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Petosemtamab (MCLA-158) Monotherapy in Previously Treated (2L+) Recurrent/Metastatic (r/m) Head and Neck Squamous Cell Carcinoma (HNSCC): Phase 2 Trial

Presenter: Christophe Le Tourneau MD, PhD,
Senior Medical Oncologist Institut Curie, Professor of Medicine Paris-Saclay University

Christophe Le Tourneau,[1] Jérôme Fayette,[2] Caroline Even,[3] Assuntina G. Sacco,[4] Amaury Daste,[5] Irene Braña,[6] Carla M. L. van Herpen,[7] Thibault Mazard,[8] Stephanie Henry,[9] Michael Saerens,[10] Fabian Zohren,[11] Eduardo Pennella,[11] Yu-Ming Shen,[11] Kees Bol,[11] Lokesh Jain,[11] Marina Magin Ferrer,[11] Renée de Leeuw,[11] Antoine Hollebecque[3]

[1]Department of Drug Development and Innovation (D3i), Institut Curie, INSERM U900 Research Unit, Paris-Saclay University, Paris, France; [2]Department of Medical Oncology, Léon Bérard Center, University of Lyon, Lyon, France; [3]Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France; [4]Department of Internal Medicine, Division of Hematology-Oncology, UC San Diego Health, La Jolla, CA, USA; [5]Oncology, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France; [6]Vall d'Hebron Hospital Campus and Institute of Oncology (VHIO), IOB-Quirón, UVic-UCC, Barcelona, Spain; [7]Department of Medical Oncology, Radboud Institute for Medical Innovation, Radboud University Medical Center, Nijmegen, Netherlands; [8]Institut Régional du Cancer de Montpellier (ICM), Montpellier, France; [9]Department of Oncology-Hematology, Radiotherapy, and Nuclear Medicine, CHU UCL Namur, Namur, Belgium; [10]Department of Medical Oncology, Ghent University Hospital, Ghent, Belgium; [11]Merus N.V., Utrecht, Netherlands.

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DECLARATION OF INTERESTS

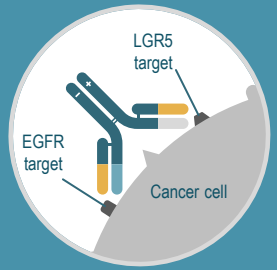
Christoph Le Tourneau

- Advisory boards: ALX Oncology, BMS, Exscientia, GSK, MSD, Merck Serono, Nanobiotix, Roche, Rakuten, Seattle Genetics

Petosemtamab Monotherapy in 2L+ r/m HNSCC

MoA and Phase 2 Trial Design (NCT03526835)

PETOSEMTAMAB



Petosemtamab is a human common light chain IgG1 bispecific antibody with ADCC-enhanced activity, targeting EGFR and LGR5[1]

Key HNSCC inclusion criteria

- 2L+ r/m HNSCC
- ECOG PS 0–1
- Measurable disease

Single-arm cohort

Petosemtamab 1500 mg (n=54)[a]
IV, Q2W; 28-day cycle

Initial cohort presented[2]

Dose-comparison cohort

Petosemtamab 1500 mg (n=28)
IV, Q2W; 28-day cycle

Petosemtamab 1100 mg (n=28)
IV, Q2W; 28-day cycle

Key objectives

- **Efficacy:** ORR (RECIST v1.1 per investigator), DOR, PFS, OS
- **Safety**, tolerability, and PK characterization
- **Efficacy evaluable population:** patients with ≥2 treatment cycles and ≥1 postbaseline tumor assessment or who discontinued early due to PD or death

Enrollment and analysis population

Data cutoff date
July 5, 2024

Enrollment at 1500 mg
N=82

Enrollment at 1100 mg
N=28

1500 mg efficacy evaluable population
- 75 patients
- 7 patients excluded[b]

1100 mg efficacy evaluable population
- 27 patients
- 1 patient excluded[c]

[a]Initial cohort (n=49) presented at AACR 2023[2] plus 5 enrolled after Feb. 1, 2023 data cutoff. [b]6 patients withdrew due to IRR to first infusion and 1 patient with exclusion criterion deviation. [c]1 patient withdrew consent (<2 months treatment). 2L+: second or subsequent line of therapy; ADCC: antibody-dependent cellular cytotoxicity; DOR: duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; EGFR: epidermal growth factor receptor; HNSCC: head and neck squamous cell carcinoma; IgG1: immunoglobulin G1; IRR: infusion-related reaction; IV: intravenous; LGR5: leucine-rich repeat-containing G-protein coupled receptor 5; MoA: mechanism of action; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PK: pharmacokinetic; Q2W: every 2 weeks; RECIST: Response Evaluation Criteria in Solid Tumors; r/m: recurrent/metastatic.

1. Herpers et al. Nat Cancer. 2022;3:418–36; 2. Cohen et al. Cancer Res. 2023;83 (8_suppl): Abst CT012.

Baseline Characteristics, Disposition and Exposure

Baseline characteristics	1500 mg Q2W (N=82)[a]	1100 mg Q2W (N=28)
Age (years), median (range)	60 (31–77)	64 (39–80)
Male / female, n (%)	65 (79) / 17 (21)	22 (79) / 6 (21)
ECOG PS 0 / 1, n (%)	25 (31) / 57 (70)	7 (25) / 21 (75)
Main tumor location, n (%)		
Oropharynx	37 (45)	6 (21)
Oral cavity	25 (31)	11 (39)
Hypopharynx	10 (12)	2 (7)
Larynx	5 (6)	8 (29)
Other[b]	3 (4)	1 (4)
p16 (HPV) status[c] (oropharynx), n (%)		
Positive / negative / unknown	17 (46) / 17 (46) / 3 (8)	1 (17) / 5 (83) / 0 (0)
EGFR (IHC) H-score, median (range)	200 (0–300)	255 (0–300)
Prior systemic therapy, median (range)	2 (1–4)	2 (1–4)
Prior platinum chemotherapy, n (%)	78 (95)	26 (93)
PD-(L)1 inhibitor, n (%)	80 (98)	28 (100)

Disposition and duration of exposure	1500 mg Q2W (N=82)[a]	1100 mg Q2W (N=28)
Petosemtamab treatment ongoing, n (%)	10 (12)	9 (32)
Reason for treatment discontinuation, n (%)		
Disease progression	57 (70)	15 (54)
Symptomatic deterioration	3 (4)	2 (7)
Withdrawal by subject	3 (4)	2 (7)
Study drug-related adverse event	7 (9)	0
Death[d]	1 (1)	0
Other[e]	1 (1)	0
Petosemtamab exposure duration (months), median (range)	4.0 (0.0–37.3)	3.9 (1.3–9.8)

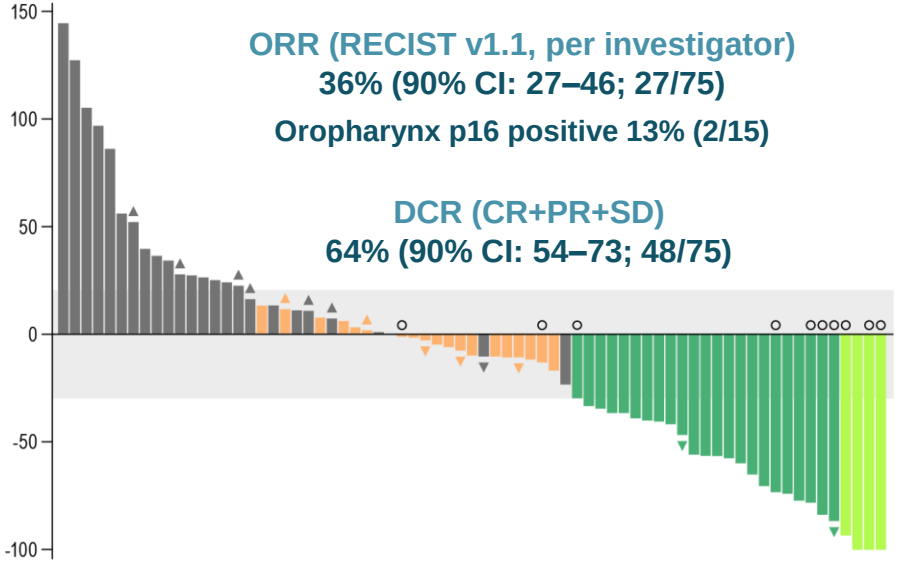
[a]The 1500 mg group includes 54 patients from the single-arm cohort, and 28 patients from the randomized cohort. [b]Other tumor locations included: vocal cord, unknown origin, unknown primary tumor. [c]p16 status is presented only for the 37 and 6 patients with oropharyngeal tumors in the 1500 mg group and 1100 mg group, respectively, and is based on central results. If no central results were available, p16 status was based on local results. [d]Discontinuation due to death was deemed unrelated to treatment. [e]Discontinuation due to investigator's judgement.

HPV: human papillomavirus; IHC H-score: immunohistochemistry histological score; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1.

Petosemtamab Antitumor Activity in 2L+ HNSCC

Petosemtamab 1500 mg Q2W, efficacy evaluable population (N=75)

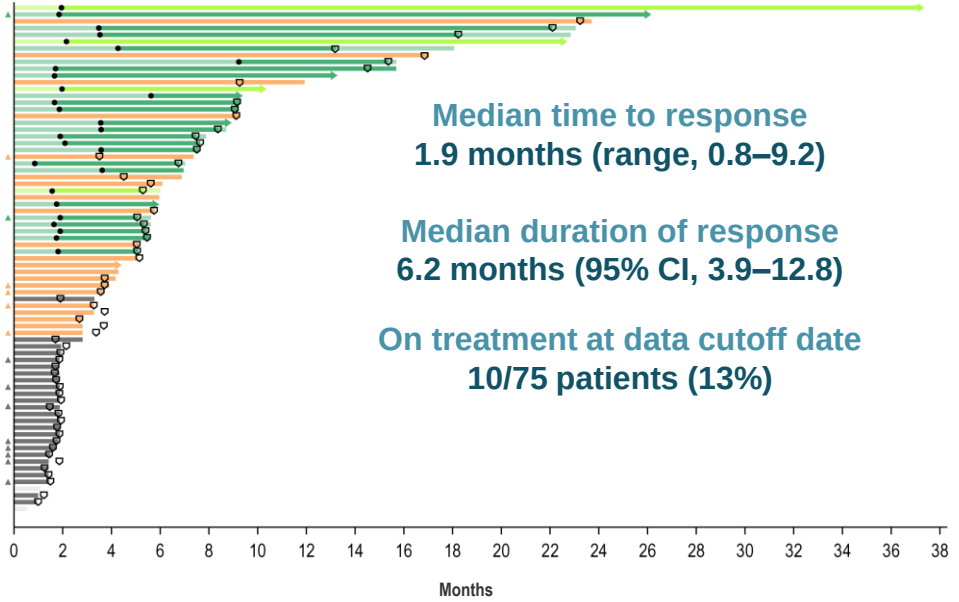
Best percentage change in sum of target lesions from baseline (N=75)[a]



ORR (RECIST v1.1, per investigator)
36% (90% CI: 27–46; 27/75)
Oropharynx p16 positive 13% (2/15)

DCR (CR+PR+SD)
64% (90% CI: 54–73; 48/75)

Time to response and duration of exposure (N=75)



Median time to response
1.9 months (range, 0.8–9.2)

Median duration of response
6.2 months (95% CI, 3.9–12.8)

On treatment at data cutoff date
10/75 patients (13%)

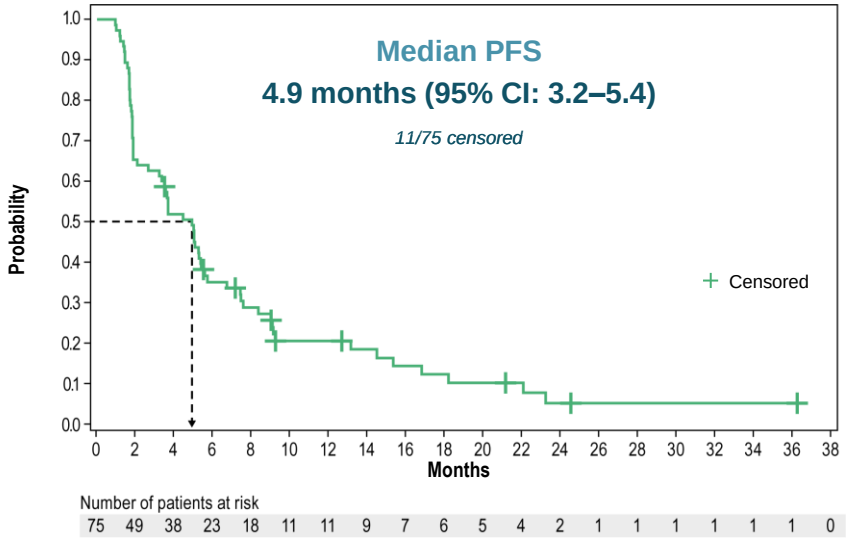
CR | PR | SD | PD | NE | ○ Treatment ongoing | • First CR/PR | ▽ Progressive disease | △ Oropharynx p16+ (local/central)

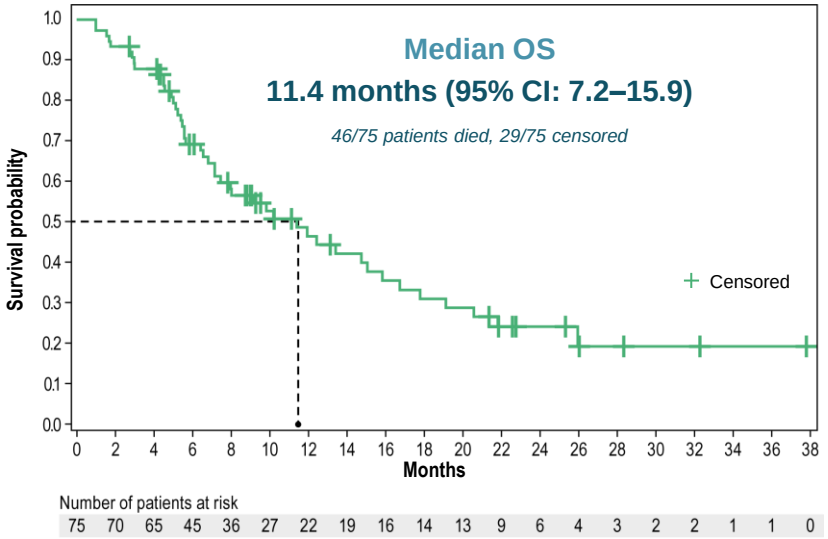
[a]There were 4 patients (including 1 patient who was oropharynx p16+) excluded from the waterfall plot. Two patients were excluded as the target lesions were not assessed, or assessed partially. One patient assessed as PD died prior to the first tumor assessment; the final patient discontinued study treatment due to PD/symptomatic deterioration.

CI: confidence interval; CR: complete response; DCR: disease control rate; NE: not evaluable; PR: partial response; SD: stable disease.

Petosemtamab Antitumor Activity in 2L+ HNSCC

Petosemtamab 1500 mg Q2W, efficacy evaluable population (N=75)





In the single-arm cohort, initially presented at AACR 2023[1], among 48 evaluable patients[a], the median DOR, PFS, and OS were 6.7, 5.2, and 12.5 months, respectively

[a]Efficacy-evaluable population from single-arm cohort, excludes 5 patients who withdrew due to IRR to first infusion and 1 patient with exclusion criterion deviation without clinical evidence of progression.

1. Cohen et al. Cancer Res. 2023;83 (8_suppl): Abst CT012

Petosemtamab Safety and Pharmacokinetics in 2L+ HNSCC

Petosemtamab 1500 mg Q2W, safety-evaluable population (N=82)

AEs irrespective of causality (>20% of patients)

Preferred Term	1500 mg Q2W N=82	
	All grades, n (%)	Grade ≥3, n (%)
At least one TEAE	82 (100)	48 (59)
Dermatitis acneiform	34 (41)	3 (4)
Blood magnesium decreased	32 (39)	7 (9)
Rash	24 (29)	0
Fatigue	22 (27)	1 (1)
Nausea	21 (26)	0
Hypotension	20 (24)	4 (5)
Pruritus	20 (24)	1 (1)

Infusion-related reactions (>10% of patients)

Preferred Term	Prior administration regimen N=49		Updated administration regimen N=33	
	All grades, n (%)	Grade 3–4, n (%)	All grades, n (%)	Grade 3, n (%)
At least one TEAE of IRR	33 (67)	12 (24)	15 (45)	3 (9)
Infusion-related reaction	12 (24)	7 (14)	7 (21)	2 (6)
Hypotension	10 (20)	4 (8)	4 (12)	0
Flushing	8 (16)	2 (4)	2 (6)	1 (3)
Nausea	6 (12)	0	2 (6)	0
Dyspnea	5 (10)	1 (2)	0	0
Erythema	5 (10)	0	0	0

Safety

- Petosemtamab 1500 mg Q2W in HNSCC was well tolerated with a manageable safety profile
- IRRs were generally only seen on day 1 of cycle 1; the IRR mitigation strategy reduced the severity and frequency of IRRs

Pharmacokinetics

- Geometric mean steady state C_{trough} was 68% higher with 1500 mg Q2W vs. 1100 mg Q2W
  - No positive exposure–safety (Grade ≥3 TEAE) relationship was observed
- 1500 mg Q2W was projected to achieve superior target engagement (*i.e.* ≥98%) for EGFR compared with 1100 mg Q2W dose

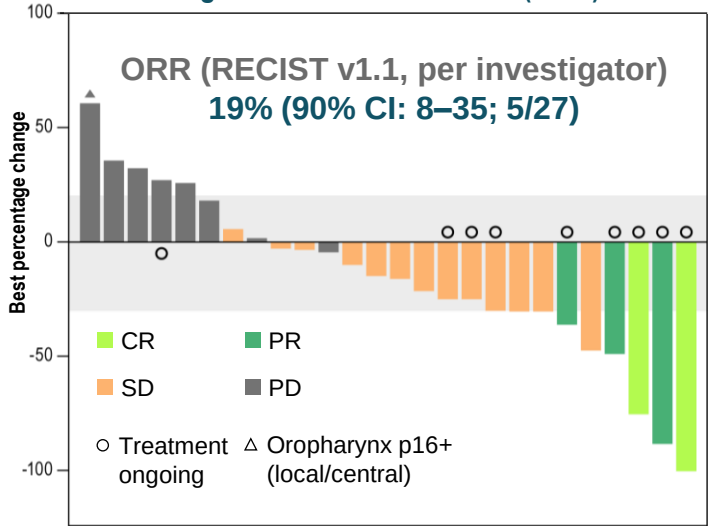
AE: adverse event; C_{trough}: trough concentration; TEAE: treatment-emergent adverse event.

Petosemtamab 1100 mg Q2W in 2L+ HNSCC

AEs irrespective of causality (>20% of patients)

Preferred Term	1100 mg Q2W N=28	
	All grades, n (%)	Grade 3–4, n (%)
At least one TEAE	28 (100)	14 (50)
Dermatitis acneiform	12 (43)	1 (4)
Rash	9 (32)	1 (4)
Asthenia	8 (29)	0
Blood magnesium decreased	8 (29)	1 (4)
Dry skin	7 (25)	0
Constipation	6 (21)	0
Skin fissures	6 (21)	0
Fatigue	5 (18)	0
Infusion-related reaction (Grouped term)	11 (39)	0

Best percent change in sum of target lesions from baseline (n=27)[a]



Petosemtamab 1500 mg Q2W confirmed as dose for phase 3

[a]Efficacy-evaluable population, one patient excluded from the waterfall plot as there was no postbaseline tumor assessment due to progressive disease.

Petosemtamab Monotherapy in 2L+ HNSCC: Conclusions

- Clinically meaningful efficacy and durability observed, with a well tolerated and manageable safety profile
  - Clinical benefit observed across HPV-related and -unrelated cancer
- Potential new first and best in class treatment for patients with 2L+ HNSCC
- Petosemtamab 1500 mg Q2W confirmed as dose for phase 3
- Clinical development continues:
  - 1L HNSCC phase 3 registration trial with pembrolizumab (NCT06525220)
  - 2L/3L HNSCC phase 3 registration trial as monotherapy (NCT06496178)
  - 2L CRC phase 1/2 trial with chemotherapy (NCT03526835)

1L: first line.

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European Society for Medical Oncology (ESMO)
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org