Clinical activity of MCLA-158 (petosemtamab), an IgG1 bispecific antibody targeting EGFR and LGR5, in advanced head and neck squamous cell carcinoma (HNSCC)

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Disclosure Information

Ezra EW Cohen

I have the following relevant financial relationships to disclose

Consultant for: Adagene, Astellas, Cidara, Eisai, Genmab, Gilboa, iTeos, Eli Liily, MSD, Merck, Nectin Tx, Novartis, Nykode, Pangea Therapeutics, PCI Biotechn Replimune, Roche, Soteria, Tempus, Viracta

Stock/equity in: Kinnate Biopharma, Primmune Therapeutics

My additional financial relationship disclosures are:

Board of Directors: Akamis Bio

Scientific Advisory Board: Kinnate Biopharma, Pangea Therapeutics

DSMB: Kura

Background

Petosemtamab is a Bispecific Antibody Targeting EGFR and LGR5

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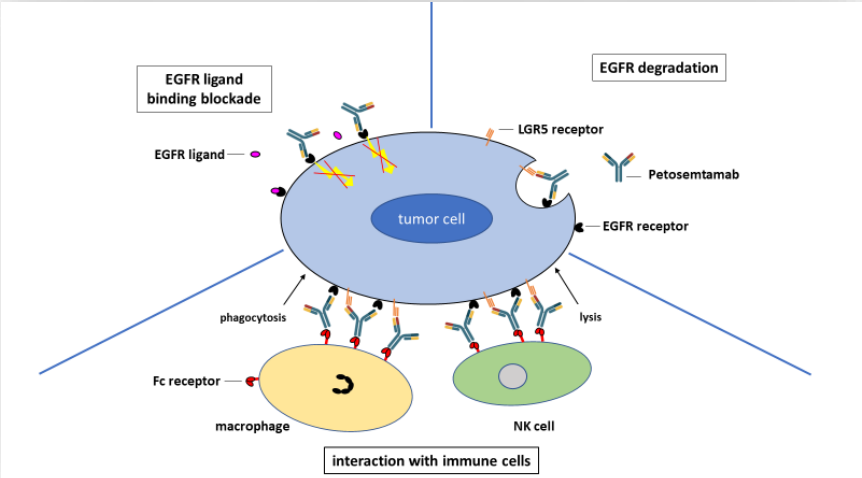
Mechanism of Action[1]

- Inhibition of EGFR-dependent signaling
- EGFR degradation (via LGR5/E3 ligase)
- Facilitates interaction with immune cells (ADCC and ADCP enhanced antibody)



- EGFR and WNT are oncogenic and mitogenic drivers in several cancer types, including HNSCC
- LGR5 is expressed mainly on cancer stem cells (CSCs). It is upregulated in many tumors (CRC, HNSCC, GC, NSCLC, HCC, OC)[2,3]
- Petosemtamab has effective antitumor activity against tumor initiating cells and CSCs (1-5% of all cancer cells) that express LGR5
- Petosemtamab demonstrated significant growth inhibition in multiple head and neck cancer PDX models with high EGFR expression[1]

1. *Herpers et al. Nature Cancer, 3:418–36, 2022;* **2.** *Xu et al. Stem Cell Res Ther, 10:219, 2019;*
3. *Katoh. Int J Onc, 51:1357–69, 2017*

Background

Head and Neck Squamous Cell Carcinoma

- High prevalence and mortality with dismal prognosis
  - 6th most common cancer worldwide in 2020
  - ~930,000 new cases and 467,000 deaths[1]
- Unmet medical need in the platinum and anti-PD-(L)1 refractory setting
  - Limited treatment options after platinum-based chemotherapy and pembrolizumab
  - 5-13% ORR and median OS ~6 months in 2nd line with cetuximab, docetaxel or methotrexate[2-4]
- LGR5 expression in 52-89% of HNSCC[5,6]
- EGFR overexpression in up to 90% of HNSCC tumors[7,8]

1. *Sung et al. CA Cancer J Clin, 71:209-49, 2021;* ***2.*** *Cohen et al. Lancet, 393:156-67, 2019;* ***3.*** *Ferris et al. N Engl J Med, 375:1856-67, 2016;*
4. *Vermorken et al. J Clin Oncol, 25:2171-7, 2007;* ***5.*** *Wu et al. Int J Clin Exp Pathol, 10:11267-75, 2017;* ***6.*** *Dally et al. Oral Surg Oral Med Oral Pathol Oral Radiol, 119:436-40, 2015;*
7. *Byeon et al. Exp Mol Med, 16;51:1-14, 2019;* ***8.*** *Xu et al. Cancer Metastasis Rev, 36:463-73, 2017*

Petosemtamab Dose Selection

Modeling and Simulation of PK and Target Occupancy

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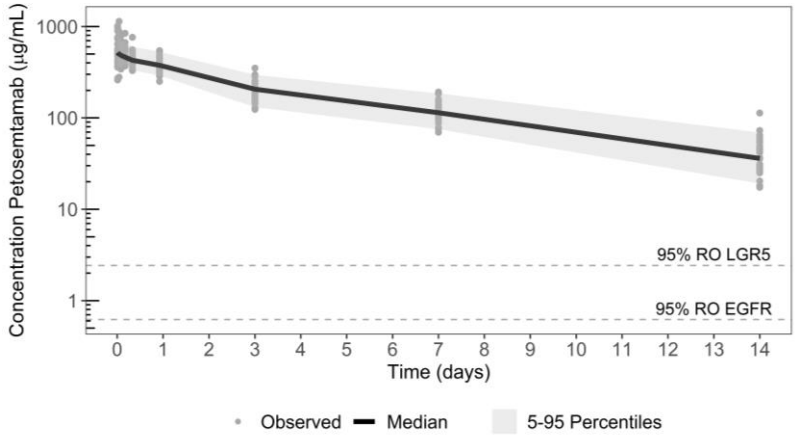
PK and Immunogenicity

- PK data from a broad dose range (90 - 1500 mg Q2W)
- PK profile consistent with fully human IgG1 mAb
  - Median half-life at steady-state is ~8 days
  - Estimated effect of body weight on CL supports fixed-dosing approach
- At the dose of 1500 mg Q2W, >95% receptor occupancy (RO)[1] was predicted for EGFR and LGR5 targets in tumor tissue[2] for the entire dosing interval
- Treatment-emergent positive antidrug antibodies in <5% patients (N=62)

Petosemtamab Serum Concentration vs Time Profile
in HNSCC Patients Treated at 1500 mg Q2W (N=38)



Horizontal lines indicate serum concentrations for 95% RO of EGFR and LGR5 receptors based on in vitro KD values for binding affinities

[1] *RO is based on in vitro KD values for binding affinities. Herpers et al. Nature Cancer, 3:418–36, 2022*
[2] *Using a tumor distribution model based on Baxter et al. Cancer Res, 55:4611-22, 1995*

Phase 1/2 Study
Cohort Expansion in HNSCC

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Dose escalation is completed: No DLTs were reported; the dose of 1500 mg Q2W was selected based on safety, PK, and predicted receptor occupancy.[1]

Key HNSCC Inclusion Criteria

- Progression on or intolerant to anti-PD-(L)1 and platinum-based therapy in incurable recurrent or metastatic disease
- ECOG PS 0-1
- Measurable disease

Treatment Plan

- Petosemtamab 1500 mg IV, Q2W, 28-day cycle
- Until PD or toxicity
- Tumor assessment Q8W

Follow-Up

Survival follow-up for up to 18 months

Objectives and Analysis Population

- **Primary objective:** ORR using RECIST 1.1 per investigator
- **Secondary objectives:** ORR (per central review), DOR and PFS (per investigator and central review), OS, safety, PK, immunogenicity, and biomarkers
- **Efficacy evaluable population:** patients with ≥2 treatment cycles (≥8 weeks) with ≥1 post-baseline tumor assessment or discontinued early due to disease progression or death

Enrollment and Interim Analysis

Data cutoff date

01-Feb-2023

Enrollment

49 patients

Efficacy evaluable population

43 patients

6 patients excluded per protocol:

- 5 patients withdrew due to IRR on Day 1
- 1 patient with excl. criterion deviation

1. Argiles et al. J Clin Oncol. 39(3_suppl):Abst 62, 2021

HNSCC Patient Population

Demographics and Disease Features

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Demographics and Disease Features	N=49
Age (years), median (range)	63 (31 - 77)
Male / female	38 (78%) / 11 (22%)
ECOG PS 0 / 1	14 (29%) / 35 (71%)
Squamous cell carcinoma histology	48 (98%)[1]
Tumor location	
▪ Oropharynx	17 (35%)
▪ Oral cavity	15 (31%)
▪ Larynx	8 (16%)
▪ Hypopharynx	4 (8%)
▪ Other	5 (10%)[2]
Measurable disease	48 (98%)

1. *One patient had p16-negative epidermoid cancer with unknown origin*
2. *Other: nasal cavity and paranasal sinuses, nasopharynx, supraglottis, vocal cord, unknown origin*

Tumor Biomarkers	N=49
EGFR	
▪ H-score[3], median (range) (n=35)	170 (0 - 300)
PD-L1	
▪ Positive (CPS[3] ≥1) / negative	20 (41%) / 9 (18%)
▪ Unknown[4]	20 (41%)
p16 status: oropharynx	**N=17**
▪ p16 positive / negative[3]	6 (35%) / 3 (18%)
▪ Unknown[4]	8 (47%)

3. *By immunohistochemistry*
4. *Unknown: not yet available or analyzed, not collected, or inadequate quality*

HNSCC Patient Population

Prior Therapy, Disposition, and Exposure

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Prior Cancer Therapy	N=49
No. lines prior systemic therapy, median (range)	2 (1 - 4)
▪ PD-(L)1 inhibitor	47 (96%)
▪ Chemotherapy	46 (94%)
▪ Platinum-based therapy	45 (92%)
▪ Cetuximab	2 (4%)
Last therapy prior to petosemtamab	
▪ Immunotherapy	27 (55%)
▪ Immunotherapy + chemotherapy	14 (29%)
▪ Chemotherapy	7 (14%)
▪ Investigational	1 (2%)

Patient Disposition	N=49
Petosemtamab treatment	
Treatment continuing	12 (25%)
Treatment discontinuation	37 (75%)
▪ Disease progression	31 (63%)
▪ Related adverse event[1]	4 (8%)
▪ Other[2]	2 (4%)
Petosemtamab exposure duration, months	
▪ Median (range)	4.1 (0.5 - 20.8)

1. *Grade 3-4 IRR*
2. *End of study reason was physician decision following IRR on Day 1 for one patient and one patient died due to underlying disease*

Petosemtamab Antitumor Activity in HNSCC

Overall Response Rate (RECIST 1.1, per Investigator)

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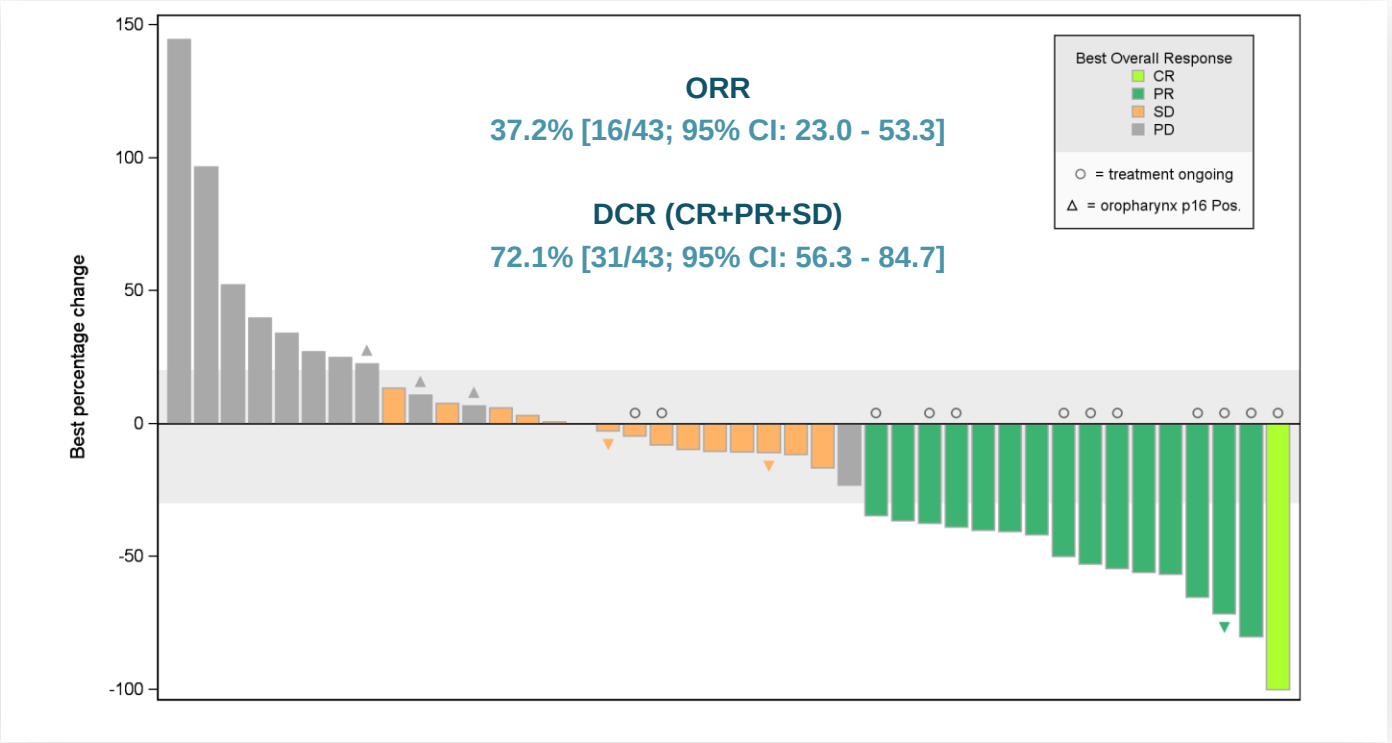
Best Percent Change in Sum of Target Lesions From Baseline (N=43)



One patient with best overall response of not evaluable not included due to no post-baseline tumor assessment
p16 status was available in 9 of the 15 oropharynx patients (6 positive and 3 negative) in the efficacy evaluable population

Petosemtamab Antitumor Activity in HNSCC

Time to Response and Duration of Exposure

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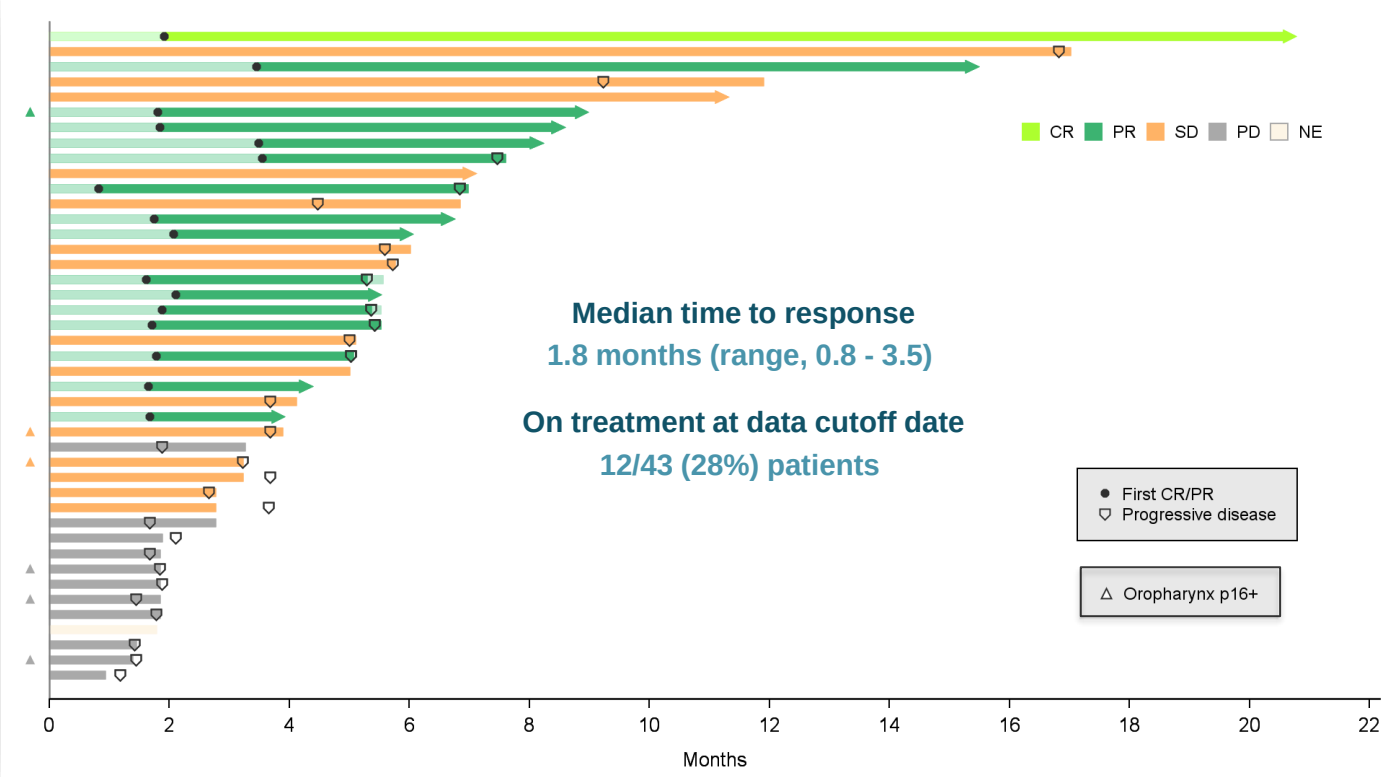

Arrows indicate treatment is ongoing at data cutoff date

p16 status was available in 9 of the 15 oropharynx patients (6 positive and 3 negative) in the efficacy evaluable population

Petosemtamab Antitumor Activity in HNSCC

DOR, PFS (RECIST 1.1, per Investigator), and OS

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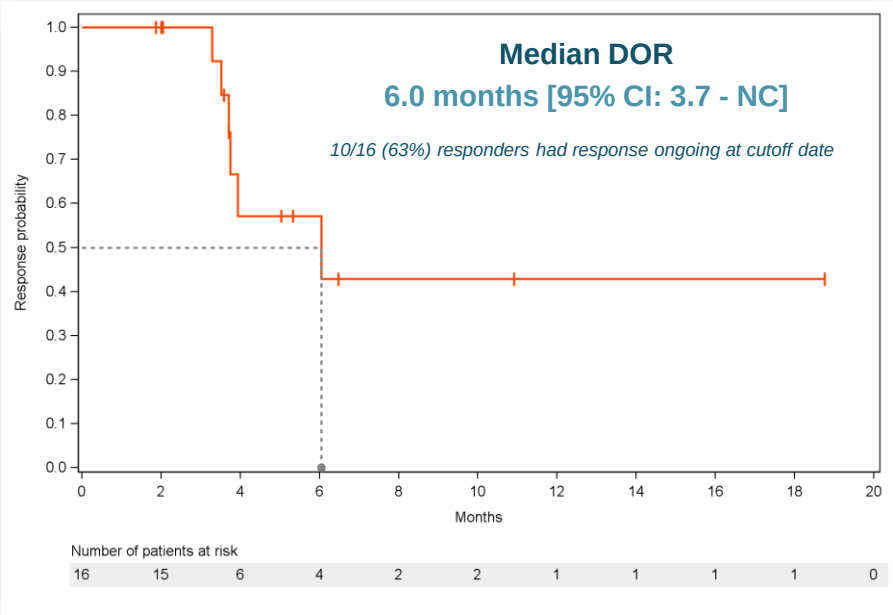

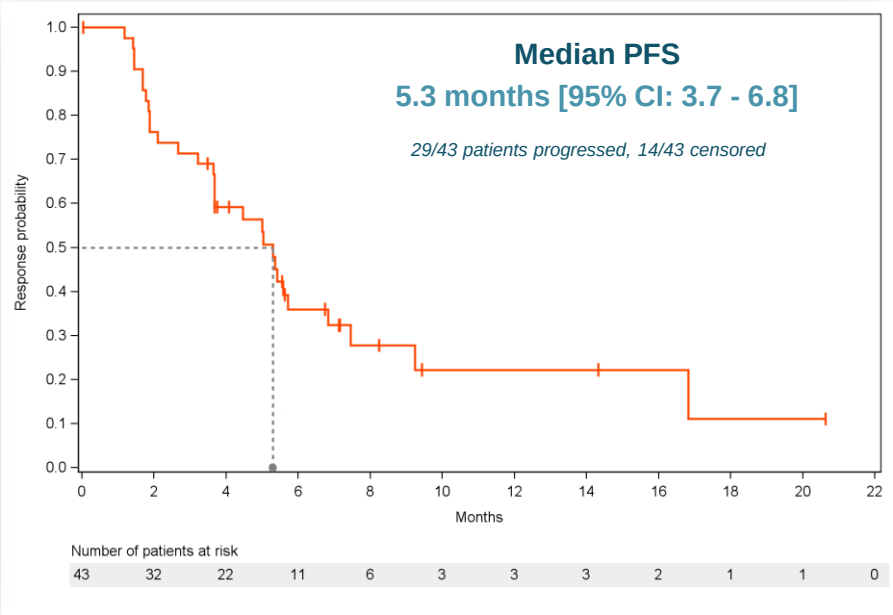

Median OS

11.5 months [95% CI: 7.2 - 20.6]

29/49 patients still alive at data cutoff date

Clinical Response to Petosemtamab

57-Year-Old Male with Oral Cavity SCC Stage IVA

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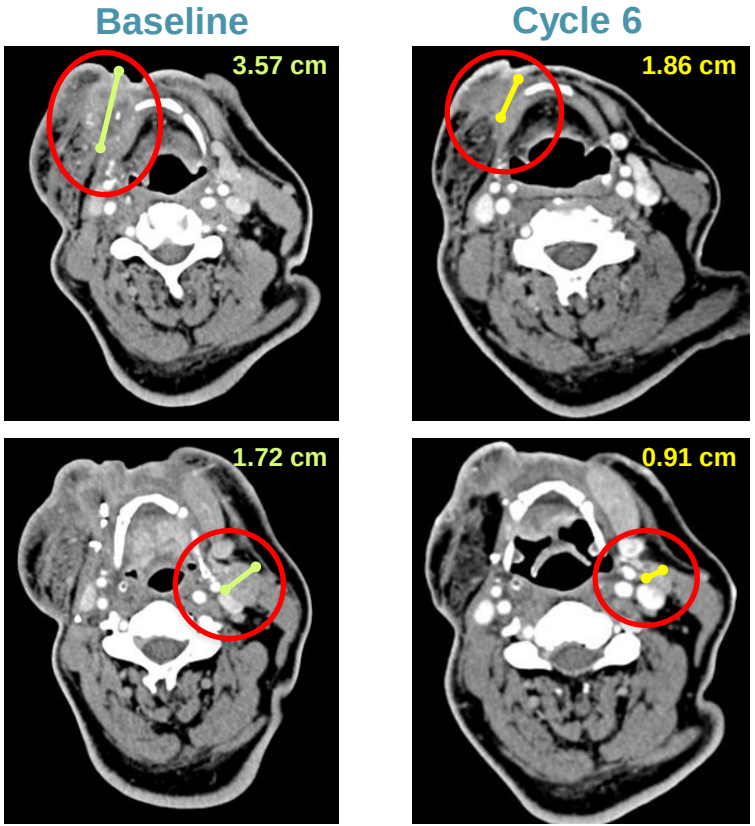
Patient Data	
Baseline status	ECOG PS 1 Incurable local recurrence
Prior treatment	**1.** Surgery **2.** Cisplatin + radiotherapy **3.** Carboplatin + paclitaxel + durvalumab; BOR = PR PD 6 months after 1st dose
Peto monotherapy	6 cycles (ongoing)
RECIST 1.1	Partial response (53% tumor reduction)



Tumor assessment (#3) after data cutoff date

Clinical Response to Petosemtamab

73-Year-Old Female with Oropharynx SCC Stage III

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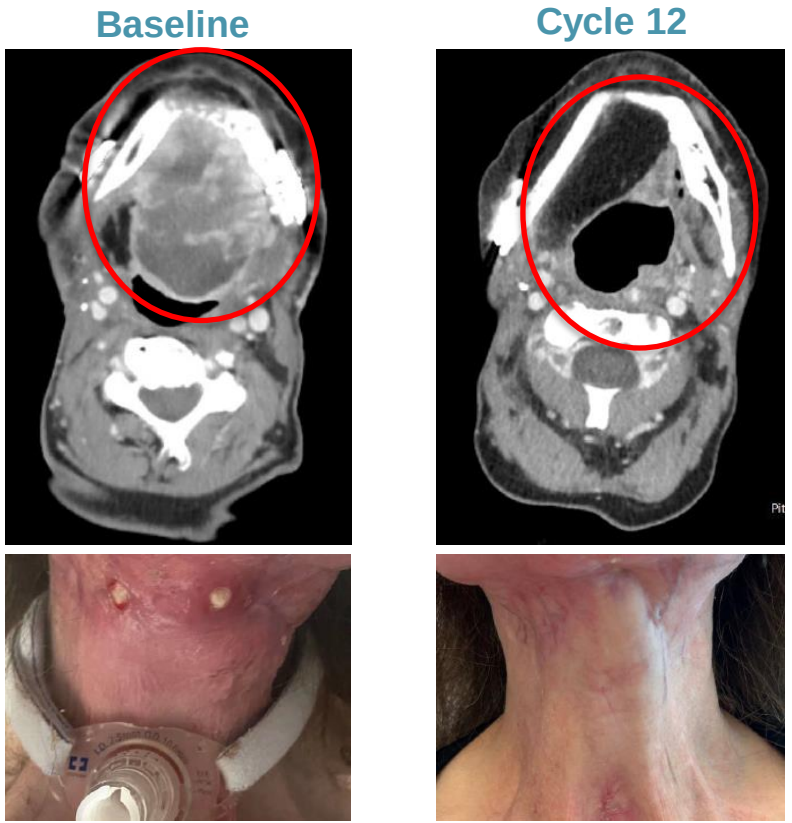
Patient Data	
Baseline status	ECOG PS 1 Incurable locoregional disease p16 positive
Prior treatment	**1.** Radical surgery **2.** Radiotherapy **3.** Pembrolizumab + TLR9 agonist; BOR = PD
Peto monotherapy	10 cycles (ongoing)
RECIST 1.1	Partial response (71% tumor reduction)



Tumor assessment (#6) after data cutoff date

Safety Profile of Petosemtamab 1500 mg Q2W

- Safety profile among 80 patients treated with petosemtamab at 1500 mg Q2W across dose escalation and expansion cohorts of the study
- Well tolerated and manageable safety profile at 1500 mg Q2W
- Most frequent related AEs were signs and symptoms of infusion-related reactions
- Gastrointestinal and skin toxicities were mostly mild to moderate
- No treatment-related Grade 5 AEs

[1] 2 patients had Grade 5 AEs not related to treatment

Preferred Term	Irrespective of Causality (>10% Patients) (N=80)		Suspected Related (N=80)	
	All Grades	Grades 3-5[1]	All Grades	Grades 3-5
N patients with ≥1 AE	**80 (100%)**	**42 (53%)**	**80 (100%)**	**26 (33%)**
Rash	29 (36%)	0	29 (36%)	0
Dyspnea	22 (28%)	3 (4%)	13 (16%)	3 (4%)
Hypotension	21 (26%)	5 (6%)	20 (25%)	5 (6%)
Nausea	21 (26%)	1 (1%)	14 (18%)	0
Dermatitis acneiform	20 (25%)	1 (1%)	20 (25%)	1 (1%)
Infusion-related reaction	17 (21%)	10 (13%)	16 (20%)	10 (13%)
Blood Mg decreased	16 (20%)	4 (5%)	13 (16%)	3 (4%)
Diarrhoea	16 (20%)	0	7 (9%)	0
Erythema	15 (19%)	0	15 (19%)	0
Fatigue	13 (16%)	1 (1%)	5 (6%)	0
Asthenia	12 (15%)	2 (3%)	5 (6%)	1 (1%)
Pruritus	11 (14%)	0	11 (14%)	0
Constipation	11 (14%)	0	2 (3%)	0
Skin fissures	11 (14%)	0	11 (14%)	0
Decreased appetite	9 (11%)	2 (3%)	0	0
Dry skin	9 (11%)	0	8 (10%)	0
Flushing	9 (11%)	2 (3%)	8 (10%)	2 (3%)
Headache	9 (11%)	0	7 (9%)	0
Hypoxia	9 (11%)	2 (3%)	7 (9%)	1 (1%)
Pyrexia	9 (11%)	0	3 (4%)	0
Stomatitis	9 (11%)	0	8 (10%)	0

Infusion-Related Reactions

IRR Composite Term

Composite term for signs and symptoms during 24 h after initiating the petosemtamab infusion, that investigators judge as an infusion-related reaction (IRR); includes the AE PT “IRR” and other PTs

- 74% Grade 1-4 IRR and 21% Grade 3-4 IRR among 80 patients
- Mainly occurred during first infusion
- All IRR PTs resolved
- 6 of 80 patients discontinued on Day 1 due to a Grade 3-4 IRR
- For all patients rechallenged after an IRR, rechallenge was successful
- IRRs were manageable with prophylaxis/ prolonged infusion (necessary on Day 1 only)

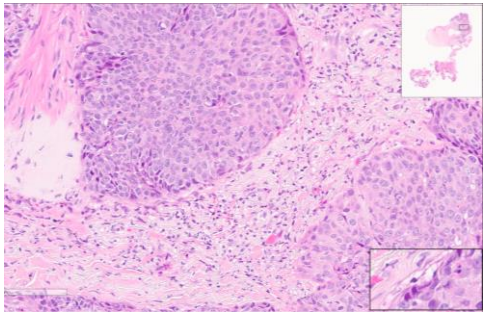
IRR[1] Preferred Term (PT) (>3% Patients)	All Grades (N=80)	Grade 3-4 (N=80)
N patients with ≥1 AE of IRR[1]	**59 (74%)**	**17 (21%)**
Hypotension	19 (24%)	5 (6%)
Infusion-related reaction	17 (21%)	10 (13%)
Dyspnea	12 (15%)	3 (4%)
Erythema	11 (14%)	0
Nausea	10 (13%)	0
Flushing	8 (10%)	2 (3%)
Hypoxia	7 (9%)	1 (1%)
Chills	4 (5%)	0
Hyperhidrosis	4 (5%)	1 (1%)
Pruritus	4 (5%)	0
Tachycardia	4 (5%)	0
Vomiting	4 (5%)	0
Back pain	3 (4%)	1 (1%)
Bradycardia	3 (4%)	2 (3%)
Headache	3 (4%)	0
Syncope	3 (4%)	1 (1%)
Throat irritation	3 (4%)	0

[1] *Composite term*

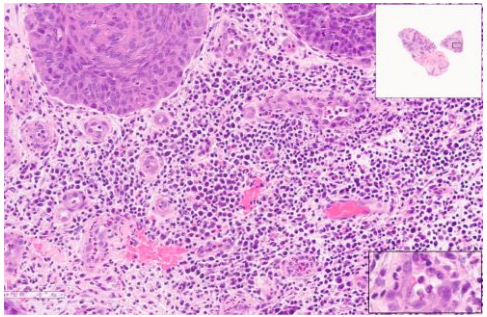
Increased Immune Cell Infiltration in Tumor Samples

Oropharyngeal SCC Patient (p16-Negative) with PR

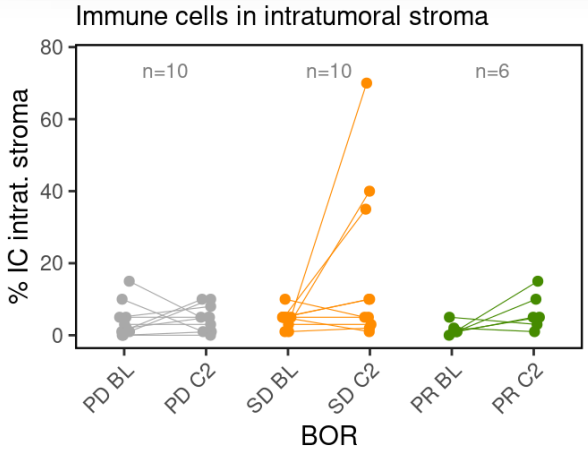
Baseline

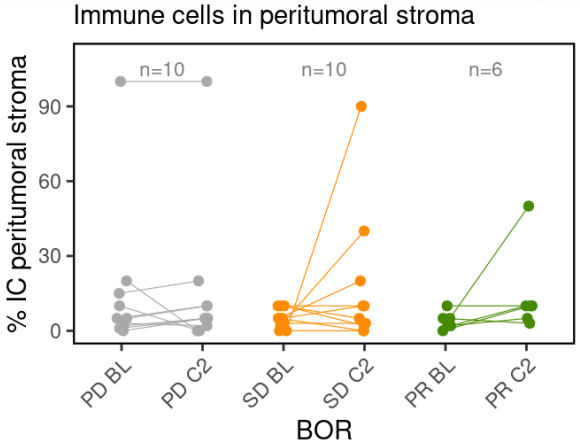


Cycle 2 Day 1



- Biopsy H&E evaluation showed increased mononuclear immune infiltrate in tumor area at Cycle 2 vs baseline in some patients with PR or SD
- Baseline immune cell presence did not correlate with response





Methods as described in Salgado et al. Ann Oncol, 26:259-71, 2015
Intratumoral stroma: complete stromal compartment within the tumor area
Peritumoral stroma: stromal compartment immediately surrounding the tumor
C2 = Cycle 2; BL = baseline; BOR = best overall response; IC = immune cell

Petosemtamab Conclusions

- Clinically meaningful activity observed with durable responses in advanced HNSCC previously treated with immunotherapy and platinum-based chemotherapy
  - **ORR 37%** (95% CI: 23 - 53; N=43)
  - **Median DOR 6.0 months** (95% CI: 3.7 - NC), with 10/16 responders continuing in response
  - **DCR 72%** (95% CI: 56 - 85; N=43)
- Novel dual targeting of EGFR and LGR5; validation of earlier clinical report
- Well tolerated and manageable safety profile
- Responses observed across biomarker expression levels (EGFR H-score 12-280); further biomarker evaluation is ongoing
- Development of petosemtamab in HNSCC is ongoing (NCT03526835)
  - Monotherapy in previously treated recurrent/metastatic disease
  - Combination with pembrolizumab as initial systemic therapy in recurrent/metastatic disease

Acknowledgments

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