Lung Cancer UPDATES
ASCO HIGHLIGHTS
31 MAYO-04 JUNIO 2024
Chicago, USA

Iniciativa científica de:
GECP
lung cancer research

Enfermedad metastásica, terapias dirigidas: ALK, KRAS, ROS1, HER2 y FGFR

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Enfermedad metastásica con alteración molecular: ALK

Abstract LBA8503: Crown

Iniciativa científica de: GECP lung cancer research

Current Post Hoc Analyses at 5 Years

Endpoint evaluation by BICR stopped after the 3-year analysis

Key eligibility criteria

- Stage IIIB/IV *ALK*+ NSCLC
- No prior systemic treatment for metastatic disease
- ECOG PS 0-2
- Asymptomatic treated or untreated CNS metastases were permitted
- ≥1 extracranial measurable target lesion (RECIST 1.1) with no prior radiation required

Randomized 1:1 N=296

Lorlatinib 100 mg QD n=149

Stratified by:

- Presence of brain metastases (yes vs no)
- Ethnicity (Asian vs non-Asian)

Crizotinib 250 mg BID n=147

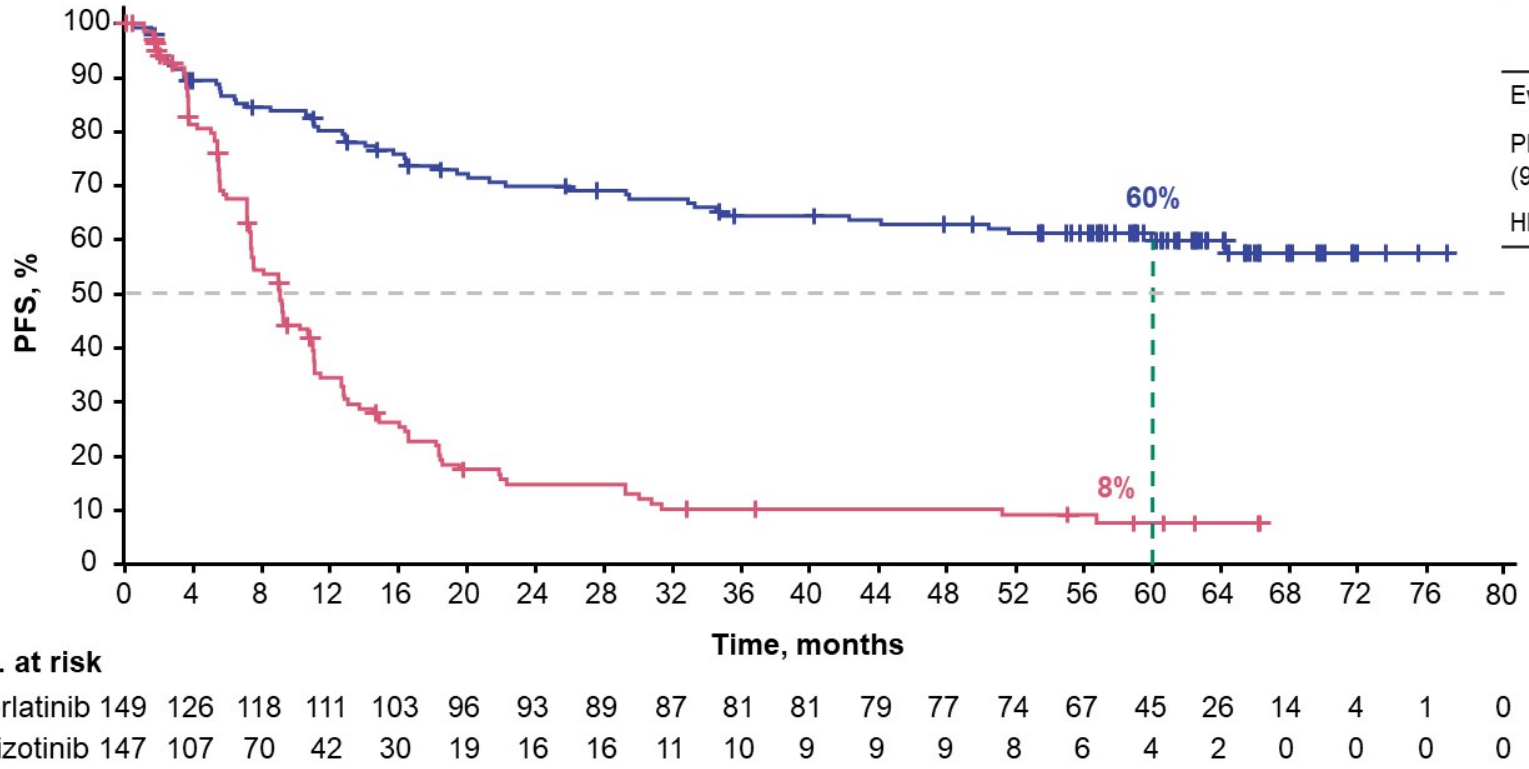
No crossover between treatment arms was permitted

Current analyses

Data cutoff: October 31, 2023

- PFS[a] by investigator
- ORR and IC ORR by investigator
- DOR and IC DOR by investigator
- IC TTP by investigator
- Safety
- Biomarker analyses

At 60.2 Months of Median Follow-Up, Median PFS by Investigator Was Still Not Reached With Lorlatinib



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	55	115
PFS, median (95% CI), months	NR (64.3-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.27)**	

HR, hazard ratio; ITT, intention to treat; NR, not reached; PFS, progression-free survival.

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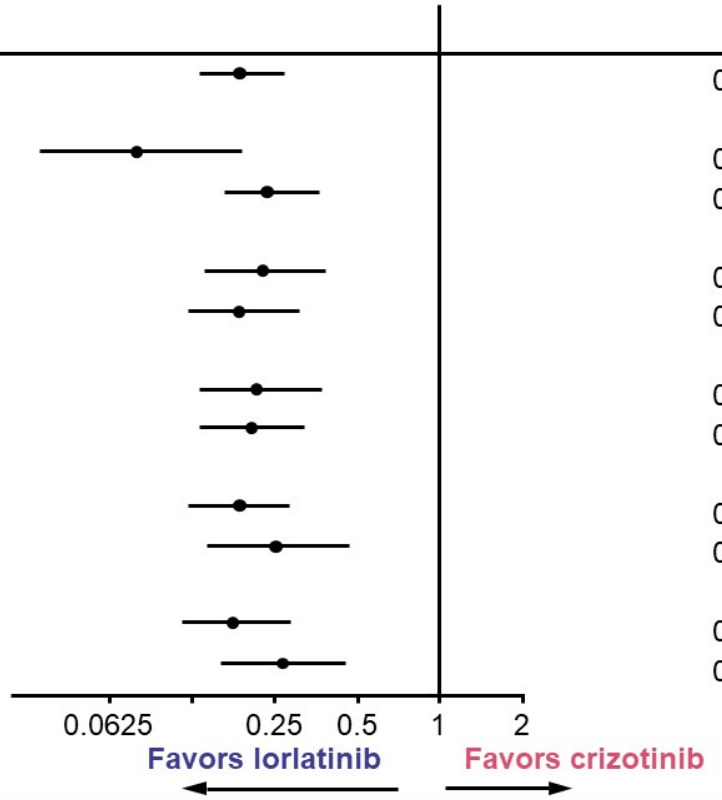
PFS Benefit With Lorlatinib Was Observed Across Patient Subgroups

Subgroup	Patients, n (%)		Events, n		HR (95% CI)
	Lorlatinib	Crizotinib	Lorlatinib	Crizotinib	
All patients (stratified)	149 (100)	147 (100)	55	115	0.19 (0.13-0.27)
Presence of brain metastases					
Yes	35 (23)	38 (26)	16	34	0.08 (0.04-0.19)
No	114 (77)	109 (74)	39	81	0.24 (0.16-0.36)
Ethnic origin					
Asian	66 (44)	65 (44)	25	50	0.23 (0.14-0.38)
Non-Asian	83 (56)	82 (56)	30	65	0.19 (0.12-0.31)
Sex					
Male	65 (44)	56 (38)	24	48	0.22 (0.13-0.37)
Female	84 (56)	91 (62)	31	67	0.21 (0.13-0.32)
Age					
<65 years	96 (64)	110 (75)	33	88	0.19 (0.12-0.28)
≥65 years	53 (36)	37 (25)	22	27	0.26 (0.14-0.47)
Smoking status					
Never	81 (54)	94 (64)	30	75	0.18 (0.12-0.29)
Current/former	68 (46)	52 (35)	25	39	0.27 (0.16-0.45)



PFS, progression-free survival.

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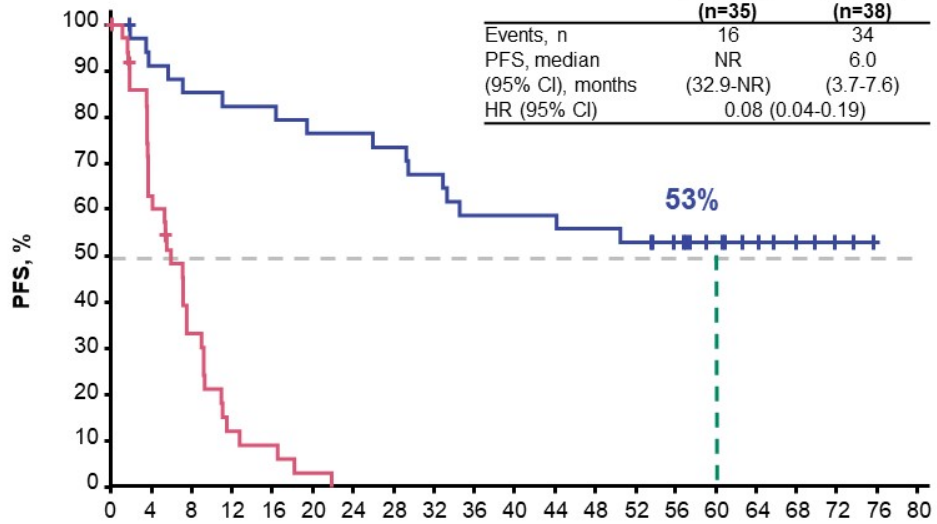
Lorlatinib Showed Superior PFS Benefit Irrespective of Presence or Absence of Baseline Brain Metastases

With Baseline Brain Metastases

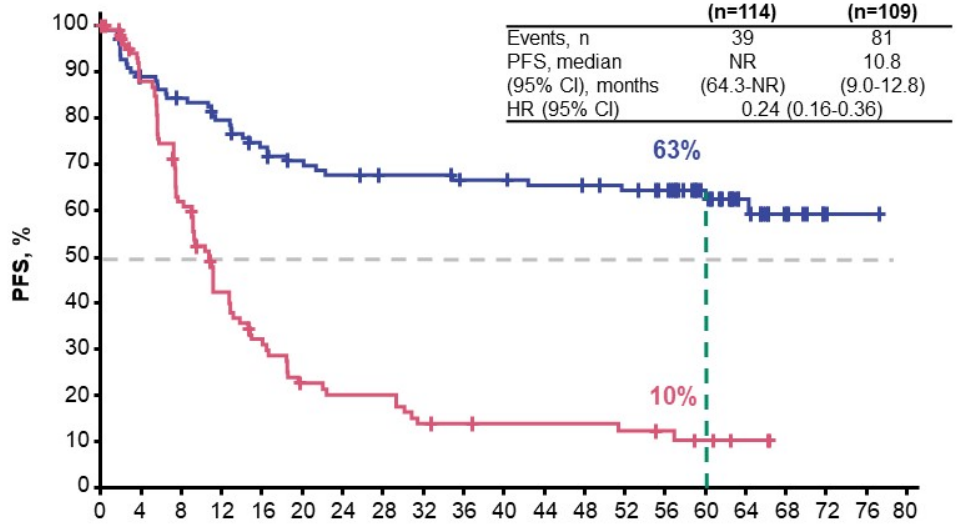
	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	16	34
PFS, median (95% CI), months	NR (32.9-NR)	6.0 (3.7-7.6)
HR (95% CI)	0.08 (0.04-0.19)	



No. at risk																					
Lorlatinib	35	31	29	28	28	26	26	25	23	20	20	20	19	18	15	10	7	5	2	0	-
Crizotinib	38	22	11	4	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-

Without Baseline Brain Metastases

	Lorlatinib (n=114)	Crizotinib (n=109)
Events, n	39	81
PFS, median (95% CI), months	NR (64.3-NR)	10.8 (9.0-12.8)
HR (95% CI)	0.24 (0.16-0.36)	



No. at risk																					
Lorlatinib	114	95	89	83	75	70	67	64	64	61	61	59	58	56	52	35	19	9	2	1	0
Crizotinib	109	85	59	38	27	18	16	16	11	10	9	9	9	8	6	4	2	0	0	0	0

HR, hazard ratio; NR, not reached; PFS, progression-free survival.

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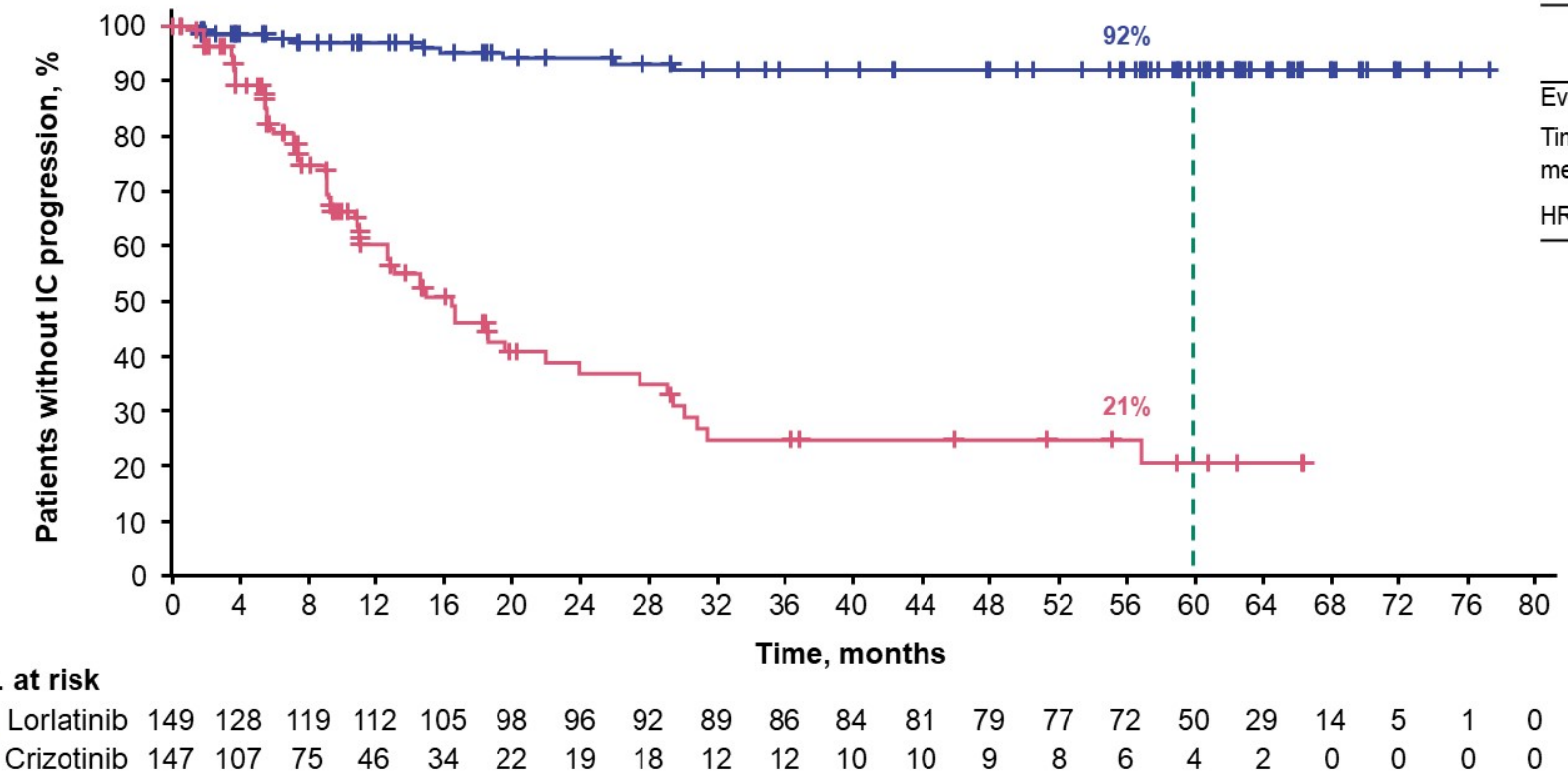
Time to IC Progression by Investigator Was Longer With Lorlatinib Than Crizotinib (ITT Population)



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	9	65
Time to IC progression, median (95% CI), months	NR (NR-NR)	16.4 (12.7-21.9)
HR (95% CI)	0.06 (0.03-0.12)	

Tumor assessments, including brain MRI, have been performed every 8 weeks in all patients throughout the study.
HR, hazard ratio; IC, intracranial; ITT, intention to treat; NR, not reached.

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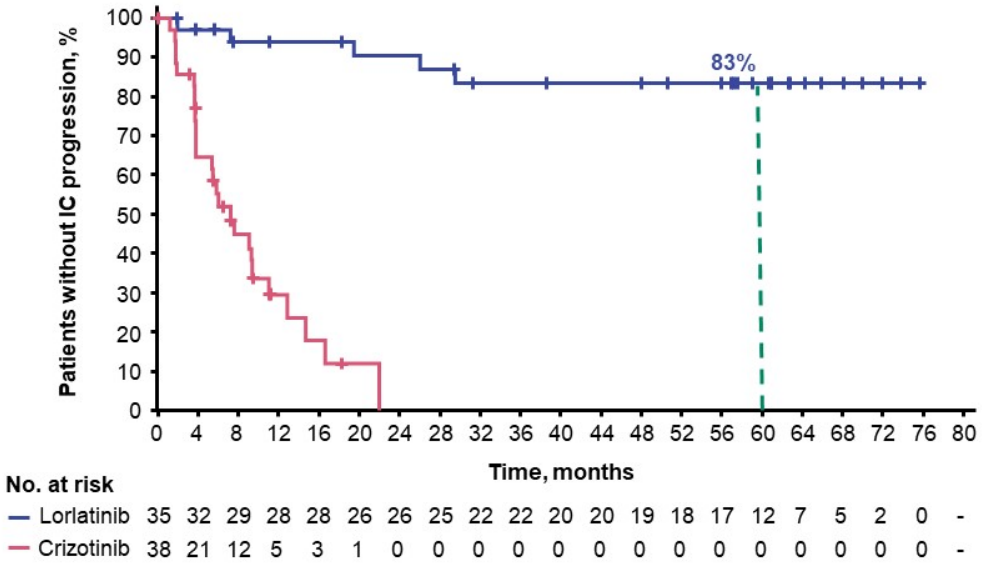
Time to IC Progression Was Longer With Lorlatinib in Presence or Absence of Baseline Brain Metastases

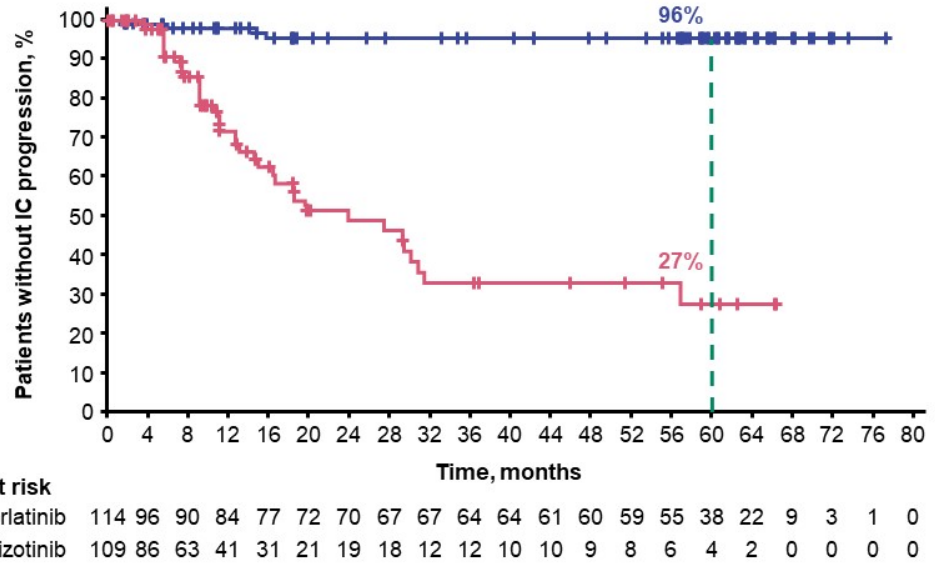
With Baseline Brain Metastases

	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	5	26
Time to IC progression, median (95% CI), months	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	39
Time to IC progression, median (95% CI), months	NR (NR-NR)	23.9 (16.4-30.8)
HR (95% CI)	0.05 (0.02-0.13)	



HR, hazard ratio; IC, intracranial; NR, not reached.

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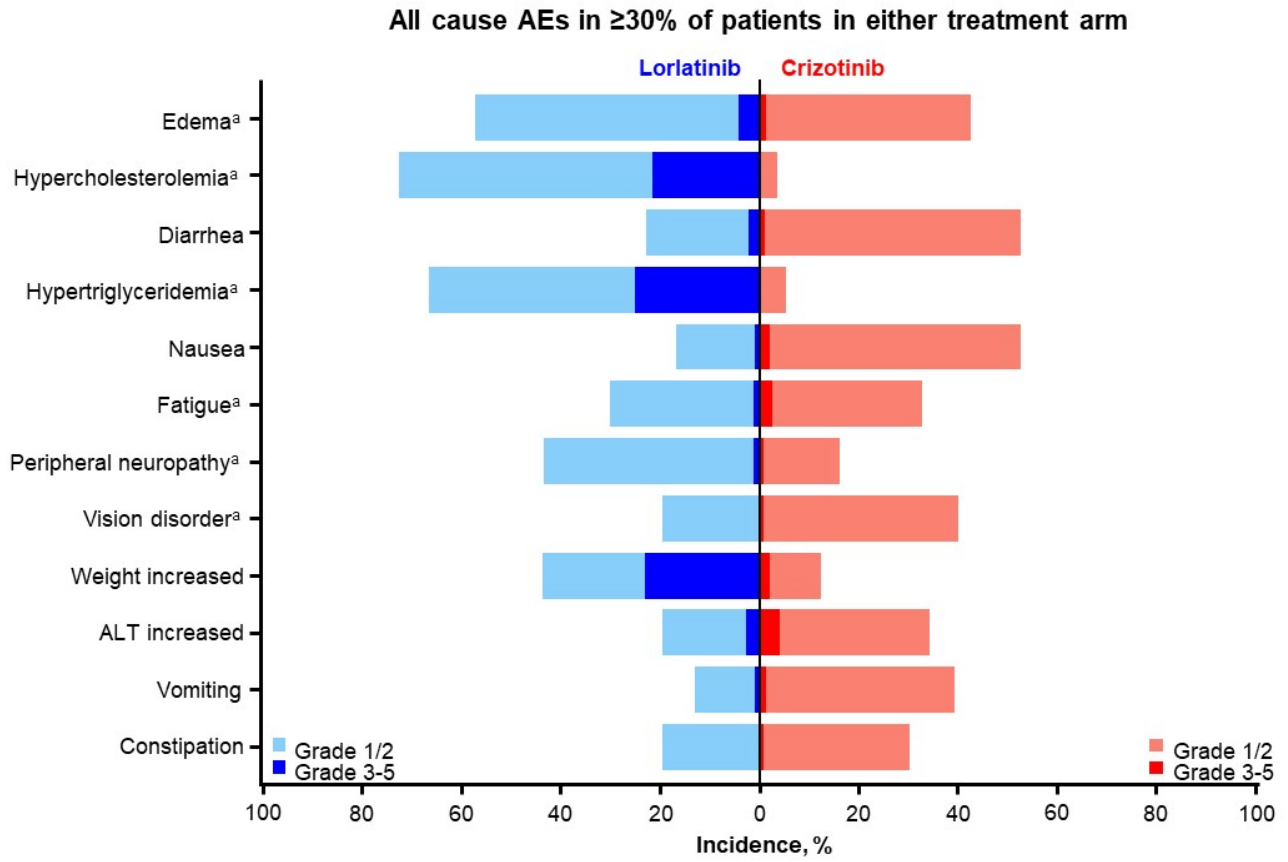
Safety Profile of Lorlatinib Was Consistent With That Observed in Prior Analyses

- All-cause any-grade AEs occurred in all patients in the lorlatinib arm and in 99% in the crizotinib arm
  - Grade 3/4 AEs occurred in 77% and 57% of patients, respectively
- Serious AEs occurred in 44% and 32% of patients in the lorlatinib and crizotinib arms, respectively
- In the lorlatinib arm, all-cause AEs led to dose reduction in 23% of patients, temporary treatment discontinuation in 62%, and permanent discontinuation in 11%
- With lorlatinib, treatment-related AEs led to permanent treatment discontinuation in 5% of patients, all reported during the first 26 months



AE, adverse event.
[a]This category comprised a cluster of AEs that may represent similar clinical symptoms or syndromes.

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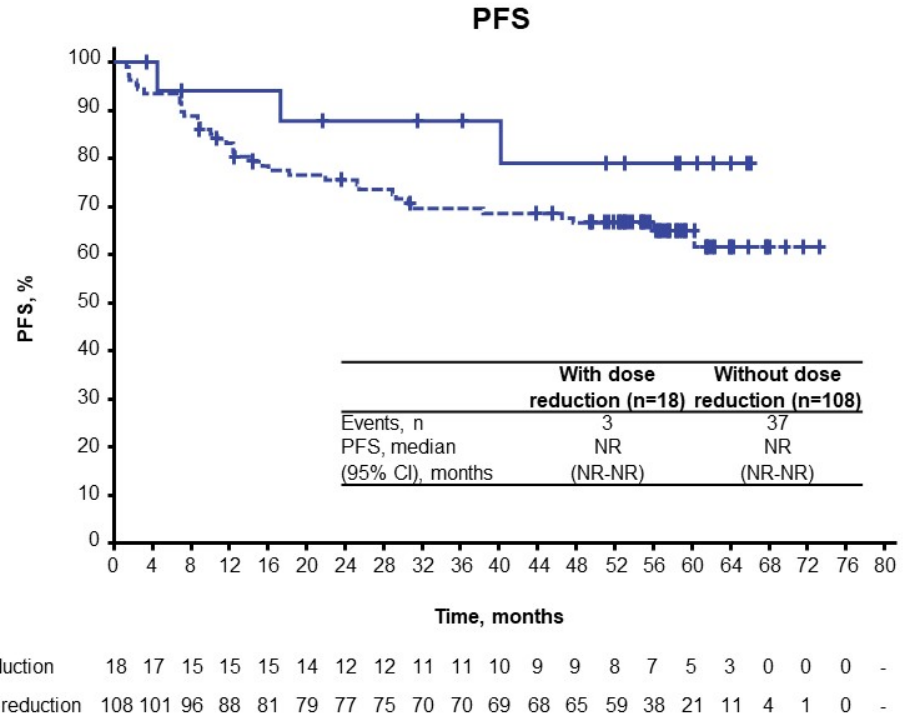
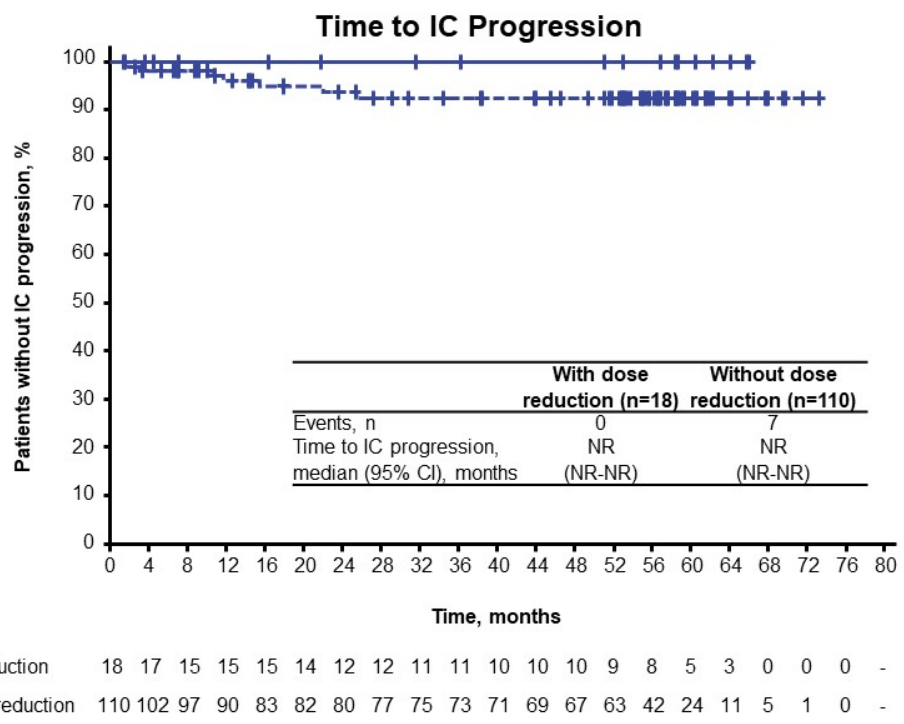
Dose Reduction Did Not Impact Efficacy of Lorlatinib in Patients Who Had Dose Reduction in the First 16 Weeks





IC, intracranial; NR, not reached; PFS, progression-free survival.

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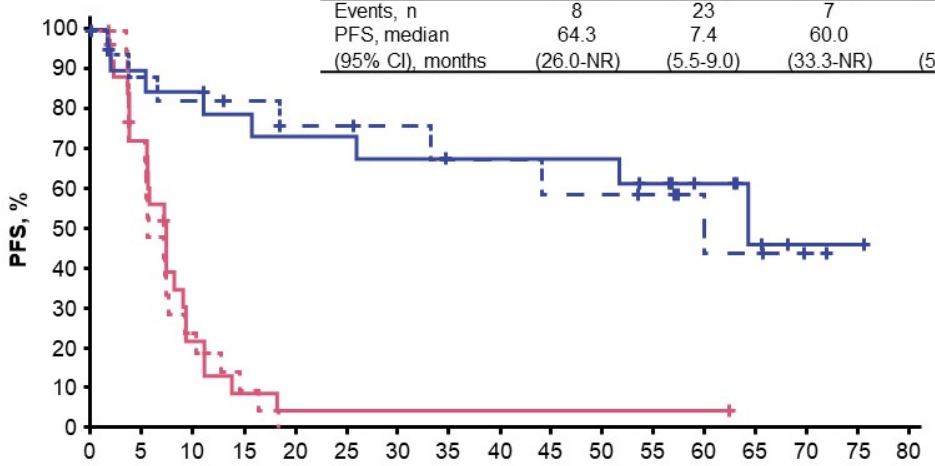
Lorlatinib Treatment Benefited Patients With Poor Prognostic Biomarkers

	Variant 1		Variant 3a/b	
	Lorlatinib (n=20)	Crizotinib (n=26)	Lorlatinib (n=18)	Crizotinib (n=23)
Events, n	8	23	7	21
PFS, median (95% CI), months	64.3 (26.0-NR)	7.4 (5.5-9.0)	60.0 (33.3-NR)	5.6 (5.3-7.6)



***EML4::ALK* variant 1**

No. at risk

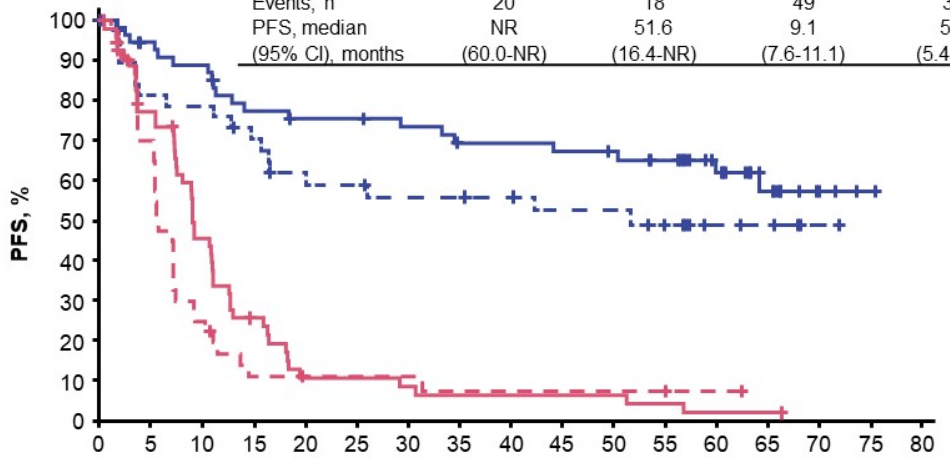
Lorlatinib	20	17	16	14	13	13	12	11	11	11	11	9	6	3	1	1	0
Crizotinib	26	18	5	2	1	1	1	1	1	1	1	1	1	0	0	0	0

***EML4::ALK* variant 3**

No. at risk

Lorlatinib	18	15	14	13	11	11	9	8	8	7	7	6	3	3	1	0	-
Crizotinib	23	15	5	2	0	0	0	0	0	0	0	0	0	0	0	0	-

	Lorlatinib		Crizotinib	
	TP53 mut (-) (n=56)	*TP53* mut (+) (n=41)	*TP53* mut (-) (n=58)	*TP53* mut (+) (n=42)
Events, n	20	18	49	36
PFS, median (95% CI), months	NR (60.0-NR)	51.6 (16.4-NR)	9.1 (7.6-11.1)	5.7 (5.4-7.2)



Lorlatinib

No. at risk

TP53 mut (-)	56	50	47	40	38	38	36	33	33	32	31	28	20	12	4	1	0
TP53 mut (+)	41	30	29	25	21	20	18	18	17	15	15	12	6	4	1	0	0

Crizotinib

No. at risk

TP53 mut (-)	58	40	23	12	5	5	4	3	3	3	3	2	1	1	0	-	-
TP53 mut (+)	42	28	10	4	3	3	3	2	2	2	2	2	1	0	0	-	-

mut, mutation; NR, not reached; PFS, progression-free surviva

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Emerging New *ALK* Mutations Were Not Detected in ctDNA Collected at the End of Lorlatinib Treatment

n (%)	Lorlatinib (n=31)	Crizotinib (n=89)
Resistance mechanisms		
New single ALK mutation	0	8 (9)
ALK compound mutation	0	2 (2)
Bypass mechanism	9 (29)	10 (11)
MAPK pathway aberration	3 (10)	1 (1)
PI3K/MTOR/PTEN pathway aberration	2 (6)	0
RTK pathway aberration	4 (13)	5 (6)
Cell cycle pathway aberration	2 (6)	5 (6)
Other gene aberration	11 (35)	19 (21)
Unknown	13 (42)	56 (63)

ctDNA from plasma collected at screening was analyzed with a validated, commercially available, 74-gene ctDNA next-generation sequencing assay (Guardant360 panel version 2.11; bioinformatics pipeline version 3.5.3; Guardant Health, Inc., Redwood City, CA).
ctDNA, circulating tumor DNA.

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Enfermedad metastásica con alteración molecular: KRAS

Iniciativa científica de: GECP lung cancer research

Segunda línea

· Abstract LBA8509: Sotorasib

Primera línea

· Abstract 8510: Olomorasib + Pembrolizumab

· Abstract 8512: Carboplatino + Pemetrexed + Sotorasib

· Abstract LBA8511: Fulcerasib

· Abstracts 4088 y 3008: Glecirasib

Enfermedad metastásica con alteración molecular: KRAS

Segunda línea: LBA8509

Iniciativa científica de: GECP lung cancer research

KRYSTAL-12: phase 3 study of adagrasib versus docetaxel in patients with previously treated locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring a *KRAS*^{G12C} mutation

Tony S. K. Mok,[1] Wenxiu Yao,[2] Michaël Duruisseaux,[3-5] Ludovic Doucet,[6] Aitor Azkárate Martínez,[7]

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 brain metastases allowed

N = 453

R 2:1

ADA 600 mg BID PO[d]

DOCE 75 mg/m^2 Q3W IV

Stratified by:

- **Region (non-Asia-Pacific vs Asia-Pacific)**
- **Prior treatment (sequential vs concurrent chemotherapy and immunotherapy)**

Crossover from DOCE to ADA was allowed in cases where disease progression per RECIST v1.1 was confirmed by real-time BICR[e]

- 44 (29%) patients crossed over from DOCE to ADA after BICR-confirmed disease progression

Primary endpoint

- PFS by BICR (RECIST v1.1)

Secondary endpoints

- ORR by BICR (RECIST v1.1)
- DOR
- OS
- Safety
- Patient-reported outcomes

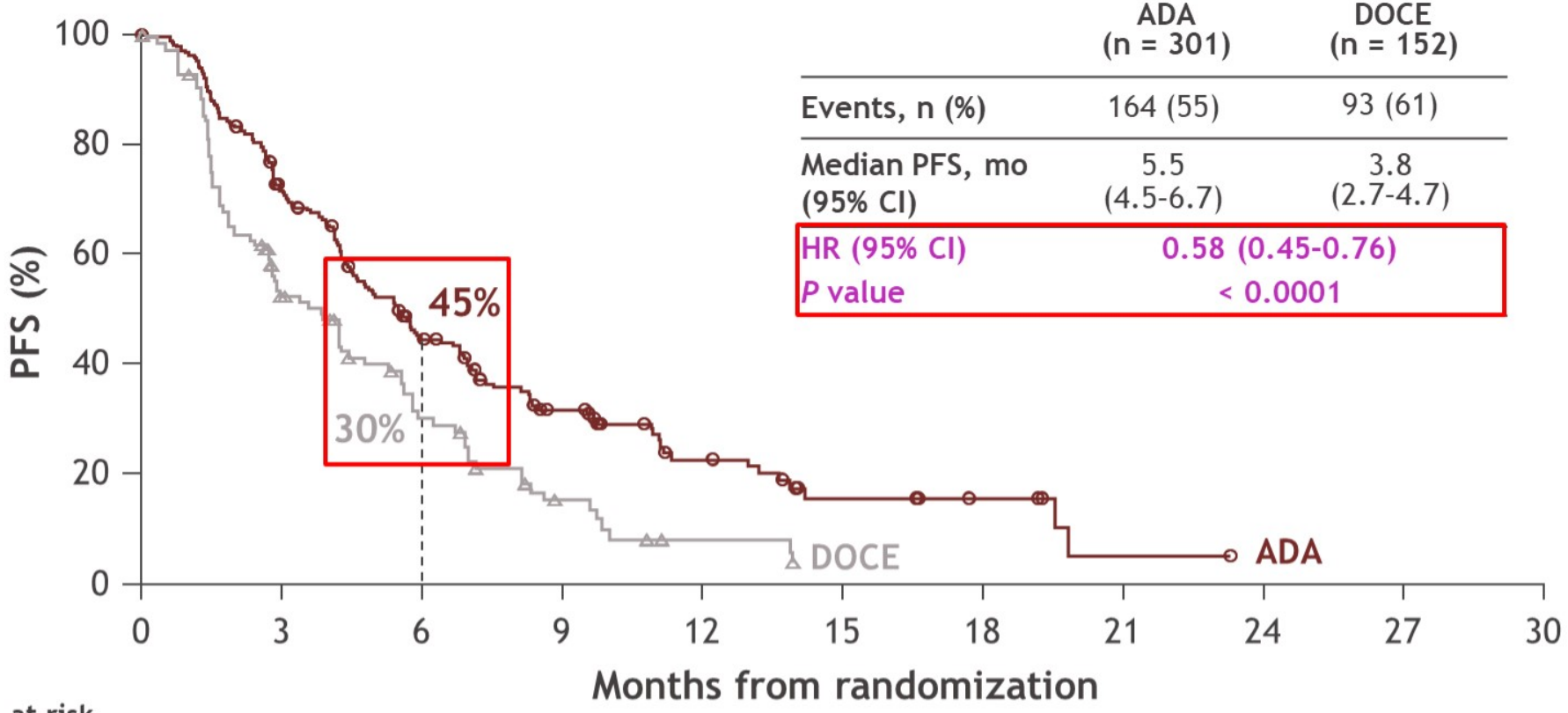
Baseline patient characteristics

	ADA (n = 301)	DOCE (n = 152)
Median age, years (range)	64 (34-83)	65 (45-80)
Age category, %		
< 65 years	53	49
≥ 65 years	47	51
Male, %	64	72
Region, %		
Non-Asia-Pacific	74	74
Asia-Pacific	26	26
ECOG PS, %[a]		
0	32	31
1	68	68
Disease stage, %		
Locally advanced	6	5
Metastatic	94	95
Histology, %		
Adenocarcinoma	94	97
Other[b]	6	3

	ADA (n = 301)	DOCE (n = 152)
Smoking status, %[a]		
Current	19	20
Former	76	74
Never	6	6
Metastases at baseline, %[c]		
Brain	17	18
Liver	15	12
Bone	23	26
Tumor PD-L1 expression, %		
< 1%	20	22
1-49%	42	45
≥ 50%	24	19
Not evaluated	14	13
Prior chemo-immunotherapy, %		
Sequential	27	27
Concurrent	73	73

Percentages may not total 100 due to rounding. [a]Data missing for 1 patient in DOCE arm. [b]Other histologies in ADA/DOCE arms, respectively, were large-cell (n = 4/n = 1), unclassified or undifferentiated (n = 6/n = 1), squamous (n = 6/n = 0) and other (n = 2/n = 3). [c]In accordance with RECIST v1.1 per BICR.

Primary endpoint: PFS[a] per BICR



	ADA (n = 301)	DOCE (n = 152)
Events, n (%)	164 (55)	93 (61)
Median PFS, mo (95% CI)	5.5 (4.5-6.7)	3.8 (2.7-4.7)
HR (95% CI)	0.58 (0.45-0.76)	
P value	< 0.0001	

No. at risk

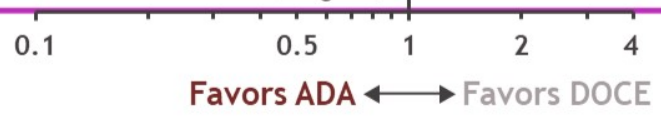
ADA	301	160	77	41	19	8	5	1	0	0	0
DOCE	152	51	24	9	2	0	0	0	0	0	0

Median follow-up: 7.2 months.

[a]Time from randomization to the date of disease progression per BICR or death due to any cause, whichever occurs first. For patients who started a subsequent anticancer therapy prior to disease progression or death, PFS was censored at the date of the last tumor assessment prior to the start of the new therapy.

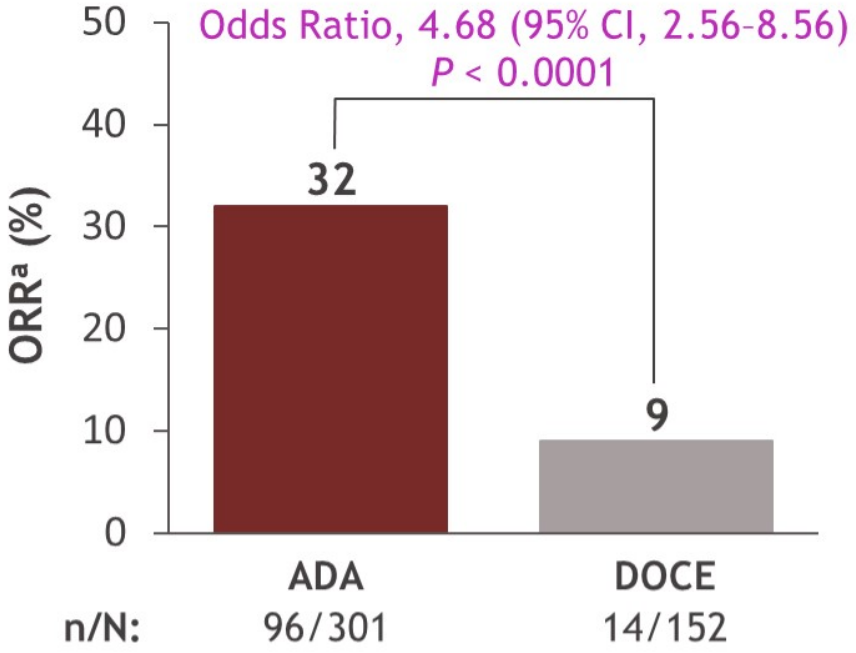
PFS subgroup analysis per BICR

	Median PFS, mo		Unstratified HR (95% CI)	Unstratified HR
	ADA (n = 301)	DOCE (n = 152)		
Overall (N = 453)	5.5	3.8		0.58
< 65 years (n = 234)	5.4	2.9		0.56
≥ 65 years (n = 219)	5.9	4.2		0.60
Male (n = 303)	5.4	2.9		0.55
Female (n = 150)	5.6	5.6		0.64
Non-Asia-Pacific (n = 335)	5.7	3.4		0.55
Asia-Pacific (n = 118)	5.4	3.9		0.66
ECOG PS 0 (n = 143)	11.1	5.8		0.44
ECOG PS 1 (n = 309)	4.6	2.8		0.61
Current smoker (n = 86)	4.2	4.4		0.89
Former smoker (n = 340)	5.8	3.6		0.51
Never smoker (n = 26)	5.5	6.2		0.70
Brain metastases at baseline (n = 80)[a]	4.1	4.2		0.71
No brain metastases at baseline (n = 373)[a]	5.8	3.6		0.55
Liver metastases at baseline (n = 64)[a]	4.5	1.4		0.43
No liver metastases at baseline (n = 389)[a]	5.6	4.2		0.59
Bone metastases at baseline (n = 107)[a]	4.4	2.8		0.56
No bone metastases at baseline (n = 346)[a]	5.8	4.2		0.58
PD-L1 < 1% (n = 95)	5.8	2.8		0.44
PD-L1 1-49% (n = 195)	5.9	3.6		0.56
PD-L1 ≥ 50% (n = 100)	5.0	3.9		0.62
Sequential chemo-immunotherapy (n = 121)	5.8	2.9		0.53
Concurrent chemo-immunotherapy (n = 332)	5.4	3.9		0.60

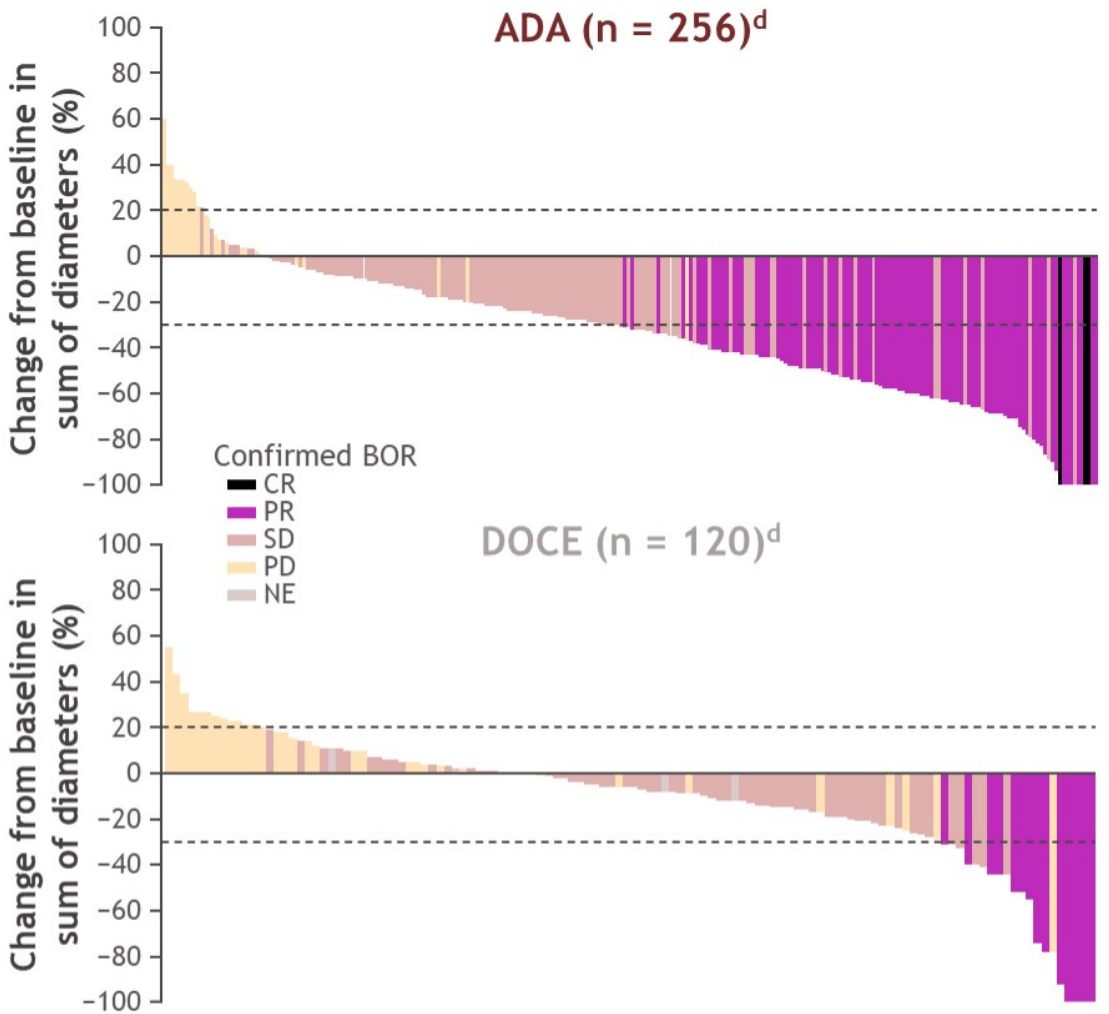


Median follow-up: 7.2 months.
Bold text indicates stratification factors. [a]In accordance with RECIST v1.1 per BICR.

Tumor response per BICR



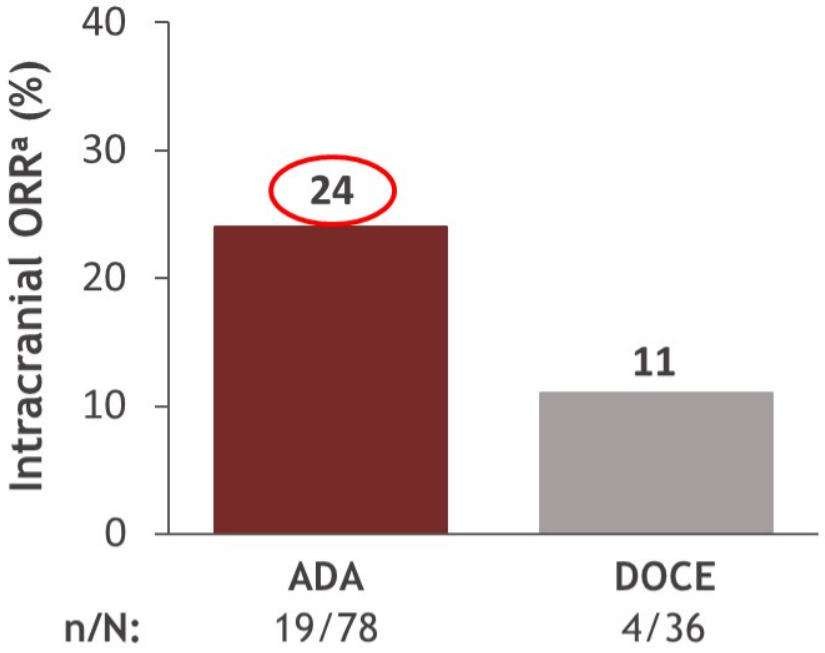
Tumor response	ADA (n = 301)	DOCE (n = 152)
DCR,[b] n (%)	236 (78)	89 (59)
Median DOR,[c] mo (95% CI)	8.3 (6.1-10.4)	5.4 (2.9-8.5)
Remaining in response at 6 mo, %	64	39



[a]ORR is defined as the percent of patients documented to have a confirmed CR/PR by BICR (per RECIST v1.1). [b]Disease control rate (DCR) is defined as the percent of patients documented to have a confirmed CR/PR/SD by BICR (per RECIST v1.1). [c]DOR is defined as the time from the date of first documentation of CR/PR to the first documentation of PD or death due to any cause in the absence of documented PD. DOR is only calculated for patients with confirmed CR/PR. [d]Waterfall plots include patients with at least one target lesion at baseline and at least one post-baseline tumor assessment.

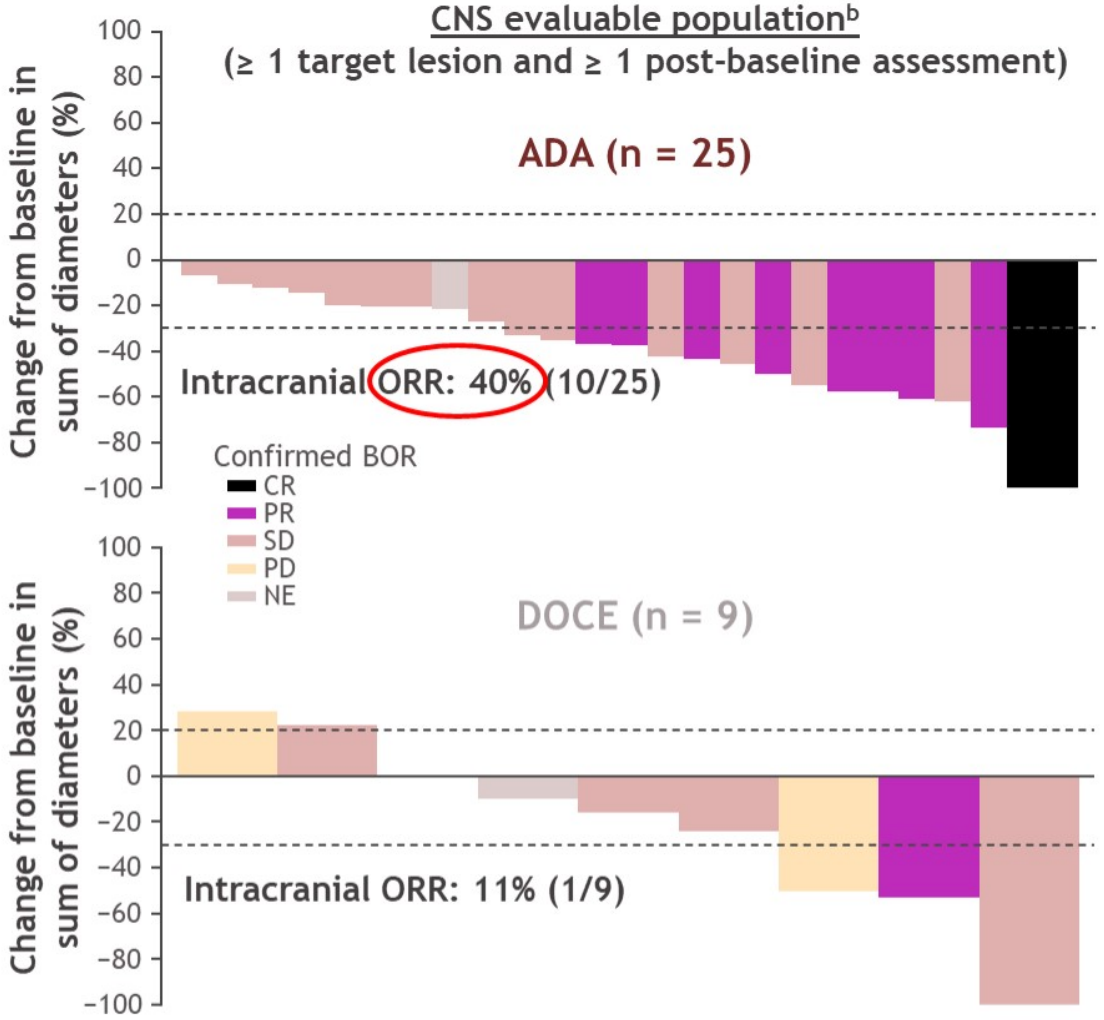
Intracranial response per BICR[a]

All patients with baseline CNS metastases[a]



Intracranial response[a]	ADA (n = 78)	DOCE (n = 36)
Intracranial DCR, n (%)	64 (82)	20 (56)

CNS evaluable population[b]
(≥ 1 target lesion and ≥ 1 post-baseline assessment)



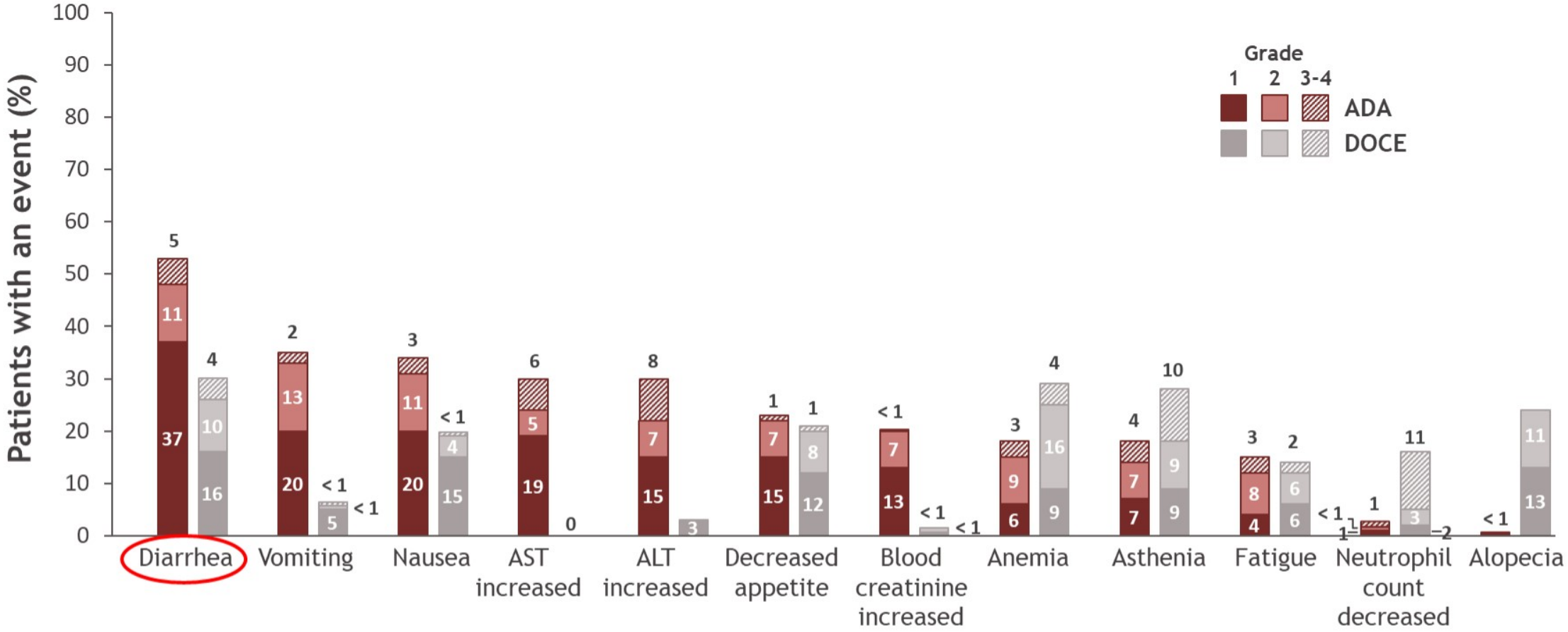
[a]In accordance with CNS-adapted RECIST v1.1. CNS RECIST data (including identification of patients with baseline CNS metastases) were based on a separate CNS imaging charter and neuroradiologist review. [b]Waterfall plots show CNS evaluable population including patients with at least one CNS target lesion at baseline and at least one post-baseline CNS tumor assessment. For lesions to be considered target lesions, they must have been measurable and either not previously treated with CNS-directed therapy or must have progressed after prior CNS-directed therapy.

Safety summary[a]

Patients, %	ADA (n = 298)	DOCE (n = 140)
TRAEs	94	86
Grade ≥ 3 TRAEs	47	46
TRAEs leading to discontinuation[b]	8	14
TRAEs leading to dose reduction	48	24
TRAEs leading to dose interruption	59	19
Treatment-related SAEs	21	16
Treatment-related deaths[c]	1	< 1

[a]AEs per CTCAE v5.0 and MedDRA v26.0. Includes events reported between the first dose and 28 days after the last dose, and prior to the initiation of subsequent anticancer therapy. For each category, patients are included only once, even if they experienced multiple events in that category. [b]Most common TRAEs leading to treatment discontinuation were ALT increased (n = 3), neutropenia, diarrhea, and pneumonitis (n = 2 each) with ADA, and asthenia, fatigue, and peripheral neuropathy (n = 3 each) with DOCE. [c]Treatment-related deaths were due to epilepsy, hepatic failure, hepatic ischemia, and unknown cause with ADA, and sepsis with DOCE (n = 1 each).

Most frequent TRAEs (> 15% in either treatment arm[a])



[a]For each TRAE, patients are included only once at the maximum severity.

Enfermedad metastásica con alteración molecular: KRAS

Primera línea: Abstract 8510

Iniciativa científica de: GECP lung cancer research

Efficacy and safety of olomorasib (LY3537982), a second-generation KRAS G12C inhibitor (G12Ci), in combination with pembrolizumab in patients with KRAS G12C-mutant advanced NSCLC

Phase 1a[a]
Dose Escalation

Phase 1b[a]
Dose Expansion (Olomorasib monotherapy and combination therapy)

Part A[b]
KRAS G12C mutant advanced solid tumors

Part B: NSCLC
- B1: Olomorasib
- B4[b]: Olomorasib + pembrolizumab[c]
- B8: Olomorasib: NSCLC with Brain metastases
- B9: Olomorasib + pembrolizumab + pemetrexed + platinum

Part C: CRC
- C2: Olomorasib + cetuximab

Part D: Other solid tumors
- Part D1: Olomorasib

Part E: NSCLC
- E1: Olomorasib: NSCLC with prior KRAS G12Ci

Part G: 1L NSCLC
- G: Olomorasib + pembrolizumab[c]

Phase 1a Design
- mTPI-2 design
- 21-day cycle (DLT evaluation period)
- Intrapatient dose escalation allowed

Phase 1a/b Eligibility
- Age ≥18
- ECOG PS 0-1
- Measurable disease per RECIST v1.1
- Locally advanced/metastatic solid tumor
- Presence of KRAS G12C mutation
- KRAS G12C inhibitor naive except where indicated

Key Objectives
- Safety and Tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- ORR and DoR per RECIST v1.1

- In this analysis, we study 2 doses of olomorasib (50 mg and 100 mg BID) which are under ongoing investigation in combination with pembrolizumab
- As previously disclosed, 150 mg olomorasib in combination with pembrolizumab was found to be suboptimal due to elevated LFTs and is no longer under investigation[1]

Part B: NSCLC

B4
Olomorasib + pembrolizumab[a]
(n=48)

Part B4 Eligibility

- Prior chemotherapy, anti-PD-(L)1, and KRAS G12C inhibitor therapy was allowed

Part G: 1L NSCLC

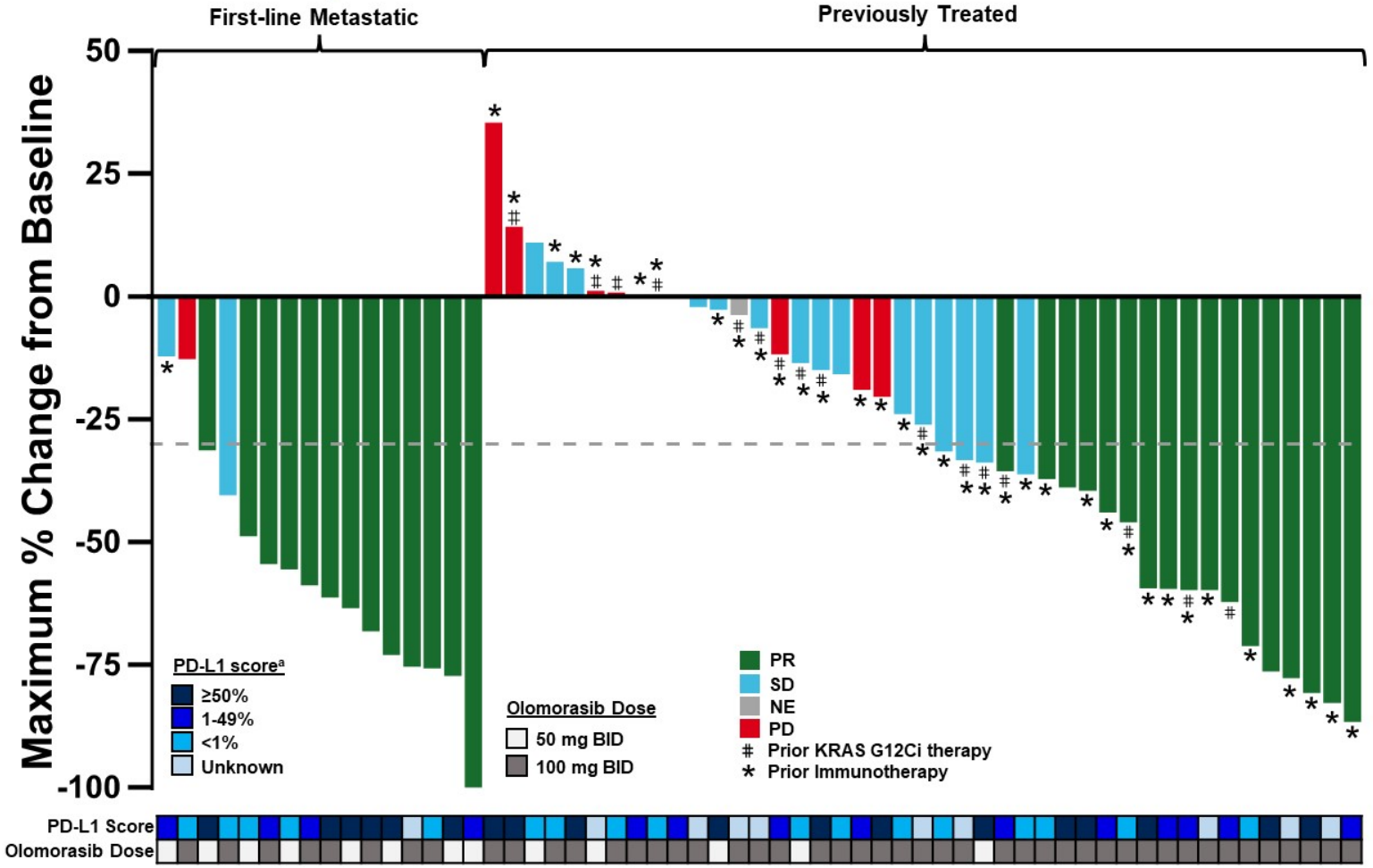
G
Olomorasib + pembrolizumab[a]
Randomized 1:1[b]
(n=16)

Part G Eligibility

- No prior therapy for metastatic disease

Median number of prior systemic therapies (range)	2 (0-8)
First-line metastatic, n (%)	20 (31)
Previously treated, n (%)[c]	44 (69)
Platinum-based chemotherapy/anti-PD-(L)1 therapy	36 (82)
Platinum-based chemotherapy alone	8 (18)
KRAS G12C inhibitor	17 (39)
Reason discontinued most recent KRAS G12C inhibitor, n (%)[d]	
Progressive disease / Toxicity / Other	13 (76) / 3 (18) / 1 (6)

Efficacy of Olomorasib + Pembrolizumab



Efficacy Evaluable Patients[b]	First-line Metastatic (N=17)	Previously Treated (N=43)
Objective Response Rate[c], % (n/N)	**77% (13/17)**	**40% (17/43)**
Best overall response		
CR, n (%)	-	-
PR, n (%)	13 (77)	17 (40)
SD, n (%)	2 (12)	18 (42)
PD, n (%)	1 (6)	7 (16)
NE, n (%)	1 (6)	1 (2)
DCR, % (n/N)	**88% (15/17)**	**81% (35/43)**

- 81% (35/43) of previously treated patients had received prior immunotherapy
- Median time to response was 1.4 months; median duration of response was NE

Data cutoff date of 18 Mar 2024. [a]PD-L1 frequency - 30% with ≥50%, 25% with 1-49%, 28% with <1%, and 17% unknown. [b]Efficacy evaluable patients are those treated at 50 and 100 mg olomorasib doses who had at least one post-baseline response assessment or had discontinued treatment before the first post-baseline response assessment. Data for 5 patients are not shown in the waterfall plot; 1 discontinued prior to first post-baseline response assessment, and 4 did not have a first post-baseline response assessment and are ongoing. [c]ORR includes patients with a best response of PR (confirmed, and pending confirmation and ongoing). 2 patients in first-line metastatic and 1 patient in previously treated have unconfirmed PRs pending confirmation and ongoing. Investigator assessed response per RECIST v1.1.

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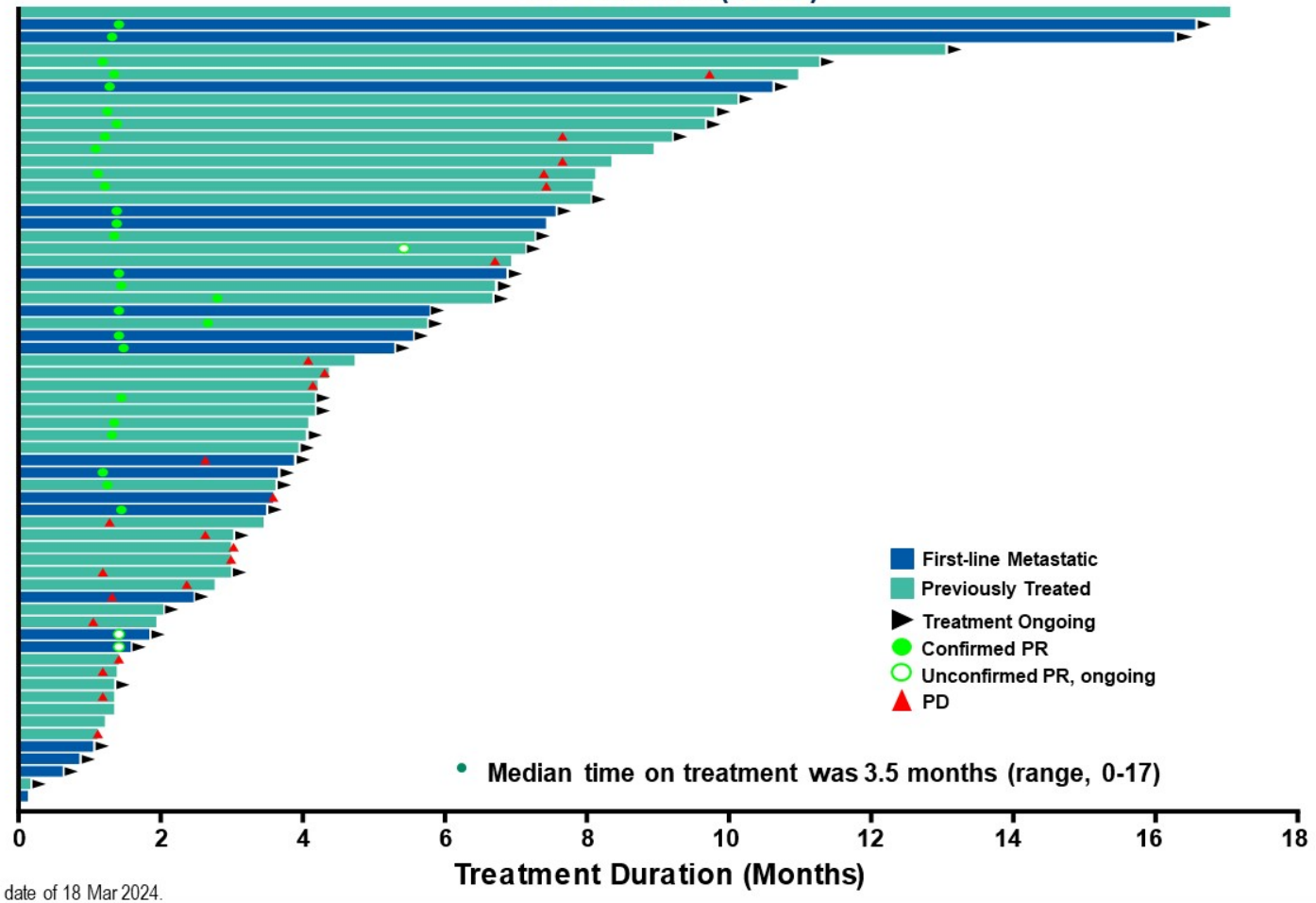
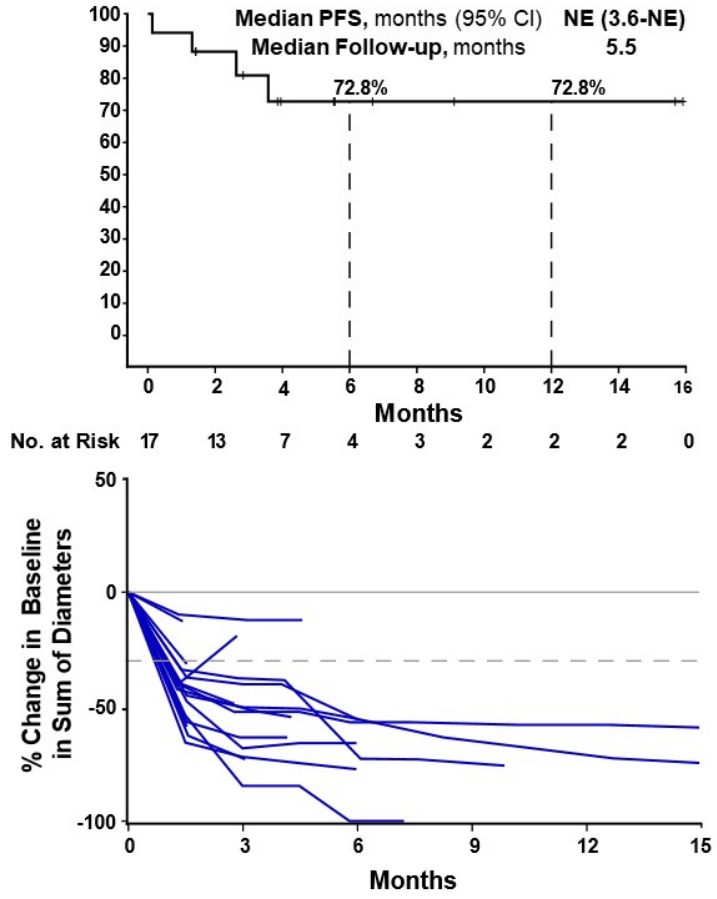
Response and Progression Free Survival in Olomorasib + Pembrolizumab

All Patients (N=64)



First-line Metastatic (n=17)



Data cutoff date of 18 Mar 2024.

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Safety Profile: Olomorasib + Pembrolizumab

All Doses and Patients (50 + 100 mg BID, N = 64)							
	Treatment-Emergent AEs (>10%), %		Treatment-Related AEs[a], %				
Adverse Event	Any grade	Grade ≥3	Any grade	Grade 1	Grade 2	Grade 3	Grade 4[b]
Any AE	86%	47%	70%	20%	23%	25%	2%
Diarrhea	28%	13%	23%	8%	3%	13%	-
Fatigue	27%	-	16%	8%	8%	-	-
ALT increased	25%	8%	20%	11%	3%	6%	-
Pruritus	25%	3%	19%	11%	5%	3%	-
Nausea	23%	-	14%	6%	8%	-	-
Arthralgia	19%	-	8%	8%	-	-	-
AST increased	17%	8%	16%	6%	2%	8%	-
Vomiting	17%	-	8%	5%	3%	-	-
Anemia	16%	2%	3%	3%	-	-	-
Decreased appetite	14%	2%	9%	8%	-	2%	-
Cough	13%	-	-	-	-	-	-
Dyspnea	11%	5%	-	-	-	-	-
Headache	11%	-	2%	2%	-	-	-
Hypokalemia	11%	3%	-	-	-	-	-

- TRAEs led to olomorasib dose holds in 25% of patients (16/64) and olomorasib dose reductions in 17% of patients (11/64)
- TRAEs led to permanent discontinuation of olomorasib only in 3% of patients (2/64) and pembrolizumab only in 11% of patients (7/64); 5% of patients (3/64) discontinued both drugs due to TRAEs
- Grade ≥2 diarrhea was usually brief (median 9 days), and 92% resolved to grade 1/baseline with dose modification and antidiarrheals

Data cutoff date of 18 Mar 2024. [a]TRAEs are olomorasib and/or pembrolizumab related. [b]1 patient had a grade 4 TRAE (pneumonitis). Total % may be different from the individual components due to rounding. AE, adverse event; ALT alanine aminotransferase; AST, aspartate aminotransferase.

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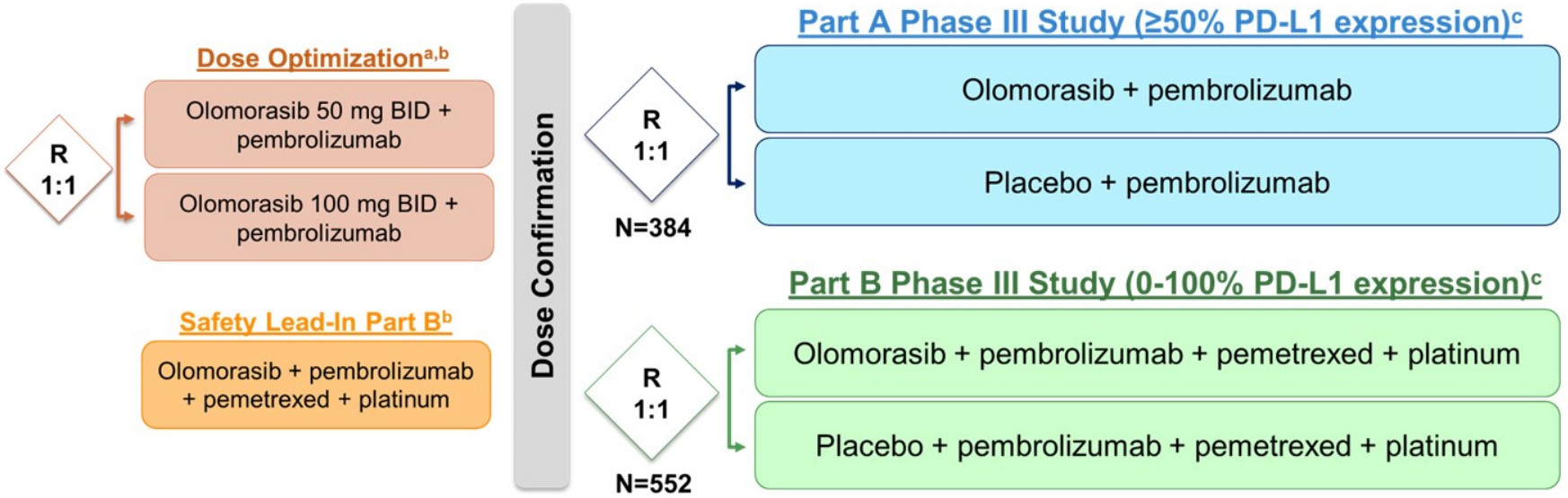
SUNRAY-01 Phase 3 Study Design

Poster #TPS8649, Poster board 512b
Monday, June 3, 1:30 - 4:30 PM

SUNRAY-01 is a pivotal, global, phase 3 study in 1L advanced KRAS G12C-mutated NSCLC (NCT06119581)



- Olomorasib/placebo are administered orally (PO), twice daily
- Pembrolizumab, pemetrexed, and platinum (cisplatin or carboplatin) are each administered intravenously per label. After completing 4 cycles of chemotherapy without disease progression, patients will receive maintenance therapy with olomorasib/placebo, pembrolizumab and pemetrexed

[a]Participants should be suitable for pembrolizumab monotherapy
[b]PD-L1 expression 0-100%, N~40 for each study part (randomized Dose Optimization and Safety Lead-In Part B)
[c]Participants with PD-L1 ≥50% are eligible to be enrolled to Part A or Part B at the discretion of the investigator

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Enfermedad metastásica con alteración molecular: KRAS

Primera línea: Abstract 8512

Iniciativa científica de: GECP lung cancer research

Sotorasib Plus Carboplatin and Pemetrexed in *KRAS* G12C Advanced NSCLC: Updated Analysis From the International CodeBreaK 101 Trial

Key eligibility criteria

- *KRAS* G12C–mutated advanced NSCLC, identified through molecular testing
- Patients were treatment-naive or previously treated*
- Measurable disease per RECIST v1.1
- ECOG ≤ 2
- No active brain metastases

→

Up to 4 cycles†

Sotorasib 960 mg PO daily
+
Carboplatin AUC 5 IV Q3W
+
Pemetrexed 500 mg/m^2 IV Q3W

→

Maintenance†

Sotorasib 960 mg PO daily
+
Pemetrexed 500 mg/m^2 IV Q3W

Data were pooled from dose exploration and expansion cohorts and analyzed by exposure to prior therapy in the locally advanced/metastatic setting: **1L (n = 37) and 2L+ (n = 21)‡**

Primary endpoints: Safety and tolerability (including DLT)
Secondary endpoints: ORR, DCR, DOR, TTR, OS, PFS, duration of SD, and PK

Baseline Characteristics

	Sotorasib + Carboplatin + Pemetrexed	
	1L (n = 37)	2L+ (n = 21)
Median age, years (range)	64 (46–82)	67 (44–76)
Male, n (%)	15 (41)	11 (52)
White / Black or African American / Other, n (%)	34 (92) / 2 (5) / 1 (3)	16 (76) / 3 (14) / 2 (10)
Hispanic or Latino, n (%)	1 (3)	4 (19)
Current / former smoker, n (%)	5 (14) / 30 (81)	5 (24) / 14 (67)
ECOG performance status 0 / 1, n (%)	15 (41) / 22 (59)	7 (33) / 14 (67)
Stage III / IV at screening, n (%)	1 (3) / 36 (97)	1 (5) / 20 (95)
History of brain metastasis, n (%)	6 (16)	5 (24)
History of liver metastasis, n (%)	3 (8)	4 (19)
Prior neoadjuvant / adjuvant chemotherapy, n (%)	2 (5)	2 (10)
Prior anti–PD-(L)1, n (%)	0	18 (86)
PD-L1 protein expression,* n (%)		
< 1%	22 (59)	5 (24)
1% – 49%	9 (24)	4 (19)
≥ 50%	5 (14)	12 (57)

Data cutoff, December 1, 2023. Patients were enrolled from the United States, Spain, and Belgium.
*1 patient (3%) in the 1L cohort had unknown PD-L1 protein expression.

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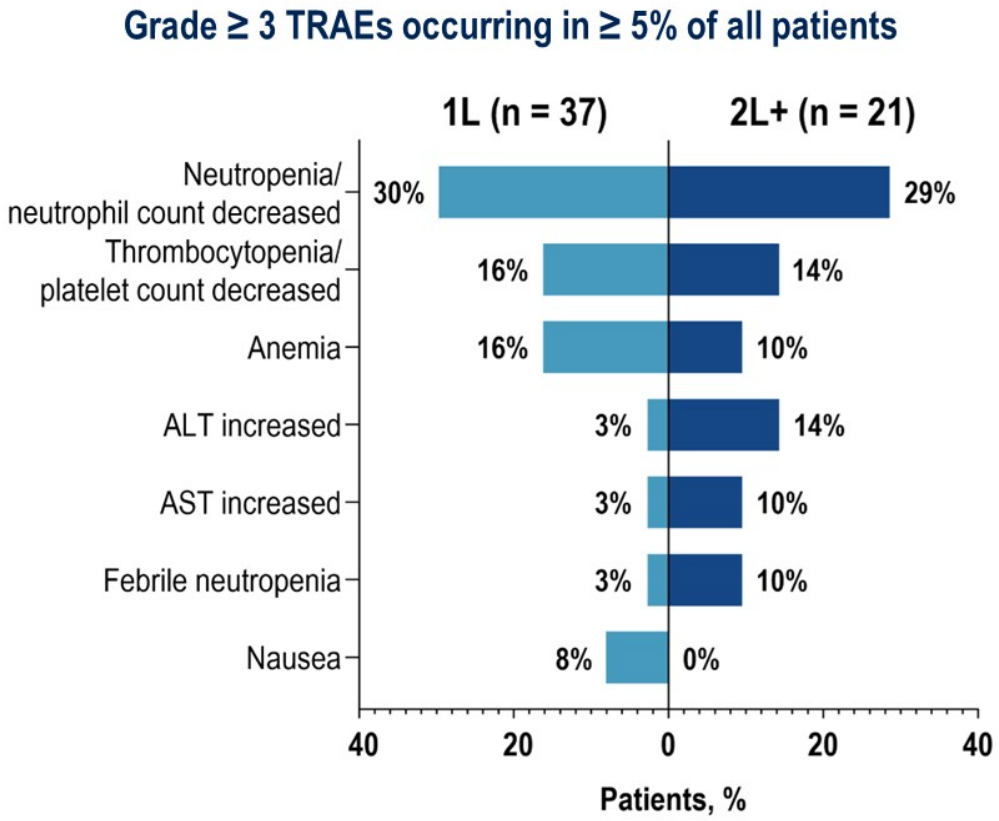
Treatment-Related Adverse Events

	Sotorasib + Carboplatin + Pemetrexed	
	1L (n = 37)	2L+ (n = 21)
Any-grade TRAEs, n (%)	34 (92)	20 (95)
Grade ≥ 3	18 (49)	13 (62)
Leading to dose reduction / interruption of any treatment	24 (65)	15 (71)
Sotorasib	19 (51)	13 (62)
Carboplatin	12 (32)	10 (48)
Pemetrexed	18 (49)	9 (43)
Leading to discontinuation of any treatment	8 (22)	6 (29)
Sotorasib	2 (5)	3 (14)
Carboplatin	0	1 (5)
Pemetrexed	7 (19)	5 (24)
Fatal*	0	1 (5)



Most common TRAEs in ≥ 20% of all patients were neutropenia / neutrophil count decreased (48%), anemia (41%), nausea (41%), thrombocytopenia / platelet count decreased (40%), asthenia (33%), diarrhea (29%), ALT increased (29%), fatigue (28%), AST increased (26%), vomiting (26%), and decreased appetite (26%)

Data cutoff, December 1, 2023.
*Fatal TRAE was febrile neutropenia, attributed to carboplatin and pemetrexed.

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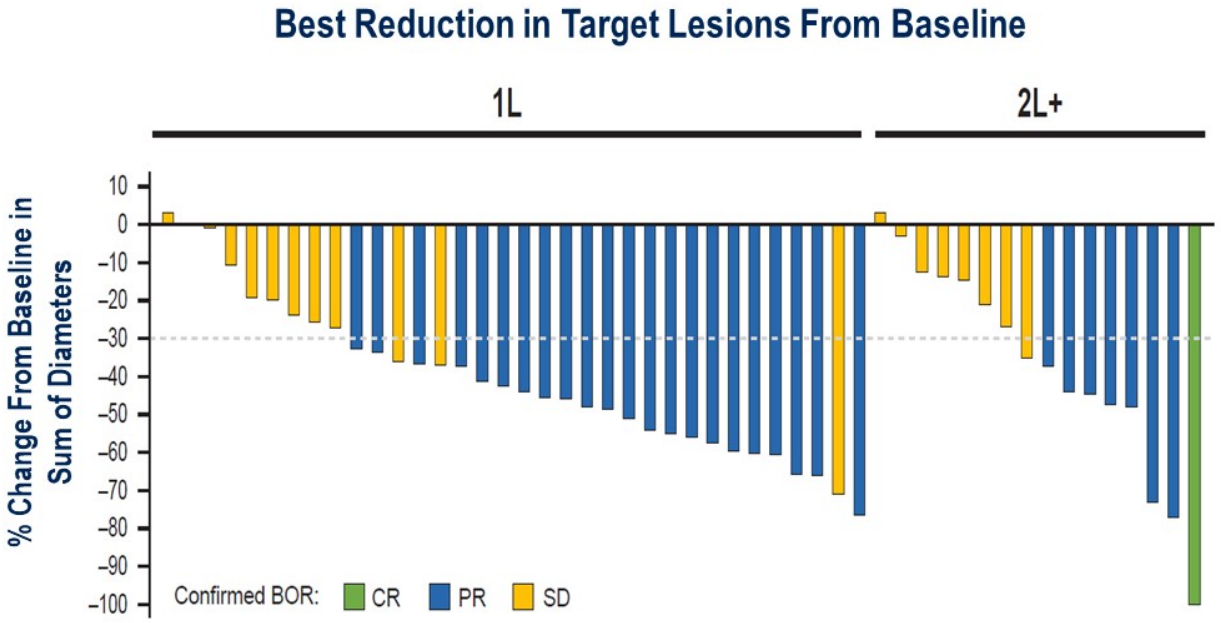
Efficacy

Confirmed response by investigator assessment*	Sotorasib + Carboplatin + Pemetrexed	
	1L (n = 34)	2L+ (n = 19)
ORR, n (%)	22 (65)	8 (42)
Best overall response, n (%)		
Complete response	0	1 (5)
Partial response	22 (65)	7 (37)
Stable disease	12 (35)†	8 (42)
Progressive disease	0	1 (5)
Not evaluable / not done	0	2 (11)
DCR, n (%)	34 (100)	16 (84)



- **Among patients treated in the 1L setting, ORR was 65% and DCR was 100%**
- **94% of all patients had reduction in target lesions**

Data cutoff, December 1, 2023.

*Included all patients who received ≥ 1 dose of study drug, had ≥ 1 measurable lesion at baseline per RECIST v 1.1, and could be followed for ≥ 7 weeks starting from day 1.

†One 1L patient with stable disease had an unconfirmed partial response awaiting confirmatory scan.

PRESENTED BY: Bob T. Li, MD, PhD, MPH

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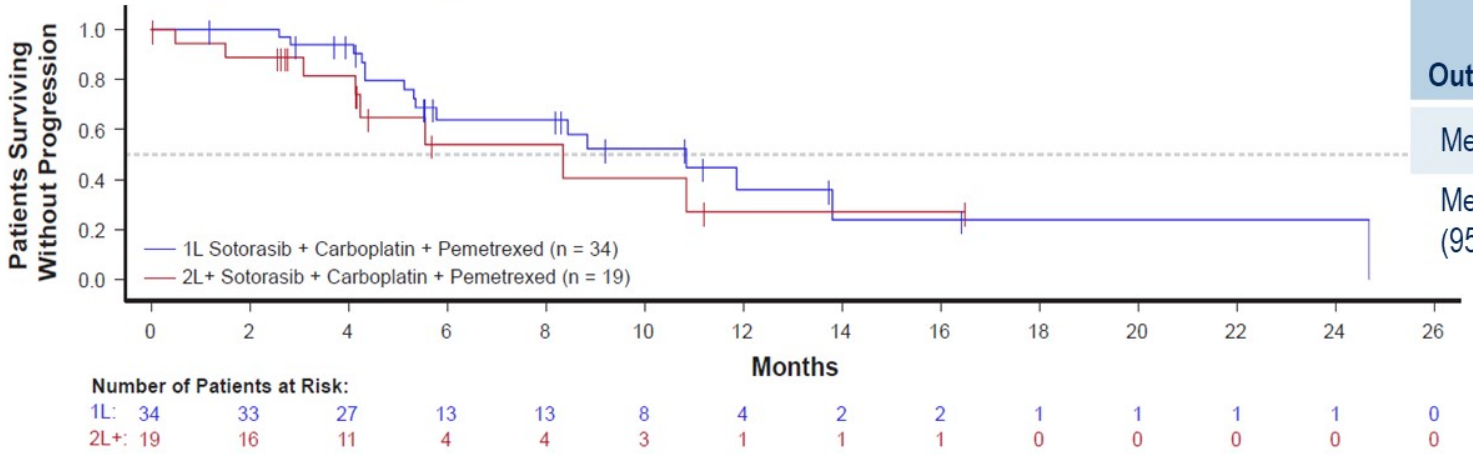
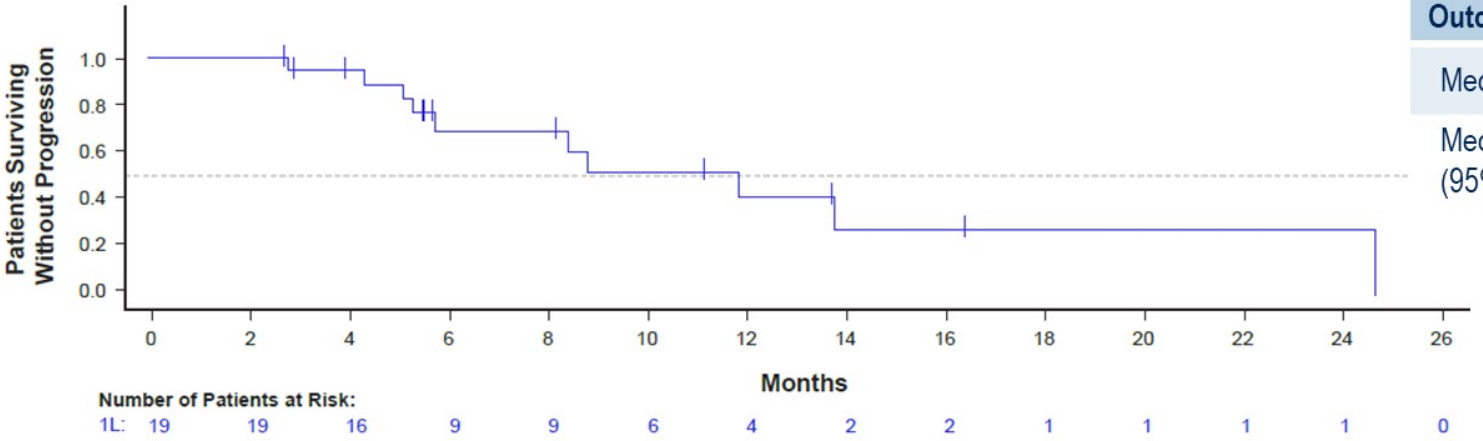
Progression-Free Survival*

PFS by Line of Therapy



Outcome	Sotorasib + Carboplatin + Pemetrexed	
	1L (n = 34)	2L+ (n = 19)
Median PFS, months (95% CI)	10.8 (5.4–NE)	8.3 (4.1–NE)
Median follow-up, months (95% CI)	9.2 (5.6–13.7)	4.4 (2.7–NE)

PFS for PD-L1 < 1% in 1L Setting



Outcome	PD-L1 < 1% in 1L Setting (n = 19)
Median PFS, months (95% CI)	11.9 (5.3–NE)
Median follow-up, months (95% CI)	13.7 (5.6–NE)

*Included all patients who received ≥ 1 dose of study drug, had ≥ 1 measurable lesion at baseline per RECIST v 1.1, and could be followed for ≥ 7 weeks starting from day 1.

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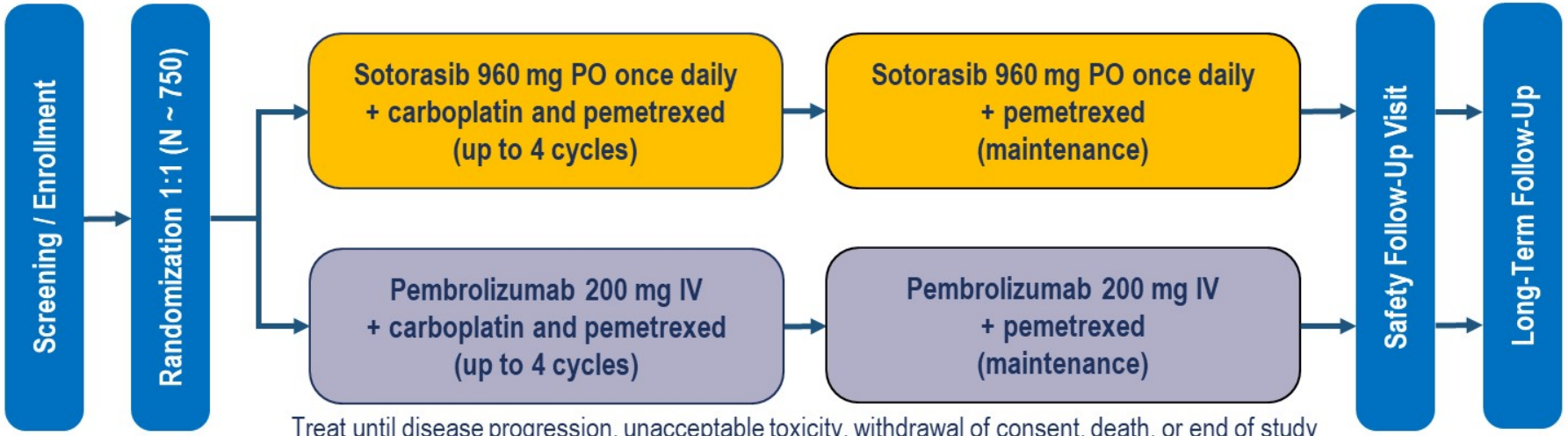
CodeBreaK 202 Study Design

Key inclusion criteria:

- *KRAS* G12C–positive stage IV (metastatic) or advanced stage IIIB or IIIC NSCLC
- No history of systemic therapy in metastatic / non-curable settings
- PD-L1 tumor cells < 1%
- ECOG performance status ≤ 1

Key exclusion criteria:

- Symptomatic (treated or untreated) brain metastases*
- Actionable alterations other than *KRAS* G12C



Primary endpoint: PFS per BICR (assessed per RECIST v1.1)
Secondary endpoints: ORR, OS, DCR, DOR, TTR, PFS2,‡ PRO, safety, PK
Exploratory endpoint: intracranial PFS per RANO-BM criteria

NCT05920356.

*Patients with untreated brain metastases will be allowed into the study if asymptomatic without systemic steroids, and radiation therapy is not indicated.

†Continues until patient is removed from study due to either decision by sponsor, end of study, withdrawal of consent, lost to follow-up, or death, whichever occurs first; patients who discontinue treatment for a reason other than disease progression will continue imaging and tumor assessment until BICR-confirmed progressive disease, unacceptable toxicity, death, withdrawal of consent, or end of study.

‡Defined as time from randomization to progression per investigator after initiation of new anticancer therapy or treatment beyond progression (i.e., second progression) or death from any cause.

PRESENTED BY: Bob T. Li, MD, PhD, MPH

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Enfermedad metastásica con alteración molecular: KRAS

Primera línea: Abstract LBA8511

Iniciativa científica de: GECP lung cancer research

KROCUS: a Phase II study investigating the efficacy and safety of fulzerasib (GFH925) in combination with cetuximab in patients with previously untreated advanced KRAS G12C mutated NSCLC

KROCUS (NCT05756153) Objectives and Study Design

Abstract number: LBA8511
KROCUS: fulzerasib in previously untreated KRAS G12C NSCLC

Key eligibility criteria

- Pathologically confirmed, advanced G12C KRAS mutated NSCLC[a]
- Treatment naive
- ECOG PS 0 - 1

Single-arm
Open-label

Fulzerasib 600 mg BID +
Cetuximab 500 mg/m^2 Q2W
N ≈ 45

Progressive disease, intolerable toxicity or other reasons to withdrawal

Long-term Follow up

- **Primary endpoint:** ORR[b] per RECIST 1.1
- **Secondary endpoints:** PFS per RECIST 1.1, adverse events
- **Exploratory endpoints:** PD-L1 and EGFR expression levels, co-mutations at baseline and EoT.

[a] KRAS G12C status was detected in tumor tissue using sponsor-approved local testing.
[b] An ORR of 40% is considered for the KRAS G12C inhibitor monotherapy; the expected ORR of the study combination treatment is ≥ 60%.

Abbreviations: BID, twice daily; Q2W, every two weeks; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; PFS, progression-free survival; EoT, end of treatment.

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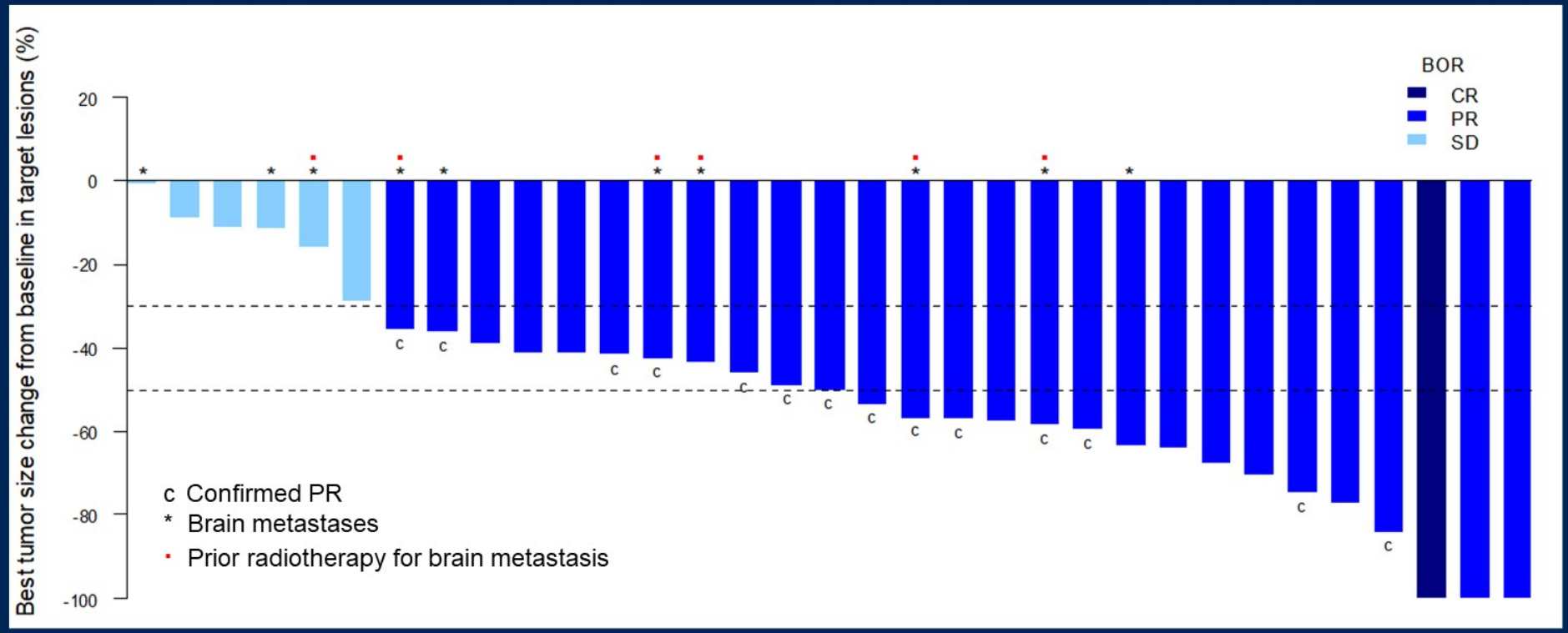
Abstract number: LBA8511
KROCUS: fulzerasib in previously untreated KRAS G12C NSCLC

Primary Endpoint: Best Overall Response

- A total of 33 pts had at least one available post-treatment tumor assessment as of data cut-off date.
- Investigator-assessed ORR was 81.8% (95% CI: 64.5, 93.0) and DCR was 100% (95% CI: 89.4, 100); in pts with brain mets ORR was 70%.



Data cut-off date: 19Apr2024

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Abstract number: LBA8511
KROCUS: fulzerasib in previously untreated KRAS G12C NSCLC

Safety Overview

	Fulzerasib + cetuximab (N=40) n (%)
All TRAE	35 (87.5)
All ≥ G3 TRAE	7 (17.5)
All TRSAE	
Fulzerasib	0
Cetuximab	1 (2.1)
TRAE leading dose reduction	
Fulzerasib	1 (2.1)
Cetuximab	1 (2.1)
TRAE leading dose interruption	
Fulzerasib	4 (10.0)
Cetuximab	5 (12.5)
TRAE leading permanent discontinuation	
Fulzerasib	0
Cetuximab	3 (7.5)*
Fatal TRAE	0

Data cut-off date: 19Apr2024. CTCAE 5.0
*Three pts discontinued cetuximab permanently due to G2, G3 infusion related reaction and G3 ulcerative keratitis, respectively.
Abbreviations：TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event.

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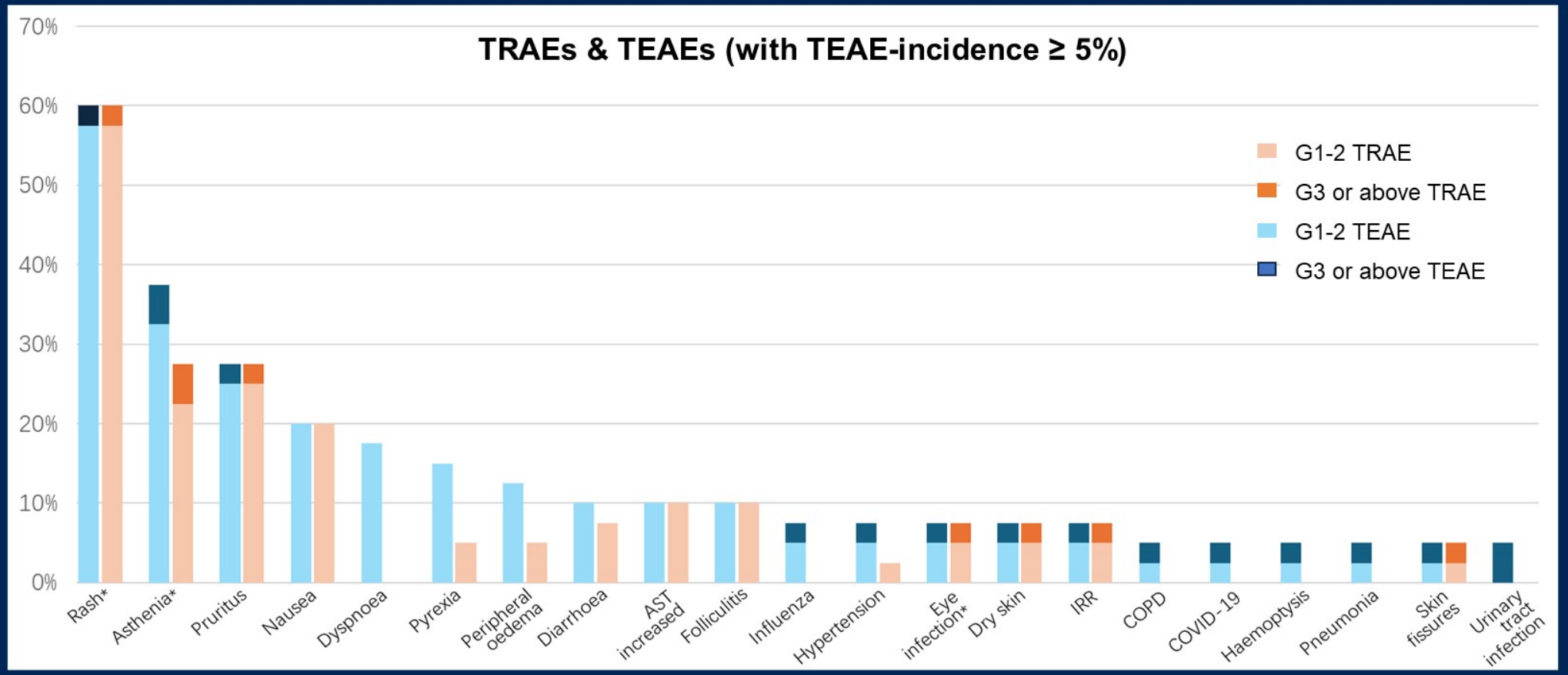
Abstract number: LBA8511
KROCUS: fulzerasib in previously untreated KRAS G12C NSCLC

Summary of Adverse Events

- No new safety signals were identified compared with fulzerasib or cetuximab as single agent.



Data cut-off date: 19Apr2024. MedDRA v27.0. CTCAE 5.0 Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
*Grouped terms: Rash (acne, dermatitis, dermatitis acneiform, rash, perioral dermatitis, and rash pustular); Asthenia (asthenia and fatigue); Eye infection (eye infection, conjunctives, and ulcerative keratitis).

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Enfermedad metastásica con alteración molecular: KRAS

Primera línea: Abstract 4088

Iniciativa científica de: GECP lung cancer research

Efficacy and Safety of Glecirasib (JAB-21822) Monotherapy in Patients with Advanced NSCLC Harboring *KRAS* G12C Mutation: Top-Line Results from a Pivotal Phase 2 Study

Study Design of Glecirasib Monotherapy in ≥ 2L NSCLC

Key eligibility criteria

- Advanced or metastatic NSCLC with *KRAS* G12C mutation
- Refractory or intolerable to IO and platinum-based regimen
- No active brain or spinal metastases

Glecirasib Monotherapy
≥ 2L NSCLC (800mg QD)
N=119

Primary endpoint:

- ORR per IRC

Secondary endpoints:

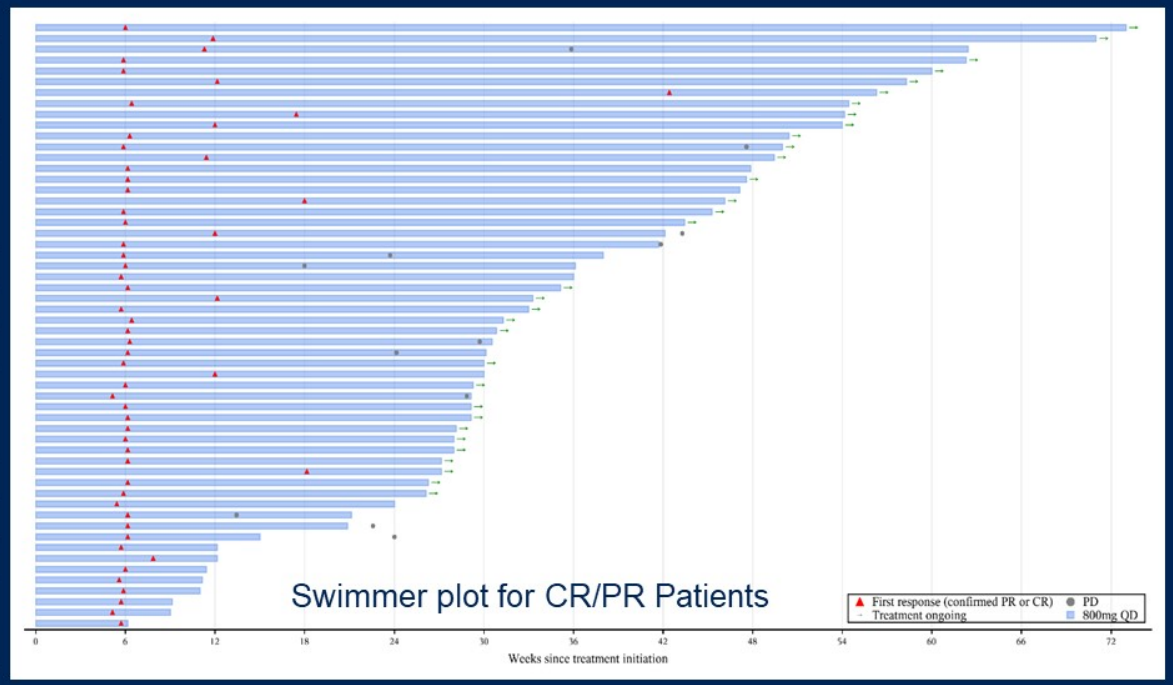
- ORR per investigator
- DoR, DCR, TTR, PFS per investigator and IRC
- OS
- Safety and tolerability, PK

The study provided 90% power to ensure that the lower limit of 95% confidence interval for ORR exceeds the benchmark ORR of 23%.

Efficacy by IRC: Glecirasib has met the study primary endpoint

Efficacy Outcome	800mg QD (N=117) *
Best overall response	
CR	4 (3.4%)
PR	52 (44.4%)
SD	45 (38.5%)
PD	12 (10.3%)
NE	4 (3.4%)
ORR	
n (%)	56 (47.9%)
95% CI	38.5%, 57.3%
DCR	
n (%)	101 (86.3%)
95% CI	78.7%, 92.0%

* 2 patients did not have target lesion at baseline per IRC.



- Confirmed ORR was 47.9% (56/117) , CR rate was 3.4% (4/117)
- 34.2% (40/117) patients are still on treatment.
- Median TTR was 1.41 months (range, 1.2- 9.8).
- The majority of CR/PR patients are ongoing. The median DoR has not been reached (95% CI, 7.2 – NE). 6-month and 12-month DoR rates were 73.6% and 56.6%, respectively.

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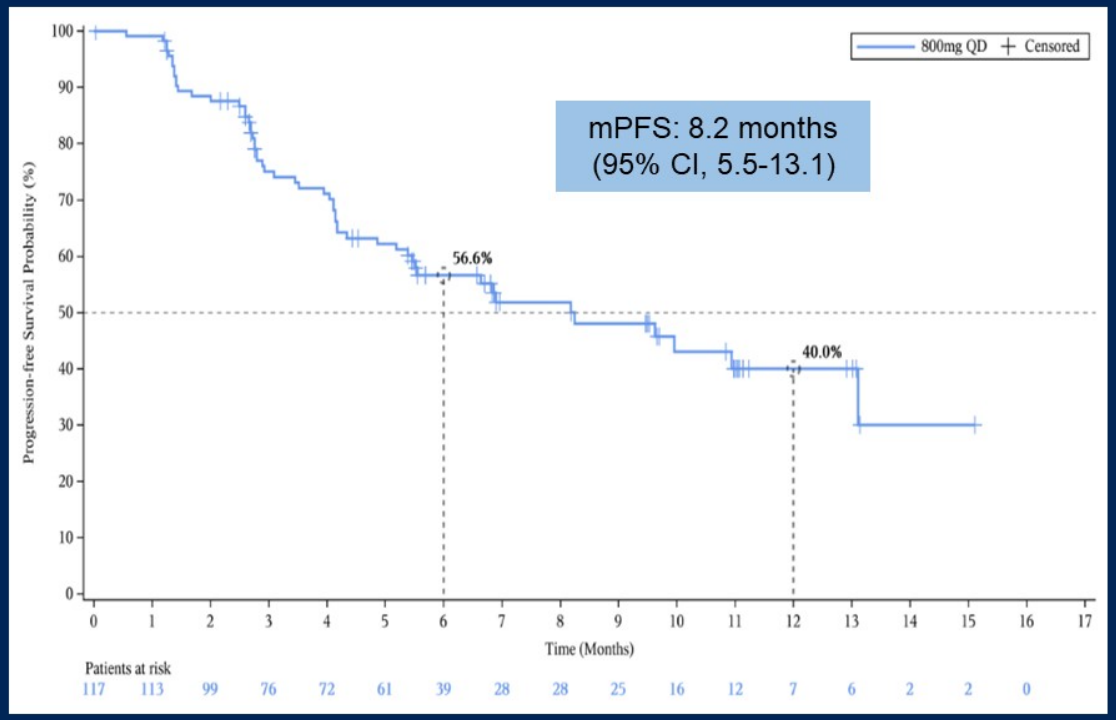
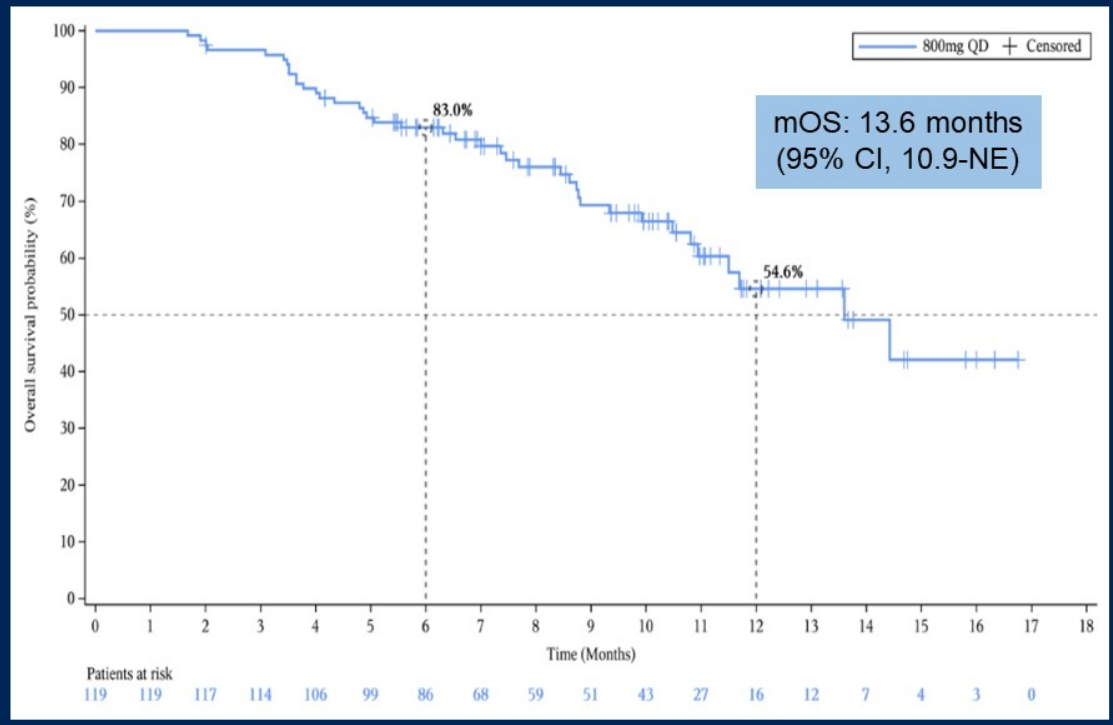
Progression-Free Survival and Overall Survival

- Median PFS per IRC was 8.2 months（95%CI: 5.5, 13.1).
- Median OS was 13.6 months（95%CI, 10.9, NE). The 12-month OS rate was 54.6%.





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Common TRAEs in ≥ 10% of Patients (n=119)

Adverse Event	All Grade n (%)	Grade 3-4 n (%)
Anemia	67 (56.3%)	5(4.2%)
Blood bilirubin increased	58 (48.7%)	8(6.7%)
Alanine aminotransferase increased	42 (35.3%)	13(10.9%)
Aspartate aminotransferase increased	42 (35.3%)	13(10.9%)
Hypertriglyceridemia	34 (28.6%)	9(7.6%)
Gamma-glutamyltransferase increased	19 (16%)	7(5.9%)
Bilirubin conjugated increased	16 (13.4%)	2(1.7%)
Weight decreased	15 (12.6%)	0
Anorexia	15 (12.6%)	2(1.7%)
ALP increased	13 (10.9%)	0
White blood cell count decreased	14 (11.8%)	2(1.7%)
Neutrophil count decreased	12 (10.1%)	5(4.2%)
Hypoalbuminemia	12 (10.1%)	0
Proteinuria	12 (10.1%)	0

- 97.5% (116/119) of patients experienced at least one TRAE.
- 38.7% (46/119) of patients had at least one of grade 3/4 TRAE.
- No grade 5 (fatal) TRAE occurred.
- 5.0% patients discontinued the treatment due to TRAE.

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Gastrointestinal AEs with Glecirasib

Reported GI-related AEs Comparison with other approved KRAS G12C inhibitors

GI Relate AEs	Glecirasib[1] N=119 (800mg QD) Jacobio	Sotorasib[2] N=126 (960 mg QD) Amgen	Adagrasib[3] N=116 (600 mg BID) BMS/Mirati
diarrhea	3.4%	31.7%	62.9%
nausea	6.7%	19%	62.1%
vomiting	7.6%	7.9%	47.4%

In addition to the lower GI related AEs of all grades, glecirasib study had only one grade 3 nausea observed.

Lower GI related AEs were observed from glecirasib phase II trial. However the comparison is not from head to head trial.

Glecirasib has lower RP2D with 800mg QD, 4 pills per day, which is favorable to the patients.

1. 2024 ASCO Planery Series in April (Pivotal trial) 2. 2021 NEJM: CodeBreak100. 3. 2022 NEJM: KRYSTAL-1.

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Enfermedad metastásica con alteración molecular: KRAS

Primera línea: Abstract 4088

Iniciativa científica de: GECP lung cancer research

Updated Safety and Efficacy Data of Combined KRAS G12C inhibitor (Glecirasib, JAB-21822) and SHP2 Inhibitor (JAB-3312) in Patients with *KRAS p.G12C* Mutated Solid Tumors

Study Design

Phase 1/2a [NCT05288205]

Dose exploration/optimization
- Primary objective: Safety and tolerability
- Secondary objective: Efficacy, PK

Dose expansion
- Primary objective: Efficacy
- Secondary objective: Safety and tolerability

Glecirasib + JAB-3312

Key eligibility criteria
- Locally advanced or metastatic advanced solid tumors harboring KRAS p.G12C mutation who have failed or lack SOC or are unwilling to undergo or intolerant to SOC
- At least one measurable lesion as defined by RECIST v1.1
- ECOG 0-1
- No active brain metastases

800mg QD
- 3mg [1/1]
- 2mg [1/1]
- 2mg [1/2]

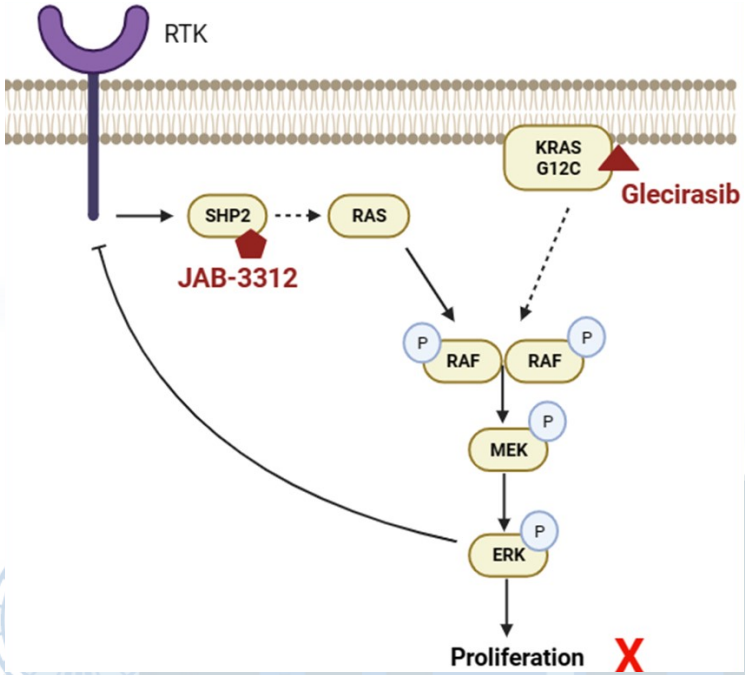
400mg QD
- 3mg [1/1]
- 2mg [1/1]
- 2mg [2/1]
- 2mg QD

Cohort 1-NSCLC
- KRAS G12C inhibitor naïve
- ≤ 2 Lines of prior systemic therapy

Cohort 2-NSCLC
- KRAS G12C inhibitor treated
- ≤ 3 Lines of prior systemic therapy

Cohort 3-Other solid tumors
- KRAS G12C inhibitor naïve

- SOC: Standard-of-care; ECOG: Eastern Cooperative Oncology Group; PK: Pharmacokinetics; QD: Once daily;
- [1/1]: Once daily for 1 week on, then 1 week off; [1/2]: Once daily for 1 week on, then 2 weeks off; [2/1]: Once daily for 2 weeks on, then1 week off.



Safety Overview

	All N=194	Frontline NSCLC N=102
Patients with any TRAE*, n(%)	190 (97.9%)	102 (100%)
Grade 3 or 4 TRAE	85 (43.8%)	45 (44.1%)
SAE (related to treatment)	23 (11.9%)	12 (11.8%)
TRAE leading to glecirasib reduced	17 (8.8%)	13 (12.7%)
TRAE leading to JAB-3312 reduced	27 (13.9%)	13 (12.7%)
TRAE leading to glecirasib discontinuation	5 (2.6%)	2 (2.0%)
TRAE leading to JAB-3312 discontinuation	21 (10.8%)	14 (13.7%)

*Related to either or both drugs.

No grade 5 (fatal) TRAE occurred.

TRAE: Treatment-related adverse event; SAE: Serious adverse event

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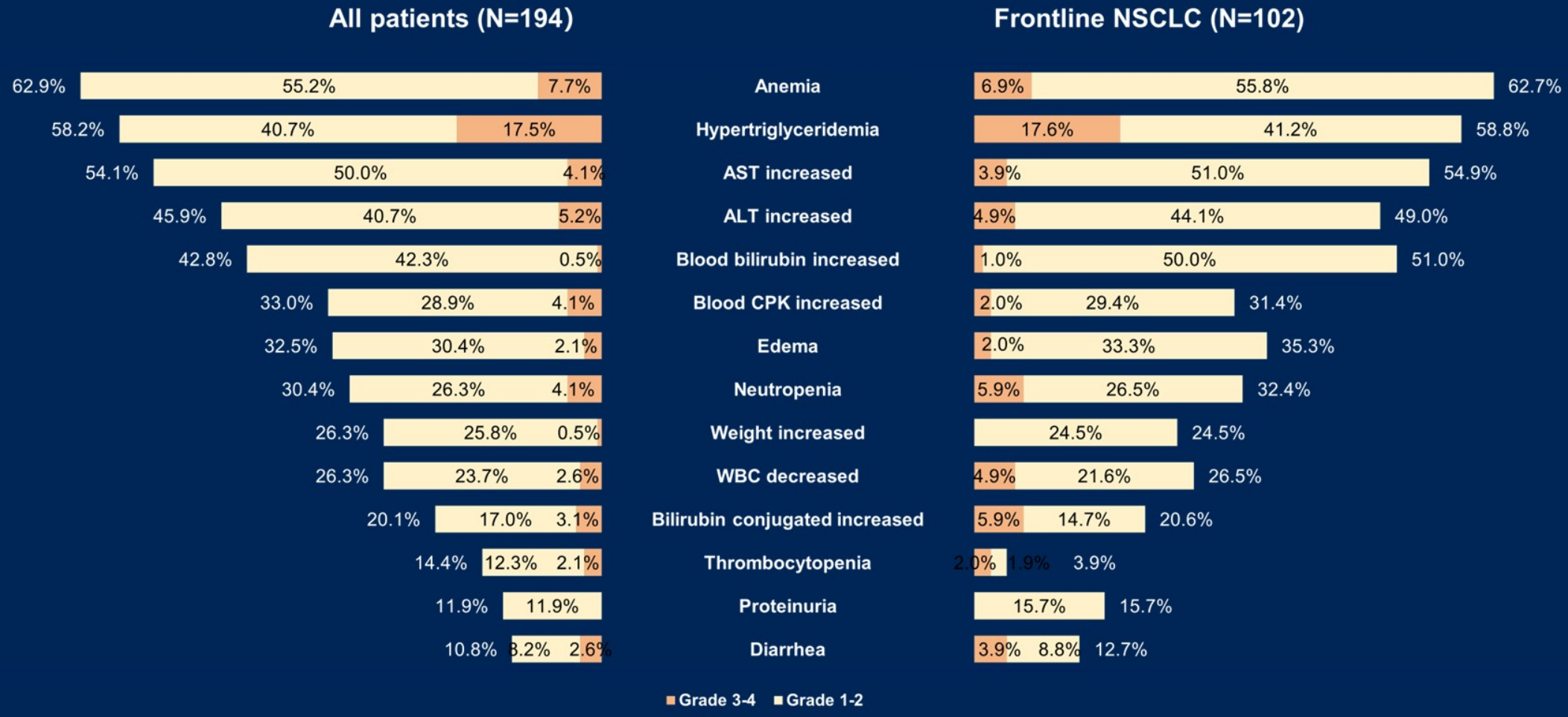
Treatment-related Adverse Events (incidence＞10% in all patients)



- Safety profile in the frontline NSCLC population was similar to that of the overall population.

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CPK : Creatine phosphokinase; WBC: White blood cell

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Efficacy in the Frontline NSCLC

	All dosage groups (N=102)	800mg QD + 2mg [1/1] (N=31)
Best overall response[a]	n (%)	n (%)
Complete Response (CR)	0	0
Partial Response (PR)	75 (73.5%) [c]	25 (80.6%) [d]
Stable Disease (SD)	20 (19.6%)	3 (9.7%)
Progressive Disease (PD)	3 (2.9%)	2 (6.5%)
Not Evaluable (NE)	4 (3.9%) [e]	1 (3.2%)[f]
Objective Response Rate (ORR)	75 (73.5%)	25 (80.6%)
• Confirmed ORR	66 (64.7%)	24 (77.4%)
• 95% CI[b]	56.5, 75.8	58.9, 90.4
Disease Control Rate (DCR)	95 (93.1%)	28 (90.3%)
• 95% CI	90.0, 98.9	74.2, 98.0

- Amongst all frontline NSCLC enrolled, the confirmed ORR was 64.7% and DCR was 93.1%.
- In 800mg QD + 2mg [1/1] group, the confirmed ORR was 77.4% and DCR was 90.3%.

[a] Assessed by investigator per RECIST v1.1; [b] Exact 95% CI is calculated using the Clopper Pearson method; [c] Nine patients currently have unconfirmed PRs. Six patients had a single PR and discontinued treatment. Three patients are still receiving treatment. [d] One patients had a single PR and discontinued treatment. [e] One SD was assessed less than 5 weeks after start of study treatment. Three patients discontinued treatment without efficacy results. [f] One SD was assessed less than 5 weeks after start of study treatment.

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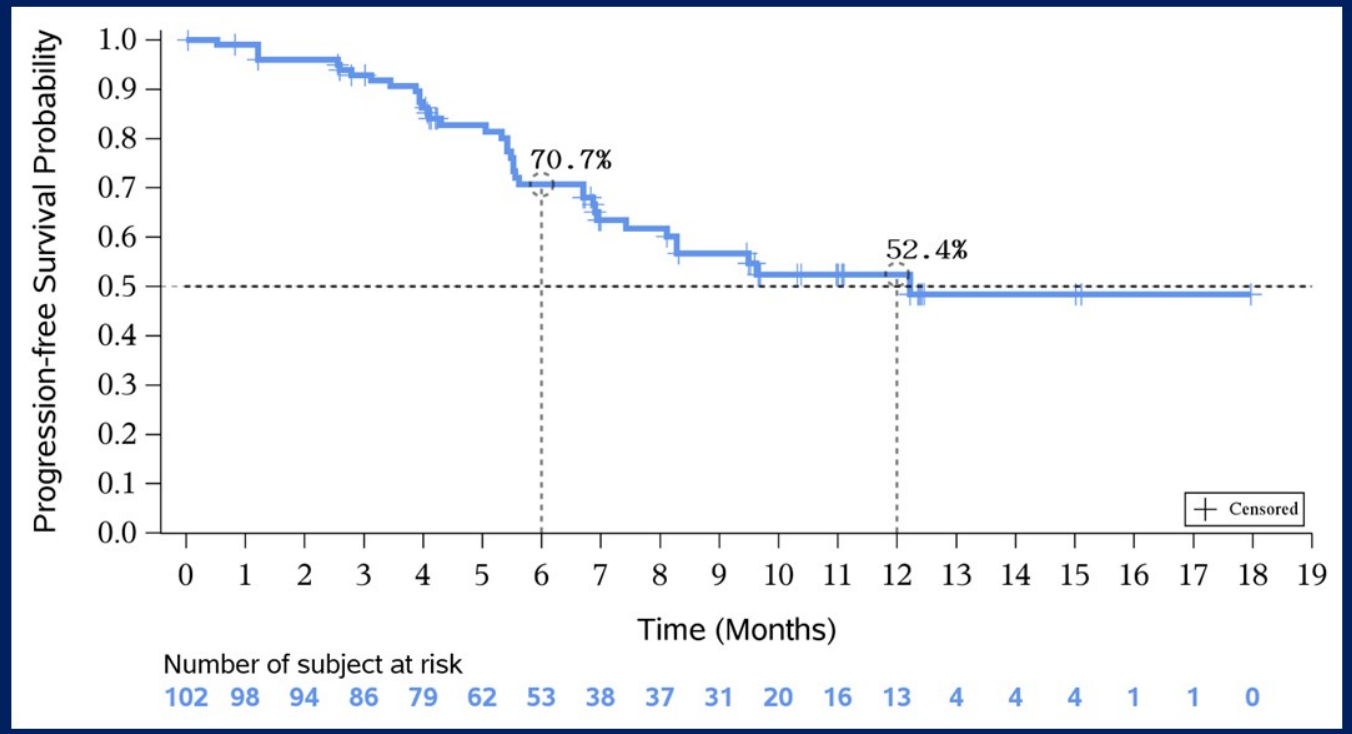
Progression-Free Survival in the Frontline NSCLC



In the frontline setting		N= 102
Median Follow-up duration （m）(range)		10.1 (1.2-20.9)
mPFS (Kaplan-Meier)	Median (m)	12.2
	95% CI	(7.4, NE)
	6 months rate	70.7%
	12 months rate	52.4%

Assessed by investigator

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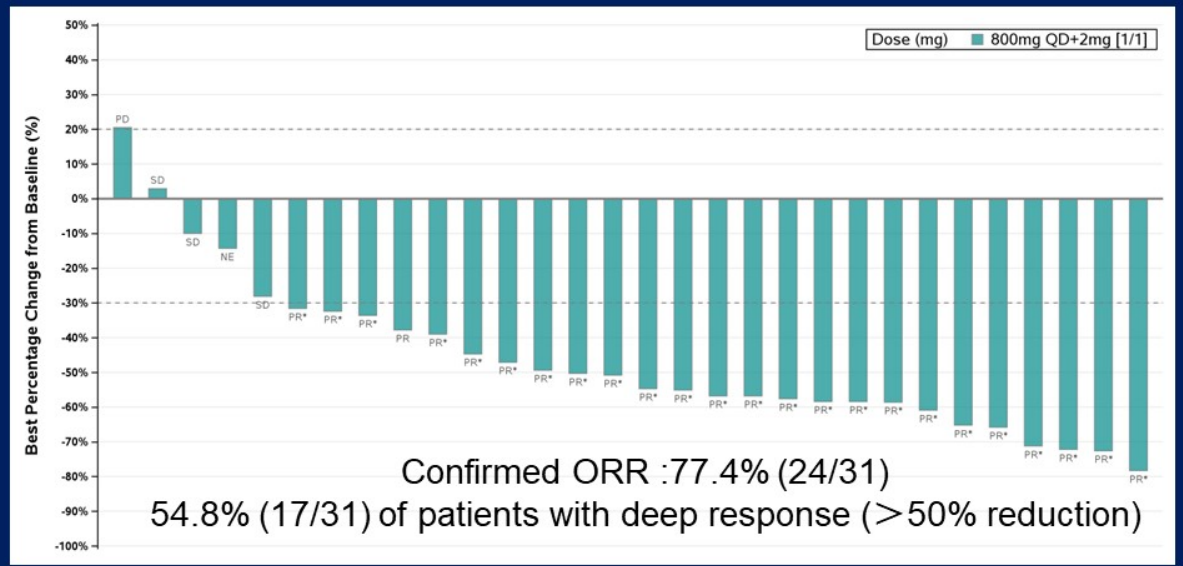
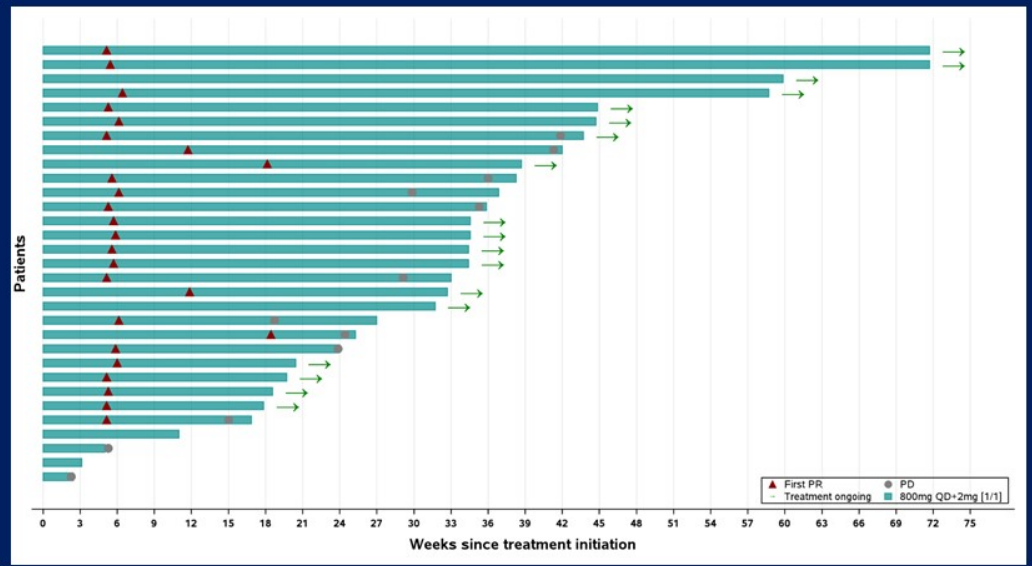
Efficacy in 800mg QD+2mg [1/1] Dosage Group (Frontline NSCLC)





- 58.1% (18/31) of patients were still on treatment.
- The median PFS in 800mg QD + 2mg [1/1] group was not mature.

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Enfermedad metastásica con alteración molecular: ROS1

Abstract 8519

Iniciativa científica de: GECP lung cancer research

Lorlatinib in TKI naïve, advanced ROS1-positive non-small cell lung cancer: a multicenter, open-label, single-arm, phase 2 trial

Methods

Study design : Multi-center, single arm, phase II study (NCT03612154)

Select inclusion criteria

- Age ≥18 years
- Locally advanced or metastatic NSCLC
- ROS1+ by local testing
- TKI naïve
- ≤1 prior platinum based systemic anticancer therapy in the advanced setting

Lorlatinib 100 mg once daily

Continue Lorlatinib until:

- Progression (PD)
- Unacceptable toxicity
- Withdrawal of consent
- Death

Disease assessment every 8 weeks until 6cycles than every 12weeks

Primary endpoint	Secondary endpoints	Select exploratory endpoints
• Objective response rate (ORR)	• Progression free survival (PFS) • Overall survival (OS) • Disease control rate (DCR) • Safety	• Pre treatment/Post PD tissue and blood NGS to find out : Fusion partner Resistance mechanism Variant allele frequency

Statistical considerations

- Null hypothesis: 40%
- Alternative hypothesis: 60%
- Type I error (α):10%
- Type II error (β): 20%
- Drop rate: 10 %
- Calculated sample size: 32 patients

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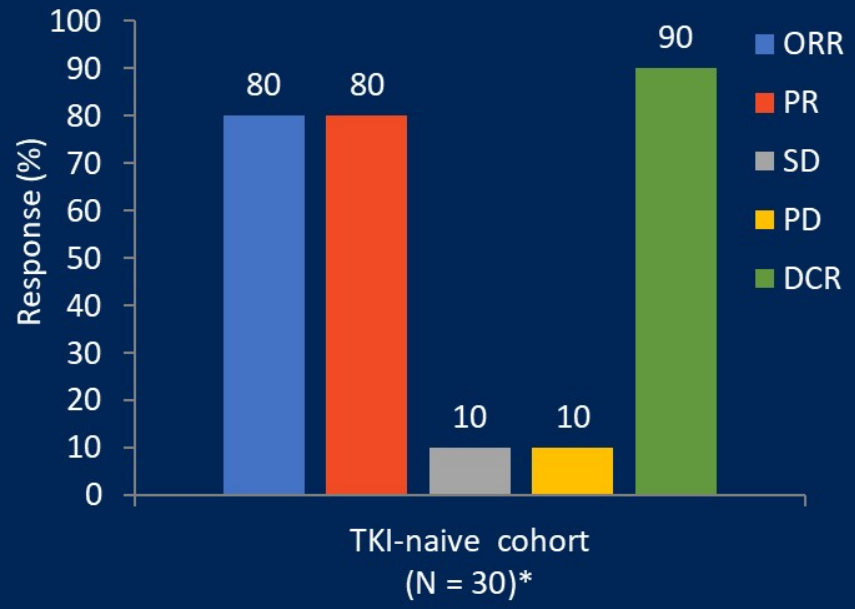
Results: ORR



Confirmed ORR was 80% (95% CI 63% - 91%)

3 PD patients
- 2 pts: false positive RT PCR (confirmed by tissue NGS)
- 1 pt: ROS1-ABCC5 by tissue NGS
  but called by a total of only 5 reads

*2 patient withdraw before 1st response evaluation and excluded from final analysis

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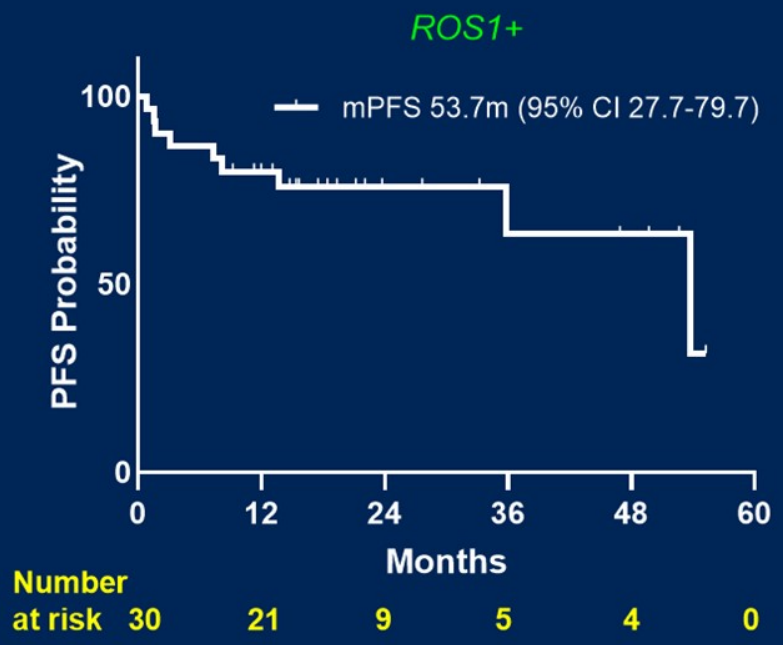
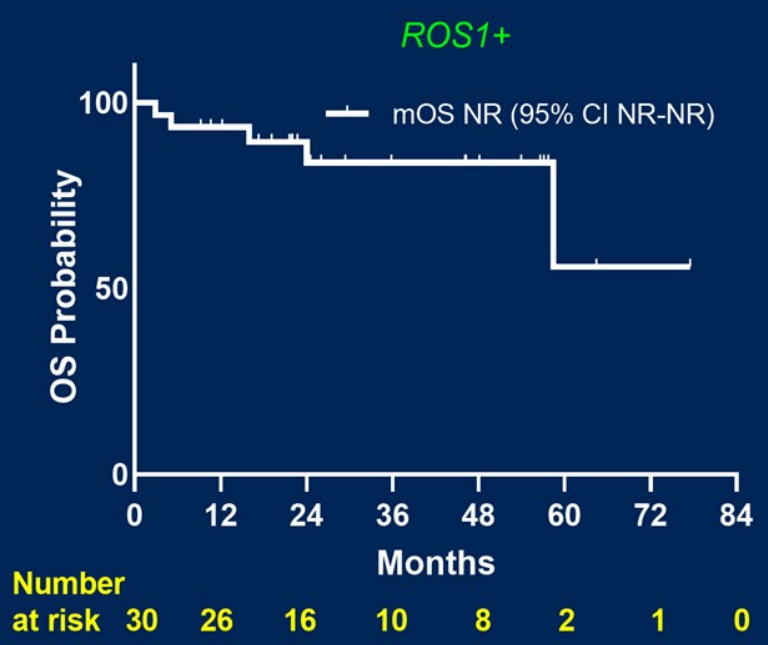
Results: PFS & OS

Systemic PFS in final analysis cohort (N=30)
Data cut off Mar 2024



OS from diagnosed as advanced disease



CI, confidence interval; NR, Not Reached

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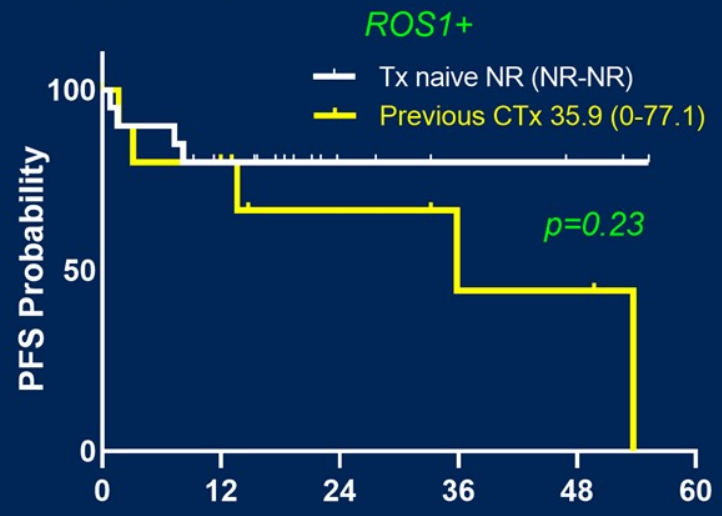
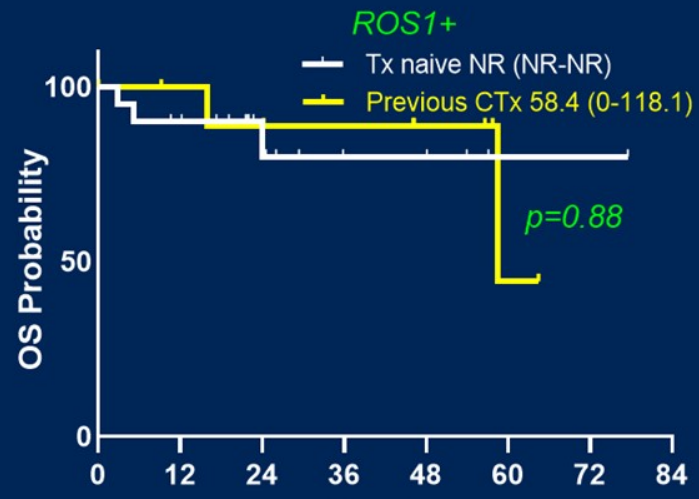
Results

PFS Regarding Previous Chemotherapy month, (95%CI)



Number at risk						
Treat naive	20	14	5	3	2	0
Previous CTx	10	7	4	2	2	0

OS Regarding Previous Chemotherapy month, (95%CI)



Number at risk								
Treat naive	20	17	9	4	4	1	1	0
Previous CTx	10	9	7	6	4	1	0	0

CI, confidence interval; NR, Not Reached; Tx, Treatment; CTx, Chemotherpay

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Results : Adverse Event

TEAEs reported

TEAE, %	Lorlatinib (N=32)	
	ALL GRADE	GRADE ≥3
Hypertriglyceridemia	78	25
Hypercholesterolemia	78	16
Increased ALT level	25	0
Increased AST level	22	0
Peripheral sensory neuropathy	19	0
Dizziness	13	0
Nervous system disorders	13	0
Edema	13	0
Diarrhea	13	0
Eye disorders	9	0
Stroke	6	3
Memory impairment	6	0
Hypothyroidism	6	0
Weight gain	6	0
Hypertension	6	0

There were no Grade 5 events related to lorlatinib

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Limitations

- Single arm, no comparator
- Small in number and only Korean patients
- Further maturation is needed as a few more events may vary PFS & OS
- Brain MRI was not mandatory during follow-up

- Further analysis of Pre Treatment/Post PD tissue and blood NGS will reveal detailed information (fusion partner, resistance mechanism, allele frequency)

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Enfermedad metastásica con alteración molecular: ROS1

Abstract 8520

Iniciativa científica de: GECP lung cancer research

EFFICACY AND SAFETY OF TALETRECTINIB IN PATIENTS WITH ADVANCED OR METASTATIC ROS1+ NON-SMALL CELL LUNG CANCER: THE PHASE 2 TRUST-I STUDY

TRUST-I (NCT04395677): Phase 2 Trial of Taletrectinib in ROS1+ NSCLC

Key Eligibility Criteria

Inclusion Criteria:
- Locally advanced or metastatic NSCLC
- Age ≥18 years
- ECOG PS 0-1
- Evidence of ROS1 fusion in tumor tissue

Cohort A: ROS1 TKI naive
Taletrectinib 600 mg QD[b]

Cohort B: Crizotinib pretreated
Taletrectinib 600 mg QD[b]

Endpoints

Primary:
- IRC-assessed cORR per RECIST v1.1

Secondary:
- DOR
- IC-ORR
- BOR
- DCR
- TTR
- PFS
- Safety[a]

Category	TKI Naive n=106	Crizotinib Pretreated n=67	Overall n=173
Median age, years (range)	56.0 (26–78)	51.0 (31–77)	55.0 (26–78)
Female, n (%)	59 (55.7)	41 (61.2)	100 (57.8)
ECOG PS 0/1, n (%)	20 (18.9)/86 (81.1)	19 (28.4)/48 (71.6)	39 (22.5)/134 (77.5)
Stage IV disease	97 (91.5)	65 (97.0)	162 (93.6)
Prior anticancer chemotherapy, n (%)	22 (20.8)	23 (34.3)	45 (26.0)
Never smoker	78 (73.6)	49 (73.1)	127 (73.4)
Brain metastasis, n (%)	18 (17.0)	28 (41.8)	46 (26.6)

[a]Safety was analyzed in patients receiving ≥1 dose of taletrectinib until 30 days after the last dose of taletrectinib or the start date of new anticancer therapy minus 1 day, whichever occurred first.
[b]A dose confirmation lead-in stage evaluated the safety of taletrectinib 400 mg QD (n=3) and 600 mg QD (n=3).
BOR, best overall response; cORR, confirmed objective response rate; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, intracranial; IRC, independent review committee; NSCLC, non-small cell lung cancer; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; TTR, time to response.

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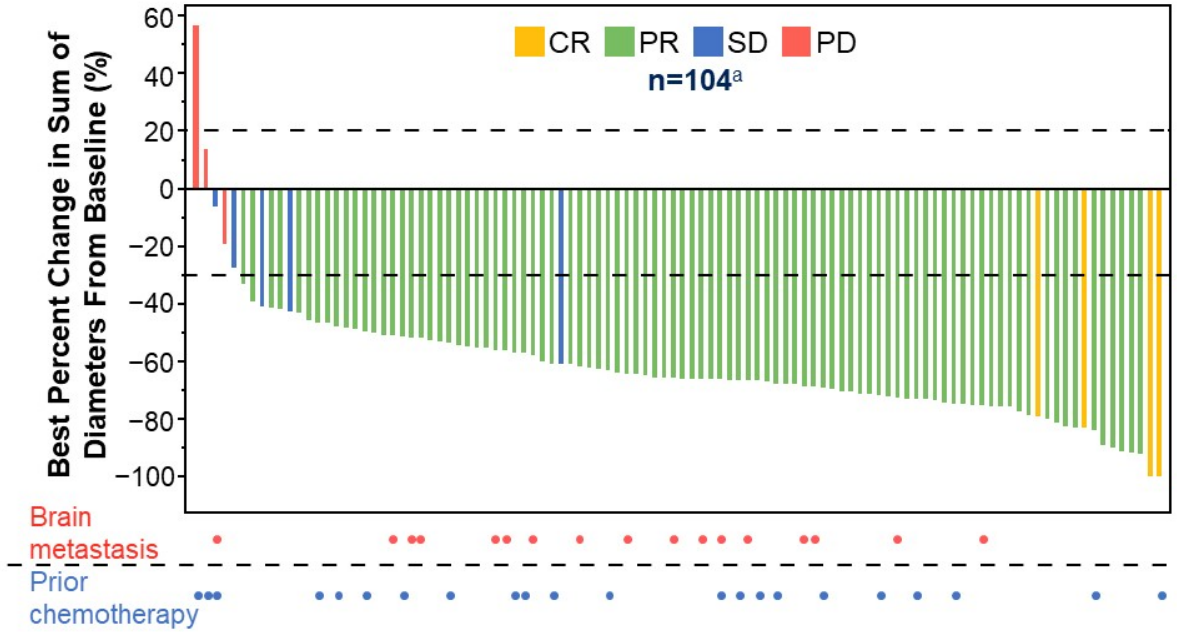
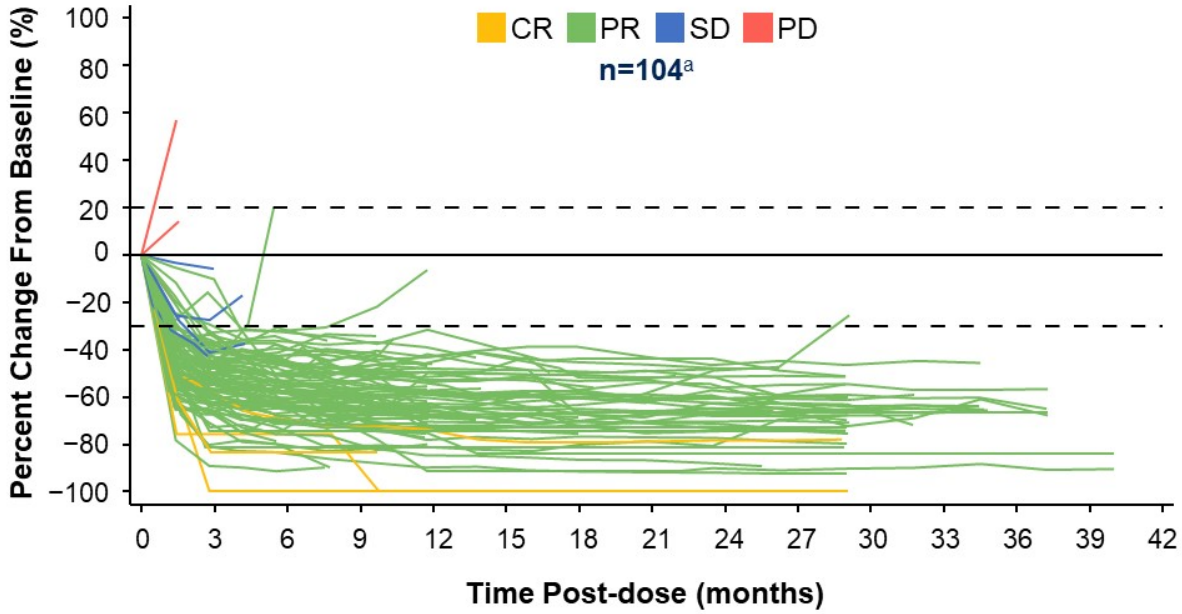
Taletrectinib: Efficacy in ROS1+ TKI-Naive NSCLC

Responses	TKI Naive n=106
IRC-assessed cORR, % (95% CI)	90.6 (83.33, 95.38)
DCR, % (95% CI)	95.3 (89.33, 98.45)
Median TTR, months (95% CI)	1.4 (1.38, 1.41)





Data cutoff: November 29, 2023. [a]Two patients with confirmed BOR as not evaluable are not displayed in the waterfall and spider plots.
BOR, best overall response; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; IRC, independent review committee; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TTR, time to response.

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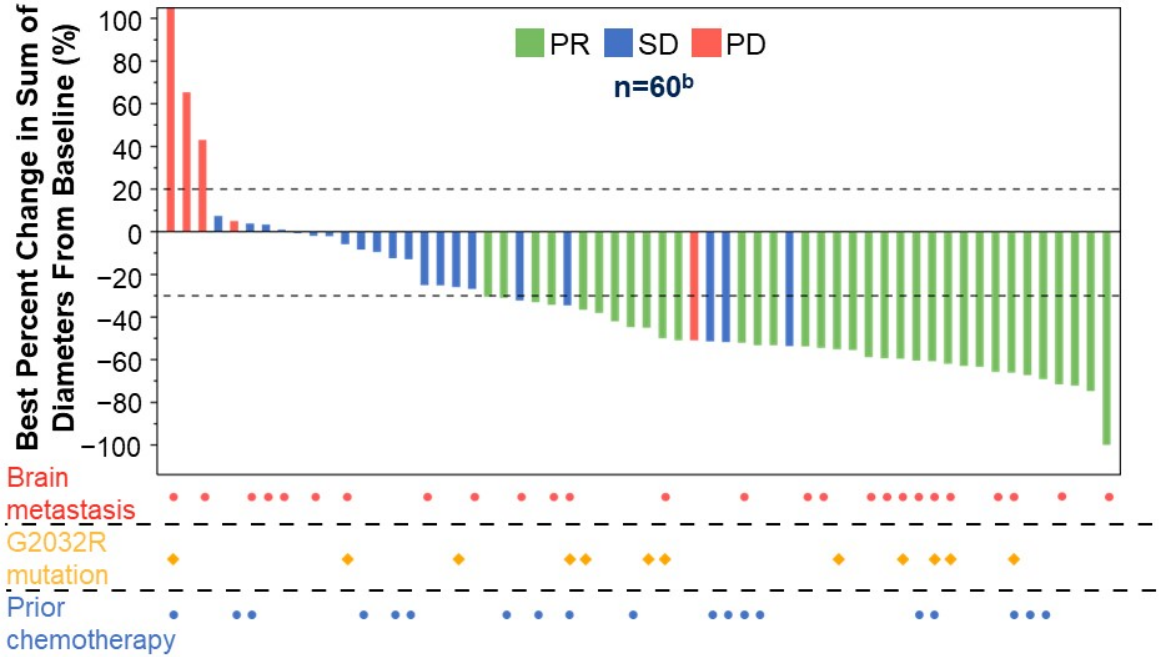
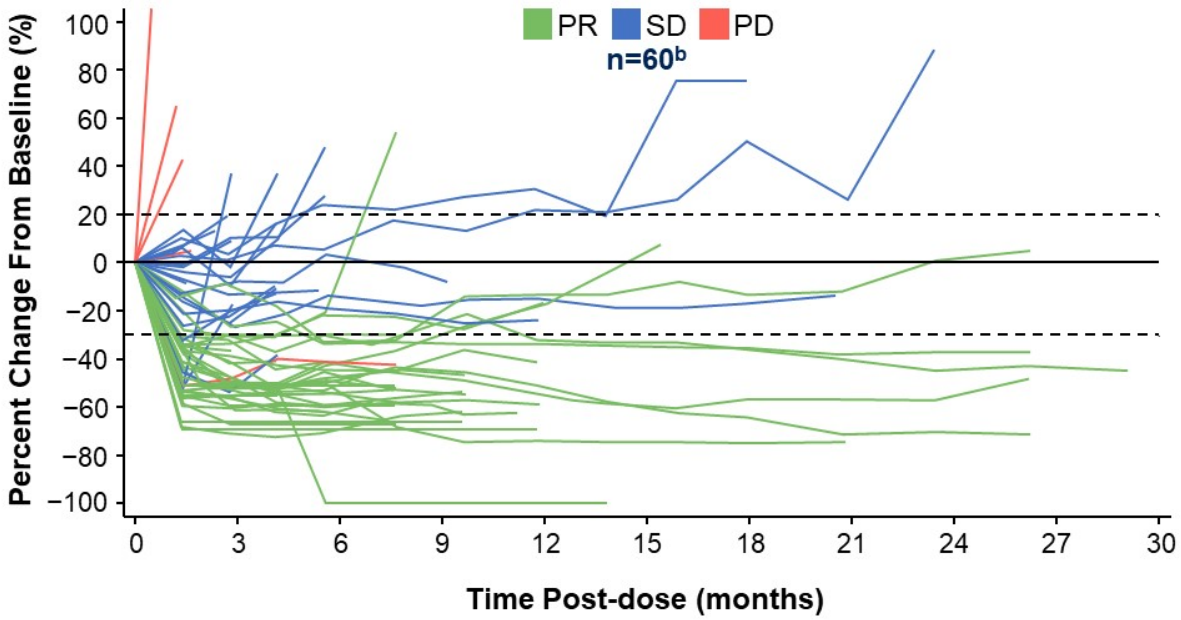
Taletrectinib: Efficacy in ROS1+ Crizotinib-Pretreated NSCLC

Responses	Crizotinib Pretreated n=66[a]
IRC-assessed cORR, % (95% CI)	51.5 (38.88, 64.01)
DCR, % (95% CI)	83.3 (72.13, 91.38)
Median TTR, months (95% CI)	1.4 (1.38, 1.41)
cORR: G2032R mutations, % (n/N)	66.7 (8/12)





Data cutoff: November 29, 2023. [a]One patient was excluded from the response-evaluable population in the crizotinib-pretreated group due to the presence of secondary cancer. [b]Six patients with confirmed BOR as not evaluable are not displayed in the waterfall and spider plots.

BOR, best overall response; cORR, confirmed objective response rate; DCR, disease control rate; IRC, independent review committee; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TTR, time to response.

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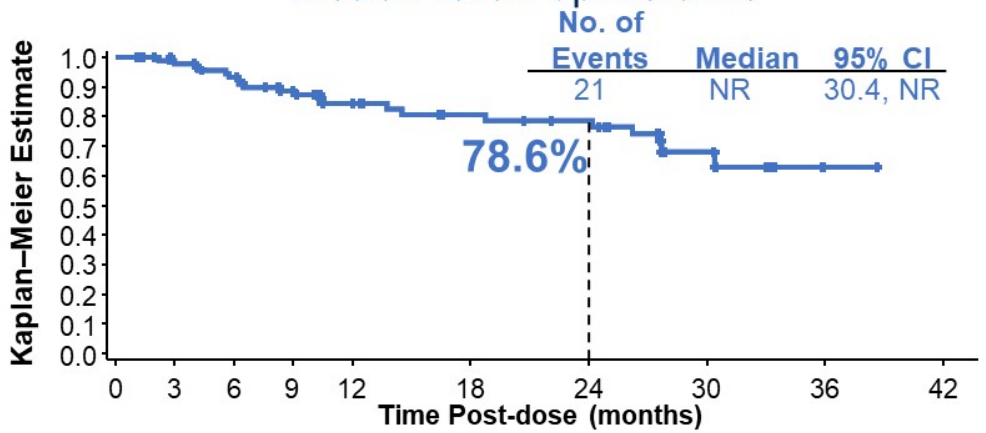
Taletrectinib: Duration of Response and Progression-Free Survival

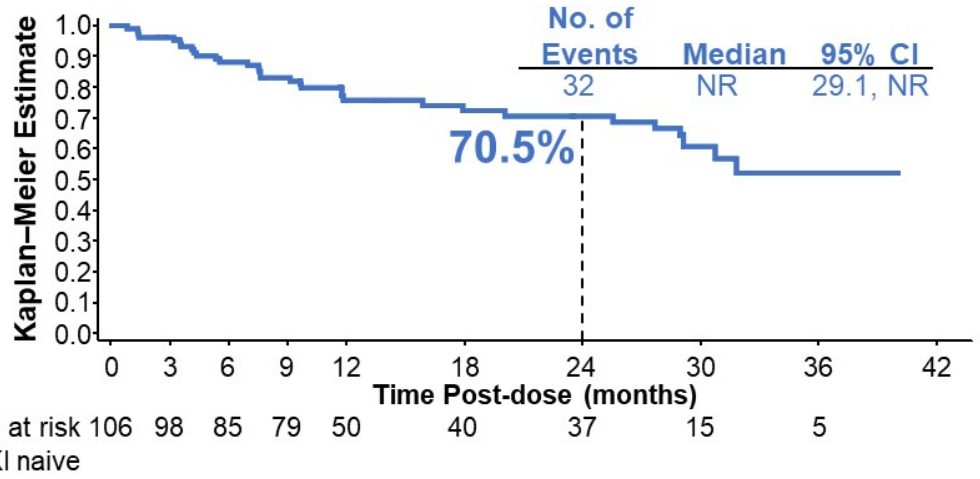
TKI Naive (n=106)

Median follow-up: 23.5 mo

DOR

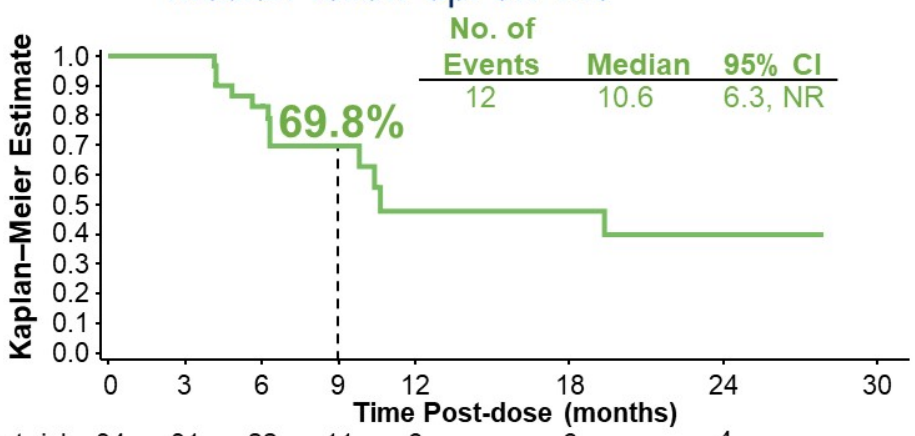


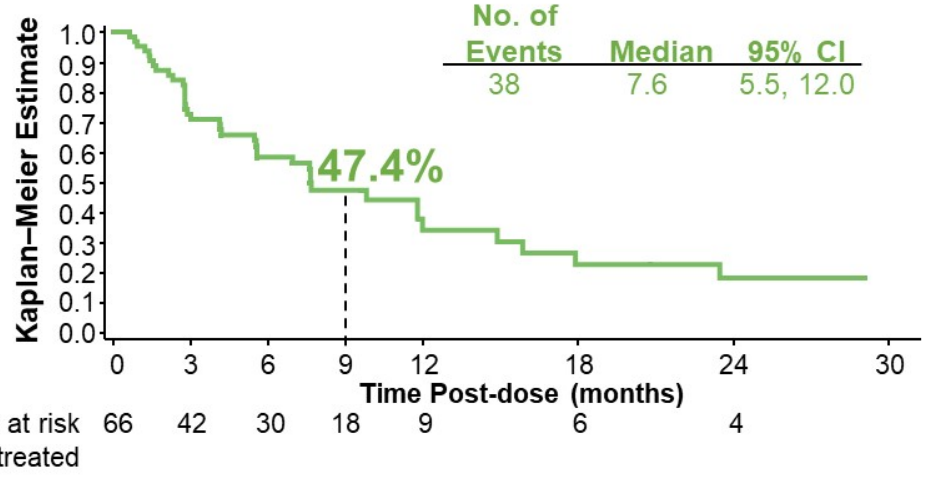
PFS



Crizotinib Pretreated (n=66)

Median follow-up: 9.7 mo





Data cutoff: November 29, 2023. DOR, duration of response; NR, not reached; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

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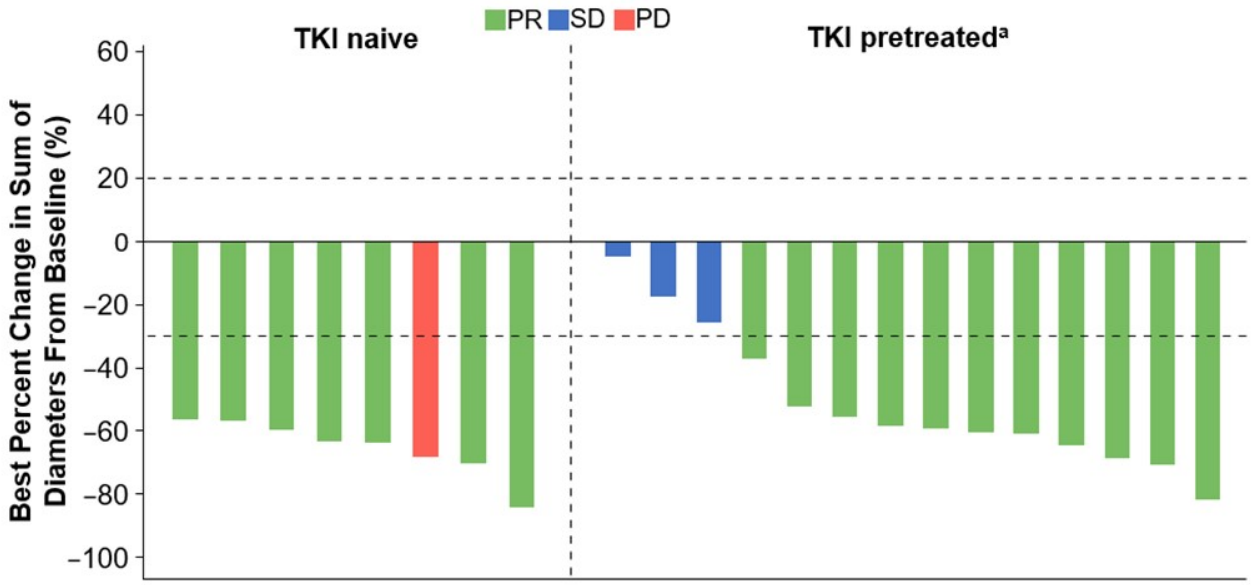
Taletrectinib: Responses in Measurable Baseline Brain Metastases

Responses	TKI Naive n=8	Crizotinib Pretreated n=15
IC-cORR, % (95% CI)	87.5 (47.35, 99.68)	73.3 (44.90, 92.21)
DCR, % (95% CI)	100.0 (63.06, 100.0)	93.3 (68.05, 99.83)



Data cutoff: November 29, 2023. [a]One patient with confirmed best overall response as not evaluable is not displayed in the waterfall plot.
cORR, confirmed objective response rate; DCR, disease control rate; IC, intracranial; IRC, independent review committee; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

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Taletrectinib Safety: TEAEs in ≥15% of Patients[a] (N=173)

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5[b] n (%)	Any grade n (%)
Increased AST	92 (53.2)	26 (15.0)	14 (8.1)	0	0	132 (76.3)
Diarrhea	99 (57.2)	16 (9.2)	6 (3.5)	0	0	121 (69.9)
Increased ALT	79 (45.7)	29 (16.8)	8 (4.6)	1 (0.6)	0	117 (67.6)
Vomiting	75 (43.4)	16 (9.2)	1 (0.6)	0	0	92 (53.2)
Anemia	52 (30.1)	30 (17.3)	3 (1.7)	0	0	85 (49.1)
Nausea	64 (37.0)	8 (4.6)	1 (0.6)	0	0	73 (42.2)
Decreased neutrophil count	25 (14.5)	10 (5.8)	6 (3.5)	4 (2.3)	0	45 (26.0)
Abnormal hepatic function	21 (12.1)	8 (4.6)	14 (8.1)	0	1 (0.6)	44 (25.4)
Decreased WBC count	27 (15.6)	14 (8.1)	3 (1.7)	0	0	44 (25.4)
Increased blood bilirubin	34 (19.7)	6 (3.5)	2 (1.2)	1 (0.6)	0	43 (24.9)
Dizziness	36 (20.8)	3 (1.7)	1 (0.6)	0	0	40 (23.1)
Proteinuria	34 (19.7)	5 (2.9)	0	0	0	39 (22.5)
Increased weight	17 (9.8)	16 (9.2)	3 (1.7)	0	0	36 (20.8)
Increased blood creatinine	33 (19.1)	2 (1.2)	0	0	0	35 (20.2)
QT prolongation	26 (15.0)	4 (2.3)	5 (2.9)	0	0	35 (20.2)
Hypercholesterolemia	29 (16.8)	4 (2.3)	0	0	0	33 (19.1)
Hyperuricemia	30 (17.3)	2 (1.2)	0	0	0	32 (18.5)
Decreased weight	23 (13.3)	8 (4.6)	0	0	0	31 (17.9)
Constipation	28 (16.2)	2 (1.2)	0	0	0	30 (17.3)
Decreased appetite	26 (15.0)	3 (1.7)	0	0	0	29 (16.8)
Increased conjugated bilirubin	22 (12.7)	3 (1.7)	2 (1.2)	1 (0.6)	0	28 (16.2)
COVID-19	10 (5.8)	15 (8.7)	3 (1.7)	0	0	28 (16.2)
Pyrexia	23 (13.3)	3 (1.7)	1 (0.6)	0	0	27 (15.6)
Increased blood CPK	21 (12.1)	5 (2.9)	0	0	0	26 (15.0)
Hypertriglyceridemia	24 (13.9)	2 (1.2)	0	0	0	26 (15.0)

- Median exposure of taletrectinib was 12.2 months (range: 0.23–40.04)
- 40.5% (70/173) of patients had a TEAE leading to treatment interruption
- 19.1% (33/173) of patients had a TEAE leading to a dose reduction
- 5.2% (9/173) of patients had a TEAE leading to treatment discontinuation
- Rates of neurologic TEAEs were low (dizziness: 23%; dysgeusia: 10%) and mostly grade 1

Data cutoff: November 29, 2023. [a]Worst grade per patient is reported. [b]Taletrectinib-related grade 5 TEAEs occurred in 3 patients: 2 TKI naive (1 hepatic failure, 1 pneumonia) and 1 crizotinib pretreated (abnormal hepatic function).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatinine phosphokinase; TEAE, treatment-emergent adverse event; WBC, white blood cell.

PRESENTED BY: Wei Li, MD

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Enfermedad metastásica con alteración molecular: ROS1

Abstract 8522

Iniciativa científica de: GECP

Repotrectinib in tyrosine kinase inhibitor (TKI)-naïve patients with advanced *ROS1* fusion-positive (*ROS1*+) NSCLC in the phase 1/2 TRIDENT-1 trial: clinical update, treatment beyond progression and subsequent therapies

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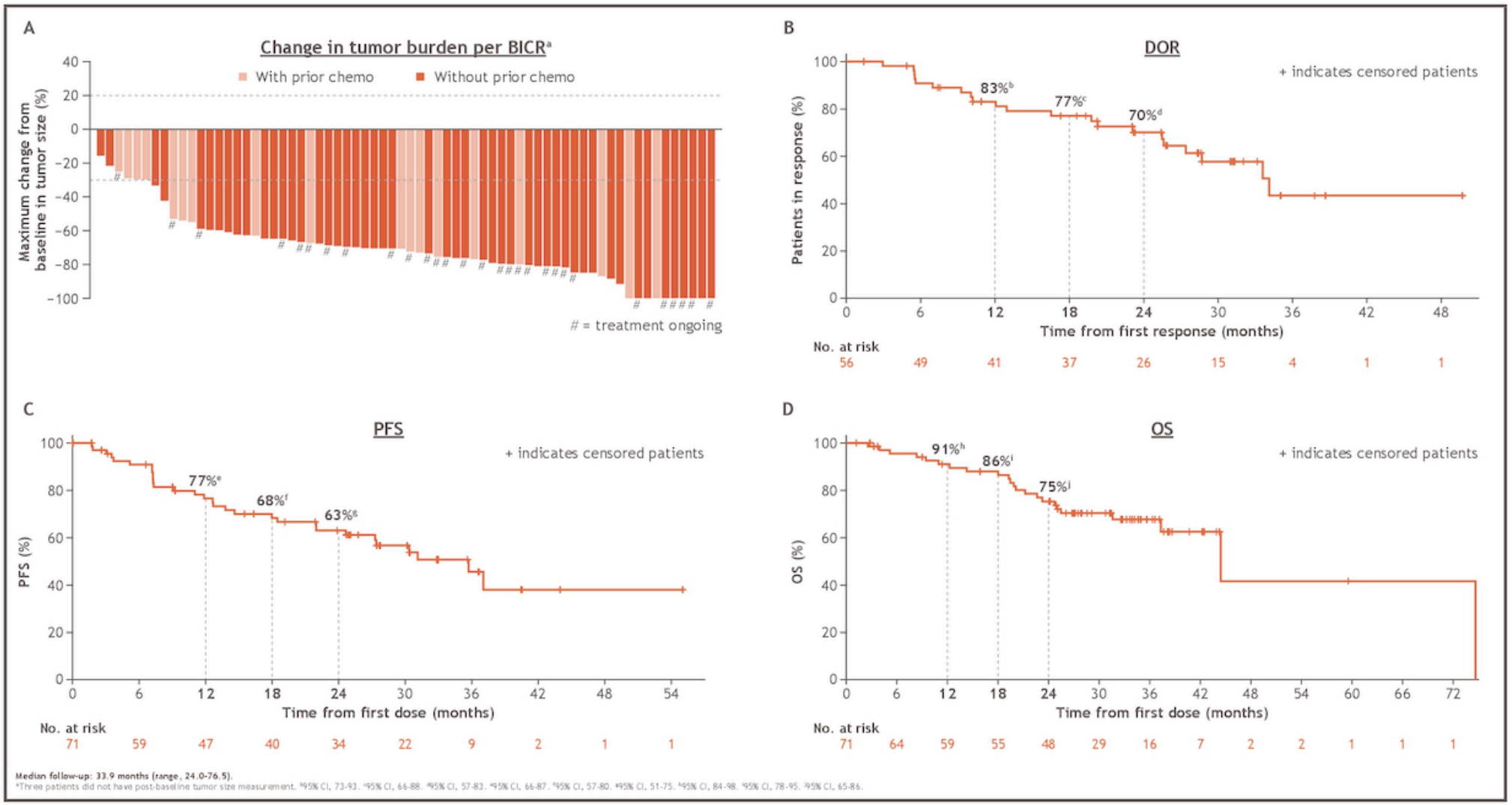
Figure 2. Change in tumor burden (A), DOR (B), PFS (C) per BICR, and OS (D)



Median follow-up: 33.9 months (range, 24.0-76.5).

[a]Three patients did not have post-baseline tumor size measurement. [b]95% CI, 73-93. [c]95% CI, 66-88. [d]95% CI, 57-83. [e]95% CI, 66-87. [f]95% CI, 57-80. [g]95% CI, 51-75. [h]95% CI, 84-98. [i]95% CI, 78-95. [j]95% CI, 65-86.

Enfermedad metastásica con alteración molecular: ROS1

Abstract 8522

Iniciativa científica de: GECP

Repotrectinib in tyrosine kinase inhibitor (TKI)-naïve patients with advanced *ROS1* fusion-positive (*ROS1*+) NSCLC in the phase 1/2 TRIDENT-1 trial: clinical update, treatment beyond progression and subsequent therapies

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Table 2. Efficacy summary

	ROS1 TKI-naïve (n = 71)
cORR,[a] % (95% CI) With prior chemo (n = 20) Without prior chemo (n = 51)	79 (68–88) 70 (46–88) 82 (69–92)
BOR,[a] n (%) CR PR PD SD	 9 (13) 47 (66) 2 (3) 11 (15)
CBR,[a,b] % (95% CI)	94 (86–98)
Median time to response, months (range)	1.8 (1.5–5.6)
Median PFS,[c] months (95% CI) With prior chemo Without prior chemo	35.7 (24.6–NE) 35.7 (18.0–NE) 37.1 (22.0–NE)
Median DOR,[d] months (95% CI) With prior chemo Without prior chemo	34.1 (27.4–NE) 34.1 (23.1–NE) 33.6 (25.6–NE)
icORR, % (95% CI) [n/N]	89 (52-100) [8/9]

Enfermedad metastásica con alteración molecular: HER2

Abstract 8514

Iniciativa científica de:

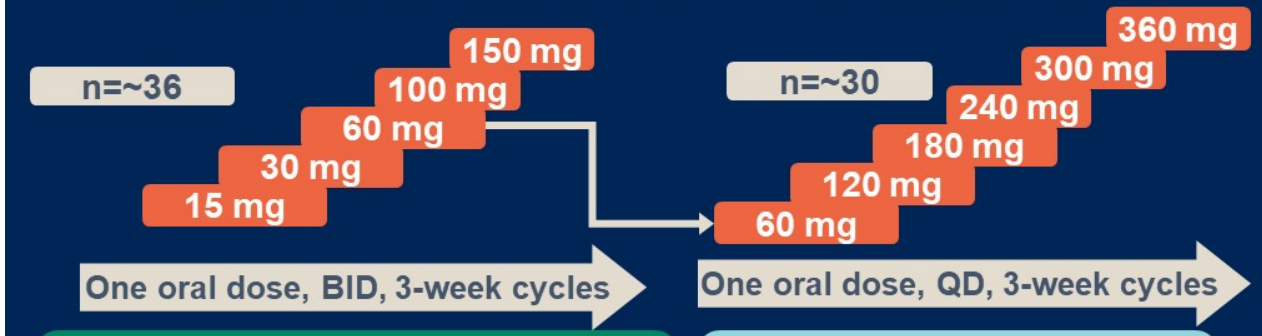
GECP lung cancer research

Phase Ia/Ib trial of zongertinib (BI 1810631), a HER2-specific tyrosine kinase inhibitor in patients with HER2 aberration-positive solid tumors: updated Phase Ia data from Beamion LUNG-1, including progression-free survival data

Beamion LUNG-1 (NCT04886804): trial design/endpoints

- Zongertinib (BI 1810631) is a novel TKI that covalently and selectively binds to the TKD of HER2, and is under investigation as an oral treatment for NSCLC tumors harboring *HER2* TKD mutations, including ex20ins mutations

Phase Ia: dose escalation (in patients with advanced solid tumors with HER2 aberrations)



Phase Ia endpoints

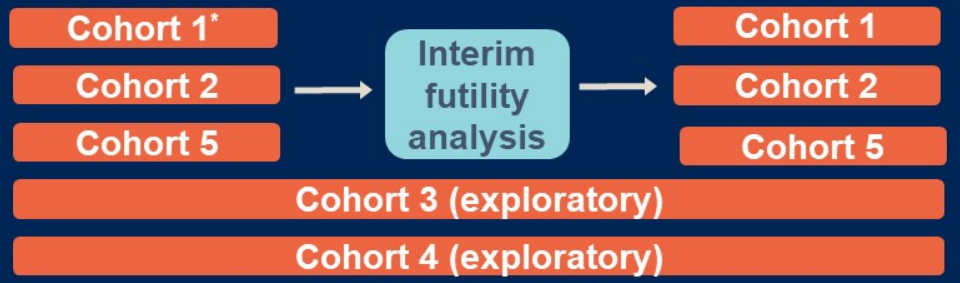
Primary: MTD and DLTs
Further: preliminary efficacy (ORR)†

Key inclusion criteria

HER2 aberration: overexpression, amplification, somatic mutation, or gene rearrangement involving *HER2* or *NRG1*

Exhausted or not suitable for existing standard treatment options

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



Phase Ib primary endpoint

ORR†

Key inclusion criteria

Patients with *HER2* mutation-positive NSCLC

Received ≥1 line of platinum-based combination chemotherapy (Cohorts 1, 3, 5)

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

PRESENTED BY: Dr John Heymach

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*Randomized to receive either 120 mg or 240 mg QD. One dose will be selected after interim analysis; †RECIST v1.1; ‡Excluding patients treated with ADCs
ADC, antibody-drug conjugate; BID, twice daily; DLTs, dose-limiting toxicities; ex20ins, exon 20 insertion; HER2, human epidermal growth factor receptor 2; MTD, maximum tolerated dose; NRG1, neuregulin 1; NSCLC, non-small cell lung cancer; ORR, objective response rate; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; TKD, tyrosine kinase domain; TKI, tyrosine kinase inhibitor

Phase Ia: baseline characteristics

Characteristic	Total (N=83)
Median age, years (range)	59.0 (31–81)
Male, n (%)	38 (45.8)
Race, n (%)	
Asian	39 (47.0)
White	35 (42.2)
Missing	9 (10.8)
ECOG PS, n (%)	
0	31 (37.3)
1	52 (62.7)
Previous lines of therapy, n (%)	
≤2	32 (38.6)
>2	47 (56.6)
Missing	4 (4.8)

Characteristic	Total (N=83)
Diagnosis, n (%)	
NSCLC	43 (51.8)
Breast cancer	9 (10.8)
Colorectal cancer	7 (8.4)
Esophageal cancer	5 (6.0)
Other tumors*	15 (18.1)
Unknown†	4 (4.8)
HER2 aberration, n/N tested (%)	
Mutation	42/75 (56.0)
Amplification	9/11 (81.8)
Overexpression‡	24/28 (85.7)
Rearrangement involving *HER2* or *NRG1*	12/75 (16.0)

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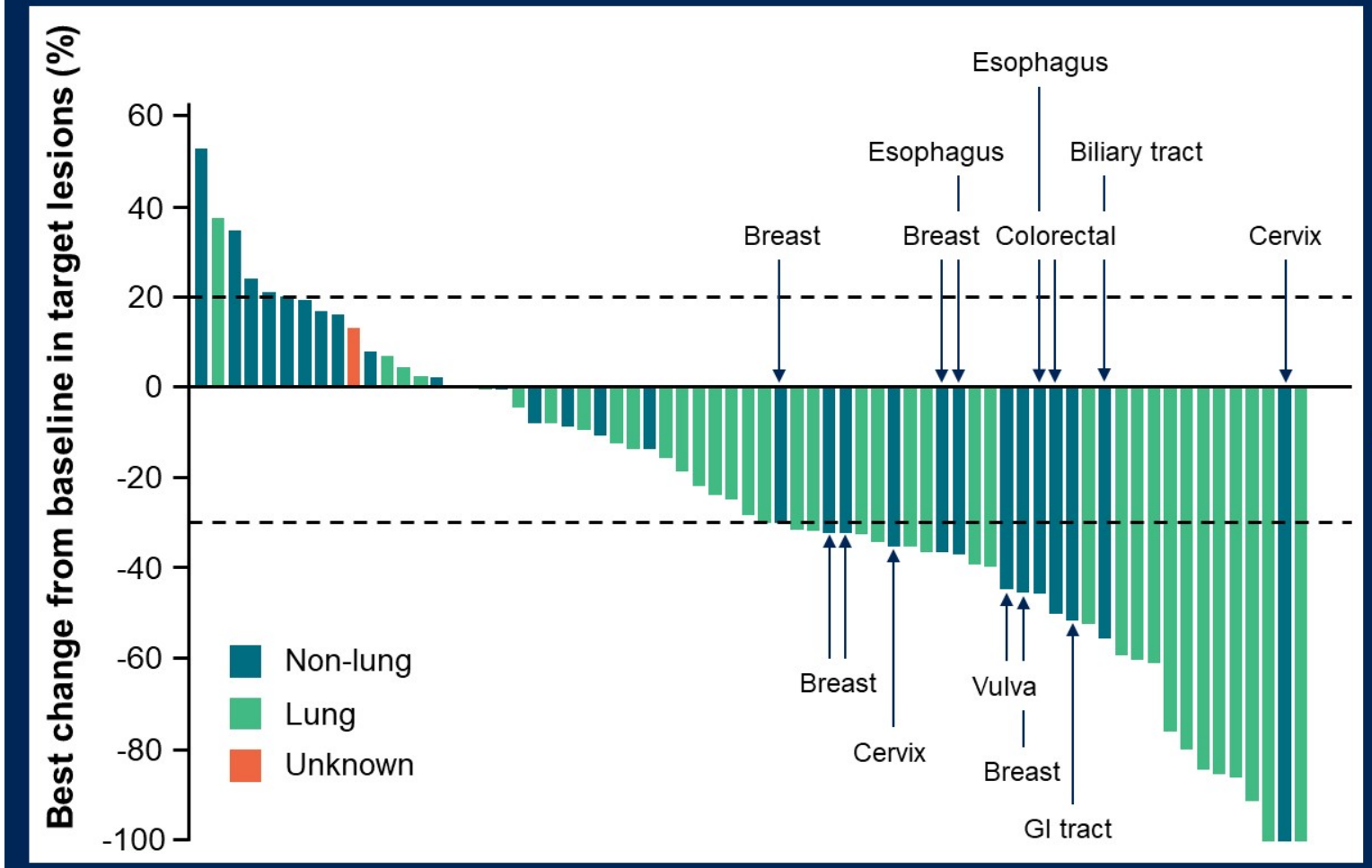
Data cut-off: January 29, 2024. *Cervical (n=3), endometrial (n=3), gastrointestinal tract (n=2), genitourinary system (n=1), small intestine, (n=1), biliary tract (n=1), mediastinum (n=1), pancreas (n=1), vulva (1), and other (n=1); †Tumor type was not listed for four patients; ‡1+, 2+, or 3+ on immunohistochemistry
ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; NRG1, neuregulin 1; NSCLC, non-small cell lung cancer

Phase Ia: antitumor response across all dose levels*



Best confirmed tumor response

	ORR	DCR
Overall (N=74)	35%	85%
NSCLC (N=41)	44%	93%

Unconfirmed response rates

	ORR	DCR
Prior trastuzumab deruxtecan (n=14)	36%	79%
Prior HER2 tx† (n=32)	38%	84%

Data cut-off: January 29, 2024.*Responses are restricted to non-CNS lesions by RECIST 1.1.†Prior treatment with other HER2 therapies was permitted
CNS, central nervous system; DCR, disease control rate; GI, gastrointestinal; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, objective response rate; tx, treatment

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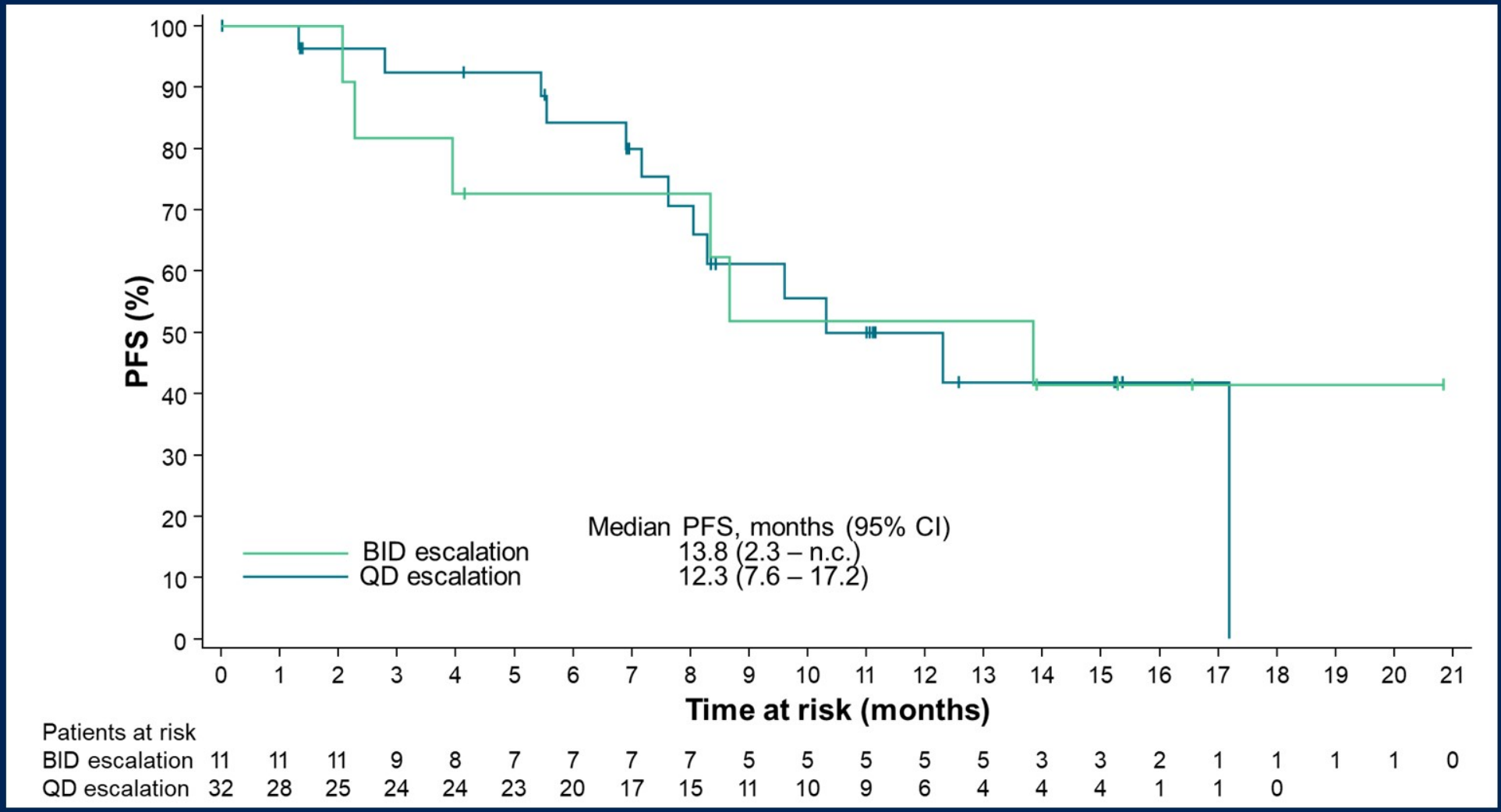
Phase Ia: PFS in patients with NSCLC*



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Data cut-off: January 29, 2024
BID, twice daily; CI, confidence interval; n.c., not reached; NSCLC, non-small cell lung cancer; PFS, progression-free survival; QD, once daily

Phase Ia dose escalation and safety

TRAEs (%)	Total (N=83)	
	All grades	G≥3
Any TRAE*	**75.9**	**9.6**
Diarrhea	42.2	1.2
Rash†	12.0	0.0
Decreased appetite	9.6	0.0
ALT increased	8.4	3.6
AST increased	8.4	1.2
Anemia	8.4	0.0
Fatigue	8.4	0.0
Dysgeusia	7.2	0.0
Paronychia	7.2	0.0
Dry skin	6.0	0.0
Nausea	6.0	0.0

Dose-limiting toxicities	
60 mg BID	G2 edema
150 mg BID	G2 diarrhea
180 mg QD	G2 elevated AST and elevated bilirubin G3 elevated ALT
240 mg QD	**G3 diarrhea (MTD period)** G4 thrombocytopenia
300 mg QD	**G4 neutropenia (MTD period)** G4 hypokalemia
360 mg QD	**G3 decreased platelet count (MTD period)**

- **Only one grade 4 TRAE (thrombocytopenia; 240 mg)**
- **No grade 5 TRAEs**
- **MTD was not reached with either BID or QD schedule**
- **Doses taken to optimization: 120/240 mg QD**

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Data cut-off: January 29, 2024. *TRAEs that occurred in ≥5 patients are listed;
†Combined term, includes rash, rash maculo-papular, dermatitis acneiform
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; G, grade; MTD, maximum tolerated dose; QD, once daily; TRAEs, treatment-related adverse events

Enfermedad metastásica con alteración molecular: FGFR

Abstract 8515

Iniciativa científica de: GECP lung cancer research

Efficacy and Safety of Erdafitinib in Adults With NSCLC and Prespecified Fibroblast Growth Factor Receptor Alterations in the Phase 2 Open-label, Single-arm RAGNAR Trial

RAGNAR (NCT04083976) : A tumor-agnostic, phase 2, single arm, open-label study

Patients

Inclusion criteria

- Age ≥12 years
- Advanced or metastatic squamous or non-squamous NSCLC with prespecified *FGFR*1-4 alterations (mutations/fusions)
- Documented disease progression after exhausting standard therapies
- Received ≥1 prior line of systemic therapy

Exclusion criteria

- Previous *FGFR* inhibitor treatment
- Other targetable alterations (e.g., *EGFR, ALK, ROS1*)

Intervention

Oral erdafitinib once-daily

- Given in continuous 21-day cycle until disease progression or intolerable toxicity as per pharmacodynamically guided up-titration:
  - Age ≥15 years: 8 mg to 9 mg
  - Age 12-14 years: 5 mg to 8 mg

Endpoints
by independent review committee

Primary*
- Objective response rate

Secondary
- DOR
- DCR#
- PFS
- OS
- Safety

Baseline Characteristics

- Overall, 23 patients with NSCLC received erdafitinib
- 96% of patients had metastatic disease
- Patients were heavily pretreated
  - Only 2 (9%) patients had responded to their last therapy

Characteristics	Squamous (n=14)	Non-squamous (n=9)	Total (N=23)
Age, years, median (range)	60.0 (52.0-77.0)	63.0 (50.0-79.0)	63.0 (50.0-79.0)
Male, n (%)	11 (78.6)	6 (66.7)	17 (73.9)
Current/former smoker, n (%)	12 (85.7)	7 (77.8)	19 (82.6)
Metastasis, n (%)	14 (100)	8 (89)	22 (96)
***FGFR* gene, n (%)**			
*FGFR*2	2 (14.3)	5 (55.6)	7 (30.4)
*FGFR*3	12 (85.7)	4 (44.4)	16 (69.6)
***FGFR* alteration type, n (%)**			
Mutation	7 (50.0)	3 (33.3)	10 (43.5)
Fusion	7 (50.0)	6 (66.7)	13 (56.5)
Prior lines of therapies, median (range), n (%)	2.0 (1.0-6.0)	3.0 (1.0-7.0)	2.0 (1.0-7.0)
1	2 (14.3)	1 (11.1)	3 (13.0)
2	6 (42.9)	3 (33.3)	9 (39.1)
≥3	6 (42.9)	5 (55.6)	11 (47.8)
Response to last line of therapy, n (%)	2 (14.3)	0	2 (8.7)

FGFR, fibroblast growth factor receptor; NSCLC, non-small cell lung cancer

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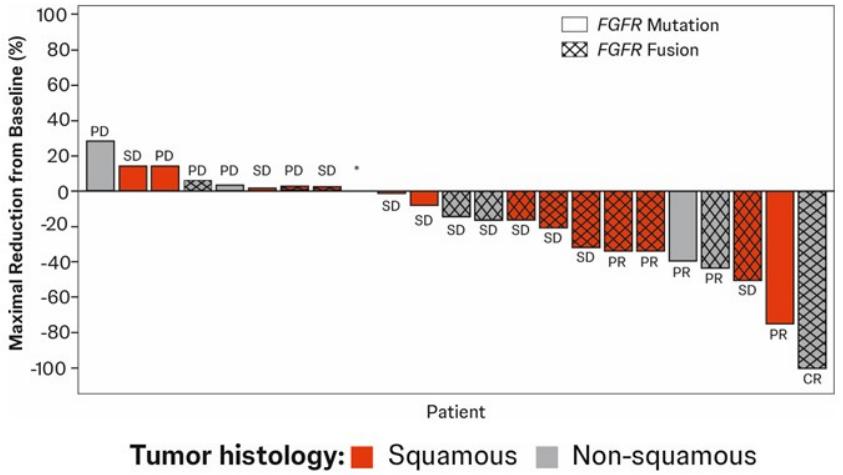
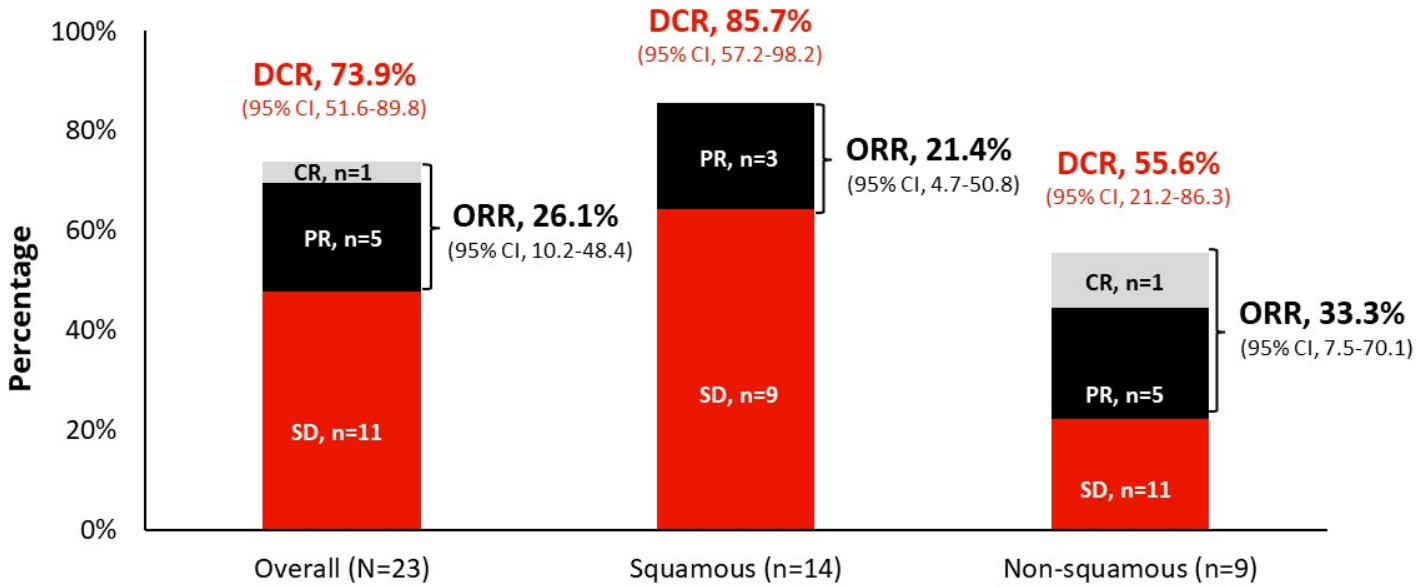
Tumor Response and Disease Control (per IRC)





- Median time to response was 1.5 (95% CI, 1.1-2.9) months
- ORR was 28.6% and 25.0% in patients with *FGFR*2 and *FGFR*3 gene alterations, respectively
- ORR was 30.8% and 20.0% in patients with *FGFR* fusions and mutations, respectively

*Squamous with *FGFR* mutation and non-CR/non-PD
CR, complete response; DCR, disease control rate; *FGFR*, fibroblast growth factor receptor; IRC, independent review committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

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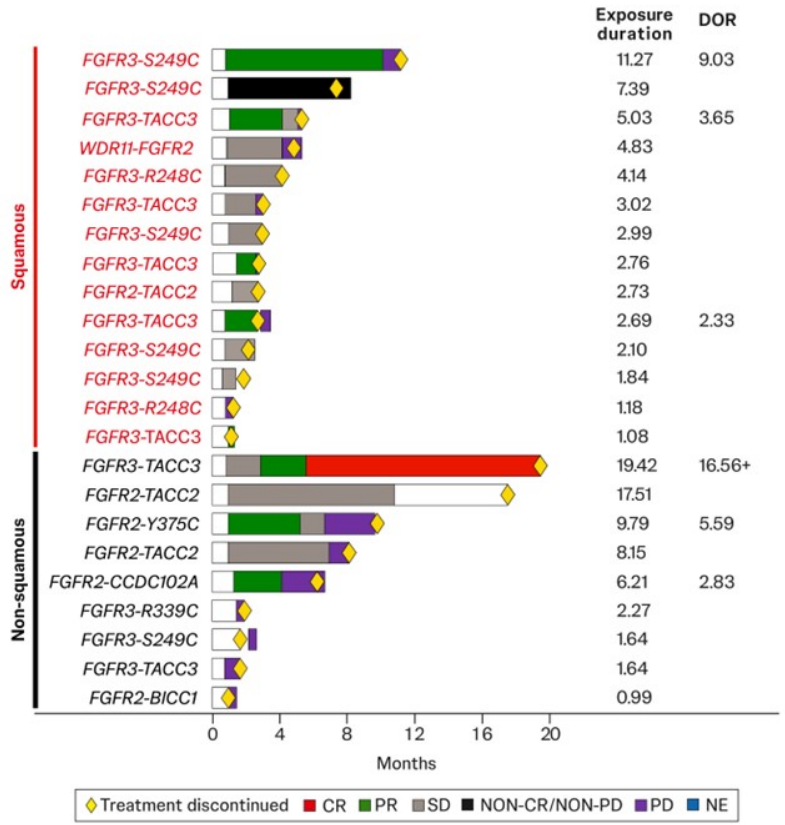
Duration of Response, PFS and OS

Median (95% CI)	Overall (N=23)	Squamous (n=14)	Non-squamous (n=9)
DOR	4.6 (2.3-NE)	3.7 (2.3-NE)	5.6 (2.8-NE)
PFS	4.1 (2.4-6.9)	4.1 (2.4-NE)	4.1 (1.4-NE)
OS	10.5 (4.4-14.8)	10.5 (2.4-14.5)	9.9 (2.4-NE)



DOR, duration of response; CR, complete response; NE, not evaluable; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease

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Safety

- 91.3% erdafitinib-treated patients had at least 1 drug-related TEAE
- Drug-related TEAEs of grade ≥3 occurred in 39.1% of patients and were manageable with supportive care and treatment interruptions or reductions
- 8.7% of patients discontinued due to drug-related TEAEs
- 8.7% of patients had serious drug-related TEAEs
- 56.5% of patients had dose reduction due to drug-related TEAEs
- 78.3% of patients had dose interruption due to drug-related TEAEs
- No treatment-related deaths were observed

TEAE by preferred term in ≥30% of patients, n (%)	N=23	
	Any grade	Grade ≥3
Hyperphosphatemia	15 (65.2)	0
Diarrhea	13 (56.5)	1 (4.3)
Stomatitis	13 (56.5)	3 (13.0)
Dry mouth	10 (43.5)	1 (4.3)
Nail disorder	8 (34.8)	1 (4.3)
Dry skin	7 (30.4)	0
Palmar-plantar erythrodysesthesia syndrome	7 (30.4)	2 (8.7)

TEAE, treatment-emergent adverse event

Pant C, et al. *Lancet Oncol* 2023; 24: 925–35

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Iniciativa científica de:

GECP lung cancer research

Gracias