Nivolumab (Opdivo®) as monotherapy for the treatment of unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OESCC)

General information

Drug description [1]	Indication [2]
Nivolumab is a IgG4 monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2	Nivolumab as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic OESCC after prior fluoropyrimidine- and platinum-based combination chemotherapy.

Current treatment [3]

❖ Standard treatment options for stage II oesophageal cancer:
- Chemoradiation followed by surgery
- Surgery alone
- Chemotherapy followed by surgery
- Definitive chemoradiation

❖ Standard treatment options for stage III oesophageal cancer:
- Chemoradiation followed by surgery
- Preoperative chemotherapy followed by surgery
- Definitive chemoradiation

❖ Treatment options for stage IV oesophageal cancer:
- Chemoradiation followed by surgery (for patients with stage IVA disease).
- Chemotherapy, which has provided partial responses for patients with metastatic distal oesophagal adenocarcinomas
- Nd: YAG[1] endoluminal tumour destruction or electrocoagulation
- Endoscopic-placed stents to provide palliation of dysphagia
- Radiation therapy with or without intraluminal intubation and dilation
- Intraluminal brachytherapy to provide palliation of dysphagia

❖ Standard treatment options for recurrent oesophageal cancer:
- Palliative use of any of the standard therapies, including supportive care.

Regulatory status

EMA [2]

Approval status for this indication: On 15 October 2020, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Opdivo®. The CHMP adopted a

new indication in oesophageal squamous cell carcinoma:

❖ Nivolumab as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic OESCC after prior fluoropyrimidine- and platinum-based combination chemotherapy.

Other indications:

❖ Melanoma: Nivolumab as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

❖ Adjuvant treatment of melanoma: Nivolumab as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

❖ Non-small cell lung cancer (NSCLC):
- Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic NSCLC in adults whose tumours have no sensitising EGFR mutation or ALK translocation.
- Nivolumab as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults.

❖ Renal cell carcinoma (RCC):

FDA [4, 5]

Approval status for this indication: On 10 June 2020, the FDA approved nivolumab for patients with unresectable advanced, recurrent or metastatic OESCC after prior fluoropyrimidine- and platinum-based chemotherapy.

✓ Accelerated approval
✓ Priority review
✓ Orphan drug designation

Other indications: Nivolumab is indicated for the treatment of:

❖ Melanoma:
- Patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab.
- Patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.

❖ NSCLC:
- Adult patients with metastatic NSCLC expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumour aberrations, as first-line treatment in combination with ipilimumab.
- Adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumour aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.
- Patients with metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab.

❖ Malignant Pleural Mesothelioma: Adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab.

❖ RCC:

[1] Laser therapy

- Nivolumab as monotherapy is indicated for the treatment of advanced RCC after prior therapy in adults.
- Nivolumab in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced RCC.

❖ Classical Hodgkin lymphoma (cHL): Nivolumab as monotherapy is indicated for the treatment of adult patients with relapsed or refractory cHL after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.

❖ Squamous cell cancer of the head and neck (SCCHN): Nivolumab as monotherapy is indicated for the treatment of recurrent or metastatic SCCHN in adults progressing on or after platinum-based therapy.

❖ Urothelial carcinoma (UC): Nivolumab as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic UC in adults after failure of prior platinum-containing therapy.

- Patients with advanced RCC who have received prior antiangiogenic therapy.
- patients with intermediate or poor risk advanced RCC, as a first-line treatment in combination with ipilimumab
- patients with advanced RCC, as a first-line treatment in combination with cabozantinib.

❖ cHL: Adult patients with cHL that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or 3 or more lines of systemic therapy that includes autologous HSCT.

❖ SCCHN: Patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy.

❖ UC: Patients with locally advanced or metastatic UC who: have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

❖ Colorectal Cancer : Adult and paediatric (12 years and older) patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab.

❖ Hepatocellular Carcinoma (HCC): Patients with HCC who have been previously treated with sorafenib, as a single agent or in combination with ipilimumab.

Costs

24 ml **Opdivo®** concentrate for solution for infusion10mg/ml = **€3,432.00** (ex-factory price) [6]

Study characteristics [7, 8]

Trial name	n	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ATTRACTION-3 ONO-4538-24/CA209473, NCT02569242	419	nivolumab (240 mg for 30 min every 2 weeks)	investigator's choice of chemotherapy (paclitaxel or docetaxel)	OS in the ITT population	randomised, multicentre, open-label, phase 3 trial	-	ONO Pharmaceutical Company and Bristol-Myers Squibb	Link

Efficacy (I vs. C)

Median OS (at a minimum follow-up time of 17.6 months): 10.9 m (95% CI, 9.2-13.3) vs. 8.4 m (7.2-9.9), HR for death 0.77 (95% CI, 0.62-0.96, p=0.019).
Objective response rate: 19% (95% CI, 14–26) vs. 22% (15–29)
Median duration of response: substantially longer with nivolumab compared with chemotherapy, 6.9 (5.4–11.1) vs. 3.9 (2.8–4.2) m
Patients with ongoing response: 21% vs. 6%
Median time to response: 2.6 vs. 1.5 m
Median PFS: 1.7 m versus 3.4 m, HR 1.08 (0.87–1.34)
QoL: overall improvement in the nivolumab group; Patients treated with nivolumab had a decreased risk of deterioration in QoL compared with patients treated with chemotherapy for the VAS (HR 0.65, 95% CI 0.49–0.86, p=0.0030; median time to deterioration 4.3 m vs. 2.7 m) and the utility index (HR 0.73, 95% CI 0.55–0.97, p=0.032; median time to deterioration 4.2 m vs. 2.9 m)
Subsequent therapy for advanced oesophageal cancer: 57% vs. 55%

Safety (I vs. C)

AEs grade 3: n=33 (16%) vs. n=85 (41%)
AEs grade 4: n=5 (2%) vs. n=46 (22%)
SAEs grade 3: n=16 (8%) vs. n=31 (15%)
SAEs grade 4: n=4 (2%) vs. n=8 (4%)
AEs leading to death: n=5
Discontinuation[2]: n=18 (9%) vs. n=19 (9%)

ESMO-MCBS version 1.1

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	≤12 m	OS: +2.5 m	OS: 0.77 (0.62-0.96)	HR ≤0.65 AND gain ≥2.0,<3 m	3	-	improved	+1	4
Adapted	NC	2a	≤12 m	OS: +2.5 m	OS: 0.77 (0.62-0.96)	HR >0.70 OR gain <1.5 m	1	-	improved	+1	2

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	unclear	no	yes	yes[3]	high

[2] Due to AE(s) of any grade
[3] The funders of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the clinical study report.

Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ASCT=autologous stem cell transplant, C=comparator, cHL=classical Hodkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HCC=hepatocellular carcinoma, HR=hazard ratio, HSCT=hematopoietic stem cell transplantation, I=intervention, IgG4=human immunoglobulin G4, Int.=intention, ITT=intention-to-treat, m=months, MG=median gain, n=number of patients, NSCLC=non-small cell lung cancer, SCLC=small cell lung cancer, SAE=serious adverse event, OESCCOS=oesophageal squamous cell carcinoma, overall survival, PD-1=programmed death-1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RCC=renal cell carcinoma, SAE=serious adverse event, SCCHN=squamous cell cancer of the head and neck, ST=standard treatment, UC=urothelial carcinoma, VAS=visual analogue scale

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