Nivolumab (Opdivo®) in combination with ipilimumab (Yervoy®) for the first-line treatment of patients with unresectable malignant pleural mesothelioma

General information

Drug description [1]	Indication [2]
Nivolumab (a fully human anti-programmed cell death 1 antibody) and ipilimumab (a fully human anti-cytotoxic T-lymphocyte 4 antibody) are immune checkpoint inhibitors. Ipilimumab induces T-cell proliferation and de-novo anti-tumour T-cell responses, including in-memory T cells, whereas nivolumab restores the function of existing anti-tumour T cells.	Nivolumab in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

Current treatment [3]

- NICE recommends pemetrexed as a treatment option for malignant pleural mesothelioma only in people who have a WHO performance status of 0 or 1, who are considered to have advanced disease and for whom surgical resection is considered inappropriate.
- Patients currently receiving pemetrexed who do not fall into the patient population as defined above should have the option to continue therapy until they and their clinicians consider it appropriate to stop.
- Pemetrexed is licensed in the UK for the treatment of unresectable MPM which has not previously been treated with chemotherapy (in combination with cisplatin).

Regulatory status

EMA

Nivolumab (Opdivo)

Approval status for this indication: On 22 April 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for the Opdivo®.

The CHMP adopted a new indication:

- Opdivo® in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

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.
- Renal cell carcinoma (RCC)

FDA [7-9]

Approval status for this indication: On 2 October 2020, the FDA approved the combination of nivolumab (Opdivo®) plus ipilimumab (Yervoy®) as first-line treatment for adult patients with unresectable malignant pleural mesothelioma.

- ✓ Priority review
- ✓ Orphan product designation

Nivolumab (Opdivo)

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®.
- RCC
  - patients with intermediate or poor risk advanced renal cell carcinoma, 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.

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

Ipilimumab (Yervoy®)

Approval status for this indication: On 22 April 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Yervoy®.

The CHMP adopted a new indication:

❖ Yervoy® in combination with nivolumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

Other indications: Yervoy® is indicated:

❖ Melanoma
- as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults, and adolescents 12 years of age and older.
- adult patients with cHL that has relapsed or progressed after (indication approved under accelerated approval based on overall response rate and duration of response):
  - o autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
  - o 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.

❖ Urothelial Carcinoma
- patients with locally advanced or metastatic urothelial carcinoma who (indication approved under accelerated approval based on overall response rate and duration of response):
  - o have disease progression during or following platinum-containing chemotherapy
  - o 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 MSI-H or dMMR metastatic colorectal cancer 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, as a single agent or in combination with ipilimumab (indication approved under accelerated approval based on overall response rate and duration of response).

❖ Oesophagal Cancer
- Patients with completely resected oesophagal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy. Patients with unresectable advanced, recurrent or metastatic oesophagal squamous cell carcinoma 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.

Ipilimumab (Yervoy®)

Other indications: Yervoy® is indicated for:

❖ Melanoma
- Treatment of unresectable or metastatic melanoma in adults and paediatric patients 12 years and older.
- Treatment of adult patients with unresectable or metastatic melanoma, in combination with nivolumab.
- Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

❖ RCC
- Treatment of patients with intermediate or poor risk, previously untreated advanced RCC, in combination with nivolumab.

❖ Colorectal Cancer
- Treatment of adult and paediatric patients 12 years and older with MSI-H or dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and

- in combination with nivolumab 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.

❖ RCC
- in combination with nivolumab for the first-line treatment of adult patients with intermediate/poor-risk advanced RCC.

❖ NSCLC
- in combination with nivolumab and 2 cycles of platinum-based chemotherapy for the first-line treatment of metastatic NSCL in adults whose tumours have no sensitising EGFR mutation or ALK translocation.

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

irinotecan, in combination with nivolumab (approved under accelerated approval based on overall response rate and duration of response).

❖ HCC
- Treatment of patients with HCC who have been previously treated with sorafenib, in combination with nivolumab (approved under accelerated approval based on overall response rate and duration of response).

❖ NSCLC
- Treatment of 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 nivolumab.
- Treatment of adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumour aberrations as first-line treatment, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy.

Costs

24 ml Opdivo® concentrate for solution for infusion10 mg/ml = € 3,432.00 (ex-factory price) [10]
10 ml Yervoy® concentrate for solution for infusion 5 mg/ml = € 4,250.00 (ex-factory price) [10]

CheckMate 473 patients (nivolumab + ipilimumab group) received nivolumab at a dose of 3 mg/kg IV once every 2 weeks and ipilimumab at a dose of 1 mg/kg IV once every 6 weeks. The median number of nivolumab doses received was 12.0 and of ipilimumab was 4.0 [1]. Assuming an average body weight of 80 kg, one dose of nivolumab and ipilimumab would cost approx. € 3,432.00 and € 8,500.00, respectively.

Warnings and precautions [7, 8]

Yervoy®

❖ **Severe and Fatal Immune-Mediated Adverse Reactions**
- Immune-mediated adverse reactions (IMAR) can occur in any organ system or tissue, including the following: immune-mediated colitis, immune-mediated hepatitis, immune-mediated dermatologic adverse reactions, immune-mediated endocrinopathies, immune-mediated pneumonitis, and immune-mediated nephritis with renal dysfunction, and can occur at any time during treatment or after discontinuation.
- Monitor for symptoms and signs that may be clinical manifestations of IMAR. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone level and thyroid function at baseline and before each dose.
- In general, withhold Yervoy® for severe (grade 3) and permanently discontinue for life-threatening (Grade 4) immune-mediated adverse reactions.

❖ **Infusion-Related Reactions**
- Discontinue for severe and life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions.

❖ **Complications of allogeneic HSCT**
- Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with Yervoy®.

❖ **Embryo-Foetal Toxicity**
- Can cause foetal harm. Advise of the potential risk to a foetus and use of effective contraception.

Opdivo®

❖ **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.
❖ 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

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
CheckMate 743, CA209743 NCT02899299	605	nivolumab (3 mg/kg IV once every 2 weeks) + ipilimumab (1 mg/kg IV once every 6 weeks)	cisplatin IV (75 mg/m²) or carboplatin (area under the concentration time curve 5 mg/mL per min) + pemetrexed (500 mg/m²) every 3 weeks for a maximum of six cycles	OS[1]	global, open-label, randomised, controlled, phase 3 study	-	Bristol Myers Squibb	[1]

Efficacy (I vs. C)[2]

Median OS: 18.1 months (95% CI 16·8–21.4) vs. 14.1 months (95% CI 12.4-16.2); HR 0.74 (96.6% CI 0.60–0.91; p=0.0020)
OS rates at 1 year: 68% vs. 58%
OS rates at 2 years: 41% vs. 27%

Median PFS: 6.8 months (95% CI 5.6–7.4) vs. 7.2 months (95% CI 6.9–8.0); HR 1.00 (95% CI, 0.82–1.21)
PFS rates at 2 years: 16% vs. 7%

Objective response: 40% vs. 43%
Complete responses (only observed in I): 2%
Disease control: 77% (with a median time to response of 2.7 months vs. 85% (with a median time to response of 2.5 months)
Median duration of response: 11.0 months vs. 6.7 months
2-year duration of response rate: 32% vs. 8%

Subsequent systemic therapy: 44.2% vs. 40.7%
Subsequent immunotherapy (including anti-PD-1, anti-PD-L1, and anti-CTLA-4): 3.3% vs. 20.2%
Patient-reported outcomes (PROs) [13]:

❖ PRO completion rates were >80% for most on-treatment timepoints across arms for ≥10 patients (up to week 96 for nivolumab+ipilimumab and week 36 for chemotherapy).

Safety (I vs. C)[3]

Grade 3 TRAEs: n=79/300 (26.3%) vs. n=73/284 (25.7%)
Grade 4 TRAEs: n=12/300 (4.0%) vs. n=18/284 (6.3%)
Serious Grade 3-4 TRAEs: n=46/300 (15.3%) vs. n=17/284 (6.0%)
Treatment-related deaths: n=3/300 (1%)[4] vs. n=1/284 (<1%)[5]
Discontinuation[6]: n=45/300 (15.0%) vs. n=21/284 (7.4%)

[1] The study protocol was revised on 25 April 2019 to change PFS from a co-primary endpoint to a secondary endpoint. This was based on guidance from the FDA, which stated that tumour assessments can be imprecise where there is a lack of demarcated margins, such as with malignant pleural mesothelioma.
[2] Pre-specified interim analysis data. The study met its primary endpoint at the pre-specified interim analysis according to the recommendation of the independent Data Monitoring Committee. Given that the study was able to reject the null hypothesis at the interim analysis, this analysis is considered final.
[3] Pre-specified interim analysis data. The study met its primary endpoint at the pre-specified interim analysis according to the recommendation of the independent Data Monitoring Committee. Given that the study was able to reject the null hypothesis at the interim analysis, this analysis is considered final.
[4] Death due to pneumonitis, encephalitis, and heart failure.
[5] Death due to myelosuppression.
[6] Discontinuation due to Grade 3-4 TRAEs

- ❖ Symptoms (Lung Cancer Symptom Scale-Meso average symptom burden index) trended to improve over time with nivolumab+ipilimumab and deteriorate with chemo, although the mean changes did not meet clinically important difference thresholds (±10 score change).
- ❖ HRQoL (mean EQ-5D-3L VAS scores) improved over time with nivolumab+ipilimumab; patients remaining on treatment over 2 years had scores in line with UK population norms (82.8) with a similar trend for the EQ-5D-3L UI.
- ❖ With both on-treatment and follow-up data, nivolumab+ipilimumab significantly delayed deterioration in HRQoL and showed a trend in symptom delay vs. chemotherapy.

ESMO-MCBS version 1.1 [14]

Scale	Int.	Form	MG ST	MG	HR (96.6% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	>12months, <24 months	OS: +4.0 months	0.74 (0.60–0.91)	HR ≤0.70 AND gain ≥3-<5 months	3	x	NA	x	3
Adapted	NC	2a	>12months,<24 months	OS: +4.0 months	0.74 (0.60–0.91)	HR >0.70-0.75 AND gain ≥1.5 months	2	-2% grade 3-4 AEs, +7.6 discontinuation	NA	x	2

Risk of bias (study level) [15]

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, open-label	unclear[7]	yes[8]	unclear

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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, dMMR= mismatch repair deficient, EGFR=Epidermal Growth Factor Receptor, EMA=European Medicines Agency, ESCC=esophageal squamous cell carcinoma, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, EQ-5D-3L= European Quality of Life 5 Dimensions 3 Level questionnaire, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HCC=hepatocellular carcinoma, HR=hazard ratio, HRQoL=health-related quality of life, HSCT=hematopoietic stem-cell transplantation, I=intervention, IMAR=Immune-mediated adverse reactions, Int.=intention, IV=intravenous, MG=median gain, MSH-I=microsatellite instability-high, n=number of patients, NA=not applicable, NICE=National Institute for Health and Care Excellence, NSCLC=Non small-cell lung cancer, OS=overall survival, OSCC=Oesophageal squamous cell carcinoma, PD L1=Programmed cell death 1 ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PROs=patient-reported outcomes, QoL=quality of life, RCC=renal cell carcinoma, SAE=serious adverse event, SCCHN=Squamous cell cancer of the head and neck, ST=standard treatment, TRAE=treatment-related adverse event, UK=United Kingdom, UI=utility index, VAS=visual analogue scale, WHO=World Health Organization

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[7] Interim analysis data available; CheckMate 743 is ongoing until 04/2023
[8] The study was designed by the funder and study steering committee. The funder had a role in data collection with the investigators, data analysis and interpretation in collaboration with the authors, and the writing of the report by funding professional medical writing assistance.

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