Treating resistance mechanisms in oncogenic disease

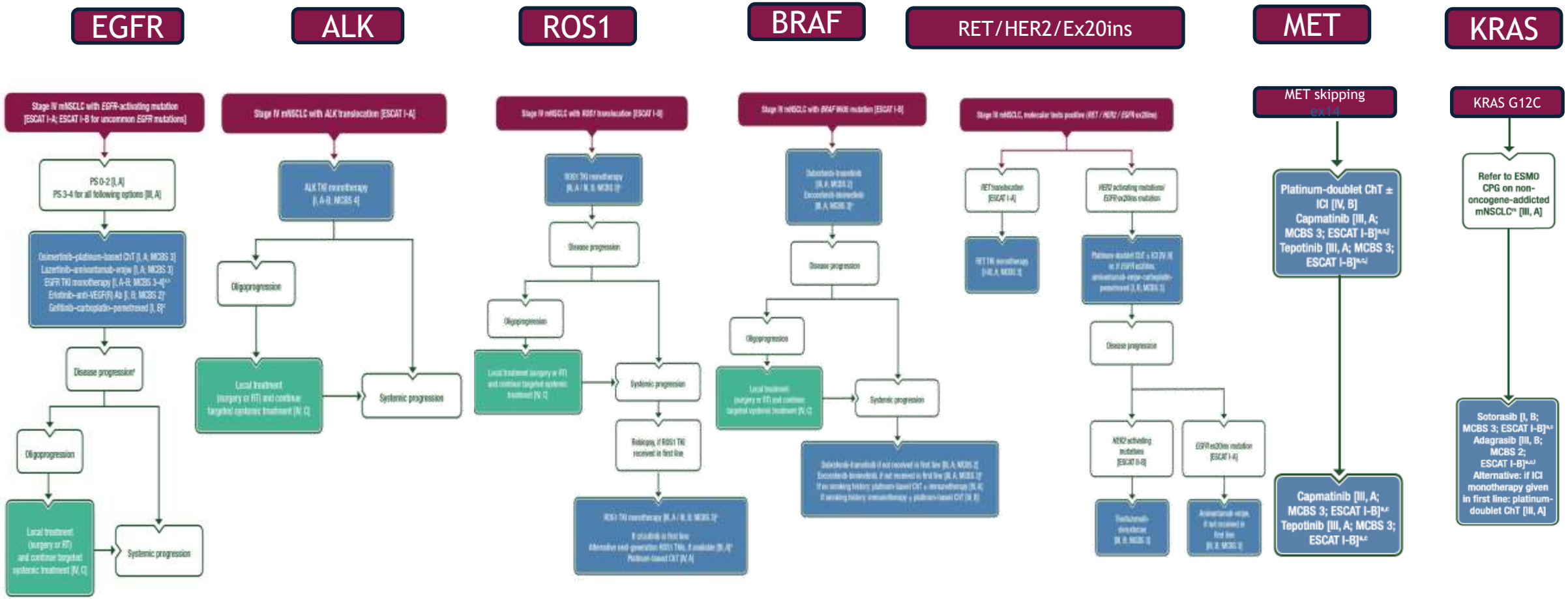
Oscar Juan-Vidal

Hospital Universitari i Politècnic La Fe de Valencia

CONFLICTO DE INTERESES

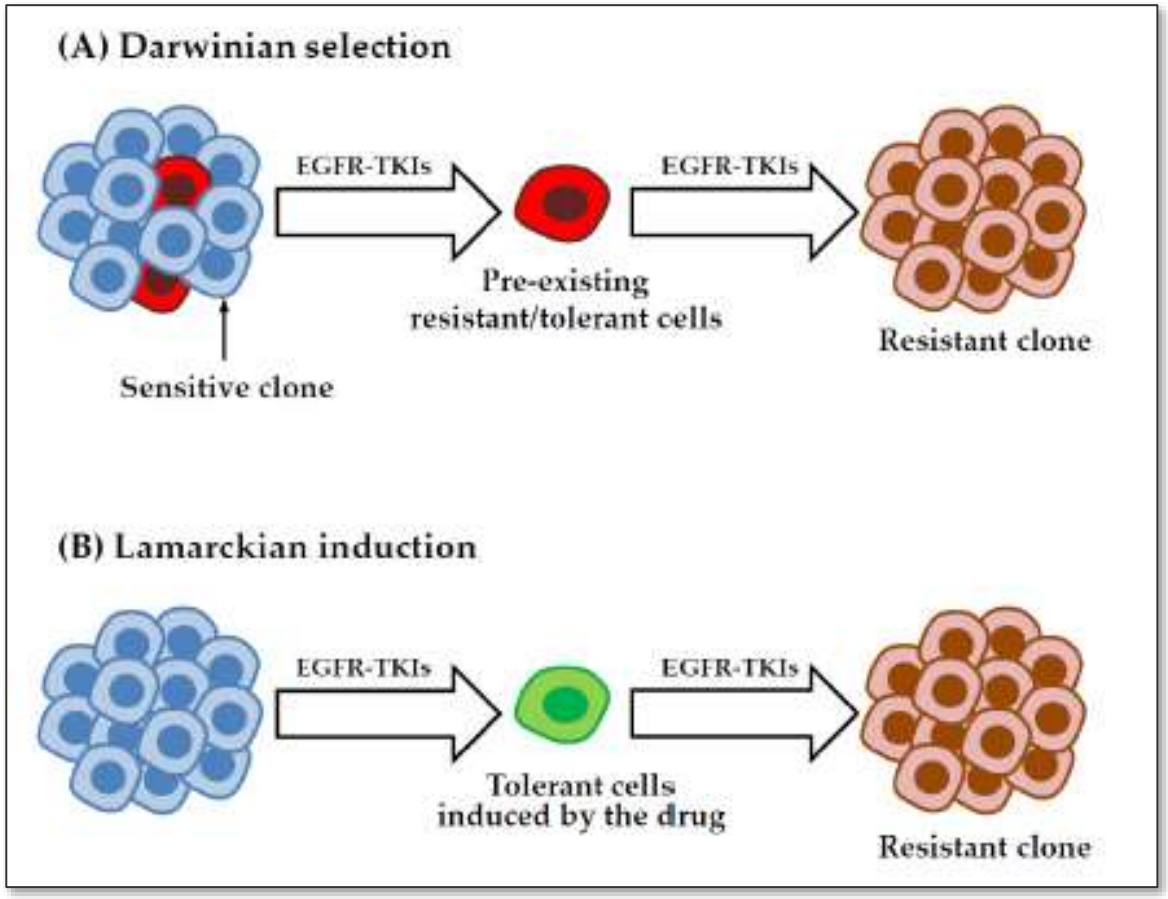
Consultant or Advisory role: Bristol-Myers Squibb, Roche/genetech, Daixhi, Astra-Zeneca, Pfizer, Eli Lilly, Novartis, Johnso&Johnson.
Speaking: Bristol-Myers Squibb, Roche/genetech, Daixhi, Astra-Zeneca, Pfizer, Eli Lilly, Novartis, Johnso&Johnson.
Institution Research Funding: Astra-Zeneca, BeOne.
Travel expenses: Daixhi/Astra-Zeneca, Pfizer, Roche/Genetech, Pharmamar, MSD
Employment: Conselleria de Sanitat, Pivotal S.L.U.

Treatment algorithm for stage IV NSCLC with positive molecular test

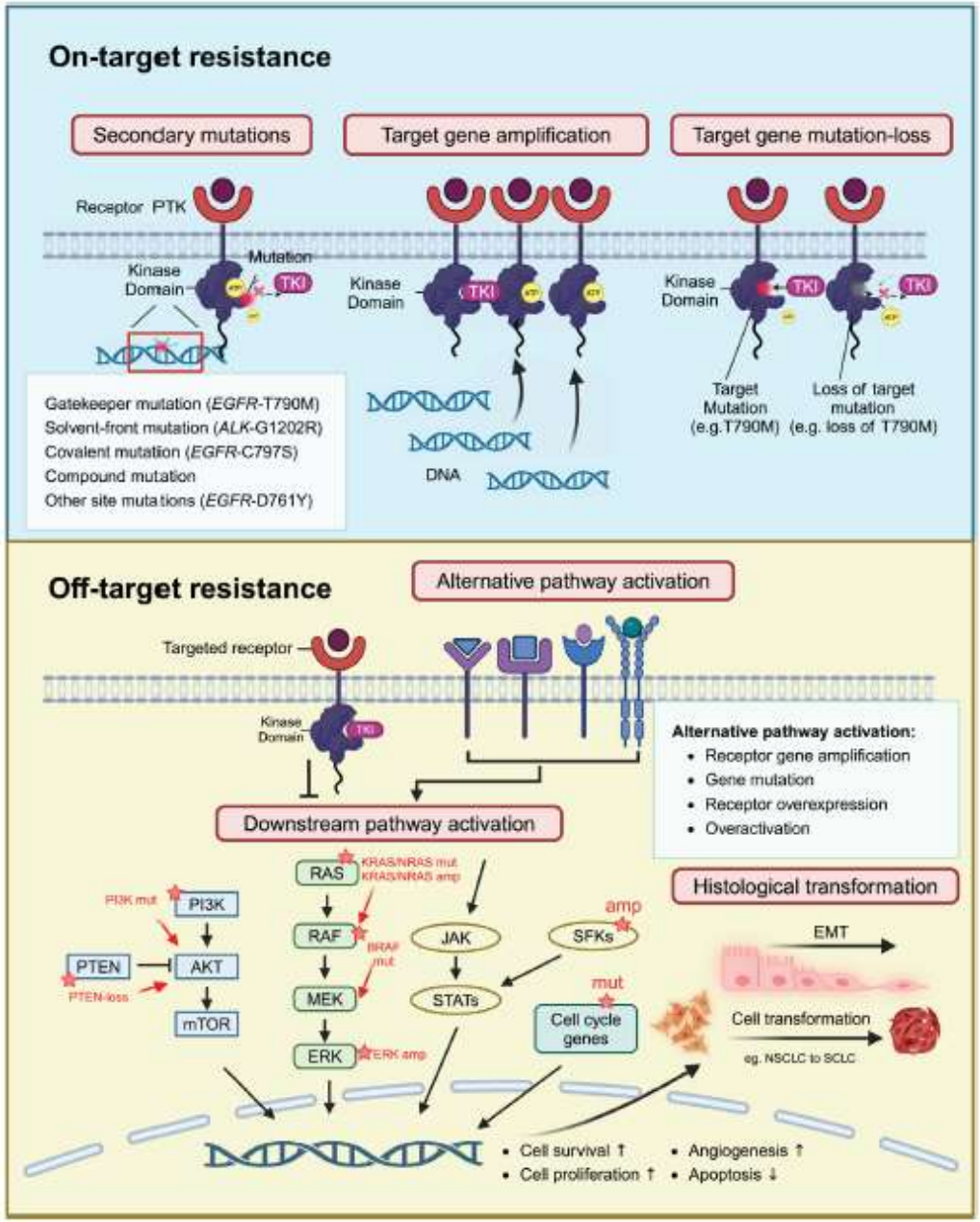


Hendricks L, et al. Clinical Practice Guidelines ESMO Living Guidelines, v1,2 January 2025

Mechanisms of Acquired Resistance



Chhouri H et al. Cancers 2023

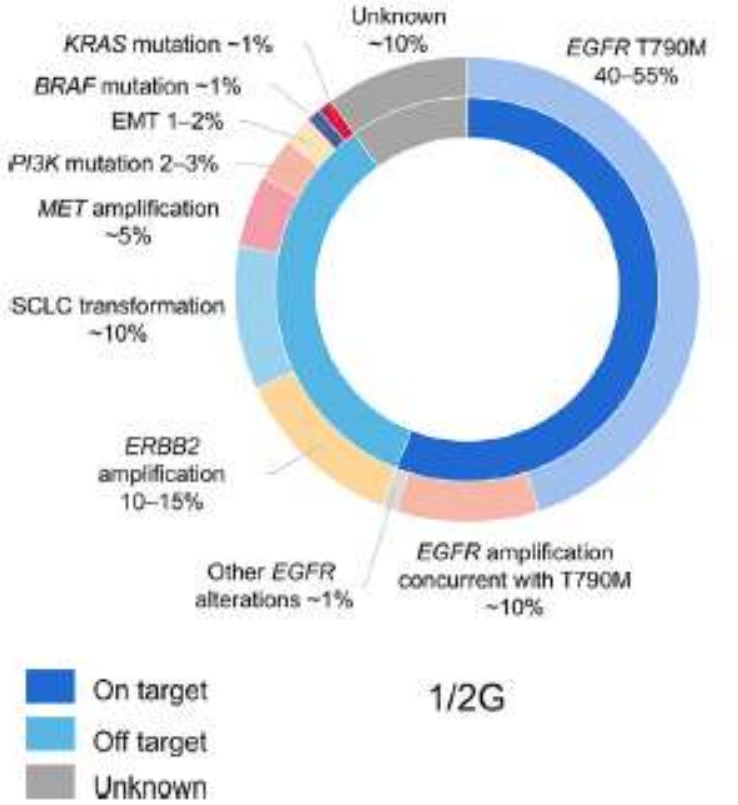


Ou X et al. Cancers 2023

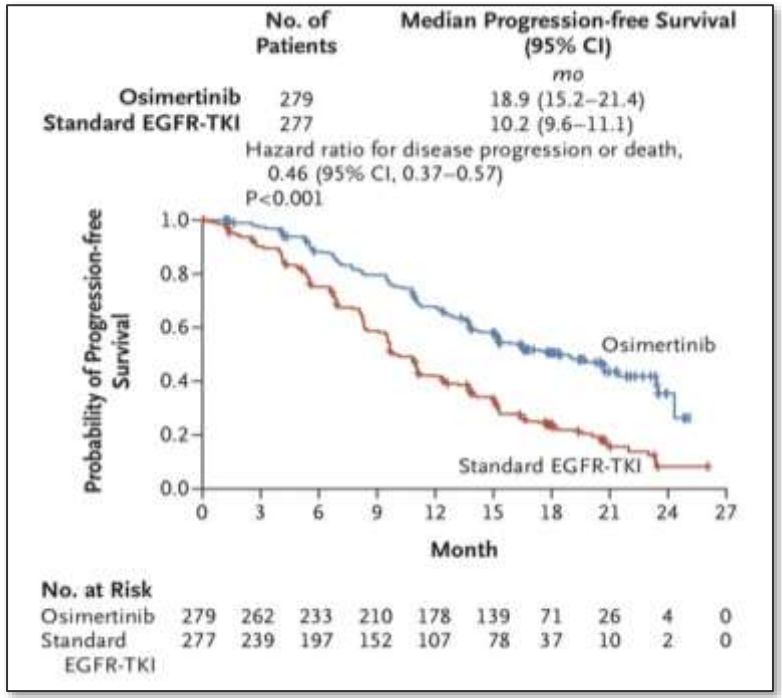
Resistance to EGFR TKIs

Combating resistance mechanisms from the 1st line of therapy: New drugs

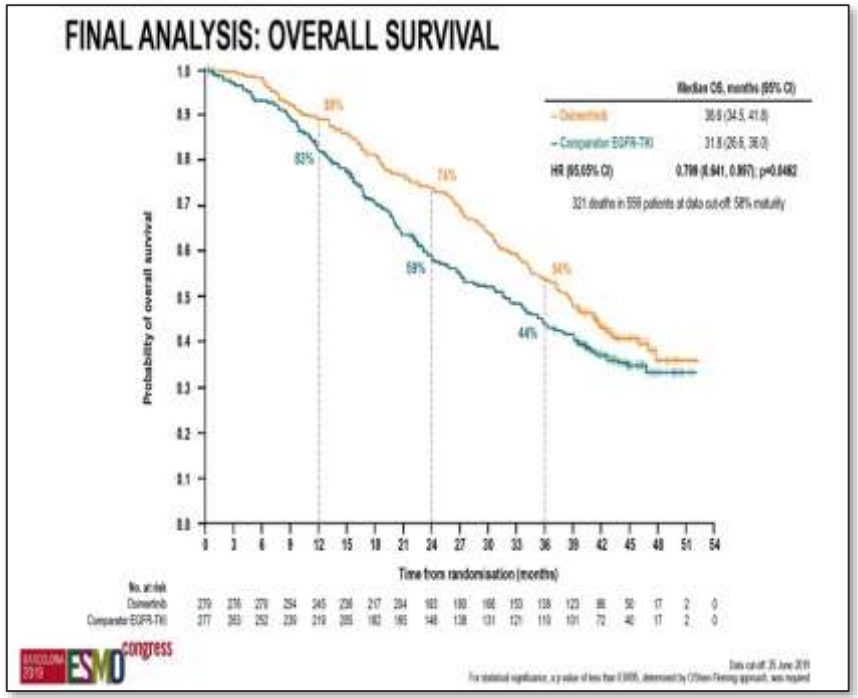
Osimertinib in untreated EGFR+ disease (FLAURA)



Progression-free Survival



Overall Survival

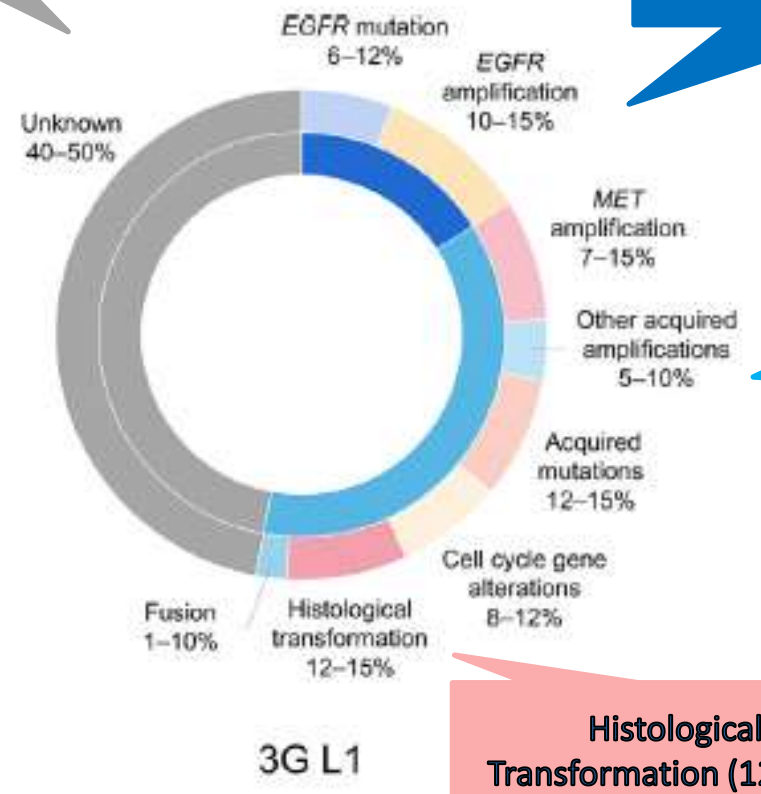


Soria et al. NEJM 2017 *Ramalingam et al. NEJM 2020*

The same drug, different resistance mechanisms

Unknown
40-50%

On target (16-32%)
G797X, L792X, G798X, L178O, G724S, S768i, EGFR amp



Bypass (35-62%)
MET amp, HER2 amp, KRAS, BRAF; Fusions

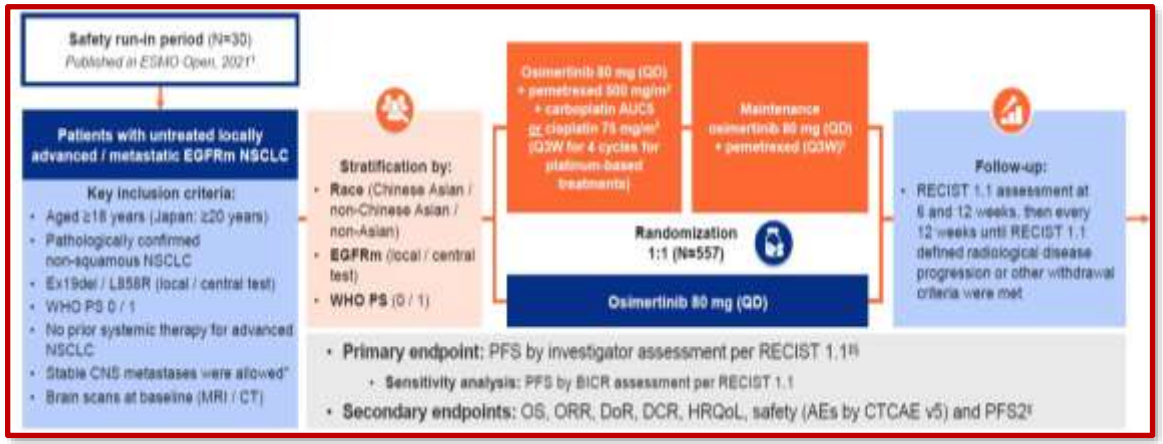
Histological Transformation (12-15%)
SCLC 5-15%, SCC 15%

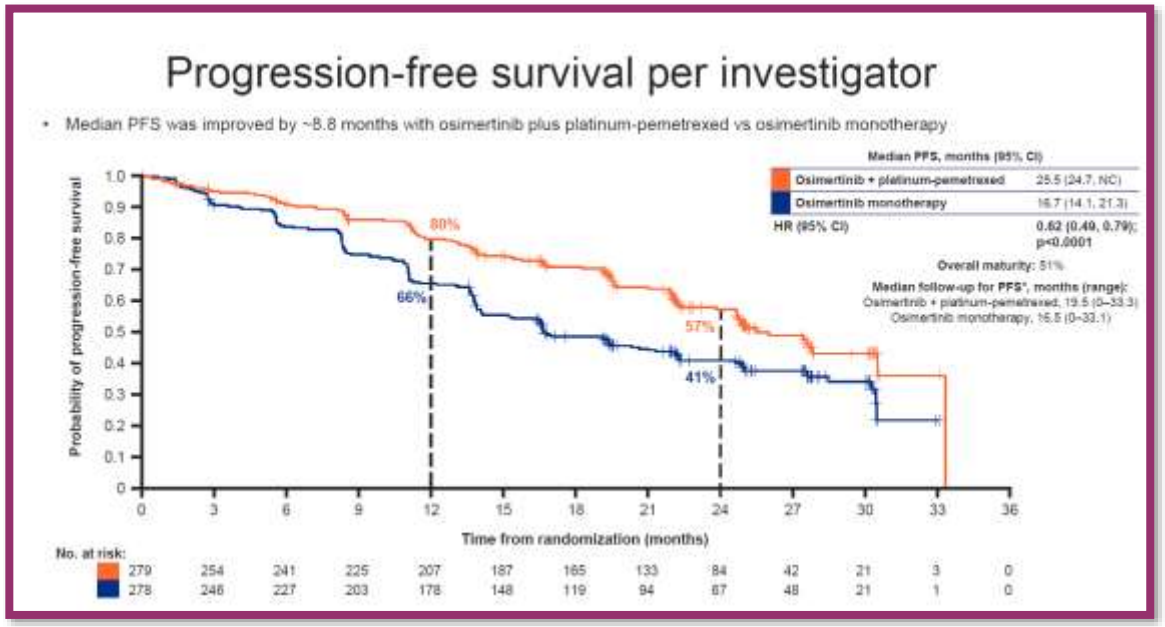
Treatment with EGR-TKIs is associated with changes in the tumor microenvironment

Zhang J et al. *Chinese Medical Journal Pulmonary and Critical Care Medicine* 2023

Combating resistance mechanisms from the 1st line of therapy: Combinations

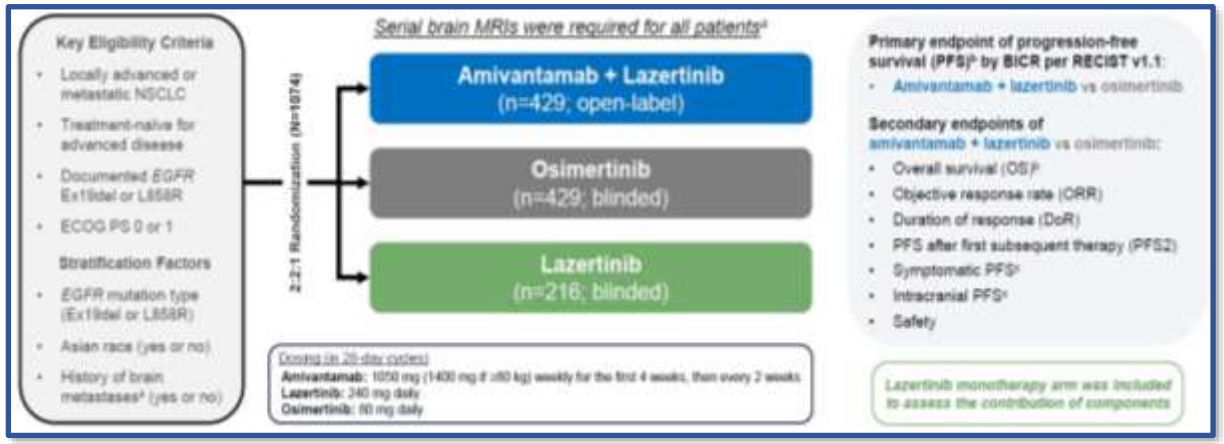
Osimertinib + Chemotherapy (FLAURA 2)

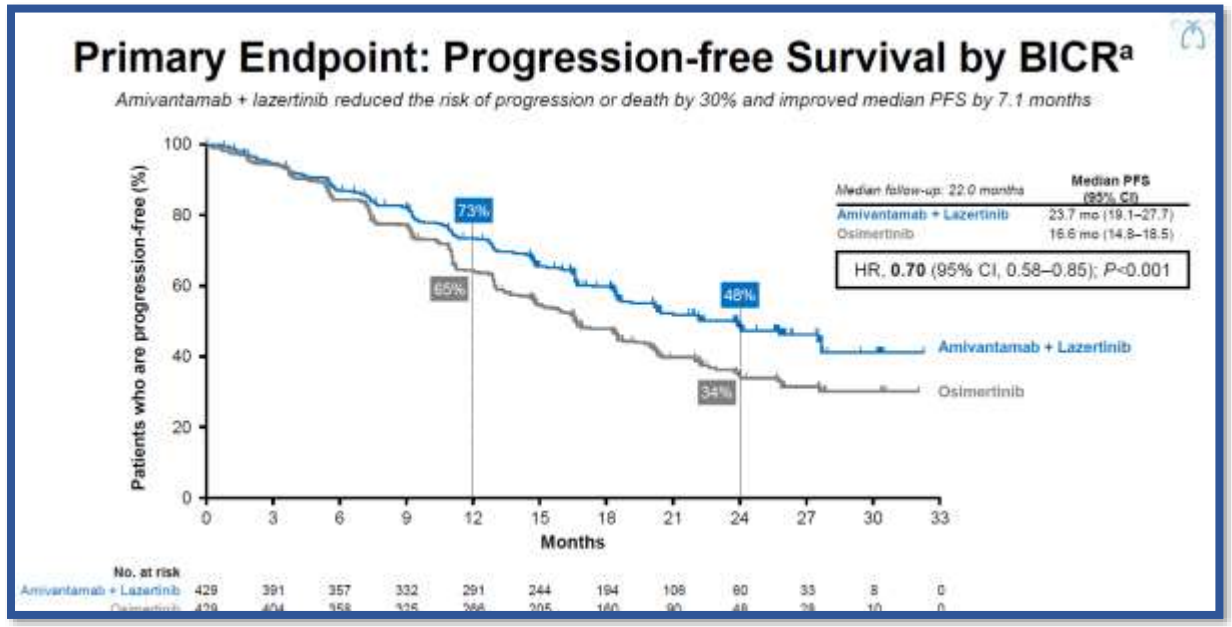




Planchard D, et al.. N Engl J Med. 2023;389(21):1935-1948.

Lazertinib + Amivantamab (MARIPOSA)





Cho BC, et al.. N Engl J Med. 2024 Oct 24;391(16):1486-1498

Combating resistance mechanisms from the 1st line of therapy: Combinations

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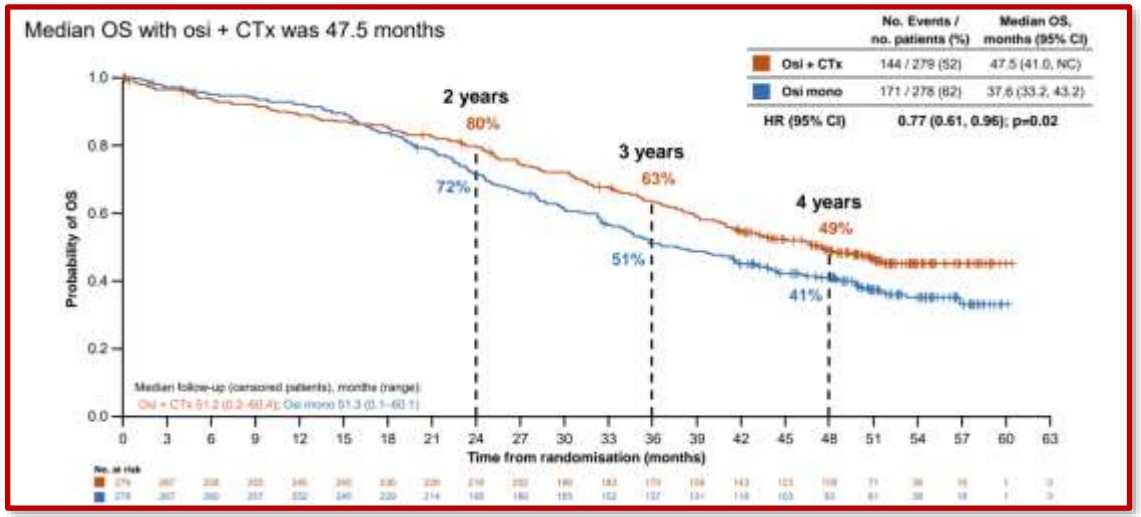
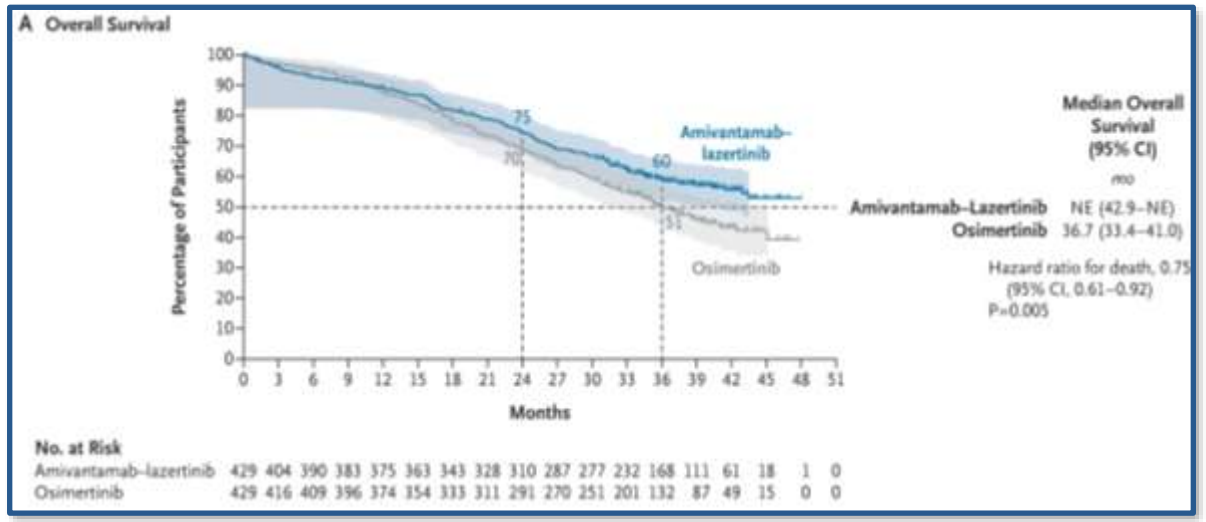


Lazertininb + Amivantamab (MARIPOSA)



FLAURA2 OS HR = 0.77 (0.61,0.96) p=0.02			
	24M	36M	48M
Osi - CTx	80%	63%	49%
Osi	72%	51%	41%

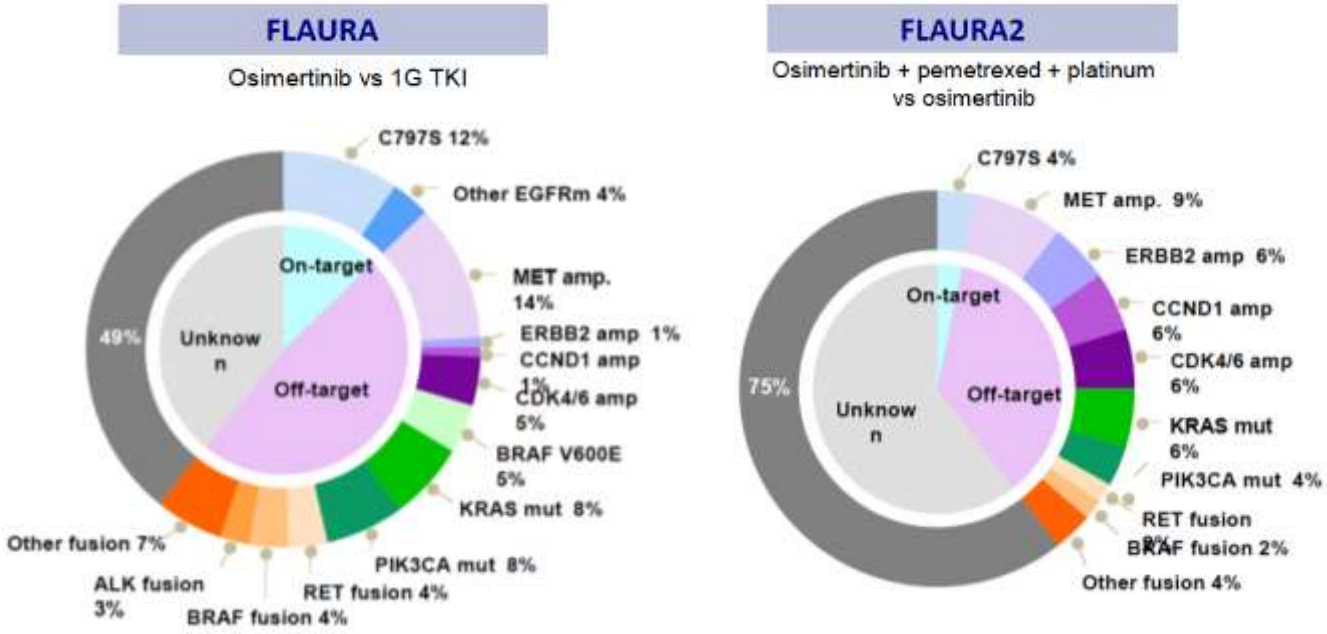
MARIPOSA OS HR 0.75 (0.61, 0.92) p=0.005		
	24M	36M
Lazer+Ami	75%	60%
Lazer	70%	51%

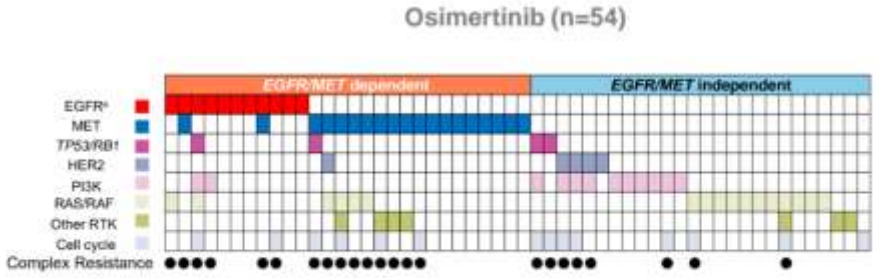
Planchard D, et al.. N Engl J Med.; Janne P et al. NEJM 2025

Cho BC, et al.. N Engl J Med. 2024; Yang JC et al. NEJM 2025

Combating resistance mechanisms from the 1st line of therapy: Combinations

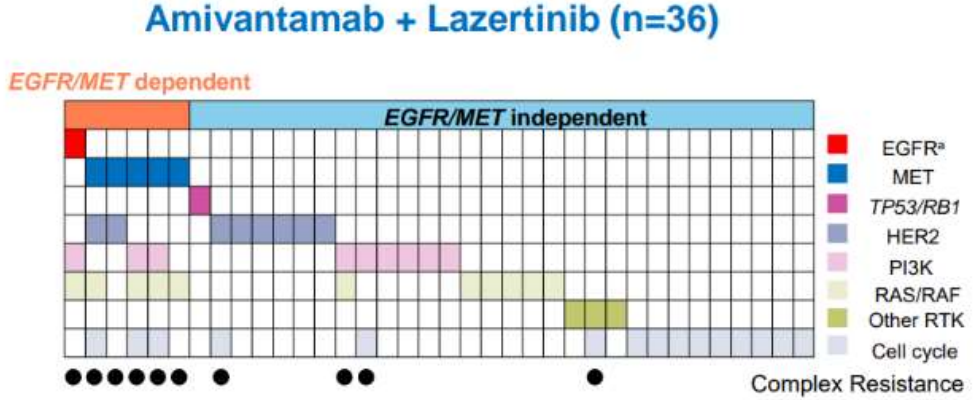
Osimertinib + Chemotherapy (FLAURA 2)



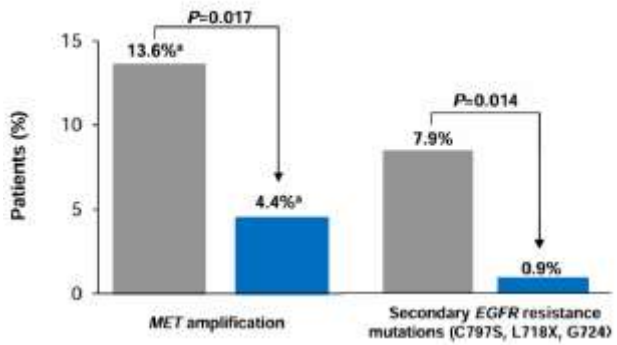


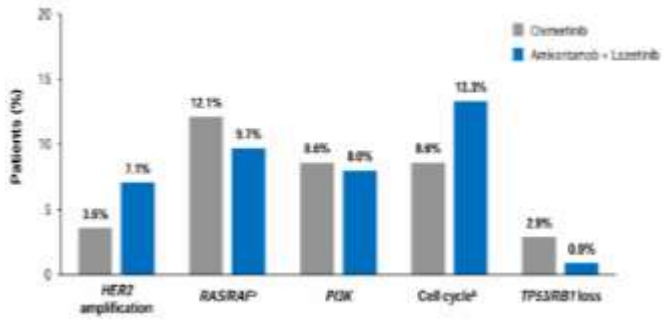
42.6% had alterations in ≥2 resistance pathways

Lazertininb + Amivantamab (MARIPOSA)



27.8% had alterations in ≥2 resistance pathways





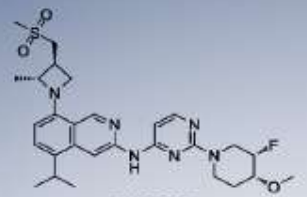
Yang et al. ESMO 2024 ; *Besse B, et al. ESMO 2024; Hayashi H, et al. WCLC 2025*

Treating resistance at the time of progression to osimertinib

On target resistance: C797S mutation

FOURTH-GENERATION EGFR TKIs

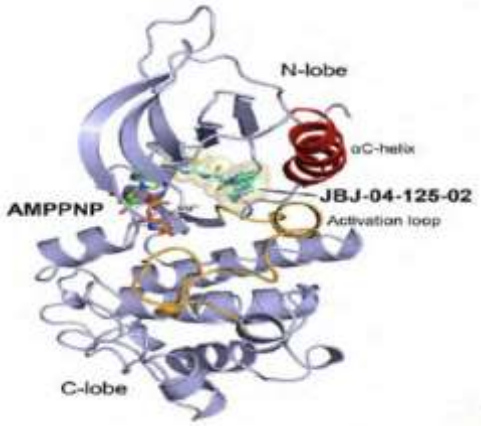
THIAZOLE AMID-BASED



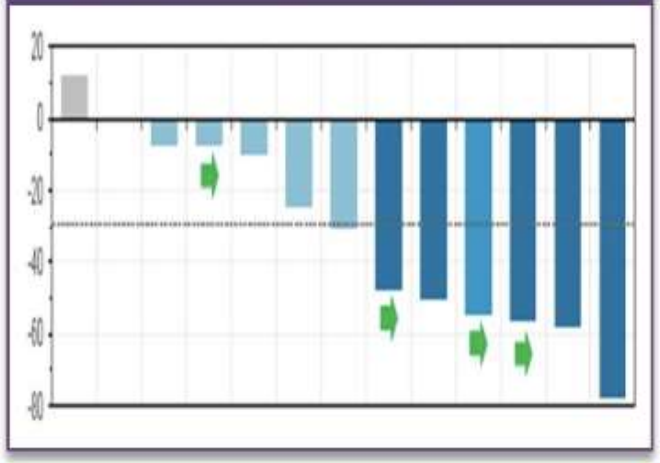
BLU-945
TRX-221
BDTX-1535
BAY 2927088
H002
JIN-A02*

REVERSIBLE ALLOSTERIC INHIBITION

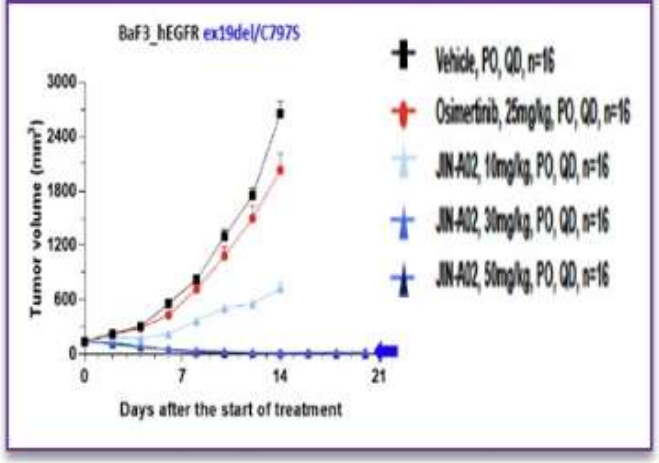
EGFR Ex19Del/L858R	●
EGFR wild type	×
EGFR uncommon	▲
ERBB2/ERBB4	×
EGFR T790M	●
c*EGFR*/T790M/C797S	●
c*EGFR*/C797S	●
CNS	●



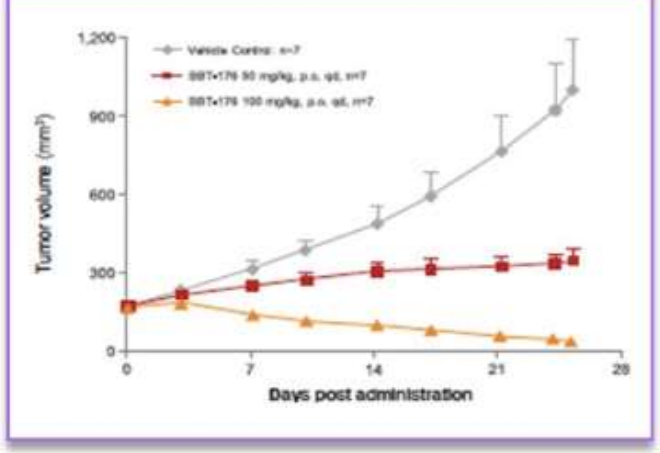
BDTX-1535, 4G *EGFR* TKI



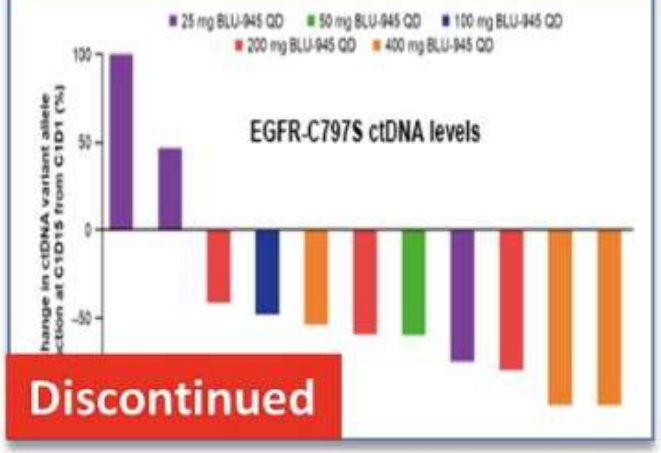
JIN-A02, 4G *EGFR* TKI



BBT-176, 4G *EGFR* TKI



BLU945, 4G *EGFR* TKI

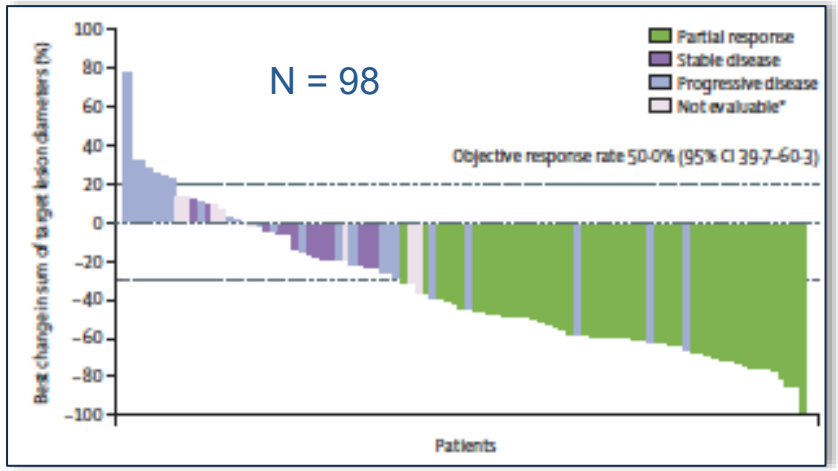


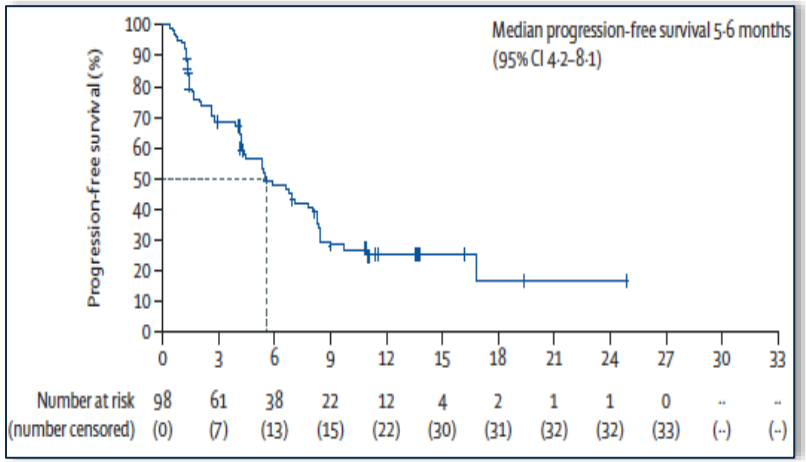
Janne P et al. Cancer Discovery 2019

Treating resistance at the time of progression to osimertinib

Off-target resistance. Bypass mechanisms: MET amplification

TKI inhibitor: Tepotinib + Osimertinib (INSIGHT 2)





TRAEs, n (%)†	Any Grade	Grade ≥3
Any	88.3 (113)	34.4 (44)
Diarrhoea	49.2 (63)	0.8 (1)
Peripheral oedema	40.6 (52)	4.7 (6)
Paronychia	22.7 (29)	0.8 (1)
Nausea	21.1 (27)	2.3 (3)
Decreased appetite	20.3 (26)	3.9 (5)
Hypoalbuminaemia	18.0 (23)	0.8 (1)
AST increase	12.5 (16)	0
Anaemia	11.7 (15)	1.6 (2)
Vomiting	11.7 (15)	0.8 (1)
sCr increase	11.7 (15)	0
Lipase increase	10.9 (14)	2.3 (3)
ALT increase	10.9 (14)	1.6 (2)
Rash	10.9 (14)	0

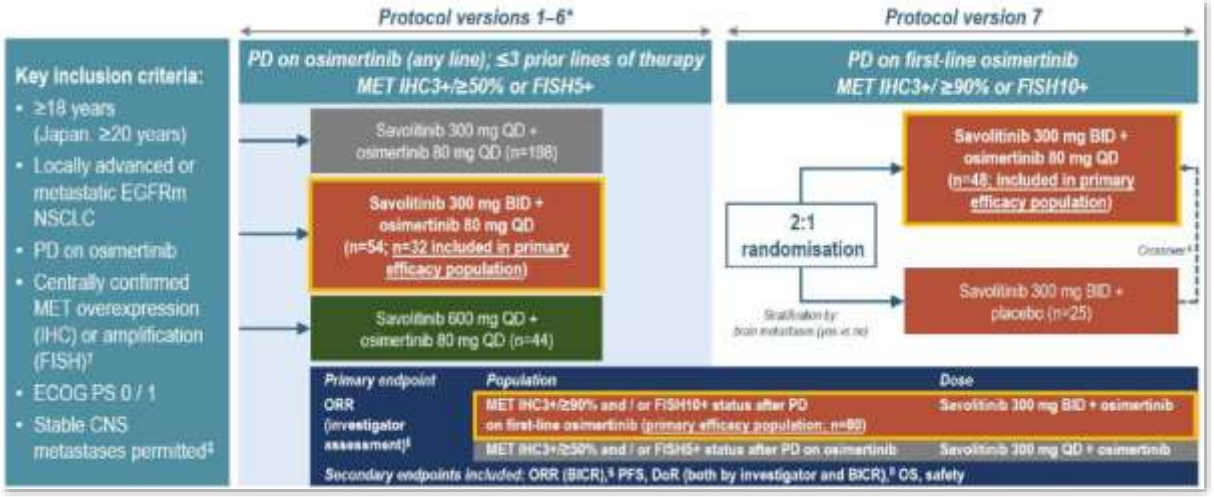
Tepotinib + osimertinib demonstrated an **ORR of 50%** in patients with *EGFR*-mutant NSCLC who progressed on osimertinib and had *MET*amp (central TBx FISH)
mPFS 5.6 months and mOS 17.8 months

Wu Y et al. Lancet Oncol 2024

Treating resistance at the time of progression to osimertinib

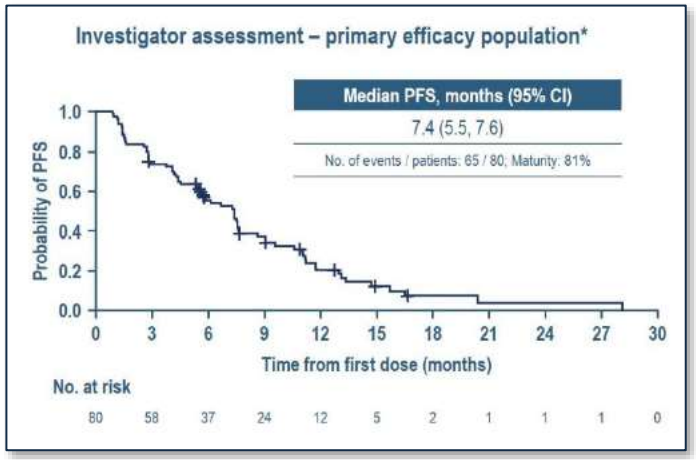
Off-target resistance. Bypass mechanisms: MET amplification

TKI inhibitor: Savolitinib + Osimertininb (SAVANNAH)

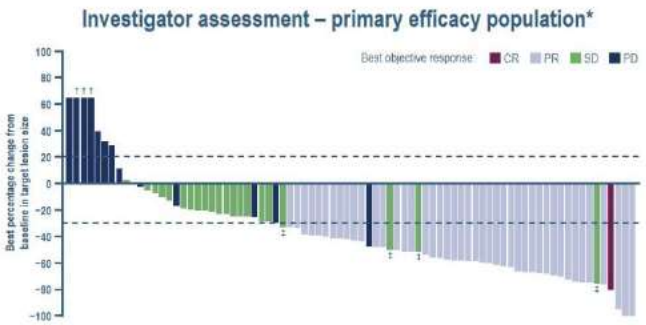


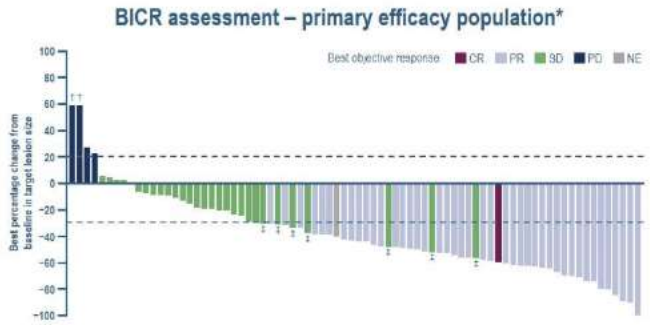
In a preliminary analysis of SAVANNAH, estimated prevalence of MET IHC3+/≥90% and / or FISH10+ was 34% in patients with EGFR-mutated NSCLC and progression on osimertinib[1]

Progression-free Survival



	Primary efficacy population (n=80)*	
	Investigator assessment	BICR assessment
Confirmed ORR, % (95% CI)	56 (45, 67)	55 (43, 66)
CR, %	1	1
PR, %	55	54
Median DoR, months (95% CI)	7.1 (5.6, 9.6) months	9.9 (6.0, 13.7) months
Median time to onset of response, weeks (IQR)	6.1 (6.0–6.7) weeks	6.0 (5.7–6.6) weeks





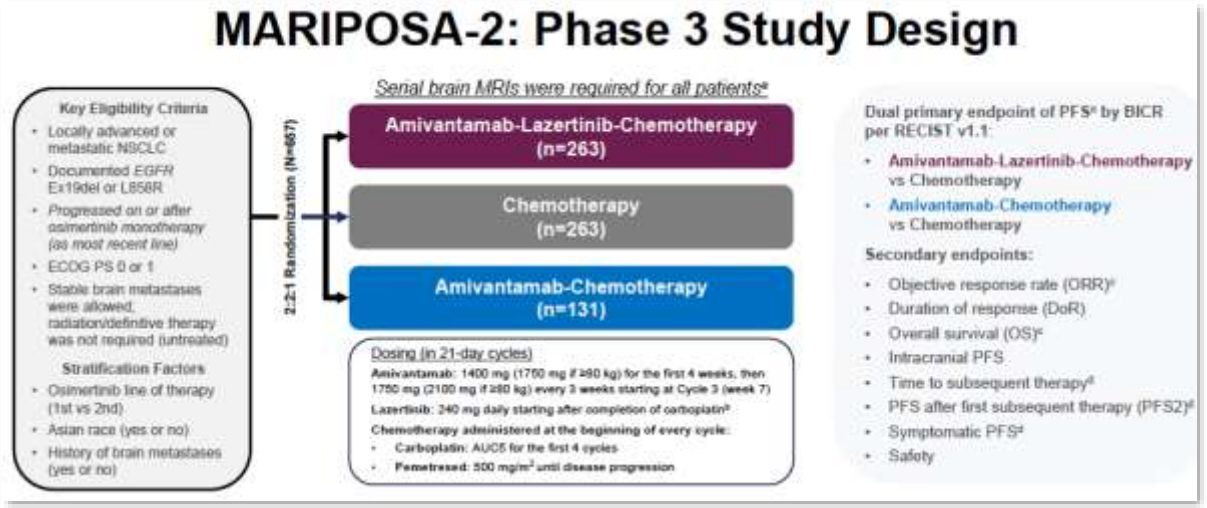
	ORR	mDOR	mPFS
By investigator	55%	7.1 mo	7.4 mo
By BICR	56%	9.9 mo	7.5 mo

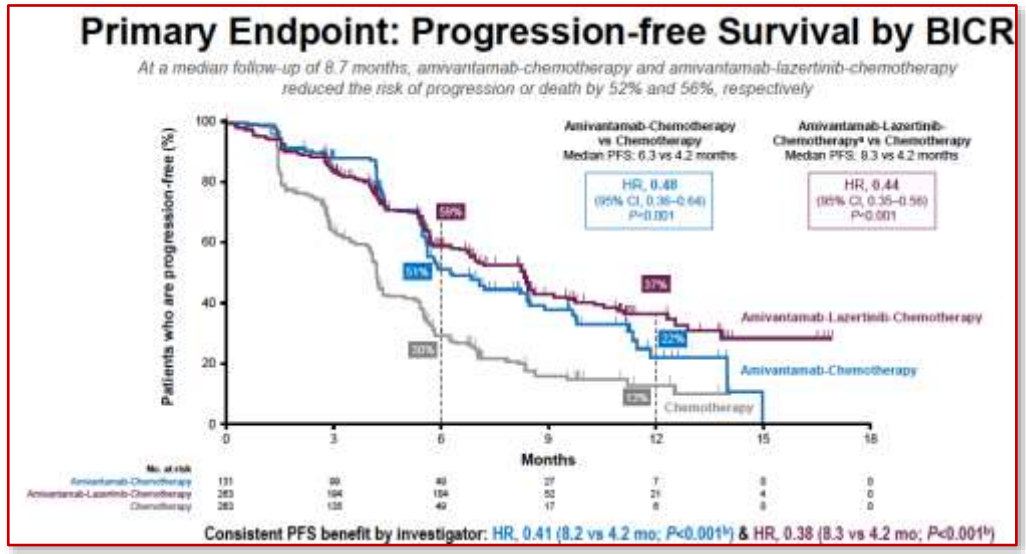
Ahn M et al. ELCC 2025

Treating resistance at the time of progression to osimertinib

Off-target resistance. Bypass mechanisms: MET amplification

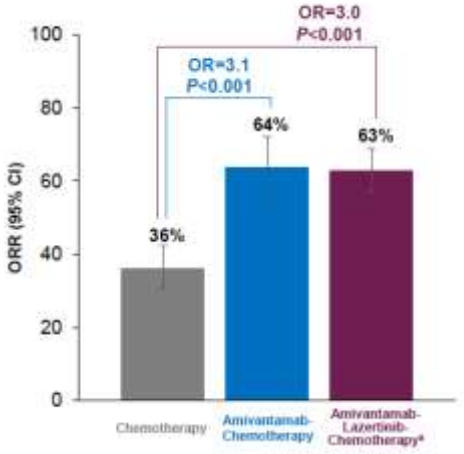
Biespecific antibodies: Amivantamab + Chemotherapy (MARIPOSA 2)





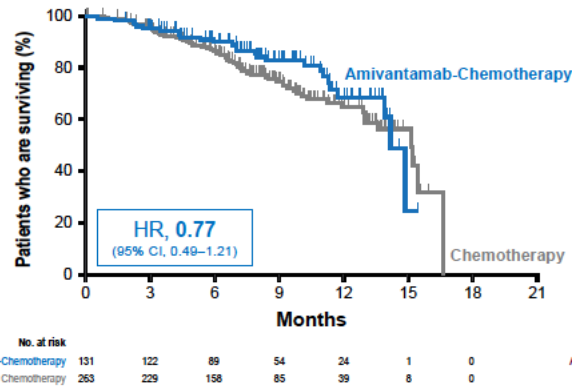
ORR

mPFS: Ami + CTx 6.3 vs CTx 4.2 months



BICR-assessed Response, n (%)[b]	Chemotherapy (n=263)	Amivantamab-Chemotherapy (n=131)	Amivantamab-Lazertinib-Chemotherapy (n=263)
Best Response			
CR	1 (0.4)	2 (2)	6 (2)
PR	93 (36)	81 (62)	157 (61)
SD	82 (32)	30 (23)	61 (24)
PD	52 (20)	10 (8)	14 (5)
NE/UNK	32 (12)	7 (5)	21 (8)
Median DoR[c]	5.6 mo (95% CI, 4.2–9.6)	6.9 mo (95% CI, 5.5–NE)	9.4 mo (95% CI, 6.9–NE)

Overall Survival



Passaro A et al. ESMO 2023

Treating resistance at the time of progression to osimertinib

Off-target resistance. Bypass mechanisms: MET amplification

Biespecific antibodies: MCLA-129

Study Design

MCLA-129 Development Program

Ongoing Phase 1/2 global, open-label clinical trial

*EGFR*mut NSCLC

Inclusion Criteria

- Locally advanced unresectable or metastatic NSCLC
- With sensitizing mutations[a] and no prior treatment (1L), or progressed on or after osimertinib (2L+)
- Measurable disease at baseline per RECIST v1.1
- ≥ 18 years of age, ECOG PS of 0 or 1
- Life expectancy ≥ 12 weeks, as per the investigator

Treatment Plan

- MCLA-129 1500 mg IV Q2W until PD or unacceptable toxicity
- Osimertinib 80 mg QD
- Tumor imaging Q8W

Endpoints and Population

Primary endpoint
ORR[b] using RECIST v1.1 per investigator assessment

Secondary endpoints
DoR, DCR,[c] PFS, OS, and safety[d]

Primary analysis population
≥ 2 MCLA-129 cycles, with baseline and ≥ 1 postbaseline scan

Enrollment and Analysis

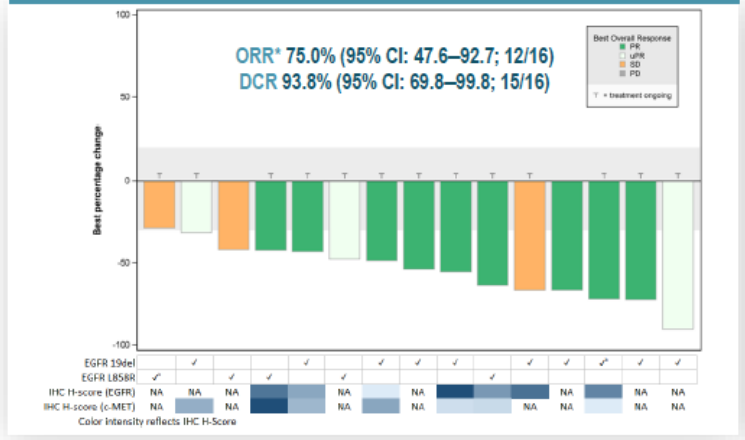
Data cutoff date
August 10, 2023

Enrollment
60 *EGFR*mut NSCLC patients
- 16 patients in 1L
- 44 patients in 2L+

Primary efficacy analysis population
- 16 patients in 1L
- 34 patients in 2L+
- 9 patients in 2L+ excluded, with < 2 cycles and discontinued for reasons not related to PD
- 1 patient in 2L+ with < 2 cycles ongoing at the data cutoff date was not part of the efficacy analysis population

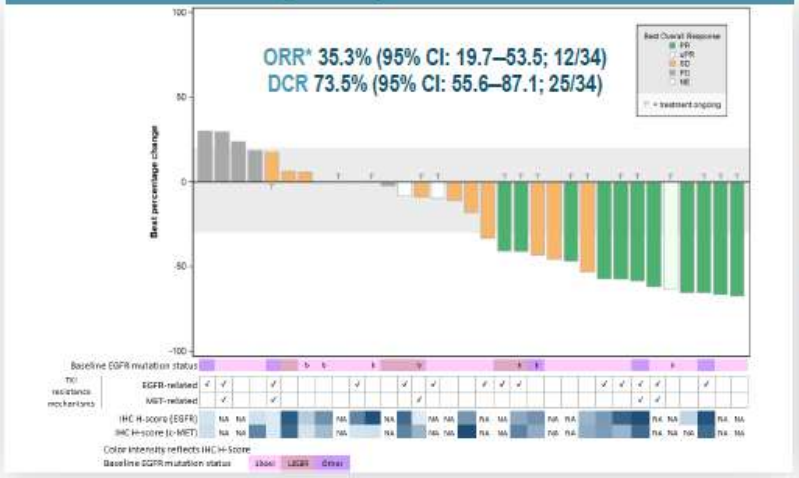
MCLA-129 Activity in 1L *EGFR*mut NSCLC

Best % change in target lesions from baseline[a]

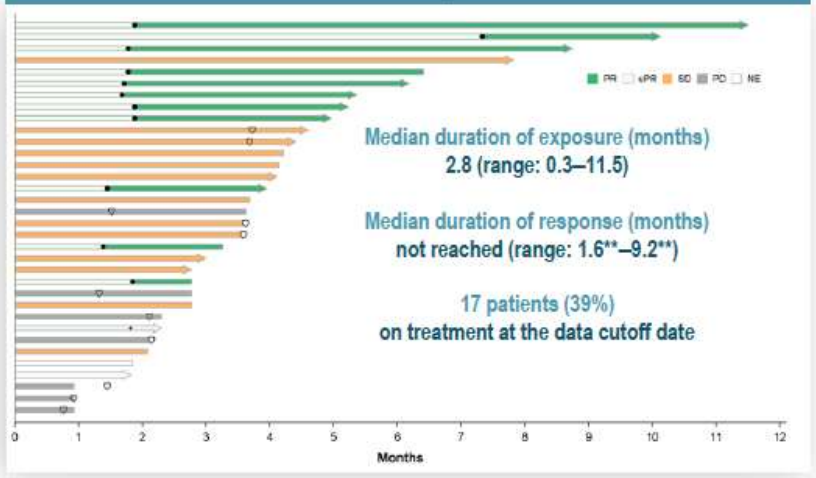


MCLA-129 Activity in 2L+ *EGFR*mut NSCLC

Best % change in target lesions from baseline[a]



Duration of exposure[a]

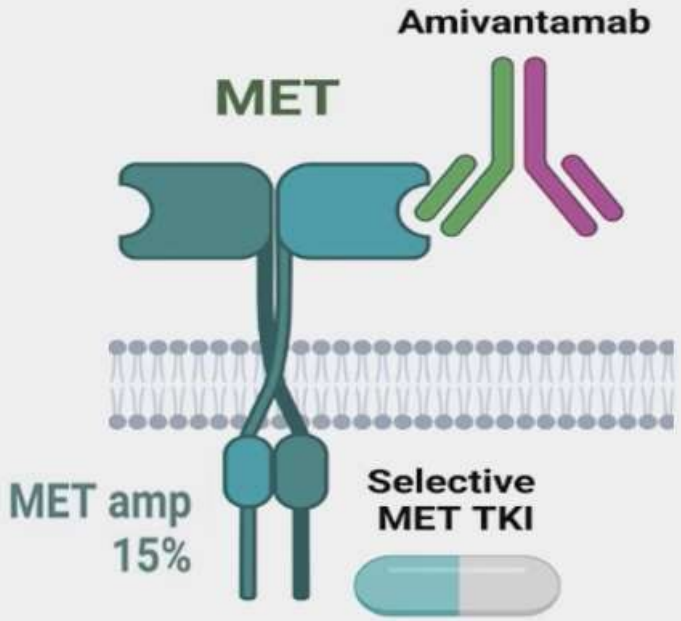


Cappuzzo F et al. ESMO Asia 2023

Treating resistance at the time of progression to osimertinib

Off-target resistance. Bypass mechanisms: MET amplification

Summary TKIs and Biespecific antibodies



MET gene copy number (GCN) ≥5
MET/CEP7 ratio ≥2
Liquid biopsy, no clear consensus

	Trial	Drug	N	RR (%)	DoR (mo)	PFS (mo.)
MET TKI	TATTON	Osimertinib + Savolitinib (B1 cohort)	69	33	9.5	5.5 (OS: 30.3)
	ORCHARD	Osimertinib + Savolitinib	17	41	NR	NR
	SAVANNAH	Osimertinib + Savolitinib	193	32	8.3	5.3
	INSIGHT2	Osimertinib + Tepotinib	98 Tissue 31 Lx Bx	50 52	8.5 5.6	5.6 4.6
	INSIGHT2	Tepotinib	12	8.3	NR	NR
EGFR/ MET mAb	CHRYSALIS-E	Amivantamab + Lazertinib	45	36	9.6	4.9
	CHRYSALIS-D	Amivantamab + Lazertinib	108	30	10.8	5.7
	CHRYSALIS-A (Post Osi & PBC)	Amivantamab + Lazertinib	162	33	8.4	5.1

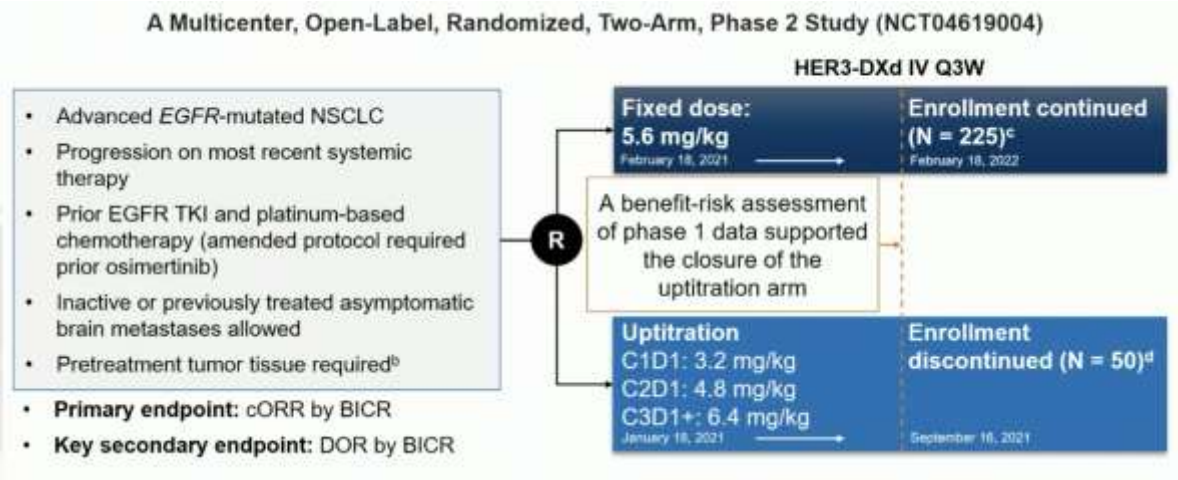
Remon J et al. ASCO 2024

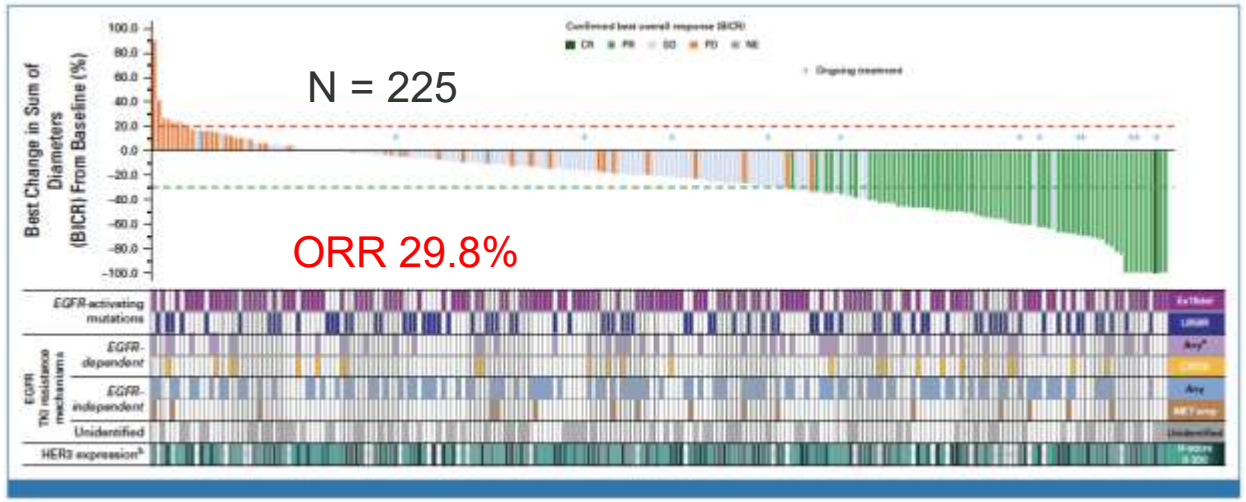
Treating resistance at the time of progression to osimertinib

On-target resistance and Bypass mechanisms: Antibody Drug Conjugates (ADCs)

Anti HER3: Patritumab Deruxtecan

HERTHENA-Lung01: Phase 2 trial of Patritumab Deruxtecan in EGFR-m NSCLC who have progresses to prior therapy





- **Not** a know **mechanism of resistance** to EGFR TKIs
- **Expressed in 60%** of EGFRm NSCLC

Efficacy was observed across diverse mechanisms of EGFR TKI resistance

EGFR-dependent -> ORR 32.4%.

EGFR-independent ->ORR 27.2%

CNS ORR 20% (33.3% in patients without RT)

Camidge R et al. ASCO 2020; Yu et al. JCO 2023

Treating resistance at the time of progression to osimertinib

On-target resistance and Bypass mechanisms: Antibody Drug Conjugates (ADCs)

Anti Trop2: Datopotamb Deruxtecan (TROPION-Lung 05)

Study Design

Screening

Key inclusion criteria

- Stage IIIB, IIIC, or IV NSCLC
- Presence of ≥1 actionable genomic alteration (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*)
- ECOG PS of 0 or 1
- ≥1 line of targeted therapy
- 1 or 2 prior cytotoxic agent–containing therapies including platinum-based therapy in the metastatic setting
- Radiographic disease progression after targeted therapy

Treatment

Dato-DXd
6 mg/kg
Q3W

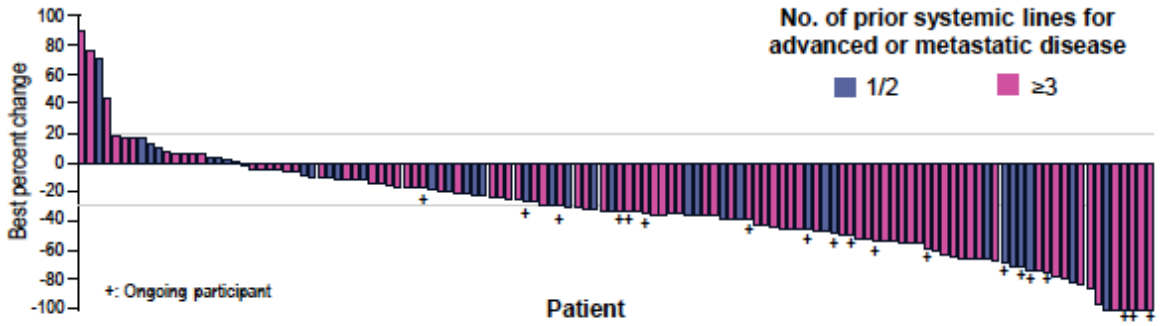
Endpoints[a]

Primary: ORR by BICR

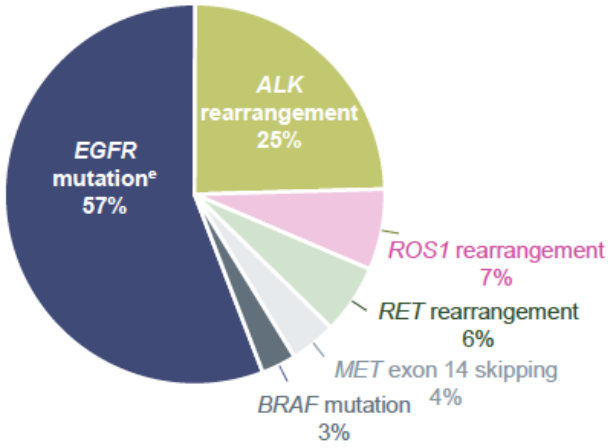
Secondary:

- By BICR and investigator: DOR, DCR, CBR, PFS, TTR
- By investigator: ORR
- OS, safety, PK, immunogenicity

Best Percent Change From Baseline in Sum of Diameters of Target Lesions



Relative Frequency of Genomic Alterations[b-d]



Response per BICR	All treated patients (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
Median DOR (95% CI), months	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)
DCR confirmed, n (%) [95% CI][a]	108 (78.8) [71.0-85.3]	64 (82.1) [71.7-89.8]	25 (73.5) [55.6-87.1]
Median PFS, (95% CI), months[b]	5.4 (4.7-7.0)	5.8 (5.4-8.3)	4.3 (2.6-6.9)

BOR: In the overall population (N=137), 4 patients (3%) achieved a CR and 45 (33%) achieved a PR

***EGFR* subset:** Among patients with sensitizing or T790M mutations (N=68), the ORR was 49.1% in those previously treated with osimertinib

Paz-Ares L et al. ESMO 2023

Treating resistance at the time of progression to osimertinib

On-target resistance and Bypass mechanisms: Antibody Drug Conjugates (ADCs)

Anti Trop2: Sacituzumab tirumotecan

OptiTROP-Lung03 Study Design

Open-label, randomized, multicenter, registrational trial (NCT05631262)

Key Eligibility
- ECOG score 0 or 1
- Nsq-NSCLC (stage IIIB/IIIC ineligible for surgery or radical radiotherapy or stage IV)
- EGFR-sensitizing mutations, including 19-Del and L858R
- Progression after prior combination or sequential treatment with EGFR-TKIs and platinum-based chemotherapy

Stratification factors:
- Brain metastases (present vs. absent)

R 2:1

- Sac-TMT 5 mg/kg IV, Q2W
- Docetaxel 75 mg/m² IV, Q3W

Treatment until disease progression, intolerable toxicity, or any other reason for discontinuation.

After PD verified by BIRC, patients could be permitted to cross over to receive sac-TMT

Primary Endpoint*
- ORR* assessed by BIRC

Secondary endpoints*
- PFS
- OS
- ORR assessed by investigator
- DOR, DCR, TTR
- Safety

* Tumor assessments will be performed every 6 weeks (± 7 days) within 48 weeks after randomization.
* After 48 weeks of randomization, tumor assessments will be performed every 12 weeks (± 7 days).

OptiTROP-Lung04 Study Design

Randomized, multicenter, open-label, phase 3 trial (NCT05870319)

Key Eligibility
- ECOG score 0 or 1
- Nsq-NSCLC (stage IIIB/IIIC or stage IV)
- EGFR-sensitive mutations
- Progression after 3rd gen TKI therapy or progression after 1st or 2nd gen TKIs with negative T790M

R 1:1

- Sac-TMT 5 mg/kg IV, Q2W
- Pemetrexed 500 mg/m² + Carboplatin AUC 5 or Cisplatin 75 mg/m² Q3W for up to 4 cycles
- Pemetrexed 500 mg/m² maintenance, Q3W

Treatment until disease progression, intolerable toxicity, or patient request to discontinue treatment.

Primary endpoints*
- PFS assessed by BICR

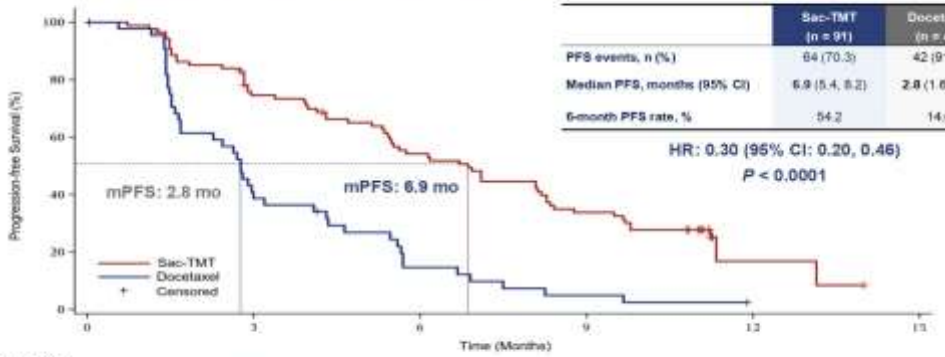
Secondary endpoints*
- OS (key secondary endpoint)
- PFS assessed by investigator
- ORR, DCR, DOR, etc.
- Safety

Stratification factors:
1. Prior EGFR-TKI therapy (**3rd gen TKI in 1st line** *vs* **in 2nd line** *vs* **no 3rd gen TKI**)
2. Brain metastases (**yes** *vs* **no**)

Statistical considerations:
- Hierarchical testing was conducted for PFS by BICR and OS.
- Pre-specified interim analysis for OS:
  at approximately 50% maturity,
  or 24 months after the first patient randomized.

Progression-Free Survival by BIRC

Sac-TMT significantly improved PFS over docetaxel with 70% lower risk of disease progression or death.

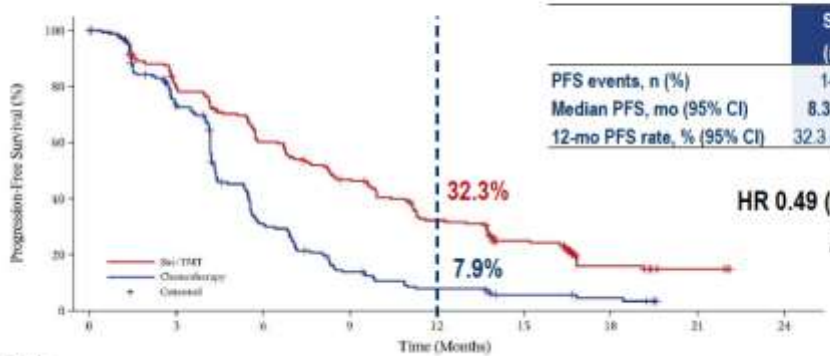


	Sac-TMT (n = 91)	Docetaxel (n = 40)
PFS events, n (%)	64 (70.3)	42 (91.3)
Median PFS, months (95% CI)	6.9 (5.4, 8.2)	2.8 (1.6, 4.1)
6-month PFS rate, %	54.2	14.6

HR: 0.30 (95% CI: 0.20, 0.46)
P < 0.0001

Progression-Free Survival by BICR

Sac-TMT significantly improved PFS over chemotherapy with 51% lower risk of disease progression or death.



	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

Zhang L et al. ASCO 2025

Zhang L et al. ESMO 2025

Treating resistance at the time of progression to osimertinib

On-target resistance and Bypass mechanisms: Immunotherapy

HARMONi-A: Ivonescimab + chemotherapy

Study Design

Key Eligibility Criteria

- Non-squamous NSCLC (Stage IIIB/C ineligible for surgery or local therapy and IV)
- EGFR sensitive mutation positive
- ECOG PS 0 or1
- Regardless PD-L1 expression

Stratification Factors:

- Exposure to 3rd EGFR-TKI before (yes vs. no)
- Brain metastases (yes vs. no)

Enrollment: Jan 2022 - Nov 2022

R 1:1

Ivonescimab 20mg/kg + Pemetrexed 500 mg/m² Carboplatin AUC5 Q3W for 4 cycles → **Ivonescimab** 20mg/kg + Pemetrexed 500 mg/m² Q3W

Placebo + Pemetrexed 500 mg/m² Carboplatin AUC5 Q3W for 4 cycles → **Placebo** + Pemetrexed 500 mg/m² Q3W

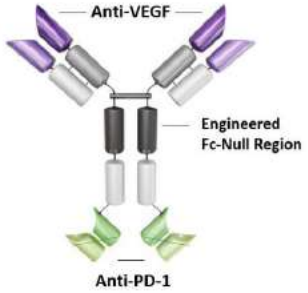
Treatment until:

- Intolerable toxicity
- No clinical benefit
- Initiation of new anti-tumor therapy

Up to 24 months

Endpoint

- Primary endpoint: progression-free survival (PFS) by IRRC
- Key secondary endpoint: overall survival (OS)

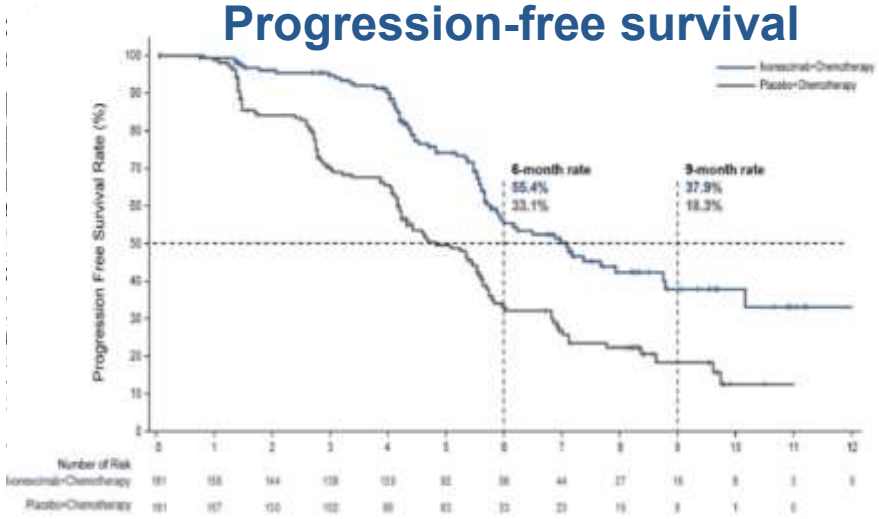


Data cut-off date: April 2025
(median follow-up of 32.5 months)

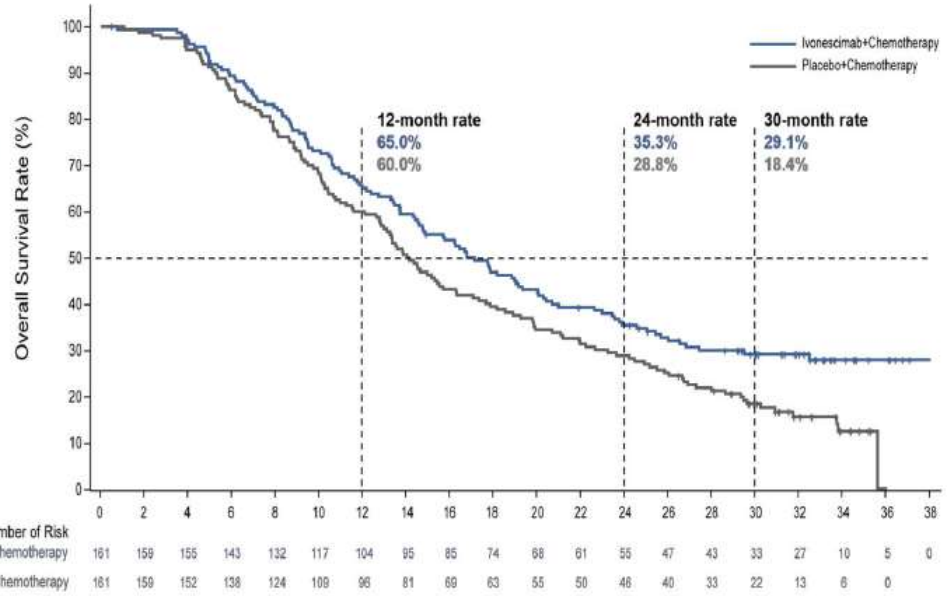
	Ivonescimab + chemotherapy	Placebo + chemotherapy
ORR[1], % (95% CI)	**50.6** (42.6, 58.6)	**35.4** (28.0, 43.3)
DCR[1], % (95% CI)	**93.1** (88.0, 96.5)	**83.2** (76.5, 88.6)
mPFS[1], months (95% CI)	**7.1** (5.9, 8.7)	**4.8** (4.2, 5.6)
PFS HR[1] (95% CI)	**0.46** (0.34, 0.62) **p<0.001**	
mOS[2], months (95% CI)	**16.8** (14.5, 20.0)	**14.1** (12.8, 16.3)
OS HR[2] (95% CI)	**0.74** (0.58, 0.95) **p=0.019** (two-side)	

[1]Interim analysis
[2]Final analysis

Progression-free survival



Overall survival



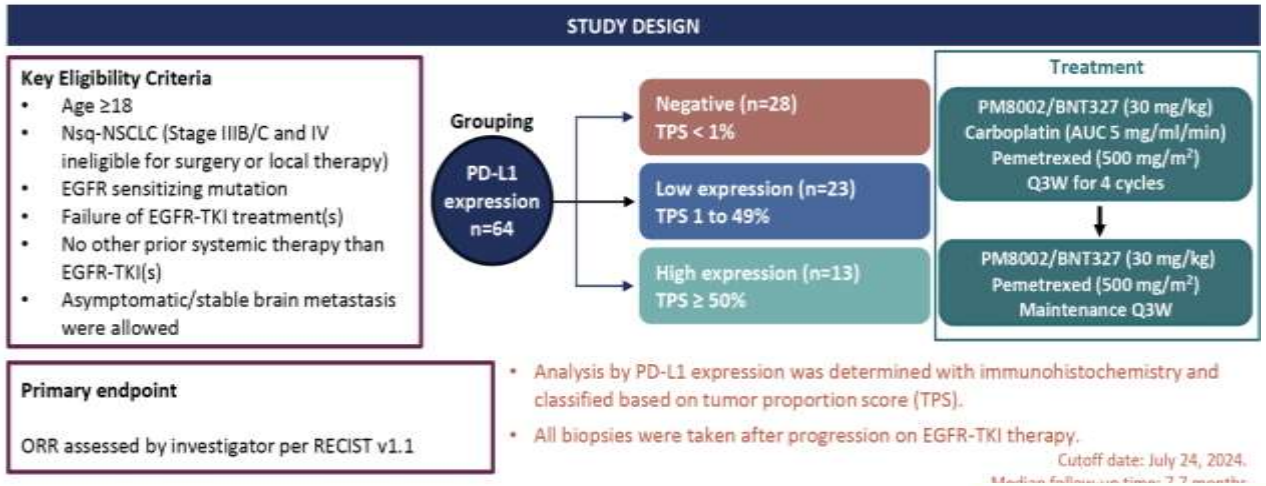
Zhang L. et al. STIC 2025

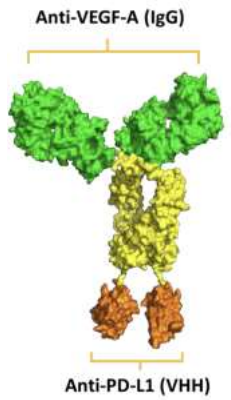
Treating resistance at the time of progression to osimertinib

On-target resistance and Bypass mechanisms: Immunotherapy

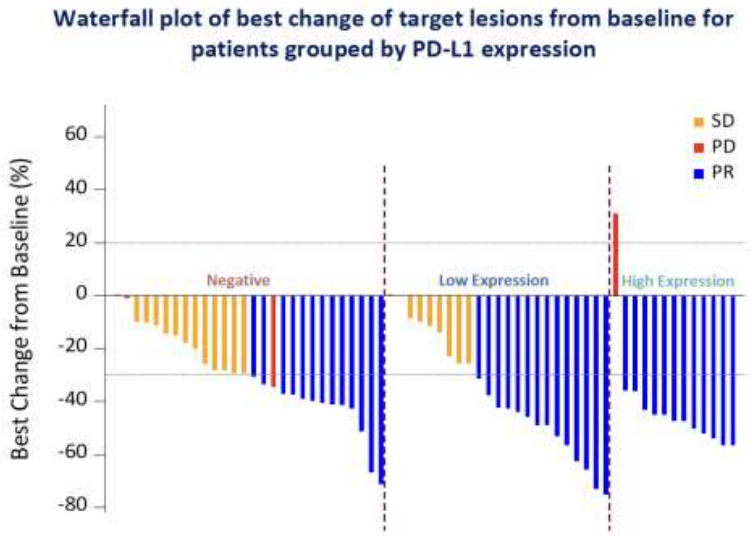
PM8002/BNT327 + chemotherapy

Study Design





ORR



Response Assessment	Overall n=64	PD-L1 negative n=28	PD-L1 low expression n=23	PD-L1 high expression n=13
ORR by investigator, n (%) [95% CI]	39 (60.9) [47.9,72.9]	13 (46.4) [27.5,66.1]	14 (60.9) [38.5,80.3]	12 (92.3) [64.0,99.8]
Confirmed ORR by investigator, n (%) [95% CI]	37 (57.8) [44.8,70.0]	11 (39.3) [21.5,59.4]	14 (60.9) [38.5,80.3]	12 (92.3) [64.0,99.8]
Best overall response, n (%)				
PR	37 (57.8)	11 (39.3)	14 (60.9)	12 (92.3)
SD	24 (37.5)	15 (53.6)	9 (39.1)	0 (0)
PD	3 (4.7)	2 (7.1)	0 (0)	1 (7.7)
DCR, n (%) [95% CI]	61 (95.3) [86.9,99.0]	26 (92.9) [76.5,99.1]	23 (100) [85.2,100.0]	12 (92.3) [64.0,99.8]
Median TTR, months [95% CI]	2.9 [1.5,4.1]	5.8 [2.7, NE]	2.9 [1.4, NE]	1.6 [1.5,2.9]

Wu YL. et al. ESMO 2024

Treating resistance at the time of progression to osimertinib

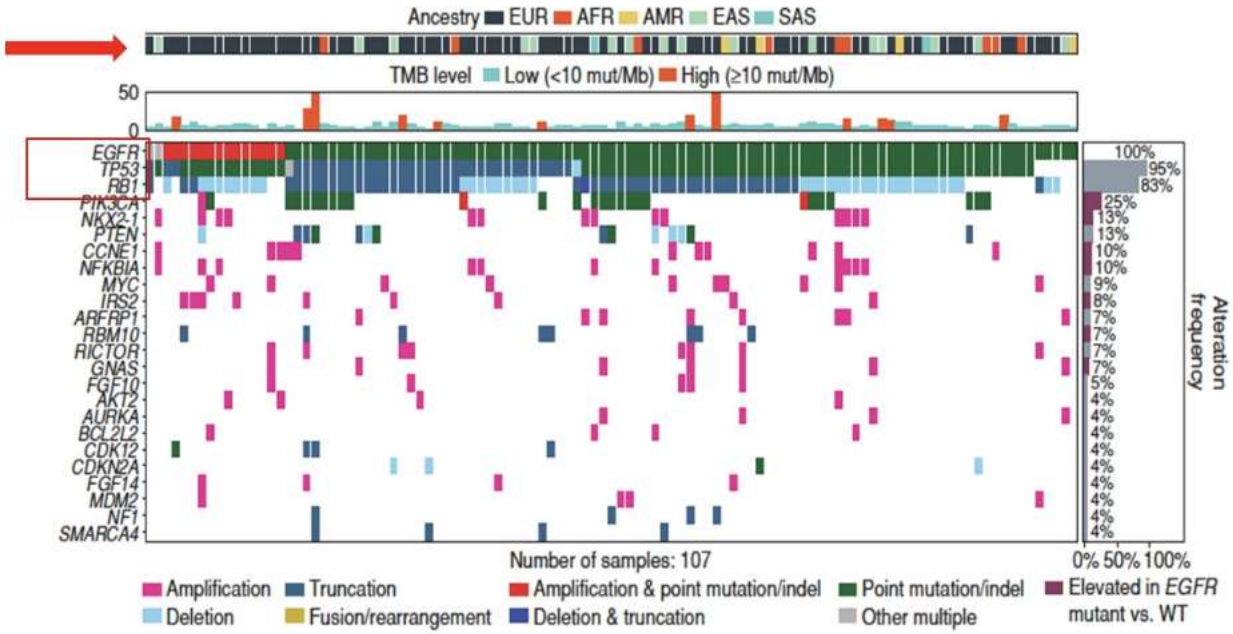
On-target resistance and Bypass mechanisms: Immunotherapy

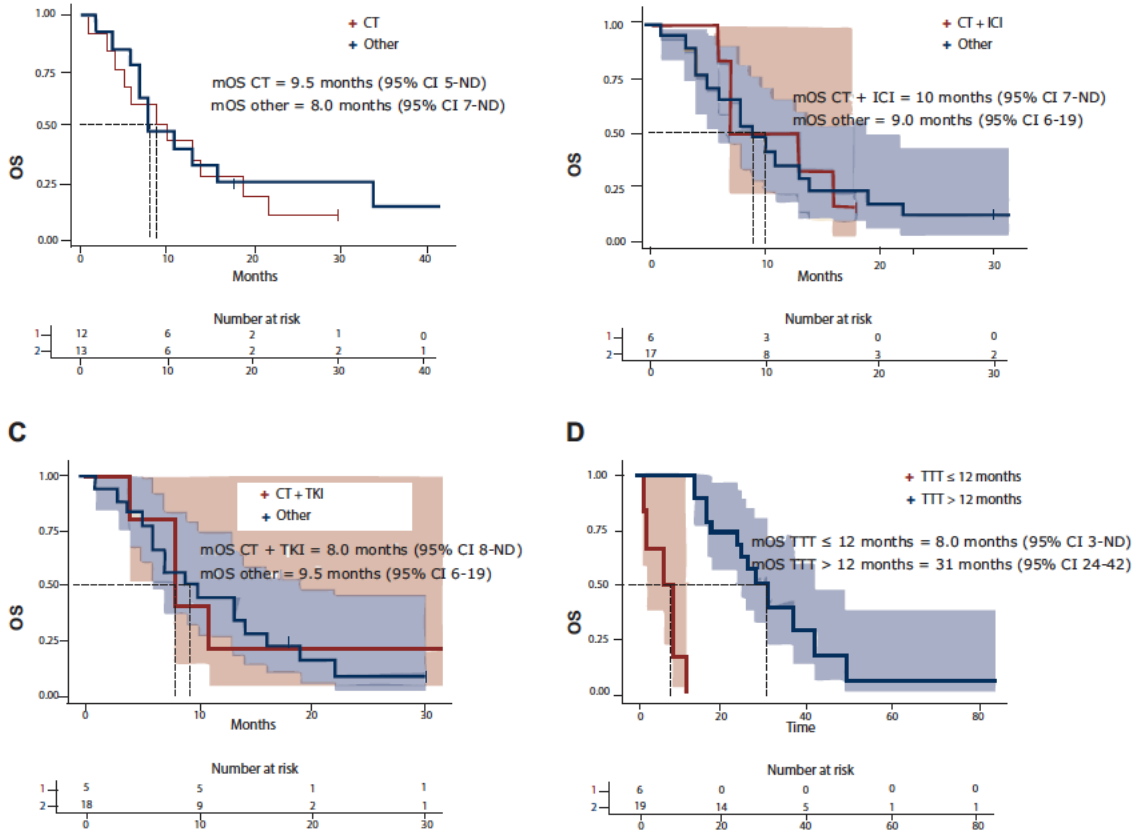
Study	Treatment	N	PFS	HR; 95%IC	OS	HR, 95%IC
CheckMate 722	**Nivolumab** + PBC vs. PBC	296	**5.6 vs. 5.4**	0.75; 0.56-1.00	**19.4 vs. 15.9**	0.82; 0.61-1.10
KEYNOTE 789	**Pembrolizumab** + PBC vs PBC	480	**5.6 vs. 5.5**	0.80; 0.65-0.97	**15.9 vs. 14.7**	0.84; 0.69 -1.02
ORIENT 31	**Sintilimab** + PBC vs. PBC	318	**5.5 vs. 4.3**	0.72; 0.55-0.94	**20.5 vs. 19.2**	0.97; 0.71 -1.32
IMPOWER 150	**Atezolizumab + BVZ** + PBC vs. BVZ + PBC	58	**10.3 vs. 6.1**	0.41; 0.23-0.75	**29.4 vs. 18.1**	0.60; 0.31 -1.14
IMPOWER 151	**Atezolizumab + BVZ** + PBC vs. BVZ + PBC	163	**8.5 vs. 8.3**	0.86; 061-1.21	NR	NR
ATLAS	**Atezolizumab + BVZ** + PBC vs. PBC	215	**8.4 vs. 5.6**	0.62; 0.45-0.86	**20.6 vs. 20.3**	1.01; 0.69 -1.46
ORIENT 31	**Sintilimab + IBI305** + PBC vs. PBC	318	**7.2 vs. 4.3**	0.51; 0.39-0.67	**21.1 vs. 19.2**	0.98; 0.72 -1.34
ABC-Lung	**Atezolizumab + BVZ** + PBC vs. Atezolizumab + BVZ + Pem	95	**6.3 vs. 7.5**	NR	**15.4 vs. 15.5**	NR
HARMONi-A	**Ivonescimab** + PBC vs. PBC + Placebo	322	**7.1 vs. 4.8**	0.46; 0.34-0.62	**17.1 vs. 14.5**	0.80; 0.59-1.08

Remon J et al. ASCO 2024

Treating resistance at the time of progression to osimertinib

Treating histologic transformation





- Histologic transformation can occur across all subtypes
- Patients with co-occurring **EGFR/RB1/TP53** alterations had a higher risk of transformation
- TP53 95%, RB1 83%. PIK3CA 25%.
- Histologic transformation **EGFR Del19 vs. L858R (64% vs. 26%)**

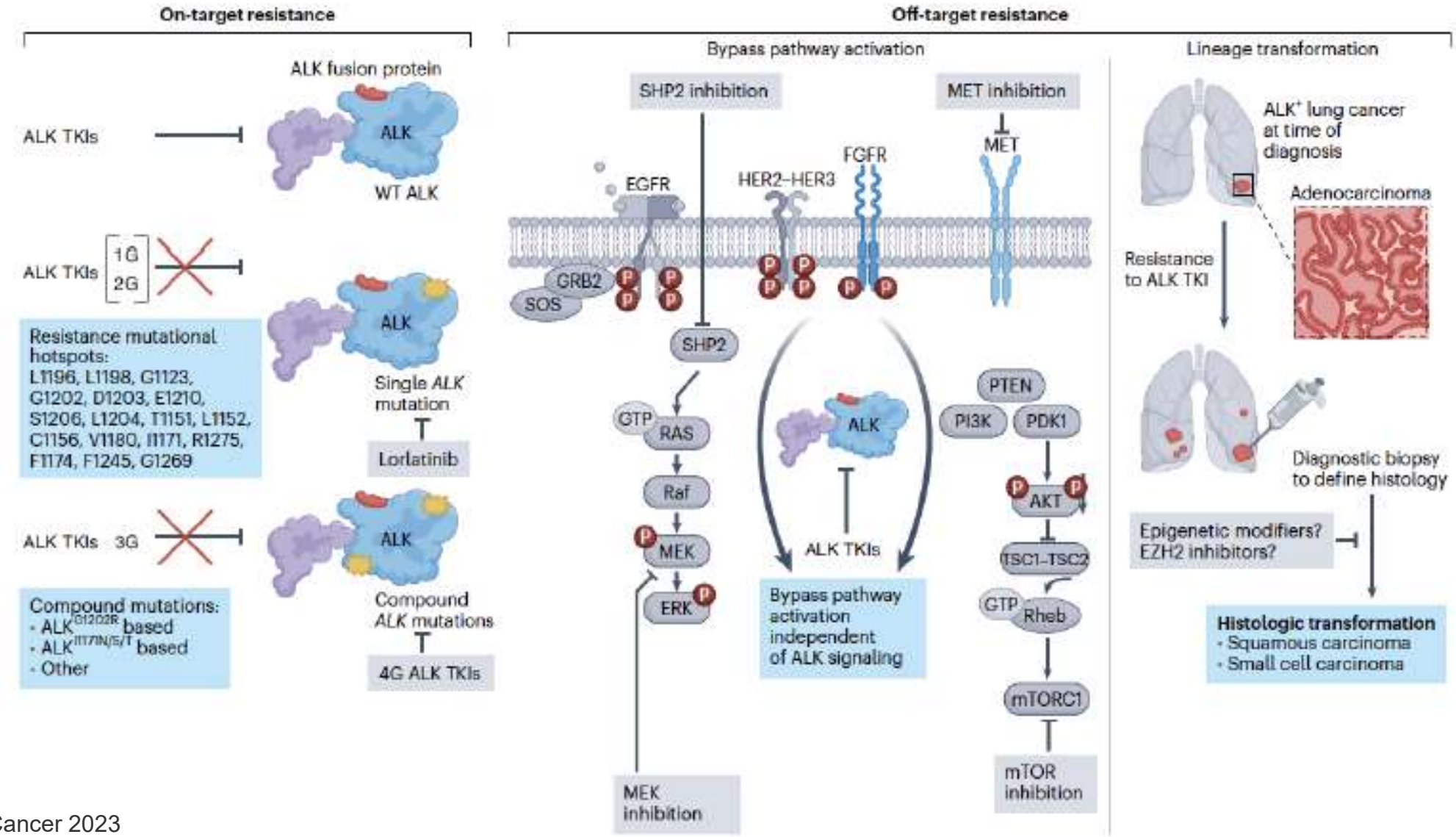
- The prognosis after histologic transformation is poor
- **mOS 9 months, mPFS 2 months**
- No differences according to the treatment

Offin M et al. JTO 2019; Catania C et al ESMO Open 2025

Resistance to ALK inhibitors

Resistance to ALK TKIs

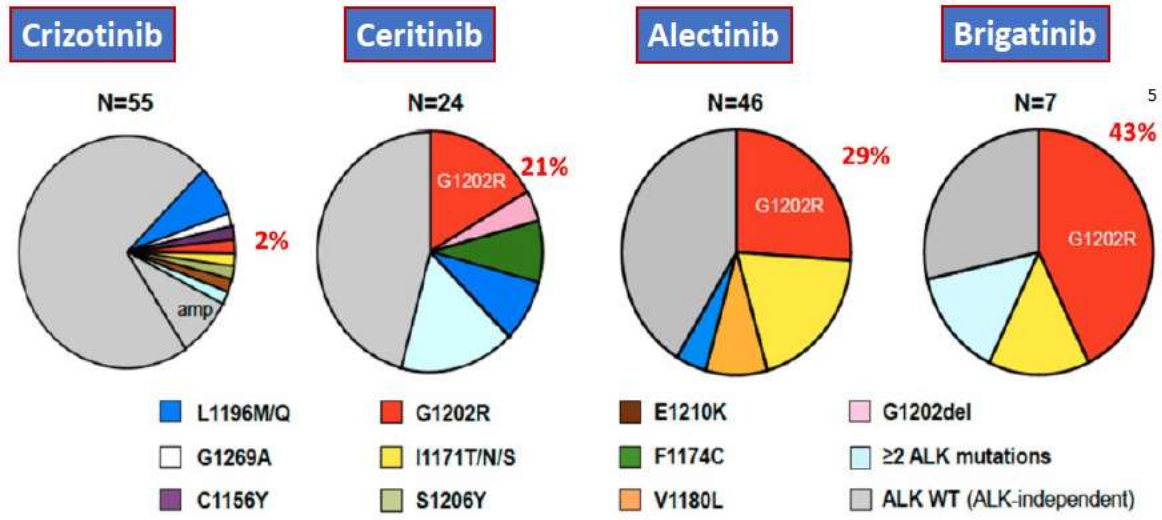
Mechanisms of resistance to ALK TKI therapy



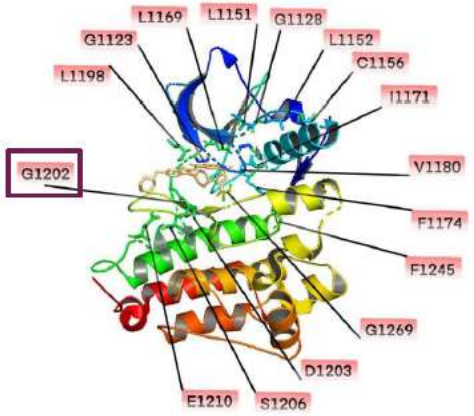
Schneider JL et al. Nat Cancer 2023

Resistance to ALK TKIs

On target Resistance to first and second generation TK



30-40% mutations in the kinase domain



G1202R Primary resistance to alectinib, brigatinib, ceritinib

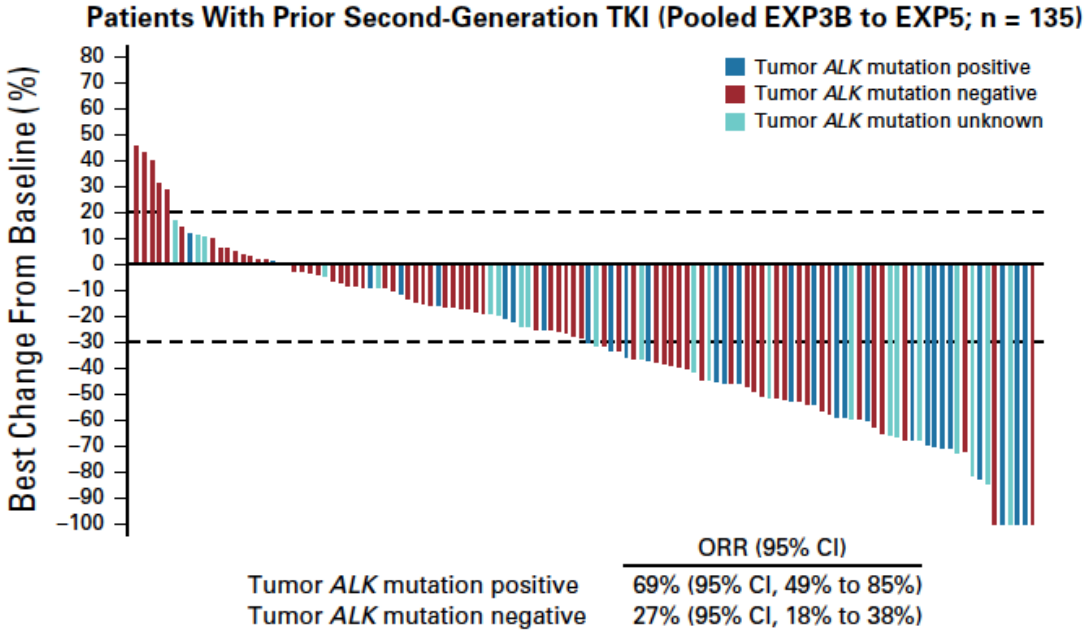
Cellular ALK Phosphorylation Mean IC50 (nM)					
Mutation status	**Crizotinib**	**Ceritinib**	**Alectinib**	**Brigatinib**	**Lorlatinib**
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4-ALK V1	38.6	4.9	11.4	10.7	2.3
EML4-ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4-ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4-ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4-ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4-ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4-ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4-ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4-ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4-ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4-ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4-ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4-ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4-ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4-ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

Gainor JF et al. Cancer Discovery 2016

Resistance to ALK TKIs

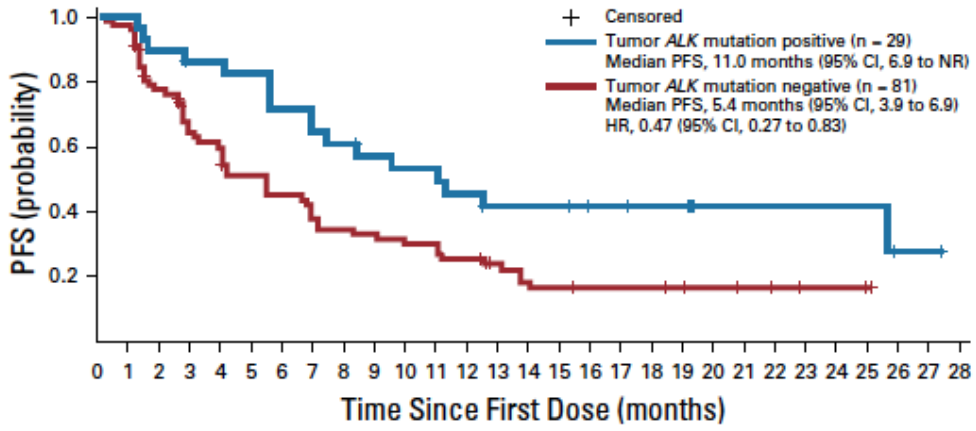
On target Resistance to first and second generation TKIs

Lorlatinib after 2G ALK TKIs (e.g. Alectinib)



	ORR (95% CI)
Tumor *ALK* mutation positive	69% (95% CI, 49% to 85%)
Tumor *ALK* mutation negative	27% (95% CI, 18% to 38%)

Progression-free Survival



No. at risk																											
Tumor *ALK* mutation positive	29	29	26	24	24	23	20	18	17	15	14	14	12	10	10	10	8	8	7	7	3	3	3	3	3	1	1	0
Tumor *ALK* mutation negative	81	76	56	44	37	34	30	25	23	22	20	20	17	13	9	9	8	8	8	7	6	4	3	2	2	1	0	0	0

ORR in 139 pts ≥1 2G ALK TKI: 39.6% (95% CI 31.4-48.2)
Median DOR 9.6 months (95% CI 5.6-16.7)
Median PFS 6.6 months (95% CI 5.4-7.4)

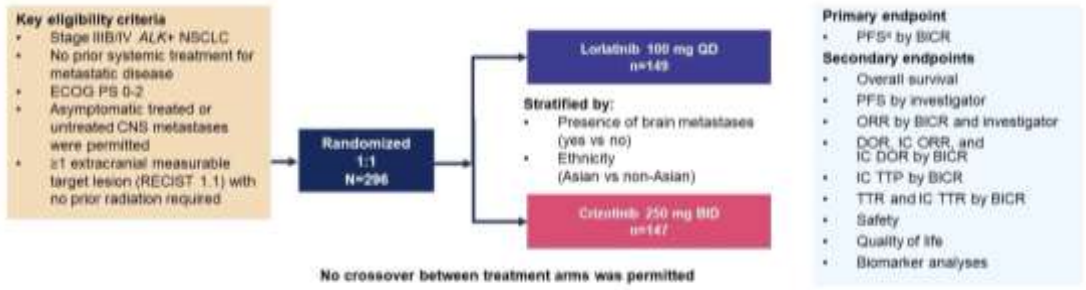
Felip E, et al. Ann Oncol 2001; Shaw AT JCO 2019

Resistance to ALK TKIs

ON target Resistance to first and second generation TKIs

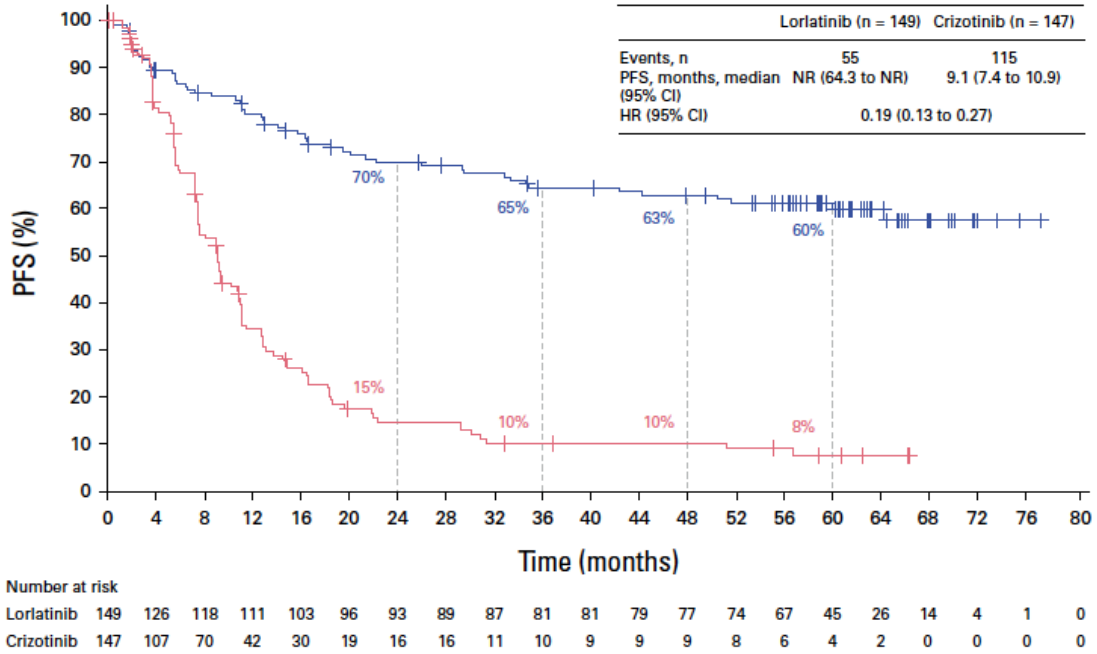
Lorlatinib as fisrt line: CROWN

Study Design



- In a subsequent post hoc analysis, at 3 years of follow-up, median PFS by BICR was still not reached (95% CI, NR-NR) with lorlatinib and 9.3 months (95% CI, 7.6-11.1 months) with crizotinib (HR, 0.27; 95% CI, 0.18-0.39)

Progression-free Survival

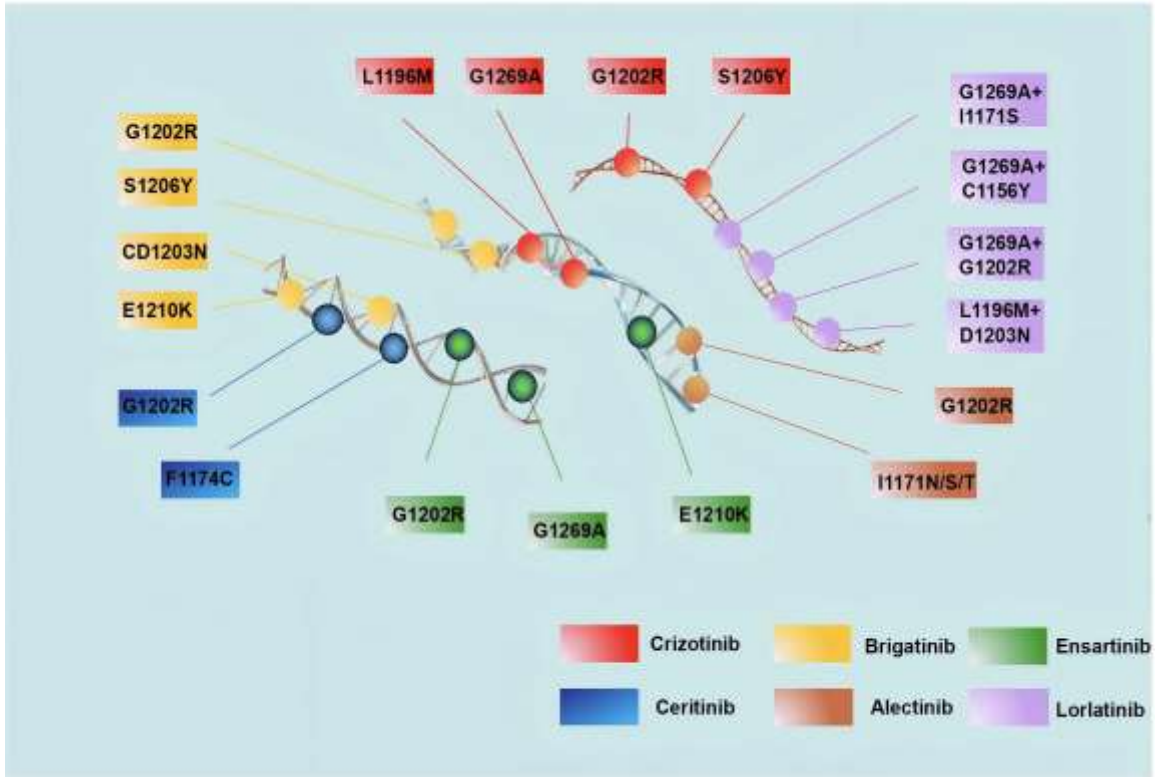


With a median follow-up for PFS of 60.2 and 55.1 months, respectively, median PFS was not reached (NR [95% CI, 64.3 to NR]) with lorlatinib and 9.1 months (95% CI, 7.4 to 10.9) with crizotinib (hazard ratio [HR], 0.19 [95% CI, 0.13 to 0.27])

Shaw AT, et al. NEJM 2002; Salomon BJ JCO 2024

Resistance to ALK TKIs

On target Mechanisms of resistance to Lorlatininb



Resistance mutations associated with therapeutic resistance to different generations of ALK TKI agents

Crizotinib
L1196M
G1202R
L1152R/P
1151Tins
G1269A/S
C1156Y/T
S1206Y
F1174C/L/V
V1180L

1st-generation TKI

Alectinib
V1180L
I1171T/N/S
G1202R
L1196M

CERITINIB
G1202R
F1174C/L/V
L1152P/R
F1174C/L/V

2nd-generation TKI

Lorlatinib
L1198F + C1156Yc
G1269A + G1202R
L1196M/D1203N

3rd-generation TKI

LORLATINIB
New single mutations 0%
ALK compound mutatiions 0%
MAPK pathwat aberration 12%
PI3K/mTOR/PTEN 8%
RTK pathway aberration 8%

3rd-generation TKI

Brigatinib
E1210K + S1206C
E1210K + D1203N
G1202Ra

Lorlatinib is primarily associated with compound resistance mutations.
G1202R+L1196M mutation is currently the most resistant
Loss of neurofibromatosis type 2 (NF2) function and upregulation of miR-100-5p are recognized mechanisms of resistance to Lorlatinib

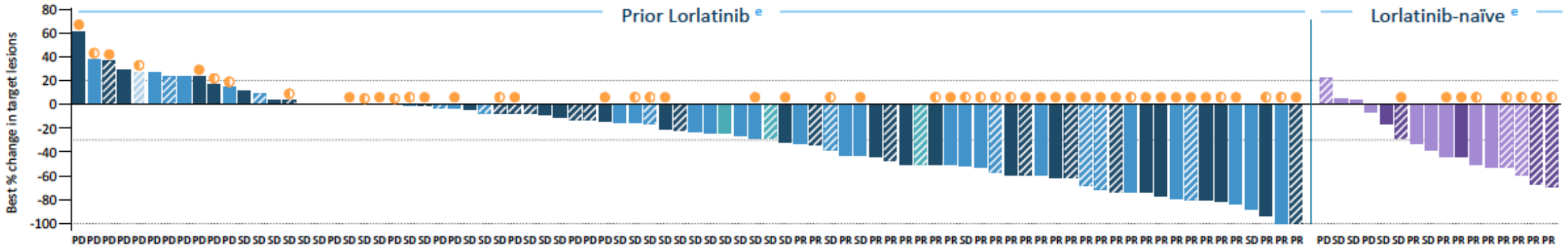
Xie J, et al. Interrnational J General Med 2025

Resistance to ALK TKIs

On target resistance to Lorlatinib

Neladalkib (NVL-655), 4G ALK TKI: Preliminary Efficacy Ph 2 trial (ALKOVe-1)

RECIST 1.1 ORR, % (n/N) *All patients ± chemotherapy*	NSCLC Response-Evaluable (Any Prior ALK TKI, range 1 – 5)			Prior Lorlatinib (≥2 ALK TKIs)			Lorlatinib-naive (≥1 2G ± 1G)	
	All	Any ALK mutation [a]	G1202R [b]	All	Any ALK mutation	Compound ALK mutation [c]	All	Any ALK mutation
All Doses	**38%** (39/103)	**52%** (30/58)	**69%** (22/32) [d]	**35%** (30/85)	**47%** (23/49)	**54%** (15/28)	**53%** (9/17)	**88%** (7/8)
RP2D	**38%** (15/39)	**55%** (12/22)	**71%** (10/14)	**35%** (11/31)	**50%** (8/16)	**64%** (7/11)	**57%** (4/7)	**80%** (4/5)



Data cut-off: 15 June 2024. Response-evaluable patients with NSCLC. All responses were confirmed.

NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; RP2D, Recommended Phase 2 dose (150 mg QD); SD, stable disease; TKI, tyrosine kinase inhibitor.

[a] Includes all patients with ≥1 identified ALK resistance mutation as per local or central testing of blood (ctDNA) or tissue. Responses observed in patients with ALK I1171N/S, V1180L, L1196Q, L1198F, D1203N, or E1210K mutations, including where multiple mutations co-occur, in addition to those with G1202R.

[b] Includes patients with G1202R single and compound (≥2) mutations.

[c] Cis-allelic configuration has not been confirmed for all patients with compound (≥2) ALK resistance mutations.

[d] ORR = 67% (20/30) for G1202R patients with prior lorlatinib, and ORR= 100% (2/2) for lorlatinib-naïve G1202R patients.

[e] Five response-evaluable patients (4 with no known ALK mutations and 1 with single ALK mutation) not shown due to incomplete or missing post-baseline tumor assessments in the setting of PD or symptomatic deterioration.

KEY: PATIENT DETAILS

Lorlatinib Pre-treated:
- ≥ 3 prior ALK TKI
- 2 prior, 2G + lorlatinib
- 2 prior, 1G + lorlatinib
- 1 prior (lorlatinib only)

Lorlatinib-naïve:
- ≥ 2 prior ALK TKIs
- 1 prior, alectinib

Patient treated at RP2D

- ALK single resistance mutation
- ALK compound (≥2) resistance mutation

Drilon A. et al. ESMO 2024

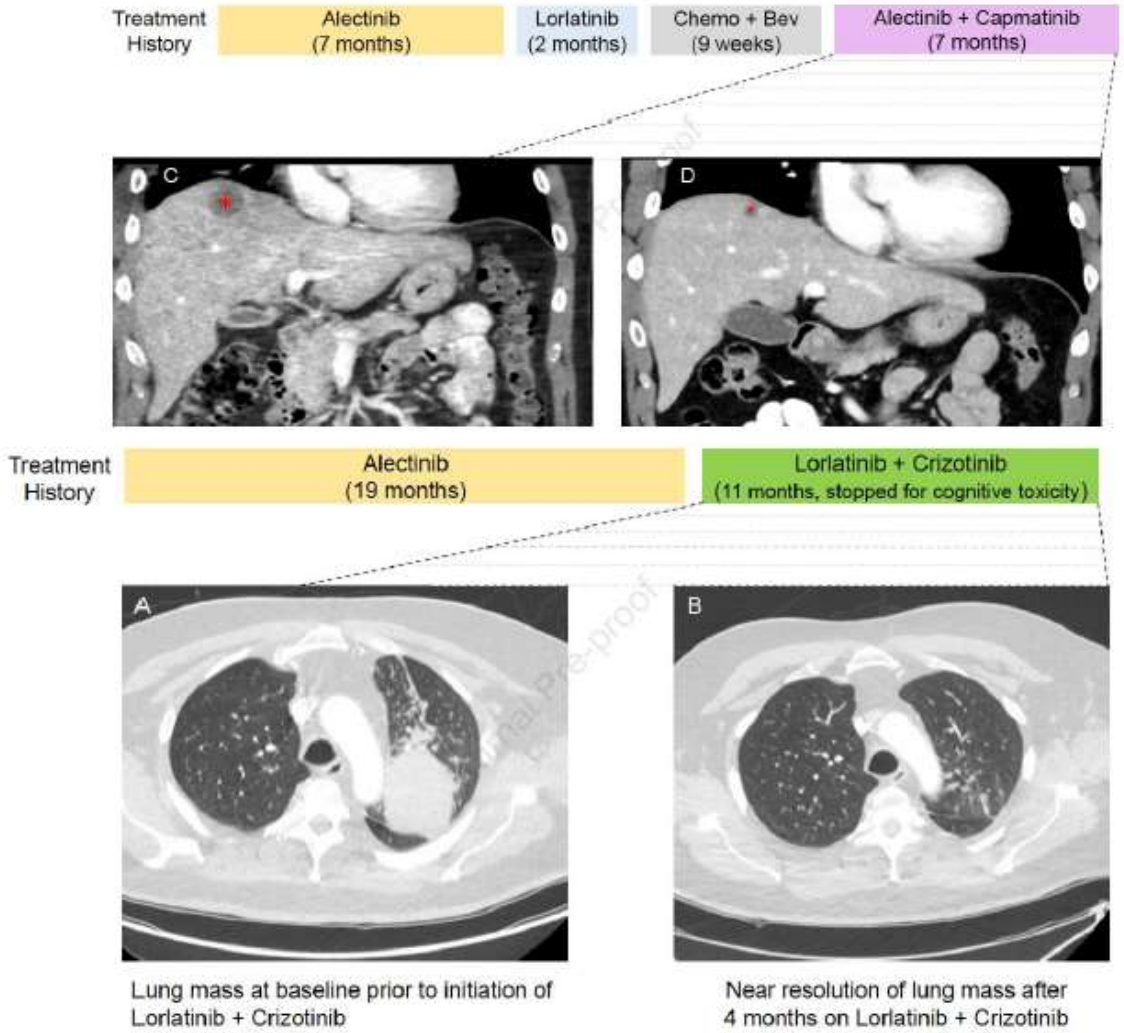
Resistance to ALK TKIs

Bypass Pathways of resistance to ALK TKI

Bypass mechanism	Prior ALK TKI[a]	Prevalence	Refs
MET amplifications	Second-generation TKIs	12% in first or later lines	121
	Lorlatinib	22% in later lines	121
MET rearrangements	Alectinib or lorlatinib	3% in later lines	121
MET exon 14 mutations	Alectinib	Unknown, data limited to case reports	146
RET rearrangements	Brigatinib	Unknown, data limited to case reports	125
EGFR activation	Crizotinib	44% in first line	151
EGFR mutations	Crizotinib	9–14% in first line	152,153
HER2 amplifications	Crizotinib, alectinib	Unknown, data limited to case reports	148,149
KIT amplifications/activation	Crizotinib	15% in first line	151
IGF1R activation	Crizotinib	80% in first line	154
SHP2 signalling	Ceritinib	Preclinical data only	157
NF2 mutations	Lorlatinib	20% in later lines	107
YES1 amplifications	Crizotinib, ceritinib	11.8% in later lines	141
KRAS mutations	Crizotinib	18% in first line	153
BRAF^{V600E} mutations	Alectinib	Unknown, data limited to case reports	147
MAP2K1 mutations	Ceritinib	Unknown, data limited to case reports	150
DUSP6 loss	Crizotinib	83%	166
PIK3CA mutations	Lorlatinib or ceritinib	Unknown, data limited to case reports	100,150
AXL overexpression	Earlier-generation TKIs	Preclinical data only	155,156

This table includes selected studies and is not intended to reflect the entirety of clinical and preclinical work on bypass mechanisms in *ALK*-rearranged NSCLC. NSCLC, non-small-cell lung cancer; TKI, tyrosine kinase inhibitor. [a]The ALK TKI received immediately before biopsy sampling is reported here.

ALK TKI + METi Therapy in *MET* amp



Cooper AJ. et al. Nat Rev Clin Oncol 2022; Dagogo-Jack I et al. JTO Clin Res Rep 2023

Resistance to ALK TKIs

On-target resistance and Bypass mechanisms: Antibody Drug Conjugates (ADCs)

Activity of patritumab deruxtecan in NSCLC with non-classical EGFRmut AGAs[1]

Activity of datopotamab deruxtecan in NSCLC with AGAs[2] including EGFR and ALK

Response per BICR	All treated patients (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
Median DOR (95% CI), months	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)
DCR confirmed, n (%) [95% CI][a]	108 (78.8) [71.0-85.3]	64 (82.1) [71.7-89.8]	25 (73.5) [55.6-87.1]
Median PFS, (95% CI), months[b]	5.4 (4.7-7.0)	5.8 (5.4-8.3)	4.3 (2.6-6.9)

- **Patritumab deruxtecan** (anti-HER3 ADC)1 & **datopotamab deruxtecan** (anti-TROP2 ADC)2 have shown signals of activity in patients with ALK+ NSCLC
- Clinical activity of ADCs across AGA subsets appears irrespective of the spectrum of known or unknown resistance mechanisms

Steuer C. et al. ASCO 2022; Paz-Ares L et al ESMO 2023; Ha et al. WCLC 2023

Resistance to other targeted therapies

Resistance to ROS1 TKIs in NSCLC

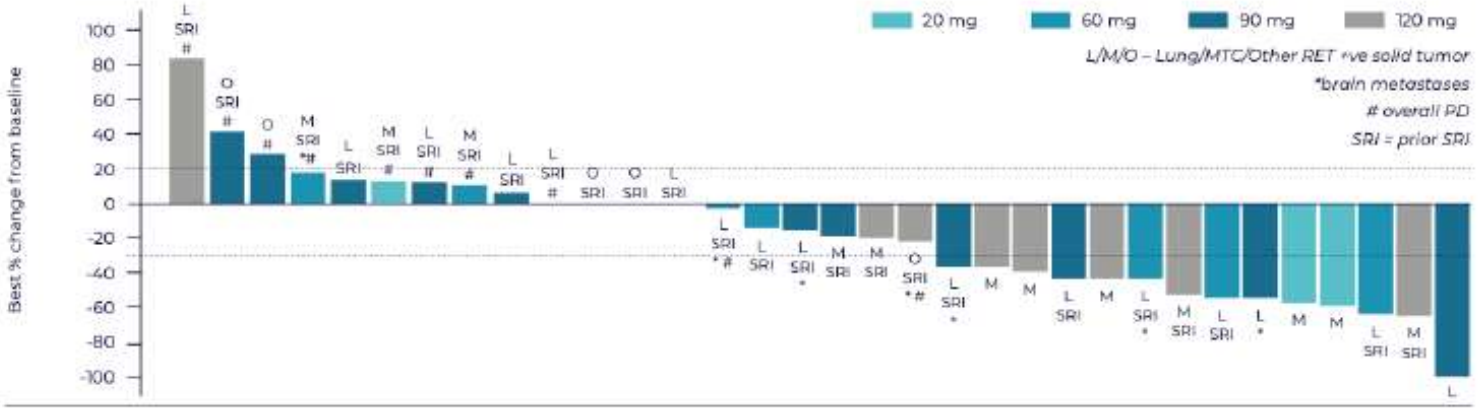
New generation ROS1 TKIs

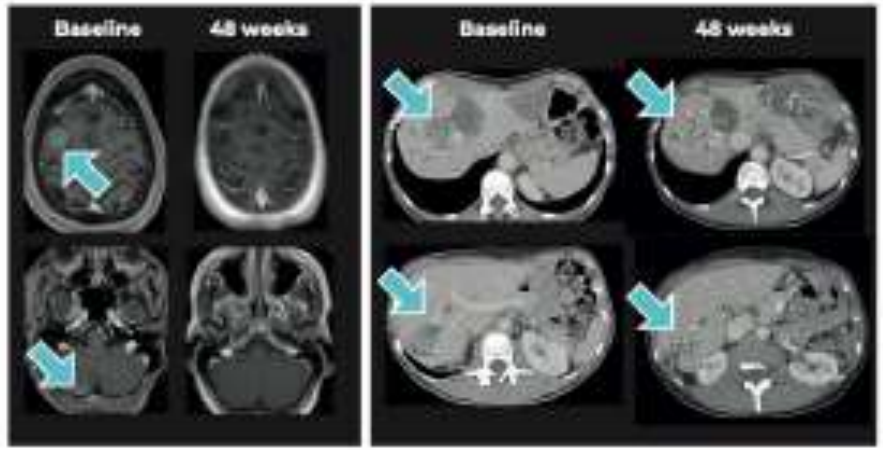
	Lorlatinib (Phase 1/2)	Repotrectinib (TRIDENT-1 Phase 1/2)	Taletrectinib (TRUST China Phase 2)	NVL-520 (ARROS-1 Phase 1)
Patients	N=40	N=56	N=38	N=21
ORR	**35%** **(prior crizotinib)**	**38%** **(only 1 prior ROS1 TKI and no prior chemo)*** *FDA breakthrough therapy designation	**50%** **(prior crizotinib)*** *FDA breakthrough therapy designation	**48%** • **53% (9/17) with ≥2 prior ROS1 TKI, ≥1 chemo** • **50% (9/18) with prior lorlatinib or repotrectinib**
Median PFS	**8.5 months**	**9.0 months**	**9.8 months**	**Not reported**
CNS activity	12/24 (50%) with measurable or nonmeasurable CNS disease	5/13 (38%) with measurable CNS metastases	11/12 (92%) with measurable CNS metastases (TKI-naïve & crizotinib-pretreated)	CNS responses reported
Clinical ROS1 G2032R activity	Response in 0/6 **(0%)** patients with a baseline ROS1 G2032R in plasma	Responses in 10/17 (**59%**) patients with a baseline ROS1 G2032R	Responses in 4/5 (**80%**) patients with a baseline ROS1 G2032R	Responses in 7/9 (**78%**) patients with a baseline ROS1 G2032R
Most common TRAEs or TEAEs (all grades)	Hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy, cognitive/mood effects, weight increased	Dizziness, dysgeusia, constipation, paresthesia, dyspnea, anemia, fatigue, nausea, muscular weakness, ataxia	Diarrhea, nausea, vomiting, ALT increase, AST increase, anemia, neutrophil count decrease	No DLTs or treatment-related SAEs or dizziness reported
Reference	Shaw AT et al., Lancet Oncol 2019	Cho BC et al., WCLC 2023	Li W et al., ELCC 2023	Drilon A et al., EORTC-NCI-AACR 2022

Resistance to RET inhibitors in NSCLC

New generation RET inhibitors

EP0031 (A400(KL590586)

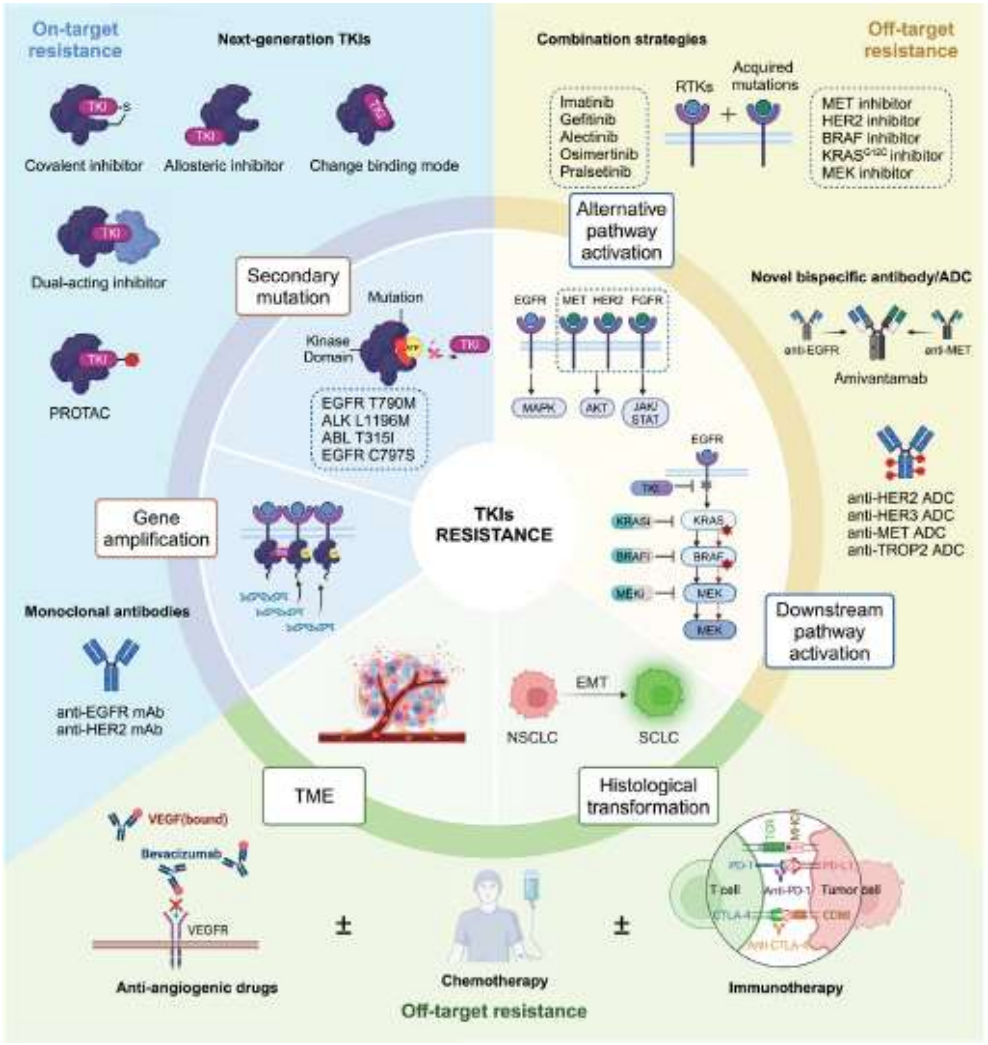




RET+ NSCLC post selective RET inhibitor: RR 36%, DCR 71% including complete CNS response in 3 of 4 patients

Garralda et al. ESMO 2024

Conclusions



- The current SOC 1L therapy for most targeted alterations are TKIs
- Mechanisms of resistance include on-target mutation, bypass pathways, and histological transformation
- Next-generation TKIs can overcome on-target resistance to previous treatments
- Combination therapy is an approach to delay the development of resistance
- After progression to TKIs, chemotherapy with or without immunotherapy remains the standard of care
- New therapies like TILs, CAR-T, cancer vaccines, etc., may be an alternative for these patients

Ou X et al. Medd Comm 2024

16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

THANK YOU

GECP lung cancer research