RXADVANCE
2 Park Central Drive
Southborough, MA 01772

Keytruda (pembrolizumab) for Injection
Clinical Update

Clinical update: FDA Approves Second Biomarker-Based Indication for Merck's Keytruda (pembrolizumab), Regardless of Tumor Type.
FDA approval date: June 16, 2020

Keytruda is an anti-PD-1 therapy that works by increasing the ability of the body's immune system to help detect and fight tumor cells. Keytruda is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes which may affect both tumor cells and healthy cells. It is indicated for the treatment of melanoma, non-small cell lung cancer, small cell lung cancer, head and neck squamous cell carcinoma, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability-high cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, tumor mutational burden-high (TMB-H) cancer, and cutaneous squamous cell carcinoma.

The accelerated approval was based on data from a prospectively-planned retrospective analysis of 10 cohorts (A through J) of patients with various previously treated unresectable or metastatic solid tumors with TMB-H, who were enrolled in KEYNOTE-158 (NCT02628067), a multicenter, non-randomized, open-label trial evaluating Keytruda (200 mg every three weeks). The trial excluded patients who previously received an anti-PD-1 or other immune-modulating monoclonal antibody, or who had an autoimmune disease, or a medical condition that required immunosuppression. TMB status was assessed using the FoundationOne CDx assay and pre-specified cutpoints of ≥10 and ≥13 mut/Mb, and testing was blinded with respect to clinical outcomes. Tumor response was assessed every nine weeks for the first 12 months and every 12 weeks thereafter. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) in the patients who received at least one dose of Keytruda as assessed by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, modified to follow a maximum of 10 target lesions and a maximum of five target lesions per organ.

In KEYNOTE-158, 1,050 patients were included in the efficacy analysis population. TMB was analyzed in the subset of 790 patients with sufficient tissue for testing based on protocol-specified testing requirements. Of the 790 patients, 102 (13%) had tumors identified as TMB-H, defined as TMB ≥10 mut/Mb. The study population characteristics of these 102 patients were: median age of 61 years (range, 27 to 80); 34% age 65 or older; 34% male; 81% White; and 41% Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 and 58% ECOG PS of 1. Fifty-six percent of patients had at least two prior lines of therapy.

In the 102 patients whose tumors were TMB-H, Keytruda demonstrated an ORR of 29% (95% CI, 21-39), with a complete response rate of 4% and a partial response rate of 25%. After a median follow-up time of 11.1 months, the median DOR had not been reached (range, 2.2+ to 34.8+ months). Among the 30 responding patients, 57% had ongoing responses of 12 months or longer, and 50% had ongoing responses of 24 months or longer.

In a pre-specified analysis of patients with TMB ≥13 mut/Mb (n=70), Keytruda demonstrated an ORR of 37% (95% CI, 26-50), with a complete response rate of 3% and a partial response rate of 34%. After a median follow-up time of 11.1 months, the median DOR had not been reached (range, 2.2+ to 34.8+ months). Among the 26 responding patients, 58% had ongoing responses of 12 months or longer, and 50% had ongoing responses of 24 months or longer. In an exploratory analysis in 32 patients whose cancer had TMB ≥10 mut/Mb and <13 mut/Mb, the ORR was 13% (95% CI, 4-29), including two complete responses and two partial responses.

Immune-mediated adverse reactions, which may be severe or fatal, can occur with Keytruda, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, severe skin reactions, solid

organ transplant rejection, and complications of allogeneic hematopoietic stem cell transplantation (HSCT). Based on the severity of the adverse reaction, Keytruda should be withheld or discontinued.
Keytruda can cause fetal harm when administered to a pregnant woman.