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Keytruda (pembrolizumab) Injection
Clinical Update

Clinical Update: FDA approved Keytruda (pembrolizumab) as First line treatment of Patients with Unresectable or Metastatic MSI-H or dMMR Colorectal Cancer.
FDA approval date: June 29, 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.

Keytruda (pembrolizumab) 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.

U.S. Food and Drug Administration (FDA) has approved Keytruda, Merck's anti-PD-1 therapy, as monotherapy for the first-line treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer.
The approval was based on data from KEYNOTE-177 (NCT02563002), a multi-center, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR colorectal cancer.
Patients were randomized 1:1 to receive Keytruda 200 mg intravenously every three weeks or investigator's choice of the following chemotherapy regimens given intravenously every two weeks:

- mFOLFOX6 (oxaliplatin, leucovorin, and fluorouracil) or mFOLFOX6 in combination with either bevacizumab or cetuximab: oxaliplatin 85 mg/m2, leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2), and fluorouracil 400 mg/m^2 bolus on Day 1, then fluorouracil 2,400 mg/m2 over 46-48 hours; plus bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m^2 on first infusion, then 250 mg/m^2 weekly.
- FOLFIRI (irinotecan, leucovorin, and fluorouracil) or FOLFIRI in combination with either bevacizumab or cetuximab: irinotecan 180 mg/m^2, leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2), and fluorouracil 400 mg/m^2 bolus on Day 1, then fluorouracil 2,400 mg/m2 over 46-48 hours; plus bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m^2 on first infusion, then 250 mg/m^2 weekly.

Treatment with Keytruda or chemotherapy continued until Response Evaluation Criteria in Solid Tumors (RECIST) v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with Keytruda without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every nine weeks. Patients randomized to chemotherapy were offered Keytruda at the time of disease progression. The main efficacy outcome measure was progression-free survival (PFS) as assessed by blinded independent central review (BICR) according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of five target lesions per organ, and overall survival (OS). Additional efficacy outcome measures were objective response rate (ORR) and duration of response (DOR).

Patients were enrolled and randomized to Keytruda (n=153) or chemotherapy (n=154). The baseline characteristics of these 307 patients were: median age of 63 years (range, 24 to 93), 47% age 65 or older; 50% male; 75% White and 16% Asian; 52% had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, and 48% had an ECOG PS of 1; and 27% received prior adjuvant or neoadjuvant chemotherapy. Among the 154 patients randomized to receive chemotherapy, 143 received chemotherapy per the protocol. Of these 143 patients, 56% received

mFOLFOX6, 44% received FOLFIRI, 70% received bevacizumab plus mFOLFOX6 or FOLFIRI, and 11% received cetuximab plus mFOLFOX6 or FOLFIRI. The median follow-up time was 27.6 months (range, 0.2 to 48.3 months).

In this study, Keytruda monotherapy significantly reduced the risk of disease progression or death by 40% (HR=0.60 [95% CI, 0.45-0.80; p=0.0004]) and showed a median PFS of 16.5 months (95% CI, 5.4-32.4) compared with 8.2 months (95% CI, 6.1-10.2) for patients treated with chemotherapy. For PFS, in the Keytruda arm, there were 82 patients (54%) with an event versus 113 patients (73%) in the chemotherapy arm. For patients treated with Keytruda, the ORR was 44% (95% CI, 35.8-52.0), with a complete response rate of 11% and a partial response rate of 33%, and for patients treated with chemotherapy, the ORR was 33% (95% CI, 25.8-41.1), with a complete response rate of 4% and a partial response rate of 29%. Median DOR was not reached (range, 2.3+ to 41.4+) with Keytruda versus 10.6 months (range, 2.8 to 37.5+) with chemotherapy. Based on 67 patients with a response in the Keytruda arm and 51 patients with a response in the chemotherapy arm, 75% in the Keytruda arm had a duration of response greater than or equal to 12 months versus 37% in the chemotherapy arm, and 43% in the Keytruda arm had a duration of response greater than or equal to 24 months versus 18% in the chemotherapy arm.

Among the 153 patients with MSI-H or dMMR colorectal cancer treated with Keytruda, the median duration of exposure to Keytruda was 11.1 months (range, 1 day to 30.6 months). Adverse reactions occurring in patients with MSI-H or dMMR colorectal cancer were similar to those occurring in 2,799 patients with melanoma or non-small cell lung cancer treated with Keytruda as a single agent.