HOW DO I TREAT PATIENTS WITH HER2 MUTATIONS, BRAF MUTATIONS, MET MUTATIONS

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DECLARATION OF INTERESTS

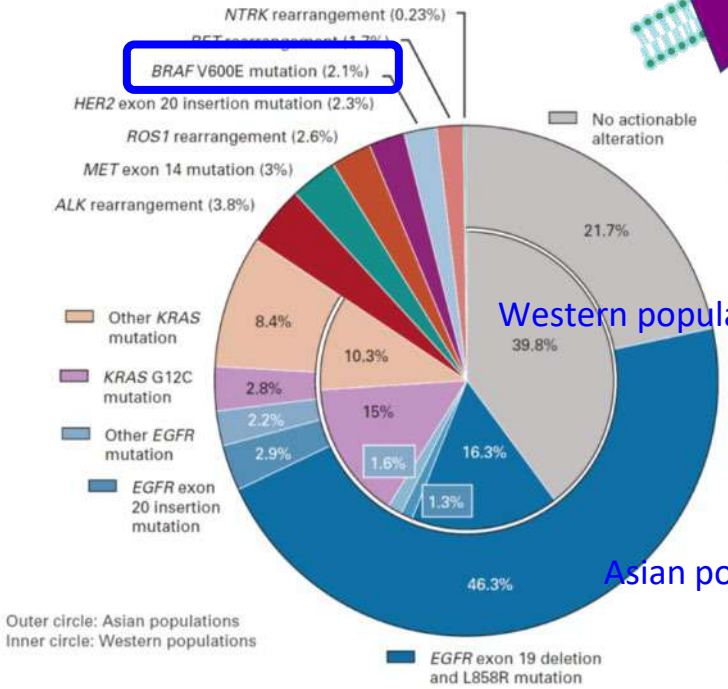
Consulting, advisory role or lectures: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche, Janssen, Abbvie

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

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, Janssen, Abbvie

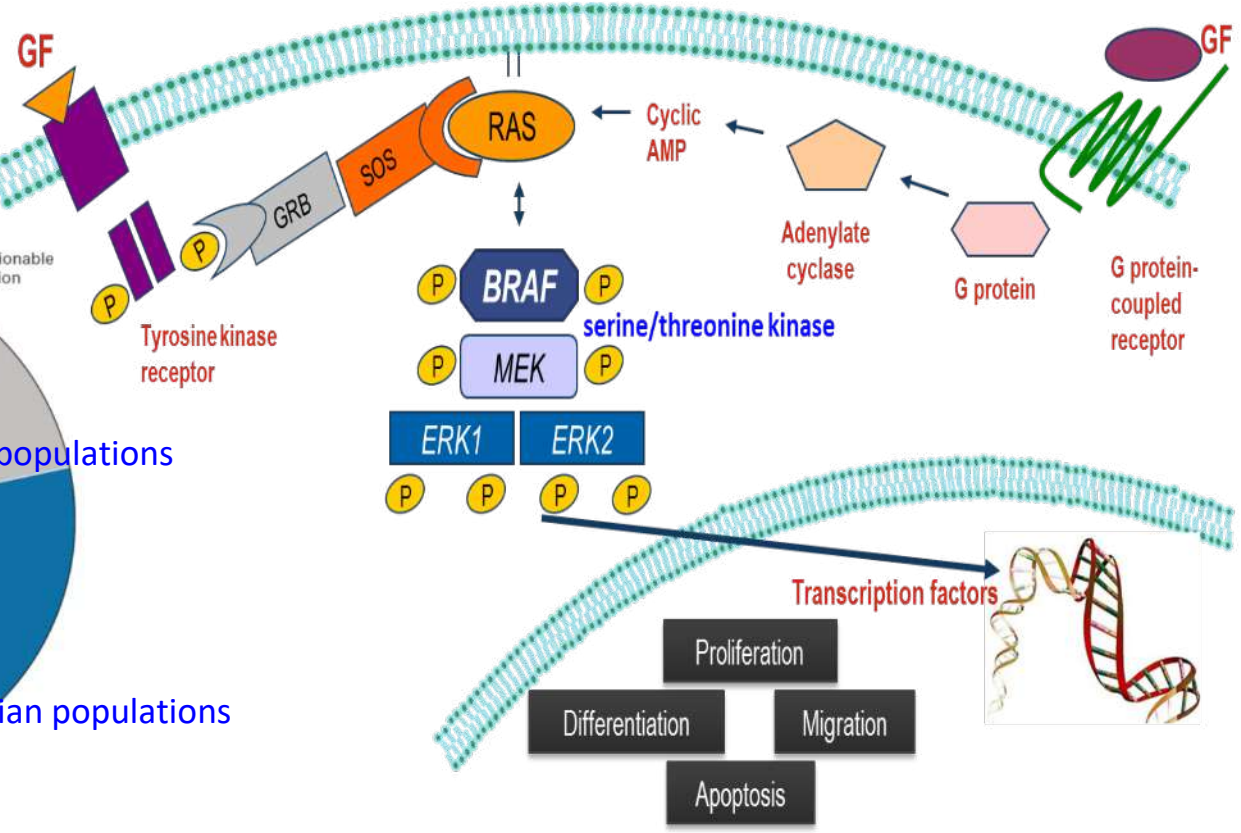
Travel, Accommodations, Expenses: AstraZeneca, Roche, Novartis, prIME Oncology, Pfizer

BRAF MUTATIONS IN NSCLC



Western populations

Asian populations



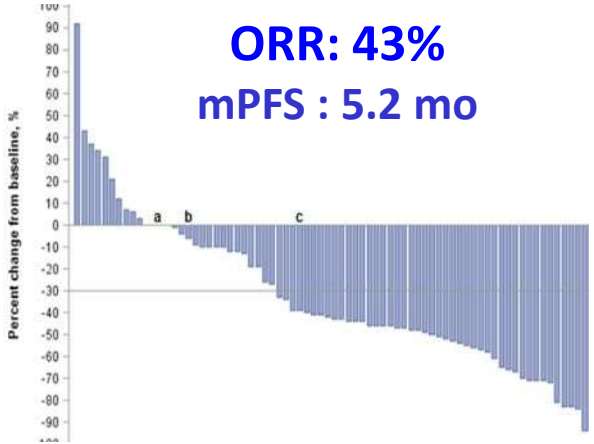
1. Barlesi F *et al. Lancet* 2016;387:1415–1426;

Vemurafenib and Dabrafenib in *BRAF* mutant NSCLC

AcSé trial

Vemurafenib

79 BRAF^{V600} NSCLC



ORR: 43%

mPFS : 5.2 mo

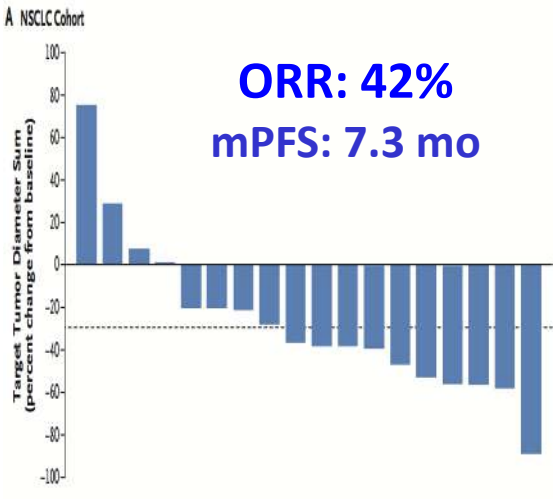
Mazières – WCLC 2018

J.Mazieres et al, annals of onco 2020

VE-Basket trial

Vemurafenib

20 BRAF^{V600} NSCLC



ORR: 42%

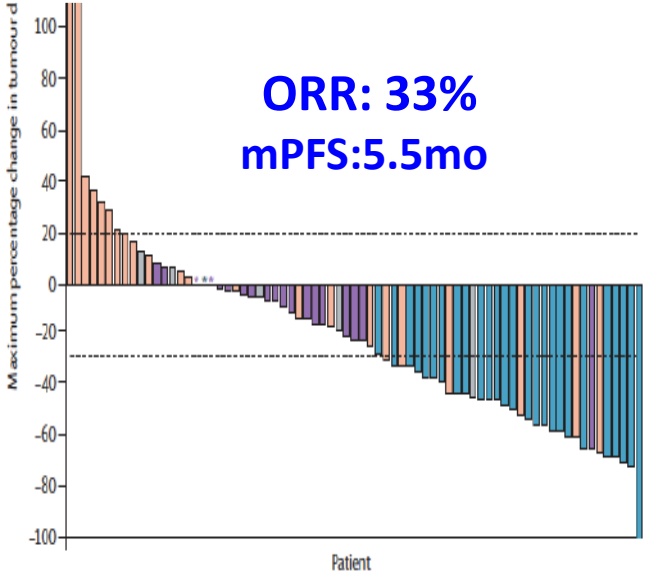
mPFS: 7.3 mo

Hyman – NEJM 2015

BRF113928 Study

Dabrafenib

84 BRAF^{V600E} NSCLC

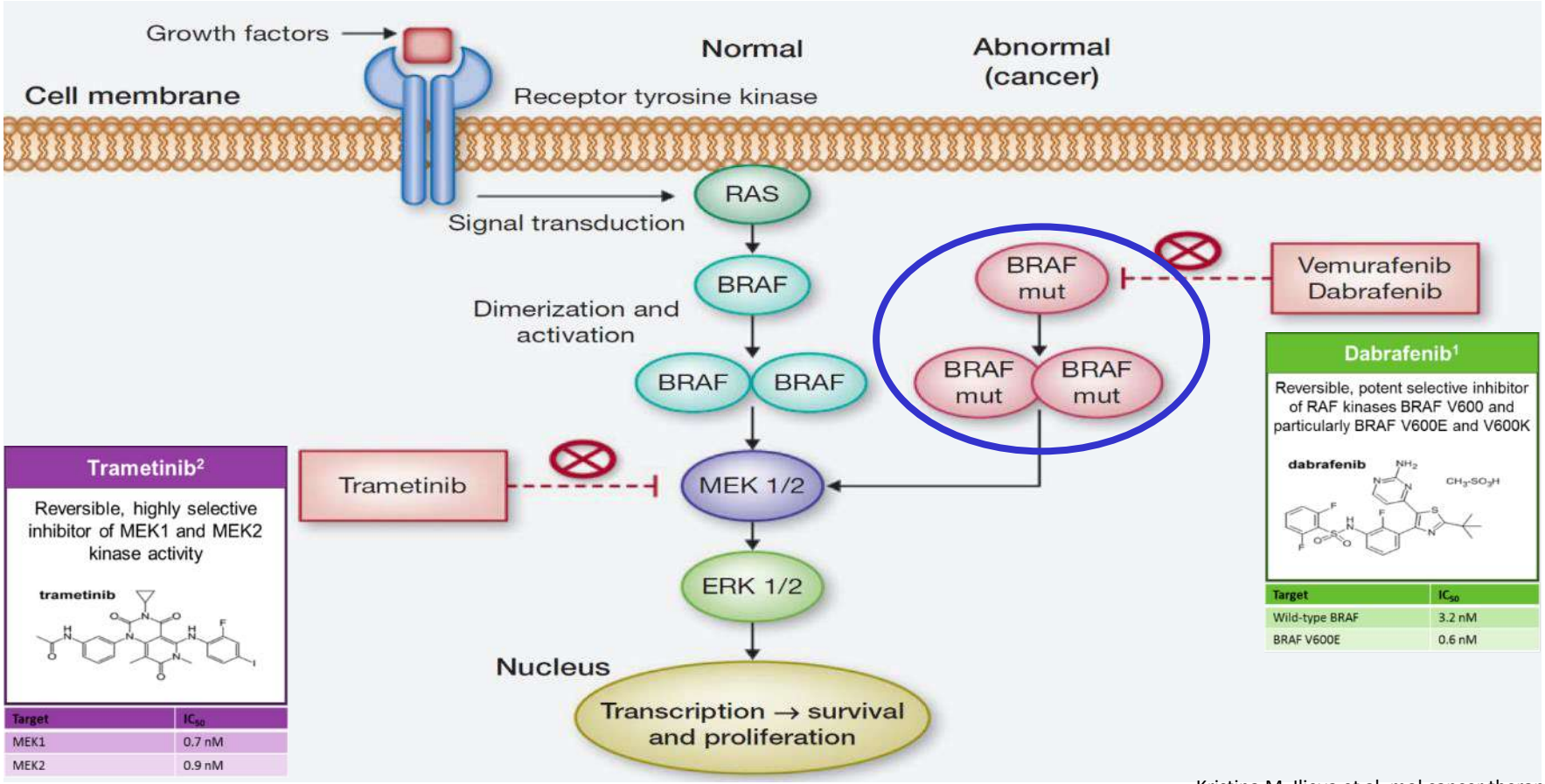


ORR: 33%

mPFS:5.5mo

D. Planchard et al – lancet Oncol 2016

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



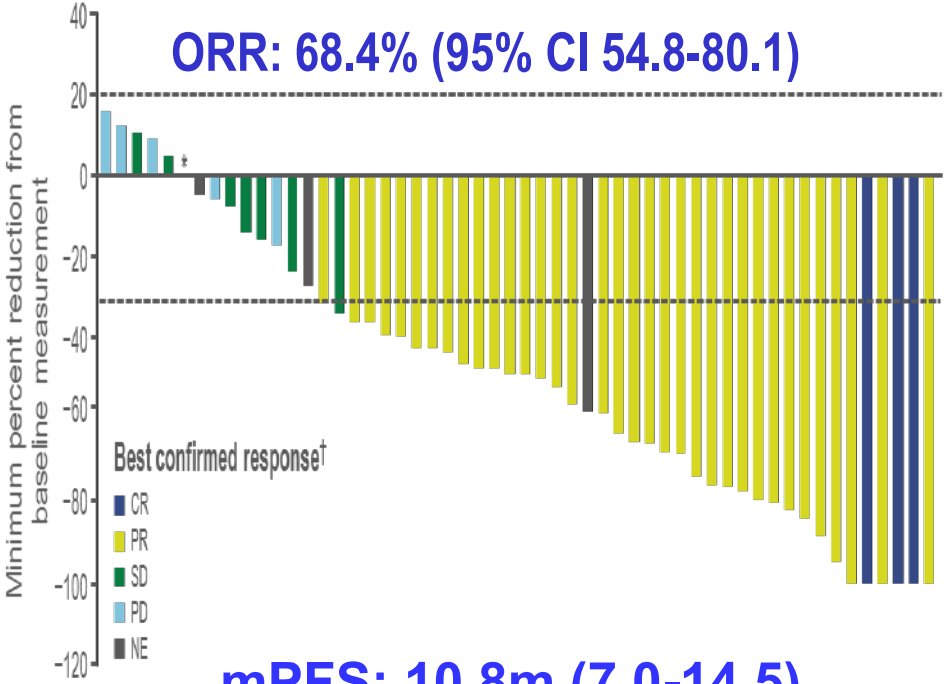
Kristina M. Ilieva et al, mol cancer therapeutics

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

Cohort B (N=57 NSCLC BRAF V600E)

2ND LINE

ORR: 68.4% (95% CI 54.8-80.1)



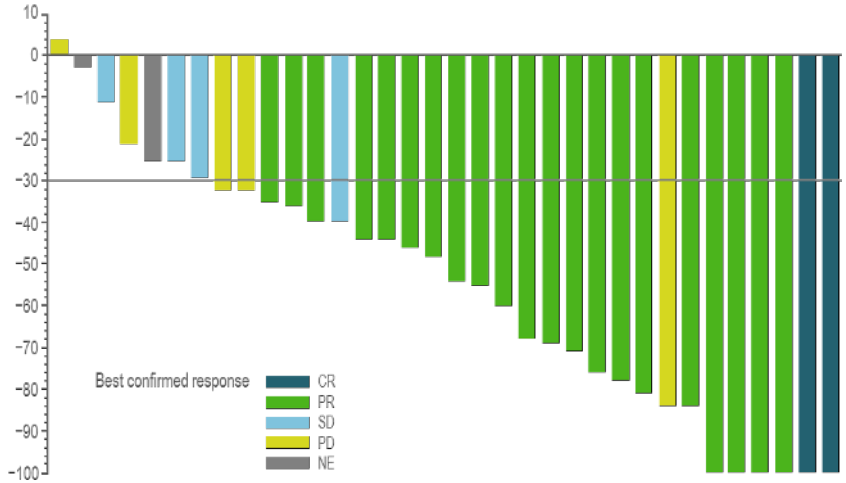
mPFS: 10.8m (7.0-14.5)

Planchard D *et al. Lancet Oncol* 2016;17:984–993;

Cohort C (N=36 NSCLC BRAFV600E)

1ST LINE

ORR: 63.9% (95% CI 46.2- 79.2)



mPFS: 10.2m (6.9-16.7)

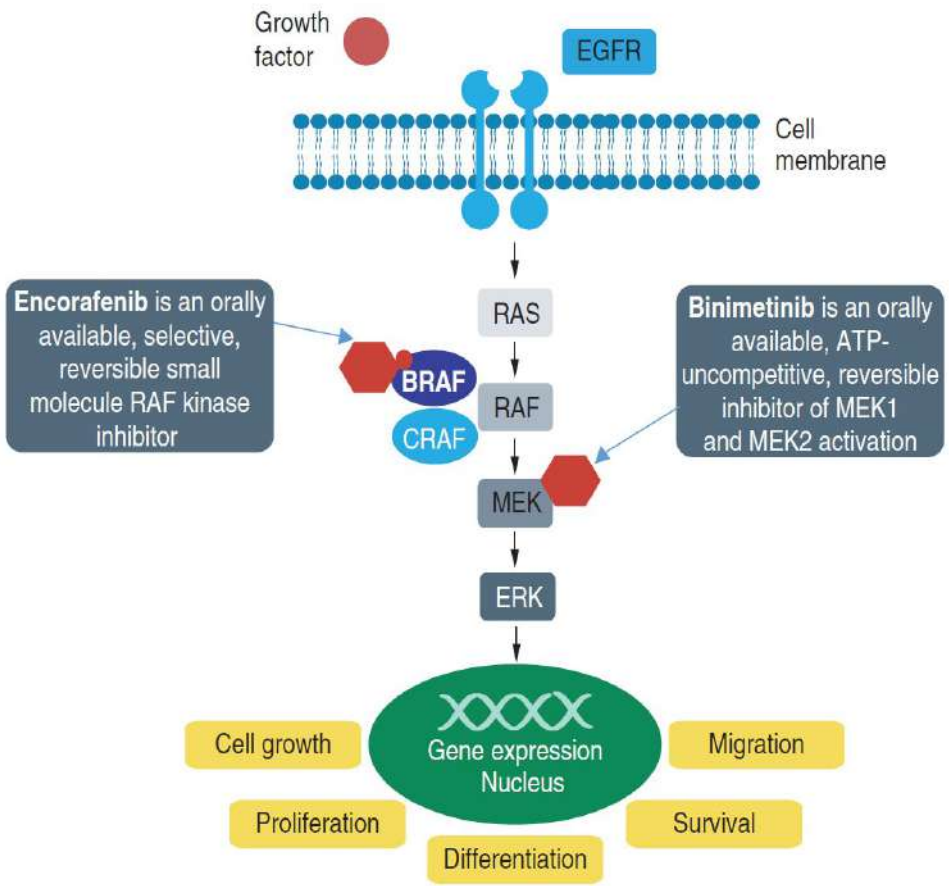
Planchard D *et al. Lancet Oncol* 2017;18:1307–1316

THE SAFETY PROFILE FOR DABRAFENIB, OR DABRAFENIB + TRAMETINIB

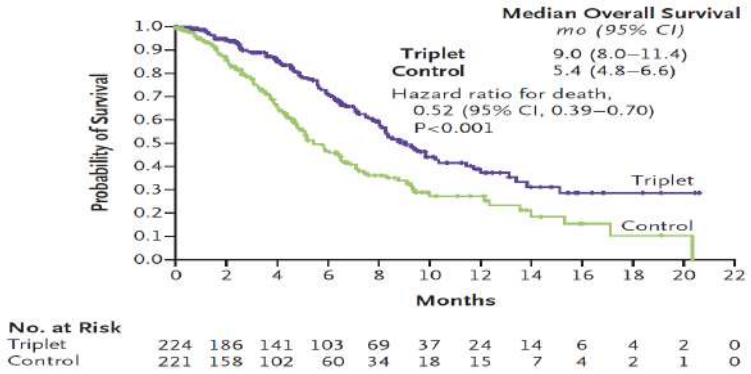
		Dabrafenib + trametinib 1st line[1]		Dabrafenib + trametinib 2nd line[2]		Dabrafenib monotherapy 2nd line[2]	
Category	**AEs, n (%)**	**All grades**	**Grade 3**	**All grades**	**Grade 3**	**All grades**	**Grade 3**
General	Pyrexia	23 (64)	4 (11)	26 (46)	1 (2)	30 (36)	2 (2)
	Asthenia	4 (11)	1 (3)	18 (32)	2 (4)	25 (30)	3 (4)
	Decreased appetite	12 (33)	0	17 (30)	0	24 (28)	1 (1)
	Chills	9 (25)	0	13 (23)	1 (2)	13 (15)	1 (1)
	Peripheral edema	13 (36)	0	13 (23)	0	–	–
	Arthralgia	5 (14)	1 (3)	11 (19)	0	14 (17)	1 (1)
Skin	Dry skin	12 (33)	0	15 (26)	1 (2)	19 (23)	0
	Rash	8 (22)	1 (3)	12 (21)	1 (2)	17 (20)	1 (1)
	Hyperkeratosis	–	–	6 (10)	1 (2)	25 (30)	1 (1)
	Basal-cell carcinoma	–	–	2 (2)	1 (2)	4 (5)	4 (5)
	Squamous-cell carcinoma	–	–	2 (4)	2 (4)	10 (12)	10 (12)
	Skin papilloma	–	–	–	–	22 (26)	0
Digestive	Nausea	20 (56)	0	23 (40)	0	23 (27)	1 (1)
	Vomiting	12 (33)	3 (8)	20 (35)	0	17 (20)	1 (1)
	Diarrhea	13 (36)	1(3)	19 (33)	1 (2)	14 (17)	1 (1)

1. Planchard D *et al. Lancet Oncol* 2017;18:1307–1316;
2. Planchard D *et al. Lancet Oncol* 2016;17:984–993

The combination of encorafenib plus binimetinib

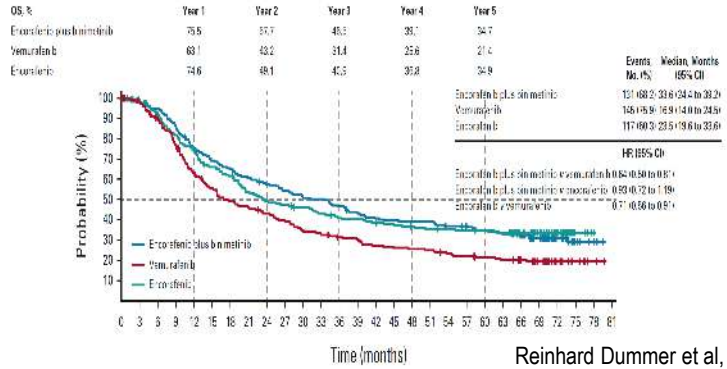


Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer



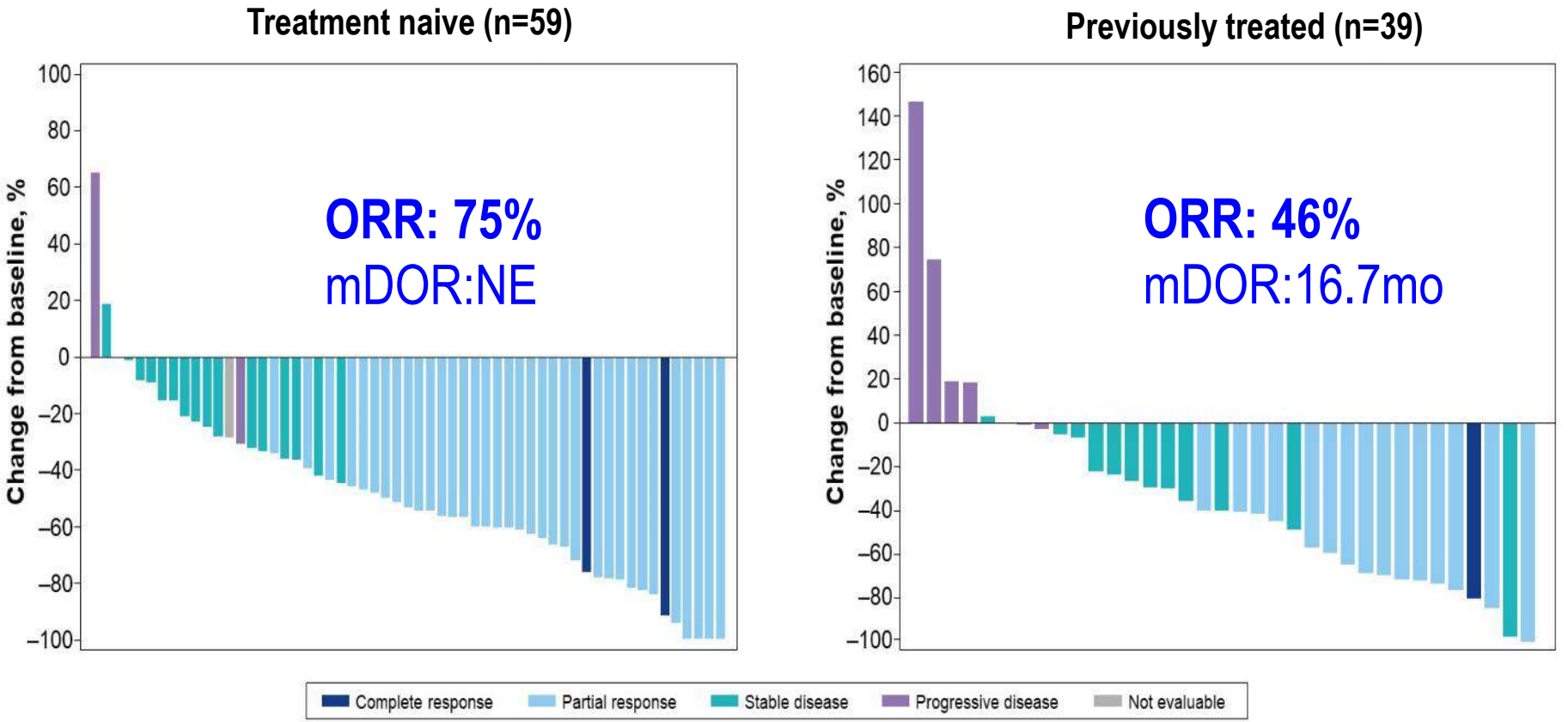
S. Kopetz, A et al, NEJM 2019

COLUMBUS: Encorafenib Plus Binimetinib Versus Vemurafenib or Encorafenib in Patients With BRAF V600–Mutant Melanoma



Reinhard Dummer et al, JCO 2022

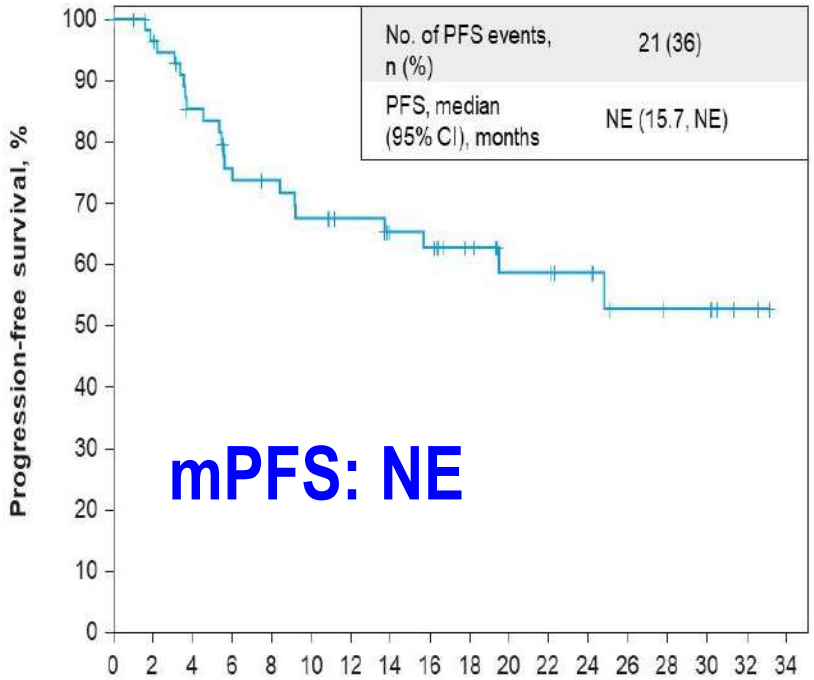
Encorafenib + Binimetinib in metastatic BRAF-V600E NSCLC
PHAROS Trial (Phase 2 Study)



GJ.Riely et al, ASCO2023, JCO 2023

PFS by IRR

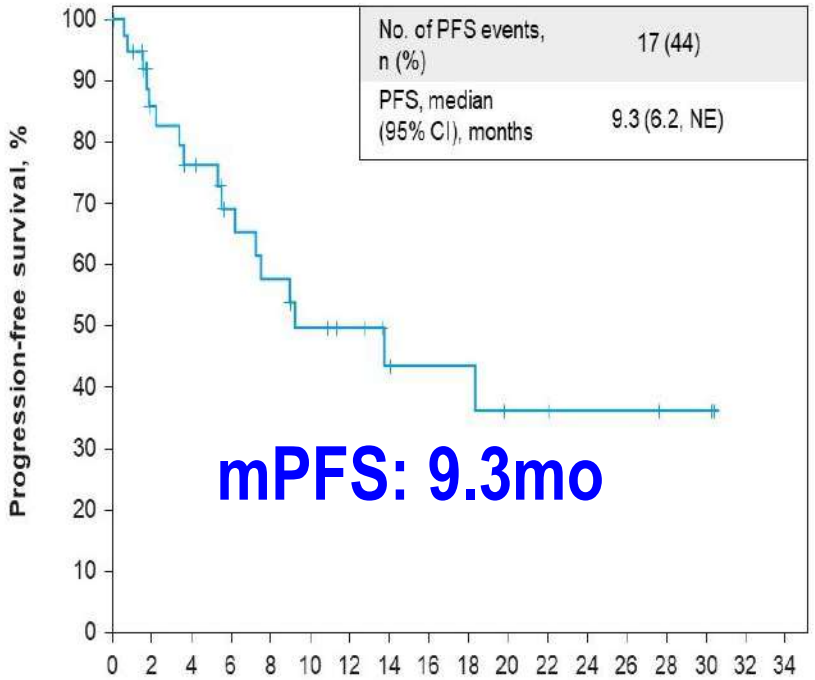
Treatment naive (n=59)



No. at risk

Treatment naïve	59	54	45	38	36	33	30	26	25	19	14	14	12	8	7	7	2	0

Previously treated (n=39)



No. at risk

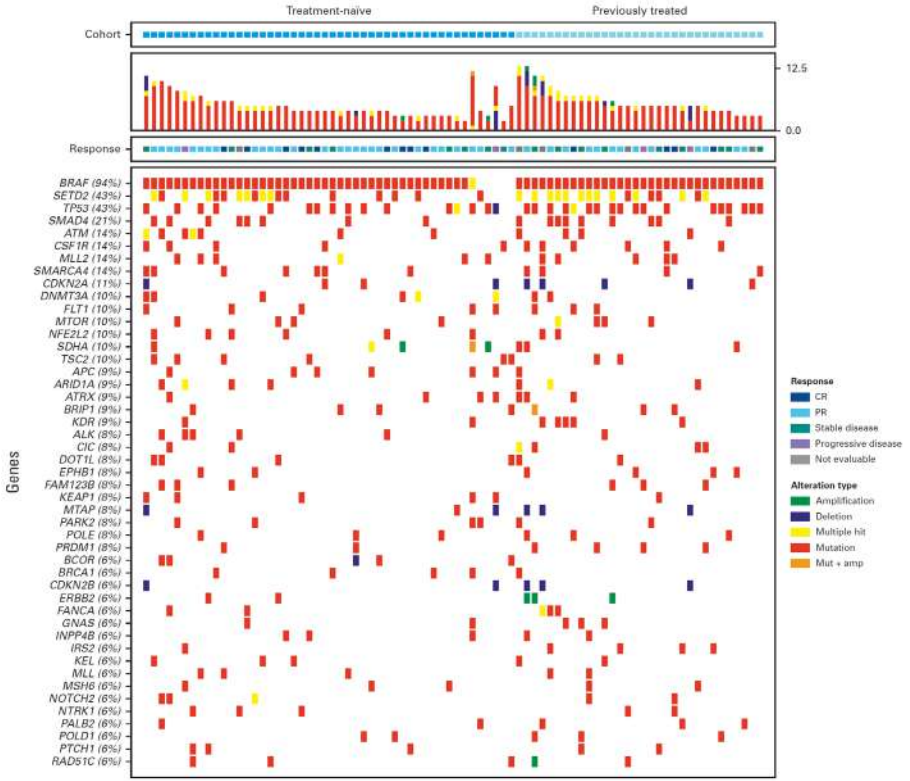
Previously treated	39	27	23	18	15	12	10	7	6	6	4	4	3	3	2	2	0	0

GJ.Riely et al, ASCO2023, JCO 2023

Incidence of TRAEs of Any Grade ≥10%

AE Preferred Term	Overall (N = 98) Any Grade	Grade 3	Grade 4
Any TRAEs, No. (%)	92 (94)	37 (38)	3 (3)[a]
Nausea	49 (50)	3 (3)	0
Diarrhea	42 (43)	4 (4)	0
Fatigue	31 (32)	2 (2)	0
Vomiting	28 (29)	1 (1)	0
Anemia	18 (18)	3 (3)	0
Vision blurred	17 (17)	1 (1)	0
Constipation	13 (13)	0	0
ALT increased	12 (12)	5 (5)	0
AST increased	12 (12)	7 (7)	0
Pruritus	12 (12)	0	0
Blood creatine phosphokinase increased	11 (11)	0	0
Peripheral edema	11 (11)	0	0
Abdominal pain	10 (10)	0	0
Alopecia	10 (10)	0	0
Asthenia	10 (10)	3 (3)	0
Dry skin	10 (10)	0	0

Tumor molecular alterations in baseline biopsy



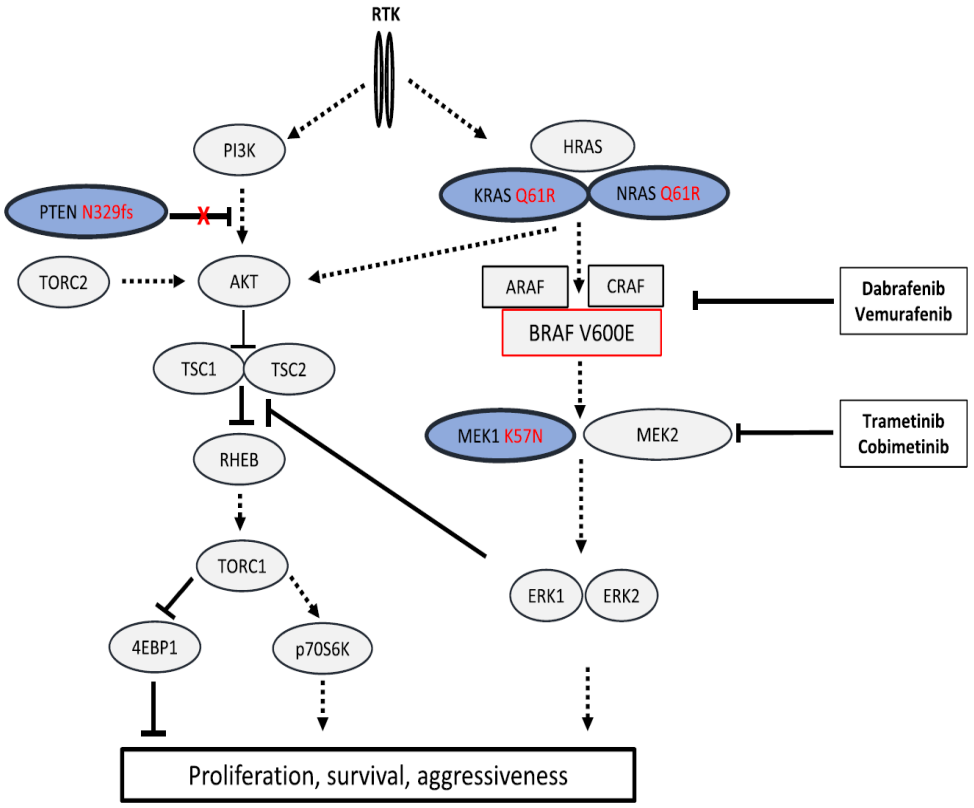
Most frequent genomic alterations identified at baseline:
SETD2 and TP53 (43% each), SMAD4 (21%), ATM, MLL2, CSF1R, SMARCA4 (14% each), and CDKN2A (11%).
None of these alterations associated with outcome

GJ.Riely et al, ASCO2023, JCO 2023

PI3K-AKT-mTOR and RAS-RAF-MEK pathways

WES, RNA sequencing (RNAseq) (Illumina Integragen) and comparative genomic hybridisation (CGH) array

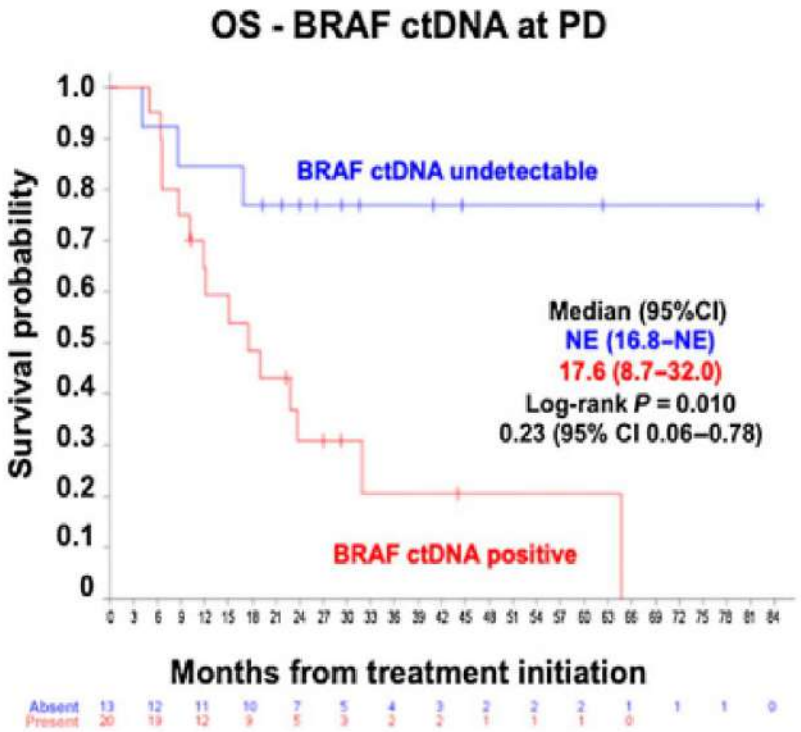
Patient	Tumour cell proportion	Targeted NGS	WES	RNAseq	CGH array	TMB (mut/Mb)
MR113	50%	*BRAF* V600E ***MEK1* K57N**	*BRAF* V600E ***MEK1* K57N** *FANCD2* Q706* *LRP1B* P203Q *GRIN2A* M960I *RARA* T285I	*ZNF354C-RGS7*	No hints	3.04
MR159	30%	*BRAF* V600E ***PTEN* N329fs**	*BRAF* V600E ***PTEN* N329fs** *SETD2* D1537Ifs *SETD2* T1171Kfs *MEN1* G230V *PTCD3* E114Rfs *ATXN1* P485A *AKAP6* D668G	No fusion transcripts	No hints	1.42
MR279	50%	*BRAF* V600E *AKT1* E17K ***NRAS* Q61R**	*BRAF* V600E *AKT1* E17K *(see baseline NGS)* *ERBB4* S303Y *SETD2* G1081Vfs	No fusion transcripts	No hints	1.71
MR372	50%	*BRAF* V600E ***KRAS* Q61R** *TP53* R280I	*BRAF* V600E ***KRAS* Q61R** *TP53* R280I *KMT2E* L1610Ffs *MPL* Q247Sfs *ZFHX3* S2515* *MED12* Q2160* *ARID1A* F1809fs *KMT2A* S754F *KMT2A* S2319C *MYOD1* R281C *SETD2* C1520F *NCOR1* L866V	No fusion transcripts	No hints	3.75

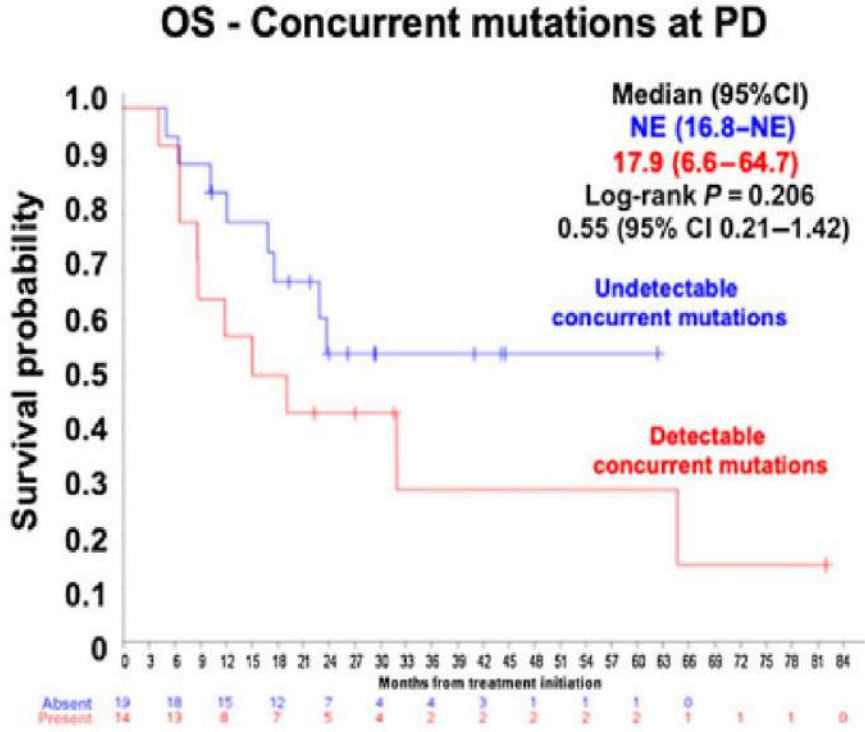


F. Facchinetti et al, EJC 2020

OS according to BRAF-mutant ctDNA status or concurrent genomic alterations, at PD

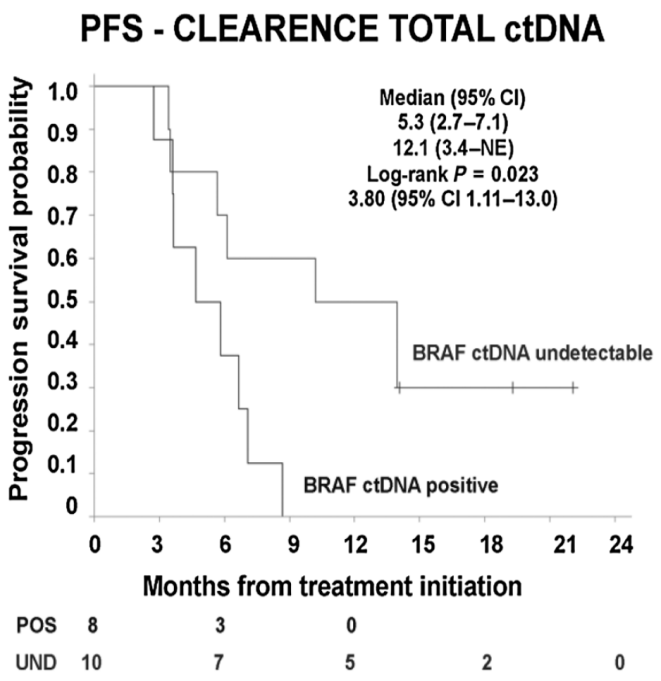
Prospective cohort of 78 BRAF-mutant NSCLC patients (N=208 samples)

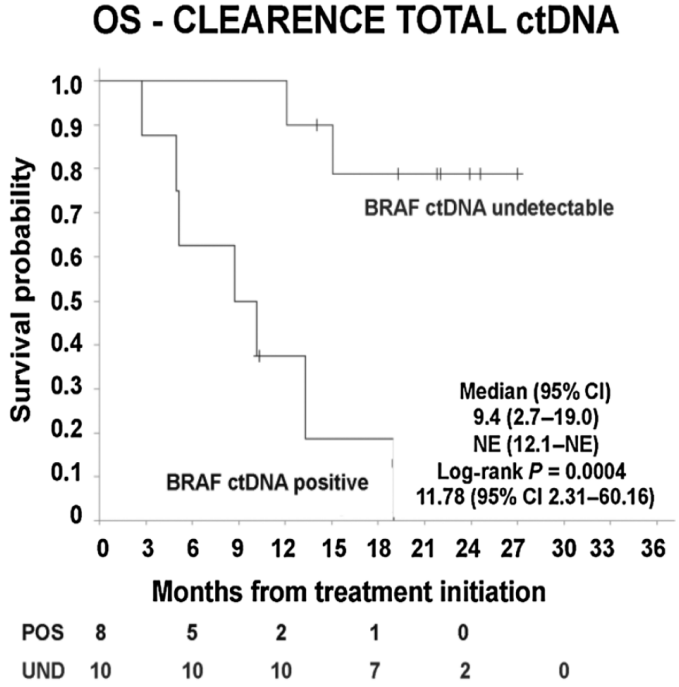


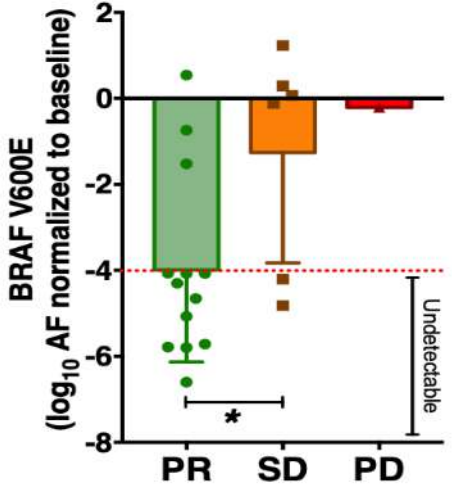


S. Ortiz-Cuaran et al. IASLC 2019, CCR 2020

PFS and OS by ctDNA status at the first radiographic evaluation
(<100 days after start of targeted therapy)





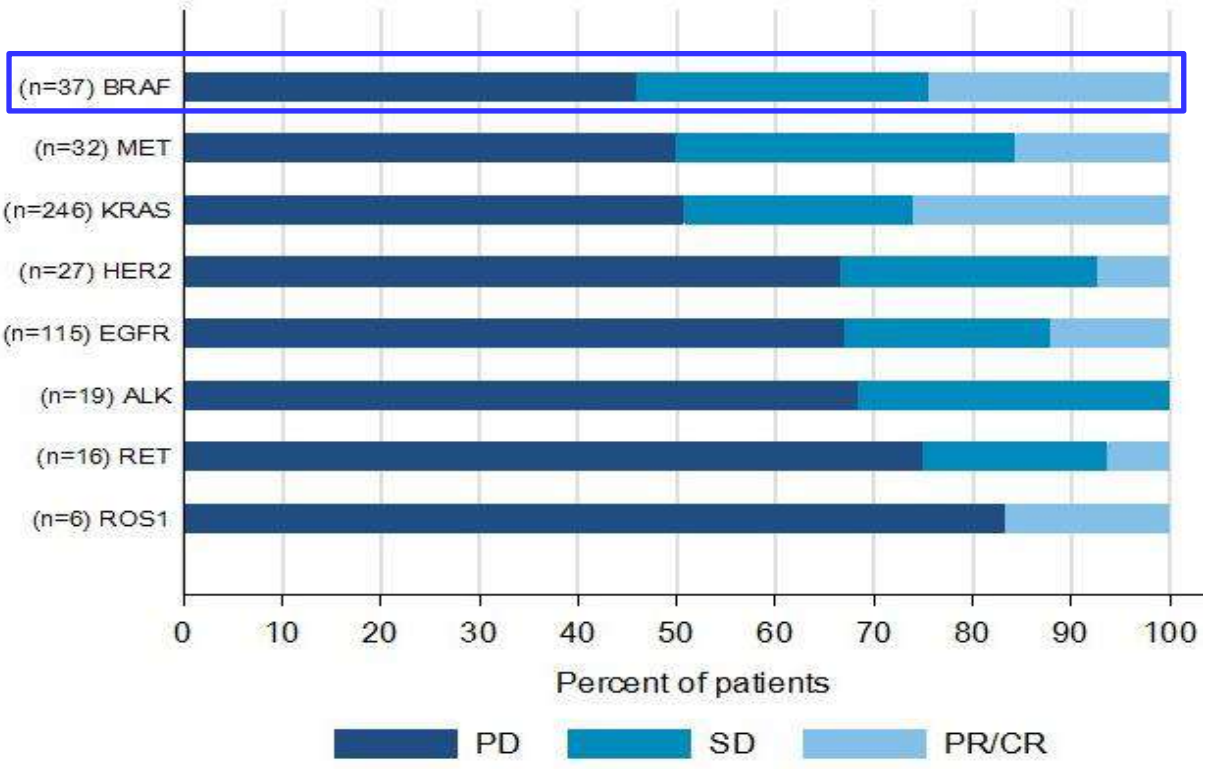


Complete clearance of BRAF V600E at the first CT-scan evaluation* in 12/20 (60%)

S. Ortiz-Cuaran et al. IASLC 2019, CCR 2020

IMMUNOTARGET registry (BRAF, n=37 pts)

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

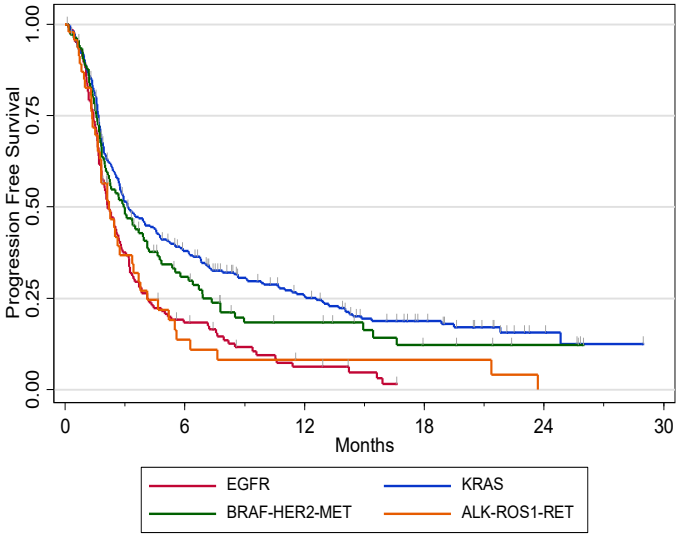


J. Mazieres et al, Annals of onco 2019

IMMUNOTARGET COHORT: PFS

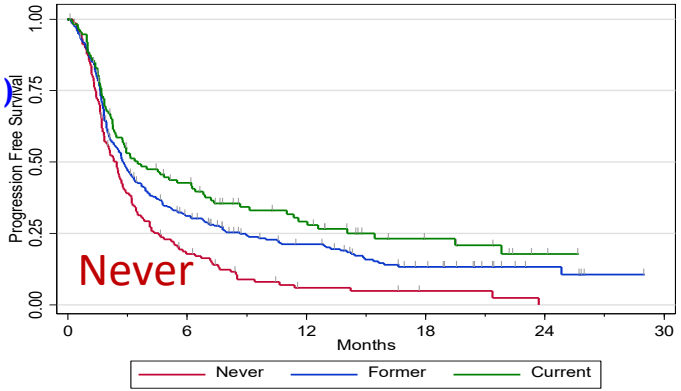
Driver	PFS (months)	
KRAS	3.2	3.2
EGFR	2.1	2.1
BRAF	3.1	2.9
MET	3.4	
HER2	2.5	
ALK	2.5	2.2
RET	**2.1**	
ROS1	-	
TOTAL	**2.8**	

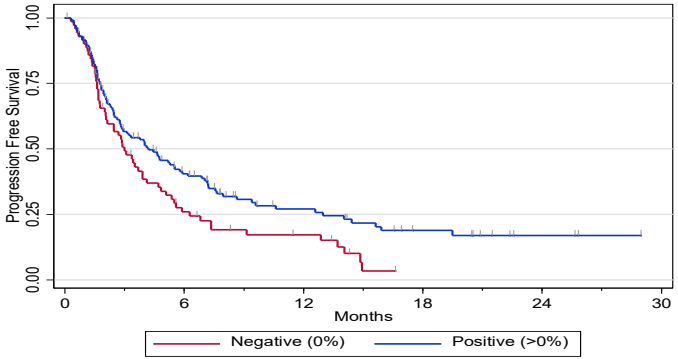
PFS according to driver alteration (p < 0.001)



Median follow-up 16.1 months

PFS by smoking (p < 0.001)





PFS by PDL1 (p = 0.02)

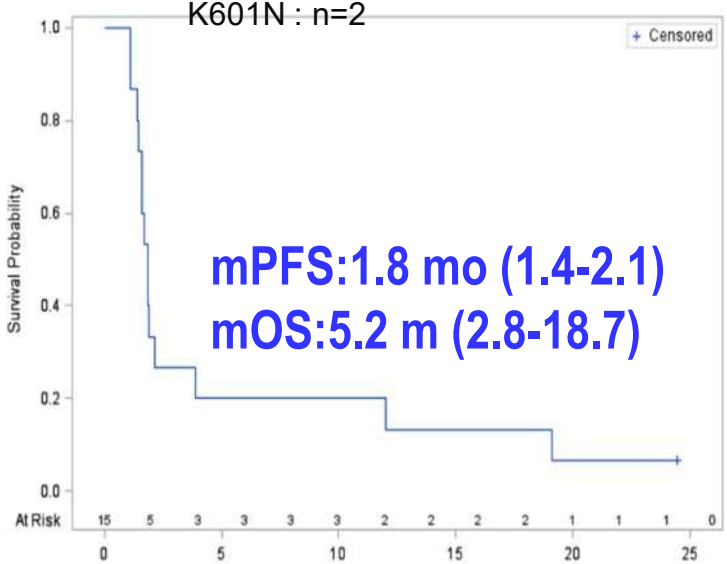
J. Mazieres et al, Annals of onco 2019

BRAF non V600 cohort (AcSé Vemu)

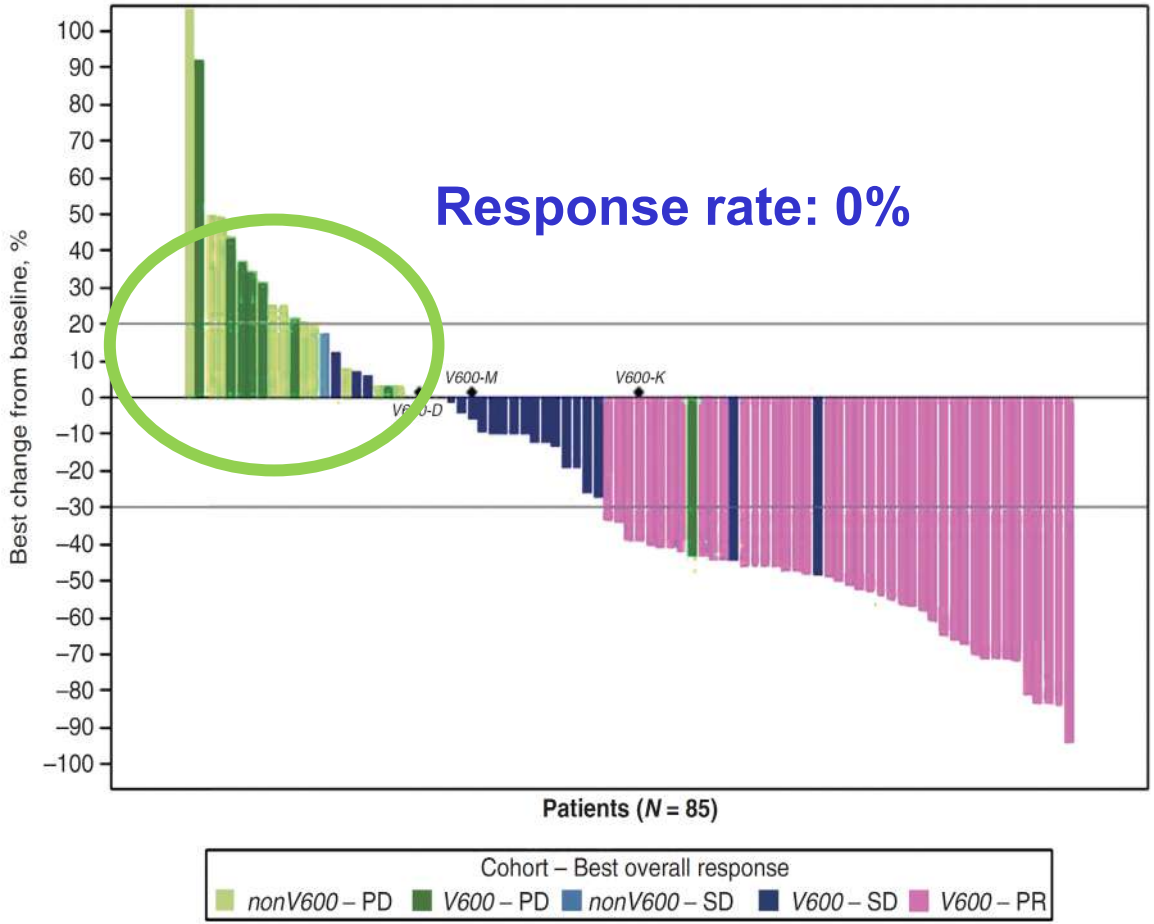
Non V600 mutations

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



mPFS:1.8 mo (1.4-2.1)
mOS:5.2 m (2.8-18.7)

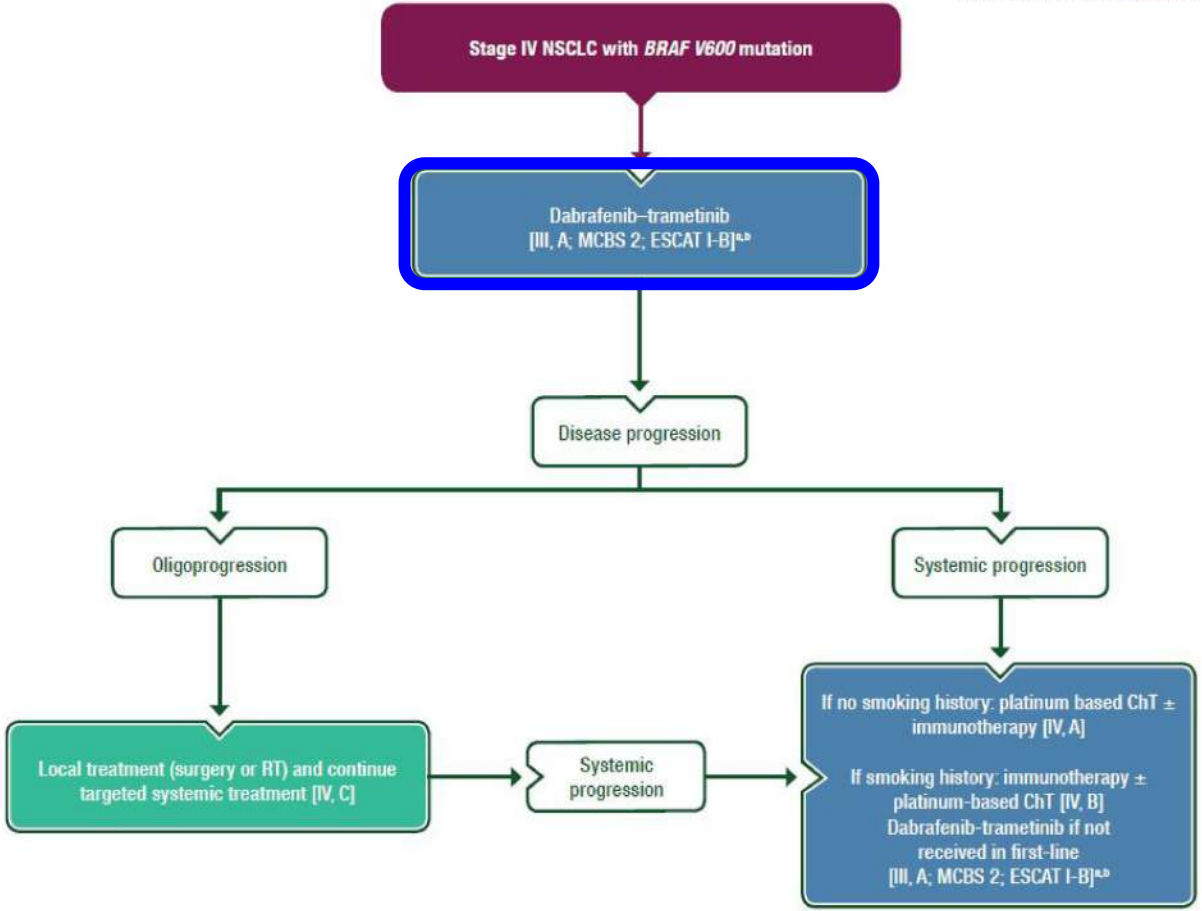


J.Mazieres et al, annals of onco 2020

BRAFV600mut NSCLC

ESMO
ANNALS OF ONCOLOGY
SPECIAL ARTICLE
Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up

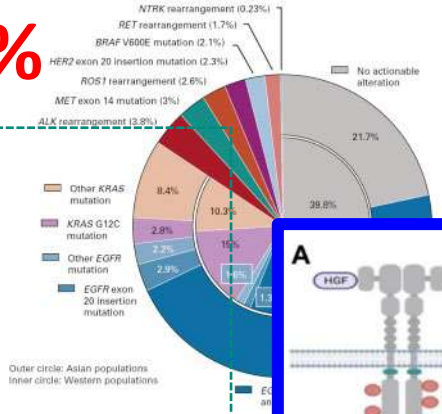
GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS



D.Planchard et al, annals onco 2018; L.Hendriks et al, 2023

MET Ex14 mutant NSCLC

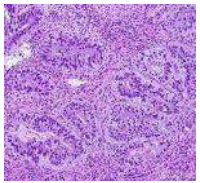
≈2%



Clinical characteristics

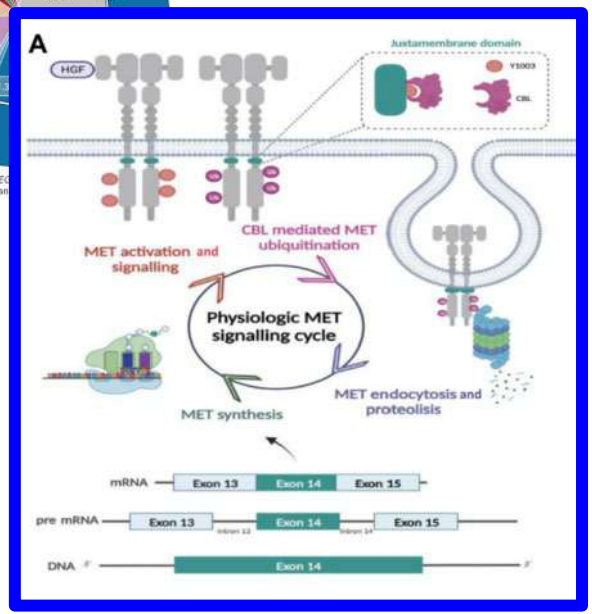
Median age 75 years

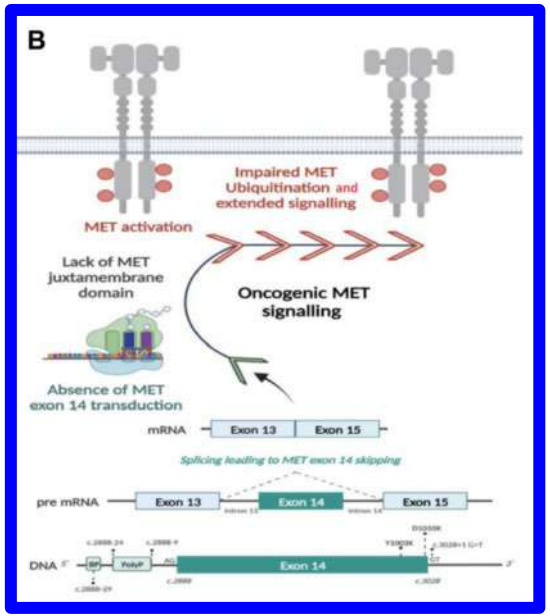
Never smokers, 50%



Non-Squamous: ∽ 80%
(Sarcomatoid: 20% METex[14])
Squamous: ∽ 10%

METexon 14 skipping mutation





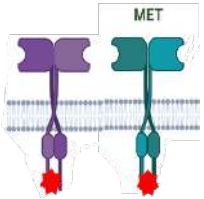
Awad – JCO PO 2021 * Sabari – Ann Oncol 2018 *Kron – JTO 2021

J.Remon et al, JTO 2022

MET Agents – A Broad Therapeutic Landscape

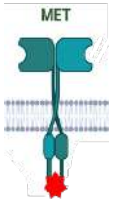
MET KINASE INHIBITORS

MULTI-TARGETED



CRIZOTINIB
CABOZANTINIB
GLESATINIB (MGCD265)
MERESTINIB (LY2801653)
SAR125844
FORETINIB (GSK1363089)
ELZOVANTINIB (TPX-022)

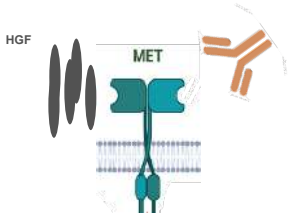
SELECTIVE



TEPOTINIB
CAPMATINIB
SAVOLITINIB
BOZITINIB (APL-101)
GLUMETINIB (SCC244)

MONOCLONAL ANTIBODIES (MET/HGF)

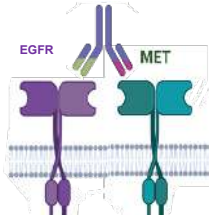
MONOSPECIFIC



HGF
FICLATUZUMAB (AV299)
RILOTUMUMAB (AMG-102)

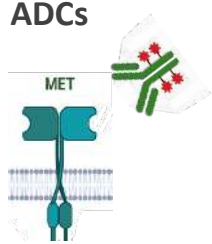
MET
HLX55

POLYSPECIFIC



EGFR-MET
AMIVANTAMAB
EMB-01
METx MET
Sym015
UBAMATAMAB (REGN5093)
EMIBETUZUMAB (LY2875358)
EGFR-MET-MET
GB263T

ADCs

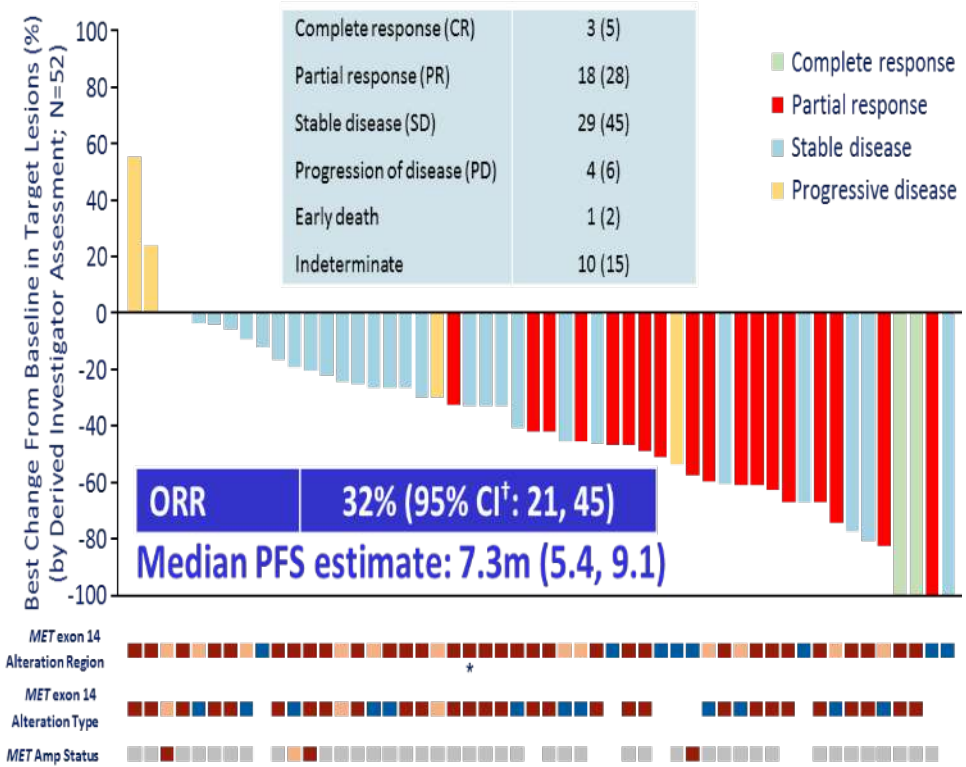


TELISO-V (ABBV-399)
SHR-A1403
TR1801-ADC

Slide courtesy of Dr. Reguart / J.Remon

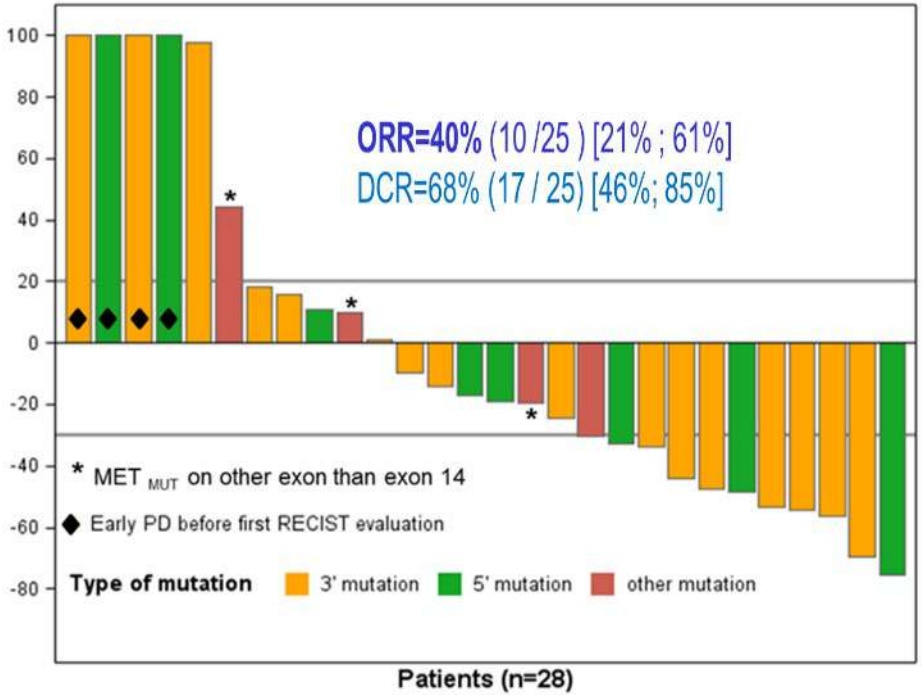
Antitumor Activity of Crizotinib *MET* Exon 14-Altered NSCLC

Profile 1001



Alexander Drilon et al , Nat Med 2020

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



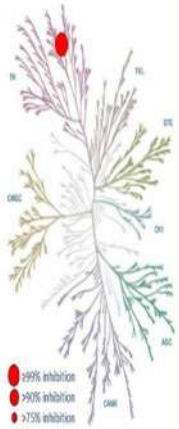
D. Moro-Sibilot et al, Annal ono 2019

VISION Study (Tepotinib)

Selective MET Kinase Inhibitor

- 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 $K_{p,uu}$ (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]



Key inclusion criteria

- Advanced NSCLC (*EGFR/ALK* wild-type, all histologies)
- Central confirmation of *MET*ex14 skipping by liquid and/or tissue biopsy
- First, second, or third line of therapy

Cohort A* *MET*ex14 skipping (primary)

Cohort C† *MET*ex14 skipping (confirmatory)

Tepotinib 500 mg‡ once daily

Selected endpoints

Primary:

Objective response by IRC (RECIST v1.1)

Secondary:

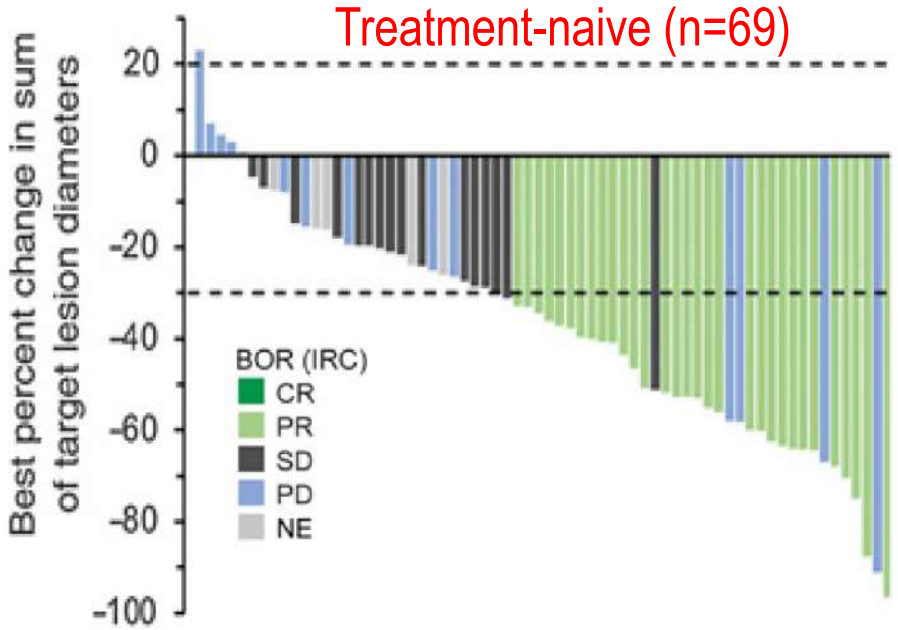
DOR, PFS, OS, Safety

Exploratory RANO-BM analysis§:

BOR per RANO-BM (patients with ≥1 evaluable post-baseline tumor assessment): disease control was defined as CR/PR/SD, or non-CR/non-PD

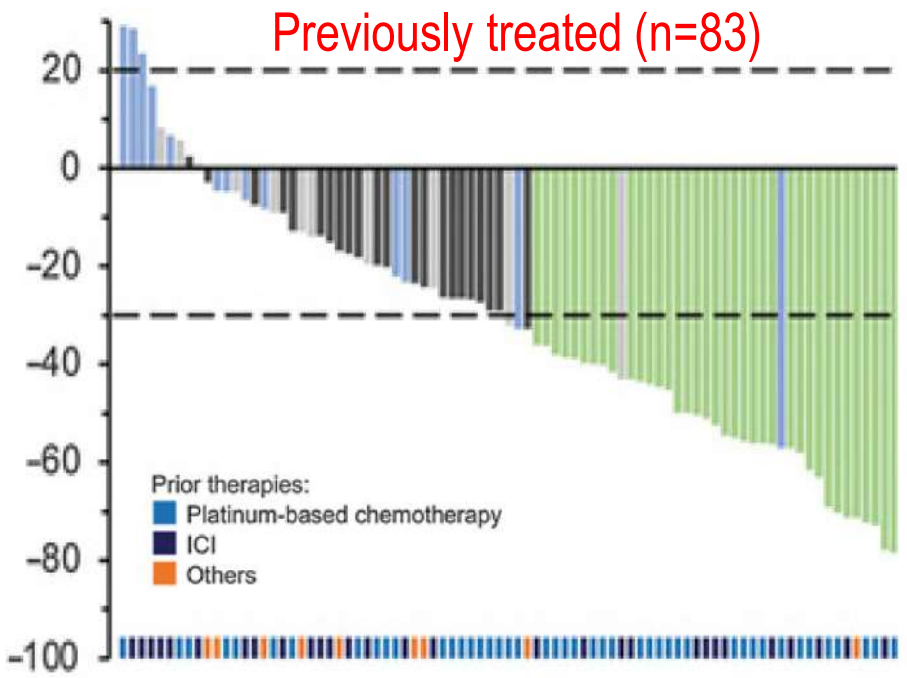
METex14 mutation: Tepotinib

VISION Study (cohort A)



ORR: 44.9%

mPFS: 8.5mo



ORR: 44.6%

mPFS: 10.9mo

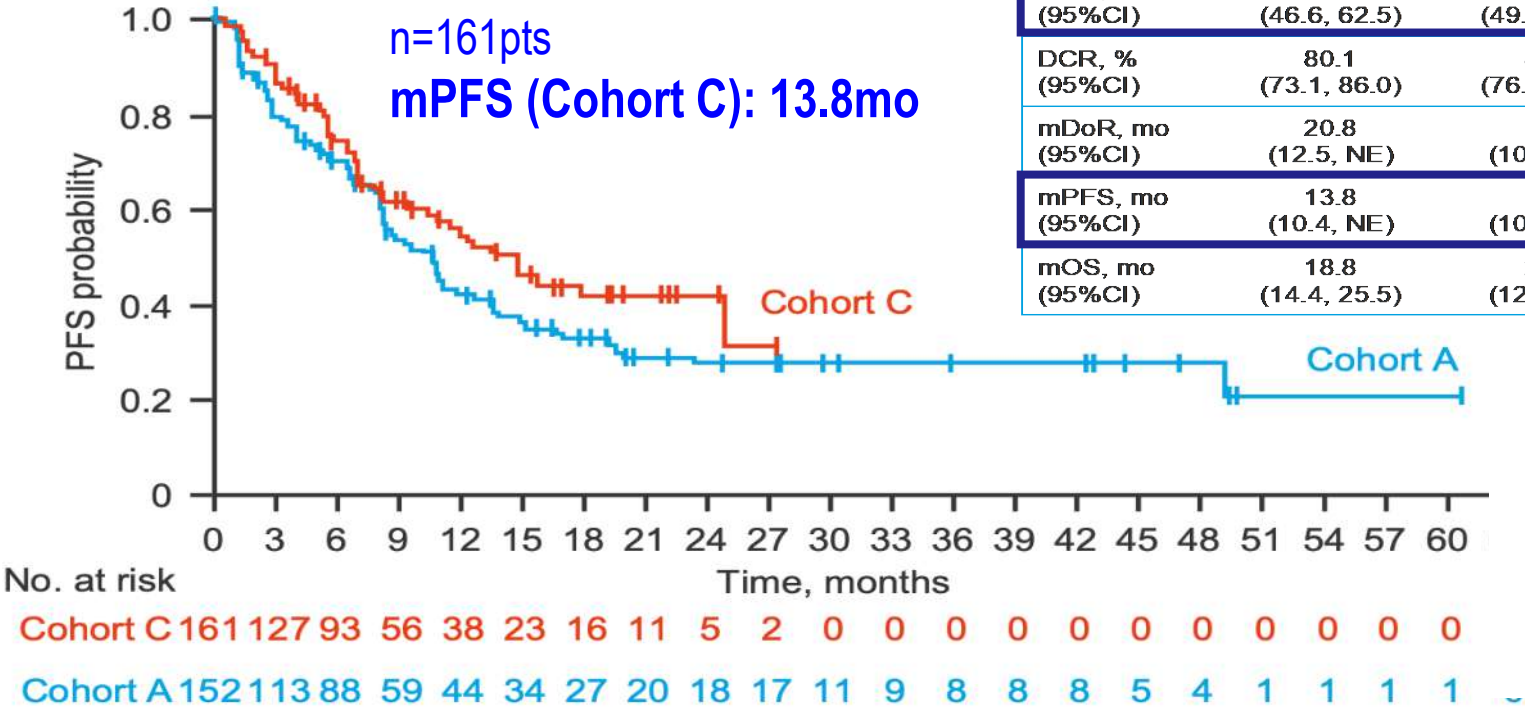
Xiuning Le et al, CCR 2021

METex14 mutation: Tepotinib

VISION Study (confirmatory cohort C)

ORR: 54.7% **62.3%** **51%**

Response in Cohort C	All (n=161)	1L (n=69)	2L (n=51)
ORR, % (95%CI)	54.7 (46.6, 62.5)	62.3 (49.8, 73.7)	51.0 (36.6, 65.2)
DCR, % (95%CI)	80.1 (73.1, 86.0)	87.0 (76.7, 93.9)	82.4 (69.1, 91.6)
mDoR, mo (95%CI)	20.8 (12.5, NE)	NE (10.4, NE)	12.6 (4.3, NE)
mPFS, mo (95%CI)	13.8 (10.4, NE)	15.9 (10.8, NE)	13.8 (6.9, NE)
mOS, mo (95%CI)	18.8 (14.4, 25.5)	22.7 (12.7, NE)	19.6 (14.6, NE)

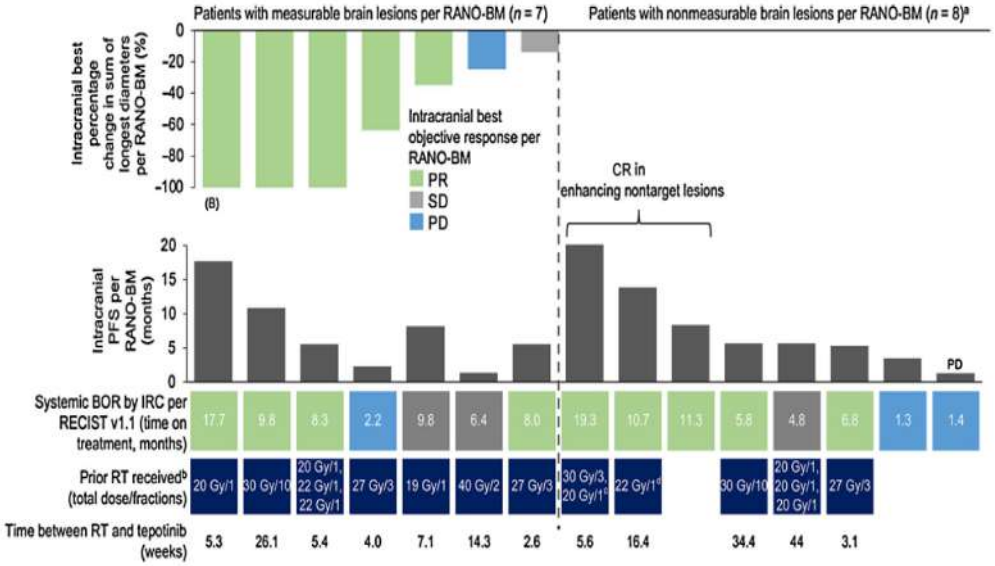


Thomas M, et al. WCLC 2022

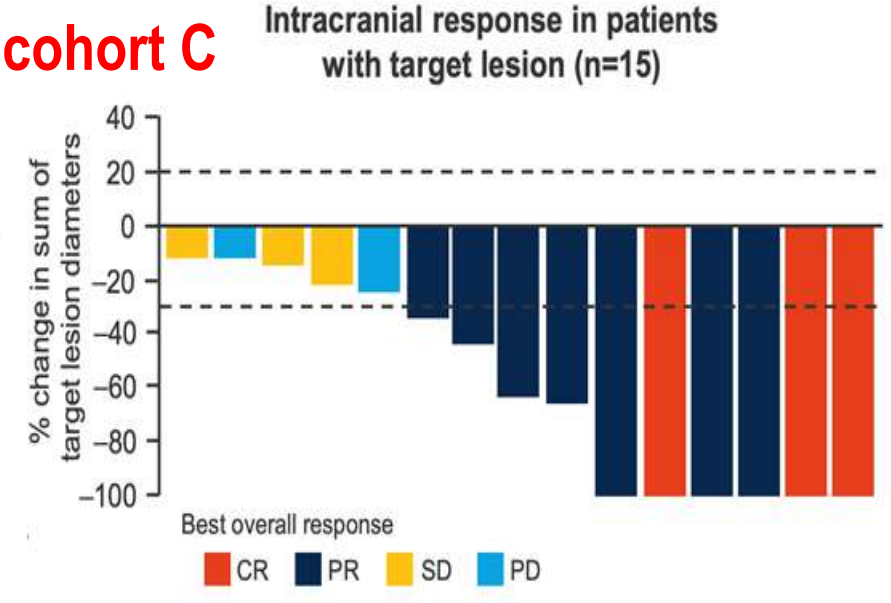
Intracranial activity of Tepotinib (METex14, VISION trial)

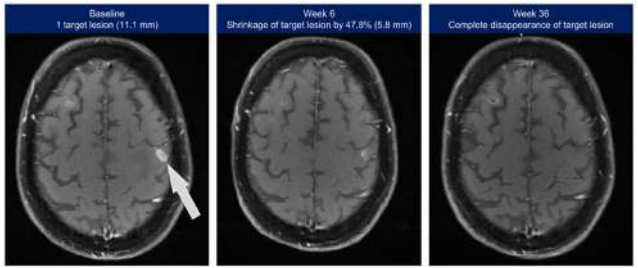
cohort A

5/7 patients



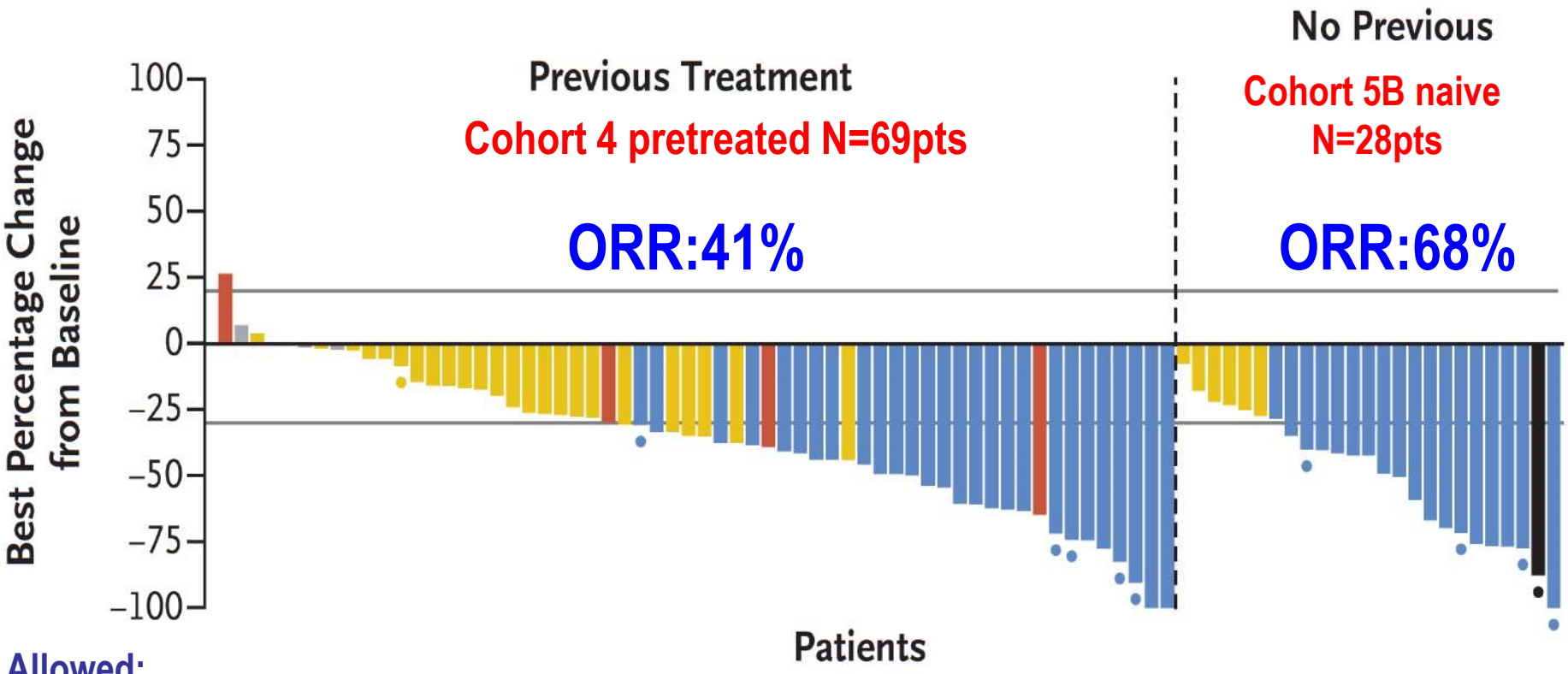
cohort C





Xiuning Le et al, CCR 2021

GEOMETRY Study (Capmatinib)



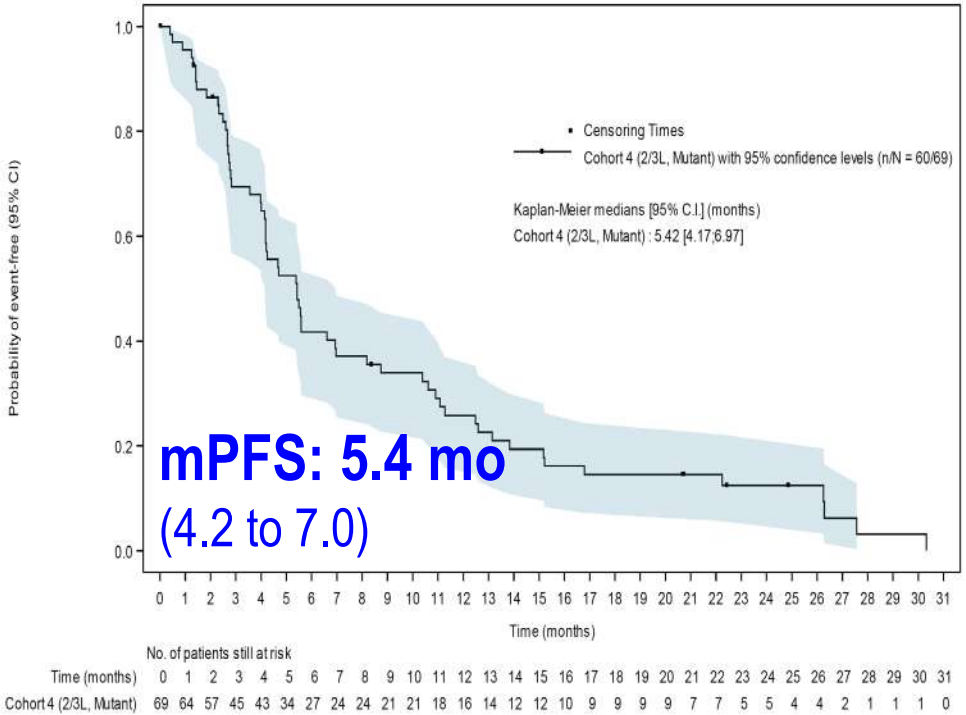
Allowed:
-stable CNS mets
-asymtomatic CNS mets

Primary endpoint: ORR by IRC

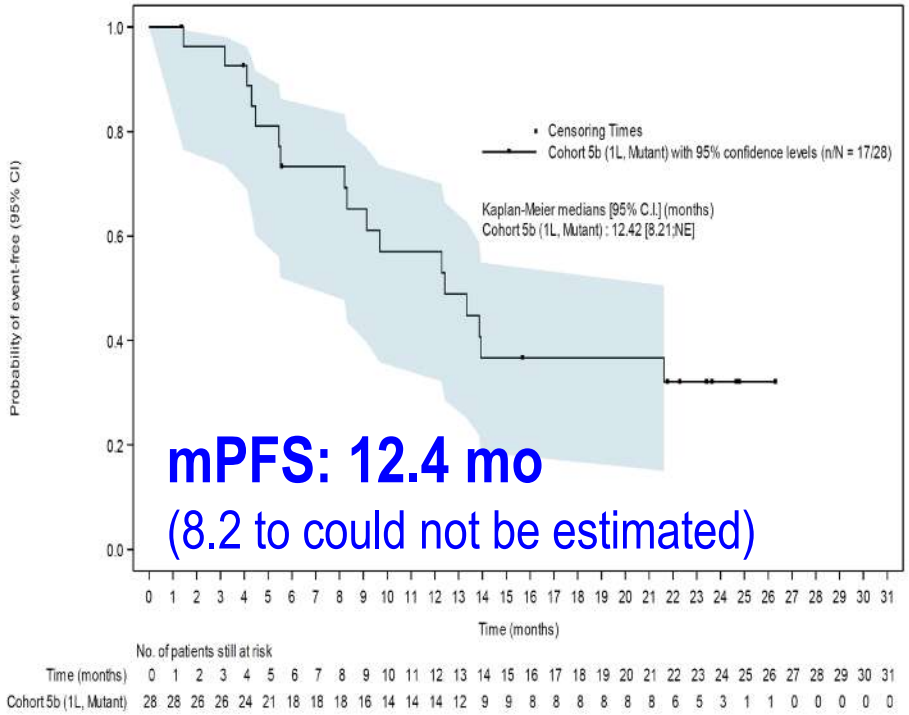
J.Wolf et al, ASCO 2021
J.Wolf et al, NEJM 2020

Capmatinib - PFS per BIRC assessment

2/3 L



1L

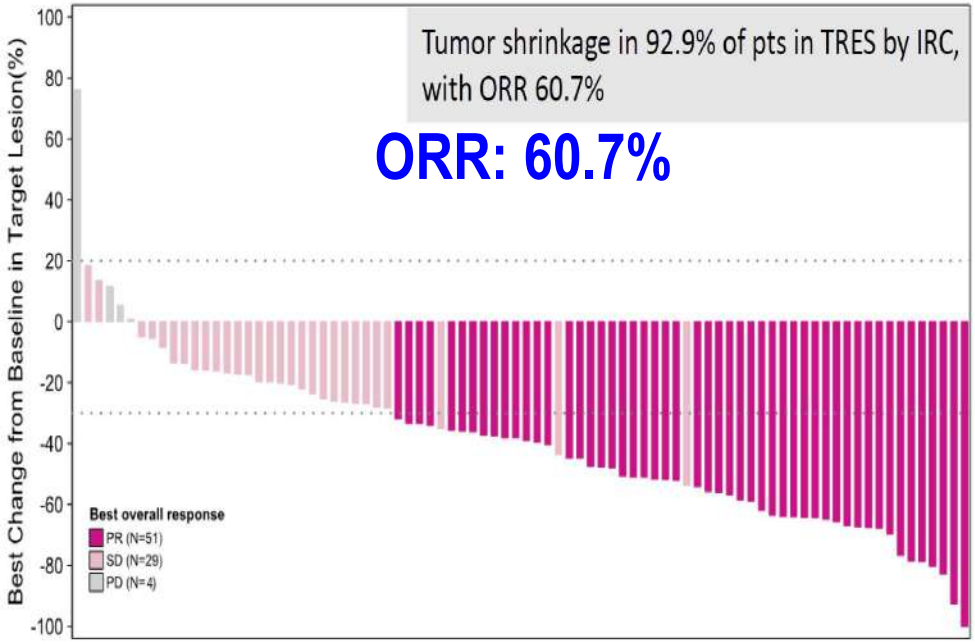


J.Wolf et al, NEJM 2020

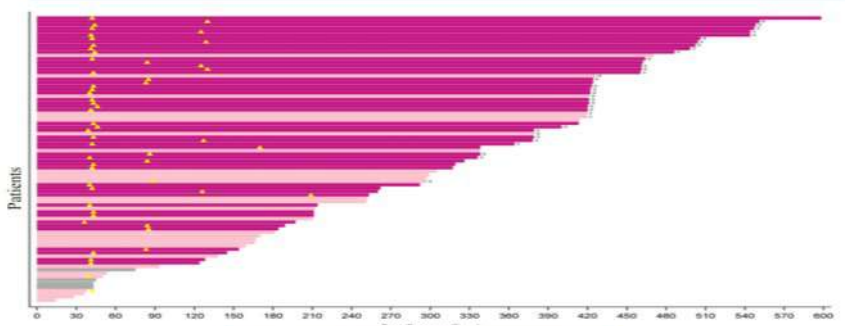
Savolitinib 1L – MET Exon14 mutation NSCLC

Deep and Durable Response (IRC assessment)

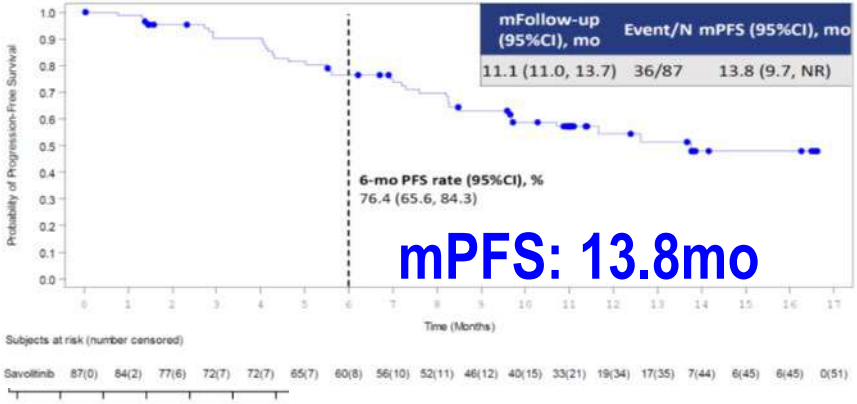
Waterfall Plot - Tumor Shrinkage of Target Lesion (IRC Assessment) - Tumor Response Evaluable Set



Swimmer Plot - (IRC Assessment) - Tumor Response Evaluable Set



KM plot of PFS- (IRC Assessment) FAS



Shun Lu et al, WCLC 2023

METex14 tyrosine kinase inhibitors

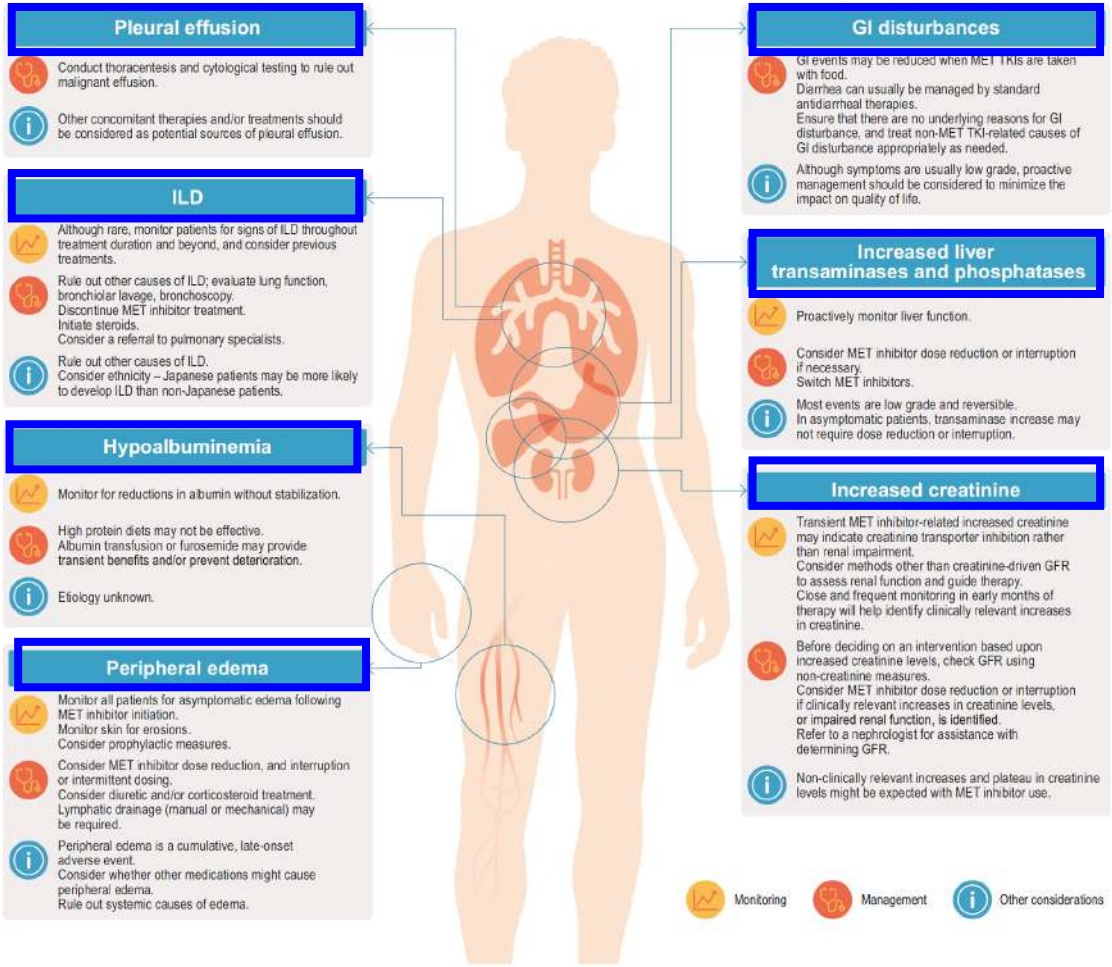
	Non-Selective	Selective TKI							
	CRIZOTINIB PROFILE 1001	CAPMATINIB GEOMETRY Mono-1		TEPOTINIB VISION (C) (TBx)		SAVOLITINIB		GLUMETINIB GLORY	
IC_{50} (nM)	26,5	0.6		3.0		2.1		0.42	
Dose	250 mg BID	400 mg BID		500 mg QD		400-600 mg QD		300 mg QD	
Line	≥1	1	≥2	1	≥2	1	≥2	1	≥2
N	69	60	100	161	51	87	42	42	27
RR (%)	32	**68.3**	**44**	**62.3**	**51**	**60.7**	40.5	66.7	51.9
DoR (mo.)	9.1	16.6	9.7	NE	12.6	NR	9.7	NE	5.1
PFS (mo.)	7.3	**12.4**	**5.4**	**15.9**	**13.8**	**13.8**	**6.9**	NE	5.7
OS (mo.)	20.5	25.5	13.6	22.7	19.6	NR	19.4	NR	NR
Comments	Shorter PFS in ctDNA positive at baseline	Higher activity in 1st line vs. ≥2nd line		The RR regardless Age, line & type of previous therapy		Sarcom. vs. others RR: 40% vs. 44% PFS: 5.5 vs. 6.9			

2022 2022 (2nd) 2021 2021 (2nd) 2021

J.Remon Slide

Drilon –Nature Med 2020 * Wolf –ELCC 2022 * Wolf – ASCO 2021 * Thomas – WCLC 2022 * Lu – Lancet Resp Med 2021 * Lu – ELCC 2022 * Lu – AACR 2022

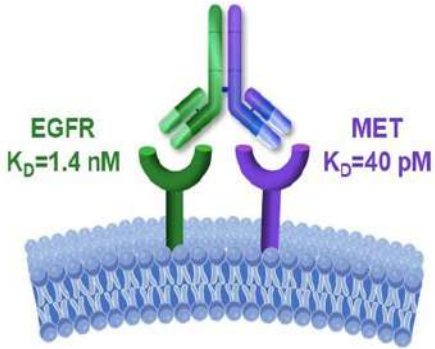
Overview - key adverse events

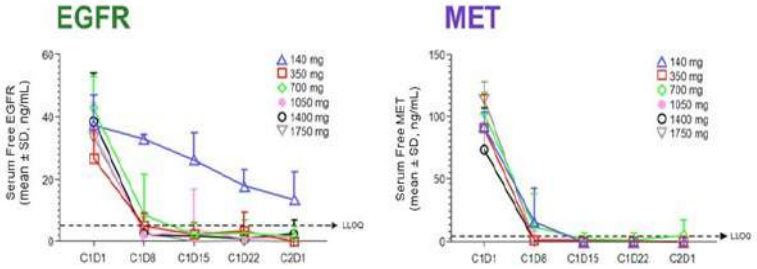


A.Cortot et al, Clinical Lung cancer 2022

Bispecific mAb anti-EGFR & anti-MET

Amivantamab





CHRYSALIS Study Phase 1

Part 1: Dose Escalation

140–1750 mg

Objective: Establish RP2D

RP2D

Amivantamab
1050 mg (<80 kg)
1400 mg (≥80 kg)

Intravenous dosing
C1 QW, C2+ Q2W

Part 2: Dose Expansion

MET-2 Cohort: *METex14* n=55[a]
(up to 100 planned)

Objective: Safety and efficacy at the RP2D

Eligibility

- Metastatic or unresectable/advanced NSCLC
- Failed or ineligible for standard of care therapy

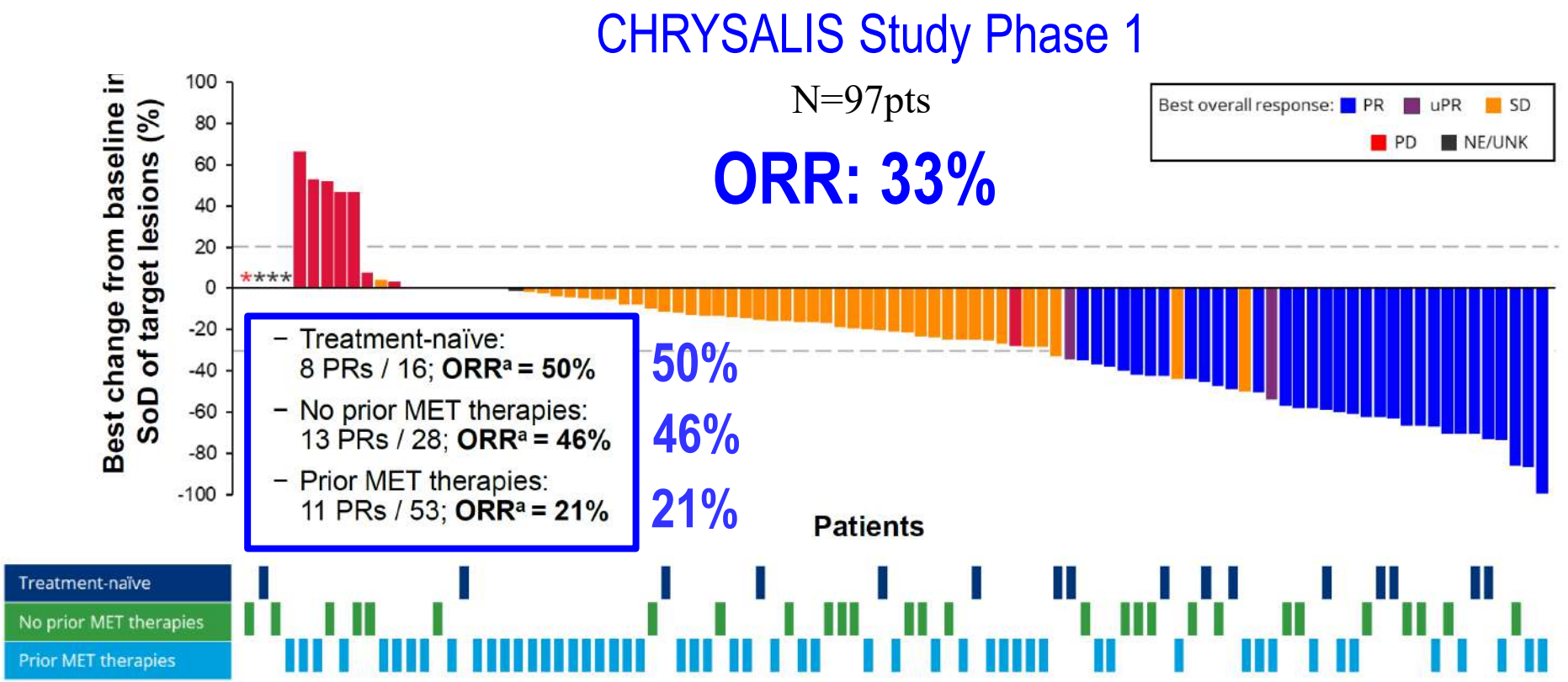
Eligibility for METex14 Cohort

- Measurable disease
- Primary METex14 mutation by NGS of tumor or ctDNA

Mattew G.Krebs et al, ASCO 2022

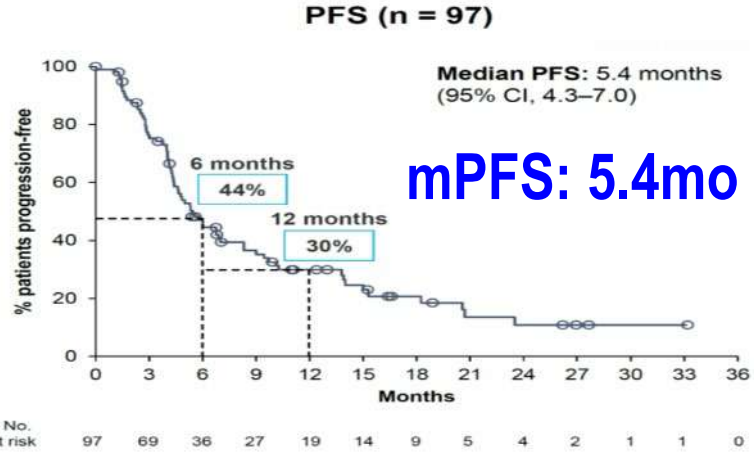
Bispecific mAb anti-EGFR & anti-MET

METex14 mutation: Amivantamab

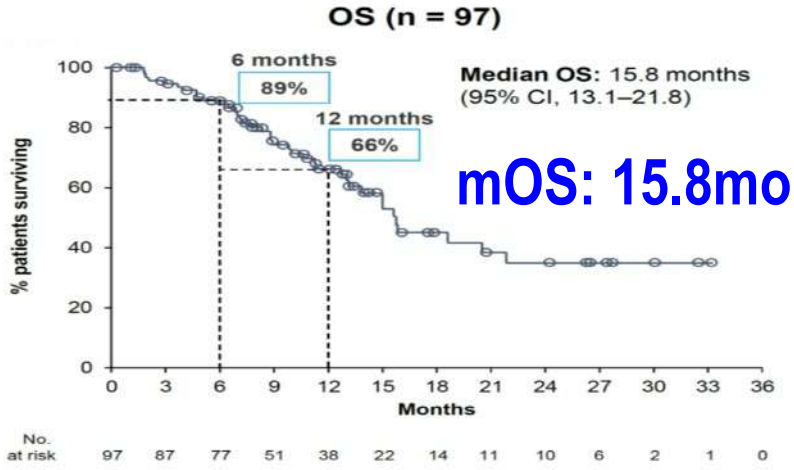


N.B.Leighl et al, WCLC 2023

PFS and OS of amivantamab monotherapy



mPFS: 5.4mo



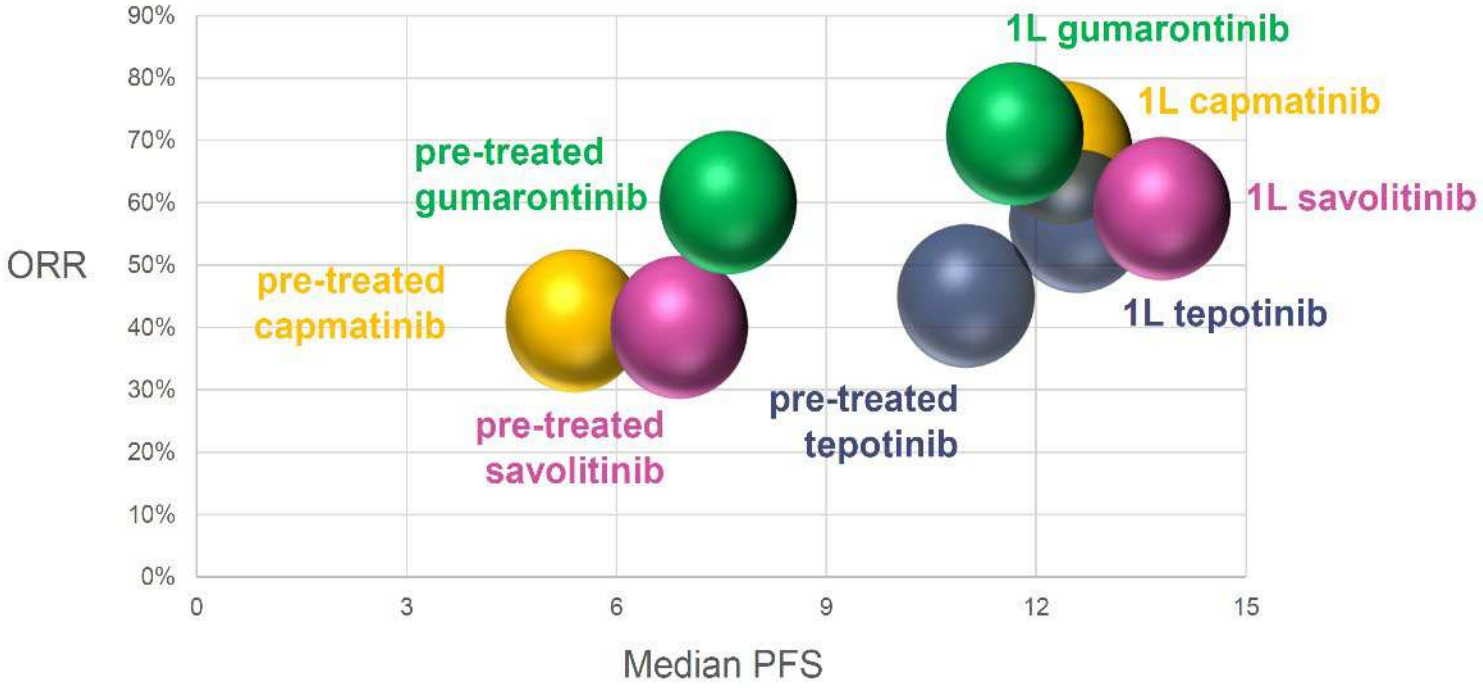
mOS: 15.8mo

Safety Profile

AEs (≥20%) by preferred term, n (%)	Median follow-up: 10.0 months (n = 97) Total	Grade ≥3
Associated with EGFR inhibition		
Paronychia	47 (48.5)	0
Dermatitis acneiform	40 (41.2)	1 (1.0)
Rash	37 (38.1)	1 (1.0)
Stomatitis	27 (27.8)	0
Pruritus	20 (20.6)	0
Associated with MET inhibition		
Hypoalbuminemia	37 (38.1)	2 (2.1)
Peripheral edema	36 (37.1)	4 (4.1)
Other		
Infusion-related reaction	70 (72.2)	4 (4.1)
Fatigue	28 (28.9)	2 (2.1)
Dyspnea	22 (22.7)	5 (5.2)
Hypokalemia	22 (22.7)	3 (3.1)
Nausea	21 (21.6)	0
Decreased appetite	21 (21.6)	0
Alanine aminotransferase increased	20 (20.6)	2 (2.1)
AEs of special interest by grouped term, n (%)		
Rash[a]	76 (78.4)	3 (3.1)
Venous thromboembolism[b]	8 (8.2)	2 (2.1)
Interstitial lung disease[c]	4 (4.1)	1 (1.0)

N.B.Leighl et al, WCLC 2023

First line MET TKI therapy appears to be associated with higher ORRs and PFS medians

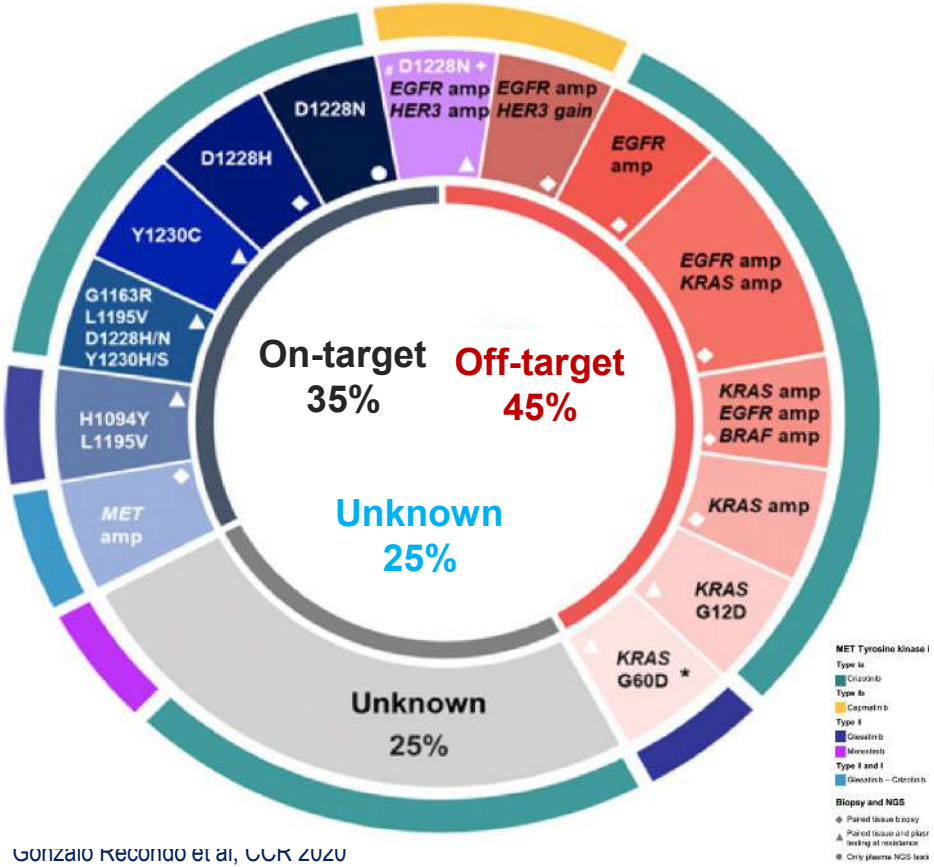


Ref/s: Lu et al, WCLC 2023; Lu et al, Lancet Resp Med 2021; Mazieres et al, JAMA Onc 2023; Wolf et al, NEJM 2020; Yu et al eClinicalMedicine 2023

A.Drilon, WCLC 2023

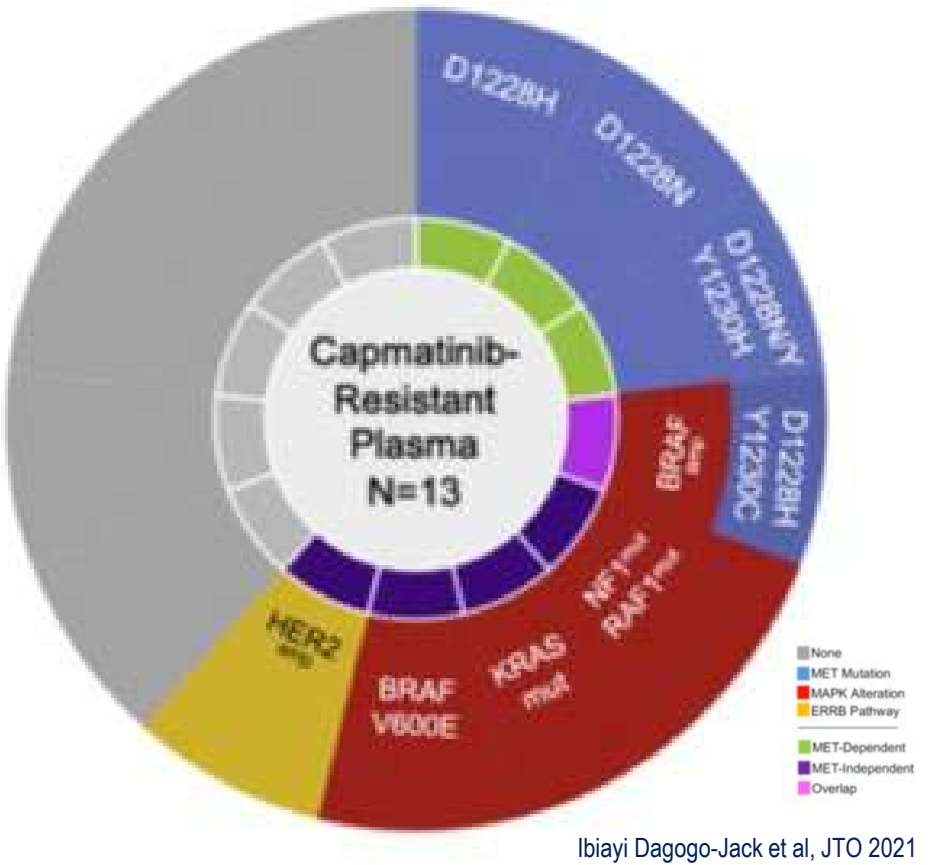
Molecular Mechanisms of Acquired Resistance to MET TKIs

Post MET TKIs plasma specimens



Gonzalo Recondo et al, CCR 2020

Postcapmatinib plasma specimens



Ibiayi Dagogo-Jack et al, JTO 2021

MET TKI and resistance mutations

Drug name	Inhibitor type	Selectivity	Activity against other kinases	RESISTANCE MUTATION ACTIVITY (steric hindrance / conformational resistance)				References
				Solvent-Front	Activation-Loop	Beta-9 strand	Hydrophobic-core	
Crizotinib	DFG-Din	Multi kinase inhibitor	ALK; ROS1	G1163R	Y1230C/H/N/S; D1231Y	D1228N/H/E	L1995V	Cosmic drug resistance dataset; Recondo et al CCR 2020; Fujino et al JTO 2019
Tepotinib	DFG-Din	MET selective		G1163E	Y1230X	D1228X	L1995V	Fujino et al JTO 2019
Capmatinib	DFG-Din	MET selective		Active on cell lines	Y1230H	D1228N/H	L1995V	Cosmic drug resistance dataset; Recondo et al CCR 2020; Fujino et al JTO 2019
Savolitinib	DFG-Din	MET selective		Active on cell lines	Y1230S	D1228N/V	L1995V	Cosmic drug resistance dataset; Fujino et al JTO 2019
Cabozantinib	DFG-Dout	Multi kinase inhibitor	VEGFR; KIT; RET; AXL; FLT3: ROS1	Variably active on cell lines	Known to be active	D1228Y/A/N	L1195V; F1200L	Fujino et al JTO 2019;Fujino et al JHO 2022; Kang et al Lung Cancer 2023;
Merestinib	DFG-Dout	Multi kinase inhibitor	FLT3; AXL; ROS1	Active on cell lines	Known to be active	D1228Y	F1200I	Fujino et al JTO 2019
Glesatinib	DFG-Dout	Multi kinase inhibitor	VEGFR: TIE2: SMO	H1094Y	Known to be active	D1228Y/A	L1195V	Recondo et al CCR 2020; Fujino et al JTO 2019

Clinical evidence of resistance

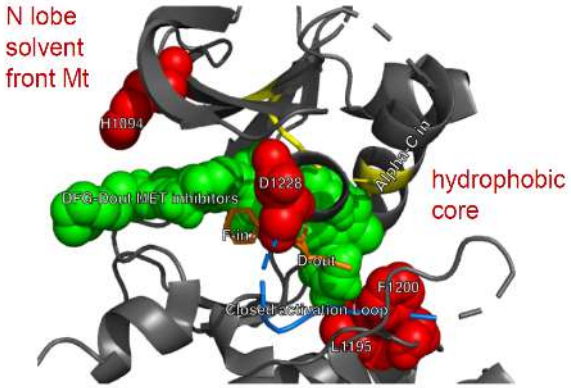
Preclinical evidence of resistance

Evidence of activity

Ref/s: table courtesy of Matteo Repetto MD, Univ Milan/MSKCC

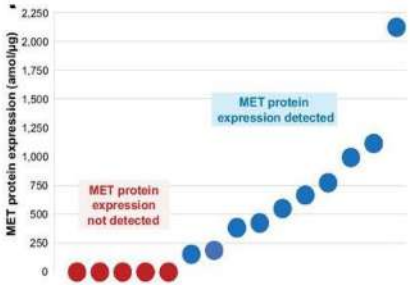
A.Drilon, WCLC 2023

Antibody-based therapeutics may address complex ontarget and off-tatget resistance



MET Ab	Targets
Onartuzumab, telisotumab, HLX55	MET
REGN5093, Sym015	MET, MET
Amivantamab, MCLA-129, CKD702	MET, EGFR
GB263T	MET, MET, EGFR
TAVO412	MET, EGFR, VEGF

MET ADC	Warhead (if disclosed)
Telisotumab vedotin (MET)	MMAE
TR1801 (MET)	PBD
SHR-A1403 (MET)	Microtubule inhibitor
RC108 (MET)	
ABBV-400 (MET)	Topo I inhibitor
BYON3521 (MET)	Duocarmycin based
AZD9592 (MET-EGFR)	Topo I inhibitor
MYTX-011 (MET)	MMAE
REGN5093-M114 (MET-MET)	Maytansine derivative



Ref/s: Bachall et al, Cancer Discov 2017; green - volumes occupied by: Merestinib (4EEV), Foretinib (6SD9) and Cabozantinib (Docked)

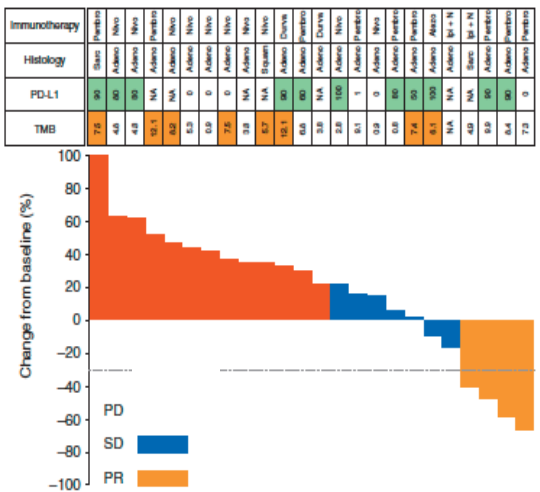
Attenuated efficacy of ICI in *MET*ex14

MSKC cohort

147MET+

ORR: 17%

PFS: 1.9 mo

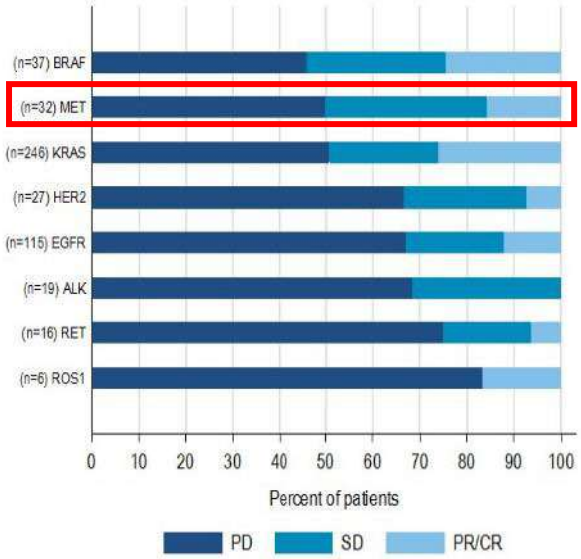


IMMUNOTARGET

36 *MET+*

ORR: 16%

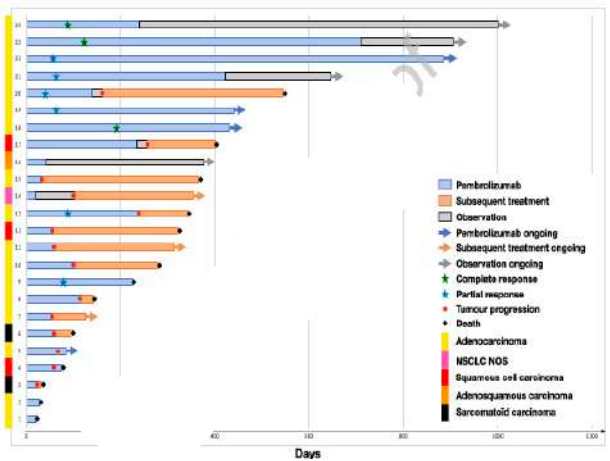
PFS: 3.4 mo



GFPC 01-20

30 *MET+* & PD-L1≥50%

ORR: 43%



RR not enriched in PD-L1 ≥ 50% nor high TMB

J.Remon Slide

Awad – JCO PO 2021 * Sabari – Ann Oncol 2018 * Mazières- Ann Oncol 2019 * Guisier – JTO 2020 * Guisier – Clin Lung Cancer 2022 * Mayenga –Lung Cancer 2020

ESMO
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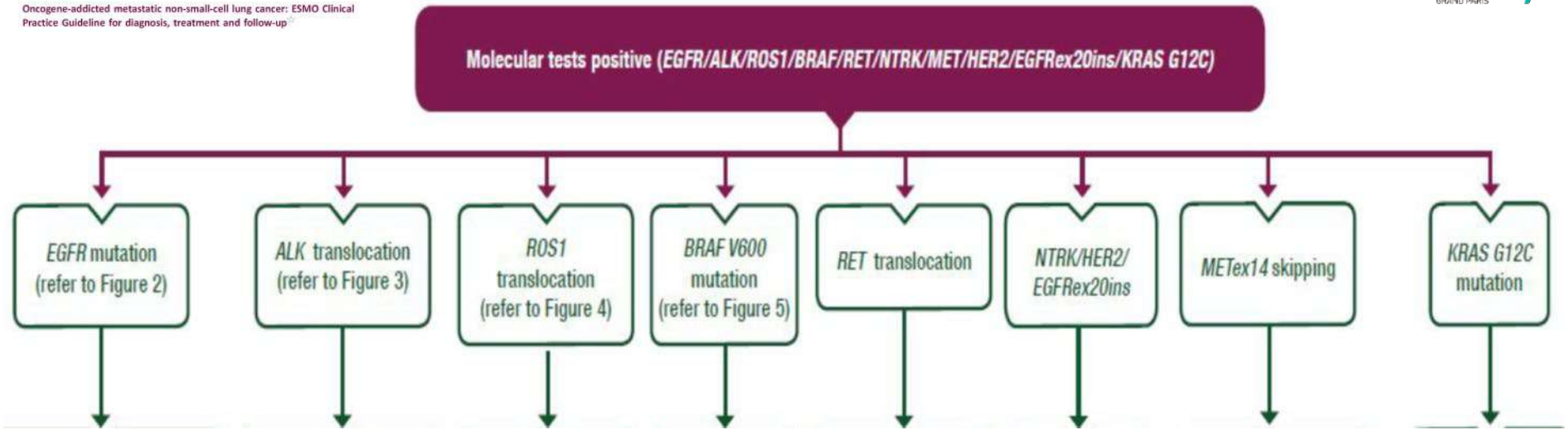
SPECIAL ARTICLE
Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS



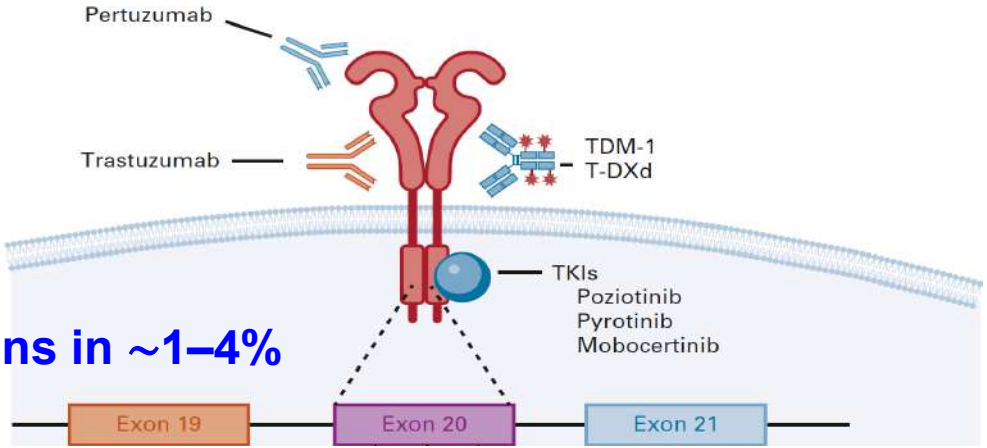
2nd line

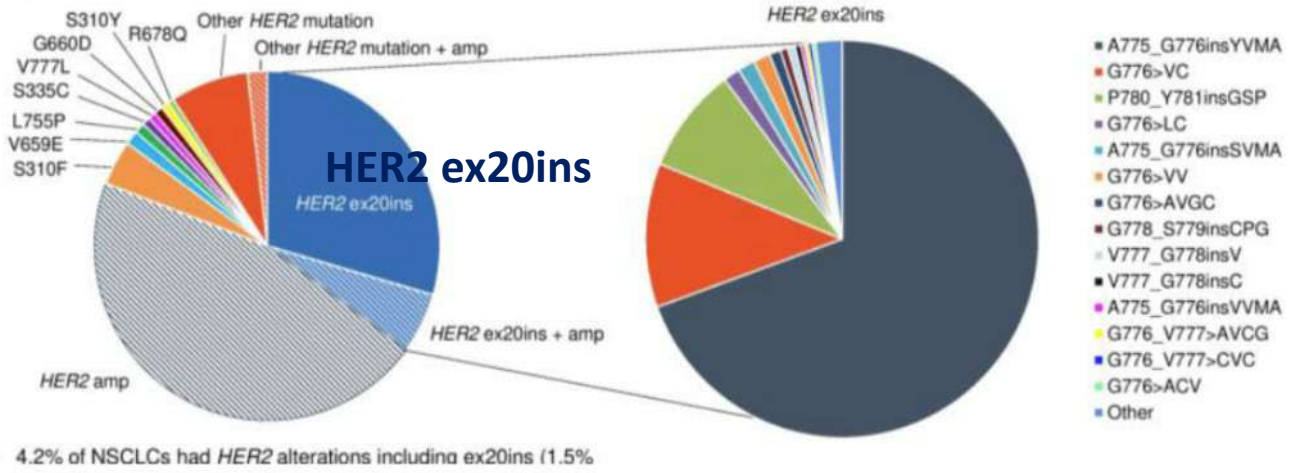
Capmatinib [III, A; MCBS 3; ESCAT I-B][a,c]
Tepotinib [III, A; MCBS 3; ESCAT I-B][a,c]

L. E. Hendriks, K. Kerr, J. Menis, T. S. Mok, U. Nestle, A. Passaro, S. Peters, D. Planchard, E.F Smit, B. J. Solomon, G. Veronesi & M. Reck, Annals of onco 2023

HER2 mutations occur mainly in the tyrosine kinase domain

***HER2* mutations in ~1–4%**





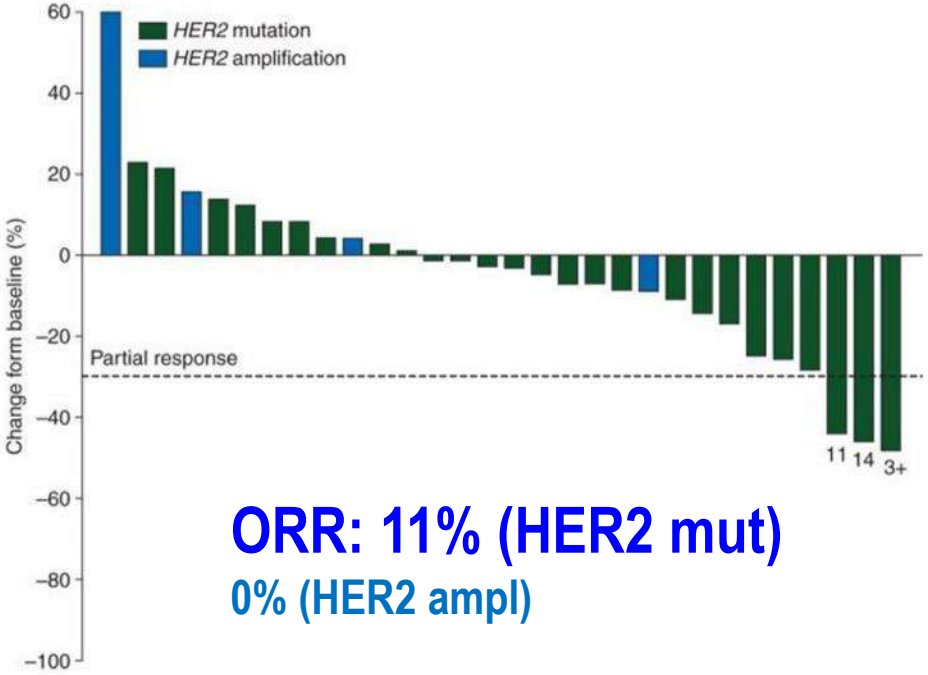
- 4.2% of NSCLCs had *HER2* alterations including ex20ins (1.5%

Robichaux et al, AACR 2019

Alissa J.Cooper et al, JCO 2022

Dacomitinib and Afatinib for HER2 mutated NSCLC

Dacomitinib

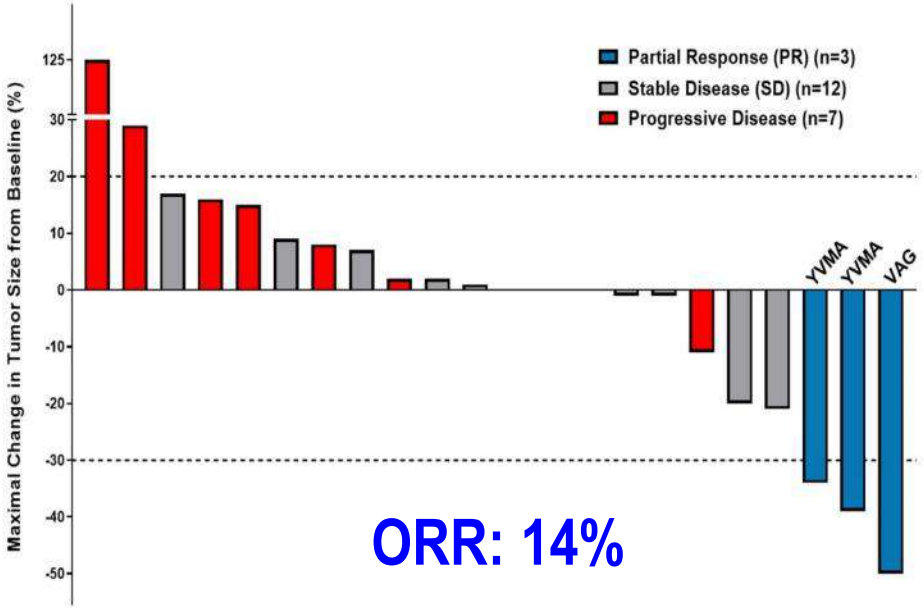


ORR: 11% (HER2 mut)

0% (HER2 ampl)

Kris et al, Annals onco 2014

Afatinib 2)



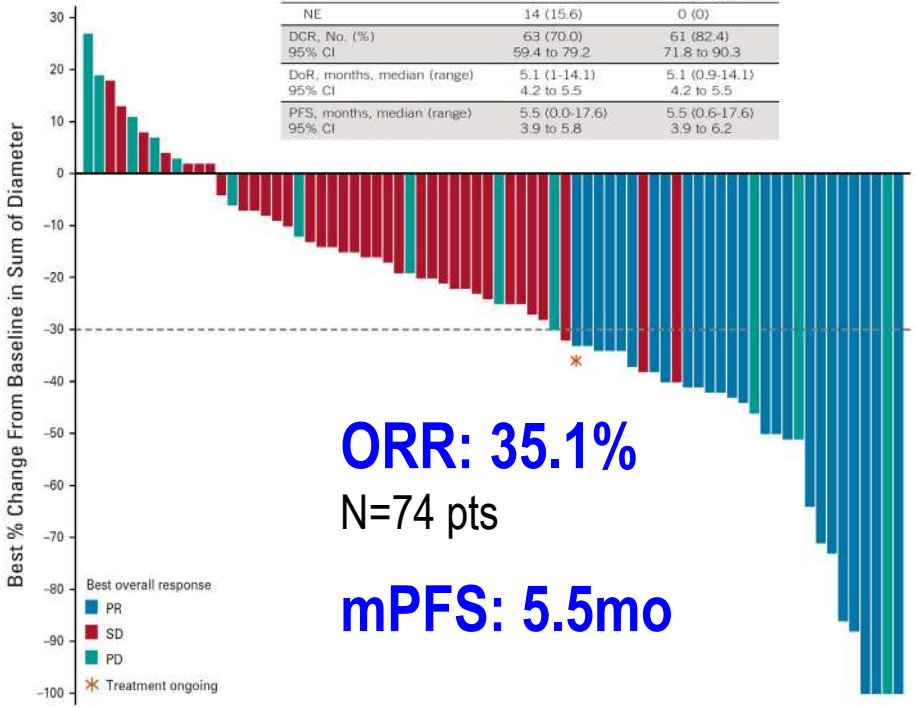
ORR: 14%

Lai et al, Eur J Cancer 2019

Poziotinib - HER2 Exon 20 Insertion after Prior Therapies:

ZENITH20-2 Trial

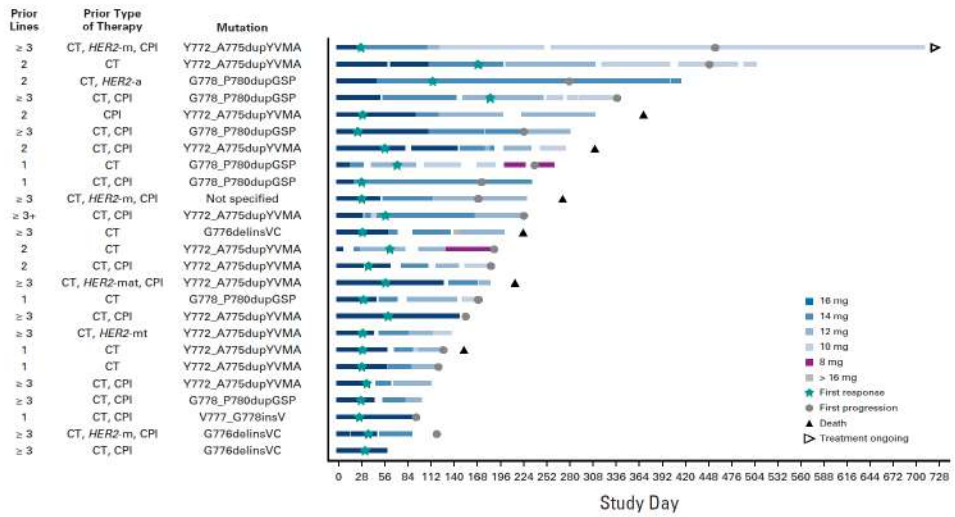
Parameter	As-Treated[a] (N = 90)	Evaluable[b] (n = 74)
ORR, No. (%) 95% CI	25 (27.8)[c] 18.9 to 38.2	26 (35.1)[d] 24.4 to 47.1
Best overall response, No. (%)		
CR	0 (0)	0 (0)
PR	25 (27.8)[c]	26 (35.1)[d]
SD	38 (42.2)	35 (47.3)
PD	13 (14.4)	13 (17.6)
NE	14 (15.6)	0 (0)
DCR, No. (%) 95% CI	63 (70.0) 59.4 to 79.2	61 (82.4) 71.8 to 90.3
DoR, months, median (range) 95% CI	5.1 (1-14.1) 4.2 to 5.5	5.1 (0.9-14.1) 4.2 to 5.5
PFS, months, median (range) 95% CI	5.5 (0.0-17.6) 3.9 to 5.8	5.5 (0.6-17.6) 3.9 to 6.2



ORR: 35.1%

N=74 pts

mPFS: 5.5mo



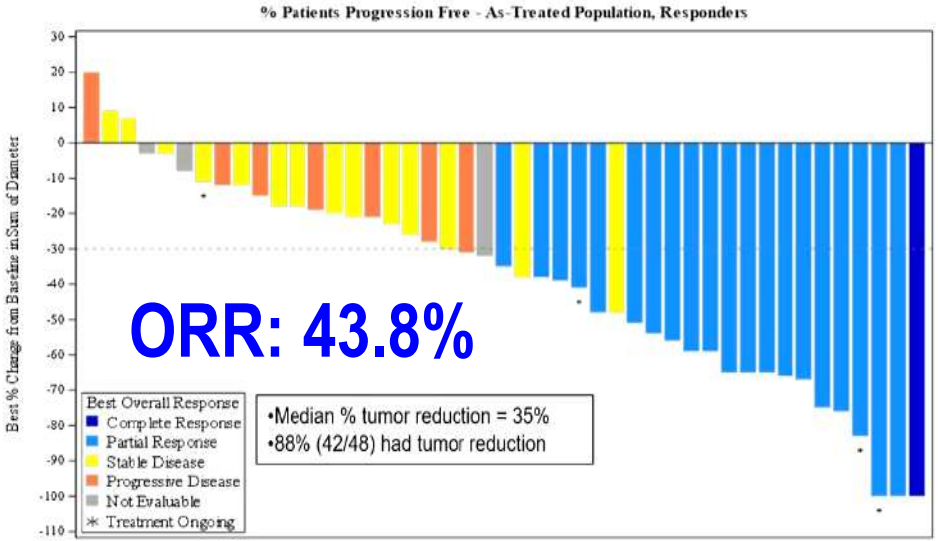
	N=90, n (%)
Treatment-related AE	88 (98)
Dose interruptions	78 (87)
Dose reductions	70 (78)

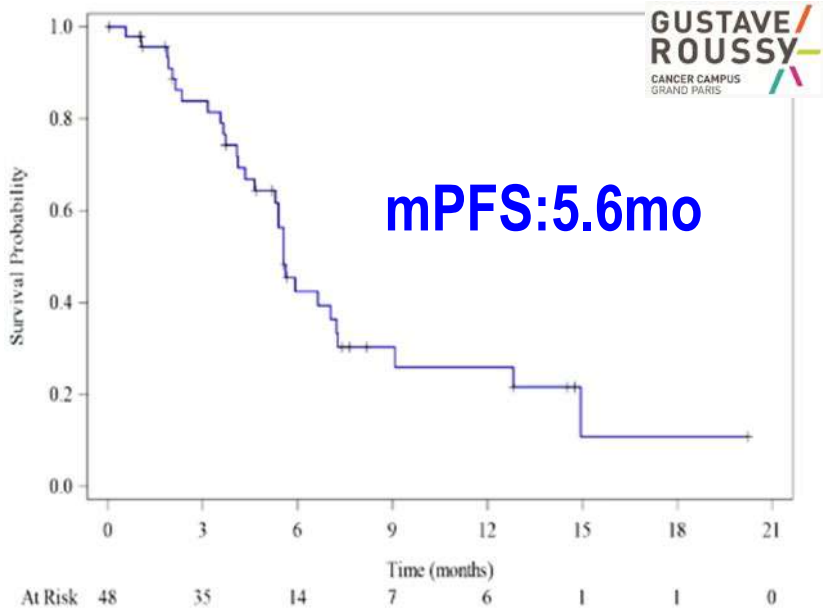
Preferred Term (PT)	N=90, n (%)		
	Any Grade	Grade 3	G4
Diarrhea	74 (82)	23 (26)	0
Rash	61 (68)	27 (30)	0
Stomatitis	59 (66)	20 (22)	1 (1)
Paronychia	34 (38)	1 (1)	0
Pneumonitis	1 (1)	0	0

Xiuning Le, et al, JCO 2022

POZIOTINIB: First Line HER2 exon 20

Best %Change from Baseline in Target Tumor Size

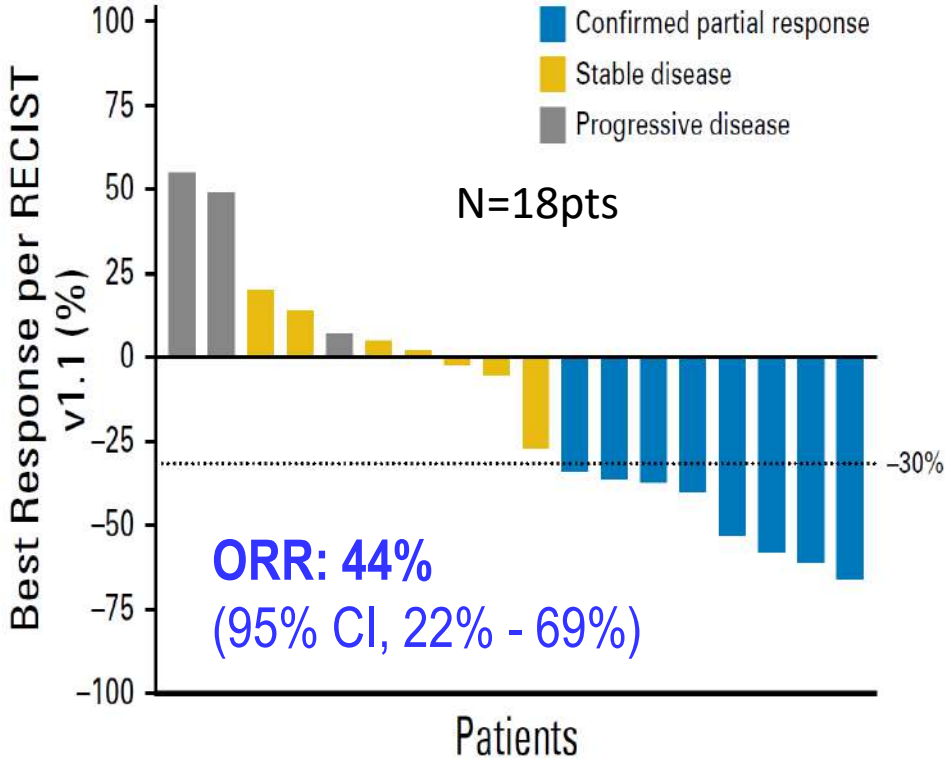


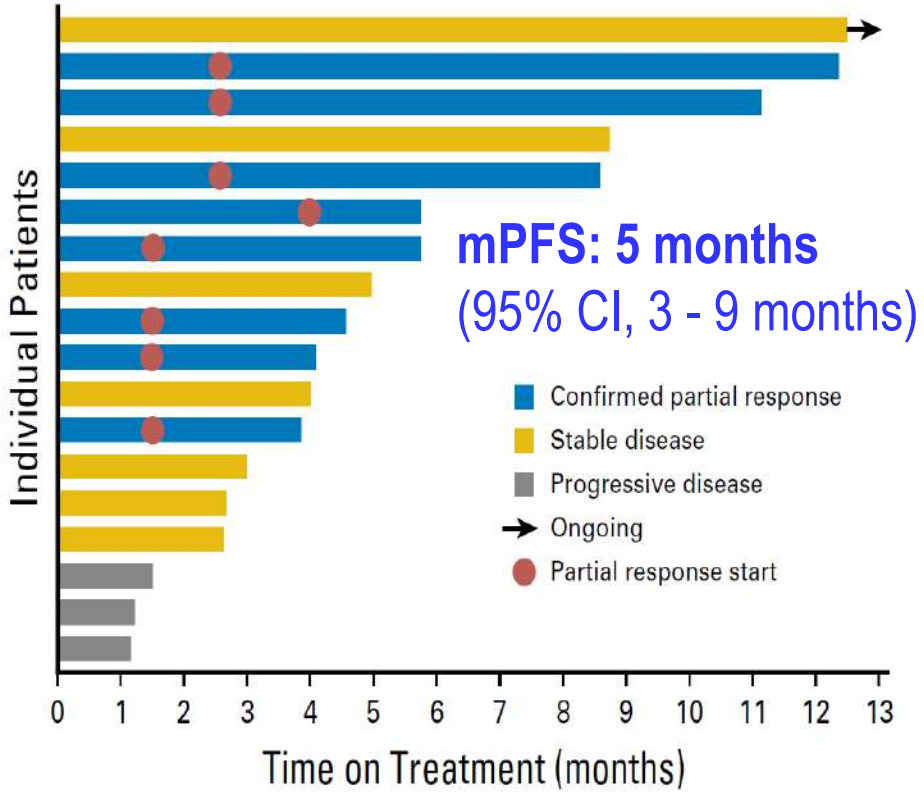


	Any Grade	Grade 3	Grade 4 / 5
Diarrhea	40 (83)	7 (15)	0
Rash	34 (69)	17 (35)	0
Stomatitis / Mucosal Inflammation	39 (81)	10 (21)	0
Paronychia	22 (46)	4 (8)	0
Pneumonitis	2 (4)	1 (2)	0

R.Cornelissen et al, ESMO 2021

Ado-Trastuzumab Emtansine (T-DM1)
in HER2-Mutant Lung Cancers (Phase II Basket Trial)

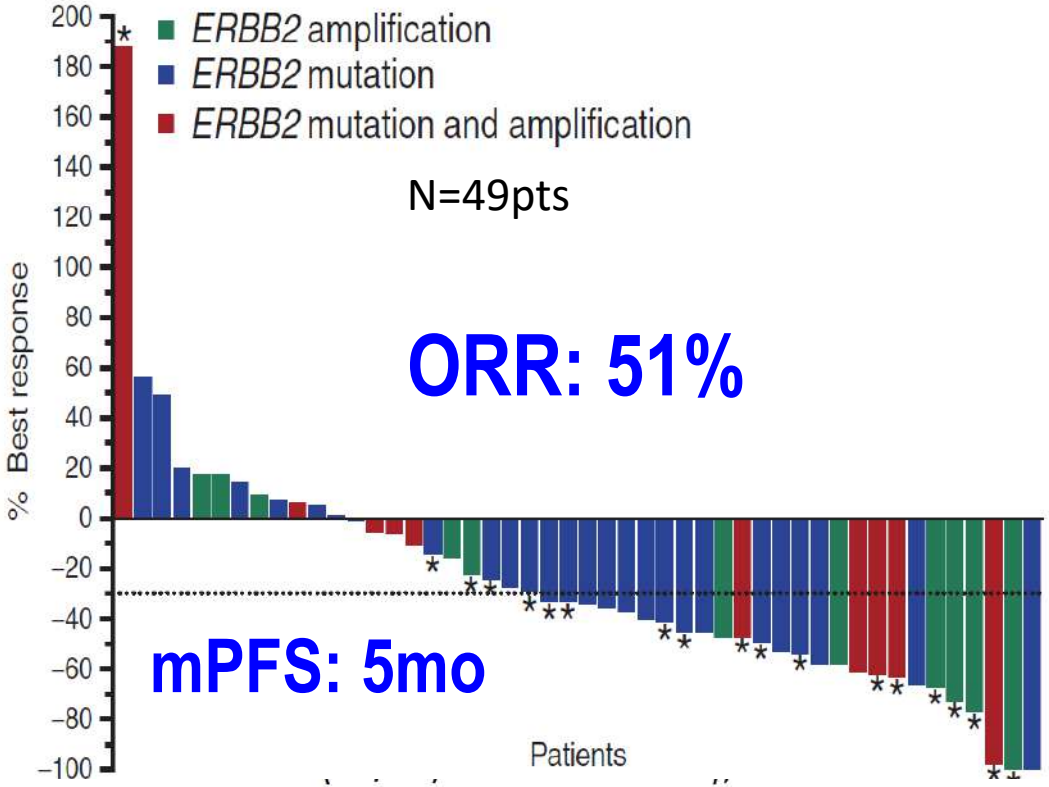


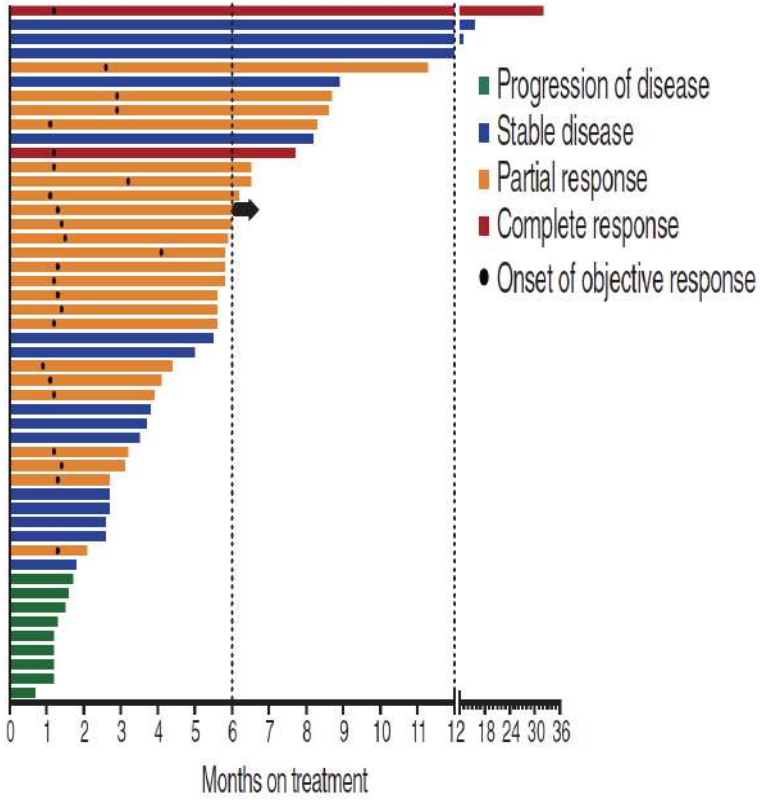


HER2 immunohistochemistry ranged from 0 to 2+ and did not predict response

Bob T. Li et al, JCO 2018

Clinical activity of T-DM1 in NSCLC





55% (6/11, 95% CI 23-83%) for *ERBB2*-amplified patients,
50% (14/28, 95% CI 31 to 69) for *ERBB2*-mutant patients
50% (5/10, 95% CI 19-81) for concurrently *ERBB2*-mutant and amplified patients

Li et al, cancer discovery 2020

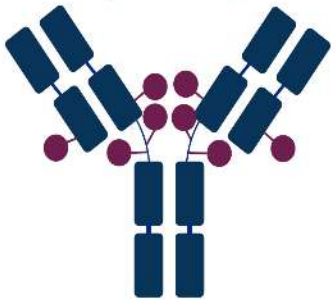
Differences between T-DXd and T-DM1

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

HER2-Targeting ADCs With a Similar mAB Backbone

Next- generation ADCs

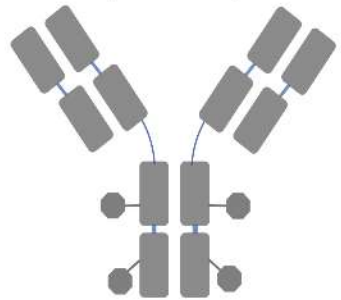
Trastuzumab deruxtecan (T-DXd)



T-DXd	ADC Attributes	T-DM1
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander antitumor effect?**	No

First generation ADCs

Trastuzumab emtansine (T-DM1)



1. Nakada T et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-85. 2. Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097-108.
3. Trail PA et al. *Pharmacol Ther*. 2018;181:126-42. 4. Ogitani Y et al. *Cancer Sci*. 2016;107:1039-46. 5. LoRusso PM et al. *Clin Cancer Res*. 2011;17:6437-47.

DESTINY-Lung01

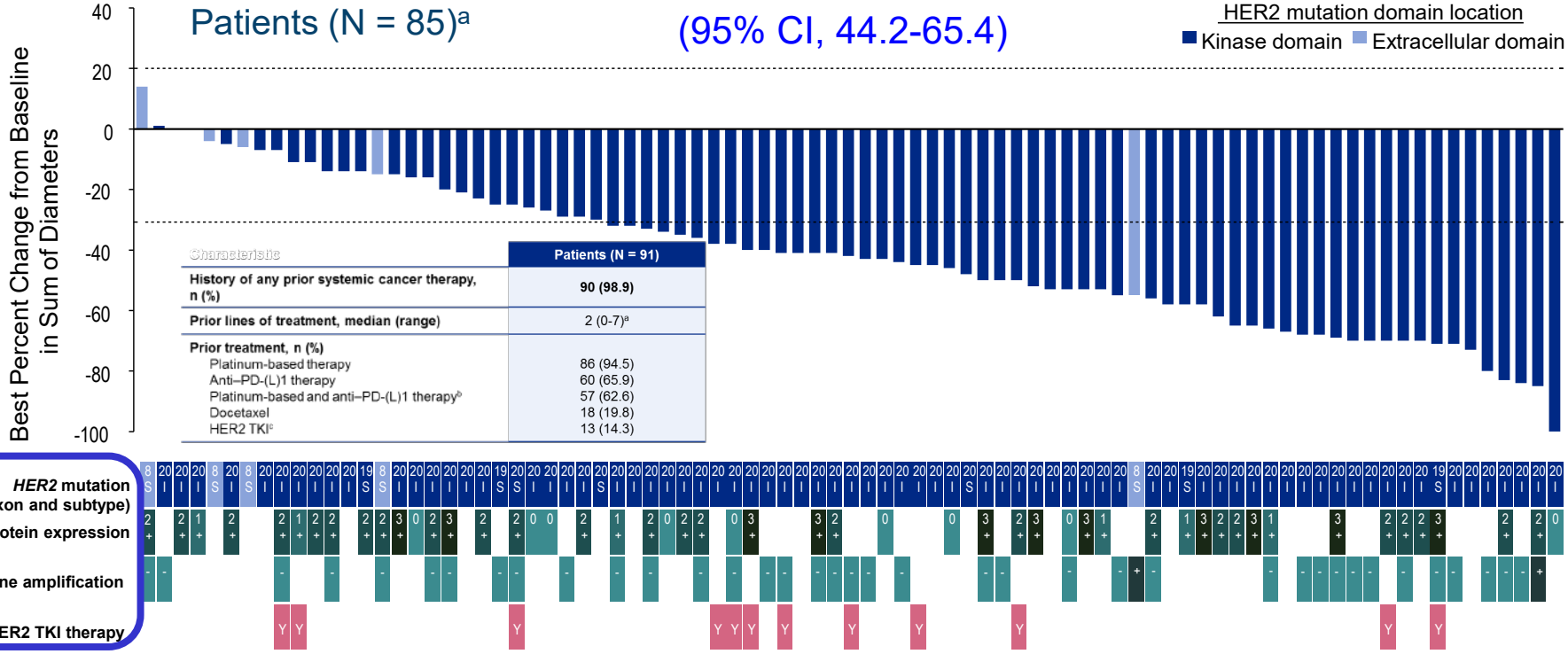
Trastuzumab-Deruxtecan (T-DXd)

54.9%

(95% CI, 44.2-65.4)

Patients (N = 85)[a]

HER2 mutation domain location
Kinase domain Extracellular domain

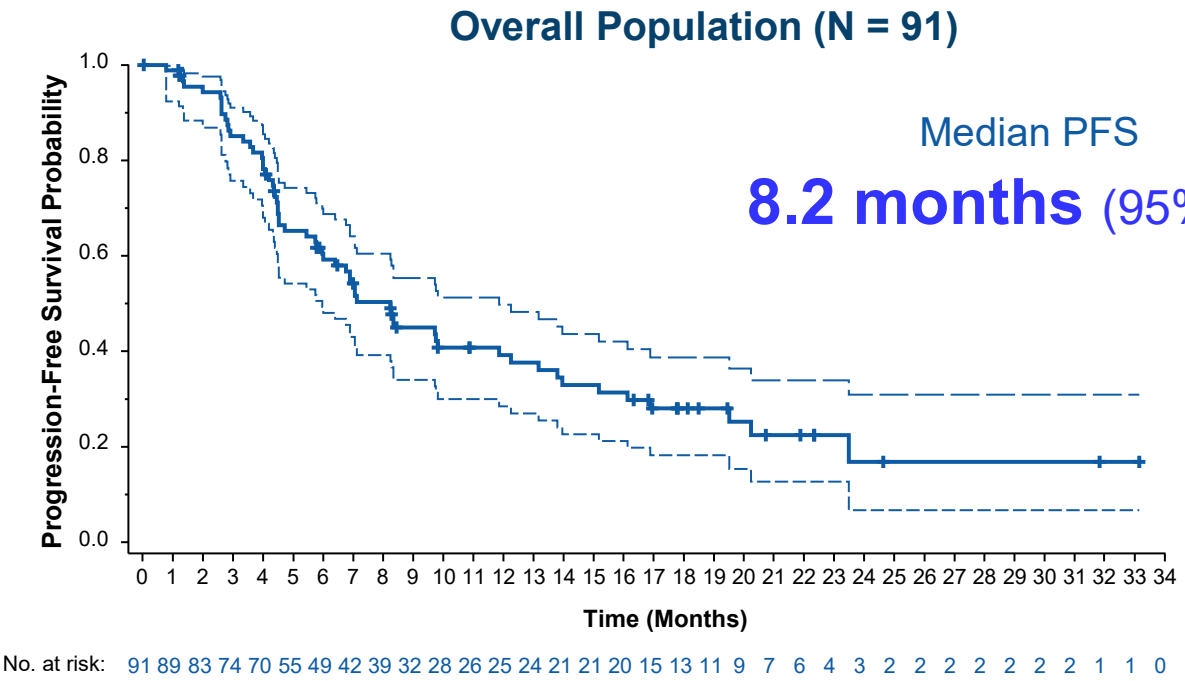


Characteristic	Patients (N = 91)
History of any prior systemic cancer therapy, n (%)	90 (98.9)
Prior lines of treatment, median (range)	2 (0-7)[a]
Prior treatment, n (%)	
Platinum-based therapy	86 (94.5)
Anti–PD-(L)1 therapy	60 (65.9)
Platinum-based and anti–PD-(L)1 therapy[b]	57 (62.6)
Docetaxel	18 (19.8)
HER2 TKI[c]	13 (14.3)

Li BT et al, NEJM 2022

PFS in the overall *HER2*m NSCLC Population

T-DXd



Median PFS

8.2 months (95% CI, 6.0-11.9)

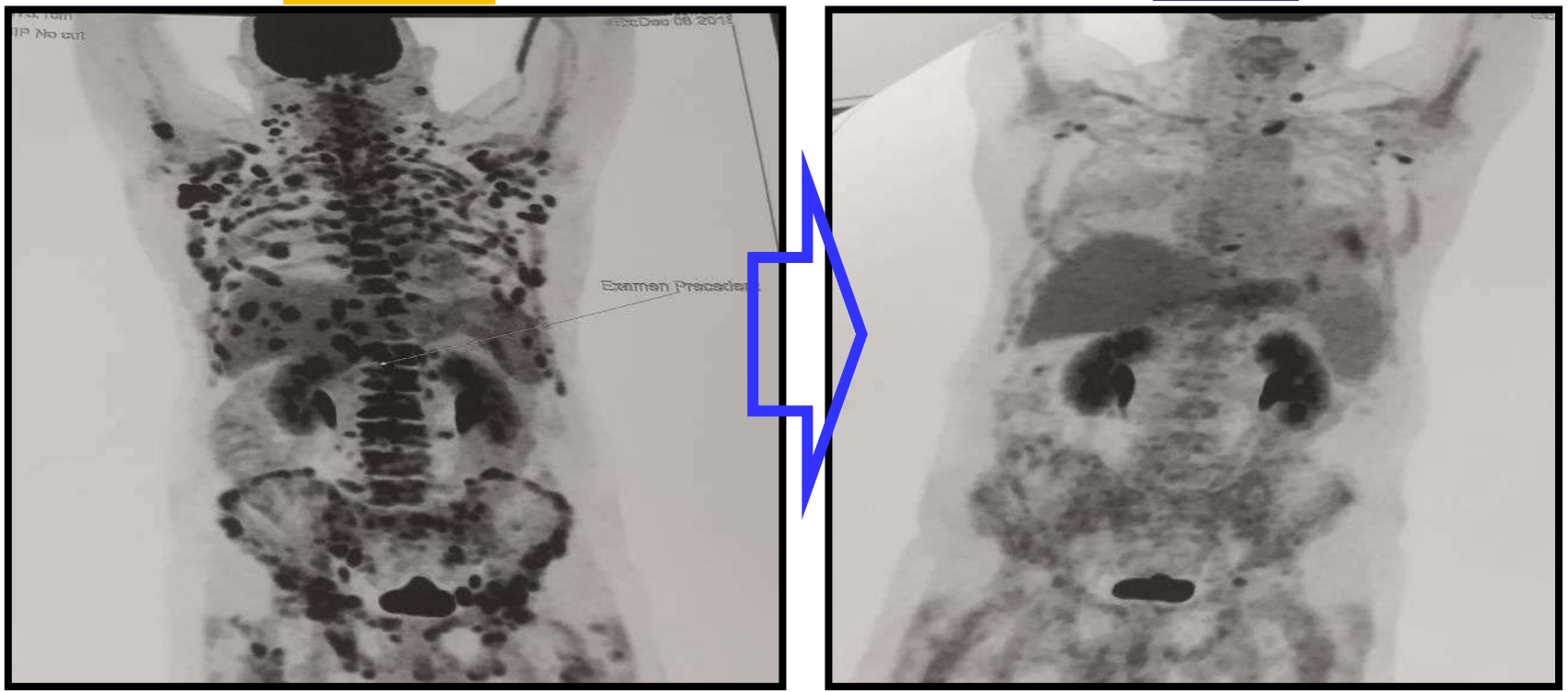
Bob T.Li et al, ESMO 2022

NSCLC adenocarcinoma HER2-insertion in exon 20

- Lymph node metastases, adrenal glands, hepatic, spleen, brain, bone...
- **1st line carboP-pemetrexed and 2nd line pembrolizumab**

Baseline

T-DXd C7D1

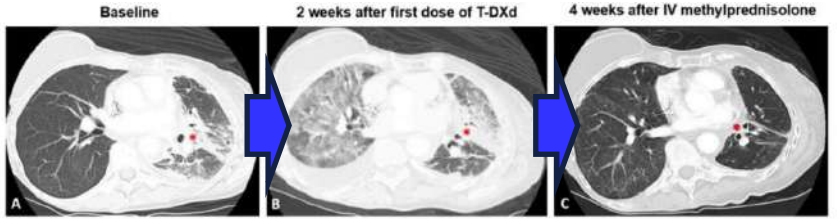


D.Planchard, Throacic Group, Gustave Roussy, 2022

Drug-related TEAEs Reported by Investigator

n (%)	Patients (N = 91) Any grade	Grade ≥3
Patients with ≥1 drug-related TEAEs	88 (96.7)	42 (46.2)
Drug-related TEAEs with ≥20% incidence in all patients		
Nausea	66 (72.5)	8 (8.8)
Fatigue[a]	48 (52.7)	6 (6.6)
Alopecia	42 (46.2)	0
Vomiting	36 (39.6)	3 (3.3)
Neutropenia[b]	32 (35.2)	17 (18.7)
Anemia[c]	30 (33.0)	9 (9.9)
Diarrhea		
Decreased appetite		
Leukopenia[d]		
Constipation		

Drug-Related ILD/Pneumonitis



	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
n (%)	3 (3.3)	**15 (16.5%)**	4 (4.4)	0	2 (2.2)	**24 (26.4%)**

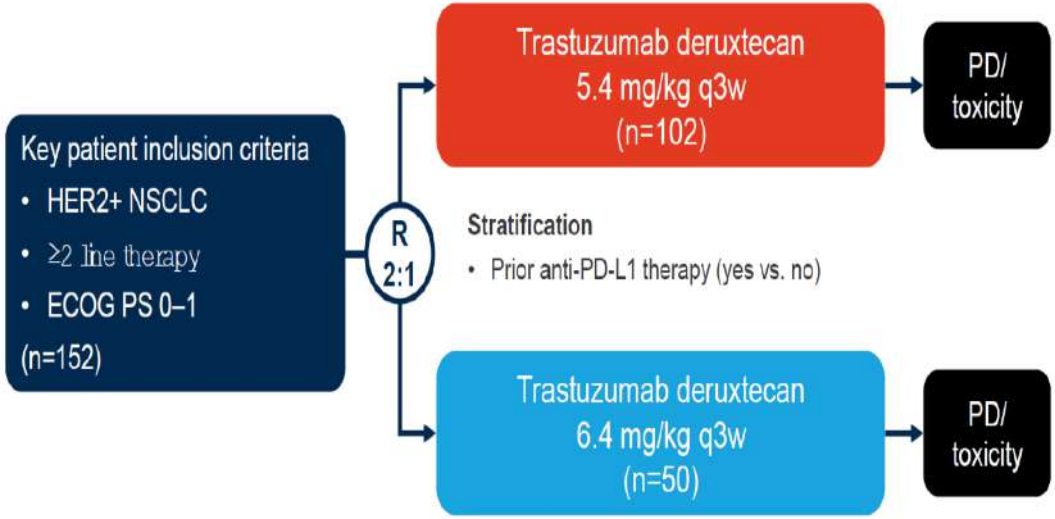
Median time to onset of first reported drug-related **ILD/pneumonitis:141 days** (range, 14-462 days) with a median duration of 43 days (95% CI, 24-94 days)

Li BT et al, NEJM 2022

DESTINY-Lung02 (HER2 mut)

KEYPOINTS

- ***HER2* mut** advaced NSCLC (PS 0-1)
- **≥ 1 prior therapy** (platinum based chemo)
- **Adecuate washout** of prior treatment
- **CNS+ allowed** if treated/asymphomatic
- **Stratification:** prior PD-(L)1 inhibitor



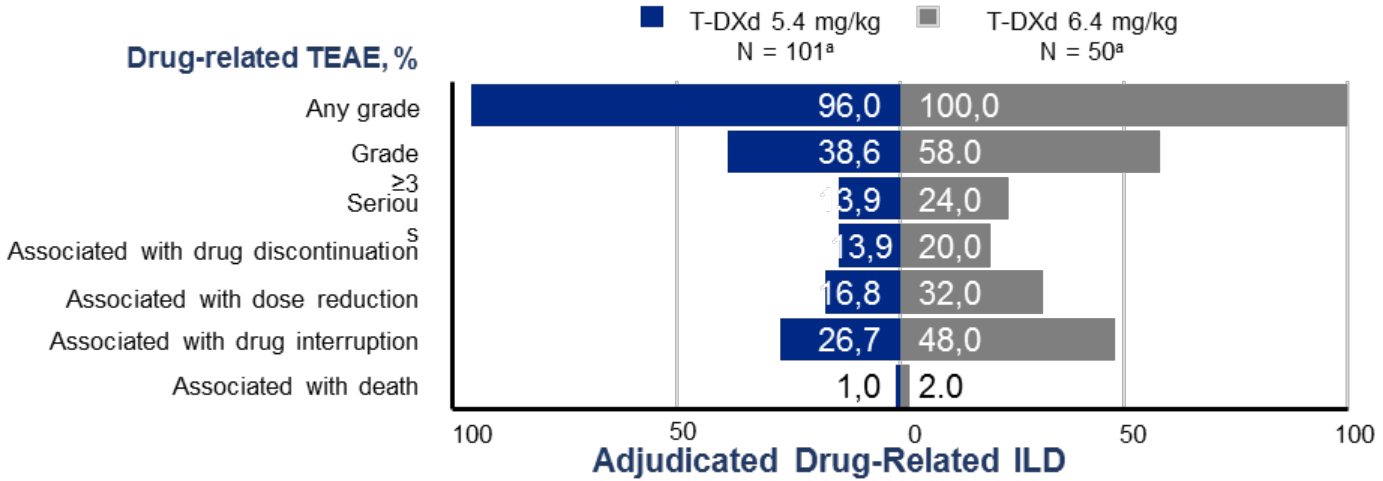
- **DESTINY-Lung02 is a randomized, phase 2 trial** assessing the efficacy and safety of 2 doses of **T-DXd (5.4 and 6.4 mg/kg)** in previously patients with metastatic *HER2*m NSCLC

The study was not powered to statistically compare the 2 arms

Goto K et al, ESMO 2022

Trastuzumab Deruxtecan in Patients With HER2-Mutant Metastatic NSCLC: Primary Results of DESTINY-Lung02

Overall Safety



Adjudicated Drug-Related ILD

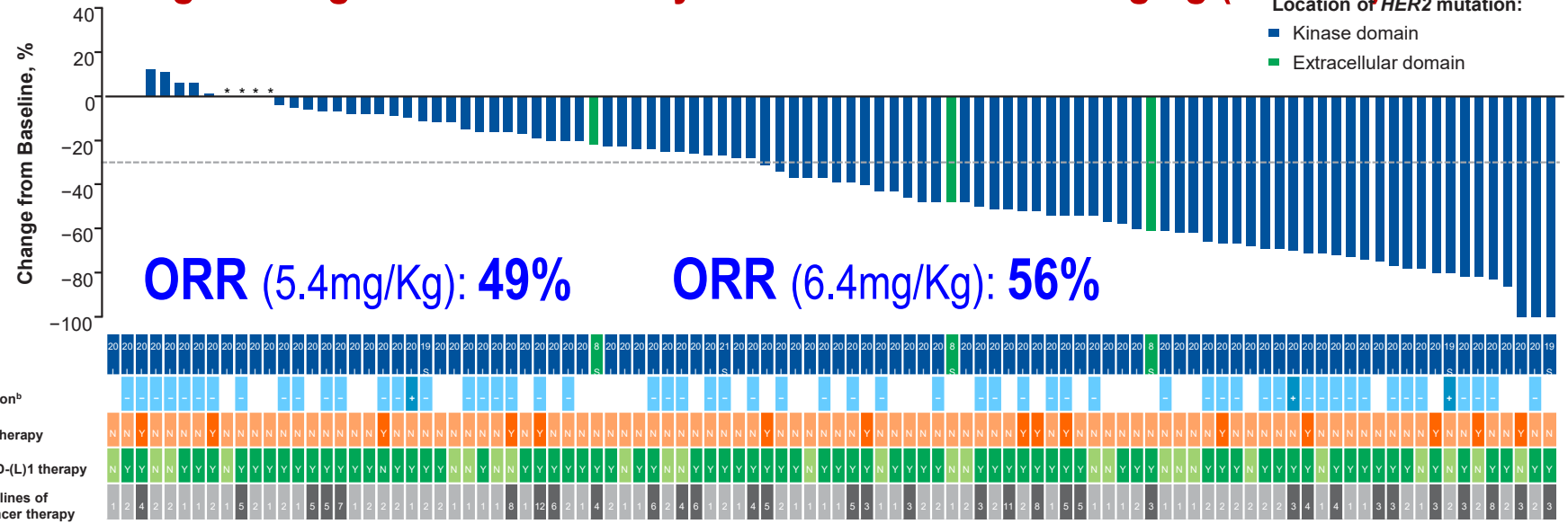
Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101[a]	T-DXd 6.4 mg/kg N = 50[a]
Any grade, n (%)	**13 (12.9)**	**14 (28.0)**
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

12.9%

28%

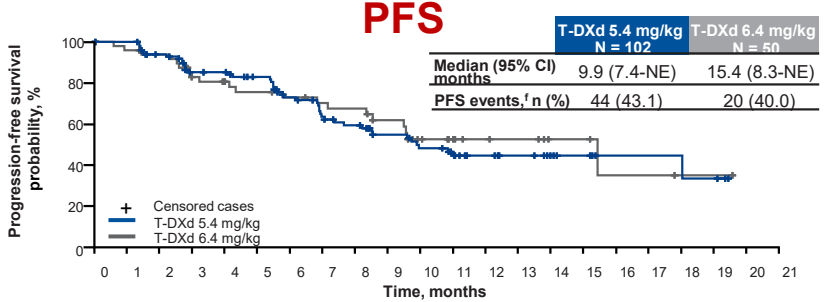
P.A.Janne et al, WCLC 2023 – JCO2023

Best Percentage Change in Tumor Size by BICR with T-DXd 5.4 mg/kg (N = 102)



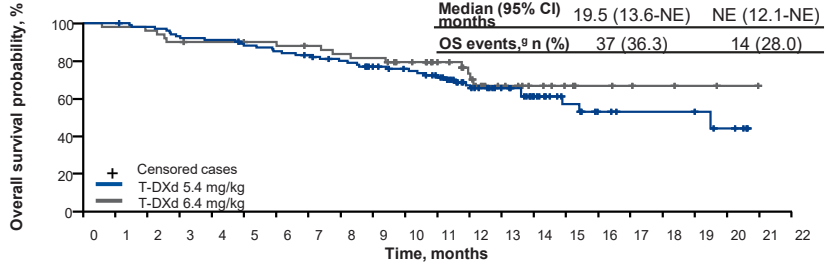
Responses observed regardless of *HER2* mutation type, *HER2* amplification status, and number or type of prior therapies

PFS



	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Median (95% CI) months	9.9 (7.4-NE)	15.4 (8.3-NE)
PFS events,[f] n (%)	44 (43.1)	20 (40.0)

OS



	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Median (95% CI) months	19.5 (13.6-NE)	NE (12.1-NE)
OS events,[g] n (%)	37 (36.3)	14 (28.0)

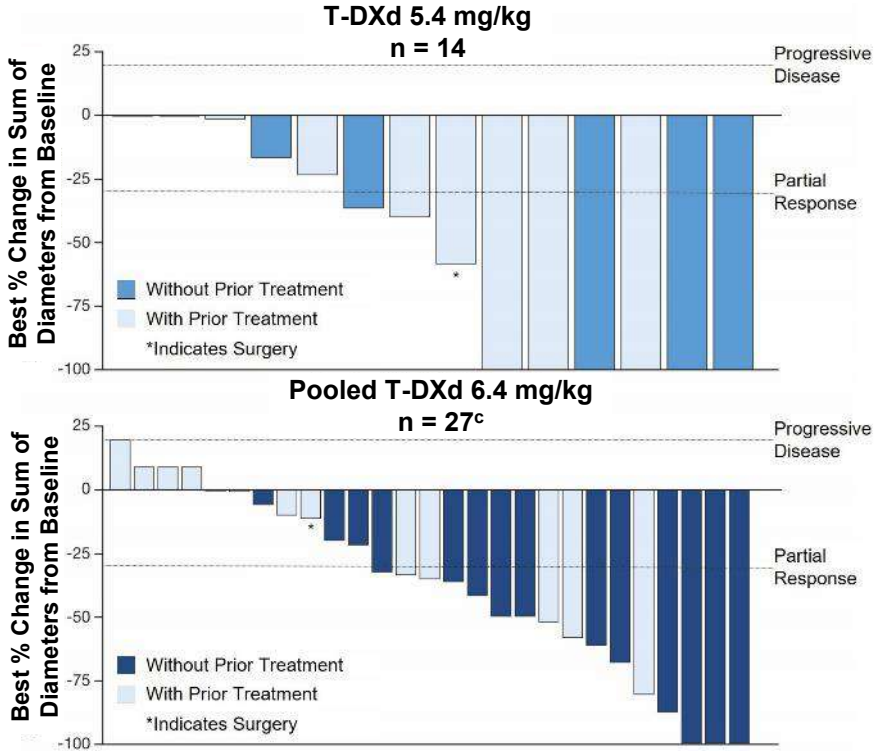
P.A.Janne et al, WCLC 2023 – JCO2023

IC Objective Response Rates & Best Overall Response (BICR)

Measurable BM at Baseline

	T-DXd 5.4 mg/kg DL-02 BM n = 14	Pooled T-DXd 6.4 mg/kg DL-01 *HER2m*/DL-02 BM n = 30
IC-cORR, n (%)[a]	**7 (50.0)**	**9 (30.0)**
95% CI[b]	23.0-77.0	14.7-49.4
CR	3 (21.4)	0
PR	4 (28.6)	9 (30.0)
SD	6 (42.9)	13 (43.3)
PD	1 (7.1)	4 (13.3)
NE[c]	0	2 (6.7)
Missing	0	2 (6.7)
IC-DCR, n (%)[a]	**13 (92.9)**	**22 (73.3)**
95% CI[b]	66.1-99.8	54.1-87.7
IC-DoR, months[d]		
Median, (95% CI)[e]	9.5 (3.6-NE)	4.4 (2.9-10.2)

12/14 (86%) patients with measurable BM receiving T-DXd 5.4 mg/kg and 21/27 (78%) in the pooled 6.4 mg/kg group experienced a reduction in brain lesion size from baseline as their best overall response



FDA and EMA approval

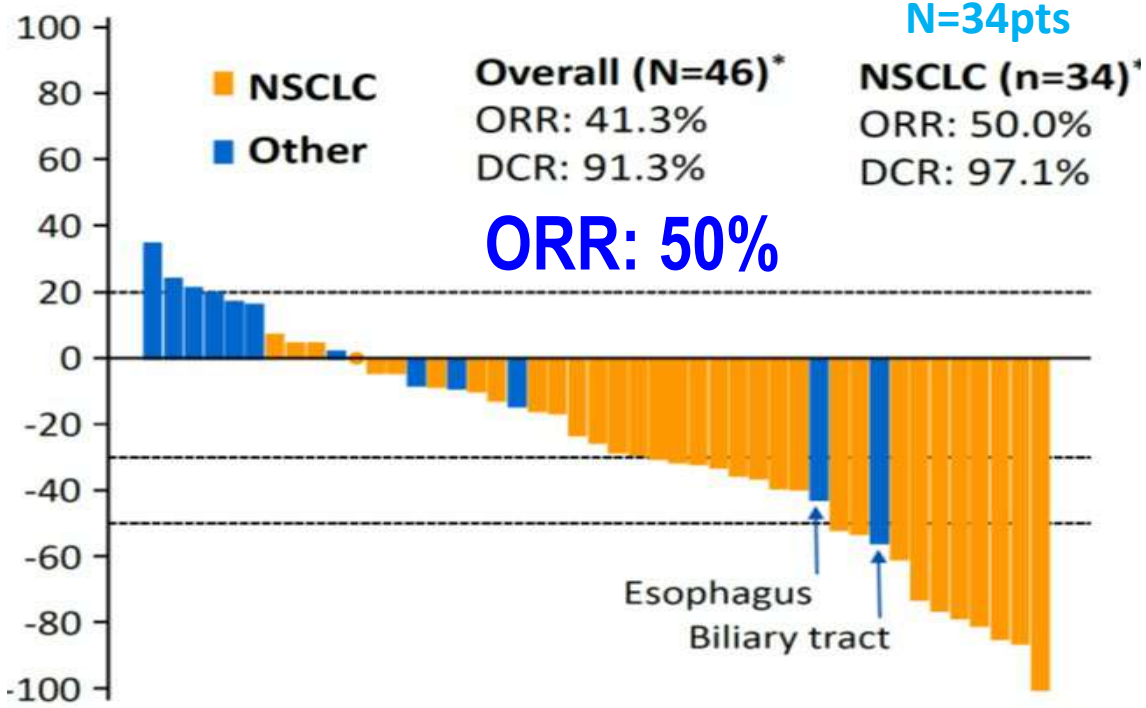
First drug approved for HER2-mutant NSCLC

On August 11, 2022, the FDA granted accelerated approval to fam-trastuzumab deruxtecan-nxki for adult patients with **unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations**, and who have received a prior systemic therapy.

September 2023, Enhertu as monotherapy is indicated for the treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy.

Drug	Study	N	Patient population	Study arm	Control arm	Endpoints
Trastuzumab-deruxtecan	DESTINY-Lung04	264	• First-line advanced NSCLC • HER2 ex19 or ex20 mutations	Trastuzumab-deruxtecan	Pembrolizumab + pemetrexed + platinum	PFS

BEAMING Lung-1, Phase I of ZONGERTINIB (BI 1810631), in pts with HER2 aberrations

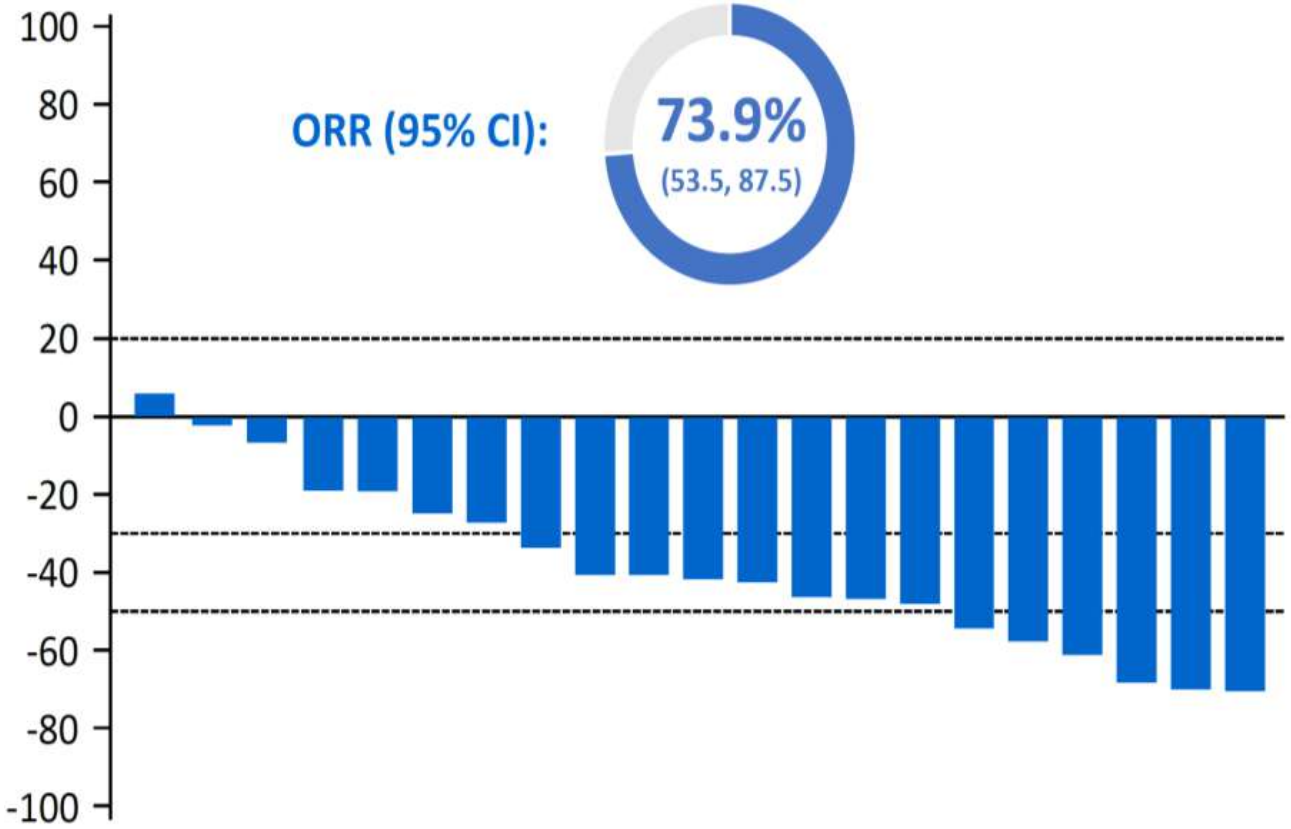


Phase Ia dose escalation and safety

Phase Ia TRAEs (%*)	Zongertinib BID (n=17)		Zongertinib QD (n=33)		Total (N=50)	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Any TRAE	**76.5**	**5.9**	**84.8**	**12.1**	**82.0**	**10.0**
Diarrhea	47.1	–	36.4	–	40.0	–
AST increased	5.9	–	18.2	3.0	14.0	2.0
Rash†	11.8	–	15.2	–	14.0	–
ALT increased	5.9	5.9	15.2	6.1	12.0	6.0
Paronychia	5.9	–	12.1	–	10.0	–
Dry skin	11.8	–	6.1	–	8.0	–
Anemia	11.8	–	6.1	–	8.0	–

N. Yamamoto et al, WCLC 2023

Antitumor activity in Phase Ib - ZONGERTINIB (BI 1810631)



Overall (N=23)*

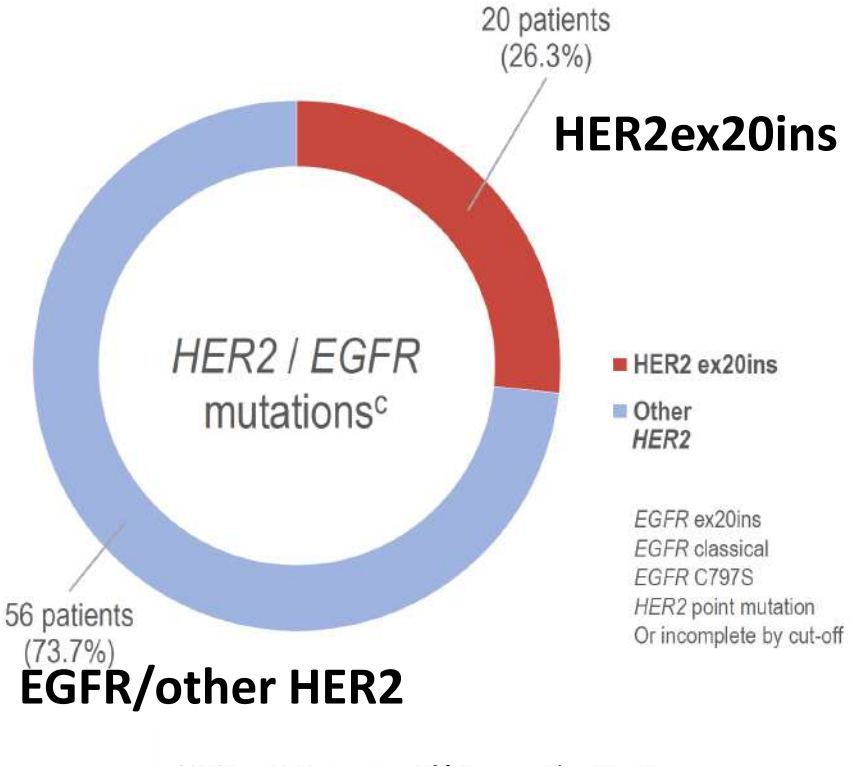
- The first interim analysis in Cohort 1 was passed
- Patients included in the efficacy analysis all had between 2–5 cycles of treatment at cut off
- DCR: 91.3%
- Median best percentage change from baseline in target lesions: -41.2%

N. Yamamoto et al, WCLC 2023

Early evidence of efficacy in pts with HER2 exon20ins in phase I with BAY292088

Patient characteristics

	All treated patients (*N*=76)
Females, *n* (%)	45 (59.2)
Median age, years (range)	60.0 (35.0-81.0)
Baseline ECOG PS, *n* (%)	
1	49 (64.5)
Patients who have never smoked, *n* (%)	55 (72.4)
Number of previous systemic anti-cancer treatments, *n* (%)	
0	2 (2.6)
1	20 (26.3)
2	16 (21.1)
≥3	38 (50.0)
NSCLC histology, *n* (%)	
Squamous cell carcinoma, small cell, non-keratinizing	1 (1.3)
Adenocarcinoma, not otherwise specified	70 (92.1)
Adenocarcinoma with mixed subtypes	1 (1.3)
Papillary adenocarcinoma, not otherwise specified	1 (1.3)
Missing	3 (3.9)
Median time since initial diagnosis, months (range)[a]	28.2 (2.1-195.2)
Median time since most recent progression / relapse to first administration of study treatment, months (range)[b]	1.5 (0-30.0)



Herbert H.Loong et al, ESMO 2023

Best % change in target lesion size across all dose levels

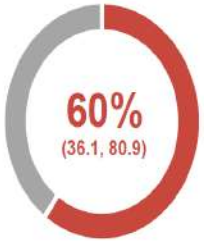
N=69pts

All patients

ORR (95% CI)

N=20pts

HER2 ex20ins



ORR (95% CI)

ORR: 60%

n (%)	All evaluable patients[a] (*n*=69)	*HER2* ex20ins subgroup[b] (*n*=20)
CR	1 (1.4)	1 (5.0)
PR	13 (18.8)	8 (40.0)
uPR	4 (5.8)	3 (15.0)
SD[c]	27 (39.1)	6 (30.0)
PD	20 (29.0)	1 (5.0)
NE	3 (4.3)	1 (5.0)
NA[d]	1 (1.4)	0
ORR	**18 (26.1)**	**12 (60.0)**
95% CI	**16.3, 38.1**	**36.1, 80.9**
DCR[e]	38 (55.1)	16 (80.0)
95% CI	42.6, 67.1	56.3, 94.3

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Dose escalation / backfill: safety

n (%)	All grades (*N*=76)	Grade ≥3 (*N*=76)
Any TRAE	66 (86.8)	19 (25.0)
Most common TRAEs occurring in ≥10% of patients		
Diarrhea	57 (75.0)	12 (15.8)
Paronychia	19 (25.0)	0
Dry skin	17 (22.4)	0
Dermatitis acneiform	16 (21.1)	0
Stomatitis	14 (18.4)	1 (1.3)
Pruritus	12 (15.8)	2 (2.6)
Vomiting	12 (15.8)	1 (1.3)
Rash	12 (15.8)	0
Decreased appetite	11 (14.5)	0
Increased amylase	11 (14.5)	2 (2.6)
Nausea	10 (13.2)	0
Hypokalemia	10 (13.2)	5 (6.6)
Increased alanine aminotransferase	8 (10.5)	2 (2.6)

Safety summary

- 76 patients have been treated in dose-escalation / backfill cohorts at the cut-off
- 5 patients with dose-limiting toxicities (3/5 in 40 mg BID, 1/9 in 30 mg BID, and 1/5 in 60 mg QD)
- No discontinuation due to TRAEs
- 20 patients (26.3%) with dose reductions due to TRAEs
- 2 patients (2.6%) with serious TRAEs (diarrhea, vomiting)
- Most AEs were reversible and manageable

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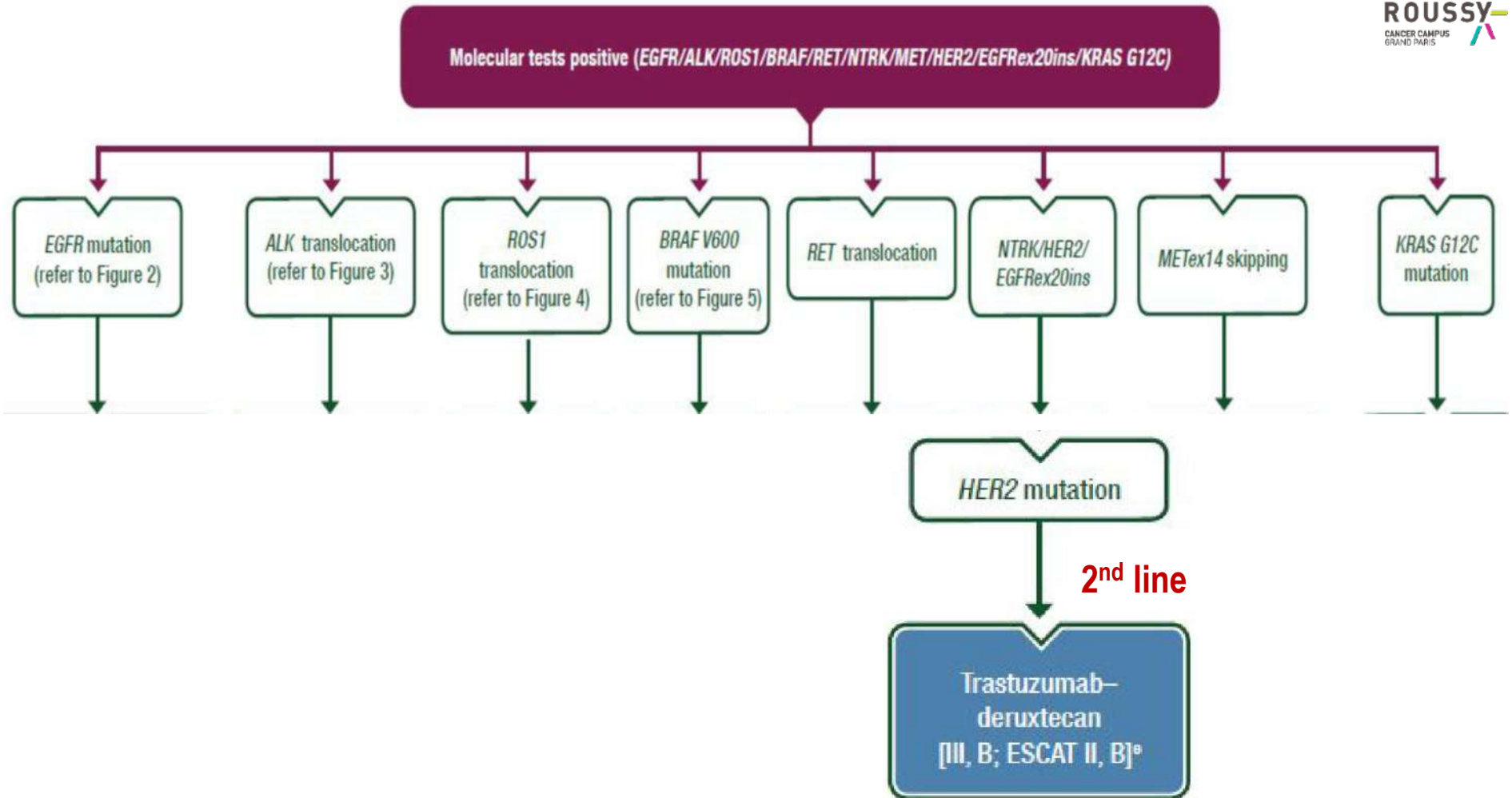
Next Generation of EGFRwt sparing HER2 TKIs

Investigational Compounds	IC50	NCT Number	Trial Status	Indication	Sponsor
ELVN-002[2,3]	4.2 nM	NCT05650879	Phase 1 Recruiting	Advanced/metastatic *HER2* mutation–positive NSCLC	Enliven Therapeutics
JIN-A04[4,5]	11.1 nM	N/A	Preclinical	N/A	J INTS BIO
NVL-330[6]	<20 nM	N/A	Preclinical	N/A	Nuvalent
ENT-H1[7]	NR	N/A	Preclinical	N/A	Entos

2. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05650879. Accessed July 25, 2023; 3. Aujay M, et al. Presented at the AACR Annual Meeting 2023, Orlando, USA, April 14–19, 2023. Poster 4019; 4. Yu M, et al. Presented at the AACR Annual Meeting 2023, Orlando, USA, April 14–19, 2023. Abstract 4029; 5. Chang M. Korea Biomedical Review. Accessed on July 27, 2023; 6. Andrews KL, et al. *Eur J Cancer*. 2022;174S1:S3–S128. 7. Zhao, C, et al. Presented at the AACR Annual Meeting 2023, Orlando, USA, April 14–19, 2023. Poster 4034.

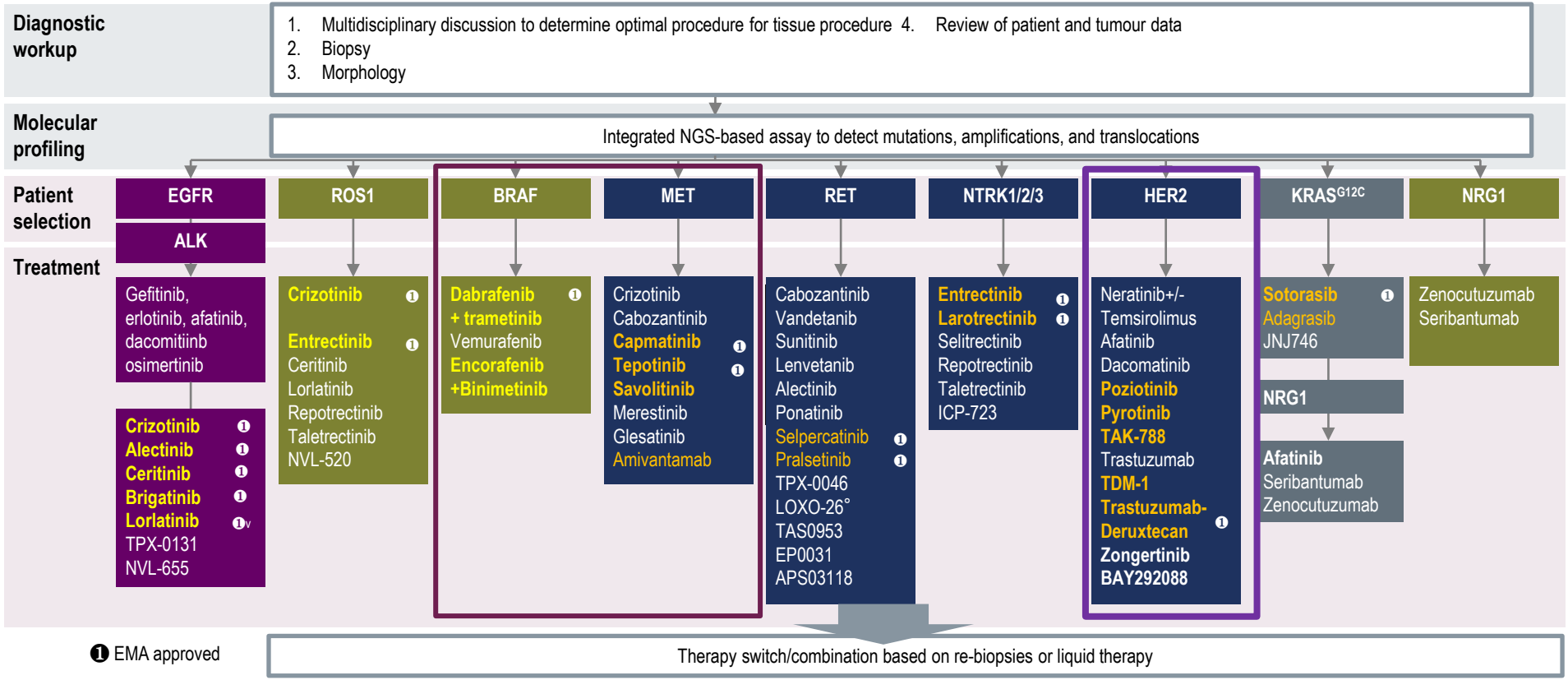


L. E. Hendriks, K. Kerr, J. Menis, T. S. Mok, U. Nestle, A. Passaro, S. Peters, D. Planchard, E.F Smit, B. J. Solomon, G. Veronesi & M. Reck, Annals of onco 2023

GREAT ADVANCES HAVE BEEN MADE IN LUNG CANCER THERAPY FOR BRAF, MET AND HER2…

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

Personalised therapy in advanced-stage NSCLC



THANK YOU !

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