KEYNOTE-689: Phase 3 Study of Neoadjuvant and Adjuvant Pembrolizumab Combined With Standard of Care in Patients With Resectable, Locally Advanced Head and Neck Squamous Cell Carcinoma

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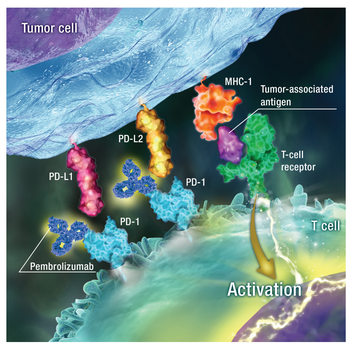
BACKGROUND

- Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide[1]
  - The most frequent tumor sites of HNSCC are the larynx, pharynx, and oral cavity[1]
- Standard-of-care (SOC) treatment for patients with locally advanced (LA) HNSCC include combinations of surgery, radiation therapy (RT), and chemotherapy or cetuximab[2]
  - Although these multimodality treatments are aggressive, 40%-60% of patients will experience relapse[3]
- Pembrolizumab is a potent, high-affinity monoclonal antibody that directly blocks the interaction between programmed death 1 (PD-1) and its ligands, PD-L1 and PD-L2 (**Figure 1**)[4]
  - Pembrolizumab is approved in >80 countries for 1 or more advanced malignancies
  - It is approved in the United Stated for recurrent or metastatic HNSCC in patients exhibiting disease progression on or after receiving platinum-containing chemotherapy[4]
- Given the activity in recurrent and/or metastatic HNSCC, integrating checkpoint inhibitor therapy for patients with surgically treated LA HNSCC represents a new strategy to improve outcomes
- Supporting this approach, 2 trials have demonstrated the efficacy and safety of pembrolizumab in the neoadjuvant and adjuvant settings in patients with high-risk, resectable LA HNSCC[5,6]
  - In a phase 2 trial (ClinicalTrials.gov, NCT02296684), patients received 1 dose of neoadjuvant pembrolizumab (200 mg) before surgery; patients with high-risk pathological features then received postoperative adjuvant cisplatin and RT followed by adjuvant pembrolizumab
    - Preliminary analyses revealed that neoadjuvant and adjuvant pembrolizumab were well tolerated and showed antitumor activity, including pathological tumor response and clinical-to-pathological downstaging
  - In another phase 2 trial (ClinicalTrials.gov, NCT02641093), patients received neoadjuvant pembrolizumab before surgery; after surgery, patients received concurrent adjuvant pembrolizumab and RT, and those with high-risk features also received weekly cisplatin
    - Pathological response was observed after 1 dose of pembrolizumab, and the adjuvant treatment combination demonstrated an acceptable safety profile
- KEYNOTE-689 (ClinicalTrials.gov, NCT03765918) is a randomized, open-label, phase 3 trial designed to evaluate the efficacy and safety of pembrolizumab as neoadjuvant and adjuvant therapy in combination with SOC in patients with previously untreated, resectable LA HNSCC

Figure 1. Pembrolizumab and the PD-1 Pathway



MHC-1, major histocompatibility complex 1; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2.

OBJECTIVES

Primary

- To compare the rate of major pathological response (mPR; ≤10% invasive SCC within the resected primary tumor specimen and all sampled regional lymph nodes) as assessed by the central pathologist at the time of definitive surgery between patients who receive neoadjuvant pembrolizumab (arm A) and those who do not (arm B)
- To compare event-free survival (EFS) as assessed by blinded independent central review between patients who receive pembrolizumab neoadjuvant therapy and postoperative adjuvant pembrolizumab with RT ± cisplatin and patients who receive only postoperative adjuvant RT ± cisplatin

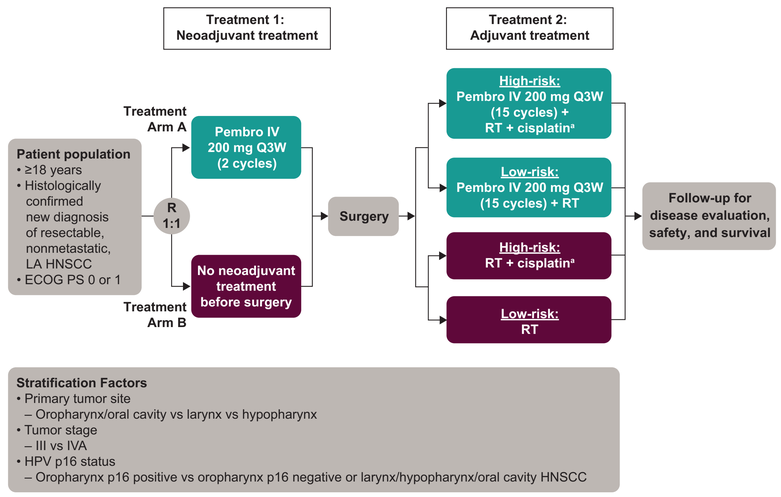
Secondary

- To compare overall survival (OS) between patients who receive neoadjuvant pembrolizumab and postoperative adjuvant pembrolizumab with RT ± cisplatin and patients who receive only postoperative adjuvant RT ± cisplatin
- To evaluate the rate of pathological complete response (pCR) as assessed by the central pathologist at the time of definitive surgery
- To evaluate global health status/quality of life (QoL) scores using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and swallowing, speech, and pain symptoms using the EORTC Head and Neck-Specific QOL questionnaire (EORTC QLQ-H&N35)
- To determine the safety and tolerability of neoadjuvant pembrolizumab and postoperative adjuvant pembrolizumab in combination with RT ± cisplatin

METHODS

- KEYNOTE-689 is a randomized, open-label phase 3 study of neoadjuvant and adjuvant pembrolizumab added to SOC for patients with stage III-IVA resectable LA HNSCC (**Figure 2**)
  - SOC includes surgery followed by postoperative adjuvant RT
    - Participants at low risk will receive 2 Gy/fraction × 30 fractions
    - Participants at high risk will receive 2 Gy/fraction × 33 fractions and cisplatin (100 mg/m^2 every 3 weeks [Q3W] for 3 doses)
    - Participants with gross residual disease after surgery will receive 2 Gy/fraction × 35 fractions and cisplatin (100 mg/m^2 Q3W for 3 doses)
- Approximately 600 eligible patients will be enrolled and randomly assigned 1:1 to either of 2 treatment arms (**Figure 2**)
  - Patients in arm A will receive neoadjuvant pembrolizumab (2 cycles) followed by surgical resection and then adjuvant pembrolizumab (15 cycles) plus SOC
  - Patients in arm B will undergo surgical resection followed by adjuvant SOC
- Treatment will continue until disease progression, unacceptable toxicity, or decision to withdraw

Figure 2. Study Design



ECOG PS, Eastern Cooperative Oncology Group performance status; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; IV, intravenous; LA; locally advanced; Pembro, pembrolizumab; Q3W, every 3 weeks; R, randomly assigned; RT, radiation therapy.

[a]Cisplatin will be given intravenously at 100 mg/m^2 Q3W for 3 cycles; if there are any delays in cisplatin treatment, cisplatin may be administered up to 1 week after the completion of RT.

Patient Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 • Histologically confirmed new diagnosis of resectable, nonmetastatic SCC that is[a] – Stage III oropharyngeal p16 positive T4 (N0-N2), M0 **OR** – Stage III or IVA oropharyngeal p16 negative **OR** – Stage III or IVA larynx/hypopharynx/oral cavity (independent of p16) • Eligible for primary surgery • Evaluable tumor burden based on RECIST v1.1 • Newly obtained core or excisional biopsy of a tumor • p16 test results for oropharyngeal cancer • ECOG PS 0 or 1 • Adequate organ function	• Stage T4B and/or N3 LA HNSCC and/or distant metastases • Cancer outside the oropharynx, larynx, hypopharynx, or oral cavity • Receipt of prior therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent or with an agent directed to another coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137) • Receipt of prior RT or systemic anticancer therapy • Current participation in a study of an investigational agent or use of an investigational device within 4 weeks before the first dose of study treatment • Immunodeficiency or systemic steroid therapy within 7 days before the first dose • Additional malignancy within the past 3 years[b] • CNS metastases and/or carcinomatous meningitis • Grade ≥2 audiometric hearing loss or grade ≥2 neuropathy • Previous allogeneic tissue or solid organ transplant • Active autoimmune disease or active infection necessitating systemic therapy • History of HIV, hepatitis B, or hepatitis C

CNS, central nervous system; CTLA-4, cytotoxic T lymphocyte–associated protein 4; ECOG PS, Eastern Cooperative Oncology Group performance status; HIV, human immunodeficiency virus; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; LA, locally advanced; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2; RT, radiation therapy; SCC, squamous cell carcinoma.

[a]Patients with multiple primary HNSCC tumors are eligible for the study if ≥1 of the tumors meets eligibility criteria based on staging after consultation with and approval by the sponsor.
[b]Patients with basal cell carcinoma of the skin, SCC of the skin, or carcinoma in situ (eg, in situ cervical cancer or breast carcinoma) who have undergone potentially curative therapy are not excluded.

Assessments and Follow-Up

- Tumor imaging (head and neck, chest, and upper abdomen) will be performed by computed tomography (CT) or magnetic resonance imaging (when CT is contraindicated)
- Patients in arm A will undergo radiologic imaging assessment after 2 cycles of neoadjuvant pembrolizumab before surgery
- Postoperative imaging will be performed in both arms 12 weeks after the completion of RT, then every 3 months for the first 3 years and every 6 months thereafter
- Adverse events (AEs) will be monitored throughout the study and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, from the time of allocation to 30 days (90 days for serious AEs) after the last pembrolizumab dose
- Patients who discontinue pembrolizumab for any reason other than disease progresssion or initiation of a new anticancer therapy will continue to be assessed every 3 months for the first 3 years and every 6 months thereafter
- Patients who experience disease progression or start a new anticancer therapy will be contacted by telephone every 12 weeks to assess survival status until death, withdrawal of consent, or end of the trial

Efficacy

- The intention-to-treat population will be used for the primary efficacy analyses
- Analysis of mPR and pCR will include all patients who have been randomly assigned at least 8 weeks before the completion of enrollment
  - mPR will be evaluated by comparing arm A and arm B using the stratified Miettinen and Nurminen method with strata weighting by sample size; the between-treatment differences in percentages, 95% CIs, and *P* values will be provided
- All randomly assigned patients will be included in the EFS and OS analyses based on the treatment group to which they are randomly assigned
  - EFS and OS will be evaluated by comparing arm A and arm B using a stratified log-rank test
  - Hazard ratio will be estimated using a stratified Cox regression model
  - Event rates will be estimated within each treatment group using the Kaplan-Meier method

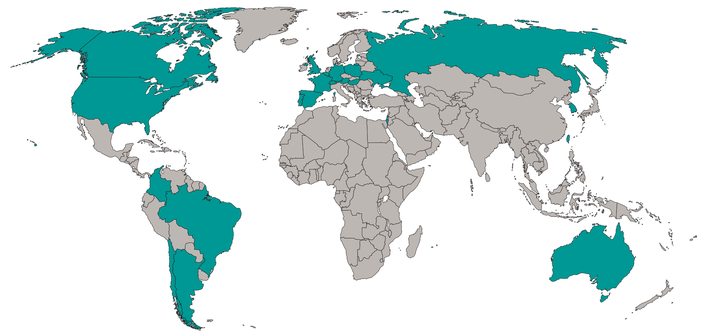
Safety

- Safety will be assessed in the all-patients-as-treated population, which consists of all randomly assigned patients who received study treatment (surgery is considered part of study treatment)
- The safety analysis will follow a tiered approach based on the number of AEs observed
  - No events warrant inferential testing as tier 1 safety end points in this study
  - Point estimate and 95% CI for between-treatment comparisons by the Miettinen and Nurminen method will be provided for tier 2 safety end points
  - Only point estimates by treatment group will be provided for tier 3 safety end points

STATUS

- KEYNOTE-689 is ongoing in 22 countries (**Figure 3**)

Figure 3. Countries With Sites of Enrollment for KEYNOTE-689 (shown in green)



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