KEYNOTE-826: A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Pembrolizumab Plus Chemotherapy for First-line Treatment of Persistent, Recurrent, or Metastatic Cervical Cancer

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BACKGROUND

- Cervical cancer arises in the setting of persistent infection with high-risk human papillomavirus subtypes¹
- Women with recurrent/metastatic disease represent a poor prognostic group with unmet clinical needs¹
 - Incorporation of antiangiogenesis therapy to standard treatment has emerged as a therapeutic option, but the survival benefit of 3.7 months over chemotherapy alone is modest¹
- Pembrolizumab is a selective, humanized immunoglobulin G4k monoclonal antibody that prevents the interaction between programmed death receptor-1 (PD-1), expressed by lymphocytes, and its ligands, PD-L1 and PD-L2, expressed by tumor cells (**Figure 1**)²
- On the basis of the 14.3% objective response for pembrolizumab monotherapy in the cervical cancer cohort of KEYNOTE-158,³ the US Food and Drug Administration granted accelerated approval to pembrolizumab in June 2018 for treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (combined positive score ≥ 1)²
 - On the basis of these promising results and the unmet clinical needs, combination therapy with pembrolizumab and chemotherapy will be investigated in a first-line setting for advanced cervical cancer

Figure 1. Pembrolizumab and the PD-1 Pathway

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

OBJECTIVES

Primary

- Evaluate overall survival (OS) and progression-free survival (PFS), as assessed by blinded independent radiology review via RECIST v1.1, of frontline chemotherapy with and without pembrolizumab in women with recurrent and/or metastatic cervical cancer

Secondary

- Evaluate objective response, duration of response, 12-month PFS, health-related quality of life, and safety and tolerability

DESIGN

- KEYNOTE-826 is a phase 3, randomized, double-blind, placebo-controlled, multinational trial of pembrolizumab + chemotherapy vs placebo + chemotherapy for first-line treatment of recurrent, persistent, or metastatic cervical cancer (ClinicalTrials.gov identifier, NCT03635567)
- Eligible patients will be randomized 1:1 to pembrolizumab + chemotherapy 200 mg intravenously (IV) or placebo + chemotherapy every 3 weeks (**Figure 2**)
 - The chemotherapy regimen (paclitaxel 175 mg/m² IV + cisplatin 50 mg/m² or carboplatin AUC 5 IV, with or without bevacizumab 15 mg/kg IV) will be selected by the investigator before randomization
- Patients will be stratified according to metastatic status at diagnosis (primary metastatic or recurrent disease), planned bevacizumab use (yes or no), and PD-L1 status (combined positive score <1 , 1 to <10 , or ≥ 10)

Figure 2. KEYNOTE-826 Study Design

Study treatments administered on day 1 of each 3-week treatment cycle; cisplatin may be administered on day 2 of each cycle per local practice. CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; PD-L1, programmed death ligand-1; PS, performance status; Q3W, every 3 weeks.

Endpoints and Assessments

- Primary endpoints
 - PFS per RECIST v1.1 (assessed by blinded independent central review)
 - OS
- Secondary endpoints
 - Objective response
 - Duration of response
 - 12-month PFS
 - Patient-reported quality of life using the European Organisation for Research and Treatment of Cancer global score (questionnaires administered before dosing on day 1 of cycles 1-14, every other cycle thereafter, at end of treatment, and at safety follow-up)
 - Safety and tolerability
- Imaging assessments of disease status will be performed every 9 weeks from the date of randomization through week 54 and every 12 weeks thereafter

Patient Eligibility Criteria

Key Inclusion Criteria
<ul style="list-style-type: none">Women aged ≥ 18 yearsPersistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix not previously treated with systemic chemotherapy and not amenable to curative treatment (eg, surgery or radiation)^aMeasurable disease per RECIST v1.1 criteriaECOG PS of 0 to 1
Key Exclusion Criteria
<ul style="list-style-type: none">Pregnant or positive urine pregnancy test within 72 hours before randomization, breastfeeding, or of childbearing potential and not using contraception during treatment periodActive central nervous system metastases, carcinomatous meningitis, or additional malignancy that is progressing or has required active treatmentDiagnosis of immunodeficiency or receiving immunosuppressive therapyActive infection requiring systemic therapyPrior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed at another stimulatory or co-inhibitory T-cell receptor

ECOG, Eastern Cooperative Oncology Group; PD-1, programmed death receptor-1; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; PS, performance status.
^aPrior chemotherapy utilized as a radiosensitizing agent and completed ≥ 2 weeks before randomization with resolution of all radiation-related toxicities is allowed.

STATUS

- Planned enrollment is approximately 600 patients from 126 sites in the United States, Argentina, Australia, Canada, Chile, Colombia, France, Germany, Israel, Italy, Japan, Republic of Korea, Mexico, Peru, Russia, Spain, Taiwan, Turkey, and Ukraine (**Figure 3**)

Figure 3. Countries with Planned Enrollment Sites for KEYNOTE-826 (shown in green)

References

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