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 **OrphanStatus:** **Eu:** No **Us:** No **Mechanism of action:** pembrolizumab is a humanised monoclonal antibody which binds to the PD-1 receptor and blocks its interaction with ligands PD-L1 and PD-L2[1].	**Authorized Indication:** **EMA:** pembrolizumab, in combination with chemotherapy, isindicated for the treatment of locally recurrent unresectable or metastatic TNBC in adults whose tumors express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease[2]. **FDA:** In combination with chemotherapy, for the treatment of pts with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 [CPS≥10]as determined by an FDA approved test [3]. **Route of administration:**IV **Licensing status** **EU CHMP M.A. date:**19/10/2021 **FDA M.A. date:** 13/11/2020 **EU Speed Approval Pathway:** - **FDA Speed Approval Pathway:** Yes **-----** **ABBREVIATIONS:** **BICR:** blinded independent central review **CHMP:** Committee for Medicinal Products for Human Use **CPS**: combined positive score **ESMO:** European Society for Medical Oncology **HR:** hazard ratio **ITT:**intention-to-treat **M.A.:** Marketing Authorization **OS:** overall survival **p:** p-Value **PARPis:** polyadenosine diphosphate-ribose polymerase inhibitors **PD-1:**programmed cell death protein 1 **PD-L1**: Programmed Cell Death Receptor- Ligand 1 **PD-L2**: Programmed Cell Death Receptor- Ligand 2 **PFS:** progression-free survival **pts:** patients **RECIST 1.1:** Response Evaluation Criteria in Solid Tumors version 1.1 **TNBC**: Triple-Negative Breast Cancer **TRAE:** Treatment-related adverse events **vs.:** versus	**Summary of clinical EFFICACY:** **KEYNOTE-355 (NCT02819518)**is a placebo-controlled, double blind, phase 3 trial, in pts with untreated locally recurrent inoperable or metastatic TNBC. Pts were randomly assigned (2:1) to pembrolizumab 200 mg every three weeks plus chemotherapy (nab-paclitaxel; paclitaxel; or gemcitabine/carboplatin) or placebo every three weeks plus chemotherapy.Among the 847 enrolled pts: 636 (75%) had tumors that expressed PD-L1with a CPS ≥ 1 and 323 (38%) had tumor PD-L1 expression CPS ≥ 10 based on the PD-L1 IHC22C3 pharmDxTM Kit.The dual primary endpoints included PFS as assessed by BICR using RECIST 1.1 and OS.The study demonstrated an improvement in PFS at itspre-specified interim analysisamong pts with CPS ≥ 10: the median PFS was 9.7 months inthe pembrolizumab–chemotherapy arm vs 5.6 months in the placebo–chemotherapy arm (HR: 0.65, 95% CI 0.49–0.86; one-sided p=0·0012). In the final analysis OS was 23.0 months in pembrolizumab–chemotherapy arm vs. 16.1 months in placebo–chemotherapyarm[HR0.73; 95% CI 0.55-0.95; p=0.0093]. [3]. **Summary of clinical SAFETY:** TRAE occurred in 96% of the pts in the pembrolizumab–chemotherapy arm and 95% of the subjects in the placebo–chemotherapy arm, and included (pembrolizumab-chemotherapy vs. placebo-chemotherapy, respectively): anemia (49% vs 46%), neutropenia (41% vs 38%), and nausea (39% vs 41%). TRAE led to death in two pts(<1%) in the pembrolizumab–chemotherapy group (one from acute kidney injury and one from pneumonia) and no pts in the placebo–chemotherapy group. Immune-mediated AESs occurred in 26% of the subjects in the pembrolizumab–chemotherapy armvs 6% of the pts in the placebo–chemotherapy arm [4-5]. **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/assessment-report/keytruda-epar-public-assessment-report_en.pdf 2. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/keytruda-4 3. https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf 4. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s088lbl.pdf 5. Cortes, Javier et al. "Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial." Lancet (London, England) vol. 396,10265 (2020): 1817-1828. doi:10.1016/S0140-6736(20)32531-9 6. https://gallery.farmadati.it/Home.aspx 7. https://www.aiom.it/wp-content/uploads/2020/10/2020_Numeri_Cancro-operatori_web.pdf 8. Gennari, A et al. "ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer." Annals of oncology official journal of the European Society for Medical Oncology, S0923-7534(21)04498-7. 19 Oct. 2021, doi:10.1016/j.annonc.2021.09.019 9. https://clinicaltrials.gov/ct2/results?cond=&term=&type=Intr&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=Pembrolizumab&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= 10. https://clinicaltrials.gov/ct2/results?cond=Triple+Negative+Breast+Cancer&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=Intr&rslt=&phase=2&Search=Apply	**Cost of therapy:** In Italy, IV 4 mL vial (25 mg/mL) of pembrolizumabcosts 3,428.00 €(*ex-factory price*) [6]. The recommended dose of pembrolizumab is200 mg every three weeks,therefore one cycle costs6,856.00€[3]. **Epidemiology:** In Italy, among women, breast cancer is the most common cancer, with 54,976 new diagnoses estimated for 2020. Around 15%-20% of breast cancers are classifiedas TNBC. More thanone-third of pts with TNBC will presentdistant metastases, either recurrent or denovo metastatic disease. [7-8] ----- **POSSIBLE PLACE IN THERAPY** For pts PD-L1-positive mTNBC ESMO recommends 1st-line of treatment: atezolizumab–nab-paclitaxelorpembrolizumab–chemotherapy; 2nd-line of treatment: sacituzumabgovitecan 3rd-line: chemotherapy(eribulin, capecitabine or vinorelbine) .[8] **OTHER INDICATIONS IN DEVELOPMENT:** squamous cell carcinoma of head and neck, non-small-cell lung carcinoma, Merkel cell carcinoma, hepatocellular carcinoma, melanoma, urinary bladder cancer, urothelial carcinoma, renal cell carcinoma, Hodgkin lymphoma, and other[8] **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:**- **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION** camrelizumab, olaparib+pembro, serplulimab, etoposide+anlotinib,anlotinib+tislelizumab+anthracycline/nab-paclitaxel, zoledronate, ipatasertib, toripalimab+nab-paclitaxel,trilaciclib, epetraborole, capivasertib, eryaspase+chemotherapy, alpelisib + nab-paclitaxel [9] *Service reorganization Y/N: Yes *Possible off label use Y/N: Yes

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