Report OPDIVO® nivolumab

Product & Mechanism of action

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.

Authorized indications Licensing status

Authorized Indication:
EMA: Nivolumabin combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%[2].

Route of administration: IV

Licensing status
EU CHMP P.O. date:24/02/2022
FDA M.A. date: -
EU Speed Approval Pathway: No
FDA Speed Approval Pathway: -----

ABBREVIATIONS:
AEs: Adverse events
CHMP: Committee for Medicinal Product for Human Use
CI: Confidence Interval
CPS: combined positive score
CTLA-4: Cytotoxic T-lymphocyte-associated antigen 4
IV: intravenous
GOJ: gastro oesaphageal cancer
MA: Marketing Authorization
OS: Overall Survival
PD-1: Programmed Death-1
PD-L1: Programmed Death-Ligand 1
PFS: Progression-free survival
PO: Positive Opinion
Pts: patients
SAEs: Serious Adverse Events
TRAEs: Treatment-related adverse events
vs.: versus

Essential therapeutic features

Summary of clinical EFFICACY:
CheckMate-648(NCT03143153):is an open-label, randomized, phase III trial that enrolled adult pts who had unresectable, advanced, recurrent, or metastatic esophageal squamous-cell carcinoma, regardless of PD-L1 expression status; had disease that was not amenable to curative treatments; and had not received previous systemic therapy for advanced disease. Pts (n=970) were randomly assigned in a 1:1:1 ratio to receive:
- Nivolumab (240 mg IV every two weeks) + chemotherapy (four week-cycle of IV fluorouracil at a dose of 800 mg per square meter of body surface area on days 1 through 5 and IV cisplatin at a dose of 80 mg per square meter on day 1) (n=321);
- Nivolumab (administered IV at a dose of 3 mg per kg of body weight every two weeks) + ipilimumab (administered IV at a dose of 1 mg per kg every six weeks) (n=325);
- Chemotherapy alone (n=324);

Treatment continued until disease progression, unacceptable toxic effects, withdrawal of consent, or the end of the trial. The primary endpoints were OS and PFS.
Results were collected at a 13-month minimum follow up:

	OS (months)	**PFS** (months)
N+C	15.4 (95% CI, 11.9 to 19.5)	6.9 (95% CI, 5.7 to 8.3)
Ch	9.1 (95% CI, 7.7 to 10.0)	4.4 (95% CI, 2.9 to 5.8)
HR	0.54 (99.5% CI, 0.37 to 0.80; p<0.001)	0.65 (98.5% CI, 0.46 to 0.92; p=0.002)
N+I	13.7 (95% CI, 11.2 to 17.0)	4.0 (95% CI, 2.4 to 4.9)
Ch	9.1 (95% CI, 7.7 to 10.0)	4.4 (95% CI, 2.9 to 5.8)
HR	0.64 (98.6% CI, 0.46 to 0.90; p=0.001)	1.02 (98.5% CI, 0.73 to 1.43; p=0.90)

[3].

Summary of clinical SAFETY:
TRAEs of any grade occurred in 96% of pts in the nivolumab + chemotherapy arm, 80% in the nivolumab + ipilimumab arm and 90% in the chemotherapy arm. The most frequently reported TRAEs were nausea (59% vs. 8% vs. 52%), decreased appetite (43% vs. 6% vs. 43%), stomatitis (32% vs. 4% vs. 23%), anemia (30% vs. 4% vs. 22%). TRAEs of grade 3 and 4 occurred respectively in 47% vs. 32% vs. 36% pts in the three study arms. Treatment-related SAEs of any grade were more common with nivolumab + chemotherapy (24%) and nivolumab + ipilimumab (32%) than with chemotherapy alone (16%). The incidence of treatment-related deaths was similar across the groups: 2 % in all treatment arms [3].

Ongoing studies:
- ***For the same indication:*** No.
- ***For other indications:*** Yes.

Discontinued studies (for the same indication): No.

References:

1. https://www.ema.europa.eu/en/medicines/human/EPAR/yervoy
2. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/yervoy-3
3. https://pubmed.ncbi.nlm.nih.gov/35108470/
4. https://gallery.farmadati.it/
5. WHO. GLOBOCAN 2012 estimated cancer incidence, mortality and prevalence worldwide. http://globocan.iarc.fr/Def ault.aspx
6. LineeGuida AIOM Tumoridell'Esofago, Edizione 2019
7. 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
8. 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).
9. https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda
10. https://adisinsight.springer.com/drugs/800006680
11. https://clinicaltrials.gov/ct2/home

NHS impact

Cost of therapy:
Nivolumab 24 ml (10 mg/ml) vial costs €3,226.01 (ex-factory price) [4].
Price for one-month cycle (70 Kg patient): €6,452.02.

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) [5]. 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 [6].

POSSIBLE PLACE IN THERAPY
Treatment options for pts with unresectable advanced or metastatic esophageal or GOJ cancer are limited. Currently for the first-line treatment of advanced or metastatic disease platinum-based chemotherapy in combination with fluoropyrimidine is recommended [7,8]. Pembrolizumab has recently been approved in combination with chemotherapy, for the first-line treatment of adults whose tumours express PD-L1 with a CPS ≥10 [9].

OTHER INDICATIONS IN DEVELOPMENT: Yes (Non-Hodgkin's lymphoma, Bladder cancer, Breast cancer, Multiple myeloma, Prostate cancer) [10].

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT: -

OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION: Yes (Tislelizumab, CS1001) [11].

*Service reorganization Y/N: Yes
*Possible off label use Y/N: Yes

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