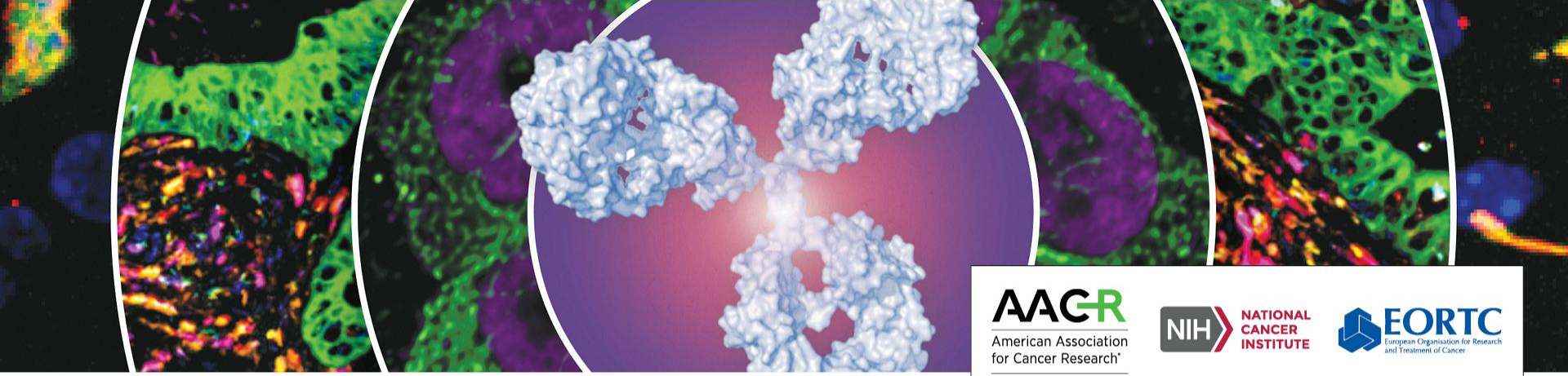

Petosemtamab (MCLA-158) monotherapy or with chemotherapy in metastatic colorectal cancer: Preliminary antitumor activity and safety data from a phase 2 trial

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AACR-NCI-EORTC MOLECULAR TARGETS AND CANCER THERAPEUTICS

October 22-26, 2025 | Hynes Convention Center | Boston, MA

Disclosure Information

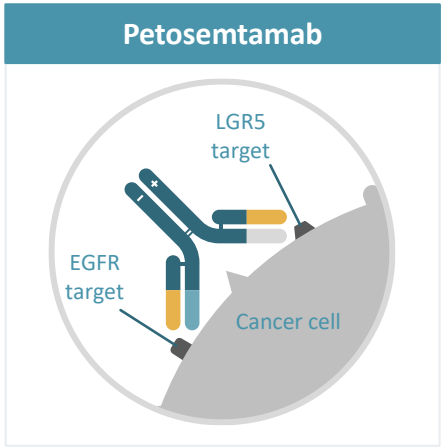
Moh’d Khushman

I have the following relevant financial relationships to disclose:

Consultant/Advisor for:	TriSalusLife Sciences, Cardinal Health, BMS, AbbVie, Exelixis, Elevar Therapeutics, Guardant Health, Merus N.V.
Grant/Research Support:	AbbVie, FOGPharma, IgM Biotherapeutics, Merus N.V., GlaxoSmithKline, BeiGene

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[5,6]
- 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



1L, first line; 2L, second line; ADCC, antibody-dependent cellular toxicity; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HNSCC, head and neck squamous cell carcinoma; PD-L1+, programmed death-ligand 1 positive; r/m, recurrent/metastatic.

1. Douillard JY, et al. *N Engl J Med*. 2013;369(11):1023-1034. 2. Watanabe J, et al. *JAMA*. 2023;329(15):1271-1282. 3. Katoh M. *Int J Oncol.* 2017; 51(5): 1357–1369. 4. Xu L, et al. *Stem Cell Res Ther*. 2019;10(1):219. 5. Shimokawa M, et al. *Nature*. 2017;545:187-192. 6. Slobodnyuk K, et al. Presented at 2025 AACR-NCI-EORTC international conference [poster B042]. 7. Herpers B, et al. *Nat Cancer*. 2022;3(4):418–436. 8. Lundberg AS, et al. *Cancers (Basel).* 2025;17(10):1665. 9. Merus N.V. News release. 2025. Available at https://ir.merus.nl/news-releases/news-release-details/petosemtamab-granted-breakthrough-therapy-designation-us-fda-1l/. Accessed August 4, 2025.

Phase 2 Trial Design and Objectives (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[a]; KRAS, NRAS, BRAF WT, EGFR ectodomain WT, no ERBB2/HER2 amplification by baseline central ctDNA NGS

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

2L: Petosemtamab 1500 mg IV + FOLFOX[b] or FOLFIRI[c], 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 combo: 14 patients

2L combo: 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 combo:** 10 patients; 4 patients excluded[d]
- **2L combo:** 13 patients; 1 patient excluded[d]
- **3L+ monotherapy:** 20 patients; 6 patients excluded[d]

[a]Oxaliplatin-, Irinotecan-, 5-FU-pretreated; [b]FOLFOX: oxaliplatin 85 mg/m^2 IV 120 min, leucovorin 400 mg/m^2 IV 90-120 min, 5-FU bolus 400 mg/m^2 IV 5 min, and 5-FU 2400 mg/m^2 IV 46 h; [c]FOLFIRI: irinotecan 180 mg/m^2 IV 90-120 min, leucovorin 400 mg/m^2 IV 90-120 min, 5-FU bolus 400 mg/m^2 IV 5 min, and 5-FU 2400 mg/m^2 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; CRC, colorectal cancer; ctDNA, circulating tumor DNA; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFRi, epidermal growth factor receptor inhibitor; IV, intravenously; NGS, next generation sequencing; ORR< overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q2W, every 2 weeks; Q8W, every 8 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SOC, standard of care; VEGFRi, vascular endothelial growth factor receptor; WT, wild type.

Patient Characteristics and Disposition

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)

1L, first-line, 2L, second-line, 3L+, third-line and beyond; ECOG PS, Eastern Cooperative Oncology Group performance status.

Safety

Most Common TEAEs Irrespective of Causality

TEAEs (≥20%), n (%) Preferred Term	Petosemtamab + FOLFOX (N=12)		Petosemtamab + FOLFIRI (N=16)		Petosemtamab monotherapy (N=26)	
	All grades	Grades 3-5	All grades	Grades 3-5	All grades	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)		Petosemtamab + FOLFIRI (N=16)		Petosemtamab monotherapy (N=26)	
	All grades	Grade 3-5	All grades	Grade 3-5	All grades	Grade 3
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 G4 or G5 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] observed to be well tolerated and manageable without pharmacologic prophylaxis
- IRRs were managed with premedication and prolonged infusion on C1D1; no discontinuations due to IRRs

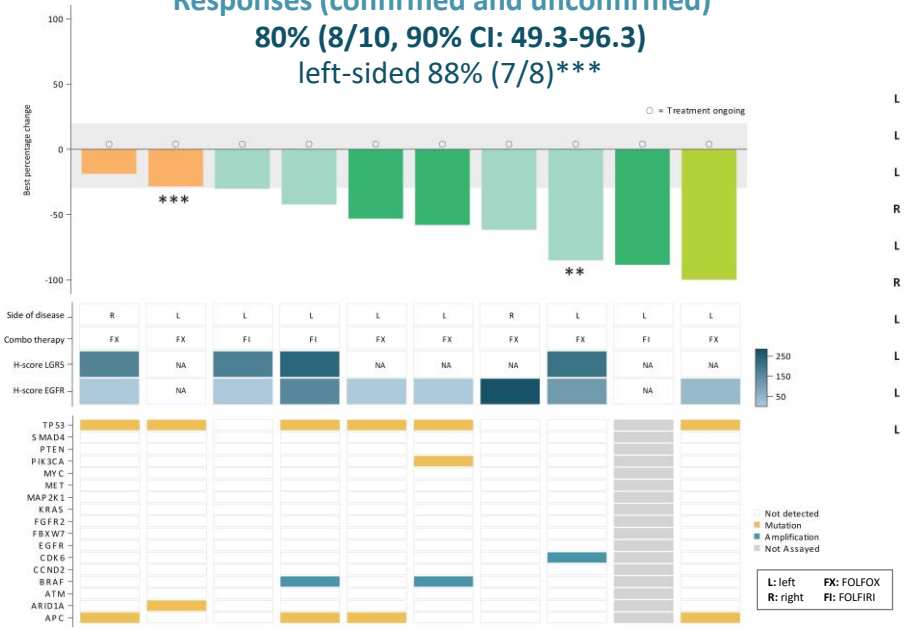
[a]Most common TEAEs, irrespective of causality, are defined as AEs with onset date on or after date of first administration of study drug and ≤30 days post-treatment;
[b]IRR is a composite term for one or multiple signs/symptoms during the 24-hour period after initiating the petosemtamab infusion, judged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

C1D1, cycle 1 day 1; G, Grade; IRR, infusion-related reaction; K, potassium; Mg, magnesium; PPE, palmar-plantar erythrodysesthesia; TEAE, treatment-emergent adverse event.

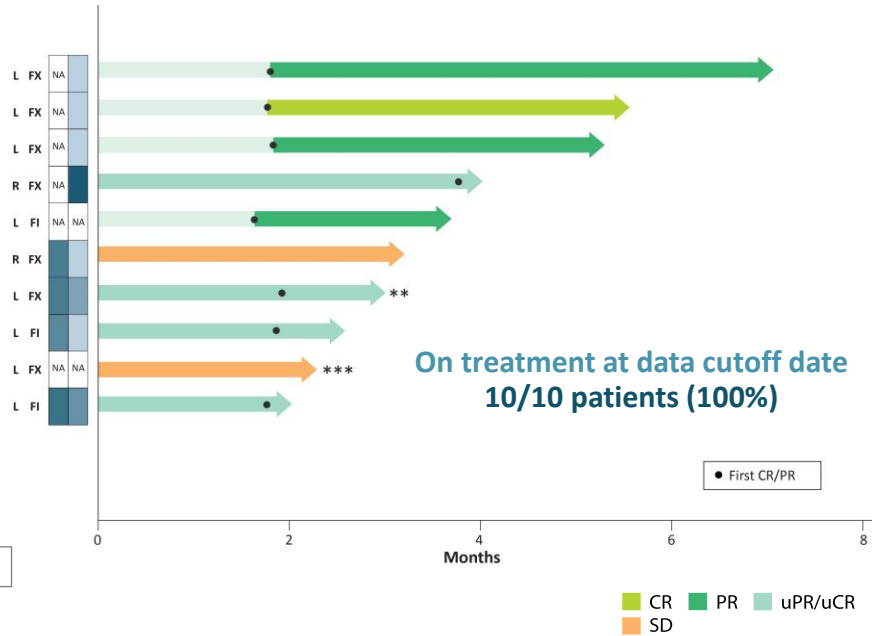
Efficacy: Petosemtamab + FOLFOX/FOLFIRI in 1L mCRC (n=10)

Best percent change in sum of target lesions from baseline

Responses (confirmed and unconfirmed)*
80% (8/10, 90% CI: 49.3-96.3)
left-sided 88% (7/8)***



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% responses left-sided (8/8).

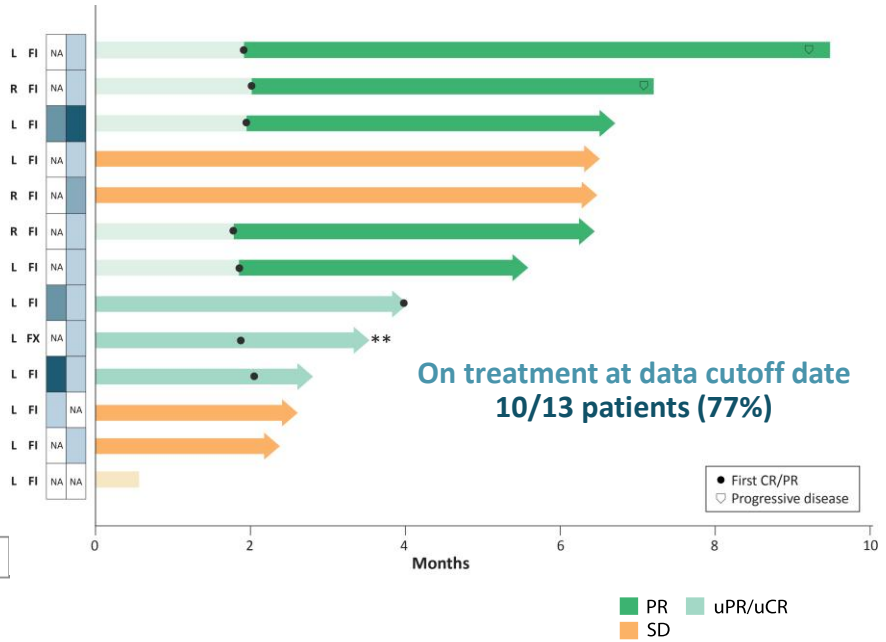
1L, first-line; CI, confidence interval; CR, complete response; mCRC, metastatic colorectal cancer; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; uCR, unconfirmed complete response uPR, unconfirmed partial response.

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

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

Responses (confirmed and unconfirmed)*
62% (8/13, 90% CI: 35.5-83.4)

Time to response and duration of exposure

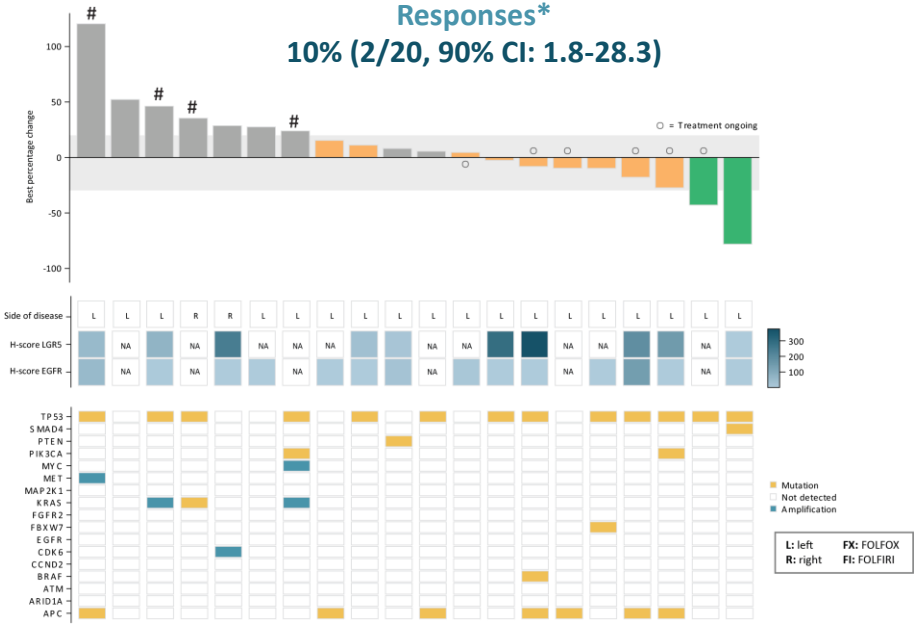


[a]One patient with early symptomatic deterioration and no post-baseline scan not included in the waterfall plot.
*RECIST v1.1, per investigator; **Unconfirmed response was confirmed post data cutoff.

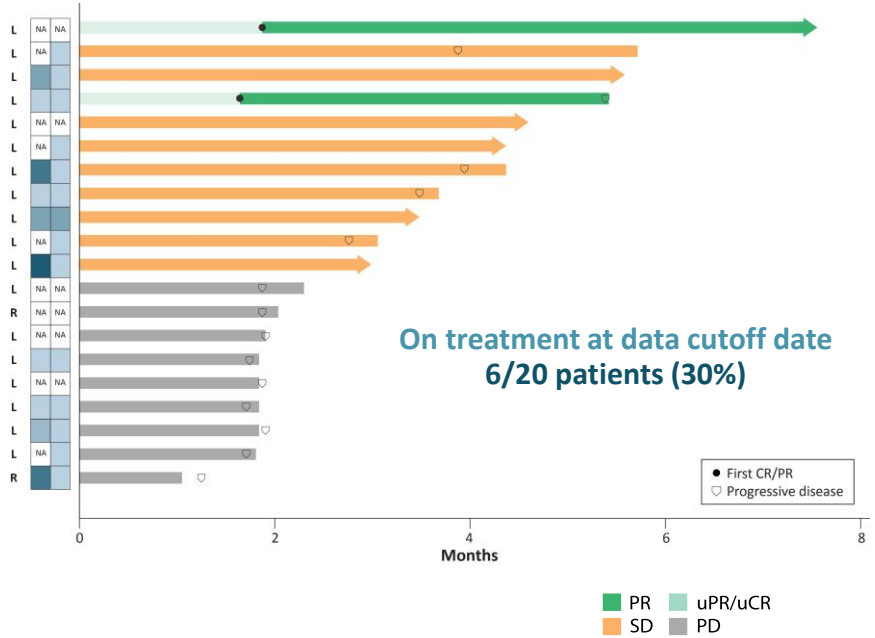
2L, second-line; CI, confidence interval; CR, complete response; mCRC, metastatic colorectal cancer; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; uCR, unconfirmed complete response uPR, unconfirmed partial response.

Efficacy: 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.

3L+, third-line and beyond; CI, confidence interval; CR, complete response; CRC, colorectal cancer; PD, progressive disease; PR, partial response;
RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; uCR, unconfirmed complete response uPR, unconfirmed partial response.

Intrahepatic tumor responses with petosemtamab + FOLFOX/FOLFIRI

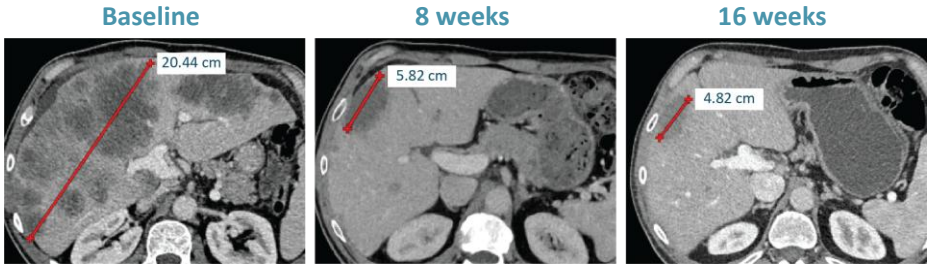
Case studies

Among 14 patients with measurable target liver lesions, 10 (71%) showed intrahepatic objective response

- 1L: 6/8 (75%)
- 2L: 4/6 (67%)

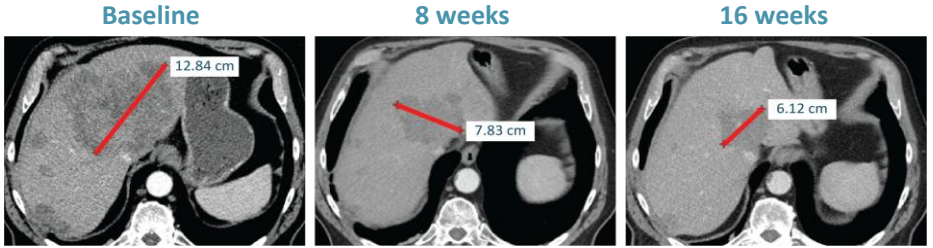
67-year-old male with metastatic sigmoid adenocarcinoma

- 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



PR, partial response.

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 observed to be well tolerated 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)

1L, first-line; 2L, second-line; 3L+, third-line and beyond; HNSCC, head and neck squamous cell carcinoma; IRRs, infusion-related reactions; L-side: left side; mCRC, metastatic colorectal cancer; PD-L1+, programmed death-ligand 1 positive; r/m, recurrent/metastatic; SD, stable disease;

Acknowledgments

Thanks to:

We thank the patients and their families, the investigators and their teams, Merus colleagues (including Marina Magin Ferrer); clinical research organizations, and vendors. Study sponsored by Merus N.V.