

Precision Treatment Pathways in NSCLC: Navigating Rare and Actionable Mutations

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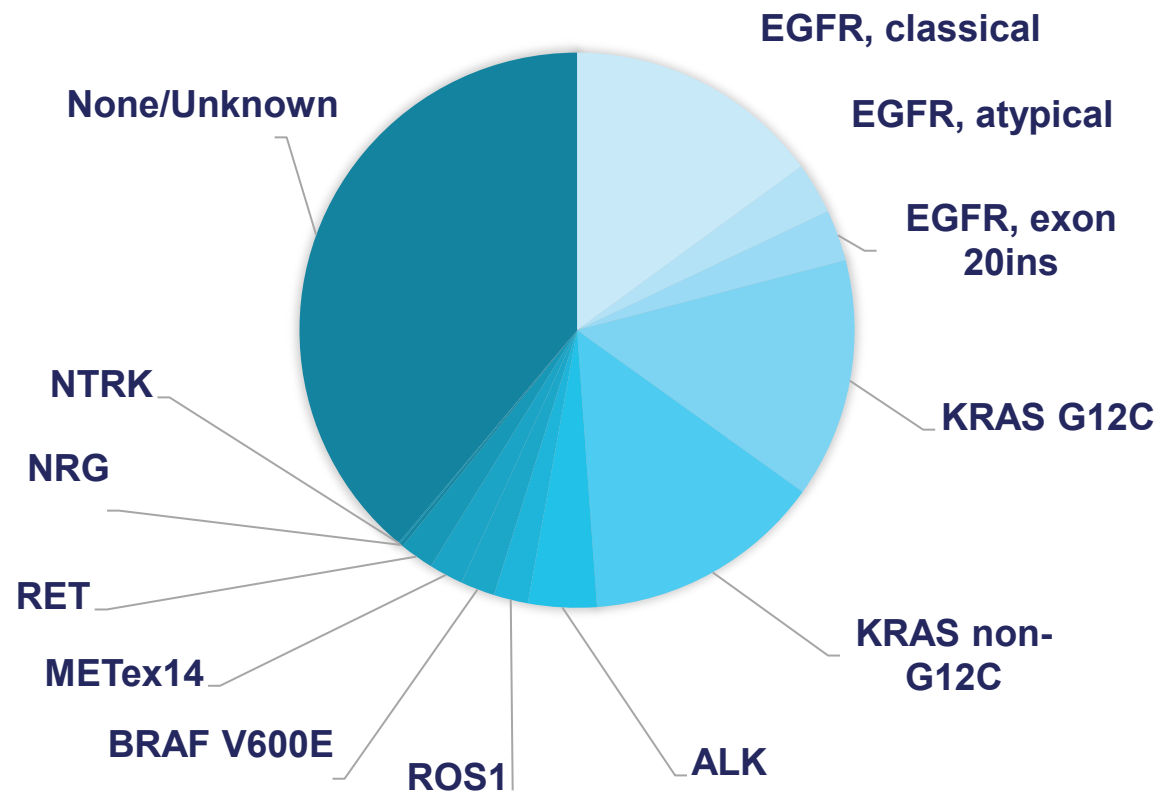
Disclosures

Julia Rotow, MD: Consulting—AbbVie, Amgen, AstraZeneca, BioAtla, BioNTech, Blossom Hill, Bristol Myers Squibb, Boehringer Ingelheim, Caris, Catalyst, Daiichi Sankyo, Genentech, Gilead, G1 Therapeutics, Guardant Health, Johnson & Johnson, Jazz Pharmaceuticals, Merck, Merus, Novocure, Nuvalent, Nuvation Bio, ORIC, Ottimo, Pfizer, Regeneron, Sanofi-Genzyme, Summit Therapeutics, Takeda; honoraria—AstraZeneca, Daiichi Sankyo, Johnson & Johnson, Pfizer; institutional research—AbbVie, Altor Bioscience, AstraZeneca, Bicycle Therapeutics, BioAtla, BioNTech, Black Diamond, Blossom Hill, Blueprint Medicines, Bristol Myers Squibb, Daiichi Sankyo, Duality, Enliven Therapeutics, EpimAb, Immunity Bio, LOXO Oncology, Nuvalent, ORIC Pharmaceuticals, RedCloud Bio, Regeneron Summit, SyntheKine

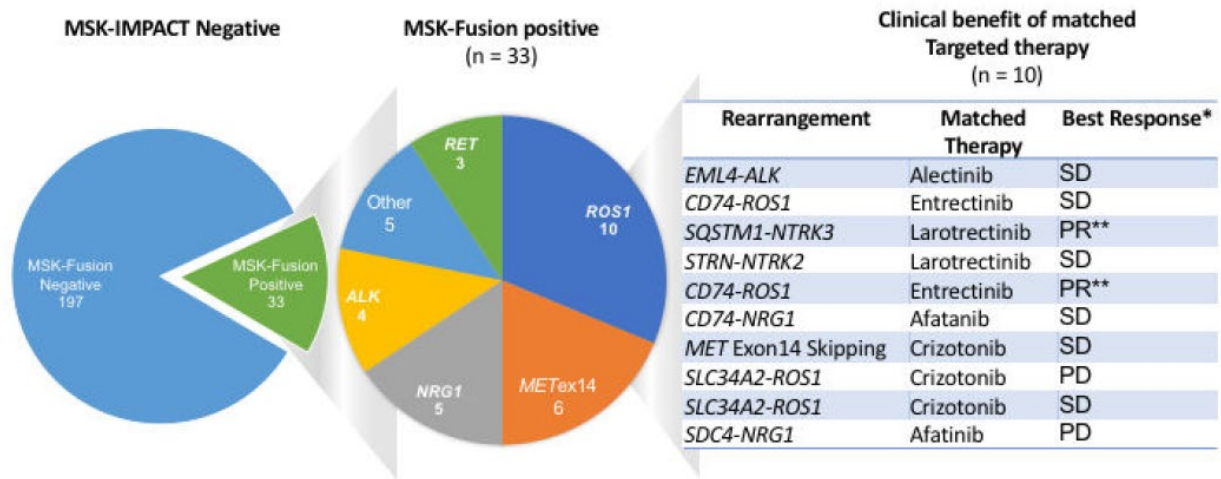
Learning Objectives

- Differentiate the molecular characteristics and clinical implications of rare or unique driver mutations in non-small cell lung cancer (NSCLC), including EGFR exon 20 insertions, ALK alterations, KRAS variants, and RET fusions
- Evaluate current and emerging targeted therapies for rare NSCLC mutations based on efficacy, safety, and patient-specific considerations
- Apply evidence-based sequencing strategies for patients with uncommon oncogenic drivers following progression or intolerance to prior therapy

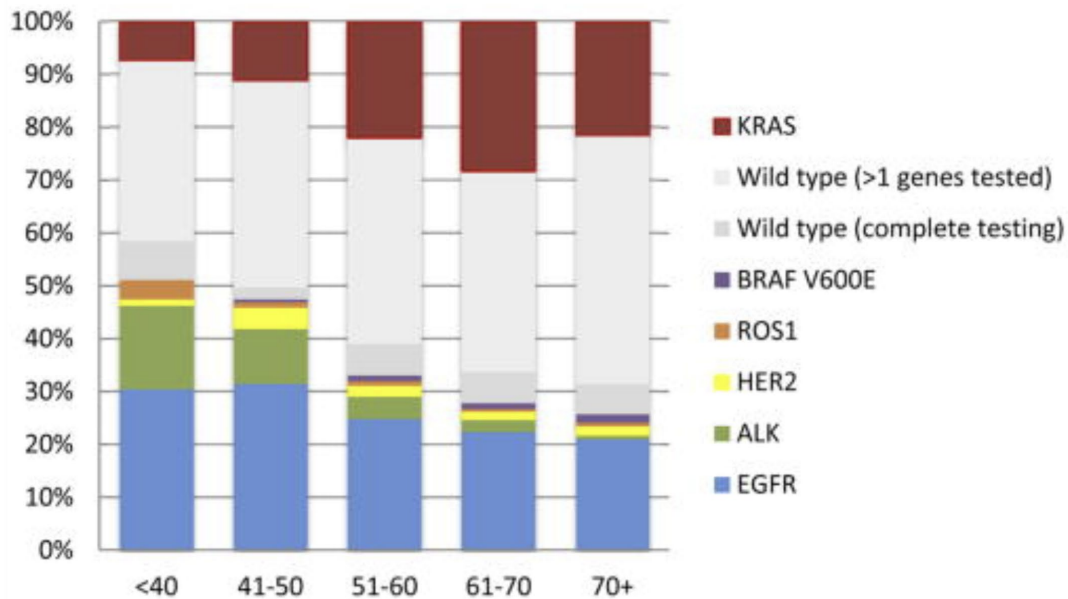
The Rare Oncogenes in NSCLC as a Group Are Common



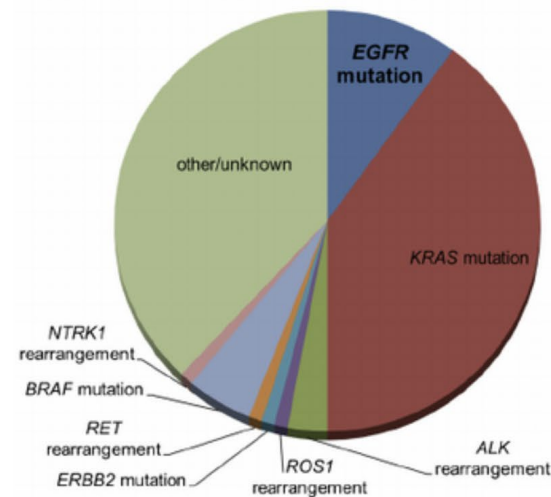
And become more common with optimal biomarker testing (DNA and RNA)



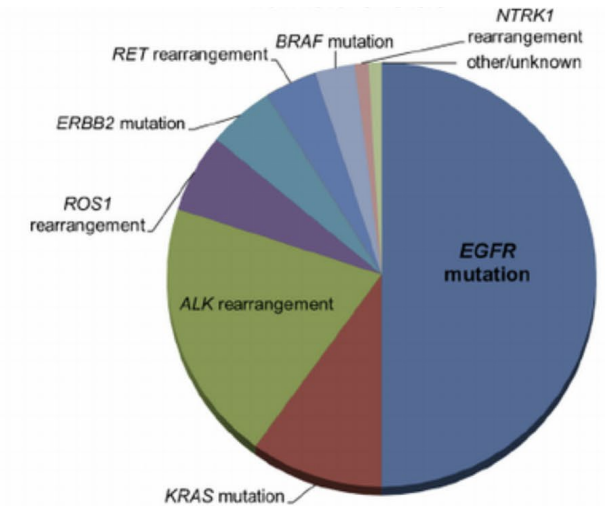
Distinct Profiles by Age and Tobacco Use History



Former or Current Tobacco Use

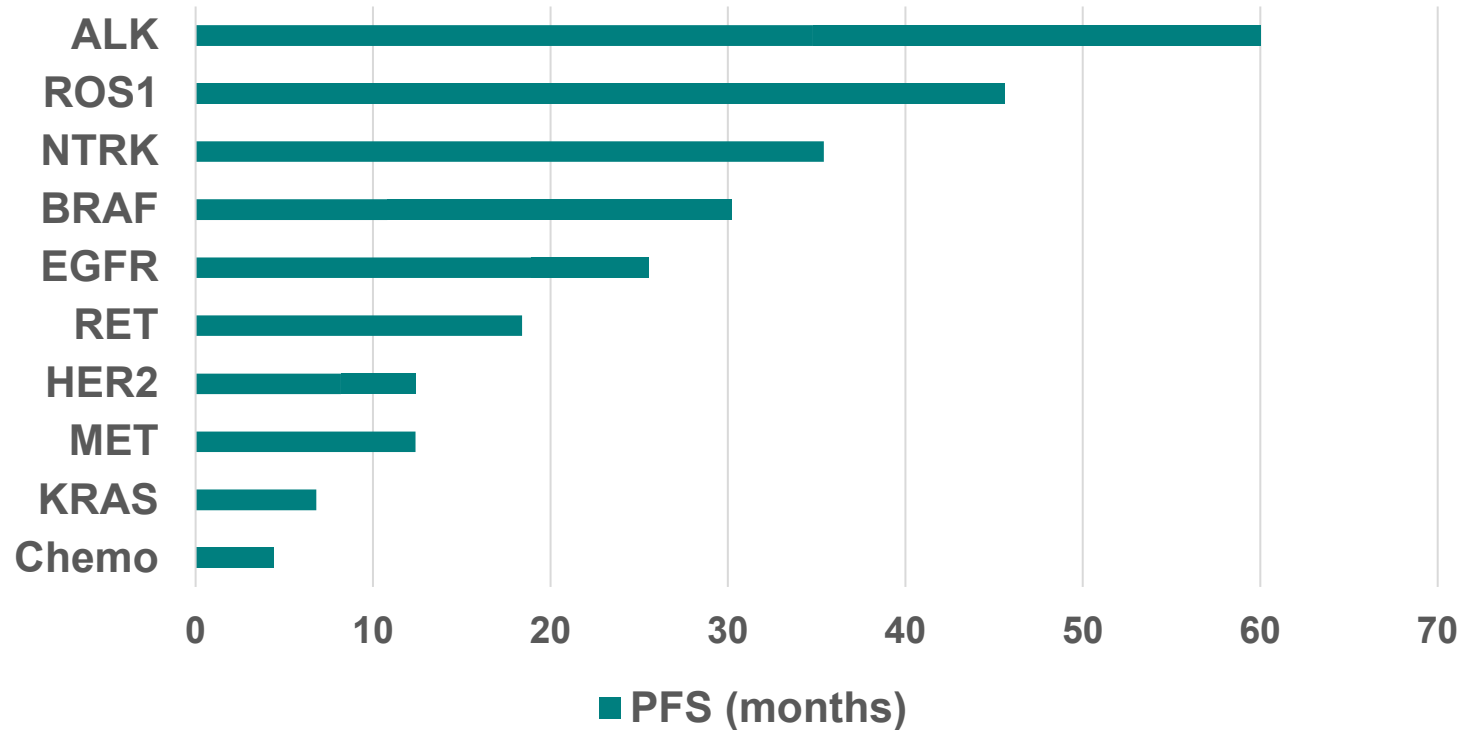


No History Tobacco Use



Camidge DR, Doebele RC. *Nat Rev Clin Oncol*. 2012;9(5):268-77. Sacher AG, et al. *JAMA Oncol*. 2016;2(3):313-320. Jorge SEDC, et al. *Braz J Med Biol Res*. 2014;47(11):929-939.

Significant and Increasing Impact on for Those Patients with Actionable Driver Oncogenes



Covering today

- EGFR uncommon
- EGFR exon 20ins
- KRAS
- ALK
- RET

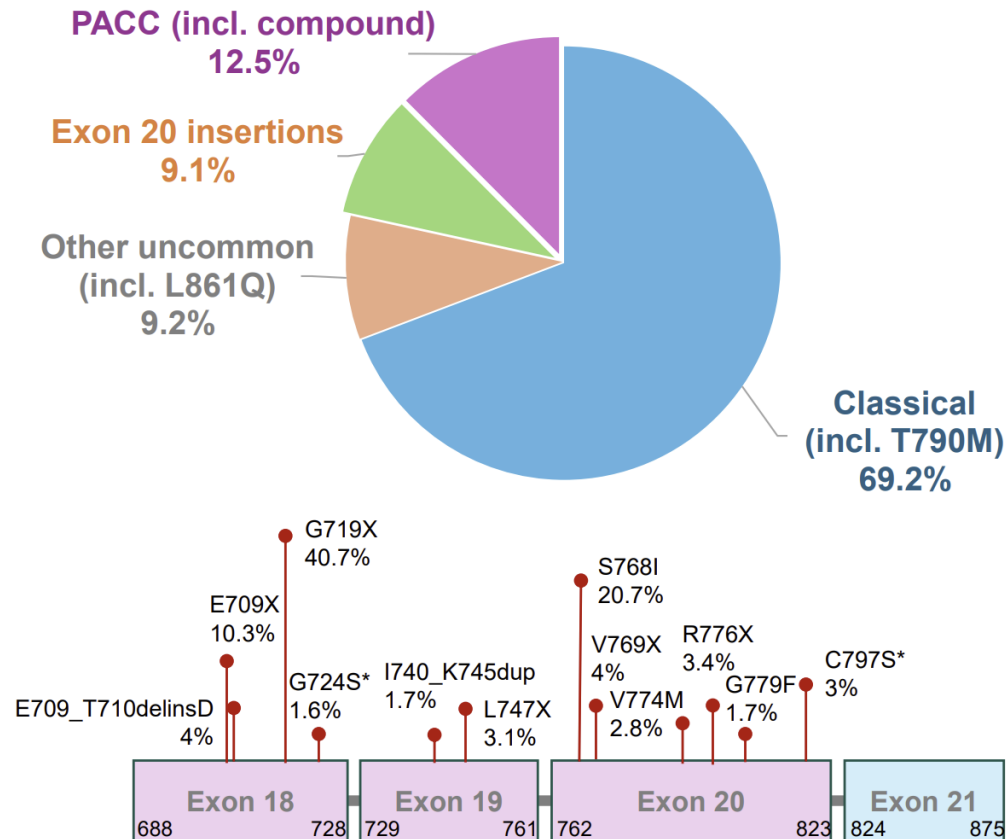
PFS = progression-free survival.

Soria JC, et al. *N Engl J Med.* 2018;378(2):113-125. Wolf J, et al. *J Clin Oncol.* 2021;39(Suppl 15):9020. Mok TSK, et al. *Ann Oncol.* 2020;31(8):1056-1064. Drilon A, et al. *N Engl J Med.* 2020;383(9):813-824. Drilon A, et al. *JTO Clin Res Rep.* 2022;3(6):100332. Planchard D, et al. *J Thorac Oncol.* 2022;17(1):103-115. Drilon A, et al. *J Clin Oncol.* 2023;41(2):385-394. Li F, et al. *Front Oncol.* 2022;12:968517. Skoulidis F. *Clin Cancer Res.* 2021;27(4):913-915. Drilon A, et al. *N Engl J Med.* 2024;390(2):118-131. Riely GJ, et al. *Ann Oncol.* 2024;35(Suppl 2):S1246-S1247. Solomon BJ, et al. *J Clin Oncol.* 2024;42(29):3400-3409. Planchard D, et al. *N Engl J Med.* 2023;389(21):1935-1948.

EGFR Atypical and Exon 20 Insertions



The Spectrum of EGFR Mutations



PACC
Ex G719X

- **Afatinib** alone
- Off-label **Osimertinib +/- chemotherapy**
- Off-label **amivantamab + lazertinib**
- **Clinical trials**

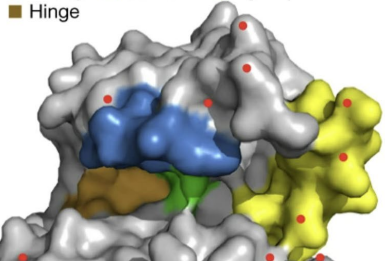
Classical-Like
Ex: L861Q

- Reasonable to use similar strategy to L858R/del19
- Eg, **osimertinib monotherapy or 1L combinations**

1L = first-line.

Le X, et al. Presented at: International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer (WCLC); 2024. Abstract PL04.07. Robichaux JP, et al. *Nature*. 2021;597(7878):732-737. Yang JCH, et al. *Lancet Oncol*. 2015;16(7):830-838. Yang G, et al. *Lung Cancer*. 2020;145:186-194. Bar J, et al. *J Oncol*. 2021;2021:7836264. Cho BC, et al. *J Clin Oncol*. 2024;42(16 Suppl):8516.



Classical-like	Description	Representative mutations	Drug selectivity
	Distal to drug-binding pocket	L858R Ex19dels S720P L861Q/R	Selective
	Modest to no impact on drug binding	S811F K754E T725M L833F/V A763insFQEA A763insLQEA	Intermediate Resistant 3rd gen 2nd gen 1st gen Ex20ins-active
T790M-like	At least one mutation in hydrophobic core	T790M-3S Classical/T790M G719X/T790M L747_K745del insATSPE S768I/T790M	T790M-3S 3rd gen PKCi ALKi 2nd gen 1st gen
	Increased affinity for ATP compared to classical-like mutations		
	Two subgroups: T790M-like-3S T790M-like-3R	T790M-3R Ex19del/T790M/L792H L858R/T790M/L718X Classical/T790M/ C797S	T790M-3R PKCi ALKi 3rd gen 2nd gen 1st gen
Exon 20 loop insertion	C-terminal loop of alphaC-helix	Ex20ins-NL S768dupSVD A767dupASV D770insNPG D770del insGY	Ex20ins-NL Ex20ins-active 2nd gen 1st gen 3rd gen
	Indirect and substantial impact on drug binding (P-loop and alphaC-helix)	Ex20ins-FL H773insNPH H773dupH V774insAV V774insPR	Ex20ins-FL Ex20ins-active 2nd gen 1st gen 3rd gen
	Two subgroups: Ex20ins-near loop Ex20ins- far loop		
P-loop alphaC-helix compressing	Proximal to drug-binding pocket	Primary G719X S768I L747P/S V769L E709_T710 delinsD	2nd gen 1st gen Ex20ins-active
	Direct or indirect impact on drug binding via moderate displacement of P-loop and/or alphaC-helix	Acquired C797S L792H G724S L718X T854I	3rd gen

Using Structure-Based Classification for Uncommon EGFR Mutations to Select Therapy

Classification of uncommon mutations as

- Classical-like → 1st-3rd-gen TKIs
Includes L861Q
- T790M-like → 3rd-gen TKIs
- Exon 20 insertions
- P-loop alphaC helix → 2nd-gen
Includes G719X, S768I

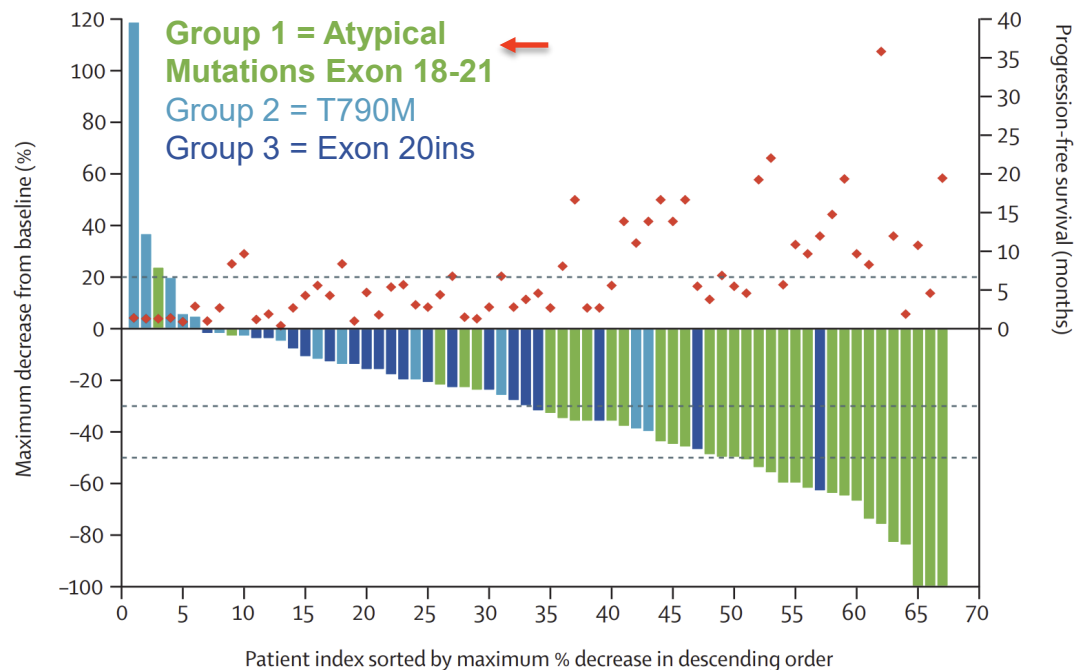
Predict for treatment response by mutation class

TKI = tyrosine kinase inhibitor.
Robichaux JP, et al. *Nature*. 2021;597(7878):732-737

The Uncommon EGFR Mutations— Selecting a First-Line Therapy



Afatinib for the atypical EGFR mutations (FDA-approved)



ORR 71.1%
Median 10.7 months

Osimertinib for the atypical EGFR mutations (UNICORN Study)

Patient Subgroups	n (%)	RR ^a (95% CI)	, mo (95% CI)
Uncommon	44	60 (45-74)	8.6 (7.3-13.5)
G719X	16 (27)	53 (30-75)	8.6 (6.9-NA)
L861Q	11 (18)	78 (45-94)	15.7 (8.9-18.8)

PACC

Classical-Like

FDA = US Food and Drug Administration.
Yang JCH, et al. *Lancet Oncol.* 2015;16(7):830-838. Yang G, et al. *Lung Cancer.* 2020;145:186-194. Bar J, et al. *J Thorac Oncol.* 2023;18(2):169-180.

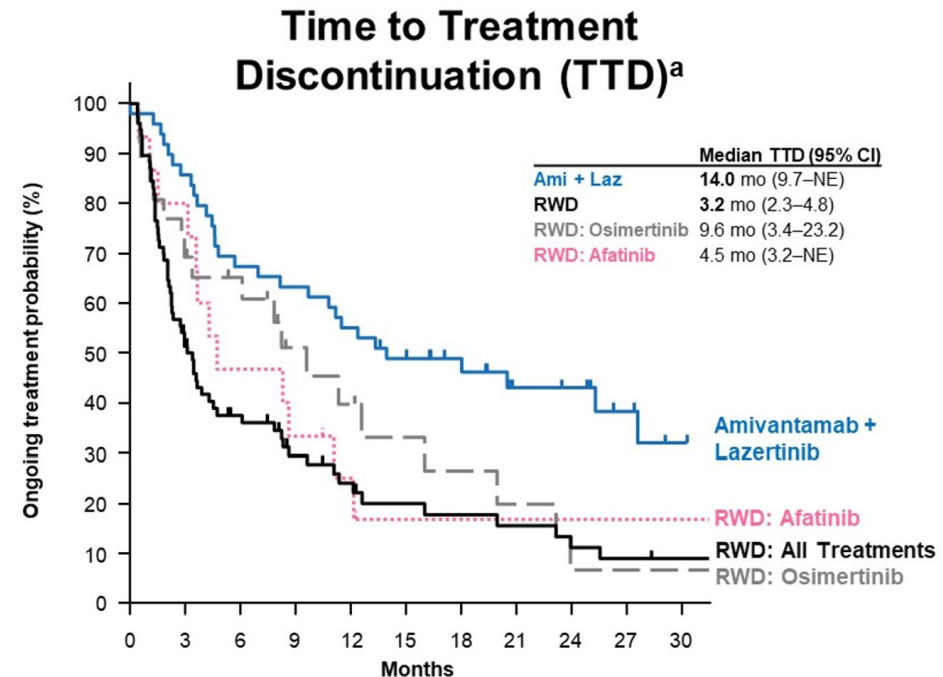
Amivantamab/Lazertinib for Uncommon EGFR Mutations

CHRYSLIS-2 Cohort C: First-Line for Uncommon EGFR mutations

Investigator-assessed response (n=49)	
Median follow-up	17.3 mo (range, 0.1–31.5)
ORR	57% (95% CI, 42–71)
Median DoR	20.7 mo (95% CI, 9.9–NE)
DoR ≥6 mo, n (%) ^a	21 (75)
CBR ^b	84% (95% CI, 70–93)
Median PFS	19.5 mo (95% CI, 11.2–NE)
Median OS	NE (95% CI, 26.3–NE)

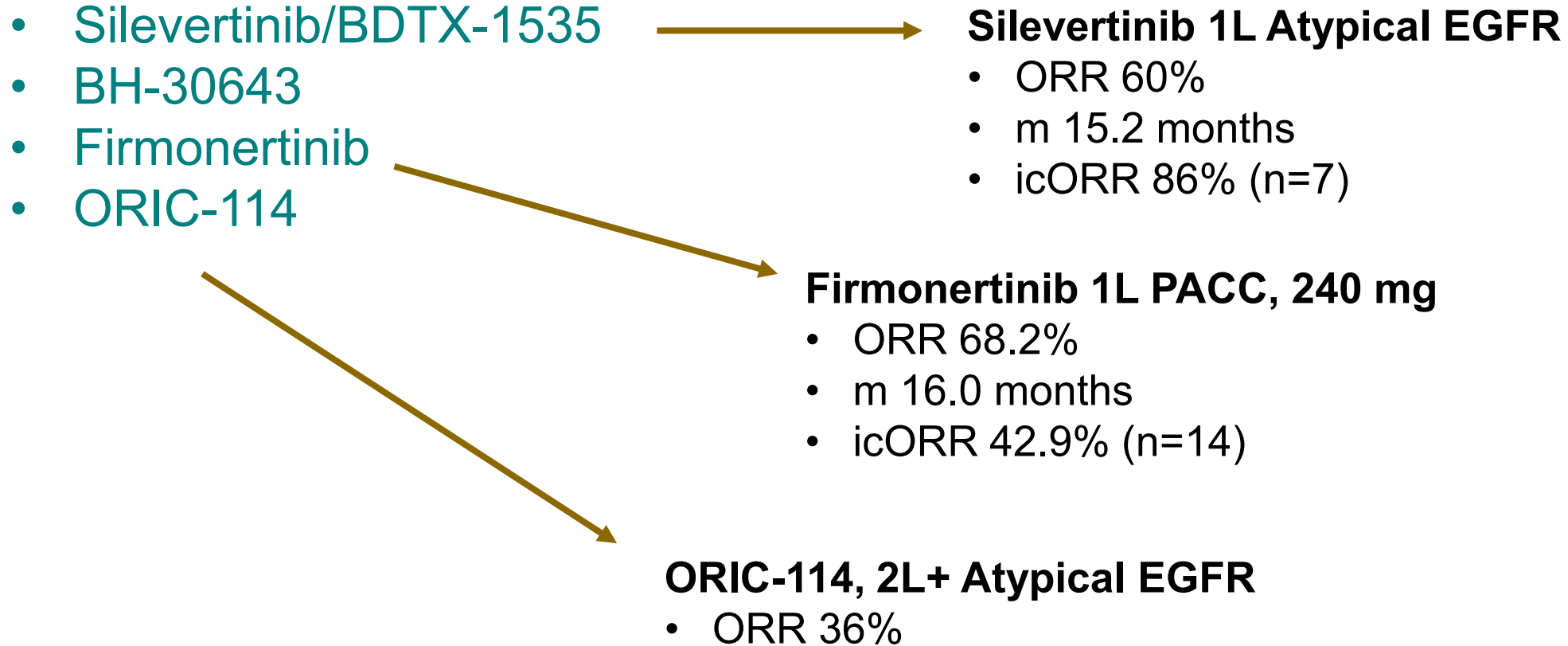
OS 41.0 months (ASCO 2026)

Real-World Data Cohort



ORR = objective response rate; DoR = duration of response; CBR = clinical benefit rate; OS = overall survival; RWD = real-world data; NE = not estimable. Cho BC, et al. *J Clin Oncol*. 2024;42(16 Suppl):8516. Le X, et al. Presented at: IASLC WCLC; 2024. Abstract PL04.07. Tomasini P, et al. *J Clin Oncol*. 2026;44(1):54-65.

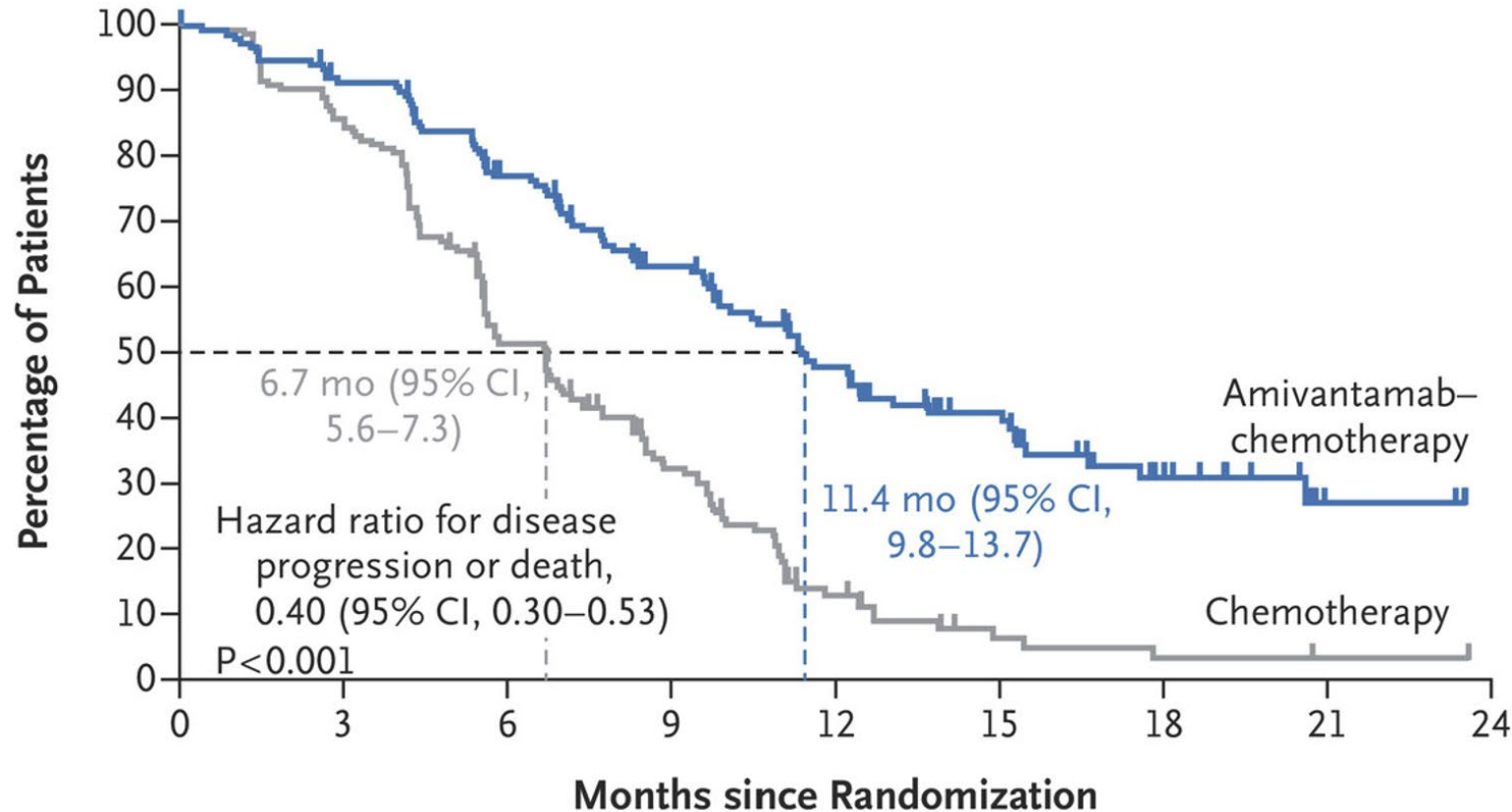
Next-Generation EGFR TKIs for Uncommon Mutations



m = median ; icORR = intracranial ORR.

Rotow JK, et al. *J Clin Oncol*. 2026;44(16 Suppl):8519. Le X, et al. *J Clin Oncol*. 2026;44(Suppl 16):TPS8675. Hong MH, et al. Presented at: European Society for Medical Oncology (ESMO) Asia Congress; 2025.

PAPILLON: Amivantamab + Chemotherapy vs Chemotherapy 1L EGFR Exon 20ins+ NSCLC



11.4 vs 6.7 months
HR 0.40 (0.30-0.53)

ORR 73% vs 47.%

PAPILLON Safety Outcomes

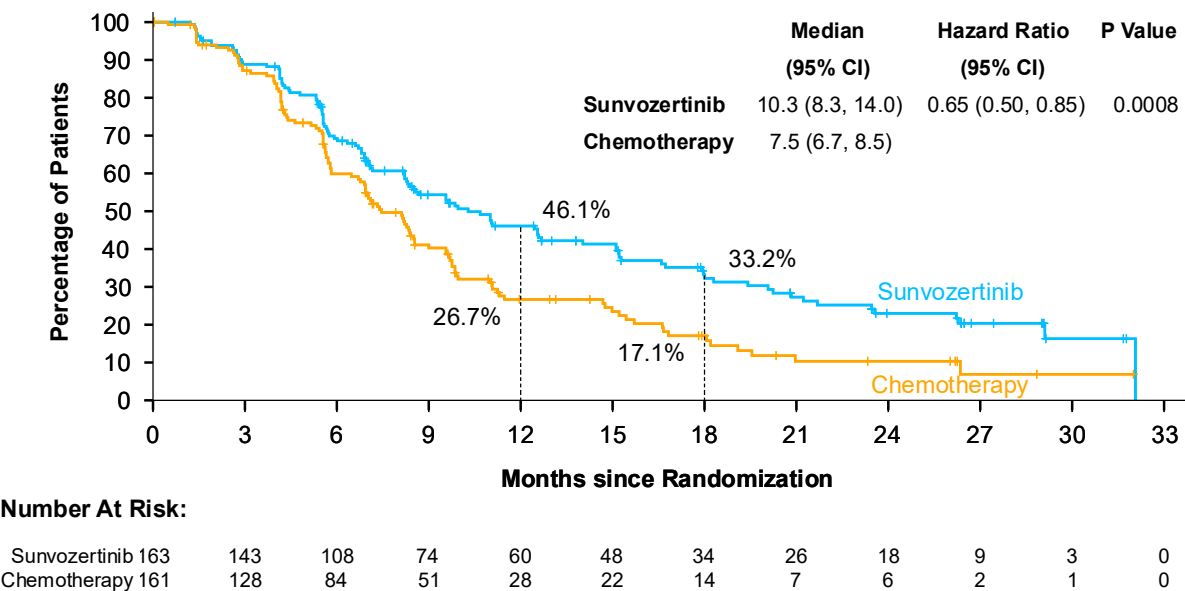
Most common AEs of any cause by preferred term (≥20%), n (%)	Amivantamab-Chemotherapy (n=151)		Chemotherapy (n=155)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition				
Paronychia	85 (56)	10 (7)	0	0
Rash	81 (54)	17 (11)	12 (8)	0
Dermatitis acneiform	47 (31)	6 (4)	5 (3)	0
Stomatitis	38 (25)	2 (1)	9 (6)	0
Diarrhea	31 (21)	5 (3)	20 (13)	2 (1)
Associated with MET inhibition				
Hypoalbuminemia	62 (41)	6 (4)	15 (10)	0
Peripheral edema	45 (30)	2 (1)	16 (10)	0
Other				
Neutropenia	89 (59)	50 (33)	70 (45)	35 (23)
Anemia	76 (50)	16 (11)	85 (55)	19 (12)
Infusion-related reaction	63 (42)	2 (1)	2 (1)	0
Constipation	60 (40)	0	47 (30)	1 (1)
Leukopenia	57 (38)	17 (11)	50 (32)	5 (3)
Nausea	55 (36)	1 (1)	65 (42)	0
Thrombocytopenia	55 (36)	15 (10)	46 (30)	16 (10)
Decreased appetite	54 (36)	4 (3)	43 (28)	2 (1)
Alanine aminotransferase increased	50 (33)	6 (4)	56 (36)	2 (1)
Aspartate aminotransferase increased	47 (31)	1 (1)	51 (33)	1 (1)
COVID-19	36 (24)	3 (2)	21 (14)	1 (1)
Hypokalemia	32 (21)	13 (9)	13 (8)	2 (1)
Vomiting	32 (21)	5 (3)	29 (19)	1 (1)

AE = adverse event.

Zhou C, et al. *N Engl J Med*. 2023;398(22):2039-2051.

WU-KONG28: Sunvozertinib vs Platinum/Pemetrexed

(BICR)



m 10.3 vs 7.5 months (HR 0.65)

BICR = blinded independent central review.
Heymach JV, et al. *J Clin Oncol*. 2026;44(17 Suppl):LBA8500.

Response to Treatment

	Sunvozertinib (N=163)	Chemotherapy (N=161)
Best Objective Response Rate, % (95% CI)	68.1 (60.4, 75.2)	35.4 (28.0, 43.3)
Confirmed Objective Response Rate, % (95% CI)	58.9 (50.9, 66.5)	31.1 (24.0, 38.8)
Odds Ratio (95% CI); P value	3.2 (2.0, 5.0); P<0.0001	
Disease Control Rate, % (95% CI)	94.5 (89.8, 97.4)	85.7 (79.3, 90.7)

Common Treatment-Related Adverse Events (≥20%)

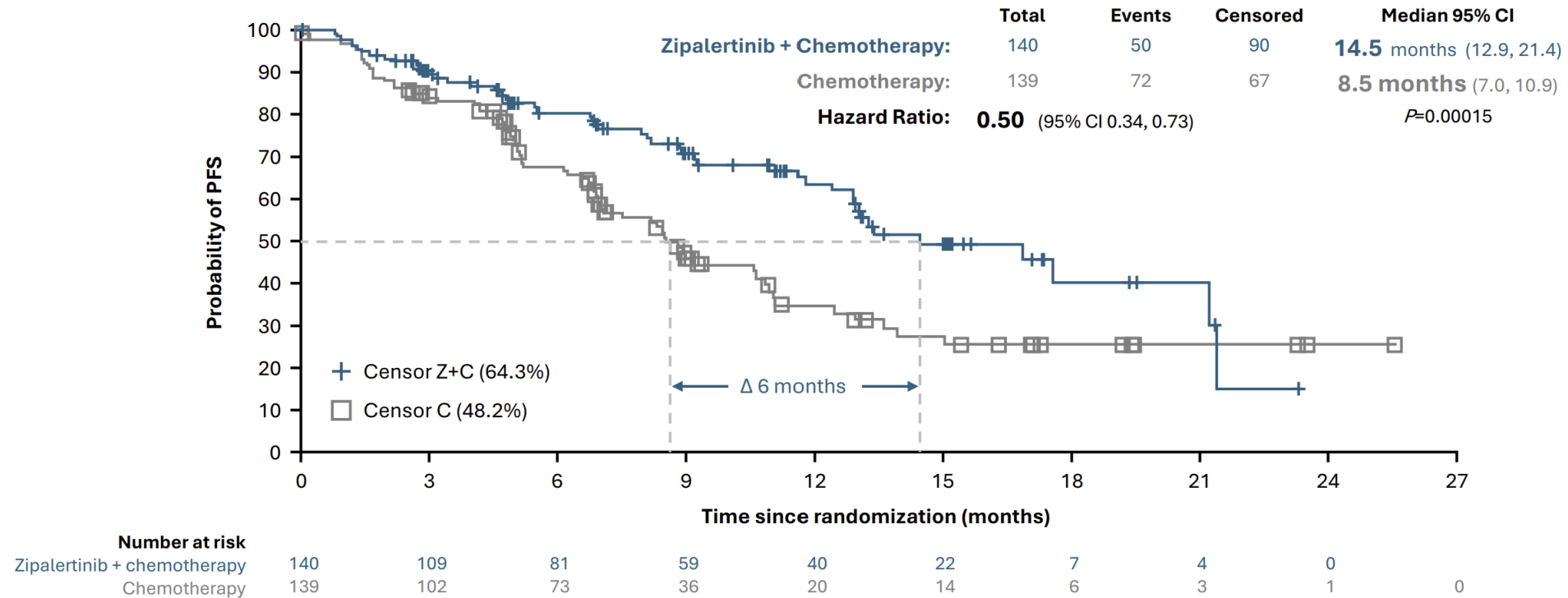
	Sunvozertinib (N=163)		Chemotherapy (N=150)	
	All Grade	≥ Grade 3	All Grade	≥ Grade 3
Participants with Any TRAE	163 (100.0)	100 (61.3)	146 (97.3)	74 (49.3)
Diarrhea	137 (84.0)	22 (13.5)	15 (10.0)	0 (0.0)
Blood creatine phosphokinase increased	90 (55.2)	33 (20.2)	5 (3.3)	1 (0.7)
Rash	84 (51.5)	1 (0.6)	8 (5.3)	0 (0.0)
Paronychia	79 (48.5)	6 (3.7)	0 (0.0)	0 (0.0)
Anemia	75 (46.0)	10 (6.1)	91 (60.7)	15 (10.0)
Weight decreased	56 (34.4)	5 (3.1)	15 (10.0)	1 (0.7)
Decreased appetite	52 (31.9)	1 (0.6)	39 (26.0)	2 (1.3)
Blood creatinine increased	50 (30.7)	1 (0.6)	12 (8.0)	0 (0.0)
Vomiting	40 (24.5)	3 (1.8)	32 (21.3)	3 (2.0)
Nausea	38 (23.3)	3 (1.8)	66 (44.0)	2 (1.3)
Aspartate aminotransferase increased	35 (21.5)	3 (1.8)	52 (34.7)	1 (0.7)
Lipase increased	35 (21.5)	9 (5.5)	8 (5.3)	1 (0.7)
Amylase increased	34 (20.9)	2 (1.2)	11 (7.3)	0 (0.0)
Alanine aminotransferase increased	25 (15.3)	2 (1.2)	50 (33.3)	2 (1.3)
Neutrophil count decreased	22 (13.5)	4 (2.5)	68 (45.3)	28 (18.7)
White blood cell count decreased	20 (12.3)	1 (0.6)	58 (38.7)	10 (6.7)
Platelet count decreased	11 (6.7)	2 (1.2)	32 (21.3)	10 (6.7)
Constipation	4 (2.5)	0 (0.0)	30 (20.0)	0 (0.0)

TRAE = treatment-related adverse event.

Heymach JV, et al. *J Clin Oncol*. 2026;44(17 Suppl):LBA8500.

REZILIENT 3: 1L Zipalertinib + Chemotherapy vs Chemotherapy

(BICR)



m 14.5 vs 8.5 months (HR 0.50)
 ORR 65.0% vs 40.3%

REZILIENT 3: 1L Zipalertinib + Chemotherapy vs Chemotherapy

REZILIENT 3: Safety Summary

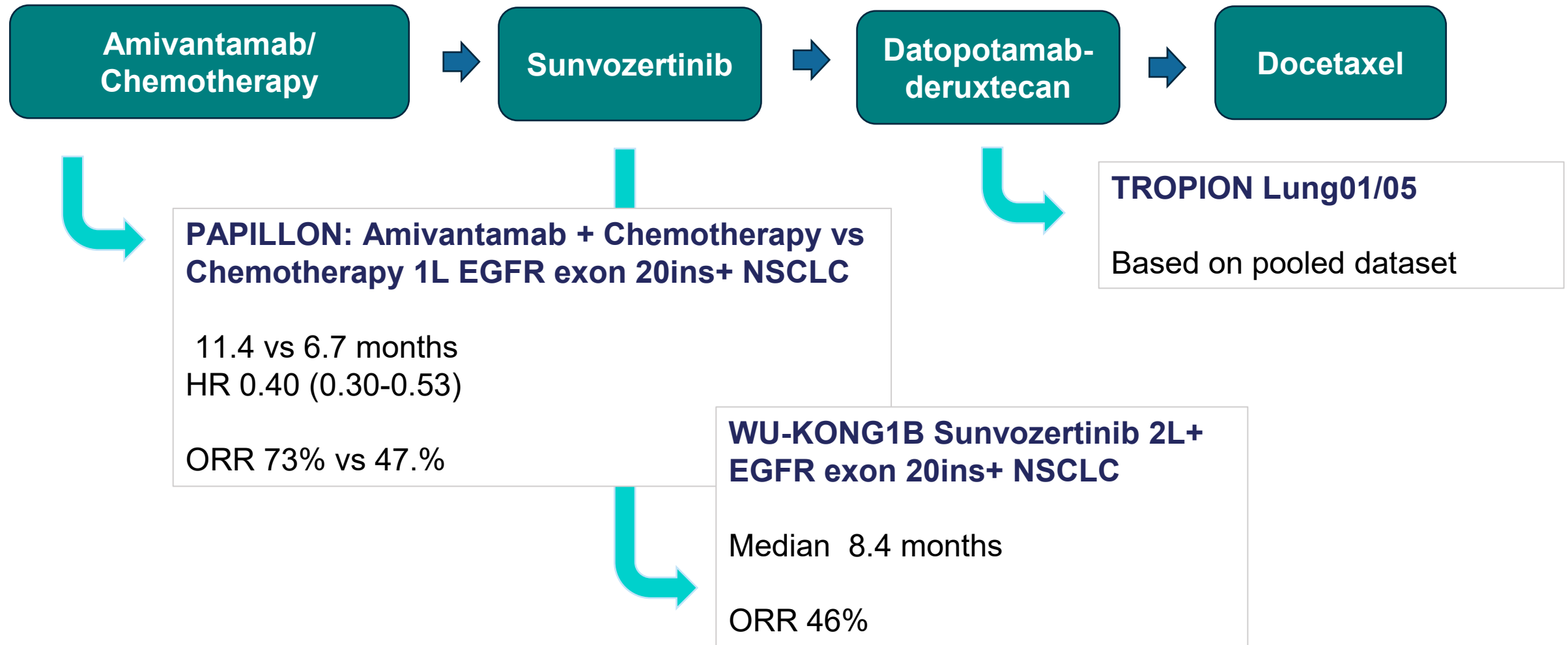
	Zipalertinib + Chemotherapy (n=140), n (%)			Chemotherapy (n=136), n (%)	
Treatment-Related Adverse Events	138 (98.6)			120 (88.2)	
Grade ≥3 treatment-related adverse events	113 (80.7)			55 (40.4)	
Serious Adverse Events	71 (50.7)			45 (33.1)	
Treatment-related serious adverse events	53 (37.9)			17 (12.5)	
	Zipalertinib	Pemetrexed	Carbo/ cisplatin	Pemetrexed	Carbo/ cisplatin
AE Leading to Treatment Interruption	116 (82.9)	104 (74.3)	70 (50)	60 (44.1)	40 (29.4)
AE Leading to Dose Reductions	61 (43.6)	68 (48.6)	46 (32.9)	29 (21.3)	21 (15.4)
AE Leading to Drug Discontinuation ^a	24 (17.1)	44 (31.4)	22 (15.7)	16 (11.8)	7 (5.1)
Adverse Events With Outcome of Death ^b	13 (9.3)			4 (2.9)	
TRAЕ with outcome of death	3 (2.1)			0	
Sepsis/septic shock	3 (2.1)			0	
Chemotherapy Administration					
Platinum choice: Carboplatin/cisplatin	138/4 ^c			123/14 ^c	
Pemetrexed number of cycles (median , range)	7 (1-35)			8 (1-36)	

REZILIENT 3: Summary of Adverse Events

Adverse Event in ≥25% ^a , %	Zipalertinib + Chemotherapy (n=140)		Chemotherapy (n=136)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anemia^a	80.7	48.6	50.0	12.5
Neutropenia^b	50.7	33.6	40.4	22.1
Thrombocytopenia^c	56.4	30.0	19.9	8.1
Rash	45.7	10.7	6.6	0
Nausea	44.3	3.6	41.9	0.7
Constipation	32.1	0	30.9	0
Paronychia	31.4	1.4	0	0
Stomatitis	28.6	5.0	7.4	0.7
Diarrhea	27.1	1.4	8.8	0
Pneumonitis^d	5.7	2.1	2.2	1.5

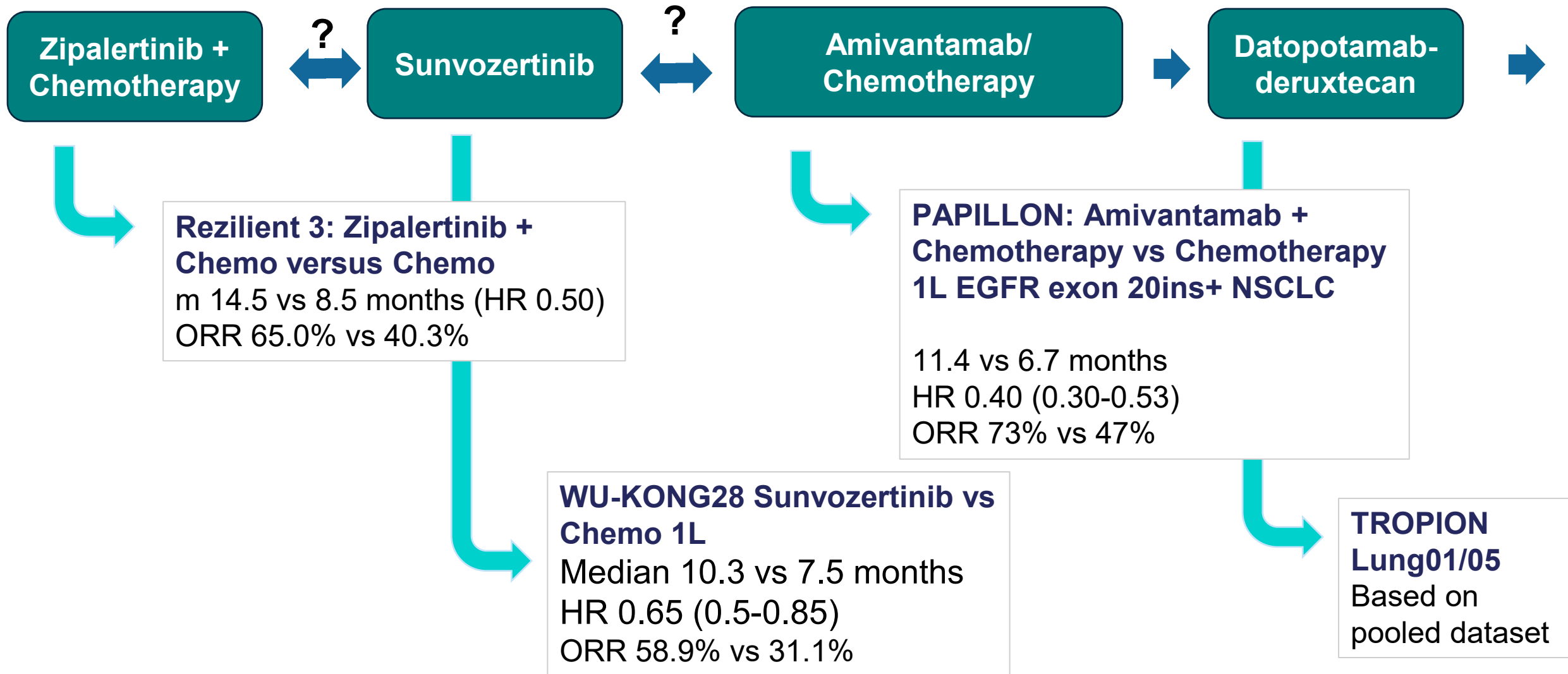
Tan D, et al. Presented at: IASLC WCLC; 2026.
Abstract PL03.04.

Updates for EGFR Exon 20 Insertions



Zhou C, et al. *N Engl J Med*. 2023;398(22):2039-2051. Yang G, et al. *Lung Cancer*. 2020;145:186-194. Ahn MJ, et al. Presented at: ESMO Asia Congress; 2024. Yang JCH, et al. *J Clin Oncol*. 2025;43(29):3198-3208.

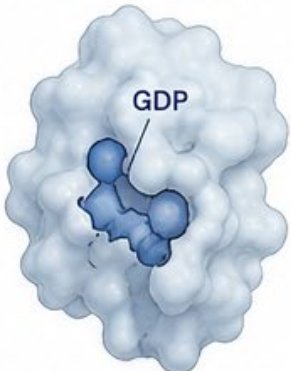
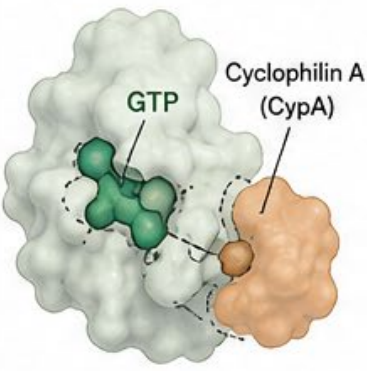
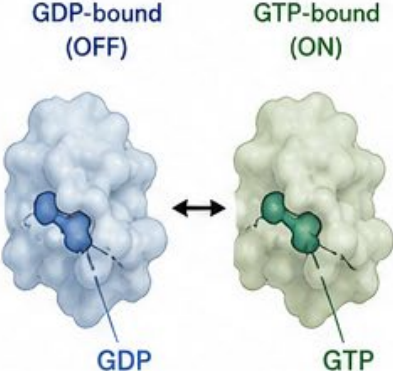
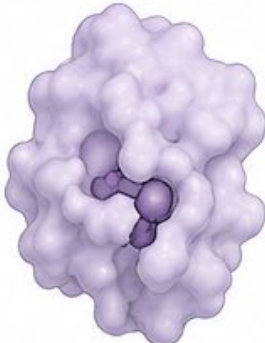
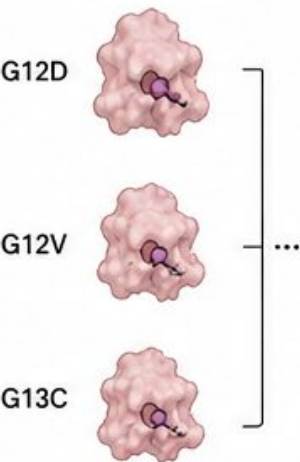
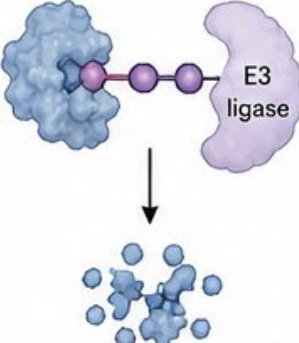
Updates Post-ASCO/WCLC for EGFR Exon 20 Insertions



Zhou C, et al. *N Engl J Med*. 2023;398(22):2039-2051. Yang G, et al. *Lung Cancer*. 2020;145:186-194. Ahn MJ, et al. Presented at: ESMO Asia Congress; 2024. Yang JCH, et al. *J Clin Oncol*. 2025;43(29):3198-3208. Heymach JV, et al. *J Clin Oncol*. 2026;44(17 Suppl):LBA8500.

KRAS

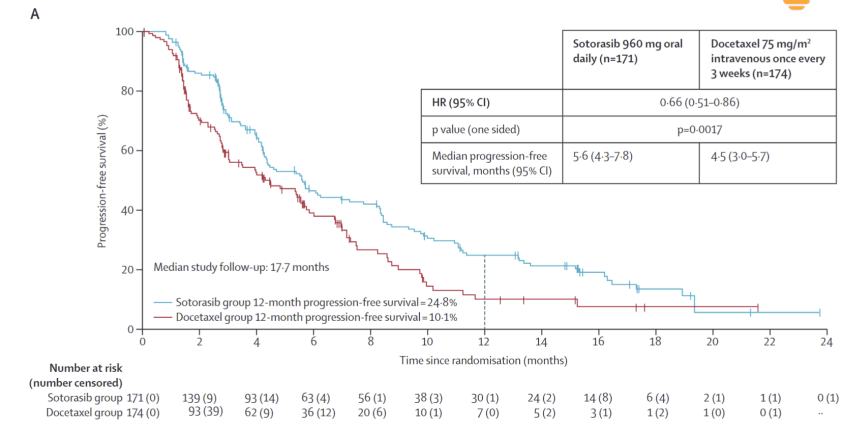
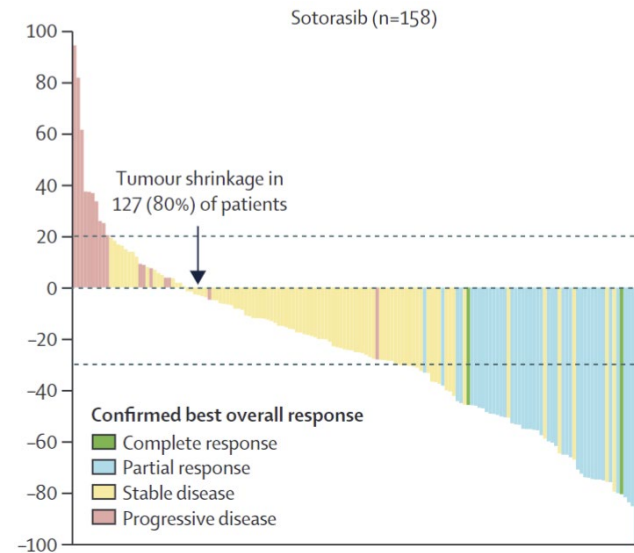
The Spectrum of KRAS Inhibitors

1. OFF-State Inhibitors (G12C Selective)	2. ON-State Inhibitors (Tri-Complex)	3. Dual-State Inhibitors (Non-Tri-Complex)	4. Pan-KRAS / Pan-RAS Inhibitors	5. Mutation-Specific (Non-G12C) Inhibitors	6. KRAS Degraders (PROTAC / Molecular Glue)
Bind inactive GDP-bound KRAS G12C	Bind active GTP-bound KRAS using cyclophilin A (CypA)	Bind KRAS in both GDP and GTP states directly	Inhibit multiple KRAS mutations or RAS isoforms	Selective for specific KRAS mutations	Induce degradation of KRAS protein
 Switch-II pocket	 Tri-complex formation blocks effector binding	 Direct binding to both inactive and active states	 Broad binding across KRAS variants or RAS isoforms	 G12D G12V G13C	 Degrader brings KRAS to E3 ligase → ubiquitination and proteasomal degradation



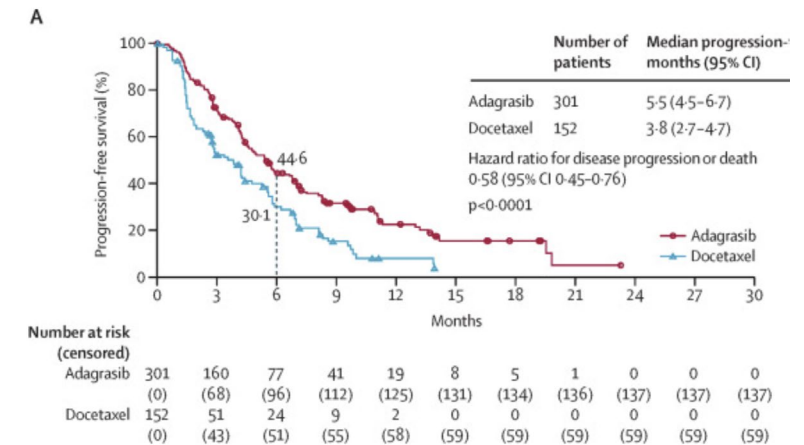
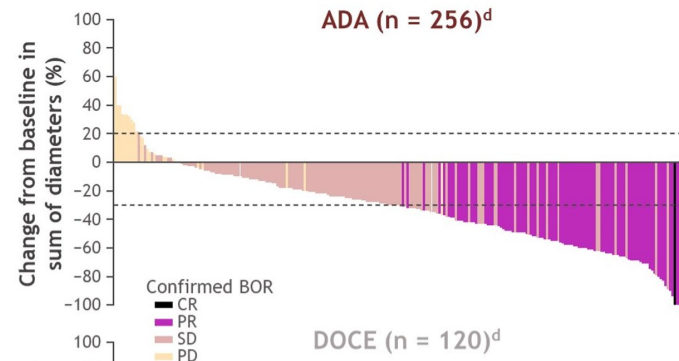
Sotorasib vs Docetaxel: CodeBreakK 200

	Sotorasib	Docetaxel
ORR	28.1%	13.2%
	5.6 months	4.5 months
	HR 0.66 (0.51-0.86)	
OS	10.6 months	11.3 months
	HR 1.01 (0.77-1.33)	



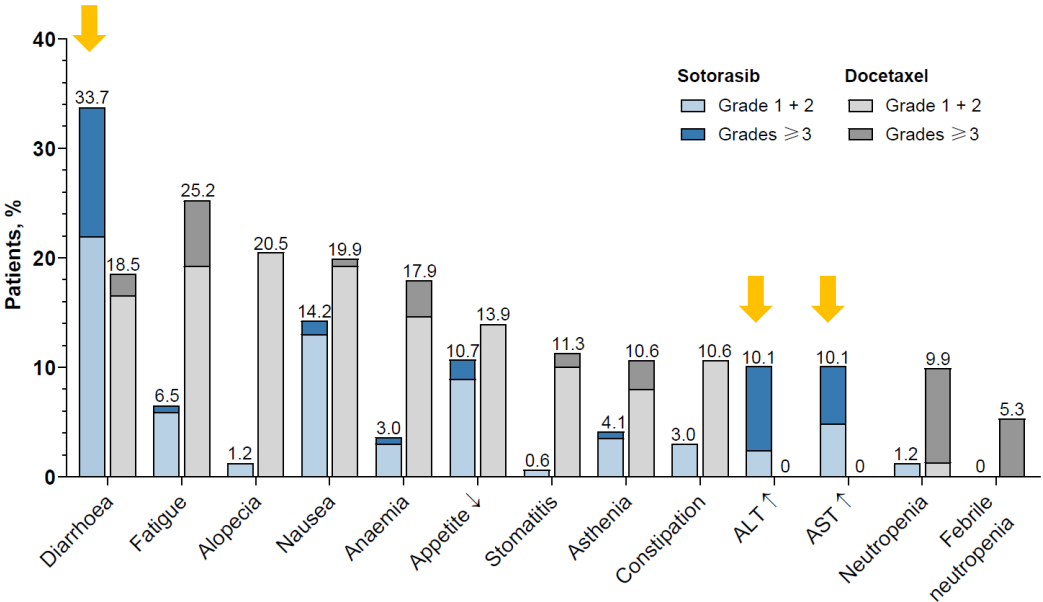
Adagrasib vs Docetaxel: KRYSTAL-12

	Adagrasib	Docetaxel
ORR	32%	9%
	5.5 months	3.8 months
	HR 0.58 (0.45-0.76)	

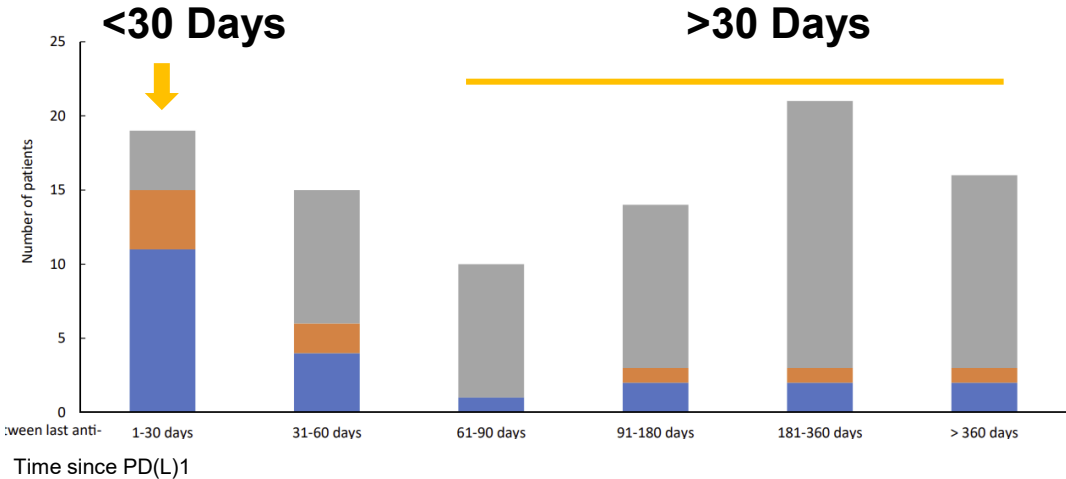


CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.
De Langen AJ, et al. *Lancet*. 2023;401(10378):733-746. Mok TSK, et al. *J Clin Oncol*. 2024;42(Suppl 17):LBA8509.
Barlesi F, et al. *Lancet*. 2025;406(10503):615-626.

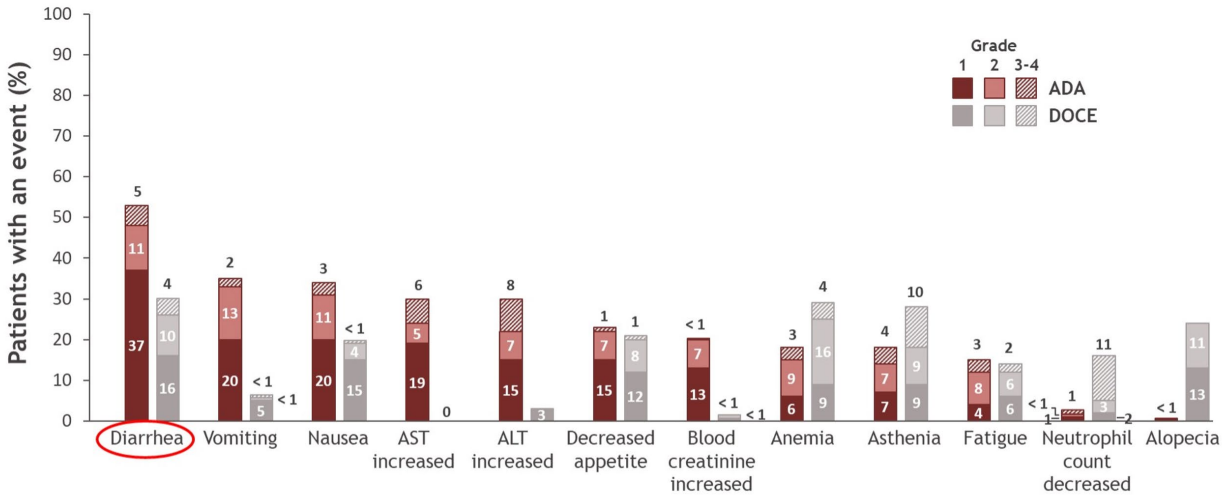
Sotorasib vs Docetaxel: CodeBreakK 200, TRAEs



Greater Rates of Hepatotoxicity with Prior ICI in Retrospective Series



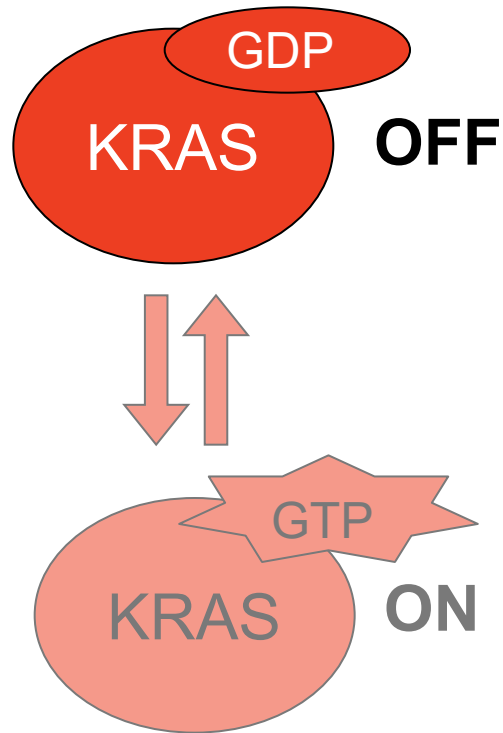
Adagrasib vs Docetaxel: KRYSTAL-12, TRAEs



	Adagrasib	Docetaxel	Sotorasib	Docteaxel
D/c Rate	8%	14%	10%	11%
Dose Reduc. Rate	48%	24%	15%	27%

ICI = immune checkpoint inhibitor; AST = aspartate transaminase; ALT = alanine transaminase; d/c = discontinuation.
Mok TSK, et al. *J Clin Oncol.* 2024;42(Suppl 17):LBA8509. Johnson ML, et al. Presented at: ESMO Congress; 2022. Abstract LBA10.

Emerging G12C Drugs—KRAS(OFF) Inhibitors



FDA-Approved, Previously-Treated KRAS G12Cm NSCLC

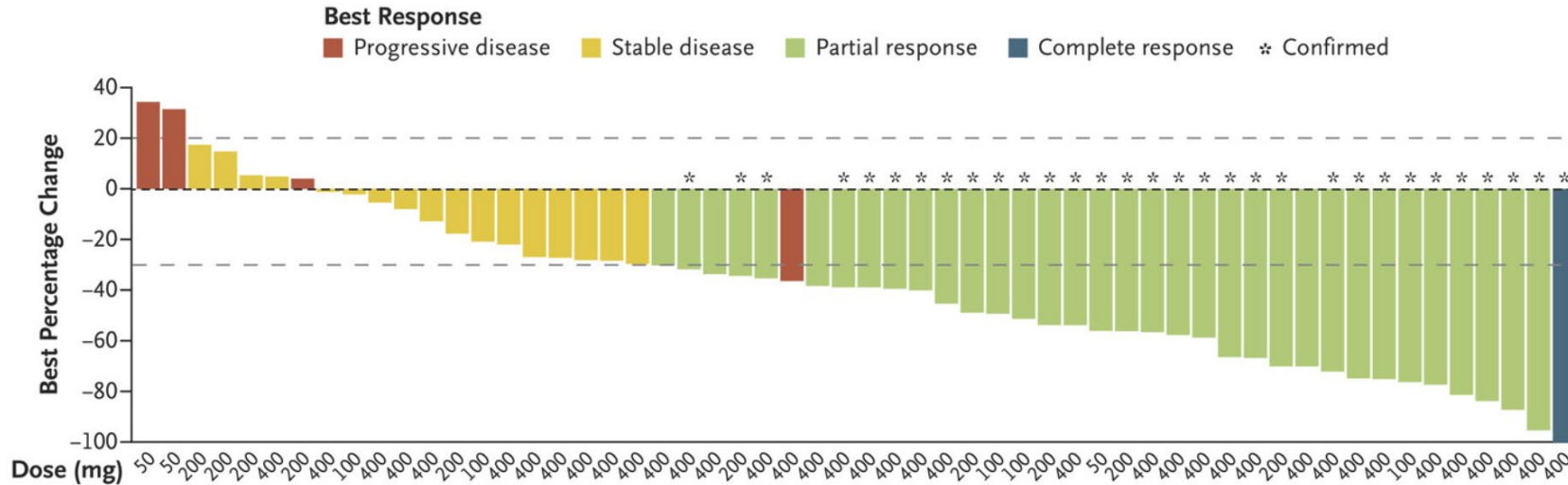
- Sotorasib (2021)
- Adagrasib (2022)

Investigational KRAS G12C (OFF) Inhibitors

- Divarasib
- Olomorasib
- Calderasib
- Glecirasib
- Garsorasib
- Fulzerasib
- Elisrasib

Divarasilb

Best Change from Baseline in Tumor Burden



Confirmed response rate:
53.4%
: 13.1 months

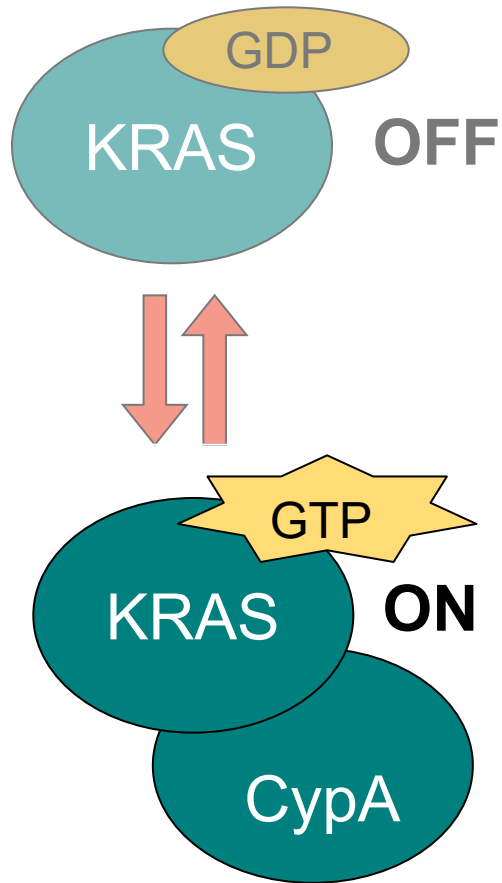
Treatment-Related Adverse Event	Any Grade	Grade 3-4
Nausea	47 (78)	1 (2)
Diarrhea	36 (60)	2 (3)
Vomiting	38 (63)	0
Fatigue	16 (27)	1 (2)
Decreased appetite	11 (18)	0
Aspartate aminotransferase level increased	9 (15)	4 (7)

Press Release

Krascendo 1 Phase 3 of Divarasilb vs Sotorasilb/Adagrasilb with positive PFS and OS



RAS(ON) Tri-Complex Inhibitors



KRAS G12C

- Elironrasib (RMC-6291, investigational)

Pan-RAS

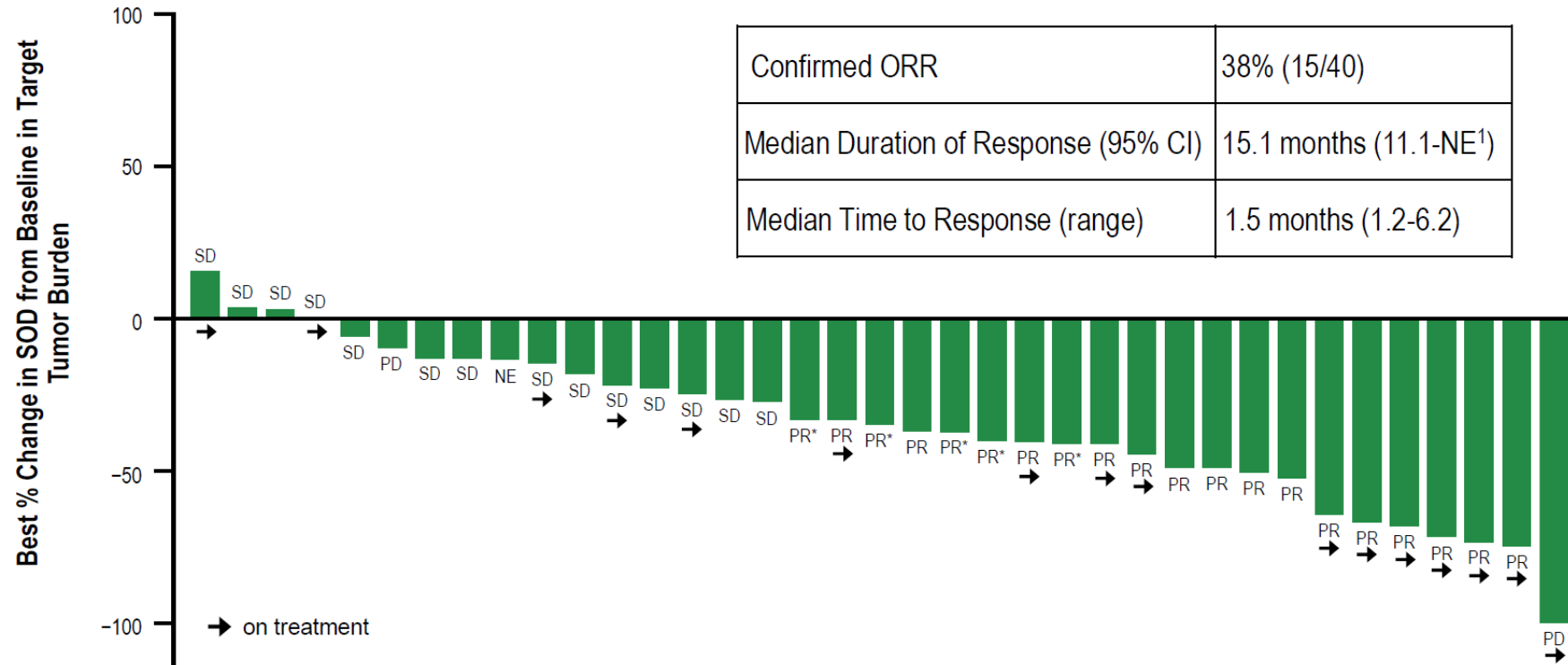
- Daraxonrasib (RMC-6236, investigational)

Other Mutation-Specific

- Eg, Zoldonrasib (KRAS G12D, investigational)

Daraxonrasib: A Pan-RAS “ON” Inhibitor

Activity in RAS G12X NSCLC



Median 9.8 months (6-12.3)

Clinical activity assessed in patients with NSCLC (n=40) that

- Harbor RAS G12X mutations
- Have received 1 or 2 prior lines of therapy (prior immunotherapy and platinum chemotherapy)
- Have not received docetaxel previously

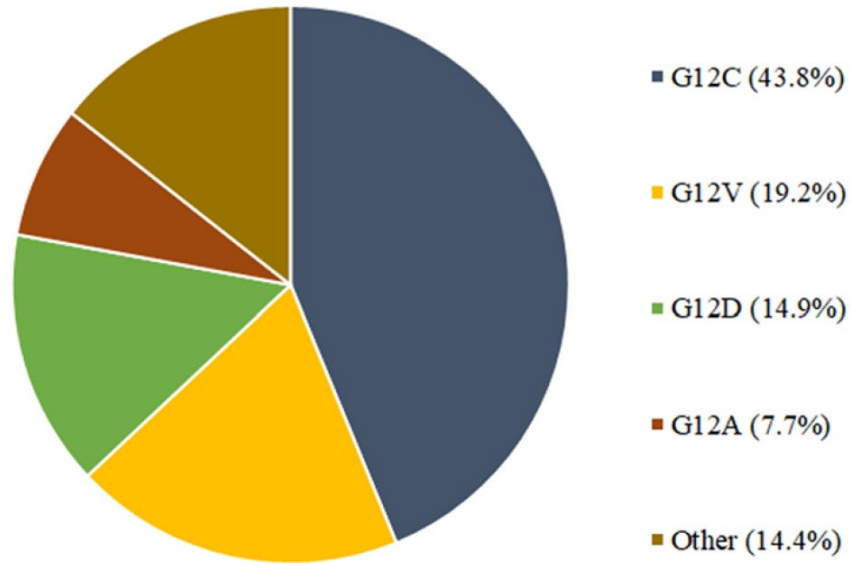
SOD = sum of diameters.

Punekar S, et al. Presented at: European Lung Cancer Congress (ELCC); 2025. Abstract 6MO.

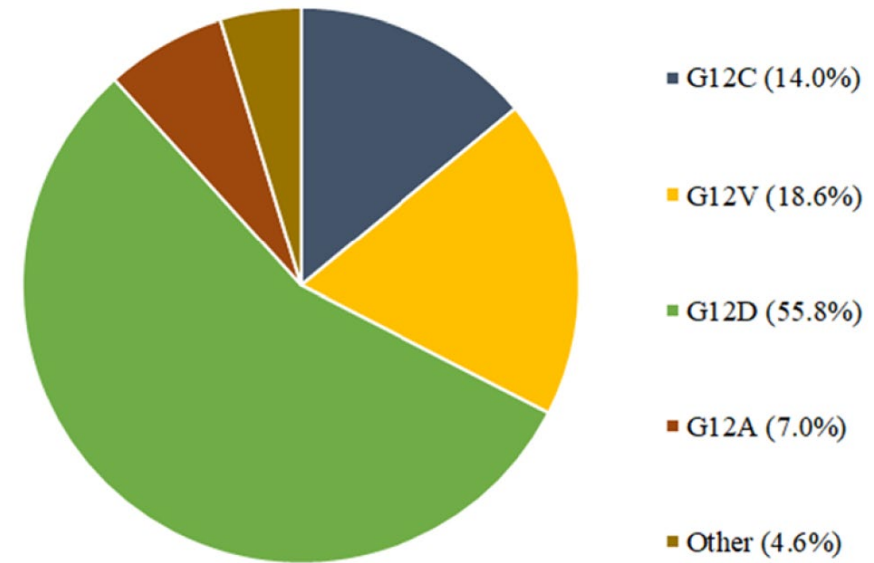
KRAS G12D as a Therapeutic Target in NSCLC



Current Tobacco Use



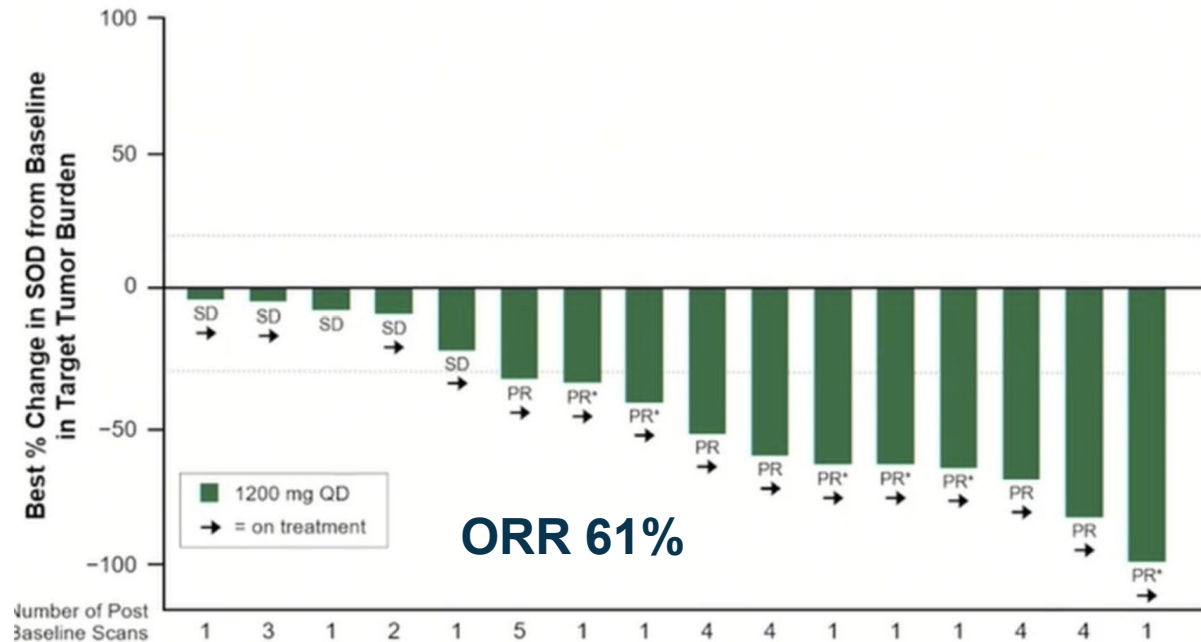
No Tobacco Use History



- *KRAS* G12D mutations are present in ~4% of NSCLC
- Among the *KRAS* mutations, more common in patients without history of tobacco use



Zoldonrasib for KRAS G12Dm NSCLC



Patients Treated with 1200 mg QD Zoldonrasib (N = 90) ¹				
Maximum Severity of Treatment-Related AEs	Grade 1	Grade 2	Grade 3	Any Grade
Any TRAE	49 (54%)	16 (18%)	2 (2%)	67 (74%)
TRAEs occurring in ≥10% of patients, n (%)				
Nausea	30 (33%)	5 (6%)	0	35 (39%)
Diarrhea	18 (20%)	3 (3%)	1 (1%)	22 (24%)
Vomiting	12 (13%)	4 (4%)	0	16 (18%)
Rash ²	11 (12%)	0	0	11 (12%)
Other select TRAEs, n(%)				
AST increased	5 (6%)	2 (2%)	0	7 (8%)
ALT increased	4 (4%)	1 (1%)	1 (1%)	6 (7%)
Stomatitis/mucositis ³	1 (1%)	0	0	1 (1%)
TRAEs leading to dose reduction, n (%)	2 (2%)	2 (2%)	0	4 (4%)
TRAEs leading to dose interruption, n (%)	3 (3%)	3 (3%)	2 (2%)	8 (9%)
TRAEs leading to treatment discontinuation, n (%)	1 (1%)	0	0	1 (1%)
Mean dose intensity	98%			

For patients treated at 1200 mg dose

Is There a Role for KRASi + ICI First-Line in *KRAS* G12C NSCLC?

Strategy/Agent	Key Clinical Signal	Ongoing / Planned Study
Sotorasib + ICI	Excess hepatotoxicity observed with combination approaches	CodeBreakK 202: sotorasib + platinum doublet vs ICI + platinum doublet in PD-L1 negative NSCLC
Adagrasib + pembrolizumab	ORR 32%; median 27.7 months in PD-L1 high NSCLC	KRYSTAL-7: phase 3 adagrasib + pembrolizumab vs pembrolizumab alone in PD-L1 high NSCLC
Olomorasib + pembrolizumab	ORR 78% in PD-L1 high NSCLC	SUNRAY-01: olomorasib vs placebo + pembrolizumab (± chemotherapy)
Calderasib + pembrolizumab	ORR 88% in PD-L1 high NSCLC	KANDLELIT-004: calderasib vs placebo + pembrolizumab in PD-L1 high NSCLC
Elisrasib + pembrolizumab	ORR 81.3%, any PD-L1	
Divarasib + pembrolizumab	Combination strategy under active investigation	KRASCENDO-2: divarasib + pembrolizumab vs chemotherapy + pembrolizumab

Li Z, et al. Presented at: IASCL WCLC; 2022. Abstract 907. Garassino MC, et al. Presented at: ELCC; 2025. Abstract 5MO. Johnson ML, et al. Presented at: WCLC; 2025. Abstract MA02.06. Sacher AG, et al. *J Clin Oncol*. 2025;43(16 Suppl):8605. Lu S, et al. *J Clin Oncol*. 2026;44(16 Suppl):8511.

KRAS Inhibitors in the Curative-Intent Setting

Study	Strategy	Population/Setting
SUNRAY-02	Olomorasib + ICI vs placebo + ICI	• Stage II/III resected NSCLC • No prior therapy or no pCR to neoad chemo-ICI or • Prior chemoradiation for stage III disease
KRASCENDO-3	Adjuvant divarasib vs ICI	• Stage II/III resected NSCLC • No pCR to neoadjuvant chemo-ICI
KANDLELIT-013	Adjuvant calderasib vs placebo + ICI	• Stage IIA-IIIB resected NSCLC • Prior neoadjuvant chemo-ICI or adjuvant chemo

pCR = pathologic CR.

ALK

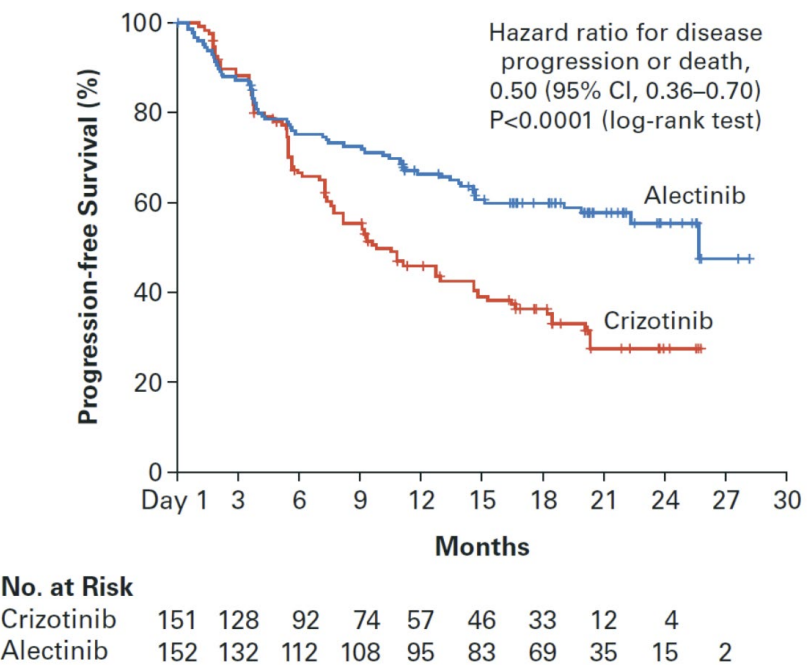
First-Line TKIs for ALK+ NSCLC

Drug	Trial Name	Median (BICR)
Crizotinib >> Chemotherapy 1L	PROFILE 1014	10.9 vs 7.0 mo
Ceritinib >> Chemotherapy 1L	ASCEND-4	16.6 vs 8.1 mo
Alectinib >> Crizotinib 1L	ALEX	25.7 vs 10.4 mo
Brigatinib >> Crizotinib 1L	ALTA-1L	24.0 vs 11.1 mo
Lorlatinib >> Crizotinib 1L	CROWN	5 yr 60% vs 8%

Peters S, et al. *N Engl J Med*. 2017;377(9):829-838. Solomon BJ, et al. *Lancet Respir Med*. 2023;11(4):354-366. Soria JC, et al. *Lancet*. 2017;389(10072):917-929. Solomon BJ, et al. *J Clin Oncol*. 2018;36(22):2251-2258. Camidge DR, et al. *N Engl J Med*. 2018;379(21):2027-2039. Solomon BJ, et al. *J Clin Oncol*. 2024;42(17 Suppl):LBA8503.

ALEX

Alectinib vs crizotinib 1L (BICR)



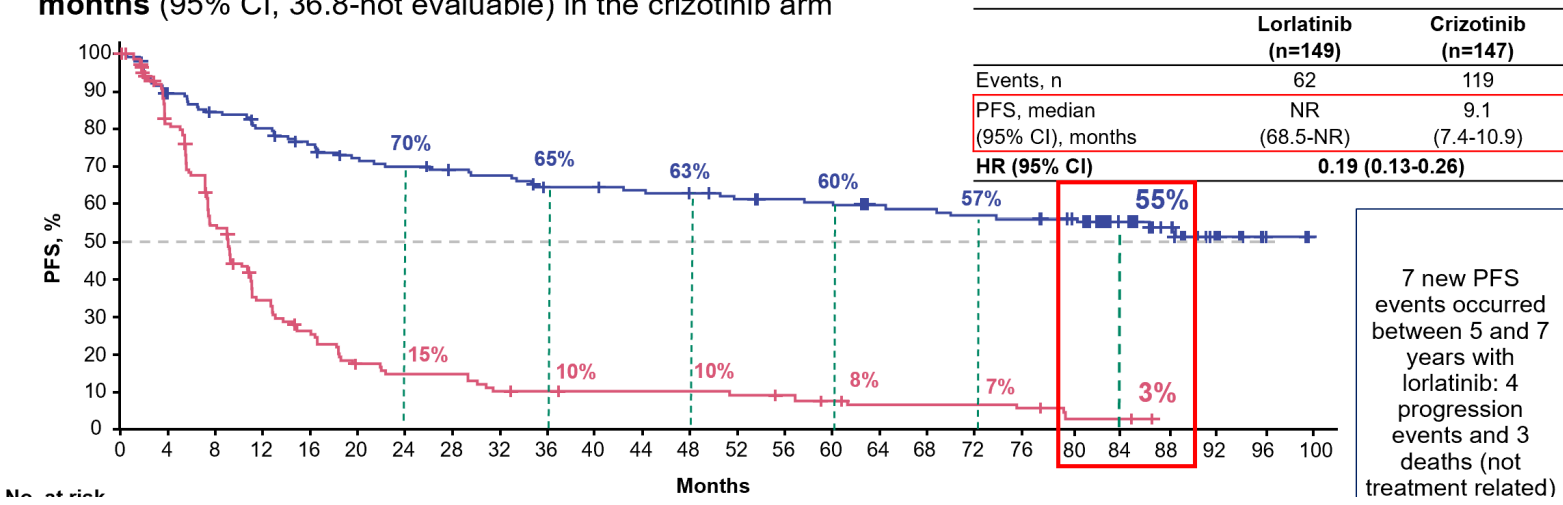
25.7 vs 10.4 mo
HR 0.50 (0.36-0.70)

NR = not reached.
 Peters S, et al. *N Engl J Med.* 2017;377(9):829-838. Solomon BJ, et al. *J Clin Oncol.* 2024;42(17 Suppl):LBA8503. Mok TSK, et al. *J Clin Oncol.* 2026;44(16 Suppl):8502.

CROWN—7-year update

Lorlatinib vs crizotinib 1L (BICR)

- The median duration of follow-up for PFS was **83.0 months** (95% CI, 81.2-86.3) in the lorlatinib arm and **77.2 months** (95% CI, 36.8-not evaluable) in the crizotinib arm

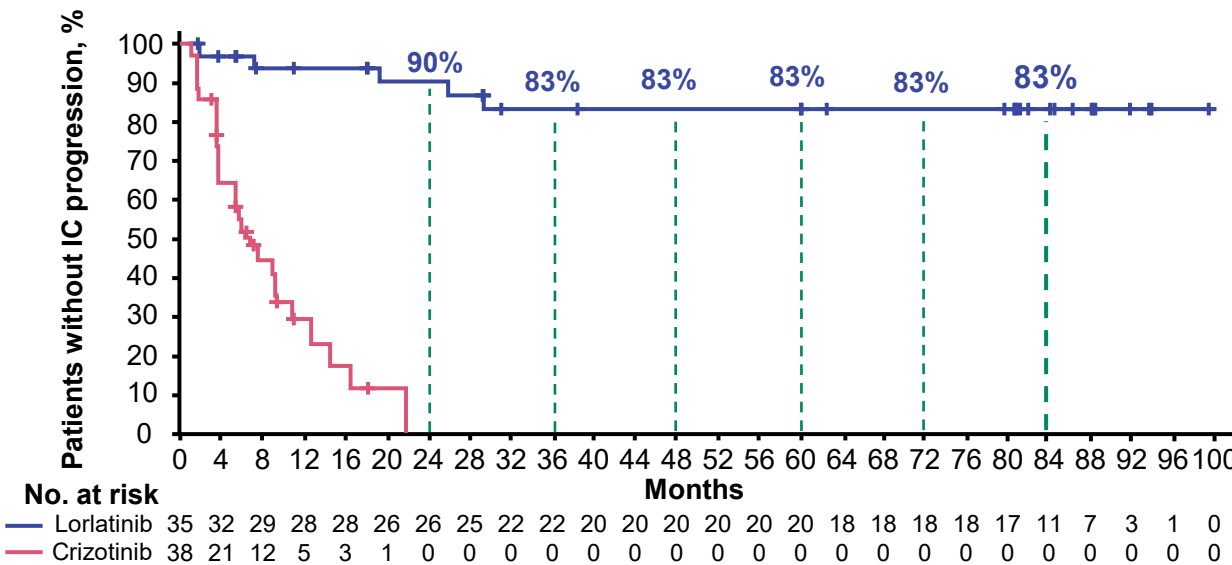


NR vs 9.1
HR 0.19 (0.13-0.26)

CROWN: Time to IC Progression by Brain Metastases

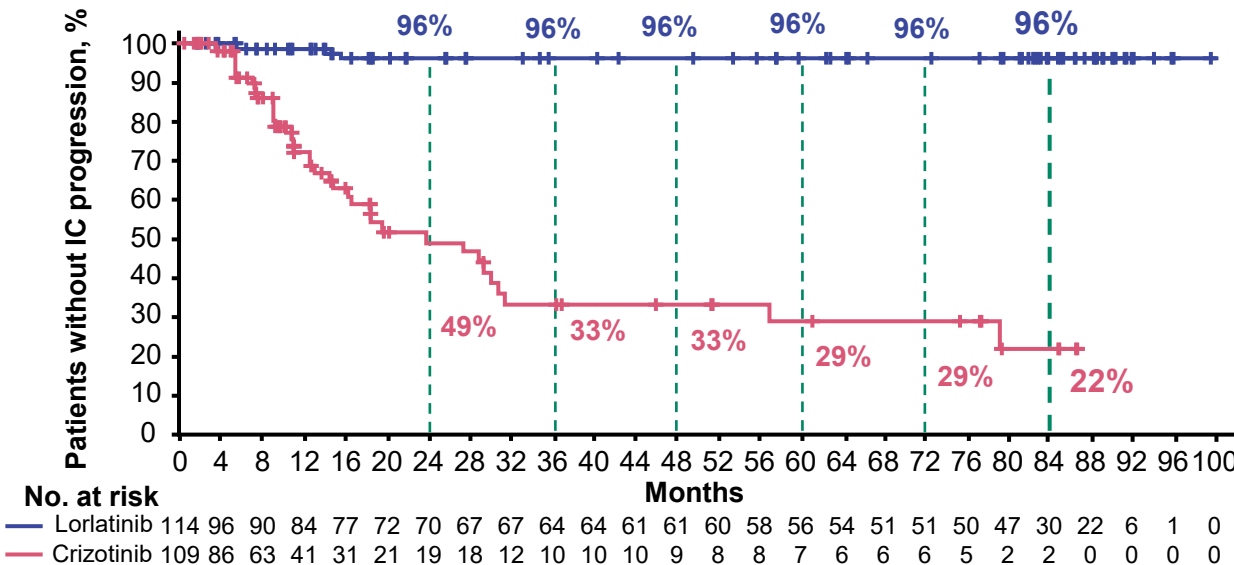
With baseline brain metastases

	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	5	26
Time to IC progression, months, median (95% CI)	NR (NR-NR)	7.2 (3.7-11.0)
HR (95% CI)	0.03 (0.01-0.13)	



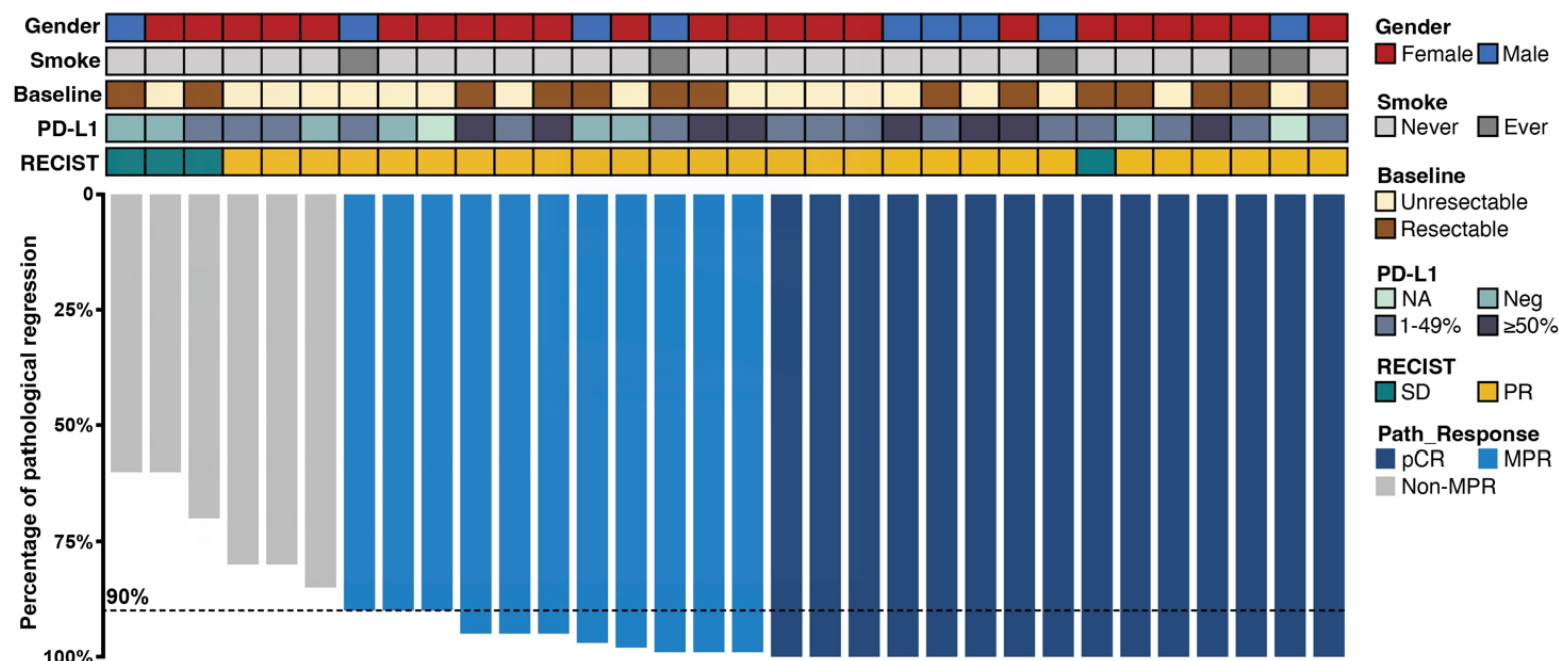
Without baseline brain metastases

	Lorlatinib (n=114)	Crizotinib (n=109)
Events, n	4	40
Time to IC progression, months, median (95% CI)	NR (NR-NR)	23.9 (16.4-30.8)
HR (95% CI)	0.04 (0.02-0.12)	



IC = intracranial.
Mok TSK, et al. *J Clin Oncol*. 2026;44(16 Suppl):8502.

pCR Rate to 3 Months Neoadjuvant Lorlatinib



Overall	N=32 (n, %)
pCR	15 (47)
MPR	26 (81)
Median/Mean RVT	1%/7%

Resectability	pCR/MPR
Resectable	50%/86%
Unresectable	44%/78%

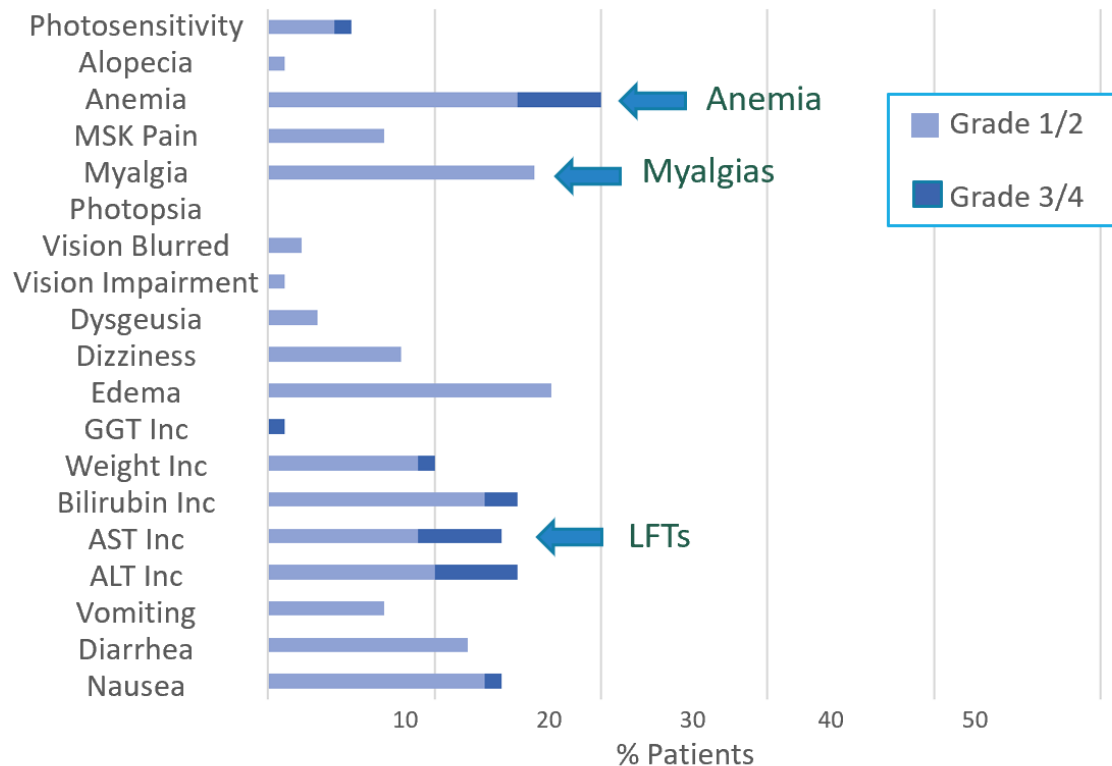
Median PD-L1 exp.	
MPR/pCR	25%
Non-MPR	1%
<i>p</i> value <0.01	

Among patients who underwent surgery, the pCR and MPR rates were **46.9% (15/32) (95%CI, 29.1%-65.2%) [34.9% for ITT]** and **81.3% (26/32) [60.5% for ITT]**, respectively, reaching the primary endpoint.

ITT = intention-to-treat; MPR = major pathologic response; NA = not available; RVT = residual viable tumor.
Zhang C, et al. *J Clin Oncol*. 2026;44(16 Suppl):8002.

Adverse Effects

Alectinib (ALEX)



11% d/c rate for adverse effects

16% dose reduction rate

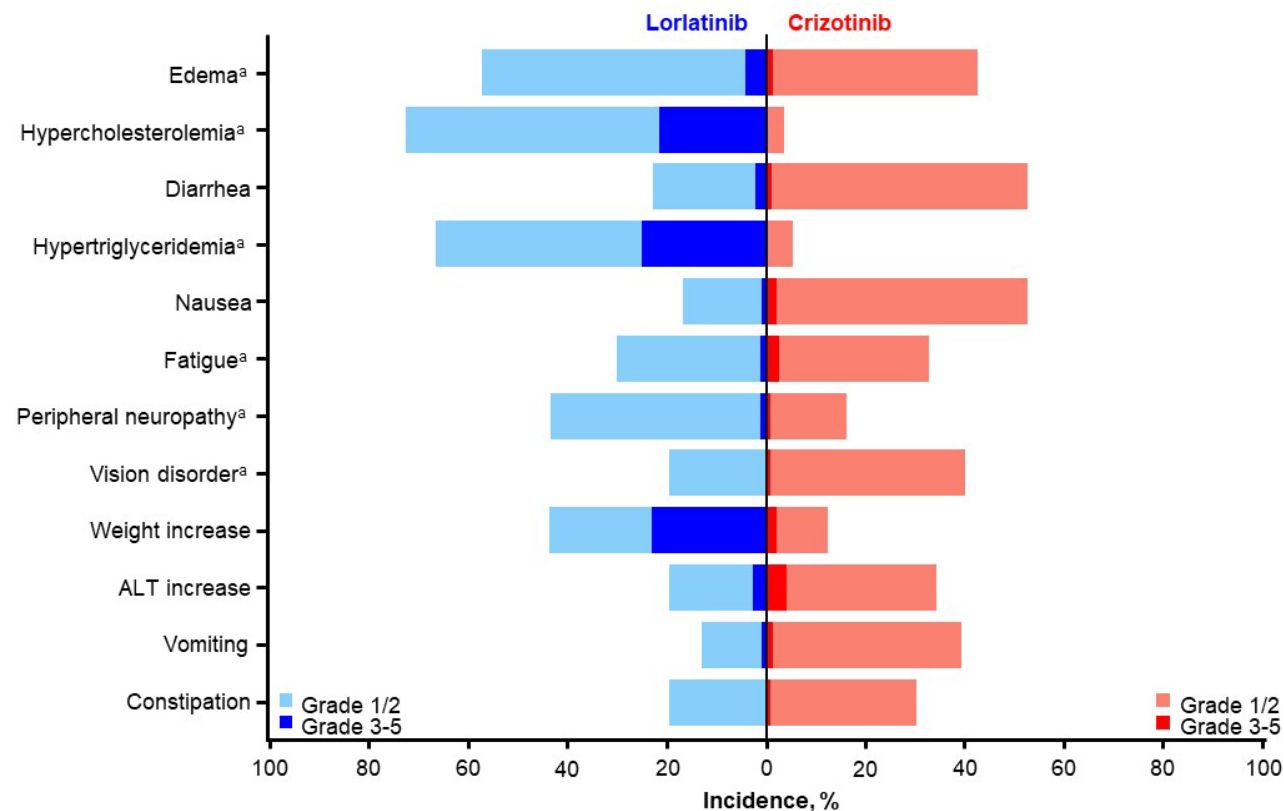
MSK = musculoskeletal; GGT = gamma-glutamyl transferase (GGT).

Peters S, et al. *N Engl J Med*. 2017;377(9):829-838. Solomon BJ, et al. *J Clin Oncol*. 2024;42(17 Suppl):LBA8503.

Liu G, et al. *Lung Cancer*. 2024;191:107535.

Lorlatinib (CROWN)

All cause AEs in ≥30% of patients in either treatment arm

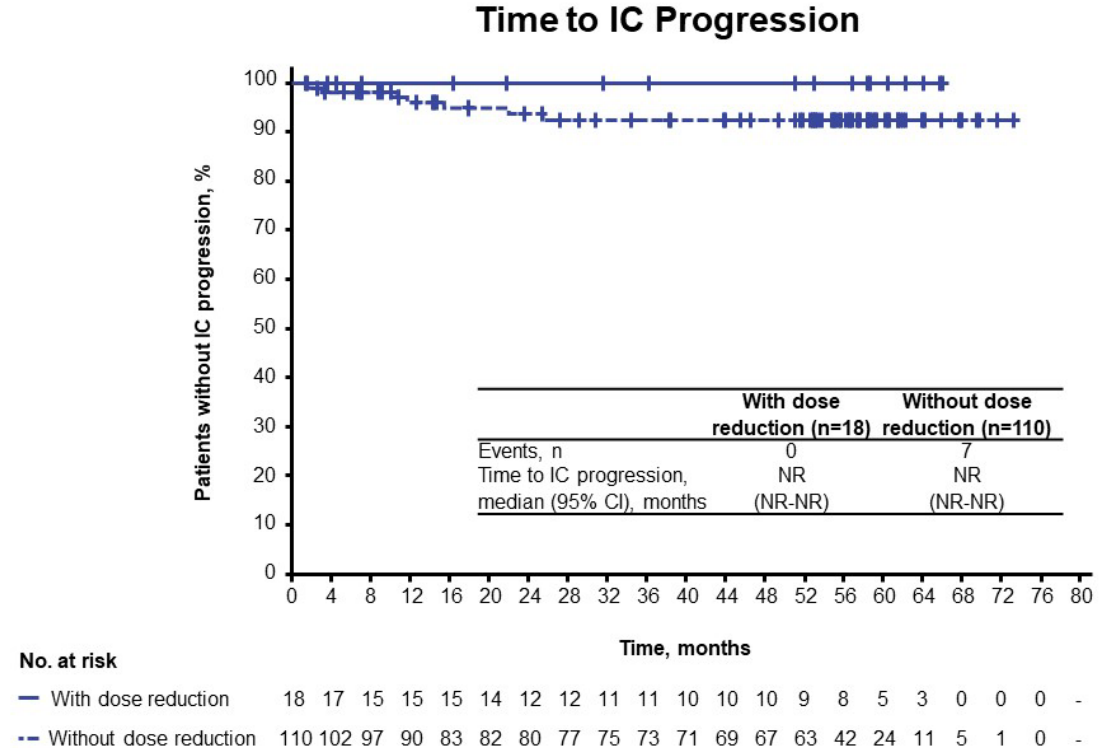
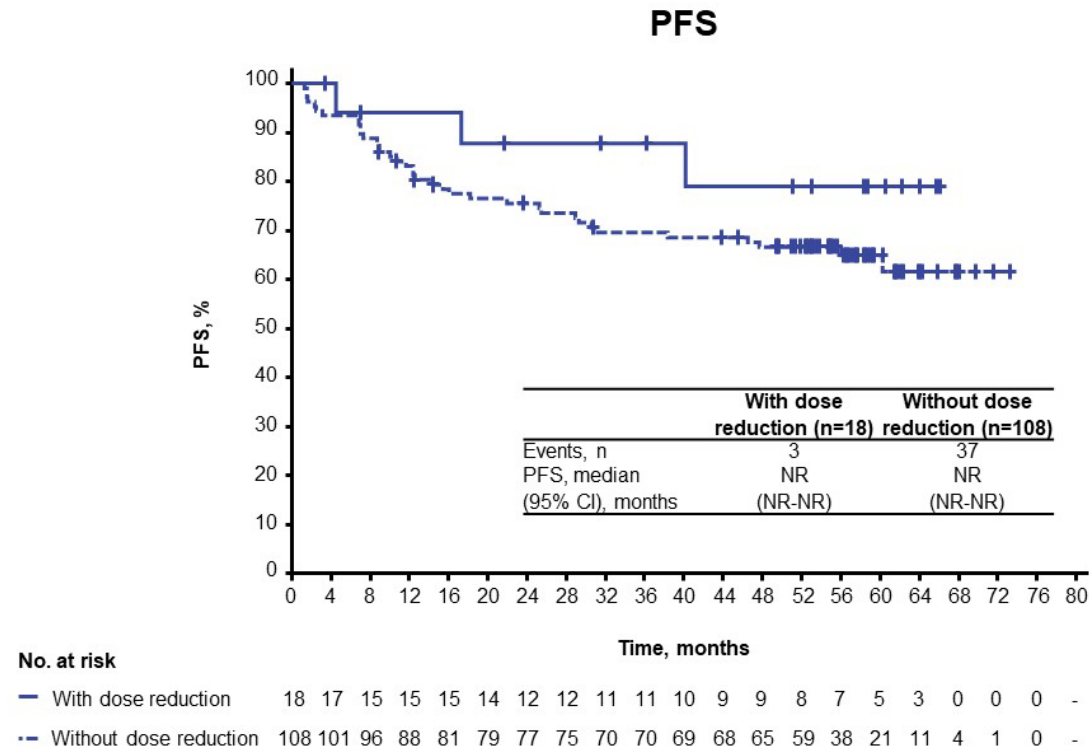


Cognition (26%), mood (17%), speech (5%), psychotic effects (5%)

5% d/c rate for TRAEs

23% dose reduction rate

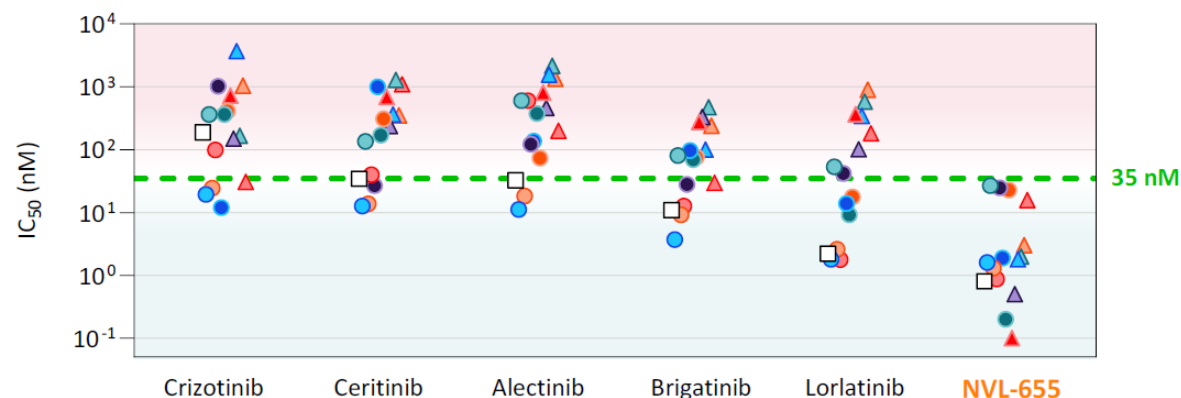
Early Dose Reduction Did Not Significantly Impact Long-Term Outcomes



Novel Therapies for ALK: Neladalkib

ALK Fusion and ALK Single/Compound Mutation Activity

Potent activity ($IC_{50} = 0.1 - 30$ nM) against ALK-driven cell lines, including ALK single and compound mutants



Cell lines harboring EML4-ALK fusion
3-day cell viability assay

Single ALK mutations

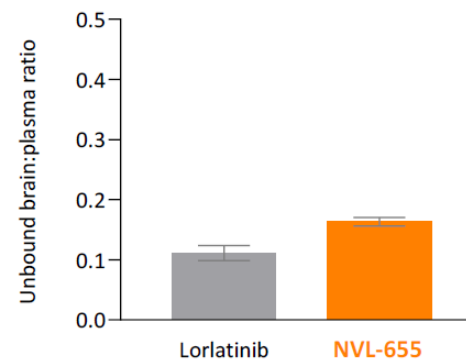
- T1151M | Ba/F3 (v3)
- I1171N | Ba/F3 (v1)
- F1174L | Ba/F3 (v3)
- V1180L | Ba/F3 (v1)
- L1196M | MGH045-1 (v1)
- L1198F | Ba/F3 (v1)
- G1202R | YU-1077 (v3)
- D1203N | Ba/F3 (v1)

Compound ALK mutations

- ▲ G1202R/T1151M | MR448re (v3)
- ▲ G1202R/F1174L | Ba/F3 (v3)
- ▲ G1202R/L1196M | MGH953-7 (v3)
- ▲ G1202R/L1198F | Ba/F3 (v1)
- ▲ G1202R/G1269A | Ba/F3 (v1)
- ▲ I1171N/L1198F | Ba/F3 (v1)

Brain Penetrance

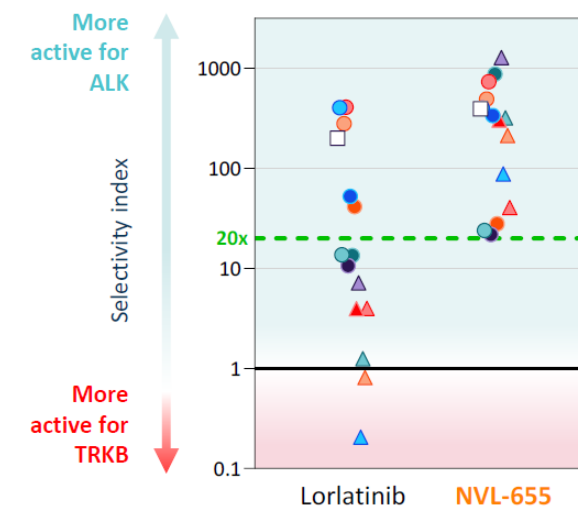
Preclinical pharmacokinetic data similar to lorlatinib



Wistar Han rats
10 mg/kg, single dose PO
1-hour timepoint

Avoidance of TRK Inhibition

Selective inhibition of ALK and ALK mutants over TR.



$$\text{Selectivity index} = \frac{IC_{50} (\text{pTRKB})}{IC_{50} (\text{Ba/F3 EML4-ALK})}$$

ALKOVE-1: Objective Response in ALK TKI-Pretreated Patients

- **Prior alectinib only ± chemotherapy:**
ORR = **48%** (21/44, 5% CR)
- **≥ 2 prior ALK TKIs ± chemotherapy:**
ORR = **28%** (56/198)^b

^c Includes 2 single-timepoint CR pending confirmation in ongoing patients with prior confirmed PR. ^d Includes 1 single-timepoint CR pending confirmation in ongoing patient with prior confirmed PR.



RECIST = response evaluation criteria in solid tumors.
Lin JJ, et al. *J Clin Oncol*. 2026;44(16 Suppl):8503.

Neladalkib CNS and Safety Outcomes

ALKOVE-1: CNS Activity

TKI-Pretreated CNS Response- Evaluable ^a RECIST 1.1, BICR [95% CI]	Any prior ALK TKI ± chemotherapy N = 92	Lorlatinib- naive ± chemotherapy N = 24	Lorlatinib- experienced ± chemotherapy N = 68
IC-ORR, % (n/N)	32% (29/92) ^b [22, 42]	63% (15/24) ^b [41, 81]	21% (14/68) [12, 32]
IC-CR, % (n/N)	13% (12/92) ^c	21% (5/24) ^c	10% (7/68)
IC-DOR ≥ 6 months ^d	81% [59, 91]	92% [57, 99]	71% [41, 88]
IC-DOR ≥ 12 months ^d	71% [48, 85]	92% [57, 99]	55% [26, 77]
IC-DOR ≥ 18 months ^d	71% [48, 85]	92% [57, 99]	55% [26, 77]

^a Includes patients with measurable (≥5mm) CNS lesions by BICR at baseline and no brain radiation within 2 months before first dose of neladalkib. ^b Includes 2 single-timepoint IC-PR pending confirmation in ongoing patients. ^c Includes 1 single-timepoint IC-CR pending confirmation in ongoing patient with prior confirmed IC-PR. ^d Analyses of DOR based on Kaplan-Meier estimates.

- **CNS response-evaluable after prior alectinib only ± chemotherapy:** IC-ORR = **60%** (9/15; 1 IC-uPR); no intracranial progressors among confirmed intracranial responders.
- **CNS response-evaluable after ≥ 2 prior ALK TKIs ± chemotherapy:** IC-ORR = **25%** (19/75; 1 IC-uPR); IC-DOR at 6 months = **78%** (95% CI: 51, 91) and at 12 and 18 months = **66%** (95% CI: 39, 83).

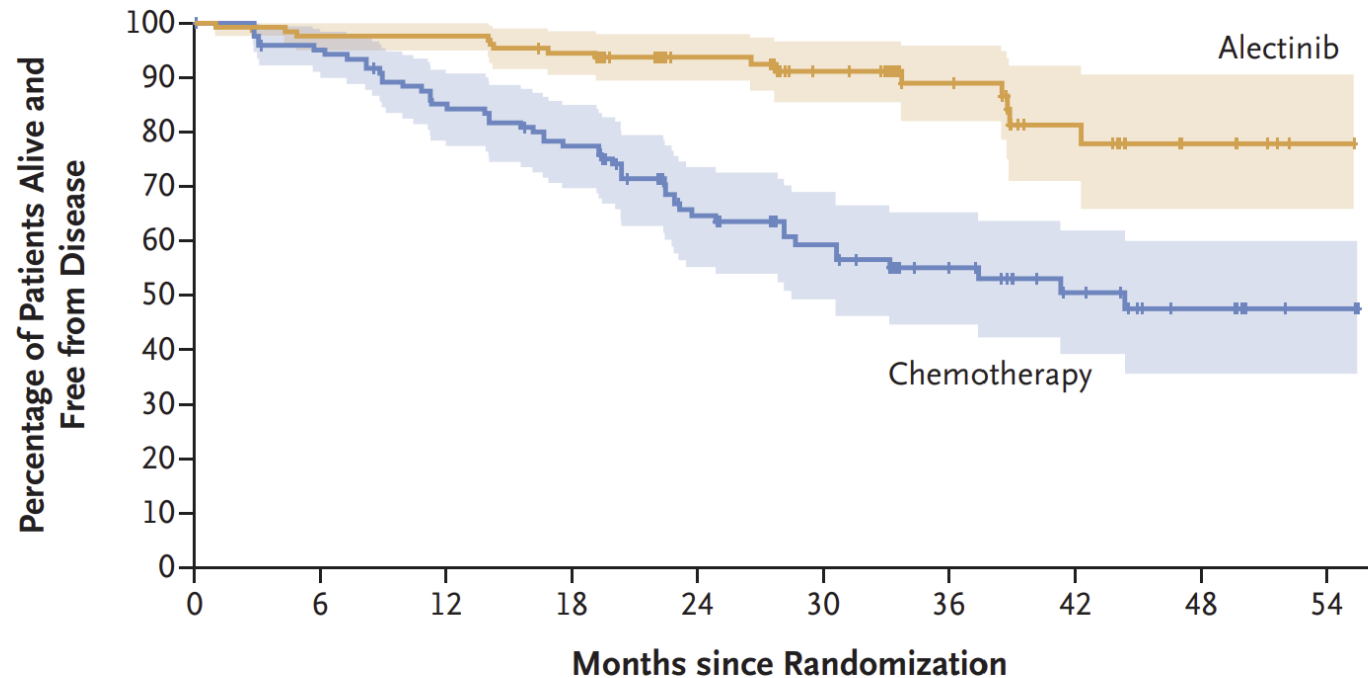
All Treatment-Emergent Adverse Events (TEAEs) in ≥ 15% of TKI-Naïve or TKI-Pretreated Patients with Advanced ALK+ NSCLC Receiving Neladalkib 150 mg QD (N = 656)

Preferred Term	Any Grade	Grade ≥3
ALT increased	47%	20%
AST increased	44%	16%
Constipation	28%	0.2%
Dysgeusia	23%	0
Peripheral edema	18%	0.3%
Cough	16%	0.5%
Nausea	16%	0.8%

CNS = central nervous system.
Lin JJ, et al. *J Clin Oncol*. 2026;44(16 Suppl):8503.

ALINA: 2 Years Adjuvant Alectinib

B Intention-to-Treat Population



Median Disease-free Survival (95% CI)
mo

Alectinib
Not reached

Chemotherapy
41.3 (28.5–NE)

Hazard ratio for disease recurrence or death, 0.24 (95% CI, 0.13–0.43)
P<0.001

No. at Risk

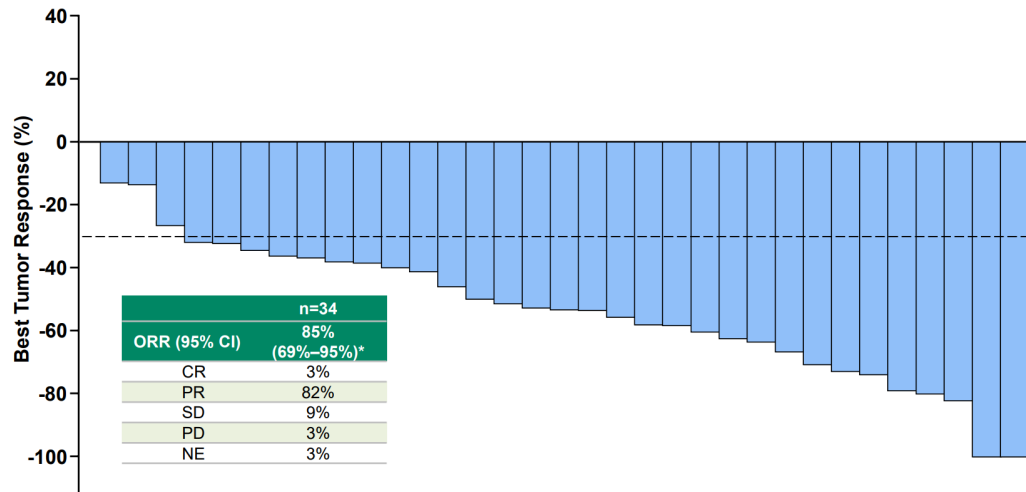
Alectinib	130	123	123	118	74	55	39	22	10	3
Chemotherapy	127	112	98	89	55	41	27	18	11	2

RET

RET Fusions

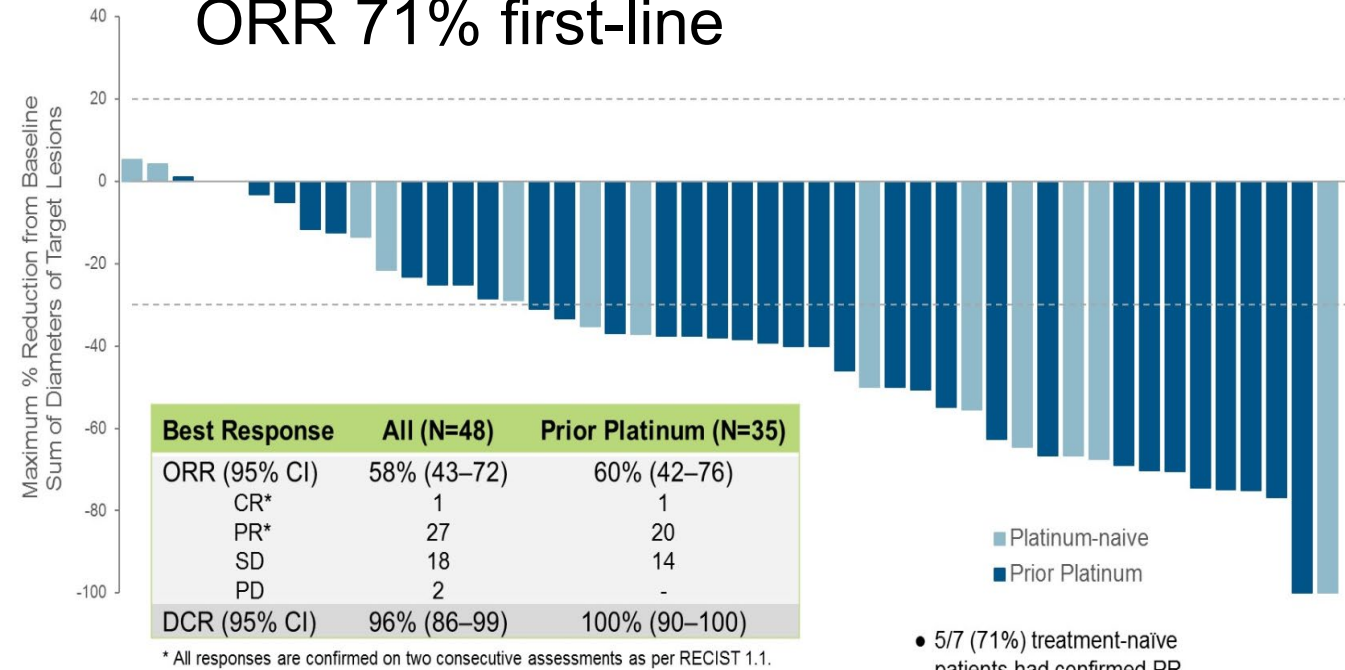
Selpercatinib (LIBRETTO-001)

ORR 85% first-line



Pralsetinib (ARROW)

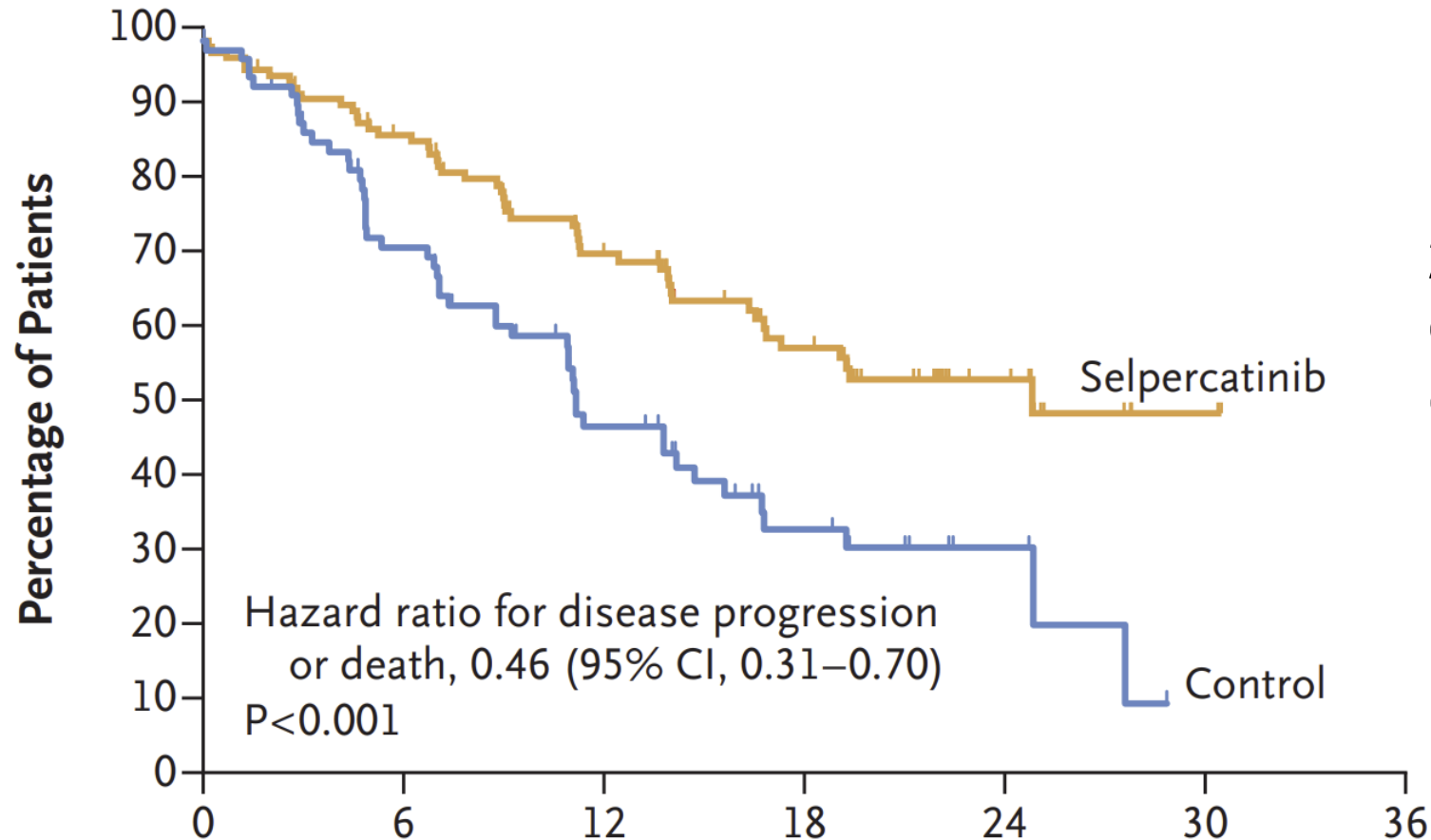
ORR 71% first-line



DCR = duration of complete response.

Drilon A, et al. Presented at: IASLC WCLC; 2019. Abstract PL02.08. Gainor JF, et al. *J Clin Oncol*. 2019;37(15 Suppl):9008.

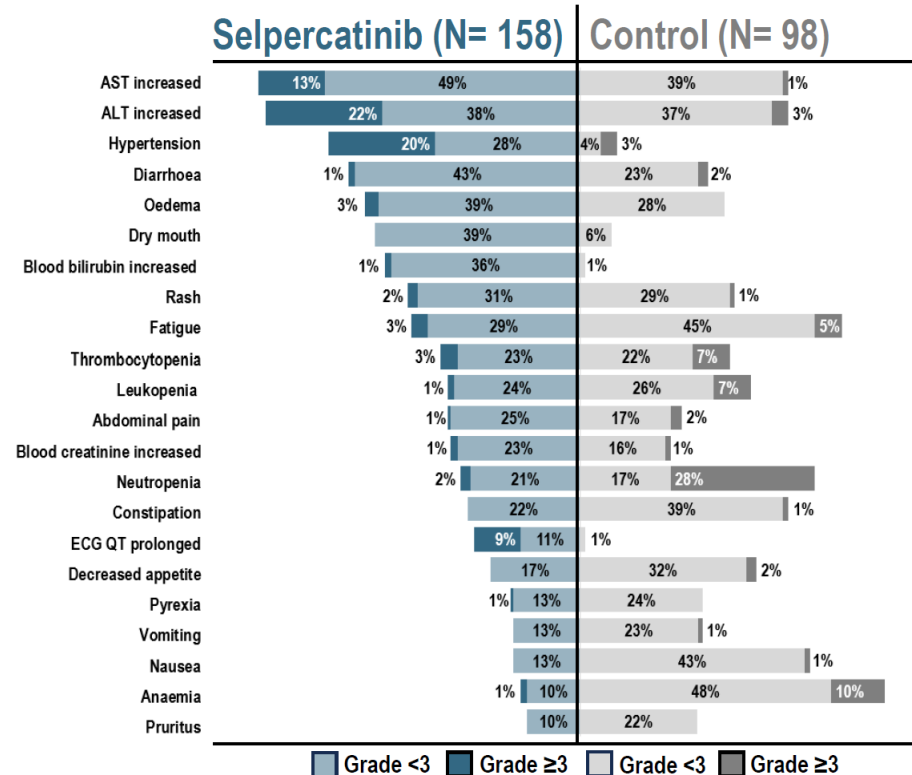
LIBRETTO-431: First-Line Selpercatinib versus Chemoimmunotherapy



24.8 vs 11.2 months
ORR 84% vs 65%
CNS ORR 82%

LIBRETTO-431: Safety Outcomes

Safety



Any grade treatment-emergent adverse events (TEAEs) occurring in ≥20% of patients in either study arm

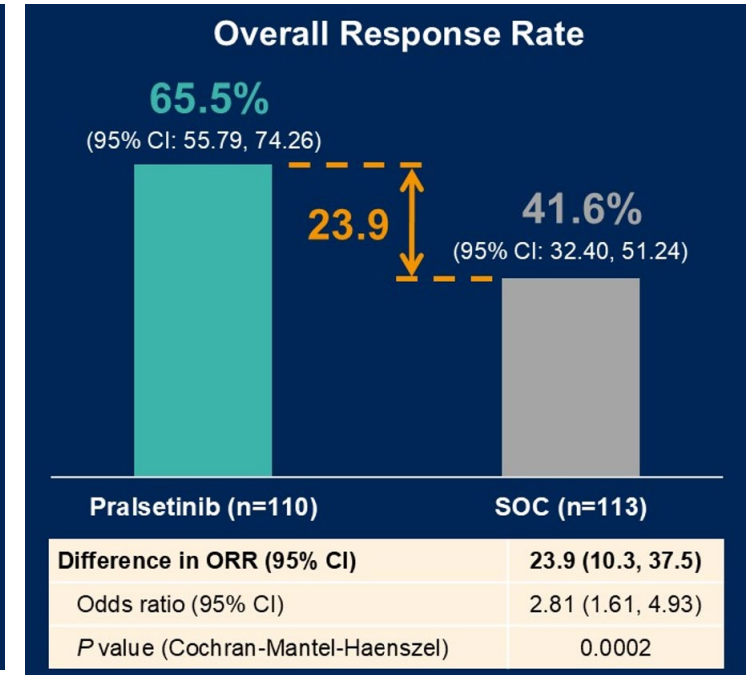
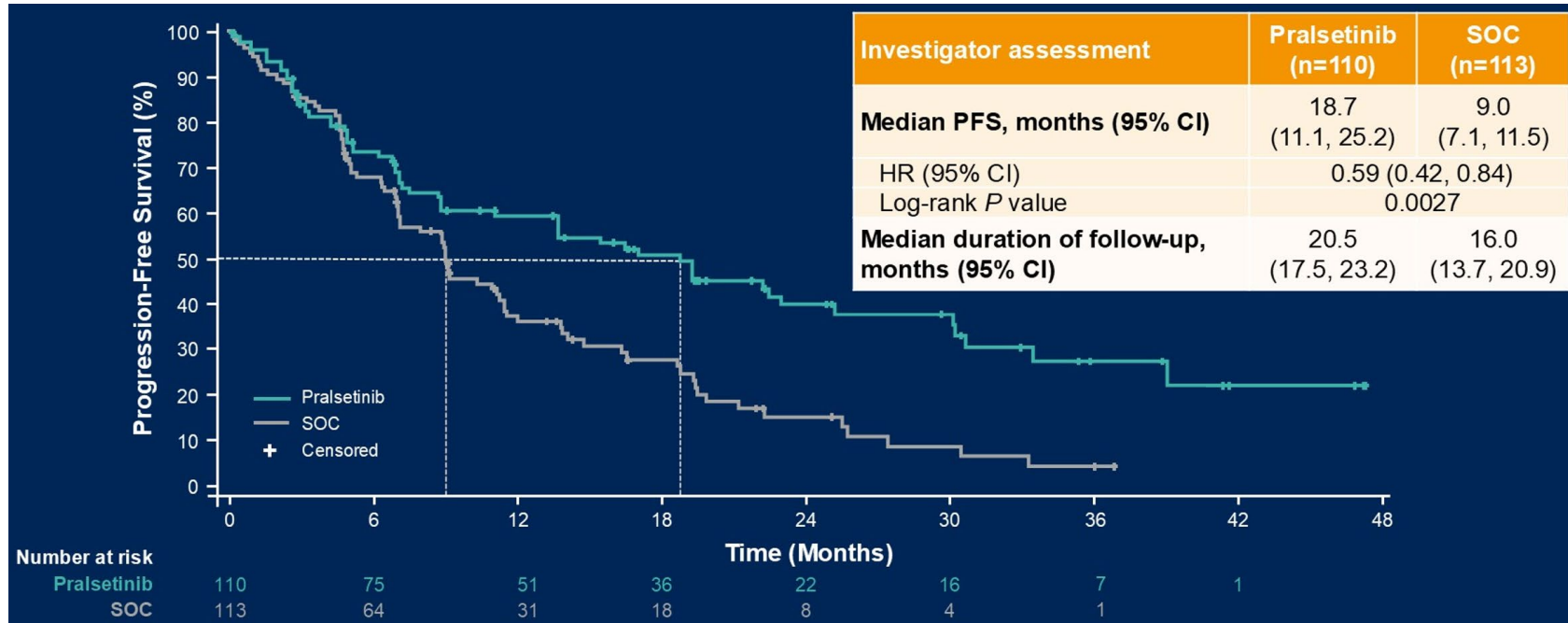
- Median time on selpercatinib was approximately 70% longer than control (16.7 vs 9.8 months)
- TEAEs observed with selpercatinib were generally consistent with those previously reported, and the majority were managed with dose modifications

	Selpercatinib N= 158	Control N= 98
Median time on treatment, months ± SD	16.7 ± 8.3	9.8 ± 7.2
Any AE, n (%)	158 (100.0)	97 (99.0)
AE Grade ≥3	111 (70.3)	56 (57.1)
Deaths due to AE, n (%)	7 (4.4)	0
Related AE (malnutrition and sudden death)	2 (1.3)	0
AEs leading to discontinuation, n (%)	16 (10.1)	2 (2.0)
AEs leading to any dose adjustment, n (%)	123 (77.8)	74 (75.5)
AEs leading to dose reduction	81 (51.3)	28 (28.6)

ECG = electrocardiogram.

Loong HHF, et al. Presented at: ESMO Congress; 2023.

AcceleRET-Lung: First-Line Pralsetinib versus Platinum Doublet



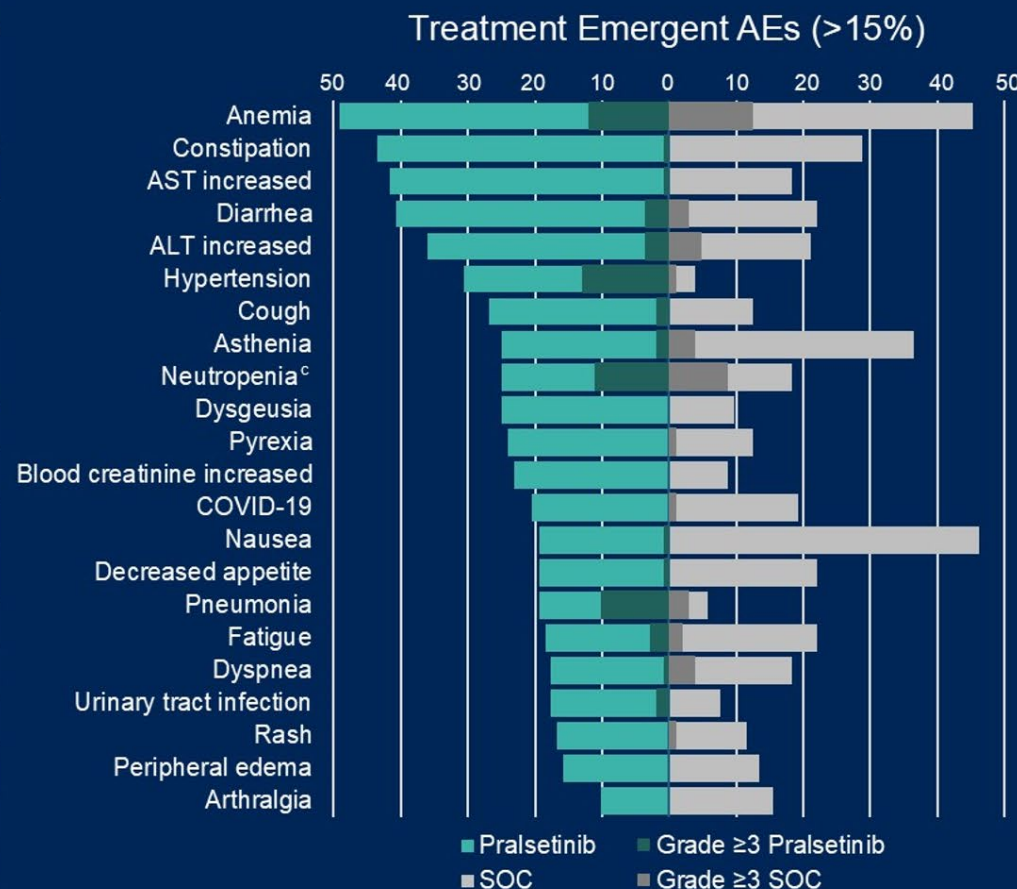
SOC = standard of care.
 Popat S, et al. *J Clin Oncol*. 2026;44(16 Suppl):8504.

AcceleRET-Lung: Safety Outcomes

Treatment exposure	Pralsetinib (n=108)	SOC	
		Chemotherapy ^a (n=35)	Chemotherapy + Pembrolizumab (n=69)
Median duration, months (range)	12.9 (0-50)	6.9 (0-25)	8.8 (0-25)

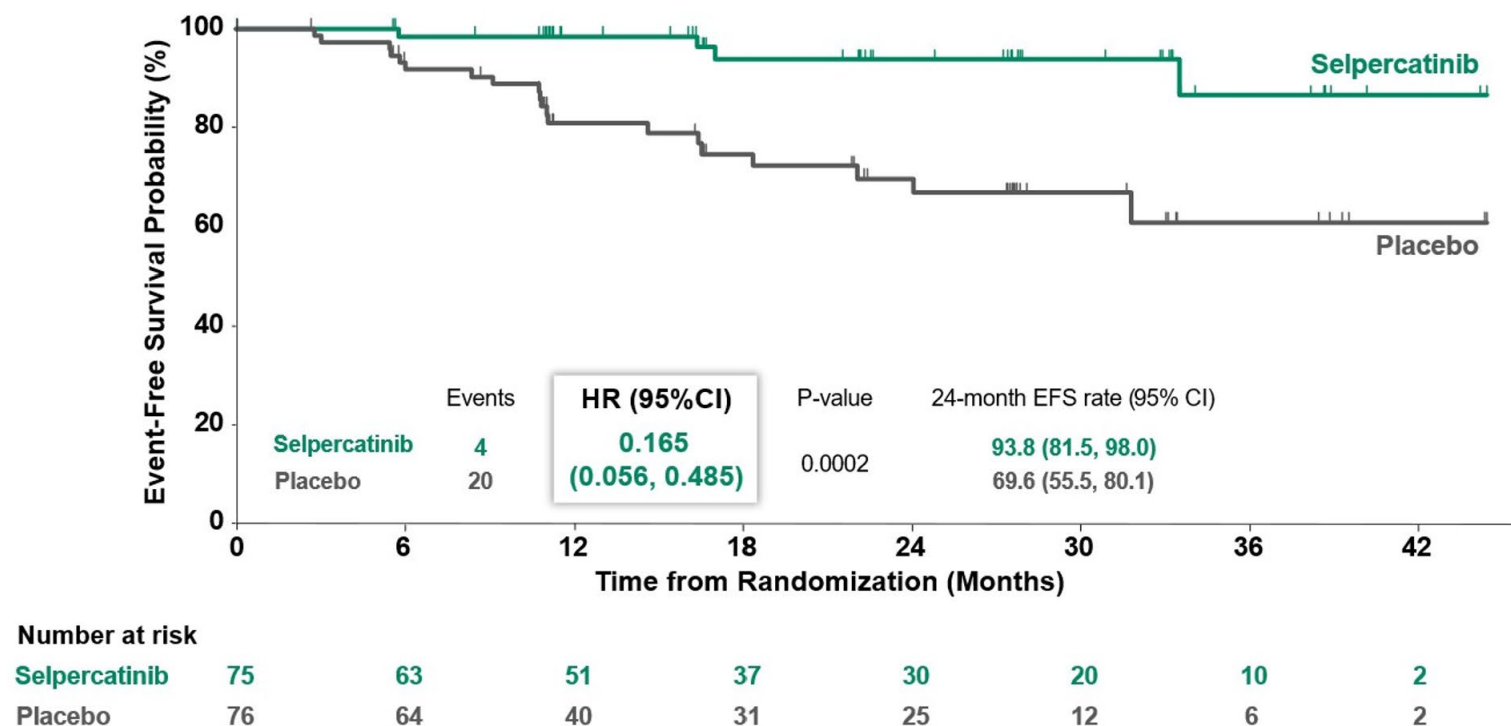
- Time on treatment was 87% longer for pralsetinib vs chemotherapy alone and 47% longer for pralsetinib vs chemotherapy + pembrolizumab

Adverse events (main treatment period)	Pralsetinib (n=108)	SOC (n=104)
Patients with ≥1 AE	108 (100)	104 (100)
Related AEs	101 (93.5)	96 (92.3)
Serious AEs	67 (62.0)	38 (36.5)
Related serious AEs	23 (21.3)	9 (8.7)
Grade 3-5 AEs	84 (77.8)	60 (57.7)
Deaths due to AEs ^b	16 (14.8)	5 (4.8)
Deaths due to infections ^b	8 (7.4)	0
Grade ≥3 QT prolongation	3 (2.8)	0
AEs leading to withdrawal from treatment	18 (16.7)	25 (24.0)
AEs leading to dose modification/interruption	80 (74.1)	57 (54.8)



LIBRETTO-432: 3 Years Adjuvant Selpercatinib

Event-Free Survival by Investigator Assessment Overall Population, Stage IB-IIIA *RET* fusion-positive NSCLC



EFS = event-free survival.
Goldman J, et al. *J Clin Oncol*. 2026;44(17 Suppl):LBA3.



Key Learning Points

- An increasing proportion of NSCLC has or is anticipated to have clinically actionable oncogenic driver alterations
- Comprehensive and high-quality biomarker profiling remains critical; some rare biomarkers predict for prolonged survival on targeted therapies
- The uncommon and exon 20ins EGFR mutations carry unique treatment implications
- Novel KRAS G12C and non-G12C inhibitors may offer improved outcomes in the future and address a larger fraction of the NSCLC population
- Emerging perioperative TKI therapies are impacting optimal genomic profiling in the resectable setting