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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)

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Declarations of Interests

Mariana Brandão

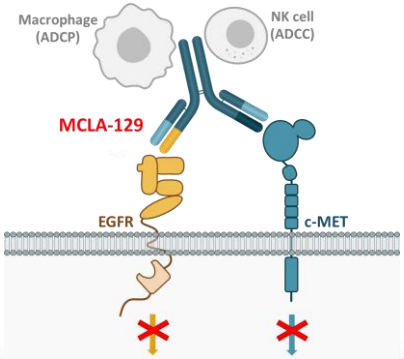
- Data Safety Monitoring Boards and Advisory Boards: Amgen, Janssen
- Research grants: AstraZeneca, Boehringer Ingelheim, iTeos, and Roche/GNE
- Meeting attendance: Sanofi, Takeda
- Speakers' bureau, manuscripts, or educational events: BMS, Merus N.V., Janssen, and Takeda

Background

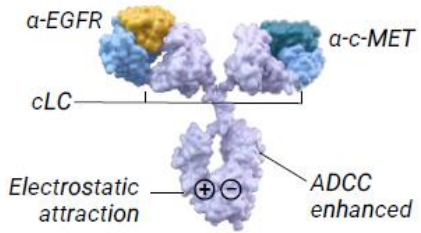
MCLA-129 is a Bispecific Antibody Targeting EGFR and c-MET

- 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+)

MCLA-129 mechanism of action



MCLA-129 structure



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.

1. Tsuji T, et al. *Oncotarget*. 2017;8(42):71805-71816. 2. Melosky B, et al. *Mol Diagn & Ther*. 2022;26:7-18. 3. Liang H, and Wang M. *OncoTargets & Ther*. 2020;13:2491-2510. 4. Kishikawa T, et al. *Thorac Cancer*. 2020;11:935-942. 5. De Gorter DJ, et al. *Cancer Res*. 2021;81(13 suppl):952. 6. ClinicalTrials.gov Identifier: NCT04868877.

Study Design

MCLA-129 Development Program

Ongoing Phase 1/2 global, open-label clinical trial

*EGFR*mut NSCLC

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

Treatment Plan

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

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

Enrollment and Analysis

Data cutoff date
August 10, 2023

Enrollment
60 *EGFR*mut 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

[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.

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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.

Patients With *EGFR*mut NSCLC

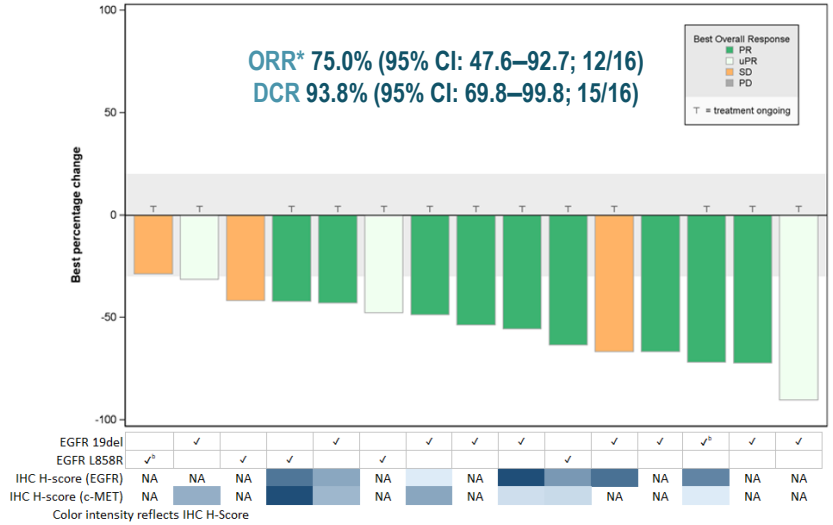
Demographics and prior therapy	1L NSCLC N = 16	2L+ NSCLC N = 44
Age, median (range), years	60 (40–80)	61 (35–81)
Gender, male / female, n (%)	6 (38) / 10 (63)	16 (36) / 28 (64)
ECOG PS, 0 / 1 / missing, n (%)	8 (50) / 8 (50) / 0	14 (32) / 28 (64) / 2 (5)
Race, White / Asian / Other, n (%)	7 (44) / 3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

Prior therapy of patients with *EGFR*mut NSCLC

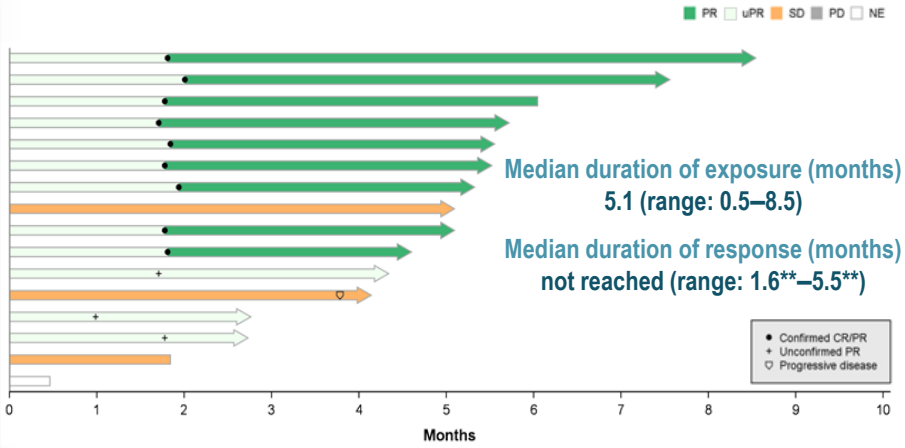
- All 2L+ patients had received osimertinib as prior therapy
- 22 (50%) of these received osimertinib as the only prior therapy
- 16 (36%) 2L+ patients had received prior chemotherapy

MCLA-129 Activity in 1L *EGFR*mut NSCLC

Best % change in target lesions from baseline[a]



Duration of exposure

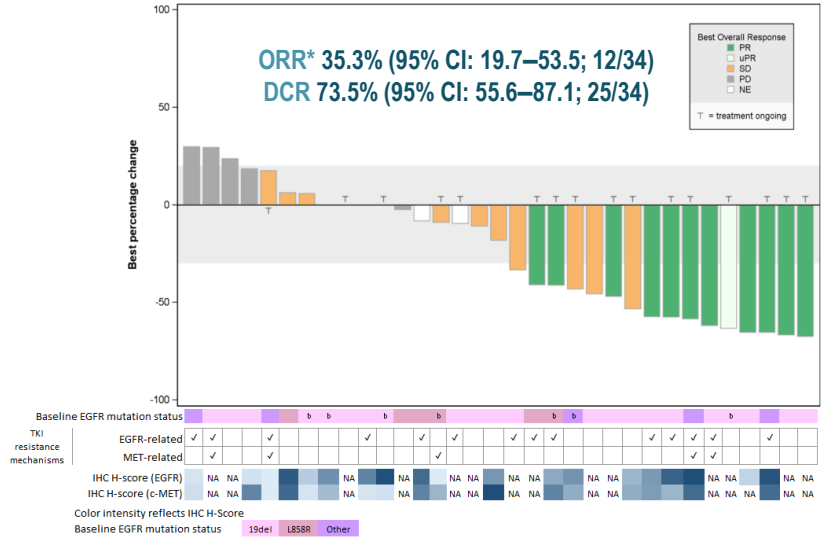


13 patients (81%) on treatment at the data cutoff date

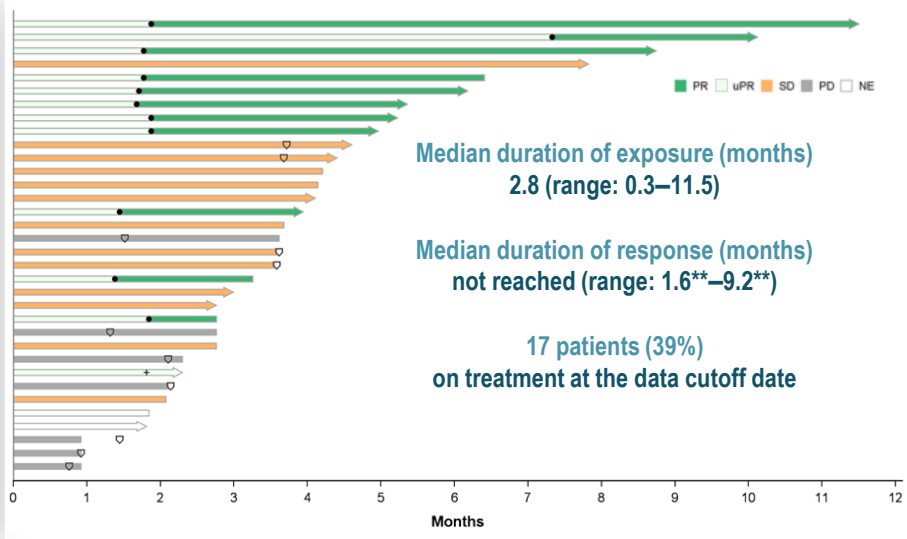
[a]Excludes 1 patient who died without postbaseline scan. [b]EGFR mutation status (ex19del or L858R) provided by site at screening that is not confirmed by ctDNA NGS testing.
CI: confidence interval; DCR: disease control rate; IHC: immunohistochemistry; NA: not available; NE: not evaluable; ORR: overall 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+ *EGFR*mut NSCLC

Best % change in target lesions from baseline[a]



Duration of exposure[a]



[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. [b]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, EGFR^{amp}; MET-related, including MET^{amp}

MCLA-129 + osimertinib Safety Profile

- 60[a] *EGFR*mut 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%)			
	Treatment-related TEAEs n (%)		TEAEs irrespective of causality n (%)	
	All grades	Grade ≥3	All grades	Grade ≥3
≥1 TEAE	60 (100)	23 (38)	60 (100)	38 (63)
Nausea	21 (35)	0	27 (45)	0
Dyspnea	12 (20)	0	18 (30)	0
Hypotension	16 (27)	1 (2)	17 (28)	1 (2)
Rash	16 (27)	1 (2)	17 (28)	1 (2)
Asthenia	6 (10)	0	15 (25)	0
Cough	8 (13)	0	15 (25)	0
Flushing	15 (25)	2 (3)	15 (25)	2 (3)
Vomiting	10 (17)	0	15 (25)	0
Decreased appetite	9 (15)	0	14 (23)	0
Dermatitis acneiform	13 (22)	1 (2)	14 (23)	1 (2)
ILD / pneumonitis	13 (22)	7 (12)	14 (23)	8[c] (13)
Diarrhea	10 (17)	0	13 (22)	0
Headache	6 (10)	0	12 (20)	1 (2)
Paronychia	8 (13)	0	12 (20)	0
Thrombocytopenia	9 (15)	0	10 (17)	0
Anemia	2 (3)	0	9 (15)	1 (2)
Mucosal inflammation	6 (10)	0	9 (15)	0
Stomatitis	7 (12)	1 (2)	9 (15)	1 (2)
Fatigue	4 (7)	0	8 (13)	0
Pyrexia	4 (7)	0	8 (13)	0
Abdominal pain	4 (7)	1 (2)	7 (12)	1 (2)
Constipation	4 (7)	0	7 (12)	0

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[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 *EGFR*mut (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

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