Lung Cancer UPDATES
ESMO HIGHLIGHTS
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Berlin, Germany

GECP lung cancer research

CPNCP avanzado con mutaciones driver (II)

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INDICE

KRAS

Intracranial efficacy of olomorasib, a next-generation KRAS G12C-mutant NSCLC and active untreated brain metastases.

Phase 1/2 LOXO-RAS-20001

Cohort B8: NSCLC
Olomorasib (150 mg BID)
(N=21)

Eligibility

- Age ≥18
- ECOG performance status of 0 or 1
- Measurable intracranial disease per mRECIST v1.1
- Locally advanced/metastatic NSCLC
- Presence of a *KRAS* G12C mutation
- **At least 1 untreated, active, brain lesion (≥5 mm)**
- No prior KRAS G12C inhibitor
- Leptomeningeal disease was excluded

Key objectives

- Safety and Tolerability
- Pharmacokinetics
- Intracranial ORR and DoR
- ORR, DoR, DCR and PFS per modified RECIST v1.1

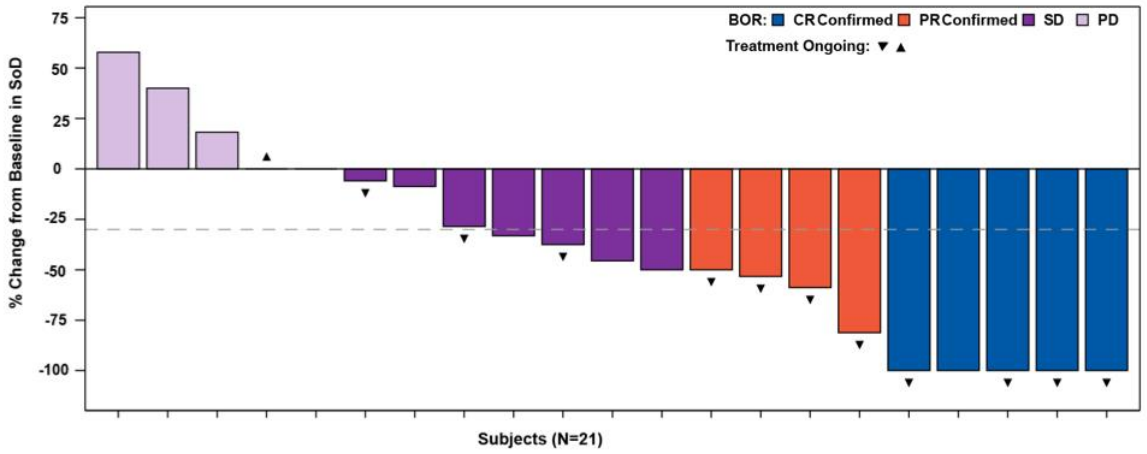
Patient and Disease Characteristics

Characteristics	Olomorasib[a] (n=21)
Age, median, years (range)	65 (42, 80)
Sex, n (%)	
Male / Female	8 (38) / 13 (62)
Race, n (%)	
White / Asian / Black or African American / other / unknown	11 (52) / 3 (14) / 1 (5) /1 (5) / 5 (24)
ECOG, PS[b], n (%)	
0 / 1 / 2	7 (33) / 13 (62) / 1 (5)
Smoking history, n (%)	
Former / Current / Never	15 (71) / 3 (14) / 3 (14)
Number of baseline intracranial lesions, n (%)	
Target: 1 / 2-5	12 (57) / 9 (43)
Non-target: 0 / 1 / 2-5	5 (24) / 14 (67) / 2 (10)
Prior brain radiotherapy[c], n (%)	
Yes / No	11 (52) / 10 (48)
Prior lines of systemic therapy, n (%)	
0 / 1 / 2 / 3+	4 (19) / 5 (24) / 6 (29) / 6 (29)
Prior systemic therapy[d], n (%)	
Platinum-based chemotherapy + anti-PD-(L)1	14 (67)
Platinum-based chemotherapy alone / Anti-PD-(L)1 alone	1 (5) / 2 (10)

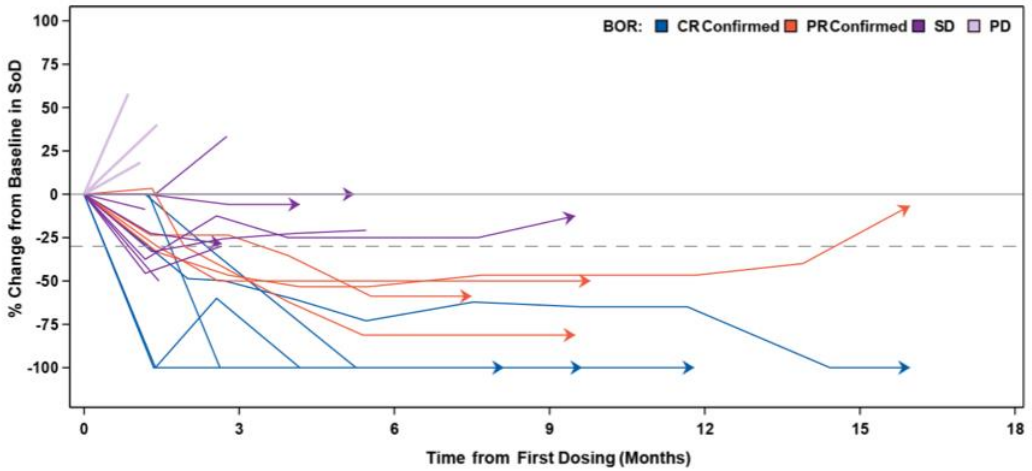
Intracranial efficacy of olomorasib, a next-generation KRAS G12C-mutant NSCLC and active untreated brain metastases.

Intracranial Response of Olomorasib in NSCLC Patients with Active, Untreated Brain Metastases

Intracranial ORR[a]: 43% (95% CI 21.8, 66.0)



Intracranial Rate of DoR ≥6 months: 100%



5 patients (24%) with an intracranial complete response

Intracranial efficacy of olomorasib, a next-generation KRAS G12C-mutant NSCLC and active untreated brain metastases.

Olomorasib (150 mg BID, N=201)[a]		
Parameter n (%)	**Most Common TRAEs**	
	Any Grade	**Grade ≥3**
Any TRAE	140 (70)	14 (7)
Diarrhea	56 (28)	1 (1)
Nausea	24 (12)	-
Fatigue	19 (9)	1 (1)
ALT increased	19 (9)	2 (1)
AST increased	19 (9)	3 (2)

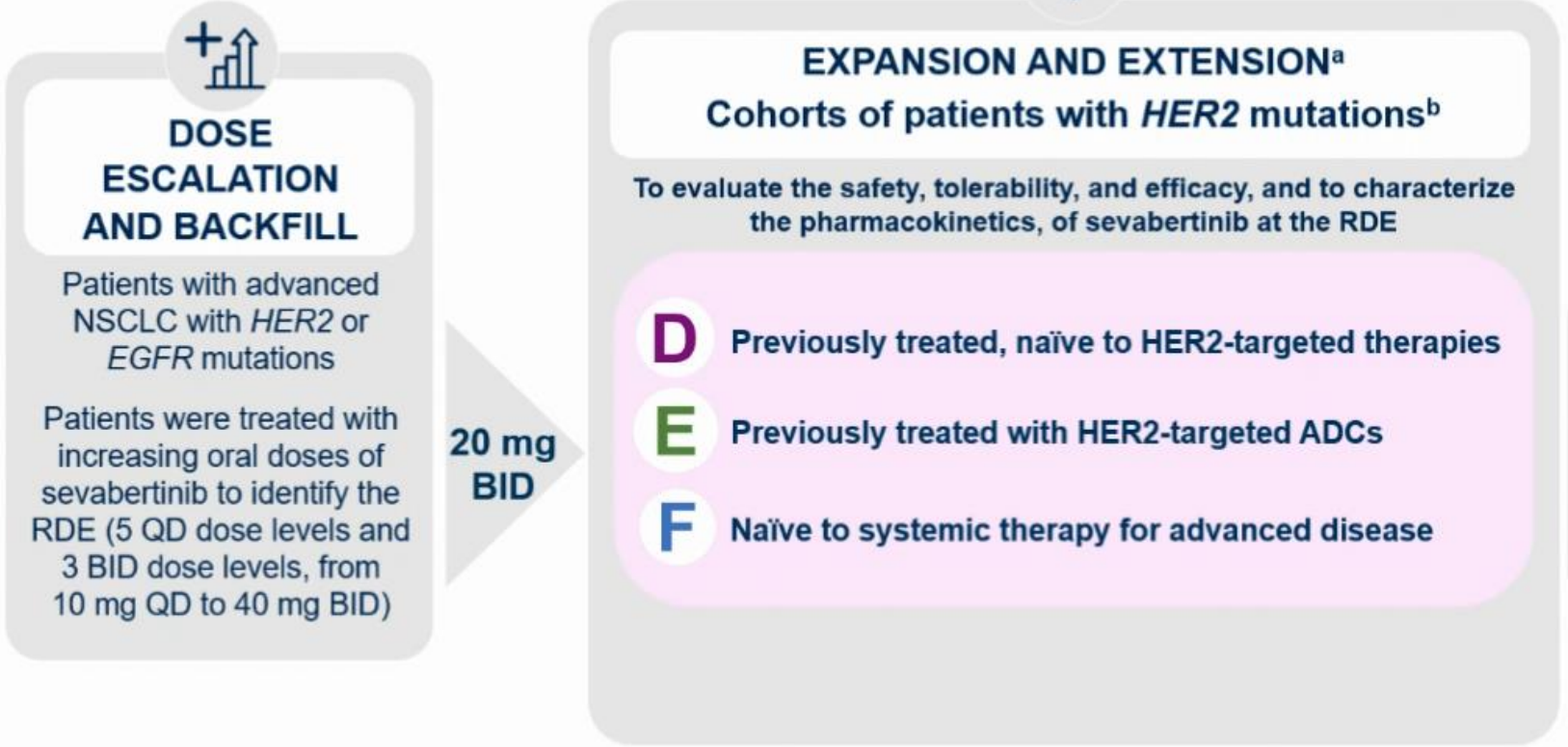
- TRAEs led to dose reductions of olomorasib in 15 patients (7.5%)
- TRAEs led to permanent discontinuation of olomorasib in 2 patients (1.0%)

Safety profile in the subpopulation of NSCLC patients with brain mets (n=21) is consistent with the overall population receiving monotherapy at 150 mg BID, with no safety concerns identified.

HER2

Sevabertinib in advanced HER2-mutant NSCLC: results from the SOHO-01 study

SOHO-01 study design (NCT05099172)



PRIMARY ENDPOINT (extension phase)

- ORR per RECIST v1.1 by BICR

SECONDARY ENDPOINTS

- DoR, DCR, and PFS (per RECIST v1.1) by BICR and investigator assessment
- Safety and tolerability

Sevabertinib in advanced HER2-mutant NSCLC: results from the SOHO-01 study

Baseline characteristics (Cohorts D E F: 209 pts with *HER2*-mut NSCLC)

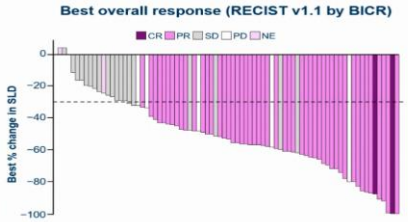
	Cohort D[a] (*n*=81)	Cohort E[b] (*n*=55)	Cohort F[c] (*n*=73)
Female, *n* (%)	50 (62)	36 (65)	46 (63)
Race, *n* (%)			
Asian	57 (70)	32 (58)	51 (70)
White	18 (22)	15 (27)	19 (26)
Black or African American	1 (1)	4 (7)	0
Not reported	5 (6)	4 (7)	3 (4)
Median age, years (range)	60 (29-82)	65 (35-91)	65 (31-82)
Baseline ECOG PS, *n* (%)			
0	31 (38)	15 (27)	18 (25)
1	50 (62)	40 (73)	54 (74)[d]
Smoking habits at informed consent, *n* (%)			
Never	50 (62)	35 (64)	57 (78)
Former or current	31 (38)	20 (36)	16 (22)
Adenocarcinoma histology[e]	77 (95)	55 (100)	71 (97)
Brain metastases at baseline, *n* (%)[f]	18 (22)	15 (27)	9 (12)

	Cohort D[a] (*n*=81)	Cohort E[b] (*n*=55)	Cohort F[c] (*n*=73)
Activating *HER2* mutations, *n* (%)			
Y772_A775dupYVMA	49 (60)	40 (73)	58 (79)
Other *HER2* ex20ins	19 (23)	9 (16)	11 (15)
HER2 point mutation	12 (15)	5 (9)	1 (1)
Not applicable[g]	1 (1)	1 (2)	3 (4)
***HER2* TKD mutation, *n* (%)**			
Yes	73 (90)	52 (95)	71 (97)
No	7 (9)	3 (5)	2 (3)
Not applicable[h]	1 (1)	0	0
Number of previous systemic anti-cancer therapies, *n* (%)			
0	0	0	67 (92)
1	46 (57)	12 (22)	4 (5)[i]
≥2	35 (43)	43 (78)	2 (3)[i]
Previous anti-cancer therapies, *n* (%)			
Chemotherapy	78 (96)	44 (80)	6 (8)
Platinum and no immunotherapy	20 (25)	12 (22)	3 (4)
Platinum and immunotherapy	56 (69)	31 (56)	3 (4)
Trastuzumab deruxtecan	2 (2)[j]	41 (75)	0

Sevabertinib in advanced HER2-mutant NSCLC: results from the SOHO-01 study

Cohort D (previously treated, *n*=81): Objective response (ORR) by BICR

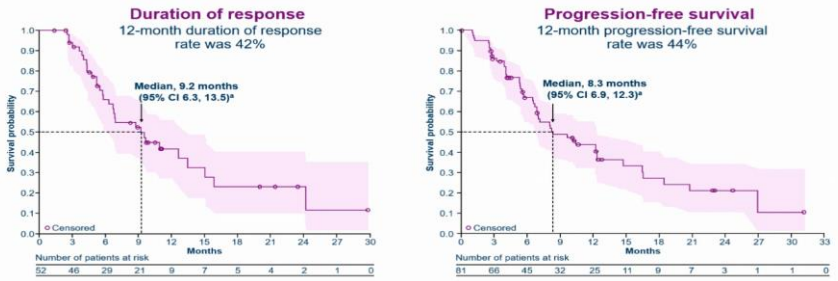
Median follow-up: 13.8 months (range 1-32)



n (%)	
CR	2 (2)
PR	50 (62)
SD	20 (25)
PD	6 (7)
Not evaluable[a]	3 (4)
ORR[b] [95% CI]	**52 (64)** [53, 75]
DCR[c] [95% CI]	**66 (81)** [71, 89]
DoR, median (months) [95% CI]	**9.2** [6.3, 13.5]
PFS, median (months) [95% CI]	**8.3** [6.9, 12.3]

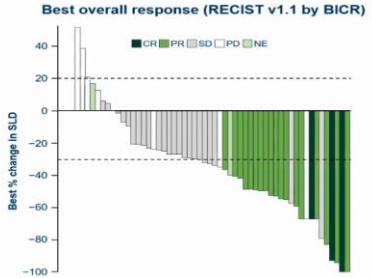
Cohort D (previously treated, *n*=81): DoR and PFS by BICR

Median follow-up: 13.8 months (range 1-32)



Cohort E (previous HER2 ADCs, *n*=55): Objective response by BICR

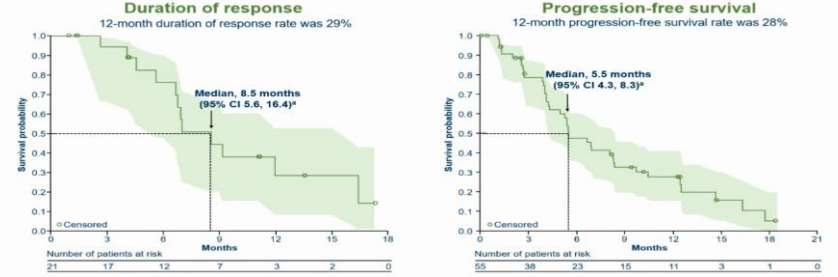
Median follow-up: 11.6 months (range 2-22)



n (%)	
CR	3 (5)
PR	18 (33)
SD	23 (42)
PD	7 (13)
Not evaluable[a]	4 (7)
ORR[b] [95% CI]	**21 (38)** [25, 52]
DCR[c] [95% CI]	**39 (71)** [57, 82]
DoR, median (months) [95% CI]	**8.5** [5.6, 16.4]
PFS, median (months) [95% CI]	**5.5** [4.3, 8.3]

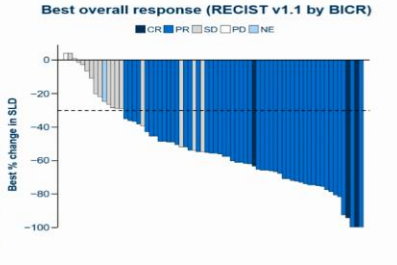
Cohort E (previous HER2 ADCs, *n*=55): DoR and PFS by BICR

Median follow-up: 11.6 months (range 2-22)



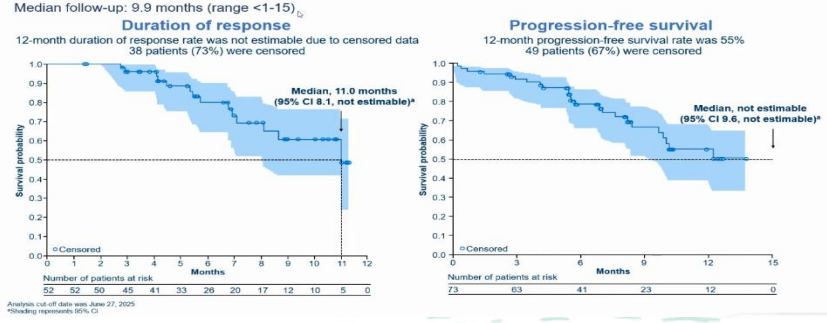
Cohort F (treatment-naïve, *n*=73): Objective response by BICR

Median follow-up: 9.9 months (range <1-15)



n (%)	
CR	3 (4)
PR	49 (67)
SD	16 (22)
PD	2 (3)
Not evaluable[a]	1 (1)
Not available[b]	2 (3)
ORR[c] [95% CI]	**52 (71)** [59, 81]
DCR[d] [95% CI]	**65 (89)** [80, 95]
DoR, median (months) [95% CI]	**11.0** [8.1, not estimable]
PFS, median (months) [95% CI]	Not estimable [9.6, not estimable]

Median follow-up: 9.9 months (range <1-15)



Sevabertinib in advanced HER2-mutant NSCLC: results from the SOHO-01 study

Cohorts D E F: ORRs (RECIST v1.1) in patients *with* and *without* brain metastases at baseline

- Brain metastases were present in 22% and 27% of previously treated patients (Cohort D and Cohort E, respectively) and in 12% of treatment-naïve patients (Cohort F)
- Systemic responses in patients with and without brain metastases were similar

	Cohort D[b]	Cohort E[c]	Cohort F[d]	Total
Brain metastases at baseline, *n/N* (%)[a]	18/81 (22)	15/55 (27)	9/73 (12)	42/209 (20)
ORR by BICR (RECIST v1.1), *n/N* (%)				
All patients	52/81 (64)	21/55 (38)	52/73 (71)	125/209 (60)
Brain metastases	11/18 (61)	4/15 (27)	7/9 (78)	22/42 (52)
No brain metastases	41/63 (65)	17/40 (43)	45/64 (70)	103/167 (62)

Zongertinib as first-line treatment in patients with advanced HER2-mutant NSCLC: Beamion LUNG-1

Beamion LUNG-1 Study Design

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

In Phase Ia, the MTD was not reached at 360 mg QD
In Phase Ib, the selected dose after interim futility analysis was zongertinib 120 mg QD

Current analysis

Cohort 2 — **Treatment-naïve patients with TKD mutations**

Primary endpoint: Objective response by BICR (RECIST v1.1)

Secondary endpoints: DC, DoR, and PFS by BICR (RECIST v1.1)

Key inclusion criteria: aged ≥18 years, advanced/metastatic non-squamous *HER2*-mutant NSCLC (TKD mutation), ≥1 measurable non-CNS lesion (RECIST v1.1) and ECOG PS of 0/1. Patients with stable/asymptomatic brain metastases were eligible

Here we present the efficacy and safety of zongertinib 120 mg given as a first-line therapy

Additional cohorts not included in the current analysis

Cohort 1	Previously treated patients with TKD mutations
Cohort 3	Previously treated patients with non-TKD mutations
Cohort 4	Treatment-naïve or previously treated patients with TKD mutations and active brain metastases at baseline
Cohort 5	Patients previously treated with HER2-directed ADC and with TKD mutations

Zongertinib was recently approved in the United States (accelerated), China (conditional), and Japan for patients with previously treated advanced *HER2*-mutant NSCLC

Baseline Patient and Disease Characteristics

- At data cut-off, 74 patients had received first-line zongertinib 120 mg; two of these patients had received prior treatment*
- Of note:
  - 58% were ≥65 years old
  - 50% were female
  - 45% were non-Asian
  - 35% had a history of tobacco exposure
  - 30% had baseline brain metastases

	N = 74*
Median age, years (range)	67 (35–88)
Age group, n (%)	
65–<75 years	30 (40)
≥75 years	13 (18)
Female, n (%)	37 (50)
Race, n (%)†	
Asian	34 (46)
Non-Asian	33 (45)
ECOG PS, n (%)	
0	34 (46)
1	40 (54)
Tobacco use, n (%)‡	
Never	47 (64)
Former	25 (34)
Current	1 (1)
Brain metastases, n (%)	22 (30)
HER2 TKD mutation type, n (%)‡	
A775_G776insYVMA	49 (66)
Other	24 (32)
Median time since diagnosis, months (range)	1.7 (0.4–127.4)

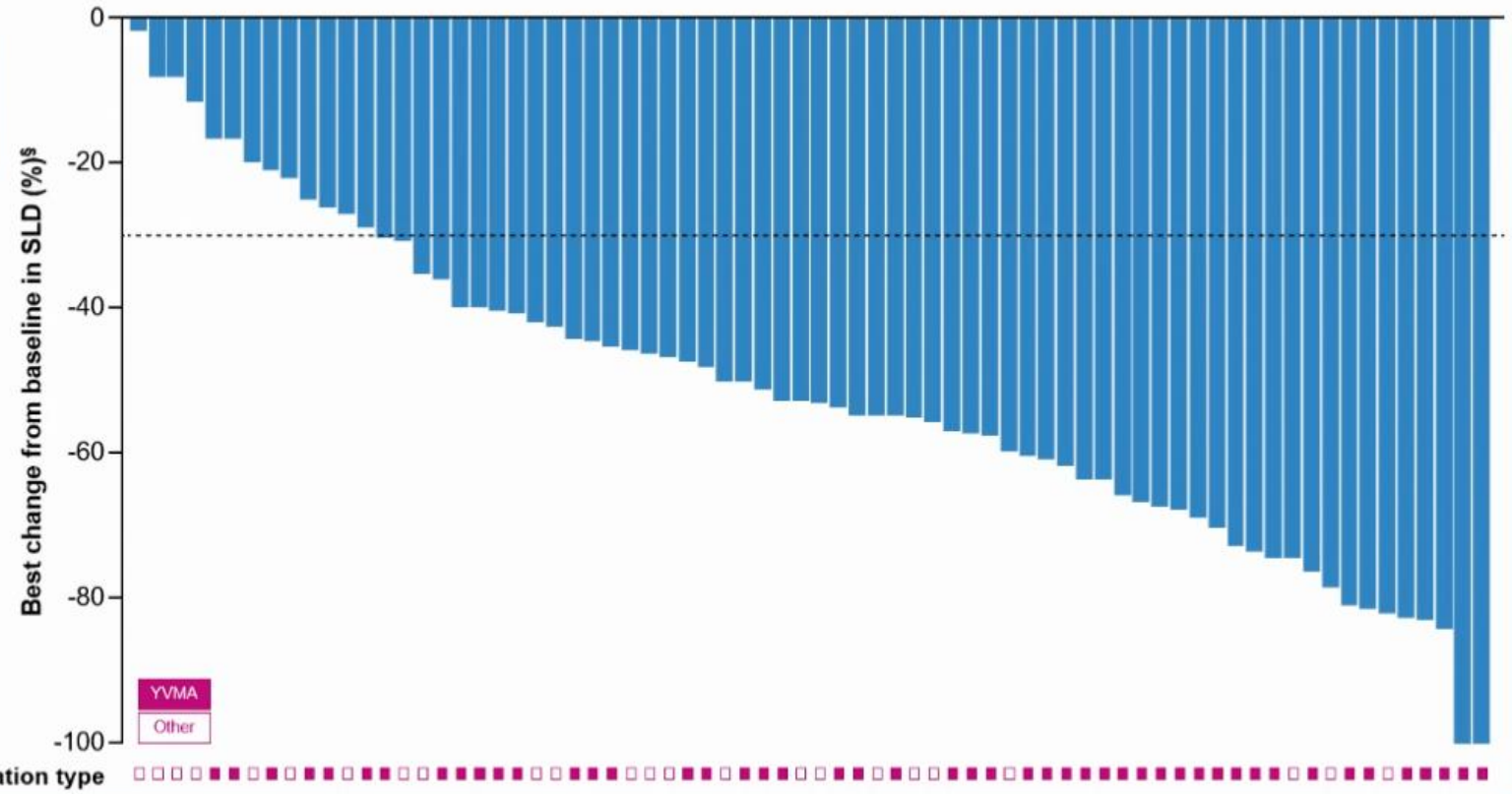
Data cut-off: May 8, 2025

*Two patients had received prior treatment and had protocol deviations;

Zongertinib as first-line treatment in patients with advanced HER2-mutant NSCLC: Beamion LUNG-1

Zongertinib in Treatment-Naïve Patients: Tumor Response

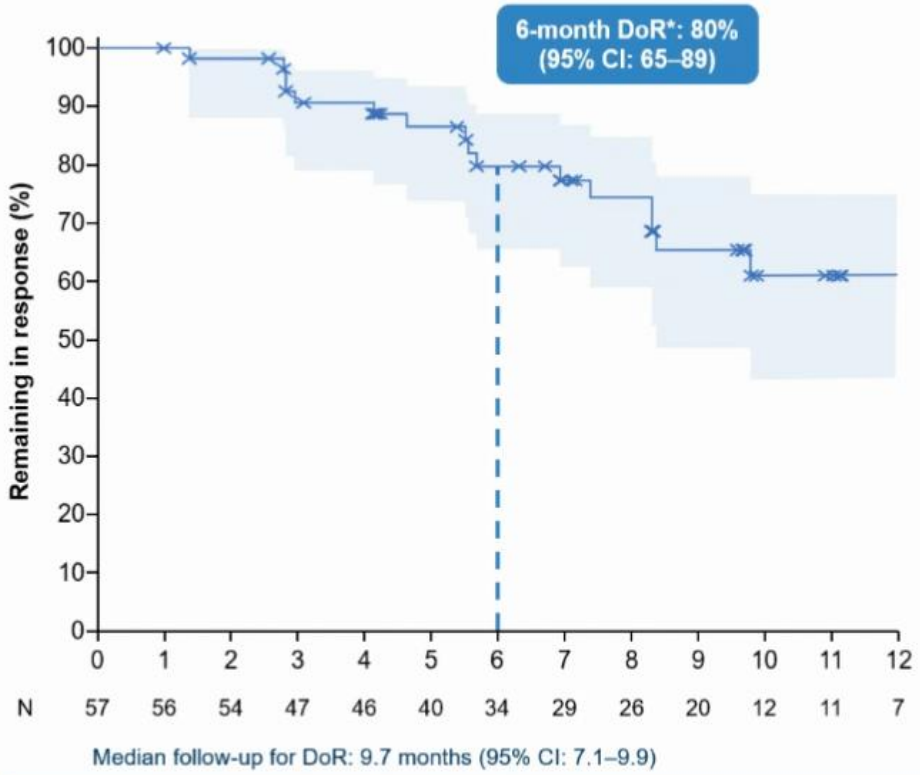
Confirmed response by BICR (RECIST v1.1)	N = 74*
ORR	**77%**
95% CI	66–85
p value†	<0.0001
CR, n (%)	6 (8)
PR, n (%)	51 (69)
DCR	**96%**
95% CI	89–99
SD, n (%)	14 (19)
PD, n (%)	1 (1)‡



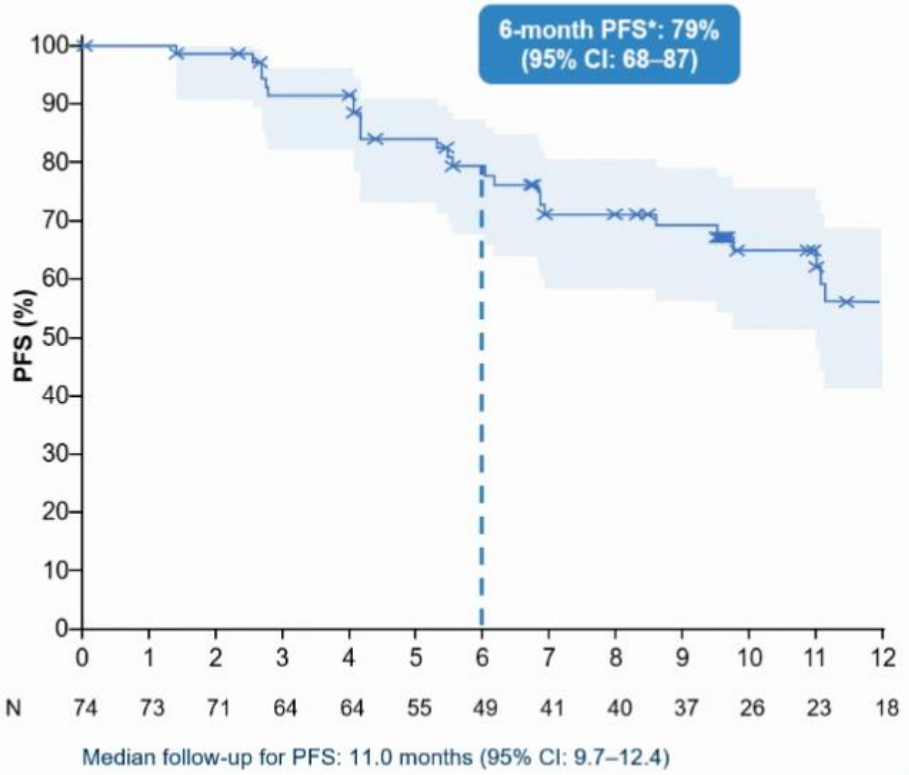
Clinical benefit was observed with zongertinib in all patients, irrespective of *HER2* mutation type

Zongertinib as first-line treatment in patients with advanced HER2-mutant NSCLC: Beamion LUNG-1

Zongertinib in Treatment-Naïve Patients: DoR and PFS Rates



Median follow-up for DoR: 9.7 months (95% CI: 7.1–9.9)



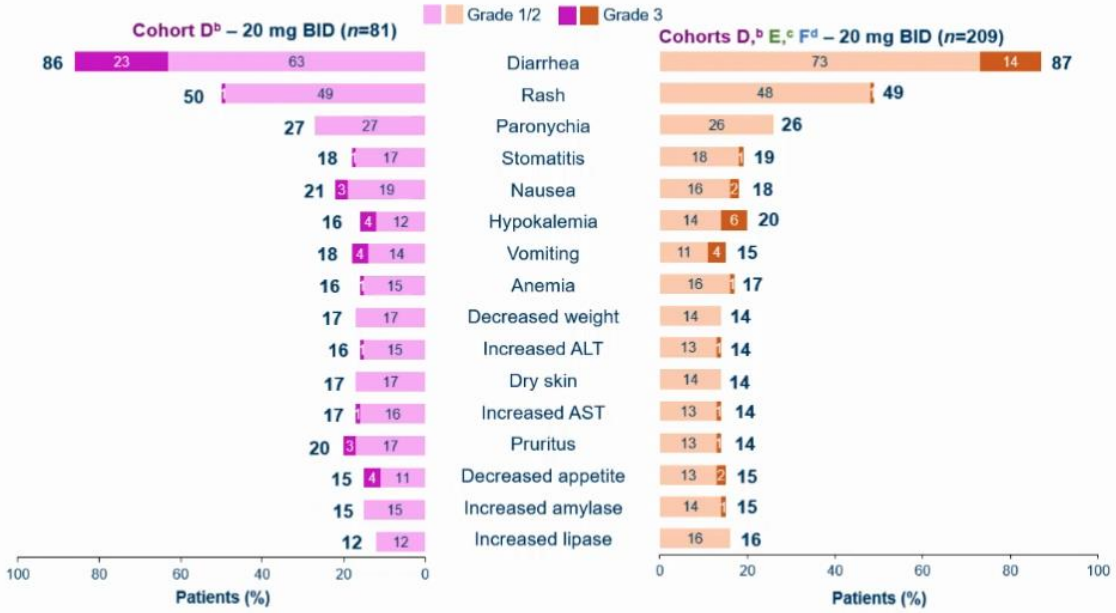
Median follow-up for PFS: 11.0 months (95% CI: 9.7–12.4)

Zongertinib demonstrated marked and durable response and PFS

Perfil de toxicidad con Sevabertinib y Zongertinib

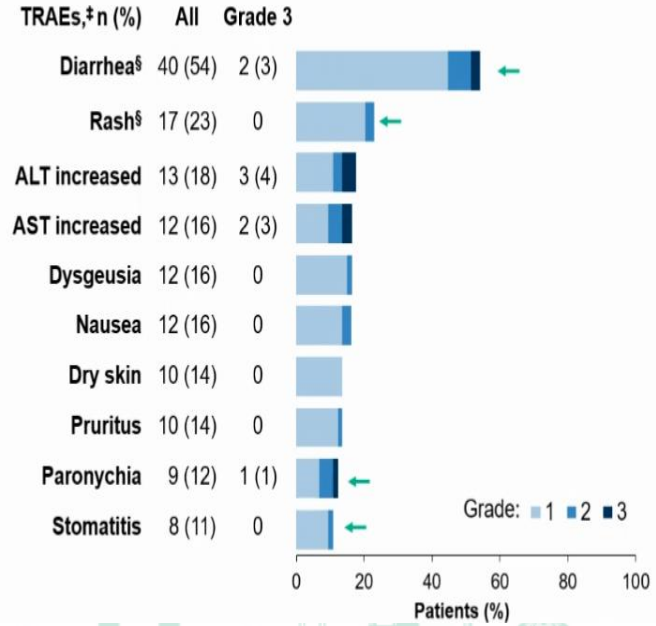
Sevabertinib safety and tolerability

Most frequent treatment-related adverse events (≥10% of total)[a]



Zongertinib in Treatment-Naïve Patients: Safety Profile

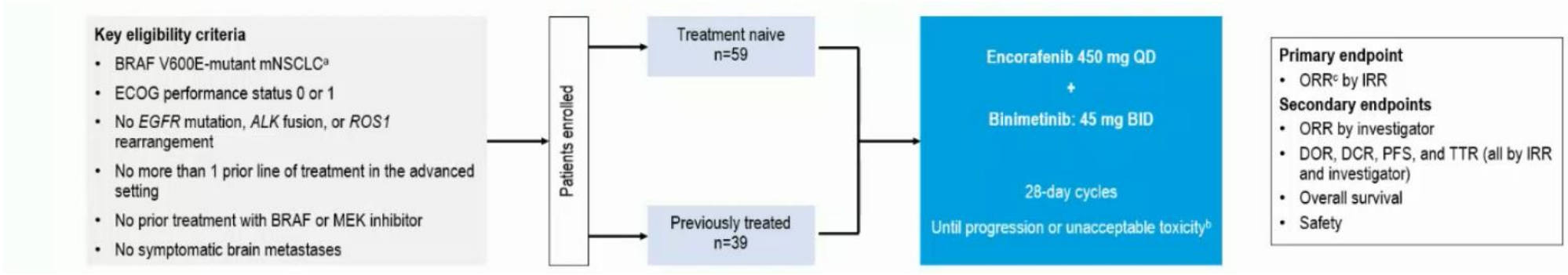
- TRAEs were reported in 67 (91%) patients, including grade 3 TRAEs in 13 (18%) patients
- There were no grade 4/5 TRAEs
- AEs leading to dose reduction occurred in 11 (15%) patients*
- AEs leading to dose discontinuation occurred in 7 (9%) patients†
- Two cases (3%) of ILD/pneumonitis were reported (both grade 2)
- The safety profile was consistent with previously reported safety data



Bajo % de neumonitis y en cualquier caso, leves, en comparación con otros ADCs contras HER2.

BRAF

Updated OS analysis from the phase 2 PHAROS study of encorafenib plus binimetinib in patients with BRAF V600E-mutant metastatic NSCLC.



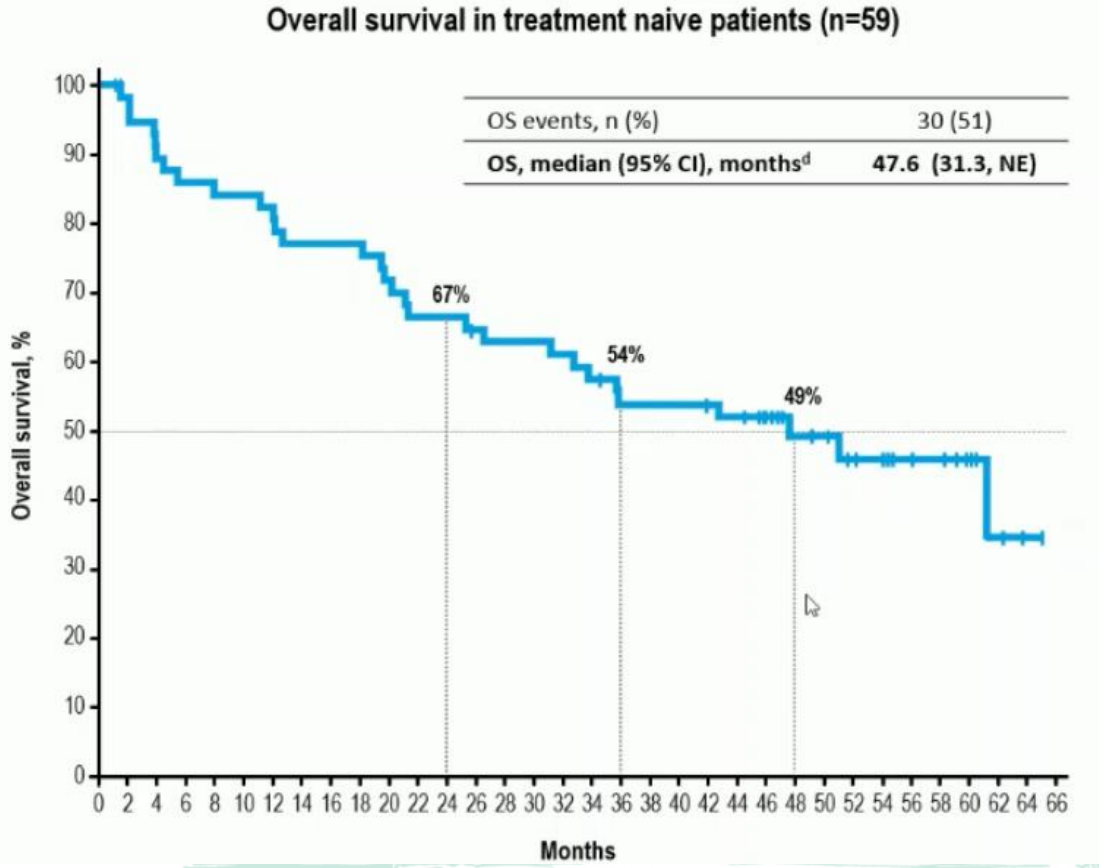
Baseline characteristics

	Treatment naive (n=59)	Previously treated (n=39)
Age, median (range), years	68 (47-83)	71 (53-86)
Sex, n (%)		
Female	33 (56)	19 (49)
Male	26 (44)	20 (51)
Race, n (%)		
White	53 (90)	33 (85)
Asian	3 (5)	4 (10)
Other or unknown	3 (5)	2 (5)
ECOG performance status, n (%)		
0	19 (32)	7 (18)
1	40 (68)	32 (82)

	Treatment naive (n=59)	Previously treated (n=39)
Smoking status, n (%)		
Current/former	41 (69)	28 (72)
Never	18 (31)	11 (28)
Brain metastases, n (%)		
No	55 (93)	35 (90)
Yes	4 (7)	4 (10)
Prior systemic treatment for metastatic disease, n (%)		
Immunotherapy	Not applicable	24 (62)[a]
Monotherapy	Not applicable	12 (31)
Combination therapy[b]	Not applicable	12 (31)
Chemotherapy	Not applicable	18 (46)

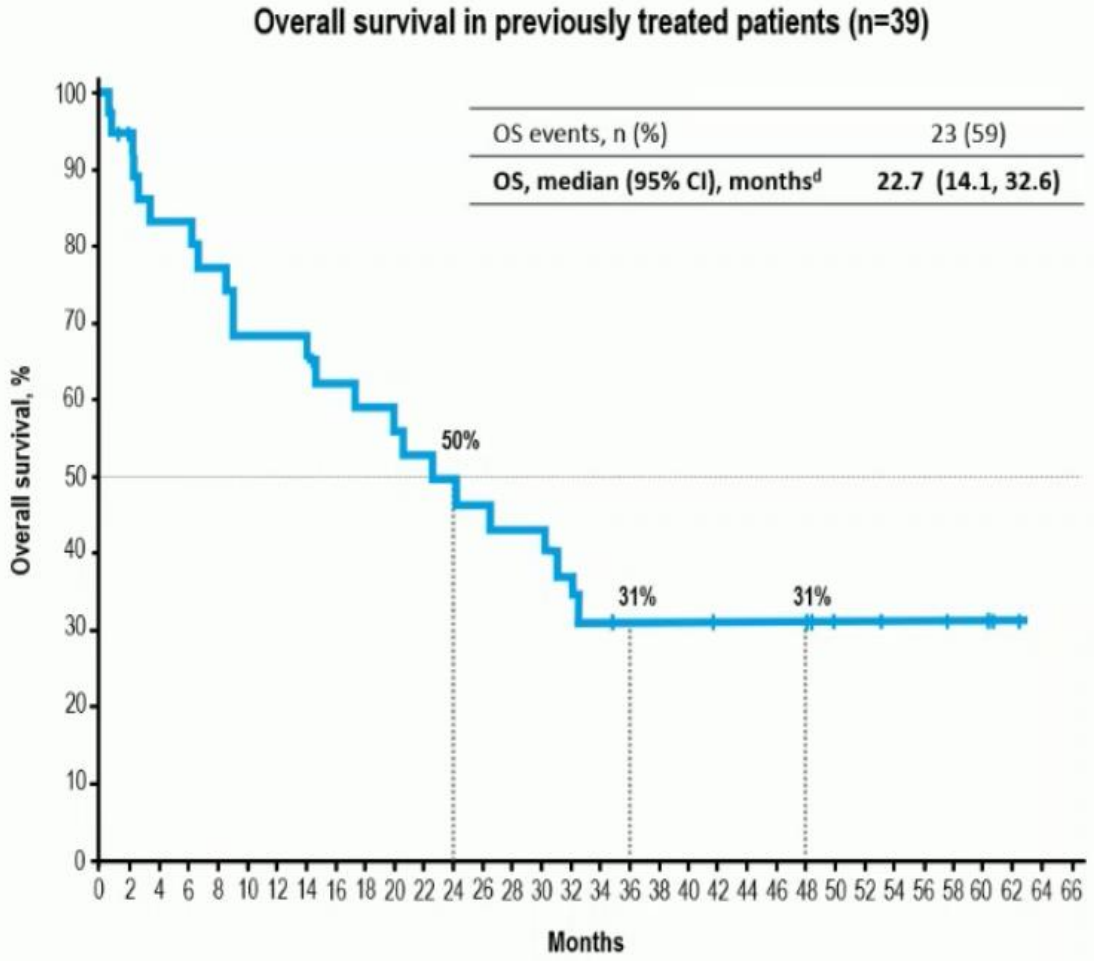
Updated OS analysis from the phase 2 PHAROS study of encorafenib plus binimetinib in patients with BRAF V600E-mutant metastatic NSCLC.

Endpoint by IRR	Treatment naive (n=59)
Objective response rate (95% CI), %[a]	**75 (62, 85)**
Complete response, n (%)	12 (20)
Partial response, n (%)	32 (54)
Stable disease, n (%)	10 (17)
Progressive disease, n (%)	2 (3)
Time to response, median (range), months[b]	1.9 (1.1-5.6)
DOR, median (95% CI), months[b]	**40.0 (23.2, NE)**
PFS, median (95% CI), months[c]	**30.4 (15.7, NE)**



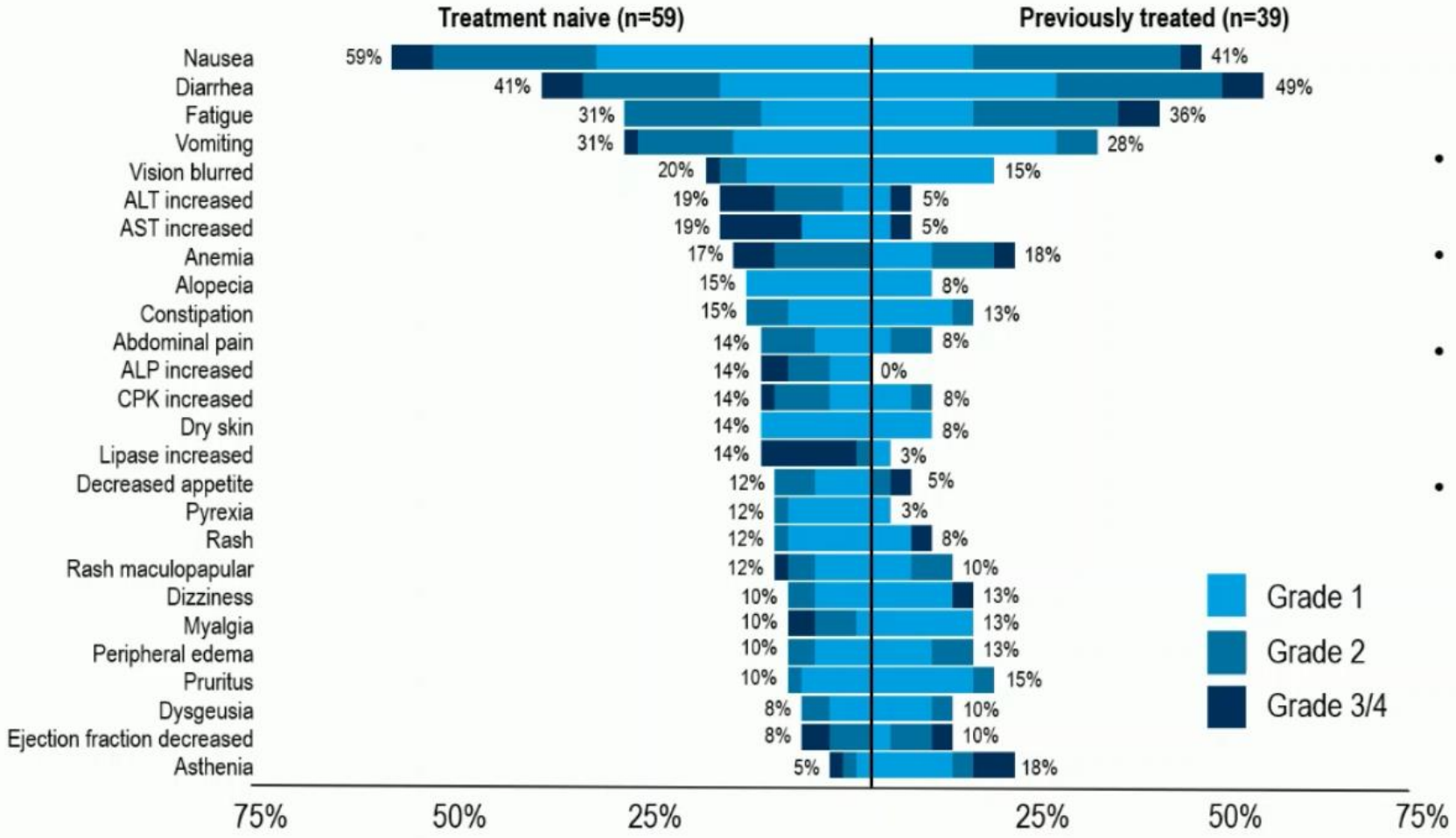
Updated OS analysis from the phase 2 PHAROS study of encorafenib plus binimetinib in patients with BRAF V600E-mutant metastatic NSCLC.

Endpoint by IRR	Previously treated (n=39)
Objective response rate (95% CI), %[a]	**49 (32, 65)**
Complete response, n (%)	5 (13)
Partial response, n (%)	14 (36)
Stable disease, n (%)	12 (31)
Progressive disease, n (%)	3 (8)
Time to response, median (range), months[b]	1.7 (1.2-16.5)
DOR, median (95% CI), months[b]	**16.7 (7.4, NE)**
PFS, median (95% CI), months[c]	**9.3 (6.2, 24.8)**



Updated OS analysis from the phase 2 PHAROS study of encorafenib plus binimetinib in patients with BRAF V600E-mutant metastatic NSCLC.

Treatment-related AEs (≥10%) by treatment line



- Safety profile was consistent with prior analyses[1,2]
- No new safety signals were observed with longer follow-up
- Treatment-related AE profiles were comparable across both treatment lines
- Similar to the prior analysis,[2] any-grade treatment-related pyrexia occurred in 8% of patients; all were grade 1/2 in severity

ROS1

Efficacy of Lorlatinib after failure of a first-line ROS1 TKI in patients with advanced ROS1-positive NSCLC. IFCT-2003 ALBATROS trial.

IFCT-2003 ALBATROS trial design

Single-arm, multicenter phase II trial

- ROS1-positive advanced NSCLC according to IHC and confirmed with FISH or NGS (local)
- Progression after a first-line therapy with ROS1 TKI
- PS 0, 1 or 2
- Stable and asymptomatic brain metastases allowed
- Measurable disease according to RECIST 1.1

Mandatory centralized tumor tissue and blood samples

- Lorlatinib 100 mg once daily
- Planned inclusion of 84 patients *
- Until progression or intolerable toxicity
- Required blood samples at time of progression

Primary endpoint: investigator-assessed confirmed Overall Response Rate (cORR)

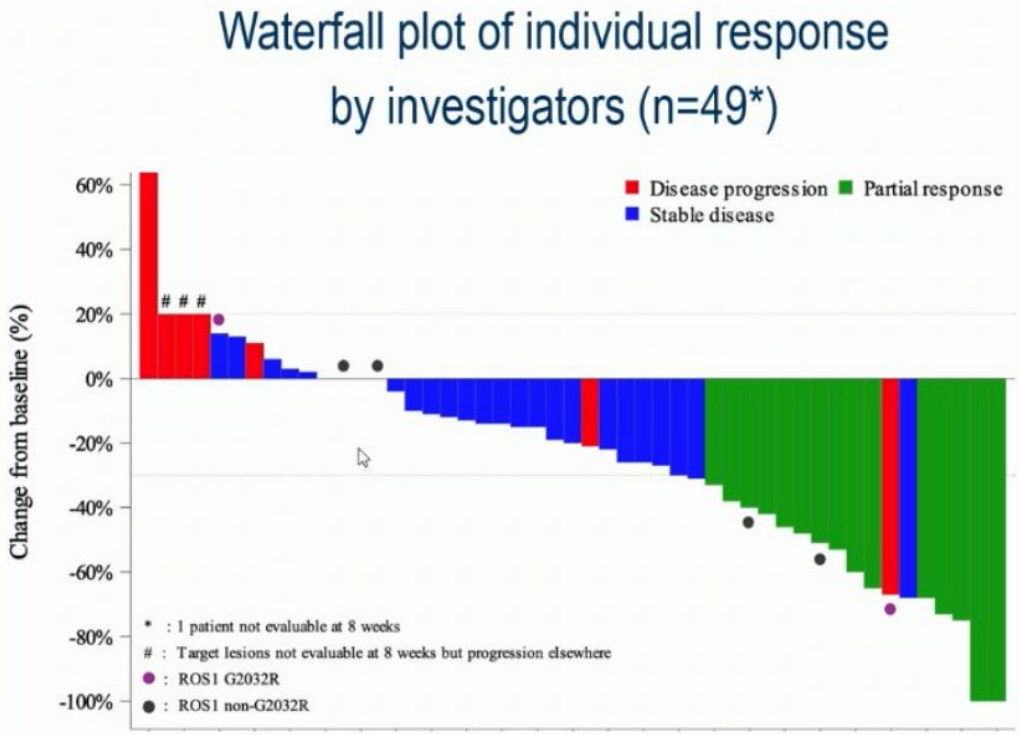
Secondary endpoint: BICR cORR, DCR, PFS, DoR, OS, CNS ORR, safety

		ITT (N = 54)
Female	N (%)	32 (59.3)
Age	Median	63.0
Smoking status		
Current	N (%)	5 (9.3)
Former		19 (35.2)
Never		30 (55.6)
Adenocarcinoma	N (%)	54 (100)
ROS1 Rearrangement	N (%)	54 (100)
Resistance Mutation ROS1 on tissue		
ROS1 G2032R	N (%)	2 (8.3)
ROS1 non-G2032R		4 (16.7)
No ROS1 resistance mutation		18 (75.0)
Unknown	N	30
Brain metastasis	N (%)	31 (57.4)
Number of previous lines		
1	N (%)	38 (70.4)
2		14 (25.9)
3		2 (3.7)
Last antineoplastic treatment		
Crizotinib	N (%)	51 (94.4)
Repotrectinib		2 (3.7)
Entrectinib		1 (1.9)

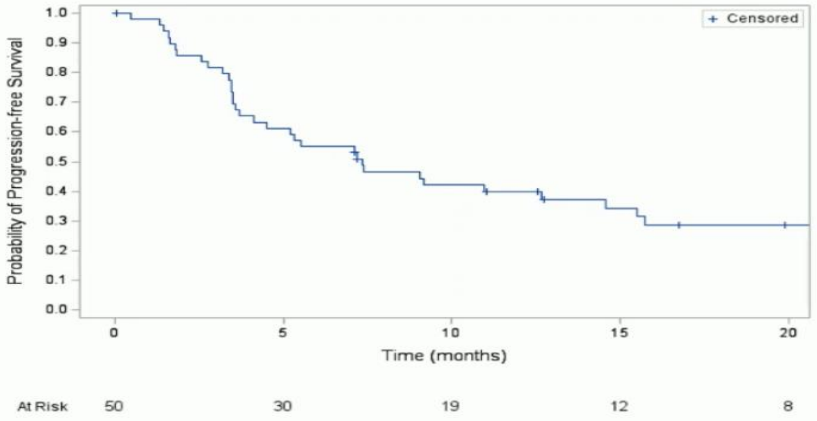
Efficacy of Lorlatinib after failure of a first-line ROS1 TKI in patients with advanced ROS1-positive NSCLC. IFCT-2003 ALBATROS trial.

Primary endpoint: inv-assessed cORR

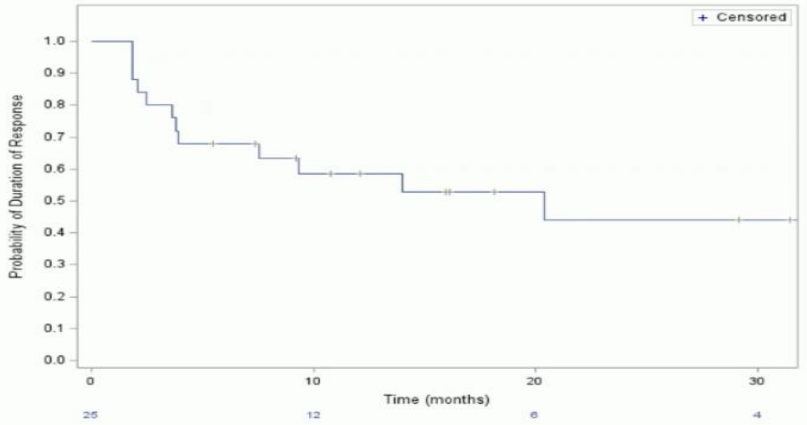
	Investigator assessed N = 50	BICR assessed N = 50
Complete Response	0	0
Partial Response	15 (30.0%) [17.3% ; 42.7%]	17 (34.0%) [20.9% ; 47.1%]
Objective Response	**15 (30.0%) [17.3% ; 42.7%]**	**17 (34.0%) [20.9% ; 47.1%]**
Disease Control Rate	42 (84.0%) [73.8% ; 94.2%]	37 (74.0%) [61.8% ; 86.2%]



Secondary endpoints: inv-assessed PFS and DoR

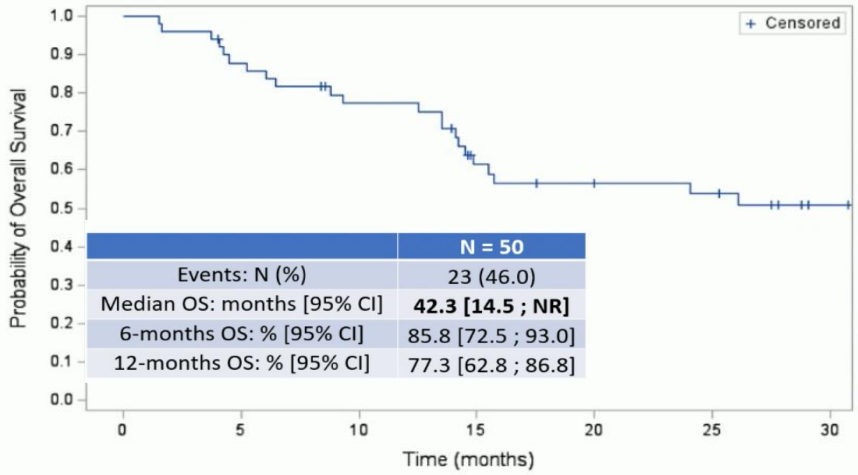


	N = 50
Events: N (%)	36 (72.0)
Median PFS: months [95% CI]	**7.4 [4.1-14.6]**
12-months PFS: % [95% CI]	39.9 [26.1 ; 53.3]



	Patients with an Objective Response N = 25
Events : N (%)	14 (56)
Median DOR: months [95% CI]	**20.4 [3.9-34.5]**

Secondary endpoints: OS



	N = 50
Events: N (%)	23 (46.0)
Median OS: months [95% CI]	**42.3 [14.5 ; NR]**
6-months OS: % [95% CI]	85.8 [72.5 ; 93.0]
12-months OS: % [95% CI]	77.3 [62.8 ; 86.8]

Secondary endpoints: inv-assessed CNS ORR

	Investigator assessed N = 13 patients with measurable CNS disease
Complete Response	7 (53.8%) [26.7% ; 80.9%]
Partial Response	5 (38.5%) [12.0% ; 64.9%]
Objective Response	**12 (92.3%) [77.8% ; 100.0%]**
Stable Disease	1 (7.7%) [0.0% ; 22.2%]
Disease Control	**13 (100.0%) [100.0% ; 100.0%]**
Progressive Disease	0

CONCLUSIONES

- Olomorasib ha demostrado datos prometedores de eficacia intracraneal en pacientes con CPNCP avanzado con mutación en KRAS G12C y metástasis cerebrales activas.

- En HER2 mutado, tanto sevabertinib como zongertinib presentan altas tasas de respuesta así como duración de la misma, tanto en primera línea como en pacientes pre-tratados, con un perfil de toxicidad muy favorable.

- Tras un seguimiento a 4 años, la combinación de encorafenib-binimetinib ha demostrado beneficio en SG (mediana: 4 años) en primera línea, siendo los mejores datos reportados hasta la fecha en esta población.

- Lorlatinib es una buena opción en pacientes con CPNCP avanzado con mutación en ROS1 tras progresión a TKIs de primera línea, con especial actividad a nivel del SNC.

MUCHAS GRACIAS