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Genetic preditors associated with brain metastasis of non-small cell lung cancer using next-generation sequencing

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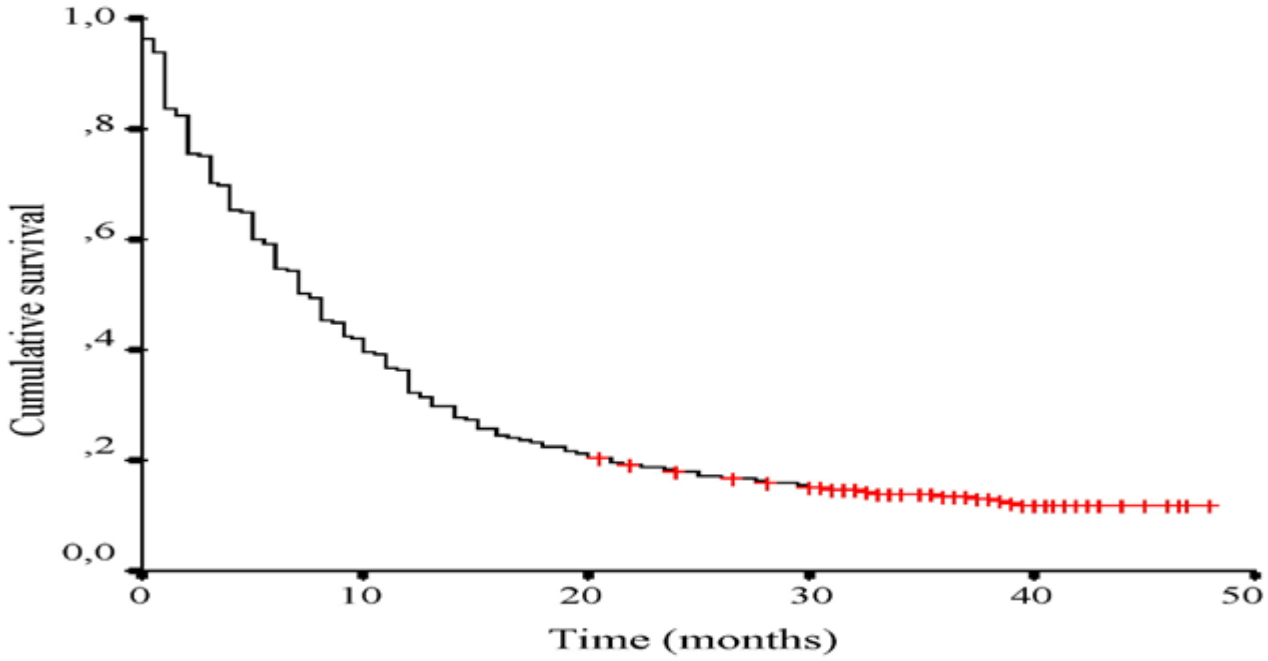
Background

- Brain metastasis (BM)
  - is associated with increased morbidity and mortality in NSLCL



1 year survival : 14%, 2 year survival 7.6%

Julio Sánchez de Cos et al. Lung Cancer 63 (2009) 140-145

Background

	brain recurrence (Column %)	no brain recurrence (Column %)	Odds Ratio Φ (95 % CI)	P values
LKB1 mutation ζ				
Mutant	3(17.6)	18(11.6)	1.63	0.47
Wild type	14(82.4)	137(88.4)	(0.35–5.62)	
LKB1 expression ζ			0.574	0.32
mean	0.447	0.570	(0.187–1.65)	
LKB1 copy number ζ			0.103	0.039
(mean)	−0.051	0.120	(0.01–0.81)	
KRAS mutation ζ				
Mutant	6(35.3)	16(10.4)	4.71	0.007
Wild type	11(64.7)	138(89.6)	(1.46–14.2)	
KRAS expression ζ			0.83	0.63
mean	−0.127	−0.041	(0.388–1.69)	
KRAS copy number ζ			0.552	0.67
mean	0.0506	0.0776	(0.024–5.52)	

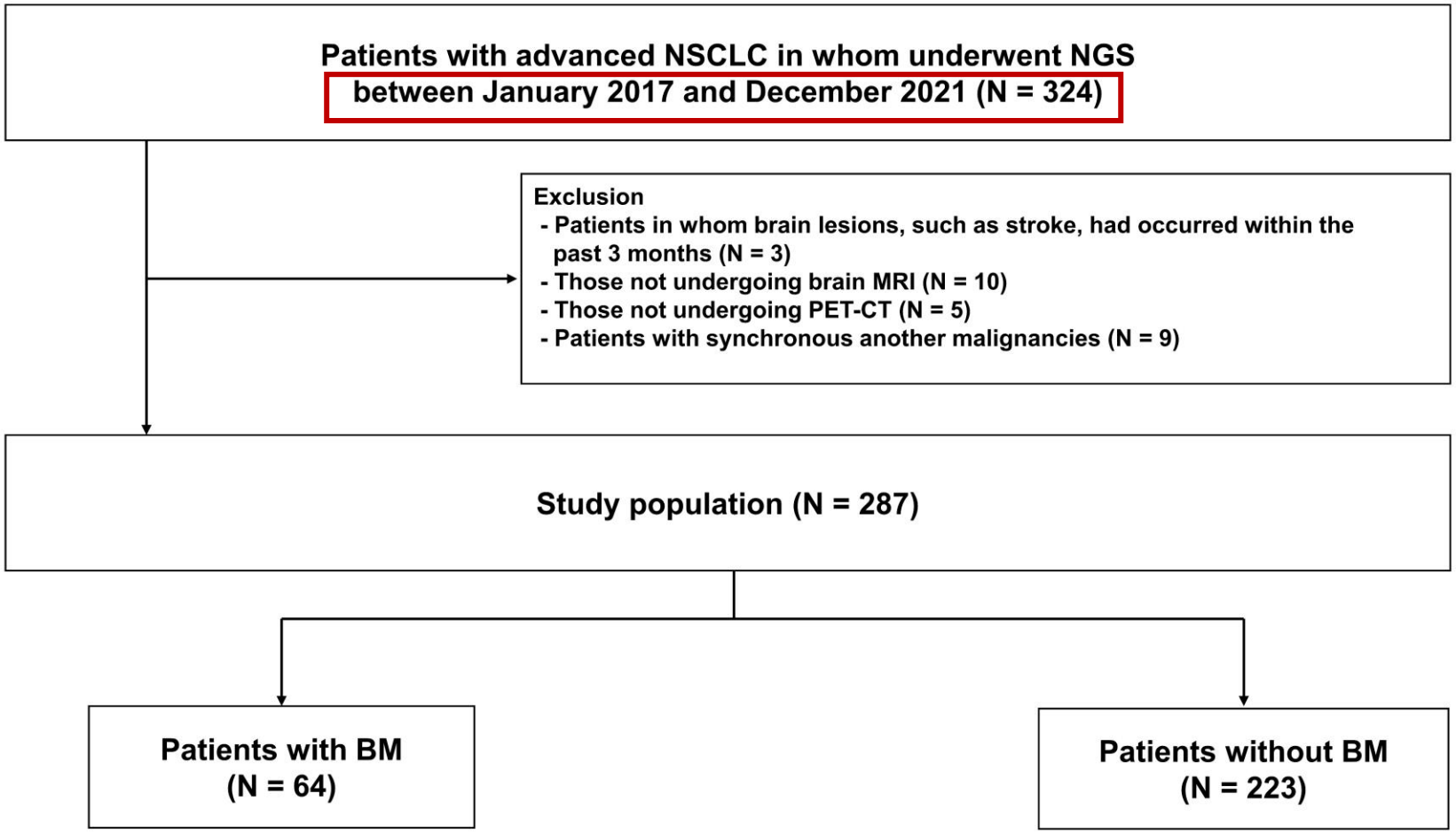
Lung cancer (Amsterdam, Netherlands) 2014, 86, 255-261

Aim

- To **analyze next-generation sequencing (NGS) results**, a targeted genome sequencing, in patients with NSCLC

- To evaluate **genetic predictors for BM** in patients with NSCLC

Methods


Patients with advanced NSCLC in whom underwent NGS
between January 2017 and December 2021 (N = 324)
Exclusion
- Patients in whom brain lesions, such as stroke, had occurred within the past 3 months (N = 3)
- Those not undergoing brain MRI (N = 10)
- Those not undergoing PET-CT (N = 5)
- Patients with synchronous another malignancies (N = 9)
Study population (N = 287)
Patients with BM
(N = 64)
Patients without BM
(N = 223)

Methods

- **NGS**

CancerSCAN

- ✓ The CancerSCAN™ panel is designed to **target 375 cancer-related genes**
- ✓ SNV, Indel, CNV, translocation
- ✓ Matched-normal free analysis

ABL1	CASP8	EGFR	FLT4	KMT2A	NTRK3	RICTOR	TNKS
ABL2	CBFB	ELMO1	FOXA1	KRAS	NUP93	RNF43	TNKS2
ACVR1B	CBL	EP300	FOXL2	LMO1	PAK3	ROBO1	TOP1
AKT1	CCND1	EPHA3	FUBP1	LRP1B	PAK7	ROBO2	TP53
AKT2	CCND2	EPHA5	GATA1	LRP6	PALB2	ROS1	TRAF7
AKT3	CCND3	EPHA6	GATA2	LTK	PARP1	RPA1	TRRAP
ALK	CCNE1	EPHA7	GATA3	MAML1	PARP2	RPTOR	TSC1
ALOX12B	CD79A	EPHB1	GID4	MAP2K1	PARP3	RUNX1	TSC2
APC	CD79B	EPHB4	GNA11	MAP2K2	PARP4	RUNX1T1	TSHR
APCDD1	CDC42	EPHB6	GNA13	MAP2K4	PAX5	SEMA3A	U2AF1
APOBEC3A	CDC73	ERBB2	GNAQ	MAP3K1	PBRM1	SEMA3E	U2AF2
APOBEC3B	CDH1	ERBB3	GNAS	MAP3K13	PDGFRA	SETBP1	USP9X
AR	CDH2	ERBB4	GPR124	MCL1	PDGFRB	SETD2	VHL
ARAF	CDH20	ERCC2	GRIN2A	MDM2	PDK1	SF3A1	WHSC1L1
ARFRP1	CDH5	ERG	GSK3B	MDM4	PGR	SF3B1	WISP3
ARID1A	CDK12	ESR1	GUCY1A2	MED12	PHF6	SFRS7	WT1
ARID1B	CDK4	ETV1	H3F3A	MEF2B	PHLPP2	SH2B3	WWP1
ARID2	CDK6	ETV4	HGF	MEN1	PIK3C3	SKP2	XBP1
ASXL1	CDK8	ETV5	HIST1H3B	MET	PIK3CA	SLIT2	XPO1
ATM	CDKN1B	ETV6	HLA-A	MITF	PIK3CG	SMAD2	XRCC3
ATR	CDKN2A	EWSR1	HNF1A	MLH1	PIK3R1	SMAD3	ZNF217
ATRX	CDKN2B	EYA2	HOXA3	MLL	PIK3R2	SMAD4	ZNF703
AURKA	CDKN2C	EZH2	HRAS	MLL2	PKHD1	SMARCA1	ZRSR2
AURKB	CDX2	FAM123B	HSP90AA1	MLL3	PLCG1	SMARCA4	CARD11
AXIN1	CEBPA	FAM46C	IDH1	MPL	PMS2	SMARCB1	DOT1L
AXL	CHD1	FANCA	IDH2	MRE11A	PNRC1	SMARCD1	FLT3
B2M	CHD2	FANCC	IGF1	MSH2	PPP2R1A	SMO	KLHL6
BACH1	CHD4	FANCD2	IGF1R	MSH6	PRDM1	SOCS1	NTRK2
BAP1	CHEK1	FANCE	IGF2R	MTOR	PRKAR1A	SOX10	RET
BARD1	CHEK2	FANCF	IKBKE	MUTYH	PRKDC	SOX2	SUFU
BCL2	CHUK	FANCG	IKZF1	MYC	PRPF40B	SOX9	C15ORF55
BCL2A1	CIC	FANCI	IL7R	MYCL1	PRSS8	SPEN	DOCK2
BCL2L1	CRBN	FANCL	INHBA	MYCN	PTCH1	SPOP	FLT1
BCL2L2	CREBBP	FANCM	INPP4B	MYD88	PTCH2	SRC	KLF4
BCL6	CRKL	FAT3	INSR	NCOA3	PTEN	SRSF1	NTRK1
BCOR	CRLF2	FBXW7	IRF4	NCOR1	PTPN11	SRSF2	REL
BCORL1	CSF1R	FGF10	IRS2	NF1	PTPRD	STAG2	TNFRSF14
BCR	CTCF	FGF12	ITK	NF2	RAB35	STAT3	C11ORF30
BLM	CTNNA1	FGF14	JAK1	NFE2L2	RAC1	STAT4	DNMT3A
BRAF	CTNNB1	FGF19	JAK2	NFKBIA	RAD50	SUFU	FGFR4
BRCA1	CUL4A	FGF23	JAK3	NKX2-1	RAD51	SYK	KIT
BRCA2	CUL4B	FGF3	JUN	NKX3-1	RAD51B	TBX22	NSD1
BRD2	CYLD	FGF4	KAT6A	NOTCH1	RAD51C	TBX3	RB1
BRD3	CYP17A1	FGF6	KDM5A	NOTCH2	RAD51D	TET2	TNFAIP3
BRD4	DAXX	FGF7	KDM5C	NOTCH3	RAD52	TERT	
BRIP1	DDR2	FGFR1	KDM6A	NOTCH4	RAD54L	TGFBR2	
BTG1	DIS3	FGFR2	KDR	NPM1	RAF1	TIPARP	
BTK	DNMT1	FGFR3	KEAP1	NRAS	RARA	TMPRSS2	

Statistical analyses

- Gene similarity: **Unsupervised hierarchical clustering**
- **To evaluate genes associated with BM** in patients with NSCLC, **logistic regression analyses** were performed
- We assessed the **co-mutation of genes** in patients diagnosed with BM and without BM using **logistic regression**
- Gene interrelationships : Factor analysis

  -> All genes were classified into **three groups**, and **logistic regression** was performed to determine the association between BM and gene clusters

Results - Baseline characteristics

	Total (N = 287)	BM		P-value
		No (N = 223)	Yes (N = 64)	
Age, years	63.3 (10.3)	63.4 (10.6)	62.9 (9.1)	0.727
Sex, male	194 (67.6)	154 (69.0)	40 (62.5)	0.323
Smoking history				0.143
Never smoker	112 (39.0)	86 (38.6)	26 (40.3)	
Ex-smoker	107 (37.2)	89 (39.9)	18 (28.3)	
Current smoker	68 (23.6)	48 (21.5)	20 (31.4)	
Type of histology				0.174
Adenocarcinoma	226 (78.7)	176 (78.9)	50 (78.1)	
SqCC	58 (20.2)	46 (20.6)	12 (18.8)	
Others	3 (1.1)	1 (0.5)	2 (3.1)	
T stage (N = 286)				0.028
T1	53 (18.5)	47 (21.2)	6 (9.3)	
T2	108 (37.7)	76 (34.2)	12 (18.8)	
T3	52 (18.1)	38 (17.1)	14 (21.9)	
T4	73 (25.5)	61 (27.5)	32 (50.0)	
N stage (N = 222)				0.751
N1	29 (13.1)	23 (14.0)	6 (10.4)	
N2	90 (40.5)	65 (39.6)	25 (43.1)	
N3	103 (46.4)	76 (46.4)	27 (46.5)	
M stage (N = 212)				0.010
Malignant pleural effusion or pericardial effusion	43 (20.3)	43 (29.05)	48 (52.1)	
Pleural seeding	138 (65.1)	74 (50.0)	54 (88.4)	

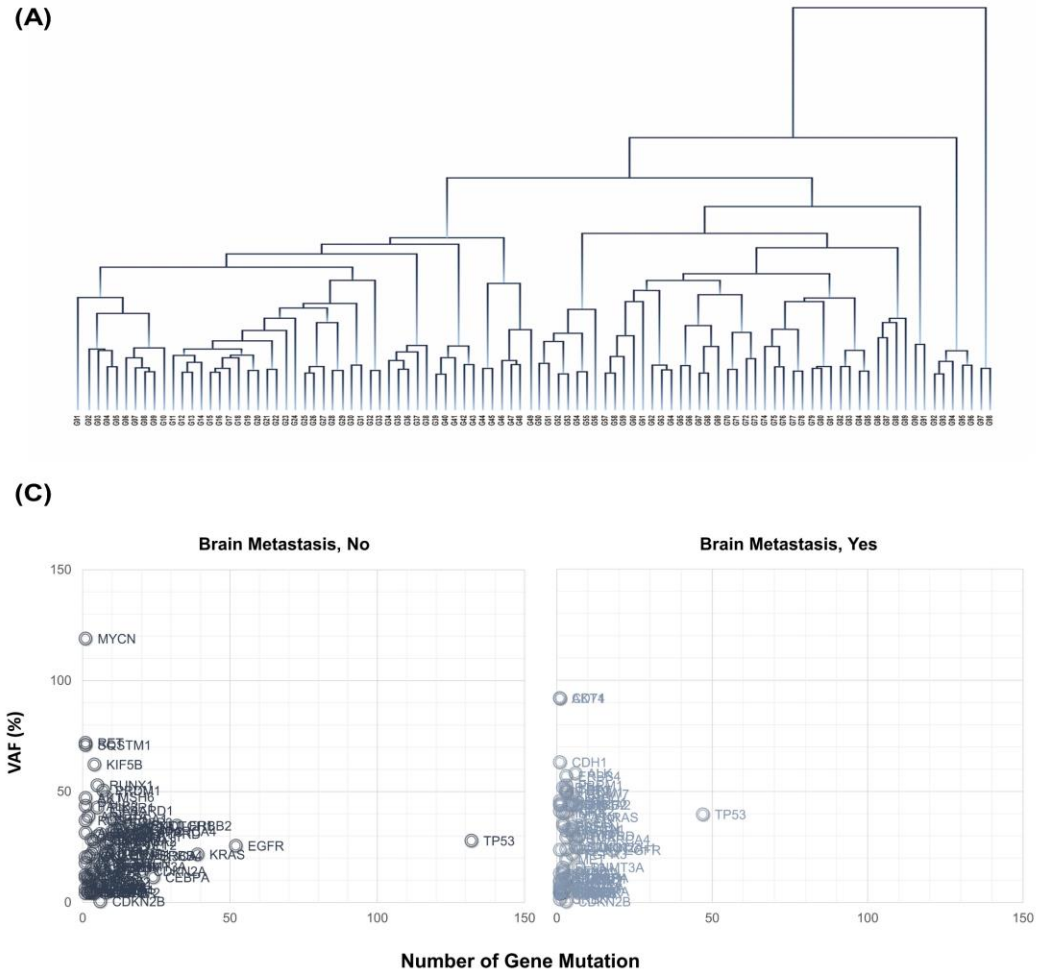
Results - Baseline characteristics

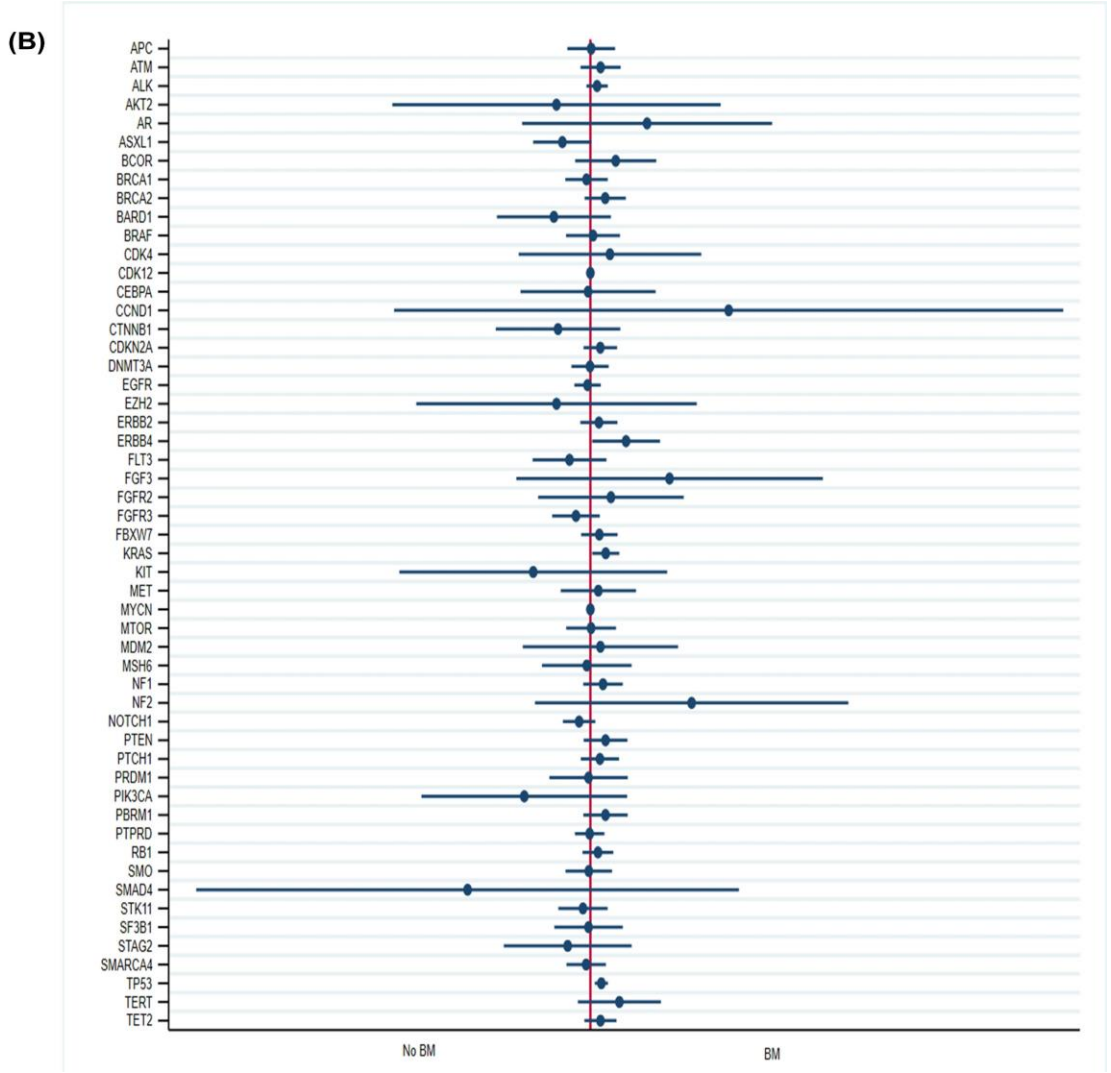
	Total (N = 287)	BM		P-value
		No (N = 223)	Yes (N = 64)	
Extra-pulmonary metastasis				
Bone	56 (19.5)	41 (18.4)	15 (23.4)	0.369
Adrenal gland	19 (6.6)	12 (5.4)	7 (10.9)	0.115
Liver	19 (6.6)	14 (6.3)	5 (7.8)	0.663
Abdominal lymph node	11 (3.8)	9 (4.0)	2 (3.1)	0.738
Comorbidities				
DM	48 (16.7)	43 (19.2)	10 (15.6)	0.130
HTN	62 (21.6)	48 (21.5)	14 (21.8)	0.952
Dyslipidemia	16 (5.6)	13 (5.8)	3 (4.6)	0.726
COPD, asthma	54 (18.8)	40 (17.9)	14 (21.8)	0.477
TB	10 (3.5)	6 (2.6)	4 (6.2)	0.171

Results - Number of genes according to presence of BM in patients with NSCLC

		BM	
No. of gene	Overall (N = 287)	No (N = 223)	Yes (N = 64)
0	4 (1.4)	4 (1.8)	0 (0)
1	18 (6.3)	15 (6.7)	3 (4.7)
2	51 (17.8)	41 (18.4)	10 (15.6)
3	52 (18.1)	40 (17.9)	12 (18.8)
4	55 (19.2)	48 (21.5)	7 (10.9)
5	41 (14.3)	34 (153)	7 (10.9)
6	25 (8.7)	18 (8.1)	7 (10.9)
7	16 (5.6)	7 (3.1)	9 (14.1)
8	14 (4.9)	7 (3.1)	7 (10.9)
9	6 (2.1)	5 (2.2)	1 (1.6)
10	2 (0.7)	2 (0.9)	0 (0)
12	1 (0.3)	0 (0)	1 (1.6)
13	1 (0.3)	1 (0.4)	0 (0)
15	1 (0.3)	1 (0.4)	0 (0)

Results - (A) Unsupervised hierarchical clustering of gene. (B) Gene alterations associated with BM using NGS. (C) Gene mutation according to BM in patients with NSCLC





Results - Cluster gene associated with BM

	No. of patients	No. of gene included in group (%)	Percentage of gene expression, Mean (SD)	OR (95% CI)	P-value	Gene
Cluster 1	256	53 (55.79)	28.72 (16.41)	1.02 (1.01, 1.04)	0.02	APC, ALK, AKT1, AKT2, AKT3, AURKA,BTK, BAP1, BRCA1, BRCA2, BARD1, CDH1, CHD2, CDK12, CEBPA, CCND1, CCNE1, CTNNB1, EGFR, EZH2, ERBB4, FLT3, FGF3, FGFR1, FGFR2, FGFR3, KDR, KIF5B, MET, MTOR, MSH6, NF2, NOTCH1, PTEN, PTCH1, PRDM1, PIK3CA, PBRM1, PDGFRA, RB1, REL, RET, RUNX1, SOX2, SMAD4, SF3B1, STAG2, STAT3, SQSTM1, TP53, TOP1, TET2, U2AF1
Cluster 2	141	22 (23.16)	28.91 (21.22)	1.00 (0.99, 1.02)	0.597	ARID1A, BRAF, CRBN, CD74, CDKN2A, FBXW7, GNA11, GNAQ, IDH1, IDH2, KIT, MYCN, PKHD1, PALB2, PIK3R1, PTPRD, RAF1, ROS1, SMO, STK11, SMARCA4, WT1
Cluster 3	170	20 (21.05)	20.53 (18.47)	1.01 (0.99, 1.03)	0.469	ATM, AR, ASXL1, BCOR, BCL2, CDK4, CDKN2B, DNMT3A, ERBB2, HRAS, KRAS, MYC, MCL1, MDM2, NF1, NCOA3, RICTOR, SRSF2, TERT, VHL

Results - Paired gene group associated with BM

No. of patients	No. of gene included in group (%)	Percentage of gene expression, Mean (SD)	OR (95% CI)	P-value	Gene
205	3 (3.16)	29.87 (20.59)	1.03 (1.02, 1.05)	<0.001	ERBB4, KRAS, TP53

Conclusion

- **22.3% of advanced NSCLC patients had BM.**

- 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**.