



Post WCLC-ESMO targeted therapy

Anne-Marie Dingemans

Longarts

19-11-2018



**Oncologisch Netwerk
Zuidoost-Nederland**



Disclosure

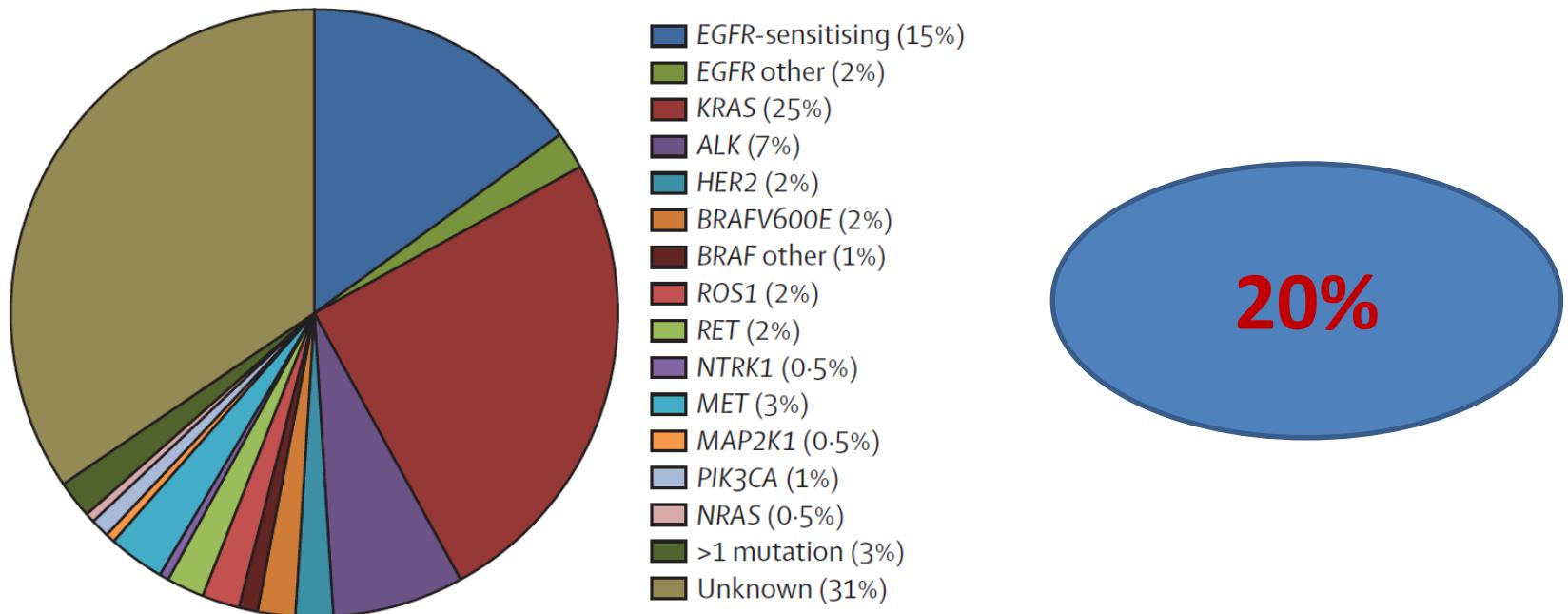
I attended advisory boards and/or provided lectures for: Roche, Eli Lilly, Boehringer Ingelheim, Astra Zeneca, Pfizer, BMS, Amgen, Novartis, MSD, Takeda;
for which my institute received honoraria

Met dank aan Joop de Langen

INHOUD

- Welke targets testen?
- Welke targets zijn behandelbaar?
- Rol van immunotherapie in ‘mutatie-positief’ NSCLC
- (EGFR) TKI resistantie
- Take home messages

Molecular alterations in NSCLC



14-09-2018 09:53

Geachte collega,

*Reden van verwijzing,
vraagstelling*

Graag uw second opinion ivm mogelijk uitbehandeld Longcarcinoom. Onderstaand verslag
van het laatste mdo uit

Kunt u eens meedenken of er nog

CONCLUSIE

Ter revisie ontvangen van
adenocarcinoom.

, lobectomie rechter bovenkwab: conform,

Therapiekeuzetest longadenocarcinoom:

NGS (CHPv2+):

- KRAS: niet aangetoond
- EGFR: niet aangetoond
- BRAF: niet aangetoond
- HER2: niet aangetoond
- Overige genen: niet aangetoond

-ALK fusie: immunohistochemisch (clone 5A4): negatief

-ROS1 fusie: immunohistochemisch (clone D4D6): deels positief, score 1+. FISH: WEL een ROS1 translocatie aangetoond

-TRKpan fusie: immunohistochemisch (clone A7H6R): negatief

-RET fusie: vervalt

-MET exon 14 skipping: RT-PCR: vervalt

-PD-L1 immunohistochemie (clone 22C3 LDT):

Sterk positief (meer dan 50% van de tumorcellen). In dit materiaal (membraneus) positief in 55% van de tumorcellen

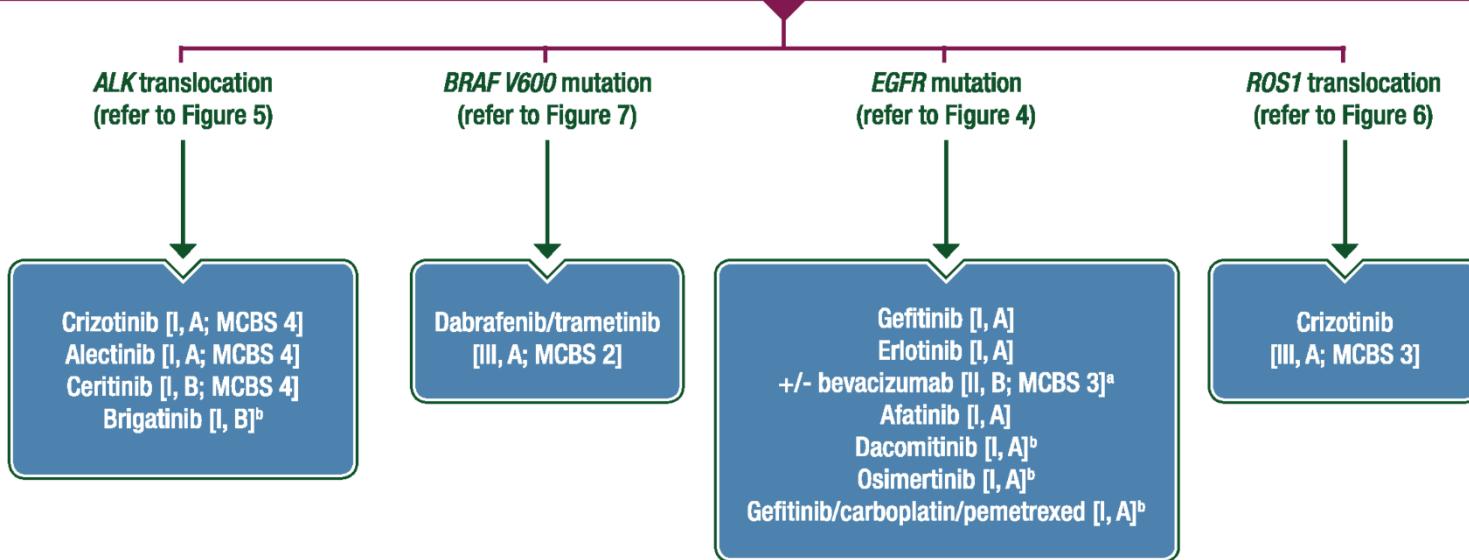
0. zonder beperkingen in staat alle normale activiteiten uit te voeren

Conclusie
Progressie na immunotherapie.

Molecular diagnostic workup

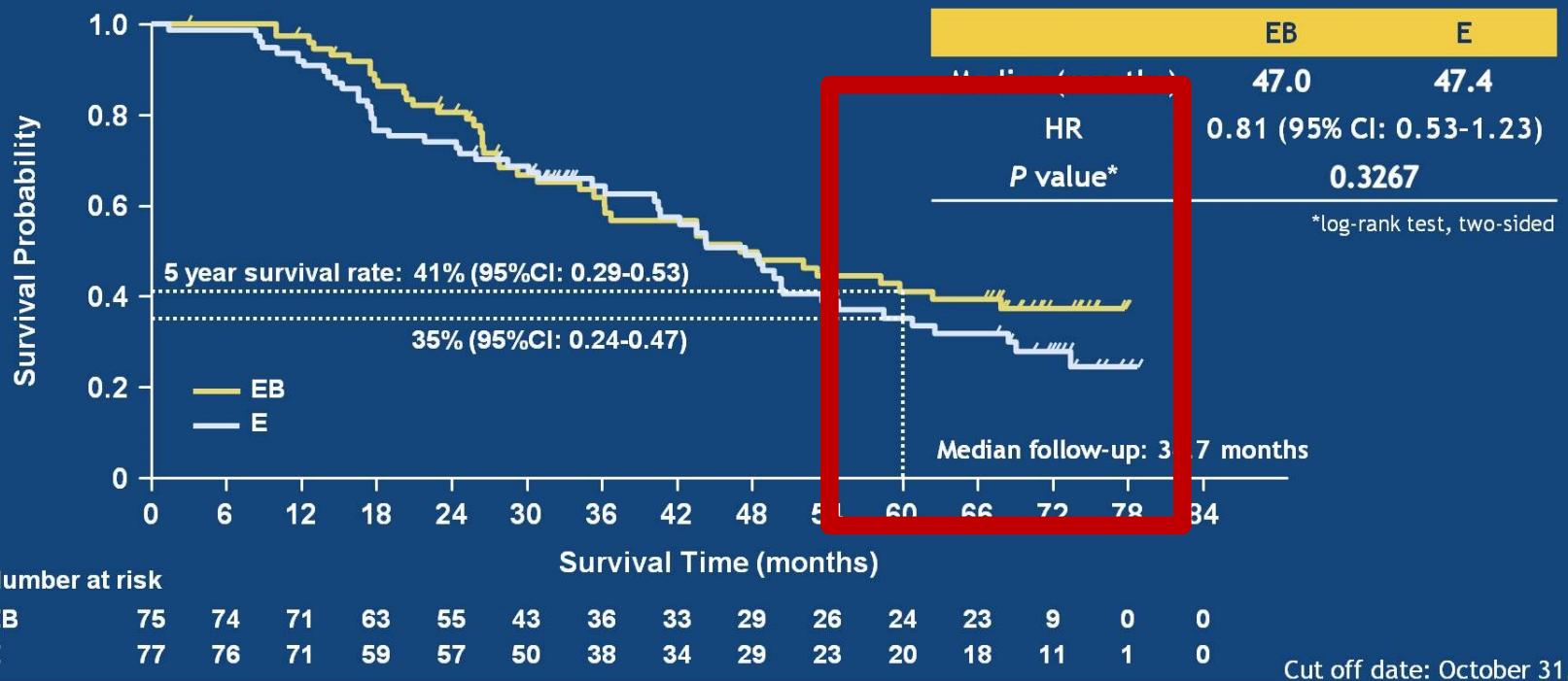
- NGS, including **EGFR**, HER2, **BRAF**, **KRAS**, MAP2K1 (MEK)
- Fusion analysis for **ALK**, **ROS1**, RET, NTRK1
- MET amplification and exon 14 skipping
- **Net zo belangrijk als PD-L1**

Stage IV NSCC: Molecular tests positive (*ALK/BRAF/EGFR/ROS1*)

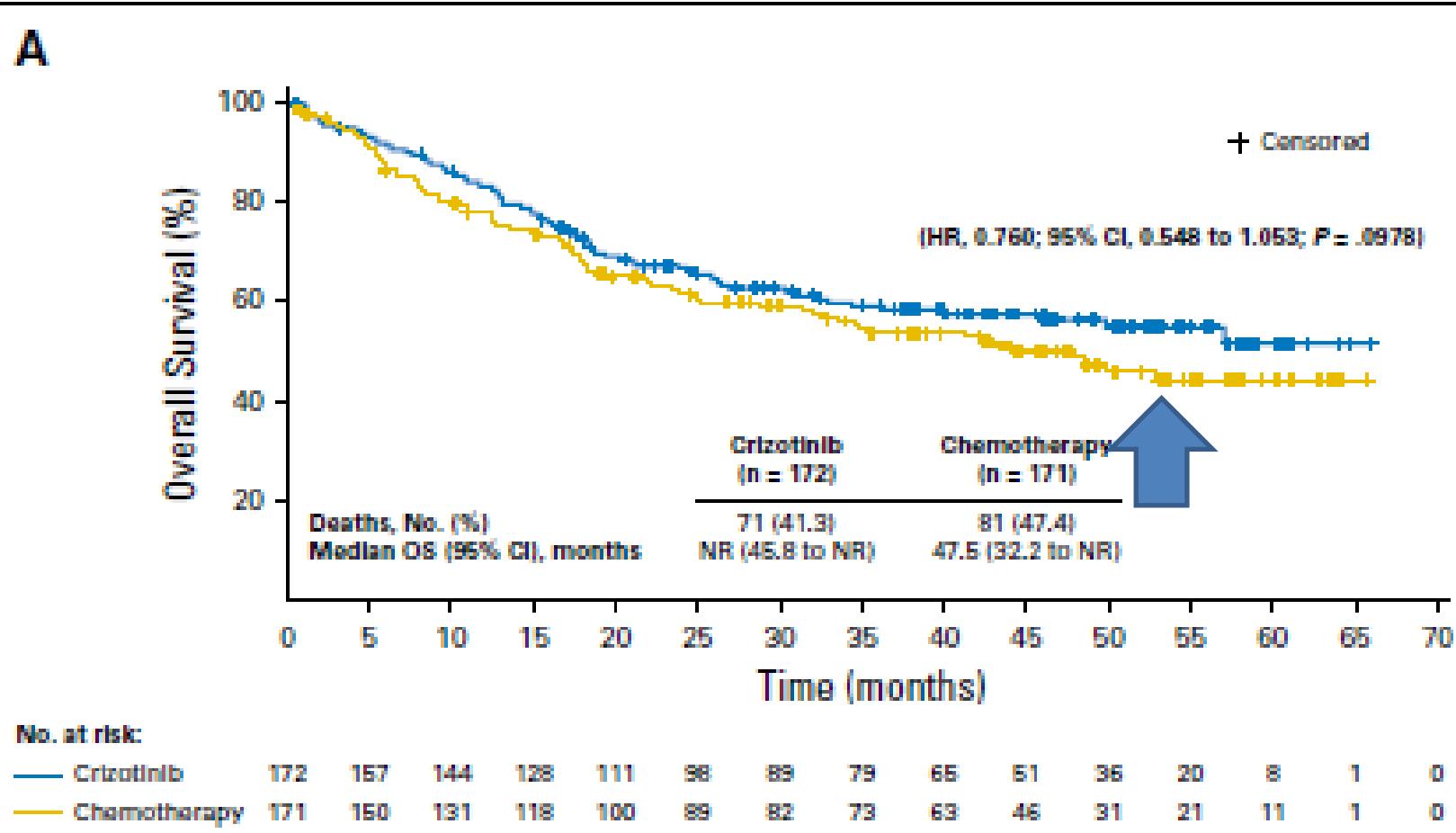


EGFR mutatie: 5 yr OS 40%!

Final Overall survival



ALK translokatie: 5 yr OS > 50%





Efficacy and Safety of Entrectinib in Locally Advanced or Metastatic *ROS1*-Positive Non-Small Cell Lung Cancer (NSCLC)

Robert C. Doebele,¹ Myung-Ju Ahn,² Salvatore Siena,^{3,4} Alexander Drilon,⁵ Matthew G. Krebs,^{6,7} Chia-Chi Lin,^{8,9} Filippo G. De Braud,¹⁰ Thomas John,¹¹ Daniel S.W. Tan,¹² Takashi Seto,¹³ Rafal Dziadziuszko,¹⁴ Hendrick-Tobias Arkenau,¹⁵ Fabrice Barlesi,¹⁶ Christian Rolfo,¹⁷ Jürgen Wolf,¹⁸ Edna Chow-Manevel,¹⁹ Pratik S. Multani,¹⁹ Na Cui,²⁰ Todd Riehl,²⁰ Byoung Chul Cho¹¹

¹University of Colorado, Aurora, CO, USA; ²Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea;

³Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, and Università degli Studi di Milano, Milan, Italy; ⁴Università degli Studi di Milano, Milan, Italy;
⁵Memorial Sloan Kettering Cancer Center, New York, NY, USA; ⁶The University of Manchester, Manchester, UK; ⁷The Christie NHS Foundation Trust, Manchester, UK; ⁸National Taiwan University Hospital, Taipei, Taiwan; ⁹National Taiwan University College of Medicine, Taipei, Taiwan;

¹⁰Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; ¹¹Olivia Newton-John Cancer Centre, Austin Health, Melbourne, Australia; ¹²National Cancer Centre Singapore, Singapore; ¹³National Kyushu Cancer Center, Fukuoka, Japan; ¹⁴Medical University of Gdańsk, Gdańsk, Poland; ¹⁵Sarah Cannon Research Institute, London, UK; ¹⁶Aix Marseille University, Assistance Publique-Hôpitaux de Marseille, Marseille, France; ¹⁷Antwerp University Hospital, Antwerp, Belgium;

¹⁸Center for Integrated Oncology Köln-Bonn, University Hospital of Cologne, Cologne, Germany; ¹⁹Ignyta, Inc., San Diego, CA, USA;

²⁰Genentech, South San Francisco, CA, USA



Objective response rate (BICR assessment)

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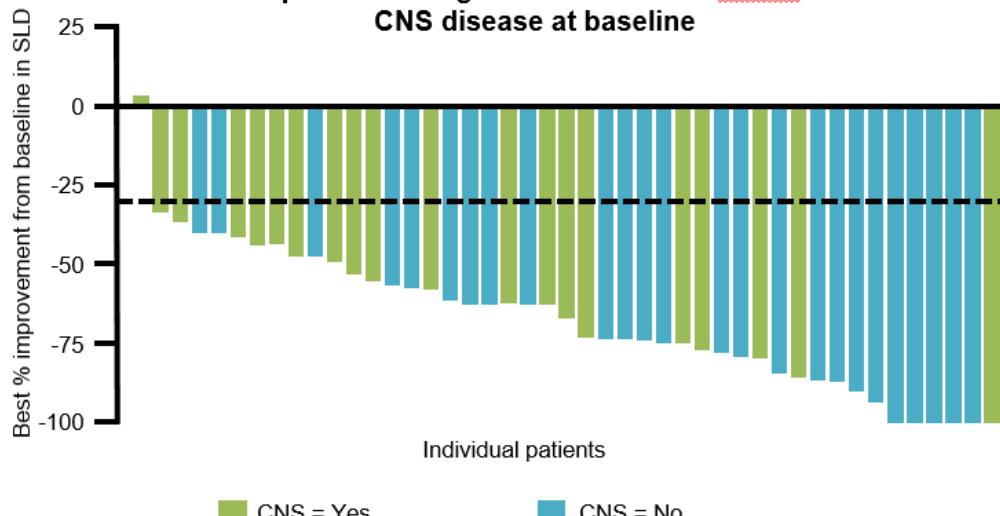
WCLC2018.IASLC.ORG

<http://bit.ly/2xw1EA7>

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Change in tumor size: *ROS1+* NSCLC population

Best percent change from baseline in tumor size CNS disease at baseline



Subjects with missing SLD percent change were excluded from plot

n (%)	Total (N=53)	CNS disease at baseline (n=23)	No CNS disease at baseline (n=30)
ORR (95% CI)	41 (77.4) (63.8, 87.7)	17 (73.9) (51.6, 89.8)	24 (80.0) (61.4, 92.3)
CR	3 (5.7)	0	3 (10.0)
PR	38 (71.7)	17 (73.9)	21 (70.0)
SD	1 (1.9)	0	1 (3.3)
PD	4 (7.5)	4 (17.4)	0
Non-CR/PD	3 (5.7)	0	3 (10.0)
Missing or unevaluable	4 (7.5)	2 (8.7)	2 (6.7)
Clinical benefit rate* (95% CI)	41 (77.4) (63.8, 87.7)		

*Includes SD for at least 6 months. Data cut-off date: May 31 2018 (median follow up: 15.5 months), ROS1-inhibitor-naïve patients with *ROS1+* NSCLC (integrated analysis population)



Overall survival

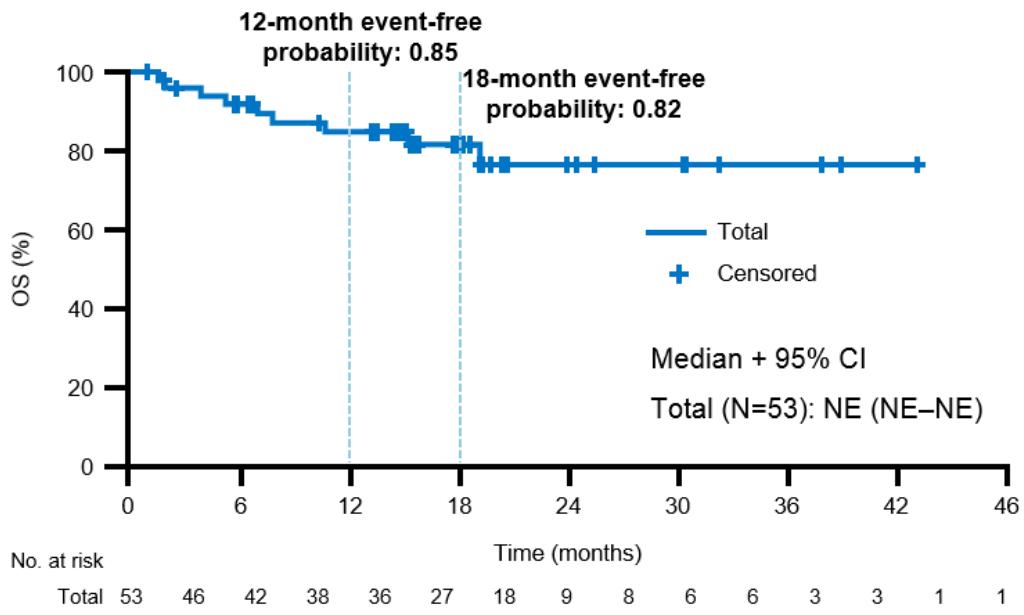
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<http://bit.ly/2xw1EA7>

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Overall survival, ROS1+ NSCLC



	Total (N=53)
Pts with event	9 (17.0%)
Death	9
Time to event	
Median	NE
95% CI	NE

**Median OS NE months
(95% CI NE, NE)**

**Median survival follow up:
15.5 months**

Data cut-off date: May 31 2018, ROS1-inhibitor-naïve patients with ROS1+ NSCLC (integrated analysis population)





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September 23–26, 2018 Toronto, Canada

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Phase II trial of poziotinib for EGFR and HER2 exon 20 mutant NSCLC

John V. Heymach, MV Negrao, JP Robichaux, BW Carter, A Patel, M Altan, DL Gibbons, F Fossella, G Simon, V Lam, G Blumenschein, AS Tsao, JM Kurie, F Mott, DM Jenkins, D Mack, L Feng, B Roeck, Z Yang, V Papadimitrakopoulou, YY Elamin

**University of Texas MD Anderson Cancer Center
Houston, Tx, USA**

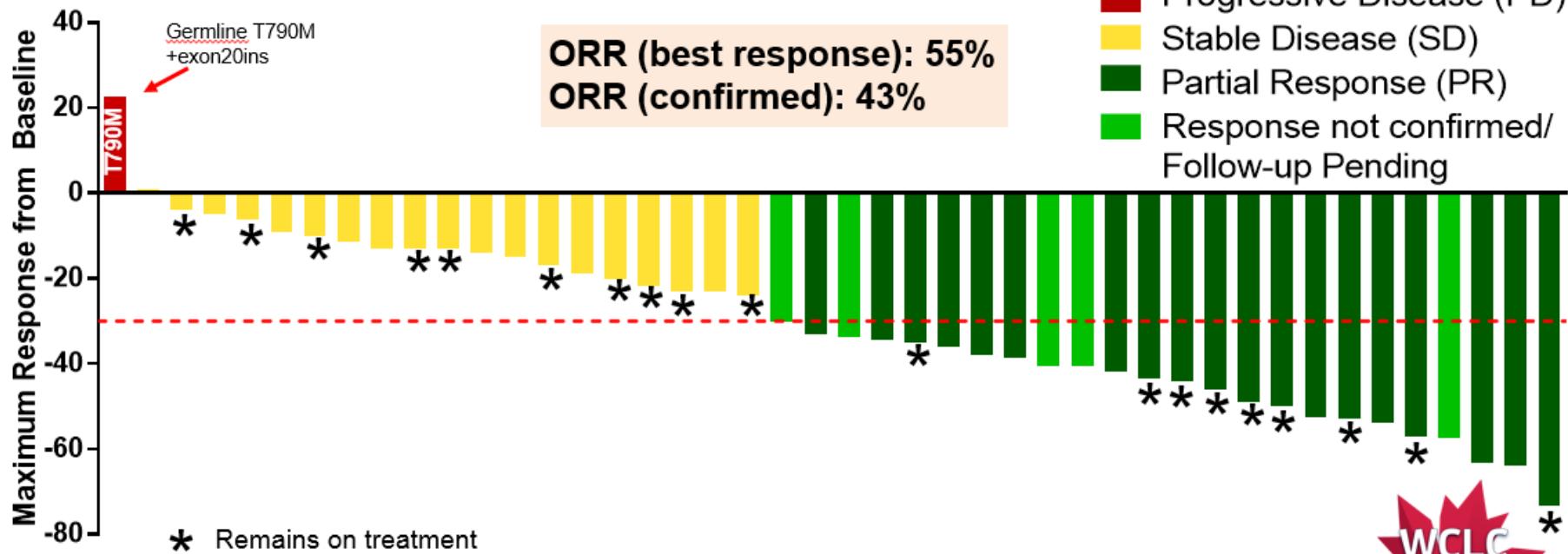
JV Heymach, University of Texas MD Anderson Cancer Center, USA





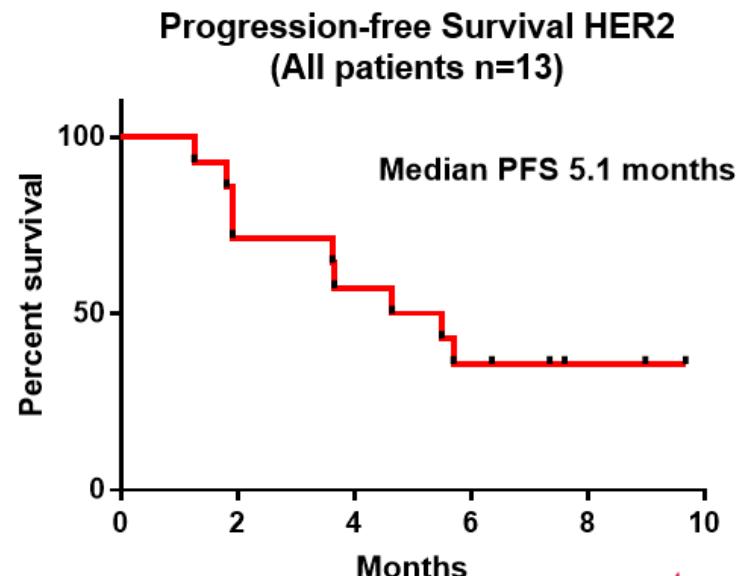
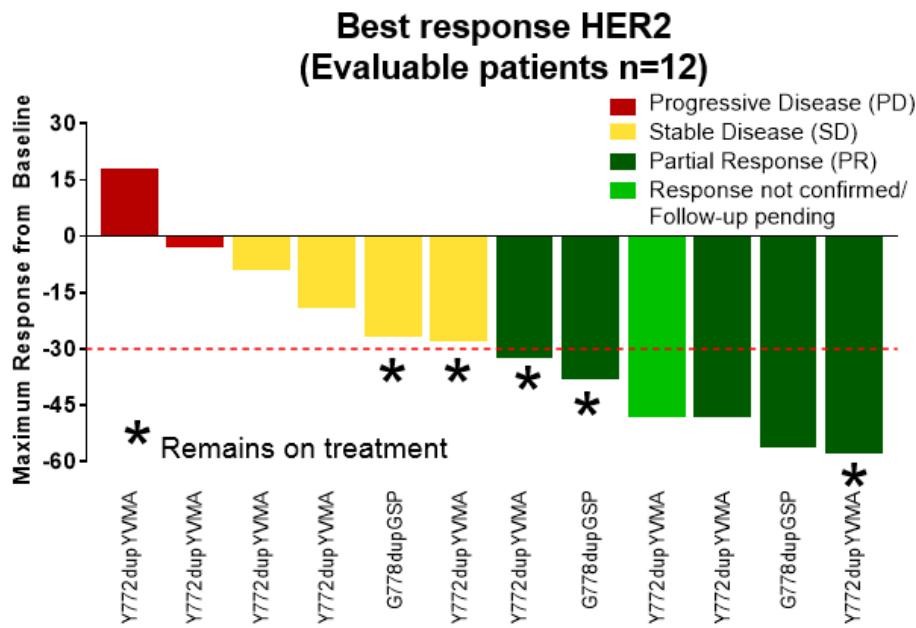
Poziotinib efficacy in EGFR Exon 20 mutant NSCLC

(Evaluable patients n=44)





Poziotinib efficacy in HER2 Exon 20 insertion mutant NSCLC



JV Heymach, University of Texas MD Anderson Cancer Center, USA





Clinical Activity of LOXO-292, a Highly Selective RET Inhibitor, in Patients with *RET* Fusion+ Non-Small Cell Lung Cancer

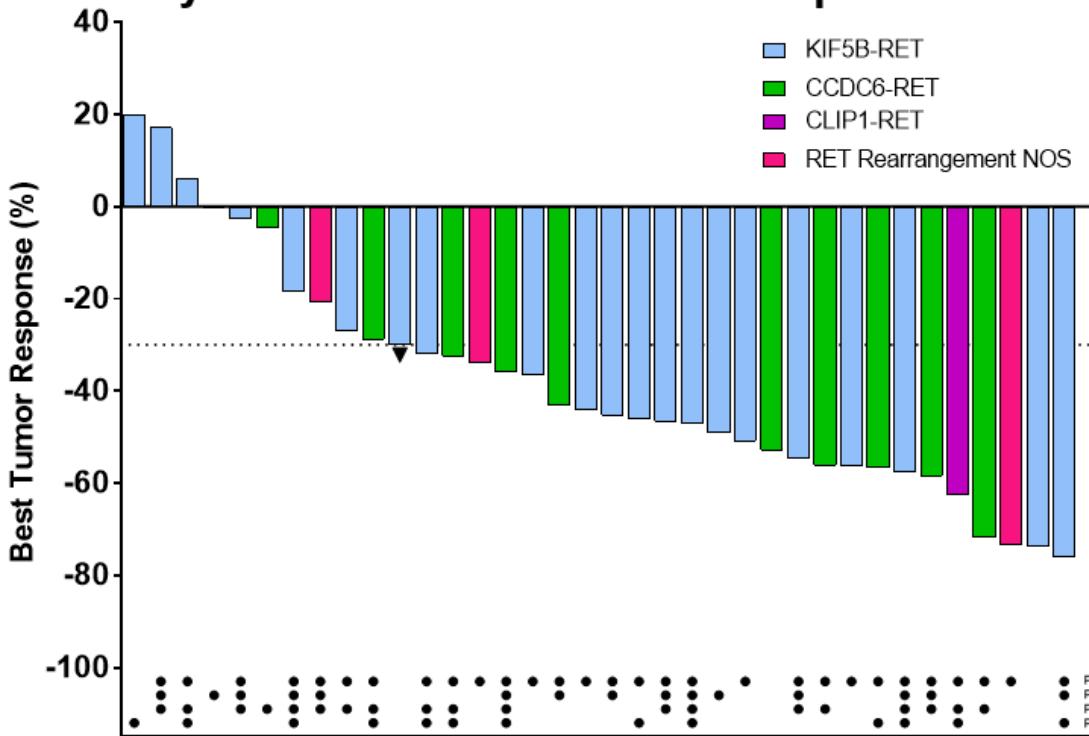
An Update from ASCO 2018

Geoffrey R. Oxnard, Vivek Subbiah, Keunchil Park, Todd M. Bauer, Lori J. Wirth, Vamsidhar Velcheti, Manisha Shah, Benjamin Besse, Valentina Boni, Karen L. Reckamp, Herbert H. F. Loong, Lyudmila Bazhenova, Ben Solomon, Daniel S. W. Tan, Jyoti D. Patel, Melissa L. Johnson, Anas Gazzah, Tony Mok, Steve Smith, Brian Tuch, Kevin Ebata, Edward Y. Zhu, Michele Nguyen, Xin Huang, Scott Cruickshank, S. Michael Rothenberg, and Alexander Drilon





Efficacy of LOXO-292 in *RET* fusion-positive NSCLC



RET fusion-positive NSCLC	
Enrolled	38
Eligible for response evaluation	38
Overall Response Rate (95% CI)	26/38 68% (51% - 83%)
Confirmed ORR*	25/37 68% (50% - 82%)
CR	-
PR**	26
SD	8
PD	2
NE	2

4/4 confirmed intracranial responses (1 CR, 3 PR) in patients with measurable (> 5 mm) intracranial lesions





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Phase II Data for the MET Inhibitor Tepotinib in Patients with Advanced NSCLC and *MET*exon14-Skipping Mutations

Enriqueta Felip¹, Hiroshi Sakai², Jyoti Patel³, Leora Horn⁴, Remi Veillon⁵,
Frank Griesinger⁶, Rolf Bruns⁷, Jürgen Scheele⁷, Paul K. Paik⁸

¹Vall d'Hebron University Hospital, Barcelona/Spain, ²Saitama Cancer Center, Saitama/Japan, ³University of Chicago,
Chicago, IL/United States of America, ⁴Vanderbilt-Ingram Cancer Center, Nashville, TN/United States of
America, ⁵Hôpital Haut-Lévêque, Pessac/France, ⁶Pius Hospital Oldenburg, Oldenburg/Germany, ⁷Merck KGaA,
Darmstadt/Germany, ⁸Memorial Sloan Kettering Cancer Center, New York, NY/United States of America

Dr Enriqueta Felip, Vall d'Hebron University Hospital, Spain

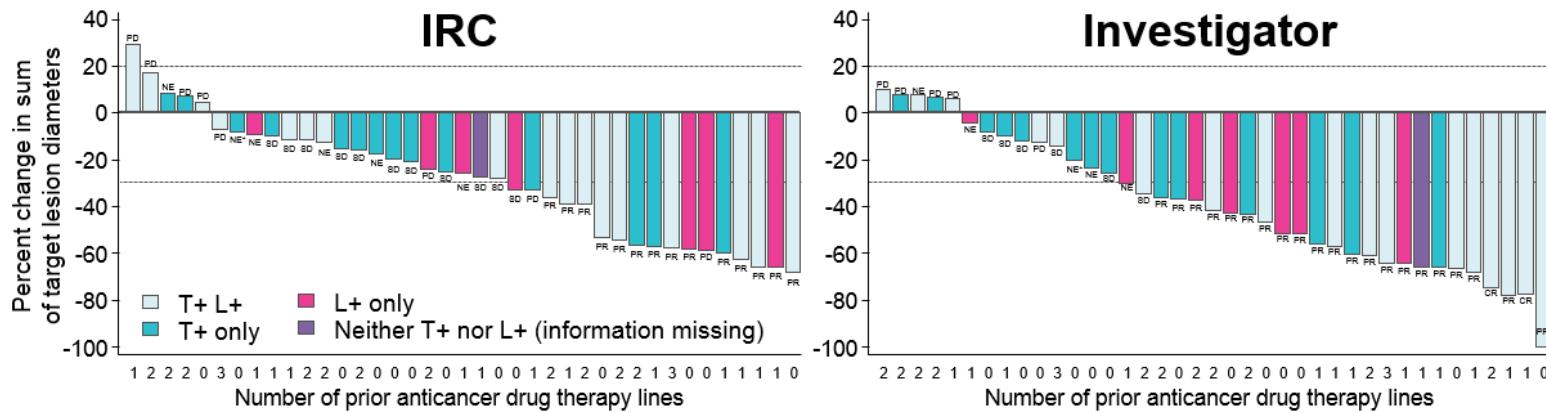
Abstract: 12896





Change in Sum of Target Lesion Diameter

Evidence of tumor shrinkage in 34 patients (87.2%) in both IRC and Investigator read

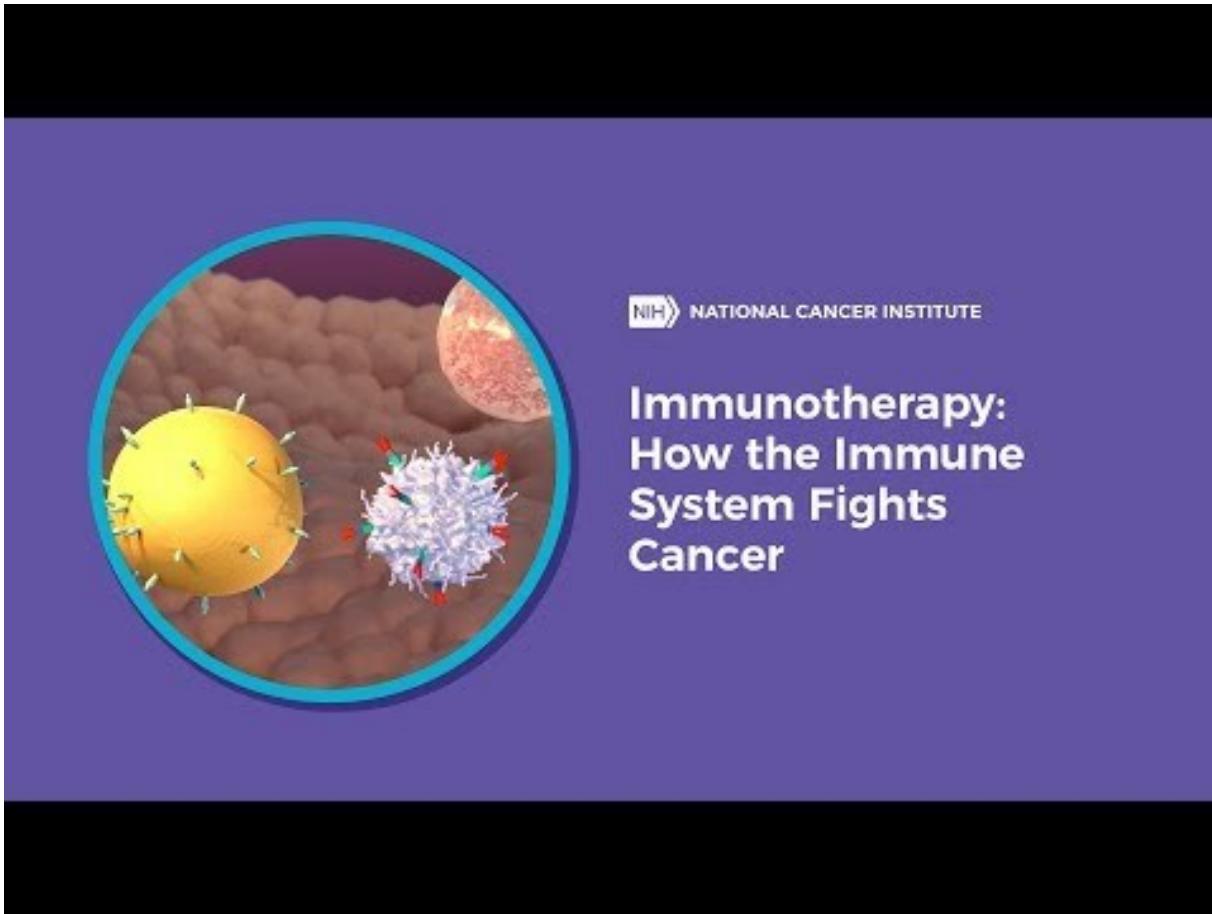


n=39. Seven patients were excluded due to baseline/on-treatment measurement not being available.

BOR displayed at the end of the bar. NE*, BOR non-evaluable where ongoing patient has not had 2 post-baseline tumor assessments.

BOR, best overall response; CR, complete response; IRC, independent review committee; L, liquid biopsy; NE, non-evaluable;

PD, progressive disease; PR, partial response; SD, stable disease; T, tumor biopsy.



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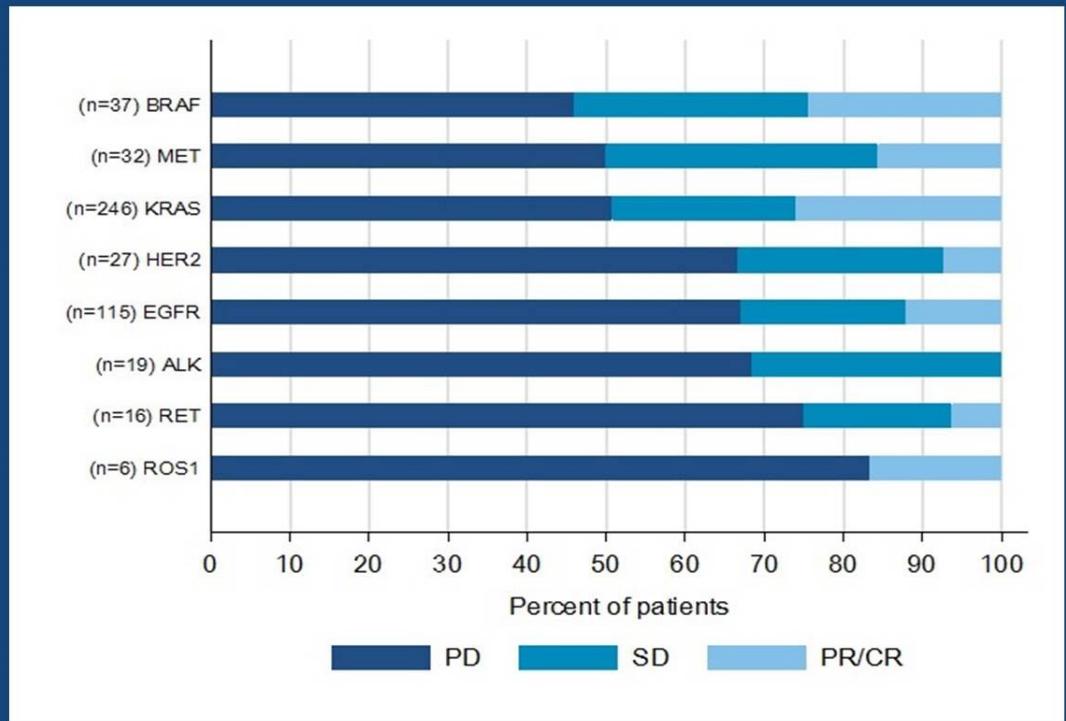
Efficacy of immune-checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC) patients harboring activating molecular alterations (ImmunoTarget).

Julien MAZIERES, Alexander DRILON, Laurent MHANNA, Julie MILIA, Amelie LUSQUE, Alexis CORTOT, Laura MEZQUITA, Alesha THAI, Sébastien COURAUD, Remi VEILLON, Celine MASCAUX, Robert SCHOUTEN, Joel NEAL, Terry NG, Martin FRUEH, Nir PELED, Valérie GOUNANT, Sanjay POPAT, Viola ZHU, Oliver GAUTSCHI, for the IMMUNOTARGET group.

Academic Funding: Toulouse University Hospital and Lucerne Cantonal Hospital

IMMUNOTARGET COHORT: Response

Driver	PD	SD	CR/PR
BRAF	46%	30%	24%
MET	50%	34%	16%
KRAS	51%	23%	26%
HER2	67%	26%	7%
EGFR	67%	21%	12%
ALK	68%	32%	0
RET	75%	19%	6%
ROS1	83%	0	17%
TOTAL	57%	24%	19%



PRESENTED AT: **2018 ASCO®**
ANNUAL MEETING

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PRESENTED BY: Julien MAZIERES

Presented By Julien Mazieres at 2018 ASCO Annual Meeting

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Conclusion

Driver	n	RR	PFS	OS	Impact (+/X) on PFS of				Comments
					PDL1	Smoking	Nb line	Subtype	
Total		19%	2.8	13.3					Outcome consistent with registration trials for ICI
KRAS	271	26%	3.2	13.5	+	X	X	X	Clear benefit across all subgroups
EGFR	125	12%	2.1	10	+	X	X	X	Could be considered in PDL1 + after TKIs exhaustion
BRAF	43	24%	3.1	13.6	X	+	X	NA	Could be considered in smokers
MET	36	16%	3.4	18.4	NA	X	NA	X	Could be considered after conventional treatment
HER2	29	7%	2.5	20.3	NA	+	X	NA	
ALK	23	0	2.5	17					
RET	16	6%	2.1	21.3	X	X	X	NA	Poor outcome. New biomarker needed.
ROS1	7	17%	-	-					

EGFR and IO

A Phase II Study of Pembrolizumab in EGFR-Mutant, PD-L1+, Tyrosine Kinase Inhibitor Naïve Patients With Advanced NSCLC

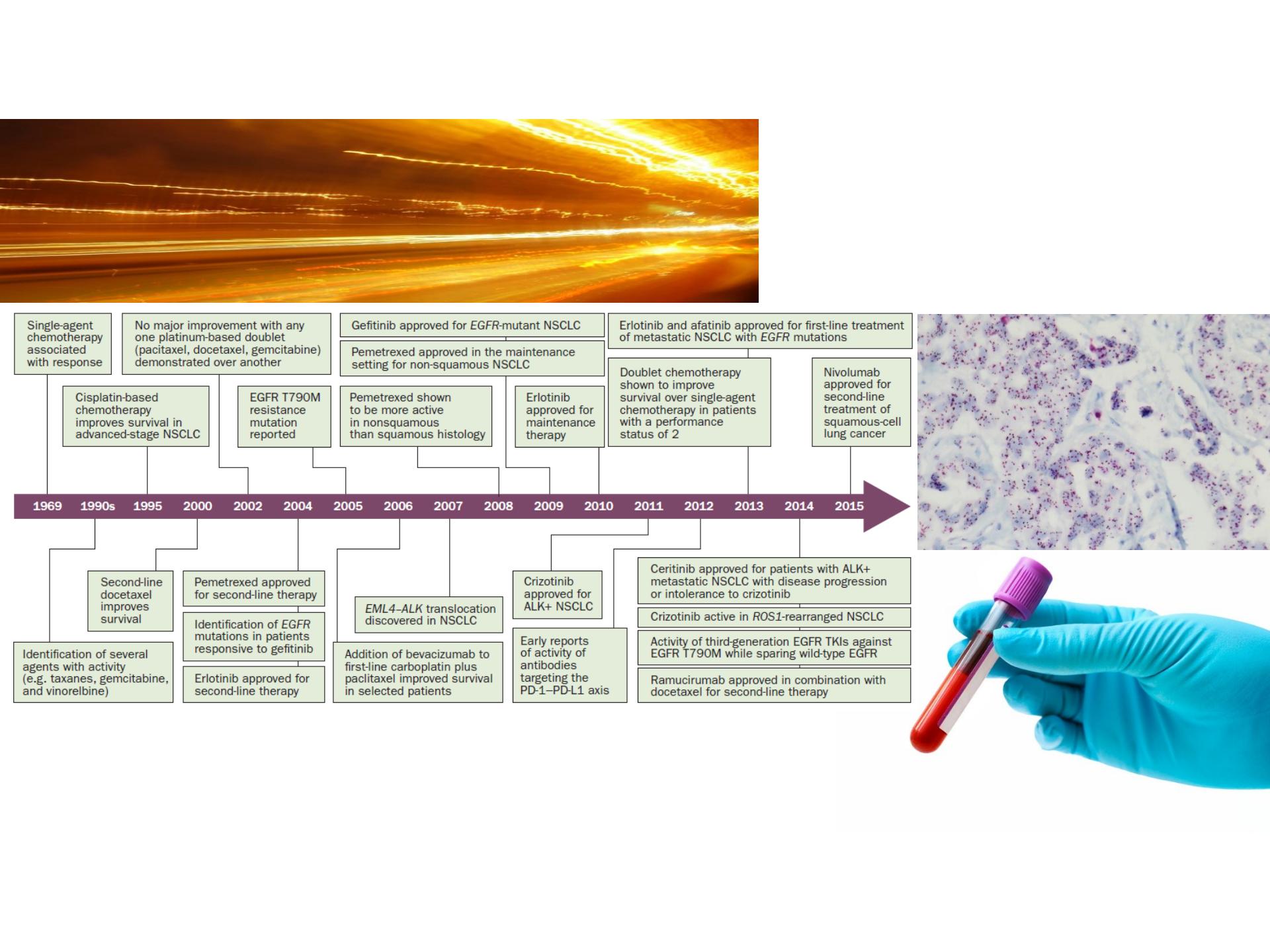
Table 1. Subject Characteristics by Patient

Age (y)	Sex	Race	Smoker	Histology	EGFR Mutation	PD-L1 (%)	trAE (Grade)	Best Response	Time on Trial (m)	Reason Off Trial	TKI After Trial	TKI-Related AE (Grade)
54	F	Asian	Never	ADC	L858R	5	Decreased TSH (1)	SD	3.2	PD	Y	Transaminitis (1, 3) Diarrhea (3)
61	F	White	Prior	ADC	E330K	95	Rash (1) Flu-like symptoms (1) Chills (1) Diarrhea (1, 2) Transaminitis (1-3)	SD	3.0	trAE	N	N/A
35	M	Asian	Never	SCC	Exon 20 ins	50	None	PD	2.0	PD	N	N/A
56	M	Asian	Prior	ADC	Exon 19 del	55	None	SD	4.0	PD	Y	Rash (2)
71	F	Asian	Never	ADC	L858R	10	Rash (1, 1) Fatigue (2) Adrenal insufficiency (2)	SD	4.0	PD	Y	Rash (2)
61	M	White	Prior	ADC	Exon 19 del	30	None	SD	4.0	PD	Y	Rash (1)
67	M	Asian	Active	ADC	None ^a	80	Rash (1) Flu-like symptoms (1)	PR	8.2	OT	N/A	N/A
52	F	White	Never	ADC	Exon 19 del	90	Diarrhea (1)	N/A ^b	1.4	trAE	Y	Pneumonitis (5), Diarrhea (2)
61	F	White	Never	ADC	L858R	55	None	SD	4.1	PD	Y	Rash (1)
65	F	White	Never	ADC	Exon 20 ins	70	None	PD	1.9	PD	Y	None
63	F	White	Prior	ADC	L858R	80	Rash (1)	SD	2.1	OT	N/A	N/A

^aSubject found not to have EGFR mutation.

^bSubject only received 1 dose of study treatment.

ADC, adenocarcinoma; AE, adverse event; del, deletion; F, female; inc, increased; ins, insertion; M, male; N, no; N/A, not applicable; OT, continues on trial; PD, progressive disease; SCC, squamous cell carcinoma; SD, stable disease; TKI, tyrosine kinase inhibitor; trAE, treatment-related AE; TSH, thyroid stimulating hormone; Y, yes; PR, partial response; PD-L1, programmed death ligand 1.



MECHANISMS OF ACQUIRED RESISTANCE TO FIRST-LINE OSIMERTINIB: PRELIMINARY DATA FROM THE PHASE III FLAURA STUDY

Suresh S Ramalingam¹, Ying Cheng², Caicun Zhou³, Yuichiro Ohe⁴, Fumio Imamura⁵, Byoung Chul Cho⁶, Meng-Chih Lin⁷, Margarita Majem⁸, Riyaz Shah⁹, Yuri Rukazenkov¹⁰, Alexander Todd¹¹, Aleksandra Markovets¹², Carl Barrett¹², Juliann Chmielecki¹³, Jhanelle E Gray¹⁴

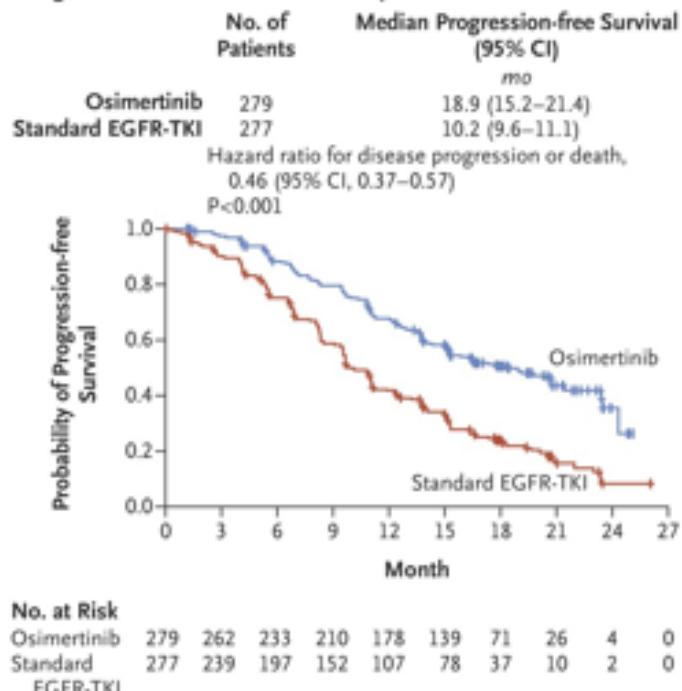
¹Winship Cancer Institute, Emory University, Atlanta, GA, USA; ²Jilin Provincial Cancer Hospital, Changchun, China; ³Department of Oncology, Pulmonary Hospital of Tongji University, Shanghai, China; ⁴Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; ⁵Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan; ⁶Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; ⁷Division of Pulmonary and Critical Care Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; ⁸Medical Oncology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; ⁹Kent Oncology Centre, Maidstone Hospital, Maidstone and Tunbridge Wells NHS Trust, Maidstone, UK; ¹⁰Global Medicines Development, GMED Oncology, AstraZeneca, Cambridge, UK; ¹¹Biometrics and Information Sciences, AstraZeneca, Cambridge, UK; ¹²Oncology Bioscience, IMED Biotech Unit, AstraZeneca, Boston, MA, USA; ¹³Translational Sciences, IMED Biotech Unit, AstraZeneca, Waltham, MA, USA; ¹⁴Department of Thoracic Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA.

Study funded by AstraZeneca, the manufacturer of osimertinib

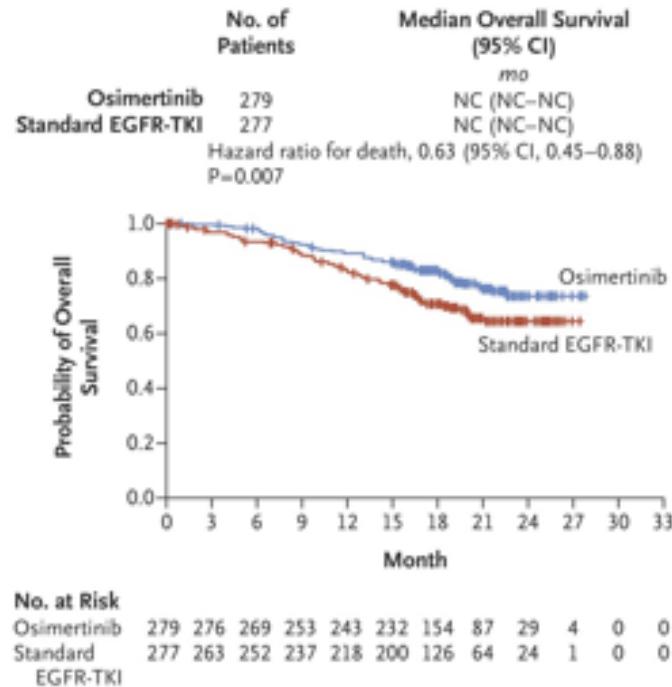
esmo.org

Improved PFS with osimertinib first line

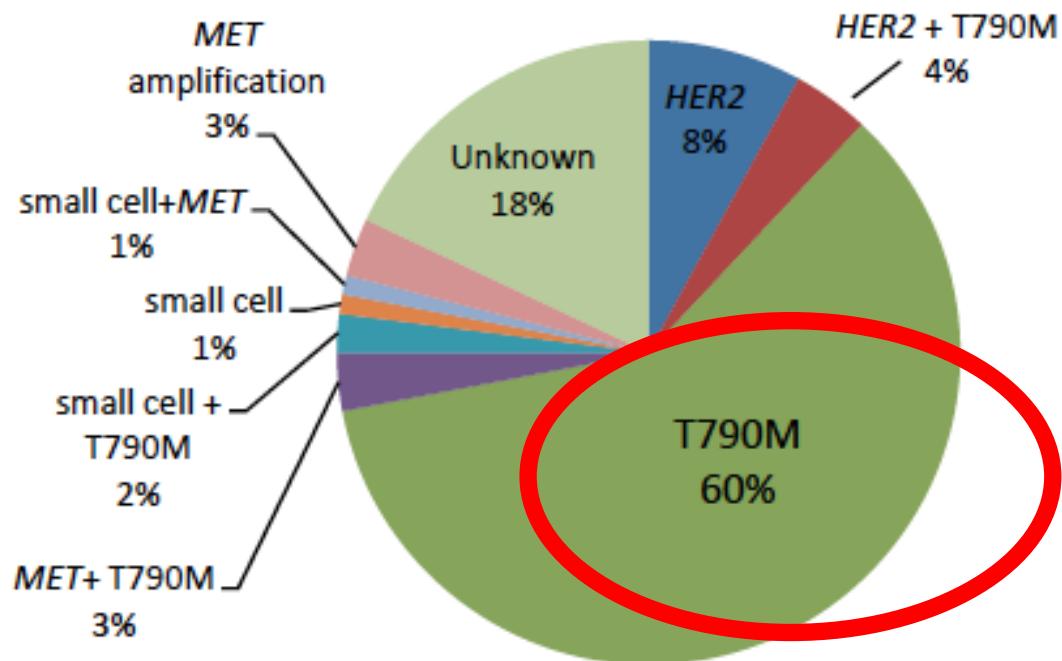
A Progression-free Survival in Full Analysis Set



D Overall Survival

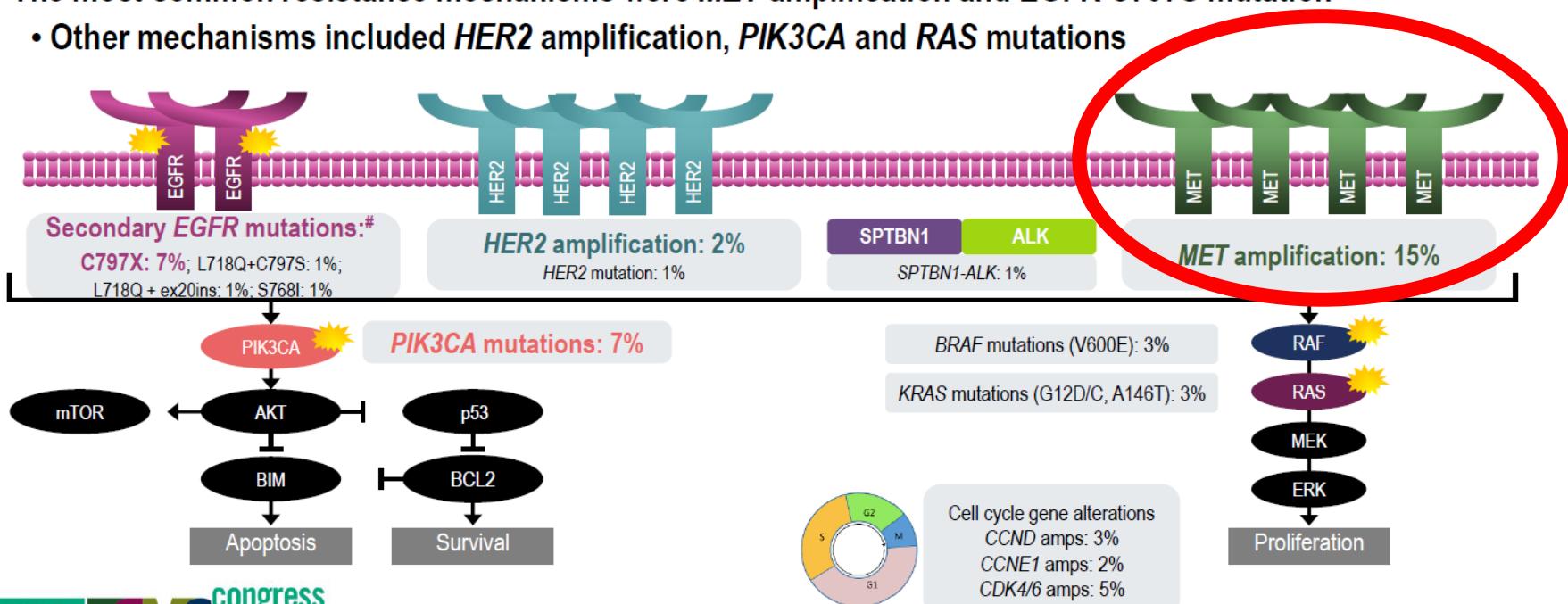


Resistance 1st/2nd generation EGFR-TKI



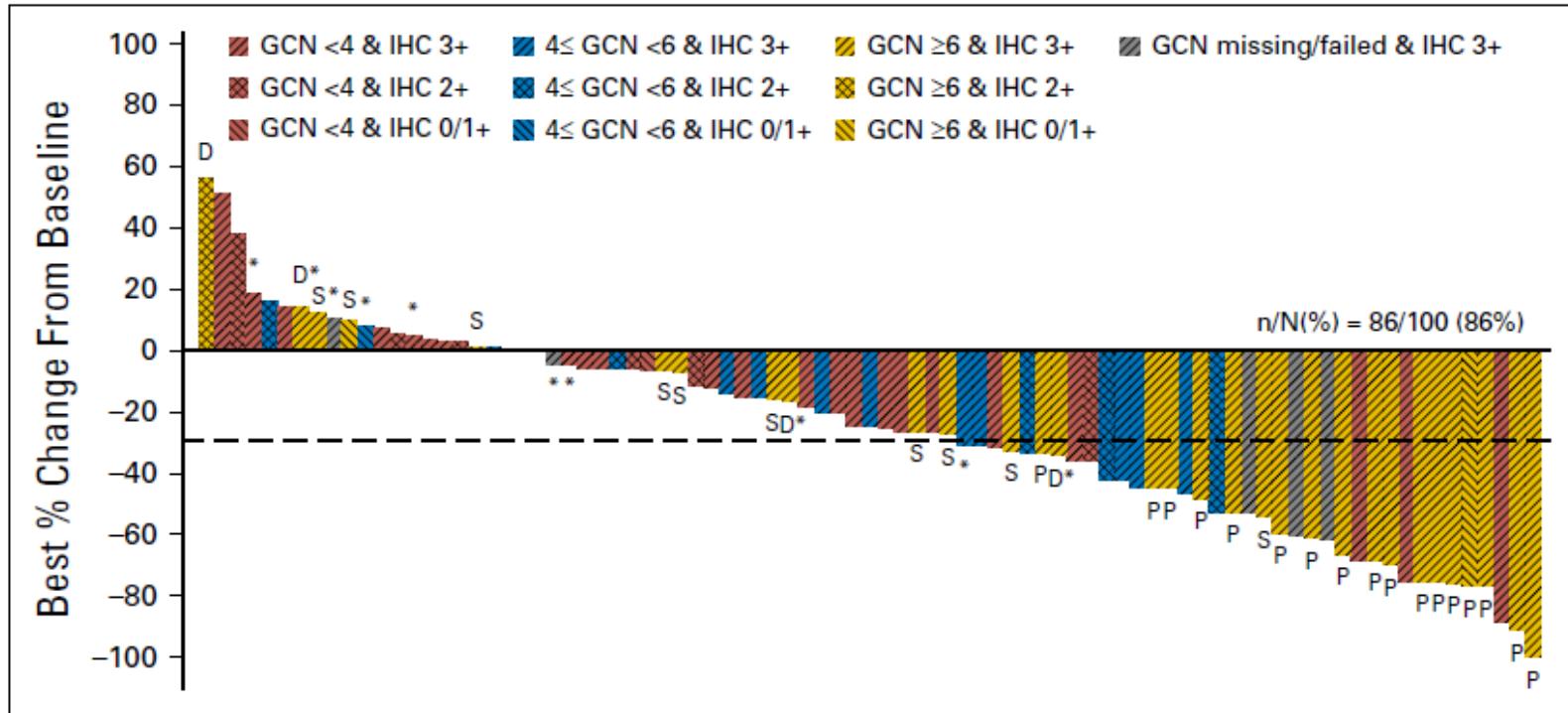
RESULTS: CANDIDATE ACQUIRED RESISTANCE MECHANISMS WITH OSIMERTINIB (n=91)*

- No evidence of acquired EGFR T790M
- The most common resistance mechanisms were *MET* amplification and *EGFR C797S* mutation
 - Other mechanisms included *HER2* amplification, *PIK3CA* and *RAS* mutations



*Resistance mechanism reported may overlap with another; #Two patients had *de novo* T790M mutations at baseline of whom one acquired C797S at progression

Capmatinib + gefitinib



Wu, JCO 2018



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Activity of osimertinib and the selective RET inhibitor BLU-667 in an EGFR-mutant patient with acquired RET rearrangement.

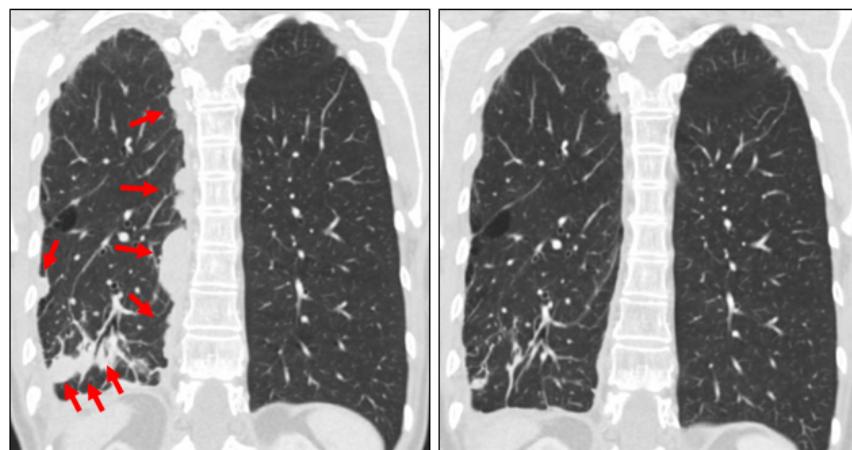
Z Piotrowska¹, H Isozaki¹, JK Lennerz¹, S Digumarthy¹, JF Gainor¹, N Marcoux¹, M Banwait¹, D Dias-Santagata¹, AJ Iafrate¹, M Mino-Kenudson¹, R Nagy², RB Lanman², E Evans³, C Clifford³, B Wolf³, AN Hata¹, LV Sequist¹.

1. Massachusetts General Hospital, Boston, MA
2. Guardant Health, Redwood City, CA
3. Blueprint Medicines Corporation, Cambridge, MA.

Response to Osimertinib (osi) + BLU-667 in the Clinic

- 60yo F with EGFR del19 NSCLC received afatinib x 1 year, then osi for T790M x 18 mos.
 - Post-osi biopsy (MGH NGS/Rearrangement Panel)- *CCDC6-RET* fusion, T790M “lost”
 - Treated with Osimertinib + BLU-667 on single-patient IND protocol.
 - Osimertinib 80mg QD
 - BLU-667 200mg QD x 2 weeks, then 300 mg QD
 - To date, the safety profile of Osi/BLU-667 includes only grade 1 AE’s, including:
 - Fatigue, leukopenia, high BP, dry mouth, AST/ALT elevation
 - Treatment with Osi/BLU-667 is ongoing.

RECIST 1.1 Partial Response (-78%)*



Baseline

8 weeks

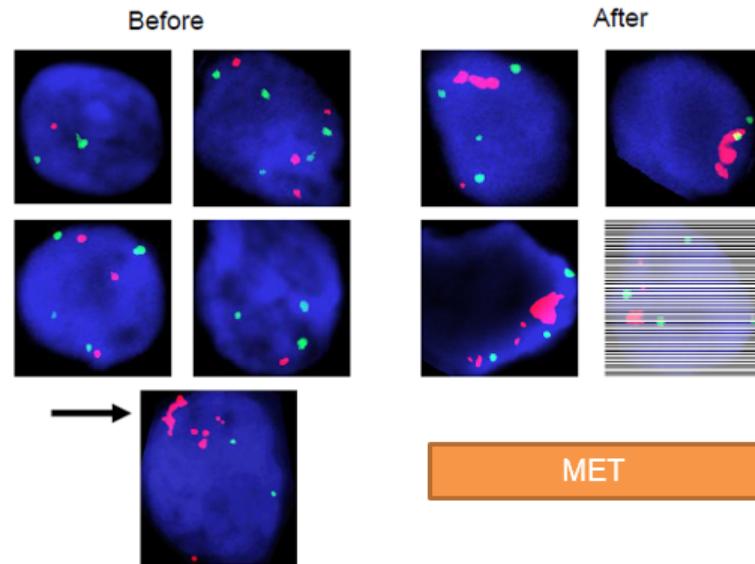
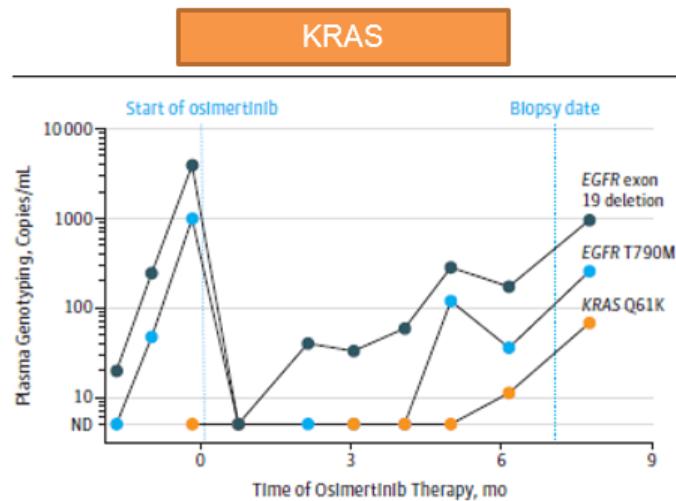
**PR Pending confirmation*



EGFR and resistance



What do we know about post Osi resistance



Take home messages WCLC en ESMO 2018

- Significante 5 jaars overleving met gericht therapie!
- Test uitgebreid! En wacht test uitslag af
- Resistent op 1^e / 2^e EGFR TKI
 - T790M positief: osimertinib
 - T790M negatief: aanvullende diagnostiek met HER2 IHC en MET FISH.
- Immunotherapie in combinatie met chemotherapie en alleen als TKI geen alternatief is

Patients with driver mutations

Goal: 5 yr OS with Good QoL!

