Nivolumab (Opdivo®) in combination with ipilimumab (Yervoy®) for the treatment of patients with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer

General information

Drug description	Indication [1]
Nivolumab and ipilimumab are immune checkpoint inhibitors.	Nivolumab in combination with ipilimumab is indicated for the treatment of adult patients with dMMR or MSI-H metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.

Current treatment [2]

- The management of metastatic colorectal cancer is largely palliative, combining specialist treatments (palliative surgery, chemotherapy and radiation) with control of symptoms and psychosocial support.
- The majority of patients with metastases have a disease that is initially not suitable for potentially curative resection; therefore, treatment aims to convert initially unresectable disease to resectable disease with combination chemotherapy.
- Treatment may include:
  - Chemotherapy
    - FOLFOX (folinic acid, 5-fluorouracil and oxaliplatin) as first or second-line treatment
    - XELOX (capecitabine and oxaliplatin) as first-line or second-line treatment
    - Irinotecan as second-line treatment
    - FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first or second-line treatment
    - Raltitrexed – for patients who are intolerant to folinic acid, 5-fluorouracil, or for whom these drugs are not suitable
    - Trifluridine/tipiracil
  - Biological agents

    According to current NICE guidance:
    - Cetuximab is recommended, within its marketing authorisation, as an option for previously untreated EGFR-expressing, RAS wild-type metastatic colorectal cancer in adults in combination with FOLFOX or FOLFIRI
    - Panitumumab is recommended, within its marketing authorisation, as an option for previously untreated RAS wild-type metastatic colorectal cancer in adults in combination with FOLFOX or FOLFIRI
- Other licensed biologics include bevacizumab and aflibercept.

Regulatory status

EMA [1, 3, 4]

Nivolumab (Opdivo®)

Approval status for this indication: On 20 May 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Opdivo®.

The CHMP adopted a new indication as follows:

- Nivolumab in combination with ipilimumab is indicated for the treatment of adult patients with dMMR or MSI-H metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.

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. 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.

FDA [5-7]

Approval status for this indication: On 10 July 2018, the FDA granted accelerated approval to ipilimumab (Yervoy®) for use in combination with nivolumab for the treatment of patients 12 years of age and older with MSI-H or dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This new use has also been added to the nivolumab (Opdivo®) labelling. Nivolumab received accelerated approval for this indication as a single agent on 31 July 2017.

Nivolumab (Opdivo®)

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

- 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.
- 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.
- 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®)

- 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 malignant pleural mesothelioma, 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 is 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 platinum-based therapy.
- Urothelial Carcinoma
  - adjuvant treatment of patients with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection of urothelial carcinoma.
  - patients with locally advanced or metastatic urothelial carcinoma who (indication is approved under accelerated approval based on overall response rate and duration of response:
    - have disease progression during or following platinum-containing chemotherapy
    - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- Hepatocellular Carcinoma (HCC)
  - patients with hepatocellular carcinoma who have been previously treated with sorafenib, as a single agent or in combination with ipilimumab.
- 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 (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy
- Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma
  - patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and oesophagal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.

Ipilimumab (Yervoy®)

Approval status for this indication: On 20 May 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 as follows:

- Ipilimumab in combination with nivolumab is indicated for the treatment of adult patients with dMMR or MSI-H metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.

Other indications: Ipilimumab 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.

Other indications: Ipilimumab is indicated for the treatment of

- Melanoma
  - unresectable or metastatic melanoma in adults and paediatric patients 12 years and older.
  - adult patients with unresectable or metastatic melanoma, in combination with nivolumab.
  - patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy (adjuvant treatment).
- RCC
  - patients with intermediate or poor risk advanced RCC, as first-line treatment in combination with nivolumab.
- HCC
  - patients with HCC who have been previously treated with sorafenib, in combination with nivolumab (indication is approved under accelerated approval based on overall response rate and duration of response).
- NSCLC
  - 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.
  - 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
  - adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivolumab.

Costs [8]

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

Warnings and precautions [5, 6]

Nivolumab (Opdivo®)

- **Immune-Mediated Adverse Reactions (IMAR):**
  - IMARs, 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 patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody.

- ❖ **Embryo-Fetal toxicity:**
  - Can cause fetal 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

Ipilimumab (Yervoy®)

- ❖ **Severe and Fatal IMARs:**
  - IMARs 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) IMARs.
- ❖ **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-Fetal Toxicity:**
  - Can cause fetal harm. Advise of the potential risk to a foetus and use of effective contraception.

Study characteristics [9, 10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
CheckMate 142, Study CA209142 NCT02060188	82	Ipilimumab 1 mg/kg IV and nivolumab 3 mg/kg IV every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg IV as a single agent every 2 weeks, until unacceptable toxicity or radiographic progression	-	Investigator-assessed objective response as per RECIST 1.1	Multi-centre, non-randomised, multiple parallel-cohort, open-label, phase 2 study	-	Bristol-Myers Squibb	[9]

Efficacy (I vs. C)

ORR among 82 patients (by an independent radiographic review committee using RECIST 1.1): 46% (95% CI: 35,58), with 3 complete and 35 partial responses.

Response duration of ≥ 6 months: 89% of responding patients.

Separate cohort of 58 patients with dMMR/MSI-H mCRC with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy who received nivolumab alone: ORR of 28% with 67% having response durations of ≥ 6 months [7].

Safety, n=119 [11]

Grade ≥3 TRAEs: n=38/119 (32%)
Select TRAEs (sTRAEs) Grade 3 or 4: n= 29/119 (24%)
Deaths attributed to study drug-related toxicity: n=0
Discontinuation due to TRAEs: n=15/119 (13%)

2-year clinical update [12]:

- ORR (95% CI) in 45 patients with median follow-up of 29.0 months increased to 69% (53–82) from 60% (44.3–74.3)
- CR rate increased to 13% from 7%; PR: 56%, SD: 16%, PD:13%
- The concordance rate of investigator-assessed and blinded independent central review was 89%.
- Disease control rate: 84%
- Median DOR was not reached
- Median PFS and OS were not reached, and 24-month rates were 74% and 79%, respectively.
- 19 patients discontinued study treatment without subsequent therapy.

Clinical update [13]

- ORR for all 45 patients (median follow-up was 13.8 months): 60% (95% CI 44.3–74.3).
- Responses were consistent with the overall population across subgroups including age, ECOG performance status, prior adjuvant/neoadjuvant therapy, and mutation status.

UPDATE: Efficacy results (minimum follow-up 46.9 months; median follow-up 51.1 months, n=119) [4]:
Confirmed objective response: 64.7% (95% CI, 55.4-73.2)
CR: 12.6%
PR: 52.1%
Stable disease: 21.0%
Median DOR: NR (range 1.4-58.0+)
Median time to response: 2.8 months (range 1.1-37.1)

ESMO-MCBS version 1.1 [14]

The ESMO-MCBS is not applicable since no statistically significant endpoints were reported in the analyses.

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**
Not appropriate, single-arm study	Not appropriate, single-arm study	No, open-label	unclear[1]	yes[2]	high

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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, CR=complete response, dMMR=mismatch repair deficient, DOR=duration of response, ECOG= Eastern Cooperative Oncology Group, 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=haematopoietic stem cell transplantation, I=intervention, IMAR=immune-Mediated Adverse Reactions Int.=intention, MG=median gain, MPM=malignant pleural mesothelioma MSI-H= microsatellite instability high, PR=partial response, n=number of patients, NICE=National Institute for Health and Care Excellence, NSCLC=non small cell lung cancer, ORR=objective response rate, OS=overall survival, OSCC=oesophageal squamous cell

[1] CheckMate 142 trial is ongoing until 07/2022.

[2] The funder provided the study drug and worked with the investigators to design the study and to collect, analyse, and interpret the data. All authors made the decision to submit the report for publication, and all drafts of the report were prepared by the corresponding author with input from coauthors and editorial assistance from professional medical writers, funded by the funder.

carcinoma, PD=pogressive disease, PD-L1=programmed death-ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=quality of life, RCC=renal cell carcinoma, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, SCCHN=squamous cell cancer of the head and neck, SD=stable disease, ST=standard treatment, sTRAE=select treatment-related adverse event, TRAE=treatment-related adverse event

References:

1. European Medicines Agency (EMA). Medicines. Opdivo. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/opdivo-4].
2. National Institute for Health Research (NIHR). Nivolumab (Opdivo) + Ipilimumab (Yervoy) for metastatic colorectal cancer patients with deficient DNA mismatch repair mechanism (dMMR) or high microsatellite instability (MSI-H). [Available from: http://www.io.nihr.ac.uk/wp-content/uploads/migrated_new/12638-Nivolumab-+-ipilimumab-for-metastatic-colorectal-cancer.pdf].
3. European Medicines Agency (EMA). Medicines. Yervoy. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/yervoy-2].
4. European Medicines Agency (EMA). Opdivo: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf].
5. U.S. Food and Drug Administration (FDA). Opdivo. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125554s092lbl.pdf].
6. U.S. Food and Drug Administration (FDA). Yervoy. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125377s121lbl.pdf].
7. U.S. Food and Drug Administration (FDA). FDA grants accelerated approval to ipilimumab for MSI-H or dMMR metastatic colorectal cancer. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-ipilimumab-msi-h-or-dmmr-metastatic-colorectal-cancer].
8. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
9. Overman MJ, McDermott R, Leach J, Lonardi S, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol 2017; 18: 1182–91 Published Online July 19, 2017. [Available from: https://linkinghub.elsevier.com/retrieve/pii/S1470204517304229].
10. U.S.National Library of Medicine, ClinicalTrials.gov. An Investigational Immuno-therapy Study of Nivolumab, and Nivolumab in Combination With Other Anti-cancer Drugs, in Colon Cancer That Has Come Back or Has Spread (CheckMate142). [Available from: https://clinicaltrials.gov/ct2/show/NCT02060188].
11. Morse MA, Overman MJ, Hartman L, et al. Safety of Nivolumab plus Low-Dose Ipilimumab in Previously Treated Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer. The Oncologist 2019;24:1453–1461.
12. Lenz H, Lonardi S, Zagonel V. Nivolumab (NIVO) + low-dose ipilimumab (IPI) as first-line (1L) therapy in microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Two-year clinical update. [Available from: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.4040].
13. Lenz H, Lonardi S, Zagonel V, et al. Nivolumab plus low-dose ipilimumab as first-line therapy in microsatellite instability-high/DNA mismatch repair deficient metastatic colorectal cancer: Clinical update. [Available from: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.4_suppl.11].
14. Cherny NI DU, Bogaerts J., et al.,. ESMO-Magnitude of Clinical Benefit Scale version 1.1. . Annals of Oncology 28: 2340–2366, 2017.

15. European Network for Health Technology Assessment (EUnetHTA). LEVELS OF EVIDENCE. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].