Nivolumab (Opdivo®) plus ipilimumab (Yervoy®) and chemotherapy as first-line treatment for metastatic non-small cell lung cancer (NSCLC)

General information

Drug description	Indication [1, 2]
❖ Ipilimumab is an anti-CTLA-4 monoclonal antibody (IgG1κ) ❖ Nivolumab is a programmed death receptor-1 (PD-1) inhibitor	Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic NSCLC in adults whose tumours have no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation.

Current treatment [3]

- ❖ NICE recommends that chemotherapy is offered to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100), to improve survival, disease control and QoL.
- ❖ Chemotherapy for advanced NSCLC should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug.
- ❖ Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience.
- ❖ Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug.
- ❖ Pembrolizumab is recommended for use in some patients with untreated PD-L1-positive metastatic NSCLC.

Regulatory status

EMA [1, 2]

Approval status for this indication: On 17 September 2020, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Opdivo®.

The CHMP adopted an extension to the existing indication for NSCLC:

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

Other indications: Nivolumab is indicated in:

- ❖ Melanoma
  - as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults
- ❖ 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
- ❖ NSCLC
  - as monotherapy for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults.
- ❖ Renal cell carcinoma (RCC)
  - as monotherapy for the treatment of advanced RCC after prior therapy in adults.
  - in combination with ipilimumab is for the first-line treatment of adult patients with intermediate/poor-risk advanced RCC
- ❖ Classical Hodgkin lymphoma (cHL)

FDA [4-6]

Approval status for this indication: On 26 May 2020, the FDA approved the combination of nivolumab plus ipilimumab and 2 cycles of platinum-doublet chemotherapy as first-line treatment for patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations.

Other indications: Nivolumab 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 tumor aberrations, as first-line treatment in combination with ipilimumab.
  - patients with metastatic NSCLC and progression on or after platinum-based chemotherapy.
- ❖ Malignant Pleural Mesothelioma
  - adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab
- ❖ RCC
  - patients with advanced RCC who have received prior antiangiogenic therapy
  - patients with intermediate or poor risk, previously untreated advanced RCC in combination with ipilimumab
- ❖ Classical Hodgkin Lymphoma (cHL)
  - adult patients with cHL lymphoma that has relapsed or progressed after:
    - 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 a platinum-based therapy
- ❖ UC
  - patients with locally advanced or metastatic UC who:
    - o have disease progression during or following platinum-containing chemotherapy

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

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

On 17 September 2020, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Yervoy®.

The CHMP adopted a new indication as follows:

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

Other indications: Ipilimumab is indicated in:

❖ 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 is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

❖ RCC
- in combination with nivolumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced RCC.
  - 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 microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab.

❖ Hepatocellular Carcinoma (HCC)
- patients with hepatocellular carcinoma who have been previously treated with sorafenib, as a single agent or in combination with ipilimumab.

❖ Esophageal Squamous Cell Carcinoma (ESCC)
  - patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy.

Other indications: Ipilimumab is indicated for:

❖ Melanoma
- Treatment of unresectable or metastatic melanoma in adults and pediatric patients 12 years and older
- 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 pediatric patients 12 years and older with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab (accelerated approval).

❖ Hepatocellular Carcinoma
- Treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib, in combination with nivolumab (accelerated approval).

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

❖ Malignant Pleural Mesothelioma
- Treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivolumab.

Costs

10 ml **Opdivo®** concentrate for solution for infusion 10 mg/ml **= €1,430.00** (ex-factory price) [7]
Yervoy®: currently no cost information available

Study characteristics [4, 8-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)

CHECKMATE-9LA, CA2099LA, NCT03215706	719	Nivolumab (360 mg every 3 weeks) plus ipilimumab (1 mg/kg every 6 weeks) and platinum-doublet chemotherapy every 3 weeks for 2 cycles	Platinum-doublet chemotherapy every 3 weeks for four cycles	OS	Randomized, open-label trial	-	Bristol-Myers Squibb	Link[1]

Efficacy (I vs. C)[2]	**Safety** (I vs. C)
Median OS: 14.1 months vs. 10.7 months, HR 0.69; 96.71% CI: 0.55-0.87, p=0.0006 **Median PFS per BICR:** 6.8 months vs. 5 months, HR 0.70; 95% CI: 0.57-0.86, p=0.0001 **Confirmed ORR per BICR:** 38% vs. 25% **Median response duration:** 10 months vs. 5.1 months **Median time to response:** 2.5 vs. 1.6 months **Subsequent systemic therapy** received by 28.8% vs. 41.1% of patients **Subsequent immunotherapy** received by 3.9% vs. 27.9% of patients	**Grade 3–4 treatment-related AEs:** 47% vs 38% **SAEs:** n=203/358 (56.70%) vs. n=144/349 (41.26%) **All-cause mortality**: n=203/358 (56.70%) vs. n=144/349 (41.26%)

ESMO-MCBS version 1.1

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	≤12 m	OS: +3.4 m	HR 0.69 (0.55-0.87)	HR >0.65 AND Gain ≥3 m	4	-	NA	-	4
Adapted	NC	2a	≤12 m	OS: +3.4 m	HR 0.69 (0.55-0.87)	HR >0.65-0.70 OR Gain ≥1.5m	2	+9% grade3-4 AEs	NA	-	2

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
Not applicable, only abstract available					

First published: 10/2020
Last updated: 01/2021

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, 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, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HCC=hepatocellular carcinoma, HR=hazard ratio, HSCT= hematopoietic stem cell transplantation, I=intervention, Int.=intention, NA=not available, m=months, MG=median gain, n=number of patients, NICE=National Institute for Health and Care Excellence, NSCLC=non-small cell lung cancer, ORR=overall response rate, OS=overall survival, 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, SCCH=squamous cell cancer of the head and neck, SCLC=small cell lung cancer, ST=standard treatment, UC=urothelial carcinoma

[1] Only abstract available.
[2] Interim analysis data; CheckMate 9LA is ongoing until 11/2020

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