Nivolumab (Opdivo®) in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the treatment of patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma

General information

Drug description [1]	Indication [1]
Nivolumab is a programmed cell death (PD)-1 inhibitor.	Nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated 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 (CPS) ≥ 5.

Current treatment [2]

- As first-line palliative chemotherapy for locally advanced or metastatic oesophageal or gastric cancer, NICE recommends the following:
  - Trastuzumab
    - Trastuzumab, in combination with cisplatin and capecitabine or 5-fluorouracil, is recommended as an option for the treatment of people with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who:
      - have not received prior treatment for their metastatic disease and
      - have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3.
    - People who are currently receiving treatment with trastuzumab for HER2-positive metastatic gastric cancer who do not meet the criteria above should have the option to continue treatment until they and their clinicians consider it appropriate to stop.
  - Capecitabine
    - Capecitabine in combination with a platinum-based regimen for the first-line treatment of inoperable advanced gastric cancer.

Regulatory status

EMA [1]

Approval status for this indication: On 16 September 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Opdivo®.

<u>The CHMP adopted a new indication as follows:</u>

- Opdivo® in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated 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 CPS ≥ 5.

Other indications: Opdivo® is indicated in

- 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.

FDA [3, 4]

Approval status for this indication: On 16 April 2021, the FDA approved nivolumab (Opdivo®) in combination with fluoropyrimidine- and platinum-containing chemotherapy for advanced or metastatic gastric cancer, gastroesophageal junction cancer, and oesophageal adenocarcinoma.

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

- as monotherapy for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults.

❖ Malignant pleural mesothelioma (MPM)
- in combination with ipilimumab for the first-line treatment of adult patients with unresectable MPM.

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

❖ Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer (OC or GEJC)
- as monotherapy for the adjuvant treatment of adult patients with OC or GEJC who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.
- 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 (indication approved under accelerated approval based on ORR and DOR):
  - 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 platinum-based therapy.

❖ UC
- adjuvant treatment of patients with UC who are at high risk of recurrence after undergoing radical resection of UC.
- patients with locally advanced or metastatic urothelial carcinoma who:
  - have disease progression during or following platinum-containing chemotherapy
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

❖ CRC
- adult and paediatric (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 (indication approved under accelerated approval based on ORR and DOR).

❖ Hepatocellular Carcinoma (HCC)
- patients with HCC who have been previously treated with sorafenib in combination with ipilimumab.

❖ 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 after prior fluoropyrimidine- and platinum-based chemotherapy.

✓ **Priority review**
✓ **Orphan drug designation**

Costs [5]

4 ml Opdivo® concentrate for solution for infusion 10 mg/ml = € 572.00 (ex-factory price)
10 ml Opdivo® concentrate for solution for infusion 10 mg/ml = € 1,430.00 (ex-factory price)
24 ml Opdivo® concentrate for solution for infusion 10 mg/ml = € 3,432.00 (ex-factory price)

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 the severity of the reaction.

❖ **Complications of allogeneic HSCT:**
- Fatal and other serious complications can occur in a 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 the potential risk to a foetus and to use effective contraception.

Study characteristics [6-8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
CheckMate 649, CA209649 NCT02872116	1,581: 789 vs. 792	nivolumab (360 mg every 3 weeks or 240 mg every 2 weeks) + investigator's choice of chemotherapy[1]	chemotherapy alone	OS or PFS by BICR in patients whose tumours had a PD-L1 CPS of ≥5	multicentre, randomised, open-label, phase 3 trial	HER2	Bristol Myers Squibb, in collaboration with Ono Pharmaceutical	[7]

Efficacy (I vs. C)

OS (at a minimum follow-up of 12.1 months): nivolumab plus chemotherapy showed superior OS, with a 29% reduction in the risk of death compared with chemotherapy alone; HR 0.71 (98.4% CI 0.59–0.86), p<0.0001
Median OS in patients with a PD-L1 CPS ≥5: 14.4 months (95% CI 13.1–16.2) vs. 11.1 months (10.0–12.1), HR 0.71 (98·4% CI 0.59–0.86); p<0·0001
Patients alive at 12 months: 57% (95% CI 53–62) vs. 46% (42–51)
PFS in patients with a PD-L1 CPS of ≥5: 32% reduction in the risk of progression or death with nivolumab plus chemotherapy vs. chemotherapy alone; HR 0.68 (98% CI 0.56–0.81), p<0.0001
Median PFS: 7.7 months (95% CI 7.0–9.2) vs. 6.0 months (5.6–6.9)
12-month PFS estimate: 36% (95% CI 32–41) vs. 22% (18–26)
OS in patients with a PD-L1 CPS of ≥1: HR 0.77 (99.3% CI 0.64–0.92); p<0.0001
OS in all randomly assigned patients: HR 0.80 (0.68–0.94); p=0.0002
PFS benefit with nivolumab in patients with a PD-L1 CPS of ≥1: HR 0.74 (95% CI 0.65–0.85)
PFS benefit in all randomly assigned patients: HR 0.77 (0.68–0.87)
Unstratified HR for OS for patients with a PD-L1 CPS of <1: 0.92 (95% CI 0.70–1.23)
HR for OS for patients with a PD-L1 CPS of <5: 0.94 (95 % CI 0.78–1.13)

Safety (I vs. C)

Grade 3-4 treatment-related AEs: n=462/782 (59%) vs. n=341/767 (44%)
Serious treatment-related AEs of any grade: n=172/782 (22%) vs. n=93/767 (12%)
Serious treatment-related grade 3-4 AEs: n=131/782 (17%) vs. n=77/767 (10%)
Serious treatment-related grade 5 AEs: n=4 vs. n=0
Discontinuation[2]: n=284/782 (36%) vs. n=181/767 (24%)
Deaths that were considered treatment related[3]: n=16/782 (2%) vs. n=4/767 (1%).

[1] XELOX [capecitabine 1000 mg/m² twice a day, days 1–14 and oxaliplatin 130 mg/m², day 1, every 3 weeks] or FOLFOX [leucovorin 400 mg/m², day 1, fluorouracil 400 mg/m², day 1 and 1200 mg/m², days 1–2, and oxaliplatin 85 mg/m², day 1, every 2 weeks].
[2] Discontinuation due to any-grade treatment-related AE(s).
[3] **Nivolumab plus chemotherapy group**: 12 treatment-related deaths were due to 3 cases of pneumonitis, 2 cases of febrile neutropenia or neutropenic fever, and 1 case each of gastrointestinal bleeding, gastrointestinal toxicity, infection, intestinal mucositis, pneumonia, septic shock, and stroke. An additional 4 deaths due to other reasons were specified as related to treatment by the investigator; these included 1 case each of acute cerebral infarction, mesenteric thrombosis, disseminated intravascular coagulation, and pneumonitis. **Chemotherapy alone group**: 4 treatment-related deaths were due to diarrhoea, asthenia and severe loss of appetite, pulmonary thromboembolism, and pneumonitis.
Of the 16 deaths in the nivolumab plus chemotherapy group, four were deemed to be related to nivolumab, five to nivolumab plus chemotherapy, and seven to chemotherapy alone.

Unstratified HRs for PFS: 0.93 (0.69–1.26) for patients with a PD-L1 CPS of <1 and 0.93 (0.76–1.12) for patients with a PD-L1 CPS of
ORR by BICR: 60% (95% CI 55–65) vs. 45% (40–50)
Patients with a CR: 12% vs. 7%
Median DOR: 9.5 months (95% CI 8.0–11.4) vs. 7.0 months (5.7–7.9)
Patients who received **at least one subsequent therapy** for advanced gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma: 38% vs. 41%

Updated descriptive analysis with a minimum follow-up of 19.4 months [9]:
OS events: 344 (73%) vs. 397 (82%), HR 0.69 (0.60-0.81)
Median OS: 14.4 months (95% CI, 13.1-16.3) vs. 11.1 months (95%CI, 10.0-12.1)
OS rate at 12 months: 57.3 (95% CI, 52.6-61.6) vs. 46.4 (95% CI, 41.8-50.8)
PFS events: 342 (72.3%) vs. 366 (75.9%), HR 0.68 (0.59-0.79)
Median PFS: 8.31 months (95% CI, 7.03-9.26) vs. 6.05 months (5.55-6.90)
PFS rate at 12 months: 36.3 (31.7-41.0) vs. 21.9 (17.8-26.1)
Objective response rate: 60% vs. 45%
Complete response: 12.2% vs. 6.7%
Partial response: 47.9% vs. 38.5%
Median duration of response: 9.69 (95%CI, 8.25-12.22) vs. 6.97 (95%CI, 5.62-7.85)

QoL:

- The proportion of patients with a PD-L1 CPS of ≥5 and all randomly assigned **patients completing the FACT-Ga questionnaire** was **90%** or more at baseline and **80%** or more at most subsequent assessments for which at least ten patients responded (until week 109).
- Baseline mean FACT-Ga total scores were **similar** between the nivolumab plus chemotherapy (127.6; SD 27.4) and chemotherapy alone groups (127.6; 26.4) for patients with a PD-L1 CPS of ≥5 and between the nivolumab plus chemotherapy (126.6; 28.3) and chemotherapy alone groups (126.8; 26.8) for all randomly assigned patients, with an improvement from baseline in FACT-Ga total score at all on-treatment assessments.
- In patients with a PD-L1 CPS of ≥5 and all randomly assigned patients, the least squares mean difference between treatment groups **favoured nivolumab** plus chemotherapy vs. chemotherapy alone (at timepoints with ≥50 patients in each group). **This result was less than the minimally important difference of 15.1 points**.
- Patients in the nivolumab plus chemotherapy group had **decreased risk of symptom deterioration** than the chemotherapy alone group while on treatment (patients with a PD-L1 CPS ≥5, HR 0.64 (95% CI 0.49–0.83) and all randomly assigned patients (HR 0.77; 0.63–0.95).

ESMO-MCBS version 1.1 [10]

Scale	Int.	Form	MG ST	MG	HR (98.4% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2A	≤12 months	OS: +3.3 months	HR 0.71 (0.59–0.86)	HR ≤0.65 AND gain ≥3 months	4	-	-	-	4
Adapted	NC	2A	≤12 months	OS: +3.3 months	HR 0.71 (0.59–0.86)	HR >0.70 or gain <1.5 months	1	+ 15% grade 3-4 treatment-related AEs, + 12% discontinuation due to AEs	-	-1	0

Risk of bias (RCT) [11]

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	no	No, open-label	unclear[4]	yes[5]	high
					First published: 10/2021 **Last updated**: 01/2022

Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ASCT=autologous stem cell transplant, BICR=blinded independent central review, C=comparator, cHL=classical Hodgkin lymphoma, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CPS=combined positive score, CRC=colorectal carcinoma, dMMR=mismatch repair deficient, DOR=duration of response, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FACT-Ga= Functional Assessment of Cancer Therapy-Gastric, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, GEJC=gastro-oesophageal junction cancer, HCC=hepatocellular carcinoma, HER=human epidermal growth receptor 2, HSCT=hematopoietic stem cell transplantation, HR=hazard ratio, I=intervention, Int.=intention, MG=median gain, MPM=malignant pleural mesothelioma, MSI-H=microsatellite instability-high, n=number of patients, NSCLC= non-small cell lung cancer, OC=oesophageal cancer, ORR=overall response rate, OS=overall survival, OSCC=oesophageal squamous cell carcinoma PD=programmed cell death, PD-L1=programmed cell 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 carcinoma of the head and neck, ST=standard treatment, UC=urothelial carcinoma,

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[4] CheckMate649 trial is currently ongoing; estimated study completion date is 10/2022.
[5] The funder of the study was involved in study design, data collection, data analysis, data interpretation, and writing of the clinical study report.