Phase 3 KEYNOTE-630 Study of Adjuvant Pembrolizumab Versus Placebo in Patients With High-Risk Locally Advanced Cutaneous Squamous Cell Carcinoma

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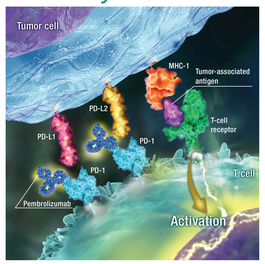
Background

- Cutaneous squamous cell carcinoma (cSCC) is the second most common nonmelanoma skin cancer and accounts for approximately 20%-50% of all skin cancer cases in the world. The incidence of cSCC is increasing yearly in the United States[1]
- The current standard of care for patients with resectable cSCC is surgical resection of the primary tumor and any involved lymph nodes, with consideration of adjuvant radiation therapy (RT) for tumors with high-risk features.[2] However, approximately 20% of patients with high-risk features develop recurrence within 5 years following RT[3]
- Pembrolizumab is a potent, high-affinity monoclonal antibody that directly inhibits the interaction between PD-1 and its ligands, PD-L1 and PD-L2, releasing PD-1 pathway–mediated inhibition of the antitumor immune response[4,5] (**Figure 1**)
- Pembrolizumab is approved in >80 countries for the treatment of 1 or more advanced malignancies, including, in the United States, recurrent or metastatic cSCC that is not curable by surgery or radiation[4]
- Cemiplimab, another PD-1 monoclonal antibody, has also shown encouraging antitumor activity and manageable safety in patients with unresectable locally advanced or metastatic cSCC,[6] suggesting that inhibition of the PD-1 pathway could be a promising treatment approach for this disease
- KEYNOTE-630 (ClinicalTrials.gov, NCT03833167) is a phase 3 trial designed to evaluate the efficacy and safety of adjuvant pembrolizumab in patients with high-risk locally advanced cSCC

Figure 1. Pembrolizumab and the PD-1 Pathway



MHC-1, major histocompatibility complex 1.

Objectives

Primary

- To compare recurrence-free survival (RFS; assessed by the investigator and confirmed by biopsy) in patients treated with pembrolizumab and in patients treated with placebo as adjuvant therapy

Secondary

- To compare the following in patients treated with pembrolizumab and in patients treated with placebo as adjuvant therapy
  - Overall survival (OS)
  - Mean change from baseline in patient-reported health-related quality of life (HRQoL) scores from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)
  - Safety and tolerability

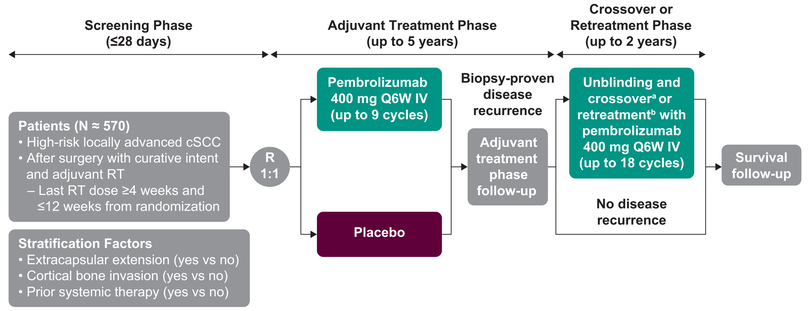
Exploratory

- To identify molecular biomarkers indicative of clinical response, resistance, safety, pharmacodynamic activity, and/or mechanism of action of pembrolizumab
- To compare changes from baseline in HRQoL scores in the Skindex-16 questionnaire in patients treated with pembrolizumab or placebo as adjuvant therapy
- To characterize utilities using the EuroQol 5-dimension, 5-level questionnaire (EQ-5D-5L)

Methods

- KEYNOTE-630 is a global, randomized, double-blind, placebo-controlled phase 3 study of pembrolizumab versus placebo as adjuvant therapy in patients with high-risk locally advanced cSCC who have undergone surgery with curative intent and adjuvant RT
- Approximately 570 eligible patients will be randomly assigned 1:1 to receive intravenous (IV) pembrolizumab (400 mg every 6 weeks [Q6W]) or placebo for up to 9 cycles (approximately 1 year) and will be followed up for as long as 5 years (**Figure 2**)
  - Based on modeling and simulation analyses, pembrolizumab 400 mg Q6W is expected to have a similar benefit-risk profile as 200 mg every 3 weeks (Q3W), the approved dose for several indications[4,5,7,8]
- Patients will be stratified by presence or absence of extracapsular extension, cortical bone invasion, and prior systemic therapy
- On first biopsy-proven disease recurrence, study treatment will be unblinded, and eligible patients who experience recurrence within 5 years may cross over to or receive retreatment with open-label pembrolizumab 400 mg Q6W for up to 18 cycles (approximately 2 years)
  - If recurrence occurs >6 months after completing 1 year (9 cycles) of adjuvant pembrolizumab and before the end of year 5, patients not eligible for surgical resection may receive retreatment with pembrolizumab (≤18 cycles)
- Treatment will be discontinued during either phase upon disease recurrence, start of new anticancer treatment, unacceptable toxicity, or investigator or patient decision to withdraw

Figure 2. Study Design



R, randomization.
[a]Patients randomly assigned to receive placebo are eligible for crossover to pembrolizumab if disease recurrence occurs before the end of year 5 and must begin treatment with pembrolizumab within 12 weeks of disease recurrence.
[b]Patients randomly assigned to receive pembrolizumab are eligible for retreatment if disease recurs >6 months after completion of 9 cycles of adjuvant therapy and before the end of year 5.

Patient Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 years • Histologically confirmed cSCC as the primary site of malignancy[a] • Complete macroscopic resection of all known cSCC disease, with or without microscopic positive margins • Histologically confirmed, locally advanced cSCC with ≥1 of the following high-risk features – Histologically involved nodal disease that has extracapsular extension, with either ≥1 lymph node >2 cm in greatest diameter or ≥2 lymph nodes involved – Any index tumor with ≥2 of the following features • Tumor ≥4 cm with a depth >6 mm or invasion beyond subcutaneous fat • Multifocal perineural invasion for nerves of <0.1 mm diameter (3 or more foci) or any involved nerve ≥0.1 mm diameter • Poor differentiation and/or sarcomatoid and/or spindle cell histology • Recurrent disease (any cSCC that recurs within 3 years in the previously surgically or topically treated area) • Satellite lesions (satellitosis) and/or in transit metastases – Gross cortical bone invasion or skull base and/or skull base foramen invasion • Completed adjuvant RT (≥45 Gy) for locally advanced cSCC, with last dose of RT ≥4 weeks and ≤16 weeks from randomization • Disease-free as assessed by the investigator, with complete radiographic staging assessment ≤28 days from randomization • Adequate tumor tissue sample for PD-L1 testing as determined by central laboratory[b] • Life expectancy >3 months • ECOG PS 0 or 1 • Adequate organ function	• Macroscopic residual disease after surgery and/or recurrence with active cSCC disease before randomization • Presence of any histologic type of skin cancer other than invasive cSCC • Prior therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent, or with an agent directed to another co-stimulatory or co-inhibitory T-cell receptor • Prior systemic anticancer therapy, including investigational agents, for cSCC ≤4 weeks before randomization[c] • Not yet recovered from all acute RT-related toxicities, or had radiation pneumonitis • Receipt of a live vaccine within 30 days before first dose of study treatment • Diagnosis of immunodeficiency or receipt of long-term systemic steroid therapy or any other form of immunosuppressive therapy within 7 days before first dose of study drug • Active central nervous system metastases and/or carcinomatous meningitis • Active autoimmune disease that necessitated systemic treatment in the past 2 years • Current pneumonitis or history of noninfectious pneumonitis that necessitated steroids • Active infection necessitating systemic therapy

ECOG PS, Eastern Cooperative Oncology Group performance status.
[a]Metastatic skin involved from another primary cancer or an unknown primary cancer is not permitted; patients with tumors arising on cutaneous nonglabrous (hair-bearing) lip with extension onto vermillion (dry red lip) or for whom the primary site is the nose (skin, not nasal mucosa with outward extension to skin) may be eligible.
[b]Tissue sample may be obtained from the surgical resection or an earlier archival tissue specimen not previously irradiated. Patients for whom PD-L1 testing cannot be performed because of the infeasibility of testing the sample will not be eligible; patients will not be excluded if tissue was initially thought to be adequate but a PD-L1 result could not be reported for any reason. Central pathologic review for PD-L1 will not be performed before randomization.
[c]Patients must have recovered to grade 1 or baseline from all adverse events caused by previous therapies; patients with grade 2 neuropathy may be eligible. If patients underwent major surgery, they must have adequately recovered from toxicity, complications from the intervention, or both.

Assessments and Follow-Up

- Computed tomography or magnetic resonance imaging will be performed during screening and subsequently every 12 weeks (±7 days) until year 2, then every 6 months (±14 days) until the end of year 5, or more frequently if clinically indicated during treatment
  - Tumor imaging will continue to be performed until biopsy-proven disease recurrence, the start of new anticancer treatment, withdrawal of consent, pregnancy, death, or the end of the study
- In the crossover or retreatment phase, radiographic imaging will be performed before treatment with pembrolizumab (≤28 days) and every 12 weeks (±7 days) after the restart of treatment until year 2 or until disease progression, the start of new anticancer treatment, withdrawal of consent, pregnancy, death, or notification by the sponsor
- Patient-reported outcomes (PROs) will be administered by trained site personnel on day 1 of cycles 1-3, then every 12 weeks until the end of year 2
- Adverse events (AEs) will be monitored throughout the study from the time of randomization to 30 days after the last dose of study treatment (90 days for serious AEs), and severity will be graded according to the guidelines outlined in the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0

Analyses

Efficacy

- All randomly assigned patients will be included in the intention-to-treat population, and their data will be analyzed for efficacy
- Comparison of RFS and OS in the pembrolizumab and placebo treatment arms will be performed using a stratified log-rank test; the hazard ratio will be estimated using a stratified Cox proportional hazards model with the Efron method of tie handling
  - The Kaplan-Meier method will be used to estimate RFS and OS event rates over time

Safety

- Data of all randomly assigned patients who received ≥1 dose of study treatment will be analyzed for safety
- The analysis of safety results will follow a tiered approach based on the number of events observed to provide point estimates with 95% CIs for differences in the proportion of patients with events or point estimates only

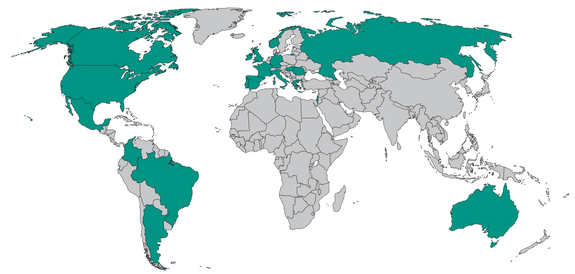
PROs

- Patients who have ≥1 PRO assessment and receive ≥1 dose of study drug will be included in the PRO analysis population
- A constrained longitudinal data analysis model will be applied to the PRO data to assess the treatment effects on the change from baseline in global health status and physical function scores; differences in the least squares mean change from baseline will also be evaluated

Status

- KEYNOTE-630 is ongoing in 20 countries (**Figure 3**)

Figure 3. Countries With Sites of Enrollment for KEYNOTE-630 (shown in green)



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