Merus closing in on cancer

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

Jérôme Fayette,[1] Florian Clatot,[2] Irene Braña,[3] Esma Saada,[4] Carla M. L. van Herpen,[5] Thibault Mazard,[6] Cesar A. Perez,[7] Josep Tabernero,[8] Christophe Le Tourneau,[9] Antoine Hollebecque,[10] Virginia Arrazubi,[11] Elisa Fontana,[12] Shumei Kato,[13] Assuntina G. Sacco,[13] Amir Harandi,[14] Jan Paul de Boer,[15] Jessica Ann Hellyer,[16] Eduardo Pennella,[17] Andrew K. Joe,[17] Amaury Daste[18]

[1]Department of Medical Oncology, Léon Bérard Center, University of Lyon, Lyon, France; [2]Department of Medical Oncology, Henri Becquerel Cancer Institute, Rouen, France; [3]Vall d'Hebron Institute of Oncology (VHIO) and Vall d'Hebron University Hospital, Barcelona, Spain; [4]Department of Medical Oncology, Centre Antoine Lacassagne, Nice, France; [5]Department of Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands; [6]Institut Régional du Cancer de Montpellier (ICM), Montpellier, France; [7]Sarah Cannon Research Institute at Florida Cancer Specialists, Orlando, FL, USA; [8]Vall d'Hebron Hospital Campus and Institute of Oncology (VHIO), IOB-Quirón, UVic-UCC, Barcelona, Spain; [9]Department of Drug Development and Innovation (D3i), Institut Curie, Paris-Saclay University, Paris, France; [10]Gustave Roussy, University of Paris-Saclay, Villejuif, France; [11]Servicio de Oncología Médica, Hospital Universitario de Navarra, Pamplona, Spain; [12]Sarah Cannon Research Institute, London, UK; [13]Department of Medicine, Division of Hematology-Oncology, University of California San Diego Health, Moores Cancer Center, La Jolla, CA, USA; [14]Florida Cancer Specialists and Research Institute, Lakewood Ranch, FL, USA; [15]Department of Medical Oncology, Netherlands Cancer Institute, Antoni van Leeuwenhoek, Amsterdam, Netherlands; [16]Cancer Care Northwest (Tempus), Spokane, WA, USA; [17]Merus N.V., Utrecht, Netherlands; [18]Oncology, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France.

PRESENTED BY: Dr. Jérôme Fayette

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

- Clinically meaningful activity and favorable safety observed:
  - 67% response rate overall (13/24 confirmed and 3/24 unconfirmed* responses)
  - Responses observed across HPV-related and -unrelated cancer; and across PD-L1 CPS subgroups
  - Favorable safety profile including manageable IRRs (38% all Grades, 7% Grade 3; no Grade 4 or 5)
- Potential first- and best-in-class treatment for 1L HNSCC
- Petosemtamab clinical development in HNSCC and CRC is ongoing:
  - 1L HNSCC phase 3 registration trial with pembrolizumab planned to start by year end 2024
  - 2L/3L HNSCC phase 3 registration trial as monotherapy planned to start mid-2024
  - 2L CRC phase 1/2 trial with chemotherapy planned

*All 3 uPR were confirmed as PR after data cutoff date.
2L, second-line; 3L, third-line; CRC, colorectal cancer.

Merus

Petosemtamab

A Biclonics® bispecific antibody targeting EGFR and LGR5

- EGFR and WNT are oncogenic and mitogenic drivers in several cancer types, including HNSCC[1-3]
- LGR5 is a receptor of WNT signaling and is upregulated in many cancer types[4,5]
- Petosemtamab monotherapy demonstrated meaningful preclinical and clinical antitumor activity in HNSCC[1]

Mechanisms of action[1]

- Inhibition of EGF ligand binding and downstream signaling
- Degradation of EGFR via LGR5 internalization
- Engagement of host immune cells via enhanced ADCC

Rationale

- Combining an EGFR antibody with an anti-PD-1 agent such as pembrolizumab in HNSCC may improve efficacy without significantly increased toxicity[6-8]
- Petosemtamab demonstrated substantial monotherapy efficacy in 2L+ HNSCC (ORR 37%, mOS 11.5 months)[9] supporting the rationale for the present clinical trial

2L+, second or subsequent line of therapy; ADCC, antibody-dependent cellular cytotoxicity; EGF, epidermal growth factor; EGFR, EGF receptor; LGR5, leucine-rich repeat-containing G-protein coupled receptor 5; mOS, median overall survival; ORR, overall response rate; PD-1, programmed cell death protein 1; WNT, wingless/integrated.

1. *Herpers B, et al. Nat Cancer. 2022;3(4):418-436;* ***2.*** *Schinke H, et al. Mol Cancer. 2022;21(1):178;* ***3.*** *Parsons MJ, et al. Cancer Discov. 2021;11(10):2413-2429;* ***4.*** *Xu L, et al. Stem Cell Res Ther. 2019;10:219;* ***5.*** *Katoh M. Int J Oncol. 2017;51(5):1357-1369;* ***6.*** *Sacco AG, et al. Lancet Oncol. 2021;22(6):883-892;* ***7.*** *Chung CH, et al. Cancers (Basel). 2021;13(5):1180;* ***8.*** *Gulati S, et al. Clin Cancer Res. 2023;29(10):1906-1915;* ***9.*** *Cohen E, et al. AACR 2023 (oral).*

PRESENTED BY: Dr. Jérôme Fayette

Merus

Phase 2 study (NCT03526835)

1L petosemtamab in combination with pembrolizumab

Key HNSCC inclusion criteria

- 1L r/m PD-L1+ HNSCC*
- ECOG PS 0-1
- Measurable disease

Treatment plan

- Petosemtamab 1500 mg IV, Q2W (28-day cycle) with pembrolizumab 400 mg IV Q6W
- Until PD or toxicity
- Tumor assessment Q8W

Follow-up

- Survival follow-up for up to 3 years

Objectives

- **Primary objectives:** ORR using RECIST 1.1 per investigator, and safety and tolerability
- **Secondary objectives:** DOR and PFS (per investigator and central review), ORR (per central review), OS, PK, immunogenicity, and biomarkers
- **Efficacy evaluable population:** Patients treated as of the abstract cutoff date (who had the opportunity for ≥4 months follow-up), with ≥2 treatment cycles and ≥1 post-baseline tumor assessment, or who discontinued early due to disease progression or death

Enrollment and analysis

Data cutoff date
06-Mar-2024

Enrollment
45 patients

Efficacy evaluable population
24 patients

- 19 patients enrolled after abstract cutoff date
- 2 patients were excluded per protocol:
  - 1 patient withdrew consent prior to first tumor assessment
  - 1 patient discontinued due to toxicity with <2 cycles of treatment

**PD-L1+ is defined as a patient with a PD-L1 CPS ≥1.*
CPS, combined positive score; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; OS, overall survival; PD, progressive disease; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PK, pharmacokinetics; Q2W, every 2 weeks; Q6W, every 6 weeks; Q8W, every 8 weeks; RECIST, response evaluation criteria in solid tumors.

PRESENTED BY: Dr. Jérôme Fayette

Merus

Patient demographics and disposition

Safety set (N=45)

Demographics and disease features	
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*	2 (4)
PD-L1 status (local), n (%)	
PD-L1 positive	45 (100)
CPS 1-19 / ≥20	19 (42) / 25 (56)
p16 (HPV) status (local): Oropharynx (n=14), n (%)	
p16 positive	8 (57)
p16 negative	5 (36)
p16 unknown	1 (7)
IHC H-score (EGFR), n (%)†	
0 - <100	6 (13)
100 - <200	7 (16)
200 - 300	28 (62)

Patient disposition	
Petosemtamab treatment, n (%)	
Treatment ongoing	32 (71)
Treatment discontinuation	13 (29)
Disease progression	9 (20)
Withdrawal of consent	2 (4)
Death (unrelated to treatment)	1 (2)
Related AE‡	1 (2)
Petosemtamab exposure duration (months), median (range)	3.32 (0.5-10.3)
Duration of follow-up (months), median (range)	3.58 (0.5-10.3)

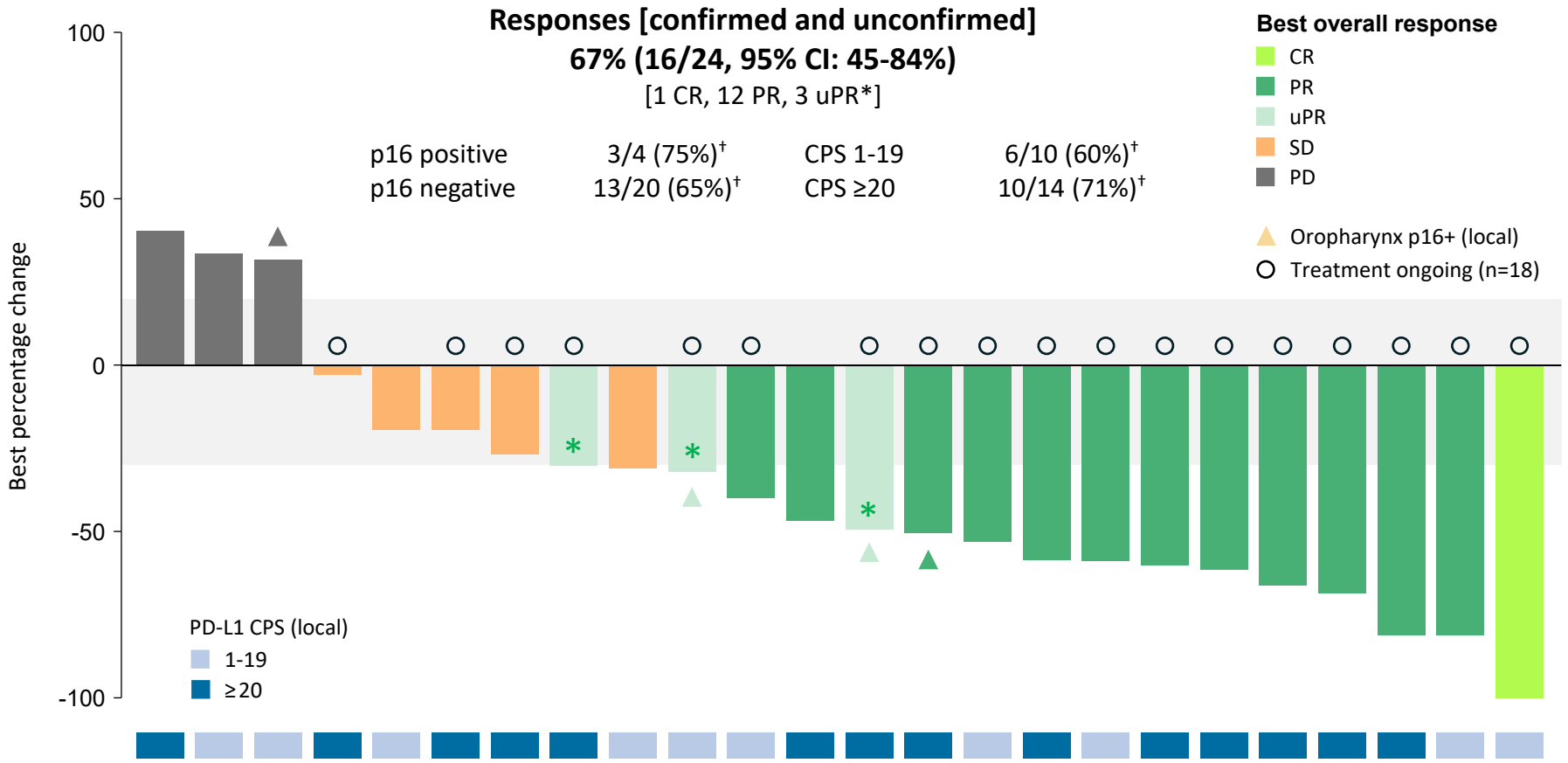
**One patient with HNSCC from unknown primary tumor location, one patient with HNSCC from sinonasal primary tumor;*
†4 patients had no IHC H-score (EGFR) available; ‡Patient discontinued due to adverse events (asthenia, diarrhea, creatinine increase; all Grade <3).
AE, adverse event; HPV, human papillomavirus; IHC, immunohistochemistry.

PRESENTED BY: Dr. Jérôme Fayette

Merus

Overall response rate (RECIST 1.1, per investigator)

Best percent change in sum of target lesions from baseline (n=24)



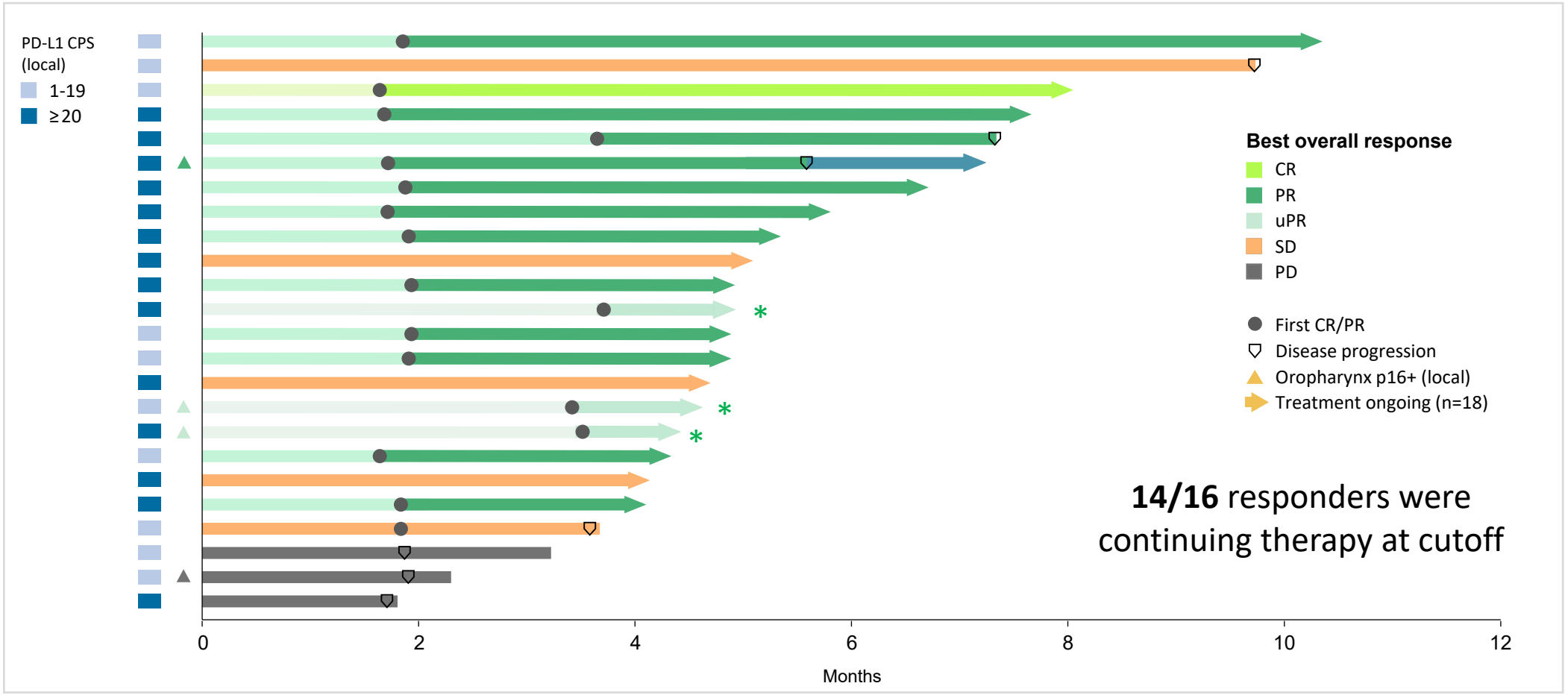
**All 3 uPR were confirmed as PR after data cutoff date; †Response values for p16 and PD-L1 CPS subgroups include CR, PR, and uPR.*
CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; uPR, unconfirmed partial response.

PRESENTED BY: Dr. Jérôme Fayette

Merus

Time to response and duration of exposure

Response status and exposure duration in individual patients over time (n=24)



*All 3 uPR were confirmed as PR after data cutoff date.

Merus

Safety profile

Overall safety

- Treatment-emergent AEs (TEAEs) were reported in 45 patients; most were Grade 1 or 2
- Treatment-related TEAEs* led to study discontinuation in 2 patients (4%), both were Grade 1-2
- Grade ≥3 TEAEs occurred in 18 (40%) patients, 11 (24%) of which were treatment related
- No significant overlapping toxicities

IRRs (composite term)†

- IRR occurred in 38% of patients, with 7% Grade 3; no Grade 4 or 5
- Mainly occurred during first infusion and were resolved
- Rechallenge after an IRR was successful in all patients and no patients discontinued due to a Grade 3-5 IRR
- IRRs were managed with premedication and prolonged infusion

Preferred term	Irrespective of causality (>15% of patients) (N=45)	
	All Grades, n (%)	Grades 3-5, n (%)
At least 1 TEAE‡§	**45 (100)**	**18 (40)**
Acneiform dermatitis	20 (44)	1 (2)
Rash	18 (40)	0
Asthenia	16 (36)	3 (7)
Skin fissures	15 (33)	0
Constipation	12 (27)	0
Folliculitis	12 (27)	0
Nausea	12 (27)	1 (2)
Blood magnesium decreased	10 (22)	1 (2)
Diarrhea	10 (22)	1 (2)
Dry skin	10 (22)	0
Pruritus	10 (22)	0
Stomatitis	10 (22)	1 (2)
Cough	7 (16)	0
Fatigue	7 (16)	1 (2)
Infusion-related reaction	7 (16)	1 (2)
Paronychia	7 (16)	0
Tumor pain	7 (16)	1 (2)

*One patient had asthenia (Grade 2), diarrhea (Grade 1), and creatinine increase (Grade 1); one patient had dyspnea, tachycardia, nausea, and IRR (all Grade 2); †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; ‡Most common (>15% of patients) TEAEs, irrespective of causality, are listed; §TEAEs are defined as AEs with onset date on or after date of first administration of study drug and ≤30 days post-treatment. IRR, infusion-related reaction.

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

- Clinically meaningful activity and favorable safety observed:
  - 67% response rate overall (13/24 confirmed and 3/24 unconfirmed* responses)
  - Responses observed across HPV-related and -unrelated cancer; and across PD-L1 CPS subgroups
  - Favorable safety profile including manageable IRRs (38% all Grades, 7% Grade 3; no Grade 4 or 5)
- Potential first- and best-in-class treatment for 1L HNSCC
- Petosemtamab clinical development in HNSCC and CRC is ongoing:
  - 1L HNSCC phase 3 registration trial with pembrolizumab planned to start by year end 2024
  - 2L/3L HNSCC phase 3 registration trial as monotherapy planned to start mid-2024
  - 2L CRC phase 1/2 trial with chemotherapy planned

**All 3 uPR were confirmed as PR after data cutoff date.*
2L, second-line; 3L, third-line; CRC, colorectal cancer.

Acknowledgments

Thanks to:

- Patients and their families
- Investigators and their teams
- Merus colleagues:
  - Yu-Ming Shen
  - Renée de Leeuw
  - Marina Magin Ferrer
- CROs and vendors
- Sophie Houten at LiNK Health Group

CRO, contract research organization.

Merus