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 **OrphanStatus:** **Eu:** No **Us:** No **Mechanism of action:** Nivolumab is a monoclonal antibody, which binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which may be expressed by tumours or other cells in the tumour environment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands [1].	**Authorized Indication:** **EMA:**nivolumab as monotherapy is indicated for the adjuvant treatment of adults with MIUC with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC [2]. **FDA**: nivolumab is indicated as adjuvant treatment of pts with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection [3]. **Route of administration:** IV **Licensing status** **EU CHMP P.O. date:**24/02/2022 **FDA M.A. date:** 19/08/2021 **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** No ----- **ABBREVIATIONS:** **AEs:** Adverse events **BCG:** bacillus Calmette-Guérin **CHMP**: Committee for Medicinal Product for Human Use **CI**: Confidence Interval **HR**: Hazard Ratio **ITT**: Intention-to-treat **IV**: intravenous **MA**: Marketing Authorization **MIBC**: muscle-invasive bladder carcinoma **MIUC:** muscle Invasive Urothelial Carcinoma **NMIBC:** non-muscle-invasive bladder carcinoma **PD-1:** Programmed Death-1 **PD-L1:** Programmed Death-Ligand 1 **PO**: Positive Opinion **Pts**: patients **TRAEs**: Treatment-related adverse events **Vs**.: versus	**Summary of clinical EFFICACY:** **CheckMate-274 (NCT02632409):**Phase III, multicenter, double-blind, randomized, controlled trial of adjuvant nivolumab as compared with placebo. Eligible pts must have had radical surgery within 120 days before randomization, with or without neoadjuvant cisplatin-based chemotherapy, and pathological evidence of urothelial carcinoma with a high risk of recurrence. Pts (n=709) were assigned in a 1:1 ratio to receive nivolumab 240 mg (n=353) or placebo (n=356) every two weeks as a 30-minutes IV infusion for up to one year or until disease recurrence or discontinuation from the trial. The two primary endpoints were disease-free survival (defined as the time between the date of randomization and the date of first recurrence) among all the pts who underwent randomization and among those with a tumor PD-L1 expression level of 1% or more. The median disease-free survival was 20.8 months (95% CI, 16.5 to 27.6) in the nivolumab group and 10.8 months (95% CI, 8.3 to 13.9) in the placebo group in the ITT population*. The percentage of pts who were alive and disease free at six months was 74.9% with nivolumab and 60.3% with placebo in the ITT population (HR, 0.70; 98.22% CI, 0.55 to 0.90; p<0.001). Among pts with a PD-L1 expression level of 1% or more, the percentage who were alive and disease-free at six months was 74.5% with nivolumab and 55.7% with placebo (HR, 0.55; 98.72% CI, 0.35 to 0.85; p<0.001)[4]. *As for the pts with PD-L1 expression level of 1% or more, there are insufficient number of events to calculate the median disease free-survival. Upper limit number not reached. **Summary of clinical SAFETY:** AEs of any cause occurred in 98.9% of pts in the nivolumab group vs. 95.4% of those in the placebo group; events of grade 3 or higher occurred in 42.7% and 36.8% of the pts in the respective groups. TRAEs of any grade occurred in 77.5% of pts in the nivolumab group vs. 55.5% of those in the placebo group; TRAEs of grade 3 or higher occurred in 17.9% vs. 7.2% of pts in the respective groups. The most common TRAE of any grade in the nivolumab group were pruritus (23.1%), fatigue (17.4%) and diarrhea (16.8%). The most common TRAE of grade 3 or higher in the nivolumab group were elevation in the serum levels of lipase (5.1%) and amylase (3.7%) as well as diarrhea (0.9%), colitis (0.9%), and pneumonitis (0.9%). Treatment-related deaths due to pneumonitis occurred in two pts in the nivolumab group. One treatment-related death due to bowel perforation in the nivolumab group was reported [4]. **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/product-information/opdivo-epar-product-information_en.pdf 2. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/opdivo-7 3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125554s097lbledt.pdf 4. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2034442?articleTools=true 5. https://gallery.farmadati.it/ 6. https://pubmed.ncbi.nlm.nih.gov/28543959/ 7. https://www.cancer.net/cancer-types/bladder-cancer/introduction 8. https://www.aiom.it/wp-content/uploads/2020/12/2020_LG_AIOM_Urotelio.pdf 9. https://pubmed.ncbi.nlm.nih.gov/28489981/ 10. https://pubmed.ncbi.nlm.nih.gov/31443960/ 11. https://pubmed.ncbi.nlm.nih.gov/32360052/ 12. https://www.ioveneto.it/pathology/tumore-della-vescica/ 13. https://clinicaltrials.gov/ct2/home	**Cost of therapy:** Nivolumab 24 ml (10 mg/ml) vial costs €3,226.01 (ex-factory price) [5]. Price for one-month cycle: €6,452.02. **Epidemiology:** Nearly all cases of urothelial carcinoma are represented by bladder cancer, whereas upper tract urothelial carcinoma is a rare subset, accounting for 5-10% of all urothelial malignancies [6]. On the other hand, approximately 90% of bladder tumors are urothelial carcinomas, and other less frequent types of bladder cancer are represented by squamous cell carcinoma and adenocarcinoma [7]. In Italy, it has been estimated that almost 280,000 living people have a previous diagnosis of bladder cancer, and in 2019 29,700 new cases of bladder cancer were recorded (24,000 among men vs 5,700 women). The proportion of pts who recover is approximately 59% of men and 69% of women, and on average 16 years are required to consider a patient recovered [8]. Most pts present non–muscle-invasive disease at diagnosis, but up to 25% have muscle-invasive disease and present or subsequently develop metastatic disease [9]. **POSSIBLE PLACE IN THERAPY** For early-stage/in situ urothelial NMIBC, surgical resection represents the first therapeutic approach, followed by adjuvant intravesical instillations of a chemotherapeutic agent (mitomycin) or of BCG, which stimulates the local immune response. Radical cystectomy is the recommended treatment in highest-risk NMIBC and nonmetastatic MIBC, preceded by cisplatin-based neoadjuvant chemotherapy. For metastatic MIBC, standard 1st-line treatment for fit pts (e.g. with good renal function) is represented by cisplatin-based combination chemotherapy, such as gemcitabine plus cisplatin regimen. 2nd-line therapy is mainly based on immunotherapy with PD-1/PD-L1 inhibitors, including pembrolizumab, nivolumab and atezolizumab [8, 10-12]. **OTHER INDICATIONS IN DEVELOPMENT:** metastatic castration-resistant prostate cancer; other locally advanced or metastatic malignant solid tumors (HR+/HER2- breast cancer, triple negative breast cancer, squamous non-small cell lung cancer, non-squamous non-small cell lung cancer, head and neck cancer, gastric or gastroesophageal junction or esophageal adenocarcinoma) [12]. **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:** No. **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** Yes (rogaratinib, cabazitaxel, retifanlimab + epacadostat) [13]. *Service reorganization Y/N: Yes *Possible off label use Y/N: Yes

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