Tremelimumab (Imjudo®) with durvalumab (Imfinzi®) and platinum-based chemotherapy for the first-line treatment of metastatic non-small cell lung cancer (NSCLC)

General information

Drug description [1]

Tremelimumab (Imjudo®) is a selective, fully human IgG2 antibody that blocks CTLA-4 interaction with CD80 and CD86, thus enhancing T-cell activation and proliferation, resulting in increased T-cell diversity and enhanced antitumour activity. The combination of tremelimumab, a CTLA-4 inhibitor and durvalumab (Imfinzi®), a PD-L1 inhibitor results in improved anti-tumour responses in metastatic NSCLC in murine syngeneic tumour models, dual blockade of PD-L1 and CTLA-4 resulted in enhanced anti-tumour activity.

Indication [2]

Tremelimumab (Imjudo®) in combination with durvalumab (Imfinzi®) and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations.

Incidence

In Austria, in 2020, a total of 4,799 patients were newly diagnosed with cancer of the lung, bronchia and trachea. The age standardised incidence rate[1] was 67.4/100,000 men and 41.1/100,00 women [2].

The age-specific incidence of lung cancer increases with age up to the 8th decade of life; the median age was most recently 69 years, and only about 2% of those affected develop the disease before the age of 50. In 50% of new cases with sufficient documentation of tumour stages, distant metastases are already present at the initial diagnosis of NSCLC, and only 27% of cases are diagnosed in early stages I or II according to UICC [3].

Current treatment

For the first-line therapy for NSCLC without activating EGFR-, ROS1-, or ALK aberrations, Onkopedia recommends [3]:

- In patients without genetic aberrations for whom targeted drugs are approved, the following recommendations apply:
  - Expression of the immune marker PD-L1 on >50% of tumour cells:
    - Monotherapy with the anti-PD1 antibody pembrolizumab vs. platinum-containing chemotherapy resulted in prolonged OS (HR 0.62; 26.3 vs. 13.4 months), prolonged PFS (HR 0.50; median 4.3 months), and reduced rates of SAEs. These data are supported by the results of the KEYNOTE-042 trial. Data from a direct comparison of pembrolizumab monotherapy vs. pembrolizumab + combination chemotherapy are not yet available.
    - Monotherapy with the anti-PDL1 antibody atezolizumab was tested in patients with PD-L1 on ≥50% of tumour cells or a rate of PD-L1 positive tumour-infiltrating immune cells (IC) of ≥10%. Compared with platinum-containing chemotherapy, atezolizumab prolonged OS (HR 0.59; 20.2 vs. 13.1 months), and PFS (HR 0.63; median 3.1 months) and reduced the rate of SAEs (52.5 vs. 30.1%).
    - Monotherapy with the anti-PDL1 antibody cemiplimab resulted in prolongation of OS (HR 0.57; median not reached vs. 14 months), prolongation of PFS (HR 0.63; median plus 2.5 months), and in the overall study, a reduction in the rate of SAEs (28 vs. 39%) in patients with PD-L1 expression >50% vs. platinum-containing chemotherapy.
    - The combination of an immune checkpoint inhibitor (ICI) with chemotherapy is a potential alternative especially in patients in urgent need of treatment due to distressing symptoms, high tumour burden and/or rapid tumour growth. A meta-analysis by the FDA showed no significant differences in OS between monotherapy and combination therapy, but a slight numerical advantage in favour of immunochemotherapy and a significant advantage in PFS. In patients > 75 years, there is evidence of an advantage in favour of immunomonotherapy. In addition, there appears to be an impact of gender on the efficacy of immune checkpoint inhibitor monotherapy vs. ICI + chemotherapy. Women appear to consistently benefit less than men from ICI monotherapy, as do non-smokers. These observations require confirmation to guide treatment decisions.
  - Independent of PD-L1 expression on tumour cells or tumour-infiltrating IC:
    - In non-squamous cell carcinoma, the combination of pembrolizumab with chemotherapy (platinum/pemetrexed) vs. chemotherapy resulted in prolonged OS (HR 0.56; median 11.3 months) and prolonged PFS (HR 0.48; median 3.9 months). The relative gain by pembrolizumab increases with the degree of PD-L1 expression but is also significant in

[1] European Standard Population 2013.

terms of OS (HR 0.52) in the group of PD-L1 negative patients. In the subgroup of TTF1 negative patients the use of other cytostatic agents instead of pemetrexed should be considered.
    - In squamous cell carcinoma, the combination of pembrolizumab with chemotherapy (platinum/(nab)paclitaxel) vs. chemotherapy was shown to prolong OS (HR 0.63; median 4.6 months) and PFS (HR 0.56; median 1.6 months). Thereby, no significant benefit was seen for the subgroup of patients with PD-L1 expression <1% in the final survival analysis of the KEYNOTE-407 trial.
    - In non-squamous cell carcinoma, the combination of atezolizumab with carboplatin/paclitaxel/bevacizumab (BCP) vs. BCP resulted in prolonged OS (HR 0.78; median 5.5 months) and PFS (HR 0.62; median 1.5 months). The need for bevacizumab in this combination is unclear. This combination is the only approved combination therapy with immune checkpoint inhibitors for patients with EGFR and ALK alterations. There is no approval in Switzerland. However, this combination should only be used in this indication if the options for targeted therapy have been exhausted. One group of patients who may particularly benefit from atezolizumab-BCP therapy versus BCP are patients with liver metastases.
    - In non-squamous cell carcinoma, the combination of atezolizumab with carboplatin / nab-paclitaxel also resulted in prolonged OS (HR 0.79; median 4.7 months) and PFS (HR 0.64; median 1.5 months).
    - In squamous or non-squamous cell carcinoma regardless of PD-L1 expression, the combination of nivolumab / ipilimumab in combination with chemotherapy for 2 cycles and continuation of immune combination therapy vs. conventional chemotherapy for 4 cycles resulted in significant prolongation of OS (HR 0.66; median 15.6 vs. 10.9 months), for approval see the currently valid regulatory information. Side effects of immune combination therapy are higher than with immune monotherapy or combination of immunotherapy with chemotherapy and mainly involve liver, skin, and endocrine toxicities. In the study, patients with low PD-L1 expression and squamous histology benefited particularly well. A direct comparison of dual ICI chemotherapy vs. single ICI chemotherapy is not available.
- When chemotherapy alone is chosen, combination chemotherapy with two cytostatic agents is more effective than monotherapy in terms of remission rate, PFS, and OS. Combinations are burdened with higher therapy-associated toxicity. Most experience is with platinum-containing combinations. Previous studies have shown that significantly higher remission rates are achieved with cisplatin than with carboplatin; however, these differences are not evident in combinations with third-generation drugs. In terms of OS, the two platinum derivatives are equieffective. The choice is mainly based on the individual expected toxicity. Non-platinum combinations have lower remission rates than platinum-containing combinations.
- In patients with non-squamous cell carcinoma, the combination of bevacizumab with carboplatin/paclitaxel, cisplatin/gemcitabine, or another platinum-containing two-drug combination increased remission rates and prolonged PFS compared with chemotherapy alone, but also increased the rate of side effects. The paclitaxel/carboplatin/bevacizumab combination also resulted in an increase in OS.
- In stable disease, first-line platinum-containing therapy should be stopped after 4 cycles. If there is a response, combination therapies should be stopped after 4-6 cycles.
- If disease is at least stable, therapy with single agents can be continued in terms of maintenance therapy. In some randomised trials, survival was significantly prolonged compared to controls. Current options are:
    - Pemetrexed for non-squamous cell carcinoma
    - Pembrolizumab - monotherapy (for TPS >50%) every 3 or every 6 weeks in continuation of the induction immune monotherapy; in the pivotal trial, pembrolizumab was given for up to 35 cycles
    - Pembrolizumab + pemetrexed every 3 or every 6 weeks following combination immunochemotherapy; in the pivotal study, pembrolizumab was given for up to 35 cycles
    - Nivolumab + ipilimumab following induction with combination immunotherapy and chemotherapy; in the pivotal trial, nivolumab + ipilimumab was given for 2 years
- An alternative to maintenance chemotherapy is the initiation of second-line therapy at progression. Close monitoring, e.g., at 6–8-week intervals, is necessary to diagnose progression early. However, in this concept only about 60% of patients receiving first-line therapy are treated with second-line therapy.

Regulatory status

EMA [4]	FDA [5, 6]
Approval status for this indication: On 22 June 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Imjudo®. The CHMP adopted a new indication as follows: ❖ Imjudo® in combination with durvalumab (Imfinzi®) and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations.	**Approval status for this indication**: On 10 November 2022, the FDA approved tremelimumab (Imjudo®) in combination with durvalumab (Imfinzi®) and platinum-based chemotherapy for adult patients with metastatic NSCLC with no sensitizing EGFR mutation or ALK genomic tumour aberrations.

Other indications: ❖ Imjudo® in combination with durvalumab (Imfinzi®) is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC). ✓ **Medicine under additional monitoring**	**Other indications**: Imjudo® is indicated ❖ in combination with durvalumab, for the treatment of adult patients with unresectable HCC.

Manufacturer

Imjudo® is manufactured by AstraZeneca.

Costs [7]

15 ml Imjudo® concentrate for solution for infusion 20 mg/ ml = € 22,020.00 (ex-factory price)
10 ml Imfinzi ® concentrate for solution for infusion 50 mg /ml = € 3,088.00 (ex-factory price)

Posology [1]

Imjudo® in combination with durvalumab and platinum-based chemotherapy

- When Imjudo® is given in combination with durvalumab and platinum-based chemotherapy, Imjudo® is given first, followed by durvalumab and then platinum-based chemotherapy on the day of dosing.
- When Imjudo® is given as a fifth dose in combination with durvalumab and pemetrexed maintenance therapy at week 16, Imjudo® is given first, followed by durvalumab and then pemetrexed maintenance therapy on the day of dosing.
- Imjudo®, durvalumab, and platinum-based chemotherapy are administered as separate intravenous infusions. Imjudo® and durvalumab are each given over 1 hour. For platinum-based chemotherapy, refer to the SmPC for administration information. For pemetrexed maintenance therapy, refer to the SmPC for administration information. Separate infusion bags and filters for each infusion should be used.
- During cycle 1, Imjudo® is to be followed by durvalumab starting approximately 1 hour (maximum 2 hours) after the end of the Imjudo® infusion. Platinum-based chemotherapy infusion should start approximately 1 hour (maximum 2 hours) after the end of the durvalumab infusion. If there are no clinically significant concerns during cycle 1, then at the physician's discretion, subsequent cycles of durvalumab can be given immediately after Imjudo® and the time period between the end of the durvalumab infusion and the start of chemotherapy can be reduced to 30 minutes.

Warnings and precautions [1, 5]

- **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, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions and immune-mediated pancreatitis.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, adrenocorticotropic hormone level and thyroid function at baseline and before each dose.
  - Withhold or permanently discontinue based on severity and type of reaction.
- **Infusion-related reactions**
  - Interrupt, slow the rate of infusion, or permanently discontinue treatment based on the severity of the reaction.
- **Embryo-foetal toxicity**
  - Can cause foetal harm.
  - Advise females of reproductive potential of the potential risk to a foetus and use of effective contraception.
- **Traceability**
  - In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.
- **Disease-specific precaution: Metastatic NSCLC**
  - Limited data are available in elderly patients (≥ 75 years) treated with tremelimumab in combination with durvalumab and platinum-based chemotherapy. Careful consideration of the potential benefit/risk of this regimen on an individual basis is recommended.

- ❖ **Patients excluded from clinical studies: Metastatic NSCLC**
  - Patients with the following were excluded from clinical studies: active or prior documented autoimmune disease; active and/or untreated brain metastases; a history of immunodeficiency;
    administration of systemic immunosuppression within 14 days before the start of tremelimumab or durvalumab, except physiological dose of systemic corticosteroids (< 10 mg/day prednisone or equivalent); uncontrolled intercurrent illness; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of tremelimumab or durvalumab. In the absence of data, tremelimumab should be used with caution in these populati on after careful consideration of the potential benefit/risk on an individual basis.
- ❖ **Sodium content**
  - This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Study characteristics [8, 9]

Trial name	*n*	Intervention (I): T+D+CT	Intervention (I2): D+CT	Comparator (C): CT	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
POSEIDON NCT03164616	1,013 (1:1:1)	tremelimumab 75 mg + durvalumab 1,500 mg + platinum-based chemotherapy for up to four 21-day cycles, followed by durvalumab once every 4 weeks until progression and 1 additional tremelimumab dose	durvalumab + chemotherapy for up to four 21-day cycles, followed by durvalumab once every 4 weeks until progression	chemotherapy for up to six 21-day cycles (with or without maintenance pemetrexed)	PFS (BICR) + OS for D+CT vs. CT[2]	10.3 months for PFS; 34.0 months for OS	**ongoing**[3], global, randomised, open-label three-arm, phase 3 trial	PD-L1	AstraZeneca	POSEIDON trial [8]

Inclusion criteria[4]	Exclusion criteria	Patient characteristics at baseline (I vs. I2 vs. C)
❖ Patients ≥18 years (in Japan ≥20 years) with histologically or cytologically documented stage IV NSCLC not amenable to curative surgery or radiation ❖ Tumours that lack activating EGFR mutations and ALK fusions; if a patient has squamous histology or is known to have a tumour with a KRAS mutation, then EGFR and ALK testing is not required ❖ No prior chemotherapy or any other systemic therapy for metastatic NSCLC. ❖ Patients who have received prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation for advanced disease are eligible, provided that progression has occurred >12 months from end of last therapy	❖ Mixed small-cell lung cancer and NSCLC histology, sarcomatoid variant ❖ Any concurrent chemotherapy, investigational product, biologic, or hormonal therapy for cancer treatment ❖ No radiation therapy is allowed, unless it is • definitive radiation that had been administered at least 12 months prior • palliative radiation to brain, with associated criteria for stability or lack of symptoms • palliative radiation to painful bony lesions (this must comprise <30% of the bone marrow) ❖ Major surgical procedure within 28 days prior to the first dose of investigational product	❖ Median age: 63.0 vs. 64.5 vs. 64.0 years ❖ Male sex: 79.6% vs. 74.9% vs. 73.6% ❖ ECOG PS: • 0: 32.5% vs. 32.2% vs. 35.3% • 1: 67.5% vs. 67.8% vs. 64.4% • Missing: 0% vs. 0% vs. 0.3% ❖ Histology: • Squamous: 36.7% vs. 37.9% vs. 36.2% • Non-squamous: 63.3% vs. 61.8 vs. 63.5%

2 Key alpha-controlled secondary endpoints were PFS and OS for T + D + CT vs. CT.
[3] The POSEIDON trial is currently ongoing; estimated study completion date is 05/2025.
[4] For detailed in- and exclusion criteria, please see POSEIDON trial data supplement.

❖ Tumour PD-L1 status must be known prior to randomisation ❖ ECOG performance status of 0 or 1 at enrolment and randomisation ❖ Life expectancy ≥12 weeks at randomisation (day 1) ❖ Body weight >30 kg ❖ At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis ≥15 mm) with CT or MRI and that is suitable for accurate repeated measurements as per RECIST v1.1 guidelines ❖ No prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-programmed cell death ligand-2 antibodies, excluding therapeutic anticancer vaccines ❖ Adequate organ and marrow function ❖ Evidence of post-menopausal status or negative urinary or serum pregnancy test for female premenopausal patients	❖ History of allogeneic organ transplantation ❖ Active or prior documented autoimmune or inflammatory disorders ❖ Uncontrolled intercurrent illness ❖ Medical contraindication to platinum-based doublet chemotherapy ❖ History of another primary malignancy (for exception, please see data supplement) ❖ History of leptomeningeal carcinomatosis ❖ Spinal cord compression ❖ Brain metastases ❖ History of active primary immunodeficiency ❖ Active infection ❖ Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab ❖ Receipt of live, attenuated vaccine within 30 days prior to the first dose of investigational product ❖ Female patients who are pregnant or breast-feeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of tremelimumab plus durvalumab combination therapy ❖ Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients	• Other or missing: 0% vs. 0.3% vs. 0.3% ❖ AJCC disease stage: • IVA: 50.6% vs. 50.3% vs. 49.3% • IVB: 48.8% vs. 49.4% vs. 50.4% • Other or missing[5]: 0.6% vs. 0.3% vs. 0.3% ❖ Smoking history: • Current smoker: 24.9% vs. 18.9% vs. 19.6% • Former smoker: 57.7% vs. 56.2% vs. 56.7% • Never smoker: 17.5% vs. 24.9 vs. 23.4% • Missing: 0% vs. 0% vs. 0.3% ❖ CNS metastases: 9.8% vs. 8.3% vs.13.4% ❖ Liver metastases: 20.4% vs. 18.3% vs. 23.7%

Efficacy	**Safety** (I vs. I2 vs. C)
PFS/OS With D+CT vs. CT: **PFS** (HR 0.74; 95% CI, 0.62-0.89; p=0.0009) and **OS** (HR, 0.86; 95% CI, 0.72-1.02; p=0.0758) **Median PFS**: 5.5 months (95% CI, 4.7-6.5) vs. 4.8 (95% CI, 4.6-5.8) **12-month PFS rates**: 24.4% vs. 13.1% **Median OS**: 13.3 months (95% CI, 11.4 to 14.7) vs. 11.7 (95% CI, 10.5-13.1) **24-months OS rates**: 29.6% vs. 22.1% **PFS/OS with T+D+CT vs. CT[6]:** **PFS** (HR 0.72; 95% CI, 0.60-0.86; p=0.0003) and **OS** (HR 0.77; 95% CI, 0.65-0.92; p=0.0030): statistically significant improvement for T+D+CT vs. CT **Median PFS**: 6.2 months (95% CI, 5.0-6.5) vs. 4.8 months (95% CI, 4.6-5.8) **12-month PFS rates**: 26.6% vs. 13.1% **Median OS:** 14.0 months (95% CI, 11.7-16.1) vs. 11.7 months (95% CI, 10.5-13.1) **24-month OS rates**: 32.9% vs. 22.1%	**Treatment-related AEs of any grade**: 92.7% vs. 88.6% vs. 89.5% **TRAEs of grade 3 or 4**: 51.8% vs. 44.6% vs. 44.4% **Serious TRAEs of any grade**: 27.6% vs. 19.5% vs. 17.7% **Treatment-related deaths**: 3.3% vs. 2.1% vs. 2.4% **TRAEs leading to treatment discontinuation**: 15.5% vs.14.1% vs. 9.9% **Immune-mediated AEs of any grade**: 33.6% vs. 19.2% vs. 5.1% **Immune-mediated AEs of grade 3 or 4**: 10.0% vs. 6.9% vs. 1.5% **Serious immune-mediated AEs**: 9.7% vs. 6.0% vs. 1.2% **Immune-mediated AEs leading to treatment discontinuation**: 5.8% vs. 4.2% vs. 0.6% **Immune-mediated AEs leading to death**: 0.6% vs. 0.3% vs. 0%

[5] 2 patients in the tremelimumab + durvalumab and chemotherapy arm and 1 in the durvalumab + chemotherapy arm were incorrectly randomly assigned with stage III disease; these were reported as protocol deviations.

[6] Results from primary and secondary analysis; the data cutoff was 24 July 2019, for PFS and other RECIST-related end points, and 12 March 2021, for OS, safety, and all other data.

ORR and DoR:
Unconfirmed ORR: 46.3% with T+D+CT, 48.5% with D+CT and 33.4% with CT
Confirmed ORR: 38.8% with T +D+CT, 41.5% with D+CT and 24.4% with CT
Median DoR among patients with a confirmed response: 9.5 months (95% CI, 7.2-not estimable) with T+D +CT, 7.0 months (95% CI, 5.7-9.9) with D+CT, and 5.1 months (95% CI, 4.4-6.0) with CT

Patient-reported outcomes [10]

- Global health status/QoL, functioning and symptoms were assessed as a secondary endpoint using EORTC QLQ-C30/LC13.
- Time to deterioration (TTD) was assessed using a stratified log-rank test with a Cox proportional-hazards model, with medians estimated by the Kaplan-Meier method, and improvement rates by logistic regression.
- As of 12 March 2021, 338, 338 and 337 patients were randomised to T+D+CT, D+CT and CT, respectively.
- Compliance was ≥60% for C30 and LC13 up to 88 weeks, 64 weeks and 24 weeks for the T+D +CT, D+CT and CT arms, respectively.
- Baseline global health status/QoL, functioning and symptom scores were generally similar across treatment arms.
- HRs indicated longer TTD with T+D +CT and D+CT vs. CT across nearly all PROs, including prespecified symptoms/domains of interest (with exception of appetite loss for D+CT vs. CT)
- Improvement rates in PROs, including prespecified symptoms/domains of interest, were greater for T+D+CT and D+CT vs. CT alone.
- The addition of D (+/- T) to CT improved efficacy while delaying deterioration in health-related QoL in patients with metastatic NSCLC.
- Patients in the T+D+CT and D+CT arms tended to have longer TTD and greater rates of improvement in global health status/QoL, functioning and symptoms vs. patients in the CT arm.

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	≤12 months	OS: +2.3 months; Increase in 2-year survival: +10.8%	0.77 (0.65-0.92)	Increase in 2-year survival: ≥10%	4	-	improved	+1[7]	5
Adapted	NC	2a	≤12 months	OS: +2.3 months; Increase in 2-year survival: +10.8%	0.77 (0.65-0.92)	Increase in 2-year survival: ≥10%	4	-	improved	+1	5

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	-	no[8] high risk	unclear[9]/ unclear risk	yes[10]/ high risk	**unclear**

Ongoing trials [13]

NCT number/trial name	Description	Estimated study completion date
NCT03164616/ POSEIDON	Please see above.	05/2025
NCT02352948/ ARCTIC	A phase III, open-label, randomised, multi-centre, international study of MEDI4736 (durvalumab), given as monotherapy or in combination with tremelimumab determined by PD-L1 expression vs. SoC in patients with locally advanced or metastatic NSCLC (Stage IIIB-IV) who have received at least 2 prior systemic treatment regimens including one platinum-based chemotherapy regimen and do not have known EGFR TK activating mutations or ALK rearrangements.	06/2023

[7] Upgrade 1 level due to improved QoL.
[8] POSEIDON was designed as an open-label study.
[9] POSEIDON trial is currently ongoing; final analysis data is currently not available.
[10] Industry-funded.

NCT02453282/ MYSTIC	A phase III randomised, open-label, multi-centre, global study of MEDI4736 (durvalumab) in combination with tremelimumab therapy or MEDI4736 monotherapy vs. SoC platinum-based chemotherapy in first-line treatment of patients with advanced or metastatic NSCLC.	12/2023
NCT02542293/ NEPTUNE	A phase III randomised, open-label, multi-centre, global study of MEDI4736 (durvalumab) in combination with tremelimumab therapy vs. SoC platinum-based chemotherapy in first-line treatment of patients with advanced or metastatic NSCLC.	12/2023

Available assessments

- According to NICE, the Department for Health and Social Care has asked NICE to carry out a single technology appraisal of durvalumab with tremelimumab for untreated EGFR- and ALK-negative locally advanced and metastatic NSCLC. For information, the company have advised that they are no longer pursuing a Marketing Authorisation Application from the Medicines and Healthcare products Regulatory Agency for this indication currently. Therefore, NICE has decided to suspend this appraisal from its current work programme in August 2022 [14].
- On behalf of G-BA, IQWIG published an assessment "Tremelimumab und Durvalumab (NSCLC). Nutzenbewertung gemäß § 35a SGB V" in April 2023 [15].
- No further assessments were identified.

Other aspects and conclusions

- In June 2023, the **CHMP adopted a new indication** for tremelimumab (Imjudo®) in combination with durvalumab (Imfinzi®) and platinum-based chemotherapy for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations. The **FDA approved** Imjudo® for this indication in November 2022.
- **POSEIDON** (NCT03164616) is an **ongoing,** open-label, phase III study evaluating tremelimumab plus durvalumab and chemotherapy vs. durvalumab plus chemotherapy vs. chemotherapy alone in first-line metastatic NSCLC. Patients age ≥18 years with stage IV NSCLC were included, provided they had not previously received systemic therapy for metastatic NSCLC; had ECOG PS 0 or 1; and had measurable disease according to RECIST v1.1. The tumours were to have no sensitizing EGFR mutations or ALK rearrangements and PD-L1expression status. For detailed in- and exclusion criteria, please see study protocol.
- **Primary endpoints** of POSEIDON were PFS and OS for durvalumab + chemotherapy vs. chemotherapy alone: PFS was significantly improved (HR 0.74; 95% CI, 0.62-0.89; p=0.0009; median, 5.5 vs. 4.8 months); a trend for improved OS did not reach statistical significance (HR, 0.86; 95% CI, 0.72-1.02; p=0.0758; median, 13.3 vs. 11.7 months; 24-month OS, 29.6% vs. 22.1%). Key alpha-controlled secondary endpoints were **PFS and OS for tremelimumab + durvalumab + chemotherapy vs. chemotherapy alone**: PFS (HR 0.72; 95% CI, 0.60-0.86; p=0.0003; median, 6.2 vs. 4.8 months) and OS (HR 0.77; 95%CI, 0.65-0.92; p=0.0030; median, 14.0 vs. 11.7 months; 24-month OS, 32.9% vs. 22.1%) were **significantly improved**.
- Across nearly all **PROs**, HRs indicated longer TTD with tremelimumab + durvalumab + chemotherapy and durvalumab + chemotherapy vs. chemotherapy alone, including prespecified symptoms/domains of interest. Improvement rates in PROs (including prespecified symptoms/domains of interest) were greater for tremelimumab + durvalumab + chemotherapy and durvalumab + chemotherapy vs. chemotherapy alone.
- The original and adapted **ESMO-MCBS** were applied and resulted in a final adjusted magnitude of clinical benefit grade of 5 and 4, respectively. This indicates a substantial magnitude of clinical benefit of the combination of tremelimumab + durvalumab + chemotherapy vs. chemotherapy alone.
- Since the POSEIDON trial is currently ongoing and final analysis data is lacking, the **risk of bias was considered unclear**. However, the risk of bias is increased by the open-label design and industry-funded background of the study.
- Beside POSEIDON, three further phase III trials, assessing the efficacy and safety of tremelimumab and durvalumab in patients with NSCLC were identified.
- Final analysis data from POSEIDON and further phase III data is required to determine the role of tremelimumab and durvalumab in NSCLC patients.

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Abbreviations: AE=adverse event, AJ=adjustment, AJCC=American Joint Committee on Cancer, ALK=anaplastic lymphoma kinase, BCP= carboplatin/paclitaxel/bevacizumab, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CT=chemotherapy, CTLA-4=cytotoxic T-lymphocyte–associated antigen 4, D=durvalumab, DoR=duration of response, ECOG=Eastern Cooperative Oncology Group, EGFR=epidermal growth factor receptor, 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, I=intervention, IC=immune cell, ICI=immune checkpoint inhibitor, ICER=Institute for Clinical and Economic Review, Int.=intention, IQWIG=Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, MG=median gain, 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-L1=programmed cell death ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, SoC=standard of care, ST=standard treatment, T=tremelimumab, TRAEs=treatment-related adverse events, TTD=time to deterioration, TTF1=thyroid transcription factor 1, UICC=Union for International Cancer Control,

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