Lung Cancer UPDATES
IASLC HIGHLIGHTS
09-12 SEPTIEMBRE 2023
Singapore

Iniciativa científica de:
GECP
lung cancer research

TRATAMIENTOS DIRIGIDOS A DIANAS

Dra. Virginia Calvo de Juan

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DISCLOSURES

Iniciativa científica de: GECP lung cancer research

- **Advisory board:** Roche, AstraZeneca, MSD, BMS, Takeda, Sanofi, AMGEN

- **Speaking**: Roche, AstraZeneca, MSD, BMS, Takeda, Pfizer, Janssen

ORAL COMUNICATIONS

Iniciativa científica de: GECP lung cancer research

- **EGFR (Ex19del, L858R)**
  - OA03.03: Aumolertinib plus anlotinib in advanced NSCLC with brain metastasis: a single-arm, phase II study
  - **PL03.13: FLAURA 2: Osimertinib with/without platinum-based chemotherapy as first-line treatment in patients with EGFRm advanced NSCLC**
  - **MA13.06: Amivantamab, Lazertinib plus platinum-based chemotherapy in EGFR-mutated advanced NSCLC: Updated results from CHRYSALIS-2**
  - **OA05.03: Patritumab Deruxtecan (HER3-DXd) in EGFR-mutated NSCLC following EGFRTKI and platinum-based chemotherapy: HERTHENA-Lung01**
  - MA13.03: BBT-176, a 4th generation EGFR TKI, for progressed NSCLC after EGFR TKI therapy: updated report from a phase 1 study
  - MA04.04: A novel anti-EGFR/CD3 bispecific antibody exhibits potent efficacy for Osimertinib-resistant NSCLC

PL03.13: FLAURA 2: Osimertinib with/without platinum-based chemotherapy as first-line treatment in patients with EGFRm advanced NSCLC

IASLC 2023 World Conference on Lung Cancer
SEPTEMBER 9-12, 2023 | SINGAPORE

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Osimertinib With / Without Platinum-Based Chemotherapy as First-Line Treatment in Patients with EGFRm Advanced NSCLC (FLAURA2)

Prof Pasi A. Jänne[1], Prof David Planchard[2], Prof Ying Cheng[3], Dr James Chih-Hsin Yang[4], Dr Noriko Yanagitani[5], Prof Sang-We Kim[6], Dr Shunichi Sugawara[7],

FLAURA2 Phase III study design

Safety run-in period (N = 30)
Published in ESMO Open, 2021[1]

Patients with untreated locally advanced / metastatic EGFRm NSCLC

Key inclusion criteria:
- Aged ≥18 years (Japan: ≥20 years)
- Pathologically confirmed non-squamous NSCLC
- Ex19del / L858R (local / central test)
- WHO PS 0 / 1
- No prior systemic therapy for advanced NSCLC
- Stable CNS metastases were allowed*
- CT/MRI scan at baseline

Stratification by:
- **Race** (Chinese Asian / non-Chinese Asian / non-Asian)
- **EGFRm** (local / central test)
- **WHO PS** (0 / 1)

Randomization 1:1 (N = 557)

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75mg/m² (Q3W for 4 cycles for platinum-based treatments)

Maintenance osimertinib 80 mg (QD) + pemetrexed (Q3W)†

Osimertinib 80 mg (QD)

Follow-up:
- RECIST 1.1 assessment at 6 and 12 weeks, then every 12 weeks until RECIST 1.1 defined radiological disease progression or other withdrawal criteria were met

- **Primary endpoint:** PFS (by investigator and BICR assessment per RECIST 1.1)‡§
- **Secondary endpoints:** OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5) and PFS2‡

PL03.13: FLAURA 2: Osimertinib with/without platinum-based chemotherapy as first-line treatment in patients with EGFRm advanced NSCLC

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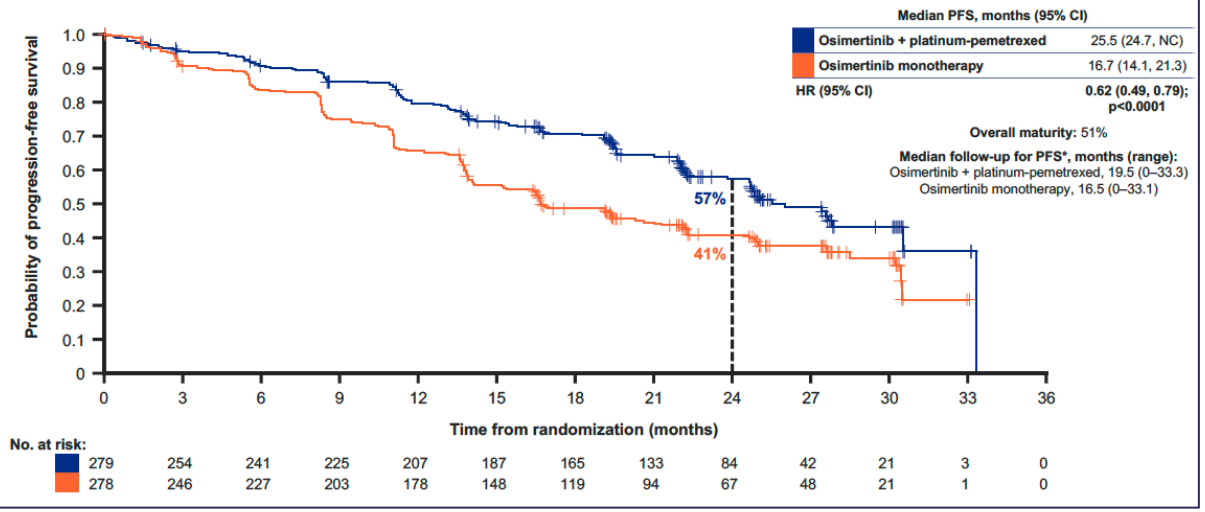
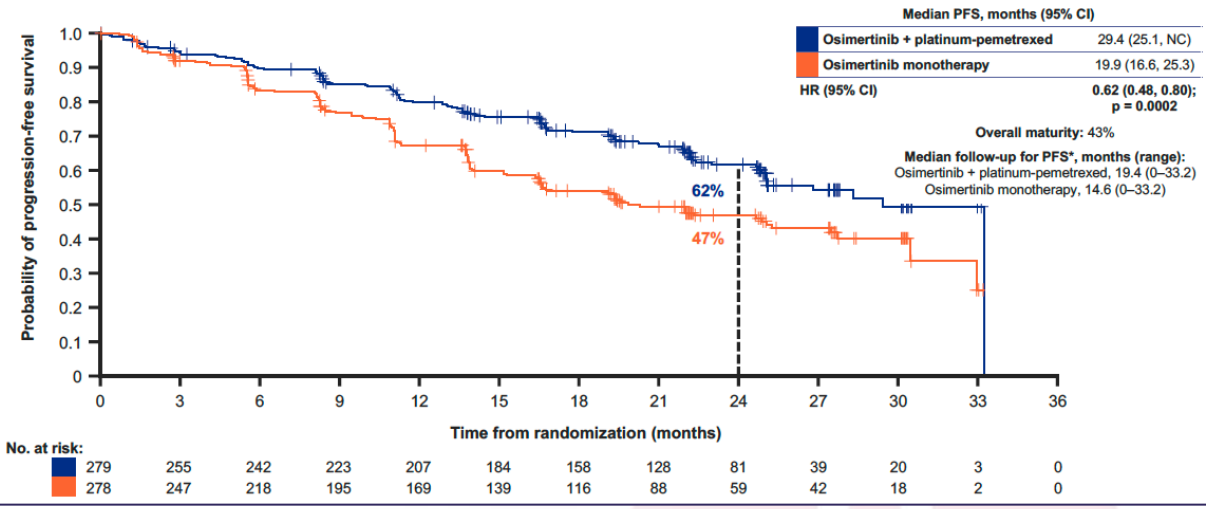
Progression-free survival per investigator

- Median PFS was improved by 8.8 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy



Progression-free survival per BICR

- Median PFS was improved by 9.5 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy



PL03.13: FLAURA 2: Osimertinib with/without platinum-based chemotherapy as first-line treatment in patients with EGFRm advanced NSCLC

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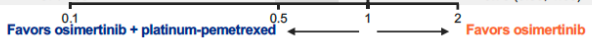
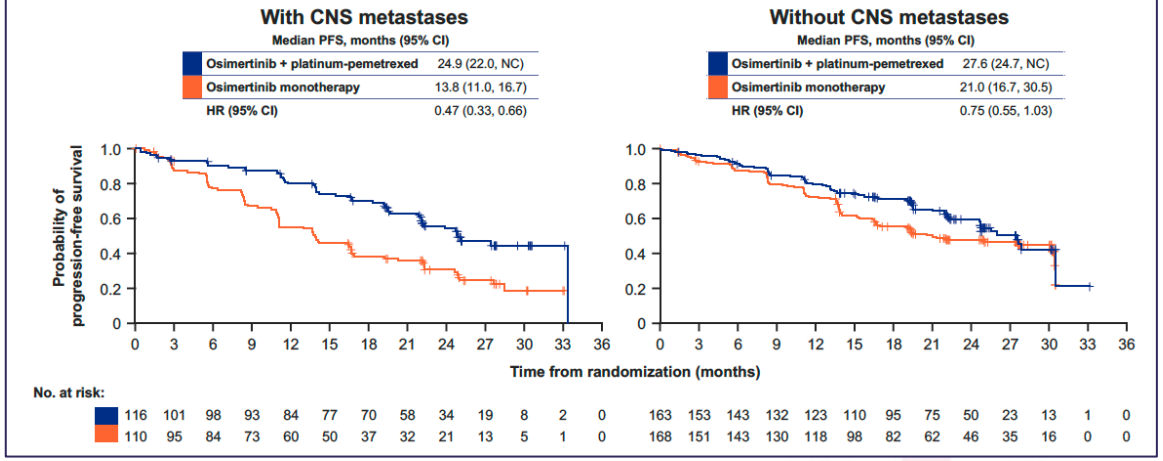
Progression-free survival across subgroups

- PFS benefit was consistent across all pre-defined subgroups

Subgroup		Osimertinib + platinum-pemetrexed (Events / patients)	Osimertinib monotherapy (Events / patients)	HR (95% CI)
All patients	Stratified log-rank	120 / 279	166 / 278	**0.62** (0.49, 0.79)
	Unadjusted Cox PH	120 / 279	166 / 278	**0.62** (0.49, 0.78)
Sex	Male	51 / 106	73 / 109	**0.54** (0.37, 0.77)
	Female	69 / 173	93 / 169	**0.67** (0.49, 0.92)
Race	Chinese Asian	26 / 71	43 / 69	**0.49** (0.30, 0.81)
	Non-Chinese Asian	54 / 107	65 / 107	**0.76** (0.53, 1.09)
	Non-Asian	40 / 101	58 / 102	**0.55** (0.37, 0.83)
EGFR mutation test method	Central	52 / 121	67 / 119	**0.73** (0.51, 1.05)
	Local	68 / 158	99 / 159	**0.55** (0.40, 0.74)
Age at screening	<65 years	73 / 174	97 / 166	**0.59** (0.44, 0.80)
	≥65 years	47 / 105	69 / 112	**0.68** (0.47, 0.98)
Smoking history	Yes	43 / 91	57 / 97	**0.63** (0.42, 0.94)
	No	77 / 188	109 / 181	**0.61** (0.46, 0.82)
EGFR mutation type*	Ex19del	65 / 172	94 / 169	**0.60** (0.44, 0.83)
	L858R	55 / 106	70 / 107	**0.63** (0.44, 0.90)
WHO PS	0	48 / 101	57 / 102	**0.79** (0.54, 1.16)
	1	72 / 178	109 / 176	**0.53** (0.39, 0.72)
CNS status at baseline	Yes	52 / 116	79 / 110	**0.47** (0.33, 0.66)
	No	68 / 163	87 / 168	**0.75** (0.55, 1.03)



PFS* with / without CNS metastases at baseline

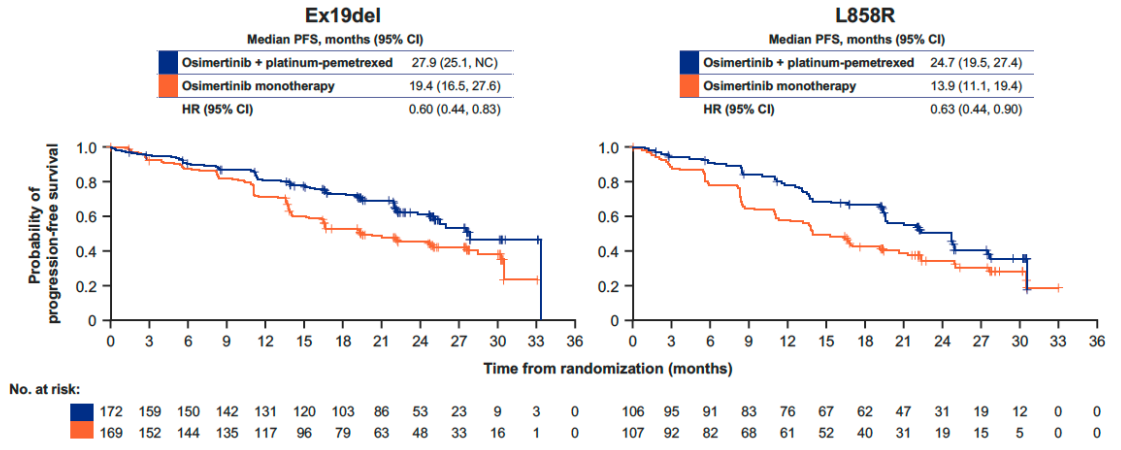


Baseline characteristics

- Patient demographics / clinical characteristics were balanced between arms, and almost half of patients had CNS metastases at baseline

Characteristics, %*	Osimertinib + platinum-pemetrexed (n = 279)†	Osimertinib monotherapy (n = 278)†
Sex: male / female	38 / 62	39 / 61
Age: median (range), years	61 (26–83)	62 (30–85)
Race: Chinese Asian / non-Chinese Asian / non-Asian	25 / 39 / 35	25 / 38 / 36
WHO PS: 0 / 1‡	37 / 62	37 / 63
Smoking status: never / current / former	67 / 1 / 31	65 / 1 / 33
Histology: adenocarcinoma / adenosquamous / other	99 / 1 / 1	99 / 0 / 1
EGFR mutation at randomization§: Ex19del / L858R	61 / 38	60 / 38
Locally advanced / metastatic	5 / 95	3 / 97
CNS metastases	42	40
Extra-thoracic visceral metastases	53	54
Baseline tumor size, mean (SD) / median (range), mm	65 (42) / 57 (10–284)	64 (39) / 57 (11–221)

PFS* by EGFR mutation type at baseline



PL03.13: FLAURA 2: Osimertinib with/without platinum-based chemotherapy as first-line treatment in patients with EGFRm advanced NSCLC

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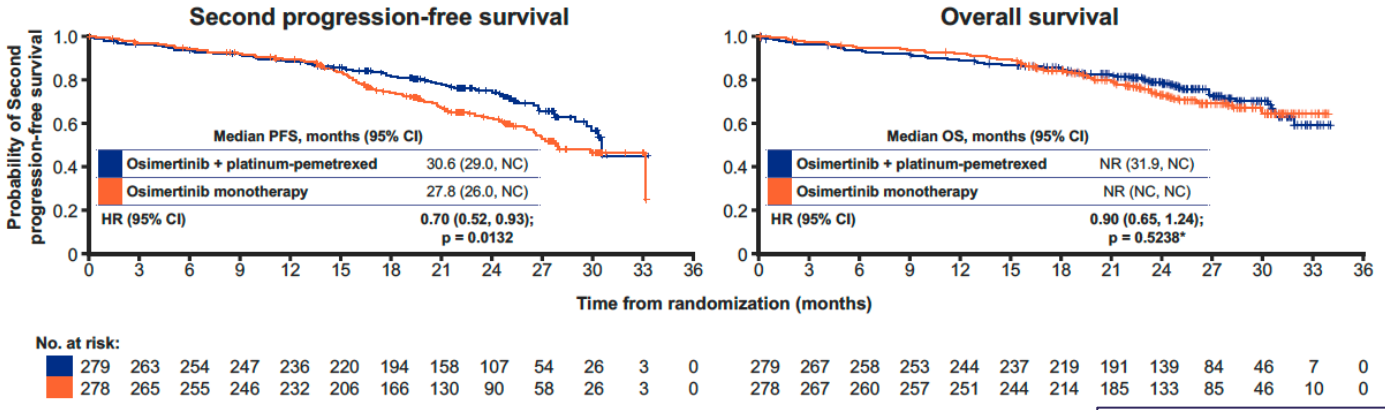
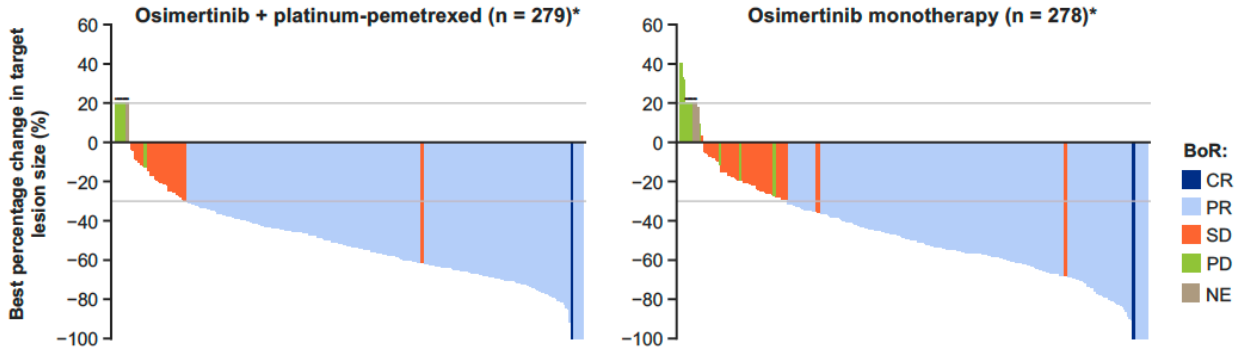
PFS2 and OS interim analysis



- PFS2 and OS were immature at this interim analysis (34% and 27% data maturity, respectively)

Tumor response per investigator



	Osimertinib + platinum-pemetrexed (n = 279)	Osimertinib monotherapy (n = 278)
Objective response rate, % (95% CI)	83.2 (78.2, 87.4)	75.5 (70.1, 80.5)
Odds ratio (95% CI)	1.61 (1.06, 2.44)	
Complete response, n (%)	1 (<1)	2 (1)
Partial response, n (%)	231 (83)	208 (75)
Stable disease ≥35 days, n (%)	34 (12)	51 (18)
Progression, n (%)	7 (3)	12 (4)
Median duration of response, months (95% CI)	24.0 (20.9, 27.8)	15.3 (12.7, 19.4)

PL03.13: FLAURA 2: Osimertinib with/without platinum-based chemotherapy as first-line treatment in patients with EGFRm advanced NSCLC

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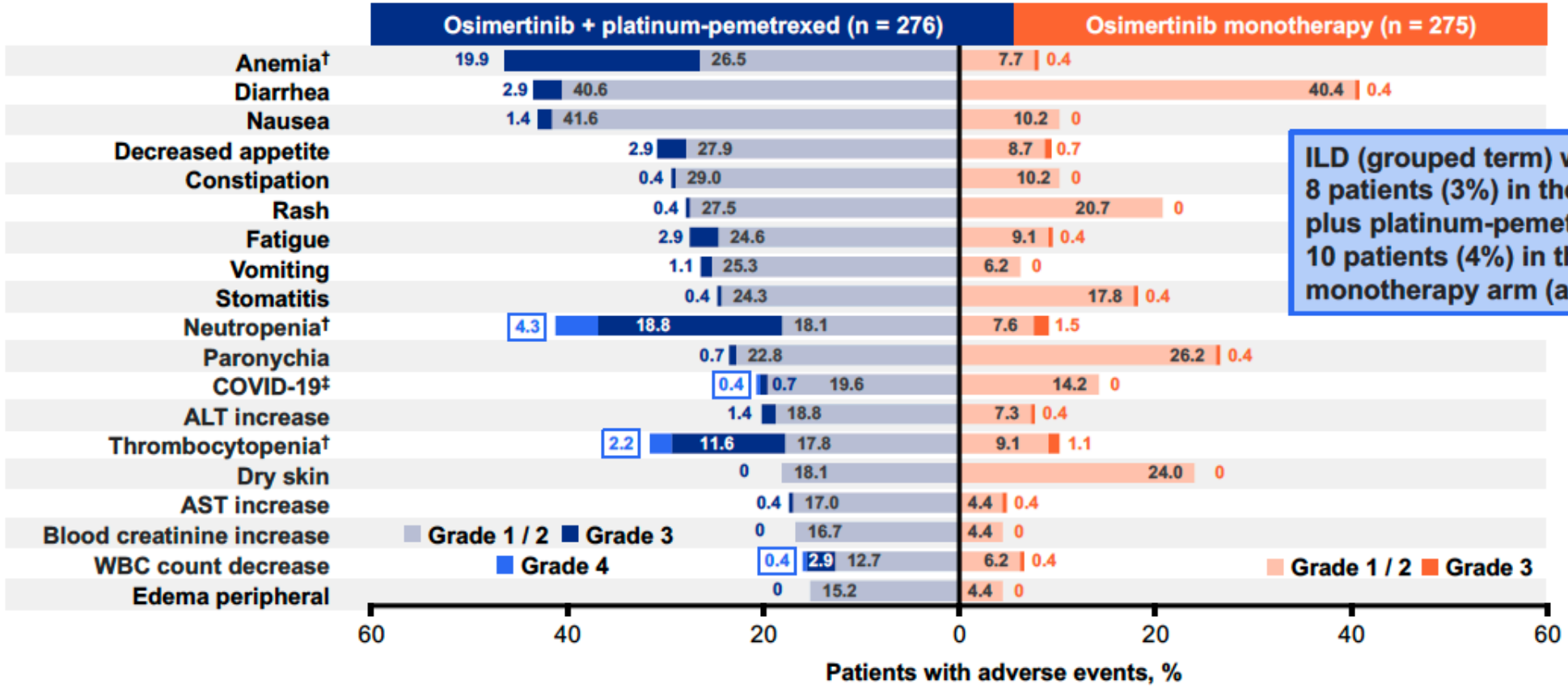
Common adverse events (≥15% of patients)*



ILD (grouped term) was reported in 8 patients (3%) in the osimertinib plus platinum-pemetrexed arm and 10 patients (4%) in the osimertinib monotherapy arm (all grades)†

- Of most common AEs (occurring in ≥15% of patients in either arm), all Grade 4 AEs in the osimertinib plus platinum-pemetrexed arm were hematological toxicities, known to be associated with chemotherapy; there were no common Grade 4 AEs in the monotherapy arm

PL03.13: FLAURA 2: Osimertinib with/without platinum-based chemotherapy as first-line treatment in patients with EGFRm advanced NSCLC

Iniciativa científica de: GECP lung cancer

Conclusions

- Osimertinib in combination with platinum-pemetrexed has demonstrated a statistically significant and clinically meaningful improvement in PFS over osimertinib monotherapy in patients with EGFRm advanced NSCLC (HR: 0.62 [95% CI 0.49, 0.79])
  - **Median improvements in PFS were 8.8 and 9.5 months with combination vs monotherapy, per investigator and BICR, respectively (median 25.5 vs 16.7 and 29.4 vs 19.9 months per investigator and BICR, respectively)**
- PFS benefits were consistent across all pre-defined subgroups
- PFS2 and OS data were immature at this interim analysis
- The safety profiles were as expected for each treatment and were manageable with standard medical practice
- Further ongoing analyses include CNS response and progression, post-progression endpoints, subsequent therapies, and ctDNA analyses

Osimertinib plus platinum-pemetrexed offers a new first-line treatment option for patients with EGFRm advanced NSCLC

MA13.06: Amivantamab, Lazertinib plus platinum-based chemotherapy in EGFR-mutated advanced NSCLC: Updated results from CHRYSALIS-2

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- **Amivantamab** is an EGFR-MET bispecific antibody with immune cell–directing activity[1-3]
- **Lazertinib** is a CNS-penetrant, 3rd-generation EGFR TKI with efficacy in activating *EGFR* mutations, T790M, and brain metastases[4,5]
- The combination of targeted inhibition of EGFR/MET signaling with platinum-based chemotherapy could address the diverse and polyclonal resistance after progression on osimertinib

CHRYSALIS-2 (NCT04077463)

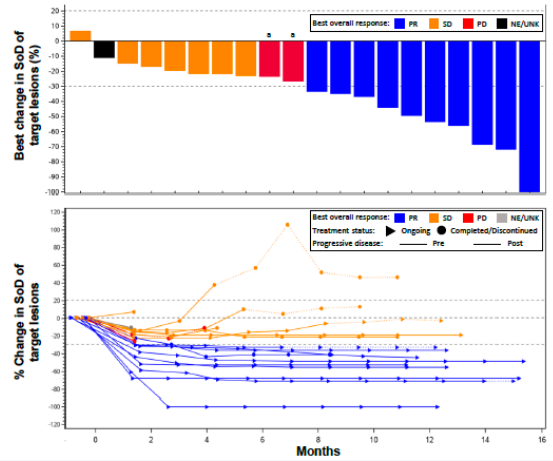
Eligibility
EGFR-mutated, advanced NSCLC post-TKI (max of 3 prior lines)

Dosing (21-day cycle)	
Lazertinib	240 mg daily
Amivantamab	1400/1750[b] mg on C1 D1/D2, C1D8, C1D15, C2D1; 1750/2100[b] mg C3+ Q3W
Chemotherapy	Carboplatin (AUC5; stopped after 4 cycles)
	Pemetrexed (500 mg/m²) until disease progression

Endpoints
- Adverse events (primary)
- Objective response rate
- Duration of response
- Clinical benefit rate[c]
- Progression-free survival
- Overall survival

Demographic and baseline disease characteristics, n (%)	n = 20
Median age, years (range)	61 (38–76)
Female / male	11 (55) / 9 (45)
Race	
Asian	11 (55)
White	8 (40)
Black	1 (5)
Exon 19 deletion / L858R	13 (65) / 7 (35)
ECOG PS 0 /1	4 (20) / 16 (80)
History of brain metastases	12 (60)
Median no. of prior lines[d] (range)	1 (1–3)
Prior therapy[d]	
1st/2nd-generation EGFR TKI	9 (45)
Osimertinib	14 (70)
Platinum-based chemotherapy[e]	5 (25)

ORR and Durability

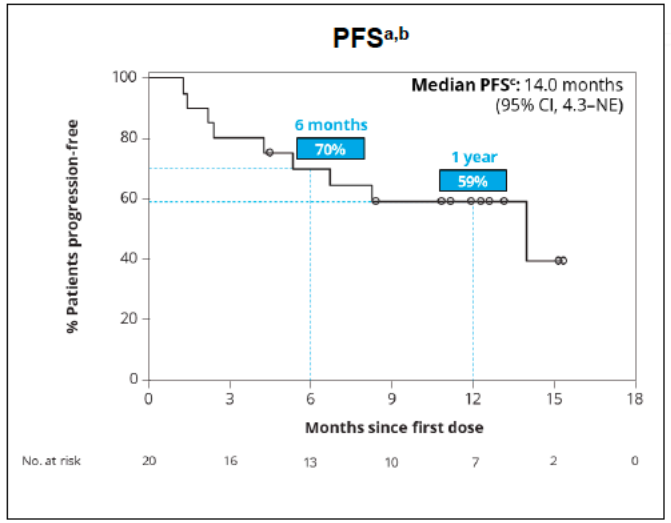


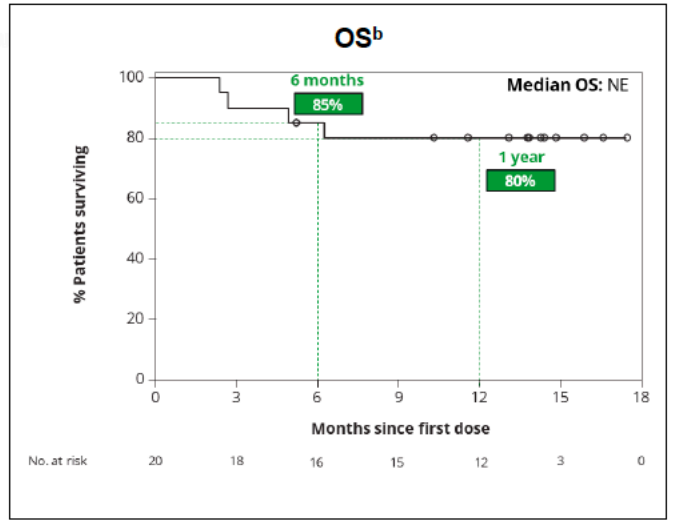
Investigator-assessed response (n=20)	
ORR	50% (95% CI, 27–73)
Median DOR	Not estimable
Ongoing response	8 of 10 responders
DOR ≥6 months	8 of 10 responders
CBR[b]	80% (95% CI, 56–94)

- At a median follow-up of 13.1 months, 11 (55%) patients remain on treatment
- 3 of 7 patients with SD as best response had SD duration ≥6 months, 2 of which remain on treatment
- A total of 5 patients were treated beyond investigator-assessed progression,[c] with incremental median treatment duration after progression of 4.2 months (range, 3.1–7.1)

AEs (≥20%) by preferred term, n (%)	Total[a]	Grade ≥3
Associated with EGFR inhibition		
Rash	15 (75)	1 (5)
Paronychia	12 (60)	0
Stomatitis	12 (60)	0
Dermatitis acneiform	8 (40)	2 (10)
Diarrhea	6 (30)	1 (5)
Associated with MET inhibition		
Hypoalbuminemia	8 (40)	2 (10)
Other		
Neutropenia	18 (90)	14 (70)
IRR	13 (65)	0
Fatigue	10 (50)	5 (25)
Nausea	10 (50)	0
COVID-19	8 (40)	0
Thrombocytopenia	8 (40)	5 (25)
Constipation	7 (35)	0
Decreased appetite	7 (35)	1 (5)
Leukopenia	7 (35)	4 (20)
Alanine aminotransferase increased	6 (30)	0
Anemia	6 (30)	2 (10)
Pulmonary embolism	6 (30)	1 (5)
Aspartate aminotransferase increased	5 (25)	0
Back pain	5 (25)	0
Epistaxis	5 (25)	0
Hemorrhoids	5 (25)	0
Peripheral sensory neuropathy	5 (25)	0

PFS and OS





MA13.06: Amivantamab, Lazertinib plus platinum-based chemotherapy in EGFR-mutated advanced NSCLC: Updated results from CHRYSALIS-2

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Treatment benefits	• Amivantamab, lazertinib plus chemotherapy[a] among *EGFR*-mutant NSCLC after TKI demonstrated: – An ORR of 50% and median PFS of 14.0 months – The median DOR and OS were not estimable, with 80% of patients alive at 1 year, suggesting immune-driven durability
Safety	• No new safety signals were seen; the safety profile was consistent with that of the individual components • Given the reduction in cytopenia events after completion of carboplatin therapy, additive cytotoxicity arising from carboplatin plus targeted therapies requires further investigation
Key takeaway & next steps	• Combining amivantamab, lazertinib plus chemotherapy[a] is promising and likely addresses the diverse and polyclonal resistance emerging after progression on osimertinib • The safety and efficacy of this regimen is being evaluated in the phase 3, randomized, MARIPOSA-2 study (NCT04988295) in the post-osimertinib setting

OA05.03: Patritumab Deruxtecan (HER3-DXd) in EGFR-mutated NSCLC following EGFRTKI and platinum-based chemotherapy: HERTHENA-Lung01

Iniciativa científica de: GECP lung cancer research

Patient population

- Advanced *EGFR*-mutated NSCLC
- Progression on most recent systemic therapy
- Prior EGFR TKI and prior platinum-based chemotherapy (amended protocol required prior osimertinib)
- Inactive or previously treated asymptomatic brain metastases allowed
- Pretreatment tumor tissue required[a]

R 1:1

HER3-DXd IV Q3W

Fixed dose 5.6 mg/kg
February 18, 2021 → February 18, 2022

Enrollment continued (N=225)[b]

Decision point
A benefit-risk assessment of phase 1 data supported the closure of the uptitration arm

Uptitration
C1D1: **3.2 mg/kg**
C2D1: **4.8 mg/kg**
C3D1 and later cycles: **6.4 mg/kg**
January 18, 2021 → September 16, 2021

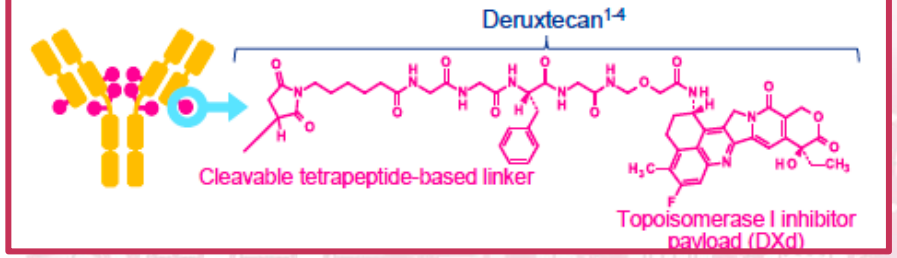
Enrollment discontinued (N=50)[c]

Primary endpoint
- cORR by BICR

Key secondary endpoint
- DOR by BICR

Primary data cutoff, 21 Nov 2022[d]
Snapshot data cutoff, 18 May 2023 (additional 6 months follow-up)
Data are presented for the 5.6-mg/kg fixed-dose arm
- Efficacy from snapshot data cutoff—median study follow-up, 18.9 (range, 14.9-27.5) months
- Safety from primary data cutoff—median treatment duration, 5.5 (range, 0.7-18.2) months

HER3-DXd is an ADC composed of 3 parts[1-4]:
- A fully human anti-HER3 IgG1 mAb (patritumab)
- A topoisomerase I inhibitor payload (DXd)
- A tetrapeptide-based cleavable linker that covalently bonds the other 2 components



OA05.03: Patritumab Deruxtecan (HER3-DXd) in EGFR-mutated NSCLC following EGFRTKI and platinum-based chemotherapy: HERTHENA-Lung01

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Confirmed responses and survival		Prior EGFR TKI (any) and PBC (N=225)	Subset with prior 3G EGFR TKI and PBC (n=209)
cORR (95% CI), %		**29.8 (23.9-36.2)**	**29.2 (23.1-35.9)**
Best overall response (BICR), n (%)	CR	1 (0.4)	1 (0.5)
	PR	66 (29.3)	60 (28.7)
	SD[a]	99 (44.0)	91 (43.5)
	PD	43 (19.1)	41 (19.6)
	NE[b]	16 (7.1)	16 (7.7)
DCR (95% CI), %		73.8 (67.5-79.4)	72.7 (66.2-78.6)
DOR, median (95% CI), mo		6.4 (4.9-7.8)	6.4 (5.2-7.8)
PFS, median (95% CI), mo		5.5 (5.1-5.9)	5.5 (5.1-6.4)
OS, median (95% CI), mo		11.9 (11.2-13.1)	11.9 (10.9-13.1)

Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

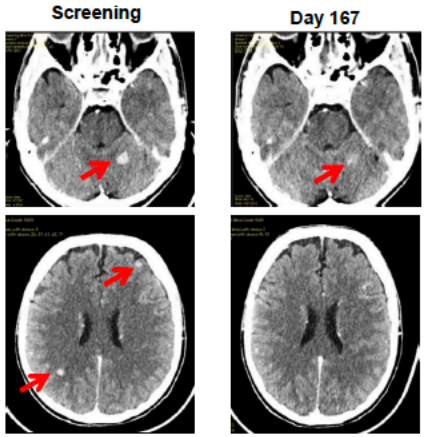
Intracranial Responses (by CNS BICR) Observed With HER3-DXd

Intracranial Efficacy of HER3-DXd in Patients With Brain Metastases at Baseline

Intracranial response by CNS BICR per CNS RECIST	Patients with brain metastasis at baseline and no prior radiotherapy (N=30)[a]
Confirmed ORR (95% CI), %	33.3 (17.3-52.8)
CR, n (%)	9 (30.0)[b]
PR, n (%)	1 (3.3)
SD, n (%)[c]	13 (43.3)
PD, n (%)	4 (13.3)
NE, n (%)	3 (10.0)
DCR (95% CI), %	76.7 (57.7-90.1)
DOR, median (95% CI), mo	8.4 (5.8-9.2)

Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

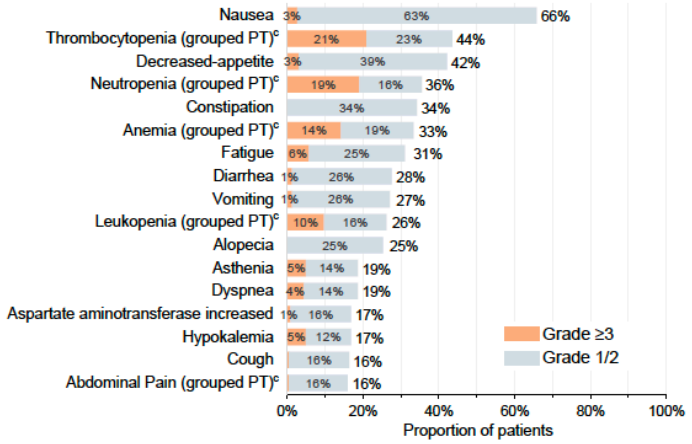
Partial CNS Response in a Patient With a Measurable CNS BICR Target Lesion



Safety summary	HER3-DXd 5.6 mg/kg (N=225)
Any TEAE, n (%)	224 (99.6)
Associated with treatment discontinuation[a]	16 (7.1)
Associated with treatment dose reduction	48 (21.3)
Associated with treatment dose interruption	91 (40.4)
Grade ≥3 TEAE, n (%)	146 (64.9)
Treatment-related TEAE, n (%)	215 (95.6)
Associated with death[b]	4 (1.8)
Grade ≥3	102 (45.3)
Serious TEAE	34 (15.1)
Adjudicated interstitial lung disease, n (%) [All were adjudicated as treatment-related]	12 (5.3)
Grade 1	1 (0.4)
Grade 2	8 (3.6)
Grade 3	2 (0.9)
Grade 4	0
Grade 5	1 (0.4)

Primary data cutoff, 21 Nov 2022.
Median treatment duration: 5.5 (range, 0.7-18.2) months.

Most Common TEAEs Occurring in ≥15% of Patients (N=225)



Any hematologic toxicities typically occurred early in treatment, were transient, and were not associated with clinical sequelae

OA05.03: Patritumab Deruxtecan (HER3-DXd) in EGFR-mutated NSCLC following EGFRTKI and platinum-based chemotherapy: HERTHENA-Lung01

Iniciativa científica de: GECP lung cancer research

- HER3-DXd provided clinically meaningful and durable efficacy (cORR, 29.8%) in patients with advanced *EGFR*-mutated NSCLC that progressed following EGFR TKI and platinum-based chemotherapy; efficacy was observed across diverse mechanisms of EGFR TKI resistance and across a broad range of pretreatment tumor HER3 membrane expression
- HER3-DXd showed clinically meaningful intracranial antitumor activity in patients with untreated brain metastases
  - Intracranial cORR, 33.3%
  - Intracranial DCR, 76.7%
- The safety profile of HER3-DXd in this population of heavily pretreated patients was manageable and tolerable and was consistent with previous reports
  - TEAE associated with treatment discontinuation, 7.1%
  - Adjudicated treatment-related ILD, 5.3%
- HER3-DXd has emerged as a promising therapy for patients with *EGFR*-mutated NSCLC after the failure of EGFR TKI and platinum-based chemotherapy, for whom available treatment options provide only limited efficacy

HERTHENA-Lung01, a Phase II Trial of Patritumab Deruxtecan (HER3-DXd) in Epidermal Growth Factor Receptor–Mutated Non–Small-Cell Lung Cancer After Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and Platinum-Based Chemotherapy

Helena A. Yu, MD[1]; Yasushi Goto, MD[2]; Hidetoshi Hayashi, MD, PhD[3]; Enriqueta Felip, MD, PhD[4]; James Chih-Hsin Yang, MD, PhD[5];

ORAL COMUNICATIONS

Iniciativa científica de: GECP lung cancer research

- **EGFR (uncommon mutations)**
  - MA13.04: Final overall survival analysis of osimertinib for patients with NSCLC harboring uncommon EGFR mutations (KCSG-LU15-09)
  - MA13.11: Lazertinib for patients with NSCLC harboring uncommon EGFR mutations: a single-arm, phase II multi-center trial

MA13.04: Final overall survival analysis of osimertinib for patients with NSCLC harboring uncommon EGFR mutations (KCSG-LU15-09)

Iniciativa científica de: GECP lung cancer research

Study design (NCT03424759)

Phase 2, open-label, single arm, multi-center study.

First patient dosed : April 5, 2016

36 patients, 7 hospitals, Mar 2016 ~ Oct 2017.

Data cut-off : Nov 30, 2021

Key inclusion criteria :

- Histological confirmed metastatic or recurred NSCLC (stage IV)
- Activating EGFR mutation other than exon 19 deletion, L858R, T790M and Exon 20 insertion
- EGFR-TKI näive
- Age 19 years or older
- ECOG PS 0-2

→ **Osimertinib 80mg QD** →

Study objectives :

- Primary endpoint
  : Objective response rate
- Secondary endpoint
  : Progression-free survival,
  Overall survival,
  Safety profile,
  Quality of life

Adverse events

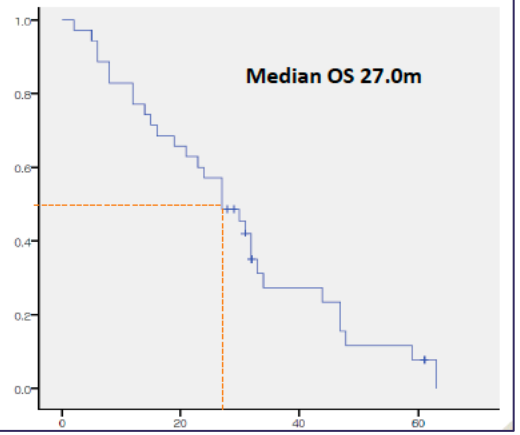
- Cycle delay : 7/35 (20%)
  - reason for dose delay
  : 3 (adverse event),
  2 (schedule conflict),
  2 (disease evaluation)
- Dose adjustment : 1/35 (3%)
  : 1 (adverse event)
- Treatment discontinuation : 1/35 (3%)
  : 1 (adverse event, G3 pneumonitis)

Adverse event category, n (%)	All grade	G1	G2	G3	G4
Rash	12 (34)	9 (26)	3 (9)	0	0
Anorexia	8 (23)	3 (9)	5 (14)	0	0
Diarrhea	7 (20)	6 (17)	1 (3)	0	0
Pruritis	5 (14)	4 (11)	1 (3)	0	0
Constipation	4 (11)	2 (6)	2 (6)	0	0
Mucositis	3 (9)	1 (3)	2 (6)	0	0
Elevated AST/ALT	2 (6)	0	0	0	2 (6)
Thrombocytopenia	3 (9)	1 (3)	0	2 (6)	0
dyspnea	2 (6)	1 (3)	2 (6)	0	0

Final Overall Survival Analysis

Clinical response	Osimertinib (n=35)
Objective response rate (95% CI)	51% (34, 68)
Disease control rate (95% CI)	89% (78, 99)
Median progression-free survival, months (95% CI)	8.0 (5.7, 10.3)
Median overall survival, months (95% CI)	27.0 (19.3, 34.7)
Median duration of response, months (95% CI)	13.0 (9.1, 16.9)
Median progression-free survival 2, months (95% CI)	16.0 (8.5, 23.5)

•Median follow-up duration: 61.0 months



Conclusions

- Osimertinib continued to show favorable activity after long-term follow-up in patients with NSCLC harboring uncommon EGFR mutations
  - Median OS 27.0m (95%CI, 18.5-33.5), Median DOR 13.5m (range 1.0-43.0)
- Osimertinib had manageable safety profile, consistent with previous reports; no new safety signals were identified

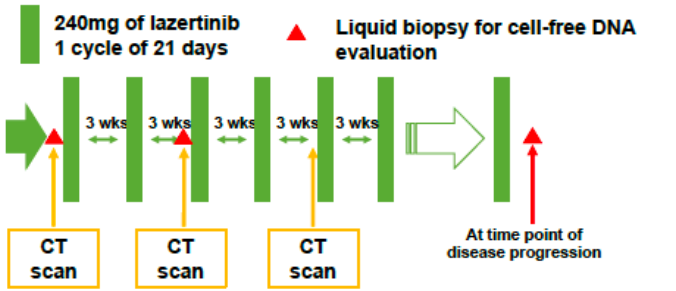
MA13.11: Lazertinib for patients with NSCLC harboring uncommon EGFR mutations: a single-arm, phase II multi-center trial

Iniciativa científica de: GECP lung cancer research

STUDY DESIGN

Key Inclusion Criteria (n=36)

1. Biopsy proven NSCLC
2. TKI naïve patients
3. Confirmed uncommon *EGFR* mutations without common *EGFR* mutations (19del, L858R, T790M, and exon 20 insertion) via liquid or tissue



Thoracic (+/- abdomen, neck) radiological assessment will be conducted every 6 weeks until cycle 8 and every 12 weeks thereafter

- Uncommon *EGFR* mutation is defined as point mutation or duplication in exon 18-21 other than *EGFR* del19, L858R, T790M and exon 20 insertion.
- **List of uncommon *EGFR* mutations eligible for the study:**
  G719X, S768I, L861Q, G719X + S768I, G719X + L861Q, L861Q + S768I, L747S, S720A, E709A, exon 18 deletion
- **Primary endpoint:** Objective response rate (H0: 20%, H1: 40%)
  Secondary endpoint: PFS, OS, safety profile, resistance mechanisms based on the liquid NGS test

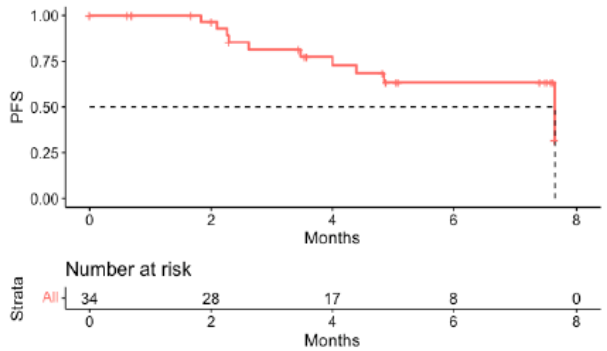
SAFETY PROFILE

Patients with dose modification	N (%)
Temporally dose interruption	9 (26.5)
Dose reduction to 160mg	12 (35.3)
Permanent discontinuation	1 (2.9)

- **Reason for permanent discontinuation:**
  Gr 2 pneumonitis
- **Reasons for dose reduction include following Gr 1 or 2 AEs:**
  Peripheral neuropathy, Fatigue, Mucosal inflammation, Myalgia, Bone pain, Paronychia, Dermatitis, Muscle spasm, Paresthesia, Asthenia, Decreased appetite, Headache, Insomnia, Nausea, Rash, Skin laceration

RESULT (Data cut-off, Mar 24th 2023)

- Median follow-up duration: 6.83 months (95% CI 4.76 – 8.08)
- Objective response rate: 44.1%
- Disease control rate: 85.3%



Median PFS: 7.69 months (95% CI 4.44 - NA)
Number of events: 10

Type	N(%)	Best response	N(%)	ORR
G719X	13 (38.24)	Complete response	-	53.8%
		Partial response	7(53.85)	
		Stable disease	6(46.15)	
		Progressive disease	-	
S768I	1 (2.94)	Complete response		100%
		Partial response	1(100.00)	
		Stable disease	-	
		Progressive disease	-	
L861Q	11 (32.35)	Complete response	-	54.6%
		Partial response	6(54.55)	
		Stable disease	3(27.27)	
		Progressive disease	-	
		NA	2(18.18)	
G719X + S768I	3 (8.82)	Complete response		33.3%
		Partial response	1(33.33)	
		Stable disease		
		Progressive disease		
		NA	2(66.67)	
Exon18 del	5 (14.71)	Complete response		0%
		Partial response		
		Stable disease	4(80.00)	
		Progressive disease	1(20.00)	
Exon 19 ins	1 (2.94)	Complete response		0%
		Partial response		
		Stable disease	1(100.00)	
		Progressive disease		

CONCLUSIONS

- **This study includes the preliminary results of 34 patients (out of 36 patients) with uncommon EGFR mutation who were treated with 240mg Lazertinib as 1st line.**
  Median follow-up duration 6.83 months (95% CI 4.76 – 8.08)
- **The objective response rate was 44.1%, the disease control rate was 85.3%, and median PFS was 7.69 months (95% CI 4.44-NA)**
  G719X (n = 13): ORR 53.8%
  L861Q (n = 11): ORR 54.6%
- **The safety profile of Lazertinib in the study population was similar to previous reports.**
- **42.4% of baseline liquid biopsy detects the same uncommon EGFR mutation that has been detected with other methods used for screening tests.**
- **The final analysis including the resistance mechanism will be presented in the future**

Sehhoon Park, et al.

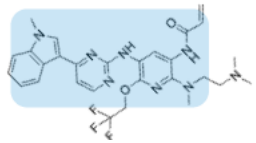
ORAL COMUNICATIONS

Iniciativa científica de:
GECP lung cancer research

- **EGFR Exon 20 insertions**
  - OA03.04: A phase 1b study of furmonertinib, an oral, brain penetrant, selective EGFR inhibitor, in patients with advanced NSCLC with EGFR Exon 20 insertions

• Novel 3rd gen-EGFR-TKI

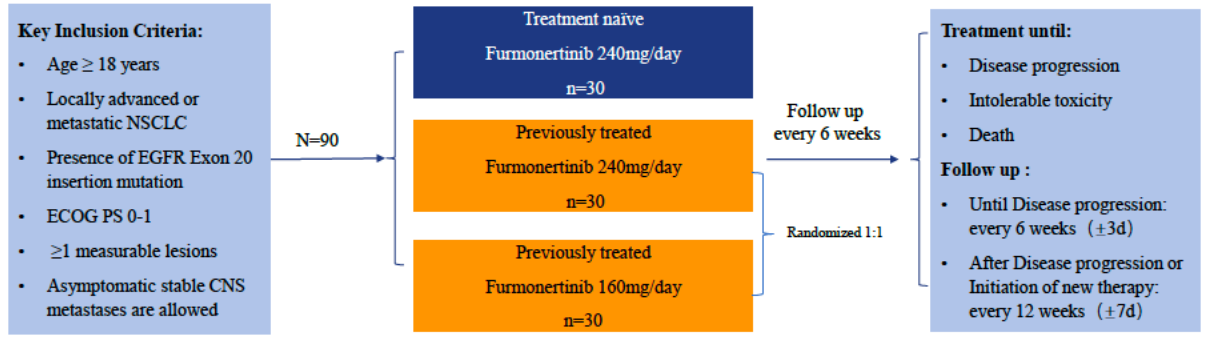
Furmonertinib



OA03.04: FAVOUR: A phase 1b study of furmonertinib, an oral, brain penetrant, selective EGFR inhibitor, in patients with advanced NSCLC with EGFR Exon 20 insertions

Iniciativa científica de: GECP lung cancer research

FAVOUR Study Design in NSCLC EGFR Exon 20 Insertion



Endpoints

➢ **Primary**: ORR by IRC assessment; **Secondary**: DCR, DoR, PFS, OS, Depth of response, safety, quality of life

Most Frequent TRAEs (Incidence ≥ 20%)

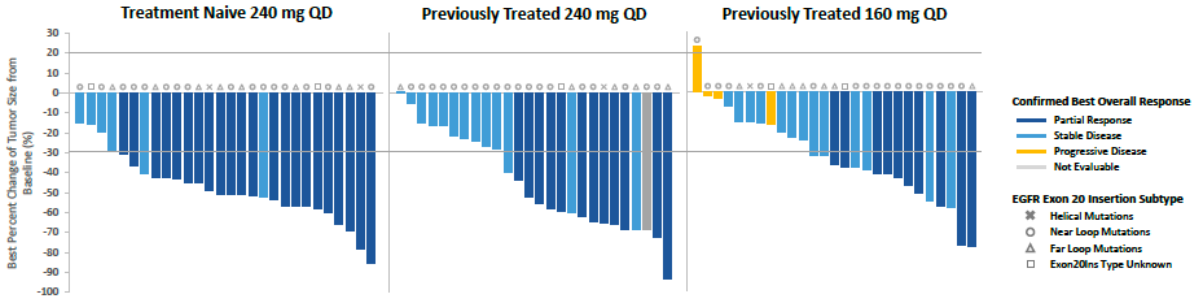
Preferred Term, Number of Patient(s) (%)	Treatment-naive 240 mg (N = 30)		Previously Treated 240 mg (N = 28)		Previously Treated 160 mg (N = 28)	
	Total	Grade≥3	Total	Grade≥3	Total	Grade≥3
Diarrhea	22 (73%)	0	24 (86%)	0	9 (32%)	2 (7%)
Anemia	13 (43%)	0	7 (25%)	1 (4%)	4 (14%)	1 (4%)
Aspartate aminotransferase increased	8 (27%)	0	7 (25%)	0	10 (36%)	0
Alanine aminotransferase increased	7 (23%)	0	7 (25%)	1 (4%)	8 (29%)	0
Blood creatinine increased	6 (20%)	0	8 (29%)	0	7 (25%)	0
Mouth ulceration	9 (30%)	1 (3%)	4 (14%)	0	5 (18%)	0
Rash	7 (23%)	0	6 (21%)	0	4 (14%)	0
Electrocardiogram QT prolonged	8 (27%)	1 (3%)	4 (14%)	2 (7%)	2 (7%)	0
White blood cell count decreased	6 (20%)	1 (3%)	5 (18%)	0	6 (21%)	0
Decreased appetite	3 (10%)	0	8 (29%)	0	0	0
Weight decreased	3 (10%)	0	7 (25%)	1 (4%)	3 (11%)	0
Skin fissures	6 (20%)	0	3 (11%)	0	0	0
Paronychia	6 (20%)	0	2 (7%)	0	1 (4%)	0

Safety profile was consistent with the 80mg dose approved in China for classical EGFR mutations

Confirmed ORR by IRC by Cohort

Efficacy by IRC	Treatment Naïve 240mg N=28*	Previously Treated 240mg N= 26#	Previously Treated 160mg N= 26#
Confirmed ORR, % (95% CI)	78.6% (59.05%, 91.70%)	46.2% (26.59%, 66.63%)	38.5% (20.23%, 59.43%)
Best Response, n (%)			
Partial response (PR)	22 (78.6%)	12 (46.2%)	10 (38.5%)
Stable disease (SD)	6 (21.4%)	12 (46.2%)	12 (46.2%)
Progressive disease (PD)	0	0	4 (15.4%)
Not evaluable/Not done	0 / 0	1 (3.8%) / 1 (3.8%)	0 / 0
DoR, median (months) (95% CI)	15.2 (8.74, 24.84)	13.1 (5.62, 13.80)	9.7 (5.59, NA)
DCR (CR+PR+SD), % (95% CI)	100.0% (87.66%, 100.00%)	92.3% (74.87%, 99.05%)	84.6% (65.13%, 95.64%)

Depth of Response by Cohort and EGFR Exon20ins Mutation Subtype



- Responses observed across near loop, far loop and helical Exon20ins mutations
- Median maximum tumor reductions are 50.9% (treatment naïve), 54.2% (previously treated 240 mg) and 36.2% (previously treated 160 mg)

- Promising efficacy in both treatment naïve and previously treated patients
- Well-tolerated safety profile: the most common TRAE observed at the 240mg dose was low-grade diarrhea
- Phase III study in first-line patients (FURVENT/FURMO-004; NCT05607550)

Baohui Han, et al.

ORAL COMUNICATIONS

Iniciativa científica de:
GECP lung cancer research

- **ALK**
  - OA03.05: A randomized, phase 3 study of iruplinalkib (WX-0593) vs crizotinib in locally advanced or metastatic ALK+ non-small cell lung cancer (NSCLC)
  - MA06.11: Lorlatinib for previously treated ALK-positive advanced NSCLC: updated efficacy and safety data from a phase 2 study in China

OA03.05: A randomized, phase 3 study of iruplinalkib (WX-0593) vs crizotinib in ALK TKI-naïve, locally advanced or metastatic ALK+ non-small cell lung cancer (NSCLC): INSPIRE

Iniciativa científica de: GECP lung cancer research

INSPIRE: Phase Ⅲ, Open-Label, Randomized, Multicenter Study

Key Eligibility Criteria
- Stage ⅢB/IV NSCLC
- ALK positive centrally confirmed by FISH (Abbott Molecular), or by local NMPA-approved tests
- ECOG PS 0-1
- ALK TKI-naïve
- Previously treated with ≤1 chemotherapy regimen

Randomized 1:1 (N=292)

Iruplinalkib 180 mg qd with 7-day lead-in at 60 mg qd

Crizotinib 250 mg bid

Stratification factors:
- Previous chemotherapy regimens (0/1)
- Baseline CNS metastases (present/no)
- Previous radiotherapy to CNS metastases (yes/no)

Treatment until PD, intolerable toxicity, and other reasons for discontinuation

100% Asian

Primary endpoint
- IRC-assessed PFS per RECIST v1.1

Key secondary endpoints
- Investigator-assessed PFS
- ORR and DoR (IRC and investigator)
- Intracranial ORR (IRC and investigator)
- OS
- Safety

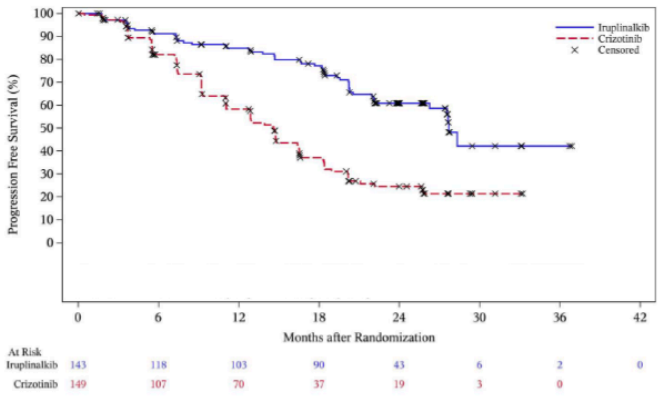
Trial fully accrued in 2 December 2020
Data cutoff date: 13 November 2022
This study is registered with Center for Drug Evaluation of NMPA (CTR20191231) and Clinicaltrials.gov (NCT04632758).

Abbreviations: NSCLC, non-small cell lung cancer; NMPA, National Medical Products Administration; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committees; CNS, central nervous system; PFS, progression-free survival; ORR, objective response rate; DoR, duration of response; OS, overall survival; PD, progressive disease

Conclusions

- Iruplinalkib demonstrated significantly improved progression-free survival (PFS) vs crizotinib in this preplanned interim analysis
  - median PFS 27.70 vs 14.62 months; hazard ratio (HR)=0.344
- Iruplinalkib showed high objective response rate (ORR) (93.0%) and responses were durable (median DoR 26.78 months)
- Iruplinalkib showed improved central nervous system (CNS) efficacy vs crizotinib
  - Intracranial ORR 90.9% vs 60.0%
  - Intracranial response was durable with iruplinalkib (median intracranial DoR 20.14 vs 9.26 months)
- Iruplinalkib was well tolerated without new safety signals
- Iruplinalkib may be a new treatment option for patients with advanced *ALK*-positive and ALK TKI-naïve non-small cell lung cancer (NSCLC)

Primary Endpoint: IRC-Assessed PFS (ITT)



	Iruplinalkib (N=143)	Crizotinib (N=149)
Median PFS (95% CI), mo	27.70 (26.25-NE)	14.62 (11.07-16.49)
Hazard ratio (98.02% CI)	0.344 (0.226-0.523)	
P value (log-rank test)	<0.0001	

	Median follow-up (range), mo
Iruplinalkib	23.98 (0-36.9)
Crizotinib	24.54 (0-33.2)

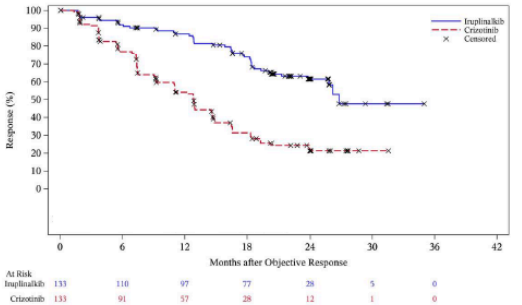
IRC-assessed objective response

IRC-assessed objective response rate (ITT Population)

	Iruplinalkib (N=143)	Crizotinib (N=149)
Objective response, n (%)		
PR	133 (93.0)	133 (89.3)
ORR, n (%)	133 (93.0)	133 (89.3)
95% CI	87.5-96.6	83.1-93.7
Difference in ORR, %	3.7 (P=0.2694)	
SD*, n (%)	5 (3.5)	9 (6.0)
Time to objective response, months, median (range)	1.84 (0.5-11.1)	1.84 (0.9-9.1)

Abbreviations: ITT, Intention-To-Treat; CI, confidence interval; IRC, independent review committee; ORR, objective response rate; PR, partial response; SD, stable disease
*Including non-CR/non-PD
Note: Miettinen-Nurminen method was used to analyze the difference in ORR.

IRC-assessed DoR (ITT)



	Iruplinalkib (N=133)	Crizotinib (N=133)
Median DoR (95% CI), mo	26.78 (25.79-NE)	12.88 (10.97-14.72)
Hazard ratio (95% CI)	0.312 (0.215-0.452)	
P value (log-rank test)	<0.0001	

Iruplinalkib approved in China (June 2023) for Tx of *ALK*-positive, crizotinib resistant or intolerable advanced NSCLC

Runxiang Yang, et al.

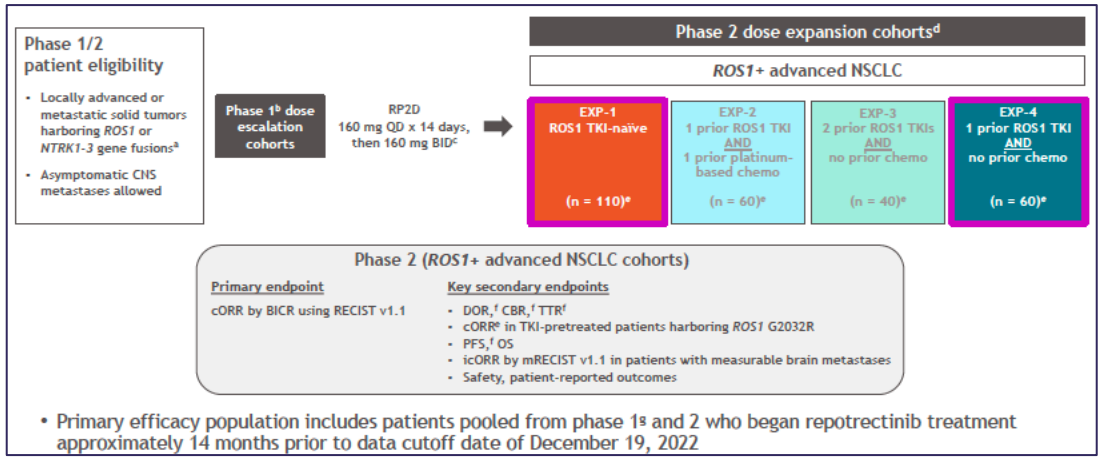
ORAL COMUNICATIONS

Iniciativa científica de:
GECP lung cancer research

- **ROS-1**
  - **OA03.06: Repotrectinib in patients with ROS1 fusion-positive (ROS1+) NSCLC: Update from the pivotal phase 1/2 TRIDENT-1 trial**

OA03.06: Repotrectinib in patients with ROS1 fusion-positive (ROS1+) NSCLC: Update from the pivotal phase 1/2 TRIDENT-1 trial

Iniciativa científica de: GECP lung cancer research

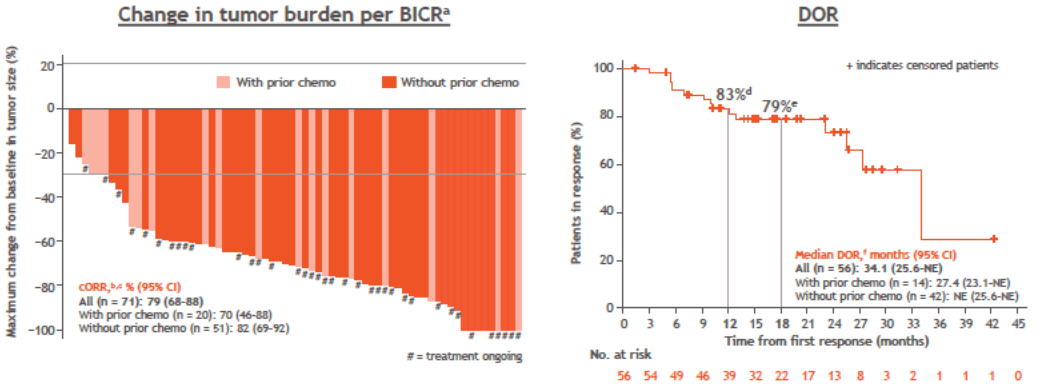


- Primary efficacy population includes patients pooled from phase 1[a] and 2 who began repotrectinib treatment approximately 14 months prior to data cutoff date of December 19, 2022

	TKI-naïve (N = 71)	1 TKI and no chemo (N = 56)
ORR	79%	38%
CR	10%	5%
PR	69%	32%
SD	15%	41%
mPFS	35 .7 months	9 months
Intracranial ORR	89%	38%

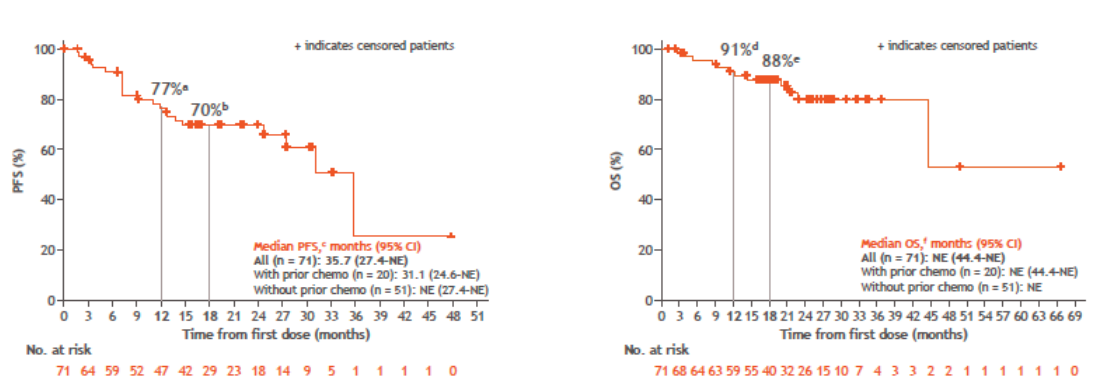
Tumor response per BICR in TKI-naïve patients with *ROS1*+ advanced NSCLC

TRIDENT-1 update: Repotrectinib in *ROS1*+ NSCLC



- Of patients in the ROS1 TKI-naïve cohort treated at the RP2D (n = 63), cORR was 78% (95% CI, 66-87) and median DOR was NE (95% CI, 25.6-NE)[g]

PFS and OS in TKI-naïve patients with *ROS1*+ advanced NSCLC



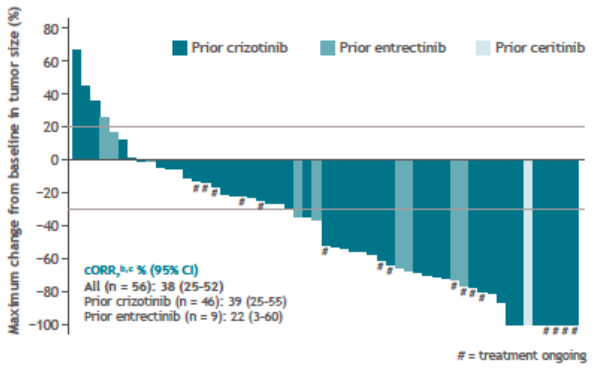
- Of patients in the ROS1 TKI-naïve cohort treated at the RP2D (n = 63), median PFS was NE months (95% CI, 27.4-NE)[g] and median OS was NE[h]

OA03.06: Repotrectinib in patients with ROS1 fusion-positive (ROS1+) NSCLC: Update from the pivotal phase 1/2 TRIDENT-1 trial

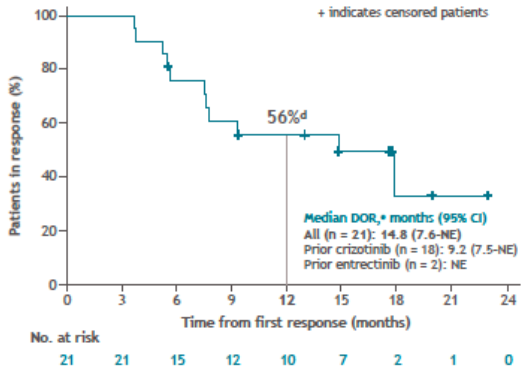
Iniciativa científica de: GECP lung cancer research

Tumor response per BICR in patients with *ROS1*+ advanced NSCLC pretreated with 1 prior ROS1 TKI and no prior chemo

Change in tumor burden per BICR[a]



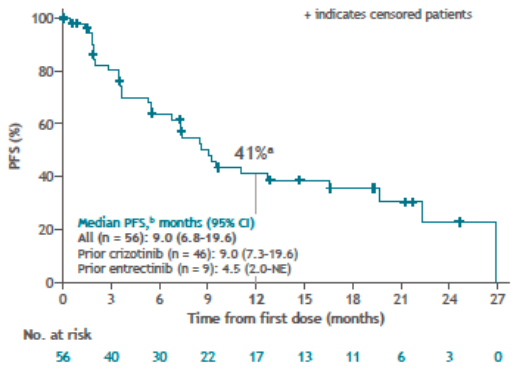
DOR



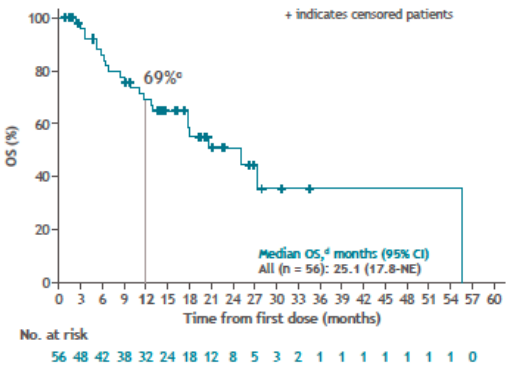
- Of patients in the 1 prior ROS1 TKI and no prior chemo cohort treated at the RP2D (n = 53), cORR was 38% (95% CI, 25-52) and median DOR was 14.8 months (95% CI, 7.5-NE)[f]

PFS and OS in patients with *ROS1*+ advanced NSCLC pretreated with 1 prior ROS1 TKI and no prior chemo

PFS



OS



- Of patients in the 1 prior ROS1 TKI and no prior chemo cohort treated at the RP2D (n = 53), median PFS was 9.0 months (95% CI, 6.8-19.6)[e] and median OS was 20.5 months (95% CI, 17.8-NE)[f]

Conclusions

- In TRIDENT-1, with a median follow-up of over 20 months, repotrectinib continued to demonstrate durable clinical activity in patients with *ROS1*+ NSCLC
  - In TKI-naïve patients, median DOR and PFS (95% CI) were 34.1 (25.6-NE) months and 35.7 (27.4-NE) months, respectively; no patient developed an emergent *ROS1* resistance mutation at disease progression
  - Clinically meaningful activity was also seen in TKI-pretreated patients, including in the presence of solvent front mutation
- Repotrectinib led to durable intracranial responses, and may have delayed or prevented the development of brain lesions in patients without baseline brain metastases
- Repotrectinib safety in patients treated at the RP2D was manageable and consistent with previous reports in all treated patients
- These results from TRIDENT-1 demonstrate repotrectinib as a potential new standard of care option for TKI-naïve and TKI-pretreated patients with *ROS1*+ locally advanced or metastatic NSCLC

ORAL COMUNICATIONS

Iniciativa científica de:
GECP
lung cancer research

- **KRAS G12C**
  - **MA06.04: KRYSTAL-1: Two-year follow-up of adagrasib (MRTX849) monotherapy in patients with advanced/metastatic KRASG12C-mutated NSCLC**
  - **MA06.05: CodeBreak 101: Safety and efficacy of sotorasib with carboplatin and pemetrexed in KRAS G12C-mutated advanced NSCLC**

MA06.04: KRYSTAL-1: Two-year follow-up of adagrasib (MRTX849) monotherapy in patients with advanced/metastatic KRASG12C-mutated NSCLC

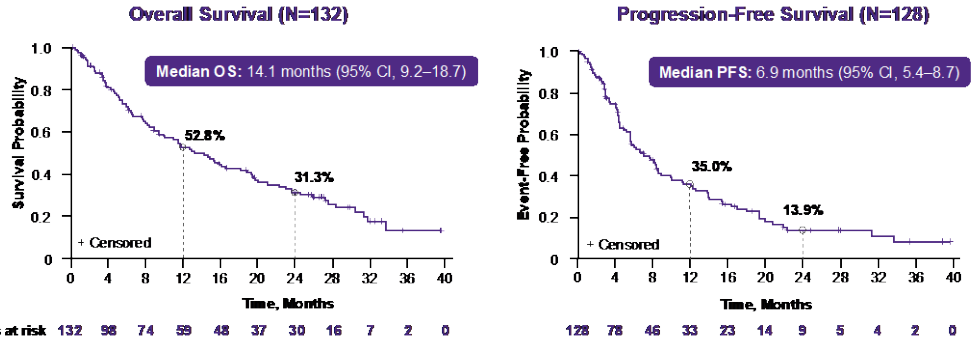
Iniciativa científica de: GECP lung cancer research

Key Eligibility Criteria[a]
- $KRAS^{G12C}$-mutated unresectable or metastatic NSCLC[b,c]
- ≥18-years-old
- ECOG PS 0–1
- Treated, stable CNS metastases were allowed

Phase 1/1b[5] Dose Escalation and Expansion	Phase 2 Cohort A[7] NSCLC Monotherapy Treatment
Adagrasib 600 mg BID N=16	**Adagrasib 600 mg BID N=116**
Key Endpoints: Safety, tolerability, recommended Phase 2 dose, and efficacy	**Primary Endpoint:** ORR (RECIST v1.1) per BICR **Secondary Endpoints:** DOR, PFS, 1-year survival rate, OS, and safety **Exploratory Endpoints:** Clinical activity in patients with CNS metastases and co-mutations[d]

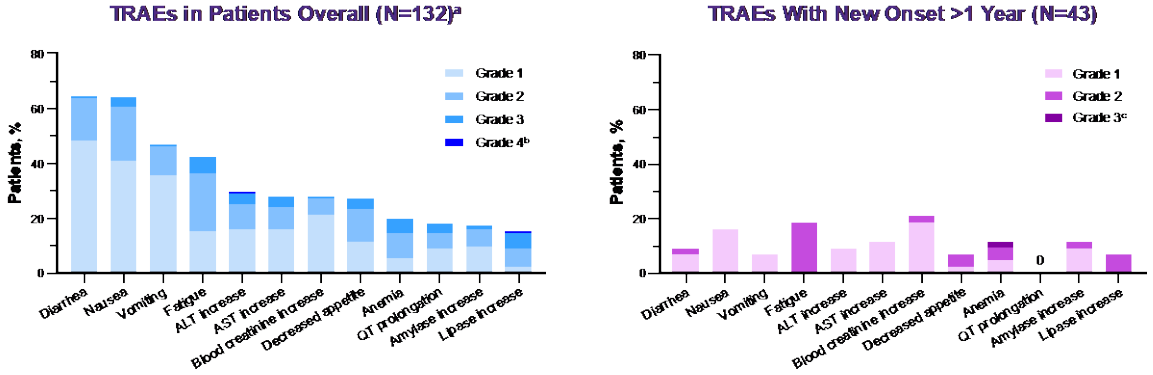
- Here we report 2-year follow-up data for 132 patients in Phase 1/1b dose escalation and expansion cohorts and Phase 2 Cohort A of KRYSTAL-1 (Data as of 1 January 2023; median follow-up: 26.9 months)
- Patients were administered adagrasib 600 mg BID orally (capsule, fasted)
- Baseline characteristics were consistent with those previously reported[5,7]

Efficacy Outcomes at Two-Years



- Objective responses were observed in 43% of patients (55/128); DCR was 80%
- Median DOR was 12.4 months (95% CI, 7.0–15.1)[a]

Treatment-Related Adverse Events and Long-Term Safety



- ≥1 TRAE occurred in 128/132 (97%) patients
- 0/12 (0%) patients[d] who received IO <30 days before adagrasib had Grade ≥3 hepatotoxicity[e]
- One patient discontinued treatment due to Grade 3 hepatotoxicity
- 43/132 patients (32.6%) received adagrasib for >1 year
- 29 of these 43 patients (67%) had a new onset TRAE after >1 year
- New onset Grade ≥2 GI TRAEs occurred in 1 patient (2%; Grade 2 diarrhea); no patients had Grade ≥2 hepatotoxicity with onset >1 year

Conclusions and Future Directions

- In this pooled analysis of patients with previously treated $KRAS^{G12C}$-mutated NSCLC, adagrasib demonstrated durable efficacy, with a median OS of 14.1 months and 2-year OS rate of 31%
- Exploratory analyses suggested durable clinical benefit in patients with treated, stable CNS metastases at baseline (median OS of 14.7 months), with clinical benefit noted across most baseline co-mutations
- Adagrasib had a manageable long-term safety profile; most TRAEs with onset >1 year were of low grade and included fewer GI TRAEs
- Treatment management by dose modification did not lead to a decrease in OS (2-year OS rate of 32%)
- Adagrasib was associated with a low rate of Grade ≥3 hepatotoxicity and was not observed in any patients who received adagrasib within 30 days of prior IO
- A confirmatory Phase 3 study is evaluating adagrasib vs docetaxel in previously treated patients with $KRAS^{G12C}$-mutated NSCLC, in North America, Europe, Asia, and Australia (KRYSTAL-12; NCT04685135)

Shirish Gadgeel, et al.

MA06.05: CodeBreak 101: Safety and efficacy of sotorasib with carboplatin and pemetrexed in KRAS G12C-mutated advanced NSCLC

Iniciativa científica de: GECP lung cancer research

Phase 1b CodeBreaK 101 Study

Key eligibility criteria
- *KRAS* G12C–mutated advanced NSCLC, identified through molecular testing
- Measurable disease per RECIST v1.1
- ECOG ≤ 2
- No active brain metastases

→ **Induction phase**: Sotorasib: 960 mg oral daily + Carboplatin: AUC 5 IV Q3W* + Pemetrexed: 500 mg/m² IV Q3W

→ **Maintenance phase†**: Sotorasib: 960 mg oral daily + Pemetrexed: 500 mg/m² IV Q3W

→ Data were pooled and analyzed by exposure to prior therapy in the locally advanced/metastatic setting‡

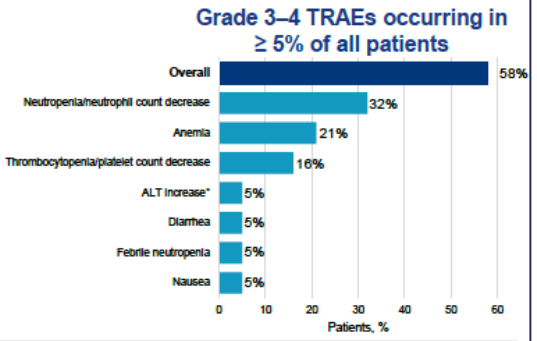
First-line (n = 25)

Second-line (n = 13)

Primary Endpoints: Safety and tolerability (including DLT)
Secondary Endpoints: Anti-tumor efficacy (ORR, DCR, DOR, TTR, OS, PFS, duration of SD) and PK

Safety

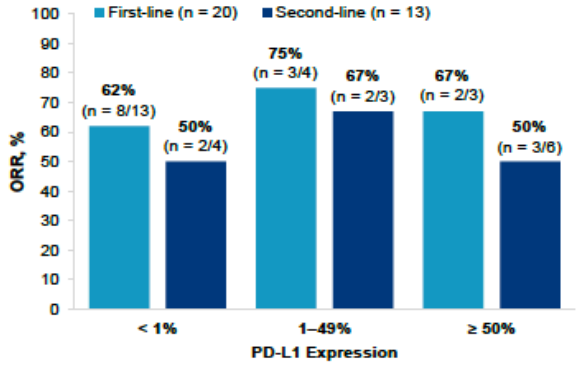
TRAEs, n (%)	Sotorasib + Carboplatin + Pemetrexed	
	First-line (n = 25)	Second-line (n = 13)
Any grade	23 (92)	13 (100)
Grade 1	4 (16)	1 (8)
Grade 2	7 (28)	2 (15)
Grade 3	10 (40)	8 (62)
Grade 4	2 (8)	2 (15)
TRAEs leading to discontinuation of any treatment	3 (12)	4 (31)
Discontinuation of sotorasib	2 (8)	2 (15)
Discontinuation of carboplatin	1 (4)	2 (15)
Discontinuation of pemetrexed	3 (12)	3 (23)



- The most common TRAEs were neutropenia/neutrophil count decrease (53%), anemia (39%), and thrombocytopenia/platelet count decrease (37%)
- TRAEs were consistent with sotorasib and platinum doublet-based regimens,[3,4] and no fatal AEs were observed

Efficacy

Response by Investigator Assessments*	Sotorasib + Carboplatin + Pemetrexed	
	First-line (n = 20)	Second-line (n = 13)
ORR, n (%)	13 (65)†	7 (54)
Best overall response, n (%)		
Complete response	0	1 (8)
Partial response	13 (65)	6 (46)
Stable disease	7 (35)	4 (31)
Progressive disease	0	1 (8)
Not evaluable / not done	0	1 (8)
DCR (95% CI)	20 (100) (83.2, 100)	11 (85) (54.6, 98.1)



- ORR was 65% in the first-line setting and 54% in the second-line setting
- ORR was similar across PD-L1 expression levels

Conclusions

- Sotorasib in combination with pemetrexed and carboplatin showed promising clinical activity in *KRAS* G12C–mutated advanced NSCLC among patients treated in the first- and second-line settings
  - Common TRAEs were consistent with sotorasib and platinum doublet-based regimens[3,4]
  - ORR was 65% and 54% in the first- and second-line settings, respectively
  - DCR was 100% and 85% in the first- and second-line settings, respectively
- Longer follow-up is ongoing to assess the durability of this combination
- Sotorasib with pemetrexed and carboplatin versus pembrolizumab with pemetrexed and carboplatin is being evaluated in the first-line setting in patients with *KRAS* G12C-mutated advanced NSCLC, negative for PD-L1 (Phase 3 CodeBreaK 202 trial; NCT05920356)

ORAL COMUNICATIONS

Iniciativa científica de: GECP lung cancer research

- **HER-2**
  - **MA13.11: Trastuzumab Deruxtecan in patients with HER2-mutant metastatic non-small cell lung cancer: primary results of DESTINY-Lung02**
- **HER-2 Exon 20 Insertion**
  - MA13.09: Efficacy and safety of poziotinib in HER2 Exon 20 Insertion NSCLC patients who received at least 2 previous systemic therapies

MA13.11: Trastuzumab Deruxtecan in patients with HER2-mutant metastatic non-small cell lung cancer: primary results of DESTINY-Lung02

Iniciativa científica de: GECP lung cancer

DESTINY-Lung02

Blinded, randomized, multicenter, international, noncomparative, phase 2 trial (NCT04644237)

Study Design

Key Eligibility Criteria[a]
- Metastatic *HER2*m[b] NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

Stratification Factor:
- Prior anti–PD-(L)1 treatment

R 2:1 → N = 152

- T-DXd 5.4 mg/kg Q3W N = 102[c]
- T-DXd 6.4 mg/kg Q3W N = 50

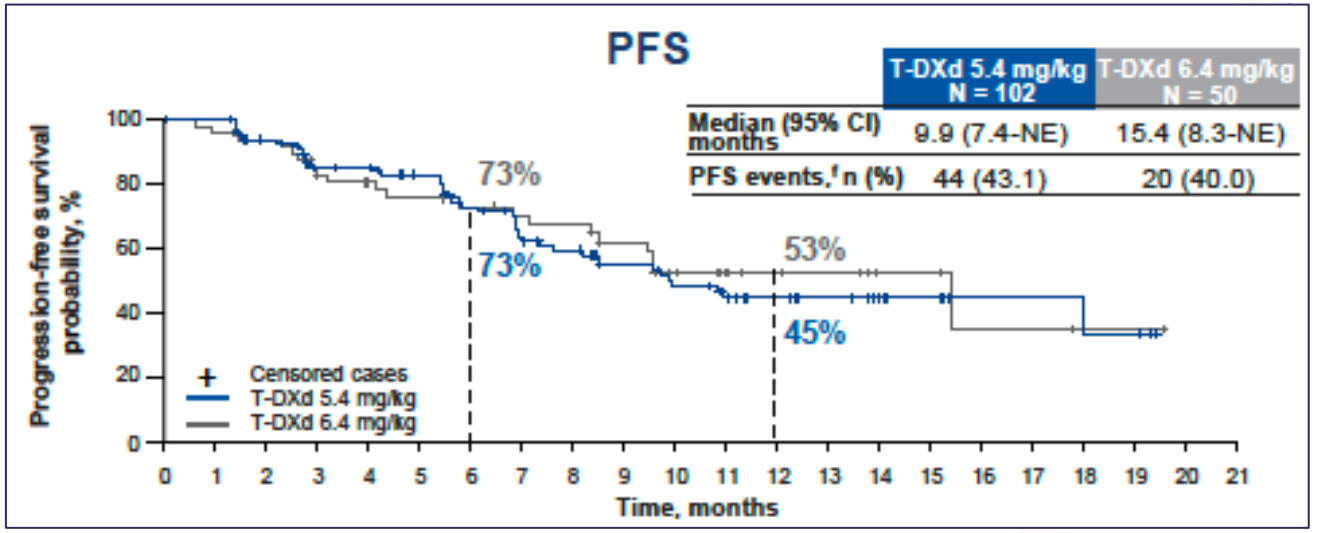
Primary Endpoint
- Confirmed ORR by BICR

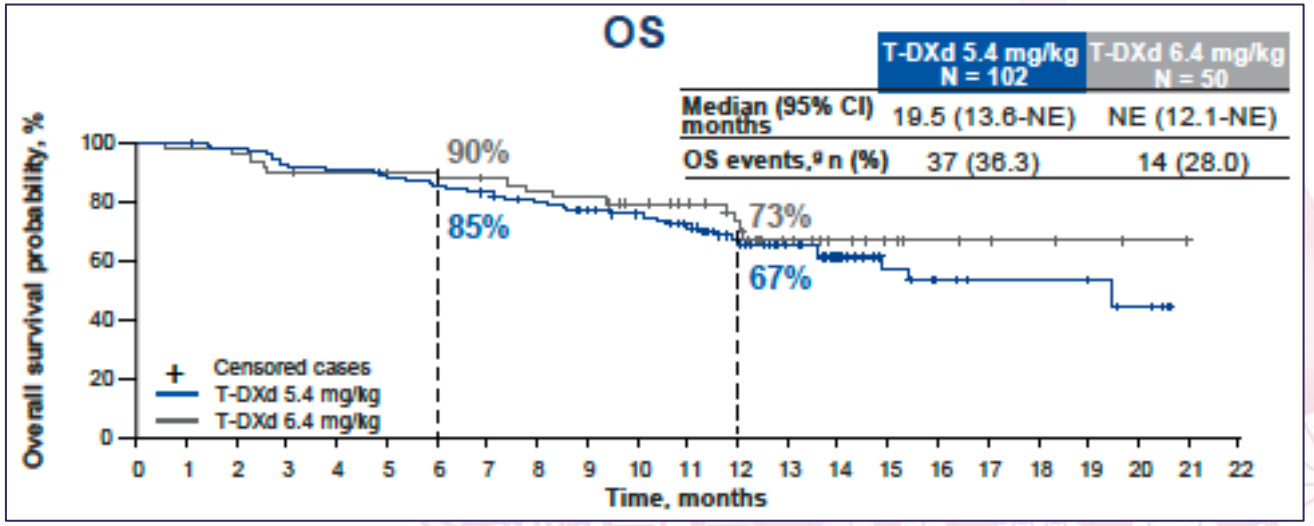
Secondary Endpoints
- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

Patients and investigators were blinded to the dose level

Primary analysis data cutoff: 23 December 2022

Efficacy summary	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Confirmed ORR,[a] n (%) [95% CI]	**50 (49.0)** [39.0-59.1]	**28 (56.0)** [41.3-70.0]
CR | PR	1 (1.0) | 49 (48.0)	2 (4.0) | 26 (52.0)
SD | PD	45 (44.1) | 4 (3.9)	18 (36.0) | 2 (4.0)
Non-evaluable[b]	3 (2.9)	2 (4.0)
DCR,[c] n (%) [95% CI]	95 (93.1) [86.4-97.2]	46 (92.0) [80.8-97.8]
Median DoR,[d,e] months (95% CI)	16.8 (6.4-NE)	NE (8.3-NE)
Median TTIR,[d] months (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Median follow-up, months (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)



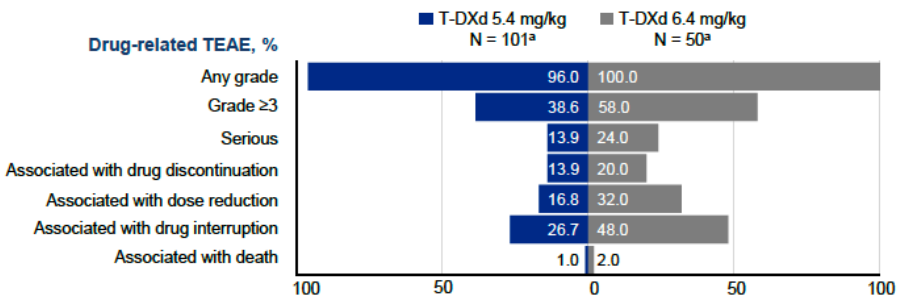


MA13.11: Trastuzumab Deruxtecan in patients with HER2-mutant metastatic non-small cell lung cancer: primary results of DESTINY-Lung02

Iniciativa científica de: GECP lung cancer research

Overall Safety Summary

Overall Safety



Adjudicated Drug-Related ILD

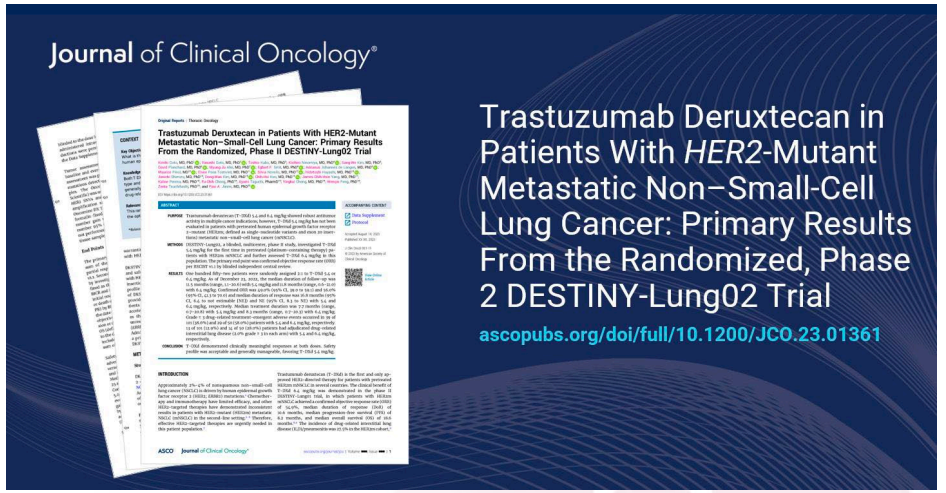
Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101[a]	T-DXd 6.4 mg/kg N = 50[a]
Any grade, n (%)	**13 (12.9)**	**14 (28.0)**
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

- **Median treatment duration** was 7.7 months (range, 0.7-20.8) with T-DXd 5.4 mg/kg and 8.3 months (range, 0.7-20.3) with T-DXd 6.4 mg/kg
- The **most common any-grade TEAEs** in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms included **nausea** (67.3% and 82.0%), **neutropenia** (42.6% and 56.0%), and **fatigue** (44.6% and 50.0%)
- The **most common grade ≥3 TEAEs** in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms included **neutropenia** (18.8% and 36.0%) and **anemia** (10.9% and 16.0%)

Conclusions

- **T-DXd** demonstrated **deep and durable responses** at **both the 5.4 mg/kg and 6.4 mg/kg dose**
  - The lower limit of the ORR 95% CI of both doses exceeded the benchmark of 26.4%
  - Responses were consistent regardless of *HER2* mutation type, *HER2* amplification status, and prior systemic anticancer therapy
- The **safety profile** was **acceptable and generally manageable at both doses** and **favored the 5.4 mg/kg dose**
  - The observed safety profile was consistent with previous studies and no new safety signals were observed
  - Lower incidence of drug-related grade ≥3 TEAEs, serious TEAEs, and TEAEs associated with study drug discontinuations, dose reductions, and drug interruptions were observed with the 5.4 mg/kg dose
  - Adjudicated drug-related ILD rate was lower in the T-DXd 5.4 mg/kg arm than in the 6.4 mg/kg arm

Primary analysis results of DESTINY-Lung02 support the use of T-DXd 5.4 mg/kg for patients with previously treated *HER2*m NSCLC and reinforce T-DXd as the standard of care in this population



Trastuzumab Deruxtecan in Patients With *HER2*-Mutant Metastatic Non–Small-Cell Lung Cancer: Primary Results From the Randomized, Phase II DESTINY-Lung02 Trial

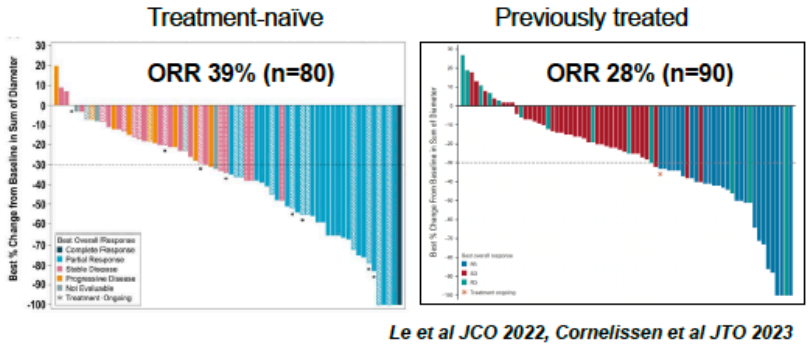
Koichi Goto, MD, PhD[1]; Yasushi Goto, MD, PhD[2]; Toshio Kubo, MD, PhD[3]; Kiichiro Ninomiya, MD, PhD[4]; Sang-We Kim, MD, PhD[5];

MA13.09: Efficacy and safety of poziotinib in HER2 Exon 20 Insertion NSCLC patients who received at least 2 previous systemic therapies

Iniciativa científica de: GECP lung cancer research

Poziotinib for HER2 exon20 insertion NSCLC in ZENITH20 trial

	Treatment-naïve	Previously treated
ORR %	39	28 (19-38)
CR	1%	0
PR	38%	28%
SD	34%	42%
PD	11%	14%
NE	16%	16%
DCR %	73	70
PFS (mon)	5.6	5.5
DoR (mon)	5.7	5.1



Le et al JCO 2022, Cornelissen et al JTO 2023

- In ZENITH20 trial, patients with HER2 exon 20 insertion NSCLC who previously received at least two lines of systemic therapy were identified (n=69)
- All patients received poziotinib 16mg daily

Drug exposure and side effects

- Median dose intensity 74%
- Rash, diarrhea, stomatitis, and paronychia are common

	16 mg QD (N = 69)
Duration of Treatment (Days), median (min, max)	114 (1, 972)
Relative Dose Intensity, median (min, max)	74 (21, 100)
Patients with Dose Interruption, n (%)	57 (83)
Days to First Dose Interruption, median (min, max)	18 (3, 174)
Patients with Dose Reduction, n (%)	50 (72)
Days to First Dose Reduction, median (min, max)	36 (9, 204)

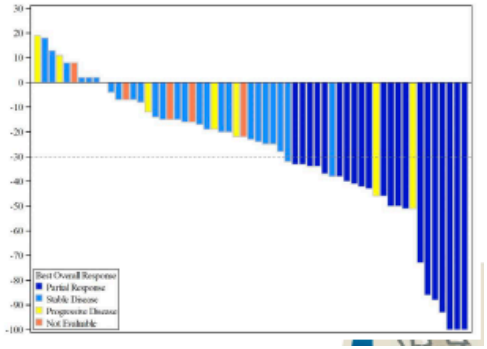
AE terms	16 mg QD (N = 69)	
	Any Grade	Grade 3-4 AE
Rash-type	61 (88)	32 (46)
Diarrhea	57 (83)	19 (28)
Stomatitis / mucositis	46 (67)	17 (25)
Paronychia	29 (42)	0

Clinical efficacy

- In this heavily pre-treated population, the ORR was 30% DCR 71% PFS 5.5 months, similar to entire cohort 2 outcome.

	16 mg QD (N = 69)	Cohort 2 Pre-treated (N=90)
Confirmed Best Overall Response, n (%)		
CR	0	0
PR	21 (30.4)	27.8%
SD	28 (40.6)	42.2%
PD	7 (10.1)	14.4%
NE	13 (18.8)	15.6%
ORR, % (95% CI)	30.4 (19.9, 42.7)	27.8 (18.9, 38.2)
DCR, % (95% CI)	71.0 (58.8, 81.3)	70 (59.4, 79.2)
Median DoR, months (95% CI)	5.5 (4.9, 8.4)	5.1 (4.2, 5.5)
Median PFS, months (95% CI)	5.6 (3.9, 7.2)	5.5 (3.9, 5.8)

Best % tumor size change



- Poziotinib demonstrated clinically meaningful efficacy (ORR 30%) in patients who received and progressed on prior two or more lines of therapy
- The responses were observed regardless of types and sequence of treatment, including in patients who received prior anti-HER2 antibody or ADC therapies.

ORAL COMUNICATIONS

Iniciativa científica de:
GECP lung cancer research

- **MET Exon 14 mutation**
  - OA21.03: A phase 3b study of 1L savolitinib in patients with locally advanced or metastatic NSCLC harboring MET Exon 14 mutation
  - OA21.04: Amivantamab in patients with advanced NSCLC and MET Exon 14 skipping mutation: results from the CHRYSALIS study
  - OA21.05: Tepotinib + Osimertinib in EGFR-mutant NSCLC with MET amplification following 1L Osimertinib: INSIGHT 2 primary analysis

OA21.03: A phase 3b study of 1L savolitinib in patients with locally advanced or metastatic NSCLC harboring MET Exon 14 mutation

Iniciativa científica de: GECP lung cancer research

Study design – 1L patients (treatment naive)

Study population:
- Locally advanced or metastatic NSCLC
- *MET*ex14+ & EGFR/ALK/ROS1-
- Naïve to systemic anti-tumor treatment
- Naïve to *MET* inhibitor

→

Savolitinib treatment:
- 600mg (BW≥50kg), or
- 400mg (BW<50kg)

Orally, once daily, 21 days/cycle

Tumor evaluation by investigators
- Within 1 year: every 6 weeks
- After 1 year: every 12 weeks

(Independent review retrospectively)

→

EOT

Treatment until disease progression, death, or unacceptable toxicity

Primary Endpoint:
- ORR (RECIST v1.1) by IRC

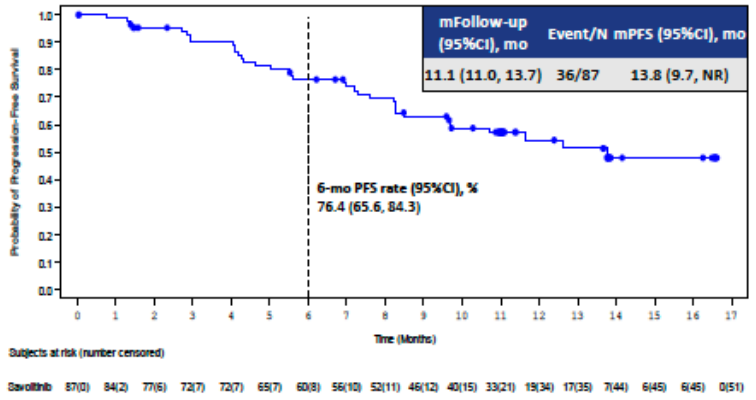
Secondary Endpoints:
- ORR by investigator, DCR, DoR, TTR, PFS, 6-month PFS rate, OS
- Safety and tolerability

Efficacy (IRC assessment)

	FAS N=87, n (%)	TRES N=84, n (%)
BOR		
PR	51 (58.6)	51 (60.7)
SD	29 (33.3)	29 (34.5)
PD	5 (5.7)	4 (4.8)
NE*	2 (2.3)	-
ORR	51 (58.6)	51 (60.7)
Exact 95%CI	(47.6, 69.1)	(49.5, 71.2)
DCR	80 (92.0)	80 (95.2)
Exact 95%CI	(84.1, 96.7)	(88.3, 98.7)
mDoR (mo) (95%CI)	NR (9.7, NR)	-
mTTR (mo) (95%CI)	1.4 (1.4, 1.5)	-

ORR 58.6% by IRC in FAS (60.7% in TRES), indicating a better response in 1L patients

KM plot of PFS- (IRC Assessment) FAS



Responses occurred early and mDoR not reached (95%CI: 9.7, NR)

*Reasons for NE: all post-baseline assessments have overall response NE/No post-baseline assessments
BOR: best overall response; mDCR: median disease control rate; mDoR: median duration of response; FAS: Full Analysis Set; IRC: independent review committee; mPFS: median progression free survival; NE: not evaluable; NR: not reached; ORR: objective response rate; PD: disease progression; PR: partial response; SD: stable disease; TTR: time to response

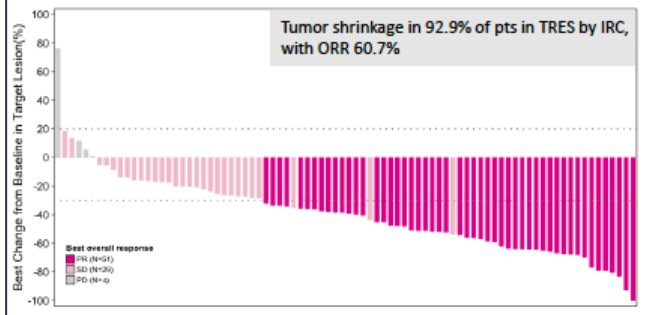
OA21.03: A phase 3b study of 1L savolitinib in patients with locally advanced or metastatic NSCLC harboring MET Exon 14 mutation

Iniciativa científica de: GECP lung cancer research

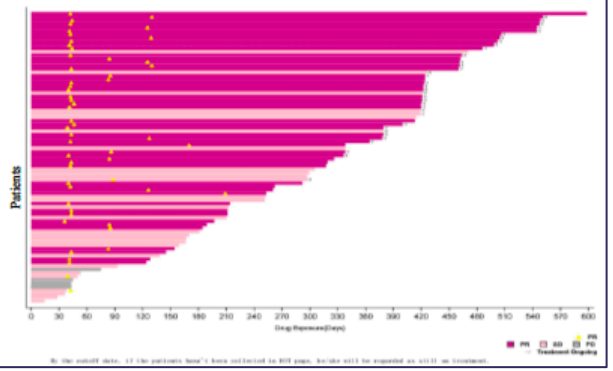
Deep and Durable Response (IRC assessment)

Waterfall Plot - Tumor Shrinkage of Target Lesion (IRC Assessment) - Tumor Response Evaluable Set

Tumor shrinkage in 92.9% of pts in TRES by IRC, with ORR 60.7%

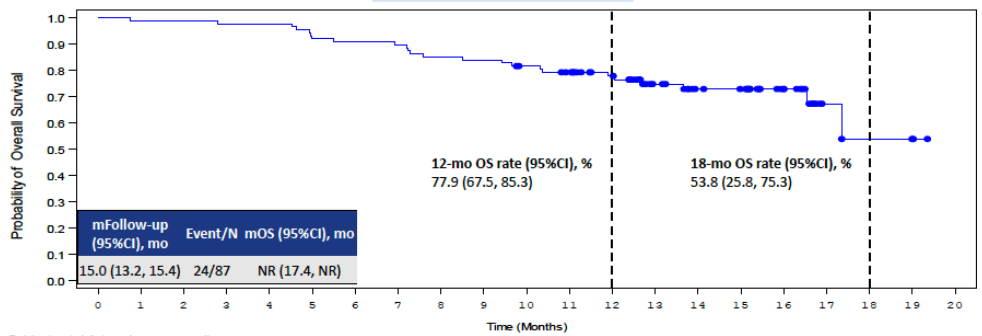


Swimmer Plot - (IRC Assessment) - Tumor Response Evaluable Set



Overall Survival (OS)

KM plot of OS - Full Analysis Set



mFollow-up (95%CI), mo	Event/N	mOS (95%CI), mo
15.0 (13.2, 15.4)	24/87	NR (17.4, NR)

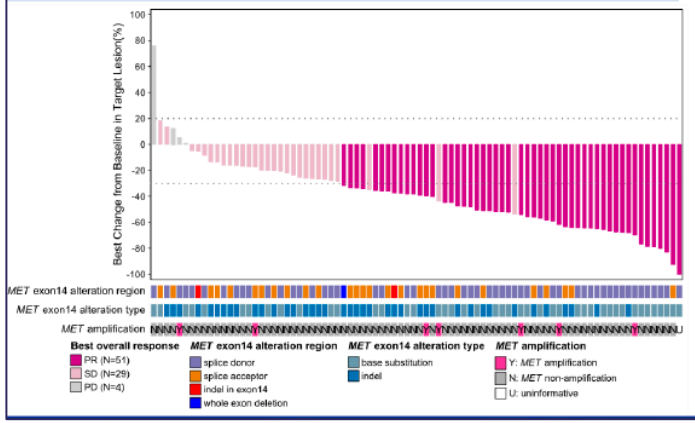
Subjects at risk (number censored)

Savolitinib	87(0)	86(0)	86(0)	85(0)	85(0)	80(0)	79(0)	78(0)	74(0)	73(0)	69(2)	65(4)	56(12)	41(25)	33(32)	31(34)	19(46)	5(59)	3(60)	2(61)	0(63)

Note: OS maturity is 27.6%

All types of METex14 could benefit from Savolitinib

Waterfall Plot - Tumor Shrinkage of Target Lesion (IRC Assessment) - Tumor Response Evaluable Set



TRES (N=84)	ORR, n (%)	(95%CI)
MET exon14 alteration type		
Base substitution (N=44)	31 (70.5)	(54.8, 83.2)
Indel (N=40)	20 (50.0)	(33.8, 66.2)
MET exon14 alteration region		
INDEL in exon14 (N=2)	1 (50.0)	(1.3, 98.7)
Splice acceptor (N=27)	15 (55.6)	(35.3, 74.5)
Splice donor (N=54)	34 (63.0)	(48.7, 75.7)
Whole exon deletion (N=1)	1 (100.0)	(2.5, 100.0)
MET amplification		
Yes (N=7)	4 (57.1)	(18.4, 90.1)
No (N=76)	46 (60.5)	(48.6, 71.6)
Unknown (N=1)	1 (100.0)	(2.5, 100.0)

Safety

Overall Safety	N=87, n (%)
Any TEAE	86 (98.9)
CTCAE grade ≥3 TEAE	70 (80.5)
Treatment related TEAE (TRAE)	85 (97.7)
CTCAE grade ≥3 TRAE	58 (66.7)
Serious TEAE (TESAE)	44 (50.6)
Treatment related TESAE	27 (31.0)
TRAE leading to dose interruption	27 (31.0)
TRAE leading to dose reduction	63 (72.4)
TRAE leading to drug discontinuation	7 (8.0)
TRAE leading to death	1 (1.1)
AESI	82 (94.3)
Treatment related AESI	81 (93.1)

Treatment related TEAE	N=87, n (%)	
PT	Total (≥20%)	Grade ≥3
Oedema peripheral	52 (59.8)	6 (6.9)
Aspartate aminotransferase increased	40 (46.0)	12 (13.8)
Alanine aminotransferase increased	36 (41.4)	14 (16.1)
Hepatic function abnormal*	30 (34.5)	19 (21.8)
Hypoalbuminaemia	30 (34.5)	0
Nausea	29 (33.3)	0
Platelet count decreased	20 (23.0)	2 (2.3)
Blood creatinine increased	20 (23.0)	0
White blood cell count decreased	19 (21.8)	2 (2.3)
Gamma-glutamyltransferase increased	18 (20.7)	5 (5.7)
Neutrophil count decreased	18 (20.7)	4 (4.6)
Blood bilirubin increased	18 (20.7)	2 (2.3)
Rash	18 (20.7)	1 (1.1)

*Hepatic function abnormal included "elevated transaminase with or without bilirubin/ALP increased".
AESI: adverse event of special interest; ALP: alkaline phosphatase; CTCAE: Common Terminology Criteria for Adverse Events; PT: Preferred Term; TEAE: treatment-emergent adverse event.

OA21.04: Amivantamab in patients with advanced NSCLC and MET Exon 14 skipping mutation: results from the CHRYSALIS study

Iniciativa científica de: GECP lung cancer

CHRYSALIS Study Design

- As of June 19, 2023, 97 patients had been enrolled in the *MET*ex14 cohort, with a median follow-up of 10.0 months

Dose-escalation phase

RP2D was identified:
Amivantamab
1050 mg IV
(1400 mg if ≥80 kg)

Dose-expansion cohorts

- Cohort A: Post–any EGFR TKI (T790M+, C797S+)
- Cohort B: Post–any EGFR TKI (T790M–, C797S–)
- Cohort C: Post-osimertinib (C797S+)
- Cohort D: *EGFR* Ex20ins[a]
- Cohort MET-1: Post–any EGFR TKI (*MET* amplified)
- **Cohort MET-2: *MET*ex14[b]**
- Cohorts WT: *EGFR* wild-type status

Endpoints

- Objective response rate (primary)
- Duration of response
- Clinical benefit rate[c]
- Progression-free survival
- Overall survival
- Adverse events

Focus of this presentation

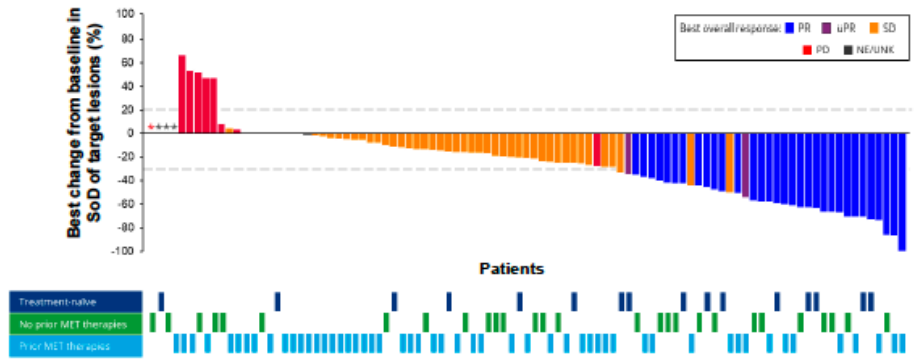
All cohorts are now closed

CHRYSALIS also included 2 additional combination cohorts:

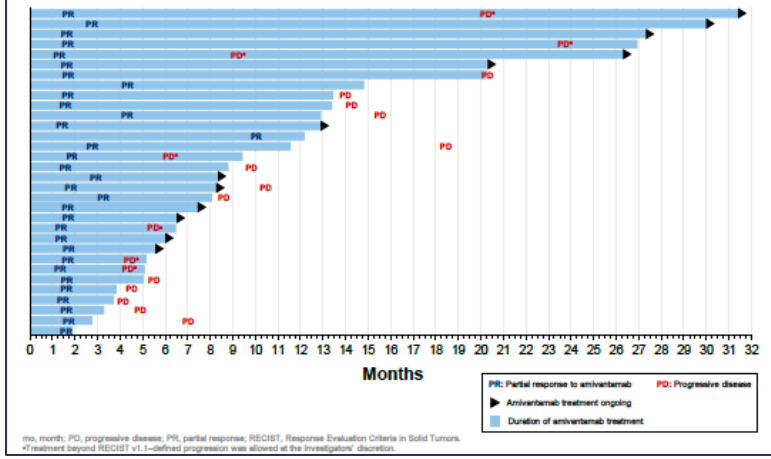
- *Amivantamab + lazertinib*
- *Amivantamab + carboplatin-pemetrexed*

- The **ORR[a] was 33%**, with a total of 32 PRs observed
- Responses to amivantamab were observed in both treatment-naïve and prior treatment settings
  - Treatment-naïve: 8 PRs / 16; **ORR[a] = 50%**
  - No prior MET therapies: 13 PRs / 28; **ORR[a] = 46%**
  - Prior MET therapies: 11 PRs / 53; **ORR[a] = 21%**

Best change from baseline in SoD of target lesions

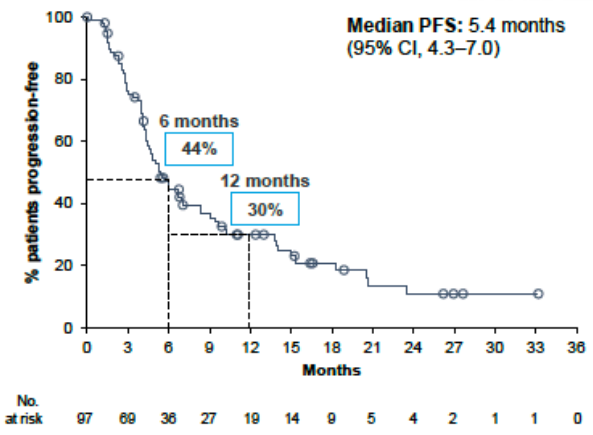


Duration of response and treatment in patients responding to amivantamab (n = 32)

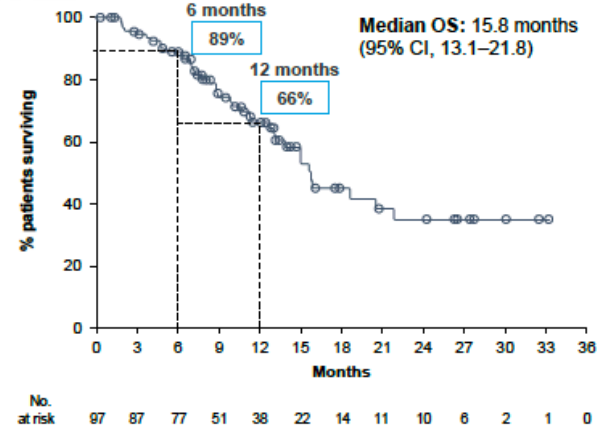


- Median duration of exposure was 8.6 mo (range, 1.9–31.4)
- The median duration of response was 11.2 mo (95% CI, 5.3–19.0)
- 15/32 patients (47% of responders) had a response duration ≥6 months
- Among 15 patients with responses ≥6 months:
  - 10 had durable responses at 12 mo
  - 6 had durable responses at 18 mo
  - 3 had durable responses at 24 mo
- 38% (12/32) of responders remain on treatment at the time of data cutoff

PFS (n = 97)



OS (n = 97)



OA21.04: Amivantamab in patients with advanced NSCLC and MET Exon 14 skipping mutation: results from the CHRYSALIS study

Iniciativa científica de: GECP lung cancer research

AEs (≥20%) by preferred term, n (%)	Median follow-up: 10.0 months (n = 97)	
	Total	Grade ≥3
Associated with EGFR inhibition		
Paronychia	47 (48.5)	0
Dermatitis acneiform	40 (41.2)	1 (1.0)
Rash	37 (38.1)	1 (1.0)
Stomatitis	27 (27.8)	0
Pruritus	20 (20.6)	0
Associated with MET inhibition		
Hypoalbuminemia	37 (38.1)	2 (2.1)
Peripheral edema	36 (37.1)	4 (4.1)
Other		
Infusion-related reaction	70 (72.2)	4 (4.1)
Fatigue	28 (28.9)	2 (2.1)
Dyspnea	22 (22.7)	5 (5.2)
Hypokalemia	22 (22.7)	3 (3.1)
Nausea	21 (21.6)	0
Decreased appetite	21 (21.6)	0
Alanine aminotransferase increased	20 (20.6)	2 (2.1)
AEs of special interest by grouped term, n (%)		
Rash[a]	76 (78.4)	3 (3.1)
Venous thromboembolism[b]	8 (8.2)	2 (2.1)
Interstitial lung disease[c]	4 (4.1)	1 (1.0)

Treatment benefits

- Amivantamab demonstrated meaningful antitumor activity in patients with *MET*ex14 advanced NSCLC
  - Treatment-naïve: ORR = 50%
  - No prior MET therapies: ORR = 46%
  - Prior MET therapies: ORR = 21%
- Amivantamab provided durable clinical benefit (median DOR, 11.2 months), with 38% of patients who responded ongoing; the longest response is 29 months to date

Safety

- Safety profile was consistent with prior reports[1]
- No new safety signals were observed

Key takeaway & next steps

- Amivantamab is a bispecific EGFR-MET antibody with immune cell–directing activity and the ability to target *MET*ex14 NSCLC in treatment-naïve patients and those with acquired resistance to prior MET therapies due to a unique mode of action
- METalmark (ClinicalTrials.gov Identifier: NCT05488314) is evaluating amivantamab plus capmatinib in patients with *MET*ex14 or *MET* amplification

OA21.05: Tepotinib + Osimertinib in EGFR-mutant NSCLC with MET amplification following 1L Osimertinib: INSIGHT 2 primary analysis

Iniciativa científica de: GECP lung cancer research

INSIGHT 2: an Open-label, Two-arm Phase II Study[1]

- *MET*amp is a common driver of secondary resistance in patients with *EGFR*m NSCLC following treatment with 1L osimertinib,[2,3] that may be responsive to MET inhibition
- TBx FISH is the gold standard for *MET*amp detection, with rates of ~50% compared with ~15% by LBx NGS testing[4,5]

Key inclusion criteria

- Locally advanced/metastatic *EGFR*m NSCLC
- Acquired resistance to 1L osimertinib
- ***MET*amp by:**
  - **TBx FISH** (GCN ≥5 and/or *MET*:*CEP7* ≥2) and/or **LBx NGS** (≥2.3 Archer®)
- ECOG PS of 0 or 1

Tepotinib 500 mg QD
+
Osimertinib 80 mg QD

Tepotinib monotherapy 500 mg QD*

Endpoints

Primary endpoint
- **Objective response by IRC** in patients with **TBx FISH** *MET*amp

Selected secondary endpoints
- Objective response in patients with LBx NGS *MET*amp
- DOR
- PFS
- OS
- HRQoL
- Safety
- Biomarkers

Selected tertiary endpoints
- RANO-BM

- The trial aims for an ORR in the range of ~50% with a lower limit of the corresponding exact 2-sided 95% CI (according to Clopper–Pearson) to exceed an ORR of 35%
- Subgroup analysis of Asian patients† was preplanned
- Data cut-off: March 28, 2023
- Efficacy population has ≥9 months follow-up

We now report the primary analysis

OA21.05: Tepotinib + Osimertinib in EGFR-mutant NSCLC with MET amplification following 1L Osimertinib: INSIGHT 2 primary analysis

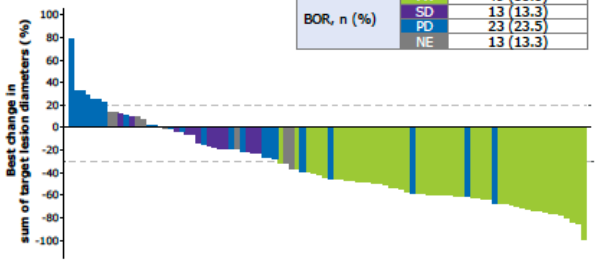
Iniciativa científica de: GECP

INSIGHT 2 Primary Analysis: Objective Response by IRC

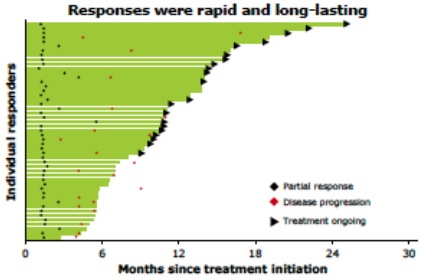
- The INSIGHT 2 primary analysis showed an ORR of 50% in patients with *EGFR*m NSCLC who have progressed on 1L osimertinib and had *MET*amp (central TBx FISH)

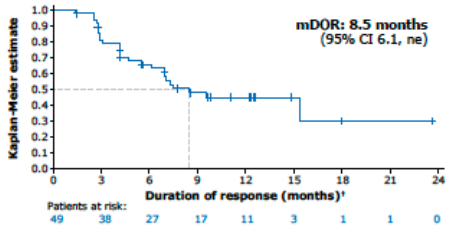
Tumor shrinkage (n=98*)

ORR, % (95% CI)		50.0 (39.7, 60.3)
BOR, n (%)	PR	49 (50.0)
	SD	13 (13.3)
	PD	23 (23.5)
	NE	13 (13.3)



Responses were rapid and long-lasting





- Patients in the monotherapy arm (n=12) showed an ORR of 8.3% (95% CI 0.2, 38.5), which has been reported previously[1]

*Four patients were excluded due to baseline/post-baseline measurement not being available.
†Only patients with a response were included in Kaplan-Meier analyses.
Abbreviations defined on last slide.
1. Mazieres J, et al. *Ann Oncol*. 2022;33:S808–S869.

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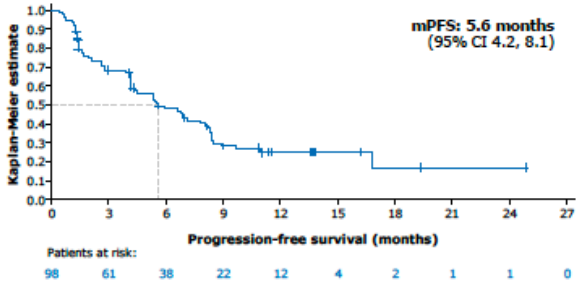
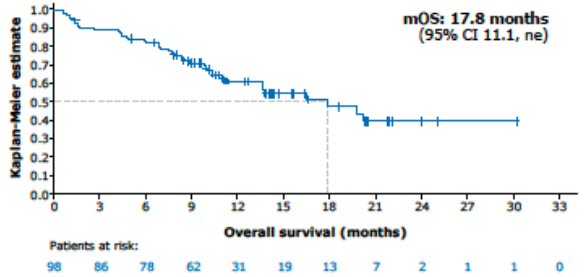
INSIGHT 2 Secondary Objectives: PFS, OS, and LBx NGS Efficacy

- PFS and OS were clinically meaningful in patients with *EGFR*m NSCLC who have progressed on 1L osimertinib and had *MET*amp (central TBx FISH)





In patients with LBx NGS *MET*amp (n=31)

- ORR: 54.8% (95% CI 36.0, 72.7)
- mDOR: 5.7 months (95% CI 2.9, 15.4)
- mPFS: 5.5 months (95% CI 2.7, 7.2)
- mOS: 13.7 months (95% CI 9.6, ne)

- In the primary analysis (TBx FISH), **ORR was 50.0%** (95% CI 39.7, 60.3), **mDOR was 8.5 months** (95% CI 6.1, ne), **mPFS was 5.6 months** (95% CI 4.2, 8.1), and **mOS was 17.8 months** (95% CI 11.1, ne)
- In Asian patients, ORR was 59.6% (95% CI 45.1, 73.0), mDOR was 7.3 months (95% CI 4.7, ne), mPFS was 6.9 months (95% CI 5.4, 8.4) and mOS was 19.8 months (95% CI 13.6, ne)
- Efficacy outcomes were meaningful in patients with LBx NGS METamp (ORR 54.8%; 95% CI 36.0, 72.7)
- Better outcomes were observed when there were no co-occurring mechanisms of osimertinib resistance
- Tepotinib + osimertinib demonstrated a **manageable safety profile**, while maintaining HRQoL

Tepotinib + osimertinib provides a potential chemotherapy-sparing oral targeted treatment option for patients with *EGFR*m NSCLC with *MET*amp after progression on 1L osimertinib, who have a high unmet need

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