Adjuvant nivolumab (Opdivo®) as monotherapy for the treatment of patients with oesophageal (OC) or gastro-oesophageal junction cancer (GEJC)

General information

Drug description [1]	Indication [2]
Nivolumab (Opdivo®) is a human immunoglobulin G4 (IgG4) monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2.	Nivolumab (Opdivo®) as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.

Current treatment [3]

- Neoadjuvant chemoradiotherapy followed by surgery is a widely used standard of care for patients with resectable, locally advanced oesophageal or gastro-oesophageal junction cancer.
- However, the risk of recurrence after neoadjuvant chemoradiotherapy and surgery remains high, especially among the 70 to 75% of patients who do not have a pathological complete response.
- The median overall survival among patients without a pathological complete response is shorter than that among those with pathological complete response, and outcomes are even worse in patients with lymph node-positive disease.
- The standard of care after neoadjuvant chemoradiotherapy and surgery is surveillance.

Regulatory status

EMA [2]

Approval status for this indication: On 24 June 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Opdivo®.

The CHMP adopted a new indication as follows:

- Opdivo® as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.

Other indications: Opdivo® is indicated:

- Melanoma
  - as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults. Relative to nivolumab monotherapy, an increase in PFS and OS for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression.
- Adjuvant treatment of melanoma
  - as monotherapy 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)
  - in combination with ipilimumab and 2 cycles of platinum-based chemotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours have no sensitising EGFR mutation or ALK translocation.
  - as monotherapy for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults.
- Malignant pleural mesothelioma (MPM)

FDA [4, 5]

Approval status for this indication: On 20 May 2021, the FDA approved nivolumab (Opdivo®) for patients with completely resected oesophageal or GEJC with residual pathologic disease who have received neoadjuvant chemoradiotherapy.

Other indications: Opdivo® 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 NSCLC 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 Opdivo®.
- MPM
  - adult patients with unresectable MPM, as first-line treatment in combination with ipilimumab.
- RCC
  - 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.
  - patients with advanced RCC who have received prior anti-angiogenic therapy.
- cHL
  - adult patients with cHL that has relapsed or progressed after (this indication is approved under accelerated approval based on overall response rate and duration of response):
    - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or

- in combination with ipilimumab for the first-line treatment of adult patients with unresectable MPM.

❖ Renal cell carcinoma (RCC)
- as monotherapy is indicated for the treatment of advanced RCC after prior therapy in adults.
- in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced RCC.
- in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced RCC.

❖ Classical Hodgkin lymphoma (cHL)
- as monotherapy 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)
- as monotherapy for the treatment of recurrent or metastatic SCCHN in adults progressing on or after platinum-based therapy.

❖ Urothelial carcinoma
- as monotherapy for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

❖ Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC)
- in combination with ipilimumab for the treatment of adult patients with dMMR or MSI-H metastatic CRC after prior fluoropyrimidine-based combination chemotherapy.

❖ Oesophageal squamous cell carcinoma (OSCC)
- as monotherapy for the treatment of adult patients with unresectable advanced, recurrent or metastatic OSCC after prior fluoropyrimidine- and platinum-based combination chemotherapy.

❖ Gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma
- in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score ≥ 5.
  - 3 or more lines of systemic therapy that includes autologous HSCT.

❖ SCCHN
- patients with recurrent or metastatic SCHNN with disease progression on or after platinum-based therapy.

❖ Urothelial Carcinoma
- adjuvant treatment of patients with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection of urothelial carcinoma.
- patients with locally advanced or metastatic urothelial carcinoma who (this indication is approved under accelerated approval based on overall response rate and duration of response):
  - have disease progression during or following platinum-containing chemotherapy.
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

❖ Colorectal Cancer
- adult and pediatric (12 years and older) patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab (this indication is approved under accelerated approval based on overall response rate and duration of response).

❖ Hepatocellular Carcinoma (HCC)
- patients with hepatocellular carcinoma who have been previously treated with sorafenib, as a single agent or in combination with ipilimumab (this indication is approved under accelerated approval based on overall response rate and duration of response).

❖ Oesophageal Cancer
- patients with completely resected oesophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy.
- patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

❖ Gastric Cancer, Gastroesophageal Junction Cancer, and Oesophageal Adenocarcinoma
- patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and oesophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.

Costs

24 ml **Opdivo®** concentrate for solution for infusion 10mg/ml= **€ 3,432.00** [6]

Warnings and precautions [4]

❖ **Immune-mediated adverse reactions:**
- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis and hepatotoxicity, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, and immune-mediated nephritis and renal dysfunction.
- Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
- Withhold or permanently discontinue based on severity and type of reaction.

- **Infusion-related reactions**:
  - Interrupt, slow the rate of infusion, or permanently discontinue Opdivo® based on severity of reaction.
- **Complications of allogeneic HSCT:**
  - Fatal and other serious complications can occur in patient who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody.
- **Embryo-foetal toxicity:**
  - Can cause foetal harm. Advise females of reproductive potential of potential risk to a foetus and to use effective contraception.
- Treatment of patients with **multiple myeloma** with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials [4].

Study characteristics [3, 7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
CheckMate 577, CA209577, NCT02743494	794	nivolumab 240 mg every 2 weeks for 16 weeks, followed by nivolumab 480 mg every 4 weeks	matching placebo	disease-free survival	global, randomised, double-blind, placebo-controlled phase 3 trial	PD-L1	Bristol Myers Squibb and Ono Pharmaceutical	[3]

Efficacy (I vs. C)

Interim analysis data; clinical data cut-off date 05/2020:

Median disease-free survival: 22.4 months (95% CI, 16.6-34.0) vs. 11.0 months (95% CI, 8.3-14.3); HR for disease recurrence or death 0.69; 96.4% CI, 0.56-0.86; p<0.001)

Distant recurrence: n=145/532 (29%) vs. n=103/262 (39%)

Locoregional recurrence: n=65/532 (12%) vs. n=44/262 (17%)

Median distant metastasis–free survival: 28.3 months (95% CI, 21.3-could not be estimated) vs. 17.6 months (95% CI, 12.5-25.4); HR 0.74; 95% CI, 0.60-0.92

Patients who received subsequent therapy, including systemic anticancer therapy, radiotherapy, and surgery: n=157/532 (30%) vs. n=111/262 (42%)

Patients who received subsequent immunotherapy: n=4/532 (<1%) vs. n=19/262 (7%)

Data cutoff 02/2021 [10]:

Median disease-free survival: 22.4 months (95% CI, 17.0-33.6) vs. 10.4 months (95% CI, 8.3-13.9); HR 0.67 (96.4% CI, 0.55-0.81)

Rate at 6 months: 72.6 vs. 61.5

Rate at 12 months: 61.8 vs. 45.5

Rate at 24 months: 48.3 vs. 36.0

Patient-Reported Outcomes

- At least **95%** of the patients **completed the FACT-**E assessment and the EQ-5D-3L questionnaire at baseline, and approximately **90% completed these assessments at 12 months** during the treatment period.

Safety (I vs. C)

Grade 3 or 4 AEs of any cause: n=183/532 (34%) vs. 84/260 (32%)

SAEs of any grade: n=158/532 (30%) vs. n=78/260 (30%)

in the placebo group, and serious adverse events

AEs that were considered by the investigators to be related to the trial regimen (including grade 3 or 4 events)[1]: n=71/532 (13%) vs. 15/260 (6%)

Related AEs leading to discontinuation: 48/532 (9%) vs. 8/260 (3%)

SAEs of any grade related to the trial regimen: n=40/532 (8%) vs. n=7/260 (3%)

[1] One grade 5 nivolumab-related adverse event was recorded (a cardiac arrest in the nivolumab group that was deemed to be not related to nivolumab by the investigator after database lock).

- ❖ A longitudinal mixed-model analysis that was used to compare the least-squares mean score differences between the two groups showed **similar improvement from baseline at most time points through week 53** with both nivolumab and placebo in the FACT-E total score, on the EQ-5D-3L visual analogue scale, and in the EQ-5D-3L utility index score.
- ❖ A **clinically meaningful improvement** with both nivolumab and placebo was observed at several time points on the EQ-5D-3L visual analogue scale, but neither group had a clinically meaningful improvement in the FACT-E total score or the EQ-5D-3L utility index score.
- ❖ These findings indicate that **HRQoL was maintained** during the treatment period.
- ❖ The percentages of patients who replied "I am not at all bothered by side effects of treatment" on the FACT-E GP5 item were similar in the two groups.

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (96.4% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	adjuvant	1	x	DFS: +11.4 months	DFS: 0.69 (0.56-0.86)	HR<0.65	A	+2% grade ≥3 AEs	ND	x	A
Adapted	adjuvant	1	x	DFS: +11.4 months	DFS: 0.69 (0.56-0.86)	HR 0.65-0.80	B	+2% grade ≥3 AEs	ND	x	B

Risk of bias (study level) [12]

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[2]	yes	unclear[3]	yes[4]	high

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Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ASCT= autologous stem cell transplant, C=comparator, cHL=classical Hodgkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CRC=colorectal cancer, dMMR=mismatch repair deficient, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, EQ-5D-3L=European Quality of Life–5 Dimensions questionnaire, ESCC=esophageal squamous cell carcinoma, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FACT-E= Functional Assessment of Cancer Therapy–Esophageal, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, GEJ=gastroesophageal junction, GEJC= gastro-oesophageal junction cancer, HR=hazard ratio, HRQoL=health-related quality of life, HSCT= hematopoietic stem cell transplantation, I=intervention, Int.=intention, MG=median gain, MPM=malignant pleural mesothelioma, n=number of patients, ND=no difference, NSCLC=non-small cell lung cancer, OC=oesophageal cancer, OS=overall survival, PD=programmed-death, PD-L1=programmed-death-ligand 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

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[2] According to the supplementary appendix, the treatment allocation list was generated by the sponsor.

[3] CheckMate 577 trial is ongoing until 10/2025.

[4] The sponsor funded the trial, provided the trial agents, and collaborated with the academic authors on the design of the trial and the collection, analysis, and interpretation of the data. Medical-writing support, including development of the first draft of the manuscript under the guidance of the first and last authors, was funded by the sponsor.

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