POSTER
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Petosemtamab plus pembrolizumab vs. pembrolizumab for first-line (1L) treatment of recurrent/metastatic (r/m) PD-L1–positive head and neck squamous cell carcinoma (HNSCC): A randomized, open-label, phase 3 trial

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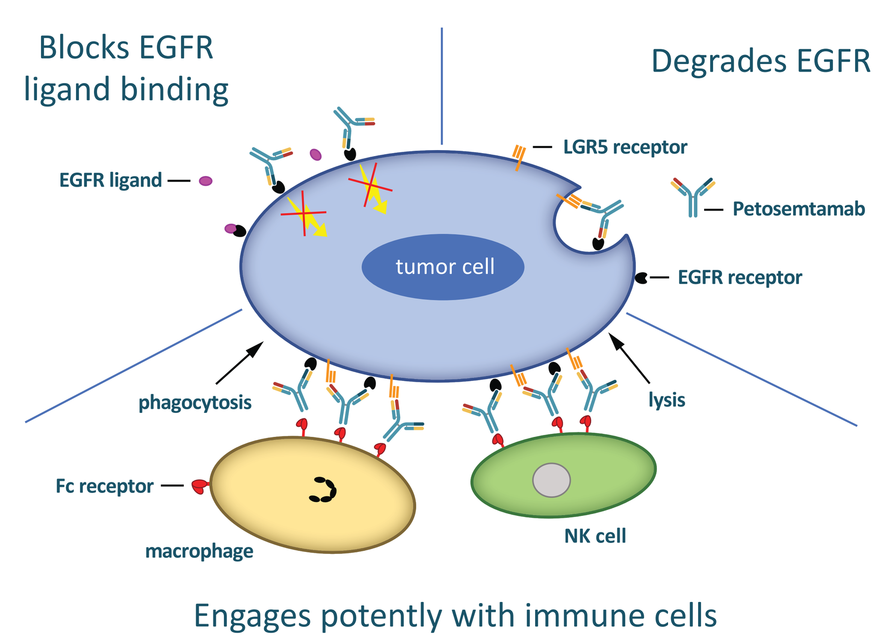
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LiGeR HN1
Bispecific antibody that targets EGFR & LGR5

INTRODUCTION

Petosemtamab is a human, common light chain, IgG1 bispecific antibody with ADCC-enhanced activity, 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[1,6]
- The combination of petosemtamab plus pembrolizumab demonstrated clinically meaningful activity in 1L PD-L1+ HNSCC[7]



Blocks EGFR ligand binding
Degrades EGFR
EGFR ligand
LGR5 receptor
Petosemtamab
tumor cell
EGFR receptor
phagocytosis
lysis
Fc receptor
macrophage
NK cell
Engages potently with immune cells

Figure 1 | Petosemtamab mechanism of action

Mechanism of action[1]

Petosemtamab was designed to:

- Block EGFR ligand binding and inhibit signaling
- Degrade EGFR (via LGR5/E3 ligase)
- Facilitate interaction with immune cells via ADCP and enhanced ADCC

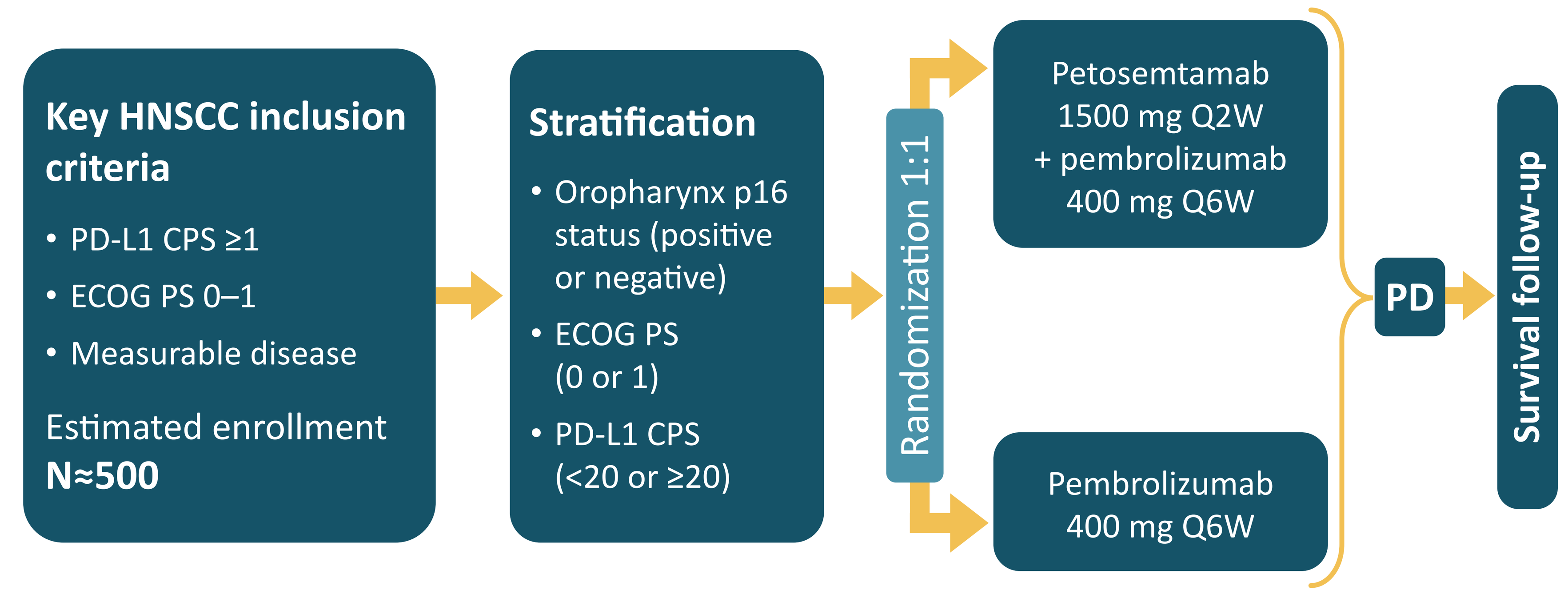
Head and neck squamous cell carcinoma

- High prevalence and mortality with dismal prognosis[8]
 - Sixth most common cancer worldwide in 2020 with ~930,000 new cases and 467,000 deaths[8]
- Unmet need for a more effective and tolerable 1L treatment of PD-L1+ r/m HNSCC
 - Pembrolizumab with or without chemotherapy is the current standard of care for 1L treatment of PD-L1+ r/m HNSCC[9]
 - In a study evaluating pembrolizumab in 1L PD-L1+ HNSCC, ORR was 19% and median OS was 12.3 months[10]
 - This highlights poor survival prognosis and an unmet need for improved therapies for this patient population
- LGR5 expression reported in 52–89% of HNSCC[11,12]
- EGFR overexpression reported in ~90% of HNSCC[13,14]

1L: first-line; ADCC: antibody-dependent cellular cytotoxicity; ADCP: antibody-dependent cellular phagocytosis; EGFR: epidermal growth factor receptor; Fc: fragment crystallizable; HNSCC: head and neck squamous cell carcinoma; IgG1: immunoglobulin G1; LGR5: leucine-rich repeat-containing G-protein coupled receptor 5; NK: natural killer; ORR: overall response rate; OS: overall survival; PD-L1(+): programmed cell death ligand 1 (positive); r/m: recurrent/metastatic; WNT: wingless/integrated.

LiGeR-HN1 PHASE 3 TRIAL DESIGN

LiGeR-HN1 is a randomized, open-label, phase 3 trial to evaluate the efficacy and safety of petosemtamab plus pembrolizumab vs. pembrolizumab monotherapy in patients with 1L r/m PD-L1+ HNSCC



Key HNSCC inclusion criteria
• PD-L1 CPS ≥1
• ECOG PS 0–1
• Measurable disease
Estimated enrollment
N≈500
Stratification
• Oropharynx p16 status (positive or negative)
• ECOG PS (0 or 1)
• PD-L1 CPS (<20 or ≥20)
Randomization 1:1
Petosemtamab 1500 mg Q2W + pembrolizumab 400 mg Q6W
Pembrolizumab 400 mg Q6W
PD
Survival follow-up

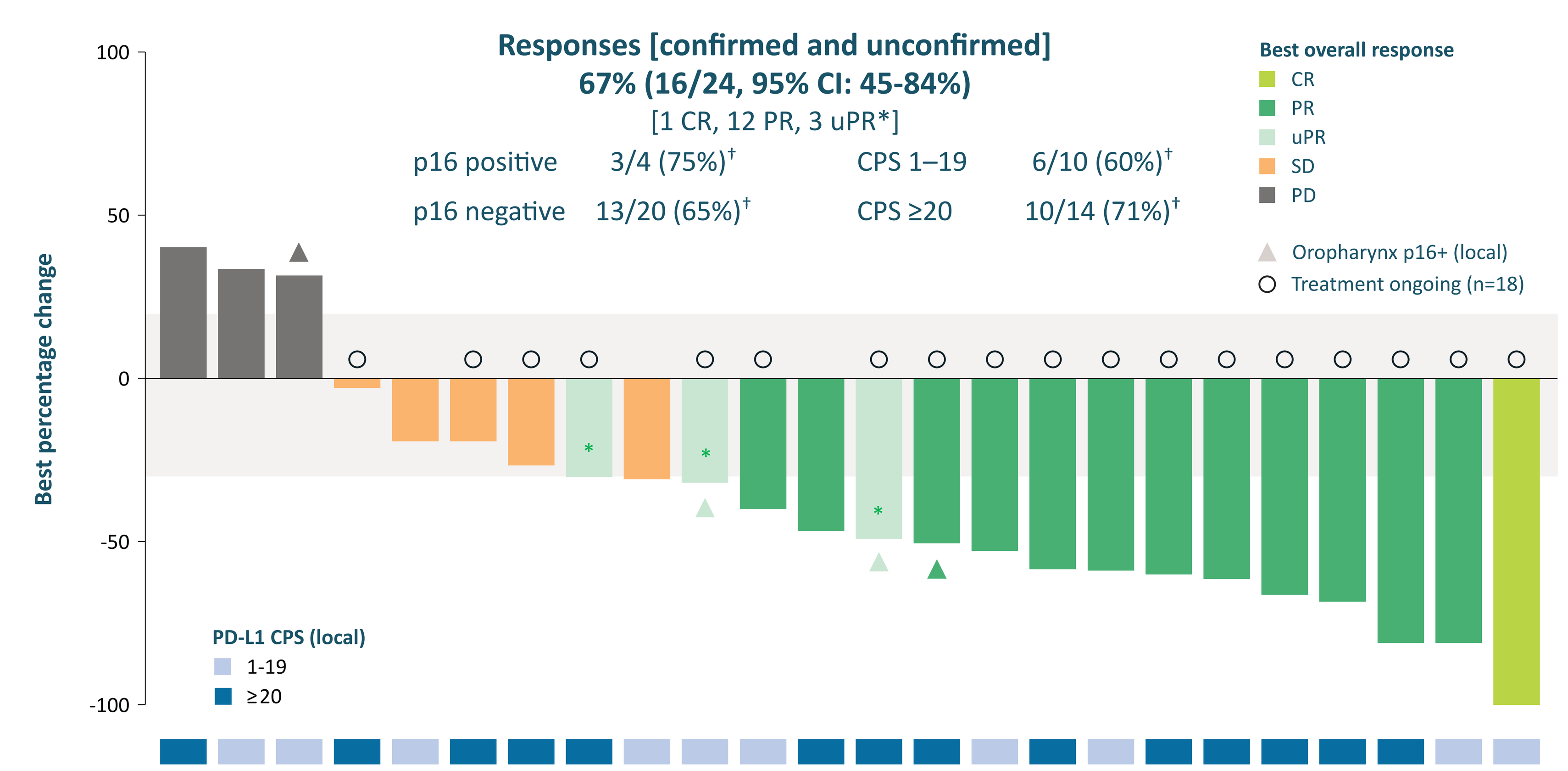
Figure 2 | LiGeR-HN1 trial design

No crossover is permitted. CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group performance status; PD: progressive disease; Q2W: once every 2 weeks; Q6W: once every 6 weeks.

PHASE 2 TRIAL INTERIM DATA: 2024 ASCO®

Overall response rate (RECIST v1.1, per investigator)

Best percent change in sum of target lesions from baseline (N=24)[7]



Responses [confirmed and unconfirmed]
67% (16/24, 95% CI: 45-84%)
[1 CR, 12 PR, 3 uPR*]
p16 positive 3/4 (75%)†
p16 negative 13/20 (65%)†
CPS 1–19 6/10 (60%)†
CPS ≥20 10/14 (71%)†
Best overall response
CR
PR
uPR
SD
PD
Oropharynx p16+ (local)
Treatment ongoing (n=18)
Best percentage change
100
50
0
-50
-100
PD-L1 CPS (local)
1-19
≥20

Figure 3 | Petosemtamab plus pembrolizumab in 1L r/m HNSCC: Phase 2 data (NCT03526835)

Petosemtamab plus pembrolizumab was observed to have a favorable safety profile including manageable infusion-related reactions[7]

Data cutoff date: 06 Mar 2024.
*All three uPRs were confirmed as PR after data cutoff date. †Response values for p16 and PD-L1 CPS subgroups include CR, PR, and uPR.
ASCO: American Society of Clinical Oncology; CI: confidence interval; CR: complete response; PR: partial response;
RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease; uPR: unconfirmed partial response.

LiGeR-HN1 METHODS

Inclusion criteria

- Age ≥18 years at signing of ICF
- Histologically confirmed HNSCC with evidence of metastatic or locally recurrent disease not amenable to local therapy with curative intent
- HNSCC primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx; both HPV+ and HPV– are allowed
- Eligible to receive pembrolizumab as 1L monotherapy with tumors expressing PD-L1, CPS ≥1
- No previous systemic therapy administered in the incurable r/m setting
- Measurable disease as defined by RECIST v1.1 by radiologic methods
- ECOG PS of 0–1

Exclusion criteria

- CNS metastases that are untreated or already treated but symptomatic, or require radiation, surgery, or continued steroid therapy to control symptoms within 21 days of study entry
- Known leptomeningeal involvement
- Any systemic anticancer therapy within 4 weeks of the first dose of study treatment
- History of prior malignancies*
- Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any form of immunosuppressive therapy within 7 days prior to the first dose
- Primary tumor site of nasopharynx, or sinonasal carcinoma (any histology)

Primary outcome measures

- Objective response rate per RECIST v1.1 as assessed by BICR
- Overall survival

Secondary outcome measures

- Progression-free survival per RECIST v1.1 as assessed by BICR
- Duration of response per RECIST v1.1 as assessed by BICR
- Safety of petosemtamab plus pembrolizumab (incidence and severity of AEs and SAEs)

*With the exception of excised local cancer, or treated cancer deemed at low risk for recurrence with no evidence of disease for ≥3 years.
AE: adverse event; BICR: blinded independent central review; CNS: central nervous system; HPV: human papillomavirus; ICF: informed consent form; SAE: serious AE.

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Presenting Author Disclosures

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