2024 World Conference on Lung Cancer

SEPTEMBER 7-10, 2024 | SAN DIEGO, CA USA

Other Oncogene-Driven Cancers

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October 5, 2024

Discussion Agenda

- HER2 Alterations
  - PL04.04 & MA12.10 Phase 1b Beamion LUNG-1 (Zongertinib)

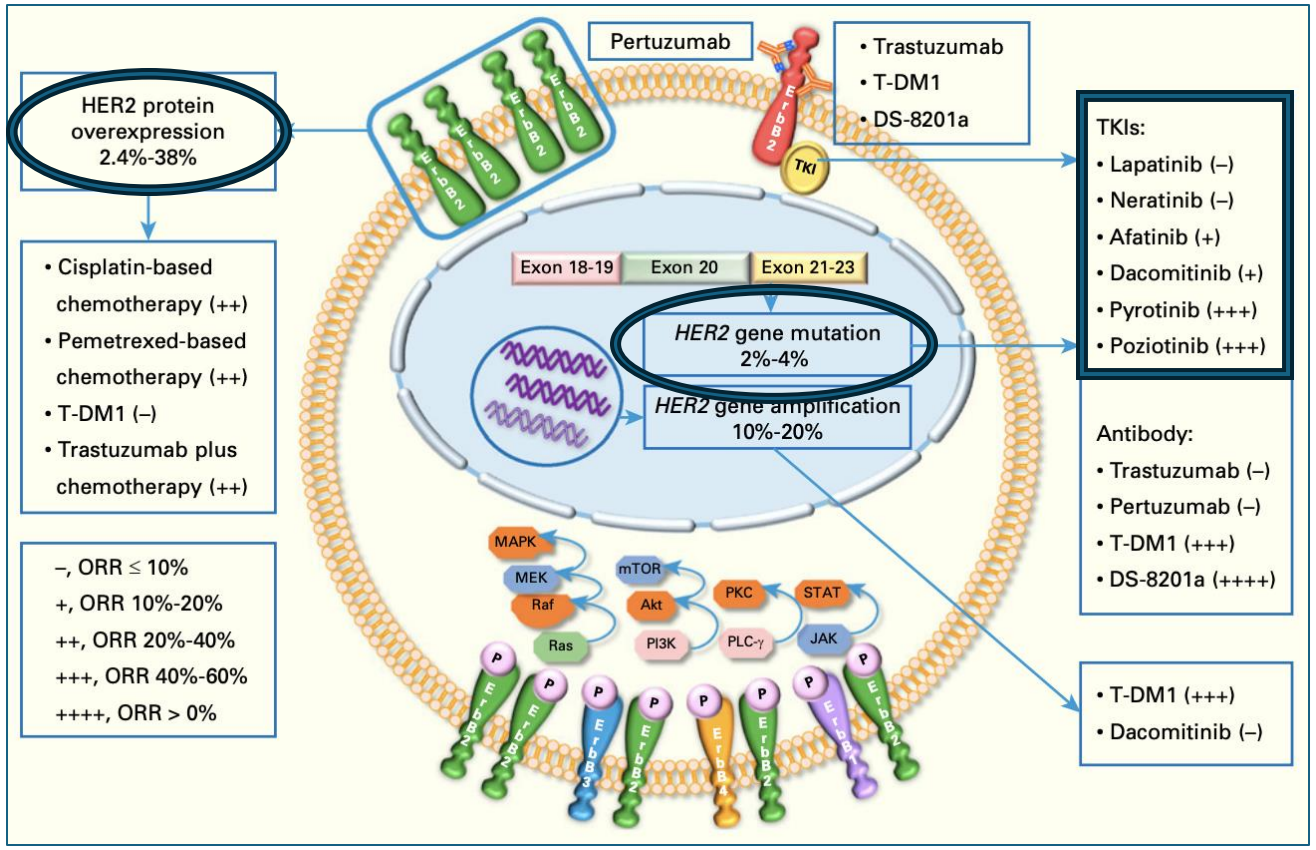
  PL04.03 Phase I/II SOHO-01 (BAY 2927088)

- *KRAS* G12C
  - OA09.06 Quality of Life Metrics for Adagrasib vs Docetaxel
  - OA14 Novel *KRAS* G12C Inhibitors

- Rare “other-oncogenes”: *NTRK* fusions
- MA06.12 Updated Analysis of Larotrectinib in *TRK*-fusion NSCLC

Historical Landscape of *HER2* Therapy

"New in Class": Enhertu
- *HER2*-mutant
- HER2 overexpression



"Unmet Need": oral targeted therapies

Zhao & Xia, *JCO Precis Oncol*, 2020

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Phase Ib Analysis of Beamion LUNG-1: Zongertinib (BI 1810631) in Patients with *HER2*-Mutant NSCLC

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Zongertinib (BI 1810631) for HER2-positive Solid Tumors with Brain Metastases: Subanalysis of the Beamion LUNG-1 Trial

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Beamion LUNG-1: Zongertinib

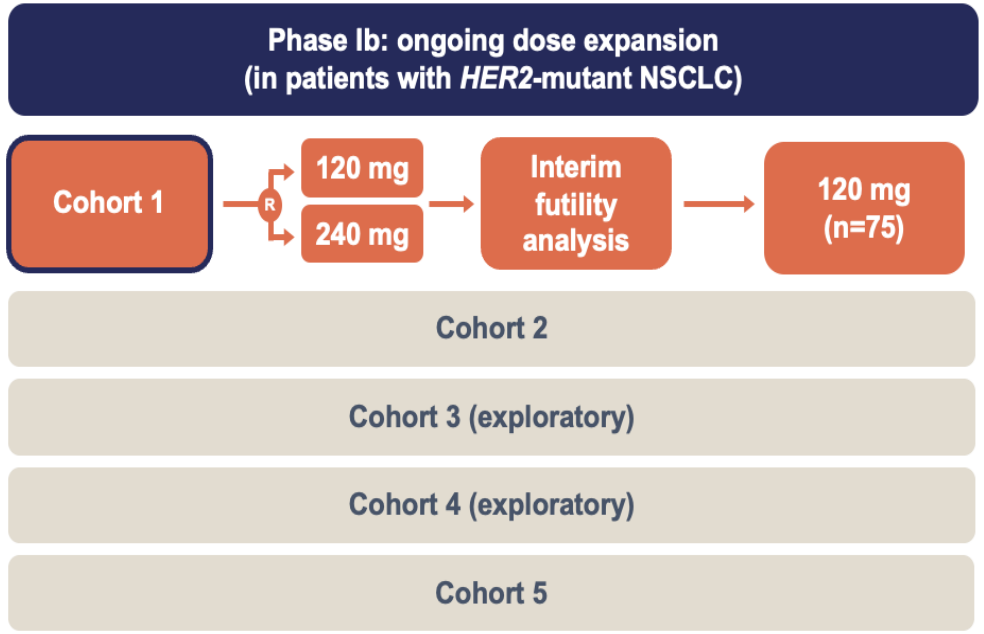
Zongertinib: tyrosine kinase inhibitor of mutant and wild-type HER2

Phase Ib primary endpoint

Confirmed objective response (RECIST v1.1) by central independent review

Key inclusion criteria

Cohort 1:	**Pre-treated*† NSCLC with a *HER2* TKD mutation**
Cohort 2:	Treatment-naïve NSCLC with a *HER2* TKD mutation
Cohort 3:	Pre-treated* NSCLC with a non-TKD *HER2* mutation or *HER2* TKD-mutant squamous NSCLC
Cohort 4:	NSCLC with active brain metastases with a *HER2* TKD mutation
Cohort 5:	Pre-treated* NSCLC with a *HER2* TKD mutation and prior treatment with HER2-directed ADCs



Patient Demographics

	120 mg n = 75	240 mg n = 57
Median age, years (range)	62 (30–80)	62 (36–82)
Sex, n (%)		
Female	51 (68)	25 (44)
Male	24 (32)	32 (56)
Race, n (%)		
Asian	40 (53)	33 (58)
White	24 (32)	15 (26)
Missing	11 (15)	9 (16)
Lines of prior systemic anticancer treatment*, n (%)		
1	42 (56)	28 (49)
2	12 (16)	16 (28)
≥3	21 (28)	13 (23)

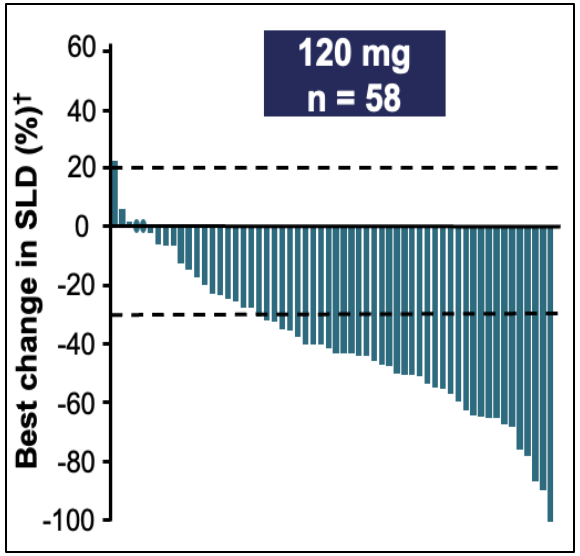
	120 mg n = 75	240 mg n = 57
ECOG PS, n (%)		
0	28 (37)	17 (30)
1	47 (63)	40 (70)
Mutation type, n (%)		
A775_G776insYVMA	49 (65)	34 (60)
P780_Y781insGSP	8 (11)	4 (7)
Other	23 (31)	23 (40)
Brain metastases, n (%)	28 (37)	26 (46)
Tobacco use, n (%)		
Never	49 (65)	32 (56)
Current	2 (3)	0
Former	24 (32)	25 (44)

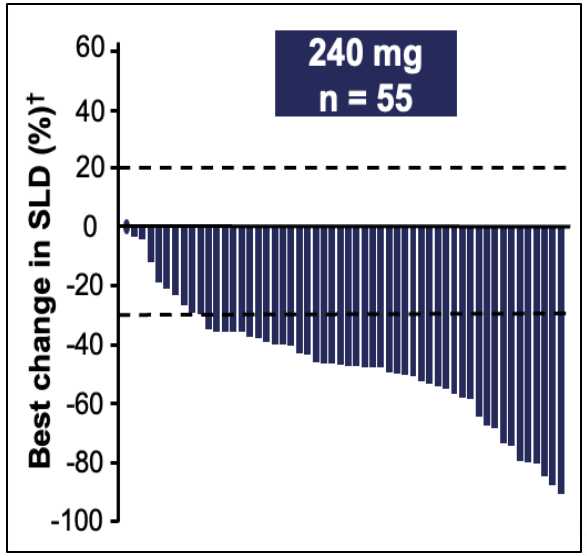
*Over 75% of patients received prior immune checkpoint inhibitor therapy, 9% prior HER2 therapy

Efficacy Endpoints

- ORR 66.7% (97.5% CI 53.8-77.5) for all patients (n = 75) treated at the 120 mg dose.
- Two-thirds of patients remain on therapy at the time of data cut-off (PFS immature).

Confirmed Best Overall Response by Central Review, n (%)	120 mg n = 58	240 mg n = 55
ORR	42 (72.4)	43 (78.2)
CR	1 (1.7)	2 (3.6)
PR	41 (70.7)	41 (74.5)
DCR	55 (94.8)	55 (100.0)
SD	13 (22.4)	12 (21.8)
PD	3 (5.2)	0
NE	0	0





Safety Endpoint

TRAEs, n (%)	120 mg n = 75		240 mg n = 57	
	All	Grade ≥3	All	Grade ≥3
Any TRAE*	69 (92)	13 (17)	57 (100)	11 (19)
Diarrhea	36 (48)	1 (1)	37 (65)	1 (2)
Rash†	18 (24)	0	17 (30)	0
ALT increased	14 (19)	6 (8)	16 (28)	6 (11)
AST increased	16 (21)	4 (5)	14 (25)	4 (7)
Anemia	8 (11)	0	10 (18)	0
Nausea	10 (13)	0	4 (7)	0
Neutrophil count decreased	7 (9)	1 (1)	7 (12)	3 (5)
Pruritus	6 (8)	0	8 (14)	0
Serious TRAE	3 (4)	3 (4)	7 (12)	5 (9)

- Most common adverse events regardless of dose were diarrhea, rash, and elevated liver enzymes.
- Many adverse events were numerically more frequent in patients receiving zongertinib 240 mg, including diarrhea, rash, elevated liver enzymes, anemia, and serious treatment-related adverse events.
- 11% required dose reduction and 3% discontinued treatment.

Intracranial Efficacy

Phase Ib: ongoing dose expansion (in patients with *HER2*-mutant NSCLC)

Cohort 1:*	***HER2* TKD mutation: pretreated**
Cohort 2:	*HER2* TKD mutation: treatment naïve
Cohort 3:†	Non-TKD *HER2*: pretreated
Cohort 4:†	*HER2* TKD mutation: active brain metastases
Cohort 5:	*HER2* TKD mutation: prior HER2-directed ADCs

Patients with brain metastases permitted if asymptomatic (Cohorts 1, 2, 3, 5)

Secondary Endpoint: CNS response by RANO-BM

Phase 1b (*HER2*+ NSCLC): n = 132 (41% w/ CNS metastases)

Confirmed BOR (RECIST v1.1) BICR

Patients with brain metastases (n = 54)
ORR: 70% (1 CR, 37 PR)
DCR: 94%

Patients without brain metastases (n = 78)
ORR: 73% (2 CR, 55 PR)
DCR: 96%

Intracranial Efficacy

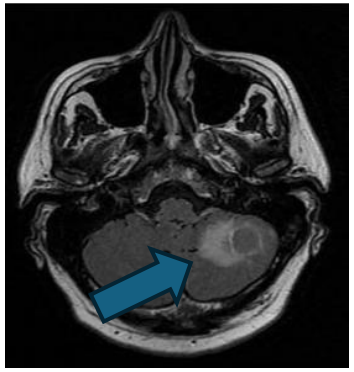
Confirmed BOR (RECIST v1.1) BICR

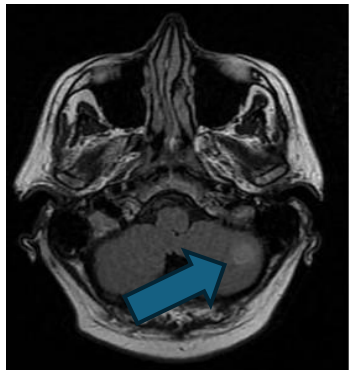
Overall phase 1b cohort (n = 52):
- iORR 37%
- iDCR 83%

Patients who received 120 mg (n = 27)
ORR: 33% (4 CR, 5 PR)
DCR: 74%

Patients who received 240 mg (n = 25)
ORR: 40% (5 CR, 5 PR)
DCR: 92%

Clinical Example:
51 yo M w/ *HER2* exon 20 insertion receiving zongertinib 240 mg daily





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Safety and Efficacy of BAY 2927088 in Patients with *HER2*-Mutant NSCLC: Expansion Cohort from the Phase I/II SOHO-01 Study

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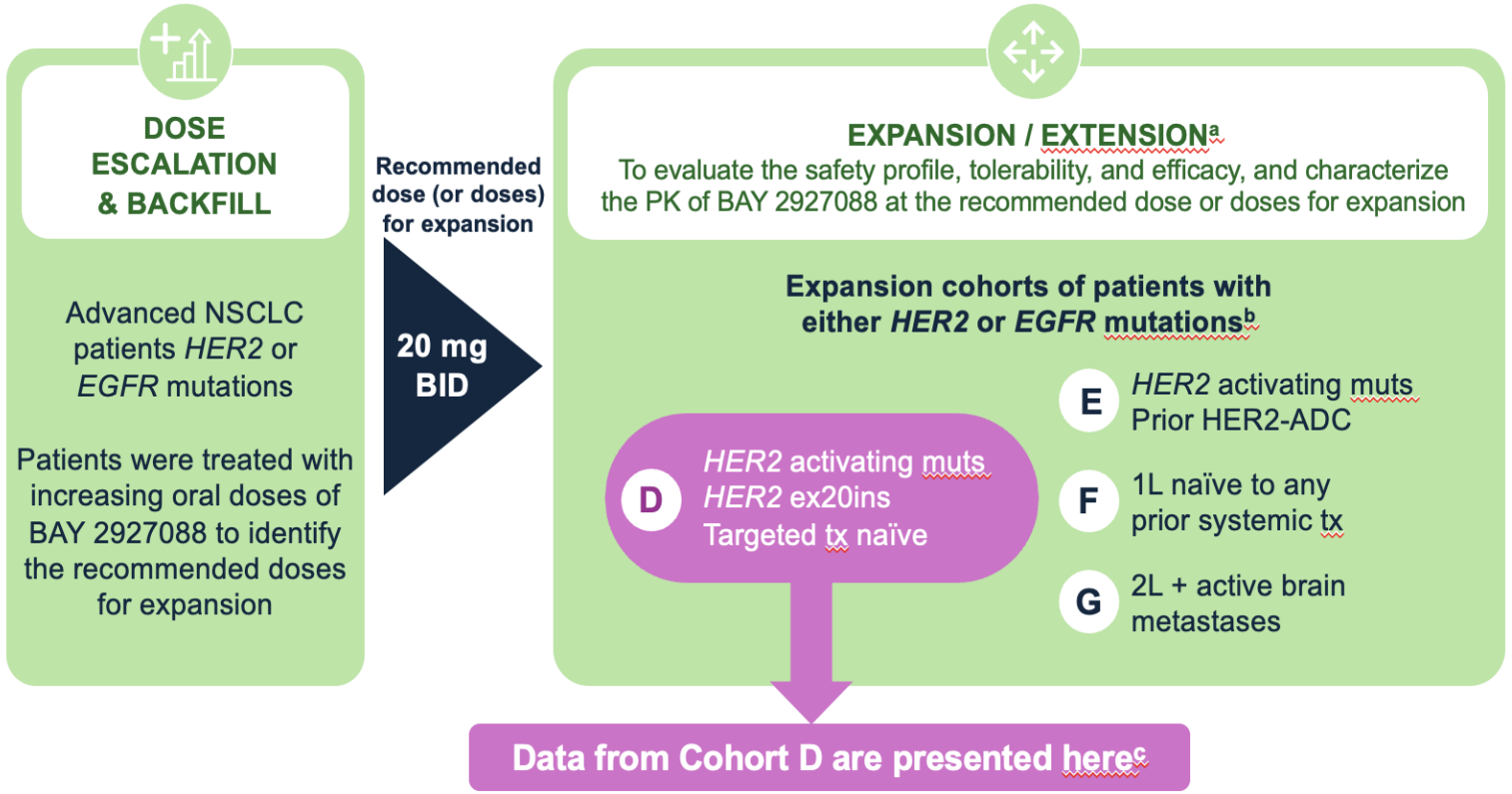
SOHO-01 Study: BAY 2927088

- BAY 2927088: oral, reversible tyrosine kinase inhibitor of *HER2 (ERBB2)*
- SOHO-01 study: open-label, first-in-human phase I/II trial of BAY 2927088 in patients with advanced *HER2*-mutant NSCLC



Primary Endpoint:
- Safety/tolerability
- Pharmacokinetics

Secondary Endpoint:
- ORR
- PFS, DCR, DOR

Patient Demographics

	Cohort D (*N*=44)*
Female, *n* (%)	28 (63.6)
Race, *n* (%)	
White	10 (22.7)
Asian	30 (68.2)
Not reported	4 (9.1)
Median age, years (range)	62.0 (29-82)
Baseline ECOG PS, *n* (%)	
0	19 (43.2)
1	25 (56.8)
Smoking habits at informed consent, *n* (%)	
Never	31 (70.5)
Former	11 (25.0)
Current	2 (4.5)
NSCLC histology, *n* (%)	
Squamous cell carcinoma, not otherwise specified	2 (4.5)
Adenocarcinoma, mixed or not otherwise specified	42 (95.5)
Median time since initial diagnosis, months (range)	16.0 (3.9-77.2)

	Cohort D (*N*=44)
***HER2* mutations**	
Y772_A775dup (YVMA) insertion	31 (70.5)
Point mutations	3 (6.8)
Other	10 (22.7)
Brain metastases at baseline	
Yes	8 (18.2)
No	36 (81.8)
Number of previous systemic anti-cancer treatments, *n* (%)	
1	20 (45.5)
2	10 (22.7)
≥3	14 (31.8)

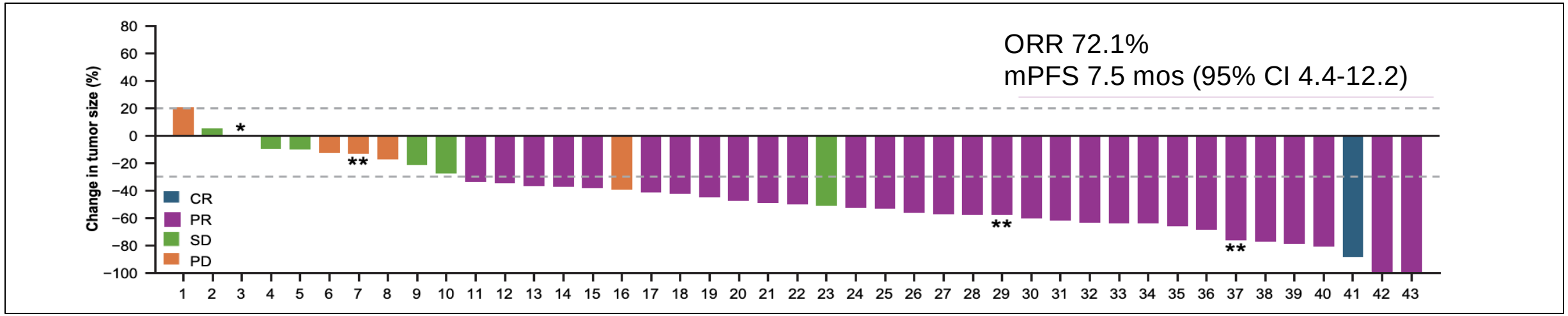
Primary Safety Endpoint

n (%)	All grades (*N*=44)	Grade ≥3 (*N*=44)
Any TRAE	42 (95.5)	19 (43.2)
Most common TRAEs occurring in ≥10% of patients		
Diarrhea	38 (86.4)	11 (25.0)
Rash	19 (43.2)	0
Paronychia	11 (25.0)	0
Nausea	11 (25.0)	1 (2.3)
Vomiting	9 (20.5)	2 (4.5)
Dermatitis acneiform	8 (18.2)	0
Stomatitis	8 (18.2)	1 (2.3)
Dry skin	7 (15.9)	0
Increased aspartate aminotransferase	6 (13.6)	1 (2.3)
Decreased appetite	6 (13.6)	2 (4.5)
Increased amylase	5 (11.4)	0
Anemia	5 (11.4)	0
Increased lipase	5 (11.4)	0
Decreased weight	5 (11.4)	0
Pruritis	5 (11.4)	1 (2.3)

[a]≥2 patients: diarrhea (*n*=6), hepatic function abnormal (*n*=2), ALT increase (*n*=2), decreased appetite (*n*=2)
ILD, interstitial lung disease; TRAE, treatment-related adverse event

- Most reported adverse events were grade 1-2, but grade 3 diarrhea was frequent (25%) (per CTCAE v5: ≥7 stools/day above baseline or hospitalization indicated or limited self-care ADL's).
- 31.8% required dose reduction and 6.8% discontinued treatment.
- No ILD or pneumonitis reported.

Secondary Efficacy Endpoints



- Median follow-up: 10.9 months (range 0.9-20.2)
  - Treatment ongoing in 16 of 44 (36.4%) patients
  - Treatment duration >12 mos in 14 patients (31.8%)

Outcomes in Selected Subgroups

Subgroup		Patients,[a] *n*	ORR, *n* (%; 95% CI)
All evaluable patients in cohort D		43	31 (72.1; 56.3, 84.7)
***HER2* YVMA insertion**	Yes	30	27 (90.0; 73.5, 97.9)
	No	13	4 (30.8; 9.1, 61.4)
Brain metastases at baseline	Yes	8	5 (62.5; 24.5, 91.5)
	No	35	26 (74.3; 56.7, 87.5)
Previous therapy	Previous platinum, no previous immunotherapy	17	12 (70.6; 44.0, 89.7)
	Previous platinum and immunotherapy	25	18 (72.0; 50.6, 87.9)

HER2 YVMA (Y772_A775dup

Median DoR:
9.7 months (95% CI 5.5, NE)

Median PFS:
9.9 months (95% CI 6.9, NE)

Conclusions

- For a molecular subgroup (*HER2*) that has lacked tyrosine kinase inhibitor options, zongertinib and BAY 2927088 represent novel effective therapies with high response rates (~70%).
- Zongertinib demonstrates effective intracranial activity.
- Adverse events should not be minimized, particularly with respect to diarrhea, which can impact quality of life.

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Health-Related Quality of Life (HRQoL) Outcomes with Adagrasib vs Docetaxel in *KRAS*^{G12C}-Mutated NSCLC: KRYSTAL-12 study

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KRYSTAL-12 Schema and PRO Tools

Key eligibility criteria

- Locally advanced or metastatic NSCLC with *KRAS*^{G12C} mutation[b]
- Prior treatment with platinum-based chemotherapy and anti-PD-(L)1 therapy[c]
- ECOG PS 0-1
- Stable and treated brain metastases allowed

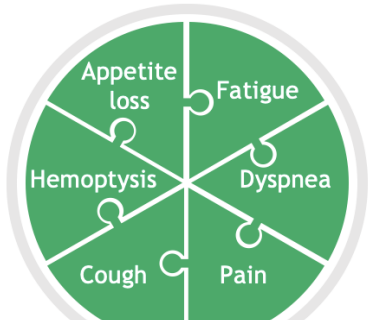
N = 453

R[d] 2:1

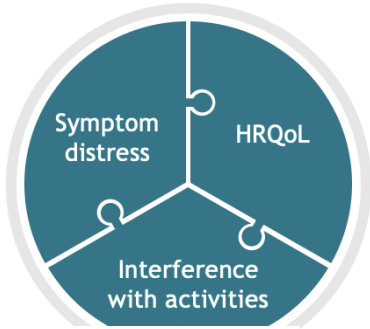
- ADA 600 mg BID PO[e]
- DOCE 75 mg/m^2 Q3W IV[f]

Patient-reported outcomes (LCSS and EQ-5D-5L)

- Data collected on days 1 and 15[g] for cycles 1-4, then at day 1 of every cycle until the end of treatment visit (28-35 days after last dose)



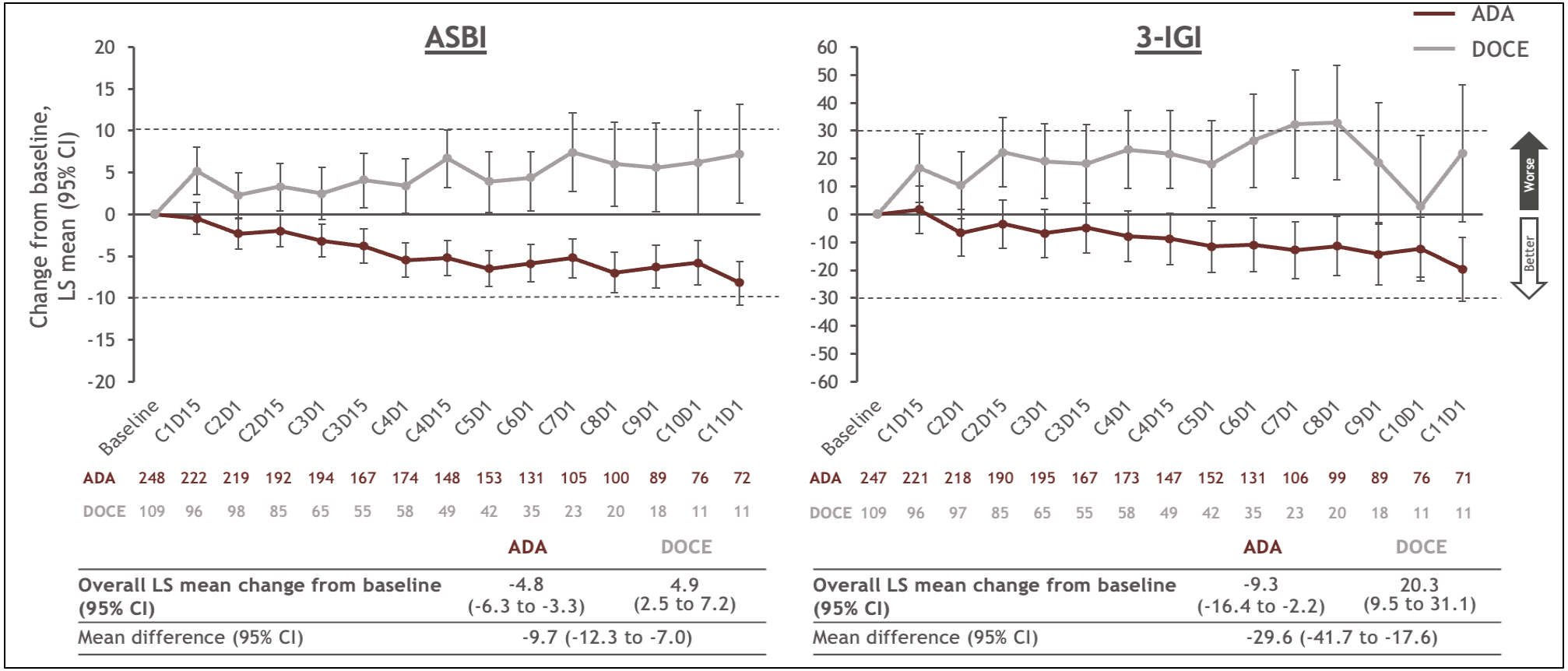
LCSS ASBI



LCSS 3-IGI

EQ-5D-5L

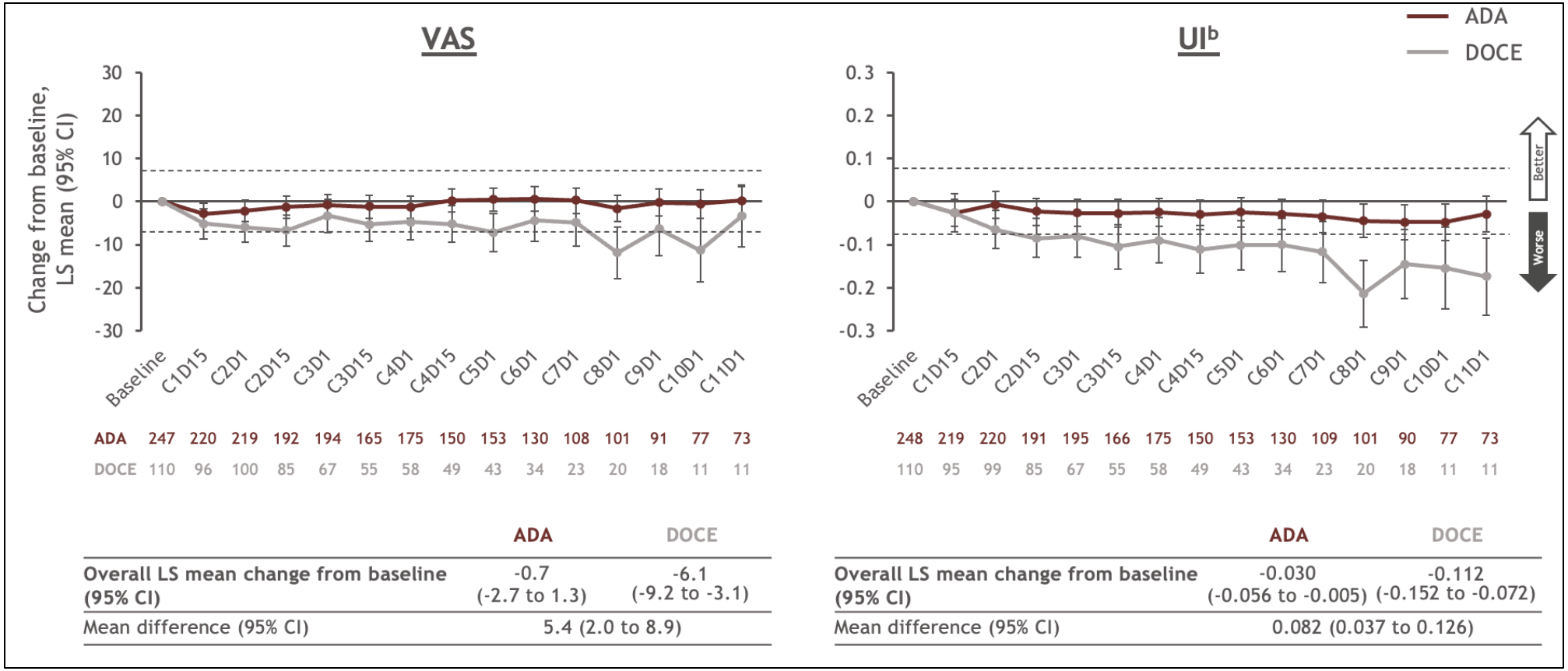
Change in Scores by Treatment Arm



	ADA	DOCE
Overall LS mean change from baseline (95% CI)	-4.8 (-6.3 to -3.3)	4.9 (2.5 to 7.2)
Mean difference (95% CI)	-9.7 (-12.3 to -7.0)	

	ADA	DOCE
Overall LS mean change from baseline (95% CI)	-9.3 (-16.4 to -2.2)	20.3 (9.5 to 31.1)
Mean difference (95% CI)	-29.6 (-41.7 to -17.6)	

Change in Scores by Treatment Arm



	ADA	DOCE
Overall LS mean change from baseline (95% CI)	-0.7 (-2.7 to 1.3)	-6.1 (-9.2 to -3.1)
Mean difference (95% CI)	5.4 (2.0 to 8.9)	

	ADA	DOCE
Overall LS mean change from baseline (95% CI)	-0.030 (-0.056 to -0.005)	-0.112 (-0.152 to -0.072)
Mean difference (95% CI)	0.082 (0.037 to 0.126)	

Novel *KRAS* G12C Inhibitors

Abstract	Drug	ORR	PFS
OA14.03, Li et al, World Lung, 2024	Garsorasib 600 mg BID	52.0%	9.1 mos (5.6-10.3)
OA14.05, Zhou et al, World Lung, 2024	IBI351 600 mg BID	49.1%	9.7 mos (5.6-11.0)
OA14.06, Sacher et al, World Lung, 2024	Divarasib 400 mg daily	59.1%	15.3 mos (12.3-26.1)
Skoulidis et al, *N Engl J Med*, 2021	Sotorasib 960 mg daily	37.1%	6.8 mos (5.1-8.2)
Janne et al, *N Engl J Med*, 2022	Adgarasib 600 mg BID	42.9%	6.5 mos (4.7-8.4)

ORR = objective response rate
PFS = progression free survival

Conclusions

- Adagrasib and sotorasib represent existing targeted therapy options for patients with progressive *KRAS* G12C-positive NSCLC.
- In KRYSTAL-12, adagrasib was associated with improvement in symptoms and metrics of health-related quality of life as compared to docetaxel.
- Nonetheless, more effective targeted therapy options are needed. Several agents are under current study with early encouraging results (e.g., divarasib).

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Updated Efficacy, Safety, and Biomarker Analysis in Patients with TRK Fusion Lung Cancer Treated with Larotrectinib

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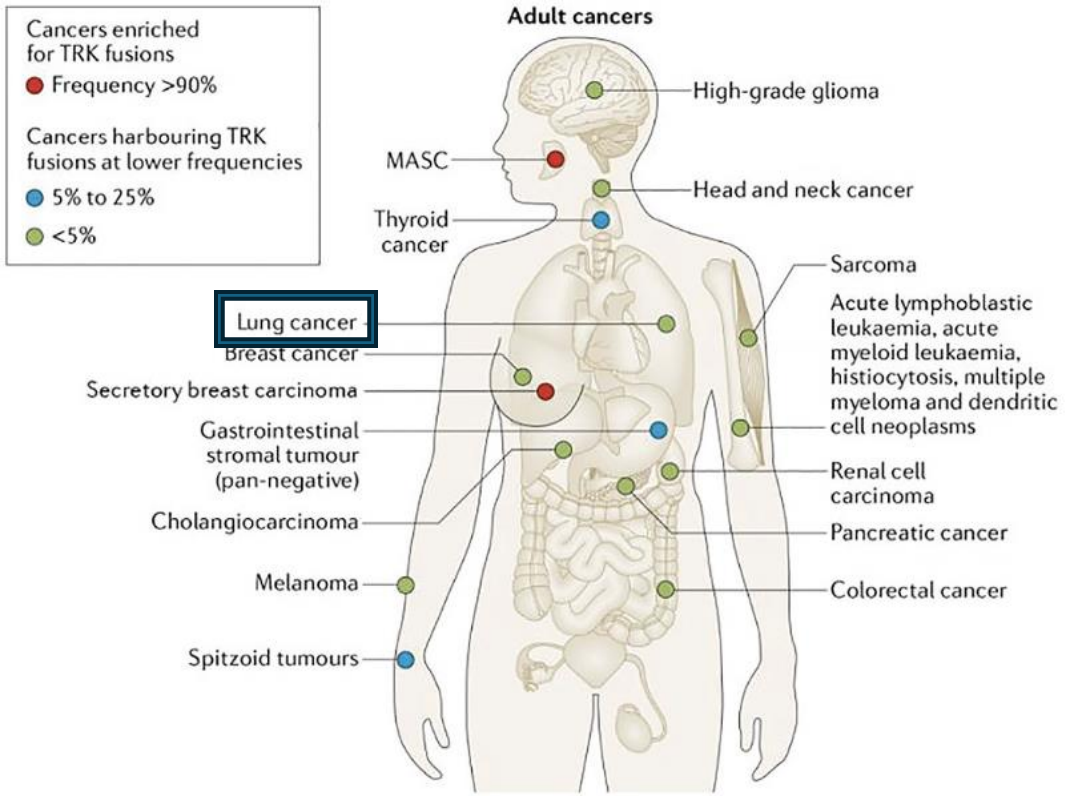
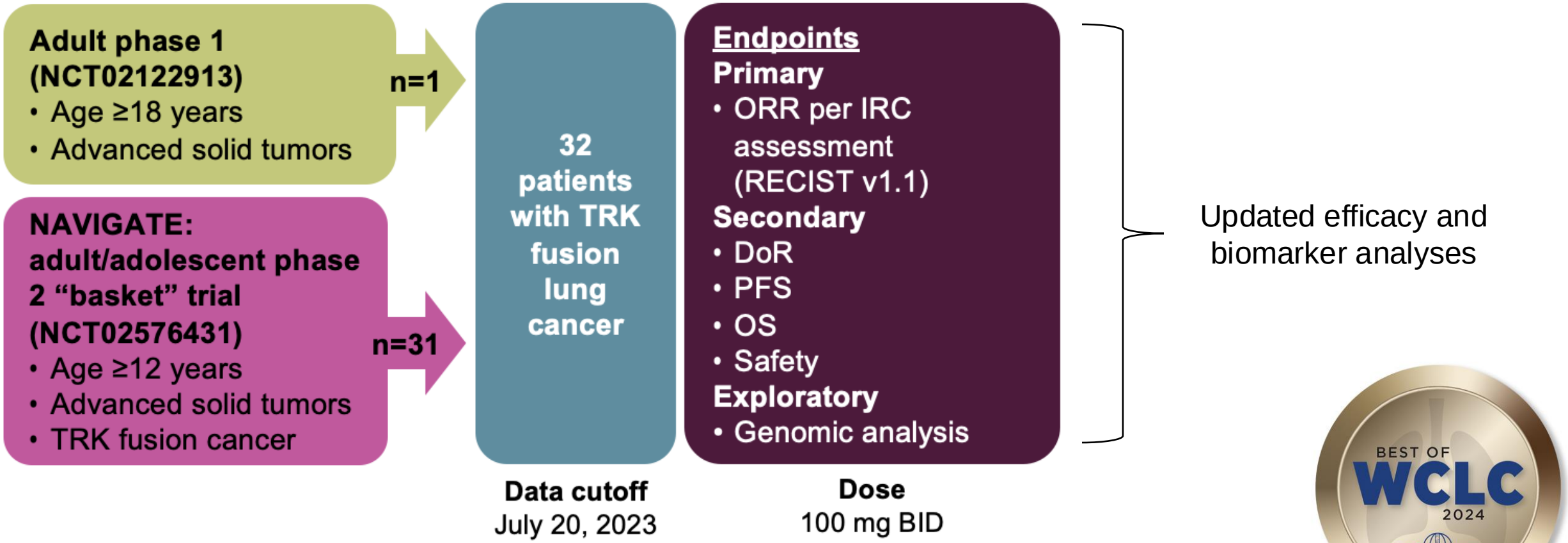
NTRK Fusions in NSCLC



- The incidence of *NTRK* fusion in NSCLC is low (<1%).
- Larotrectinib is a selective small molecular inhibitor of TRKA, TRKB, and TRKC proteins that is approved for patients with solid tumors harboring *NTRK* fusions.
- However, in the pivotal study leading to Larotrectinib's approval (Drilon et al, *N Engl J Med*, 2018), only 4 of 55 enrolled patients had a diagnosis of lung cancer.

Cocco et al, *Nat Rev Clin Oncol*, 2018
Drilon et al, *N Engl J Med*, 2018

Study Design



Patient Demographics

	N=32
Age, years, median (range)	55.5 (25–81)
Sex, n (%)	
Male	13 (41)
Female	19 (59)
***NTRK* gene fusion**, n (%)†	
NTRK1	24 (75)
NTRK2	0
NTRK3	8 (25)
Tumor histology, n (%)	
Adenocarcinoma	30 (94)
Atypical carcinoid	1 (3)
Neuroendocrine	1 (3)‡
Known CNS metastases at baseline, n (%)	
No	20 (63)
Yes	12 (38)

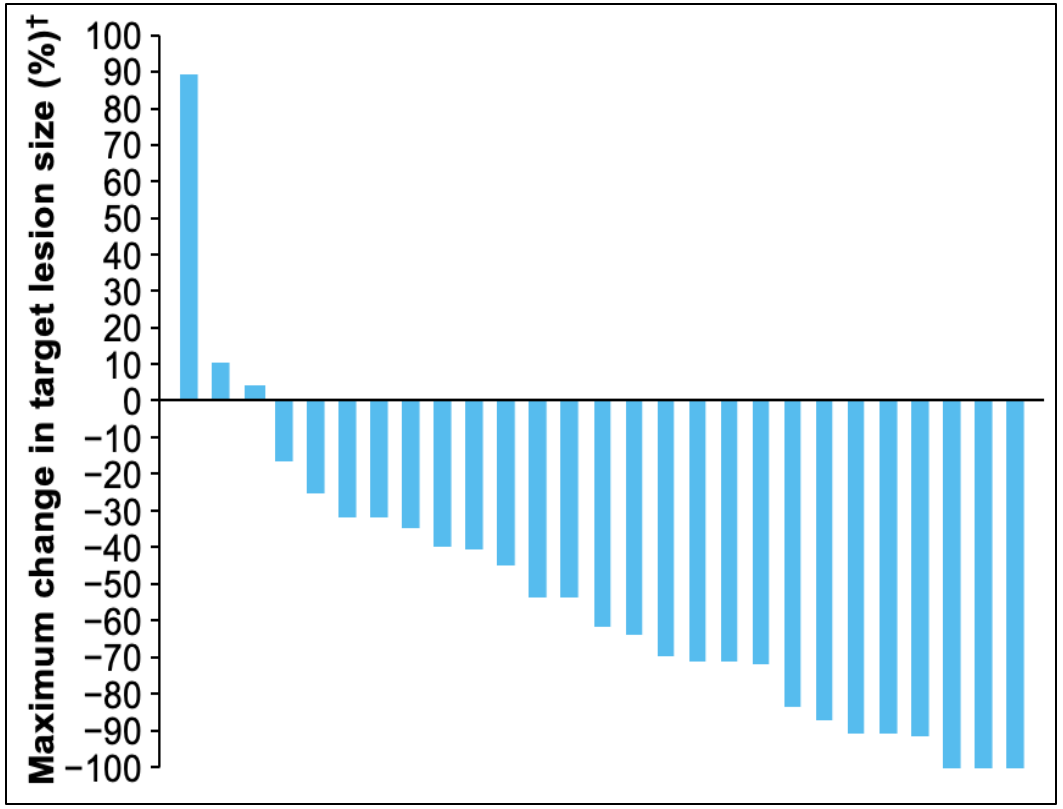
	N=32
Prior therapies, n (%)§	
Surgery	16 (50)
Radiotherapy	15 (47)
Systemic therapy‖,¶	31 (97)
Immunotherapy¶	13 (41)
Prior systemic therapies, median (range)‖,¶	2 (0–8)
Prior systemic therapies, n (%)‖,¶	
0	1 (3)
1	12 (38)
2	7 (22)
≥3	12 (38)

Best response to prior therapy, n (%)#,¶	**Immunotherapy**	**Systemic**
Complete response	1 (8)	1 (3)
Partial response	0	3 (9)
Stable disease	1 (8)	7 (22)
Progressive disease	4 (31)	6 (19)
Other††	7 (54)	14 (44)

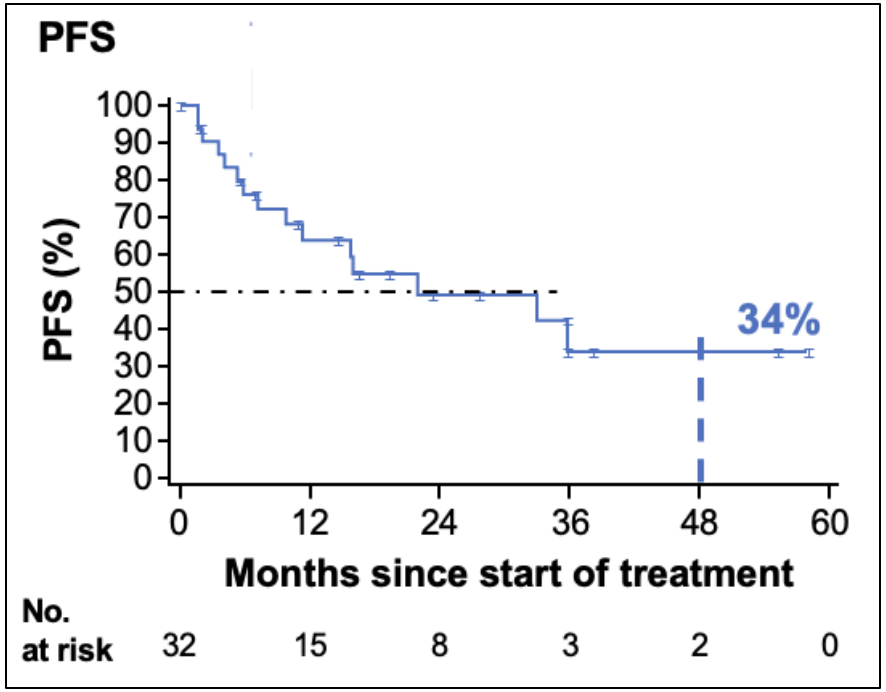
†*NTRK* gene fusions were identified locally by NGS in all patients. ‡This patient was originally diagnosed with small cell lung cancer that was subsequently assessed as neuroendocrine carcinoma. §Patients may be counted in more than 1 row. ‖Excludes patients who received RAI. ¶Includes patients with any prior immunotherapy. #Includes patients who received RAI. ††Includes unknown and not evaluable.
CNS, central nervous system; NGS, next-generation sequencing; RAI, radioactive iodine.

Efficacy

Objective Response Rate

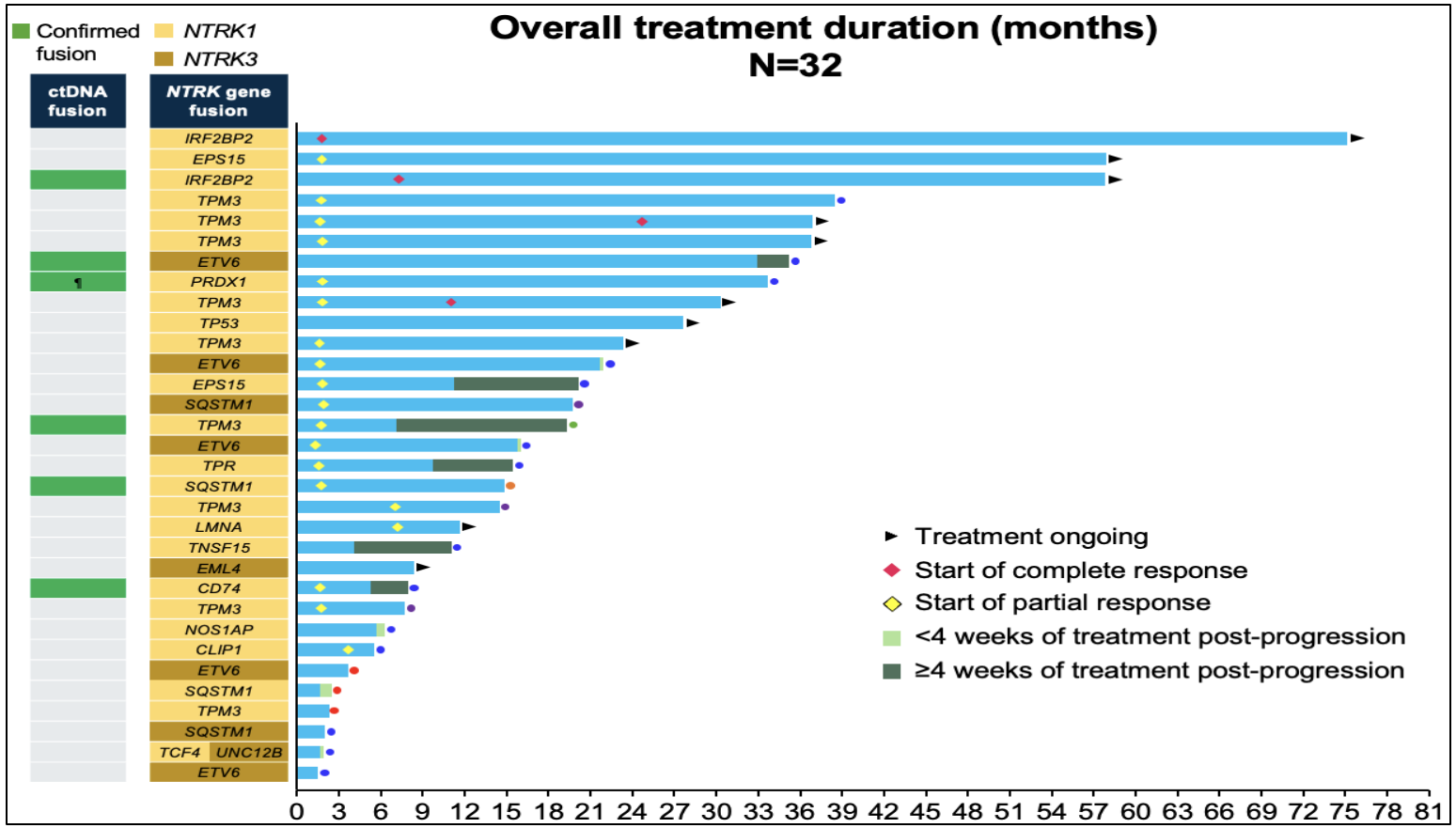


Progression Free Survival



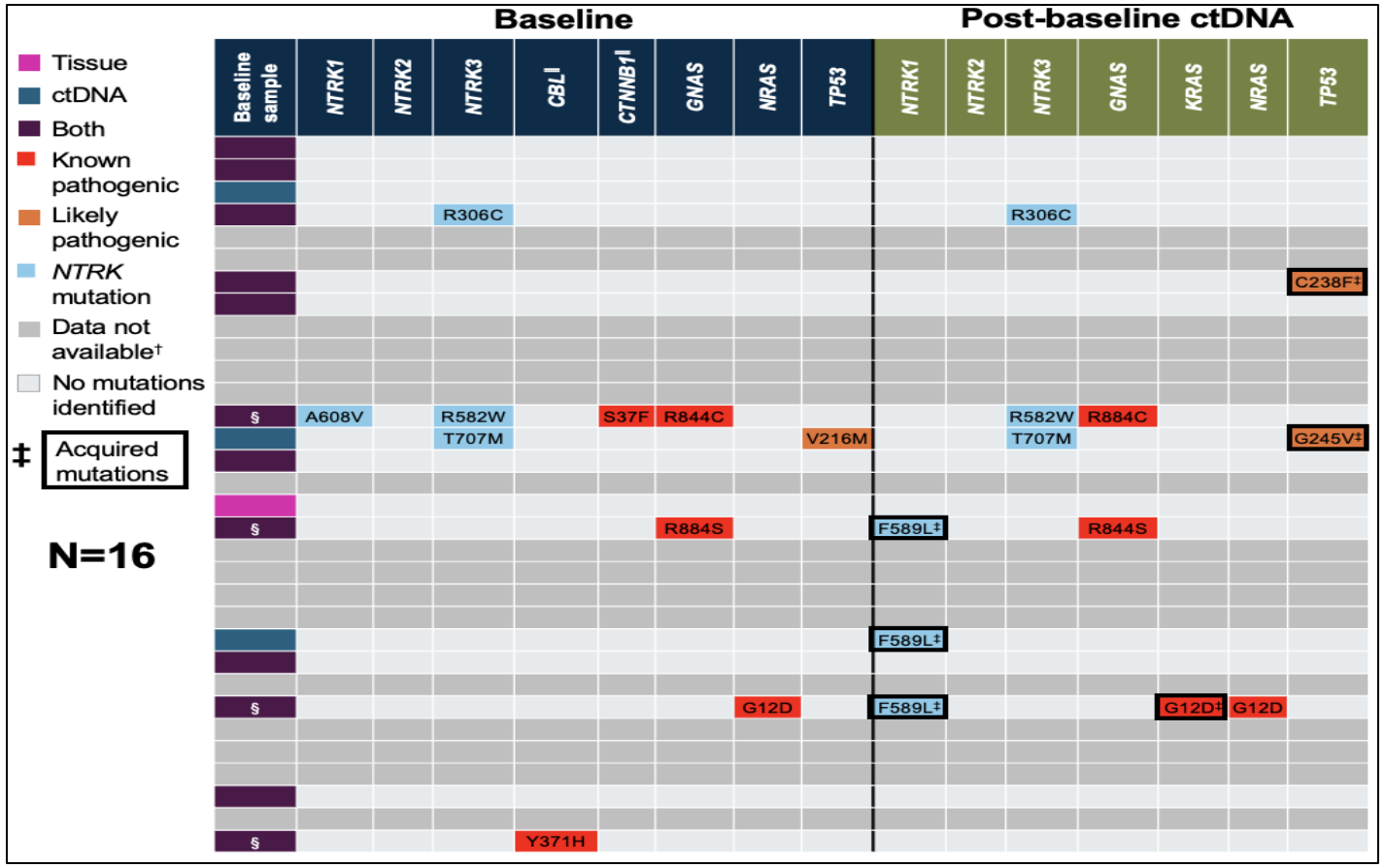
mPFS 22 mos (95% 10-NE)
mOS 39 mos (95% CI 17-NE)

Durability of Response Across Fusion Partners



- Median duration of response (DoR) 34 mos (95% CI 10-NE).
- Durable treatment responses were seen across a range of *NTRK* fusion partners.

Acquired Mechanism of Resistance?



- Paired post-baseline ctDNA sample identified new mutations in the **NTRK kinase domain, *KRAS*, and *TP53***, potentially representing mechanisms of acquired resistance to larotrectinib.

Thank you!

Conclusions

- Although *NTRK* fusions are uncommon in NSCLC, they represent an important targetable driver alteration.
- While approved across tumor types, larotrectinib shows effective and durable activity against *NTRK*-fusion NSCLC in particular.
- Molecular testing (liquid or biopsy) in NSCLC should include an assessment of *NTRK* fusions.