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Randomized Double-blind Placebo-controlled trial of Nicotinamide and EGFR-TKIs for EGFR-mutated Lung Adenocarcinoma

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INTRODUCTION

- Runt-related gene 3 (RUNX3) inactivation by promoter hypermethylation correlates with poor clinical outcome and occurs in 70% of lung adenocarcinomas.[1]

- Nicotinamide, a well-known sirtuin inhibitor, re-activates the epigenetically silenced tumor suppressor RUNX3 in cancer cells. [2]

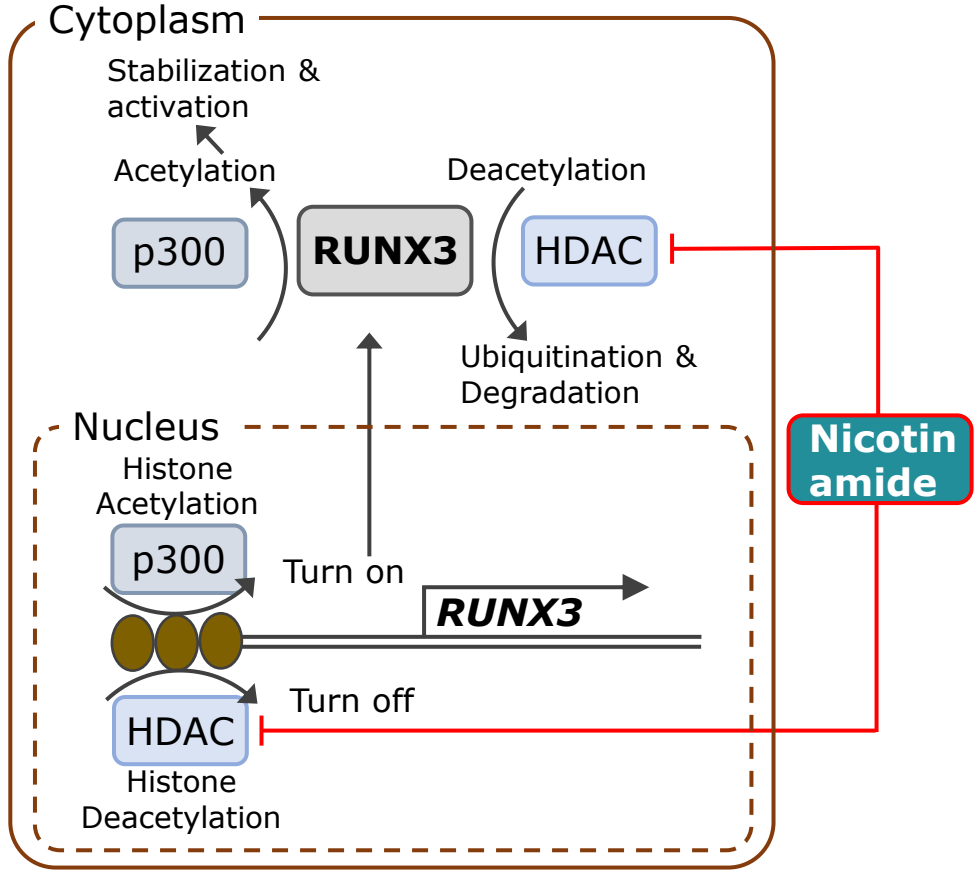
- We examined whether the addition of nicotinamide to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) increases the survival of patients with stage IV lung cancer with EGFR mutations (exon 19 deletion or L858R).

1. Omar MF, et al. *Pathol Oncol Res*. 2012;18(4):783-792.
2. Kim WJ, et al. *J Urol*. 2011;185(6):2366-2375.

BACKGROUND

- RUNX3 is a downstream effector of the transforming growth factor-β (TGF-β) signaling pathway and activates ARF-p53 pathway in response to aberrant oncogene activation. And it is known as a pioneer factor for the restriction-point deciding cell proliferation or death.[3]
- RUNX3 deletion facilitates oncogene-induced lung adenocarcinoma in mice.[4] And RUNX3 is downregulated in K-RAS or EGFR activated human lung adenocarcinoma.[1]
- Nicotinamide has preventive and therapeutic effects on tumorigenesis through RUNX3 expression up-regulation (Fig 1).[2] And it suppresses the growth of carcinogen-induced cancers in mice.[5] And it also reduces the rates of skin cancer in high-risk patients.[6]

Figure 1. RUNX3 activation by nicotinamide

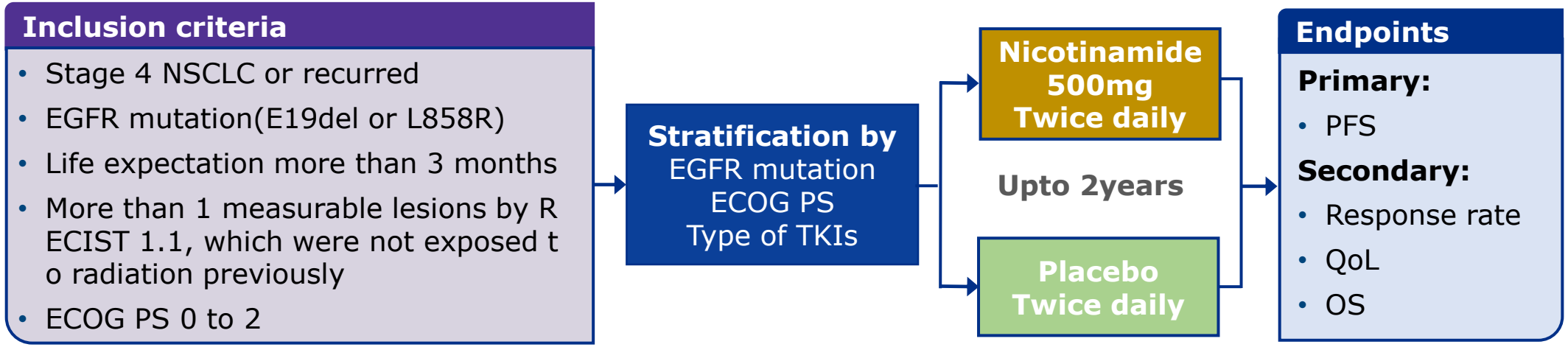


3. Chen F, et al. *Oncol Rep*. 2016;35(3):1227-1236.
4. Y-S Lee, et al. *Cancer Cell. 2013 Nov 11;24(5):603-16.*
5. SY Park, et al. *J Cell Physiol. 2012 Mar;227(3):899-908.*
6. Chen AC, et al. *N Engl J Med*. 2015;373(17):1618-1626.

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.

Figure 2. Study design. (NCT02416739)



RESULTS

Patients

- 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 (Table1). Gefitinib was used in 59.1% of patients and erlotinib in the remaining 40.9%, resulting in an objective response of 56.0%.

Table 1. Characteristics of patients in the Nicotinamide and Placebo groups

		Total (n=110)	Nicotinamide (n=55)	Placebo (n=55)	P value
Age (years ± SD)		68.5 ± 10.4	67.7 ± 10.0	69.2 ± 10.9	0.450
Sex (Female)		70 (63.6)	34 (61.8)	36 (65.5)	0.843
Smoking	Never	84 (76.4)	39 (70.9)	56 (81.8)	0.251
	Current	11 (10.0)	8 (14.5)	3 (5.5)	
	Ex-smoker	15 (13.6)	8 (14.5)	7 (12.7)	
ECOG PS score	0-1	89 (80.9)	45 (81.8)	44 (80.0)	0.622
	2	21 (19.1)	10 (18.2)	11 (20.0)	
EGFR mutation	Ex19del	66 (60.0)	33 (60.0)	33 (60.0)	0.489
	L858R	44 (40.0)	22 (40.0)	22 (40.0)	
EGFR-TKI	Erlotinib	45 (40.9)	23 (41.8)	22 (40.0)	1.000
	Gefitinib	65 (59.1)	32 (58.2)	33 (60.0)	
Response	CR or PR	61 (56.0)	31 (56.4)	30 (55.6)	0.098
	SD	43 (39.4)	20 (36.4)	23 (42.6)	
	PD	2 (1.8)	2 (3.6)	0 (0.0)	
T790M mutation		44 (40.0)	20 (36.4)	24 (43.6)	0.659
3rd generation EGFR-TKI		42 (38.2)	20 (36.4)	22 (40.0)	0.292
Progression		22 (20.0)	15 (27.3)	7 (12.7)	0.280
Survival		22 (20.0)	15 (27.3)	7 (12.7)	0.160

RESULTS

- **Efficacy-Survival**

- 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).

Figure 3A. Median progression free survival

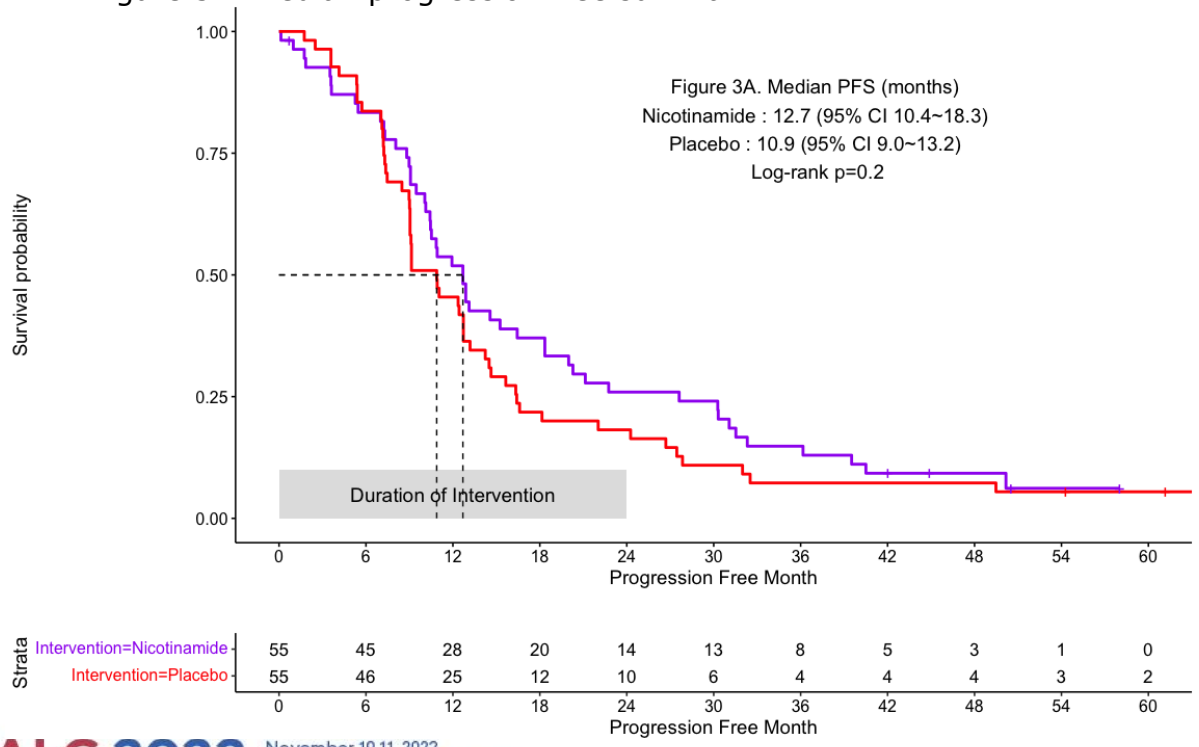
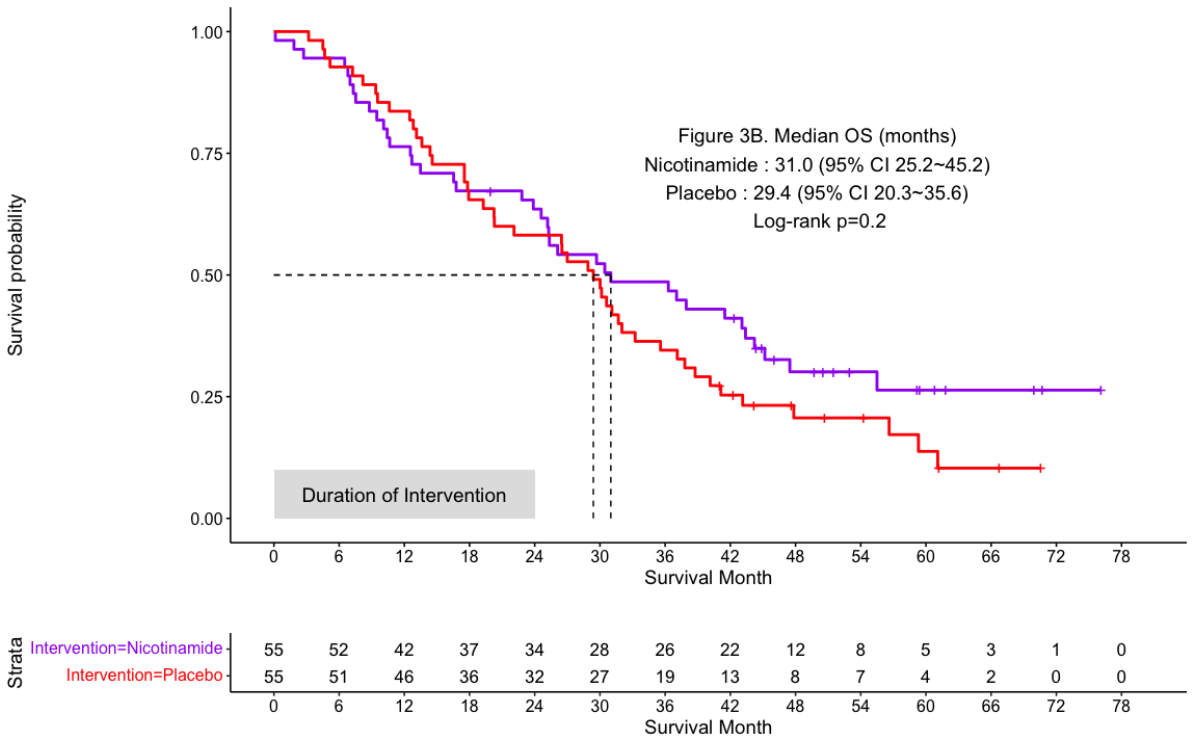


Figure 3B. Median overall survival



RESULTS

- **Efficacy-Survival, subgroup analysis**

Figure 5A. Subgroup analysis of progression free survival

Subgroup	Nicotinamide Event/Total	Placebo Event/Total	ard Ratio % CI)
Male	19/21	17/19	(0.48-1.78) p=0.8
Female	31/34	35/36	(0.43-1.14) p=0.1
Never smoker	36/39	42/45	(0.52-1.27) p=0.4
Smoker	14/16	10/10	(0.32-1.69) p=0.5
Exon19del	28/23	39/33	(0.41-1.15) p=0.2
L858R	22/22	22/22	(0.57-1.90) p=0.9
Gefitinib	28/32	23/33	(0.46-1.28) p=0.3
Erlotinib	22/23	20/22	(0.45-1.51) p=0.5
Overall	**50/55**	**52/55**	(0.53-1.17) p=0.2

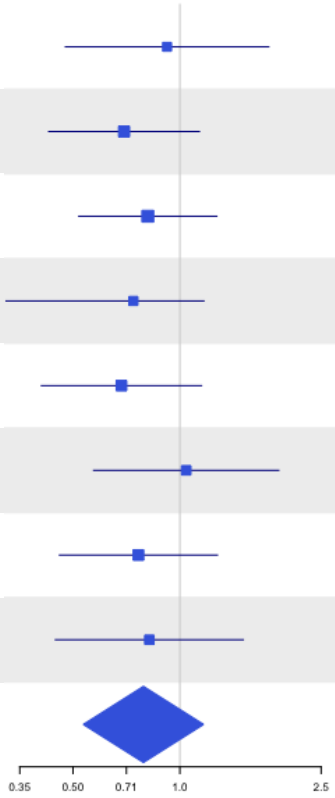
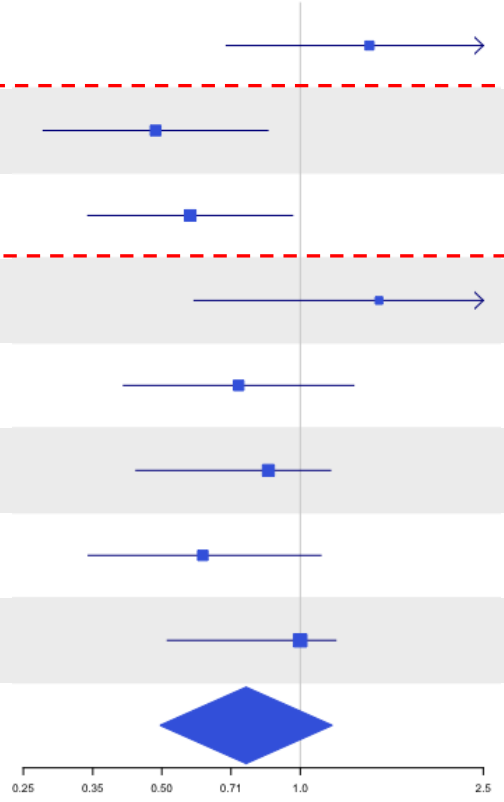


Figure 5B. Subgroup analysis of overall survival

Subgroup	Nicotinamide Event/Total	Placebo Event/Total	Hazard Ratio (95% CI)
Male	19/21	13/19	1.41(0.69-2.89) p=0.3
Female	20/23	33/36	0.48(0.28-0.85) p=0.01
Never smoker	24/39	39/45	0.58(0.35-0.96) p=0.03
Smoker	14/16	7/10	1.48(0.59-3.74) p=0.4
Exon19del	21/33	26/33	0.76(0.41-1.31) p=0.3
L858R	22/22	22/22	0.85(0.44-1.65) p=0.6
Gefitinib	21/32	28/33	0.61(0.35-1.09) p=0.09
Erlotinib	17/23	18/22	0.99(0.51-1.19) p=1.0
Overall	**38/55**	**46/55**	0.76(0.50-1.17) p=0.2



RESULTS

- **Efficacy-Survival, subgroup analysis**

- In subgroup analysis, more patients survived with nicotinamide than placebo in female (HR: 0.48, 95% CI: 0.28-0.85, p=0.01) and never smoker group (HR: 0.58, 95% CI: 0.35-0.96, p=0.03, Fig 5B).

- In female, the median OS of nicotinamide group was 43.4 months (95% CI: 31.0-NA) and that of placebo group was 30.1 (22.1-37.1) (p=0.01, Fig 4A) In never smoker group, the median OS of nicotinamide group was 43.1 (25.3-NA) and that of placebo group was 29.4 (20.3-37.1) (p=0.03, Fig 4B)

Figure 4A. Median overall survival of female subgroup

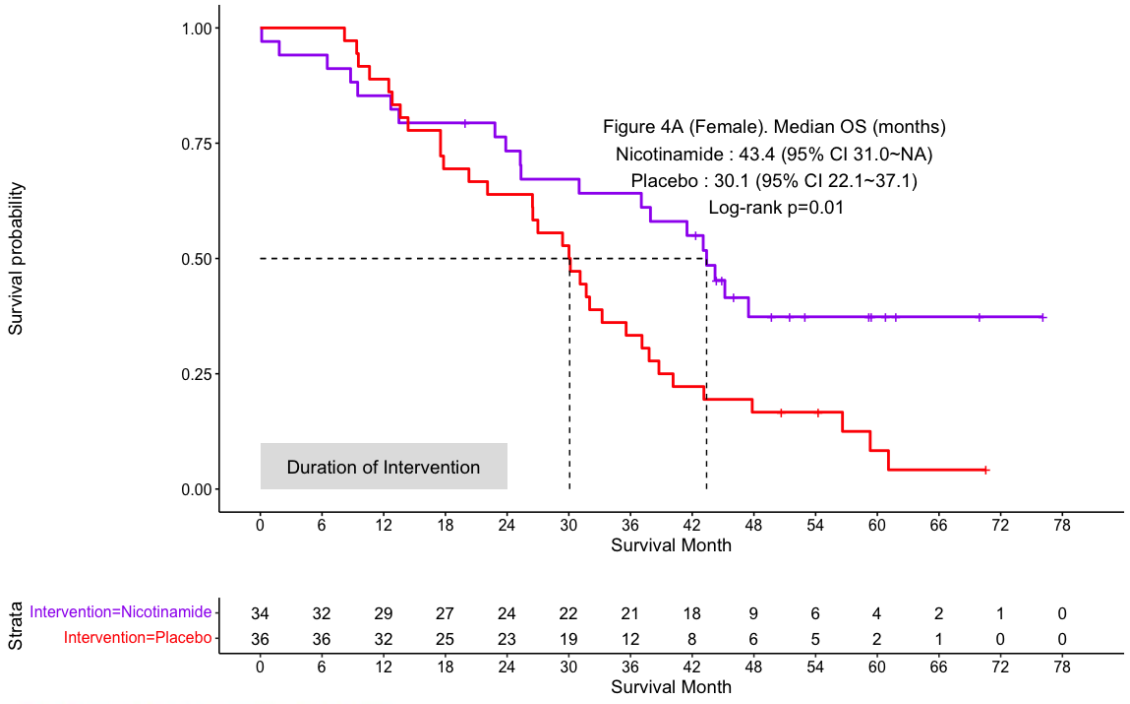
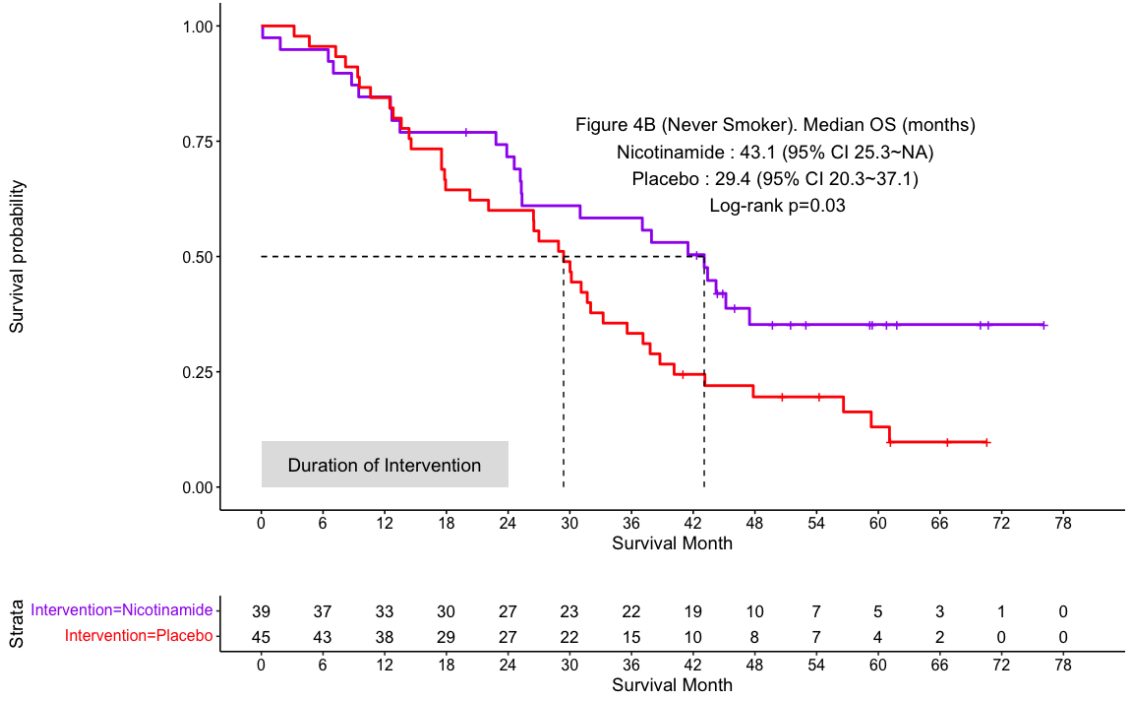


Figure 4B. Median overall survival of never smoker subgroup



RESULTS

- **Efficacy-Survival, subgroup analysis**
- All female patient was never smoker. And there was no difference of clinical characteristics between nicotinamide and placebo groups in never smoker. (Table 2)

Table 2. Characteristics of never smoked patients.

		Nicotinamide (N=39)	Placebo (N=45)	P value
Age (years ± SD)		69.7 ± 8.7	69.6 ± 10.2	0.958
Sex (Female)		34 (87.2)	36 (80.0)	0.557
ECOG PS score	0	4 (10.3)	6 (13.3)	0.887
	1	28 (71.8)	32 (71.1)	
	2	7 (17.9)	7 (15.6)	
EGFR mutation	Ex19del	22 (56.4)	27 (60.0)	0.912
	L858R	17 (43.6)	18 (40.0)	
EGFR-TKI	Erlotinib	10 (25.6)	15 (33.3)	0.596
	Gefitinib	29 (74.4)	30 (66.7)	
Response	CR	3 (7.7)	0 (0.0)	0.075
	PR	20 (51.3)	26 (57.8)	
	SD	14 (35.9)	18 (40.0)	
	PD	0 (0.0)	0 (0.0)	
T790M mutation		16 (41.0)	19 (42.4)	0.558
3rd generation EGFR-TKI		15 (38.5)	17 (37.8)	0.551

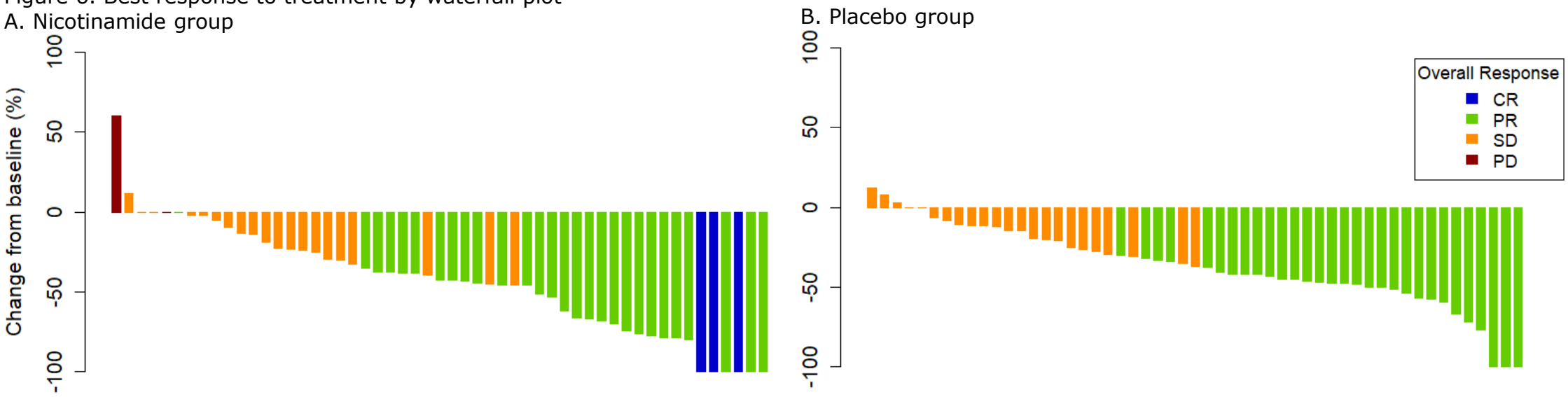
RESULTS

- **Efficacy-Response**
- 3 patients in nicotinamide group showed complete response. Otherwise there was no difference in response of each groups.

N(%)	CR	PR	SD	PD	NE	Total
Nicotinamide	3 (5.4)	28 (50.9)	20 (36.4)	2 (3.6)	2 (3.6)*	55
Placebo	0 (0)	30 (54.5)	23 (41.8)	0 (0)	2 (3.6)†	55

*;lost to follow up, Adverse event, †; Adverse event, Withdrawal of consent

Figure 6. Best response to treatment by waterfall plot



RESULTS

- **Safety**

Table 3. Adverse events

	Nicotinamide, n=55		Placebo, n=55	
Adverse events, N(%)				
Any grade	52 (94.5)		54 (98.2)	
Grade 3-5	9 (16.4)		7 (12.7)	
Serious	3 (5.5)		4 (7.3)	
Adverse events occurring in ≥10% of patients in either group, N(%)				
	Any grade	Grade 3 or 4	Any grade	Grade 3or 4
Abdominal pain	6 (10.9)	0 (0)	6 (10.9)	0 (0)
Acute kidney injury	7 (12.7)	1 (1.8)	3 (5.5)	0 (0)
ALT elevation	12 (21.8)	1 (1.8)	11 (20)	2 (3.6)
Alopecia	4 (7.3)	0 (0)	6 (10.9)	0 (0)
Anemia	8 (14.5)	0 (0)	12 (21.8)	1 (1.8)
Anorexia	20 (36.4)	0 (0)	23 (41.8)	0 (0)
AST elevation	9 (16.4)	0 (0)	8 (14.5)	2 (3.6)
Constipation	9 (16.4)	0 (0)	5 (9.1)	0 (0)
Diarrhea	38 (69.1)	1 (1.8)	29 (52.7)	0 (0)
Dry skin	10 (18.2)	0 (0)	14 (25.5)	0 (0)
Fatigue	10 (18.2)	0 (0)	9 (16.4)	1 (1.8)
Epigastric pain	5 (9.1)	0 (0)	11 (20)	0 (0)
Insomnia	6 (10.9)	0 (0)	4 (7.3)	0 (0)
Nasal mucositis	11 (20)	0 (0)	8 (14.5)	0 (0)
Nausea	3 (5.5)	0 (0)	7 (12.7)	0 (0)
Oral mucositis	29 (52.7)	1 (1.8)	25 (45.5)	0 (0)
Pain in extremity	8 (14.5)	0 (0)	2 (3.6)	0 (0)
Paronychia	24 (43.6)	0 (0)	22 (40)	0 (0)
Productive cough	4 (7.3)	0 (0)	11 (20)	0 (0)
Pruritus	28 (50.9)	0 (0)	32 (58.2)	0 (0)
Skin rash	33 (60)	1 (1.8)	31 (56.4)	1 (1.8)
Sore throat	6 (10.9)	0 (0)	4 (7.3)	0 (0)

CONCLUSION

- PFS and OS were numerically longer when EGFR TKIs were used in combination with nicotinamide than when patients were treated with EGFR TKIs alone.

- In female or never-smoker groups, OS was significantly longer in nicotinamide group. Further evaluation is needed to explain the effect of nicotinamide in these group.