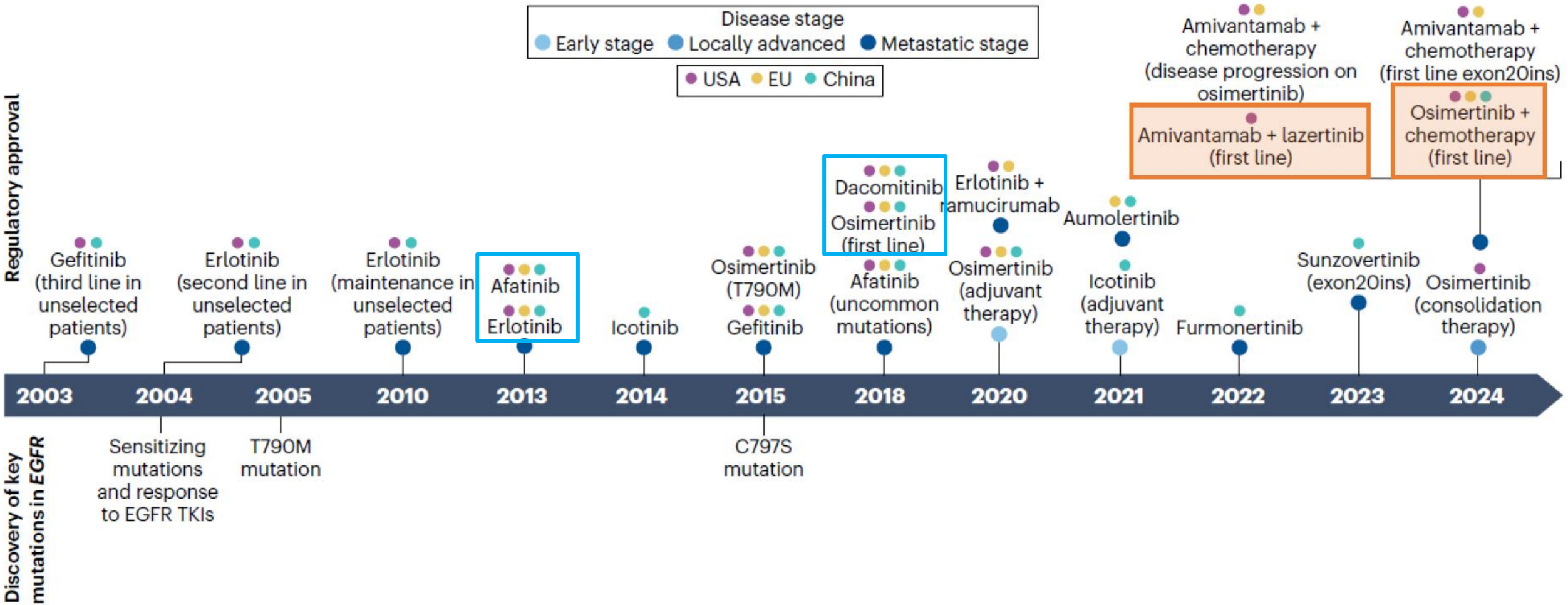
Optimizing for post 3rd Gen EGFR-TKI management in advanced EGFR mutant NSCLC

건국대병원

김 인 애

[Timeline of genomic discoveries and drug development in EGFR mutation]



First-Line EGFR TKIs Landmark Studies

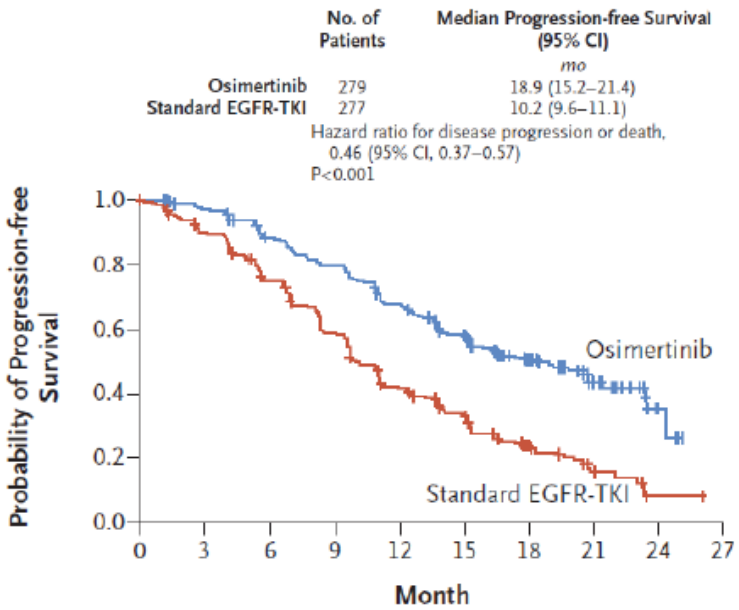
Trial	Year	Phase	Race	EGFR-TKI	ORR (%)	PFS (months, median)	OS (months, median)
IPASS	2009	III	Asian	Gefitinib	71.2	9.6	21.6
WJTOG 3405	2010	III	Asian	Gefitinib	62.1	9.2	35.5
NEJ002	2010	III	Asian	Gefitinib	73.7	10.8	27.7
OPTIMAL	2011	III	Asian	Erlotinib	83.0	13.1	22.8
First-SIGNAL	2012	III	Asian	Gefitinib	84.6	8.0	27.2
EURTAC	2012	III	Caucasian	Erlotinib	58.0	9.7	19.3
LUX-Lung3	2013	III	Asian, Caucasian	Afatinib	56.1	11.1	28.2
LUX-Lung6	2014	III	Asian	Afatinib	66.9	11.0	23.1
ARCHER1050	2015	III	Asian, Caucasian	Dacomitinib	75.0	14.7	34.1
FLAURA	2015	III	Asian, Caucasian	Osimertinib	80.0	18.9	38.6
LASER301	2020	III	Asian, Caucasian	Lazertinib	76.0	20.6	NR
FLAURA2	2023	III	Asian, Caucasian	Osimertinib/Chemotherapy	83.0	25.5	47.5
MARIPOSA	2024	III	Asian, Caucasian	Lazertinib/Amivantamab	86.0	23.7	More than 48.7

Contents

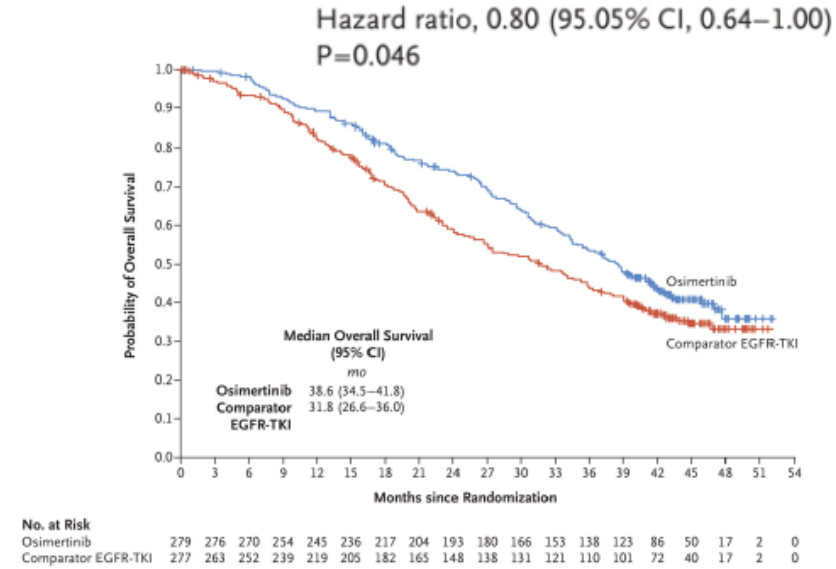
- **Post –3rd Gen EGFR-TKIs treatment**
  - **Target therapy**
    - 4th Gen EGFR-TKI, C797S…
    - Combined MET inhibitors
  - **All comer 2L**
    - ADC- Dato-Dxd, Sci-TMT, Iza-Bran
    - Bispecific antibody- Ivonescimab

Osimertinib as 1L

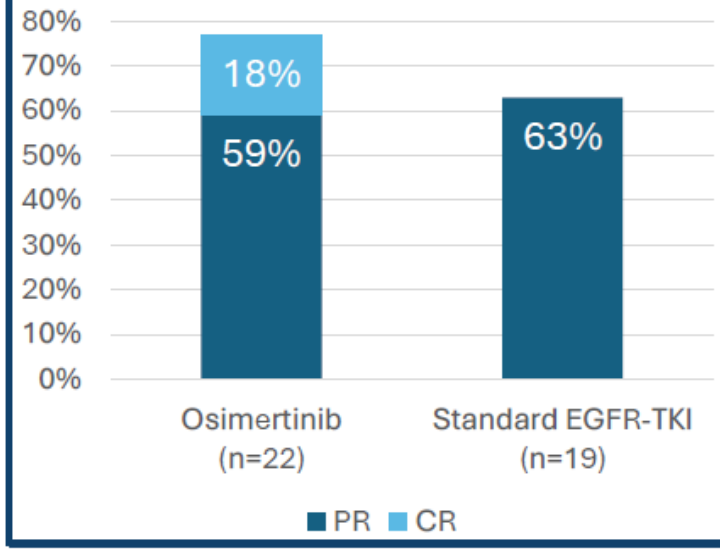
PFS



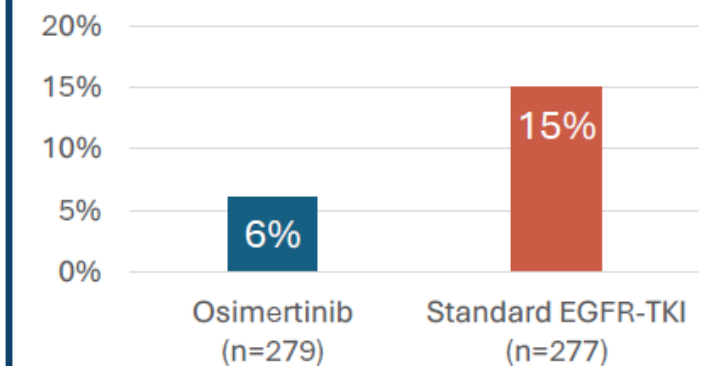
OS



CNS ORR



Rate of CNS PD



Soria, NEJM 2018; Ramalingam, NEJM 2019

Combination Therapy

MARIPOSA

MARIPOSA Study has more enrollment patients with 8w follow up (by 30 months)

FLAURA2

MARIPOSA Phase 3 Study Design

Serial brain MRIs were required for all patients[a]

Key Eligibility criteria
- Local advanced or metastatic NSCLC
- Treatment-naïve for advanced disease
- Document *EGFR* EX19del or L858R
- ECOG PS 0 or 1

Stratification Factors
- EGFR mutation type (Ex19del or L858R)
- Asian race (yes or no)
- History of brain metastatses[a] (yes or no)

2:2:1 Randomization (N= 1074)

- Amivantamab + Lazertinib (n=429; open-label)
- Osimertinib (n=429; blinded)
- Lazertinib (n=216; blinded)

Primary endpoint of PFS[b] by BICR per RECIST v1.1:
- **Amivantmab + lazertinib** vs Osimertinib

Secondary endpoints of amivantamab + lazertinib vs Osimertinib:
- OS[b]
- ORR
- DoR
- PFS after first subsequent therapy (PFS2)
- Symptomatic PFS[c]
- Intracranial PFS[c]
- Safety

Dosing (in 28-day cycles)
Amivantamab: 1050 mg (1400 mg if ≥ 80 kg) weekly for the first 4 weeks, then every 2 weeks.
Lazertinib:240 mg daily
Osimertinib: 80 mg daily

Lazertinib monotherapy arm was included to assess the contribution of components

[a]Baseline brain MRIs were mandatory for all patients and performed ≤28 days prior to randomization. Patients without the capability f or MRIs were allowed CT scans as a substitute. **Brain MRIs were conducted every 8 weeks for the first 30 months and every 12 weeks thereafter**. Extracranial tumour assessments followed the same schedule, aiming to confirm disease progression per BICR.
[b]The study was powered at 90%, with a two-sided alpha of 0.05. This ensures statistical rigor in detecting differences in PFS and OS
[c]These secondary endpoints (symptomatic PFS and intracranial PFS) will be presented at future congresses, implying that additional results may be forthcoming.

Figure adapted from amivantamab-plus-lazertinib-vs-osimertinib-longer-follow-up-of-the-mariposa-study.pdf. Copyright © 2024 The Authors. Published by World Conference on Lung Cancer

FLAURA2 Phase III study design

Safety run-in period (N=30)
Published in ESMO Open,2021[3]

Patients with untreated locally advanced/metastatic EGFRm NSCLC

Key inclusion criteria:
- Aged ≥ 18years (Japan: ≥ 20years)
- Pathologically confirmed non-squamous NSCLC
- Ex19del/L858R (local/central test)
- WHO PS 0/1
- No prior systemic therapy for advanced NSCLC
- Stable CNS metastases were allowed*
- Brain scans at baseline (MRI/CT)

Stratification by:
- **Race** (Chinese Asian/non-Chinese Asian/non-Asian)
- **EGFRm** (local/central test)
- **WHO PS** (0/1)

Randomization 1:1 (n=557)

- Osimertinib 80 mg (QD)
- Osimertinib 80mg (QD) + pemetrexed500 mg/m²+ carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles for platinum based treatments)
- Maintenance Osimertinib 80 mg (QD) + pemetrexed (Q3W) †

Follow-up:
- RECIST 1.1. assessment at 6 and **12 weeks, then every** 12 weeks until RECIST 1.1 defined radiological disease progression or other withdrawal criteria were met.

- **Primary Endpoint:** PFS by Investigator Assessment per RECIST 1.1
- **Sensitivity analysis:** PFS by BICR Assessment per RECIST 1.1.
- **Secondary endpoints**: OS, ORR, DoR, DCR, HRQoL, Safety (AEs by CTCAE v5), and PFS2

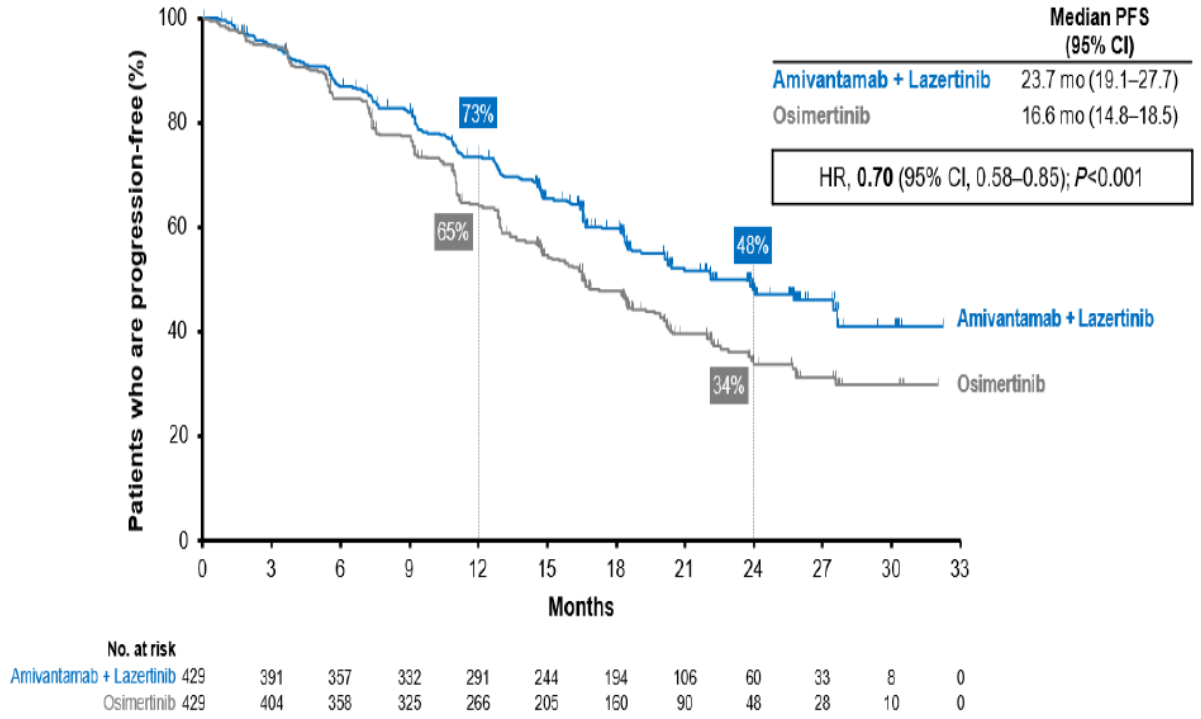
Figure adapted from Planchard D, et al. *N Engl J Med*. 2023;389(21):1935-1948. Copyright © 2023 Massachusetts Medical Society; Planchard D, et al. *ESMO Open*. 2021;6(5):10027.Copyright © 2021 The Authors. Published by Elsevier Ltd.

1. Cho BC, et al, N Engl J Med. 2024;391 (16):1486-1498.; 2. Planchard D, et al. N Engl J Med. 2023;389(21):1935-1948; 3. Planchard D, et al. ESMO Open. 2021;6(5):100271.

Primary Endpoint: Progression-Free Survival

MARIPOSA

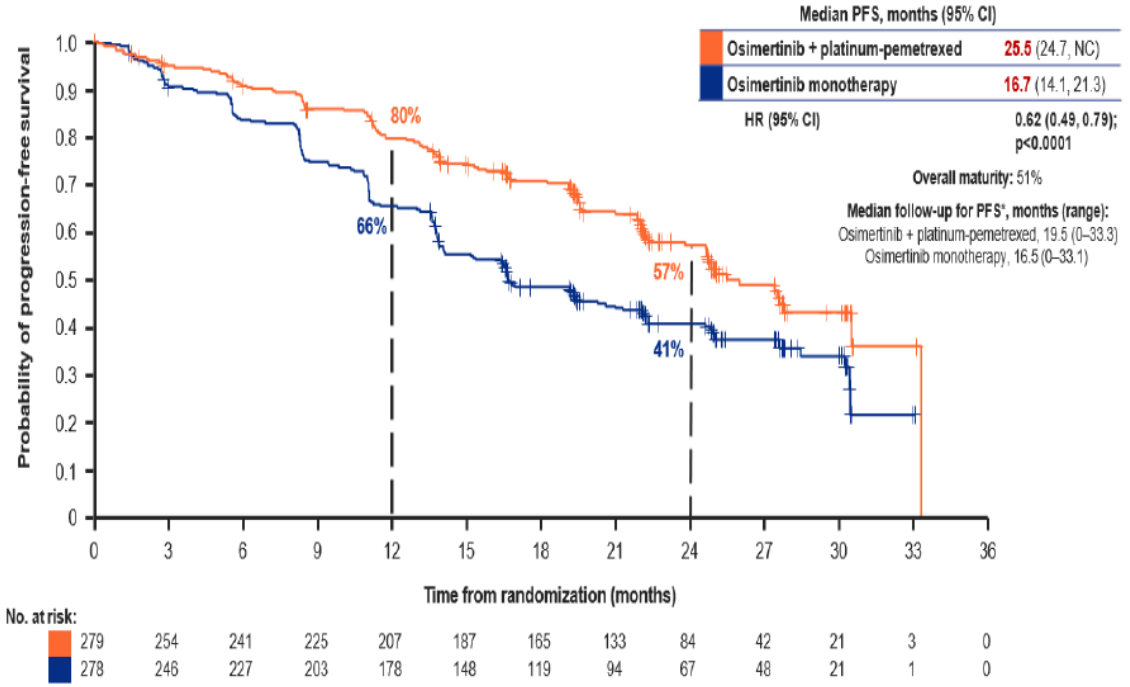
PFS by Blinded Independent Central Review



[a]At the time of prespecified final PFS analysis, there were a total of 444 PFS events in the amivantamab+ lazertinib and osimertinib arms combined.

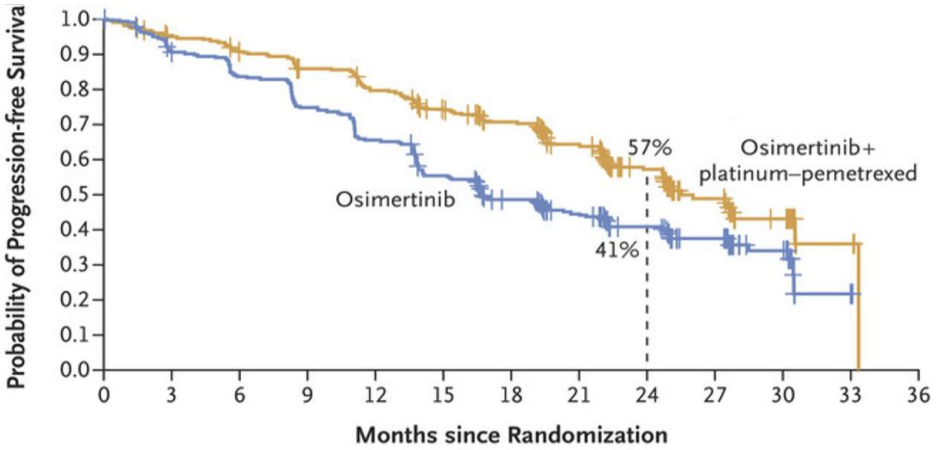
FLAURA2

PFS by Investigator Assessment



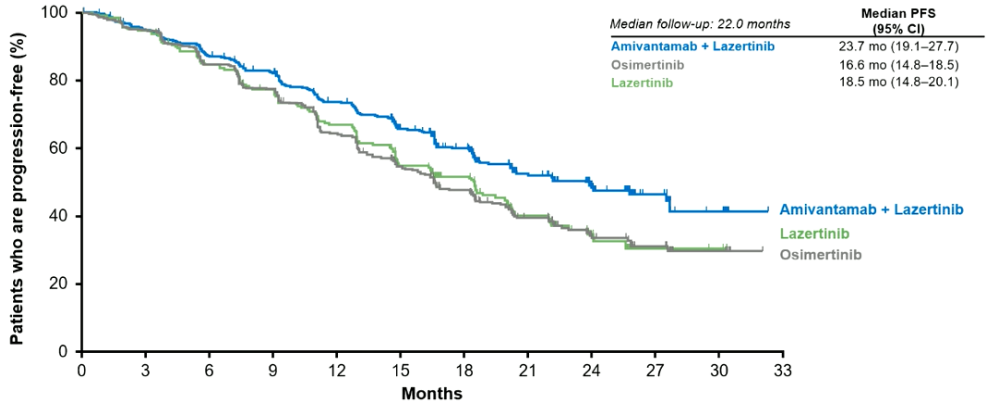
Upfront combination therapy improves PFS

FLAURA2:
Osimertinib + Platinum Doublet vs Osimertinib



Median PFS 16.7 → 25.5 months
HR 0.62; 95% CI, 0.49 to 0.79

MARIPOSA:
Amivantamab + Lazertinib vs Osimertinib

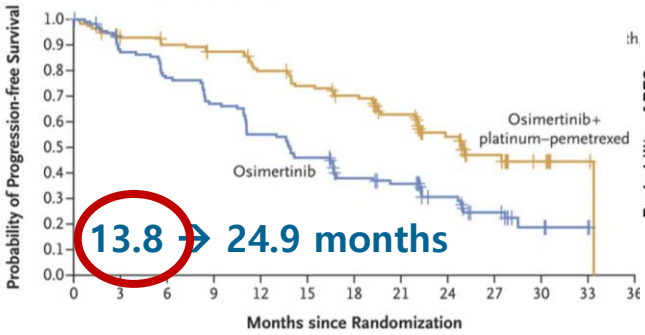


Median PFS 16.6 → 23.7 months
HR 0.70; 95% CI, 0.58 to 0.85

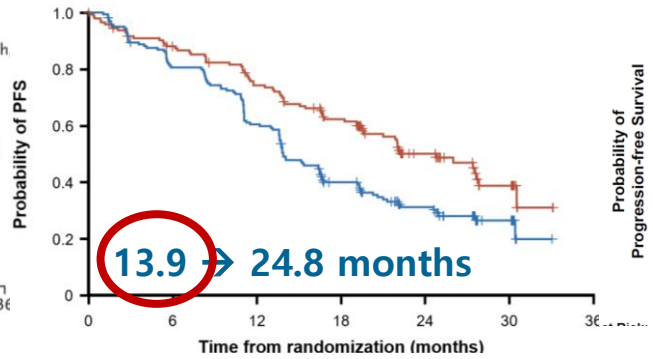
But the potential benefit is not the same for all patients.
What does it mean to have “higher-risk” EGFR lung cancer?

FLAURA2 Subgroup Analysis

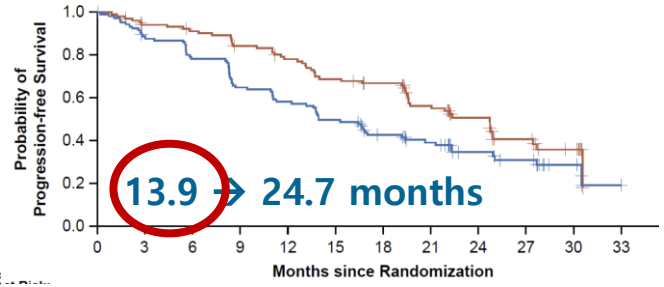
With Brain Metastases



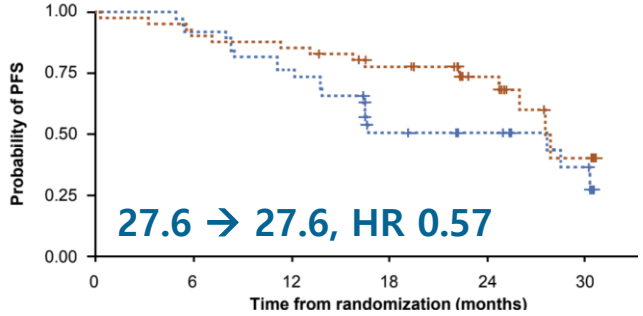
Plasma EGFR Detectable



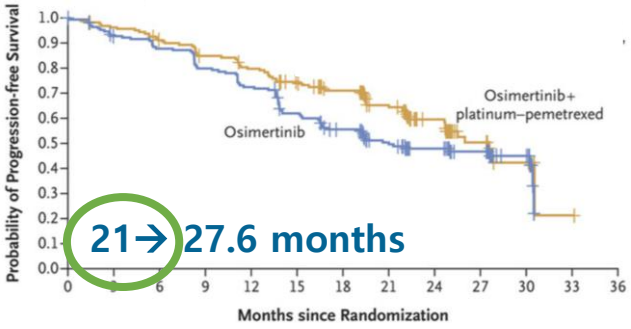
EGFR L858R



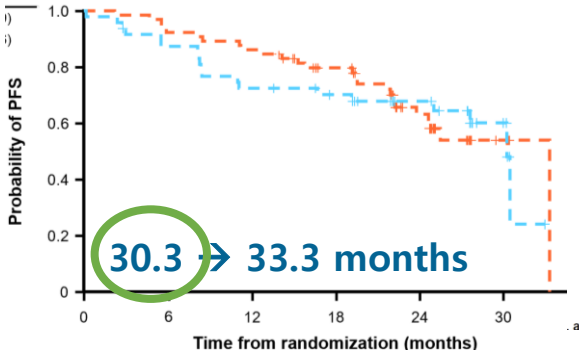
TP53 Mutated



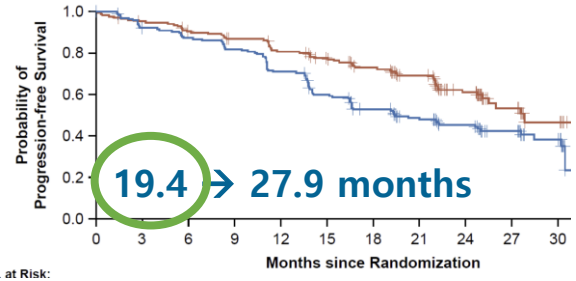
Without Brain Metastases



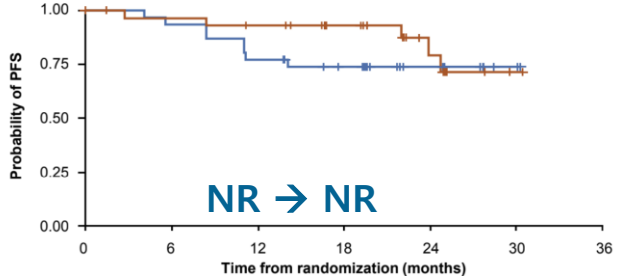
Plasma EGFR Undetectable



EGFR Exon 19 Deletions



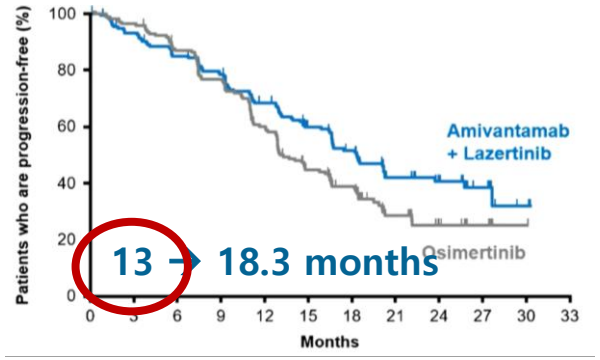
TP53 Wild Type



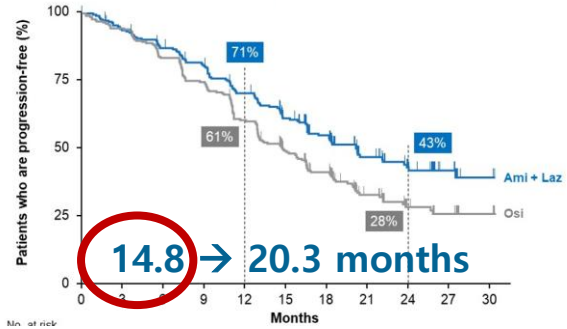
Planchard et al. *N Engl J Med*. 2023;389(21):1935-1948; Janne, AACR 2024

MARIPOSA Subgroup Analysis

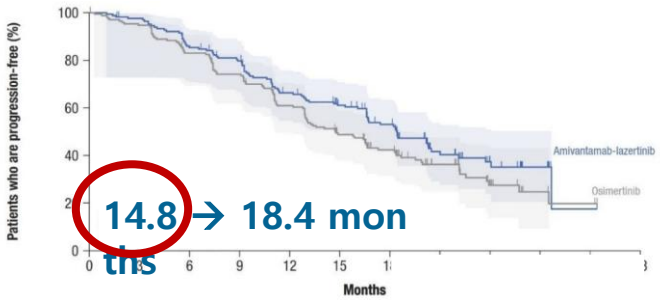
With Brain Metastases



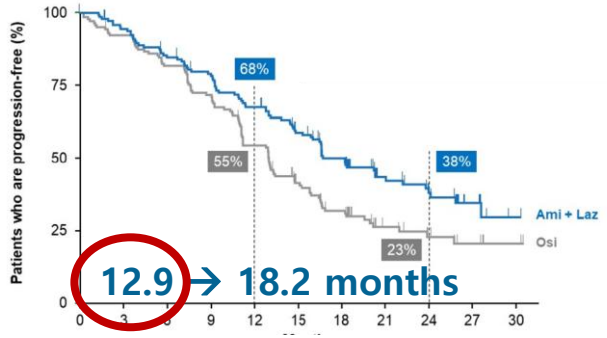
Plasma EGFR Detectable



EGFR L858R



TP53 Mutated



Without Brain Metastases

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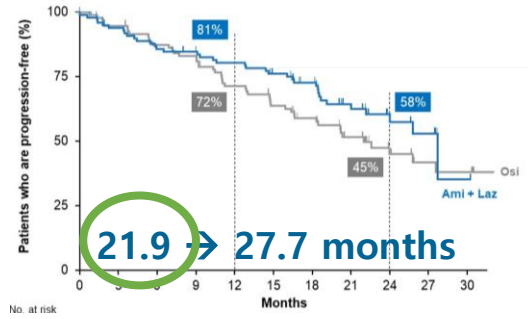
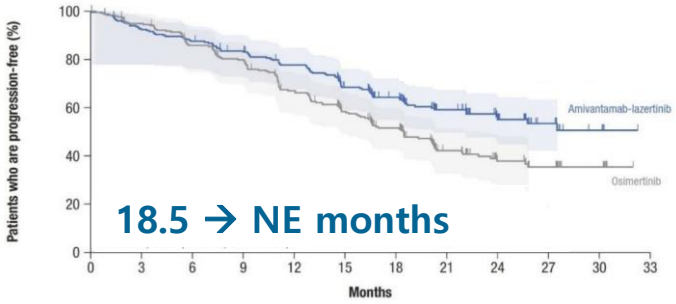
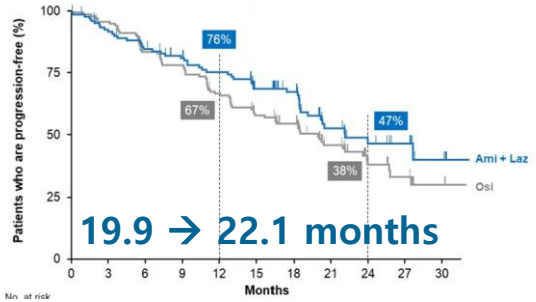


EGFR Exon 19 Deletions



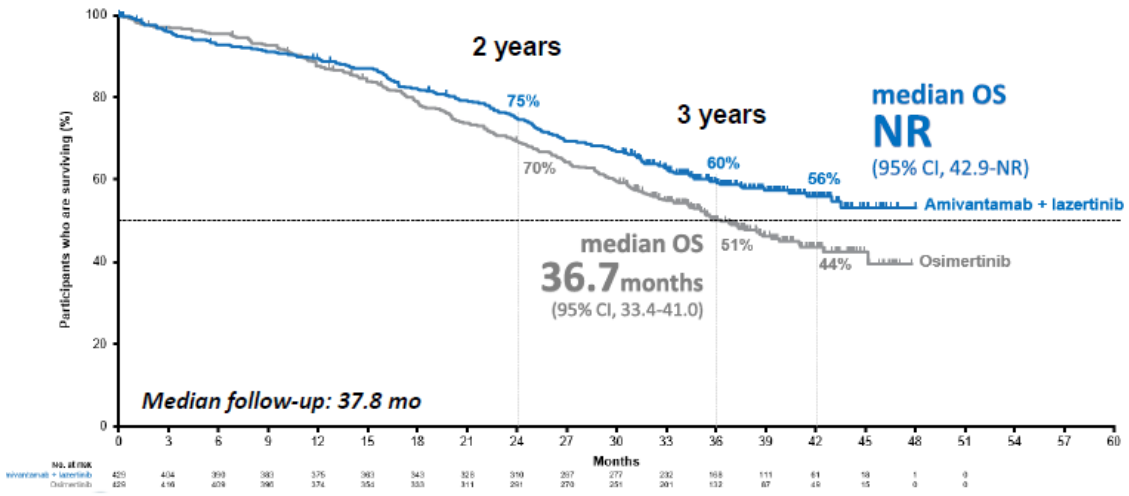
TP53 Wild Type



Cho et al. ESMO 2023. LBA14; Felip et al ASCO 2024; Cho et al NEJM 2024

Overall survival

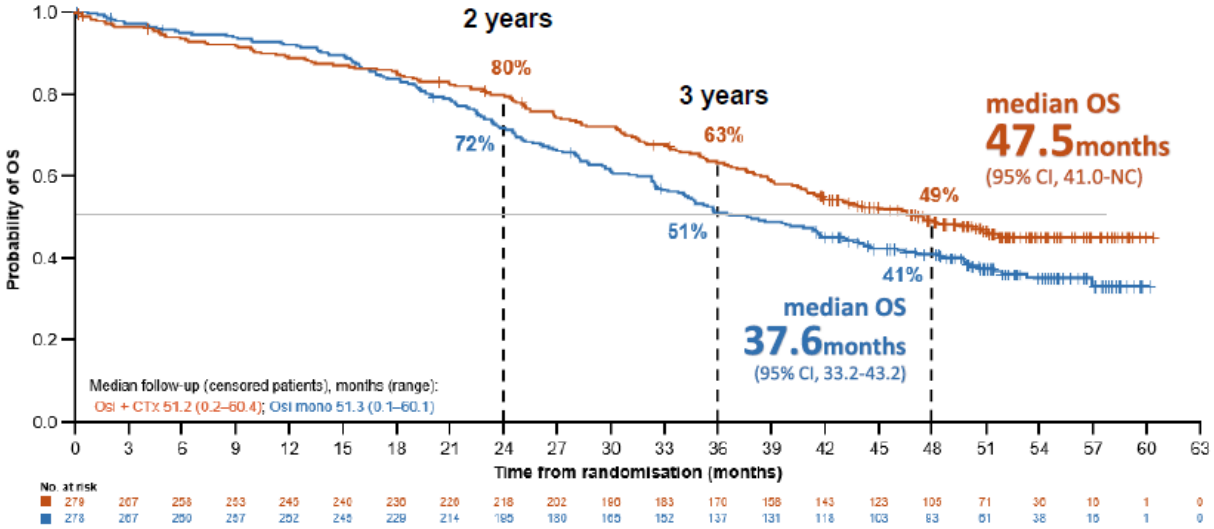
MARIPOSA



Median follow-up: 37.8 mo	Median OS (95% CI)
Amivantamab + lazertinib	Not reached (42.9–NR)
Osimertinib	36.7 mo (33.4–41.0)

HR, 0.75; (95% CI, 0.61–0.92); *P*<0.005

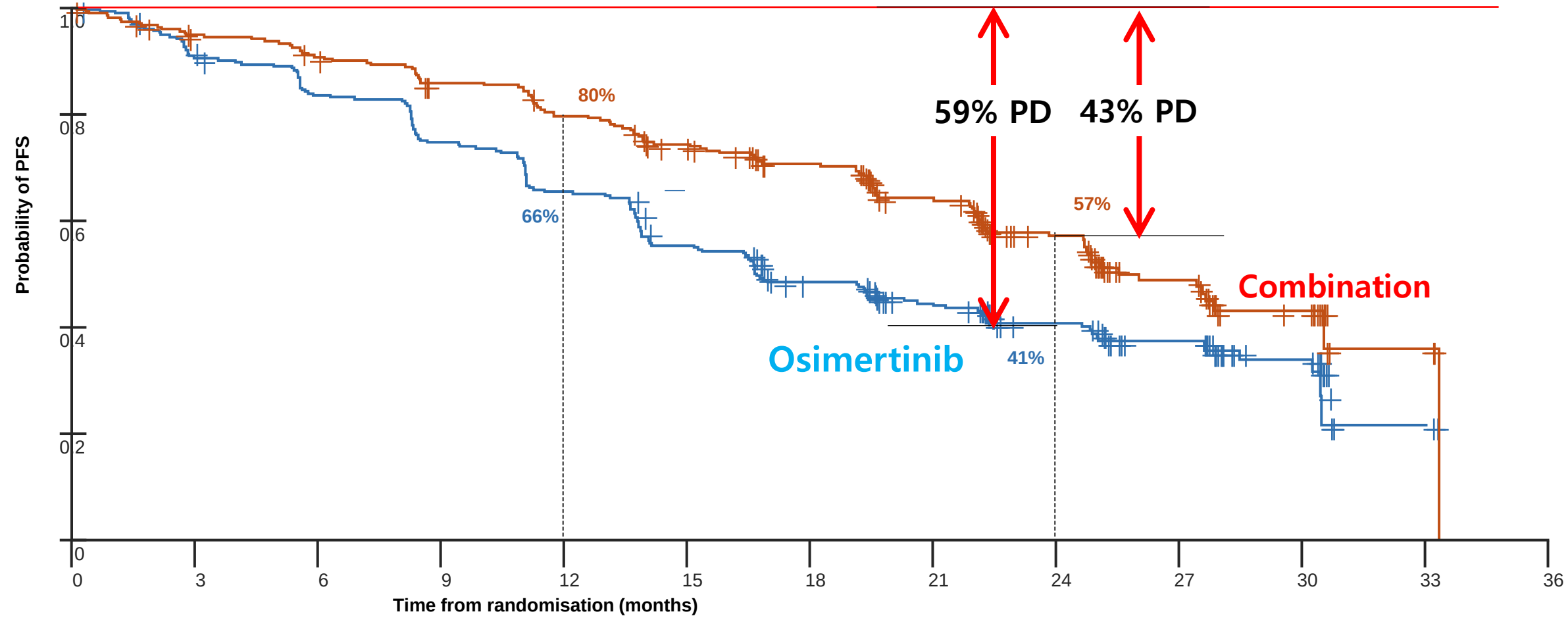
FLAURA2



	No. Events / no. patients (%)	Median OS, months (95% CI)
Osi + CTx	144 / 279 (52)	47.5 (41.0, NC)
Osi mono	171 / 278 (62)	37.6 (33.2, 43.2)
HR (95% CI)	0.77 (0.61, 0.96); p=0.02	

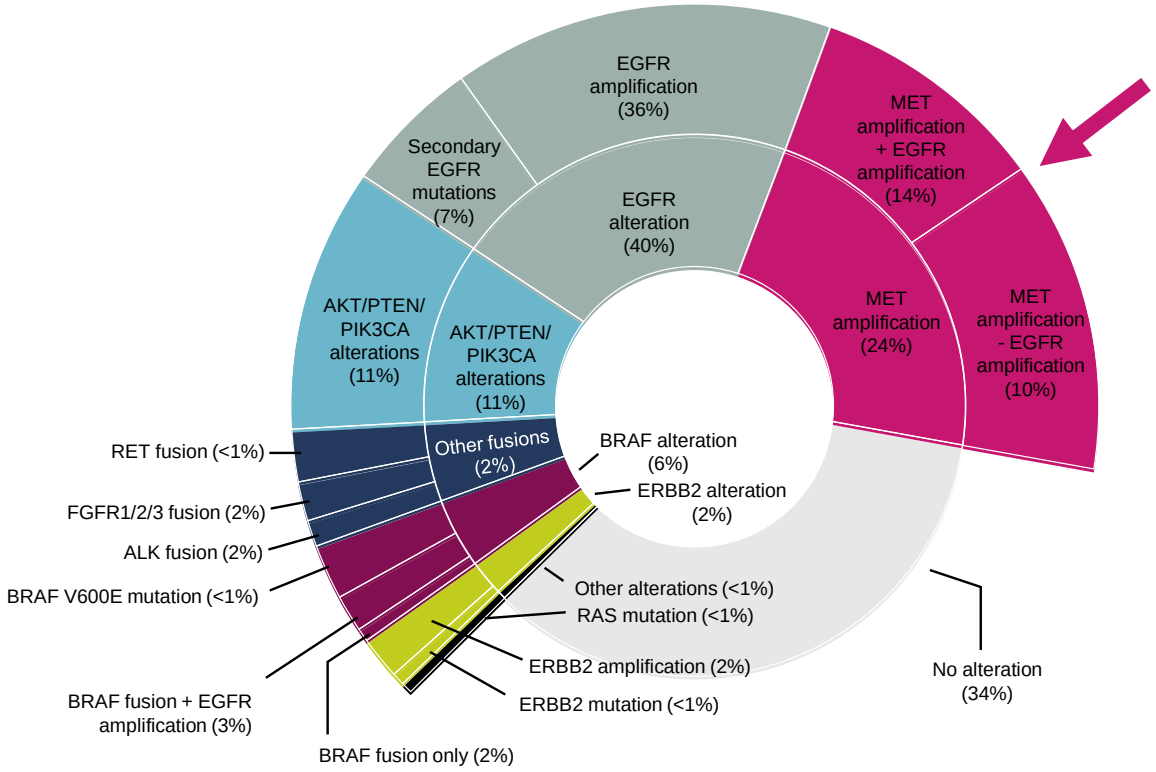
Crossover allowed → 초기에 intensified tx 생존에 이익

Primary analysis: Progression-free survival (FLAURA2)



Osi +Chemo combination 을 해도 2년 후 43% PD

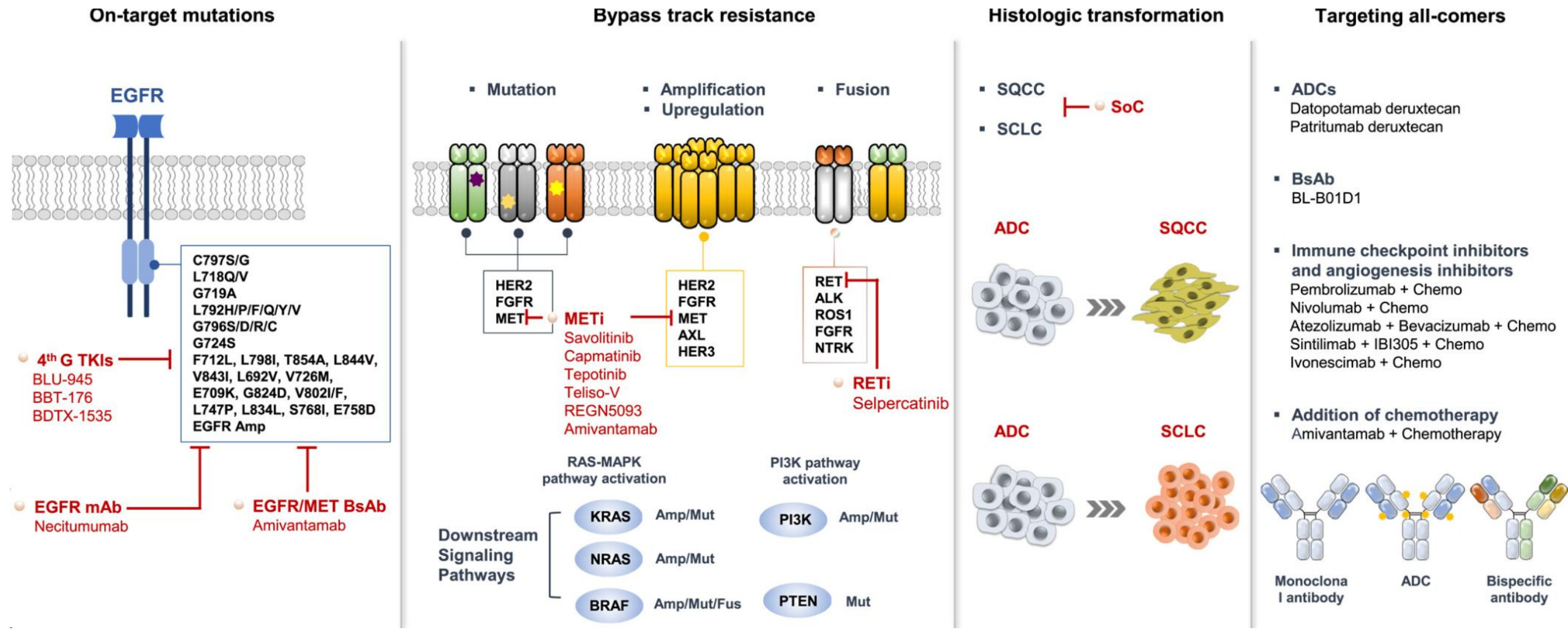
Resistance mechanism to 1L osimertinib



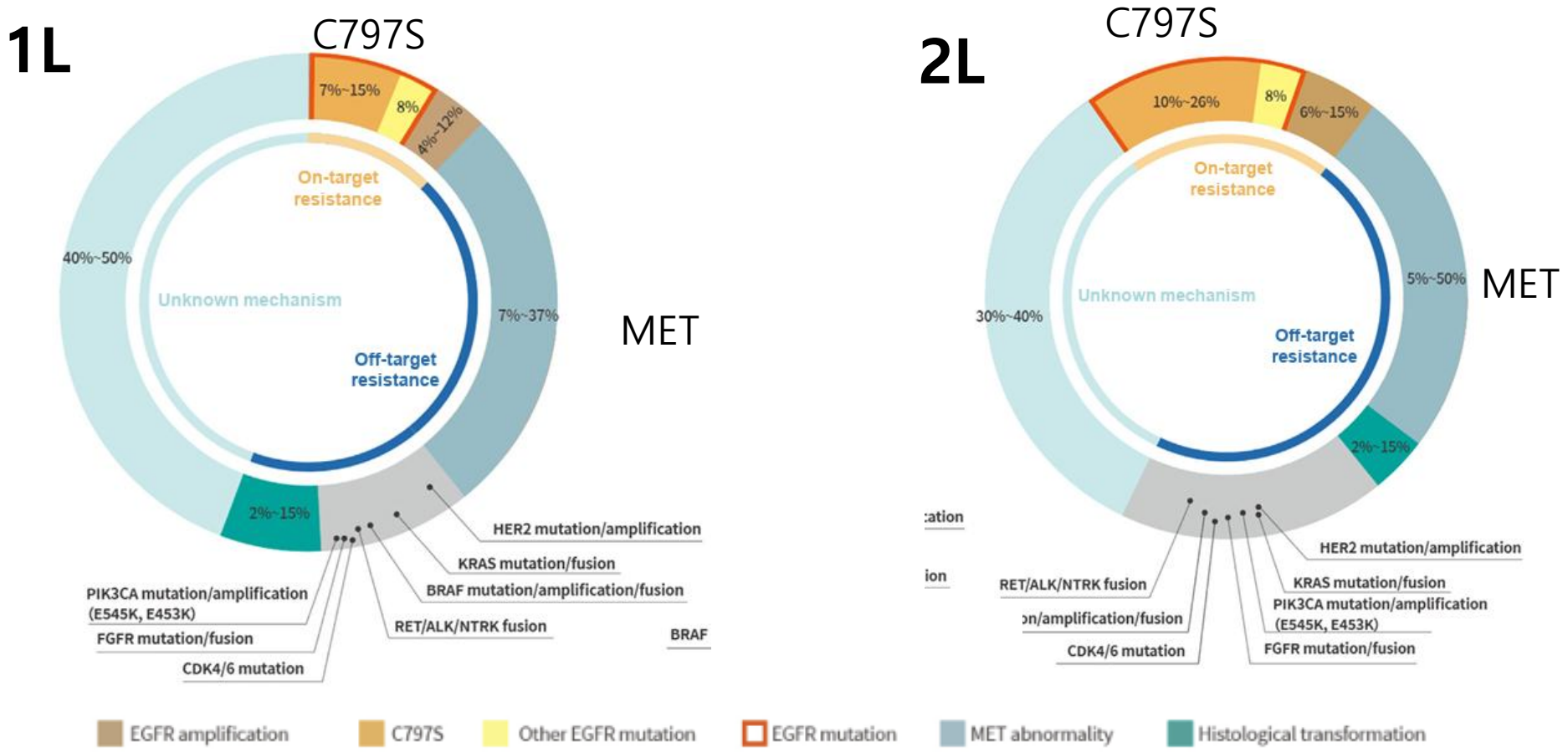
- Orchard Trial: 174 patients had tumor tissue biomar ker status available by central testing
- MET amplification was the most prevalent resistance mechanism (42/174, 24%)
- AKT / PTEN / PIK3CA mutations were found in 19/174 (11%) tissue samples
- BRAF fusions were found in 9/174 (5%) tissue sampl es
- Other potentially targetable genetic alterations were rare

Okamoto, Japan Lung Cancer Society, 2022.
Riess J, 2023 Texas Lung Conference, 2023.

Mechanism of post-osimertinib resistance



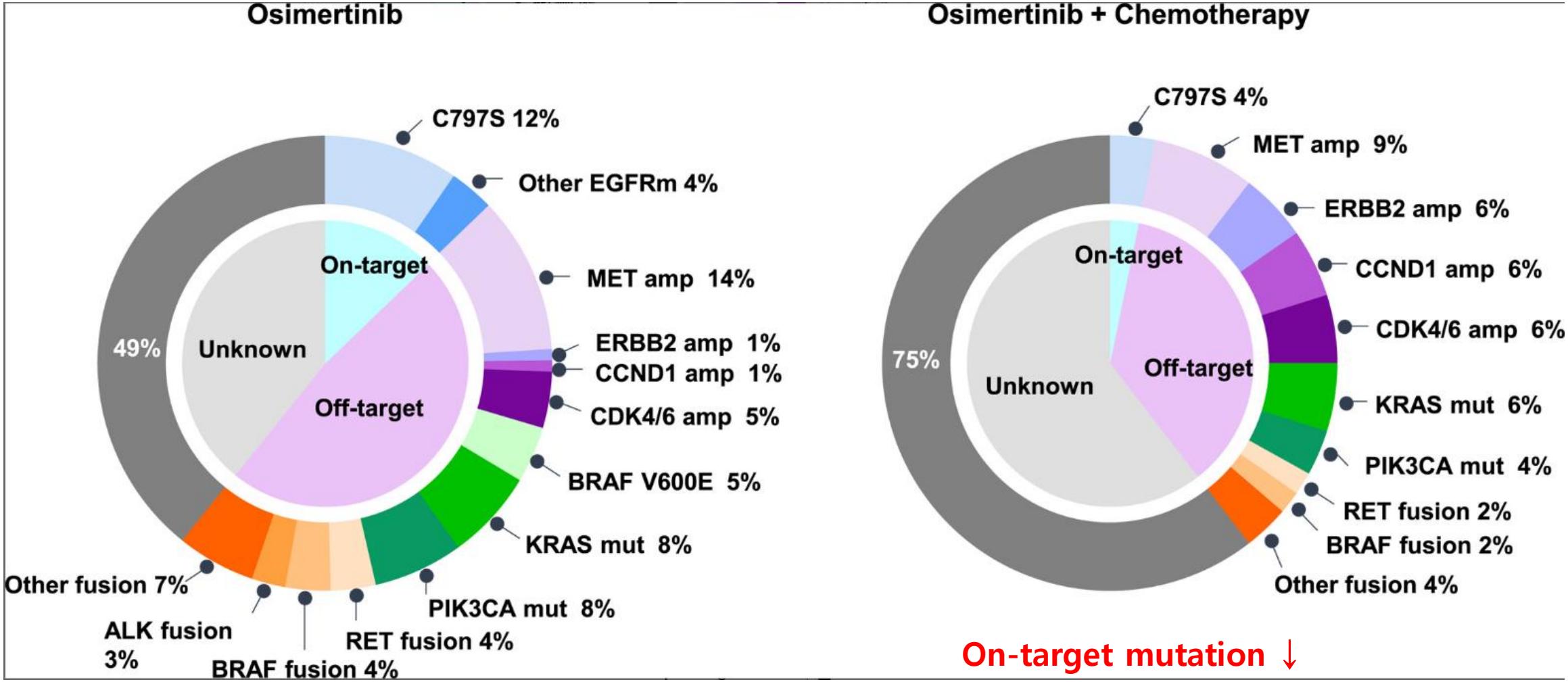
Third-generation EGFR-TKI resistance



Mechanism of resistance to osimertinib.

Zhou Q et al. Lancet Reg Health West Pac. 2024 Dec 11;53:101260.

Acquired mechanisms of resistance to osimertinib and osimertinib plus chemotherapy (FLAURA 2 study)

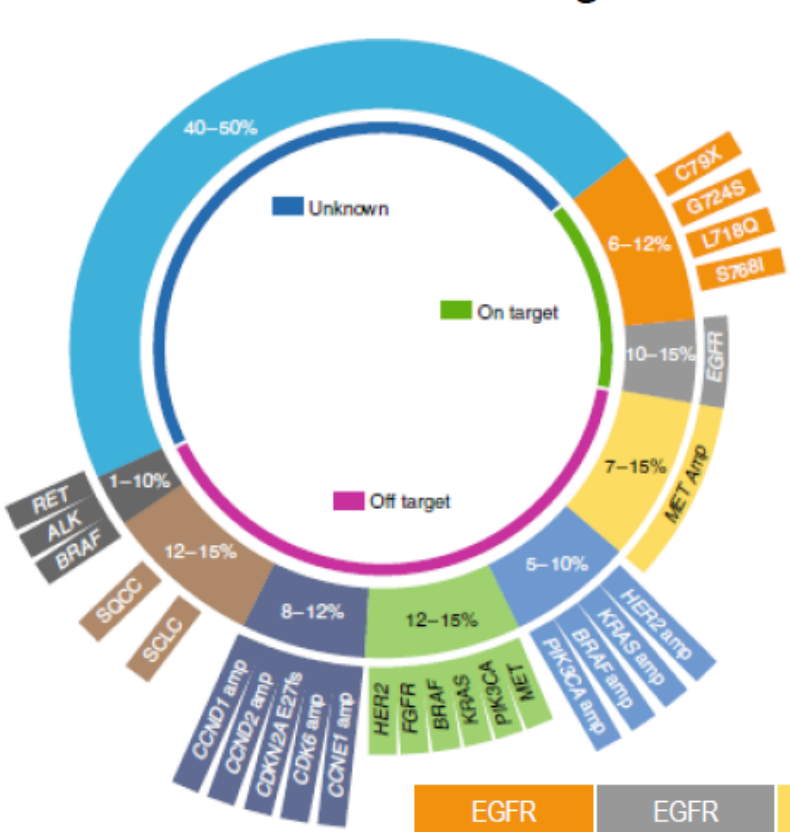


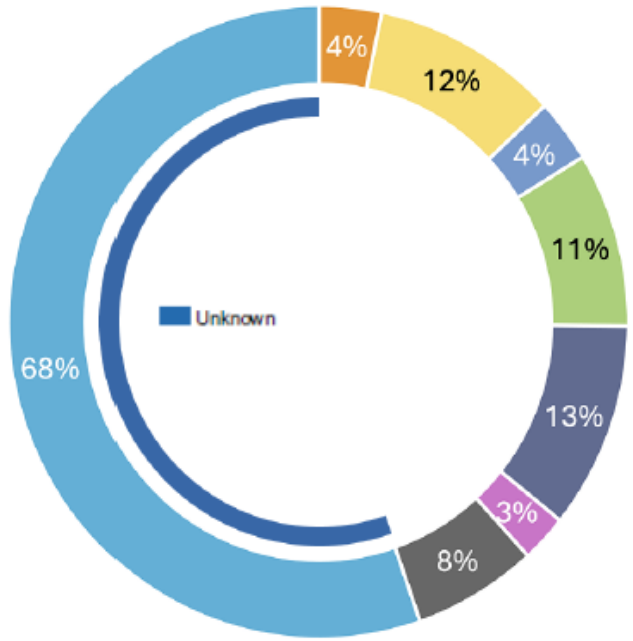
1L therapy shapes resistance

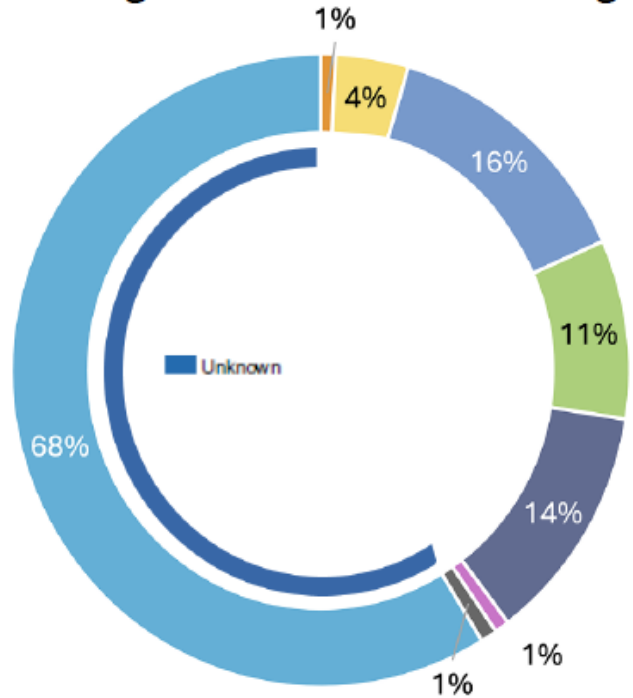
Osimertinib | Osimertinib + chemotherapy | Amivantamab + Lazertinib

New tumor sample or ct DNA at PD

The lack of an actionable target in the majority of patients validates the development of agnostic treatment strategies







EGFR mutation | EGFR amplification | MET amplification | Other acquired amplifications | Acquired mutations | Cell cycle gene alteration | Histological transformation | Fusion | TP53 loss

Adapted from Passaro A, Nature Cancer 2021; Yang J, Presented at WCLC 2024; Besse B, Presented at ESMO 2024

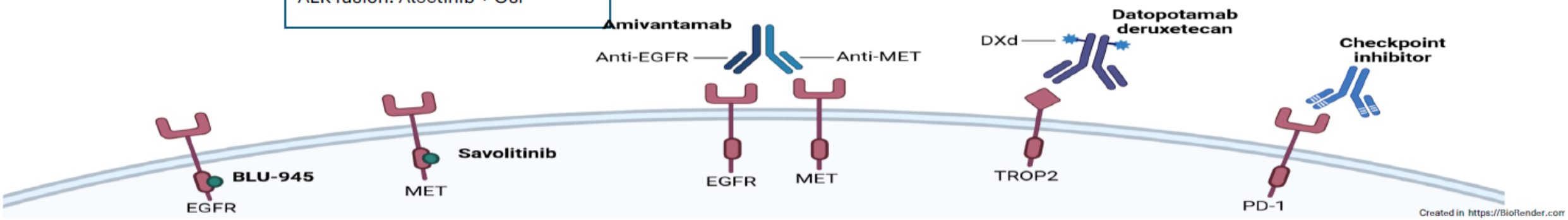
Post-Osimertinib Novel Treatment Strategies

Genotype-matched strategies

Mechanism-agnostic strategies

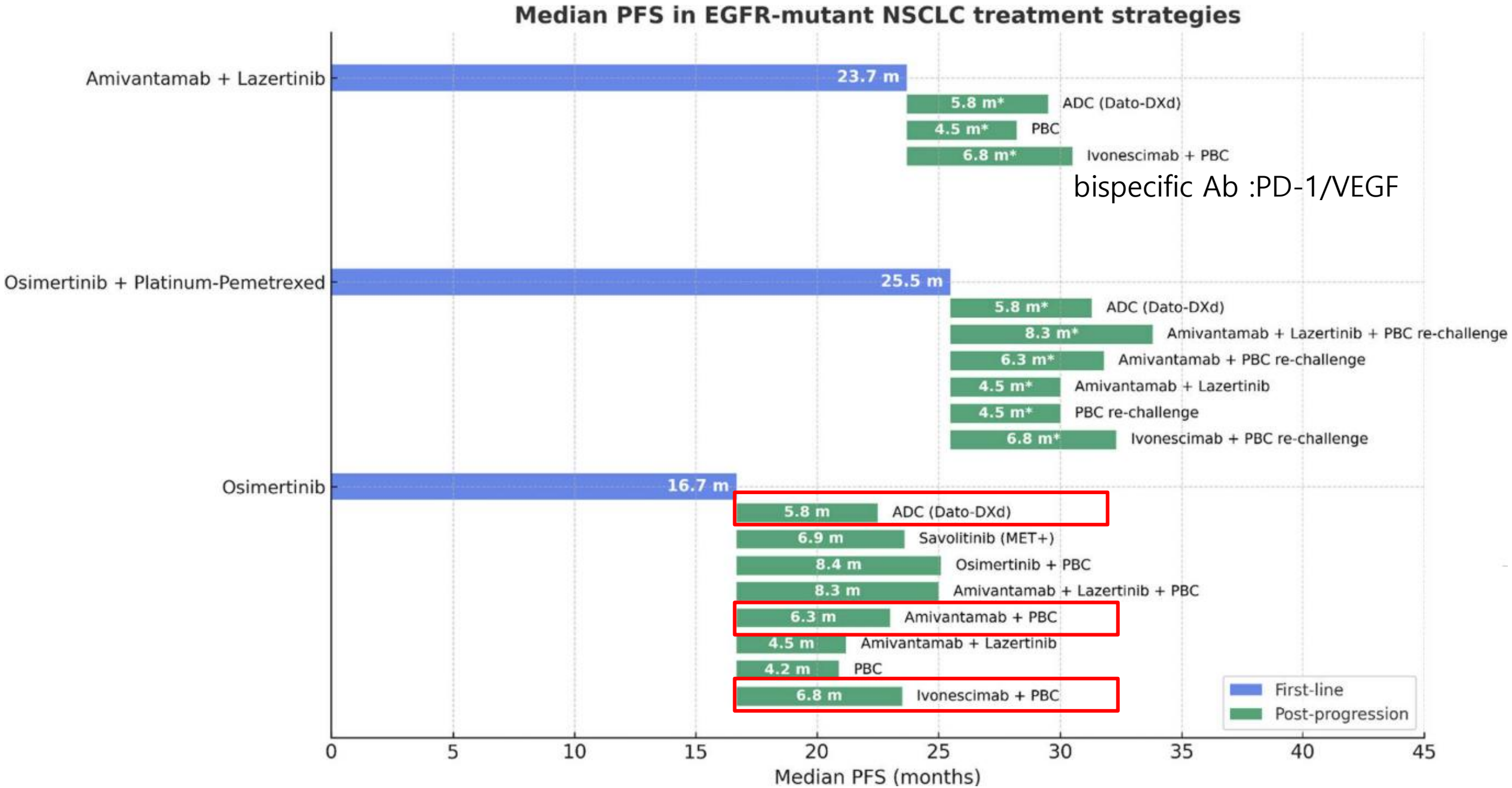
(non-genotype based)

On-target inhibition	Bypass pathway inhibition	On-target + bypass pathway inhibition	Targeting tumor-associated antigen	Targeting common escape routes
EGFR TKI/mAB	**Resistance-matched agents**	**Biespecific mAB/ADC targeting EGFR + bypass pathway**	**ADCs**	**mAB**
C797X mut: Gefitinib Gefitinib + Osi	cMET amp: Savolitinib + Osi Capmatinib + Osi Tepotinib + Osi cMET over-exp: Teliso V +/- Osi	Amivantamab (EGFR + cMET)	Datopotomab DXd (TROP2) Sacituzumab tirumotecan	Ivonescimab (PDL1 + VEGF) + Chemo
EGFR alt: Necitumumab + Osi 4G EGFR TKI	HER2 over-exp: TDM1 + Osi	Izalontamab brengitecan (EGFR + HER3)	Patritumab DXd (HER3)	Anti PD1/L1 + Antiangiogenic + Chemo
	RAS-MAPK act: Selumetinib + Osi			
	ALK fusion: Alectinib + Osi			



Two primary strategy for managing EGFR TKI resistance

Resistance Matched strategy	“ All-Comer” 2L Strategy
+ Personalized, may offer higher ORR/favorable toxicity	+ Rapid initiation, No waiting for genomic IHC
- Delay In Rx to permit resistance testing	+ TKI backbone may not be needed
- Biopsy/NGS required	+ Biopsy/NGS not required
- TKI backbone typically required post-progression	- Best ORR far fall short of matched targeted therapy, but long DOR.
- May miss the tumor heterogeneity	- Higher off target toxicity
Ex) Met inhibitors, C797S Inhibitors	Ex) BiAb (Amivantamab, Ivonescimab) ADC (Dato-DXD, Sac-TMT)



PBC: Platinum-based chemotherapy

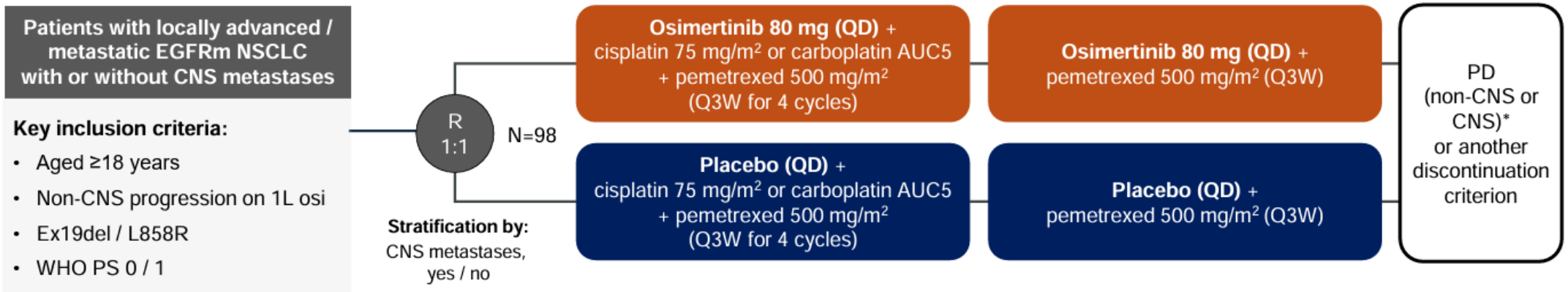
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL ARTICLE

COMPEL: osimertinib plus platinum-based chemotherapy in patients with EGFR-mutated advanced NSCLC and progression on first-line osimertinib

COMPEL: Global, randomised, phase III double-blind study

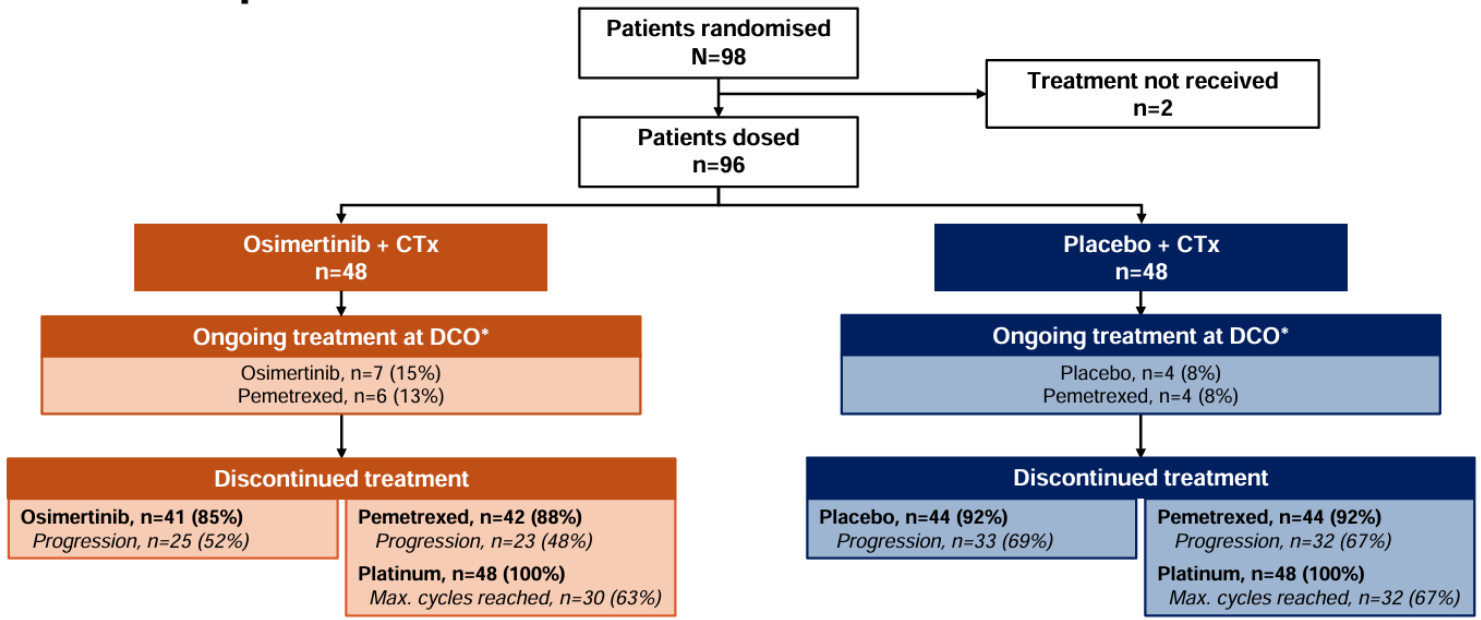


The COMPEL study explored whether osimertinib + chemo improves outcomes vs placebo + chemo in patients with EGFRm advanced NSCLC following **non-CNS progression on 1L osimertinib**

- **Primary endpoint: PFS (investigator-assessed)**
- **Secondary endpoints: CNS PFS**

Peled et al. ESMO open 2025

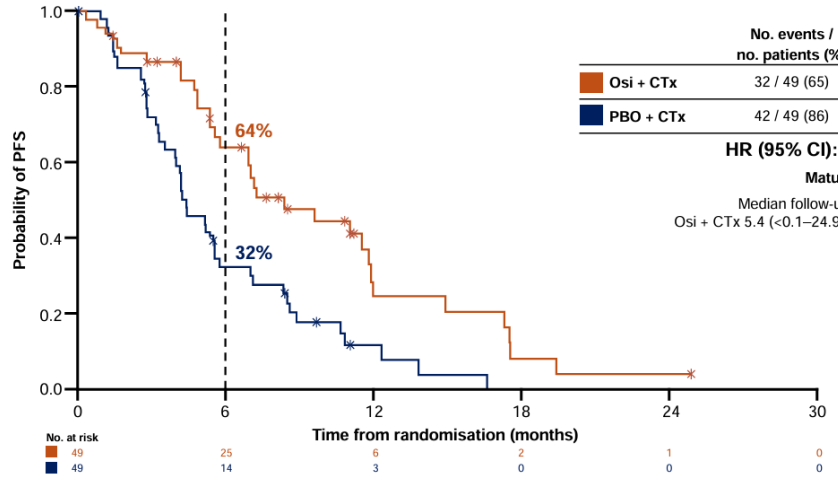
Patient disposition



Baseline characteristics

Characteristic, %*	Osi + CTx (n=49)	PBO + CTx (n=49)
Sex: male / female	39 / 61	20 / 80
Age: median (range), years	63 (37–85)	61 (42–88)
Race: Asian / White / other / not reported	12 / 80 / 2 / 6	18 / 78 / 2 / 2
WHO PS: 0 / 1†	45 / 53	49 / 51
Smoking status: never / current / former	65 / 8 / 27	67 / 4 / 29
EGFR mutation type: Ex19del / L858R‡	65 / 35	55 / 45
Disease stage at study entry (AJCC): IIIB / IV	0 / 100	2 / 98
Number of metastatic sites at study entry: median (range)	2 (1–6)	2 (1–7)
CNS metastases present at baseline	22	24
Time on 1L osimertinib: median (range), months§	21.3 (3.2–51.3)	19.6 (7.4–52.3)

Primary analysis: Progression-free survival (PFS)*



	No. events / no. patients (%)	Median PFS, months (95% CI)
Osi + CTx	32 / 49 (65)	8.4 (5.7, 11.8)
PBO + CTx	42 / 49 (86)	4.4 (3.5, 5.6)

HR (95% CI): 0.43 (0.27, 0.70)

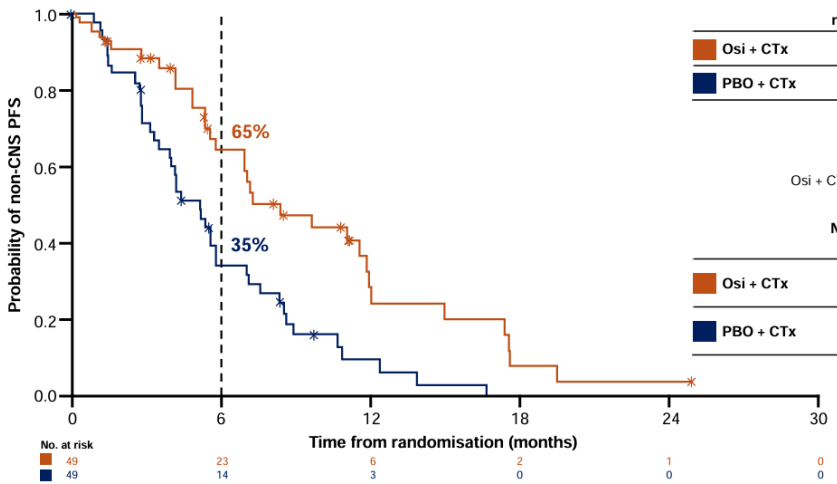
Maturity: 76%

Median follow-up,† months (range):
Osi + CTx 5.4 (<0.1–24.9); PBO + CTx 5.5 (<0.1–11.1)

Osi + CTx was associated with improved PFS versus PBO + CTx

Osi+Chemo vs chemo
mPFS: **8.4 vs 4.4 months**

Non-CNS (extracranial) PFS*



	No. events / no. patients (%)	Median non-CNS PFS, months (95% CI)
Osi + CTx	31 / 49 (63)	8.4 (5.7, 11.8)
PBO + CTx	41 / 49 (84)	5.2 (3.5, 5.8)

HR (95% CI): 0.43 (0.26, 0.71)

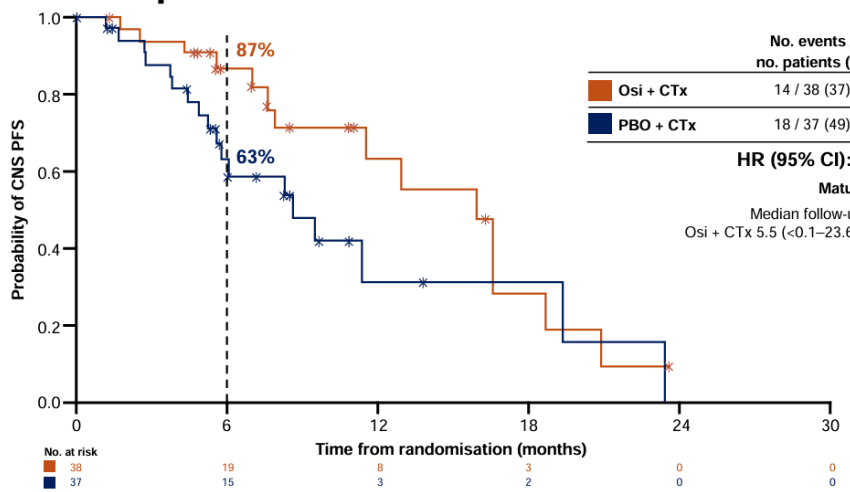
Maturity: 73%

Median follow-up,† months (range):
Osi + CTx 3.6 (<0.1–24.9); PBO + CTx 3.6 (<0.1–9.7)

	Non-CNS ORR,‡ n (%) [95% CI]	Median non-CNS DOR,‡ months (IQR)
Osi + CTx	17 (35) [22, 50]	8.2 (4.4–12.2)
PBO + CTx	14 (29) [17, 43]	4.2 (3.1–7.6)

Osi + CTx was associated with improved non-CNS PFS versus PBO + CTx

CNS PFS* in patients without baseline CNS metastases



	No. events / no. patients (%)	Median CNS PFS, months (95% CI)
Osi + CTx	14 / 38 (37)	15.9 (7.9, 18.6)
PBO + CTx	18 / 37 (49)	8.6 (5.6, 19.4)

HR (95% CI): 0.56 (0.27, 1.13)

Maturity: 43%

Median follow-up,† months (range):
Osi + CTx 5.5 (<0.1–23.6); PBO + CTx 5.6 (<0.1–13.8)

CNS PFS was longer with osi + CTx versus PBO + CTx in patients without baseline CNS metastases

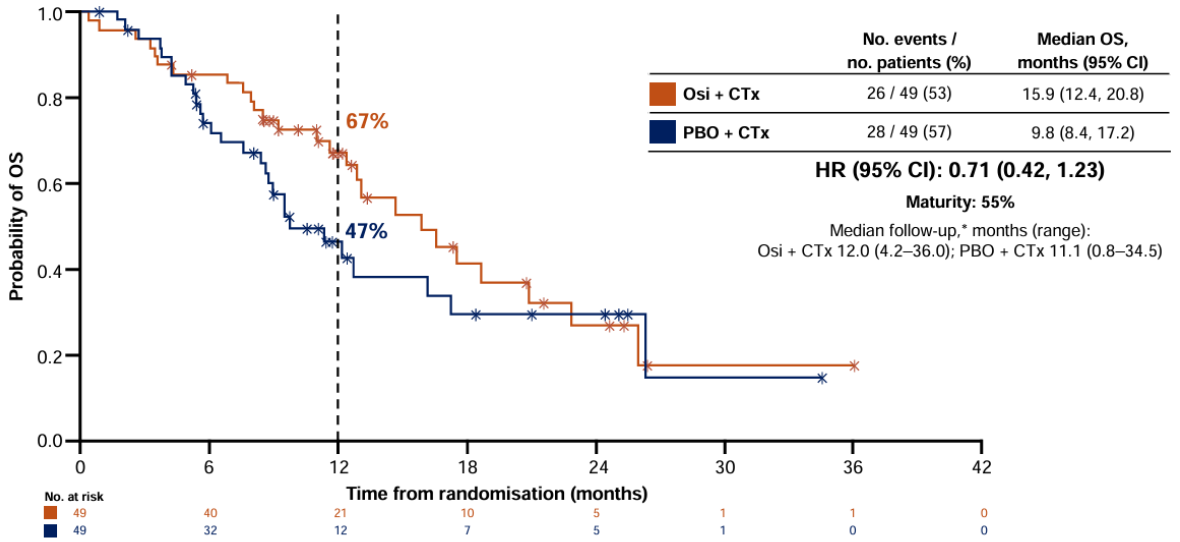
New brain meta 가 생기는 경우-
Osi 유지 brain meta 늦춤

New lesions*

	Osi + CTx (n=49)	PBO + CTx (n=49)
Patients with new lesions, n (%)†	18 (37)	25 (51)
Brain	5 (10)	13 (27)
Liver	6 (12)	7 (14)
Lung	6 (12)	3 (6)
Bone	2 (4)	4 (8)
Adrenal gland	1 (2)	2 (4)
Pleural effusion	1 (2)	2 (4)

Fewer patients had new brain lesions with osi + CTx versus PBO + CTx

Overall survival (OS)



OS was longer with osi + CTx versus PBO + CTx

Osi+ Chemo : Chemo
mOS 15.9 mon vs 9.8 mon

PFS. OS 이득
Brain meta 억제

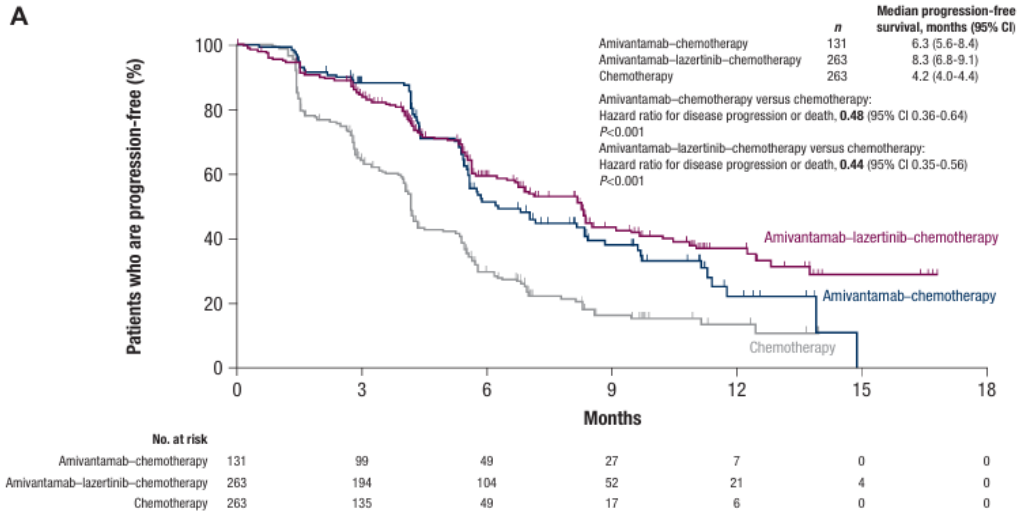
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

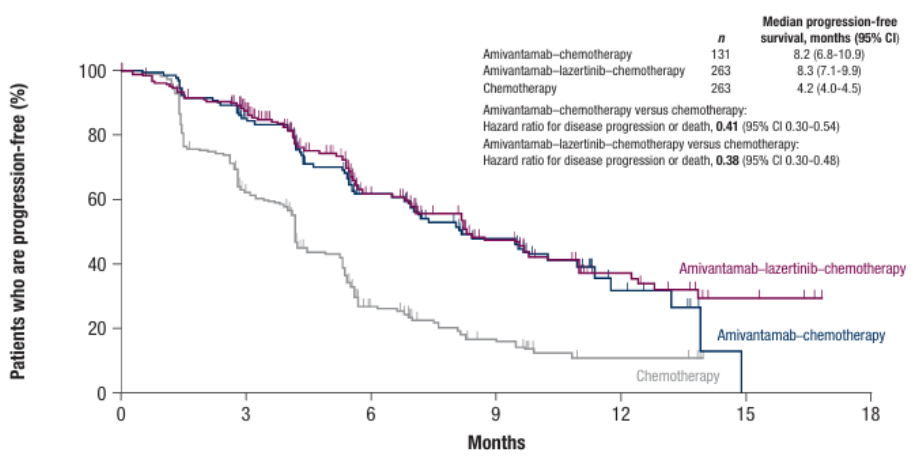
ANNALS OF ONCOLOGY driving innovation in oncology

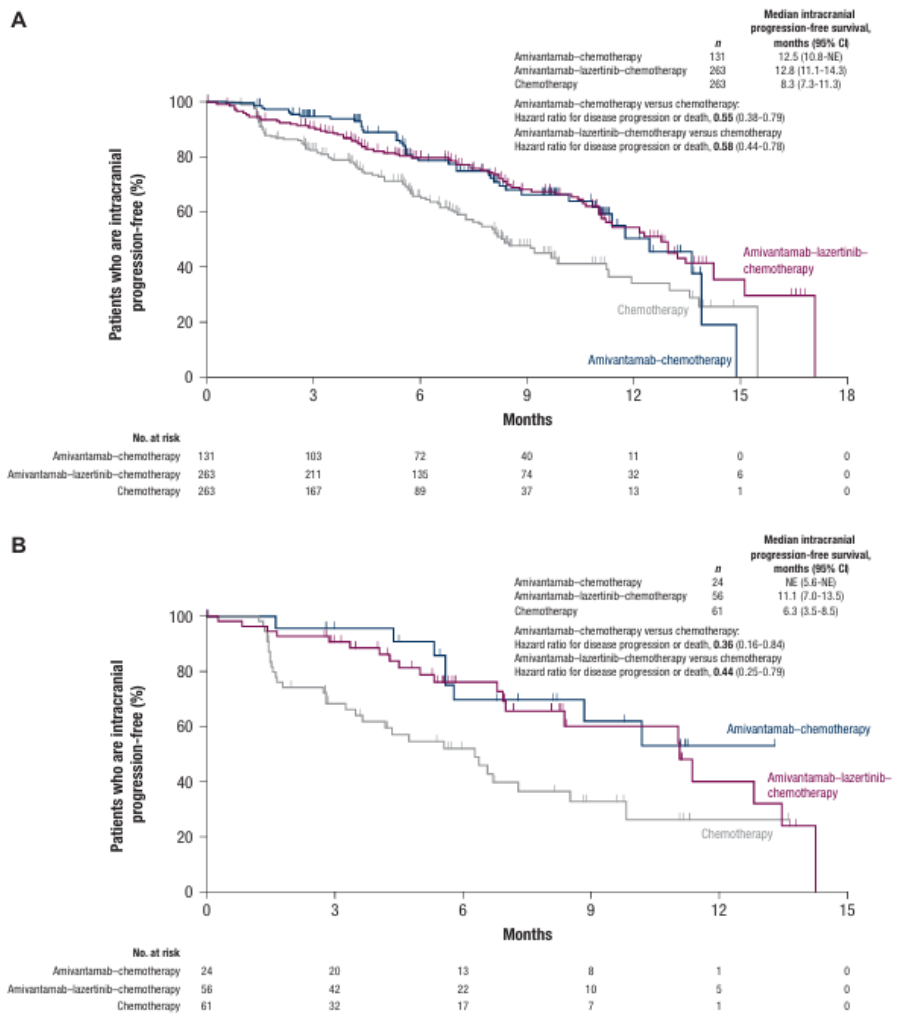
ORIGINAL ARTICLE

Amivantamab plus chemotherapy with and without lazertinib in *EGFR*-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study☆

Ami +Chemo ≒ Ami + Laz+ Chemo>> Chemo







Passaro et al. 2024

Treatment-emergent adverse events

Event, *n* (%)	Chemotherapy (*n* = 243)		Amivantamab–chemotherapy (*n* = 130)		Amivantamab–lazertinib–chemotherapy (*n* = 263)	
Any event	227 (93)		130 (100)		263 (100)	
Grade ≥3	117 (48)		94 (72)		242 (92)	
Any serious event	49 (20)		42 (32)		137 (52)	
Any event resulting in death	3 (1)		3 (2)		14 (5)	
Any event leading to:						
Interruptions of any study agent	81 (33)		84 (65)		202 (77)	
Reductions of any study agent	37 (15)		53 (41)		171 (65)	
Discontinuations of any study agent	9 (4)		24 (18)		90 (34)	
Adverse events[a]	All	Grade ≥3	All	Grade ≥3	All	Grade ≥3
Neutropenia[b]	101 (42)	52 (21)	74 (57)	59 (45)	181 (69)	144 (55)
Thrombocytopenia[b]	72 (30)	22 (9)	57 (44)	19 (15)	158 (60)	96 (37)
Infusion-related reaction	1 (0.4)	0	76 (58)	7 (5)	148 (56)	9 (3)
Anemia	97 (40)	23 (9)	51 (39)	15 (12)	141 (54)	48 (18)
Paronychia	1 (0.4)	0	48 (37)	3 (2)	133 (51)	11 (4)
Nausea	90 (37)	2 (1)	58 (45)	1 (1)	131 (50)	16 (6)
Rash	12 (5)	0	56 (43)	8 (6)	126 (48)	17 (6)
Stomatitis	21 (9)	0	41 (32)	1 (1)	120 (46)	24 (9)
Leukopenia	68 (28)	23 (9)	37 (28)	26 (20)	106 (40)	71 (27)
Hypoalbuminemia	21 (9)	1 (0.4)	29 (22)	3 (2)	104 (40)	12 (5)
Constipation	72 (30)	0	50 (38)	1 (1)	96 (37)	3 (1)
Decreased appetite	51 (21)	3 (1)	40 (31)	0	85 (32)	7 (3)
Peripheral edema	15 (6)	0	42 (32)	2 (2)	85 (32)	1 (0.4)
Vomiting	42 (17)	1 (0.4)	32 (25)	1 (1)	76 (29)	10 (4)
Fatigue	47 (19)	4 (2)	36 (28)	4 (3)	69 (26)	15 (6)
Diarrhea	16 (7)	1 (0.4)	18 (14)	1 (1)	68 (26)	10 (4)
Asthenia	40 (16)	5 (2)	34 (26)	1 (1)	67 (25)	14 (5)
Dermatitis acneiform	7 (3)	0	26 (20)	5 (4)	62 (24)	17 (6)
Alanine aminotransferase increased	67 (28)	10 (4)	26 (20)	7 (5)	55 (21)	14 (5)
Hypokalemia	15 (6)	6 (2)	24 (18)	6 (5)	55 (21)	16 (6)
COVID-19	25 (10)	0	27 (21)	2 (2)	44 (17)	0
Hypocalcemia	9 (4)	0	16 (12)	1 (1)	44 (17)	3 (1)
Aspartate aminotransferase increased	57 (23)	0	19 (15)	1 (1)	43 (16)	7 (3)
Hyponatremia	16 (7)	2 (1)	13 (10)	5 (4)	42 (16)	10 (4)
Pruritus	17 (7)	0	20 (15)	0	30 (11)	0
Adverse events of special interest	All	Grade ≥3	All	Grade ≥3	All	Grade ≥3
Rash[c]	30 (12)	0	92 (71)	13 (10)	197 (75)	40 (15)
Venous thromboembolism[d]	11 (5)	7 (3)	13 (10)	3 (2)	58 (22)	17 (6)
Interstitial lung disease[e]	0	0	2 (2)	1 (1)	7 (3)	5 (2)

MARIPOSA-2 (NCT04988295) **demonstrated improved PFS versus chemotherapy** after disease progression on osimertinib in patients with *EGFR*-mutated advanced NSCLC

MARIPOSA-2 is a randomized,[a] open-label, Phase 3 study

evaluating the efficacy and safety of 2 regimens of amivantamab (with and without lazertinib) and chemotherapy

1. Amivantamab-Chemotherapy (n=131)
2. Amivantamab-Lazertinib-Chemotherapy (n=263)
3. Chemotherapy (n=263)

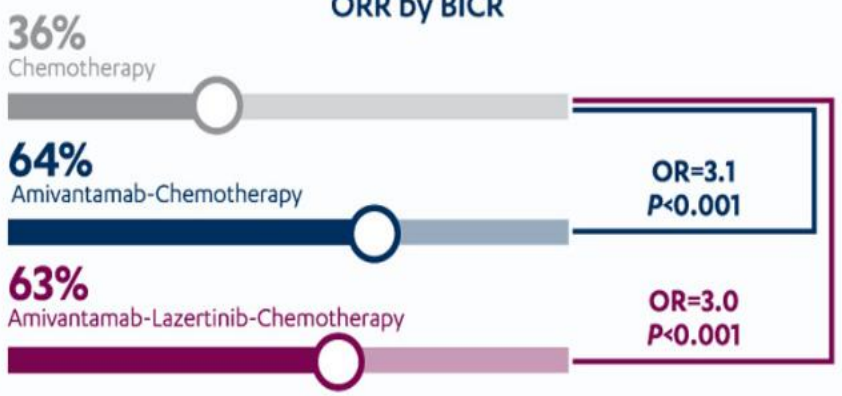
There are currently no targeted therapies approved for patients who progress on osimertinib

[a]Patients were randomized 1:2:2 to Amivantamab-Chemotherapy, Amivantamab-Lazertinib-Chemotherapy, and Chemotherapy, respectively.

Amivantamab + Lazertinib + Chemotherapy and **Amivantamab + Chemotherapy** improved PFS, intracranial PFS, ORR, and other key endpoints versus **Chemotherapy** alone

Amivantamab-Chemotherapy vs Chemotherapy	Amivantamab-Lazertinib-Chemotherapy vs Chemotherapy
HR for disease progression or death, **0.48** (95% CI, 0.36–0.64); *P*<0.001	HR for disease progression or death, **0.44** (95% CI, 0.35–0.56); *P*<0.001

ORR by BICR



BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; PFS, progression-free survival.

Predominant AEs in the amivantamab-containing arms were hematologic and EGFR-and MET-related

Most hematologic AEs were transient, with majority occurring in Cycle 1

The safety profile of amivantamab-chemotherapy is consistent with that of its individual components

Most common EGFR-, MET-, and chemotherapy-associated AEs, n (%)		Chemotherapy (n=243)		Amivantamab-Chemotherapy (n=130)		Amivantamab-Lazertinib-Chemotherapy (n=263)	
		All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
	Any AEs	227 (93)	117 (48)	130 (100)	94 (72)	263 (100)	242 (92)
EGFR	Paronychia	1 (0.4)	0	48 (37)	3 (2)	133 (51)	11 (4)
	Rash	12 (5)	0	56 (43)	8 (6)	126 (48)	17 (6)
MET	Hypoalbuminemia	21 (9)	1 (0.4)	29 (22)	3 (2)	104 (40)	12 (5)
	Peripheral edema	15 (6)	0	42 (32)	2 (2)	85 (32)	1 (0.4)
Chemotherapy	Neutropenia	101 (42)	52 (21)	74 (57)	59 (45)	181 (69)	144 (55)
	Thrombocytopenia	72 (30)	22 (9)	57 (44)	19 (15)	158 (60)	96 (37)
Other	Infusion-related reaction	1 (0.4)	0	76 (58)	7 (5)	148 (56)	9 (3)

AE, adverse event; EGFR, epidermal growth factor receptor; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Second line regimens after Osimertinib +/- Chemotherapy

	MARIPOSA-2			CHRYSALIS-2 (Cohort A)
	Chemo (n=263)	**Chemo+Ami (n=131)**	**Chemo+Ami+Laz (n=263)**	**Ami+Laz (n=162)**
Prior therapy		**Osimertinib monotherapy**		**Osimertinib+ chemotx**
ORR % (95% CI)	36 (30-42)	**64** (55-72)	63 (57-69)	35 (27-42), BICR
PFS, mo (BICR)	4.2 (4.0-4.4)	**6.3** (5.6-8.4)	8.3 (6.8-9.1)	4.5 (4.1-5.8)
PFS, mo (investigator)	4.2 (4.0-4.5)	**8.2** (6.8-10.9)	**8.3** (7.1-9.9)	--
PFS HR (BICR)	0.48 (0.36-0.64) Ami+chemo vs chemo			--
IC-PFS, mos	8.3 (7.3-11.3)	**12.5** (10.8-NE)	**12.8** (11.1-14.3)	IC RR 28% (retrospective)
OS, mos	HR 0.73 (0.54-0.99) Ami+ chemo vs chemo, 2nd interim			14.8 (12.2-18.0)

Passaro et al. Ann Oncol 2024;35(1):77 Popat et al. LBA54 ESMO 2024 Besse et al JTO 2025

Should EGFR Pathway Blockade Be Maintained Throughout Treatment in Advanced NSCLC with *EGFR* Mutation?

	COMPEL		MARIPOSA-2	
	CT + osimertinib	CT + placebo	CT + amivantamab	CT
N	48	48	131	263
ORR, %	35*	29*	**64**	36
mDOR, months	8.2	4.2	6.9	5.6
mPFS, months	8.4	4.4	6.3	4.2
CNS-PFS	15.9°	8.6°	12.5	8.3
mOS	15.9	9.8	17.7	**15.3**
TEAEs, G3+	63%	46%	72%	48%

CT: chemotherapy; *: non-CNS ORR and DOR; °CNS-PFS in pts without brain metastases at baseline

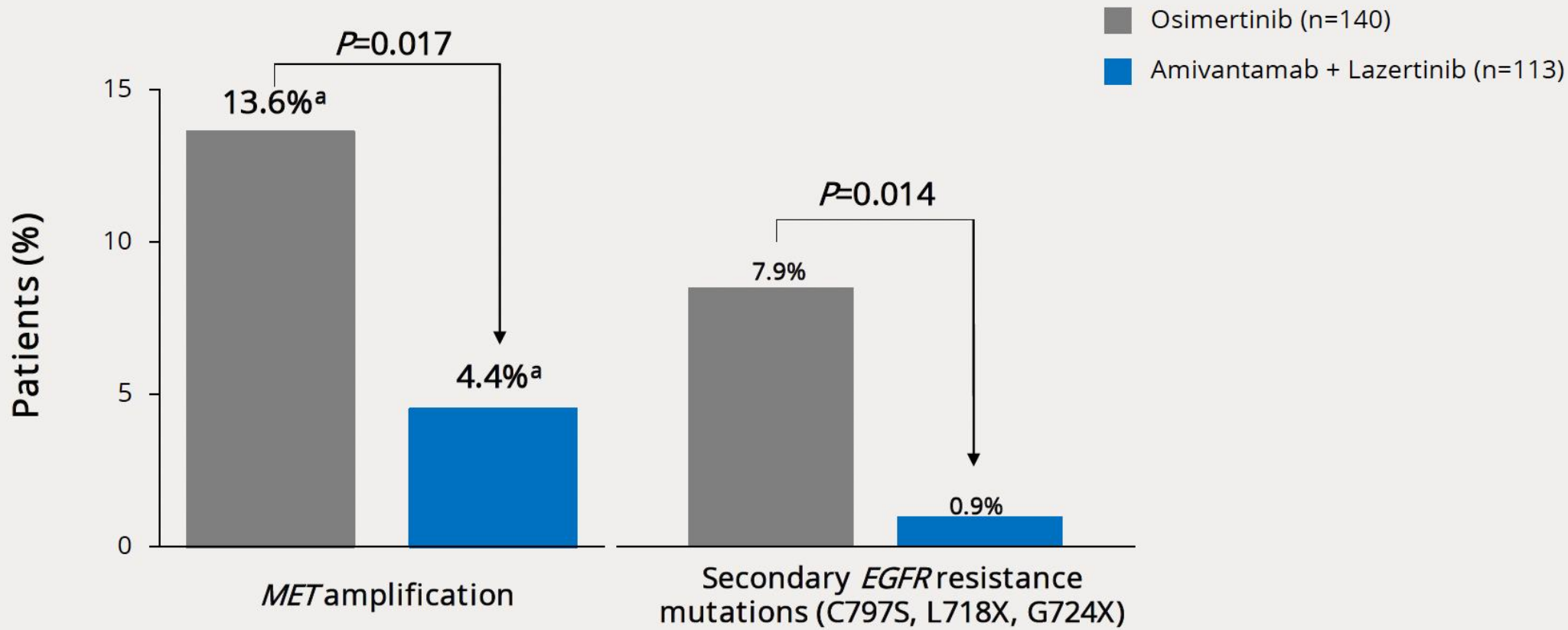
Passaro A et al. Ann Oncol 2023
Popat S et al., ESMO 2024
Pasello G et al., WCLC 2025

MET Amplification

MET and *EGFR*-based Resistance Mechanisms

MARIPOSA
Ami + Laz in
1L *EGFR*+ NSCLC

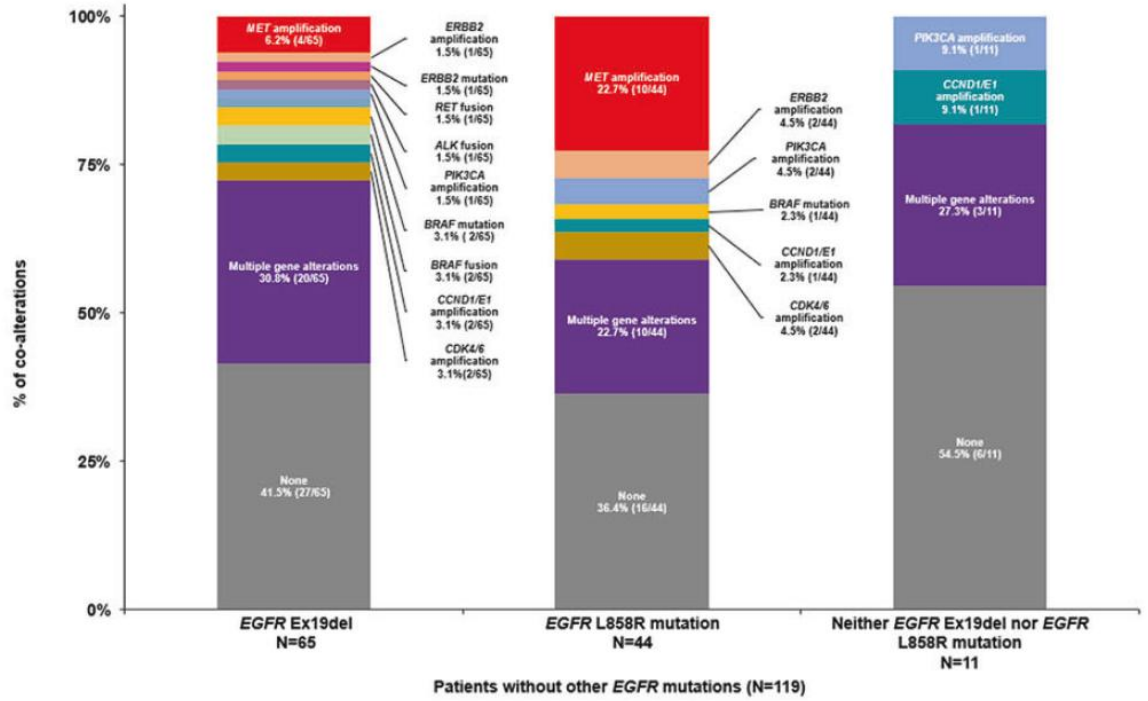
Amivantamab + lazertinib significantly reduced the incidence of acquired MET amplifications and EGFR resistance mutations vs osimertinib

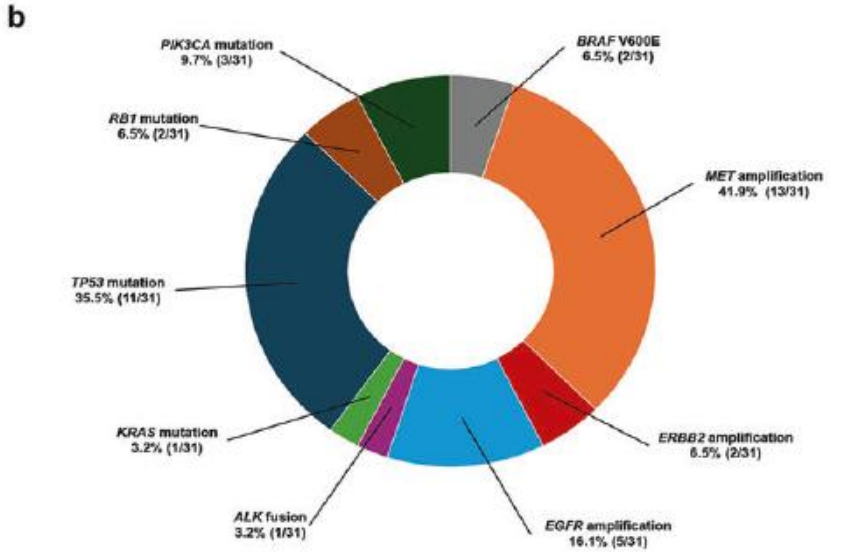


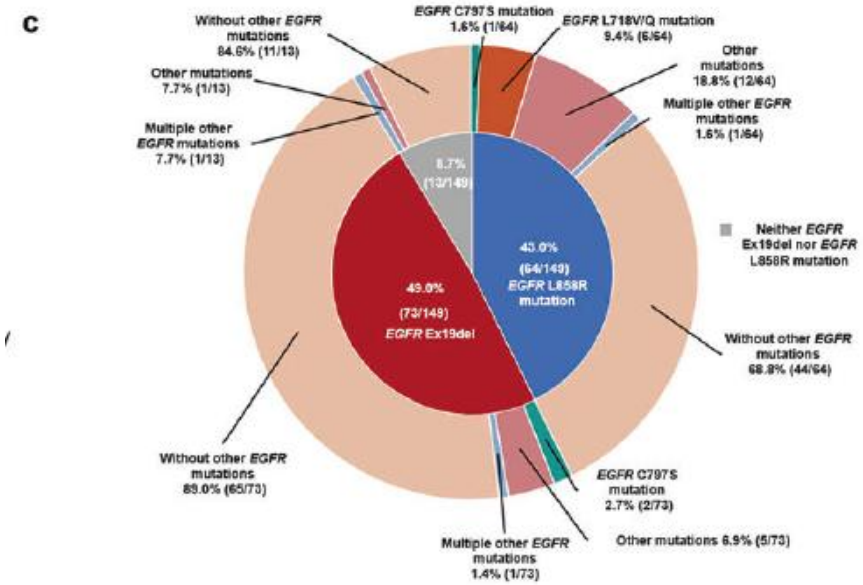
ARTICLE OPEN

A prospective, multicenter, comprehensive genomic profile signature study in patients with *EGFR*-mutant advanced non-small cell lung cancer at the first-line treatment failure of osimertinib

Yuankai Shi[1], Dongqing Lv[2], Weineng Feng[3], Shuoyan Liu[4], Puyuan Xing[1], Yan Yu[5], Jun Yin[6], Xiubao Ren[7], Junqiang Zhang[8],







TP53 mutation (69.8%, 104/149) and **MET amplification (30.9%, 46/149**) were the most frequent bypass signaling activation and downstream pathway activation

Shi et al. Signal Transduction and Targeted Therapy 2025

Osimertinib+MET TKI (SACHI and SAVANNAH)

Savolitinib combined with osimertinib versus chemotherapy in EGFR-mutant and MET-amplified advanced NSCLC after disease progression on EGFR tyrosine kinase inhibitor: results from a randomized phase 3 SACHI study

Shun Lu[1], Jie Wang[2], Nong Yang[3], Dongqing Lv[4], Lijuan Chen[5], Lin Wu[3], Xingya Li[6], Longhua Sun[7], Yongfeng Yu[1], Bo Jin[8], Lin Yang[9], Yubiao Guo[10], Haipeng Xu[11], Tienan Yi[12], Aiping Zeng[13], Xiaorong Dong[14], Jianhua Chen[3], Ziping Wang[15], Tony Mok[16], Weiguo Su[17]

Savolitinib + Osimertinib > Chemotherapy

International-only enrollment

Prior EGFR TKI with MET amplification

Phase 3

Efficacy and CNS results from a randomized subset of the Phase 2 SAVANNAH study comparing savolitinib + osimertinib combination with savolitinib + placebo

Benjamin Levy,[1] Filippo de Marinis, Laura Bonanno, Adrian G. Sacher, Quincy S. Chu, Christina S. Baik, Paolo Bironzo, Lyudmila Bazhenova, Marcello Tiseo, Claudia Proto, Cheng-Ta Yang, Jonathan W. Riess, Konstantinos Leventakos, James Chih-Hsin Yang, Lecia V. Sequist, Karen Barrett, Ryan Hartmaier, Ike Igwegbe, Wanning Xu, Myung-Ju Ahn

Savolitinib + Osimertinib > Savolitinib + Placebo

Prior EGFR TKI with MET amplification or MET overexpression

Phase 2

Savolitinib plus osimertinib versus chemotherapy for advanced, *EGFR* mutation-positive, *MET*-amplified non-small-cell lung cancer in China (SACHI): interim analysis of a multicentre, open-label, phase 3 randomised controlled trial

Shun Lu, Jie Wang*, Nong Yang*, Dongqing Lv*, Lijuan Chen, Lin Wu, Xingya Li, Longhua Sun, Yongfeng Yu, Bo Jin, Lin Yang, Yubiao Guo, Haipeng Xu, Tienan Yi, Aiping Zeng, Xiaorong Dong, Jianhua Chen, Ziping Wang, Hongrui Niu, Ying Cheng, Pinhua Pan, Pengbo Deng, Hongming Pan, Xuhong Min, Jun Bai, Laiyu Liu, Tongmei Zhang, Juan Li, Songhua Fan, Michael M Shi, Tony Mok, Weiguo Su, on behalf of the SACHI Study Group†*

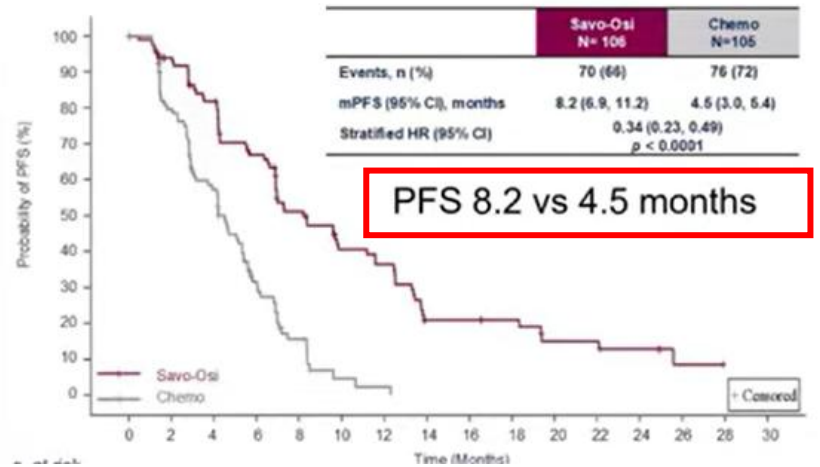
- 68 Chinese hospitals (106 VS 105 pts)

- Metastatic EGFR mutation-positive NSCLC &MET amplification after first-line EGFR TKI failure.
  (1st, 2nd, 3rd generation)

- MET amplification defined as either
  - (a) MET copy number ≥**5** or MET to CEP7 ratio ≥2 after disease progression on previous EGFR TKI therapy,
  - (b) MET copy number ≥**10** for those with previous third-generation EGFR TKI therapy,
  - **FISH using the AmoyDx** c-Met Gene Amplification Analysis Kit
    (3세대 TKI 사용시 더 높은 Copy number 여야 driver mutation 으로 가정, passenger target 감별).

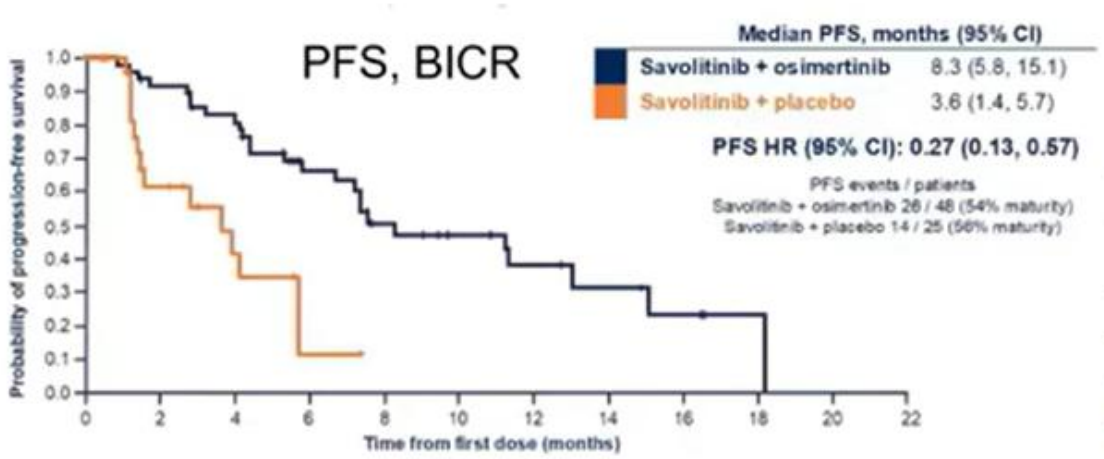
Lancet 2026; 407: 375–87

SACHI : Osi/Savolitinib vs Platinum Doublet



	Savo-Osi N=106	Chemo N=105
ORR, % (95% CI)	58 (49-68)	34 (25-44)
DCR, % (95% CI)	89 (81-94)	67 (57-76)
Median DoR, month (95% CI)	8.4 (5.9-11.1)	3.2 (2.8-4.2)

SAVANNAH：Osi/Savolitinib vs Savolitinib/Placebo

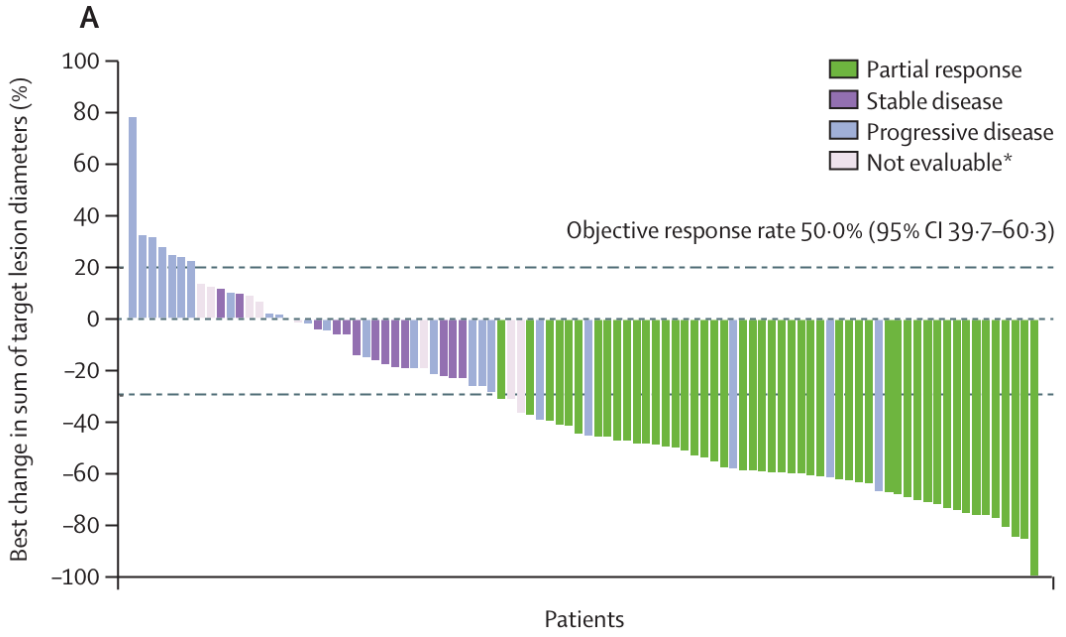


PFS 8.3 vs 3.8 months

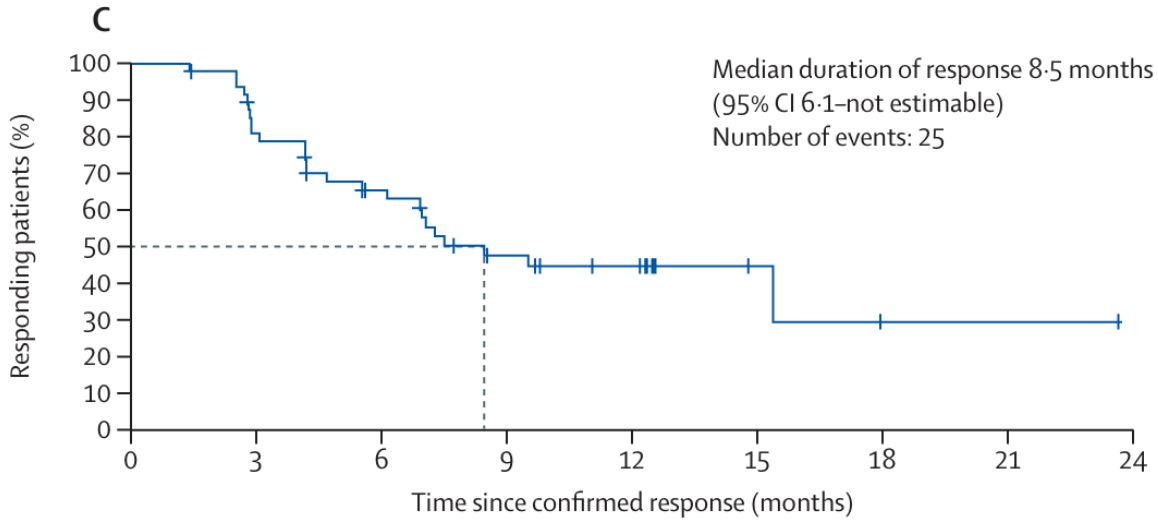
	BICR-assessed	
	Savolitinib + osimertinib (n=48)	Savolitinib + placebo (n=25)
Confirmed ORR, % (95% CI)	58 (43, 72)	16 (5, 36)
	(n=28)	(n=4)
Median DoR, months (95% CI)	11.8 (6.0, NC)	4.5 (2.6, NC)
Median time to onset of response, weeks (IQR)	6.0 (5.7–6.2)	6.1 (5.8–6.3)

Tepotinib plus osimertinib in patients with *EGFR*-mutated non-small-cell lung cancer with *MET* amplification following progression on first-line osimertinib (INSIGHT 2): a multicentre, open-label, phase 2 trial

*Yi-Long Wu, Valentina Guarneri, Pei Jye Voon, Boon Khaw Lim, Jin-Ji Yang, Marie Wislez, Cheng Huang, Chong Kin Liam, Julien Mazieres, Lye Mun Tho, Hidetoshi Hayashi, Nguyen Viet Nhung, Puey Ling Chia, Filippo de Marinis, Jo Raskin, Qinghua Zhou, Giovanna Finocchiaro, Anh Tuan Le, Jialei Wang, Christophe Dooms, Terufumi Kato, Ernest Nadal, How Soon Hin, Egbert F Smit, Martin Wermke, Daniel Tan, Masahiro Morise, Aurora O'Brate, Svenja Adrian, Boris M Pfeiffer, Christopher Stroh, Dilafruz Juraeva, Rainer Strotmann, Kosalaram Goteti, Karin Berghoff, Barbara Ellers-Lenz, Niki Karachaliou, Xiuning Le, Tae Min Kim, for the INSIGHT 2 investigators**



- MET amplification (FISH) or liquid biopsy
- **ORR : 50.0%**
- **PFS : 5.6 months**
- **DOR : 8.5 months**



Lancet Oncol 2024;

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

Results from a phase Ib study of telisotuzumab vedotin in combination with osimertinib in patients with c-Met protein-overexpressing, *EGFR*-mutated locally advanced/metastatic non-small-cell lung cancer (NSCLC) after progression on prior osimertinib

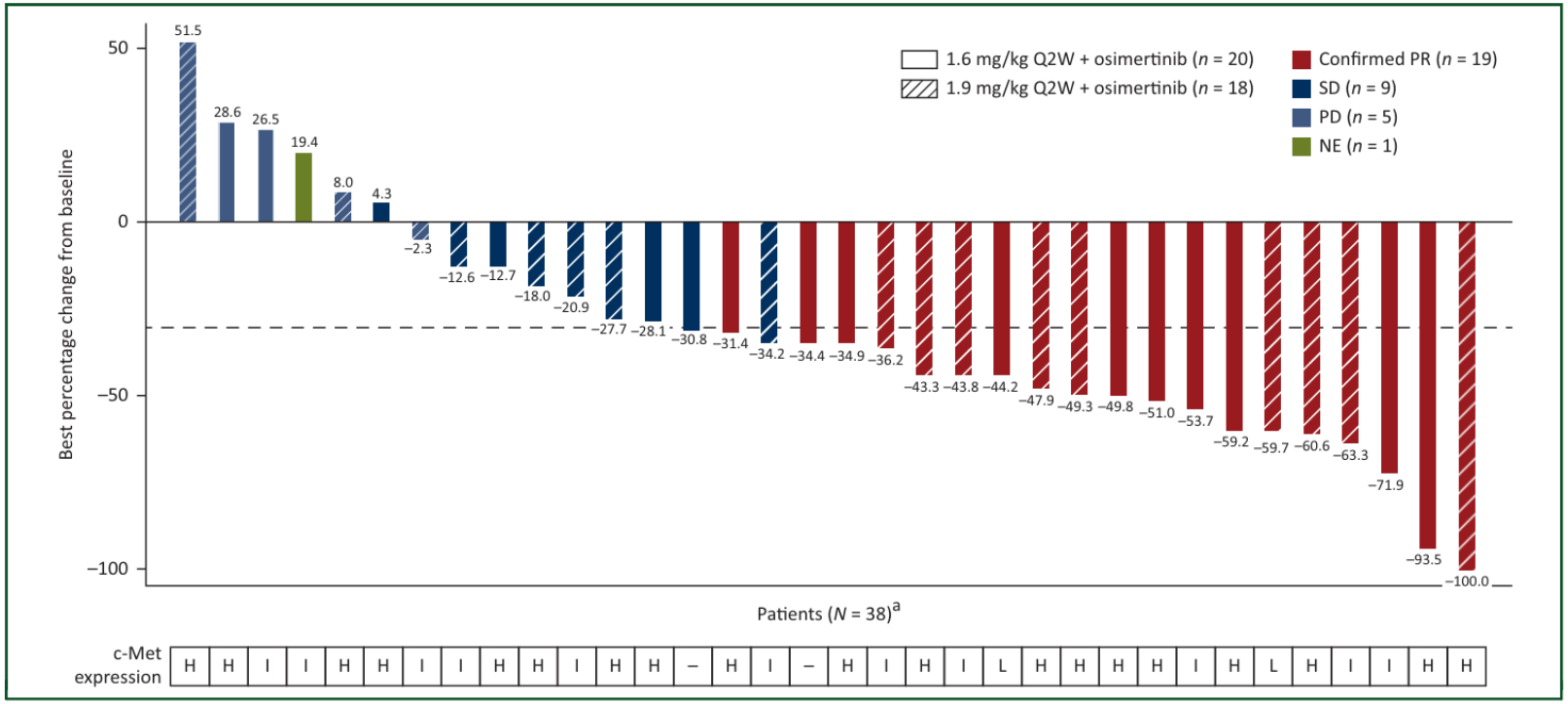
- **Telisotuzumab vedotin** (Teliso-V, ADC): c-Met mAb + monomethyl auristatin E (microtubule inhibitor)
- c-Met protein overexpression : 25% of tumor cells with membrane staining
- Teliso-V +osimertinib in pts with metastatic EGFR-mutated & c-Met protein-overexpressing NSCLC after progression on osimertinib
- 1.6 mg/kg Q2W or 1.9 mg/kg Q2W
- ORR : 50%
- PFS : 7.4 months
- TEAEs : peripheral sensory neuropathy(50%), peripheral edema(32%), nausea (24%)
- Grade3/4 TEAEs: anemia (11%), pulmonary embolism(8%)

2025 *Annals of Oncol*

Efficacy

Table 3. Efficacy outcomes

	ICR			Inv		
	Teliso-V		Total ($N = 38$)	Teliso-V		Total ($N = 38$)
	1.6 mg/kg Q2W plus osimertinib ($n = 20$)	1.9 mg/kg Q2W plus osimertinib ($n = 18$)		1.6 mg/kg Q2W plus osimertinib ($n = 20$)	1.9 mg/kg Q2W plus osimertinib ($n = 18$)	
Response						
ORR, *n* (%)	10 (50.0)	9 (50.0)	19 (50.0)	11 (55.0)	9 (50.0)	20 (52.6)
(95% CI)	(27.2-72.8)	(26.0-74.0)	(33.4-66.6)	(31.5-76.9)	(26.0-74.0)	(35.8-69.0)
Confirmed PR	10 (50.0)	9 (50.0)	19 (50.0)	11 (55.0)	9 (50.0)	20 (52.6)
DCR, *n* (%)	15 (75.0)	14 (77.8)	29 (76.3)	13 (65.0)	14 (77.8)	27 (71.1)
(95% CI)	(50.9-91.3)	(52.4-93.6)	(59.8-88.6)	(40.8-84.6)	(52.4-93.6)	(54.1-84.6)
DOR						
Patients with events, *n* (%)	—	3 (33.3)	3 (15.8)	3 (27.3)	6 (66.7)	9 (45.0)
Patients censored, *n* (%)	10 (100)	6 (66.7)	16 (84.2)	8 (72.7)	3 (33.3)	11 (55.0)
Median DOR, months (95% CI)	—	11.0 (3.7, NR)	— (5.6, NR)	27.7 (3.7, NR)	7.4 (3.7-12.9)	8.0 (5.6, NR)
PFS						
Patients with events, *n* (%)	7 (35.0)	10 (55.6)	17 (44.7)	11 (55.0)	13 (72.2)	24 (63.2)
Patients censored, *n* (%)	13 (65.0)	8 (44.4)	21 (55.3)	9 (45.0)	5 (27.8)	14 (36.8)
Median PFS, months (95% CI)	31.1 (1.9, NR)	6.8 (4.7, NR)	7.4 (5.4, NR)	7.4 (3.5, NR)	5.6 (5.3-9.2)	6.8 (5.3, 9.2)



ORR : 50%

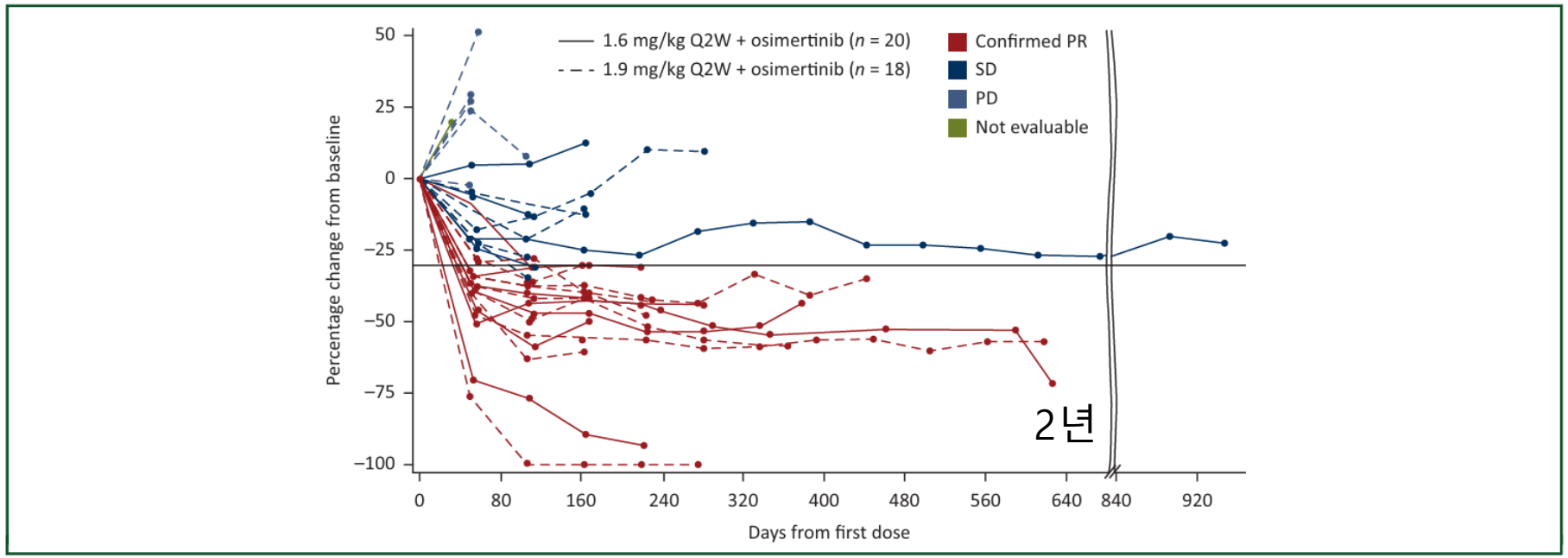


Figure 2. Change in target lesion size over time per ICR.[a]

Safety

Grade 3/4 TEAE			
Any	7 (35)	12 (67)	19 (50)
Anemia	2 (10)	2 (11)	4 (11)
Pulmonary embolism	0	3 (17)	3 (8)
Deep vein thrombosis	0	2 (11)	2 (5)
Hemoptysis	1 (5)	1 (6)	2 (5)
Hypoalbuminemia	2 (10)	0	2 (5)
Malignant neoplasm progression	0	2 (11)	2 (5)
Peripheral motor neuropathy	1 (5)	1 (6)	2 (5)
Peripheral sensory neuropathy	1 (5)	1 (6)	2 (5)
Pneumonia	1 (5)	1 (6)	2 (5)

	Teliso-V		Total ($N = 38$) *n* (%)
	1.6 mg/kg Q2W plus osimertinib ($n = 20$) *n* (%)	1.9 mg/kg Q2W plus osimertinib ($n = 18$) *n* (%)	
TEAE			
Peripheral sensory neuropathy	11 (55)	8 (44)	19 (50)
Peripheral edema	7 (35)	5 (28)	12 (32)
Nausea	2 (10)	7 (39)	9 (24)
Anemia	4 (20)	4 (22)	8 (21)
Fatigue	5 (25)	3 (17)	8 (21)
Hypoalbuminemia	5 (25)	2 (11)	7 (18)
Muscle spasms	4 (20)	3 (17)	7 (18)
Paronychia	5 (25)	2 (11)	7 (18)
Vision blurred	3 (15)	4 (22)	7 (18)
Decreased appetite	4 (20)	2 (11)	6 (16)
Myalgia	2 (10)	4 (22)	6 (16)
Alopecia	3 (15)	2 (11)	5 (13)
Diarrhea	2 (10)	3 (17)	5 (13)
Dizziness	1 (5)	4 (22)	5 (13)
Paresthesia	2 (10)	3 (17)	5 (13)
Back pain	2 (10)	2 (11)	4 (11)
Constipation	1 (5)	3 (17)	4 (11)
Cough	2 (10)	2 (11)	4 (11)
Dry eye	1 (5)	3 (17)	4 (11)
Dyspnea	1 (5)	3 (17)	4 (11)
Hemoptysis	2 (10)	2 (11)	4 (11)
Malignant neoplasm progression	1 (5)	3 (17)	4 (11)
Edema	2 (10)	2 (11)	4 (11)
Peripheral motor neuropathy	2 (10)	2 (11)	4 (11)
Rash	2 (10)	2 (11)	4 (11)

Post-Osimertinib Therapies With MET as a Target

	Amivantanab + Lazertinib (N = 45)[1]	Amivantanab + Lazertinib Chemotherapy (N = 162)[2]	Osimertinib + Savolitinib (N = 69)[3]	Teliso-V + Osimertinib (N = 25)[4]	Tepotinib + Osimertinib
Study	CHRYSALIS	CHRYSALIS-2	SACHI/SAVANNAH	M14-237	INSIGHT2 (Ph2)
Target	*EGFR/MET*	*EGFR/MET*	*EGFR/MET*	*MET*	MET
ORR, %	36	33	30	58	50
Median DOR, mo	9.6	9.6	7.9	Not reported	8.5
Median PFS, mo	4.9	5.1	8.3	7.4	5.6
Grade ≥3 TRAE, %	16	38	57	32	34

1. Sequist LV et al. *Lancet Oncol*. 2020;21:373-386. 2. Cho BC et al. ASCO 2021. Abstract 9006. 3. Shu CA et al. ASCO 2022. 4. Goldman JW et al. ASCO 2022. Abstract 9013.

Antibody-drug conjugate

ADCs are being evaluated in Phase III trials in patients with *EGFR*m mNSCLC and actionable genomic alterations

Examples of ADCs in Phase III trials for treatment of *EGFR*m mNSCLC

Sacituzumab tirumotecan (SKB264)[1–4]

Target antigen: TROP2

Payload: T030 (topoisomerase I inhibitor)

Linker: CL2A (pH cleavable)

DAR: ≈7–8:1

Ongoing Phase III trials in *EGFR*m mNSCLC:
NCT05870319
MK-2870-009
MK-2870-004

Datopotamab deruxtecan (Dato-DXd)[5–8]

Target antigen: TROP2

Payload: DXd (topoisomerase I inhibitor)

Linker: GGFG tetrapeptide (enzymatically cleavable)

DAR: ≈4:1

Ongoing Phase III trials in *EGFR*m mNSCLC:
TROPION-Lung14
TROPION-Lung15

Izalontamab brengitecan (BL-B01D1)[9,10]

Target antigens: HER3 and EGFR

Payload: Ed-04 (topoisomerase I inhibitor)

Linker: N/D (enzymatically cleavable)

DAR: ≈8:1

Ongoing Phase III trials in *EGFR*m mNSCLC:
BL-B01D1-301

Patritumab deruxtecan (HER3-DXd)[6,11,12]

Target antigen: HER3

Payload: DXd (topoisomerase I inhibitor)

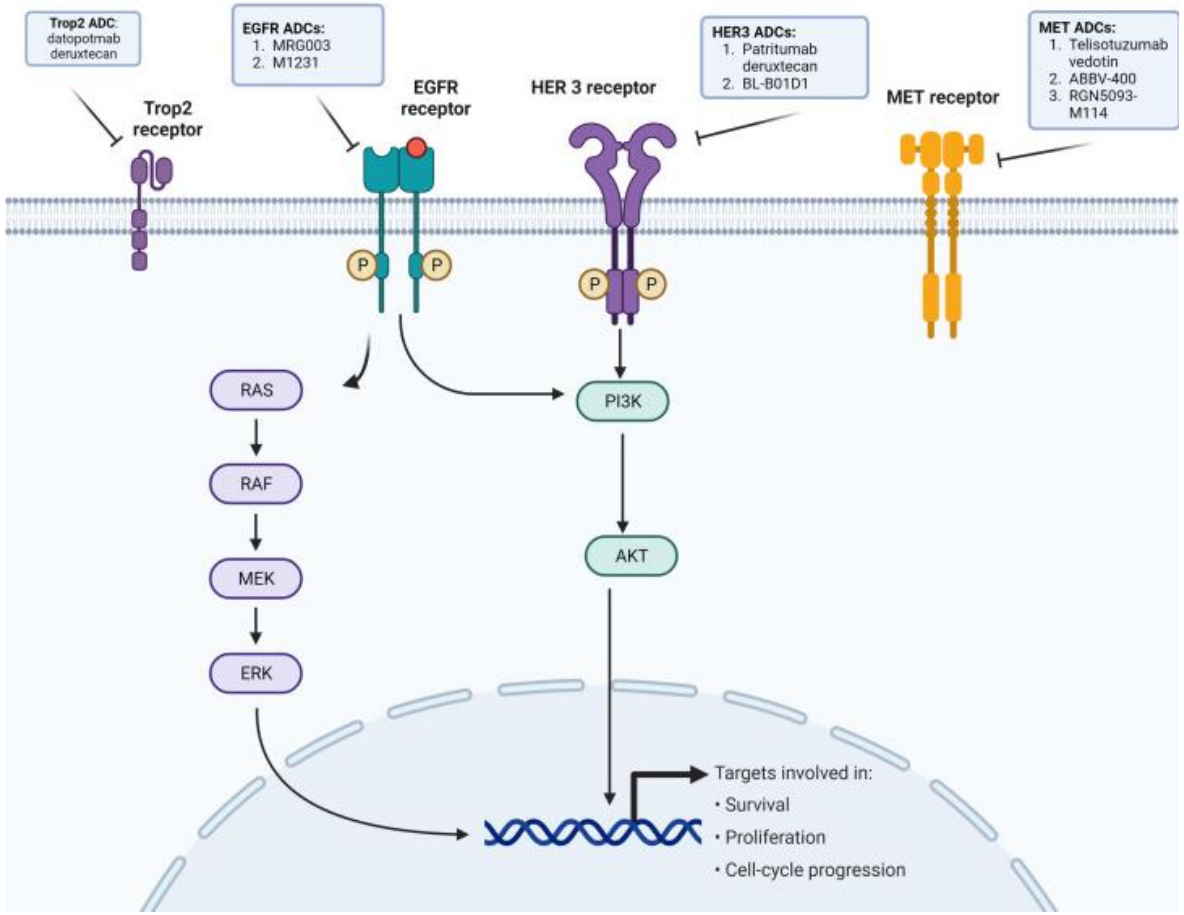
Linker: GGFG tetrapeptide (enzymatically cleavable)

DAR: ≈8:1

Ongoing Phase III trials in *EGFR*m mNSCLC:
HERTHENA-Lung02: **실패**

Other ongoing Phase III trials include both patients with and without actionable genomic alterations:
TROPION-Lung01 (Dato-DXd), TeliMET NSCLC-01 (telisotuzumab vedotin), EVOKE-01 (SG), EVOKE-03 (SG), SGNB6A-002 (SGN-B6A)

1.Target-independent cytotoxicity
2.Eradicating EGFR-TKI-DTPs



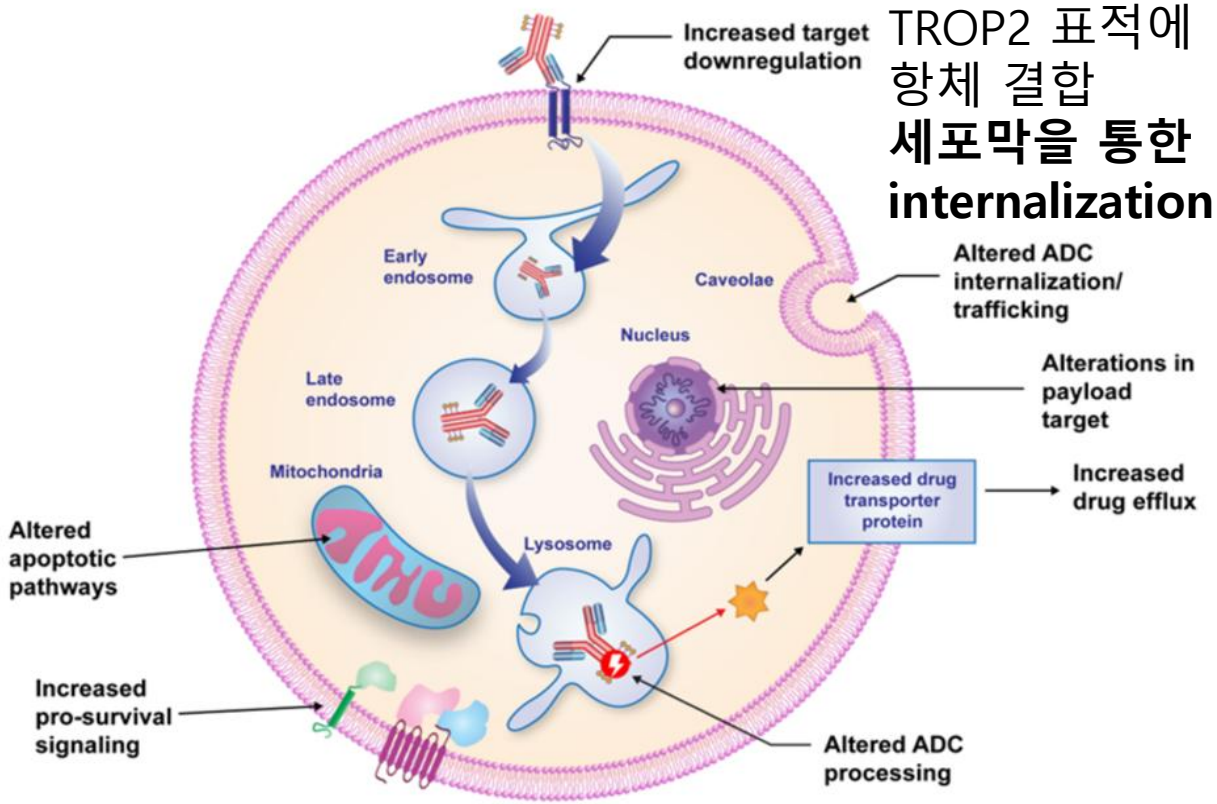


Fig. 2. Proposed mechanisms of ADC resistance. ADC, antibody-drug conjugate.

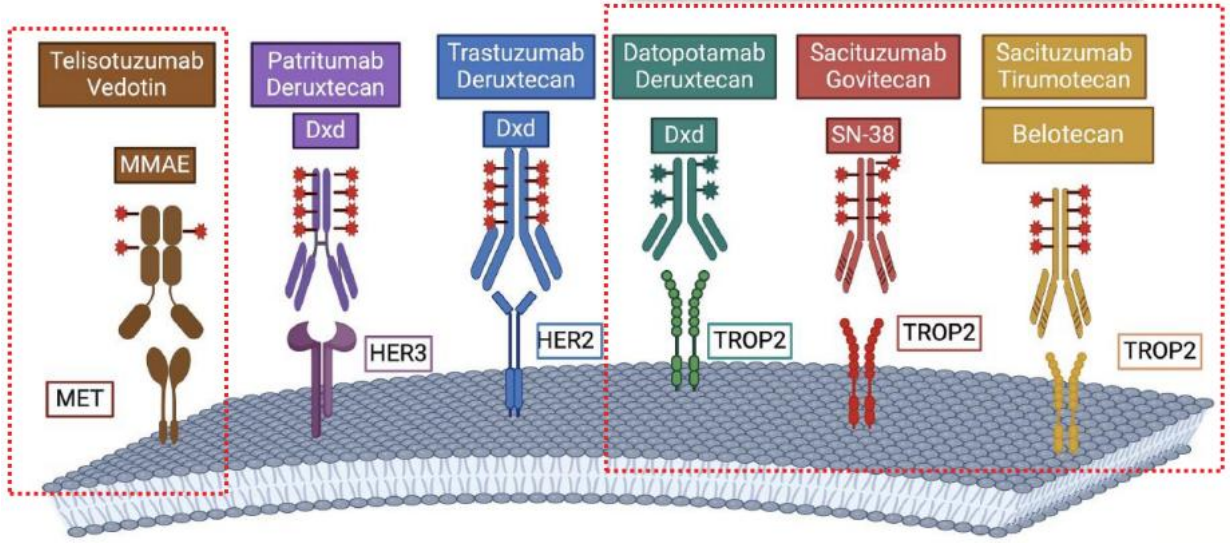
TROP2 표적에 항체 결합
세포막을 통한 internalization

•Lysosomal cleavage → payload release
•DNA 손상·세포사멸

EGFR cellular pathway and purpose, and receptors with ADCs in development against *EGFR*-mutated NSCLC.

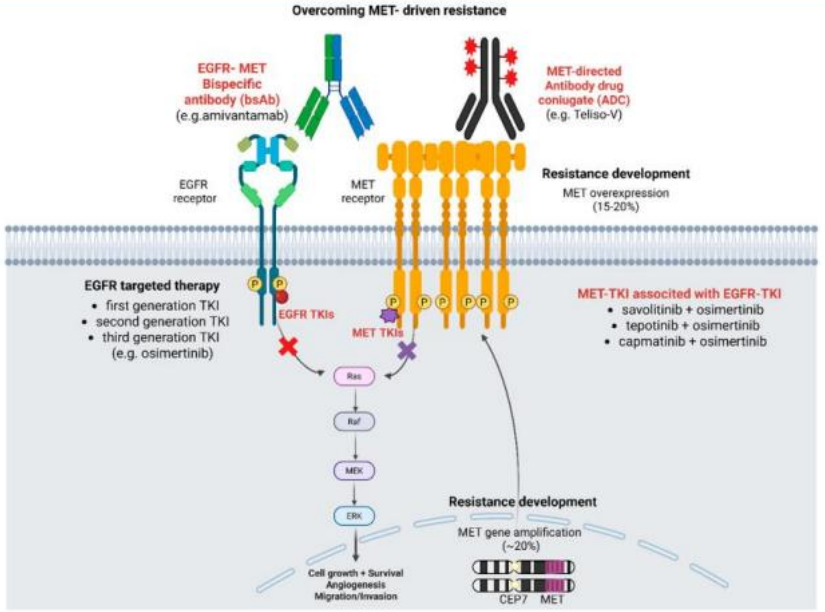
Emerging biomarkers in *EGFR*m NSCLCs

TROP-2 expression?

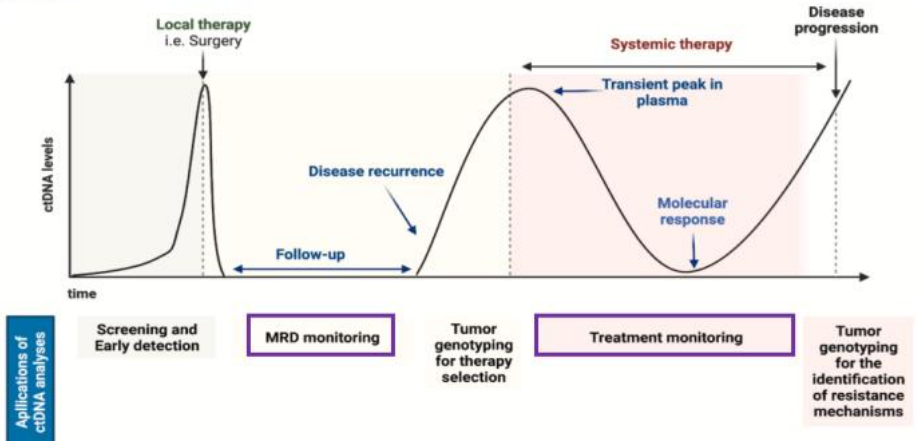


MMAE= monomethyl auristatin E
Dxd=Deruxtecan
SN-38= Camptothecin Derivative
TROP2= trophoblast cell surface antigen 2.

MET overexpression?



Acquired *MET*-ampl?



MRD and ctDNA changes?

Mountzios G, et al. Cancer Treat Rev 2025; Malapelle U, et al. Lung Cancer 2022

TROP2 : epithelial cell 표면에 존재하는 당단백질, 암세포에 과발현 (80-90%)
정상 조직에는 낮게 발현(피부, 각막, 타액선 존재), 기능 : 세포간 접착 및 신호 전달 역할

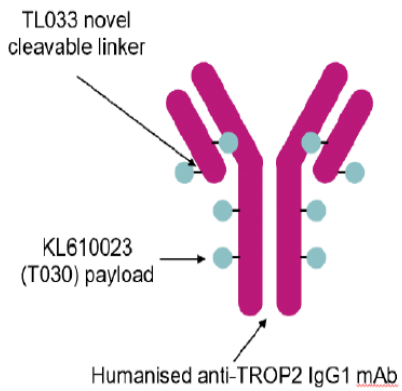
Trop2 ADCs in NSCLC

All use humanised IgG1 mAb

Payloads are all TOP1 inhibitors

Sacituzumab tirumotecan[1,2]

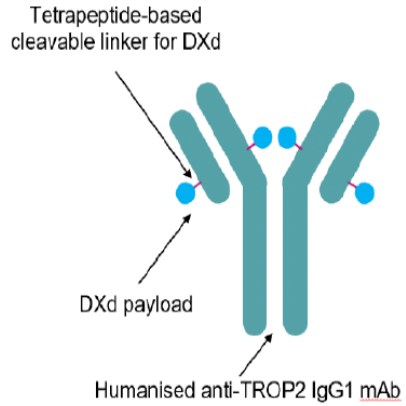
DAR ≈ 7.4:1



- Payload mechanism of action: topoisomerase I inhibitor
- Payload with short systemic half-life
- Bystander antitumour effect

Datopotamab deruxtecan[3]

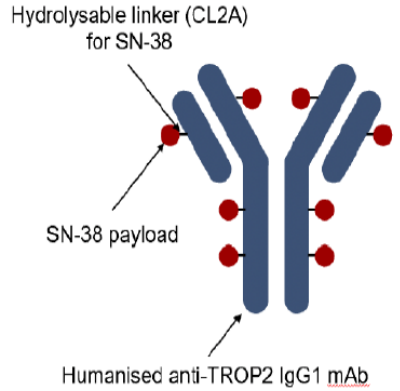
DAR ≈ 4:1



- Payload mechanism of action: topoisomerase I inhibitor
- Payload with short systemic half-life
- Bystander antitumour effect

Sacituzumab govitecan[3,4]

DAR ≈ 8.1:1



- Payload mechanism of action: topoisomerase I inhibitor
- Payload with long systemic half-life
- Bystander antitumour effect

Different DAR

Different linkers

Different payload

Different half-life

TROP2 is highly expressed in NSCLC;[5] ADCs in development differ in their characteristics[6,7]

No TROP2-directed agents are licensed for NSCLC. Sacituzumab govitecan is currently approved globally for patients with 2L and later mTNBC and pre-treated 3L HR+/HER2-ve mBC.[8,9] Please check local prescribing guidelines. Figure partially adapted from Parisi C, et al. (2023).

DAR, drug-to-antibody ratio; DXd, deruxtecan; HR+/HER2- mBC, unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer; mTNBC, unresectable or metastatic triple-negative breast cancer

1. Cheng Y, et al. Front Oncol 2022;12:951589; 2. Fang W, et al. Poster presented at AACR 2024 (Abstract CT247); 3. Parisi C, et al. Cancer Treat Rev 2023;118:102572; 4. Shastry M, et al. Am Soc Clin Oncol Educ Book 2023;43:e390094; 5. Omori S, et al. J Cancer Res Clin Oncol 2022;148:2455–2463; 6. Passaro A, et al. J Clin Oncol 2023;41:3747–3761; 7. Coleman N, et al. NPJ Precis Oncol 2023;7:5; 8. Sacituzumab govitecan summary of product characteristics. 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/trodelvy-epar-product-information_en.pdf (Accessed 30 August 2024); 9. Sacituzumab govitecan prescribing information. 2023. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761115s035lbl.pdf (Accessed 30 August 2024)

L Hendriks
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Organisers: ESMO, IASLC

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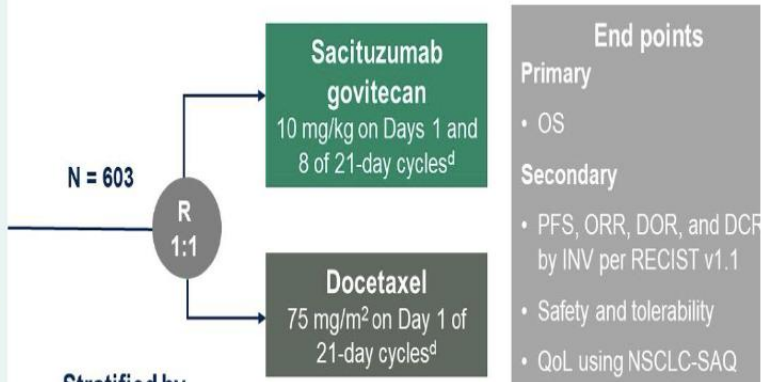
Adapted from Lizza Hendriks, ELCC 2025

Early days of biomarker-unselected Ph3 trials

EVOKE-01: Global, Randomized, Open-Label, Phase 3 Study

Key eligibility criteria

- Measurable stage IV NSCLC
- ECOG PS 0–1
- Radiographic progression after platinum-based and anti-PD-(L)1–containing regimen[a]
- In addition, patients with known AGAs must have received ≥ 1 approved TKI[b]
  - *EGFR/ALK* test required. Testing of other AGAs recommended[c]
- Previously treated stable brain metastases were included
- No prior treatment with Topo-1 inhibitors, Trop-2–targeted therapies, or docetaxel



End points

Primary

- OS

Secondary

- PFS, ORR, DOR, and DCR by INV per RECIST v1.1
- Safety and tolerability
- QoL using NSCLC-SAQ

Stratified by

- **Histology** (squamous vs nonsquamous)
- **Response to last anti-PD-(L)1–containing regimen** (responsive [best response CR/PR] vs nonresponsive [PD/SD])
- **Received prior targeted therapy for AGA** (yes vs no)

At data cutoff (29 November 2023), the study median follow-up was 12.7 months (range, 6.0–24.0)

Presented by Luis Paz-Ares, ASCO 2024

TROPION-Lung01 Study Design

Randomized, Phase 3, Open-Label, Global Study (NCT04656652)

Key Eligibility Criteria

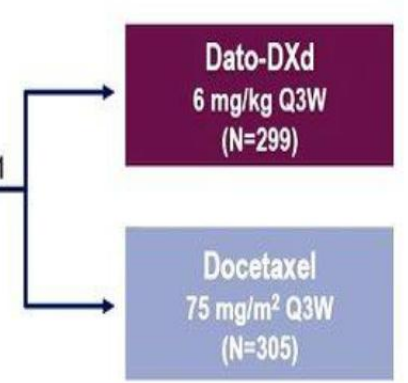
- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without actionable genomic alterations[a]

- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With actionable genomic alterations

- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb



Dual Primary Endpoints

- PFS by BICR
- OS

Secondary Endpoints

- ORR by BICR
- DOR by BICR
- Safety

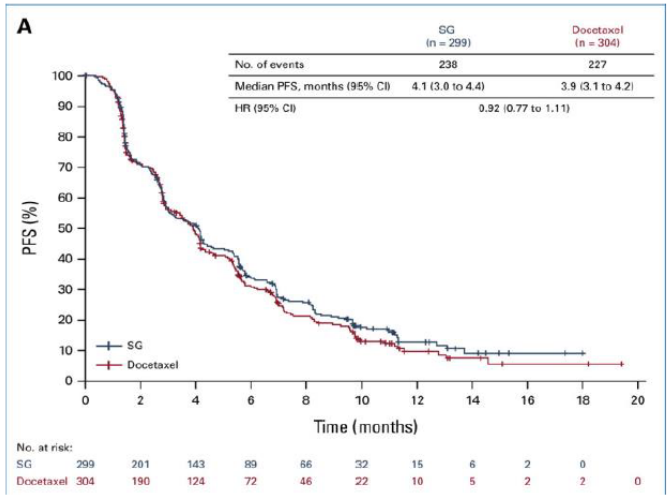
Stratified by: histology,[b] actionable genomic alteration,[c] anti–PD-(L)1 mAb included in most recent prior therapy, geography[d]

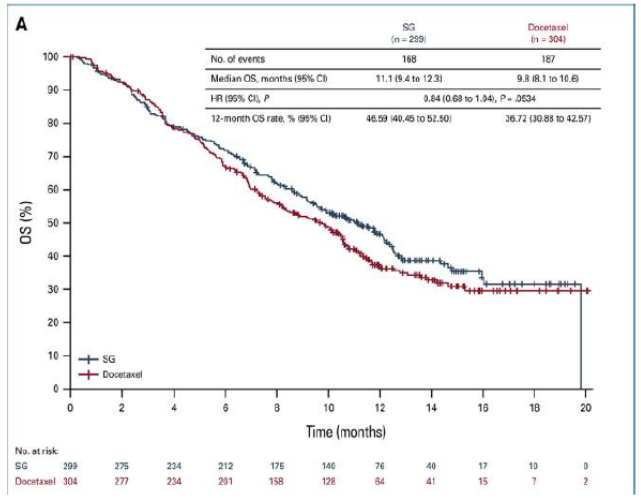
Enrollment period: 19 February 2021 to 7 November 2022.
BICR, blinded independent central review; CT, chemotherapy; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death 1 (ligand 1); PFS, progression-free survival; Q3W, every 3 weeks; R, randomized.
[a]Patients with *KRAS* mutations in the absence of known actionable genomic alterations are eligible; must meet prior therapy requirements for patients without actionable genomic alterations. [b]Squamous vs non-squamous. [c]Presence vs absence. [d]United States/Japan/Western Europe vs rest of world.

Presented by Aaron Lisberg, ESMO 2023

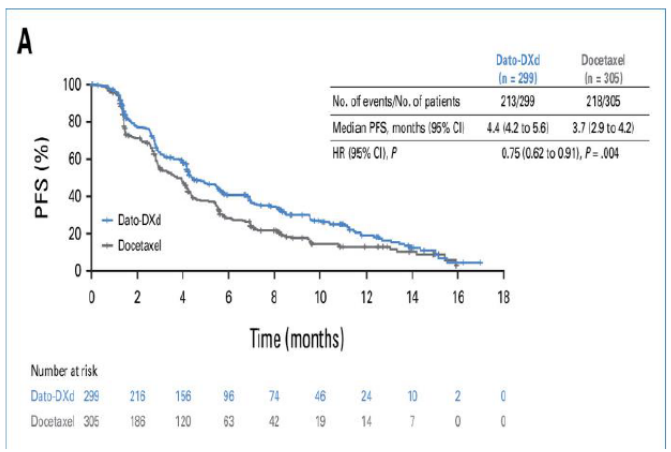
Both with rather disappointing results

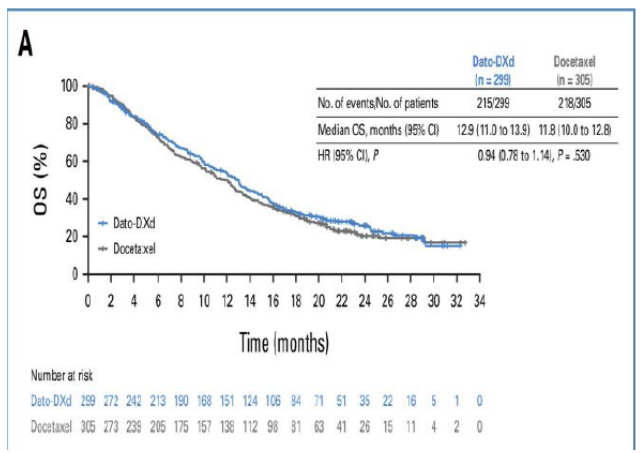
EVOKE-01





TROPION-Lung01





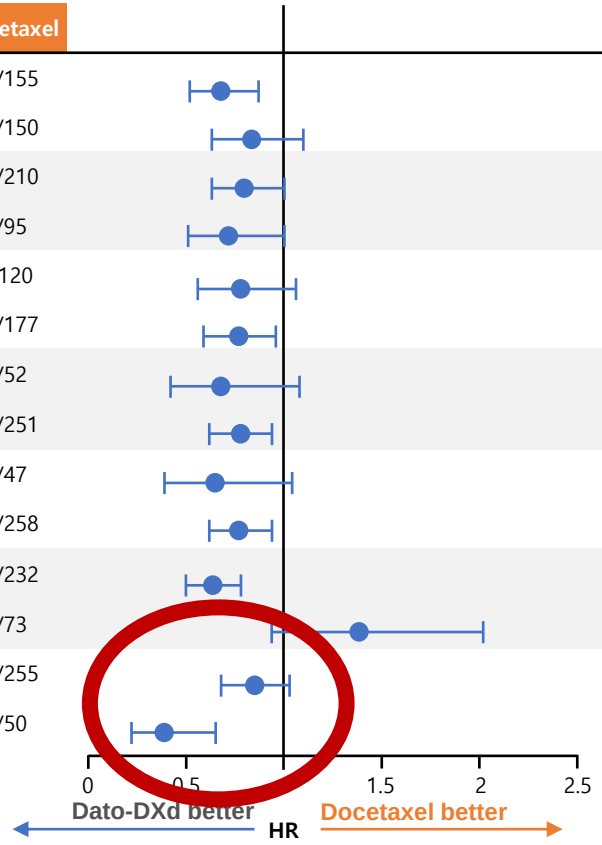
No significant improvement in OS (primary endpoint) or PFS comparing SG against Docetaxel

Dato-DXd marginally improved PFS but not OS (dual primary endpoints) over Docetaxel

Paz-Ares et al, JCO 2024; Ahn et al, JCO 2024

PFS in key subgroups[1]

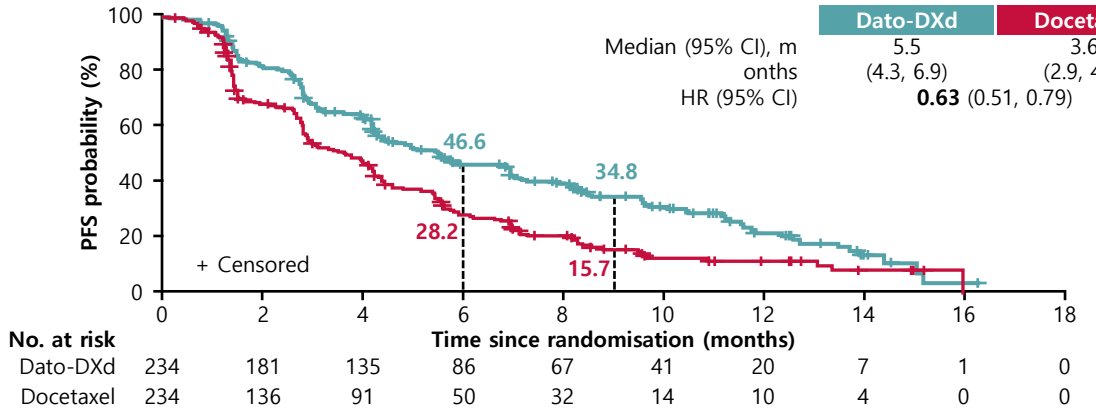
		Events, n Dato-DXd	Events, n Docetaxel	HR
Age at randomisation	<65 years	118/162	115/155	0.67
	≥65 years	95/137	103/150	0.83
Sex	Male	136/183	158/210	0.79
	Female	77/116	60/95	0.71
Race	Asian	76/119	82/120	0.77
	Non-Asian	131/172	129/177	0.76
Smoking status	Never	36/61	33/52	0.67
	Former/current	177/238	184/251	0.77
Brain metastasis at baseline	With	33/50	31/47	0.64
	Without	180/249	187/258	0.76
Histology	Non-squamous	156/229	168/232	0.63
	Squamous	57/70	50/73	1.38
Actionable genomic alterations[a]	Absent	189/252	184/255	0.84
	Present	24/47	34/50	0.38



Activity of Dato-DXd was primarily driven by patients with NSQ histology[1]

Pre-planned subgroup analysis in patients with NSQ histology[2]

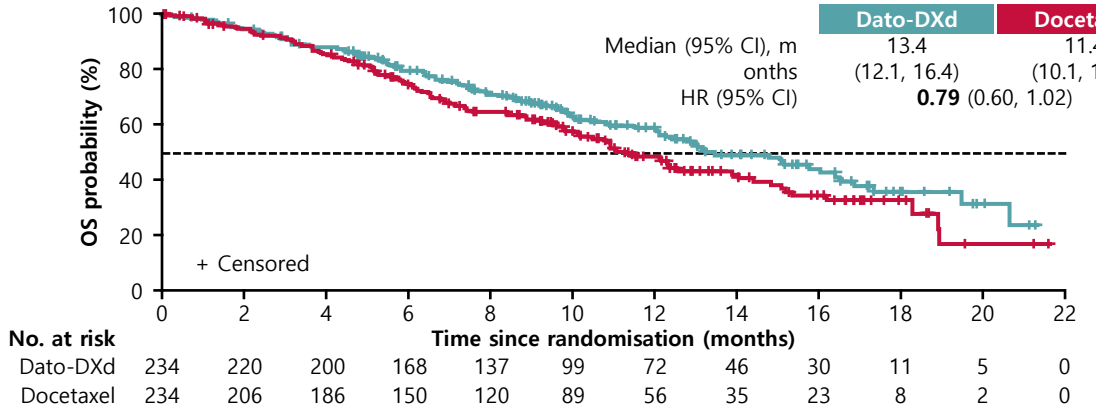
PFS by BICR – NSQ population



	Dato-DXd	Docetaxel
Median (95% CI), months	5.5 (4.3, 6.9)	3.6 (2.9, 4.2)
HR (95% CI)	**0.63** (0.51, 0.79)	

No. at risk										
Dato-DXd	234	181	135	86	67	41	20	7	1	0
Docetaxel	234	136	91	50	32	14	10	4	0	0

OS (interim) – NSQ population



	Dato-DXd	Docetaxel
Median (95% CI), months	13.4 (12.1, 16.4)	11.4 (10.1, 13.8)
HR (95% CI)	**0.79** (0.60, 1.02)	

No. at risk												
Dato-DXd	234	220	200	168	137	99	72	46	30	11	5	0
Docetaxel	234	206	186	150	120	89	56	35	23	8	2	0

This investigational agent is not approved for use. No TROP2-directed agents are licensed for NSCLC.

[a]Regardless of histology. BICR, blinded independent central review; Dato-DXd, datopotamab deruxtecan; TROP2, trophoblast cell surface antigen 2

1. Ahn M-J, et al. Ann Oncol 2023;34(Suppl. 4):S1665–S1666 (Abstract LBA12; oral presentation at ESMO 2023); 2. Girard N, et al. Poster 59P presented at ELCC 2024

A much-awaited breakthrough and approval

A pooled analysis of datopotamab deruxtecan in patients with *EGFR*–mutated NSCLC

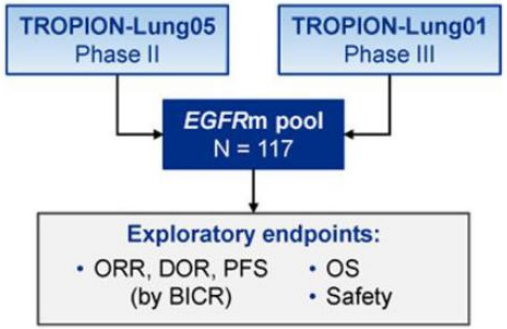
Journal of Thoracic Oncology

Background

A critical unmet need exists for effective later-line treatment options for patients with *EGFR*m advanced NSCLC

Methods

Pooled analysis from two trials assessing the TROP2-directed ADC Dato-DXd in pretreated patients with *EGFR*m NSCLC



Results

Pooled study population (N = 117)

63 years MEDIAN AGE

62% FEMALE

69% ASIAN

23% WHITE

Median 3 prior lines of therapy (EGFR-directed and platinum chemotherapy)

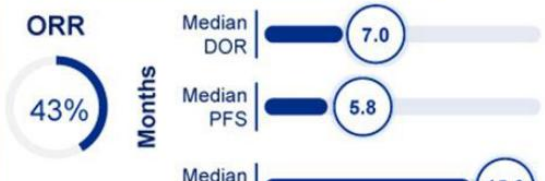
Prior osimertinib 82%

Most common *EGFR* mutations

• Patients may have had tumors with >1 *EGFR*m

*Occurring as co-mutations.

Dato-DXd elicited robust and durable clinical efficacy



Safety profile consistent with the individual studies

	Any grade	Grade 3
Oral mucositis/stomatitis	69%	9%
Ocular surface events	32%	3%
Adjudicated drug-related ILD/pneumonitis	4%	1%

• No new safety signals
• No grade 4 or 5 AESIs

CONCLUSION: Dato-DXd demonstrated clinically meaningful activity and had a manageable safety profile in previously treated patients with advanced *EGFR*m NSCLC

IASLC

Ahn M-J, et al. *J Thorac Onc* (2025)

FDA grants accelerated approval to datopotamab deruxtecan-dlnk for EGFR-mutated non-small cell lung cancer

On June 23, 2025, the Food and Drug Administration granted accelerated approval to datopotamab deruxtecan-dlnk (Datroway, Daiichi Sankyo, Inc.) for adults with locally advanced or metastatic epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) who have received prior EGFR-directed therapy and platinum-based chemotherapy.

Dato-DXd is the 2nd ADC to be FDA approved in NSCLC after T-DXd

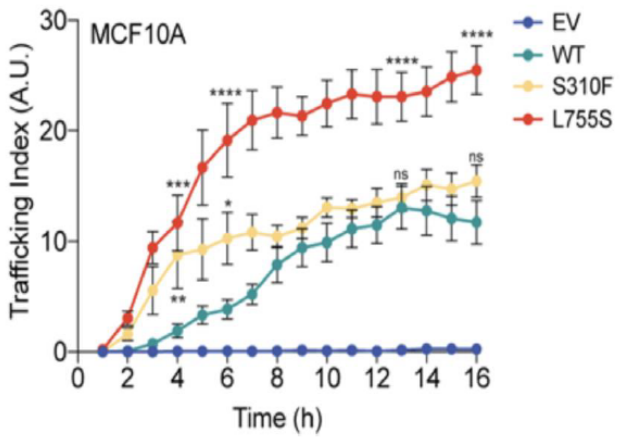
Ahn et al, JTO 2025

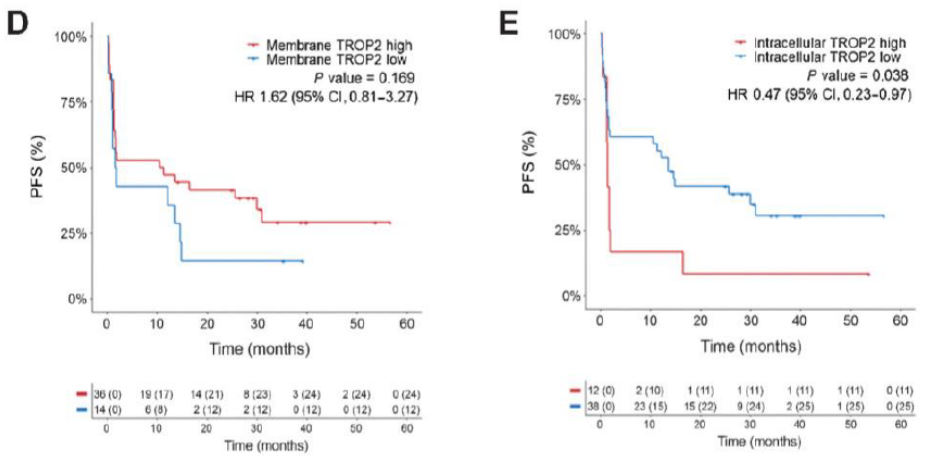
Why does Trop2 ADC work in EGFRm NSCLC?

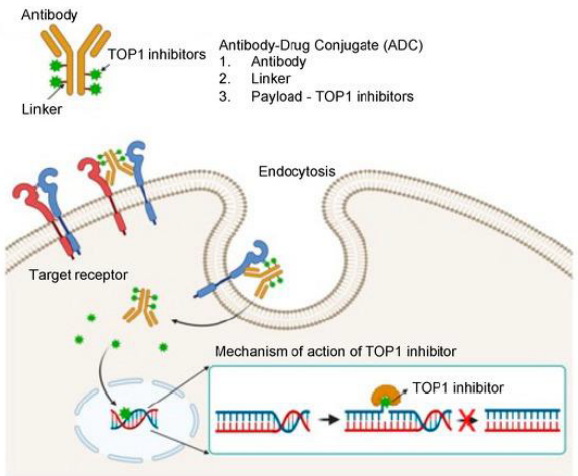
Enhanced receptor internalisation?

Increased Trop2 expression? (Intracellularly vs membranous)

Sensitivity to TOP1 payload? (Deruxtecan, Tirumotecan)







Enhanced receptor internalisation in HER2m NSCLC to explain T-DXd efficacy

Trop2 intracellular expression (but not membranous) is associated with worse outcomes to ICI

MOA of TOP1 ADCs

Still many unknowns about mechanism of action and underlying tumour biology

Li et al, Cancer Discov 2020; Bessede et al, Clin Cancer Res 2024; Han et al, Pharmaceutics 2022

Datopotamab Deruxtecan in Advanced or Metastatic Non–Small Cell Lung Cancer With Actionable Genomic Alterations: Results From the Phase II TROPION-Lung05 Study

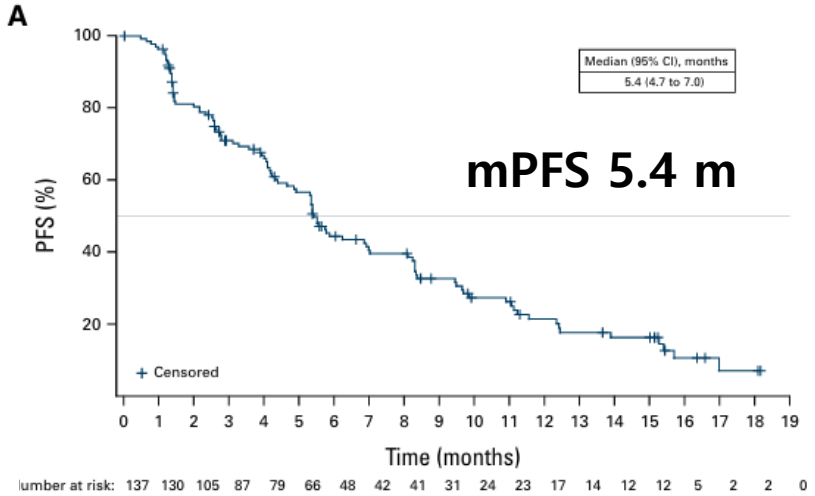
Jacob Sands, MD[1]; Myung-Ju Ahn, MD[2]; Aaron Lisberg, MD[3]; Byoung Chul Cho, MD, PhD[4]; George Blumenschein Jr, MD[5];

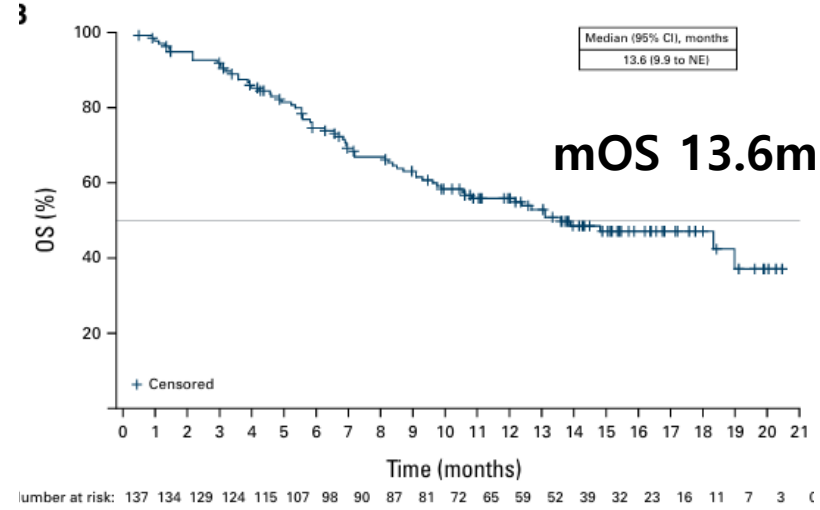
Datopotamab deruxtecan (**Dato-DXd**) in patients with pretreated advanced/metastatic NSCLC (6mg/kg, every 3 weeks)
AGAs: **EGFR**, ALK, ROS1, NTRK, BRAF, MET exon 14 skipping

TABLE 2. Antitumor Activity Assessed by Blinded Independent Central Review

Variable	Overall (N = 137)	*EGFR* Mutations (n = 78)	*ALK* Rearrangements (n = 34)
Confirmed ORR, No. (%)	49 (35.8)	34 (43.6)	8 (23.5)
95% CI[a]	27.8 to 44.4	32.4 to 55.3	10.7 to 41.2
CR, No. (%)	4 (2.9)	4 (5.1)	0
PR, No. (%)	45 (32.8)	30 (38.5)	8 (23.5)
SD, No. (%)	56 (40.9)	27 (34.6)	17 (50.0)
PD, No. (%)	19 (13.9)	10 (12.8)	5 (14.7)
Non-CR/non-PD, No. (%)	3 (2.2)	3 (3.8)	0
NE for BOR, No. (%)	10 (7.3)	4 (5.1)	4 (11.8)
DCR, No. (%)	108 (78.8)	64 (82.1)	25 (73.5)
95% CI[a]	71.0 to 85.3	71.7 to 89.8	55.6 to 87.1
DOR, months, median	7.0	7.0	7.0
95% CI[b]	4.2 to 9.8	4.2 to 10.2	2.8 to 8.4
CBR, No. (%)	64 (46.7)	42 (53.8)	12 (35.3)
95% CI[b]	38.1 to 55.4	42.2 to 65.2	19.7 to 53.5
Time to response, months, median	1.5	1.5	1.4
Range	1.1-11.3	1.2-11.3	1.1-4.1
PFS, months, median[b]	5.4	5.8	4.3
95% CI[b]	4.7 to 7.0	5.4 to 8.3	2.6 to 6.9

CR=4

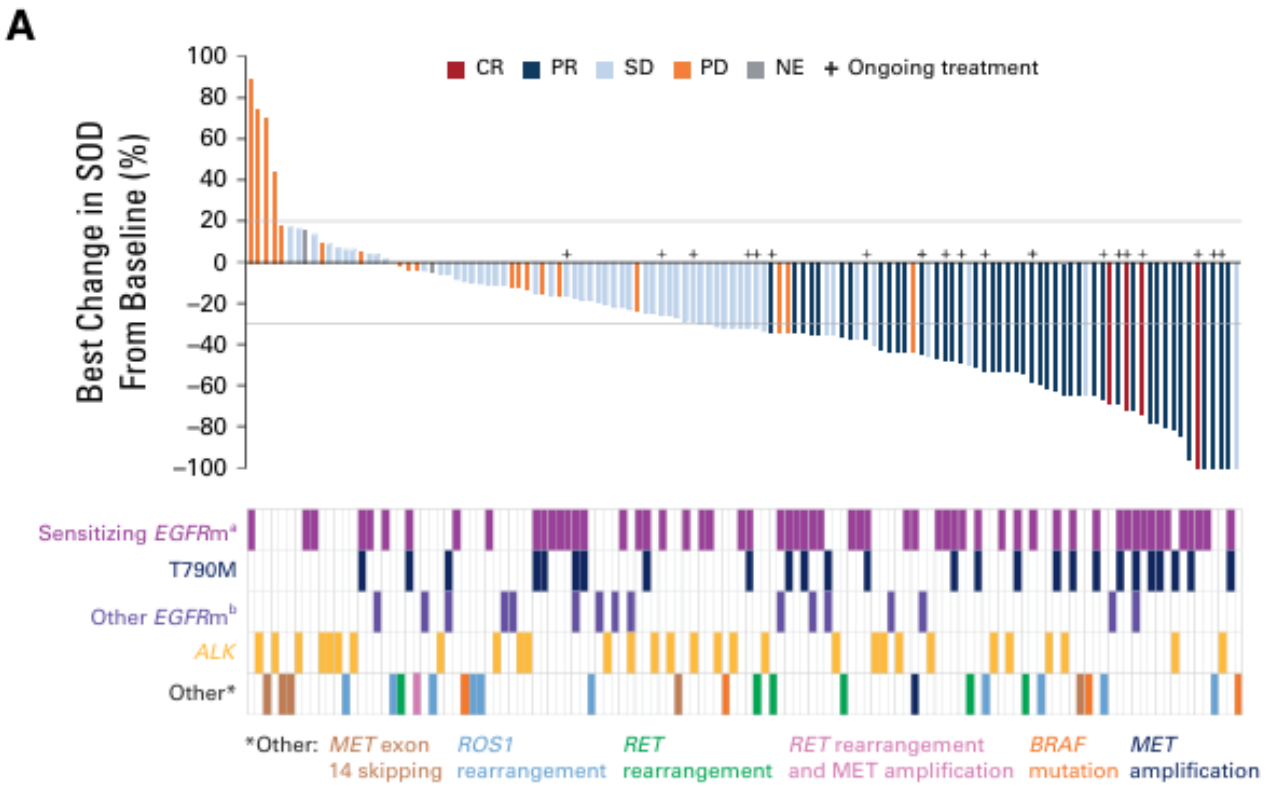


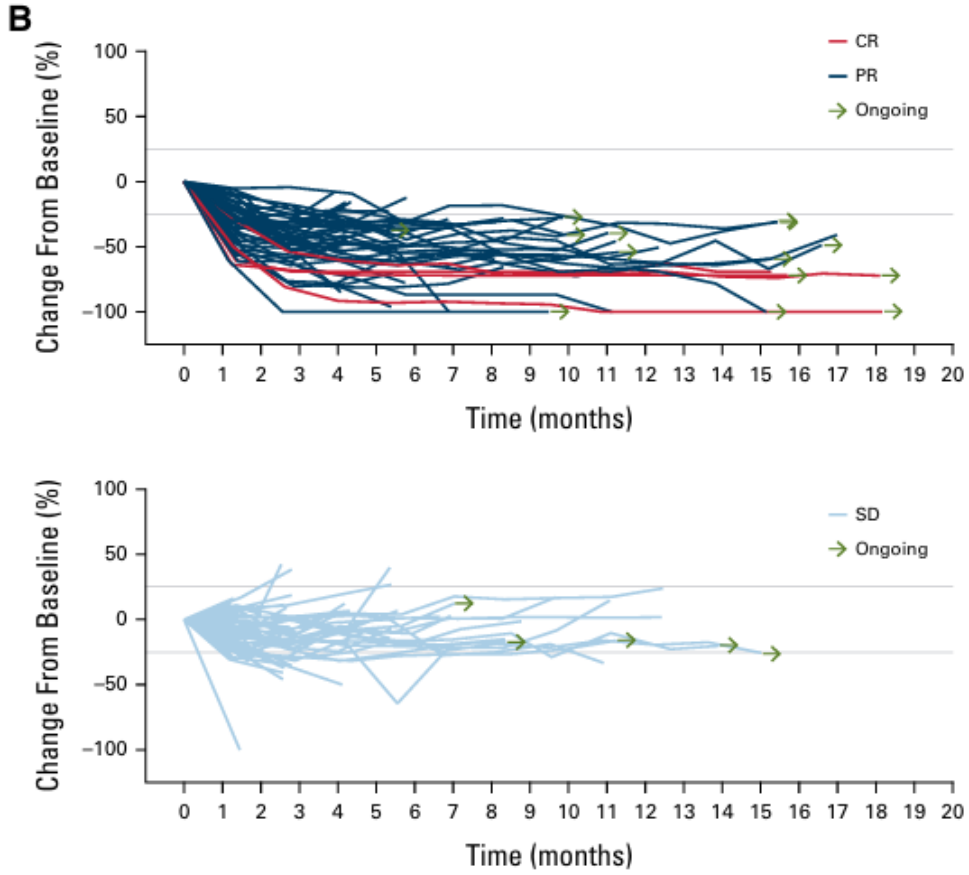


Efficacy : ORR 36%, **EGFR ORR 44%(n=78) CR=4**

Sands et al, ***J Clin Oncol*** **2025**

Efficacy





Efficacy : ORR 36%, **EGFR ORR 44%(n=78)**
DCR : 78.8%

DOR : 7 months
PR,SD 반응지속시간이 길다

Safety

TABLE 3. Safety Summary

	N = 137, No. (%)			
Adverse Event	Any Grade	Grade 3	Grade 4	Grade 5
TRAEs	129 (94.2)	38 (27.7)	1 (0.7)	0
Dose adjustments because of TRAEs				
Dose reductions	27 (19.7)	10 (7.3)	0	0
Dose delay	29 (21.2)	11 (8.0)	0	0
Treatment discontinuation	7 (5.1)	1 (0.7)	1 (0.7)	0
Serious TRAEs	11 (8.0)	6 (4.4)	1 (0.7)	0
AESIs				
Oral mucositis/stomatitis	90 (65.7)	15 (10.9)	0	0
Mucosal inflammation	1 (0.7)[a]	0	0	0
Ocular surface events	36 (26.3)	3 (2.2)	0	0
Infusion-related reactions	22 (16.1)	0	0	0
Adjudicated ILD/pneumonitis	5 (3.6)	0	0	1 (0.7)
Dose adjustments because of AESIs				
Dose reductions	17 (12.4)	6 (4.4)	0	0
Dose delay	16 (11.7)	5 (3.6)	0	1 (0.7)
Treatment discontinuations	5 (3.6)	0	0	1 (0.7)
Serious AESIs	5 (3.6)	3 (2.2)	0	1 (0.7)
AESI-associated death	1 (0.7)	0	0	1 (0.7)

Abbreviations: AESI, adverse event of special interest; ILD, interstitial lung disease; TRAE, treatment-related adverse event.
[a]The verbatim term of the mucosal inflammation event was nasal mucositis.

TABLE 4. Treatment-Related Adverse Events (≥10%)

	N = 137, No. (%)			
TRAE	Any Grade	Grade 1	Grade 2	Grade ≥3
Stomatitis (PT)	77 (56.2)	37 (27.0)	27 (19.7)	13 (9.5)
Nausea	75 (54.7)	44 (32.1)	28 (20.4)	3 (2.2)
Alopecia	68 (49.6)	48 (35.0)	19 (13.9)	1 (0.7)
Decreased appetite	28 (20.4)	11 (8.0)	14 (10.2)	3 (2.2)
Fatigue	26 (19.0)	14 (10.2)	10 (7.3)	2 (1.5)
Constipation	21 (15.3)	16 (11.7)	5 (3.6)	0
Rash	19 (13.9)	14 (10.2)	5 (3.6)	0
Vomiting	19 (13.9)	10 (7.3)	8 (5.8)	1 (0.7)
Asthenia	15 (10.9)	8 (5.8)	5 (3.6)	2 (1.5)

The most common TRAE :stomatitis 56%
ILD 3.6%

Low incidence of hematologic or treatment related grade ≥3 toxicities

TROP2 정상 조직 :피부, 각막, 타액선 존재

ADVANCED NSCLC · Volume 20, Issue 3, Supplement 1, S2-S4, March 2025

1O: Osimertinib (osi) + datopotamab deruxtecan (Dato-DXd) in patients (pts) with EGFR-mutated (EGFRm) advanced NSCLC (aNSCLC) whose disease progressed on first-line (1L) osi: ORCHARD

X. Le [1] · L. Hendriks [2] · A. Morabito [3] · ... · J.M. Lehman [18] · P.G. Fraenkel [19] · S.B. Goldberg [20] ... Show more

Affiliations & Notes Article Info

Methods

Pts received oral osi (80 mg QD) + IV Dato-DXd (4 or 6 mg/kg Q3W in two cohorts). Enrolment started in the 4 mg cohort and was extended to the 6 mg cohort, followed by simultaneous enrolment to both dose levels. Primary endpoint: ORR (RECIST v1.1; by investigator). Secondary endpoints: DoR, PFS, OS, and safety. DCO: 12 Oct 2024.

Results

Overall, 69 pts received osi + Dato-DXd. Median tx duration was 9.0 and 9.8 mo for the 4 mg (n = 35) and 6 mg (n = 34) cohorts, respectively; median duration of follow-up was 13.4 and 13.8 mo, respectively. Among 68 evaluable pts, ORR was similar between the cohorts (4/6 mg: 43/36%); DoR (4/6 mg: 15/64% remaining in response at 9 mo) and PFS (4/6 mg: median, 9.5/11.7 mo) favoured

the 6 mg cohort (Table). OS was immature (37% maturity). More pts in the 6 mg cohort had grade ≥3 AEs related to any tx (4/6 mg: 34/56%), AEs leading to Dato-DXd dose reduction (4/6 mg: 23/59%), and adjudicated ILD/pneumonitis (4/6 mg: any grade, 3/15%; grade ≥3, 3/6%).

ADVANCED NSCLC · Volume 20, Issue 3, Supplement 1, S2-S4, March 2025

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Affiliations & Notes Article Info

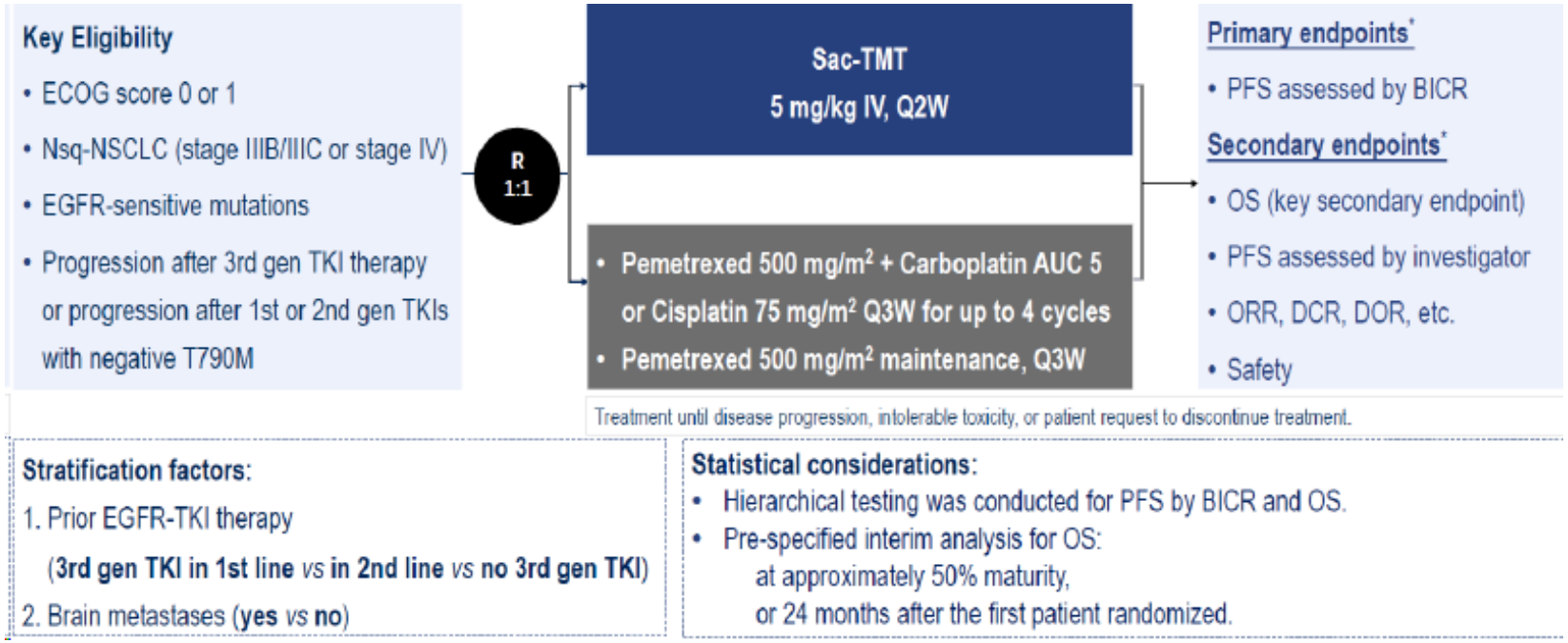
		Dato-DXd dose cohort	
		4 mg/kg(n = 35)	6 mg/kg (n = 33)
ORR	Pts with a response, n	15	12
	ORR, % (80% CI)	43 (31, 55)	36 (25, 49)
	Median time to onset of response, mo (Q1, Q3)	2.7 (1.5, 4.1)	1.4 (1.2, 2.1)
DoR	DoR events, n (%)	13 (87)	6 (50)
	Pts remaining in response at 9 mo, % (95% CI)*	15 (2, 38)	64 (30, 85)
PFS	PFS events, n (%)	28 (80)	19 (58)
	Median PFS, mo (95% CI)*	9.5 (7.2, 9.8)	11.7 (8.3, NC)
	PFS rate at 9 mo, % (95% CI)*	50 (33, 65)	70 (49, 83)
	PFS rate at 12 mo, % (95% CI)*	21 (9, 35)	39 (21, 57)

mPFS 9.5 mon, 11.7 months

OptiTROP-Lung04 study

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 1, 2026 VOL. 394 NO. 1

Sacituzumab Tirumotecan in EGFR-TKI–Resistant, *EGFR*-Mutated Advanced NSCLC



- TROP2 :82% of patients with EGFR-mutant NSCLC
- Sac-TMT -TROP2-targeted ADC with linker that delivers a belotecan-derived topo I inhibitor to tumor cells.
- showing enhanced uptake and internalization in EGFR-mutant and TKI-resistant models in preclinical studies

§ 중국 Kelun biotech- 머크 (MSD) 합작 (Keytruda + Sac-TMT 임상도 진행 중)

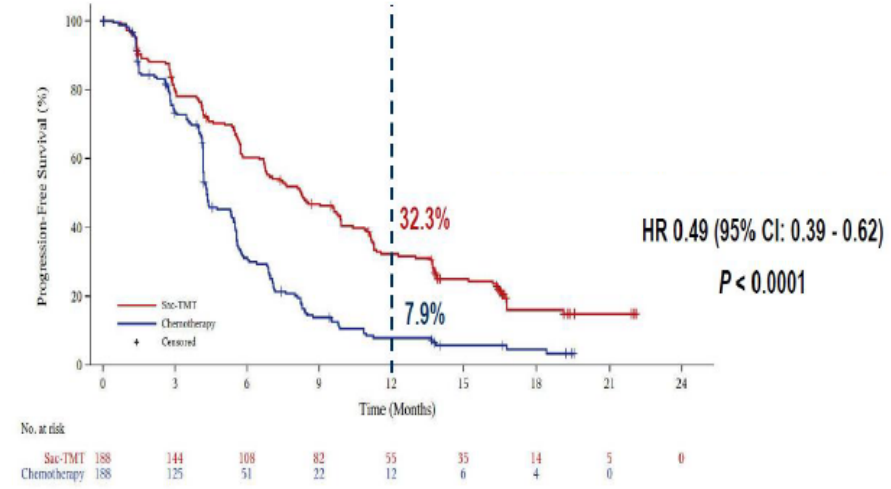
Patient characteristic

Characteristic	Sac-TMT (n = 188)	Chemotherapy (n = 188)
Median age (range), years	60 (31-75)	59 (33-75)
≥ 65 years, n (%)	58 (30.9)	51 (27.1)
Male, n (%)	66 (35.1)	83 (44.1)
ECOG PS 1, n (%)	153 (81.4)	145 (77.1)
Smoking history, n (%)		
Never smoked	145 (77.1)	135 (71.8)
Current or former smoker	43 (22.9)	53 (28.2)
Clinical stage at enrollment, n (%)		
Stage IIIB/IIIC	6 (3.2)	3 (1.6)
Stage IV	182 (96.8)	185 (98.4)
≥ 3 metastatic sites, n (%)	128 (68.1)	126 (67.0)
Brain metastases, n (%)	33 (17.6)	36 (19.1)
Liver metastases, n (%)	25 (13.3)	33 (17.6)

Characteristic	Sac-TMT (n = 188)	Chemotherapy (n = 188)
***EGFR* mutation subtype*, n (%)**		
Exon 19 deletion	106 (56.4)	118 (62.8)
Exon 21 L858R	84 (44.7)	71 (37.8)
T790M mutation status, n (%)		
Positive	29 (15.4)	36 (19.1)
Negative	48 (25.5)	40 (21.3)
Unknown	111 (59.0)	112 (59.6)
Prior 3rd generation EGFR-TKI, n (%)		
1st line	118 (62.8)	117 (62.2)
2nd line	60 (31.9)	60 (31.9)

Efficacy

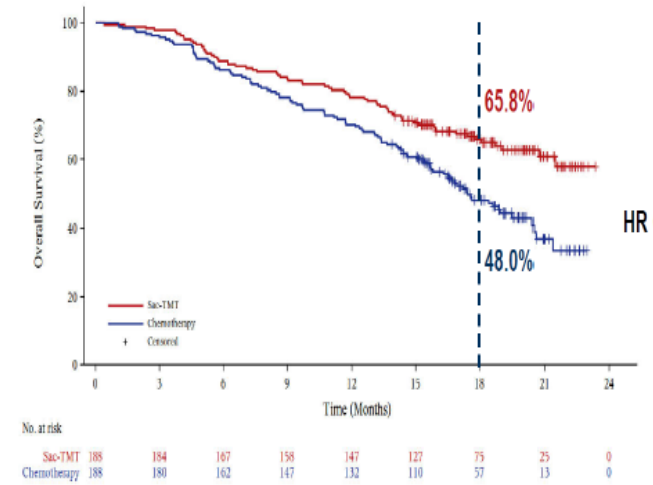
	Sac-TMT (n = 188)	Chemotherapy (n = 188)
PFS events, n (%)	144 (76.6)	159 (84.6)
Median PFS, mo (95% CI)	**8.3** (6.7 - 9.9)	**4.3** (4.2 - 5.5)
12-mo PFS rate, % (95% CI)	32.3 (25.5 - 39.2)	7.9 (4.4 - 12.8)



HR 0.49 (95% CI: 0.39 - 0.62)

P < 0.0001

	Sac-TMT (n = 188)	Chemotherapy (n = 188)
OS events, n (%)	67 (35.6)	101 (53.7)
Median OS, mo (95% CI)	**NR** (21.5 - NE)	**17.4** (15.7 - 20.4)
18-mo OS rate, % (95% CI)	65.8 (58.3 – 72.3)	48.0 (40.2 - 55.4)



HR 0.60 (95% CI: 0.44 - 0.82)

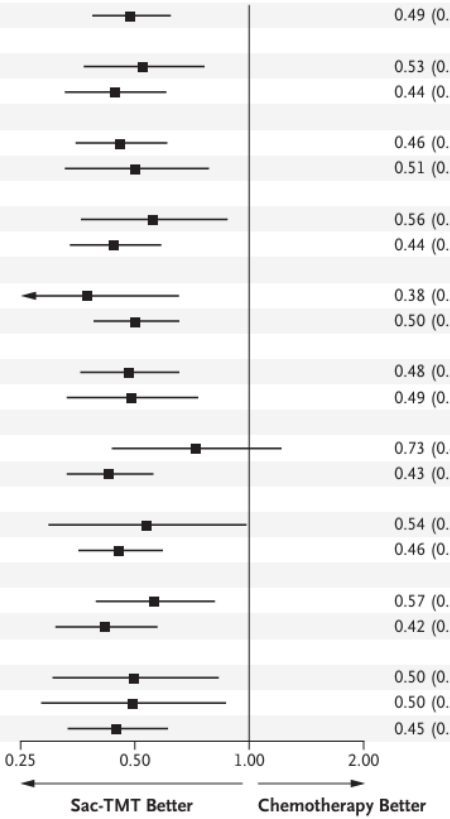
two-sided *P* = 0.001*

PFS 8.3 mon vs 4.3 months (cf. Dato-Dxd ORR 5.4 mon)
OS NR vs 17.4 months
ORR 60.6% vs 43.1% (cf. Dato-Dxd ORR 44%)

Sac-TMT is better than Chemotx

B Analysis of Progression-free Survival in Prespecified Subgroups

Subgroup	Sac-TMT	Chemotherapy	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/total no. of patients		
All patients	144/188	159/188	0.49 (0.39–0.62)
Sex			
Male	54/66	75/83	0.53 (0.37–0.76)
Female	90/122	84/105	0.44 (0.33–0.60)
Age			
<65 yr	100/130	118/137	0.46 (0.35–0.61)
≥65 yr	44/58	41/51	0.51 (0.33–0.78)
History of smoking			
Current or former smoker	36/43	49/53	0.56 (0.36–0.88)
Never smoked	108/145	110/135	0.44 (0.34–0.59)
ECOG performance-status score			
0	24/35	35/43	0.38 (0.22–0.65)
1	120/153	124/145	0.50 (0.39–0.65)
Previous third-generation EGFR-TKI therapy			
First-line therapy	89/118	95/117	0.48 (0.36–0.65)
Second-line therapy	49/60	55/60	0.49 (0.33–0.73)
Brain metastases			
Yes	30/33	31/36	0.73 (0.43–1.21)
No	114/155	128/152	0.43 (0.33–0.56)
Liver metastases			
Yes	18/25	28/33	0.54 (0.30–0.98)
No	126/163	131/155	0.46 (0.35–0.59)
EGFR mutation subtype			
Exon 21 L858R substitution	68/84	59/71	0.57 (0.39–0.81)
Exon 19 deletion	77/106	101/118	0.42 (0.31–0.57)
T790M mutation status			
Negative	39/48	32/40	0.50 (0.30–0.83)
Positive	23/29	30/36	0.50 (0.28–0.87)
Unknown	82/111	97/112	0.45 (0.33–0.61)



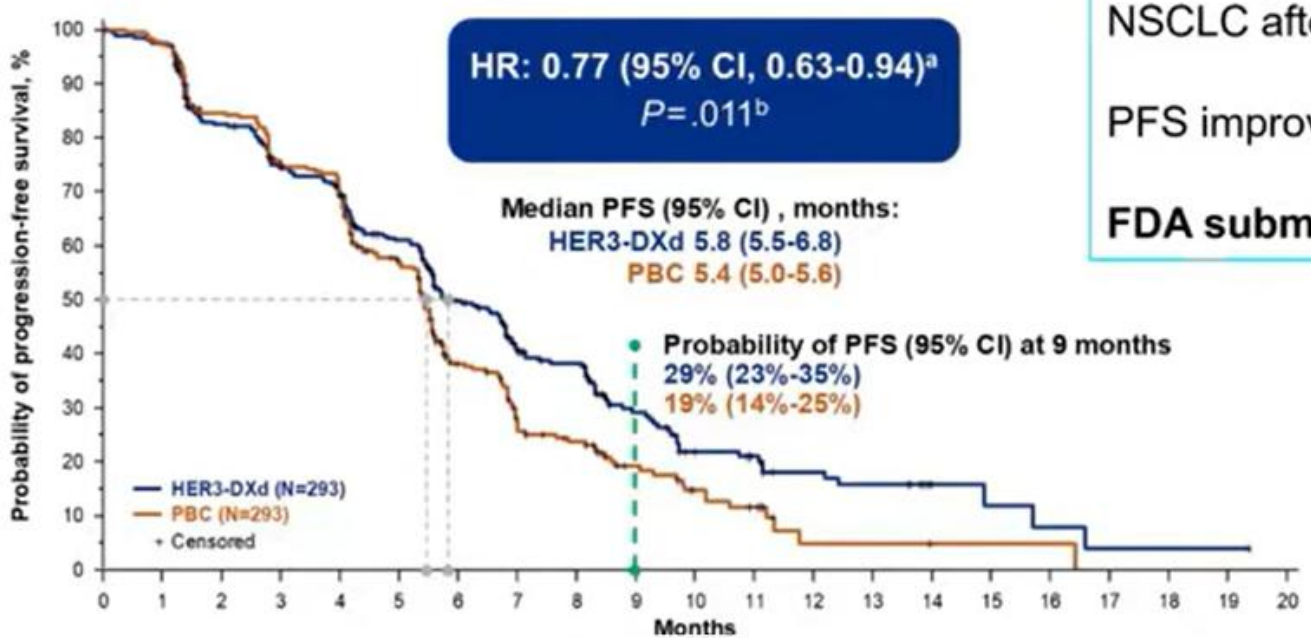
Hematologic toxicity, alopecia, stomatitis
TROP2 : epithelial cell 표면에 존재하는 당단백질

Table 3. Treatment-Related Adverse Events (Safety Population).*

Event	Sacituzumab Tirumotecan (N=188)		Chemotherapy (N=182)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
	number of patients (percent)			
Any treatment-related adverse event	188 (100.0)	109 (58.0)	179 (98.4)	98 (53.8)
Leading to dose reduction	57 (30.3)	—	41 (22.5)	—
Leading to dose interruption	69 (36.7)	—	60 (33.0)	—
Leading to treatment discontinuation	0	—	1 (0.5)	—
Leading to death†	0	—	1 (0.5)	—
Any treatment-related serious adverse event	17 (9.0)	—	32 (17.6)	—
Treatment-related adverse event with an incidence of ≥10% in either group				
Anemia	159 (84.6)	21 (11.2)	139 (76.4)	26 (14.3)
White-cell decreased	157 (83.5)	52 (27.7)	127 (69.8)	40 (22.0)
Alopecia	157 (83.5)	0	17 (9.3)	0
Neutrophil count decreased	142 (75.5)	75 (39.9)	126 (69.2)	60 (33.0)
Stomatitis‡	121 (64.4)	9 (4.8)	9 (4.9)	0
Nausea	89 (47.3)	1 (0.5)	86 (47.3)	2 (1.1)
Anorexia	78 (41.5)	0	58 (31.9)	0
Fatigue	72 (38.3)	7 (3.7)	73 (40.1)	4 (2.2)
Weight loss	52 (27.7)	0	28 (15.4)	1 (0.5)
Thrombocytopenia	51 (27.1)	4 (2.1)	85 (46.7)	30 (16.5)
Vomiting	50 (26.6)	0	39 (21.4)	1 (0.5)
Alanine aminotransferase increased	46 (24.5)	1 (0.5)	63 (34.6)	2 (1.1)
Constipation	39 (20.7)	0	31 (17.0)	0
Aspartate aminotransferase increased	35 (18.6)	1 (0.5)	63 (34.6)	2 (1.1)
Constipation	39 (20.7)	0	31 (17.0)	0
Aspartate aminotransferase increased	35 (18.6)	1 (0.5)	63 (34.6)	2 (1.1)
Rash	35 (18.6)	0	14 (7.7)	0
Lymphocyte count decreased	30 (16.0)	6 (3.2)	23 (12.6)	7 (3.8)
Hypoalbuminemia	23 (12.2)	0	27 (14.8)	0
γ-Glutamyltransferase increased	20 (10.6)	2 (1.1)	27 (14.8)	3 (1.6)
Hyperuricemia	20 (10.6)	0	17 (9.3)	0
Diarrhea	19 (10.1)	1 (0.5)	6 (3.3)	0
Hypokalemia	14 (7.4)	4 (2.1)	23 (12.6)	7 (3.8)

Patritumab Deruxtecan (HER3-DXd) in Resistant *EGFR*-Mutated Advanced NSCLC After a Third-Generation EGFR TKI: The Phase 3 HERTHENA-Lung02 Study

Tony S. K. Mok, MD, FRCPC, FASCO[1]
Helena A. Yu, MD,[2] Sun Min Lim, MD, PhD,[3] Isamu Okamoto, MD, PhD,[4] Maurice Pérol, MD,[5] Silvia Novello, MD, PhD,[6] Christophe Dooms, MD, PhD,[7] Jong-Mu Sun, PhD,[8] Steven Kao, BHB, MBChB, PhD, FRACP,[9] Pasi A. Jänne, MD, PhD,[10] Martin Reck, MD, PhD,[11] Conor Steuer, MD,[12] Makoto Nishio, MD, PhD,[13] Yi-Long Wu, MD,[14] Ronan Fougeray, MS,[15] Ragini Kudchadkar, MD,[15] Jian Yu Wu,[16] Stephen Esker, PharmD,[15] Antonio Passaro, MD, PhD[17]



HER3-DXd vs Platinum Doublet in EGFRm NSCLC after 3rd Gen EGFR TKI

PFS improvement of 0.4 months

FDA submission withdrawn

IASLC 2025 World Conference on Lung Cancer

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Phase I/II Study of iza-bren (BL-B01D1) as Monotherapy in Patients with Locally Advanced or Metastatic EGFR Mutated NSCLC

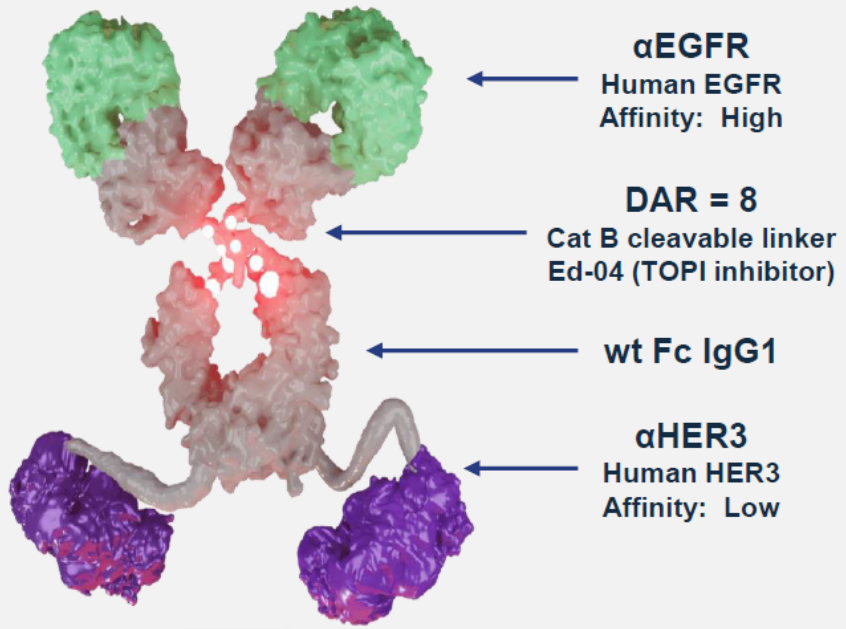
Presented by: Wenfeng Fang[1]

H. Zhao[2], Y. Zhao[2], Y. Ma[2], Y. Huang[2], Y. Yang[2], L. Chen[2], X. Hou[2], Y. Wang[3], S. Xiao[4], H. Zhu[5], Y. Zhu[5], L. Zhang[2]

[1]Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangzhou, China; [2]Sun Yat-sen University Cancer Center, Guangzhou, China; [3]West China Hospital Sichuan University, Sichuan, China; [4]Baili-Bio (Chengdu) Pharmaceutical Co., Ltd., Sichuan, China; [5]SystImmune, Inc., Redmond, WA, United States

Background

Iza-bren (BL-B01D1)



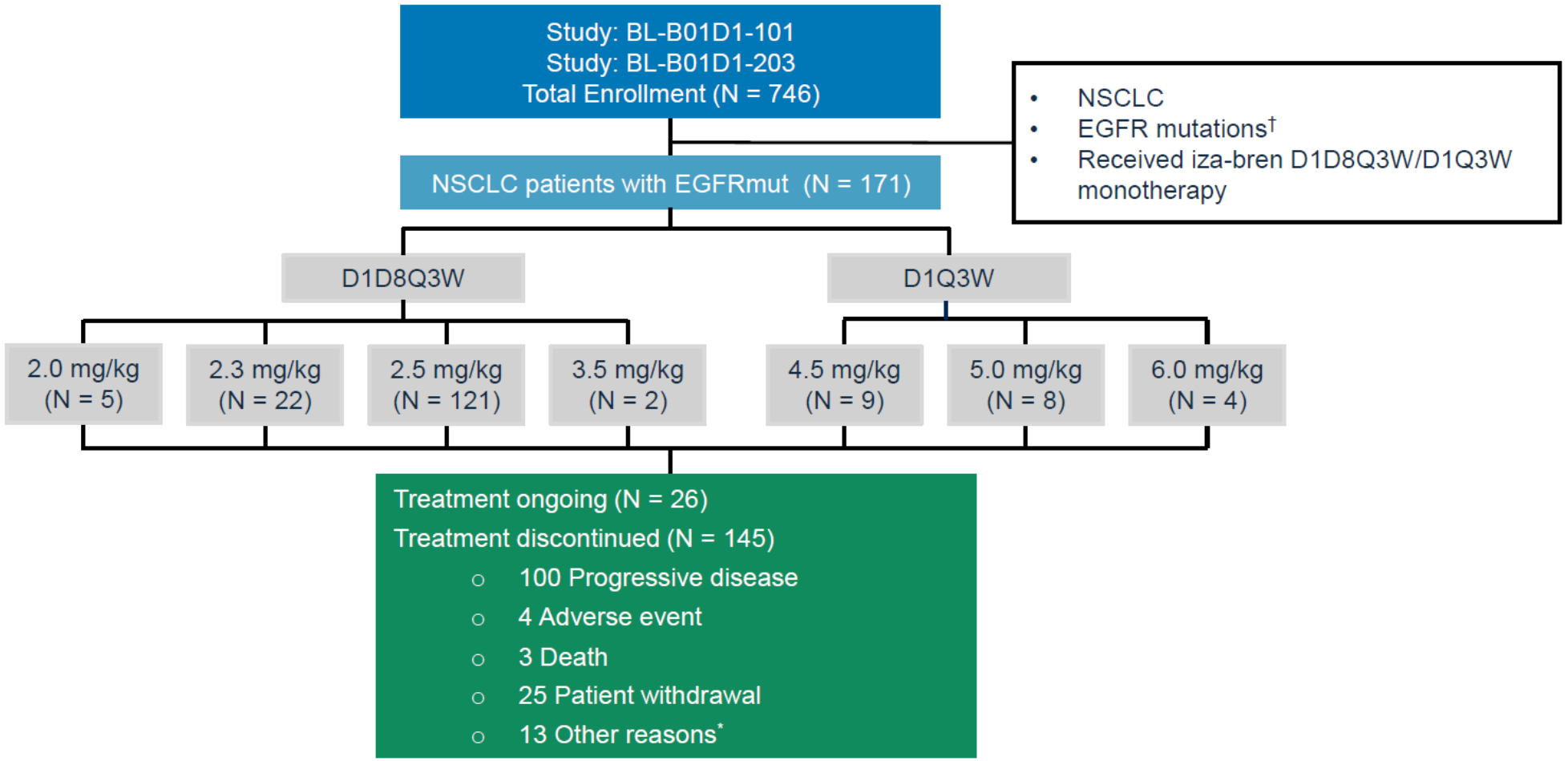
- Third generation (3G) EGFR-TKI is one of the standard first-line therapy for patients with EGFRmt NSCLC, and most patients inevitably developed drug resistance. Subsequent therapeutic options following 3G EGFR-TKI remain limited.
- Iza-bren is a potential first-in-class ADC comprised of an EGFR x HER3 bispecific antibody conjugated to a novel topo-I inhibitor payload (Ed-04) via a stable tetrapeptide-based cleavable linker.
- Iza-bren has shown promising clinical activity and a manageable safety profile in solid tumors including pretreated EGFRmt NSCLC[1].

Here, we report the latest efficacy and safety results of iza-bren as monotherapy in pretreated EGFRmt NSCLC from two phase I/II studies (NCT05194982, NCT05880706).

wt: wild type; **Cat B:** cathepsin B; **TOPI:** Topoisomerase I.

[1] Ma, Yuxiang et al. The Lancet Oncology, Volume 25, Issue 7, 901-911.

Study Design & Patient Disposition



†: Including EGFR exon19del, L858R, T790M, Exon 20ins, etc.
*: Including 5 with treatment delay >28 days; 5 discontinued per investigator decision; 2 started new anti-cancer therapy; 1 non-compliant.

Data cutoff: June 30, 2025

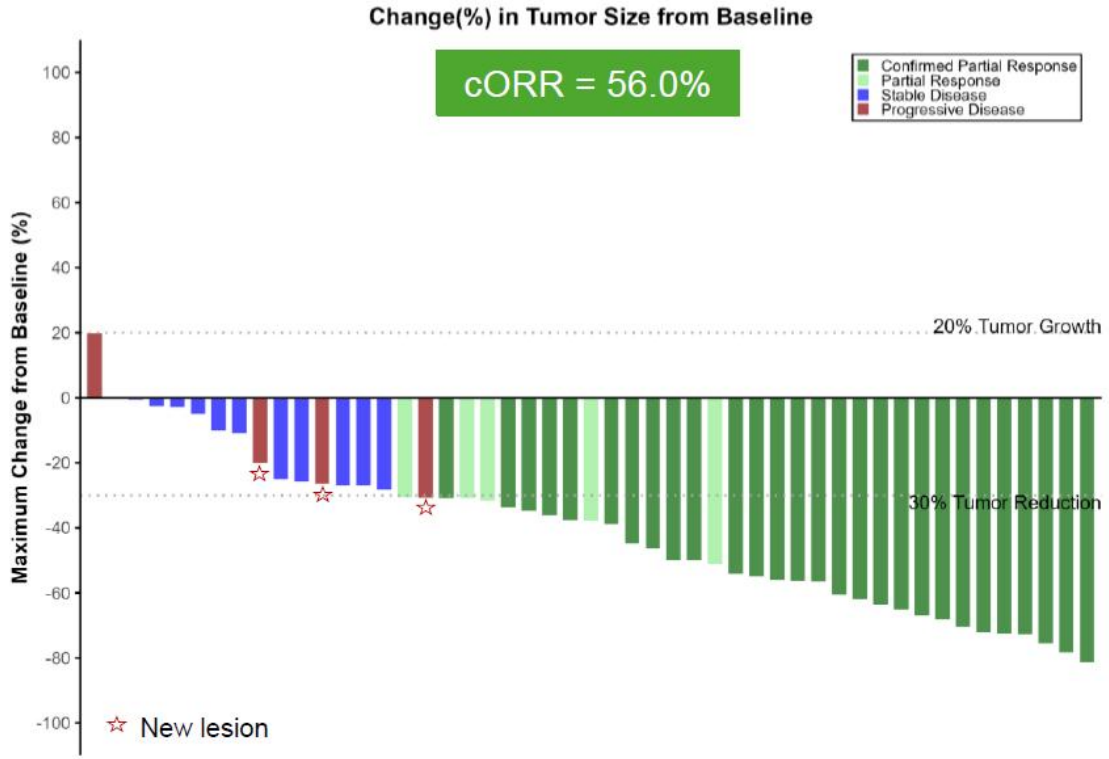
Baseline Characteristics

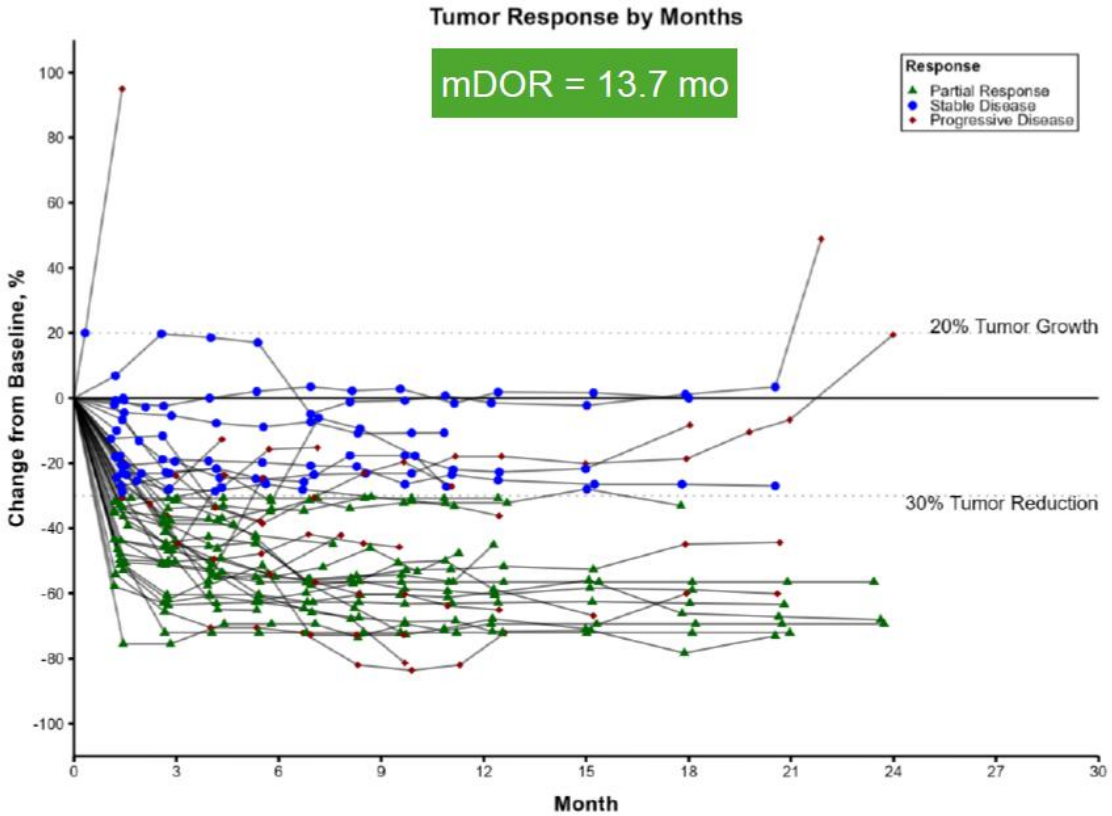
	Total (N = 171)	D1D8Q3W				D1Q3W		
		2.0 mg/kg (N = 5)	2.3 mg/kg (N = 22)	2.5 mg/kg (N = 121)	3.5 mg/kg (N = 2)	4.5 mg/kg (N = 9)	5.0 mg/kg (N = 8)	6.0 mg/kg (N = 4)
Median (range) age, years	57.0 (35.0, 82.0)	58.0 (40.0, 69.0)	61.5 (37.0, 72.0)	57.0 (37.0, 82.0)	39.0 (39.0, 39.0)	54.0 (42.0, 71.0)	60.5 (35.0, 73.0)	61.0 (53.0, 67.0)
Male, n (%)	72 (42.1)	3 (60.0)	10 (45.5)	51 (42.1)	1 (50.0)	2 (22.2)	3 (37.5)	2 (50.0)
Median (range) baseline sum of diameters, mm	45.5 (10.0, 181.0)	64.7 (52.0, 120.0)	41.5 (18.0, 133.0)	42.0 (10.0, 181.0)	64.5 (16.0, 113.0)	58.0 (27.0, 94.0)	40.5 (26.0, 91.0)	63.0 (42.0, 117.0)
ECOG-PS Score, n (%)								
0	14 (8.2)	0	1 (4.5)	9 (7.4)	0	2 (22.2)	1 (12.5)	1 (25.0)
1	157 (91.8)	5 (100)	21 (95.5)	112 (92.6)	2 (100)	7 (77.8)	7 (87.5)	3 (75.0)
EGFR exon19del mutation, n (%)	91 (53.2)	3 (60.0)	10 (45.5)	65 (53.7)	1 (50.0)	5 (55.6)	6 (75.0)	1 (25.0)
EGFR L858R mutation, n (%)	67 (39.2)	2 (40.0)	12 (54.5)	44 (36.4)	0	4 (44.4)	2 (25.0)	3 (75.0)
Brain metastasis at baseline, n (%)	61 (35.7)	2 (40.0)	3 (13.6)	44 (36.4)	1 (50.0)	6 (66.7)	3 (37.5)	2 (50.0)
Prior line of therapy, n (%)								
1L	44 (25.7)	1 (20.0)	12 (54.5)	30 (24.8)	1 (50.0)	0	0	0
2L	53 (31.0)	3 (60.0)	8 (36.4)	36 (29.8)	0	2 (22.2)	4 (50.0)	0
3L and above	74 (43.3)	1 (20.0)	2 (9.1)	55 (45.5)	1 (50.0)	7 (77.8)	4 (50.0)	4 (100)
Prior line of chemotherapy, n (%)								
0L	74 (43.3)	1 (20.0)	16 (72.7)	50 (41.3)	1 (50.0)	0	5 (62.5)	1 (25.0)
1L	60 (35.1)	3 (60.0)	4 (18.2)	42 (34.7)	1 (50.0)	5 (55.6)	3 (37.5)	2 (50.0)
2L	18 (10.5)	1 (20.0)	1 (4.5)	16 (13.2)	0	0	0	0
3L and above	19 (11.1)	0	1 (4.5)	13 (10.7)	0	4 (44.4)	0	1 (25.0)
Prior 3G EGFR-TKI, n (%)	158 (92.4)	5 (100)	22 (100)	110 (90.9)	1 (50.0)	9 (100)	7 (87.5)	4 (100)
Prior PBC, n (%)	90 (52.6)	4 (80.0)	1 (4.5)	69 (57.0)	1 (50.0)	9 (100)	3 (37.5)	3 (75.0)
Prior anti-PD(L)-1, n (%)	31 (18.1)	0	0	25 (20.7)	1 (50.0)	4 (44.4)	0	1 (25.0)

Most patients were pretreated with 3G EGFR-TKI; predominant EGFR mutations in our population were exon19del and L858R.

Data cutoff: June 30, 2025

Depth & Duration of Response – Post TKI & chemo naïve (N = 50)

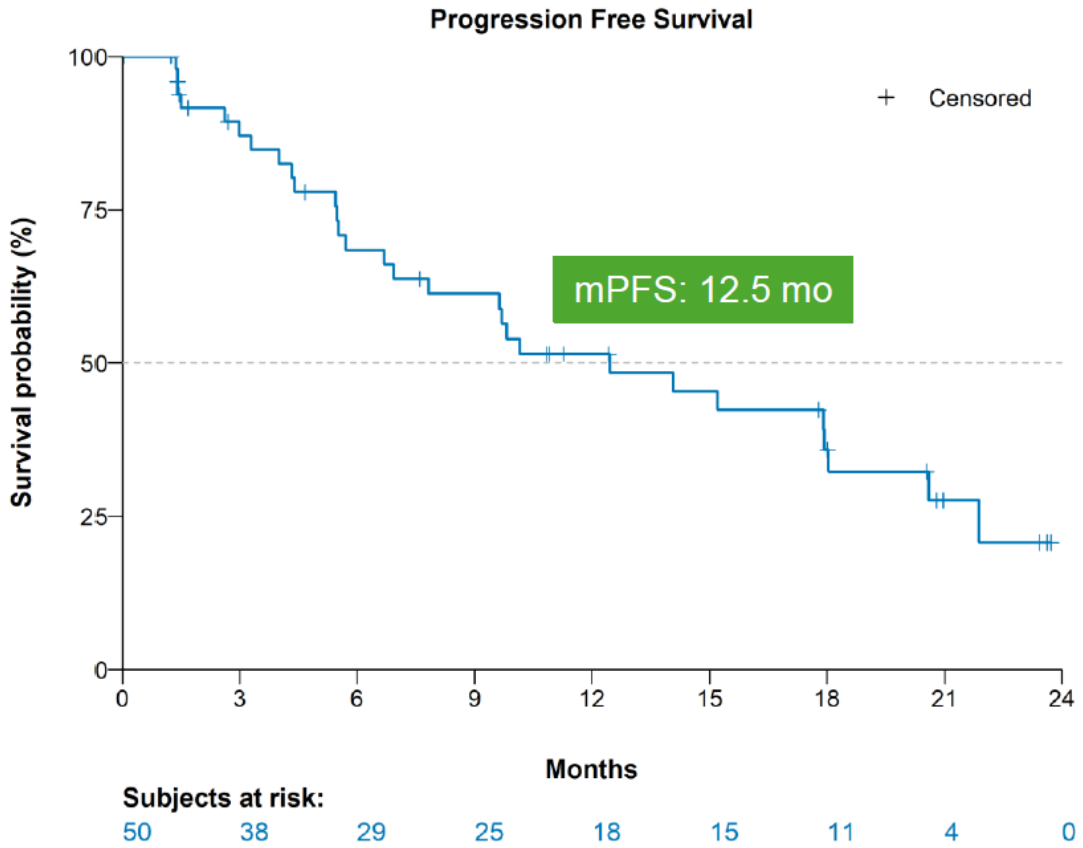


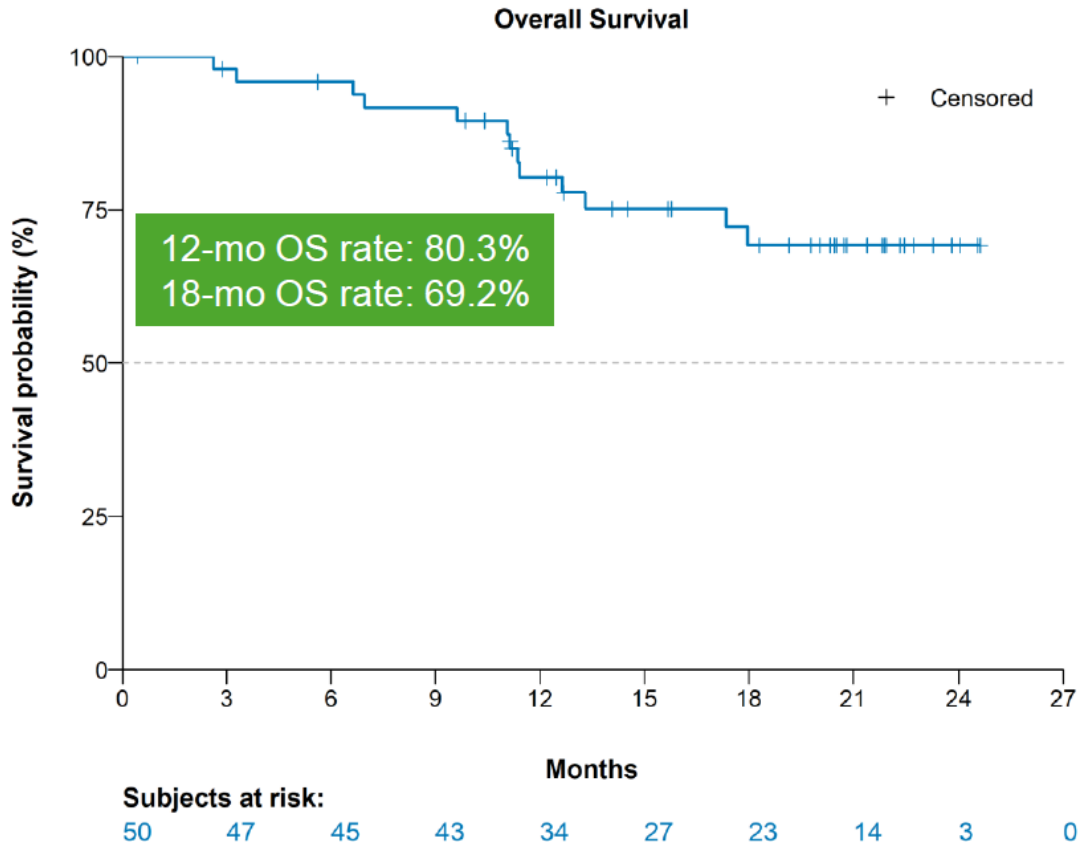


94.0% of patients with tumor shrinkage and the median (range) shrinkage (%) was -38.9 (-81.3, -0.7).

Data cutoff: June 30, 2025

PFS & OS – Post TKI & chemo naïve (N = 50)

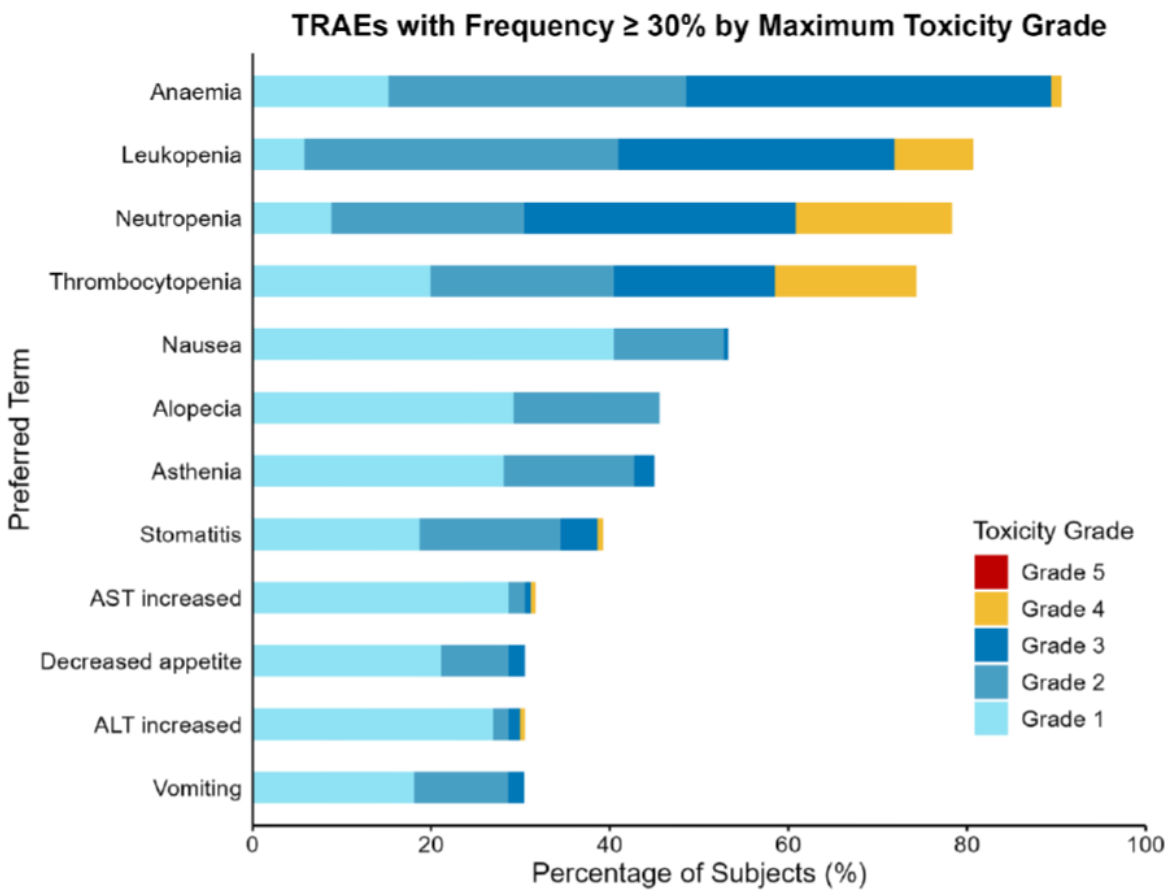




The mPFS in post TKI and chemo naïve patients was 12.5 mo, and the 18-mo OS rate was 69.2%.

Data cutoff: June 30, 2025

TRAEs with Frequency ≥ 30% (N = 171)



- Most common Grade 3 and above AEs were hematologic toxicities*, which were effectively managed with standard supportive care, as demonstrated by the low rate (1.2%) of TRAE leading to drug discontinuation.
- Among patients with Grade 3 or above neutropenia, most patients had one or two episodes. The median time to resolution of Grade 3 or 4 neutropenia was 4-6 days.
- Febrile neutropenia rate was 1.8%.
- Primary G-CSF prophylaxis was not mandatory in this cohort.
- Only one case of Grade 1 interstitial lung disease (ILD) was observed (0.6%). No new safety signals were identified.

* Patients were frequently monitored with weekly CBC.

Data cutoff: June 30, 2025

Conclusions

- In heavily pre-treated EGFRmt NSCLC patients, iza-bren demonstrated promising efficacy with a manageable safety profile.
  - In total of 171 patients, ORR: 57.9%; cORR: 47.4%; mPFS: 6.9 mo; mOS: 24.8 mo.
  - In post-TKI and chemo naïve patients, ORR: 66.0%; cORR: 56.0%; mPFS: 12.5 mo; mOS was not reached.
  - In post-TKI and chemo naïve patients, comparable efficacy was observed in patients with different EGFRmt subtypes, which was consistent with total population.
- Two phase III registrational studies of iza-bren as monotherapy in EGFRmt NSCLC after progression on a 3G EGFR-TKI are ongoing in China (NCT06382116) and globally (IZABRIGHT-Lung01, NCT07100080).

Bispecific antibody
- Ivonescimab

IASLC 2025 World Conference on Lung Cancer

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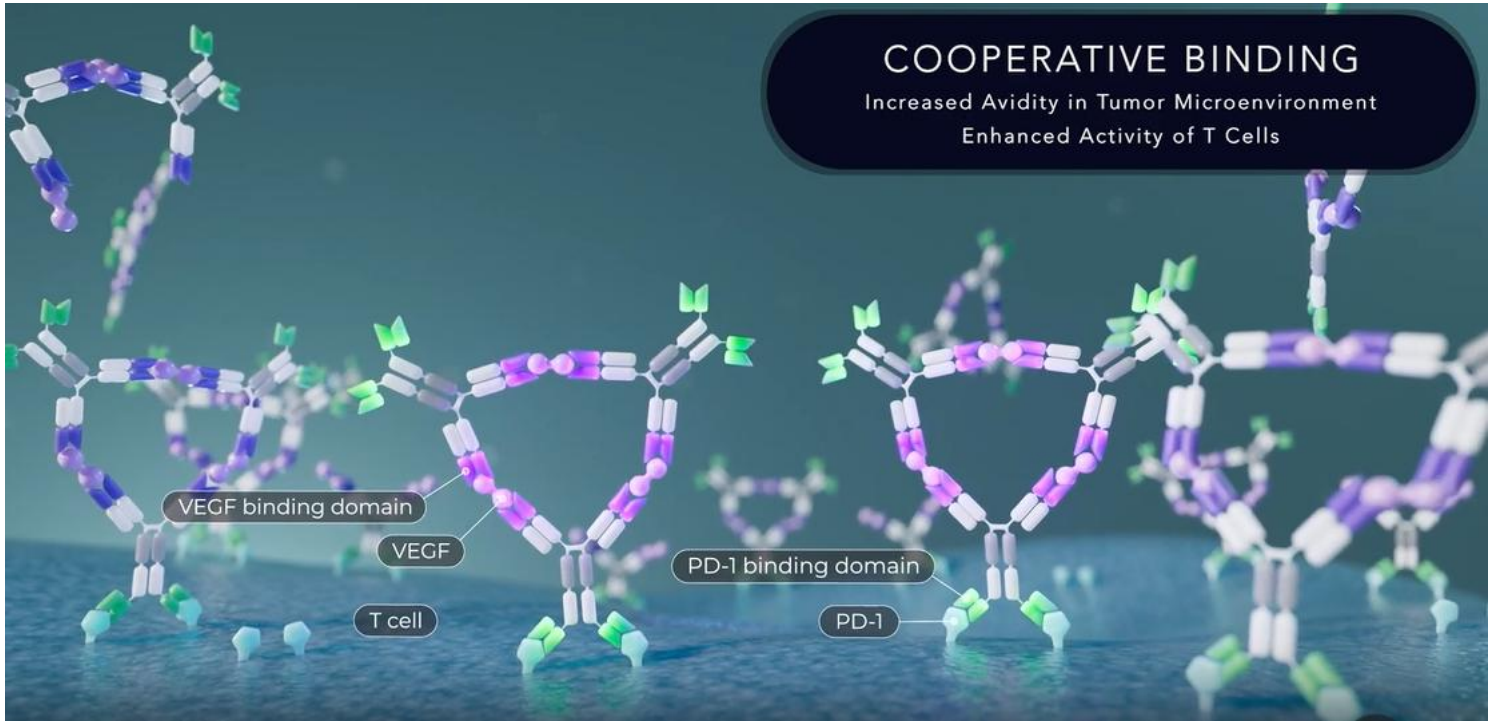
Ivonescimab vs Placebo Plus Chemo, Phase 3 in Patients with EGFR+ NSCLC Progressed with 3rd gen EGFR-TKI Treatment: HARMONi

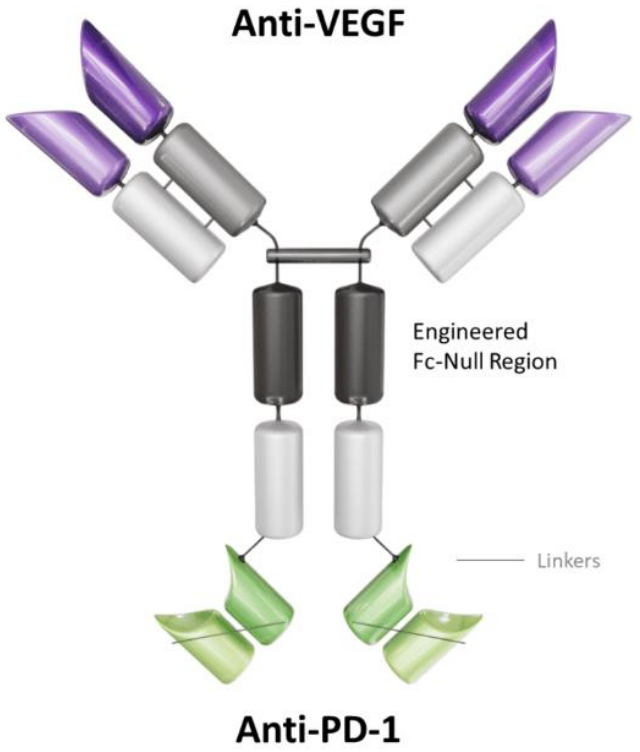
Jonathan W. Goldman[1], Antonio Passaro[2], Janessa Laskin[3], Delvys Rodrigues-Abreu[4], Antonio Calles[5], Lyudmila Bazhenova[6], Giuseppe Lo Russo[7], Natasha Leighl[8], Frederico Cappuzzo[9], Nicolas Girard[10], Sanjay Popat[11], Wenfeng Fang[12], Yongzhong Luo[13], Runxiang Yang[14], Wenting Li[15], Jianling Li[16], Lori Styles[16], Benjamin Thompson[16], Li Zhang[17], Xiuning Le[18].

[1]UCLA Health, Santa Monica, CA, USA; [2]European Institute of Oncology, Milan, Italy; [3]British Columbia Cancer Research Institute, Vancouver, Canada; [4]Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain; [5]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [6]UC San Diego Moores Cancer Center, San Diego, CA, USA; [7]Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [8]Princess Margaret Cancer Centre University of Toronto, Toronto, Ontario, Canada; [9]Regina Elena National Cancer Institute, Rome, Italy; [10]Institut Curie, Paris, France; [11]Lung Unit, Royal Marsden Hospital, London, UK; [12]Sun Yat-sen University Cancer Center, Guangzhou, China; [13]Hunan Cancer Hospital, Changsha, China; [14]Yunnan Cancer Hospital, Kunming, China; [15]Akeso Biopharma, Inc., Zhongshan, China; [16]Summit Therapeutics, Menlo Park, CA, USA; [17]Sun Yat-sen University Cancer Center, Guangzhou, China; [18]The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

Ivonescimab



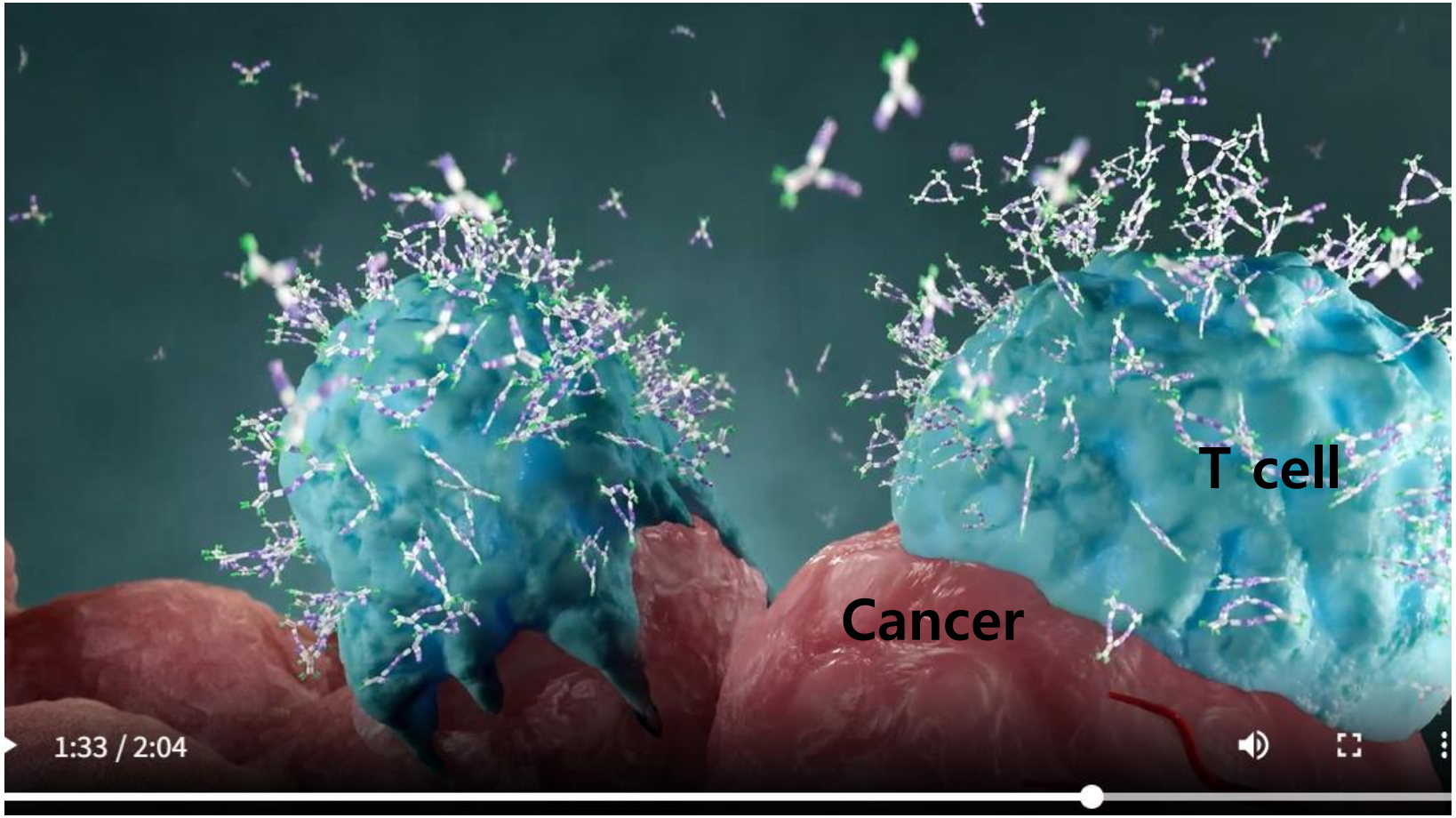
Summit therapeutics homepage



Synergistic activity of increasing T-cells → antitumor effect

https://smmttx.com/ivonescimab-smt112/ivonescimab-overview/default.aspx

Ivonescimab



Cooperative Binding Offers Potential to Drive Synergistic Anti-Tumor Activity

Dual Blocking of PD-1 & VEGF

Increased Avidity in TME[1*]

VEGF-A efficiently enhances the binding affinity to PD-1 by several fold

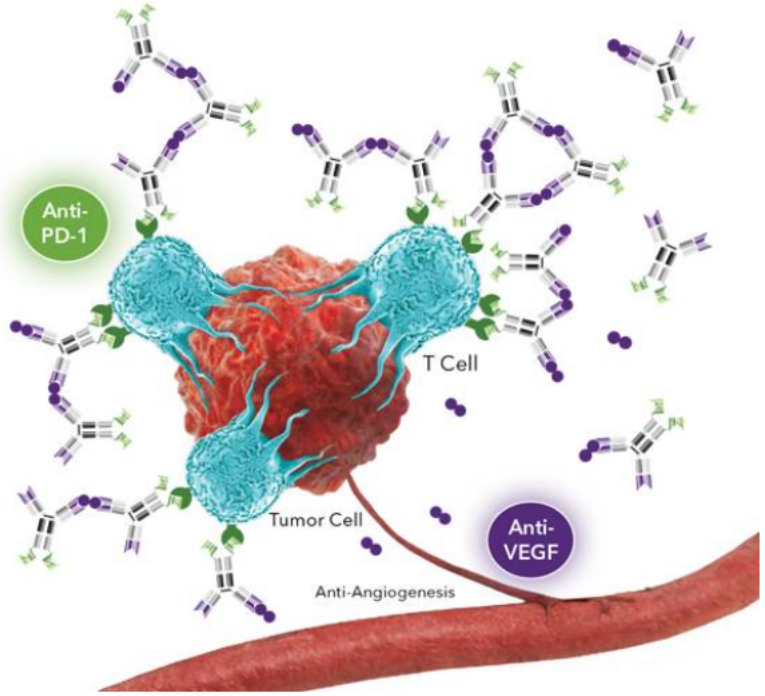
Enhanced Activity of T Cells[1*]

VEGF dimer leads to potential interconnection of ivonescimab molecules, which may increase activity of T cells

T1/2 ~10 days[2] and Fc-null region[1]

Could potentially lead to a favorable safety profile

*in vitro



Images for illustrative purposes only.

https://smmttx.com/ivonescimab-smt112/ivonescimab-overview/default.aspx

Phase 3 Study Design

HARMONi

Key Eligibility Criteria

Locally advanced or metastatic NSCLC:

- EGFR sensitizing mutation+
- Progressed on 3rd gen EGFR-TKI
- ECOG 0 or 1
- Any PD-L1 expression

Stratification factor by geographic region:

- Brain metastases (yes or no)

R 1:1

N=438

Ivonescimab + Chemotherapy (N = 219)

Placebo + Chemotherapy (N = 219)

Ivonescimab: 20 mg/kg Q3W

Chemotherapy:

- Carboplatin: AUC5 Q3W x 4 cycles (21 day/cycle)
- Pemetrexed: 500 mg/m^2 Q3W

Endpoints:

Primary

- OS, PFS by IRRC per RECIST 1.1

Secondary

- ORR by IRRC, DoR, safety and tolerability

Planned Efficacy Analyses

- PFS primary (at ~231 events) & OS interim analyses
- OS final analysis (at ~261 events)

FPI: Jan 2022 (overall)
LPI Asia: Nov 2022
LPI NA & EU (and overall): Oct 2024

Note: Positive outcomes were reported from the single-region (Asia) study HARMONi-A, with PFS as the primary endpoint.

DoR=duration of response; ECOG=eastern cooperative oncology group; EGFR= Epidermal growth factor receptor; EU=Europe; FPI=first patient in; IRRC= independent radiology review committee; LPI=last patient in; mets=metastases; NA=North America; ORR=overall response rate; OS=overall survival; NSCLC=non-small cell lung cancer; TKI=tyrosine kinase inhibitor; PD-L1= programmed cell death ligand; PFS=progression-free survival; Q3W=every 3 weeks; RECIST=response evaluation criteria in solid tumors.

Demographic and Baseline Characteristics

HARMONi

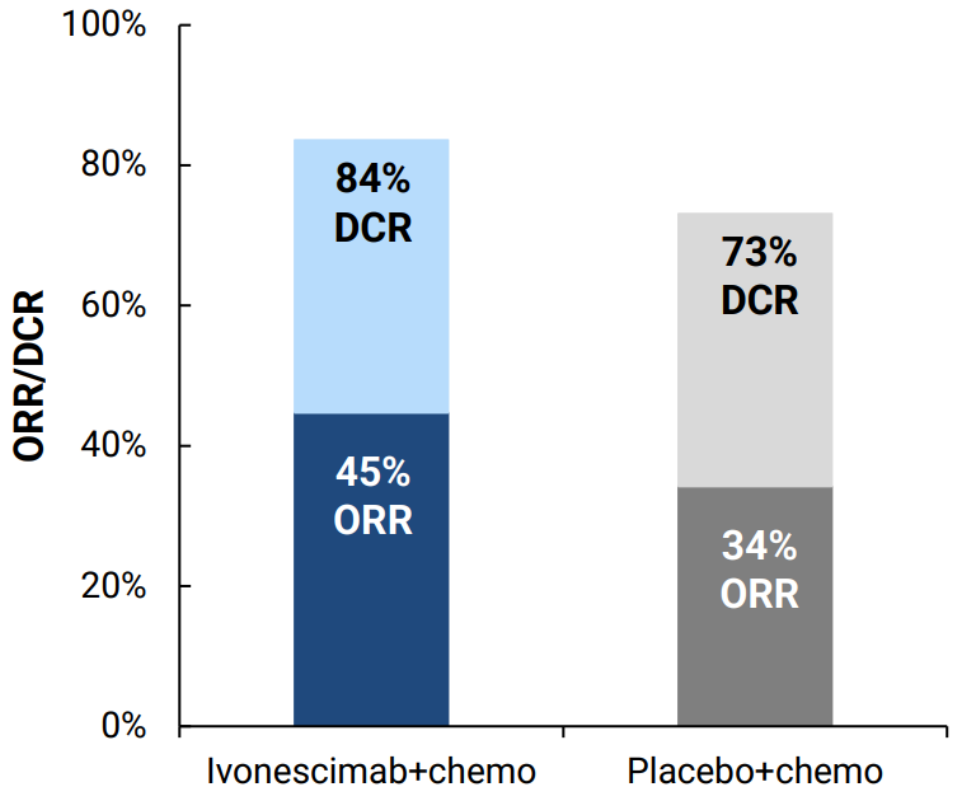
Arms were well-balanced; majority were females, ECOG 1, never smokers; 25% with brain mets

Characteristic, n (%)	Ivonescimab+chemo (N=219)	Placebo+chemo (N=219)
Age – Median (range)	62 (32-84)	60 (36-84)
≥65 yr	83 (37.9)	88 (40.2)
Female	130 (59.4)	127 (58.0)
Region – NA & Europe	83 (37.9)	82 (37.4)
Asia	136 (62.1)	137 (62.6)
Race – Asian	153 (69.9)	153 (69.9)
White	51 (23.3)	54 (24.7)
ECOG - 1	162 (74.0)	157 (71.7)
Smoking - Never	143 (65.3)	155 (70.8)
Stage - IV	215 (98.2)	214 (97.7)
Brain metastasis	54 (24.7)	54 (24.7)
Liver metastasis	32 (14.6)	23 (10.5)
Prior line of systemic cancer therapy (median)	1.0	1.0
Prior EGFR-TKI		
1st/2nd generation	95 (43.4)	92 (42.0)
3rd generation	219 (100)	218 (99.5)
4th generation	1 (0.5)	0
EGFR Mutation		
19del	131 (59.8)	118 (53.9)
L858R	74 (33.8)	90 (41.1)
Non-19del/L858R*	15 (6.8)	11 (5.0)

* Non-19del/L858R mutations include G719X, L861Q, S768I, etc.

Overall Response Rate and Duration of Response

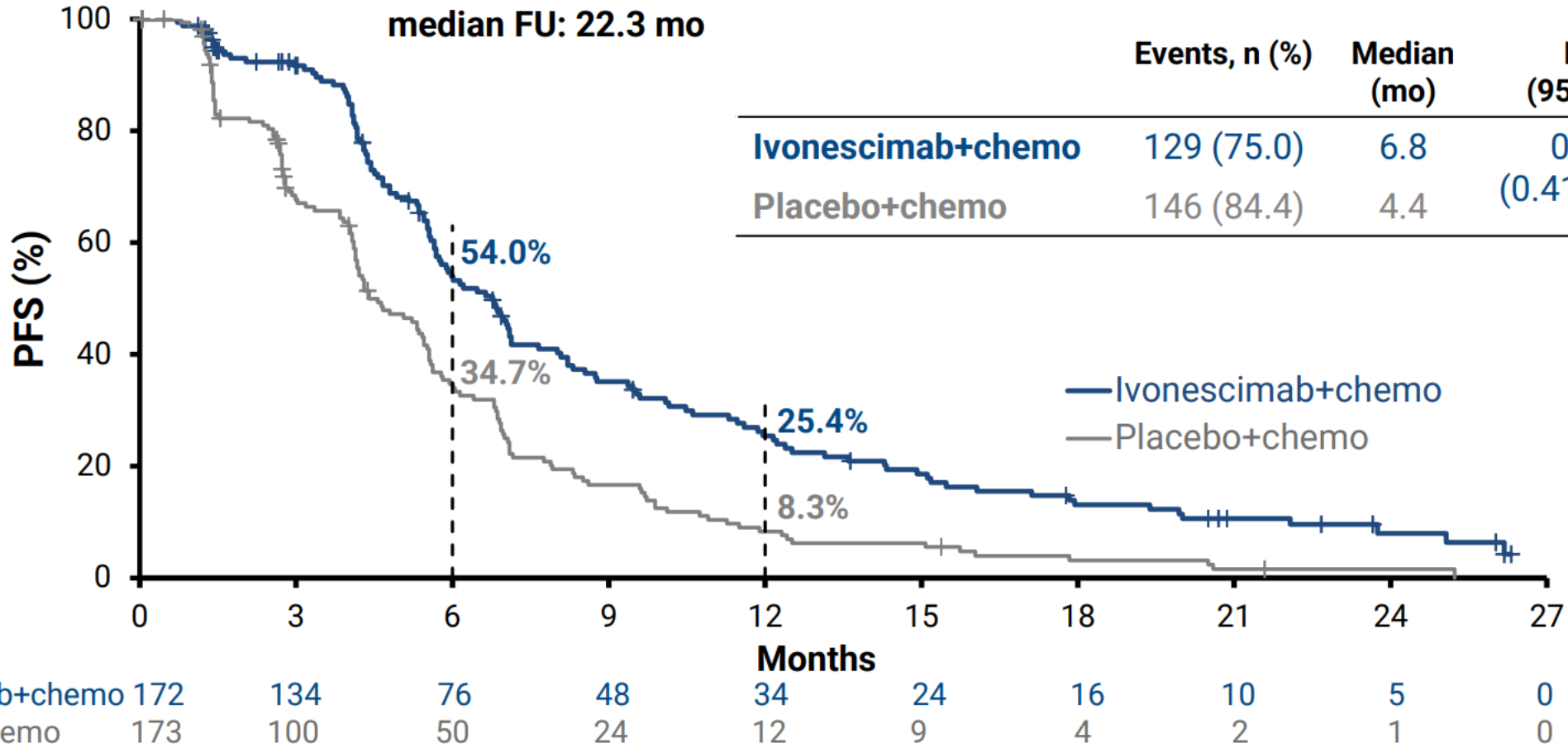
By IRRC



DoR (mo)	Ivonescimab + chemo	Placebo + chemo
n	98	75
Median (95% CI)	**7.6** (5.5-10.6)	**4.2** (2.9-4.7)

Primary Endpoint: PFS by IRRC

Statistically significant and clinically meaningful benefit with ivonescimab



	Events, n (%)	Median (mo)	HR (95% CI)	*P* Value
Ivonescimab+chemo	129 (75.0)	6.8	0.52 (0.41-0.66)	<0.0001
Placebo+chemo	146 (84.4)	4.4		

No. at risk

Ivonescimab+chemo	172	134	76	48	34	24	16	10	5	0
Placebo+chemo	173	100	50	24	12	9	4	2	1	0

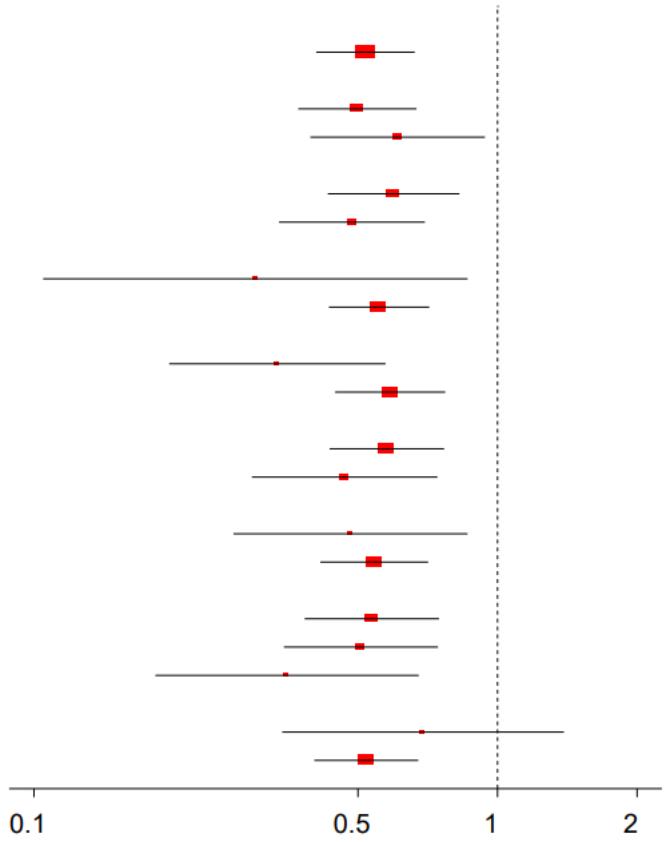
Consistent PFS benefit by investigator: HR = 0.58 (95% CI: 0.45-0.73)

PFS by IRRC – Subgroup Analysis

Consistent across pre-defined subgroups

HARMONi

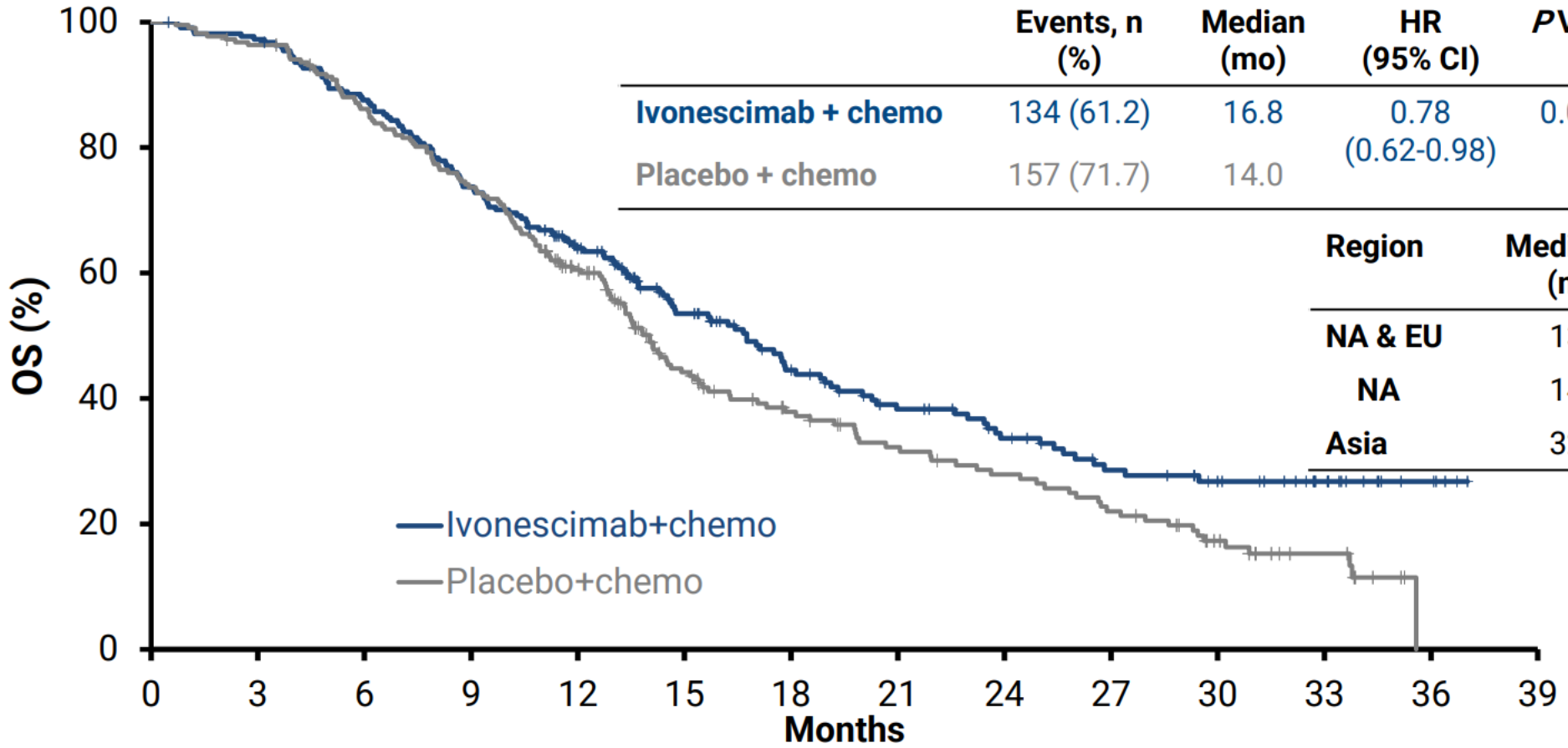
	Ivonescimab + chemo (Events/N)	Placebo + chemo (Events/N)	Hazard Ratio (95% CI)
Overall population	129/172	146/173	0.52 (0.41-0.66)
Age			
<65 years	89/115	101/110	0.50 (0.37-0.67)
>=65 years	40/57	45/63	0.61 (0.39-0.94)
Sex			
Female	74/97	74/92	0.60 (0.43-0.83)
Male	55/75	72/81	0.49 (0.34-0.70)
Geographic region			
NA & EU	6/36	12/36	0.30 (0.10-0.86)
Asia	123/136	134/137	0.56 (0.43-0.71)
Brain metastases prior to study entry			
Present	28/41	34/42	0.34 (0.20-0.57)
Absent	101/131	112/131	0.59 (0.45-0.77)
Smoking history			
Never	95/117	101/121	0.58 (0.43-0.77)
Former/Current	34/55	45/52	0.47 (0.30-0.74)
Baseline ECOG performance status			
0	19/35	33/43	0.48 (0.27-0.86)
1	110/137	113/130	0.54 (0.41-0.71)
Baseline EGFR mutation			
19Del	77/104	69/86	0.54 (0.38-0.75)
L858R	45/56	73/78	0.51 (0.35-0.74)
T790M	25/27	17/21	0.35 (0.18-0.68)
Liver metastases prior to study entry			
Present	19/26	15/20	0.69 (0.34-1.39)
Absent	110/146	131/153	0.52 (0.40-0.67)



Overall Survival: Longer Term Western Follow-up

HARMONi

OS stable with longer term Western data, nominal p=0.0332



	Events, n (%)	Median (mo)	HR (95% CI)	*P* Value
Ivonescimab + chemo	134 (61.2)	16.8	0.78 (0.62-0.98)	0.0332
Placebo + chemo	157 (71.7)	14.0		

Region	Median FU (mo)	Median OS (mo)
NA & EU	13.7	17.0 vs. 14.0
NA	14.6	NR vs. 14.0
Asia	32.7	16.7 vs. 14.0

Data cutoff
NA&EU: Sep 2025
Asia: Apr 2025

No. at risk

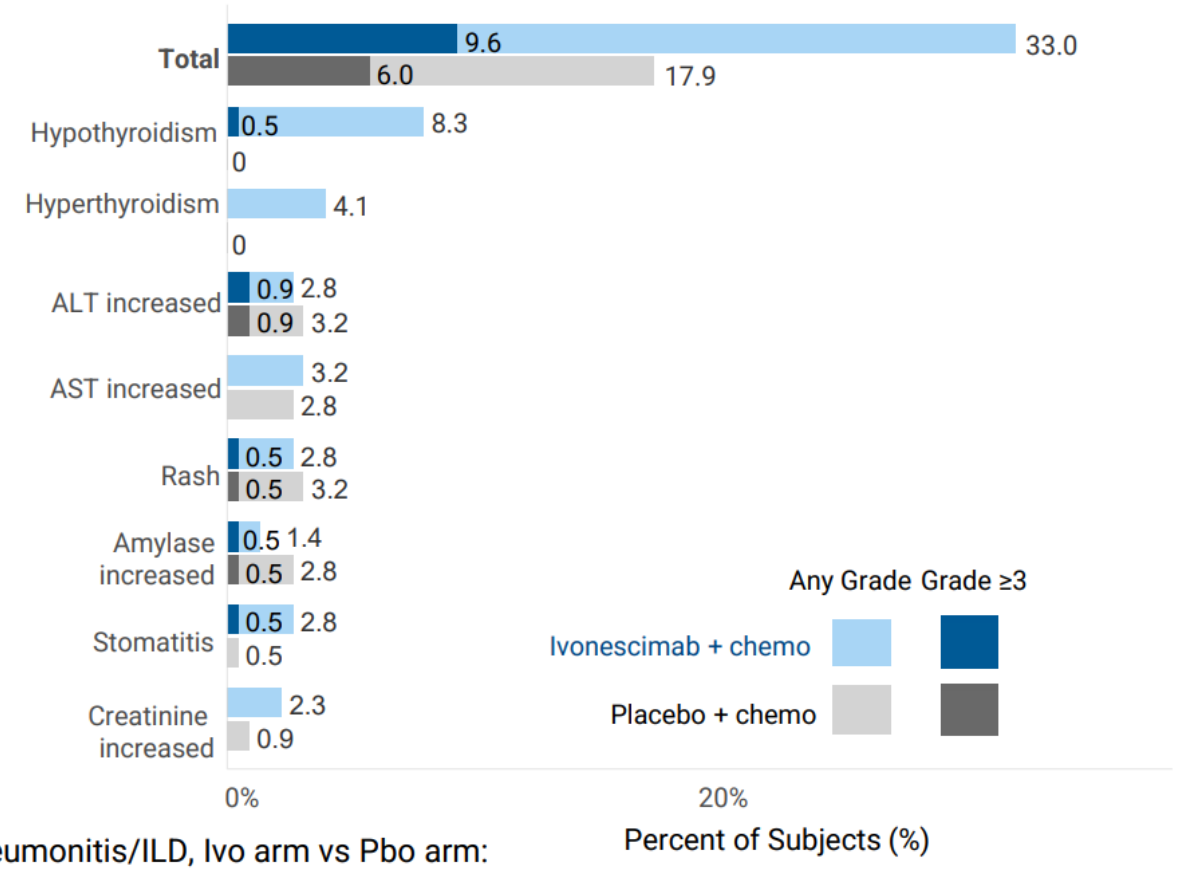
Ivonescimab+chemo	219	212	190	160	127	92	68	53	43	33	26	16	5	0
Placebo+chemo	219	210	186	159	119	74	56	45	38	30	18	9	0	

Immune-related and VEGF-related TRAEs

HARMONi

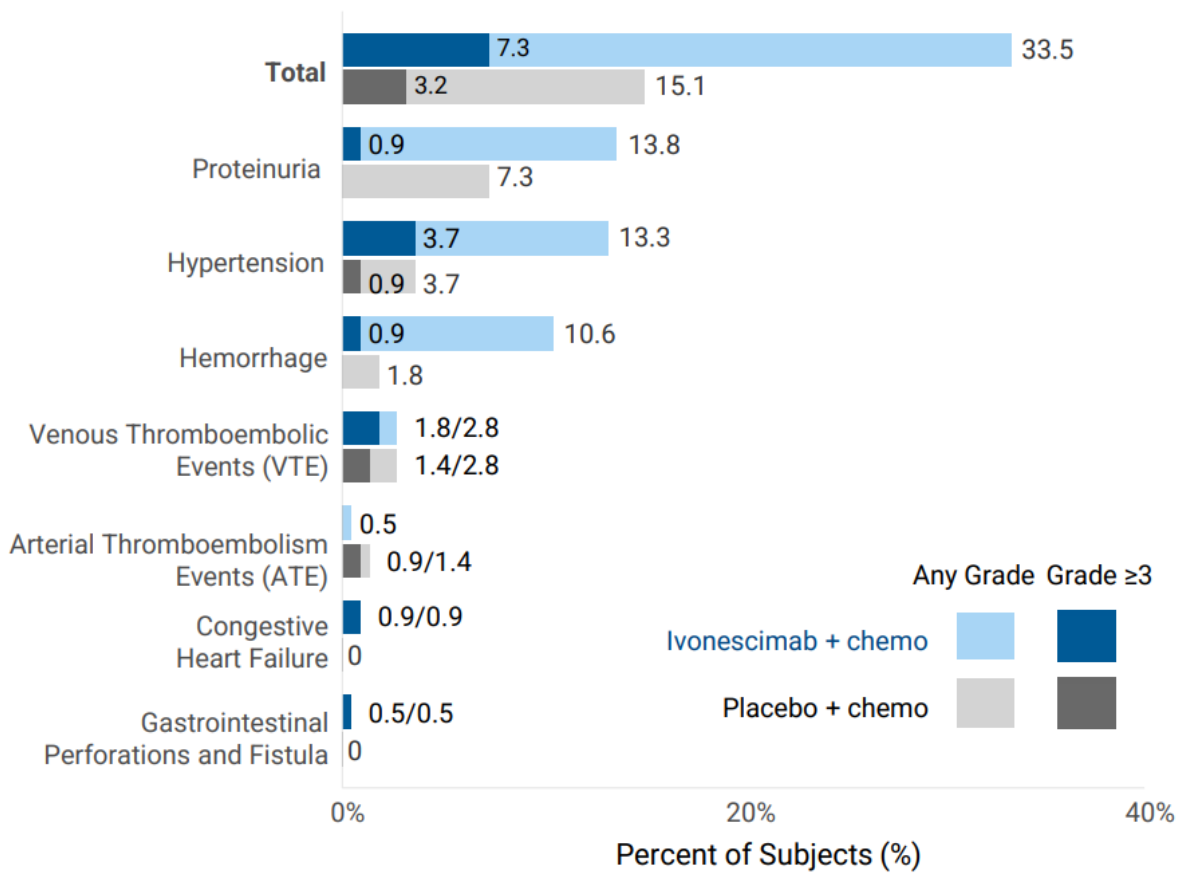
Most common irAEs: hypo/hyperthryroidism, transaminase elevation, rash; mostly low grade
Most common VEGF-related TRAEs: proteinuria, hypertension, hemorrhage; mostly low grade

irAE



Pneumonitis/ILD, Ivo arm vs Pbo arm:
2.8% (1.4% Grade ≥3) vs **1.8%** (1.4% Grade ≥3)

VEGF-related



Summary

HARMONi

- Ivonescimab had a significant and clinically meaningful PFS benefit in EGFRm+ NSCLC patients post-3rd gen TKI
  - Reduced risk of progression or death by 48% vs chemotherapy, HR=0.52
  - Consistent efficacy across pre-defined subgroups
  - Increased ORR and DoR
- OS final analysis showed favorable trend; HR=0.79 with p=0.0570
  - Longer-term follow-up of Western patients showed stable OS; HR=0.78 with nominal p=0.0332
  - Western patients' median OS was numerically higher by 3 months
- Ivonescimab well tolerated, with no new safety findings
  - <1% Grade 3+ bleeding and comparable rates of discontinuation and death between arms

SINGAPORE 2025 ESMO ASIA

Safety Profile and Anti-Tumor Efficacy of VRN110755, a Highly Selective, Brain Penetrant EGFR Inhibitor for Patients with EGFR-Driven Non-Small Cell Lung Cancer

Phase 1/2 study of VRN110755

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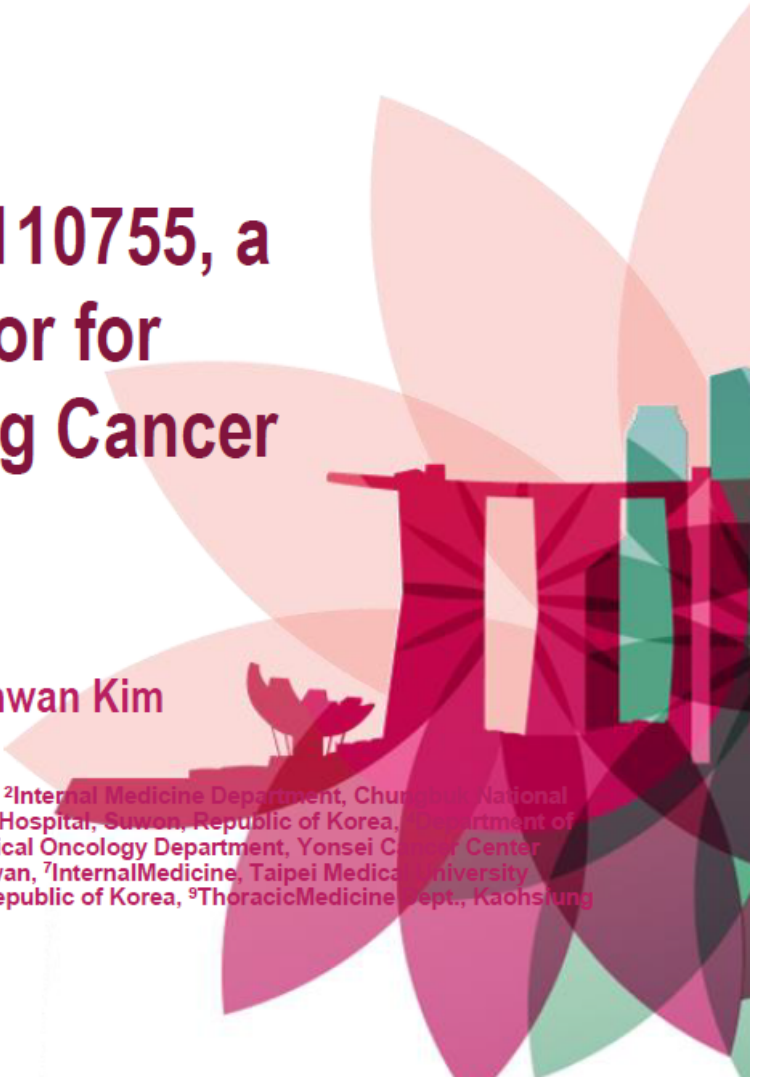

06 Dec 2025

EGFR activating mutation in non-small cell lung cancer (NSCLC)

- Approximately 25~30% of NSCLC patients harbor EGFR activating mutations.
- Third-generation EGFR TKIs are widely used as a standard of care for EGFR-mutant NSCLC, but on-target EGFR resistance mutations still arise.
- EGFR-C797S is one of the most common acquired resistant mechanisms against 3G EGFR TKI; however, there is no approved treatment available.
- CNS metastasis is associated with poor prognosis in EGFRm NSCLC, and 20% of patients treated with osimertinib develop CNS progression[1].
- VRN11 is a mutant-selective EGFR inhibitor characterized by high brain permeability.

[1]Wang C, Zhao K, Hu S, Dong W, Gong Y, Xie C. Clinical Outcomes of Afatinib Versus Osimertinib in Patients With Non-Small Cell Lung Cancer With Uncommon EGFR Mutations: A Pooled Analysis. Oncologist. 2023 Jun 2;28(6):e397-e405. doi: 10.1093/oncolo/oyad111. PMID: 37116899; PMCID: PMC10243768.

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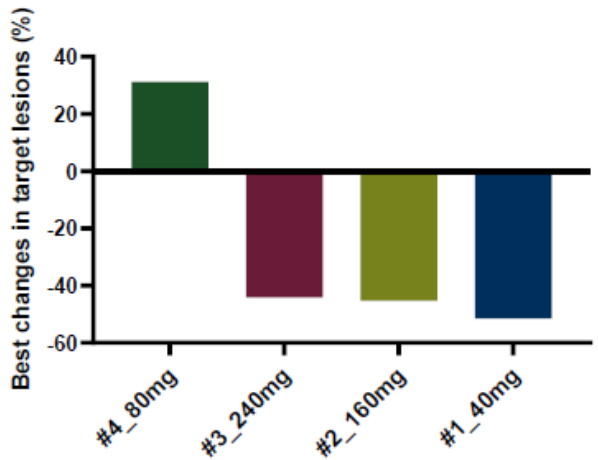
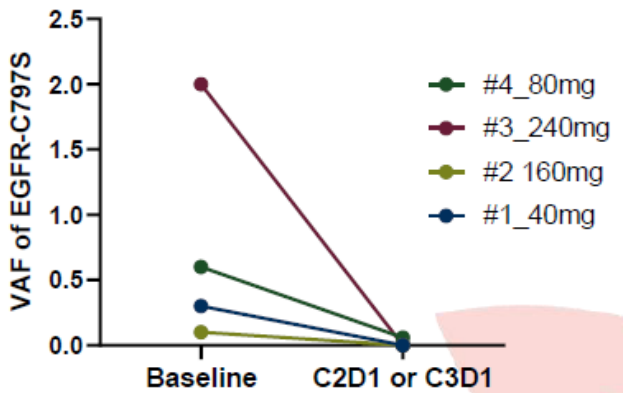
Clinical efficacy in patients with C797S-positive

Patient ID	Dose level	EGFR mutants	Prior TKIs	ctDNA clearance (C797S)	Best changes in Target lesions (%)	Brain lesion response	Best response
1	40 mg	L858R/C797S/R776H	Dacomitinib – Osimertinib	100%	-51.4	Response	PR
2	160 mg	Del19/C797S	Osimertinib	100%	-45.3	Response	PR
3	240 mg	Del19/C797S	Lazertinib Osimertinib	100%	-44.1	Response	PR
4	80 mg	Del19/C797S	Osimertinib	90%	31.2	Non-response	PD

Tumor assessment (C797S+ patients)



Molecular response (C797S+ patients)



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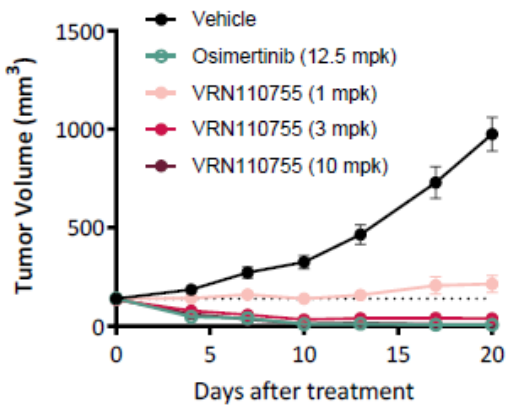
VRN110755, potent EGFRm inhibitor with high CNS activity in preclinical model

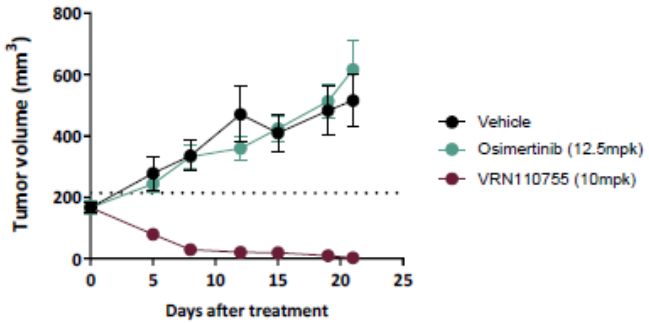
EGFR Common: Del19, Xenograft



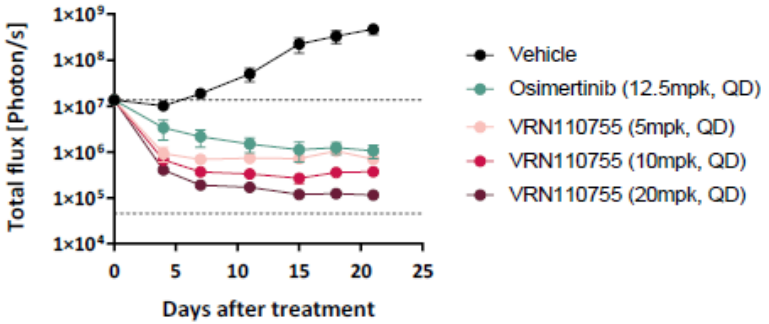
+ C797S

Brain

EGFR, Del19 + C797S, Xenograft

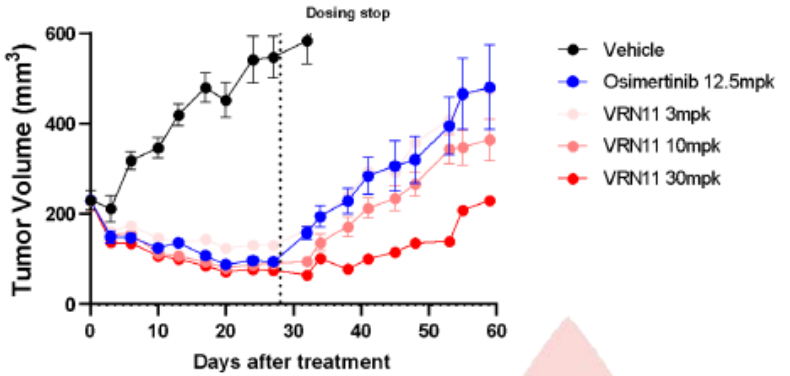


EGFR, Del19, Xenograft in Brain



	Mouse	Monkey
$K_{p,uu,brain}$	0.6	1.7
$K_{p,uu,csf}$	N.D.	2.6

EGFR Uncommon: G719A-S768I PDX



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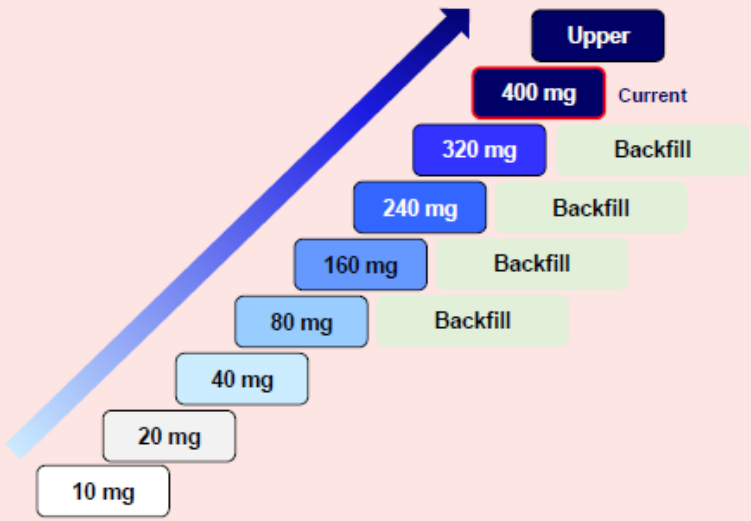
VRN110755-01 study design (Phase 1/2)_Monotherapy

Key Eligibility Criteria

- Age ≥ 18 years
- Diagnosis of advance (Stage IIIB/IV or recurrent) NSCLC, harboring EGFR mutation
- Measurable disease per RECIST v1.1
- Prior EGFR TKI treatment with disease progression
- ECOG 0-1
- Advanced NSCLC with EGFR mutation
- Without other driver mutations, e.g. KRAS G12X, cMET amp, etc
- Without EGFR/HER2 exon20 insertion mutation
- Asymptomatic brain metastasis can be enrolled

Dose escalation



Primary endpoints:
Maximal Tolerable Dose, Serious Adverse Events, DLT
Secondary endpoints:
Pharmacokinetics, Anti-tumor responses, ctDNA changes

Dose expansion

Cohort-1
Common EGFRm
Treatment naive

Cohort-2
Common EGFRm with CNS metastasis
TKI-naïve

Cohort-3
Common EGFRm with C797S after 1L
3rd Gen TKI (Osi, Laz, Ami+Laz)

Cohort-4
Atypical/uncommon EGFRm
TKI-naïve

Cohort-5
Atypical/uncommon EGFRm
One prior TKI (allow ≤ 1 prior systemic regimen)

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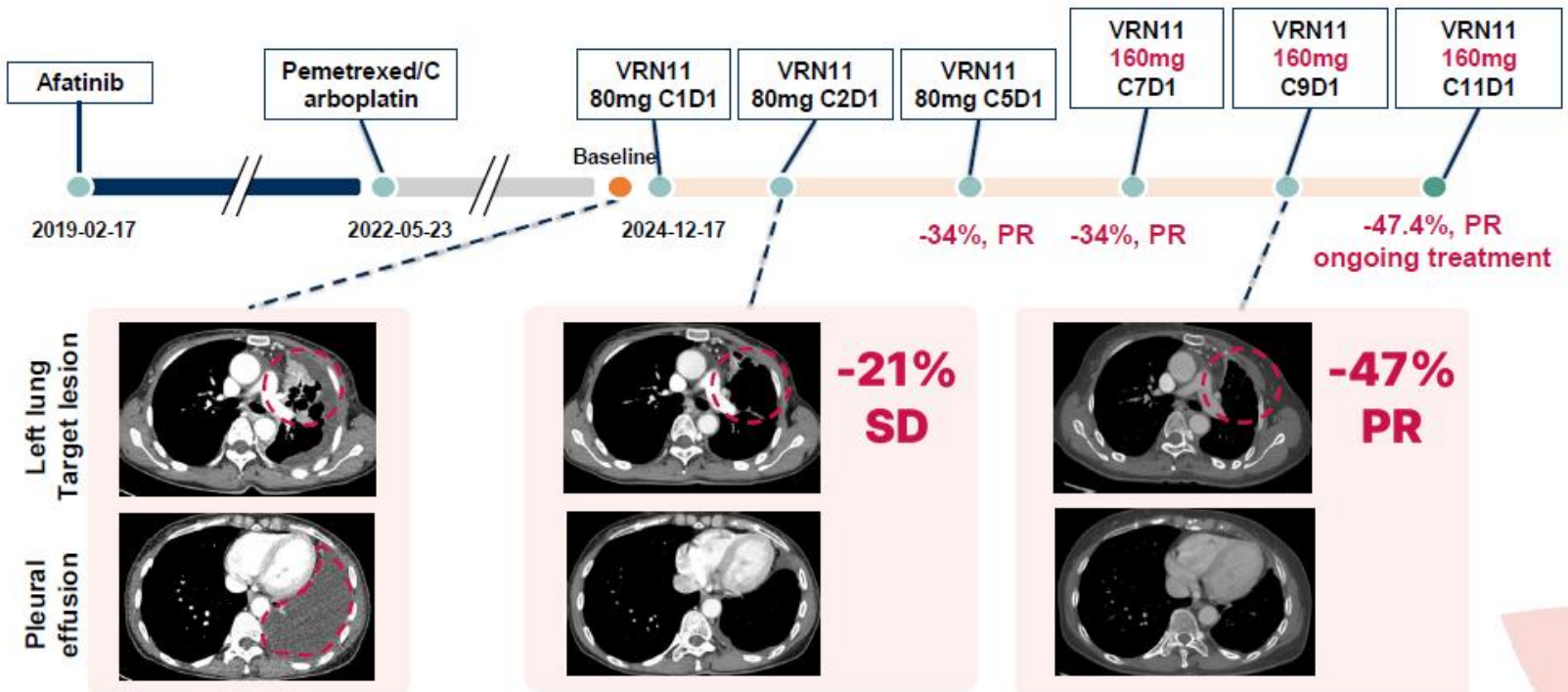
The EGFR common driver mutation progressed after EGFR TKI, without resistance mutations

Case Study at 80 mg cohort: 53 years old, female patient harboring EGFR Del19 progressed on Platinum, following Afatinib. Dose escalation to 160mg further reduced size of the tumor.



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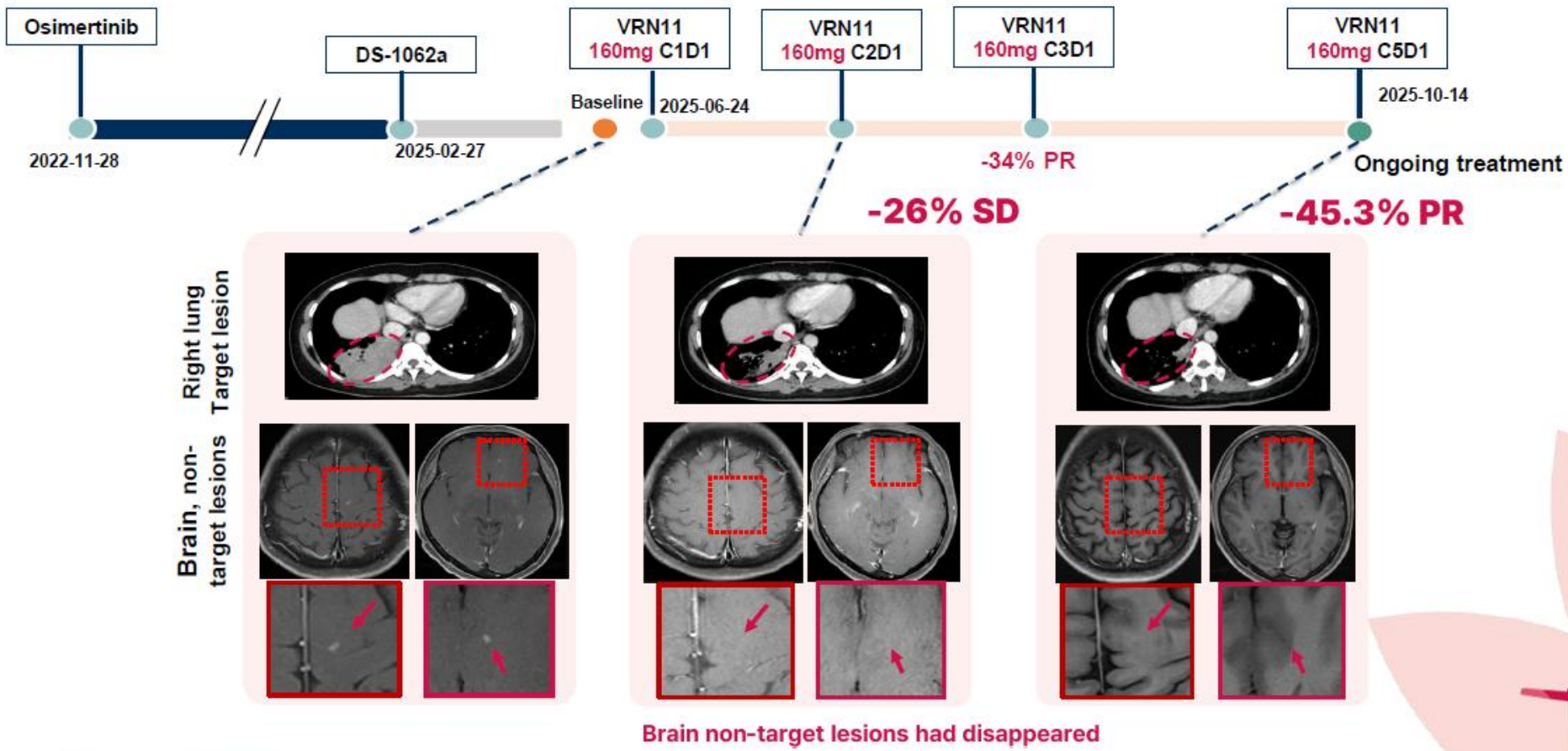
C797S-Positive patients with brain metastases

Case Study at 160 mg cohort: 47 years old female patient harboring EGFR Del19/C797S progressed on DS-1062a, following Osimertinib.



Brain non-target lesions had disappeared

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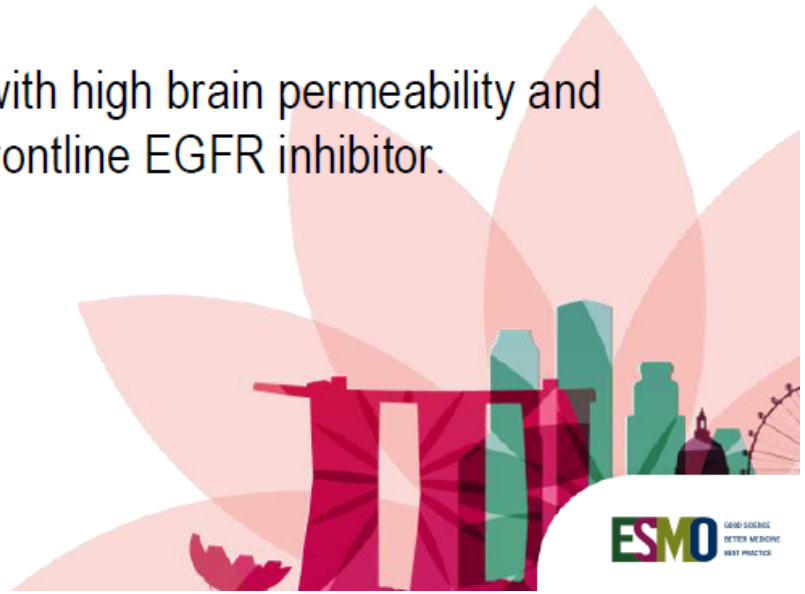
Simplify the document for me

Conclusions

- VRN110755 demonstrates favorable pharmacokinetics and high CNS penetration, promising high target engagement (4x) compared to osimertinib
- The most common adverse events were diarrhea, skin rash, and dry skin, but mostly grade 1-2. No dose-limiting toxicity was observed up to 400mg
- Promising anti-tumor efficacy (ORR 19% and DCR 90%) was observed with VRN110755 treatment, ≥80mg in heavily pretreated patients (≥ 2, median 3 prior systemic therapies)
- Its robust activity in 3G TKI–resistant EGFR-mutant (C797S), together with high brain permeability and intracranial efficacy, supports VRN110755 as a potential best-in-class frontline EGFR inhibitor.



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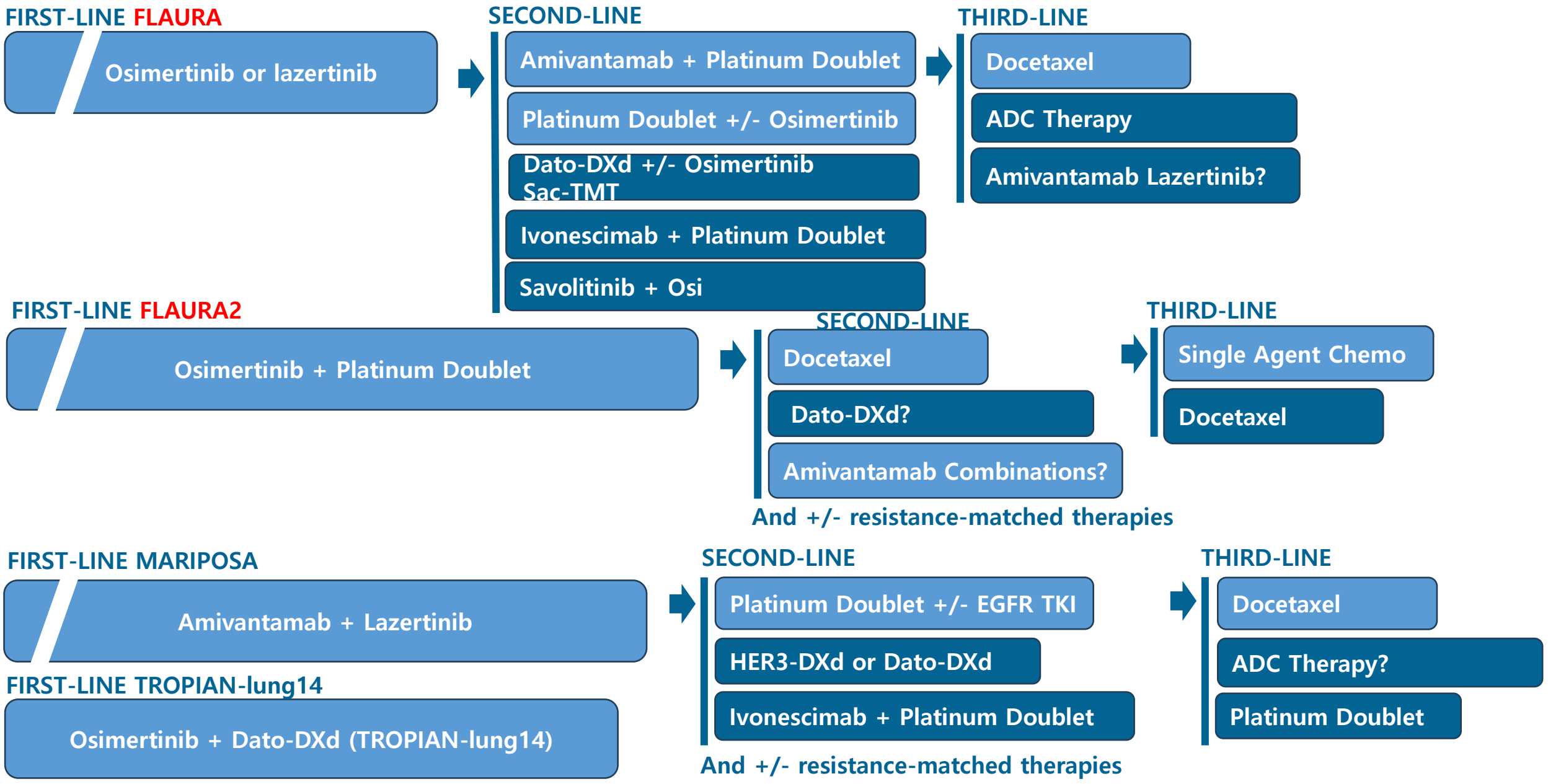
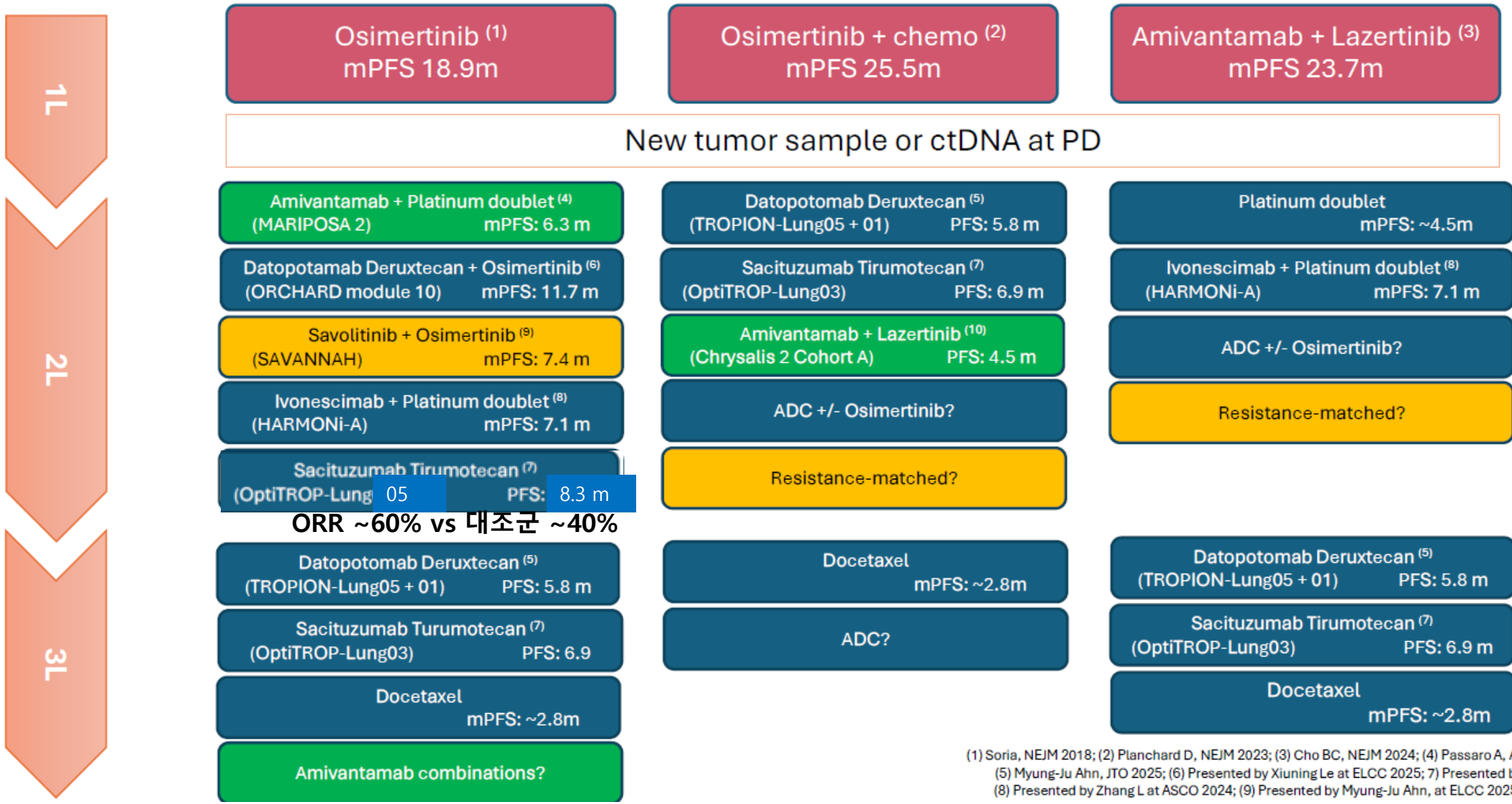
2L Therapy EGFRm NSCLC





(1) Soria, NEJM 2018; (2) Planchard D, NEJM 2023; (3) Cho BC, NEJM 2024; (4) Passaro A, Annals of Oncology 2023; (5) Myung-Ju Ahn, JTO 2025; (6) Presented by Xiuning Le at ELCC 2025; 7) Presented by Zhang L at ASCO 2025; (8) Presented by Zhang L at ASCO 2024; (9) Presented by Myung-Ju Ahn, at ELCC 2025; (10) Besse B, JTO 2025

- 감사합니다