Report OPDIVO® Nivolumab

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: nivolumab **Brand Name:** Opdivo® **Originator/licensee:** Bristol-Myers Squibb Pharma EEIG **Classification:** NI **ATC code:** L01XC17 **Orphan Status:** **Eu:** No **Us:** Yes **Mechanism of action:** nivolumab is a human IgG4 monoclonal anti-body that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response [1].	**Authorized Indication:** **EMA:** nivolumab, in combination with ipilimumab, is indicated for the first line treatment of adult pts with unresectable MPM [2]. **FDA:** nivolumab is indicated for the treatment of adult pts with unresectable MPM, as first-line treatment in combination with ipilimumab [1]. **Route of administration:** IV **Licensing status** **EU CHMP P.O. date:** 22/04/2021 **FDA M.A. date:** 2/10/2020 **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** No --- **ABBREVIATIONS:** **AEs:** Adverse Events **SAEs:** serious adverse events **CHMP:** Committee for Medicinal Products for Human Use **HR:** hazard ratio **IgG4:** immunoglobulin G4 **IV:** intravenous **M.A.:** Marketing Authorization **MPM:** malignant pleural mesothelioma **N+I:** nivolumab plus ipilimumab **OS**: overall survival **P.O.:** Positive Opinion **PD-1:** Programmed Death-1 **PD-L 1 or 2:** Programmed Death-Ligand 1 or 2. **pts:** patients **Q2W** = Every Two Weeks **Q6W** = Every Six Weeks **SEs:** serious events **vs.:** versus	**Summary of clinical EFFICACY:** **CheckMate743 (NCT02899299):** a global open-label, randomized, controlled, phase III study. Pts were randomly assigned (1:1) to experimental group (n= 303) to receive nivolumab as first line (3 mg/kg IV Q2W) plus ipilimumab (1 mg/kg IV Q6W) and to chemotherapy group (n=302) to receive an IV infusion of cisplatin (75 mg/m ^{2}) or carboplatin (5 mg/mL / min) plus pemetrexed (500 mg/m ^{2}) every three weeks for a maximum of six cycles. Treatment was continued until disease progression, unacceptable toxicity, or for two years in the case of immunotherapy. The primary endpoint was OS; median OS was 18.1 months (95% CI 16.8–21.4) for N+I group vs. 14.1 months (95% CI 12.4–16.2) for chemotherapy group, with HR (stratified by sex and histology) of 0,74 (96.6% CI 0.60–0.91; p=0·002). Overall survival rates at year one were 68% (95% CI 62.3–72.8) vs. 58% (51.7–63.2) and at year two were 41% (35.1–46.5) vs. 27% (21.9–32.4), respectively [3]. **Summary of clinical SAFETY:** Any-grade treatment-related SAEs were reported in 21% pts treated with N+I vs. 8% pts treated with chemotherapy; the most frequently reported SAEs were colitis (3% N+I group vs. <1% chemotherapy group) and anemia (2% N+I group vs. 36% chemotherapy group). Grade 3–4 treatment-related SAEs were reported in 15% pts treated with N+I vs. 6% treated with chemotherapy. Grade 3–4 treatment-related AEs were reported in 30% of pts treated with N+I and 32% of pts treated with chemotherapy. The most frequent any-grade treatment-related AEs were diarrhea (21% N+I group vs. 7% chemotherapy group) and nausea (10% N+I group vs. 37% chemotherapy group). Any-grade treatment-related AEs that led to discontinuation were reported in 23% pts treated with N+I and 16% pts treated with chemotherapy, respectively; grade 3–4 events that led to discontinuation were reported in 15% pts from the N+I group and 7% pts from the chemotherapy group [3]. **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/2021/125554s090lbl.pdf 2. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/opdivo-3 3. https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S0140673620327148?scrollTo=%23hl0001017 4. https://gallery.farmadati.it/Home.aspx 5. https://www.aiom.it/wp-content/uploads/2018/11/2018_LG_AIOM_Mesotelioma.pdf 6. https://link.springer.com/article/10.1007/s12094-020-02532-2#Sec26 7. https://www.aiom.it/wp-content/uploads/2019/10/2019_LG_AIOM_Mesotelioma.pdf 8. https://clinicaltrials.gov/ct2/results?cond=&term=&type=Intr&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=Nivolumab%2FIpilimumab&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= 9. https://clinicaltrials.gov/ct2/results?cond=Malignant+Pleural+Mesothelioma	**Cost of therapy:** Nivolumab Q2W 24ml (10mg/ml): € 5324.15*. The cost for one month-therapy is € 10,648.44 [4]. **Retail price including VAT.* **Epidemiology:** In Italy, in the period 2012-2015 1,495 cases of MPM per year were identified, with a higher incidence in the northern regions, where the use of asbestos has been greater. The frequency of MPM is higher in men, with about 2/3 of all cases [5]. --- **POSSIBLE PLACE IN THERAPY** The first-line treatment for MPM is an association of cisplatin plus pemetrexed for 4-6 cycles. In pts who don't tolerate cisplatin, carboplatin can be used. Gemcitabine or vinorelbine are second-line treatments, while pemetrexed is recommended in pts who have not received it as first-line approach [6][7]. **OTHER INDICATIONS IN DEVELOPMENT** Yes Diffuse Large B-Cell Lymphoma, Metastatic Hormone-Sensitive Prostate Cancer (phase I), Metastatic Uveal Melanoma [8]. **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:** - **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** Yes [9] *Service reorganization: Yes *Possible off label use: Yes

Issued on May 2021