Lung Cancer UPDATES
IASLC HIGHLIGTHS
06-09 AGOSTO 2022
Viena, Austria

Iniciativa científica de:
GECP
lung cancer research

TARGETED THERAPIES 2

Rosario García Campelo

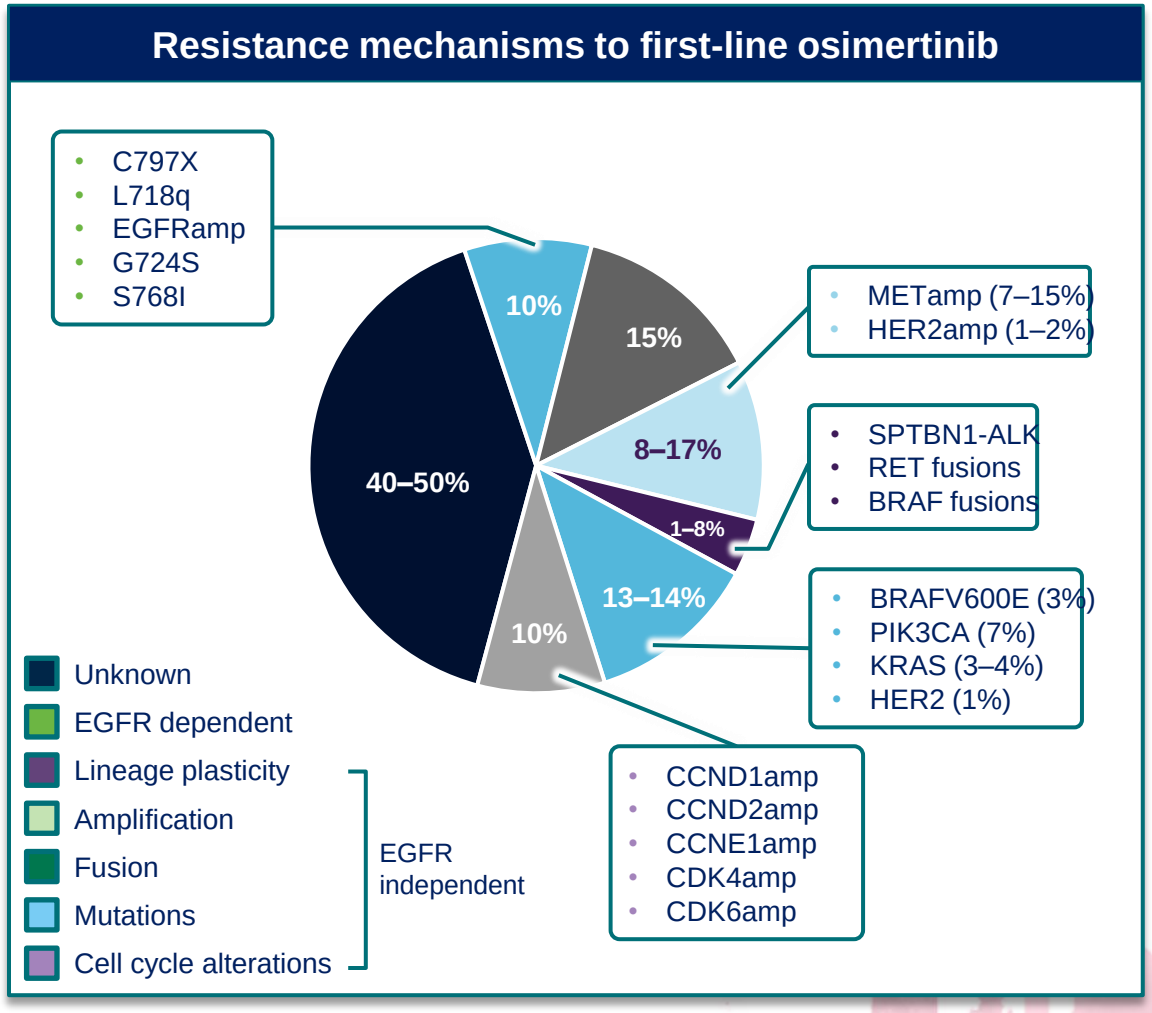
Servicio de Oncología Médica

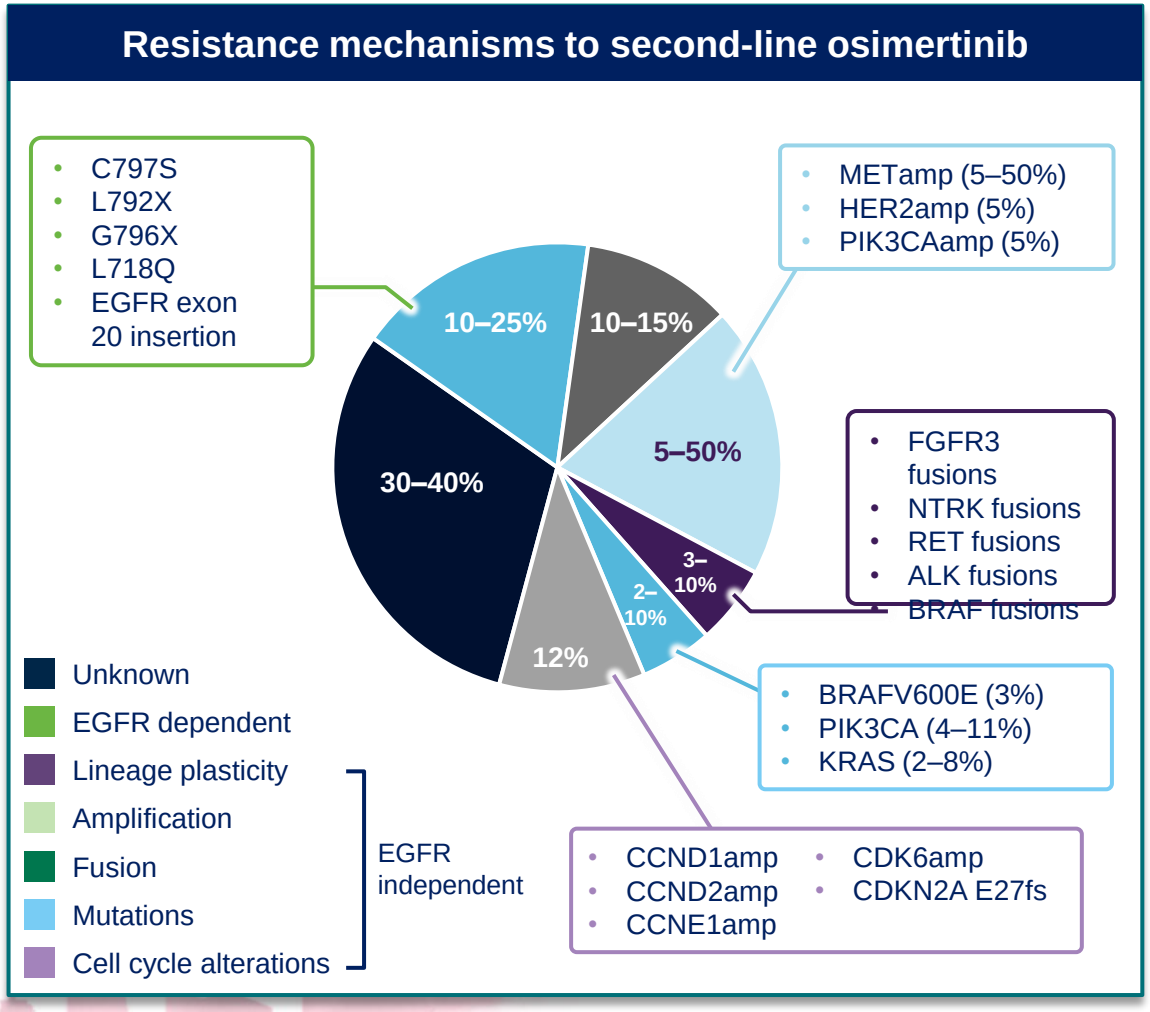
Complejo Hospitalario Universitario A Coruña

Disclosures

- Advisory boards: MSD, Bristol-Myers, Roche, Boehringer Ingelheim, Pfizer, Novartis, AstraZeneca, Lilly, Takeda
- Consultancy: MSD, Bristol-Myers, Roche, Boehringer Ingelheim, Pfizer, Novartis, AstraZeneca, Lilly, Takeda
- Speaker honoraria: MSD, Bristol-Myers, Roche, Boehringer Ingelheim, Pfizer, Novartis, AstraZeneca, Lilly, Takeda

We are not curing our patients…





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Real-World Landscape of EGFR C797X Mutation as a Resistance Mechanism to Osimertinib in NSCLC

Suresh S. Ramalingam[1], Nicole Zhang[2], Junhua Yu[2], Carin Espenschied[2], Teresa Green[3], Joshua Infantine[3], Brenton G. Mar[3]

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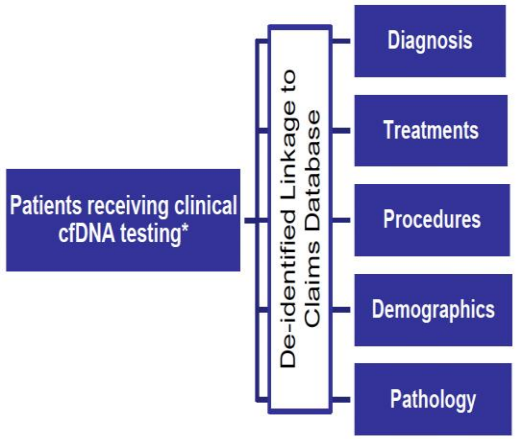
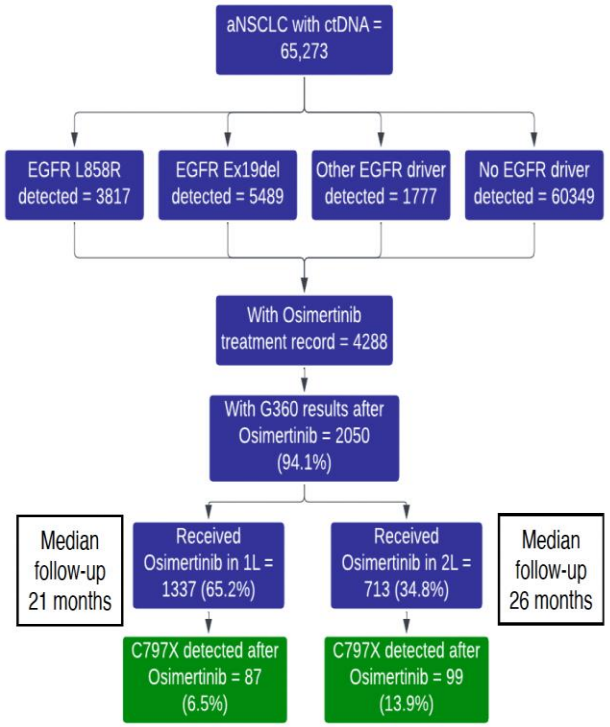
Real world data integrating Guardant360 cfDNA and INFORM data

- INFORM is an aggregated commercial payer claims database with de-identified records of over 174,000 U.S.-based advanced cancer patients with clinical cfDNA* results.

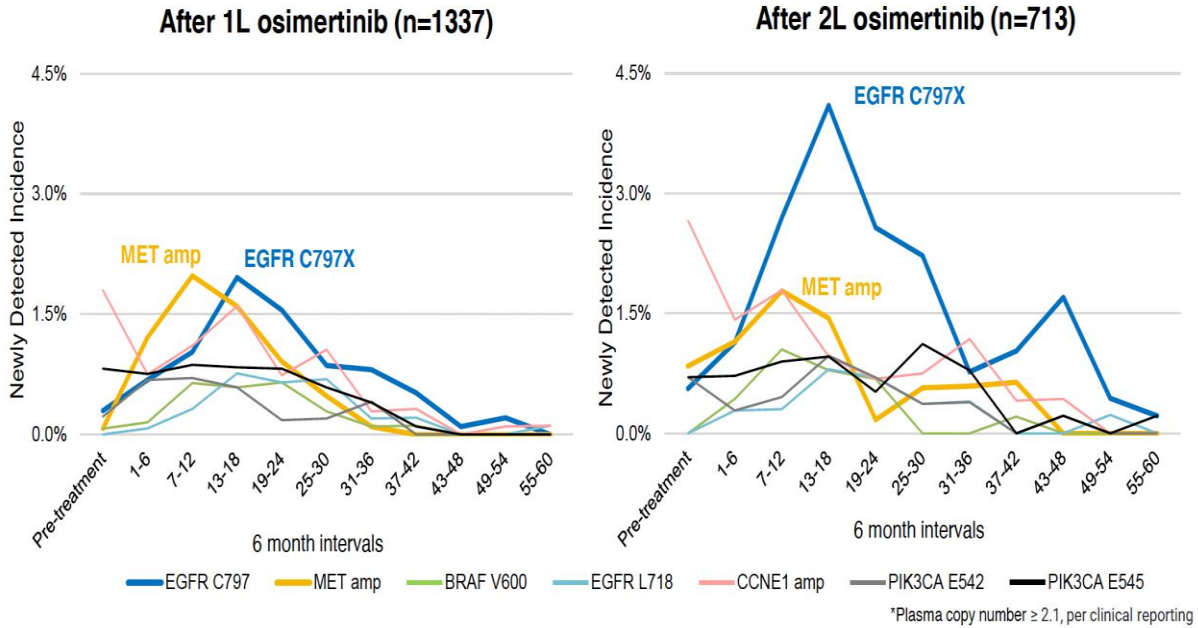




Early vs late resistance

MET amp is most common acquired resistance mechanism in 1st year of 1L osimertinib, while EGFR C797X is most common after the 1st year

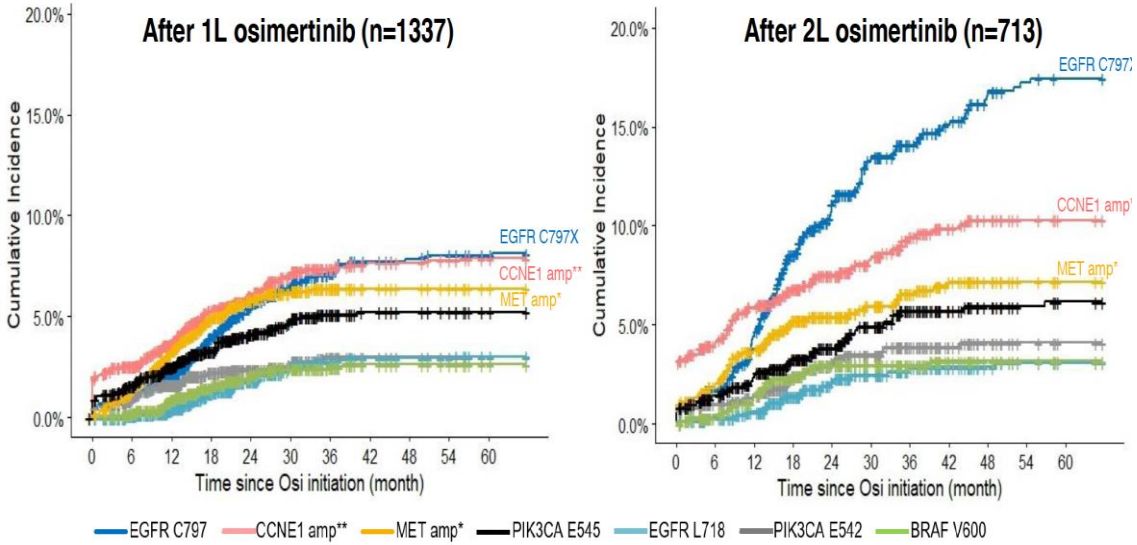
6-month Incidence of Common Acquired Resistance Mutations after osimertinib



*Plasma copy number ≥ 2.1, per clinical reporting

EGFR C797X is the most common on-target or off-target resistance mutation, cumulatively, after osimertinib treatment

Cumulative incidence of common resistance mutations after osimertinib initiation#



- The cumulative incidence of EGFR C797X in a subset of likely 1L osi progressors (n=600) was 12.5%&

#Including pts who were sequenced anytime after osimertinib. &When analysis limited to those who discontinued osimertinib within 60 days of G360 (likely progressors).
*Including focal MET amp, per clinical reporting. **including both focal and aneuploidy of CCNE1 amplification, per clinical reporting.

- MET amplification is the most common initial resistance mutation in the first year of 1L osimertinib, but EGFR C797X mutations subsequently emerge and are the most common resistance after the first year
- Cumulatively, EGFR C797X mutations were 1.25 times more common than MET amplification after 1L osimertinib and 2.4 times more common after 2L osimertinib
- In patients likely progressing after 1L osimertinib, the cumulative incidence of EGFR C797X was 12.5%

Ramalingam S, et al. MA 07.03

4th GENERATION EGFR TKI: JIN-AOS

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JIN-A02, a Highly Effective 4th Generation EGFR-TKI, Targeting EGFR C797S Triple Mutation in NSCLC

Byoung Chul Cho
Yonsei Cancer Center
Korea

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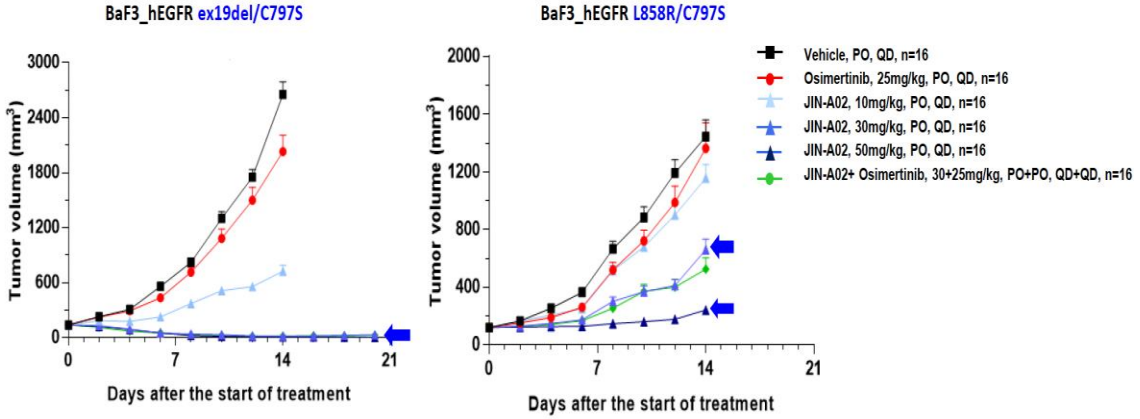
▶ **The antitumor efficacy of JIN-A02 in xenograft mouse model**



▶ **Conclusions:** JIN-A02 showed robust activities against **EGFR resistant mutations including C797S and T790M and sensitizing mutations.** JIN-A02 is a potential best-in-class fourth-generation EGFR TKI with high potency and selectivity.

JIN-A02 showed robust activities against EGFR resistant mutations including C797S and T790M and sensitizing mutations.

Cho et al. MA 07.08

4th GENERATION EGFR TKI: BBT-176

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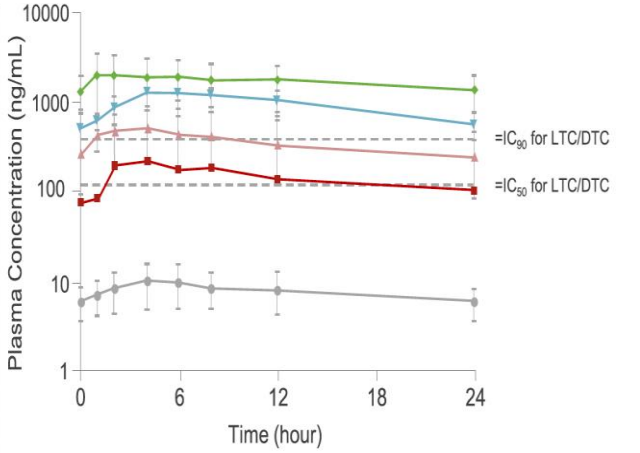
Baseline Characteristics of Enrolled Patients

CHARACTERISTIC	ALL PATIENTS (N=25)
Median age (range)	63 (38-79)
Female	17 (68%)
Asian	25 (100%)
ECOG PS (0, 1)	7 (28%), 18 (72%)
Number of prior systemic anticancer regimens	
1 (%)	2 (8%)
2 (%)	7 (28%)
≥3 (%)	16 (64%)
Prior EGFR TKI treatment	25 (100%)
Prior Gefitinib, Erlotinib, Afatinib or Dacomitinib	25 (100%)
Prior Osimertinib or Lazertinib	20 (80%)
Brain metastasis, stable (%)	10 (40%)
EGFR mutation detected by ctDNA (19del, L858R)	14 (56%), 9 (36%)*
containing C797S	8 (32%)

* In two patients, *EGFR* mutation was not detected from repeated assessment of ctDNA

PK Profile by Dose Level on Cycle 2 Day 1



- Dose escalation by 3+3 with Bayesian Logistic Regression Model
- Intra-patient dose escalation was allowed after the first cycle
- BBT-176 shows apparently dose-proportional increase in exposure
- BBT-176 achieves IC_{90} efficacy levels (in vitro Ba/F3 cells of *EGFR* triple mutation) at 160 mg QD or higher

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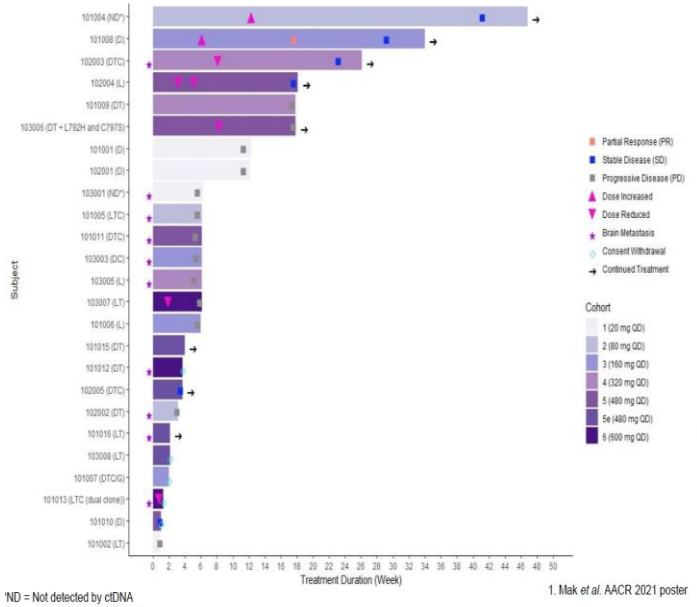
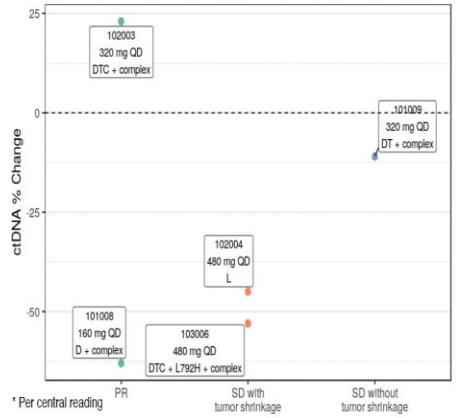
Duration of Treatment and Tumor Response, All Patients by Dose Level



*ND = Not detected by ctDNA
Data cut-off on May 23rd, 2022

1. Mak *et al.* AACR 2021 poster

Correlation between Molecular Response[1] and Radiologic Response*



* Per central reading

- Treatment-related adverse events ≥ grade 3 occurred from 320 mg QD
- Some patients withheld dosing due to diarrhea or nausea
- Common treatment-emergent AE's (≥ 10% of total patients) are nausea, diarrhea, vomiting, anorexia, constipation, dizziness, dyspepsia and platelet count decrease

Preclinical efficacy of next generation TKIs noted in both double and triple mutant models
Clinical efficacy to date modest

Lim et al. MA 07.09

Amivantamab+Lazertinib+Platinum based CT in relapsed EGFR mut NSCLC

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Amivantamab and lazertinib in combination with platinum-based chemotherapy in relapsed/refractory EGFR-mutant NSCLC

Melina Marmarelis[1], Se-Hoon Lee[2], Alexander I. Spira[3], Sai-Hong Ignatius Ou[4], Saiama Waqar[5], Shengting Li[6], Meena Thayu[6], Roland E. Knoblauch[6], Joshua M. Bauml[6], Byoung Chul Cho[7]

[1]University of Pennsylvania Perelman Center for Advanced Medicine, Philadelphia, PA, USA; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Virginia Cancer Specialists Research Institute, US Oncology Research, Fairfax, VA, USA; [4]University of California Irvine School of Medicine, Chao Family Comprehensive Cancer Center, Orange, CA, USA; [5]Washington University School of Medicine, St Louis, MO, USA; [6]Janssen R&D, Raritan, NJ, USA; [7]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

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Amivantamab and Lazertinib + Carboplatin/Pemetrexed (LACP)

- **Amivantamab**[a] is an EGFR-MET bispecific antibody with immune cell-directing activity[1-3] and **lazertinib** is a highly selective, brain-penetrant, third-generation EGFR TKI with efficacy in activating EGFR mutations, T790M, and CNS disease[4,5]
- Combining **platinum-based chemotherapy** with targeted inhibition of EGFR/MET signaling may lead to improved outcomes

CHRYSALIS-2 (NCT04077463) LACP Cohort

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

Dosing (21-day cycle)	
Lazertinib	240 mg QD
Amivantamab	1400/1750[b] mg on C1 D1/D2, C1 D8, C1 D15, and C2 D1; then 1750/2100[b] mg C3 +Q3W
Chemotherapy	Pemetrexed (500 mg/m^2)
	Carboplatin (AUC5; stopped after 4 cycles)

Primary Endpoint
- Safety (adverse events)

Other Endpoints
- Overall response rate
- Duration of response
- Clinical benefit rate[c]
- Progression-free survival
- Overall survival

Demographics and Baseline Disease Characteristics, n (%)	Total (n=20)
Median age, years (range)	61 (38–83)
Male / female	9 (45) / 11 (55)
Race	
Asian	11 (55)
White	8 (40)
Black	1 (5)
Exon 19 del/L858R	13 (65) / 7 (35)
ECOG PS 0 /1	4 (20) / 16 (80)
Brain metastases at baseline[d]	10 (50)
Median no. of prior lines (range)	2 (1–3)
Prior therapy	
1st/2nd-generation EGFR TKI	9 (45)
Osimertinib	14 (70)
Platinum-based chemotherapy[e]	5 (25)
Median follow-up = 7.1 months (range, 2.4–10.4)	

[a]Amivantamab is approved (in the United States and other countries) for the treatment of EGFR exon 20 insertion NSCLC that progressed on or after platinum-based chemotherapy.
[b]Doses for <80kg/≥80 kg.
[c]Defined as the percentage of patients achieving complete or partial response, or durable stable disease (duration of ≥11 weeks) as defined by RECIST v1.1 (response was investigator assessed).
[d]Classified via imaging of brain/CNS lesion at screening.
[e]The range of time between completion of prior platinum-based chemotherapy and LACP was 49 to 1602 days.

50% CNS+
70% post-Osimertinib

Marmarelis M, et al. MA 07.04

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Safety Profile

TEAEs (≥15%) by Preferred Term, n (%)	n=20	
	All grade	Grade ≥3
EGFR-related		
Rash	15 (75)	1 (5)
Stomatitis	12 (60)	0
Paronychia	10 (50)	0
Dermatitis acneiform	7 (35)	2 (10)
Diarrhea	5 (25)	1 (5)
MET-related		
Hypoalbuminemia	3 (15)	1 (5)
Other		
Neutropenia	17 (85)	14 (70)
Infusion related reaction (IRR)	12 (60)	0
Fatigue	10 (50)	5 (25)
Nausea	8 (40)	0
Thrombocytopenia	8 (40)	5 (25)
Constipation	7 (35)	0
Decreased appetite	7 (35)	1 (5)

TEAEs (≥15%) by Preferred Term, n (%)	n=20	
	All grade	Grade ≥3
Other continued		
Anemia	5 (25)	1 (5)
Epistaxis	5 (25)	0
Hemorrhoids	5 (25)	0
Leukopenia	5 (25)	3 (15)
Dyspepsia	4 (20)	0
Insomnia	4 (20)	0
Pulmonary embolism	4 (20)	1 (5)
Vomiting	4 (20)	0
Weight decreased	4 (20)	0
Back pain	3 (15)	0
COVID-19	3 (15)	0
Dizziness	3 (15)	0
Hypomagnesemia	3 (15)	0
Hyponatremia	3 (15)	1 (5)
Paresthesia	3 (15)	0
Peripheral Edema	3 (15)	0

- Median follow up of 7.1 months (range, 2.4–10.4) and the median number of cycles was 10 (range, 2–15)[a]
- Individual AEs were mostly low grade 1-2
- EGFR- and MET-related AEs were consistent with previously reported data on amivantamab + lazertinib
- Median cycles of carboplatin / pemetrexed were 4 and 7.5 respectively

- Rates of cytopenias were numerically high and mostly occurred within the 1st cycle however small sample size, scheduled testing on C1D8 and C1D15, and heterogenous prior treatments limit interpretation
- No patients had pneumonitis/ILD
- 1 grade 5 AE – sudden death, not attributed to any of the study drugs
- No new safety signals identified

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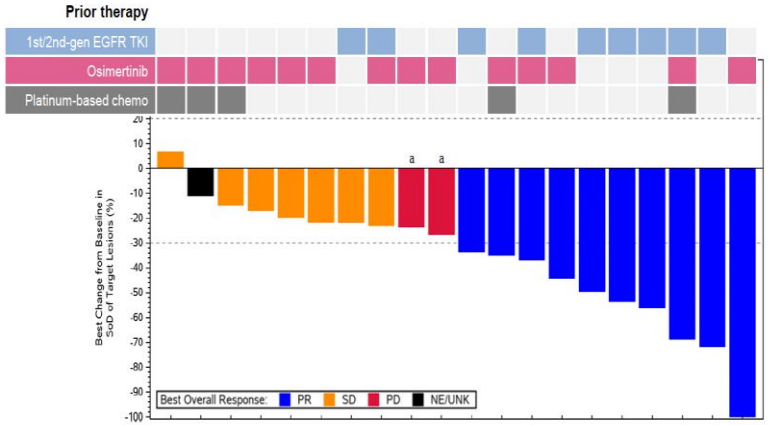
Best Antitumor Response



- For all patients (n=20):
  - **ORR is 50%** (95% CI, 27–73)
  - **CBR[b] is 80%** (95% CI, 56–94)
- In those with baseline brain metastases (n=10):
  - **ORR is 50%** (95% CI, 19–81)
  - **CBR[b] is 80%** (95% CI, 44–98)

- 2 out of 5 patients with prior platinum-based chemotherapy had a PR
  - Of the 2 PRs, 1 responded to prior chemotherapy and 1 did not; the remaining 3 did not respond to prior chemotherapy
- Of the 6 patients who received 1st/2nd-gen EGFR TKI without osimertinib, 5 of 6 (83%) had a PR; 5 of 6 tested negative for T790M
  - Of these 5 PRs, 1 tested positive for the rare T790I mutation

Amivantamab in combination with lazertinib and chemotherapy is being evaluated in the ongoing phase 3, randomized MARIPOSA-2 study (NCT04988295) in post-osimertinib settings

Marmarelis M, et al. MA 07.04

Osimertinib+Necituzumab+Trastuzumab in refractory EGFR mut NSCLC

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Phase 1b/2 study of combined HER inhibition in refractory EGFR-mutated metastatic non-small cell lung cancer (NSCLC)

J. Goldman[1], H.K.T. Huang[1], A. Cummings[1], Z. Noor[1], S. Slomowitz[1], E. Kirimis[1], O. Olevsky[1], K. Arzoo[1], S. Ashouri[1], B. DiCarlo[1], E.H-L. Hu[1], D.J. Wong[1], J. Chauv[1], E.B. Garon[1], Y. Yarden[2], D. Slamon[1]

[1]David Geffen School of Medicine at UCLA, Los Angeles/CA/USA
[2]Weizmann Institute of Science, Rehovot/IL

University of California, Los Angeles (UCLA), USA

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Trial Introduction, Objectives and Design

Trial Background:

- Preclinical models (A, western blot; B, orthotopic murine model) show that osimertinib, cetuximab, and trastuzumab overcome osimertinib resistance. Necitumumab was substituted for cetuximab due to higher binding affinity and lower hypersensitivity reactions. (Romaniello, Yarden, et al. Clin Can Res, 2018)

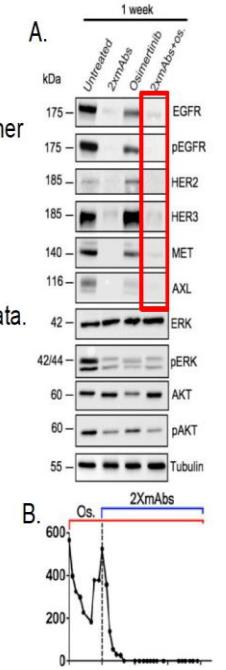
Key Objectives:

- Determine the recommended phase 2 dose (RP2D), safety, tolerability, and preliminary efficacy of the combination of osimertinib, necitumumab and trastuzumab (ONT).
- Exploratory endpoints include patient reported outcomes (PRO-CTCAE) and quality of life (FACT-L) data.

Study Design:

- In phase 1b, we utilized an accelerated dose-escalation to determine the RP2D.
- In phase 2, a Simon's two-stage optimum design will be used to treat up to 20 patients at the RP2D.

Dose Level	Osimertinib (mg)	Necitumumab (mg)	Trastuzumab (mg/kg)
-1	40 qd	400 q2w	6, followed by 4 q2w
1	40 qd	600 q2w	6, followed by 4 q2w
2	80 qd	600 q2w	6, followed by 4 q2w
3	80 qd	800 q2w	6, followed by 4 q2w

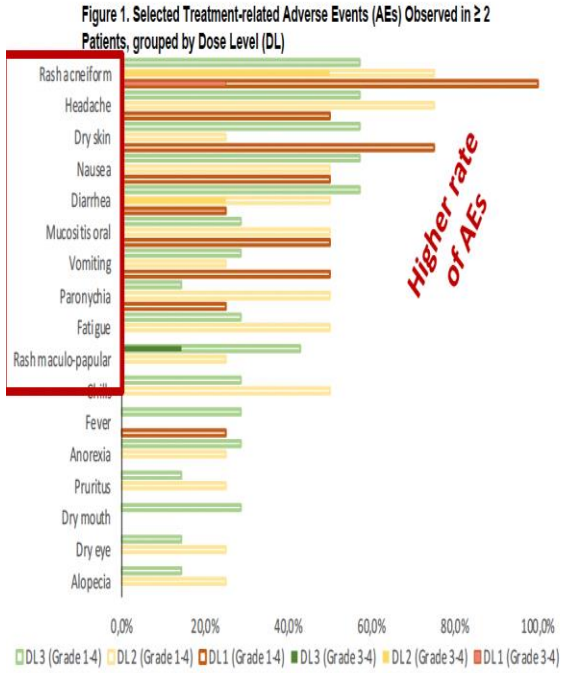


Patient Demographics

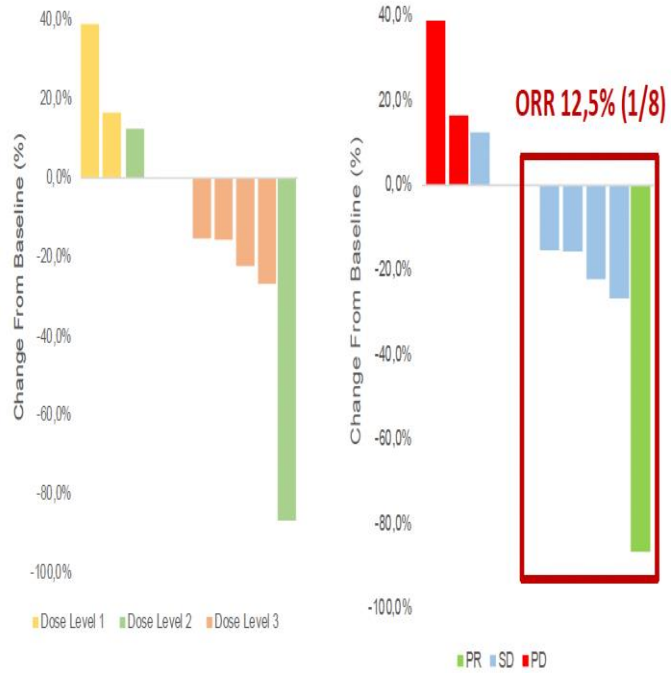
- Number of patients: 15
- Median Age: 61, Range: 54 – 82

Gender	Total = 15	%
Male	3	20.0%
Female	12	80.0%
Age Group	**Total = 15**	**%**
> 50 & ≤ 60	7	46.7%
> 60 & ≤ 70	3	20.0%
> 70 & ≤ 80	4	26.7%
> 80 & ≤ 90	1	6.7%
Race	**Total = 15**	**%**
Asian	5	33.3%
Decline to Answer	1	6.7%
Other	1	6.7%
White	7	46.7%
Unknown	1	6.7%
Ethnicity	**Total = 15**	**%**
Hispanic or Latino	1	6.7%
Not Hispanic or Latino	14	93.3%
Smoking History	**Total = 15**	**%**
Former Smoker	3	26.7%
Current Smoker	1	6.7%
Never Smoker	11	73.3%

Treatment-related AEs



Objective responses



Goldman J, et al. MA 07.05

Integrated Efficacy and Safety of Brigatinib Following Alectinib Treatment in the ALTA-2 and J-ALTA Studies

Overview of Integrated Study Design

ALTA-2 (NCT03535740), post-alectinib cohort (n=86)[1]

Single arm, open-label study conducted in Asia, Europe, North America, and Australia

- Locally advanced or metastatic *ALK*+ NSCLC[a]
- Disease progression on alectinib
- ≤3 lines of systemic therapy for metastatic disease (included crizotinib prior to alectinib)

Brigatinib 180 mg QD (7-day lead-in at 90 mg QD)

Primary endpoint:
Confirmed BIRC-assessed ORR
Secondary endpoints:
DoR, PFS, OS, safety

J-ALTA (NCT03410108), main cohort (n=47)[2]

Single arm, open-label study conducted in Japanese patients

- Locally advanced or metastatic *ALK*+ NSCLC[a]
- Disease progression on alectinib ± prior crizotinib

Baseline Patient Characteristics

Characteristic, n (%)	Integrated Population N = 133
Age, median (range), years	54 (22–82)
Female, n (%)	68 (51)
Brain metastases at baseline by BIRC	66 (50)
Stage IV disease at study entry	131 (98)
Prior anticancer therapies	
Alectinib only	77 (58)
Crizotinib and alectinib	56 (42)
Chemotherapy for metastatic disease	41 (31)
2 prior therapies	53 (40)
3 prior therapies	24 (18)
Duration of prior alectinib, median (range), mo	15 (1–65)
Best response to prior alectinib as CR/PR	96 (72)

CR, complete response; CI, confidence interval; CNS, central nervous system; DCR, disease control rate; iORR, intracranial objective response rate; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

BIRC-Assessed Efficacy

Parameters	Integrated Population N = 133
Confirmed ORR, n (%) [95% CI]	41 (31) [23–39]
CR	1 (1)
PR	40 (30)
SD	42 (32)
PD	33 (25)
Not Evaluable/Not Reported	17 (13)
DCR, n (%) [95% CI]	83 (62) [54–71]
Median DoR, mo (95% CI)	9.2 (5.5–NE)
Median PFS, mo (95% CI)	5.2 (3.7–7.3)
Median OS, mo (95% CI)	NE (16.2–NE)
Patients with baseline CNS metastases, n (%)	66 (50)
Confirmed iORR, n (%) [95% CI]	9 (14) [6–24]
Intracranial CR/PR	6 (9) / 3 (5)

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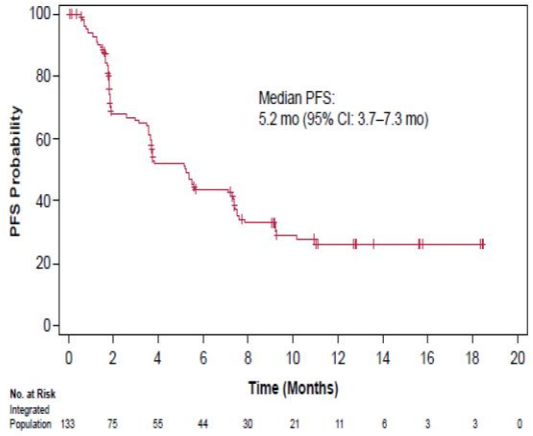
Brigatinib in alectinib resistant ALK+ NSCLC : Results from integrated analysis ALTA2/J-ALTA

Efficacy measures by BIRC

Parameters	Integrated Population N = 133
Confirmed ORR, n (%) [95% CI]	41 (31) [23–39]
Not Evaluable/Not Reported	17 (13)
Median DoR, mo (95% CI)	9.2 (5.5–NE)
Median PFS, mo (95% CI)	5.2 (3.7–7.3)
Patients with baseline CNS metastases, n (%)	66 (50)
Confirmed iORR, n (%) [95% CI]	9 (14) [6–24]

BIRC-Assessed Progression-Free Survival



Ou S-H I, et al WCLC 2022

Safety profile in line with previous reports

ORR: 31%
mPFS 5.2m
icORR 14%

Ou I, et al. MA 13.03

Entrectinib in ROS1 NSCLC: Updated efficacy and safety analysis

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Entrectinib in Patients with *ROS1* Fusion-Positive NSCLC: Updated Efficacy and Safety Analysis

Yun Fan,[1] Alexander Drilon,[2] Chao-Hua Chiu,[3*] Daniel W. Bowles,[4] Herbert H.F. Loong,[5] Salvatore Siena,[6,7] Koichi Goto,[8] Maciej Krzakowski,[9] Myung-Ju Ahn,[10] Haruyasu Murakami,[11] Rafal Dziadziuszko,[12] Harald Zeuner,[13] Bethany Pitcher,[14] Diarra Cheick,[15] Matthew G. Krebs[16]

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**Currently at Taipei Cancer Center and Taipei Medical University Hospital, Taipei, Taiwan*

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Patient demographics and baseline characteristics

	Overall efficacy population N=172	First-line population* n=67
Median age, years (range)	54.5 (20–86)	55.0 (33–86)
Female, n (%)	113 (65.7)	41 (61.2)
ECOG PS, n (%) 0 / 1 / 2	66 (38.4) / 90 (52.3) / 16 (9.3)	25 (37.3) / 37 (55.2) / 5 (7.5)
Smoking status, n (%) Never smoker / Previous or current smoker	111 (64.5) / 61 (35.5)	42 (62.7) / 25 (37.3)
Prior lines of systemic therapy in metastatic setting, n (%) 0 / 1 / ≥2	67 (39.0) / 65 (37.8) / 40 (23.3)	NA
CNS metastases at baseline by investigator, n (%) Yes / No	60 (34.9) / 112 (65.1)	26 (38.8) / 41 (61.2)

Data cut-off: 02 Aug 2021. *Patients who had not received any prior lines of systemic therapy in the metastatic setting
CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology group performance status; NA, not applicable

Fan et al. MA 13.04

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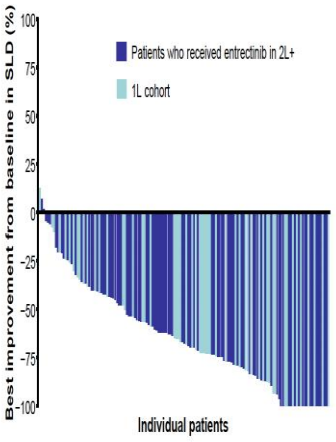
Entrectinib demonstrated robust and durable responses regardless of baseline CNS status



	Overall efficacy population (N=172)	Baseline CNS metastases* (n=60)	No baseline CNS metastases* (n=112)	First-line population† (n=67)
ORR, n (%) [95% CI]	**116 (67.4)** [59.9–74.4]	**38 (63.3)** [49.9–75.4]	**78 (69.6)** [60.2–78.0]	**46 (68.7)** [56.2–79.4]
CR	23 (13.4)	4 (6.7)	19 (17.0)	10 (14.9)
PR	93 (54.1)	34 (56.7)	59 (52.7)	36 (53.7)
SD	16 (9.3)	6 (10.0)	10 (8.9)	7 (10.4)
PD	16 (9.3)	8 (13.3)	8 (7.1)	5 (7.5)
Non CR / PD	10 (5.8)	2 (3.3)	8 (7.1)	6 (9.0)
Missing / unevaluable	14 (8.1)	6 (10.0)	8 (7.1)	3 (4.5)
Median DoR, months [95% CI]	**20.4** [14.8–34.8]	**14.6** [11.0–20.4]	**28.6** [14.9–38.6]	**35.6** [13.9–38.8]

Data cut-off: 02 Aug 2021. *Investigator-assessed CNS metastases; †Exploratory analysis. 1L, first line; 2L, second line; CI, confidence interval; CR, complete response; DoR, duration of response; ORR, objective response rate, PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameters

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Entrectinib demonstrated intracranial efficacy in patients with *ROS1* fusion-positive NSCLC

Intracranial efficacy	Overall efficacy population (n=51)*	First-line cohort (n=23)*†
IC-ORR, n (%) [95% CI]	**25 (49.0)** [34.8–63.4]	**14 (60.9)** [38.5–80.3]
CR	8 (15.7)	3 (13.0)
PR	17 (33.3)	11 (47.8)
SD	0	0
PD	10 (19.6)	2 (8.7)
Non-CR / PD	12 (23.5)	6 (26.1)
Missing / non evaluable	4 (7.8)	1 (4.3)
Median IC-DoR, months [95% CI]	**12.9** [7.6–22.5]	**12.9** [7.6–22.2]
No. remaining at risk (% event free): 6 / 12 mos	19 (79) / 14 (58)	12 (86) / 9 (64)
Median IC-PFS, months [95% CI]	**12.0** [6.7–15.6]	**15.6** [7.7–21.1]
No. remaining at risk (% event free): 6 / 12 mos	33 (70) / 23 (48)	18 (78) / 13 (57)

Data cut-off: 02 Aug 2021. *In patients with BICR-assessed CNS metastases at baseline; †Exploratory analysis.
BICR, blinded independent central review; IC, intracranial

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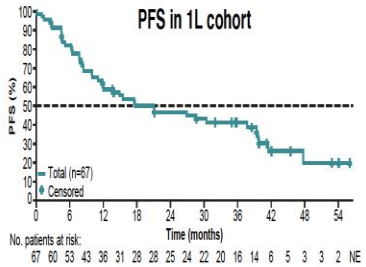
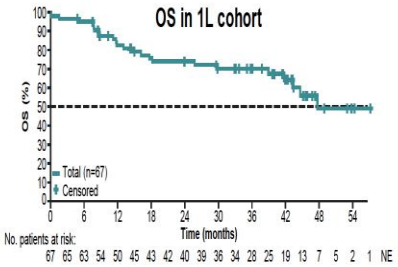
Entrectinib demonstrated prolonged survival in patients with *ROS1* fusion-positive NSCLC

	Overall efficacy population (N=172)	Baseline CNS metastases* (n=60)	No baseline CNS metastases* (n=112)	First-line population† (n=67)
Median PFS, months [95% CI]	**16.8** [12.2–22.4]	**11.8** [7.2–15.7]	**25.2** [15.7–36.6]	**17.7** [11.8–39.4]
Median OS, months [95% CI]	**44.1** [40.1–NE]	**28.3** [17.0–44.6]	**NE** [41.8–NE]	**47.7** [43.2–NE]





Data cut-off: 02 Aug 2021. *Investigator-assessed CNS metastases; †Exploratory analysis.
OS, overall survival; PFS, progression-free survival

Entrectinib demonstrated robust and durable responses regardless of baseline CNS status
<u>1st line cohort:</u>
mDoR 35.6m, mPFS 17.7m, mOS 47.7m
ic-ORR:60.9%, ic DoR 12.9m, icPFS 15.6m

Fan et al. MA 13.04

VISION TRIAL
MET EXON 14 AND TEPOTINIB

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Tepotinib in patients with *MET* exon 14 skipping NSCLC: Primary analysis of the confirmatory VISION Cohort C

Michael Thomas,[1] Marina C. Garassino,[2,3] Enriqueta Felip,[4] Hiroshi Sakai,[5] Xiuning Le,[6] Remi Veillon,[7] Egbert F. Smit,[8] Julien Mazieres,[9] Alexis B. Cortot,[10] Jo Raskin,[11] Santiago Viteri,[12] James CH Yang,[13] Myung-Ju Ahn,[14] Yi-Long Wu,[15] Rui Ma,[16] Jun Zhao,[17] Aurora O'Brate,[18] Karin Berghoff,[19] Rolf Bruns,[20] Gordon Otto,[21] Paul K. Paik[22,23]

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Tepotinib is a once daily and highly selective MET TKI approved for *MET*ex14 skipping NSCLC based mainly on Cohort A of the multi-cohort Phase II VISION study[1]

Key inclusion criteria

- Advanced NSCLC (*EGFR/ALK* wild-type, all histologies)
- Central confirmation of *MET*ex14 skipping by liquid and/or tissue biopsy
- First, second, or third line of therapy

Cohort A* *MET*ex14 skipping (primary)

Cohort C† *MET*ex14 skipping (confirmatory)

Tepotinib 500 mg‡ once daily

Selected endpoints

Primary:
Objective response by IRC (RECIST v1.1)

Secondary:
DOR, PFS, OS, Safety

Exploratory RANO-BM analysis§:
BOR per RANO-BM (patients with ≥1 evaluable post-baseline tumor assessment): disease control was defined as CR/PR/SD, or non-CR/non-PD

Here, we report the primary analysis (>9-months' follow-up) of the independent confirmatory Cohort C; data cut-off February 20, 2022‡

Thomas M, et al. OA 03.05

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MET EXON 14 AND TEPOTINIB

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Patients in the confirmatory Cohort C had a median age of 71 years, about half were male, about half had smoking history, and most had adenocarcinoma histology

Baseline characteristics		Cohort C (N=161)	Cohort A (N=152)
Median age, years (range)		71.0 (42–91)	73.1 (41–94)
Sex, %	Male	46.6	52.0
Race, %	White/Asian	54.0/42.2	71.1/25.0
ECOG PS, %	0/1	24.8/74.5	27.0/73.0
Smoking history, %	Yes	43.5	52.0
Histology, %	Adenocarcinoma	75.2	86.2
Brain metastases at baseline, %	Yes	21.1	15.1
Line of therapy, %	Treatment-naïve/previously treated	59.0/41.0	45.4/54.6
*MET*ex14 skipping detection*	T+/L+	74.5/49.1	57.9/65.1

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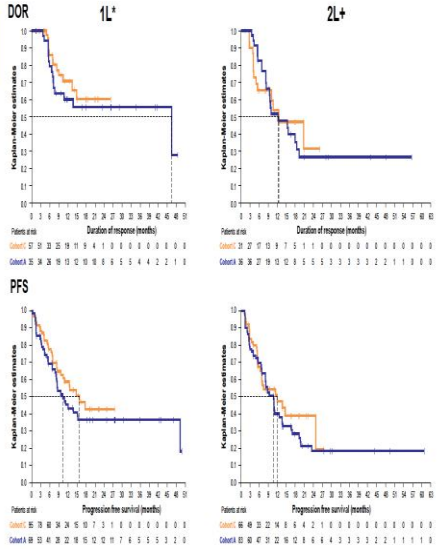
Overall efficacy in Cohort C and Cohort A was robust and durable across therapy lines

	1L* (T+ and/or L+)	2L+ (T+ and/or L+)
	Cohort C (n=95)	Cohort C (n=66)
ORR, % (95% CI)	60.0 (49.4, 69.9)	47.0 (34.6, 59.7)
Median DOR, months (95% CI)	ne (13.4, ne)	12.6 (5.1, ne)
Median PFS, months (95% CI)	15.9 (10.4, ne)	12.1 (6.9, ne)
Median OS, months (95% CI)	21.1 (12.7, ne)	18.8 (13.5, ne)



*1L enrollment began approximately 8 months later than 2L+.
1L, first line; 2L+, second-or-later line; CI, confidence interval; DOR, duration of response; L+, *MET*ex14 skipping detected in liquid biopsy; ne, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T+, *MET*ex14 skipping detected in tissue biopsy.

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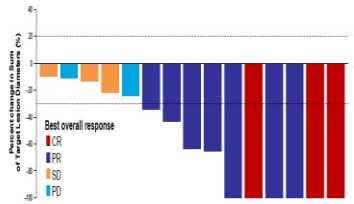
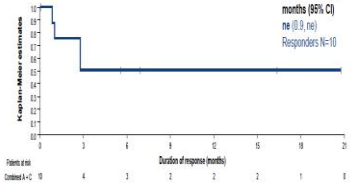
Tepotinib showed promising intracranial activity in patients with brain metastases (RANO-BM analysis)

- Tepotinib crosses the blood brain barrier to a significant extent, leading to concentrations of unbound tepotinib in the brain of 25% compared to plasma (Kp_{uu}=0.25), within a similar range to other CNS–penetrant TKIs[1]
- Across Cohorts A+C, 43 patients with brain metastases were evaluable by RANO-BM (1L, n=23; 2L+, n=20)
- 30 patients (69.8%) received prior brain radiotherapy or surgery
- In patients with target or non-target lesions (n=43), **intracranial disease control rate was 88.4%** (95% CI: 74.9, 96.1) with **intracranial mPFS of 20.9 months** (95% CI: 5.7, ne)
- In patients with target lesions (n=15), **intracranial ORR was 66.7%** (95% CI: 38.4, 88.2) with **intracranial mDOR ne** (95% CI: 0.9, ne)

Intracranial response in patients with target lesions (n=15)



Intracranial duration of response



1L, first line; 2L+, second-or-later line; CI, confidence interval; CNS, central nervous system; CR, complete response; DOR, duration of response; Kp_{uu}, unbound partition coefficient; m, median; ne, not estimable; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; SD, stable disease; TKI, tyrosine kinase inhibitor.
1. Friese-Hamim M, et al. *Lung Cancer*. 2022;163:77–86.

1L: ORR 60%. mDOR NE mPFS 15.9m. mOS 21.1m
2L: ORR: 47% mDOR 12.6m, mPFS 12.1m mOS 18.8m
Brain: icORR 66.7%, icPFS 20.9m

Thomas M, et al. OA 03.05

TAS0493/HM06

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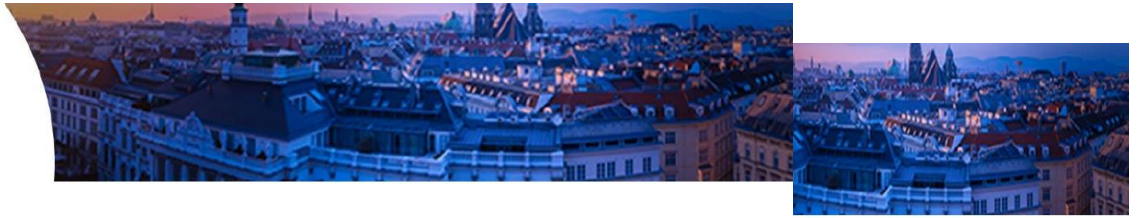
The 5 Ws of vepafestinib



Study of RET Inhibitor TAS0953/HM06 in Patients With Advanced Solid Tumors With RET Gene Abnormalities ((MARGARET))

STATUS	END DATE	PARTICIPANTS NEEDED	SPONSOR
Recruiting	Aug 5, 2024	202	Helsinn Healthcare SA

WHO?

Ph. I
- Solid Tumors *RET* abnormalities
- ECOG PS 0-1

Ph. I Exp – Ph. II
- RET + NSCLC w/wo prior RET-TKIs
- BMs/leptomen. disease allowed
- Measurable disease

WHAT ?
- TAS0953/HM06
- Orally starting dose 20 mg BID, until RD2 dose, continuous daily dosing, cycles lasting 21 days

WHEN ?
- 2021 - 2024

WHERE ?
- US
- Japan

WHY?
- Ph. I: MTD, DLTs and RP2D
- Ph. II: ORR, DCR, TTR, PFS, TTP, DOR, OS, CNS ORR, CNS PD

cenetrwatch.com; clinicaltrials.gov;

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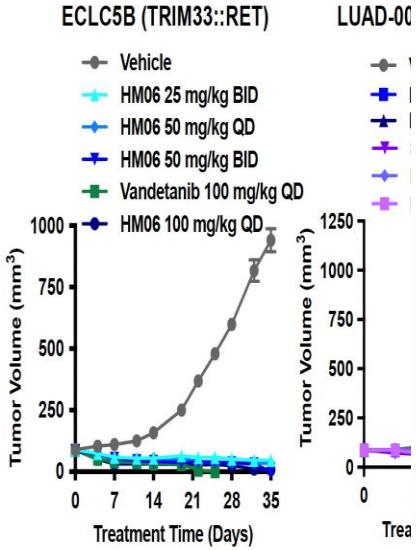
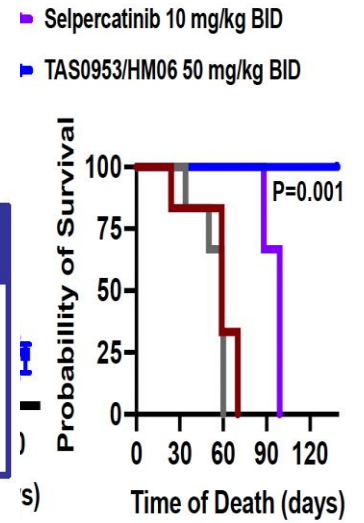
TAS0953/HM06 is Effecti



tinib in the CNS



TAS0953/HM06 is effective in preclinical model of RET-resistant NSCLC

Odintsov et al. MA 13.05

SOME NOTES TO CONCLUDE

- Multiple ongoing strategies to overcome EGFR TKI resistance (Amivantamab combinations, 4th generation TKI…)
- In VISION –the largest clinical trial of a MET TKI in *MET*ex14 skipping NSCLC –the Cohort C primary analysis provided confirmation for robust and durable efficacy of tepotinib, with comparable or improved outcomes across endpoints compared to Cohort A
- Brigatinib could be an option after alectinib failure
- Entrectinib confirms its efficacy even in untreated ROS1+ patients
- In RET+ NSCLC, new strategies are needed at selpercatinib or pralsetinib failure