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LiGeR-HN phase III trials of petosemtamab + pembrolizumab and petosemtamab monotherapy in recurrent or metastatic HNSCC

Jean-Pascal Machiels [a], Jérôme Fayette [b], Robert Haddad [c], Douglas Adkins [d], Maura Gillison [e], Kevin J Harrington [f], Sung-Bae Kim [g], Christophe Le Tourneau [h], Amanda Psyrri [i], Ari Rosenberg [j], Lillian L Siu [k], Makoto Tahara [l], William N. William Jr [m], Jim Ford[n], Shekeab Jauhari[o], Rebecca Pyle[n], Yu-Ming Shen[p], David Yao[o], Fabian Zohren[o] and Everett Vokes [q]

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ABSTRACT

Patients with recurrent/metastatic (r/m) head and neck squamous cell carcinoma (HNSCC) have limited treatment options and a dismal prognosis, especially when their cancer is resistant to standard treatments like anti-programmed cell death protein 1 and platinum-based therapies. Petosemtamab – a human, common light chain, bispecific antibody with enhanced antibody-dependent cellular cytotoxicity targeting epidermal growth factor receptor (EGFR) and leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5) – demonstrated antitumor activity in r/m HNSCC. In many tumor types, including HNSCC, EGFR is an oncogenic driver, while LGR5 is upregulated. LGR5 can potentiate the wingless-type integration site (WNT)/β-catenin signaling pathway in response to ligand binding, stimulating cancer stem cell proliferation and self-renewal. This article describes two registration-intent, open-label, randomized phase III trials evaluating efficacy and safety of petosemtamab. LiGeR-HN1 (NCT06525220) evaluates petosemtamab plus pembrolizumab versus pembrolizumab as first-line therapy for patients with programmed cell death ligand 1–positive r/m HNSCC. LiGeR-HN2 (NCT06496178) evaluates petosemtamab versus investigator's choice of monotherapy (cetuximab, methotrexate, or docetaxel) in patients with previously treated r/m HNSCC. Primary endpoints in both trials are objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1 by blinded independent central review, and overall survival. Both trials are recruiting at the time of publication.

Clinical Trial Registration: NCT06525220 and NCT06496178 (ClinicalTrials.gov).

PLAIN LANGUAGE SUMMARY

Head and neck squamous cell carcinoma (HNSCC) is a common cancer located in the head or neck, particularly in the mouth, throat, and nasal cavity. People living with HNSCC whose cancer has come back after treatment (recurrent) or spread to other parts of the body (metastatic) have limited treatment options, especially when their cancer does not respond to available therapies. Petosemtamab is a drug that targets receptors called epidermal growth factor receptor (EGFR) and leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5) – two key drivers of tumor cells that contribute to tumor growth and spread. In a phase II trial, petosemtamab showed clinically meaningful benefit with manageable side effects for patients with recurrent or metastatic HNSCC. This article describes two phase III trials studying petosemtamab's ability to reduce tumors and improve survival. LiGeR-HN1 will include approximately 500 patients who have not yet been treated for recurrent or metastatic HNSCC, and whose tumors have a protein called programmed cell death ligand 1 on the cell surface. Patients will be split into two groups: one group will receive petosemtamab with pembrolizumab, an immunotherapy; the other group will receive only pembrolizumab. LiGeR-HN2 will include approximately 500 patients whose disease has progressed on or after receiving anti-programmed cell death protein 1 and platinum-based treatment for recurrent or metastatic HNSCC. Patients will be split into two groups: one group will receive petosemtamab; the other group will receive either cetuximab (targeted therapy), methotrexate (chemotherapy), or docetaxel (chemotherapy). Both trials are recruiting participants at the time of publication.

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Article highlights

- Petosemtamab, a bispecific antibody targeting epidermal growth factor receptor (EGFR) and leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5), has demonstrated clinically meaningful activity in patients with recurrent/metastatic (r/m) head and neck squamous cell carcinoma (HNSCC) in a multi-cohort phase II trial (NCT03526835), and has the potential to become a first- and best-in-class treatment.
- LiGeR-HN1 (NCT06525220) and LiGeR-HN2 (NCT06496178) are open-label, randomized, multicenter, parallel-group, phase III trials evaluating the efficacy, safety, pharmacokinetics, immunogenicity, and health-related quality of life outcomes of petosemtamab in patients with r/m HNSCC.
- Approximately 500 patients with programmed cell death ligand 1–positive (combined positive score of ≥ 1) r/m HNSCC will be randomized to receive either petosemtamab plus pembrolizumab, or pembrolizumab alone, as first-line therapy in the LiGeR-HN1 trial.
- LiGeR-HN2 will randomize approximately 500 previously treated patients with r/m HNSCC to receive either petosemtamab monotherapy or investigator's choice of monotherapy (cetuximab, methotrexate, or docetaxel).
- The two primary endpoints of both trials are overall response rate per Response Evaluation Criteria in Solid Tumors version 1.1 by blinded independent central review, and overall survival.
- The results of these trials could potentially transform the treatment landscape for patients with r/m HNSCC in both the first-line and previously treated settings.

1. Introduction

Head and neck cancer accounted for more than 940,000 new cases and over 480,000 deaths globally in 2022, making it the sixth most prevalent and the fifth deadliest tumor type [1]. Notably, over 90% of these cases are classified as head and neck squamous cell carcinoma (HNSCC) [2]. HNSCC is often diagnosed at later stages, where the risk of recurrence and metastasis is high, resulting in considerable challenges for treatment and patient survival [3,4].

The current standard of care for first-line systemic treatment of recurrent or metastatic (r/m) HNSCC is pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, either as monotherapy or in combination with platinum-based therapy and fluorouracil [5,6]. This standard therapy also applies to HNSCC tumors expressing programmed cell death ligand 1 (PD-L1), defined as having a combined positive score (CPS) of ≥ 1 [5,6], with a prevalence of approximately 78–85% observed in large clinical trials [7]. Despite modern therapeutic advancements, only around 15–20% of these patients will survive past 4 years [8]. In the second-line setting and beyond, for patients whose disease is resistant to anti-PD -1 and platinum-based therapies, treatment options are limited, and no uniform standard of care exists; therapies including methotrexate, docetaxel, or cetuximab are commonly used [5,6]. However, clinical trials evaluating these therapies have shown that only 17–27% of patients are alive at 12 months [9,10]. The high prevalence of HNSCC, combined with the dismal survival prognosis in the r/m setting, underscores the urgent need for novel therapeutic strategies to improve outcomes for this patient population.

Epidermal growth factor receptor (EGFR) is a tyrosine kinase receptor expressed in many adult tissues and serves as a versatile signal transducer involved in numerous cellular processes essential for cell survival, growth, motility, and apoptosis [11,12]. EGFR has been established as an oncogenic driver in the pathogenesis of multiple tumor types, and given its central role in tumorigenesis, it has emerged as an important therapeutic target [11]. Over 80% of HNSCC cases demonstrate EGFR overexpression, which is frequently associated with poor clinical outcomes, decreased chemosensitivity, high recurrence rates, and low survival rates [13,14]. Leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5) is a seven-transmembrane protein expressed on stem-like cells, including cancer stem cells (CSCs) [15]; CSCs have been shown to cause tumor growth and metastasis, with LGR5-positive cells contributing to metastatic growth after seeding [16,17]. LGR5 plays a critical role in cell-fate determination by modulating the wingless-type integration site (WNT)/β-catenin signaling pathway [15,18], and stimulating CSC proliferation and renewal in the presence of a ligand [19]. Mutations in LGR5 and related pathway genes occur in multiple cancers [15], and overexpression of LGR5 correlates with poor response to chemotherapy [20,21]. LGR5 is upregulated in many solid tumors and is known to be expressed at higher levels when EGFR is inhibited [22]. Therefore, targeting both EGFR and LGR5 could represent a more effective strategy for treating tumor cells compared with EGFR inhibition alone.

Petosemtamab is a high-affinity, human, common light chain, immunoglobulin G1 bispecific antibody targeting EGFR and LGR5 [23]. Its activity has been demonstrated preclinically through a threefold mechanism of action: (i) direct inhibition of EGFR signaling, (ii) binding to LGR5-positive stem cell-like tumor cells and generating EGFR degradation via LGR5 internalization, and (iii) through antibody-dependent cell-mediated phagocytosis (ADCP) plus enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) (Figure 1). Through inhibition of EGFR, LGR5 may be upregulated by differentiating cells to effectively overcome EGFR treatment as a resistance mechanism [24–28]. This upregulation in the context of petosemtamab administration may lead to enhanced activity through secondary targeting of the emergent LGR5 antigen, serving as a further anchor for the above mechanisms of action, such as ADCP and ADCC.

A phase II trial (ClinicalTrials.gov identifier: NCT03526835) evaluated the efficacy, safety, and tolerability of petosemtamab administered intravenously (IV) at a dosage of 1500 mg every 2 weeks (Q2W) across various solid tumor types, including HNSCC [29]. Petosemtamab monotherapy demonstrated promising results in patients with previously treated r/m HNSCC, achieving an overall response rate (ORR) of 36% based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by investigator assessment (27 of 75 patients; Figure 2). Furthermore, the treatment was well tolerated, displaying a manageable safety profile [30].

The trial also investigated the combination of petosemtamab and pembrolizumab as a first-line treatment for PD-L1–positive r/m HNSCC. Interim clinical data demonstrated a favorable safety profile, including manageable infusion-related reactions (IRRs). Additionally, the ORR was 67%, with 16 of 24 patients responding, as assessed using RECIST v1.1 by the investigators (Figure 3) [31].

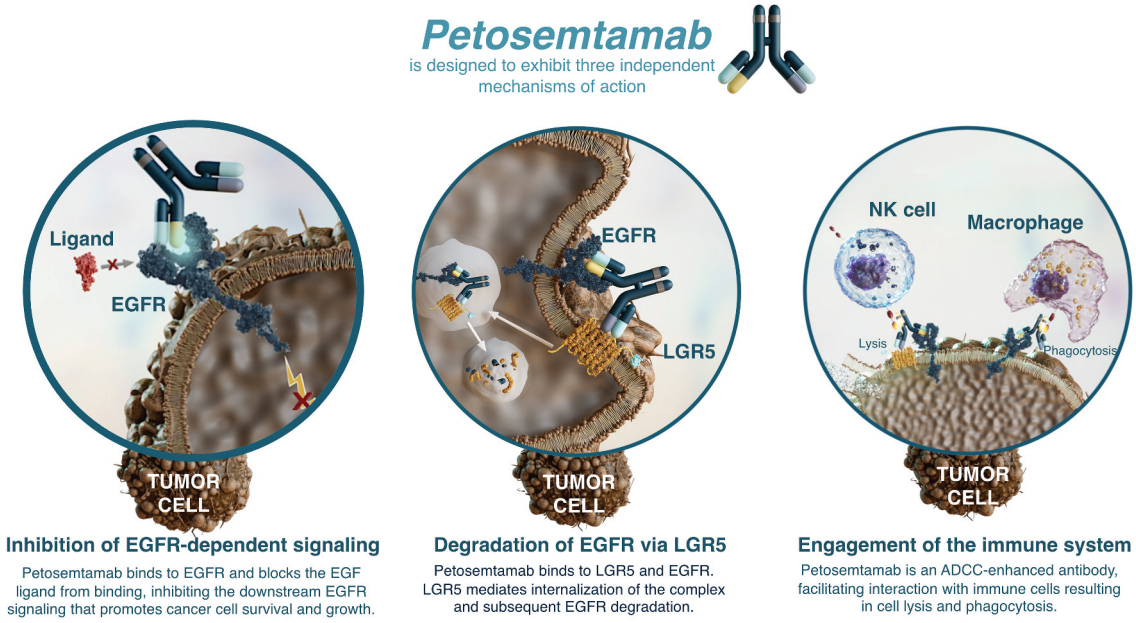

Figure 1. Petosemtamab mechanism of action [23].

ADCC: antibody-dependent cellular cytotoxicity, EGF: epidermal growth factor; EGFR: epidermal growth factor receptor; LGR5: leucine-rich repeat-containing G-protein coupled receptor 5; NK: natural killer.

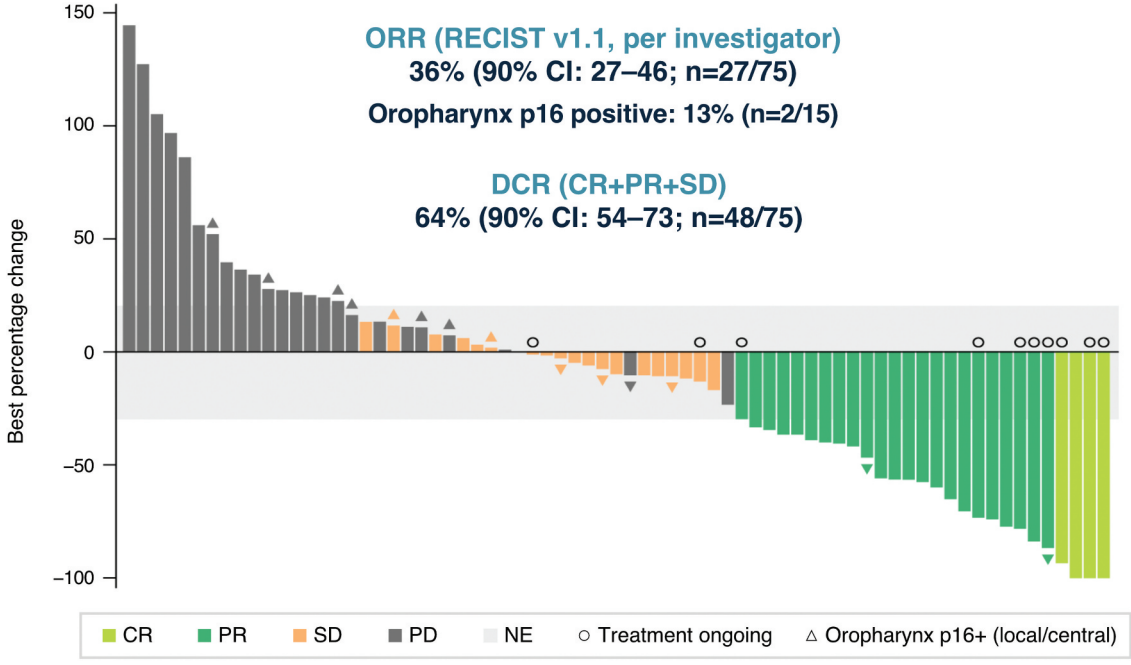

Figure 2. Petosemtamab monotherapy in previously treated recurrent or metastatic head and neck squamous cell carcinoma: phase II data (NCT03526835) [31].

The lighter gray shaded region indicates the threshold for confirmed objective response, as defined by the RECIST v1.1 response criteria.

The waterfall plot excludes four patients (including one patient who had oropharynx p16+ status). Two patients were excluded as the target lesions were not assessed or assessed partially. One patient assessed as having 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; ORR: objective response rate; PD: progressive disease; PR: partial response; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1; SD: stable disease.

Based on these promising phase II data in r/m HNSCC, two phase III trials were initiated. LiGeR-HN1 (ClinicalTrials.gov identifier: NCT06525220) is evaluating the efficacy and safety of petosemtamab plus pembrolizumab versus pembrolizumab alone as first-line therapy for PD-L1–positive r/m HNSCC. LiGeR-HN2 (ClinicalTrials.gov identifier: NCT06496178) is evaluating the efficacy and safety of petosemtamab versus investigator's choice of monotherapy in patients with r/m HNSCC whose disease has progressed on or after receiving anti-PD-1 and platinum-based treatment. These trials are sponsored by Merus N.V.

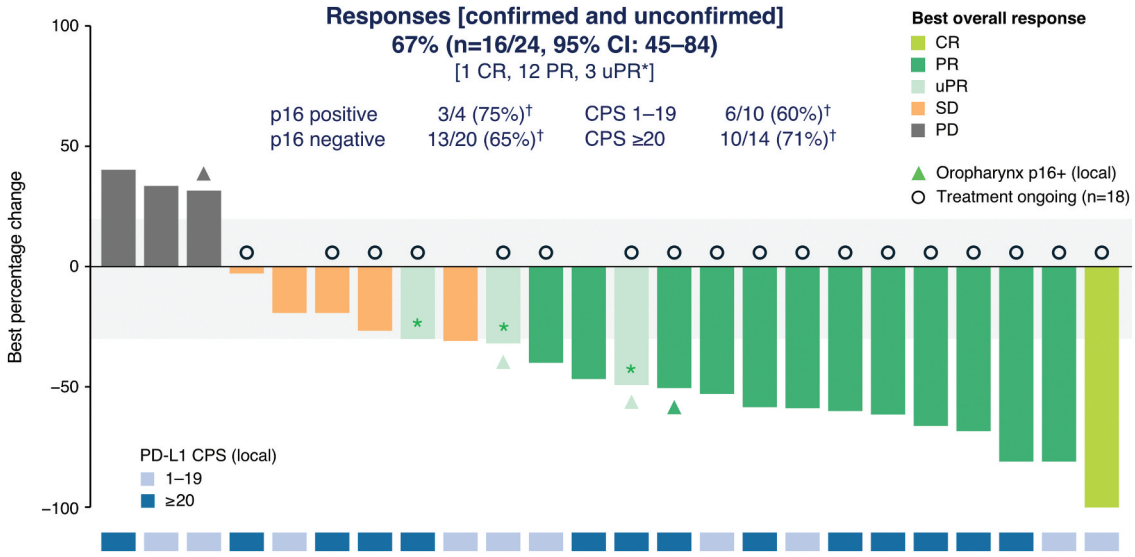

Figure 3. Petosemtamab plus pembrolizumab in first-line programmed cell death ligand 1–positive recurrent or metastatic head and neck squamous cell carcinoma: phase II data (NCT03526835) [30].

The lighter gray shaded region indicates the threshold for confirmed objective response, as defined by the RECIST v1.1 response criteria.

Sixteen of 24 patients demonstrated treatment responses.

*Three PRs were unconfirmed as of the March 2024 data cutoff but were subsequently confirmed post-cutoff. †Response values for p16 and PD-L1 CPS subgroups include CR, PR, and uPR.

CI: confidence interval; CPS: combined positive score; CR: complete response; PD: progressive disease; PD-L1: programmed cell death ligand 1; PR: partial response; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1; SD: stable disease; uPR: unconfirmed partial response.

2. Methods

2.1. Trial design

Both LiGeR-HN trials are open-label, randomized, multicenter, parallel-group, phase III trials evaluating the efficacy, safety, pharmacokinetics, immunogenicity, and health-related quality of life outcomes of petosemtamab in r/m HNSCC. LiGeR-HN1 will investigate petosemtamab plus pembrolizumab versus pembrolizumab alone as first-line treatment of PD-L1–positive r/m HNSCC (Figure 4), while LiGeR-HN2 will compare petosemtamab versus investigator's choice of monotherapy in patients who have progressed on or after anti-PD-1 and platinum-based therapy (Figure 5). The trials are designed to demonstrate the superiority of petosemtamab, either in combination with pembrolizumab or as monotherapy, in r/m HNSCC compared with the current standards of care.

Approximately 175 sites are planned to be involved in each trial across North and South America, Europe, and Asia-Pacific regions; a list of trial locations can be found on the respective trial pages on the ClinicalTrials.gov website.

2.2. Participants

The LiGeR-HN1 and LiGeR-HN2 trials will enroll patients aged ≥18 years with histologically or cytologically confirmed HNSCC, measurable disease per investigator

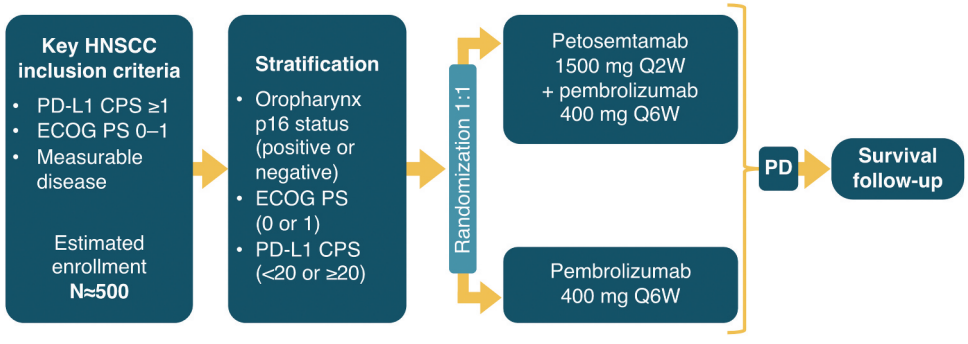

Figure 4. LiGeR-HN1 trial design.

p16 status is measured only in patients with oropharyngeal tumors; all other tumor locations are designated as p16 negative for the purposes of stratification.

CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group performance status; HNSCC: head and neck squamous cell carcinoma; PD: progressive disease; PD-L1: programmed cell death ligand 1; Q2W: every 2 weeks; Q6W: every 6 weeks.

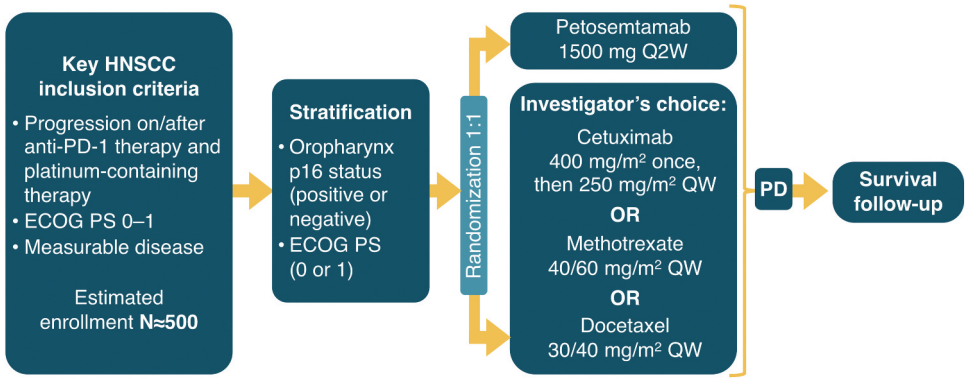

Figure 5. LiGeR-HN2 trial design.

Methotrexate will be administered initially at a dose of 40 mg/m^2 IV in a short infusion weekly, which may be increased to 60 mg/m^2 if tolerated as per local practice. Docetaxel will be administered initially at a dose of 30 mg/m^2 IV weekly, which may be increased to 40 mg/m^2 if tolerated as per local practice.

ECOG PS: Eastern Cooperative Oncology Group performance status; HNSCC: head and neck squamous cell carcinoma; IV: intravenous; PD: progressive disease; PD-1: programmed cell death protein 1; Q2W: every 2 weeks; QW: once weekly.

assessment as defined by RECIST v1.1, and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Eligible patients will be required to have r/m HNSCC that is not amenable to local or standard therapy with curative intent, and have primary disease located in either the oropharynx, oral cavity, hypopharynx, or larynx. The key eligibility criteria of the trials are summarized in Tables 1 and 2.

Table 1. LiGeR-HN1 eligibility criteria.*†

LiGeR-HN1 inclusion criteria	LiGeR-HN1 exclusion criteria
• Signed ICF before initiation of any study procedures • 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 • The eligible HNSCC primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx • Patients with HNSCC eligible to receive pembrolizumab as 1 L monotherapy with tumors expressing PD-L1, CPS of ≥ 1 • Patients with HNSCC should not have had previous systemic therapy administered in the incurable recurrent or metastatic setting • A new tumor biopsy unless the patient has an available archival tumor sample with sufficient material • Measurable disease per investigator assessment as defined by RECIST v1.1 by radiologic methods • ECOG PS of 0 or 1 • Life expectancy of ≥12 weeks, as per investigator assessment • Left ventricular ejection fraction ≥ 50% or greater than or equal to the institutional normal limit, whichever is higher, by echocardiogram or multigated acquisition scan • Adequate organ function as defined per protocol	• CNS metastases that are untreated or already treated but symptomatic, or require radiation, surgery, or continued steroid therapy to control symptoms within 21 days prior to randomization • Known leptomeningeal involvement • Any systemic anticancer therapy or investigational drug within 4 weeks or five half-lives, whichever is shorter, before randomization • Requirement for immunosuppressive medication • Major surgery or radiotherapy within 3 weeks of randomization • Clinically significant toxicities related to prior anticancer therapy that have not returned to grade ≤ 1 or baseline except for grade ≤ 2 myalgia, alopecia, and prior therapy-related endocrinopathies • History of hypersensitivity reaction to any of the excipients of petosemtamab or pembrolizumab • Unstable angina; history of congestive heart failure of NYHA Class II – IV criteria, or serious cardiac arrhythmia requiring treatment; or history of myocardial infarction within 6 months prior to randomization • History of prior malignancies within the last 5 years, with the exception of excised local cancer • Current dyspnea at rest of any origin, or other diseases requiring continuous oxygen therapy • Current serious illness or medical conditions including, but not limited to, uncontrolled active infection, clinically significant pulmonary, metabolic, or psychiatric disorders • Patients with known infectious diseases as per protocol • Pregnant or breastfeeding patients • The patient has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy of prednisone >10 mg/day or equivalent or any other form of immunosuppressive therapy • The patient has an active autoimmune disease that has required systemic immune suppressive treatment in the past 2 years; replacement therapy is not considered immune suppressive treatment • The patient has had an allogeneic tissue/solid organ transplant • Patient has a primary tumor site of nasopharynx, or sinonasal carcinoma (any histology)

*Other protocol-defined eligibility criteria may apply. †Please see ClinicalTrials.gov listing for country-specific criteria.

1 L: first-line; CNS: central nervous system; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group performance status; HNSCC: head and neck squamous cell carcinoma; ICF: informed consent form; NYHA: New York Heart Association; PD-L1: programmed cell death ligand 1; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1.

Table 2. LiGeR-HN2 eligibility criteria.*†

LiGeR-HN2 inclusion criteria	LiGeR-HN2 exclusion criteria
• Signed ICF before initiation of any study procedures • Age ≥18 years at signing of ICF • Histologically previously confirmed HNSCC with evidence of metastatic or locally advanced disease not amenable to standard therapy with curative intent • Patients with HNSCC that has progressed on or after anti-PD-1 therapy and platinum-based therapy • The eligible HNSCC primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx • Documentation of p16 status (positive or negative) by local laboratory IHC for patients with primary oropharyngeal cancer • A baseline new tumor biopsy unless the patient has an available archival tumor sample with sufficient material • Measurable disease per investigator assessment as defined by RECIST v1.1 by radiologic methods • ECOG PS of 0 or 1 • Life expectancy of ≥12 weeks, as per investigator • Adequate organ function (as per protocol) • Judged appropriate by the investigator to receive investigator's choice monotherapy, if randomized to that treatment arm	• CNS metastases that are untreated or symptomatic, or require radiation, surgery, or continued steroid therapy to control symptoms within 14 days prior to randomization • Known leptomeningeal involvement • Any systemic anticancer therapy, investigational drug, or live or live attenuated vaccine within 4 weeks or five half-lives (if known), whichever is shorter, prior to randomization • Major surgery or radiotherapy within 3 weeks of randomization • Clinically significant toxicities related to prior anticancer therapy that have not returned to grade ≤ 1 or baseline except for alopecia, and grade ≤ 2 prior therapy-related endocrinopathies • History of hypersensitivity reaction to any of the excipients of treatment required for this study • Unstable angina; history of congestive heart failure of NYHA Class II – IV criteria, or serious cardiac arrhythmia requiring treatment or history of myocardial infarction within 6 months prior to randomization • History of prior malignancies within the last 5 years, with the exception of excised local cancer (e.g., cervical intraepithelial neoplasia, non-melanoma skin cancers) • Current dyspnea at rest of any origin, or other diseases requiring continuous oxygen therapy • Current serious illness or medical conditions including, but not limited to, uncontrolled active infection, clinically significant pulmonary, metabolic, or psychiatric disorders • Patients with known infectious diseases (as per protocol) • Pregnant or breastfeeding patients • Patient has a primary tumor site of nasopharynx or sinonasal (any histology)

*Other protocol-defined eligibility criteria may apply. †Please see ClinicalTrials.gov listing for country-specific criteria.
CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group performance status; HNSCC: head and neck squamous cell carcinoma; ICF: informed consent form; IHC: immunohistochemistry; NYHA: New York Heart Association; PD-1: programmed cell death protein 1; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1.

2.3. Treatment and dosing

2.3.1. LiGeR-HN1 treatment design

Approximately 500 patients with previously untreated PD-L1–positive (defined as having a CPS of ≥ 1) r/m HNSCC will be randomized 1:1 to either the investigational arm, where they will receive petosemtamab 1500 mg IV Q2W plus pembrolizumab 400 mg every 6 weeks (Q6W), or the control arm, where they will receive pembrolizumab 400 mg IV Q6W for up to 24 months or until progressive disease is confirmed by blinded independent central review (BICR) per RECIST v1.1. Full intervention details are listed in Table 3.

Randomization will be stratified based on p16 status (positive vs. negative) and PD-L1 CPS (<20 vs. ≥20), as determined by central laboratory testing, and ECOG PS (0 vs. 1). Patients will be treated in 28-day cycles for up to 2 years, after which they may continue to be treated with petosemtamab if clinical benefit is observed. Safety follow-up will occur at a minimum of 30 days after the last study treatment administration, and survival follow-up will occur every 3 months until the end of the study, when all patients have had the opportunity to be followed up for at least 36 months. All other efficacy measures will be evaluated until the end of the trial.

2.3.2. LiGeR-HN2 treatment design

Around 500 patients with previously treated r/m HNSCC will be randomized 1:1 to either the investigational arm, where they

Table 3. LiGeR-HN1 and LiGeR-HN2 study interventions.

Trial	
LiGeR-HN1	
Arm 1 (investigational arm):	Petosemtamab 1500 mg IV Q2W plus pembrolizumab 400 mg IV Q6W
Arm 2 (control arm):	Pembrolizumab 400 mg IV Q6W
LiGeR-HN2	
Arm 1 (investigational arm):	Petosemtamab 1500 mg IV Q2W
Arm 2 (control arm):	One of three investigator's choice of monotherapies: • Cetuximab 400 mg/m^2 IV once, then 250 mg/m^2 weekly OR • Methotrexate 40 mg/m^2 IV weekly, which may be increased to 60 mg/m^2 if tolerated as per local practice OR • Docetaxel 30 mg/m^2 IV weekly, which may be increased to 40 mg/m^2 if tolerated as per local practice

IV: intravenously; Q2W: every 2 weeks; Q6W: every 6 weeks.

will receive petosemtamab 1500 mg IV Q2W as monotherapy, or to the control arm, where they will receive one of three possible investigator's choice of available monotherapies (cetuximab IV 400 mg/m^2 once, then 250 mg/m^2 once weekly [QW]; methotrexate IV 40/60 mg/m^2 QW; or docetaxel IV 30/40 mg/m^2 QW). Full intervention details are listed in Table 3.

Randomization will be stratified based on p16 status (positive vs. negative) as determined by local laboratory testing or the central laboratory if local results are unavailable, and ECOG PS (0 vs. 1). Patients will be treated in 28-day cycles until protocol-defined discontinuation criteria are met. Safety follow-up will occur at a minimum of 30 days after the last study treatment administration; survival follow-up will occur every 3 months and continue until all patients have had the opportunity to be followed up for ≥18 months, or until all patients either have discontinued or completed 18 months of survival follow-up. All other efficacy measures will be evaluated until the end of the trial.

2.3.3. Dosing and management

In both trials, a required premedication for petosemtamab, including antipyretics, antihistamines, and corticosteroids, will be administered. In the event of IRRs, hypersensitivity, or allergic reactions, treatment to control symptoms, including but not limited to antihistamines or corticosteroids, should be administered according to standard local clinical practice. Study treatment will be discontinued in the case of disease progression, unacceptable adverse events (AEs), withdrawal of consent, patient noncompliance with trial requirements, investigator's decision for safety or clinical deterioration, interruption of petosemtamab treatment for more than 6 consecutive weeks due to treatment-related toxicity, intercurrent illness that prevents administration of further treatment, confirmed positive serum pregnancy test, patient lost to follow-up, or administrative reasons. Petosemtamab dose interruptions, symptom-directed treatment measures, and dose adjustments will be implemented in the event of AEs associated with targeting the EGFR pathway.

2.4. Trial endpoints

The two primary endpoints of the LiGeR-HN1 and LiGeR-HN2 trials are ORR per RECIST v1.1 by BICR, and overall survival (OS).

Secondary efficacy endpoints include progression-free survival, duration of response, and clinical benefit rate, all assessed per investigator and BICR, in addition to ORR per investigator. Other key secondary endpoints include the incidence of treatment-emergent adverse events (TEAEs) and serious TEAEs, study discontinuations and dose modifications due to TEAEs, and health-related quality of life as measured by generic and disease-specific assessments from the European Organisation for Research and Treatment of Cancer, EuroQol 5-Dimension 5-Level questionnaire, and the patient global impression of change scales. Health-related quality of life will be assessed using the same assessment instruments across both trials. The key endpoints for LiGeR-HN1 are listed in Table 4, and key endpoints for LiGeR-HN2 are listed in Table 5.

Table 4. LiGeR-HN1 trial endpoints.

LiGeR-HN1 primary endpoints
• Overall survival • Objective response rate per RECIST v1.1 as assessed by BICR
LiGeR-HN1 secondary endpoints
• Progression-free survival per RECIST v1.1 as assessed by BICR • Duration of response per RECIST v1.1 as assessed by BICR • Objective response rate per RECIST v1.1 as assessed by investigator review • Progression-free survival per RECIST v1.1 as assessed by investigator review • Duration of response per RECIST v1.1 as assessed by investigator review • Clinical benefit rate per RECIST v1.1 as assessed by BICR • Clinical benefit rate per RECIST v1.1 as assessed by investigator review • Number of participants who experienced at least one TEAE • Number of participants who experienced at least one serious TEAE • Number of participants who discontinued study treatment due to TEAEs • Number of participants who had dose modification due to TEAEs • To evaluate patient-reported outcomes for health-related quality of life • Pharmacokinetic parameters • Incidence of ADAs against petosemtamab

ADA: anti-drug antibody; BICR: blinded independent central review; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1; TEAE: treatment-emergent adverse event.

Table 5. LiGeR-HN2 trial endpoints.

LiGeR-HN2 primary endpoints
• Overall survival • Objective response rate per RECIST v1.1 as assessed by BICR
LiGeR-HN2 secondary endpoints
• Progression-free survival per RECIST v1.1 as assessed by BICR • Duration of response per RECIST v1.1 as assessed by BICR • Objective response rate per RECIST v1.1 as assessed by investigator review • Progression-free survival per RECIST v1.1 as assessed by investigator review • Duration of response per RECIST v1.1 as assessed by investigator review • Time to response per RECIST v1.1 as assessed by BICR • Time to response per RECIST v1.1 as assessed by investigator review • Clinical benefit rate per RECIST v1.1 as assessed by BICR • Clinical benefit rate per RECIST v1.1 as assessed by investigator review • Number of participants who experienced at least one TEAE • Number of participants who experienced at least one serious TEAE • Number of participants who discontinued study treatment due to TEAEs • Number of participants who had dose modification due to TEAEs • To evaluate patient-reported outcomes for health-related quality of life • Pharmacokinetic parameters • Incidence of ADAs against petosemtamab

ADA: anti-drug antibody; BICR: blinded independent central review; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1; TEAE: treatment-emergent adverse event.

2.5. Assessments

2.5.1. Efficacy assessments

For both trials, in all treatment arms, tumor response will be evaluated according to RECIST v1.1. Baseline tumor assessments will be performed within 42 days prior to the first dose of study treatment. Baseline imaging of the head, neck, chest, and abdomen using computed tomography or magnetic resonance imaging scan will be conducted ≤28 days prior to study treatment. Tumor assessments will then be performed every 8 weeks after the start of study treatment until disease progression or up to 12 months, after which they will be conducted every 12 weeks.

2.5.2. Safety assessments

Patients will be monitored for signs and symptoms of AEs throughout the trial. Patient data will be analyzed for evidence of cumulative toxicity with repeated cycles of therapy in both trials. AEs, along with signs and symptoms of disease, will be recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Incidence, severity, and relationship of AEs, as well as laboratory abnormalities, serious AEs, discontinuations, and dose adaptations due to AEs, will be recorded.

2.6. Statistical methods

Each trial plans to enroll approximately 500 patients to detect a statistically significant difference in the two primary efficacy endpoints, ORR and OS.

3. Conclusion

Patients with r/m HNSCC have limited treatment options and a dismal prognosis when treated with current standard of care therapies. Based on phase II interim clinical data, petosemtamab has the potential to become a first- and best-in-class treatment for this patient population. Petosemtamab is being evaluated in combination with pembrolizumab as first-line treatment of PD-L1–positive r/m HNSCC in the LiGeR-HN1 trial, and as monotherapy in patients who have progressed on or after anti-PD-1 and platinum-based therapy in the LiGeR-HN2 trial. Enrollment of patients in LiGeR-HN1 and LiGeR-HN2 began in September 2024 and July 2024, respectively, and at the time of this publication are actively recruiting. Please refer to ClinicalTrials.gov (NCT06525220 [LiGeR-HN1] and NCT06496178 [LiGeR-HN2]) for more information. The outcomes of these trials have the potential to impact the treatment paradigm, possibly offering more effective therapeutic options in both the first-line and previously treated settings.

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Study conception and design: JPM and MG. Methodology: JF, SJ, RP, YS, DY, and FZ. Writing – original draft: All authors. Writing – review & editing: All authors. Funding acquisition: JF, SJ, RP, YS, DY, and FZ.

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Ethical declaration

These clinical trials will be conducted in compliance with the protocol; Good Clinical Practice (GCP) as defined in the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use Guidance E6(R2): Good Clinical Practice: Consolidated Guidance; the Declaration of Helsinki; the European Union (EU) Clinical Trials Directive 2001/20/EC or EU Clinical Trials Regulation 536/2014/EC (whichever is applicable, based on the relevant circumstances); the GCP Directive 2005/28/EC, and applicable national and local regulatory requirements.

Both trials will be conducted across various sites globally, and approvals have been obtained from all relevant national/local Independent Ethics Committees/Institutional Review Boards for all active sites. Approval numbers for each site, and a detailed list of these can be provided upon request.

Before enrolling in both the clinical trials, each screened participant will receive an informed consent form (ICF) containing all necessary details to support a fully informed decision. The ICF will adhere to the requirements outlined in the ICH E6(R2) Guideline for GCP and will include any additional elements required by local regulations.

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