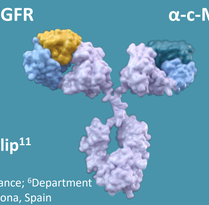
POSTER
447

Efficacy and Safety of MCLA-129, an Anti-EGFR/c-MET Bispecific Antibody, in Non-Small Cell Lung Cancer (NSCLC) With Hepatocyte Growth Factor Receptor (c-MET) Exon 14 Skipping Mutations (*MET*ex14)



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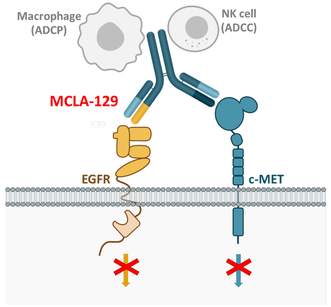
BACKGROUND

- Hepatocyte growth factor receptor (c-MET) is dysregulated in many tumors, including in non-small cell lung cancer (NSCLC)[1]
  - Splice-site alterations resulting in the loss of transcription of exon 14 in the oncogenic driver c-MET (*MET*ex14 skipping mutations) occur in 3–4% of all NSCLCs and lead to oncogenic MET activation[2–4]
  - Alongside chemotherapy, MET tyrosine kinase inhibitors (TKIs; capmatinib and tepotinib) provide therapeutic options for c-MET–driven NSCLC but resistance can occur via multiple pathways[4,5]
- MCLA-129 is a human bispecific antibody targeting epidermal growth factor receptor (EGFR) and c-MET, with multiple mechanisms of action, including inhibition of EGFR and c-MET signaling (**Figure 1**), antibody-dependent cellular phagocytosis (ADCP), and enhanced antibody-dependent cellular cytotoxicity (ADCC)[6]
- In a Phase 1/2 trial (NCT04868877)[7], the initial recommended Phase 2 dose of MCLA-129 was established at 1500 mg intravenously every 2 weeks with 28-day cycles
- Here, MCLA-129 is explored as a monotherapy in patients with previously treated locally advanced/metastatic NSCLC with *MET*ex14 skipping mutations

Figure 1 | MCLA-129 mechanisms of action[6]



ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; c-MET, hepatocyte growth factor receptor; EGFR, epidermal growth factor receptor; NK, natural killer.

TRIAL DESIGN AND OBJECTIVES

- This is an open cohort in an ongoing, Phase 1/2, global, open-label, multicenter trial in adult patients with NSCLC with *MET*ex14 skipping mutations (**Figure 2**)
  - Eligible patients had at least 1 prior line of systemic therapy, and were naïve or previously treated with MET TKI

Figure 2 | Phase 2 dose-expansion study design[7]

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

*MET*ex14 NSCLC

Inclusion Criteria
- Advanced/metastatic NSCLC with *MET*ex14 skipping mutation
- Previously treated with ≥1 prior systemic therapy
- Age ≥18 years
- ECOG PS of 0 or 1
- Life expectancy ≥12 weeks, as per investigator

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

Endpoints and Population

Primary Endpoint
ORR† using RECIST v1.1 per investigator assessment

Secondary Endpoints
DoR, DCR,‡ PFS, OS, and safety

Primary Efficacy Analysis Population
≥2 MCLA-129 cycles, measurable disease at baseline, and ≥1 post-baseline scan

Enrollment and Analysis

Data Cutoff Date
February 16, 2024

Enrollment
22 patients

Primary Efficacy Analysis Population
15 patients

7 patients excluded:
- 4 discontinued due to AEs within <2 cycles
- 3 are ongoing with <2 cycles at data cutoff

*Safety assessment: chest computed tomography scan at Week 4. †Defined as the proportion of patients with a best overall response of CR or PR per RECIST v1.1 based on investigator assessment in patients with measurable disease at baseline. ‡Defined as the proportion of patients with CR, PR, or SD as the best overall response per RECIST v1.1 based on investigator assessment. AE, adverse event; CR, complete response; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; *MET*ex14, MET exon 14 skipping mutations; NSCLC, non-small cell lung cancer; 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; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

NSCLC *MET*ex14 COHORT

- At the data cutoff date of February 16, 2024, 22 patients were treated, and 14 patients (64%) were continuing treatment
- Baseline demographics and disease history are presented in **Table 1**
  - Median (range) exposure was 2 (0.5–11) months with a median (range) of 5 (1–24) administrations

Table 1 | Baseline demographics and disease characteristics

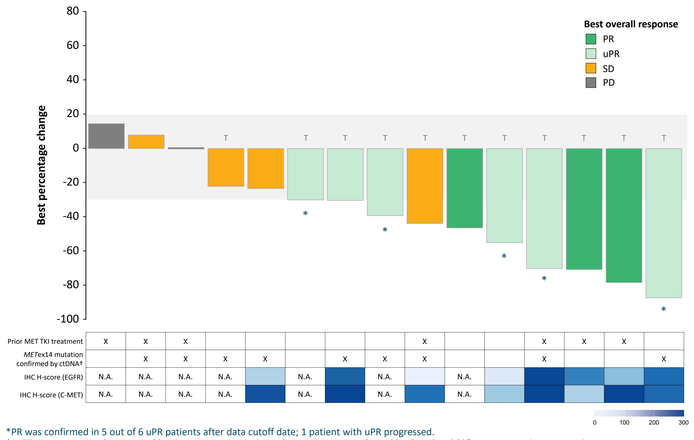
	N=22
Age, years, median (range)	73 (54–83)
Gender, male / female, n (%)	10 (45) / 12 (55)
Race, White / Asian / other / not reported, n (%)	14 (64) / 1 (5) / 6 (27) / 1 (5)
ECOG PS 0 / 1, n (%)	4 (18) / 18 (82)
Locally advanced / metastatic, n (%)	2 (9) / 20 (91)
Number of metastatic sites, median (range)	3 (1–5)
Number of prior systemic anticancer therapy regimens, median (range)	2 (1–5)
Number of prior systemic anticancer therapy regimens, 1 / 2 / >2, n (%)	10 (45) / 5 (23) / 7 (32)
TKI-naïve / prior MET TKIs,* n (%)	10 (45) / 12 (55)

*Includes prior therapy with capmatinib or tepotinib only; patients treated with other therapies were considered TKI-naïve.
ECOG PS, Eastern Cooperative Oncology Group performance status; TKI, tyrosine kinase inhibitor.

ANTITUMOR ACTIVITY

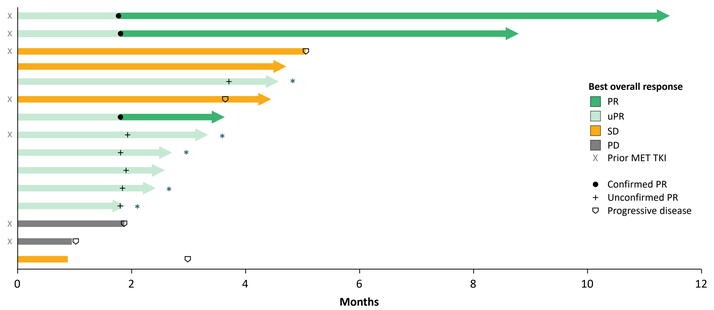
- Of 15 evaluable patients, best overall response of 3 partial responses (PRs) and 6 unconfirmed PRs was observed (overall response rate [ORR] of 60% [9/15]; 90% confidence interval [CI]: 36–81) (**Figure 3**), all with ongoing treatment at the data cutoff date (**Figure 4**):
  - Two of the 3 patients with confirmed PRs were previously treated with MET TKIs
- Reduction in target lesion tumor size from baseline was demonstrated in 12 patients (80%)
- ORR and disease control rate (DCR) were higher in TKI-naïve patients than in patients previously exposed to MET-TKI therapy (**Table 2**)

Figure 3 | Best percent change from baseline in sum of diameters of target lesions (N=15)



*PR was confirmed in 5 out of 6 uPR patients after data cutoff date; 1 patient with uPR progressed.
†*METex14* status was documented by site at screening; ctDNA alterations were evaluated by Guardant360® next-generation sequencing.
ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; METex14, MET exon 14 skipping mutations; N.A., not applicable; PD, progressive disease; PR, partial response; SD, stable disease; T, treatment ongoing; TKI, tyrosine kinase inhibitor; uPR, unconfirmed partial response.

Figure 4 | Duration of exposure (N=15)



*PR was confirmed in 5 out of 6 uPR patients after data cutoff date; 1 patient with uPR progressed.
PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; uPR, unconfirmed partial response.

ANTITUMOR ACTIVITY

Table 2 | ORR and DCR of TKI-naïve patients and patients who received prior MET-TKI therapy (N=15)

	TKI-naïve (n=8)	Prior MET TKI (n=7)
ORR, n (%) [90% CI]	6 (75) [40–95]	3 (43) [13–78]
DCR, n (%) [90% CI]	8 (100) [69–100]	5 (71) [34–95]

CI, confidence interval; DCR, disease control rate; MET, mesenchymal–epithelial transition factor; PR, partial response; TKI, tyrosine kinase inhibitor; uPR, unconfirmed partial response; ORR, overall response rate (including PR and uPR).

SAFETY PROFILE

- Overall, 19 of 22 patients (86%) experienced infusion-related reactions (IRRs), 4 (18%) with Grade ≥3 IRRs (**Table 3**)
- One patient (5%) had treatment-related interstitial lung disease (Grade 2)
- Venous thromboembolism was recorded in 2 patients (1 Grade 3 possibly treatment-related, the other Grade 2 and not related to treatment)

Table 3 | Safety profile in patients with *MET*ex14 NSCLC (N=22)

	All grades, n (%)	Grade ≥3, n (%)
≥1 TEAE	**22 (100)**	**10 (46)**
TESAEs	8 (36)	7 (32)
TEAEs leading to discontinuation	4 (18)	4 (18)
TEAEs leading to dose adjustment/infusion interruption	17 (77)	5 (23)
TEAEs leading to death*	1 (5)	1 (5)
TEAE occurring in >15% of patients		
IRR†	19 (86)	4 (18)
Dermatitis acneiform	6 (27)	1 (5)
Stomatitis	6 (27)	0
Hypoalbuminemia	5 (23)	1 (5)
Peripheral edema	5 (23)	0
Asthenia	4 (18)	0
TEAE of special interest		
ILD‡	1 (5)	0
VTE	2 (9)	1 (5)

*Pneumonia. †Composite term covering preferred terms (reported in ≥10% of patients are hypotension, hypoxia, IRR, nausea, flushing, vomiting) considered by the investigator to be IRRs occurring within 24 hours of infusion start. ‡ILD assessed by investigator as treatment-related; all other TEAEs are presented regardless of relationship to study drug.
ILD, interstitial lung disease; IRR, infusion-related reaction; *MET*ex14, MET exon 14 skipping mutations; NSCLC, non-small cell lung cancer; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent severe adverse event; VTE, venous thromboembolism.

CONCLUSIONS

- **MCLA-129 demonstrated promising single-agent efficacy in patients with locally advanced/metastatic NSCLC with *MET*ex14 skipping mutations, with or without previous treatment with MET TKI**
- **This cohort confirmed the manageable safety profile of MCLA-129 monotherapy**
- **Further clinical investigation is warranted in patients with NSCLC with METex14 skipping mutations**

References

1. Tsuji et al. (2017) Oncotarget *8*, 71805–71816; 2. Frampton et al. (2015) Cancer Discov *5*, 850–859; 3. Hong et al. (2021) Ther Adv Med Oncol *13*, 17588359211992976; 4. Ettinger, et al. (2022) J Natl Compr Canc Netw *20*, 497–530; 5. Recondo et al. (2020) Clin Cancer Res *26*, 2615–2625; 6. De Gorter et al. (2021) Cancer Res *81*, 952; 7. ClinicalTrials.gov. NCT04868877. Available at: https://www.clinicaltrials.gov/study/NCT04868877. Accessed April 16, 2024.

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