Nivolumab (Opdivo®) in combination with platinum-based chemotherapy for the neoadjuvant treatment of resectable non-small cell lung cancer (NSCLC)

General information

Drug description	Indication [1]
Nivolumab (Opdivo®) is a fully human anti–programmed death 1 (PD-1) antibody	Nivolumab (Opdivo®) in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable NSCLC at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥1%.

Incidence

- In Austria, in 2020, the age-standardised incidence rate[1] of lung cancer was 67.4/100,000 in men and 41.1/100,000 in women [2].
- NSCLC accounts for more than 80% of all lung cancer cases; approximately 20–35% of NSCLC cases will be diagnosed as stage III. Median age at diagnosis of patients with stage III NSCLC ranged from 65 to 79 years (50.4% of patients) [3].
- Approximately 20-25% of patients who receive a diagnosis of NSCLC have resectable disease; however, 30-55% of patients who undergo curative surgery have recurrence and ultimately die of their disease [4].

Current treatment [5]

- For the treatment of **NSCLC stage IB**, Onkopedia recommends the following:
  - The therapeutic intent is curative.
  - Surgery is the treatment of choice in the absence of contraindications.
  - The postoperative 5-year survival rate for stage IB in the now valid TNM edition is 73%. The change in classification also affected stage IB, with tumours >4 cm now classified as stage II.
  - Adjuvant chemotherapy may be considered for stage IB patients. Recommendations from various guidelines derived from the data are not consistent. Retrospective analyses suggest that possibly stage IB (TNM, version 7) patients with additional risk factors such as micropapillary or solid subtyping of adenocarcinomas, pleural infiltration, lymphatic or vascular infiltration may also benefit from adjuvant chemotherapy. These additional parameters have not been prospectively validated. In this context, special attention should be paid to potential contraindications and comorbidities.
  - In stage IB patients with an EGFR mutation del19 or L858R, adjuvant therapy with osimertinib may also be considered. It should be noted that the inclusion criteria of the ADAURA trial were based on the UICC 7 criteria. Most patients classified according to UICC 7 are also stage IB according to UICC 8. This must be considered when determining the indication.
  - Adjuvant radiation is only indicated after incomplete resection when re-excision is not possible. In the postoperative situation after R0 resection, it has a negative impact on prognosis and is not indicated.
  - Radiotherapy is an alternative as a primary therapeutic measure in inoperable patients.
- For the treatment of **NSCLC stages IIA and IIB**, the following is recommended:
  - The therapeutic intent is curative.
  - Surgery is the key curative therapeutic modality in the absence of contraindications.
  - Postoperative 5-year survival rates range from 60 to 65% for stage IIA and from 53 to 55% for stage IIB.
  - In stage IIA and IIB, systemic therapy, adjuvant or induction, should be given.
  - After R0 resection, adjuvant chemotherapy is recommended.
  - The value of adjuvant systemic therapy with molecular-targeted and immune checkpoint inhibitors is currently the subject of numerous studies.
  - An alternative to adjuvant systemic therapy is induction chemotherapy, also referred to as preoperative or neoadjuvant therapy.
  - Results of direct randomised trials comparing induction chemotherapy versus adjuvant chemotherapy are largely lacking. Only one Spanish study performed a three-arm comparison of surgery alone versus neoadjuvant or adjuvant therapy, with no difference in overall survival between study arms. The argument for induction therapy is the higher treatment adherence, relative to systemic therapy. Also, the morbidity of postoperative chemotherapy after pneumonectomy is increased.
  - Currently, the first data on the combination of neoadjuvant chemotherapy with an immune checkpoint inhibitor are available. The CheckMate 816 trial also enrolled stage II patients; however, the data are not yet mature for evaluation in this stage of disease.
  - In the postoperative setting after R0 resection, radiotherapy has a negative impact on prognosis and is not indicated. Radiation therapy is an alternative as a primary therapeutic measure in inoperable patients. It may also be indicated in an R1 or R2 situation when reoperation is not possible.
- For **NSCLC stage IIIA T3 N1, T4 N0, T4 N1** the following is recommended:

[1] European standard population 2013.

- The treatment recommendations for clinical stage T3 N1, T4 No and T4 N1 patients are essentially the same as for stage IIB.
- Surgery is the local therapy of choice if there are no contraindications due to tumour location or comorbidities.
- In general, patients with infiltration of thoracic wall, vertebral body, pulmonary artery, mediastinum, trachea, or bifurcation should be presented to an experienced thoracic surgeon for evaluation of potential resectability. In cases of infiltration of the aorta or oesophagus, surgical procedures should be evaluated with caution because of the highly complex procedures with high mortality. It is strongly recommended to discuss the procedure in an interdisciplinary tumour conference.
- In the case of a T4 stage caused by involvement of multiple ipsilateral lobes of the lung, the integration of surgery should be considered. In this case, lung-sparing procedures should be preferred.
- After Ro resection, adjuvant chemotherapy is recommended, followed by adjuvant therapy with atezolizumab if PD-L1 expression is high and EGFR/ALK WT is present.
- Patients with a common EGFR mutation should be treated with osimertinib after chemotherapy. According to the design of the pivotal trial, osimertinib administration is recommended until recurrence, unacceptable toxicity, for a maximum of 3 years.
- An alternative to adjuvant is **induction chemotherapy**:
    - Induction chemotherapy is an alternative to adjuvant chemotherapy in stages II and III, based on randomised trials and meta-analyses. The results can be summarised as follows:
        - Randomised trials and meta-analyses show no difference between preoperative versus postoperative chemotherapy.
        - Therapy adherence may be higher preoperatively than postoperatively.
        - Postoperative chemotherapy after pneumonectomy is associated with significantly lower treatment adherence and has a significantly higher morbidity rate than after lobectomy.
    - Effective combinations of drug tumour therapy for the induction modality include:
        - cisplatin / paclitaxel; cisplatin / docetaxel; cisplatin / gemcitabine; cisplatin / pemetrexed; cisplatin / vinorelbine; carboplatin / paclitaxel
        - The above combination chemotherapies plus nivolumab; not approved in this indication.
    - The choice of drugs is based on the comorbidity of the patients.
    - Generally, four cycles of induction chemotherapy (as in adjuvant therapy) are applied, and surgery is scheduled approximately 4 weeks after day 1 of the 3rd or 4th cycle of chemotherapy.
    - Molecular-targeted therapies (kinase inhibitors and antibodies) do not, at this time, replace perioperative chemotherapy in patients with a curative approach to therapy. Such therapeutic approaches should be applied within clinical trials. Data on induction chemotherapy in combination with the immune checkpoint inhibitor nivolumab show a significant increase in the rate of pathological complete remissions and EFS as well as a numerical prolongation of OS.
    - Meta-analysis of 3 prospective randomised trials showed that induction chemotherapy and induction radiochemotherapy have a favourable impact on response, mediastinal downstaging, and pathologic CR of mediastinal lymph nodes without affecting periinterventional mortality. More patients in the radiochemotherapy group achieved Ro resection. However, no long-term differences were found between chemotherapy and radiochemotherapy in terms of PFS and OS at 2, 4, and 6 years.
    - Currently, the first data on the **combination of neoadjuvant chemotherapy with an immune checkpoint inhibitor** are available. In the **CheckMate 816 trial**, the combination of platinum-containing chemotherapy with nivolumab versus chemotherapy resulted in an increase in the rate of pathohistologic complete remission from 2.2 to 24.0%, prolongation of event-free survival (HR 0.63; p=0.005), and OS (HR 0.57; p=0.008), but the data are immature. Nivolumab has not yet been approved in this indication. In the current evaluation, the positive effect in terms of EFS and OS is limited to stage IIIA patients and to patients with PD-L1 expression >1% on tumour cells. 83.2% of patients in the immunochemotherapy arm and 75.4% of patients in the chemotherapy arm underwent surgery with curative intent. An advantage of neoadjuvant therapy is that potentially all patients can be directed to such, ICI-containing therapy. Close monitoring is critical to identify non-responders in time and not to miss the window for curative surgery.
- The basic prerequisite for interdisciplinary discussion and critical evaluation in the presence of thoracic surgeons should always be the likelihood of achieving complete tumour resection (Ro) by surgery. If the risk of R1 or R2 resection is high, definitive simultaneous radiochemotherapy with ablative intensity should be chosen as the definitive local therapy for these patients (with the alternative of definitive or induction treatment).

Regulatory status

EMA [1]	FDA [6, 7]
Approval status for this indication: On 25 May 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Opdivo®. <u>The CHMP adopted a new indication as follows:</u> ❖ Opdivo® in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable NSCLC at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%.	**Approval status for this indication**: On March 4, 2022, the FDA approved nivolumab (Opdivo®) with platinum-doublet chemotherapy for adult patients with resectable NSCLC in the neoadjuvant setting. This represents the first FDA approval for neoadjuvant therapy for early-stage NSCLC. ✓ Priority review **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.

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.
- 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 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.
- in combination with ipilimumab for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.
- 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.
- as monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with brentuximab vedotin.
- as monotherapy for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy.
- as monotherapy for the treatment of locally advanced unresectable or metastatic UC in adults after failure of prior platinum-containing therapy.
- as monotherapy for the adjuvant treatment of adults with 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 dMMR or MSI-H metastatic colorectal cancer 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 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 oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.
- adult and paediatric (12 years and older) patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.
- 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 cancer 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 that has relapsed or progressed after (this indication is approved under accelerated approval based on ORR and DoR):
    - autologous HSCT and brentuximab vedotin, or
    - 3 or more lines of systemic therapy that includes autologous HSCT.
- adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.
- adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing radical resection of UC.
- adult patients with locally advanced or metastatic UC 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.
- adult and paediatric (12 years and older) patients with MSI-H or dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab (this indication is approved under accelerated approval based on ORR and DoR).
- adult patients with hepatocellular carcinoma 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 CRT.
- adult patients with unresectable advanced or metastatic oesophageal squamous cell carcinoma as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy.
- adult patients with unresectable advanced or metastatic oesophageal squamous cell carcinoma as first-line treatment in combination with ipilimumab.
- adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma 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 (this indication is approved under accelerated approval based on ORR and DoR).

❖ as monotherapy for the treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma 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 CRT. ❖ 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.	

Manufacturer

Opdivo® is manufacturer by Bristol-Myers Squibb.

Costs [8]

4 ml Opdivo® concentrate for solution for infusion 10 mg/ml = € 572.00 (ex-factory price)
10 ml Opdivo® concentrate for solution for infusion 10 mg/ml = € 1,430.00 (ex-factory price)

Posology [6]

- ❖ Administer by intravenous infusion after dilution based upon recommended infusion rate for each indication.
- ❖ Neoadjuvant treatment of resectable (tumours ≥4 cm or node positive) NSCLC:
  - 360 mg with platinum-doublet chemotherapy on the same day every 3 weeks for 3 cycles.

Warnings and precautions [6, 9]

- ❖ **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.
- ❖ Disease-specific precaution: Neoadjuvant treatment of NSCLC
  - Patients with a baseline performance score ≥2, active autoimmune disease, symptomatic interstitial lung disease, medical conditions requiring systemic immunosuppression, unresectable or metastatic disease, who received prior anti-cancer treatment for resectable disease, or who had known EGFR mutations or ALK translocations were excluded from the pivotal trial in neoadjuvant treatment of resectable NSCLC.
  - In the absence of data, nivolumab in combination with chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Study characteristics [4, 10-12]

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

CheckMate 816, CA209816 NCT02998528	358[2] (1:1[3])	nivolumab (360 mg) plus platinum-doublet chemotherapy (every 3 weeks for three cycles)[4]	platinum-doublet chemotherapy alone (every 3 weeks for three cycles)[5]	event-free survival (EFS) + pathological complete response[6,7]	29.5 months	**ongoing**[8], international, randomised, open-label, phase 3 trial	PD-1	Bristol Myers Squibb	CheckMate 816 [4]

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline (I vs. C, n=179 vs. n=179)
❖ Adults with resectable stage IB (≥4 cm) to IIIA NSCLC ❖ ECOG PS score of 0 or 1 ❖ No previous anticancer therapy ❖ Measurable disease according to RECIST (version 1.1) and pre-treatment tumour tissue available to assess the expression of PD-L1 ❖ Adequate pulmonary function capable of tolerating the proposed lung resection ❖ Sampling of suspicious mediastinal lymph nodes for pathological confirmation ❖ Not pregnant or breastfeeding ❖ Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger were also eligible. ❖ Patients with stage II or higher NSCLC and those with suspected brain metastases were required to have a MRI or CT scan of the brain with pre- and post-contrast within 28 days prior to randomisation. ❖ An FDA-approved test was recommended if patients were tested for EGFR mutations or ALK translocations, and testing was performed locally. ❖ EGFR testing was mandatory in Asia for patients with non-squamous histology and was performed at the investigator's discretion in all other regions.	❖ Patients with known ALK translocations or EGFR mutations ❖ Locally advanced unresectable (regardless of stage) or metastatic disease (stage IV) ❖ Brain metastases ❖ Grade ≥2 peripheral neuropathy ❖ Large-cell neuroendocrine carcinoma tumour histology ❖ Known human immunodeficiency virus/acquired immunodeficiency syndrome ❖ Serious or uncontrolled medical disorders ❖ Patients with conditions requiring systemic corticosteroids (>10 mg daily prednisone or equivalent) or immunosuppressive medication within 14 days of the first dose of study drug (exceptions were inhaled or topical steroids and adrenal-replacement steroids)	❖ Median years (range): 64 (41–82) vs. 65 (34–84) ❖ Male sex: 71.5% vs. 70.9% ❖ Female: 51 (28.5) vs. 52 (29.1) ❖ ECOG PS score: • 0: 69.3% vs. 65.4% • 1: 30.7% vs. 34.6% ❖ Disease stage: • IB or II: 36.3% vs. 34.6% • IIIA: 63.1% vs. 64.2% ❖ Histologic type of tumour: • Squamous: 48.6% vs. 53.1% • Non-squamous: 51.4% vs. 46.9% ❖ Smoking status: • Never smoked: 10.6% vs. 11.2% • Current or former smoker: 89.4% vs. 88.3% ❖ PD-L1 expression level: • Could not be evaluated: 6.7% vs. 7.3% • <1%: 43.6% vs. 43.0% • ≥1%: 49.7% vs. 49.7% • 1–49%: 28.5% vs. 26.3% • ≥50%: 21.2% vs. 23.5% ❖ Type of platinum therapy: • Cisplatin: 69.3% vs. 74.9% • Carboplatin: 21.8% vs. 18.4%

Efficacy (I vs. C)	**Safety** (I vs. C)

[2] 176 patients in each group received treatment.
[3] A third group that received nivolumab (3 mg per kilogram of body weight every 2 weeks for three cycles) plus ipilimumab (1 mg per kilogram, cycle 1 only) closed enrolment early based on external trial data reported during the trial.
[4] Followed by resection.
[5] Followed by resection.
[6] 0% viable tumour in resected lung and lymph nodes.
[7] Both PEs were evaluated by blinded independent review.
[8] The CheckMate 816 trial is currently ongoing; estimated study completion date is 11/2028.

Surgery summary: **Patients with definitive surgery**: 83.2% vs. 75.4% **Patients with cancelled definitive surgery[9]:** 15.6% vs. 20.7% **Patients with delayed surgery[10]:** 20.8% vs. 17.8% **Median duration of surgery**: 185.0 min vs. 213.5 min **Surgical approach**: thoracotomy (59.1% vs. 63.0), minimally invasive (29.5% vs. 21.5%), minimally invasive to thoracotomy (11.4% vs. 15.5%) **Type of surgery**: lobectomy (77.2% vs. 60.7%), sleeve lobectomy (1.3% vs. 7.4%), bilobectomy (2.0% vs. 3.0%), pneumonectomy (16.8% vs. 25.2%), other (16.1% vs. 15.6%) **Completeness of resection**: R0 (no residual tumour: 83.2% vs. 77.8%), R1 (microscopic residual tumour: 10.7% vs. 15.6%), R2 (macroscopic residual tumour: 3.4% vs. 3.0%), Rx (unknown: 2.7% vs. 3.7%) **Efficacy:** **Median EFS:** 31.6 months (95% CI, 30.2-not reached) vs. 20.8 months (95% CI, 14.0-26.7); HR for disease recurrence, or death 0.63 (97.38% CI, 0.43-0.91; p= 0.005). **Estimated percentage of patients surviving without disease progression or disease recurrence at 1 year:** 76.1% vs. 63.4% **Estimated percentage of patients surviving without disease progression or disease recurrence at 2 years**: 63.8% vs. 45.3% **Median EFS in patients with PD-L1 expression ≥1%:** NR vs. 21.1. months; HR 0.41 (95% CI, 0.24-0.70) **Patients with a pathological CR**: 24.0% (95% CI, 18.0-31.0) vs. 2.2% (95% CI, 0.6-5.6); odds ratio, 13.94 (99% CI, 3.49-55.75; p<0.001) **Patients with a major pathological response[11]:** 36.9% vs. 8.9%; odds ratio 5.70 (95% CI, 3.16-10.26) **Incidence of radiographic downstaging[12]**: 30.7% vs. 23.5% **Median OS**: NR vs. NR (HR for death 0.57; 99.67% CI, 0.30-1.07; p= 0.008) **Median EFS in patients without a pathological CR:** 26.6 months vs.18.4 months (HR for disease progression, disease recurrence, or death 0.84; 95% CI, 0.61-1.17) **Analysis of ctDNA (evaluated in n=89):** **Patients with ctDNA clearance**: 56% (95% CI, 40-71) vs. 35% (95% CI, 21 to 51) **Efficacy results in patients with tumour PD-L1 ≥ 1% and stage II-IIIA disease[13] (n=81 vs. n=86) [9]:** **Median EFS by BICR:** NR (95% CI, 44.42-NR) vs. 26.71 (95%CI, 13.40-NR) **Pathologic CR per BIPR:** 32.1% (95% CI, 22.2-43.4) vs. 2.3% (95% CI, 0.3-8.1) **Difference of pCR:** 29.8% (95% CI, 19.0-40.7)	**AEs of any cause:** n=163/176 (92.6%) vs. n=171/176 (97.2%) **TRAEs of grade 3 or 4:** n=59/176 (33.5%) vs. n=65/176 (36.9%) **TRAEs of any grade leading to treatment discontinuation:** n=18/176 (10.2%) vs. 17/176 (9.7%) **Treatment-related deaths[14]:** n=0 vs. n=3/176 (1.7%) **AEs of any grade leading to delayed surgery:** n=6/176 (3.4%) vs. n=9/176 (5.1%) **AEs of any grade that were identified as surgical complications:** n=62/149 (41.6%) vs. n=63/135 (46.7%) **Grade 3 or 4 surgery-related AEs[15]:** n=17/149 (11.4%) vs. n=20/135 (14.8%)
Patient-reported outcomes [13]	
❖ HRQoL (exploratory endpoint) was evaluated using the 3-level version of the EQ-5D (EQ-5D-3L).	

[9] Reasons for cancellation included disease progression, AEs, patient refusal, unresectability, and poor lung function.
[10] Time from last dose to neoadjuvant surgery >6 weeks.
[11] Major pathological response: ≤10% residual viable tumour cells in the primary tumour and sampled lymph nodes.
[12] Reduction of disease stage from baseline.
[13] Minimum follow-up for EFS was 32.9 months, data cut-off: 6 September 2022; pCR data cut-off: 28 July 2020.
[14] Treatment-related deaths in the chemotherapy-alone group were due to pancytopenia, diarrhea, acute kidney injury (all in one patient), enterocolitis, and pneumonia.
[15] Grade 5 surgery-related AEs were reported in two patients treated with nivolumab plus chemotherapy and were deemed to be unrelated to the trial drugs by the investigator (one each due to pulmonary embolism and aortic rupture).

- A mixed-effects model repeated measures analysis evaluated longitudinal changes from baseline in EQ-5D visual analogue scale (VAS; range 0 to 100) and utility index (UI; range -0.594 to 1) scores during the neoadjuvant period (week 4, week 7, and post-neoadjuvant visit 1); higher scores reflect better HRQoL.
- EQ-5D-3L completion rates were >80% in both treatment arms at baseline and during the neoadjuvant period.
- Baseline EQ-5D-3L VAS and UI scores were consistent with UK population norms.
- Scores during the neoadjuvant period were generally similar to baseline for both treatment arms; there were no clinically meaningful differences between I and C.
- In both treatment arms, most patients reported "no problems" for individual EQ-5D-3L dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) at baseline and during treatment.
- Analyses from the postsurgical period will be presented.
- In conclusion, the addition of nivolumab to neoadjuvant chemotherapy for resectable NSCLC had no detrimental impact on HRQoL during the neoadjuvant period.

ESMO-MCBS version 1.1 [14]

Scale	Int.	Form	MG ST	MG	HR (97.38 CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	potentially curative	1	-	EFS: +10.8 months	0.63 (0.43-0.91)	Improvements in EFS alone (HR<0.65) in studies without mature survival data	A	-	-	-	A
Adapted	potentially curative	1	-	EFS: +10.8 months	0.63 (0.43-0.91)	Improvements in EFS alone (HR<0.65) in studies without mature survival data	A	-	-	-	A

Risk of bias (RCT) [15]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes (low risk)	yes (low risk)	no[16] (high risk)	unclear[17] (unclear risk)	yes[18] (high risk)	unclear risk

Ongoing trials [16]

NCT number/trial name	Description	Estimated study completion date
NCT02998528 / CheckMate 816	Please see above.	11/2028
NCT04025879/ CheckMate 77T	A phase 3, randomised, double-blind study of neoadjuvant chemotherapy plus nivolumab vs. neoadjuvant chemotherapy plus placebo, followed by surgical resection and adjuvant treatment with nivolumab or placebo for participants with resectable stage II-IIIB NSCLC.	09/2024

Available assessments

- In February 2023, NICE published a final draft guidance "Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer" [17].
- The Health Technology Briefing "Nivolumab in combination with chemotherapy for early-stage non-small cell lung cancer – neoadjuvant" was published by NIHR in January 2020 [18].

Other aspects and conclusions

- In May 2023, the **CHMP adopted a new indication** for nivolumab (Opdivo®) in combination with platinum-based chemotherapy indicated for the neoadjuvant treatment of resectable NSCLC at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥1%. In March 2022, the FDA approved Opdivo® with platinum-doublet chemotherapy for adult patients with resectable NSCLC in the neoadjuvant setting.

[16] CheckMate 816 is an open-label trial.
[17] CheckMate 816 is currently ongoing; only interim analysis results are currently available.
[18] The sponsor and a steering committee designed the trial and analysed the data with participation from all the authors. The manuscript was developed with medical writing support funded by the sponsor.

- **CheckMate 816** is an open-label, randomised phase 3 trial to evaluate the efficacy and safety of neoadjuvant nivolumab plus chemotherapy as compared with chemotherapy alone. Adults with resectable stage IB to IIIA NSCLC, an ECOG PS score of 0 or 1 and no previous anticancer therapy were enrolled. Patients had to have measurable disease according to RECIST, version 1.1, and pre-treatment tumour tissue available to assess the expression of programmed death ligand 1 (PD-L1). Patients with known ALK translocations or EGFR mutations were excluded.
- The **median EFS** was 31.6 months vs. 20.8 months (HR for disease progression, disease recurrence, or death 0.63; 97.38% CI, 0.43-0.91; p=0.005). The percentage of patients with a pathological CR was 24.0% vs. 2.2% (odds ratio, 13.94; 99% CI, 3.49-55.75; p<0.001).
- Evaluation of **HRQoL** by using the EQ-5D (EQ-5D-3L) showed that the addition of nivolumab to neoadjuvant chemotherapy for resectable NSCLC had no detrimental impact on HRQoL during the neoadjuvant period.
- The **ESMO-MCBS** form 1 was applied, indicating a substantial magnitude of clinical benefit of nivolumab (Opdivo®) in combination with platinum-based chemotherapy versus platinum-based chemotherapy alone (score A).
- Since the CheckMate 816 is currently ongoing and no final analysis data is available, the **risk of bias** was considered unclear. The open-label design and the involvement of the sponsor in trial design and data analysis increase the risk of bias.
- In addition to the ongoing CheckMate 816 trial, another phase 3, double-blind study of neoadjuvant chemotherapy plus nivolumab vs. neoadjuvant chemotherapy plus placebo, followed by surgical resection and adjuvant treatment with nivolumab or placebo for participants with resectable stage II-IIIB NSCLC was identified. Study completion is expected in September 2024.

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Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, ASCT=autologous stem cell transplant, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CPS=combined positive score, CRT=chemoradiotherapy, CT=computed tomography, ctDNA=circulating tumor DNA, dMMR=mismatch repair deficient, DoR=duration of response, ECOG PS=Eastern Cooperative Oncology Group performance-status, EFS=event-free survival, EGFR=Epidermal growth factor receptor, EMA=European Medicines Agency, EQ-5D-3L=European Quality of Life 5 Dimensions 3 Level Version, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, HRQoL=health-related quality of life, HSCT=hematopoietic stem cell transplantation, I=intervention, ICI=immune checkpoint inhibitor, Int.=intention, IV=intravenous, MG=median gain, MIUC=muscle invasive urothelial carcinoma, MSI-H=microsatellite instability-high, MRI=magnetic resonance imaging, n=number of patients, NICE=National Institute for Health Care Excellence, NSCLC=non-small cell lung cancer, ORR=overall response rate, OS=overall survival, PD-1=anti–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, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, ST=standard treatment, TRAE=treatment-related adverse event, UC=urothelial carcinoma, UICC=Union for International Cancer Control, VAS=visual analogue scale

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