Other Oncogenic Drivers (BRAF, MET, RET, HER2, NTRK)

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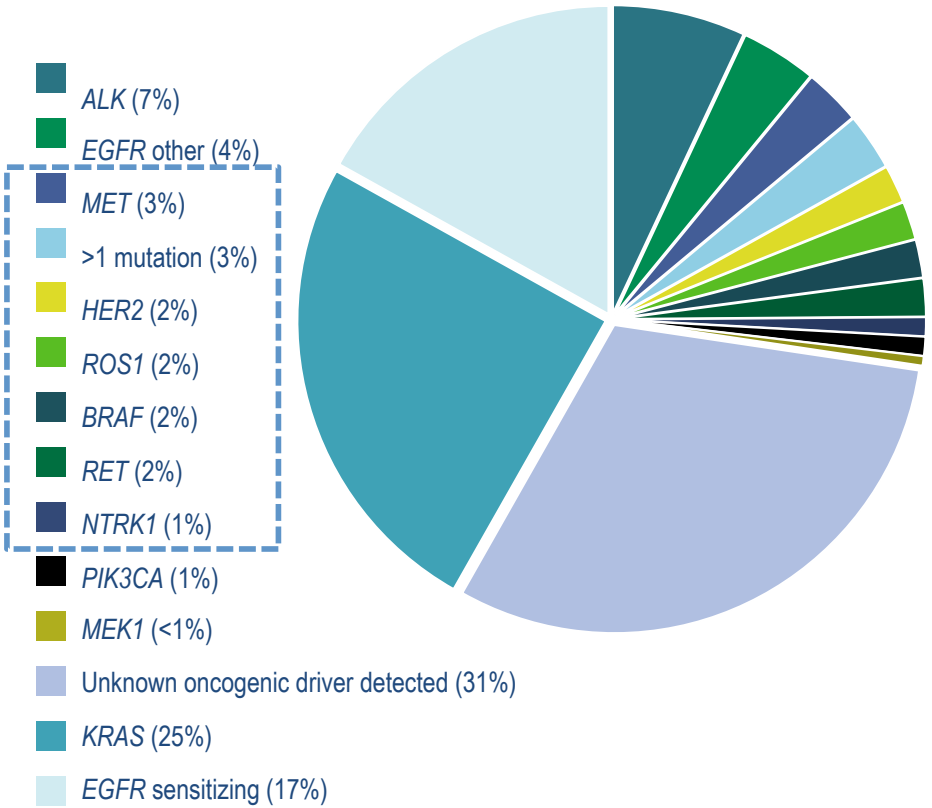
Disclosure Slide

- **Honoraria:** AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, MSD Oncology, Novartis, Pfizer, prIME Oncology, Roche
- **Consulting, advisory role or lectures:** AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, MSD Oncology, Novartis, Pfizer, prIME Oncology, Roche
- **Travel, Accommodations, Expenses:** AstraZeneca, Roche, Novartis, prIME Oncology, Pfizer

Great advances have been made in lung cancer therapy: targeting of oncogenic drivers



PRESENTED AT: 2018 ASCO ANNUAL MEETING

***EGFR* sensitizing**
Gefitinib; Erlotinib; Afatinib; Osimertinib; Dacomitinib

ALK
Crizotinib; Alectinib; Ceritinib; Lorlatinib; Brigatinib

ROS1
Crizotinib; Cabozantinib; Ceritinib; Lorlatinib; Entrectinib; Ropotrectinib, DS-6051b

BRAF
Vemurafenib;Dabrafenib; Dabrafenib + Trametinib

MET
Crizotinib; Cabozantinib; Capmatinib; Savolitinib; Tepotinib; Merestinib; Glesatinib

HER2
Trastuzumab emtansine; Afatinib; Neratinib-temsirolimus; Dacomitinib; Poziotinib; XMT-1522; TAK-788; DS-8201a,

RET
Cabozantinib; Alectinib; Apatinib; Vandetanib; sunitinib; Ponatinib; Lenvatinib; BLU-667; LOXO-292

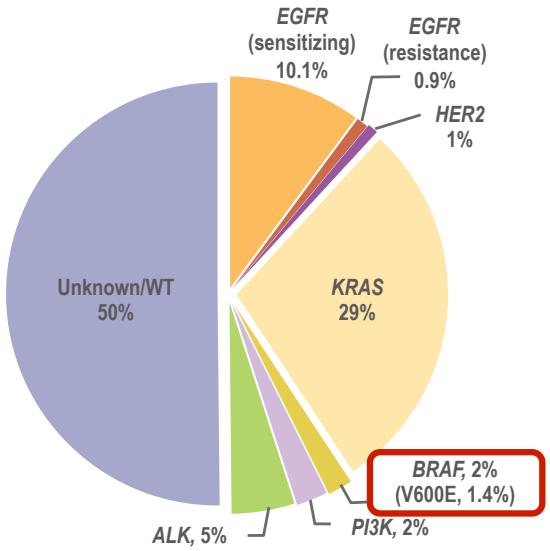
NTRK1
Entrectinib; LOXO-101 (larotrectinib); loxo-195; DS-6051b; ropotrectinib

PIK3CA
LY3023414; PQR 309

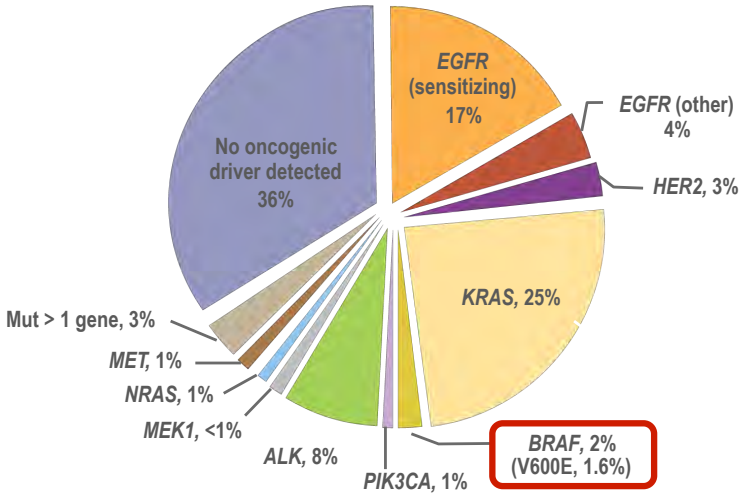
MEK1
Trametinib; Selumetinib;Cobimetinib

BRAF MUTATIONS IN NSCLC

France[1]
NSCLC
(Biomarkers France [IFCT]; N=17,664)



US[2]
Adenocarcinoma
(Lung Cancer Mutation Consortium; N=733)

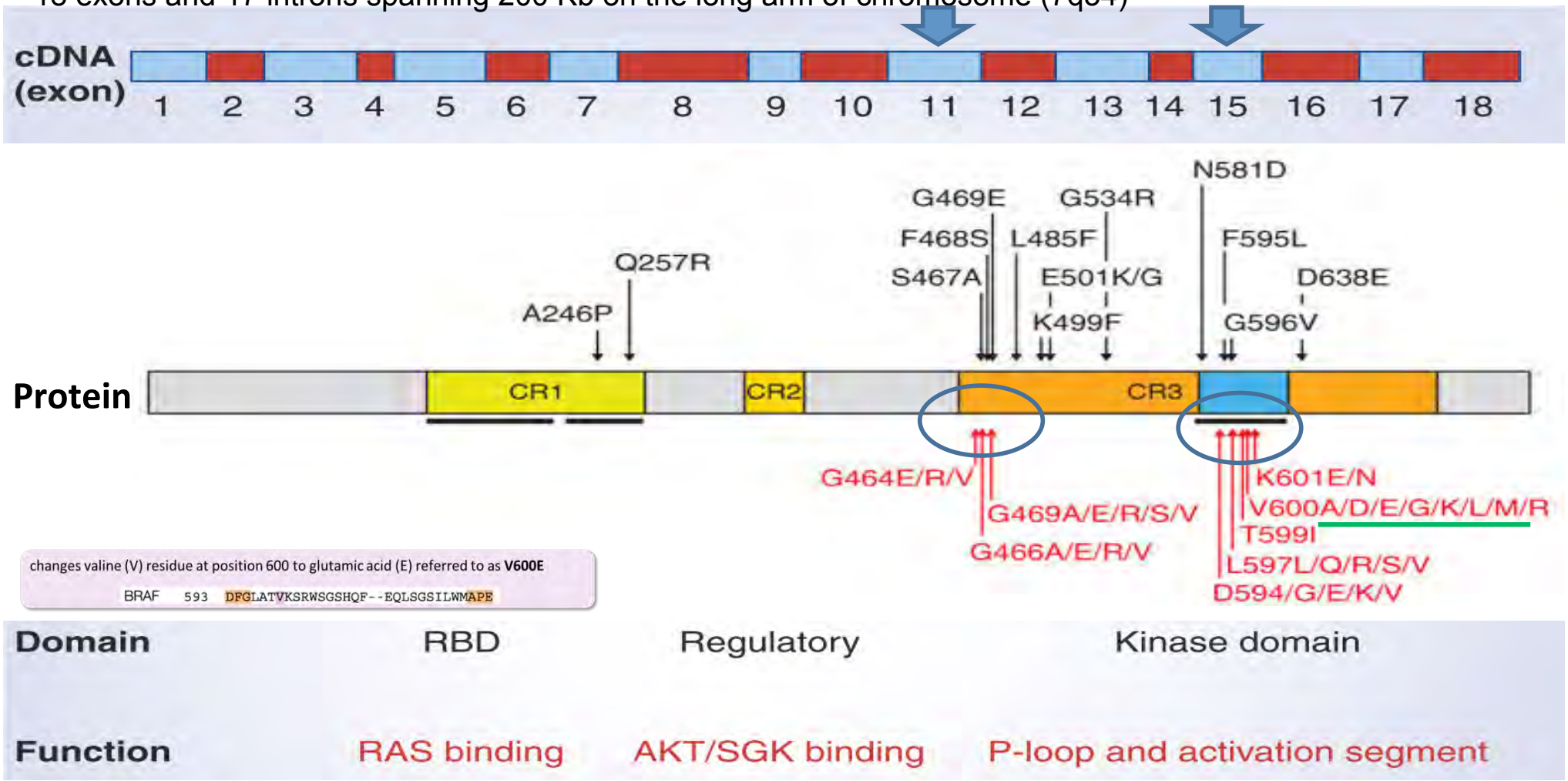


- NSCLC with *BRAF* V600E mutations has histological features suggestive of an aggressive tumor[3]
- Patients with *BRAF* V600E–mutant NSCLC demonstrated less-favorable outcomes with platinum-based chemotherapy[3,4]

1. Barlesi F *et al. Lancet* 2016;387:1415–1426; 2. Kris MG *et al. JAMA* 2014;311:1998–2006;
3. Marchetti A *et al. J Clin Oncol* 2011;29:3574–3579; 4. Cardarella S *et al. Clin Cancer Res* 2013;19:4532–4540

BRAF gene and protein structures with related biological aspects

18 exons and 17 introns spanning 200 Kb on the long arm of chromosome (7q34)



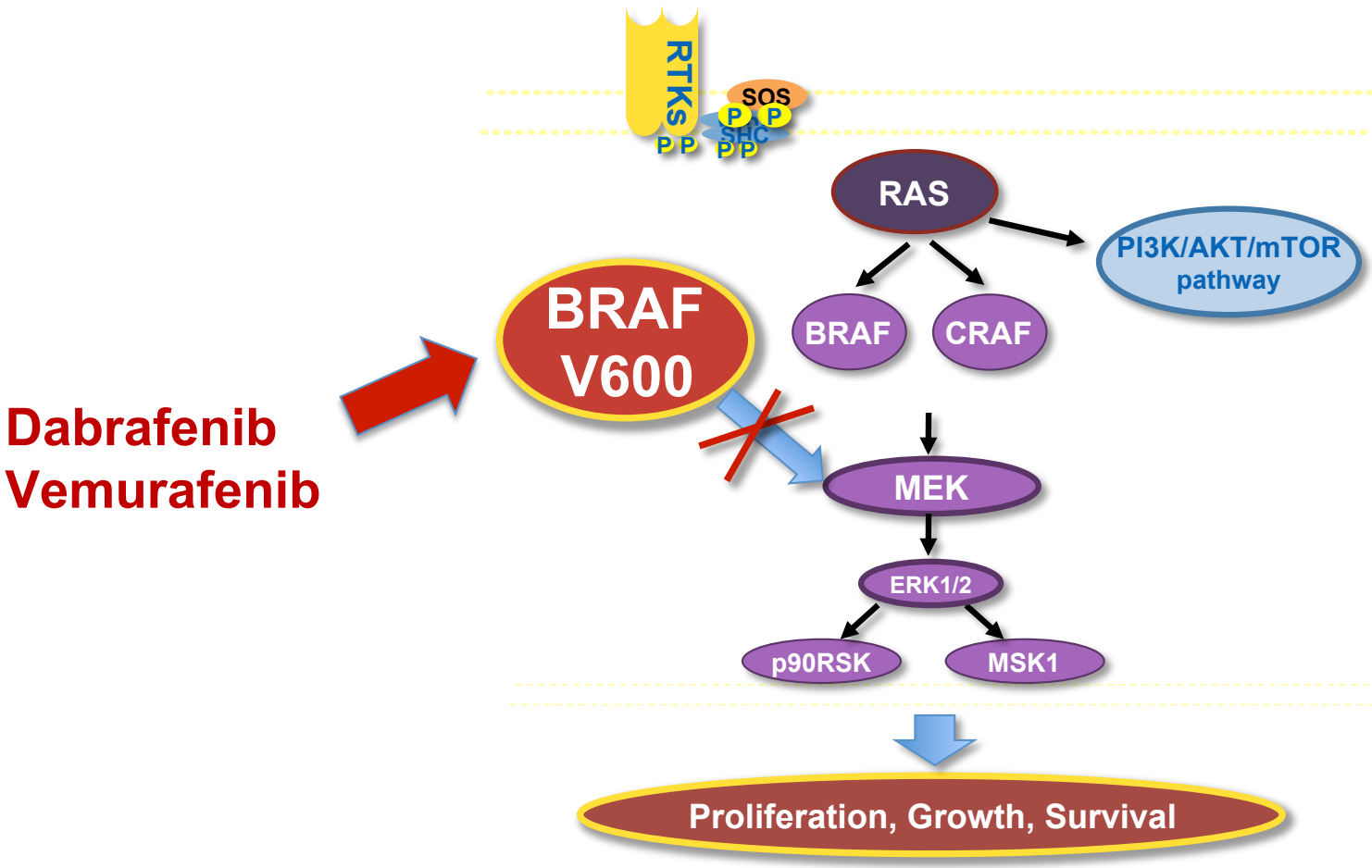
BRAF-ASSOCIATED PATIENT CHARACTERISTICS

	ALK[1–4]	*EGFR*[1,3,4,7]	*KRAS*[4,7]	*BRAF*[5–8]
Age	Younger (~50)	Older (~60)	Older (~60)	Older (~65)
Male or female	None	Female predominant	Female predominant	None
Smoker or non-smoker	Never or light	Never or light	Heavy	Smoker and non-smoker
Histology	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma
Pattern of spread	Pericardial,* pleural metastases,* liver,* intra- or extrathoracic lymph nodes,* CNS	Liver,* CNS	CNS	?

1. Shaw AT *et al. J Clin Oncol* 2009;27:4247–4253; 2. Wang Y *et al. PLoS One* 2014;9:e116017;
3. Tsao A *et al. J Thorac Oncol* 2006;1:231–239; 4. Doebele RC *et al. Cancer* 2012;118:4502–4511;
5. Kinno T *et al. Ann Oncol* 2014;25:138–142; 6. Cardarella S *et al. Clin Cancer Res* 2013;19:4532–4540;
7. Barlesi F *et al. Lancet* 2016;387:1415–1426; 8. Nguyen-Ngoc T *et al. J Thorac Oncol* 2015;10:1396–1403

*Compared with triple-negative, wild-type patients

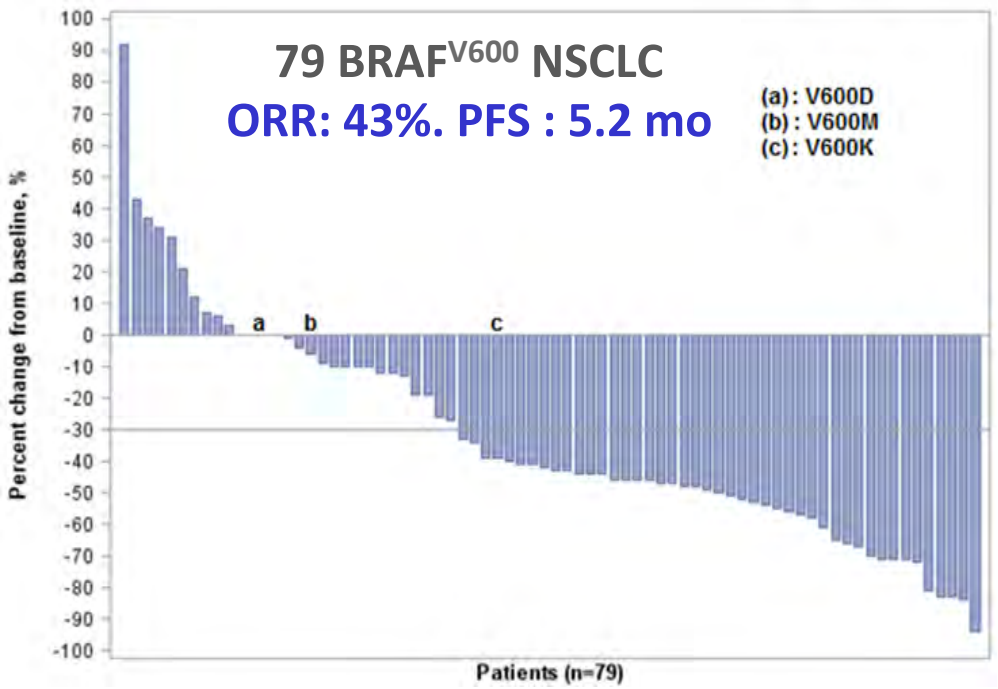
Inhibition of BRAF V600 Kinase



Vemurafenib in *BRAF* mutant NSCLC

AcSé trial

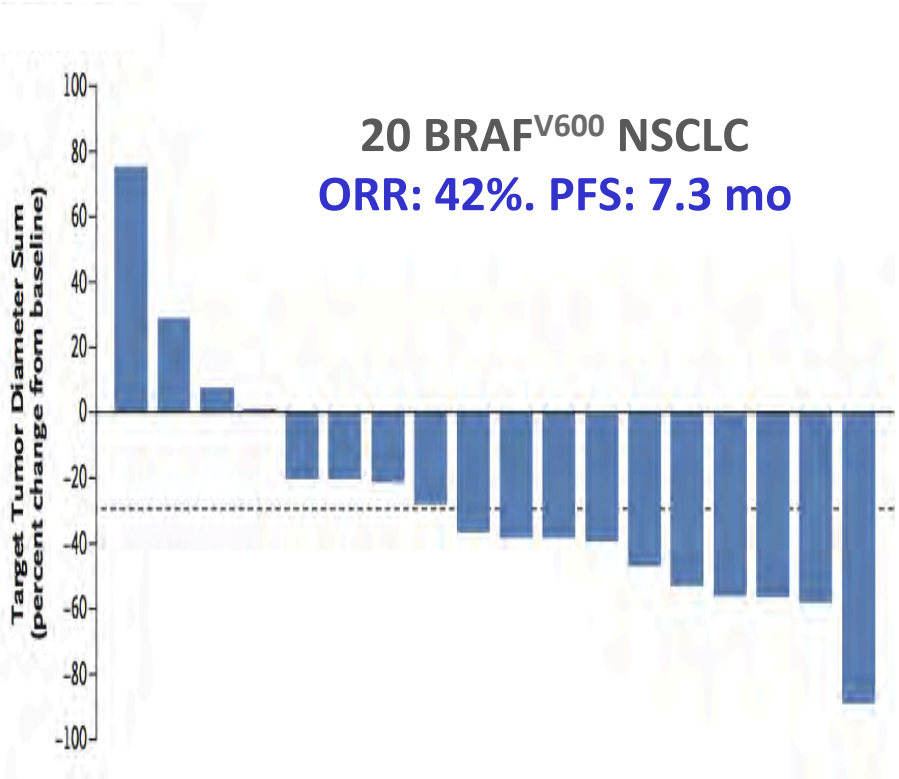
Vemurafenib



Mazières – WCLC 2018

VE-Basket trial

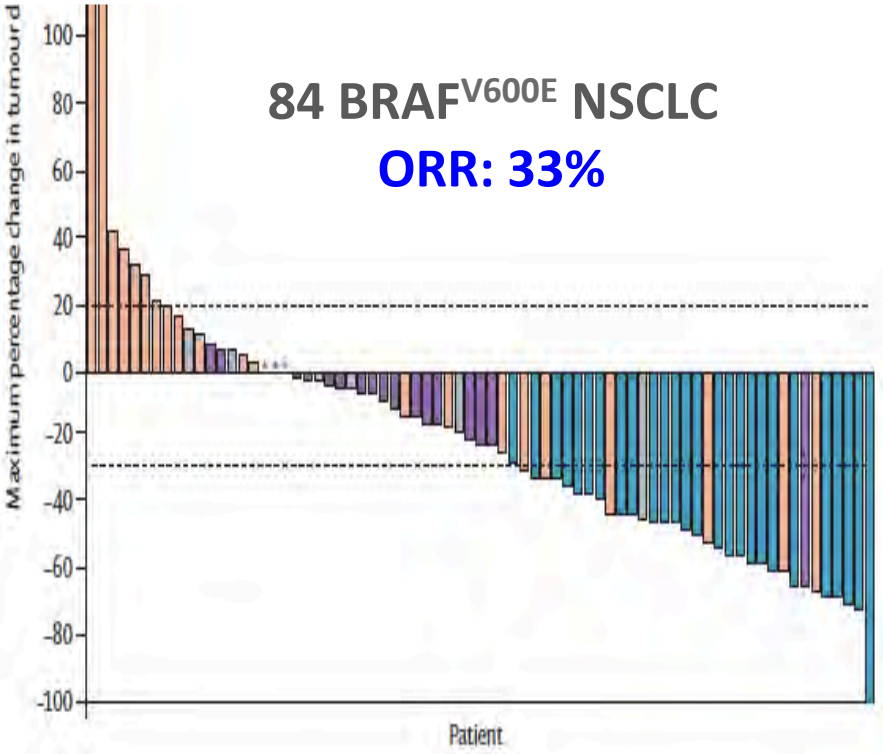
Vemurafenib



Hyman – NEJM 2015

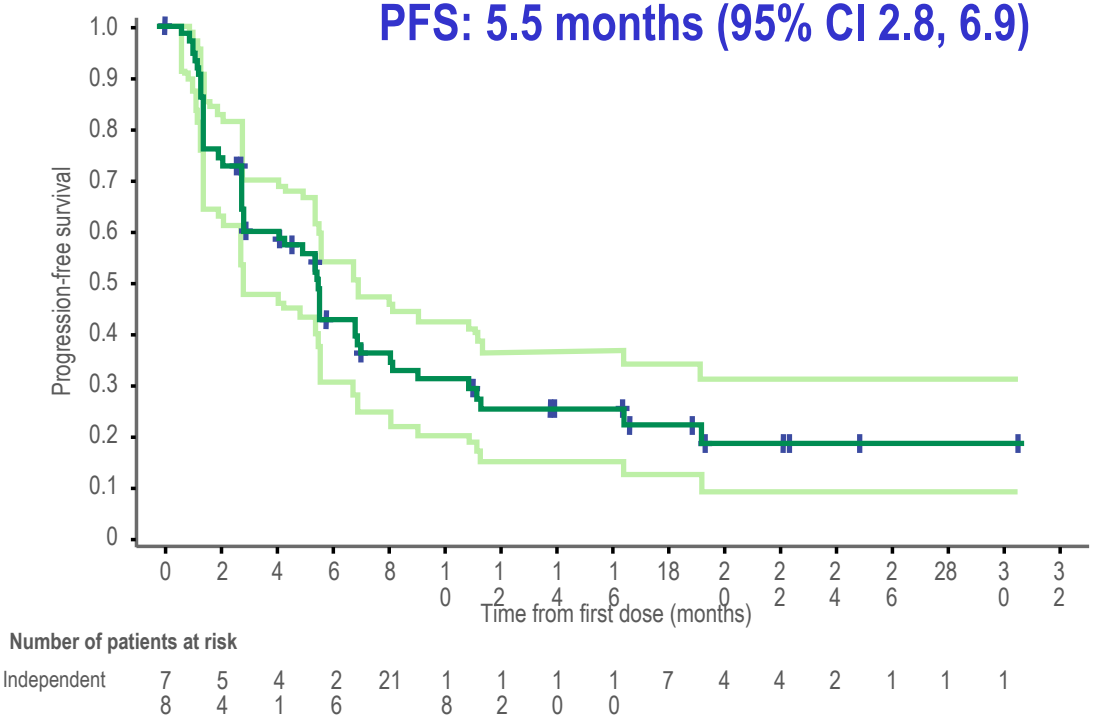
BRF113928 STUDY : DABRAFENIB IN BRAF MUTANT NSCLC IN 2ND LINE

Cohort A



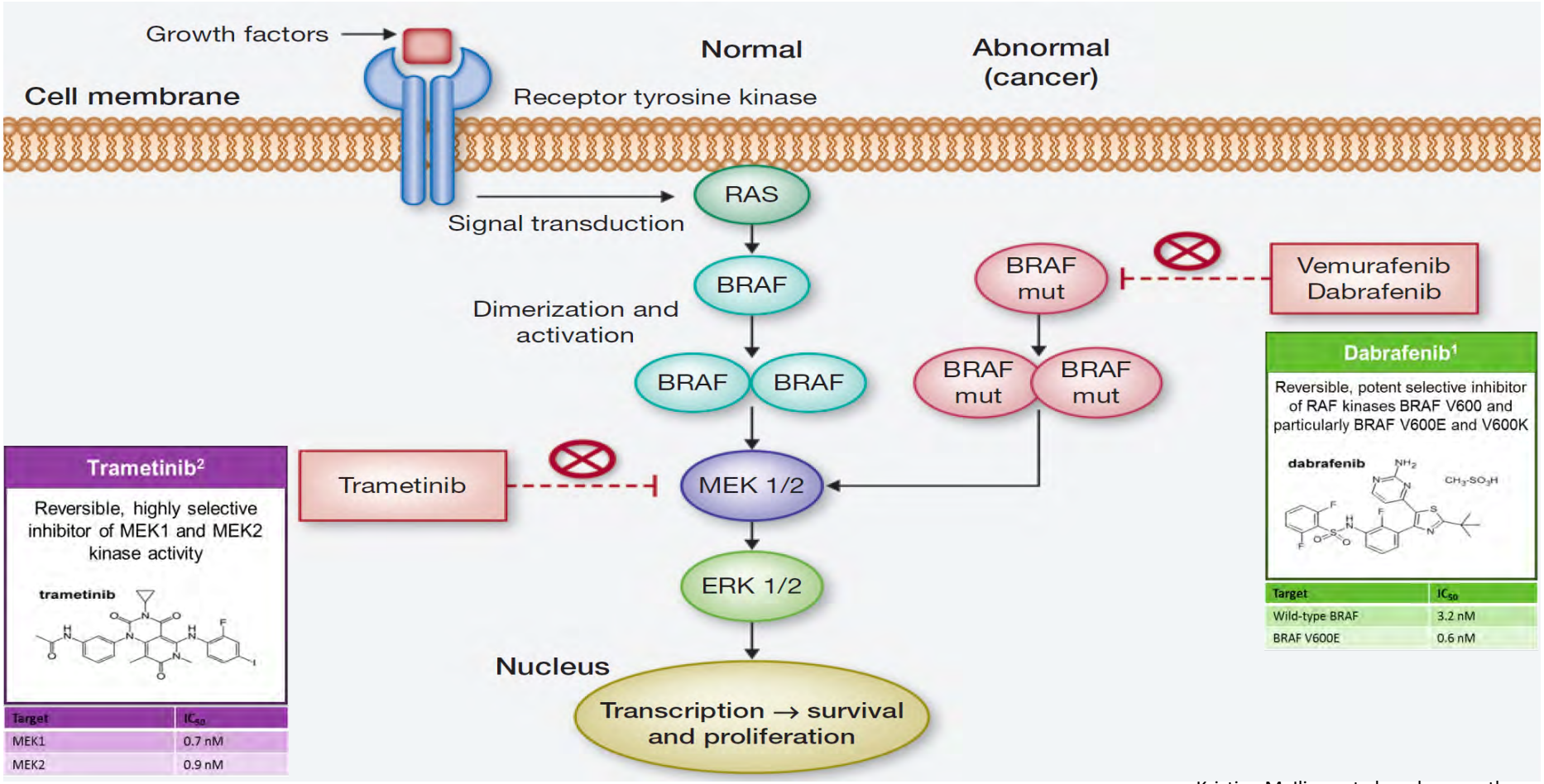
84 BRAF^{V600E} NSCLC

ORR: 33%



D. Planchard et al – lancet Oncol 2016

MECHANISM OF ACTION FOR DUAL MAPK PATHWAY INHIBITION WITH DABRAFENIB + TRAMETINIB TO OVERCOME *ERK* ESCAPE MECHANISM



Kristina M. Ilieva et al, mol cancer therapeutics

BRF113928 STUDY : MAXIMUM CHANGE IN TARGET LESION BY BEST CONFIRMED RESPONSE WITH DABRAFENIB + TRAMETINIB IN 2ND LINE

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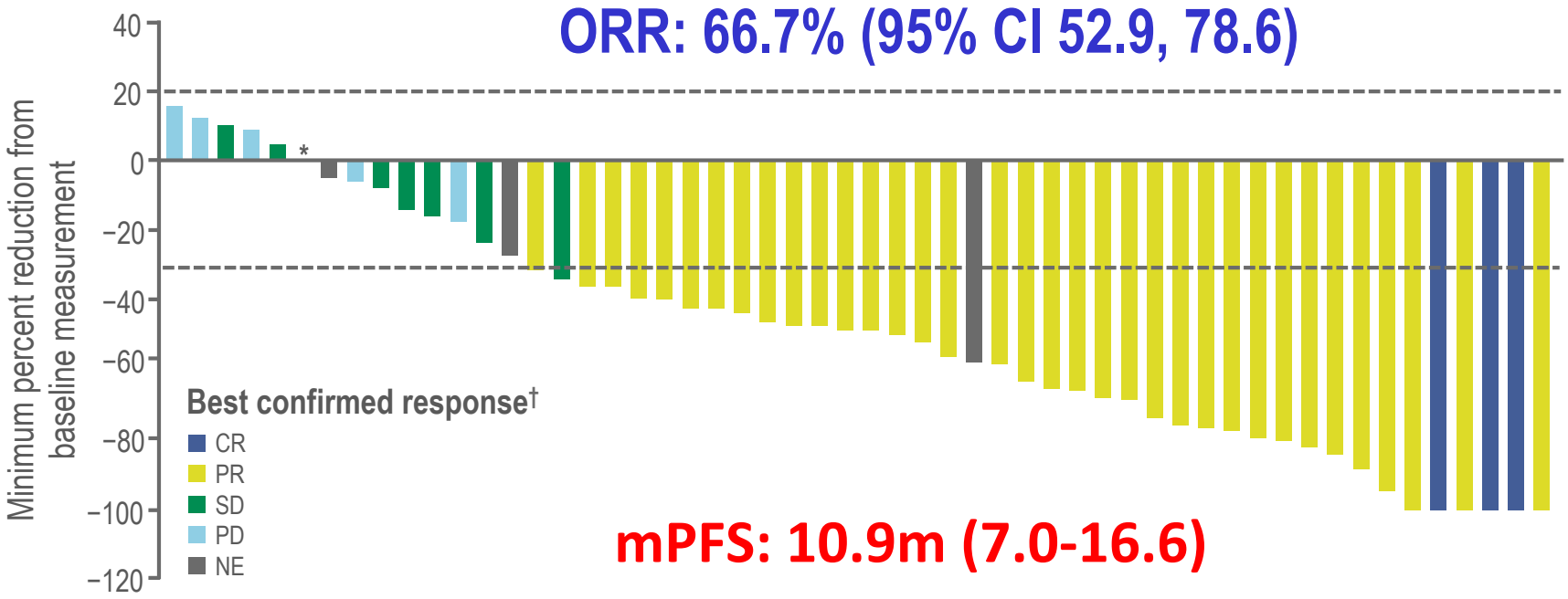
Cohort B



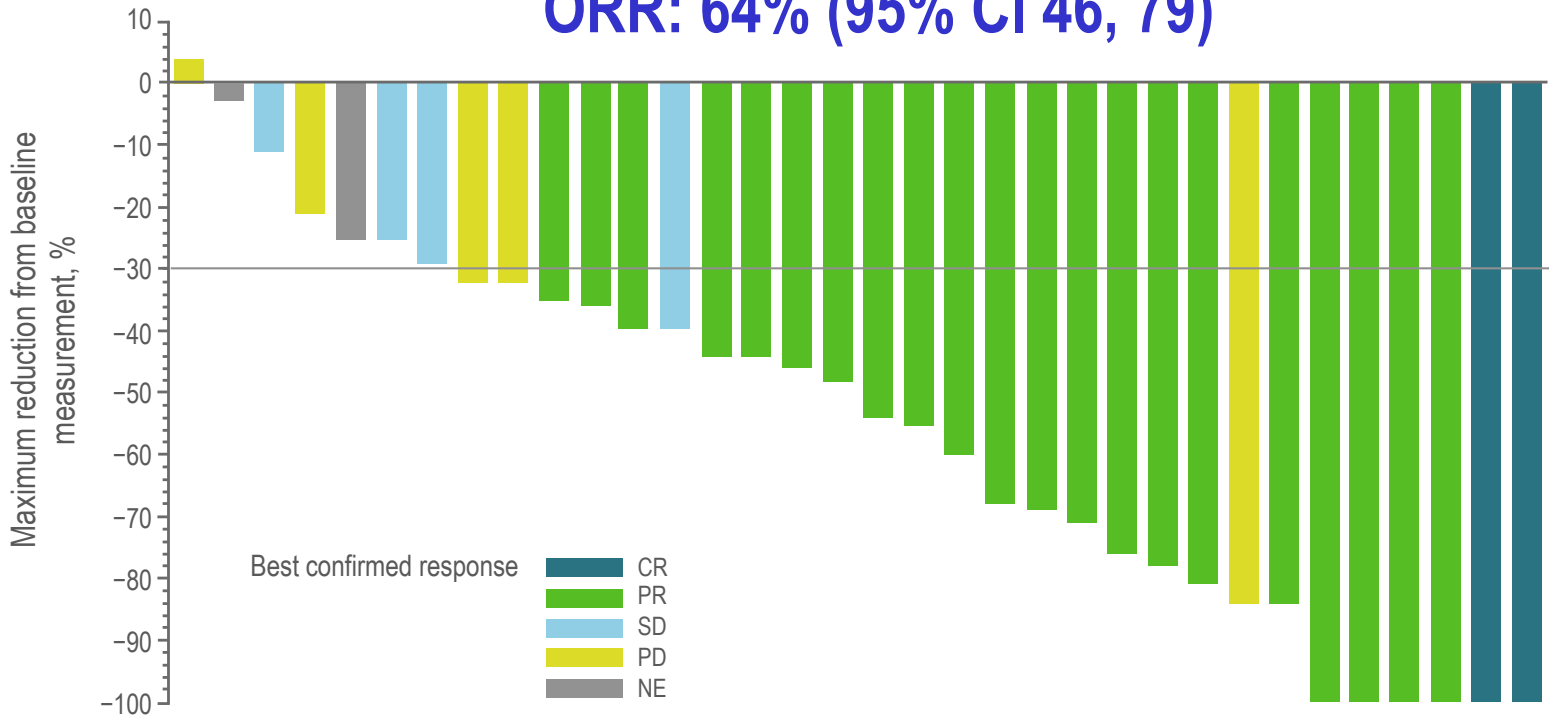
Planchard D *et al. Lancet Oncol* 2016;17:984–993;
Planchard D *et al. J Clin Oncol* 2017;35(Suppl):Abst 9075

BRF113928 STUDY : MAXIMUM CHANGE IN TARGET LESION BY BEST CONFIRMED RESPONSE WITH DABRAFENIB + TRAMETINIB IN 1ST LINE

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

Cohort C

ORR: 64% (95% CI 46, 79)



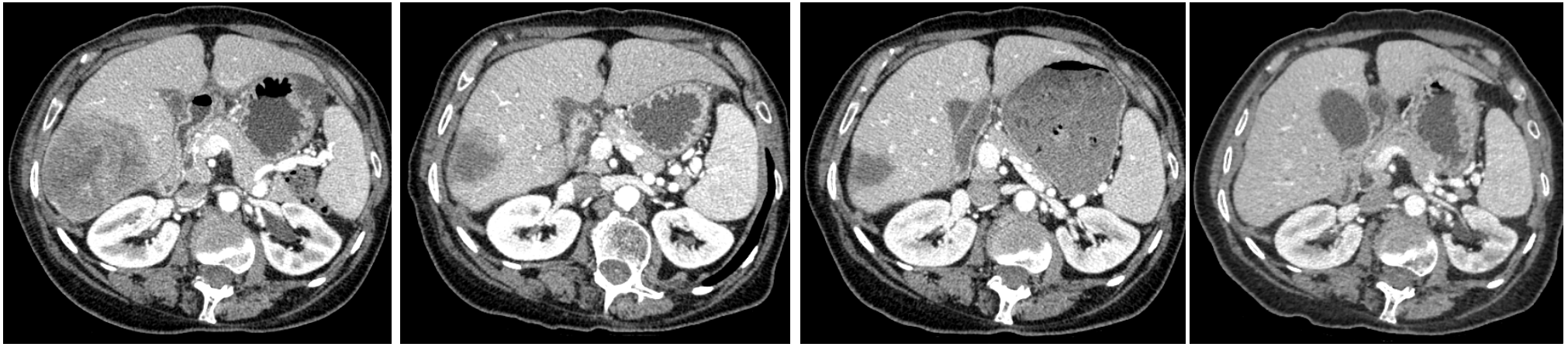
mPFS: 10.2m (6.9-16.7)

Planchard D *et al. Lancet Oncol* 2017;18:1307–1316

The patient received the association: Dabrafenib (150mg twice a day) + Trametinib (2mg/day)

July 2014

February 2017



+ 31 months

D.Planchard et al, Gustave Roussy

BRAF mutated patients

Author	n	Drug	ORR	PFS (months)	OS (months)
Hyman (BASKET-trial)	20	Vemurafenib	42%	7.3	NR
Gautschi (EU-RAF, retrospective)	35	Vemurafenib	53%	5	10.8
Mazières (AcSé Vemu)	100	Vemurafenib	44.9%	5.2	9.3
Planchard (BRF cohort A)	78	Dabrafenib	33%	5.5	12.7
Planchard (BRF cohort B)	57	Dabrafenib + trametinib	66.7%	10.9	12.7
Planchard (BRF cohort C)	36	Dabrafenib + trametinib 1L	64%	10.2	24.6

EMA and FDA approvals 2017

J.Mazieres, WCLC 2018

BRAF non V600 cohort (AcSé Vemu)

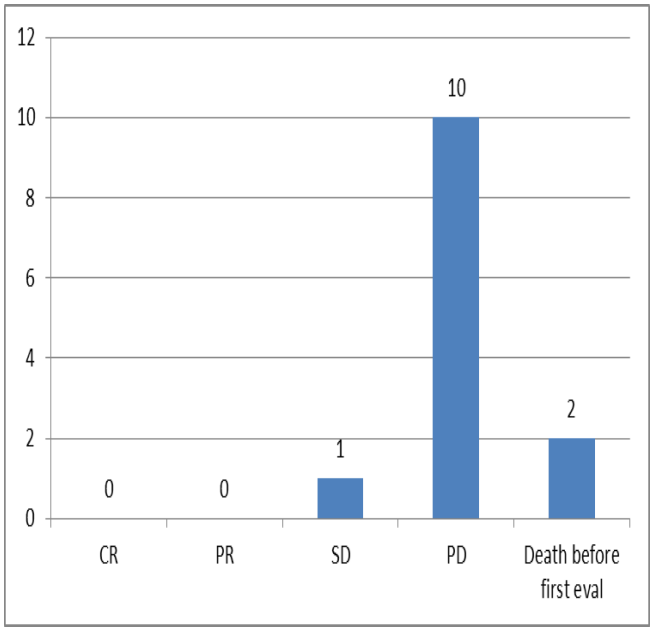
- Mean Bayesian Estimated Success rate : **5.9%** ; credibility 95%CI : [0.2%; 20.6%]
- Prob ORR < futility bound (10%): 81.5% - **study stopped**

Non V600 mutations

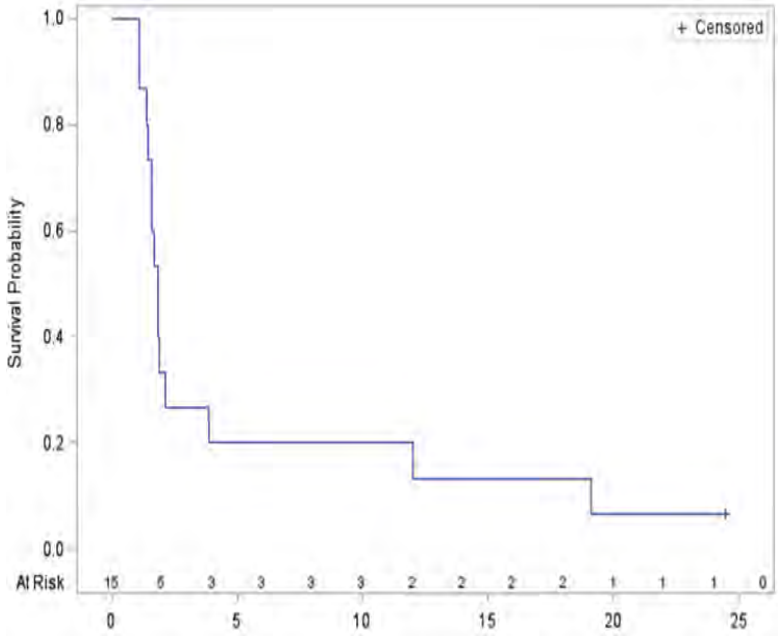
n = 17

G466A : n=1
G466V : n=3
G469A : n=3
G469V : n=1
N581S : n=3
G596R : n=1
K601E : n=3
K601N : n=2

Response rate: 0%



PFS: 1.8 m. [1.4;2.1]



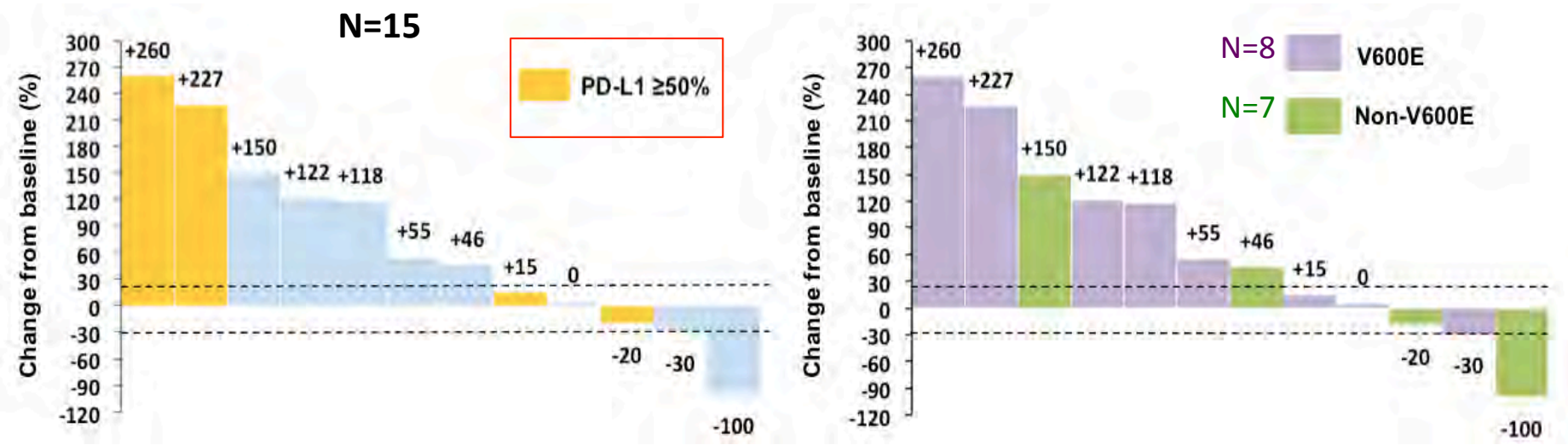
J.Mazieres et al, WCLC 2018

BRAF and immunotherapy

45% of *BRAF*-mutant & high PD-L1 expression levels (≥ 50% by 22C3 IHQ)
10% of cases associated with **high tumor mutational burden (≥20 Mb)**

ORR: 17%

N=15



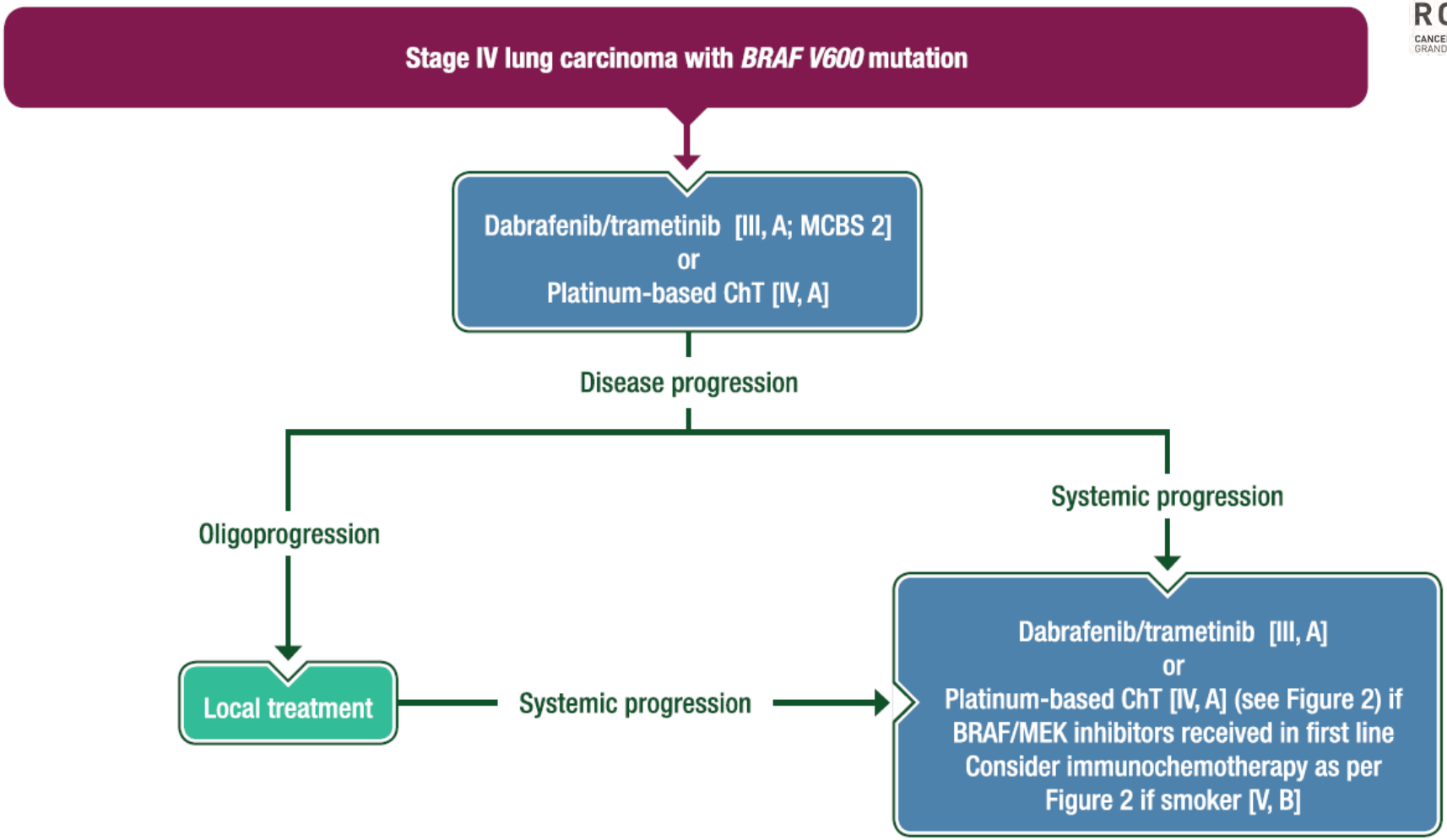
PFS / OS V600E *vs*. Non-V600E: 6.1 mo. *vs*. 2.6 mo. (p=0.67) / NR vs. 33.9 (p=0.47)

Dudnik – WCLC 2017

Immunotarget- Low benefit of immunotherapy in case of molecular alteration...need for specific studies

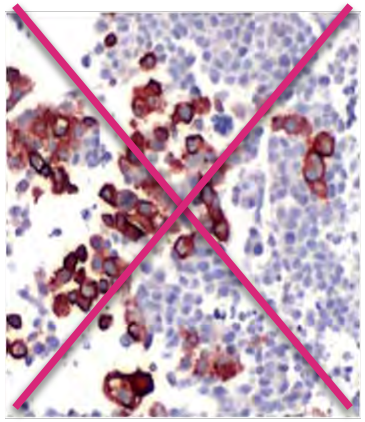
Driver	n	RR	PFS	OS	Impact (+/X) on PFS of				Comments
					PDL1	Smoking	Nb line	Subtype	
Total		19%	2.8	13.3					Outcome consistent with registration trials for ICI
KRAS	271	26%	3.2	13.5	+	X	X	X	Clear benefit across all subgroups
EGFR	125	12%	2.1	10	+	X	X	X	Could be considered in PDL1 + after TKIs exhaustion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

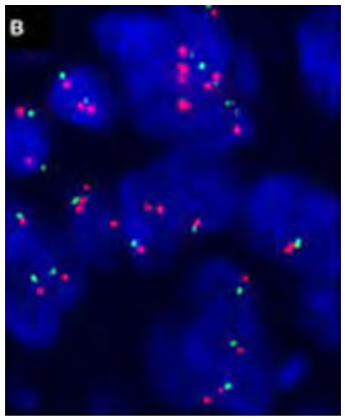
Julien MAZIERES et al, ASCO 18

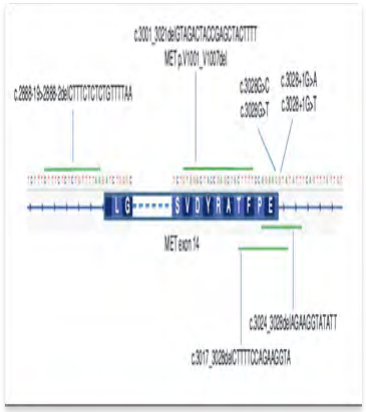


D.Planchard et al, annals onco 2018

MET aberrations in NSCLC



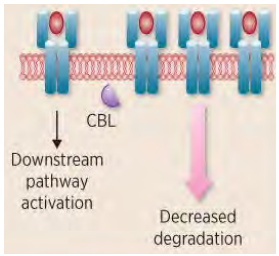




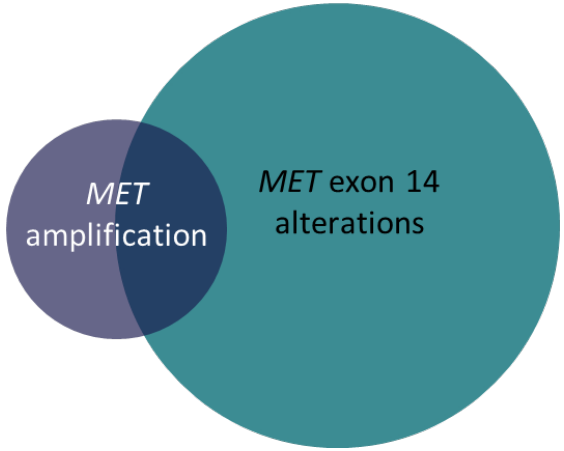
MET Overexpression 25-75%

MET Amplification 3-7%

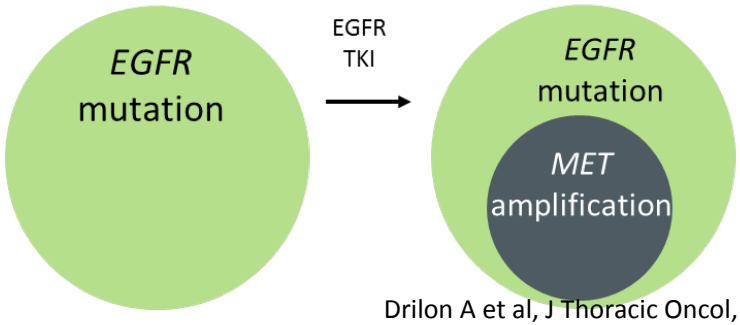
MET exon14 Skipping 3%



MET as a primary driver



MET as a secondary/co-driver



Paik – Cancer Discovery 2015 * Tong - Clin Cancer Res 2016

Drilon A et al, J Thoracic Oncol, 2016

Type 1 MET Inhibitors

Good Drug	Criz	Tep
• High ORR	Modest	
• Potent	✓	✓
• Selective	✓	✓
• Tolerable		
• CNS Activity		

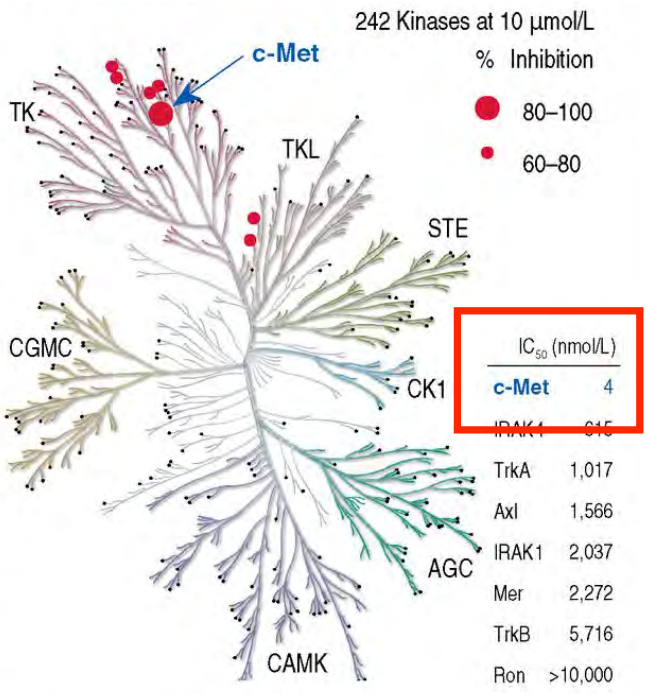
Capmatinib

Savolitinib

Crizotinib

Kinase	IC_{50} (nM) mean*	Selectivity ratio
c-MET	8	–
ALK	20	2X
RON	298	34X
	189	22X
Axl	294	34X
	322	37X
Tie-2	448	52X
Trk A	580	67X
Trk B	399	46X
Abl	1,159	166X

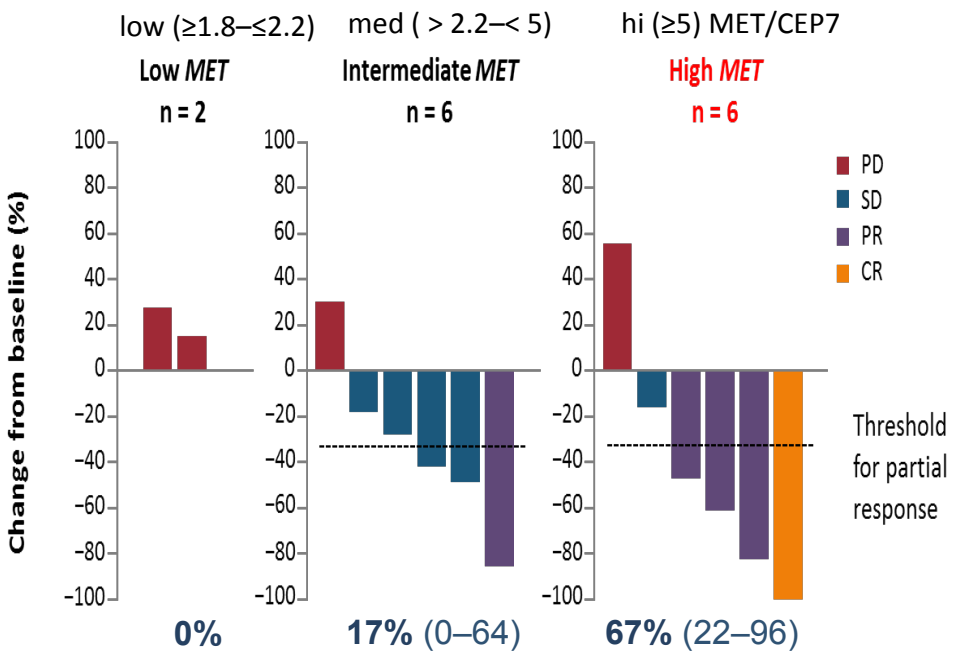
Tepotinib



Cui JJ, et al, *J Med Chem*. 2011 Sep 22;54(18):6342-63; Bladt F, et al, *Clin Cancer Res*. 2013 Jun 1;19(11):2941-51.

Tumour shrinkage seen with crizotinib or capmatinib treatment in intermediate and high *MET* amplified

Crizotonib



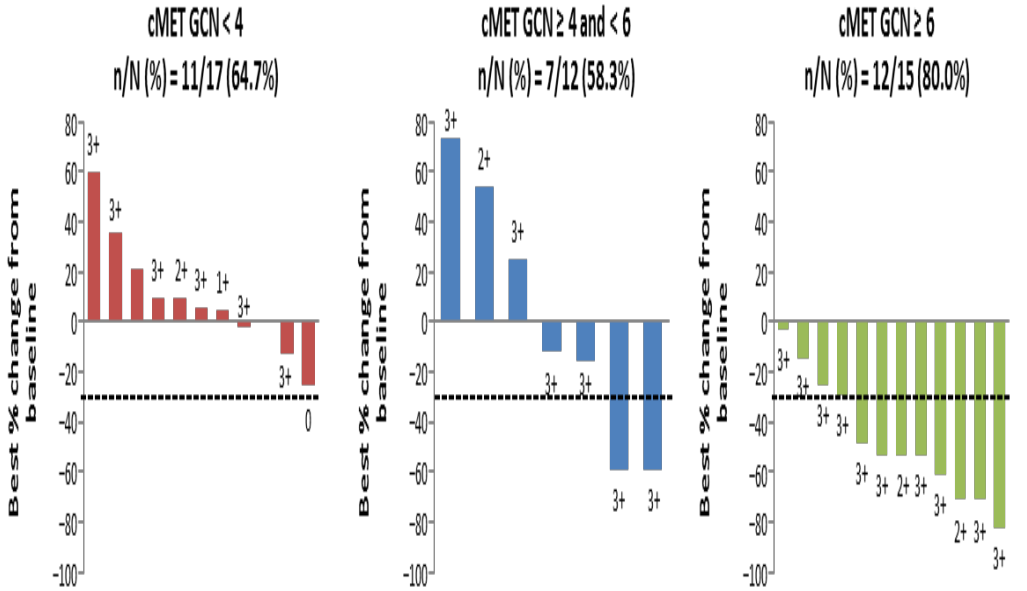
0% **17%** (0–64) **67%** (22–96)

ORR	**33.3% (0.8-90.6)**	**14.3% (1.8-42.8)**	**40.0% (19.1-63.9)**
PFS	1.8 (0.8-14.0)	6.7 (3.4-7.4)	6.7 (3.4-7.4)
	n = 3	n = 14	n = 20

UpDate ASCO
D. Ross Camidge
(Abst 9062)

Camidge DR, et al. ASCO 2014. J Clin Oncol. 2014;32:5s (suppl; abstract 8001).

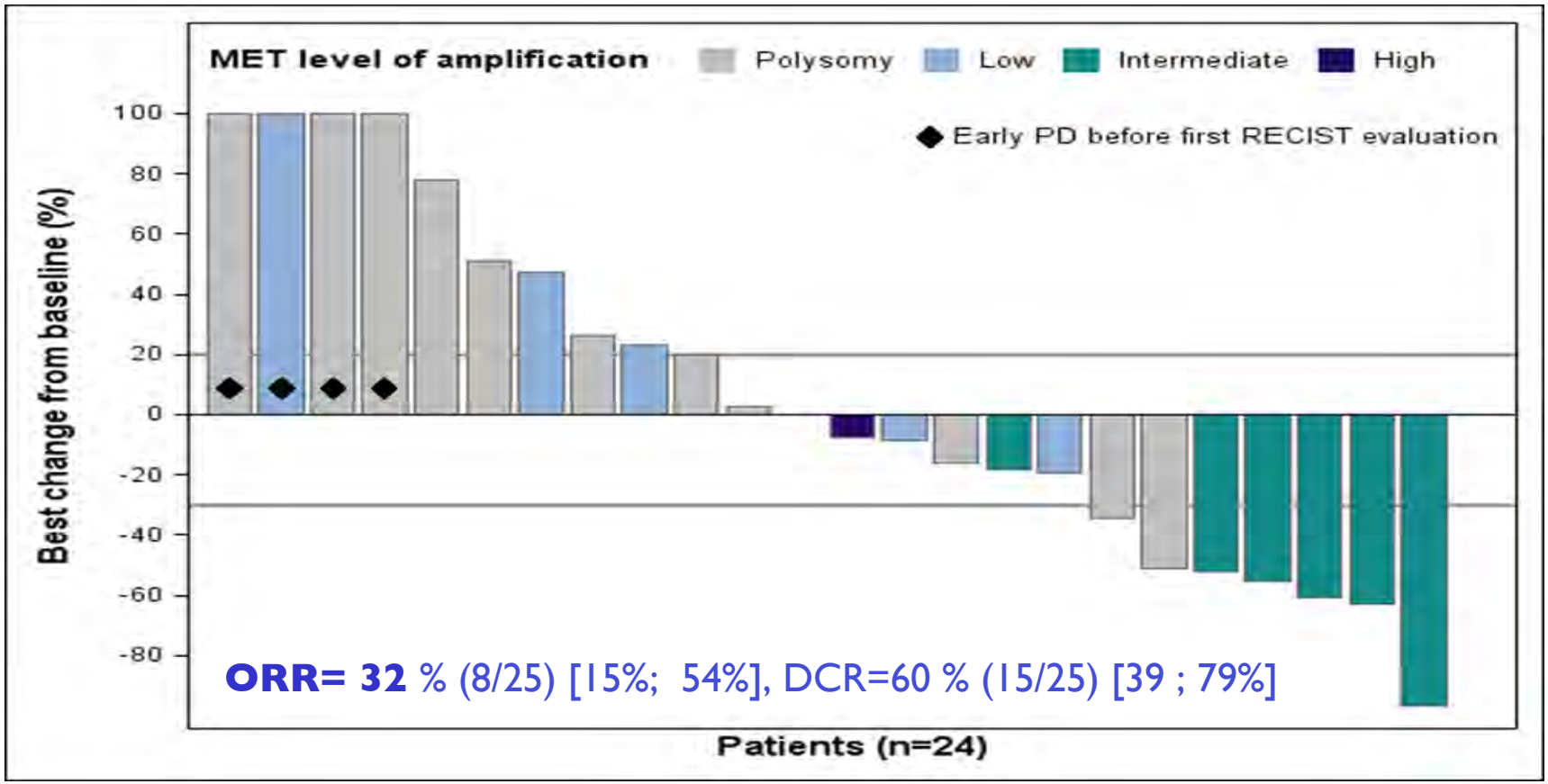
Capmatinib



17% (2.1–48.4) **47% (21.3–73.4)**

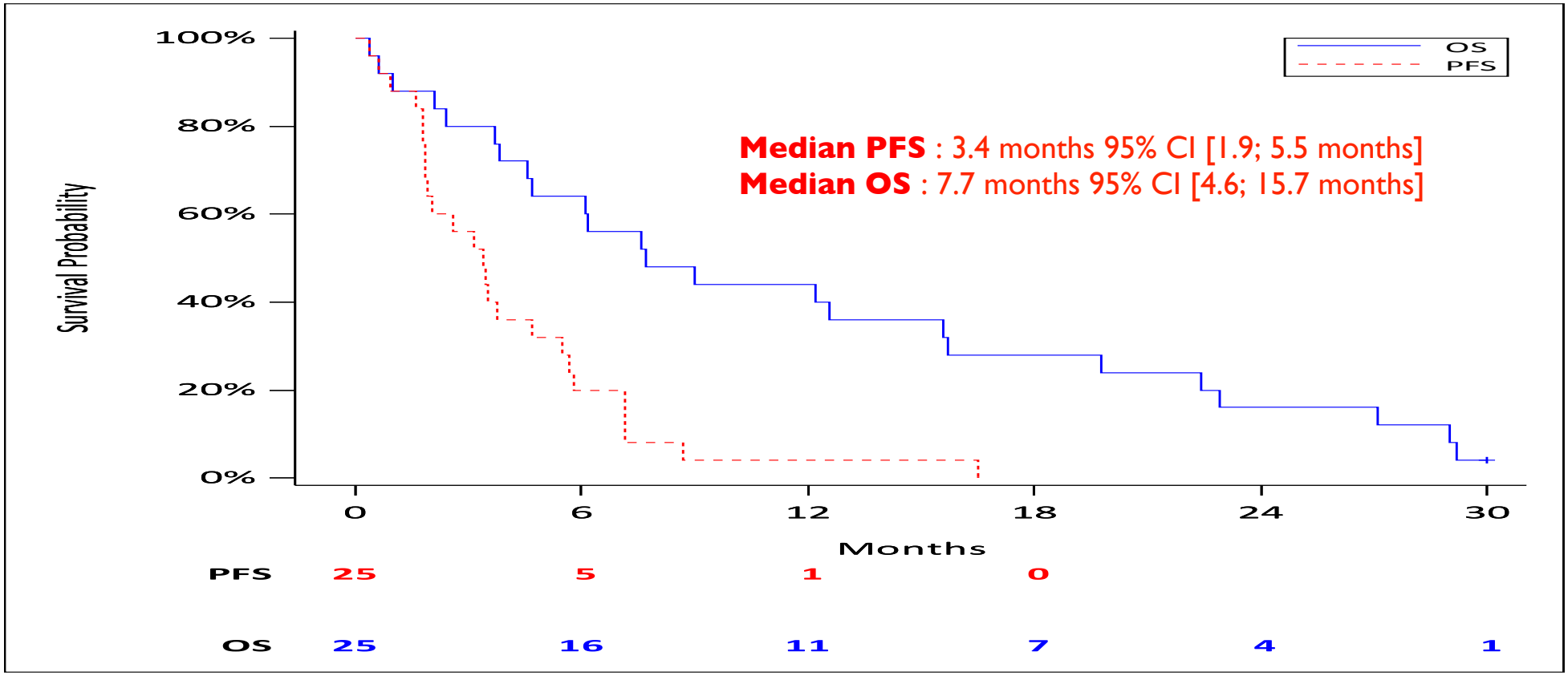
Schuler M, et al. ASCO 2016. J Clin Oncol. 2016;34 Suppl:abstract 9067.

AcSé trial, Response rate MET amplification



Abstract ID: #12937. Activity of crizotinib in MET or ROS1 positive (+) NSCLC: results of the AcSé trial. D. Moro-Sibilot

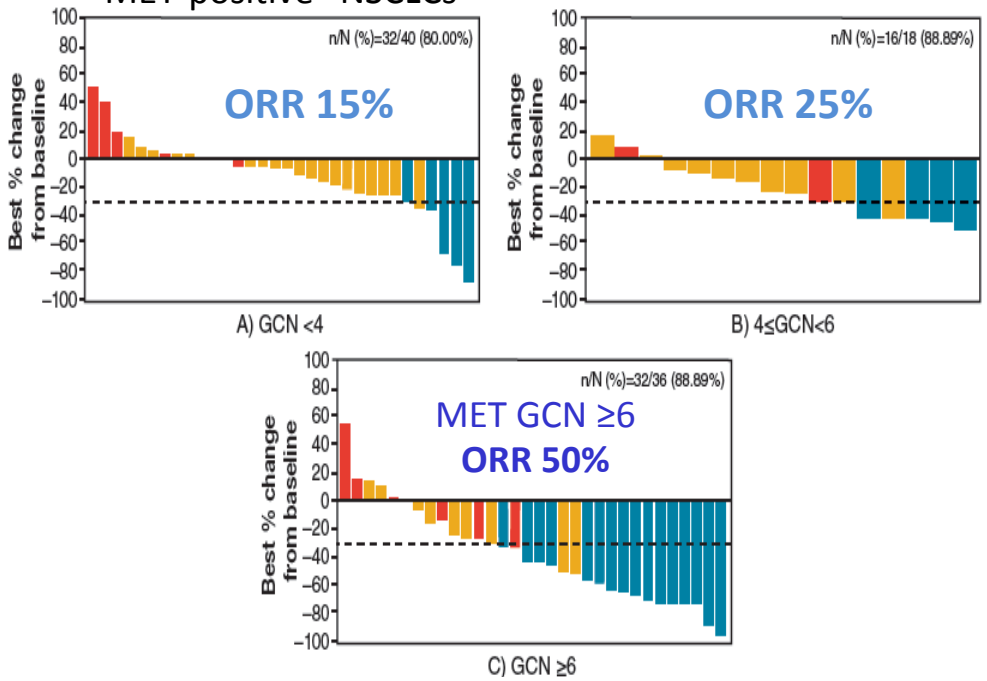
MET amplification



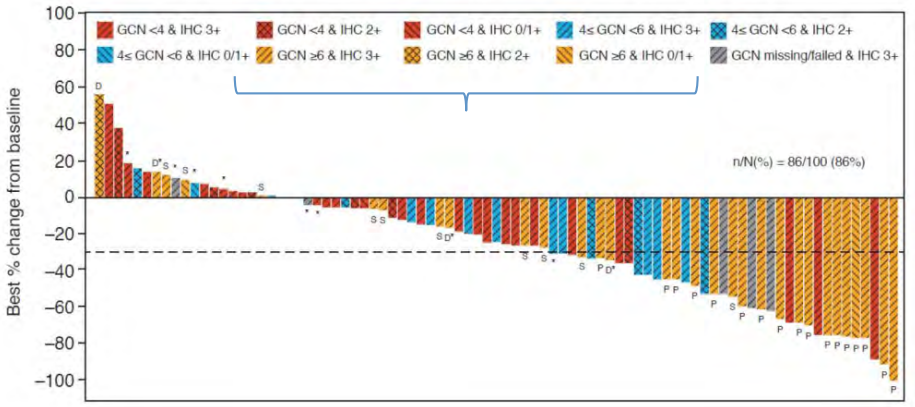
Abstract ID: #12937. Activity of crizotinib in MET or ROS1 positive (+) NSCLC: results of the AcSé trial. D. Moro-Sibilot

Response to Combined EGFR- and MET-Directed Targeted Therapy (MET amplified)

- **Capmatinib + Gefitinib**
  - Phase 2 expansion cohort
  - *EGFR*-mutant lung cancers with acquired resistance and "MET-positive" NSCLCs



Phase Ib/II Study



ORR: 47% in patients with MET gene copy number ≥6

JOURNAL OF CLINICAL ONCOLOGY | EDITORIAL

Have We Really MET a New Target?

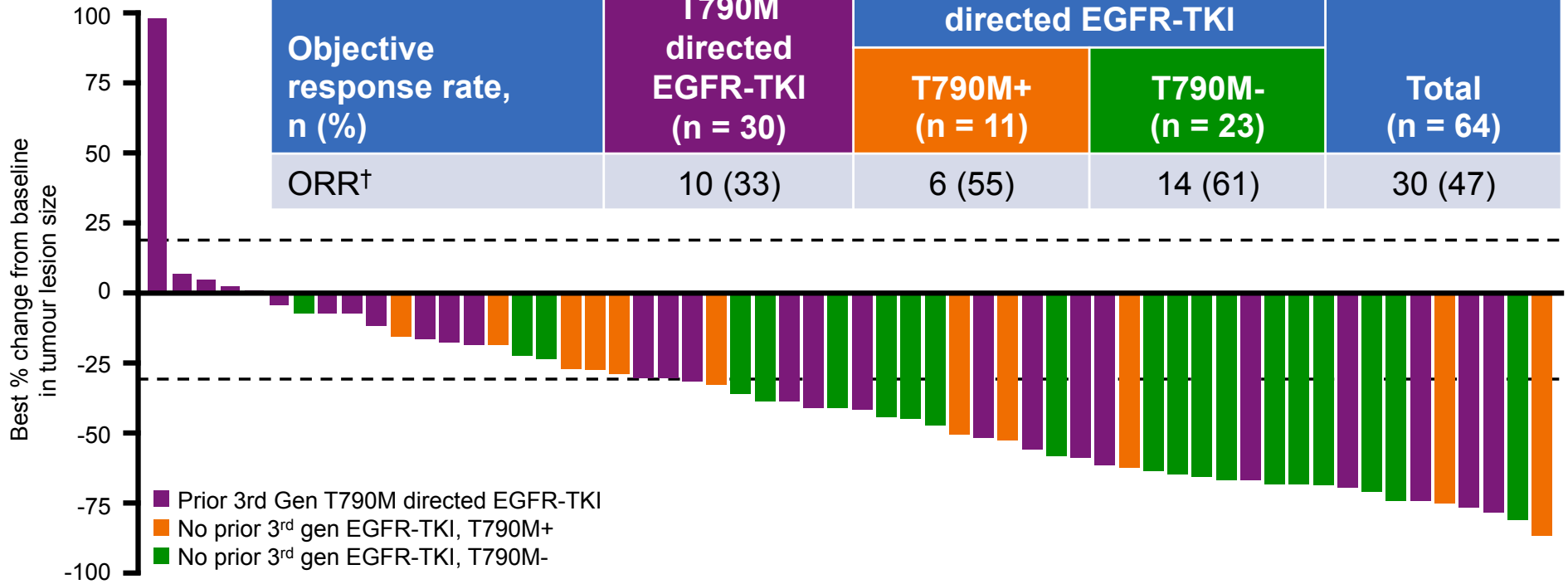
David Planchard, *Gustave Roussy, Villejuif, France*

Yi-Long Wu et al, JCO 2018

TATTON (osimertinib+ Savolitinib)

Preliminary anti-tumour activity in all MET-positive patients*, n = 64

Objective response rate, n (%)	Prior 3rd Gen T790M directed EGFR-TKI (n = 30)	No prior 3rd Gen T790M directed EGFR-TKI		Total (n = 64)
		T790M+ (n = 11)	T790M- (n = 23)	
ORR†	10 (33)	6 (55)	14 (61)	30 (47)

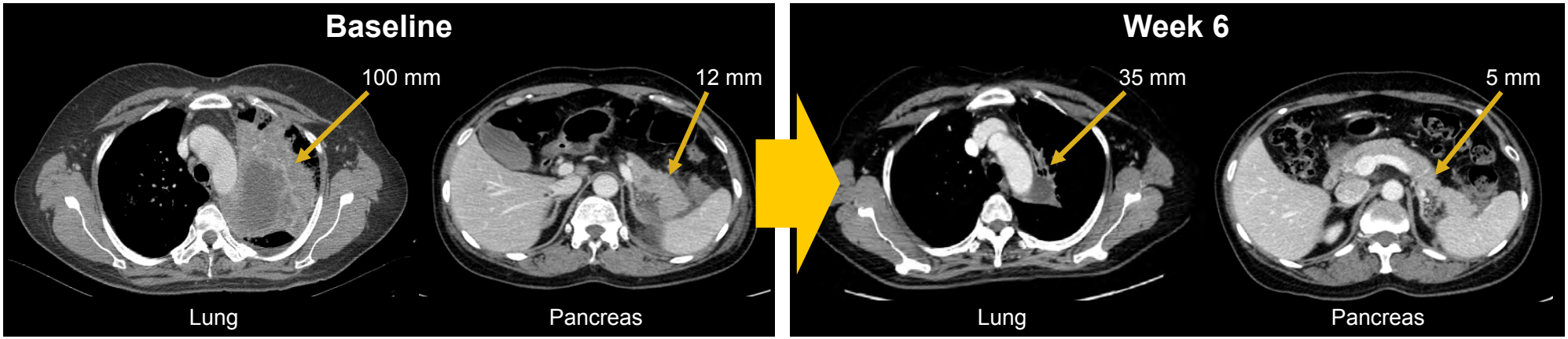


Waterfall plot based on evaluable patients (n = 64): all patients dosed and with on-treatment assessment or discontinuation prior to first tumour assessment
Data cut-off 31 Aug 2017
*17 patients did not have central FISH confirmation of MET-positive status (n = 6 MET-negative; n = 11 unknown by central lab); †Confirmed by a later scan performed at least 4 weeks after initial response observed

TATTON Part B
NCT02143466

Myung-Ju Ahn et al, IASLC 2017

57 year old female never smoker with NSCLC adenocarcinoma histology, ECOG PS 1



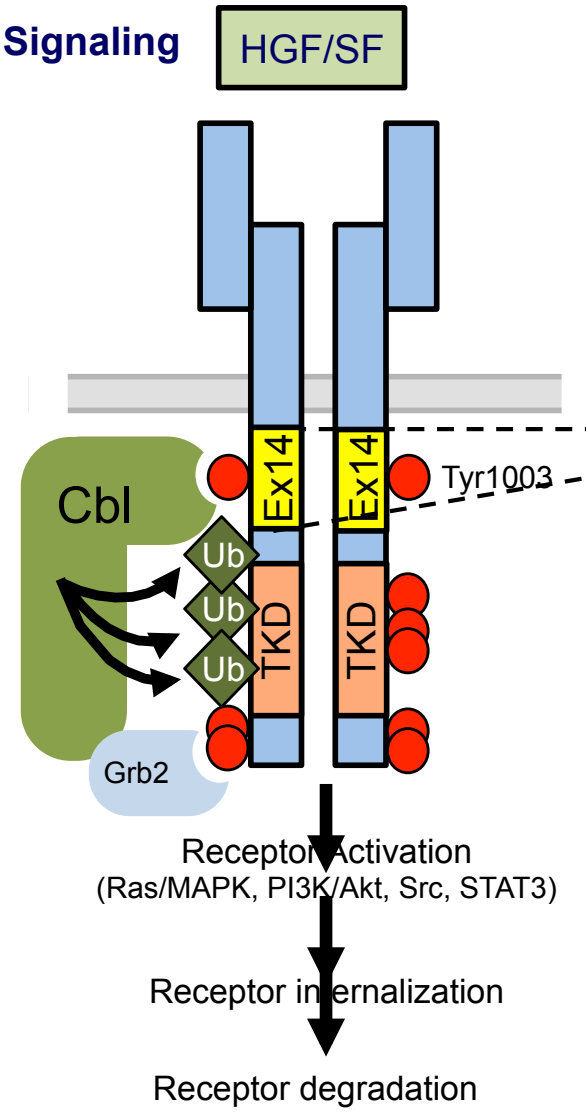
Nov 2016		Jun 2017	Jul 2017	Sep 2017	
Diagnosis of adenocarcinoma T3N3M1b with brain metastasis; EGFR Ex19Del	First-line gefitinib 250 mg QD for 6 months BOR: PR	Post-PD biopsy: **T790M-, MET+** (FISH). First dose on TATTON study	**PR** **6 week RECIST scan**	**Confirmed PR** **12 week RECIST scan**	Ongoing

Ex19Del, exon 19 deletion

TATTON Part B
NCT02143466

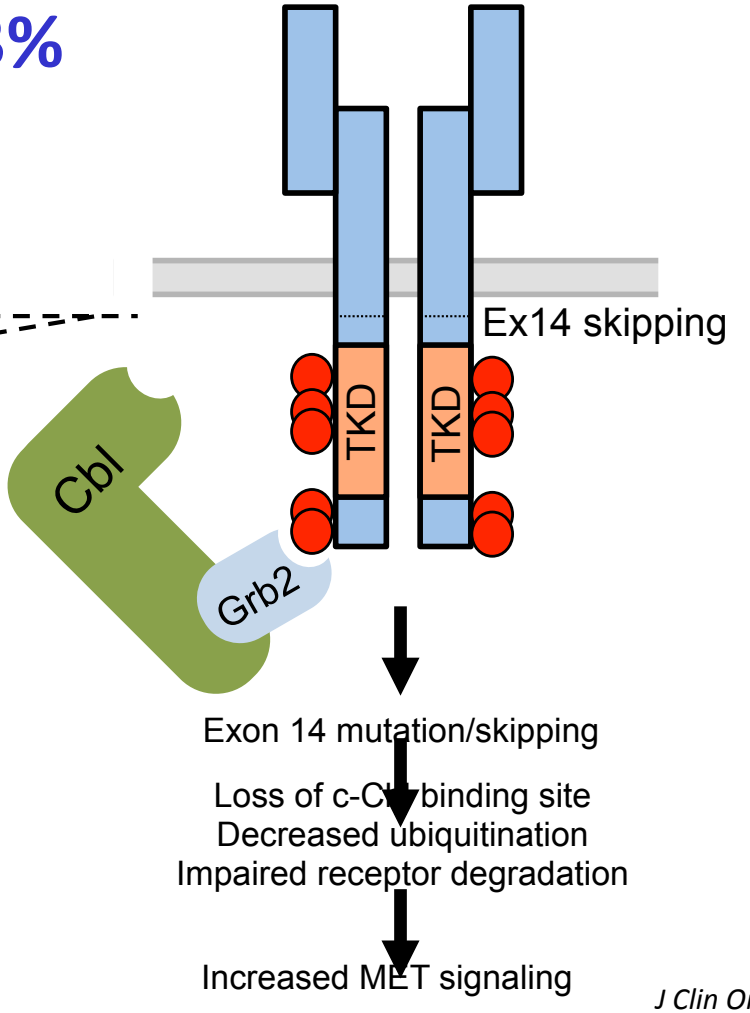
Myung-Ju Ahn et al, IASLC 2017

Normal MET Signaling



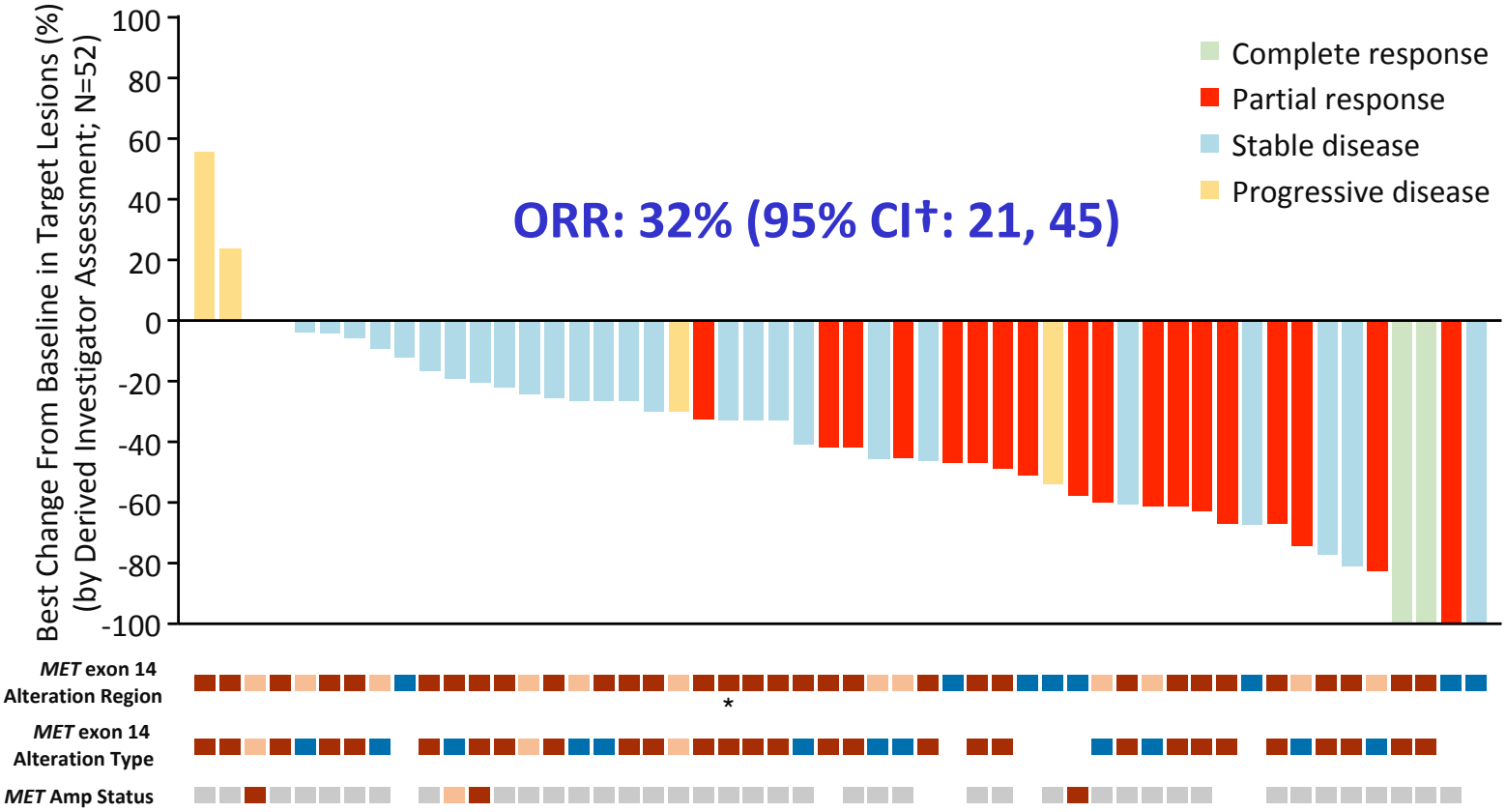
Exon 14 Mutated/Skipped

3%



Awad MM,
J Clin Oncol. 2016 Jan 19.

Updated Antitumor Activity and Safety of Crizotinib in Patients With *MET* Exon 14-Altered Advanced NSCLC



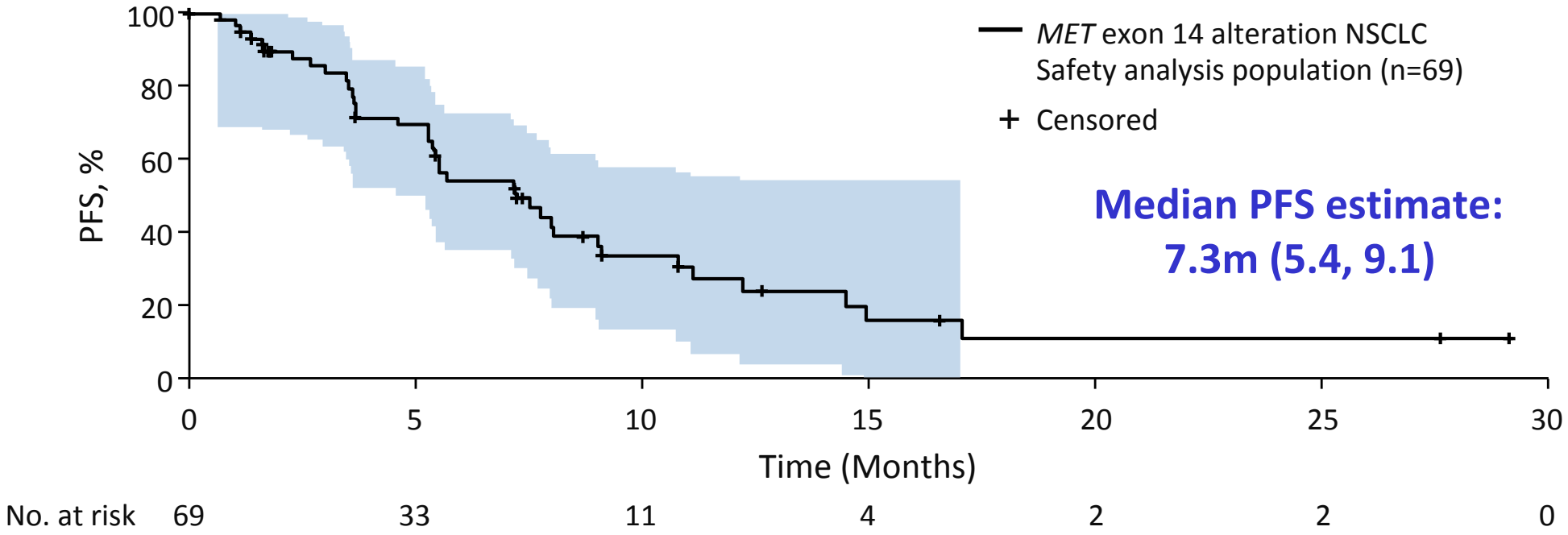
Biomarker Data Key[§]

	MET exon 14 alteration region	*MET* exon 14 alteration type	*MET* amp status
	Splice donor	Base substitution	Detected
	Splice acceptor[†]	Large indel (>35 bp)	UIF
	Canonical[‡]	Indel	–
	Not detected	–	Not detected

*Alterations in both splice donor and acceptor regions. [†]Includes alterations in the Splice Acceptor Region, Polypyrimidine Tract, and Branching Point. [‡]Includes *MET* exon 14 alterations that are not associated with DNA coding region information. [§]White space in biomarker data rows indicates no available sample for testing, not analyzable or no results reported. bp, base pairs; UIF, uninformative.

Alexander Drilon et al, WCLC 2018

Progression-Free Survival (PFS) by Derived Investigator Assessment

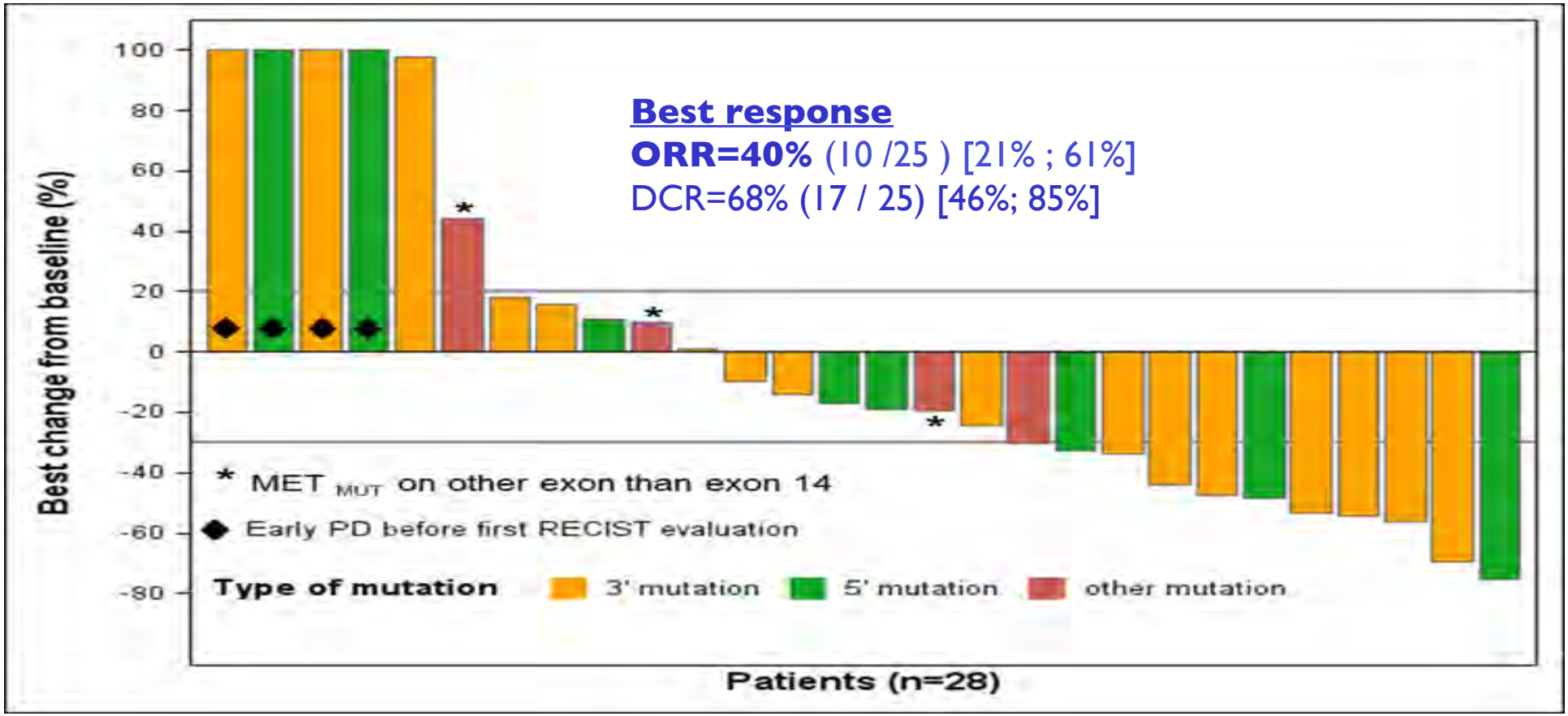


- OS data were not mature at time of data cutoff: 34.8% patients had died; 40.6% still in follow-up
- Median Overall Survival (OS) estimate, months (95% CI): 20.5 (14.3, 21.8)

Shaded area in PFS Kaplan-Meier plot above represents 95% Hall-Wellner band. 95% CI estimates for PFS and OS based on Brookmeyer and Crowley method.

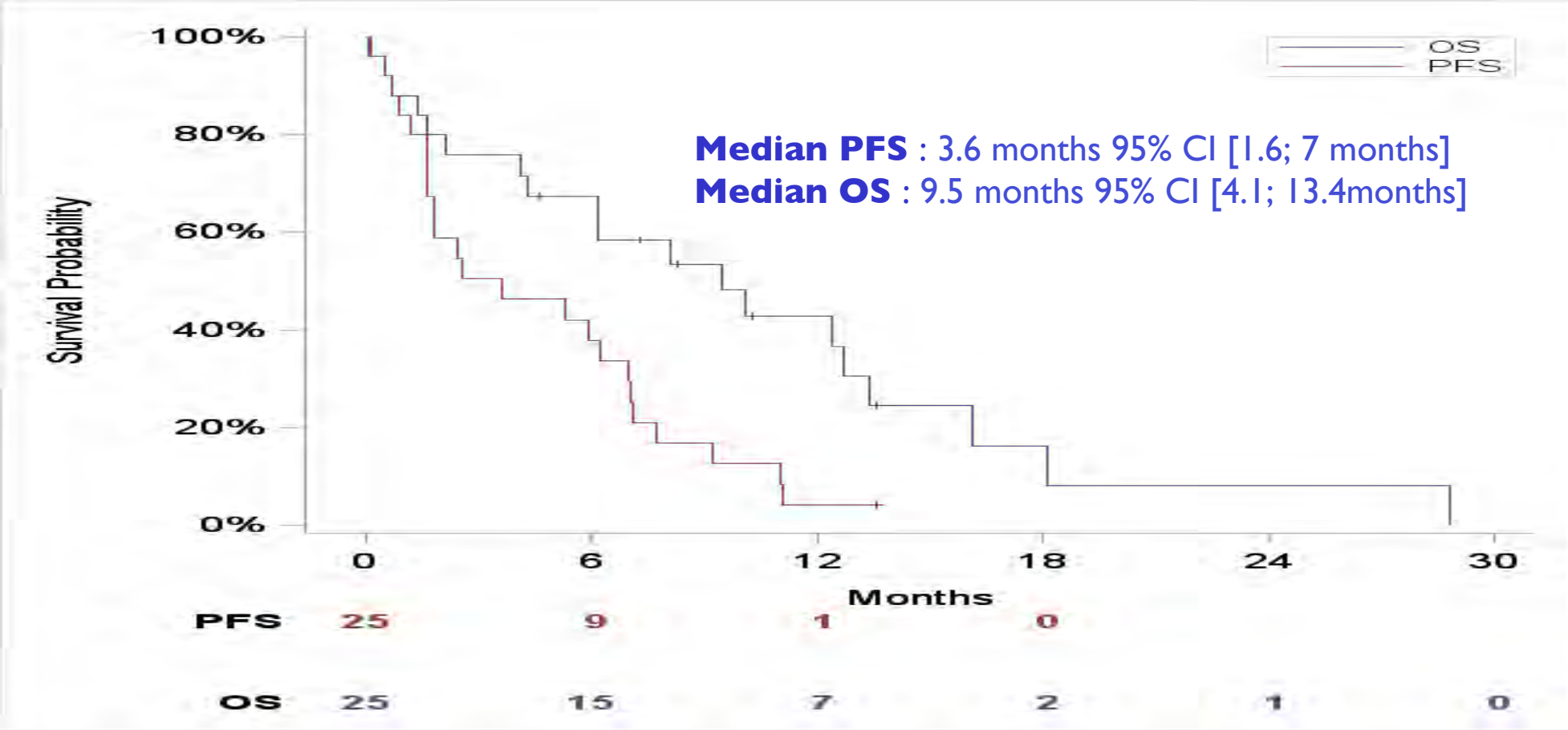
Alexander Drilon et al, WCLC 2018

AcSé trial, Response rate *MET* exon 14 mutation



Abstract ID: #12937. Activity of crizotinib in MET or ROS1 positive (+) NSCLC: results of the AcSé trial. D. Moro-Sibilot

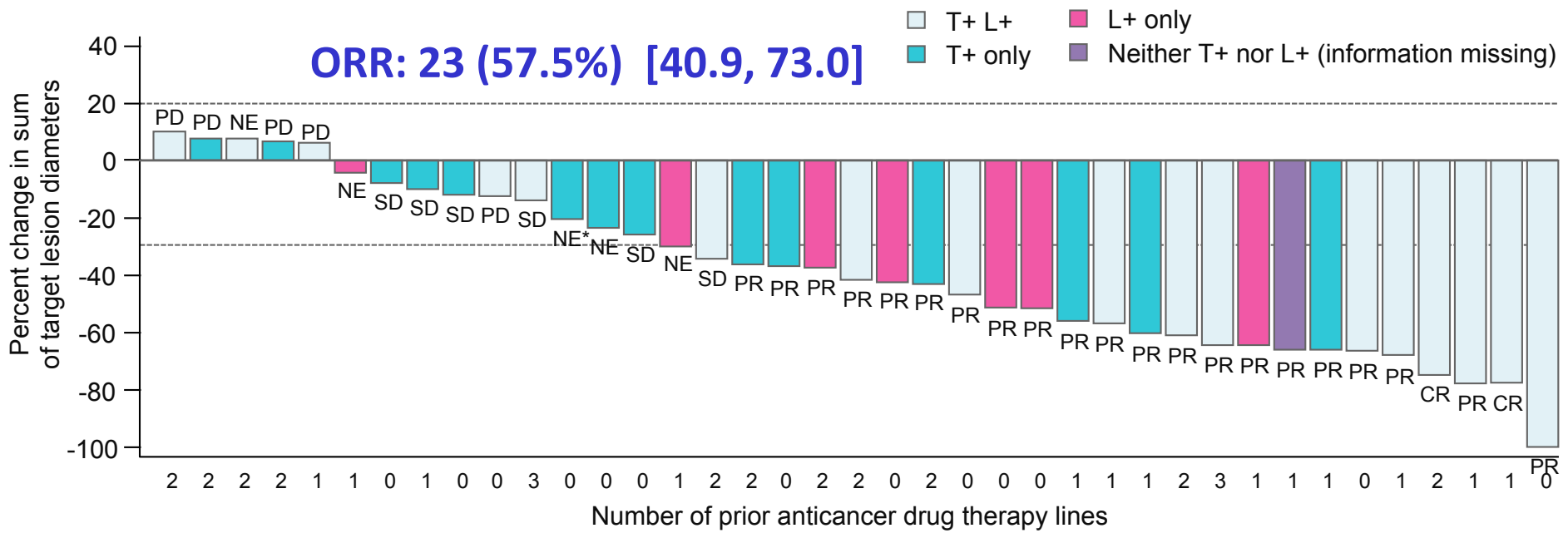
Response rate *MET* exon 14 mutation



Median PFS : 3.6 months 95% CI [1.6; 7 months]
Median OS : 9.5 months 95% CI [4.1; 13.4months]

Abstract ID: #12937. Activity of crizotinib in MET or ROS1 positive (+) NSCLC: results of the AcSé trial. D. Moro-Sibilot

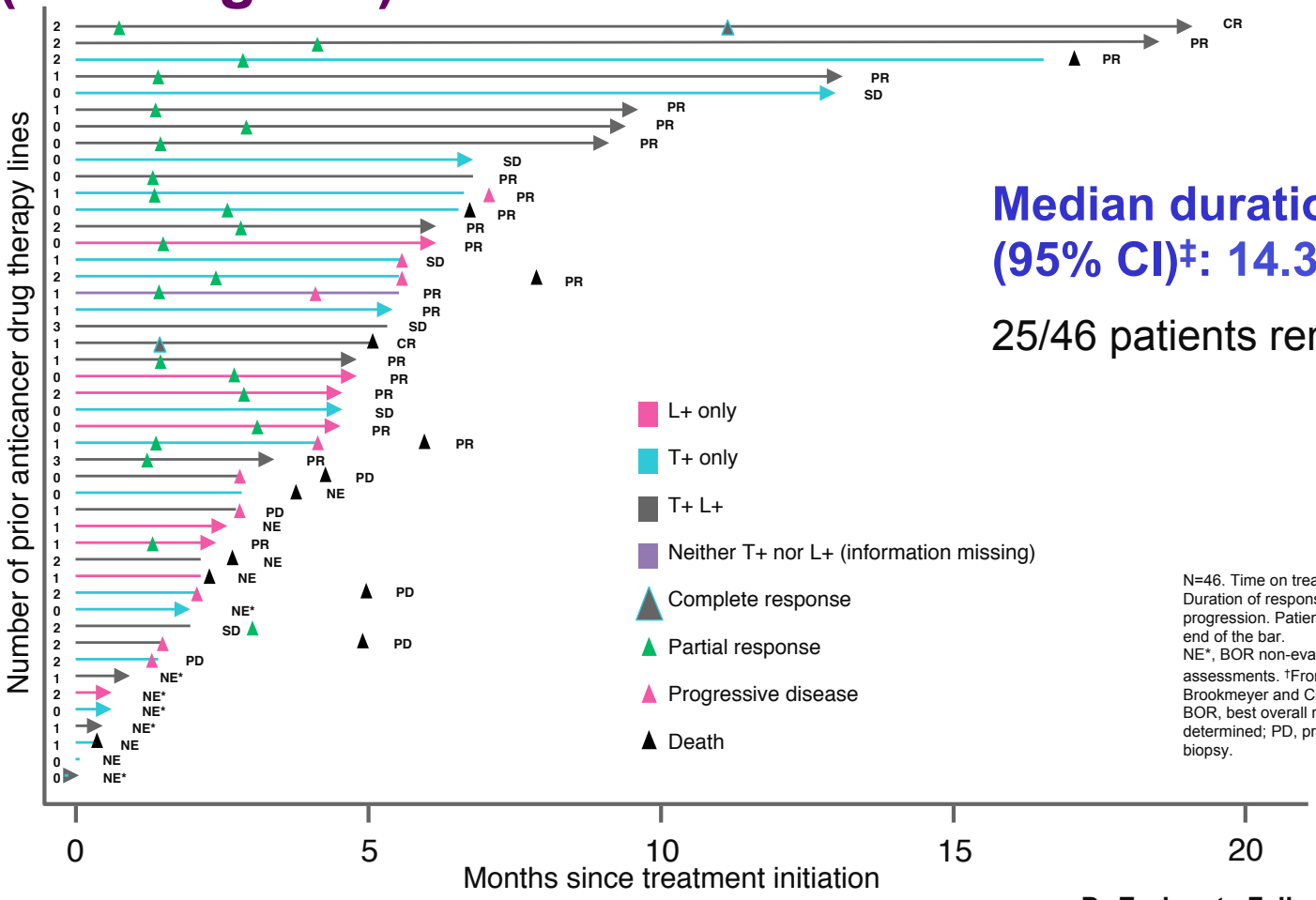
VISION: A Phase II, Single-arm Trial to Investigate Tepotinib in Advanced NSCLC with METexon14-Skipping Alterations



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; L, liquid biopsy; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease; T, tumor biopsy.

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

Time on Treatment and Duration of Response (Investigator)



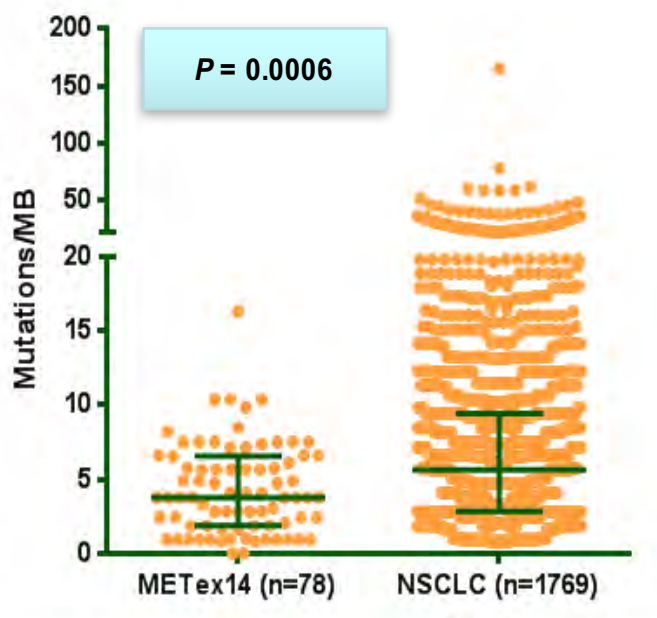
Median duration of response† (95% CI)‡: 14.3 (3.7, nd) months

25/46 patients remain on-treatment

N=46. Time on treatment is the time from treatment initiation until treatment termination. Duration of response is measured from time of initial response until documented tumor progression. Patients denoted with an arrow remain on-treatment. BOR displayed at the end of the bar.
NE*, BOR non-evaluable where ongoing patient has not had two post-baseline tumor assessments. †From Kaplan-Meier survival analysis. ‡95% CI for the interval using the Brookmeyer and Crowley method.
BOR, best overall response; CR, complete response; L, liquid biopsy; nd, not determined; PD, progressive disease; PR, partial response; SD, stable disease; T, tumor biopsy.

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

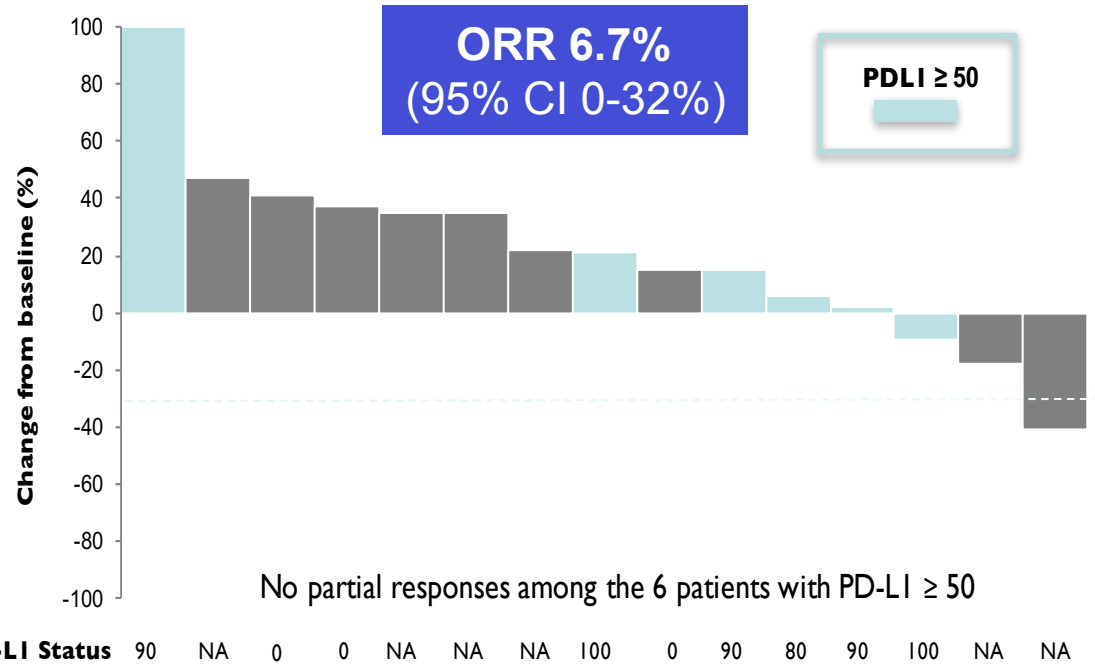
Poor Response to Immunotherapy in MET exon 14-altered NSCLCs



TMB is lower in patients with *MET* exon 14 altered NSCLCs compared to other NSCLCs

MET exon 14-altered cancers can express high levels of PD-L1

PD-L1, Cell Signaling, Clone E1L3N assay, n=54			
	0 %	1 – 49 %	≥50 %
n, (%)	19 (35)	10 (19)	25 (46)



Sabari et al, ASCO 2017

Low benefit of immunotherapy in case of molecular alteration...need for specific studies

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 conventionnal treatment
HER2	29	7%	2.5	20.3	NA	+	X	NA	
ALK	23	0	2.5	17	X	X	X	NA	Poor outcome. New biomarker needed.
RET	16	6%	2.1	21.3					
ROS1	7	17%	-	-					

Julien MAZIERES et al, ASCO 18

Resistance to MET-Directed Targeted Therapy

Drug Administered	MET alteration	Putative resistance mechanism	Notes
Crizotinib 8 mo of disease control	MET D1010H	**MET D1228N** (acquired second site mutation on tumor rebiopsy)	high total MET and phospho-MET IHC+ on post-PD biopsy
Crizotinib 13 mo of disease control	MET D1010H (MET Y1230C)	**MET Y1230C** (detected in ctDNA on PD)	
Crizotinib 8 mo of disease control	MET c.3028delG	**MET Y1230H** (acquired in tumor, MET amp + MET D1228N, Y1230H, Y1230S, and G1163R in plasma)	thereafter responded to Glesatinib
Savolitinib + Osimertinib 9 mo of disease control	MET amplification (+EGFR ex19 del)	**MET D1228V** (acquired second site mutation on tumor rebiopsy)	thereafter responded to Cabozantinib + Erlotinib

Mechanisms of acquired resistance to MET TKIs in MET exon 14mutant NSCLC

Presented Sunday, June 3, 2018. Mark M. Awad (Abst 9069)

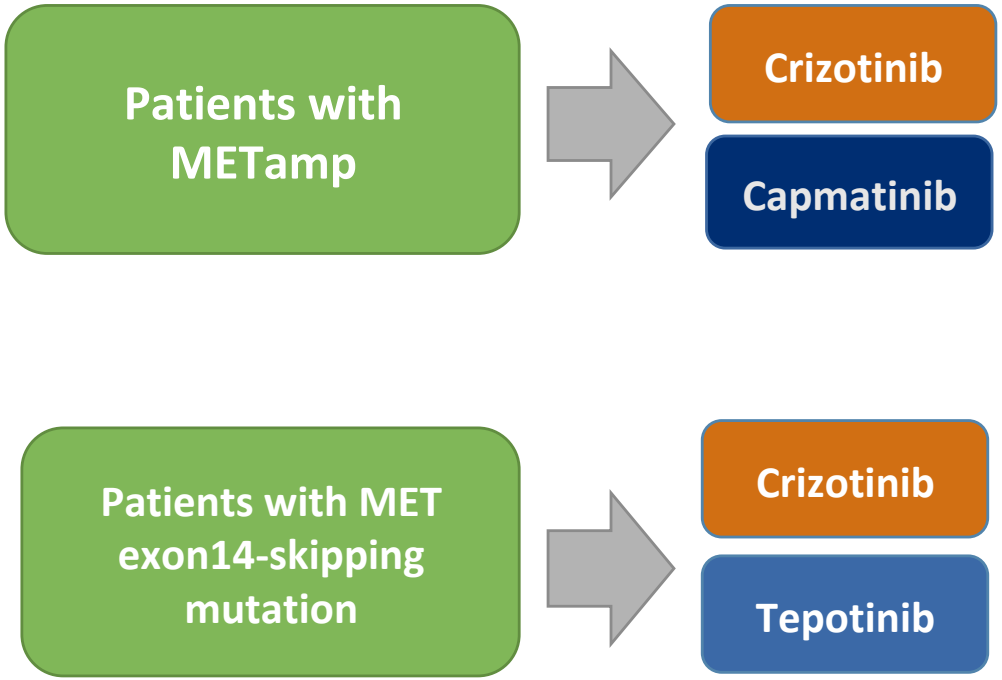
-Secondary mutations in MET included H1094Y, G1163R, L1195F, L1195V, D1228N, Y1230H, and Y1230S.

-bypass track activation : amplification of wild-type KRAS, BRAF, and/or EGFR.

- acquired amplification of the mutated METex14 allele

Heist R et al, J Thoracic Oncol, 2016; Ou et al, J Thoracic Oncol, 2017; Bachall et al, Cancer Discov, 2017; Qi et al, Cancer Res, 2011; Tiedt et al, Cancer Res 2011; Engstrom et al, Clinical Cancer Res 2017

In summary for MET NSCLC



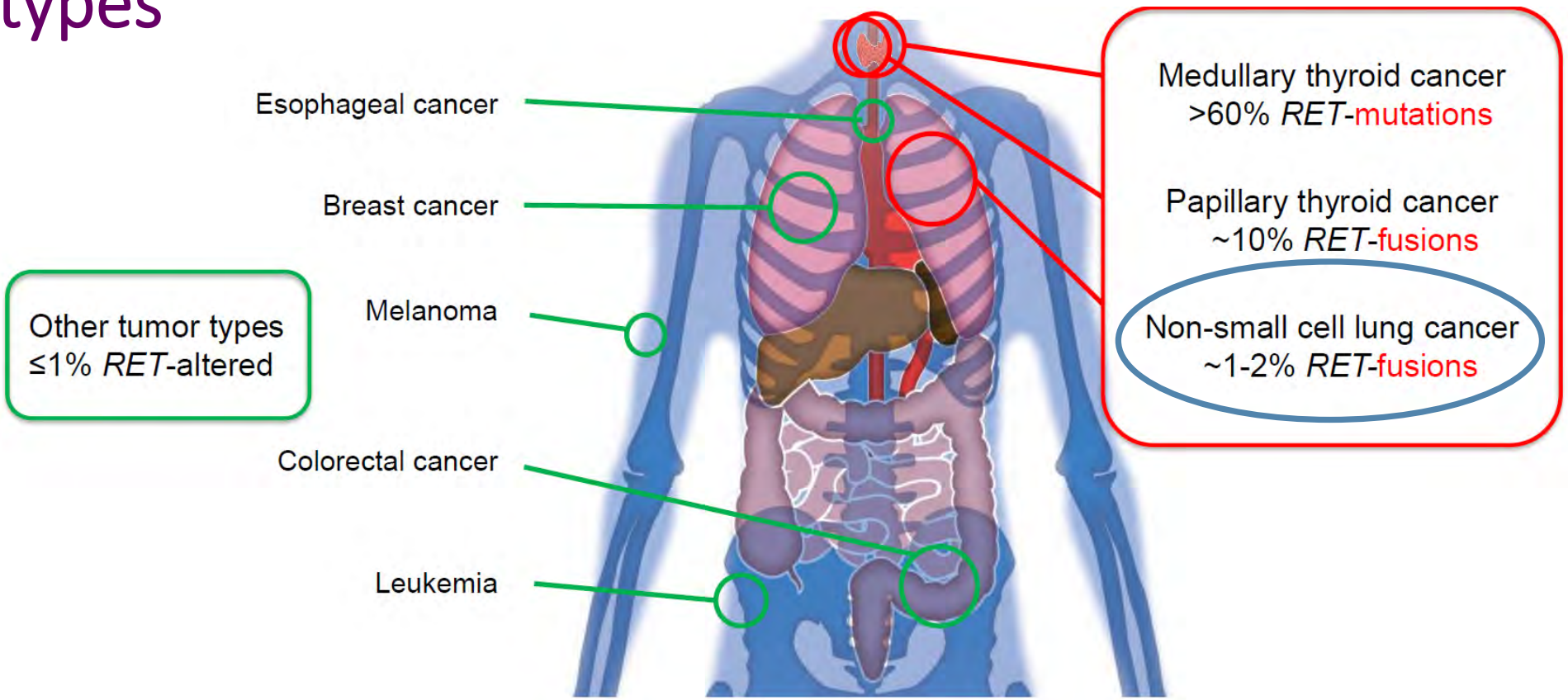
Savolitinib | Tepotinib

Cabozantinib | AMG337

Glesatinib | Merestinib

Second line
MET TKI therapy post crizotinib ??

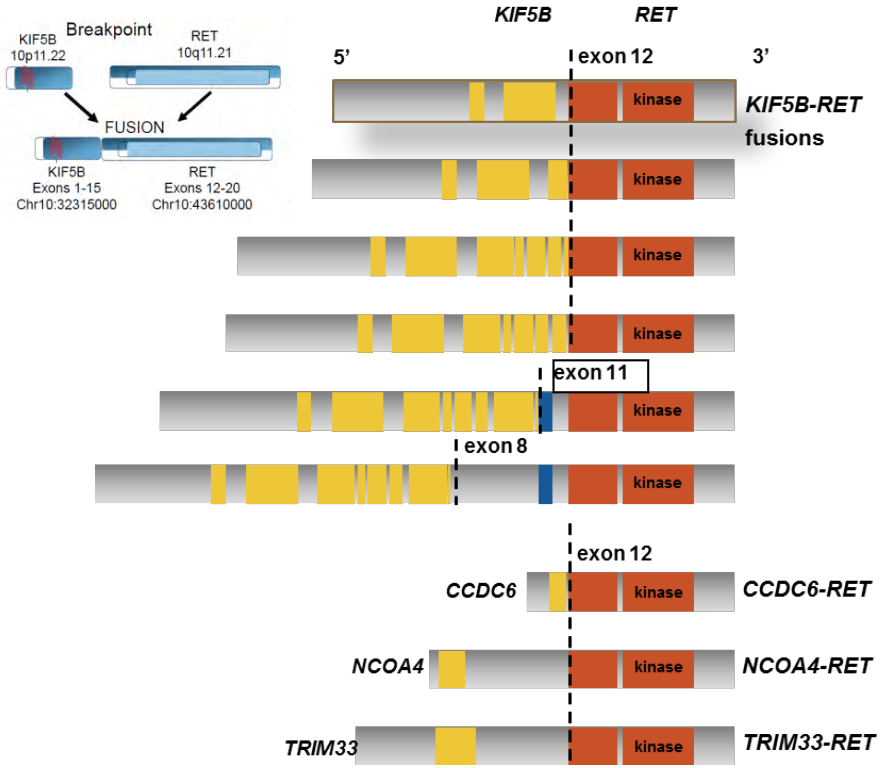
RET is a rare driver of multiple, diverse tymor types



1. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15:151-67 2.Kato S, et al. *Clin Cancer Res* 2017;23:1988-1997.

RET rearrangements

- **1–2% of unselected NSCLCs**
- Clinical features: young, never or former light cigarette smokers

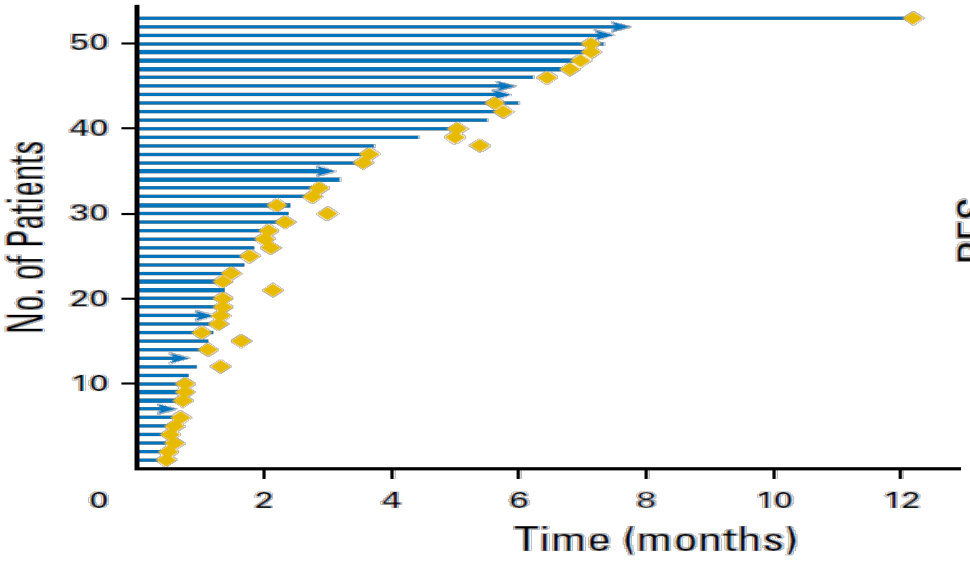


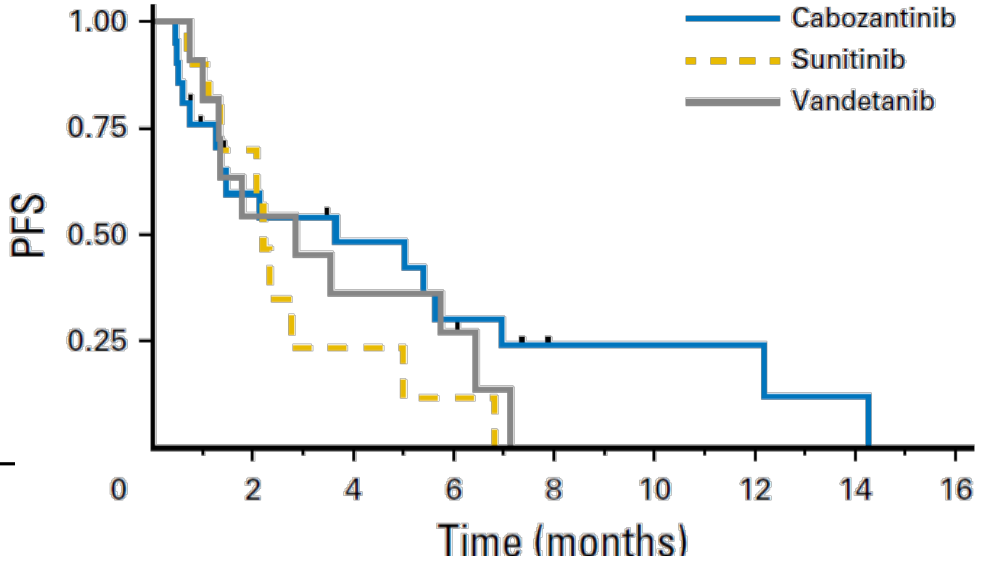
Multi-tyrosine kinase inhibitors

Compound	IC_{50} (nM) In vitro kinase	IC_{50} (nM) Cellular kinase	IC50 (nM) In vitro kinase RET V804M	Other targets
Regorafenib	1.5	~10	NR	VEGFR1-3, BRAF, c-kit, PDGF-b
Levantinib	1.5	48	NR	VEGFR1-3, FGFR1-3, c-kit, PDGFR
Alectinib	4.8	?	53 V804L (32)	ALK (1.9 nM)
Cabozantinib	5.2	27-85	4094	VEGFR2, MET
Ponatinib	7	0.7-11	12	Bcr-abl, FGFR1-4
Sunitinib	30	40-164	55	VEGFR, PDGFR, c-kit, Flt-3
Sorafenib	47	~20-50	12	RAF, VEGFR2-3, PDGFR, c-kit, Flt-3
Vandetanib	100	NR	> 10,000	VEGFR, EGFR

Drilon A, et al. Cancer Discov. 2013;3:630-5. Kohno T, et al. Nat Med. 2012;18:375-7. Lipson D, et al. Nat Med. 2012;18:382-4. Saito M, et al. Carcinogenesis. 2014;35:2452-6. Suehara Y, et al. Clin Cancer Res. 2012;18:6599-608. Takeuchi K, et al. Nat Mec 2012;18:378-81.

Global RET Registry



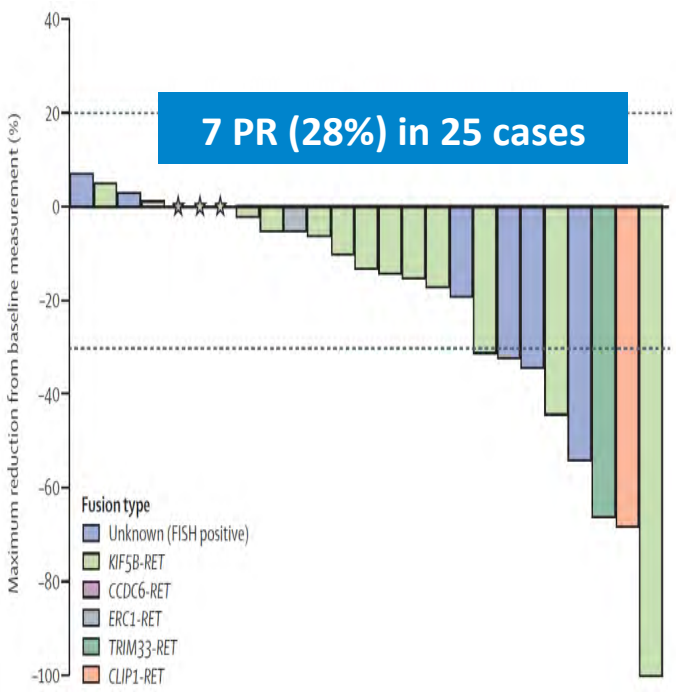


RET inhibitor	Best response (% ; 95 % CI)	Median DoT (range	Median PFS (95% CI)	Median OS (95% CI)
Cabozantinib	37% (16.3 - 61.6)	1.6 months (0.5 -12.2)	3.6 months (1.3 - 7.0)	4.9 months (1.9 - 14.3)
Vandetanib	18% (2.3 - 51.8)	2.9 months (0.8 - 7.1)	2.9 months (1.0 - 6.4)	10.2 months (2.4 - NR)
Sunitinib	22% (2.8 - 60.0)	2.2 months (0.7 - 6.6)	2.2 months (0.7 - 5.0)	6.8 months (1.1 - NR)

Gautschi et al, JCO 2017

Need of more potent drugs

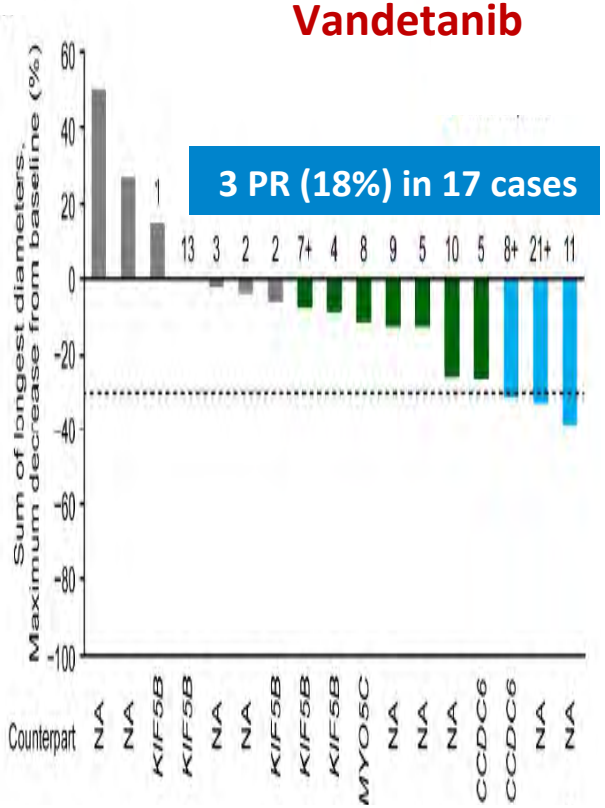
Cabozantinib



mPFS: 5.5 months (95% CI 3.8–8.4)

Drilon et al, Lancet Oncol, 2016

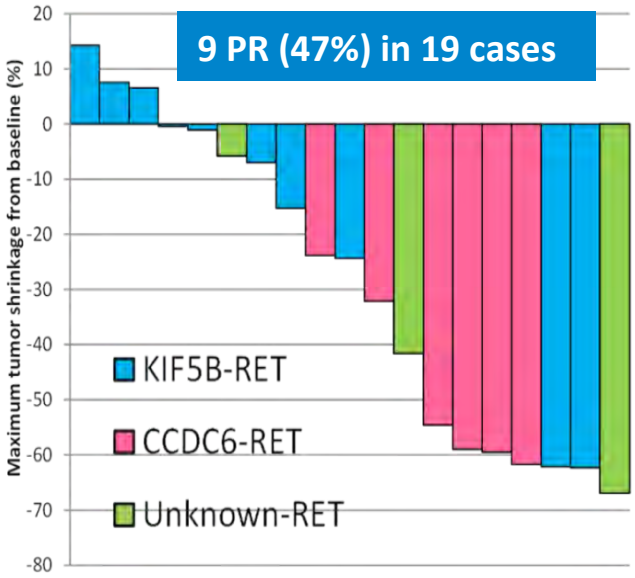
Vandetanib



mPFS: 5.5 months

Lee et al, Ann Oncol, 2017

Vandetanib



mPFS: 4.7 months (95% CI 2.8–8.5)

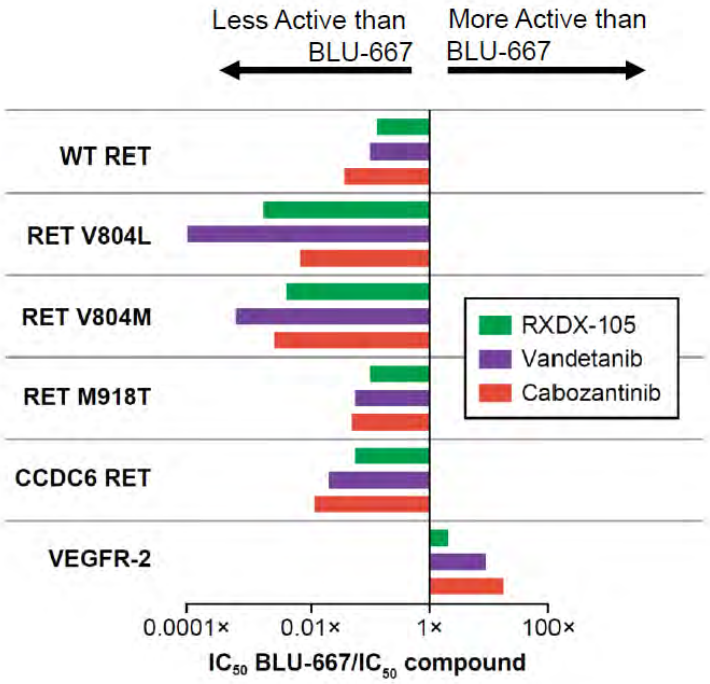
Yoh et al, Lancet Resp Med, 2017

BLU-667 designed to treat RET-altered cancers

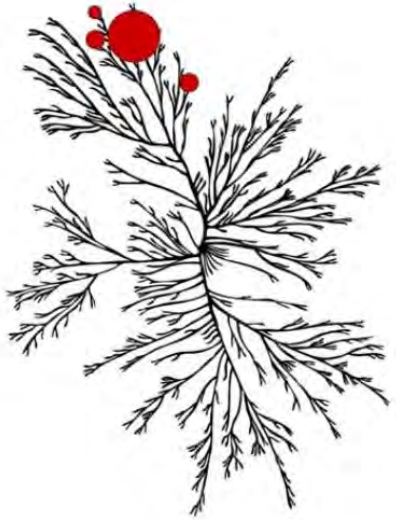
Subnanomolar potency[1]

Variant	Biochemical IC_{50} (nM)
RET wildtype	0.4
RET V804L	0.3
RET V804M	0.4
RET M918T	0.4
CCDC6-RET	0.4

More Potent than MKI

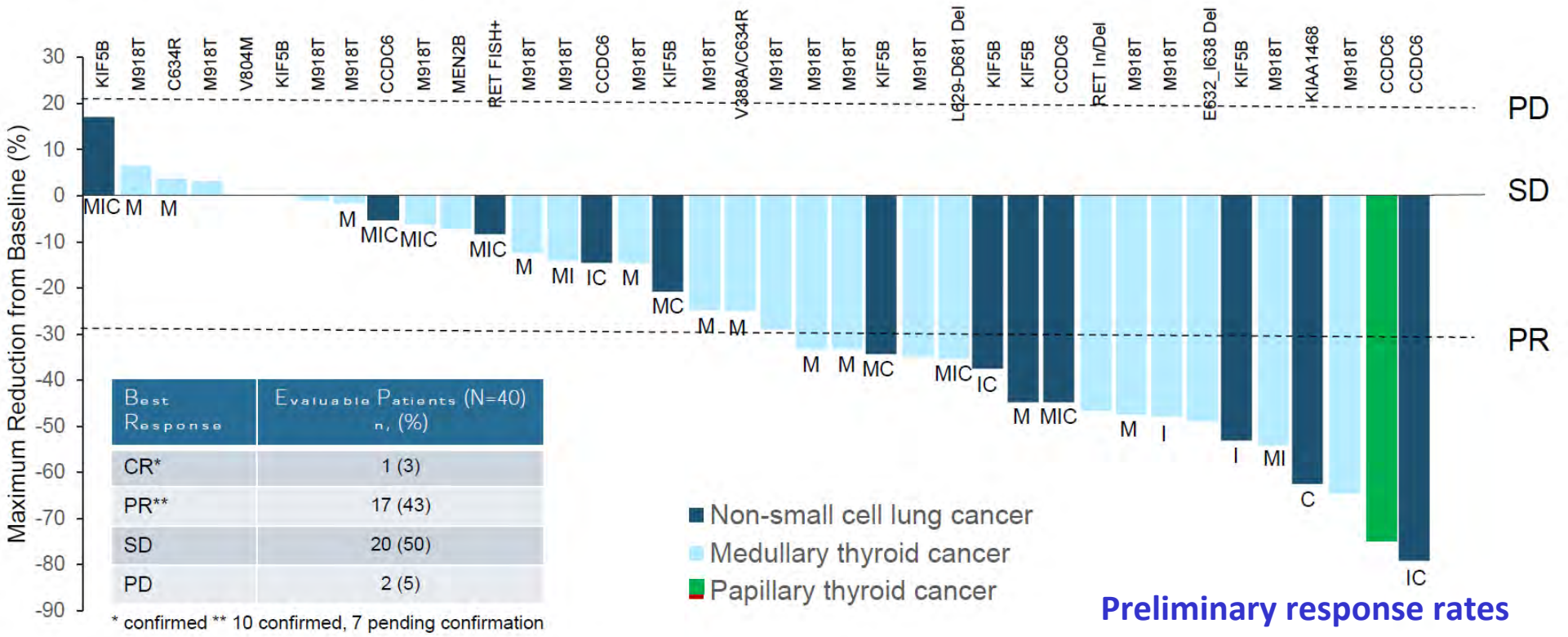


Kinome selectivity for RET



1. Subbiah V et al. *Cancer Discovery* April 15 2018

Broad anti-tumor activity against RET-altered cancers



Best Response	Evaluable Patients (N=40) n, (%)
CR*	1 (3)
PR**	17 (43)
SD	20 (50)
PD	2 (5)

* confirmed ** 10 confirmed, 7 pending confirmation

Preliminary response rates

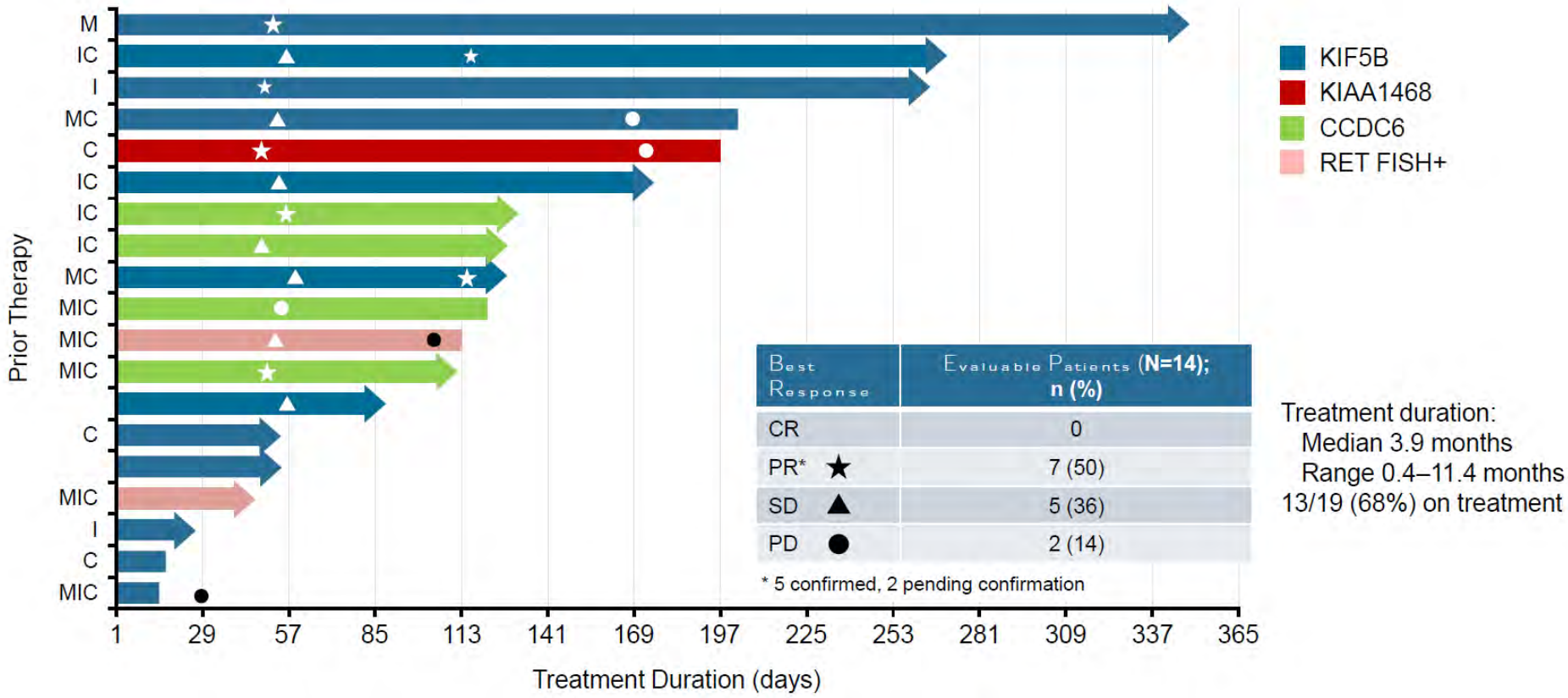
-ORR RET-fusion NSCLC 50%

-ORR RET-fusion MTC 40%

Vivek Subbiah et al, Cancer discovery 2018

Vivek Subbiah et al, AACR 2018

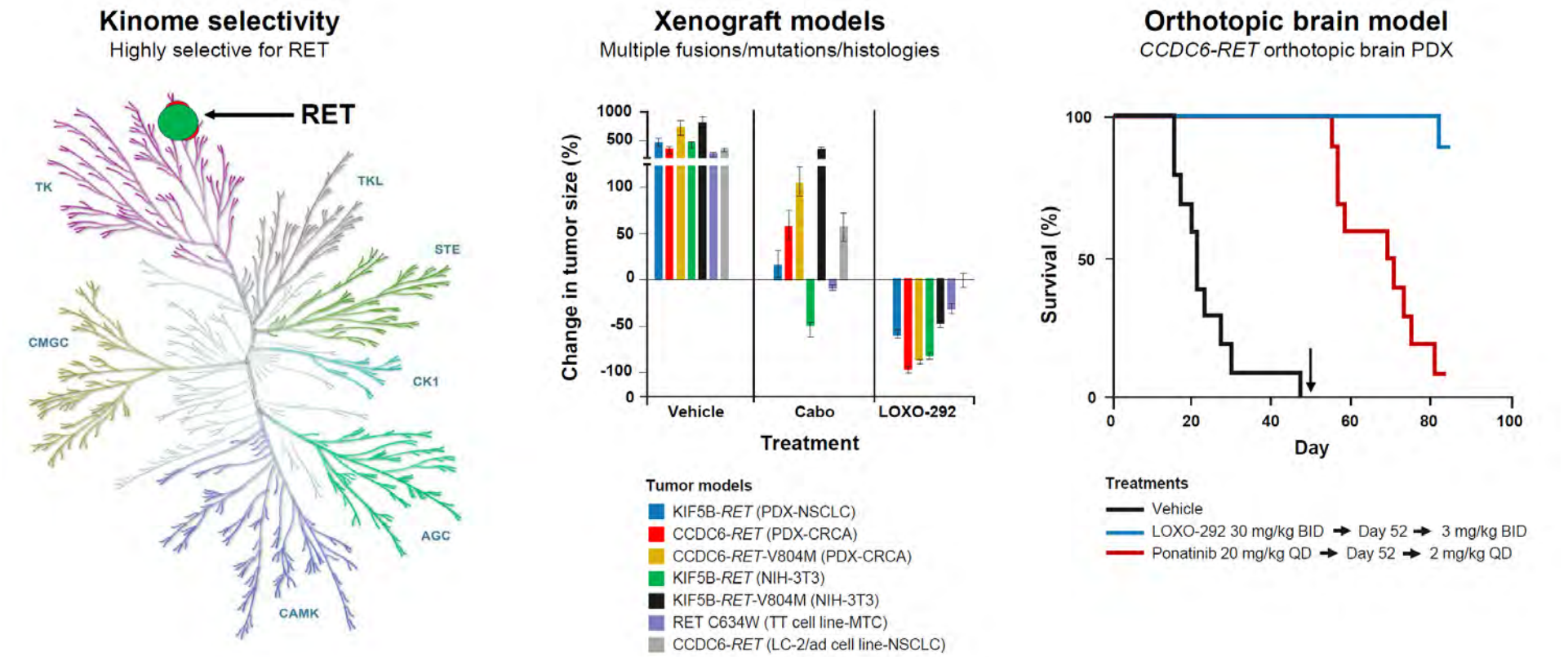
Durable activity



Vivek Subbiah et al, Cancer discovery 2018

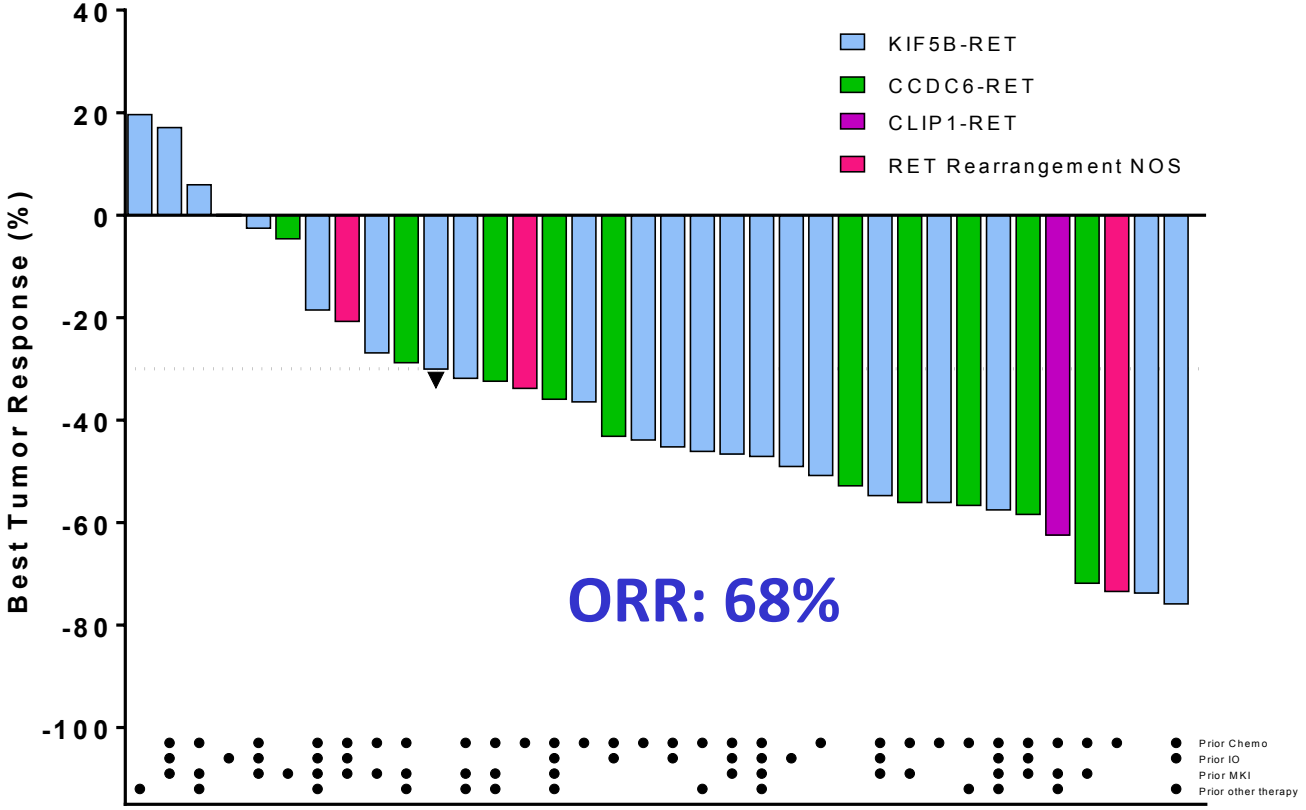
Vivek Subbiah et al, AACR 2018

LOXO-292 is a potent and selective RET inhibitor



Subbiah et al. Ann Oncol 2018; Cabo = cabozantinib; PDX = patient-derived xenograft; NSCLC = non-small cell lung cancer; CRC = colorectal cancer; MTC = medullary thyroid cancer; BID = twice-daily; QD = once-daily

LOX-292: a new potent inhibitor of RET



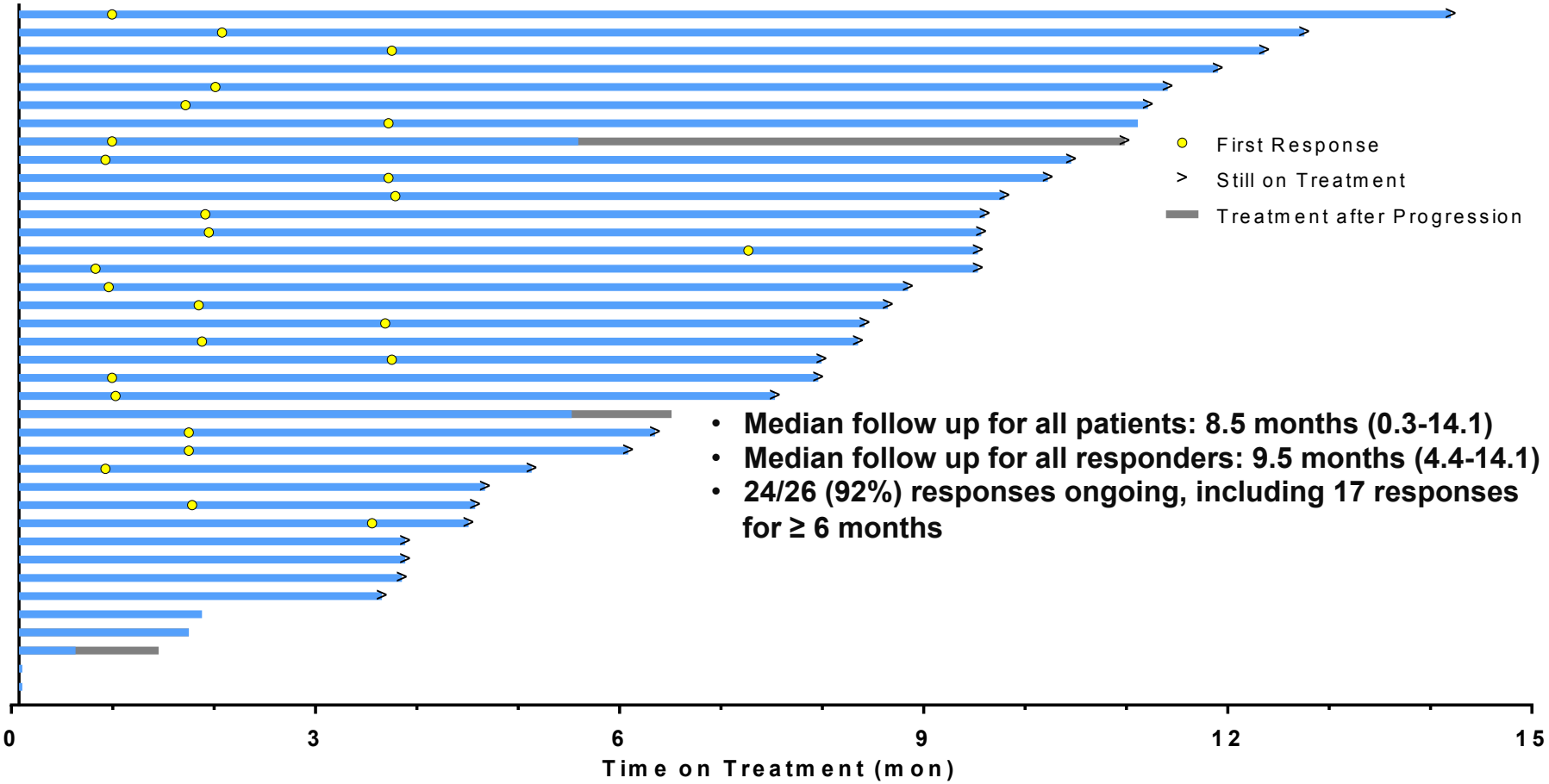
RET fusion-positive NSCLC	
Enrolled	38
Eligible for response evaluation	38
Overall Response Rate (95% CI)	**26/38 68% (51% - 83%)**
Confirmed ORR*	**25/37 68% (50% - 82%)**
CR	-
PR**	26
SD	8
PD	2
NE	2

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

▼ pending confirmation; * Excludes one patient with unconfirmed PR pending confirmation at time of data cut-off; ** 25 confirmed PR, 1 unconfirmed PR pending confirmation
Follow-up as of July 19, 2018.

Geoffrey R. Oxnard et al, WCLC 2018

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



NSCLC Patients enrolled as of April 2, 2018. Follow-up as of July 19, 2018.

Geoffrey R. Oxnard et al, WCLC 2018

RET: the next big target…

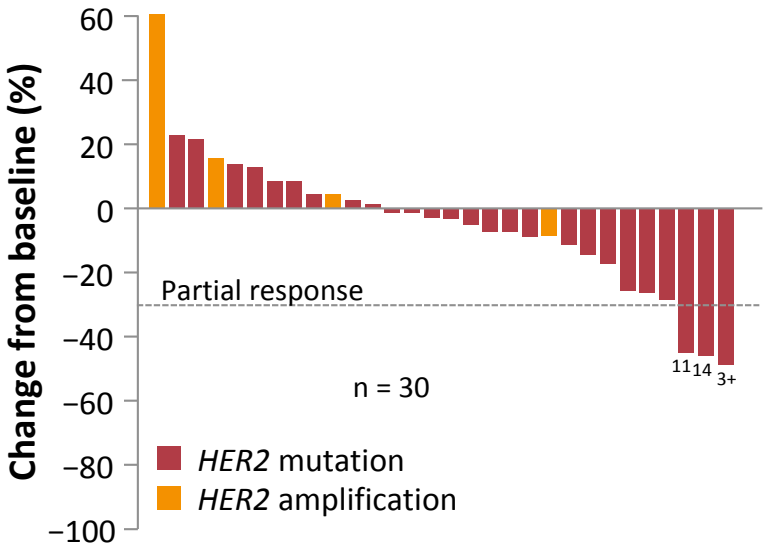
Study	Drug	n	Response rate	PFS
Drilon A, 2016	**Cabozantinib**	25	28%	NR
Lin JJ, 2016	**Alectinib**	4	50%	Duration trtt: 6m
Lee SH, 2017	**Vandetanib**	18	18%	4.5 m.
Yoh, K, 2017	**Vandetanib**	19	53%	4.7 m.
Velcheti, 2016	**Lenvatinib**	25	18%	7.3 m.
Gaustchi O, 2017	**Various (registry)**	53	18 to 37%	2.3 m.
Subbiah V, 2018 (ASCO)	**vandetanib + everolimus**	13	**54%** (7/13)	4.4m
Subbiah V, 2018 (AACR)	**BLU-667**	53 (19 NSCLC)	**50%** (NSCLC)	Duration trtt: 3.9m
Drilon A, 2018 (ASCO)	**LOXO-292**	82 (38 NSCLC)	**68%**	N.A

Drilon A, Lancet Oncol 2016; Lin JJ, JTO 2016; Lee SH, Lancet Resp Med 2016; Yoh K, Lancet Respir Med 2016; Gaustchi O, JCO 2017

Targeting *HER2* aberrations

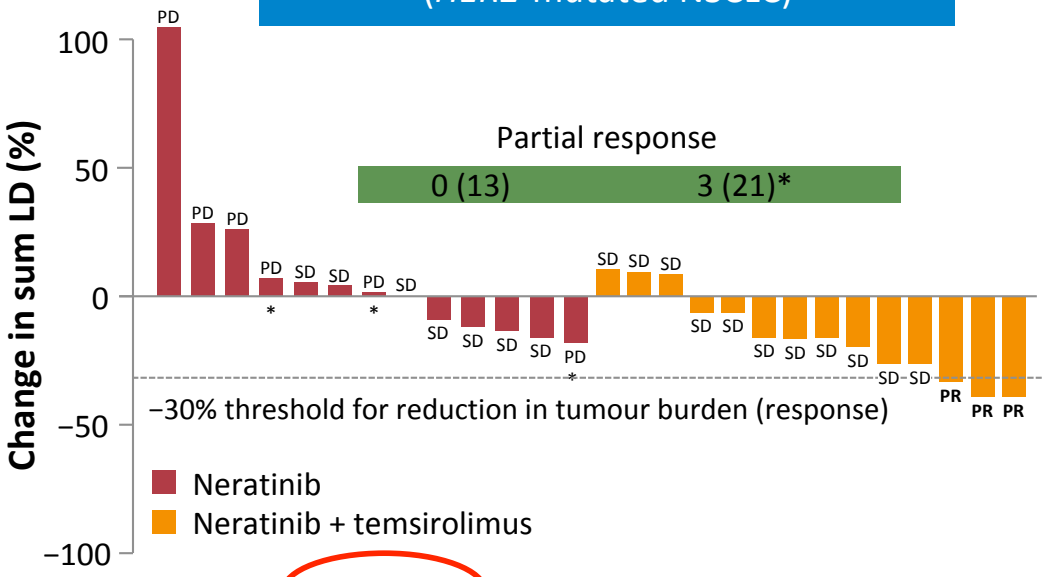
HER2 mutations in ~1–4% and *HER2* amplifications in 2–5%

Dacomitinib (pan-HER inhibitor)
(*HER2*-mutated or amplified NSCLC)



Only 3/26 of *HER2*-mutant patients had a response **(ORR 12%)**

Neratinib (pan-HER inhibitor)
± temsirolimus (mTOR inhibitor)
(*HER2*-mutated NSCLC)



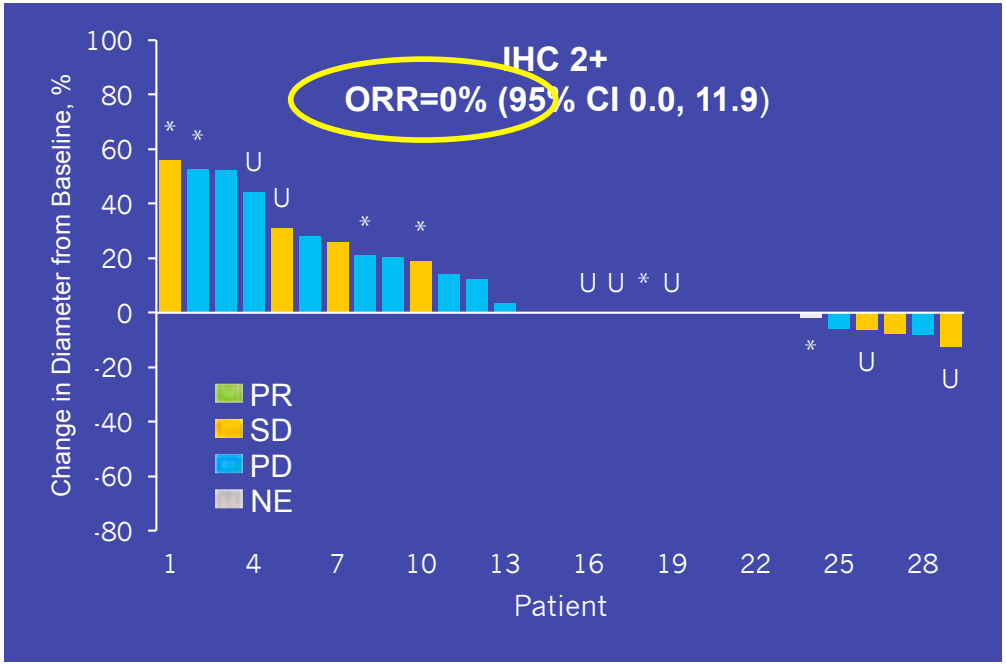
21% ORR and mPFS of 4 months

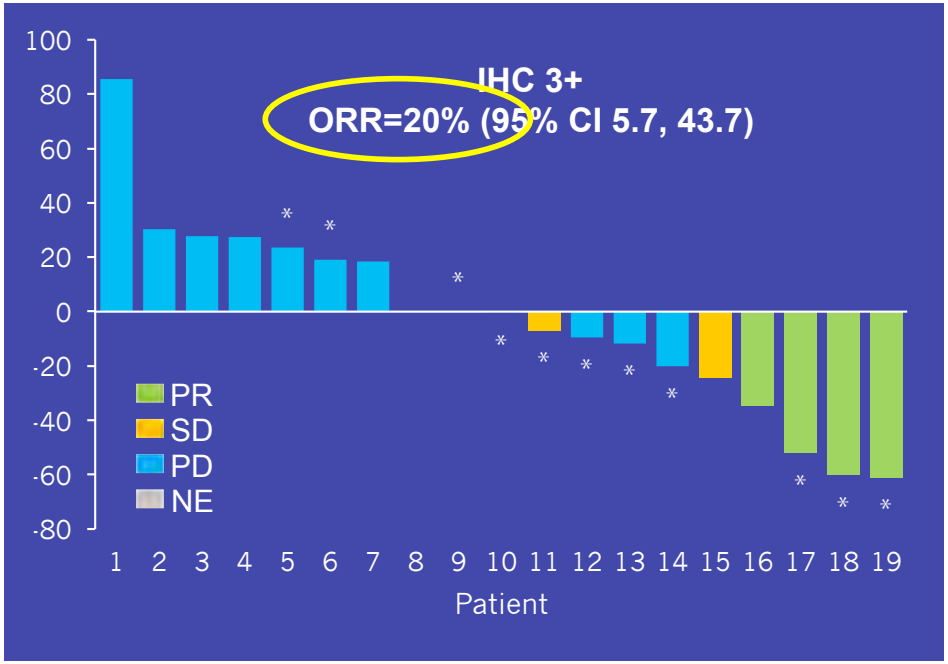
* Patients had < 20% increase in tumour burden, but were considered PD due to the appearance of new lesions

Kris MG, et al. Ann Oncol. 2015; 26:1421-7. Besse B, et al. Presented at ESMO 2014. Abstract LBA 39.

Antibody-drug ConjugateTrastuzumab Emtansine (T-DM1) in Pts with Previously Treated HER2-Overexpressing

	IHC 2+ (n=29)	IHC 3+ (n=20)	All (N=49)
Median PFS, mo (95% CI)	**2.6** (1.4, 2.8)	**2.7** (1.4, 8.3)	**2.6** (1.4, 2.8)



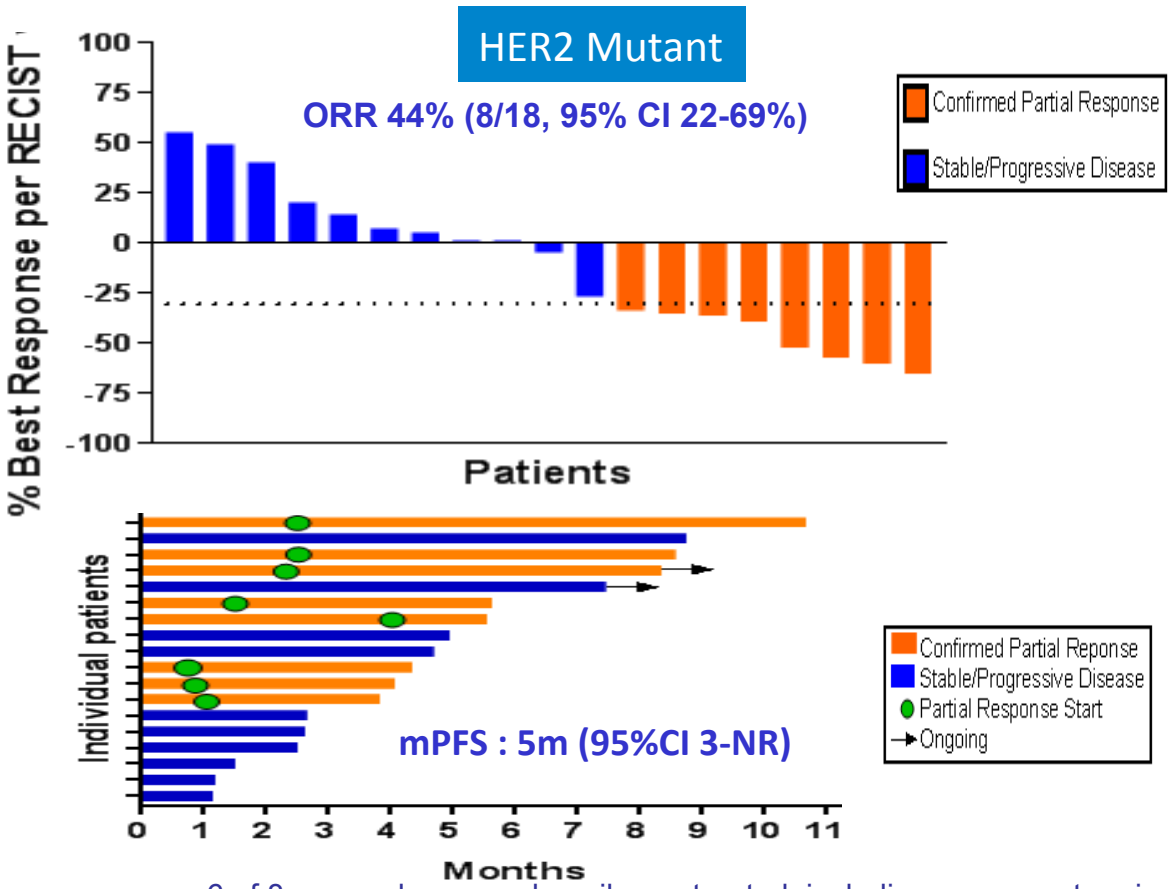


***Indicates positive HER2 amplification; U indicates unknown HER2 amplification; All other patients' ISH status is negative**

Thomas Stinchcombe et al, ASCO 2017

Phase 2 trial of ado-trastuzumab emtansine for pts with *HER2* amplified or mutant cancers

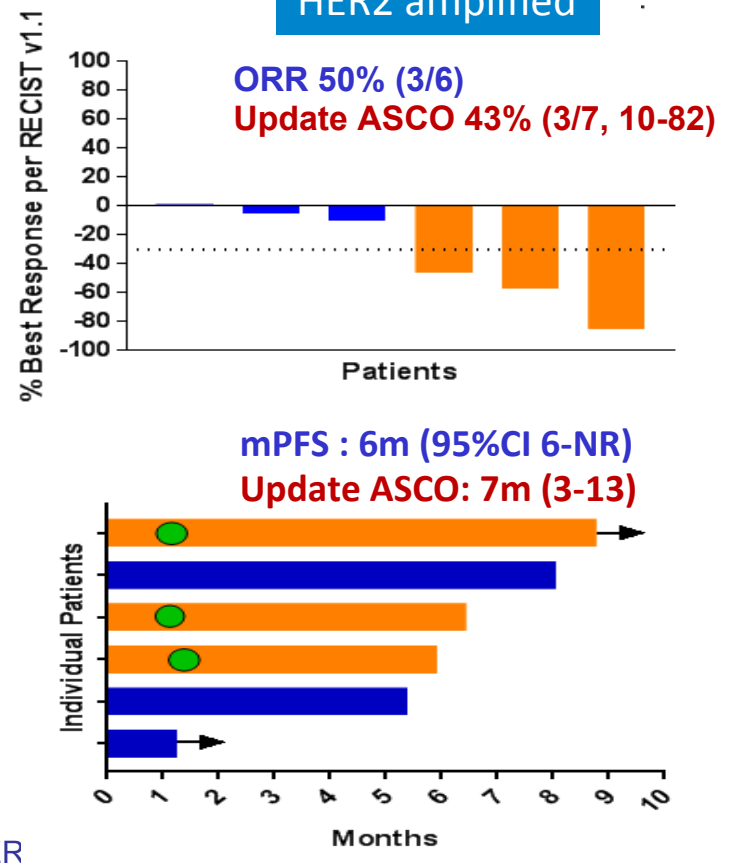
HER2 Mutant



6 of 8 responders were heavily pre-treated, including response to prior HER therapy neratinib, afatinib, trastuzumab

Bob T.Li et al, JCO 2018

HER2 amplified



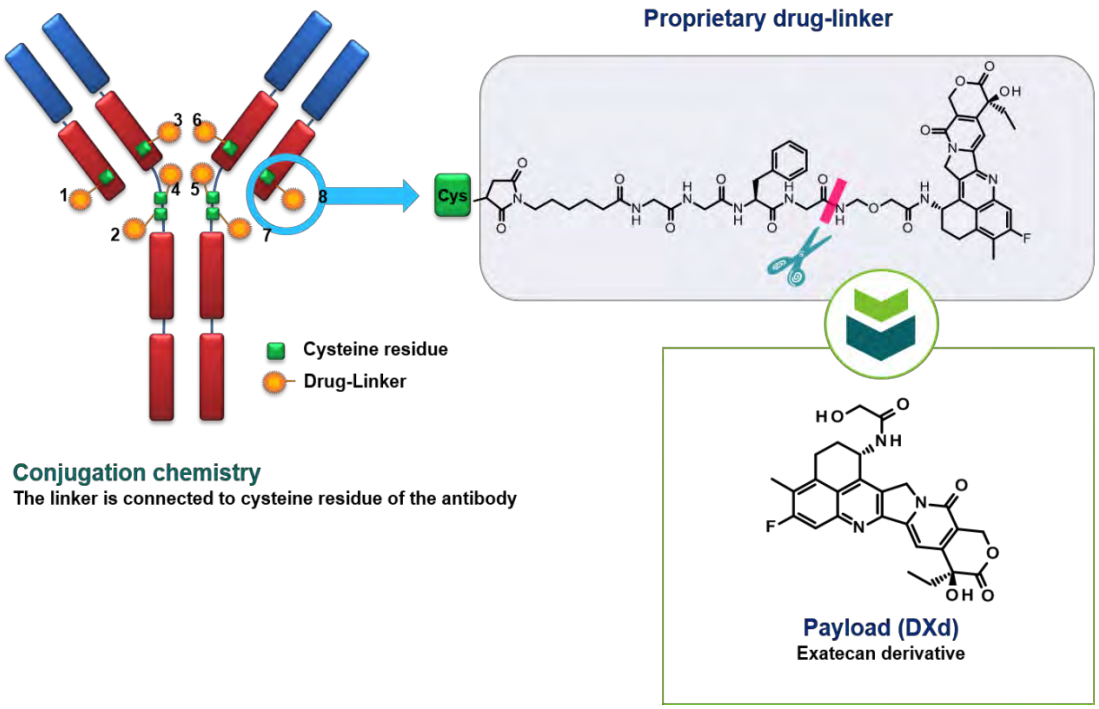
Bob T. Li, MD et al, WCLC 2017, Bob T.Li et al, ASCO 2018

Concurrent HER2 amplification observed in 2 of 18 (11%)

NGS	FISH (HER2/CEP17)	IHC	Mass spectrometry (amol/ug)	Partial Response
Exon 20 p.A775_G776insYVMA	1.1 (2.7/2.5)	0	NA	Yes
Exon 20 p.A775_G776insYVMA	1.8 (8.1/4.5)	2+	642	
Exon 20 p.A775_G776insYVMA	NA	NA	NA	
Exon 20 p.A775_G776insYVMA	1.4 (4.5/3.3)	1+	586	Yes
Exon 20 p.A775_G776insYVMA	1.9 (5.6/2.9)	1+	548	Yes
Exon 20 p.G778_P780dup	1.6 (7.6/4.8)	1+	0	
Exon 20 p.G778_P780dup	1.8(4.6/2.5)	2+	507	Yes
Exon 20 p.G778_P780dup	1.4 (5.8/4.2)	2+	NA	
Exon 20 p.G778-779 insCPG	1.6(4.3/2.7)	0	NA	
Exon 20 p.G776_V777>VCV	NA	NA	NA	Yes
Exon 20 p.G776delinsVC	1.6 (5.7/3.6)	0	205	Yes
Exon 19 p.L755P	1.5 (3.2/2.1)	2+	434	
Exon 19 p.L755P	NA	0	NA	
Exon 17 p.V659E	1.2 (2.4/2.0)	2+	NA	
Exon 17 p.V659E	1.1 (2.3/2.0)	2+	688	Yes
Exon 8 p.S310F amplification fold change 2.8	4.1 (8.4/2.5)	2+	1495	Yes
Exon 8 p.S310F	1.8 (3.2/1.8)	0	0	
Exon 8 p.S335C	2.4 (4.8/2.0)	2+	902	

Bob T.Li et al, JCO 2018

Updated results of a phase 1 study of DS-8201a in HER2-expressing or -mutated advanced NSCLC



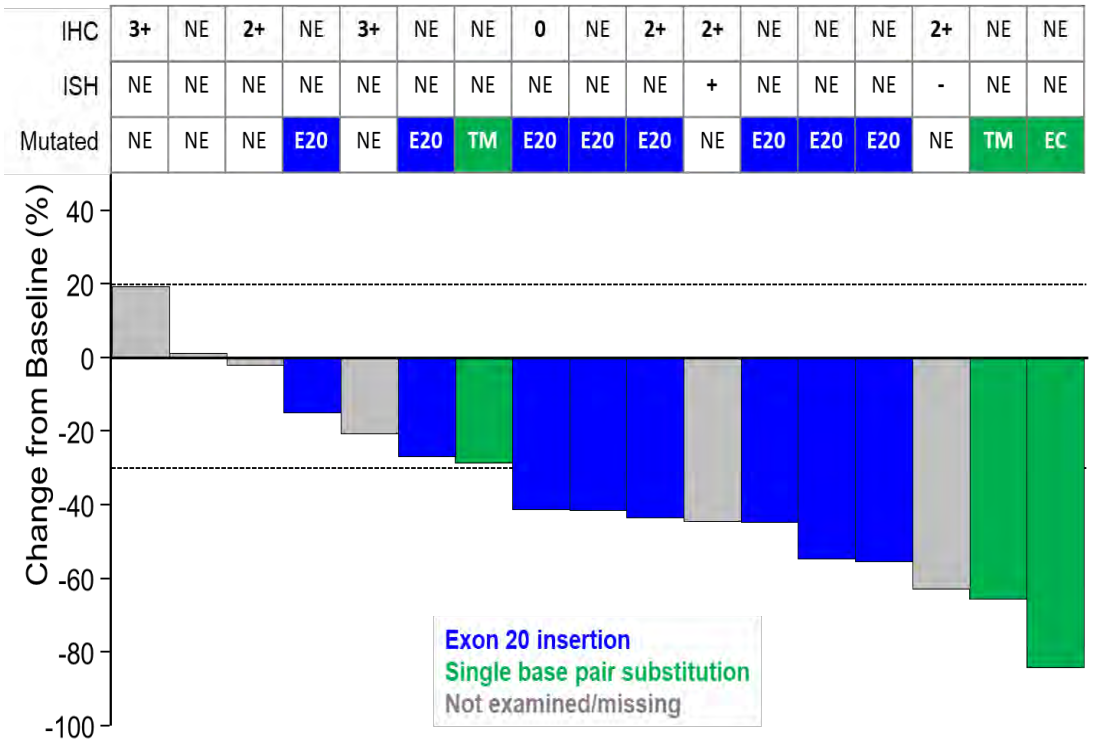
- *Payload with a different mechanism of action*
- *High potency of payload*
- *Payload with short systemic half-life*
- *Bystander effect*
- *Stable linker-payload*
- *Tumor-selective cleavable linker*
- *High drug-to-antibody ratio (7–8)*

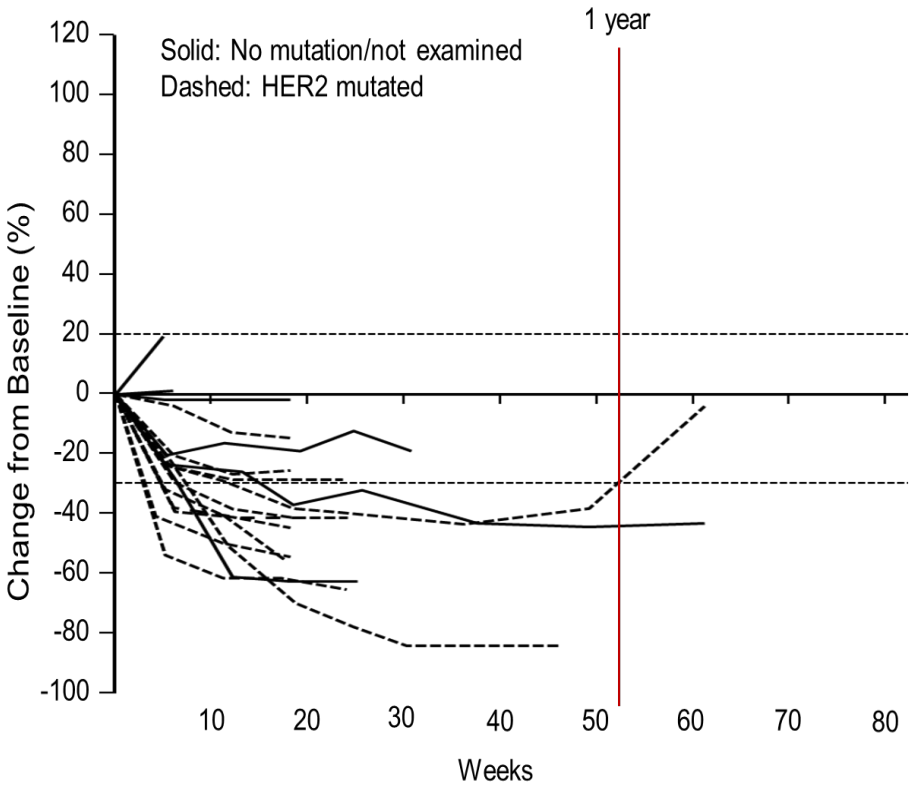
- DS-8201a was designed with the goal of improving critical attributes of an ADC

ADC, antibody drug conjugate.

Junji Tsurutani et al, WCLC 2018

Updated results of a phase 1 study of DS-8201a in HER2-expressing or -mutated advanced NSCLC





IHC by local laboratory testing.
E20, exon 20 insertion; EC, single base pair substitution at extracellular domain; IHC, immunohistochemistry; ISH, in situ hybridization; NSCLC, non-small cell lung cancer; NE, not examined or missing; TM, single base pair substitution in transmembrane domain.

Junji Tsurutani et al, WCLC 2018

Efficacy Outcomes (Efficacy Evaluable Subjects)

	Confirmed ORR*, % (n/N)	DCR, % (n/N)	DOR, median (range), months	TTR, median (range), months	PFS, median (range), months
HER2-expressing or HER2-mutated NSCLC N = 18	**58.8% (10/17)**	83.3% (15/18)	9.9 (0.0+, 11.5)	1.4 (1.0, 4.2)	**14.1 (0.9, 14.1)**
HER2-mutated NSCLC n = 11	**72.7% (8/11)**	100% (11/11)	11.5 (0.03+, 11.5)	1.4 (1.0, 4.2)	**14.1 (4.0+, 14.1)**

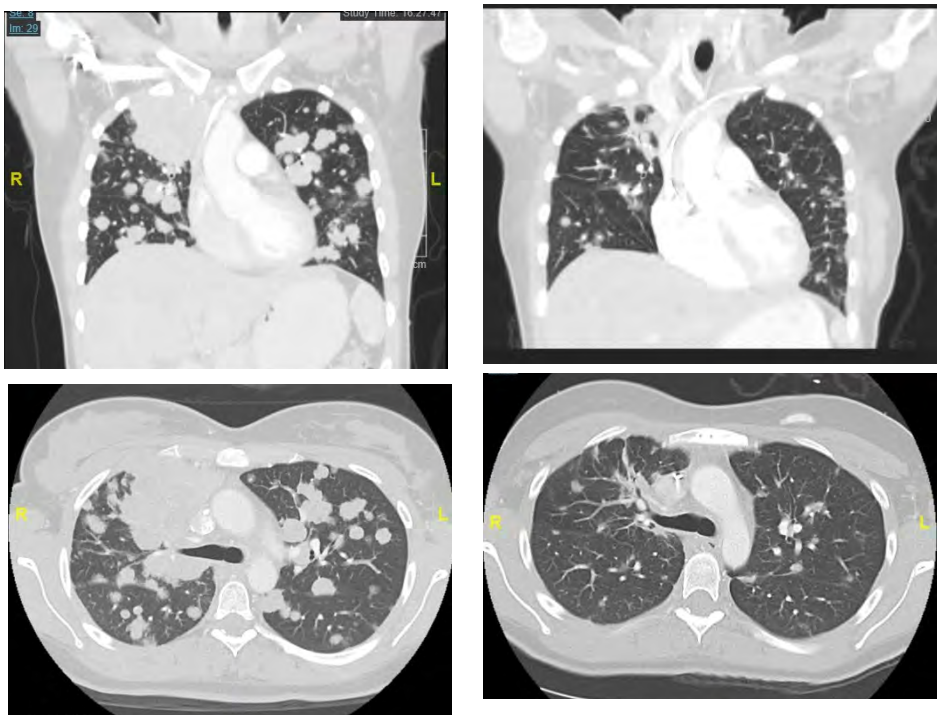
Data cutoff, August 24, 2018.
*Confirmed response includes subjects who had ≥2 postbaseline scans, had progressive disease, or discontinued treatment for any reason prior to second postbaseline scan.
+ after value indicates censoring.
DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; TTR, time to response.

Junji Tsurutani et al, WCLC 2018

Example CT Image from Responder to DS-8201a

- 23 years old
- Female
- Nonsmoker
- History of Type 1 Diabetes
- HER2 12 bp insertion in exon 20
- **January 2017:** presented with cough and SOB
  - Diagnosed with stage IV nonsquamous NSCLC
  - Carbo/Pem 1 cycle
- **February–June 2017:** switched to Carbo/Nab-paclitaxel due to LFT elevations
  - Best response SD
- **September–December 2017:** switched to Carbo/Pem due to progression
  - Four cycles
  - Best response SD
  - Last scan with slight increase in disease
  - Recommended HER2 targeted therapy; came to DFCI
- **February 2018:** started DS-8201a
  - Symptomatic with cough and DOE
  - Status: PR (confirmed)

HER2 insertion exon 20



February 2018 – baseline

May 2018 – C5D1

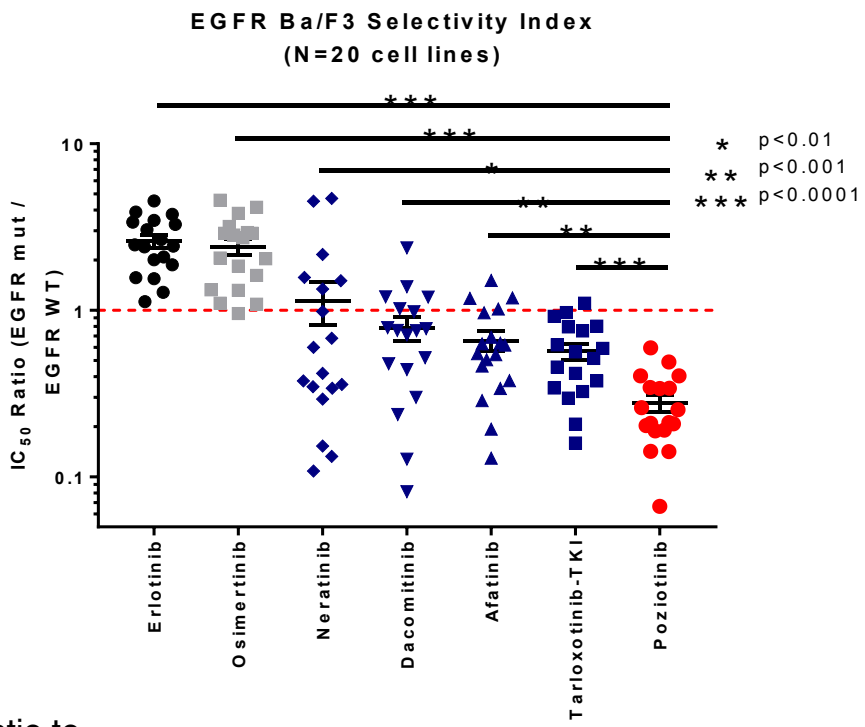
Images courtesy of Dr. Pasi Jänne. Special thanks to Dr. Pasi Jänne and Dr. Ian Krop of DFCI.

bp, base pair; Carbo, carboplatin; CT, computed tomography; DFCI, Dana-Farber Cancer Institute; DOE, dyspnea on exertion; HER2, human epidermal growth factor 2; IV, intravenous; LFT, liver function test; Nab, nab-paclitaxel; NSCLC, non-small cell lung cancer; Pem, pemetrexed; PR, partial remission; SD, stable disease; SOB, shortness of breath.

Junji Tsurutani et al, WCLC 2018

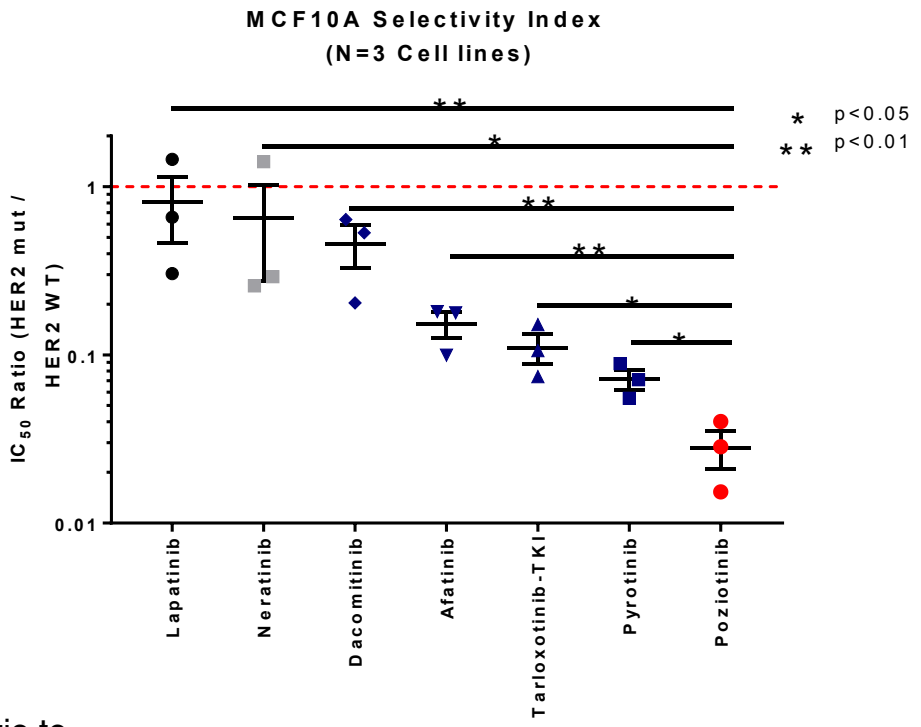
Poziotinib is a selective (mut vs wt) inhibitor of EGFR and HER2 exon 20 mutations *in vitro*

EGFR



Ratio to Poziotinib	9.4	8.7	4.1	2.8	2.4	2.0

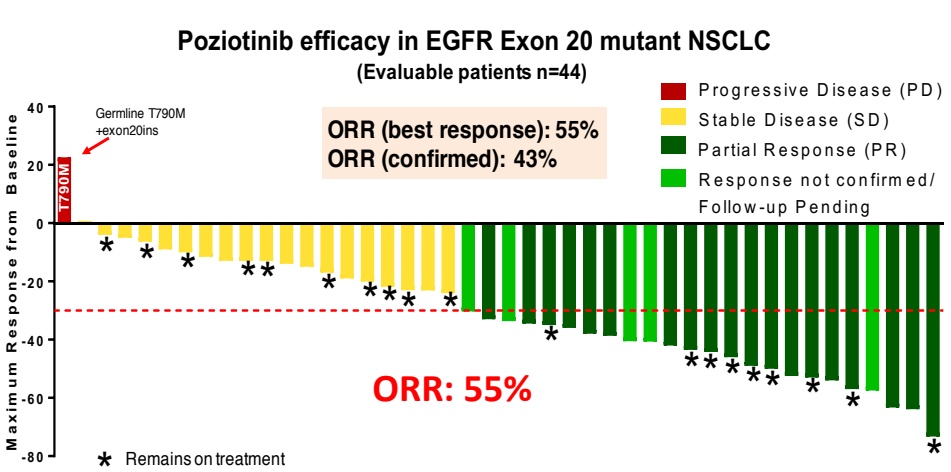
HER2

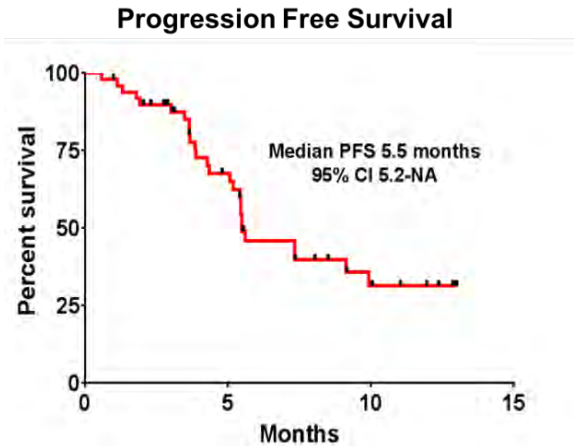


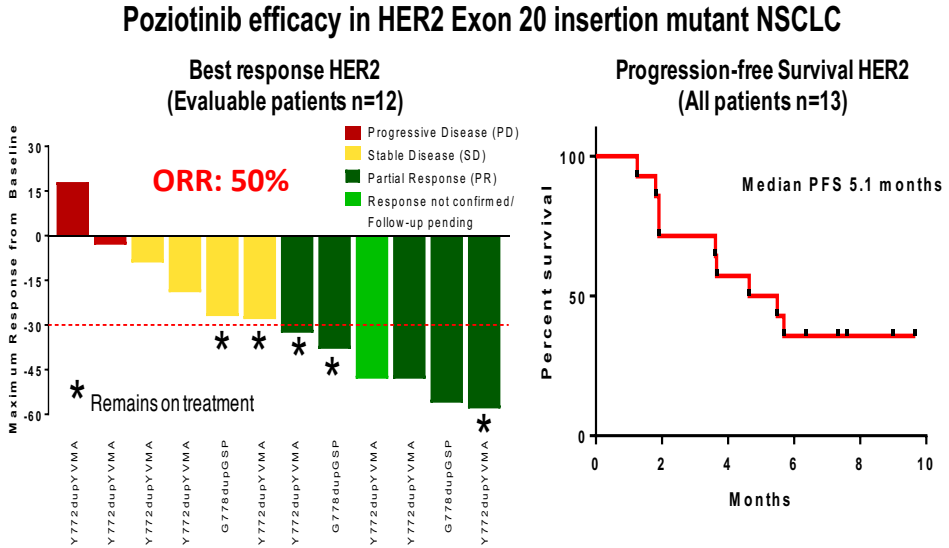
Ratio to Poziotinib	28.7	23.3	16.3	5.4	4.0	2.6

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

A Phase II Trial of Poziotinib in EGFR and HER2 exon 20 Mutant Non-Small Cell Lung Cancer (NSCLC)





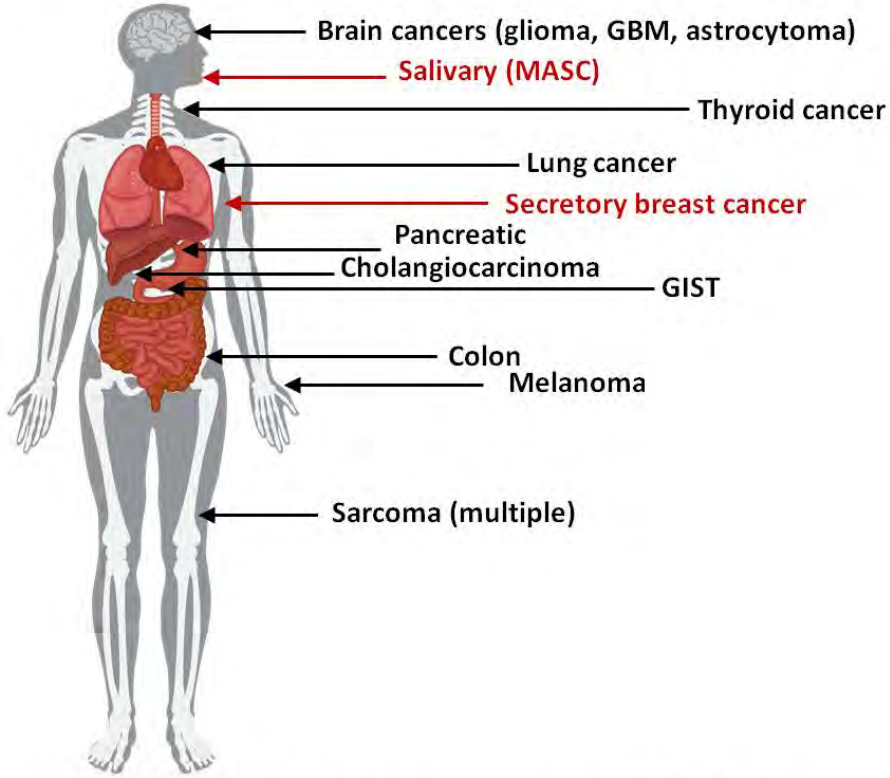


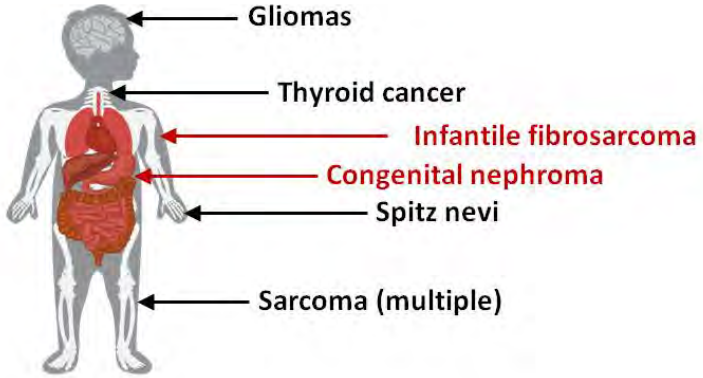
Conclusions:

Encouraging activity has prompted a confirmatory, international, multicenter study in *EGFR* and *HER2* exon 20 mutant NSCLC patients which is currently enrolling (NCT03318939) including a first-line cohort and development of a pan-tumor basket study

Adapted from Heymach JV. OA 02.06 (WCLC 2018)

TRK fusions found in diverse cancer histologies





■ Common cancer with low TRK fusion frequency

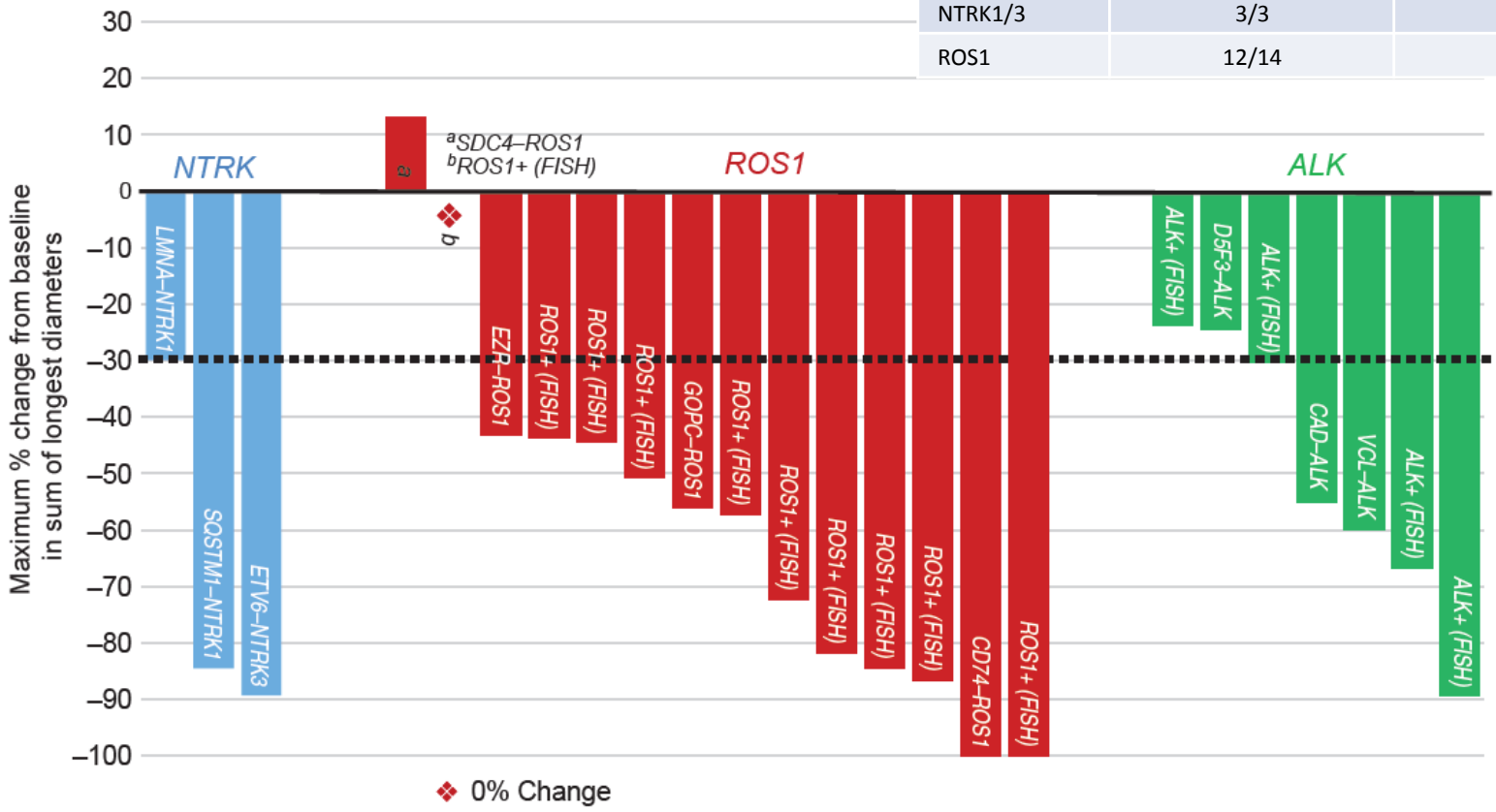
■ Rare cancer with high TRK fusion frequency

Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually

Hyman ASCO 2017

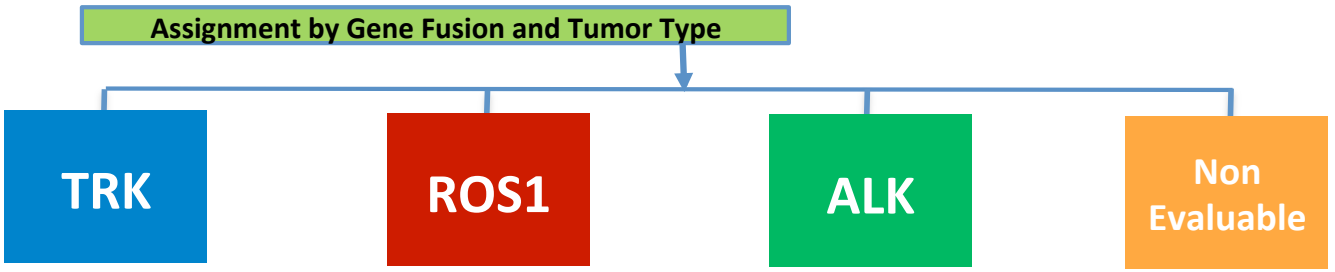
Entrectinib, first in class, antitumor activity in NTRK1/2/3 fusions

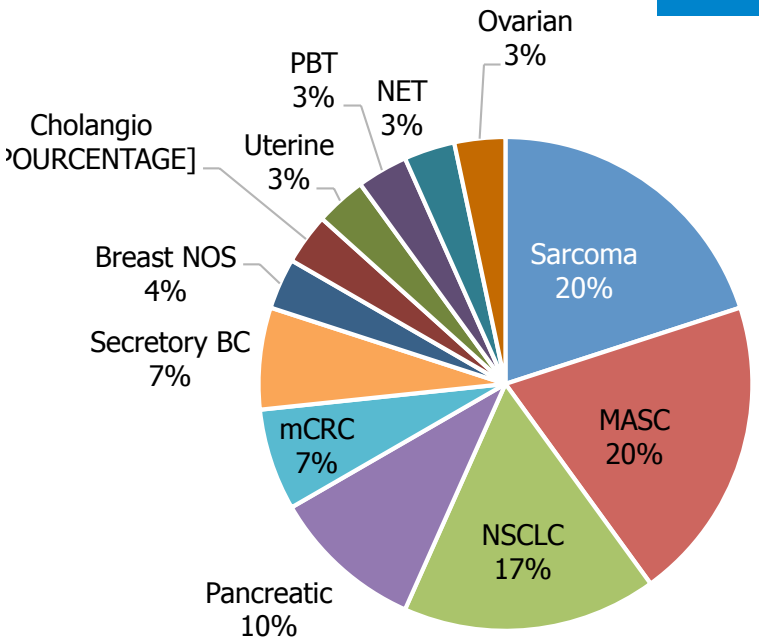
Fusion	Confirmed Responses (n)	ORR (%)
NTRK1/3	3/3	100%
ROS1	12/14	86%



A.Drilon et al, Can Disc 2017

STARTRK-2 NTRK Enrollment





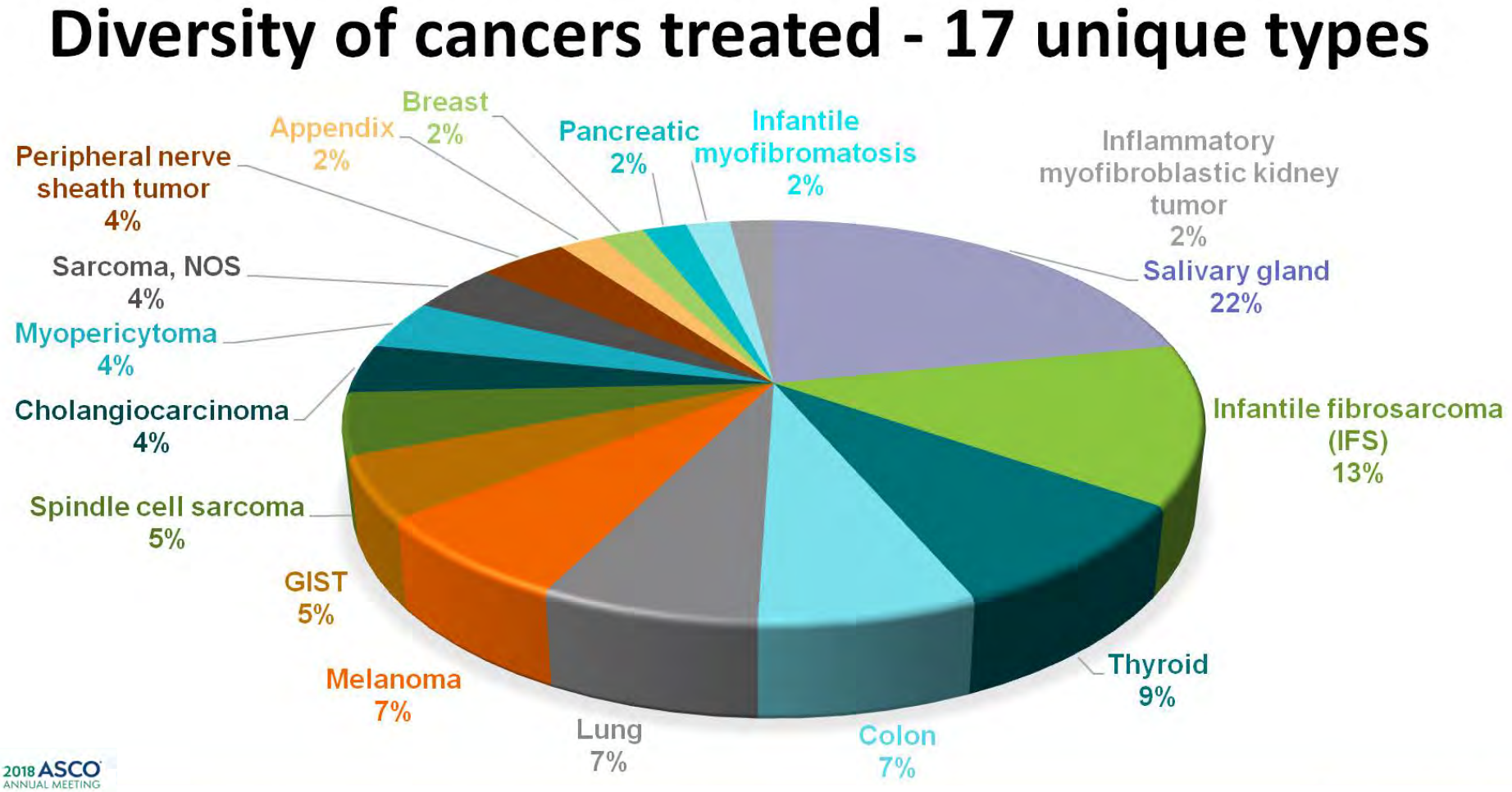
TRK by Histology

TRK enrollment in STARTRK-2 has been consistent with the diffuse distribution pattern described in the literature

- Patients with TRK fusions enrolled across >15 different tumor types
- All of these patients were identified using next generation sequencing (NGS)

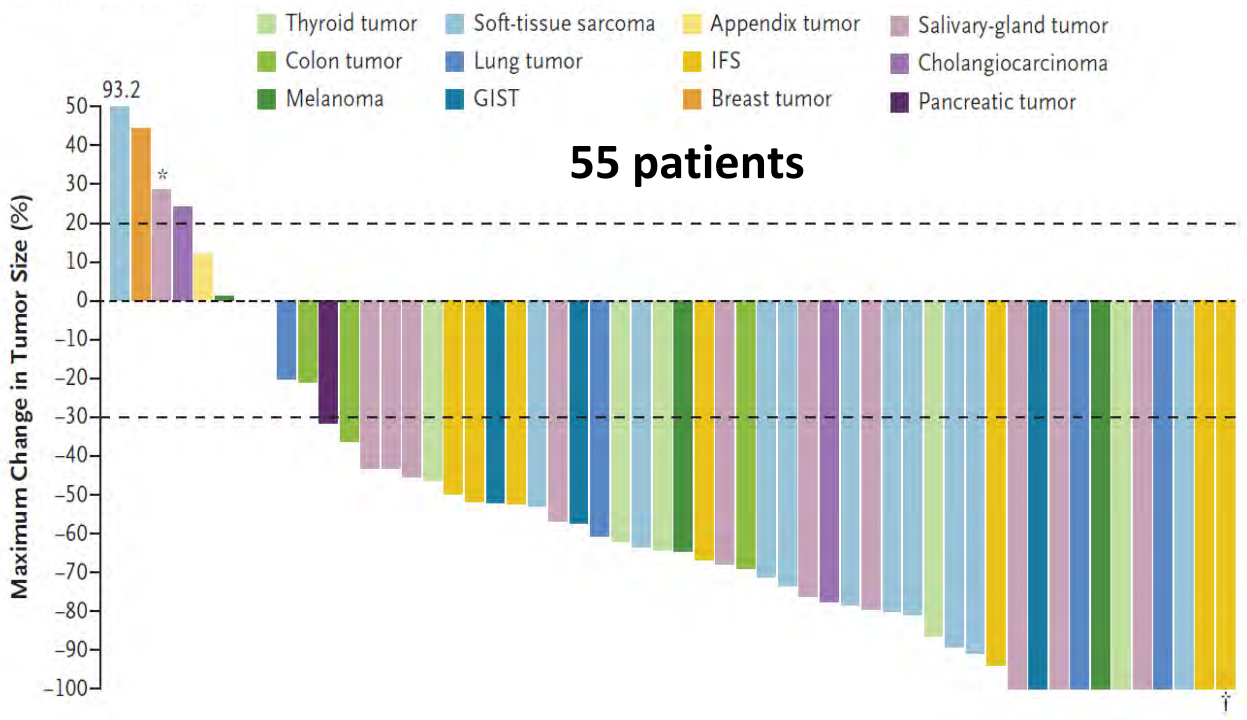
A. Drilon et al, Can Disc 2017

Larotrectinib (LOXO-101), a selective TRK inhibitor



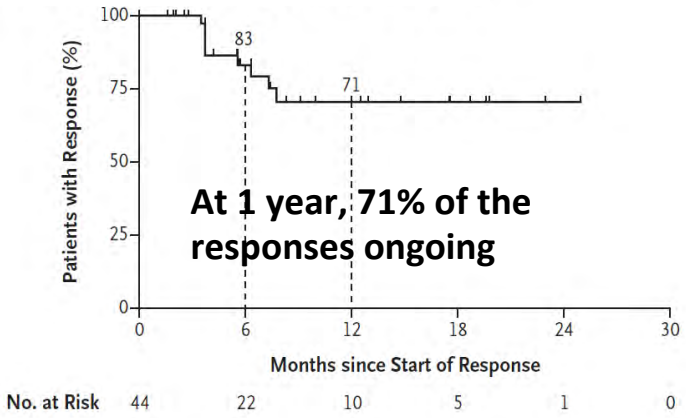
PRESENTED AT: 2018 ASCO ANNUAL MEETING

Efficacy of Larotrectinib in TRK Fusion– Positive Cancers in Adults and Children

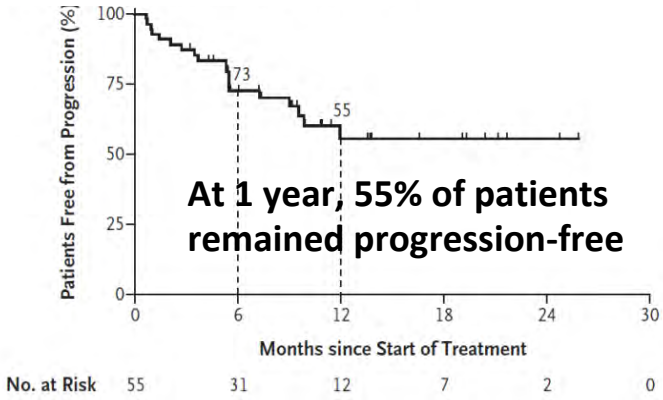


ORR: 75% (95%CI, 61-85), independent review
ORR: 80% (95% CI, 67-90), investigator assessment

DOR

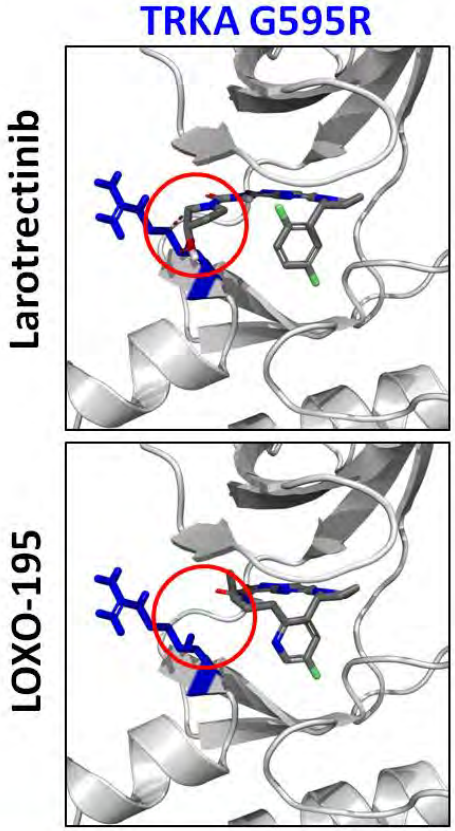


PFS



A. Drilon et al, NEJM 2018

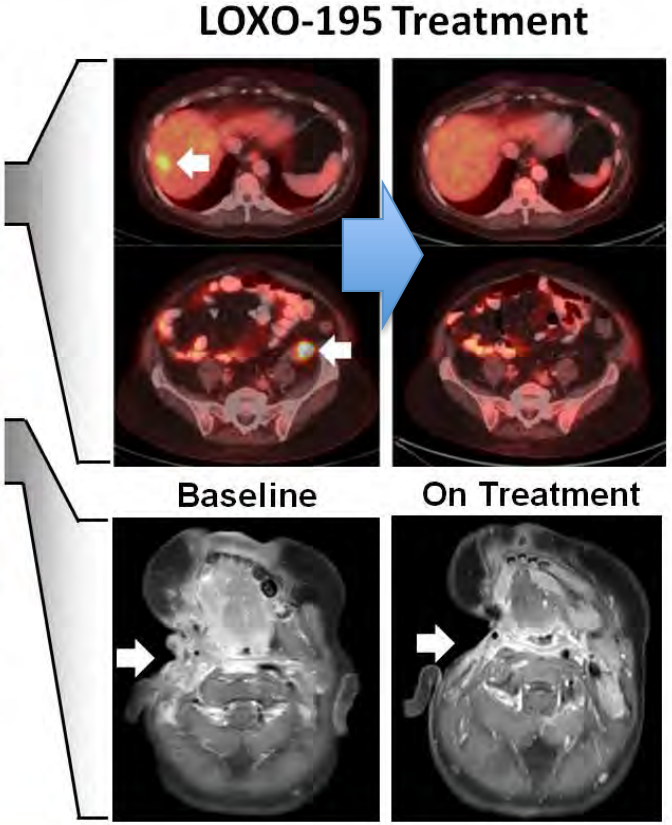
LOXO-195 to Address TRK Acquired Resistance



Larotrectinib (LOXO-101)

Tumor type	Fusion	Resistance mutation
Colorectal	TPM3-NTRK1	TRKA G595R
Colorectal	LMNA-NTRK1	TRKA G595R
NSCLC	TPR-NTRK1	TRKA G595R
Sarcoma❃	TPM3-NTRK1	TRKA G595R
IFS	ETV6-NTRK3	TRKC G623R
Cholangio❃	LMNA-NTRK1	TRKA F589L* + GNAS Q227H

TRK solvent front mutations detected in 5 of 6 patients with acquired resistance. First 2 patients successfully treated with LOXO-195.



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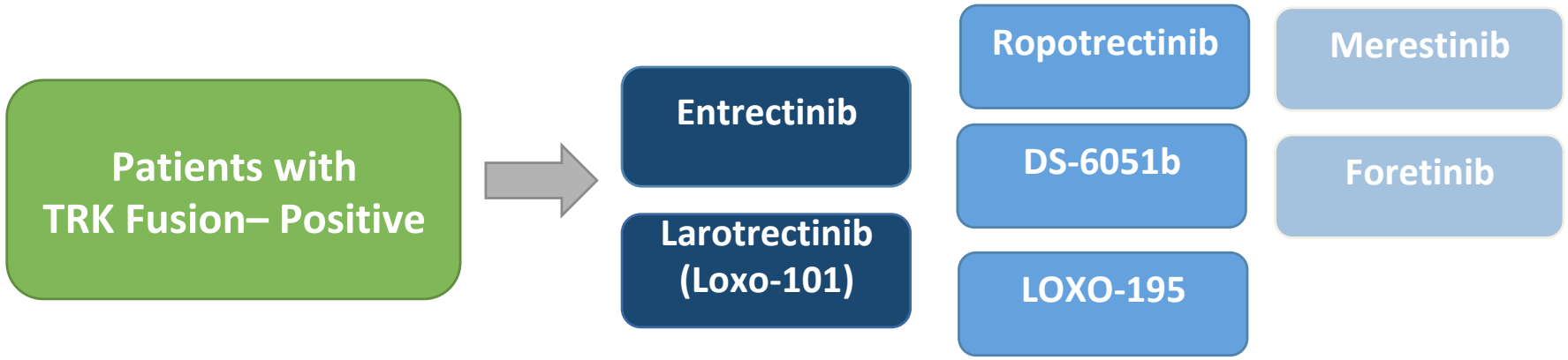
Hyman ASCO 2017, Drilon Can Disc 2017

New data to come…



A phase 1 study of the next-generation ALK/ROS1/TRK inhibitor ropotrectinib (TPX-0005) in patients with advanced ALK/ROS1/NTRK+ cancers (TRIDENT-1)

Presented Monday, June 4, 2018. Alexander E. Drilon (Abst 2513) 65 pts (28 ALK+, 29 ROS1+, and 8 NTRK+)

DS-6051b is an oral, small molecule receptor TKI with high affinity for ROS1 and NTRK kinases

First-in-human study of DS-6051b in patients (pts) with advanced solid tumors (AST) conducted in the US

Presented Monday, June 4, 2018. Kyriakos P. Papadopoulos (Abst 2514)

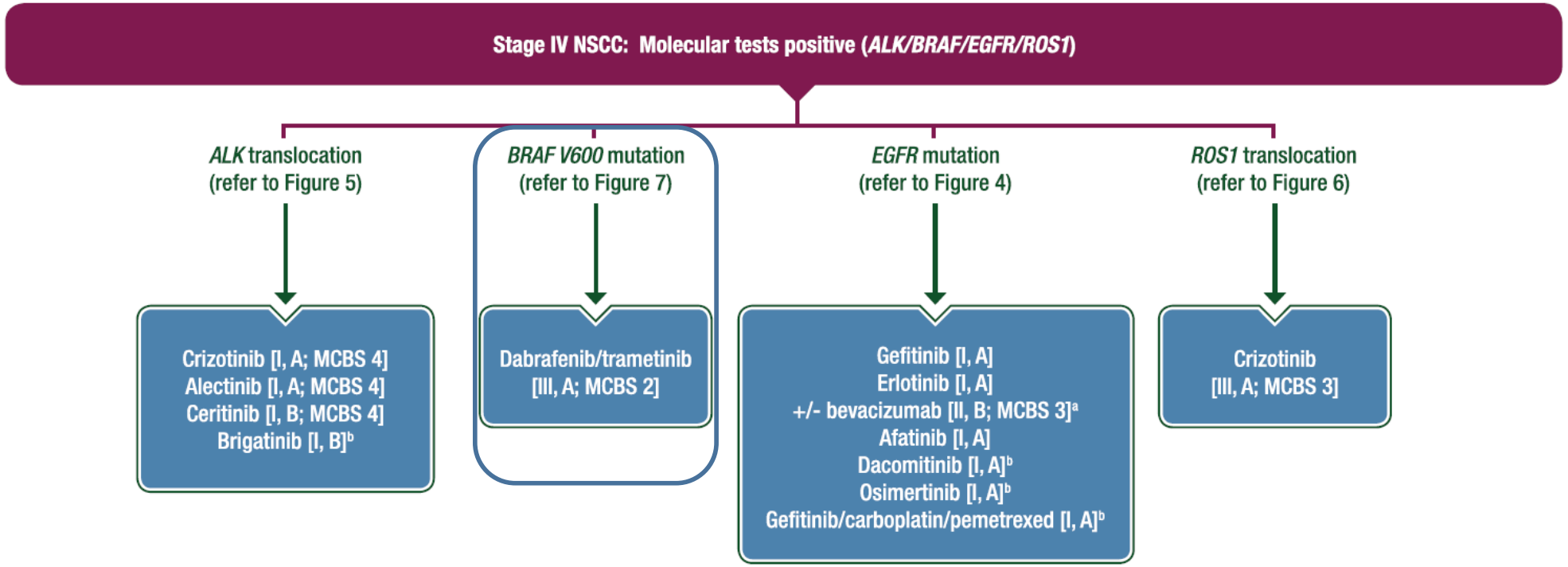
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29 (Supplement 4): iv192–iv237, 2018
doi:10.1093/annonc/mdy275

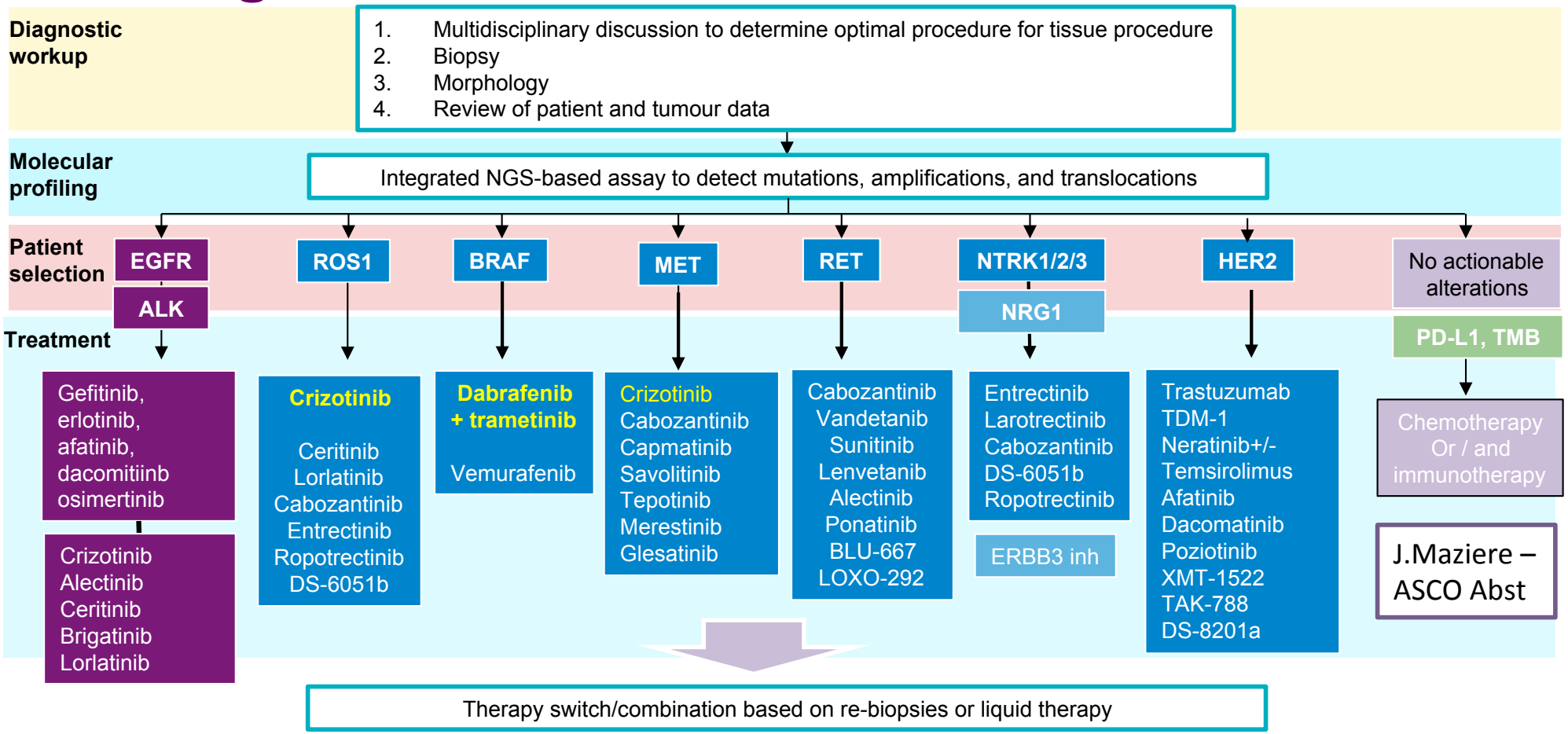
CLINICAL PRACTICE GUIDELINES

Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

D. Planchard[1], S. Popat[2], K. Kerr[3], S. Novello[4], E. F. Smit[5], C. Faivre-Finn[6], T. S. Mok[7], M. Reck[8], P. E. Van Schil[9], M. D. Hellmann[10] & S. Peters[11], on behalf of the ESMO Guidelines Committee*



In summary, promizing new drugs for old or new targets…



THANK YOU !

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