Lung Cancer UPDATES
ASCO HIGHLIGTHS
02-06 JUNIO 2023
Chicago, USA

Iniciativa científica de:
GECP
lung cancer research

Novedades en terapia dirigida para CPNM con enfermedad avanzada (excepto KRAS)

Dr. Santiago Viteri

UOMI Cancer Center, Clinica Mi Tres Torres

DECLARACIÓN DE RELACIONES COMERCIALES

Iniciativa científica de: GECP lung cancer research

CONSULTORIA: ABBVIE, BMS, ROCHE, TAKEDA, ASTRAZENCA, MSD

PONENCIAS: MERCK Serono, JANSSEN, BMS, ROCHE, ASTRAZENECA, MSD

ASISTENCIA A CONGRESOS: OSE IMMUNOTHERAPEUTICS, ROCHE, MSD, MERCK

ORAL COMMUNICATIONS + RAPID ORALS

Iniciativa científica de: GECP lung cancer research

#9001 Randomized phase 3 study of first-line AZD3759 (zorifertinib) versus gefitinib or erlotinib in EGFR-mutant (*EGFR*m+) non–small-cell lung cancer (NSCLC) with central nervous system (CNS) metastasis

#9002 Sunvozertinib for the treatment of NSCLC with EGFR Exon20 insertion mutations: The first pivotal study results.

#9011 BLU-945 monotherapy and in combination with osimertinib (OSI) in previously treated patients with advanced *EGFR*-mutant (*EGFRm*) NSCLC in the phase 1/2 SYMPHONY study.

POSTER DISCUSSION 1

Iniciativa científica de: GECP lung cancer research

#9014 Safety and preliminary efficacy of YK-029A, a novel EGFR TKI, in patients with advanced NSCLC harboring ex20ins, T790M or rare mutations.

#9015 FAK inhibition with novel FAK/ALK inhibitor APG-2449 could overcome resistance in NSCLC patients who are resistant to second-generation ALK inhibitors.

#9017 Intracranial and systemic efficacy of repotrectinib in advanced ROS1 fusion-positive (ROS1+) non-small cell lung cancer (NSCLC) and central nervous system metastases (CNS mets) in the phase 1/2 TRIDENT-1.

POSTER DISCUSSION 2

Iniciativa científica de: GECP lung cancer research

#9018 Efficacy and safety of encorafenib (enco) plus binimetinib (bini) in patients with BRAF V600E-mutant (BRAFV600E) metastatic non-small cell lung cancer (NSCLC) from the phase 2 PHAROS study.

#9019 LIBELULE: A randomized phase III study to evaluate the clinical relevance of early liquid biopsy (LB) in patients with suspicious metastatic lung cancer.

#9021 Tepotinib + osimertinib for EGFR mutant (EGFRm) NSCLC with MET amplification (METamp) after first-line (1L) osimertinib.

EVEREST: Randomized phase 3 study of first-line AZD3759 (zorifertinib) versus gefitinib or erlotinib in EGFR-mutant (*EGFR*m+) non-small-cell lung cancer (NSCLC) with central nervous system (CNS) metastasis

Iniciativa científica de: GECP lung cancer research

Study Design: Randomized, Controlled, Open-label, Phase 3

Patient population

- Confirmed EGFRm+ (L858R and/or Exon 19Del), advanced NSCLC
- Documented MRI-confirmed CNS metastases (asymptomatic/stable symptoms)
- No prior first-line systemic therapy
- No prior brain radiotherapy
- ≥1 non-irradiated measurable CNS lesion or (in patients with no measurable CNS lesions) ≥1 nonirradiated extracranial lesion
- No EGFR T790M, KRAS, or cMET mutations
- ECOG PS 0–1

N=439

R* 1:1

Zorifertinib 200 mg BID
***N*=220**

Gefitinib 250 mg QD or Erlotinib 150 mg QD
***N*=219†**

Primary endpoint:

- PFS by BICR (RECIST 1.1)

Secondary endpoints:

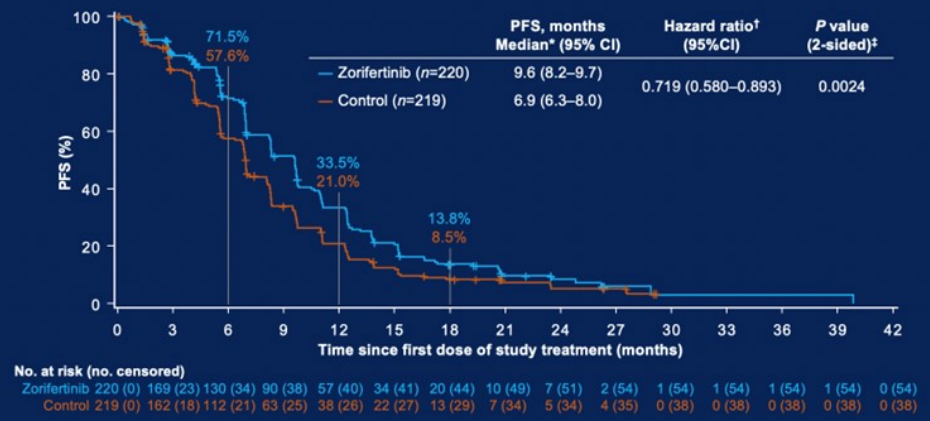
- PFS by INV (RECIST 1.1) and BICR (mRECIST 1.1)
- IC and EC PFS‡
- ORR, DCR, DoR, and TTR (Overall, IC and EC)‡
- OS, QoL, safety

This trial is registered at ClinicalTrials.gov: NCT03653546

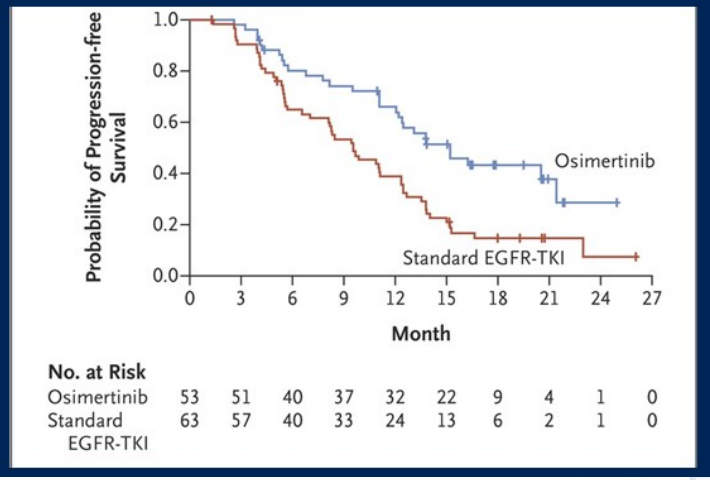
OBJETIVO PRIMARIO

Iniciativa científica de: GECP lung cancer research

Primary Endpoint: PFS Assessed by BICR per RECIST 1.1 (ITT)



Osimertinib PFS Pts with CNS Disease in FLAURA (Inv)



mPFS 15.2 mo. (12.1-21.4) vs 9.6 mo. (7-12.4) (95% CI)

ACTIVIDAD INTRACRANEAL

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IC variable	Assessor	AZD3759	The control group	HR/OR (95% CI)	*p*
median PFS (mo)	BICR[a]	15.2	8.3	HR 0.467 (0.352–0.619)	<0.0001
	INV[b]	17.9	11.1	HR 0.627 (0.466–0.844)	0.0018
ORR (%)[c]	BICR[a]	75.0	64.2	OR 1.658 (0.993–2.768)	0.0534
	INV[b]	75.6	62.3	OR 1.904 (1.098–3.302)	0.0218
median DoR (mo) [c]	BICR[a]	12.4	7.0	HR 0.521 (0.352–0.773)	0.0009
	INV[b]	13.8	11.1	HR 0.789 (0.501–1.244)	0.3037

[a]IC lesions were evaluated separately per RECIST 1.1. [b]Evaluated per Response Assessment in Neuro-Oncology Brain Metastases (*RANO-BM*). [c]Confirmed responses. INV, investigator; OR, odds ratio.

OBJETIVO EXPLORATORIO: MECANISMOS DE RESISTENCIA

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Drug-Resistance-Associated Biomarkers (Exploratory)*

- EGFR T790M mutation was the most common secondary resistance mutation

Data are n (%)	Zorifertinib (N=24)		Control (N=25)	
EGFR-T790M	8	(33.3)	3	(12.0)
EGFR-T790M with 19Del	5	(20.8)	0	
EGFR-T790M with L858R	3	(12.5)	0	
EGFR-T790M with exon 19 complex mutation	0		2	(8.0)
EGFR-T790M	0		1	(4.0)
EGFR exon 19 complex mutation	0		1	(4.0)

*Total population from the entire phase 2–3 study (NCT03653546).

POTENCIAL IMPACTO CLÍNICO

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Basic Components of a Successful EGFR TKI

Inhibit of EGFR E19del and L858R

Yes

CNS Penetration

Yes

EGFR WT Sparing (comparatively)

No

Diarrhea - 63.6% (13.2% G3) vs 39.9% (0.5% G3)
Rash – 55.6% (13.6% G3) vs 37.6% (0.5% G3)

Suppression of Major EGFR TKI Resistance Mechanisms (EGFR-T790M)

No

1/3 of patients (8/24) with EGFR-T790M resistance

WU-KONG6 Sunvozertinib for the treatment of NSCLC with EGFR Exon20 insertion mutations: The first pivotal study results.

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WU-KONG6 Study Design

Key inclusion criteria:

- Locally advanced or metastatic NSCLC
- Confirmed EGFR exon20ins in tumor tissues
- Received 1 – 3 lines of prior systemic therapies
- Disease progressed on or after platinum-based chemotherapy

DZD9008

300 mg, QD

Primary endpoint:

- IRC assessed† ORR

Secondary end point:

- IRC assessed† DoR
- ORR (investigator assessed), PFS, DCR, tumor size changes
- OS
- Safety and tolerability
- Pharmacokinetics

† According to RECIST 1.1. Tumor assessment every 6 weeks

IRC, independent review committee; ORR, objective response rate; DoR, duration of response; PFS, progression free survival; DCR, disease control rate; OS, overall survival.

Data cut-off for analysis: October 17, 2022

EFICACIA Y SEGURIDAD EN CONTEXTO

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Efficacy

	Mobocertinib[1] (N=114)	Amivantamab[2] (N=81)	Sunvozertinib (DZD9008) (N=97) WUKONG6[3]
Investigator assessed			
ORR, %	35%	36%	46.4%
Disease control rate, %	78%	73%	
Duration of response, mos	11.2 mo	-	
IRC assessed (95% CI)			
ORR, % (95% CI)	28% (20-37%)	40% (29-51%)	60.8% (50.4-70.6%)
Disease control rate, %	78%	74%	87.6%
Duration of response, months	17.5 mo	11.1 mo	64.4% responding at median fup of 5.6 mo.
PFS, months	7.3 mo	8.3 mo	-
Brain Mets, ORR (N=)	-	-	44% (N=25) [4]

1. Zhou C. et al. *JAMA Oncol.* 2021 Oct 14;e214761. 2. Park K, et al. *J Clin Oncol.* 2021;39:3391-3404. 3. M. Wang et al ASCO 2023. ABS7 9002. 4. L. Bazhenoza et al NACLC 2022.

Safety

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EGFR Exon 20 Tx	Trial	Diarrhea	Rash	Other Major Notable
Amivantamab	CHRYSALIS[2]	12% (2% G3+)	86% (4% G3+)	Infusion-related reaction 66% (8% G3+), Paronychia
Mobocertinib	EXCLAIM[1]	93% (16% G3+)	45% (0% G3+)	lipase, amylase, other GI, lipase, amylase elevation
Sunvozertinib	WUKONG6[4]	67.3% (7.7% G3+)	53.8% (1% G3+)	CPK Elevation (57.7%, 17.3% G3+)

*WUKONG 1,2,6 pooled at 300 mg dose [5]

Other EGFR Exon 20 ins TKI with Putative CNS Penetration in Development

- TAS6417 (CLN-081)
- Blu-451
- Oric-114
- Furmonertinib

EFICACIA EN TODOS LOS TIPOS DE INSERCIONES

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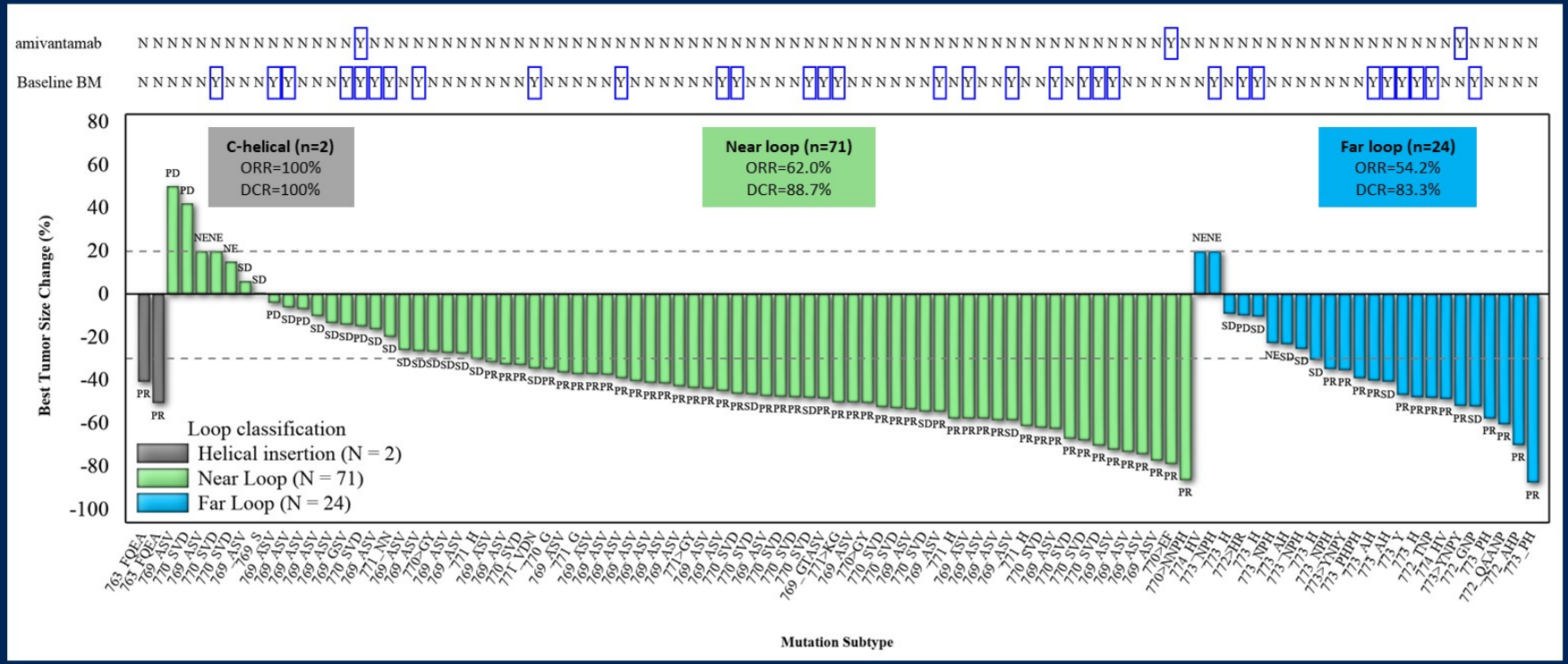
Anti-tumor Efficacy in Different EGFR Exon20ins Subtypes



- A total of 30 different subtypes of EGFR exon20ins were enrolled. Anti-tumor efficacy was observed regardless of mutation subtypes and insertion locations.

POTENCIAL IMPACTO CLÍNICO

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Basic Components of a Successful EGFR Exon 20 ins TKI

Inhibit Wide Range of EGFR Exon 20 ins (C-Helix, Near and Far loop)

Yes

CNS Penetration

Yes

EGFR WT Sparing (comparatively)

Yes

Suppression of Resistance Mechanisms for EGFR Exon 20 ins TKI

? (anti-T790M preclinical activity)

SYMPHONY: BLU-945 monotherapy and in combination with osimertinib (OSI) in previously treated patients with advanced *EGFR*-mutant (*EGFRm*) NSCLC in the phase 1/2 SYMPHONY study

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SYMPHONY (NCT04862780) study design and patient characteristics

Key eligibility criteria

- **Adults with metastatic *EGFR*m NSCLC**
- **No other known oncogenic tumor drivers**
- **ECOG status 0-1**
- **Prior treatment with ≥1 EGFR TKI with activity against T790M; progression on osimertinib as last therapy (part 1B only)**

Phase 1 (dose escalation)

Part 1A (N=112)
BLU-945 monotherapy
BOIN design
Starting dose: 25 mg QD[a]
Initiated May 2021

Part 1B (N=55)
BLU-945 + osimertinib (80 mg)
Starting dose:
BLU-945 200 mg QD[a]
Initiated June 2022

All combination patients received osimertinib as last line of therapy without a washout period

Primary endpoints
MTD, RP2D, safety

Characteristic	BLU-945	
	Monotherapy[b] (n=112)	Combination[c] (n=55)
Age, years, median (min, max)	63 (34, 84)	62 (28, 87)
Age group, n (%)		
<65 years	63 (56.3)	32 (58.2)
≥65 years	49 (43.8)	23 (41.8)
Female, n (%)	74 (66.1)	34 (61.8)
CNS metastases at baseline, n (%)	43 (38.4)	17 (30.9)
Prior LOT, median (min, max)	3.5 (1, 13)	2 (1, 7)

- Patients enrolled in the phase 1 dose escalation were heavily pretreated
- 94% of monotherapy and 89% of combination patients had an additional EGFR and/or detectable additional genetic alteration
- Combination dose escalation is ongoing

[a]BID dosing was also evaluated. [b]25–600 mg QD; 100–300 mg BID. [c]200–400 mg QD;100–200 mg BID with OSI 80 mg QD.
BID, twice daily; BOIN, Bayesian optimal interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ex19del, exon 19 deletion; LOT, line of therapy; MTD, maximum tolerated dose; QD, every day; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor.

SEGURIDAD DE LA COMBINACIÓN

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BLU-945 + osimertinib combination is well tolerated with limited EGFR WT AEs

TRAEs, (N=55)		
TRAEs, n (%) Safety population	**Any grade**	**Grade ≥3**
Any TRAEs	52 (94.5)	6 (10.9)
EGFR-associated TRAEs		
Diarrhea	16 (29.1)	0
Dry skin	9 (16.4)	0
Dermatitis acneiform	8 (14.5)	1 (1.8)
Paronychia	6 (10.9)	0
TRAEs in ≥10% of patients		
Headache	19 (34.5)	0
Nausea	19 (34.5)	0
Fatigue	12 (21.8)	1 (1.8)
Decreased appetite	7 (12.7)	0
Vomiting	6 (10.9)	0

- Exposure of BLU-945 and osimertinib when coadministered are comparable to PK data from BLU-945 given alone and published osimertinib data[1,2]
- EGFR-WT associated AEs were infrequent, and the majority were Grade 1
- Three patients had DLTs across 200 – 400 mg total daily doses
  - 100 mg BID + 80 mg osi, Grade 3 acute respiratory failure
  - 300 mg QD + 80 mg osi - Grade 4 pneumonitis
  - 400 mg QD + 80 mg osi- Grade 3 dermatitis acneiform
- Two patients (3.6%) discontinued due to TRAEs
- There were no treatment-related deaths
- Dose escalation is on-going with MTD/RP2D yet to be determined

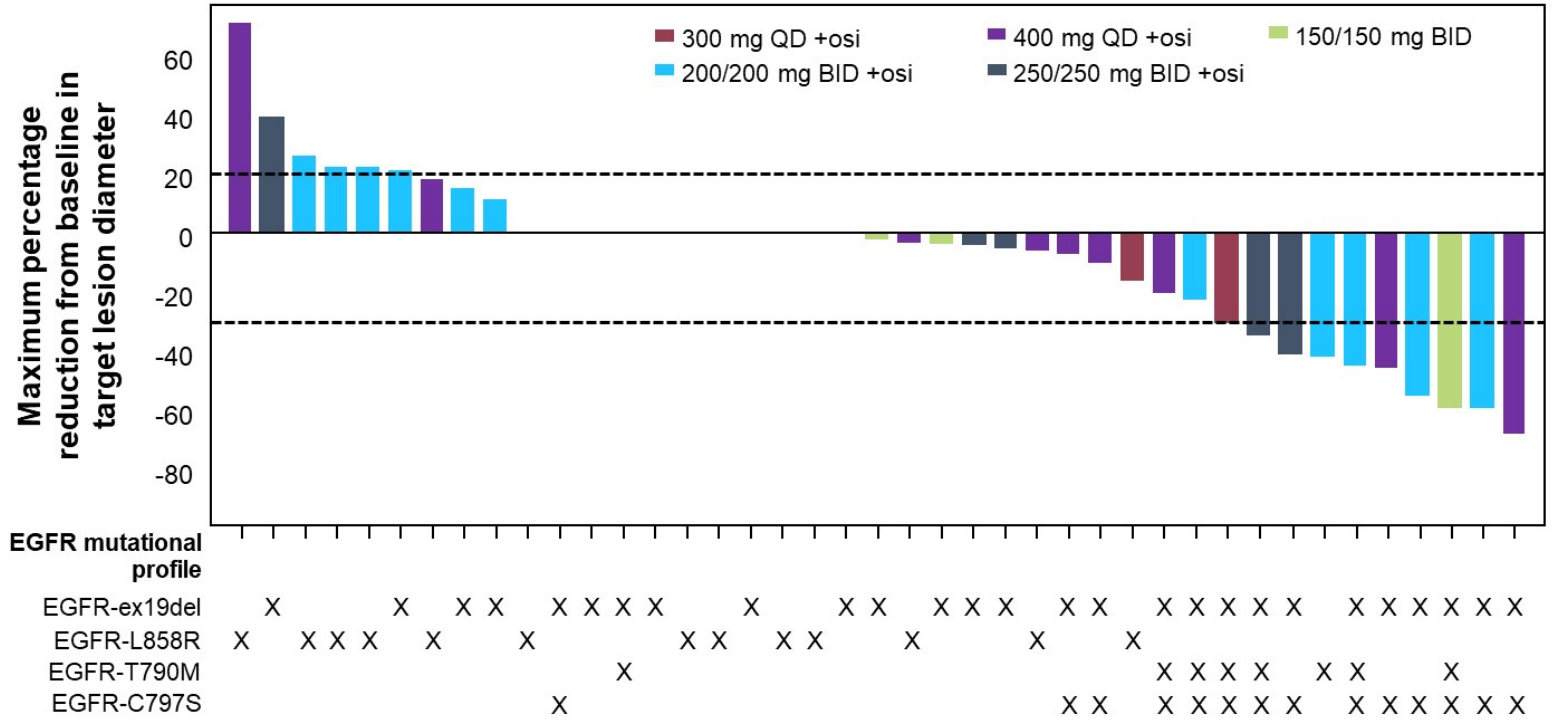
AE, adverse event; BID, twice daily; DLT, dose limiting toxicity; EGFR, epidermal growth factor receptor; MTD, maximum tolerated dose; QD, once daily; RP2D, recommended phase 2 dose; TRAE, treatment-related adverse event; WT, wild type.

1. Brown K, et al. *Br J Clin Pharmacol*. 2017;83(6):1216-1226. **2.** Planchard D, et al. *Cancer Chemother Pharmacol*. 2016;77: 767-776.

EFICACIA DE LA COMBINACIÓN

Iniciativa científica de: GECP lung cancer research

Early BLU-945 + osimertinib antitumor activity[a]



- In the ongoing dose-escalation, tumor shrinkage, including 4 confirmed PRs, was observed in patients who had progressed on osimertinib as the last therapy line

[a]Patients with EGFR-mutant positive NSCLC were enrolled based on local mutation assessment of tumor biopsy or blood ctDNA with a follow-up central ctDNA assessment at C1D1. Patients were counted only once.
BID, twice daily; EGFR, epidermal growth factor receptor.

POTENCIAL IMPACTO CLÍNICO

Iniciativa científica de: GECP lung cancer research

Conclusions

- In heavily pretreated EGFR-mutant NSCLC patients, BLU-945 monotherapy was active and well-tolerated; however, due to genomic heterogeneity, responses were not durable
- Emerging BLU-945 + osimertinib combination data demonstrated clinical activity post progression on osimertinib and was well tolerated with infrequent EGFR WT toxicity
- A correspondence between reduction of the resistance mutation alleles by ctDNA and tumor shrinkage was observed in both cohorts
- Phase 1 data support BLU-945 + osimertinib as a differentiated, fully oral, novel combination for treatment of EGFR-mutant NSCLC, warranting further clinical development
    - Combination escalation is ongoing with RP2D/MTD yet to be established

Abstract 9014: Safety and preliminary efficacy of YK-029A, a novel EGFR TKI, in patients with advanced NSCLC harboring ex20ins, T790M or rare mutations.

Duan J, Zhao J, Li M, Lin Wu, Chengzhi Zhou, Qitao Yu, Yanyan Xie, Jie Wang

Iniciativa científica de:

GECP lung cancer research

2023 ASCO ANNUAL MEETING

Abstract #9014
Poster Bd #2

Safety and preliminary efficacy of YK-029A, a novel EGFR TKI, in patients with advanced NSCLC harboring ex20ins, T790M or rare mutations

Jianchun Duan[1], Jun Zhao[2], Mingjun Li[3], Lin Wu[4], Chengzhi Zhou[5], Qitao Yu[6], Yanyan Xie[7], Jie Wang[1]

[1]State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer Hospital, Beijing, China; [2]Peking University Cancer Hospital and Institute, Beijing, China; [3]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China;[4]Hunan Cancer Hospital, Changsha, China; [5]The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; [6]Department of Respiratory Oncology, Affiliated Tumor Hospital of Guangxi Medical University, Nanning City, Nanning, China; [7]The People's Hospital of Guangxi Zhuang Autonomous Region, Guangxi, Nanning, China;

Puhe BioPharma 浦合医药

June 2-6, 2023
McCormick Palace, Chicago, IL & Online
#ASCO2023

Background

- In the Asia-Pacific population, the prevalence of EGFR ex20ins mutation is estimated to be as high as 4%[1].
- Patients with ex20ins mutation have poor outcomes than those with more common EGFR mutations. First- and second-generation EGFR tyrosine kinase inhibitors (TKI) have demonstrated limited efficacy against EGFR ex20ins mutation[2].
- Two FDA-approved treatments, amivantamab and mobocertinib, are currently available to patients with EGFR ex20ins mutation after chemotherapy failure[3, 4]. Platinum-based chemotherapy remains the first-line treatment for patients with ex20ins mutation.

Objective

To evaluate the safety, tolerability, pharmacokinetics of YK-029A, a third-generation EGFR tyrosine kinase inhibitor, and the preliminary efficacy of YK-029A in treatment-naïve patients with EGFR ex20in mutation.

Methods

- This dose-escalation and dose-expansion phase 1 trial(NCT05767866)
- recruited previously untreated or treated patients with EGFR ex20ins mutant locally advanced or metastatic NSCLC and previously treated patients with EGFR T790M or rare mutations.
- In dose-escalation phase, patients with EGFR T790M mutation were enrolled. YK-029A was given at doses of 50, 100, 150, 200 to 250 mg/day (3+3 design).
- In dose-expansion phase, patients with EGFR T790M, EGFR ex20ins, or rare mutations were enrolled. The primary objective was safety. Dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) were explored. In the treatment-naïve cohort of EGFR ex20ins mutant NSCLC, patients were administered oral YK-029A 200 mg once daily in a 28-day cycle, and efficacy was assessed by the independent review committee(IRC).

Results

- A total of 108 were included in the safety analysis set. DLT did not occur in dose-escalation phase. MTD was not reached.
- At the cut-off date on October 30, 2022, 19 patients (73.1%) had partial remission, five patients (19.2%) had stable disease, and two patients (7.7%) developed disease progression. The confirmed objective response rate per IRC achieved 73.1% (95% confidence interval [CI], 52.21% to 88.43%). The median progression-free survival was 9.3 months (95% CI, 5.85 to not evaluated).
- Baseline characteristics are shown in Table 2.

References

1.Burnett, H., et al. PLoS One, 2021. 16(3): p. e0247620.
2.Morita, C., et al. Sci Rep, 2021. 11(1): p. 18762.
3. Riely, G.J., et al. Cancer Discov, 2021. 11(7): p. 1688-1699.
4. Yun, J., et al.Cancer Discov, 2020. 10(8): p. 1194-1209.

Results

Table 1. Efficacy of treatment-naive patients with EGFR ex20ins mutation

Cohort 6 (200mg, treatment-naive patients)		
Outcomes	By INV(n=26)	By IRC(n=26)
Confirmed Best response, n(%)		
PR	15	19
SD	10	5
PD	1	2
Confirmed ORR, n(%,95%CI)	57.7% (95% CI, 36.92 , 76.65)	73.1% (95% CI, 52.21 , 88.43)
DCR, n(%, 95%CI)	96.2% (95% CI, 80.36 , 99.90)	92.3% (95% CI, 74.87 , 99.05)
mDoR, m(95%CI)	9.4 (95% CI, 3.75, NE)	7.5 (95% CI, 3.75, NE)
6-month DOR rate (95% CI)	65.2 (95% CI, 30.36, 85.76)	59.8 (95% CI, 23.28, 83.37)
mPFS, m (95% CI)	11.1 (95% CI, 5.85, NE)	9.3 (95% CI, 5.85, NE)
6-month PFS rate, % (95% CI)	69.7% (95% CI, 45.71, 84.63)	72.8 % (95% CI, 44.48, 88.28))
9-month PFS rate,% (95% CI)	69.7% (95% CI, 45.71, 84.63)	63.7% (95% CI, 33.76, 82.90)
1-year OS rate, %(95%CI)	83.1 %(95% CI, 47.17, 95.53)	
Median follow-up time(month)	7.6	

Table 2. Baseline characteristic(treatment-naïve patients)

EGFR ex20ins (treatment-naive patients)	Cohort 6 (200mg) (N=28)
Median age(range)	59.2 (10.7)
Gender, Male, n(%)	15 (53.6%)
ECOG PS	
0	5 (17.9%)
1	22 (78.6%)
2	1 (3.6%)
Histological subtype, n(%)	
squamous cell carcinoma	1 (3.6%)
Adenocarcinoma	27 (96.4%)
Baseline brain metastasis	
Yes	4 (14.3%)
Smoking status	
None	20 (71.4%)

Figure 1. Waterfall plot of IRC-assessed best percentage change in sum of target lesion diameters(treatment-naïve patients)

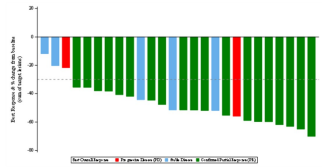


Figure 2. Waterfall plot of IRC-assessed best percentage change in sum of target lesion diameters(treatment-naïve patients)

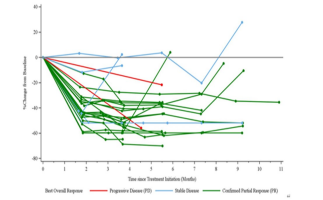


Figure 3. Time on treatment in confirmed responders to YK-029A (treatment-naive patients, n=28, IRC)

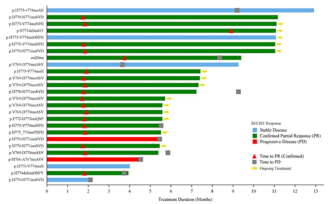
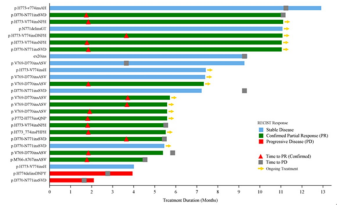


Figure 4. Time on treatment in confirmed responders to YK-029A (treatment-naive patients, n=28, INV))



Results

Figure 5. PFS by IRC assessment (A) and by INV(B)

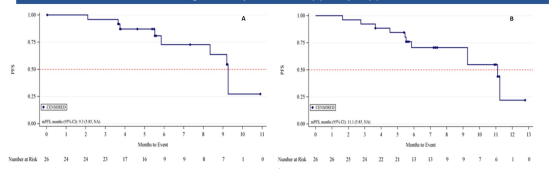


Table 3. Overview of AEs (N=108)

Events, n(%)	50mg QD (N=9)	100mg QD (N=13)	150mg QD (N=41)	200mg QD (N=41)	250mg QD (N=3)	150mg BID (N=1)	All (N=108)
At least one TRAE	9 (100)	13 (100)	39(85.4)	41 (100)	3 (100)	1(100)	106 (98.1)
Grade ≥3 TRAE	1 (11.1)	2 (15.4)	8 (19.5)	17(41.5)	1 (33.3)	1(100)	30 (27.8)
TRSAE	0	1 (7.7)	6 (14.6)	10(24.4)	0	1(100)	18 (16.7)
TRAE leading to suspension	1 (11.1)	2 (15.4)	6 (14.6)	11(26.8)	1 (33.3)	1(100)	22 (20.4)
TRAE leading to discontinuation	0	0	1 (2.4)	2 (4.9)	0	0	3 (2.8)
TRAE leading to dose reduction	0	0	1(2.4)	9(22)	0	0	10(9.3)
TRAE leading to death	0	0	1 (2.4)	0	0	0	1 (0.9)

Table 4. TRAEs of Grade ≥3 occurred in ≥1% patients

	50mg QD (N=9)	100mg QD (N=13)	150mg QD (N=41)	200mg QD (N=41)	250mg QD (N=3)	150mg BID (N=1)	All (N=108)
TRAE of grade≥3	1 (11.1%)	2 (15.4%)	8 (19.5%)	17 (41.5%)	1 (33.3%)	1 (100%)	30 (27.8%)
diarrhea	0	0	0	6 (14.6%)	0	0	6 (5.6%)
anemia	0	0	2 (4.9%)	2 (4.9%)	0	0	4 (3.7%)
QT prolongation	1 (11.1%)	1 (7.7%)	1 (2.4%)	0	0	0	3 (2.8%)
Spinal inhibition	0	0	1 (2.4%)	2 (4.9%)	0	0	3 (2.8%)
thrombocytopenia	0	0	1 (2.4%)	1 (2.4%)	0	0	2 (1.9%)
hypokalemia	0	0	1 (2.4%)	1 (2.4%)	0	0	2 (1.9%)
oral mucositis	0	0	0	2 (4.9%)	0	0	2 (1.9%)

Conclusions

- YK-029A, a novel oral EGFR TKI, demonstrated rapid, deep, and durable responses in patients with treatment-naïve EGFR ex20ins+ mNSCLC.
  - Confirmed ORR was 73.1% per IRC and 57.7% per INV.
  - Median DoR was 7.5 months and median PFS was 9.3 months (per IRC).
  - 9-month PFS rate was 63.7% (33.76, 82.90) and 1-year OS rate was 83.1%(95% CI: 47.17, 95.53).
- Responses were observed in all evaluated subgroups, including patients with brain metastases, and across EGFR ex20ins mutation subtypes.

Acknowledgments

- The Sponsor wishes to thanks all the patients and their families for participation in this study, as well as investigators and staff at participating institutions for their support in executing this study
- This trial was sponsored by Puhe Biopharma Co.,Ltd

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EFICACIA EN CONTEXTO

Iniciativa científica de: GECP lung cancer research

Existing and upcoming EGFR exon20 treatment options

	Mobocertinib	Amivantamab	Sunvozertinib DZD9008	Zipalertinib CLN081/TAS6417	YK-029A
	FDA accelerated approval 2021	FDA accelerated approval 2021	FDA BTD	FDA BTD	
		Phase 3 PAPLLON	1L phase 3 trial ongoing	1L phase 3 trial ongoing	1L phase 3 trial ongoing (vs. chemo)
ORR	28% (post-chemo)	40% (post-chemo)	61% (2L) 78% (treatment-naïve)	41%	**73%** **(Treatment-Naïve)**
PFS (months)	7.3	8.3	NR	12	9.3
DoR (months)	17.5	11.1	NR	NR	7.5
CNS activities	No	No	Not known	Not known	Not known
Common Toxicities All grade (G3+)	Diarrhea, 91% (21%) Rash, 45% (0%)	Diarrhea 11% (2%) Rash 86% (4%)	Diarrhea, 59% (6.5%) Rash 39% (1%)	Diarrhea, 30% (3%) Rash, 80% (1%)	Diarrhea 46% (14.6%) Rash 32%(0%) Mucositis (4.9%)
	QTc prolongation (Black Box)	Infusion reaction (66%)	CPK elevation 31%		
Dose discontinuation	17%	10%	NR	5%	4.9%
Dose reduction	25%	13%	NR	13%	22%

Blu-451, ORIC-114, BAYER7088, PLB004, furmonertinib, and many others in clinical development

Zhou C et al JAMA Oncol 2021, Park K et al JCO 2021,* Bazhenova LA *et al NALC 2022, Yu H et al ASCO 2022, Wang et al ASCO 2023, Xu et al ASCO 2023, Duan J et al ASCO 2023

Abstract 9015: FAK inhibition with novel FAK/ALK inhibitor APG-2449 could overcome resistance in NSCLC patients who are resistant to second-generation ALK inhibitors

Yuxiang Ma, Hongyun Zhao, Jianhua Chen, Zhengbo Song, Yanqiu Zhao, Yubiao Guo, Gang Wu, Wenwei Zhou, Xiaoqing Yu, Fangfang Gao, Ruiguang Zhang, Jian Fang, Xiaoyan Lin, Wu Zhuang, Xiaohong Tian, Yanhua Tu, Juan Yu, GuangLin Liu, Yifan Zhai, and Li Zhang

Iniciativa científica de: GECP lung cancer research

2023 ASCO ANNUAL MEETING

FAK inhibition with novel FAK/ALK inhibitor APG-2449 could overcome resistance in NSCLC patients who are resistant to second-generation ALK inhibitors

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2023 ASCO ANNUAL MEETING

INTRODUCTION

- APG-2449 is a novel, orally active FAK inhibitor and an ALK/ROS1 tyrosine kinase inhibitor (TKI) that has shown potent activity in preclinical models.
- It has been demonstrated that APG-2449 is well tolerated, and preliminary efficacy was observed in patients who were resistant to second-generation ALK/ROS1$^+$ inhibitors.[1]
- We provide updated safety and efficacy results and potential mechanisms of action(s) of this therapy.

OBJECTIVE

- This is a first-in-human dose escalation and dose expansion study to evaluate APG-2449 in patients with second-generation TKI-resistant ALK/ROS1 non-small-cell lung cancer (NSCLC), mesothelioma, or ovarian cancer (NCT03917043).
- Study aims were to assess the safety/tolerability, recommended phase 2 dose (RP2D), pharmacokinetics (PK), pharmacodynamics (PD), and efficacy.

METHODS

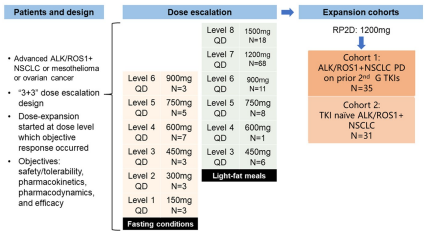


Figure 1. Study design.

RESULTS

Table 1. Baseline characteristics (N = 136)

Age, yr	
Median (range)	53.0 (21-78)
Sex, n (%)	
Female	74 (54.4)
Male	62 (45.6)
ECOG performance status, n (%)	
0	44 (32.4)
1	92 (67.6)
Tumor, n (%)	
Mesothelioma	5 (3.7)
NSCLC	122 (89.7)
Ovarian cancer	9 (6.6)
Molecular subtype,* n (%)	
ALK	90 (73.8)
ROS1	32 (26.2)
Lines of prior systemic therapy,* n (%)	
0	27 (22.1)
1	28 (23.0)
2	30 (24.6)
≥3	37 (30.3)
ALK/ROS1 TKI,* n (%)	
0	34 (27.9)
1	36 (29.5)
2	32 (26.2)
≥3	20 (16.4)
Prior chemotherapy,* n (%)	42 (34.4)
Brain metastasis at baseline,* n (%)	70 (57.4)

*Patients with mesothelioma were excluded.

SAFETY

Table 2. Common treatment-related AEs (TRAEs; ≥ 10%)

	APG-2449	
	Any Grade	≥ Grade 3
Population	136	136
Subjects with at least one TRAE, n (%)	123 (90.4)	19 (14.0)
Preferred term, no. (%)		
Increased blood creatinine	63 (46.3)	0
Increased alanine aminotransferase	55 (40.4)	4 (2.9)
Increased aspartate aminotransferase	45 (33.1)	1 (0.7)
Nausea	37 (27.2)	1 (0.7)
Vomiting	31 (22.8)	2 (1.5)
Decreased leukocyte-count	30 (22.1)	1 (0.7)
Diarrhea	29 (21.3)	0
Decreased neutrophil count	24 (17.6)	1 (0.7)
Rash	17 (12.5)	0

EFFICACY

Figure 2. Best tumor response (%) in patients with second-generation TKI-resistant ALK$^+$ NSCLC treated at the RP2D of APG-2449.

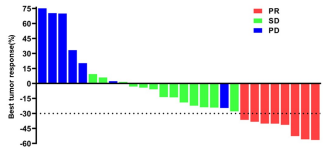
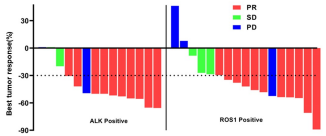


Figure 3. Best tumor response (%) in patients with TKI-naïve ALK/ROS1$^+$ NSCLC treated at the RP2D of APG-2449.



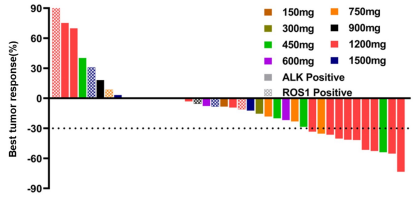


Figure 4. Best tumor response (%) of brain metastases observed in patients with second-generation TKI-resistant ALK$^+$ NSCLC treated with APG-2449 at different assigned doses.

Correlation of phosphorylated FAK (pFAK) with best tumor response

Figure 5. Peripheral blood mononuclear cells (PBMCs) were collected from patients with NSCLC who received prior treatment with ALK TKI and were treated at different doses of APG-2449. pFAK fold change from baseline was evaluated based on best tumor response.

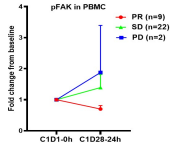
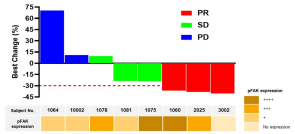


Figure 6. pFAK expression based on best tumor response after treatment with APG-2449 at RP2D. Baseline tumor tissues were from 8 patients with NSCLC previously treated with ALK TKIs.



CONCLUSIONS

- APG-2449 showed a favorable preliminary safety profile and antitumor activity in patients with NSCLC.
- Preliminary efficacy was observed in those whose disease was TKI naïve and resistant to second-generation ALK inhibitors.
- FAK inhibition may be a novel approach to overcome ALK resistance in patients with NSCLC resistant to second-generation ALK inhibitors.

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ACKNOWLEDGMENTS

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EFICACIA EN CONTEXTO

Iniciativa científica de: GECP lung cancer research

Existing ALK-rearranged NSCLC treatment options

	Ceritinib	Alectinib	Brigatinib	Ensartinib	Lorlatinib (3G)	APG-2449
ORR	72%	81-91%	74%	74%	77%	**78% (Treatment-Naïve)**
PFS (months)	16.6	25.7-34.1	24.0	25.8	NR (f/u 37m)	NR
CNS ORR	73%	81-94%	78%	64%	83%	Promising
Common Toxicities All grade (G3+)	Nausea 66-83% ALT/AST 20-45%	Nausea 10-21% ALT/AST 12-28% Constipation 24-33%	Nausea 40-55% ALT/AST 15%	Nausea 22% ALT/AST 48% Rash 68% Elevated creatinine 14%	Nausea 15% ALT/AST 17% Edema 55% Hyperlipidemia 70% Cognitive 21%	Nausea 27% (0.7%) ALT/AST 40% (3%) Elevated Creatine (46%)
Dose discontinuation	5% (80% dose interruption)	11-13%	8-13%	9%	7%	NR

NVL-655 and other ALK inhibitors in clinical development

FAK inhibitor defactinib (VS6063), BI 853520, GSK2256098 in clinical development with combination strategies.

Soria JC et al Lancet 2017, Hida T et al Lancet 2017, Peters S. e t al NEJM 2017, Mok T e t al Ann Oncol 2020, Zhou et al Lancet Respir Med. 2019, Camidge DR, et al. J Thorac Oncol, Camidge DR, et al. J Clin Oncol. 2020, Horn L, et al. JAMA Oncol. 2021, Shaw AT, et al. NEJM 2020, Solomon BJ, et al. Lancet Resp Med. 2022, Ou SH et al unpublished data

Iniciativa científica de:

GECP lung cancer research

Intracranial and systemic efficacy of repotrectinib in advanced *ROS1* fusion-positive non-small cell lung cancer and central nervous system metastases in the phase 1/2 TRIDENT-1 trial

9017

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Background

- Oncogenic driver gene fusions involving *ROS1* have been identified in up to 2% of non-small cell lung cancer (NSCLC),[1] and ROS1 tyrosine kinase inhibitor (TKI) therapy is the current standard of care[1,2]; response rates with currently approved therapies (crizotinib and entrectinib) range from 66%–74% but achieving durable benefit remains a challenge[3-5]
- Central nervous system (CNS) metastases have been detected in up to 36% of patients at the time of diagnosis and up to 56% of TKI-pretreated patients[6-8]; CNS was the first and only site of progression in >50% of patients pretreated with crizotinib[9]
- Repotrectinib is a next-generation ROS1 and TRK TKI with a compact macrocyclic structure that is designed to improve durability of benefit by decreasing the potential for developing resistance mutations (TKI-naïve and -pretreated patients) and circumventing known resistance mutations (TKI-pretreated patients), and has favorable CNS drug-like properties for human brain penetration[10]
- Repotrectinib monotherapy is currently under evaluation in the ongoing, global, pivotal phase 1/2 TRIDENT-1 trial (NCT03093116) and the pediatric CARE trial (NCT04094610)[11,12]; preliminary data from both trials have been presented[13-15]
- Here, we report the first efficacy and safety data for repotrectinib in TKI-naïve and TKI-pretreated patients with *ROS1* fusion-positive (*ROS1+*) NSCLC by baseline CNS metastasis status

Methods

- TRIDENT-1 is an ongoing phase 1/2 trial of repotrectinib in patients with *ROS1+* and *NTRK* fusion-positive (*NTRK+*) advanced solid tumors
- Patients with *ROS1+* NSCLC were enrolled in 4 expansion cohorts by treatment history in the phase 2 portion (**Figure 1**) and analyzed by CNS metastases at baseline (**Figure 2**)
- Treated or untreated asymptomatic CNS metastases and/or asymptomatic leptomeningeal carcinomatosis at baseline were permitted if ≥ 14 days have elapsed since whole brain radiation treatment and ≥ 7 days have elapsed since stereotactic radiosurgery prior to starting repotrectinib treatment

Figure 1. Efficacy analysis of the phase 1/2 TRIDENT-1 study design

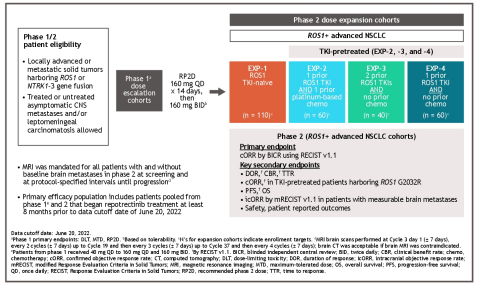
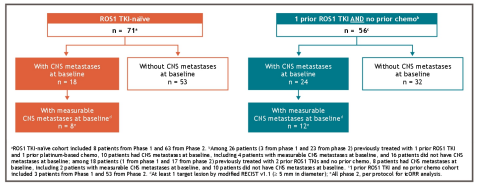


Figure 2. Efficacy analysis population per BICR



Results

Baseline characteristics

- CNS metastases at baseline were present in 18 of 71 patients (25%) in the TKI-naïve cohort and 24 of 56 patients (43%) in the 1 prior ROS1 TKI and no prior chemo cohort; baseline characteristics are shown in **Table 1**
- Baseline characteristics of more heavily pretreated cohorts were generally consistent with the cohorts shown in **Table 1**
  - Of 26 patients in the 1 ROS1 TKI and 1 chemo cohort:
    - Ten (38%) had CNS metastases per BICR; 9 of 10 had received prior crizotinib and 1 received entrectinib
    - Sixteen (62%) did not have CNS metastases per BICR; 12 of 16 had received prior crizotinib, 3 received entrectinib, and 1 received ceritinib
  - Of 18 patients in the 2 ROS1 TKI and no chemo cohort:
    - Eight (44%) had CNS metastases per BICR; all had received prior crizotinib, 6 received lorlatinib and 2 ceritinib
    - Ten (56%) did not have CNS metastases per BICR; all had received prior crizotinib, 5 had received lorlatinib, 3 had received entrectinib, and 1 each had received foretinib and taletrectinib

Table 1. Demographics and baseline characteristics of patients with *ROS1+* advanced NSCLC with or without baseline CNS metastases per BICR

	ROS1 TKI-naïve (n = 71[a])		1 prior ROS1 TKI AND no prior chemo (n = 56[b])	
	With CNS metastases (n = 18)	Without CNS metastases (n = 53)	With CNS metastases (n = 24)	Without CNS metastases (n = 32)
Age				
Median (range), years	56 (31-73)	57 (28-80)	57 (33-75)	57 (37-78)
≥ 65 years, n (%)	3 (17)	16 (30)	5 (21)	10 (31)
Region, n (%)				
US	0	11 (21)	4 (17)	13 (41)
Asia	13 (72)	28 (53)	13 (54)	10 (31)
Other	5 (28)	14 (26)	7 (29)	9 (28)
Female, n (%)	11 (61)	32 (60)	17 (71)	21 (66)
ECOG PS, n (%)				
0	4 (22)	20 (38)	8 (33)	10 (31)
1	14 (78)	33 (62)	16 (67)	22 (69)
Never smoked, n (%)	12 (67)	33 (62)	19 (79)	17 (53)
***ROS1* resistance mutation,[c] n (%)**				
Solvent front (G2032R)	0	0	2 (8)	4 (12)
Gatekeeper	0	0	0	0
Prior TKI treatment, n (%)				
Crizotinib	Not applicable		23 (96)	23 (72)
Entrectinib			1 (4)	8 (25)
Ceritinib			0	1 (3)

[a]8 (phase 1) + 63 (phase 2). [b]2+50. [c]Identified in tumor tissues by local HGS testing or in plasma ctDNA using the GuardantG360 CDx HGS test performed by Guardant Health. CDx, companion diagnostic; ECOG PS, Eastern Cooperative Oncology Group performance status; ctDNA, circulating tumor DNA; HGS, next-generation sequencing.

Efficacy

Confirmed ORR, DOR, and PFS in patients with or without baseline CNS metastases

- At data cutoff, median follow-up was 18.1 months in the TKI-naïve cohort (n = 71) and 15.5 months in the 1 prior TKI and no prior chemo cohort (n = 56)
- In TKI-naïve patients with and without CNS metastases, respectively, cORR was 89% (95% CI, 65-99) and 75% (62-86), with responses ongoing at 12 months in 93% and 84% of responders (**Table 2**)
- cORR, DOR, and PFS results for TKI-pretreated cohorts are shown in **Table 2**

Table 2. Systemic efficacy in patients with *ROS1+* NSCLC with or without baseline CNS metastases per BICR

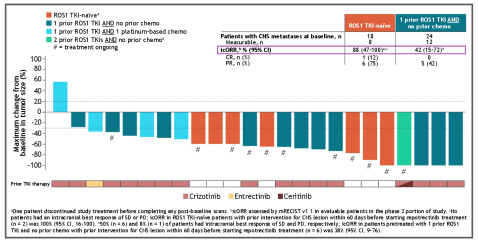
	ROS1 TKI-naïve (n = 71)	1 prior ROS1 TKI AND no prior chemo (n = 56)	1 prior ROS1 TKI AND 1 prior platinum-based chemo (n = 26)	2 prior ROS1 TKIs AND no prior chemo (n = 18)
Median follow-up, months	18.1	15.5	21.3	14.1
Patients with CNS mets,[a] n (%)	18 (25)	24 (43)	10 (38)	8 (44)
cORR,[b] % (95% CI)	89 (65-99)	33 (16-55)	40 (12-74)	12 (0.3-53)
CR, n (%)	1 (6)	0 (0)	0 (0)	1 (12)
PR, n (%)	15 (83)	8 (33)	4 (40)	0 (0)
SD,[c] n (%)	1 (6)	11 (46)	3 (30)	1 (12)
DOR,[b] % (95% CI)				
≥ 6 months	100 (100-100)	62 (29-96)	50 (1-99)	100 (100-100)
≥ 12 months[d]	93 (79-100)	–	–	–
PFS,[b] % (95% CI)				
≥ 6 months	94 (83-100)	57 (35-78)	40 (10-70)	12 (0-35)
≥ 12 months[d]	87 (71-100)	–	–	–
Patients without CNS mets, n (%)	53 (75)	32 (57)	16 (62)	10 (56)
cORR,[b] % (95% CI)	75 (62-86)	41 (24-59)	44 (20-70)	40 (12-74)
CR, n (%)	3 (6)	3 (9)	1 (6)	0 (0)
PR, n (%)	37 (70)	10 (31)	6 (38)	4 (40)
SD,[c] n (%)	10 (19)	14 (44)	5 (31)	2 (20)
DOR,[b] % (95% CI)				
≥ 6 months	87 (77-98)	92 (76-100)	71 (38-100)	50 (1-99)
≥ 12 months[d]	84 (72-96)	–	–	–
PFS,[b] % (95% CI)				
≥ 6 months	90 (81-98)	75 (59-91)	38 (12-63)	30 (2-58)
≥ 12 months[d]	77 (65-89)	–	–	–

[a]Including patients with measurable and non-measurable lesions. [b]By RECIST v1.1. DOR and PFS were calculated by Kaplan-Meier estimates. [c]Not reported for TKI-pretreated cohorts due to small number of patients at risk. CR, complete response; mets, metastases; PR, partial response; SD, stable disease.

Intracranial efficacy

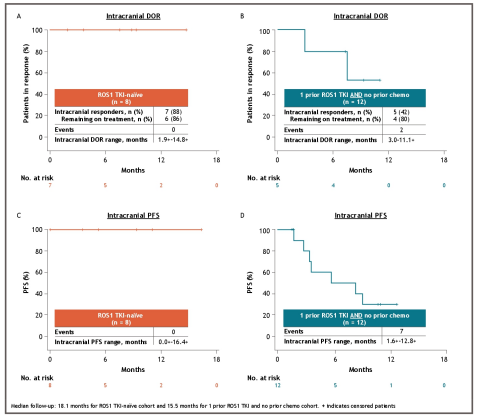
- Seven of 8 TKI-naïve patients with measurable baseline CNS metastases had a response; IcORR was 88% (95% CI, 47-100) and 1 patient was not evaluable (**Figure 3**)
- Among patients pretreated with 1 prior ROS1 TKI and no prior chemo with measurable baseline CNS metastases, IcORR was 42% (95% CI, 15-72); 50% (n = 6) and 8% (n = 1) of patients had intracranial SD and PD, respectively
- Of the 18 patients with CNS metastases at baseline in the pooled cohorts of patients with 1 prior ROS1 TKI and 1 prior chemo or 2 prior ROS1 TKIs and no prior chemo, intracranial responses were observed in 2 of 6 patients with measurable baseline CNS metastases (both were in the 1 prior ROS1 TKI and 1 chemo cohort and had intracranial PR)
- Among patients with intracranial response, 0 of 7 in the TKI-naïve cohort and 2 of 5 in 1 prior ROS1 TKI and no prior chemo cohort had intracranial progression or died; intracranial DOR range was 1.9+ to 14.8+ months and 3.0 to 11.1+ months (**Figure 4A and 4B**)
- Intracranial PFS range was 0.0+ to 16.4+ months (TKI-naïve) and 1.6+ to 12.8+ months (1 prior ROS1 TKI and no prior chemo)
- Results for TKI-naïve and TKI-pretreated patients who developed a first new brain metastasis are shown in **Figure 5**

Figure 3. icORR and reduction in intracranial tumor burden in TKI-naïve and TKI-pretreated patients with *ROS1+* advanced NSCLC and measurable baseline CNS metastases



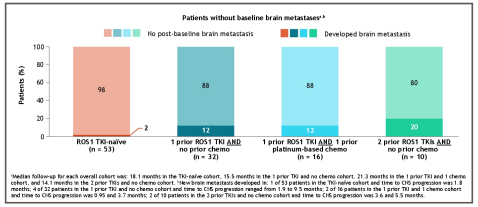
[a]One patient discontinued study treatment before completing any post-baseline scans. [b]IcORR assessed by mRECIST v1.1 in evaluable patients in the phase 2 portion of study. His patients had an intracranial best response of SD or PD; tcORR in ROS1 TKI-naïve patients with prior intervention for CNS lesion within 60 days before starting repotrectinib treatment (n = 2) was 100% (95% CI, 16-100); 50% (n = 6) and 8% (n = 1) of patients had intracranial best response of SD and PD, respectively; tcORR in patients pretreated with 1 prior ROS1 TKI and no prior chemo with prior intervention for CNS lesion within 60 days before starting repotrectinib treatment (n = 6) was 38% (95% CI, 9-76).

Figure 4. Intracranial DOR and intracranial PFS in TKI-naïve (A, C) and TKI-pretreated (B, D) patients with *ROS1+* advanced NSCLC and measurable baseline brain metastases per BICR



Median follow-up: 18.1 months for ROS1 TKI-naïve cohort and 15.5 months for 1 prior ROS1 TKI and no prior chemo cohort. + indicates censored patients

Figure 5. Development of new brain metastasis in TKI-naïve and TKI-pretreated patients without baseline brain metastases per BICR



[a]Median follow-up for each overall cohort was: 18.1 months in the TKI-naïve cohort, 15.5 months in the 1 prior TKI and no chemo cohort, 21.3 months in the 1 prior TKI and 1 chemo cohort, and 14.1 months in the 2 prior TKIs and no chemo cohort. [b]New-brain metastasis developed in: 1 of 53 patients in the TKI-naïve cohort and time to CNS progression was 1.8 months; 4 of 32 patients in the 1 prior TKI and no chemo cohort and time to CNS progression ranged from 1.9 to 9.5 months; 2 of 16 patients in the 1 prior TKI and 1 chemo cohort and time to CNS progression was 5.95 and 7.7 months; 2 of 10 patients in the 2 prior TKIs and no chemo cohort and time to CNS progression was 2.6 and 5.5 months.

Safety summary

- Safety, including the rate of nervous system adverse events (AEs), was generally consistent in patients with *ROS1+* NSCLC with or without CNS metastases (**Table 3** and **4**)
- Dizziness was observed in 57% and 63% of patients with or without baseline CNS metastases, respectively (mostly grade 1-2), and did not lead to treatment discontinuation (**Table 4**)

Table 3. Safety summary in patients with *ROS1+* NSCLC with or without baseline CNS metastases per investigator assessment[a]

	With baseline CNS metastases (n = 118)		Without baseline CNS metastases (n = 178)	
AE, n (%)	**TEAEs**	**TRAEs**	**TEAEs**	**TRAEs**
Any AEs	116 (98)	109 (92)	178 (100)	169 (95)
Any grade ≥ 3 AEs	52 (44)	27 (23)	96 (54)	41 (23)
Serious AEs	31 (26)	6 (5)	74 (42)	11 (6)
AEs leading to dose reduction	38 (32)	34 (29)	62 (35)	54 (30)
AEs leading to drug interruption	48 (41)	32 (27)	92 (52)	61 (34)
AEs leading to treatment discontinuation	8 (7)	3(3)	18 (10)	9 (5)
AEs leading to death	7 (6)	0	8 (4)	0

[a]Safety analysis population includes all patients with *ROS1+* NSCLC in phase 1 and phase 2 who received at least 1 dose of repotrectinib. TEAE, treatment-emergent AE; TRAE, treatment-related AE.

Table 4. Nervous system AEs in patients with *ROS1+* NSCLC with or without baseline CNS metastases per investigator assessment[a]

	With baseline CNS metastases (n = 118)			Without baseline CNS metastases (n = 178)		
TEAEs in ≥10% of patients in either group, n (%)	**All grades**	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
Nervous system disorders	103 (87)	12 (10)	2 (2)	160 (90)	15 (8)	0
Dizziness[a]	67 (57)	3 (3)	0	112 (63)	2 (1)	0
Dysgeusia	49 (42)	0	0	94 (53)	0	0
Paraesthesia	38 (32)	0	0	61 (34)	2 (1)	0
Headache	32 (27)	1 (1)	0	21 (12)	0	0
Ataxia	20 (17)	0	0	39 (22)	0	0
Memory impairment	16 (14)	0	0	18 (10)	1 (1)	0

[a]Safety analysis population includes all patients with *ROS1+* NSCLC in phase 1 and phase 2 who received at least 1 dose of repotrectinib. [a]Among the 296 patients with or without baseline CNS metastases who received at least 1 dose of repotrectinib, 84% of eligible patients (n = 264) were titrated up to 160 mg BID. treatment-emergent dizziness (including dizziness, vertigo, dizziness postural, dizziness exertional, and vertigo positional) was reported in 63% of patients; grade 3 treatment-emergent dizziness was reported in 2% of patients. The median time to onset of any-grade treatment-emergent dizziness was 7.0 days (range, 1.0-504.0). Dose reduction was required in 10% of patients and 6% required dose interruption of repotrectinib due to treatment-emergent dizziness. No patients discontinued repotrectinib due to dizziness.

Conclusions

- In the global, pivotal phase 1/2 TRIDENT-1 trial, repotrectinib, a next-generation ROS1 and TRK inhibitor, demonstrated durable clinical activity in both ROS1 TKI-naïve and TKI-pretreated patients with *ROS1+* advanced NSCLC with or without baseline CNS metastases
- Systemic efficacy with repotrectinib was seen in both ROS1 TKI-naïve and TKI-pretreated patients with baseline CNS metastases per BICR
  - ROS1 TKI-naïve: cORR, 89% (95% CI, 65-99); estimated 12-month systemic DOR, 93% (95% CI, 79-100)
  - One ROS1 TKI and no prior chemo: cORR, 33% (95% CI, 16-55); estimated 6-month systemic DOR, 62% (95% CI, 29-96)
- Across both TKI-naïve and TKI-pretreated cohorts, in patients with measurable CNS metastases at baseline, intracranial response was durable, with deep reductions in intracranial tumor volume
- Repotrectinib safety profile (including nervous system AEs) was similar in patients with *ROS1+* NSCLC with or without CNS metastases; dizziness was observed in 57% and 63% of patients with or without CNS metastases, respectively (mostly grade 1-2), and did not lead to treatment discontinuation
- Data presented here from the ongoing TRIDENT-1 trial are the first analysis of outcomes on repotrectinib in patients with *ROS1+* NSCLC with or without baseline CNS metastases and suggest that repotrectinib could represent a potential new treatment option for patients with *ROS1+* advanced NSCLC, including those with CNS metastases

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EFICACIA INTRACRANEAL EN CONTEXTO (NAIVE)

Iniciativa científica de: GECP lung cancer research

ROS1 TKIs in TKI naïve patients

ROS1 TKI	Study	Transporter effect	K_{puu} brain: plasma	Overall outcomes ORR (n)	mDOR	mPFS	intracranial ORR	intracranial PFS
ROS1 TKI naive								
Crizotinib	METROS	P-gp	-	65% (17/26)	21.4m	22.8m	33% (2/6)	-
Ceritinib	Lim et al	Pgp/ BRCP	-	67% (20/30)	21.0m	19.3m	29% (2/7)	-
Entrectinib	Drilon et al	-	-	77% (41/53)	24.6m	19.0m	55% (11/20)	7.7m
	Drilon et al			68% (114/168)	20.5m	15.7m	80% (20/25)	8.8m
Lorlatinib	Shaw et al	No Pgp	0.11	62% (13/21)	25.3m	21.0m	64% (7/11)	
Repotrectinib	Lin et al	P-gp	-	89% (16/18)	93% at12m	87%at12m	88% (7/8)	100% at 12m
Taletrectinib	Li et al	-	-	92.8% (62/67)	87% at12m	33.2m	91.7% (11/12)*	-
NVL-520	Cho et al	-	0.15	78.9% (56/71)	86% at 12m	80% at 12m	87.5%(7/8)	-

* Combined TKI naïve and pretreated

EFICACIA INTRACRANEAL EN CONTEXTO (PRETREATED)

Iniciativa científica de: GECP lung cancer research

ROS1 TKIs in TKI-Pretreated patients

	Study	Overall outcomes			IC ORR	IC PFS
		ORR (n)	mDOR	mPFS		
ROS1 TKI pre-treated						
Lorlatinib	Shaw et al	Prior crizotinib 35% (14/40) ≥2 prior TKI; 0% (0/6)	Prior crizotinib:13.8m; ≥2 prior TKI;-	Prior crizotinib:8.5m; ≥2 prior TKI; -	Prior crizotinib:50% (12/24); ≥2 prior TKI; 66% (2/3)	-
Repotrectinib	Lin et al	43% (8/24)	60% at 6m	57% at 6m	42% (5/12)	30% at 12m
Taletrectinib	Li W et al	52.6% (20/38)	56.9% at 12m	11.8m	91.7% (11/12)*	-
NVL-520	Cho et al	37.5% (21/56)	80% at 6m	67% at 6m	41.7%(5/12)	-

* Combined TKI naïve and pretreated

Abstract 9018

Efficacy and safety of encorafenib plus binimetinib in patients with *BRAF* V600E-mutant (*BRAF*^{V600E}) metastatic non-small cell lung cancer (NSCLC) from the phase 2 PHAROS study

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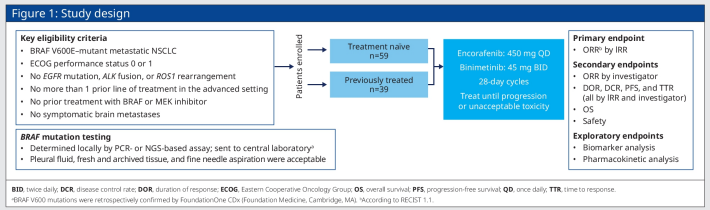
Background

- The combination of encorafenib (BRAF inhibitor) plus binimetinib (mitogen-activated protein kinase kinase [MEK] inhibitor) has demonstrated clinical efficacy with an acceptable safety profile in patients with BRAF V600E/K–mutant metastatic melanoma[1,2]
- In 2017, dabrafenib plus trametinib was approved by the US Food and Drug Administration (FDA) for patients with BRAF V600E–mutant metastatic NSCLC and is a current standard of care[3,4]
  - This approval was based on the results of a single-arm, phase 2 study that showed meaningful antitumor activity and a manageable safety profile[5,6]
    - The ORR by IRR was 64% in treatment-naïve patients and 63% in previously treated patients
    - The median DOR by IRR was 15.2 months in treatment-naïve patients and 9.0 months in previously treated patients
- Given the observed efficacy and safety profile of encorafenib plus binimetinib in patients with BRAF V600E/K–mutant metastatic melanoma, this combination therapy was assessed in patients with BRAF V600E–mutant metastatic NSCLC

Methods

- PHAROS (NCT03915951) is an ongoing, single-arm, open-label, multicenter, phase 2 trial evaluating the efficacy and safety of encorafenib plus binimetinib in treatment-naive and previously treated patients with BRAF V600E–mutant metastatic NSCLC (**Figure 1**)
- Tumor samples were required to have V600 class 1 *BRAF* mutations by next-generation sequencing (NGS)– or polymerase chain reaction (PCR)–based local testing before patients were enrolled
- The primary endpoint was confirmed ORR, assessed by IRR according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)

Figure 1: Study design



BID, twice daily; **DCR**, disease control rate; **DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **OS**, overall survival; **PFS**, progression-free survival; **QD**, once daily; **TTR**, time to response.
[a]*BRAF* V600 mutations were retrospectively confirmed by FoundationOne CDx (Foundation Medicine, Cambridge, MA). [b]According to RECIST 1.1.

Results

- Between June 4, 2019, and June 2, 2022, 98 patients were enrolled and treated with encorafenib plus binimetinib
  - Of these, 59 patients were treatment naïve, and 39 were previously treated
- Baseline characteristics are shown in **Table 1**
- The median duration of treatment was 9.2 months (range, 0-35.1 months) with encorafenib and 8.4 months (range, 0-35.1 months) with binimetinib
- At the data cutoff of September 22, 2022, treatment was ongoing in 25 treatment-naïve patients (42%) and 8 previously treated patients (21%)

Table 1: Patient characteristics

	Treatment naïve n=59	Previously treated n=39	Overall N=98
Age, median (range), years	68 (47-83)	71 (53-86)	70 (47-86)
Sex, n (%)			
Women	33 (56)	19 (49)	52 (53)
Men	26 (44)	20 (51)	46 (47)
Race, n (%)			
White	53 (90)	33 (85)	86 (88)
Asian	3 (5)	4 (10)	7 (7)
Black	1 (2)	2 (5)	3 (3)
Other	2 (3)	0	2 (2)
ECOG performance status, n (%)			
0	19 (32)	7 (18)	26 (27)
1	40 (68)	32 (82)	72 (73)
Smoking status, n (%)			
Current	8 (14)	5 (13)	13 (13)
Former	33 (56)	23 (59)	56 (57)
Never	18 (31)	11 (28)	29 (30)
BRAF V600 status, n (%)			
V600E	59 (100)	39 (100)	98 (100)
V600D[a]	0	1 (3)	1 (1)

[a]Cumulation with V600E.

Antitumor activity

- The ORR per IRR was 75% (95% CI, 62%, 85%) in treatment-naïve patients and 46% (95% CI, 30%, 63%) in previously treated patients (**Table 2**)

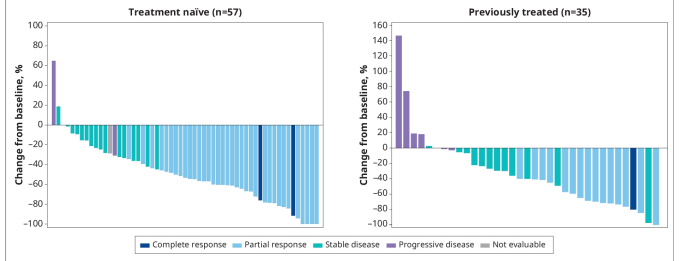
Table 2: Efficacy endpoints by IRR

	Treatment naïve n=59	Previously treated n=39
Objective response rate, n/N (%)[a] (95% CI), %	44/59 (75) (62, 85)	18/39 (46) (30, 63)
Complete response	9 (15)	4 (10)
Partial response	35 (59)	14 (36)
Stable disease	10 (17)	13 (33)
Progressive disease	2 (3)	3 (8)
Disease control rate at 24 weeks (95% CI), %	64 (51, 76)	41 (26, 58)
Duration of response, median (95% CI), months	NE (23.1, NE)	16.7 (7.4, NE)
Duration of response ≥12 months, n/N (%)	26/44 (59)	6/18 (33)
Time to response, median (range), months	1.9 (1.1-19.1)	1.7 (1.2-7.3)

[a]Response of 3 patients were not evaluable in the treatment-naïve group, and 5 were not evaluable in the previously treated group.

- Investigator-assessed ORR was 63% in treatment-naïve patients and 41% in previously treated patients (**Figure 2**)

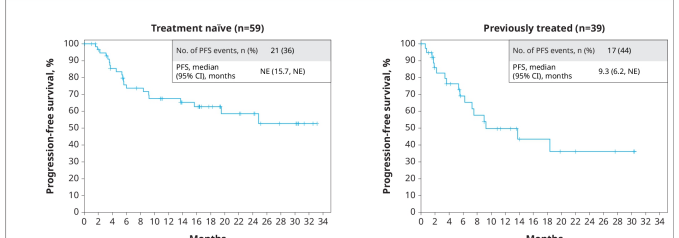
Figure 2: Change from baseline in the sum of diameters of target lesions by investigator assessment[a]



[a]Patients for whom an assessment response was not evaluable at all tumor assessments were not included in this analysis.

- The median duration of follow-up for PFS by IRR was 18.2 months (95% CI, 16.4, 22.3 months) in treatment-naïve patients and 12.8 months (95% CI, 9.0, 19.8 months) in previously treated patients
- Median PFS by IRR was NE (95% CI, 15.7 months, NE) in the treatment-naïve group and 9.3 months (95% CI, 6.2 months, NE) in the previously treated group (**Figure 3**)
- OS was immature at the time of data cutoff; the median OS was NE in both patient groups

Figure 3: Progression-free survival by IRR



Safety

- Treatment-related adverse events (TRAEs) of any grade, grade 3, and grade 4 occurred in 92 (94%), 37 (38%), and 3 (3%) of 98 patients, respectively (**Table 3**)
- TRAEs led to permanent discontinuation of both encorafenib and binimetinib in 15 of 98 patients (15%)
  - The most frequent TRAEs that led to permanent discontinuation were diarrhea, nausea, and vomiting (2 patients each)

Table 3: Incidence of TRAEs of any grade >10% in all patients

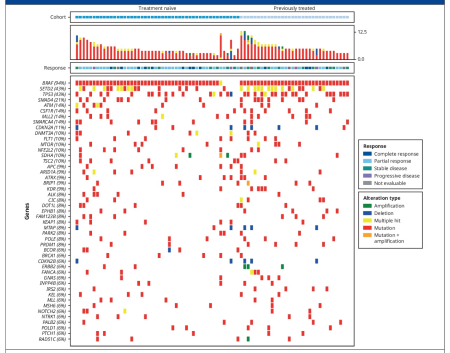
	Overall (N=98)		
	Any grade	Grade 3	Grade 4
Any TRAEs, n (%)[a]	92 (94)	37 (38)	3 (3)[b]
Nausea	49 (50)	3 (3)	0
Diarrhea	42 (43)	4 (4)	0
Fatigue	31 (32)	2 (2)	0
Vomiting	28 (29)	1 (1)	0
Anemia	18 (18)	3 (3)	0
Vision blurred	17 (17)	1 (1)	0
Constipation	13 (13)	0	0
ALT increased	12 (12)	5 (5)	0
AST increased	12 (12)	7 (7)	0
Pruritus	12 (12)	0	0
Blood creatine phosphokinase increased	11 (11)	0	0
Edema peripheral	11 (11)	0	0

Note: Any-grade abdominal pain, alopecia, asthenia, and dry skin occurred in 10 (10%) patients; any-grade pyrexia occurred in 8 (8%) patients. **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase.
[a]One patient died due to intracranial hemorrhage, which was assessed as treatment related by the investigator. [b]Grade 4 TRAEs were colitis, disseminated intravascular coagulation, increased γ-glutamyl transferase, and hyponatremia. One patient can have multiple TRAEs.

Biomarker analyses

- All available baseline tumor biopsy samples were submitted for analysis; data from NGS analysis were obtained from 48 treatment-naïve and 32 previously treated samples
- The most frequent genomic alterations identified at baseline, in addition to *BRAF*, were *SETD2* and *TP53* (43% each), *SMAD4* (21%), *ATM*, *MLL2*, *CSF1R*, *SMARCA4* (14% each), and *CDKN2A* (11%) (**Figure 4**)
- None of these alterations were associated with outcome after false discovery correction (corrected p-value <0.05)

Figure 4: Tumor molecular alterations in baseline biopsy samples[a]



[a]The most frequently altered genes (altered in 5 or more cases) are shown.

Conclusions

- The combination of encorafenib plus binimetinib showed a meaningful clinical benefit with an acceptable safety profile in patients with BRAF V600E–mutant metastatic NSCLC in the phase 2 PHAROS study
  - Efficacy benefit was observed in both treatment-naïve and previously treated patients
    - Objective response rate (ORR) by independent radiology review (IRR) was 75% in treatment-naïve patients and 46% in previously treated patients
    - Median duration of response (DOR) by IRR was not estimable (NE) in treatment-naïve patients and 16.7 months in previously treated patients
  - The safety profile was consistent with that observed in the approved indication in melanoma
- Encorafenib plus binimetinib represents a potential new treatment option for patients with BRAF V600E–mutant metastatic NSCLC

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Presented at the 2023 ASCO Annual Meeting, June 2-6, 2023; Chicago, IL, and Online

Iniciativa científica de:

GECP lung cancer research

EFICACIA EN CONTEXTO

Iniciativa científica de: GECP lung cancer research

Dabrafenib plus Trametinib *vs* Encorafenib plus Binimetinib in *BRAF* ^{V600E} NSCLC : Efficacy

	Dabrafenib/trametinib		Encorafenib/binimetinib	
Study	Single arm phase II		Single arm phase II	
Pts	Treatment naive	Previously treated	Treatment naive	Previously treated
No of Pts	36	57	59	39
Med age	67	64	68	71
Never smoker	28%	28%	31%	28%
Evaluation	Investigator-assess	Investigator-assess	BICR	BICR
Median follow-up	5 yrs	5 yrs	18.2m	12.8m
ORR	64%	68%	75%	46%
DOR	10.2m	9.8m	NE	16.7m
mPFS	10.8m	10.2m	NE	9.3m
OS	17.3m	18.2m	NA	NA

Iniciativa científica de:

GECP lung cancer research

Abstract #9019

LIBELULE: a randomized phase III study to evaluate the clinical relevance of early liquid biopsy in patients with suspicious metastatic lung cancer

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OBJECTIVES

First "real-life" randomized study to evaluate the feasibility and clinical relevance of early liquid biopsy (LB) to shorten Time to Treatment Initiation (TTI), in frontline setting of advanced lung cancer

CONCLUSIONS

- **Early LB significantly reduces the time to initiation of an appropriate 1st-line therapy in patients eligible for systemic treatment, especially for those with actionable alterations indicating targeted 1st-line therapy**
- **Early LB significantly reduces the time to a contributive molecular analysis by an average of 8 days**
- **Performing a liquid biopsy as early as possible for suspected advanced lung cancer helps to obtain a genomic profile and accelerates the initiation of appropriate treatment**
- **Further analyses will include progression-free survival, quality of life analyses, cost-effectiveness and budget impact analyses**

Clinical trial information: Supported by a PHRC-K 2018, NCT03721120

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BACKGROUND

Genomic testing is a major component of the therapeutic decision in 1st-line treatment of advanced NSCLC. Timeliness of biomarker testing is essential to minimize the time to treatment initiation (TTI) or avoid inappropriate treatment. We hypothesized that early liquid biopsy (LB)-based molecular testing performed at the patient's first visit could reduce this TTI.

METHODS

LIBELULE is a multicenter, randomized, comparative, open-label study, enrolling pts with radiological suspicion of stage IV lung cancer, and no prior biopsy or cytology for advanced NSCLC diagnosis.

DESIGN (Figure 1)

- **Arm A (experimental arm): LB performed at the 1st visit. We identified 3 situations:**
  - ✓ *Category 1 alterations* with targeted therapies available in 1st line (*EGFR*-, *BRAF* V600E mutation, *ALK*- or *ROS1*-rearrangement) identified on LB → LB results only were sufficient to initiate targeted treatment
  - ✓ *Category 2 alterations* without targeted therapies available in 1st line (*ERBB2*, *MET* exon 14, *KRAS*, *BRAF* non V600 and/or *LKB1* mutation, *RET*- or *NTRK*-rearrangement) identified on LB → LB **and** pathological report (including PD-L1) were mandatory to initiate treatment
  - ✓ *Other or no molecular alterations* detected on LB → LB **and** pathological report **and** molecular report on tissue were mandatory to initiate treatment
- **Arm B (control arm): histological sampling was planned with genomic analysis when indicated (local LB allowed)**

LB: InVisionFirst®-Lung assay is an amplicon-based NGS panel covering 37-NSCLC associated genes, including SNVs, CNVs, indels and fusions (Figure 2.).

Figure 2.

SAMPLE SIZE

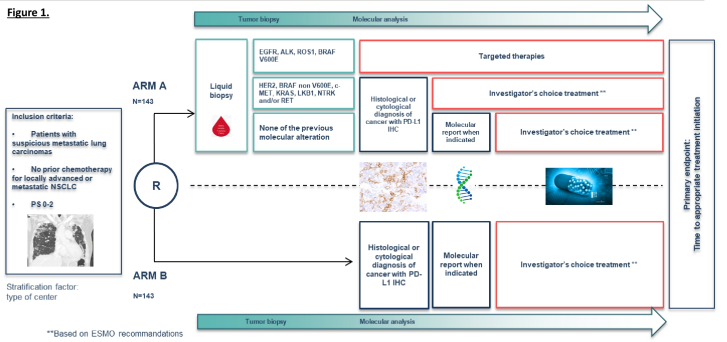
Based on a French retrospective study on ~250 advanced NSCLC patients, the mean TTI was 42 days (associated standard deviation: 22.5 days)[1].

The expected decrease of the mean TTI in the experimental group is based on the following hypotheses:

- a 21 days diminution in the category 1 alterations (expected to represent 13% of the population[2])
- a 17 days diminution in the category 2 (expected to represent 36% of the population[2])

It results in a mean TTI in the experimental group of 33 days (21% reduction of TTI). The sample size calculation is based on a non-parametric 2-sided Wilcoxon Mann and Whitney test. Assuming a type I error alpha of 5% and 90% power, 286 patients are needed to reject the null hypothesis H0: the TTI distributions are not different experimental and control groups.

Figure 1.



ENDPOINTS

- **The primary endpoint** was the time from randomization to initiation of appropriate treatment based on informative genomic and pathological results.
- Secondary endpoints were time to availability of informative molecular pathology results, rate of treatment initiated before obtaining molecular results, progression-free survival, safety of diagnosis procedures, quality of life, anxiety and depression level, the concordance between the molecular status on tissue and liquid biopsies, the rebiopsy avoidance rate for molecular status determination with the use of liquid biopsy, cost-effectiveness and budget impact analyses.

RESULTS

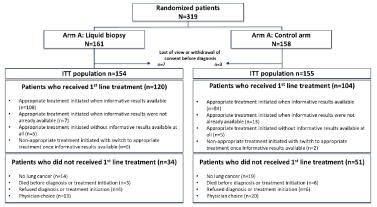
- 319 pts were randomized between Arm A (n=161) and B (n=158): median age was 68 years (39-97), 56.1% were male, 28.5% were non-smokers, 18.1% were PS≥2. Histologies were distributed as follow: adenocarcinoma (56.7%), squamous cell carcinoma (11%), SCLC (10%), other tumor types (5%). 5.3% of patients were found to be cancer-free at the end of the workup.

Baseline patients' characteristics

		Arm A Liquid Biopsy N=161	Arm B Control N=158
Median age, years (range)		68 (39-97)	68 (43-94)
Sex female, n(%)		65 (40.4%)	75 (47.5%)
Smoking history			
	Never	49(30.4%)	42 (26.6%)
	Current	40 (24.8%)	40 (25.3%)
	Former	72 (44.7%)	76 (48.1%)
Histology, N (%)			
SCLC		14 (8.7%)	18 (11.4%)
NSCLC		121 (75.2%)	113 (71.5%)
	Adenocarcinoma	94 (58.4%)	87 (55.1%)
	Squamous	18 (11.7%)	17 (10.8%)
	Other	9 (5.6%)	9 (5.7%)
No lung cancer		14 (8.7%)	19 (12%)
No cancer		9 (5.6%)	8 (5.1%)
No diagnosis obtained		12 (7.5%)	8 (5.1%)
PS			
	0	46 (28.6%)	50 (31.6%)
	1	84 (52.2%)	78 (49.4%)
	≥2	29 (18%)	28 (17.7%)
	Missing	2 (1.2%)	2 (1.3%)

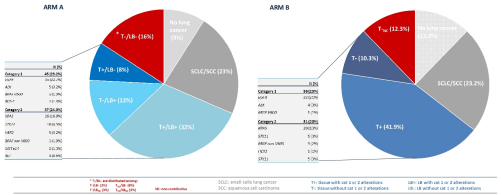
Treatment initiation in each arm

- Systemic treatment was initiated in 74.5% and 65.8% of patients in Arm A and B, respectively. Main reasons for not initiating treatment were diagnosis other than cancer, local treatment and palliative care.



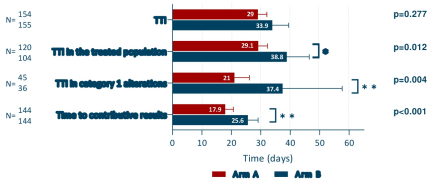
Patients' molecular profile

- In Arm A, 81% of patients had ctDNA findings.
- ✓ **Turn-around time for LB analysis was 6 days** (9 days including shipment to the US).
- ✓ Category 1 and category 2 alterations were identified on tissue and/or LB in 29.2% and 24%, respectively. *EGFR* mutations were found in 21.7% of patients.
- In Arm B, 23.2% of patients had category 1 and 20% had category 2 alterations detected. *EGFR* mutations were found in 20.3% of patients.

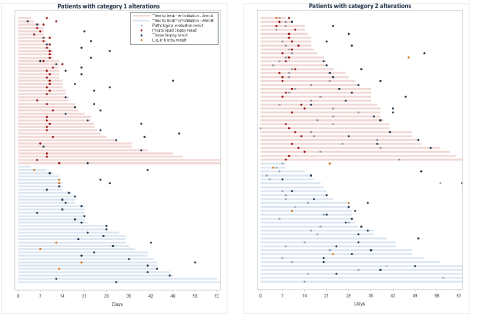


Time to treatment initiation

- If no systemic lung therapy was initiated, TTI used the physician decision (surveillance, local therapy), death or patient refusal date.
- The mean TTI was 29.0 days (95%CI 25.9-32.1) in Arm A versus 33.9 days (95%CI 28.4-39.5) in Arm B in the intention-to-treat population.
- The mean TTI was **9.7 days shorter** in Arm A for **patients who received systemic treatment.**
- It was also **16.4 days shorter in patients with category 1 alterations**.
- **The time to contributive genomic analysis was also reduced by 7.7 days**.



Representation of time to contributive genomic profile in patients with category 1 and 2 alterations



- In Arm A,
  - ✓ In patients with category 1 alterations (left graph), treatment could have theoretically been initiated at the time of liquid biopsy report reception (red dots). As shown by the red bars and blue dots, some physicians tend to wait for the molecular report on tissue to initiate treatment, which tends to increase the TTI.
  - ✓ In patients with category 2 alterations (right graph), pathological results (grey stars) were obtained 4.9 days (-9.0-36.0) after liquid biopsy results (red dots), which could allow to initiate faster an appropriate treatment based on informative results.
- In both arms, **mean time between informative results and treatment initiation was 12.9 days** (0-346) similar between category 1 (14 days (0-346)) and 2 (12.4 days (0-61)) alterations patients'. 29,1% of patients initiated treatment ≥15 days following reception of informative results including 10.8% in more than 30 days.
- In Arm A, **7.4% of patients versus 13.3% in Arm B initiated a treatment without genomic analysis available**.

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[2]**Barlesi F, Mazieres J, Merlio JP, Debieuvre D, Mosser J, Lena H, et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). The Lancet. avr 2016;387(10026):1415-26.**

Tepotinib + osimertinib for *EGFR* mutant (*EGFR*m) NSCLC with *MET* amplification (*MET*amp) after first-line (1L) osimertinib

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CONCLUSIONS

- **Tepotinib + osimertinib was highly active in patients with *EGFR*m NSCLC with acquired resistance to 1L osimertinib and *MET*amp**
- **The combination treatment was well tolerated with no new safety signals observed**
- **Tepotinib + osimertinib provides a potential chemotherapy-sparing oral targeted therapy option in this population with a high unmet need, regardless of the method used for detecting *MET*amp**

INTRODUCTION

- *MET*amp is a common resistance mechanism in patients with *EGFR*m NSCLC following treatment with 1L osimertinib[1]
- Clinical studies suggest that tepotinib, an oral, once daily, highly selective MET inhibitor, when combined with EGFR TKIs in *EGFR*m *MET*amp NSCLC may be an effective treatment following osimertinib resistance[2–4]
- Here we report new interim data from the INSIGHT 2 study evaluating the efficacy and safety of tepotinib + osimertinib in patients with *EGFR*m NSCLC harboring *MET*amp and resistance to 1L osimertinib with ≥3 months' follow-up by September 26, 2022 (data cut-off)

METHODS

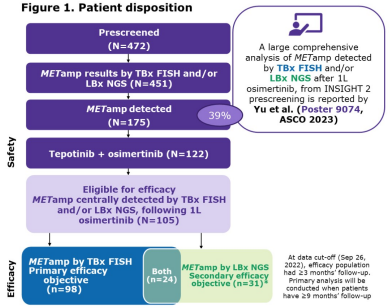
- Enrolled patients received tepotinib 500 mg (450 mg active moiety) + osimertinib 80 mg once daily (**Supplementary Figure 1**)
- *MET*amp was detected centrally by **TBx FISH** (*MET* GCN ≥5 and/or *MET*/*CEP7* ≥2) and/or by **LBx NGS** (*MET* GCN ≥2.3; Archer®)
- The primary endpoint was objective response by IRC for patients with centrally detected *MET*amp by **TBx FISH**, treated with tepotinib + osimertinib
- Secondary endpoints included objective response for patients with *MET*amp detected by **LBx NGS**, DOR, PFS, OS, and safety

RESULTS

Patients

- Efficacy data are reported for patients with ≥3 months' follow-up, and safety data for all patients who received at least one dose of tepotinib + osimertinib
- *MET*amp is commonly detected by NGS or by FISH, but FISH has been shown to be the most sensitive diagnostic tool of the two[4]

Figure 1. Patient disposition



A large comprehensive analysis of *MET*amp detected by **TBx FISH** and/or **LBx NGS** after 1L osimertinib, from INSIGHT 2 prescreening is reported by **Yu et al. (Poster 9074, ASCO 2023)**

At data cut-off (Sep 26, 2022), efficacy population had ≥3 months' follow-up. Primary analysis will be conducted when patients have ≥9 months' follow-up

[a]Seven patients had *MET*amp detected by central LBx NGS only ('TBx FISH was not evaluable in five patients; TBx FISH was negative in two patients).

Table 1. Demographics and characteristics of patients receiving tepotinib + osimertinib

Baseline characteristics		Tepotinib + osimertinib (N=122)
Median age, years (range)		61 (20–84)
Sex, n (%)	Female	73 (59.8)
	Male	49 (40.2)
Race, n (%)	Asian	73 (59.8)
	White	43 (35.2)
	Others/Not collected	6 (4.9)
Smoking status, n (%)	Never	83 (68.0)
	Former/Current	39 (32.0)
ECOG PS, n (%)	0	34 (27.9)
	1	88 (72.1)
Brain metastases by IRC, n (%)	Yes	21 (17.2)
***EGFR* mutation, n (%)**	Del19	72 (59.0)
	L858R	44 (36.1)
	Other exon 21 mut.	5 (4.1)
	Other	1 (0.8)
Mean SOLD, mm ± SD		72.1 ± 43.8
Time on 1L osimertinib*, n (%)	<12 months	35 (28.7)
	≥12 months	79 (64.8)

*Eight patients did not receive 1L osimertinib.

RESULTS

Efficacy

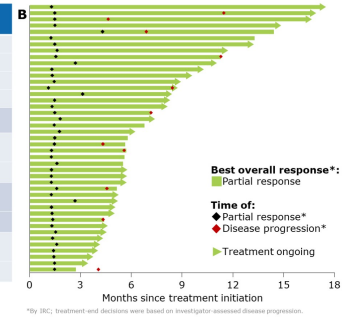
- Of 98 patients with **TBx FISH⁺** *MET*amp (primary analyses set), median *MET* GCN was 11 (range 5.0–50.6) and baseline tumor load (mean SOLD ± SD) was 73.2 ± 47.1 mm
- BOR was PR in 43 patients, for an ORR of 43.9% (95% CI: 33.9, 54.3); as the data matures, six additional PRs have been confirmed. Treatment was still ongoing in 42 patients

Figure 2. Efficacy outcomes in patients with *MET*amp detected centrally by TBx FISH receiving tepotinib + osimertinib (primary analysis set). A. Summary, **B.** Time on treatment in patients with objective response, **C.** Tumor shrinkage, **D.** DOR, and **E.** PFS.

A

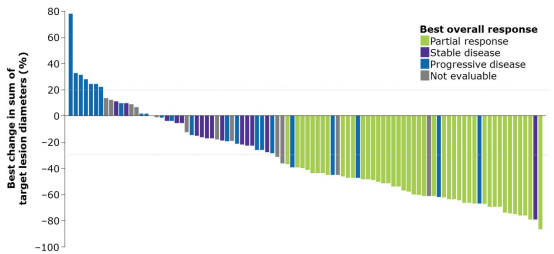
		TBx FISH⁺ (n=98)
BOR, n (%)	PR	43 (43.9)
	SD	15 (15.3)
	PD	23 (23.5)
	NE	17 (17.3)
ORR	% (95% CI)	**43.9** (33.9, 54.3)
DOR	Median, months (95% CI)	**9.7** (5.6, ne)
	Events, n (%)	11 (25.6)
PFS	Median, months (95% CI)	**5.4** (4.2, 7.1)
	Events, n (%)	51 (52.0)
OS	Median, months (95% CI)	**ne** (11.1, ne)
	Events, n (%)	23 (23.5)

B



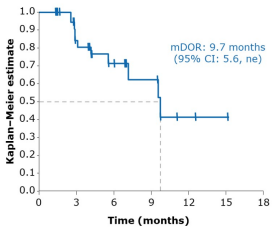
*By IRC; treatment-end decisions were based on investigator-assessed disease progression.

C

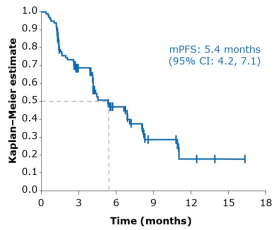


*Four patients were excluded due to baseline/post-baseline measurement not being available.

D



E



*Only patients with a response (n=43) were included in Kaplan–Meier analyses.

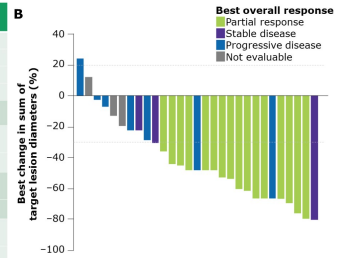
- Of 31 patients with **LBx NGS⁺** *MET*amp, including 24 who were also **TBx FISH⁺**, median *MET* GCN was 16.4 (range 2.1–45.3) and mean SOLD ± SD was 93.9 ± 51.4 mm

Figure 3. Efficacy outcomes in patients with *MET*amp detected centrally by LBx NGS receiving tepotinib + osimertinib. A. Summary and **B.** Tumor shrinkage.

A

		LBx NGS⁺ (n=31)
BOR, n (%)	PR	16 (51.6)
	SD	3 (9.7)
	PD	7 (22.6)
	NE	5 (16.1)
ORR	% (95% CI)	**51.6** (33.1, 69.8)
DOR	Median, months (95% CI)	**5.6** (2.9, ne)
	Events, n (%)	7 (43.8)
PFS	Median, months (95% CI)	**4.6** (2.7, 6.9)
	Events, n (%)	19 (61.3)
OS	Median, months (95% CI)	ne (6.8, ne)
	Events, n (%)	9 (29.0)

B



*Two patients were excluded due to baseline/post-baseline measurement not being available.

Safety

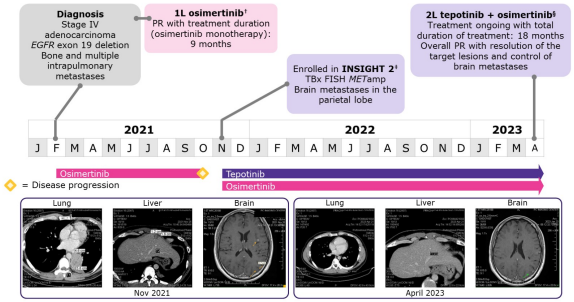
- Tepotinib + osimertinib was well tolerated
- Treatment-related adverse events led to dose reduction in 21 (17.2%) patients
  - Tepotinib dose was reduced in 19 patients
  - Osimertinib dose was reduced in four patients
- Seven patients (5.7%) discontinued treatment due to treatment-related adverse events

Table 2. Most common TRAEs in patients treated with tepotinib + osimertinib

TRAEs, n (%)	Tepotinib + osimertinib (N=122)	
Any grade	99 (81.1)	
Grade ≥3	34 (27.9)	
Leading to dose reduction	21 (17.2)	
Leading to treatment discontinuation	7 (5.7)	
Leading to death	2 (1.6)*	
TRAEs in >15% of patients, n (%)	**All grades**	**Grade ≥3**
Diarrhea	57 (46.7)	0
Peripheral edema	42 (34.4)	5 (4.1)
Paronychia	25 (20.5)	1 (0.8)
Decreased appetite	22 (18.0)	4 (3.3)
Nausea	20 (16.4)	2 (1.6)

*Two patients had AEs leading to death that were considered potentially related to either trial drug by the investigator (pneumonia/pneumonitis and dyspnea/pneumonitis).

Case study: Control of brain metastases in a 33-year-old* Asian male with a durable response to tepotinib + osimertinib



Courtesy of Pongwut Danchaivijitr. *Age at INSIGHT 2 study entry. †Osimertinib 80 mg QD. ‡RANO-BM analysis planned at the time of the primary analysis. §Tepotinib 500 mg QD plus osimertinib 80 mg QD.

Abbreviations: 1L, first line; AE, adverse event; BOR, best overall response; CEP7, centromere 7; CI, confidence interval; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FISH, fluorescent in situ hybridization; GCN, gene copy number; IRC, independent review committee; LBx, liquid biopsy; MET, mesenchymal–epithelial transition factor; *MET*amp, *MET* amplification; ne, not evaluable; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; SD, stable disease; SD, standard deviation; SOLD, sum of longest diameters of target lesion; TBx, tissue biopsy; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event.

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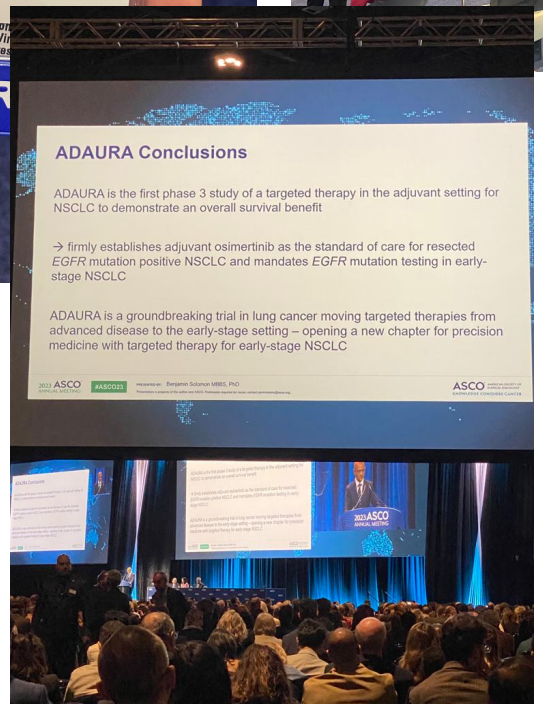

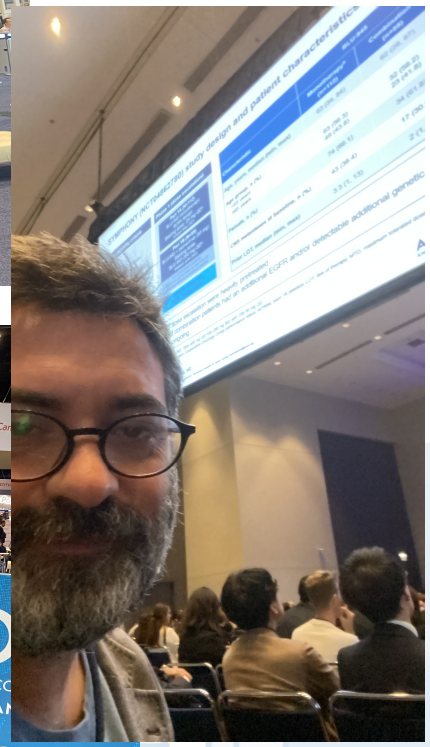

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Novedades en terapia dirigida para CPNM con enfermedad avanzada (excepto KRAS)

DR. SANTIAGO VITERI

UOMI CANCER CENTER, CLÍNICA MI TRES TORRES