BRAF, MET, and Her2 mutations in lung cancer

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GUSTAVE ROUSSY

CANCER CAMPUS GRAND PARIS

DISCLOSURE SLIDE

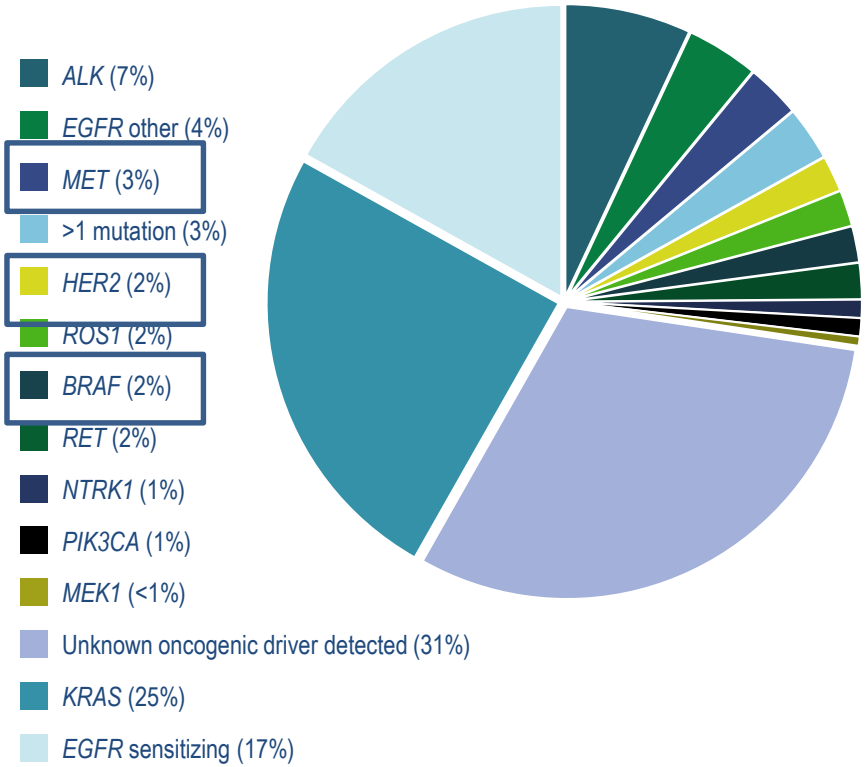
Consulting, advisory role or lectures: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche

Honoraria: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche

Clinical trials research as principal or co-investigator (Institutional financial interests): AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmun, Sanofi-Aventis, Taiho Pharma, Novocure, Daiichi Sankyo

Travel, Accommodations, Expenses: AstraZeneca, Roche, Novartis, prIME Oncology, Pfizer

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



***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; repotrectinib

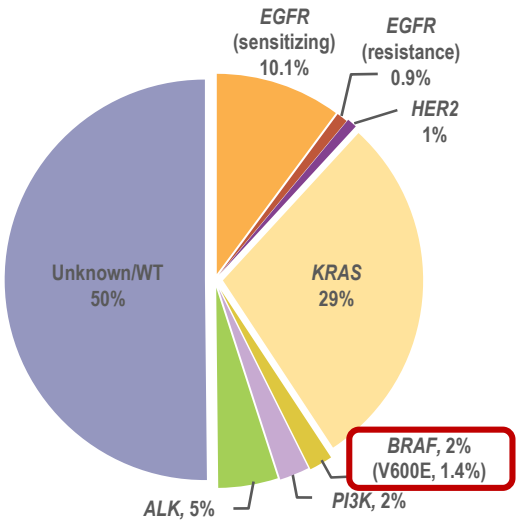
PIK3CA
LY3023414; PQR 309

MEK1
Trametinib; Selumetinib;Cobimetinib

BRAF MUTATIONS IN NSCLC

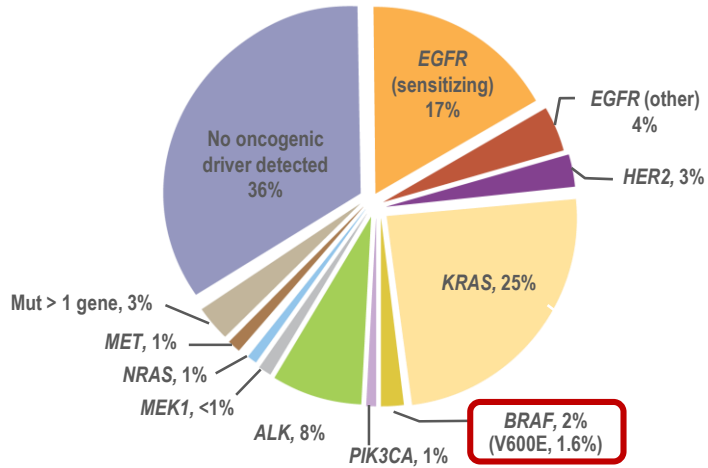
France[1]

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



US[2]

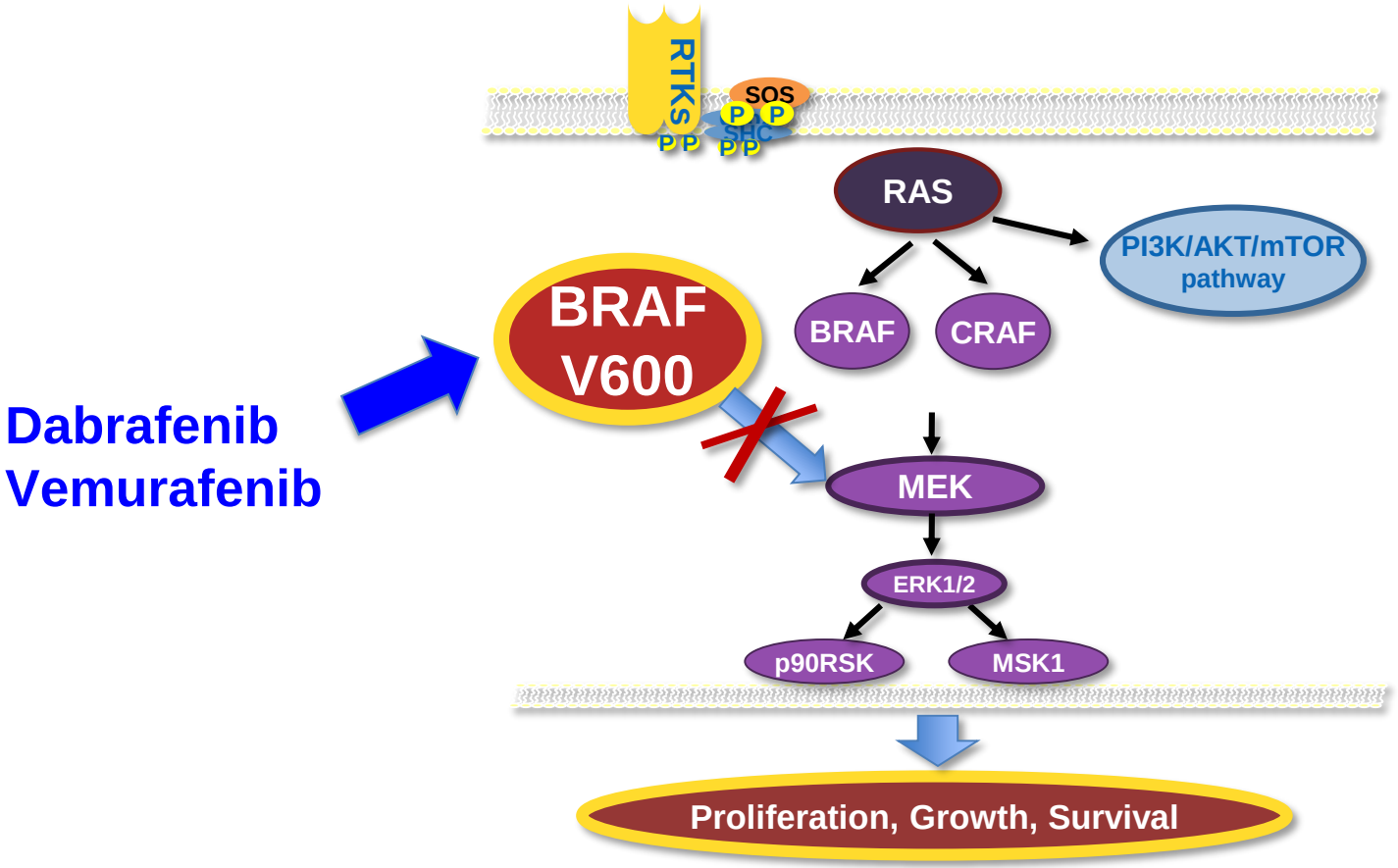
Adenocarcinoma
(Lung Cancer Mutation Consortium; N=733)



- 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

Inhibition of BRAF V600 Kinase



Dabrafenib
Vemurafenib

Vemurafenib in *BRAF* mutant NSCLC

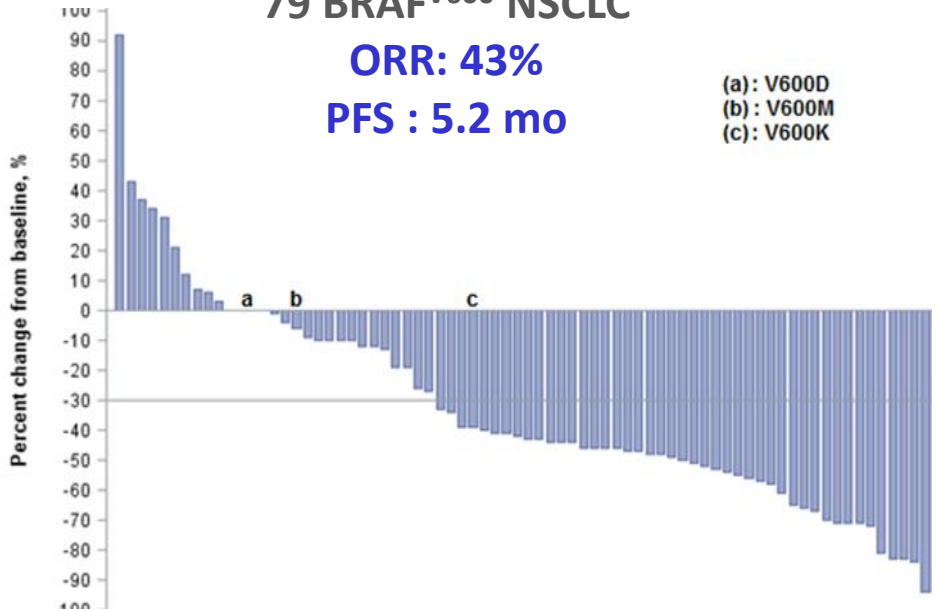
AcSé trial

Vemurafenib

79 BRAF^{V600} NSCLC

ORR: 43%

PFS : 5.2 mo



Mazières – WCLC 2018

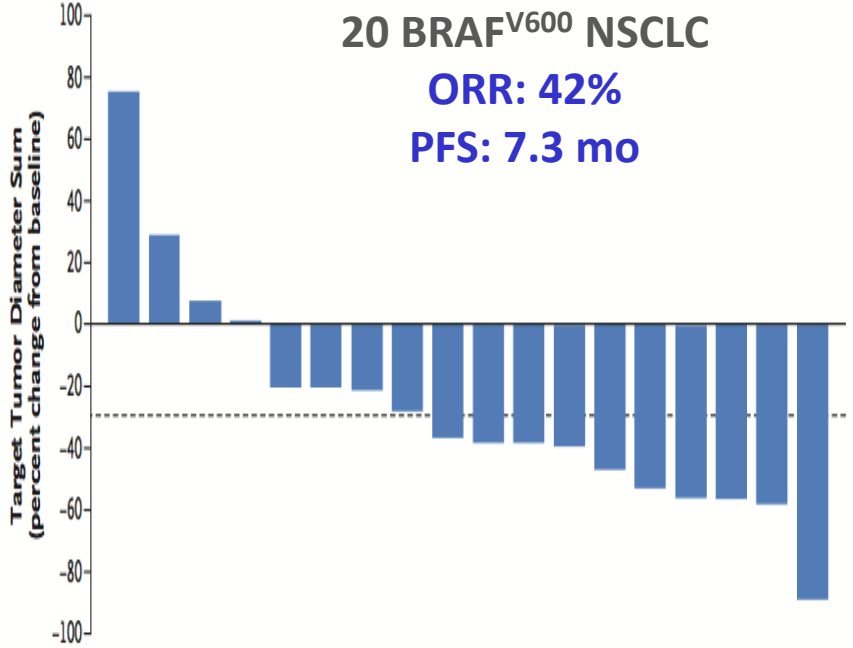
VE-Basket trial

Vemurafenib

20 BRAF^{V600} NSCLC

ORR: 42%

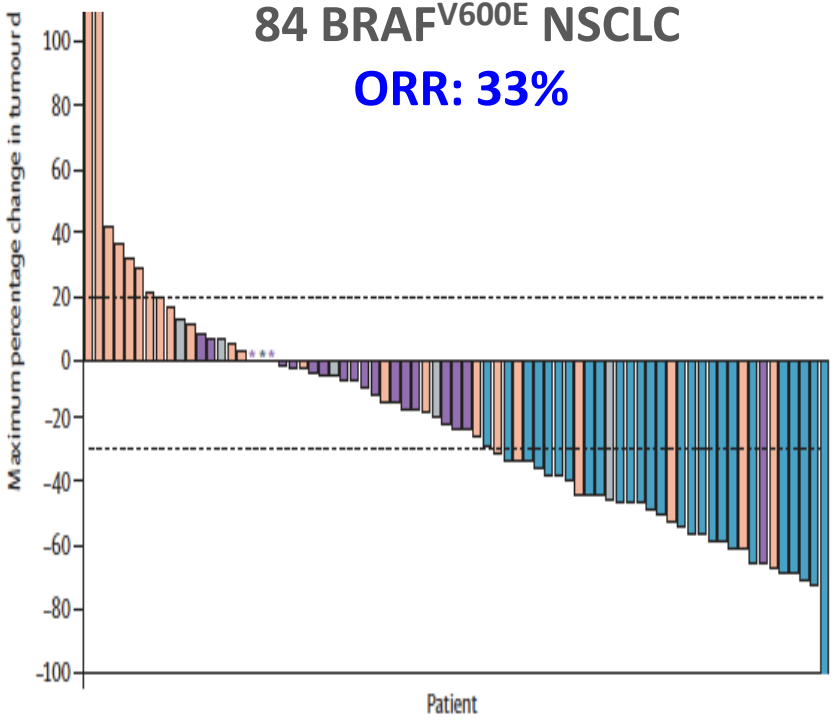
PFS: 7.3 mo

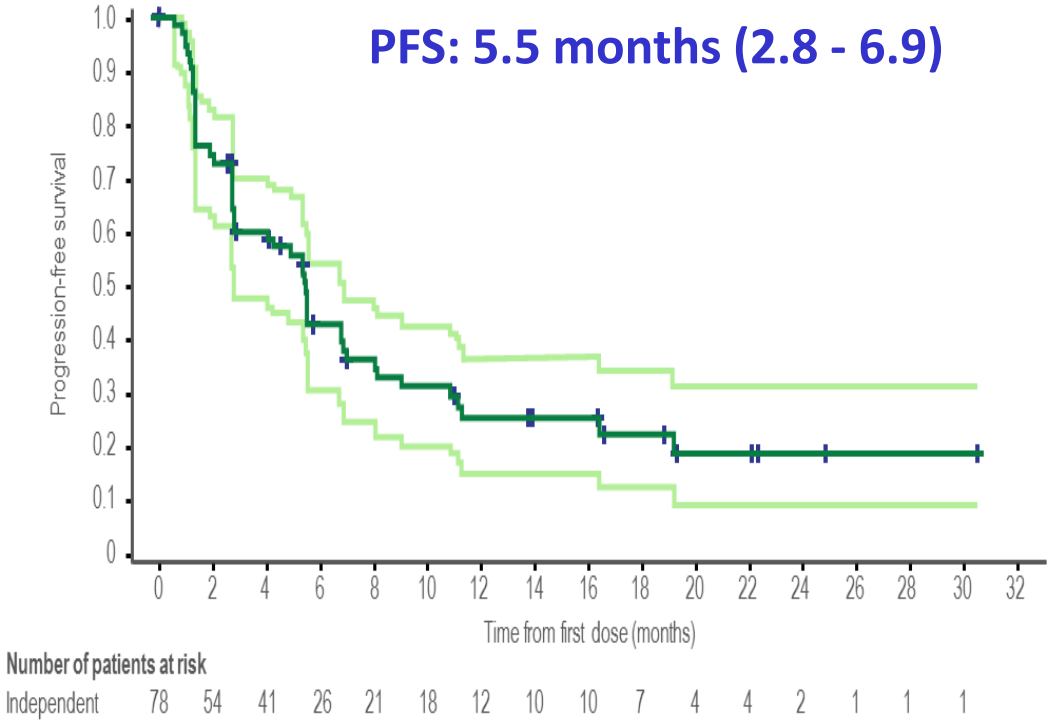


Hyman – NEJM 2015

Dabrafenib in BRAF NSCLC in 2nd line

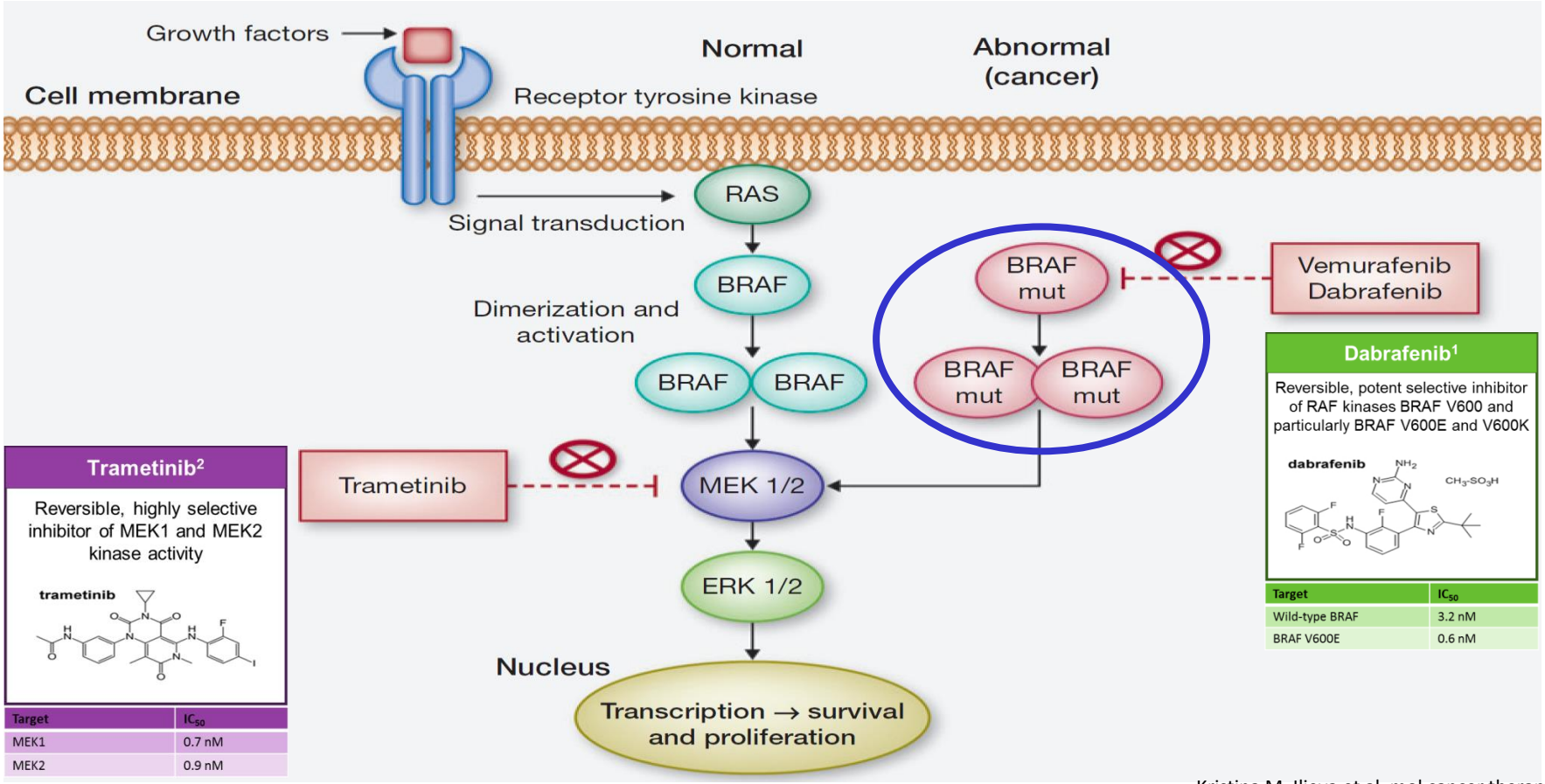
(BRF113928 Study)





D. Planchard et al – lancet Oncol 2016

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

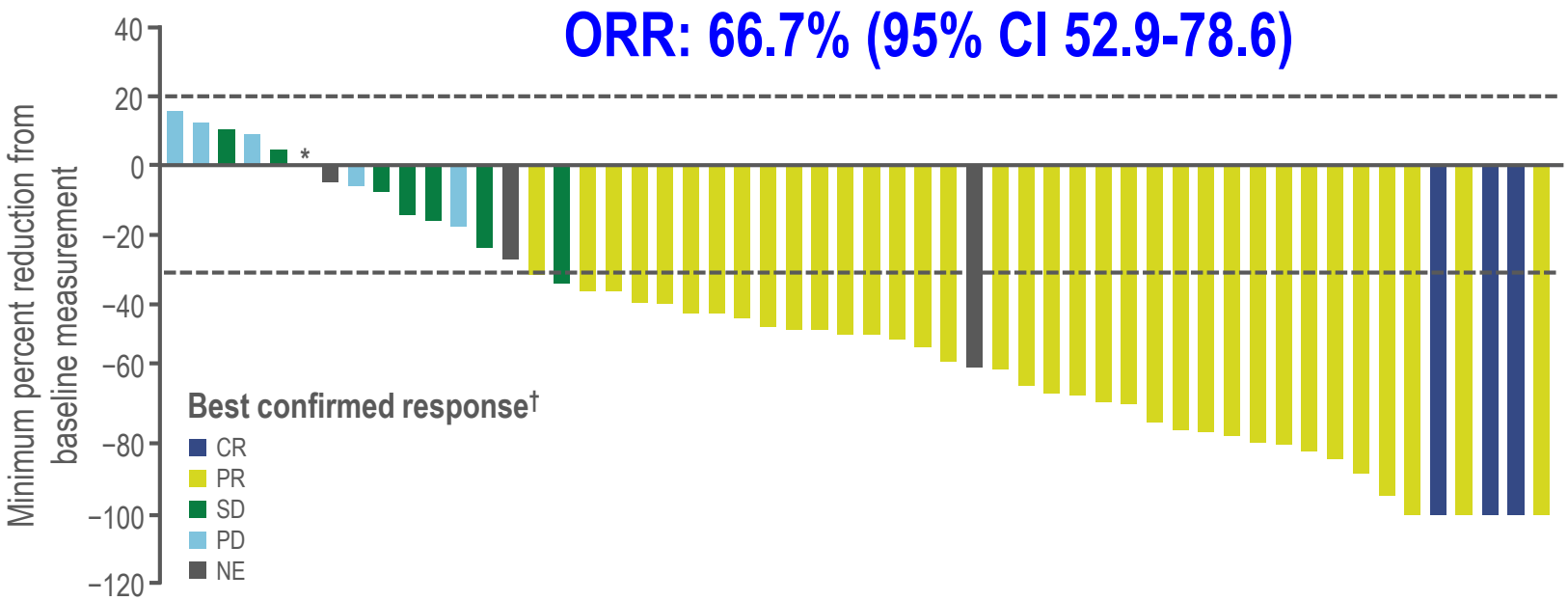


Kristina M. Ilieva et al, mol cancer therapeutics

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

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

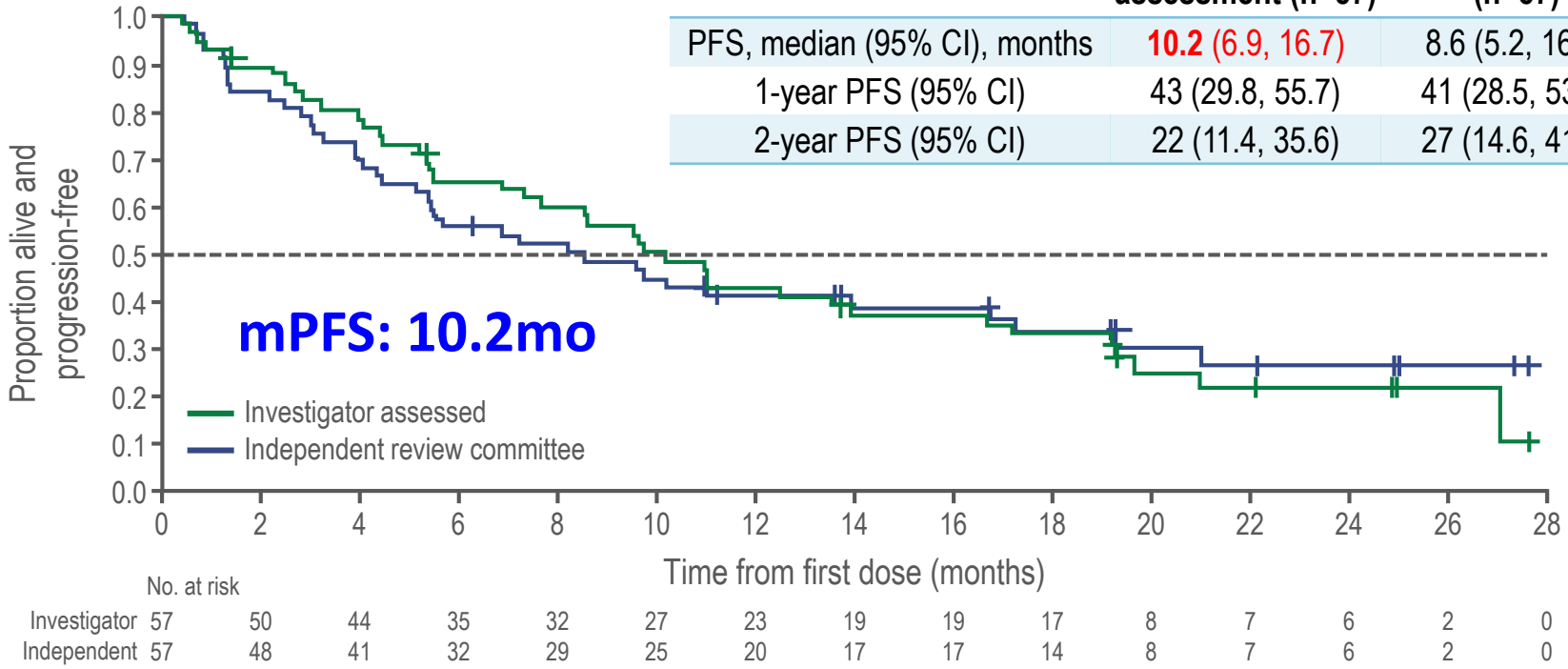
Cohort B (N=57 NSCLC BRAF V600E)



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

PFS WITH DABRAFENIB + TRAMETINIB AS 2ND LINE

	Investigator assessment (n=57)	IRC assessment (n=57)
PFS, median (95% CI), months	**10.2** (6.9, 16.7)	8.6 (5.2, 16.8)
1-year PFS (95% CI)	43 (29.8, 55.7)	41 (28.5, 53.9)
2-year PFS (95% CI)	22 (11.4, 35.6)	27 (14.6, 41.1)



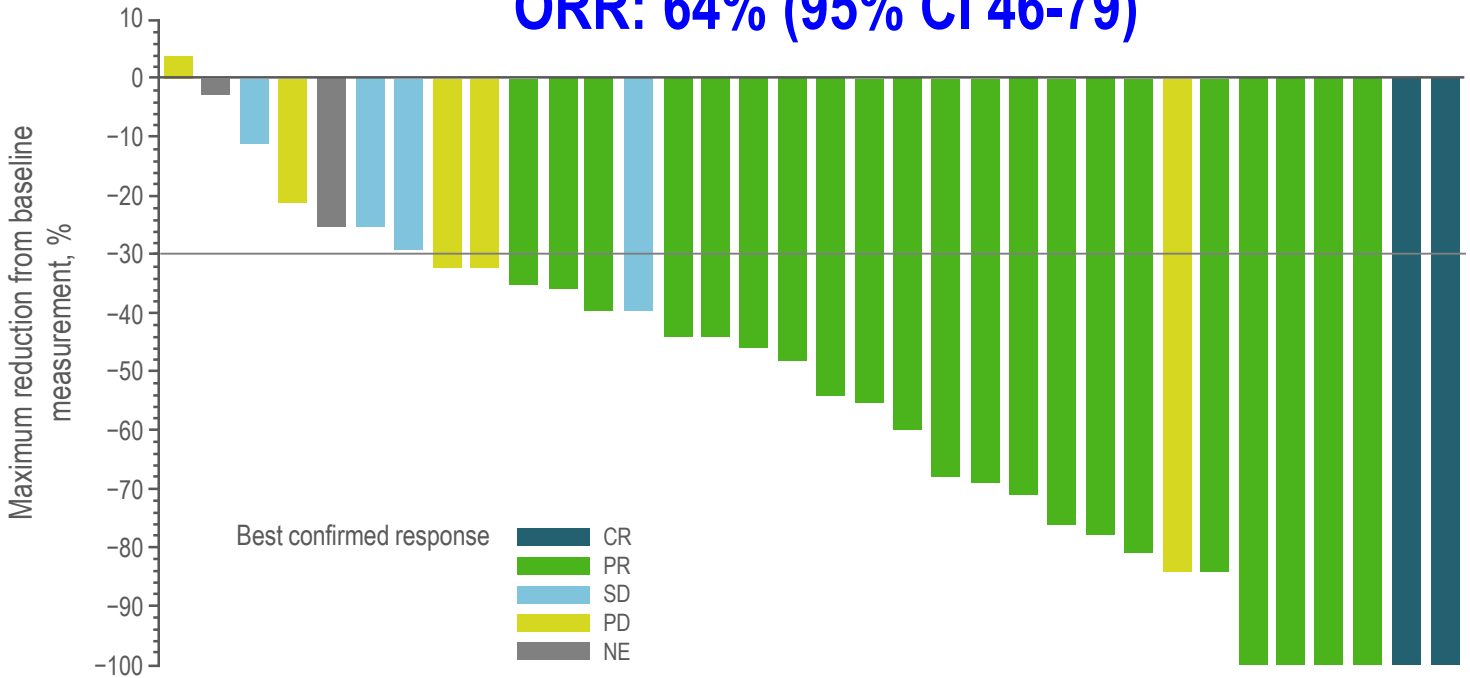
Planchard D *et al. Lancet Oncol* 2016;17:984–993;
Planchard D *et al. J Clin Oncol* 2017;35(Suppl):Abst 9075

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 (N=36 NSCLC BRAFV600E)

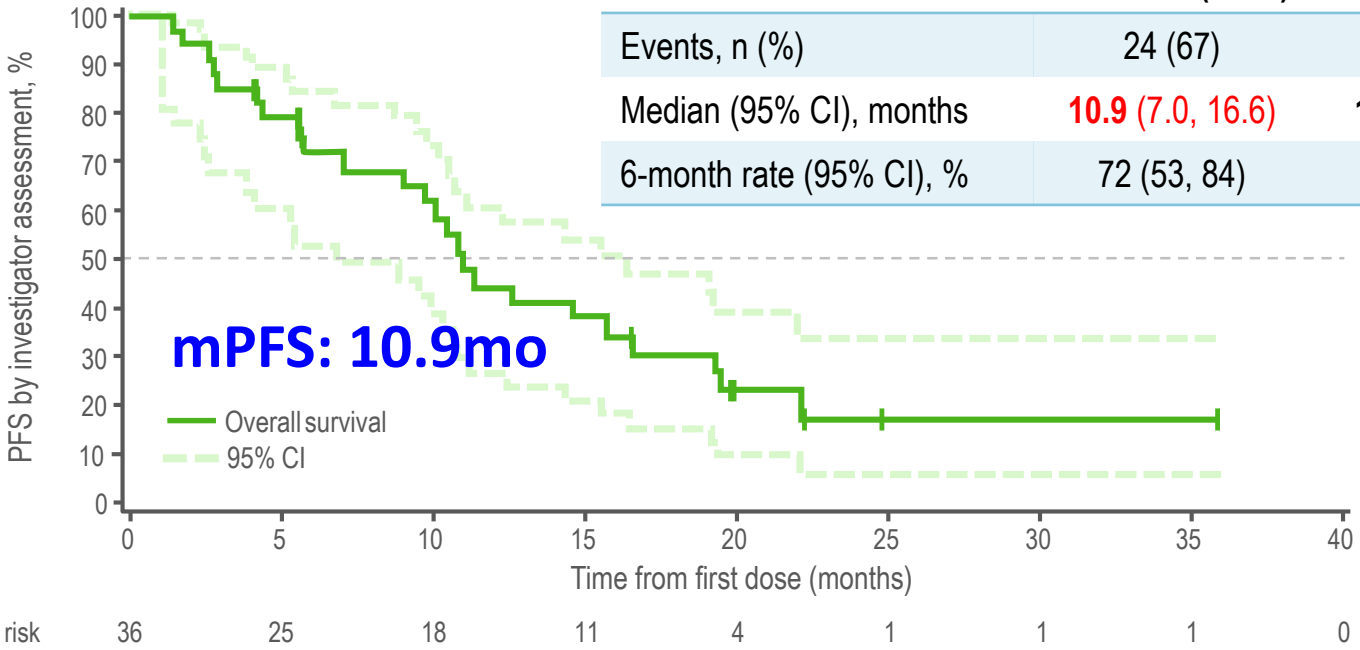
ORR: 64% (95% CI 46-79)



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

PFS WITH DABRAFENIB + TRAMETINIB IN 1ST LINE

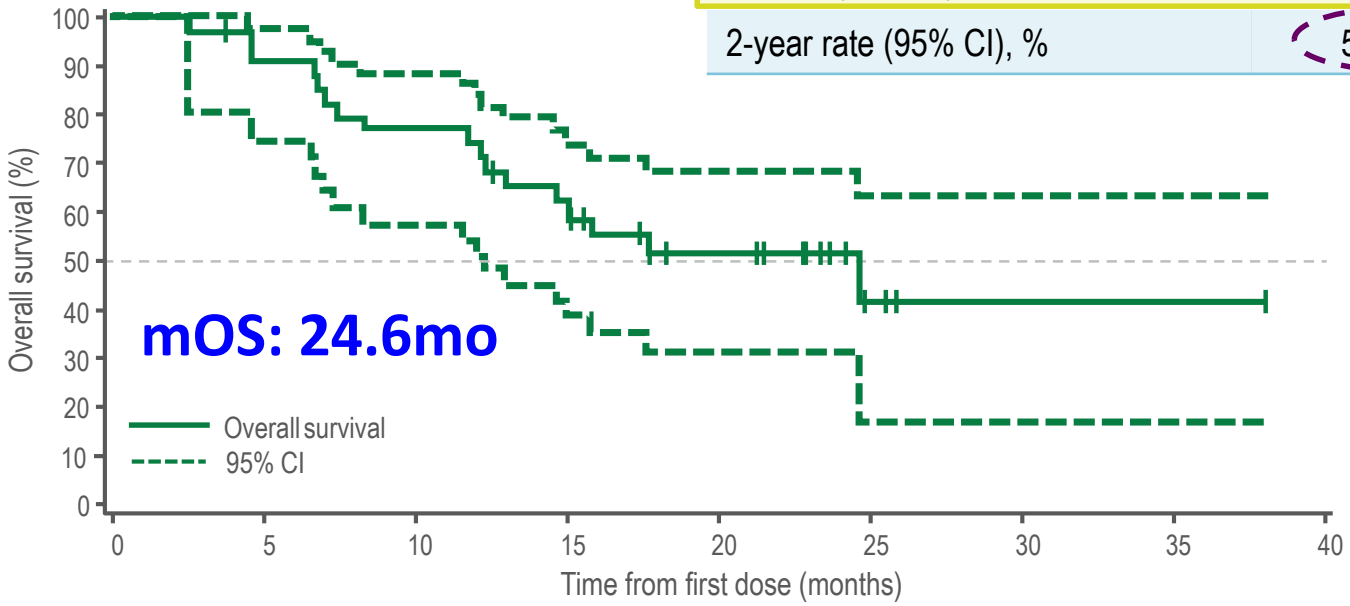
	Investigator assessed (n=36)	IRC assessed (n=36)
Events, n (%)	24 (67)	22 (61)
Median (95% CI), months	**10.9** (7.0, 16.6)	**14.6** (7.0, 22.1)
6-month rate (95% CI), %	72 (53, 84)	69 (51, 82)



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

OVERALL SURVIVAL WITH DABRAFENIB + TRAMETINIB IN 1ST LINE

	n=36
Events, n (%)	17 (47)
Median (95% CI), mo	**24.6** (12.3, NE)
2-year rate (95% CI), %	51 (33, 67)

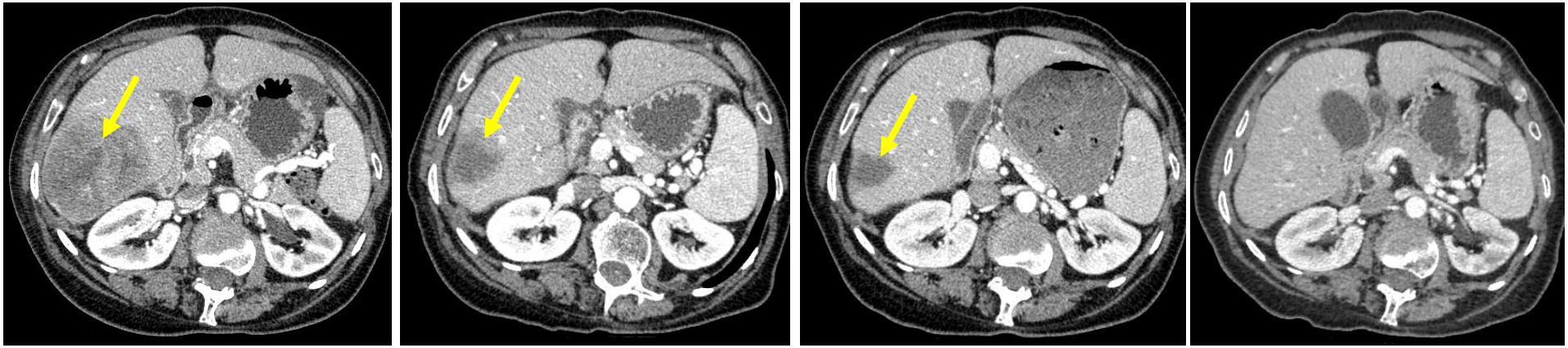


Planchard D *et al. Lancet Oncol* 2017;18:1307–1316

Lady, 58-year, BRAFV600E:
Dabrafenib (150mg twice a day) + Trametinib (2mg/day)

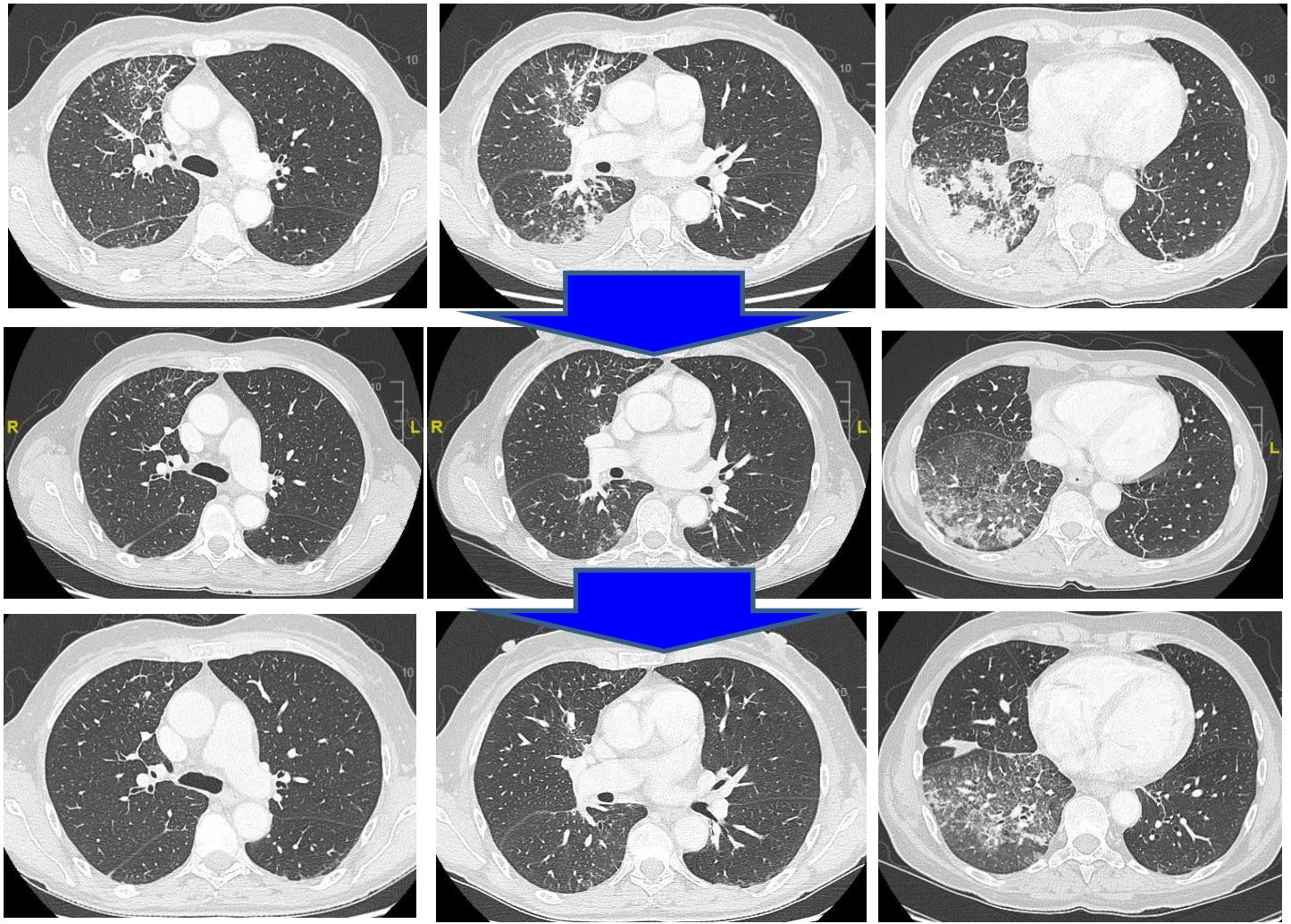
July 2014

February 2018



+ 4 years

D.Planchard et al, Gustave Roussy

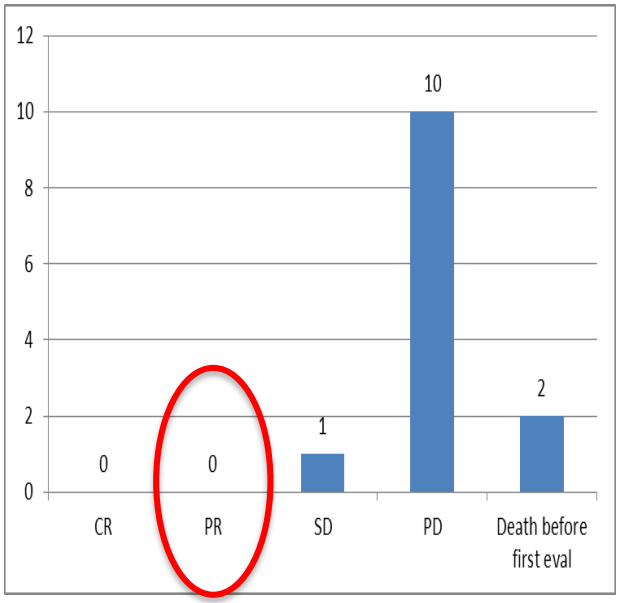

2 months
3 years
R
L

BRAF non V600 cohort (AcSé Vemu)

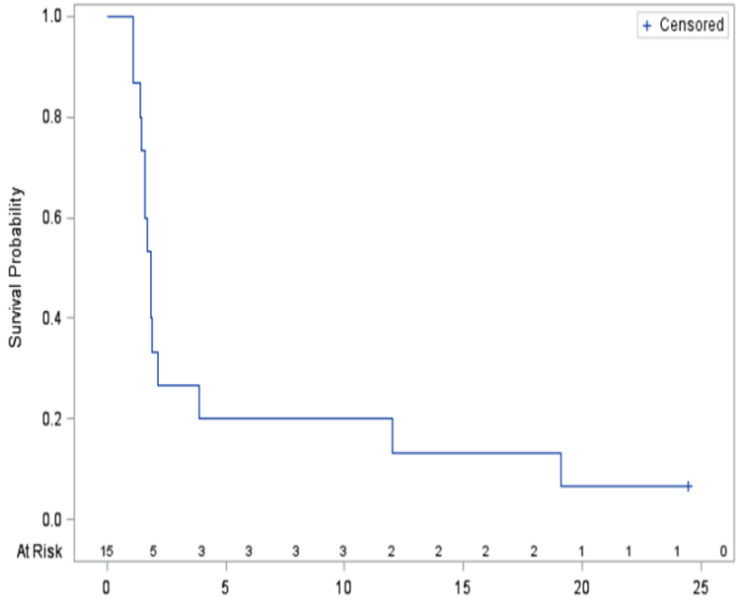
- Mean Bayesian Estimated Success rate : **5.9%** ; credibility 95%CI : [0.2%; 20.6%]
- Prob ORR < futility bound (10%): 81.5% - **study stopped**

<u>Non V600</u> 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

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

Italien Expanded Access Program of 2nd line Nivolumab

Retrospective trial

Best response to Nivolumab	BRAF-mutated N=11 (%)	BRAF Wild Type N=199 (%)	BRAF Not evaluated N=1378 (%)
CR	0	1 (0.5%)	9 (0.6%)
PR	**1 (9.1%)**	**38 (19.1%)**	**241 (17.5%)**
SD	0	45 (22.6%)	369 (26.8%)
PD	**8 (72.7%)**	**92 (46.2%)**	**588 (42.7%)**
Death	1 (9.1%)	16 (8.1%)	113 (8.2%)
NE	1 (9.1%)	7 (3.5%)	58 (4.2%)

Rihawi K et al, JTO 2019

BRAF and immunotherapy

Multi-institutional retrospective

39 pts BRAF mutant NSCLC

-54%: V600E (group A, n = 21)

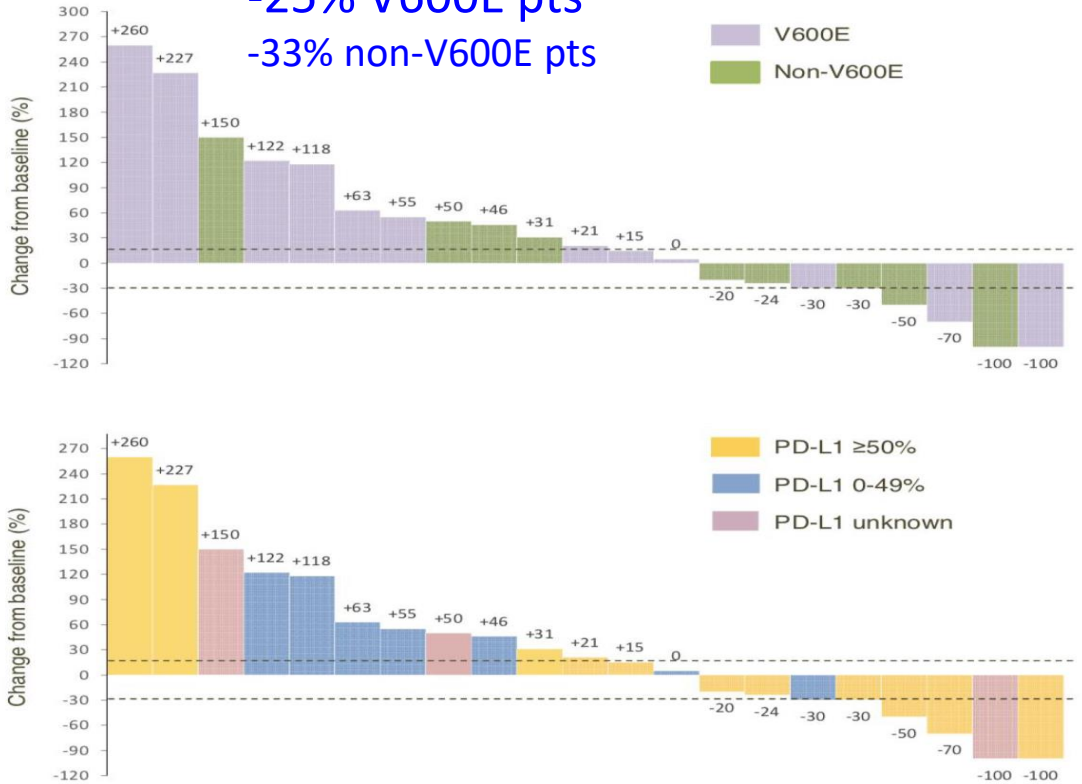
-non-V600E (group B, n = 18)

-38% never-smokers

ORR:

-25% V600E pts

-33% non-V600E pts



PD-L1 high (≥50%):

-in 42% -V600E pts

-50% non –V600E pts

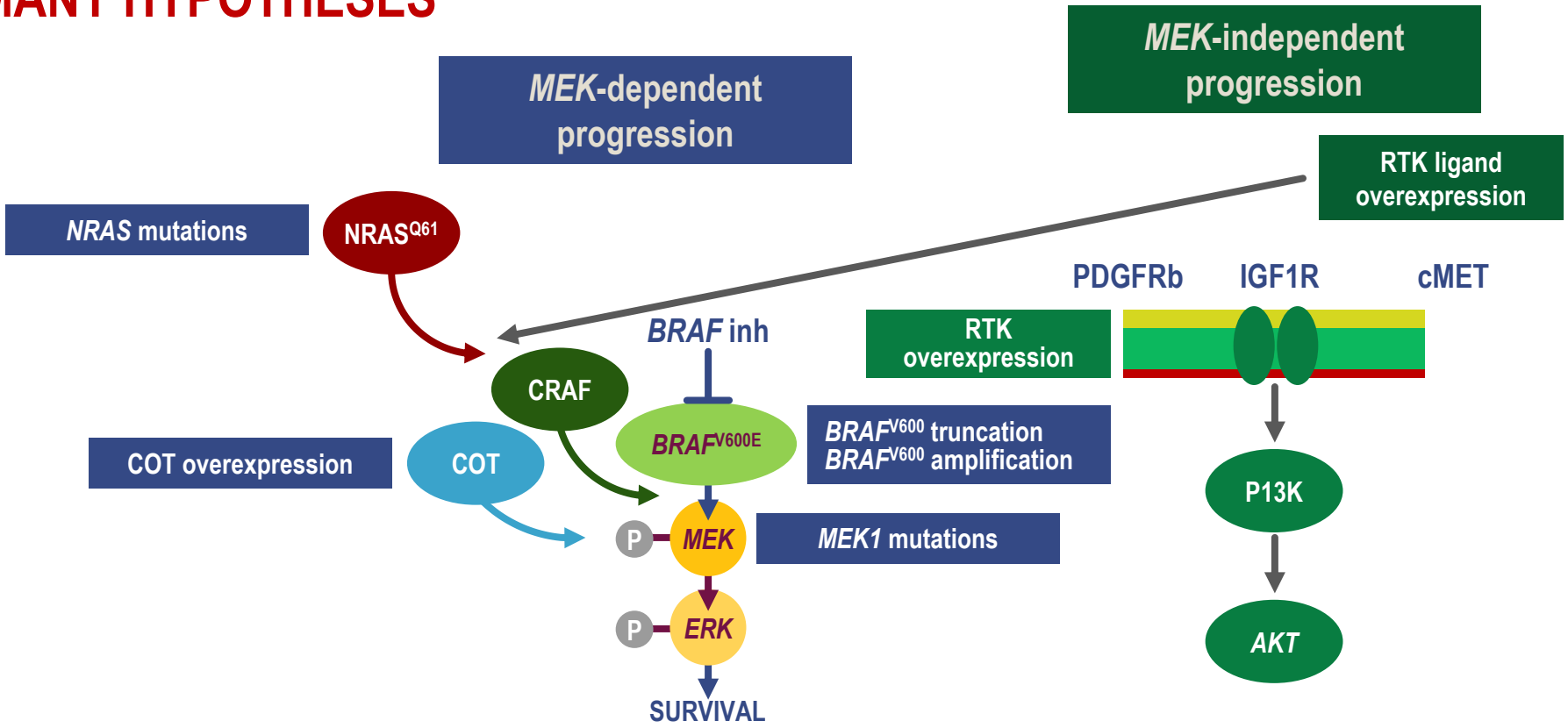
PFS:

-3.7 mo V600E pts

-4.1 mo non-V600E pts

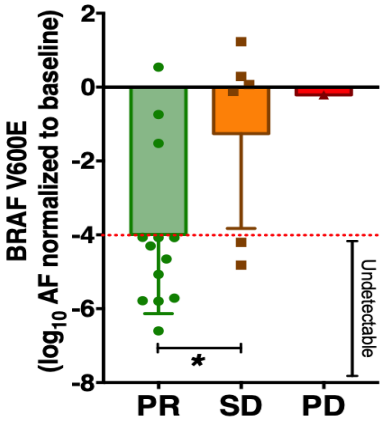
Dudnik E et al, JTO 2018

ACQUIRED RESISTANCE TO *BRAF* INHIBITION: MANY HYPOTHESES

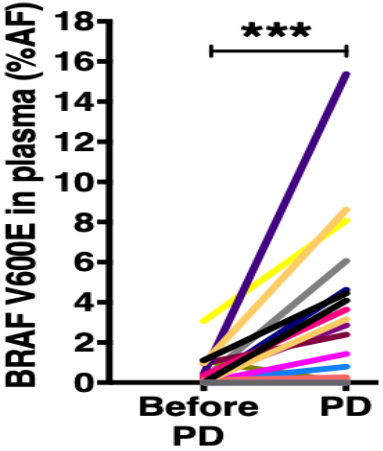


Johannessen CM *et al. Nature* 2010;468:968–972; Nazarian R *et al. Nature* 2010;468:973–977; Poulikakos PI *et al. Nature* 2011;480:387–390; Shi H *et al. Nature Commun* 2012;3:724; Straussman R *et al. AACR* 2012;abstract 4837; Villanueva J *et al. Cancer Cell* 2010;18:683–695; Wagle N *et al. J Clin Oncol* 2011;29:3085–3096

Genomic ctDNA profiling of disease progression on BRAF-targeted therapies



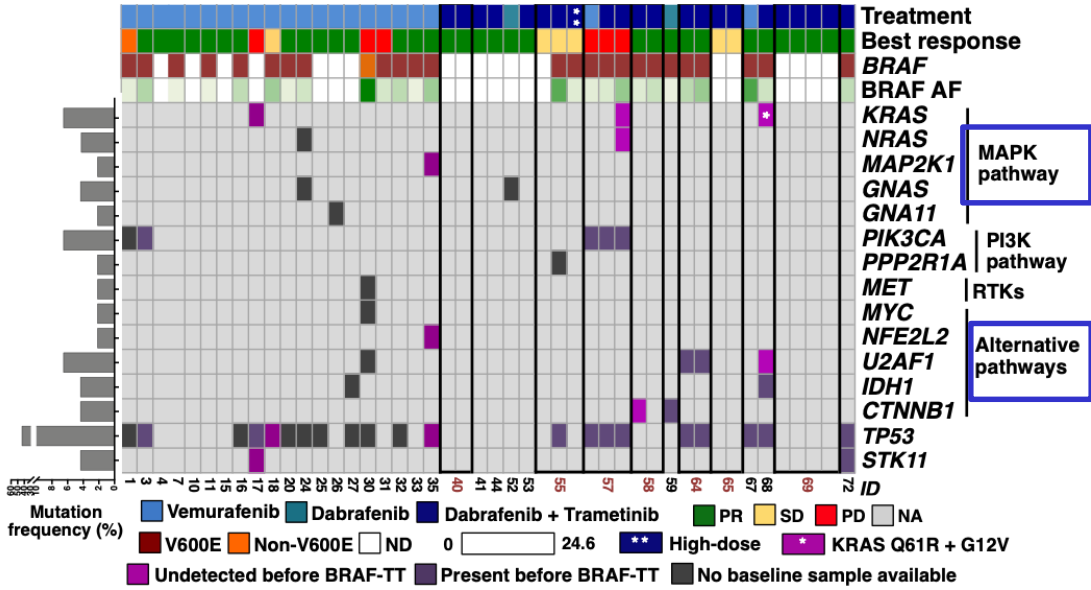
Complete clearance of BRAF V600E at the first CT-scan evaluation* in 12/20 (60%)



Consistent rebound in BRAF V600E at PD in **17/27 (63%)** patients

Molecular progression observed in 3 patients with a median of **57 days** before confirmation of radiographic progression

35 patients
(46 samples)



***BRAF* mutation in 56.5% (16/46) of samples**

So where we are in 2019…BRAFV600-mutant

	Previously Treated				Treatment Naive
	VE-Basket trial **vemurafenib** (n=20)	AcSé trial **vemurafenib** (n=100)	BRF113928 **dabrafenib** (n = 78)	BRF113928 **Dabrafenib Plus Trametinib** (n = 57)	BRF113928 **Dabrafenib Plus Trametinib** (n = 36)
Male	14 (70%)	-	39 (50%)	29 (51%)	14 (39%)
Never smoker	7 (35%)	-	29 (37%)	16 (28%)	10 (28%)
ORR % (95% CI)	42 (20-67)	44.9	33 (23–45)	67 (53–79)	64 (46-79)
PFS, median (95% CI)	**7.3** (3.5-10.8)	**5.2**	**5.5** (3.4–7.3)	**10.2** (6.9–16.7)	**10.9** (7.0-16.6)
OS, median (95% CI)	NA	9.3	12.7 (7.3–16.3)	18.2 (14.3–NE)	24.6 (12.3-NE)

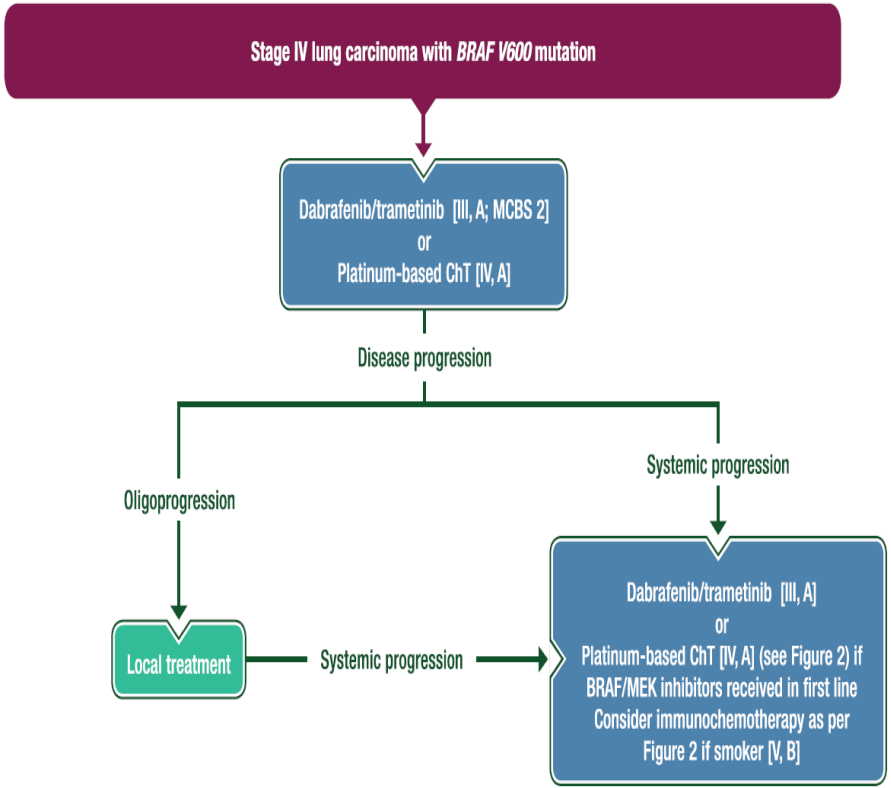
Dabrafenib+trametinib mPFS (10.9 months) → Platinum-based CT+/-IO → Immunotherapy…

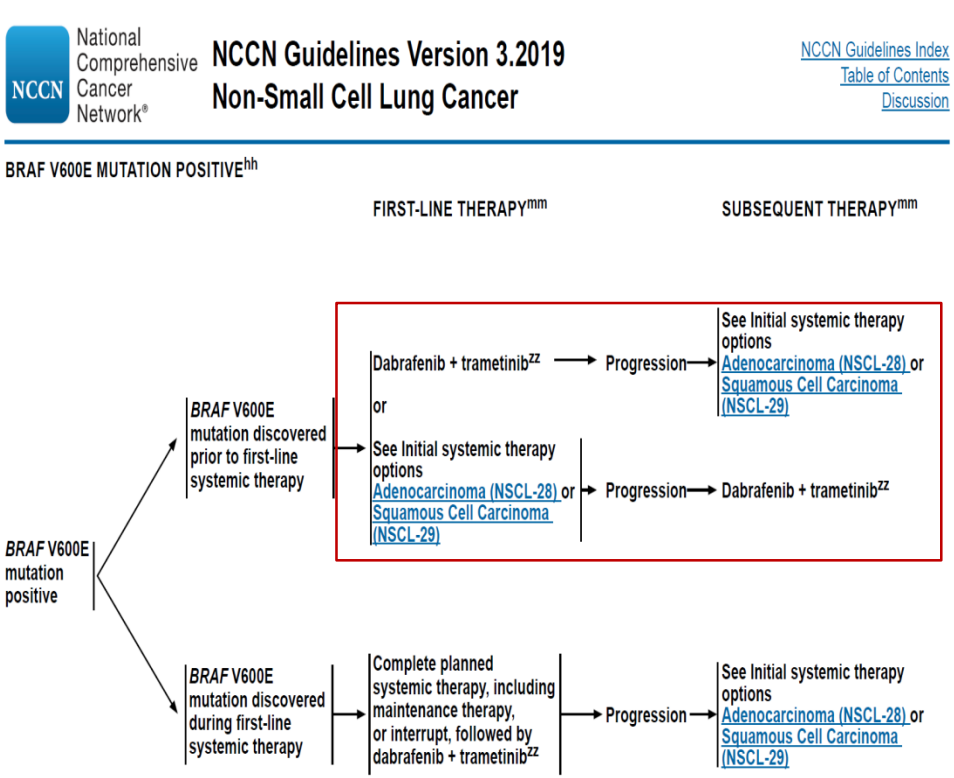
EMA and FDA approvals 2017

Platinum-based CT+/-IO → Dabrafenib+trametinib mPFS (10.2 months) → Immunotherapy…

D.Planchard et al, ASCO 18

ESMO and NCCN Guidelines

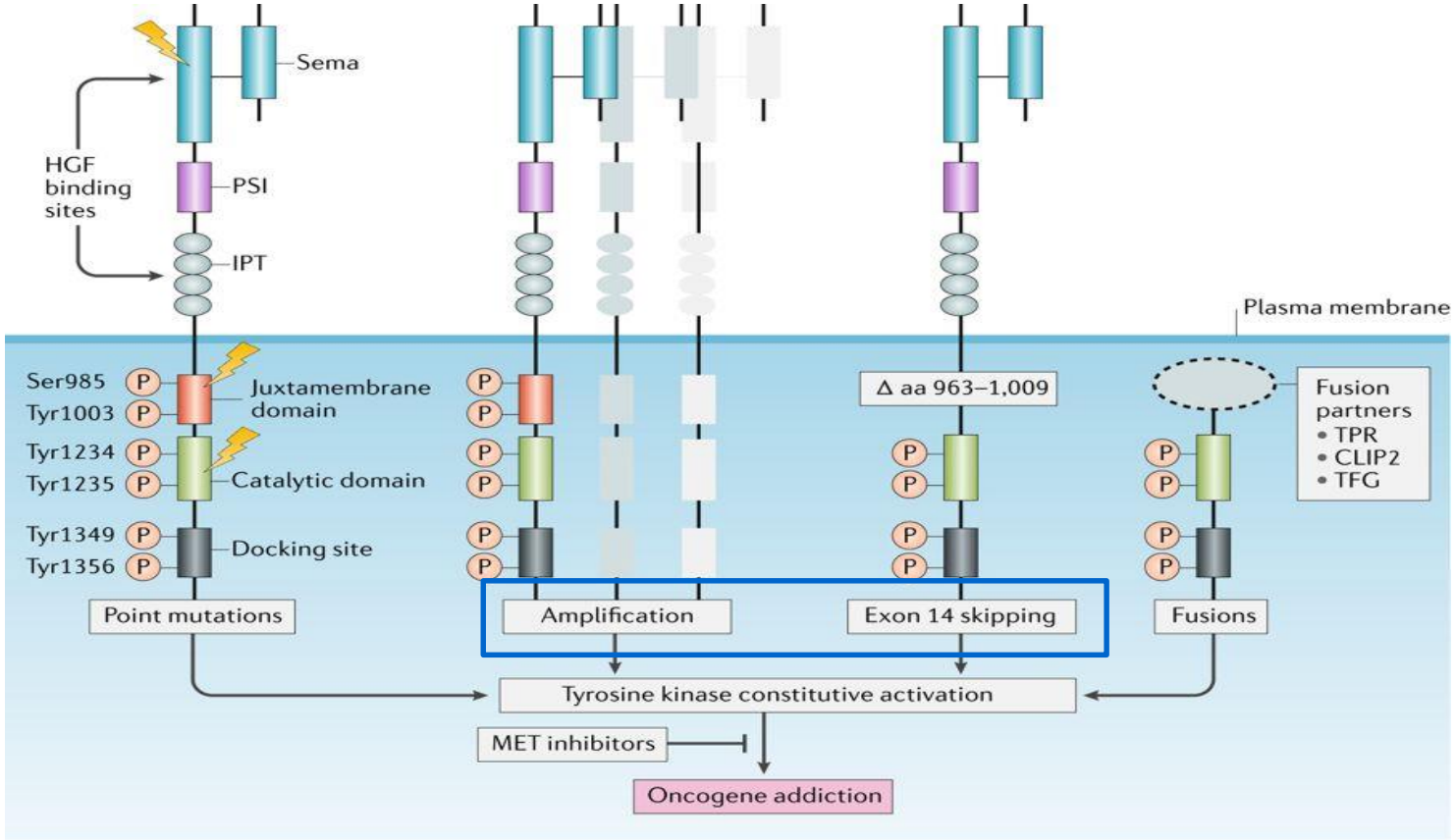




D.Planchard et al, annals onco 2018

EMA and FDA approvals 2017

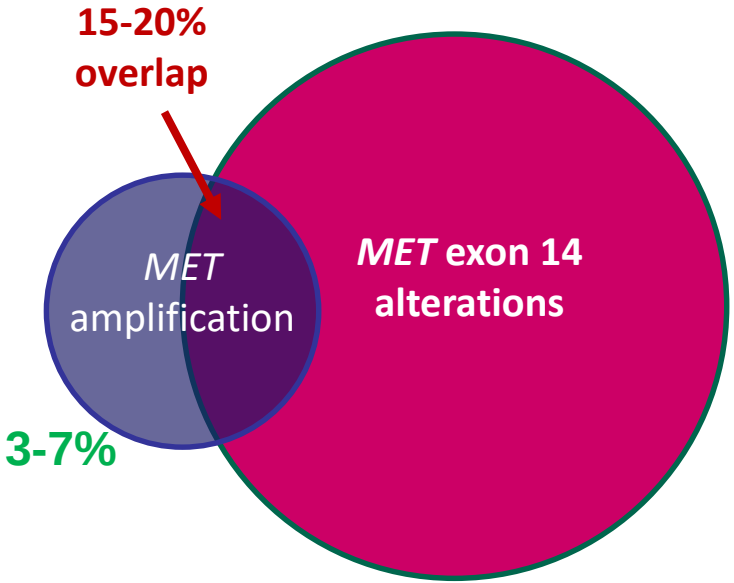
Activation of MET pathway in lung cancer



Comoglio, Trusolino & Boccaccio Nat Rev Cancer 2018; 341-358

MET aberrations in NSCLC

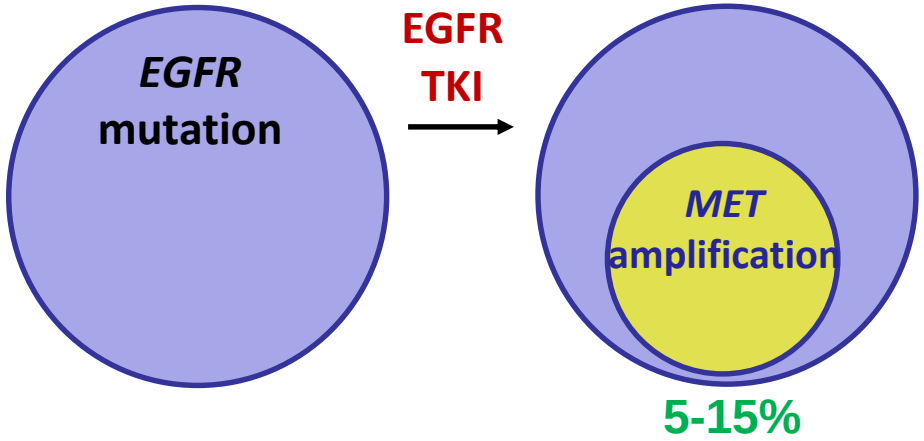
MET as a primary driver



3-4% of nonsquamous NSCLCs

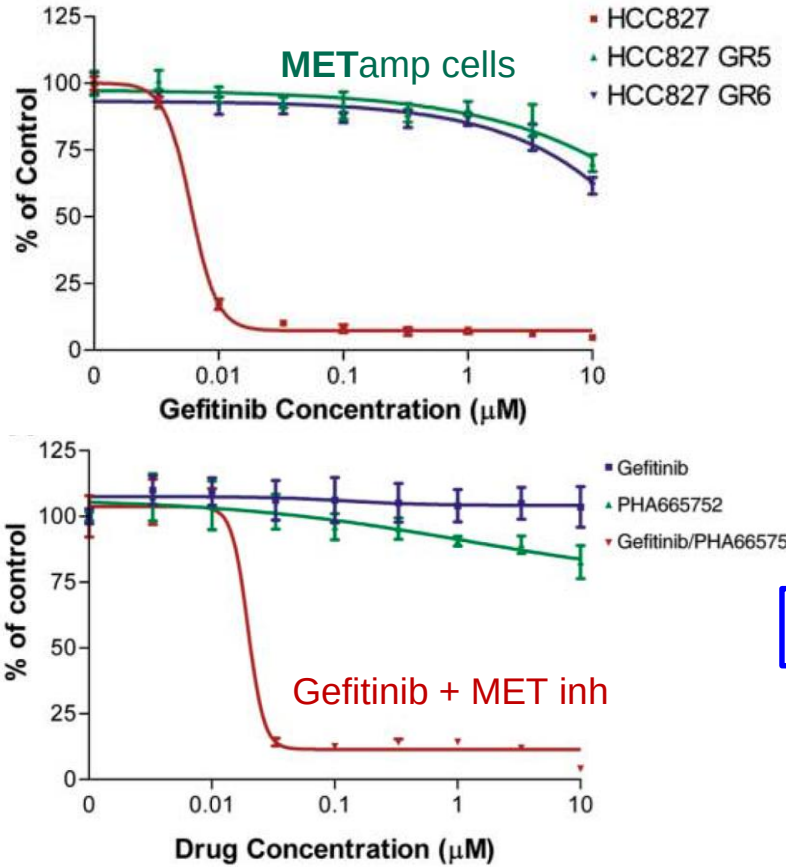
8-30% sarcomatoid lung carcinomas

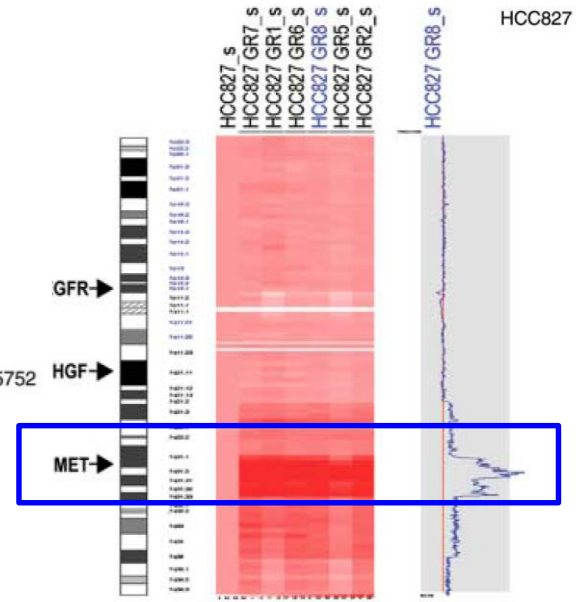
MET as a secondary/co-driver

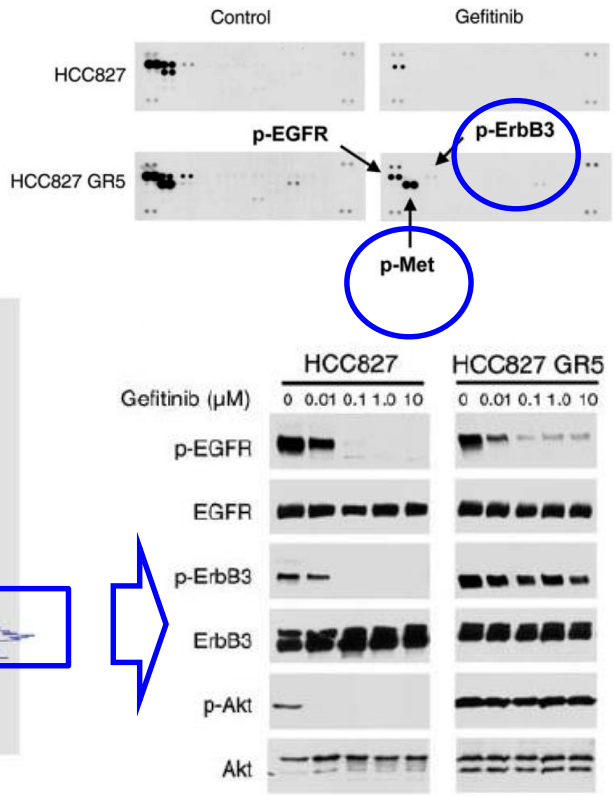


Drilon A et al, J Thoracic Oncol, 2016

First report of MET amplification as bypass track to circumvent EGFR inhibition: ERBB 3-dependent PI3K activation

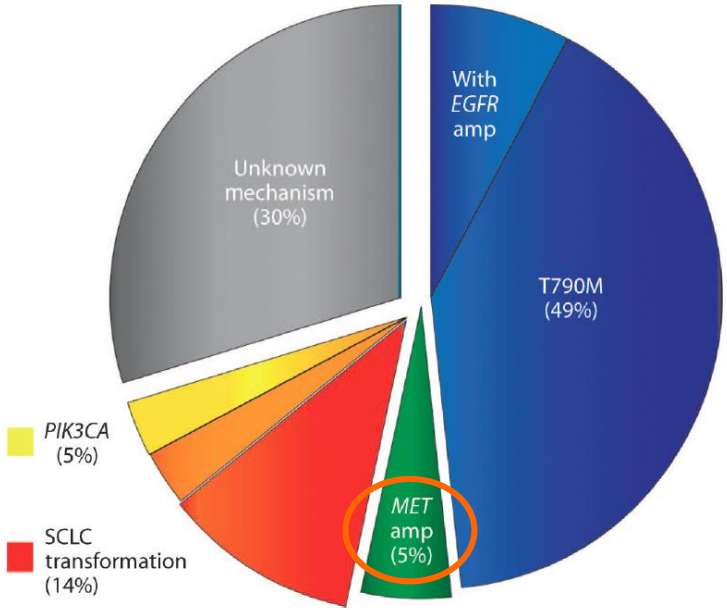


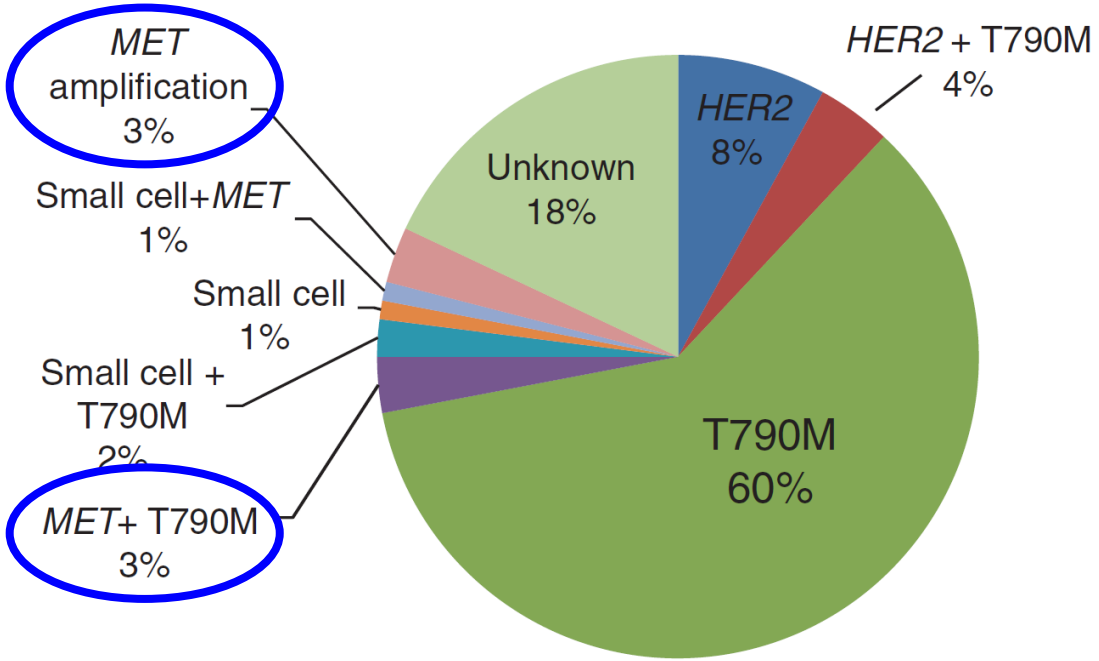




Jeffrey A. Engelman et al, Science 2007

Acquired resistance to 1st –2nd generation EGFR-TKI





≈ 5-10%

Lecia V. Sequist et al, Science translational medecine 2011

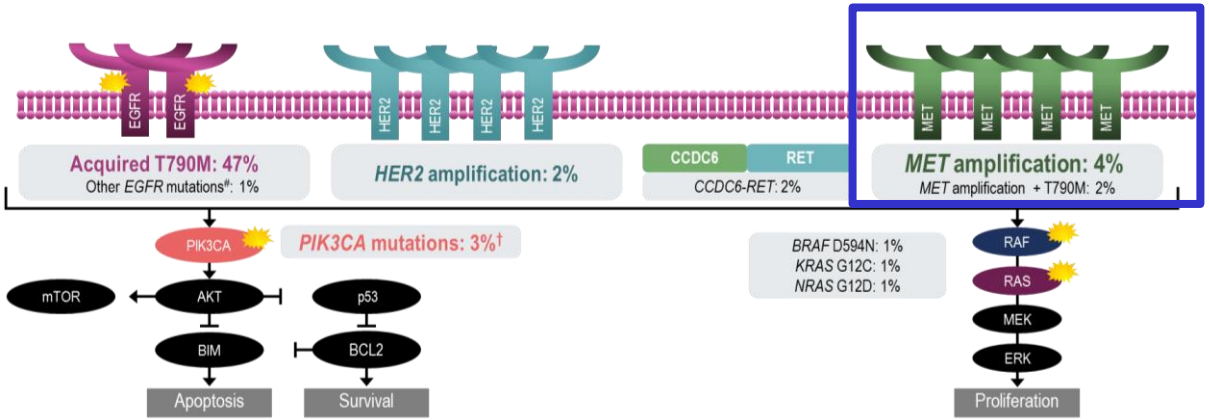
Helena A. Yu et al, CCR 2013

FLAURA-RESULTS: ACQUIRED RESISTANCE MECHANISMS

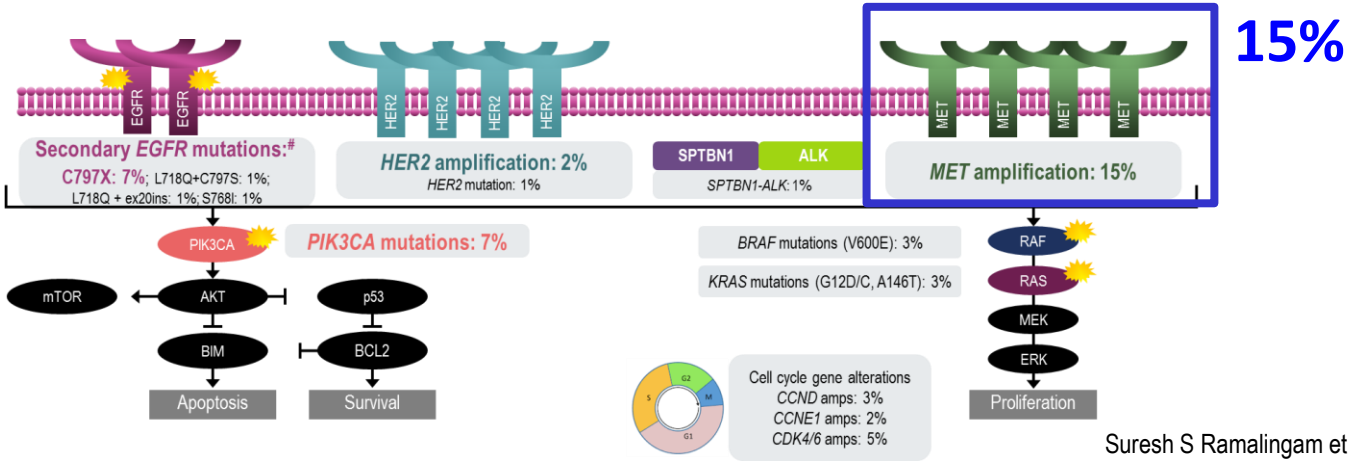
GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

ctDNA analysis

Post-Erlotinib or Gefitinib



Post-Osimertinib



Suresh S Ramalingam et al, ESMO 2018

MET inhibitors in clinical trial

Agent	Other Molecular Targets	IC_{50} (nM)[1]
Type I		
Crizotinib	MET (type Ia), ALK, ROS1	<1
Capmatinib	selective MET (type Ib)	0.13
Tepotinib	selective MET (type Ib)	3
Savolitinib	selective MET (type Ib)	5
Type II		
Cabozantinib	MET (type II), VEGFR, RET, TIE2, AXL, FLT3, KIT	1.3
Merestinib	MET (type II), MST1R, FLT3, MERTK, TEK, ROS1, DDR, NTRK, AXL	4.7

Highly selective MET TKI

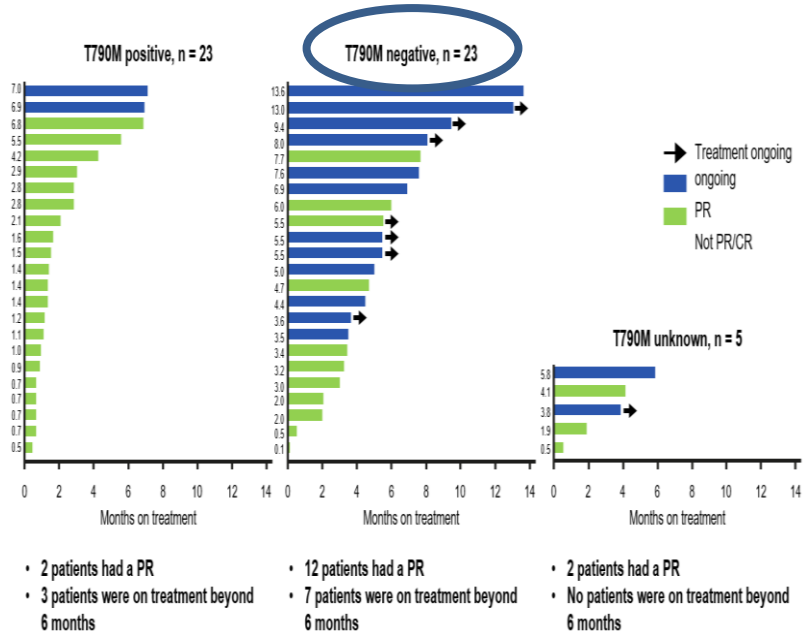
Type I: binds ATP-binding pocket in the active conformation, Ib more highly specific
Type II: binds ATP-binding pocket in the inactive conformation; potency is mora variable

Reungwetwattana et al, lung cancer 2017

Savolitinib + Gefitinib (phase Ib)

EGFR mut pts MET amplified

RECIST (v 1.1) response	T790M positive (n = 23)	T790M negative (n = 23)	T790M unknown (n = 5)
BoR, n (%)			
CR	0	0	0
PR	2 (9)	12 (52)	2 (40)
SD ≥6 weeks	9 (39)	7 (30)	2 (40)
PD/death*	7 (30)	3 (13)	0
NE	5 (22)	1 (4)	1 (20)



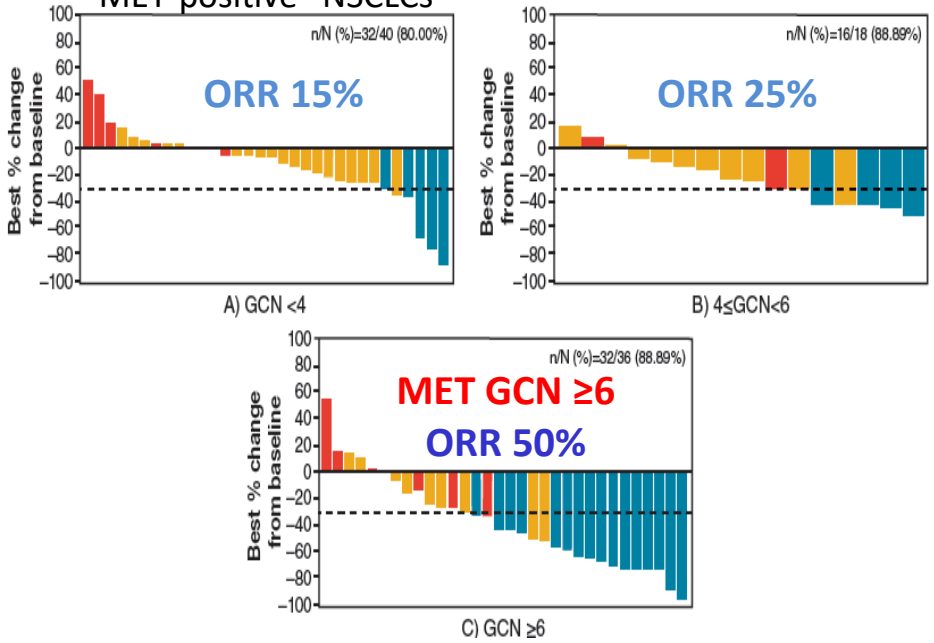
- *MET*-amplification = *MET*/*CEP7* ratio ≥2 or *MET* gene number ≥5 (central tumour tissue FISH)'
- **Primary endpoints:** Safety and tolerability, recommended Phase II dose

Yang J.J et al, IASLC 2017

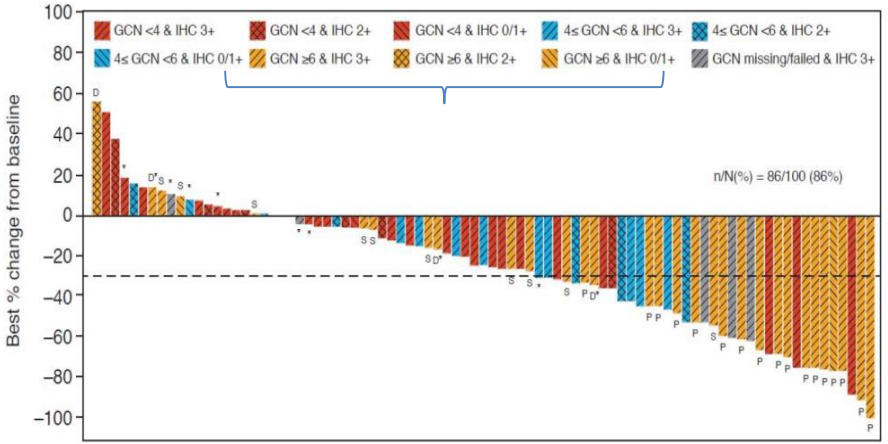
Capmatinib + Gefitinib (Phase Ib/II)

EGFR mut pts 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

Yi-Long Wu et al, JCO 2018

Tepotinib + Gefitinib (phase Ib) EGFR-mut pts METamp

Gefitinib + Tepotinib. Phase II. N=55

EGFR TKI-resistant Asian patients with locally advanced/metastatic NSCLC, ***EGFR*+, T790M–, MET+**

- **MET2+ or 3+** by IHC (D1C1 antibody)
- ***MET* amplification** by ISH (GCN ≥5 and/or *MET/CEP-7* ≥2)

R

Tepotinib 500 mg + **gefitinib** 250 mg orally once daily*

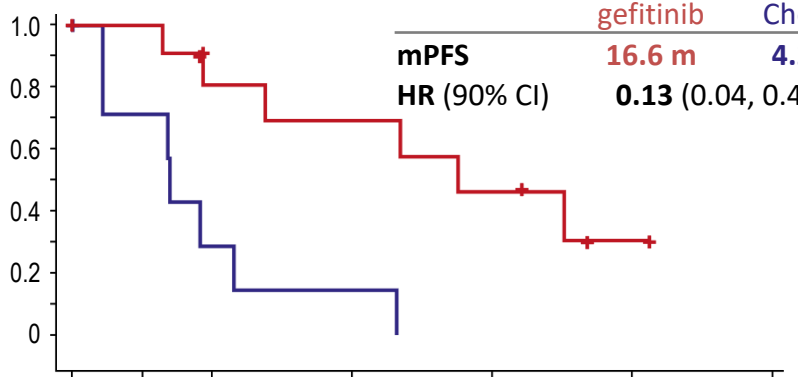
Chemotherapy: **Pemetrexed** 500 mg/m^2 + **cisplatin** 75 mg/m^2 or **carboplatin** AUC 5 or 6 i.v. on Day 1†

ORR, n (%) [90% CI]

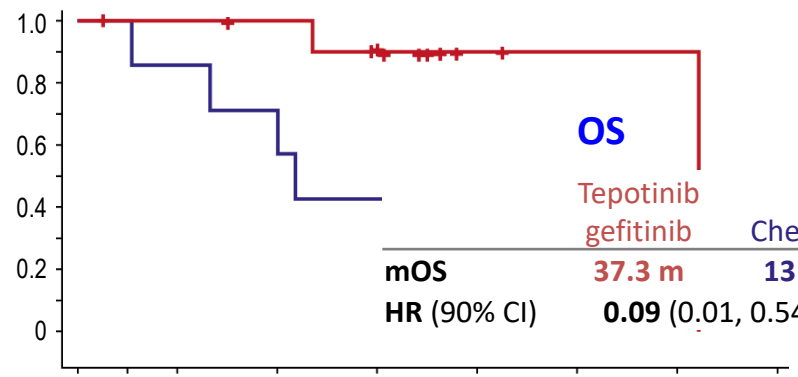
Tepotinib + gefitinib n=12	Chemotherapy n=7	OR (90% CI)
8 (66.7%) [39.1, 87.7]	3 (**42.9**) [12.9, 77.5]	**2.67** (0.37, 19.56)

PFS

***MET* amplification, N=19**



	Tepotinib gefitinib	Chemo
mPFS	**16.6 m**	**4.2 m**
HR (90% CI)	**0.13** (0.04, 0.43)	



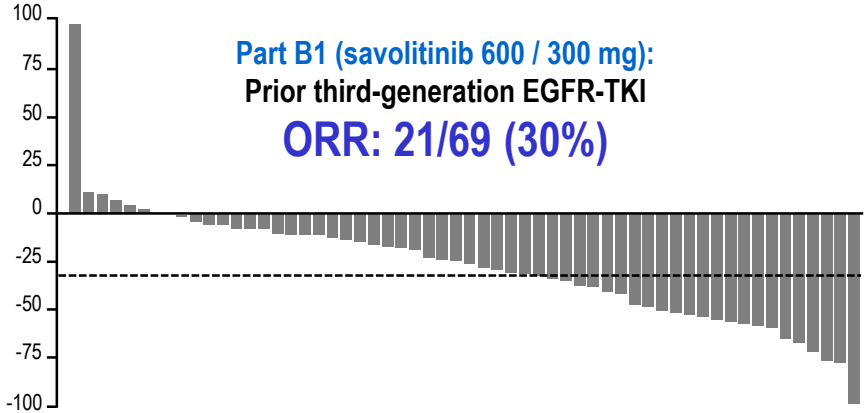
OS

	Tepotinib gefitinib	Chemo
mOS	**37.3 m**	**13 m**
HR (90% CI)	**0.09** (0.01, 0.54)	

Wu – WCLC 2019

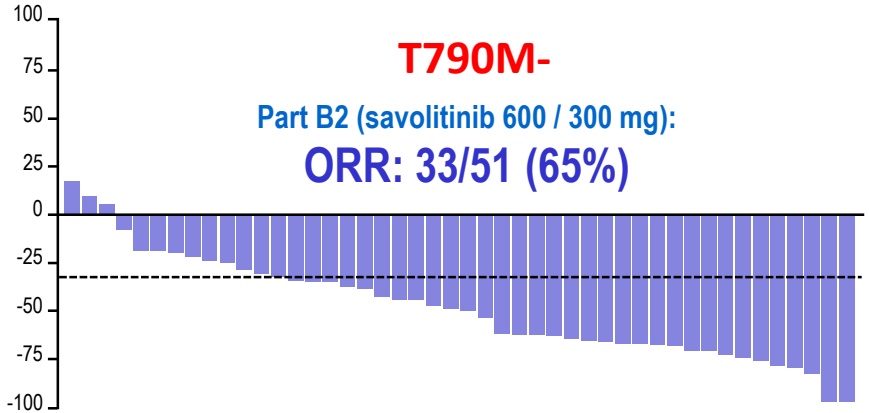
TATTON (osimertinib + Savolitinib)

Post-3nd Generation

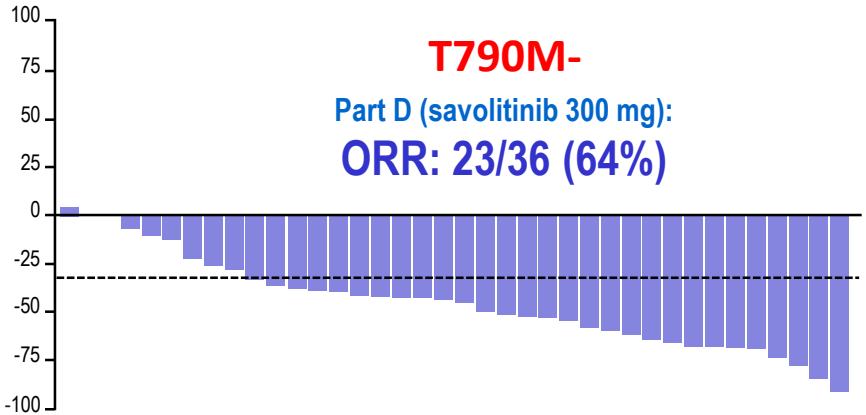


Part B1 (savolitinib 600 / 300 mg):
Prior third-generation EGFR-TKI
ORR: 21/69 (30%)

No prior 3nd-generation



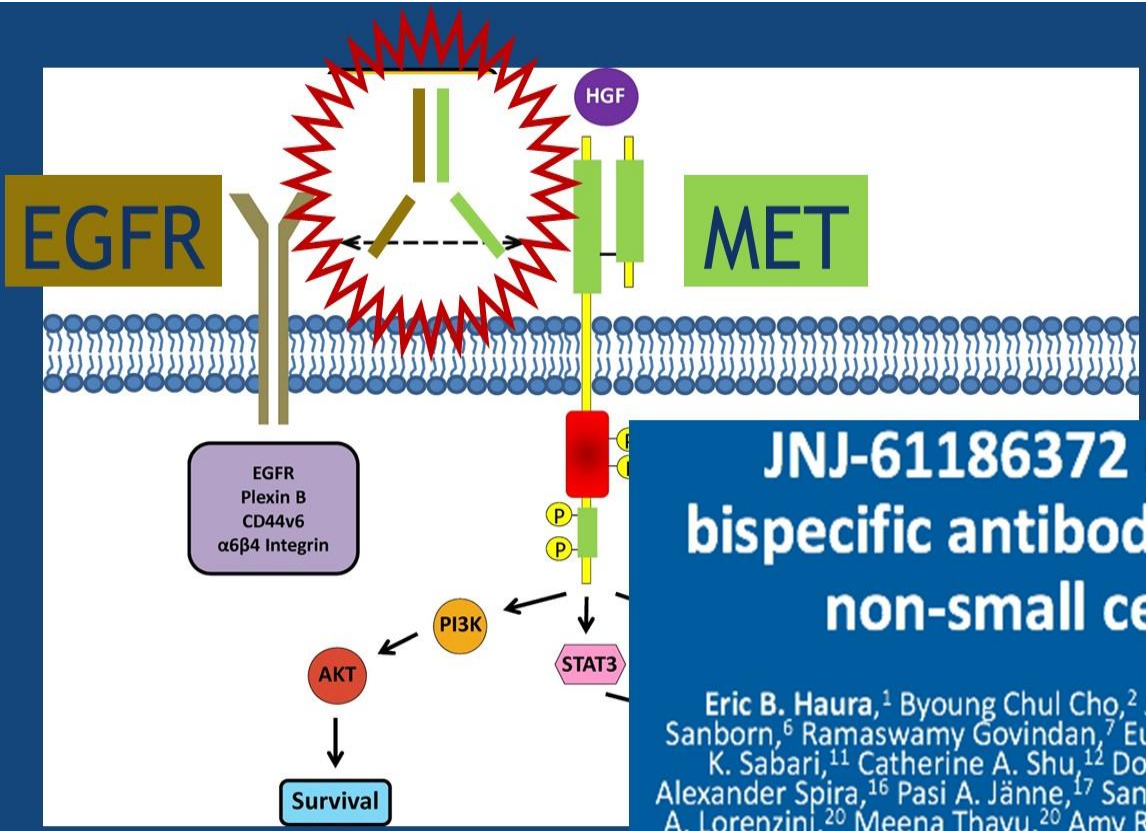
T790M-
Part B2 (savolitinib 600 / 300 mg):
ORR: 33/51 (65%)



T790M-
Part D (savolitinib 300 mg):
ORR: 23/36 (64%)

Ji-Youn Han et al, ESMO Asia 2019

Novel approach: bispecific antibody JNJ-372

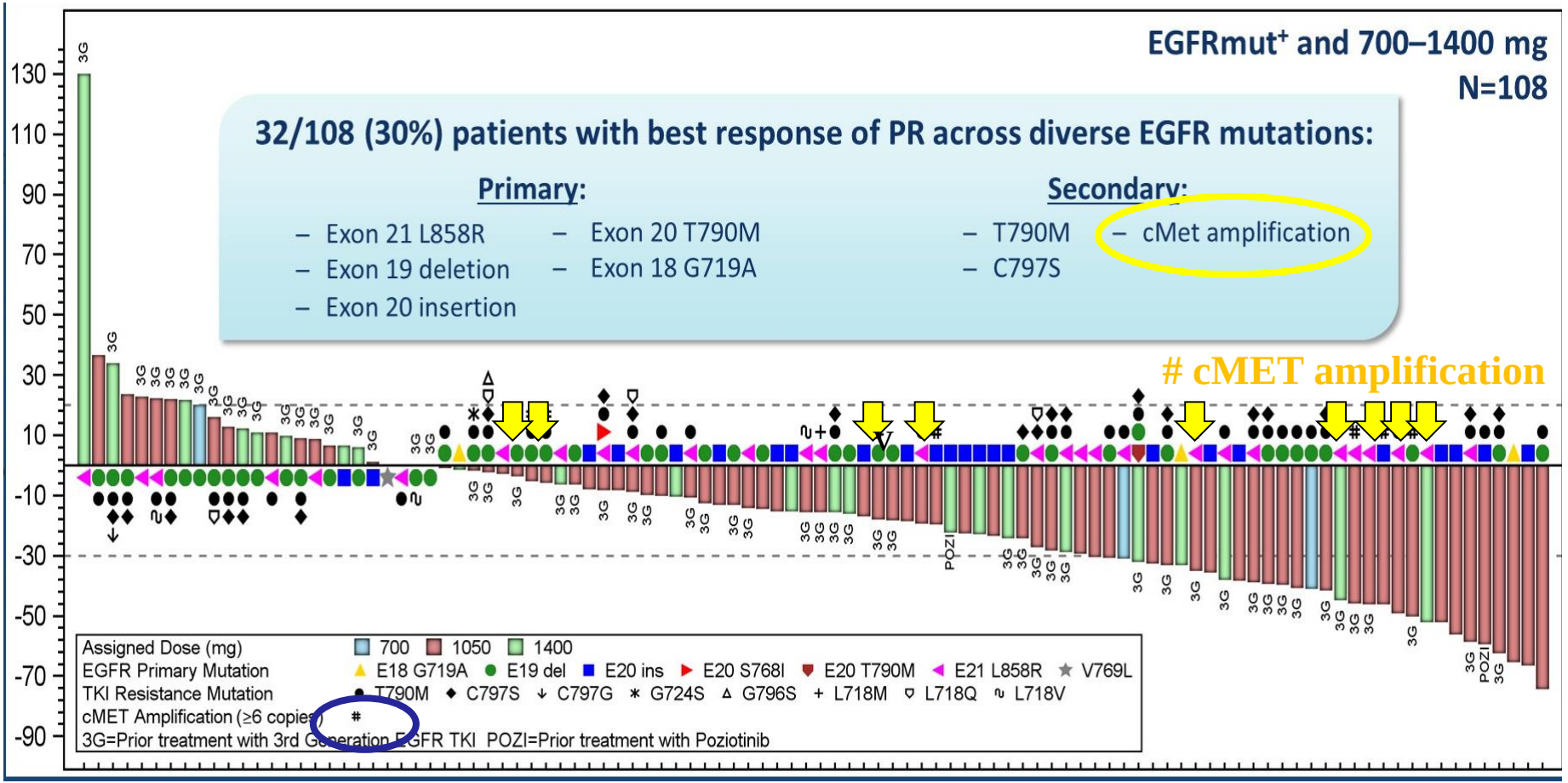


JNJ-61186372 (JNJ-372), an EGFR-cMet bispecific antibody, in EGFR-driven advanced non-small cell lung cancer (NSCLC)

Eric B. Haura,[1] Byoung Chul Cho,[2] Jong-Seok Lee,[3] Ji-Youn Han,[4] Ki Hyeong Lee,[5] Rachel E. Sanborn,[6] Ramaswamy Govindan,[7] Eun Kyung Cho,[8] Sang-We Kim,[9] Karen L. Reckamp,[10] Joshua K. Sabari,[11] Catherine A. Shu,[12] Dong-Wan Kim,[13] Jorge E. Gomez,[14] Aaron S. Mansfield,[15] Alexander Spira,[16] Pasi A. Jänne,[17] Santiago Viteri,[18] Jose Manuel Trigo,[19] Martin Curtis,[20] Patricia A. Lorenzini,[20] Meena Thayu,[20] Amy Roshak,[20] Kyounghwa Bae,[20] Roland E. Knoblauch,[20] Joshua C. Curtin,[20] Nahor Haddish-Berhane,[20] Matthew V. Lorenzi,[20] Keunchil Park,[21] Joshua M. Bauml[22]

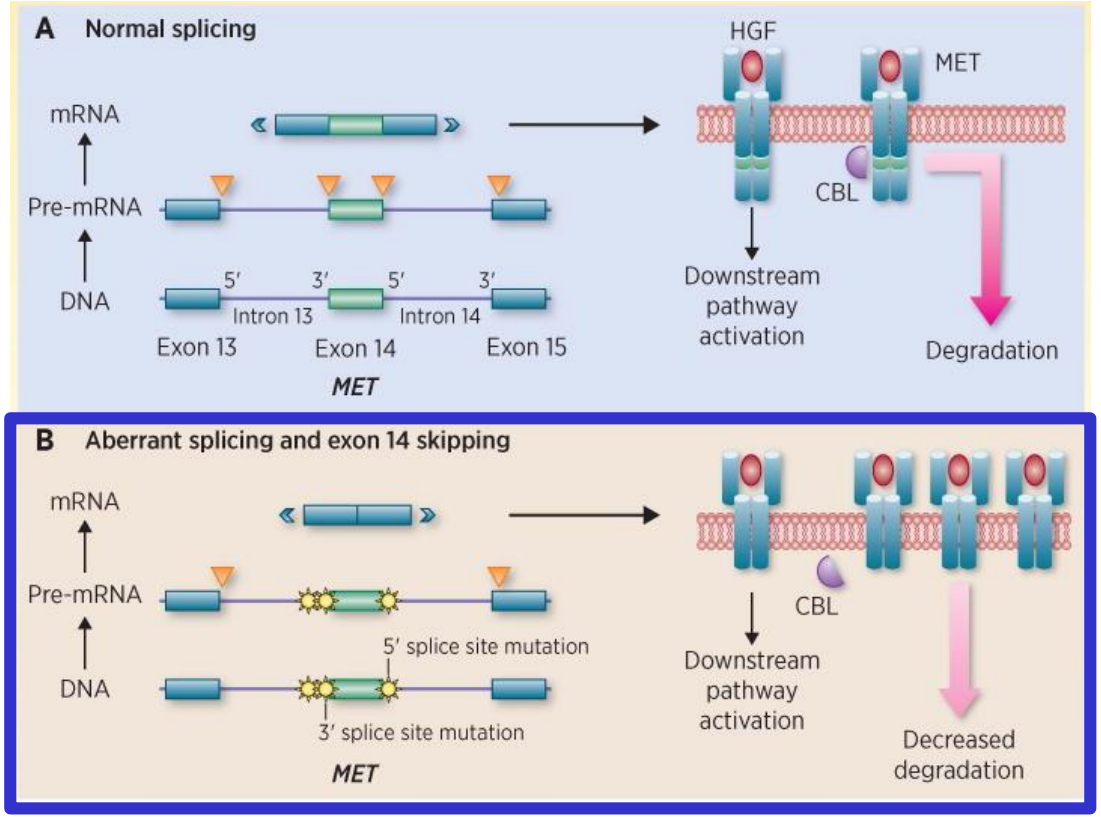
Gelsomino, et al, *Critical Reviews O/H* 2014

Results


EGFRmut+ and 700–1400 mg
N=108
32/108 (30%) patients with best response of PR across diverse EGFR mutations:
Primary:
– Exon 21 L858R
– Exon 19 deletion
– Exon 20 insertion
– Exon 20 T790M
– Exon 18 G719A
Secondary:
– T790M
– C797S
– cMet amplification
cMET amplification
Assigned Dose (mg) 700 1050 1400
EGFR Primary Mutation E18 G719A E19 del E20 ins E20 S768I E20 T790M E21 L858R V769L
TKI Resistance Mutation T790M C797S C797G G724S G796S L718M L718Q L718V
cMET Amplification (≥6 copies) #
3G=Prior treatment with 3rd Generation EGFR TKI POZI=Prior treatment with Poziotinib

MET Exon 14 Alteration Biology

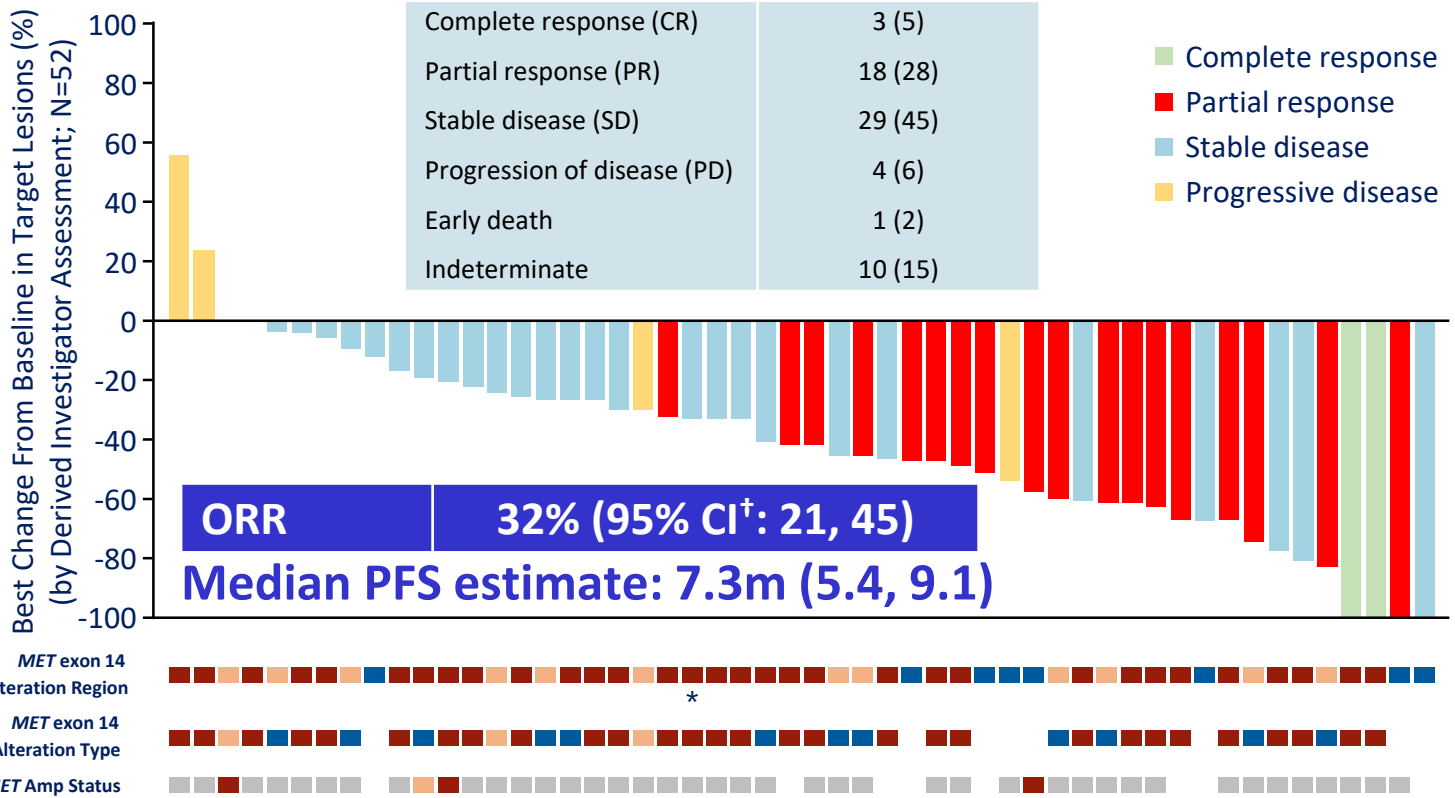
- **Result of *MET* mutation**
  - disrupt splicing sites (5' or 3')
  - causes alternative splicing to occur and exclusion of *MET* exon 14
  - highlights association between abnormal splicing and oncogenesis
- **Decreases MET degradation**
  - lack of Y1003-containing region
  - ↓MET ubiquitination
  - ↑MET on cell surface driving oncogenesis



Drilon A, Clin Cancer Res, 2016

Updated Antitumor Activity of Crizotinib in Pts With *MET* Exon 14-Altered NSCLC

Complete response (CR)	3 (5)
Partial response (PR)	18 (28)
Stable disease (SD)	29 (45)
Progression of disease (PD)	4 (6)
Early death	1 (2)
Indeterminate	10 (15)

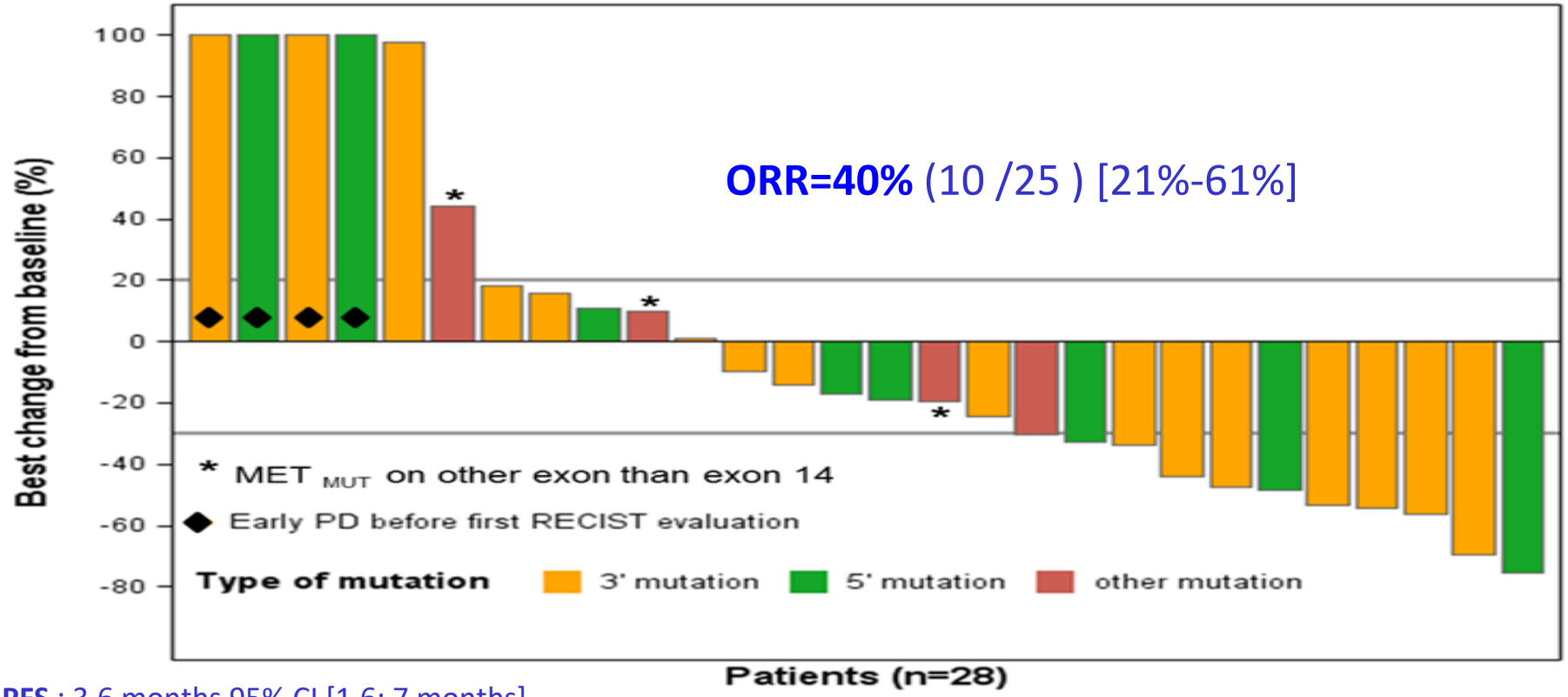


Biomarker Data Key§

	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

29 May 2018: FDA granted Breakthrough Therapy designation for crizotinib for the treatment of patients with metastatic NSCLC MET exon 14 alterations

AcSé trial (crizotinib), *MET* exon 14 mutation



mPFS : 3.6 months 95% CI [1.6; 7 months]

mOS : 9.5 months 95% CI [4.1; 13.4months]

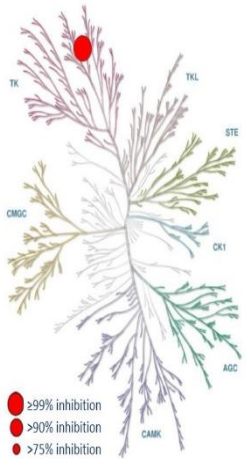
Abstract ID: #12937. Activity of crizotinib in MET or ROS1 positive (+) NSCLC: results of the AcSé trial. D. Moro-Sibilot

Phase II study of tepotinib in NSCLC patients with *MET*ex14 mutations

Paul K. Paik[1], Remi Veillon[2], Alexis B. Cortot[3], Enriqueta Felip[4], Hiroshi Sakai[5], Julien Mazieres[6], Frank Griesinger[7], Leora Horn[8], Helene Senellart[9], Jan Van Meerbeeck[10], Javier de Castro Carpeño[11], Jyoti Patel[12], Marina Chiara Garassino[13], Masahiro Morise[14], Niels Reinmuth[15], Santiago Viteri[16], Takaaki Tokito[17], Tomohiro Sakamoto[18], Jürgen Scheele[19], Xiuning Le[20], on behalf of the VISION Study Group

- Tepotinib is a highly selective, ATP-competitive, reversible, potent MET tyrosine kinase inhibitor (TKI)
  - IC_{50} ~1.7 nM
  - At 1 μM, only MET is inhibited out of a panel of over 300 kinases
- No MTD reached at 1400 mg QD; RP2D is 500 mg QD
- Preclinical brain penetration
  - High binding to rat brain tissue ($f_{u\ br}$ = 0.4%)
  - The $K_{p\ u,u}$ (ratio of free brain vs plasma concentration) in rats was 0.25, i.e. 25% of free tepotinib levels in brain, relative to levels found in plasma
- Complete brain and systemic response lasting almost 1 year in patient with NSCLC harboring MET-RB1 translocation treated with tepotinib as compassionate use (*Dr Marie Florescu, MD, and Dr Raafat Alameddine at CHUM Montreal, Canada*)

Tepotinib kinome[1]



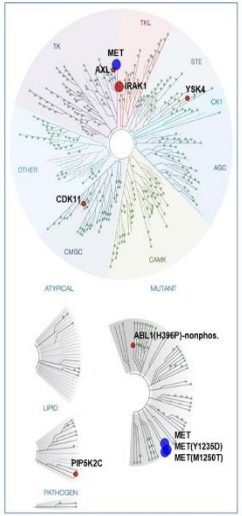
Capmatinib in *METΔex14*-mutated advanced non-small cell lung cancer (NSCLC): Efficacy data from the phase II GEOMETRY mono-1 study

Juergen Wolf,[1] Takashi Seto,[2] Ji-Youn Han,[3] Noemi Reguart,[4] Edward B. Garon,[5] Harry J. M. Groen,[6] Daniel S. W. Tan,[7] Toyoaki Hida,[8] Maja de Jonge,[9] Sergey V Orlov,[10] Egbert F. Smit,[11] Pierre-Jean Souquet,[12] Johan Vansteenkiste,[13] Sylvie Le Mouhaer,[14] Anna Robeva,[15] Maeve Waldron-Lynch,[16] Alejandro Balbin,[17] Lauren Fairchild, [17] Monica Giovannini,[15] Rebecca S. Heist[18]

- *MET* exon 14 skipping mutations (*METΔex14*) are reported in 3–4% of patients with NSCLC[1-4] and associated with both poor prognosis and poor responses to standard therapies including immunotherapy.[5-9]
- Capmatinib is a highly selective *MET* inhibitor with *in vitro* and *in vivo* activity seen against preclinical cancer models with *MET* activation.[10]
- Capmatinib is the most potent inhibitor against MET compared to other inhibitors.[11]

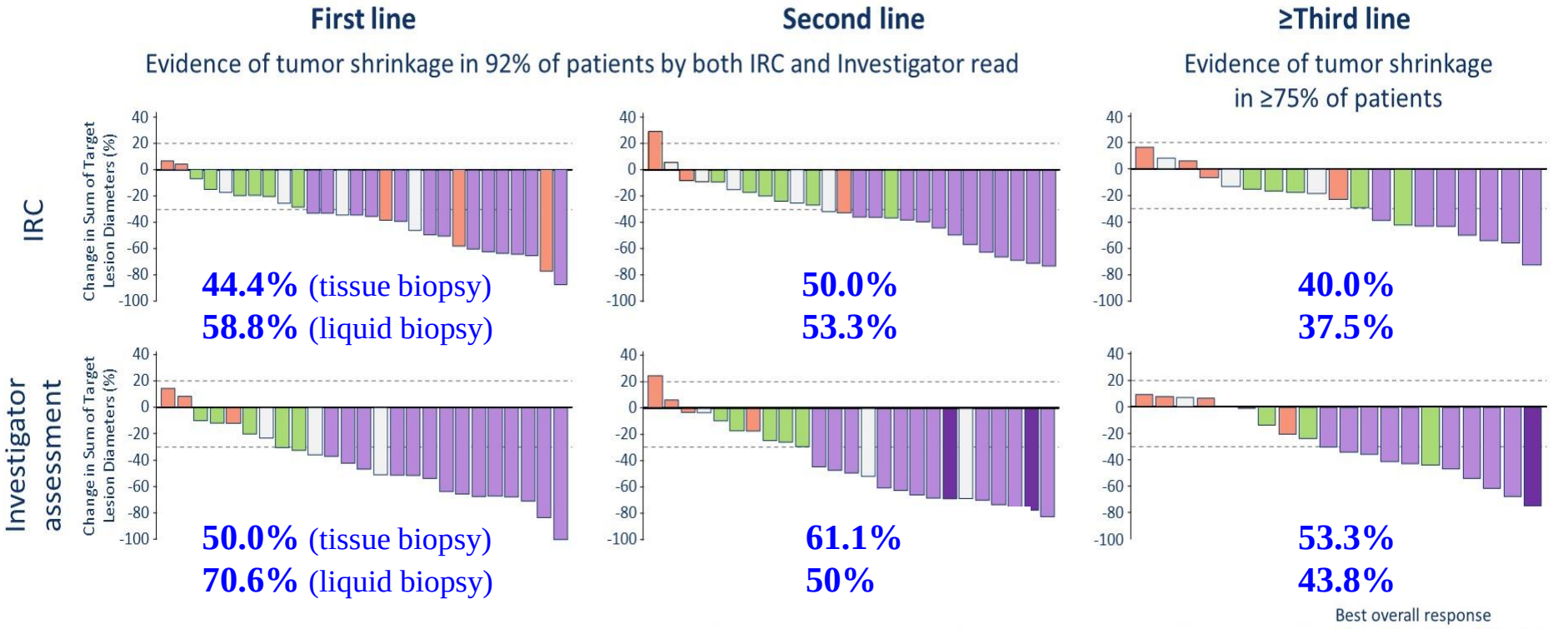
	Capmatinib	Savolitinib	Tepotinib	Cabozantinib	Crizotinib
IC_{50} (nM)	**0.6**	2.1	3.0	7.8	22.5

- Preliminary efficacy data from the phase 2, multi-cohort, multicenter GEOMETRY mono-1 study showed **deep responses** with capmatinib irrespective of the line of treatment as well as **activity in the brain lesions** in patients with *METΔex14* mutated advanced NSCLC.[12]



ASCO 2019

Tepotinib: tumor shrinkage by line of therapy (Phase II – VISION Study)



Patients excluded due to baseline/on-treatment measurement not being available (IRC/investigator assessment): first line 5/8, second line 4/5, ≥third line 4/3.
One patient was excluded from all efficacy analyses due to insufficient METex14 data.
CR, complete response; IRC, independent review committee; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

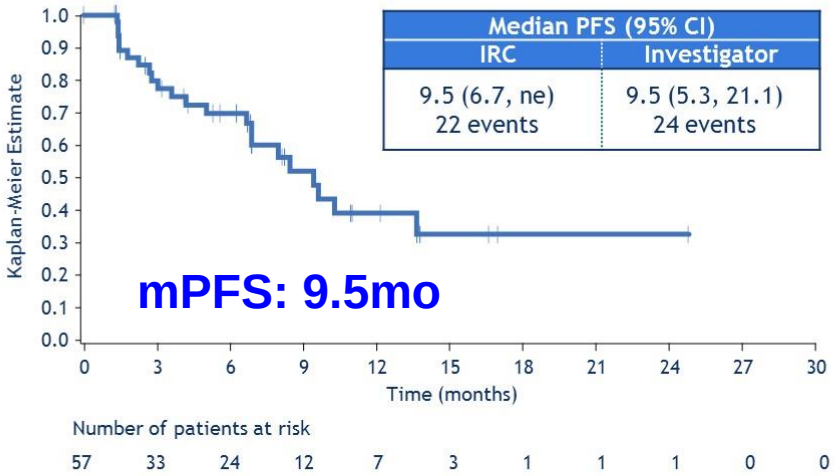
P.K. Paik et al, ASCO 2019

Tepotinib: PFS

PFS across all treatment lines

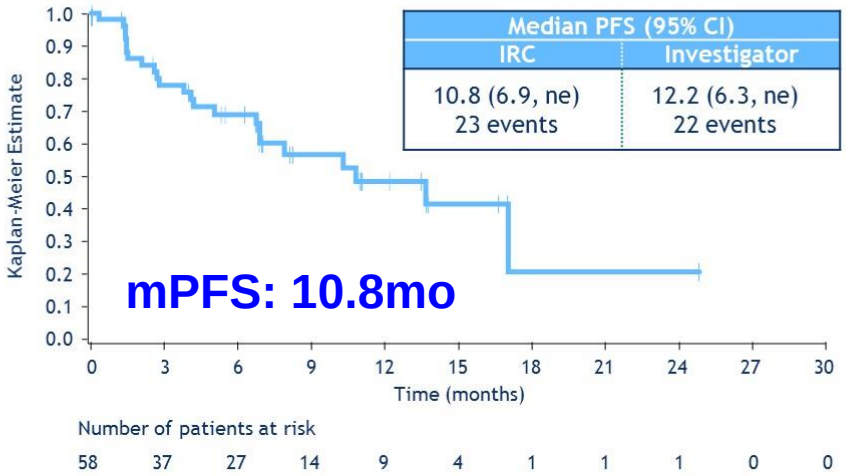
Liquid biopsy (L+) (n=57)

PFS by IRC



Tissue biopsy (T+) (n=58)

PFS by IRC



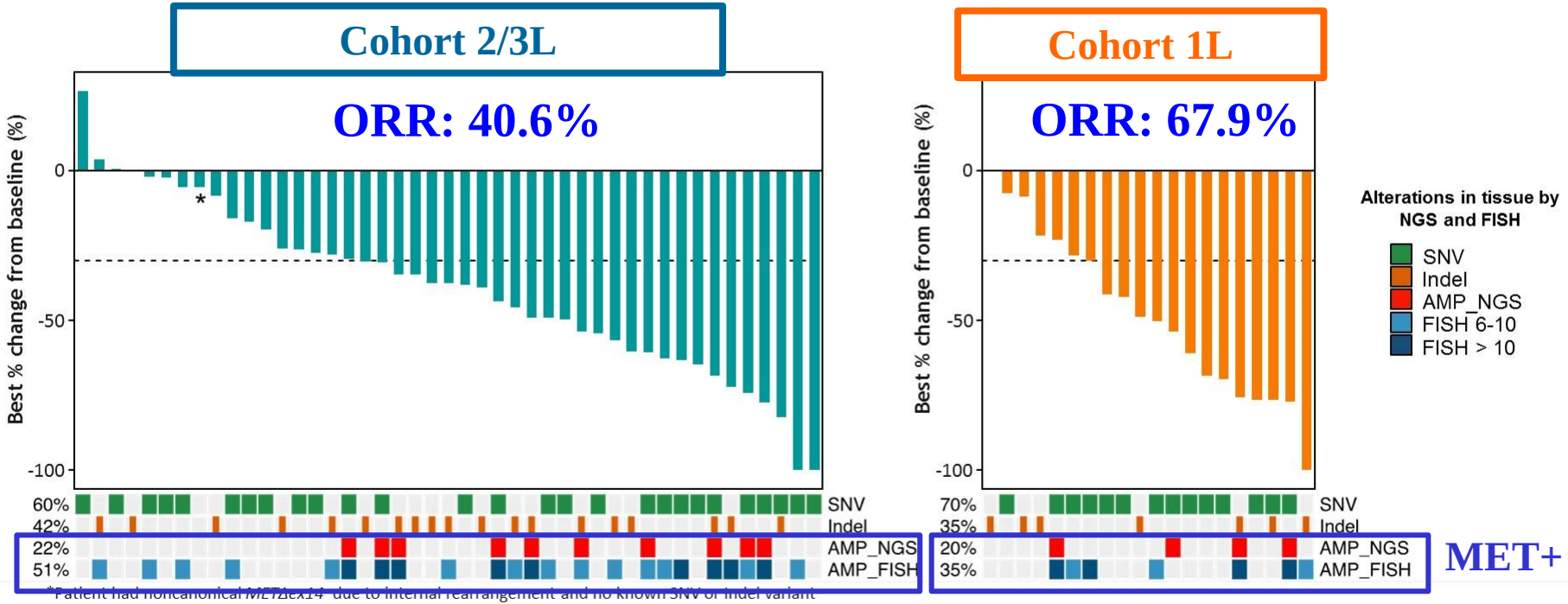
33/57 L+ patients and 31/58 T+ patients remain on treatment.

11 sept 2019: FDA Breakthrough Therapy Designation for Investigational Therapy Tepotinib in Patients with Metastatic NSCLC with METex14 Skipping Alterations

P.K. Paik et al, ASCO 2019

Capmatinib: tumor shrinkage per BIRC
(Phase II – GEOMETRY Trial)

- ***MET mutations could be detected by both RT-PCR and NGS***
  - High concordance (99%) between NGS and RT-PCR† in detection of *METΔex14* in tumor tissue



*Patient had noncanonical *METΔex14* due to internal rearrangement and no known SNV or indel variant

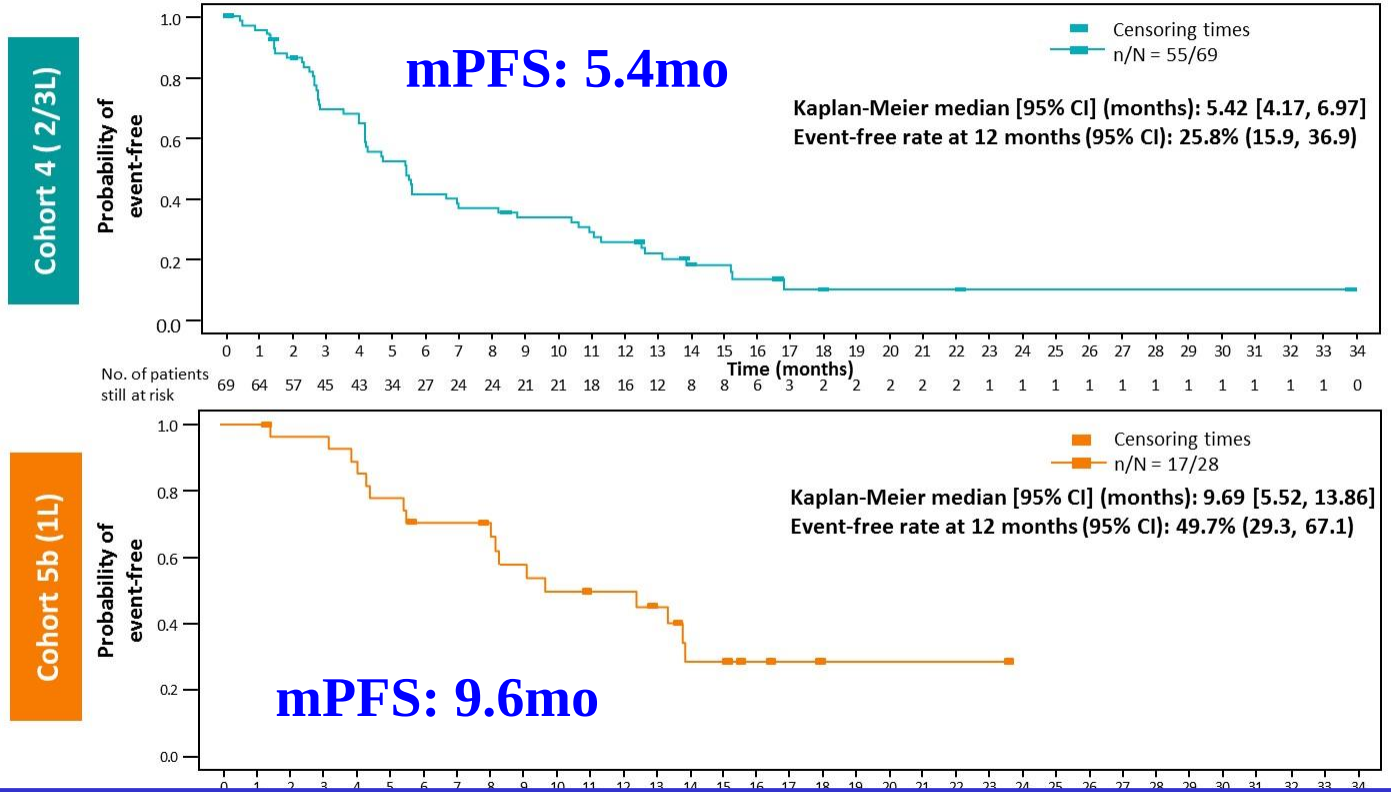
†73 tissue samples, Cohort 4=53 (Including 1 patient with a noncanonical METΔex14 rearrangement and no canonical variants), Cohort 5b=20.

SNV, Single nucleotide variant in MET leading to Ex14 skipping; Indel, Insertion or deletion leading to METEx14; AMP_NGS, amplification detected by FM NGS panel ≥ 6 *GCN*; AMP_FISH, MET FISH copy number

J.Wolf et al, ASCO 2019

Capmatinib: PFS per BIRC

Median PFS was 5.42 months in Cohort 4 (2/3L) and 9.69 months in Cohort 5b (1L)

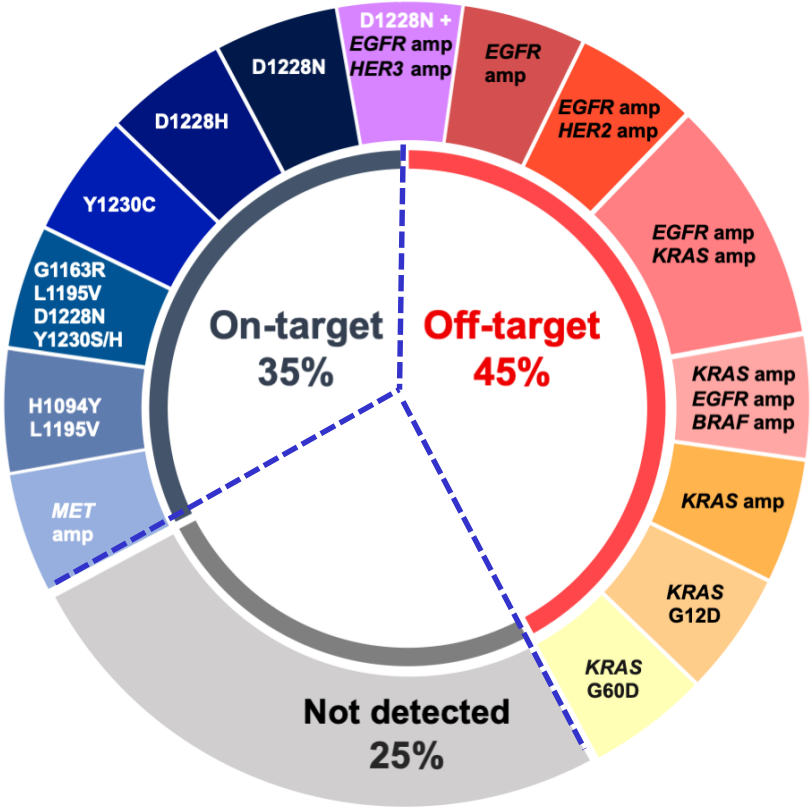


6 Sept 2019, cancer therapy capmatinib (INC280) granted FDA Breakthrough Therapy Designation for pts with MET-mutated advanced NSCLC

J.Wolf et al, ASCO 2019

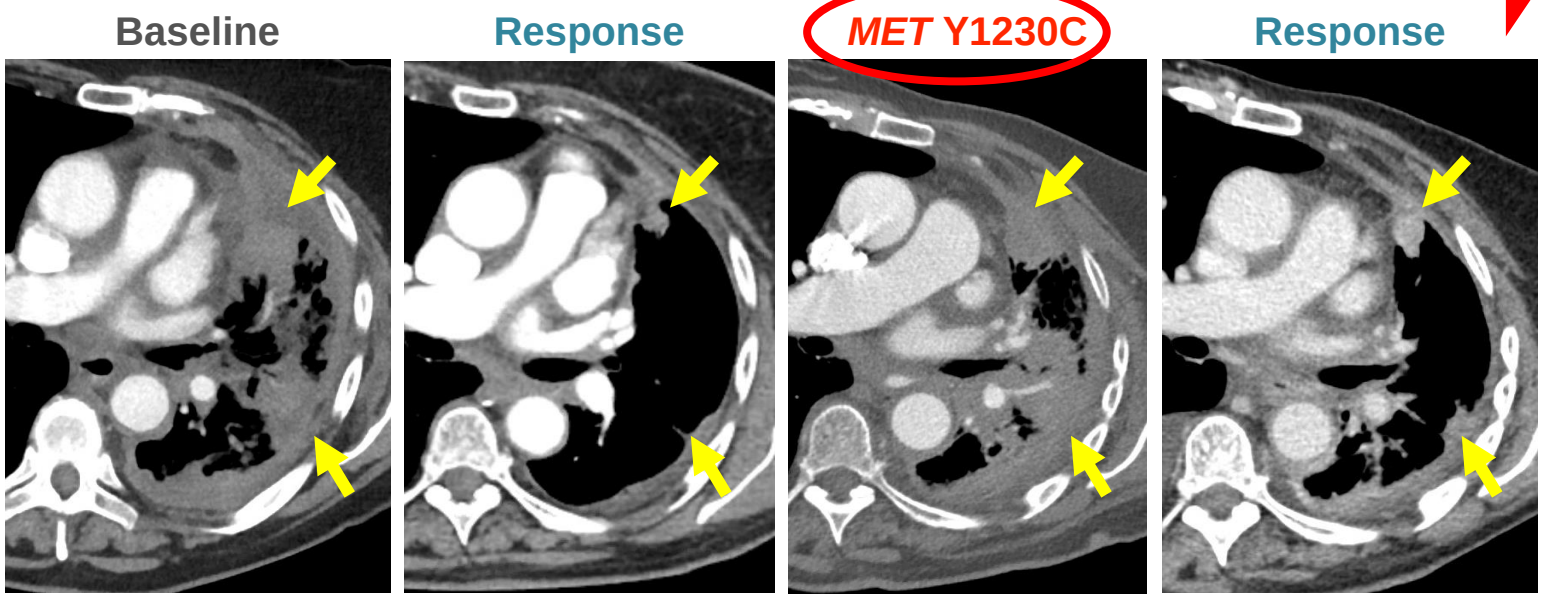
Next step…mechanisms of resistance

- Genomic **on-target** and **bypass mechanisms of resistance** were frequently found in the setting of resistance to MET TKI.
- ***MET*-dependent** resistance include single and polyclonal **kinase domain mutations** in frequent hotspots (D1228X, Y1230X and L1195X) and high levels of ***MET* amplification** (type I and II).
- Genomic **bypass mechanisms of resistance** involved recurrent gene amplification in ***EGFR, HER2, HER3 and* MAPK *pathway genes (KRAS/BRAF)*** and ***KRAS* mutations**.
- Novel treatment strategies like sequential MET TKI for on-target resistance, and EGFR-MET or MET-MEK dual combinations for bypass activation should be explored to overcome resistance to MET TKIs.



MET Y1230C resistance can be overcome with type II MET TKIs

Crizotinib PFS 15 months → **Merestinib Ongoing**



In summary for MET NSCLC

Patients with METamp

- **Crizotinib** (ORR:40%)
- **Capmatinib** (ORR: 47%)
- **Savolitinib**
- **Tepotinib**

Patients with MET exon14-skipping mutation

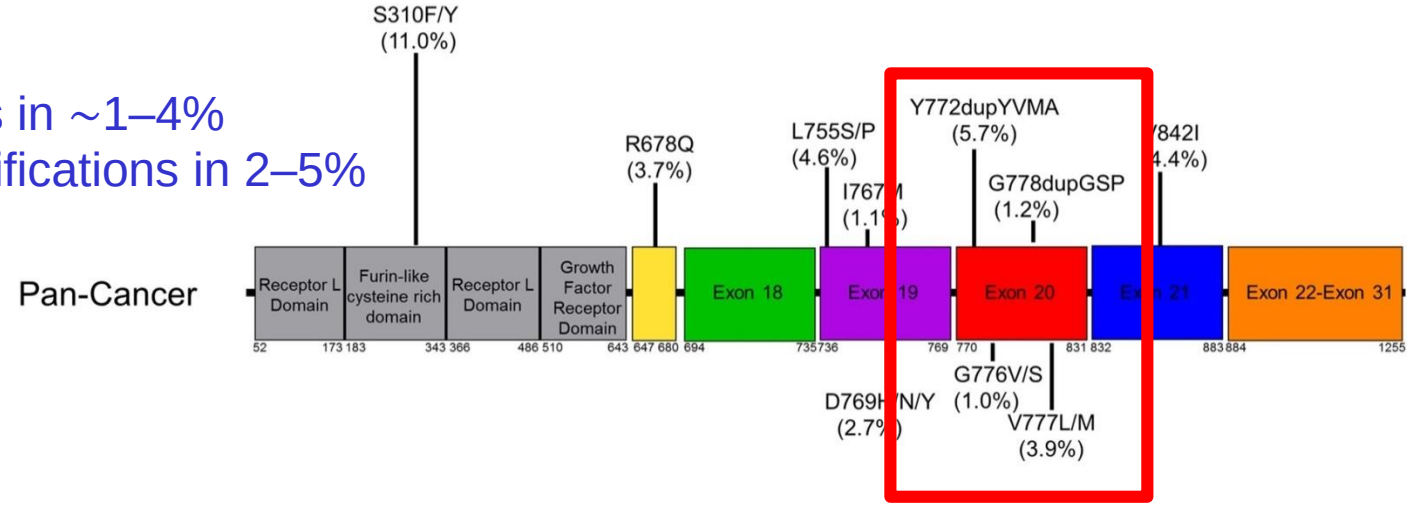
- **Crizotinib** (ORR:32%, mPFS:7.3mo)
- **Tepotinib** (ORR 1st L:44%, 2nd:L 50% (mPFS:10.8mo)
- **Capmatinib** (ORR 1st L:67%, 2/3nd:40%) (mPFS 1st L:9.6, 2/3nd L: 5.4mo)
- **Savolitinib** **(ORR: 54%)** (Lu et al, AACR 2019)

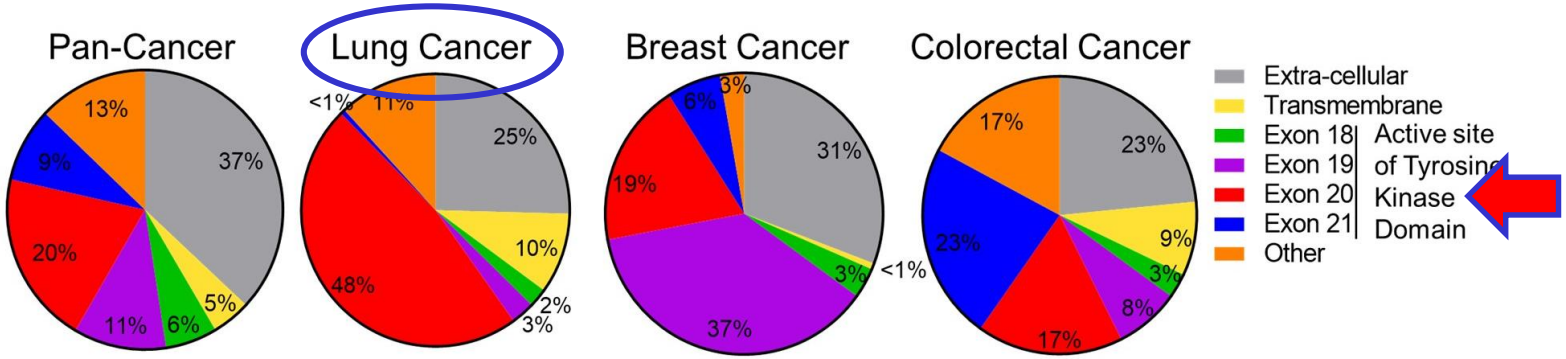
2nd line at resistance ?

- **Cabozantinib**
- **AMG337**
- **Glesatinib**
- **Merestinib**

HER2 mutations occur mainly in the tyrosine kinase domain

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

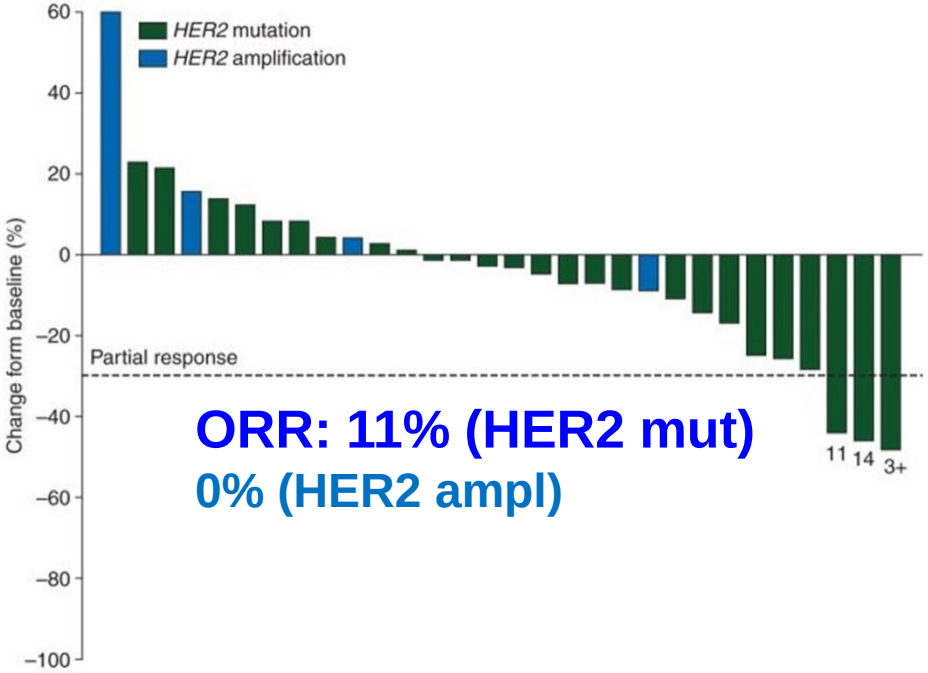




Robichaux et al, AACR 2019

Dacomitinib and Afatinib for HER2 mutated NSCLC

Dacomitinib

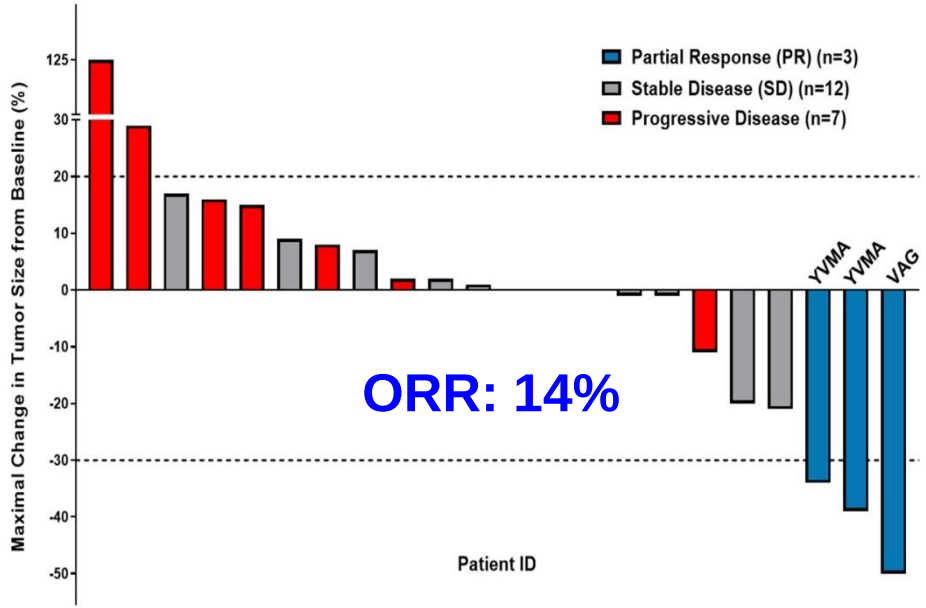


ORR: 11% (HER2 mut)

0% (HER2 ampl)

Kris et al, Annals onco 2014

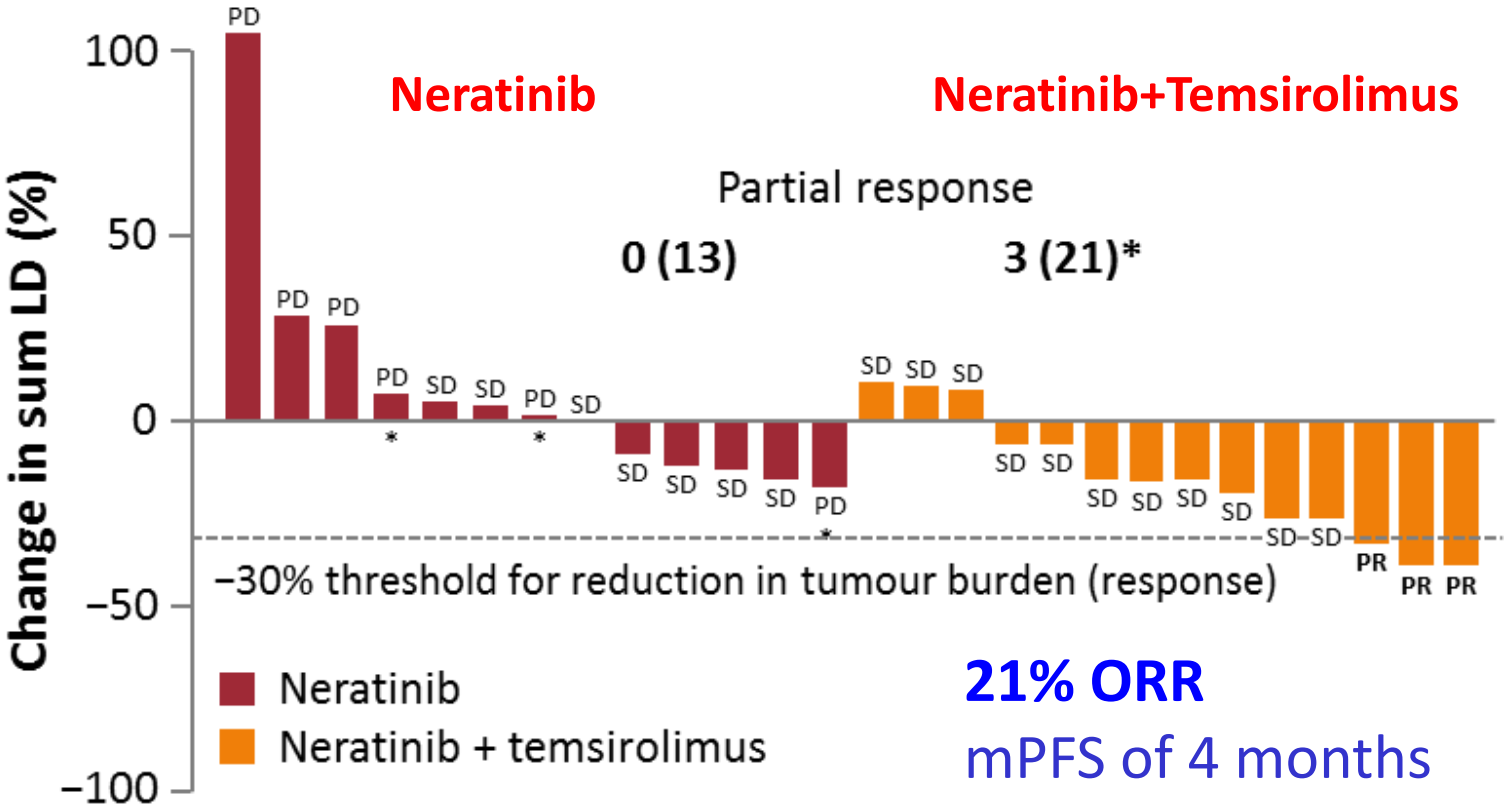
Afatinib



ORR: 14%

Lai et al, Eur J Cancer 2019

Neratinib +/- Temsirolimus for HER2 mutated NSCLC



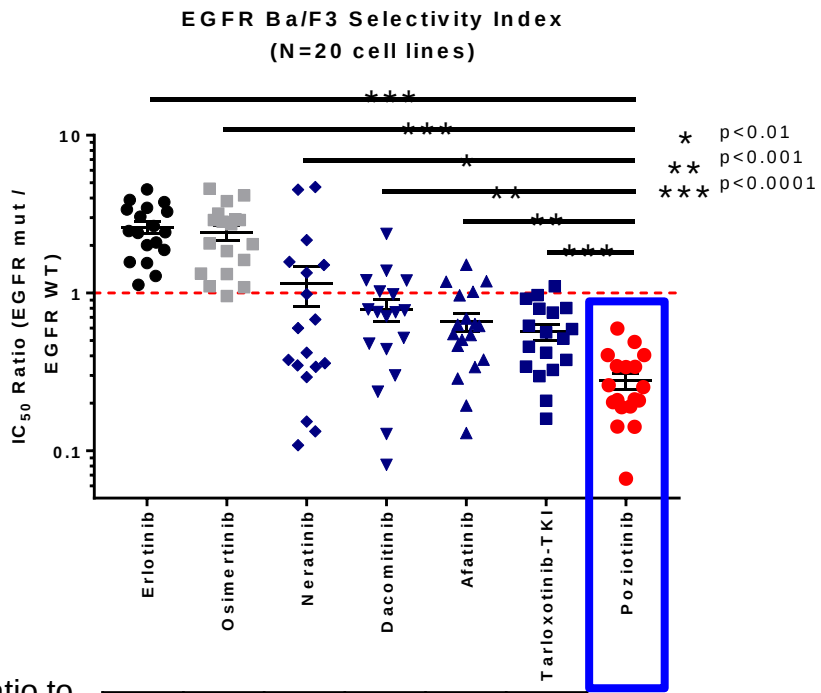
21% ORR

mPFS of 4 months

Besse B, et al. Presented at ESMO 2014. Abstract LBA 39

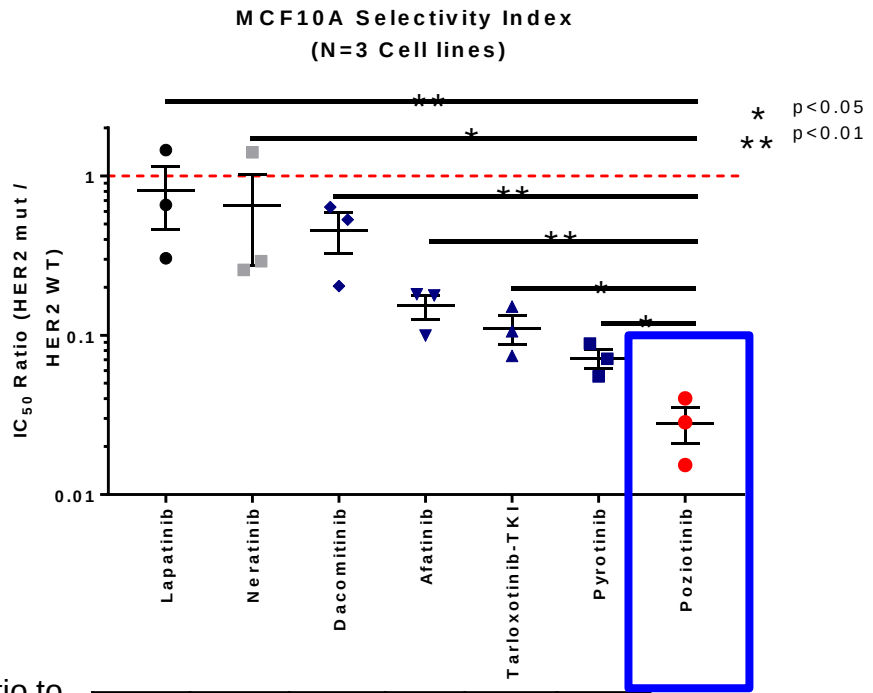
Poziotinib is a selective (mut vs wt) inhibitor of EGFR and HER2 exon 20 mutations *in vitro*

EGFR



Ratio to Poziotinib	9.4	8.7	4.1	2.8	2.4	2.0

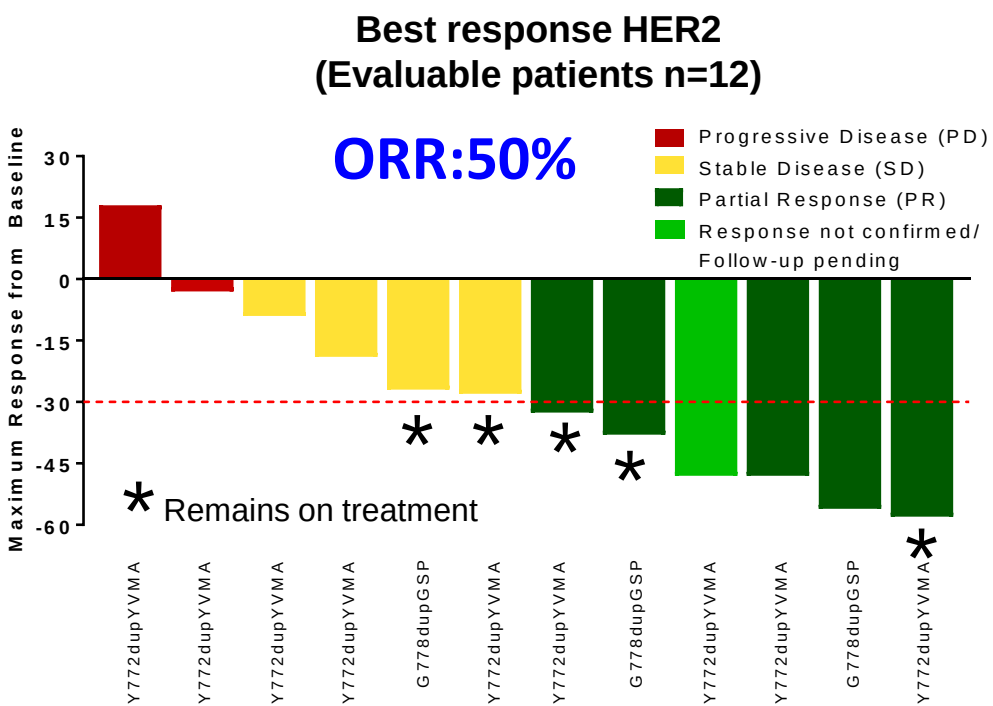
HER2

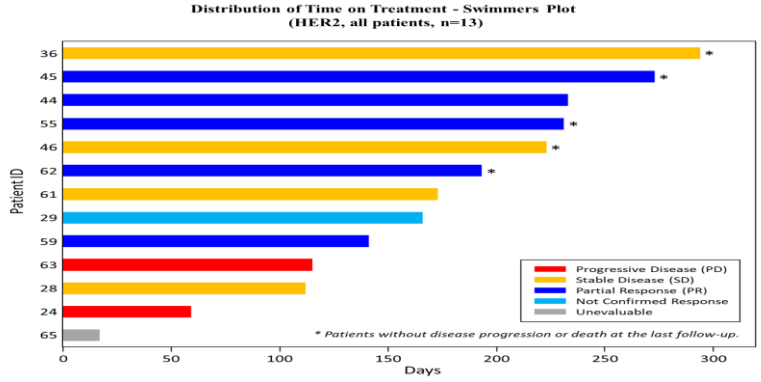


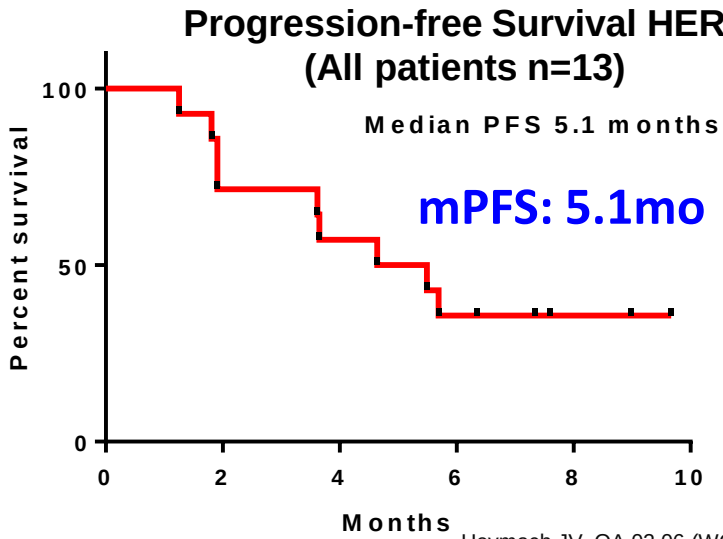
Ratio to Poziotinib	28.7	23.3	16.3	5.4	4.0	2.6

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

Poziotinib efficacy in HER2 Exon 20 insertion mutant NSCLC







Heymach JV. OA 02.06 (WCLC 2018)

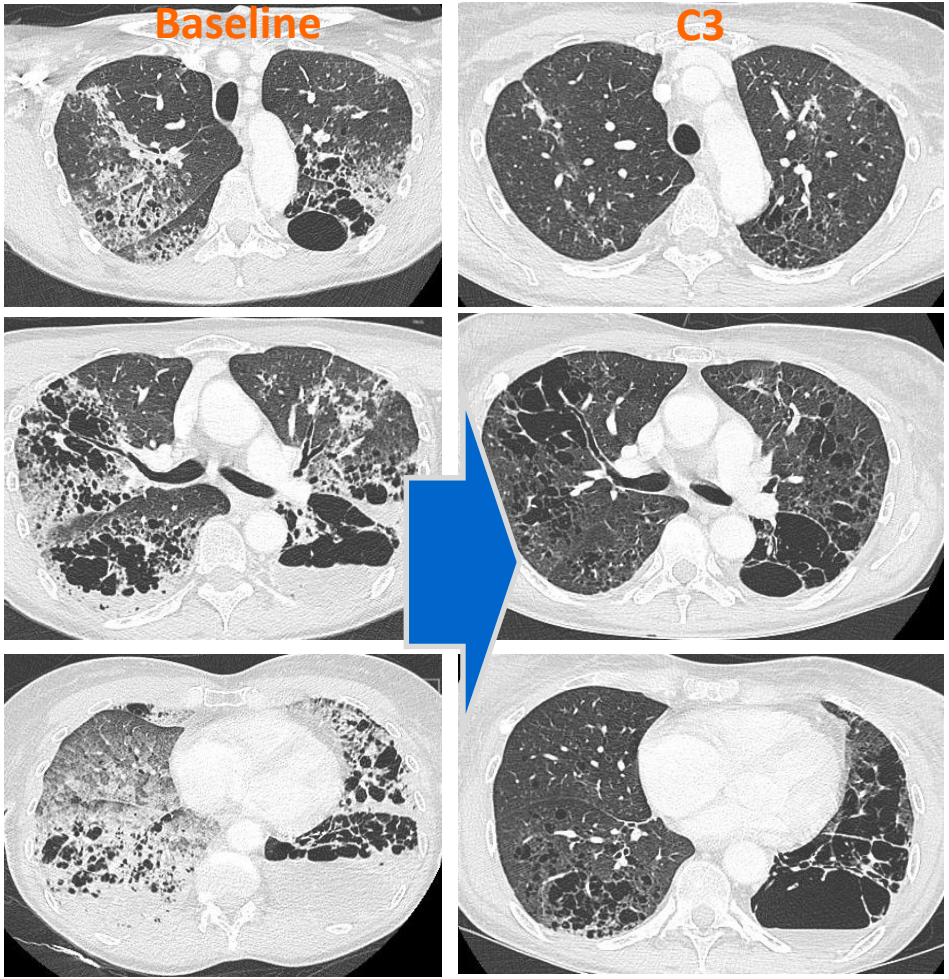
52-year, non-smoker patient, adenocarcinoma HER2 exon 20, with pulmonary metastasis:

- cisplatin+pem
- pacliatxel+herceptin
- nivolumab
- paclitaxel+herceptin
- vinorelbine+herceptin

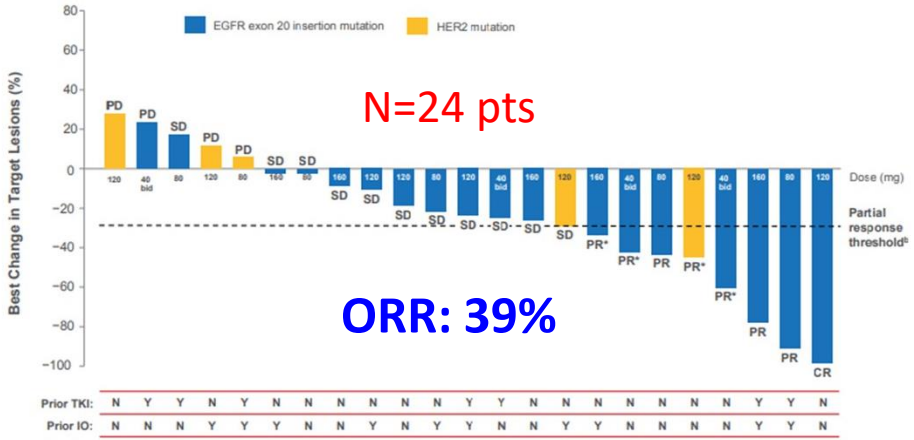
- **Poziotinib**

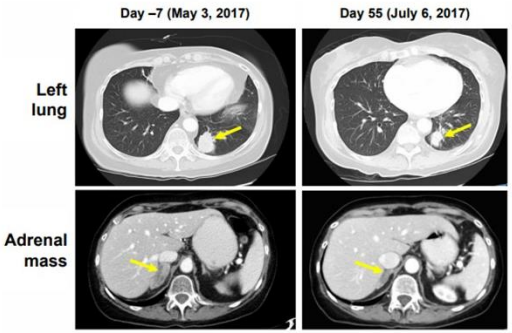
Toxicities grade 3-4 …

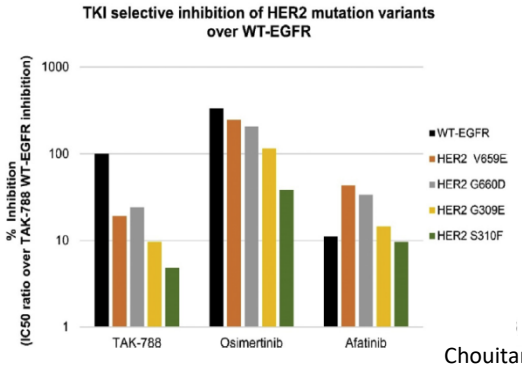
Poziotinib



Activity of the EGFR/HER2 exon 20 inhibitor TAK788 in NSCLC







Chouitar J et al IASLC 2018

Table 6. Responses to TAK-788 in NSCLC Patients With *EGFR* Exon 20 Insertions

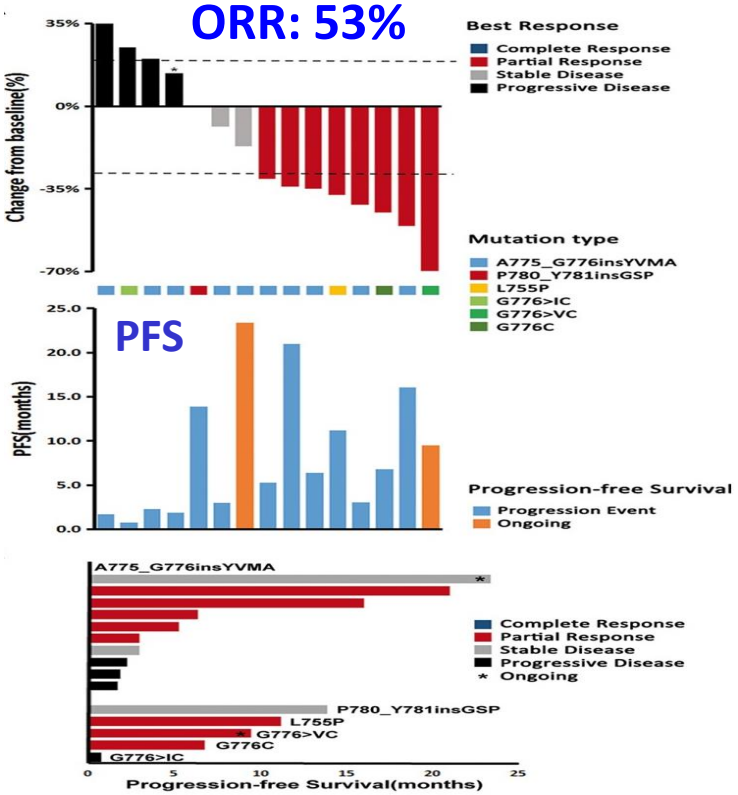
	5–40 mg qd (n=12)	80 mg qd; 40 mg bid (n=9)	120 mg qd; 60 mg bid (n=9)	160 mg qd (n=6)	80–160 mg Total Daily Dose (n=24)
Patients with ≥1 post-baseline scan	n=10	n=9	n=4	n=5	n=18
ORR, n (%)	0	4 (44)[a]	1 (25)	2 (40)[b]	7 (39)
CR	0	0	1 (25)	0	1 (6)
PR	0	4 (44)[a]	0	2 (40)[b]	6 (33)[c]
DCR, n (%)	3 (30)	8 (89)	4 (100)	5 (100)	17 (94)

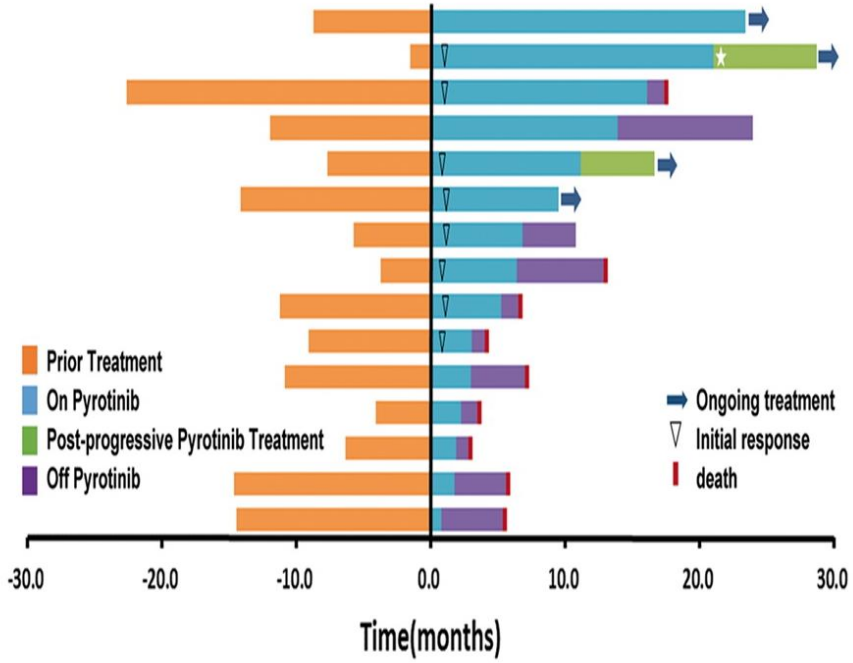
Patients are presented under their initial dose cohort

[a] 2 PRs awaiting confirmation; [b] 1 PR awaiting confirmation; [c] 3 PRs awaiting confirmation

Neal, J et al, IASLC 2018

Pyrotinib in pts with HER2-mutant NSCLC (phase 2)



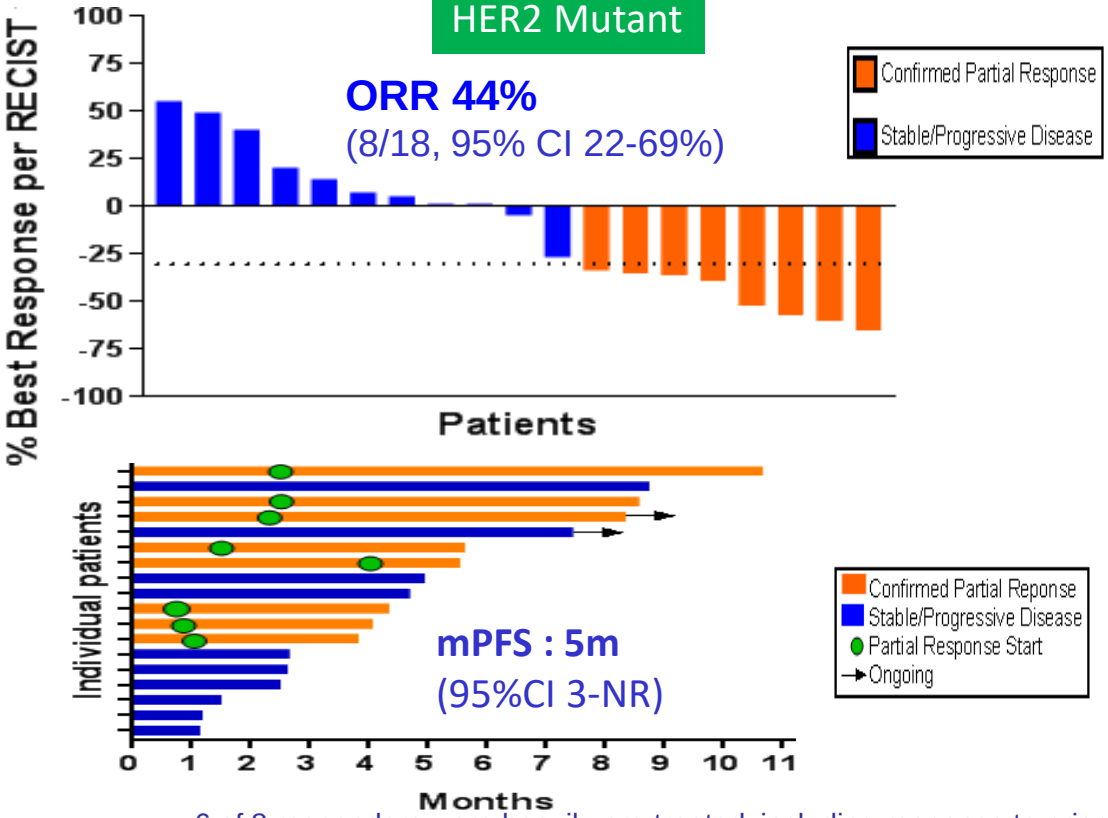


Wang Y et al, annals of onco 2019

Antibody-drug conjugate ado-trastuzumab emtansine (TDM1) for pts with *HER2* amplified or mutant NSCLC

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

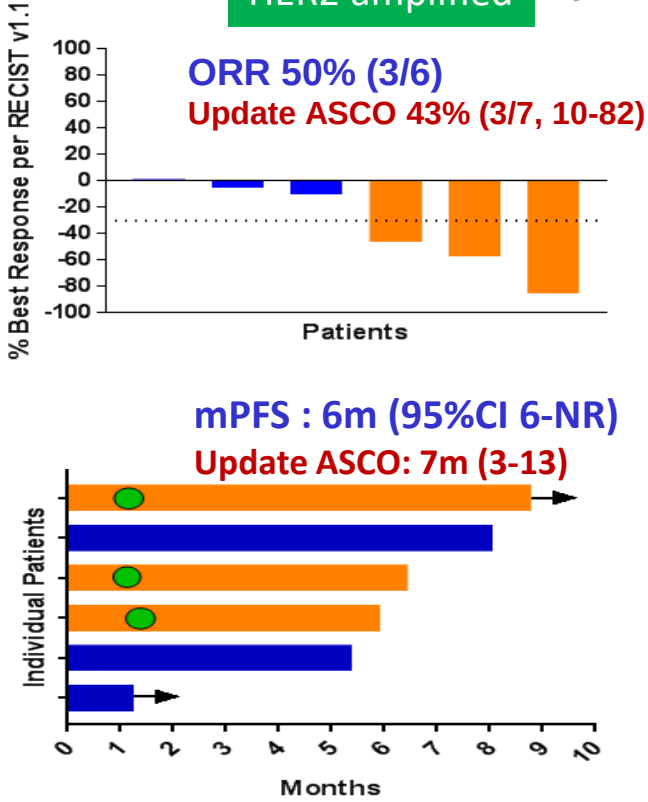
HER2 Mutant



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

Bob T.Li et al, JCO 2018

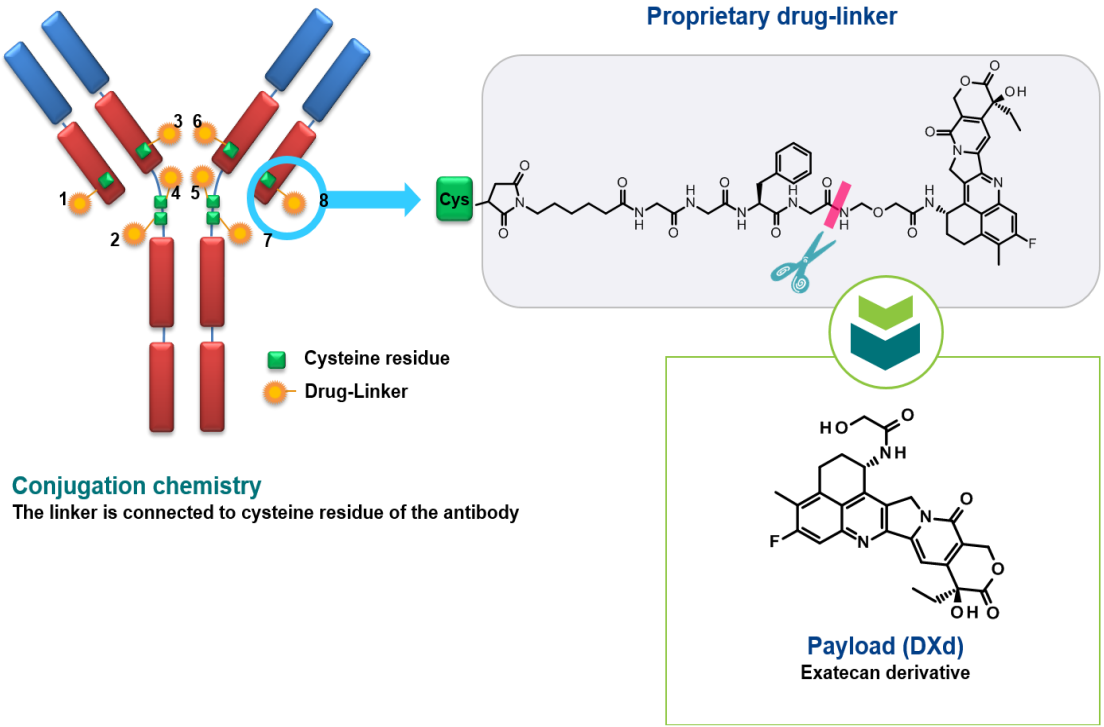
HER2 amplified



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

Novel HER2-targeted antibody-drug conjugate

DS-8201a in HER2-expressing or -mutated advanced NSCLC



[Fam-] trastuzumab deruxtecan (DS-8201a)

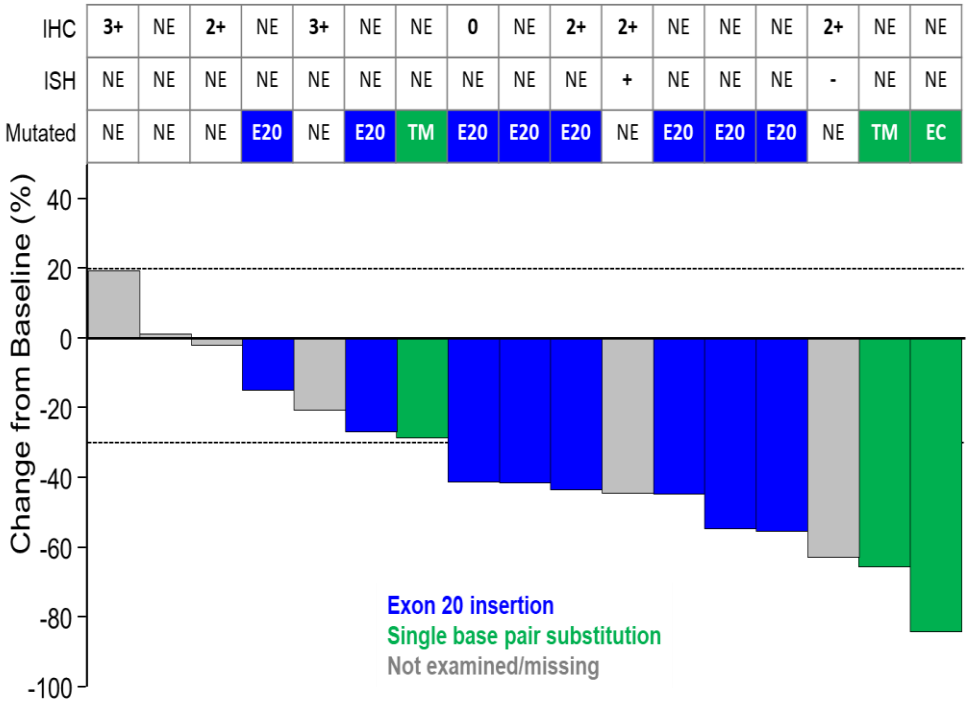
- HER2-targeted antibody-drug conjugate with a humanized HER2-targeted antibody attached to a potent topoisomerase I inhibitor payload by a proprietary peptide-based cleavable linker

- 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 NSCLC



	HER2-expressing or -mutated NSCLC (N = 18)	HER2-mutated NSCLC (n = 11)
Confirmed ORR[a] % (n/N)	58.8%(10/17)	88.2% (15/17)
Confirmed DCR[a] % (n/N)	72.7% (8/11)	100% (11/11)
PFS, median (range), months	14.1 (0.9, 14.1)	14.1 (4.0+, 14.1)

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.

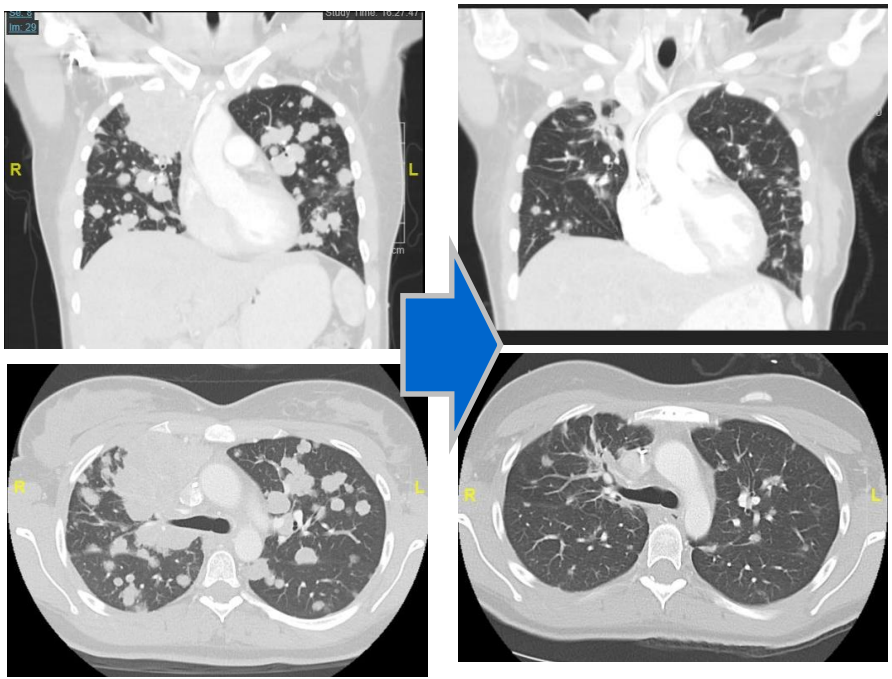
Junji Tsurutani et al, WCLC 2018

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



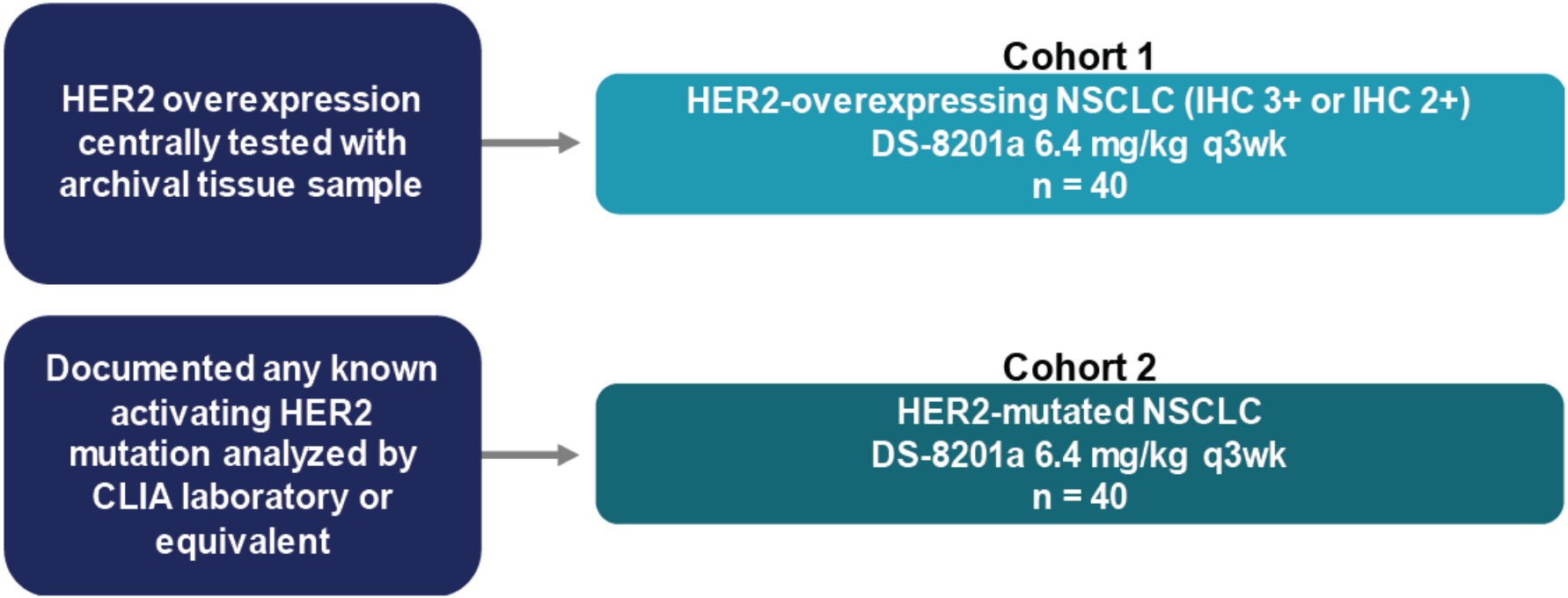
February 2018 – baseline

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

Phase 2 trial with DS-8201a, ongoing in NSCLC (HER2)



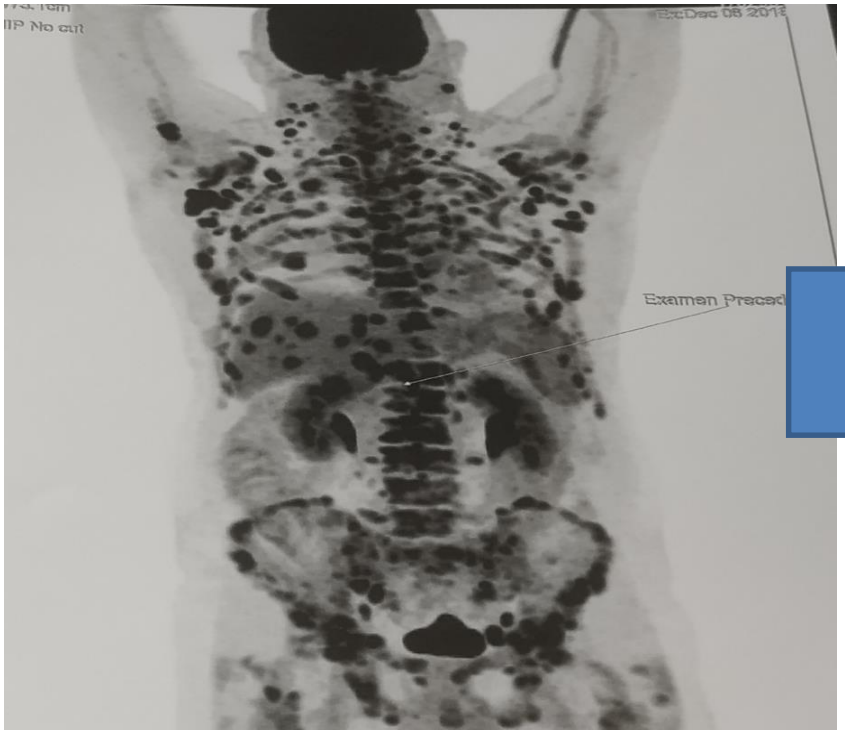
D.Planchard et al, ELCC 2019

NSCLC adenocarcinoma HER2-insertion in exon 20

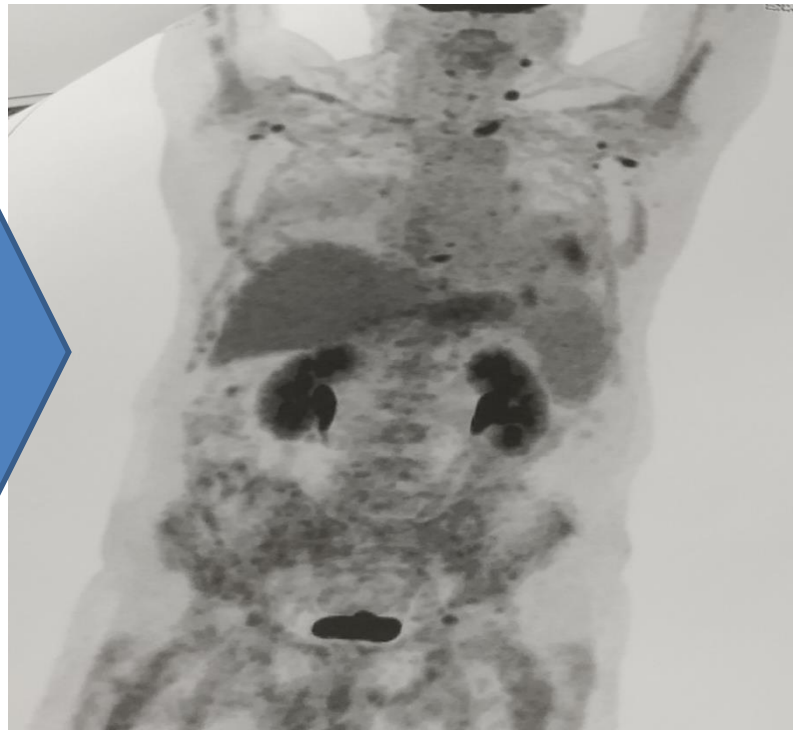
-lymph node metastases, adrenal glands, hepatic, spleen, brain, bone...

-First line carbo-pem and second line pembrolizumab

Baseline – December 2018



June 2019 – C7J1



Patients HER2-mutant NSCLC

Pan HER inhibitors

- Dacomitinib (ORR:11%)
- Neratinib-Temsirolimus (ORR:21%)
- Afatinib (ORR:14%)

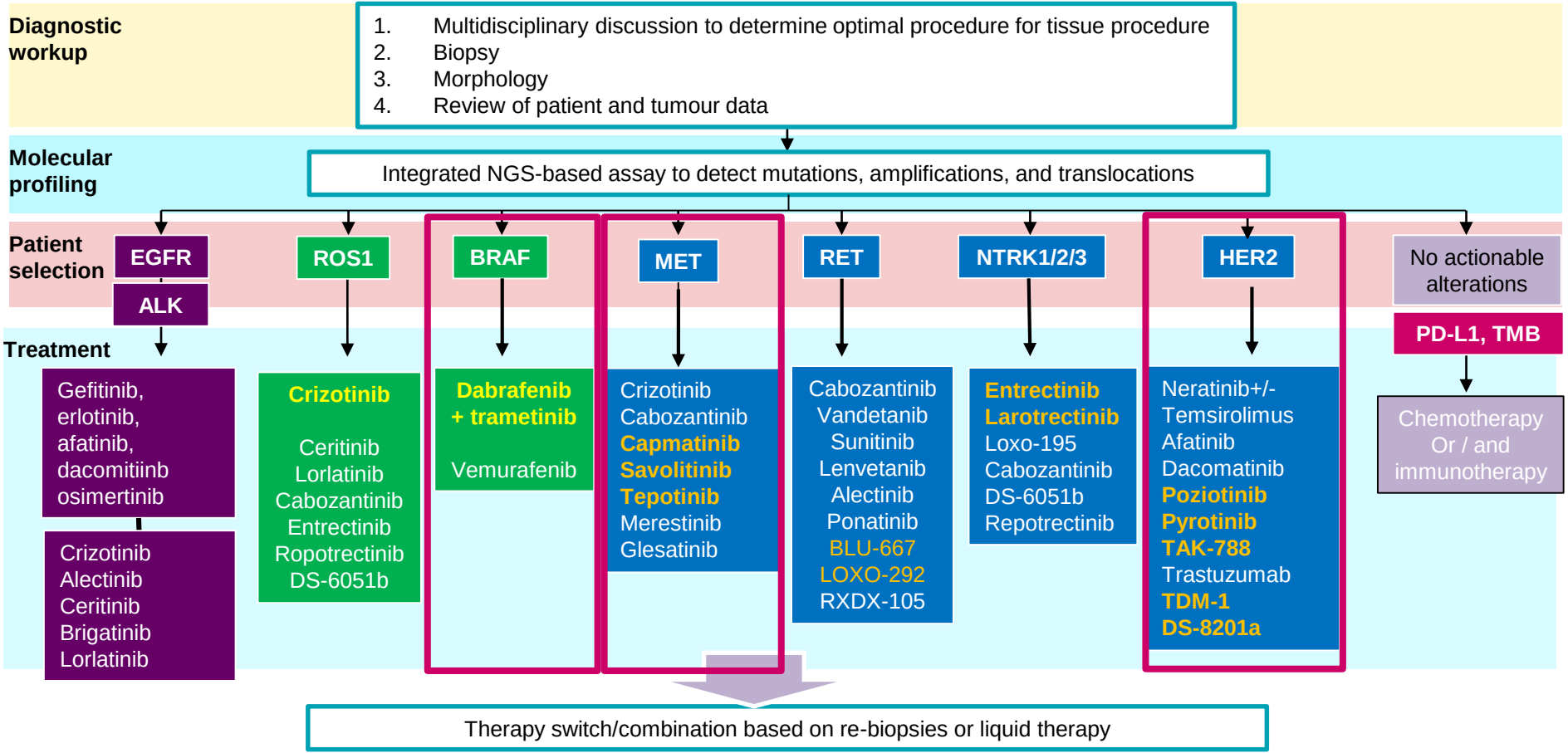
Selective inhibitor HER2 exon 20

- Poziotinib (ORR:42%)
- Pyrotinib (ORR:53%)
- TAK788 (ORR:39%)

Antibody and Antibody-drug conjugate

- Trastuzumab
- T-DM1 (ORR:44%)
- DS-8201a (ORR:88%)

In summary, many new options for BRAF, MET and HER2 NSCLC pts…



THANK YOU !

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Cécile LE PECHOUX
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GUSTAVE ROUSSY
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