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KALC 2022

Breakthrough and Excellence in Lung Cancer

November 10-11, 2022

Lotte Hotel World, Seoul, Korea

Korean Association for Lung Cancer

KALC

KOREAN ASSOCIATION FOR LUNG CANCER INTERNATIONAL CONFERENCE

Welcome Message

Dear Colleagues and Friends,

As the COVID-19 infections continue to decline and various restrictions have been lifted, we are very excited to invite you to this face-to-face and online conference. We believe that the members of our society who treat thoracic cancer must have had a harder time than anyone else. I would like to express my deep gratitude and respect to those who endured difficult times and did their best in patient care and research.

Last year, thanks to the support of many colleagues, we were able to host the KALC-IC successfully. Based on our experience, this year, we will continue to hold our annual meeting as an international event, and try to make it a more interesting, informative, and safe conference.

We prepared many lectures that summarize the rapidly changing sciences across all fields of thoracic tumors. Like last year, there will be a joint meeting with the Korean Association of Immunologists. In addition, we will have a session with the Health Insurance Review and Assessment Service to discuss issues related to medical insurance in Korea.

We hope that you will participate in the KALC-IC 2022 and welcome you to Seoul on November 10-11, 2022.

Thank you.

Dong Kwan Kim
President
Korean Association for Lung Cancer

Young Chul Kim
Chairman
Korean Association for Lung Cancer

Korean Association for Lung Cancer
KALC

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Program at a Glance

DAY 1 Thursday, November 10, 2022

TIME	Room A	Room B	Room C	Room D
	Opening 07:40-07:50			
08:00	**Plenary Session I** 07:50-08:40			
	Break 08:40-08:50			
09:00	Session I (A) **Clinical Genomics** 08:50-10:10	Session I (B) **Details and Challenges in Sublobar Resection** 08:50-10:10	Session I (C) **Radiology: AI-Enhanced Medical Imaging in Lung Cancer** 08:50-10:10	
10:00	Coffee Break 10:10-10:30			
11:00	Session II (A) **Oral Presentation I** 10:30-11:50	Session II (B) **Upcoming Novel Therapeutics** 10:30-11:50	Session II (C) **Bronchoscopy** 10:30-11:50	
12:00	Break 11:50-12:00			
	Satellite Symposium I [Yuhan] 12:00-12:40			
	Coffee Break 12:40-13:00			
13:00	Session III (A) **Indocyanine Green and Fluorescence Image-Guided Thoracic Surgery** 13:00-14:40	Session III (B) **KALC-KAI Joint Symposium** 13:00-14:40	Session III (C) **Targeting Lung Cancer with Bioconjugates** 13:00-14:40	
14:00	Coffee Break 14:40-15:00			
15:00	Session IV (A) **Advances in Radiation Oncology** 15:00-16:40	Session IV (B) **Treatment-Related Pneumonitis** 15:00-16:40	Session IV (C) **Biomarkers in Immune Checkpoint Inhibitor** 15:00-16:40	
16:00	Break 16:40-16:50			
17:00	Satellite Symposium II (AB) [MSD] 16:50-17:40		Satellite Symposium II (C) [Takeda] 16:50-17:40	Satellite Symposium II (D) [ONO BMS] 16:50-17:40

Program at a Glance

DAY 2 Friday, November 11, 2022

(*K): Session in Korean

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	Break 08:40-08:50		
09:00	Session V (A) **Liquid Biopsy** 08:50-10:10	Session V (B) **Lung Cancer Screening** 08:50-10:10	Session V (C) **KALC-HIRA Joint Symposium** (*K) 08:50-10:30
10:00	Coffee Break 10:10-10:30		
			Coffee Break 10:30-10:50
11:00	Session VI (A) **Oral Presentation II** 10:30-11:50	Session VI (B) **Multiple Primary Lung Cancer - Multidisciplinary Review** 10:30-11:50	Session VI (C) **NHIS Big Data and Lung Cancer Fact Sheet** (*K) 10:50-11:50
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12:00	Satellite Symposium III [AstraZeneca] 12:00-12:40		
	KALC General Meeting 12:40-13:00		
13:00	Session VII (A) **Oral Presentation III** 13:00-14:40	Session VII (B) **Optimal Models for Lung Cancer Research** 13:00-14:40	Session VII (C) **Immunotherapy** 13:00-14:40
14:00			
	Coffee Break 14:40-15:00		
15:00	Session VIII (A) **Recent Advances in the Treatment of Oligometastatic Lung Cancer** 15:00-16:40	Session VIII (B) **Cellular Immunotherapy** 15:00-16:40	Session VIII (C) **Small Cell Lung Cancer and Others** 15:00-16:40
16:00			
	Break 16:40-16:50		
17:00	Satellite Symposium IV (A) [MSD] 16:50-17:40	Satellite Symposium IV (B) [Pfizer] 16:50-17:40	Satellite Symposium IV (C) [Lilly] 16:50-17:40
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Session II (A). Oral Presentation I

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★ Scientific Committee's Pick

E-Poster Presentation

E-Poster Presentation

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E-Poster Presentation

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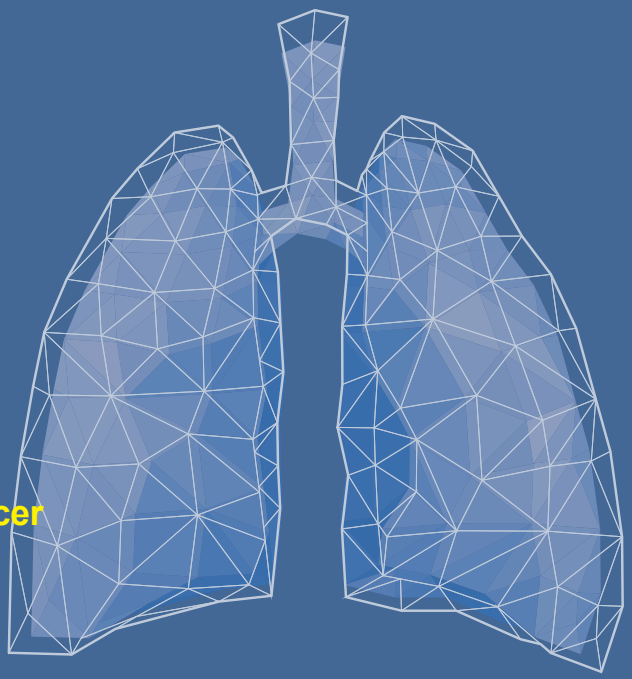

| November 10 (Thu), 2022 | Room A

07:50-08:40

Plenary Session I

Chair: Myung-Ju Ahn *(Sungkyunkwan Univ.)*

Overcoming Resistance after 3rd Generation TKI Treatment in EGFR Mutant Non-Small Cell Lung Cancer

Suresh S. Ramalingam

Emory Univ., USA

EGFR mutations account for approximately 15% and 40% of lung adenocarcinoma among Caucasian and Asian patients respectively. Mutations involving exon 19 or 21 account for approximately 85% of EGFR mutations. EGFR tyrosine kinase inhibitors (TKI) are used for the treatment of EGFR mutated advanced stage non-small cell lung cancer (NSCLC). Treatment with EGFR TKI results in improvements in response rate and progression-free survival relative to platinum-based chemotherapy. More recently, Osimertinib, a third generation EGFR TKI has demonstrated improvement in progression-free survival and overall survival compared to gefitinib, a first generation TKI in this patient population. Osimertinib has higher selectivity to the mutant receptor and is also associated with activity against brain metastasis. Osimertinib is now considered the standard first line therapy for EGFR mutated lung adenocarcinoma.

Regardless of the extent of initial response, acquired resistance invariably occurs following TKI therapy in advanced stage NSCLC; therefore, developing novel approaches to improve outcomes following acquired resistance has emerged as a major clinical priority. The mechanisms of acquired resistance to Osimertinib has been described by multiple investigators. Secondary mutation in EGFR C797 is noted in approximately 6-10% of patients treated with Osimertinib; MET amplification has been reported in approximately 20% of patients. A small subset of patients undergoes histological transformation to small cell or squamous cell histology. The emergence of ct-DNA platform for molecular analysis has allowed for non-invasive determination of acquired resistance mechanism; however, tissue biopsy is necessary to establish histological transformation. In addition, new oncogenic fusion abnormalities have also been reported in the setting of acquired resistance. Based on these observations, several efforts are underway to develop mechanism-based treatment approaches in the setting of acquired resistance.

The clinical presentation of acquired resistance may occur in the form of oligoprogression or

widespread systemic progression; progression within the brain is another form of acquired resistance that can be challenging to treat. For patients with oligoprogression, studies have noted clinical benefit with local therapy to the progressing lesion followed by continuation of Osimertinib. However, if progression is widespread, switching therapy to platinum-based chemotherapy remains the current standard therapy. In the event of conversion to small cell histology, treatment with platinum-etoposide based combination therapy is the recommended approach. Presently there is no proven role for continuation of Osimertinib after progression when patients are switched to another line of therapy; however, in patients with stable brain metastasis and extra-cranial progression, continued use of Osimertinib may be beneficial in addition to another line of therapy. The COMPEL study is presently ongoing to determine whether continuation of Osimertinib with platinum-based chemotherapy is superior to chemotherapy alone. The role of immune checkpoint inhibitors in the setting of acquired resistance remains unproven. Single agent therapy with PD-1 or PD-L1 inhibition offers minimal to no clinical benefit. A post-hoc analysis of the IMpower 150 study noted potential benefit with the combination of chemotherapy, bevacizumab and atezolizumab in patients with EGFR mutation; this observation was substantiated by the results of the ORIENT 31 study that noted improved progression-free survival with chemotherapy, sintilimab and a bevacizumab-biosimilar agent. However, the survival results have not been reported. An ongoing phase 3 study (Keynote 789) will report on the utility of adding pembrolizumab to chemotherapy in patients who develop acquired resistance to EGFR TKI therapy.

Promising results have been observed with the combination of EGFR TKI with MET inhibition in the setting of acquired resistance. A recent report noted an objective response rate of approximately 45% with Osimertinib and tepotinib (MET inhibitor) for patients with MET amplification. Another combination targeting MET and EGFR with amivantamab and lazertinib noted a response rate of 25-30% and a median progression-free survival of 5.1 months. The MARIPOSA-2 study will evaluate if the addition of amivantamab and lazertinib to chemotherapy results in favorable efficacy.

Patritumab deruxtecan is an antibody drug conjugate targeted against HER3; a recent study of patritumab in patients with acquired resistance to EGFR TKI therapy has demonstrated promising response rate of nearly 40% with a median progression-free survival of approximately 8 months. Larger confirmatory studies are presently underway to determine the role of patritumab for the treatment of patients with acquired resistance. More recently, the 4th generation of TKIs have entered clinical evaluation; BLU-945 is a novel agent that targets EGFR (L858R or exon 19 deletion), T790M and C797S; this agent has high potency and kinase selectivity in addition to penetrance into the brain. Taken together, based on increasing knowledge on resistance to Osimertinib, sev-

eral novel approaches are presently under evaluation. While more work remains to be done, we have made tremendous progress in targeting EGFR since the discovery of the mutations in the year 2004; patients are living longer and experiencing better quality of life.

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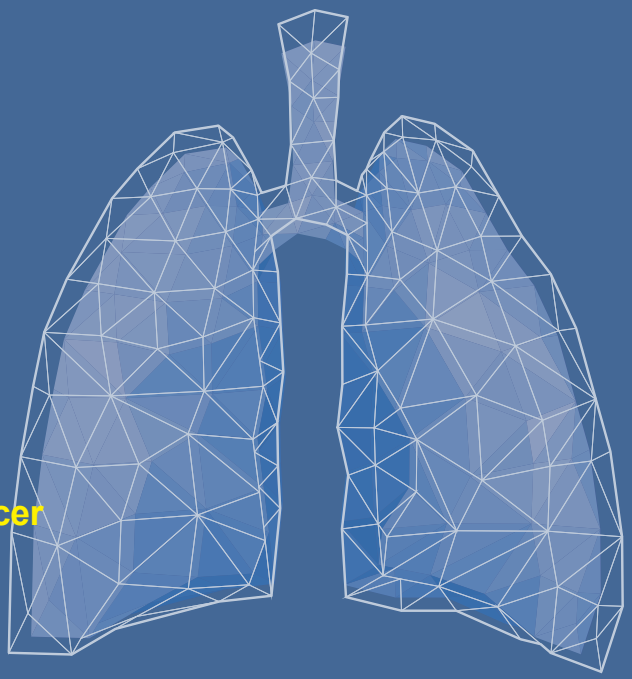

| November 10 (Thu), 2022 | Room A

08:50-10:10

Session I (A)

Clinical Genomics

Chair: Geon Kook Lee *(National Cancer Center)*

Lung Pathology in the Era of Targeted Therapies in Patients with Advanced Non-Small Cell Lung Cancer

Trishe Leong

St. Vincent's Hospital Melbourne, Australia

The advent of targeted therapies has significantly altered the requirements of the biopsy and lung cancer pathology report. The pathologist remains crucial to patient management, but our role has evolved from morphology alone to encompass molecular classification and interpretation. Tumour diagnosis, grading and staging are now only the first steps in the pathology journey, with the biopsy also required to provide sufficient tissue for molecular testing to identify driver mutations for prediction of response to personalized therapies.

The availability of reimbursement for therapeutics and companion diagnostics varies internationally and influence what is tested for routinely. Nonetheless, the number of druggable gene targets is increasing, and around half of advanced non-squamous non small cell carcinomas have a driver mutation that is currently targetable. From only 3 routinely druggable gene targets in 2018, in 2022 there are targeted therapies available for BRAF V600E, NTRK, RET and MET exon 14 skipping variants, and more recently EGFR exon 20 insertions and KRAS G12C.[1,2]

Life expectancy for the patient with advanced stage lung cancer is measured in months, so molecular testing for these driver mutations must be time-efficient so that treatment can be accessed as soon as possible. This is best achieved through optimization not only of the processes utilized by the laboratory, but also the samples provided for testing and the clinical information provided with the sample.

Sample optimization

All molecular testing requires a certain absolute quantity of DNA and percentage of tumour content in order to ensure test success and avoid false negative results. Lung tumour samples often present challenges in this regard as they are frequently core biopsies or fine needle aspirate specimens of limited volume.

Multidisciplinary guidelines from the USA regarding the collection and handling of thoracic small biopsy and cytology specimens for ancillary studies recommend that to achieve optimal diagnostic yield, the proceduralist should attempt to obtain a minimum of 3 core samples, if technically and clinically feasible.[3] An average of 2 to 3 samples collected demonstrated a diagnostic yield of 94.6% with molecular adequacy of 96.8% to 98.6%.[4]

Placing individual core specimens in separately numbered containers rather than a single container also improves tissue adequacy for molecular testing by altering subsequent specimen blocking in the laboratory.[5] It is recommended that in cases with fewer than five cores, each core should be placed in its own container and if more than five cores, two cores should be submitted per container.[6]

For fine needle aspirate specimens, the use of rapid on-site assessment and appropriate triage to allocate all material to the needle rinse once diagnostic material is identified in smears can improve the cellularity of cell blocks and the molecular adequacy rate significantly.[7]

In order to ensure that DNA is well preserved, cold ischaemia time for specimens should be minimized.3 Routine molecular diagnostics are optimized for formalin fixed, paraffin-embedded tissue so unless microbiological or other testing is required, samples should be placed into fixative immediately rather than sent in the unfixed fresh state to the laboratory.

Clinical information provision

The clinical history provided on the pathology request form can also impact the success and speed of molecular testing. When a biopsy has been performed specifically for molecular testing for a patient with known NSCLC, this should be indicated on the test request form so that the laboratory is alerted not to waste tissue on unnecessary levels or immunohistochemistry to establish a histologic diagnosis that is already known. Clinical urgency should also be communicated to the laboratory as it may be possible to prioritise testing of the sample, which otherwise may be delayed due to the need to batch specimens for cost efficiency. It is also of importance to indicate if a specific gene mutation is of interest as this influences the type of testing performed (e.g. RNA sequencing rather than DNA sequencing for gene fusions).

Laboratory process optimization

Laboratory processes should be standardised in order to ensure that lung cancer specimens are handled in a way that preserves as much tissue as possible for molecular testing, and minimises turnaround times. Staff at all levels of the laboratory should be educated regarding the need to

preserve material and procedures developed for an optimal approach based on local workflows and testing requirements.

Routine division of specimens between two or more blocks at specimen accessioning, so that levels and immunohistochemical stains are performed on one block only, may assist in ensuring that there is at least one block preserved solely for molecular. Minimisation of the amount of facing done on the paraffin block and hence tissue wastage when slides are sectioned is also essential. Sectioning slides for molecular up front on every lung cancer specimen at the same time as when the slides for diagnosis are being cut may assist tissue conservation and efficient molecular testing. Performing molecular testing as reflex upon the diagnosis of non squamous NSCLC is also recommended to minimise testing delays.[5]

As the number of relevant genes and the complexity of the genetic alterations requiring detection increases, next generation sequencing with a combined DNA and RNA workflow is increasingly becoming the method of choice over single gene methods because of its sensitivity, greater accuracy in detecting fusions and skipping events, and its ability to detect all types of mutations in parallel from small amounts of tissue.[8,9] NGS also becomes more cost-efficient than multiple single-gene tests when greater than three gene targets are being investigated.[10]

Routine use of liquid biopsies to test circulating tumour DNA is yet to replace direct testing of tumour tissue and is only recommended in certain settings. Although specificity is near 100%, liquid biopsy lacks sensitivity and negative results still require reflex to tissue testing to exclude false negative results.[11]

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Experience of ROS1 CDx Platforms in the Central Laboratory of South Korea

Tae Jung Kim

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Lung cancer is the most common type of cancer worldwide and the leading cause of cancer - related death.[1] Approximately 85% of individuals with lung cancer have non - small - cell lung cancer (NSCLC), with 70% of NSCLC tumors being inoperable, locally advanced, or metastatic at diagnosis.[2] Molecular targeting agents such as epidermal growth factor receptor (*EGFR*) - tyrosine kinase inhibitors (TKIs), anaplastic lymphoma kinase (*ALK*) - TKIs, c - ros oncogene 1 (*ROS1*) - TKIs, and v - raf murine sarcoma viral oncogene homolog B1 (*BRAF*) - TKIs have markedly improved progression - free survival (PFS) and overall survival (OS) in patients with NSCLC who are positive for the corresponding genetic alterations. [3,4,5,6,7] Testing for these driver oncogene alterations in advanced NSCLC, especially in non - squamous - cell carcinoma, is essential for making informed treatment decisions. Among them, ROS1 is ROS1-rearranged (*ROS1*+) non-small-cell lung cancer (NSCLC) is a rare lung cancer with limited treatment options.[8]

Three different assays, including fluorescent in situ hybridization (FISH), Amoy Dx reverse transcription polymerase chain reaction (RT-PCR), and Oncomine Dx Target Test (ODXTT), were routinely performed as part of a nationwide screening in South Korea to detect ROS1 rearrangement in NSCLC. The clinicopathologic and analytic features were assessed. 257 (1.9%) of 13,673 NSCLC confirmed positive for ROS1 rearrangement using RT-PCR or FISH. In consecutive 155 NSCLC cases with assessing both ROS1 RT-PCR and ODxTT, additional four ROS1-positive cases were found using ODXTT. The average age of patients in the ROS1-positive group was 61 years old, Female patients (58.4%) with ROS1-positive occurred more than male patients (41.6%). Turnaround time for each method were 5.2 days by FISH, 4.8 days by RT-PCR, and three weeks by ODXTT, respectively. RNA based test failure rate was 65 (0.6%) of 11745 NSCLC with ROS1 RT PCR and 1 (0.8%) of 116 cases with upfront ODxTT and 7 (4.2%) of 47 cases with serial ODxTT. We anticipate that using upfront ODxTT or RT-PCR in conjunction with ODxTT can increase the screening sensitivity for ROS1 mutations.

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Clinician's View on Next-Generation Sequencing for Rare Mutations in Lung Cancer

Shinkyo Yoon

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Next-generation sequencing (NGS) and its increased cost efficiency have allowed for the rapid panel testing of hundreds of genes and the selection of tumor mutations and targeted anticancer drugs[1]. With advances of NGS, the molecular characterization of non-small cell lung cancer (NSCLC) has revealed a slew of oncogenic alterations, of which several have become targets for drug development[2]. For a relevant therapeutic decision, we need to focus on several issues about tissue acquisition, sequencing platform, and the operation of molecular tumor board (MTB).

First, target areas of DNA extraction are the most important consideration, and enrichment of tumor cells is vital when selecting the region of interest. Extracting DNA from locations below the standard for tumor cell fraction can lead to false negatives. Tissue storage and fixation is crucial to achieve high-quality samples suitable for NGS. Delayed or insufficient fixation in surgical samples, in particular, may lead to DNA degradation. Liquid biopsies have been introduced into clinical practice for non-invasive genome analysis, treatment response monitoring, identification of drug-resistant mechanisms, early detection of recurrence, and overcoming intra-tumoral heterogenicity by supplementing the limitations of NGS examinations using existing tumor tissues[3]. Second, for accurate detection of fusions, gene panels should be designed with optimization to cover either whole regions of a gene or specific exonic/intronic regions where fusions frequently occur. However, intronic regions are hardly covered by the sequencing due to repeated sequences. In this respect, no fusion is detected if breakpoints are located in the uncovered regions. To overcome these limitations, the use of RNA panels has been gradually expanded recently[4]. Lastly, operation of MTB will be crucial for the optimal delivery of precision medicine[5]. Reviewing the use of an appropriate sample and correct test methods comprise the discussions concerning quality within the MTB. Moreover, reviewing appropriate sample selection, cellularity, and mean target depth is important to assess the quality of the NGS. When clinically significant genetic abnormalities arise from the NGS, single nucleotide variants, copy number variation, and structural

variation should be examined. Additionally, when interpreting each genetic aberrations, knowledge databases, such as OncoKB, cBioportal.

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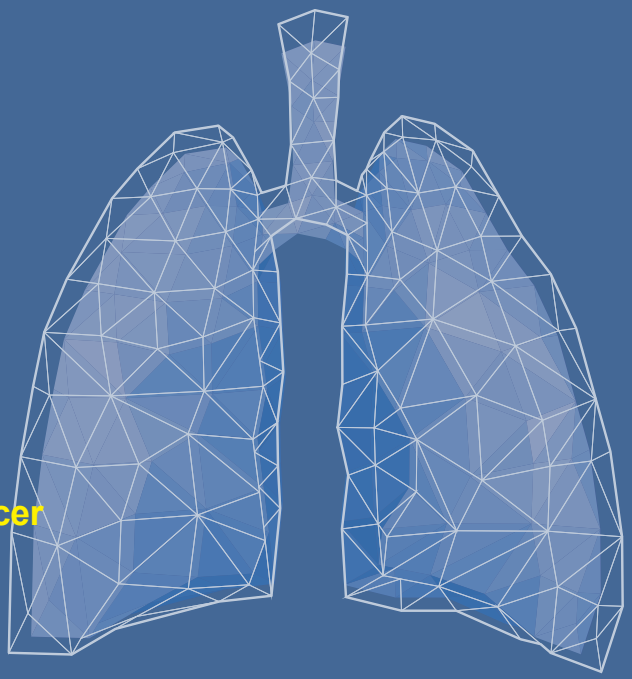


| November 10 (Thu), 2022 | Room A

10:30-11:50

Session II (A)

Oral Presentation I

Chair: In Kyu Park *(Seoul National Univ.)*

Exosome-GCC2 as a Promising Biomarker and Therapeutic Target for Lung Adenocarcinoma: A Multicenter Study

Byeong Hyeon Choi[1,2], Hyonggin An[3], Sukki Cho[4,5], Sungsoo Lee[6], Hyeong Ryul Kim[7], Jong Ho Cho[8], Ok Hwa Jeon[2,9], Hyunku Shin[10], Yeonho Choi[10, 11], and Hyun Koo Kim[2,9]

[1]Korea Artificial Organ Center, Korea University, Seoul, Republic of Korea; [2]Department of Thoracic and Cardiovascular Surgery, Korea University Guro Hospital College of Medicine, Korea University, Seoul, Republic of Korea; [3]Department of Biostatistics, Korea University College of Medicine, Seoul, Republic of Korea; [4]Department of Thoracic and Cardiovascular Surgery, Seoul National University College of Medicine, Seoul, Republic of Korea; [5]Department of Thoracic and Cardiovascular Surgery, Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do, Republic of Korea; [6]Department of Thoracic and Cardiovascular Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [7]Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [8]Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [9]Department of Biomedical Sciences, College of Medicine, Korea University, Seoul, Republic of Korea; [10]Exopert corporation, Seoul, Republic of Korea; [11]Department of Biomedical Engineering, Korea University, Seoul, Republic of Korea

Aims: An early lung cancer diagnosis is essential for patients to receive optimal treatment as early as possible and improve survival rates. Liquid biopsy is a noninvasive technique that allows cancer detection using body fluids as samples, with the added advantage of real-time monitoring of cancer treatment. Exosomes are 30 – 200 nm nano-sized vesicles secreted by all types of cells and involved in biological functions. In a pilot study, we previously reported the discovery of GRIP and coiled-coil domain containing 2 (GCC2) expressed exosomes as a predictive biomarker and therapeutic target for early detection of lung adenocarcinoma. In this study, we evaluated the potential biomarker of exosome-GCC2 for lung adenocarcinoma by comparing lung adenocarcinoma patients who underwent surgery with healthy controls through a multicenter clinical study. Moreover, we demonstrated the association with tumor growth of exosome-GCC2 *in vitro* and *in vivo*.

Methods: A total of 470 blood plasma samples (age, sex-matched 150 healthy controls, and 320 lung adenocarcinoma patients who received lung cancer surgery and pathologically diagnosed lung adenocarcinoma) were retrospectively obtained from five institutions: Korea University Guro Hospital, Seoul National University Bundang Hospital, Gangnam Severance Hospital, Asan Medical Center, and Samsung Medical Center in the Republic of Korea. Exosome isolation from conditioned media and blood plasma was isolated by size exclusion chromatography. The expression of exosome-GCC2 was evaluated using western blot, nano tracking analysis (NTA), transmission electronic microscopy (TEM), immunohistochemistry (IHC) staining, and ELISA assay. A series of

in vitro research investigated the biological functions of exosome GCC2. Moreover, mouse xenograft models were used to demonstrate the clinical relevance of exosome-GCC2 *in vivo*.

Results: The concentration of exosome-GCC2 in lung adenocarcinoma patients was significantly higher than in healthy controls; the AUC value was 0.856, sensitivity was 90.67%, and specificity was 72.50%. According to the statistical analysis, exosome GCC2 was significantly associated with c-stage, p-TNM stage, tumor size, visceral pleural invasion, and ECOG score. Moreover, GCC2 expression of lung adenocarcinoma tissues was significantly overexpressed than non-cancerous lung tissues result of GCC2 IHC staining. The concentration of GCC2 of exosomes in PC9 cells knockdown with GCC2 siRNA was decreased than in those treated with control siRNA. We found that treatment with GCC2-depleted exosomes for 72h significantly decreased the proliferation of PC9 cells. Moreover, GCC2 depleted exosomes suppressed tumor growth and lymph node metastasis in the mouse cancer model.

Conclusions: Our study identified Exosome-GCC2 might be a promising biomarker with a therapeutic target for lung adenocarcinoma.

Keywords: Extracellular vesicles, Biomarker, Lung adenocarcinoma, Liquid biopsy

AXL Affects Tumor Growth of Lung Cancer through Regulating of Dendritic Cells

Kyungtaek Im[1], Yun Jung Choi[1], Dong Ha Kim[1], Cha Won Lee[2], Da-Som Kim[2], Chang-Min Choi[3,4], Wonjun Ji[3], Jae Cheol Lee[4], Jin Kyung Rho[5]

[1]Asan Institute for Life Sciences, [2]Department of Biomedical Sciences, AMIST, [3]Department of Pulmonology and Critical Care Medicine, and [4]Department of Oncology, [5]Department of Convergence Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

AXL is a receptor tyrosine kinase (RTK) that has a various role in tumor progression such as proliferation, metastasis, angiogenesis, drug resistance and immune tolerance. Although targeting AXL exhibits an anti-cancer effects partially depending on the immune system, their molecular mechanisms have not been fully elucidated. To search the roles of AXL in immune tolerance of tumor, we generated AXL knockout (KO) mice. These AXL KO mice showed the reduced tumor growth in syngeneic LLC-1 model compared to wild type mice. To validate the mechanisms underlying the inhibition of AXL KO-derived tumor growth, we examined tumor-infiltrating lymphocytes (TIL). Compared with tumor-bearing wild type mouse, CD45-positive cells were significantly enhanced in tumor-bearing AXL KO mouse. Especially, these results were dominant in CD8-positive cells and dendritic cells (DCs). Tumor-infiltrating DCs showed the altered expression of surface receptors in AXL KO mouse. In addition, the inhibition of AXL led to induce the DCs migration. In conclusion, our data demonstrated that targeting AXL may inhibit tumor growth through the activation of DCs including the enhancement of migration and reduced expression of receptors in DCs.

The Expression of CEACAMs and Serum CEA Levels as Biomarkers of Postoperative Cancer Recurrence in Non-Small Cell Lung Cancer

Bubse Na[1], Onyou. Lee[2], Yun Ho Kim[2], Yoojin Jung[2], Kwon Joong Na[1,2], Hyun Joo Lee[1], Samina Park[1], In Kyu Park[1], Chang Hyun Kang[1], Young Tae Kim[1,2]

[1]Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul/KR; [2]Cancer Research Institute, Seoul National University College of Medicine, Seoul/KR

Aims: The serum carcinoembryonic antigen (CEA) levels have been used as a prognostic biomarker and a diagnostic tool for non-small cell lung cancer (NSCLC). However, no study has been conducted to compare the gene expression of CEA-related cell adhesion molecules (CEACAMs) in surgically resected cancer specimens matching CEA levels. We hypothesized that the expression of CEACAMs and postoperative serum CEA levels may be utilized as a biomarker to predict postoperative cancer recurrence in NSCLC.

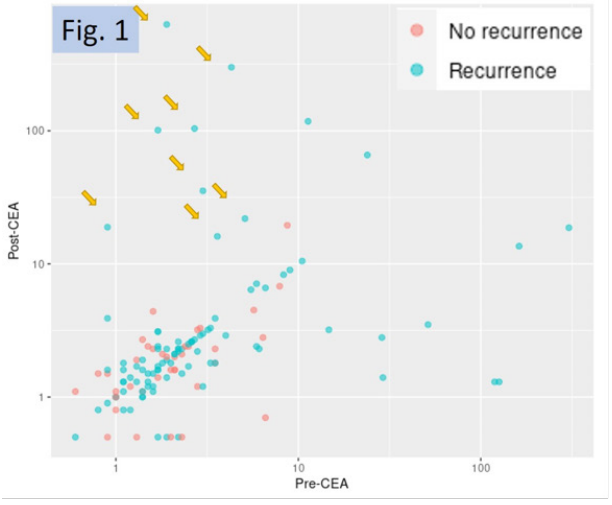
Methods: We identified 157 patients who underwent surgery for NSCLC and had access to cancer specimens for whole transcriptome sequencing (WTS) and CEA levels. Using the STAR aligner, WTS data were aligned to the reference genome hg19. The "DESeq2" R software was utilized to evaluate differentially expressed genes. CEA levels were determined preoperatively (pre-CEA) and at the time of recurrence (post-CEA). The most recent postoperative CEA levels were used as the post-CEA in those who did not experience recurrence. Normal lung tissue WTS data were also available for 79 cases. By comparing data on lung cancer and normal lung tissue, we could determine the extent to which the transcripts were differentially expressed

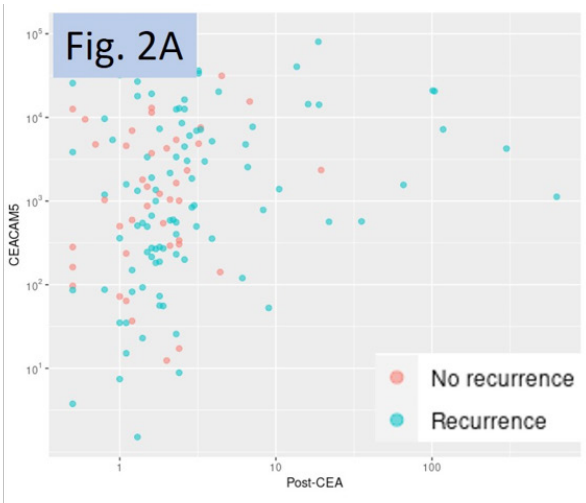
Results: Elevated pre- or post-CEA levels (>10ng/ml) were associated with recurrence (p=0.035, HR=7.341 pre-CEA; p=0.064, HR=6.265 post-CEA). When a patient whose pre-CEA level was elevated (>10ng/ml) developed a recurrence, the post-CEA level was increased. Even while the pre-CEA level was low, the post-CEA level increased in many patients at the time of recurrence, which we thought to be an intriguing finding (arrow) (Fig.1). CEACAMs were frequently overexpressed in the majority of cases (79.7% CEACAM5, 53.2% CEACAM6). The levels of CEACAM5 and CEACAM6 expression were significantly correlated (R2=0.73, p<0.001). The majority of patients with elevated CEA levels (>10ng/ml) expressed high levels of CEACAM5 and CEACAM6, implying that the elevated serum CEA level was caused by CEA leaking from cancer tissue into the blood-

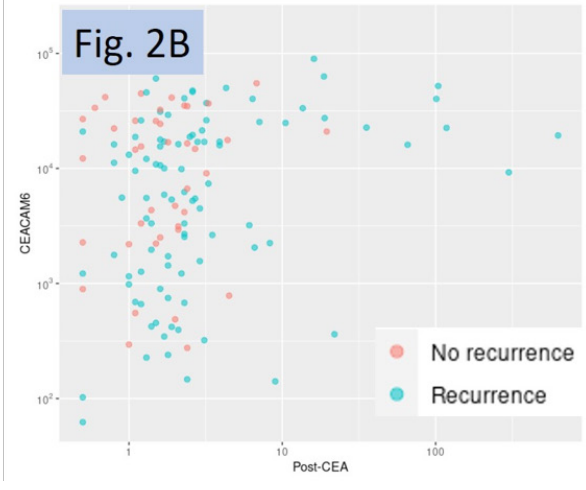
stream. Interestingly, many patients with elevated CEACAM expression showed low post-CEA levels(≤10ng/ml) at the time of recurrence, implying the existence of a novel molecular mechanism regulating the cancer cell's protein entry into the bloodstream (Fig.2).

Conclusions: Our data established that pre- or post-CEA levels greater than 10 ng/ml were a significant predictor of recurrence, particularly in patients with high CEACAMs expression in their cancer tissue. The occurrence of individuals with recurrence who had low post-CEA levels despite elevated CEACAMs levels demonstrated that CEA levels may not be an ideal marker for detecting recurrence in NSCLC, indicating the existence of a novel molecular mechanism controlling the cancer cell protein leaking into the bloodstream.

Keywords: Lung cancer, CEA, NGS







Plasma GDF15 Levels are Associated with PD-1+ T Cells in Advanced NSCLC Patient Who Treated Immunotherapy

Da Hyun Kang[1], Green Hong[1], Pureum Sun[2], Chaeuk Chung[1], Dongil Park[1], Song-I Lee[1], Nayoung Kim[2], Jeong Eun Lee[1]

[1]Department of Internal Medicine, College of Medicine, Chungnam National University, Daejeon, Korea; [2]Institute for Medical Sciences, College of Medicine, Chungnam National University, Daejeon, Korea

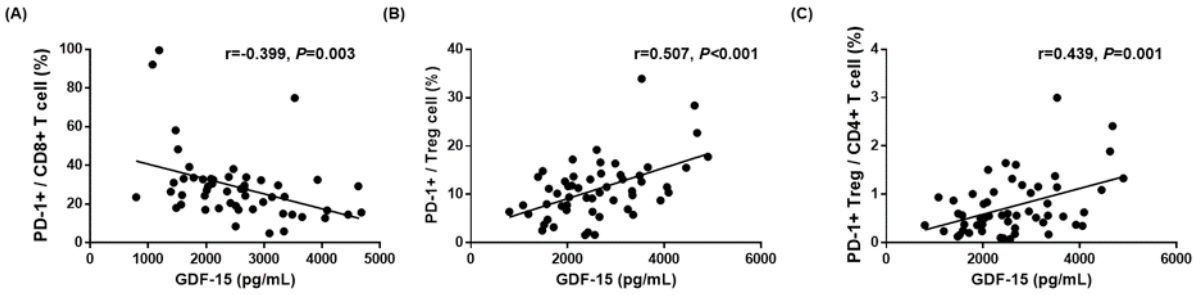
Aims: GDF15 is a stress-induced cytokine that secreted by tumor cells and affected by tumor-promoting inflammation, and immune infiltration. Although it is reported that GDF15 expression in human tumor tissues is associated with CD3+ or CD8+ T cell infiltrations, the effect of circulating GDF15 on immune escape signaling remain largely unknown. We identified the association of circulating GDF15 levels with immune cell populations of peripheral blood mononuclear cells (PBMCs).

Methods: This study is a prospective study included 87 patients with advanced NSCLC receiving PD-1/PD-L1 inhibitors from March 2018 to May 2020 in Chungnam National University Hospital (CNUH). Blood samples for measuring plasma GDF15 level were obtained from patients immediately before PD-1/PD-L1 inhibitor administration. Peripheral blood mononuclear cells were isolated, and multi-color flow cytometry was performed.

Results: The proportion of PD-1$^+$CD8$^+$ T cells in CD8$^+$ T cells (PD-1$^+$/CD8$^+$) were significantly lower in the high GDF15 group than low GDF15 group, and the proportion of PD-1$^+$ Treg cells in Treg cells (PD-1$^+$/Treg) and the proportion of PD-1$^+$Treg cells in CD4$^+$ T cells (PD-1$^+$Treg/CD4$^+$) were significantly higher in the high GDF15 group than low GDF15 group. We investigated the correlation analysis of plasma GDF15 levels with immune cell subpopulations, sPD-1, and sPD-L1. Plasma GDF15 level was negatively correlated with PD-1$^+$/CD8$^+$ ($r = -0.399, p = 0.003$), and positively correlated with PD-1$^+$/Treg ($r = 0.507, p<0.001$), and PD-1$^+$Treg/CD4$^+$ ($r = 0.439, p<0.001$).

Conclusions: Plasma GDF15 levels were associated with the proportion of PD-1$^+$CD8$^+$ T cells and PD-1$^+$ Treg cells in advanced NSCLC patients underwent immunotherapy.

Keywords: GDF15, NSCLC, Immunotherapy


(A)
PD-1+ / CD8+ T cell (%)
r=-0.399, P=0.003
GDF-15 (pg/mL)
(B)
PD-1+ / Treg cell (%)
r=0.507, P<0.001
GDF-15 (pg/mL)
(C)
PD-1+ Treg / CD4+ T cell (%)
r=0.439, P=0.001
GDF-15 (pg/mL)

Preoperative Mediastinal Lymph Node Evaluation with Cancer-Associated Fibroblast Imaging Using Ga-68 FAPI PET/CT in Non-Small Cell Lung Cancer: A Prospective Pilot Study

Kwon Joong Na[1], Yeon-koo Kang[2], Nakwon Kwak[3], Jimyung Park[3], Hongyoon Choi[2], Young Tae Kim[1]

[1]Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [2]Department of Nuclear Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [3]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea

Aims: Conventional diagnostic imaging modalities have limitations in accurate lymph node staging for non-small cell lung cancer (NSCLC). Fibroblast activation protein inhibitor (FAPI) PET has been proposed as a promising imaging method for the evaluation of various kinds of malignant disorders. We aimed to investigate the feasibility of Ga-68 FAPI PET in preoperative mediastinal lymph node staging in NSCLC.

Methods: As a pilot study, eight patients (mean age 64±9 years, M:F=6:2) who were planned to undergo curative surgery for NSCLC were enrolled in this prospective study. F-18 FDG PET and Ga-68 FAPI PET were performed within three months before surgery. In a patient-wise analysis, two experienced nuclear medicine physicians read the images to evaluate the stage based on each imaging modality. In a lesion-wise quantitative analysis, radiotracer uptake of each node was measured as maximum standardized uptake value (SUV_{max}) and TBR_{max} (SUV_{max}/mediastinal blood pool activity).

Results: Based on the postoperative pathologic examination, one patient was proven to be in N1 stage, one in N2 and the rest in N0. In the patient-wise analysis, FAPI PET exhibited higher diagnostic accuracy than FDG PET in mediastinal lymph node staging (100.0% vs. 87.5%). FDG PET underestimated an "N2" patient as "N0", who was estimated correctly by FAPI PET (Figure 1). In the lesion-wise analysis, a total of eighteen nodes were evaluated. Tracer uptake in FAPI PET was higher in all metastatic nodes (TBR_{max} 7.53±4.62 vs. 3.17±1.94) and lower in all benign nodes (1.72 ±0.77 vs. 2.38±0.64) in comparison with FDG PET (Figure 2). The lesion-wise sensitivity and specificity were 100.0% and 93.3% in FAPI PET, and 66.7% and 80.0% in FDG PET.

Conclusions: FAPI PET exhibited the potential to provide additional benefits with higher accuracy in lymph node staging of NSCLC. Further studies with larger sample sizes are warranted to vali-

date diagnostic performance.

Keywords: Lung cancer, Cancer-associated fibroblast, Positron emission tomography

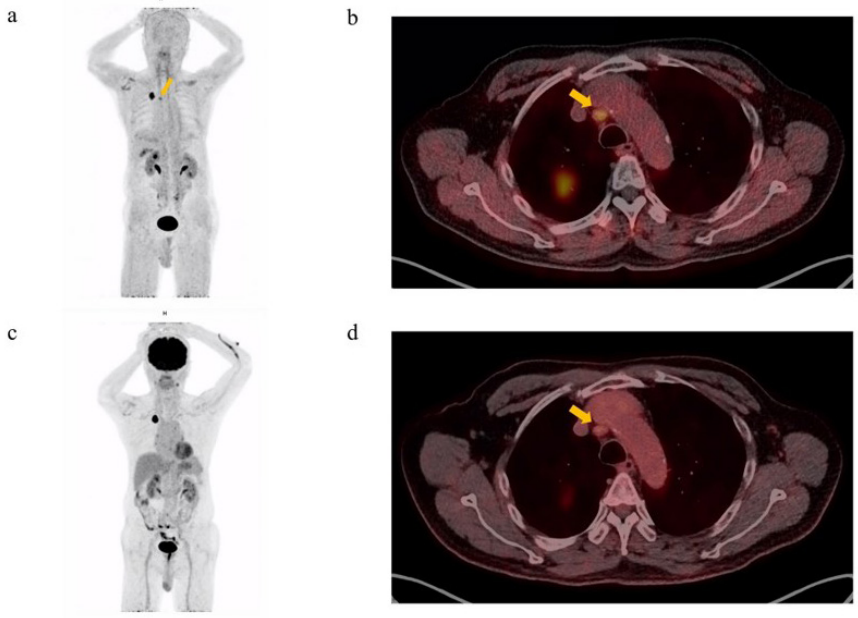


Figure 1. Comparison of Ga-68 FAPI PET and F-18 FDG PET images in a single patient Ga-68 FAPI PET (a-b) and F-18 FDG PET (c-d) images in a patient who were planned to receive right upper lobectomy. The right paratracheal node exhibited significant increase of uptake only in FAPI PET, which was confirmed to be the only metastatic lesion by postoperative pathologic examination.

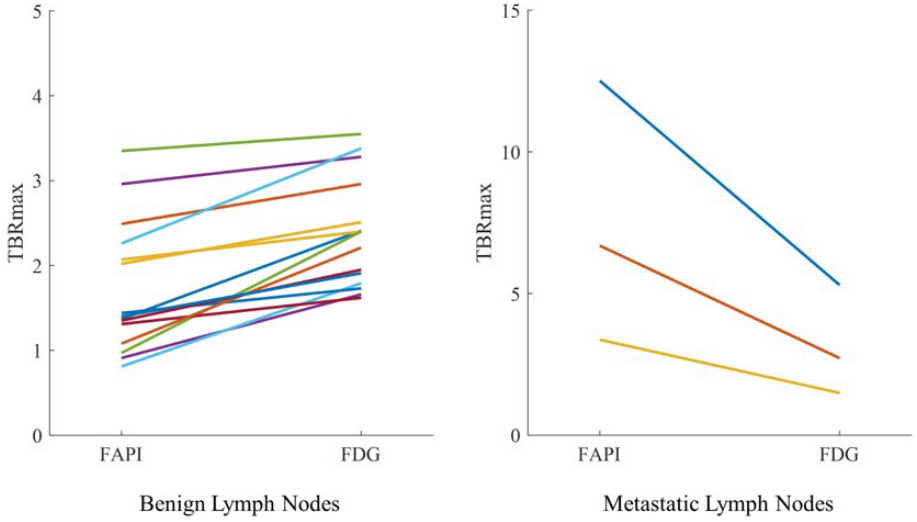


Figure 2. Comparison of nodal tracer uptake in Ga-68 FAPI PET and F-18 FDG PET images Tracer uptake measured as TBR_{max} in benign (left plot) or metastatic (right plot) lymph nodes from all patients are described for FAPI (left column of each plot) and FDG (right column of each plot) PET images. FAPI uptake is lower in all benign nodes but higher in all metastatic nodes in comparison with FDG uptake.

Augmented Reality Eye Glasses Display for Real-time Fluorescent Imaging-Guided Surgery

Ok Hwa Jeon[1,2], Sungjoon Kim[3], Seung Hyun Lee[4], Beop-Min Kim[4], PhD, Kwanghoon Lee[3], Hyun Koo Kim[1,2]

[1]Department of Thoracic and Cardiovascular Surgery, Korea University Guro Hospital, College of Medicine, Korea University, Seoul, Korea; [2]Department of Biomedical Sciences, College of Medicine, Korea University, Seoul, Korea; [3]Spatiacl optical information research center, Korea photonics technology institute, Gwangju, Korea; [4]Department of Bio-Convergence, Korea University, Seoul, Korea

Aims: Indocyanine green (ICG)-based near-infrared (NIR) fluorescence imaging technology has been actively used to intraoperative visualize various types of cancer and lymph nodes as well as perfusion of blood in target organs in patients. Up to now, most of NIR imaging systems provide information the fluorescent imaging on the surgical monitor which can interrupts the surgeons' attention and results in increasing the probability of errors and the overall surgery time. Here, we develop an Augmented Reality Eye Glasses Display (AR-EGD) that not only provides the user with a near-infrared fluorescence image of the target area in real-time using an AR optical system, but also matches the real surgical area by matching the calibration module.

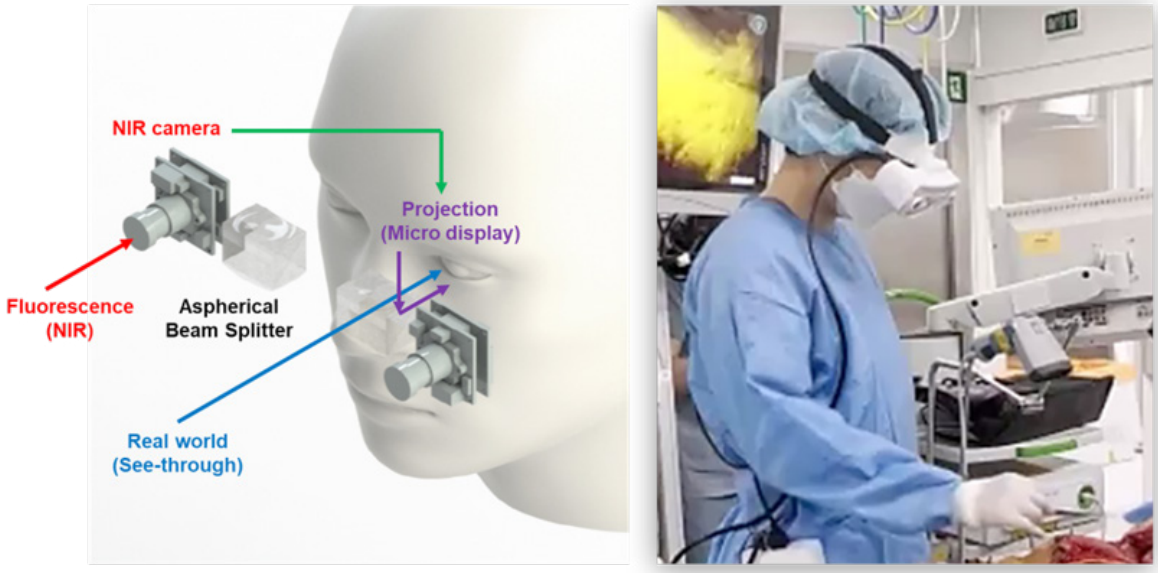
Methods: The fluorescence signal acquired from the NIR camera is post-processed through a calibration module for matching of AR fluorescence images and real-space objects, and was developed using Visual Studio 2017 (Microsoft, Redmond, WA, USA), C++. We also confirmed the practical applicability by optimizing the real-time object and real-time AR image matching through the fluorescence image matching calibration module. Next, the feasibility of using AR-EGD for intraoperative indocyanine green-based detection of sentinel lymph nodes (SLN), intersegmental planes, and lung cancers was evaluated in rabbit model. We also evaluated the utility of AR-EGD to detect pseudo lung cancer and segmental plane of target segment in a canine model. Lastly, to improve the clinical applicability of AR-EGD, we detected lung cancer with AR-EGD in 10 patients preoperatively labelled with ICG for lung cancer in ex vivo, and compared its fluorescence signal with the NIR fluorescent imaging system used in the clinic.

Results: The AR optical system can acquire fluorescent-guided cancer images with NIR cameras through the beam-splitter optics located at the front of the surgeon's eye. And acquired fluorescent images are finally delivered to the surgeon's eye in real time through the micro-display and beam-splitter optics, and a matched AR image with the same position, size and depth as the can-

cer site can be viewed simultaneously in the surgery site. AR-EGD provided accurate fluorescence images of the SLN, intersegmental planes, and lung cancers, and it was consistently matched with the real image of rabbit models. The pseudo lung cancer and segmental plane of the canine models were also detected by AR-EGD, and segmentectomy were successfully performed. In 10 patients, all lung cancers were successfully detected using AR-EGD. In addition, the fluorescence images of lung cancer detected in AR-EGD were consistent with near-infrared fluorescence imaging systems used in the clinic.

Conclusions: AR-EGD can be potentially very useful and fully integrated by the surgeon for optimizing many aspects of oncologic surgery.

Keywords: Augmented reality eye glasses display , Indocyanine green , Real-time



The 10-Year Journey of Non-Small Cell Lung Cancer: Real-World Experience

Daeho Choi[1]; Hyeyeon Yu[2], Yoon-La Choi[3], Sehhoon Park[2], Jong-Mu Sun[2], Se-Hoon Lee[2], Jin Seok Ahn[2], Myung-Ju Ahn[2], Kyunga Kim[4,5,6†], Hyun Ae Jung[2†], Keunchil Park[2]

[1]Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences & Technology, Sungkyunkwan University, Seoul, Korea; [2]Division of Hematology Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [3]Department of Pathology and Translational Genomics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [4]Biomedical Statistics Center, Research Institute for Future Medicine, Samsung Medical Center, Seoul, Korea; [5]Department of Data Convergence & Future Medicine, Sungkyunkwan University School of Medicine, Seoul, Korea; [6]Department of Digital Health, Samsung Advanced Institute for Health Sciences & Technology, Sungkyunkwan University, Seoul, Korea

Aims: Over the past 10 years, the treatment of NSCLC has been revolutionized with the development of molecular test and targeted therapy and immunotherapy. This study evaluated how this revolution of treatment of NSCLC improved outcomes in the real-world.

Methods: We collected and analyzed a comprehensive clinical, pathological, and molecular data of NSCLC in our cohort. The primary outcome was overall survival by clinical stage, histology, and molecular biomarker between two period (Period I: 2010-2015 versus Period II: 2016-2021).

Results: Among 21,978 NSCLC patients, adenocarcinoma (AD) was the predominant histology (70.3% in Period I vs. 74.3% in Period II) (standardized mean difference [SMD] = 0.09, $p < .001$). In Period I, 37.0%, 10.5%, 15.9%, and 34.3% patients were in clinical stages I, II, III, and IV, respectively. In Period II, 45.1%, 9.7%, 15.2%, and 29.3% were in each stage, respectively (SMD = 0.16, $p < .001$). Patients during Period II were more likely to undergo molecular tests for *EGFR*, *ALK*, and/or others than those during Period I in both the AD (79.8% in Period I vs. 97.9% in Period II) and non-AD (53.8% in Period I and 89.0% in Period II) groups. In AD patients, 40.5% in Period I and 56.6% in Period II had any major druggable mutations. Among non-AD patients, 2.9% and 5.7% of patients had any major druggable mutations in Periods I and II, respectively. In patients with AD in Period I, the 3-year survival rates were 92.8 %, 72.4%, 56.7%, and 28.7% for each stage (I, II, III, and IV), respectively. In Period II, the 3-year survival rates of AD patients were 95.1 %, 82.5%, 65.1%, and 42.4% for each stage, respectively (all $p < .05$). In patients with non-AD, the 3-year survival rates were 72.0%, 60.0%, 38.9%, and 9.7% for each stage in Period I. In Period II, the 3-year survival rates of non-AD were 79.3%, 67.3%, 48.2%, and 18.1% for each stage (all $p < .05$).

Conclusions: Our study is meaningful as a large-scale study that reflects the changes in survival

outcomes in a timely manner. Through our real-world experience of over 10 years, the incidence of never-smokers and early-stage NSCLC has been increasing. Moreover, the implementation of molecular testing has increased. Notably, survival outcomes remarkably improved across all stages, especially in patients with stage III–IV disease.

Keywords: Non–small-cell lung cancer, Medical big data, Clinical data warehouse

Application of Exosomal miRNAs as Diagnosis Biomarkers for Small Cell Lung Cancer

Dong Ha Kim[1], Yun Jung Choi[1,2], Kyungtaek Im, Cha Won Lee, Da-Som Kim, Chan-Gi Pack[2], Chang-Min Choi[1,7], Wonjun Ji, Jae Cheol Lee[7,†,*], Jin Kyung Rho[2,†,*]

[1]Asan Institute for Life Sciences, [2]Department of Convergence Medicine, [3]Department of Biomedical Sciences, AMIST, [4]Department of Pulmonology and Critical Care Medicine, and [5]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Korea

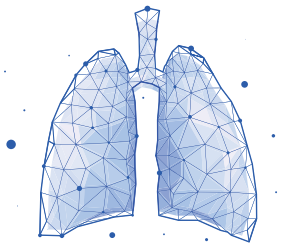
Aims: Small cell lung cancer (SCLC) have an exceptionally poor prognosis because the most of them are initially diagnosed as extensive disease (ED) with hematogenous metastasis. Thus, early diagnosis of SCLC seems very important, and may lead to improve its prognosis. To investigate the possibility of early diagnosis of SCLC, we examined exosomal miRNAs in serum from patients with SCLC.

Methods: Firstly, exosomes were isolated in serum from patients with SCLC and healthy individuals, and were characterized using particle size and protein markers. And then miRNA array was performed to define SCLC-specific exosomal miRNAs. From the results of miRNA array, we selected 19 up-regulated miRNAs and 12 down-regulated miRNAs based on p-values, and top 10 differentially expressed. Of these 51 miRNAs, 25 miRNAs were validated using quantitative reverse transcription-polymerase chain reaction (RT-PCR). Secondly, 25 miRNAs were further validated using large cohort.

Results: Among them, 7 miRNAs were significantly changed in only SCLC-derived exosomes. 6 miRNAs (miR-3565, miR3124-5p, miR-200b-3p, miR-6515, miR-3126-3p and miR-9-5p) were up-regulated and 1 miRNA (miR-92b-5p) was down-regulated. Finally, the ability to diagnose SCLC of 7 miRNAs was estimated by AUC. The AUC of each miRNA exhibited the value from 0.64 to 0.76, however the combined application of 3 miRNAs (miR-200b-3p, miR-3124-5p and miR-92b-5p) dramatically improved the diagnostic value (AUC=0.93). In addition, 3 miRNA panel was associated with various oncogene pathway and nervous system development in gene ontology analysis, and a worse prognosis.

Conclusions: In conclusion, our study identified SCLC-specific exosomal miRNAs. The 3-miRNA panel (miR-200b-3p, miR-3124-5p and miR-92b-5p) may serve as a diagnostic and prognostic marker for SCLC.

Keywords: Small cell lung cancer, Diagnosis, Exosome, MiRNAs



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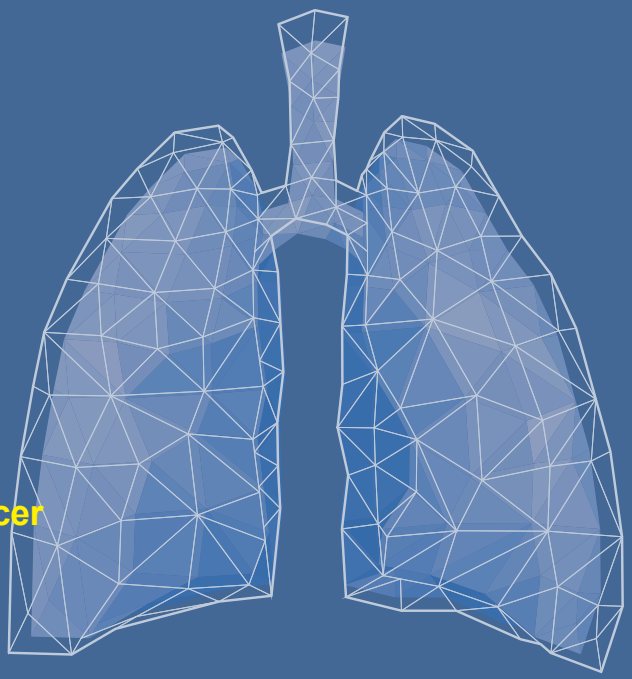

| November 10 (Thu), 2022 | Room A

12:00-12:40

Satellite Symposium I

[YUHAN]

Chair: Jin-Hyoung Kang *(The Catholic Univ. of Korea)*

Spotlighting the New 3rd Generation EGFR TKI, Lazertinib: Updated Clinical Study Results & Real World Outcomes

Sun Min Lim

Yonsei Univ., Korea

Lazertinib is an oral, irreversible, third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that exhibits a high selectivity for sensitizing and T790M EGFR mutations. In January 2021, it was first approved for the treatment of advanced or metastatic non-small cell lung cancer (NSCLC) patients with EGFR T790M who had previously received EGFR TKI therapy based on LASER201, a phase I/II trial. At a recommended dose of 240 mg, lazertinib achieved an encouraging anti-tumor activity in both extra- and intracranial lesions. With a high half-maximal inhibitory concentration for EGFR wild type tumors, it is anticipated to pose a lower risk of skin and cardiac adverse events compared to osimertinib.[1] Lazertinib was studied in a first-in-human, open-label, multicenter, phase 1-2 trial, and the recommended phase 2 dose was determined to be 240mg.[2] Lazertinib 240mg daily has a manageable safety profile with durable anti-tumor efficacy, including brain metastases, in patients with advanced T790M-positive NSCLC after previous EGFR TKI therapy.[3] The updated overall survival data showed a median of 38.9 months (30.2-NR).[3] Lazertinib is currently being investigated as a monotherapy in first-line treatment in a global, phase III trial aiming to compare the efficacy of lazertinib to gefitinib as a first-line treatment (NCT04248829), and several studies are ongoing with lazertinib as a single agent or in combination with stereotactic radiotherapy or chemotherapy or Amivantamab. In this symposium, I will systemically summarize the preclinical and clinical data of lazertinib and discuss recent real world outcomes from Yonsei Cancer Center.

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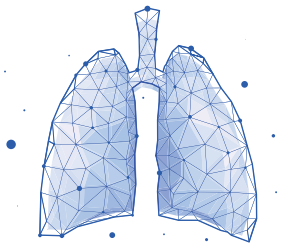

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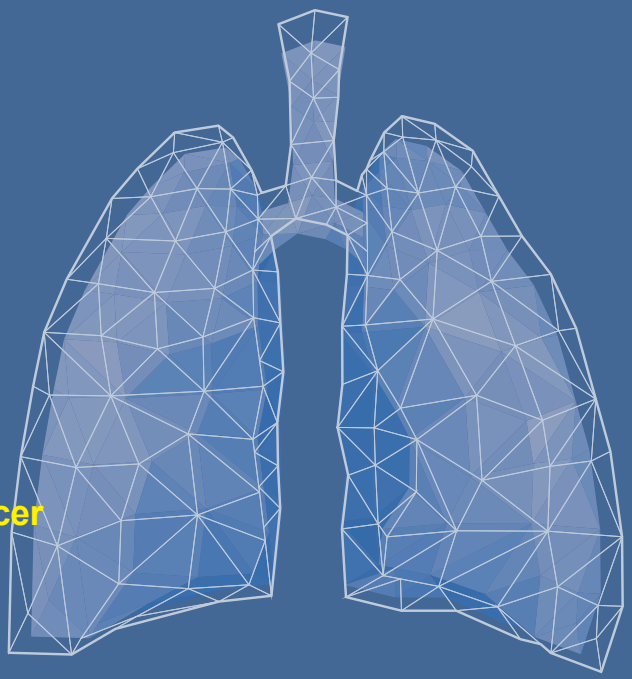


| November 10 (Thu), 2022 | Room A

13:00-14:40

Session III (A)

Indocyanine Green and Fluorescence Image-Guided Thoracic Surgery

Chair: Sukki Cho *(Seoul National Univ.)*

Indocyanine Green Guided VATS/RATS Segmentectomy

Kwon Joong Na

Seoul National Univ., Korea

Recent research suggests that segmentectomy is a suitable alternative for lobectomy in the surgical treatment of early-stage lung cancer. According to a recent clinical trial (JCOG0802), segmentectomy performed as well as lobectomy in terms of long-term overall survival and recurrence-free survival in patients with early-stage lung cancer. As a result, we may anticipate that segmentectomy will play a bigger part in the surgical management of lung cancer.

Intraoperative interpretation of segmental anatomy is one of the key technical challenges while doing segmentectomy. The development of CT reconstruction allowed for a more detailed understanding of segmental anatomy by surgeons prior to surgery. We must determine anatomic segment boundaries to divide the lung parenchyme once segmental arteries and bronchi are transected. The intersegmental plane was traditionally identified using the ventilation-inflation approach. However, it is known that this method requires 10-20 minutes during the operative procedure, and the inflated segments become an obstacle to perform minimally invasive surgery in narrow intrathoracic space.

Near-infrared fluorescence-guided surgery by indocyanine green (ICG) injection is an emerging technique for lung segmentectomy. The ICG-fluorescence technology is safe and effective for verification of anatomic segment borders for minimally invasive surgery. The use of ICG might demarcate the intersegmental plane more restricted to the target segment compared with air injection. Delineation of the intersegmental plane by ICG is feasible regardless of the type of segmentectomy or the presence of obstructive lung disorder, and it can be commonly applicable in pulmonary segmentectomy.

In this lecture, I will briefly review the general application of ICG in minimally invasive surgery and introduce some cases of lung segmentectomy using ICG in both VATS and RATS.

Utility and Pitfalls of Intersegmental Visibility Using Indocyanine Green in VATS Segmentectomy

Chang Young Lee

Yonsei Univ., Korea

Differential ventilation (inflation/deflation) has been reported to be relatively easy to perform and is commonly used. However, the inflation/deflation border may be unclear due to collateral ventilation. Furthermore, cauterisation of the intersegmental surface may cause air to escape resulting in deflation of the inflated lung (Sato et al., 2019).

Intravenous indocyanine green injection is similarly an efficient technique, although diffusion of the dye may obscure demarcation of the target segment. Accessory bronchial branches may also lead to incorrect ICG stains (Sato et al., 2019).

In addition, there are some limitations such as hypoperfusion of emphysematous lung and fast washout of systemic injected ICG resulting in diminishing ICG contrast between target segment and preserving segment.

In this presentation, I am going to introduce my tips on how to maximize the visibility of intersegmental plane to achieve adequate surgical margin during VATS segmentectomy for primary lung cancer.

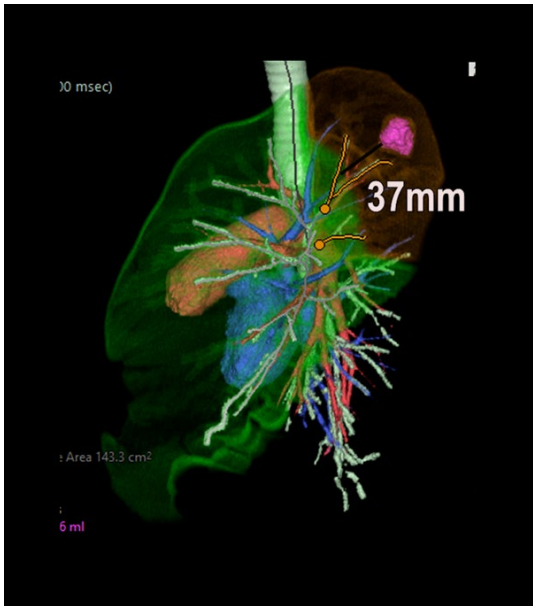


Fig. 1. 3D simulation of left apicoposterior segmentectomy (virtual surgical margin: 37mm, preserved lung volume: 1042ml (74% of total LUL volume).

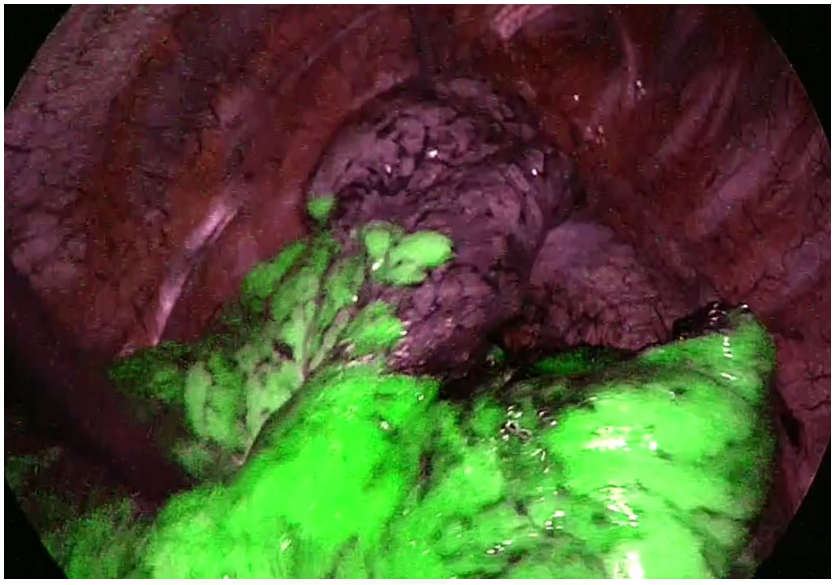
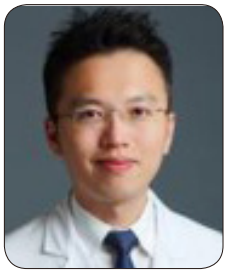


Fig. 2. Corresponding surgical image after systemic ICG injection through near infrared thoracoscopy.



Indocyanine Green Technique for Preoperative Tumor Localization in Lung Cancer

Yin-Kai Chao

Chang Gung Univ., Taiwan

Intraoperative Fluorescence Imaging in Thoracic Cancer Surgery

Hyun Koo Kim

Korea Univ., Korea

With advancement of biotechnology, even patients with cancer have wanted to have better quality of life after treatment for cancer. Therefore, use of less invasive treatment modality including surgery must be considered.

Recently, real-time imaging technologies could offer the possibility to put the images right under the hands of the surgeons, warranting intra-operative image-guided surgery during cancer surgery. This technology would make it possible to discriminate between tumor and normal tissue and consequently determine an adequate tumor-free margin during surgery. The use of intraoperative imaging that provides the unique advantage of a single procedure, whereby the nodule is both localized and wedged during operation. For these types of imaging-guided surgeries, clinicians have been using intravenous injection of indocyanine green (ICG), 1.0 to 5.0 mg/kg.

A minimal effective dose and immediate imaging after lung-specific delivery are important in ICG-based intraoperative visualization of malignant lung tumors. Therefore, we first examined an intraoperative fluorescence imaging technique that may be used to detect lung tumor margin via inhalation delivery of ICG. This technique appears to facilitate rapid and prolonged visualization of the tumor margin of a lung tumor on the pleural surface with a low dosage of ICG, which cannot be achieved using the intravenous injection method. We suggest that the ICG inhalation method will not only provide more accurate resection of lung tumors but also may improve patient safety during surgery.

Although intraoperative molecular imaging is safe and uses non-ionizing radiation, improvements in depth of penetration (the ability to localize deep lung nodules) is a significant area of weakness for this method to date.

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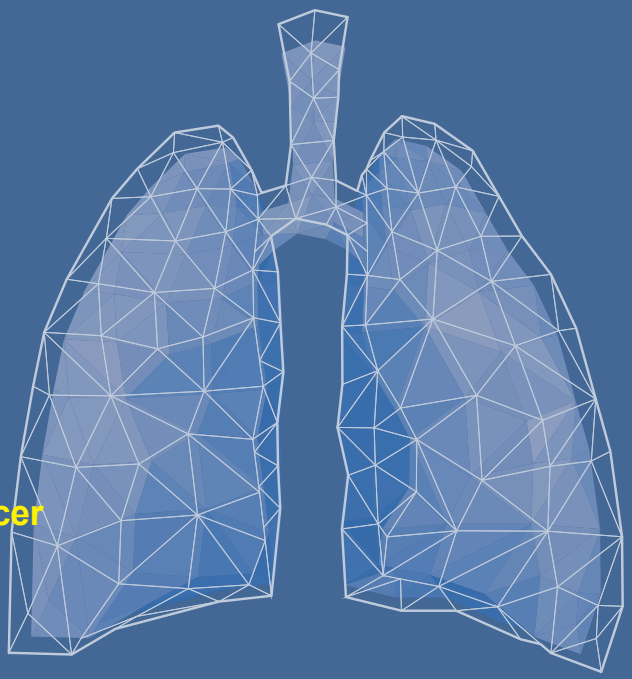

| November 10 (Thu), 2022 | Room A

15:00-16:40

Session IV (A)

Advances in Radiation Oncology

Chair: Hak Choy *(UT Southwestern Medical Center, USA)*

FLASH : A New Paradigm in Cancer Radiation Therapy and Novel Technology for Its Clinical Translation

Billy Loo

Stanford Univ., USA

This presentation will describe the novel concept of FLASH radiation therapy and its potential to increase the therapeutic index in cancer treatment. It will review the range of preclinical biological observations demonstrating improved sparing of normal tissues while maintaining anti-cancer efficacy of ultra-rapid FLASH radiation compared to conventional dose rate radiation. It will then review new advances in linear accelerator technology that can translate this approach to clinical treatment in humans, addressing general cancer indications treated with radiation therapy.

AI in Radiation Oncology

Hak Choy

UT Southwestern Medical Center, USA

Artificial intelligence (AI) has the potential to fundamentally alter current health care pattern. In the past several years, AI recognize the complex patterns in medical data and provided a quantitative, rather than qualitative, assessment. The technology and techniques in radiation oncology have been continuously evolved in the past several decades. Especially the development of new imaging modalities and advanced imaging processing techniques provided better care of our patients and provided an increasing amount of data available to medical physicists and radiation oncologists. The clinical applications of AI in radiation oncology can be deployed into the entire adiation therapy workflow, including initial treatment decision-making, treatment planning and preparation, QA, delivery of radiation therapy and follow up of patients. AI generated model potentially enable clinical procedure automation and improv patient safety and clinical workflow. While, we have seen a lot of exciting research work, very few of which have been used in routine clinical practice. Eventually, we can make AI models very accurate, much more accurate than human doctors, medical physicists and radiation ethnologists, perhaps replace them with AI driven humanoid robot. But this maybe still many years if not decades away, due to the complexity of the clinical problems. Whatever the model generated by AI research need to show benefit of treatment outcome and toxicity and not just trying to replace human with machine.

In this talk, I will discuss the challenges associated with the clinical development and implementation of AI platforms in radiation oncology and provide perspective on how these platforms might change the roles of radiation oncology medical professionals.

Passive Scattering or Pencil Beam Scanning Proton Therapy for Lung Cancer

Sung Ho Moon

National Cancer Center, Korea

Proton therapy (PT) can effectively deliver the radiation dose to the tumor while minimizing normal tissue injury, thanks to the physical property of "Bragg peak" and has theoretical advantages over photon radiotherapy. In the treatment of lung cancer, both early and locally advanced stages, PT is expected to have potential benefits in terms of reduction of cardiopulmonary and hematological toxicity and survival outcomes. However, there also exist some technical issues to be solved for the use of PT to moving organ tumor, such as lung cancer. There are two available delivery techniques of PT, passive scattering PT (PSPT) mainly in the early period and pencil beam technique (PBS), and both techniques have their own strength and weakness. In this presentation, the achievements so far and the future prospects of PT in the treatment of lung cancer and the solutions to technical problems of PSPT or PBS.

Heavy Charged Particle Therapy

Hong In Yoon

Yonsei Univ., Korea

Heavy ions exhibit a characteristic energy distribution in depth, known as the "Bragg Peak," where low levels of energy are deposited in tissues proximal to the target, and the majority of energy is released in the target.[1] Additionally, a steeper lateral dose penumbra is observed at greater depths with carbon, than with photons or protons.[2,3] Furthermore, carbon exhibits a higher linear energy transfer (LET) than photons and protons. This leads to a higher relative biological effectiveness (RBE), where damage caused by carbon ions is clustered in the DNA, overwhelming the cellular repair systems.[3] Among the heavy particles currently being investigated, carbon ion has been applied to cancer treatment. With a higher LET and the characteristics of the Bragg Peak, carbon ion radiation therapy (CIRT) is a promising treatment of choice by providing higher doses to targets while reducing irradiation to organs at risk.[1] The National Institute for Quantum Science and Technology (QST) opened the first heavy ion accelerator for clinical use, in 1994 in Japan.[4] Since then, over 20,000 patients have been treated with CIRT in QST.[5] Today, there are six countries and a total of 15 centers treating with CIRT.

Historically, heavy particle therapy was introduced for medically inoperable patients with peripheral early stage lung cancer.[6,7] Based on a number of studies, CIRT for peripheral early stage lung cancer is considered an alternative treatment option which is safe and effective.[7-12] Many studies regarding CIRT have demonstrated that CIRT demonstrates local control and survival rates that are comparable to current standard treatments with low rates of severe toxicity. CIRT showed an excellent treatment outcome compared to the radical surgery even in operable peripheral early stage lung cancer patients.[8,9]

In central type tumors, local control and survival rates of CIRT were also comparable to other treatment modalities according to a small number of studies.[13] However, caution is required in lung cancer patients with underlying pulmonary disease such as severe chronic obstructive pulmonary disease.

A few studies evaluated the safety and efficacy of CIRT for locally advanced lung cancer.[14,15] Although the results are promising, since only a few studies of CIRT alone have been reported for a small number of patients, further studies with larger sample size to prove the effectiveness of CIRT combined with systemic treatment are needed.

In early stage lung cancer, although randomized trials have not yet been conducted, CIRT can serve as an alternative treatment option to standard treatment based on several prospective and retrospective studies. However, in central early stage or locally advanced lung cancer, further studies are required to prove the safety and effectiveness of CIRT.

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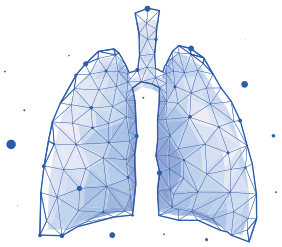

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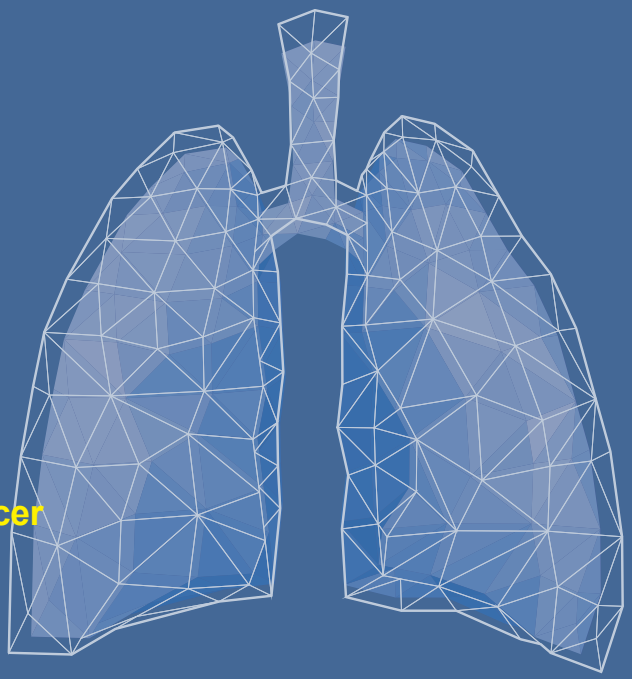

| November 10 (Thu), 2022 | Room A

16:50-17:40

Satellite Symposium II

[MSD]

Chair: Seung Hun Jang *(Hallym Univ.)*

Pembrolizumab Combination Strategies in Lung Cancer: Present and Future

Bin Zhao

MSD Global Clinical Research

Significant progress has been made in oncology over the past few years.

At ESMO 2022, long term survival data from N189 and KN407 were presented. 5-yr survival rate is doubled compared to chemotherapy, which continues to support pembrolizumab plus chemotherapy as a standard-of-care first line treatment option for advanced nsq and sq NSCLC.

However, although long-term survival and cure is now possible, it is only realized in a subset of patients.

Several strategies have been implemented to test the hypotheses that whether adding another new MOA on top of pembrolizumab will further improve the treatment outcome. These include pembrolizumab in combination with Lenvatinib, Olaparib, anti-TIGIT, ADCs etc. in the first line NSCLC setting. High-level study designs will be presented.

In the early stage NSCLC, we are investigating pembrolizumab in combination with concurrent chemoradiation therapy in unresectable, locally advanced, Stage III NSCLC, and as neoadjuvant and adjuvant setting in the operable disease.

Another frequently asked question is, with more patients treated now with first line immune checkpoint inhibitors, will rechallenge with IO-based therapy resume the sensitivity to pembrolizumab. We are currently addressing this question with pembrolizumab and lenvatinib combination and other combinations.

Small cell lung cancer is a difficult to treat disease. Long-term follow up data from KN604 presented at WCLC this year showed that pembrolizumab in combination with etoposide platinum continued to show clinically meaningful improvement in OS and PFS vs. chemo alone in ES SCLC, justifying continuing study pembrolizumab based therapy in SCLC.

Lastly, early oncology pipeline includes more than 20 investigational therapeutic candidates. Anti-Lag3, ADCs and KRAS G12C are actively under investigation in thoracic malignancies program.

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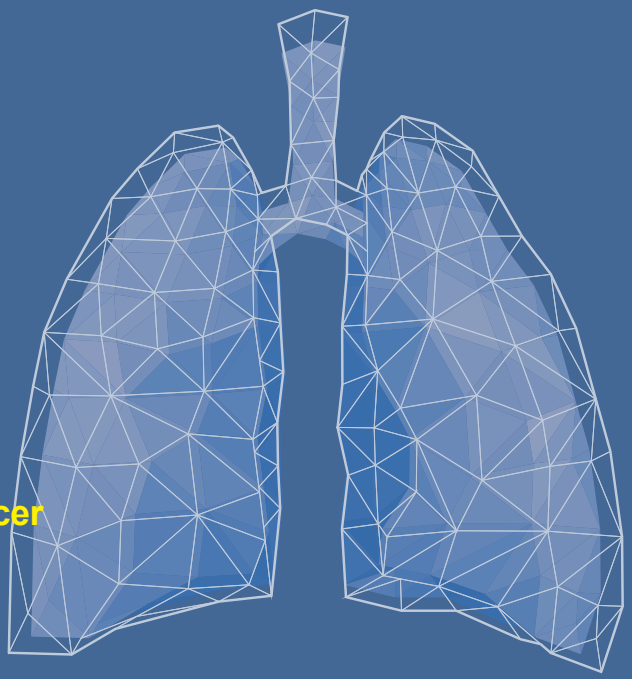

| November 10 (Thu), 2022 | Room B

08:50-10:10

Session I (B)

Details and Challenges in Sublobar Resection

Chair: Sungsoo Lee *(Yonsei Univ.)*

Extent of Lymph Node Dissection during Sublobar Resection

Yoohwa Hwang

Seoul National Univ., Korea

Since more than 20 years, lobectomy combined with mediastinal lymph node dissection, has been standardized as the surgical treatment for localized non-small cell lung cancer.[1] Nowadays, the early-stage lung cancer population is delineated on the basis of 18FDG positron-emission tomography, routine brain imaging, and high-resolution CT scan findings, which result in more reliable staging of the disease. Furthermore, launching of low-dose helical CT scan screening programs leads to the diagnosis of lung cancer at a smaller tumor size and at an earlier stage. Changes in the epidemiology of the disease, as well as precise identification of minor changes in the density within ground-glass nodules combined with a better understanding of histological tumor biology introduced subgroups with indolent behavior, low propensity to spread to LNs, and finally more favorable outcomes.[2]

The surgical approach to mediastinal lymph nodes at the time of sublobar resection for lung cancer has long been a subject of interest. The European Society of Thoracic Surgeons Guidelines in 2006 stated 'adherence to these guidelines will standardize the intraoperative lymph node staging and pathologic evaluation, and improve pathologic staging, which will help decide on the best adjuvant therapy'.[3] The opening statement of the International Association for the Study of Lung Cancer staging project's proposals for the revision of the N Descriptors in the eighth Edition of the tumor-node-metastasis (TNM) Classification for Lung Cancer reads: 'Nodal status is considered to be one of the most reliable indicators of the prognosis in patients with lung cancer and thus is indispensable in determining the optimal therapeutic options'.[4] The extent of nodal dissection and the number of nodes removed and sent to the pathology laboratory is used as a quality standard in some jurisdictions.

Some argue that complete mediastinal lymph node dissection contributes to more accurate lymph node staging and survival benefit, whereas others believe that systematic mediastinal lymph node sampling is adequate for accurate staging and that formal dissection of the me-

diastinal nodes does not provide any survival advantage as patients with positive N2 nodes die from systemic disease.

A large prospective study showed no difference between mediastinal lymph node dissection, sampling, and selective lymph node dissection in the prognosis of early NSCLC.[5] However, numerous studies have shown that mediastinal lymph node dissection leads to lower rates of local recurrence in the general population, [6,7] and another study found that mediastinal lymph node dissection had survival benefit for patients with early NSCLC in teaching hospitals. Also, Gonfiotti et al. found that postoperative complications incidence among patients who underwent mediastinal lymph node dissection were no more significant than those among non-dissection patients.[8] However, Mokhles et al. reported that mediastinal lymph node dissection was associated with more complications than sampling or no dissection.[9]

Although the results of studies so far have been inconsistent, the current NCCN guidelines recommend treatment according to the pN stage. According to prospective data derived from the Dutch Lung Surgery Audit in 2013 and 2014, 6.2% of patients presenting with a cT1aN0 tumor had a pN1 disease, and 4.6% a pN2 disease, leading to an overall 10.8% LN upstaging rate.[10] Accurate lymph node staging is of guiding significance for postoperative adjuvant therapy. Additionally, several recent studies have suggested that the higher the number of lymph nodes removed, the better the prognosis. Either formal mediastinal lymph node dissection, lymph node sampling or lobe-specific sampling are considered appropriate. Based on the available literature, mediastinal lymph node dissection and lobe-specific lymph node dissection appear equally efficacious with respect to overall survival. Mediastinal lymph node dissection is favored for larger or more central tumors or if N1 disease is identified.

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Sublobar Resection in Compromized Patients with Lung Cancer

Jeong Su Cho

Pusan National Univ., Korea

Surgical treatment for lung cancer is known as an important treatment among various treatment modalities for lung cancer. However, it is known that the risk of surgical treatment is relatively high for patients comparing to other treatments, so it is burdensome for compromised patients to perform lobectomy, which is currently known as the standard surgical extent for resectable lung cancer. Therefore, I would like to say the surgical treatment of compromised patient with resectable lung cancer, especially sublobar resection.

The first thing to consider is what kind of compromised patients there are, and among them, we need to know which cases require sublobar resection.

Types of compromised patients

A compromised patient generally refers to an old age, poor lung function due to underlying lung disease, cardiovascular problems or other problems such as liver cirrhosis, chronic renal failure or immunocompromised conditions. However, the cases in which sublobar resection should be considered among these might be the elderly or those with cardiopulmonary dysfunction.

As for the age of patients, people in their 70s or older are classically considered to be old, but recent studies have reported that people in their 70s are no longer classified as a high-risk group. There are reports that there is no significant difference in recovery even if lobectomy, and in other studies, there are reports that sublobar resection in the elderly does not have a significant effect on the prognosis.[1-4] However, if there is a problem with cardiopulmonary function, the risk group is evaluated through a cardiopulmonary exercise test, and if the high-risk group is identified, sublobar resection or non-surgical treatment is recommended.[5,6]

Is sublobar resection in compromised patient with resectable lung cancer oncological acceptable?

The reason for considering sublobar resection in compromised patients is that it is expected to make a safe recovery after surgery. However, it is also necessary to confirm whether actual sublobar resection can expect a comparable prognosis compared to nonsurgical treatments.

In patients with stage I lung cancer, several studies including RCTs such as JCOG 0802/WJOG4607L[7] and study reported by G Stamatis etc.[8] suggest that although several conditions must be met for stage I lung cancer, sublobar resection can also expect a relatively good prognosis. However, in the case of advanced stages such as stage II and III, there is not enough evidence that sublobar resection is a superior treatment compared to other treatment modalities, and there are many cases where other treatments must also be accompanied, so a multidisciplinary discussion is essential.

Types of sublobar resection : Segmentectomy versus Wedge resection

Finally, the technical and oncological aspects of sublobar resection would be explained.

Sublobar resection usually refers to wedge resection and segmentectomy, and in the aspect of the time required for the operation and the damage to the patient, lung wedge resection is much better than segmentectomy. However, many studies have reported that wedge resection is oncologically inferior to segmentectomy, so, when sublobar resection is necessary, it is recommended to perform segmentectomy whenever possible.[9-11]

There is some consensus on the role of sublobar resection in compromised patient with resectable lung cancer, but there are still areas that require further research. However, the role of sublobar resection in some compromised patient is clear, and if sublobar resection through multidisciplinary discussion is applied to the patient, the better prognosis can be expected.

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Additional Management (for Incomplete or Local Recurrence) after Sublobar Resection

Seong Yong Park

Sungkyunkwan Univ., Korea

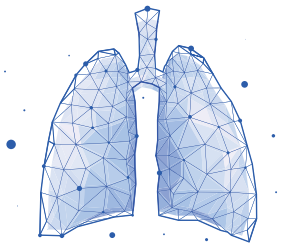
Recently, the JCOG0802 study showed the benefits of segmentectomy versus lobectomy in the overall survival of patients with small peripheral non-small cell lung cancer (NSCLC), tumor diameter ≤ 2cm, and consolidation-to-tumor ratio >0.5. However, the patients received the segmentectomy showed more locoregional recurrences than patients with lobectomy. Although the segmentectomy may play a leading role in the early NSCLC in the future, there will be many cases to perform completion lobectomy or additional segmentectomy after a previous segmentectomy, due to not only locoregional recurrences, but also second primary lung cancer on the ipsilateral side or the same lobe. Among the wide array of reoperation options, completion lobectomy after segmentectomy in the same lobe is particularly difficult because of dense adhesions that are generated from hilar dissections and destroyed hilar structures. In addition, few studies have reported surgical outcomes on completion lobectomy after segmentectomy. In this presentation, the rationale of completion lobectomy will be reviewed with previous case series and institutional data, and technical tips and pitfalls will also be discussed.

Japan Clinical Oncology Group Studies about Sublobar Resection

Hisashi Saji

St. Marianna Univ., Japan

Surgical resection is the gold standard of treatment for early-stage lung cancer, with lobectomy being the standard mode of surgery since 1960. With the increased frequency of CT screening and advances in diagnostic modalities, including thin-section CT, the early detection rate of small-sized or ground-glass opacity lung tumors has increased. Consequently, the practical indications of sublobar resections have been extended to early-stage lung cancer. To select radiologically non-invasive lung cancer without pathological lymph node involvement or lympho-vascular invasion, JCOG0201 that investigated the association between radiological findings and prognosis in early-stage non-small-cell lung cancer (NSCLC). Given the results of the JCOG0201 and specific features of sublobar resection, JCOG and WJOG conducted three prospective multi-institutional studies (JCOG0802/WJOG4607L, JCOG1211, and JCOG0804/WJOG4507L) to investigate the optimal surgical modality for early-stage NSCLC. After confirming the hypotheses of the three studies, a standard mode of surgery for early-stage NSCLC can be established. In 2022, these studies were opened and resulted showing all positive results. Additionally, CALGB140503 were also presented and showed positive results of primary endpoint, DFS. Finally, it's a time of paradigm shift to sublobar resections must be considered as a standard surgical procedure for small-sized peripheral lung cancer.



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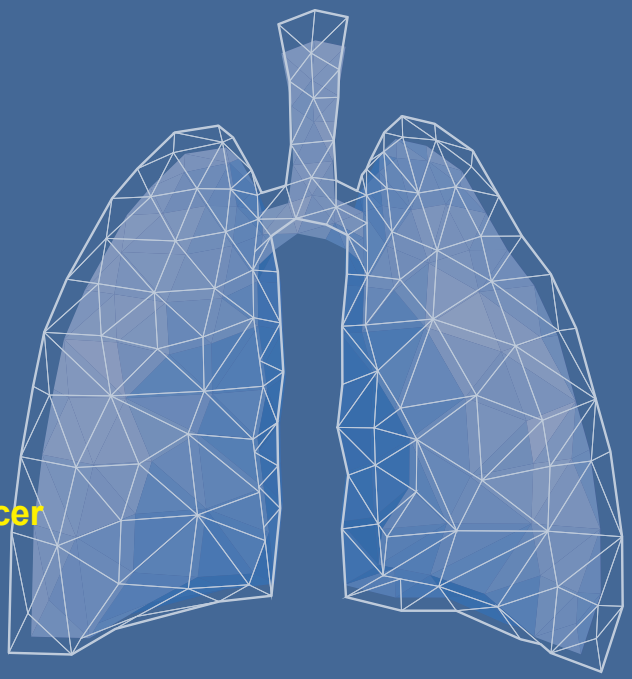

| November 10 (Thu), 2022 | Room B

10:30-11:50

Session II (B)

Upcoming Novel Therapeutics

Chair: In-Jae Oh (Chonnam National Univ.)

Antibody-Drug Conjugates: A Promising Novel Therapeutic Approach in Lung Cancer

David Planchard

Gustave Roussy, France

Antibody drug conjugates (ADCs) are a new generation of smart bio-pharmaceutical compounds composed of monoclonal antibodies linked to cytotoxic drugs. They are among the fastest growing drug classes in oncology. They have shown promising preliminary data in lung cancer with impressive response rates and survival outcomes in previously treated patients. ADCs are arguably the most complex platform in oncology with 4 main concerns, i.e., target antigen selection, antibody optimization, linker chemistry and stability and payload efficacy and toxicity. The objective is to maximize antitumor activity while limiting both on-target and off-target toxicities. There are several ADCs currently in clinical trials for NSCLC and small cell lung cancer (SCLC). These ADCs often have different targets which include HER2, HER3, TROP2, CEACAM5, and MET in NSCLC and DLL3 in SCLC. We will focus on the use of ADCs in advanced or metastatic lung cancer.

J2H-2002, an Oral, Selective, and Potent Protein Degrader for the Treatment of Non-Small Cell Lung Cancer with Osimertinib-Resistant EGFR C797S Mutations

Sumi Lee

J2HBiotech, Korea

Lung cancer is the leading cause of cancer-related mortality with the 5-year relative survival of 22.9%.[1] Non-small cell lung cancer (NSCLC), known as the most common type of lung cancer, accounts for roughly 80~85% of all cases.[2] Epidermal growth factor receptor (EGFR) mutations are the most prevalent in NSCLC and occur in approximately 10-35% of NSCLC patients.[3] Among them, EGFR gene mutations, such as EGFR exon 19 deletion (del19) and a point mutation (L858R) in exon 21, account for approximately 90% of all EGFR mutations.[4] These are associated with favorable clinical responses to EGFR tyrosine kinase inhibitors (TKIs). According to Datamonitor Healthcare (2020), there were 1.8 million incident cases of NSCLC worldwide in 2018, predicting that the number increases to 1.9 million incident cases by 2027.[2] In 2020, GlobalData estimated that the global NSCLC market, mainly including 8MM (US, 5EU and Japan), will grow from $19.6B in 2019 to 14.8B in 2019 by a 2-fold increase.[5] Similarly, the global EGFR market was valued at $3.38B and will increase by a 2.7-fold to $9.2B in 2029.[5]

Targeted cancer therapy has emerged as an important means of disease management for patients with non-small cell lung cancer (NSCLC). Since the approval of the first EGFR TKI gefitinib in 2003, there have been developed first to third generation EGFR TKIs for the treatment of EGFR-mutant NSCLC patients. Unfortunately, such treatment method still has an inevitable issue of drug resistance development.[6] EGFR T790M mutation has been identified as the main mechanism of acquired resistance to first- and second-generation inhibitors. Although osimertinib has provided clinical benefits in patients with the T790M double mutation, drug resistance to osimertinib has also emerged through development of EGFR C797S mutations.[6] Generally, the drug resistance inevitably emerges within one year of targeted cancer therapy, leaving patients with no further treatment options for disease progression. Accordingly, there is an unmet medical need to devel-

op next-generation EGFR TKI for the treatment of NSCLC with osimertinib-resistant EGFR C797S mutations. Recently, several fourth-generation EGFR tyrosine kinase inhibitors, including BBT-176, BLU-945 and BLU-701, entered clinical development. Furthermore, EGFR protein degraders J2H-2002 and CFT8919 with a new drug modality have been developed as a promising anticancer drug, which are different from the existing EGFR small molecule inhibitors.[7-10]

PROTAC (proteolysis targeting chimera), also known as TPD (targeted protein degradation), is a novel and innovative chemical tool that has been gaining attention with its ubiquitin-proteasome system (UPS) redirected by small-molecule ligands. PROTAC is composed of a protein of interest (POI) ligand, E3 ligase ligand, and a linker.[11] Since the PROTAC concept was first published by Sakamoto group, there have been a number of research activities including discovery of various E3 ligase ligands and PROTAC-mediated drug development.[12] Remarkably, androgen receptor (AR)-targeting PROTAC degrader ARV-110 has first entered phase I clinical trials in 2019 and is currently in phase II trial, suggesting that PROTAC technology can be a novel therapeutic strategy in drug discovery and development.[12] PROTAC binds to a protein of interest while simultaneously tagging it with ubiquitin via the cell's proteolytic machinery, eventually forming a ternary POI-PROTAC-E3 complex for POI degradation. The TPD material is then dissociated and recycled for another decomposition.[13] The catalytic mechanism of action (MOA) of PROTAC technology offers several advantages over traditional small molecule drugs, including the degradation of undruggable targets, high potency against drug-resistant mutations, high selectivity, and low off-target toxicity.[14, 15] Importantly, PROTAC may potentially overcome the unavoidable problem of drug resistance development by eliminating target proteins via our body's ubiquitin proteasome system (UPS).

Considering the benefits of the PROTAC technology, J2H Biotech has developed J2H-2002 that is an orally available 4th-generation EGFR mutant targeted protein degrader with the potential to treat NSCLC with osimertinib-resistant C797S mutations. J2H-2002 is a highly potent and mutant-selective EGFR degrader targeting EGFR activating mutations (de19, L858R) as well as all drug-resistant mutations (T790M, C797S, and T790M/C797S). Additionally, J2H-2002 exhibits robust cellular potencies against 8 types of EGFR mutations in the nanomolar range, potentially encompassing the therapeutic effects of first- to third-generation EGFR inhibitors. In Ba/F3 cell-derived allograft mouse models, J2H-2002 significantly inhibits tumor growth. Significant tumor growth regression was also shown in the patient-derived xenograft (PDX) model, which best resembles the human tumor, referring that J2H-2002 is potential to have a clinically significant effect in patients with EGFR mutant NSCLC. Interestingly, the PROTAC J2H-2002 has an excellent pharmacokinetic profile in animals and can cross the blood-brain barrier indicating the potential

to treat patients with brain metastases. Collectively, J2H-2002 has exhibited promising research data to advance into a best-in-class 4th-generation EGFR degrader.

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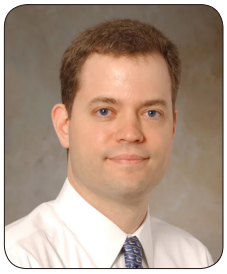

LAG 3 Immunotherapy in Lung Cancer

Scott Nicholas Gettinger

Yale Univ. Medical Center, USA

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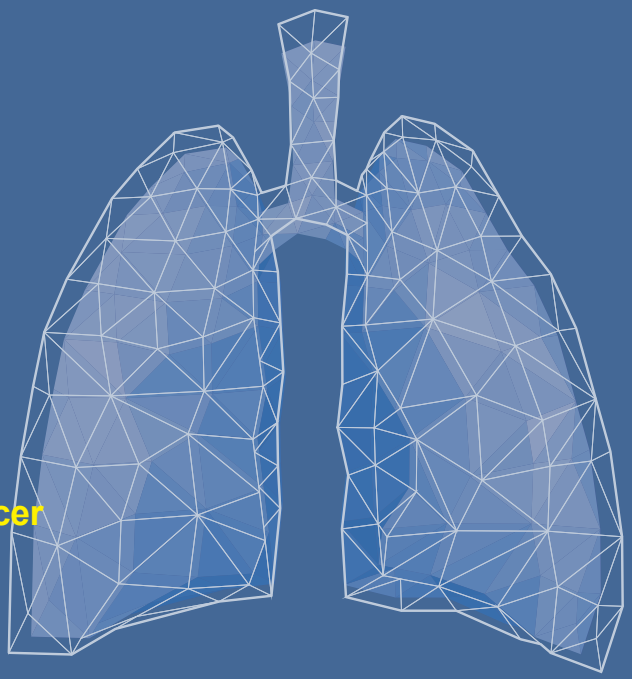

| November 10 (Thu), 2022 | Room B

13:00-14:40

Session III (B)

KALC-KAI Joint Symposium: New Insight for Cancer Immunotherapy

Chair: Yeon Suk Chung *(Seoul National Univ.)*,
Sei-Hoon Yang *(Wonkwang Univ.)*

Expanding the Benefits of Immunotherapy for Cancer: Combine and Conquer

Dan G. Duda

Harvard Medical School, USA

Surgical treatments offer the chance for cures in some primary or metastatic cancers. However, many patients experience disease progression after surgical interventions or cannot undergo surgery as they present with unresectable disease at diagnosis. In such cases, available treatment options – local and systemic – have been limited in efficacy for most cancers, which led to dismal survival rates. Immunotherapy has emerged as a major therapeutic modality for advanced cancers. However, most patients with cancer do not derive benefit from this treatment alone.

More recent developments in oncology have offered renewed hope for using immunotherapy in combination with other treatments for advanced cancers. Some involve chemotherapy-based regimens, which have traditionally been the standard of care. Others involve hypofractionated radiation, which has shown feasibility and promise in unresectable settings and is now being tested in randomized phase III trials (e.g., clinicaltrials.gov identifier NCT03186898). Last but not least, combinations with antiangiogenic agents are attractive, as these drugs have strongly impacted the management of several advanced cancers, such as lung, liver, and renal malignancies.

Immune checkpoint blockade therapy relies on the infiltration and activation of immune effector cells within the tumor microenvironment, and immune responses and vascular function are reciprocally regulated. Structural and functional abnormalities in tumor vasculature are hallmarks of cancer and facilitate immune evasión and treatment resistance. The vascular endothelial growth factor (VEGF) is crucial in inducing these abnormalities. Posited by Prof. Rakesh K. Jain (Harvard University) in 2001, the concept that blocking the VEGF pathway could partially restore vascular function (a process called "vascular normalization") was recently validated in clinical studies. A consequence of vascular normalization in cancer is improved therapeutic responsiveness to other treatments. Significantly, vascular normalization can increase the infiltration of immune effector cells into tumors and convert the immunosuppressive tumor microenvironment to an immune-supportive one. On the other hand, cytotoxics such as radiation or chemotherapy may

impact the immune tumor microenvironment as well as immunotherapy efficacy.

Combinations of these strategies are very attractive, as they promise durable and profound responses in advanced disease and potentially in earlier stages of cancer. But to achieve this promise more broadly, these concepts require greater understanding based on mechanistic preclinical studies and validation in correlative studies in clinical trials as a basis to establish optimal combinatorial strategies. I will summarize the results from clinical correlative studies and preclinical models of these diseases performed at our institution and in collaboration with other American, Asian, and European investigators.

The insights gained from this "bench-to-the-bedside and back" approach raise the hope for more efficient development of targeted agents in combination and in earlier stages of the disease to increase survival in patients afflicted with these aggressive and deadly diseases.

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Atezolizumab-Grab: Beyond the PD-L1 Blockade in Cancers

Keehoon Jung

Seoul National Univ., Korea

Pancreatic ductal adenocarcinoma (PDAC) has a poor 5-year overall survival rate. Patients with PDAC display limited benefits after undergoing chemotherapy or immunotherapy modalities. Herein, we reveal that chemotherapy upregulates placental growth factor (PlGF), which directly activates cancer-associated fibroblasts (CAFs) to induce fibrosis-associated collagen deposition in PDAC. Patients with poor prognosis have high PlGF/VEGF expression and an increased number of PlGF/VEGF receptor-expressing CAFs, associated with enhanced collagen deposition. We also develop a multi-paratopic VEGF decoy receptor (Ate-Grab) by fusing the single-chain Fv of atezolizumab (anti-PD-L1) to VEGF-Grab to target PD-L1-expressing CAFs. Ate-Grab exerts anti-tumor and anti-fibrotic effects in PDAC models via the PD-L1-directed PlGF/VEGF blockade. Furthermore, Ate-Grab synergizes with gemcitabine by relieving desmoplasia. Single-cell RNA sequencing identifies that the CD141+ CAF population is reduced upon Ate-Grab and gemcitabine combination treatment. Overall, our results elucidate the mechanism underlying chemotherapy-induced fibrosis in PDAC and highlight a combinatorial therapeutic strategy for desmoplastic cancers.

Combination of Two Distinct Subsets of Peripheral Blood CD8+ T Cells from Patients with Non-Small Cell Lung Cancer Predicts Response Outcome to Immune Checkpoint Blockade Therapy

Sung-Woo Lee[1], Ju Sik Yun[2], Hee-Ok Kim[3], Hyun-Ju Cho[4], Cheol-Kyu Park[4], Woo Kyun Bae[4], Ik Joo Chung[4], Joon Haeng Rhee[1], Sook Jung Yun[5], Sang Yun Song[2], In-Jae Oh[4], and Jae-Ho Cho[1,6]

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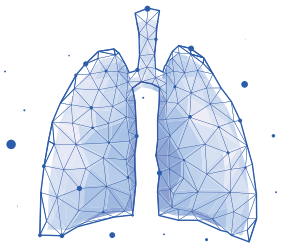
Background: Immune checkpoint blockade (ICB) has achieved a great success as a promising regime for the treatment of patients with many types of solid malignancies, associated with predictive biomarker of PD-L1 expression. However, generally a low rate of ICB therapy response remains a critical hurdle to overcome for expanding its versatile therapeutic efficacy, and necessitates importance of developing a biomarker better predicting response outcome after ICB.

Method: Peripheral blood $CD8^+$ T cell compartment from patients with stage IV of non-small cell lung cancer (n=119 (Atezolizumab) + 19 (Pembrolizumab)) before ICB treatment targeting programmed cell death 1 (PD-1) or its ligand 1 (PD-L1) was analyzed and correlated with patients' ICB treatment outcome.

Results: Strong correlation between the patients' response outcome after ICB and the proportion of two distinct subsets of blood $CD8^+$ T cells, namely $CD27^+$ $CD28^+$ $CD45RA^-$ $CCR7^-$ and $CD27^+$ $CD28^+$ $CD45RA^+$ $CCR7^-$ cells was observed. Using these two cellular parameters combined with machine learning based probability graph, we found that both initial discovery (n=70) and later validation cohorts of patients (n=49) showed a power of predicting approximately 57.14% of ICB responders (95% CI, 20.5-93.8%; PR based on the RECISTv1.1 criteria) compared to that of ~17.1% (95% CI, 8.3-26.0%; no biomarker included) and of ~25.0% (95% CI, 5-55.0%; biomarker based on

tumor PD-L1 expression). Mechanistically, the observed strong correlation was due to the basal functional fitness and reactive capacity of responding $CD8^+$ T cells, which was characterized by lower initial levels of perforin, granzyme B and interferon-γ expression in these cells before ICB treatment. As such, the patients with enhanced proportion of this subset in their bloods showed greater capacity to enhance ICB-driven upregulation of cytotoxic molecules and accordingly better ICB response outcomes.

Conclusion: These observations are in line with current notion that a relatively less differentiated subset of $CD8^+$ T cells would be a major target for ICB and provide a potential of developing this non-invasive blood-based approach as an ICB response predictor for patients with cancer.



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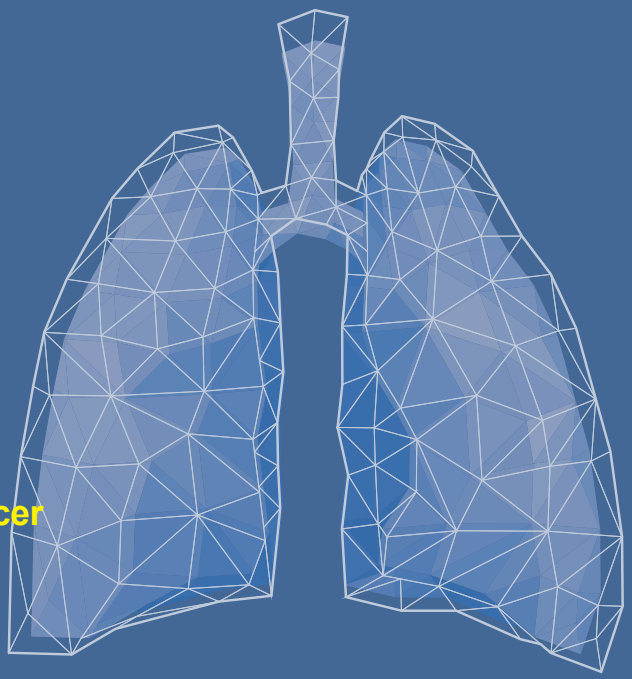

| November 10 (Thu), 2022 | Room B

15:00-16:40

Session IV (B)

Treatment-Related Pneumonitis

Chair: Jeong Eun Lee *(Chungnam National Univ.)*

Chest Imaging of Treatment-Related Pneumonitis

Hyae Young Kim

National Cancer Center, Korea

The management of cancer has been advanced with the development of new chemotherapeutic agents and improved techniques of radiation therapy. Those interventions have the potentials of adverse effects, although new therapeutic management have improved survival in cancer patients.

The increasing use of molecular targeting agents and ICI has increased the frequency and broadened the spectrum of lung toxicity. The clinical symptoms of drug related pneumonitis (DRP) are generally nonspecific, including dyspnea, cough, malaise, and low-grade fever. The time course is variable, but in most cases, it occurs relatively early within the first weeks or months after initiation of therapy. Clinical courses of pneumonitis are also variable among patients. Drug-related pneumonitis is ultimately a diagnosis of clinical correlation and exclusion as radiographic and pathologic findings are typically nonspecific, and there is no specific test. Mimics of DRP include a progression of malignancy, infection, cardiogenic and non-cardiogenic pulmonary edema. A broad differential is warranted.

A radiographic pattern-based approach offers a practical aid to recognize and characterize DRP and may help guide treatment decisions. Each drug can be associated with multiple injury patterns at CT, which are typically not specific. The CT patterns reflect acute (diffuse alveolar damage) interstitial pneumonia and transient (simple pulmonary eosinophilia) lung abnormality, subacute interstitial disease (organizing pneumonia and hypersensitivity pneumonitis), and chronic interstitial disease (nonspecific interstitial pneumonia).

The Fleischner's society proposed diagnostic criteria of DRP, recently. (a) newly-identified pulmonary parenchymal opacities at CT or chest radiography, commonly in a bilateral nonsegmental distribution; (b) temporal association of presentation with the initiation of a systemic therapeutic agent; and (c) exclusion of other likely causes. Multidisciplinary diagnosis is particularly important

in patients suspected DRP because there is no individual feature that is required or sufficient for the diagnosis of DRP.

Chronic immune check-point inhibitor pneumonitis was defined as pneumonitis that persists or worsens with steroid tapering. And it necessitates more than 12 weeks of immunosuppression, after ICI discontinuation. Subsequent episodes of pneumonitis from ICI rechallenge are called recurrent pneumonitis. Pneumonitis flare is a unique phenomenon where ICI-related pneumonitis recurs after the termination of corticosteroid taper without ICI rechallenge.

Radiation recall pneumonitis is a rare reaction occurring in previously irradiated areas of the lungs after administration of triggering agents. It is not likely to be due to the direct effect of radiation. It should be suspected in any patient with a history of radiation therapy with new airspace changes sharply demarcated from the adjacent lung in the appearance of a radiation field.

Modern precision radiotherapy techniques, including three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), and proton therapy, have been developed to conform the radiation dose to the tumor and may reduce normal tissue exposure to radiation. However, adverse effects are still common. Radiation-induced toxicity is dependent on many factors including radiotherapy techniques, the dose and irradiated volume, the tumor location, the functional status of an organ, and others. Concurrent or concomitant systemic therapy sensitize to radiation-induced lung injury (RILD) or worsen pre-existing co-morbidities. Radiation induced lung injury should be differentiated from recurrent tumoral disease, infection and radiation-induced tumors.

Early exudative phase typically occurs 2 weeks to 3 months after treatment and is usually limited to the irradiated field. Mild injury often resolves without treatment. However, when the injury is severe, radiation induced lung injury progresses into a proliferative/organizing phase, which occurs about 3–9 months. The final fibrotic phase typically is seen more than 9 months after the completion of radiotherapy. Lesions are usually considered as stable and definite after 2 years.

Radiation induced lung injury are usually confined to the radiation port. Though the typical pattern of RILD is easily recognized after conventional two-dimensional radiation therapy (RT), RILD may present with nontraditional patterns of radiation-induced changes to the lungs after use of newer radiation therapy delivery techniques, including 3D-CRT, IMRT, SBRT, and proton therapy.

Imaging findings of typical patterns show homogenous, patchy or slightly nodular areas of ground-glass infiltration or consolidation in the early phase. From the exudative to organizing phases, the findings change into more homogenous and discrete consolidation that conforms better to the shape of the portals. When the lung injury is more severe, consolidation eventual-

ly shrinks and shows a sharper delineation and conformation to the irradiated fields in fibrotic phase.

Three nontraditional patterns in chronic phase of RILD with newer techniques are reported: (a) A modified conventional pattern is characterized by consolidation, volume loss, and bronchiectasis. (b) The mass-like pattern involves a focal opacity confined to the site of the original tumor. (c) The scar-like pattern is characterized by a linear opacity, associated with possible volume loss, in the region of the original tumor.

Knowledge of the treatment planning, including the arrangement of the beams and the dose distribution, may help the interpretation of RILD.

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How to Deal with Treatment-Related Pneumonitis

Sun Min Lim

Yonsei Univ., Korea

With the increasing use of immune-checkpoint inhibitors, the incidence of treatment-related pneumonitis is increasing. Treatment-related pneumonitis is rare with commonly used targeted therapies, and tyrosine kinase inhibitors inhibiting EGFR may cause interstitial lung disease in up to 3.5%.[1] Treatment-related pneumonitis also occurs as an immune-related adverse events (irAEs), and corticosteroids are the mainstay of treatment of most irAEs related to immunotherapy. Early intervention with corticosteroids is a key goal in general management of immune-related toxicity. Use of corticosteroids to treat irAEs has not been shown to reduce anti-tumor efficacy.

Prior to starting immune checkpoint inhibitor therapy, we need to assess patient's understanding of disease and recommendations for treatment. Educating the patients about the mechanisms of action and rationales for the treatment is necessary, and it is important to document any underlying medical conditions affecting any organ system. Assessing the patient's ability to monitor and report potential adverse events and potential toxicity profile, including presenting symptoms and timing is important.[2]

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Optimal Management of Radiation and Drug Related Pneumonitis in Unresectable Stage III Non-Small Cell Lung Cancer Patients

William N. William Jr.

Beneficencia Portuguesa de Sao Paulo, Brazil

Introduction

Concurrent chemoradiation therapy followed by consolidation durvalumab is considered the standard of care treatment for patients with unresectable, stage III, non-small cell lung cancer patients (NSCLCs), given improvements in overall survival observed with this strategy in the phase 3 PACIFIC study.[1,2]

Despite considered a major improvement for these patients, immunotherapy-based treatment intensification may lead to an increase in the incidence of adverse events, namely pneumonitis, which may adversely impact outcomes if not readily recognized and adequately managed.

Herein, we discussed recent advances in prevention, diagnosis and treatment options for radiation and drug-induced pneumonitis in the context of multimodality treatment for stage III NSCLC.

Radiation therapy-induced pneumonitis

Up to 10-30% of patients who receive radiation therapy to the lung may experience pneumonitis.[3,4] In addition to acute manifestations, radiation pneumonitis may evolve to radiation fibrosis with significant clinical impacts. A physiopathological model for radiation-induced pneumonitis has been proposed, according to which radiation would induce normal epithelial and endothelial cell damage, leading to increased vascular permeability, macrophage infiltration, release of reactive oxygen species and acute inflammation. Several cytokines may be secreted in this process of type I and II epithelial cell damage, such as transforming growth factor beta, platelet-derived growth factor, and interleukins, further perpetuating injury. This disorderly process may evolve to tissue fibrosis and necrosis, and vascular disruption. Over time, fibroblast proliferation, and stromal changes may develop into radiation fibrosis.

Radiographically, radiotherapy-induced pneumonitis may manifest as uniform patchy, small nodule-like pattern, diffuse ground glass opacities (in early stages), alveolar infiltration, diffuse or patchy (late stages), and decreased lung volumes, diffuse or patchy ground-glass opacities, and linear scar with consolidation (in fibrotic stages).[5]

Risk factors for radiation-therapy induced pneumonitis include female sex, pre-existing lung dysfunction or lung disease, as well as radiation features (such as mean lung dose, lung V20Gy, lung V5Gy, and radiation delivery technique). Compared to 3D conformal, IMRT technique may reduce radiation pneumonitis from 7.9% to 3.5%, as evidenced in one of the most controlled prospective clinical trial analysis performed to date.[6]

Treatment of radiation therapy-induced pneumonitis includes supportive care, with oxygen supplementation as needed. Steroids are commonly employed, despite the lack of randomized clinical trials assessing efficacy in this setting. As a result, the optimal glucocorticoid choice, dose, mode of administration, and treatment length are yet to be defined.

Immune checkpoint inhibitor (ICI)-induced pneumonitis

ICI-induced pneumonitis occurs in approximately 3% of patients included in most clinical trials of systemic therapy alone, with less than 1% incidence of grade 3-5 pneumonitis, and a pneumonitis-related death rate estimated at 0.2%.[7] In the real world, however, figures as high as 20% of all grade pneumonitis (and 11% of grade 3-4 pneumonitis) in NSCLC patients have been reported.[8]

Risk factors for ICI-induced pneumonitis include use of PD-1/PD-L1 inhibitors (compared to anti-CTLA4 drugs), combination immunotherapy, history of asthma/chronic obstructive pulmonary disease, previous chest radiation therapy, and smoking history. Smoking and lung disease may also be associated with a poor response to steroid therapy for pneumonitis.[9]

The pathogenesis of ICI-induced pneumonitis has not been fully characterized, but may involve overactivation of T cells, increased levels of pre-existing antibodies, and release of inflammatory cells and cytokines.[9-11]

Clinically, patients with ICI-induced pneumonitis present with dyspnea, dry cough, fever, fatigue and imaging findings may be non-specific.

Treatment of ICI-induced pneumonitis is based off of clinical experience that has been incorporated into guidelines,[12] with no comprehensive prospective study performed to date on this topic. Grade 1 pneumonitis usually requires no treatment. Grade 2 pneumonitis should be managed with ICI interruption and oral steroids (e.g., prednisone 1-2 mg/kg/day), slowly tapered over

a period not shorter than 4-6 weeks. Grade 3-4 pneumonitis requires admission to the hospital, intravenous steroids (e.g., methylprednisolone 1-2 mg/kg/day), with therapy escalation to infliximab, cyclophosphamide, or other immunomodulatory agents in case of suboptimal response. Recurrence of pneumonitis may occur during steroid taper or upon re-exposure to ICI inhibitors, thus requiring close follow-up careful considerations before re-treatment (especially after a high grade episode).

The specific case of pneumonitis in the context of stage III NSCLC treatment

Use of ICI after radiation therapy (as is the case for consolidation durvalumab after chemoradiation therapy for management of stage III NSCLCs) is associated with increased incidence of pneumonitis, compared to ICI single modality. In the PACIFIC trial, the incidence of pneumonitis was 33.6% for patients receiving durvalumab consolidation therapy compared to 24.9% in the placebo group.[2,13] Pneumonitis was self-limited, for the most part (median duration of 57-64 days). Grade 3/4 immune-mediated pneumonitis occurred in 1.9% of patients receiving durvalumab.[14]

As treatment of stage III NSCLCs advances, several issues related to pneumonitis arise. Multiple clinical trials have now been performed adding ICI concurrently to radiation therapy, with some evidence to suggest increased incidence of pneumonitis with the concurrent versus sequential approach, although still at tolerable rates.[15] Upcoming results of phase 3 trials that have already completed accrual will help determine the full safety profile of concurrent radiation therapy and immunotherapy, as well as efficacy. Additionally, efforts are under way to investigate possible blood- and/or image-based biomarkers that could be predictors of pneumonitis. Lastly, anti-fibrotic agents have been used to treat interstitial lung disease unrelated to ICIs or radiation therapy, and their possible role as preventive agents for radiation and/or ICI-induced pneumonitis remains to be determined.

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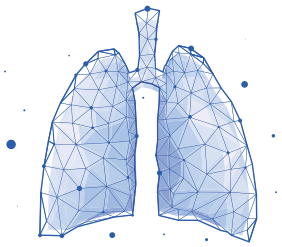

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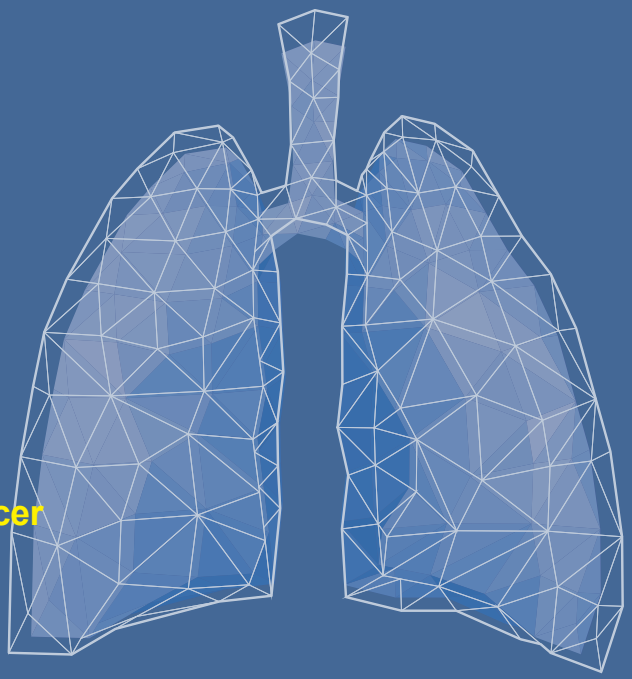


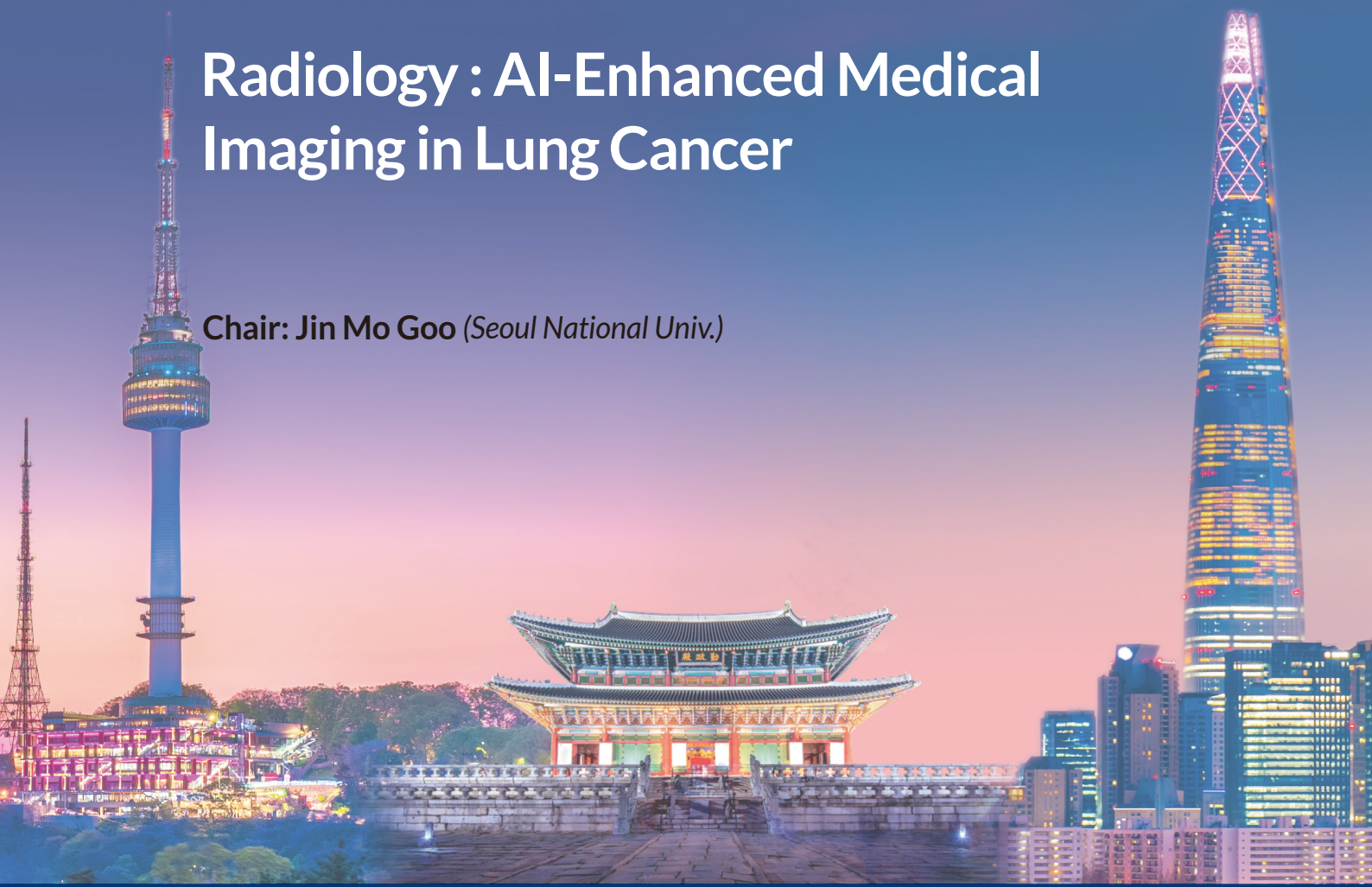
| November 10 (Thu), 2022 | Room C

08:50-10:10

Session I (C)

Radiology : AI-Enhanced Medical Imaging in Lung Cancer

Chair: Jin Mo Goo *(Seoul National Univ.)*



Artificial Intelligence in Medical Imaging

Hugo Aerts

Dana-Farber Cancer Institute, USA

Technological advances in Artificial Intelligence (AI), particularly deep learning, have demonstrated remarkable progress in image-recognition tasks. Methods ranging from convolutional neural networks to variational autoencoders have found myriad applications in various medical fields, propelling it forward at a rapid pace. In this talk, Dr. Aerts will discuss recent developments from his group and collaborators performing research at the intersection of deep learning, radiology, oncology, cardiology, bioinformatics, and data science. He will explore how these methods could impact multiple facets of medicine, with a general focus on applications in radiology, and demonstrate ways in which these methods are advancing the field. The presentation will conclude with a discussion on the need for open-source deep learning frameworks that are transparent and reproducible. Topics that will be discussed include:

Biological age quantification using medical imaging

Chronological age, defined as the number of years since birth, is a cornerstone of medical decision-making. To decide who is eligible for cancer screening based on chronological age; chronological age is among the most important inputs to current guidelines for the primary prevention of cancer and cardiovascular disease. Yet chronological age is an imperfect measure of health and longevity, as individuals age at different rates. Biological age, defined as a cumulative measure of the effects of aging on an individual, has been proposed as a better measure of longevity and susceptibility to aging-related disease. Indeed, investigators have developed biological age measures using functional (e.g., gait speed, frailty), physiological (e.g., vascular compliance), and blood (e.g., DNA methylation, telomere length) measures.

In recent work, published by Raghu et al[1] and Lu et al[2], proposed a new measure of biological age, based on a convolutional neural network (CNN) analysis of a chest radiograph (CXR or x-ray) image. Chest radiography is the most common diagnostic imaging test and thus provides ample opportunity to assess aging from existing images. CNNs, a form of artificial intelligence, have

made major advances in diagnosis from CXRs. They found that CNN's could also estimate the biological age from x-ray images and could predict long-term all-cause and cardiovascular mortality beyond chronological age. A clinical application of such a system could be by identifying individuals at risk of developing cancer. In recent work, published in the Annals of Internal Medicine[3], we demonstrate how lung cancer screening can be improved using an automated deep-learning approach based on chest radiograph images. Our model could identify smokers at high risk for incident lung cancer, beyond CMS eligibility and using information commonly available in the EMR. Extension of this work in individuals with lung diseases, such as COPD and cancer, are currently ongoing.

Evaluation of AI algorithms in clinical practice

AI and deep learning have also shown great potential in streamlining clinical tasks. However, most studies remain confined to in silico validation in small internal cohorts, without external validation or data on real-world clinical utility. In recent work, Hosny et al[4], developed a strategy for the clinical validation of deep learning models for segmenting primary non-small-cell lung cancer (NSCLC) tumours and involved lymph nodes in CT images, which is a time-intensive step with large variability among experts, that is relevant for treatment planning and improving response assessment. In a observational study, CT images and segmentations were collected from eight internal and external sources from the USA. They included 2208 patients imaged between 2001 and 2015, with 787 patients used for model discovery and 1421 for model validation, including 28 patients for end-user testing. Models showed an improvement over the interobserver benchmark, and were within the intraobserver benchmark. For primary validation, AI performance on internal data (segmented by the same expert who segmented the discovery data) was very high and within the interobserver benchmark. Performance on clinical trial data (RTOG-0617) was high and with similar results on diagnostic radiology datasets. AI assistance led to a 65% reduction in segmentation time (5·4 min; $p<0·0001$) and a 32% reduction in interobserver variability (SD; $p=0·013$). These results illustrate that in silico geometric segmentation metrics might not correlate with clinical utility of the models. Experts' segmentation style and preference might affect model performance.

Cloud-based platforms for the dissemination of deep learning models

Recent advances in artificial intelligence in medicine have led to a profusion of studies that apply deep learning to problems in radiology and pathology among others. Additionally, the availability of open-source computational frameworks has lowered the barriers to implementing state-of-

the-art methods across multiple domains. Albeit leading to major performance breakthroughs in some tasks, effective dissemination of deep learning algorithms remains challenging. These models use different AI backends, come with varying degrees of documentation, and hence are not readily usable. Other researchers often go through a long process of trial-and-error to reimplement these models, and such effort is often duplicated. This inhibits reproducibility and benchmarking studies, impeding further validation, and ultimately hindering their effectiveness in the cumulative scientific progress. Therefore, better processes for sharing and dissemination of deep learning models are required.[5]

For this reason, Dr. Aerts and colleagues are developing platforms for sharing AI-based research outputs. These community-driven container-based software engines provide a platform for the structured dissemination of deep learning models. By being domain-, data-, and framework-agnostic, this allows them to cater to different workflows and contributors' preferences and provides a flexible software template. As such, these open-source models can be used out of the box without the need for reimplementation. Additionally, this standard interface allows for smoothly integrating different models with research platforms (e.g. Imaging Data Commons [IDC]), and can be important for challenges, as AI competition organizers can utilize the platform's submission requirements. Ultimately, these efforts will bring much-needed transparency to AI and accelerate scientific discoveries, academic training, and clinical adoption of AI applications in radiology.

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AI-Powered Lung Cancer CT Screening

Sang Min Lee

Univ. of Ulsan, Korea

Artificial intelligence, especially deep learning (DL), is a rapidly evolving field and expanding to medicine. DL is a genre of machine learning that allows computational models to learn representations of data with multiple levels of abstraction using numerous processing layers. A distinctive feature of deep learning, compared to conventional machine learning methods, is that it can generate appropriate models for tasks directly from the raw data, removing the need for human-led feature extraction.

Medical images are particularly suited for deep learning applications. In chest imaging, there has been a large effort to develop and apply computer-aided detection (CAD) systems for the detection of lung nodules on chest radiographs and chest computed tomography. Finally, recent advances in deep learning enable to develop applicable solutions for clinical practice. In this presentation, I will address AI applications in lung cancer CT screening (LSC).

The first step for LCS is to determine the target population. Recently, Lu et al[1] developed and validated a DL risk prediction model to identify candidates with high risk for LCS. The model used easily obtainable inputs, including age, sex, smoking status, and a chest radiograph, and it showed overall better performance and a higher sensitivity than the Centers for Medicare and Medicaid Services eligibility criteria. Furthermore, Lee et al[2] also demonstrated the added value of the risk model to the 2021 U.S. Preventive Services Task Force recommendations.

The next step is to detect nodules and evaluate the detected nodules on CT. DL based CAD can automatically detect and segment nodules on CT.[3] Primakov et al reported a fully automated pipeline for the detection and volumetric segmentation of non-small cell lung cancer (NSCLC) developed and validated on 1328 thoracic CT scans from 8 institutions. Interestingly, on average, radiologists and radiation oncologists preferred automatic segmentations than manual segmentations in 56% of the cases. In the evaluation of subsolid nodules, CAD shows excellent

performance in detection of nodules, even better at 1-mm section thickness CT[4] and automatic measurements of solid portions of lung cancer manifesting as subsolid lesions by the DL algorithm were comparable with manual measurements and showed good agreement with invasive component size at pathologic evaluation.[5] These functions of DL based CAD allow the automatic assignment of Lung-RADS categories.

Regarding the evaluation of nodules, Venkadesh et al[6] showed that the DL algorithm significantly outperformed the PanCan model and was comparable to thoracic radiologists for malignancy risk estimation of pulmonary nodules. Moreover, DL based CAD can improve estimation of indeterminate pulmonary nodule malignancy risk on chest CT and improve interobserver agreement for both risk stratification and management recommendations.[7]

Finally, DL based image normalization can effectively reduce the effect of two different reconstruction kernels and may improve the reproducibility of radiomic features in pulmonary nodules or masses.[8] Radiomics extracts high-throughput quantitative features from medical images and use these features for diagnosis, prognostication, or prediction of treatment outcomes. Although radiomics is a promising tool, the results have been difficult to reproduce and be applied in clinical practice. Especially, the vulnerability of radiomics to variation in the acquisition parameters of imaging examinations is one of the major barriers to overcome. This limitation can be solved by DL methods and image normalization for intra-/inter-vendor CT kernel conversion is now being explored using generative adversarial networks.

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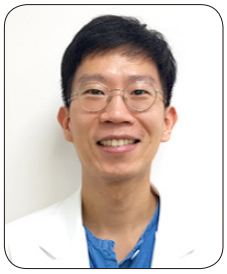

Prognostication Using Imaging Features in Patients with Lung Cancer

Hyungjin Kim

Seoul National Univ., Korea

In this session, preoperative CT-based prognostic features in early-stage lung cancers will be briefly introduced. First, tumor dimensions in terms of the uni-dimensional or bi-dimensional measurement are fundamental prognostic factors as a clinical T descriptor. Second, tumor margin characteristics such as spiculation and pleural tagging are CT surrogates for the desmoplastic reaction in the tumor microenvironment. Third, central tumor location is associated with mediastinal nodal metastasis, and it is associated with worse survival even in node-negative lung cancers. Fourth, sarcopenia and adipopenia are associated with postoperative survival in patients with resected lung cancer, and these features can be quantified using the chest CT or whole-body CT from PET/CT. Fifth, deep learning models can be used to extract CT features, which are independent of the semantic features or dimensional measurements. Deep learning-derived CT features do not require manual feature engineering and thus are robust to the inter-scan and inter-reader variation.

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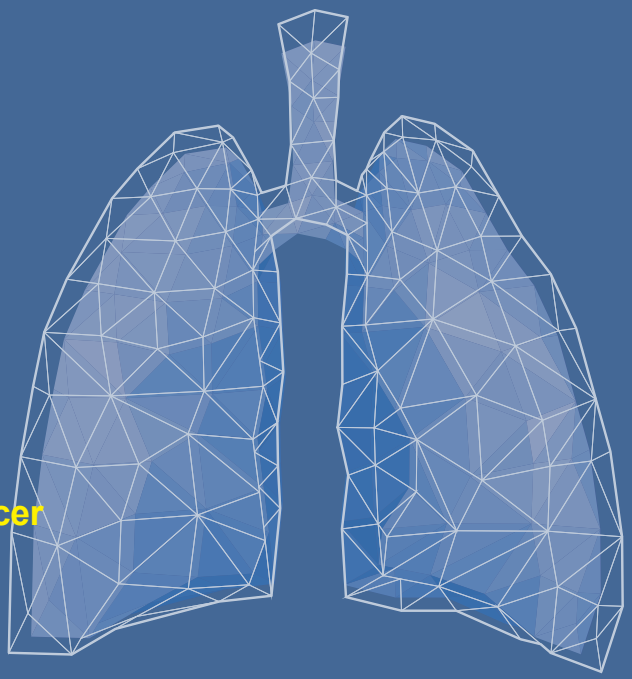


| November 10 (Thu), 2022 | Room C

10:30-11:50

Session II (C)

Bronchoscopy

Chair: Bin Hwangbo *(National Cancer Center)*

Advanced Bronchoscopic Techniques for the Peripheral Lung Cancer

Noriaki Kurimoto

Shimane Univ. Hospital, Japan

I will talk about three topics.

1. Reading CT anatomy

I will clarify how to visually trace the bronchi leading to a peripheral pulmonary lesion using CT images. Although virtual bronchoscopic navigation has become widespread, it is important that we learn how to trace the bronchi leading to a peripheral pulmonary lesion from CT images without the help of navigation. Reading CT image anatomy can provide a diagram of the bronchial branches surrounding a specific target close to the pleura and has the advantage that the doctor can get more confidence. Compared "reading CT anatomy" with Navigation, in the proximal bronchus Navigation is more accurate than Reading CT anatomy. But in the peripheral sub-pleural area, Reading CT anatomy is more accurate than Navigation, because Navigation could not show the narrow bronchus in the sub-pleural area.

There are five steps to reading CT image anatomy.
1st step: To reverse or rotate the CT images.

2nd step: To differentiate between the vertical and horizontal branches of the bronchi.

3rd step: To determine whether the patient's head is in front of or behind the screen.

4th step: To determine the long axis of the most proximal horizontal branch.

5th step: To place the point of view at the proximal site of the most proximal horizontal branch.
(The third, fourth, and fifth steps refer to the horizontal bronchial branches.)

2. EBUS using a guide sheath

For EBUS using a guide sheath (EBUS-GS), a miniature probe is covered by a guide sheath.

(1) In the procedure of EBUS-GS, the probe covered by the guide sheath is introduced into the lesion via the working channel of a bronchoscope. While scanning the peripheral lesion, we can confirm the accurate location of the lesion.

(2) The probe is withdrawn, while the guide sheath is left in situ.

(3) A brush or biopsy forceps is introduced through the guide sheath into the lesion and collected specimens.

We classified the location between the probe and the lesion into "within," "adjacent to," or "invisible."

I will explain the procedure of EBUS-GS.

1st step: To perform Reading CT Anatomy.
Before performing bronchoscopy for peripheral pulmonary lesions, we read and draw the bronchial branches leading to the lesion on CT images.

2nd step: To advance the scope more periphery.

3rd step: To guide the probe to the lesion.
When the lesion is *"invisible"* on EBUS images, we should seek another (bronchial) branch under fluoroscopy. When the lesion is *"adjacent to"* on EBUS images, we should seek another (bronchial) branch under EBUS images. After seeking the bronchial branch under fluoroscopy and EBUS images, the probe is still adjacent to the lesion and then "Pinpoint Biopsy" is useful to get specimens from the lesion.

4th step: To confirm the location of the tip of GS
While we gently pull back the probe into the GS and the part of the transducer still locates out of the GS, EBUS image is still bright. But the total of the transducer is covered by the GS, the EBUS image changes to be dark. We would like to call this phenomenon "dark phenomenon." Scanning the target, we can confirm the proximal edge of the target. At this position, we pull back and advance the probe for confirming "dark phenomenon." And then we adjust the tip of the GS to locate at the proximal area of the target.

3. Tips of the procedure of EBUS-GS

I would like to show the tips of the procedure of EBUS-GS.

Medical Thoracoscopy for Malignant Pleural Effusion

Pyng Lee

National Univ. of Singapore, Singapore

Medical thoracoscopy provides the physician a window into the pleural space. The procedure allows biopsy of the parietal pleura under direct visualization with good accuracy. In addition, it achieves therapeutic goals of fluid drainage, guided chest tube placement, and pleurodesis. Thoracoscopy as described by Jacobaeus more than a century ago was a technique to collapse underlying tuberculous lung, which fell into oblivion owing to effective anti-tuberculous drugs. Thoracoscopy enjoyed resurgence when thoracic surgeons introduced it for minimally invasive surgery also known as video-assisted thoracic surgery (VATS). VATS is performed under general anesthesia with single lung ventilation while medical thoracoscopy (MT) is performed by the pulmonologist in an endoscopy suite using rigid or flex-rigid instruments, local anesthesia and conscious sedation. MT is less invasive, and comparable diagnostic yield is achieved with the flexi-rigid instrument compared with VATS. Flexi-rigid pleuroscopy is extremely well tolerated under local anesthesia, and safe as an outpatient procedure. Biopsy quality can be further enhanced with accessories that are compatible with the flex-rigid pleuroscope such as the insulated tip knife and cryoprobe. In the era of sensitive imaging tools, image guided pleural biopsy and advances in cytopathology, MT continues to play a pivotal role in staging, and palliation of malignant pleural effusion.

Figure 1. Endoscopic findings of (a, b) polypoid masses (c, d) candle wax nodules.

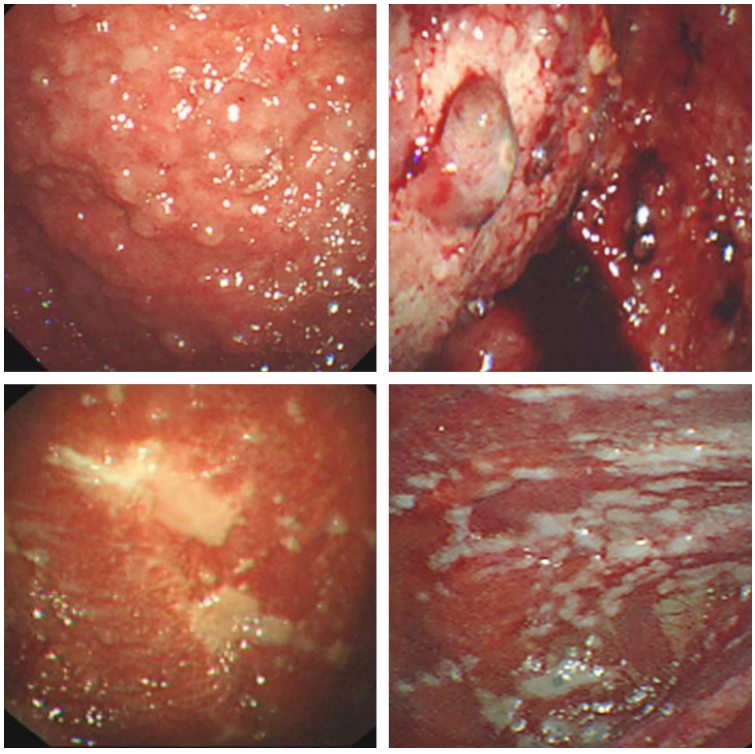


Figure 2. Biopsy of parietal pleura with (a) flexible forceps and (b) rigid optical forceps (c) cryoprobe (d) IT knife for tissue biopsy for molecular characterization of cancer.

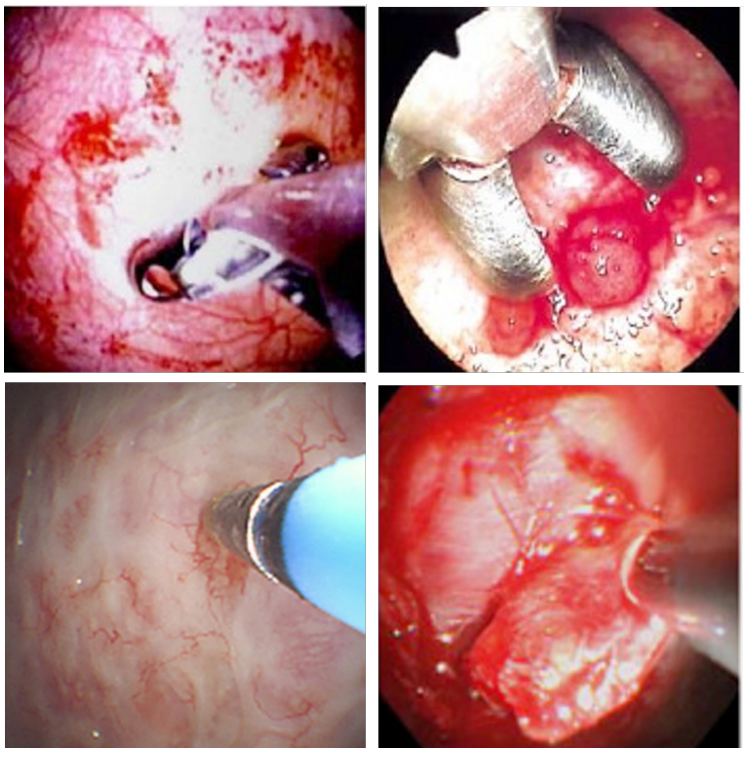
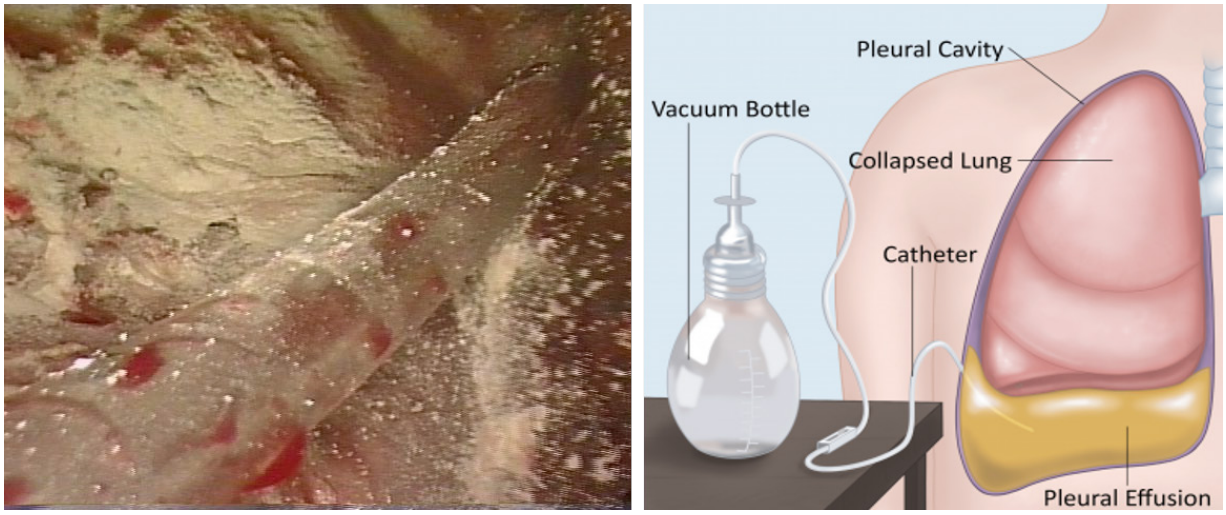


Figure 3. Thoracoscopic talc poudrage or Placement of Indwelling Pleural Catheter.



Rigid Bronchoscopy for Malignant Central Airway Obstruction

Ho Joong Kim

Sungkyunkwan Univ., Korea

Airway intervention is nowadays commonly indicated in malignant central airway obstructions, and often brings a dramatic relief from life-threatening dyspnea. Among many etiologies causing malignant central airway obstruction, non-small cell lung cancer invading large airway is by far most frequent. Airway invasion by esophageal, thyroid, and breast cancer are not infrequent, and endobronchial metastasis can become life-threatening in colon, kidney, and other cancer patients. Slowly growing tumor in large airways, such as adenoid cystic carcinoma and carcinoid tumor are rare but may require endoscopic treatment.

The growing problems of malignant central airway obstruction have led to a rapid development of interventional bronchology, including laser therapy, cryotherapy, stenting, ballooning, and brachytherapy. If curative or effective palliative therapy is available after the emergency rescue, airway intervention is strongly recommended. However, airway intervention does not bring a dramatic improvement in all patients. Good results are expected when the following conditions are met; mechanical airway obstruction being the main cause of dyspnea, intact distal airways, patient's good general condition and tolerability for the morbidity of the procedure, and presence of experienced and competent bronchoscopists. Careful patient selection is one of the most important preconditions for airway intervention.

In many clinical reports, most patients (85-90%) improved immediately after the airway intervention, and procedure-related mortality was low (<3%) in experienced centers. Massive hemoptysis, respiratory failure, pneumothorax, pneumomediastinum are potential complications.

It should be remembered that airway intervention is not a curative measure for malignant central airway obstruction. It doesn't prolong the life, and is only a kind of supportive therapy to relieve dyspnea. Standardized pathologic diagnosis and staging workup is essential and curative therapeutic modality should be selected first if possible. Only after the curative and other palliative

modalities were exhausted, the remained symptomatic airway obstruction can be treated by endobronchial measure, including stenting, laser ablation, cryotherapy, ballooning, and brachytherapy.

In conclusion, airway intervention could be a part of the comprehensive therapy for patients with malignant central airway obstruction. The interventional bronchoscopist should consider the advantages and limitations of airway intervention and carefully select indicated patients.

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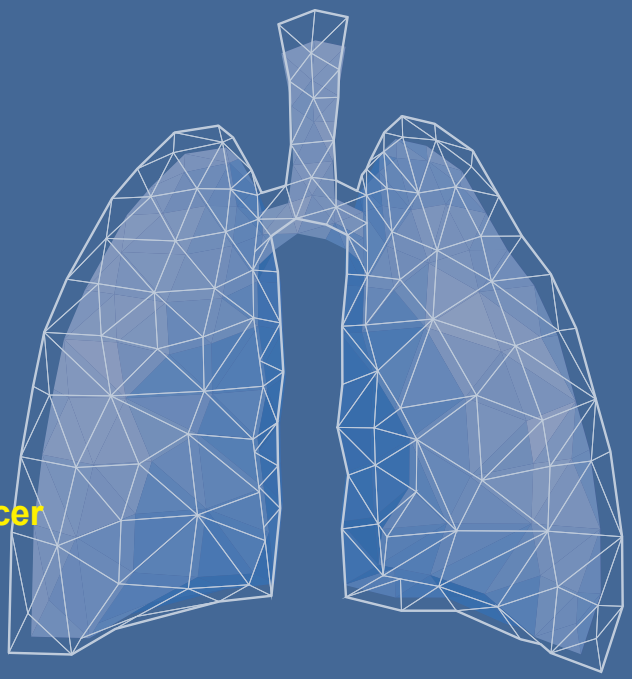


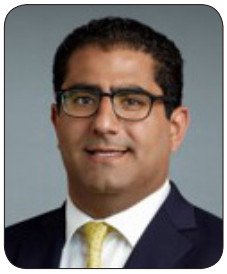
| November 10 (Thu), 2022 | Room C

13:00-14:40

Session III (C)

Targeting Lung Cancer with Bioconjugates

Chair: Yoon Soo Chang *(Yonsei Univ.)*



Amivantamab

Joshua K. Sabari

NYU Langone Health, USA

Patritumab Deruxtecan

Pasi A. Jänne

Dana-Farber Cancer Institute, USA

Trastuzumab Deruxtecan (Enhertu)

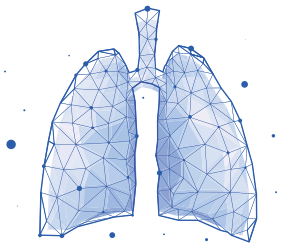
Enriqueta Felip

Vall d'Hebron Univ. Hospital, Spain

Precision Delivery of Targeted Protein Degraders for Solid Tumors

Sung Joo Lee

Orum Therapeutics



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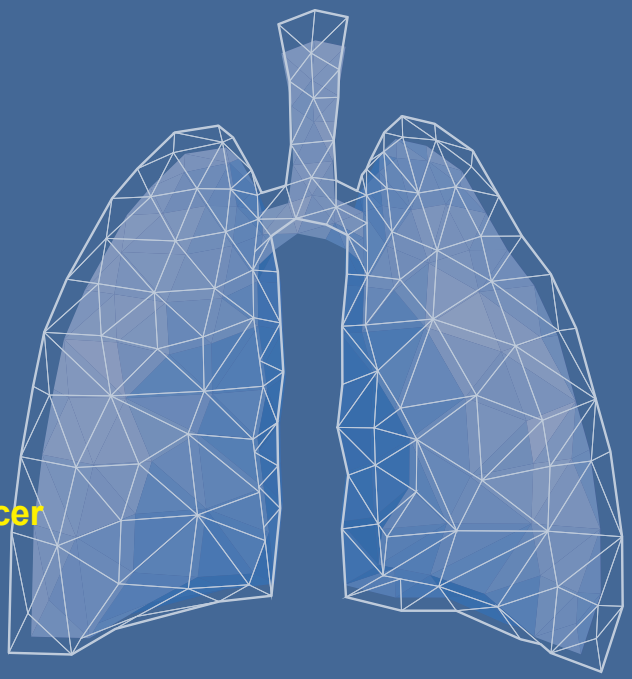

| November 10 (Thu), 2022 | Room C

15:00-16:40

Session IV (C)

Biomarkers in Immune Checkpoint Inhibitor

Chair: Yoon Kyung Chun *(Seoul National Univ.)*

Programmed Death Ligand 1 (PD-L1)

Fred R. Hirsch

Mount Sinai Health System, USA

PD-L1 expression assessed by immunohistochemistry (IHC) has been validated as a useful predictive biomarker for immunotherapy (IO) in Non-Small Cell Lung Cancer (NSCLC). For IO monotherapy it is a clear association between higher PD-L1 expression and improved response rate and outcome (e.g. KN 024 and KN 042). This seems to be the case also for IO plus chemotherapy (e.g. ImPower 189) and IO plus IO therapy (e. g Nivolumab plus Ipilumumab, CM 9LA). In most US institutions the IO treatment paradigm is based on PD-L1 expression today is: PD-L1≥50% : IO monotherapy (in some patients with high tumor burden: IO+CT) ; PD-L1 1-49%: IO+ Chemotherapy (CT); PD-L1<1%: IO+ CT or IO+IO. However, PD-L1 expression is not made for cut-off values! PD-L1 expression is a dynamic process and might be we should assess the expression pattern as a continuous variable? A potential difference in PD-L1 biology and predictive capability between non-squamous and squamous histologies needs also to be better understood.

Why do PD-L1 negative tumors/patients respond to IO? This topic will be discussed, but heterogeneity of PD-L1 expression in the tumor(s) needs to be considered as a (main) cause for IO-response in PD-L1 negative tumors. Discrepancies between PD-L1 expression in primary tumors versus metastases have been seen in several studies, including paired sample studies from the same patient (s). Whether this represents a biological phenomenon, or a technical phenomenon remains to be studied. If this represents a biological phenomenon, it might indicate that the biology of PD-L1 expression might differ from early-stage NSCLC compared to advanced stage NSCLC. While tissue PD-L1 examination is the common assay, studies have also demonstrated that cytology specimens can be used for PD-L1 assessment and outcome on IO-monotherapy based on cytology seems to be the same as tissue-based examination.

Artificial Intelligence (AI) assessment of PD-L1 tissue expression have been studied in preliminary/retrospective studies and has already demonstrated a more nuanced assessment of PD-L1 expression compared to manual assessment and has also in retrospective analysis from Nivolumab

studies shown to result in a better survival difference to chemotherapy than manual (traditional) assessment. However, the studies are small and retrospective and need further validation. Only future studies can tell if AI assessment might improve the predictive capability of PD-L1 protein expression. Even if PD-L1 expression today is widely used and approved predictive biomarker for IO-therapy, it is not a perfect biomarker, and most likely in the future combination of biomarkers and assays need to be considered and prospectively studied.

Tumor Immune Microenvironment: Tumor Infiltrating Lymphocytes

Se-Hoon Lee

Sungkyunkwan Univ., Korea

Biomarkers on the basis of tumor-infiltrating lymphocytes (TIL) are potentially valuable in predicting the effectiveness of immune checkpoint inhibitors (ICI). However, clinical application remains challenging because of methodologic limitations and laborious process involved in spatial analysis of TIL distribution in whole-slide images (WSI). We have developed an artificial intelligence (AI)–powered WSI analyzer of TIL in the tumor microenvironment that can define three immune phenotypes (IPs): inflamed, immune-excluded, and immune-desert. These IPs were correlated with tumor response to ICI and survival in two independent cohorts of patients with advanced non–small-cell lung cancer (NSCLC). Inflamed IP correlated with enrichment in local immune cytolytic activity, higher response rate, and prolonged progression-free survival compared with patients with immune-excluded or immune-desert phenotypes. At the WSI level, there was significant positive correlation between tumor proportion score (TPS) as determined by the AI model and control TPS analyzed by pathologists (P<.001). Overall, 44.0% of tumors were inflamed, 37.1% were immune-excluded, and 18.9% were immune-desert. Incidence of inflamed IP in patients with programmed death ligand-1 TPS at <1%, 1%-49%, and ¡Ã50% was 31.7%, 42.5%, and 56.8%, respectively. Median progression-free survival and overall survival were, respectively, 4.1 months and 24.8 months with inflamed IP, 2.2 months and 14.0 months with immune-excluded IP, and 2.4 months and 10.6 months with immune-desert IP. The AI-powered spatial analysis of TIL correlated with tumor response and progression-free survival of ICI in advanced NSCLC. This is potentially a supplementary biomarker to TPS as determined by a pathologist.

Keywords: immune checkpoint inhibitor, lymphocyte, spatial analysis, artificial intelligence

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Tumor Immunogenicity: Tumor Mutational Burden, Microsatellite Instability

Yasushi Goto

National Cancer Center Hospital, Japan

Most successful immunotherapy until now is targeting immune checkpoints. $CD8^+$ T cells are the primary mediators of anti-cancer immunity. $CD8^+$ T cells recognize the antigenic peptides to become activated and kill the tumor cells. Candidates of cancer rejection antigens are tumor-associated antigens (self-antigens encoded in the germline genome and preferentially expressed in tumor), viral antigens, and tumor specific antigens (TSA; antigens raised by tumor-specific irregularities). TSAs also called neoantigens, are generally tumor specific and derived from of genomic aberrations. TSA arise because of somatic, tumor-specific nonsynonymous DNA mutations.[1] Tumor mutation burden is the indicator of mutation load and may increase the possibility of generating the cancer rejection neoantigens. Microsatellite instability (MSI) is the accumulation of insertion or deletion errors at microsatellite repeat sequences in cancerous cells. Functional deficiency within one or more major DNA mismatch repair proteins is the cause of this status.[2] Compared with MSI-stable tumors, MSI-H tumors are associated with a higher mutational burden, accumulation of non-synchronous mutation, and therefore tumor neoantigen load.

We are still unable to precisely detect the neoantigen of personal tumor yet, but high mutation burden is indirectly suggesting the likelihood of generating neoantigens and activating $CD8^+$ T cells. From the origin, it will never become the clear biomarker of immune checkpoint inhibitor (ICI), but has syllogistic emerged as a predictive marker of ICI. However, early enthusiasm is negated by several studies in NSCLC, where PD-L1 expression in tumors are established as a biomarker.

I will review the biomarker of ICI and its actual use in clinic. Tumor immunogenicity will be discussed from the standpoint of future clinical use, including expected next generation treatment of neoantigen specific cancer vaccines.

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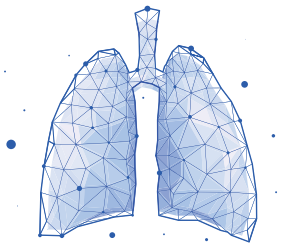
Tumor Cell Gene Mutation: Druggable Mutations, STK11, MDM2, DNMT3A, CDKN2A/B, etc.

Yun-Gyoo Lee

Sungkyunkwan Univ., Korea

Immune checkpoint inhibitors (ICIs) have been established as the stand- ard treatment for patients with locally advanced/meta- static non-small cell lung cancer (NSCLC), whether in monotherapy or combination therapy. Despite this, substantial patients do not benefit from ICIs. Even in patients who initially respond to ICIs, disease may eventually progress. Thus, identifying predictive biomarkers may help select those patients who are most likely to benefit from ICIs. Although PD-L1 expression and tumor mutation burden have been widely used as predictive biomarkers for ICI, both are incomplete. Today, we will discuss potential predictive biomarkers for ICIs in patients with NSCLC including druggable Mutations such as EGFR, ALK, K-RAS, TP53, STK11/KEAP1, MDM2, DNMT3A, CDKN2A/B etc.



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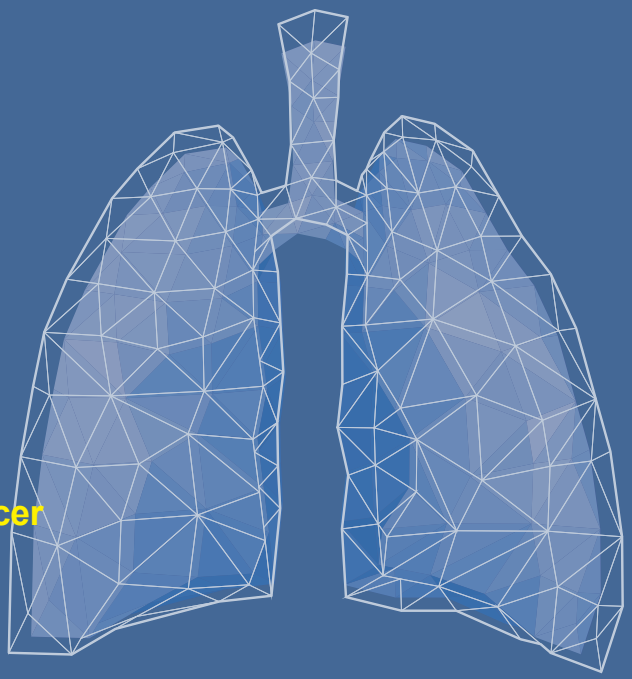

| November 10 (Thu), 2022 | Room C

16:50-17:40

Satellite Symposium II (C)

[TAKEDA]

Chair: Sang-We Kim *(Univ. of Ulsan)*

1L Treatment Approach for Patients with ALK+Advanced Non-Small Cell Lung Cancer

Hyun Ae Jung

Sungkyunkwan Univ., Korea

In the recent version of NCCN guideline, three ALK-TKI (alectinib, brigatinib, and loratinib) are recommended for first-line therapy in patients with ALK + NSCLC as category 1.[1] ALTA-1L study is a phase 3, open-label, randomized, multicenter study of brigatinib. With median follow-up was 40.4 (range 0-52.4) months, median BIRC assessed PFS was 24.0 months (95% CI, 18.5-43.2) for brigatinib and 11.1 month (95% CI, 9.1-13.0) (HR 0.48), P<0.0001).[2] Intracranial PFS was 44.1 months for brigatinib and 21.2 months for crizotinib (HR 0.44, P<0.0001) in ITT population. In patients with baseline brain metastases, intracranial PFS was 24.0 months for brigatinib and 5.5 months for crizotinib (HR, 0.29, P<0.001). The final overall survival was not reached in both arms. The 3-yr OS rate was 71% vs. 68% and the 4-yr OS rate was 66% vs. 60% for brigatinib and crizotinib, respectively (HR, 0.54, P=0.02) in ITT population. In patients with brain metastasis at baseline, the 3-ys OS rate was 71% vs. 55% and 4-yr OS rate was 71% vs. 44% for brigatinib and crizotinib, respectively (HR 0.43, P=0.02). In the brigatinib arm, 3% of patients had early-onset pulmonary event within 14 days of treatment initiation. In the ALTA-1L study, 59% of patients was white and 39% of patients with Asian. Brigatinib showed comparable improvement in PFS over crizotinib in both Asian and non-Asian patients with ALK + NSCLC.[3] ALEX study is a phase 3 trial of alectinib, median BIRC assessed PFS was 25.7 months (95% CI, 19.9-NE) for alectinib and 10.4 months for crizotinib (HR 0.50, P<0.001).[4] In Korea, as first line of therapy for ALK + NSCLC, brigatinib and alectinib were reimbursed and loratinib was reimbursed after failing brigatinib treatment. In the retrospective study of BrigALK2, among the patients who progressed to brigatinib treatment, 68 patients received loratinib treatment.[2] The median OS from loratinib start was 14.1 months. Through the long-term follow-up data of ALTA-1L, brigatinib showed promising efficacy and manageable safety profile. Brigatinib followed by loratinib would be feasible treatment sequence.

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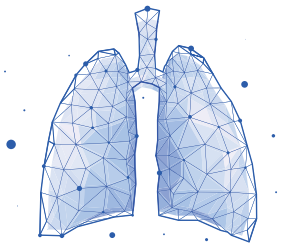

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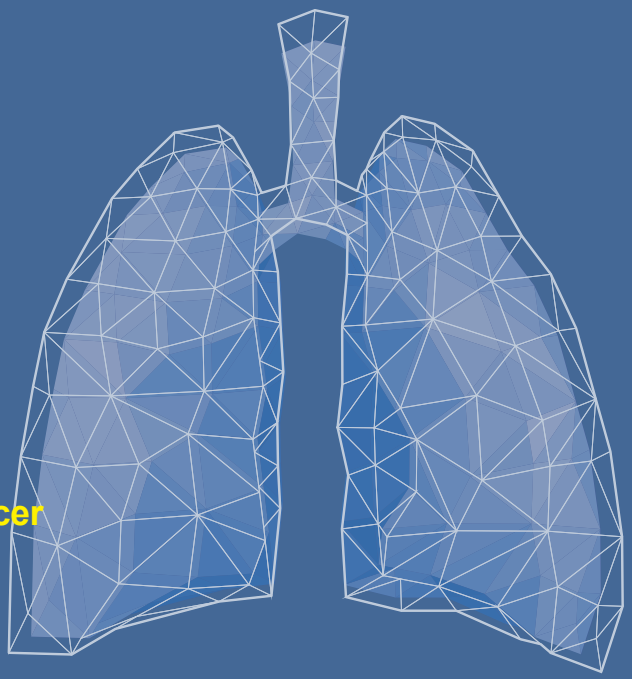


| November 10 (Thu), 2022 | Room D

16:50-17:40

Satellite Symposium II (D)

[ONO BMS]

Chair: Myung-Ju Ahn *(Samsung Medical Center)*

Changing Treatment Paradigm of Neoadjuvant Non-Small Cell Lung Cancer with Newly Approved OPDIVO + Chemotherapy

Mariano Provencio

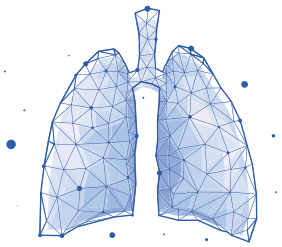
Puerta de Hierro Majadahonda Univ. Hospital, Spain

Background: Neoadjuvant or adjuvant chemotherapy confers a modest benefit over surgery alone for resectable non–small-cell lung cancer (NSCLC). In early-phase trials, nivolumab-based neoadjuvant regimens have shown promising clinical activity; however, data from phase 3 trials are needed to confirm these findings.

Methods: In this open-label, phase 3 trial, we randomly assigned patients with stage IB to IIIA resectable NSCLC to receive nivolumab plus platinum-based chemotherapy or platinum-based chemotherapy alone, followed by resection. The primary end points were event-free survival and pathological complete response (0% viable tumor in resected lung and lymph nodes), both evaluated by blinded independent review. Overall survival was a key secondary end point. Safety was assessed in all treated patients.

Results: The median event-free survival was 31.6 months (95% confidence interval [CI], 30.2 to not reached) with nivolumab plus chemotherapy and 20.8 months (95% CI, 14.0 to 26.7) with chemotherapy alone (hazard ratio for disease progression, disease recurrence, or death, 0.63; 97.38% CI, 0.43 to 0.91; P=0.005). The percentage of patients with a pathological complete response was 24.0% (95% CI, 18.0 to 31.0) and 2.2% (95% CI, 0.6 to 5.6), respectively (odds ratio, 13.94; 99% CI, 3.49 to 55.75; P<0.001). Results for event-free survival and pathological complete response across most subgroups favored nivolumab plus chemotherapy over chemotherapy alone. At the first prespecified interim analysis, the hazard ratio for death was 0.57 (99.67% CI, 0.30 to 1.07) and did not meet the criterion for significance. Of the patients who underwent randomization, 83.2% of those in the nivolumab-plus-chemotherapy group and 75.4% of those in the chemotherapy-alone group underwent surgery. Grade 3 or 4 treatment-related adverse events occurred in 33.5% of the patients in the nivolumab-plus-chemotherapy group and in 36.9% of those in the chemotherapy-alone group.

Conclusions: In patients with resectable NSCLC, neoadjuvant nivolumab plus chemotherapy resulted in significantly longer event-free survival and a higher percentage of patients with a pathological complete response than chemotherapy alone. The addition of nivolumab to neoadjuvant chemotherapy did not increase the incidence of adverse events or impede the feasibility of surgery. (Funded by Bristol Myers Squibb; CheckMate 816 ClinicalTrials.gov number)



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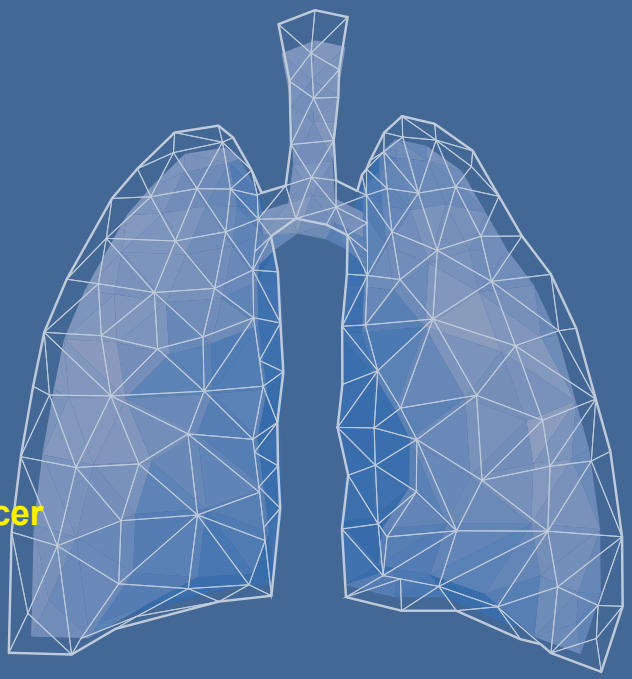

| November 11 (Fri), 2022 | Room A

07:50-08:40

Plenary Session II

Chair: Young Tae Kim *(Seoul National Univ.)*

How to Interpret the Results of Japan Clinical Oncology Group 0802 Study, a Comparison between Lobectomy and Segmentectomy for the Peripheral Non-Small Cell Lung Cancer

Hisao Asamura

Keio Univ., Japan

Since the landmark randomized trial of North American Lung Cancer Study Group, the gold standard of pulmonary parenchymal resection for lung cancer (T1N0M0) has been set as the lobectomy, and widely accepted in the thoracic surgical community. However, in these days, we encounter smaller and earlier tumors more often, and already 30 more years have passed since this landmark study. Therefore, among thoracic surgeons, there has been a surge of requests for revision of the trial comparing lobectomy to lesser sublobar resection.

Because of these, randomized studies such as CALGB 140503 and JCOG 0802 were conducted across the Pacific Ocean. If the results indicate the superiority of lesser resection, lobectomy might be replaced by segmentectomy or wedge resection. Their results are being released very recently, and **they might have the possibility to alter the standard mode of surgical resection.**

The JCOG 0802 trial is planned as the non-inferiority design with two important endpoints, **OS (overall survival) and postoperative respiratory function**. If the OS after segmentectomy is not inferior to that after lobectomy and the postoperative function of segmentectomy is significantly better than that of lobectomy, segmentectomy could be respected as the standard mode of resection for the peripheral, small-sized lung cancer. This is the fundamental scenario of the study as the **non-inferiority design**. The results of JCOG 0802 indicated the following: with regard to OS, the segmentectomy showed significantly better OS than lobectomy, which indicated that **the study has shown not only the "non inferiority" but also the "significant superiority" of segmentectomy over lobectomy.** However, with regard to postoperative respiratory function, the segmentectomy could not show the advantage over lobectomy; **the difference of FEV1.0 at 12 months was only 3%**, postoperative air leakage and postoperative recurrence were more common for segmentectomy, and segmentectomy needed longer operative time than lobectomy.

How to interpret these results is a difficult issue.

First, as the scientific experiment with non-inferiority setting, it has been concluded that the segmentectomy should be respected as the standard mode of resection for lung cancer, based on the premises in case that the superiority is shown. However, it is at the same time quite difficulty to simply recommend segmentectomy which was obviously below the expectations about postoperative respiratory function. We should remember that the **segmentectomy could not be qualified as the function preserving surgery.**

We know that our daily practice is reasonably being modified based upon the new "evidence" which were given by the scientifically fair clinical trials. For this purpose, it is necessary for us to hold the prudent attitude in changing our daily practice, and wait for the data maturation until the consistent conclusion is given by the different trials.

References

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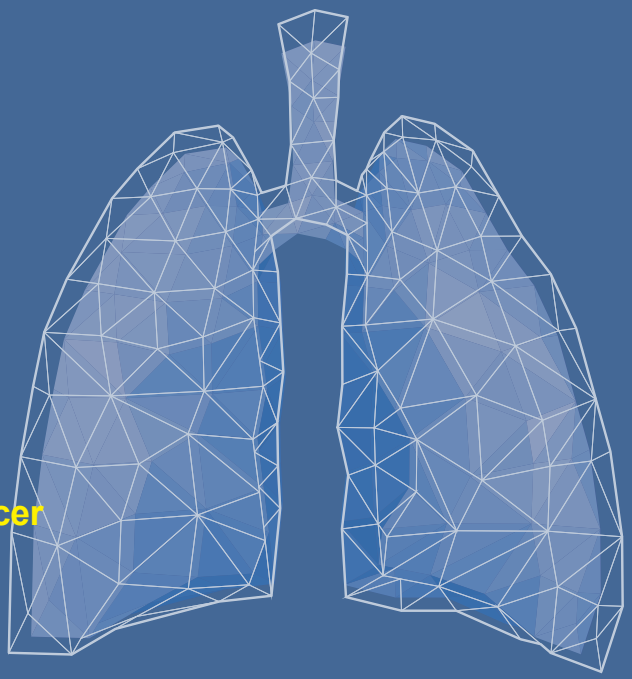


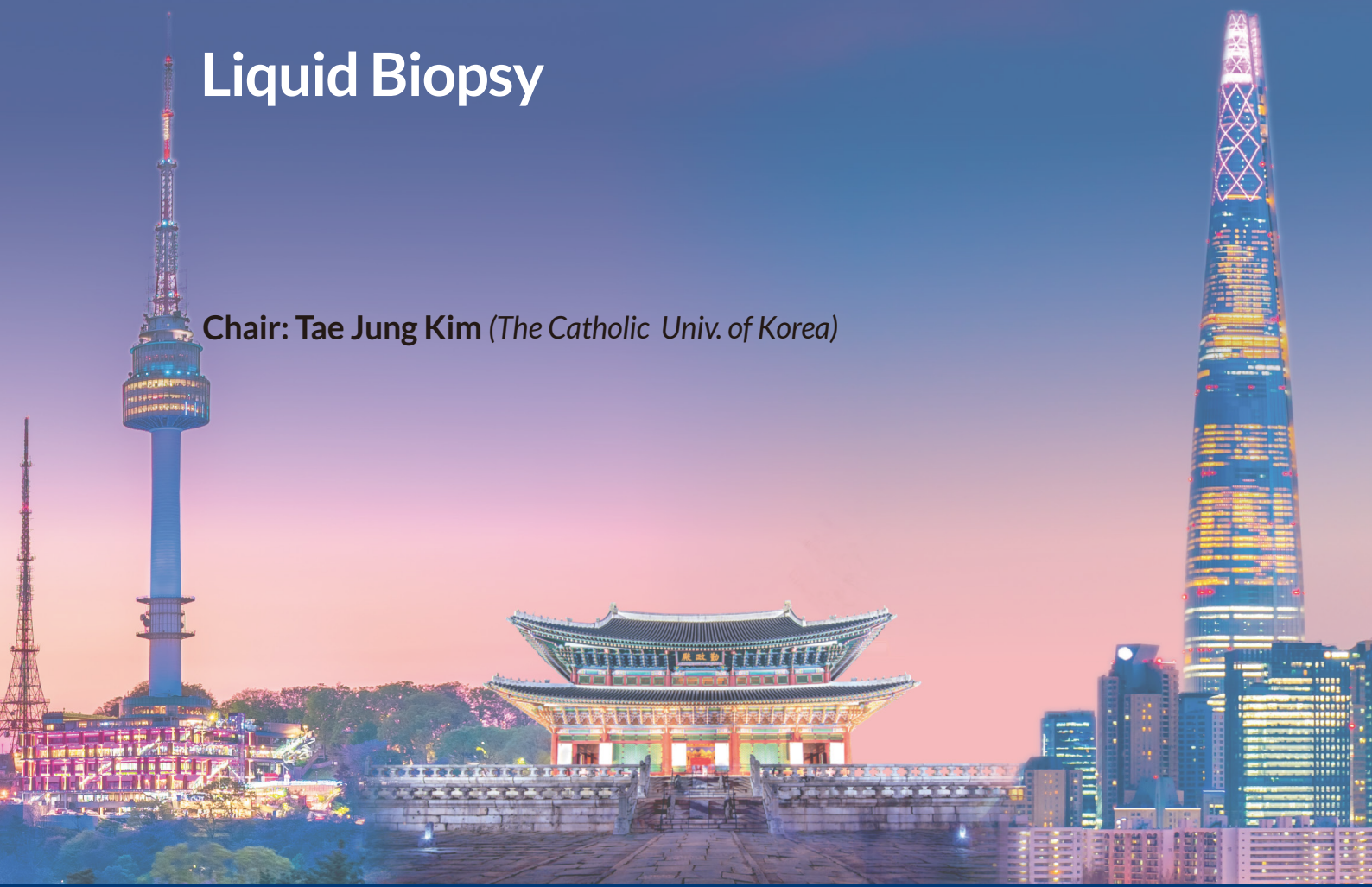
| November 11 (Fri), 2022 | Room A

08:50-10:10

Session V (A)

Liquid Biopsy

Chair: Tae Jung Kim *(The Catholic Univ. of Korea)*



Ultrasensitive Detection of Minimal Residual Disease of Non-Small Cell Lung Cancer through Whole Genome Sequencing Using AI Based Error Suppression Model

Aaron C. Tan[1], Stephanie P.L. Saw[1], Gillianne G.Y. Lai[1], Kevin L.M. Chua[1], Angela Takano[2], Boon Hean Ong[3], Tina P.T. Koh[1], Amit Jain[1], Wan Ling Tan[1], Quan Sing Ng[1], Ravindran Kanesvaran[1], Tanujaa Rajasekaran[1], Sunil Deochand[4], Dillon Maloney[4], Danielle Afterman[5], Tomer Lauterman[5], Noah Friedman[4], Imane Bourzgui[4], Nidhi Ramaraj[4], Zohar Donenhirsh[5], Ronel Veksler[5], Jonathan Rosenfeld[4], Ravi Kandasamy[4], Iman Tavassoly[4], Boris Oklander[5], Asaf Zviran[4], Wan-Teck Lim[1], Eng-Huat Tan[1], Anders J. Skanderup[6], Mei-Kim Ang[1], Daniel S.W. Tan[1]

[1]National Cancer Centre Singapore, Singapore; [2]Singapore General Hospital, Singapore; [3]National Heart Centre Singapore, Singapore; [4]C2i Genomics, Inc., New York, NY10014, USA; [5]C2i Genomics, Ltd., Haifa, Israel; [6]Genome Institute of Singapore, Singapore

Background: Early detection of recurrence and monitoring of minimal residual disease (MRD) post-surgery is critical for clinical decision-making to tailor adjuvant therapy.[1] In early-stage non-small cell lung cancer (NSCLC), circulating tumor DNA (ctDNA) detection is especially challenging, requiring highly sensitive and specific assays.[2] Therefore, we used a whole genome sequencing (WGS) approach (C2inform) for ultra-sensitive ctDNA detection in NSCLC patients undergoing curative surgery.[3] The primary objective was to determine whether C2inform status (positive/negative) at the landmark timepoint (collected at first follow-up within 6 months after surgery) was associated with relapse.

Methods: We conducted a pilot study to evaluate the C2inform approach in serial plasma samples (including pre-surgery, post-surgery and follow-up timepoints) from resected stage IB-IIIA NSCLC patients. Patients underwent routine surveillance by computed tomography (CT) scans. ctDNA was extracted from ~1mL plasma. C2inform uses WGS by a tumor-informed approach (sequencing coverage 40x for tumor, 20x for plasma DNA) combined with AI-based error suppression models (trained and calibrated with a non-cancer cohort, n=17) to increase the signal to noise ratio for precise ctDNA detection, and improve the accuracy of readouts especially for low tumor burden scenarios. The assay reports the detection and quantification of ctDNA burden in

blood with a prognostic value for risk of recurrence. The ability of the assay to predict recurrence from a single sample, taken at the clinical landmark point (median 1.6 months post-surgery, range 0.1-6.5 months) was evaluated.

Results: Overall, 52 NSCLC patients were enrolled (n=88 plasma samples) with median clinical follow-up of 32.6 months (range 3.1-98.6). There were 43 patients with post-surgery landmark samples, with median age 62 years, 70% were male, 79% were adenocarcinoma and 49% were *EGFR* mutated. 26% were stage IB and 37% each were stage II and III. There were 15/18 (sensitivity 83%) patients with confirmed radiological recurrence in which C2inform was positive, including 6/7 (86%) *EGFR* mutated patients. The median relapse-free survival (RFS) in C2inform positive patients was 15.2 months (range 3.7-33.4). Among 25 patients with no recurrence (median follow-up 25.6 months), C2inform reported 4 patients to be MRD positive (specificity 84%). These results were consistent between *EGFR* mutated (sensitivity 86%, specificity 86%) and wildtype patients (sensitivity 82%, specificity 82%). For longitudinal samples (n=17 patients), negative ctDNA was associated with absence of recurrence in 14/15 patients (specificity 93%).

Conclusion: Using a robust WGS implemented AI-based computational platform (C2inform), we demonstrate high sensitivity and specificity detection of MRD in both *EGFR* mutated and wildtype NSCLC. With an increasing number of therapeutic options in the adjuvant setting for NSCLC,[4,5] an ultra-sensitive MRD assay has the potential to facilitate personalized clinical decision-making for tailoring both the need and choice of adjuvant therapies.

Keywords: Lung cancer: non-small cell lung cancer; liquid biopsies; circulating tumor DNA

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2. Pellini and Chaudhuri. 2022; J Clin Oncol 40(6):567-75.
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Novel Plasma Based Detection of Early Stage Lung Cancer

Eun-Hae Cho

GC Genome, Korea

Liquid biopsy is an emerging technology with a potential role in lung cancer screening and early detection. A number of liquid biopsy derived biomarkers have been found and are currently the subject of ongoing research.

According to the National Lung Screening Trial (NLST), chest low dose computed tomography (LDCT) screening among high risk individuals reduced the lung cancer specific death rate by 20% compared to chest X-ray. However, the proportion of false positives, overdiagnosis, and unnecessary invasive procedures continue to be serious issues.

Researchers at Johns Hopkins Kimmel Cancer Center in the US have developed DELFI (DNA evaluation of fragments for early interception), an artificial intelligence (AI)-based blood testing technology that can detect lung cancers(1). The DELFI technology uses machine learning to analyse millions of cell-free DNA fragments in blood samples for abnormal patterns in various genomic regions, including DNA size and amount. Combining fragmentation features, clinical risk factors, and CEA levels, followed by CT imaging, detected 94% of patients with cancer across stages and subtypes, including 91% of stage I/II and 96% of stage III/IV, at 80% specificity. The potential improvement of the PPV in the combined LDCT/DELFI approach suggests that many fewer unnecessary procedures would be performed in individuals with positive results.

More than 900 healthy individuals and 200 lung cancer patients underwent cfDNA WGS at GC Genome, and an artificial intelligence model was created using these data. We used cfDNA fragment size, end motif, mutation density and copy number aberration as important features. Our algorithms are remarkably accurate in predicting the presence of cancer.

And abnormal distribution of DNA methylation is one of the hallmarks of many cancers and methylation changes occur early during carcinogenesis. Systemic analysis of cfDNA methylation profiles is being developed for cancer early detection. Burning Rock company showed that deep methylation sequencing aided by a machine-learning classifier of methylation patterns enables

the detection of tumour-derived signals at dilution factors as low as 1 in 10,000(2). For a total of 308 patients with surgery-resectable lung cancer and 261 age- and sex-matched non-cancer control individuals, the assay detected 52–81% of the patients at disease stages IA to III with a specificity of 96% (95% confidence interval (CI) 93–98%). In a subgroup of 115 individuals, the assay identified, at 100% specificity (95% CI 91–100%), nearly twice as many patients with cancer as those identified by ultradeep mutation sequencing analysis. The low amounts of ctDNA permitted by machine-learning-aided deep methylation sequencing could provide advantages in cancer screening and the assessment of treatment efficacy. The Guardant company showed the next-generation Guardant SHIELD multi-cancer screening assay achieved sensitivity (detection rates) of 87% (n=55) in stages I and II lung cancer. A high-performance blood test that can be completed as part of a routine patient workup has the potential to improve screening rates.

GC Genome analyzed TCGA methylation array and cfMeDIP seq and whole genome enzyme conversion methylation seq and then, we selected about 350 methylation markers for lung cancer early detection. We are validating our NGS panel using these markers in the retrospective and prospective cohort.

References

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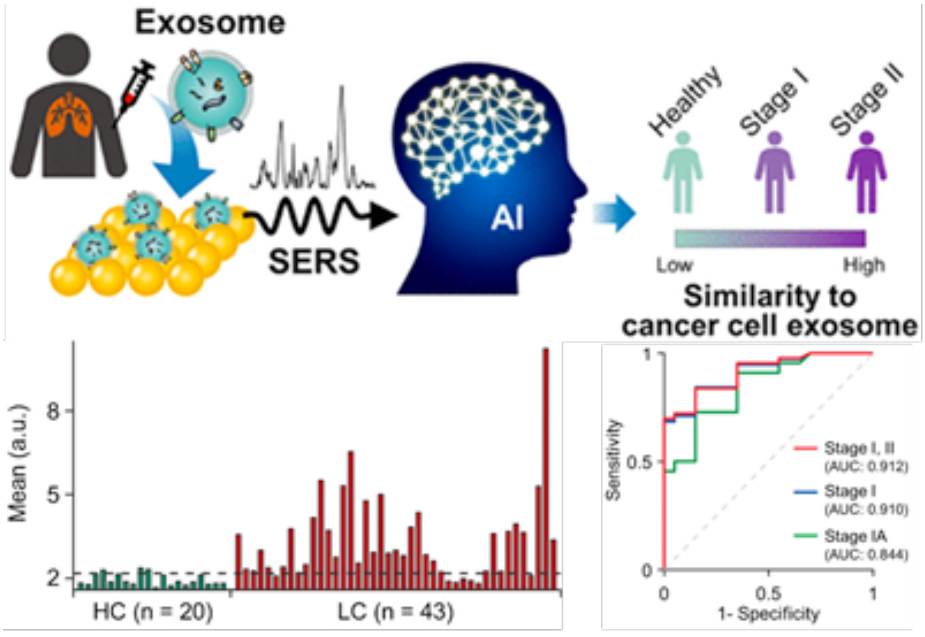
Early Stage Lung Cancer Diagnosis by AI-Based Spectroscopic Analysis of Circulating Exosomes

Yeonho Choi

Korea Univ., Korea

Early Stage Lung Cancer Diagnosis by AI-based Spectroscopic Analysis of Circulating Exosomes

Exosomes are nano-sized extracellular vesicles found in the blood that contain information about cells. Therefore, if exosomes are analysed, we could diagnose disease earlier or monitor the treatment steps, which is expected to increase the survival rate of patients. For this purpose, we showed that an accurate diagnosis of lung cancer is possible using deep learning-based surface-enhanced Raman spectroscopy (SERS) of exosomes. We built a deep learning algorithm learning system based on SERS signals from exosomes derived from normal and lung cancer cell lines. Based on the learned algorithm, we succeeded in diagnosing lung cancer by analysing the similarity between the healthy control and patient plasma exosome SERS signals with the cell



line-derived SERS signals. Briefly, plasma exosomes from 90.7% of patients showed a higher similarity to lung cancer cell exosomes than the mean of healthy controls. Moreover, these similarities were proportional to cancer progression. These results suggest that the combination of exosome analysis and deep learning has great potential as an early-stage liquid biopsy method for lung cancer.

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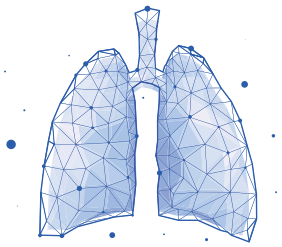
Acknowledgement (if required)

This presentation was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Republic of Korea (Grant No. HI14C3477).



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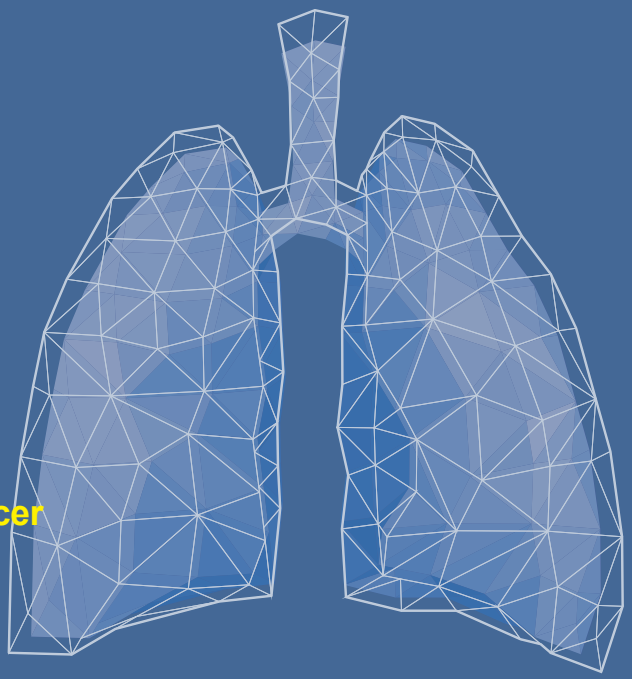


| November 11 (Fri), 2022 | Room A

10:30-11:50

Session VI (A)

Oral Presentation II

Chair: Seung Joon Kim *(The Catholic Univ .of Korea)*

Long-term Surgical Outcomes of Oligometastatic Non-Small Cell Lung Cancer: A Single-Center Study

Seungmo Yoo, Geun Dong Lee, Sehoon Choi, Hyeong Ryul Kim, Yong-Hee Kim, Dong Kwan Kim, Seung-Il Park, and Jae Kwang Yun

Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

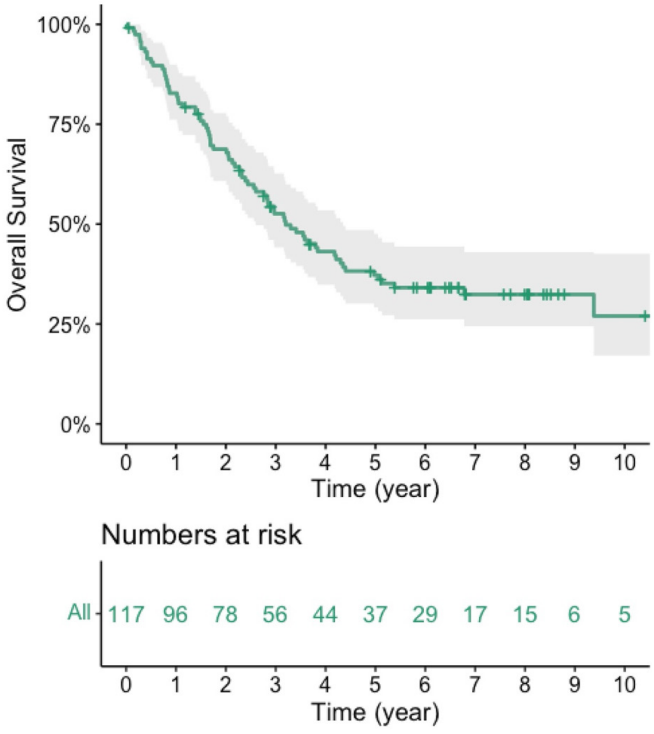
Aims: The role of surgery in the multimodal therapy for selected stage IV oligometastatic (OM) non–small cell lung cancer (NSCLC) is still openly debated. This study aims to evaluate the clinical outcomes of patients with OM NSCLC receiving multimodality therapy including lung surgery.

Methods: A retrospective analysis was performed of 117 patients with OM NSCLC who underwent complete resection of the primary tumor from 2014 to 2017.

Results: The median follow-up duration was 2.91 years (95% CI: 1.48–5.84) and the patients included 73 males (62.4%), and there were 76 patients (64.9%) under the age of 65 years. Histologically, 97 adenocarcinomas and 14 squamous cell carcinomas were included. The biomarker analysis revealed that 53 patients tested positive for epidermal growth factor receptor, anaplastic lymphoma kinase, or ROS1, while 36 tested negative. Metastases were detected in: the brain in 74 patients, adrenal gland in 12, bone in 5, vertebra in 4, and others in 12. Radiation therapy for organ metastasis was performed in 81 patients, and surgical resection in 27. The 1-year overall survival (OS) in these patients was 82.8%, and the 3- and 5-year OS was 82.8% and 37.2%, respectively. Among the patients with positive biomarker testing, 1-, 3-, and 5-year OS was 98%, 64%, and 42.7%, respectively. These patients had better OS than those with negative biomarker testing (p=0.031). Patients aged under 65 years and pT1–2 were also associated with better survival (both p=0.008).

Conclusions: Surgical resection of primary lung cancer could be a viable treatment option for selected patients with OM NSCLC in the context of multimodal therapy.

Keywords: Carcinoma, Non-small cell, lung, Oligometastatic lung cancer, Surgical resection, Survival analysis


Overall Survival
100%
75%
50%
25%
0%
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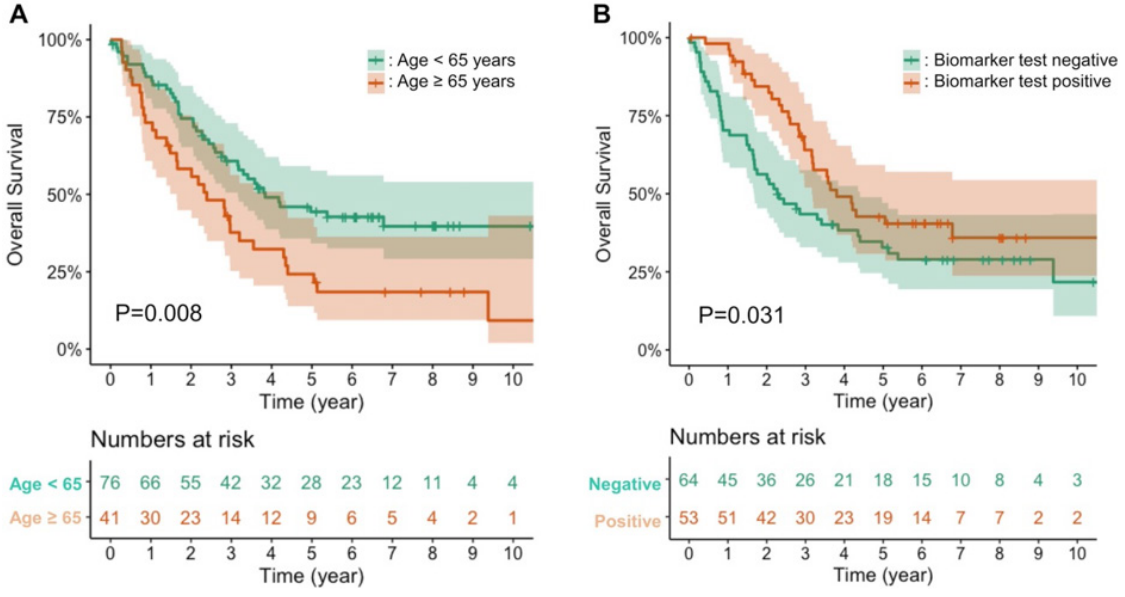
Time (year)
Numbers at risk
All 117 96 78 56 44 37 29 17 15 6 5
0 1 2 3 4 5 6 7 8 9 10
Time (year)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Overall Survival
100%
75%
50%
25%
0%
: Age < 65 years
: Age ≥ 65 years
P=0.008
0 1 2 3 4 5 6 7 8 9 10
Time (year)
Numbers at risk
Age < 65 76 66 55 42 32 28 23 12 11 4 4
Age ≥ 65 41 30 23 14 12 9 6 5 4 2 1
0 1 2 3 4 5 6 7 8 9 10
Time (year)
B
Overall Survival
100%
75%
50%
25%
0%
: Biomarker test negative
: Biomarker test positive
P=0.031
0 1 2 3 4 5 6 7 8 9 10
Time (year)
Numbers at risk
Negative 64 45 36 26 21 18 15 10 8 4 3
Positive 53 51 42 30 23 19 14 7 7 2 2
0 1 2 3 4 5 6 7 8 9 10
Time (year)

Existence of Pre-operative Clonal Hematopoiesis Is Related to Adverse Outcome in Surgically Resected Non-Small Cell Lung Cancer Patients Who Underwent Adjuvant Therapy

Jae Kwang Yun[1], Sugyeong Kim[2], Geun Dong Lee[1], Hyeong Ryul Kim[1], Yong-Hee Kim[1], Dong Kwan Kim[1], Seung-Il Park[1], Sehoon Choi[1], Youngil Koh[2,3]

[1]Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, Ulsan University College of Medicine, Seoul, Republic of Korea; [2]Genome Opinion Inc., Seoul, Korea; [3]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea

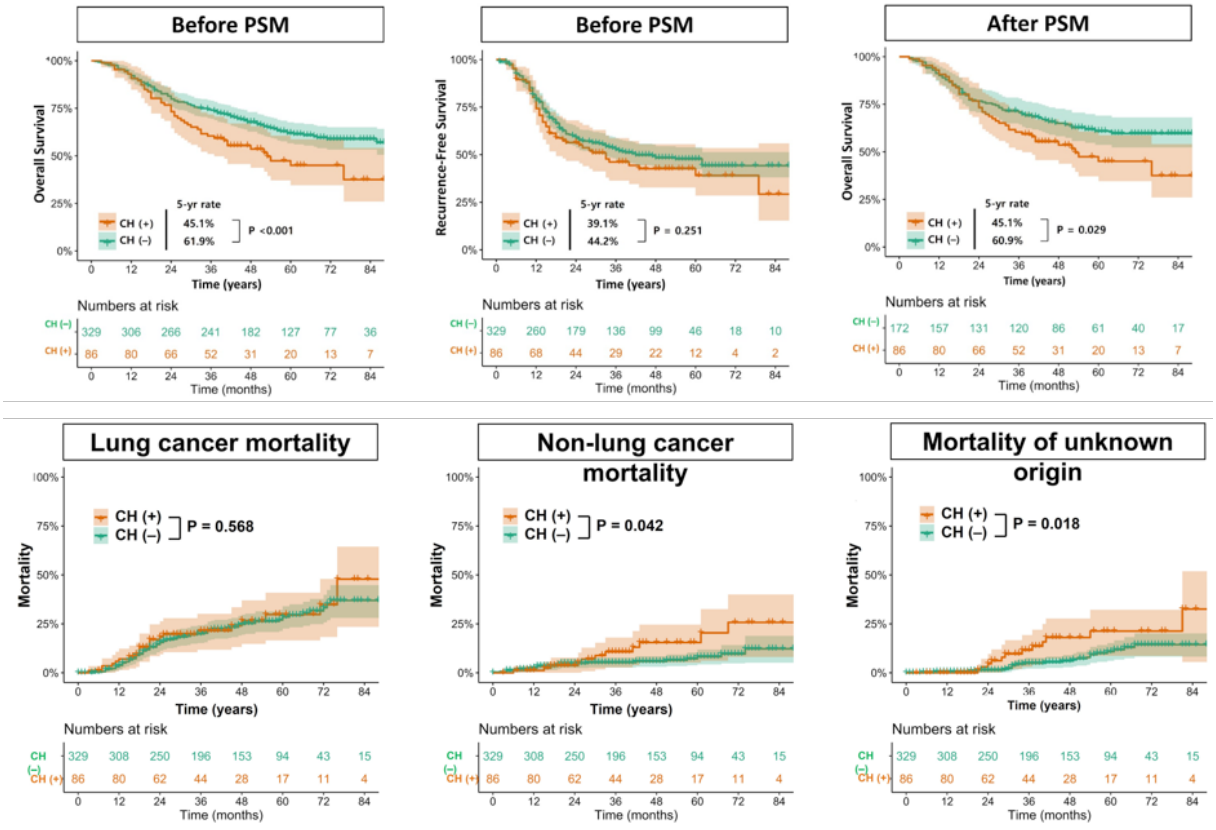
Aims: Clonal hematopoiesis (CH), an expansion of clonally derived hematopoietic stem cells with somatic mutations in leukemogenic genes, often develops after chemotherapy or radiotherapy. We evaluated the clinical impact of preoperative CH on the survival outcomes of patients with non-small cell lung cancer (NSCLC) who underwent surgical resection followed by adjuvant therapy.

Methods: This retrospective cohort study included 415 consecutive patients with NSCLC who underwent surgery followed by adjuvant therapy from 2011 to 2017. CH status was evaluated using targeted deep sequencing of blood samples collected before surgery. To minimize the possible selection bias between the two groups according to CH status, a propensity score matching (PSM) technique was adopted. Data on patient demographics, the presence of CH, and long-term survival outcomes were collected and analyzed.

Results: CH was detected in 21% (86/415) of patients with NSCLC before adjuvant therapy. Patients with CH mutations had worse overall survival (OS) than those without (hazard ratio [95% confidence interval] = 1.61 [1.14–2.27], $p = 0.006$), which remained the same after PSM (1.61 [1.03–2.21], $p = 0.034$). Of note, the presence of CH was associated with non–lung cancer mortality ($p = 0.042$) and mortality of unknown origin ($p = 0.018$). After PSM in patients with stage IIB NSCLC, the presence of CH was significantly associated with worse OS in patients who underwent adjuvant therapy (2.59 [1.26–5.33], $p = 0.011$), but it was not in patients who did not perform adjuvant therapy (1.34 [0.66–2.70], $p = 0.417$).

Conclusions: In resected NSCLC, existence of preoperative CH might amplify CH-related adverse outcomes through adjuvant treatments, resulting in poor survival results.

Keywords: Clonal hematopoesis, Non-small cell lung cancer, Adjuvant therapy, Propensity score matching



Longitudinal Monitoring of Circulating Tumor DNA from Plasma in Patients with Curative Resected Stage IA-IIIA EGFR Mutant-Non-Small Cell Lung Cancer

Hyun-Ae Jung[1], Bo Mi Ku[2], Yeon Jeong Kim[3], Sehhoon Park[1], Jong-Mu Sun[1], Se-Hoon Lee[1], Jin Seok Ahn[1], Jong Ho Cho[4], Hong Kwan Kim[4], Yong Soo Choi[4], Jin Kook Kim[4], Myung-Ju Ahn[1]

[1]Division of Hematology and Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine; [2]Research Institute for Future Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Samsung Genomic Institute, Samsung Medical Center; [4]Department of Thoracic Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine

Aims: For patients with early-stage epidermal growth factor receptor mutation-positive (*EGFR*-M+) non-small cell lung cancer (NSCLC), curative surgery followed by adjuvant chemotherapy is considered the standard of care. Recently, based on the ADAURA study, osimertinib was approved for a duration of 3 years in resected stage IB-IIIA *EGFR*-M+ NSCLC. The circulating tumor DNA (ctDNA) provides a potentially valuable biomarker for early diagnosis, prognostic stratification, detection of minimal residual disease (MRD) and recurrence. In this study, we investigated the longitudinal monitoring of ctDNA test in early-stage *EGFR*-M+ NSCLC.

Methods: Between August 2015 and October 2017, 278 patients with curative resected, stage IA-IIIA (AJCC 7th edition) *EGFR*-M+ NSCLC were enrolled at Samsung Medical Center. Radiological follow-up including chest CT or PET-CT was accompanied by serial longitudinal monitoring of ctDNA using a droplet digital PCR(BioRad) from baseline (pre-operative), post-operative follow-up (4 weeks after curative surgery), and follow-up per protocol until 5 years or radiographic recurrence.

Results: Median follow-up duration was 62.0 months (range, 1.5-77.4). Among 278 patients, stage IA, IB, IIA, IIB, and IIIA comprised 167 (60.1%), 51 (18.3%), 28 (10.1%), 6 (2.2%), and 26 (9.4%), respectively. The *EGFR* exon 19 del was 60.1% and L858R was 39.9%. The 3-year DFS rate for IA, IB, IIA, IIB, and IIIA was 95%, 78%, 58%, 50%, and 32%, respectively. A total of 627 plasma samples in the *EGFR* exon 19 del and 383 plasma samples in L858R mutation were analyzed. The median plasma volume collected at each follow-up was 4 ml (range 1 – 9 ml), while the median yield of cfDNA per ml is 9.2 ng. Among 278 patients, baseline ctDNA was detected in 67 (24.1%) patients: 23.4% (stage IA), 17.6% (IB), 17.9% (IIA), 50.0% (IIB), and 42.3% (IIIA) (p=0.06). There was no

difference in detection rate between exon 19 del and L858R. In 76.1% (51 of 67) of patients with baseline ctDNA, it was cleared up 4 weeks after surgery. Patients were classified into three groups according to the presence of positivity of ctDNA at baseline and postoperative follow-up (Group A: baseline ctDNA negative group (n=211), Group B: baseline ctDNA positive, but MRD negative group (n=51), Group C: baseline ctDNA positive, but MRD positive (n=16)). The 3-year DFS rate was significantly different among the three groups (83.3% for Group A, 78% for Group B, and 50% for Group C, respectively, p=0.02). After adjusting for clinicopathologic variables, ctDNA group (HR 1.27, 95% CI 1.03-1.57, p=0.03) still remains an independent risk factor regardless stage for DFS.

Conclusions: These results suggest that patients with baseline ctDNA positive or MRD positive were associated with poor DFS in curative resected stage IA-IIIA *EGFR* M+ NSCLC.

Keywords: Early-stage, Epidermal growth factor receptor, Non-small cell lung cancer, Circulating tumor DNA

Risk Prediction of Multiple–Station N2 Metastasis in Patients with Clinical Single–Station N2 NSCLC

Joon Young Kim, Jae Kwang Yun, Geun Dong Lee, Sehoon Choi, Hyeong Ryul Kim, Yong-Hee Kim, Dong Kwan Kim, and Seung-Il Park

Asan Medical Center

Aims: Although the standard treatment for patients with N2 non-small cell lung cancer (NSCLC) is definitive chemoradiation, several studies have demonstrated that minimal N2 disease, such as single–station N2 disease (N2 disease limited to a single mediastinal station), is a favorable prognostic indicator of resected N2 NSCLC. The objective of this study is to investigate long-term survival outcomes and develop a risk model for multiple–station N2 metastasis in patients with clinical single–station N2 NSCLC.

Methods: From 2006 to 2008, 547 patients who underwent upfront surgery for clinical single–station N2 NSCLC were analyzed. Based on the findings of the multivariable analysis using preoperative clinical variables, a risk model for predicting multiple–station N2 metastasis was developed.

Results: Among patients with clinical single–station N2 NSCLC (n=547), preoperative N2 node biopsy was performed in 125 (22.9%) patients. There were 118 (21.6%), 58 (10.6%), and 371 (67.8%) patients with pathologically N0 (pN0), pN1, and pN2 disease. When patients with pN2 NSCLC (n=371) were divided based on subdivided pN descriptors, there were 77 (20.8%), 165 (44.5%), and 129 (34.7%) patients with pN2a1 (single–station N2 without N1 involvement), pN2a2 (single–station N2 with N1 involvement), and pN2b (multiple–station N2). The 5-year overall survival rate of patients with pN2a1 (51.2%) and pN2a2 (45.8%) were significantly higher than those with pN2b (29.0%) (all p=0.041). According to the risk model, histologic type (p<0.001), age ≤ 50 years (p<0.001), preoperatively confirmed N2 metastasis (p<0.001), and clinical stage IIIB (vs. IIIA) (p = 0.003) were independent risk factors for multiple–station N2 metastasis in patients with clinical single–station N2 NSCLC. The risk scoring system based on this model showed a good discriminant ability for pN2b disease (area under the receiver operating characteristic curve: 0.779)

Conclusions: In patients with clinical single–station N2 NSCLC, those with pN2b had significantly worse prognosis than those with pN2a1 and pN2a2. Our risk scoring system for predicting pN2b has good discriminant ability in patients with clinical single–station N2 NSCLC.

Keywords: NSCLC, N2, Risk prediction

Different Prognostic Impact between Single-Zone and Multiple-Zone N2 Node Metastasis in Patients with N2b NSCLC

Shi A Kim, Geun Dong Lee, Se Hoon Choi, Hyeong Ryul Kim, Yong-Hee Kim, Dong Kwan Kim, ; Jae Kwang Yun

Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

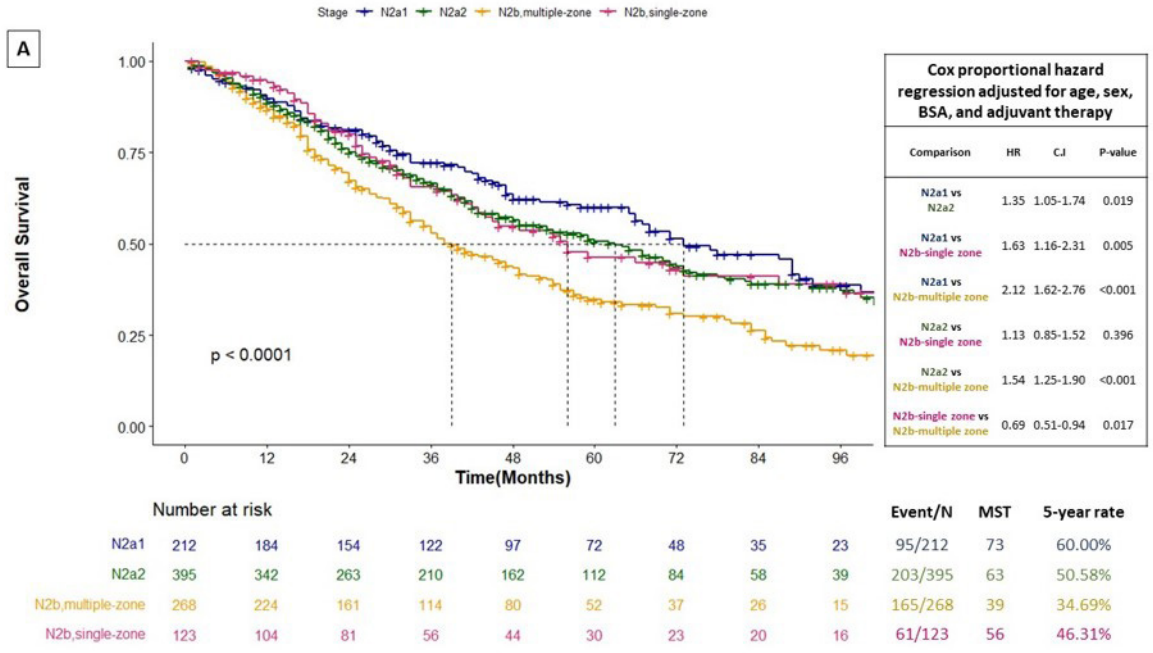
Aims: The non-small cell lung cancer(NSCLC) patients are staging determined by the pathological N description according to TNM classification. The International Association for the Study of Lung Cancer (IASLC) suggested further subdivisions of pathological N stage with including the location and the number of involved lymph node (LN) stations. Using the involved LN zones, we reclassified patients with station-based N2b into single-zone and multiple-zone N2 disease, and proved to be an applicable model.

Methods: A total of 997 patients (608 men, median age: 62 years, IQR 55-69) with pathologically confirmed N2 NSCLC were included between 2006 to 2019. N2 classification was grouped into 4 categories: single-station N2 without N1 (N2a1), single-station N2 with N1 (N2a2), multiple-station N2 with single-zone N2 involvement (N2b-single-zone) and multiple-station N2 with multiple zone N2 involvement (N2b-multiple-zone). LN zones were defined as upper mediastinal, lower mediastinal, aortopulmonary and subcarinal for N2 nodes by grouping the LN stations.

Results: The number of patients with N2a1, N2a2, and N2b who underwent lung cancer surgery was 212, 394 and 391, respectively. Patients with station-based N2b whose N2 nodes were included in a single-zone and multiple-zone were 125 and 266, respectively. Patients with single-zone N2b NSCLC showed significantly better prognosis than those with multiple-zone N2b NSCLC (5-year overall survival: 45.4% vs 30.5%, $p<0.002$), which were similar to those with N2a2 (45.4% vs 45.9%, $p=0.95$)

Conclusions: We proposed the both N descriptors (zone-based and station based) are prognostically appropriate for patients. As a result, to determine the ideal N descriptors, the abilities of zone-based LN classification among N2b could be consider with station-based LN classification.

Keywords: Lung cancer staging, Non-small cell lung cancer, N descriptors, Lymph node metastasis


Stage N2a1 N2a2 N2b,multiple-zone N2b,single-zone
A
Overall Survival
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
12
24
36
48
60
72
84
96
Time(Months)
Number at risk
N2a1 212 184 154 122 97 72 48 35 23
N2a2 395 342 263 210 162 112 84 58 39
N2b,multiple-zone 268 224 161 114 80 52 37 26 15
N2b,single-zone 123 104 81 56 44 30 23 20 16
Cox proportional hazard regression adjusted for age, sex, BSA, and adjuvant therapy
Comparison HR CJ P-value
N2a1 vs N2a2 1.35 1.05-1.74 0.019
N2a1 vs N2b-single zone 1.63 1.16-2.31 0.005
N2a1 vs N2b-multiple zone 2.12 1.62-2.76 <0.001
N2a2 vs N2b-single zone 1.13 0.85-1.52 0.396
N2a2 vs N2b-multiple zone 1.54 1.25-1.90 <0.001
N2b-single zone vs N2b-multiple zone 0.69 0.51-0.94 0.017
Event/N MST 5-year rate
95/212 73 60.00%
203/395 63 50.58%
165/268 39 34.69%
61/123 56 46.31%

Lobectomy versus Sublobar Resection for Stage I (T1-T2aN0M0) Small Cell Lung Cancer: A SEER Population-Based Propensity Score Matching Analysis

Ning Zhou[1,2*], Shuai Zhu[1,2*], Huandong Huo[1,2*], Bo Zhang[1,2], Jinling He[1,2], Lingqi Yang[1,2], Lingling Zu[1,2], Zuoqing Song[1,2#], Song Xu[1,2#]

[1]Department of Lung Cancer Surgery, [2]Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Lung Cancer Institute, Tianjin Medical University General Hospital, Tianjin 300052, China

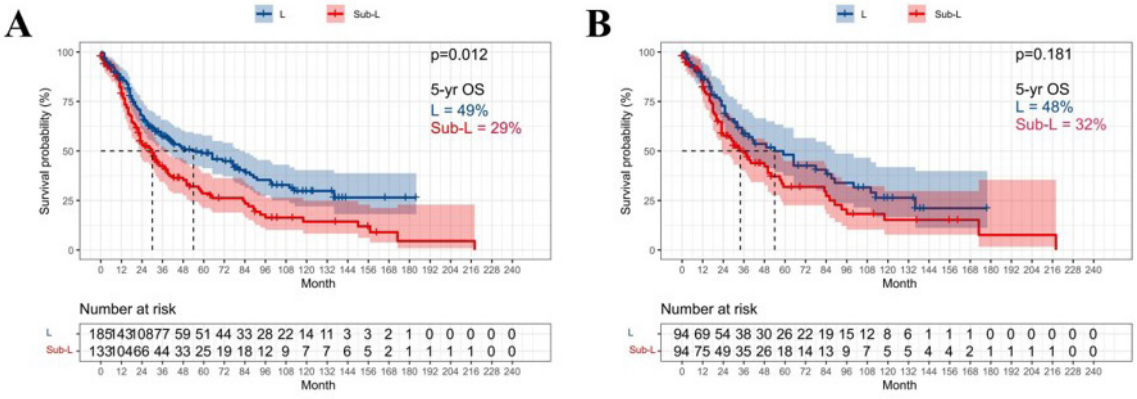
Aims: This study evaluated whether sublobar resection (sub-L) is non-inferior to lobectomy (L) for stage I (T1-T2aN0M0) small cell lung cancer (SCLC) regarding long-term overall survival (OS).

Methods: Clinicopathological and prognostic data of patients with stage I (pT1-T2aN0M0) SCLC were retrieved. Kaplan-Meier curves and Breslow tests were performed for the assessment of OS. Propensity score matching (PSM) analysis was used to mediate the inherent bias of retrospective researches.

Results: 188 patients with stage I SCLC were included in this study after PSM. For resected stage I SCLC, surgery plus adjuvant therapy was related to a better OS compared with surgery only (p=0.016). For resected stage I SCLC, no matter adjuvant therapy was performed or not, no significant difference was observed in long-term OS between the L and sub-L groups (p=0.181). Further subgroup analysis demonstrated that the OS disadvantage of sub-L over L was not statistically significant for stage I SCLC patients underwent surgery only (p=0.653), and for the patients underwent surgery plus adjuvant therapy (p=0.069). Moreover, in the subgroup analyses according to TNM stage (IA and IB), sex (male and female), and age (≥70Y and <70Y), OS did not differ between the L and sub-L groups except in female patients (p=0.008). Multivariate Cox regression analysis indicated that adjuvant therapy was positively associated with OS.

Conclusions: Surgery plus adjuvant therapy confers a better survival benefit than surgery only for stage I SCLC patients. However, as far as the range of surgical resection is concerned, sublobar resection may be non-inferior to lobectomy regarding OS. Our study could conduce to the development of optimal therapeutic strategies for stage I SCLC patients. Further validation is warranted in larger retrospective and prospective cohort studies.

Keywords: SCLC, Stage I, Surgery


A
L
Sub-L
p=0.012
5-yr OS
L = 49%
Sub-L = 29%
Survival probability (%)
Month
Number at risk
L 185 143 108 77 59 51 44 33 28 22 14 11 3 3 2 1 0 0 0 0 0
Sub-L 133 104 66 44 33 25 19 18 12 9 7 7 6 5 2 1 1 1 1 0 0
B
L
Sub-L
p=0.181
5-yr OS
L = 48%
Sub-L = 32%
Survival probability (%)
Month
Number at risk
L 94 69 54 38 30 26 22 19 15 12 8 6 1 1 1 0 0 0 0 0 0
Sub-L 94 75 49 35 26 18 14 13 9 7 5 5 4 4 2 1 1 1 1 0 0

Clinical Outcome of Stereotactic Body Radiotherapy in Early-Stage Lung Cancer Patient with Ground Glass Opacity Predominant Lesion: A Single Institution Experience

Jeong Yun Jang[1], Su Ssan Kim[1], Si Yeol Song[1], Young Seob Shin[1], Sei Won Lee[2], Wonjun Ji[2], Chang-Min Choi[2], and Eun Kyung Choi[1]

[1]Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [2]Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Aims: In recent years, with the increase in routine examination using computed tomography (CT), the frequency of detecting early-stage lung cancer with ground glass opacity (GGO) has increased. For these patients, surgery has been suggested as the standard of care. However, for patients who cannot be treated surgically, stereotactic body radiotherapy (SBRT) has been applied as an alternative. The promising results of SBRT have recently been reported in patients with early-stage lung cancer, but few reports have been published with GGO predominant lesions. Therefore, we performed a retrospective study to investigate the clinical outcome after SBRT in early-stage lung cancer patients with GGO predominant tumor in a single institution.

Methods: A total of 89 patients with 99 lesions who were treated with SBRT between July 2016 to July 2021 in Asan Medical Center were included in the analysis (Fig.1). Among patients with lung lesions suspected of being diagnosed as lung cancer, patients who could be confirmed by pathological examination and patients who were clinically confirmed as lung cancer through serial chest CT images were included. GGO predominant lesion was defined as having a consolidation/tumor ratio ≤0.5. Patients with a history of previous radiotherapy to the ipsilateral side of thorax were excluded. Median total dose of 56.0 Gy (range, 48.0 – 60.0) were delivered by using 10.0 – 15.0 Gy per fraction. The local control (LC), loco-regional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS) were calculated from the date of SBRT using the Kaplan–Meier method. Toxicity was evaluated based on CTCAE version 5.0.

Results: The median age was 72 years (range, 45 – 90), and 49 patients (55.1%) were male. Of the 89 patients, 51 (57.3%) had a previous history of non-small-cell lung cancer, and 49 (96.1%) un-

derwent surgery and the rest underwent radiotherapy. There were 72 patients (80.9%) with single primary lung cancer and 17 patients (19.1%) with multiple primary lung cancer with more than two lung lesions at time. Histological examination was performed on 44 lesions out of 99, and all were confirmed to be adenocarcinoma. Forty-three lesions were pure GGO nodules without consolidation, and 56 were subsolid nodules. Median diameters of tumors and consolidations were 15.7mm (range, 5.7 – 45.0) and 4.5 mm (range, 0.0 – 16.0), respectively. During the median follow-up period of 33 months (range, 9.9 – 65.9), there was no evidence of recurrence in any of the 99 treated lesions, showing 100% LC. Three patients had regional recurrence in the lung parenchyma or hilar lymph nodes outside the radiation field, and distant metastasis occurred in three patients. Except for one patient who was asymptomatic and had slow progression, all received chemotherapy as salvage treatment. The 3-year LRRFS, DMFS, and DFS rates were 96.3%, 93.0%, and 92.6%, respectively. During the follow-up period, a total of eight patients expired from causes unrelated to lung cancer, and the 1-year, 3-year, and 5-year OS rates were 100%, 91.6%, and 82.8%, respectively (Fig.2). Univariate analysis revealed that advanced age and low level of diffusing capacity of lung for CO was significantly associated with OS rates ($p = 0.001, 0.003$), and none of the factors were associated with LLRFS and DFS. There were no patients with acute or late toxicity ≥ grade3.

Conclusions: For patients with GGO predominant lung cancer, application of SBRT has been shown to yield high LC and appears to be a safe treatment with low toxicity data. SBRT is expected to be considered as one of the alternative treatment options for surgery in patients with multiple lesions, surgical history, or medically inoperable patients due to age or comorbidities.

Keywords: Lung cancer, Ground glass opacity, Stereotactic body radiotherapy, Clinical outcome

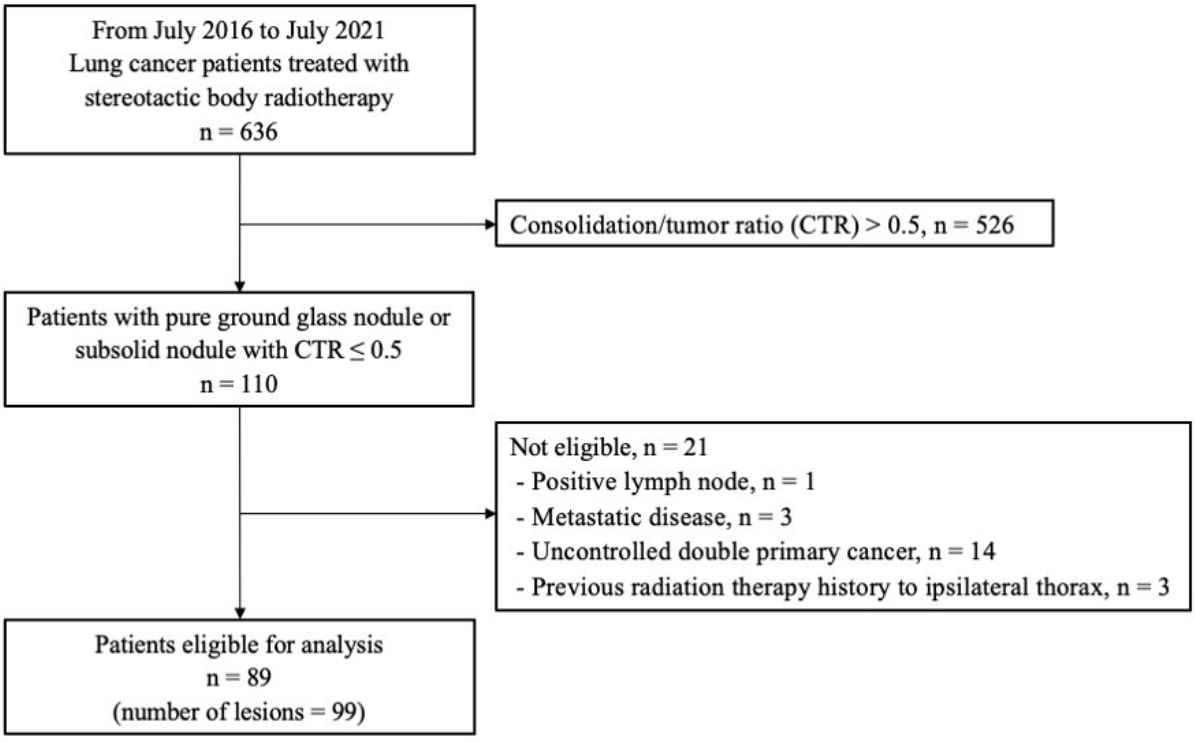


Figure 1. Flow diagram of the enrolled patients.

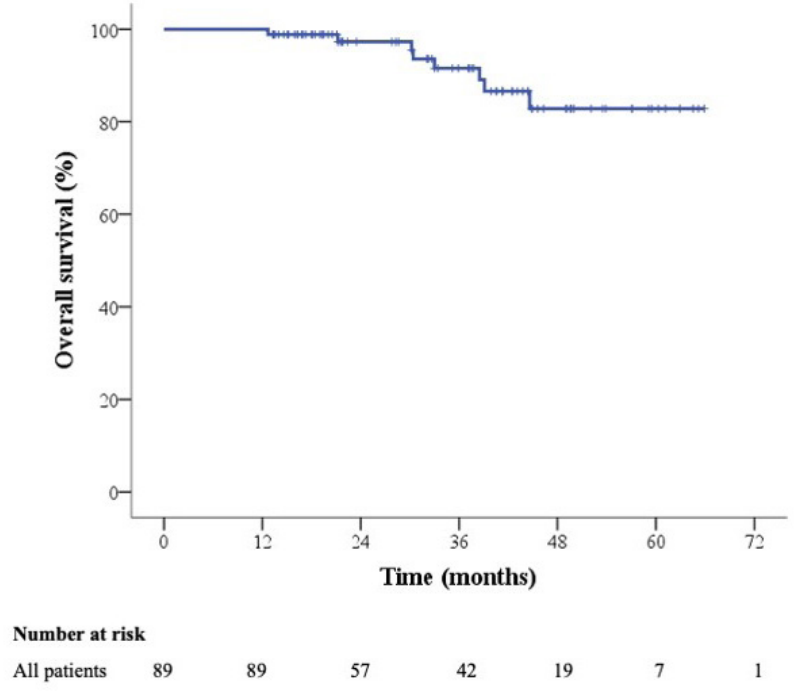


Figure 2. Overall Survival after stereotactic body radiotherapy for ground glass nodule.

Oncologic Outcomes of Stereotactic Body Radiotherapy in Early-Stage Non-Small Cell Lung Cancer Patients with Interstitial Lung Disease

Young Seob Shin, Sumin Lee, Su Ssan Kim, Si Yeol Song, Eun Kyung Choi

Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Aims: To evaluate the efficacy and toxicity of Stereotactic Body Radiotherapy (SBRT) in Early-Stage Non-Small Cell Lung Cancer (ES-NSCLC) Patients with Interstitial Lung Disease (ILD).

Methods: We retrospectively reviewed the medical records of 42 patients with ES-NSCLC and ILD who underwent definitive SBRT between January 2009 and June 2019. The median SBRT dose was 56 Gy in 4 fractions and the median biologically effective dose with α/β of 10 was 134.4 Gy (range, 95.2-150 Gy). The outcomes of survival, toxicities and the relationships between outcomes and clinical factors were investigated.

Results: The median age of all patients was 73.5 (range, 63-88), and the median follow-up period was 17.8 (range, 1.6-85.0) months. The average values for forced expiratory volume in one second (FEV1) and diffusing capacity of the lung for carbon monoxide were 74.7 and 46.6, respectively. After SBRT, six patients developed grade 3 or higher radiation induced pneumonitis, however no clinical factor was significantly associated with high grade pneumonitis. At the end of the follow-up, 34 patients had died. The most frequent cause of death was lung cancer in 17 patients, followed by other lung disease in 10 patients, such as pneumonitis, exacerbation of ILD and pneumonia. The rates of 2-year freedom from local recurrence (FFLP), progression-free survival (PFS) and overall survival (OS) were 68.9%, 24.8% and 45.2%, respectively. In multivariate analysis, the mean lung dose was significant predictor of with PFS while FEV1/forced vital capacity and lung volume receiving ≥5 Gy were significantly associated with OS.

Conclusions: Patients with ES-NSCLC and ILD had a poor prognosis and high incidence of treatment related lung toxicity after SBRT. Nevertheless, considering that lung cancer progression is the most common cause of death in these patients, cancer-directed treatment should be considered despite its toxicities.

Keywords: Lung neoplasms, Radiosurgery, Lung disease, Interstitial, Radiation pneumonitis

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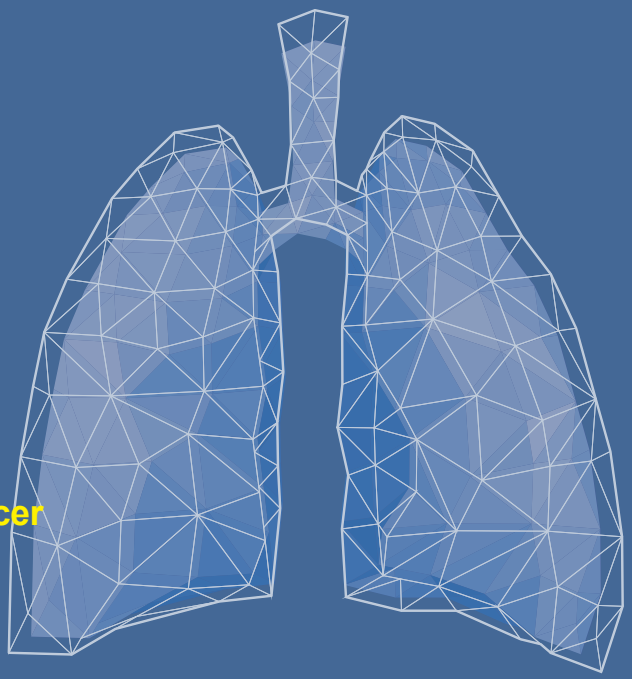


| November 11 (Fri), 2022 | Room A

12:00-12:40

Satellite Symposium III

[ASTRAZENECA]

Chair: Byoung Chul Cho *(Yonsei Univ.)*

Osimertinib and Durvalumab as Frontier Treatment for Non-Small Cell Lung Cancer Patients with Curative Intent

James Yang

National Taiwan Univ., Taiwan

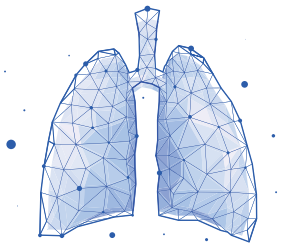
Every year more than 20,000 new cases were diagnosed with lung cancer, of which 85% are NSCLC. Only 30% of these are resectable diseases at the time of diagnosis, meaning early-stage diseases. The rest of them are regional/locally advanced disease or metastatic diseases. The standard of care for local advanced diseases obviously is radiotherapy plus chemotherapy concurrently or sequentially and for those who had metastatic disease, systemic remains the standard of care. Therefore, the treatment outcome for these patients were pretty bad.

Pacific study is the study to address whether we can improve patients with stage3 unresectable disease using immunotherapy or PD-L1 checkpoint inhibitor as adjuvant for one year. Before this Pacific study, the standard of care for patients with unresectable NSCLC stage3 was concurrent CRT. This study is a monumental and positive study that has changed the paradigm of unresectable stage3 disease. The co-primary endpoints of the study were PFS by BICR and OS. Durvalumab was shown longer PFS than placebo. At 12 months or 18 months, there was roughly 20 percent improvement in terms of PFS in Durvalumab arm. And OS HR was 0.68 and there was roughly 11 percent improvement in terms of OS at two years of time. The patients who received Durvalumab showed greater improvement in terms of TTDM, TFST, TSST.

ADAURA study is the study to evaluate the efficacy and safety of Osimertinib as adjuvant therapy. Patients who had stage1B to 3A disease with or without adjuvant chemotherapy who had EGFRm(Ex19del or L858R) of after complete resection with negative margins can be randomized. The primary endpoint was disease-free survival among patients with stage II to IIIA disease (according to investigator assessment). The secondary end points included disease-free survival in the overall population of patients with stage IB to IIIA disease, overall survival, and safety. The primary analysis showed a huge difference at the ratio of 0.17 using Osimertinib versus placebo, but the maturity of the first analysis was very low at only 33 percent. The hazard ratio of disease-free

survival in the overall population including stage1B is still very small at 0.2 and still widely separated. A DFS benefit with Osimertinib was observed across all predefined subgroups. The cumulative incidence of CNS recurrence was consistently lower in the Osimertinib arm than in the placebo arm.

In conclusion, Durvalumab 1 year adjuvant treatment improve overall survival and progression free survival in unresectable stage3 NSCLC after concurrent chemoradiotherapy as definitive treatment. 3 year of Osimertinib adjuvant treatment improve disease free survival after complete resection of stage IB-IIIA NSCLC with EGFR del19 and L858R mutation.



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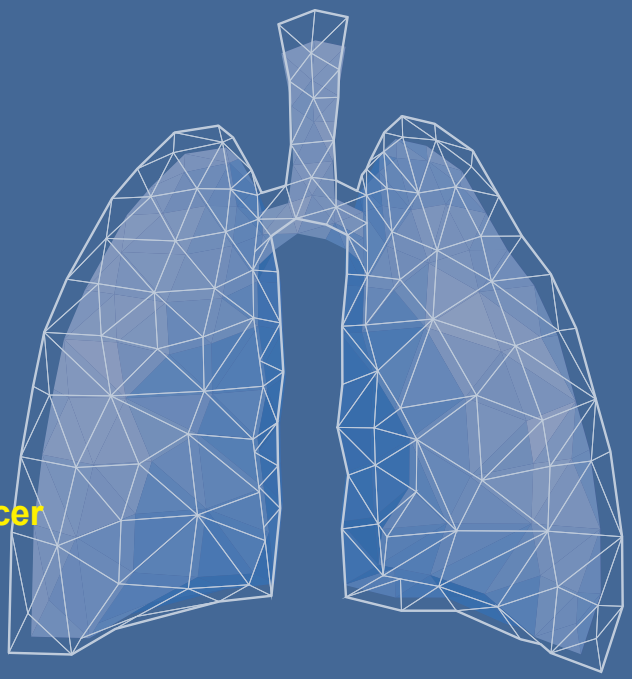

| November 11 (Fri), 2022 | Room A

13:00-14:40

Session VII (A)

Oral Presentation III

Chair: Hee Kyung Ahn *(Gachon Univ.)*

Tepotinib in Patients with MET Exon 14 (METex14) Skipping NSCLC: Analysis of All Patients from VISION Cohorts A and C

Myung-Ju Ahn[1], Hyun Ae Jung[2], Dong-Wan Kim[3,4], Michael Thomas[5], Aurora O'Brate[6], Karin Berghoff[7], Rolf Bruns[8], Gordon Otto[9], Paul K. Paik[10,11]

[1]Department of Medicine, Section of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University, Seoul, Korea; [2]Department of Medicine, Section of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University, Seoul, Korea; [3]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [4]Seoul National University Cancer Research Institute, Seoul, Korea; [5]Thoraxklinik, University Heidelberg and Translational Lung Research Center Heidelberg (TLRC-H), The German Center for Lung Research (DZL), Heidelberg, Germany; [6]Global Medical Affairs, Merck Healthcare KGaA, Darmstadt, Germany; [7]Global Patient Safety, Merck Healthcare KGaA, Darmstadt, Germany; [8]Department of Biostatistics, Merck Healthcare KGaA, Darmstadt, Germany; [9]Global Clinical Development, Merck Healthcare KGaA, Darmstadt, Germany; [10]Thoracic Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [11]Weill Cornell Medical College, New York, NY, USA

Aims: Tepotinib, a MET TKI, is approved for the treatment of *MET*ex14 skipping NSCLC. Here, we report analysis of all patients with *MET*ex14 skipping in the Phase II VISION study (Cohort A: >2-years' follow-up; confirmatory Cohort C: >9-months' follow-up); data cut-off February 20, 2022

Methods: Patients with advanced/metastatic *MET*ex14 skipping NSCLC, received tepotinib 500 mg (450 mg active moiety) once daily. Primary endpoint was objective response by IRC using RECIST v1.1. Pre-planned exploratory analysis of brain lesions was conducted by IRC using RANO-BM criteria.

Results: Patients in Cohorts A+C (N=313) had a median age of 72.0 years (range: 41–94), 49.2% were male, 62.3% were white, 33.9% were Asian, 47.6% had smoking history, 80.5% had adenocarcinoma histology, and 73.8% had ECOG PS 1. In treatment-naïve patients (1L; n=164), objective response rate (ORR) was 56.1% (48.1, 63.8) and median duration of response (mDOR) was 46.4 months (13.8, not estimable [ne]); in previously treated patients (2L+; n=149), ORR was 45.0% (36.8, 53.3) and mDOR was 12.4 months (9.5, 18.5) (Table). A total of 43 patients with brain metastases were evaluable by RANO-BM (1L, n=23; 2L+, n=20); 30 (69.8%) received prior brain radiotherapy or surgery. Intracranial (i) disease control rate was 88.4% (74.9, 96.1) with i-progression-free survival of 20.9 months (5.7, ne). In patients with target lesions only (n=15), iORR was 66.7% (38.4, 88.2) with iDOR ne (0.9, ne). Treatment-related adverse events (TRAEs) occurred in 91.7% of patients (Grade ≥3 34.2%); including (≥15%) peripheral edema (any grade/Grade ≥3: 66.5/10.9%), nausea (23.3/0.6%), hypoalbuminemia (23.0/3.2%), diarrhea (22.4/0.3%), and in-

creased blood creatinine (21.7/0.6%). Permanent discontinuation due to TRAEs occurred in 14.7% of patients.

Conclusions: In VISION – the largest clinical trial of a MET inhibitor in *MET*ex14 skipping NSCLC – tepotinib showed robust and durable efficacy across treatment lines, and promising intracranial activity was observed.

Keywords: Tepotinib, METex14, NSCLC, Adenocarcinoma, Vision

Line of therapy	Cohorts A+C	ORR, % (95% CI)	mDOR, months (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
1L	n=164	56.1 (48.1, 63.8)	46.4 (13.8, ne)	12.6 (9.6, 17.7)	19.1 (13.7, 23.7)
2L+	n=149	45.0 (36.8, 53.3)	12.4 (9.5, 18.5)	11.0 (8.2, 13.7)	19.6 (15.2, 22.3)
Overall	n=313	50.8 (45.1, 56.5)	18.0 (12.4, ne)	11.2 (9.5, 13.8)	19.3 (15.8, 22.3)

1L, first line; 2L+, second-or-later line; CI, confidence interval; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; ne, not estimable; ORR, objective response rate.

Clinical Response to Tepotinib according to Circulating Tumor (ct)DNA Biomarkers in Patients with Advanced NSCLC with High-Level MET Amplification

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Aims: Tepotinib showed meaningful activity in patients with NSCLC with high-level *MET*amp in VISION. Exploratory biomarker analyses are presented herein.

Methods: Patients had 0–2 prior therapy lines, high-level *MET*amp by LBx (Guardant360®; *MET* copy number ≥2.5), and no *MET*ex14 skipping or *EGFR/ALK* alterations received tepotinib 500 mg once daily (450 mg active moiety). Primary endpoint was objective response by independent review (RECIST v1.1); data cut-off: 20-Aug-2021. Exploratory biomarker analysis included LBx at baseline (BL), on treatment, and end of treatment (EOT).

Results: 24 pts were enrolled (median age: 63.4 yrs; smokers: 88%; ECOG PS 1: 88%; adenocarcinoma: 67%). Treatment duration was ≥1 yr in 5 pts and ≥2 yrs in 2 (both ongoing). Overall, objective response rate (ORR) was 41.7% (95% CI 22.1, 63.4). Treatment-naïve pts (n=7) had ORR 71.4% (29.0, 96.3), mDOR 14.3 months (2.8, ne) and mPFS 15.6 months (1.4, ne). BL biomarker analyses according to clinical benefit (CR/PR/SD [n=11] vs PD/NE [n=13]) showed association with better outcomes in patients with focal *MET*amp (ORR 57.1%), or without *MYC*amp (ORR 55.6%), or *RB1* wild type (ORR 52.6%) (Table). *MYC*amp/*RB1* mutation was detected in 4/7 pts with neuroendocrine/not otherwise specified histology. Low BL ctDNA mutant allele frequency (MAF) was associated with better outcomes. 14 pts had eMRs; persistent *MET*amp (n=4) was associated with lack of

clinical response. 2/9 pts with EOT biomarker profiles had emerging resistance mechanisms (MET kinase domain mutations Y1230 and D1228); both had *MET*amp re-emergence. Treatment-related AEs included edema (composite term; any grade 46%; Grade 3 13%) and constipation (any grade 17%; Grade ≥3 0%).

Conclusions: Tepotinib showed meaningful activity, especially in first line, *EGFR* WT NSCLC with high-level *MET*amp. BL biomarker analyses indicated focal *MET*amp, *MYC/RB1* WT, and low ctDNA MAF were associated with improved outcomes. Serial LBx could monitor molecular response and evaluate resistance.

Keywords: Tepotinib, Vision, Biomarker, NSCLC, MET amplification

Biomarker analyses		**ORR, n (%) [95% CI]**	**mDOR, months (95% CI)**	**mPFS, months (95% CI)**
Overall		10 (41.7) [22.1, 63.4]	14.3 (2.8, ne)	4.2 (1.4, 15.6)
BL *MYC*	WT (n=18)	10 (55.6) [30.8, 78.5]	14.3 (2.8, ne)	13.6 (1.4, ne)
	Amp (n=6)	0 [0, 45.9]	ne (ne, ne)	1.4 (0.8, ne)
BL *RB1*	WT (n=19)	10 (52.6) [28.9, 75.6]	14.3 (2.8, ne)	4.5 (1.4, ne)
	Mutation (n=5)	0 [0, 52.2]	ne (ne, ne)	1.4 (1.4, ne)
BL ctDNA MAF (>/≤ 26%; range 0.1–61.7)	Low (n=18)	10 (55.6) [30.8, 78.5]	14.3 (2.8, ne)	13.6 (4.1, ne)
	High (n=6)	0 [0, 45.9]	ne (ne, ne)	1.2 (0.6, ne)
eMR	Responder (n=14)	10 (71.4) [41.9, 91.6]	14.3 (2.8, ne)	13.6 (4.1, ne)
	Non-responder (n=4)	0 [0, 60.2]	ne (ne, ne)	1.8 (1.4, ne)

Evaluation of Blood Tumor Mutation Burden for Efficacy of Second- Line Atezolizumab Treatment in Non-Small Cell Lung Cancer: BUDDY Trial

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Aims: We aimed to investigate the feasibility of blood-based biomarkers, including blood tumor mutation burden (bTMB), to predict the atezolizumab efficacy in relapsed/advanced non-small cell lung cancer (NSCLC).

Methods: We recruited relapsed/advanced NSCLC patients with previous 1-2 platinum-doublet chemotherapy. Patients received atezolizumab 1200 mg every three weeks. Blood was collected to obtain plasma cell-free DNA (cfDNA) before the first cycle (C0) and at the fourth cycle (C4) or end-of-treatment (EOT) visit. The bTMB was measured in patients with cfDNA>10ng using CT-ULTRA, a targeted NGS panel for ctDNA analysis. Primary endpoint was to evaluate objective response rate (ORR) in bTMB-high (bTMBhi) and -low (bTMBlo) population.

Results: A total of 100 patients were enrolled. The cfDNA concentration was measured in 86 samples, and the bTMB was measured in 64 ctDNA samples at C0 and paired 48 ctDNA samples at C4/EOT. The overall ORR was 10%, and there was no difference in ORR according to bTMB (cutoff: 11.5muts/Mb) at C0 (bTMBhi 8.1% vs. bTMBlo 11.1%). However, the C4 (or EOT)/C0 bTMB ratio was significantly lower in patients with durable clinical benefit (DCB). The level at C0 and the C4/C0 ratio of cfDNA concentration, highest variant allele frequency (VAF), and standard deviation of VAF (VAF SD) were significantly lower in patients with DCB. In multivariate analysis, high cfDNA concentration at C0 (cutoff: 8.6ng/mL) and C4/C0 ratio of bTMB >1 were significant risk factors for PFS.

Conclusions: In previously treated NSCLC patients, the baseline levels and dynamic change of blood-based biomarkers including bTMB, cfDNA concentration, and VAF SD could predict the treatment efficacy of atezolizumab.

Keywords: Cell-free DNA, Blood tumor mutation burden, Atezolizumab, Non-small cell lung cancer

Distinct Characteristics and Treatment Outcomes of Exon20 Insertion Mutations Positive Non-Small Cell Lung Cancer Patients in Real World Practice

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Aims: Epidermal growth factor receptor (EGFR) exon20 insertion mutations accouts for around 10% of all EGFR mutant non-small cell lung cancer(NSCLC). The patients with these mutations are known to have poor response to conventional EGFR tyrosine kinase inhibitors (TKIs) and recently specific exon20 insertion TKIs and antibodies have been implemented into clinical practice. However, the clinical characteristics and treatment outcomes of exon20 insertion mutations are not well established. Here in, we investigated the clinical characteristics of NSCLC patients with EGFR exon20 insertion mutations.

Methods: We identified 24 consecutive cases of EGFR exon20 insertion positive NSCLC by using next-generation sequencing between April 2017 and August 2022,. Clinical data, including patient characteristics, metastatic site, response to chemotherapy, conventional EGFR-TKI or exon20 insertion targeted therapy, were retrospectively analyzed. Information regarding the specific amino acid sequence change was also available.

Results: The median patient age was 61 years, and 54.1% of the patients were female. Majority of the patients (54%) were never-smokers and all the patients were diagnosed as adenocarcinoma. About half (45.8%) of patients had an extra-thoracic metastatic lesion, and 25% had an brain metastasis at the initial presentation. The most common EGFR exon20 insertion site was in near loop following C-helix. In 58.3% of the patients who were treated with pemetrexed-based chemotherapy, the overall response rate and progression-free survival time were 35.7% and 3.3months (95% CI:0.0-6.8), respectively. The overall response rate and progression-free survival time were 28.6% and 5.5 months (95% CI: 2.3-8.8), respectively, for the 13 patients treated with exon20 insertion targeted therapy.

Conclusions: Exon20 insertion positive NSCLC has an effective and durable response to exon20 insertion targeted therapy rather than conventional pemetrexed-based chemotherapies or EGFR-TKIs. Given its novel characteristics and distinct clinical responses, the treatment strategy for exon20 insertion positive NSCLC remains to be further developed regarding treatment sequence and combinations.

Keywords: Exon 20 insertion mutation, Non-small cell lung cancer, EGFR mutation

AdvanTIG-105: Phase 1b Dose-Expansion Study of Ociperlimab plus Tislelizumab in Patients with Metastatic NSCLC

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Aims: Combination of anti-TIGIT/anti-PD-1 antibodies is a promising therapy for NSCLC. AdvanTIG-105 is a dose-escalation/-expansion study designed to assess the safety and preliminary antitumor activity of ociperlimab (investigational anti-TIGIT mAb) with tislelizumab (clinical-stage anti-PD-1 mAb) in patients with advanced, metastatic unresectable solid tumors (NCT04047862). Here, we report results from a dose-expansion cohort of AdvanTIG-105.

Methods: Treatment-naïve adult patients with histologically or cytologically confirmed metastatic squamous or nonsquamous NSCLC with PD-L1-positive (tumor cell [TC] ≥1% by VENTANA PD-L1 [SP263] Assay) and nonsquamous patients with *EGFR/ALK/ROS-1* wild-type tumors were enrolled. Patients received the RP2D of ociperlimab 900mg IV Q3W plus tislelizumab 200mg IV Q3W until disease progression, intolerable toxicity, or withdrawal of consent. Primary endpoint was investi-

gator-assessed ORR per RECIST v1.1.

Results: As of 5 April 2022, 40 patients (median age: 65.0 years [range 46-81]) were enrolled; median study follow-up was 28.1 weeks (range 3.1-61.7). Overall, ORR in the efficacy-evaluable set (N=39) was 53.8% (95% CI: 37.2, 69.9); DCR was 89.7% (95% CI: 75.8, 97.1). In patients with PD-L1 TC ≥50% (n=14), ORR was 71.4% (95% CI: 41.9, 91.6), and 44.0% (95% CI: 24.4, 65.1) in patients with PD-L1 TC 1-49% (n=25). In the safety analysis set (N=40), 38 patients (95.0%) experienced ≥1 AE and 11 (27.5%) had grade ≥3 AEs. Most common AEs were pruritus (32.5%), pyrexia (30.0%), rash (20.0%), and decreased appetite (20.0%). Serious AEs occurred in 10 patients (25.0%); AEs leading to treatment discontinuation occurred in three patients (7.5%). An AE leading to death (cerebral infarction) occurred in one patient, but the event was not considered to be related to the study drugs.

Conclusions: Combination of ociperlimab 900mg plus tislelizumab 200mg IV Q3W was well tolerated and showed preliminary antitumor activity in patients with treatment-naïve metastatic squamous or nonsquamous NSCLC with PD-L1-positive tumors (TC ≥1%).

Keywords: TIGIT antibody, PD-1 inhibitor, Metastatic NSCLC, Ociperlimab

Real-World Study of Osimertinib in Korean Patients with Epidermal Growth Factor Receptor T790M Mutation-Positive Non-Small Cell Lung Cancer

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Aims: Although osimertinib is the standard-of-care treatment of epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer, real-world evidence on the efficacy of osimertinib is not enough to reflect the complexity of the entire course of treatment. Herein, we report on the use of osimertinib in patients with EGFR T790M mutation-positive non-small cell lung cancer who had previously received EGFR tyrosine kinase inhibitor (TKI) treatment in Korea.

Methods: This study was a retrospective cohort study performed at 19 medical centers in South

Korea. Patients with confirmed EGFR T790M after disease progression of prior EGFR-TKI were enrolled and administered osimertinib 80 mg daily. The primary effectiveness outcome was progression-free survival, with time-to-treatment discontinuation, treatment and adverse effects leading to treatment discontinuation, and overall survival being the secondary endpoints.

Results: A total of 558 individuals were enrolled, and 55.2% had investigator-assessed responses. The median progression-free survival was 14.2 months (95% confidence interval (CI), 13.0–16.4), and the median time-to-treatment discontinuation was 15.0 months (95% CI, 14.1–15.9). The median overall survival was 36.7 months (95% CI, 30.9–not reached). The benefit with osimertinib was consistent regardless of the age, sex, smoking history, and primary EGFR mutation subtype. However, hepatic metastases at the time of diagnosis, the presence of plasma EGFR T790M, and the shorter duration of prior EGFR-TKI treatment were poor predictors of osimertinib treatment. Ten (1.8%) patients, including three with pneumonitis, had to discontinue osimertinib due to severe adverse effects.

Conclusions: Osimertinib demonstrated its clinical effectiveness and survival benefit for EGFR T790M mutation-positive in Korean patients with no new safety signals.

Keywords: Osimertinib, EGFR T790M, Non-small cell lung cancer, Real-world efficacy

Tepotinib in Asian Patients with Advanced NSCLC with MET Exon 14 (METex14) Skipping

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Aims: Tepotinib is a highly selective, potent MET inhibitor approved in several Asian countries for the treatment of advanced *MET*ex14 skipping NSCLC. In the VISION study (n=275; data cut-off: Feb 1, 2021), tepotinib had an objective response rate (ORR) of 49.1% (95% CI: 43.0, 55.2) by independent review (IRC), with a median duration of response (mDOR) of 13.8 months (9.9, 19.4) across treatment lines. Here, we report outcomes in Asian patients.

Methods: Patients with advanced *MET*ex14 skipping NSCLC, detected by liquid (L+) or tissue (T+) biopsy, received tepotinib 500 mg (450 mg active moiety) once daily. Primary endpoint was ORR by IRC.

Results: In 79 Asian patients assessed for efficacy (38% female, 42% smoking history, 34% treatment-naïve [1L] and 77% adenocarcinoma), ORR was 54.4% (42.8, 65.7), mDOR was 18.5 months (8.3, not estimable [ne]), mPFS was 12.1 months (6.9, ne), and mOS was 20.4 months (19.1, ne). ORR was 66.7% (46.0, 83.5) in 1L patients (n=27) and 48.1% (34.0, 62.4) in previously treated patients (2L+; n=52). Meaningful activity was observed irrespective of *MET*ex14 skipping detection method (Table). In patients analyzed for HRQoL (n=73), mean change from baseline for EORTC QLQ-C30 GHS (4.06), EQ-5D-5L VAS (-0.53), and EORTC QLQ-LC13 for cough (-6.77), dyspnea

(-0.98), and chest pain (-7.00) symptom scores, demonstrated stability in QoL. In 88 Asian patients analyzed for safety, the most common adverse events (AEs) were peripheral edema, increased blood creatinine, and diarrhea. 29.5% of patients had Grade ≥3 treatment-related (TR) AEs. TRAEs led to dose reductions in 29.5%, temporary interruption in 43.2%, and permanent discontinuation in 14.8% of patients.

Conclusions: In VISION, tepotinib showed robust and durable clinical activity in Asian patients with *MET*ex14 skipping NSCLC. TRAEs were manageable, with few leading to treatment discontinuation. Overall, VISION enrolled 106 Asian patients; analysis in this population is ongoing.

Keywords: Tepotinib, METex14, NSCLC, VISION, Asia

Efficacy in Asian pts	Overall			Treatment-naïve			Previously treated		
	L+ (n=37)	T+ (n=57)	Combined (n=79)	L+ (n=10)	T+ (n=20)	Combined (n=27)	L+ (n=27)	T+ (n=37)	Combined (n=52)
ORR, % (95% CI)	51.4 (34.4, 68.1)	57.9 (44.1, 70.9)	54.4 (42.8, 65.7)	70.0 (34.8, 93.3)	70.0 (45.7, 88.1)	66.7 (46.0, 83.5)	44.4 (25.5, 64.7)	51.4 (34.4, 68.1)	48.1 (34.0, 62.4)
DCR, % (95% CI)	70.3 (53.0, 84.1)	82.5 (70.1, 91.3)	77.2 (66.4, 85.9)	70.0 (34.8, 93.3)	85.0 (62.1, 96.8)	77.8 (57.7, 91.4)	70.4 (49.8, 86.2)	81.1 (64.8, 92.0)	76.9 (63.2, 87.5)
12-month rates*, % (95% CI)									
DOR	41 (12, 69)	54 (26, 75)	53 (29, 72)	63 (14, 89)	83 (27, 97)	79 (38, 94)	25 (1, 65)	24 (1, 62)	29 (5, 60)
PFS	41 (22, 59)	53 (35, 68)	51 (37, 64)	53 (17, 79)	74 (43, 90)	66 (40, 83)	38 (16, 59)	42 (20, 63)	44 (26, 61)
OS	71 (53, 84)	85 (71, 93)	80 (69, 88)	80 (41, 95)	89 (64, 97)	84 (63, 94)	68 (46, 83)	83 (64, 93)	78 (63, 88)

*mDOR, mPFS, and mOS were not reached for several subsets, especially in treatment-naïve patients. Hence, 12-month event-free rates from Kaplan-Meier survival analysis are shown instead of median

Application of Machine Learning Algorithms for the Prediction of Afatinib Treatment Outcome in Advanced Stage EGFR-Mutated NSCLC

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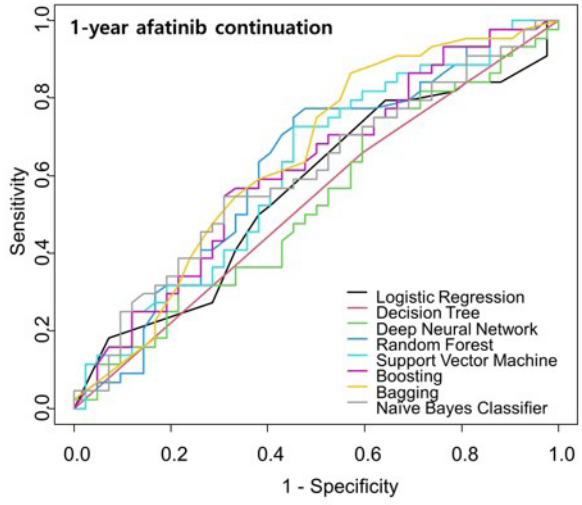
Aims: The present study aimed to evaluate the performance of several machine learning (ML) algorithms in predicting 1-year afatinib continuation and 2-year survival after afatinib initiation and to identify the differences in survival outcomes between ML-classified strata.

Methods: Data that were also used in the RESET study were employed. A stratified random sampling method was applied to split the data into training and test sets (70:30 split ratio). The training was performed using eight ML algorithms: logistic regression, decision tree, deep neural network, random forest, support vector machine, boosting, bagging, and the naïve Bayes classifier. The model performance was assessed based on sensitivity, specificity, and accuracy. The area under the receiver operator characteristic curve (AUC) was calculated and compared between the ML models using DeLong's test. A Kaplan-Meier (KM) curve was used to visualize the identified strata obtained from the ML models.

Results: No significant differences in the input variables were observed between the training and test datasets. The best-performing models were support vector machine in predicting 1-year afatinib continuation (AUC 0.626) and decision tree in 2-year survival after afatinib start (AUC 0.644), although the performances of the ML models were comparable and did not display any predictive roles. KM analysis and log-rank test revealed significant differences between the strata identified from the ML model (p<0.001) in terms of both time-on-treatment (TOT) and overall survival (OS).

Conclusions: The performances of ML models in our study found no discernible roles in predicting afatinib-related outcomes, although the identified strata revealed different TOT and OS in the KM analysis. This implies the strength of ML in predicting the survival outcome, as well as the limitation of electronic medical record-based variables in ML algorithms. Careful consideration of variable inclusion is likely to improve the general model performance.

Keywords: NSCLC, Afatinib, Machine learning, Prediction


1-year afatinib continuation
Sensitivity
1 - Specificity
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Random Forest
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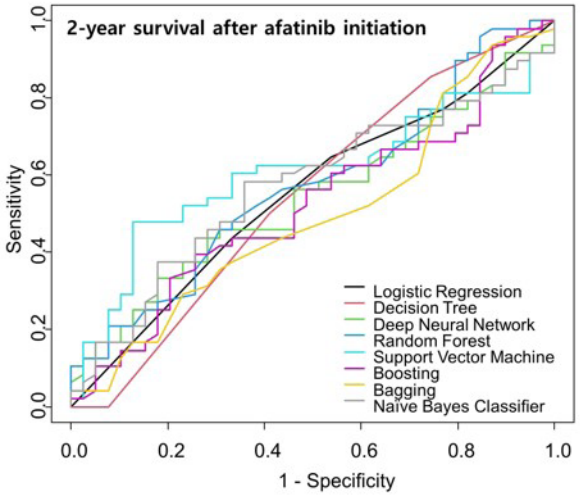
Naive Bayes Classifier


2-year survival after afatinib initiation
Sensitivity
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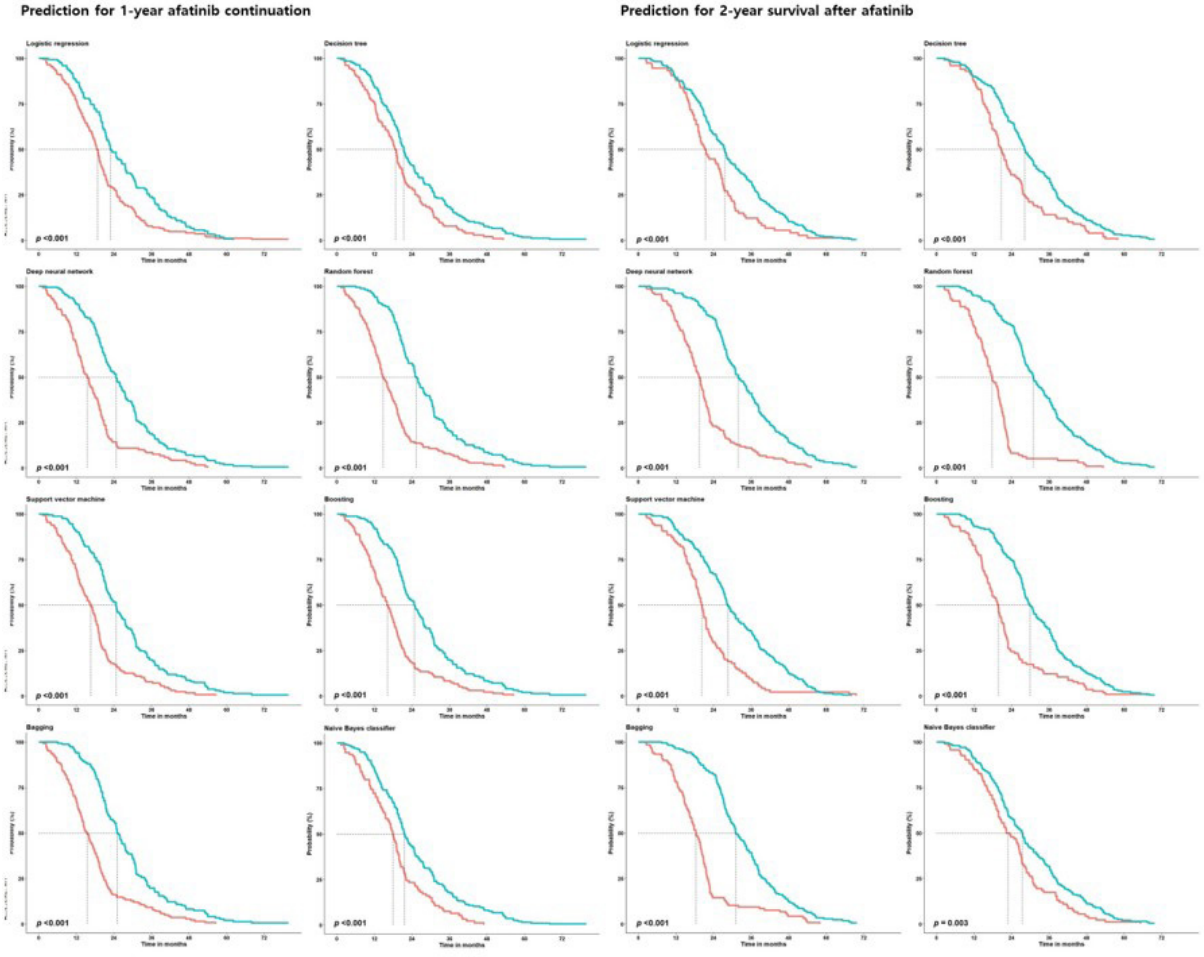
Prediction for 1-year afatinib continuation
Prediction for 2-year survival after afatinib
Logistic regression
Decision tree
Deep neural network
Random forest
Support vector machine
Boosting
Bagging
Naive Bayes classifier
p <0.001
p = 0.003

AdvanTIG-105: Phase 1b Dose-Expansion Study of Ociperlimab+Tislelizumab with Chemotherapy in Patients with Metastatic Squamous and Nonsquamous Non-Small Cell Lung Cancer

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Aims: TIGIT inhibitor plus a PD-1 antibody is a promising combination which shows potent efficacy in solid tumors. AdvanTIG-105 is an open-label dose-escalation/-expansion study designed to assess the safety and preliminary antitumor activity of ociperlimab (investigational anti-TIGIT mAb) plus tislelizumab (clinical-stage anti-PD-1 mAb) in patients with metastatic unresectable solid tumors (NCT04047862). In the dose-escalation phase, ociperlimab plus tislelizumab was well tolerated, preliminary antitumor activity was observed, and the RP2D of ociperlimab (900 mg IV Q3W) plus tislelizumab (200 mg IV Q3W) was established. Here, we report results from NSCLC dose-expansion cohorts of the AdvanTIG-105 study.

Methods: Treatment-naïve adult patients with histologically/cytologically confirmed metastatic squamous NSCLC (Cohort 1 [C1]) or nonsquamous NSCLC with *EGFR/ALK/ROS-1* wild-type tumors (Cohort 2 [C2]) were enrolled. Patients in C1 received the RP2D of ociperlimab plus tislelizumab with paclitaxel/*nab*-paclitaxel plus carboplatin; patients in C2 received the RP2D of ociperlimab plus tislelizumab with pemetrexed plus cisplatin/carboplatin until disease progression,

intolerable toxicity, or withdrawal of consent. Primary endpoint was investigator-assessed ORR per RECIST v1.1; safety/tolerability profile was a secondary endpoint.

Results: As of March 18, 2022, 84 patients were enrolled (C1: n=41; C2: n=43). The median study follow-ups were 17.7 weeks (range 1.1-42.6) and 15.0 weeks (3.0-51.1) in C1 and C2, respectively. Overall, 76 patients were evaluable for efficacy. In C1, confirmed ORR was 45.9% (95% CI: 0.3, 0.6) and 25.6% (95% CI: 0.1, 0.4) in C2. Overall, 81 patients (96.4%) experienced ≥1 adverse event (AE), and 48 patients (57.1%) had grade ≥3 AEs. Serious AEs occurred in 26 patients (31.0%). Most common AEs were anemia (41.7%), neutrophil count decreased (33.3%), and white blood cell count decreased (33.3%).

Conclusions: Ociperlimab 900 mg IV Q3W plus tislelizumab 200 mg IV Q3W in combination with chemotherapy was generally well tolerated and showed antitumor activity in patients with treatment-naïve metastatic squamous/nonsquamous NSCLC.

Keywords: TIGIT antibody, PD-1 inhibitor, Metastatic NSCLC, Dose-expansion

The Role of Brain Radiotherapy before First-Line Afatinib Therapy, Compared to Gefitinib or Erlotinib, in Patients with EGFR-Mutant Non–Small Cell Lung Cancer

Hyun Ae Jung, Sehhoon Park, Se-Hoon Lee, Jin Seok Ahn, Myung-Ju Ahn, Jong-Mu Sun

Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Aims: Brain metastasis is common in patients with epidermal growth factor receptor (*EGFR*)-mutant non–small cell lung cancer (NSCLC) at initial presentation. A previous study showed that brain radiotherapy (RT) before first-generation (first-G) *EGFR*–tyrosine kinase inhibitor (TKI) therapy is associated with longer overall survival than TKI therapy alone. However, there is no data regarding the role of additional brain RT before afatinib therapy.

Methods: Between October 2014 and June 2019, *EGFR*-mutant NSCLC patients with brain metastases who started first-G *EGFR*-TKIs (gefitinib or erlotinib) or afatinib as first-line therapy were retrospectively analyzed. This study compared overall survival and intracranial progression-free survival (PFS) between patients who received *EGFR*-TKIs alone and *EGFR*-TKIs with brain RT and either a first-G *EGFR*-TKI or afatinib, respectively.

Results: The median follow-up duration was 29.6 months (range, 1.5–116.9 months). In the first-G *EGFR*-TKI group (n = 155), 94 (60.6%) patients received the first-G *EGFR*-TKI alone and 61 (39.4%) patients received brain RT prior to their first-G *EGFR*-TKI. In the afatinib group (n = 204), 126 (61.8%) patients received afatinib alone and 78 (38.2%) patients received brain RT prior to afatinib. There was no difference in overall survival rates between the groups with RT (35.6 months: 95% confidence interval [CI], 27.9%–43.3%) and without RT (31.4 months: 95% CI, 23.9%–38.9%) in the afatinib group ($p = 0.58$), but there was a significant difference in overall survival in the first-G *EGFR*-TKI group in a manner favoring additional brain RT (41.1 months: 95% CI, 30.5%–51.7% vs. 25.8 months: 95% CI, 20.1%–31.5%; $p = 0.02$). Meanwhile, median intracranial PFS was not different between patients who received *EGFR*-TKI therapy alone vs. *EGFR*-TKI therapy with brain RT in both the first-G *EGFR*-TKI ($p = 0.39$) and afatinib ($p = 0.24$) groups.

Conclusions: Afatinib therapy alone showed comparable survival outcomes to those of afatinib

with brain RT. The current study suggests that brain RT can be delayed when first-line afatinib therapy is considered in patients with *EGFR*-mutant NSCLC.

Keywords: Non–small-cell lung cancer, Epidermal growth factor receptor, Tyrosine-kinase inhibitor, Brain

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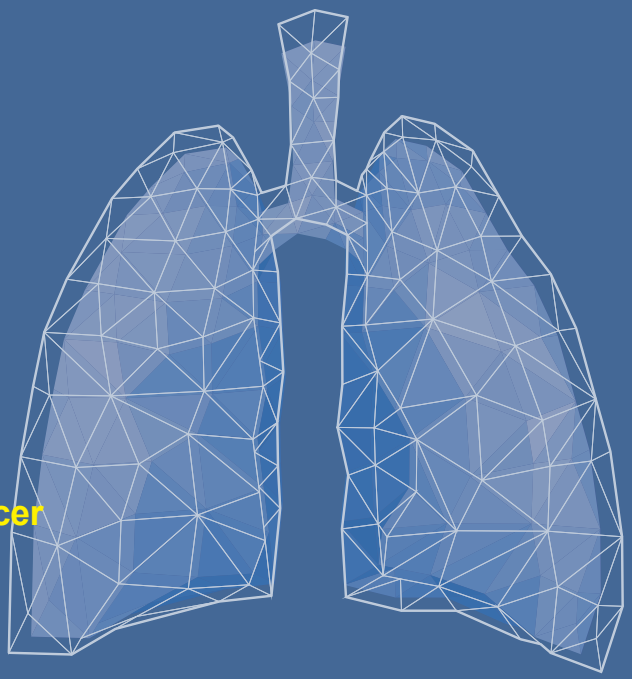


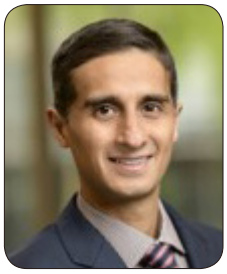
| November 11 (Fri), 2022 | Room A

15:00-16:40

Session VIII (A)

Recent Advances in the Treatment of Oligometastatic Lung Cancer

Chair: Hak Jae Kim *(Seoul National Univ.)*



Ablative Treatment for Limited Metastatic Lung Cancer: Past Lessons and Future Directions

Daniel R. Gomez

MSKCC, USA

Integrating SBRT into the Treatment of Oligometastatic Non-Small Cell Lung Cancer with Actionable Mutations: Now and the Future

Oscar S.H. Chan

Hong Kong Integrated Oncology Centre, Hong Kong

The term oligometastases was first coined by Hellmann and Weisaulbaum in 1995[1]. It is an intermediate state of metastases with limited number of lesions in limited organs. As the sophisticated and sensitive imaging like PET-CT and sensitive tumour markers testing are becoming more readily available, this intermediate state can be detected more often. Besides, there is another type of oligometastases emerging, which is known as induced oligometastases. It refers to widespread metastatic disease being controlled to limited number of foci after an effective systemic treatment. With the advent of precision medicine, more and more actionable mutations are identified. A higher response rate and more durable response can be achieved with appropriate target therapy[2]. Thus, induced oligometastases are also increasingly encountered in clinical practice nowadays.

Instead of this binary classification, in the daily practice, the types of oligometastases can vary widely in different clinical scenarios. Many different terms like oligo-progression, oligo-residual, oligo-persistent disease emerges. In light of this, the European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer OligoCare project developed a comprehensive system for characterisation and classification of oligometastatic disease. A total of nine distinct types of oligometastases were characterized[3]. A standardized classification and nomenclature would be instrumental in the future research and scientific communication.

Increasing evidence indicated that delivering local ablative therapy (LAT) to oligometastatic disease can improve progression free survival (PFS) in non-small cell lung cancer (NSCLC) with actionable mutation in the past decade[4]. Stereotactic body radiotherapy, SBRT, is the preferred form of LAT in most of the conditions as it is non-invasive and can be done in ambulatory setting,

even in relatively old and frail patients. In addition, it is precise, highly effective with limited and manageable toxicities. Compared to conventional radiotherapy, the shorter fractionations allow minimal interruption to systemic therapy.

NSCLC is a heterogenous disease driven by different actionable mutations. Epidermal growth factor receptor (EFGR) mutation, the prototype of actionable mutation, is highly prevalent in Asian populations. In general, the response rate of target therapies is much higher, and PFS is longer than conventional chemotherapy. Yet acquired mutation is inevitable. Apart from new medicines aiming to overcome selective secondary or even tertiary mutations, LAT especially SBRT can non-selectively remove the resistant clones and hence preserve the use of the original systemic therapy[5-6].

Our group has previously published a retrospective matched-cohort study comparing patients with EGFR mutation-positive stage IV NSCLC receiving radiotherapy versus chemotherapy upon progression. The OS of the radiotherapy group was significantly longer than the chemotherapy group, 28.2 versus 14.7 months (P=0.026). The median PFS was 7.0 and 4.1 months after radiotherapy and chemotherapy, respectively (P=0.0017). The use of radiotherapy was an independent predictive factor of OS and PFS in multivariate analysis. Only one patient experienced grade 3 toxicity after radiotherapy[7]. Another large retrospective study from Shanghai has showed similar findings, with a median prolongation of TKI therapy for 7.6 months. Limitations in retrospective series should not be overlooked. Therefore, randomized studies minimizing selection bias are needed[8]. The ongoing studies: STOP NSCLC and HALT Study are randomized studies addressing the true benefits of SBRT in patients with oncogenic addiction upon oligoprogression [9-10].

SINDAS is a phase III randomized study to examine the effects of upfront radiotherapy followed by EGFR TKI treatment versus TKI therapy alone. Synchronous oligometastatic (<=5 metastases) NSCLC patients were enrolled and a moderate dose of RT (25-40Gy in 5 fractions) was given. A statistically improvement in PFS (12.5 vs 20 months p<0.001) and OS (17.4 vs 25.5 months, p<0.001) were demonstrated[11].

The best timing of local treatment is debatable. While the first 2 studies delivered local therapy upon progression, SINDAS gave upfront RT before systemic therapy. And there are also a few studies giving RT/ SBRT as consolidation to oligopersistent disease. Patterns of failure study indicated half of the progression occurred in initial disease. And ATOM is a phase 2 prospective study conceptualized by our group in 2013[12]. SBRT were given to PET-avid sites 3 months post EGFR TKI. Unfortunately, the study closed due to slow accrual. The primary endpoint, one-year PFS rate (i.e. 15 month post TKI) was 68.8%. Median OS was 43.3 months. All LAT were done by SBRT, and

none experienced ≥ grade 3 SBRT related toxicities. Compared with screen failure cohort (n = 48), pre-emptive SBRT effectively reduced risk of progression (HR 0.41, p = 0.0097). Xu et al reported another large retrospective cohort of consolidative LAT after brief course (2-month) TKI. It illustrated consolidative LAT to all metastatic sites with EGFR-mutant synchronous oligometastatic NSCLC can significantly improve PFS and OS compared with consolidative LAT to partial sites or observation alone[13]. A randomized phase 2 study was at the 2019 was presented in World Conference for Lung Cancer. After three months of TKI with controlled disease, 61 patients were randomized to either SBRT combined with TKI or TKI alone. PFS of patients with SBRT combined with TKI was superior to that on TKI alone (17.4 vs. 8.9 months; P=0.042). However, the sites of irradiation were at the discretion of the investigators and not all patients received SBRT to all metastases[14].

Although accumulating data favour the use of SBRT/ LAT to oligometastatic NSCLC, there are still a lot of challenges which requires further studies in the future. First of all, oligometastases relies only on imaging at present. Though PET-CT is sensitive, it still cannot unearth minute foci of micrometastases. Sometimes the "oligometastases" is only the tip of iceberg of polymetastatic disease. MicroRNA has been studied as a potential biomarker of oligometastatic disease, but further validation is required[15]. In addition, normograms have also been developed to facilitate better selection and counselling of patients[16]. Since patients with actionable mutations has distinct driver mutation and the detection of the allelic fractions of the driver mutation may help monitoring the success of LAT on oligometastases. Second, the radiation dose fractionation and schedules vary widely in the current published data. Whether an ablative dose is required is debatable, and some anatomical locations limit the delivery of conventional ablative SBRT dosage. A fine balance between the curative and palliation dose is required. Though the current data suggested that SBRT is safe in treating oligometastases, repeated courses of SBRT in various body parts may incur some unexpected cumulative long term toxicities, especially patients with actionable mutations usually fare better in survival and long term toxicities may be more pronounced. Third, prospective large scale studies are still sparse. More phase 3 data in different distinct oligometastatic subgroups are required to address the optimal dose, toxicities and timing of initiating SBRT. Last but not least, cost effectiveness analysis of delivering LAT compared to other alternative treatments (like change of target therapy) should be studied as well.

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Advanced Radiotherapy Techniques for Oligometastatic Lung Cancer and a Pattern of Care Survey within Korean Radiation Oncologists

Yang-Gun Suh

National Cancer Center, Korea

Recently many clinical trials and retrospective studies have demonstrated that local ablative therapy (LAT) such as surgery or radiotherapy gain a survival benefit in non-small cell lung cancer (NSCLC) with limited metastatic diseases (oligometastasis). LAT options for patients with oligometastasis include surgical resection, radiotherapy, radiofrequency ablation, and cryoablation.[1-4] Among them, radiotherapy is a nonsurgical and noninvasive treatment, and high-dose radiation shows good tumor control. Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiotherapy, refers to stereotactically guided delivery of high conformal radiation with ablative dose in a limited number of fractions.[5] SABR for metastatic lesions has shown good local control rates ranging from 70 to 100% and durable treatment-related toxicities.[6-8] As a result, SABR is commonly used for small metastatic lesions in lung, spine, liver, as well as adrenal gland. To minimize radiation exposure to normal tissues adjacent to tumors, modern radiation techniques including image-guided radiotherapy (IGRT), respiratory-gated radiotherapy (RGT), and proton beam therapy (PBT) are used for SABR. To maximize tumor control, high-dose radiation during short treatment courses with 1-5 fractions are used. The ongoing randomized phase II/III trial (NRG-LU002) comparing local consolidative therapy and maintenance systemic therapy for limited metastatic NSCLC uses radiation dose of 24 Gy (acceptable variation, 21-27 Gy) with 1 fraction, 30 Gy with 3 fractions (acceptable variation, 26.5-33 Gy), and 34 Gy with 5 fractions (acceptable variation, 30-37.5 Gy) for SABR. For radiation to the primary lung tumor and involved-regional lymph nodes, SABR is inappropriate due to unacceptable toxicities, more protracted hypofractionated-radiotherapy using 45 Gy with 15 fractions (acceptable variation, 42-48 Gy) is used. Interestingly, a recent systematic study showed that the use of SABR instead of conventionally fractionated radiotherapy for oligometastatic NSCLC patients rapidly increased after 2011, and a time trend towards improved OS after 2011 was also detected.[9]

Several phase II-III prospective trials have shown beneficial effects of SABR for NSCLC patients with oligometastasis.[10-15] These studies have demonstrated that SABR can improve treatment outcomes as consolidation therapy after cytotoxic chemotherapy, EGFR-TKIs, or immune checkpoint blockades. However, in real world, the use of LAT for oligometastatic NSCLC is controversial due to complexity and variety of diseases and patients.

According to the European Society for Radiotherapy and Oncology (ESTRO) and European Organisation for Research and Treatment of Cancer (EORTC) consensus recommendation, oligometastasis is classified to de-novo oligometastasis, repeat oligometastasis, and induced oligometastasis.[16] A retrospective single center study showed the ESTRO EORTC classification system had moderate discriminatory strength for overall survival and progression-free survival.[17]

The Korean Oligometastasis Working-Group performed an online survey to investigate a pattern of care for oligometastatic lung cancer within Korean radiation oncologists specializing in lung cancer. The survey items were consisted of 4 cases of oligometastatic lung cancer representing de-novo, repeat, and induced oligometastasis. For de-novo synchronous oligometastasis, repeat oligoprogression, repeat oligopersistance, and induced oligoprogression, 68%, 86%, 73%, and 64% of responders considered radiotherapy with curative intent. A substantial proportion of radiation oncologists in Korea consider radiation therapy with curative intent for oligometastasis. Therefore, further studies are needed to define multidisciplinary consensus on the treatment for oligometastatic lung cancer.

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Role of Surgery in Oligometastatic Lung Cancer

Seong Yong Park

Sungkyunkwan Univ., Korea

The efficacy of the local consolidative therapy in oligometastatic lung cancer has been reported previously, however, those studies described the utility of the radiation therapy rather than of surgery. Furthermore, those studies included either no or few patients with oncogene-driven non-small cell lung cancer, which has distinct biological properties and treatment options. Surgery is the most reliable method of tumor removal that allows detailed examinations of resected tissue, such as comprehensive genetic analysis. The author reported that pulmonary resection for advanced non-small cell lung cancer after targeted therapy is feasible, and the surgical specimens could be used for planning further targeted therapy in the previous literatures and these experiences will be introduced in the presentation. In addition, the consideration for questions which are aroused from the experiences will be shared; is the salvage operation really helpful for the patients? How can we expect the ypT0N0? What is the best timing for the salvage surgery? Is the anatomic resection mandatory?

Timing of Local Consolidative Therapy in Oligometastatic Non-Small Cell Lung Cancer: Upfront or Later?

Jeong Uk Lim

The Catholic Univ. of Korea, Korea

Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases. In NSCLC, stage IV cancer account 35%–40% of all newly diagnosed NSCLC cases. Advances in targeted therapy and immunotherapy have significantly improved clinical outcomes in stage IV NSCLC. Despite the advent of treatment modalities, the 5-year survival rate of patients with metastatic NSCLC remains poor.

In stage IV cancer, oligometastasis is usually used to describe patients with ≤5 extrathoracic metastatic lesions in ≤3 organs, and they comprise 20%–50% of all patients with locally advanced and metastatic NSCLC. Hellmann and Weichselbaum suggested that oligometastasis is the state in which the progressing tumor cells are restricted to a single or a few organs due to the relatively limited number of seeding tumor cells and receptivity of the host organ. Accurate staging to minimize the possibility of missing lesions prior to treatment is important, because treatment approaches for disseminated and oligometastatic cancer is different. Positron emission tomography (PET)/computed tomography (CT) shows great sensitivity for the staging of mediastinal lymph nodes and finding distant and occult metastases. In combination with brain magnetic resonance imaging, detection of oligometastatic disease can be more accurate.

Recent studies suggested that local consolidative therapy (LCT) of primary or metastatic lesions in oligometastasis have potential clinical benefits in NSCLC. The Pan-Asian clinical practice guidelines for metastatic NSCLC suggest administering LCT, such as high-dose radiotherapy, or surgery to up to 3 synchronous metastatic sites after careful discussion among the multidisciplinary board. Treatment modalities mainly include radiotherapy, and several studies have shown association with overall survival (OS) or progression-free survival (PFS) in the patient groups after radiotherapy to the metastatic sites. Past studies suggested that the predictors of a good response to consolidative radiotherapy at oligometastatic sites were a T-stage of 1 to 2, the number of

metastatic organs, the absence of liver metastases, and the absence of bone metastases. In oligometastatic NSCLC, we can speculate that LCT can be more beneficial to patients with less tumor burden.

However, questions still remain when to apply LCT. Upfront LCT focuses on reducing the tumor burden at the early phase of anti-cancer treatment. Another opinion is that clinicians should wait to see the initial responses to the systemic treatment, so as to avoid unnecessary treatment-related hazards to the patients. Some researchers state that in driver mutation-positive NSCLC, aggressive treatment of both local and oligometastatic sites should be postponed for at least 6 months to allow the natural history of the oligometastatic disease to be observed. Several studies recommend that local therapy to primary and oligometastatic lesions should be considered for patients who did not show progression on systemic therapy.

Location of the metastatic lesions is an important factor when deciding the timing of LCT. Recent results support more preemptive approach in brain oligometastases. One study suggested that upfront cranial stereotactic radiosurgery prior to EGFR-TKI in patients with brain metastases resulted in a superior OS as compared with other treatment approaches. Similar results supporting the upfront definitive radiotherapy to the brain lesions were shown in a number of retrospective studies. LCT for oligometastatic bone lesions requires different approaches. Related symptoms, response to systemic treatment, whether the lesion is at the weight-bearing bone, and the possibility of complications such as pathological fractures, spinal cord compression are important factors to be considered when undergoing LCT in bone oligometastases.

In patients with oligometastases, whether LCT should be performed during the period of responsive systemic treatment or after the occurrence of oligoprogression needs to be discussed further because the number and duration of ablative therapies that can be given is limited. The timing of LCT should be decided after careful consideration of the tumor biology, anatomy and sites of metastatic lesions, and the patient's general condition.

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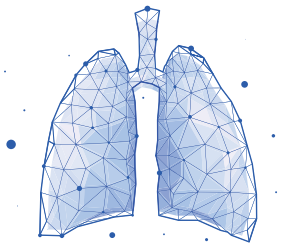

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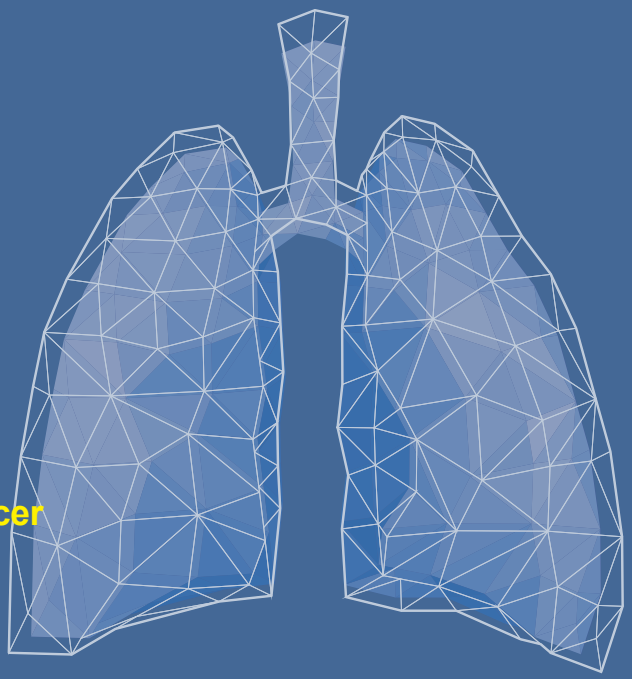


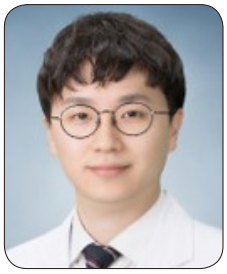
| November 11 (Fri), 2022 | Room A

16:50-17:40

Satellite Symposium IV (A)

[MSD]

Chair: Young Joo Min *(Univ. of Ulsan)*



The Indispensable Treatment Option for More TOMORROWs: Pembrolizumab for Metastatic Non–Small Cell Lung Cancer Patients in the First-Line

Beung-Chul Ahn

National Cancer Center, Korea

www.kalcic.co.kr

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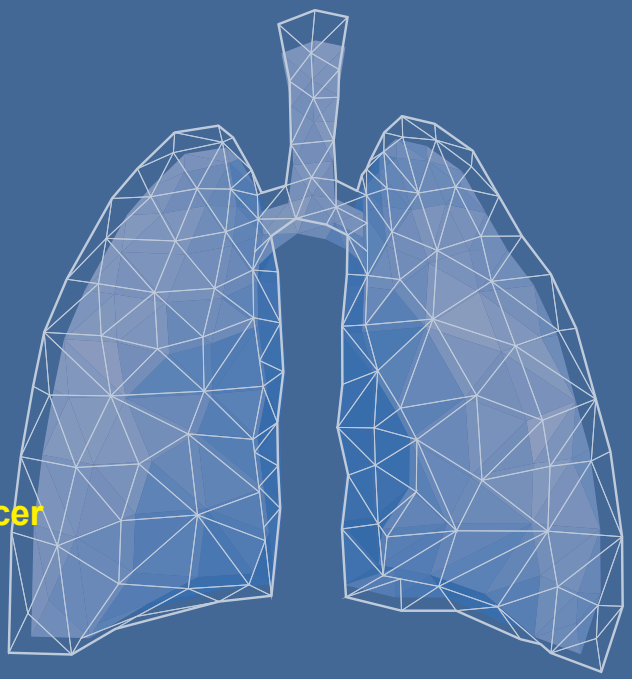

| November 11 (Fri), 2022 | Room B

08:50-10:10

Session V (B)

Lung Cancer Screening

Chair: Yeol Kim *(National Cancer Center)*

Implementation of Population Based Lung Cancer Screening in Europe

John K. Field

The Univ. of Liverpool, UK

NLST and NELSON LDCT screening trials have provided evidence of a statistically significant reduction (20%, 24% respectively) in lung cancer mortality.

The UKLS was a randomised controlled trial, comparing LDCT screening with usual care in a high-risk population selected using the LLPv2 risk model and having a unique single LDCT screening design. The mortality data was published in 2021; within the same publication a meta-analysis of nine international randomised controlled trials provided a synthesis of the latest randomised trial evidence. Results from this meta-analysis indicated a significant reduction in lung cancer mortality. LDCT screening was associated with a 16% relative reduction in lung cancer mortality, when compared against a non-LDCT control arm (RR 0·84 [0·76 – 0·92]) with no significant heterogeneity (p= 0·31, I^2=14·2%).

LDCT screening has already been implemented in the U.S. and currently there are concerted efforts to initiate lung cancer screening throughout Europe. Recently the UK National Screening committee has recommended the introduction of targeted lung cancer screening, which has built on the results from the UKLS and International lung cancer screening trials results. The European Commission have also recently produced recommendation to expand population-based cancer screening to include lung, prostate, and gastric cancers.

Looking to the future, the SPIRAL framework (as Screening Planning and Implementation RAtionale for Lung cancer) defines the scope of future implementation research on lung cancer screening programmes.

Lung Cancer Screening in Never-Smokers

Ryutaro Kakinuma

National Cancer Center, Japan

Purpose: To evaluate lung cancers detected using low-dose CT screening between February 2004 and March 2012.

Methods: The analyses were performed based on the database on September 10, 2012. The number of screenees analyzed in the observational study was 12,116. Screenees were classified into three groups based on their smoking index (SI): SI ≥ 600, SI < 600, and never-smokers. Overall, 147 lung cancers in 132 cases treated at the National Cancer Center Hospital and the National Cancer Center Hospital East were evaluated according to the smoking index. Adenocarcinomas were evaluated based on the following classification: group A (adenocarcinoma in situ and minimally invasive adenocarcinoma), and group B (invasive adenocarcinoma). Statistical analyses were performed using the chi-square test.

Results: The ages of the patients with lung cancer ranged between 42 and 85 years (mean, 61 years). Thirty-two of the 2156 male screenees (1.48%) and 2 of the 149 female screenees (1.34%) in the SI ≥ 600 group, 22 of the 2989 male screenees (0.74%) and 10 of the 796 female screenees (1.26%) in the SI < 600 group, and 16 of the 2148 male screenees (0.74%) and 50 of the 3878 female screenees (1.29%) in the never-smoker group were diagnosed as having lung cancer. Among the 147 lung cancers, 8 lesions (5.4%) did not present as nodules and instead appeared as a partial thickening of the bulla wall, a funicular-like shadow, a pneumonia-like shadow, etc. Among the remaining 139 lung cancers, 35 lesions (25.2%) presented as pure ground-glass nodules (GGNs), 64 lesions (46%) presented as part-solid nodules, and 40 lesions (28.8%) presented as solid nodules. The histology of the lung cancers was adenocarcinoma in 132 cases (89.8%), squamous cell cancer in 8 cases (5.4%), small cell cancer in 3 cases (2%), adenosquamous carcinoma in 1 case (0.7%), carcinoid tumor in 2 cases (1.4%), and NSCLC in 1 case (0.7%). The disease

stages were as follows: IA, 127 (86.4%); IB, 11 (7.5%); IIA, 2 (1.4%); IIB, 1 (0.7%); IIIA, 3 (2.0%); and IIIB, 3(2.0%). Among the 147 cancers, the number of incident cases was 10 in the SI ≥ 600 group (median follow-up period, 3.1 years), 3 in the SI < 600 group (median follow-up period, 2.9 years), and none in the never-smoker group (median follow-up period, 3.0 years). Lung cancer cases in smokers (including ex-smokers) occurred predominantly in men (male, 54; female, 12), while lung cancer cases in never-smokers occurred predominantly in women (female, 50; male,16) ($P < 0.0001$). The number of adenocarcinomas in smokers (including ex-smokers) was 29 in group A and 24 in group B, while the number of adenocarcinomas in never-smokers was 42 in group A and 23 in group B ($P = 0.274$). In the never-smoker group, the number of adenocarcinomas in men was 7 in group A and 9 in group B, while the number of adenocarcinomas in women was 35 in group A and 14 in group B ($P < 0.05$).

Conclusion: The number of invasive adenocarcinomas was not statistically different between smokers (including ex-smokers) and never-smokers. Never-smokers should also be a target population of CT lung cancer screening in Japan. Adenocarcinoma may be overdiagnosed among female never-smokers.

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Functional Genomics Approaches to Understand Genetic Susceptibility to Lung Cancer

Jiyeon Choi

National Cancer Institute, USA

What causes lung cancer? While smoking is a well-known determinant of lung cancer, only a fraction of smokers develops lung cancer, and up to 25% of lung cancer cases arise in never-smokers. Cancers are complex diseases where both inherent genetic factors and environmental exposures contribute to initiation and progression. Lung cancer also has genetic component, and genetic studies in families, twins, and general populations estimated 8-20% heritability for lung cancer[1–4]. In other words, 8-20% of the variation in lung cancer risk across different individuals could be explained by genetic factors, depending on the population and the method the effect was estimated with.

Consistent with these observations, studies of familial lung cancer cases where multiple family members develop lung cancer have identified rare but high-penetrance germline mutations including *EGFR* T790M and those in *TP53* predisposing to Li-Fraumeni syndrome[5,6]. However, these familial cases are very rare, and for most of the sporadic cases the effect of a single germline variant is considered very small. The hypothesis is that accumulation of multiple individually small-effect-size genetic variants in an individual could increase the individual's risk for lung cancer even if they have the same amount of environmental exposure, for example. How could we detect these small-effect-size genetic variants increasing lung cancer risk in the general population?

Genome-wide association studies (GWAS) is a powerful approach to detect an association between individual germline genetic variants and disease risk. The idea is to assess genotypes of all the common germline variants (e.g., minor allele frequency in the population > 1%) from tens of thousands of lung cancer cases and equivalent number of control individuals and run a regression between the genotype (i.e., minor allele count of 0, 1, or 2) and lung cancer status (i.e., cancer or no cancer) to determine the statistical significance of association. This analysis can be done for >1 million single nucleotide polymorphisms (SNP) in the human genome, and those SNPs that

reach genome-wide significance (e.g., $P < 5x10^{-8}$ based on Bonferroni correction for multiple testing of ~1 million SNPs) are declared as a genomic "locus" associated with lung cancer.

Indeed, GWAS during the last ~14 years in diverse populations identified more than 45 different genomic loci associated with lung cancer[7]. These findings suggested that several biological pathways may be important in genetic predisposition to lung cancer. For example, genomic loci were identified near the genes implicated in smoking behavior and nicotine metabolism, telomere biology, immune response, and DNA damage response pathways, among others[8]. While functional studies have provided some evidence to link the GWAS signals to biological pathways informing lung cancer etiology, linking the association signals to candidate causal variants and to target genes and their function is complex.

Currently, very few of ~45 lung cancer-associated loci have functional support, and this number will increase, as future GWAS are expected to increase the number of significant loci. One of the main challenges in GWAS follow-up functional analyses is that there are usually multiple (e.g., tens to hundreds) variants that are genetically linked (i.e., linkage disequilibrium or LD) that show similar association P-values. Because of LD, it is hard to pinpoint the candidate causal variant based on GWAS statistics alone. Further, >90% of GWAS variants are located in non-protein coding regions and considered to exert their function via gene regulation, and therefore finding target genes of the candidate causal variants is not simple (i.e., target gene might not be the nearest gene to the SNP with the lowest P-value). Moreover, function of the variants and target genes could be highly dependent on the cellular contexts including cell and tissue types as well as the presence of relevant exposures or stimuli.

While this complexity in gene regulation underlying lung cancer GWAS loci might make the number of experimental testings extremely high, various functional genomics tools and resources could enable simultaneous assessment of thousands of genetic variants to streamline this process. Our group at National Cancer Institute is adopting many of these tools to identify candidate causal variants and target genes from multiple lung cancer GWAS loci and characterize their functions to better understand the lung cancer etiology in diverse populations.

The first example of these efforts is applying massively parallel reporter assays (MPRA)[9] to identify functional variants conferring lung cancer risk from thousands of candidate variants. From three recent lung cancer GWAS[10,11], we investigated 42 genomic loci displaying genome-wide significant association with lung cancer risk (overall lung cancer, lung adenocarcinoma, or lung squamous carcinoma) in European populations of mainly smokers as well as East Asian populations including smokers and never-smokers. From these loci, we selected over 2,000 candidate variants

and performed MPRA to compare the effect of lung cancer risk and protective alleles of each variant on gene expression levels using RNA-sequencing. To maximize the chance to detect the variant function that could be context-specific, we incorporated two lung cancer cell lines representing lung adenocarcinoma and squamous cell carcinoma as well as a short-term exposure to a tobacco carcinogen, benzo(a)pyrene (BaP). Using this approach, we identified at least one functional variant showing allelic transcriptional activity from >80% of lung cancer loci.

While MPRA could reduce the number of candidate variants from each locus considerably, we further integrated functional annotation of the variant and the genomic region around the variant using lung-specific genome annotation datasets and nominated a small number of high-confidence variants. We observed that in most lung cancer loci, there were multiple equally functional variants tied by LD rather than a single prominent functional variant. We further found that a subset of functional variants associated with lung cancer risk displayed differences between cell types representing lung adenocarcinoma versus squamous cell carcinoma. In contrast, the short-term BaP exposure condition that we tested did not have significant effect in variant allelic function.

The second example of our work is investigating cell-type specific gene regulation through lung cancer-associated variants using single-cell approaches. Lung tissue has >50 different cell types[12], and lung histological subtypes arise from different types of epithelial cells in lung. Further, the roles of non-epithelial cells (e.g., immune cells) could be important in lung cancer etiology. To dissect cell-type and context-specific gene regulation underlying lung cancer susceptibility we are building a single-cell multiome dataset of normal lung tissue from smokers and never-smokers (n = 16) as well as single-cell expression quantitative loci (eQTL) dataset from never-smoking women (n = 120) in close collaboration with Dr. Eun Young Kim's group at Yonsei University. Our preliminary results show enrichment of epithelial cell populations in our samples as well as preliminary linkage between cell-type specific enhancer elements harboring GWAS variants and target gene expression levels.

Together our functional genomics approaches will help identify susceptibility genes contributing to lung cancer development, which could lead to better strategies for prevention, prediction, and therapy of lung cancer.

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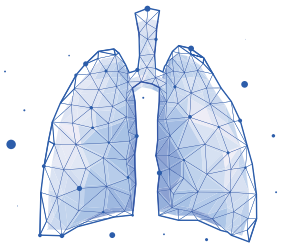

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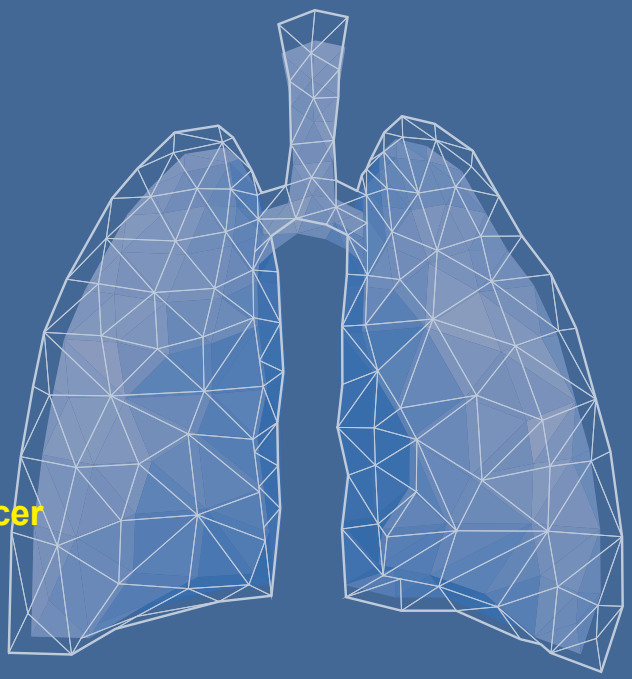


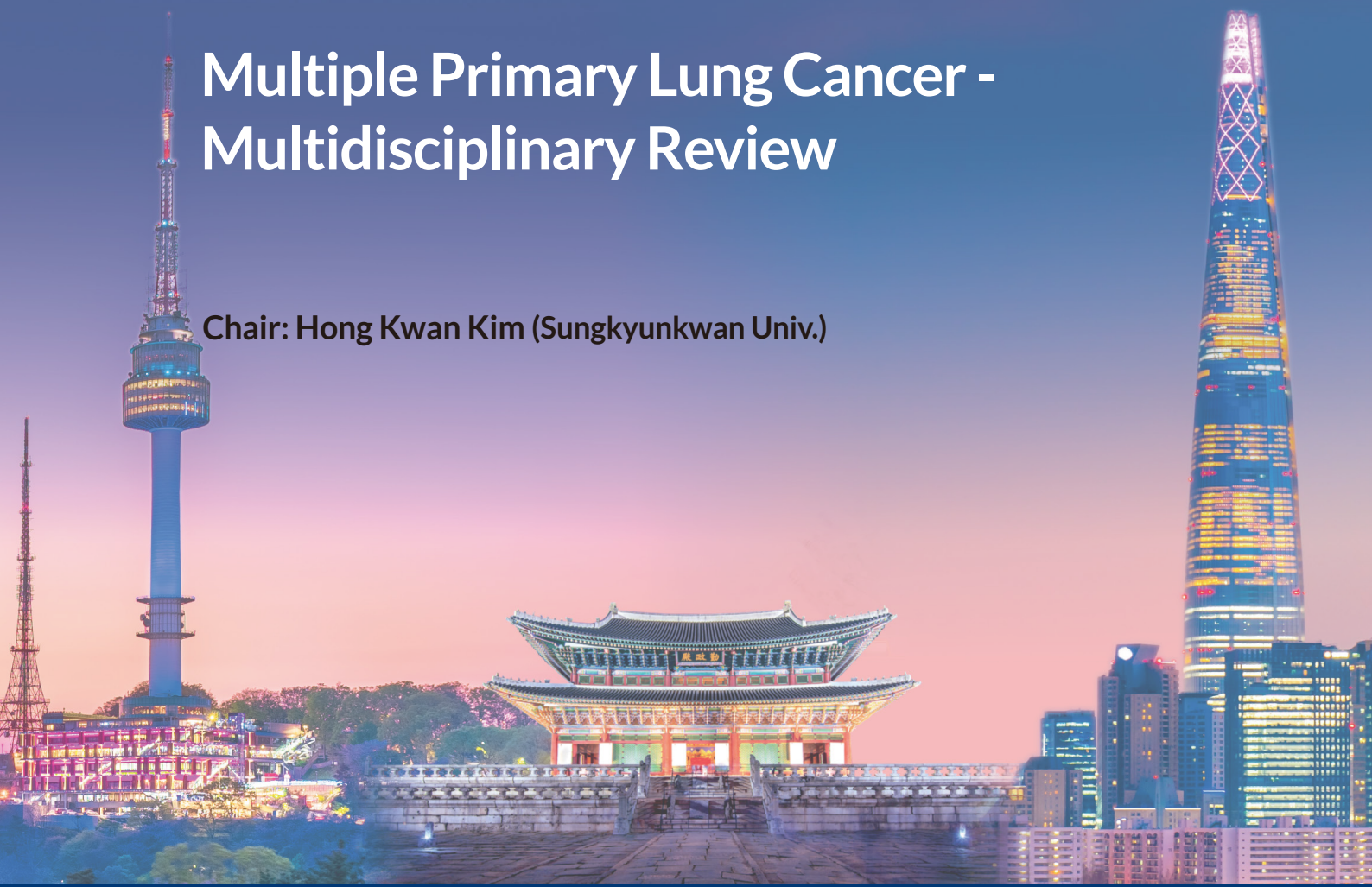
| November 11 (Fri), 2022 | Room B

10:30-11:50

Session VI (B)

Multiple Primary Lung Cancer - Multidisciplinary Review

Chair: Hong Kwan Kim (Sungkyunkwan Univ.)



Radiologic Characteristics of Multiple Primary Lung Cancer Including Ground Glass Nodules

Geewon Lee

Pusan National Univ., Korea

Lung cancers presenting with multiple lesions pose difficulties for staging and classification. Therefore, this lecture will provide an overview of updates on the radiologic characteristics and staging of lung cancer presenting with multiple lesions including ground glass nodules.

Pathologic Differentiation and Significance of Next-Generation Sequencing for Synchronous or Metachronous Lesions vs. Metastatic or Recurred Lesions in Lung Cancer

Jin-Haeng Chung

Seoul National Univ., Korea

An increasing number of lung cancers exhibit multiple lung nodules.

As the treatment strategies and prognosis of intrapulmonary metastasis (IPM) and multifocal primary lung cancer (MPLC) are different, distinguishing IPM and MPLC has clinical significance in improving the accuracy of prognosis assessment as well as therapeutic intervention. However, it might be difficult to distinguish between a MPLC and an IPM and the patients presenting with multiple lung lesions remain a diagnostic challenge with definite prognostic and therapeutic implications. There can be significant confusion and disagreement over how to manage these patients with multiple pulmonary nodules. As well as differences in morphologic features and immunophenotype between multiple pulmonary carcinomas, much is not well understood about their molecular differences or commonalities and many questions are still unanswered.

In 1975, Martini and Melamed published their recommendations on the diagnosis of multiple lung tumors based on conventional histopathological features.

In 2009, Girard et al. reported a comprehensive histologic assessment pursuing the same diagnostic goal that included a semi-quantitative grading system evaluating growth patterns and cytologic features. They were the first researchers who used genomic features in combination with a histologic assessment to establish tumor clonality.

Recently, next-generation sequencing (NGS) has been widely used in the medical practice and research field which enables deeper and more comprehensive approach in the cancer research. Several researchers used NGS to distinguish MPLC from IPM based on genomic characteristics and found that MPLC had no common genomic alterations, but IPM did, so that they could dis-

tinguish MPLC from IPM. Increasing evidence suggests that NGS techniques offer the possibility of comparing multiple tumors on a genomic level.

In this session, comprehensive analysis of the genetic characteristics of MPLC and IPM using NGS will be presented to effectively distinguish MPLC from IPM.

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Surgical Strategy for Multiple Primary Lung Cancer

Alan D. L. Sihoe

Gleneagles Hong Kong Hospital, Hong Kong

Traditionally, the appearance of more than one tumor in the lungs in a patient with non-small cell lung cancer (NSCLC) suggests that lung metastasis has occurred and that the patient is not a candidate for surgery. However, it was recognized almost 50 years ago that in a small subset of patients, each tumor focus may be an individual primary cancer rather than metastasis. Clinical evidence over the years has now confirmed that in such patients with Multifocal NSCLC, if each focus is treated surgically as an independent early-stage lung cancer, then good oncological outcomes may be achieved.

When identifying such patients with Multifocal NSCLC, key considerations include: histological confirmation of NSCLC; meticulous staging to exclude nodal metastasis; and identification of a ground-glass opacity (GGO) component within the tumors. Other considerations have been suggested to include the size of the lesion(s) and/or the presence of patient symptoms. When Multifocal NSCLC has been identified, it is now generally recognized that sublobar resection may be considered. This is to better preserve lung function when multiple lesions need to be resected, and also to anticipate the possibility of future metachronous multifocal disease requiring further surgery.

This presentation gives an overview of this niche but clinically important topic that all lung cancer surgeons should become well familiarized with.

Recent Advances in Radiotherapy for Multiple Primary Lung Cancer

Si Yeol Song

Univ. of Ulsan, Korea

Stereotactic Ablative Radiotherapy (SABR), also called stereotactic body radiation therapy (SBRT) is a type of radiation therapy with delivery of extremely high-dose radiation per treatment in a short period of time. Early-stage lung cancer or metastatic lung cancer can be ablated with minimal toxicity even in patients with reduced performance. Currently, SABR is recognized as an effective treatment modality for early-stage lung cancer in medically inoperable patients and as an alternative in some selected operable patients. There is a lot of research on the superior results of SABR for early-stage lung cancer but is usually limited to solitary tumor.

Multiple primary lung cancer (MPLC) is rising challenge in patients with impaired cardiopulmonary function, because its incidence is increasing for various reasons; increased life expectancy, improved treatment results and improved diagnostic technology or screening program. Multiple SABR has been effectively delivered to multiple metastatic lung cancer as synchronous or metachronous treatment. Although reduced lung function must be considered, multiple SABR can be safely applied in patients with MPLC. Combined SABR and surgery for each tumor is also an excellent choice according to characteristic of tumor or patient. For more effective SABR with minimal toxicity, active surveillance for lung cancer in high-risk patients may be helpful.

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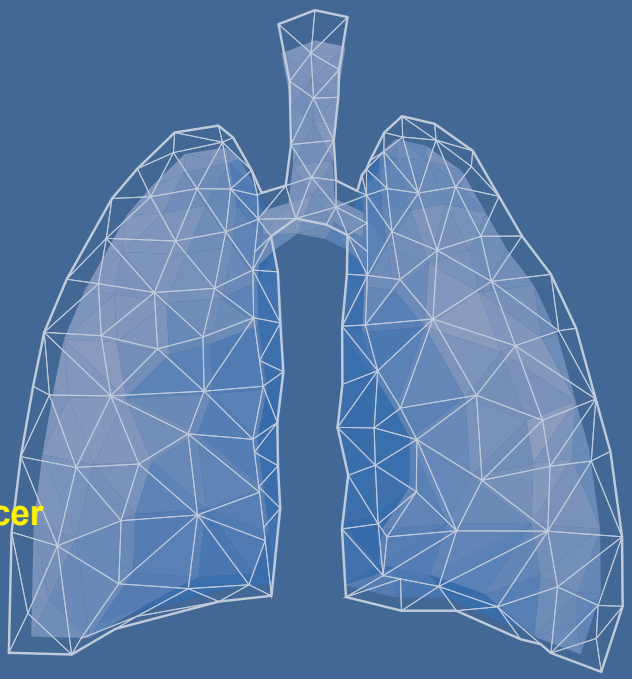

| November 11 (Fri), 2022 | Room B

13:00-14:40

Session VII (B)

Optimal Models for Lung Cancer Research

Chair: Kye Young Lee *(Konkuk Univ.)*

Lung Cancer Genomic Evolution during the Establishment and Propagation of Patient-Derived Xenograft Models

Robert E. Hynds

Univ. College London, UK

Background: Since the frequency of cell culture establishment in our non-small cell lung cancer (NSCLC) cohort was very low,[1] we investigated the establishment of patient-derived xenograft (PDX) models. PDX models have become key pre-clinical models in cancer biology.[2] They are thought to mimic tumor biology more closely than traditional cancer cell lines as a consequence of their *in vivo* heterocellularity and cell-matrix interactions, their 3D architecture and their relatively recent derivation. The genomic fidelity of PDX models is integral to their applications in both basic research and in translational medicine, and has been the subject of debate in the literature.[3-5] We created multi-region PDX models from patients enrolled in lung TRACERx – a study of the evolutionary dynamics of NSCLC that uses a multi-region deep whole-exome sequencing (WES) approach[6,7] – using spatial sampling to better understand the histological and genomic fidelity of the PDX approach.

Methods: We transplanted regional NSCLC tumor tissue subcutaneously into immunocompromised NSG mice. PDX models and matched patient tumor regions were subjected to whole exome sequencing.

Results: 145 regional tumor samples from 44 patients were attempted, resulting in 63 xenografts. Of these, 47 regional xenografts were NSCLC-derived, while 16 were B-cell lymphoproliferative disease. Cryopreservation of tumor samples prior to injection did not alter PDX take rates. Histologically, broad similarity was observed between PDX models and corresponding patient tumor regions. Analysis of WES data revealed that PDX models are frequently monoclonal, but retain genomic similarity to the region of origin compared to spatially distinct tumor regions. On-going evolution occurs within PDX models but contributes less to genomic divergence than initial bottlenecking events. Specific mutational signatures, such as those caused by mismatch repair deficiencies or APOBEC mutagenesis, can define the evolutionary trajectories of individual PDX models.

Conclusions: Overall, our study demonstrates the feasibility of systematic multi-region PDX derivation and suggests that multiple spatial sampling of tumors could improve PDX take rates and generate PDXs that represent the intratumor diversity of heterogenous NSCLCs.

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A Minimal Sufficient Condition for the Development of K-Ras-Activated Lung Cancer

You-Soub Lee[1], Ja-Yeol Lee[1], Jung-Won Lee[1], Dohun Kim[2] and Suk-Chul Bae[1]

[1]Department of Biochemistry, School of Medicine and Institute for Tumour Research, Chungbuk National University, Cheongju, South Korea; [2]Department of Thoracic and Cardiovascular surgery, School of Medicine, Chungbuk National University and Hospital, Cheongju, South Korea

The aberrant persistence of RAS activity resulting from heterozygous oncogenic mutation has been implicated in various malignancies. Because the p53 pathway plays key roles in cellular defences against oncogenic RAS, restoration of the p53 pathway has long been considered as a promising therapeutic strategy. However, in *Kras*-activated mouse lung tumour models, restoration of *p53* fails to eliminate low-grade lung tumours due to the failure of $p19^{Arf}$ (*Arf*) induction[1,2,3]. These results raised the question of why the Arf–p53 pathway is not activated in *Kras*-activated low-grade lung tumours. Recently, we reported that Runx3 recognises aberrant persistence of oncogenic Ras signal at the Restriction-point and induces apoptosis by activating the Arf–p53 pathway[4]. *Runx3* is silenced in nearly all *Kras*-activated human lung cancers[5]. Therefore, it is possible that *Runx3* silencing is responsible for failure of the Arf–p53 pathway activation in *Kras*-activated lung cancers. In this study, we investigated this possibility using mouse lung cancer models and found that *Runx3* restoration in established *Kras*-activated low-grade mouse lung tumours activated the Arf–p53 pathway, eradicated tumours and markedly increased survival. The therapeutic benefit of *Runx3* restoration was markedly decreased by deletion of *p53*, indicating that the effect was mediated through the Runx3–Arf–53 pathway. Our observations identify Runx3 inactivation and K-Ras activation as a minimal sufficient condition for the development of *K-ras*-activated lung cancer. These results also suggest that *Runx3* could be used as a therapeutic tool for the treatment of *K-ras*-activated lung cancers.

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Development of a Novel Mouse Model for Improved Evaluation of *in vivo* Anti-Cancer Effects: Targeted Therapy and Immunotherapy

Jin Kyung Rho

Univ. of Ulsan, Korea

Targeted therapies and immunotherapy for lung cancer have been hot issues in the oncology field for the past 20 years. During this time, identification of oncogenic driver alteration has led to the development of new targeted drugs. After anti-PD-1/PD-L1 immunotherapy, other immune checkpoint antibodies are being extensively investigated in clinical trials. However, various issues limit the use of these drugs. In the case of targeted therapies, the emergence of acquired resistance to existing drugs requires continuous development of new drugs. Indeed, 3rd-generation EGFR-TKIs were previously developed, and 4th generation EGFR-TKIs are currently being developed to overcome C797S-mediated resistance. Clinically meaningful animal models are continuously needed for the development of these drugs. In the case of immunotherapy, the clinical benefit of anti-PD-1/PD-L1 strategies is still limited to a minority of patients, reflecting the need to identify predictive biomarkers of response. However, models to study the mechanisms of immunotherapy response are still rare. Here, we will present the generation of genetically engineered mice for the development of new 4th generation EGFR-TKIs. The system used for generating these mice can be applied to other oncogenic proteins and to investigate tumorigenesis. In addition, we will present the generation of humanized mice for research on the mechanisms of immunotherapy. In conclusion, our presentation will provide some suggestions to help you investigate personalized therapies in lung cancer.

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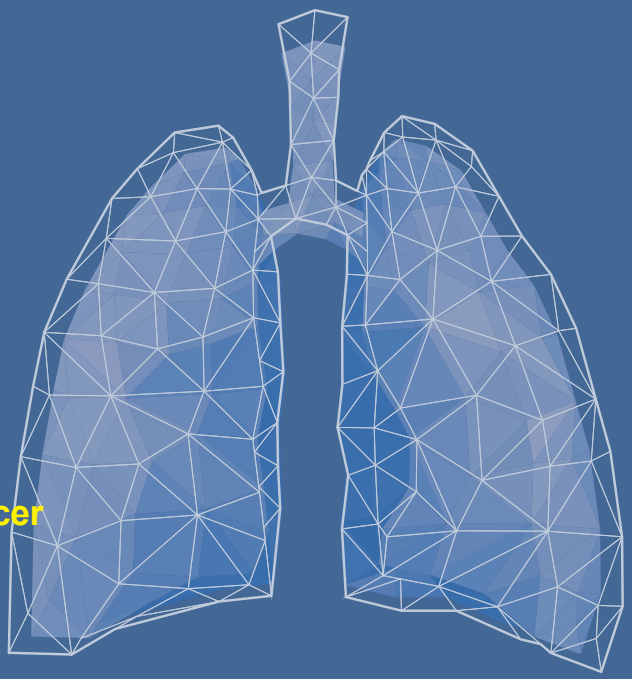

| November 11 (Fri), 2022 | Room B

15:00-16:40

Session VIII (B)

Cellular Immunotherapy

Chair: Sung-Yong Lee *(Korea Univ.)*

Clinical Application of Natural Killer T Cells to Cancer Immunotherapy

Shinichiro Motohashi

Chiba Univ., Japan

Recent advances in cancer immunotherapy have clearly shown dramatic clinical benefits in some advanced cancer patients. The clinical benefit of immune checkpoint inhibitors has thus provided proof of the concept for the efficacy of immunotherapy not only in immune responsive tumors, such as melanoma and renal cell carcinoma, but also in non-small cell lung cancer (NSCLC), which was previously considered non-responsive. On the other hand, only a limited number of patients successfully responded to immunotherapy; therefore, it remains insufficiently effective for many patients. Combination therapies will likely be required to enhance the anti-tumor activity of immune therapy.

Invariant natural killer T (iNKT) cells are unique, innate lymphocytes that have an important role in tumor immunity. iNKT cells express invariant T cell receptors (TCRs) to recognize their cognate glycolipid antigen, including α-galactosylceramide (αGalCer) presented on CD1d. Activated iNKT cells produce massive amounts of cytokines such as IFN-γ and TNF-α, and exert cytotoxicity by secreting granzymes and perforin. iNKT cells play an essential role in anti-tumor immunity; they directly target tumors and indirectly activate NK cells or cytotoxic $CD8^+$ T cells (adjuvant effects). Currently, we focus on the development of iNKT cell-targeted immunotherapy for NSCLC and head and neck cancer (HNC) to improve the clinical outcome.[1] Previous clinical studies have shown the intravenous injection of α-galactosylceramide (αGalCer)-pulsed antigen presenting cells (APCs) induced the activation of endogenous iNKT cells and iNKT cell-dependent responses.[2] Moreover, an increase in the number of IFN-γ producing cells in peripheral blood mononuclear cells has been shown to be associated with prolonged survival. A dramatic infiltration of iNKT cells and accumulation of conventional T cells in the tumor microenvironment was also observed after αGalCer-pulsed APCs.[3]

Based on these results, the phase II clinical trial of αGalCer-pulsed APCs for NSCLC was designed

under the Advanced Medical Technology System Regulation by the Japanese Ministry of Health, Labour and Welfare.[4] The patients with advanced or recurrent NSCLC who completed the first-line chemotherapy were enrolled. Out of 35 enrolled patients, 32 cases (91.4%) completed the therapy. The administration of α GalCer-pulsed APCs was well tolerated and was accompanied by the successful induction of iNKT cell-dependent immune responses. The estimated median survival time (MST) of the 35 cases was 667 days, which was considered to achieve the primary endpoint.

Previous early-phase clinical trials showed that the combination therapy with ex vivo expanded iNKT cells and α GalCer-pulsed APCs had a clear anti-tumor immune response. However, the number of iNKT cells was very small in peripheral blood, especially in patients with cancer; thus, it was difficult to prepare enough iNKT cells for adoptive transfer. Then we succeeded in establishing a robust protocol to generate iNKT cells in vitro via induced pluripotent stem cells (iPS cells), which allowed us to ensure the sufficient expansion of iNKT cells. iPS cell-derived NKT cells (iPS-NKT cells) can be activated by ligand-pulsed APCs to produce a large amount of IFN-γ upon activation. These iPS-NKT cells exhibit better cytotoxic activity against various tumors in vitro and in vivo. To assess the anti-tumor efficacy of the combination therapy of iPS-NKT cells and α GalCer-pulsed APCs preclinically, we injected human iPS-NKT cells and mouse α GalCer-pulsed APCs intratumorally in patient-derived lung cancer xenograft NSG mice. As a result, the combination therapy suppressed tumor size compared with no treatment, while the iPS-NKT monotherapy did not. Restimulated iPS-NKT cells are expected to exert potent adjuvant effects and improve anti-tumor response.

Based on these preclinical examinations, a phase I study of iPS-NKT cell monotherapy started in 2020 for patients with HNC refractory to standard treatment. Once the safety profiles of iPS-NKT cell monotherapy are confirmed, we will plan the clinical trial of the combination therapy with iPS-NKT cells plus α GalCer-pulsed APCs in patients with NSCLC in the future.

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Potential Role of Non-Genetically Modified Natural Killer Cells with Enhanced Cytotoxicity in Combination with Either Immune Checkpoint Inhibitors or Anti-Tumor Monoclonal Antibodies in Lung Cancer

Paul Y. Song[1], Yongman Kim[2]

[1]NKGen Biotech Inc., Santa Ana, CA, [2]NKMax Seoul, South Korea

Background: Natural killer (NK) cells play a key role as the main effector cells toward cancer in innate immunity. Thus, a leading approach is to boost NK-cell mediated anti-tumor activity using adoptive transfer of ex vivo activated NK cells. NK cells have always been challenging to grow ex vivo especially when derived from heavily pretreated donors, thus most have focused on universal allogenic donor derived products. SNK is a first-in-kind, non-genetically modified NK cell product with significant anti-tumor cytotoxicity and over 90% expression of CD16, NKG2D, NKp46, and DNAM-1, that can be consistently produced as an allogenic or even autologous product from heavily pre-treated cancer patients (pts). While most if not all NK cell therapy has focused on liquid malignancies, SNK has been found to have strong activity against both liquid and solid tumors preclinically. NK cells play a significant role in the ADCC (antibody dependent cellular cytotoxicity) pathway and have also been implicated in the antitumor response to immune checkpoint inhibitors (ICIs) with some evidence suggesting a role in PD-L1 negative tumors.

Methods: Here we discuss the overall prognostic role of NK cells in Lung Cancer as well as provide a detailed review our clinical and pre-clinical experience to date using SNK in combination with ICIs and antibodies, and specifically how these combinations could be applied to the treatment of lung cancer.

Engineered Cancer Immune Cell Therapy (CAR-T Cell Therapy)

Hun Ju Lee

UT MD Anderson Cancer Center, USA

Adoptive T cell therapy is a type of cellular immunotherapy in which T cells are genetically engineered to target and eradicate tumors. This technology has emerged as an exciting new approach for cancer therapeutics. This presentation will go over the history and development of chimeric antigen receptor (CAR) T cell therapy as well as the remarkable efficacy it has demonstrated in hematologic malignancies. It will also touch on CAR-T therapy's novel toxicities and logistical challenges. Furthermore, the resistance mechanisms will be discussed in addition to new approaches for improving CAR-T. The presentation will conclude with an overview of developments and obstacles of CAR-T therapy in solid tumors and provide a forecast of where the field is heading in the next decade.

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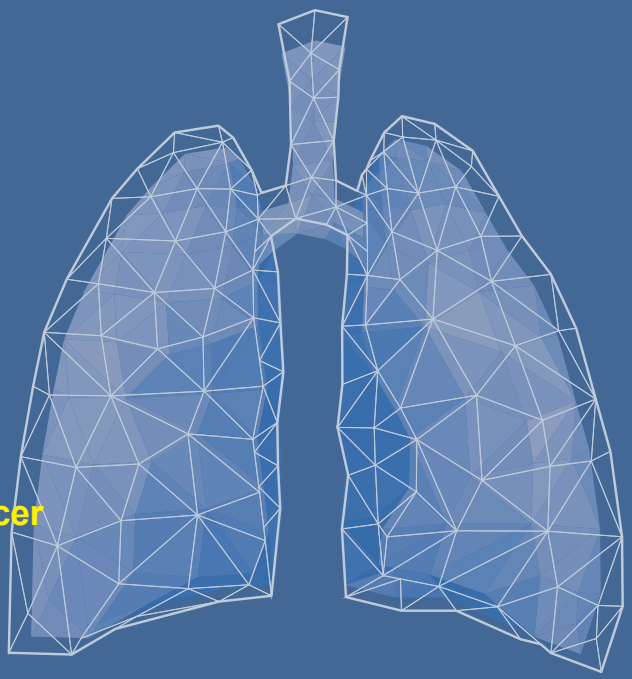

| November 11 (Fri), 2022 | Room B

16:50-17:40

Satellite Symposium IV (B)

[PFIZER]

Chair: Ji-Youn Han *(National Cancer Center)*

The Evolving Treatment Landscape of ALK+Non-Small Cell Lung Cancer with Lorlatinib

Sehhoon Park

Sungkyunkwan Univ., Korea

ALK+ non-small cell lung cancer (NSCLC) is observed around 5% of population and the incidence of brain metastases is 25 to 40%. In randomized phase 3 trial demonstrated that second-generation ALK (tyrosine kinase inhibitor) TKIs provided better efficacy results compared with first-generation crizotinib in first line setting. However resistance invariably arise and often recurrent disease develops particularly in the CNS. Therefore, there was unmet need to develop target treatment option with a broader coverage against common secondary ALK resistance mutation including G1202R, better CNS penetrance and maintenance of intracranial activity.

Lorlatinib is a novel, third generation ALK TKI that has been designed to address the two major unmet needs. From the global registry trial, B7461001 study, patients with Group B (EXP3B-5) who experienced treatment failure after one or more second generation ALK TKI were evaluated for the clinical outcomes. Among the 138 patients eligible for the analysis, objective response rate was observed in 39.6% of the patients, showing median duration of response of 9.6 months, progression-free survival of 6.6 months, and overall survival of 20.7 months. Intracranial response rate was 46.1% and median duration of response was 12.4 months. This finding was also reproduced real-world patients and promising CNS efficacy was also shown in 1st line phase III trial, CROWN study.

Based on the current clinical evidence, lorlatinib is the standard treatment in 2nd generation ALK TKI failed patients and also applicable to the treatment naïve ALK+ non-small cell lung cancer patients.

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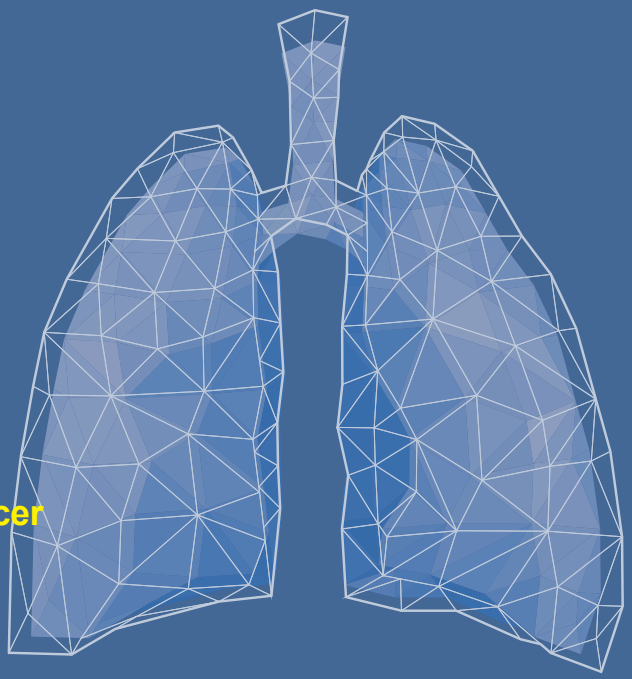


| November 11 (Fri), 2022 | Room C

08:50-10:30

Session V (C)

KALC-HIRA Joint Symposium: Reimbursement of Anticancer Agent against Lung Cancer in Korea: Current Status and Future Directions

Chair: Young Chul Kim *(Chonnam National Univ.)*

The Reimbursement Decision Process of Anticancer Agents in Korea

Kook Hee Kim
HIRA, Korea

약제는 행위, 치료재료와 달리 '선별급여' 제도를 적용하고 있어 식약처 허가 이후 보험등재 신청 없이도 비급여로 사용 가능하나, 고가인 항암제 특성 상 급여여부가 접근성을 결정하는 중요 요인이 되고 있다.

항암제 신약의 등재절차는 심평원의 급여적정성 평가, 제약사와 공단의 협상, 심평원장 공고의 3단계로 볼 수 있다.

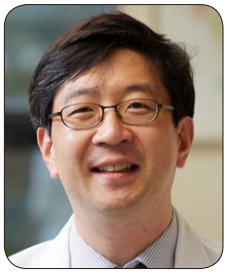
'급여적정성'은 암질환심의위원회에서 심의한 급여범위를 토대로 약제급여평가위원회에서 효과 등 임상적 측면에서의 유용성, 비용효과성, 재정영향 등을 고려하여 평가하는데, 이 중 비용효과성은 '효과 대비 비용의 적절성'을 판단하는 것으로, 효과 등이 개선된 경우 경제성평가를 통해 제약사가 이를 입증하도록 하고 있으며 근거자료 생성이 곤란한 일부 약제에 대해서는 경제성평가를 생략할 수 있는 예외적인 절차를 두고 있다.

이 과정에서 제약사는 위험분담제 적용을 요청할 수 있으며 심평원은 이를 포함하여 최종적인 급여적정성 여부를 평가한다.

급여가 적정하다고 평가된 약제는 이후 공단과 제약사간 연간 예상사용량, 가격협상, 필요 시 위험분담 조건 등에 대하여 협상을 진행하고 협상이 체결된 약제에 대하여 복지부는 급여 상한금액을 고시하고 심평원장은 급여범위(급여기준)를 공고하게 된다.

항암제에 대하여는 보장성강화 차원에서 2005년 암질환심의위원회를 별도 구성하고, 일반 약제 급여기준과 달리 복지부장관 고시가 아닌 심평원장 공고로 하여 보다 전문적인 집중검토가 가능하도록 절차를 마련하였고, 2013년12월 위험분담제도, 2015년5월 경제성평가 생략 도입 등을 통해 보장성 강화 노력을 기울여 왔다,

다만 맞춤형, 유전자치료제 등 혁신적인 항암제 개발이 가속되고 있고 등재 이후 적응증 추가가 계속 이루어지고 있는데 임상적, 비용적 불확실성도 더욱 커지고 있는 상황인 점을 고려 시, 이제는 신속한 환자 접근성 제고뿐 아니라 치료효과와 연동한 새로운 지불제도 마련 및 실제 사용자료 수집을 통한 사후관리가 필요한 시점이라 하겠다.



The Current Reimbursement Status of Lung Cancer Treating Agents in Korea

Dong-Wan Kim

Seoul National Univ., Korea

Recently, the number of newly approved drugs for the treatment of lung cancer has rapidly increased. It is important to improve the accessibility to these new agents to obtain better clinical outcomes for lung cancer patients. I will discuss the current status of new drug approval and reimbursement in Korea. In addition, I will suggest some possible ways to facilitate communication between the health authorities and physicians in the interpretation of cancer drug reimbursement standards.

Role of Companion Diagnostics in Anticancer Drug Reimbursement Decision

Yoon La Choi

Sungkyunkwan Univ., Korea

바이오마커를 통한 항암 치료요법의 선택은 더욱 강력한 효과를 가져올 수 있다. 아울러 이를 통해 특정 치료제에 대한 안전성과 효과가 입증된 환자군을 선별하는 데는 동반진단이 필수적이다. 따라서 동반진단은 정밀 의료 시대가 가능하게 한 중요한 역할을 하고 있으며, 바이오마커를 통한 항암치료제의 연구와 적용을 궁극적으로 제도권하에서 가능하게 한 것이 동반진단이다.

현재 가장 활발하게 동반진단 개발이 진행되는 분야는 항암신약 분야로, 이와 동반진단을 동시에 개발하면 임상시험 대상자 축소와 임상시험 비용을 감소할 수 있다. 특히 신약 허가 가능성과 최종 치료 효과를 높일 수 있다. 이에 따라 항암제를 비롯한 신약개발을 하는 제약사들은 진단회사와 공동으로 동반진단을 개발하는 추세다. 따라서 다국적 제약사들도 독립적으로 진단기기를 개발하기도 하지만, 대부분 진단 전문회사들과 공동으로 개발하고 있다. 국내에서도 신약개발제약회사와 진단기기 업체가 신규 약물 개발 초기 단계에서부터 전략적 파트너십 통해 협력모델을 시도하고 있다.

국내에서 동반진단이 적용되고 있는 긍정적인 면과 함께, 많은 신약들이 동반진단과 함께 허가,승인이 진행되면서 실제 진료 현장에서 어려움과 적용의 문제점들이 발생하고 있다. FDA 에서 허가된 동반진단이 국내에 적용이 어렵거나, 가격이 너무 비싸서 국내 급여여건에서 사용이 어렵기도 하다. 약물 처방을 하기 위한 필요전제조건으로 지정되어 있는 상태에서 동반진단을 사용할 수 없다는 것은 매우 황당한 상황이라고 할 수 있겠다. 또한, 다양한 약물이 같은 동반진단 방법을 사용하지만, 그 기준이나 판독법이 다름으로써 진단 현장에서는 혼란과 불편함을 유발하고 있다. 더불어, 동반보조진단 (약물의 반응성을 예측하지만, 약물처방에 필수적이지는 않은 경우) 은 약물을 처방하기 위해서 필수적이지 않지만, 국내에서는 급여의 조건으로 지정되어 있어, 허가 관점에서는 동반진단이 되어 버리고 있다. 이러한 복잡한 상황들이 의료진과 환자들에게 큰 혼란과 불편함을 과중시키고 있다.

이러한 문제점은 국내 뿐 아니라 전 세계적으로 인지되고 있고, 해결점들을 논의하고 있다. FDA 에서는 “Specific group of oncology therapeutic products” 에 한가지 동반진단을 허가하는 제도가 시행되었으며, 국내에서도 적용될 예정이다. 바이오마커의 검사는 바이오마커 자체 뿐 아니라 검출하는 방법과 기술, 검출한도의 정의, 검출결과의 해석 등에 따라 그 결과가 모두 달라질 수 있다. 하나하나의 결과가 환자의 진단과 치

료에 미치는 영향이 점점 커지고 있는 의료 현실에서 충분간 근거를 가지고 검증을 거친 허가 및 승인을 만족한 동반진단을 사용하는 것을 근본으로 하면서, 현실적인 어려움을 합리적으로 보완할 수 있는 방안 마련이 필요하겠다.

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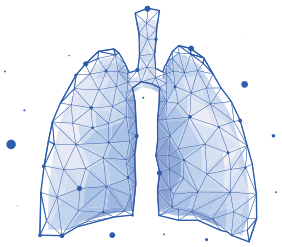

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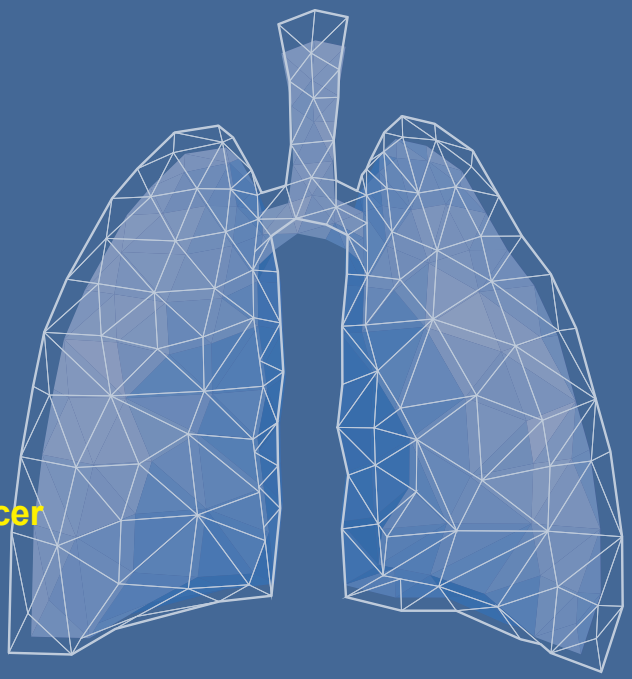

| November 11 (Fri), 2022 | Room C

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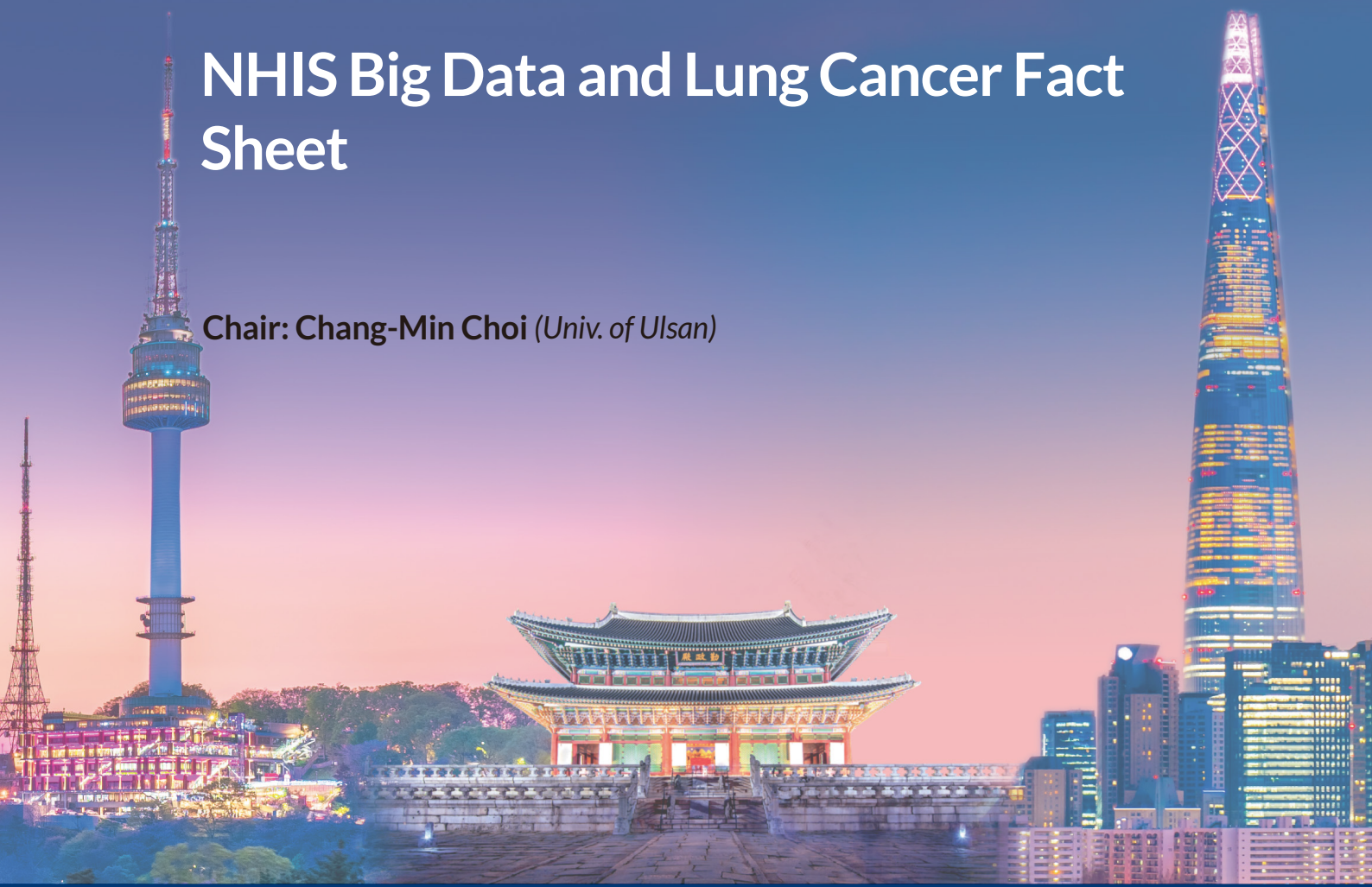
Session VI (C)

NHIS Big Data and Lung Cancer Fact Sheet

Chair: Chang-Min Choi *(Univ. of Ulsan)*



Advanced Bronchoscopic Techniques for the Peripheral Lung Cancer

Young-Eun Kim

National Health Insurance Service, Korea

국민건강보험공단은「국민건강보험법」제14조 및「노인장기요양보험법」제48조에 근거하여 전 국민을 대상으로 가입자와 피부양자의 자격관리, 보험료 부과 및 징수, 보험급여 관리 및 비용 지급, 건강검진, 장기요양 관련 업무 등을 수행하고 있다. 이 과정에서 수집·축적된 자료를 가공하여 연구용DB(국민건강정보DB)로 구축하였으며, 전 국민의 자격 및 보험료, 일반·영유아·암 건강검진 결과, 진료내역, 노인장기요양보험 자료, 요양기관 현황, 암 및 희귀난치성질환자 등록정보 등을 포함하고 있다.

국민건강정보DB는 업무를 위해 수집된 개인정보들을 가명처리하여 연구 및 정책지원을 목적으로 일반 연구자들에게 제공되며, 체계적인 연구·분석을 위하여 2002년부터 현재까지의 자료가 개인별 연계가 가능한 형태의 DB로 구축되어 있다. 뿐만 아니라 전 국민 건강보험 빅데이터를 기반으로 수요도가 높은 데이터를 표본 추출한 표본연구DB도 구축되어 있다. 표본연구DB는 전 국민을 대표할 수 있도록 구성된 표본코호트DB와, 건강검진코호트DB, 노인코호트DB 3종으로 구성되어 있다. 표본코호트DB는 2006년 1년간 건강보험 및 의료급여 수급권자 자격을 유지한 국민을 대표할 수 있도록 성, 연령군, 가입자 구분 및 보험료 분위, 거주 지역에 따라 층화계통추출법을 통해 대상자를 추출하였다. 이렇게 추출된 약110만명(전국민의 약 2%)에 대하여 2002년부터 현재까지 사회·경제적 현황(자격 및 보험료, 장애, 사망), 의료이용 현황(진료 및 건강검진), 요양기관 현황, 장기요양 이용 현황으로 구성되어 있으며, 사망자의 경우 통계청의 사망원인이 연계된 형태로 구성되어 있다. 건강검진코호트DB는 2002년 자격유지자 중 2002~2003년 40~79세 일반건강검진 수검자중 약 51만명에 대한 데이터로 구성되어 있고, 노인코호트DB는 2002년 자격유지자 중 만 60세 이상 대상자 약 55만명에 대한 데이터로 구성되어 있다. 특히 노인코호트DB의 경우 노인장기요양서비스 현황에 대한 정보도 추가로 포함되어 있다.

건강보험공단에서는 규격화된 표본DB와는 별개로 개별 연구에서 필요로 하는 데이터를 맞춤형으로 제공(맞춤형DB)하고 있다. 말 그대로 맞춤형 DB는 개별 연구에서 대상으로 하는 대상자 전수를 제공하고자 하고 있으나, 대상자 규모나 분석 데이터의 크기가 지나치게 큰 경우 연구자와의 상의를 통해 적정 수준의 데이터 규모로 조정하여 제공한다. 이 외에도 2022년부터는 질병관리청의 코로나19 확진, 백신 접종 데이터와 연계한 DB를

제공하고 있다.

건강보험 빅데이터는 단일 보험자로서 전 국민에 대한 전수 자료를 보유하고 있으며, 전 국민의 사회경제적 수준 및 전체 의료공급자의 의료서비스가 포함되어 일반화에 용이한 장점(대표성)을 가지고 있다. 또한 행위별 수가제에 기반한 상세 진료행위 및 처방내역을 보유(완결성)하고 있으며, 개인식별번호(주민등록번호)를 통해 코호트 자료를 구축 할 수 있다. 뿐만 아니라 제한적 또는 실험적 정보가 아닌 현실이 반영된 자료이며, 실제로 측정된 BMI, 콜레스테롤, 혈압 등 국가건강검진 자료를 활용할 수 있는 장점이 있다. 반면, 비급여 항목이 포함되어 있지 않으며, 진료비 상환을 위한 업코딩(up-coding), 건강 향상 및 수술성공여부와 같은 의료행위의 결과변수가 포함되어 있지 않다는 단점을 가지고 있다.

국민건강정보DB는 국민보건 향상, 사회보장 증진 등 사회적 가치 실현을 위한 공익적 목적으로 제공하고 있으며, 연구계획서와 IRB 심의 결과, 데이터 신청서를 기반으로 공단에서 운영하고 있는 국민건강정보자료제공심의위원회의 심의를 통해 제공여부를 결정하고 있다. 심의위원회에서는 공익 및 학술목적의 연구 여부, 제3자 권익 훼손 여부, 개인정보보호법 위한 여부 등을 기준으로 자료제공여부를 판단한다. 맞춤형 연구의 경우 공단에서 운영하고 있는 '건강보험 빅데이터 분석센터'에서 연구·분석이 가능하며, 표본DB 연구의 경우 개인 PC로 사전 지정된 원격 룸에서 연구·분석이 가능하다. '건강보험 빅데이터 분석센터'는 공단 지역본부(서울, 수원, 세종, 전주, 광주, 원주, 청주, 대구, 부산) 및 분석센터(서울대, 연세대 등)에서 운영하고 있으며, 국민건강정보DB의 안전한 제공을 위해 폐쇄망 분석용PC가 설치되어 있다.

국민건강정보DB의 신청과 자세한 안내사항은 '건강보험자료공유서비스' 홈페이지를 참고하기 바란다(nhiss.nhis.or.kr).

Clinical Research Using NHIS Big Data: Present and Future

Jaehun Jung

Gachon Univ., Korea

Introduction of Lung Cancer Fact Sheet Project

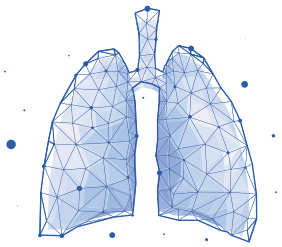
Wonjun Ji

Univ. of Ulsan, Korea

The Korean National Health Insurance (NHIS) data sharing service provides the detailed information on the health service utilization of the insured person, and it is an excellent data source comparable to the nationwide cohort. In particular, it shows high diagnostic reliability in estimation some specific diseases such as malignant tumors. In addition, the NHIS big data is possible to analyze the cost of medical examinations, procedures, surgeries, and medications that are covered by national insurance service for each disease. Furthermore, it also has the advantage of being able to evaluate the data on the entire treatment period of an individual from diagnosis to death.

On the other hand, the NHIS database is impossible to analyze uninsured items. And then, the NHIS database is difficult to access the cause of death in detail. When the researcher wants to do clinical study for lung cancer using NHIS bid data, the fact that the exact clinical stage cannot be known is a fatal disadvantage. However, some previous study was proved that the clinical stage could be presumed using operational definition according to treatment pattern for patients with lung cancer.

The research committee of the Korean Association of Lung Cancer (KALC) has been conducting the lung cancer fact sheet (LCFS) project using the NHIS big data since 2021, considering these advantages and disadvantages of NHIS database. The purpose, progress, and future plans of these LCFS projects will be presented in this part.



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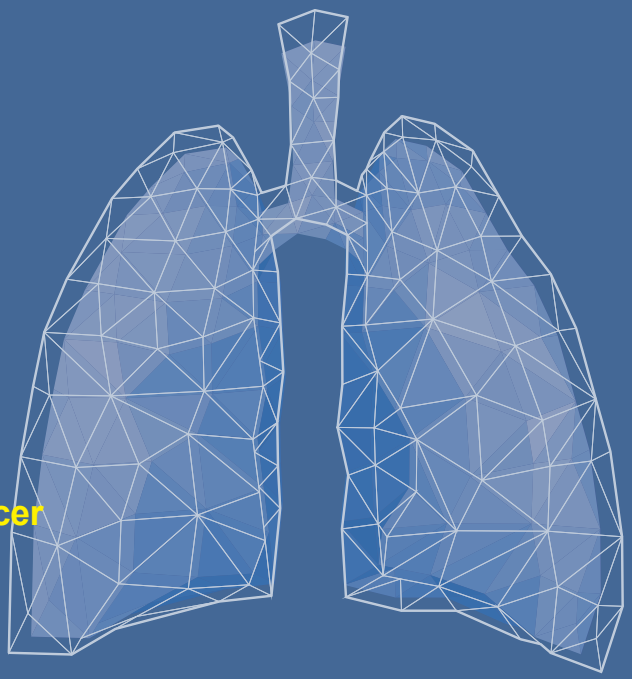

| November 11 (Fri), 2022 | Room C

13:00-14:40

Session VII (C)

Immunotherapy

Chair: Dae Ho Lee *(Univ. of Ulsan)*

Metastatic Non-Small Cell Lung Cancer: How Can We Improve Immunotherapy in Metastatic Disease

Herbert H. Loong

The Chinese Univ. of Hong Kong, Hong Kong

Locally Advanced Non-Small Cell Lung Cancer: Who Benefits from Immunotherapy with Definitive Chemoradiotherapy

Hyun Ae Jung

Sungkyunkwan Univ., Korea

Introduction

Stage III non-small cell lung cancer (NSCLC) accounted for 15-20% of all NSCLC. Stage III NSCLC comprises a heterogenous group. Treatment for stage III depend on many clinical conditions including patient's performance status, lung function, and tumor characteristics. Multimodality therapy is an appropriate treatment for resectable stage III NSCLC. For patients with unresectable stage III NSCLC, the standard of treatment is definitive concurrent chemoradiotherapy. Through PACIFIC trial, durvalumab thus fills a critical unmet need in the setting of unresectable NSCLC and provides a new option for patients treated with curative intent. Today, we review the treatment of unresectable NSCLC, with a focus on the effect of the clinical data with immunotherapy with definitive chemoradiotherapy.

5-year OS data of PACIFIC Trial

The pacific trial was a practice-changing study in management of unresectable locally advanced NSCLC. First patient was enrolled on May 2014 and last patient was enrolled on April 2016. The first data of PFS was presented in 2017 ESMO congress. The 5-year progression-free survival (PFS) and overall survival (OS) data was presented in 2021 ASCO annual meeting. Median PFS was 16.9 months (95% CI, 13.0-23.9) for durvalumab and 5.6 months (95% CI, 4.8-7.7) for placebo group [HR, 0.55 (0.45-0.68)]. The 5-year PFS rate was 33.1% for durvalumab and 19.0% for placebo group. The median OS was 47.5 months (95% CI 38.1-52.9) for durvalumab and 29.1 months (95% CI, 22.1-35.1) for placebo group [HR, 0.72 (0.59-0.89). The 5-year OS rate was 42.9% for durvalumab and 33.4% for placebo group. OS and PFS benefit with durvalumab at 5-year analysis was consistent with the findings of the primary analyses.

Real-world data of PACIFIC regimen

Pacific-R study is an international, observational study which enrolled 1,399 patients in E.U. With 23.0 months of median follow-up duration, median PFS was 21.7 months (95% CI, 19.2-24.5). Of total, 16.7% of patients discontinued durvalumab due to adverse event. Pneumonitis/interstitial lung disease was the most common adverse event leading to permanent discontinuation (9.5%). Median time to onset of pneumonitis/ILD from durvalumab initiation was 2.5 months. Corticosteroid administration was required in 71.3% of events.

Other RWD of PACIFIC regimen was the SPOTLIGHT study in USA. In the SPOTLIGHT study, 333 patients received durvalumab after completion of definitive CCRT. With 17.5 months of median follow-up duration, median PFS was 17.5 months (95% CI, 14.2-24.8).

Other study of immunotherapy with definitive chemoradiotherapy

There were several ongoing trials of immunotherapy with definitive chemoradiotherapy including induction immunotherapy concurrently with chemoradiotherapy or durvalumab plus other regimen for consolidation treatment (Table 1).

In the phase 2 KEYNOTE-799 trial, pembrolizumab plus CCRT demonstrated objective response rates of 70.5 % and grade 3 or higher pneumonitis occurred 8%.

Study Name and Phase	ClinicalTrials.gov Identifier	Estimated/Actual Enrollment (N)	Patient Population	Treatment Arms	Primary Endpoints	Estimated Primary Completion Date
PACIFIC[1] Phase III	NCT02125461	713[a]	Stage III unresectable NSCLC whose disease has not progressed following definitive platinum-based cCRT	Durvalumab vs placebo 1Yr	PFS by BICR OS	February 2017[b] (March 2021[c])
PACIFIC 2[2] Phase III	NCT03519971	300	Stage III unresectable NSCLC who have not received prior or current cancer treatment	Durvalumab given concurrently with CRT vs placebo + CRT Until PD	ORR PFS	September 2020
PACIFIC 5[3] Phase III	NCT03706690	360	Stage III unresectable NSCLC whose disease has not progressed following definitive, platinum-based chemoradiation therapy	Durvalumab vs placebo (consolidation therapy) Until PD	PFS assessed by BICR according to RECIST 1.1	May 2022
PACIFIC 6[4] Phase II	NCT03693300	150	Stage III unresectable NSCLC whose disease has not progressed following definitive, platinum based sCRT	Durvalumab (fixed dose) monotherapy 2Yrs	Safety and tolerability profile as defined by Grade 3 and Grade 4 TRAEs	February 2023
COAST[5] Phase II	NCT03822351	300	Stage III unresectable NSCLC who have not progressed following cCRT	Durvalumab Durvalumab + Oleclumab Durvalumab + Monalizumab 1Yr	ORR	October 2023
DUART[6] Phase II	NCT04249362	150	Stage III unresectable NSCLC who were treated with and did not progress on radiotherapy, are ineligible for chemotherapy, IO naive	Durvalumab + standard RT vs Durvalumab + palliative RT 1Yr	Safety and tolerability profile as defined by Grade 3 and Grade 4 PRAEs	June 2022

Supportive care in patients receiving definitive CCRT with immunotherapy

A group of experts from the European Society for Therapeutic Radiology and Oncology (ESTRO) and the European Society of Medical Oncology (ESMO) identified the following items of impor-

tance for further improvement of supportive care: smoking cessation; nutrition; physical exercise; prevention and treatment of acute esophagitis and dysphagia; treatment of cough and dyspnea; treatment of skin; prevention, diagnosis, and treatment of cardiac disease and damage; and optimization of radiotherapy techniques and chemotherapy adjustments to reduce toxicity of immune therapy

Conclusion

Immunotherapy with definitive chemoradiotherapy is a standard of care for locally advanced stage NSCLC. In Korea, durvalumab consolidation was approved and reimbursed on April 2020. RWD are important to learn about various aspects of durvalumab treatment under real-life conditions including effectiveness, safety and tolerability.

Early Non-Small Cell Lung Cancer: Where Is Immunotherapy after Curative Surgery

Min Hee Hong

Yonsei Univ., Korea

Monoclonal antibodies that target immune checkpoint proteins, so-called immune checkpoint inhibitors (ICIs), prevent tumor evasion of the immune system and are often effective in the treatment of various cancer types including lung cancer, esophageal cancer, and head and neck squamous cell carcinoma. Studies have revealed improved objective response rates, progression-free survival, and overall survival with immune checkpoint inhibitors when used in both first and subsequent-line settings in non-small lung cancer. The usage of immunotherapy is expanding from neoadjuvant to adjuvant treatment, incorporating with surgery and now we are witnessing a revolution in the treatment of resectable stage NSCLC.

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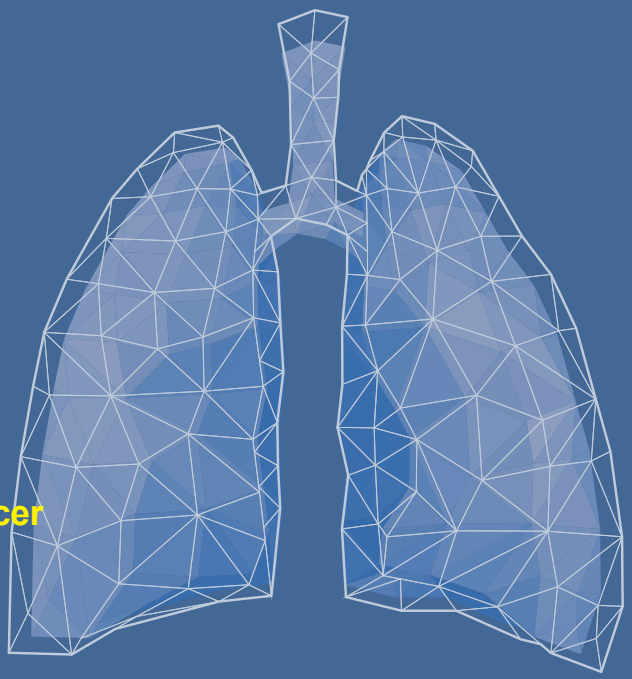

| November 11 (Fri), 2022 | Room C

15:00-16:40

Session VIII (C)

Small Cell Lung Cancer and Others

Chair: Jin Seok Ahn *(Sungkyunkwan Univ.)*

Updates of Immunotherapy in Thymic Cancers and Mesothelioma

Yong Won Choi

Ajou Univ., Korea

Mesothelioma is a rare and universally fatal cancer linked to exposure to asbestos. Until recently, standard systemic therapy for mesothelioma was combination chemotherapy with platinum and pemetrexed. In 2020, combination immunotherapy with ipilimumab and nivolumab was approved as first-line systemic therapy for mesothelioma following the results from the CheckMate 743 trial, showing improved overall survival for patients receiving ipilimumab and nivolumab over those treated with platinum and pemetrexed chemotherapy.[1] When the survival results were examined analyzed by histologic subtype, the survival benefit was most significant in those with nonepithelioid mesothelioma (8.8 v 18.1 months), a group for which combination immunotherapy is now standard of care. For those who previously received chemotherapy without immunotherapy, single agent nivolumab provides benefit over best supportive care in CONFIRM trial.[2] Similarly designed two single-arm phase II studies (DREAM,[3] PrE0505[4]) combining cisplatin and pemetrexed with durvalumab PD-L1 blockade were conducted in patients with previously untreated, unresectable mesothelioma. Response rates were 46% and 56%, respectively, the 6-month PFS was 57% for DREAM and 69% for PrE0505, and the 12-month OS was 65% and 70%, respectively. These outcomes compare favorably with chemotherapy alone and make this combination worthy of further study. Several randomized phase III trials are ongoing to validate the activity of chemoimmunotherapy in first line setting.

Thymic epithelial tumors (TETs) are rare and potentially aggressive malignant cancers of the anterior mediastinum. Platinum-based combination chemotherapy regimens are the standard treatment for metastatic, unresectable or refractory disease although options are limited in this setting with response rates ranging from 69% in thymoma to 42% in thymic carcinoma (TC). Clearly, immune checkpoint inhibitors are active, but they also present a higher risk of autoimmune toxicity than in other tumor types.[5] Since these toxic effects can be severe (particularly myocarditis), special caution must be taken, and methods to prevent these effects or predict high-risk patients are

needed. Several clinical trials with ICI alone or in combination are ongoing. In ESMO 2021 annual meeting, some results of a phase II study (the NIVOTHYM trial) to assess the efficacy of nivolumab or its combination with ipilimumab in patients with advanced, refractory type B3 thymoma or TC, after exposure of platinum-based chemotherapy are presented. Recently, results from CAVEATT study (avelumab + axitinib) in recurrent TC who had progressed after at least one line of platinum-based chemotherapy have been reported with promising outcomes (partial response and stable disease of 34% and 56% respectively and, PFS of 7.5 months) and acceptable safety profile.[6] Ultimately, a greater understanding of thymic biology and the development of novel predictive biomarkers is required to make immunotherapy a safe and feasible option for patients with thymoma and thymic carcinoma.[5]

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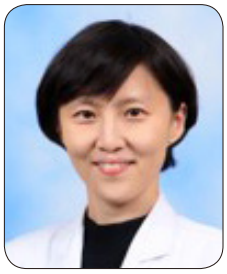

Frontline Immunotherapy in Extensive Stage Small Cell Lung Cancer

Hye Ryun Kim

Yonsei Univ., Korea

Extensive stage small cell lung cancer (SCLC) has spread too far for surgery or radiation therapy to be useful as the initial treatment. If you have extensive SCLC and are in fairly good health, chemotherapy, possibly along with an immunotherapy drug, is typically the first treatment.

The most common combination of chemo drugs is etoposide plus either cisplatin or carboplatin. The immunotherapy drugs atezolizumab or durvalumab can be used along with etoposide and a platinum drug for initial treatment and can then be continued alone as maintenance therapy.

Atezolizumab and durvalumab are humanized monoclonal anti-programmed death-ligand 1 (PD-L1) antibodies that have improved survival, when combined with a platinum agent and etoposide (E) during induction and continued as maintenance. The anti-programmed cell death protein 1 (PD-1) antibody pembrolizumab has been shown to improve PFS with a favorable but non significant survival advantage. The addition of an anti-CTLA4 inhibitor to durvalumab and Etoposide/cisplatin also showed a trend towards improved survival compared with Etoposide/cisplatin alone, but this was not statistically significant.

Cross-trial comparisons suggest similar efficacy and toxicities between durvalumab and atezolizumab when paired with chemotherapy, and a choice between them should depend on provider preference and insurance coverage. If atezolizumab is chosen, we use Etoposide/carboplatin as the accompanying chemotherapy regimen, as atezolizumab has not been evaluated in combination with etoposide/cisplatin. Durvalumab may be paired with either etoposide/cisplatin or etoposide/carboplatin.

Despite the improvements observed with the addition of immunotherapy to chemotherapy in induction, maintenance immunotherapy has not demonstrated benefits among those induced with chemotherapy alone. In CHECKMATE 451, which evaluated maintenance therapy in patients with stable disease or response after initial chemotherapy, neither of the two immunotherapy arms (nivolumab alone or nivolumab in combination with ipilimumab) improved survival relative to placebo.

Existing Treatment Options and Future Directions for Second Line and beyond in Extensive Stage Small Cell Lung Cancer

Vivek Subbiah

UT MD Anderson Cancer Center, USA

Role of Thoracic Radiotherapy Extensive Stage Small Cell Lung Cancer

Jae Myoung Noh

Sungkyunkwan Univ., Korea

Extensive-stage small cell lung cancer (ES-SCLC) accounts for approximately two-thirds of SCLC, and it has more aggressive disease course with poor survival.[1,2] As the thoracic progression is common, consolidative thoracic radiation therapy (TRT) could improve survival outcomes. There have been three randomized trials addressing the role of consolidative TRT in ES-SCLC [3-5]. Two studies demonstrated survival benefit of consolidative TRT, but one did not. Pooled meta-analysis of these studies showed significant improvements in PFS and reduction in thoracic failures [6]. As the two largest trials support OS benefit of TRT, ASCO Guideline recommends TRT for patients with ES-SCLC with a response to chemotherapy alone but residual tumor in the thorax [7].

In the CREST trial, 30 Gy (in 10 fractions) TRT was delivered, and the risk of intrathoracic recurrence was 44% despite of TRT [4]. The greatest survival benefit was observed from the randomized study with higher radiation dose (54 Gy in 36 fractions, 1.8 Gy twice a day), and several retrospective studies has shown the survival benefit of higher TRT dose [5,8,9]. Therefore, higher dose (45-54 Gy) could be considered if the patient is expected to have prolonged survival [7].

Previous studies had been conducted before the approval of immunotherapy in ES-SCLC. Since the IMpower 133 and CASPIAN trials demonstrated an improvement in overall survival with the addition of immunotherapy to first-line chemotherapy, the new standard of care in ES-SCLC has been combination chemotherapy and immune checkpoint inhibitors [10,11]. But these trials did not allow consolidative TRT, and clinical trials on RT-immunotherapy are few and limited to early phase studies focusing on toxicity in ES-SCLC [1]. While the benefit of TRT in patients with ES-SCLC treated with chemo-immunotherapy is uncertain, TRT is conditionally recommended in ASCO Guideline [7]. The optimal RT dose is also uncertain in this setting. As several prospective studies are ongoing, the results of these studies could address the role of consolidative TRT in the ear of chemo-immunotherapy for ES-SCLC (CL 2022).

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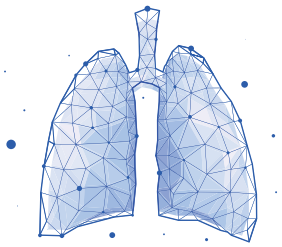

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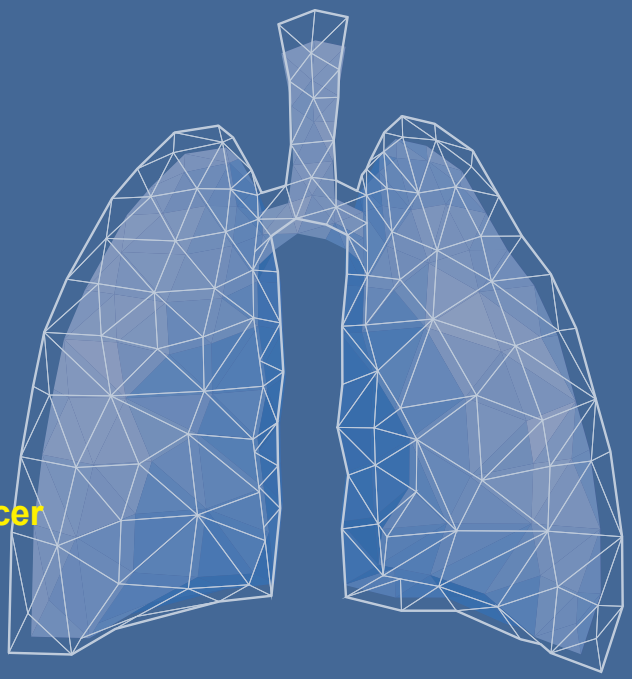

| November 11 (Fri), 2022 | Room C

16:50-17:40

Satellite Symposium IV (C)

[LILLY]

Chair: Tae Won Jang *(Kosin Univ.)*

A New Era of Treatment Opportunities for Metastatic Non-Small Cell Lung Cancer Patients : First-in-Class RET Inhibitor "Retevmo"

Kaname Nosaki

National Cancer Center Hospital East, Japan

REarranged during Transfection (RET) fusion are identified in 1-2% of non-squamous non-small cell lung cancer (NSCLC). Selpercatinib is a first-in-class highly selective and potent RET kinase inhibitor with central nervous system activity. Selpercatinib demonstrates the robust and durable efficacy with a favorable safety profile in RET fusion positive NSCLC, and is approved in multiple countries for the treatment of RET-altered NSCLC. Hypersensitivity reaction (HR) is a unique adverse event of selpercatinib. In this lecture, the latest data on selpercatinib induced HR, which occurs in 4-8 % and the incidence is more common in patients with prior immune check point inhibitors (ICI) treatment, will be presented.

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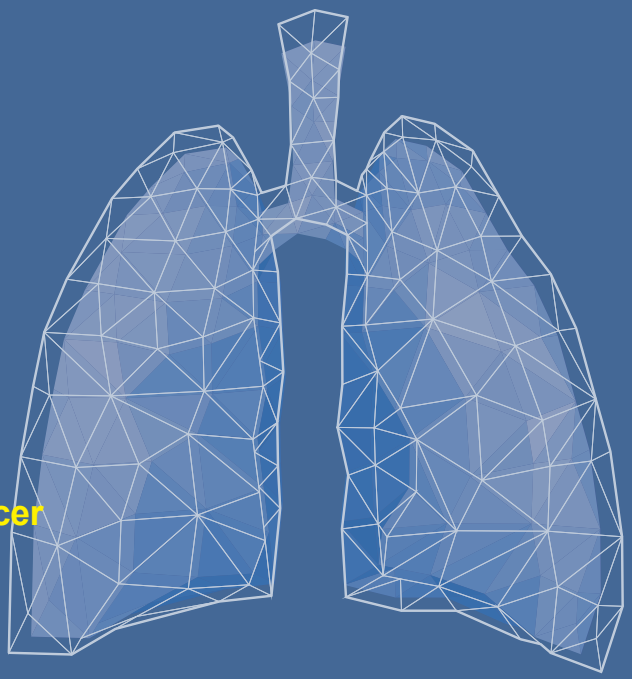

E-Poster Presentation

[PE1-01]

Pharmacological Targeting of Epithelial-to-Mesenchymal Transition in Non-Small Cell Lung Carcinoma

Paolo Ceppi

Department of Biochemistry and Molecular Biology, University of Southern Denmark, Odense, Denmark

Aims: Non-small cell lung cancer (NSCLC) represents an enormous health problem. The introduction of novel drugs has recently improved the scenario, but the patients& prognosis in many cases is still dismal because the drugs fail to prevent the metastatic spread. Hence, the development of novel targeted therapeutic for lung cancer is urgently needed. Epithelial to mesenchymal transition (EMT) is a developmental cellular program that determines the aggressiveness of tumors by causing metastasis and chemoresistance. Despite its importance in cancer, EMT has so far never been successfully targeted by any drug available for cancer therapy. Cancer cells alter their basic metabolism to support the malignant properties and therefore metabolic pathways represent attractive therapeutic targets. This work aimed at identifying metabolism pathways with association and a potential regulatory role on EMT which could be targeted to reduce the spread and the chemoresistance of lung tumors.

Methods: Whole-genome transcriptomics on large datasets, analysis of metabolic pathways and mass-spec analysis, *in vitro* treatments of lung cancer cell lines with Incucyte S3 real-time imager, western blotting, immunofluorescence, FACS, *in vivo* tumor growth and metastasis formation in nude mice, CRISPR/Cas9-based model of lung cancer (Kras/p53/LKB1), RNA-sequencing, ChIP sequencing, mass-spec profiling of histones modifications.

Results: By large-scale transcriptomics and analysis of metabolic pathways in cancer, we found that EMT can be inhibited by metabolites belonging to the class of short chain fatty acids, like propionate. These are non-toxic small metabolites produced by our commensal microbiota, and therefore potentially very interesting for therapeutic use. Treatment of human lung cancer cell lines with sodium propionate (SP) 1) increased the expression of epithelial markers, 2) reduced their metastatic ability once injected in immune-deficient mice, and 3) sensitized the cells towards cisplatin, backbone for cytotoxic chemotherapy in advanced-stage patients. RNA-sequencing and validation experiments on SP-treated cells preliminarily indicated chromatin remodeling via histone acetylation as the mechanism behind EMT attenuation. Additional work to understand the role of lung microbiota on the EMT status of lung cancer cells is currently ongoing *in vitro* and in NSCLC tissue samples.

Conclusions: This class of metabolites could be tested for chemoprevention of metastasis and for breaking EMT and chemotherapy resistance. Targeting EMT could have important potential implications in reducing the devastating effects of aggressive NSCLCs.

Keywords: Non-small cell lung cancer, Metabolism, Epithelial-to-mesenchymal transition, Metastasis, Propionate

[PE1-02]

Transformation to Small Cell Lung Cancer from an Adenocarcinoma Egfr+ as Resistance Mechanism Utility of Liquid Biopsy in Treatment Selection

MuÑoz Miguel[1,2,3], Possi Beatriz[2], Suarez Lucia[2], **Perroud Herman**[2,3]

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Aims: Tyrosine kinase inhibitors (TKIs) have been shown to be effective in advanced lung cancer with mutation of the EGFR gene. Several mechanisms of resistance to TKIs have been identified, such as: point mutation of the EGFR T790M within exon 205.6, amplification of the MET and Her2 gene, sec-

ondary mutations in BRAF-12 and very rarely the histological transformation to small cell lung cancer (SCLC).

Methods: Clinical Case Report

Results: CLINICAL CASE: 51-year-old, former tobacco user, diagnosed in 2013 with left locally advanced lung adenocarcinoma, Stage IIIB, EGFR mutated (L858R) by liquid biopsy (LB) because the lake of histological material was not enough to study EGFR in tumoral tissue. Initially received gefitinib 250 mg/day. After 4 years she progressed in 2017, with increase of lung tumor mass with bone compromise. The histological diagnose of lesion showed: Poorly differentiated lung carcinoma with features of SCLC confirmed by Immunohistochemistry, a 2nd LB was performed and informed EGFR L858R mutation in circulating DNA (cDNA). The therapeutic plan was Radiation therapy in rib cage and 6 cycles of chemotherapy platin based plus etoposide, after complete treatment response assessment (RA) showed stable disease. In March 2019 a 3rd LB was performed, an EGFR L858R + in cDNA was still present; so patient restart Gefitinib. A 6-month tomography control informed stable lung images with new liver metastases and a brain CT scan performed because neurological symptoms showed a right frontal cortical lesion of 16 mm x 19 mm. She received whole brain radiotherapy. She archived complete response in CNS by images and significant clinical improvement, but progression at the lung and liver sites. The new liver biopsy reports an infiltration of SCLC, and a 4th LB showed EGFR + L858R mutation in cDNA, based in this information it was decided to continue with gefitinib and start taxanes based chemotherapy. Thill this moment patient still alive.

Conclusions: LB has demonstrated in this patient with poor tissue sample the co existents of L858 Mutation in cDNA. The transformation of SCLC in histological tissue is a very rear mechanism of resistance to TKIs present in about 4% of the cases. LB allows us to select the best treatment for this patient and detect the absence of other mechanism of resistance like mutation of the EGFR T790M. Also, it is important to monitor the evolution of tumor with tissue samples and LB. A larger number of patients could provide a stronger basis on this issue.

Keywords: Small cell, Liquid biopsy, EGFR

[PE1-03]

Biological Potential of Artemetin in the Medicine for Their Lipoxygenase Inhibitory Potential

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Aims: Flavonoids class phytochemical are one of the most scientifically studied natural component in the modern medicine as its composed of over 6000 components having basic structure C6-C3-C6 system. Proanthocyanidins, flavanones, anthocyanins isoflavones, flavones and flavonols class phytochemicals are some of the example of the flavonoids in the medicine. Flavonoids class phytochemical have important role in the modern medicine as they are playing an important roles in the vascular diseases, diabetes, liver injury, hypertension, cancer and oxidative stress mainly due to their stabilizing power of reactive oxygen species and scavenging potential.

Methods: Biological potential of artemetin isolated from different natural sources have been studied in the present work through scientific data analysis of different scientific research work. Biological potential of artemetin in the medicine for their lipoxygenase inhibitory potential have been investigated in the present work through scientific data analysis of different scientific research work. Other pharmacological activities have been also studied in the present work in order to know the therapeutic potential of artemetin against various forms of diseases and complications.

Results: Scientific data analysis signified the biological importance of artemetin against various forms of diseases and complications. Scientific data anal-

ysis revealed the presence of artemetin in the *Vitex agnus-castus.* Scientific data analysis revealed that artemetin solated from *Vitex agnus-castus* exhibited potent lipoxygenase inhibitory activity in the medicine. Other scientific research work also signified the biological potential of the artemetin in the medicine and other allied health sectors.

Conclusions: Scientific data analysis signified the biological importance of artemetin against different diseases and associated complications.

Keywords: Biological importance, Artemetin, Diseases, Lipoxygenase

[PE1-04]

Genetic Predictors Associated with Brain Betastasis of Non-Small Cell Lung Cancer Using Next-Generation Sequencing

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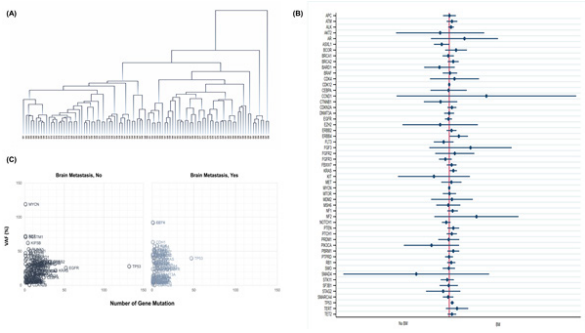
Aims: Few studies evaluated genetic alterations associated with brain metastasis (BM) using next-generation sequencing (NGS) in lung cancer. This study aimed to analyze NGS results to evaluate the genetic predictors of BM in non-small cell lung cancer (NSCLC) patients.

Methods: A total of 287 advanced NSCLC patients who underwent NGS on lung cancer tissues were included from a single referral center. The association between BM and each gene was determined using logistic regression analysis. To analyze gene similarity, the genes were divided into several groups using unsupervised hierarchical clustering. Factor analysis was performed to derive gene interrelationships from the clustering analysis results.

Results: Of the 287 patients, 64 (22.3%) had BM. Of targeted 375 cancer-related genes designed for NGS, mutations in *ERBB4* (odds ratio [OR] =1.09; 95% CI = 1.001&1.19; p=0.039), *KRAS* (OR = 1.04; 95% CI = 1.01&1.07; p=0.027), and *TP53* (OR = 1.03; 95% CI = 1.01&1.04; p=0.001) were associated with BM. Furthermore, hierarchical clustering analysis revealed that gene alterations in one subgroup 53 genes were significantly associated with BM development (p=0.020).



Conclusions: The results of NGS analysis showed that *TP53*, *KRAS*, and *ERBB4* were associated with BM development and provided a cluster of gene alterations associated with BM in NSCLC.

Keywords: Brain metastasis, Non-small cell lung carcinoma, genetic alteration, Next-generation sequencing

[PE1-05]

GWAS to Post-GWAS: In the Context of Lung Cancer Study

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Aims: Lung cancer (LC) is the second most common cancer and the leading cause of cancer death

worldwide, accounting for 18% of the total cancer deaths. It has been past more than a decade while Genome-wide association studies (GWAS) have identified approximately 45 genomic loci with a large number of genetic variants that are significantly associated with LC risk, but the biological mechanisms underlying these associations remain largely unknown due to the lack of enough functional study so far. Although, many novel computational and experimental tools now became available to accelerate the functional assessment of lung cancer-associated variants, moving beyond locus-by-locus approaches. The aim of this study to explore the current status of molecular insights from GWAS to post-GWAS era.

Methods: Over 90% of SNPs identified in GWAS of a range of human conditions and traits have been found to localize outside protein-coding regions and this has limited the rate of functional translation; this is also true for LC as well. This suggests that LC-associated variants are likely to be involved in normal and aberrant regulation of gene expression. Providing support for this, GWAS SNPs were found to be enriched in chromatin regulatory features and overrepresented in gene expression quantitative trait locus (eQTL) studies. Since gene expression signatures are cell type specific and dependent on developmental stage and epigenetic mechanisms, as well as environmental factors, it makes interpretation of putative SNPs identified in GWAS challenging. SNPs located within intergenic regions are particularly difficult to interpret.

Results: In the recent years, several high-throughput techniques like massively parallel reporter assay (MPRA), self-transcribing active regulatory region sequencing (STARR-seq) revealed the regulatory activity of genetic variants *in vitro* and *in vivo*. Later on, CHIP-seq, 3C, reporter assay, CRISPR/Cas9 technique might be used to validate the findings further.

Conclusions: To conclude, it can be said that, still these techniques are not enough to know the molecular mechanism of genetic variants over the target genes. Therefore, it is necessary to study the function of causal genetic variants of LC on their target genes to get the highest benefits in the long run.

Keywords: Lung Cancer, GWAS, Post-GWAS, Genetic Variants

[PE1-06]

A Meta-Analytic Approach to Study the Association between MDM2 SNP309 Germline Variant and Lung Cancer

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Aims: Lung cancer is the most common diagnosed malignancy and the leading cause of cancer-related mortality worldwide. Murine double minute 2 (MDM2) SNP309 polymorphisms have been reported to influence the risk of lung cancer. However, association studies on these polymorphisms in lung cancer cases have shown controversial results. In order to derive a more precise estimation of the relationship, it is important to conduct a meta-analysis that will help to get a result in a nutshell. The aim of this study was to perform a potential meta-analysis between MDM2 SNP309 and lung cancer risk based on published case-control studies.

Methods: The relevant literatures were extracted from 4 literature databases such as PubMed, Google Scholar, Web of Science and Embase up to August 2022. MetaGenyo online tool was used to perform data analysis. Pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were estimated to quantitatively evaluate the association between SNP309 and lung cancer susceptibility.

Results: A total of 17 case-control studies containing 11,764 cases and 12,891 controls were included in the current meta-analysis. We have applied 6 genetic models for pooled analysis. In multivariate

logistic regression, significantly increased risk of lung cancer was observed for MDM2 SNP309 in the dominant model. Stratification analysis revealed that age, sex, obesity, and smoking also increases the risk of lung cancer when carrying the MDM2 SNP309. Our meta-analysis revealed that MDM2 SNP309 was considerably associated with lung cancer in Asian populations.

Conclusions: To conclude, it might be stated that the current findings suggested that the MDM2 SNP 309 can be used as a potential biomarker for lung cancer susceptibility, especially for Asian ethnic people. Therefore, to get a strong summary, it is essential to conduct more case-control studies with larger sample number.

Keywords: Lung Cancer, MDM2, SNP309, Meta-analysis

[PE1-07]

Breakthrough SARS-CoV-2 Infection and COVID-19 Disease Severity in Lung Cancer Patients

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Aims: Patients with Lung Cancer (LC) are at higher risk of having complications from SARS-CoV-2 infection. Multiple studies showed that patients with solid tumors generally mount similar levels of antibodies after SARS-CoV-2 vaccination compared to healthy controls, yet the longitudinal outcomes and breakthrough infection rates remain unclear.

Methods: LC patients who were diagnosed with COVID-19 from March 2020 to September 2022 were extracted from ongoing study of SARS-CoV-2 and Lung Cancer at Mount Sinai, New York, USA. Patient&s characteristics, COVID-19 infection (either PCR confirmed or patient reported), and disease course were analyzed.

Results: Overall, 21.5% of LC patients (n=65) among 302 LC patients in our study were diagnosed with COVID-19, with 6 patients and 1 patient reporting two and three instances for a total of 73 infections. The mean age was 65.6±10.9 years. 63.1% of patients had stage 4 LC and the majority of patients (55/65) were receiving anti-cancer treatment. 95% of patients were vaccinated with primary doses (2 doses of mRNA-1273 or BNT162b2 vaccine, or 1 dose of Ad26.COV2.S); only 52% of patients completed the first booster vaccination. Among the total of 73 cases of COVID-19 diagnosis, 65.8% (n=48) were breakthrough infections, with a prevalence of 16.4% (46 patients with 48 breakthrough cases among 280 fully vaccinated LC patients). 24 cases occurred in December 2021 to January 2022 and 11 cases in April to May 2022, corresponding to Omicron variant surge periods. 10 cases (13.7%) were severe COVID-19 illnesses requiring hospitalization, 5 of which were breakthrough infections representing 1.8% (5 patients among 280 fully vaccinated LC patients).

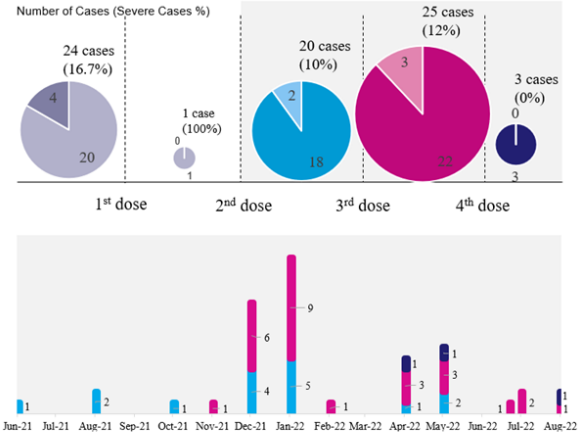

Figure 1. Breakthrough COVID-19 Infection in Lung Cancer Patients

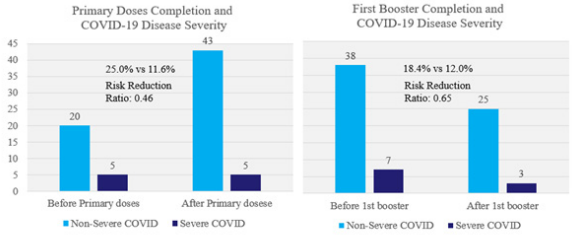

Figure 2. COVID-19 Disease Severity by Vaccination Completion Status

Conclusions: Lung cancer patients had similar breakthrough COVID-19 infection rates and higher hospitalization rates compared to the New York State general population*, thus requiring further longitudinal investigation of immunity to SARS-CoV-2 in this population.

Keywords: Breakthrough COVID-19 infection , COVID-19 disease severity, SARS-CoV-2, Lung Cancer, Vaccination

[PE1-08]

Noble Strategy for Culturing Lung Cancer Organoid with High Cancer Cell Purity in All Stages of Lung Cancer

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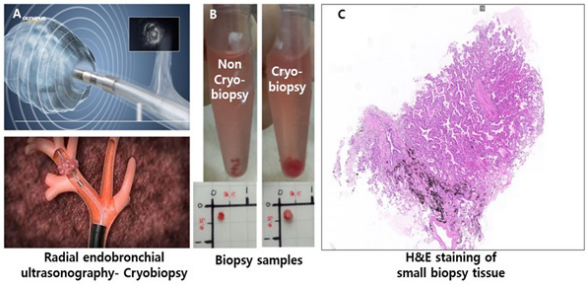
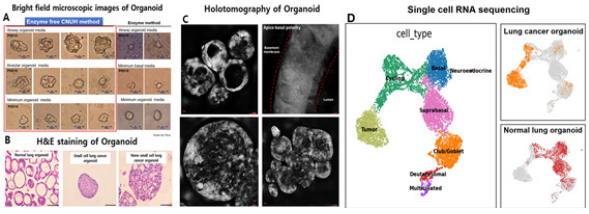
Aims: Recently, studies for personalized medicine using lung cancer organoids are being actively conducted. However, until now, most lung cancer organoids are derived from surgical tissues, so it is difficult to utilize lung cancer organoids for the treatment of advanced and metastatic lung cancer. Furthermore, in lung cancer organoids from surgical tissue, normal lung organoids often overgrow. To overcome these limitations, we utilized the tissues from cryobiopsy for lung cancer organoid.

Methods: Lung cancer tissues were obtained by cryobiopsy with radial EBUS. To improve the viabilty of cell, biopsy tissues were dissociated into single cells by only mechanical dissection and strainers without enzyme digestion. Then cells were embedded in Matrigel and submerged in airway organoid media including R-spondin, Noggin, FGF-7/10 and EGF.

Results: We successfully cultured lung cancer organoids derived from cryobiopsy tissues. Compared to conventional bronchoscopy or radial EBUS, cryobiopsy could get muh larger tissues and obtain 5 to 10 times more cells. The success rate of lung cancer organoid with cryobiopsy tissues was much higher than conventional biopsy. H&E staining shows typical morphology of normal lung organoid and lung cancer organoid. Holotomography demonstrates that the normal lung organoid and lung cancer organoid are composed of various cells, and it reveals the apical-basal polarity and cilia in several organoids. By immunhistohestry and single cell RNA sequencing, it was confirmed that lung cancer organoids recapitulate characteristics of the primary tumor and contain various cell populations.





Conclusions: Lung cancer organoids derived from cryobiopsy tissue can overcome the shortcomings of present lung cancer organoids. This method can make lung cancer organoids with high purity of cancer cells. We expect that lung cancer organoid derived from cryo-biopsy will be a breakthrough strategy of clinical application of lung cancer organoid.

Keywords: Lung cancer, Organoid, Cryo-biopsy, High cancer cell purity

[PE1-09]

Comparison for EGFR Mutant Expressions between Early Stage and Advanced Stage NSCLC

Son Lam Nguyen

Pham Ngoc Thach Hospital

Aims: The investigation of EGFR gene mutations in NSCLC is usually performed in the advanced stages of this disease, when the possibility of surgical resection on this tumor is often very low. The investigation of EGFR mutations in the early stages of NSCLC has been more recently done. Since then, there are clinical applications that is taken to many benefits to patients. We conduct research with the following objectives:

a. Investigation of EGFR mutation expression in early and advanced NSCLC.

b. Compare the results have obtained from these two pathological groups. Since then, we have been making clinical applications on NSCLC patients at Pham Ngoc Thach Hospital.

Methods: A research with retrospective, cross-sectional descriptive statistics. Analysis with SPSS 20.0 software, two-sided analysis with T-Test, test value with P <0.05.

Conclusions: There is really a need to perform the diagnosis of EGFR mutations in the early stages of NSCLC. EGFR mutations in early and advanced NSCLC have almost the same subtype distribution, except for EGFR mutations Exon 21 L861Q and Exon 20 T790M. There are broader indications for second and third generation TKIs.

Keywords: Early stage NSCLC, Advanced stage NSCLC, EGFR gene mutations, Rare EGFR mutations, EGFR Exon 20 T790M, Combined EGFR gene mutations

Results:

Genetic alternations	Early NSCLC	Advanced NSCLC	P-Value
Detective EGFR mutation rate	187 ca # 38,09%	725 ca # 39,13%	0,3783
Rare EGFR mutations	Exon 18 G719X: (5 case single mutation + 1 case compound mutation) 6 cases # 3,21%	Exon 18 G719X: (15 cases single mutation + 6 ca compound mutation) 21 cases # 2,89%	0,0907
	Exon 20 Insertion: (11 cases single mutation + 5 cases compound mutation) 16 cases # 8,56%	Exon 20 Insertion: 61 cases single mutation + 11 cases compound mutation) 72 cases # 9,93%	0,0863
	Exon 20 S768I: 9 cases # 4,81%	Exon 20 S768I: (16 cases single mutation + 2 cases compound mutation) 18 cases # 2,48%	0,0515
	Exon 21 L861Q: (13 cases single mutation + 2 cases compound mutation) 15 cases # 8,02%	Exon 21 L861Q: (13 cases single mutation + 5 cases compound mutation) 18 cases # 2,48%	0,0309 (< 0,05)
TKIs sensitive EGFR mutation	Exon 19 Deletion: (77 cases single mutation + 8 ca compound mutation) 85 cases # 45,45%	Exon 19 Deletion: (391 cases single mutation + 12 cases compound mutation) 403 cases # 55,59%	0,0817
	Exon 21 L858R: (36 ca single mutation + 4 ca compound mutation) 40 cases # 21,39%	Exon 21 L858R: 184 cases single mutation + 3 cases compound mutation) 187 cases # 25,79%	0,0829
EGFR Exon 20 T790M mutation	(17 cases single mutation + 14 cases compound mutation) 31 cases # 16,58%	(18 cases single mutation + 14 cases compound mutation) 32 ca # 4,41%	0,0265 (< 0,05)

[PE1-10]

Pilot Untargeted Blood Plasma Metabolite Profiling of Tyrosine Kinase Inhibitor Response in Filipino Non-Small Cell Lung Cancer (NSCLC) Patients

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Aims: Lung cancer was the 2nd most diagnosed malignancy in the Philippines (2020) with NSCLC accounting for about 85% of cases. Around 10-30% of NSCLC cases have EGFR mutations driving cell malignancy through the activation of downstream cell proliferation pathways. While EGFR-TKI drugs have been developed to target EGFR-mutation-positive NSCLC, resistance is still pervasive. This study aimed to use metabolomics approaches to profile the blood plasma of Filipino NSCLC patients undergoing EGFR-TKI therapy and extend the applications of omics technologies to drug response prediction.

Methods: A total of 17 consenting patients with 43 corresponding blood plasma collections were recruited in the study. Table 1 shows the patient profiles. Patients underwent CT scans every 3 months post-TKI therapy initiation. Blood plasma was collected concurrently. Response Evaluation Criteria in Solid Tumors (RECIST), an objective measure of determining response, was used to evaluate disease progression. A global extraction method (methanol and internal reference standards) and an untargeted metabolomics workflow (Waters UPLC-QtoF; positive and negative mode) were optimized. Peak spectral processing and functional annotation were performed using Metaboanalyst and xcms online.

Results: Following spectral processing, peak assignment/alignment, and annotation, multivariate statistics (unsupervised PCA) shows clustering of identified metabolite profiles according to RECIST profile (Fig. 1). Blood samples from patients with progressive disease (RECIST 4) clustered independently from patients responding to treatment (RECIST 2 and 3).

Table 1. Profile of Recruited Patients

Characteristic	Overall (n=17) (%)
Age	
Median	63
Mean	61.41
Range	38-77
Sex	
Female	13 (76.47)
Male	4 (23.53)
Smoking Status	
Nonsmoker	10 (58.82)
Firsthand	1 (5.88)
Secondhand	6 (35.29)
Stage	
III	1 (5.88)
IV	16 (94.12)
EGFR Status	
Exon 21 L858R	6 (35.29)
Exon 19 del	10 (58.82)
Exon 21 L861Q	1 (5.88)

Conclusions: Metabolomics has been used in previous studies to profile and identify potential biomarkers for oncogenic drug response. The results of this study suggest that patients undergoing EGFR-TKI therapy with progressive disease possess a distinctive blood plasma metabolite signature that may be used to distinguish them from responsive patients. Further statistical analysis is currently underway to determine the stratification potential of the identified metabolite features, as well as pathway analysis to identify possible pathways involved in disease progression.

Keywords: Targeted therapy, Drug response, NS-

CLC, Metabolomics

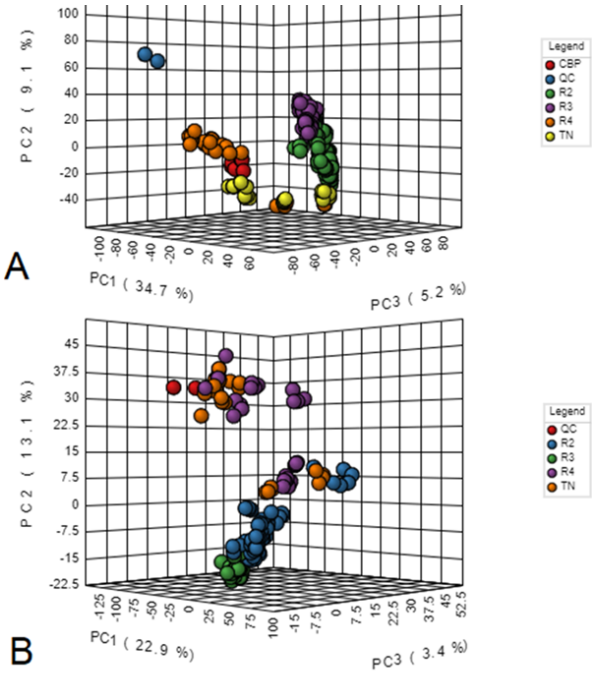

Figure 1. Unsupervised principal component analysis (PCA) of Filipino NSCLC patients undergoing EGFR-TKI Therapy. Clustering of metabolite profiles according to the degree of drug response is observed in both positive (A) and negative (B) ionization modes. TN corresponds to treatment-naive samples, CBP corresponds to commercial blood plasma control (Sigma-Aldrich P9523), while RECIST values (R2, R3, R4) correspond to partial response, stable disease, and progressive disease, respectively.

[PE1-11]

Clinical Study to Validate a Universal Panel for Liquid Biopsy

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Aims: Lung cancer has a high mortality and incidence worldwide. In Korea, the incidence rate of lung cancer ranks second, and the incidence rate is increasing every year. In particular, more than 80% of lung cancers are NSCLS. Early detection is most important for the patient survival. Recently, low-dose CT is a representative diagnostic method, but there is high false-positive rate. Therefore, many people are focusing on the development of molecular diagnostics and more accurate early diagnosis methods. More recently, liquid biopsy has been used to overcome the limitations of tissue biopsy. Liquid biopsy has been used to diagnose various diseases including cancer. Various fluids contain many substances, such as cells, proteins, and nucleic acids from normal tissues, but very few substances from the disease area. The investigation and analysis of these substances in the liquid play a pivotal role in diagnosis of various disease. Therefore, it is important to accurately isolation and analysis of the required substances, and many techniques are used for this.

Methods: Many cancer-related molecular markers are already known. Recently, NGS panels that can analyze a large number of markers at once have been widely used. However, most of the panels still mainly use tissues. The need for a panel that accurately detects a small amount of material, such as liquid biopsied substances, has emerged. In this study, we confirmed the performance of ODxTT panel that can be universally used in cfDNA and tissues. For this study, tissues and blood were collected individually from 100 lung cancer patients.

Results: In our results, the concordance rate was 58.06% (54/93) between tissue and plasma. In particular, the EGFR mutation detection result shows a sensitivity of about 85.71% (18/21) in tissue and 28.57% (6/21) in plasma compared to qRT-PCR. In addition, the specificities are approximately 89.86% (62/69) and 98.55% (68/69), respectively. PPV was 72% in tissue and 85.71% in plasma, and NPV were 95.38% and 81.61%, respectively.

Conclusions: Comparisons with more panels, such as liquid biopsy panels, are needed, but we found the possibility that ODxTT could also be used for liquid biopsy.

[PE1-12]

In-vitro Evaluation of IND126, a KRASG12C Inhibitor in Combination with Inhibitors of EGFR, Cdk 4/6 and PI3Kalpha

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VeGen Labs LLP, ASPIRE-BioNEST, University of Hyderabad, Hyderabad, Telengana, India

Aims: $KRAS^{G12C}$ mutation occurs in about 13% of NSCLC, 4% of colorectal and ~2 % of patients with other solid tumors. Treatment with KRASG12C inhibitors as single agent (such as Lumakras and Adagrasib) have shown to have a transient inhibitory effect on overall KRAS signalling because such initial oncoprotein signalling inhibition is accompanied by re-accumulation of active KRAS and/or reactivation of alternative pathways including MAPK pathway such as RAF and/or ERK. One approach towards overcoming the acquired resistance towards G12C inhibitors, is combining them with other inhibitors involved in Ras/Raf/MEK/TKI pathway. IND126 is a novel, potent and highly selective inhibitor of KRASG12C and is currently being pursued for IND enabling studies.

Methods: We report synergistic effect of IND126, with an EGFR, Cdk 4/6 and PI3K& inhibitor. Cell viability assays (3-5 days) were performed in G12C mutated cell lines using a 25 and/or 40-point dose matrix, to identify combination synergy score (CSS). Further, said combination were evaluated to understand programmed cell death using apoptotic makers in a flow cytometry-based assay. Western blot analysis of downstream markers representing the RAS/EGFR and PI3Kpathway were performed to substantiate the findings.

Results: *In vitro* combination studies of IND126 with each of the EGFR , Cdk4/6 and PI3K& inhibitor demonstrated significant synergy scores as analysed using SynergyFinder. Marked programmed cell death, as measured through apoptotic markers was observed at low nM concentrations

Conclusions: Combination of IND126, a novel, selective KRASG12C inhibitor with inhibitors of Ras/Raf/MEK/TKI pathways could be an effective approach to overcome the acquired resistance and/or reactivation of alternative pathways as reported with single agent use of KRASG12C inhibitors

Keywords: KRAS, Combination, Resistance, Targeted therapy

[PE1-13]

Utility of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration Liquid-Based Cytology in the Diagnosis and Staging of Lung Cancer: A Single Center Study

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*A***ims:** Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a preferred procedure for the diagnosis and staging of lung cancer. Diagnostic role of liquid-based cytology (LBC) compared to conventional method in EBUS-TBNA is controversial. Herein, this study compared the diagnostic yield of LBC and conventional smear (CS) of EBUS-TBNA in detection of lung cancer cells.

Methods: A total of 92 puncture sites including main mass and mediastinal lymph nodes were retrospectively analyzed in 48 histologically confirmed lung cancer patients who underwent EBUS-TBNA between April 2021 and August 2022. The histopathological result of TNBA tissue or cell blocks was considered as the gold standard and compared with the results of LBC and CS.

Results: The diagnostic positive rate for histopathology, CS, and LBC was 47.9%, 45.7%, and 35.9%, respectively. The sensitivity of LBC and CS was 70.5% and 90.9%. The specificity of LBC and CS was 95.8%. The positive predictive value of LBC and CS was 93.9% and 95.2%. The accuracy of LBC and CS was 82.7% and 93.5%.

Conclusions: Diagnostic yield of LBC in EBUS-TBNA is slightly lower than CS for diagnosis and staging of lung cancer. However, EBUS-TBNA LBC still could be considered as an alternative specimen preparation method.

Keywords: EBUS, Cytology, Liquid-based preparation

[PE1-14]

Identification of Potential Secretome Biomarkers for Early Stage Lung Adenocarcinoma in Filipino Patients

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Aims: Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small-cell lung carcinoma (NSCLC) accounting for 80-85% of all casualties. The cancer secretome is a promising source of biomarker candidates as it plays a role in various tumor-promoting processes. This study aims to identify a panel of potential secretome biomarkers for NSCLC through LC-MS/MS proteomics.

Methods: Tumor and adjacent normal tissue specimens from 7 Filipino early-stage NSCLC patients were analyzed through Orbitrap LC-MS/MS analysis of TMT-labeled tryptic peptides. Protein database search and identification of differentially expressed proteins (log 2 fold change >1, p-value >0.05) were performed using Proteome Discoverer 2.5. Secreted proteins were predicted using various in silico algorithms and databases. The transcriptional profiles of genes encoding the secreted proteins were then evaluated using lung adenocarcinoma (LUAD) datasets in the TCGA and GTEx databases using the GEPIA 2 tool. Differentially expressed secretome genes were determined by one-way ANOVA, applying log 2 fold change >1 and q-value <0.01 cutoffs. The expression of these genes across 8 cancer types (LUAD, LUSC, BRCA, PRAD, COAD, STAD, LIHC, READ) were compared and Euclidean cluster analysis of the expression profiles was performed.

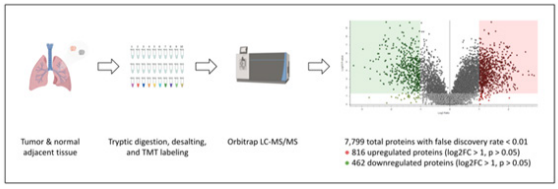

Figure 1. Sample processing, tryptic digestion, TMT labeling, and Orbitrap LC-MS/MS workflow. TMT quantification and two-sample t-test identified a total of 816 significantly upregulated and 462 significantly downregulated proteins in tumor tissues.

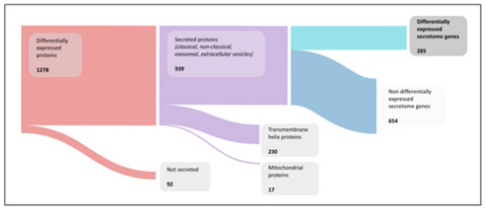

Figure 2. Filtering of candidate secretome biomarkers. Secreted proteins were predicted using various *in silico* algorithms (SignalP, SecretomeP, TargetP, TMHMM) and databases (Exocarta and Vesiclepedia). The GEPIA 2 tool was used to identify secretome genes that are differentially expressed in lung adenocarcinoma (LUAD) in the TCGA and GTEx databases.

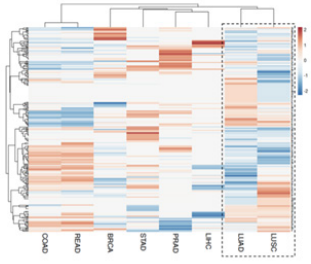

Figure 3. Lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) exhibit expression profiles that are distinct from other prevalent cancer types. Euclidean cluster analysis was performed on the expression profiles of secretome genes across the 8 most prevalent cancer types (BRCA: breast invasive carcinoma; COAD: colon adenocarcinoma; LIHC: liver hepatocellular carcinoma; LUAD: lung adenocarcinoma; LUSC: lung squamous cell carcinoma; PRAD: prostate adenocarcinoma; READ: rectum adenocarcinoma; STAD: stomach adenocarcinoma)

Results: TMT quantification and two-sample t-test identified a total of 816 significantly upregulated and 462 significantly downregulated proteins in tumor tissues. Among these proteins, 939 were predicted to be secreted. Using the GEPIA 2 tool, genes encoding 285 of the secreted proteins were determined to be differentially expressed. Cluster analysis revealed that LUAD and LUSC, the most common subtypes of NSCLC, exhibit expression profiles distinct from other cancer types.

Conclusions: This analysis demonstrates a proteomics workflow coupled with a bioinformatics pipeline to identify a shortlist of secreted proteins that may be used as non-invasive biomarkers for NSCLC. Notably, the panel of proteins exhibits an expression profile distinct from other cancer types.

Keywords: NSCLC, Lung adenocarcinoma, Secretome, Biomarkers, Proteomics

[PE1-15]

Can Antipsychotics Prevent the Progression of Non-Small Cell Lung Cancer?

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Aims: Despite great advances in diagnostic and therapeutic technologies, lung cancer remains the leading cause of cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases. Recently, some antipsychotics have been shown to possess anticancer activity. However, the effects of antipsychotics on NSCLC need to be further explored.

Methods: We analyzed publicly available clinical data to evaluate the possible association between schizophrenia and lung cancer risk. Then, we examined the effects of trifluoperazine (TFP), a commonly used antipsychotic drug, and its synthetic analogs on A549 human lung cancer cells as well as primary lung cancer cells from patients. Cell proliferation analysis, colony formation assay, flow cytometry, western blot analysis and *in vivo* xenograft experiments were performed.

Results: The clinical data analysis revealed decreased lung cancer incidence in schizophrenic patients, suggesting that antipsychotics have an anticancer effect and key genes and mechanisms possibly affected by TFP and 3dc are significantly related to better survival outcomes in lung cancer patients. Treatment with TFP and its analog 3dc significantly inhibited the proliferation, anchorage-dependent/independent colony formation and migration of A549 cells. Treatment with 3dc affected the expression of genes related to apoptosis and survival of A549 cells. Treatment with 3dc promoted apoptosis and DNA fragmentation. In all experiments, including *in vivo* studies of orthotopic lung cancer development, 3dc had stronger anticancer effects than TFP.

Conclusions: According to our analysis of publicly available clinical data and *in vitro* and *in vivo* experiments, we suggest that some kinds of antipsychotics prevent the progression of NSCLC. Furthermore, this study indicates a synthetic TFP analog that could be a potential therapeutic for lung cancer.

Keywords: Non-small cell lung canceer, Antipsychotics, Cell proliferation, Cell apopatosis

[PE1-16]

Molecular Genetic and Epigenetic Features in Smokers and Non-Smokers with Non-Small Cell Lung Cancer

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Aims: Lung cancer is one of the most common malignant tumors and the main cause of death in male patients. The most common (85%) is non-small cell lung cancer (NSCLC). The study of the molecular genetic and epigenetic features of the tumor, which makes it possible to identify markers determining the development and course of the disease, is of great importance. The aim of the study: to investigate the mutational burden of the tumor and methylation features of the promoter regions of the HOXA9, MARCH11, PTGDR, and UNCX genes in patients with NSCLC, depending on the smoking status.

Methods: Sampling consisted of 113 patients with NSCLC (81 smokers and 31 non-smokers). The material was collected in compliance with the principles of voluntariness and confidentiality and upon the authorization of the Ethics Committee. DNA was isolated from the tumor tissue by homogenization with a lysis buffer, incubation at 56°C with proteinase K, and standard phenol-chloroform extraction. DNA sample preparation for analysis was performed using TruSeq Amplicon Cancel Panel and AmpliSeq for Illumina Cancer HotSpot Panel v2 kits (Illumina, USA). The data obtained in the form of fastq files were subjected to bioinformatics analysis, the processed data were compared with GRCh38. Due to the poor quality of readings, one sample was excluded. For the variant calling, VarDict in the Amplicon mode was used. Interpretation of variants and information on the clinical significance of mutations was obtained using the recommendations of ACMG (the American College of Medical Genetics and Genomics). Analysis of methylation of the promoter regions of the HOXA9, MARCH11, PTGDR, and UNCX genes was performed by quantitative methylation-specific PCR in 73 patients with NSCLC (45 smokers, and 28 non-smokers). For each of the patients, both tumor and non-tumor tissues were tested. The relative methylation level was defined as the ratio of the fluorescence level of the studied gene to the fluorescence level of the beta-actin gene.

Results: Variants of great clinical significance for smoking patients in sampling under study were found: PIK3CA p.Glu545Lys (0.81%), EGFR p.Glu746_Ala750del, p.His773dup (0.52%), KRAS p.Gly13Val, p.Gly13Asp, p.Gly12Val, p.Gly12Asp, p.Gly12Cys (0.25%), KIT p.Phe591Leu (0.04%), and STK11 p.Tyr36Ser, p.Arg40Cys, p.Tyr60Cys, p.Ser69Thr, p.Ser69Ter, p.Thr71Ala and p.Leu80His (0.01%). In non-smokers, KRAS p.Gly12Ala, p.Gly12Cys (0.04%) and EGFR p.Asn771dup, p.Glu746_Ala750del, p.Leu747_Pro753delinsSer, and p.His773_Val774insThrHis (0.37%) variants were identified. Among the variants with potential clinical significance, missense and frameshift mutations are most common in the genes PIK3CA (7.13%), KIT (0.75%), CTNNB1 (0.31%), NRAS (0.14%), KRAS (0.14%) and TP53 (0.11%) in smoking patients. In non-smoking patients — in the genes PIK3CA (3.31%), KIT (0.86%), KRAS (0.25%), IDH1 (0.11%) and ABL (0.07%). The largest proportion among the detected spectrum of mutations constitute the variants with uncertain clinical significance: missense mutations, frameshift and protein synthesis arrest mutations, as well as splicing mutations in the genes ATM (10.80 and 10.80%), ERBB4 (10.60 and 12.25%), PIK3CA (4.20 and 4.28%), SMO (4.16 and 5.07%), MET (4.09 and 2.86%), FGFR2 (3.98 and 4 .01%), FBXW7 (3.79 and 4.99%), CDH1 (2.83 and 1.69%), APC (2.61 and 3.90%), EGFR (2.32 and 2.72 %), SMAD4 (2.28 and 2.19%), FGFR1 (1.87 and 0.38%), IDH1 (1.83 and 1.88%), PDGFRA (1.54 and 1.06%), and RB (1.08 and 1.3%) in smokers and non-smokers correspondingly. Moreover, there are other coding mutations: in the KDR and HNF1A genes with a frequency of 2.60% and 1.34% respectively in both groups of patients. In our study, positive fluorescence levels were obtained in relation to the HOXA9 gene for 61 out of 73 patients, for the MARCH11 gene — in 59 patients, for the PTGDR gene — in 50 patients, and for the UNCX gene — in 62 patients. A significant difference in the relative methylation level in tumor and non-tumor tissues was revealed: $p=4.89*10^{-8}$ (HOXA9), $p=2.67*10^{-6}$ (MARCH11), $p=7.38*10^{-8}$ (PTGDR) and $p=2.70*10^{-4}$ (UNCX). For smoking and non-smoking patients, the accurate significance of the relative methylation level was identified only in the HOXA9 gene: the standardized indicator of the Mann-Whitney U test was 1.96 ($p=0.049$).

Conclusions: Thus, as a result of the study performed, the data on the spectrum of mutations and their clinical significance for smoking and non-smoking patients with NSCLC were obtained, and the relative methylation level of the genes HOXA9, MARCH11, PTGDR, and UNCX was determined, which will allow taking into account molecular genetic and epigenetic features of the tumor in the course of diagnosing, selecting of medications

and prognosing the course of the disease.

Keywords: Non-small cell lung cancer, Tumor mutational burden, Methylation,

[PE1-17]

Comparative Study of Recurrent Neural Network and Recurrent Neuro-Fuzzy Algorithm for Lung Cancer Detection

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Aims: Lung cancer is the most commonly occurring cancer in men and the third most commonly occurring cancer in women. There were two million new cases in 2018. Therefore, it is highly necessary to take early precautions at the initial stage such that its symptoms and effect can be found at an early stage for better diagnosis. Machine learning nowadays has a great influence on the health care sector because of its high computational capability for the early prediction of diseases with accurate data analysis. This study aims to explain the procedure, application, and accuracy of machine learning algorithms both of Recurrent Neural Network and Recurrent Neuro-Fuzzy for lung cancer nodule classification from lung photo image data.

Methods: Recurrent Neural Network and Recurrent Neuro-Fuzzy modeling steps are defining input and target variables, dividing data into training data and testing data, data normalization, designing the best model, and data denormalization. The input variable used is the feature of the lung photo image extraction, while the target tissue is the description of the condition from the lung photo image, namely normal lung, benign lung tumor, or malignant lung tumor. The image extraction step begins with an image transformation, namely from the original lung image (gray image) to a binary image, followed by extracting the transformed image using the Gray Level Co-occurrence Matrix method. The design steps for the best Recurrent Neuro-Fuzzy model begin with the design steps for the best Recurrent Neural Network model followed by data clustering steps using the Fuzzy C-Means method, learning Recurrent Neural Networks related to antecedents to fuzzy inference rules and consequent fuzzy inference rules, and Simplifying the consequent part by eliminating input and finding the consequent coefficient value of each cluster using the Least Square Estimator (LSE) method.

Results: The results obtained indicate that the classification of lung cancer nodules using the Recurrent Neural Network model gives better results than the Recurrent Neuro-Fuzzy model. The sensitivity, specificity, and accuracy values of the Recurrent Neural Network model were 94%, 56%, and 81.33% for training data and 80%, 40%, and 64% for testing data, respectively.

Conclusions: The conclusion of this study is that the Recurrent Neural Network model is able to classify quite well compared to the Recurrent Neuro-Fuzzy model.

Keywords: Recurrent neural network, Recurrent neuro-fuzzy, Lung cancer detection, Machine learningLung cancer is the most commonly occurring cancer in men and the third most commonly occurring cancer in women. There were two million new cases in 2018. Therefore, it

[PE1-18]

Effectiveness of Cloud-Based Computer Aided Quality Control System in Korean National Lung Cancer Screening

Ji-Youn Song[1], **Yonghyun Kim**[1], Nayoung Lee[1], EunKyo Kang[1], Hyae Young Kim[2], Jin Mo Goo[3], Yeol Kim[1]

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Aims: Korean national lung cancer screening program (KNLCS) targeting high-risk smoking population using low-dose CT (LDCT) was implemented in

2019. A cloud-based quality control system (CQCS) using computer-aided detection program (CAD) was used to assist radiologists in LDCT lung nodules detection, measurement and categorization. In 2021, Artificial Intelligence (AI)-based CAD was launched as a developed version of CQCS. This study evaluated effectiveness of CQCS on positive rate and inter-observer variability in KNLCS.

Methods: Among 577 radiologists in total, 61 radiologists using CQCS interpreted 28,677 (18.7%) LDCTs from KNLCS in 2019-2021. The other 516 radiologists not using CQCS interpreted 124,515 (81.3%) LDCTs. This study compared the quality index measured between radiologist groups using and not using CQCS and before and after using CQCS in 2019-2021. Also, we compared the quality index measured before and after implementation of AI-based CQCS on registered units in 2021. The quality index was evaluated by positive rates (proportion of nodules classified as Lung-RADS category 3 and 4) and their variabilities across radiologists. Coefficient of quartile variation (CQV) of positive rates was used to calculate variabilities ($\theta_{CQV}=(\theta_3-\theta_1)/(\theta_1+\theta_3)$).

Results: In CQCS, positive rates were higher by 2.19% (11.40% vs. 9.21%; $p<.001$) and variability of the positive rates was lower by 0.192 (CQV, 0.261 vs. 0.453). When positive rates were compared before and after using CQCS, positive rates increased by 4.90% (11.41% vs. 6.51%; $p<.001$) and CQV decreased from 0.448 to 0.330 after utilization of CQCS among 29 radiologists. After adopting AI-based CAD program in CQCS, positive rates increased by 1.75% (11.71% vs. 9.96%; $p=.044$) and CQV increased from 0.233 to 0.272 for 35 radiologists.

Conclusions: The CQCS showed effectiveness in assisting in lung nodule detection and lowering variabilities of screening results across radiologists and screening units. Further studies on quality control strategies for newly implemented AI-based CAD are required.

Keywords: Lung cancer, Screening, Low-dose CT, Quality control

[PE1-19]

Application of Artificial Intelligence in Detecting Lung Cancer in Asia: Systematic Review

Ferza Alfath, Fidya Annisha[1], Devi Yulia Rahmi[2]

Department of Law, Alumnus of Universitas Andalas, [1]Madina Hospital, Indonesia, [2]Department of Management, Universitas Andalas

Aims: Artificial intelligence is reported to have a significant role and accuracy in diagnosing and treating cancer. Lung cancer is one of the most deadly cancers, with a five-year survival rate of 16 per cent (Asianscientist, 2017). A clinical trial shows that using artificial intelligence can help doctors predict how cancer will develop. On Lung Cancer, AI has the potential to help to treat lung cancer from detection, diagnosis and decision-making to prognosis prediction (Chiu et al., 2022). The aim of the study is to see how IE is used for lung cancer in Asia.

Methods: This research uses a systematic review method. We collected articles from 2010-2022 from an electronic database. The keywords used are artificial intelligence, lung cancer and Asia. Then as many as ten selected articles were reviewed to answer the purpose of this study.

Results: In Asian countries, artificial intelligence for lung cancer has developed. For Example, in Chinese, the Lung Cancer Artificial Intelligence Detector may play a part in the early detection of lung cancer or large-scale screening of high-risk cancer populations. The research from Liu et al. (2022) finds that epidemiological characteristics should be considered in lung cancer screening, which can significantly improve the efficiency of the artificial intelligence model alone. Furthermore, in Indonesia, Auto ID has developed as an interface between medicine and artificial intelligence and opens the door to a future in which care is delivered more efficiently and precisely (Fahmy, 2021).

Conclusions: A for lung cancer has developed. Several countries in Indonesia, like China, Indonesia, and Taiwan, have developed lung cancer diagnoses

and screening.

Keywords: Artificial intelligence, Asia, Lung cancer

[PE1-20]

How Was Big Data Predicting Lung Cancer - Several Studies from Country in Asia

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Management Department, Universitas Andalas

Aims: Lung cancer is a disease characterized by uncontrolled cell growth in lung tissue. Lung cancer is Asia's deadliest and most common cancer (Pakzad et al., 2015). Nowadays, science has been developing. Many researchers use big data to predict lung cancer. The study aims to identify research in Asia using big data for predicting lung cancer.

Methods: This research uses the bibliometric systematic review method. We collected articles from 2010-2022 from an electronic database (pubmed.gov, springer, science direct, Gleneagles). We see the conclusion, and we get the keywords using &big data&, &lung cancer&, and &Asia&. Then as many as ten selected articles were reviewed to answer the aim of this study.

Results: Researchers in Asia have used big data to predict lung cancer. For example, in Singapore, researchers found personalized risk assessment tools that can predict the survival rate and treatment outcomes of early-stage lung cancer patients (Asianscientist, 2018). Research from Pakzad et al. (2015) using the HDI index found that the five countries with the highest standardized incidence and mortality rates of lung cancer were the Democratic Republic of Korea, China, Armenia, Turkey, and Timor-Leste, respectively. Researchers in Indonesia also analyzed big data (Purnawati, 2021). The study results showed variations in the picture of the pattern of primary lung cancer in Indonesia compared to theories and results from previous studies. This is due to differences in lung cancer risk factors in various regions in Indonesia.

Conclusions: Big data has been developed for predicting lung cancer in Asia. Several countries try to research using big data-for example, Singapore and other countries.

Keywords: Asia, Big data, Lung cancer

[PE1-21]

Implementation of Artificial Intelligence for Lung Cancer Diagnosis : A Literature Review

Nahya Nur

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Aims: Lung cancer is the second most common type of cancer after breast cancer, which is the most common in the world. Based on data obtained from WHO, there were 2.21 million cases in 2020. Cases of death caused by lung cancer were ranked first with 1.80 million deaths. In its early stages, this disease does not show any symptoms so it is very difficult to detect. This also makes the disease dangerous and can lead to death. To minimize the risk that can occur, early detection can be done by screening patients. To perform screening, there are obstacles that can occur such as the objectivity of the radiologist and the time used to make a diagnosis. These problems can be overcome by utilizing artificial intelligence by using the analyzed CT Scan image data. In this study, we will discuss several implementations of artificial intelligence in diagnosing lung cancer.

Methods: In this case, we are looking for some literature that discusses the use of artificial intelligence methods online through several reference sources such as sciencedirect, nature, hindawi, as well as several websites that discuss about cancer. We select the articles that we collect according to several criteria including: the articles were published in the last five years, discuss about lung cancer, and the implementation of artificial intelligence methods.

Results: The data used in diagnosing lung cancer,

including chest radiographs and CT scan images. The data is then processed using artificial intelligence methods. Artificial intelligence makes it possible to identify data based on models that have been built from training data. in this case the training data is used to find patterns contained in the image so that if there is new data, it can be analyzed using a model that has been built from that data. the more data used in the training process, the more efficient the results of the system diagnosis will be. Several artificial intelligence methods that can be used to diagnose include artificial neural network (ANN), long short-term memory (LSTM) neural network, and the latest algorithm using deep learning in this case convolutional neural network which is a development of previous methods.

Conclusions: The technological approach in this case utilizes artificial intelligence algorithms to assist radiologists in diagnosing lung cancer. In this case, only as a second opinion and not to replace the role of the doctor. The results of the diagnosis using this method are expected to help the process of identifying lung cancer more objectively and efficiently.

Keywords: Artificial intelligence, Lung cancer, Digital imaging, CAD

[PE1-22]

The Place of 18F-FDG PET/CT in the Diagnosis of Lung Cancer and Correlation with Histopathological Results

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Ankara University Faculty of Medicine

Aims: The aim of our study is to determine the sensitivity and specificity of 18F-FDG PET/CT in lung cancers and to reveal the relationship of lung cancer with age, sex, smoking, localization and histopathological methods used for diagnosis.

Methods: 1173 patients who underwent 18F-FDG PET/CT with diagnosis or pre-diagnosis of lung cancer were examined at Ankara University Faculty of Medicine Department of Nuclear Medicine between January 2019-July 2021 and 552 patients were included in our study, 621 patients were decommissioned due to lack of histopathological examination. Of the patients included in this study, 137 (24.8%) were female and 415 (75.2%) were male. The mean age of all patients was 64.8±10.5 (17-97) years. The data of these patients was evaluated retrospectively.

Results: According to the histopathological results of these patients, for 126 patients no neoplasia was detected (22.8%); 154 patients had adenocarcinoma (27.9%) , 111 had squamous cell carcinoma (20.1%), 56 poorly differentiated adenocarcinoma (10.1%), 51 patients had small cell carcinoma (9.2%), 56 (by 10.1%), 10 had large cell carcinoma (1.8%), 14 had metastasis from different organs (2.5%), 30 had other pathologies (5.4%) was revealed. The false positive rate of 18F-FDG PET/CT was 14.1% and the false negative rate was 1.51%. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rates of 18F-FDG PET/CT in detecting lung cancer were found to be 98.4%, 85.8%, 94.6%, 95.7%, and 94.9% respectively. The presence of lung cancer in 18F-FDG PET/CT was found to be statistically significant ($p<0.001$, $p=0.002$).

Conclusions: We believe that 18F-FDG PET/CT should be used routinely together with histopathology in the diagnosis of lung cancers and may be sufficient on its own.

Keywords: Lung cancer imaging, Lung cancer diagnosis, 18FDG-PET/CT

[PE1-23]

Nature Course of Screening Detected Pure Ground-Glass Nodules

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Aims: We have reported a natural course of 122

screening detected pure ground-glass nodules (GGNs) in 2013 and the frequency of growth was 9.8% per-nodule basis during a median follow-up duration of 59 months. In this study, we aimed to report further changes of pure GGNs after the initial evaluation.

Methods: This is a single center retrospective cohort study. We reviewed data on cases in which pure GGNs were detected among patients who underwent screening low-dose CT scans between June 1997 and September 2006.

Results: After the previous evaluation, a total of 102 pure GGNs in 70 patients were further followed up for a median duration of 177 (Interquartile range [IQR] 127-211) months. Ninety GGNs were detected at the first screening CT, and 12 GGNs were newly detected during follow-up. Of 102 pure GGNs, 11 increased in size and the median follow-up period to the first detection of size change was 118 (IQR 96-134) months. Among 11 growing pure GGNs, nine were detected at the first screening CT, and two were newly detected in the follow-up CT scan. Six of 11 growing GGNs also showed a change in appearance to part-solid nodules. Three GGNs were histologically confirmed as adenocarcinoma by surgery and two GGNs were treated by proton therapy and radiation therapy without the confirmation of histology. Among pure GGNs which were stable for 10 years (n = 78), five increased in size and one was histologically confirmed as adenocarcinoma.

Conclusions: This study is the longest-term cohort study with a median follow-up duration of 15 years regarding the natural course of pure GGNs. The growth rate pure GGNs after stability of 10 years was 6.4%. Therefore, we suggest that the screening detected pure GGNs need to be followed up more than 10 years.

Keywords: Pure ground-glass nodules, Screening, Natural courrse

[PE1-24]

Lung Cancer after Successful Treatment of Hodgkin's Lymphoma: Early Detection on Follow-Up CT

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Aims: Hodgkin&s lymphoma (HL) is a B-cell malignancy. The evolution of combined modality therapy (CMT) improved cure and survival rates of HL patients. However, it is associated with increased risk of secondary malignancies such as lung cancer (LC). Incidental findings on follow-up scans for HL survivors can help early detection. Here, we report the presentation and imaging findings of four patients who developed LC after successful treatment of HL.

Methods: We queried the electronic health records for HL survivors who developed LC. Only those whose LC diagnosis followed incidental CT findings were included.

Results: Two males and two females met the eligibility criteria. All patients received 4-6 cycles of AVD based therapies for HL, and two received radiotherapy in addition. Median age at HL diagnosis was 66 (52-75), and at LC diagnosis was 74 (54, 79). All the patients achieved complete remission after frontline HL treatment without relapse. All patients underwent CT scans as part of follow-up for HL recurrence. Only one patient, who has been a heavy smoker, had low-dose CT screening for LC. Three of the patients had LC within four years of HL treatment, while one patient was diagnosed after 13 years. The earliest presentation of LC in all patients was sub centimeter solid pulmonary nodule(s) detected on follow-up chest CT. The Median time from first incidental CT findings and lung biopsy was 14 (12, 34) months (Figure 1 and 2). Histopathology of lung lesions revealed adenocarcinoma in all patients except for one having SCC.

Conclusions: HL survivors with history of smoking are at increased risk of developing LC. Special atten-

tion should be paid for incidental lung findings in this population. In addition, screening and awareness programs should be developed for this high-risk population to ensure early detection and treatment of LC.

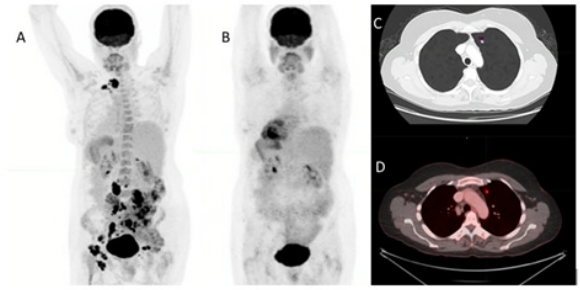
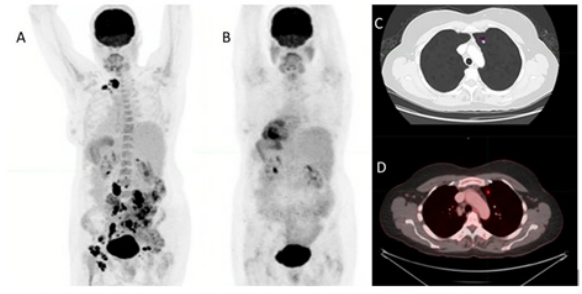


Figure 2: Images of 62 years old male with HL who subsequently developed lung cancer after treatment **A:** Baseline PET scan showing FDG-avid uptake in right-sided level II cervical nodes. No other nodal or extranodal FDG-avid lesions identified on the current scan. **B:** post treatment PET scan showing no evidence of FDG-avid disease. **C:** A low dose CT chest without contrast after 13 years showing new 6 mm nodule in the middle lobe **D:** An axial cut of PET CT fusion showing middle cavity associated nodule that was biopsy-proven to represent tumor is not FDG avid.



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Keywords: Hodgkin's, PET, CT, Lung, FDG

[PE1-25]

Prognostic Significance of Radiomic Features from 18F-FDG PET/CT in Patients with Stage III Non-Small Cell Lung Cancer Undergoing Neoadjuvant Chemoradiation Therapy Followed by Surgery

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Aims: We evaluated prognostic significance of radiomic features extracted from ^{18}F-FDG PET/CT to predict overall survival (OS) in patients with stage III non-small cell lung cancer (NSCLC) undergoing neoadjuvant chemoradiation therapy followed by surgery, and compared the predictive performance of radiomics from conventional PET parameters.

Methods: We retrospectively enrolled 300 patients with stage III NSCLC who underwent two ^{18}F-FDG PET/CT scans at initial work-up (PET1) and after neoadjuvant concurrent chemoradiotherapy (PET2). Radiomic features of primary tumor from both PET/CT images were subjected to the least absolute shrinkage and selection operator (LASSO) regression to select the most useful prognostic features. The prognostic significance of LASSO score and conventional PET parameters was assessed by cox proportional hazards regression analysis. To evaluate and compare the prognostic prediction between LASSO score and conventional PET parameters, time-dependent receiver operating characteristic (ROC) curve analysis was performed. Decision curve analysis (DCA) examined the potential net benefit of using LASSO score in the real clinical practice.

Results: The mean follow-up duration was 43.2 months. Eighty four patients (28.0%) had died, and remaining 216 patients (72.0%) were alive. Their sex, histological cell type, T stage, and tumor stage were significant prognostic factors. In conventional PET parameters, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) of each PET1 and PET2 were significantly associated with an increased risk of death. Also, both PET1-LASSO score and PET2-LASSO score were significantly associated with OS. In multivariate cox regression analysis, only PET2-LASSO score was independently significant

factor for OS (p <0.001) after adjusting for clinical characteristics. In time-dependent ROC curve analysis, LASSO score could predict OS better than conventional PET parameters. In addition, the DCA using LASSO score showed a higher net benefit across the entire spectrum of probability thresholds than that of conventional PET parameters.

Conclusions: The radiomic feature of stage III NSCLC using 18F-FDG PET/CT was independent prognostic factor for the estimation of OS. Moreover, the newly developed LASSO score using radiomic features revealed the better performance for individualized OS estimation than conventional PET parameters.

Keywords: Radiomics, Overall survival, Non-small cell lung cancer, LASSO score, 18F-FDG PET/CT

[PE1-26]

Current Status of High-Risk Smokers Participating in Population-Based National Lung Cancer Screening Program in Korea

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Aims: Following assessment of the effectiveness and feasibility based on the results from a two-year population-based nationwide prospective multi-center trial, the Korean government implemented a national lung cancer screening program using low-dose computed tomography (LDCT) for high-risk smokers in 2019.

Methods: National Health Insurance Corporation selected high risk targets who are current smokers aged 54 to 74 years with 30 packs per year or more smoking history on the basis of national health-screening database (Figure 1). Those eligible were offered lung cancer screening by invitation letters in every two years. Screening units provide LDCT using radiation less than 3mGy by at least 16-row multi-detector CT scanners. Screening results were reported by Lung Imaging Reporting and Data System (Lung-RADS). The examinee received results by mail or e-mail; after then, counseling on results and mandatory smoking cessation counselling were provided by certified doctors. National Cancer Center monitored participation rates, post-counseling rates and statistics of screening result for quality control.

Results: The participation rate gradually increased from 24.8% among 332,244 eligible targets in 2019, 25.9% in 2020, to 38.7% among 310,260 targets in 2021, however, the proportion of examinees who participated in post-counseling decreased from 46.3% in 2019 to 35.0% in 2021 due to the COVID-19 pandemic. The positive rates slightly decreased from 9.1% in 2019 to 8.7% in 2021. The variation in positive rates of screening units showed a tendency to decrease (in 2019, the 1st quartile was 4.2%, and the 3rd quartile was 12.7%; and in 2021, 4.6% and 11.0% respectively).

Conclusions: National lung cancer screening program has been implemented successfully in Korea with controlling screening positive rates not so high. Controlling false negatives and strengthening post-screening management including smoking cessation counselling needs to improve.

Keywords: Lung cancer, Screening, Low-dose CT, Smoking cessation

[PE1-27]

Impact of COVID-19 Pandemic in Motivation and Perception Towards Smoking Cessation among Lung Cancer Screening Participants in Korea

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Aims: Korean National Lung Cancer Screening Program (KNLCS) is a nationwide population-based lung cancer screening program using low-dose computed tomography (LDCT), targeting high-risk smokers between the ages of 54 and 74 with at least 30 pack-years of smoking history. KNLCS provides a mandatory in-person smoking cessation counselling following LDCT screening results counselling after screening. We aimed to access how much participants& motivation and perception towards smoking cessation changed through lung cancer screening program during the COVID-19 pandemic.

Methods: We conducted an annual telephone survey for participants in KNLCS by sampling 1,000 of them randomly from 2019 to 2021. The survey questionnaire included participants& satisfaction on screening program, whether participants attended LDCT screening results counselling after lung cancer screening, changes in motivation to quit smoking after lung cancer screening, and changes in smoking status after lung cancer screening.

Results: Among survey participants, 82.0% in 2019, 76.3% in 2020, and 74.2% in 2021 were satisfied with lung cancer screening program. During the COVID-19 pandemic, the rate of visits for screening results counselling provided after screening decreased from 61.3% in 2019, 47.8% in 2020 to 42.9% in 2021. Participants& motivation to quit smoking was 51.8% in 2019, 27.0% in 2020, and 48.6% in 2021. The rate of those who smoked less after participating in lung cancer screening program were 41.5% in 2019, 25.3% in 2020, and 22.9% in 2021. The rate of those who quit smoking after participating in lung cancer screening program was 9.8% in 2019, 11.9% in 2020, and 7.6% in 2021 respectively.

Conclusions: Impact of COVID-19 diminished visits to LDCT screening results counselling, and thus reduced its benefits such as screening participants& motivation to quit smoking. Efforts are needed to increase rates of visits to LDCT screening results counselling to promote smoking cessation after lung cancer screening.

Keywords: Screening, Lung cancer, Smoking cessation, Public health

[PE1-28]

Pretreatment Frailty Index Based on Routine Laboratory Tests: A Useful Predictor of Two-Year Mortality in Elderly Patients Diagnosed with Non-Small Cell Lung Cancer

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Aims: Frailty in older adults is associated with treatment complications and mortality. Frailty index measured by routine laboratory tests was uncomplicated and approachable in busy clinical settings. However, there are limited studies on its application in cancer survivors. Therefore, this study aimed to evaluate two frailty measurements based on laboratory data (FI-LAB) in predicting two-year survival for older patients with non-small cell lung cancer (NSCLC).

Methods: We enrolled 3347 patients aged 65 and older who were newly diagnosed with NSCLC in 2007-2018 at National Cancer Center, Korea (NCC), and followed up for 2 years. Using data of examination before initial treatment in NCC, we generated frailty scores in 2 tools: FI-22 (including 21 blood tests and 1 urine test) and FI-27 (including 27 blood tests), then categorized patients into non-frail (<0.25), prefrail (0.25-0.4), and frail (>0.4) groups. The predictive ability of FI-22 and FI-27 were estimated by Cox proportional hazards models, adjusted for age, sex, and SEER stage.

Results: FI-22 and FI-27 showed moderate agreement in classifying frailty (weighted kappa =0.67). In overall, frailty score was significantly associated with mortality risk. For FI-22, compared to non-frail

group, aHRs (95% CI) were 1.70 (1.51-1.91) for pre-frail and 2.76 (2.35-3.24) for frail groups. For FI-27, aHRs were 1.76 (1.56-1.98) and 2.67 (2.26-3.17) respectively. When stratifying by stage and treatment, adding FI-LAB could improve the c-index of models with the highest increase observed in the distant stage (p-value <0.05). In the surgery subgroup, FI-22 showed significantly higher predictive ability than FI-27 (c-index =0.80 versus 0.77, p-value =0.01).

Conclusions: FI-LAB assessed before treatment with its useful prognostic values can be considered in screening and counseling for older non-small cell lung cancer patients.

Keywords: Frailty, Prognosis, Mortality, Elderly, Non-small cell lung cancer

[PE1-29]

Biological Potential of Isolinderalactone on Human Non Small Cell Lung Cancer: Medicinal Importance in the Health Sectors

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Aims: Herbal medicines have been widely used by large sections of the population throughout world for the treatment of human disorders and associated complications. Further, in the past few decades, herbal medicines have become increasingly popular in the health sectors globally. Traditional medicine has enormous potential benefits in the development of public health. Phytochemicals are pure, active plant chemicals found to be present in the plants which have been utilized as a source of medicine and Nutraceuticals by human beings for a long time to treat diseases and associated secondary complications. Commercial products prepared from natural herbs have always been valuable for society in the form of health supplements to medicament.

Methods: Biological potential of isolinderalactone on Human non small cell lung cancer have been investigated in the present work through scientific data analysis of different scientific research in order to know their biological potential in medicine. Biological potential of isolinderalactone to exhibit anticancer potential in human non-small cell lung cancer cells has been investigated through scientific data analysis of different research work. Other pharmacological activity of isolinderalactone has been also investigated in the present work.

Results: Isolinderalactone is an active sesquiterpenes extracted from root tubers of Lindera aggregate and Neolitsea daibuensis. Isolinderalactone have iNOS inhibitory activity and anti-inflammatory activity of isolinderalactone in the medicine. Biological effect of isolinderalactone for their anticancer effect have been investigated through scientific data analysis and demonstrated that isolinderalactone could induce p21 expression and cell cycle arrest of human non-small cell lung cancer cells.

Conclusions: Scientific data analysis revealed the biological potential of isolinderalactone on human non small cell lung cancer.

[PE1-30]

Therapeutic Potential of Neobavaisoflavone against Non-Small Cell Lung Cancer: Biological Importance of Phytochemical in Medicine

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Aims: Phytochemicals are pure, active plant chemicals found to be present in the flower, leaf, seed, stem, root, vegetables, herbs, and fruits. Phytochemicals have been utilized as a source of Nutraceuticals by human beings for a long time to treat disease in medicine. Demand of plant-based products, including pure phytochemicals, has increased in medicine, Nutraceuticals, pharmaceuticals, biotechnological, and other allied health sectors. Lung cancer is one of the leading causes of the death in the world and the most commonly occurring cancer in the human

being. However non-small-cell lung cancer (NSCLC) accounts most cases of the lung cancer. Neobavaisoflavone is an important class of phytochemical found to be present in the Psoralea corylifolia belong to the flavonoid class secondary metabolites.

Methods: In order to know the medicinal importance and pharmacological activities of neobavaisoflavone in the medicine for the treatment of non-small-cell lung cancer, here we have collected scientific data from different databases and analyzed. Medicinal value of neobavaisoflavone has been investigated in the present work through literature data analysis of different scientific research to know their effectiveness against non-small-cell lung cancer. Pharmacological data of neobavaisoflavone were collected from different databases and analyzed in the present work.

Results: Scientific data analysis revealed the biological importance and therapeutic effectiveness of neobavaisoflavone against non-small-cell lung cancer. Neobavaisoflavone was found to inhibit STAT3 signaling in the non-small-cell lung cancer which signified its biological potential in the medicine for the treatment of non-small-cell lung cancer. Present work data analysis revealed the anti-non-small-cell lung cancer efficacy of neobavaisoflavone in the medicine.

Conclusions: Present work data revealed the biological effectiveness of neobavaisoflavone against non-small-cell lung cancer.

Keywords: Medicine, Neobavaisoflavone, Non-small-cell lung cancer, Phytochemical

[PE1-31]

Screening of Potential Anticancer Phytochemicals against Lung Cancer by Molecular Docking Studies

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Aims: In recent years, lung cancer has been the leading cause of death worldwide. Although there are various synthetic drugs available on the market, plant derivatives are known to have better efficacy and lesser side effects in the treatment of multiple cancers. Various molecular docking studies have been performed on the phytochemicals to evaluate their anticancer potency and are helpful in providing insights into molecular identification.

Methods: Those phytochemicals which are known to have medicinal properties are taken as ligands. Ligand structures were first determined by structural techniques. The chemical structure of shortlisted phytochemicals was accessed from the Pubchem database and drawn in Advanced Chemistry Development&s Chemsketch which was converted into the 3D structure using the software application. These ligands are further used for molecular docking analysis. The crystallographic structure of the cancer target proteins was retrieved from the protein data bank. The proteins were then cleaned by removing the bound inhibitor, non-essential molecules like heteroatoms and hydrogen atoms. Finally, optimisation of protein structure was done by Weblab Viewer, Argus Lab 4.0, Dockprep or Swiss PDB Viewer. The active site prediction is used to identify the best ligand binding site. The possible active binding sites of the proteins were obtained using DoGSiteScorer.

Results: In the docking studies, computed drug-likeness of phytochemicals revealed that maximum compounds were in the range of favourable candidates for good bioavailability per Lipinski's five rules. The phytochemical constituents of medicinal plants behave as antagonists to cancer which may be further investigated *in vitro* and *in vivo* models.

Conclusions: Molecular docking study is the important tools in the process of drug discovery for searching the potential hits. This unit aims to focus on the finding of the molecular docking study performed on various phytochemicals and different cancerous proteins and their future drug discovery potential.

Keywords: Molecular docking, Medicinal plants,

Phytochemicals, Lung cancer

[PE1-32]

Assessment of 2-Year Treatment-Related Cardiovascular Toxicity Risks in Non-Small Cell Lung Cancer Patients Utilizing Electronic Health Records

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Aims: Understanding cancer treatment-related cardiovascular (CV) toxicity has become an important issue for cancer survivorship care; however, comprehensive evaluation of CV toxicities in lung cancer patients is limited. We aim to assess the cumulative incidence of various CV toxicity types and associated risks in non-small cell lung cancer (NSCLC) patients.

Methods: We assessed CV toxicities in 7,868 individuals aged 40 or older newly diagnosed with NSCLC (2007-2018) from Clinical Research Data Warehouse at National Cancer Center, Korea. CV toxicities, including secondary hypertension, ischemic heart disease, venous thromboembolic, pericardial effusion, cardiomyopathy, atrial fibrillation and flutter (AF), cerebrovascular disease (CeVD), arterial embolism, and thrombosis were accessed. The 2-year cumulative incidence of CV toxicities was estimated with death as a competing event. The risks of CV toxicities were assessed by sub-distribution hazards ratio (sHR) in the Fine-Gray competing risks model.

Results: About 8% developed CV toxicities 2 years after cancer diagnosis. The most common types were AF (3%) and CeVD (2%). The overall CV toxicity was the highest in the chemotherapy population (2-year cumulative incidence of 10.6%), while the surgery population showed the highest AF (5.7%). The older patients and those with poor performance status had elevated risks of CV toxicities. Individuals with chemotherapy were significantly related to CeVD (sHR 4.12, 95% confidence interval (CI) 1.66-10.23). Risk of AF was significantly lower among patients with chemotherapy (sHR 0.58, 95% CI 0.34-0.98), radiotherapy (sHR 0.29, 95% CI 0.12-0.70) and combined treatment (sHR 0.20, 95% CI 0.13-0.31) than those with surgery.

Conclusions: Our study findings reveal diverse risks of treatment-related CV toxicities in clinical practice, suggesting oncologists and cardiologists should be aware of the risks of AF in surgery and CeVD in chemotherapy to achieve a better prognosis and quality of life for NSCLC patients.

Keywords: Cardiovascular toxicity, Non-small cell lung cancer, Surgery, Chemotherapy, Cardio-oncology

[PE1-33]

Mannosylated Poly (Propylene Imine) Dendrimer Mediated Lung Delivery of Anticancer Bioactive

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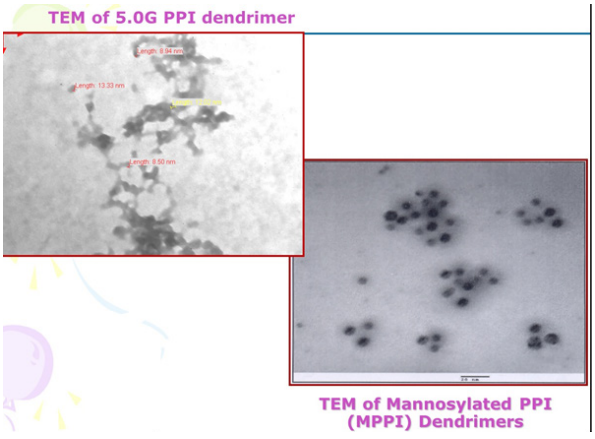
Aims: Tumors originating in lung tissues or in the bronchi invade adjacent tissue and cause infiltration beyond the lung. Lung macrophages express mannose-specific endocytosis receptor that might binds or internalize mannose terminated dendrimer. Therefore, it is hypothesized that incorporation of anticancer drug into mannose anchored dendrimer will transport the drug effectively to the tumor cells via receptor mediated endocytosis. Dendrimer are easy to synthesis and better stability, Nanoscopic size range, High drug loading propensity, Dose reduction possible, Number of free surface groups

available for further conjugation. The project aimed to investigate the targeting potential of mannose conjugated Poly Propyl Imine (PPI) dendrimer having potent anticancer drug, Gemcitabine in lung cancer cells. The dendrimers were conjugated so as to enhance the therapeutic potential and reduce adverse effect of anticancer drug.

Methods: The 5.0 generation dendrimers were synthesized and were characterized by FTIR and Nuclear Magnetic Resonance (NMR). The PPI dendrimers prepared were then conjugated with mannose and drug was loaded. The shape and size were characterized by Transmission Electron Microscopy (TEM), drug loading efficiency, In-vitro drug release and stability studies. The ex-vivo studies constituted Hemolytic toxicity study and Cell cytotoxic study by MTT Cytotoxicity Assay on A-549 (Lung adenocarcinoma epithelial) cell line. The in-vivo studies were performed on albino rats and Pharmakokinetic parameters were studied, also Biodistribution Studies were done to access gemcitabine level attained in different organs.



Results: Thus Mannosylated PPI dendrimers showed high gemcitabine loading, sustained release and excellent biocompatibility as evident by low hemolytic toxicity. MTT assay suggested high cytotoxicity of GmcH-MPPI against A549 cancer cell lines. The Presence of ligand on dendrimer molecule, elevated receptor mediated binding or internalization in AM. The developed ligand conjugated dendritic system targeted higher concentration of GmcH to lung than the free drug.

Conclusions: Thus, we concluded that GmcH loaded mannosylated PPI dendritic system could have higher potential to target anticancer drug to lungs for effective chemotherapy of lung tumor.

Keywords: Dendrimer, Gemcitabine, Anticancer

[PE1-34]

Religion and Health Care: Muslim Community in Mobilizing against Lung Cancer

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Aims: Currently the lung cancer is one of health problem in Indonesia. Therefore, muslim community raise awareness of the importance of changing perceptions and behavior for health in preventing lung cancer. The purpose of this paper is to present an approach of da&wah aimed at mobilizing civil society in reducing the lung cancer problem

Methods: This study used the descriptive method and qualitative analysis. The data source was secondary data collected from documents and texts related to the topic, be it books, articles, newspapers and journals.

Results: This study found that mobilizing against lung cancer of muslim community through da&wa had significant role in providing healthy lifestyle for certain cancers among members to reduce the depth and severety of lung cancer.

Conclusions: The themes may have utility for development of support intervention to prevent lung cancer risk to the indonesian communities.

Keywords: Religion, Health care, Muslim community, Lung cancer

[PE1-35]

Tobacco Use and Smoke Exposure: Preventive Children and Pregnant Women from Lung Cancer

Nuraliah

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Aims: Lung cancer is the leading cause of global cancer incidence and mortality, accounting for an estimated 2 million diagnoses and 1.8 million deaths. Neoplasms of the lung are the second most common cancer diagnosis in men and women (after prostate and breast cancer, respectively). With increasing access to tobacco and industrialization in developing nations, lung cancer incidence is rising globally. Does not rule out the possibility of children also experience cases of lung cancer. We cannot close our eyes, there are many children who have been passive smokers in the family since they were babies and cause them to develop lung cancer. The purpose of this study was to determine the harmful effects of cigarette smoke on children and pregnant women which can cause lung cancer.

Methods: The research method used is a literature review approach by using several sources of journals or articles selected based on predetermined criteria used in this study. Searching for the journal literature was taken from electronic-based indexes such as Google Scholar, PubMed, ProQuest, and Ebsco. The requirement for the inclusion of articles was that they were published from 2012-2022. The keywords used are smoke exposure and prevention of lung cancer for children and pregnant women, available in PubMed and SCOPUS, published 2012-2022 in English.

Results: Children of smokers and secondhand smoke are exposed to nicotine and other harmful tobacco smoke chemicals in utero as well as in their environment. This passive exposure to tobacco smoke has various adverse effects on children. In-utero exposure to tobacco smoke causes poor birth outcomes and influences lung, cardiovascular, and brain development, placing children at increased risk of a number of adverse health outcomes later in life, such as obesity, behavioral problems, and cardiovascular disease. The primary effects of maternal smoking on offspring lung function and health are decreases in forced expiratory flows, decreased passive respiratory compliance, increased hospitalization for respiratory infections, and an increased prevalence of childhood wheeze and asthma. Nicotine appears to be the responsible component of tobacco smoke that affects lung development. Because nicotine is the key agent affecting lung development, e-cigarette usage during pregnancy is likely to be as dangerous to fetal lung development as maternal smoking. Knowledge of the risks of second-hand smoke exposure is limited, and very few respondents perceived risk from third-hand smoke exposure.

Conclusions: Therefore, it is important for health workers to be aware of the risks of secondhand smoke during pregnancy and to prevent exposure to cigarette smoke in children. so that it can avoid various diseases that can be caused, especially lung cancer in mothers and children.

Keywords: Children, Lung cancer, Smoke, Tobacco

[PE1-36]

Dual Inhibitory Effects of Resveratrol in Tobacco-Carcinogen Induced Lung Cancer via Down-Regulation of PI3K/Akt/mTOR Pathway

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Aims: Phosphoinositide 3- kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathways is considered as the singling pathway which activates the diverse cellular function viz., survival, cell expansion, vesicular transport and proliferation and found fre-

quently dysregulated pathway in lung cancer. Consequently, flavonoids-based inhibitors play a key kinase role in the pathway including mTOR, PI3K and AKT, have been extensively scrutinized in targeting the oncology in recent years. The common pathway to PI3K-Akt-mTOR used to target during the lung cancer therapy. Therefore, the current study was aimed to peruse the resveratrol as dual PI3K/mTOR for lung cancer.

Methods: In the current experimental study mice were randomly divided into different groups. The oxidative stress was evaluated in term of antioxidant parameters, interleukin (IL)-1&, tumor necrosis factor-& (TNF-&) and interleukin (IL)-6 were measured via using the standard enzyme-linked immunosorbent assay kits. The concentration of PI3K, P-PI3K, mTOR, P-mTOR Akt and P-Akt were determined via using the Western blot techniques. We also performed the histopathological study to identify the changes during the disease.

Results: Resveratrol significantly suppressed the oxidative stress via improving the status of endogenous antioxidant parameters such as SOD (43.4%), CAT (48.5%), GSH (52.4%) and MPO (47.6%); proinflammatory cytokines including TNF-& (49.5%), IL-6 (43.4%), IL-1 & (53.4%) in a dose dependent manner. Disease control group mice confirmed the change in protein levels of PI3K/Akt/mTOR pathway in lung as compared to normal control, which were significantly down-regulated by the Resveratrol in a dose dependent manner. In the histological study, we observed that the Resveratrol substantially reduced the benzopyrene induced neutrophils in lung tissue.

Conclusions: It can be concluded that Resveratrol has shown promising anticancer effect via attenuation of PI3K/Akt/mTOR against lung cancer and signifies the potential therapeutic relevance for further development.

Keywords: Resveratrol, Phosphoinositide 3- kinase, mTOR, Lung cancer

[PE1-37]

Prevalence of Pulmonary TB Disease and Its Correlation as Lung Cancer Risk Factors in Indonesia

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Aims: Pulmonary TB disease was a contagious infectious disease caused by the bacterium Mycobacterium tuberculosis that can enter the respiratory tract, digestive tract, and open wounds in the skin area. In Indonesia, Pulmonary TB disease take fourth place for the highest number of cases in the world. This study aimed to analyze prevalence of Pulmonary TB disease and its correlation as lung cancer risk that occur in Indonesia.

Methods: This literature study method was carried out using a search through Google schoolar, kemenkes data and reputable health journals by reviewing some previous article which published in the last five years, from 2017 to 2022 with the keywords risk factor of lung cancer, prevalence of Pulmonary TB disease, and Indonesia.

Results: The incidence of pulmonary TB disease can be identified based on age, gender, nutritional status, alcohol consumption, smoking habits, education and knowledge. Based on the similarity of the dependent variables there are that correlation significant between prevalence of Pulmonary TB disease with respondents of productive age (15-64 years) (96.6%), and male (61.0%), having higher smoking habits than female patients, namely 24.3%. The others literature explained that level of education and knowledge also affects the increase of the prevalence of Pulmonary TB disease in Indonesia, reaching 69.5%.

Conclusions: Pulmonary TB disease in Indonesia is still relatively high. Efforts are needed to prevent the spread of pulmonary TB disease by eating nutritious foods, improving environmental health and checking phlegm if coughing is more than 2 weeks.

Keywords: Risk factor, Lung cancer, Pulmonary TB, Indonesia

[PE2-01]

Clinical Significance of Preoperative Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio in the Prognosis of Resected Early-Stage Patients with Non-Small Cell Lung Cancer: A Meta-Analysis

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Aims: Poor prognosis is linked to peripheral blood levels of preoperative platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) in many advanced cancers. Nevertheless, whether the correlation exists in resected early-stage cases with non-small cell lung cancer (NSCLC) stays controversial. Consequently, we performed a meta-analysis to explore the preoperative NLR and PLR&s prognostic significance in early-stage patients with NSCLC undergoing curative surgery.

Methods: Relevant studies that validated the link between preoperative NLR or PLR and survival results were found via the proceeding databases: PubMed, Embase, Cochrane Library, and Web of Science. The merged 95% confidence interval (CI) and hazard ratio (HR) was employed to validate the link between the NLR or PLR&s index and overall survival (OS) and disease-free survival (DFS) in resected NSCLC cases. We used sensitivity and subgroup analyses to assess the studies& heterogeneity.

Results: An overall of 21 studies were attributed to the meta-analysis. The findings indicated that great preoperative NLR was considerably correlated with poor DFS (HR = 1.58, 95% CI: 1.37&1.82, p<0.001) and poor OS (HR = 1.51, 95% CI: 1.33&1.72, p<0.001), respectively. Subgroup analyses were in line with the pooled findings. In aspect of PLR, raised PLR was indicative of inferior DFS (HR = 1.28, 95% CI: 1.04&1.58, p=0.021) and OS (HR = 1.37, 95% CI: 1.18&1.60, p<0.001). In the subgroup analyses between PLR and DFS, only subgroups with a sample size <300 (HR = 1.67, 95% CI: 1.15&2.43, p=0.008) and TNM staging of mixed (I-II) (HR = 1.47, 95% CI: 1.04&2.07, p=0.028) showed that the link between high PLR and poor DFS was significant.

Conclusions: Preoperative elevated NLR and PLR may act as prognostic biomarkers in resected early-stage NSCLC cases and are therefore valuable for guiding postoperative adjuvant treatment.

Keywords: Non-small cell lung cancer, Neutrophil-lymphocyte ratio, Platelet-lymphocyte ratio, Operation, Prognosis, Meta-analysis

[PE2-02]

Therapeutic Effect of Trilobatin in the Medicine for the Treatment of Lung Cancer: Biological Importance of Polyphenols in the Medicine

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Aims: Plant and derived herbal drugs have been used in the traditional medicine system to treat various human health complications from a very early age. A large number of useful drugs for the treatment of human health complications were mainly derived from herbal drugs. Medicinal plants and natural products derived from these plants material including some of the pure phytochemicals has been used in the medicine mainly because of their therapeutic potential and pharmacological activities. Polyphenols constitute one of the largest and most diverse classes of secondary metabolites in plants.

Methods: In order to know the biological potential of trilobatin on lung cancer, here in the present work numerous scientific data has been searched

and analyzed. Biological effect of trilobatin on lung cancer has been investigated through scientific data analysis of various research works. Other pharmacological activities of trilobatin has been has been also correlated with the present work in order to know the biological importance of trilobatin on lung cancer.

Results: Trilobatin also called phloretin-40-O-glucoside were found to be accumulated in different combinations in the stems, leaves, flowers and fruits of apple plants. Biological potential of trilobatin on gefitinib resistant lung cancer cells has been investigated in the scientific research work and revealed significant potential mainly due to its inhibitory potential on proliferation of gefitinib resistant lung cancer cells. Scientific data analysis also revealed its effectiveness on the suppression of activity of NF-&B in lung cancer cells.

Conclusions: Scientific data analysis signified the biological potential of trilobatin for the treatment of lung cancer.

Keywords: Trilobatin, Lung cancer, Phytoconstituents, Medicine

[PE2-03]

Localization of Lung Nodules by Electromagnetic Navigation Bronchoscopy

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Aims: Diagnosis of an early stage lung cancer is important and many small nodules are found through recency health checkups. It is important to accurately check and examine the small nodules, but it is challenging to clarify the resection lesion, so preoperative localization is necessary in some cases. One of the ways to localize is to use electromagnetic navigation bronchoscopy (ENB) guided localization. We decided to analyze the ENB localization data, performed in our center.

Methods: From march 2017 to August 2022, a retrospective study was conducted on 89 patients with 114 markings who underwent lung surgery with pulmonary nodules. We tried to compare patients characteristics, nodule size, location, depth, pulmonary segment, pathology and ENB data. Navigation time and failures with ENB were identified and anlyazed.

Results: A total of 89 patients underwent resection after marking lesions under ENB guided localization. There were a total of 37 men (41.6%) and the average age was 63.8 years. There were 68 patients who marked only one lesion, and 21 people who marked two or more nodules, marking a total of 114 nodules. RUL was the most frequently marked lobe with 30.7% and RML was the least at 7%. As a result of pathology, metastasis of other cancers was the most common with 46 nodules(40.4%), and primary lung cancer also accounted for a large portion with 45 nodules. Among the characteristics of nodule, solid lesion was the most common at 63.2%. On CT examination, the average size was 9.5±4.6 mm, and the depth was 8.1±5.6 mm. Surgical margin was 9.5 ±9.1 mm, the tumor size confirmed through pathology was 9.0±5.4 similar to that of CT. The average time taken to perform navigation was 19.3±2.2 minutes. Of the total marking, 6 cases were failed and lesions were not confirmed, corresponding to 5.5% and 6 cases were confirmed with dye leakage. Finally, through ENB localization, small lung lesions could be identified and removed with a 94.5% probability

Conclusions: In small nodules, ENB localization can be used as one of the acceptable methods for minimal lung resection and accurate targeting. Depending on the location of the lesion, localization may be difficult, but in most cases, the lesion can be checked with a lower failure rate.

Keywords: Localization, ENB, Lung cancer

[PE2-04]

Prognostic Impact of Preoperative Maximum Standardized Uptake Value in Clinical Stage O-IA Non-Small Cell Lung Cancer Treated by Segmentectomy

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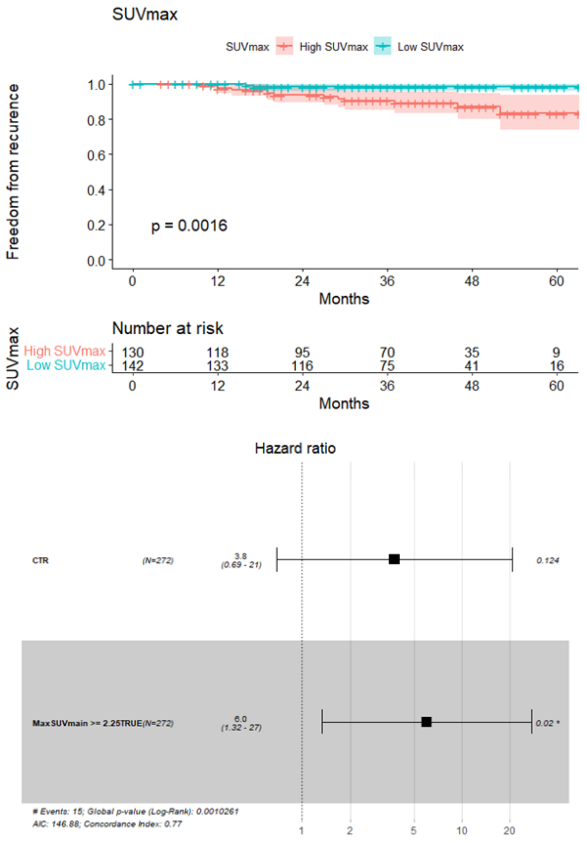
Aims: The maximum standardized uptake value (SUVmax) is a main component of positron emission tomography that represents the level of metabolic activity of tissues. High level of SUVmax has been reported that it is associated with increased risk of recurrence and poor overall survival. This study was aimed to investigate the prognostic impact of maximum standardized uptake value in clinical stage 0-IA non-small cell lung cancer treated by segmentectomy.

Methods: We retrospectively investigated the data from patients with clinical stage 0-IA non-small cell lung cancer who underwent preoperative positron emission tomography followed by segmentectomy between 2011 and 2019. A receiver operating characteristic curve was used to identify the optimal SUVmax for predicting recurrence. The prognostic impact of SUVmax was evaluated by the Cox proportional hazard analyses and Kaplan-Meier curves.

Results: This study included 272 clinical stage 0-IA non-small cell lung cancer patients, 15 (5.5%) of whom had recurrence. Tumor stages were Tis in 52, T1mi/T1a in 82, T1b in 89, and T1c in 49 patients. The receiver operating characteristic curve had an area under the curve of 0.713 and identified 2.25 as the optimal SUVmax cut-value. On multivariable study of pre-operative factors, only high-SUVmax (SUVmax & 2.25) was associated with freedom from recurrence (hazard ratio [HR], 6.0; 95% confidence interval [CI], 1.32&27.0; p=0.02). Five-year freedom from recurrence rates in tumors with standardized uptake value <2.25 and & 2.25 were 98.4% and 83.3%, respectively (p=0.002).



Conclusions: Preoperative maximum standardized uptake value of positron emission tomography is independently associated with freedom from recurrence of clinical stage 0-IA non-small cell lung cancer treated by segmentectomy.

Keywords: Lung adenocarcinoma, Positron emission tomography, Segmentectomy

[PE1-05]

Reactive Oxygen Species Modulator 1 as a Novel Predictive Biomarker for Unfavorable Clinical Outcome in Epidermal Growth Factor Receptor-Mutant Lung Adenocarcinoma Treated with Surgical Resection

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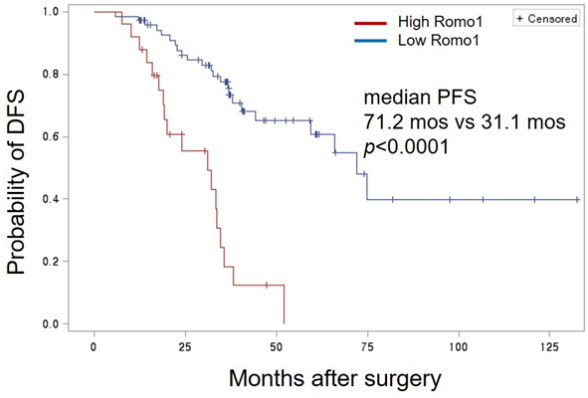
Aims: Reactive oxygen species modulator-1 (Romo1) is a key regulator of intracellular reactive oxygen species production. Previous studies have shown that Romo1 expression has been associated with poor clinical outcomes in several human malignancies. However, the clinical implication of the protein in oncogene-driven tumors has been scarcely explored. This study aimed to investigate the predictive value of Romo1 expression in epidermal growth factor receptor (EGFR)-mutant lung cancer treated with surgery.

Methods: Romo1 expression was evaluated immunohistochemically using the histologic score (H-score) in 98 tumor tissues from patients with stages I to IIIA EGFR-positive lung adenocarcinoma patients who received curative resection in a referral hospital in South Korea from March 2014 to July 2020. We investigated the possible relationship between Romo1 expression and clinicopathological parameters, and which parameters, including Romo1 expression, are associated with early postoperative recurrence.

Results: The median follow-up period was 38.9 months (range: 7.3&93.8 months). Romo1 expression was associated with advanced stage and lymph node metastasis (all $p<0.05$), but not with other parameters, including age, sex, smoking status, and EGFR mutational subtype. Using the H-score cut-off value of 200, the population was classified into the high (n = 25, 25.5%) and low (n = 73, 74.5%) Romo1 groups. In the univariate analysis, advanced stage, poorly differentiated tumor, and high Romo1 expression were significantly associated with shorter disease-free survival (DFS, all $p<0.005$). Multivariate analysis showed that high Romo1 expression was independently associated with shorter DFS (hazard ratio = 2.63; 95% confidence interval; 1.14&6.09). The overall survival data were undeveloped to be analyzed.

Conclusions: Romo1 overexpression was significantly associated with early recurrence in patients with EGFR-mutant lung adenocarcinoma patients who underwent surgical resection. Our data suggest that Romo1 may be a promising predictive biomarker for this treatment setting.



Keywords: Reactive oxygen species modulator 1, Lung cancer, EGFR, Surgery, Recurrence

[PE2-06]

Impact of Adjuvant Chemotherapy on Prognosis of Patients with Stage IB Non-Small Cell Lung Cancer with Visceral Pleural Invasion

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Aims: This study aims to explore the prognostic significance of adjuvant chemotherapy (ACT) in stage IB (1 to <4cm) non&small cell lung cancer (NSCLC) with visceral pleural invasion (VPI).

Methods: This retrospective multicenter study included 251 patients who received complete resection with pathologic stage IB and visceral pleural

invasion according to the 8th edition tumor, node, metastasis (TNM) classification from four academic hospitals. The relationship between adjuvant chemotherapy and overall survival (OS) or recurrence-free survival (RFS) was analyzed using the Kaplan&Meier method and Cox proportional hazards model.

Results: Of the 251 patients, 122 (48.6%) underwent ACT after surgical resection and 129 (51.4%) were placed under observation. Multivariate Cox analysis indicated that ACT was independent factor for improving RFS (HR, 0.568, 95% CI, 0.334-0.968, *p*=0.0375). The presence of lymphovascular invasion and micropapillary histologic pattern were associated with a higher risk of recurrence (HR, 2.207, 95% CI, 1.279-3.810, *p*=0.0045; HR, 1.969; 95% CI, 1.159-3.344, *p*=0.0122). On multivariable Cox analysis for OS, ACT was associated with significantly longer 5-year OS (HR, 0.230, 95% CI 0.085-0.618, *p*=0.0036). However, different tumor sizes (1 to <2, 2 to <3 and 3 to <4 cm) were not an independent prognostic factors in IB NSCLC with VPI.

Conclusions: Our study suggested that ACT might be an appropriate option for stage IB NSCLC patients (1 to <4cm) with VPI.

Keywords: Adjuvant, NSCLC, Visceral pleural invasion

[PE2-07]

The Curative Role of Surgery in Treating Patients with Thymic Tumours and Pleural Seeding

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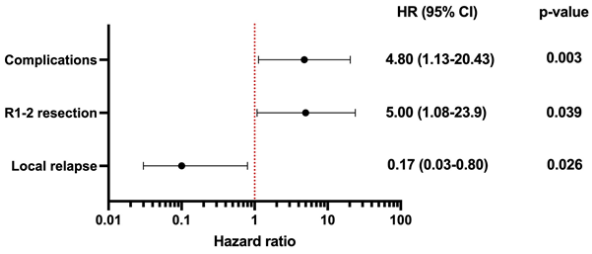
Aims: Pleural metastases of thymic epithelial tumours are diagnosed in 5-7% of patients at initial staging and in 10% of patients during follow-up after radical surgery. A cornerstone of treatment is a partial pleurectomy providing radical resection of all viable tumour deposits. We conducted a study to determine the role of surgery in treating patients with thymic epithelial tumours and pleural seeding.

Methods: Twenty-one patients with resectable thymic epithelial tumour (thymoma & 13, thymic cancer & 8) and pleural implants (initial stage IVa& 11; isolated pleural metastases as tumour progression after radical surgery & 10) were operated in our clinic in a 10-year period from 2010. Partial pleurectomy was performed in all patients along with the diaphragm and lung resection when necessary. Intraoperative photodynamic therapy was performed on 4 and intrapleural hyperthermic chemotherapy on 4 patients.

Results: R0 resection was achieved in 12 (57,2%) patients. Postoperative complications were detected in 6 (28,6%) patients, mortality equalled 7,5%. Overall 1-, 3- and 5-year survival was 78% (95% CI 61-95), 49% (95% CI 23-75), 41% (95% CI 15-67) respectively. The median overall survival was 29 months (95% CI 0-60,6). Recurrence was diagnosed in 10 (47,6%) patients. Recurrence-free 1-year survival equalled 60% (95% CI 30-90). Independent negative predictors for overall survival were: thymic cancer, incomplete resection (HR: 5; 95% CI 1,08-23,9; *p*=0,03) (fig. 1), postoperative complications (HR: 4,8; 95% CI 1,13-20,43; *p*=0,03), and local recurrence (HR: 0,172; 95% CI 0,03-0,8; *p*=0,026).



Conclusions: Surgery is the method of choice in the treatment strategy for patients with pleural metastases of thymic epithelial tumours at stage IVa or pleural progression after radical surgery. Thymic cancer histology and incomplete resection are unfavourable prognostic factors. Partial pleurectomy is the most frequent type of surgery performed with

radical intent, significantly influencing the prognosis.

Keywords: Thymoma, Pleural metastasis, Thymoma metastasis

[PE2-08]

Plural Malignant Mesothelioma Analysis, Diagnosis and Treatment

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Aims: Mesothelioma or commonly called malignant mesothelioma is a cancer or malignant tumor that develops from a thin layer of tissue that covers various visceral organs (known as mesothelium). diagnosis of malignant pleural mesothelioma is difficult. At the onset of the disease, functional or general manifestations may be unspecific. Pleural effusion is not especially large or painful. In many patients, radiograph fails to detect any mass, and computed tomography scan results are normal except for the presence of fluid. In nonpleural tumoral forms, moderate localized pain is the most common prodromal sign. Diagnosis depends primarily on histologic findings. Because patients with MPM have a poor outcome and, to our knowledge, an optimal treatment has not been clearly defined to date, MPM will remain a major public health problem for many years. Cancer ranks as a leading cause of death and an important barrier to increasing life expectancy in every country of the world.1 According to estimates from the World Health Organization (WHO) in 2019,2 cancer is the first or second leading cause of death before the age of 70 years in 112 of 183 countries and ranks third or fourth in a further 23 countries (Fig. 1). Cancer&s rising prominence as a leading cause of death partly reflects marked declines in mortality rates of stroke and coronary heart disease, relative to cancer, in many countries.

Methods: The author reviewed and analyzed several journals and summarized them, so that new conclusions were obtained.

Results: Pleural thickening that leads to benign has characteristics that depend on the cause. Pleural thickening caused by asbestos infiltration into the lungs and pleura has the appearance of a scar on the hemithorax wall with its specific location being anywhere on this wall. Asbestosis is a classification of bilateral pleural and diffuse pleural thickening. Pleural thickening due to tuberculosis infection is characterized by fibrotic tissue with classification and location usually at the lung apex. This benign pleural thickening usually involves lesions of the lung parenchyma with consolidation with fibroinfiltrates and calcifications.

Conclusions: The incredible diversity of cancers continues to provide clues to the underlying causes but also reinforces the need for a global escalation of efforts to control this disease. Resource-sensitive and effective package of preventive and curative interventions available for cancer,183,242 and their tailored integration into national health planning can serve to reduce the future burden and suffering of cancer worldwide, while narrowing the real cancer inequalities between countries. transition states and transitional states are observed today. Besides, the true significance of the false negative the diagnosis of biphasic subtype should be assessed in terms of prognosis. Indeed, this prognosis can varies depending on the biphasic spread subtypes in the pleural cavity correlated with diagnostic results of histological diagnosis of the disease by thoracoscopy. True predictive prognostic MPM biphasic subtype value should be assessed in future studies.

Keywords: Mesothelioma, Lung cancer, Pleural maglignant

[PE2-09]

Hypoalbuminemia Can Strongly Predict Severe Acute Lung Morbidity in Locally Advanced Non-Small Cell Lung Cancer

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**These authors contributed equally to this work.*

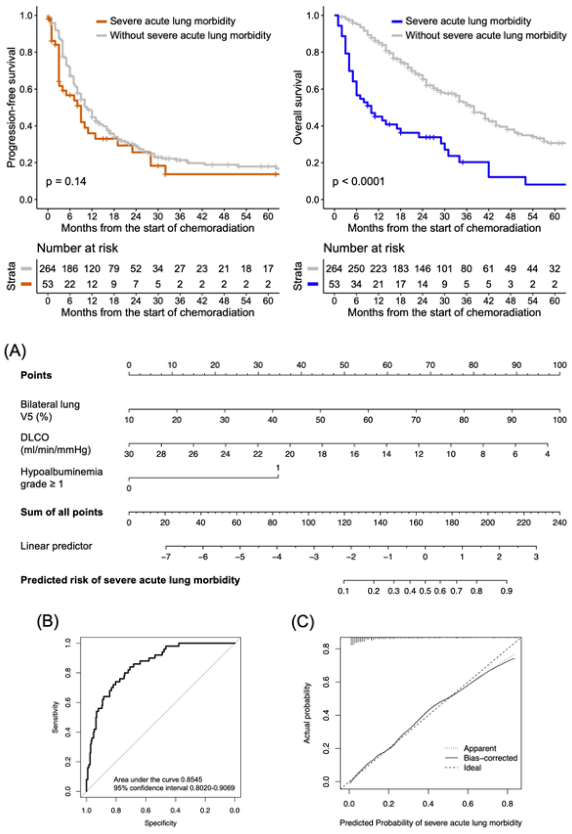
Aims: To investigate the clinical effects and predictive factors of severe acute lung morbidity (SALM) during or after concurrent chemoradiation (CCRT) for locally advanced non-small cell lung cancer (NSCLC).

Methods: Medical records of 317 patients who underwent definitive CCRT for locally advanced NSCLC were reviewed retrospectively. SALM was defined as an event of admission or emergency department visit for acute lung toxicities during CCRT or within 6 months from CCRT. The acute lung toxicities included pneumonitis and pneumonia. Patient characteristics, baseline lung function tests, radiation dosimetric parameters, and laboratory tests were analyzed to investigate the association with SALM. Prognostic endpoints were progression-free survival (PFS) and overall survival (OS).

Results: SALM was reported in 53 (16.7%) patients. Patients with SALM showed significantly worse OS (33.8% in 2 years) than those without SALM (65.3% in 2 years, P <0.001). However, the 2-year PFS rates were 25.7% with SALM and 29.1% without SALM, with no significant difference (p=0.140). In the multivariate logistic regression model, SALM was independently associated with grade & 1 hypoalbuminemia during CCRT (odds ratio [OR] 5.670, 95% confidence interval [CI] 2.487-13.40, p<0.001), diffusing capacity of carbon monoxide (DLCO) (per ml/min/mmHg, OR 0.855, 95% CI 0.743-0.974, p=0.022), and bilateral lung V5 (per 10%, OR 1.872, 95% CI 1.336-2.699, p=<0.001).

Conclusions: SALM could be recognized as a clinical endpoint to evaluate the toxicity and predict survival of CCRT in the NSCLC. Hypoalbuminemia might strongly predict SALM in locally advanced NSCLC.

Keywords: Lung cancer, Chemoradiotherapy, Hypoalbuminemia, Pulmonary diffusing capacity



[PE2-10]

Thoracic Re-Irradiation Using Hypofractionated Radiotherapy (HFRT) or Stereotactic Body Radiotherapy (SBRT) in Non-Small Cell Lung Cancer

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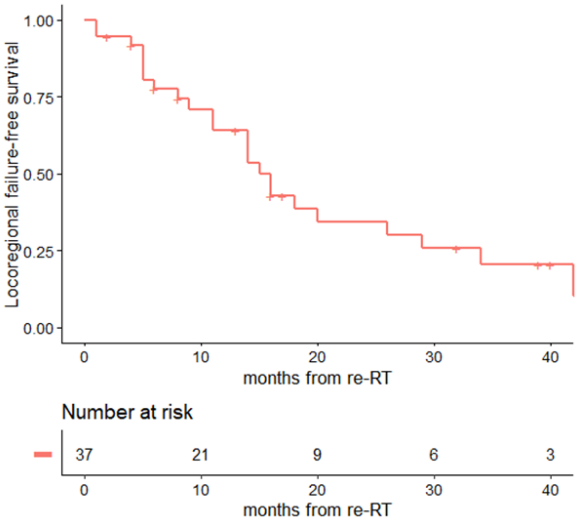
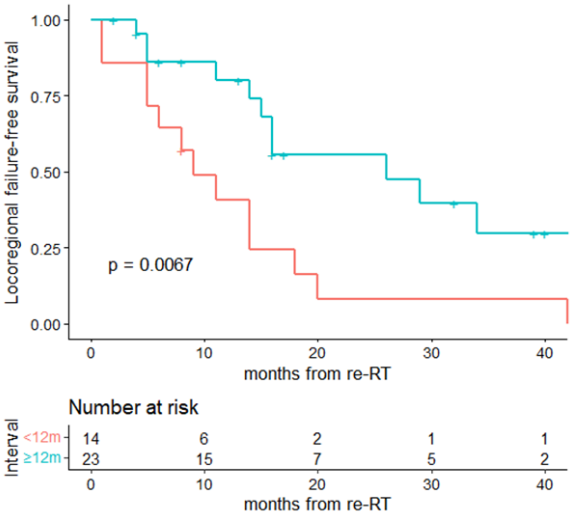
Aims: Re-irradiation (re-RT) has been increasingly important treatment option for local recurrence. The purpose of this study is to analyze treatment outcomes and toxicities of thoracic re-RT using hypofractionated radiotherapy (HFRT) or stereotactic body radiotherapy (SBRT) in non-small cell lung cancer (NSCLC) patients previously treated with HFRT or SBRT.

Methods: Patients diagnosed with NSCLC who re-

ceived more than two courses of lung RT between January 2011 and June 2021 were retrospectively analyzed. Re-RT was defined as the overlap of the 50% isodose line of the two courses of HFRT or SBRT and 37 patients were enrolled. The median re-RT dose of HFRT was 60 Gy (range, 50-70) and SBRT was 52 Gy (range, 48-60). The median interval between initial and re-RT was 13 months (range, 3-74) and the median cumulative biologically equivalent dose for &/&=10 (BED_{10}) was 239 Gy_{10} (range, 168-300).





Results: The 1- and 2-year local control rates were 87.2% and 71.1%, respectively. The 1- and 2-year locoregional failure-free survival rates (LRFFS) were 64.2% and 34.3%, respectively. The interval between initial and re-RT more than 1 year was significant factor for LRFFS (p=0.0067). The 1- and 2-year overall survival (OS) rates were 97.1% and 77.4%, respectively and the BED of re-RT dose>100 Gy_{10} was associated with longer survival (p=0.036). The crude grade 2 toxicity was seen in 14 cases (18.9%) and most common toxicity was chest wall pain (9.5%). No grade 3 or higher toxicities were observed.

Conclusions: Treatment shows favorable outcomes and acceptable toxicities for thoracic re-RT NSCLC patients using HFRT or SBRT who received HFRT or SBRT in advance. Re-RT using HFRT or SBRT can be a promising treatment option for recurrent lung cancer patients with limited treatment options.

Keywords: Non-small cell lung cancer, Re-irradiation, SBRT, HFRT

[PE2-11]

Efficacy and Safety of Cytokine-Induced Killer Cells (CIK) Therapy with Radiotherapy for Patients with Advanced Non-Small Cell Lung Cancer

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University Andalas

Aims: One of the treatments for advanced non-small-cell lung cancer patients is the administration of Cytokine-induced killer cells (CIK) therapy together with radiotherapy. There is debate about the efficacy of combining these two treatments so that the results are not always clear. This study aims to identify the safety and efficacy of cytokine-induced killer cells (CIK) therapy with radiotherapy in patients with advanced non-small-cell lung cancer.

Methods: Several databases (PubMed, Cochrane Library) were used to look for randomized clinical trials (RCTs), systematic review or meta-analysis studies with keywords of "Cytokine-Induced Killer Cells plus Radiotherapy", "Advanced non-small-cell lung cancer", "Efficacy", and "Safety". Studies were

appraised using Mendeley and publish or Perish. Data were then summarized descriptively.

Results: The results show that overall survival (OS), time to progression significantly affects the patient's survival for the better. The results of the study revealed that in some patients after combined treatment, cancer cells were more difficult to enter. There are side effects such as fever, joint pain and insomnia but the risk is low for leukopenia. Quality of life and longer survival for patients with advanced lung cancer with tolerable side effects after combined CIK plus radiotherapy.

Conclusions: The results show that Treatment CIK plus radiotherapy is an effective therapeutic strategy to prevent cells, and prolong the survival of patients with advanced NSCLC. so there is efficacy and safety in this treatment

Keywords: Efficacy, Safety, Cytokine-induced killer cells, Radiotherapy, Advanced non-small-cell lung cancer

[PE2-12]

Clinical Outcomes Following Proton and Photon Stereotactic Body Radiation Therapy for Early-Stage Lung Cancer

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Aims: We aimed to report the clinical outcomes following stereotactic body radiation therapy (SBRT) using photon or proton equipment in early-stage lung cancer.

Methods: We retrospectively reviewed 202 cT1-2N0M0 lung cancer patients who underwent SBRT with 60 Gy in 4 consecutive fractions between 2010 and 2019 at our institution: 168 photon-SBRT and 34 proton-SBRT. Local control, progression-free survival, overall survival, cause-specific survival, and toxicity were analyzed and compared between treatment modalities.

Results: Patients who underwent proton-SBRT had relatively poor baseline lung condition compared to photon-SBRT. Clinical outcomes were comparable between treatment modalities: 5-year local control (90.8% vs. 83.6%, p=0.602); progression-free survival (61.6% vs. 57.8%, p=0.370); overall survival (51.7% vs. 51.9%, p=0.475); and cause-specific survival (70.3% vs. 62.6%, p=0.618). There was no statistically significant difference in grade ≥ 2 toxicities: radiation pneumonitis (19.6% vs. 26.4%, p=0.371); musculoskeletal (13.7% vs. 5.9%, p=0.264); and skin (3.6% vs. 0.0%, p=0.604). In the binary logistic regression analysis of grade ≥ 3 radiation pneumonitis, poor performance status and poor baseline diffusion capacity of lung for carbon monoxide were significant.

Conclusions: Though patients with high risk of developing lung toxicity underwent proton-SBRT more frequently, both SBRT techniques resulted in comparable oncologic outcomes with similar toxicity profiles. Proton-SBRT could be considered for patients with high risk of radiation pneumonitis.

Keywords: Early-stage lung cancer, Stereotactic body radiation therapy, Proton beam, Photon beam

[PE2-13]

Surgical Treatment of Lung Cancer in Patients Over the Age of 75 Years: Single Cancer Centre Experience

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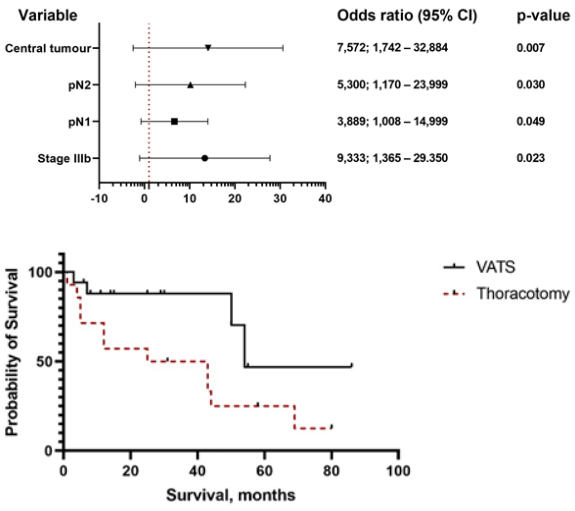
Aims: Lung cancer is diagnosed 2–3 times more often in patients over 70 years of age and is a leading cause of cancer-specific mortality. Surgery is the main treatment, but in numerous cases it cannot be performed due to a high risk of morbidity and mortality. In some patients, extensive comorbidities make surgical treatment impossible. It is of main importance to understand the factors that can influence the outcome in this population to optimize

patient selection and thus improve surgical treatment outcomes. The main aim of this research was to study the outcome of surgery in patients with non-small cell lung carcinoma (NSCLC) over the age of 75 years and to determine the major risk factors for a complicated postoperative period and poor long-term survival.

Methods: The study population included 73 patients, the age of the participants ranged from 75 to 84 years (Me = 78, IQR: 77–79). Lobectomy was performed in 50 (68.5%) patients, segmentectomy – 14 (19.2%), pneumonectomy – 4 (5.5%), bilobectomy – 3 (4.1%), wedge resection – 2 (2.7%). The most common clinical scenario was lobectomy for peripheral stage I lung adenocarcinoma. Lymph node metastases were found in 25 (32.9%). Among 9 (12.9%) patients with pN2, enlarged or hypermetabolic lymph nodes were detected preoperatively in only 4 (44%) patients, given the 7% rate of occult N2 disease. Tumour size ranged from 1 to 14 cm (Me = 3.6 cm, IQR: 2.1–4.5).



Results: Morbiditiy ratio was 16.4%, mortality 5.5%. The multivariate analysis revealed the most significant predictors of the complicated postoperative period, such as stage IIIb (OR 9.3, 95% CI [1.365, 63.816], p = .023), pN1 (OR 3.889, 95% CI [1.008, 14.999], *p*=.049), pN2 (OR 5.300, 95% CI [1.170, 23.999], *p*=.030), central location (OR 7.572, 95% CI [1.742, 32.884], *p*=.007). Overall survival was mostly affected by the CCI ^{3} 6 (OR 0.27, 95% CI [0.063, 0.864]), *p*=.044), stage Ia2 (OR 0.02, 95% CI [0, 0.712], *p*=.033), need for thoracotomy (OR 1.63, 95% CI [1.010, 2.630], *p*=.045).

Conclusions: In each case of lung cancer in patients above 75 years of age, an individualized approach is essential. An increased mortality rate requires a careful and detailed assessment of risk factors and preoperative compensation for any existing comorbidities with the participation of an anesthesiologist, cardiologist and other related specialists if necessary. A rigorous discussion at the tumour board is of equal importance. In the presence of negative predictors, such as stage IIIb, lymph node metastases, central location, squamous cell histology, need for thoracotomy, the absolute risk of postoperative complications is significantly increased.

Keywords: Lung cancer, Elderly patients, Lung resection, Surgery

[PE2-14]

Sleeve Lobectomy in Routine Clinical Practice: Single Cancer Centre Experience

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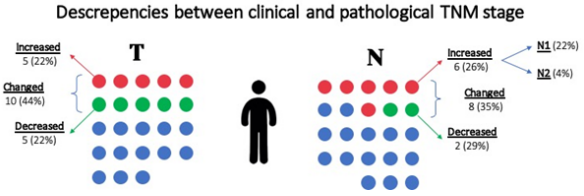
P. Hertsen Moscow Oncology Research Institute

Aims: Sleeve lobectomy is a widely used alternative to pneumonectomy in for lung cancer involving the orifice of main and lobar bronchi or carina itself. The aim of this study was to evaluate the surgical outcome of sleeve lobectomy in routine clinical practice, implementated in the National Cancer Centre in Russia and to figure out the incidence of sleeve lobectomy in Russia.

Methods: The study included 25 patients who underwent sleeve lobectomy for lung cancer in the single Thoracic Department of P. Hertsen Moscow Oncology Research Institute in 2021. All patients were assessed by the tumour board after PET/CT

scan and decision to operate was made according to the international guidelines. In addition, we conducted a survey among the leading thoracic centres and evaluated the frequency and details of technique of sleeve lobectomy and angioplasty in Russian Federation.

Results: The most common clinical pattern for sleeve lobectomy was stage IIb squamous cell lung carcinoma with N1 involvement (n = 11; 44%). The second most common indication was central carcinoid tumour (n = 9; 36%). The incidence of postoperative morbidity was 8%, with no mortality. A sleeved lobectomy was planned preoperatively in only 12 (48%) patients, in others the decision was made after precise intraoperative assessment. The result of the Pearson correlation showed that there was a significant negative association between FEV1 and tumour size, $r(23) = -0.41$, $p=0.01$. Angioplasty was more common for squamous cell carcinoma, $\chi^2(1) = 4.59$, $p=0.032$. Pathological T criteria differed from clinical ones in 10 (44%), N criteria in 8 (35%) of the patients (figure 1). According to the survey, the average frequency of sleeve lobectomy performed in a single thoracic unit is 17 surgeries per year, and that of angioplasty is 12 surgeries per year. The rate of bronchial stump insufficiency was between 0 and 10%.



Conclusions: Sleeve lobectomy is a safe and well-established procedure in the treatment of lung cancer patients. A thorough intraoperative revision of the tumour extension is essential in all patients with central location. Squamous cell carcinoma is more challenging, requiring angioplasty more frequently compared to carcinoid tumours. The extent of the N1 lymph node involvement can be underestimated despite preoperative PET/CT. Sleeve lobectomy needs to be implemented in each thoracic department treating lung cancer patients.

Keywords: Sleeve lobectomy, Routine, Surgery, Lung cancer

[PE2-15]

Hybrid Operative Room

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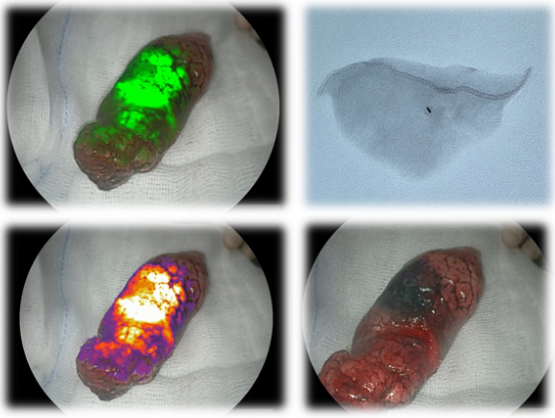
Aims: VATS wedge resection may require conversion to thoracotomy when pulmonary lesions cannot be visually identified. Hybrid operating rooms (H-OR) can provide real-time targeting of the lung lesion, allowing a spectrum of intraoperative marking techniques to help locate non-palpable nodules. We aim to present our triple contrast technique based on the simultaneous use of gold seeds, methylene blue, and indocyanine green to help detect lung lesions in patients without a histological diagnosis.

Methods: Nine patients with non-palpable lung lesions requiring VATS wedge resection underwent lesional targeting in the H-OR with at least one technique, including gold seeds, methylene blue or indocyanine green. Lesions were considered non-palpable due to size, subsolid aspect, or deep location. Lesion were identified using intraoperative CT targeting. The correct intralesional needle positioning and gold seed positioning were verified using intraoperative fluoroscopy. Before surgery, 5 out of 9 patients underwent a preoperative lung lesion biopsy in H-OR to obtain a preliminary pathological report.

Results: The gold seed was visualized correctly in all patients except in one due to dislocation. Methylene blue was visible in 7 out of 9 patients, in 2 patients blue-lake effect was observed. The indocyanine green was not visualized in 3 patients. Minimally invasive wedge resections were then performed and

sent for a preliminary pathological report resulting in lung adenocarcinoma in 6 patients who underwent VATS lobectomy. Three patients were diagnosed with inflammatory lung lesions not requiring a primary pulmonary resection. In 80 % of the cases, the preoperative core biopsy was coherent with the final pathologic report.



Conclusions: Our experience confirms that the H-OR can represent a suitable tool to locate hard-to-find lung lesions if a VATS resection is planned. A multiple marking approach seems advisable to maximize the detecting rate by direct vision, therefore reducing the VATS conversion rate.

Keywords: Hybrid operative room, VATS, Marking tecnique, Lung cancer

[PE2-16]

The Complications, Infections and Other Risk Factors after Lung Surgery: The Literature Review

Zulfa Saumia

Universitas Jambi

Aims: According to the P2PTM Ministry of Health of the Republic of Indonesia, lung cancer often occurs in people who smoke. There are two types of cancer, namely small cell lung cancer and non-small cell lung cancer. The cause of lung cancer can occur due to smoking, passive smoking, exposure to certain toxins and heredity. Symptoms include coughing up blood, chest pain, wheezing, asthma, and weight loss. Various treatments for this cancer range from traditional to lung surgery. Surgery is often the last resort if conventional treatments don't work. Unfortunately, there are various complications that occur after surgery. What and how are these complications?

Methods: The data in this abstract were obtained from reading and analysing various literature research.

Results: The first postoperative pulmonary complication is Nosocomial Infection. According to Daniel et al, the results of a sample of 295 patients with 60% of them underwent surgical resection. These patients had a severe infection (pneumonia or empyema) and a 60% mortality rate. Second, postoperative pulmonary complications. The rate of postoperative pulmonary complications was less in the fast-track group 6.6%. Morbidity and mortality are not much different. Post thoracic surgery for lung cancer can cause acute lung injury (ALI) and become the leading cause of postoperative death.

Conclusions: Nosocomial infection occurs because of the long operation time and postoperative ICU admission. Post-pulmonary care is important to reduce complications following major lung surgery. To avoid death, the index of intraoperative ventilation pressure, intravenous fluids, and alcohol use should be considered.

Keywords: Compications, Infections, Lung surgery

[PE2-17]

Factors Affecting Prolonged Drainage after Lobectomy in Patients with Lung Cancer

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Aims: The number of patients undergoing surgery for lung cancer is on the rise. Determining the length of hospitalization after lung cancer surgery

is the period of maintaining a chest tube drainage. We decided to reduce the hospitalization length by identifying the factors that increase the chest tube indwelling time and reviewing the factors

Methods: From January 1, 2008 to December 31, 2020, a retrospective study was conducted on 748 patients who underwent lung cancer surgery with non-small cell lung cancer or small cell lung cancer. We tried to compare those who had the chest tube for more than a week with those who had the chest tube removed before a week. Through multivariate analysis, elements before surgery, characteristics during surgery, and postoperative pathological results were compared, respectively

Results: There were a total of 226 patients(30%) who maintained the chest tube for more than a week. Among the factors before surgery, the group, characterized by male, elderly(mean age of 69.6), and lowered albumin levels, had a chest tube for a longer time. The prolonged airleak group showed mean blood loss of 489.1 cc, which was more than 299.4 in the control group.In addition, if the difference between input and output is too positive (1146.9 vs 1445.5cc), the chest tube has been maintained for a relatively long time. Adhesion group (focal and diffuse) showed a significant difference in chest tube indwelling time compared to the case without adhesion($p < 0.01$). The comparison of the prolonged air leak in terms of the incision approach also showed no difference between VATS and thoracotomy, but the conversion showed a significantly higher prolonged airleak ratio ($p<0.01$). In pathological findings, the chest tube was maintained for a longer time when the squamous cell type($p<0.01$) and the lymph node metastasis were N2 or higher($p=0.019$).

Conclusions: Through this, it was found that it was necessary to correct elements that could be corrected, such as albumin, through the laboratory findings before surgery. However, since the adhesion and pathological test results identified during surgery are elements that cannot be changed, adjustable elements during surgery must be changed. It is necessary to reduce the excessive difference in input output to be positive and minimize blood loss. Through this, the chest tube indwelling time may be reduced.

Keywords: Lung cancer, Airleak, chest tube

[PE3-01]

Clinicopathologic Characteristics of NSCLC Patients with Uncommon EGFR Mutations in Korea

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Aims: Limited clinicopathologic data are available in patients with non-small cell lung cancer (NSCLC) harboring uncommon epidermal growth factor receptor (EGFR) mutations.

Methods: We retrospectively analyzed the NSCLC patients who had uncommon EGFR mutations, which were categorized as follows: exon 20 insertions, "major" uncommon mutations (G719X, L861Q, and S768I, with or without any other mutation except T790M or an exon 20 insertion), compound mutations and other uncommon mutations.

Results: This study used a lung cancer cohort of the Catholic Medical Center of Korea between january 2018 and December 2021. In 589 EGFR harboting NSCLC mutations, 76 (12.9%) were patients with uncommon mutations. In uncommon mutations, the

composition was as follows: &major& uncommon mutations (50.7%), compound mutations (13.7%) and other mutations (35.6%). Exon 20 ins mutations were 15 (19.7%). The progression free survival (PFS) was shorter in patients with uncommon EGFR mutations compared to patients with common mutations (843.9±58.6 vs. 517.4±118.1, p=0.001). The PFS was not different among major uncommon, compound and other uncommon mutations (except exon 20 ins). The proportion of male (38.6% vs. 53.9%, p=0.011), squamous cell type (2.5% vs. 11.8%, p=0.001), COPD (16.6% vs. 33.3%, p=0.003) were higher, but that of never smoker (63.0% vs. 43.4%, p=0.005) was lower in patients with uncommon EGFR mutations. The mean values of SP263 (10.7 vs. 16.5, p=0.015), total lung capacity (94.9±16.4 vs. 102.4±47.9, p=0.015), residual volume (85.9±28.5 vs. 99.8±107.9, p=0.001) were higher, but that of DLco (86.9±20.2 vs. 85.3±19.9, p=0.027) was lower in patients with uncommon EGFR mutations. In metastatic pattern, pleural metastasis (82.7% vs. 92.1%, p=0.036), pericardial effusion (0.0% vs. 1.3%, p=0.009) were frequent in patients with uncommon EGFR mutations.

Conclusions: The uncommon EGFR mutations had different clinico-pathologic characteristics compared to common EGFR mutations in NSCLC patients. Further investigations are needed to confirm the responsiveness of immunotherapy in this subgroup.

Keywords: Carcinoma, Non-small cell lung, Epidermal growth factor receptor, Mutation

[PE3-02]

The Real-World Clinical Evidence of Lazertinib in Acquired EGFR T790M Mutated Non-Small Cell Lung Cancer

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Aims: Lazertinib is a 3rd generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) designed to overcome EGFR T790M mutation. Currently, 240mg of lazertinib is approved for usage in the acquired EGFR T790M mutation population based on promising clinical and safety profiles. In this study, we evaluated the clinical outcomes of lazertinib in acquired EGFR T790M mutated non-small cell lung cancer patients in a real-world clinical setting.

Methods: From July 2021 to May 2022, clinical outcomes from 89 patients with acquired EGFR T790M mutation patients who were treated with lazertinib at Samsung Medical Center were analyzed. EGFR T790M mutation was confirmed using either a cell-free EGFR test (49.4%) or a tissue-based test (50.6%), and clinical outcomes and adverse events were captured in a retrospective manner.

Results: The median age of the study population was 65 (range 42 & 86), and female (64.0%), never-smoker (67.4%) patients were predominant. Initial EGFR status was mostly confined to either exon 19 deletion (67.4%) or L858R (30.3%). Prior to the lazertinib, patients were treated with gefitinib (43.8%), erlotinib (9.0%), afatinib (41.6%), and dacomitinib (5.6%). The median follow-up duration was 7.2 months (95% CI 5.8 & 8.0), and 79.8% of patients remained on treatment at the time point of data analysis. Eighteen patients (20.2%) discontinued the treatment due to disease progression (12.4%), adverse events (5.6%), other reasons (2.2%). The overall response rate was 66.3%. The PFS rate at 6 and 12 months was 82.5% and 74.2%, respectively. Five patients discontinued the treatment due to grade 3 AST/ALT elevation (n=1), rash (n=1), grade 2 paresthesia (n=1), neuropathy (n=1), nausea and diarrhea (n=1). Otherwise, all the adverse event was tolerable and manageable with appropriate supportive care.

Conclusions: Despite the limited follow-up duration, this result demonstrates that real-world clinical efficacy and safety of 240mg lazertinib in acquired EGFR T790M mutation were similar to previous clini-

cal trial outcomes.

Keywords: Lazertinib, T790M

[PE3-03]

Cancer Immunotherapy by Immune Checkpoint Blockade and Its Advanced Application Using Nanomaterials

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Aims: Cancer is the second leading cause of death worldwide. Traditional approaches, such as surgery, chemotherapy, and radiotherapy have been the main cancer therapeutic modalities in recent years. Cancer immunotherapy is a novel therapeutic modality that potentiates the immune responses of patients against malignancy.

Methods: Immune checkpoint proteins expressed on T cells or tumour cells serve as targets for inhibiting T cell overactivation, maintaining the balance between self-reactivity and autoimmunity. Tumours essentially hijack the immune checkpoint pathway in order to survive and spread. Immune checkpoint inhibitors (ICIs) are being developed as a result to reactivate the anti-tumour immune response.

Results: Recent advances in nanotechnology have contributed to the development of successful, safe, and efficient anticancer drug systems based on nanoparticles. Nanoparticle-based cancer immunotherapy overcomes numerous challenges and offers novel strategies for improving conventional immunotherapies.

Conclusions: The fundamental and physiochemical properties of nanoparticles depend on various cancer therapeutic strategies, such as chemotherapeutics, nucleic acid-based treatments, photothermal therapy, and photodynamic agents.

[PE3-04]

Expanded Access Program (EAP) Use of Pralsetinib in Advanced NSCLC with RET Rearrangement

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Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Aims: Rearranged during transfection (RET) gene rearrangement is a well-known driver event in non-small cell lung cancer (NSCLC). Pralsetinib is a potent and selective inhibitor of RET kinase and has shown its efficacy in oncogenic RET altered tumors. This study evaluated the efficacy and safety of EAP use of pralsetinib in pretreated, advanced NSCLC patients with RET-rearrangement.

Methods: The patients with advanced NSCLC received pralsetinib 400 mg once daily as part of the EAP at Samsung Medical Center, South Korea. Baseline characteristics, treatment history, efficacy and safety outcomes were evaluated through retrospective chart review. The primary endpoint was investigator-assessed overall response rate (ORR) per RECIST version 1.1. Secondary endpoints were duration of response, progression-free survival (PFS), overall survival (OS) and safety profiles.

Results: Between April 2020 to September 2021, 27 patients with NSCLC received pralsetinib. Seven patients who died within three months and 1 patient who arbitrarily refrained after 7 days were excluded from this analysis. The following analysis included 19 patients. Median age was 51 (range, 29-74), median follow-up was 14.0 (range, 10.7-17.3) months. The median number of previous systemic treatment lines was 2 (range, 1-8). The ORR was 57.9% (11 of PR) and median duration of response was 12.7 months (range 4.8-26.0). The median PFS was 22.2 months (95% CI, 17.6-26.8), 12-month PFS rate was 77.7% and 12-month OS rate was 83.1%. The most frequent treatment-related adverse events (AEs)

were edema (8, [42.1%]), pneumonitis (7, [36.8%]). Two (10.5%) patients experienced extra-pulmonary tuberculosis. Among hematologic AEs, anemia (17, [89.5%]) and thrombocytopenia (17, [89.5%]) were reported. Common grade 3 or worse treatment-related AEs were anemia (6, [31.6%]), neutropenia (3, [15.8%]) and elevated ALT (3, [15.8%]). Dose reduction was required in nine patients (47.4%).

Conclusions: Pralsetinib was found to have clinical benefit which is consistent with a pivotal study, when used in EAP in patients with RET-rearranged NSCLC.

Keywords: NSCLC, Pralsetinib, RET rearrangement

[PE3-05]

Durability of Efficacy with Selpercatinib in Patients (pts) with RET Fusion+ Non-Small Cell Lung Cancer (NSCLC)

A Ri Jeon (Non-author Presenter)[1], Alexander Drilon[2], Vivek Subbiah[3], Oliver Gautschi[4], Pascale Tomasini[5], Filippo de Braud[6], Benjamin Solomon[7], Daniel Shao-Weng Tan[8], GuzmÁn Alonso[9], JÜrgen Wolf[10], Keunchil Park[11], Koichi Goto[12], Victoria Soldatenkova[13], Sylwia Szymczak[13], Scott S. Barker[13], Tarun Puri[13], Aimee Bence Lin[13], Herbert Loong[14], Benjamin Besse[15]

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Aims: Selpercatinib is approved in multiple countries for treatment of RET fusion+ NSCLC.

Methods: Updated analysis of selpercatinib in pts with RET fusion+ NSCLC in LIBRETTO-001 was conducted with a 15-month (mo) interval between preceding and current analyses. Primary endpoint: ORR by IRC. Secondary endpoints included DoR, PFS, clinical benefit rate (CBR; CR+PR+SD≥16 weeks), OS and safety.

Results: Efficacy results for treatment naïve pts (N=69) are: ORR% (95%CI)=84.1 (73.3–91.8) and CBR% (95%CI)=92.8 (83.9–97.6); efficacy results for pts previously treated with platinum chemotherapy (N=247) are: ORR% (95%CI)= 61.1 (54.7–67.2) and CBR% (95%CI)=85.4 (80.4–89.6). Despite a median follow-up (f/u) of ~24 mo in the treatment naïve and platinum chemotherapy pretreated populations, median DoR (mDoR) and PFS (mPFS) estimates are still not mature. Among all NSCLC pts, 26 had measurable CNS metastases at baseline per IRC. Selpercatinib treatment resulted in a CNS ORR=84.6%(95%CI=65.1–95.6), (CNS mDoR=9.4 mo[95%CI=7.4–15.3] at a median follow-up [f/u]=25.8 mo). safety population (NSCLC pts with ≥1 dose, N=356),most common AEs in ≥25% pts: dry mouth, diarrhea, hypertension, increased ALT/AST, peripheral edema, constipation, rash, headache, fatigue. 34 pts discontinued treatment due to AEs, including 11 due to drug-related AEs per investigator.

Conclusions: With longer f/u and additional patients, selpercatinib demonstrates durable efficacy and intracranial activity regardless of line of therapy. The safety profile of selpercatinib remains consistent with prior reports. Previously presented at the IASLC-ESMO European Lung Cancer Conference - 12th ELCC: March 2022, "FPN (Final Publication Number): 27P", "Alexander Drilon et al." - Reused with permission.

Keywords: Efficacy, LIBRETTO-001, Non-small cell lung cancer, RET fusion+ NSCLC

[PE3-06]

Biological Importance of Tetrahydrofuran Lignan Grandisin in the Medicine for Their Chemoprotective Effect

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Technology and Sciences, Payagraj, India

Aims: Lignans are natural compounds formed in the nature through polymerization of two phenylpropanoid (C6–C3) derivatives in different ways. Lignans are mostly free in the nature, but some of them are also found in the form of glycosides. Lignans have been studied in the scientific field mostly because of their important chemical characteristic and pharmacological activities including anti-inflammatory potential. Lignans are believed to be responsible for inhibiting the growth of different human prostate cancer cell.

Methods: Therapeutic effectiveness of tetrahydrofuran lignan grandisin in the medicine has been investigated through scientific data analysis of different scientific research work. Biological importance of grandisin in the medicine against human disorders and complications has been investigated here through scientific data analysis of different research work. Detailed pharmacological activities scientific data have been analyzed in the present work through scientific data analysis to know the therapeutic potential of grandisin in the medicine.

Results: Scientific data analysis revealed the therapeutic effectiveness of tetrahydrofuran lignan grandisin in the medicine. Biological importance of tetrahydrofuran lignan grandisin in the medicine for their chemoprotective effect have been investigated in the present work through scientific data analysis and signified their positive potential in the medicine as in the scientific research grandisin showed dose-dependent protective effect against mutagenicity. Other pharmacological activities data also support the chemoprotective effect of tetrahydrofuran lignan grandisin in the medicine.

Conclusions: Scientific data analysis revealed the chemoprotective effect of tetrahydrofuran lignan grandisin in the medicine.

Keywords: Chemoprotective effect, Tetrahydrofuran lignan, Grandisin, Medicine

[PE3-07]

Randomized Double-Blind Placebo-Controlled Trial of Nicotinamide and EGFR-TKIs for EGFR-Mutated Lung Adenocarcinoma

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Aims: Runt-related gene 3 (RUNX3) inactivation by promoter hypermethylation correlates with poor clinical outcome and occurs in 70% of lung adenocarcinomas. Nicotinamide, a well-known sirtuin inhibitor, re-activates the epigenetically silenced tumor suppressor RUNX3 in cancer cells. We examined whether the addition of nicotinamide to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) increases the survival of patients with stage IV lung cancer with EGFR mutations (exon 19 deletion or L858R).

Methods: Stage 4 or recurred NSCLC with EGFR positive patients were included and stratified by EGFR mutation status, ECOG performance status, and type of TKIs. Nicotinamide or placebo was administered upto 2 years.

Results: From 2015 to 2018, a total of 110 consecutive patients were randomized into nicotinamide (1g/day, n=55) or placebo (n=55) groups. The mean age was 68.5 years, and 63.6% were female and 76.4% were never-smokers. Gefitinib was used in 59.1% of patients and erlotinib in the remaining 40.9%, resulting in an objective response of 56.0%.

After a median follow up duration of 54.3 months, the median PFS of the nicotinamide group was 12.7 months (95% confidence interval: 10.4~18.3) whereas that of the placebo group was 10.9 months (9.0~13.2) (Log-rank p=0.2, Fig 3A). After a median follow up duration of 58.4 months, the median

OS of the nicotinamide group was 31.0 months (25.2~45.2) whereas that of the placebo group was 29.4 months (20.3~35.6) (p=0.2, Fig 3B).

The number of adverse events, such as skin rash, mucositis, and diarrhea, was not significantly different between the two groups.

Conclusions: PFS and OS were numerically longer when EGFR TKIs were used in combination with nicotinamide than when patients were treated with EGFR TKIs alone.

Keywords: Nicotinamide, EGFR-TKI, Adenocarcinoma

[PE3-08]

Clarification of Oligometastasis Showing Survival Benefit from Local Ablative Therapies during Tyrosine Kinase Inhibitor Treatment

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Aims: In non-small cell lung cancer (NSCLC) with oligometastasis (OM), the lack of universal criteria for assessing OM has hindered the application of local ablative therapy (LAT). We aimed to investigate the feasibility of four criteria on OM concerning clear survival benefits from LAT during tyrosine kinase inhibitor (TKI) treatment.

Methods: This single-center, retrospective study included patients with advanced NSCLC who received LAT because of OM during TKI treatment at Asan Medical Center from January 2011 to December 2020. At the application of LAT OM was classified according to four criteria: TNM, EORTC-LCG, NCCN, and ORGAN. We compared survival outcomes between patients with and without OM.

Results: The overall survival of the 117 patients included in the analysis was 70.8 months (95% confidence interval [CI]: 56.6–85.1), which was greater than that of the historic controls. The patients with OM meeting all four criteria (hazard ratio [HR] with 95% CI of TNM criteria 0.24 with 0.10–0.57; p = 0.001, EORTC-LCG criteria 0.34 with 0.17–0.67; p = 0.002, NCCN criteria 0.41 with 0.20–0.86; p = 0.018 and ORGAN criteria 0.33 with 0.18–0.60; p < 0.001) had significantly longer survival compared with patients who did not after adjusting for confounding factors. Furthermore, increasing the number of extra-thoracic metastatic organs to two or more were independent predictive factors for worse survival outcomes (2 organs: HR 3.51; 95% CI: 1.01–12.14; p = 0.048, 3 organs: HR 4.31; 95% CI: 0.94–19.73; p = 0.060, 4 organs: HR 24.47; 95% CI: 5.08–117.80; p < 0.001).

Conclusions: Patients with OM defined by all four criteria showed prognostic benefits from LAT during TKI therapy. The number of extra-thoracic metastatic organs involved should be considered for the application of LAT because of its prognostic implication.

Keywords: Lung neoplasm, Non-small cell lung carcinoma, Metastasis, Prognosis

[PE3-09]

Lazarus Effect of Capmatinib in MET Exon 14 Skipping Mutation-Positive Lung Adenocarcinoma with Extensive Central Nervous System Metastasis

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Aims: Several selective mesenchymal-epithelial transition (MET) inhibitors have recently demonstrated favorable systemic efficacy in MET exon 14 skipping mutation-positive non-small cell lung

cancer. However, their efficacy data against central nervous system (CNS) metastasis, especially leptomeningeal seeding, is limited.

Methods: Here, we report a case of MET exon 14 skipping-positive metastatic lung adenocarcinoma with extensive brain and leptomeningeal metastasis, which dramatically responded to capmatinib.

Results: Recently, we encountered a case of a 65-year-old woman who was diagnosed with metastatic lung adenocarcinoma. As routine molecular testing showed no genomic alterations, including epidermal growth factor receptor mutation and anaplastic lymphoma kinase translocation, the patient received a frontline platinum-doublet followed by paclitaxel. However, the tumor did not respond to these therapies, and her condition became deleterious owing to extensive brain and leptomeningeal metastases. Plasma genotyping revealed that the tumor harbored a MET exon 14 skipping mutation, and we started capmatinib, a selective MET inhibitor. The CNS lesions markedly decreased and the performance status of the patient dramatically improved.

Conclusions: Our report highlights the significant CNS activity of capmatinib, even in cases of leptomeningeal metastasis. In addition, this report emphasizes the importance of the active utilization of molecular profiling to detect rare but druggable genetic alterations for the better management of patients with lung cancer.

Keywords: Lazarus effect, Capmatinib, MET exon 14 skipping mutation, Leptomeningeal metastasis

[PE3-10]

Psychological Problems of Elderly Lung Cancer Patients Undergoing Chemotherapy

Ardela Iga Pratiwi

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Aims: According to data from the Global Burden of Cancer Study from WHO, lung cancer in Indonesia in 2020 is in third place with 34,783 cases. Lung cancer in elderly patients should receive special attention because it affects the general condition of the patient. Chemotherapy is one of the therapeutic modalities used in the treatment of elderly lung cancer patients. Undergoing chemotherapy with hospitalization will have a psychological impact on elderly patients. At least elderly lung cancer patients experience symptoms of stress. This study aims to describe the psychological problems of elderly patients with lung cancer undergoing chemotherapy.

Methods: This study used electronic data base as a method by reviewing some previous article published in 2015 to 2021.

Results: The results showed that elderly lung cancer patients who were hospitalized showed behaviors and moods such as anxiety, fear, boredom, sadness and anger, stress and depression. Undergoing a series of chemotherapy causes severe stress in the elderly. This is caused by stressors related to disease conditions and chemotherapy procedures, the effects of chemotherapy, long and repeated treatment times in the hospital, activity restrictions, diet, fluid intake, loss of self-control and independence, these circumstances make lung cancer patients advanced. They feel unmotivated to face everyday life, despair with the conditions they are experiencing and have low life expectancy.

Conclusions: Psychological problems such as stress, anxiety and depression in elderly lung cancer patients are stressors that can lower the body's immunity. This has implications for long treatment times and increased treatment costs. Therefore, the management of elderly lung cancer patients does not only focus on treatment the disease, but also how the patient's needs during hospitalization are holistically. Good social support is needed, both to prevent psychological comorbidities and to help control and manage symptoms.

Keywords: Lung cancer, Elderly, Chemotherapy, Psychological

[PE3-11]

Nivolumab as Maintenance Therapy Following Platinum-Based Chemotherapy in Non-small Cell Lung Cancer Patients after Tyrosine Kinase Inhibitor Therapy

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Aims: Although several studies have reported the improved response rate of immunotherapy and cytotoxic chemotherapy combination, a therapeutic role of salvage treatment after failure of targeted therapy in the patients with epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) is unclear.

Methods: In this open-label, single arm phase 2 trial, we enrolled patients aged 18 years or older with EGFR mutant NCSLC who failed 1st or 2nd line EGFR tyrosine kinase inhibitor (TKI) treatment. Patients received platinum based chemotherapy followed by nivolumab maintenance therapy. A 240mg nivolumab was intravenously administered every 2 weeks for 3 months followed by 480mg every 4 weeks until disease progression and unacceptable toxic effects, or other protocol-defined reasons. The primary endpoint was progression-free survival (PFS). Secondary outcomes were overall survival (OS), and incidence of grade 3-4 treatment-related adverse events (AEs).

Results: The total number of 26 patients were enrolled between May, 2020 and July, 2021.The median PFS was 5.8 months (95% CI, 4.18-7.42 months). Median OS was not reached; 12-month and 24-month OS rates were 80.8% and 49.8%, respectively. Overall response rate was 7.7 % (2/26) and disease control rate was 19.2% (5/26). Grade 3-4 treatment-related AEs occurred in 4 (15.4%) patients; the most frequent AEs was increased alanine aminotransferase (7.7%).

Conclusions: A nivolumab maintenance treatment after platinum-based chemotherapy did not seemed to provide a treatment benefit after EGFR-TKI failure in patients with EGFR mutant NSCLC. There was no new unexpected toxicity to nivolumab.

Keywords: Non-small cell lung cancer, Tyrosine kinase inhibitor therapy, Platinum-based chemotherapy, Nivolumab

[PE3-12]

Leptin Gene Inhibitor Using Curcumin Potency with Silibinin (Cur-Sil) Modified Magnetic Nanoparticles (Fe3O4) [Poly(Ethylene Caprolactone)-Poly(Ethylene Glycol) (PCL-PEG)] Co-Polymer in Lung Cancer Management

Andi Nursanti

Andini Persada College of Health Sciences Indonesia

Aims: Leptin, an adiposity-derived cytokine, plays a role in the carcinogenesis of lung cancer. *In vitro* and *in vivo* studies have shown that curcumin, a combination of silibinin based on PCL-PEG modified magnetic nanoparticles, has great potential in the treatment of lung cancer. The purpose of this study was to describe the potential of Silibinin (Cur-Sil)-Loaded Combination Curcumin Modified Magnetic (Fe3O4) Nanoparticles [Poly(Ethylene Caprolactone)-Poly(Ethylene Glycol) (PCL-PEG)] Copolymer as Leptin Gene Inhibitor in Cancer Management Lungs.

Methods: The method studied is a narrative method by grouping journal article data, the extraction results are the same as the results measured to answer the objectives whose sources have been tested for validity, relate to each other, and support the description or analysis of the discussion. Materials include published research journals on Lung Cancer, Curcumin, Silibinin, Magnetic Nanoparticles (Fe3O4), Polyethylene-Caprolactone (PCL), and Polyethylene-Glycol.

Results: Curcumin and silibinin are natural herbal

components with multitarget anticancer characteristics. The combination of curcumin and silibinin has an inhibitory effect on the leptin/LEP gene and its receptors, thereby inhibiting the activation of the JAK/STAT pathway which results in inhibition of cell proliferation, and angiogenesis, and triggers cell apoptosis. The weakness of this combination is due to natural herbal compounds with hydrophobic structures with low water solubility so the administration of high doses is very limited. To overcome this, a drug delivery system based on nanoparticle technology was applied as a nanocarrier of curcumin and silibinin (Cur-Sil) compounds to cancer targets with appropriate special features. In addition, silibinin can act as a bioenhancer, and can also act as a specific inhibitor of leptin, so it is synergistic with curcumin with higher pharmacological effects. *in vitro* and *in vivo* studies have shown that curcumin combined silibinin based on PCL-PEG modified magnetic nanoparticles has great potential in the treatment of lung cancer. The advantages of PCL-PEG modified magnetic nanoparticles in carrying the active compounds curcumin and silibinin as specific inhibitors of leptin expression, include good chemical stability in water, biodegradability, biocompatibility, good targeting of lung cancer cells, and no toxicity.

Conclusions: Pharmacology of curcumin and silibinin encapsulated magnetic nanoparticles based on modified PCL-PEG copolymer as an effective inhibitor of leptin expression without toxicity to normal tissues. This finding can be used as an alternative treatment and become the latest therapeutic modality for lung cancer.

Keywords: Curcumin, Leptin gene, Lung cancer, Nanoparticle, Silibinin

[PE3-13]

Efficacy of Chamomile for Preventing Chemo- and Radiotherapy-induced Oral Stomatitis

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Aims: This review aims to compare the efficacy of chamomile in preventing chemo- or radiotherapy-induced oral stomatitis vs. placebo, no treatment, or another active intervention, in terms of prevalence, severity, and presence of adverse events.

Methods: Findings from randomized controlled trials (RCT) and previous systematic reviews were searched from databases such as Science Direct, PubMed, CNKI, Lancet, Herdin, Ovid, and Cochrane library, and websites such as UpToDate and Google Scholar. The participants in the studies must be cancer patients scheduled for chemotherapy or radiotherapy. Participants must be given chamomile oral. The control group must be placebo, standard medical, or single factor intervention. The outcome must be change in incidence of oral mucositis. As for the secondary outcome, severity based on the WHO 5-point scale, adverse events, and median time before the disease is prevented, in days, were used. Data were analyzed using Review Manager 5.4.1. Subgroup analyses based on age, chamomile formulation and administration, presence of adjunct care, treatment duration, type of control, and type of tumor was conducted.

Results: Eight randomized controlled trials were used for pooled estimates analysis of the incidence of oral mucositis after chamomile prophylaxis. Results showed that there was a 22% reduction in incidence of oral mucositis, however, this was not

significantly different [RR 0.78, 95% CI 0.61, 1.01, p=0.06]. Subgroup analysis of the included studies showed that chamomile prophylaxis is more effective in the pediatric population [RR 0.88, 95% CI 0.64 to 1.21, p=0.43]. There is also a significant reduction in incidence when chamomile is administered as a mouthwash [RR 0.77, 95% CI 0.60 to 0.99, p=0.04]. As for secondary outcomes, overall severity was significantly reduced after chamomile prophylaxis [MD -0.34, 95% CI -0.60, -0.08, p=0.010]. In terms of duration of oral mucositis, there was no significant difference after chamomile prophylaxis, however, there seemed to be an increase in dryness as compared to the control group [MD -3.71, 95% CI -7.43 to 0.01, p=0.05]. Incidence of adverse effects was also significantly reduced [RR 0.41, 95% CI 0.27 to 0.61, P <0.0001]. This study is limited by the study population, inconsistent chamomile preparation and administration, and differing standard oral care given to the patients. To address this, there should be more randomized controlled trials employing similar protocols.

Conclusions: Pooled analysis of the eight randomized controlled trials in this review did not provide adequate evidence supporting the use of chamomile preparation as a prophylactic compound for radio- or chemotherapy-induced oral mucositis. There was a decrease in the risk for developing oral mucositis in patients receiving prophylactic chamomile treatment but this was not significant based on the random effects model. However, subgroup analysis revealed that chamomile when given as a mouthwash, and used in pediatric populations or ages below 18 years old, results in significant reduction in the incidence of oral mucositis.

Keywords: Chamomile, Oral mucositis, Mouthwash, Meta-Analysis

[PE3-14]

How the Caregiver Status Could Increase the Quality of Life among Elderly with Lung Cancer and Dementia Status?

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Alumnus of Universitas Gadjah Mada

Aims: The elderly are the most vulnerable group to lung cancer. The potential curative treatment is surgery, chemotherapy, radiation, targeted therapy, or combination treatment although the long-term survival is varied from below one year to five years or longer. Indonesia will become the second-largest Silver Economy in the world after China and the prevalence of Elderly with independence barriers reaches 3.7%. The elderly with post-treatment are very dependent on the presence of a caregiver to maintain their quality of life. However, the availability of certified informal caregivers is not available in Indonesia.

Methods: This study uses Indonesia Family Life Survey (IFLS) to explore the availability of caregivers in maintaining the quality of life of the Elderly post-treatment with Dementia.

Results: Indonesian elderly reach 10.8% of the total population and 48% of them have chronic diseases. 34.7% of elderly with post-treatment were identified as having dementia symptoms moderate to severe which were assessed using mini-cognitive test scoring. The elderly needing long-term care due to these health conditions reached 9.7% and 88% of them did not have a caregiver or took care of themselves. Only less than 1% of the elderly are cared for by paid caregivers and are concentrated in urban areas. 36% of post-treatment elderly with dementia are holders of government health assistance. Using the Geriatric Depression Scale (GDS) it was found that the percentage of elderly post-treatment with dementia who had a caregiver with mental health problems was lower than respondents who did not have a caregiver.

Conclusions: Indonesia is an aging market that is

pressed to meet the availability of certified informal caregivers. A comprehensive strategy is needed to improve the quality of life of the post-treatment elderly with dementia through the availability of certified caregivers and community services such as the realization of standardization policies for training institutions, curriculum, accreditation mechanisms, and senior living.

Keywords: Certified caregiver, Elderly with dementia, Mental health, Silver economy

[PE3-15]

Nurses Attitudes and Knowledge Regarding Palliative Care at Banyubening Hospital

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Aims: Palliative care in Indonesia is not yet popular when compared to curative and rehabilitative care. This is reinforced by WHO data which shows that 86% of patients who require palliative care have not received it. According to Tampubolong, N.R, et. all (2021), several obstacles in implementing palliative care in Indonesia, namely the absence of a palliative care module in the education curriculum and training of health workers in health services, the lack of palliative care education for nurses, the lack of perception of care providers, and the lack of facilities to provide palliative care. The aim of this study was to determine the level of attitudes and knowledge of the medical team about palliative care in Banyubening Hospital Boyolali Indonesia.

Methods: This research is quantitative research by distributing questionnaires to 21 nurses. Measuring the level of attitudes, The Frommelt's Attitude Toward Care of the Dying (FATCOD) scale questionnaire was used and Knowledge measured used, the Palliative Care Quiz for Nursing (PCQN) questionnaire.

Results: By using the rho sperm test, it was found that there was no significant relationship between attitudes and knowledge with a value of $p>0.05$ (0.207> 0.05), and the level of strength of the relationship between the attitude variable and palliative nursing knowledge was 0.287 or in the sufficient category and the direction of the relationship was negative. Attitude is in the negative category (70.7 <112) while knowledge is in the sufficient category (10.4 <10.9).

Conclusions: Based on the results of the study, it can be concluded that there is a need for a palliative care module, improving facilities to provide palliative care, and training for health workers who present professional nurses who are able to facilitate palliative care.

Keywords: Palliative care

[PE3-16]

Palliative Care for Patients with Non-Small Cell Lung Cancer

Nuraliah

West Sulawesi Research and Empowerment Center

Aims: One of the leading causes of death in cancer cases in the world is lung cancer. It is estimated that by 2030, 26 million people will die from cancer. Non-Small Cell Lung Cancer (NSCLC) is the most common lung cancer with a percentage of about 80% of all lung cancers. Palliative care, especially for lung cancer patients, is needed in assessing and evaluating patient complaints so that they can develop and implement a comprehensive treatment plan to improve the patient's quality of life. The purpose of this study was to determine how quality palliative care in patients with lung cancer is in accordance with relevant nursing diagnoses.

Methods: The research method used is a literature review approach by using several sources of journals or articles selected based on predetermined criteria used in this study. The process of searching for the journal literature was taken from electronic-based

indexes such as Google Scholar, PubMed, ProQuest, and Ebsco. The criteria for the inclusion of articles was that they were published from 2012-2022. The keywords used are "Lung cancer", "Palliative care", and "Non&small-cell".

Results: Patients assigned to early palliative care had a better quality of life than patients assigned to standard care. In addition, fewer patients in the palliative care group than in the standard care group had depressive symptoms. Despite the fact that fewer patients in the early palliative care group than in the standard care group received aggressive end-of-life care median survival was longer among patients receiving early palliative care.

Conclusions: Among patients with metastatic non&small-cell lung cancer, early palliative care led to significant improvements in both quality of life and mood. As compared with patients receiving standard care, patients receiving early palliative care had less aggressive care at the end of life but longer survival.

Keywords: Lung cancer, Palliative care, Indonesia

[PE3-17]

Cancer-Related Dysfunctional Beliefs about Sleep Mediate the Influence of Sleep Disturbance on Fear of Progression among Patients with Surgically Resected Lung Cancer

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Aims: Lung cancer is associated with significant psychological distress, including fear of progression (FoP). Evaluation of FoP and other distresses is important in disease prognosis. Because insomnia and depression are both highly prevalent and associated with FoP, we examined the association between FoP, insomnia, and depression in cancer patients. Further, we tested the mediation effect of cancer-related dysfunctional beliefs (C-DBS) on this association.

Methods: We analyzed collected data of patients with surgically resected non-small cell lung cancer from a single center randomized controlled study for digital healthcare applications. Baseline demographic and clinical variables were collected. In addition, self-report questionnaires including FoP-Q-SF, PHQ-9, ISI, and C-DBS were performed. Linear regression was used to explore the association between FoP and other variables. Mediation analysis was performed to examine the mediation effect of C-DBS.

Results: The mean scores of self-report questionnaires of 320 participants were as follows: FoP-Q-SF (36.5 $\pm$ 12.2), C-DBS (11.7 $\pm$ 6.0), ISI (15.5 $\pm$ 6.9), and PHQ-9 (11.4 $\pm$ 6.6). A regression model showed FoP was predicted by age (β = -0.13, p = 0.007), PHQ-9 (β = 0.35, p < 0.001), and C-DBS (β = 0.28, p < 0.001). C-DBS mediated the association between insomnia and FoP, whereas depression directly influenced FoP without a mediation effect.

Conclusions: Among patients with surgically resected lung cancer, C-DBS mediated the effect of insomnia severity on FoP. Depression directly influenced FoP, but C-DBS did not mediate this association. To reduce FoP among patients with lung cancer, C-DBS should be addressed in the cognitive behavioral therapy module.

Keywords: Fear of progression, Insomnia, Lung cancer, Psychological distress

[PE3-18]

Support to Improve Quality of Life with Self Efficacy in Lung Cancer Patients in Indonesia

Mega Dwi Septivani

Politeknik Negeri Padang

Aims: Based on the records of the Global Burden of Cancer Study, the prevalence of cases of death from cancer in Indonesia increased to 8.8 percent, including mortality caused by lung cancer. Lung cancer is the cause of about 11 percent of new cancer cases and number one cancer deaths in the world and in Indonesia. Lung Cancer patients experience physical and psychosocial changes. Self-efficacy is one of the most important candidates, as their influence on health outcomes is based on a solid theoretical and empirical basis. In addition to demonstrating that self-efficacy explain quality of life, it is important to find out if these factors are somehow related, either receiving support that drives self-efficacy or receiving support that promotes self-efficacy. Establishing operational procedures for self-efficacy and social support would help design better psychosocial interventions.

Methods: Articles starting from 2002-2022 are collected from an electronic database. Then as many as ten selected articles were reviewed to answer the objecives of this study.

Results: Two cross-sectional studies have shown an association between improved self-efficacy and quality of life (physical andfunctional aspects), better adjustment to disease, and diseasemanagement behaviors in lung cancer treatment. Liao et al., (2014) found that pretreatment self-efficacy in diseasemanagement explained emotional, social, and overall quality of life, whereas quality of life did not predict the physical and functional aspects of A longitudinal studyconducted on a mixed patient population (including lung cancersurvivors as well as patients with other types of cancer) foundthat self-efficacy in coping with disease-related symptoms wasassociated with emotional well-being. It has been shown to predict but not physical well-being. The results of this study show that there is a significant correlation between self-efficacy, improved quality of life for lungcancer patients, and physical and functional support, which increases patient motivation. Additionally, self-efficacy is an important factor in protecting against negative mental states and reducing unpredictable behavior and mortality.

Conclusions: It can be concluded that self efficacy as a supporting factors for improving the quality of live of lung cancer patients

Keywords: Self efficacy, Quality of life, Indonesia, Lung cancer patients

[PE3-19]

Palliative Care for Lung Cancer Patient during Covid19

Fitri Kurnia

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Aims: The COVID-19 pandemic has changed all existing settings, almost every aspect of making change and innovation work as it should. Especially in the health sector, the most urgent thing that must be a concern, various health procedures have been adapted to current conditions to minimize unwanted conditions. Lung cancer sufferers are one of the groups most at risk of exposure to COVID-19. Cancer treatment is not only in the form of medical measures, but also with palliative care. Palliative care is required for terminally ill patients. Has this pandemic condition also changed palliative care procedures in lung cancer patients? This study aims to present information about palliative care during a pandemic and what changes have been made.

Methods: Literature review.

Results: The demand for palliative care services is increasing during the pandemic, because it is based on anxiety and concern by the current conditions. The system of changes in health facilities also mini-

mizes the possibility of face-to-face contact with patients. So that palliative care is done virtually. Changes in the pillars of palliative care during the covid19 pandemic: 1. Physical (guidelines for palliative care during the pandemic, and priority handling), 2. Psychological and Social (big psychosocial impact on patients), 3. Spiritual (spirituality in uncertainty).

Conclusions: The COVID-19 pandemic has changed the method of health care, as face-to-face contact is minimized, with the risk of a lack of specialized resources in palliative care.

Keywords: Palliative care, Lung cancer, Covid19, Pillars of palliative care

[PE3-20]

Real World Evidence of First-Line Atezolizumab/Etoposide/Carboplatin in Patients with Extensive-Stage Small-Cell Lung Cancer: A Single-Institutional Clinical Experience

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Aims: Atezolizumab plus etoposide and carboplatin regimen is used as the first-line treatment for extensive-stage small cell-lung cancer (SCLC). However, real-world data are limited. This study aimed to analyze the characteristics, clinical efficacy, and safety of atezolizumab plus etoposide and carboplatin in the first-line treatment of extensive-stage SCLC.

Methods: We retrospectively reviewed medical records of patients with extensive-stage SCLC who underwent first-line treatment atezolizumab plus etoposide and carboplatin at Samsung Medical Center between October 2019 and June 2021. We analyzed the patient characteristics, clinical efficacy, and adverse events.

Results: A total of 122 patients, 113 (92.6%) were men, and the median age was 61 years (ranging from 42 to 82). Thirty-six (29.5%) patients had brain metastasis at baseline. As best response to treatment, one (0.8%) patient showed complete response, 103 (84.4%) patients showed partial response, and 11 (9.0%) showed stable disease. Of these, 19 (15.6%) patients had ongoing response. The median duration of response was 3.9 months (95% confidence interval [CI], 3.4 to 4.4). At a median follow-up 14.0 months, the median overall survival was 14.4 months (95% CI, 12.4 to 16.1). The median progression-free survival was 5.3 months (95% CI, 4.5 to 5.8). In terms of adverse events, neutropenia (8.2%), pneumonitis (4.9%), and hypothyroidism (4.1%) were the most common adverse events. Eighteen (14.8%) patients had immune-related adverse events (IRAEs), with hypothyroidism as the most common. Four (3.2%) patients experienced grade 3 IRAEs (pneumonitis and liver enzymes elevation) and one (0.8%) patient had grade 4 pneumonitis.

Conclusions: Atezolizumab plus etoposide and carboplatin showed efficacy and safety in this real-world data.

Keywords: Small cell lung cancer, Atezolizumab, First line

[PE3-21]

Efficacy and Safety of First-Line Immunotherapy in Combination with Chemotherapy for Small Cell Lung Cancer Patients

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Aims: Lung cancer is a dangerous disease in the world. The results show that more men suffer from lung cancer than women. One of the efforts to treat this disease is chemotherapy. The results of the prognosis show that chemotherapy has an impact on longer survival and better quality of life. If the addition of an Immune Checkpoint Inhibitor in che-

motherapy, a synergistic effect is seen and survival is better. However, there is controversy regarding the efficacy of this immunotherapy. This study aims to analyze the efficacy and safety of small cell lung cancer patients with immunotherapy and chemotherapy treatment.

Methods: The method used is literature search through Pubmed/MEDLINE, Cochrane Library, EBSCO, and PROQUEST was conducted to find studies about the effectiveness of Line Immunotherapy in Combination with Chemotherapy for Small Cell Lung Cancer Patient's, of especially in terms of extensive SCLC Stadium. Two studies were selected and critically appraised. The data were then summarized descriptively.

Results: The results showed that immunotherapy in the form of ipilimumabm plus chemotherapy is better than OS (hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.4-1.02; risk ratio (RR) 0.90, 95% and Reck (2013) found (HR: 0.95, 95% CI 0.59 -1.54, 95% CI 0.75 (0.48-1.19) than placebo plus chemotherapy. The combination of immunotherapy with chemotherapy was better than standard chemotherapy.

Conclusions: In both the results suggest that immunotheray with ipilimumabm suggests that PD-L1 inhibitors may be preferred. The results prove that Immune Checkpoint Inhibitors in first-line treatment for extensive-stage SCLC patients should be required.

Keywords: Efficacy, Safety, Immunotherapy, Chemotheraphy, Lung cancer

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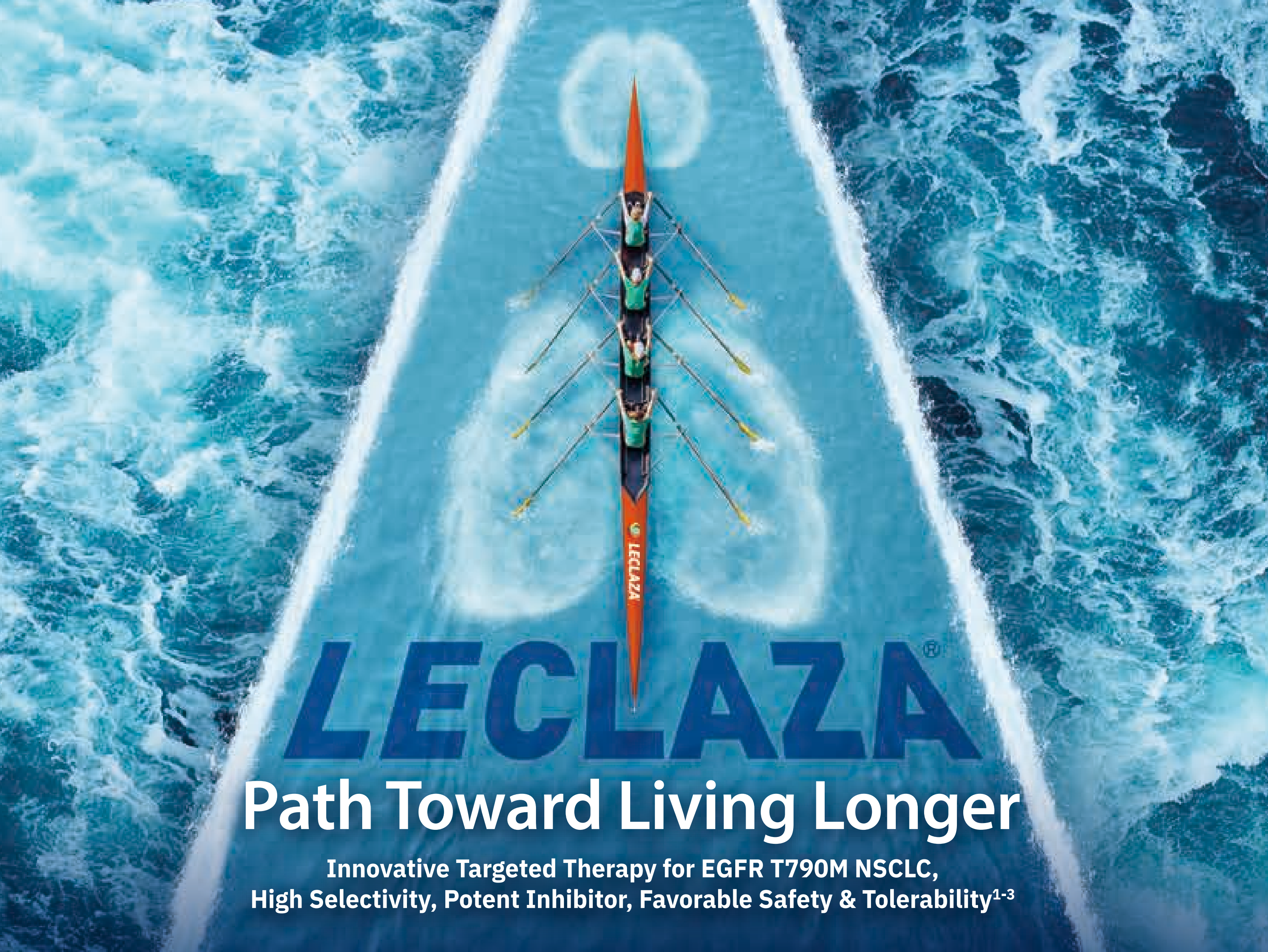

EGFR, Epidermal Growth Factor Receptor ; **NSCLC,** Non-Small-Cell Lung Cancer

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(lazertinib mesylate monohyrate) Tablets 80mg

【원료약품 및 분량】 1정 중
- **유효성분 :** 레이저티닙메실산염일수화물(별규)············96.48 mg (레이저티닙으로서 80 mg)
- **첨가제 :** 미결정셀룰로오스, D-만니톨, 크로스카멜로오스나트륨, 스테아르산마그네슘, 오파드라이AMB노란색(80W62680)

【성상】 노란색의 원형 필름코팅정

앞면	LZ	앞면	80

【효능·효과】
이전에 EGFR-TKI로 치료받은 적이 있는 EGFR T790M 변이 양성 국소 진행성 또는 전이성 비소세포폐암 환자의 치료
이 약의 유효성은 반응률 및 반응기간에 근거하였으며, 생존기간의 개선을 입증한 자료는 없다.

【용법·용량】
국소 진행성 또는 전이성 비소세포폐암의 치료로 이 약을 투여하는 경우, 치료 시작 전에 EGFR T790M 변이 상태를 평가해야 한다.
EGFR T790M 변이 상태는 충분히 검증된 신뢰성 있는 실시간 중합효소연쇄반응 시험방법을 사용하여 확인하여야 한다.
이 약의 권장 용량은 1일 1회 240 mg(80 mg, 3정)이며 매일 일정한 시간에 식사와 관계없이 경구 복용한다. 질병의 진행 또는 수용할 수 없는 독성이 나타날 때까지 복용을 지속한다.

1. 투여방법
이 약은 경구투여하며 물과 함께 통째로 삼켜야 한다. 정제를 부수거나 쪼개거나 씹어서는 안 된다.
환자가 정제를 삼킬 수 없는 경우, 정제를 물(비탄산수)에 분산시켜 복용할 수 있다. 정제 3정을 부수지 않고 약 50 ml의 물에 넣고 잘 분산되도록 저은 후 즉시 마신다. 그 다음, 잔류물이 남지 않도록 약 50 ml의 물을 추가하여 즉시 마신다. 다른 액체는 사용하지 않도록 한다. 저용량(160 mg[80 mg, 2정])을 복용하는 경우에도 동일한 물의 양을 사용한다.
비위관(Nasogastric tube)을 통한 투여가 필요한 경우, 위와 같은 방법으로 처음 녹일 때 약 50 ml의 물을 사용하고 추가로 잔류물을 헹구는데 약 50 ml의 물을 사용하여 투여한다. 약물을 녹인 용액과 잔류물을 헹군 용액은 정제를 물에 넣은 지 30분 안에 투여해야 한다.

2. 투여 누락
이 약의 복용을 누락한 경우, 다음 투여까지 12시간 이상 남았으면 즉시 복용한다.

3. 용량 조절
각 환자의 안전성 및 내약성에 근거하여 투여 중단 및/또는 용량 감소가 필요할 수 있다. 용량 감소가 필요한 경우, 이 약의 용량은 1일 1회 160 mg(80 mg, 2정)로 감량되어야 한다. 이 약과 관련한 이상반응 독성에 대한 용량 조절 방법은 표 1에 제시되어 있다.

<표 1. 권장 용량 조절>

표적 기관	이상반응[a]	용량 변경
폐	간질성 폐질환(ILD)/ 간질성 폐렴	이 약을 영구 중단한다.
기타	3등급 이상의 이상반응	최대 3주간 이 약을 중단한다.
	3등급 이상의 이상반응이 이 약을 최대 3주간 중단한 이후 0-2등급으로 개선되는 경우	이 약을 동일 용량 (240 mg[80 mg, 3정]) 또는 저용량(160 mg [80 mg, 2정])으로 다시 시작 할 수 있다.
	최대 3주간 이 약을 중단한 이후 0-2등급으로 개선되지 않는 3등급 이상의 이상반응	이 약을 영구 중단한다.

[a] 비고: 미국 국립암연구소(National Cancer Institute, NCI) 이상반응 표준 용어 기준(Common Terminology Criteria for Adverse Events, CTCAE) 버전 4.0에 의해 등급이 분류된 임상적 이상반응의 중증도.

【사용상의주의사항】

1. 경고
1) **간질성 폐질환(Interstitial Lung Disease, ILD)/간질성 폐렴**
레이저티닙 임상1/2상 시험(YH25448-201)의 2차 치료 환자 181명중 1.2%(2명)의 환자에서 간질성 폐렴이 보고되었으며, 각각 투여 후 9.8개월과 2.8개월 후에 투여 중단을 야기하였다. 따라서 이 약 투여 시, 환자에게 이 약의 이상반응에 대해 충분히 설명을 하고, 임상 증상(예: 호흡곤란, 기침 및 발열 등)에 대해 유의하여 관찰한다. 간질성 폐질환/간질성 폐렴을 의심할 수 있는 호흡기 증상이 나타나는 경우에는 투여를 중지하고 이러한 증상에 대해 신속히 조사한다. 간질성 폐질환/간질성 폐렴이 확진 되는 경우, 이 약을 영구중단하고 적절한 치료를 실시하여야 한다.

2. 다음 환자에는 투여하지 말 것
1) 이 약의 주성분이나 부형제에 대해 중증의 과민증이 있는 환자

3. 다음 환자에는 신중히 투여할 것
1) 간질성 폐질환/간질성 폐렴의 발병 위험인자를 가지고 있는 환자나 급성 폐장애, 특발성 폐섬유증, 간질성 폐렴, 진폐증, 방사선 유도성 폐렴, 약물유도성 폐렴 환자 또는 이들 질환의 병력이 있는 환자(치료로 인한 유익성이 위험성을 상회한다고 판단되는 경우에만 투여한다).

4. 이상반응
이 약의 안전성 데이터는 임상개발 프로그램 경험을 근거로 하며, 이전에 치료받은 적이 있는 상피세포 성장인자 수용체 돌연변이 양성(EGFRm+) 진행성 비소세포폐암 환자 중 20 mg, 40 mg, 80 mg, 120 mg, 160 mg, 240 mg, 320 mg 용량의 이 약을 최소한 1회 투여 받은 총 181명의 노출을 반영한다. 대부분의 이상반응 중증도는 1등급 또는 2등급이었다. 20%이상에서 발생한 가장 빈번하게 보고된 이상반응은 발진(28.7%), 가려움증(27.6%), 변비(22.1%), 감각 이상(21.0%)이었다. 환자의 24.9%에서 중증 이상반응(Common Terminology Criteria for Adverse Events, CTCAE grade 3 이상)이 나타났다. 이상반응으로 인한 용량 감소는 8.3%의 환자들에서 나타났으며 3.9%가 이상반응으로 인하여 투약을 중단하였다. 간질성 폐렴은 환자의 약 1.2%(2명)에서 발생하였으며, 중대한 이상반응으로는 한 명에게 보고되었다(CTAE 등급 3).
이 약의 240 mg 용량을 투여 받은 대상자(78명) 중 75명(96.2%)에서 이상반응이 보고되었으며, 대부분의 이상반응 중증도는 1등급 또는 2등급 이었다. 20% 이상에서 발생한 가장 빈번하게 보고된 이상반응은 발진(34.6%), 가려움증(33.3%), 감각 이상(32.1%), 근육 연축(25.6%), 두통(24.4%), 설사(21.8%), 식욕 감소(20.5%)이었다. 환자의 28.2%에서 중증 이상반응(CTCAE grade 3 이상)이 나타났다. 이상반응으로 인한 용량 감소는12.8%의 환자들에서 나타났으며 5.1%가 이상반응으로 인하여 투약을 중단하였다.
다음 표 2에 임상1/2상 시험의 240 mg 용량을 투여 받은 환자에서 이 약에 대해 보고된 이상반응을 체내 기관별로 분류하여 빈도 별로 정리하였다. 빈도가 높은 이상반응부터 나열하였다. 빈도는 다음 기준에 의해 정의하였다: 매우 흔하게(10% 이상), 흔하게(1% 이상 10% 미만), 흔하지 않게(0.1% 이상 1% 미만), 드물게(0.01% 이상 0.1% 미만), 매우 드물게(0.01% 미만), 빈도 불명(가용한 데이터로부터 추정 불가능함).

<표 2. 이상반응 (임상시험 번호: YH25448-201)>

MedDRA 기관계	MedDRA 용어	이상반응 발생한 환자수(비율) N=78	빈도
각종 위장관 장애	설사	17 (21.8)	매우 흔하게
	변비	13 (16.7)	매우 흔하게
	오심	12 (15.4)	매우 흔하게
	구토	8 (10.3)	매우 흔하게
	구내염	7 (9.0)	흔하게
	발진[a]	35 (44.9)	매우 흔하게
피부 및 피하조직 장애	가려움증	26 (33.3)	매우 흔하게
	손발톱 주위염	13 (16.7)	매우 흔하게
	피부 건조	8 (10.3)	매우 흔하게
각종 신경계 장애	감각 이상	25 (32.1)	매우 흔하게
	두통	19 (24.4)	매우 흔하게
	어지러움	8 (10.3)	매우 흔하게
	말초 신경 병증[b]	6 (7.7)	흔하게
	감각 저하	4 (5.1)	흔하게
근골격 및 결합 조직 장애	근육 연축	20 (25.6)	매우 흔하게
	근육통	10 (12.8)	매우 흔하게
감염 및 기생충 감염	상기도 감염[c]	9 (11.5)	매우 흔하게
호흡기, 흉곽 및 종격 장애	기침[d]	15 (19.2)	매우 흔하게
	간질성 폐렴	1 (1.3)	흔하게
임상 검사	알라닌 아미노 전이 효소 증가	9 (11.5)	매우 흔하게
	아스파르트산 아미노 전이 효소 증가	9 (11.5)	매우 흔하게
	심전도 QT 연장	4 (5.1)	흔하게
대사 및 영양 장애	식욕 감소	16 (20.5)	매우 흔하게
전신 장애 및 투여 부위 병태	피로	12 (15.4)	매우 흔하게
각종 눈 장애	눈 건조	4 (5.1)	흔하게

[a] 다음의 군집 용어 중에서 보고된 사례를 포함한다: 발진, 홍반성 발진, 반상-구진 발진, 반상 발진, 여드름양 피부염
[b] 다음의 군집 용어 중에서 보고된 사례를 포함한다: 말초 신경 병증, 다발 신경 병증
[c] 다음의 군집 용어 중에서 보고된 사례를 포함한다: 상기도 감염, 비인두염, 기관지염, 편도염
[d] 다음의 군집 용어 중에서 보고된 사례를 포함한다: 기침, 젖은 기침

5. 일반적 주의
1) **T790M 돌연변이 검사**
국소 진행성 또는 전이성 비소세포폐암의 치료제로서 이 약의 사용을 고려할 때, 이러한 기술의 사용이 능숙한 실험실에서 EGFR T790M 변이 상태를 확인하는 것이 중요하다. 임상시험에서는 EGFR T790M 변이 양성 비소세포폐암을 진단하기 위해, 로슈진단(주)의 Cobas® EGFR Mutation Test를 사용하였다.
2) **QTc 간격연장**
이 약을 투여 받은 환자 중 6명(3.3%) 환자에서 심전도 QT 연장이 나타났으며 이 중 240 mg을 투여한 환자는 4명(5.1%)이다. 이 중 중대한 이상반응은 없었으며, 중증도는 모두 1등급이었다. 대부분 별다른 치료 없이 회복되었으나 QTc 간격이 연장되는 것으로 알려진 약물과 병용 투여 시에는 면밀한 모니터링을 고려해야 한다.
3) **심장독성 변화**
이 약을 투여 받은 환자 중 심박출률 감소(1명, 0.6%)가 흔하지 않게 나타났으며 중증도는 1등급이었다. 240 mg을 투여 받은 환자에서는 나타나지 않았으나, 심질환의 위험인자가 있는 환자에서는 좌심실 구출율 평가를 포함한 심장모니터링을 고려할 수 있다.
4) **눈 영향**
이 약을 투여 중에 눈 건조증상, 눈물 분비 증가, 빛에 민감한 눈, 시야 흐림, 눈의 통증 및/또는 눈의 충혈과 같은 각막염의 징후 및 증상을 보이는 환자들은 즉시 안과 전문의에게 상담을 받아야 한다.
5) **간기능 이상**
이 약 투여 받은 환자 중 알라닌 아미노 전이효소(ALT), 아스파르트산 아미노 전이효소(AST) 증가가 각각 13명(7.2%), 12명(6.6%) 나타났다. 이중 240 mg을 투여 받은 환자는 각 9명(11.5%)에서 나타났다. 중대한 이상반응은 없었으며, 중증도는 모두 1-2등급이었다. 이 약을 투여 중에 AST, ALT 등, 간수치 증가와 함께 간기능 이상이 일어날 수 있다. 간기능의 변화를 관찰하기 위한 주기적인 혈액검사가 고려될 수 있으며, 중증의 간기능 변화가 있을 경우, 이 약의 감량이나 중단하는 등 적절한 조치를 취해야 한다.

6. 상호작용
1) 이 약은 주로 글루타티온 S-전이효소 Mu 1(glutathione S-transferase Mu 1, GST M1) 및 cytochrome P450 3A4(CYP3A4)에 의해 대사된다. 따라서 이 약을 GST M1 및 CYP3A4의 활성에 영향을 미치는 약제와의 병용투여 시 주의를 요한다.
2) CYP3A4 저해제(이트라코나졸, 케토코나졸, 포사코나졸, 보리코나졸 등 아졸계 진균제, 에리스로마이신, 텔리스로마이신 등 마크로라이드 항생제, 리토나비어, 인디나비르 등 단백분해효소억제제, 딜티아젬 및 베라파밀 등, 자몽주스)와의 병용투여에 의해 레이저티닙의 혈중 농도가 증가할 수 있다. 따라서 이 약은 강력한 CYP3A4 저해제와 가능한 병용하지 않도록 한다. 대체 약물이 부재하여 강력한 CYP3A4 저해제와 병용투여 시에는, 레이저티닙의 내약성 변화의 징후에 대해 면밀히 모니터링 하여야 한다.
3) 이 약을 CYP3A4 유도제(페니토인, 카바마제핀, 리팜피신, 바르비튜레이트 및 세인트존스워트(St. John's Wort[Hypericum perforatum]등)와 병용투여 시 레이저티닙의 혈중 농도가 감소되어 이 약의 효과가 감소할 수 있다. 따라서 이 약은 CYP3A4 유도제와 가능한 병용하지 않도록 한다.
4) 생체 외 실험 결과, 이 약은 P-당단백(P-glycoprotein, P-gp)의 기질이다. 현재 자료로는 이러한 생체 외 실험 결과에 임상적 유의성은 없다.
5) 이 약은 사람의 유방암 저항단백질(breast cancer resistance protein, BCRP) 저해제로 추정되어, BCRP 기질로 알려진 약물(로수바스타틴, 메토트렉세이트, 설파살라진, 플루바스타틴, 아토르바스타틴)과의 병용 투여, 한약재 혹은 식품의 섭취는 피해야 한다.
6) 이 약은 CYP3A4 저해제로 추정되어 CYP3A4의 기질(미다졸람, 알프라졸람 등 항정신병 및 항불안제, 로바스타틴, 심바스타틴과 등 지질조절제, 디소피라마이드, 드로네다론 등 항부정맥제, 베프리딜, 펠로디핀 등 칼슘채널차단제)과의 병용투여에 의해 CYP3A4 기질의 혈중 농도가 증가할 수 있다. 따라서 대표적인 CYP3A4 기질과의 병용투여 시, 기질의 내약성 변화의 징후에 대해 면밀히 모니터링 하여야 한다.
7) 이 약과 위산분비억제제와의 상호작용을 확인하기 위한 임상시험은 수행되지 않았다. 다만, 비소세포폐암 환자에서 위산분비억제제의 영향을 탐색한 결과, 위산분비억제제가 이 약의 생체 이용률에 미치는 영향은 낮았다.

7. 임부 및 수유부에 대한 투여
1) **임부**
이 약을 임부에게 투여한 자료는 없다. 동물시험에서는 생식독성을 보였다. 임신 랫드에 레이저티닙 투여 시 사람 예상 노출도의 4.3배 높은 수준에서 태자의 착상 후 손실 증가와 태자 중량 감소가 관찰되었다. 작용기전 및 비임상시험 결과에 근거할 때, 이 약은 임신한 여성에게 투여 시 태아 독성을 유발할 수 있다. 이 약은 임부에게 투여하지 않는다.
2) **수유부**
레이저티닙 또는 그 대사체가 사람 모유로 분비되는지는 알려져 있지 않다. 모유를 통한 레이저티닙 또는 그 대사체 배출을 동물을 대상으로 조사하지 않았다. 젖먹이 아이에게의 위험을 배제할 수 없다. 수유부에게 이 약 치료 중 수유를 중단하도록 해야 한다.
3) **수태능**
사람의 수태능에 이 약이 미치는 영향에 대한 자료는 없다. 동물실험 결과 이 약이 남성 및 여성 생식기관에 영향을 주어 생식능력을 저하시킬 수 있는 것으로 나타났다.
4) **남성/가임 여성**
가임 여성은 이 약 투여 중 임신을 피하여야 한다. 환자는 이 약 투여 완료 후 여성 및 남성은 최소 3개월 동안 효과적인 피임법을 계속 사용하도록 해야 한다.

8. 소아에 대한 투여
소아 환자에서 이 약의 안전성 및 유효성이 확립되지 않았다.

9. 고령자에 대한 투여
이 약의 240 mg 용량을 투여 받은 환자 78명 중 65세 이상의 환자는 27명(34.6%)이었다. 240 mg군에서의 약물 관련 이상반응 및 3등급 이상 이상반응 발생률은 65세 미만에서 86.3%(44/51명)와 7.8%(4/51명), 65세 이상 고령자에서는 88.9%(24/27명)와 7.4%(2/27명)로 유사하게 보고되었다. 전반적인 안전성 측면에서 65세 미만 환자군과 65세 이상의 환자군 간 차이는 확인되지 않았다. 65세 이상 고령자에서 이 약의 안전성과 유효성평가를 위한 충분한 수의 환자에서 임상시험은 수행되지는 않았으나, 고령자(만 65세 이상)에서 이 약의 시작용량 조절은 필요치 않다.

10. 간장애 환자에 대한 투여
중증의 간장애 환자에서 이 약의 안전성과 유효성은 확립되지 않았다. 기저시점에서의 알라닌 아미노 전이 효소(ALT) 또는 아스파르트산 아미노 전이 효소(AST)수치가 2.5 x 정상상한치(upper limit normal, ULN)를 초과하거나(증명 가능한 간 전이가 없는 경우) 5 x 정상상한치(간 전이가 있는 경우)인 환자 또는 빌리루빈 수치가 1.5 x 정상상한치(증명 가능한 간 전이가 없는 경우) 또는 3 x 정상상한치(간 전이가 있는 경우)를 초과하는 환자는 임상시험에서 제외되었으므로 이들에 대한 안전성 및 유효성은 확립되지 않았다. 기저시점에서 간장애를 가진 환자는 이 약의 독성 징후를 모니터링 해야 한다.

11. 신장애 환자에 대한 투여
신질환 환자(Cockcroft and Gault 방정식에 의해 계산된 크레아티닌 청소율[CrCL]이 50 ml/min 미만) 에 대한 이 약의 안전성과 유효성은 확립되지 않았다. 중등증, 중증 및 말기 신장애 환자에게 투약 시 주의해야 한다.

12. 임상검사치에의 영향
임상검사치에 미치는 레이저티닙의 영향은 확립 되어있지 않았다.

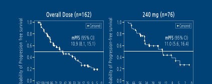
13. 과량투여시의 처치
임상 1/2상 시험의 용량제한독성 파트에서 레이저티닙 20 mg에서 320 mg까지 용량 증량 단계 동안 용량제한독성(dose limiting toxicities, DLT)이 관찰되지 않았다. 이 약의 과량투여에 대한 특이적 치료는 없으며, 과량투여에 의한 증상은 확립되지 않았다. 과량투여와 관련된 이상반응은 일반적인 보조 조치를 실시하고 대증적으로 치료해야 한다.

14. 보관 및 취급상의 주의사항
1) 어린이의 손이 닿지 않는 곳에 보관하도록 주의한다.
2) 다른 용기에 바꾸어 넣는 것은 사고 원인이 되거나 품질 유지 면에서 바람직하지 않으므로 이를 주의한다.

15. 전문가를 위한 정보
1) **약리작용**
레이저티닙은 타이로신 키나아제 억제제(Tyrosine Kinase Inhibitor, TKI)이다. 이 약은 EGFR 돌연변이 선택성이 높은 비가역적 EGFR-TKI로 야생형 EGFR을 보존하면서 활성 EGFR 돌연변이 Ex19del, L858R 및 T790M 돌연변이를 표적으로 하고 뇌혈관장벽(blood brain barrier, BBB)을 통과한다.
In vitro 실험에서 레이저티닙은 단일 돌연변이(Del19, L858R, T790M)와 이중 돌연변이(Del19/T790M 및 L858R/T790M)를 포함하는 돌연변이 EGFR 키나아제에서 강력한 저해 효과를 보였다(IC_{50} 값: 1.7-20.6 nM). 반면 레이저티닙은 Her2, Her4 또는 EGFR 야생형에 대하여 우수한 선택성을 보였다. EGFR 돌연변이 비소세포폐암 세포주를 이용한 기전연구에서 레이저티닙은 EGFR, AKT 및 ERK의 인산화 활성을 현저하게 감소시켰고, 세포사멸 전구체 단백질인 BimEL 및 caspase-3/7의 유도 활성을 보였다. 결론적으로 레이저티닙은 야생형 EGFR 비소세포폐암 세포의 증식에 최소한의 영향을 주면서 EGFR 돌연변이 암 세포 증식에 강력한 저해 효과를 보였다.
In vivo 실험에서 이 약의 경구 투여로 단일 EGFR 돌연변이 또는 T790M 이 포함된 이중돌연변이를 갖는 비소세포폐암 이종이식 마우스 모델에서 우수한 항종양 효과를 보였다.
2) **약동학적 정보**
레이저티닙의 약동학 파라미터는 건강한 시험대상자 및 비소세포폐암 환자들에서 확인되었고, 240 mg 단회 투여 시 두 집단 간 레이저티닙의 전신 노출은 유사하게 관찰되었다. 레이저티닙의 최고 혈장 농도(C_{max}) 및 농도-시간 곡선하 면적(AUC)은 20-320 mg 용량 범위에서 용량 비례에 가깝게 증가하였다. 이 약을 1일 1회 반복 투여한 결과, 항정상태는 투여 15일째에 도달하였고 단회 투여 시와 비교하여 2-3배의 축적이 나타났다.
(1) **흡수**
이 약을 경구 투여한 후, 레이저티닙의 최고 혈장 농도 도달 시간(T_{max})의 중앙값은 2-4시간이었다. 240 mg 투여 시 음식물이 레이저티닙의 전신 노출에 미치는 영향을 평가한 결과, C_{max} 및 AUC에 대한 전신 노출 비(식후/공복)의 90% 신뢰구간은 80-125% 한도 내에 포함되어, 음식물은 레이저티닙의 생체 이용률에 임상적으로 의미 있는 영향을 주지 않았다. 비소세포폐암 환자에서 위산분비억제제가 레이저티닙의 전신 노출에 미치는 영향을 탐색적으로 평가한 결과, C_{max} 및 AUC에 대한 전신 노출 비(위산분비억제제 병용함/병용하지 않음)는 각각 85.55%(90% 신뢰구간, 67.28-108.77%) 및 79.91%(90% 신뢰구간, 64.12-99.59%)로 관찰되어, 위산분비억제제가 레이저티닙의 생체 이용률에 미치는 영향은 낮았다.
(2) **분포**
이 약을 비소세포폐암 환자에게 240 mg 단회 투여 시 레이저티닙의 평균 분포용적은 4263.97L로 신체 내 광범위한 분포가 예상되었다. *In vitro* 시험에서 레이저티닙의 혈장 단백질 결합률은 99.1-99.7%이었다.
(3) **대사**
In vitro 시험에서 레이저티닙의 주요 대사 경로는 GST M1에 의한 글루타티온 포합이었고, 상대적으로 더 작은 산화 대사는 주로 CYP3A4에 의한 것이었다. 비소세포폐암 환자에게 이 약을 투여한 후, 항정 상태에서 레이저티닙 노출에 대비 10% 이상의 노출이 관찰되는 대사체는 없었다.
(4) **배설**
이 약을 비소세포폐암 환자에게 투여 시 레이저티닙의 혈장 농도는 이중 지수적 (bi-exponentially) 으로 감소하였고, 240 mg 단회 투여 후 레이저티닙의 평균 말단 소실 반감기는 64.72시간이었다. 쥐에게 ^{14}C-레이저티닙을 투여하여 배설되는 방사성능을 측정한 결과, 담즙, 분변, 소변으로 각각 60%, 24%, 4.4%가 배설되었다.

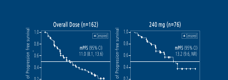
3) **임상시험 정보**
유효성 및 안전성 결과는 상피세포 성장인자 수용체 돌연변이 양성(EGFRm+) 진행성 비소세포폐암환자 중 레이저티닙을 2차 치료제로 투여 받은 대상자에서 도출된 데이터에 기반한다. 레이저티닙 임상1/2상 자료 중도 절단일자는 2019년 9월 30일이다. 전체 용량군 T790M 돌연변이 양성 대상자(162명)에서 독립 중앙 검토(ICR)와 시험자 평가(IA)에 따른 객관적 반응률(ORR)은 59% 및 68%이었다. 독립 중앙 검토와 시험자 평가에 따른 무진행-생존 기간(PFS) 중앙값은 10.9 개월(95% 신뢰구간, 8.1-15.1) 및 11.0 개월(95% 신뢰구간, 8.1-13.6)이었다(그림 1, 그림 2). 레이저티닙 240 mg 용량군에 배정된 대상자(78명) 중, T790M 돌연변이 양성 대상자(76명)에 대한 독립 중앙 검토와 시험자 평가에 따른 객관적 반응률은 58% 및 72%이었다. 독립 중앙 검토와 시험자 평가에 따른 무진행 생존 기간은 11.0 개월(95% 신뢰구간, 5.6-16.4) 및 13.2 개월(95% 신뢰구간, 9.6-도달되지 않음(not reached))이었다(그림 1, 그림 2).

<그림 1. T790M 돌연변이 양성 환자에서 독립 중앙 검토(ICR)에 따른 무진행 생존기간 (임상시험 번호: YH25448-201)>



CI: 신뢰구간(confidence interval);
ICR: 독립 중앙 검토(independent central review);
mPFS: 무진행 생존 기간 중앙값(median progression-free survival)

<그림 2. T790M 돌연변이 양성 환자에서 시험자 평가(IA)에 따른 무진행 생존 기간 (임상시험 번호: YH25448-201)>



CI: 신뢰구간(confidence interval);
IA: 시험자 평가(investigator assessment);
mPFS: 무진행 생존 기간 중앙값(median progression-free survival);
NR: 도달되지 않음(not reached)

전체 용량군 대상 독립 중앙 검토와 시험자 평가에 따른 측정 가능한 뇌 병변(measurable brain lesion)이 있는 대상자의 수는 모두 22명 이었다. 독립 중앙 검토와 시험자 평가에 따른 두개강 내 객관적 반응률(intracranial objective response rate은 55% 및 64% 이었다. 전체 용량군 대상 독립 중앙 검토와 시험자 평가에 따른 평가 가능 뇌 병변(evaluable brain lesion)이 있는 대상자 수는 각각 64명, 89명 이었다. 독립 중앙 검토와 시험자 평가에 따른 두개강 내 무진행 생존 기간(intracranial PFS)의 중앙값은 모두 도달하지 않았다(독립 중앙 검토 95% 신뢰구간, 14.0개월-도달하지 않음(not reached), 시험자 평가 95% 신뢰구간, 13.7개월-도달하지 않음(not reached)).

4) **독성시험정보**
(1) **일반독성**
랫드와 개의 반복투여 독성시험에서 상피세포를 가진 대부분의 조직과 기관에서 미약한 상피 위축에서 퇴행성 미란, 염증, 괴사까지의 변화가 관찰되었다. 이러한 결과는 240 mg 치료 용량의 환자들 노출도보다 높은 노출도에서 발생하였고, 대부분의 독성변화들은 회복기간에 완전하거나 부분적으로 회복되었다.
(2) **유전독성 및 발암성**
레이저티닙은 *In vitro* 복귀돌연변이시험, 염색체이상시험 및 in vivo 랫드 소핵시험에서 모두 유전독성을 보이지 않았고, 발암성 시험은 실시되지 않았다.
(3) **생식독성**
레이저티닙은 랫드 수태능 초기배 발생시험에서 30 mg/kg 투여군에서 태자의 착상 후 손실 증가와 생존 태자 수의 감소가 관찰되었다. 또한, 임신 랫드 배태자 발생시험에서 60 mg/kg 투여군에서 태자의 착상 후 손실 증가와 태자 중량 감소가 보였으나, 태자의 외형, 내장, 골격 검사에서 최기형성은 관찰되지 않았다. 임신 토끼를 이용한 배태자 발생시험에서도 레이저티닙 관련 최기형성은 보이지 않았다.
(4) **광독성**
레이저티닙은 *In vitro* 3T3 NRU 광독성 시험에서 광독성을 보이지 않았다.
5) **기타**
이 약의 유효성은 반응률 및 반응기간에 근거하였으며, 생존기간의 개선을 입증한 자료는 없다.

【저장방법】 기밀용기, 실온(1~30℃)보관
【사용기한】 외부포장에 표기
【포장단위】 84 정

※ 이 제품은 정부의 "소비자분쟁해결기준"에 의거 구입처를 통하여 교환 또는 환불 받을 수 있습니다.

※ 이 첨부문서의 개정연월일 이후 변경내용은 의약품통합정보시스템(http://nedrug.mfds.go.kr)에서 확인할 수 있습니다.

※ 이 제품 사용 후 부작용(이상반응)이 발생한 경우 한국의약품안전관리원(1644-6223)에 문의하여 부작용 피해구제 신청을 할 수 있습니다.

첨부문서 개정연월일 2021.12.01
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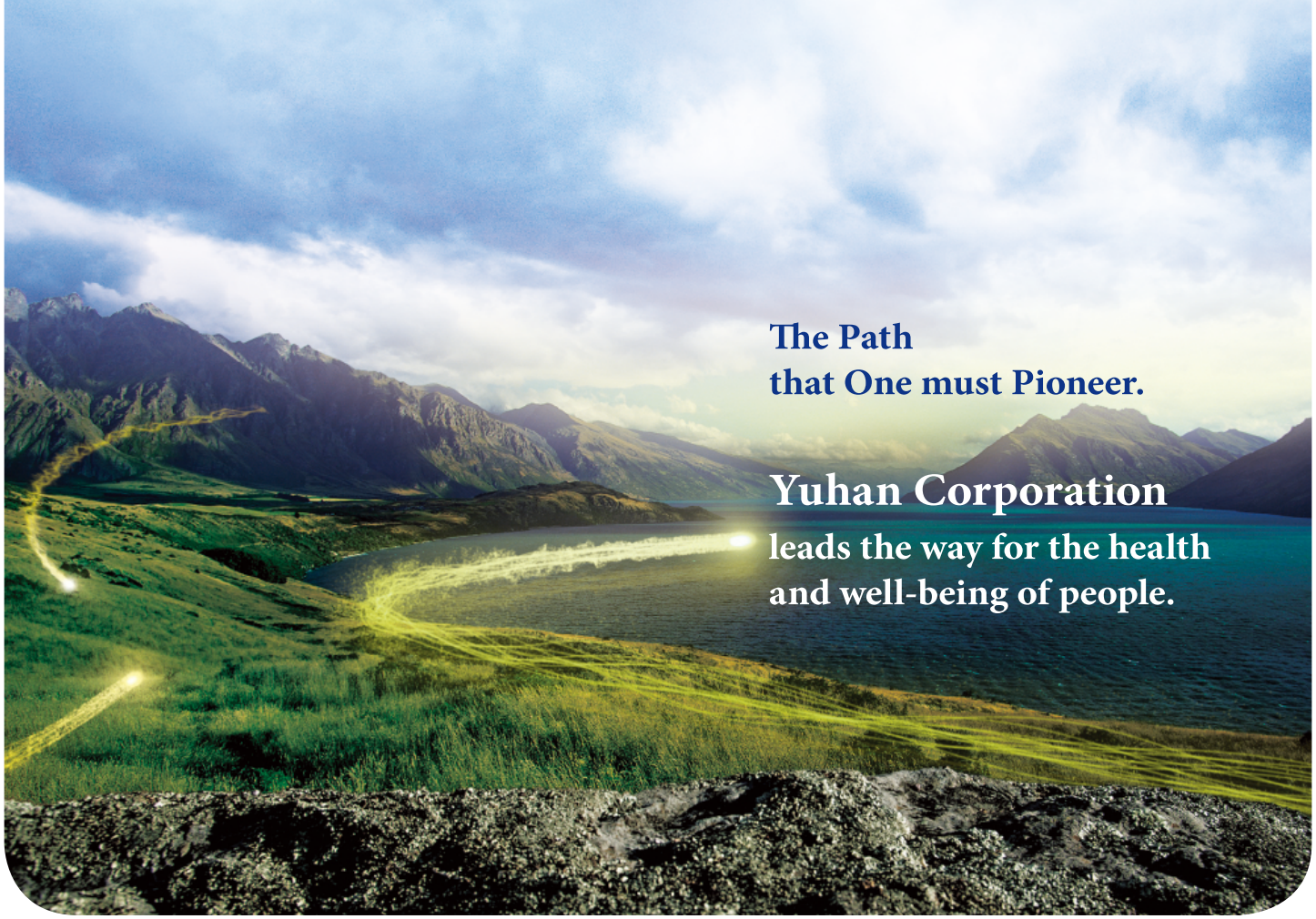

The Way of Yuhan

Yuhan Corporation, a group loved by the people and grown together with the people
For the last 90 years, the corporate culture of honesty and integrity,
and the strong beliefs in social responsibility are what made Yuhan what it is today.

Looking back on the path that we moved on and thinking of the path ahead,
Yuhan will make the leap as a global pharmaceutical company through innovative new drug development,
and by enabling healthiness and happiness for all the people in the world.

In the next 100 years, Yuhan Corporation will follow the noble spirit of our founder, Dr. New Ilhan,
and write the history of challenge and development moving forward.

Our challenge has already begun.

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durvalumab
Injection for Intravenous Use 50 mg/mL

THE STANDARD OF CARE[1] FOR STAGE III UNRESECTABLE NSCLC

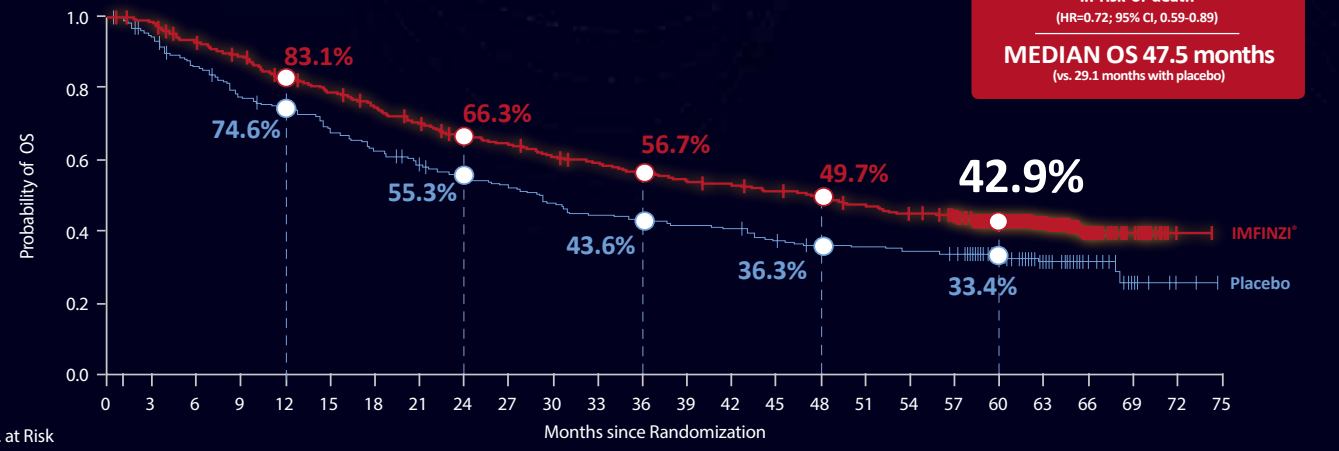
Following cCRT

임핀지™는 PACIFIC 연구에서 5년 전체생존율(OS rate) 42.9%로, 장기적인 생존개선 이점을 나타냈습니다.[2]

28% REDUCTION
in risk of death
(HR=0.72; 95% CI, 0.59-0.89)

MEDIAN OS 47.5 months
(vs. 29.1 months with placebo)

UPDATED 5-YEARS OVERALL SURVIVAL IN THE ITT POPULATION



No. at Risk

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

임핀지(durvalumab) 보험 적용 적응증[3,4]

PD-L1 발현 양성(발현 비율 ≥ 1%)이면서 백금 기반 동시적 항암화학 방사선요법 2주기 이상 투여 후 질병진행이 없는 안정병변 이상의 절제 불가능한 국소 진행성(stage III) 비소세포폐암 환자로 cCRT 치료 종료 이후 42일 내에 투여하는 경우 ※ 이전 PD-1 inhibitor 등 면역관문억제제 치료를 받지 않은 경우에 한함

- 급여 인정 기간 최대 12개월
- cCRT 치료 종료(마지막 방사선 요법 기준) 이후 42일 이내 투여할 경우
- 유도화학요법과 동시적 항암화학방사선요법의 항암요법 종류가 동일할 경우
- 방사선 요법은 54 Gy 이상, 항암화학요법은 weekly regimen 기준 4주기 이상 또는 3주기 regimen 기준 2주기 이상 투여할 경우

STUDY DESIGN The PACIFIC study design, eligibility criteria and assessments have been fully described previously. Eligible patients had histologically and/or cytologically documented Stage III, unresectable NSCLC, with a WHO performance score of 0 or 1. Patients had to have received at least two cycles of platinum-based chemotherapy concurrently with definitive radiation therapy without progression, and the last radiation dose was 1-42 days before randomization. Tumor tissue collection was not a prerequisite for inclusion in PACIFIC and enrollment was notrestricted to any threshold levels for PD-L1 expression. Patients were randomized 2:1 to durvalumab 10 mg/kg intravenously or placebo every two weeks for up to 12 months or until confirmed disease progression, initiation of alternative cancer therapy, unacceptable toxicity, or consent withdrawal. Randomization was stratified by age of the patient (<65 years vs ≥65 years), sex, and smoking history (current or former vs never smoked). The primary end points were progression free survival (as assessed by blinded independent central review) and overall survival.

NSCLC, nonsmall-cell lung cancer; cCRT, concurrent chemoradiation therapy; OS, overall survival; ITT, intent-to-treat; HR, hazard ratio; CI, confidence interval; PD-L1, programmed cell death-ligand 1; PD-1, programmed cell death protein-1.

Reference **1.** Botticella A, et al. Durvalumab for stage III non-small-cell lung cancer patients: clinical evidence and real-world experience. Ther Adv Respir Dis. 2019 Jan-Dec;13:1753466619885530; **2.** Spigel DR, et al. Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. J Clin Oncol. 2022 Feb 2. doi: 10.1200/JCO.21.01308; **3.** 건강보험심사평가원 공고 제2020-81호(시행일: 2020년 4월 1일); **4.** 건강보험심사평가원. 암질환 사용약제 및 요법: FAQ - 'Durvalumab (품명: 임핀지주)' 급여기준(공고) 관련 질의 응답[Accessed 20 Feb 2022]. Available from: https://www.hira.or.kr/bbsDummy.do?pgmid=HIRAA030023080000&brdScnBltNo=4&brdBltNo=45645&pageIndex=1

PRESCRIBING INFORMATION

임핀지주 (더발루맙) [용능• 용과] 국소 진행성 비소세포폐암: 백금 기반 동시적 항암화학방사선요법 이후 질병이 진행되지 않은 절제불가능한 국소 진행성 비소세포폐암 환자의 치료 소세포폐암: 확장병기 소세포폐암 환자의 1차 치료로서 에토포시드 및 카보플라틴 또는 시스플라틴과의 병용 요법 [용법• 용량] 이 약은 1시간에 걸쳐 정맥 점적 주입한다. 국소 진행성 비소세포폐암: 권장 용량은 이 약 10mg/kg을 2주 간격으로 투여하는 것이며, 질환의 진행되거나 허용 불가능한 독성 발생 전까지 투여한다. 소세포폐암: 권장 용량은 이 약 1500 mg을 화학요법과 병용하여 3주 간격으로 4주기 동안 투여한 뒤, 이 약 1500 mg 단독요법을 4주 간격으로 투여하는 것이며, 질환의 진행되거나 허용 불가능한 독성 발생 전까지 투여한다. 체중 30 kg 이하의 환자는 체중에 따라 이 약 20 mg/kg을 화학요법과 병용하여 3주 간격으로 4주기 동안 투여한 뒤, 이 약 20 mg/kg을 단독요법으로서 4주 간격으로 체중이 30 kg을 초과할 때까지 투여한다. 이 약을 화학요법과 병용할 때에는 에토포시드 및 카보플라틴 또는 시스플라틴의 허가된 용법•용량 정보를 참조한다. 화학요법과 같은 날 투여하는 경우 이 약을 먼저 투여한다. 용법조절: 이 약의 용량 증가나 감소는 권장되지 않는다. 일반적으로 중증(3등급) 면역 매개 이상사례의 경우 이약의 투여를 보류한다. 생명을 위협하는 (4등급) 면역 매개 이상사례와, 전신 면역 억제 치료가 필요하거나 코르티코스테로이드 시작 12주 이내에 프레드니손 또는 등가량 하루 10 mg 이하로 감량할 수 없는 중증 (3등급) 면역 매개 이상사례의 경우 이 약의 투여를 중단한다. 면역 매개 이상사례가 다음 표에 요약되어 있다. [이 약의 용법 조절 및 관리 권장 사항]

이상사례	중증도 (CTCAE v4.03*)	용법 조절	코르티코스테로이드 요법 및 기 타†
면역 매개 폐렴증/간질성 폐질환	2등급	투여 보류	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3 또는 4등급	투여 중단	
면역 매개 간염	2등급이고, 알려진 이미노전이중소 (ALT) 또는 아스파르테이트 아미노전이효소 (AST)가 정상상한치의 3-5배를 초과하거나 총 빌리루빈이 정상상한치의 1.5-3배를 초과	투여 보류	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3등급이고, ALT 또는 AST가 정상상한치의 5배 초과, 8배 이하 또는 총 빌리루빈이 정상상한치의 3배 초과, 5배 이하		
	3등급이고, ALT 또는 AST가 정상상한치의 8배를 초과 또는 총 빌리루빈이 정상상한치의 5배를 초과	투여 중단	
	4등급 (생명을 위협하는 (ALT 또는 AST가 정상상한치의 20배를 초과하거나 총 빌리루빈이 정상상한치의 10배를 초과하는 경우		
면역 매개 대장염	2 또는 3등급	투여 보류	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
또는 장사	4등급	투여 중단	
면역 매개 내분비병: 갑상선 기능 장애증, 갑상선염	2-4등급	임상적으로 안정할 때까지 투여 보류	대증적 관리
면역 매개 내분비병: 갑상선 기능 저하증.	2-4등급	변경하지 않음	갑상 지시대로 갑상선 호르몬 대체 개시
면역 매개 내분비병: 부신 기능 부전, 뇌하수체염/뇌하수체 저하증	2-4등급	임상적으로 안정할 때까지 투여 보류	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량 및 임상 지시대로 호르몬 대체 개시
면역 매개 내분비병: 제1형 당뇨병	2-4등급	변경하지 않음	갑상 지시대로 인슐린 치료 개시
면역 매개 신장염	2등급이고, 혈청 크레아티닌이 정상상한치 또는 기저치의 1.5-3배를 초과	투여 보류	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3등급이고 혈청 크레아티닌이 기저치의 3배를 초과 또는 정상상한치의 3-6배를 초과하거나, 4등급이고 혈청 크레아티닌이 정상상한치의 6배를 초과	투여 중단	
면역 매개 발진 또는 피부염 (모든 하장치 포함)	2등급으로 1주일 초과 또는 3등급	투여 보류	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	4등급	투여 중단	
면역 매개 침근염	2-4등급	투여 중단	2-4 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량.
면역 매개 근육염/다발근염증	2 또는 3등급	투여 보류	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	4등급	투여 중단	
주입 관련 반응	1 또는 2등급	주입률 줄이거나 느리게 주입	주속 주입 반응의 예방을 위해 사전 약물 치료를 고려할 수 있음
	3 또는 4등급	투여 중단	-
중증 근육 무력증	2등급	투여 보류	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3 또는 4등급, 또는 호흡 부전이나 치료 신경 침조증의 징후가 있는 모든 등급	투여 중단	
기타 면역 매개 이상사례‡	2등급	투여 보류	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3등급	투여 중단	

* 이상사례 표준 용어기준 (Common Terminology Criteria for Adverse Events; CTCAE), 버전 4.03• 1등급 이하로 개선되면, 코르티코스테로이드의 감량을 시작하여 최소 1개월 간 지속하여야 한다. 악화되거나 개선이 없다면, 코르티코스테로이드의 용량 증가 및/또는 다른 전신 면역 억제제 사용을 고려한다. † 투여 보류 후, 1등급 이하로 개선되고 코르티코스테로이드•용량이 (용량 10mg 프레드니손 또는 등가량 이하로 감소되었을 경우, 12주 이내에서 이 약의 투여를 다시 시작할 수 있다. 3등급 이상사례 재발의 경우 이 약을 중단한다. ‡ 코르티코스테로이드 투여에도 불구하고 수 일 이내에 개선이 없다면, 신속히 추가적인 면역억제 치료를 시작한다. 외복(의료)되면, 코르티코스테로이드의 감량을 시작하고 최소 1개월 간 지속한다. § 이상사례가 30일 이내에 1등급 이하로 회복되지 않거나 호흡기 기능부전의 징후가 있는 경우에는 이 약 투여를 중단한다. * 면역 형소한 감소증, 뇌염 포함 의심되는 면역 매개 이상사례에 대해, 뱅안 확인 또는 대체 병인을 배제하기 위한 적절한 평가가 수행되어야 한다. 비-면역 매개 이상사례에 대해, 2등급과 3등급 이상사례의 경우 1등급 이하가 될 때까지 이 약의 투여를 보류한다. 4등급 이상사례의 경우 이 약 투여를 중단한다 (예외적으로 4등급 실험실 검사수치 이상의 경우, 수반된 임상 징후 및 임상적 판단에 근거하여 투여 중단을 결정한다). 이 약은 경증도 간장애 환자에서는 용량 조정이 권장되지 않으며, 중등도 또는 중증 간장애 환자에서는 연구되지 않았다. 투여되었던 투여 전 이 약약물의 하석에 대한 지시 사항은 사용상의 주의사항, "13. 허료상의 주의사항"을 참고한다. 멤근된 저 단백질 결합 0.2 또는 0.22 마이크로미터 인라인 혈(in-line filter)를 포함하는 정맥 주사 라인을 통해 1시간에 걸쳐 주사액을 정맥 내 투여한다. 같은 주입 라인으로 다른 약물을 동시 투여하지 않는다. 사용하고 남은 약물이나 물품은 관련 규정에 따라 폐기되어야 한다. [사용상의 주의사항] 1.다음 환자에는 투여하지 말 것 이 약의 주성분 또는 첨가제에 과민증 병력이 있는 환자. 2.다음 환자에는 신중히 투여할 것 자가면역질환 또는 자가면역질환 병력이 있는 환자 3.약물이상반응 1) 임상시험에서 보고된 이상사례 이상사례는 MedDRA의 기준개 분류에 따라 기재되었다. 각 기준개 분류에서, 이상사례는 빈도가 높은 순으로 표기되었다. 각 빈도 군에서, 이상사례는 중증도가 높은 순으로 표기되었다. 또한, 각 이상사례의 해당 빈도 분류는 CIOMS III 원칙에 따르며 다음과 같이 정의된다: 매우 흔하게 (≥1/10); 흔하게 (≥1/100 ~ <1/10); 흔하지 않게 (≥1/1,000 ~ <1/100); 드물게 (≥1/10,000 ~ <1/1,000); 매우 드물게 (<1/10,000); 빈도 불명. 즉 이런 가능한 자료로부터 측정될 수 없음. 국소 진행성 비소세포폐암 – PACIFIC 연구 (4756명에서 국소 진행성 절제 불가능한 비소세포폐암 환자로 이 연구 시작 전 1-42일 내에 2주기 이상의 항암화학방사선요법을 완료한 환자들을 대상으로 이 약(10 mg/kg)의 안전성이 평가되었다. 이 환자 집단에서 가장 흔한 이상사례는 기침 (40.2%, 위약군 30.3%), 상부 호흡기 감염 (26.1%, 위약군 11.5%) 및 발진 (21.7%, 위약군 12.0%)이었다. 3 또는 4등급 이상사례의 발생률은 이 약 투여군에서 12.8%, 위약군에서 9.8%이었다. 가장 흔한 3 또는 4등급 이상사례는 폐렴 (6.5%, 위약군 5.6%)이었다. 이 약 투여군의 8.2% 및 위약군의 5.6%에서 이상사례로 인해 투약을 중단하였다. 이 약의 투약 중단으로 이어진 가장 흔한 이상사례는 폐렴증 (4.8%)이었다. 중대한 이상사례는 이 약 투여군 12.8% 및 위약군 11.1%의 환자에서 발생하였다. 가장 흔한 중대한 약물이상반응은 2% 이상의 환자에서 보고된 폐렴증과 폐렴이었다. 치명적인 폐렴증과 치명적인 폐렴은 이 약 투여군과 위약군 간에 유사하게 1% 미만의 환자에서 보고되었다. 공장 분기. 소세포폐암 – CASPIAN 연구 CASPIAN 연구에서 이전에 치료받지 않은 확장 병기 소세포폐암 환자에게 이 약과 에토포시드 및 카보플라틴 또는 시스플라틴을 병용투여 했을 때의 안전성이 평가되었다 (265명). 이 약과 화학요법을 병용, 시작 안전성 프로파일은 이 약 단독요법 및 화학요법의 알려진 프로파일과 일관되게 나타났다. 이 임상연구에서 보고되지 않았다라도, 이 약 또는 화학요법 단독으로 발생한다고 알려진 이상사례는 병용요법 중에도 발생할 수 있다. [저장방법] 밀봉용기, 2-8°C에서 차광하여 보관 [포장단위] 2.4 mL × 1 바이알 / 박스, 10 mL × 1 바이알 / 박스 ※ 만약 구입시 사용기한이 경과되었거나 변질, 변패 또는 오손된 제품인 경우에는 구입처를 통하여 교환하여 드리며, 공정거래위원회 고시 "소비자분쟁해결기준" 에 의거 소비자의 정당한 피해는 보상하여 드립니다. 의약품 부작용 발생 시 한국얀약품안전관리원에 피해구제를 신청하실 수 있습니다. 문헌개정연월일: 2022년 03월 04일 수립(수입자): 한국아스트라제네카 서울시 강남구 영동대로517 아셈타워 21층, 전화 02-2188-0800 •보다 자세한 사항은 제품설명서 전문을 참고하시기 바랍니다. aFZ20220310

한국아스트라제네카 서울시 강남구 영동대로 517 아셈타워 21층
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KR-105241 Exp.2024-02 (Prep.2022-02)

The First EGFR-TKI for adjuvant treatment in patient with EGFRm NSCLC after complete tumor resection

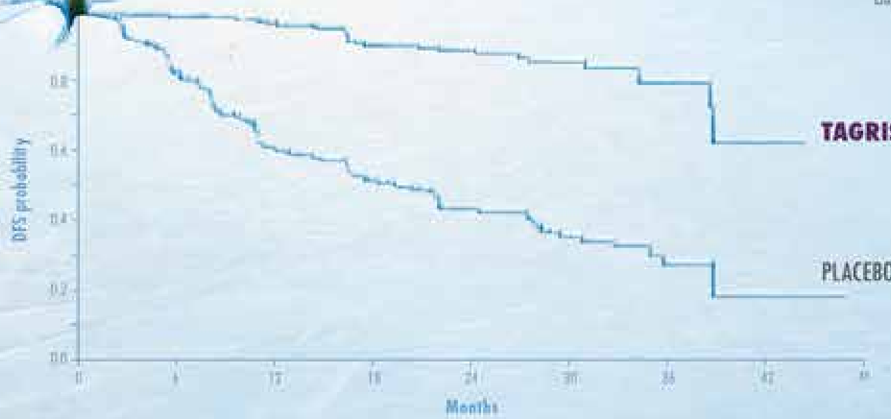
ADJUVANT TAGRISSO DELIVERS GROUNDBREAKING EFFICACY

Disease Free Survival in patients with Stage II and IIIA resected EGFRm NSCLC (primary endpoint),

adjuvant TAGRISSO reduced the risk of recurrence or death by 83%

vs placebo (HR=0.17 [99.06% CI: 0.11, 0.26] P<0.001)[1]

Data cut off: Jan 17, 2020



TAGRISSO®
osimertinib

DFS, Disease Free Survival; EGFR, Epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation-positive; EGFR TKI, Epidermal growth factor receptor–tyrosine kinase inhibitor; NSCLC, Non small cell lung cancer

STUDY DESIGN : In this phase 3, double-blind, placebo-controlled, randomized, international trial, patients were stratified according to disease stage (IB, II, or IIIA), EGFR mutational status (Ex19del or L858R), and race (Asian or non-Asian) and were randomly assigned in a 1:1 ratio to receive either oral osimertinib (at a dose of 80 mg once daily) or placebo. Screening and randomization occurred after the patients had undergone surgery and received chemotherapy. Patients received osimertinib or placebo for 3 years or until disease recurrence or fulfillment of a criterion for discontinuation.

Prescribing Information

SCAN ME

REFERENCES: 1. Wu YL, Tsuboi M, He J, et al; ADAURA Investigators. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med. 2020 Oct 29;383(18):1711-1723.

References 1. 키트루다 허가사항. 식품의약품안전처.

키트루다®주 (펨브롤리주맙) 100 mg [효능・효과] 흑색종: 1. 수술이 불가능하거나 전이성인 흑색종의 치료 2. 완전 절제술을 받은 림프절 침범을 동반한 흑색종의 수술 후 보조요법(adjuvant) 치료 **비소세포폐암:** 1. EGFR 또는 ALK 변이가 없는 전이성 비편평 비소세포폐암 환자에서의 1차 치료로서 페메트렉시드 및 백금 화학요법과의 병용 요법 2. 전이성 편평 비소세포폐암 환자에서의 1차 치료로서 카보플라틴 및 파클리탁셀(혹은 알부민 결합 파클리탁셀)과의 병용 요법 3. PD-L1 발현 양성(Tumor Proportion Score(TPS) ≥50%)으로서, EGFR 또는 ALK 변이가 없는 진행성 비소세포폐암 환자에서의 1차 치료 4. PD-L1 발현 양성(TPS ≥1%)으로서, 백금 기반 화학요법제 치료 도중 또는 이후에 진행이 확인된 진행성 비소세포폐암의 치료. 다만 EGFR 또는 ALK 변이가 확인된 환자는 이 약을 투여하기 전에 이러한 변이에 대한 승인된 치료제를 투여한 후에도 질병의 진행이 확인된 경우여야 한다. **두경부암:** 1. 전이성 또는 수술이 불가능한 재발성 두경부 편평상피세포암 환자에서의 1차 치료로서 PD-L1 발현 양성(CPS ≥1)인 환자에서의 단독 요법, 백금 및 플루오로우라실(5-FU) 화학요법과의 병용 요법 2. PD-L1 발현 양성(TPS ≥50%)으로서, 백금 기반 화학요법제 치료 도중 또는 이후에 진행이 확인된 전이성 또는 수술이 불가능한 재발성 두경부 편평상피세포암의 치료로서 단독 요법. **전형적 호지킨 림프종:** 자가조혈모세포이식에 실패하거나, 자가조혈모세포이식이 치료 옵션이 아닌 경우 최소 두 가지 이상의 이전 요법에 실패한 재발성 또는 불응성인 전형적 호지킨 림프종 성인 및 2세 이상의 소아 환자의 치료. **요로상피암:** 1. PD-L1 발현 양성(Combined Positive Score(CPS) ≥10)이며 시스플라틴 기반 항암화학요법이 불가능한 국소 진행성 또는 전이성 요로상피암의 치료 2. 백금 기반 화학요법제 치료 도중 또는 이후에 진행이 확인되거나, 백금 기반의 수술 전 보조요법(neoadjuvant) 또는 수술 후 보조요법(adjuvant) 치료 12개월 이내에 진행이 확인된 국소 진행성 또는 전이성인 요로상피암의 치료. 3. 방광 절제술이 불가능하거나 시행을 선택하지 않았으며, 유두종 유무에 상관없이 상피내암을 동반한 BCG-불응 고위험 비근침습성 방광암의 치료 **식도암:** PD-L1 발현 양성(CPS ≥10)으로서, 수술이 불가능한 국소 진행성 또는 전이성 식도암이나 HER-2 음성인 위식도 접합부 선암(병변의 중심(epicenter)이 위식도 접합부 1-5 cm 위에 위치) 환자에서의 1차 치료로서 백금 및 플루오로피리미딘 기반 화학요법과의 병용 요법 **신세포암:** 1. 진행성 신세포암 환자에서의 1차 치료로서 엑시티닙과의 병용 요법 2. 진행성 신세포암 환자에서의 1차 치료로서 렌바티닙과의 병용 요법 3. 신장 절제술 이후 재발 위험이 중등-고위험 또는 고위험이거나 신장 절제술 및 전이 병변 절제 이후인 신세포암 환자의 수술 후 보조요법(adjuvant) 치료로서 단독요법 (사용상의 주의사항 14. 임상시험 정보방 참고) **자궁내막암:** 이전의 전신 요법 이후 진행이 확인되고 수술적 치료 또는 방사선 치료가 부적합한, 고빈도-현미부수체 불안정성(MSI-H, microsatellite instability high) 또는 불일치 복구 결함(dMMR, mismatch repair deficient)이 없는 진행성 자궁내막암 치료로서 렌바티닙과의 병용 요법 **고빈도-현미부수체 불안정성(MSI-H)암:** 이전의 치료를 받은 후 진행하였고 만족스러운 대체 치료 옵션이 없는, 고빈도-현미부수체 불안정성(MSI-H) 또는 불일치 복구 결함(dMMR)을 나타내며 수술이 불가능하거나 전이성인 자궁내막암, 위암, 소장암, 난소암, 췌장암, 담도암 환자의 치료 **고빈도-현미부수체 불안정성(MSI-H) 직결장암:** 고빈도-현미부수체 불안정성(MSI-H) 또는 불일치 복구 결함(dMMR)을 나타내며 수술이 불가능하거나 전이성인 직결장암 환자의 치료 **삼중음성 유방암:** 1. 고위험 조기 삼중음성 유방암 환자의 치료로서 수술 전 보조요법(neoadjuvant)으로 항암화학요법과 병용 요법, 그리고 이어서 수술 후 보조요법(adjuvant)으로 단독 요법 2. PD-L1 발현 양성(CPS≥ 10)이며, 수술이 불가능한 국소 재발성 또는 전이성 삼중음성 유방암 환자의 치료로서 항암화학요법과의 병용 요법 **[용법・용량]** 이 약을 30분에 걸쳐 정맥 점적주입한다. 이 약의 성인 권장용량은 다음 중 하나를 따른다. 200mg을 매 3주마다 투여 또는 400mg을 매 6주마다 투여. 전형적 호지킨 림프종 소아 환자에서 이 약의 권장용량은 2 mg/kg(최대 200 mg)이다. 병용 요법으로 투여하기 위해서는 해당 병용 약제의 처방정보를 참고한다.(사용상의 주의사항 14. 임상시험 정보 항 참고) 이 약을 정맥주사용 화학요법제와 병용하여 투여하는 경우 이 약이 먼저 투여되어야 한다. 고위험 조기 삼중음성 유방암에서 수술 전 보조요법으로 항암화학요법과 병용하여 매 3주마다 200mg 8 회 또는 매 6주마다 400mg 4회 투여한다. 수술 후 보조요법으로 이약을 매 3주마다 200mg 9 회 또는 매 6주마다 400mg 5회 투여한다. **[금기] 다음 환자에는 투여하지 말 것** 이 약 및 그 구성 성분에 과민증인 환자 **[신중투여] 다음 환자에는 신중히 투여할 것** 자가면역질환이 있거나 만성적 혹은 재발성 자가면역질환의 기왕력이 있는 환자 **[약물이상반응] 1) 임상시험에서 보고된 이상사례** 대조 및 비대조 임상시험에서 총 2799명을 대상으로 이 약의 안전성을 분석하였다. 치료 기간의 중앙값은 4.2개월(범위: 1일 ~ 30.4개월)이었고, 6개월 이상 치료받은 환자는 1153명, 1년 이상 치료 받은 환자는 600명이었다. 환자의 5%가 치료 관련 약물이상반응으로 이 약 투여를 중단하였다. 최종 투여 후 90일째까지 보고된 치료 관련 중대한 이상사례(SAE)는 이 약을 투여 받은 환자의 10%에서 발생하였다. 발생한 치료 관련 중대한 이상사례 중 가장 흔하게 발생한 이상사례는 다음과 같다; 폐렴증, 결장염, 설사, 발열. 치료 관련 중대한 이상사례로 자가면역성 간염과 부신기능저하증도 보고되었다. **2) 시판 후 이상사례** 이 약의 시판 후 사용 동안 아래와 같은 이상사례가 확인되었다. 이러한 이상사례는 불특정한 인구에서 자발적으로 보고되었기 때문에 발생빈도를 확실히 추정하거나 이 약 노출과의 상관관계를 확립하기 어렵다. 눈 장애: 보그트-고야나기-하라다 증후군, 면역계 장애: 혈구 탐식성 림프 조직구증 **3) 면역-매개 약물이상반응 내분비병증:** 부신 부전이 발병하는 시간의 중앙값은 5.3개월(범위: 26일 ~ 16.6개월)이었다. 지속기간의 중앙값은 아직 도달하지 않았다(범위: 4일 ~ 1.9+년). 부신 부전으로 인해 이 약을 중단한 환자는 1명(<0.1%)이었다. 5명의 환자는 부신 부전 증상으로부터 회복하였다. 뇌하수체염이 발병하는 시간의 중앙값은 3.7개월(범위: 1일 ~ 11.9개월)이었다. 지속기간의 중앙값은 4.7개월(범위: 8+일 ~ 12.7+개월)이었다. 뇌하수체염으로 인해 이 약을 중단한 환자는 4명(0.1%)이었다. 7명의 환자는 뇌하수체염 증상으로부터 회복하였다. 갑상선기능항진증이 발병하는 시간의 중앙값은 2.1개월(범위: 3일 ~ 15.0+개월)이었다. 지속기간의 중앙값은 1.8개월(범위: 1일 ~ 12.8개월)이었다. 갑상선기능항진증으로 인해 이 약을 중단한 환자는 2명(<0.1%)이었다. 71명의 환자는 갑상선기능항진증 증상으로부터 회복하였다. 갑상선 저하증이 발병하는 시간의 중앙값은 3.5개월(범위: 1일 ~ 18.9개월)이었다. 지속기간의 중앙값은 아직 도달하지 않았다(범위: 2일 ~ 27.7+개월). 갑상선 저하증으로 이 약을 중단한 환자는 1명(<0.1%)이었다. **폐렴증:** 폐렴증이 발병하는 시간의 중앙값은 3.3개월(범위: 2일 ~ 19.3개월)이었다. 지속기간의 중앙값은 1.5개월(범위: 1일 ~ 17.2+개월)이었다. 폐렴증으로 인해 이 약을 중단한 환자는 36명(1.3%)이었다. 55명의 환자는 폐렴증 증상으로부터 회복하였다. **결장염:** 결장염이 발병하는 시간의 중앙값은 3.5개월(범위: 10일 ~ 16.2개월)이었다. 지속기간의 중앙값은 1.3개월(범위: 1일 ~ 8.7+개월)이었다. 결장염으로 인해 이 약을 중단한 환자는 15명(0.5%)이었다. 41명의 환자는 결장염 증상으로부터 회복하였다. **간염:** 간염이 발병하는 시간의 중앙값은 1.3개월(범위: 8일 ~ 21.4개월)이었다. 지속기간의 중앙값은 1.8개월(범위: 8일 ~ 20.9+개월)이었다. 간염으로 인해 이 약을 중단한 환자는 6명(0.2%)이었다. 15명의 환자는 간염 증상으로부터 회복하였다. **신장염:** 신장염이 발병하는 시간의 중앙값은 5.1개월(범위: 12일 ~ 12.8개월)이었다. 지속기간의 중앙값은 3.3개월(범위: 12일 ~ 8.9+개월)이었다. 신장염으로 인해 이 약을 중단한 환자는 3명(0.1 %)이었다. 5명의 환자는 신장염 증상으로부터 회복하였다. **4) 면역원성** 이 약 2 mg/kg을 매 3주마다 투여하거나 200 mg을 매 3주마다 투여하거나 10 mg/kg을 매 2주 또는 3주마다 투여한 임상시험에 참여한 환자 중에서 이 약 치료 중 항약물항체 존재 여부를 평가한 2034명의 환자 중 36명(1.8%)에게서 양성이 보고되었고, 이 중 9명(0.4%)의 환자에서는 펨브롤리주맙에 대한 중화 항체가 양성이었다. 항-펨브롤리주맙 결합 또는 중화 항체 발생에 따라 약동학 또는 안전성 프로파일이 변경된다는 증거는 확인되지 않았다. **5)** 국내 시판 후 수집된 중대한 이상사례 분석・평가 결과 확인된 이상사례는 다음과 같다. 다만, 이로써 곧 해당성분과 다음의 이상사례 간에 인과관계가 입증된 것을 의미하는 것은 아니다. 감염: 폐렴(pneumonia) **[일반적 주의]** 1) 면역-매개 약물이상반응 **① 면역-매개 폐렴증:** 이 약 투여 환자에서 치명적인 사례를 포함한 폐렴증이 보고되었다. 폐렴증의 징후와 증상에 대해 환자를 모니터링해야 한다. 폐렴증이 의심되면 방사선영상 검사를 실시한다. 중등증(2등급) 이상의 폐렴증의 경우 코르티코스테로이드를 투여(프레드니손으로 초회 용량 1-2 mg/kg/day 또는 이에 상응하는 양을 투여하고 이후 점감)한다. 중등증(2등급) 폐렴증의 경우 이 약 투여를 보류하며, 중증(3등급), 생명을 위협하는(4등급) 폐렴증 또는 재발성 중등증(2등급) 폐렴증의 경우에는 이 약 투여를 영구 중단한다. **② 면역-매개 결장염:** 이 약 투여 환자에서 결장염이 보고되었다. 결장염의 징후와 증상에 대해 환자를 모니터링해야 한다. 중등증(2등급) 이상의 결장염의 경우 코르티코스테로이드를 투여(프레드니손으로 초회 용량 1-2 mg/kg/day 또는 이에 상응하는 양을 투여하고 이후 점감)한다. 중등증(2등급) 또는 중증(3등급)의 결장염의 경우 이 약 투여를 보류하며, 생명을 위협하는(4등급) 결장염의 경우 이 약 투여를 영구 중단한다. **③ 면역-매개 간염 (이 약) 및 간독성 (이 약과 엑시티닙 병용 요법):** 면역-매개 간염 이 약 투여 환자에서 간염이 보고되었다. 간 기능의 변화(치료 시작 시점, 치료 기간 중에는 정기적으로 실시 및 임상 평가를 토대로 필요한 경우 실시)와 간염의 증상에 대해 환자를 모니터링해야 한다. 코르티코스테로이드를 투여(프레드니손으로 초회 용량을 2등급 간염의 경우 0.5-1 mg/kg/day, 3등급 이상의 간염의 경우 1-2 mg/kg/day 또는 이에 상응하는 양을 투여하고 이후 점감)하고 간 효소 상승의 중증도에 따라 이 약 투여를 보류 또는 중단한다. 엑시티닙과의 병용 시 간독성 이 약의 단독 투여 시와 비교하여 이 약과 엑시티닙의 병용 투여 시에는 예상되었던 발생률보다 높은 빈도의 3등급 및 4등급의 ALT 및 AST 상승과 같은 간독성이 발생할 수 있다. 치료를 시작하기 전과 치료하는 동안 정기적으로 간 효소를 모니터링해야 한다. 단독 요법으로 사용될 때에 비해 간 효소를 더 자주 모니터링할 것을 고려한다. 간 효소 상승 시 이 약 및 엑시티닙의 투여를 일시 중단하고, 필요 시 코르티코스테로이드의 투여를 고려한다(용법용량 참고). 이 약과 엑시티닙의 병용 투여 시 3등급 및 4등급의 ALT 증가(20%) 및 AST 증가(13%)가 보고되었다. ALT 증가가 발병하는 시간의 중앙값은 2.3개월(범위: 7일 ~ 19.8개월)이었다. ALT 증가인 환자들 중 59%는 전신 코르티코스테로이드를 투여받았다. ALT가 정상 상한치의 3배 이상인 환자들(2~4등급, n=116) 중 94%에서 ALT가 0~1등급으로 회복되었다. 이 약(3%) 또는 엑시티닙(31%) 단독 요법, 또는 두 약의 병용 요법(50%)으로 재투여한 92명의 환자들 중 55%는 ALT가 정상 상한치의 3배 초과로 상승하는 재발을 보이지 않았다. **④ 면역-매개 신장염:** 이 약 투여 환자에서 신장염이 보고되었다. 신기능의 변화에 대해 환자를 모니터링한다. 중등증(2등급) 이상의 신장염의 경우 코르티코스테로이드를 투여(프레드니손으로 초회 용량 1-2 mg/kg/day 또는 이에 상응하는 양을 투여하고 이후 점감)한다. 중등증(2등급) 신장염의 경우 이 약 투여를 보류하며, 중증(3등급) 내지 생명을 위협하는(4등급) 신장염의 경우 이 약 투여를 영구 중단한다. **⑤ 면역-매개 내분비병증:** 이 약 투여 환자에서 부신 부전(원발성 및 속발성)이 보고되었다. 이 약 투여 환자에서 뇌하수체염도 보고되었다. 부신 부전 및 뇌하수체염(뇌하수체기능저하증 포함)의 징후와 증상에 대해 환자를 모니터링한다. 코르티코스테로이드를 투여하고 임상적으로 필요한 경우 다른 호르몬 대체요법을 실시한다. 중등증(2등급) 부신 부전 또는 뇌하수체염의 경우 이 약 투여를 보류하며, 중증(3등급) 내지 생명을 위협하는(4등급) 부신 부전 또는 뇌하수체염의 경우 이 약 투여를 보류 또는 중단한다. 이 약 투여 환자에서 당뇨병성 케토산증을 포함하는 제1형 당뇨병이 보고되었다. 고혈당증 또는 다른 당뇨병의 징후와 증상에 대해 환자를 모니터링해야 한다. 제1형 당뇨병의 경우 인슐린을 투여하고 중증의 고혈당증의 경우 대사조절에 도달할 때까지 이 약 투여를 보류한다. 이 약 투여 환자에서 갑상선기능항진증, 갑상선 저하증 및 갑상선염을 포함하는 갑상선 장애가 보고되었으며 치료 중 언제라도 발생할 수 있다. 그러므로 갑상선 기능의 변화(치료 시작 시점, 치료 기간 중에는 정기적으로 모니터링 및 임상 평가를 토대로 필요한 경우 모니터링)와 갑상선 장애의 임상적 징후와 증상에 대해 모니터링해야 한다. 갑상선 저하증의 경우 호르몬 대체요법을 실시한다. 갑상선기능항진증은 티오나마이드 및 베타 차단제로 적절히 관리한다. 중증(3등급) 또는 생명을 위협하는(4등급) 갑상선기능항진증의 경우 투여를 일시 또는 영구 중단한다. **⑥ 중증의 피부반응:** 이 약 투여 환자에서 면역-매개의 중증의 피부반응이 보고되었다. 중증의 피부반응이 의심되면 환자를 모니터링하고 다른 원인들을 배제한다. 약물이상반응의 중증도에 따라 이 약 투여를 보류 또는 영구 중단하고 코르티코스테로이드를 투여한다(용법용량 참고). 이 약 투여 환자에서 스티븐스-존슨 증후군(SJS)과 독성표피괴사용해증(TEN)이 보고되었으며, 일부는 치명적인 경과를 보였다. 스티븐스-존슨 증후군 또는 독성표피괴사용해증의 징후 또는 증상이 있으면, 이 약 투여를 보류하고 보다 전문적인 평가와 치료를 위한 기관에 위탁한다. 만약 스티븐스-존슨 증후군 또는 독성표피괴사용해증이 확진되면, 이 약 투여를 영구 중단한다(용법용량 참고). **⑦ 기타 면역-매개 약물이상반응:** 이 약을 투여받은 환자 2799명 중 1% 미만(별도의 표시가 없는 경우)에서 다음의 임상적으로 중요한 면역관련 약물이상반응이 확인되었다: 관절염(1.5%), 포도막염, 근염, 길랑-바레증후군, 중증근무력증(악화 포함), 혈관염, 췌장염, 용혈성 빈혈, 사르코이드증, 뇌염, 척수염, 부갑상선 저하증. 다음은 이 약의 다른 임상시험 또는 시판 후 사용에서 보고되었다: 심근염, 경화성 담관염. 면역-매개 약물이상반응 중 일부는 중증이었으며 임상시험 중 또는 시판 후 사용에서 보고되었다. **⑧ 이식 관련 약물이상반응:** 시판 후 사용에서 이 약을 투여받은 환자에서 고형 장기 이식 거부가 보고되었다. 이 약은 고형 장기 이식 거부의 위험성을 증가시킬 수 있다. 이러한 환자에게 투여할 경우, 이 약 투여에 따른 유익성 대비 이식 거부 가능성에 따른 위험성을 고려해야 한다. 이 약을 투여받은 동종이형 조혈모세포이식수술(HSCT) 이력이 있는 환자에서 치명적인 이식편대숙주질환(GVHD)을 포함한 급성 이식편대숙주질환이 보고되었다. 이식 수술 후 이식편대숙주질환을 경험한 환자들은 이 약 투여 이후 이식편대숙주질환의 위험이 증가할 수 있다. 동종이형 조혈모세포이식수술 이력이 있는 환자에서는 이 약 투여에 따른 유익성 대비 이식편대숙주질환의 위험성을 고려해야 한다. **[상호작용]** 이 약에 대해 공식적인 약동학적 약물 상호작용 연구는 수행된 바 없다. 펨브롤리주맙은 혈액에서 이화작용을 통해 소실되므로 대사적 약물-약물 상호작용은 예상되지 않는다. 이 약의 약력학적 활성 및 유효성이 저해될 가능성이 있으므로 이 약 투여를 시작하기 전에 전신 코르티코스테로이드 또는 면역억제제의 사용을 피해야 한다. 하지만 이 약 투여를 시작한 이후에 면역-매개 약물이상반응의 치료를 위해서는 전신 코르티코스테로이드 또는 면역억제제를 사용할 수 있다. 이 약을 화학요법제와 병용하여 투여할 때, 예방적 항구토제 및/또는 화학요법제와 관련된 약물이상반응 완화의 목적으로 코르티코스테로이드를 전치료로 사용할 수 있다. **[임부, 수유부, 가임여성]** 1) 임부 및 가임여성: 이 약의 임신 중 투여에 관한 안전성은 확립되어 있지 않으므로 임부 또는 임신하고 있을 가능성이 있는 여성에게는 투여하지 않는다. 2) 수유부: 이 약이 사람 모유로 분비되는지 여부는 알려지지 않았다. 인간 IgG는 모유 중으로 이행되므로 수유부에게 투여하는 경우에는 수유를 중단하도록 한다. **[소아]** 소아 환자에서 이 약의 안전성 프로파일은 성인에서와 유사하였다. 가장 빈번한 약물이상반응(적어도 20%의 소아 환자에서 보고됨)은 발열, 구토, 두통, 복통, 빈혈, 기침 그리고 변비였다. **[고령자]** 전반적으로 고령자(65세 이상)와 65세 미만 성인 간에 안전성 또는 유효성의 차이는 보고되지 않았다. 이 환자군에서 용량 조절은 필요하지 않다. **[신장애 환자]** 경증 또는 중등증 신장애 환자에게는 용량 조절이 필요하지 않다. 중증 신장애 환자를 대상으로 한 이 약에 대한 연구는 수행된 바 없다. **[간장애 환자]** 경증 간장애 환자에게는 용량 조절이 필요하지 않다. 중등증 또는 중증 간장애 환자를 대상으로 한 이 약에 대한 연구는 수행된 바 없다. 작성일자: 2022년 8월 22일 **※ 키트루다를 처방하시기 전에 제품설명서를 참조하시기 바랍니다.**

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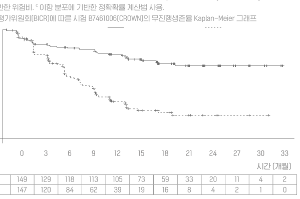
ALK, anaplastic lymphoma kinase; NSCLC, Non-small cell lung cancer; TKI, tyrosine kinase inhibitor ; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network;

References 1. Solomon BJ, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol. 2018;19(12):1654-67. **2.** Felip E, et al. Intracranial and extracranial efficacy of lorlatinib in patients with ALK-positive non-small-cell lung cancer previously treated with second-generation ALK TKIs. Ann Oncol. 2021;32(5):620-630. **3.** Planchard D, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (Originally published in 2018 – Ann Oncol (2018) 29(Suppl 4): iv192–iv237 & Updated version published 15 September 2020 by the ESMO Guidelines Committee). Available at https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-smallcell-lung-cancer. Accessed May, 2022. **4.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Non-Small Cell Lung Cancer Version 3.2022-March 16. 2022. **5.** Johnson TW, et al. Discovery of (10R)-7-Amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a Macrocyclic Inhibitor of Anaplastic Lymphoma Kinase (ALK) and cros Oncogene 1 (ROS1) with Preclinical Brain Exposure and Broad-Spectrum Potency against ALK-Resistant Mutations. J Med Chem. 2014;57(11):4720-4744. **6.** Ganior JF, et al. Molecular Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in ALK-Rearranged Lung Cancer. Cancer Discov. 2016;6(10):1118-1133. **7.** 로비큐아 제품설명서(허가사항변경일 2022.05.11)

로비큐아 제품설명서

[주요 안전성 정보] 이 약을 투여받은 환자에게 보고된 중대한 이상반응 중 가장 빈번한 것은 인지영향과 폐렴이었고, 가장 빈번하게 보고된 이상반응은 고콜레스테롤혈증, 고중성지방혈증, 부종, 말초신경병증, 체중증가, 인지영향, 피로, 관절통, 설사 및 기분영향이었다. 빈번하게 보고된 이상 반응 중 용량 감소로 이어진 가장 흔한 이상반응은 부종 및 말초신경병증이었고, 영구 투여중단으로 이어진 가장 빈번한 이상반응은 인지영향, 말초신경병증, 폐렴이었다. 또한, 이 약 투여 시 간질성 폐질환(ILD)/폐렴과 일치하는 중증 또는 생명을 위협하는 폐 이상반응이 나타났다. ILD/폐렴을 나타내는 호흡기 증상 (예:호흡곤란, 기침, 발열)의 악화가 나타난 환자는 즉시 ILD/폐렴에 대해 평가하고, 중증도에 근거하여 이 약 투여를 잠정중단 및/또는 영구중단해야 한다.



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옵디보®주 100mg / 20mg (니볼루맙, 유전자재조합) **[원료약품 및 그 분량]** 옵디보®주 20mg 중 유효성분 니볼루맙(별규) 20mg, 옵디보®주 100mg 중 유효성분 니볼루맙(별규)100mg, 옵디보®주 240mg 중 유효성분 니볼루맙(별규)240mg **[성상]** 무색~미황색의 투명 또는 유백광을 나타내는 액이 무색투명한 바이알에 든 주사제. 미립자가 확인되는 경우가 있음. **[효능효과] 흑색종** 1. 수술이 불가능하거나 전이성인 흑색종 치료의 단독요법 또는 이필리무맙과의 병용요법 2. 완전 절제술을 받은 림프절을 침범하거나 전이성인 흑색종 환자에서 수술 후 보조요법(adjuvant)으로 단독 요법 **비소세포폐암** 1.절제 가능한(종양크기 4cm 이상 또는 양성 림프절) 비소세포폐암에서 백금 기반 화학요법과의 병용투여로 수술 전 보조요법(neoadjuvant) 2.PD-L1 발현 양성(≥1%)으로서, EGFR 또는 ALK 변이가 없는 전이성 또는 재발성 비소세포폐암의 1차 치료로서 이필리무맙과의 병용 요법 3.EGFR 또는 ALK 변이가 없는 전이성 또는 재발성 비소세포폐암의 1차 치료로서 이필리무맙, 백금 기반 화학요법 2주기와의 병용 요법 4.EGFR 또는 ALK 변이가 없는 전이성 또는 재발성 비편평 비소세포폐암의 1차 치료로서 카보플라틴, 파클리탁셀, 베바시주맙과의 병용요법 5.이전 백금기반 화학요법에 실패한 국소 진행성 또는 전이성 비소세포폐암의 치료로 단독요법 **신세포암** 1.이전 치료에 실패한 진행성 신세포암 치료로 단독요법 2.이전 치료경험이 없는 중간 혹은 고위험 진행성 신세포암 치료로 이필리무맙과의 병용요법 3.진행성 신세포암의 1차 치료로서 카보잔티닙과의 병용요법 **전형적 호지킨 림프종** 자가조혈모세포이식(Hematopoietic Stem Cell Transplantation, HSCT) 전 또는 후에 브렌톡시맙베도틴의 투여에도 재발하거나 진행된 전형적 호지킨 림프종의 치료 **두경부 편평세포암** 이전 백금기반 화학요법 치료 중 또는 후에 진행된 재발성 또는 전이성 두경부 편평세포암의 치료 **요로상피세포암** 국소 진행성 또는 전이성 요로상피세포암 환자로서 다음 중 하나에 해당하는 경우 1. 백금기반 화학요법 투여 중 또는 후에 질병 진행 2. 백금기반의 수술 전 보조요법(neoadjuvant) 또는 수술 후 보조요법(adjuvant) 치료 12개월 이내에 질병 진행 2.근치절제 후 재발 위험이 높은 근육 침습성 방광암(MIBC) 환자에서 수술 후 보조요법 (adjuvant) **위 선암 또는 위식도 접합부 선암** 이전 두 가지 이상의 항암화학요법 후에도 재발하거나 진행된 위 선암 또는 위식도 접합부 선암의 치료 **식도암** 1.이전 플루오로피리미딘계 및 백금기반 화학요법 치료를 지속할 수 없거나 투여 이후에 재발 또는 진행된 수술이 불가능한 식도 편평세포암의 치료 2.수술 전 보조요법(neoadjuvant)으로 화학방사선요법(CRT)을 받고 완전 절제술을 시행 후 잔류 병리학적 질환을 동반한 식도암 또는 위식도접합부암의 수술 후 보조요법(adjuvant) **고빈도-현미부수체 불안정성(MSI-H) 또는 불일치 복구 결함(dMMR) 전이성 직결장암** 플루오로피리미딘, 옥살리플라틴 및 이리노테칸 치료 후 재발한, 고빈도-현미부수체 불안정성(microsatellite instability-high, MSI-H) 또는 불일치 복구 결함(mismatch repair deficient, dMMR)이 있는 전이성 직결장암 성인 환자에서 이필리무맙과의 병용요법 **[용법용량] 환자 선별** 전이성 비소세포폐암의 치료로서 이 약과 이필리무맙의 병용투여 시, 종양세포의 PD-L1 발현 상태를 확인하여 환자를 선별해야 한다. PD-L1 발현은 식품의약품안전처에서 동 의약품의 사용에 적합하게 허가된 체외진단 의료기기를 사용하여 평가한다. **권장용량** 단독요법으로서 이 약의 권장용량은 표 1과 같다.

표 1. 이 약의 단독요법 투여 시 권장 용량

적응증	이 약의 권장 용량	투여 기간
수술이 불가능하거나 전이성인 흑색종,국소 진행성 또는 전이성 비소세포폐암, 진행성 신세포암, 전형적 호지킨 림프종, 두경부 편평세포암, 국소 진행성 또는 전이성요로상피세포암, 요로상피세포암, 위 선암 또는 위식도 접합부 선암	다음과 같이 30분에 걸쳐 정맥 점적주입 – 3mg/kg을 2주 간격 또는 240mg을 2주 간격 또는 480mg을 4주 간격	질환이 진행되거나 허용 불가능한 독성 발생 전까지 투여한다.
흑색종의 수술 후 보조요법	다음과 같이 30분에 걸쳐 정맥 점적주입 – 3mg/kg을 2주 간격 또는 240mg을 2주 간격 또는 480mg을 4주 간격	질환이 재발하거나 허용 불가능한 독성 발생 전까지 투여하며, 최대 1년까지 투여 가능하다.
근육 침습성 방광암(MIBC) 수술 후 보조요법	다음과 같이 30분에 걸쳐 정맥 점적주입 – 240mg을 2주 간격 또는 480mg을 4주 간격	질환이 재발하거나 허용 불가능한 독성 발생 전까지 투여하며, 최대 1년까지 투여 가능하다.
식도암 또는 위식도 접합부암 수술 후 보조요법	다음과 같이 30분에 걸쳐 정맥 점적주입 – 240mg을 2주 간격 또는 480mg을 4주 간격	질환이 진행되거나 허용 불가능한 독성 발생 전까지 투여하며, 최대 1년까지 투여 가능하다.
식도 편평세포암	다음과 같이 30분에 걸쳐 정맥 점적주입 – 240mg을 2주 간격 또는 480mg을 4주 간격	질환이 진행되거나 허용 불가능한 독성 발생 전까지 투여한다.

이필리무맙 또는 다른 약제와의 병용 요법으로서 이 약의 권장용량은 표 2와 같다. 이 약과 병용 요법으로 투여되는 약제 각각의 처방정보 및 허가사항을 잘 숙지한다.

표 2. 다른 약제와의 병용요법 투여 시 권장 용량

적응증	이 약의 권장 용량	투여 기간
수술이 불가능하거나 전이성인 흑색종	이 약 1mg/kg을 3주 간격으로 30분에 걸쳐 정맥 점적주입한 후 이필리무맙 3mg/kg을 같은 날에 90분에 걸쳐 3주 간격으로 4회 정맥 점적주입. 이 후, 단독요법으로 이 약을 다음과 같이 30분에 걸쳐 정맥 점적주입 3mg/kg을 2주 간격 또는 240mg을 2주 간격 또는 480mg을 4주 간격	이필리무맙은 4회 투여한다. 4회의 이필리무맙 병용요법 투여완료 이후 단독요법으로 이 약을 질환이 진행되거나 허용 불가능한 독성 발생 전까지 투여한다.
절제 가능한(종양크기 4cm 이상 또는 양성 림프절) 비소세포폐암의 수술 전 보조요법(neoadjuvant)	다음을 병용 투여 : 이 약 360mg을 3주 간격 (30분 간 정맥 점적 주입) 및 같은 날 백금 기반 화학요법 3주 간격	백금 기반 화학요법과의 병용요법으로 3주기 투여한다.
PD-L1을 발현하는 전이성 또는 재발성 비소세포폐암	다음을 병용 투여 : 이 약 3mg/kg을 2주 간격 (30분 간 정맥 점적 주입) 및 이필리무맙 1mg/kg을 6주 간격 (30분 간 정맥 점적 주입) 또는 – 이 약 360mg을 3주 간격 (30분 간 정맥 점적 주입) 및 이필리무맙 1mg/kg을 6주 간격 (30분 간 정맥 점적 주입)	이필리무맙과의 병용요법으로서 이 약은 질환이 재발하거나 허용 불가능한 독성 발생 전까지 투여하며, 최대 2년까지 투여 가능하다.
전이성 또는 재발성 비소세포폐암	다음을 병용 투여 : 이 약 360mg을 3주 간격 (30분 간 정맥 점적 주입) 및 이필리무맙 1mg/kg을 6주 간격 (30분 간 정맥 점적 주입) 및 조직학적 기반의 백금 기반 화학요법을 3주 간격	조직학적 기반의 백금 기반 화학 요법은 2주기 투여한다.이필리무맙과의 병용요법으로서 이 약은 질환이 재발하거나 허용 불가능한 독성 발생 전까지 투여하며, 최대 2년까지 투여 가능하다.
전이성 또는 재발성 비편평 비소세포폐암	다음을 병용 투여 : 이 약 360mg을 3주 간격 (30분 간 정맥 점적 주입) 및 카보플라틴, 파클리탁셀 및 베바시주맙을 3주 간격	카보플라틴, 파클리탁셀, 베바시주맙과 이 약의 병용요법은 최대 6주기까지 투여한다. 이 후 이 약과 베바시주맙의 병용요법은 질환이 재발하거나 허용 불가능한 독성 발생 전까지 투여 가능하다.
악성 흉막 중피종	다음을 병용 투여 : 이 약 3mg/kg을 2주 간격 (30분 간 정맥 점적 주입) 및 이필리무맙 1mg/kg을 6주 간격 (30분 간 정맥 점적 주입) 또는이 약 360mg을 3주 간격 (30분 간 정맥 점적 주입) 및 이필리무맙 1mg/kg을 6주 간격 (30분 간 정맥 점적 주입)	이필리무맙은 4회 투여한다. 4회의 이필리무맙 병용요법 투여완료 이후 단독요법으로 이 약을 질환이 진행되거나 허용 불가능한 독성 발생 전까지 투여한다. 병용요법 이후 이 약의 첫 단독요법은 이 약과 이필리무맙의 병용요법 마지막 투여일로부터 3주 후에 시작한다.
진행성 신세포암	이 약 3mg/kg을 3주 간격으로 30분에 걸쳐 정맥 점적주입한 후 이필리무맙 1mg/kg을 같은 날에 30분에 걸쳐 3주 간격으로 4회 정맥 점적주입.이 후, 단독요법으로 이 약을 다음과 같이 30분에 걸쳐 정맥 점적주입: 3mg/kg을 2주 간격 또는 240mg을 2주 간격 또는 480mg을 4주 간격	이필리무맙은 4회 투여한다. 4회의 이필리무맙 병용요법 투여완료 이후 단독요법으로 이 약을 질환이 진행되거나 허용 불가능한 독성 발생 전까지 투여한다. 병용요법 이후 이 약의 첫 단독요법은 이 약과 이필리무맙의 병용요법 마지막 투여일로부터 3주 후에 시작한다.
	다음을 병용 투여 : 이 약 240mg을 2주 간격 (30분 간 정맥 점적 주입) 또는 이 약 480mg을 4주 간격 (30분 간 정맥 점적 주입) 및 카보잔티닙 1일 1회 40mg (공복에 복용)	이 약은 질환이 진행되거나 허용 불가능한 독성 발생 전까지 투여하며, 최대 2년까지 투여 가능하다. 카보잔티닙은 질환이 진행되거나 허용 불가능한 독성 발생 전까지 투여 가능하다.
위선암, 위식도 접합부 선암 또는 식도선암	다음을 병용 투여 : 이 약 360mg을 3주 간격 (30분 간 정맥 점적 주입) 및 플루오로피리미딘계 및 백금 기반 화학요법과 3주 간격 또는 이 약 240mg을 2주 간격 (30분 간 정맥 점적 주입) 및 플루오로피리미딘계 및 백금 기반 화학요법과 2주 간격	이 약을 질환이 진행되거나 허용 불가능한 독성 발생 전까지 투여하며, 최대 2년까지 투여 가능하다.
MSI-H 또는 dMMR 있는 전이성 직결장암	다음을 병용 투여 : 이 약 3mg/kg을 3주 간격 (30분 간 정맥 점적 주입) 및 같은날 이필리무맙 1mg/kg을 30분에 걸쳐 정맥 점적 주입 4회의 병용요법 후, 이 약의 단독요법 이 약 3mg/kg을 2주 간격 (30분 간 정맥 점적 주입) 또는 이 약 240mg을 2주 간격 (30분 간 정맥 점적 주입) 또는 이 약 480mg을 4주 간격 (30분 간 정맥 점적 주입)	이필리무맙과 4회의 병용요법. 4회의 병용요법 이후 이 약의단독요법은 질환이 진행되거나 허용 불가능한 독성 발생 전까지 투여 가능하다.

이 약은 긴급 상황에 대응 가능한 의료시설에서 항암화학요법에 대한 지식과 경험이 충분한 의사에 의해 투여되어야 한다.

[사용상의 주의사항] 적용상의 주의 0.9% 생리식염주사액 또는 5% 포도당주사액으로 희석하여 최종농도가 1–10mg/mL가 되도록 한다. 총 주입량은 160mL를 넘지 않도록 한다. 체중이 40 kg 미만인 환자는 총 주입량이 체중의 4mL/kg를 넘지 않도록 한다. 희석 시 급격한 진탕을 피하고 부드럽게 섞는다. 이 약은 보존제를 포함하지 않는다. 희석된 용액은 실온에서 총 8시간 내에 사용한다. 희석 용액은 2–8℃에서 냉장보관 가능하나, 24시간을 초과해서는 안된다. 얼리지 않는다. 정맥주사용으로만 투여하고 무균, 비발열성, 저단백결합 인라인 필터(0.2–1.2㎛)를 사용하여 30분에 걸쳐 투여한다. 점적주입 라인으로 다른 약물을 함께 투여하지 않는다. 주입 종료 후 점적주입 라인을 세척한다. 이 약을 다음에 따라 다른 치료적 약물과 병용요법으로 투여한다. ·이필리무맙과의 병용요법: 이 약을 먼저 주입한 후 같은 날 뒤이어 이필리무맙을 주입한다. ·백금 기반 화학요법과의 병용요법: 이 약을 먼저 주입한 후 같은 날 뒤이어 백금 기반 화학요법을 주입한다. ·이필리무맙 및 백금 기반 화학요법과의 병용요법: 이 약을 먼저 주입한 후 같은 날 뒤이어 이필리무맙, 그리고 백금 기반 화학요법을 주입한다. ·플루오로피리미딘계 및 백금 기반 화학요법과의 병용요법: 이 약을 먼저 주입한 후 같은 날 뒤이어 플루오로피리미딘계 및 백금 기반 화학요법을 주입한다. 각각 분리된 주입용 백과 필터를 사용한다. 남은 바이알 내용물은 폐기한다. 자세한 사항은 최신의 제품설명서를 참고하여 주십시오 **[최신정보 확인방법]** 최신의 품목허가 또는 변경사항은 식약처 의약품통합정보시스템 의약품안전나라(http://nedrug.mfds.go.kr) 또는 한국오노약품공업 홈페이지 (www.onopharma.co.kr)에서 확인할수 있습니다. **[문의전화]** 02)928-8423 개정연월 : 2022년 10월 **[제조자]** (원료의약품) Lonza Biologics Incorporated, 2. Bristol-Myers Squibb Cruiserath Biologics, 아일랜드미국. (완제의약품) Ono Pharmaceutical Co., Ltd. Fujiyama Plant, 일본. **[수입판매자]** 한국오노약품공업주식회사 - 서울시 강남구 테헤란로 134 19층 **[공동판매자]** 한국BMS제약 - 서울시 강남구 테헤란로 504 해성1빌딩 12층

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RET is actionable with Retevmo[1]

레테브모는 *RET* 변이* 암 환자 대상으로 승인된 최초의 *RET* 표적 치료제입니다.[1-3]

**RET* point mutation MTC,
RET fusion-positive NSCLC / thyroid cancer(non-MTC)

Retevmo®
selpercatinib

레테브모 적응증[3†]

전이성 *RET* (REarranged during Transfection) 융합-양성 비소세포폐암

이 약은 전이성 *RET* 융합-양성 비소세포폐암 (NSCLC) 성인 환자의 치료에 사용

전신요법을 요하는 진행성 또는 전이성 *RET*-변이 갑상선 수질암

이 약은 전신요법을 요하는 진행성 또는 전이성 *RET* -변이 갑상선 수질암 (MTC)이 있는 성인 및 만 12세 이상 소아 환자의 치료에 사용

이전 소라페닙 및 렌바티닙의 치료 경험이 있는 전신요법을 요하는 *RET* 융합-양성 갑상선암

이 약은 방사성 요오드에 불응하고, 이전 소라페닙 및 렌바티닙의 치료 경험이 있으며 전신요법을 요하는 진행성 또는 전이성 *RET* 융합-양성 갑상선암이 있는 성인 환자의 치료에 사용

† 이 약의 효능·효과는 전체 반응률을 근거로 허가되었으며, 생존 기간의 증가와 같은 임상적 유익성을 입증하는 임상시험 결과는 없다.

Durable response in patients with *RET* fusion – positive NSCLC[1,6]

85% ORR (95% CI:70, 94)
- 85% PR

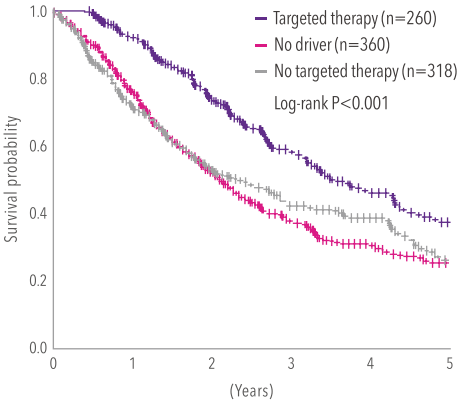
- Treatment-naive patients (n=39)
- Median DoR **not yet reached** (95% CI:12, NE) (n=39) Median follow-up: 7.4 months

64% ORR (95% CI:54, 73)
- 62% PR
- 1.9% CR

- Previously treated¶ patients (n=105)
- Median DoR **17.5 months** (95% CI:12, NE) (n=105) Median follow-up: 12.1 months

¶ Efficacy was evaluated in 105 adult patients with metastatic RET fusion-positive NSCLC who were previously treated with platinum chemotherapy enrolled into a cohort of LIBRETTO-001. All 105 patients received systemic therapy (with a median of 3 prior systemic regimens).[1]

Survival improvement for patients with NSCLC and an identified actionable oncogenic driver mutation[7]



- Patient outcome can depend on identifying a single genomic driver alteration[8]

Retevmo has showed High & Durable Intracranial Response in *RET* fusion-positive NSCLC patients[1,5]

100% Intracranial DCR

82% Intracranial ORR (95% CI: 60-95)

23% Intracranial CR

Among patients (n=22**) with measurable intracranial disease at baseline

** Including 5 patients with complete response, 13 patients with partial response and 4 patients with stable disease[5]

레테브모캡슐 40밀리그램 제품상세정보 자세히보기

레테브모캡슐 80밀리그램 제품상세정보 자세히보기

※레테브모는 정상세포에도 영향을 미쳐 부작용이 나타날 수 있으며, 일부에서는 중대할 수 있습니다.[1] ※이 제품에 대한 추가 임상적인 근거는 추후 발표 예정입니다.[4]

CI=confidence interval, **CR**=complete response, **DCR**=disease control rate, **DoR**=duration of response, **MTC**=medullary thyroid cancer, **NSCLC**=non-small cell lung cancer, **ORR**=objective response rate, **PR**=partial response; **RET**=rearranged during transfection

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ALUNBRIG® IS A PREFERRED OPTION FOR FIRST-LINE THERAPY[1]

- **Early separation** of Kaplan Myer curves and **3 X longer mPFS vs.** crizotinib (INV)[2]
- **Significant Increase in BIRC-Assessed intracranial PFS (4 X m icPFS)** evaluated in a rigorous clinical trial setting[2]
- **Long-Term safety profile** with improvement in quality of life[2]
- **The Only approved first-line ALK inhibitor** with **one-pill, once-a-day dosing** as of Jul 2021[3]

ALUNBRIG®
BRIGATINIB

ALK, anaplastic lymphoma kinase; **BIRC,** blinded independent review committee; **INV,** investigator-assessed; **NSCLC,** non-small cell lung cancer; **PFS,** progression-free survival.

REFERENCES **1.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Non-Small Cell Lung Cancer. Version 5.2021 (June 21, 2021). **2.** D. Ross Camidge, *et al.* Brigatinib Versus Crizotinib in Advanced ALK Inhibitor-Naive ALK-Positive Non-Small Cell Lung Cancer: Second Interim Analysis of the Phase III ALTA-1L Trial. *J Clin Oncol.* 2020 Aug 11;JCO2000505. **3.** 알룬브릭® 국내허가사항, 식약처 의약품안전나라, available at https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetail?itemSeq=201804848, Accessed on Jul 2021.

PRESCRIBING INFORMATION **[제품명]** 알룬브릭®정 30 mg, 90 mg, 180 mg (브리가티닙) **[효능 효과]** 역형성 림프종 인산화효소 (ALK) 양성 진행성 또는 전이성 비소세포성 폐암 환자의 치료 **[용법 용량]** **1.** ALK 검사 이 약을 투여하고자 하는 경우, 치료 시작 전에 ALK 양성 상태를 평가해야 한다. ALK 양성 진단시험은 식품의약품안전나라에서 동 의약품의 사용에 적합하게 허가된 체외 진단용 의료기기를 사용하여 평가한다. 정확하고 검증된 ALK 검사가 ALK 양성 비소세포 폐암 환자의 선택을 위해 사용되어야 한다. ALK 양성 비소세포 폐암의 평가는 활용되는 특정 기술에 대해 숙련도가 입증된 실험실에서 검사가 이루어져야 한다. **2.** 권장 용량 이 약에 대해 권장되는 용량 및 용법은 다음과 같다: • 처음 7일 동안 90 mg 1일 1회 경구투여; • 처음 7일 동안의 내약성이 좋은 경우, 용량을 180 mg 1일 1회로 증량한다. 질병이 진행되거나 관리 불가능한 독성이 발생될 때까지 이 약의 투여를 지속한다. 이상반응이 아닌 다른 이유로 14일 이상 이 약의 투여를 중단한 경우, 이전의 용량으로 증량하기 전에 90 mg 1일 1회 7일동안 투여로 치료를 재개한다. 이 약은 음식과 함께 또는 공복 상태에서 투여가 가능하다. 정제를 부수거나 씹어서는 안 되고, 그대로 삼켜야 한다. 이 약의 투여를 빠트리거나 복용 후 구토하더라도 추가 용량을 투여해서는 안 되며, 계획된 다음 투여 시간에 해당 용량을 복용해야 한다. 이상반응에 따른 권장 용량 변경 등에 대한 자세한 정보는 제품 설명서 참조. **[사용상의 주의 사항]** **1.** 경고: 1) 간질성 폐질환 (ILD)/폐렴 (자세한 정보는 제품 설명서 참조) **2.** 다음 환자에는 투여하지 말 것 1) 이 약의 주성분 또는 첨가제에 과민반응의 병력이 있는 환자 2) 이 약은 유당을 함유하고 있으므로, 갈락토오스 불내성 (galactose intolerance), Lapp 유당분해효소 결핍증 (Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수 장애 (glucose-galactose malabsorption) 등의 유전적인 문제가 있는 환자에게는 투여하면 안 된다. **3.** 이상반응: 1) 안전성 프로파일 요약 이 약을 권장 용량으로 투여한 환자에게 보고된 가장 흔한 이상반응 (≥ 25%)은 AST 증가, CPK 증가, 고혈당증, 리파아제 증가, 고인슐린혈증, 설사, ALT 증가, 아밀라제 증가, 빈혈, 오심, 피로, 저인산혈증, 림프구 수 감소, 기침, 알칼리성 인산 분해 효소 증가, 발진, APTT 증가, 근육통, 두통, 고혈압, 백혈구 수 감소, 호흡 곤란 및 구토이다. 이 약을 권장 용량으로 투여한 환자에게 종양의 진행과 관련된 증상 이외의 가장 흔하고 중대한 이상반응 (≥ 2%)은 폐렴, 간질성폐렴, 호흡 곤란 및 발열이다. (자세한 정보는 제품 설명서 참조) **4.** 일반적 주의: 1) 고혈압, 2) 서맥, 3) 시각 장애, 4) 크레아티닌 인산 분해 효소 (CPK)상승, 5) 췌장 효소 상승, 6) 간독성, 7) 고혈당증, 8)피임 (동 이상반응 관리 등에 관한 자세한 정보는 제품 설명서 참조). **5.** 상호 작용: 1) 이 약의 혈장 농도를 증가시킬 수 있는 약물: CYP3A 억제제, CYP2C8 억제제, P-gp 및 BCRP 억제제 2) 이 약의 혈장 농도를 감소시킬 수 있는 약물: CYP3A 유도제 3) 이 약에 의해 혈장 농도가 변할 수 있는 약물: CYP3A 기질 4) 수송체 기질 (동 약물 상호 작용에 따른 자세한 정보는 제품 설명서 참조) **6.** 임부, 수유부, 가임여성에 대한 투여 1) 가임기 여성 및 남성 이 약으로 치료를 받고 있는 가임기 여성에게 임신하지 않도록 권고해야 하며 이 약으로 치료를 받고 있는 남성에게 치료 중 배우자를 임신시키지 않도록 권고해야 한다. 가임기 여성에게 이 약의 투여 중과 마지막 투여 후 최소 4개월 동안은 효과적인 비호르몬 피임 방법을 사용 하도록 조언해야 한다. 가임기 여성의 남성 파트너에게 이 약의 투여 기간 중 및 마지막 투여 후 최소 3개월 동안은 효과적인 피임방법을 사용 하도록 권고한다. (임부 및 수유부, 가임력에 대한 자세한 정보는 제품 설명서 참조) 이하 **7.** 소아에 대한 투여, **8.** 고령자에 대한 투여, **9.** 간장애 환자 **10.** 신장애 환자에 대한 투여, **11.** 보관 및 취급상의 주의사항 **12.** 전문가를 위한 정보는 제품 설명서 참조 **[포장 단위]** 알룬브릭®정 30밀리그램: 28정 (14정/PTPX2), 56정 (14정/PTPX4), 알룬브릭®정 90밀리그램: 28정 (7정/PTPX4), 7정 (7정/PTPX1), 알룬브릭®정 180밀리그램: 28정 (7정/PTPX4) **[저장 방법]** 기밀용기, 실온보관 [수입자] 한국다케다제약㈜/서울특별시 송파구 올림픽로 300, 37층 (신천동, 롯데월드 타워) 전화: (02)3484-0800 이 내용은 허가사항을 요약한 것으로, 더 자세한 제품정보는 식품의약품안전나라 홈페이지 (https://nedrug.mfds.go.kr)의 제품 허가사항을 참조하시기 바랍니다.

• 이 내용은 허가사항을 요약한 것으로 자세한 정보는 제품의 첨부 문서 또는 식약처 의약품안전나라 (http://nedrug.mfds.go.kr)의 각 제품 허가사항을 확인하십시오.

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• **이상사례보고** AE.SouthKorea@takeda.com

C-APROM/KR/ALUN/0386 Date of Preparation: Jul/2021

ALECENSA

- Nearly 3 years median progression-free survival[1]

  (34.8 months (95% CI 17.7–NE))

- Demonstrated OS benefit in first-line ALK+ advanced vs. crizotinib[1]

  (5-year OS rate: Alecensa 62.5% (95% CI: 54.3–70.8) vs Crizotinib 45.5%(95% CI: 33.6–57.4))

  (stratified HR 0.67, 95% CI 0.46–0.98)

- Well-established long-term safety profile

  in patients with ALK+ advanced NSCLC [1]

ALEX study design 이전에 전신 치료 경험이 없는 ALK+ 국소 진행성 또는 전이성 NSCLC 환자(n=303)를 대상으로 Alectinib 600 mg 또는 crizotinib 250mg을 매일 2회 경구투여하여 crizotinib 대비 Alectinib의 유효성 및 안전성을 평가한 다국적, 다기관, 무작위 배정, 공개 라벨 3상 임상연구. 1차 유효성 평가변수는 연구자가 평가한(Investigator-assessed) 무진행 생존기간(PFS)이었고, 2차 유효성 평가변수는 중추신경계에서의 질병 진행까지 소요된 기간(time to CNS progression)을 포함함

Safety outcome All-grade AE의 경우, Alectinib군의 전체 152명 중 147명(96.7%), crizotinib군 전체 151명 중에서 147명(97.4%)에서 발생하였으며 Grade 3-5 AE는 Alectinib군 68명(45%), crizotinib군 77명(51%)에서 나타났음.
Median treatment duration은 Alectinib군에서는 28.1개월, crizotinib군에서는 10.8개월을 보여주었음

OS, overall survival; **ALK**, anaplastic lymphoma kinase; **NSCLC**, non-small cell lung cancer

Reference 1. Mok T et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. Ann Oncol 2020; 31(8): 1056–1064.

알레센자®캡슐 150 밀리그램(알렉티닙염산염) Selected Product Information [원료약품 및 그 분량] 이 약 1캡슐(400.00mg) 중 유효성분: 알렉티닙염산염(미분화)(별규) 161.33mg [성상] 이 약은 흰색-연한 노란색 가루 또는 덩어리진가루가 충전된 흰색-황백색의 경질캡슐제 [효능·효과] 역형성 림프종 인산화효소(ALK) 양성 국소 진행성 또는 전이성 비소세포폐암 환자의 치료 [용법·용량] 1. ALK 검사. 이 약을 투여하고자 하는 경우, 치료 시작 전에 ALK 양성 상태를 평가해야 한다. 정확하고 검증된 ALK 검사가 ALK 양성 비소세포폐암 환자의 선택을 위해 사용되어야 한다. ALK 양성 비소세포폐암의 평가는 활용되는 특정 기술에 대해 숙련도가 입증된 실험실에서 검사가 이루어져야 한다. 2. 권장용량. 이 약은 음식과 함께 복용하고 통째로 삼켜야 하며 캡슐을 개봉하거나 녹여 먹여서는 안 된다. 이 약의 권장용량은 600밀리그램(4캡슐)으로 1일 2회 경구투여한다(1일 용량 1200밀리그램). 중증 간장애 환자에서는 450밀리그램을 1일 2회 경구투여한다(1일 용량 900밀리그램). 질병 진행이 있거나 관리 불가능한 독성이 나타날 때까지 환자가 이 약으로 치료받는 것을 권장한다. 계획된 투여 용량을 놓친 경우, 환자는 다음 복용 시간까지 6시간 넘게 남았다면 바로 복용한다. 이 약 투여 후 구토를 한다면 환자는 예정된 다음 투여 시간에 해당 양을 복용한다. 3. 용량조절. 이상반응 관리를 위해 이 약 투여 중 일시적 투여 중단, 용량 감소 또는 투여 중지가 필요하다. 이 약의 용량은 내약성에 근거하여 1일 2회 150밀리그램씩 감량할 수 있다. 이 약의 투여는 환자가 1일 2회 300밀리그램에 내약성이 없다면 영구히 투여를 중지한다.간질성폐질환/폐렴(모든 등급)의 경우, 즉시 이 약 투여를 중단하고 간질성폐질환/폐렴의 다른 잠재적인 원인이 밝혀지지 않는다면 영구히 투여를 중단해야 하며 총 빌리루빈은 정상치 상한(ULN) 보다 2 배 이하로 증가하고 ALT 또는 AST 가 3 등급 이상 증가(정상치 상한보다 5 배 초과)의 경우, 기저상태 또는 1 등급 이하(정상치 상한의 3 배 이하)로 회복될 때까지 일시적으로 투여를 중단하고, 감량된 용량으로 투여를 재개(표 1 참조)한다. 담즙울체 또는 용혈 없이 총 빌리루빈이 정상치 상한 보다 2 배를 초과하여 상승하고 ALT 또는 AST 가 2 등급 이상 증가(정상치 상한보다 3 배 초과)할 시 이 약 투여를 영구히 중단한다. 3 등급 신장애 환자는 혈중 크레아티닌이 정상치 상한의 1.5 배 이하로 회복될 때까지 일시적으로 투여를 중단하고, 감량된 용량으로 투여를 재개하며 4등급 신장애 환자의 경우는 이 약 투여를 영구히 중단한다. 2 등급 또는 3 등급 서맥*(증상성, 중증이고 의학적으로 유의한, 의학적 중재가 요구되는)의 경우 1 등급(무증상) 서맥 이하 또는 심박동수 60bpm 이상으로 회복될 때까지 일시적으로 중단. 항고혈압제뿐만 아니라 서맥을 초래한다고 알려진 병용약제 투여 여부를 평가한다. 원인이 되는 병용약제가 확인되고 중지할 수 있거나 용량을 조절할 수 있다면, 1 등급(무증상) 서맥 이하 또는 심박동수 60bpm 이상으로 회복될 시 감량된 용량으로 투여를 재개한다(표 1 참조). 4등급 서맥*(생명을 위협하는 결과, 긴급한 중재가 요구되는)의 경우, 원인이 되는 병용약제를 찾을 수 없다면 영구히 이 약 투여를 중지한다. 원인이 되는 병용약제가 확인되고 중지할 수 있거나 용량을 조절할 수 있다면, 1 등급(무증상) 서맥 이하 또는 심박동수 60bpm 이상으로 회복됐을 시 감량된 용량으로 투여를 재개한다(표 1 참조). 임상적 필요에 따라 자주 모니터링 한다. 재발시 영구히 투여를 중지한다. 정상치 상한보다 5 배를 초과하는 CPK 상승 시 기저상태 또는 정상치 상한 보다 2.5 배 이하로 회복될 때까지 일시적으로 투여를 중단하고, 이전 용량으로 투여하며 정상치 상한보다 10 배를 초과하여 CPK 가 상승하거나 정상치 상한보다 5 배를 초과하는 CPK 상승이 두 번째 일어난 경우 기저상태 또는 정상치 상한 보다 2.5 배 이하로 회복될 때까지 일시적으로 투여를 중단하고, 표 1 에 따라 감량된 용량으로 투여를 재개한다 [사용상의 주의사항] 1. 경고.1) 간질성폐질환(ILD)/폐렴: 이 약의 임상시험에서 간질성폐질환/폐렴이 보고되었다. 임상시험(NP28761, NP28673, BO28984)에서, 이 약으로 투여 받은 환자 405명 중 3명(0.7%)에서 간질성폐질환/폐렴이 발생하였고, 1명(0.2%)이 3등급 간질성폐질환이었다. 이 약물 이상반응으로 이 약의 투여를 중단하였다. 어떤 임상시험에서도 간질성폐질환으로 사망한 사례는 없었다. 폐렴을 나타내는 폐 증상에 대해 모니터링 해야 한다. 간질성폐질환/폐렴으로 진단 받은 환자는 즉시 이 약 투여를 중단하고 간질성폐질환/폐렴의 다른 잠재적인 원인이 발견되지 않는다면 영구히 투여를 중지한다.

*보다 자세한 제품정보 및 제품 관련 부작용 보고는 (주)한국로슈 (02-3451-3600)로 문의하시기 바랍니다. *가장 최신 제품정보는 (주)한국로슈(www.roche.co.kr)에서 확인하실 수 있습니다.

Version: Alecensa-2021-07-29-1.0

M-KR-00001139

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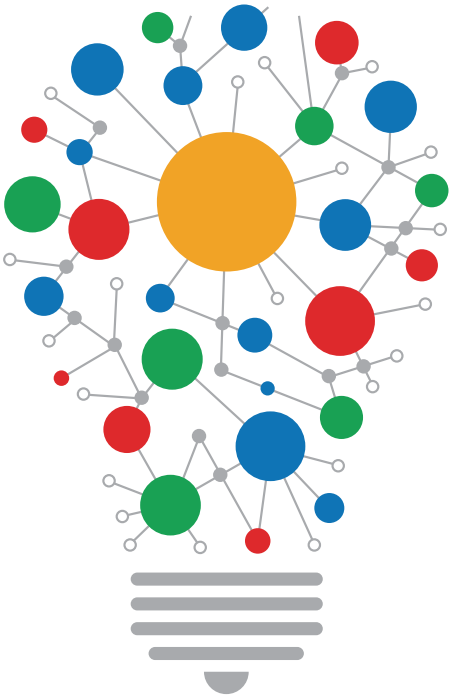

- Sequence of Treatment[1]
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EGFR=Epidermal Growth Factor Receptor; **M+**=Mutation positive; **NSCLC**=Non-small cell lung cancer; **TKI**=Tyrosine Kinase Inhibitor

Ref. 1. Hochmair MJ, et al. Future Oncol 2018, 14(27):2861-2874.

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2건의 글로벌 3상 임상 data 확보 (ADVANCE, RECOVER study)

Reference.
1) 롤론티스프리필드시린지주 제품 허가사항. 식품의약품안전처. 2) Barrett JA, *et al.* Eflapegrastim's enhancement of efficacy compared with pegfilgrastim in neutropenic rats supports potential for same-day dosing. *Exp Hematol.* 2020 Dec;92:51-61. 3) Data on file. (08-HM10460A-101) 4) Shin KH, *et al.* Pharmacokinetic and pharmacodynamic properties of a new long-acting granulocyte colony-stimulating factor (HM10460A) in healthy volunteers. *BioDrugs.* 2013 Apr;27(2):149-58. 5) Data on file. (SPI-GCF-301-PK) 6) Vacirca JL, *et al.* An open-label, dose-ranging study of Rolontis, a novel long-acting myeloid growth factor, in breast cancer. *Cancer Med.* 2018 May;7(5):1660-1669. 7) Schwartzberg LS, *et al.* Eflapegrastim, a Long-Acting Granulocyte-Colony Stimulating Factor for the Management of Chemotherapy-Induced Neutropenia: Results of a Phase III Trial. *Oncologist.* 2020 Aug;25(8):e1233-e1241. 8) Cobb PW, *et al.* A comparison of eflapegrastim to pegfilgrastim in the management of chemotherapy-induced neutropenia in patients with early-stage breast cancer undergoing cytotoxic chemotherapy (RECOVER): A Phase 3 study. *Cancer Med.* 2020 Sep;9(17):6234-6243.

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Reference

1. Choi W, et al. The Clinical Impact of Capmatinib in the Treatment of Advanced Non-Small Cell Lung Cancer with *MET* Exon 14 Skipping Mutation or Gene Amplification. *Cancer Res Treat.* 2021;53(4):1024-1032.

[Product Information]

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- 선진국(EU/JAPAN) GMP 인증 항암제 전용 시설에서 생산
- 액상제형으로 향상된 조제편의성
- 1g 함량 제품의 편리성과 경제성


RYBREVANT®
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The first targeted treatment for NSCLC patients
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PHARMACEUTICAL COMPANIES OF
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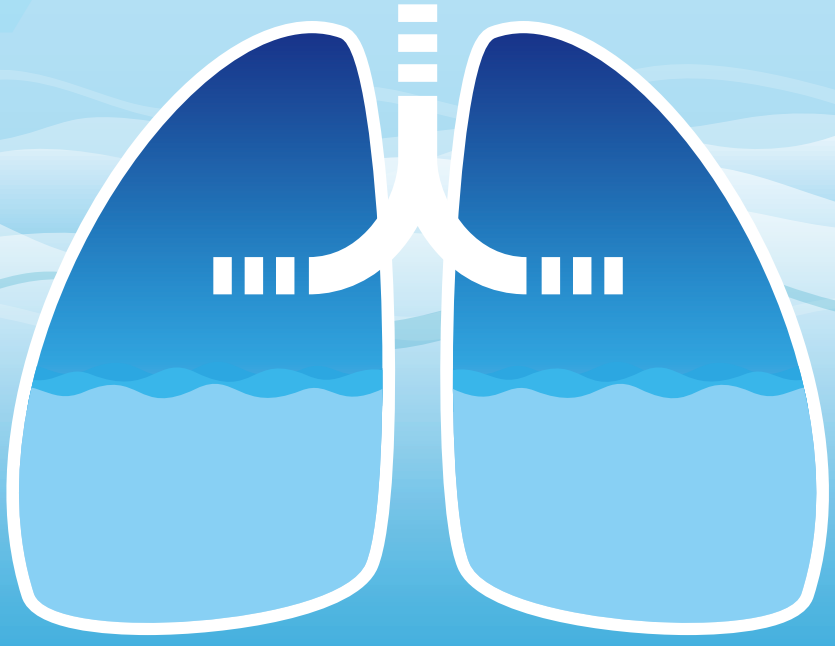
동아ST

동결건조 100mg, 300mg, 500mg | 액상제형 100mg, 800mg

MAINTA

Pemetrexed



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MAI-19K013

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Oncomine Dx Target Test

비소세포성폐암(NSCLC) 동반진단을 위한 새로운 패러다임

빠른 결과

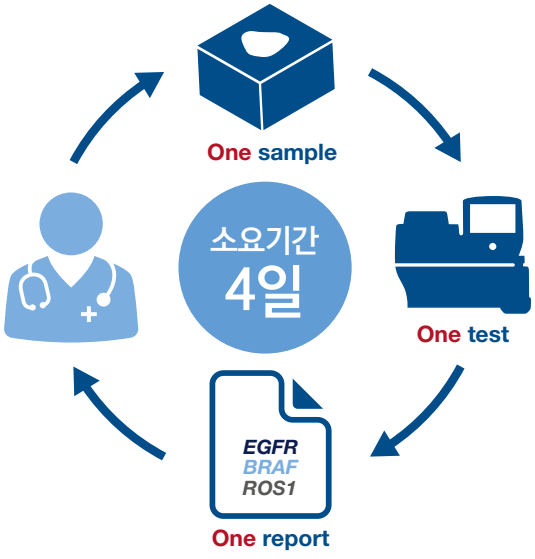
DNA와 RNA표적을 동시에 분석 가능
샘플 추출부터 임상 검사 보고까지, 전체 소요기간은 4일

임상적 성능

23개 유전자에서 369개의 변이에 대해 안정적으로
재현 가능한 결과를 제공하도록 설계

임상 보고서의 자동화

ODxTT 결과는 3개의 동반진단 바이오마커 결과와 관련된
치료약제와, 그 외 암 관련 유전자의 변이 결과를 종합한
검사 보고서 제공



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Thermo Fisher Scientific 써모 피셔 사이언티픽 솔루션스 유한회사
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ThermoFisher SCIENTIFIC

Test *KRAS G12C* status using well-validated and reliable testing methods as a first step.
Treat with LUMAKRAS® from the second line.

INDICATION:

Treatment of adult patients with *KRAS G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), who have received at least one prior therapy.

Please see full Important Safety Information and full Prescribing Information.

References:

Leighl NB, et al. Clin Cancer Res. 2019;25(15):4691-4700;
Sherwood JL, et al. ESMO Journal. 2017;2(4):e000235.
LUMAKRAS™ 120mg(sotorasib) prescribing information. MFDS, KR: (as of February 14, 2022)

ONCE-DAILY ORAL
LUMAKRAS™
(sotorasib) 120 mg tablets

AMGEN
EF-4673

석면질병 판정을 위한 흉부 CT 촬영기준 안내

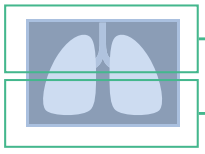
석면광산, 석면공장 인근 거주 등 **환경적인 석면 노출로 인한 건강피해자** 또는 유족을 구제하기 위해 **석면피해구제제도 운영 중** (환경부, '11.1~)

석면피해구제제도 안내 : **한국환경산업기술원 석면피해구제실**
대표전화 **1833-7690**, www.adrc.or.kr

컴퓨터 단층촬영 기준

촬영 범위

▸ **전체 폐야가 포함되도록 경부(頸部) 하부부터 상복부까지 촬영**

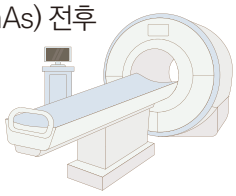


- **폐상부** : 폐 첨부가 보이지 않는 폐상부 사진이 최소 1장 이상 포함되게 촬영
- **폐하부** : 횡경막과 갈비가로막각 이하 폐가 보이지 않는 폐하부 사진이 1장 이상 포함되게 촬영

호흡과 자세, 방사선 조사량 및 조영제

가) 최대 흡기상태에서 **누운 자세(supine)와 엎드린 자세(prone)로 각각 촬영**

나) 관전압 100~120킬로볼트피크(kVp), 관전류 100밀리암페어세컨드(mAs) 전후
**주의 : 모든 촬영은 정상 방사선 조사량(저선량 아님)을 사용해야 함



다) 조영제는 사용하지 않음(사용할 필요는 없지만, 사용해도 무관함)

라) 16채널 다중검출 나선형 컴퓨터단층촬영 장치 이상의 기종으로 촬영

영상 작업

▸ **누운 자세 – 종격동창·폐창, 엎드린 자세 – 폐창 영상 모두 필요**

가) 누운자세–종격동창 컴퓨터 단층촬영 영상	나) 누운자세–폐창 컴퓨터 단층촬영 영상	다) 엎드린자세–폐창 컴퓨터 단층촬영 영상
(1) 영상 재구성의 **슬라이스 두께는 3밀리미터(㎜), 간격은 2.5밀리미터(㎜) 이하 사용**	(1) 영상 재구성의 **슬라이스 두께는 1밀리미터(㎜), 간격은 10밀리미터(㎜) 이하 사용**	(1) 영상 재구성의 **슬라이스 두께는 1밀리미터(㎜), 간격은 10밀리미터(㎜) 이하 사용**
(2) 표준연산 사용	(2) 골연산, 고공간 주파수연산 또는 폐연산 사용	(2) 골연산 또는 고공간 주파수연산을 사용
(3) 창 중심 35HU, 창 간격 350HU 전후 사용	(3) 창 중심 –700HU, 창 간격 1,500HU 사용	(3) 창 중심 –700HU, 창 간격 1,500HU 사용

*HU : 하운스필드단위

**각각은 영상조정작업이 가능한 누운자세 – 종격동창, 누운자세 – 폐창, 엎드린자세 – 폐창 영상을 반드시 포함
(즉, 폐창은 종격동창으로, 종격동창은 폐창으로 조절·변경 가능해야 함)

[1] 「석면피해구제법」에서 규정한 컴퓨터 단층촬영 기준 중 일부 전문 용어와 수치(슬라이스 두께, 간격) 등을 현행 의료 현장 상황을 반영하여 현행화

[2] 「석면피해구제법」 상 컴퓨터 단층촬영 기준은 동법 시행령 제4조 '별표1 석면질병 인정기준' 참조

환경부

KEITI 한국환경산업기술원 Korea Environmental Industry & Technology Institute