Lung Cancer UPDATES
WCLC HIGHLIGHTS
San Diego, USA
ESMO HIGHLIGHTS
Barcelona, Spain

Iniciativa científica de:
GECP
lung cancer research

CPCNP: enfermedad avanzada con driver

Ivana Sullivan, MD, PhD

Instituto Oncológico Dr. Rosell

AGENDA

- *BRAF*:
  - Encorafenib plus binimetinib in patients with previously untreated *BRAF* V600E-mutant advanced NSCLC: an open-label, multicenter phase 2 trial (IFCT-1904 ENCO-BRAF)
  - Updated efficacy and safety from the phase 2 PHAROS study of encorafenib + binimetinib in patients with *BRAF* V600E–mutant metastatic NSCLC (mNSCLC)
- *KRAS*:
  - Efficacy and safety of olomorasib with pembrolizumab + chemo as first-line treatment in patients with *KRAS* G12C mutant advanced NSCLC
  - Divarasib long-term follow-up and atezolizumab combination treatment in patients with *KRAS* G12C-positive NSCLC
  - Preliminary safety and clinical activity of ASP3082, a first-in-class, *KRAS* G12D selective protein degrader in adults with advanced pancreatic, colorectal, and non-small cell lung cancer
- *HER2*:
  - Zongertinib (BI 1810631) for *HER2*-positive solid tumors with brain metastases: subanalysis of the Beamion LUNG-1 trial
- *NTRK*:
  - Updated efficacy, safety, and biomarker analysis in patients with TRK fusion lung cancer treated with larotrectinib

- *BRAF*:
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  - Updated efficacy and safety from the phase 2 PHAROS study of encorafenib + binimetinib in patients with *BRAF* V600E–mutant metastatic NSCLC (mNSCLC)

Phase II – ENCORAFENIB + BINIMETINIB IN BRAF V600Em NSCLC – David Planchard et al.

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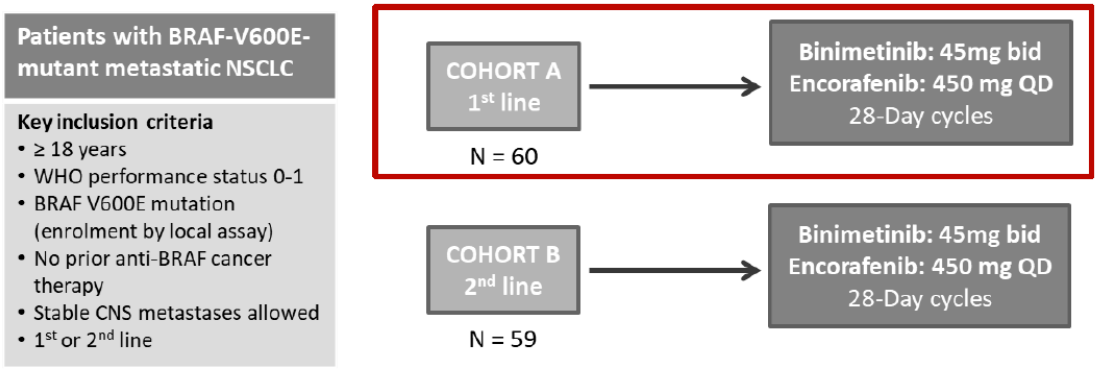

Cohort A: 1st line Encorafenib plus Binimetinib

The primary endpoint: confirmed ORR according to the investigator evaluation RECIST (v1.1) every 8 weeks (for 12months then every 12 weeks)

Secondary endpoints include PFS, DOR, DCR, OS and safety.

		Cohort A (N=64), n (%)
Age	median [range]	70.7 [39.1-90.3]
	≥ 65 years	42 (65.6)
Sex	Female	34 (53.1)
	Male	30 (46.9)
Histological type	Adenocarcinoma	63 (98.4)
PD-L1 (TPS)	≥ 50%	32 (50.0)
	≥ 1% and < 50%	17 (26.6)
	< 1%	13 (20.3)
	Not done	2 (3.1)
Smoking history	Never	23 (35.9)
	Former	33 (51.6)
	Current	8 (12.5)
ECOG, PS	0	28 (43.8)
	1	36 (56.3)
Stage	IV-A	33 (51.6)
	IV-B	31 (48.4)
Brain metastasis	Yes	11 (17.2)

Phase II – ENCORAFENIB + BINIMETINIB IN BRAF V600Em NSCLC – David Planchard et al.

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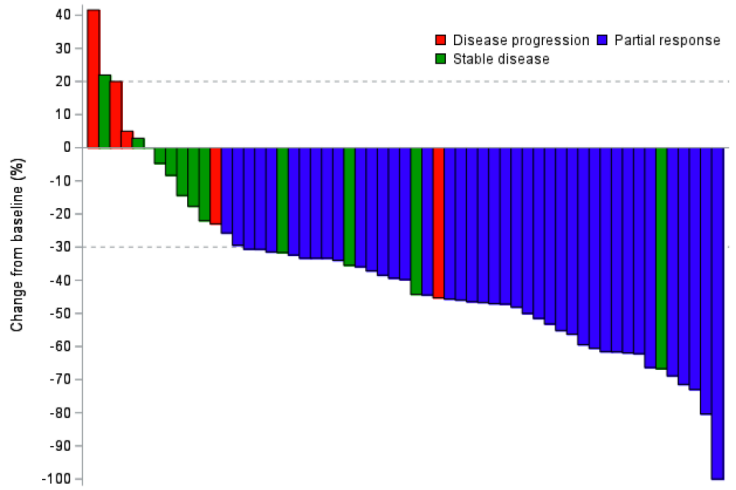
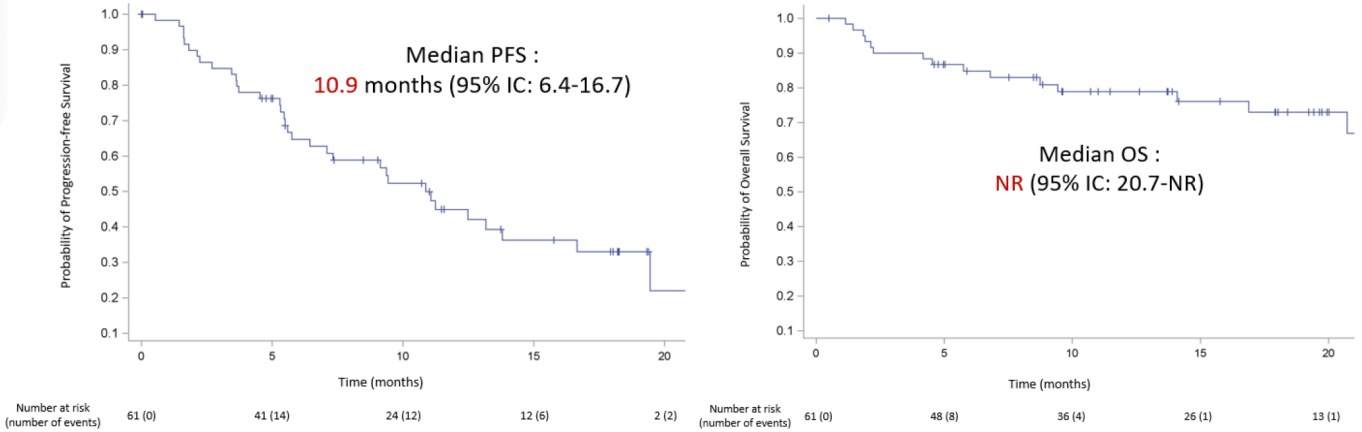


	Cohorte A (n=61)
Overall response confirmed, n (%) [95% CI]	**40 (65.6%)** [53.7% - 77.5%]
Partial response, n (%)	40 (65.6%)
Stable disease, n (%)	12 (19.7%)
Progressive disease, n (%)	5 (8.2%)
Not evaluable*, n (%)	4 (6.6%)
DOR, median [95% CI], months	**13 months** [9.1-NR]
DCR , % [95% CI]	**85.2%** [76.3% - 94.1%]

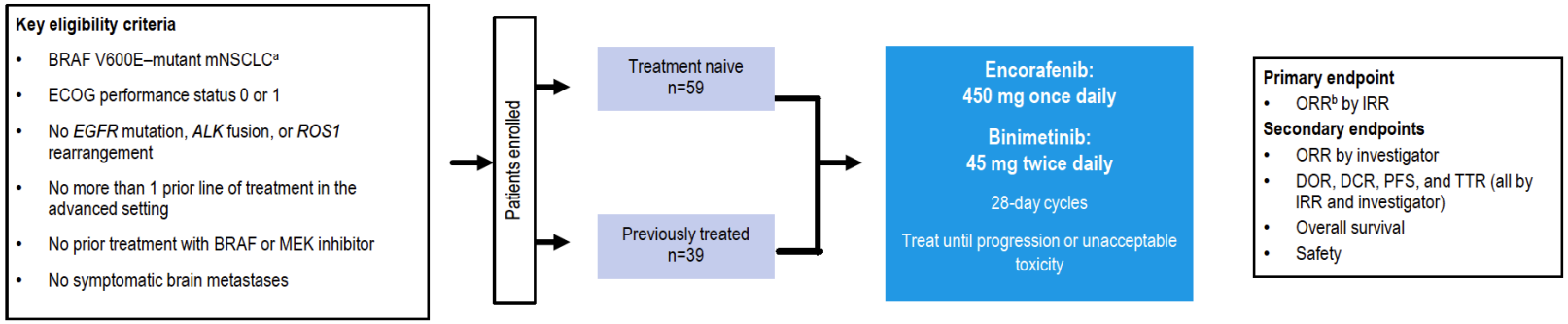
*4 patients were not evaluable

Investigator-assessed PFS and OS



Median follow-up OS of 18 months (95% IC: 12.6 – 19.4)

Phase II – ENCORAFENIB + BINIMETINIB IN BRAFm NSCLC – Gregory Riely et al.



	Treatment naive (n=59)	Previously treated (n=39)
Median age (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)
Black	1 (2)	2 (5)
American Indian	1 (2)	0
Unknown	1 (2)	0
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	8 (14)	5 (13)
Former	33 (56)	23 (59)
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)
Monotherapy	Not applicable	12 (31)
Combination therapy	Not applicable	12 (31)
Chemotherapy	Not applicable	18 (46)[a]

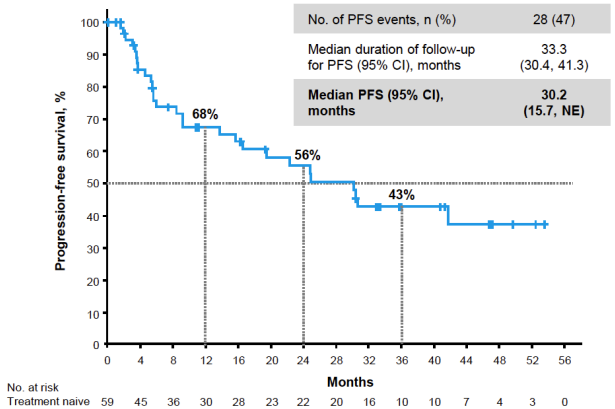
Phase II – ENCORAFENIB + BINIMETINIB IN BRAFm NSCLC – Gregory Riely et al.

Iniciativa científica de: GECP lung cancer research

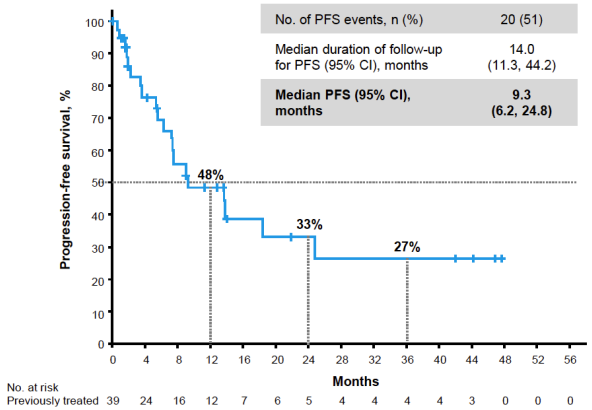
	Primary analysis (data cutoff: Sep 22, 2022)[1]		Current analysis (data cutoff: Apr 1, 2024)	
	Treatment naive	Previously treated	Treatment naive	Previously treated
Objective response rate (95% CI), %[a]	75 (62, 85)	46 (30, 63)	**75 (62, 85)**	**46 (30, 63)**
Complete response	9 (15)	4 (10)	9 (15)	4 (10)
Partial response	35 (59)	14 (36)	35 (59)	14 (36)
Stable disease	10 (17)	13 (33)	10 (17)	13 (33)
Progressive disease	2 (3)	3 (8)	2 (3)	3 (8)
Disease control rate at 24 weeks (95% CI), %	64 (51, 76)	41 (26, 58)	64 (51, 76)	44 (28, 60)
Median time to response (range), months	1.9 (1.1-19.1)	1.7 (1.2-7.3)	1.9 (1.1-19.1)	1.7 (1.2-7.3)
Median duration of response (95% CI), months	NE (23.1, NE)	16.7 (7.4, NE)	**40.0 (23.1, NE)**	**16.7 (7.4, NE)**

PFS: 30.2mo

Treatment naive (n=59)

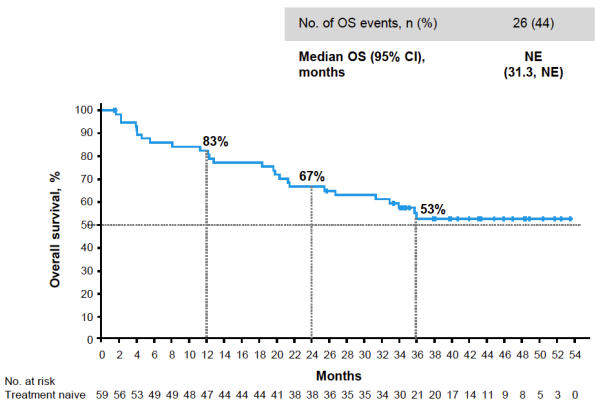


Previously treated (n=39)

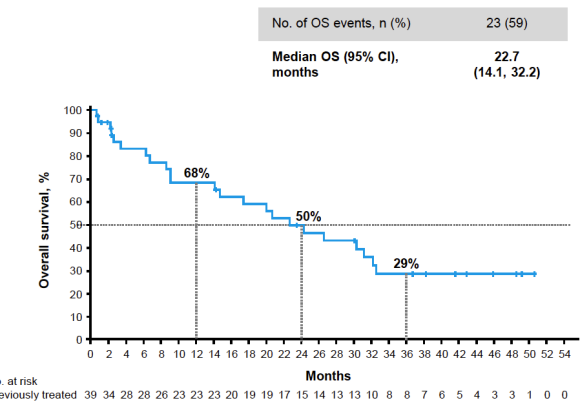


OS: NE

Treatment naive (n=59)



Previously treated (n=39)



- *KRAS*:
  - Efficacy and safety of olomorasib with pembrolizumab + chemo as first-line treatment in patients with *KRAS* G12C mutant advanced NSCLC
  - Divarasib long-term follow-up and atezolizumab combination treatment in patients with *KRAS* G12C-positive NSCLC
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Phase II - OLOMORASIB + PEMBRO + CHEMO IN KRAS G12C NSCLC - Yutaka Fujiwara et al.

Iniciativa científica de: GECP lung cancer research

Cohort B9: NSCLC

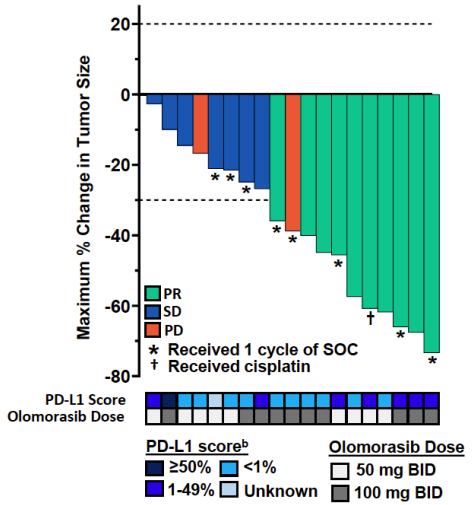
Olomorasib[a] + pembrolizumab[b] + pemetrexed[c] + platinum[d] (N=21)[e]

Cohort B9 Eligibility

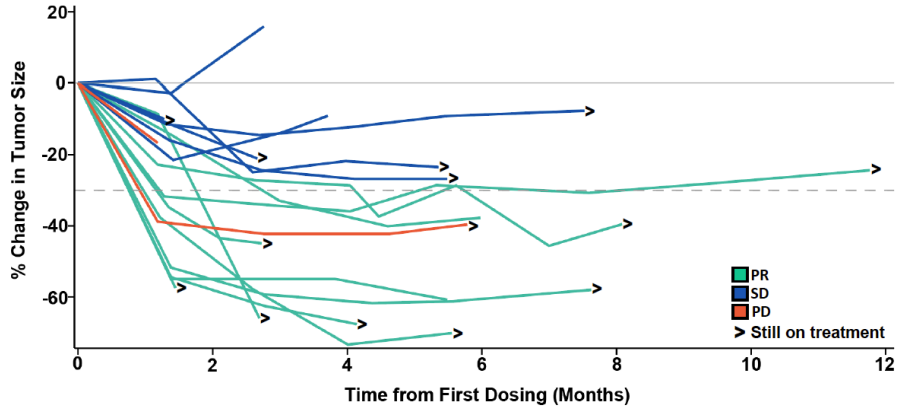
- Treatment naïve for advanced or metastatic NSCLC
- PD-L1 expression 0-100% and KRAS G12C mutation based on local testing
- **Allowance of up to one 21-day cycle of any combination of pembrolizumab, pemetrexed, and carboplatin or cisplatin**
- Prior adjuvant or neoadjuvant therapy allowed, provided last dose was completed at least 6 months prior to enrollment

Characteristics	Olomorasib 50 mg BID (n=10) and 100 mg BID (n=11) + pembrolizumab + pemetrexed + platinum N=21
Age, years	Median (range) 67 (56-81)
Sex, n (%)	Female 10 (48)
	Male 11 (52)
Race, n (%)	White 11 (52)
	Asian 7 (33)
	Not reported 3 (14)
ECOG PS, n (%)	0 9 (43)
	1 12 (57)
PD-L1 score[a], n (%)	<1% 10 (48)
	1-49% 9 (43)
	≥50% 1 (5)
	Unknown[b] 1 (5)
Brain metastases, n (%)	Yes 7 (33)
	No 14 (67)
Prior curative therapy, n (%)	No 17 (81)
	platinum-based chemotherapy/ anti-PD-(L)1 1 (5)
	platinum-based chemotherapy alone 3 (14)
Received 1 cycle SOC prior to enrollment, n (%)	Yes 9 (43)
	No 12 (57)

Objective Response Rate[a], % (n/N)	**50** (10/20)
Disease Control Rate, % (n/N)	**85** (17/20)



- Median duration of therapy was 4.5 months and 76% patients remain on study therapy at time of data-cut



Phase I – DIVARASIB +/- ATEZO IN KRAS G12C NSCLC – Adrian Sacher et al.

Iniciativa científica de: GECP lung cancer research

SINGLE AGENT

DOSE ESCALATION
Divarasib oral QD, 21-day cycles
50mg → 100mg → 200mg → 400mg
N=6 **N=5** **N=10** **N=6**
NSCLC N=27
Max Admin Dose
MTD not reached

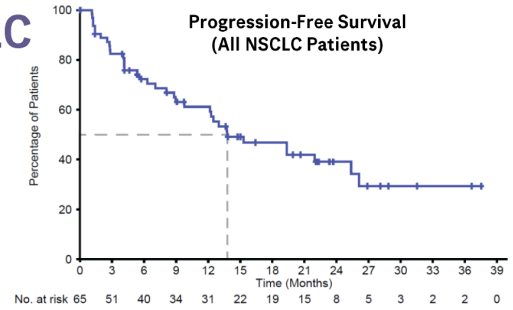
DOSE EXPANSION
Divarasib oral QD, 21-day cycles
400mg
NSCLC N=38

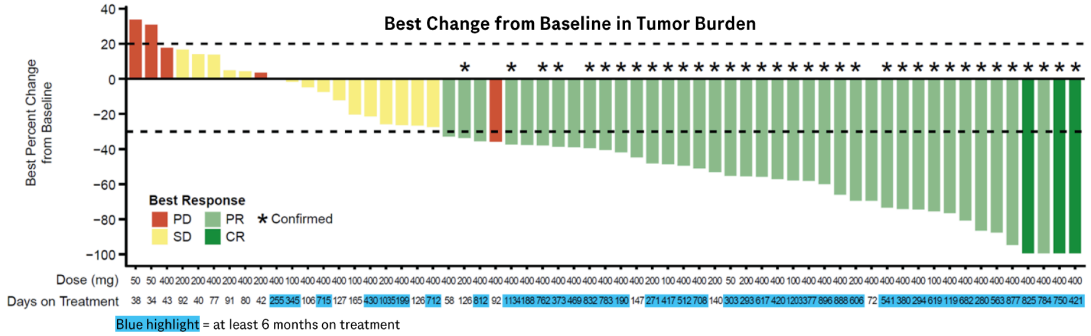
	NSCLC N=65
Age, median (range), years	66 (43-82)
Sex, female	37 (57%)
Race - White - Asian - Unknown - Black or African American	57 (88%) 4 (6%) 3 (5%) 1 (2%)
ECOG, 0 / 1	24 (37%) / 41 (63%)
PD-L1 TPS score (n=53), <1 / **(1-49) / ≥50** / NA	18 (28%) / **13 (20%)/ 21 (32%)** / 1 (1.5%)
Number of prior lines of systemic therapy, median (range)	2 (0-5)
Prior platinum chemotherapy	57 (88%)
Prior PD-1/PD-L1 inhibitor	57 (88%)
Time on treatment, median (range), months	11 (0-40)

Antitumor activity: Single-agent divarasib in NSCLC

	Confirmed ORR	Median DoR**	Median PFS
All NSCLC Patients (N=65)	**55.6%** (N=63)*	18.0 mo (95% CI 11.1, 24.9)	**13.8 mo** (95% CI 9.8, 25.4)
400 mg (N=44)	**59.1%** (N=44)*	14.0 mo (95% CI 11.1, 24.9)	**15.3 mo** (95% CI 12.3, 26.1)

* Patients with measurable disease; ** Confirmation of response not required





Blue highlight = at least 6 months on treatment

TRAEs OVERALL (≥10% PATIENTS) & CORRESPONDING GRADE 3-5 TRAEs	NSCLC N=65	
	All TRAEs	Grade 3-5 TRAEs
Patients with at least one AE	61 (94%)	11 (17%)
Nausea	51 (79%)	1 (2%)
Vomiting	43 (66%)	0
Diarrhea	40 (62%)	2 (3%)
Fatigue	16 (25%)	1 (2%)
Decreased appetite	15 (23%)	0
Amylase increased	11 (17%)	0
ALT increased	10 (15%)	4 (6%)
Lipase increased	10 (15%)	2 (3%)
AST increased	9 (14%)	3 (5%)

Phase I - DIVARASIB +/- ATEZO IN KRAS G12C NSCLC - Adrian Sacher et al.

Iniciativa científica de: GECP lung cancer research

DIVARASIB + ATEZO

DOSE ESCALATION

Divarasib oral QD, 21-day cycles
+ **atezolizumab** 1200 mg IV q3w
200mg → 400mg
N=3 **N=6** *Max Admin Dose MTD not reached*

DOSE EXPANSION

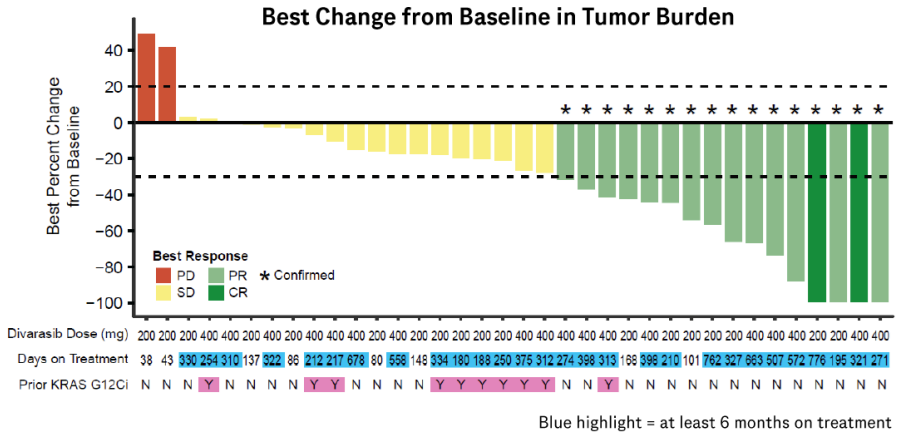
Divarasib oral QD, 21-day cycles
+ **atezolizumab** 1200 mg IV q3w
200 mg / 400mg
N=15 **N=15**

	All patients N=39
Age, median (range), years	66 (49-85)
Sex, female	19 (49%)
Race - White - Asian - Unknown	33 (85%) 3 (8%) 3 (8%)
ECOG, 0 / 1	14 (36%) / 25 (64%)
PD-L1 TPS score (n=31), <1 / **(1-49) / ≥50**	11 (28%) / **9 (23%) / 11 (28%)**
Median number of prior lines of systemic therapies (range)	2 (1-5)
Prior PD-1/PD-L1 inhibitor	35 (90%)
Prior platinum chemotherapy	37 (95%)
Prior KRAS G12C inhibitor	11 (28%)
Time on divarasib treatment, median (range), months	9.0 (0.1-25.5)

Patients enrolled	**N=39**
Patients enrolled at 400 mg	21 (54%)
Patients discontinued from study treatment	16 (41%)

Confirmed ORR*	**All Patients**	**No Prior KRAS G12Ci**
All Doses	**42.1%** (n=38)	**55.6%** (n=27)
400 mg	**45.0%** (n=20)	**61.5%** (n=13)

* Patients with measurable disease



Blue highlight = at least 6 months on treatment

TRAEs OVERALL (≥10% PATIENTS) & CORRESPONDING GRADE 3-5 AEs	**N=39**	
	All TRAEs	**Grade 3-5 TRAEs**
Patients with at least one TRAE	37 (95%)	11 (28%)
Nausea	25 (64%)	0
Diarrhea	24 (62%)	3 (8%)
Vomiting	19 (49%)	0
Decreased appetite	11 (28%)	0
AST increased	10 (26%)	2 (5%)
ALT increased	10 (26%)	2 (5%)
Asthenia	6 (15%)	0
Fatigue	5 (13%)	0
Lipase increased	5 (13%)	3 (8%)
Pruritus	5 (13%)	0
Constipation	4 (10%)	0

STUDY TREATMENT ACTION DUE TO TRAEs	**N=39**
Patients with TRAEs resulting in divarasib modification (interruption/reduction/withdrawal)	14 (36%)
Patients with TRAEs resulting in divarasib reduction	9 (23%)
Patients with TRAEs resulting in divarasib withdrawal	1 (3%)
Patients with TRAEs resulting in atezolizumab withdrawal	6 (15%)

Phase I – ASP3082 IN KRAS G12D SOLID TUMORS INCLUDING NSCLC – Wungki Park et al.

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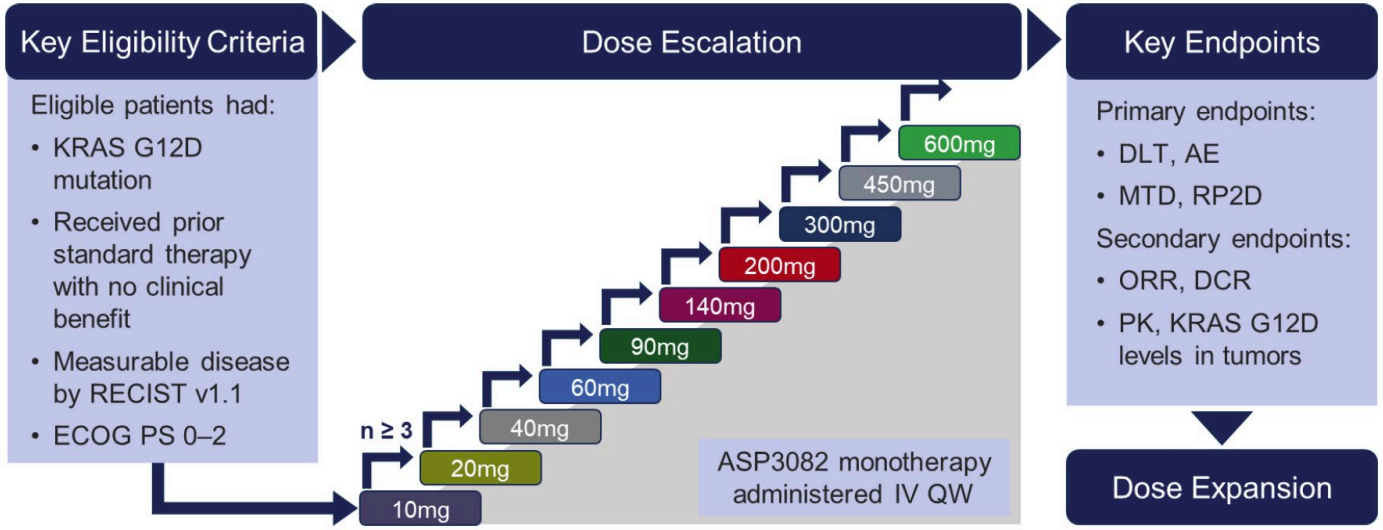
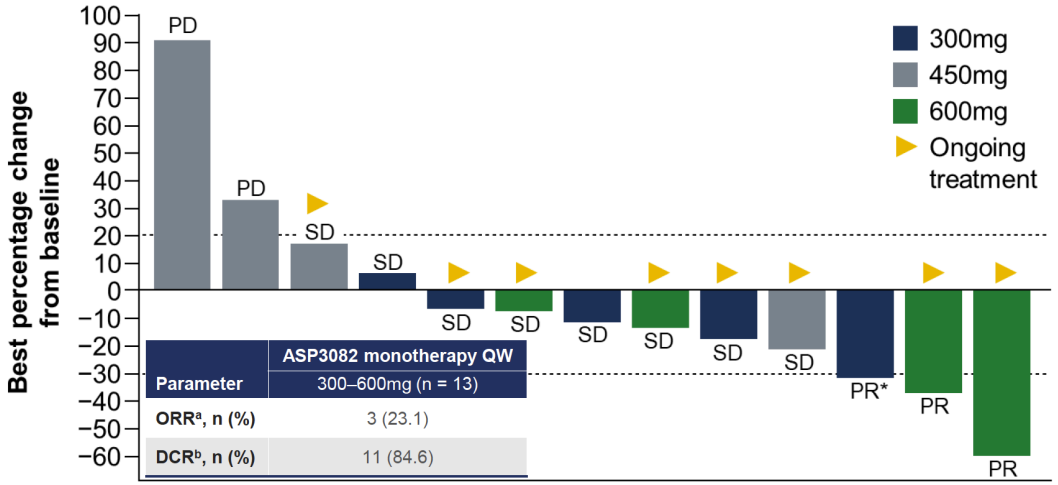


Responses to ASP3082 300–600mg in patients with NSCLC

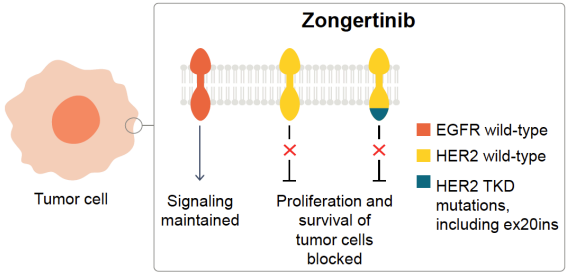


Characteristic, n (%)	ASP3082 monotherapy QW			
	Any grade		Grade 3	
	300–600mg (n = 48)	Overall (N = 111)	300–600mg (n = 48)	Overall (N = 111)
TRAEs	43 (89.6)	83 (74.8)	5 (10.4)	7 (6.3)
TRAEs occurring in ≥ 5% of all patients				
Infusion-related reaction	17 (35.4)	21 (18.9)	0	0
Fatigue	6 (12.5)	20 (18.0)	1 (2.1)	1 (0.9)
Rash[a]	10 (20.8)	13 (11.7)	0	0
Urticaria	9 (18.8)	11 (9.9)	0	0
Nausea	5 (10.4)	10 (9.0)	0	0
Pruritus	6 (12.5)	9 (8.1)	0	0
AST increased	6 (12.5)	8 (7.2)	2 (4.2)	2 (1.8)
Vomiting	3 (6.3)	6 (5.4)	0	0

- No Gr4 or Gr5 TRAEs

- *HER2*:
  - Zongertinib (BI 1810631) for *HER2*-positive solid tumors with brain metastases: subanalysis of the Beamion LUNG-1 trial

Phase I – ZONGERTINIB IN HER2+ TUMORS WITH BRAIN M1 - Frans Opdam et al.



Phase Ia: dose escalation (patients with HER2-altered, advanced solid tumors)

n = 17: 15 mg, 30 mg, 60 mg, 100 mg, 150 mg

n = 88: 60 mg, 120 mg, 180 mg, 240 mg, 300 mg, 360 mg

Selected as RDE based on all available data

One oral dose, BID, 3-week cycles

One oral dose, QD, 3-week cycles

MTD not reached with either schedule

Patients with brain metastases permitted if asymptomatic

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

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

*Randomized to 120 mg or 240 mg zongertinib; †Exploratory cohorts

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

Phase I – ZONGERTINIB IN HER2+ TUMORS WITH BRAIN M1 - Frans Opdam et al.

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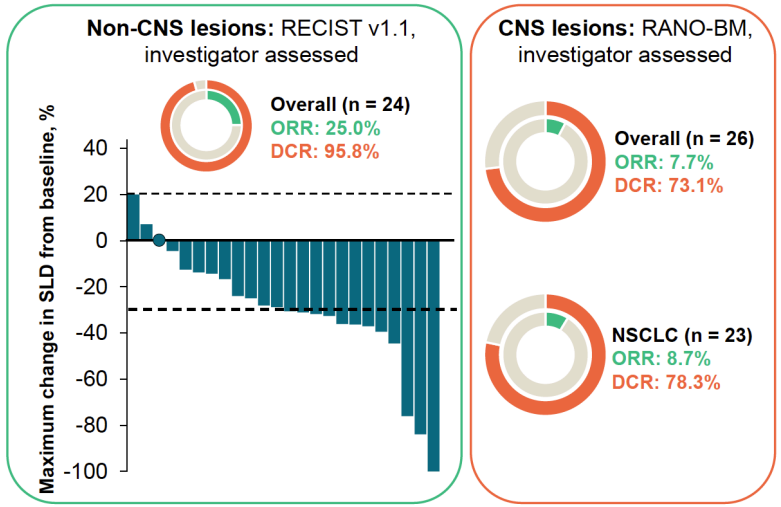
- In Phase Ia and Phase Ib, tumor response (RECIST v1.1) was assessed in patients with and without brain metastases
- In Phase Ib, CNS response (RANO-BM; BICR) was included as a secondary endpoint (primary endpoint in Cohort 4)

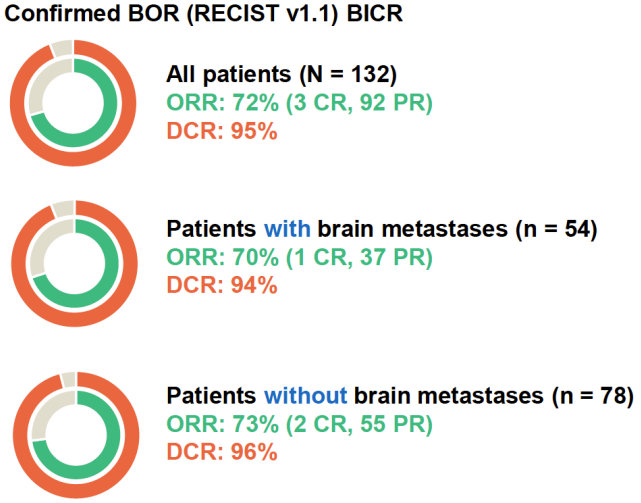
Phase Ia

- In Phase Ia (patients with solid tumors and HER2 aberrations; n = 105), 26% had brain metastases
- These patients were heavily pretreated (>2 lines of previous therapy: 67%)
- Confirmed response rate (RECIST v1.1) across all doses was similar to the overall population (25% and 32%, respectively)
- Preliminary evidence of intracranial activity was observed (RANO-BM)



Phase Ib

- In Phase Ib (patients with *HER2*-mutant NSCLC; n = 132), 41% had brain metastases
- In all patients treated with zongertinib, the confirmed ORR (RECIST v1.1) was 72%
- The response rate was very similar in patients with, and those without, brain metastases
- Zongertinib showed clinically meaningful activity in patients with pre-treated *HER2*-mutant NSCLC, regardless of the presence of brain metastases



- *NTRK*:
  - Updated efficacy, safety, and biomarker analysis in patients with TRK fusion lung cancer treated with larotrectinib

Updated data in TRK fusion NSCLC pts treated with larotrectinib - Jessica J. Lin et al.

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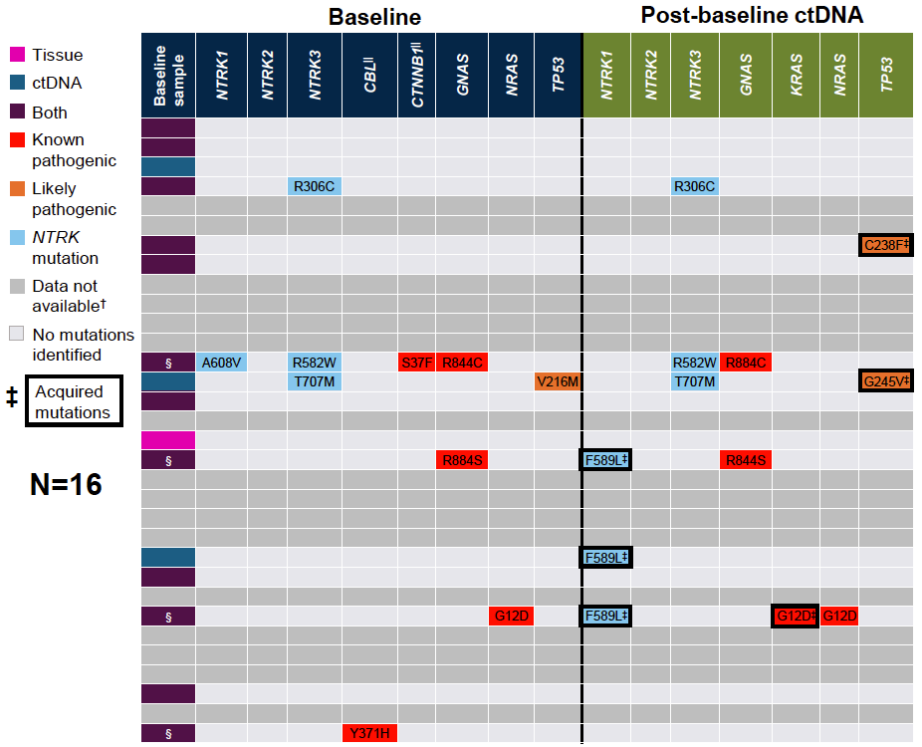
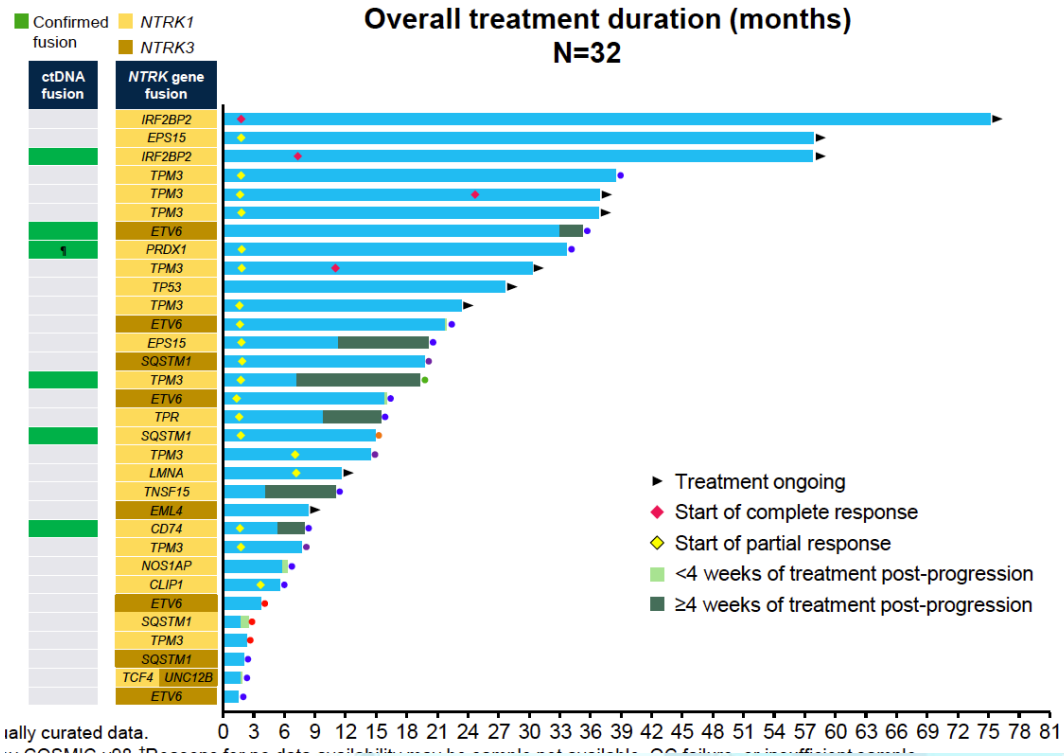
32 pts – Data cutoff July 2023 – 12 additional months FU

In patients with TRK fusion lung cancer

- **66%** ORR by IRC
- **34 months** Median DoR
- **22 months** Median PFS
- **39 months** Median OS





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Iniciativa científica de:
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CPCNP: enfermedad avanzada con driver
Parte 2

Ivana Sullivan, MD, PhD

Instituto Oncológico Dr. Rosell