Efficacy and safety of MCLA-129, an EGFR x c-MET bispecific antibody, combined with osimertinib, as first-line therapy or after progression on osimertinib in non-small cell lung cancer (NSCLC)

Federico Cappuzzo,1 Victor Moreno,2 Sai-Hong I. Ou,3 Mariana Brandão,4 Miguel F. de Sanmamed Gutierrez,5 Carole Helissey,6 Marie Wislez,7 Justin Call,8 Salvatore Grisanti,9 Melissa Johnson,10 Valentina Boni,11 Philippe Jamme,12 Isabelle Monnet,13 Salvatore Siena,14 Chris Yan,15 Benjamin A. Barasa,15 Onyinyechi Richard,15 Andrew K. Joe,15 Gianluca Laus,15 Enriqueta Felip16

1Istituto Nazionale Tumori “Regina Elena”, Roma, Italy; 2START Madrid-FJD, Hospital Fundación Jiménez Díaz, Madrid, Spain; 3University of California Irvine Health, Orange, CA, US; 4Institut Jules Bordet – Hôpital Universitaire de Bruxelles, Bruxelles, Belgium; 5Clínica Universidad de Navarra, Pamplona, Spain; 6Hôpital d’Instruction des Armées Bégin, Saint-Mandé CEDEX, France; 7Hôpital Cochin, AP-HP, Paris, France; 8START Mountain Region, West Valley City, UT, US; 9ASST degli Spedali Civili di Brescia, Brescia, Italy; 10Tennessee Oncology, Nashville, TN, US; 11NEXT Madrid, University Hospital Quironsalud Madrid, Madrid, Spain; 12Hôpital Albert Calmette, Lille, France; 13Centre Hospitalier Intercommunal de Créteil, Créteil, France; 14Salvatore Siena, Università degli Studi di Milano and Grande Ospedale Metropolitano Niguarda, Milan, Italy; 15Merus N.V., Utrecht, The Netherlands; 16Hospital Universitario Vall d’Hebron, Barcelona, Spain.
Declarations of Interests

Mariana Brandão

• Data Safety Monitoring Boards and Advisory Boards: Amgen, Janssen
• Research grants: AstraZeneca, Boehringer Ingelheim, iTeos, and Roche/GNE
• Meeting attendance: Sanofi, Takeda
• Speakers’ bureau, manuscripts, or educational events: BMS, Merus N.V., Janssen, and Takeda
Background

MCLA-129 is a Bispecific Antibody Targeting EGFR and c-MET

- EGFR and c-MET are dysregulated in many tumors, including NSCLC\(^1\)
  - *EGFR*mut NSCLC accounts for an estimated 11.9% of cases globally and 49.1% of cases among Asian patients\(^2\)
  - MET pathway overexpression occurs in 15% to 70% of NSCLC tumors\(^3\)
- Osimertinib is a third-generation EGFR tyrosine kinase inhibitor approved as 1L therapy for *EGFR* ex19del and L858R NSCLC\(^4\)
- MCLA-129 is a bispecific antibody targeting EGFR and c-MET, with multiple mechanisms of action, including inhibition of EGFR and c-MET signaling, and enhanced ADCC\(^5\)
- Here, we present data from an ongoing Phase 1/2 trial\(^6\) exploring MCLA-129 combined with osimertinib at standard dose in *EGFR*mut NSCLC, either as 1L therapy or after progression on osimertinib (2L+)

1L: first-line; 2L+: second-line or higher; ADCC: antibody-dependent cell-mediated cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; cLC: common light chain; c-MET: hepatocyte growth factor receptor; EGFR: epidermal growth factor receptor; *EGFR*mut: epidermal growth factor receptor mutant; NK: natural killer cell; NSCLC: non-small cell lung cancer.

Endpoints and Population

Primary endpoint
- ORR\(^b\) using RECIST v1.1 per investigator assessment

Secondary endpoints
- DoR, DCR,\(^c\) PFS, OS, and safety\(^d\)

Primary analysis population
- ≥ 2 MCLA-129 cycles, with baseline and ≥ 1 postbaseline scan

Inclusion Criteria
- Locally advanced unresectable or metastatic NSCLC
- With sensitizing mutations\(^a\) and no prior treatment (1L), or progressed on or after osimertinib (2L+)
- Measurable disease at baseline per RECIST v1.1
- ≥ 18 years of age, ECOG PS of 0 or 1
- Life expectancy ≥ 12 weeks, as per the investigator

Enrollment and Analysis

Data cutoff date
- August 10, 2023

Enrollment
- 60 EGFRmut NSCLC patients
- 16 patients in 1L
- 44 patients in 2L+

Primary efficacy analysis population
- 16 patients in 1L
- 34 patients in 2L+
- 9 patients in 2L+ excluded, with < 2 cycles and discontinued for reasons not related to PD
- 1 patient in 2L+ with < 2 cycles ongoing at the data cutoff date was not part of the efficacy analysis population

Treatment Plan
- MCLA-129 1500 mg IV Q2W until PD or unacceptable toxicity
- Osimertinib 80 mg QD
- Tumor imaging Q8W

AE: adverse event; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; DCR: disease control rate; DOR: duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; IV: intravenous; MedDRA: Medical Dictionary for Regulatory Activities; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; Q2W: every 2 weeks; Q8W: every 8 weeks; QD: once a day; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease.

\(^a\)Sensitizing mutations: EGFR ex19del and L858R. \(^b\)Defined as the proportion of patients with a best confirmed response of CR or PR per RECIST v1.1. \(^c\)Defined as the proportion of patients with CR, PR, or SD as the best overall response per RECIST v1.1 based on investigator assessment. \(^d\)AEs were coded using MedDRA v24.1 and graded using CTCAE v4.03.
## Patients With *EGFR*mut NSCLC

<table>
<thead>
<tr>
<th>Demographics and prior therapy</th>
<th>1L NSCLC</th>
<th>2L+ NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (range), years</strong></td>
<td>60 (40–80)</td>
<td>61 (35–81)</td>
</tr>
<tr>
<td><strong>Gender, male / female, n (%)</strong></td>
<td>6 (38) / 10 (63)</td>
<td>16 (36) / 28 (64)</td>
</tr>
<tr>
<td><strong>ECOG PS, 0 / 1 / missing, n (%)</strong></td>
<td>8 (50) / 8 (50) / 0</td>
<td>14 (32) / 28 (64) / 2 (5)</td>
</tr>
<tr>
<td><strong>Race, White / Asian / Other, n (%)</strong></td>
<td>7 (44) / 3 (19) / 6 (38)</td>
<td>36 (82) / 4 (9) / 4 (9)</td>
</tr>
<tr>
<td><strong>(Prior) smoking or tobacco products use, n (%)</strong></td>
<td>8 (50)</td>
<td>23 (52)</td>
</tr>
<tr>
<td><strong>Prior lines of systemic therapy, median (range)</strong></td>
<td>0</td>
<td>1 (1–6)</td>
</tr>
<tr>
<td><strong>Number of metastatic sites, median (range)</strong></td>
<td>2 (1–5)</td>
<td>3 (1–6)</td>
</tr>
<tr>
<td><strong>Primary tumor location, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>16 (100)</td>
<td>43 (98)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Histology, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>16 (100)</td>
<td>43 (98)</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>0</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

### Prior therapy of patients with *EGFR*mut NSCLC

- All 2L+ patients had received osimertinib as prior therapy
- 22 (50%) of these received osimertinib as the only prior therapy
- 16 (36%) 2L+ patients had received prior chemotherapy
MCLA-129 Activity in 1L EGFRmut NSCLC

Best % change in target lesions from baseline

- **ORR** 75.0% (95% CI: 47.6–92.7; 12/16)
- **DCR** 93.8% (95% CI: 69.8–99.8; 15/16)

Duration of exposure

- Median duration of exposure (months) 5.1 (range: 0.5–8.5)
- Median duration of response (months) not reached (range: 1.6**–5.5**)

13 patients (81%) on treatment at the data cutoff date

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**Excludes 1 patient who died without postbaseline scan. EGFR mutation status (ex19del or L858R) provided by site at screening that is not confirmed by ctDNA NGS testing. CI: confidence interval; DCR: disease control rate; IHC: immunohistochemistry; NA: not available; NE: not evaluable; ORR: overall response rate; PD: progressive disease; PR: partial response; SD: stable disease; uPR: unconfirmed partial response (initial assessment of PR for a patient on treatment).**

*ORR is the proportion of confirmed and unconfirmed responders out of the primary efficacy analysis population in 1L NSCLC patients with EGFR mutation; patients with RECIST progression or study discontinuation after initial CR/PR are not considered as responders. **Censored.
MCLA-129 Activity in 2L+ EGFRmut NSCLC

**Best % change in target lesions from baseline**

- **ORR**: 35.3% (95% CI: 19.7–53.5; 12/34)
- **DCR**: 73.5% (95% CI: 55.6–87.1; 25/34)

**Duration of exposure**

- Median duration of exposure (months)
  - 2.8 (range: 0.3–11.5)
- Median duration of response (months)
  - Not reached (range: 1.6**–9.2***)

17 patients (39%) on treatment at the data cutoff date

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*a*Excludes 11 patients: 10 who received <2 cycles of treatment, 9 of these discontinued treatment due to reasons other than PD, 1 was ongoing at the data cutoff date; 1 patient with PD without all baseline target lesion diameters reported at the time of data cutoff date.

**Baseline EGFR mutation status not confirmed by ctDNA NGS testing.**

**ORR** is the proportion of confirmed and unconfirmed responders out of the primary efficacy analysis population in 2L+ NSCLC patients with EGFR mutation; patients with RECIST progression or study discontinuation after initial CR/PR are not considered as responders.

**Censored. TKI resistance mechanisms: EGFR-related, including T790M, C797S, S768I, EGFRamp; MET-related, including METamp.**
**MCLA-129 + osimertinib Safety Profile**

- 60\(^a\) EGFRmut NSCLC patients treated with MCLA-129 1500 mg IV Q2W + osimertinib 80 mg QD

- Infusion-related reactions (IRRs)\(^b\) observed in 52 (87%) patients, 7 (12%) of whom experienced an AE of Gr ≥ 3

- 14 (23%) patients discontinued the study treatment due to TEAEs

- 13 (22%) patients had treatment-related ILD / pneumonitis (4 patients with Gr1, 2 with Gr2, 4 with Gr3, and 3 with Gr5)
  - Evaluation of ILD cases is ongoing
  - Venous thromboembolism (VTE, composite term) observed in 14 (23%, 7% Gr ≥ 3) patients, 3 (5%) events were treatment-related

### Most frequent TEAEs (>10%)

<table>
<thead>
<tr>
<th>TEAE</th>
<th>All grades n (%)</th>
<th>Grade ≥3 n (%)</th>
<th>All grades n (%)</th>
<th>Grade ≥3 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>21 (35)</td>
<td>0</td>
<td>27 (45)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12 (20)</td>
<td>0</td>
<td>18 (30)</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>16 (27)</td>
<td>1 (2)</td>
<td>17 (28)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Rash</td>
<td>16 (27)</td>
<td>1 (2)</td>
<td>17 (28)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6 (10)</td>
<td>0</td>
<td>15 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>8 (13)</td>
<td>0</td>
<td>15 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Flushing</td>
<td>15 (25)</td>
<td>2 (3)</td>
<td>15 (25)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (17)</td>
<td>0</td>
<td>15 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>9 (15)</td>
<td>0</td>
<td>14 (23)</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
<td>13 (22)</td>
<td>1 (2)</td>
<td>14 (23)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>ILD / pneumonitis</td>
<td>13 (22)</td>
<td>7 (12)</td>
<td>14 (23)</td>
<td>8(^c) (13)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (17)</td>
<td>0</td>
<td>13 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (10)</td>
<td>0</td>
<td>12 (20)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>8 (13)</td>
<td>0</td>
<td>12 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9 (15)</td>
<td>0</td>
<td>10 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (3)</td>
<td>0</td>
<td>9 (15)</td>
<td>1 (2)</td>
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<tr>
<td>Mucosal inflammation</td>
<td>6 (10)</td>
<td>0</td>
<td>9 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>7 (12)</td>
<td>1 (2)</td>
<td>9 (15)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (7)</td>
<td>0</td>
<td>8 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (7)</td>
<td>0</td>
<td>8 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (7)</td>
<td>1 (2)</td>
<td>7 (12)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (7)</td>
<td>0</td>
<td>7 (12)</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)Includes 1L and 2L+ patients. \(^b\)Composite term covering preferred terms (terms reported in ≥ 10% of patients are nausea, flushing, hypotension, vomiting, dyspnea, and cough) considered by the investigator to be infusion-related reactions occurring within 24 hours of infusion start. \(^c\)1 case of obstructive pneumonitis grade 3, not drug related. Gr: grade; ILD: interstitial lung disease; TEAE: treatment-emergent adverse event.
Conclusions

- MCLA-129 in combination with osimertinib demonstrated notable antitumor activity, including durable responses and prolonged stable disease in:
  - Treatment-naive NSCLC patients with EGFRmut (sensitizing mutations)
  - NSCLC patients previously treated with osimertinib
- 50% of patients were on treatment at the data cutoff date
- Safety profile shows AEs associated with EGFR and c-MET inhibition
  - IRRs, VTE and ILD / pneumonitis were observed
- Further investigation of MCLA-129 in combination with osimertinib, chemotherapy, or other therapies is planned
Acknowledgments

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