Petosemtamab (MCLA-158) monotherapy or with chemotherapy in metastatic colorectal cancer: Preliminary antitumor activity and safety data from a phase 2 trial

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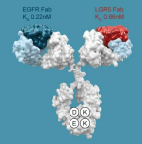


BACKGROUND

- Anti-EGFR monoclonal antibodies in combination with chemotherapy and as monotherapy are standard of care treatment for metastatic colorectal cancer (mCRC)[1,2]
- LGR5 is expressed in CRC stem-like cells that drive tumor initiation, growth and metastasis[3,4]
- Growth of CRC stem-like cells is dependent on expression of both EGFR and LGR5[3,4]
- Inhibition of EGFR on CRC cells leads to upregulation of LGR5[1,6]
- Petosemtamab: Biclonics® bispecific antibody targeting EGFR and LGR5 that inhibits tumor growth and metastasis[7,8]
- Petosemtamab mechanism of action:[6-8]
  - Inhibition of EGFR ligand binding and downstream signaling
  - Degradation of EGFR via LGR5 internalization in EGFR/LGR5-expressing cells
  - Immune system activation via enhanced ADCC
- Granted two FDA Breakthrough Therapy designations:[9]
  - As monotherapy for 2L+ r/m HNSCC
  - In combination with pembrolizumab for 1L PD-L1+ r/m HNSCC

TRIAL DESIGN AND OBJECTIVES

Phase 2 trial design (NCT03526835)

Key inclusion criteria

- Metastatic CRC
- Left and/or right sided
- Microsatellite stable
- ECOG PS 0–1
- Measurable disease by RECIST v1.1
- 1/2L: EGFRi naïve, RAS/RAF WT by local tissue NGS
- 3L+: EGFRi-, VEGFRi-, and SOC chemotherapy pretreated[1]; KRAS, NRAS, BRAF WT, EGFR ectodomain WT, no ERBB2/HER2 amplification by baseline central ctDNA NGS

1L: Petosemtamab 1500 mg IV + FOLFOX[a] or FOLFIRI[a], Q2W; 28-day cycle (planned enrollment N=40)

2L: Petosemtamab 1500 mg IV + FOLFOX[a] or FOLFIRI[a], Q2W; 28-day cycle (planned enrollment N=40)

3L+: Petosemtamab monotherapy 1500 mg IV, Q2W; 28-day cycle (planned enrollment N=60)

Follow-up

- Tumor assessments Q8W
- Survival follow-up up to 18 months

Objectives

Primary endpoint
ORR using RECIST v1.1 per investigator

Secondary and exploratory endpoints
DOR, PFS, OS, safety, tolerability, and PK characterization

Enrollment and analysis population

Data cutoff date
July 29, 2025

Enrollment
1L cohort: 14 patients
2L cohort: 14 patients
3L+ monotherapy: 26 patients

Efficacy evaluable population
Patients with ≥1 dose of petosemtamab who had opportunity for ≥8 weeks follow up and ≥1 post baseline tumor assessment or discontinued petosemtamab early due to disease progression, symptomatic deterioration and/or death
1L cohort: 10 patients; 4 patients excluded[f]
2L cohort: 13 patients; 1 patient excluded[f]
3L+ monotherapy: 20 patients; 6 patients excluded[f]

[a]Oxaliplatin ; bisotecan ; 5-FU pretreated; [b]FOLFOX: oxaliplatin 85 mg/m² IV 120 min, leucovorin 400 mg/m² IV 90-120 min, 5-FU bolus 400 mg/m² IV 5 min, and 5-FU 2400 mg/m² IV 46 h; [c]FOLFIRI: irinotecan 180 mg/m² IV 90-120 min, leucovorin 400 mg/m² IV 90-120 min, 5-FU bolus 400 mg/m² IV 5 min, and 5-FU 2400 mg/m² IV 46 h; [d]Reason for exclusion were no post-baseline tumor assessments due to insufficient follow up, unrelated AE or consent withdrawal.

1L, first line; 2L, second line; 3L+, third line and beyond; ADCC, antibody-dependent cellular toxicity; AE, adverse event; CI1D1, cycle 1 day 1; CI, confidence interval; CR, complete response; ctDNA, circulating tumor DNA; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EGFRi, EGFR inhibitor; FDA, Food and Drug Administration; h, hour; HNSCC, head and neck squamous cell carcinoma; IRR, infusion-related reaction; IV, intravenous; K, potassium; LGR5, leucine-rich repeat-containing G-protein coupled receptor; mCRC, metastatic colorectal cancer; Mg, magnesium; NA, not available; NGS, next generation sequencing; ORR, overall response rate; OS, overall survival; PD-L1+, programmed cell death-ligand 1 positive; PFS, progression-free survival; PK, pharmacokinetics; PPE, palmar-plantar erythrodysaesthesia; PR, partial response; Q2W, every 2 weeks; Q8W, every 8 weeks; r/m, recurrent/metastatic; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; SOC, standard of care; TEAE, treatment-emergent adverse event; uCR, unconfirmed complete response; uPR, unconfirmed partial response; VEGFRi, vascular endothelial growth factor receptor inhibitor; WT, wild type.

PATIENT POPULATION

Demographics and disease characteristics	1L combo (N=14)	2L combo (N=14)	3L+ monotherapy (N=26)
Age, years, median (range)	49 (35–73)	55.5 (43–76)	57.5 (30–80)
Male / female, n (%)	8 (57) / 6 (43)	8 (57) / 6 (43)	18 (69) / 8 (31)
ECOG PS, n (%)			
0	7 (50)	4 (29)	12 (46)
1	7 (50)	10 (71)	14 (54)
Race, n (%)			
White	9 (64)	9 (64)	20 (77)
Asian	0	2 (14)	0
Other/not reported	5 (36)	3 (21)	6 (23)
FOLFOX / FOLFIRI, n (%)	10 (71) / 4 (29)	2 (14) / 12 (86)	
Primary site of cancer, n (%)			
Left colon	12 (86)	11 (79)	23 (89)
Right colon	2 (14)	3 (21)	3 (12)
Liver metastases, n (%)	11 (79)	7 (50)	21 (81)
Prior lines of therapy, median (range)	0 (0–0)	1 (1–1)	3 (2-6)

Patient disposition	1L combo (N=14)	2L combo (N=14)	3L+ monotherapy (N=26)
Treatment ongoing, n (%)	13 (93)	11 (79)	11 (42)
Treatment discontinuation, n (%)			
Disease progression	0	2 (14)	13 (50)
Symptomatic deterioration	0	1 (7)	0
Withdrawal by subject	1 (7)	0	0
Study drug-related adverse event	0	0	1 (4)
Unrelated adverse event	0	0	1 (4)
Duration of follow-up, months median (range)	2.8 (0.9–7.1)	4.8 (0.6–12.0)	4.2 (0.4–7.6)

SAFETY

Most common TEAEs irrespective of causality

TEAEs (≥20%), n (%) Preferred Term	Petosemtamab + FOLFOX (N=12) All grades	Petosemtamab + FOLFOX (N=12) Grades 3-5	Petosemtamab + FOLFIRI (N=16) All grades	Petosemtamab + FOLFIRI (N=16) Grades 3-5	Petosemtamab monotherapy (N=26) All grades	Petosemtamab monotherapy (N=26) Grades 3-5
At least 1 TEAE[a]	**12 (100)**	**3 (25)**	**15 (94)**	**11 (69)**	**25 (96)**	**9 (35)**
Acneiform dermatitis	8 (67)	0	5 (31)	0	14 (54)	2 (8)
Nausea	6 (50)	0	5 (31)	0	7 (27)	0
Stomatitis	5 (42)	0	8 (50)	1 (6)	1 (4)	1 (4)
Diarrhea	4 (33)	0	9 (56)	2 (13)	2 (8)	0
Fatigue	4 (33)	0	6 (38)	1 (6)	5 (19)	0
Gastroesophageal reflux disease	4 (33)	0	1 (6)	0	0	0
Constipation	3 (25)	0	5 (31)	0	6 (23)	0
Blood Mg decreased	3 (25)	0	3 (19)	0	5 (19)	1 (4)
Blood K decreased	3 (25)	0	3 (19)	1 (6)	4 (15)	1 (4)
Dyspnea	3 (25)	0	3 (19)	0	3 (12)	0
Vomiting	3 (25)	0	3 (19)	0	4 (15)	0
Dizziness	3 (25)	0	2 (13)	0	3 (12)	0
Embolism	3 (25)	1 (8)	1 (6)	0	0	0
Peripheral sensory neuropathy	3 (25)	0	0	0	0	0
Dry skin	2 (17)	0	4 (25)	0	4 (15)	0
PPE syndrome	1 (8)	0	5 (31)	2 (13)	2 (8)	0
Neutropenia	0	0	5 (31)	3 (19)	0	0
Chills	0	0	5 (31)	0	3 (12)	0
Peripheral edema	0	0	4 (25)	0	0	0

	Petosemtamab + FOLFOX (N=12) All grades	Petosemtamab + FOLFOX (N=12) Grades 3-5	Petosemtamab + FOLFIRI (N=16) All grades	Petosemtamab + FOLFIRI (N=16) Grades 3-5	Petosemtamab monotherapy (N=26) All grades	Petosemtamab monotherapy (N=26) Grades 3-5
IRR[b]	4 (33)	0	7 (44)	0	10 (30)	1 (4)

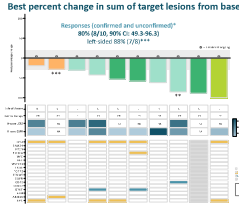
- Petosemtamab's safety profile in mCRC is consistent with its established safety profile in r/m HNSCC
- No significant overlapping toxicities identified in combination with FOLFOX/FOLFIRI
- No new safety signals identified
- No G5 or G4 treatment-related TEAEs observed in combination with FOLFOX/FOLFIRI
- No G5 treatment-related TEAEs observed with petosemtamab monotherapy
- One patient discontinued petosemtamab monotherapy due to treatment-related G4 hypomagnesemia
- Cutaneous side effect profile[c] appears favorable and manageable without pharmacologic prophylaxis
- IRRs were managed with premedication and prolonged infusion on C1D1; no discontinuations due to IRRs

[a]Most common TEAEs, irrespective of causality, are defined as AEs with onset date on or after date of first administration of study drug and ≤30 days post-treatment; [b]IRR is a composite term for one or multiple signs/symptoms during the 24-hour period after initiating the petosemtamab infusion, judged by investigator as an IRR; [c]Composite term including dermatitis acneiform, folliculitis, rash maculo-papular, skin fissures, PPE syndrome.

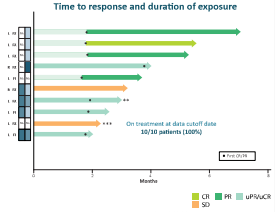
EFFICACY

Petosemtamab + FOLFOX/FOLFIRI in 1L mCRC (n=10)

Best percent change in sum of target lesions from baseline



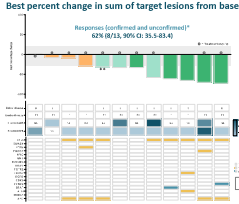
Time to response and duration of exposure



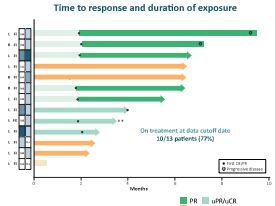
*RECIST v1.1, per investigator; **Unconfirmed response was confirmed post data cutoff; ***Unconfirmed PR documented post data cutoff leading to 100% response; left-sided (8/8).

Petosemtamab + FOLFOX/FOLFIRI in 2L mCRC (n=13)

Best percent change in sum of target lesions from baseline[a]



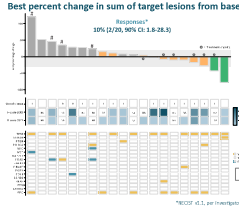
Time to response and duration of exposure



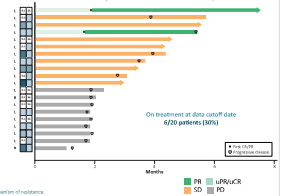
*One patient left early symptomatic deterioration and no post-baseline scan not included in the waterfall plot.
*RECIST v1.1, per investigator; **Unconfirmed response was confirmed post data cutoff.

Petosemtamab monotherapy in 3L+ mCRC (n=20)

Best percent change in sum of target lesions from baseline



Time to response and duration of exposure



*RECIST v1.1, per investigator; †Identified mechanism of resistance.

Intrahepatic tumor responses with petosemtamab + FOLFOX/FOLFIRI: Case studies

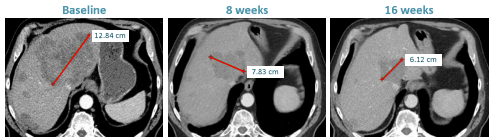
- Among 14 patients with measurable target liver lesions, 10 (71%) showed intrahepatic objective response
  - 1L: 6/8 (75%)
  - 2L: 4/6 (67%)

67-year-old male with metastatic sigmoid adenocarcinoma

- No prior systemic treatment
- Treated with petosemtamab + FOLFOX; unconfirmed PR, confirmed post data cutoff

73-year-old male with metastatic rectal adenocarcinoma

- 1 prior line of systemic treatment in the metastatic setting
- Treated with petosemtamab + FOLFIRI; confirmed PR



CONCLUSIONS

Petosemtamab in combination with FOLFOX/FOLFIRI and as monotherapy demonstrates promising efficacy and a well-tolerated safety profile in mCRC

Substantial antitumor activity:
- 1L: 8/10 (80%) confirmed + unconfirmed responses and 2 SD with tumor shrinkage continuing treatment
  - Left-side: 7/8 (88%) confirmed + unconfirmed responses
- 2L: 8/13 (62%) confirmed + unconfirmed responses and 3 SD with tumor shrinkage continuing treatment
- 3L+: 2/20 (10%) confirmed responses and 4 SD with tumor shrinkage continuing treatment

Favorable safety profile with no new safety signals identified:
- Cutaneous side effect profile appears favorable and manageable without pharmacologic prophylaxis

Clinical development continues:
- 1L and 2L mCRC in combination with FOLFOX/FOLFIRI and 3L+ mCRC monotherapy enrolling (NCT03526835)
- Phase 3 registrational trials in r/m HNSCC enrolling
  - 1L PD-L1+ with pembrolizumab (LiGeR-HN1, NCT06525220)
  - 2/3L monotherapy (LiGeR-HN2, NCT06496178)

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