Report OPDIVO® Nivolumab

Product & Mechanism of action

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 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 that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, 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 indications Licensing status

Authorized Indication:
EMA: Nivolumab in combination with ipilimumab is indicated for the treatment of adult pts with dMMR or MSI-H mCRC after prior fluoropyrimidine based combination ChT. [2]

FDA: Treatment of adult and paediatric pts 12 years of age and older with MSI-H or dMMR mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with ipilimumab. [3]

Route of administration: IV

Licensing status
EU CHMP P.O. date: 20/05/2021
FDA M.A. date: 10/07/2018

EU Speed Approval Pathway: No
FDA Speed Approval Pathway: Yes

ABBREVIATIONS:
CHMP: Committee for Medicinal Products for Human Use
ChT: Chemotherapy
CRC: colorectal cancer
dMMR: Mismatch repair-deficient
IRRC: Independent radiographic review committee
IV: Intravenous
M.A.: Marketing Authorization
mCRC: Metastatic colorectal cancer
MSI-H: Microsatellite instability-high
ORR: Overall response rate
PD-1: Programmed death-1
PD-L1: Programmed death-1 ligand
PD-L2: Programmed death-2 ligand
P.O.: Positive Opinion
Pts: Patients
TRAE: Treatment-related adverse event

Essential therapeutic features

Summary of clinical EFFICACY:
CHECKMATE-142 (NCT02060188) is a multicenter, non-randomized, multiple parallel-cohort, open-label, phase 2 study conducted in pts with recurrent or mCRC assessed as dMMR or MSI-H. Pts enrolled in the single agent nivolumab cohort (n=74) received nivolumab 3 mg/kg IV every two weeks. Pts enrolled in the nivolumab plus ipilimumab cohort (n=119) received nivolumab 3 mg/kg and ipilimumab 1 mg/kg IV every three weeks for four doses, followed by nivolumab 3 mg/kg IV as a single agent every two weeks. The primary end point was IRRC-assessed ORR per RECIST (version 1.1) [4][5][6]. Results are shown in Table 1 [3].

Table 1: Efficacy results Checkmate-142

	Nivolumab Cohort		Nivolumab + Ipilimumab Cohort	
	All pts (n=74)	Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=53)	All pts (n=119)	Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=82)
IRRC ORR; n (%)	24 (32%)	15 (28%)	58 (49%)	38 (46%)
(95% CI)	(22, 44)	(17, 42)	(39, 58)	(35, 58)

Summary of clinical SAFETY:
In the nivolumab plus ipilimumab cohort, TRAEs were reported in 73% of the enrolled pts (compared to 69% in the nivolumab cohort), with the most common being diarrhoea (22% in both cohorts), fatigue (18% vs 23%), pruritus (17% vs 14%), pyrexia (15% vs 5%), increased AST (14% vs 7%), hypothyroidism (13% vs 10%), nausea (13% vs 10%), increased ALT (12% vs 5%), rash (11% each) and hyperthyroidism (11% vs 0%). Serious any grade TRAEs were reported in 23% of pts (compared to 12% in the nivolumab cohort). Any grade TRAEs led to discontinuation in 13% of pts (compared to 7% in the nivolumab cohort) [5][6].

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-4
[3]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125554s063lbl.pdf
[4].https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-ipilimumab-msi-h-or-dmmr-metastatic-colorectal-cancer
[5]. Overman M.J., Lonardi s. et al.: Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer. Journal of Clinical Oncology. 2018; volume 36, issue 8.
[6]. Overman M.J., McDermott R. et al.: Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (Checkmate 142): an open-label, multicenter, phase 2 study. Lancet Oncol 2017;18:1182-91.
[7]. https://gallery.farmadati.it/Home.aspx
[8]. https://www.aiom.it/wp-content/uploads/2020/10/2020_LG_AIOM_Colon.pdf
[9]. https://www.aiom.it/tumori-377-000-nuovi-casi-in-italia-nel-2020-ma-aumentano-solo-nelle-donne-36-milioni-vivono-dopo-il-cancro-20-diagnosi-per-il-colon-retto-in-7-anni/
[10].https://www.aiom.it/wp-content/uploads/2020/10/2020_Numeri_Cancro-operatori_web.pdf
[11].http://www.io.nihr.ac.uk/wp-content/uploads/migrated_new/12638-Nivolumab-+-ipilimumab-for-metastatic-colorectal-cancer.pdf
[12].https://clinicaltrials.gov/ct2/results?intr=nivolumab&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&recrs=i&age_v=&gndr=&type=&rslt=&phase=2&Search=Apply
[13]. https://adisinsight.springer.com/drugs/800022442
[14].https://clinicaltrials.gov/ct2/show/study/NCT04730544?recrs=abdefi&cond=Colorectal+Cancer&intr=Nivolumab&phase=12&draw=2&rank=8
[15].https://clinicaltrials.gov/ct2/show/NCT04008030?recrs=abdefi&cond=Colorectal+Cancer&intr=Nivolumab&phase=12&draw=3&rank=17
[16].https://clinicaltrials.gov/ct2/results?cond=Colorectal+Cancer&term=&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&recrs=i&age_v=&gndr=&intr=&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=

NHS impact

Cost of Therapy:
Nivolumab 24ml (10mg/ml) vial costs €3.226,01 (ex-factory price) [7].
The monthly price is as follows (70 Kg patient):
-for the first three months: €4.301,35.
-for the following months: €6.452,02.

Epidemiology:
It is estimated that about 513,500 people are affected by CRC in Italy, with about 43,700 new cases in 2020 [8][9]. Subjects with dMMR/MSI-H represent about 4% of pts with mCRC (about 20% of pts with CRC have advanced CRC at the diagnosis). [10]

POSSIBLE PLACE IN THERAPY
No specific dMMR/MSI-H treatments are available. The treatment may include ChT with FOLFOX (folinic acid, 5-fluorouracil and oxaliplatin), XELOX (capecitabine and oxaliplatin), Irinotecan, FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) or Trifluridine/tipiracil. Biological agents, such as cetuximab or panitumumab could be used, in combination with FOLFOX or FOLFIRI. Other biologic treatments include bevacizumab and aflibercept. [11]

OTHER INDICATIONS IN DEVELOPMENT
Non-Hodgkin's lymphoma, bladder cancer, ovarian cancer, Fallopian tube cancer, prostate cancer, glioblastoma. [12][13]

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT: Yes. [14][15]

OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION: Quavonlimab, sintilimab, olaparib, toripalimab, AK104. [16]

*Service reorganization: No
*Possible off label use: Yes