Nivolumab (Opdivo®) as monotherapy for the adjuvant treatment of Stage IIB or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease

General information

Drug description [1]

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. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab (Opdivo®) potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Indication [2]

Nivolumab (Opdivo®) as monotherapy is indicated for the adjuvant treatment of adults and adolescents 12 years of age and older with stage IIB or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

Incidence [3]

In Austria, in 2020, the age-standardised incidence[1] rate of malignant melanoma was 22.1 per 100,000 men and 15.1 per 100,000 women.

Current treatment [4]

For the management of local/locoregional disease, ESMO[2] recommends:

- Wide local excision of primary tumours with safety margins of 0.5 cm for in situ melanomas, 1 cm for tumours with a tumour thickness up to 2mm and 2 cm for thicker tumours is recommended.
- SNB is recommended for all patients with pT1b or higher according to the AJCC 8th edition TNM staging system.
- CLND is not recommended for SN-positive patients. In the case of isolated locoregional clinically detectable (macroscopic, non-SN) LN metastases, CLND is indicated; removal of the tumour-bearing LN alone is insufficient.
- Patients with resected stage III melanomas should be evaluated for adjuvant therapy.
- Adjuvant RT for local tumour control can be considered in cases of inadequate resection margins of LMM, in R1 resections or after resection of bulky disease. Adjuvant RT is not recommended in the adjuvant setting.
- Anti-PD-1 adjuvant therapy, nivolumab, pembrolizumab or dabrafenib/trametinib are the preferred treatment options.

Management of advanced/metastatic disease:

- Surgical removal or stereotactic irradiation of locoregional recurrence or single distant metastasis should be considered in fit patients, as a therapeutic option, offering potential for long-term disease control.
- Patients with metastatic melanoma should have metastasis (preferably) or the primary tumour screened for detection of BRAF V600 mutation. Treatment options for the first- and second-line settings include anti-PD-1 antibodies (pembrolizumab, nivolumab), PD-1 and ipilimumab for all patients, and BRAFi/MEKi combination for patients with BRAF-mutated melanoma.
- For unresectable stage IIIB/C, IVM1a, T-VEC is also an option.
- PD-1 blockade or PD-1 and ipilimumab are now a standard of care for all patients, regardless of their BRAF status, in the first-line setting.
- For BRAF WT disease, second-line options are very limited and inclusion in clinical trials and/or personalised approaches could be discussed. If the first-line treatment was anti-PD-1 alone, ipilimumab is an option as well as ipilimumab/nivolumab.
- For BRAF-mutated disease, all the options available for WT melanoma are still valid with the addition of BRAFis/MEKis if not used in the first-line setting.
- For NRAS-mutated melanoma, due to the limited efficacy of MEK inhibitors, first-line immunotherapy options identical to those of WT melanoma are the first choice.
- If clinical trials or the approved new compounds are not available, cytotoxic drugs such as DTIC or temozolomide may be administered, with modest activity shown.

[1] European Standard Population 2013.

[2] Due to an ongoing update, the Onkopedia guideline "melanoma" is currently not available.

- For management of brain metastases, study results suggest, ipilimumab/nivolumab combination therapy as the preferred first-line treatment also in BRAF-mutated asymptomatic patients. For patients with a small number of asymptomatic metastases (<5–10), non-bulky disease (<3 cm), SRS upfront is an option. Other patients should be considered for systemic treatment first, keeping SRS for the treatment of non-responding lesions. For patients failing systemic treatment, SRS could be considered as a salvage therapy if the total number of progressing lesions is <5–10 and their maximal size <3 cm DGHO/OEGH recommendation preferred.

Regulatory status

EMA [1, 2]

Approval status for this indication: On 20 July 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Opdivo®.

The CHMP adopted an extension to an existing indication to include treatment of stage IIB or IIC melanoma:

- Opdivo® as monotherapy is indicated for the adjuvant treatment of adults and adolescents 12 years of age and older with stage IIB or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

Other indications: Opdivo® is indicated

- as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older. 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.
- in combination with ipilimumab and 2 cycles of platinum-based chemotherapy for the first-line treatment of metastatic non-small cell lung cancer (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.
- in combination with platinum-based chemotherapy for the neoadjuvant treatment of resectable NSCLC at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%.
- in combination with ipilimumab for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.
- as monotherapy for the treatment of advanced renal cell carcinoma (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.
- as monotherapy for the treatment of adult patients with relapsed or refractory cHL after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.
- as monotherapy for the treatment of recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) in adults progressing on or after platinum-based therapy.

FDA [5]

Approval status for this indication: UPDATE: On 13 October 2023, the FDA approved nivolumab (Opdivo®), for the adjuvant treatment of adult and paediatric patients 12 years and older with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma [6].

Other indications: Opdivo® is indicated for the treatment of:

- adult and paediatric (12 years and older) patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab.
- 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.
- adult 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®.
- adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab.
- adult patients with intermediate or poor risk advanced RCC, as a first-line treatment in combination with ipilimumab.
- adult patients with advanced RCC, as a first-line treatment in combination with cabozantinib.
- adult patients with advanced RCC who have received prior anti-angiogenic therapy.
- adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after
  - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
  - 3 or more lines of systemic therapy that includes autologous HSCT.
- adult patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy.
- adjuvant treatment of adult patients with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection of urothelial carcinoma.
- adult patients with locally advanced or metastatic urothelial carcinoma who:

- as monotherapy for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.
- 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.
- in combination with ipilimumab for the treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic CRC after prior fluoropyrimidine-based combination chemotherapy.
- in combination with ipilimumab 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%.
- 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.
- 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.
- in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5.
  - have disease progression during or following platinum-containing chemotherapy.
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- adult and paediatric (12 years and older) patients with microsatellite 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 (this indication is approved under accelerated approval based on ORR and DoR).
- adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib in combination with ipilimumab (this indication is approved under accelerated approval based on ORR and DoR).
- adult patients with completely resected oesophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy (CRT).
- adult patients with unresectable advanced or metastatic OSCC as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy.
- adult patients with unresectable advanced or metastatic OSCC as first-line treatment in combination with ipilimumab.
- adult patients with unresectable advanced, recurrent, or metastatic OSCC after prior fluoropyrimidine- and platinum-based chemotherapy.
- adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and oesophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.

Manufacturer

The manufacturer of Opdivo® is Bristol-Myers Squibb Pharma EEIG.

Costs [7]

12 ml Opdivo® concentrate for solution for infusion 10 mg/ml = **€1,716.00** (ex-factory price)

Disease-specific precautions [1]

Advanced melanoma

- Patients with a baseline performance score ≥2, active brain metastases or leptomeningeal metastases, autoimmune disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the pivotal clinical trials of nivolumab or nivolumab in combination with ipilimumab.
- Patients with ocular/uveal melanoma were excluded from pivotal clinical trials of melanoma. In addition, CA209037 excluded patients who have had a Grade 4 adverse reaction that was related to anti-CTLA-4 therapy.
- Patients with baseline performance score of 2, treated leptomeningeal metastases, ocular/uveal melanoma, autoimmune disease, and patients who have had a Grade 3-4 adverse reaction that was related to prior anti-CTLA-4 therapy were included in study CA209172.

- In the absence of data for patients who had been receiving systemic immunosuppressants prior to study entry, and for patients with active brain or leptomeningeal metastases, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.
- Relative to nivolumab monotherapy, an increase in PFS for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression. The improvement in OS was similar between nivolumab in combination with ipilimumab and nivolumab monotherapy in patients with high tumour PD-L1 expression (PD-L1 ≥ 1%).
- Before initiating treatment with the combination, physicians are advised to carefully evaluate the individual patient and tumour characteristics, taking into consideration the observed benefits and the toxicity of the combination relative to nivolumab monotherapy.

Use of nivolumab in melanoma patients with rapidly progressing disease

- Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with rapidly progressing disease.

Adjuvant treatment of melanoma

- There are no data on adjuvant treatment in patients with melanoma with the following risk factors:
  - patients with prior autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications,
  - patients with prior therapy for melanoma (except patients with surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥ 6 months prior to randomisation),
  - patients treated with prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways),
  - subjects under the age of 18 years.
- In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis

Study characteristics [8-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up (I vs. C)	Characteristics	Biomarker	Funding	Publication(s)
CheckMate 76K CA20976K NCT04099251	790 (2:1)	nivolumab IV 480 mg Q4W for 12 months	placebo IV Q4W for 12 months	investigator-assessed recurrence-free survival (RFS)[3]	15.8 vs. 15.9 months	**ongoing**[4], randomised, double-blind, phase 3 trial	-	Bristol-Myers Squibb	CheckMate 76K [9]

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline (I vs. C)
❖ Signed Written Informed Consent ❖ ≥ 12 years of age diagnosed with Stage IIB/C cutaneous melanoma (AJCC Staging, 8th edition) ❖ Histologically confirmed melanoma that is completely surgically resected, with documented negative margins (per local standard) for disease on resected specimens. ❖ All melanomas, except ocular/uveal and mucosal	❖ History of ocular or mucosal melanoma. ❖ Active, known, or suspected autoimmune disease. ❖ Prior malignancy active within the previous 3 years ❖ Participants with a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of randomization. ❖ Women who are pregnant or breastfeeding. ❖ Serious or uncontrolled medical disorders.	❖ Mean age: 59.9 vs. 59.3 years ❖ Male sex: 61% vs. 61% ❖ ECOG PS 0: 94% vs. 93% ❖ Stage: • IIB: 60% vs. 62% • IIC: 40% vs. 38% ❖ T category: • T3b: 39% vs. 39% • T4a: 21% vs. 22%

[3] Time between randomisation and first recurrence.
[4] Estimated study completion date is 06/2027.

melanoma, regardless of primary site of disease will be allowed. ❖ Complete resection with documented negative margins (per local standard) and sentinel lymph node assessment for presence/absence of disease, must be performed within 12 weeks prior to randomization. ❖ Negative sentinel lymph node biopsy. ❖ Disease-free status documented by a complete physical examination (within 14 days) and imaging studies within 4 weeks (28 days) prior to randomization. ❖ The complete set of baseline images must be available before randomization. ❖ Participant has not been previously treated for melanoma beyond complete surgical resection of the melanoma lesion. ❖ Participant has recovered adequately from toxicity and/or complications from surgery prior to study start. ❖ ECOG performance status of 0 or 1 at the time of enrolment. ❖ Tumour tissue from the primary diagnostic biopsy must be shipped to the central laboratory prior to randomization. ❖ Participants must be able and willing to comply with the study visit schedule and study procedures. ❖ Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatment. ❖ Women of childbearing potential must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment(s) plus 5 half-lives of study treatment plus 30 days for a total of 5 months after the last dose of study treatment	❖ Use of an investigational agent or an investigational device within 28 days before administration of first dose of study drug. ❖ Treatment directed against the resected melanoma that is administered after the complete resection. ❖ Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA-4 antibody, or agents that target IL-2 pathway any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. ❖ Treatment with complementary medications to treat the disease under study within 2 weeks prior to randomization/treatment. ❖ Participants who have received a live / attenuated vaccine within 30 days of first treatment. ❖ The concomitant use of topical Toll-like receptor 7 agonists, calcineurin inhibitors, or topical immunotherapy/contact sensitizer preparations, eg, but not limited to 2,4 dinitrochlorobenzene, squaric acic dibutylester, and diphencyprone at or near the primary tumour site, are not specifically excluded, but consultation with the Medical Monitor or designee is highly recommended prior to enrolling participants using these agents. ❖ Participants currently in other interventional trials, may not participate in BMS clinical trials until the protocol-specific ❖ washout period is achieved. ❖ Physical and Laboratory Test Findings • WBC < 2000/µ • Neutrophils < 1500/µ • Platelets < 100×103/µ • Haemoglobin < 9.0 g/dL • Serum creatinine > 1.5 x ULN, unless creatinine clearance ≥ 40 mL/min • AST/ALT: > 3.0 x UL • Total bilirubin > 1.5 x ULN • Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, • Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). ❖ Known history of allergy or hypersensitivity to study drug components. ❖ Known history of severe hypersensitivity reaction (Grade ≥ 3) to any monoclonal antibody.	• T4b: 40% vs. 39% ❖ Melanoma subtype: • Nodular: 51% vs. 50% • Superficial spreading: 29% vs. 31% • Acral lentiginous: 5% vs. 6% • Other/Not reported: 15% vs. 13% ❖ Region: • Western Europe: 58% vs. 61% • US and Canada18% vs. 17% • Australia; 13% vs. 11% • Eastern Europe: 11% vs. 11%
Efficacy (I vs. C), interim analysis data		**Safety** (I vs. C), , interim analysis data

❖ Cutoff date 28 June 2022 ❖ Nivolumab **significantly reduced** the risk of recurrence vs. placebo 12.5% vs. 26.1% had recurrence or death, with an HR for RFS of 0.42 (95% CI, 0.30–0.59; p < 0.0001) ❖ 12-month RFS rates: 89.0% (95% CI, 85.6–91.6) vs. 79.4% (95% CI, 73.5–84.1) ❖ **Median RFS:** not reached in both groups ❖ **RFS benefit** was driven by reductions in the incidence of both distant recurrences (5% vs. 12%) and regional recurrences (2% vs. 8%) ❖ New melanoma lesions occurred in 2% vs. 3% of patients, respectively, and likely did not have an impact on the observed RFS benefit. ❖ Occurrence of new primary invasive melanomas at first recurrence: 0.8% vs. 1.1% (for melanoma in situ: 1.3% vs. 1.9%) ❖ Sites of lesions/metastases at first recurrence for nivolumab vs. placebo were most commonly found in skin (3.6%) vs. 6.1%, lungs (3.2%) vs. 9.1% and lymph nodes (3.2%) vs. 12.5%; n=6 in each group had an initial local or regional recurrence or new primary melanoma and went on to have a distant recurrence. ❖ The RFS benefit of nivolumab versus placebo was consistent across stages, with an HR of 0.34 (95% CI, 0.20–0.56) for patients with stage IIB disease and 0.51 (95% CI, 0.32–0.81) for patients with stage IIC disease. ❖ The RFS forest plot shows that the RFS benefit with nivolumab was consistent across prespecified patient subgroups, which is illustrated by the clustering of HRs around the overall ITT unstratified HR of 0.43 (95% CI, 0.31–0.61) ❖ RFS benefit was consistent across T categories with an expected slightly overall worse prognosis for patients with T4b disease ❖ In a descriptive analysis, the benefit of nivolumab for reducing the risk of distant metastases or death was similar to the overall RFS benefit: HR was 0.47 (95% CI, 0.30-0.72) with 12-month distant metastasis-free survival rates of 92% vs. 87% ❖ In tumour (T)-category subgroups, 12-mont RFS rates (95% CI) for patients in the nivolumab group were 92.6% I T3b (87.2–95.7) and T4a (85.1–96.4) disease and 83.8% (77.5–88.4) in T4b disease; for patients in the placebo group, 12-month RFS rates were 83.4% (73.8–89.7), 85.2% (70.7–92.8) and 72.3% (61.9–80.2), respectively ❖ In patients with BRAFV600 mutations, RFS HR was 0.56 (95% CI: 0.30–1.04), with 12-month RFS rates (95% CI) of 87.3% (80.0–92.1) and 81.7% (70.4–89.0), respectively. ❖ In patients with BRAFV600–wild-type disease, RFS HR was 0.33 (95% CI: 0.21–0.53), with12-month RFS rates (95% CI) of 91.2% (86.8–94.1) and 77.1% (68.4–83.6). ❖ In patients with BRAFV600 mutation status not evaluable/not reported, RFS HR was 0.59 (95% CI: 0.26–1.33), with 12-month RFS rates (95% CI) of 84.2% (73.0–91.0) and 82.2% (65.7–91.3), respectively. ❖ Distant metastasis-free survival: 8.0% vs. 15.5%; HR 0.47 (95% CI: 0.30–0.72) for the ITT population; HRs 0.40 (95% CI: 0.21–0.78) and 0.52 (95% CI: 0.30–0.93) among patients with stage IIB and stage IIC disease. Efficacy results based on data cut-off 21 February 2023; minimum follow-up of 15.6 months: ❖ Median RFS: NR vs. 36.14 months; HR 0.53 (95% CI, 0.40-0.71) ❖ RFS rate at 12 months: 88.8% (95%CI, 85.6-91.2) vs. 81.1% (95% CI, 75.7-85.4) ❖ RFS rate at 18 months: 83.9% (95% CI, 80.3-86.9) vs. 70.7% (95% CI, 64.5-76.1) ❖ The exploratory RFS analyses by PD-L1 expression showed a HR for nivolumab vs. placebo of 0.43 (95% CI, 0.22-0.84) in patients (n=167) with PD- L1 expression ≥ 1%, 0.82 (95% CI, 0.44-1.54) in patients (n=135) with PD-L1 expression < 1%, and 0.50 (95% CI, 0.34-0.73) in patients (n=488) with indeterminate/not reported/not evaluable PD-L1 expression.	**Any AE grade 3-4:** 22% vs. 12% **TRAE grade 3-4:** 10.3% vs. and 2.3% **TRAE (any grade) leading to discontinuation:** 14.7% vs. 2.7% **Immune-mediated AE grade 3-4:** 8% vs. 1% **Treatment-related death:** 0.2%[5] vs 0%
Patient-reported outcomes	

[5] Due to heart failure and acute kidney injury that was not related to myocarditis.

Currently, there are no patient-reported outcomes available.

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	curative	1	-	-	RFS: 0.42 (0.30–0.59)	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	A	-	-	-	A
Adapted	curative	1	-	-	RFS: 0.42 (0.30–0.59)	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	A	-	-	-	A

Risk of bias (RCT) [12]

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 low risk	Yes low risk	Yes low risk	unclear[6] unclear risk	Yes[7] high risk	Unclear risk

Ongoing trials [13]

NCT number/trial name	Description	Estimated study completion date
NCT04099251/ CheckMate 76K	Please see above.	06/2027
NCT04309409/ NivoMela	Adjuvant nivolumab treatment in stage II high-risk melanoma - a randomised, controlled, phase III trial with biomarker-based risk stratification	01/2028
NCT05907122	A randomised, double-blind study evaluating pharmacokinetic similarity of ABP 206 compared with Opdivo® (Nivolumab) in resected stage III or stage IV melanoma subjects in the adjuvant setting	07/2025
NCT02388906/ CheckMate 238	A phase 3, randomised, double-blind study of adjuvant immunotherapy with nivolumab vs. ipilimumab after complete resection of stage IIIb/c or stage IV melanoma in subjects who are at high risk for recurrence	10/2024

Available assessments

- An efficacy assessment „Nivolumab (Melanom, adjuvant)", including patients after complete resection of stage IIIb/c or stage IV melanoma (but not stage IIb or IIc patients), was published by NIHR in April 2021 [14].
- No further assessment was identified.

Other aspects and conclusions

- In July 2023, the **CHMP adopted an extension to an existing indication** (to include treatment of stage IIB or IIC melanoma) for nivolumab (Opdivo®) as monotherapy for the adjuvant treatment of adults and adolescents 12 years of age and older with Stage IIB or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. In October 2023, the FDA approved nivolumab (Opdivo®), for the adjuvant treatment of adult and paediatric patients 12 years and older with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.
- **CheckMate 76K** (NCT04099251) is an **ongoing**, randomised, double-blind, phase 3 trial to evaluate adjuvant therapy with nivolumab vs. placebo in patients with resected stage IIB/C melanoma. Patients with histologically confirmed, resected, stage IIB/C cutaneous melanoma, a negative sentinel lymph node biopsy, with an ECOG 0 or 1 and who have not been previously treated for melanoma were **included**. Patients with a history of ocular or mucosal melanoma, pregnant or nursing women, participants with active known or suspected autoimmune disease, a known history of allergy or hypersensitivity to study drug components or prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA-4 antibody, or agents that target IL-2 pathways, T-cell stimulators, or checkpoint pathways were **excluded**.

[6] The CheckMate 76K trial is ongoing; currently, only interim analysis data is available.
[7] The trial was designed by the lead author and the sponsor. The data were collected by the sponsor and analysed in collaboration with the authors.

- ❖ **RFS is the primary endpoint** of the CheckMate 76K trial; nivolumab significantly reduced the risk of recurrence vs. placebo, with a stratified HR of 0.42 (95% CI, 0.30-0.59) and 12-month RFS rates of 89% vs. 79%.
- ❖ There is **no data** regarding patient-reported outcomes available.
- ❖ The **ESMO-MCBS was not applicable, because the primary endpoint "recurrence-free survival" could not be assessed.**
- ❖ The **risk of bias was considered unclear. However, it is increased by the involvement of the sponsor in trial design, data collection and data analysis**.
- ❖ Beside the ongoing CheckMate 76K trial, **3 further phase 3 trials**, assessing the efficacy and safety of nivolumab in the adjuvant setting in melanoma patients, were identified.
- ❖ For the assessed indication, available **evidence is rare**. Phase 3 data – from CheckMate 76K as well as from further phase 3 trials – is required to substantiate the role of nivolumab monotherapy in the adjuvant treatment of patients with stage IIb/IIC melanoma.

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Abbreviations: AE=adverse event, AJ=adjustment, AJCC=American Joint Committee on Cancer, ASCT=autologous stem cell transplant, BRAFi=BRAF inhibitor, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, cHL=classical Hodgkin lymphoma, CLND=complete lymph node dissection, CPS=combined positive score, CRC=colorectal cancer, CRT=chemoradiotherapy, DGHO=Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie, DmmR=deficient mismatch repair gene expression, DoR=duration of response, DTIC=dacarbazine, EGFR=estimated glomerular filtration rate, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HCC=hepatocellular carcinoma, HR=hazard ratio, HSCT=haematopoietic stem cell transplantation, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, LMM=lentigo maligna melanoma, LN=lymph node, MEKi=MEK inhibitor, MG=median gain, MIUC=muscle invasive urothelial carcinoma, MSI-H=microsatellite instability-high, n=number of patients, NICE=National Institute for Health Care Excellence, NSCLC=Non-small cell lung cancer, OEGH= Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie, OS=overall survival, OSCC=oesophageal squamous cell carcinoma, PD-1=programmed cell death protein 1, PD-L1=programmed death ligand 1, PD-L2=programmed death ligand 2, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RCC=renal cell carcinoma, RFS=recurrence-free survival, RT=radiotherapy, SAE=serious adverse event, SCCHN=Squamous cell carcinoma of the head and neck; SNB=sentinel lymph node biopsy, SRS=stereotactic radiosurgery, ST=standard treatment, TNM=tumour, node, metastasis, TRAE=treatment-related adverse event, T-VEC=talimogene laherparepvec, WT=wild type

References:

1. 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].
2. European Medicines Agency (EMA). Medicines. Opdivo. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/opdivo-10].
3. Statistik Austria. Krebserkrankungen. Ausgewählte Krebslokalisationen nach Inzidenz. [Available from: https://www.statistik.at/statistiken/bevoelkerung-und-soziales/gesundheit/krebserkrankungen].
4. O M, van Akkooi ACJ, Ascierto PA, Dummer R, Keilholz U, on behalf of the ESMO Guidelines Committee. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 30: 1884–1901, 2019.
5. U.S. National Food and Drug Administration (FDA). Opdivo. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125554s119lbl.pdf].
6. U.S. National Food and Drug Administration (FDA). FDA approves nivolumab for adjuvant treatment of Stage IIB/C melanoma. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-adjuvant-treatment-stage-iibc-melanoma].
7. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
8. Supplement to: Kirkwood, J.M., Del Vecchio, M., Weber, J. et al. Adjuvant nivolumab in resected stage IIB/C melanoma: primary results from the randomized, phase 3 CheckMate 76K trial. Nat Med (2023). DOI: https://doi.org/10.1038/s41591-023-02583-2

9. Kirkwood JM , Del Vecchio M, Weber J. Adjuvant nivolumab in resected stage IIB/C melanoma: primary results from the randomized, phase 3 CheckMate 76K trial. Nat Med (2023). DOI: https://doi.org/10.1038/s41591-023-02583-2
10. U.S. National Library of Medicine, ClinicalTrials.gov. Effectiveness Study of Nivolumab Compared to Placebo in Prevention of Recurrent Melanoma After Complete Resection of Stage IIB/C Melanoma (CheckMate76K). [Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04099251].
11. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. . Annals of Oncology 28: 2340–2366, 2017.
12. 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].
13. U.S. National Library of Medicine, ClinicalTrials.gov. [Available from: https://classic.clinicaltrials.gov/ct2/home].
14. Gemeinsamer Bundesausschuss, IQWIG. Nivolumab (Melanom, adjuvant) – Nutzenbewertung gemäß § 35a SGB V. [Available from: https://www.g-ba.de/downloads/92-975-4590/2021-04-01_Nutzenbewertung-IQWiG_Nivolumab_D-668.pdf].