

Nivolumab (Opdivo®) as monotherapy for the adjuvant treatment of muscle-invasive urothelial carcinoma (MIUC)

General information

Drug description [1]	Indication [2]
Nivolumab (Opdivo®) is a fully human IgG4 monoclonal antibody directed against programmed death 1.	Nivolumab (Opdivo®) as monotherapy is indicated for the adjuvant treatment of adults with muscle-invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression $\geq 1\%$, who are at high risk of recurrence after undergoing radical resection of MIUC.

Current treatment [3]

- ❖ According to the current NICE treatment pathway for patients with invasive urothelial cancer, cisplatin combination chemotherapy maybe is offered as adjuvant treatment after radical cystectomy for whom neoadjuvant chemotherapy was not suitable.
- ❖ In patients who have received radical cystectomy but are not eligible for adjuvant cisplatin-based chemotherapy (according to the European Association of Urology, over 50% of patients with urothelial cancer are likely not eligible for cisplatin-based chemotherapy), a watchful-waiting (observation) approach is taken until disease recurrence.

Regulatory status

EMA [2]	FDA [4, 5]
<p>Approval status for this indication: On 24 February 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Opdivo®.</p> <p><u>The CHMP adopted a new indication as follows:</u></p> <ul style="list-style-type: none"> ❖ Opdivo® as monotherapy is indicated for the adjuvant treatment of adults with MIUC with tumour cell PD-L1 expression $\geq 1\%$, who are at high risk of recurrence after undergoing radical resection of MIUC. <p>Other indications: Opdivo® is indicated</p> <ul style="list-style-type: none"> ❖ Melanoma <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • 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) <ul style="list-style-type: none"> • 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) <ul style="list-style-type: none"> • in combination with ipilimumab for the first-line treatment of adult patients with unresectable MPM. ❖ Renal cell carcinoma (RCC) 	<p>Approval status for this indication: On 19 August 2021, the FDA approved nivolumab (Opdivo®) for the adjuvant treatment of patients with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection.</p> <ul style="list-style-type: none"> ✓ This is the first FDA approval for adjuvant treatment of patients with high-risk urothelial carcinoma. The results supporting this approval also supported the conversion of nivolumab's accelerated approval for advanced/metastatic urothelial carcinoma to regular approval. ✓ Priority review <p>Other indications: Opdivo® is indicated for the treatment of:</p> <ul style="list-style-type: none"> ❖ Melanoma <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • adult patients with metastatic NSCLC expressing PD-L1 ($\geq 1\%$) 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 <ul style="list-style-type: none"> • adult patients with unresectable MPM, as first-line treatment in combination with ipilimumab. ❖ RCC <ul style="list-style-type: none"> • 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

- 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
 - 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)
 - in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic OSCC with tumour cell PD-L1 expression $\geq 1\%$.
 - in combination with ipilimumab for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic OSCC with tumour cell PD-L1 expression $\geq 1\%$.
 - 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.
- ❖ 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, GEJ or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5 .
- adult patients with cHL that has relapsed or progressed after (indication approved under accelerated approval based on overall response rate and duration of response):
 - 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.
- ❖ Urothelial carcinoma
 - 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 overall response rate and duration of response).
- ❖ Hepatocellular carcinoma (HCC)
 - patients with HCC who have been previously treated with sorafenib in combination with ipilimumab (indication approved under accelerated approval based on overall response rate and duration of response).
- ❖ Oesophageal cancer
 - patients with completely resected OC or GEJC 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.
- ❖ Gastric cancer, GEJ, and oesophageal adenocarcinoma
 - patients with advanced or metastatic gastric cancer, GEJ, and oesophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.

Costs [6]

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

Warnings and precautions [5]

❖ 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.

Study characteristics [1, 7-9]

Trial name	n	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
CheckMate 274 NCT02632409	709	nivolumab 240 mg every 2 weeks as a 30-minute IV infusion for up to 1 year or until disease recurrence or discontinuation from the trial	placebo	disease-free survival among all the patients (ITT population) and among patients with a tumour PD-L1 expression level of 1% or more	ongoing¹ , multicenter, double-blind, randomised, phase 3 trial	-	Bristol Myers Squibb and Ono Pharmaceutical	[1]

Efficacy (I vs. C), interim analysis data

Median follow-up: 20.9 months (range, 0.1-48.3) vs. 19.5 months (range, 0-50.0)
Median disease-free survival: 20.8 months (95% CI, 16.5-27.6) vs. 10.8 months (95% CI, 8.3-13.9)
Patients who were alive and disease-free at 6 months: 74.9% vs. 60.3%; HR for disease recurrence or death: 0.70; 98.22% CI, 0.55-0.90; p<0.001

Safety (I vs. C), interim analysis data

AEs of any cause: n=347/351 (98.9%) vs. n=332/348 (95.4%)
AEs of grade ≥3: n=150/351 (42.7%) vs. n=128/348 (36.8%)
Treatment-related AEs of any grade: 77.5% vs. 55.5%
Treatment-related AEs of grade ≥3: 17.9% vs. 7.2%
Treatment-related deaths²: n=3 vs. n=0

¹ The CheckMate 274 trial is currently ongoing; estimated study completion date is 04/2026.

² Treatment-related deaths due to pneumonitis occurred in two patients in the nivolumab group. Both patients began glucocorticoid treatment at the onset of pneumonitis; one patient began 3 days after the last dose of trial therapy, and the other began 16 days after the last dose of trial therapy. There was one treatment-related death due to bowel perforation in the nivolumab group. This patient began glucocorticoid treatment 5 days after the last dose of trial therapy.

Patients with a PD-L1 expression level of 1% or more who were alive and disease-free at 6 months: 74.5% vs. 55.7%; HR: 0.55; 95% CI, 0.35-0.85; p<0.001

Median survival free from recurrence outside the urothelial tract (in the ITT-population): 22.9 months (95% CI, 19.2-33.4) vs. 13.7 months (95% CI, 8.4-20.3)

Patients who were alive and free from recurrence outside the urothelial tract at 6 months: 77.0% vs. 62.7%; HR for recurrence outside the urothelial tract or death 0.72; 95% CI, 0.59-0.89

Patients who were alive and free from recurrence outside the urothelial tract at 6 months (among patients with a PD-L1 expression level of 1% or more): 75.3% vs. 56.7%; HR 0.55; 95% CI, 0.39-0.79

Median distant metastasis-free survival (in the ITT-population): 40.5 months (95% CI, 22.4-could not be estimated) vs. 29.5 months (95% CI, 16.7 to could not be estimated)

Patients who were alive and free from distant metastasis at 6 months: 82.5% vs. 69.8%; HR for distant metastasis or death 0.75; 95% CI, 0.59-0.94

Patients who were alive and free from distant metastasis at 6 months (among patients with a PD-L1 expression level of 1% or more): 78.7% vs. 65.7%; HR 0.61; 95% CI, 0.42-0.90

QoL:

- ❖ The percentage of patients who completed the EORTC QLQ-C30 was 85% or greater during the treatment period and 75% or greater in the follow-up period.
- ❖ Changes from baseline in the EORTC QLQ-C30 global health status score and the EQ-5D-3L visual analogue scale score over time indicated that there was **no meaningful difference in deterioration in QoL** between patients who received nivolumab and those who received placebo, both in the ITT-population and in patients with a PD-L1 expression level of 1% or more.

Discontinuation due to treatment-related AEs of any grade: 12.8% vs. 2.0%

ESMO-MCBS version 1.1 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	adjuvant	1	-	+18.8% 6-months DFS	0.55 (0.35-0.85)	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	A	-	-	-	A
Adapted	adjuvant	1	-	+18.8% 6-months DFS	0.55 (0.35-0.85)	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	A	-	-	-	A

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	yes	yes	unclear ³	yes ⁴	unclear

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³ Interim analysis data; the CheckMate 274 trial is ongoing until 04/2026.

⁴ The trial was designed by the authors in collaboration with the sponsor. The authors, with the assistance of a medical writer employed by the sponsor, drafted and provided final approval of the manuscript that was submitted.



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, CPS=combined positive score, CRC=colorectal carcinoma, DFS=disease-free survival, dMMR=mismatch repair deficient, EGFR=epidermal growth factor receptor EMA=European Medicines Agency, ESMO-MCBS=European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, EORTC-QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, EQ-5D-3L=EuroQoL Group 5-Dimension 3-Level questionnaire FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, GEJC=gastro-oesophageal junction cancer, HCC=hepatocellular carcinoma, HR=hazard ratio, HSCT=hematopoietic stem cell transplantation, I=intervention, Int.=intention, ITT=intention-to-treat, MG=median gain, MIUC=muscle invasive urothelial carcinoma, MPM=malignant pleural mesothelioma, MSI-H=microsatellite instability-high, n=number of patients, NICE=National Institute for Health and Care Excellence, NSCLC= non-small cell lung cancer , OC=oesophageal cancer, OS=overall survival, OSCC=oesophageal squamous cell carcinoma, PD-1=programmed cell death protein 1, PD-L1= programmed death ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RCC=renal cell carcinoma, SCCHN=squamous carcinoma of the head and neck, ST=standard treatment

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