Nivolumab (Opdivo®) in combination with ipilimumab (Yervoy®) for the first-line treatment of patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC)

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. Ipilimumab (Yervoy®) is a CTLA-4 immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells which mobilise to mount a direct T-cell immune attack against tumour cells.	Nivolumab (Opdivo®) in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) with tumour cell PD-L1 expression ≥ 1%.

Current treatment [3]

- For advanced OSCC, the current treatment goal is palliative.
- According to ESMO guidelines, chemotherapy for metastatic oesophageal cancer is indicated for palliative treatment in selected patients.
- In squamous cell carcinoma, the value of palliative chemotherapy is less proved compared to adenocarcinoma.

Regulatory status

EMA

Nivolumab (Opdivo®)

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®.

The CHMP adopted new indications as follows:

- Opdivo® in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic OSCC with tumour cell PD-L1 expression ≥ 1%.

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.

FDA

Nivolumab (Opdivo®)

Approval status for this indication: On 27 May 2022, the FDA approved nivolumab in combination with ipilimumab (Yervoy®) for the first-line treatment of patients with advanced or metastatic OSCC [8].

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 resectable (tumours ≥4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy.
  - 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®.

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

❖ Adjuvant treatment of urothelial carcinoma
- as monotherapy for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC.

❖ 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.

❖ 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 ≥ 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)

❖ 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 (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
- adjuvant treatment of patients with urothelial carcinoma 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 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.
- patients with unresectable advanced, recurrent or metastatic OSCC 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.

- 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.

Ipilimumab (Yervoy®)

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 Yervoy®.

The CHMP adopted a new indication as follows:

❖ Yervoy® in combination with nivolumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.

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.
- 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 NSCLC in adults whose tumours have no sensitising EGFR mutation or ALK translocation.

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

❖ dMMR or MSI-H CRC
- in combination with nivolumab for the treatment of adult patients with dMMR or MSI-H CRC after prior fluoropyrimidine-based combination chemotherapy.

Ipilimumab (Yervoy®)

Approval status for this indication: not approved

The FDA has accepted a supplemental biologic application for nivolumab plus ipilimumab and chemotherapy as a potential treatment option for unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma [5].

Other indications: Yervoy® is indicated for the

❖ 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 advanced RCC, as first-line treatment in combination with nivolumab.

❖ CRC
- treatment of adult and paediatric patients 12 years and older with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab (indication 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 (indication 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.

❖ MPM
- treatment of adult patients with unresectable MPM, as first-line treatment in combination with nivolumab.

Costs [10]

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

Warnings and precautions

Nivolumab (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 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.
- **Assessment of PD-L1 status**
  - When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is used.
- **Disease-specific precautions:**
  - First-line treatment of OSCC:
    - Patients with a baseline performance score ≥ 2, any history of concurrent brain metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, or at high risk of bleeding or fistula due to apparent invasion of tumour to organs adjacent to the oesophageal tumour were excluded from the clinical trial in OSCC.
    - In the absence of data, nivolumab in combination with ipilimumab or chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.
    - In the first-line OSCC trial, a higher number of deaths within 4 months was observed with nivolumab in combination with ipilimumab compared to chemotherapy. Physicians should consider the delayed onset of effect of nivolumab in combination with ipilimumab before initiating treatment in patients with poorer prognostic features and/or aggressive disease.

Ipilimumab (Yervoy®)

- **Severe and fatal immune-mediated adverse reactions**
  - Immune-mediated adverse reactions 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 immune-mediated adverse reactions. 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 potential risk to a foetus and use of effective contraception.

❖ **Assessment of PD-L1 status**

- When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is used.

❖ **Ipilimumab in combination with nivolumab**

- Most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications.
- Immune-related adverse reactions have occurred at higher frequencies when nivolumab was administered in combination with ipilimumab compared with nivolumab as monotherapy.
- Cardiac and pulmonary adverse events including pulmonary embolism have also been reported with combination therapy. Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during treatment.
- Ipilimumab in combination with nivolumab should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions.
- Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with ipilimumab in combination with nivolumab may occur at any time during or after discontinuation of therapy.

❖ **Disease specific precautions**: OSCC

- Patients with a baseline performance score ≥ 2, any history of concurrent brain metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, or at high risk of bleeding or fistula due to apparent invasion of tumour to organs adjacent to the oesophageal tumour were excluded from the clinical trial in OSCC.
- In the absence of data,ipilimumab in combination with nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.
- In the first-line OSCC trial, a higher number of deaths within 4 months was observed with ipilimumab in combination with nivolumab compared to chemotherapy. Physicians should consider the delayed onset of effect of ipilimumab in combination with nivolumab before initiating treatment in patientswith poorer prognostic features and/or aggressive disease.

Study characteristics [12-15]

Trial name	*n*	Intervention (I)	Intervention 2 (I2)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
CheckMate 648, CA209648, NCT03143153	970 1:1:1	nivolumab 240 mg IV every 2 weeks plus chemotherapy[1]	nivolumab IV 3 mg per kilogram of body weight every 2 weeks plus ipilimumab IV at a dose of 1 mg per kilogram every 6 weeks	chemotherapy alone	OS & PFS by BICR	**ongoing**[2], open-label, randomised, global, phase 3 trial	PD-L1	Bristol Myers Squibb and Ono Pharmaceutical	[14]

Efficacy (I2 vs. C)	**Safety** (I2 vs. C)
Median OS among patients with tumour-cell PD-L1 expression of 1% or greater: 13.7 months (95% CI, 11.2-17.0) vs. 9.1 months (95% CI, 7.7-10.0), HR 0.64; 98.6% CI, 0.46-0.90; p=0.001 **Patients who were alive at 12 months**: 57% vs. 37% **Median PFS (according to BICR) among patients with tumour-cell PD-L1 expression of 1% or greater**: 4.0 months (95% CI, 2.4-4.9) vs. 4.4 months (95% CI, 2.9-5.8), HR for disease progression or death: 1.02; 98.5% CI, 0.73-1.43; p=0.90	**Treatment-related AEs of grade 3 or 4:** n=102/322 (32%) vs. n=108/304 (36%) **Treatment-related SAEs of grade 3 or 4:** n=73/233 (23%) vs. n=38/304 (12%)

[1] Consisting of a 4-week cycle of IV fluorouracil at a dose of 800 mg per square meter of body-surface area on days 1 through 5 and IV cisplatin at a dose of 80 mg per square meter on day 1.

[2] The CheckMate 648 trial is currently ongoing; estimated study completion date is 08/2024.

Objective response (by BICR) among patients with tumour-cell PD-L1 expression of 1% or greater: 35% vs. 20%
Complete response: 18% vs. 5%
Median duration of response: 11.8 months vs. 5.7 months

Overall population:
Median OS: 12.7 months (95% CI, 11.3-15.5) vs. 10.7 months (95% CI, 9.4-11.9), HR 0.78; 98.2% CI, 0.62-0.98; p=0.01
Objective response: 28% vs. 27%
Complete response: 11% vs. 6%
Median duration of response: 11.1 months vs. 7.1 months

Patient-Reported Outcomes

- A longitudinal mixed-model analysis of FACT-E scores through week 49 showed an **overall increase** in the least-squares mean change from baseline with nivolumab plus ipilimumab (3.45 points; 95% CI, 0.96 to 5.94), and chemotherapy alone (1.54 points; 95% CI, −1.26 to 4.33) in the overall population.
- These improvements from baseline were **not clinically meaningful**, which indicates that health-related QoL was maintained during the treatment period.
- Except at baseline, the percentage of patients who reported not being bothered by treatment side effects over time was higher with nivolumab plus ipilimumab than with chemotherapy, whereas percentages with nivolumab plus chemotherapy were similar to those with chemotherapy alone.

Treatment-related AEs of grade 3 or 4 leading to trial-drug discontinuation: n=41/322 (13%) vs. n=14/304 (5%)
Treatment-related AEs leading death[3]: n=8/322 (2%) vs. n=6/304 (2%)

ESMO-MCBS version 1.1 [16]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	<12 months	OS: +4.6 months	0.64 (0.46-0.90)	HR≤0.65 AND gain ≥3 months	4	-	Not clinically meaningful	-	4
Adapted	NC	2a	< 12 months	OS: +4.6 months	0.64 (0.46-0.90)	HR≤0.65 AND gain ≥3 months	4	Treatment-related SAEs of grade 3 or 4: +11%	Not clinically meaningful	-1	3

Risk of bias (RCT) [17]

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[4]	yes[5]	unclear

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[3] Treatment-related deaths in I2 were from pneumonitis (n=2) and acute respiratory distress syndrome, interstitial lung disease, and pulmonary embolism (n=1 each). In addition, three deaths in I2 (one from other reasons and two from disease) were also reported by the investigator as treatment-related SAEs that eventually had a fatal outcome (acute kidney injury, general physical health deterioration, and internal haemorrhage). Treatment-related deaths in C were from acute kidney injury, pneumonia, sepsis, and septic shock (n=1 each). Two additional deaths in C (one from other reasons and one from an unknown cause) were also reported by the investigator as treatment-related serious adverse events that eventually had a fatal outcome (acute respiratory failure and death).

[4] CheckMate 648 is ongoing until 08/2024.

[5] The sponsor funded the trial, provided the trial drugs, and collaborated with the academic authors on the trial design and on 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 authors, was funded by the sponsor.

Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ASCT=autologous stem cell transplant, BICR=blinded independent central review, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, cHL=classical Hodgkin lymphoma, CPS=combined positive score, CTLA-4=cytotoxic T-lymphocyte-associated protein 4, 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, FACT-E= Functional Assessment of Cancer Therapy–Esophageal, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, GEJ=gastro-oesophageal junction, GEJC=gastro-oesophageal junction cancer, HCC=hepatocellular carcinoma, HR=hazard ratio, I=intervention, Int.=intention, MG=median gain, MPM=malignant pleural mesothelioma, n=number of patients, NSCLC=non-small cell lung cancer, OC=oesophageal cancer, OS=overall survival, OSCC= oesophageal squamous cell carcinoma, PD-1=programmed death-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, SAE=serious adverse event, SCCHN=squamous cell cancer of the head and neck, ST=standard treatment

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