



REUNIÓN STREAMING
Novedades
y Claves 2020
en CÁNCER de PULMÓN

BIOMARCADORES PRONÓSTICOS

Marta Domènech

Institut Català d'Oncologia- Hospital Germans Trias y Pujol

Organizado por:



INDICE

CPNCP

- BIOMARCADORES IMMUNOTERAPIA
 - PDL1
 - PIONEER
- BIOMARCADORES MOLECULARES
 - KRAS
 - Her2
 - EGFR ins 20
 - MET

CPCP

Filter: Track ▲ Type ▼ Topic ▼ Media ▼

Apply Clear X

TRACK

✓ Lung Cancer (114)

ASCO Virtual Scientific Program

Biomarker utilization in non-small cell lung cancer, are we treating after testing?

SESSION
Lung Cancer—Non-Small Cell Metastatic

AUTHOR(S)
Elias Makhoul, Jong Taek Kim, Wenjuan Zhang, Jean Rapha...

ABSTRACT / POSTER
9609 • 375



ASCO Virtual Scientific Program

Lung-MAP (SWOG S1400): Design, implementation, and lessons learned from a biomarker-driven master...

SESSION
Lung Cancer—Non-Small Cell Metastatic

AUTHOR(S)
Mary Weber Redman, Vassiliki Papadimitrakopoulou, Kath...

ABSTRACT / POSTER
9576 • 342



ASCO Virtual Scientific Program

Soluble BTN2A1 as a potential predictive biomarker of immune checkpoint inhibitor efficacy in...

SESSION
Lung Cancer—Non-Small Cell Metastatic

AUTHOR(S)
Philippe Rochigneux, Anne Sophie Chretien, Delphine Ros...

ABSTRACT / POSTER
9561 • 327



ASCO Virtual Scientific Program

Plasma-derived cfDNA to reveal potential biomarkers of response prediction and monitoring in...

ASCO Virtual Scientific Program

Primary efficacy and biomarker analyses from the VISION study of tepotinib in patients (pts) with...

ASCO Virtual Scientific Program

Impact of SWI/SNF complex mutations in patients with non-small cell lung cancer (NSCLC) treated...

SESSION

SESSION

106P - Immune checkpoint proteins as a prognostic biomarker of overall survival in non-small cell lung cancer: A meta-analysis and systematic review

Methods

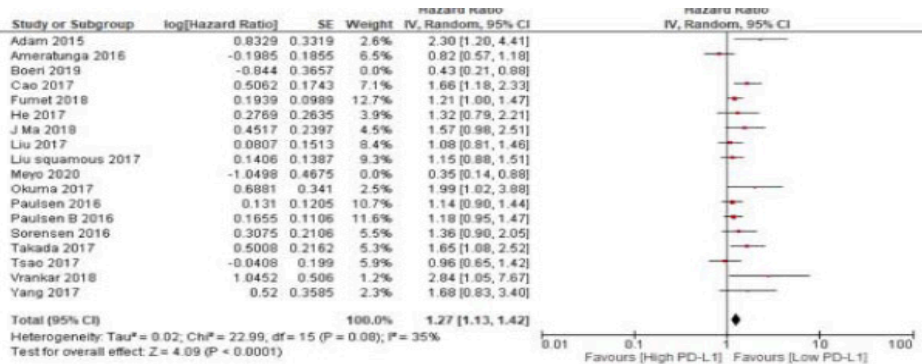
Pertinent studies were gathered via electronic search of PubMed, EMBASE, MEDLINE, Web of Science, Google Scholar and Cochrane Library databases up to April 30, 2020. Utilizing Review Manager 5.3, pooled hazard ratios and 95% confidence intervals were calculated using random or fixed effects models, contingent on the heterogeneity of studies.

Results

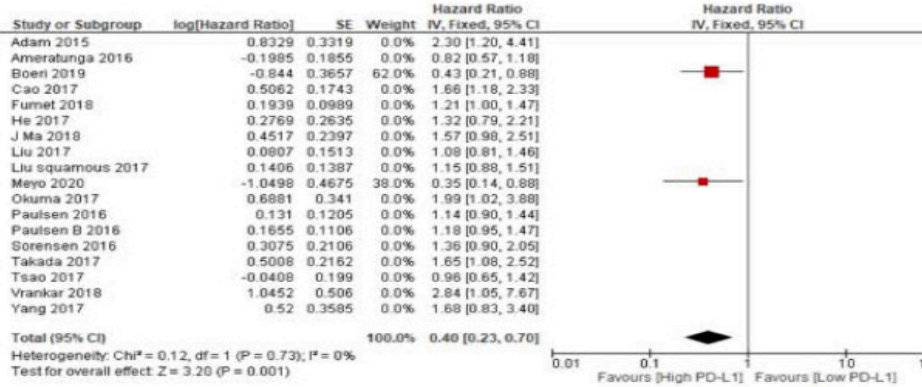
A total of 17 studies involving 6179 patients were included. Pooled analysis revealed that high PD-L1 expression was significantly associated with lower overall survival (OS), with a hazard ratio of 1.22 (95% CI, 1.06 – 1.41; p = 0.005). Subgroup analysis showed that high PD-L1 expression was significantly correlated with improved OS among patients given immune checkpoint inhibitors (HR, 0.40; 95% CI, 0.23 – 0.70; p = 0.001), albeit with worse OS among patients given adjuvant chemotherapy (HR, 1.27; 95% CI, 1.13 – 1.42; p < 0.0001). High PD-1 expression was significantly associated with inferior OS (HR, 1.23; 95% CI, 1.03 – 1.57; p = 0.02). Subgroup analysis based on tumor subtype showed that high PD-1 expression correlated with inferior OS among patients with adenocarcinoma (HR, 1.50; 95% CI 1.04 – 2.16; p = 0.03), but not among patients with squamous cell cancer. High IDO1 expression portends improved OS (HR, 0.72; 95% CI, 0.52 – 0.98; p = 0.04), while high LAG3 expression was not significantly associated with OS.

Conclusions

Immune checkpoint proteins can potentially prognosticate survival outcomes of patients with non-small cell lung cancer. Prospective studies that explore the role of immune checkpoint proteins in non-small cell lung cancer are encouraged to help

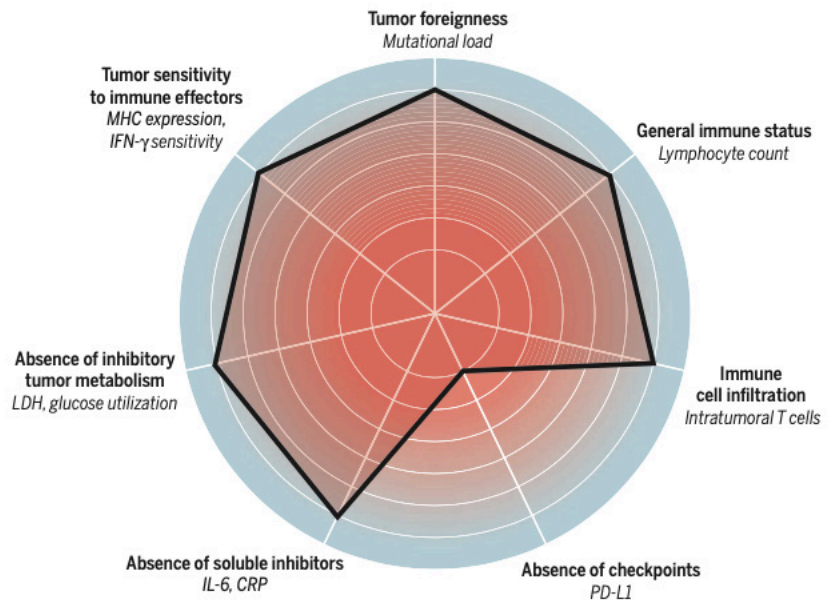
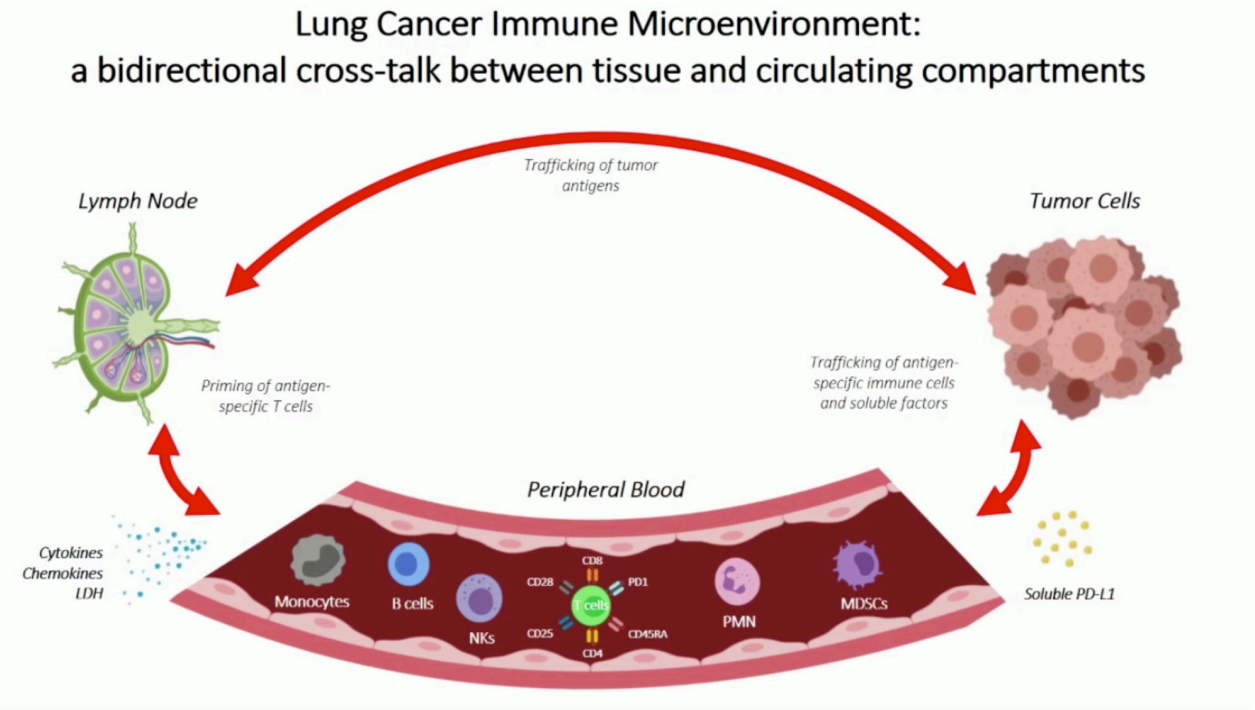


Among patients given chemotherapy, high PD-L1 portends worse OS.



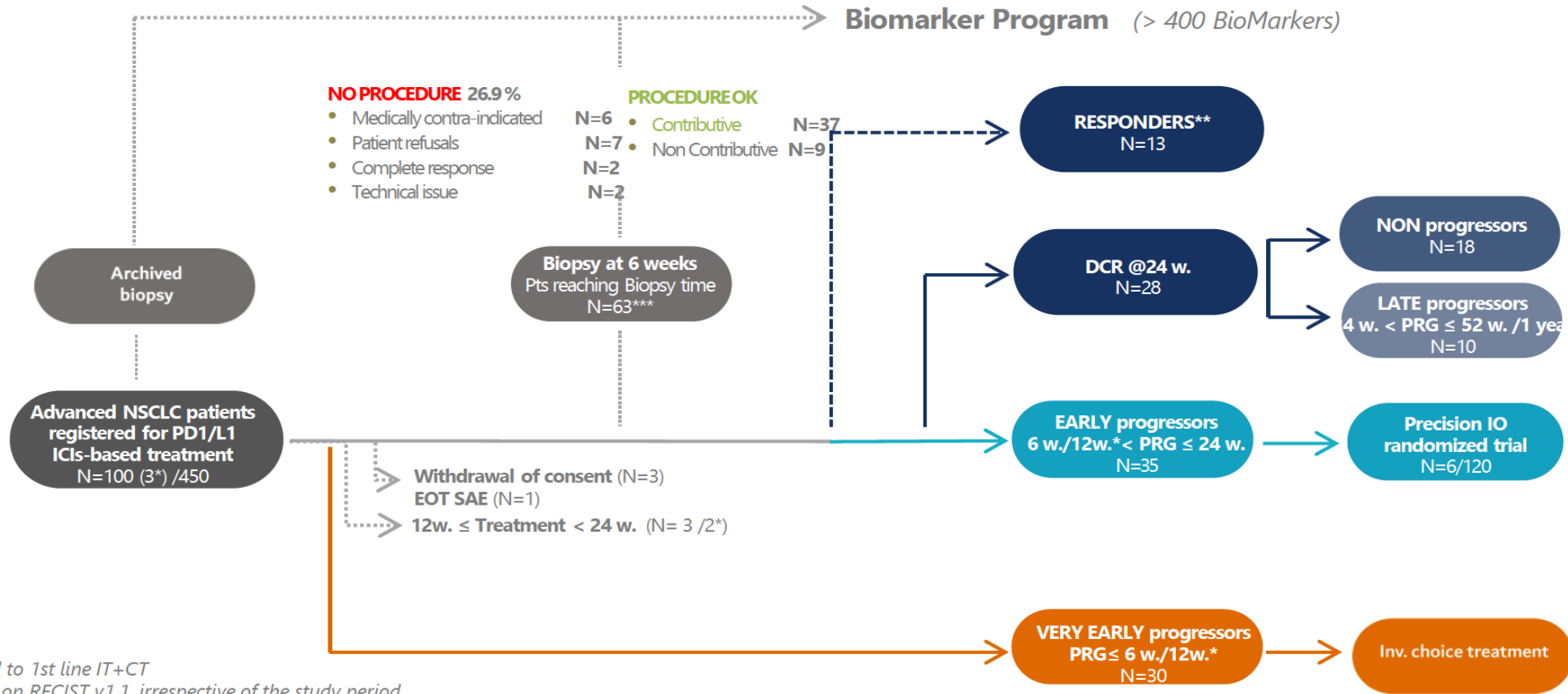
Among patients given checkpoint inhibitors, high PD-L1 associated with improved OS.

BIOMARCADOR IMMUNOTERAPIA



Precision Immuno-Oncology for advanced NSCLC patients treated with PD(L)1 immune checkpoint inhibitors (ICIs)

An analysis of the first 100 pts from the PIONeeR Project






* Related to 1st line IT+CT

** Based on RECIST v1.1, irrespective of the study period

*** Including 3 Very Early Progressors, with a radiologic progression (inclusion in clinical trial)

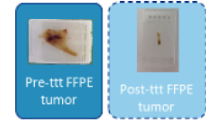
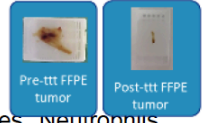
PIONEER

> 400 biomarker data planned at VS & 6W – 123 analyzed VS for at least 33 pts

 Testing initiated
 Data available
 To be initiated

Immune cells infiltration

- Mplx IHC, incl. CD3/CD8 cell densities
- Mplx IHC, incl. Monocytes, Granulocytes, Neutrophils
- Mplx Innate Immunity

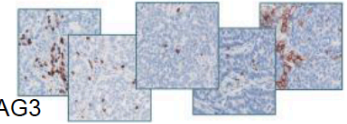


Sensitivity to immune effectors

- Immune gene expression signatures

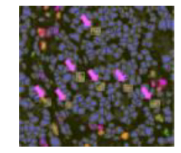
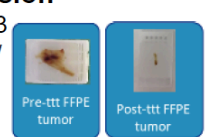
Immune checkpoints

- Immunoscore® IC PD-L1/CD8
- Mplx TCE: CD3/CD8/PD1/TIM3/LAG3



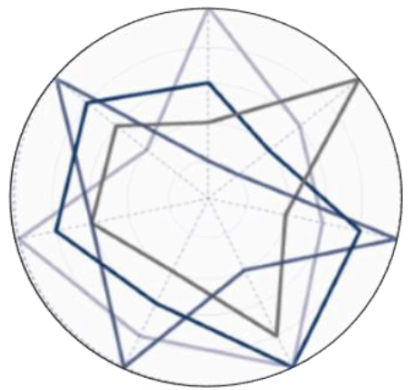
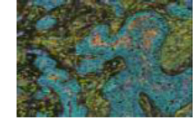
Immune suppression

- Treg – CD4/FOXP3
- Mplx PMN-MDSC / Mononuclear MDSC



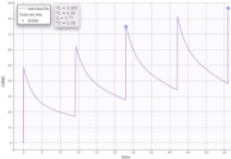
Tumor foreignness

- TMB
- T-cell clonality



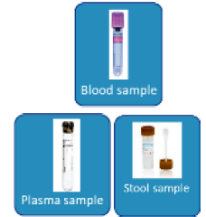
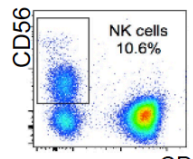
Drug response

- PK/PD modelling from longitudinal data



Peripheral markers

- Circulating immune cells
- Soluble markers
- Endothelial markers
- ctDNA
- Microbiome



PIONEER

Clinical Characteristics[§] & Biomarkers associated with **Objective Response**

Timepoint	Biomarker	Non-Responders		Responders		P-value
		N valid	Mean	N valid	Mean	
Pre-treatment	PD-L1+ tumor cell percentage*	70	14%	11	33%	0,045
	Cytotoxic T cells CD3+/CD8+ density in the Tumor	43	298 cells/mm ²	7	383 cells/mm ²	0,041
	Cytotoxic T cells at TSI (Tumor-Stroma Interface)	26	178 cells/mm ²	4	511 cells/mm ²	0,041**
	Effective T cell density in the Tumor	43	116 cells/mm ²	7	172 cells/mm ²	0,008
	Regulatory T-cell density in the Stroma	49	18 cells/mm ²	7	70 cells/mm ²	0,010
	Tissue factor blood concentration (endothelial activation)	28	21,6 fM	6	8,8 fM	0,046
6 weeks	Neutrophils in the Stroma	9	16 cells/mm ²	2	73 cells/mm ²	0,036

[§], Sex, age, ECOG PS, Histological subtypes, Smoking status, line of therapy and type of PD-(L)1 drug were not found to significantly influence the likelihood of response; * PD-L1 TC expression (<1% vs ≥1%) was significant in multivariate analysis, HR: 4,1 [1,3;14]; ** p-value F-test

Clinical Characteristics associated with Progression Free & Overall Survival

	Median PFS (months)	HR (95%CI), <i>p</i> -value
ECOG PS (2/3 vs 0/1)*	1,22 [0,49;NA] vs 3,22 [2,53;5,32]	10.8 [2.9 – 30.4], <i>p</i> =0.002
Histological Subtype (Others vs ADC)	1,51 [1,35;3,45] vs 4,63 [2,53;11,20]	2.24 [1.3 – 3.9], <i>p</i> =0.007
Type of PD-(L)1i (Pembro. vs Nivo.)	3,22 [1,77;NA] vs 2,56 [1,54;4,07]	0.58 [0.34 – 1.0], <i>p</i> =0.049
PD-L1 TC expression (<1% vs ≥1%)*	2,25 [1,58;3,71] vs 6,60 [2,99;NA]	2.0 [1.2 – 3.5], <i>p</i> =0.004

	Median OS (months)	HR (95%CI), <i>p</i> -value
ECOG PS (2/3 vs 0/1)*	3,09 [0,49;NA] vs 12,78 [8,31;NA]	3.9 [1.1 – 10.3], <i>p</i> =0.041

Sex, age, Smoking status, and line of therapy were not found to significantly influence the risk of progression; * Significant in multivariate analysis

Biomarkers associated with Progression Free & Overall Survival

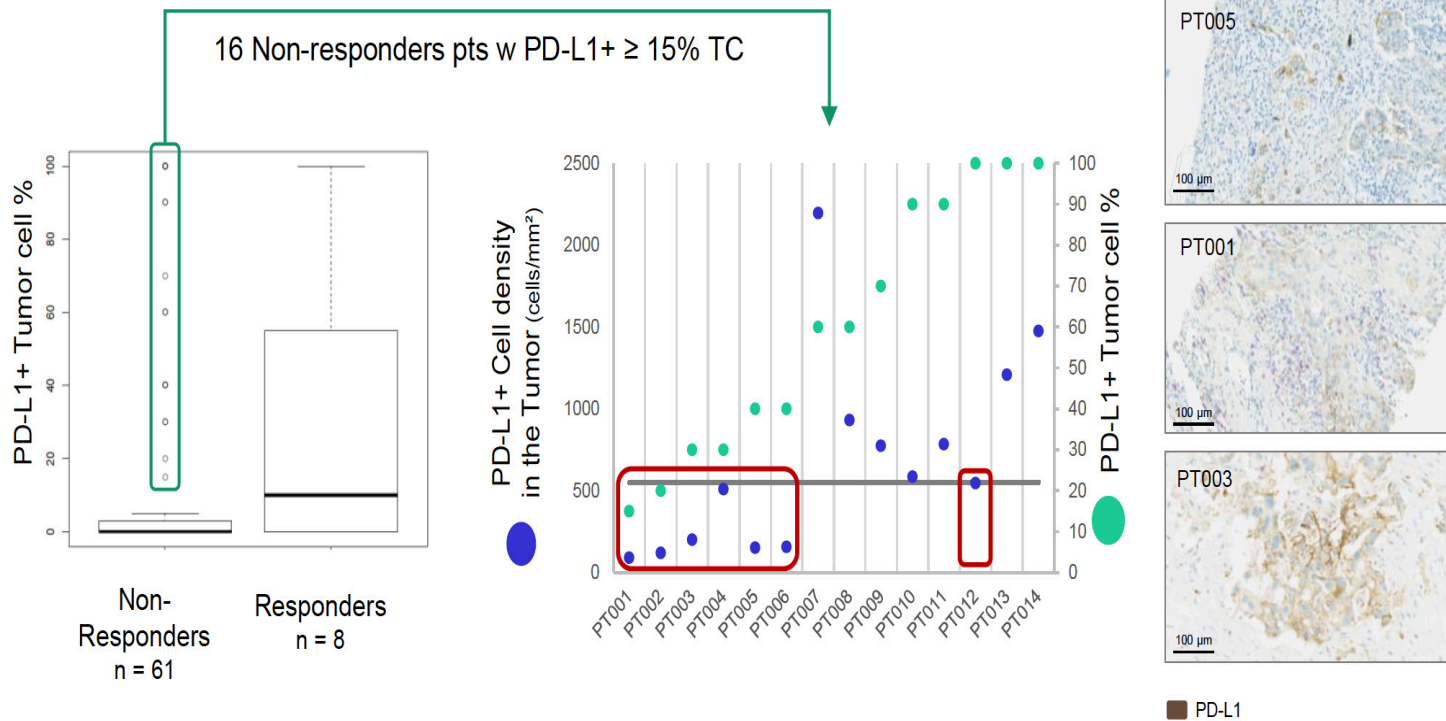
	Hazard Ratio PFS [95% IC]	<i>p</i> -value
PD-L1 expression in TC (%) *	0,98 [0,96;0,99]	0,0209
Circulating Activated T cells * **	1,06 [1,02;1,10]	0,0008
Serum IL6 *	1,00 [1,00;1,01]	0,047
Cytotoxic T cells in the tumor **	1,00 [1,00;1,01]	0,047

	Hazard Ratio OS [95% IC]	<i>p</i> -value
Circulating T cells *	0,99 [0,99;0,99]	0,039
Circulating Activated T cells *	1,07 [1,03;1,12]	0,001
Serum IL6 *	1,00 [1,00;1,01]	0,037
Serum TNFα *	1,04 [1,01;1,09]	0,031

* Multivariate analysis stratified on Sex, Age, ECOG PS, Histology, Smoking history, Line of PD-(L)1 therapy, Type of PD-(L)1 drug received, PDL1 1%; ** Multivariate analysis stratified on Sex, Age, ECOG PS, Histology, Smoking history, PDL1 1%

PIONEER

Example: PD-L1 positive cell density: a potential new and potent predictive biomarker?



Resultados de los biomarcadores pronósticos:

- Expresión tumoral de PDL1, con densidad de células conpositivas para PDL1
- Densidad de células T citotóxicas en el tumor
- Densidad de cel inmunosupresores : Cel T reguladores, MSDC

KRAS

Durability of clinical benefit and biomarkers in patients with advanced non-small cell lung cancer (NSCLC) treated with AMG 510 (sotorasib): CodeBreakK 100

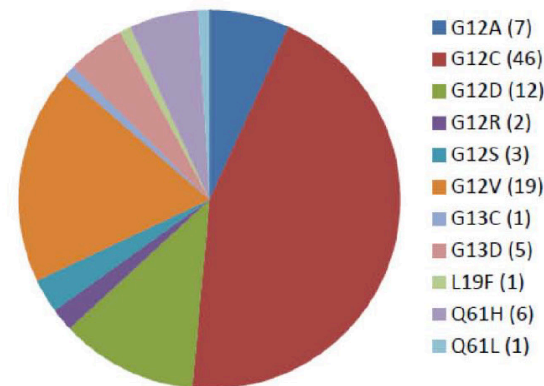
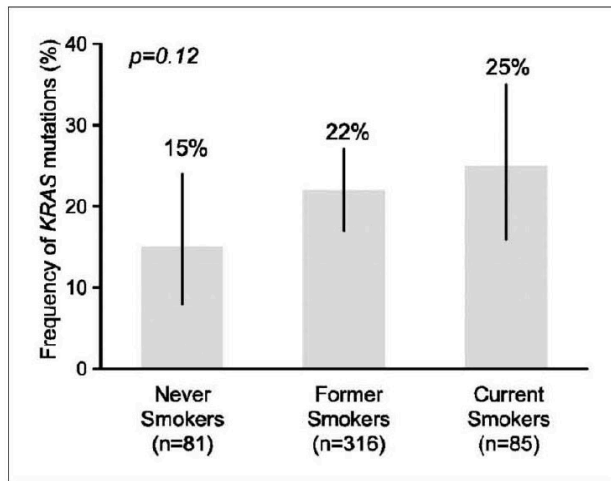
David S. Hong[†], Yung-Jue Bang, Fabrice Barlesi, Gregory A.

The NEW ENGLAND JOURNAL of MEDICINE

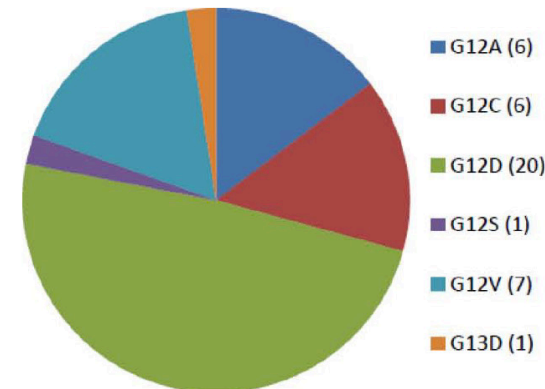
ORIGINAL ARTICLE

KRAS^{G12C} Inhibition with Sotorasib in Advanced Solid Tumors

D.S. Hong, M.G. Fakih, J.H. Strickler, J. Desai, G.A. Durm, G.I. Shapiro, G.S. Falchook, T.J. Price, A. Sacher, C.S. Denlinger, Y.-J. Bang, G.K. Dy, J.C. Krauss, Y. Kuboki, J.C. Kuo, A.L. Coveler, K. Park, T.W. Kim, F. Barlesi, P.N. Munster, S.S. Ramalingam, T.F. Burns, F. Meric-Bernstam, H. Henary, J. Ngang, G. Ngarmchamnanrith, J. Kim, B.E. Houk, J. Canon, J.R. Lipford, G. Friberg, P. Lito, R. Govindan, and B.T. Li



Current/Former Smokers



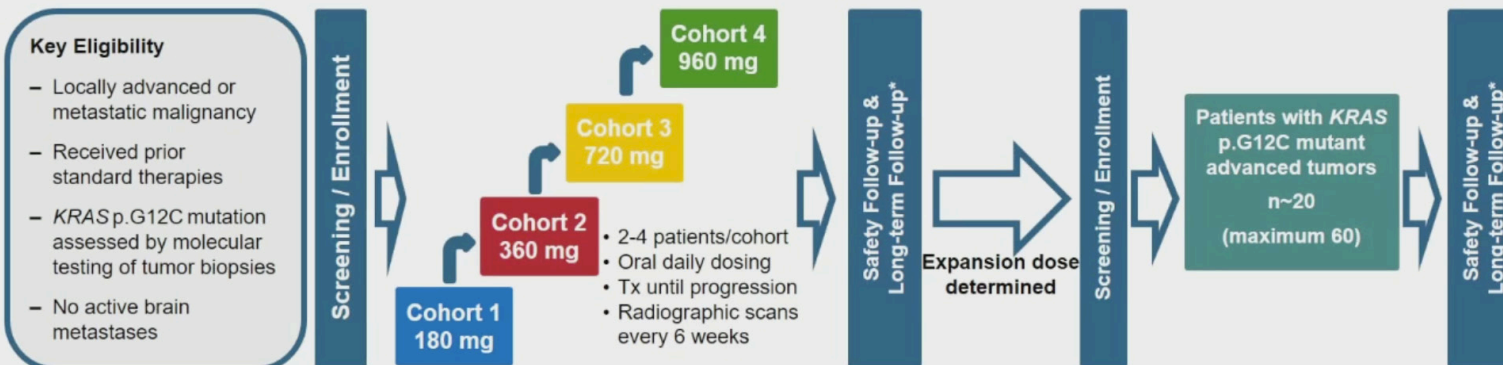
Never Smokers

KRAS

CODEBREAK 100

Phase 1, Multicenter, Open-label Study – Dose Escalation

Dose Expansion



Primary endpoint: safety

Secondary endpoints include: PK, ORR, DOR, DCR, PFS, duration of SD

Dose cohort	# patients (N = 59)
180 mg	3
360 mg	16
720 mg	6
960 mg†	34

Baseline Characteristic	960 mg (n = 34)	All Patients (N = 59)
Median age – years (range)	68 (49–83)	68 (49–83)
Female – n (%)	18 (52.9)	35 (59.3)
Current/former smoker	30 (88.2)	53 (89.8)
Prior anti-PD1/L1 therapy	28 (82.4)	53 (89.8)
Prior platinum-based chemo	34 (100.0)	59 (100.0)
ECOG PS score – n (%)		
0	8 (23.5)	12 (20.3)
1	26 (76.5)	45 (76.3)
2	0 (0.0)	2 (3.4)
Median prior systemic anticancer therapy for metastatic disease – n (range)	2 (0–10)	3 (0–10)
Prior systemic anticancer therapy – n (%)		
0	2 (5.9)	2 (3.4)
1	12 (35.3)	13 (22.0)
2	8 (23.5)	14 (23.7)
3	6 (17.7)	11 (18.6)
≥ 4	6 (17.7)	19 (32.2)
Brain metastasis	12 (35.3)	18 (30.5)

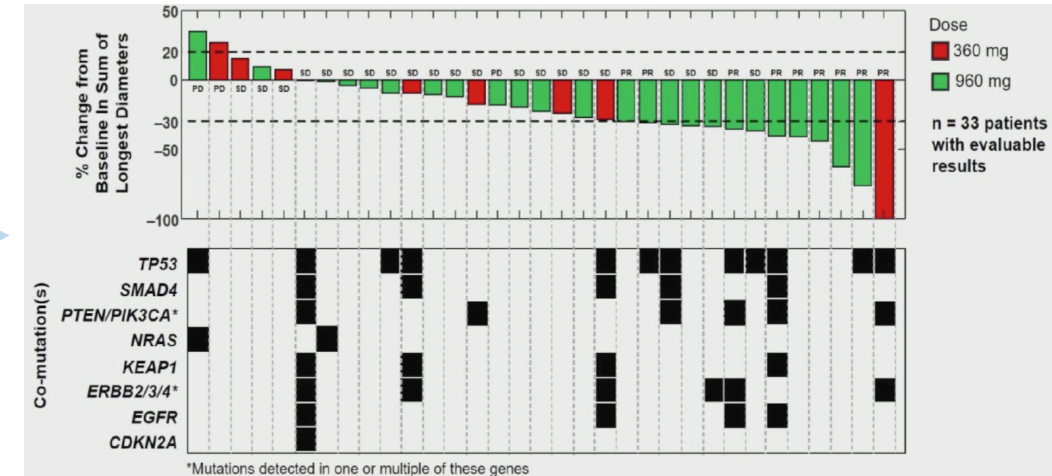
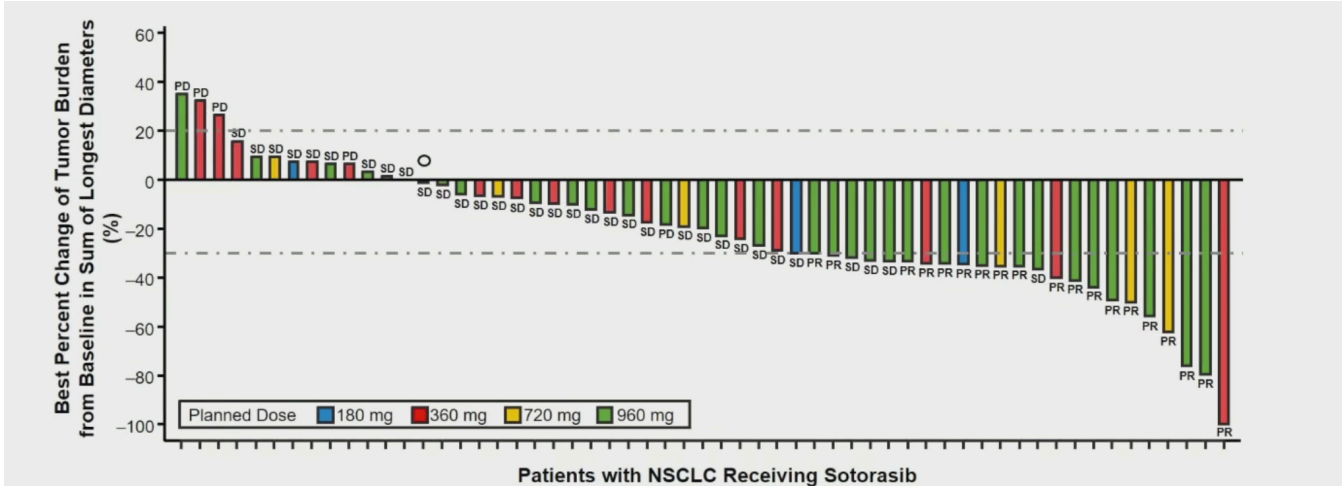
KRAS

CODEBREAK 100

Events – n (%)	All Patients (N = 59)			
	Any Grade	Grade ≥3	Grade ≥4	Fatal
Treatment-emergent AEs				
Any	58 (98.3)	37 (62.7)	17 (28.8)	13 (22.0)
Serious	30 (50.8)	27 (45.8)	16 (27.1)	13 (22.0)
Led to Discontinuation	5 (8.5)	5 (8.5)	3 (5.1)	3 (5.1)
Treatment-related AEs				
Any	39 (66.1)	11 (18.6)	1 (1.7)	0 (0.0)
Serious	2 (3.4)	1 (1.7)	1 (1.7)	0 (0.0)
Led to Discontinuation	1 (1.7)	1 (1.7)	0 (0.0)	0 (0.0)

Treatment-related Adverse Events	All Patients (N = 59) n (%)		
	Any Grade	Grade ≥3	Grade ≥4
Any	39 (66.1)	11 (18.6)	1 (1.7)
Diarrhea	15 (25.4)	3 (5.1)	0 (0.0)
ALT increased	12 (20.3)	6 (10.2)	1 (1.7)*
AST increased	12 (20.3)	3 (5.1)	0 (0.0)
Fatigue	6 (10.2)	0 (0.0)	0 (0.0)
Nausea	6 (10.2)	0 (0.0)	0 (0.0)
Alkaline phosphatase increased	5 (8.5)	2 (3.4)	0 (0.0)
Decreased appetite	4 (6.8)	0 (0.0)	0 (0.0)
Vomiting	4 (6.8)	0 (0.0)	0 (0.0)
Abdominal distension	3 (5.1)	0 (0.0)	0 (0.0)
Abdominal pain	3 (5.1)	0 (0.0)	0 (0.0)
Anemia	2 (3.4)	2 (3.4)	0 (0.0)
Lymphocyte count decreased	2 (3.4)	1 (1.7)	0 (0.0)
GGT increased	1 (1.7)	1 (1.7)	0 (0.0)
Hepatitis	1 (1.7)	1 (1.7)	0 (0.0)
Hyponatremia	1 (1.7)	1 (1.7)	0 (0.0)

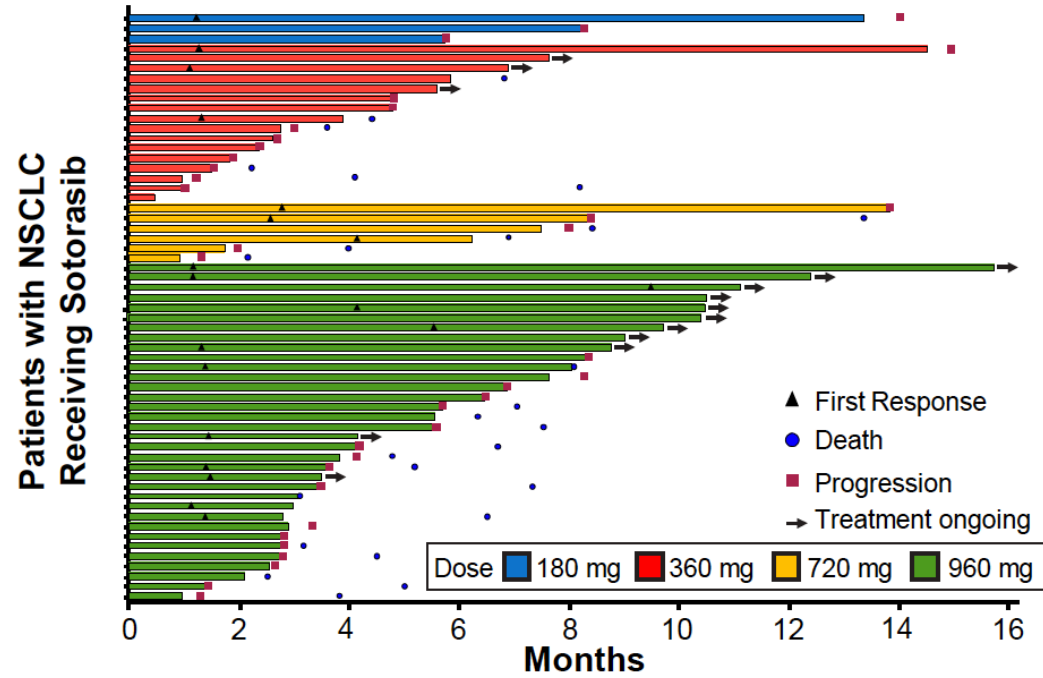
CODEBREAK 100



	960 mg (n = 34)	All patients (N = 59)
Best Overall Response per Investigators' Assessment, n (%)		
Confirmed Partial Response	12 (35.3)	19 (32.2)
Stable Disease	19 (55.9)	33 (55.9)
Progressive Disease	2 (5.9)	5 (8.5)
Not Evaluable	1 (2.9)	1 (1.7)
Not Done*	0 (0.0)	1 (1.7)
Confirmed Objective Response Rate[†], % (95% CI)	35.3 (19.8, 53.5)	32.2 (20.6, 45.6)
Disease Control Rate[‡], % (95% CI)	91.2 (76.3, 98.1)	88.1 (77.1, 95.1)

KRAS

CODEBREAK 100



Confirmed PR, n = 19

Duration of response*

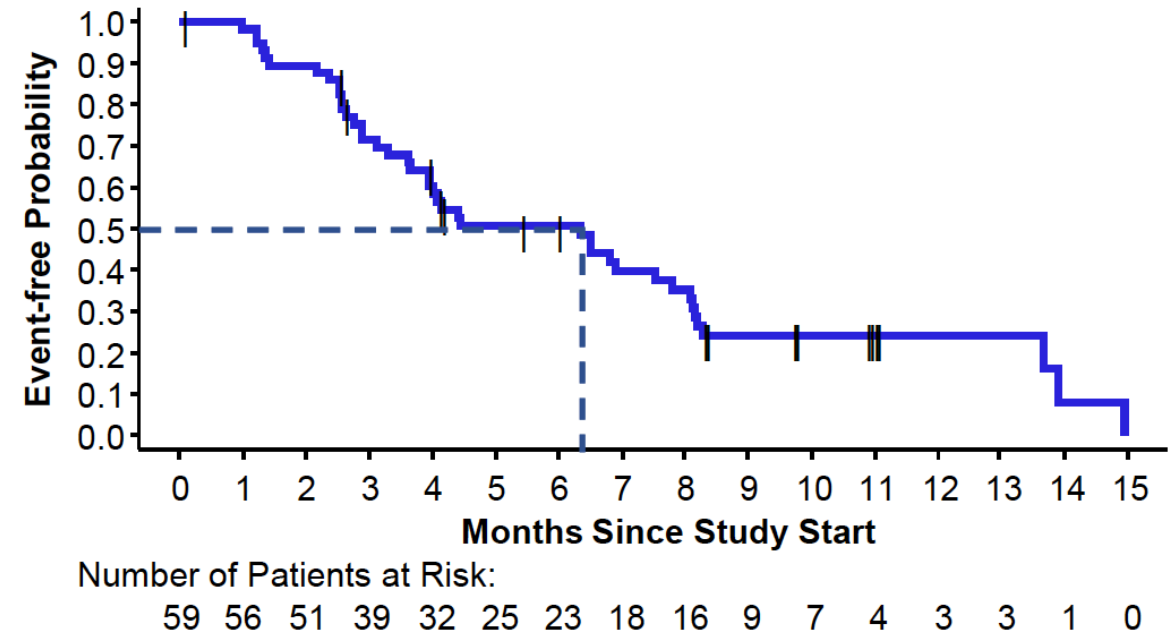
Median of 10.9
(1.1+ to 13.6) months

10/19 responders still in response†

Patients with SD, n = 33

Duration of stable disease‡

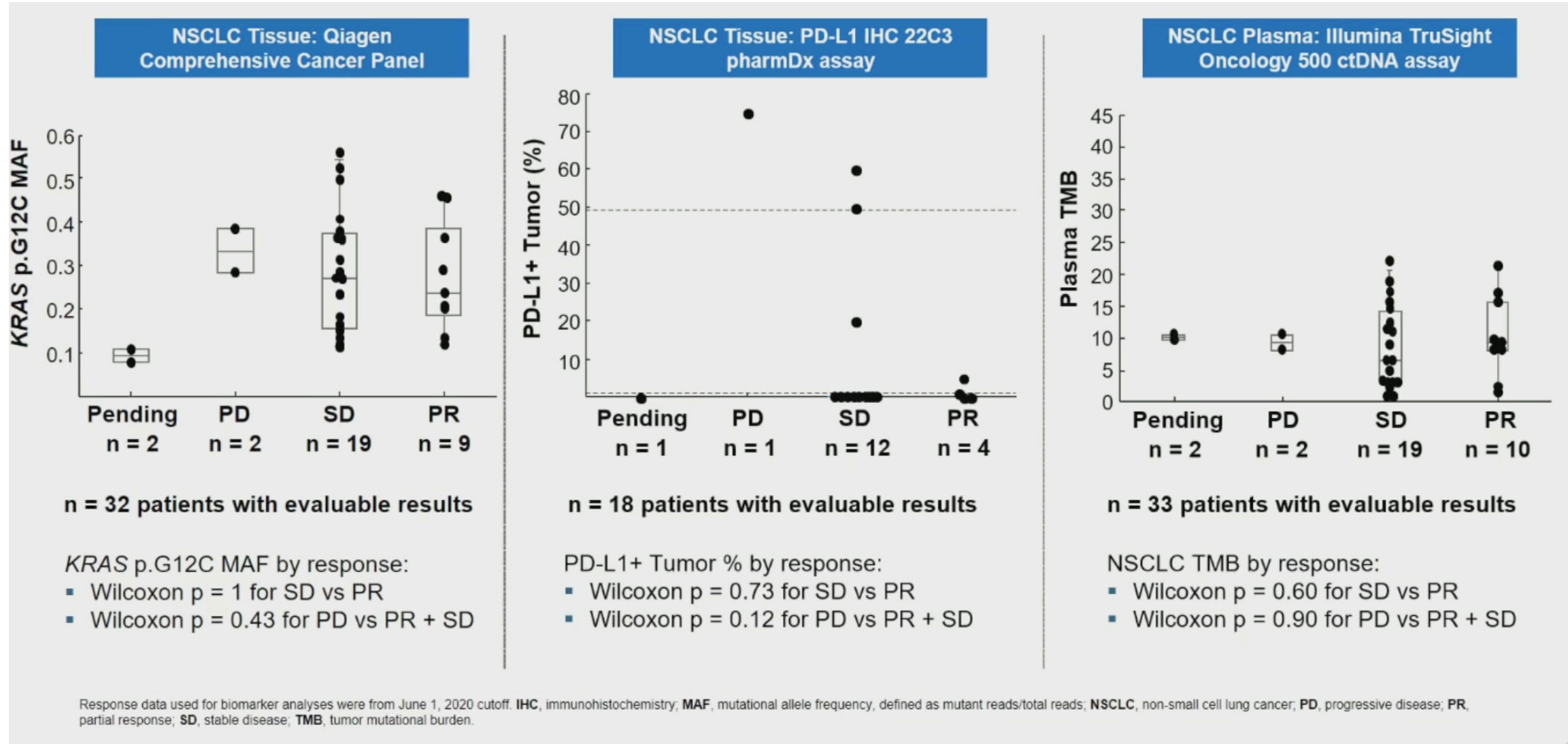
Median of 4.0
(1.4 to 10.9+) months



Median PFS: 6.3 (range 0.0+ to 14.9) months

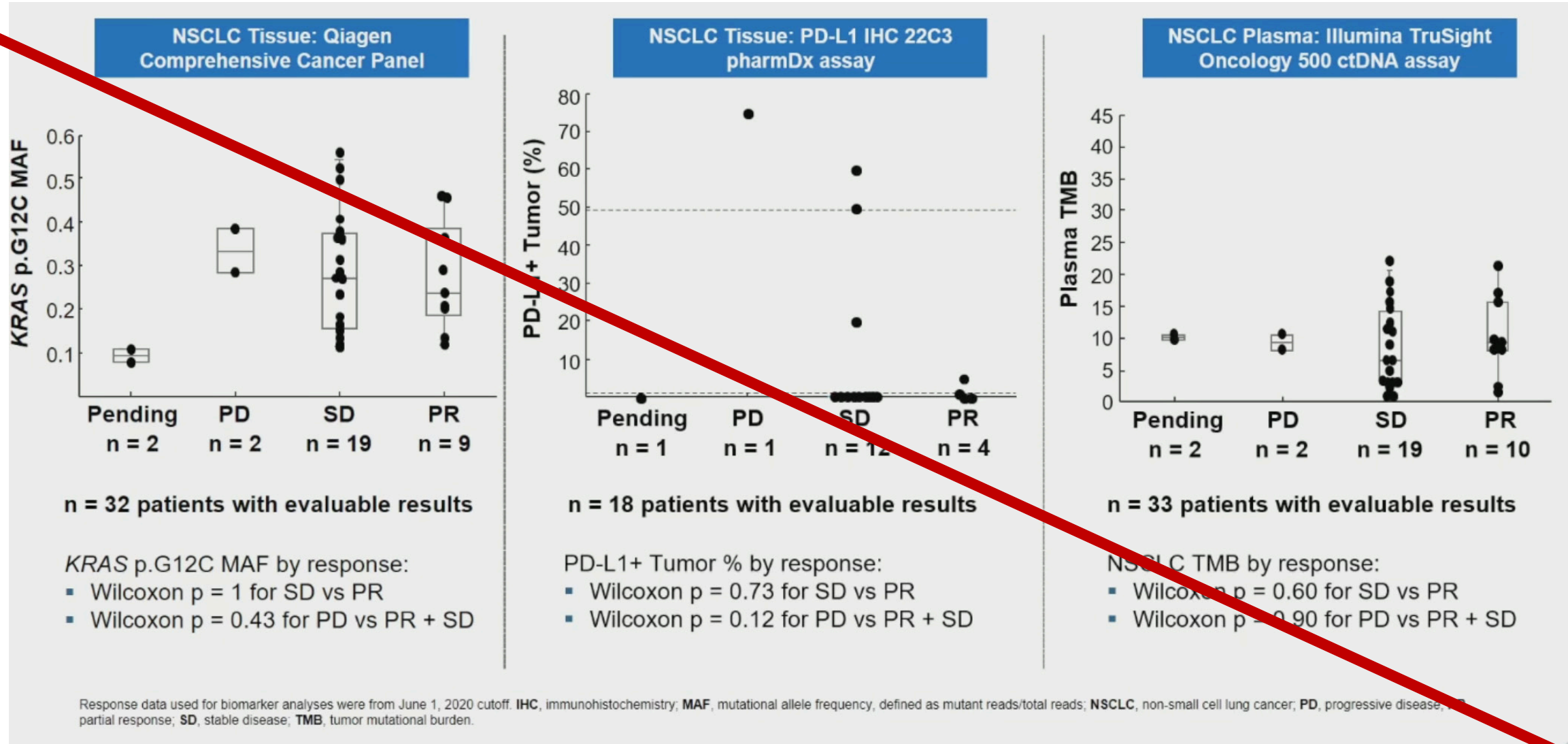
KRAS

CODEBREAK 100



KRAS

CODEBREAK 100



KRAS

1339P

Clinicopathological characteristics and treatment patterns observed in real-world care in patients with advanced non-small cell lung cancer (NSCLC) and KRAS G12C mutations in the Flatiron Health (FH)-Foundation Medicine (FMI) Clinico-Genomic Database (CGDB)

S. Aggarwal, S. Whipple, H. Hsu, H. Tu, G. Carrigan, X. Wang, G. Ngarmchamnanrith, V. Chia

Baseline Characteristics

	KRAS p.G12C (n = 743)	Triple WT* (n = 3,957)	All NSCLC (N = 7,069)
Age at advanced diagnosis – years, median (range)	68 (29–85)	69 (26–85)	68 (24–85)
Female sex – n (%)	454 (61.1)	1,665 (42.1)	3,532 (50.0)
Race – n (%)			
Asian	7 (0.9)	71 (1.8)	223 (3.2)
Black	38 (5.1)	258 (6.5)	401 (5.7)
Hispanic or Latino	2 (0.3)	2 (0.1)	4 (0.1)
White	550 (74.0)	2,800 (70.8)	4,951 (70.0)
Other	80 (10.8)	489 (12.4)	882 (12.5)
Not available	66 (8.9)	337 (8.5)	608 (8.6)
Current or former smoker – n (%)	719 (96.8)	3,430 (86.7)	5,786 (81.9)
Histology of NSCLC – n (%)			
Nonsquamous	675 (90.8)	2,506 (63.3)	5,382 (76.1)
Squamous	31 (4.2)	1,252 (31.6)	1,387 (19.6)
Not otherwise specified	37 (5.0)	199 (5.0)	300 (4.2)
Stage at initial diagnosis – n (%)			
Stage ≤ IIIA	213 (28.7)	1,078 (27.2)	1,825 (25.8)
Stage IIIB–IVB	513 (69.0)	2,776 (70.2)	5,079 (71.8)
Not reported	17 (2.3)	103 (2.6)	165 (2.3)
Diagnosed in 2015 or later – n (%) [#]	611 (82.2)	3,307 (83.6)	5,810 (82.2)
Practice type – n (%)			
Academic	46 (6.2)	245 (6.2)	537 (7.6)
Community	697 (93.8)	3,712 (93.8)	6,532 (92.4)
Number of total lines of therapy in advanced setting – n (%)			
0	149 (20.1)	681 (17.2)	1,206 (17.1)
1	293 (39.4)	1,381 (34.9)	2,479 (35.1)
2	150 (20.2)	1,015 (25.7)	1,755 (24.8)
3	83 (11.2)	491 (12.4)	871 (12.3)
≥ 4	68 (9.2)	389 (9.8)	758 (10.7)

*KRAS/EGFR/ALK wild type

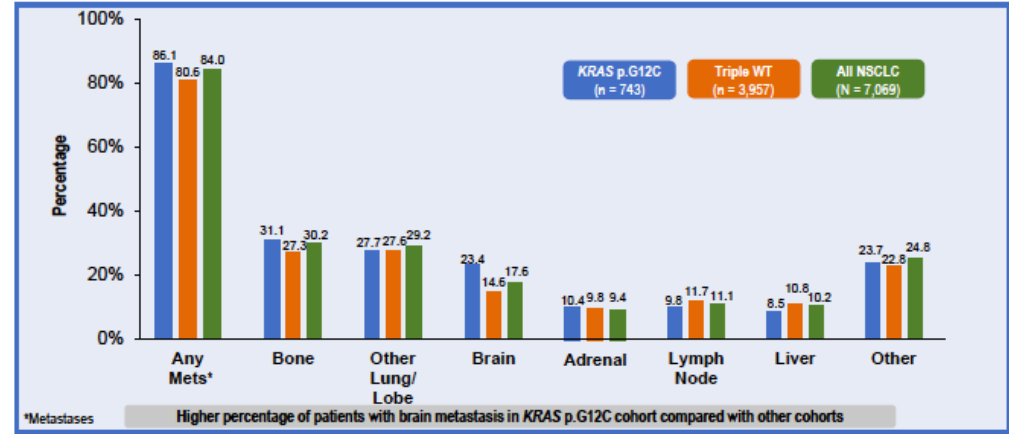
[#]Checkpoint inhibitor therapy gained its first approval in NSCLC in March 2015

743 pacientes CPCNP KRAS. G12C

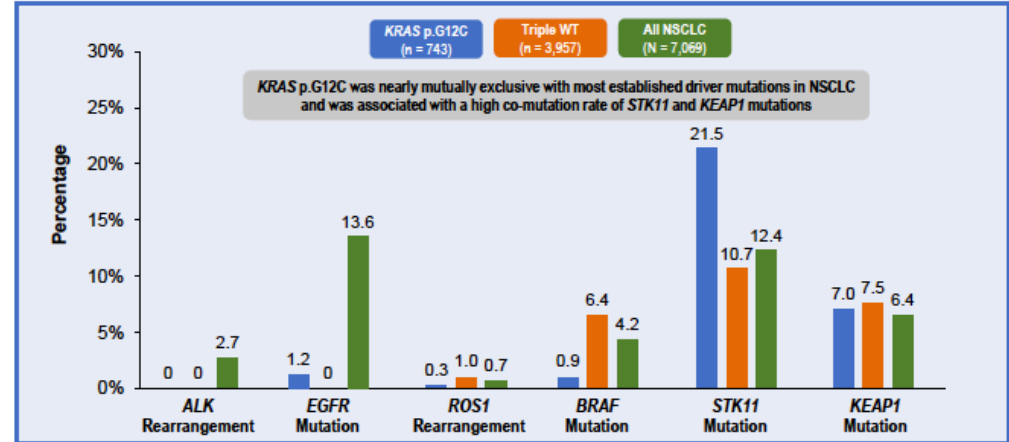
61% mujeres

97% fumadoras o exfumador

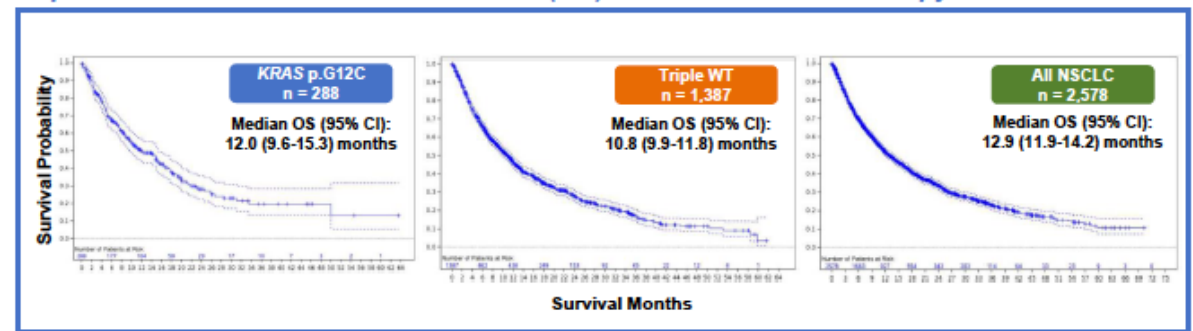
Distant Metastases at Diagnosis



Co-mutation Profiles

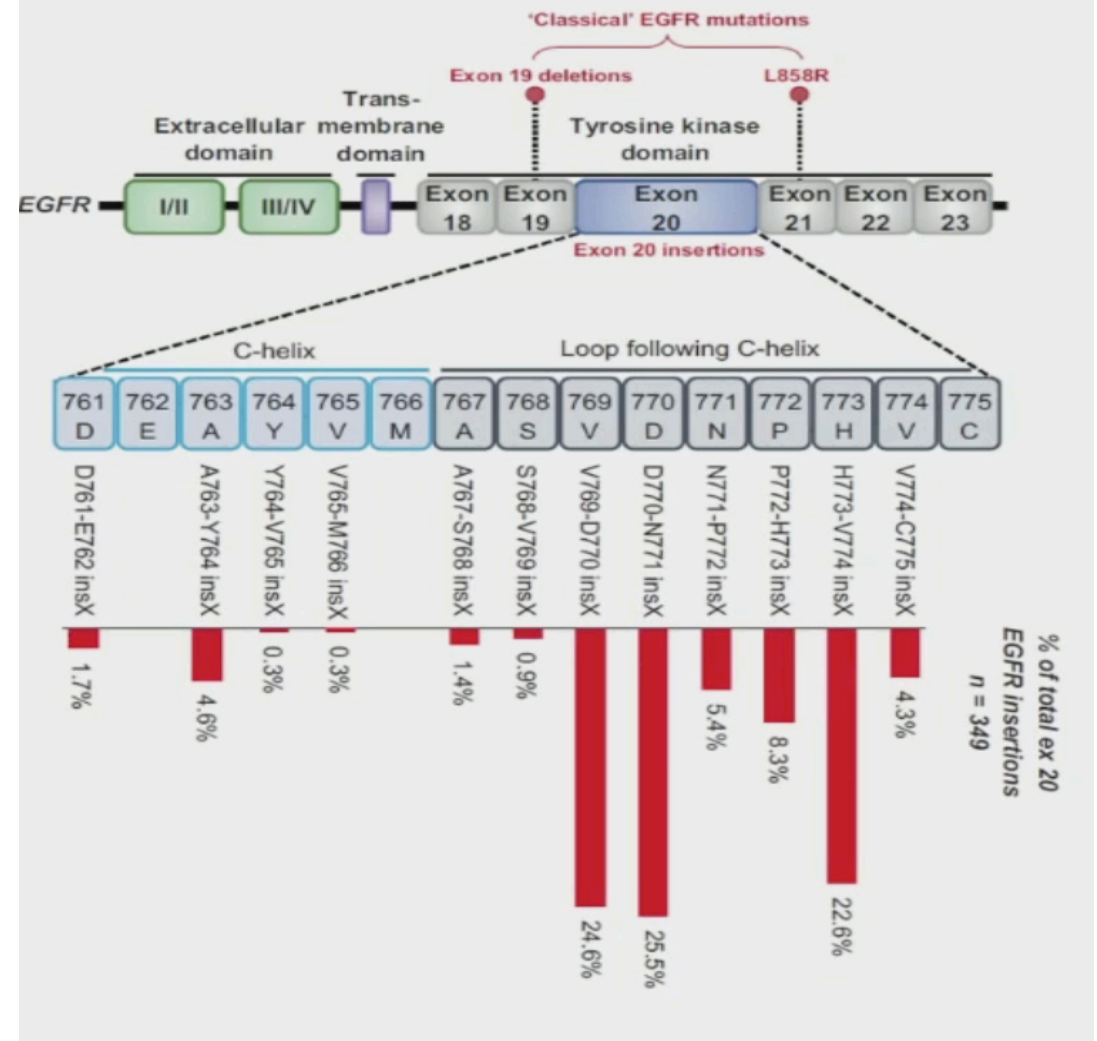
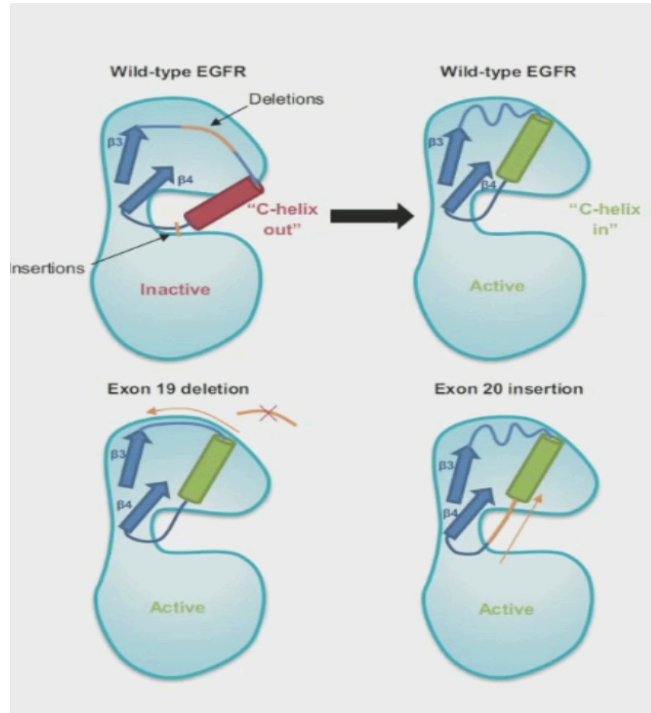
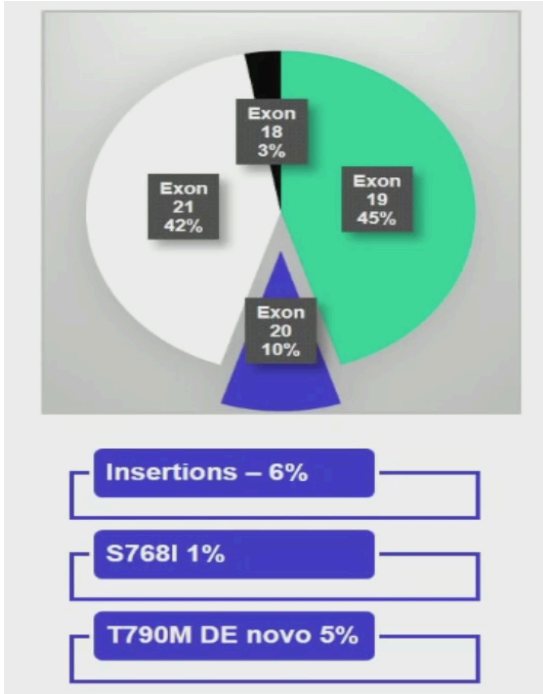


Kaplan-Meier Curves for Overall Survival (OS) After First-Line of Therapy



EGFR

Exon 20 insertions



EGFR

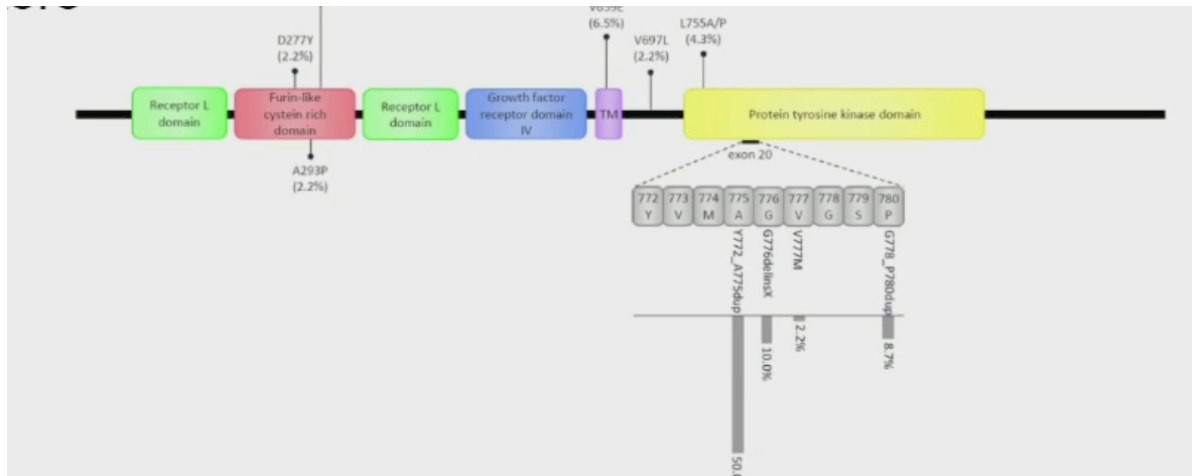
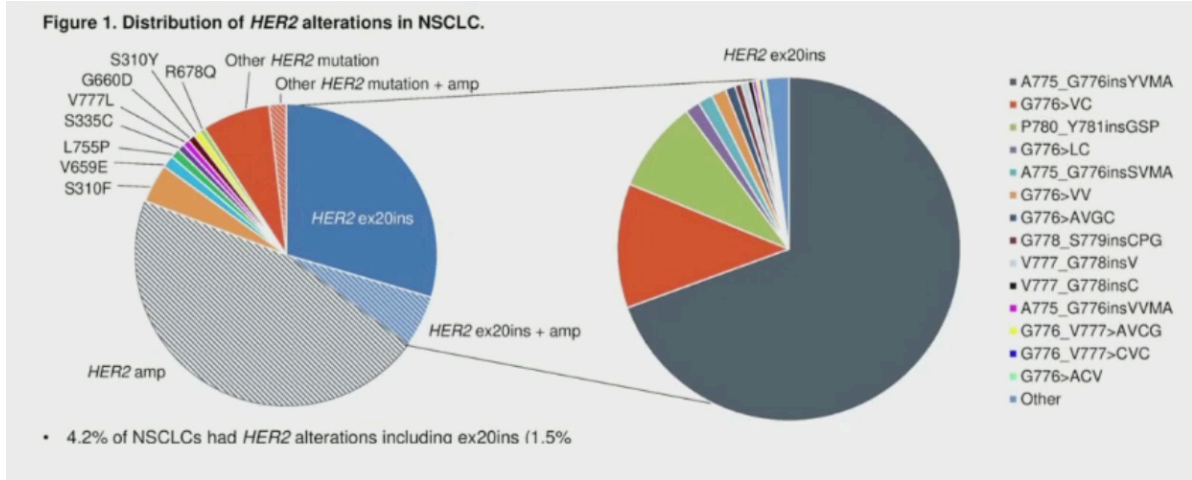
Exon 20 insertions

Drug	Group	ORR	PFS (mo)
Gefitinib/erlotinib	1 st gen <i>EGFR</i> TKI	8-27%	-
Afatinib	2 nd gen <i>EGFR/HER2</i> TKI	8%	2.7
Osimertinib	3 rd gen <i>EGFR</i> TKI	5%	3.6
Cetuximab +afatinib	Anti- <i>EGFR</i> Ab+ TKI	3/4 pts	-

Vyse et al, Signal Transduction and Targeted Therapy 2019 ;
NCT 03414814 ; Van Veggel et al, Lung Cancer 2020

HER 2

Ex ins 20



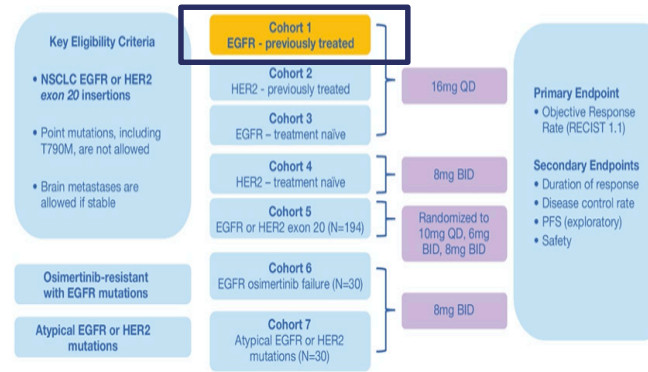
Drug	Group	ORR	PFS (mo)
Neratinib	2 nd gen EGFR/HER2 TKI	4%	3-5
Afatinib	2 nd gen EGFR/HER2 TKI	7-18%	5
Chemo+ trastuzumab	Anti-HER2 Ab	50%	4.8
TDM1	Anti-HER2 ADC	7-44%	5
T-Dxd	Anti-HER2 ADC	62%	14

EGFR

Exon 20 insertion

BACKGROUND

ZENITH20 trial



- No current approved therapy for EGFR or HER2 exon 20 mutant NSCLC patients
- ZENITH20 is a multicenter, multicohort Phase 2 trial conducted in previously treated and newly diagnosed NSCLC exon 20 patients

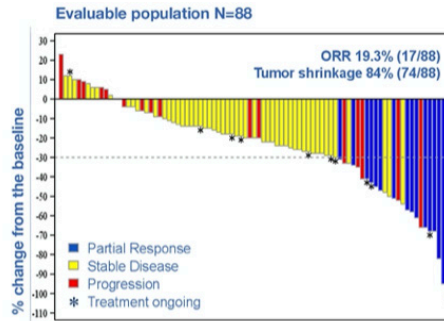
10% de las mutaciones de EGFR en CPNCP

Poziotinib* shows activity and durability of responses in subgroups of previously treated EGFR exon 20 NSCLC patients

*Poziotinib is an investigational drug not approved by the FDA

RESULTS FOR COHORT 1

	Intent-to-Treat Population (n=115)	Evaluable Population# (n=88)
Objective Response Rate [^] (ORR) (n), [95% CI]	14.8% (17) [8.9, 22.6%]	19.3% (17) [11.7, 29.1%]
Unconfirmed ORR (n), [95% CI]	18.1% (22) [12.4, 27.5%]	23.0% (22) [16.4, 35.4%]
Disease Control Rate (n), [95% CI]	68.7% (79) [59.4, 77.0%]	80.7% (71) [70.9, 88.3%]
Duration of Response, median (months), [95% CI]	7.4 [3.7, 9.7]	7.4 [3.7, 9.7]
Progression-free Survival, median (months), [95% CI]	4.2 [3.7, 6.6]	4.1 [3.7, 5.5]



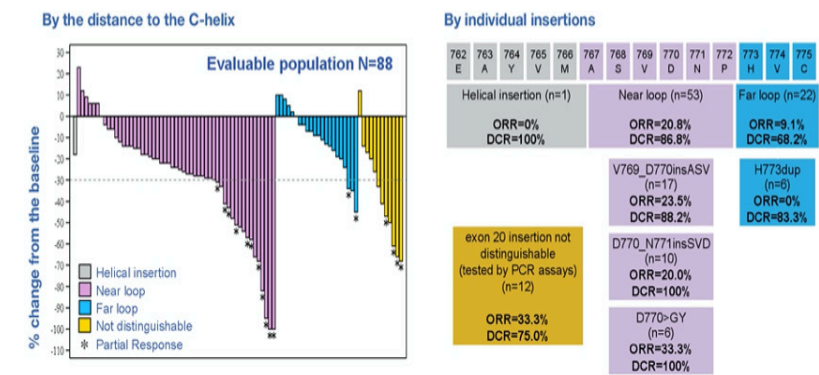
Patients with measurable tumor at baseline and evaluable post-treatment timepoints

- 115 enrolled, median age 61 years
- Common Grade 3 TRAEs: diarrhea (25%), rash (28%), stomatitis (9%), paronychia (6%)
- Efficacy was evaluated using RECIST criteria by an independent review committee
- Poziotinib showed strong clinical activity with tumor shrinkage in 84% of evaluable patients

Response by prior therapy (evaluable population)

Subgroup	N (%)	Response Rate (n)	Median Progression-free Survival (months)	Median Duration of Response (months)	
Prior lines of therapy	1	37 (42)	18.9% (7)	5.4	3.7
	2	24 (27)	16.7% (4)	3.7	6.9
	≥3	27 (31)	22.2% (6)	4.1	7.4
Prior EGFR TKI	23 (26)	8.7% (2)	3.5	Not reached	
No Prior EGFR TKI	65 (74)	23.1% (15)	5.5	7.4	
Prior osimertinib	8 (9)	12.5% (1*)	3.5	2.3	

RESPONSE BY EGFR INSERTION LOCATION (EVALUABLE POPULATION)



- Molecular distribution of EGFR exon 20 insertion is consistent with previously reported data
- Higher response rate was observed in near loop insertions that have higher prevalence

HER 2

ZENITH20

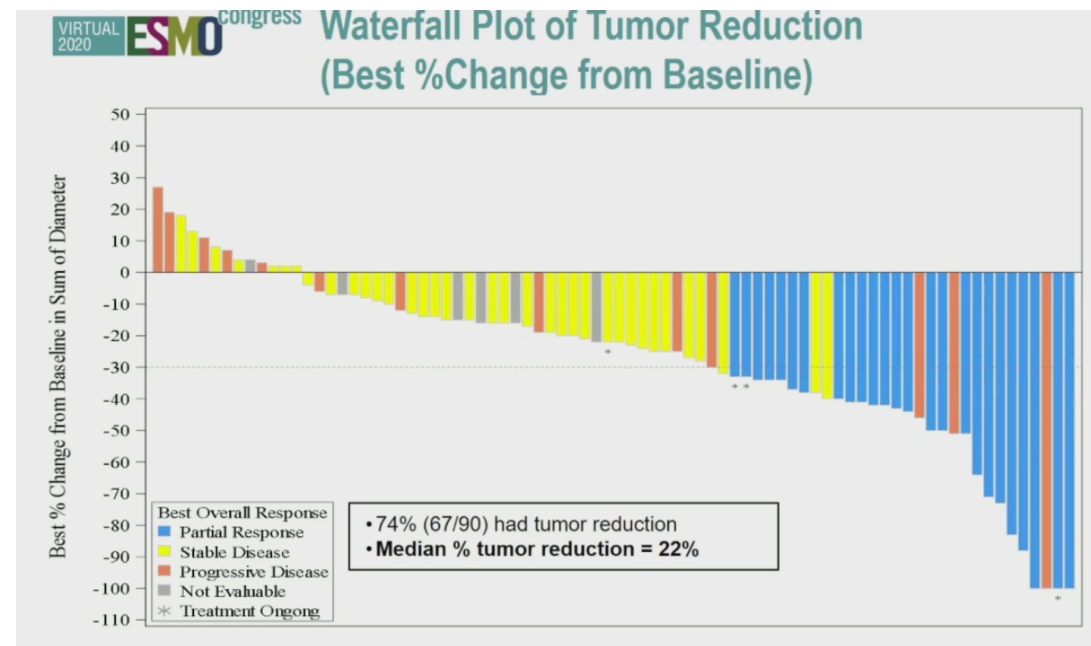
Disposition	N=90, n (%)
Treated	90 (100)
Ongoing	4 (4)
Age, median (range)	60 (25-86)
Female / Male, n	58 / 32
White /Asian / Others, n	70 / 12 / 8
Smoker / Non-Smoker, n	31 / 59
Number of therapies, median (range)	2 (1-6)
Chemotherapy only	22 (24)
Chemo / IO checkpoint inhibitors	41 (46)
Chemo / HER2 therapy / IO checkpoint inhibitors	17 (19)
Others	10 (11)
Mutations: A775_G776InsYVMA / Others, n	61 / 29

	N=90, n (%)
Treatment-related AE	88 (98)
Treatment-related Serious AE	13 (14)
Dose interruptions	78 (87)
Dose reductions	70 (78)
AE related permanent discontinuation	11 (12)

Preferred Term (PT)	N=90, n (%)		
	Any Grade	Grade 3	Grade 4
Diarrhea	74 (82)	23 (26)	0
Rash	61 (68)	27 (30)	0
Stomatitis / Mucosal Inflammation	59 (66)	20 (22)	1 (1)
Paronychia	34 (38)	1 (1)	0
Pneumonitis	1 (1)	0	0

	As-Treated (N=90)	Evaluable (N= 74)
Objective Response Rate (ORR), n (%)	25 (27.8)	26 (35.1)
95% Confidence Interval	18.9 - 38.2	24.4 - 47.1
Disease Control Rate (DCR) , n (%)	63 (70.0)	61 (82.4)
Duration of Response (months) (range)	5.1 (1 - 12.3+)	5.1 (1 - 12.3+)
Median follow up of responders (months)	8.3	8.3
Median time on treatment (months) (range)	3.7 (0 - 16.6)	3.7 (0 - 16.6)
Progression-free Survival (months) (range)	5.5 (0 - 13.1+)	5.5 (1 - 13.1+)

Primary endpoint of ORR met (Lower bound of 95% CI >17%)



EGFR

EXON 20 insertions

Updated Results From a Phase 1/2 Study of Mobocertinib (TAK-788) in NSCLC With EGFR Exon 20 Insertions

Gregory J Riely,¹ Joel W Neal,² D Ross Camidge,³ Alexander Spira,⁴ Zofia Piotrowska,⁵ Leora Horn,⁶ Daniel B Costa,⁷ Anne Tsao,⁸ Jyoti Patel,⁹ Shirish Gadgeel,¹⁰ Lyudmila Bazhenova,¹¹ Viola W Zhu,¹² Howard West,¹³ Tarek Mekhail,¹⁴ Ryan Costantino,¹⁵ David Mermel,¹⁶ Yoonhee Park,¹⁷ Chyng (Cory) Liu,¹⁷ Zhonglin Fan,¹⁷ David A. Haura,¹⁸

Characteristic	Patients With EGFR Exon 20 Insertions Treated at 160 mg qd ^a (n=28)	All Patients Treated at 160 mg qd (n=136)	All Patients ^b (N=203)
Median age, years (range)	62 (28–84)	62 (24–86)	62 (24–86)
Female, n (%)	21 (75)	90 (66)	139 (68)
Race, n (%)	White/Asian/Black/Other	103 (76)/20 (15)/9 (7)/4 (3)	148 (73)/32 (16)/14 (7)/9 (4)
Histology, n (%)	Adenocarcinoma/Other	27 (96)/1 (4)	128 (94)/5 (4) ^c
ECOG, n (%)	0/1	6 (21)/22 (79)	61 (30)/141 (69) ^e
No. of prior systemic anticancer regimens, n (%) ^f	0/1/2	0/4 (14)/9 (32)	26 (13)/23 (11)/34 (17)
	≥3	15 (54)	48 (24)
Prior EGFR/HER2 TKI therapy, n (%)		6 (21)	40 (20)
Prior checkpoint inhibitor therapy, n (%)		17 (61)	49 (24)
History of smoking, n (%)	Never/Former/Current	17 (61)/11 (39)/0	83 (61)/51 (38)/1 (<1) ^g
Baseline brain metastases, n (%)		12 (43)	86 (42)

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EGFR, epidermal growth factor receptor gene; HER2, human epidermal growth factor receptor 2; TKI, tyrosine kinase inhibitor ^a Patients who received 160 mg qd (initial dose) during dose escalation (n=6) and in expansion cohort 1 (n=22). ^b Patients who received at least 1 dose of mobocertinib (5–180 mg total daily dose) during the escalation or expansion phase. ^c Three patients missing histology classification at baseline. ^d Four patients missing histology classification at baseline. ^e One patient missing ECOG assessment at baseline. ^f Number of prior systemic anticancer regimens unknown for 53 patients treated at 160 mg qd and for 72 patients total. ^g Smoking history unknown for 1 patient

• **As of January 27, 2020, of 28 patients with EGFR exon 20 insertions treated at 160 mg qd, 7 patients (25%) remain on study**

– **Median time on treatment (range): 12 months (0.7–24.7)**

Mujeres
Adenocarcinoma
Nunca fumadoras
Metastasis SNC

EGFR

EXON 20 insertions

Any grade: ≥20% of all patients Grade ≥3: ≥5% of all patients	Patients With <i>EGFR</i> Exon 20 Insertions Treated at 160 mg qd (n=28)		All Patients Treated at 160 mg qd ^a (n=136)		All Patients Treated at Any Dose ^b (N=203)	
	Any Grade, %	Grade ≥3, %	Any Grade, %	Grade ≥3, %	Any Grade, %	Grade ≥3, %
Diarrhea	82	32	83	21	78	16
Nausea	39	11	43	4	36	3
Rash	46	0	33	1	28	<1
Vomiting	36	7	26	4	23	3
Decreased appetite	39	0	26	1	22	<1
Dry skin	18	0	21	0	21	0
Fatigue	14	4	22	1	21	1

AE, adverse event ^a Patients who received at least 1 dose of mobocertinib at 160 mg qd (initial dose) during dose escalation or expansion cohorts 1 to 7. ^b Patients who received at least 1 dose of mobocertinib (5–180 mg total daily dose) during the escalation or expansion phase

Data cutoff: 27 Jan 2020

- Dose reductions in this study occurred in 5 patients with NSCLC with *EGFR* exon 20 insertions treated at mobocertinib 160 mg qd, 23 total patients treated at 160 mg, and 28 patients treated with any dose of mobocertinib
- Mobocertinib AE profile was manageable and consistent with that of other EGFR TKIs
 - AE management measures have been updated with the potential to improve gastrointestinal tolerability
 - The AE management guideline for diarrhea has been updated to allow symptomatic treatment at first evidence of increased frequency of bowel movement or at grade 1 diarrhea

EXON 20 insertions

	Mobocertinib 5–40 mg qd (n=12)	Mobocertinib 80 mg TDD (n=9)	Mobocertinib 120 mg qd (n=21)	Patients With <i>EGFR</i> Exon 20 Insertions Treated at 160 mg qd ^a (n=28)
Best confirmed response, n (%)^b				
CR	0	1 (11)	1 (5)	0
PR	0	1 (11)	3 (14)	12 (43)
SD ^c	3 (25)	6 (67)	11 (52)	12 (43)
PD	7 (58)	1 (11)	3 (14)	2 (7)
Not evaluable	0	0	0	0
Not evaluated	2 (17)	0	3 (14)	2 (7)
Confirmed objective response, n (%) [95% CI]	0 [0–26]	2 (22) [3–60]	4 (19) [5–42]	12 (43) [24–63]
Disease control, n (%) [95% CI]	3 (25) [5–57]	8 (89) [52–100]	15 (71) [48–89]	24 (86) [67–96]
Median DoR in confirmed responders, mo (95% CI)	NR	NR	NR	13.9 (5.0–NR)

CI, confidence interval; CR, complete response; DoR, duration of response; NR, not reported; PD, progressive disease; PR, partial response; SD, stable disease; TDD, total daily dose

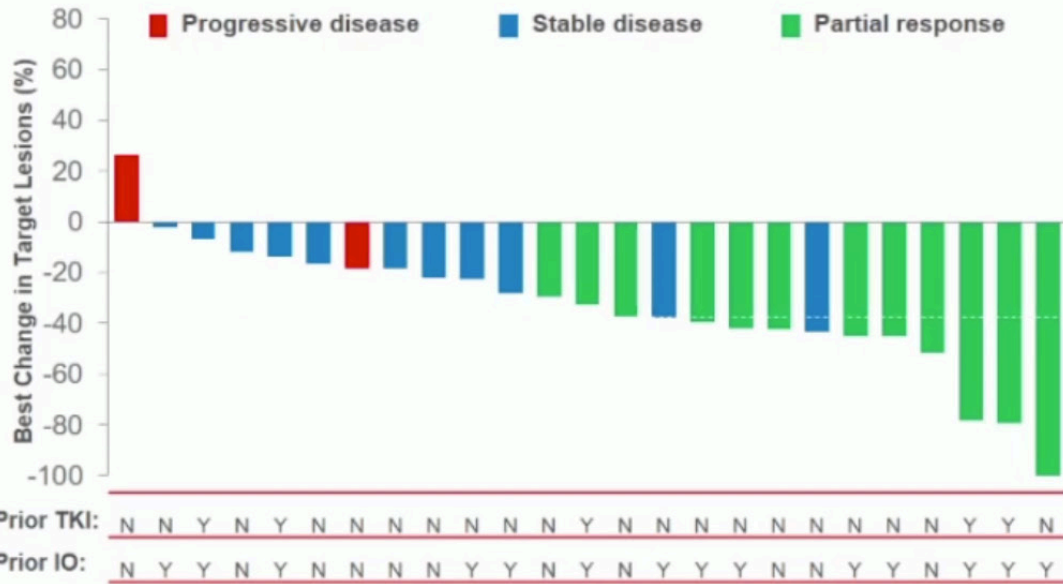
^a Patients treated with at least 1 dose of mobocertinib. ^b By RECIST v1.1. ^c SD observed ≥6 weeks after first study drug administration

Data cutoff: 27 Jan 2020

EGFR

Exon 20 insertion

Antitumor Activity

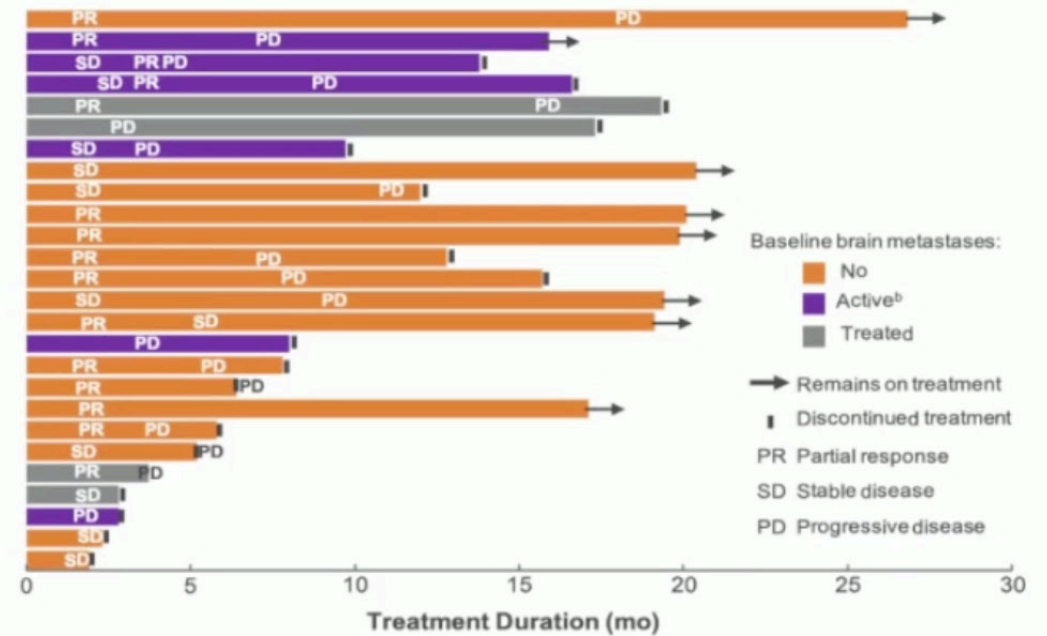


IO, immuno-oncology therapy; TKI, tyrosine kinase inhibitor

^a Two patients had no postbaseline assessment and are not included in figures

^b Active brain metastases were either never treated or progressed after radiation

Overall Response and Time on Treatment



- **Mobocertinib at recommended phase 2 dose (160 mg qd) showed antitumor activity in patients with *EGFR* exon 20 insertion mutations**
 - **43% confirmed objective response rate (n=12/28) with 13.9-month median duration of response and 7.3-month median progression-free survival in all patients, including those with baseline central nervous system metastases**

EGFR

Exon 20 insertion

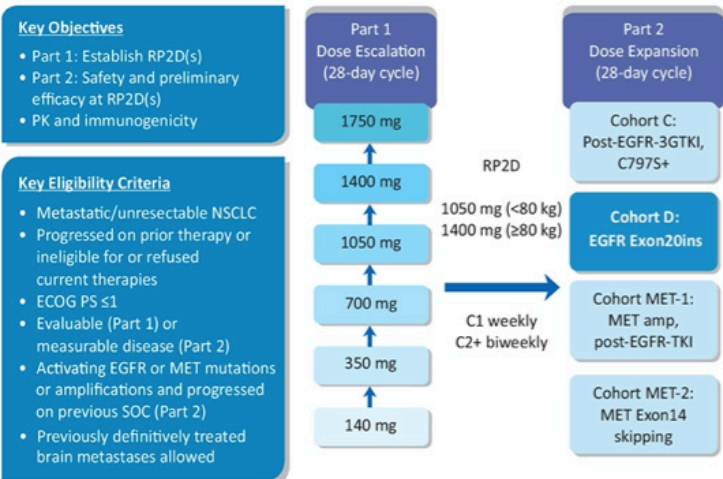
Amivantamab (JNJ-61186372), an anti-EGFR-MET bispecific antibody, in patients with EGFR Exon 20 insertion (Exon20ins)-mutated non-small cell lung cancer (NSCLC)

Keunchil Park,^{1*} Thomas John,² Sang-We Kim,³ Jong-Seok Lee,⁴ Catherine A. Shu,⁵ Dong-Wan Kim,⁶ Santiago Viteri Ramirez,⁷ Alexander I. Spira,⁸ Joshua K. Sabari,⁹ Ji-Youn Han,¹⁰ Jose Manuel Trigo Perez,¹¹ Chee Khoon Lee,¹² Ki Hyeong Lee,¹³ Nicolas Girard,¹⁴ Patricia A. Lorenzini,¹⁵ John Xie,¹⁵ Amy Roshak,¹⁵ Meena Thayu,¹⁵ Roland E. Knoblauch,¹⁵ Byoung Chul Cho¹⁵ on behalf of the CHRYSALIS Investigators

¹Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; ²Austin Hospital, Heidelberg, Australia; ³Asan Medical Center, Seoul, Republic of Korea; ⁴Seoul National University Bundang Hospital, Seongnam, Republic of Korea; ⁵Columbia University Medical Center, New York, NY, USA; ⁶Seoul National University Hospital, Seoul, Republic of Korea; ⁷Hospital Universitari Dexeus, Barcelona, Spain; ⁸Virginia Cancer Specialists, Fairfax, VA, USA; ⁹New York University School of Medicine, New York, NY, USA; ¹⁰National Cancer Center, Gyeonggi-do, Republic of Korea; ¹¹Hospital Universitario Virgen de la Victoria, Malaga, Spain; ¹²St George Hospital, Kogarah, Australia; ¹³Chungbuk National University Hospital, Cheongju, Republic of Korea; ¹⁴Institut Curie, Paris, France; ¹⁵Janssen R&D, Spring House, PA, USA; ¹⁶Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

*kpark@sksu.edu

Figure 1. CHRYSALIS Study Design



Cohorts A (EGFR-dependent resistance) and B (EGFR-independent resistance) were closed. 3GTKI=3rd-generation tyrosine kinase inhibitor; amp=amplification; C=cycle; ECOG PS=Eastern Cooperative Oncology Group performance status; Exon20ins=Exon 20 insertion; PK=pharmacokinetics; RP2D=recommended phase 2 dose; SOC=standard of care

Table 1. Demographics and Disease Characteristics of Response-Evaluable Patients

	Total (N=39)	Total (N=39)
Median age, years (range)	61 (40-78)	Median time from initial diagnosis, months (range)
Male / Female, n (%)	19 (49) / 20 (51)	12 (1-56)
Race, n (%)		Adenocarcinoma, n (%)
Asian	25 (64)	39 (100)
Black	1 (3)	Exon20ins mutation, n (%)
White	11 (28)	39 (100)
Not reported	2 (5)	Median prior lines, n (range)
ECOG PS, n (%)		1 (0-7)
0	14 (36)	Prior systemic therapies, n (%)
1	24 (62)	33 (85)
2	1 (3)	Platinum-based chemotherapy
		29 (74)
		Immuno-oncology therapy*
		13 (33)
		EGFR TKI
		9 (23)
		Bevacizumab
		4 (10)
		No prior therapy, n (%)
		6 (15)

*nivolumab, atezolizumab, pembrolizumab, durvalumab; ECOG PS=Eastern Cooperative Oncology Group performance status; EGFR=epidermal growth factor receptor; TKI=tyrosine kinase inhibitor

Table 2. Adverse Events in Patients Treated at the RP2D (Safety Population)

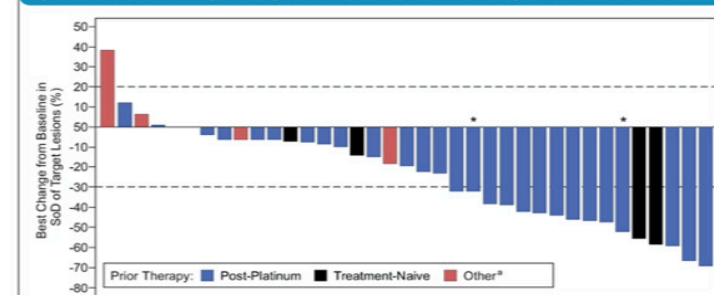
Adverse Events in the Safety Population, n (%)	Total (N=50)
Any AE	48 (96)
Serious AE	14 (28)
Grade ≥3 AE	18 (36)
AEs leading to death (all unrelated to amivantamab)	4 (8)
AEs leading to discontinuation	3 (6)
AEs leading to dose reduction	5 (10)
AEs leading to dose interruption ^a	15 (30)
All-grade AEs (≥15%), n (%)	
Rash ^b	36 (72)
Infusion related reaction	30 (60)
Paronychia	17 (34)
Constipation	13 (26)
Hypoalbuminemia	11 (22)
Dyspnea	10 (20)
Fatigue	9 (18)
Back pain	8 (16)
Stomatitis	8 (16)

PFS: 8.3 m, PFS post platino:8.6
Duración de la respuesta:10 m,
subgrupo postplatino: 7 m

Efficacy

- Reduction in target lesions was observed in post-platinum patients as well as in treatment-naive patients (Figure 2).
- Activity was observed across all 13 distinct EGFR Exon20ins alterations identified.

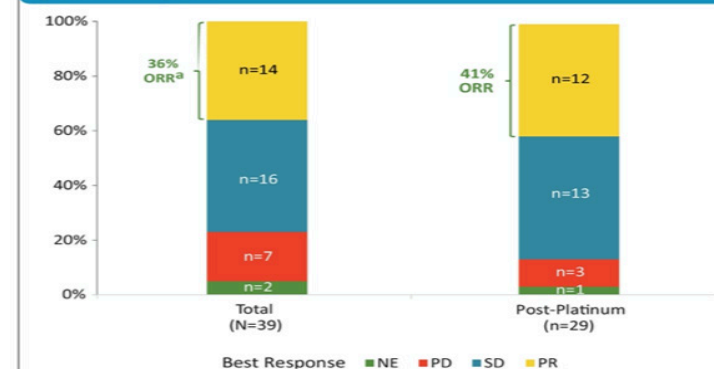
Figure 2. Best Percentage Change from Baseline in Sum of Target Lesion Diameters



*Unconfirmed partial response. ² patients treated with EGFR TKIs, 1 with bevacizumab plus radiation therapy, 1 with adjuvant immuno-oncology chemotherapy. 2 patients did not have post-baseline disease assessments and are not included in the plot. SoD=sum of diameters

- The overall response rate (ORR), confirmed responses only, was 36% (95% confidence interval [CI], 21-53), with 14/39 patients achieving a partial response (Figure 3).
- The ORR in post-platinum patients was 41% [95% CI, 24-61] (Figure 3).
- The clinical benefit rate (partial response or better or stable disease of at least 12 weeks [2 disease assessments]) was 67% (95% CI, 50-81) for all patients and 72% (95% CI, 53-87) for post-platinum patients.

Figure 3. Best Response



*Partial response or better. NE=not evaluable; ORR=overall response rate; PD=progressive disease; PR=partial response; SD=stable

EGFR y HER2

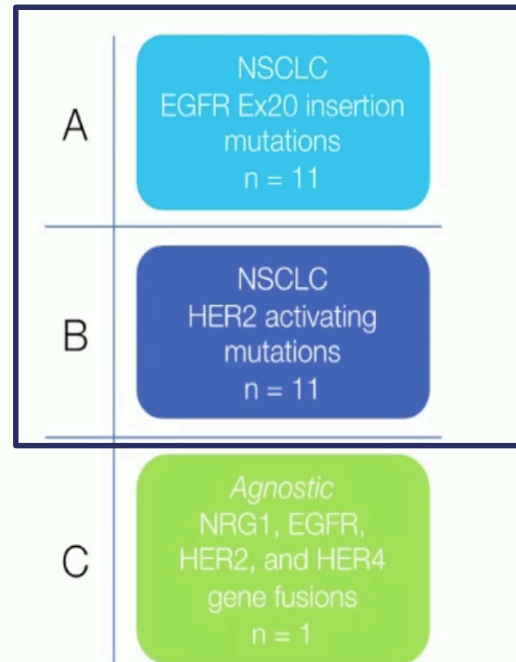
EGFR Ex20 inserción y activación de mutaciones HER2

RAIN-701 Trial Design and Patients

Protocol Overview

Tarloxotinib dose	<ul style="list-style-type: none"> 150 mg/m², IV weekly
Endpoint	<ul style="list-style-type: none"> Primary: ORR (RECIST)
Key Inclusion Criteria	<ul style="list-style-type: none"> ECOG PS 0-1 EGFR exon 20, HER2 mutation or fusion by local testing (tumor or ctDNA) PD to 1L chemotherapy (cohorts A + B only)
Key Exclusion Criteria	<ul style="list-style-type: none"> Prior EGFR/HER2 TKI/Ab (cohorts A + B only) Meds prolonging QTc; history of LQTS
Data Cutoff	<ul style="list-style-type: none"> June 12, 2020

Patient Cohorts



Patient Baseline Characteristics

	All (n=23)
Age (years)	
Median. (range)	56 (23-78)
Sex (%)	
Female	15 (65.2%)
Male	8 (34.8 %)
Race/Ethnicity (%)	
White or Caucasian	13 (56.5%)
Black or African American	3 (13.0%)
Asian	3 (13.0%)
Hispanic or Latino	2 (8.7%)
Native American	1 (4.3%)
Missing	1 (4.3%)
Baseline ECOG (%)	
0	4 (17.4 %)
1	19 (82.6%)
Brain Metastases (%)	
No	20 (87.0%)
Yes	3 (13.0%)
Prior Anticancer Therapies (%)	
Platinum-Based Chemotherapy	23 (100%)
Chemo/IO combination	18 (78.2%)
Any prior IO	19 (82.6%)
Smoking History (%)	
Current / Prior	3 (13.0%)
Never	20 (87.0%)
Histology (%)	
Adenocarcinoma	22 (95.7%)
Adenosquamous Carcinoma	1 (4.3%)

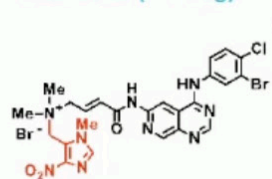
EGFR y HER2

EGFR Ex20 inserción y activación de mutaciones HER2

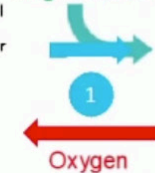
Tarloxotinib is a novel, hypoxia activated pan-HER inhibitor

- **Tarloxotinib** is a prodrug that embeds in, but cannot permeate the cell membrane
- Tarloxotinib fragments to the cell permeable tarloxotinib-E under hypoxic conditions
- Tarloxotinib-E is a potent pan-HER, covalent TKI
 - Subnanomolar potency against EGFR, HER2, and HER4 in biochemical assays
 - Cellular inhibition *in vitro* using numerous *EGFR*, *HER2*, and gene fusion cell line models
 - *In vivo* growth inhibition and regression in xenograft models of *EGFR*, *HER2* and *NRG1* fusion models
- Tarloxotinib-E is concentrated in tumor relative to normal tissues
 - Rational drug design to circumvent dose-limiting EGFR skin/GI toxicity

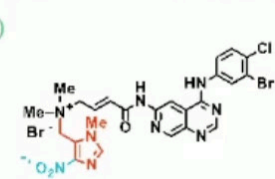
Tarloxotinib (Prodrug)



Single electron (e⁻)

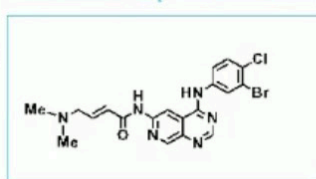


Nitro Radical Anion Intermediate

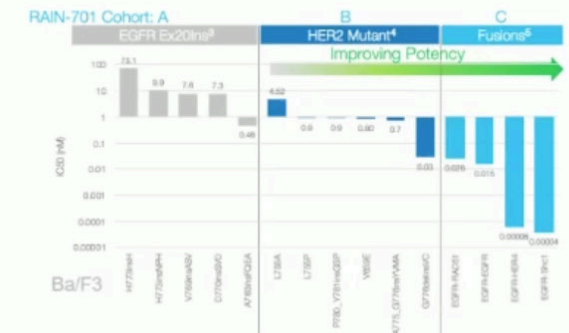
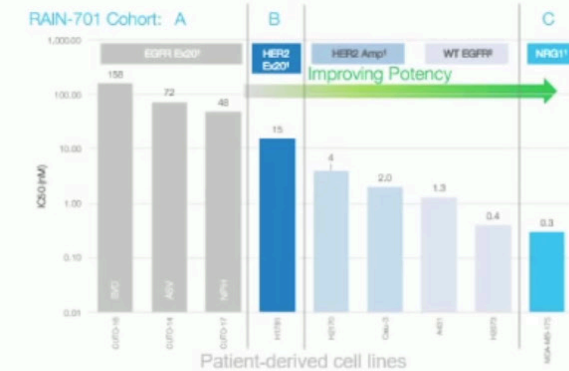


Hypoxic Fragmentation

Tarloxotinib-E (Active Metabolite)



In vitro activity of tarloxotinib-E



EGFR y HER2

EGFR Ex20 inserción y activación de mutacions HER2

TEAEs occurring in >20% of patients

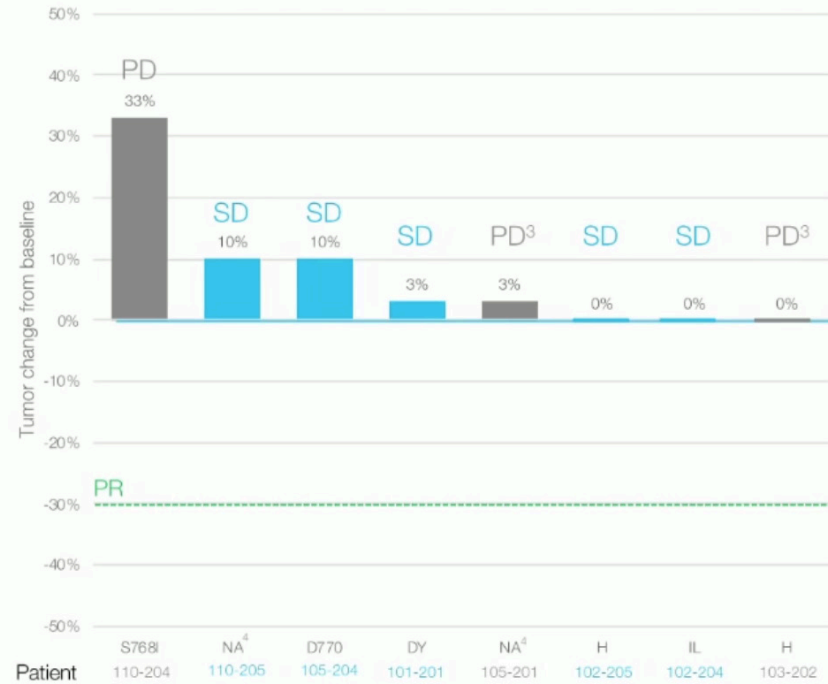
TEAE ¹	Pts (%) (n=23)	
	All Pts ² (%)	Gr ≥ 3 Pts (%)
QT Prolongation	14 (60.9%)	8 (34.8%)
Rash	10 (43.5%)	1 (4.3%)
Diarrhea	5 (21.7%)	1 (4.3%)
Nausea	5 (21.7%)	0 (0%)

- One patient (4.3%) with grade 3 transaminitis
 - Resolved after dose reduction
- Five patients (21.7%) required dose reduction
 - Two patients for infusion reaction
 - Three for QTc prolongation
 - G3 QTc resolved with single dose reduction for all 3 pts
 - **No arrhythmias observed in any patients**
- Only one patient (4.3%) discontinued therapy due to drug related AE (infusion reaction)

EGFR y HER2

EGFR Ex20 inserción y activación de mutaciones HER2

EGFR Exon 20 Insertion Mutations²

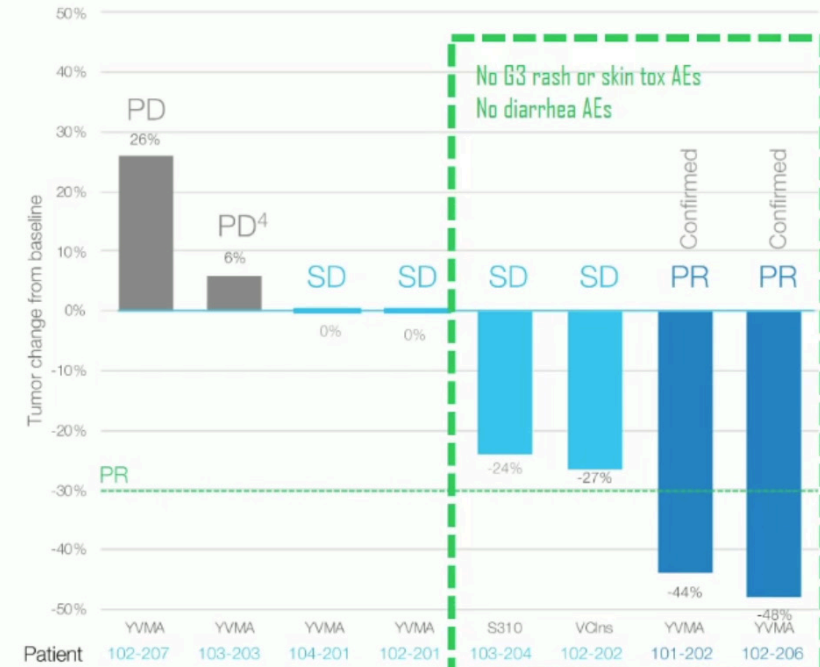


Cohort A

	% (n)
ORR	0% (0/11)
DCR	55% (6/11)

- Lack of *EGFR* exon 20 activity associated with higher IC50 for Tarloxotinib-E in *EGFR* exon 20 mutations compared to *HER2* mutations

HER2 Exon 20 Insertion Mutations^{2,3}



Cohort B

	% (n)
ORR	22% (2/9)
DCR	67% (6/9)

EGFR y HER2

EGFR Ex20 inserción y activación de mutaciones HER2

EGFR Exon 20 Insertion Mutations²

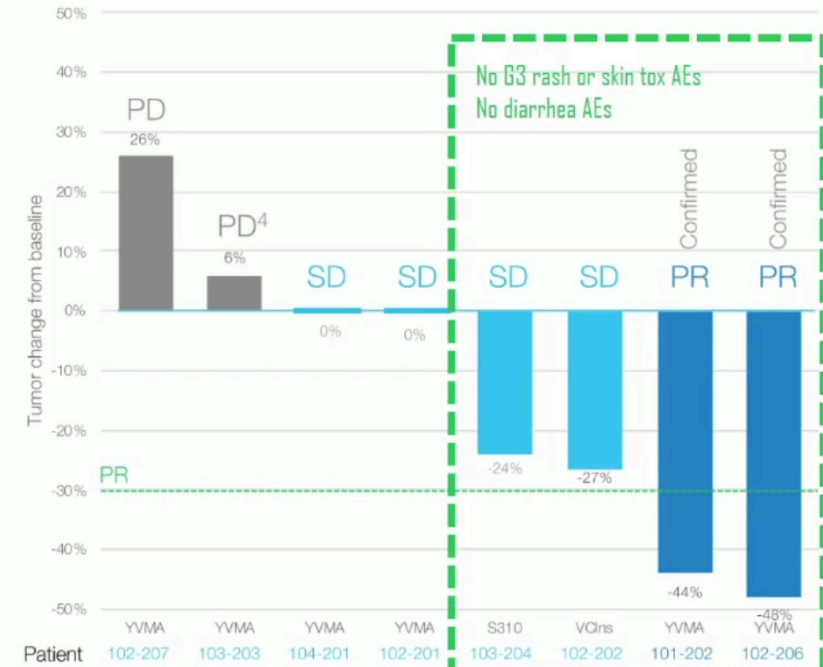


Cohort A

	% (n)
ORR	0% (0/11)
DCR	55% (6/11)

- Lack of *EGFR* exon 20 activity associated with higher IC50 for Tarloxotinib-E in *EGFR* exon 20 mutations compared to *HER2* mutations

HER2 Exon 20 Insertion Mutations^{2,3}



Cohort B

	% (n)
ORR	22% (2/9)
DCR	67% (6/9)

HER2

Mutaciones activadoras

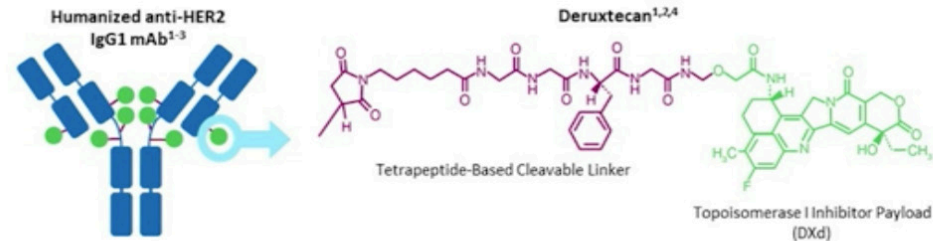
Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients With HER2-Mutated Metastatic Non-Small Cell Lung Cancer: Interim Results of DESTINY-Lung01

Egbert F. Smit, Kazuhiko Nakagawa, Misako Nagasaka, Enriqueta Felip, Yasushi Goto, Bob T. Li, Jose M. Pacheco, Haruyasu Murakami, Fabrice Barlesi, Andreas Saltos, Maurice Perol, Hibiki Udagawa, Kapil Saxena, Ryota Shiga, Ferdinand Guevara, Suddhasatta Acharyya, Javad Shahidi, David Planchard, Pasi A. Jänne

T-DXd is a Novel ADC Designed to Deliver an Optimal Antitumor Effect

T-DXd is an ADC with 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



Payload mechanism of action:
topoisomerase I inhibitor

High potency of payload

High drug to antibody ratio = 8

Payload with short systemic half-life

Stable linker-payload

Tumor-selective cleavable linker

Membrane-permeable payload

The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate.

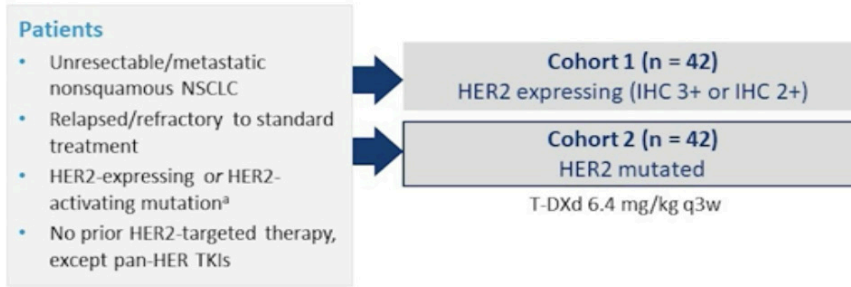
1. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142. 4. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

HER2

Mutaciones activadoras

DESTINY-Lung01 Study Design

An open-label, multicenter, phase 2 study (NCT03505710)



Primary endpoint

- Confirmed ORR by independent central review

Data cutoff: November 25, 2019

- 45.2% of patients (19/42) in Cohort 2 remained on treatment
- 54.8% discontinued, primarily for progressive disease and adverse events (21.4% each)

	Patients (N = 42)
Age, median (range), years	63.0 (34-83)
< 65 years, %	59.5
Female, %	64.3
Region, %	35.7 / 31.0 / 33.3
Asia / North America / Europe	
ECOG performance status 0 / 1, %	23.8 / 76.2
HER2 mutation, %	
Kinase domain	90.5
Extracellular domain	4.8
Not reported	4.8
Presence of CNS metastases, %	45.2

Median prior lines of treatment: 2 (range, 1-6)

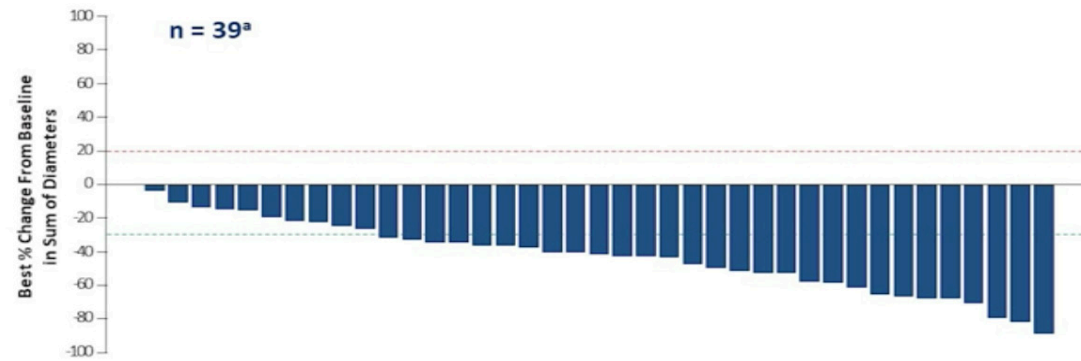
Prior Treatment, %	Patients (N = 42)
Platinum-based therapy	90.5
Anti-PD-1 or -PD-L1 inhibitor	54.8
Docetaxel	19.0

3 patients received prior poziotinib, 2 received afatinib, and 1 received mobocertinib

HER2

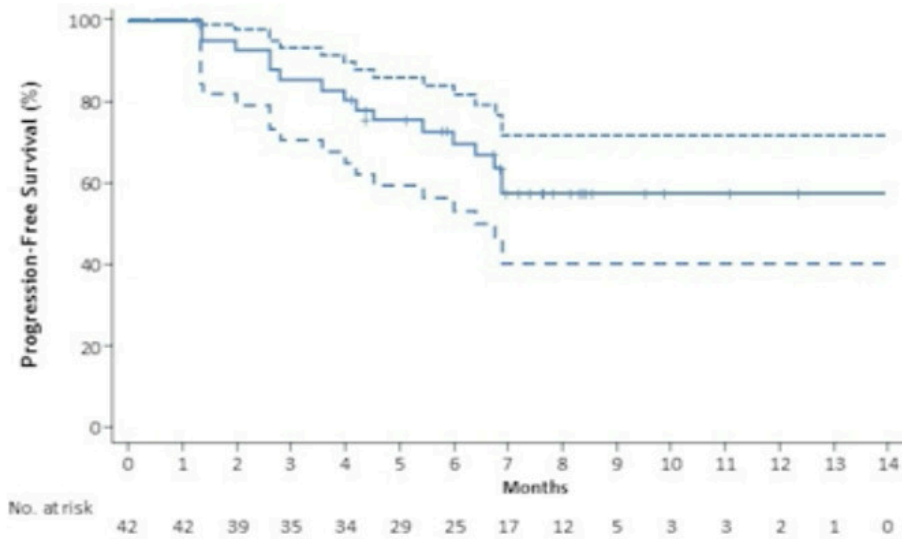
Mutaciones activadoras

Patients (N = 42)	
Confirmed ORR by ICR	61.9% (n = 26) (95% CI, 45.6%-76.4%)
CR	2.4% (n = 1)
PR	59.5% (n = 25)
SD	28.6% (n = 12)
PD	4.8% (n = 2)
Not evaluable	4.8% (n = 2)
Disease control rate	90.5% (95% CI, 77.4%-97.3%)
Duration of response, median	Not reached (95% CI, 5.3 months-NE)
PFS, median	14.0 mo (95% CI, 6.4-14.0 months)



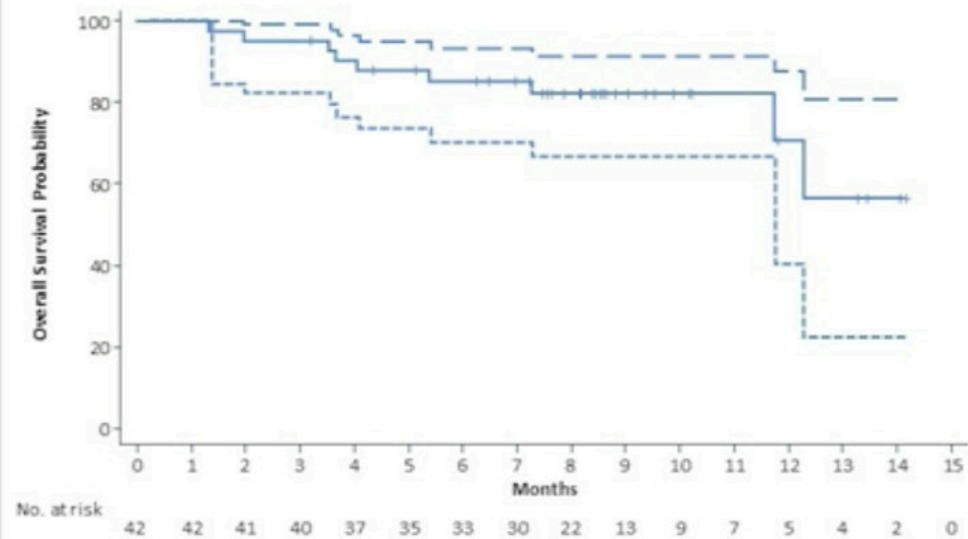
Progression-Free Survival (N = 42)^a

Median: 14.0 months (95% CI, 6.4-14.0)



Overall Survival (N = 42)

Median: Not reached (95% CI, 11.8-NE)

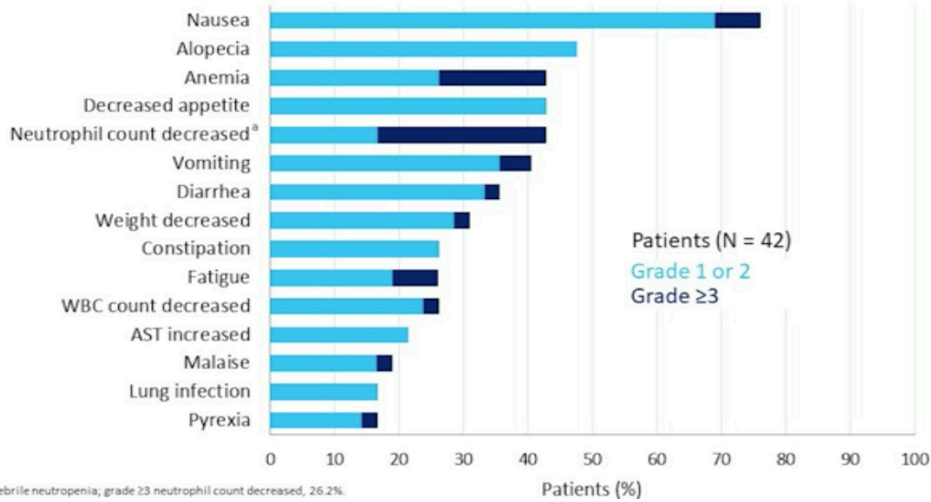


^a Patients were censored if they discontinued treatment; the median is estimated by Kaplan-Meier analysis. Median follow-up, 8.0 months (range, 1.4-14.2 months). Dashed lines indicate upper and lower 95% CI.

HER2

Mutaciones activadoras

Treatment-Emergent Adverse Events in >15% of Patients



Type of Adverse Event, n (%)^a

**Patients
(N = 42)**

Any TEAE	42 (100)
Drug-related	42 (100)
TEAE grade ≥ 3	27 (64.3)
Drug-related	22 (52.4)
Serious TEAE	14 (33.3)
Drug-related	7 (16.7)
Dose adjustments	
TEAE associated with discontinuation ^b	10 (23.8)
Drug-related	8 (19.0)
TEAE associated with dose reduction	16 (38.1)
Drug-related	16 (38.1)
TEAE associated with dose interruption	25 (59.5)
Drug-related	20 (47.6)

All Patients (N = 42)

n (%)	Grade					Any Grade/ Total
	1	Grade 2	Grade 3	Grade 4	Grade 5	
Interstitial lung disease	0 ^a	5 (11.9)	0	0	0	5 (11.9)

- Median time to onset of investigator-reported ILD was at 86 days (range, 41-255 days)
- 4 patients had drug withdrawn and 1 had drug interrupted
- All patients received steroid treatment
- 2 patients recovered, 1 recovered with sequelae, 1 was recovering, and 1 had not recovered by data-cutoff
- No grade 5 ILD was observed in this cohort

RESUMEN

	Farmaco	Fase	N	AES >o = 3	ORR	SLP	DOR	
<i>EGFR</i>	ZENITH20	Poziotinib	II	119	28% paroniquia 27% rash 25% diarreas	14.8%	4.2	7.4
		Mobocertinib TAK 788	I/II	28 (160 mg)	32% diarreas 11/7% Nauseas/vomitos	43%	7.3	13.9
	RAIN701	Tarloxotinib	II	11	34% prolongación QTc 3% Rash 3% Diarreas	0		
	CHRYSALIS	Amivantab	I/II	39	18% (3% Diarrea/ Hiperamilasemia/Hipokalemia)	36%	8	10

	Farmaco	Fase	N	AES >o = 3	ORR	SLP	DOR	
<i>HER2</i>	ZENITH20	Poziotinib (ins exón 20)	II	90	28% paroniquia 27% rash 25% diarreas	25%	5.5	5.1
	RAIN 701	Tarloxotinib (mutaciones activadoras)	II	11	34% prolongación QTc 3% Rash 3% Diarreas	22%	---	---
	DESTINY- Lung 1	Trastuzumab deruxtecan (Her2 mut)	II	42	52% Neutropenia/Anemia/Astenia/Nauseas	62%	14	NR

MET

Característica	Exon 14 skipping mutation	Met amplification
Molecular	3% CPNP 15% con ampl MET	<1% CPNPN (10% resist EGFR i 15% de resist ALK)
Patológica	Adenocarcinoma PDL1 elevado, TMB disminuido	Adenocacinoma PDL-1 elevado, TMB disminuido
Clinica	Edad media 70 Fumadores Mujeres Mal pronóstico	Edad media 60 Fumadores Hombres Mal pronóstico

Exon skipping mutation

Primary efficacy and biomarker analyses from the VISION study of tepotinib in patients with NSCLC with *MET* exon 14 skipping

Xiuning Le,¹ Enriqueta Felip,² Remi Veillon,³ Hiroshi Sakai,⁴ Alexis B. Cortot,⁵ Marina Chiara Garassino,⁶ Julien Mazieres,⁷ Santiago Viteri,⁸ Helene Senellart,⁹ Jan Van Meerbeeck,¹⁰ Niels Reinmuth,¹¹ Pierfranco Conte,¹² Dariusz Kowalski,¹³ Byoung Chul Cho,¹⁴ Josef Straub,¹⁵ Jürgen Scheele,¹⁶ Dilafruz Juraeva,¹⁷ Rolf Bruns,¹⁸ John Heymach,¹ Paul K. Paik¹⁹

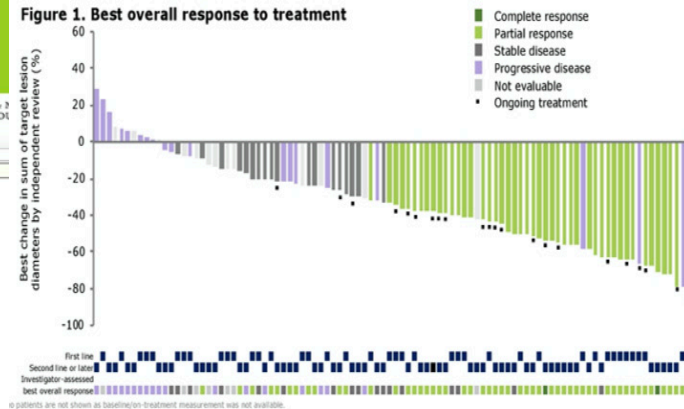
- Objective response rate by independent review (primary endpoint) was 46.5–50.0% and by investigator assessment was 55.6–61.7% (Table 2)

Table 2. Clinical response in the primary efficacy population

	Liquid-biopsy group* (n=66)		Tissue-biopsy group* (n=60)		Combined* (n=99)	
	IRC	INV	IRC	INV	IRC	INV
Objective response rate, % (95% CI)	48.5 (36.0, 61.1)	56.1 (43.3, 68.3)	50.0 (36.8, 63.2)	61.7 (48.2, 73.9)	46.5 (36.4, 56.8)	55.6 (45.2, 65.5)
Duration of response, median months (95% CI)	9.9 (7.2, ne)	14.0 (7.3, ne)	15.7 (9.7, ne)	16.4 (9.7, ne)	11.1 (7.2, ne)	14.0 (9.7, 18.3)
Disease control rate, % (95% CI)	65.2 (52.4, 76.5)	69.7 (57.1, 80.4)	68.3 (55.0, 79.7)	78.3 (65.8, 87.9)	65.7 (55.4, 74.9)	72.7 (62.9, 81.2)

*Two patients were liquid biopsy positive only; 25 patients were tissue biopsy positive only; objective response rate by independent review was 48.0% (95% CI: 21.1, 61.3) and 48.0 (95% CI: 27.8, 58.7) by investigator assessment. *Combined = liquid biopsy positive and/or tissue biopsy positive. IRC, independent review committee; ne, not estimable; CI, confidence interval.

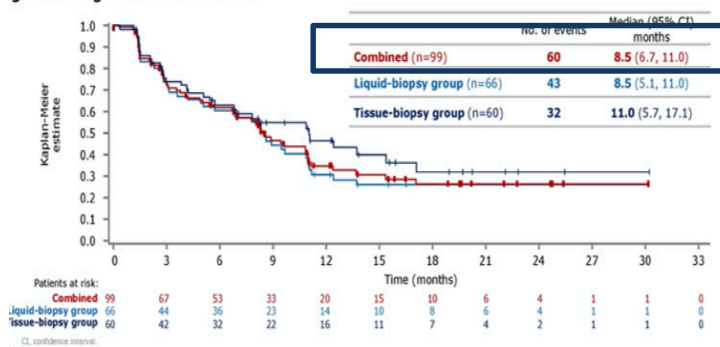
- Tumor shrinkage was observed in 89% of patients (Figure 1)



In the combined group, median (95% CI) progression-free survival was 8.5 (6.7, 11.0) months by independent review (Figure 2) and 8.6 (6.7, 11.2) months by investigator assessment

Median (95% CI) overall survival was 17.1 months (12.0, 26.8) in the combined group, 15.8 months (9.5, not estimable) in the liquid-biopsy group and 22.3 months (15.3, not estimable) in the tissue-biopsy group

Figure 2. Progression-free survival



Safety

- Grade ≥3 treatment-related adverse events were reported in 27.6% of patients (Table 3)
- Treatment-related adverse events led to dose reductions in 32.9% of patients and to permanent discontinuations in 11.2% of patients

Table 3. Treatment-related adverse events

Category, n (%)	Tepotinib (n=152)			
	All grades	Grade 1/2	Grade 3	Grade 4
Any adverse event*	135 (88.8)	93 (61.2)	38 (25.0)	3 (2.0)
Peripheral edema	96 (63.2)	85 (55.9)	11 (7.2)	0
Nausea	39 (25.7)	38 (25.0)	1 (0.7)	0
Diarrhea	33 (21.7)	32 (21.1)	1 (0.7)	0
Blood creatinine increased	27 (17.8)	26 (17.1)	1 (0.7)	0
Hypoalbuminemia	24 (15.8)	21 (13.8)	3 (2.0)	0
Amylase increased	17 (11.2)	13 (8.6)	3 (2.0)	1 (0.7)

*A 79-year-old patient had a Grade 5 adverse event of respiratory failure and *Cytopex*, secondary to interstitial lung disease.

Patients

- As of 01 January 2020, 152 patients received tepotinib (safety population) and 99 patients comprised the primary efficacy population with ≥9 months' follow-up data (Table 1)
- 60/152 and 22/99 patients were still receiving tepotinib at data cut-off

Table 1. Baseline characteristics

Baseline characteristic		Combined* (n=100)
Median age, years (range)		74.0 (41-94)
Sex (%)	Male / Female	54 / 46
Race [†] (%)	Asian / White	21 / 75
Smoking history [†] (%)	Yes	47
ECOG performance status (%)	0 / 1	73 / 27
Lines of prior therapy for advanced/metastatic disease (%)	0	43 (43.0)
	1	34 (34.0)
	2+	23 (23.0)

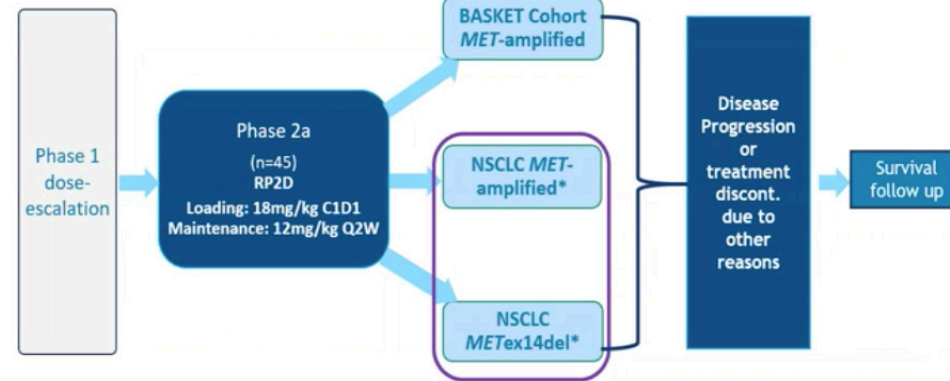
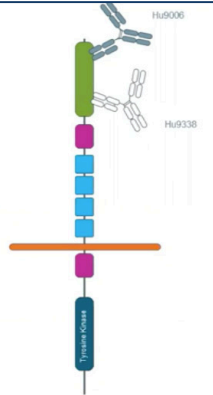
MET

Exon 14 skipping mutation and amplification

Safety and preliminary clinical activity of the MET antibody mixture Sym015 in advanced non-small cell lung cancer (NSCLC) patients with *MET*-amplification/exon 14 deletion (*MET*^{Amp/Ex14Δ})

D.R. Camidge, F. Janku, A. Martinez Bueno, D. Catenacci, J. Lee, S.H. Navarro, Y.W. Moon, M. Awad, R. Heist, T. Poulsen, Arielle Yablonovitch, Frank Nygaard, D. L. Woods, R.P. Dalal, E. Felip

- A synergistic mixture of two recombinant humanized IgG1 mAbs against non-overlapping epitopes of MET
- Blocks the HGF-MET interaction, triggers receptor internalization and degradation, and stimulates CDC and ADCC *in vitro* and *in vivo*
- An antibody approach improves MET-selectivity avoiding off-target toxicity and may circumvent intracellular acquired resistance mechanisms to MET TKIs such as kinase domain mutations



*Two NSCLC cohorts were added after preliminary data review of patients in basket cohort.

Key Inclusion Criteria

NSCLC MET-Amplified Cohort ONLY:

- Documented *MET*-amplification: ISH MET/CEP7 $\geq 2.2^*$ or NGS/qPCR >5 copies
- Prior MET and/or EGFR-targeting agents permitted

NSCLC MET^{Ex14DEL} Cohort ONLY:

- Documented MET^{Ex14DEL}
- Prior MET and/or EGFR-targeting agents permitted

*The protocol amendment #8 required ISH MET/CEP7 ≥ 3.0 .

MET

Exon skipping mutation and amplification

Parameter	Phase 2a (n=45)	NSCLC (N=20)
Age (years)		
Median	61.7	67.8
Range	29.3 ; 84.2	48.0 ; 79.9
Sex, n (%)		
Female	18 (40.0%)	11 (55.0%)
Race		
Caucasian	25 (55.6%)	17 (85.0%)
Asian	17 (37.8%)	3 (15.0%)
Other	3 (6.7%)	-
Cancer Diagnosis		
NSCLC	20 (44.4%)	20 (100%)
Gastric	12	-
CRC	4	-
Bile Duct	2	-
Breast	1	-
Other*	6	-

*One patient each with following cancer type: Hepatocellular and Cholangiocarcinoma combined, Neuroendocrine-Hepatic, Neuroendocrine-lung, Prostate, Renal cell, Uterine papillary adenocarcinoma.

Parameter	Phase 2a (n=45)	NSCLC (N=20)
≥ 2 prior Systemic Regimen, n (%)	36 (80.0%)	18 (90.0%)
Median number of prior systemic regimens, n (range)		
Prior MET TKI Targeted Therapy, n (%)	15 (33.3%)	10 (50%)
MET-Amplification, n (%)	31 (73.3%) **	8 (40%)
MET ^{Ex14Δ} , n (%)	14 (31.1%)	12 (60%)

**One Patient with MET Amplification also presented with MET^{Ex14DEL}.

NSCLC Cohort

MET TKI Naïve (N=10)
 MET-Amp (N=7)
 MET^{Ex14DEL} (N=3)

Prior MET TKI treated (N=10)
 MET-Amp (N=1)
 MET^{Ex14DEL} (N=9)

Data Cut Date: 14Apr2020

MET

Exon skipping mutation and amplification

Treatment Emergent AE >10%	Phase 2a (n=45) n (%)	NSCLC (n=20) n (%)
All	42 (93.3%)	19 (95.0%)
Oedema Peripheral	11 (24.4%)	10 (50.0%)
Fatigue	10 (22.2%)	4 (20.0%)
Nausea	10 (22.2%)	4 (20.0%)
Constipation	9 (20.0%)	4 (20.0%)
Decreased Appetite	9 (20.0%)	3 (15.0%)
Cough	8 (17.8%)	6 (30.0%)
Abdominal Pain	7 (15.6%)	1 (5.0%)
Anaemia	7 (15.6%)	1 (5.0%)
Pyrexia	7 (15.6%)	3 (15.0%)
Hypoalbuminaemia	6 (13.3%)	1 (5.0%)
Aspartate Aminotransferase Increased	5 (11.1%)	4 (20.0%)
Back Pain	5 (11.1%)	2 (10.0%)
Dyspepsia	5 (11.1%)	3 (15.0%)
Dyspnoea	5 (11.1%)	4 (20.0%)

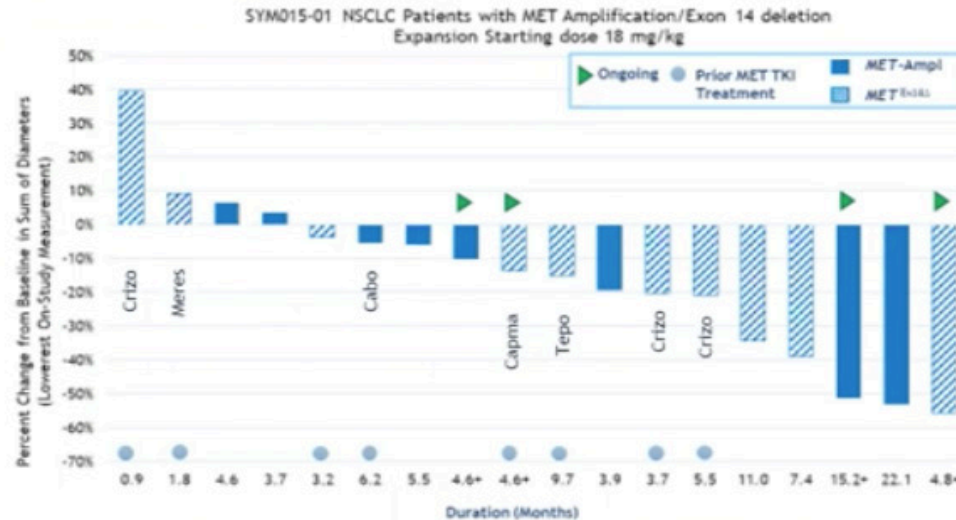
Treatment Related AE >5%	Phase 2a (n=45) n (%)	NSCLC (n=20) n (%)
All	22 (48.9%)	11 (55.0%)
Oedema Peripheral	7 (15.6%)	7 (35.0%)
Fatigue	6 (13.3%)	1 (5.0%)
Aspartate Aminotransferase Increased	4 (8.9%)	3 (15.0%)
Nausea	4 (8.9%)	2 (10.0%)
Abdominal Pain	3 (6.7%)	-
Asthenia	3 (6.7%)	2 (10.0%)
Decreased Appetite	3 (6.7%)	2 (10.0%)
Pruritus	3 (6.7%)	1 (5.0%)

- **Grade ≥ 3 related AEs reported in 6* of 45 (13.3%) pts:**
 - Anasarca and hypoalbuminemia
 - Colitis and septic shock
 - Hypophosphatemia
 - Amylase increase
 - Peripheral edema (NSCLC pt.)
 - Elevated LFTs (NSCLC pt.)
- **Dose reductions- 1 patient (NSCLC); dose reduced to 6 mg/kg q2w.**
- **No reports of treatment discontinuation due to adverse events**

MET

Exon skipping mutation and amplification

	ORR n (%)	DCR n (%)	DoR (months) median (95% CI)	mPFS (months) median (95% CI)
Overall (n=20)	5 (25%)	16 (80.0%)	13.8 (3.8-18.4)	5.5 (3.8-9.7)
MET TKI Naïve (n=10)	5 (50%)	10 (100%)	13.8 (3.8-18.4)	7.4 (3.4-21.9)
MET ^{Ex14Δ} (n=3)	3 (100%)	3 (100%)	6.5 (3.8-9.2)	9.2 (7.4-11.0)
MET-Amplification (n=7)	2 (28.6%)	7 (100%)	18.4 (NE)	5.5 (3.4-21.9)
MET TKI pre-treated (n=10)	-	6 (60.0%)	-	5.4 (1.2-9.7)
MET ^{Ex14Δ} (n=?)	-	5 (55.6%)	-	5.4 (1.2-9.7)
MET-Amplification (n=?)	-	1 (100%)	-	6.2 (NE)



- Prior Met TKI treated-MET^{Ex14Δ} subgroup: mOS 9.1 months
- mOS not reached for overall NSCLC population and other subgroups
- Range of OS- 0.13, 34.79 months

MET

MET Amplification

Capmatinib in patients with high-level MET-amplified advanced non-small cell lung cancer (NSCLC): Results from the phase 2 GEOMETRY mono-1 study

Juergen Wolf,¹ Tobias R. Overbeck,² Ji-Youn Han,³ Maximilian Hochmair,⁴ Filippo de Marinis,⁵ Kadoaki Ohashi,⁶ Egbert F. Smit,⁷ Danielle Power,⁸ Edward B. Garon,⁹ Harry J. M. Groen,¹⁰ Daniel S. W. Tan,¹¹ Maeve Waldron-Lynch,¹² Sylvie Le Mouhaer,¹³ Ngozi Nwana,¹⁴ Monica Giovannini,¹⁴ Rebecca S. Heist¹⁵

- Capmatinib is an orally, potent, and **highly selective** small-molecule MET inhibitor (type Ib)
- It prevents the **MET phosphorylation** and the downstream activation in MET-dependent tumors
- ~ 30 times more potent than crizotinib *in vitro*; capmatinib has shown regression of MET-dependent tumor models *in vivo*

- **Granted accelerated FDA approval* in MET ex14 skipping mutation (GEOMETRY study)**

Baseline characteristics (Cohorts 1a and 5a)

Demographics		Cohort 1a (2/3L, GCN ≥ 10) (N=69)	Cohort 5a (1L, GCN ≥ 10) (N=15)
Age, years	Median (range)	61 (33-76)	70.0 (49-86)
Race, n (%)	Caucasian	51 (73.9)	9 (60.0)
	Asian	17 (24.6)	6 (40.0)
	Other	1 (1.4)	0
Sex, n (%)	Female	15 (21.7)	4 (26.7)
	Male	54 (78.3)	11 (73.3)
Smoking history, n (%)	Never smoked	5 (7.2)	2 (13.3)
	Former smoker	54 (78.3)	8 (53.3)
	Current smoker	10 (14.5)	5 (33.3)
ECOG status, n (%)	0	17 (24.6)	4 (26.7)
	1	52 (75.4)	11 (73.3)

MET

MET Amplification

Best overall response (Cohorts 1a and 5a)

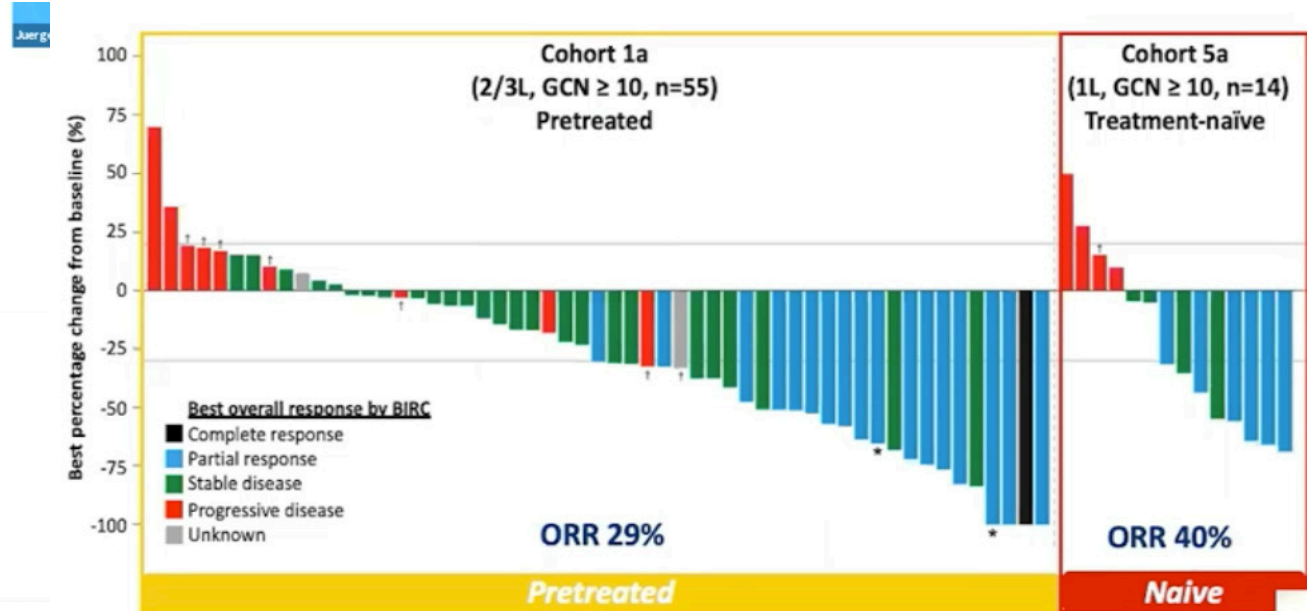
Best overall response, n (%)	Cohort 1a (2/3L, GCN ≥ 10) (N=69)		Cohort 5a (1L, GCN ≥ 10) (N=15)	
	BIRC	Investigator	BIRC	Investigator
Complete response (CR)	1 (1.4)	1 (1.4)	0	0
Partial response (PR)	19 (27.5)	18 (26.1)	6 (40.0)	6 (40.0)
Stable disease (SD)	28 (40.6)	23 (33.3)	4 (26.7)	5 (33.3)
Non-CR/non-PD	1 (1.4)	0	0	0
Progressive disease (PD)	12 (17.4)	21 (30.4)	4 (26.7)	3 (20.0)
Not evaluable*	8 (11.6)	6 (8.7)	1 (6.7)	1 (6.7)
ORR, [†] % (95% CI)	29.0 (18.7-41.2)	27.5 (17.5-39.6)	40.0 (16.3-67.7)	40.0 (16.3-67.7)
DCR, [‡] % (95% CI)	71.0 (58.8-81.3)	60.9 (48.4-72.4)	66.7 (38.4-88.2)	73.3 (44.9-92.2)

*All other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or progression within the first 12 weeks).

[†]ORR: Complete or partial response.

[‡]DCR: Patients who achieved complete response, partial response, stable disease or non-complete response/non-progressive disease.

1L/2L/3L, first/second/third-line; BIRC, Blinded Independent Review Committee; CI, confidence interval; DCR, disease control rate; GCN, gene copy number; ORR, overall response rate.



- mPFS ~4 mo.; mOS ~10 mo.; mDoR ~8 mo.

MET

MET Amplification

Most common treatment-related AEs (≥10%, all grades), n (%)	All patients N=364	
	All grades	Grade 3/4
Any	312 (85.7)	137 (37.6)
Peripheral edema	156 (42.9)	30 (8.2)
Nausea	125 (34.3)	6 (1.6)
Vomiting	68 (18.7)	7 (1.9)
Blood creatinine increased	67 (18.4)	0
Fatigue	50 (13.7)	10 (2.7)
Decreased appetite	45 (12.4)	3 (0.8)
Diarrhea	40 (11.0)	1 (0.3)

- Safety determined in the largest dataset of *MET*-dysregulated NSCLC patients (N=364)
- Median treatment exposure: 15.3 weeks
- The majority of treatment-related AEs were of grades 1 and 2
- Serious AEs suspected to be related to capmatinib occurred in 48 (13.2%) patients
- In total, 83 (22.8%) patients had at least one AE leading to dose reduction
- Treatment-related AEs leading to discontinuation occurred in 39 (10.7%) patients

MET

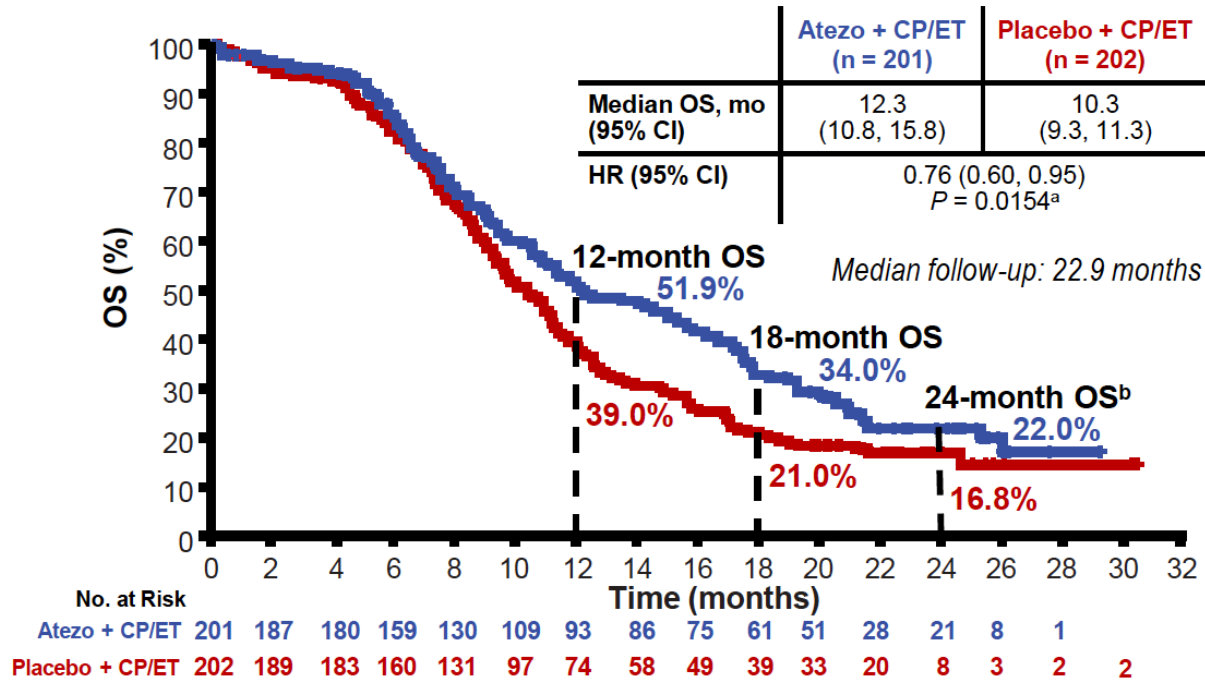
MET amp

Study	Phase	Drug	Different cut-offs	N	Line	ORR	PFS	DOR
GEOMETRY mono-1	II	Capmatinib	GCN ≥ 10	15	Naive	40%	4.07 mo.	7.5 mo.
				69	Pretreated	29%	4.17 mo.	9.56 mo.
Study	Phase	Drug	MET alteration	N	Line	ORR	PFS	DOR
METROS	II	Crizotinib	METex14 MET/CEP7 ratio > 2.2	26	Pretreated	27%	4.4 mo.	-
PROFILE 1001	I	Crizotinib	Low: ≥1.8-≤2.2 copies Medium: >2.2 to <4 High: ≥ 4 copies	37	Pretreated	33.3%	1.8 mo.	12.1 mo.
						14.3%	1.9 mo.	3.7 mo.
						40%	6.7 mo.	5.5 mo.

Efficacy,
Other MET-TKI

	Farmaco	Fase	N	AES >0 = 3	ORR (5)	SLP (m)	DOR (m)
EXON 14 SKIP MUT	Tepotinib	II	100	27%	45%	8.5	-----
EXON 14 SKIP MUT	SYM005	I/II	12	13%	100% (3/3)	9.2	6.5
MET AMPL MET/CEP7 <2.2, NGS > 5 copias	SYM005	I/II	8	13%	28% (2/7)	18.4	5.5
MET AMPL GN ≥10	Capmatinib	II	69 (pretratados) 15 (naive)	37%	29% (pretratados) 40% (naive)	4	8

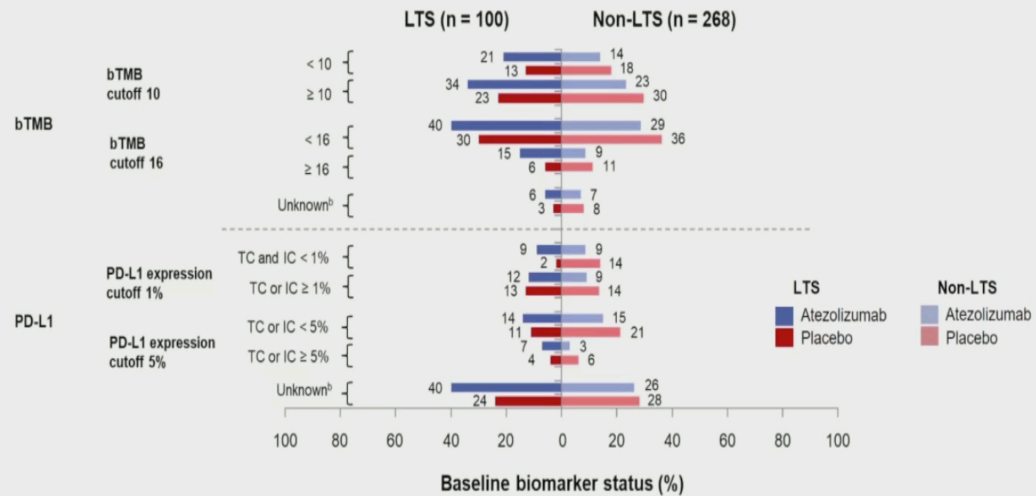
Updated OS in ITT



- **LTS** are defined as patients who lived ≥ 18 months since randomisation
- **Non-LTS** are defined as patients who died < 18 months post randomisation

	Atezo + CP/ET (n = 182)	Placebo + CP/ET (n = 191)
LTS, n (%)	61 (33.5)	39 (20.4)
95% CI	(26.7, 40.9)	(14.9, 26.8)
Non-LTS, n (%)	121 (66.5)	152 (79.6)
95% CI	(59.1, 73.3)	(73.2, 85.1)

IMpower133 LTS: baseline bTMB status and PD-L1 expression^a



Percentages are calculated for each subgroup within LTS and non-LTS, respectively

bTMB, blood tumour mutational burden; IC, tumour-infiltrating immune cell; TC, tumour cell. ^a Among patients evaluable for long-term survival, 87% were evaluable for bTMB (n = 323 of 373), and 43% were evaluable for PD-L1 (n = 160 of 373). The VENTANA SP263 assay was used to determine PD-L1 status on slide sections (regardless of age at the time of staining). ^b Unknown biomarker status irrespective of cutoff level. Data cutoff, 24 Jan 2019.

Liu et al. IMpower133 LTS. <https://bit.ly/2Ywu0bl>

Covariate	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Treatment arm (ref: atezolizumab)	0.76 (0.61, 0.96)	0.02	0.71 (0.56, 0.90)	< 0.01
Sex (ref: male)	1.11 (0.88, 1.41)	0.38	1.21 (0.94, 1.54)	0.13
Age (ref: ≥ 65 y)	1.17 (0.93, 1.47)	0.17	1.18 (0.93, 1.50)	0.17
ECOG PS (ref: 1)	1.64 (1.29, 2.10)	< 0.01	1.43 (1.11, 1.85)	0.01
Metastatic sites (ref: ≥ 3)	1.53 (1.18, 1.97)	< 0.01	1.22 (0.93, 1.61)	0.15
LDH (ref: > ULN)	1.53 (1.21, 1.94)	< 0.01	1.30 (1.01, 1.66)	0.04
SLD (ref: ≥ 111 mm)	1.69 (1.34, 2.12)	< 0.01	1.56 (1.22, 2.00)	< 0.01

TAKE HOME MESSAGES

- EL PDL1 es el marcador predictivo más fiable que tenemos hasta el momento a pesar de sus inconvenientes.
- El estudio PIONeerR nos dará más información sobre > de 400 biomarcadores (solubles y sobre tejido tumoral)
- La mutación G12C en KRAS (predominio mujeres, fumadoras) como nuevo biomarcador predictivo de respuesta de sotorasib , datos preliminares (Fase I).
- HER2(ins exón 20, mutaciones activadoras, her2 amplificado) y inserción exón 20 EGFR tiene nuevas terapias diana : Pozitotinib, Tarloxotinib, Trastuzumab deruxtecan, Amivantab; aún datos preliminares de respuesta.
- Las alteraciones de MET, biomarcador de mal pronóstico, muestran perfiles distintos según exón 14 skipping mutation (70 años, fumadores, mujeres) o amplificación de MET (60 años, fumadores, hombres).