Report KEYTRUDA® - Pembrolizumab

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: Pembrolizumab **Brand Name:** Keytruda **Originator/licensee:** Merck Sharp & Dohme B.V. **Classification:**NI **ATC code:**L01FF02 **OrphanStatus:** **Eu:** No **Us:** Yes **Mechanism of action:** Pembrolizumab, is a monoclonal antibody, a protein that has been designed to recognise and block a receptor called PD-1. Some cancers can make a protein (PD-L1) that combines with PD-1 to switch off the activity of certain cells of the immune system, preventing them from attacking the cancer. By blocking PD-1, pembrolizumab stops the cancer switching off these immune cells, thereby increasing the immune system's ability to kill the cancer cells. [1]	**Authorized Indication:** **EMA**: non-small cell lung carcinoma (NSCLC): in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults. [2] **FDA**: for the treatment of patients with resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.[3] **Route of administration:** IV **Licensing status** **EU CHMP P.O. date:**22/02/2024 **FDA M.A. date:**16/10/2023 **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** No --- **ABBREVIATIONS:** **AE:** adverse event **CI:** confidence interval **CHMP:** Committee for Medicinal Products for Human Use **C.I.**: confidence interval **EFS:** Event Free Survival **HR**: Hazard Ratio **M.A.:** Marketing Authorization **P.O.:** Positive Opinion **Pts:** patients **NSCLC:**non-small cell lung cancer **OS:** Overall Survival **TEAE:** Treatment Emergent Adverse Events	**Summary of clinical EFFICACY:** **KEYNOTE-671 (NCT03425643):**a phase III, multicenter, randomized, double-blind, placebo-controlled trial conducted in n=797 pts with previously untreated and resectable Stage II, IIIA, or IIIB (N2) NSCLC. Pts were enrolled regardless of tumor PD-L1 expression. Pts with active autoimmune disease that required systemic therapy within 2 years of treatment, a medical condition that required immunosuppression, or a history of interstitial lung disease or pneumonitis that required steroids were ineligible. Randomization was stratified by stage (II vs. III), tumor PD-L1 expression (TPS ≥50% or <50%), histology (squamous or nonsquamous), and geographic region (East Asia or non-East Asia). Pts were randomized (1:1) to one of the following treatment arms: • Treatment Arm A: neoadjuvant KEYTRUDA 200 mg on Day 1 in combination with cisplatin 75 mg/m2 and either pemetrexed 500 mg/m2 on Day 1 or gemcitabine 1000 mg/m2 on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Within 4-12 weeks following surgery, pembrolizumab 200 mg was administered every 3 weeks for up to 13 cycles. • Treatment Arm B: neoadjuvant placebo on Day 1 in combination with cisplatin 75 mg/m2 and either pemetrexed 500 mg/m2 on Day 1 or gemcitabine 1000 mg/m2 on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Within 4-12 weeks following surgery, placebo was administered every 3 weeks for up to 13 cycles. [3] The dual primary endpoints were EFS (the time from randomization to the first occurrence of local progression that precluded the planned surgery, unresectable tumor, progression or recurrence, or death) and OS. A total of 397 participants were assigned to the pembrolizumab group, and 400 to the placebo group. At the prespecified first interim analysis, the median follow-up was 25.2 months. Event-free survival at 24 months was 62.4% in the pembrolizumab group and 40.6% in the placebo group (HR for progression, recurrence, or death: 0.58; 95% CI: 0.46 - 0.72; P<0.001). The estimated 24-month OS was 80.9% in the pembrolizumab group and 77.6% in the placebo group (P=0.02, which did not meet the statistical significance)[7]. **Summary of clinical SAFETY:**serious adverse reactions occurred in 34% of patients who received pembrolizumabin combination with platinum-containing chemotherapy as neoadjuvant treatment; the most frequent (≥2%) serious adverse reactions were pneumonia (4.8%), venous thromboembolism (3.3%), and anemia (2%). Fatal adverse reactions occurred in 1.3% of patients, including death due to unknown cause (0.8%), sepsis (0.3%) and immune-mediated lung disease (0.3%). Of the patients who received single agent pembrolizumab as adjuvant treatment, 14% experienced serious adverse reactions; the most frequent serious adverse reaction was pneumonia (3.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of adjuvant pembrolizumab due to an adverse reaction occurred in 12% of patients; the most frequent (≥1%) adverse reactions that led to permanent discontinuation of adjuvant pembrolizumab were diarrhea (1.7%), interstitial lung disease (1.4%), AST increased (1%), and musculoskeletal pain (1%).[3] **Ongoing studies:** ● ***For the same indication:*** Yes ● ***For other indications:*** Yes **Discontinued studies (for the same indication):**No --- **References:** [1] https://www.ema.europa.eu/en/documents/overview/keytruda-epar-medicine-overview_en.pdf [2] https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-keytruda-ii-134_en.pdf [3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125514s139lbl.pdf [4] https://gallery.farmadati.it/Home.aspx [5] https://www.aiom.it/wp-content/uploads/2023/12/2023_AIOM_NDC-web.pdf [6] https://www.io.nihr.ac.uk/wp-content/uploads/2022/03/24150-Pembrolizumab-with-Chemotherapy-for-Non-Small-Cell-Lung-Cancer-V1.0-FEB2022-NONCONF.pdf [7] https://www.nejm.org/doi/10.1056/NEJMoa2302983?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed	**Cost of therapy:** Ex-factory price: €3,532.45 per 25 mg/ml concentrate for intravenous infusion solution.[4] **Epidemiology:**There are approximately 44,000 new lung cancer diagnoses in Italy, and about 85% of them are NSMCL. There are estimated 2900 cases per year in Veneto. [5] **POSSIBLE PLACE IN THERAPY:** Treatment options for NSCLC depend on the stage of the cancer, the patient's overall health, and other factors. The main treatments for NSCLC include: surgery that depends on the location and size of the tumor, radiotherapy, chemotherapy, target therapy (EGFR inhibitors, ALK inhibitors, ROS1 inhibitors and BRAF inhibitors).Pembrolizumab, in combination with chemotherapy as a neoadjuvant therapy, followed by pembrolizumab as adjuvant monotherapy, could offer an additional treatment option for pts with early-stage, operable NSCLC, who currently have no approved neoadjuvant/adjuvant immunotherapy treatment options [6]. **OTHER INDICATIONS IN DEVELOPMENT: (NCT02853344)** Renal Cell Carcinoma, **(NCT03713593)** Hepatocellular Carcinoma, **(NCT02674061)** Ovarian Cancer. **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT**: - **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** Yes *Service reorganization: No *Possible off label use: Yes

Issued on February 2024