BACKGROUND

Secondary Cell Carcinoma

Locally Advanced Head and Neck Squamous Standard of Care in Patients With Resectable, KEYNOTE-689: Phase 3 Study of Neoadjuvant TPS6090

Presented at the 2019 ASCO Annual Meeting (American Society of Clinical Oncology); May 31-June 4, 2019; Chicago, Illinois

• To evaluate global health status/quality of life (QoL) scores using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (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 adjunction pembrolizumab in combination with RT x cisplatin.

• 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.

• 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 modality 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.5

• It is approved in the United States for recurrent or metastatic HNSCC in patients exhibiting disease progression on or after receiving platinum-containing chemotherapy.6

• 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.7

• 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, NCT03765618) 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.

OBJECTIVES

Primary

• To compare the rate of major pathological response (mPR; ≤10%) in invasive SCC within the resected primary tumor specimen and all sampled regional lymph nodes) as assessed by the pathologist at the time of definitive surgery.

• 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 pathologist at the time of definitive surgery.

• To compare overall survival (OS) between patients who receive neoadjuvant pembrolizumab and postoperative adjuvant pembrolizumab with RT x cisplatin and patients who receive only postoperative adjuvant RT x 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 (EORTC QLQ-C30) and swallowing, speech, and pain symptoms using the EORTC Head and Neck–Specific QOL questionnaire (EORTC QLQ-H&N35).

Secondary

• To compare overall survival (OS) between patients who receive neoadjuvant pembrolizumab and postoperative adjuvant pembrolizumab with RT x cisplatin and patients who receive only postoperative adjuvant RT x cisplatin.

• To evaluate the rate of pathological complete response (pCR) as assessed by the central pathologist at the time of definitive surgery.

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 x 30 fractions

• Participants at high risk will receive 2 Gy/Fraction x 33 fractions and cisplatin (100 mg/m² every 3 weeks (Q3W) for 3 doses)

• Participants with gross residual disease after surgery will receive 2 Gy/Fraction x 35 fractions and cisplatin (100 mg/m² Q3W for 3 doses)

• Patients who discontinue pembrolizumab for any reason other than disease progression 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 planned completion of enrollment.

• mPR will be evaluated by comparing arm A and arm B using the stratified Miettinen and Numminen 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 all patients-at-treatment 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 endpoints in this study.

• Point estimate and 95% CI for between-treatment comparisons by the Miettinen and Numminen method will be provided for tier 2 safety endpoints.

• Only point estimates by treatment group will be provided for tier 3 safety endpoints.

STATUS

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

REFERENCES


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