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ABSTRACT
CT156

MCLA-158 (petosemtamab), an IgG1 bispecific antibody targeting EGFR and LGR5, in advanced gastric/esophageal adenocarcinoma (GEA)

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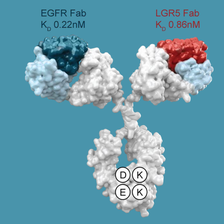
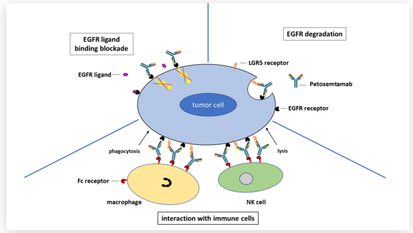


BACKGROUND

Petosemtamab (MCLA-158) is a bispecific Biclonics® low-fucose human full-length IgG1 antibody targeting the epidermal growth factor receptor (EGFR) and the leucine-rich repeat containing G-protein-coupled receptor 5 (LGR5).

Petosemtamab has 3 independent mechanisms of action (**Figure 1**)[1]: 1) inhibition of EGFR-dependent signaling, 2) LGR5 binding leading to EGFR internalization and degradation in tumor cells and cancer stem cells, and 3) enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) activity.

Figure 1 | Petosemtamab mechanism of action.



EGFR and WNT signaling are oncogenic and mitogenic drivers in several cancer types, including gastric and esophageal adenocarcinomas (GEA). EGFR amplification has been reported in ~4% of gastric adenocarcinomas.[2] Petosemtamab showed potent antitumor activity in patient-derived xenograft GEA models and blocked metastasis initiation.[1]

In a first-in-human Phase 1/2 study, the petosemtamab dose was determined to be 1500 mg every 2 weeks (Q2W) based on safety, PK data across a wide range of doses, preclinical antitumor activity, with >95% predicted receptor occupancy for EGFR and LGR5 targets in tumor tissues for the entire dosing interval.[3,4] Cohort expansion is ongoing at 1500 mg Q2W in selected solid tumor indications, including GEA and head and neck squamous cell carcinoma.[4] Data are presented for patients with GEA from the ongoing Phase 2 part.

STUDY DESIGN & OBJECTIVES

Phase 1/2, global, open-label study with expansion in advanced/metastatic solid tumor cohorts (NCT03526835)

Key GEA Inclusion Criteria
- ≥2 lines of standard therapy for advanced disease
- ECOG PS 0-1
- Measurable disease
- Baseline tumor biopsy

Treatment Plan
- Petosemtamab 1500 mg IV Q2W, 28-day cycle, with premedication
- Until PD or toxicity
- Tumor assessment Q8W

Survival Follow-up for up to 18 months

- **Primary objective:** Overall response rate (ORR) using RECIST 1.1 per investigator
- **Secondary objectives:** ORR (per central review), duration of response (DOR) and progression-free survival (per investigator and central review), overall survival, safety, PK, immunogenicity, and biomarkers
- **Efficacy evaluable population:** Patients with ≥2 treatment cycles (≥8 weeks) with ≥1 postbaseline tumor assessment or discontinued early due to disease progression or death

PATIENT POPULATION

At the data cutoff date of February 1, 2023, 15 patients with GEA were enrolled and treated in the Phase 2 part of the study. One additional patient with esophageal squamous cell carcinoma was excluded from the analysis.

Patients received a median of 2 cycles of petosemtamab (range: 1-27). Two patients were continuing therapy at the data cutoff date, and 13 patients had discontinued treatment due to tumor progression.

Table 1 | Demographics, disease features, and prior therapy in GEA patients.

	N=15
Age (years), median (range)	62 (40-80)
Male / female	12 (80%) / 3 (20%)
ECOG PS 0 / 1	4 (27%) / 11 (73%)
Tumor location	
▪ Esophagus	8 (53%)
▪ Stomach	6 (40%)
▪ Gastroesophageal junction	1 (7%)
Adenocarcinoma histology	15 (100%)
Measurable disease	15 (100%)

	N=15
No. lines of prior systemic therapy, median (range)	3 (1-5)
▪ Platinum-based chemotherapy	15 (100%)
▪ PD-(L)1 inhibitor	2 (13%)
▪ Cetuximab	0
EGFR high expression and/or amplification[a]	5 (33%)
EGFR H-score (n=11)	
▪ Median (range)	11 (0-300)
▪ 200-300 (high)	4 (27%)

[a]High expression = EGFR IHC H-score ≥ 200; amplification = ctDNA EGFR copy number ≥ 2.5.

PETOSEMTAMAB SAFETY

- Well-tolerated and manageable safety profile in 80 patients treated with petosemtamab at 1500 mg Q2W across dose-escalation and dose-expansion cohorts of the study (**Table 2**)
- Gastrointestinal and skin toxicities were mostly mild to moderate
- No treatment-related Grade 5 adverse events (AEs)

Table 2 | Main AEs in >10% patients (N=80).

Preferred term	Irrespective of causality All grades	Grades 3-5
N patients with ≥1 AE	**80 (100%)**	**42 (53%)**
Rash	29 (36%)	0
Dyspnea	22 (28%)	3 (4%)
Hypotension	21 (26%)	5 (6%)
Nausea	21 (26%)	1 (1%)
Dermatitis acneiform	20 (25%)	1 (1%)
Infusion-related reaction	17 (21%)	10 (13%)
Blood Mg decreased	16 (20%)	4 (5%)
Diarrhea	16 (20%)	0
Erythema	15 (19%)	0
Fatigue	13 (16%)	1 (1%)
Asthenia	12 (15%)	2 (3%)
Pruritus	11 (14%)	0
Constipation	11 (14%)	0
Skin fissures	11 (14%)	0
Decreased appetite	9 (11%)	2 (3%)
Dry skin	9 (11%)	0
Flushing	9 (11%)	2 (3%)
Headache	9 (11%)	0
Hypoxia	9 (11%)	2 (3%)
Pyrexia	9 (11%)	0
Stomatitis	9 (11%)	0

Infusion-related Reactions

Composite term for signs and symptoms during 24 h after initiating the petosemtamab infusion, that investigators judge as an infusion-related reaction (IRR; includes the AE preferred term [PT] "IRR" and other PTs)

- Most frequent related AEs
  - 74% Grade 1-4 IRRs and 21% Grade 3-4 IRRs among 80 patients
- Mainly occurred at first infusion
- 6/80 patients discontinued on Day 1 due to a Grade 3-4 IRR
- All IRR PTs resolved, and for all patients rechallenged after an IRR, rechallenge was successful
- Manageable with prophylaxis/ prolonged infusion (necessary on Day 1 only)

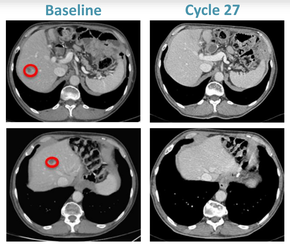
ANTITUMOR ACTIVITY

Among the 15 patients evaluable for efficacy:

- Partial response (PR) was observed in 2 patients, 1 confirmed sustained PR (70% maximal tumor reduction; response ongoing for 27 cycles), and 1 unconfirmed PR (55% maximal tumor reduction; confirmed after the data cutoff date; **Figure 2**)
- EGFR overexpression in baseline tumor biopsies was reported for both PRs, and the confirmed PR had EGFR amplification (ctDNA analysis for unconfirmed PR pending)
- 3 additional patients had a best response of stable disease, 2 had EGFR amplification (1 of whom had overexpression); 1 was not evaluable for IHC

Figure 2 | Clinical responses to petosemtamab.

62-year-old male with gastric adenocarcinoma EGFR overexpression	
Baseline status	ECOG PS 0 Liver and peritoneal metastases
Prior treatment	**1.** 5-FU **2.** Capecitabine/cisplatin
Petosemtamab	27 cycles (ongoing)
RECIST 1.1	Partial response (70% tumor reduction with complete liver remission)



58-year-old male with gastric adenocarcinoma EGFR overexpression	
Baseline status	ECOG PS 0 Incurable locoregional recurrence
Prior treatment	**1.** Irinotecan/5-FU/oxaliplatin; **2.**Capecitabine/irinotecan; **3.**Carboplatin/5-FU; **4.** SGN/TGT; **5.** Trifluridine/tipiracil
Petosemtamab	4 cycles (ongoing)
RECIST 1.1	Partial response (unconfirmed; confirmed after the data cutoff date; 55% tumor reduction)

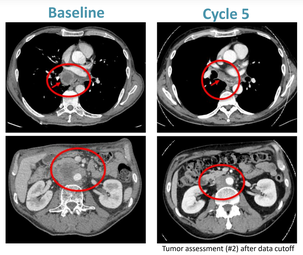
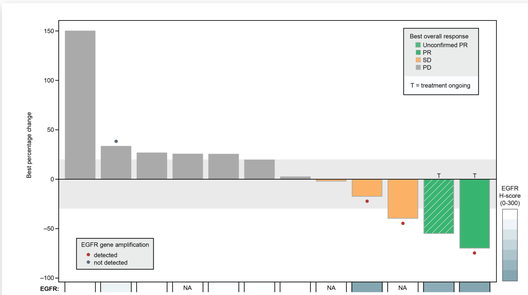
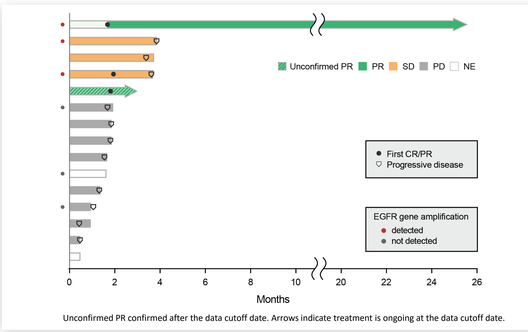


Figure 3 | Best percentage change in sum of target lesions from baseline, per EGFR expression (H-score) and amplification (N=12).



Unconfirmed PR confirmed after the data cutoff date.
3 patients were not included: 2 patients with a best overall response (BOR) of not evaluable due to no postbaseline tumor assessment, and 1 patient with a BOR of progressive disease (based on a new lesion).
NA, not available.

Figure 4 | Time to response and duration of exposure (N=15).



Unconfirmed PR confirmed after the data cutoff date. Arrows indicate treatment is ongoing at the data cutoff date.

CONCLUSIONS

- **Petosemtamab demonstrated early signals of efficacy in patients with previously treated GEA with high EGFR expression and/or amplification**
- **Biomarker analysis continues in this cohort**
- **Petosemtamab was observed to be well tolerated, with a manageable safety profile**
- **Further exploration of petosemtamab is warranted**

References

1. Herpers et al. *Nat Cancer*. 2022;3(4):418-436.
2. Cancer Genome Atlas Research Network. *Nature*. 2014;513(7517):202-209.
3. Argiles et al. *J Clin Oncol*. 2021;39(3 suppl). Abstract 62.
4. Cohen et al. AACR Annual Meeting, April 14-19, 2023; Orlando, FL, USA. Oral presentation CT012.

Presented at: AACR Annual Meeting; April 14-19, 2023; Orlando, FL, USA

ClinicalTrials.gov Identifier: NCT03526835

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