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:** L01XC18 **Orphan Status:** **Eu:** No **Us:** Yes **Mechanism of action:** Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth. [1].	**Authorized Indication:** **EMA:** pembro, in combination with platinum and fluoropyrimidine based chemo, is indicated for the first-line treatment of pts with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative GEJ adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10 [2]. **FDA:** Esophageal Cancer for the treatment of pts with locally advanced or metastatic esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either: - in combination with platinum- and fluoropyrimidine-based chemo, or - as a single agent after one or more prior lines of systemic therapy for pts with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test [1]. **Route of administration:** IV **Licensing status** **EU CHMP P.O. date:** 20/05/2021 **FDA M.A. date:** 22/03/2021 **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** No **-----** **ABBREVIATIONS:** **AE:** adverse event; **Chemo:** chemotherapy; **CPS:** combined positive score; **ESCC:** esophageal squamous cell carcinoma; **GEJ:** gastroesophageal junction; **HR:** hazard ratio; **IV:** intravenous; **M.A.:** Marketing Authorization; **NSCLC:** non small cell lung cancer; **OS:** overall survival; **PBO:** placebo; **Pembro:** pembrolizumab; **PDL-1:** programmed death-ligand1; **PFS:** progression free survival; **P.O.:** Positive Opinion; **Pts:** patients; **Q3W:** every 3 weeks	**Summary of clinical EFFICACY:** **KEYNOTE-590 (NCT03189719):** is a randomized, double-blind, PBO-controlled phase III study that enrolled 749 adult pts with a histologically or cytologically confirmed diagnosis of locally advanced unresectable or metastatic adenocarcinoma or ESCC or with advanced/metastatic Siewert Type 1 adenocarcinoma of the GEJ. Pts who received prior systemic therapy in the locally advanced or metastatic setting were ineligible. Subjects were randomized 1:1 to receive pembro 200 mg or PBO IV Q3W in combination with chemo, up to 35 cycles. The chemo regimen for both arms consisted of cisplatin 80 mg/m^2 IV Q3W (max. 6 doses) plus 5-fluorouracil 800 mg/m2 continuous IV infusion on days 1-5 Q3W. Primary endpoints were PFS and OS in all pts and in the subgroup of pts with a PD-L1 CPS ≥10. In a pre-specified formal test of OS in pts with PD-L1 CPS ≥ 10 (n=383), the median OS was 13.5 months (95% CI: 11.1, 15.6) for the pembro arm and 9.4 months (95% CI: 8.0, 10.7) for the PBO arm, with a HR of 0.62 (95% CI: 0.49, 0.78; p-Value < 0.0001). In an exploratory analysis, in pts with PD-L1 CPS < 10 (n=347), the median OS was 10.5 months (95% CI: 9.7, 13.5) for the pembro arm and 10.6 months (95% CI: 8.8, 12.0) for the PBO arm, with a HR of 0.86 (95% CI: 0.68, 1.10) [1][3][4]. **Summary of clinical SAFETY:** **KEYNOTE-590 (NCT03189719):** pembro was discontinued for AEs in 15% of pts. The most common AEs resulting in permanent discontinuation of pembro (≥1%) were pneumonitis (1.6%), acute kidney injury (1.1%), and pneumonia (1.1%). AEs leading to interruption of pembro occurred in 67% of pts and the most common (≥2%) were neutropenia (19%), fatigue/asthenia (8%), decreased white blood cell count (5%), pneumonia (5%), decreased appetite (4.3%), anemia (3.2%), increased blood creatinine (3.2%), stomatitis (3.2%), malaise (3.0%), thrombocytopenia (3%), pneumonitis (2.7%), diarrhea (2.4%), dysphagia (2.2%), and nausea (2.2%).[1] **Ongoing studies:** • ***For the same indication:*** Yes • ***For other indications:*** Yes [Phase III, but if it is an O/OE drug, also Phase II] **Discontinued studies (for the same indication):** No **References:** **[1].** https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s096lbl.pdf **[2].** https://www.ema.europa.eu/en/medicines/human/summaries-opinion/keytruda-3 **[3].** https://clinicaltrials.gov/ct2/show/NCT03189719 **[4].** Kato K, Shah MA, Enzinger P, et al. KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer. Future Oncol. 2019;15(10):1057-1066. doi:10.2217/fon-2018-0609 **[5].** https://gallery.farmadati.it/Home.aspx **[6].** WHO. GLOBOCAN 2012 estimated cancer incidence, mortality and prevalence worldwide. http://globocan.iarc.fr/Def ault.aspx **[7].** Bossetti C, Bertuccio P, Levi F et Al, "Cancer Mortality in the European Union, 1970 – 2003, with a joinpoint analysis" Ann Oncol 2008; 19: 631-640 **[8].** Linee Guida AIOM Tumori dell'Esofago, Edizione 2019 **[9].** National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Esophageal and esophagogastric junction cancers. Version 2.2018. www.nccn.org/professionals/physician gls/default.aspx **[10].** Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 27(Suppl. 5), v50–v57 (2016). **[11].**https://clinicaltrials.gov/ct2/results?cond=&term=&intr=Pembrolizumab&cntry=&state=&city=&dist=&recrs=a&recrs=b&recrs=d&recrs=e&recrs=f&type=Intr&phase=2 **[12].**https://clinicaltrials.gov/ct2/results?cond=Oesophageal+Cancer&term=&type=Intr&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=	**Economic impact:** 5,657.57 €* for 1 IV vial 4 mL (25 mg/mL) [5]. Price for 1 cycle: 11,315.14 € **retail price including VAT* **Epidemiology:** esophageal cancer is the 8th most commonly diagnosed cancer worldwide and the 6th most common cause of cancer-related death (incidence, approximately 456,000; mortality, 400,000 in 2012) [6]. In EU 43,700 new cases/year, 20,750 deaths in men and 6,950 in women, with considerable geographical variability, are estimated [7]. In Italy, the Cancer Registries recently estimate 2,025 new cases/year in males and 548 cases/year in females with higher rates in the North-Eastern regions and in Lombardy, lower in the Southern regions [8]. ----- **POSSIBLE PLACE IN THERAPY:** Treatment options for pts with unresectable advanced or metastatic esophageal or GEJ cancer are limited. Currently for the first-line treatment of advanced or metastatic disease is recommended platinum-based Chemo in combination with fluoropyrimidine [9][10]. **OTHER INDICATIONS IN DEVELOPMENT:** Head and Neck Squamous Cell Carcinoma, NSCLC; Lung Neoplasms; Merkel Cell Carcinoma; Hepatocellular Carcinoma; Melanoma, other [11]. **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:** / **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** regorafenib, nivolumab, docetaxel/paclitaxel, cetuximab, camrelizumab, other [12] [if it is ..] *Service reorganization: Yes *Possible off label use: Yes

Issued on June 2021