



2019 AIOM REVIEW: FROM CHICAGO TO VERONA

JUNE 14-15 2019

Verona,
Palazzo della Gran Guardia
Piazza Bra, 1



LUNG CANCER Highlights

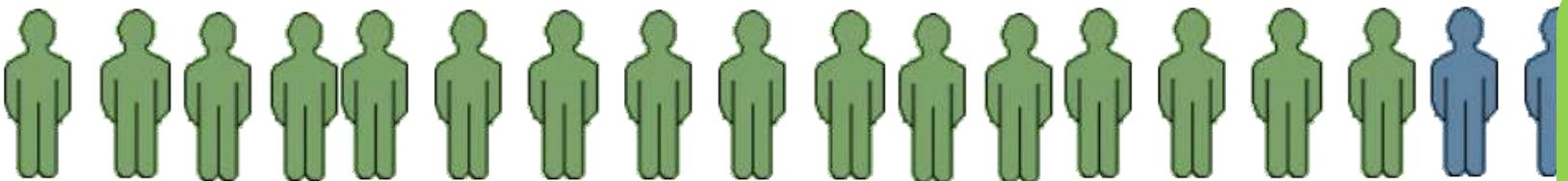
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Disclosures

- **Advisory Boards / Honoraria / Speakers' fee / Consultant for:**
 - Astra-Zeneca, BMS, Boehringer Ing., Eli Lilly, MSD, Pfizer, Roche
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 - AIRC (Associazione Italiana Ricerca sul Cancro)
 - ESMO (European Society for Medical Oncology)

What's new for wild type and oncogene-addicted NSCLC?

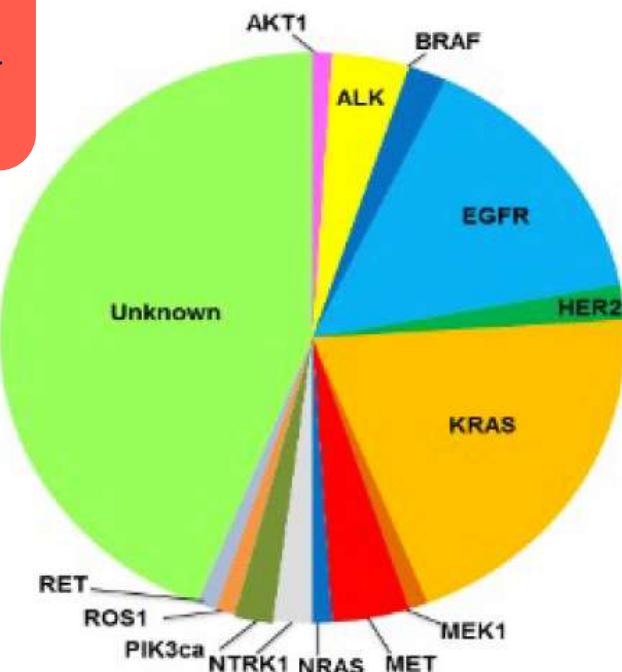


Potentially practice-changing
- Diagnostic process
- Treatment algorithm

Intriguing translational studies
but pCR and MPR with chemo-
IO more attractive

- **IO in neoadjuvant setting**
 - atezo
 - nivo vs. nivo+ipi
- **Maintenance antiangiogenics**

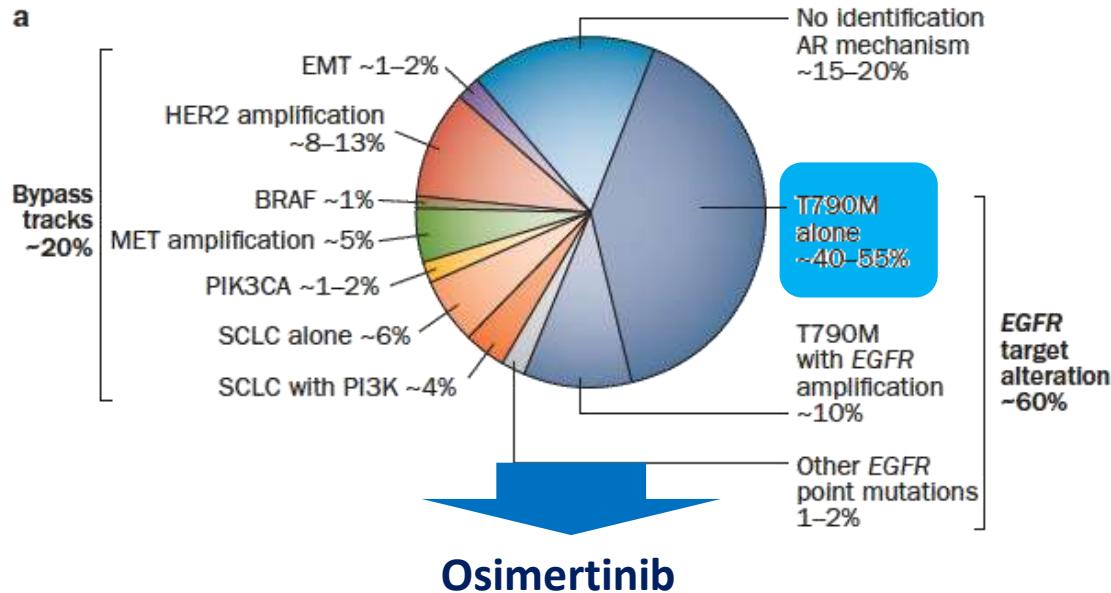
Not practice-changing



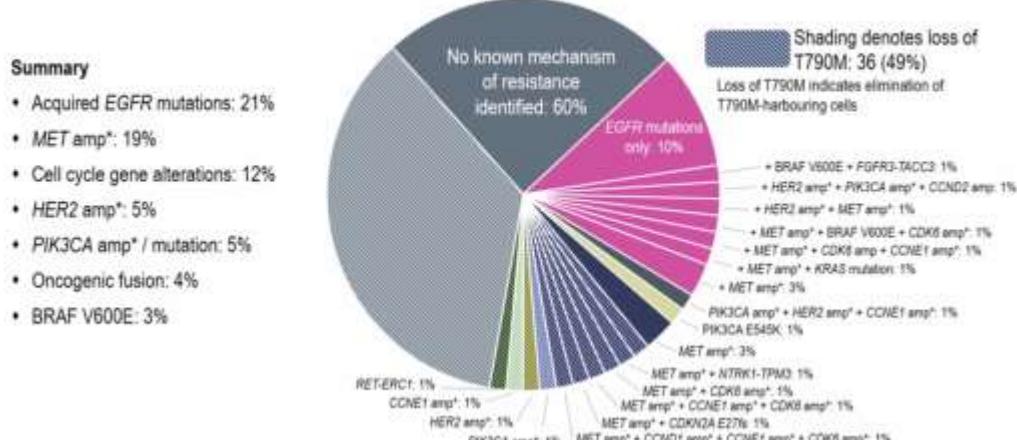
- **Old target and resistance targeting (sensitizing EGFR)**
 - TKI + antiangiogenic
 - TKI + chemo
 - HER3 Ab
 - Bispecific antibody
- **Uncommon old target (ex 20 EGFR)**
 - TAK-788
- **New targets (MET muts and RET fus)**
 - Capmatinib, Tepotinib
 - BLU-667

Old target and new resistance targeting: EGFR

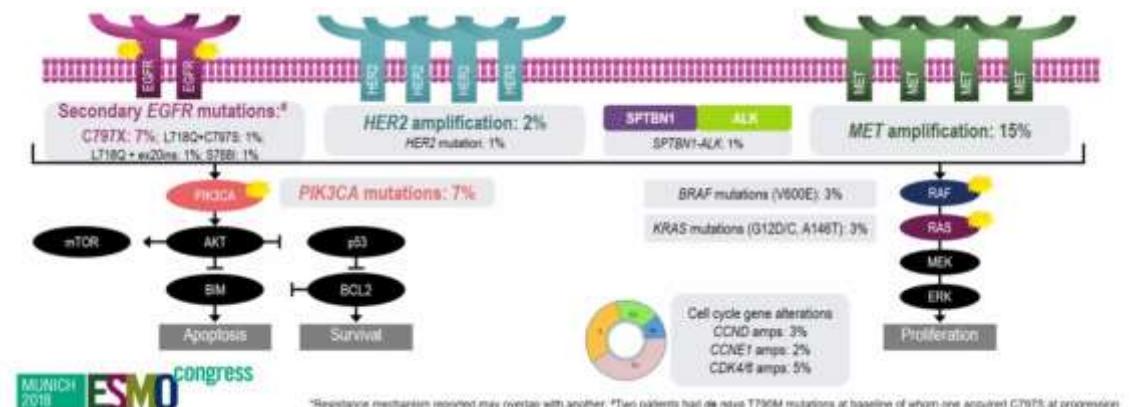
Gefitinib, Erlotinib, Afatinib



Acquired resistance mechanisms post-osimertinib (n=73)

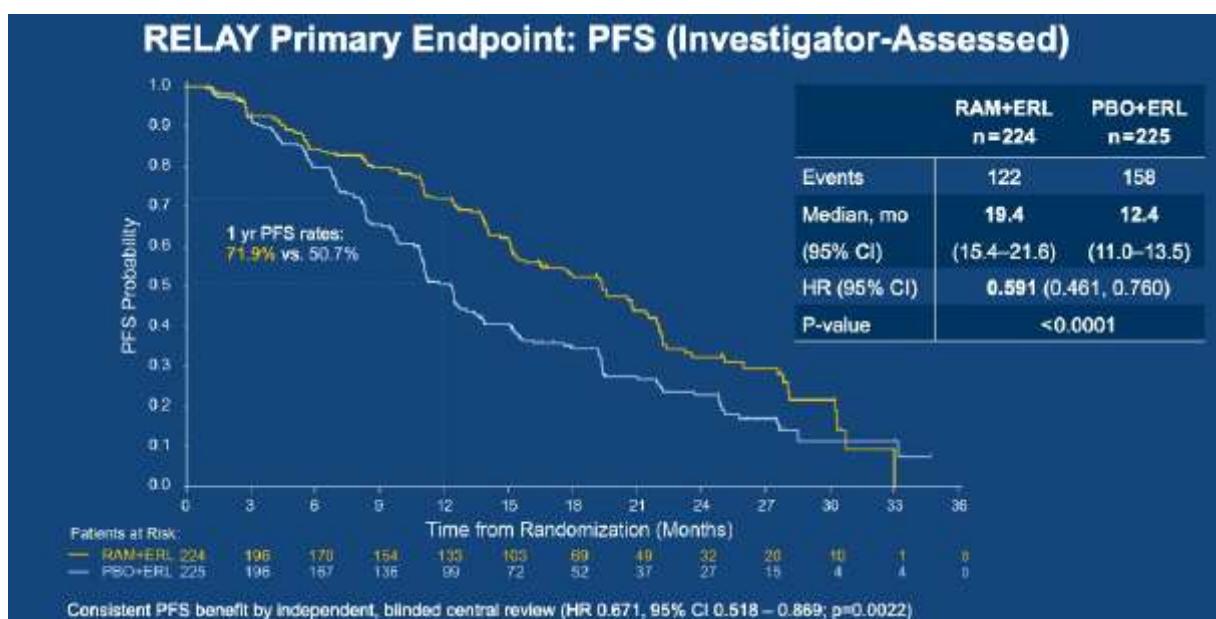
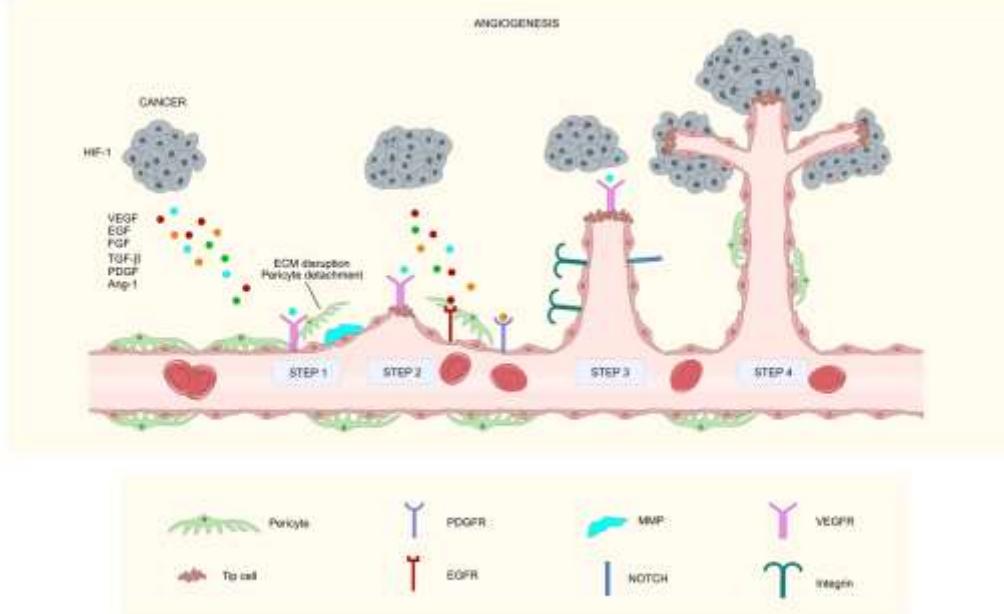
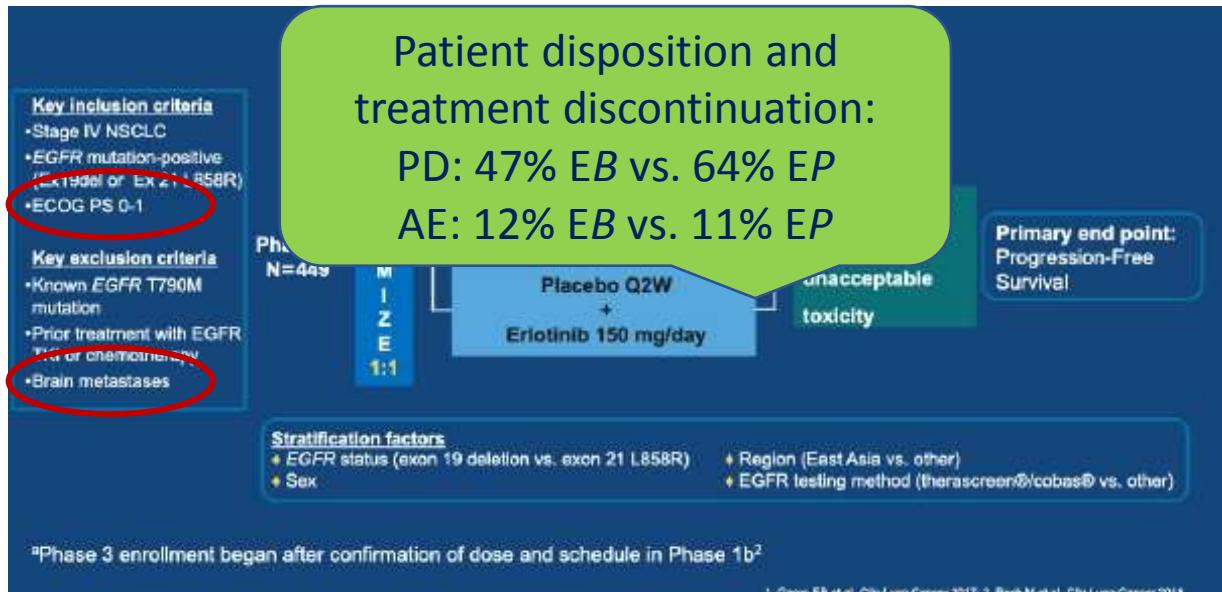


Osimertinib



- ✓ **How to delay and target on-target resistance mechanisms?(FLAURA, ARCHER1050, what else?)**
- ✓ **Unmet need for off-target resistance bypass (and for on-target after Osimertinib!)**

First generation EGFR TKI + anti-VEGFR2: RELAY STUDY



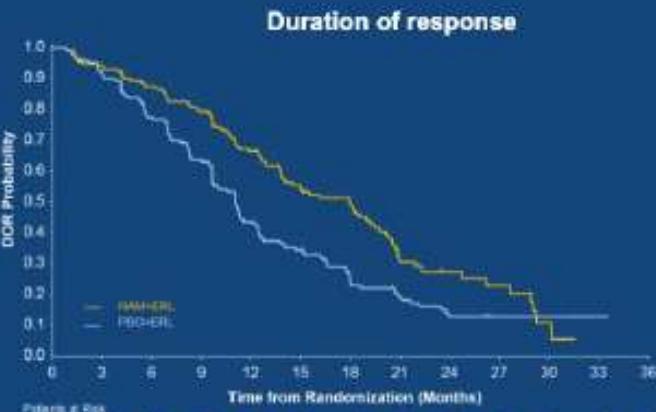
Ex19del	RAM+ERL (n=123)	PBO+ERL (n=120)
Events	64	84
Median, mo	19.6	12.5
(95% CI)	(15.1–22.2)	(11.1–15.3)
HR (95% CI)	0.651 (0.469, 0.903)	

Ex21.L858R	RAM+ERL (n=99)	PBO+ERL (n=105)
Events	58	74
Median, mo	19.4	11.2
(95% CI)	(14.1–21.9)	(9.6–13.8)
HR (95% CI)	0.618 (0.437, 0.874)	

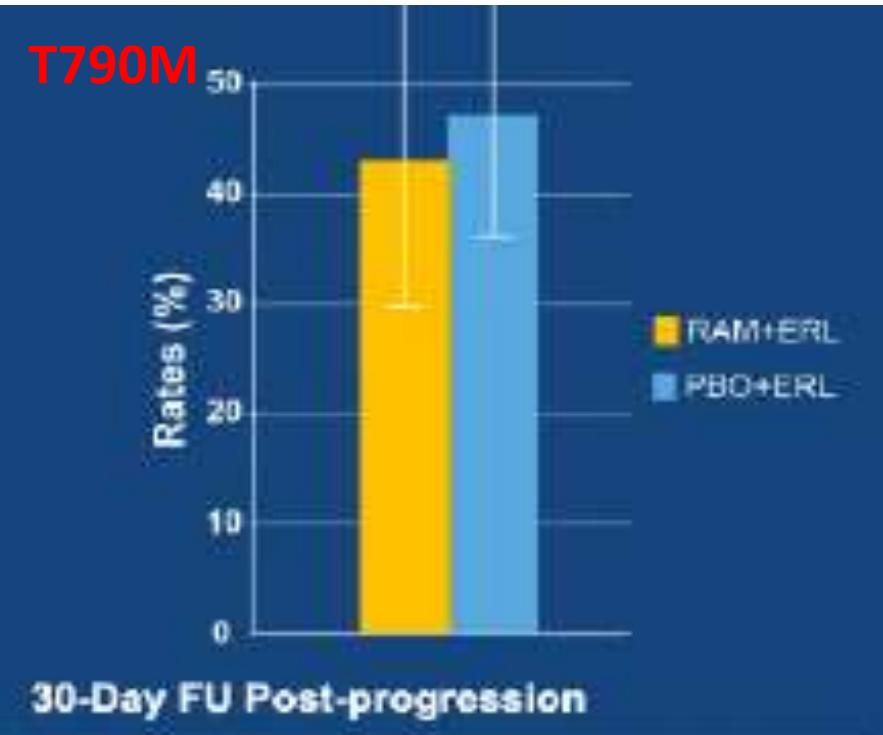
Benefit across all subgroups: liver mets yes 0.48 vs. no 0.65

First generation EGFR TKI + anti-VEGFR2: RELAY STUDY

	RAM+ERL N=224	PBO+ERL N=225
ORR % (95% CI)	76 (71–82)	75 (69–80)
DCR % (95% CI)	95 (92–98)	96 (93–98)
Duration of Response	N=171	N=168
Events	101 (59)	128 (76)
Median, mo (95% CI)	18.0 (13.9–19.8)	11.1 (9.7–12.3)
HR (95% CI)	0.619 (0.477, 0.805)	



	RAM+ERL N=224	PBO+ERL N=225
PFS2		
Events,	61	79
Censoring rate	73%	65%
Median, mo	NR	NR
HR (95% CI)	0.690 (0.490, 0.972)	
Interim OS		
Events	37	42
Censoring rate	83%	81%
Median, mo	NR	NR
HR (95% CI)	0.832 (0.532, 1.303)	



	RAM+ ERL	PBO+ERL
T790M (+)/patients with results	19/44	35/75
T790M rates (95% CI)	43 (30, 58)	47 (36, 58)
P-value		0.849

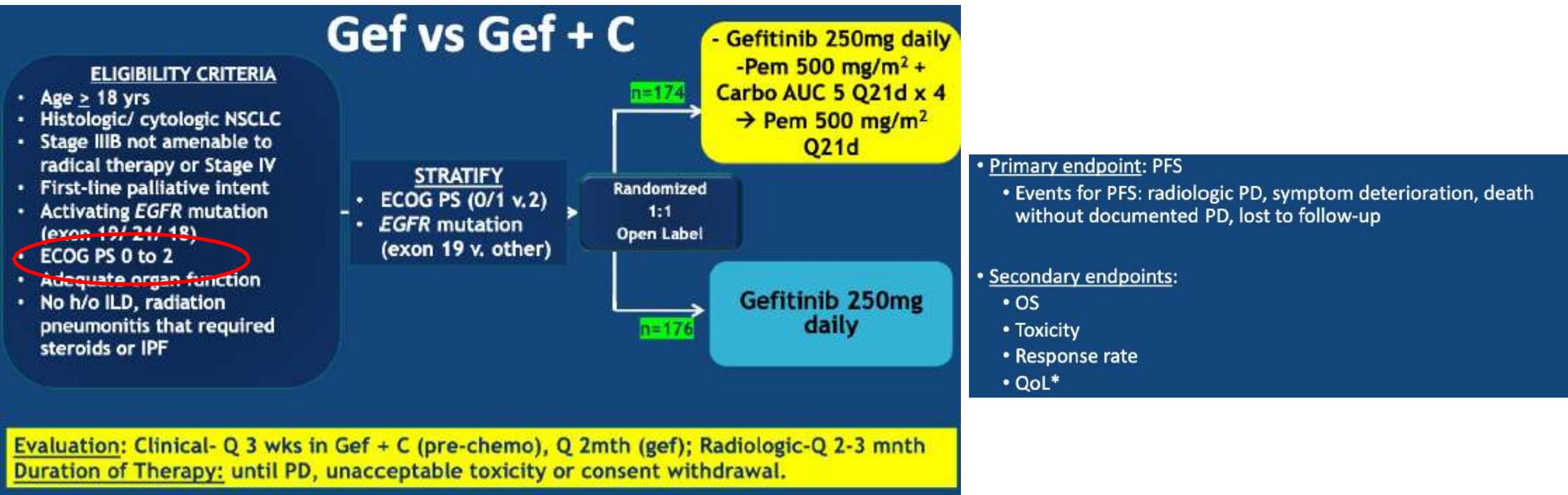
First generation EGFR TKI + anti-VEGFR2: RELAY STUDY

Preferred Term, n (%)	RAM+ERL (N=221)				PBO+ERL (N=225)			
	Any Grade	Grade 1/2	Grade 3	Grade 4	Any Grade	Grade 1/2	Grade 3	Grade 4
At least one TEAE	221 (100)	62 (28)	142 (64)	11 (5)	225 (100)	104 (46)	111 (49)	9 (4)
Diarrhea	155 (70)	139 (63)	16 (7)	0	160 (71)	157 (70)	3 (1)	0
Acneiform dermatitis	149 (67)	116 (53)	33 (15)	0	153 (68)	133 (59)	20 (9)	0
Paronychia	118 (53)	109 (49)	9 (4)	0	114 (51)	107 (48)	7 (3)	0
Hypertension	100 (45)	48 (22)	52 (24)	0	27 (12)	15 (7)	12 (5)	0
Increased ALT	94 (43)	75 (34)	17 (8)	2 (1)	70 (31)	53 (24)	14 (6)	3 (1)
Increased AST	92 (42)	81 (37)	11 (5)	0	58 (26)	48 (21)	9 (4)	1 (0.4)
Stomatitis	92 (42)	88 (40)	4 (2)	0	82 (36)	79 (35)	3 (1)	0

- G≥3 TEAEs: 72% vs. 54%
- SAEs 29% vs. 21%
- TEAEs → dose adjustment 85% vs. 71%
- TEAEs → death 1% vs. 0%

n (%)	RAM+ERL N=221		PBO+ERL N=225	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Bleeding/Hemorrhage Events				
Epistaxis	121 (55)	4 (2)	59 (26)	4 (2)
GI Hemorrhage Events ^a	74 (34)	0	27 (12)	0
Pulmonary Hemorrhage Events	23 (10)	3 (1)	6 (3)	1 (<1)
Hypertension	15 (7)	1 (<1)	4 (2)	1 (<1)
Proteinuria ^b	100 (45)	52 (24)*	27 (12)	12 (5)
Liver Failure/Liver Injury	76 (34)	6 (3)	19 (8)	0
Increased ALT	140 (63)	31 (14)	120 (53)	28 (12)
Increased blood bilirubin	94 (43)	19 (9)	70 (31)	17 (8)
Infusion-related reactions	68 (31)	3 (1)	70 (31)	2 (1)
Other TEAE of interest:	6 (3)	0	4 (2)	0
ILD events ^c	4 (2)	1 (<1)	7 (3)	3 (1)

First generation EGFR TKI + chemotherapy

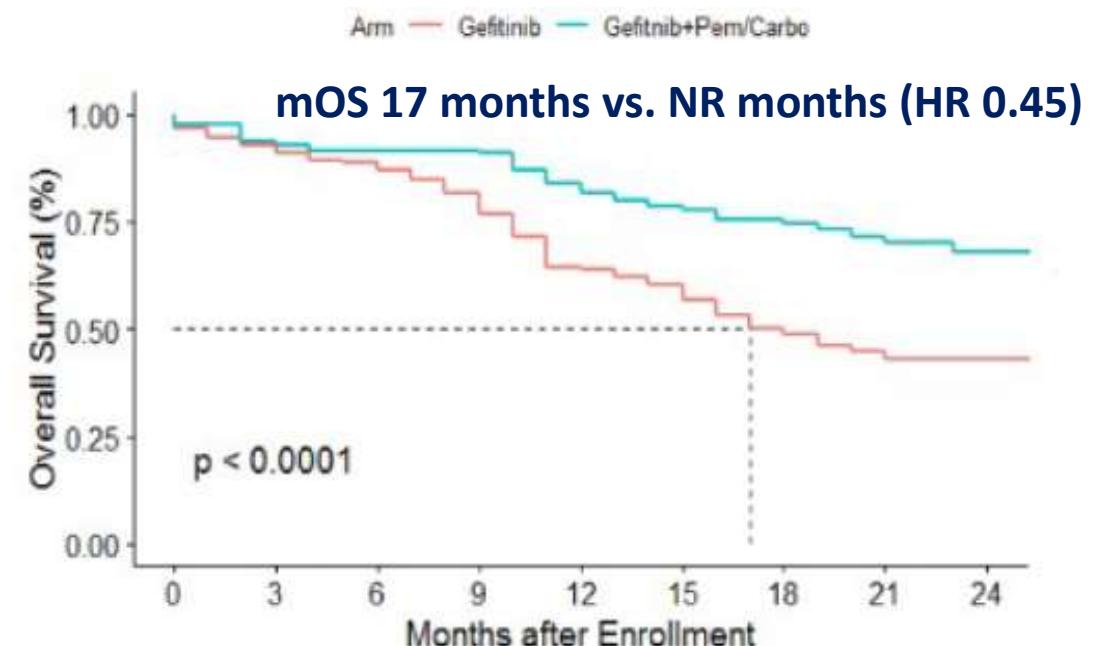
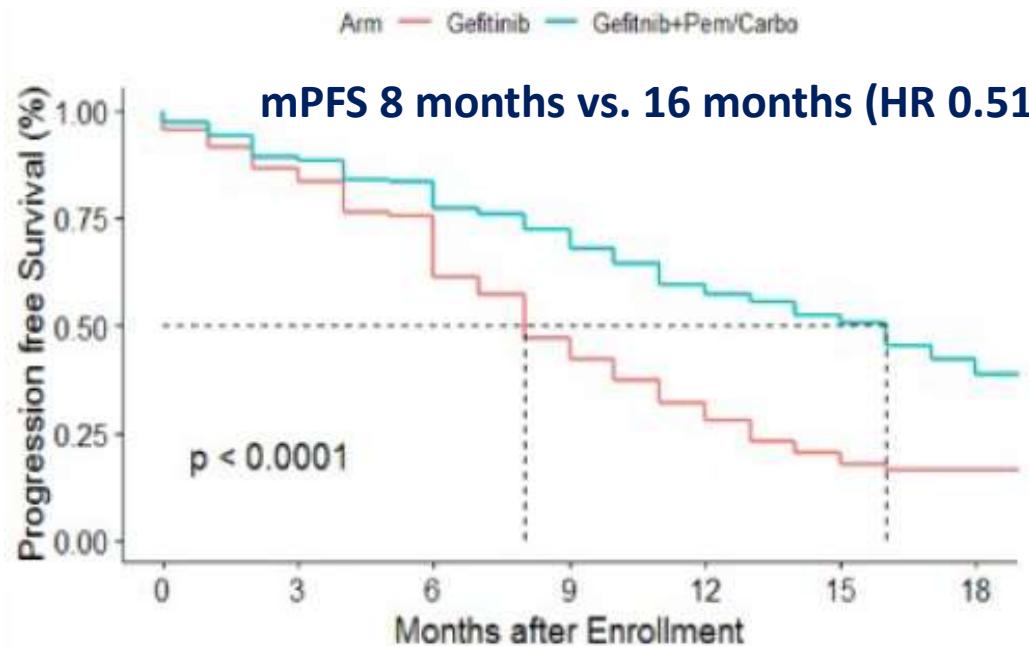


First generation EGFR TKI + chemotherapy

	Gef + C (n=174)	Gef (n=176)
Age in years: Median (Range)	54 (27-75)	56 (27-78)
Male sex-No. (%)	88 (51)	93 (53)
<u>Smoking history-No. (%)</u>		
• Never	145 (83)	150 (85)
• Former	19 (11)	21 (12)
• Current	10 (6)	5 (3)
<u>ECOG PS-No. (%)</u>		
• 0	1 (1)	7 (4)
• 1	137 (79)	130 (74)
• 2	36 (21)	39 (22)
<u>Comorbidities-No. (%)</u>		
• None	97 (56)	81 (46)
• Hypertension	21 (12)	32 (18)
• Diabetes mellitus	9 (5)	9 (5)
• COPD/ emphysema	8 (5)	5 (3)
• Prior tuberculosis	4 (2)	5 (3)
• Multiple (>1)	23 (13)	35 (20)
• Other	12 (7)	9 (5)

	Gef + C (n=174)	Gef (n=176)
<u>Histology-No. (%)</u>		
• Adenocarcinoma	170 (98)	170 (97)
• Adenosquamous	3 (2)	4 (2)
• Squamous cell CA	1 (1)	1 (1)
• Sarcomatoid CA	0	1 (1)
<u>Disease stage-No. (%)</u>		
• IV	171 (98)	171 (97)
• IIIB	3 (2)	5 (3)
<u>Metastatic site-No. (%)</u>		
• Pleura/ pericardium	30 (17)	25 (14)
• Opposite lung	20 (12)	18 (10)
• Non-regional LNs	2 (1)	5 (3)
• Bones	24 (14)	25 (14)
• Brain	2 (1)	13 (7)
• Liver/ adrenal/ omentum	3 (2)	2 (1)
• Multiple (>1)	90 (52)	83 (47)
• Non-metastatic	3 (2)	5 (3)
<u>Presence of brain metastases-No. (%)</u>	30 (17)	34 (19)
<u>Presence of pulmonary embolism-No. (%)</u>	7 (4)	2 (1)

First generation EGFR TKI + chemotherapy



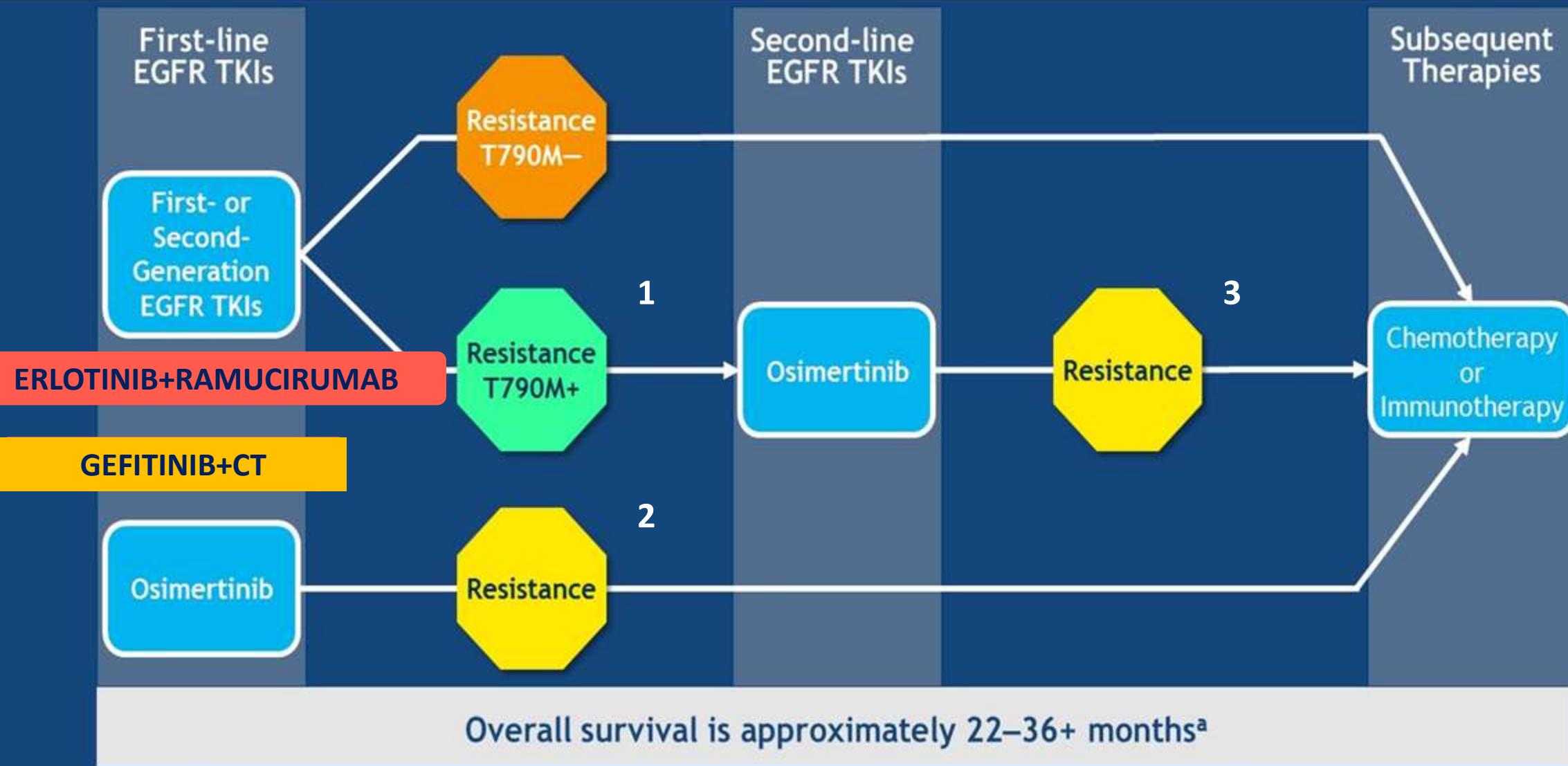
	Gef + C arm (n=174)	Gef arm (n=176)	P-value
No. of pts who had restaging scans-No. (%)	162 (93)	161 (92)	
Best radiologic response-No. (%)			
• CR	5 (2.9)	1 (0.6)	
• PR	126 (72.4)	109 (61.9)	
• SD	22 (12.6)	39 (22.2)	
• PD	9 (5.2)	12 (6.8)	
ORR (CR + PR)	75.3% (95% CI, 68.3 to 81.1)	62.5% (95% CI, 55.1 to 69.3)	0.01
Median depth of response	-56.4 (IQR, -41.2 to -69)	-43.5 (IQR, -25.2 to -60)	0.002

First generation EGFR TKI + chemotherapy

OVERALL TOXICITIES	Gef + C arm (n=164)	Gef arm (n=170)	P-value
All ≥ grade 3 toxicities	123 (75%, 95% CI, 67.8 to 81)	84 (49.4%, 95% CI, 42 to 56.9)	<0.001
Clinically relevant ≥ gr 3 toxicities (excluding asympt lab abnormalities)	83 (50.6%, 95% CI, 43 to 58.2)	43 (25.3%, 95% CI, 19.4 to 32.4)	<0.001
Fatal toxicities	1 (0.6%)-FN	1 (0.6%)-ILD	1.0
Discontinuation due to toxicities • Pemetrexed • Gefitinib	30 (16.7%) 0	N/A 2 (1.1%)	

- Anemia, thrombocytopenia, neutropenia
- Hypokalemia
- Nephrotoxicity

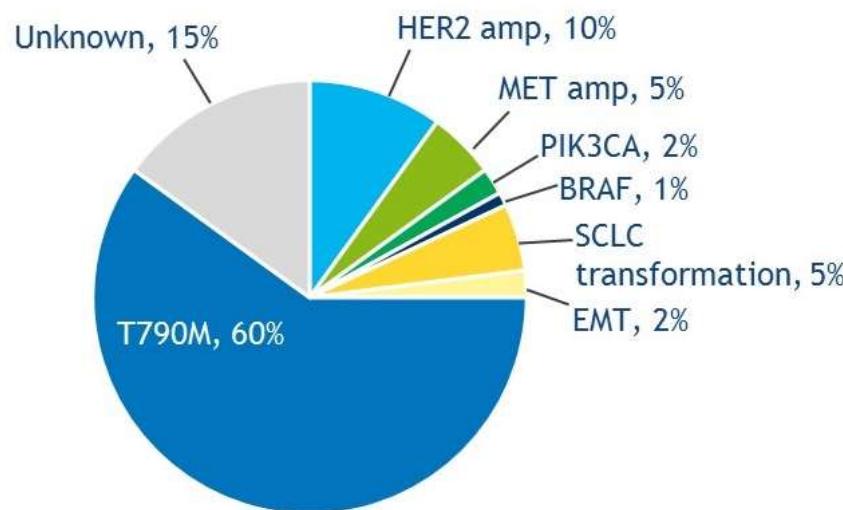
EGFR TKI Resistance Creates a Significant Unmet Need in Metastatic EGFR-mutant NSCLC



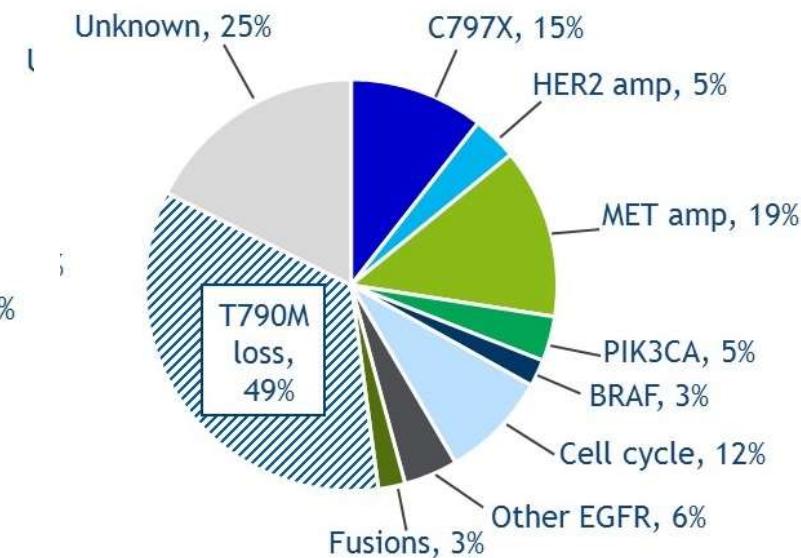
^aEstimates of patients who have progressed on EGFR TKIs and chemotherapy from Tan CS, et al. *Mol Cancer*. 2018;17:29. References: Planchard D, et al. *Ann Oncol*. 2018;29:iv192-iv237. Ettinger DS, et al. *J Natl Compr Canc Netw*. 2017;15:504-535. Jänne PA, et al. *Lancet Oncol*. 2014;15:1433-1441. EGFR, epidermal growth factor receptor; NSCLC, nonsmall cell lung cancer; TKI, tyrosine kinase inhibitor.

Old target and new resistance targeting

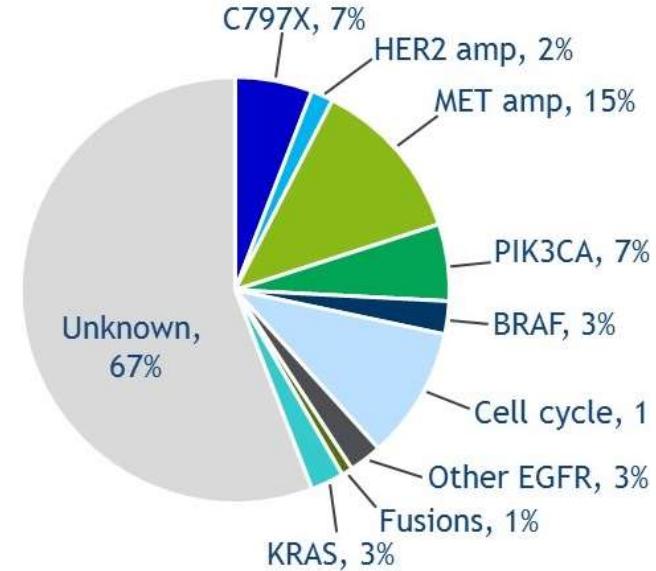
1 Gefitinib/Erlotinib/Afatinib



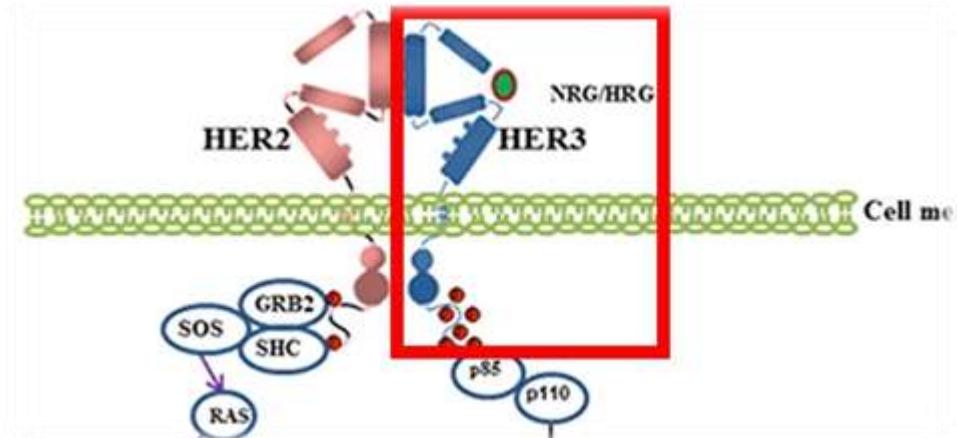
2 Osimertinib second-line



3 Osimertinib first-line



HER3 expression: 57-67%
in EGFRm resistant NSCLC



U3-1402

U3-1402, a Novel Antibody Drug Conjugate Designed to Target HER3 Expression in EGFR-mutant NSCLC

U3-1402 Design Features

Payload MOA: Topo I inhibitor

High potency of payload

High drug-to-antibody ratio (~8:1)

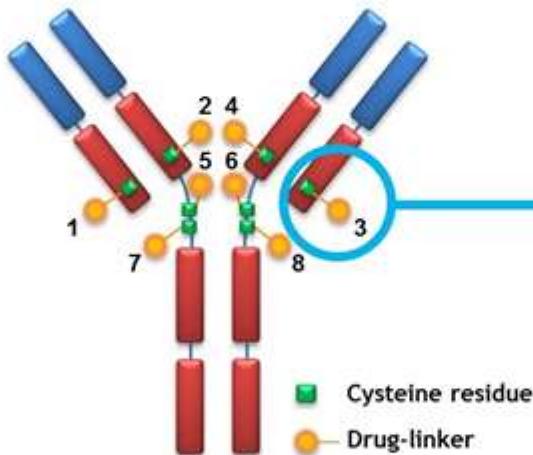
Payload with short systemic half-life

Stable linker-payload

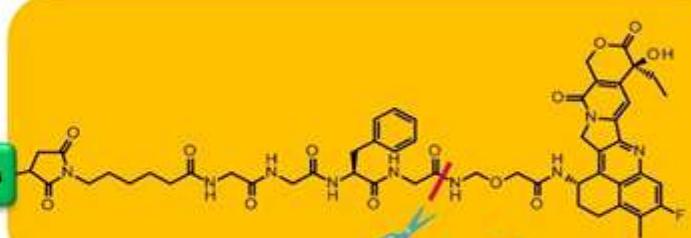
Tumor-selective cleavable linker

Bystander effect

Anti-HER3 antibody

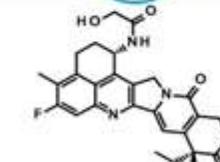


Proprietary drug-linker and payload



Conjugation chemistry

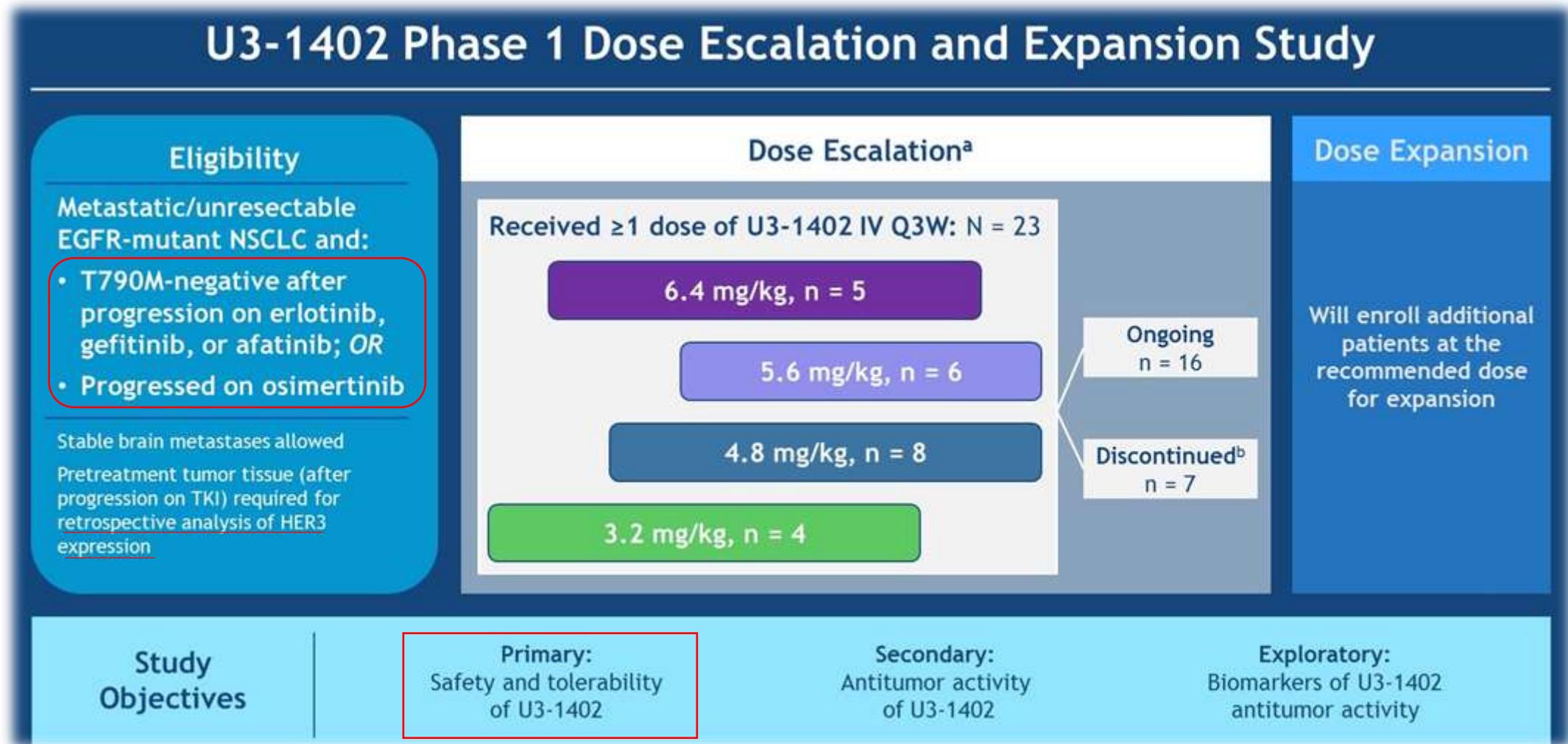
The drug-linker is conjugated to the antibody via cysteine residues



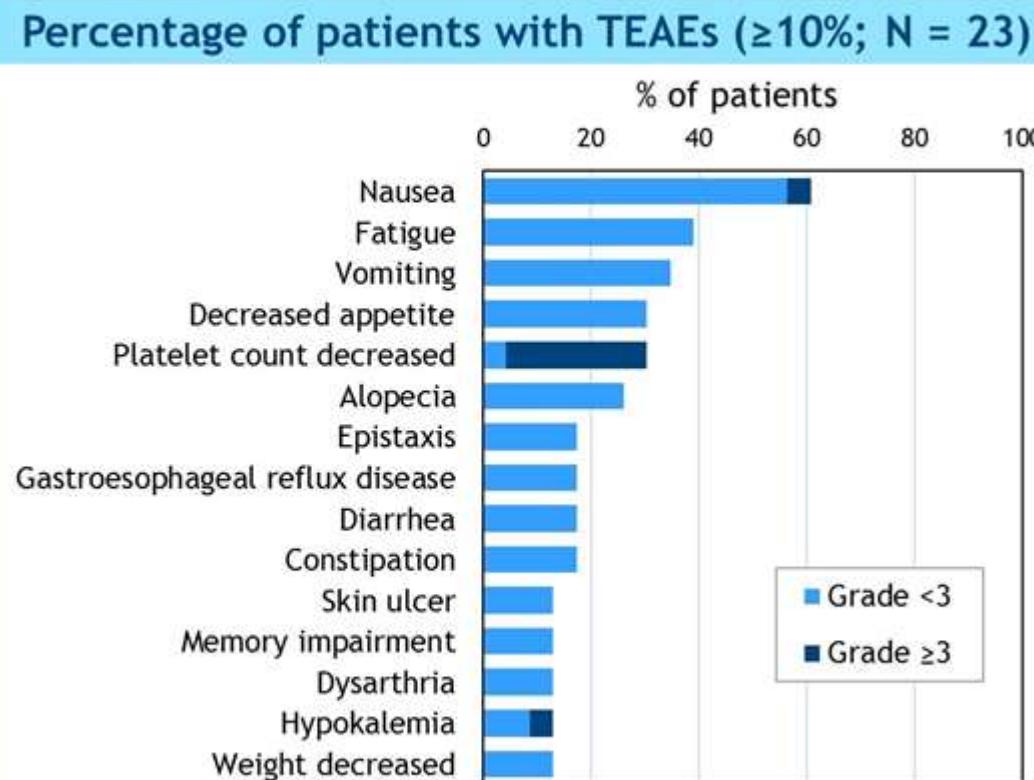
Payload (DXd)
Exatecan derivative

Topoisomerase I inhibitor

U3-1402



TEAEs and DLTs in Patients Treated with U3-1402



Dose-limiting toxicities (N = 23)

Data cutoff date of February 25, 2019. TEAE analysis used the safety analysis set, which includes all patients who received ≥ 1 dose of U3-1402 (N = 23). For TEAEs in $<10\%$ of patients, there were five Grade 3 events: ALT increased n = 1; troponin increased n = 1; confusional state n = 1; hypoxia n = 1; febrile neutropenia n = 1. DLT, dose-limiting toxicity.

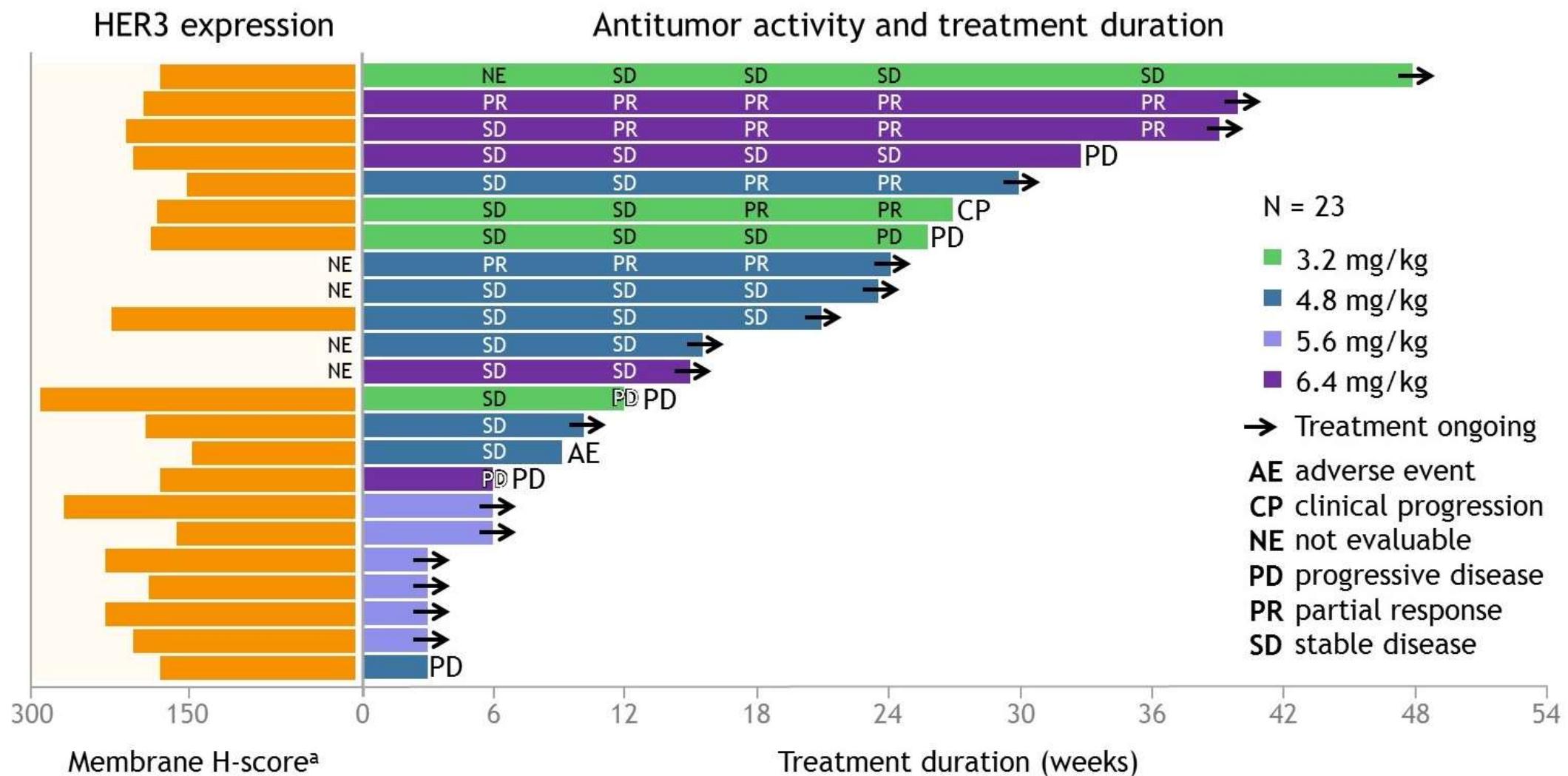
TR-AEs: 95%

TR-SAEs: 13%

TEAEs → drug discontinuation: 4.3%

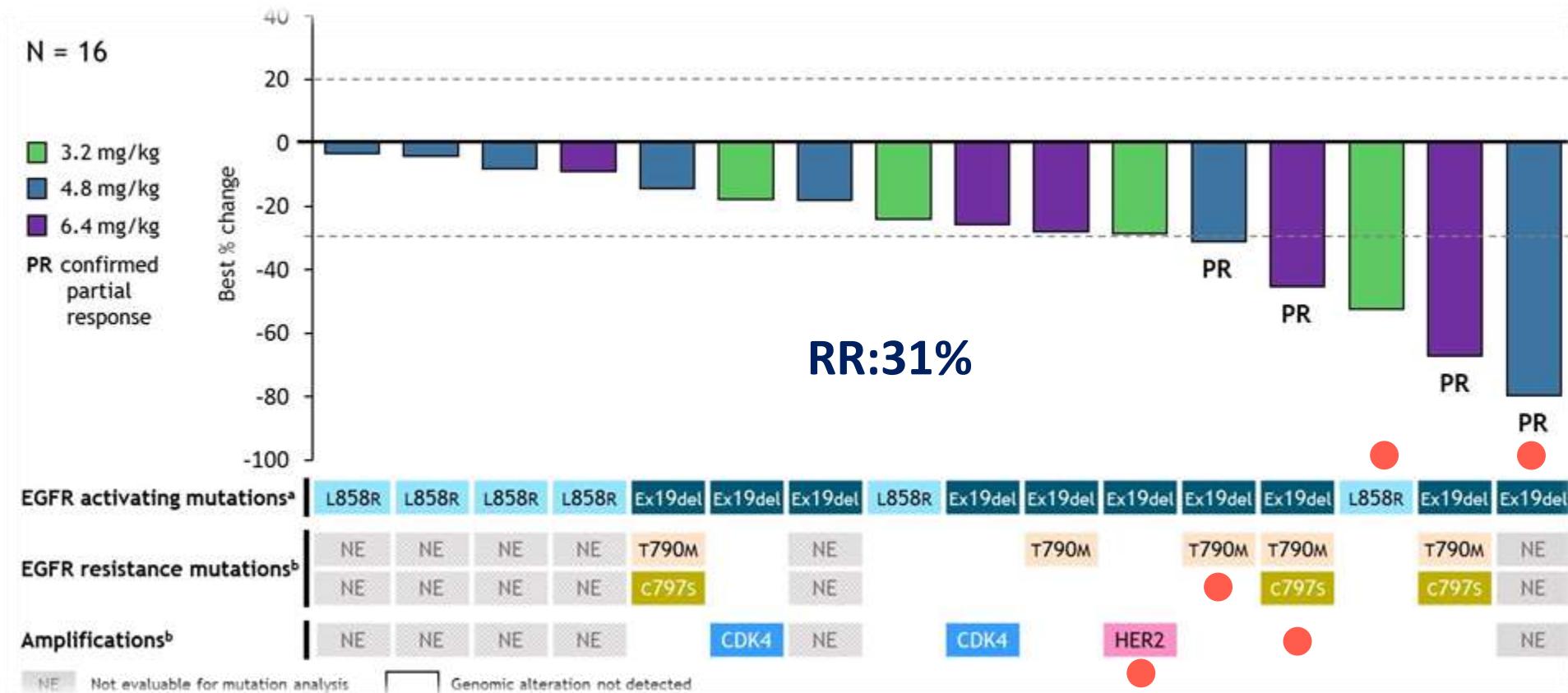
TEAEs → drug dose reduction: 30.4%

U3-1402

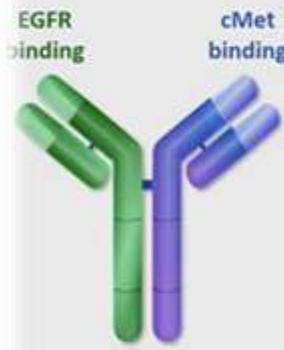


Median membrane H-score (0-300): 193

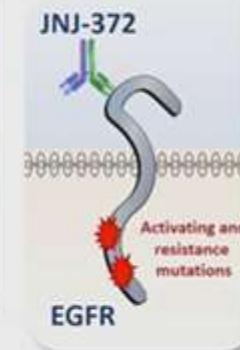
U3-1402



JNJ-372

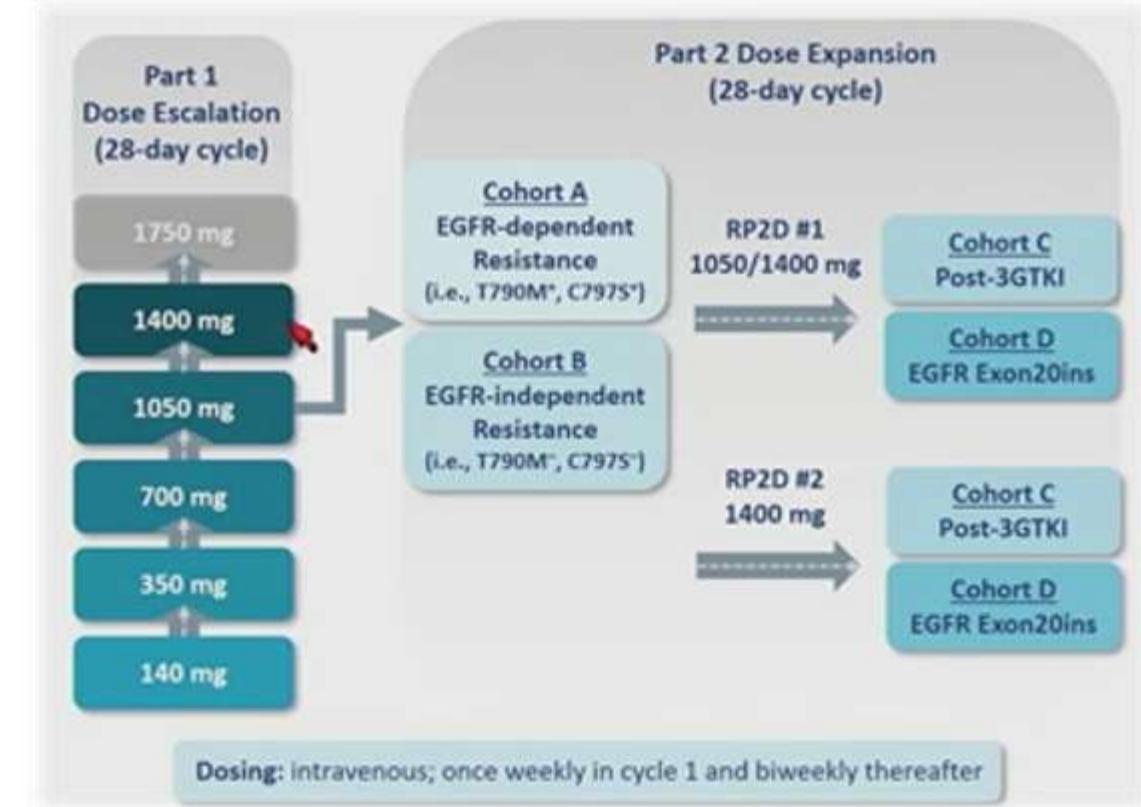


- Fully humanized, bispecific IgG1 antibody
- Targets EGFR and cMet receptors through unique mechanisms of action
- Potential to provide clinical benefit in EGFR-driven NSCLC, including TKI-resistant populations
- First-in-human study currently evaluating activity in EGFRmut-driven NSCLC



Pre-Osimertinib cohorts

Post-Osimertinib cohorts



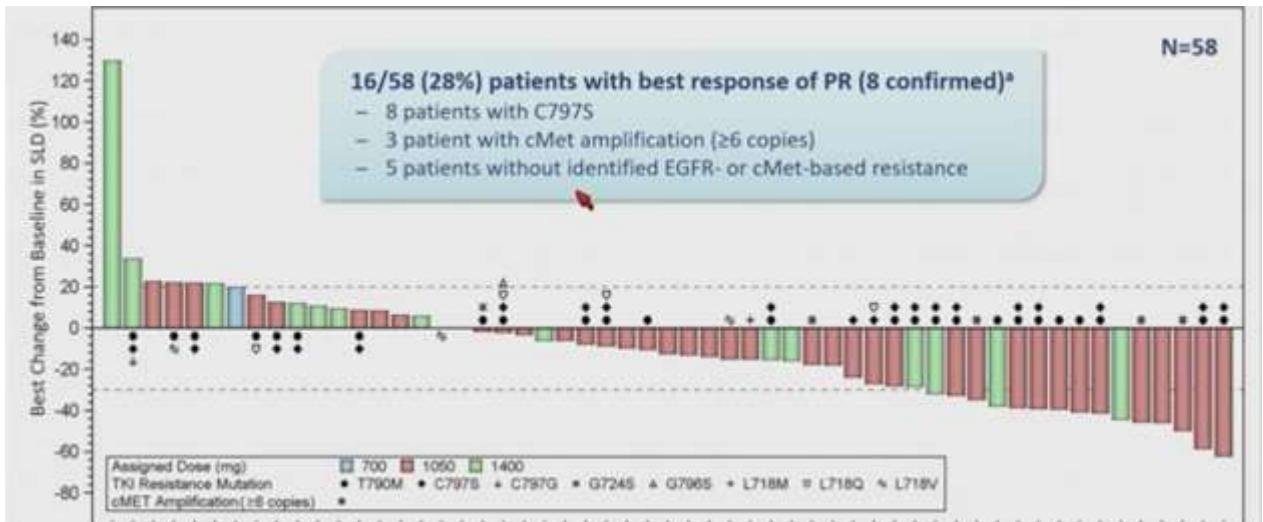
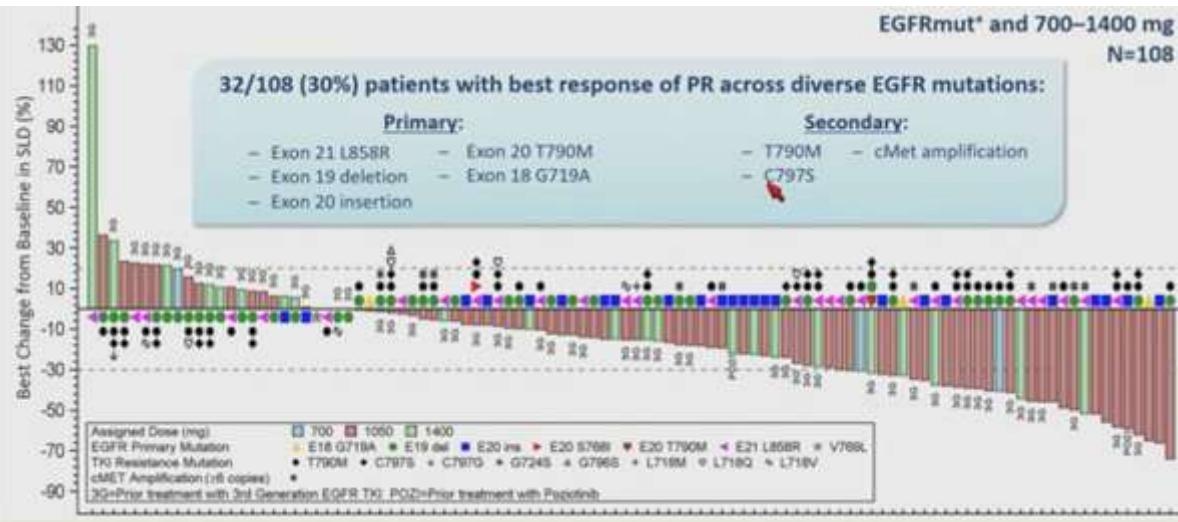
RP2D

Safety/efficacy

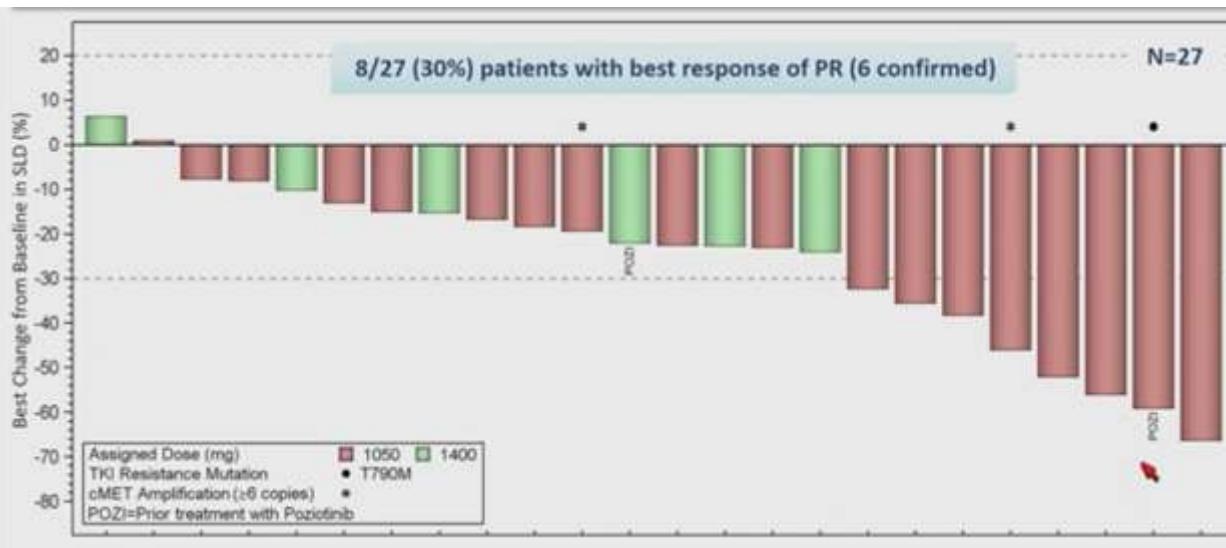
- Inhibition of EGFR and MET signaling
- Receptor degradation
- ADCC

JNJ-372

Post-Osimertinib



Exon-20



Median prior lines of tmnt: 3 (0-10)
Median prior lines of EGFR TKIs: 2 (0-6)



JNJ-372

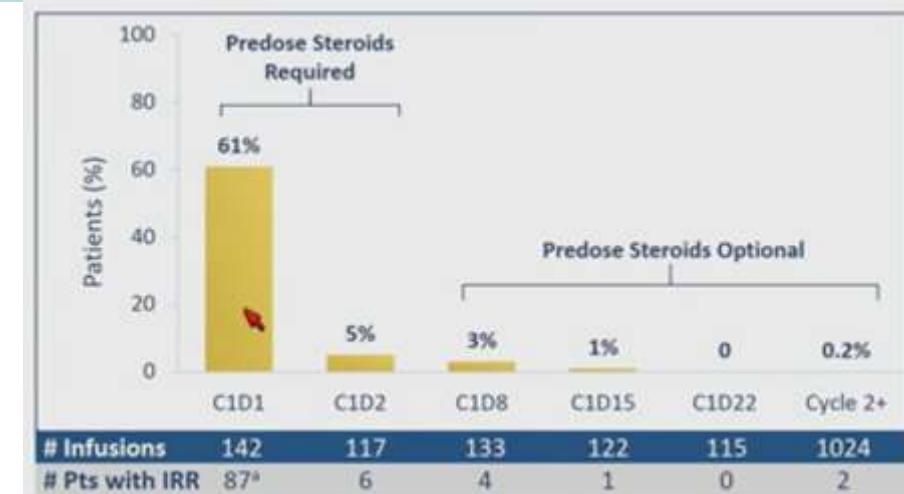
TEAE, n (%)	140 mg (n=3)	350 mg (n=3)	700 mg (n=10)	1050 mg (n=86)	1400 mg (n=40)	Total (N=142)
Infusion related reaction (IRR)	3 (100)	2 (67)	9 (90)	46 (54)	28 (70)	88 (62)
Rash*	0	2 (67)	3 (30)	55 (64)	19 (48)	79 (56)
Paronychia	0	1 (33)	2 (20)	28 (33)	6 (15)	37 (26)
Constipation	1 (33)	1 (33)	2 (20)	22 (26)	5 (13)	31 (22)
Dyspnea	0	0	2 (20)	20 (23)	5 (13)	27 (19)
Fatigue	0	1 (33)	2 (20)	14 (16)	10 (25)	27 (19)
Nausea	1 (33)	0	2 (20)	14 (16)	9 (23)	26 (18)
Stomatitis	0	0	1 (10)	16 (19)	4 (10)	21 (15)
Hypoalbuminemia	1 (33)	0	0	13 (15)	7 (18)	21 (15)
Pruritus	0	0	2 (20)	11 (13)	7 (18)	20 (14)
Decreased appetite	2 (67)	0	2 (20)	11 (13)	3 (8)	18 (13)
Dizziness	0	0	1 (10)	10 (12)	6 (15)	17 (12)
Headache	0	0	1 (10)	8 (9)	8 (20)	17 (12)
Peripheral edema	1 (33)	0	2 (20)	11 (13)	1 (3)	15 (11)
Diarrhea	1 (33)	0	2 (20)	3 (4)	4 (10)	10 (7)
Pneumonitis/ILD	0	0	0	1 (1)	2 (5)	3 (2)

- Grade ≥3 TEAEs reported in 49 (35%) patients
- Treatment-related grade ≥3 AEs reported in 12 (9%) patients

- AEs leading to treatment discontinuations=8% (4% related)
- AEs leading to dose reduction=4%

IRR-associated TEAEs (≥15%)

- Chills (20%)
- Dyspnea (20%)
- Nausea (19%)
- Flushing (17%)



Old uncommon target: EGFR exon 20

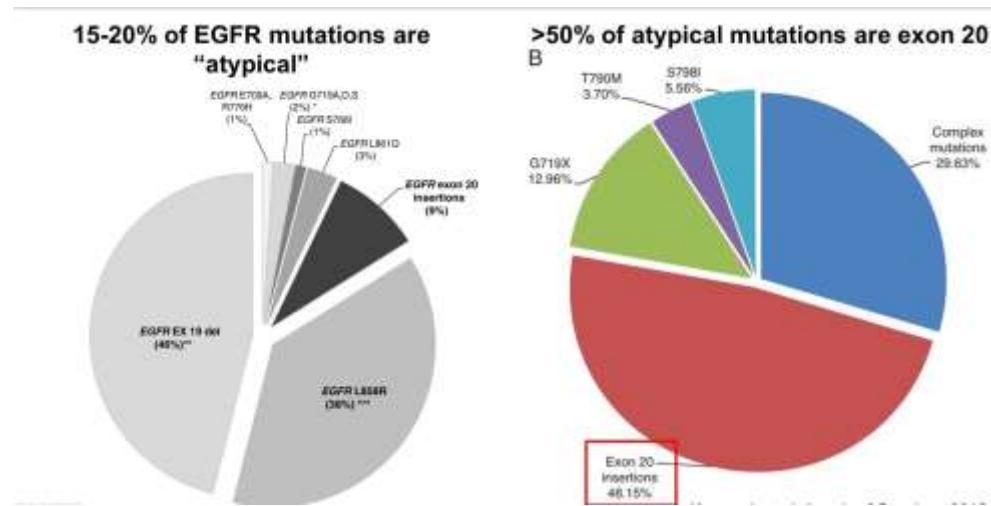


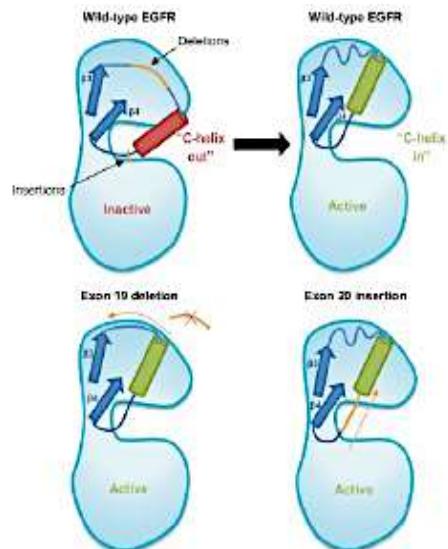
Table 1. Key clinical trials in EGFR exon 20 insertion positive NSCLC.

Inhibitor(s)	Target(s)	Clinical trial (NCT)	Key result
Gefitinib/Gefitinib	EGFR	Bretropective analysis of clinical studies	43 months PFS 9-27% PR
Dacomitinib	EGFR HER2 HER4	NCT0025121	PR for 1 patient with D770insEGFR
Afatinib	EGFR HER2 HER4	NCT00525148 NCT00649650 NCT01121393	8.7% RR, 2.7 months PFS
Neratinib	EGFR HER2 HER4	NCT00210077	0% RR
Osimertinib	EGFR T790M	NCT0144614	Ongoing
Pozotinib	EGFR HER2	NCT00946206	Ongoing, 64% RR
Cetuximab + erlotinib EGFR	EGFR	NCT00895362	D770-GF patient with 1.5 years PFS
Cetuximab + Afatinib EGFR	EGFR	NCT0372724	Preliminary report: 3 out of 4 patients with PR, 54 months PFS
Lumineptib	Hsp90	NCT0154034	17% RR, 19 months PFS
Telazosin	EGFR	-	Pre-clinical inhibition of exon20s EGFR
TAK-788	EGFR HER2 ex 20	NCT02716116	Ongoing, preliminary anti-tumor activity reported
TAK-788?	EGFR ex 20 ins	-	Pre-clinical inhibition of exon20s EGFR
Compound 1A	EGFR HER2 ex 20	-	Pre-clinical inhibition of exon20s EGFR

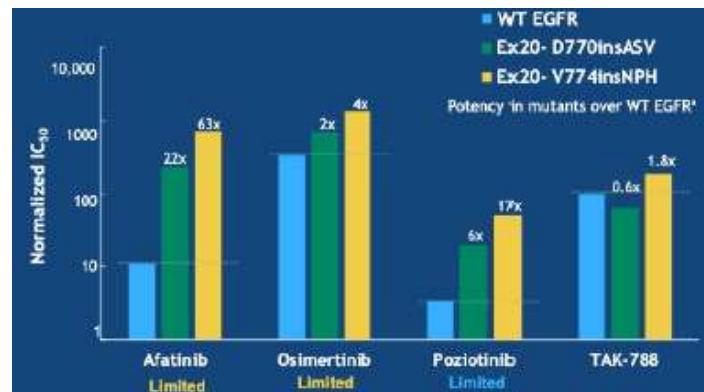
Details for trials with NCT numbers can be accessed on <https://clinicaltrials.gov/>
PR: progression-free survival; RR: response rate; ins: exon 20 insertion

Vyse et al. Signal Transduction and Targeted Therapy, 2019

The active form of EGFR exon 20 insertion mutants not too dissimilar from that of wild-type EGFR → translates to narrower therapeutic window!



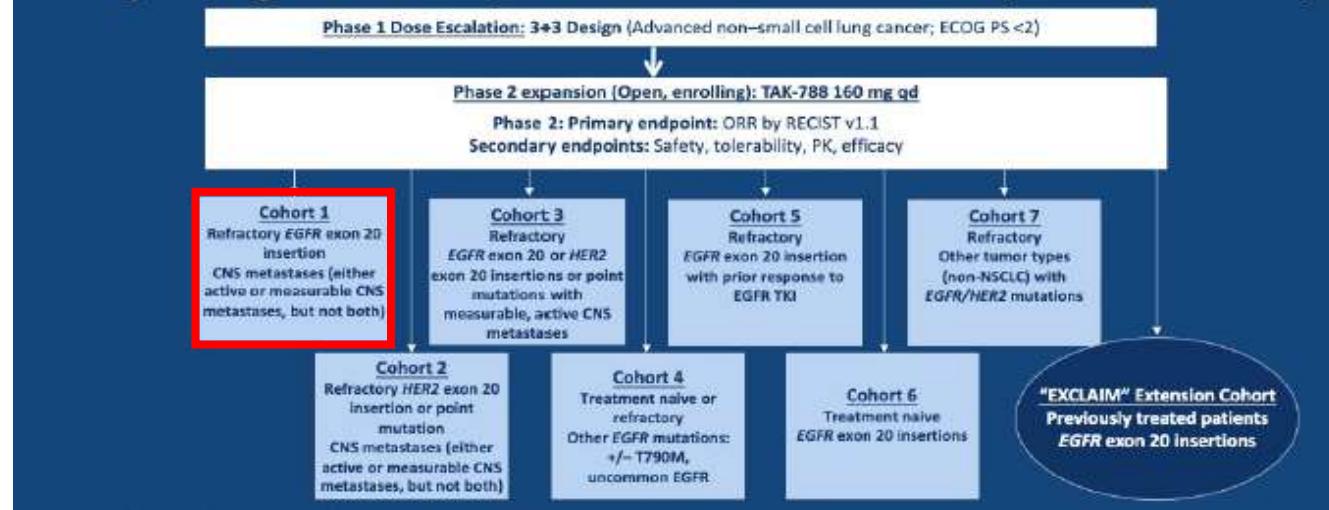
Sex	Age (years)	Smoking status	Histology	Mutation	1 st line therapy	Best response
M	71	Former	NOS	ex 18 E709K ex 21 L833V/H835L	afatinib	PR
F	69	Current	Acinar	ex 18 G719A ex 20 V769M	-	-
M	56	No	Mucinous	ex 19 I745insKIPVAI	erlotinib	SD
F	68	Former	NOS	ex 20 Q812R	CT	PD
F	68	Former	Acinar	ex 20 D770insSVD	-	-
M	62	No	NOS	ex 20 (His773G)	CT	SD
M	54	Former	Papillary	ex 20 (unspecified)	CT	SD
F	56	No	Mucinous	ex 20 Asn771_His773dup	erlotinib	PD
F	66	Current	Poorly diff.	ex 20 H773 ins PHF	erlotinib	PD
M	73	Current	Poorly diff.	ex 18 E709K	gefitinib	PD
M	86	No	NOS	ex 18 E709Stop	gefitinib	PD
F	71	Unknown	Mucinous	ex 10-1-L747-K754insSP	gefitinib	SD
F	79	No	Mucinous	ex 20 S768R	gefitinib	PD
F	56	Current	Mucinous	ex 19 del L747-P753insQ	gefitinib	SD
M	68	No	Lepidic	ex 18 E709Q	-	-
M	51	No	Acinar	ex 19 del E746-S752insV	gefitinib	PR
F	74	No	Poorly diff.	ex 19 del L747-K754	afatinib	PR
M	53	No	Mucinous	ex 18 G719A	CT	SD
F	64	Unknown	NOS	ex 20 V769insAVS	CT	SD
F	76	No	Papillary	ex 19 del S752-I759	gefitinib	PR
M	60	Former	Acinar	ex 18 G719C	gefitinib	PR
F	73	No	NOS	ex 19 L747-S752,insP	gefitinib	PR
M	79	Former	NOS	ex 18 2155G>A, pGly719Ser	gefitinib	PD
F	75	No	NOS	ex 19 del L747-P753insS	gefitinib	PR
M	54	Current	NOS	ex 19 del L747-P753insS	afatinib	PR
F	47	Current	NOS	ex 18 G719A	CT	SD



- Inhibition of WT EGFR in normal tissues is associated with DLTs^{1,2}
- TAK-788 potently inhibits EGFR exon 20 mutants with selectivity over WT EGFR
- Other EGFR TKIs have limited potency against EGFR exon 20 insertions or lack selectivity over WT EGFR

TAK-788

Study Design: Phase 1/2 Trial of Oral TAK-788 (NCT02716116)



TAK-788 Antitumor Activity in Patients With EGFR Exon 20 Insertions



Exon 20 Insertion Variant	No. of Patients	No. of Confirmed Responders, n	Confirmed ORR
769_ASV	5	2	40%
773_NPH	4	2	50%
Exact variant unknown:	4	2	50%
Other	15	6	40%

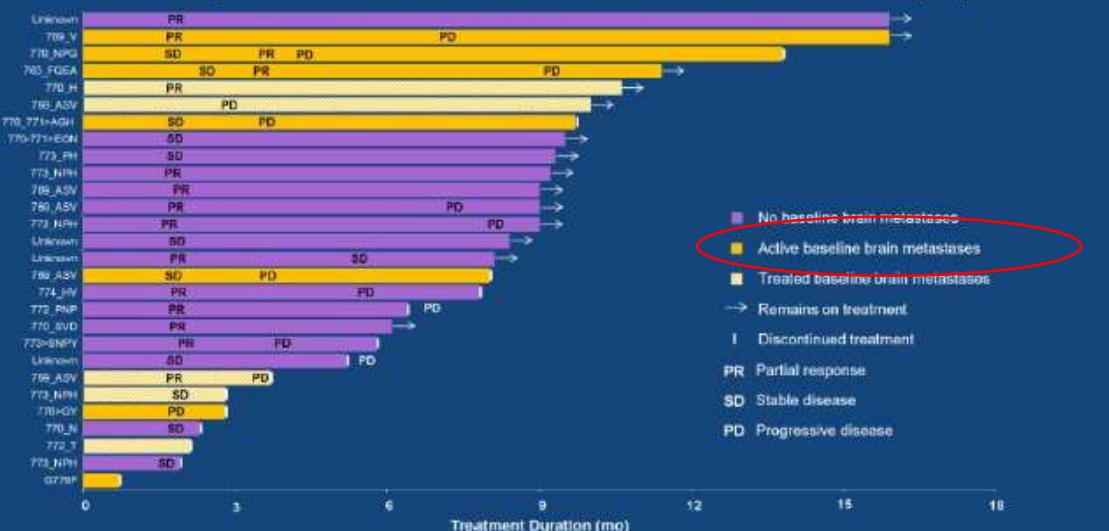
EGFR Exon 20 Insertions Treated at 160 mg qd^a

	All Patients (n=28)	With Baseline CNS Metastases ^b (n=12)	Without Baseline CNS Metastases (n=16)
Best response (confirmed), n (%) ^c			
Partial response	12 (43)	3 (25)	9 (56)
Stable disease ^d	12 (43)	5 (42)	7 (44)
Progressive disease	2 (7)	2 (18)	0
Not evaluable	2 (7)	2 (18)	0
Confirmed objective response, n (%)	12 (43)	3 (25)	9 (56)
[95% CI]	[24–63]	[5–57]	[30–80]
Disease control, n (%)	24 (86)	8 (67)	16 (100)
[95% CI]	[67–96]	[35–90]	[79–100]
Median progression-free survival, mo	7.3	3.7	8.1
[95% CI]	[4.4–NR]	[1.8–NR]	[5.6–NR]

Prior systemic treatments (median): 3; Prior EGFR/HER2 TKIs (%): 18; Prior ICI(%): 61

TAK-788

Overall Response to TAK-788 and Time on Treatment, by Patient



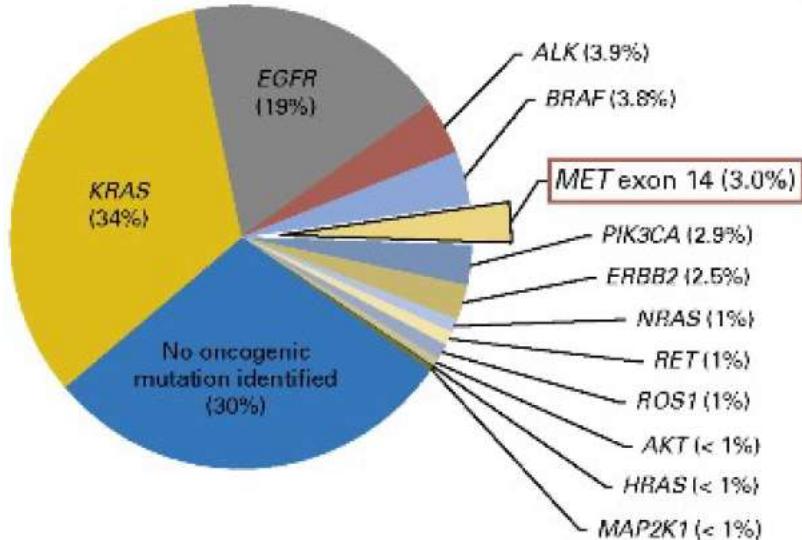
Median time on treatment: 7.9 months

Main reason for discontinuation: PD (25%); AEs (11%)

- TEAEs G \geq 3: 63%
- TR-AE G \geq 3: 43%
- TR-AE discontinuation: 14%

Any grade: \geq 20% of all patients Grade \geq 3: \geq 3% of all patients	All Patients Treated at 160 mg qd ^a (n=72)		All Patients Treated at Any Dose ^b (N=137)	
	Any Grade, %	Grade \geq 3, %	Any Grade, %	Grade \geq 3, %
Diarrhea	85	18	74	12
Nausea	43	6	33	4
Rash	36	1	26	1
Vomiting	29	3	22	2
Decreased appetite	25	1	22	1
Stomatitis	18	4	14	3
Increased lipase	10	6	8	3
Increased amylase	8	4	8	3

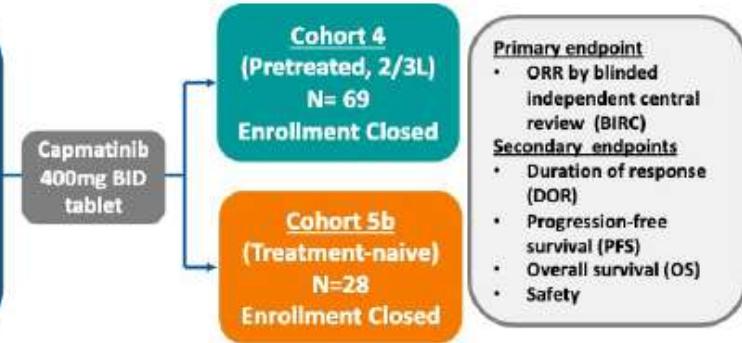
New targets: MET



	Capmatinib	Savolitinib	Tepotinib	Cabozantinib	Crizotinib
IC ₅₀ (nM)	0.6	2.1	3.0	7.8	22.5

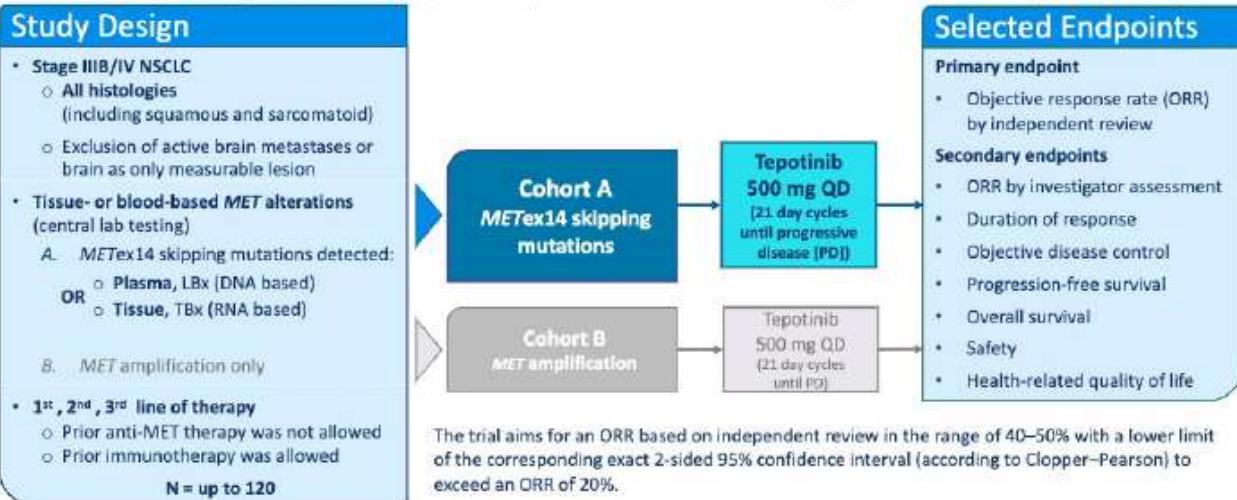
GEOMETRY

- Stage IIIB/IV NSCLC
- *METΔex14* irrespective of MET GCN by central RT-PCR
- EGFR wt (for L858R and delE19) and ALK-negative
- PS 0–1
- ≥1 measurable lesion (RECIST 1.1)
- Neurologically stable or asymptomatic brain metastases allowed



VISION

VISION is a single-arm, phase II trial of tepotinib in patients with NSCLC harboring MET alterations (NCT02864992)



Capmatinib: summary of results

Best overall response (pretreated cohort 4)

All responses confirmed per RECIST 1.1

Response rates consistent between BIRC and investigator assessment

	Cohort 4 (2/3L) N=69	
	BIRC	Investigator
Best overall response, n (%)		
Complete Response	0	1 (1.4)
Partial Response	28 (40.6)	28 (40.6)
Stable Disease	25 (36.2)	22 (31.9)
Non-CR/non-PD	1 (1.4)	2 (2.9)
Progressive Disease	6 (8.7)	7 (10.1)
Not evaluable*	9 (13.0)	9 (13.0)
Overall response rate (ORR) %, (95% CI)	40.6 (28.9, 53.1)	42.0 (30.2, 54.5)
Disease control rate (DCR) %, (95% CI)	78.3 (66.7, 87.3)	76.8 (65.1, 86.1)

mDoR: 9.7 months

Best overall response (treatment naive cohort 5b)

All responses confirmed per RECIST 1.1

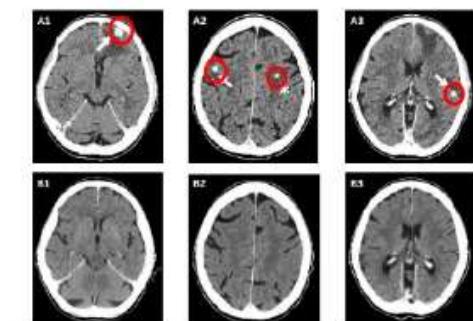
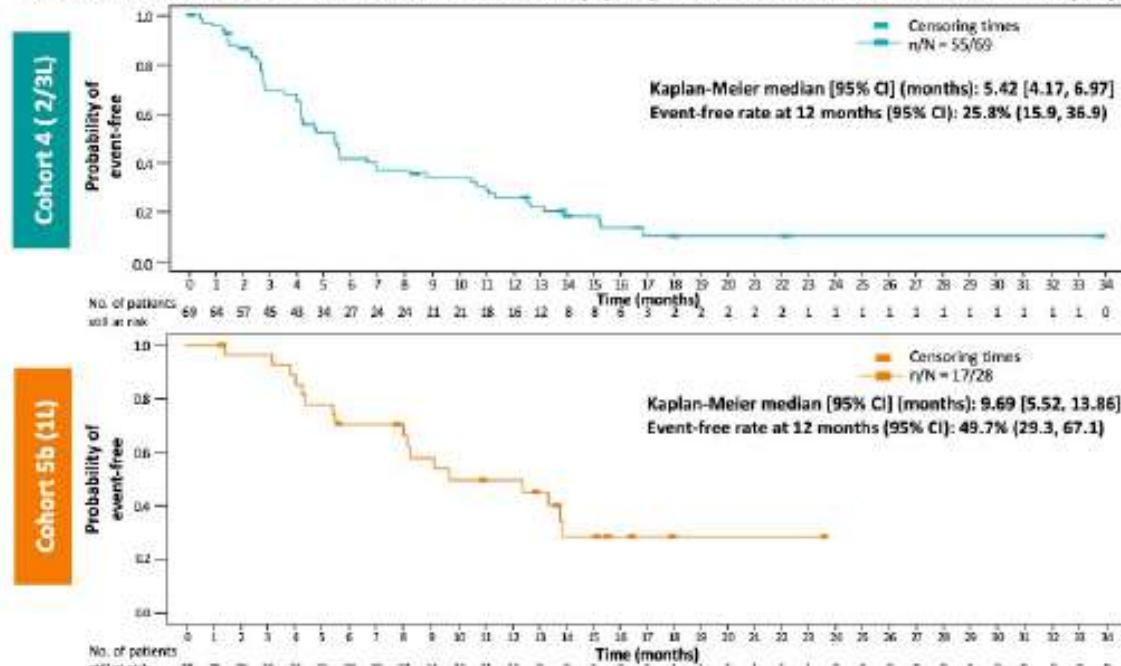
Response rates consistent between BIRC and investigator assessment

	Cohort 5b (1L) N=28	
	BIRC	Investigator
Best overall response, n (%)		
Complete Response	1 (3.6)	0
Partial Response	18 (64.3)	17 (60.7)
Stable Disease	8 (28.6)	10 (35.7)
Progressive Disease	1 (3.6)	1 (3.6)
Overall response rate (ORR) %, (95% CI)	67.9 (47.6, 84.1)	60.7 (40.6, 78.5)
Disease control rate (DCR) %, (95% CI)	96.4 (81.7, 99.9)	96.4 (81.7, 99.9)

mDoR: 11.1 months

Progression-free survival per BIRC

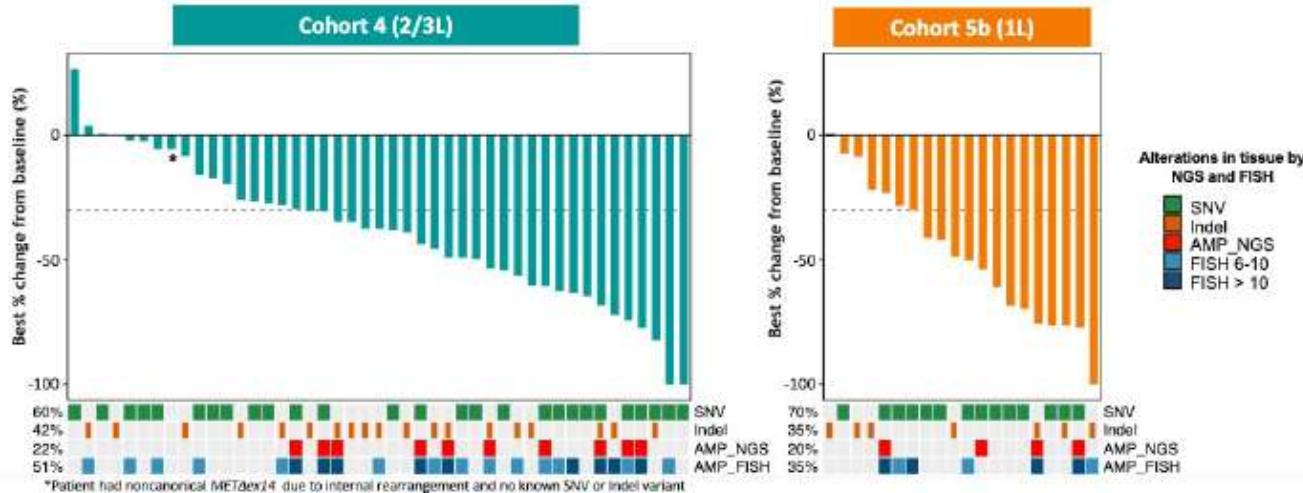
Median PFS was 5.42 months in Cohort 4 (2/3L) and 9.69 months in Cohort 5b (1L)



- 54% (n=7/13) had intracranial response*:
 - 4 patients had complete resolution of all brain lesions
 - The other 3 responding patients had:
 - complete resolution in 3 lesions, ~50% reduction in 1 lesion, stabilization in remaining 4 lesions (total of 7 lesions)
 - Complete resolution in 2 lesions, stabilization in 1 remaining lesion (total of 3 lesions)
 - Complete resolution in 1 lesion, stabilization in 3 remaining lesions (total of 4 lesions)

Capmatinib: summary of results

- Deep responses and DOR were observed independently of type of MET mutation (SNV, Indel) leading to MET Δ ex14 or co-occurrence of MET amplification.
- MET mutations could be detected by both RT-PCR and NGS
 - High concordance (99%) between NGS and RT-PCR[†] in detection of MET Δ ex14 in tumor tissue



mDoR: 14.3 months

Safety summary

Favorable and manageable safety profile

Most common adverse events-treatment related ($\geq 10\%$, all grades), n (%)	All Patients N = 334	
	All grades	Grade 3/4
Any	282 (84.4)	119 (35.6)
Peripheral edema	139 (41.6)	25 (7.5)
Nausea*	111 (33.2)	6 (1.8)
Increased blood creatinine†	65 (19.5)	0
Vomiting*	63 (18.9)	6 (1.8)
Fatigue	46 (13.8)	10 (3.0)
Decreased appetite*	42 (12.6)	3 (0.9)
Diarrhea	38 (11.4)	1 (0.3)

- Safety determined in the largest dataset of MET dysregulated[‡] NSCLC patients (N=334).
- Median treatment exposure time: 14.9 weeks
- Capmatinib was well tolerated with few Grade 3/4 events [only 15 patients (4.5%) had Grade 4 events]
- Dose adjustment due to treatment related AE: 73 (21.9%)
- Discontinuation due to treatment related AE: 37 (11.1%)
 - Most frequent ($\geq 1\%$): peripheral edema (n=6, 1.8%), pneumonitis (n=5, 1.5%) and fatigue (n=5, 1.5%)
- Serious treatment related AEs: 43 (12.9%)

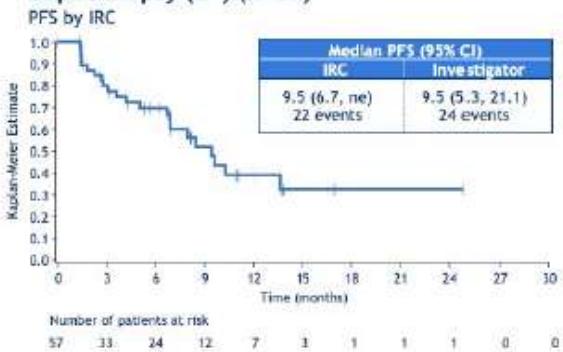
Tepotinib: summary of results

Efficacy: ORR by line of therapy (IRC/Investigator)

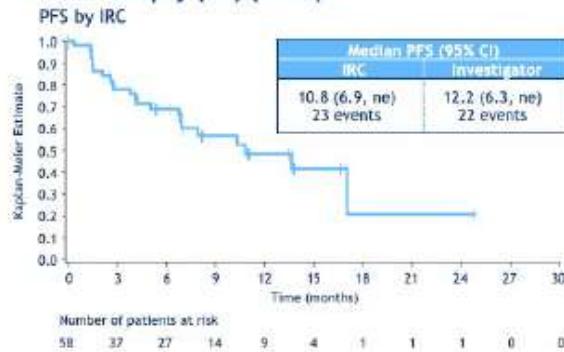
Consistent ORR across treatment lines

Tepotinib 500 mg QD		IRC (n=48)		Tissue biopsy (T+) IRC (n=51)		Investigator (n=51)	
First line	ORR,* n/N (%) [95% CI]	10/17 (58.8) [32.9, 81.6]	12/17 (70.6) [44.0, 89.7]	8/18 (44.4) [21.5, 69.2]	9/18 (50.0) [26.0, 74.0]		
Second line	ORR,* n/N (%) [95% CI]	8/15 (53.3) [26.6, 78.7]	7/14 (50.0) [27.0, 72.0]	9/18 (50.0) [26.0, 74.0]	11/18 (61.1) [35.7, 82.7]		
≥Third line	ORR,* n/N (%) [95% CI]	6/16 (37.5) [15.2, 62.0]	6/15 (40.0) [16.3, 67.7]	8/15 (53.3) [26.6, 78.7]			
≥Second line	ORR,* n/N (%) [95% CI]	14/31 (45.2) [27.3, 64.0]	14/30 (46.7) [28.3, 65.7]	15/33 (45.5) [28.1, 63.6]	19/33 (57.6) [39.2, 74.5]		
	mDOR, months [95% CI]	12.4 [5.6, ne]	ne	12.4 [3.7, ne]	17.1 [5.7, ne]		

Liquid biopsy (L+) (n=57)

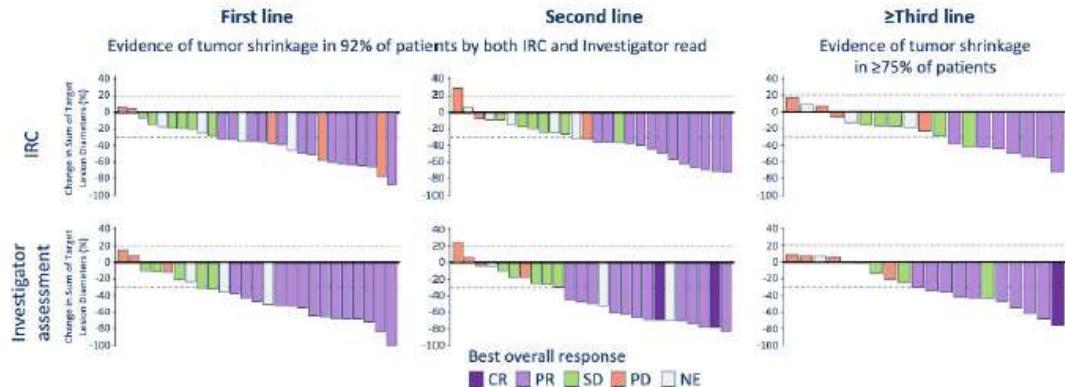


Tissue biopsy (T+) (n=58)



Efficacy: Tumor shrinkage by line of therapy

Consistent tumor shrinkage across treatment lines



Tepotinib 500 mg QD (N=87)		
	Any Grade	Grade 3
Any treatment-related AE, n (%)	71 (81.6)	17 (19.5)
Treatment-related AEs reported in ≥5% patients, n (%)		
Peripheral edema	42 (48.3)	7 (8.0)
Nausea	20 (23.0)	0
Diarrhea	18 (20.7)	1 (1.1)
Blood creatinine increased	11 (12.6)	0
Asthenia	8 (9.2)	1 (1.1)
Amylase increase	7 (8.0)	2 (2.3)
ALT increased	6 (6.9)	2 (2.3)
AST increased	5 (5.7)	1 (1.1)
Hypoalbuminemia	5 (5.7)	0

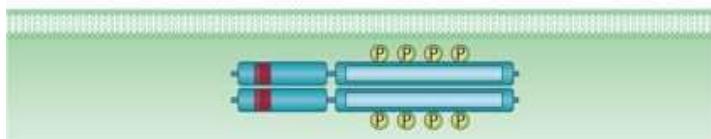
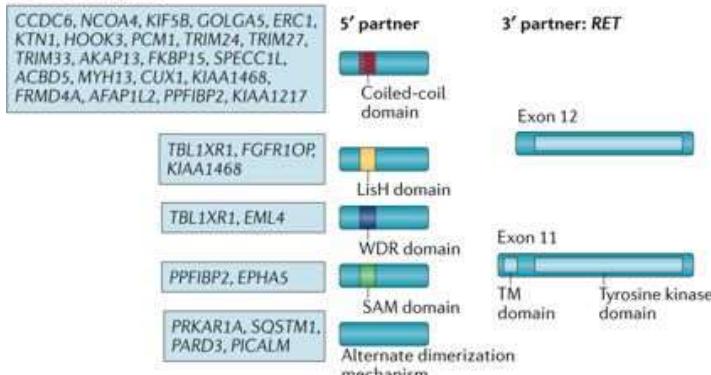
Data cut-off: February 18, 2019

- No grade 4 or grade 5 treatment-related AEs
- Other relevant treatment-related AEs (any grade) include:
 - lipase increased (4.6%)
 - fatigue (3.4%)
 - vomiting (3.4%)
- Treatment-related AEs led to permanent discontinuation in 4 patients:
 - two patients due to peripheral edema
 - one patient due to interstitial lung disease
 - one patient due to diarrhea and nausea

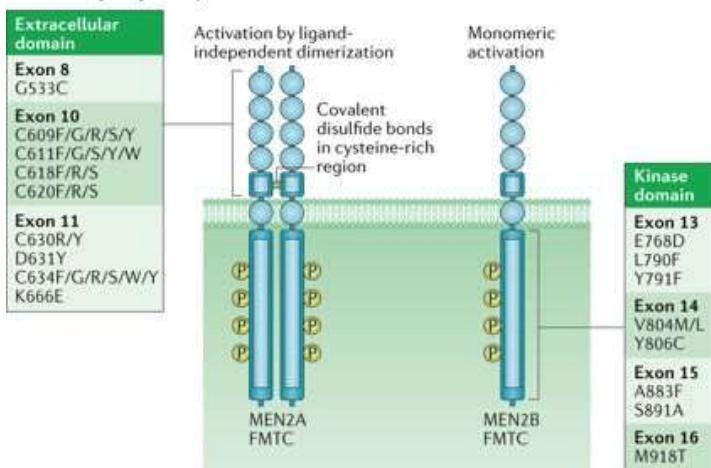
4.5%

New targets: RET

a RET fusion genes



b RET nonsynonymous point mutations

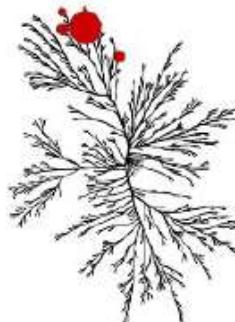


1-2%
NSCLC

Ref.	Ph.	# of pts	Detection method	RET TKI	ORR	Median PFS (months)	Median OS (months)
Drlion et al. PMID: 27925030	2	26 enrolled 25 evaluable	FISH or NGS	Cabozantinib	28% (95% CI 12-49)	5.5 (95% CI 3.8-8.4)	9.9 (95% CI 8.1-NR)
Lee et al. PMID: 27809005	2	18 enrolled 17 evaluable	FISH, NGS, RT-PCR	Vandetanib	18%	4.5	11.6
Yoh et al. PMID: 27825616	2	19 enrolled 17 evaluable	RT-PCR, FISH	Vandetanib	53% (95% CI 23-77)	4.7 (95% CI 2.8-8.5)	11.1
Velcheti et al. <i>Ann Oncol</i> (2016) 27 (Suppl_6): 1204PD	2	25	NGS	Lenvatinib	16%	7.3 (95% CI 3.6-16.2)	Not reached (95% CI 5.8-NR)
Gautschi O et al. PMID: 28447909		53	RT-PCR, FISH, NGS	Cabozantinib (n=21) Vandetanib (n=11) Sunitinib (n=10) Sorafenib (n=2) Alectinib (n=2) Lenvatinib (n=2) Nintedanib (n=2) Ponatinib (n=2) Regorafenib (n=1)	37% 18% 22%	2.3 (95% CI 1.6-5.9)	6.8 (95% CI 3.9-14.3)



BLU-667: High kinase selectivity for RET^a



BLU-667: the ARROW study

**Part 1:
Dose-Escalation
(N=62; Complete)¹**

RET-altered advanced solid tumors

BLU-667: 30-600 mg by daily oral administration (QD or BID)

Phase 2 dose determined (400 mg QD)



ARROW is registered with clinicaltrials.gov (NCT03037385)

**Part 2:
Expansion Cohorts
(Ongoing)**

BLU-667 400 mg QD

- Unresectable, advanced solid tumor
- RET alteration status by local tumor testing
- No additional driver mutation
- ECOG PS 0-1
- Asymptomatic brain metastases allowed
- Progressive disease or intolerant to SOC therapy, or not a candidate

Primary objectives:

Overall response rate (RECIST 1.1)

Safety

**RET fusion+ NSCLC,
prior platinum (n=80)**

**RET fusion+ NSCLC,
platinum naïve (n=40)**

**MTC, prior cabozantinib or
vandetanib (n=60)**

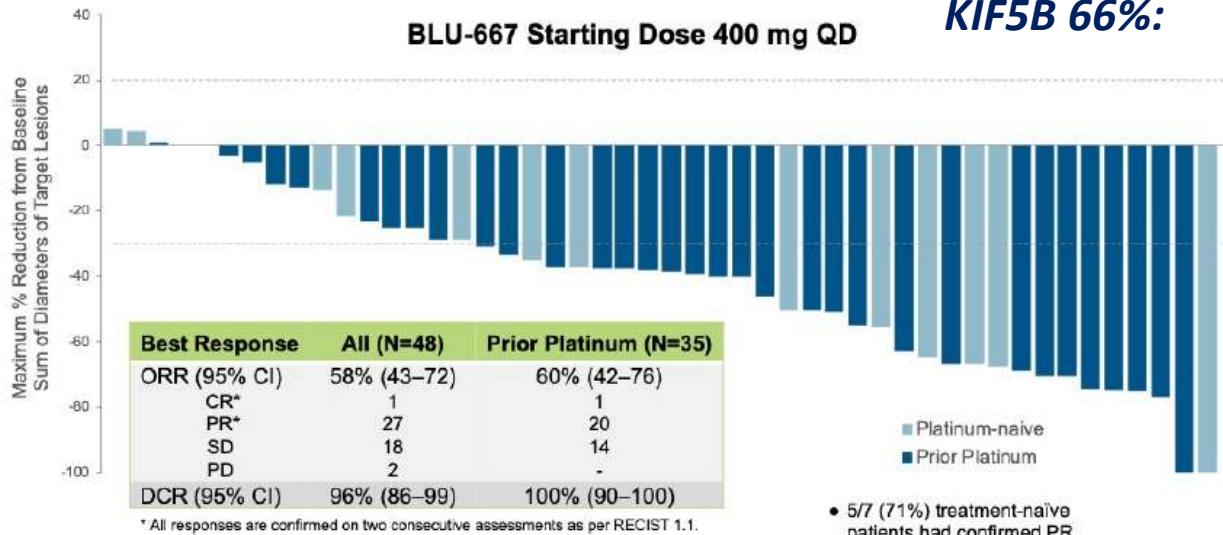
**MTC, no prior cabozantinib
or vandetanib (n=40)**

**Other RET fusion+ tumors
(n=40)**

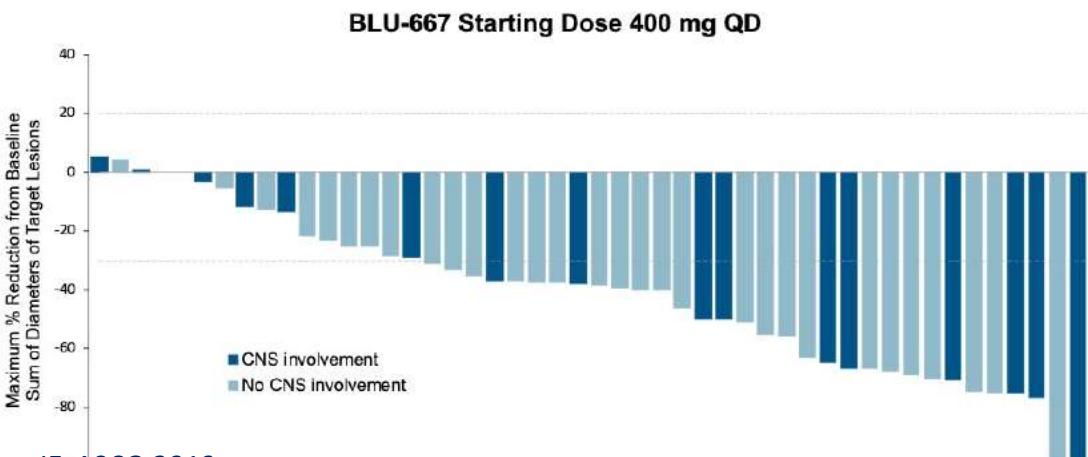
**Other RET-mutated tumors
(n=20)**

**RET-altered, prior selective
RET inhibitor (n=20)**

BLU-667



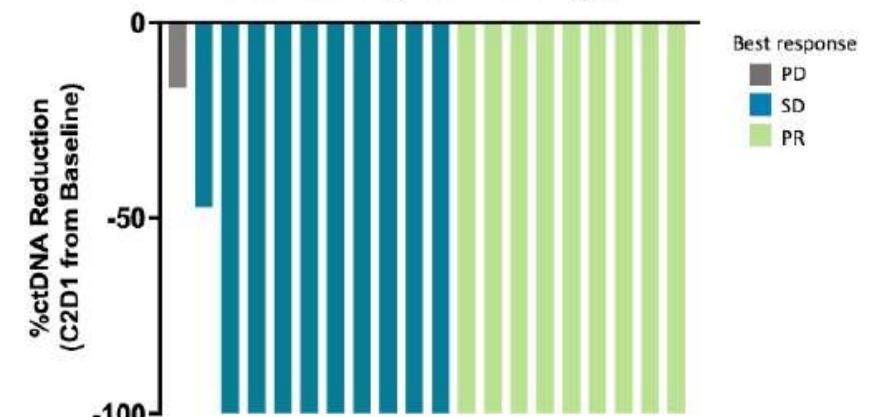
Regardless of: previous ICI; fusion partner; BM



Adverse Events	Treatment-Emergent (≥15% overall)		Treatment-Related	
	All	Grade ≥3	All	Grade ≥3
Constipation	30%	2%	17%	2%
Neutropenia*	26%	13%	26%	13%
AST increased	24%	5%	20%	2%
Fatigue	21%	3%	13%	3%
Hypertension	20%	13%	13%	10%
Anemia	18%	7%	11%	4%
Diarrhea	18%	2%	9%	-
Pyrexia	18%	-	2%	-
ALT increased	17%	3%	13%	2%

TRAE discontinuation: 7%

**RET Fusion+ Advanced NSCLC,
BLU-667 starting dose 400 mg QD**

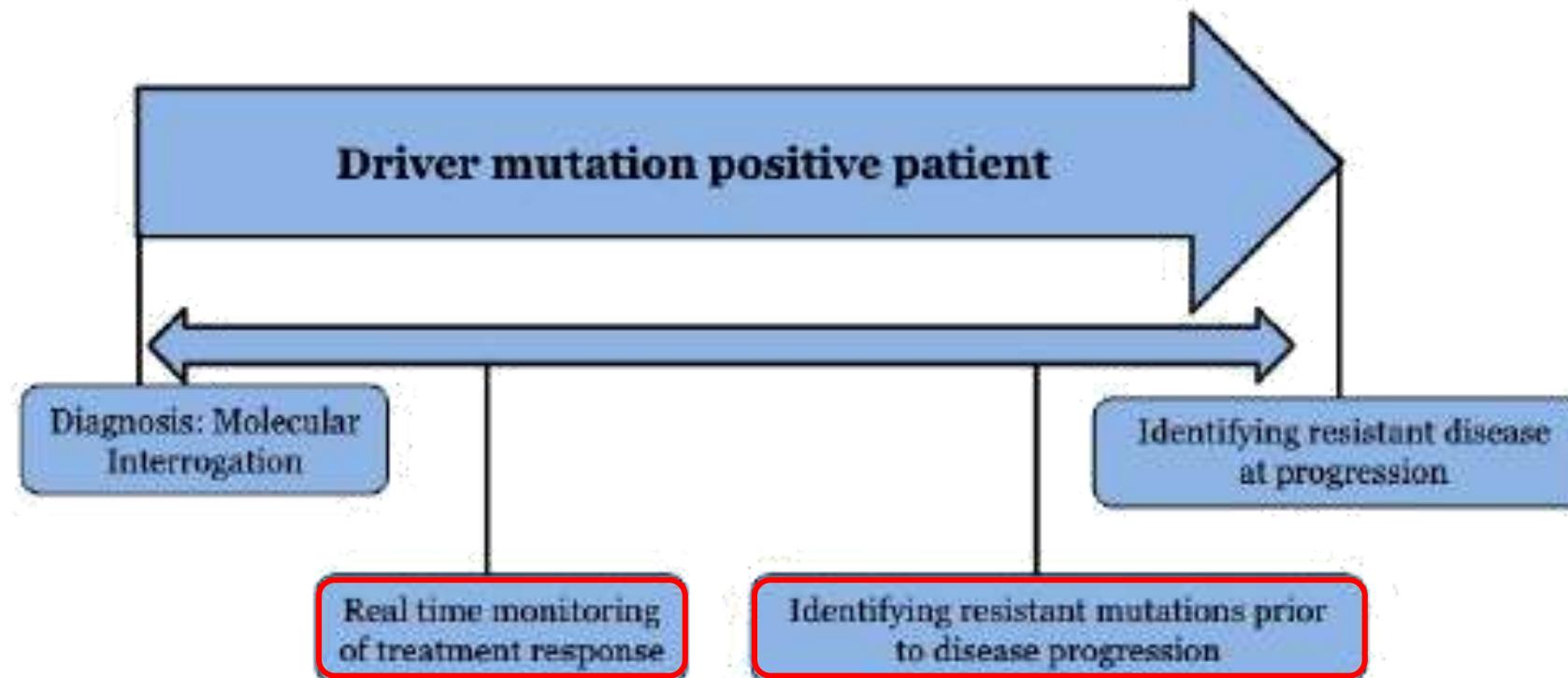


PROGRESS IN THERAPIES

- More first line options for old (EGFR, ALK) and new (MET, RET) targets
- More acquired-resistance targeting agents
- More treatment chances along the sequence

PROGRESS IN DIAGNOSTIC

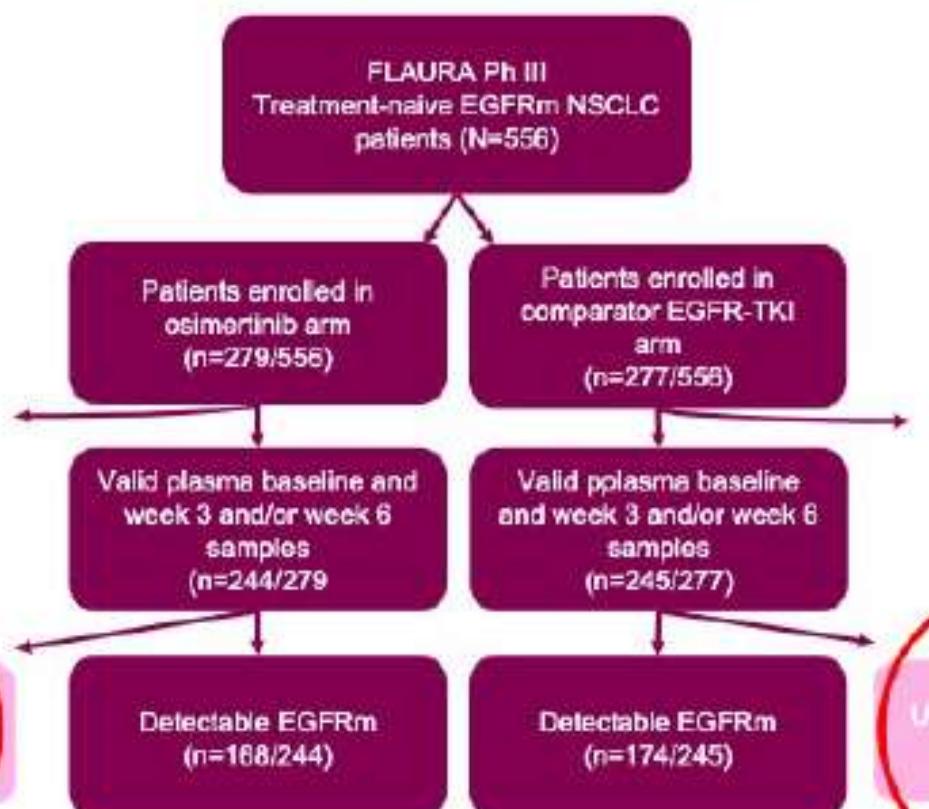
- Multigene assessment
- ctDNA detection/liquid biopsy



ctDNA detection as tool for early response assessment and treatment switch ?

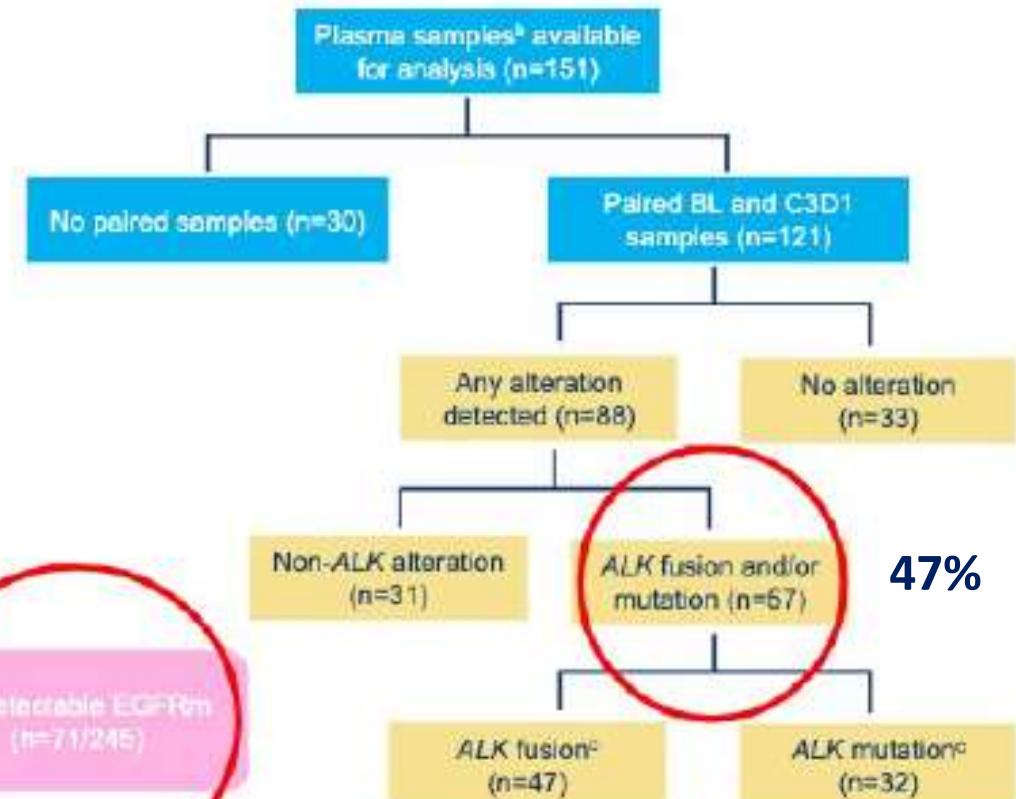
ctDNA detection as tool for early response assessment and treatment switch

Osimertinib – EGFR



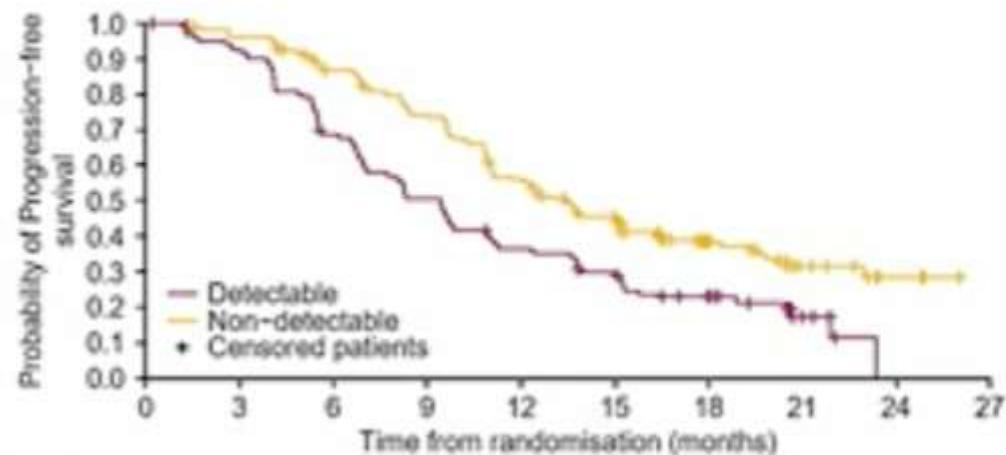
EGFRm+ detectable in 70%

Lorlatinib - ALK



47%

ctDNA detection as tool for early response assessment and treatment switch

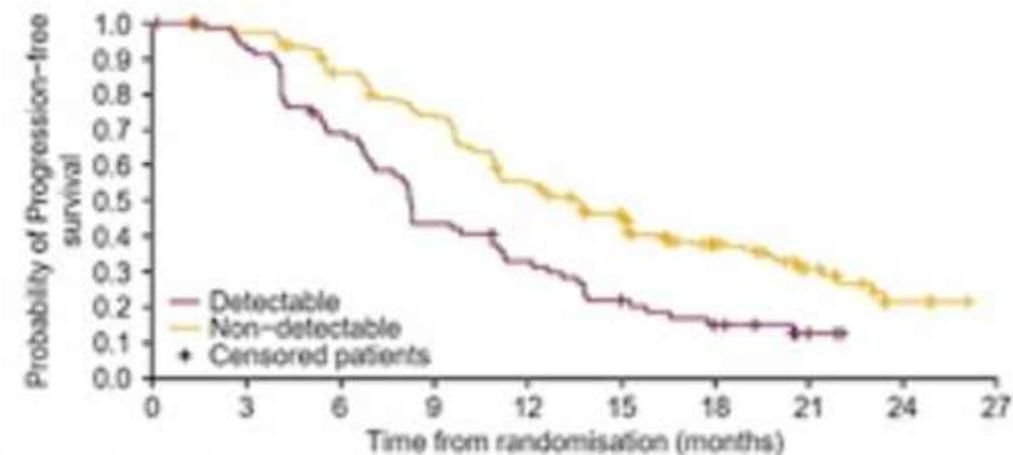


Number of patients at risk

Non-detectable	208	198	174	147	111	86	41	13	3	0
Detectable	126	114	84	62	44	34	20	6	0	0

a) Clearance of plasma EGFRm at week 3

	Detectable EGFRm (n=126)	Non-detectable EGFRm (n=208)
Events,n (maturity,%)	99 (79)	128 (62)
mPFS, months (95% CI)	9.5 (7.0, 10.9)	13.5 (11.1, 15.2)
HR (95% CI); p value	0.57 (0.4, 0.7) p<0.0001	
ORR, % (95% CI)	78 (69.5, 84.7)	87 (81.7, 91.3)



Number of patients at risk

Non-detectable	258	249	216	184	137	109	54	18	3	0
Detectable	70	63	46	29	21	13	8	2	0	0

b) Clearance of plasma EGFRm at week 6

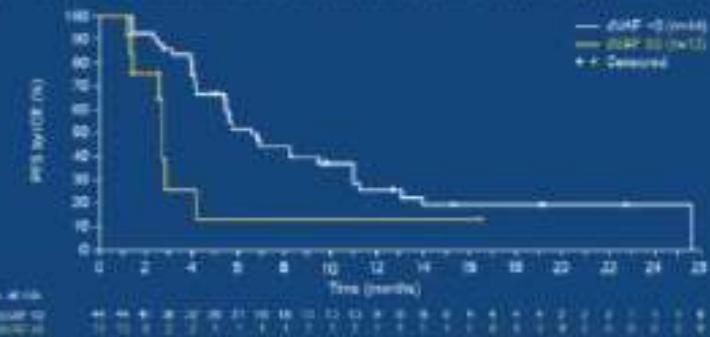
	Detectable EGFRm (n=70)	Non-detectable EGFRm (n=258)
Events,n (maturity,%)	57 (81)	165 (64)
mPFS, months (95% CI)	8.2 (6.8, 10.9)	13.5 (11.1, 15.2)
HR (95% CI); p value		0.51 (0.4, 0.7) p<0.0001
ORR, % (95% CI)	73 (60.9, 82.8)	88 (83.4, 91.7)

ctDNA detection as tool for early response assessment and treatment switch

	dVAF < 0	dVAF ≥ 0
Mean Tumor Volume Reduction	26%	12%
mPFS, months	6.6	2.6
mOS, months	18	8.6

PFS by dVAF^a

- In patients with ALK fusion and/or mutation, median PFS was 6.6 months in those with dVAF < 0 (n=44) and 2.6 months in those with dVAF ≥ 0 (n=13) (HR=2.6, 95% CI: 1.2, 5.8)



^aAnalysis is unstratified and includes patients in the progression-free group.

ALK, anaplastic lymphoma kinase; BL, brain metastasis; CDC, GCR, GCR 2; dVAF, digital tumor fraction; HR, hazard ratio; ICI, independent Clinical Review; IL, log-rank test for survival.

OS by dVAF^a

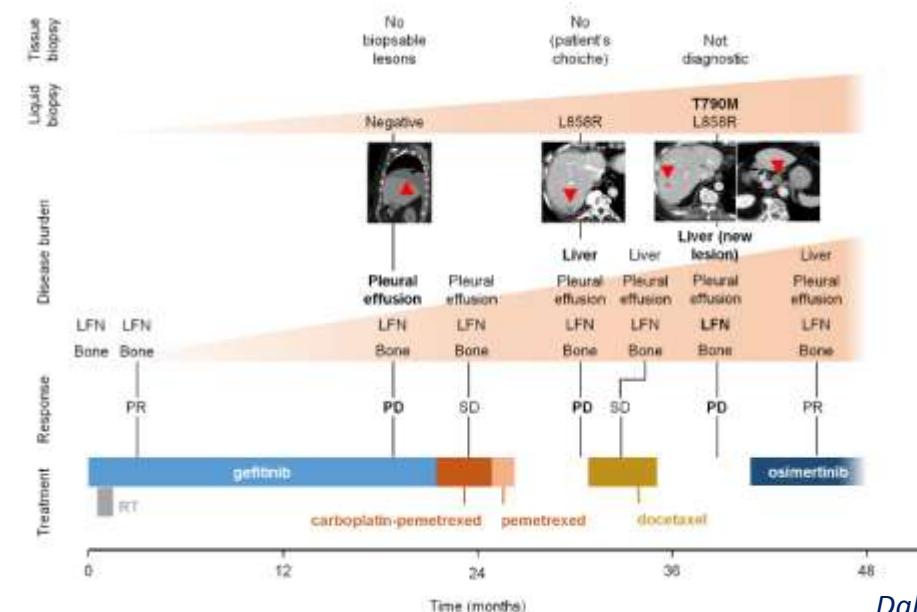
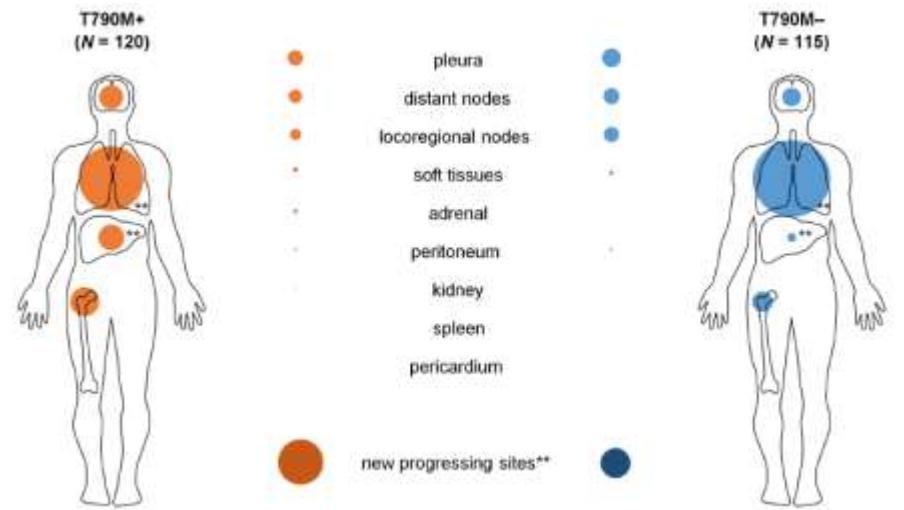
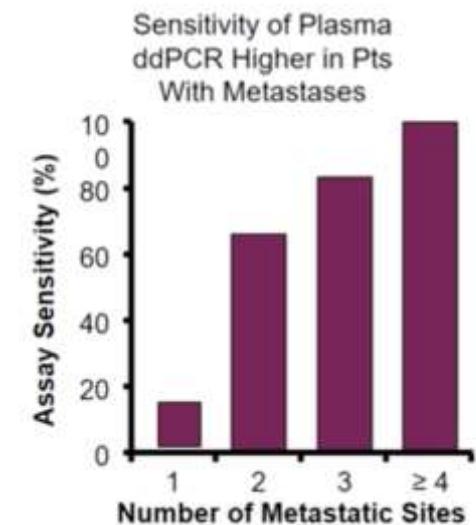
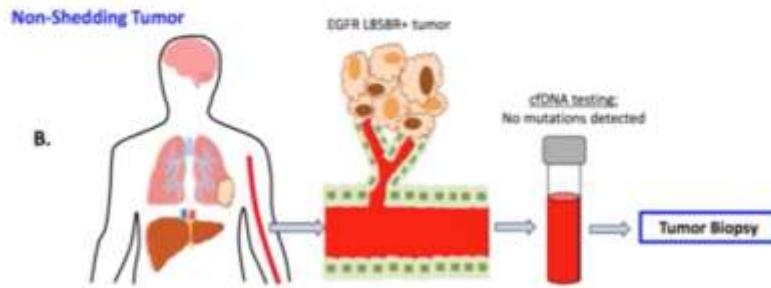
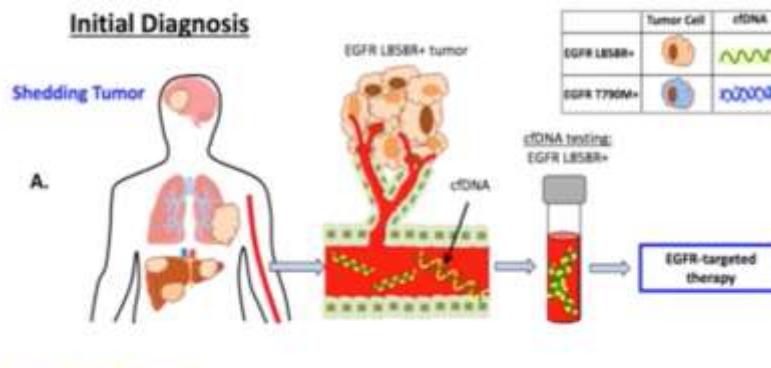
- In patients with ALK fusion and/or mutation, median OS was 18.0 months in those with dVAF < 0 (n=44) and 8.6 months in those with dVAF ≥ 0 (n=13) (HR 2.0, 95% CI, HR 0.9–4.6)



^aAnalysis is unstratified and includes patients in the progression-free group.

ALK, anaplastic lymphoma kinase; BL, brain metastasis; CDC, GCR, GCR 2; dVAF, digital tumor fraction; HR, hazard ratio; ICI, independent Clinical Review; IL, log-rank test for survival.

Number and site of metastases count for ctDNA detection



Take home messages

highlights

- **EGFR**
 - Old generation **TKIs + antiangiogenic/chemotherapy**: first line treatment options, higher toxicities, different patients population (combination with new generation EGFR-TKIs might improve safety profile)
 - **U3-1402 (HER3-targeting Ab)** and **JNJ372 (EGFR-MET Ab)**: promising agents with broad activity against heterogeneous acquired resistance mechanisms
 - **TAK-788**: potent and selective agent for unmet need in EGFRm+ NSCLC subgroup
- **MET/RET**
 - **METex14: Capmatinib, Tepotinib**: better option as first line treatment
 - **RET: BLU-667** broad activity against RET fusions, future options for naive RET+ or EGFRm+/acqRET NSCLC
- The forthcoming dynamic landscape where the possible sequence will drive first and subsequent choices might be enriched with genomic information on **early ctDNA clearance, prediction of resistant cases and subsequent treatment switch**



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