ABSTRACT
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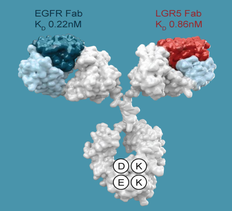
Petosemtamab (MCLA-158) with pembrolizumab as first-line (1L) treatment of PD-L1+ recurrent/metastatic (r/m) head and neck squamous cell carcinoma (HNSCC): Phase 2 trial



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BACKGROUND

- EGFR and WNT are oncogenic and mitogenic drivers in several cancer types, including HNSCC[1–4]
- LGR5 is a receptor of WNT signaling and is upregulated in many cancer types[5,6]
- Petosemtamab: Biclonics bispecific antibody targeting EGFR and LGR5[1,2]
- Mechanism of action[1,2]:
  - Inhibition of EGFR ligand binding and downstream signaling
  - Degradation of EGFR via LGR5 internalization
  - Engagement of host immune cells via enhanced ADCC
- Demonstrated substantial efficacy as a monotherapy in 2L+ r/m HNSCC (ORR 36%, mOS 11.4 months, N=75)[7]
- Demonstrated preliminary clinically meaningful activity and favorable safety in combination with pembrolizumab in 1L PD-L1+ r/m HNSCC[8]
- 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

Petosemtamab in combination with pembrolizumab is being evaluated in an ongoing Phase 2, open-label, global, multicenter trial (ClinicalTrials.gov Identifier: NCT03526835)

Phase 2 trial design

Key inclusion criteria
- 1L PD-L1+ r/m HNSCC[a]
- ECOG PS 0–1
- Measurable disease

Treatment plan
- Petosemtamab 1500 mg IV, Q2W + pembrolizumab 400 mg IV Q6W
- Until PD or toxicity
- Tumor assessment Q8W

Follow-up

Survival follow-up up to 3 years

Objectives

Primary objectives

ORR using RECIST v1.1 per investigator, safety, and tolerability

Secondary and exploratory objectives

DOR and PFS using RECIST v1.1 per investigator, OS, PK, immunogenicity, and biomarkers

Efficacy evaluable population

Patients treated (with 1 or more doses) as of the data cutoff date and either ≥1 post-baseline scan or discontinued early due to disease progression or death

Enrollment and analysis

Data cutoff date
27 February 2025

Efficacy evaluable population
43 patients

Enrollment
45 patients

2 patients were excluded that did not meet the criteria for the efficacy evaluable population

[a]PD-L1+ refers to patients with tumors expressing PD-L1 CPS ≥1.
1L: first-line; 2L: second-line; ADCC: antibody-dependent cellular cytotoxicity; CPS: combined positive score; DOR: duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; EGFR: epidermal growth factor receptor; FDA: Food and Drug Administration; HNSCC: head and neck squamous cell carcinoma; IV: intravenous; LGRS: leucine-rich repeat-containing G-protein coupled receptor 5; mOS: median overall survival; ORR: overall response rate; OS: overall survival; PD: progressive disease; PD-L1(+): programmed cell death ligand 1 (positive); PFS: progression-free survival; PK: pharmacokinetics; Q#W: every # weeks; r/m: recurrent/metastatic; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1; WNT: wingless-related integration site.

PATIENT POPULATION

Demographics and disease characteristics	N=45
Age, years, median (range)	64 (23–80)
Male / female, n (%)	35 (78) / 10 (22)
ECOG PS 0 / 1, n (%)	16 (36) / 29 (64)
Main tumor location, n (%)	
Oral cavity	17 (38)
Oropharynx	14 (31)
Larynx	7 (16)
Hypopharynx	5 (11)
Other[a]	2 (4)
PD-L1 status (local), n (%)	
PD-L1 positive	45 (100)
CPS 1–19 / ≥20	19 (42) / 26 (58)
p16 (HPV) status (local): Oropharynx (n=14), n (%)	
p16 positive	8 (57)
p16 negative[b]	6 (43)
EGFR (IHC) H-score, median (range)[c]	240 (0–300)

Patient disposition	N=45
Treatment ongoing, n (%)	14 (31)
Treatment discontinuation, n (%)	31 (69)
Disease progression	25 (56)
Withdrawal of consent	2 (4)
Related adverse event[d]	2 (4)
Symptomatic deterioration	1 (2)
Death (unrelated to treatment)	1 (2)
Petosemtamab exposure duration, months	
Median (range)	8.3 (0.5–22.1)
Mean *(with 14 patients ongoing)*	8.7
Duration of follow-up, months, median (range)	14.3 (1.5–22.1)

[a]1 patient with HNSCC from unknown primary tumor location, 1 patient with HNSCC from sinonasal primary tumor; [b]Includes 1 patient whose tumor p16 status was subsequently confirmed negative by central testing; [c]2 patients had no IHC H-score (EGFR) available; [d]1 patient discontinued due to asthenia (G2) and diarrhea (G1), 1 patient discontinued due to dermatitis acneiform (G3).

G: Grade; HPV: human papillomavirus; IHC: immunohistochemistry.

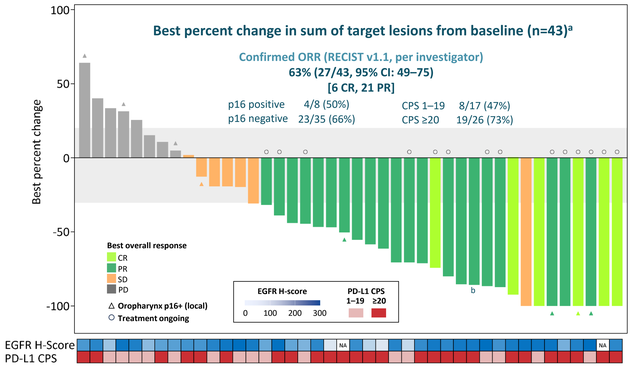
SAFETY

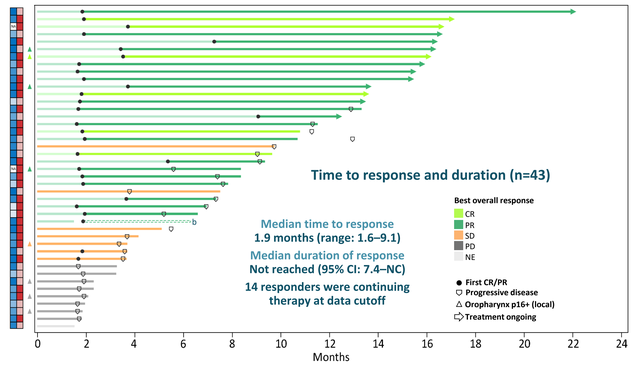
- TEAEs were reported in 45 patients; most were G1 or G2
- G≥3 TEAEs occurred in 27 patients (60%), including 20 (44%) who experienced treatment-related TEAEs
- No individual G≥3 TEAE occurred in >7% of patients
- No G5 treatment-related TEAEs were reported
- IRRs[a] occurred in 38% of patients, with 7% G3; no G4 or 5; mainly occurred during first infusion and were resolved
- IRRs were managed with premedication and prolonged infusion
- No significant overlapping toxicities were observed

[a]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; [b]Most common TEAEs, irrespective of causality, are defined as adverse events with onset date on or after date of first administration of study drug and ≤30 days post-treatment.
IRR: infusion-related reaction; Mg: magnesium; TEAE: treatment-emergent adverse event.

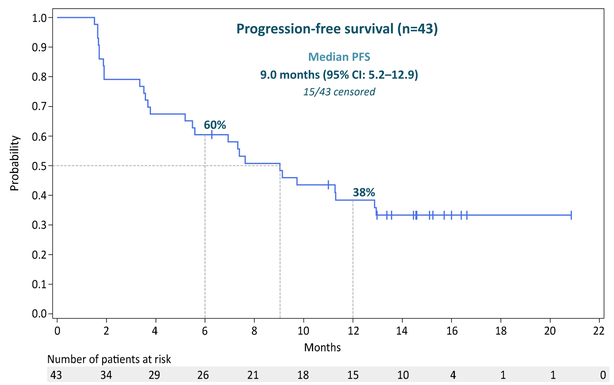
TEAEs irrespective of causality (≥20% of patients), n (%)		
Preferred term	**All grades**	**Grades 3–5**
At least 1 TEAE[b]	**45 (100)**	**27 (60)**
Asthenia	23 (51)	3 (7)
Acneiform dermatitis	22 (49)	3 (7)
Rash	20 (44)	0
Blood Mg decreased	18 (40)	3 (7)
Skin fissures	18 (40)	1 (2)
Constipation	16 (36)	0
Nausea	16 (36)	1 (2)
Folliculitis	15 (33)	1 (2)
Dry skin	14 (31)	1 (2)
Paronychia	14 (31)	1 (2)
Diarrhea	13 (29)	3 (7)
Pruritus	13 (29)	0
Stomatitis	13 (29)	2 (4)
Hypotension	10 (22)	2 (4)
Cough	9 (20)	0
Tumor pain	9 (20)	2 (4)

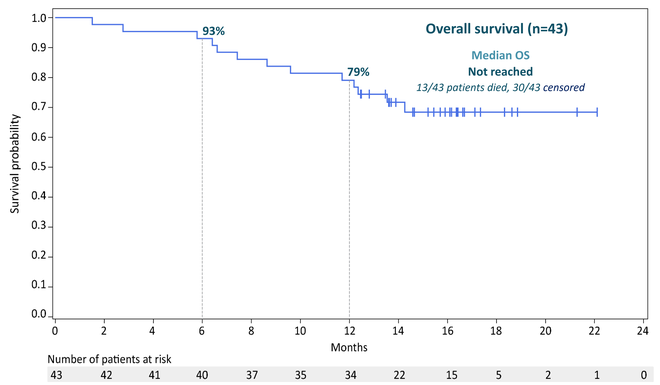
EFFICACY





[a]1 patient who died before the first post-baseline tumor assessment not included in the waterfall plot; [b]Patient received 3 infusions and discontinued petosemtamab and pembrolizumab due to treatment-related TEAEs. Confirmed, durable PR was observed after treatment discontinuation.





CI: confidence interval; CR: complete response; NA: not available; NC: not calculable; NE: not evaluable; PR: partial response; SD: stable disease.

CONCLUSIONS

Petosemtamab with pembrolizumab in 1L PD-L1+ r/m HNSCC:

- **Clinically meaningful efficacy and durability**
  - 63% ORR, with responses across p16 and CPS subgroups
  - Median PFS of 9 months, and mean duration of exposure of 8.7 months, with 14 responders still ongoing
  - 79% OS rate at 12 months
- **Favorable safety profile with no new safety signals**
- **Potential first and best-in-class treatment for 1L PD-L1+ r/m HNSCC**
- **Phase 3 registrational trials in r/m HNSCC enrolling**
  - 1L PD-L1+ r/m HNSCC with pembrolizumab (LiGeR-HN1, NCT06525220)
  - 2/3L r/m HNSCC as monotherapy (LiGeR-HN2, NCT06496178)

References

1. Herpers B, et al. *Nat Cancer*. 2022;3(4):418–436.
2. Lundberg AS, et al. *Cancers.* 2025;17 (17):1665.
3. Schinke H, et al. *Mol Cancer*. 2022;21(1):178.
4. Parsons MJ, et al. *Cancer Discov*. 2021;11(10):2413–2429.
5. Xu L, et al. *Stem Cell Res Ther.* 2019;10(1):219.
6. Katoh M. *Int J Oncol.* 2017;51(5):1357–1369.
7. Le Tourneau C, et al. *Ann Oncol*. 2024;35(Suppl 4):S1554–S1574 [mini-oral presentation 411MO at ESMO Asia 2024].
8. Fayette J, et al. *J Clin Oncol.* 2024;42(Suppl 16):6014 [oral presentation at ASCO 2024].
9. Merus N.V. News release (2025), available at: ir.merus.nl/news-releases/news-release-details/petosemtamab-granted-breakthrough-therapy-designation-us-fda-1l (accessed 06May25).

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