Atezolizumab (Tecentriq®) as monotherapy for the first-line treatment of advanced NSCLC

General information

Drug description [1]

Atezolizumab (Tecentriq®) is an Fc-engineered, humanised immunoglobulin G1 monoclonal antibody that directly binds to PD-L1 and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the antitumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction, allowing PD-L2/PD-1 mediated inhibitory signals to persist.

Indication [2]

Atezolizumab (Tecentriq®) as monotherapy is indicated for the first-line treatment of adult patients with advanced NSCLC who are ineligible for platinum-based therapy.

Incidence [3]

In Austria, in 2022, a total of 5,203 patients were newly diagnosed with cancer of the trachea, bronchia and lung. The age-standardised incidence rate was 68.0/100,000 in men and 48.8/100,000 in women.

Current treatment [4]

The Onkopedia treatment recommendation for the treatment of NSCLC in advanced stages is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [2]	FDA
Approval status for this indication: On 25 July 2024, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Tecentriq®. The CHMP adopted a new indication as follows: ❖ Tecentriq® as monotherapy is indicated for the first-line treatment of adult patients with advanced NSCLC who are ineligible for platinum-based therapy. **Other indications**: Tecentriq® is indicated: ❖ as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC): • after prior platinum-containing chemotherapy, or • who are considered cisplatin ineligible and whose tumours have a PD-L1 expression ≥ 5%. ❖ as monotherapy as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR-mutant or ALK-positive NSCLC. ❖ in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR-mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.	**Approval status for this indication**: not approved **Other indications**: Tecentriq® is indicated [5]: ❖ as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II to IIIA NSCLC whose tumours have PD-L1 expression on ≥ 1% of tumour cells, as determined by an FDA-approved test. ❖ for the first-line treatment of adult patients with metastatic NSCLC whose tumours have high PD-L1 expression (PD-L1 stained ≥ 50% of TC ≥ 50%) or PD-L1 stained tumour-infiltrating IC covering ≥ 10% of the tumour area (IC ≥ 10%), as determined by an FDA approved test, with no EGFR or ALK genomic tumour aberrations. ❖ in combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumour aberrations. ❖ in combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumour aberrations. ❖ for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA-approved therapy for NSCLC harbouring these aberrations prior to receiving Tecentriq®.

- in combination with nab paclitaxel and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR-mutant or ALK-positive NSCLC.
- as monotherapy for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR-mutant or ALK-positive NSCLC.
- as monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR-mutant or ALK positive NSCLC should also have received targeted therapies before receiving Tecentriq®.
- in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).
- in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.
- in combination with bevacizumab, for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.
- in combination with carboplatin and etoposide, for the first-line treatment of adult patients with ES-SCLC.
- in combination with bevacizumab for the treatment of adult patients with unresectable or metastatic HCC who have not received prior systemic therapy.
- in combination with cobimetinib and vemurafenib for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.
- for the treatment of adult and paediatric patients 2 years of age and older with unresectable or metastatic alveolar soft part sarcoma.

Manufacturer

Tecentriq® is manufactured by Roche.

Costs [6]

Tecentriq® concentrate for solution for infusion 1200 mg/20 ml = € 4,799.20 (ex-factory price)

Warnings and precautions [1]

- Traceability
  - In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
- Immune-mediated adverse reactions
  - Most immune-mediated adverse reactions occurring during treatment with atezolizumab were reversible with interruptions of atezolizumab and initiation of corticosteroids and/or supportive care. Immune-mediated adverse reactions affecting more than one body system have been observed. Immune-mediated adverse reactions with atezolizumab may occur after the last dose of atezolizumab. For suspected immune-mediated adverse reactions, thorough evaluation to confirm aetiology or exclude other causes should be performed. Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 1 month. Based on limited data from clinical trials in patients whose immune-mediated adverse reactions could not be controlled with systemic corticosteroid use, administration of other systemic immunosuppressants may be considered.
  - Atezolizumab must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reactions, except for endocrinopathies that are controlled with replacement hormones. In patients with pre-existing autoimmune disease (AID), data from observational studies suggest that the risk of immune-mediated adverse reactions following immune checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.
  - Immune-mediated pneumonitis
    - Cases of pneumonitis, including fatal cases, have been observed in clinical trials with atezolizumab. Patients should be monitored for signs and symptoms of pneumonitis and causes other than immune-mediated pneumonitis should be ruled out. Treatment with atezolizumab should be withheld for Grade 2 pneumonitis, and 1 to 2 mg/kg body weight (bw)/day prednisone or equivalent should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with

atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 pneumonitis.

- Immune-mediated hepatitis
  - Cases of hepatitis, some leading to fatal outcomes have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of hepatitis. AST, ALT and bilirubin should be monitored prior to initiation of treatment, periodically during treatment with atezolizumab and as indicated based on clinical evaluation. For patients without HCC, treatment with atezolizumab should be withheld if Grade 2 event (ALT or AST > 3 to 5 x ULN or blood bilirubin > 1.5 to 3 x ULN) persists for more than 5 to 7 days, and 1 to 2 mg/kg bw/day of prednisone or equivalent should be started. If the event improves to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or Grade 4 events (ALT or AST > 5.0 x ULN or blood bilirubin > 3 x ULN).
  - For patients with HCC, treatment with atezolizumab should be withheld if ALT or AST increases to > 3 to ≤ 10 x ULN from normal limits at baseline, or > 5 to ≤ 10 x ULN from > 1 ULN to ≤ 3 x ULN at baseline, or > 8 to ≤ 10 x ULN from > 3 ULN to ≤ 5 x ULN at baseline, and persists for more than 5 to 7 days, and 1 to 2 mg/kg bw/day of prednisone or equivalent should be started. If the event improves to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued if ALT or AST increases to > 10 x ULN or total bilirubin increases > 3 x ULN).
- Immune-mediated colitis
  - Cases of diarrhoea or colitis have been observed in clinical trials with atezolizumab. Patients should be monitored for signs and symptoms of colitis. Treatment with atezolizumab should be withheld for Grade 2 or 3 diarrhoea (increase of ≥ 4 stools/day over baseline) or colitis (symptomatic). For Grade 2 diarrhoea or colitis, if symptoms persist > 5 days or recur, treatment with 1 to 2 mg/kg bw/day prednisone or equivalent should be started. For Grade 3 diarrhoea or colitis, treatment with intravenous corticosteroids (1 to 2 mg/kg bw/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg bw/day of prednisone or equivalent should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 4 (life threatening; urgent intervention indicated) diarrhoea or colitis. The potential complication of gastrointestinal perforation associated with colitis should be taken into consideration.
- Immune-mediated endocrinopathies
  - Hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis and type 1 diabetes mellitus, including diabetic ketoacidosis have been observed in clinical trials with atezolizumab. Patients should be monitored for clinical signs and symptoms of endocrinopathies. Thyroid function should be monitored prior to and periodically during treatment with atezolizumab. Appropriate management of patients with abnormal thyroid function tests at baseline should be considered. Asymptomatic patients with abnormal thyroid function tests can receive atezolizumab. For symptomatic hypothyroidism, atezolizumab should be withheld and thyroid hormone replacement should be initiated as needed. Isolated hypothyroidism may be managed with replacement therapy and without corticosteroids. For symptomatic hyperthyroidism, atezolizumab should be withheld and an anti-thyroid medicinal product should be initiated as needed. Treatment with atezolizumab may be resumed when symptoms are controlled and thyroid function is improving. For symptomatic adrenal insufficiency, atezolizumab should be withheld and treatment with intravenous corticosteroids (1 to 2 mg/kg bw/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg bw/day of prednisone or equivalent should follow. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and the patient is stable on replacement therapy (if required).
  - For Grade 2 or Grade 3 hypophysitis, atezolizumab should be withheld and treatment with intravenous corticosteroids (1 to 2 mg/kg bw/day methylprednisolone or equivalent) should be started, and hormone replacement should be initiated as needed. Once symptoms improve, treatment with 1 to 2 mg/kg bw/day of prednisone or equivalent should follow. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and the patient is stable on replacement therapy (if required).
  - Treatment with atezolizumab should be permanently discontinued for Grade 4 hypophysitis. Treatment with insulin should be initiated for type 1 diabetes mellitus. For ≥ Grade 3 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L), atezolizumab should be withheld. Treatment with atezolizumab may be resumed if metabolic control is achieved on insulin replacement therapy.

- Immune-mediated meningoencephalitis
    - Meningoencephalitis has been observed in clinical trials with atezolizumab. Patients should be monitored for clinical signs and symptoms of meningitis or encephalitis. Treatment with atezolizumab must be permanently discontinued for any grade of meningitis or encephalitis. Treatment with intravenous corticosteroids (1 to 2 mg/kg bw/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg bw/day of prednisone or equivalent should follow.
- Immune-mediated neuropathies
    - Myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome, which may be life threatening, and facial paresis were observed in patients receiving atezolizumab. Patients should be monitored for symptoms of motor and sensory neuropathy. Myelitis has been observed in clinical trials with atezolizumab. Patients should be closely monitored for signs and symptoms that are suggestive of myelitis. Treatment with atezolizumab must be permanently discontinued for any grade of myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome. Initiation of systemic corticosteroids (at a dose of 1 to 2 mg/kg bw/day of prednisone or equivalent) should be considered. Treatment with atezolizumab should be withheld for Grade 1 or 2 facial paresis, and treatment with systemic corticosteroids (1 to 2 mg/kg bw/day prednisone or equivalent) should be considered. Treatment may be resumed only if the event fully resolves. Treatment with atezolizumab should be permanently discontinued for Grade 3 or Grade 4 facial paresis, or any other neuropathy that does not fully resolve while withholding atezolizumab.
    - Treatment with atezolizumab must be permanently discontinued for Grade 2, 3 or 4 myelitis.
- Immune-mediated pancreatitis
    - Pancreatitis, including increases in serum amylase and lipase levels, has been observed in clinical trials with atezolizumab. Patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis. Treatment with atezolizumab should be withheld for ≥ Grade 3 serum amylase or lipase levels increased (> 2 x ULN), or Grade 2 or 3 pancreatitis, and treatment with intravenous corticosteroids (1 to 2 mg/kg bw/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg bw/day of prednisone or equivalent should follow. Treatment with atezolizumab may be resumed when serum amylase and lipase levels improve to ≤ Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab should be permanently discontinued for Grade 4, or any grade of recurrent pancreatitis.
- Immune-mediated myocarditis
    - Cases of myocarditis, including fatal cases, have been observed with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of myocarditis. Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly. Patients with cardiac or cardiopulmonary symptoms should be assessed for potential myocarditis, to ensure the initiation of appropriate measures at an early stage. If myocarditis is suspected, treatment with atezolizumab should be withheld, prompt initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg bw/day of prednisone or equivalent should be started, and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of myocarditis is established, treatment with atezolizumab must be permanently discontinued for Grade ≥ 2 myocarditis.
- Immune-mediated nephritis
    - Nephritis has been observed in clinical trials with atezolizumab. Patients should be monitored for changes in renal function. Treatment with atezolizumab should be withheld for Grade 2 nephritis, and treatment with systemic corticosteroids at a dose of 1 to 2 mg/kg bw/day of prednisone or equivalent should be started. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 nephritis.
- Immune-mediated myositis
    - Cases of myositis, including fatal cases, have been observed with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of myositis. Patients with possible myositis should be monitored for signs of myocarditis. If a patient develops signs and symptoms of myositis, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Treatment with atezolizumab should be withheld for Grade 2 or 3 myositis and corticosteroid therapy (1-2 mg/kg bw/day prednisone or equivalent) should be initiated. If symptoms improve to ≤ Grade 1, taper corticosteroids as clinically indicated. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Treatment with atezolizumab should be permanently discontinued for Grade 4 or grade 3 recurrent myositis, or when unable to reduce the corticosteroid dose to the equivalent of ≤ 10 mg prednisone per day within 12 weeks after onset.
- Immune-mediated severe cutaneous adverse reactions (SCARs)

- Immune-mediated SCARs, including cases of SJS and TEN, have been reported in patients receiving atezolizumab. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. For suspected SCARs, patients should be referred to a specialist for further diagnosis and management. Based on the severity of the adverse reaction, atezolizumab should be withheld for Grade 3 skin reactions and treatment with systemic corticosteroids at a dose of 1-2 mg/kg bw/day of prednisone or equivalent should be started. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab should be permanently discontinued for Grade 4 skin reactions, and corticosteroids should be administered.
- Atezolizumab should be withheld for patients with suspected SJS or TEN. For confirmed SJS or TEN, atezolizumab should be permanently discontinued. Caution should be used when considering the use of atezolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immunestimulatory anticancer agents.

- Immune-mediated pericardial disorders
  - Pericardial disorders, including pericarditis, pericardial effusion and cardiac tamponade, some leading to fatal outcomes, have been observed with atezolizumab. Patients should be monitored for clinical signs and symptoms of pericardial disorders. For suspected Grade 1 pericarditis, treatment with atezolizumab should be withheld and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. For suspected Grade ≥ 2 pericardial disorders, treatment with atezolizumab should be withheld, prompt treatment with systemic corticosteroids at a dose of 1 to 2 mg/kg bw/day of prednisone or equivalent should be started and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of a pericardial disorder event is established, treatment with atezolizumab must be permanently discontinued for Grade ≥ 2 pericardial disorders.
- Haemophagocytic lymphohistiocytosis (HLH)
  - HLH, including fatal cases, has been reported in patients receiving atezolizumab. HLH should be considered when the presentation of cytokine release syndrome is atypical or prolonged. Patients should be monitored for clinical signs and symptoms of HLH. For suspected HLH, atezolizumab must be permanently discontinued and patients should be referred to a specialist for further diagnosis and management.
- Other immune-mediated adverse reactions
  - Given the mechanism of action of atezolizumab, other potential immune-mediated adverse reactions may occur, including noninfective cystitis. Evaluate all suspected immune-mediated adverse reactions to exclude other causes. Patients should be monitored for signs and symptoms of immune-mediated adverse reactions and, based on the severity of the reaction, managed with treatment modifications and corticosteroids as clinically indicated.

❖ Infusion-related reactions
- Infusion-related reactions have been observed with atezolizumab. The rate of infusion should be reduced or treatment should be interrupted in patients with Grade 1 or 2 infusion-related reactions. Atezolizumab should be permanently discontinued in patients with Grade 3 or 4 infusion-related reactions. Patients with Grade 1 or 2 infusion-related reactions may continue to receive atezolizumab with close monitoring; premedication with antipyretic and antihistamines may be considered.

❖ Disease-specific precautions
- Use of atezolizumab as monotherapy for first-line treatment in metastatic NSCLC: Physicians should consider the delayed onset of atezolizumab effect before initiating first-line treatment as monotherapy in patients with NSCLC. A higher number of deaths within 2.5 months after randomisation followed by a long-term survival benefit was observed with atezolizumab compared with chemotherapy. No specific factor(s) associated with early deaths could be identified.

❖ Patients excluded from clinical trials
- Patients with the following conditions were excluded from clinical trials: a history of autoimmune disease, history of pneumonitis, active brain metastasis, ECOG PS ≥ 2 (except for patients with advanced NSCLC ineligible for a platinum-based therapy), HIV, hepatitis B or hepatitis C infection (for non-HCC patients), significant cardiovascular disease and patients with inadequate hematologic and end-organ function. Patients who were administered a live, attenuated vaccine within 28 days prior to enrolment; systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to study entry; therapeutic oral or intravenous antibiotics within 2 weeks prior to initiation of study treatment were excluded from clinical trials.

❖ Patient card
- The prescriber must discuss the risks of Tecentriq therapy with the patient. The patient will be provided with the patient card and instructed to carry the card at all times

Study characteristics [7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
IPSOS NCT03191786	453 (2:1)	1200 mg atezolizumab IV every 3 weeks	single-agent chemotherapy[1] at 3-weekly or 4-weekly cycles	OS in the ITT population	41.0 months	phase 3, open-label, randomised controlled study	PD-L1	F Hoffmann-La Roche and Genentech Inc.	IPSOS trial [8]

Inclusion criteria[2]	Exclusion criteria	Patient characteristics at baseline (I vs. C, n=302 vs. n=151)
❖ Histologically or cytologically confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC as per the AJCC 7th edition. ❖ No sensitising EGFR mutation (L858R or exon 19 deletions) or ALK fusion oncogene detected. ❖ No prior systemic treatment for advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC as per the AJCC 7th edition. ❖ Life expectancy ≥ 8 weeks. ❖ Deemed unsuitable by the investigator for any platinum-doublet chemotherapy due to poor PS (ECOG PS of 2-3). However, participants >= 70 years of age who have an ECOG PS of 0 or 1 may be included due to: a) substantial comorbidities; b) contraindication(s) for any platinum-doublet chemotherapy. ❖ Representative FPPE tumour tissue block obtained during course of disease (archival tissue) or at screening.	**Cancer-Specific Exclusion Criteria** ❖ Participants younger than 70 years who have an ECOG PS of 0 or 1. ❖ Active or untreated CNS metastases as determined by CT or MRI evaluation of the brain during screening and prior radiographic assessments. ❖ Uncontrolled tumor-related pain. ❖ Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently). ❖ Uncontrolled or symptomatic hyerpcalcemia (ionised calcium > 1.5 mmol/L or calcium >12 mg/dL or corrected serum calcium >ULN). ❖ History of other malignancy within 5 years prior to screening, with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome. ❖ NCI CTCAE version 4.0 Grade 3 or higher toxicities due to any prior therapy (excluding alopecia), which have not shown improvement and are strictly considered to interfere with current study medication. ❖ Participants who have received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from randomisation since the last chemotherapy, radiotherapy, or chemoradiotherapy. **General Medical Exclusion Criteria:** ❖ History of autoimmune disease except autoimmune-related hypothyroidism and controlled Type I diabetes mellitus. ❖ History of idiopathic pulmonary fibrosis, organising pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis. ❖ Known positivity for HIV. ❖ Known active hepatitis B or hepatitis C.	❖ Age: 75.0 (69.0–81.0) vs. 75.0 (68.0–80.0) years ❖ ≥80 years: 32% vs. 28% ❖ 70–79 years: 41% vs. 43% ❖ <70 years: 26% vs. 28% ❖ Male sex: 73% vs. 72% ❖ Race: • White: 67% vs. 63% • Asian: 25% vs. 25% • American Indian or Alaska Native: 4% vs. 6% • Black or African American 2: 1% vs. 1% • Multiple: 2% vs. 4% • Unknown: 1% vs. 1% ❖ ECOG PS score: • 0 or 1: 19% vs. 13% • 2: 75% vs. 77% • 3: 6% vs. 11% ❖ Tobacco use history: • Previous: 69% vs. 68% • Current: 19% vs. 19% • Never: 12% vs. 13% ❖ Histology: • Non-squamous: 57% vs. 58% • Squamous: 43% vs. 42% ❖ Stage: • IIIB: 14% vs. 14% • IV: 86% vs. 86% ❖ Brain metastases:

[1] Vinorelbine (oral or IV) or gemcitabine (IV); dosing per local label.
[2] For detailed in-and exclusion criteria, please see trial protocol.

❖ Participants with treated, asymptomatic CNS metastases are eligible, provided they meet all of the following criteria: Measurable disease outside CNS; Only supratentorial and cerebellar metastases allowed; No ongoing requirement for corticosteroids as therapy for CNS disease; No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomisation; No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study. ❖ Adequate hematologic and end organ function. ❖ Female participants of childbearing potential randomised to the atezolizumab treatment arm agree to use protocol defined methods of contraception.	❖ Active tuberculosis. ❖ Severe infections within 4 weeks prior to randomisation. ❖ Significant cardiovascular disease, such as New York Heart Association NYHA cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomisation, unstable arrhythmias, or unstable angina. ❖ Major surgical procedure other than for diagnosis within 4 weeks prior to randomisation or anticipation of need for a major surgical procedure during the course of the study. ❖ Prior allogeneic bone marrow transplantation or solid organ transplant. ❖ Participants with an illness or condition that may interfere with capacity or compliance with the study protocol, as per investigator's judgment. ❖ Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to randomisation. **Exclusion Criteria Related to Atezolizumab** ❖ History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanised antibodies or fusion proteins. ❖ Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation. ❖ Oral or IV antibiotic treatment. ❖ Administration of a live, attenuated vaccine within 4 weeks before randomisation or anticipation that such a live attenuated vaccine will be required during the study. ❖ Prior treatment with cluster of differentiation 137 (CD137) agonists or immune checkpoint blockade therapies, anti-PD-1, and anti-PD-L1 therapeutic antibodies. ❖ Treatment with systemic immunostimulatory agents within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to randomisation. ❖ Treatment with systemic corticosteroids or other immunosuppressive medications. ❖ Participants not willing to stop treatment with traditional herbal medicines. **Exclusion Criteria Related to Chemotherapy** ❖ Known sensitivity and contraindications to the 2 comparative chemotherapy agents.	• Yes: 9% vs. 9% • No: 90% vs. 91% ❖ Liver metastases: • Yes: 15% vs. 17% • No: 85% vs. 83% ❖ Number of metastatic sites: • <3: 41% vs. 48% • ≥3: 47% vs. 39% • Missing: 12% vs. 13% ❖ EGFR mutation status: • Mutations other than Leu858Arg or exon 19 deletions: <1% vs. 1% • No mutation: 89% vs. 87% • Not done: 11% vs. 13% ❖ ALK rearrangement status: • No: 88% vs. 86% • Not evaluable: 1% vs. 1% • Not done: 11% vs. 13% ❖ PD-L1 expression level by SP142 immunohistochemistry assay: • TC0 and IC0: 52% vs. 52% • TC1/2/3 or IC1/2/3: 43% vs. 44% • TC2/3 or IC2/3: 18% vs. 26% • TC3 or IC3: 6% vs. 7% • Unknown: 5% vs. 4% ❖ PD-L1 expression level by SP263 immunohistochemistry assay: • TC <1%: 50% vs. 40% • TC ≥1%: 42% vs. 52% • TC 1–49%: 25% vs. 35% • TC ≥50%: 17% vs. 17% • Unknown: 8% vs. 8% ❖ Ongoing medical conditions per patient: 6.0 (3.0–9.0) vs. 5.0 (3.0–8.0) ❖ Patients with ≥1 ongoing medical condition: 97% vs. 97%
Efficacy (I vs. C)		**Safety** (I vs. C, n=300 vs. n=147)
Data cutoff 30 April 2022; median follow-up 41.0 months **Median OS**: 10.3 months (95% CI, 9.4–11.9) vs. 9.2 months (5.9–11.2); stratified HR 0.78 (0.63–0.97), p=0.028 **OS rates at 12 months**: 44% (95% CI, 37.9–49.4) vs. 39% (30.5–46.7) **OS rates at 24 months**: 24% (95% CI, 19.3–29.4) vs. 12% (6.7–18.0)		❖ **All-grade AEs:** 92% vs. 97% • **Treatment-related:** 57% vs. 80% ❖ **Grade 3–4 AEs:** 45% vs. 48% • **Treatment-related:** 16% vs. 33% ❖ **Deaths:** 12% vs. 9%

Unstratified OS HR For subgroup analyses across ECOG PS subgroups: 0.64 (95% CI, 0.36–1.13) for ECOG PS 0–1, 0.86 (0.67–1.10) for ECOG PS 2, and 0.74 (0.35–1.57) for ECOG PS 3
Unstratified OS HR across histology types: 0.77 (95% CI, 0.58–1.03) for non-squamous and 0.80 (0.58–1.12) for squamous histology
Unstratified HR across PD-L1 expression levels (SP263 assay): 0.81 (95% CI, 0.58–1.11) in the PD-L1–negative subgroup, 0.84 (0.62–1.15) in the PD-L1–positive subgroup, 0.84 (0.57–1.22) in the PD-L1–low subgroup, 0.87 (0.50–1.52) in the PD-L1–high subgroup, and 0.49 (0.21–1.14) in the PD-L1–unknown group.
Subsequent anticancer therapies: 20% vs. 30%
Subsequent chemotherapy: 16% vs. 19%
Median PFS: 4.2 months (95%, CI 3.7–5.5) vs. 4.0 months (2.9–5.4); stratified HR 0.87 (0.70–1.07)
PFS rates at 12 months: 20% vs. 14%
PFS rates at 24 months: 9% vs. 2%
ORR: 17% (95% CI, 12.8–21.6) vs. 8% (4.2–13.5)
Median duration of response: 14.0 months (95% CI, 8.1–20.3) vs. 7.8 months (4.8–9.7)

- **Treatment-related deaths:** 1% vs. 3%

❖ **Serious AEs:** 49% vs. 36%
- **Treatment-related:** 12% vs. 16%

❖ **All-grade AEs of special interest:** 34% vs. 18%
- **Grade 1–2:** 26% vs. 16%
- **Grade 3–4:** 7% vs. 2%
- **Deaths:** 1% vs. 0

❖ **All-grade AE of special interest requiring use of corticosteroids:** 11% vs. 5%
❖ **AEs leading to discontinuation of study drug:** 13% vs. 14%
❖ **AEs leading to modification or interruption of study drug:** 32% vs. 48%

Patient-reported outcomes

❖ For the patient-reported health-related QoL functioning scales and symptoms, the atezolizumab group showed clinically meaningful improvements (for appetite loss, constipation, dyspnoea, cough, and pain in chest) or maintenance in baseline health for all symptoms.
❖ By contrast, the chemotherapy group showed clinically meaningful deteriorations across several functioning domains (ie, role, social, and cognitive) and symptoms (ie, appetite loss, peripheral neuropathy, alopecia, and pain in other parts).
❖ A clinically meaningful improvement was observed in the chemotherapy group for insomnia, pain, and pain in other parts.
❖ Atezolizumab showed a benefit over chemotherapy for time-to-confirmed-deterioration in chest pain (QLQ-LC13; stratified HR 0.51, 95% CI, 0.27–0.97).

ESMO-MCBS version 1.1 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2A	≤12 months	OS: +1.1 months OS at 24 months: +12%	0.78 (0.63–0.97)	Increase in 2-year survival: ≥10%	4	-	improved (not significant)	-	4
Adapted	NC	2A	≤12 months	OS: +1.1 months OS at 24 months: +12%	0.78 (0.63–0.97)	Increase in 2-year survival: ≥10%	4	+13% serious AEs, +16% AEs of special interest	improved (not significant)	-1[3]	3

Risk of bias (RCT) [11]

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[4] high risk	no low risk	yes[5] high risk	**high**

Ongoing trials

NCT number/trial name	Description	Estimated study completion date

[3] Toxicity adjustment.
[4] This is an open-label study.
[5] F Hoffmann-La Roche and Genentech sponsored the study, provided the study drugs, and collaborated with the study investigators on the study design and the collection, analysis, and interpretation of the data. The sponsors also funded editorial and writing assistance.

For the assessed indication, no ongoing trials were identified via ClinicalTrials.gov.

Available assessments

- In August 2022, NIHR published a Health Technology Briefing "Atezolizumab for previously untreated recurrent or advanced non-small cell lung cancer unsuitable for platinum-doublet chemotherapy" [12].
- No further assessments were identified via NICE, CDA-AMC, ICER and G-BA.

Other aspects and conclusions

- In July 2024, the **CHMP adopted a new indication** for Tecentriq®, which is indicated as monotherapy for the first-line treatment of adult patients with advanced NSCLC who are ineligible for platinum-based therapy. This indication has not been **approved by the FDA**.
- **IPSOS (NCT03191786)** is a phase 3, global, multicentre, open-label, randomised controlled study assessing first-line atezolizumab monotherapy vs. single-agent chemotherapy in patients with NSCLC who are ineligible for treatment with a platinum-containing regimen. Eligible patients had stage IIIB NSCLC that was not amenable to multimodality radical treatment or stage IV NSCLC.
  Patients were deemed platinum-ineligible by the investigator if they had an ECOG PS 2–3 or were aged 70 years or older with substantial comorbidities or other contraindications for any platinum-doublet chemotherapy.
- The **primary endpoint was OS in the ITT population**. Median OS was 10.3 months (95% CI, 9.4–11.9] vs. 9.2 months (5.9–11.2); stratified HR was 0.78 (0.63–0.97), p=0.028). **2-year survival rate** was 24% (95% CI, 19.3–29.4) with atezolizumab compared with 12% (6.7–18.0) with chemotherapy.
- Among patients of the atezolizumab group, **clinically meaningful improvements** (for appetite loss, constipation, dyspnoea, cough, and pain in the chest) or maintenance in baseline health for all symptoms were shown. However, the results were not statistically significant.
- The **original and adapted ESMO-MCBS** were applied, resulting in a final adjusted magnitude of clinical benefit **grade 4 and 3**, respectively.
- The **risk of bias** was considered **high**. It is improved by the open-label trial design and the sponsor's involvement in study design, data collection, analysis and interpretation of the data.
- For the assessed indication, **no ongoing trials** were identified via ClinicalTrials.gov.
- Available data is rare for the assessed indication. More robust phase 3 data is required.

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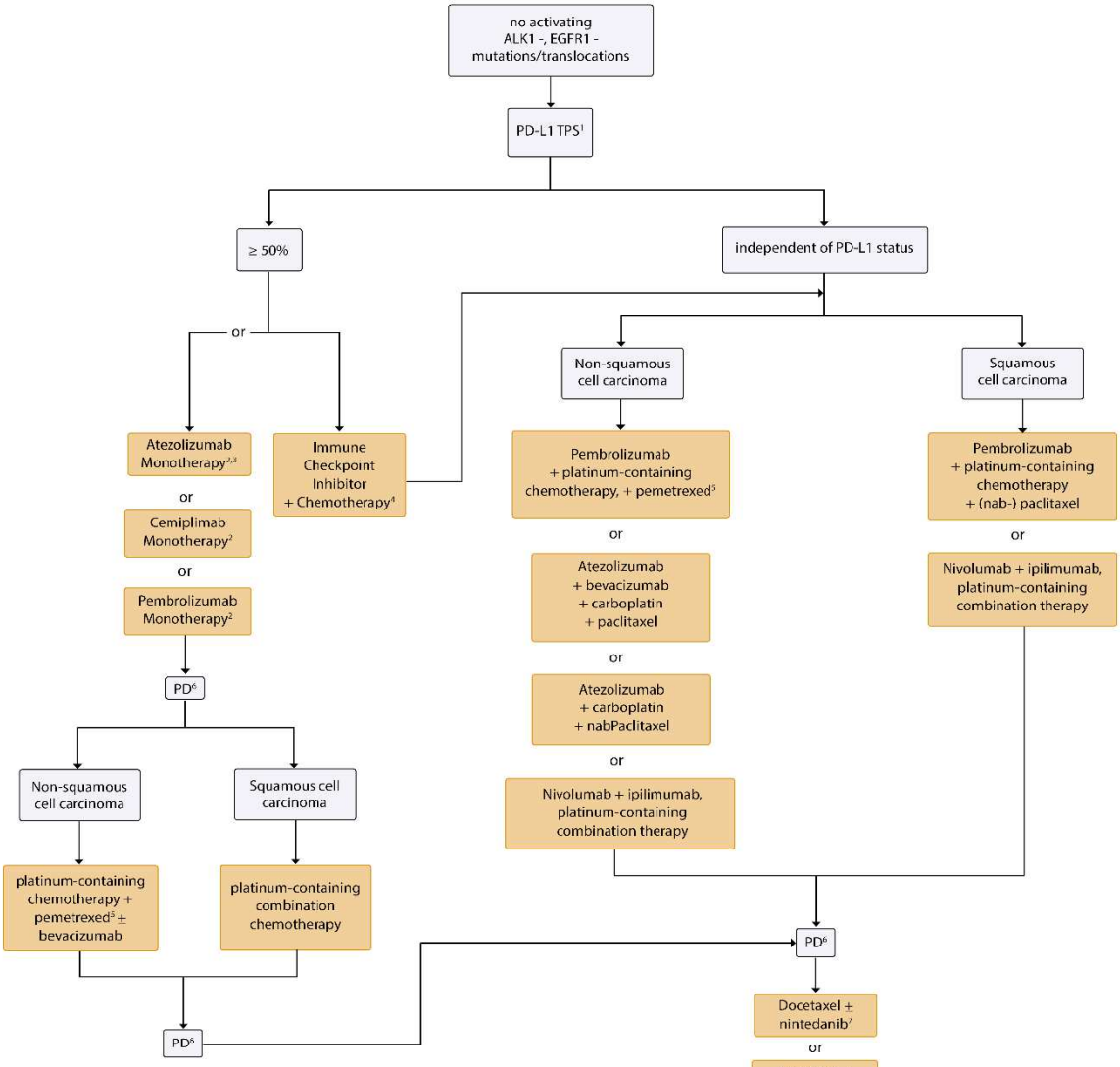
Abbreviations: AE=adverse event, AJ=adjustment, AJCC=American Joint Committee on Cancer, AID=autoimmune disease, ALK=anaplastic lymphoma kinase, ALT=alanine aminotransferase, anti-PD-1=anti-programmed death-1, AST=aspartate aminotransferase, C=comparator, CDA-AMC=Canada´s Drug Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CT=computed tomography, ECOG=Eastern Cooperative Oncology Group, EGFR= epidermal growth factor receptor, EMA=European Medicines Agency, ES-SCLC=extensive-stage small cell lung cancer, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, FPPE=formalin-fixed paraffin-embedded, G-BA=Gemeinsamer Bundesausschuss, HCC=hepatocellular carcinoma, HIV=human immunodeficiency virus, HLH=haemophagocytic lymphohistiocytosis, HR=hazard ratio, I=intervention, IC=immune cell, ICER=Institute for Clinical and Economic Review, Int.=intention, MG=median gain, MRI=magnetic resonance imaging, n=number of patients, NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, NICE=National Institute for Health Care Excellence, NSCLC=non small cell lung cancer, NYHA=New York Heart Association, OS=overall survival, PD-L1= programmed death-ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PS=performance status, QLQ-LC30= quality-of-life questionnaire Lung Cancer Module, QoL=quality of life, SAE=serious adverse event, SCARs= severe cutaneous adverse reactions, SJS=Stevens-Johnson syndrome, ST=standard treatment, TC=tumuor cells, TEN=toxic epidermal necrolysis, TNBC=triple-negative breast cancer, UC=urothelial carcinoma, ULN=upper limit of normal

References:

1. European Medicines Agency (EMA). Tecentriq: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/tecentriq-epar-product-information_en.pdf].
2. European Medicines Agency (EMA). Tecentriq - opinion on variation to marketing authorisation. [Available from: https://www.ema.europa.eu/en/medicines/human/variation/tecentriq-2].
3. Statistik Austria. Krebserkrankungen. Krebserkrankungen nach ausgewählten Lokalisationen und Geschlecht. [Available from: https://www.statistik.at/statistiken/bevoelkerung-und-soziales/gesundheit/krebserkrankungen].
4. Onkopedia, Griesinger F, et al. Onkopedia Guidelines. Lung Cancer, non small lung cancer (NSCLC). [Available from: https://www.onkopedia-guidelines.info/en/onkopedia/guidelines/lung-cancer-non-small-lung-cancer-nsclc/@@guideline/html/index.html#ID0EASAI. 2024-09-10
5. U.S. Food and Drug Administration (FDA). Tecentriq. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761034s053lbl.pdf].
6. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
7. Supplement to: Ming Lee S, Schulz C, Prabhash K, et al. First-line atezolizumab monotherapy versus single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen (IPSOS): a phase 3, global, multicentre, open-label, randomised controlled study. Lancet. 2023;402(10400):451-463.published online. DOI: 10.1016/S0140-6736(23)00774-2
8. Lee SM, Schulz C, Prabhash K, et al. First-line atezolizumab monotherapy versus single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen (IPSOS): a phase 3, global, multicentre, open-label,randomised controlled study. Lancet. 2023;402(10400):451-463. DOI: 10.1016/S0140-6736(23)00774-2
9. U.S. National Library of Medicine, ClinicalTrials.gov. A Study of Atezolizumab Compared With a Single-Agent Chemotherapy in Treatment Naïve Participants With Locally Advanced or Recurrent or Metastatic Non-Small Cell Lung Cancer Who Are Deemed Unsuitable For Platinum-Doublet Chemotherapy (IPSOS). [Available from: https://clinicaltrials.gov/study/NCT03191786?term=NCT03191786&rank=1].
10. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol. 2017;28(10):2340-2366.
11. 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].
12. National Institute for Health Research (NIHR). Atezolizumab for previously untreated recurrent or advanced non-small cell lung cancer unsuitable for platinum-doublet chemotherapy. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/11/28867-Atezolizumab-for-Non-Small-Cell-Lung-Cancer-V1.0-AUG2022-NON-CONF.pdf].

Appendix – Figure 1:



Legend:

[1] *PD-L1 TPS - expression of PD-L1 on tumor cells quantified according to the Tumor Progression Score (TPS);*
[2] *if suitable for immunotherapy and no relevant contraindications exist; see also the currently valid regulatory information;*
[3] *alternatively IC>10%;*
[4] *from an anti-PD1/-PD-L1 antibody and chemotherapy, differentiated by histology;*
[5] *TTF1 negativity is a negative predictor of pemetrexed efficacy;*
[6] *PD - progressive disease;*
[7] *Nintedanib only in adenocarcinoma;*
[8] *3rd generation cytostatic. Generation: gemcitabine, pemetrexed, vinorelbine; pemetrexed only in non-squamous cell carcinoma;*
[9] *afatinib only in squamous cell carcinoma;*
[10] *the indication was removed by the FDA in 2016;*
[11] *PD-1/PD-L1 inhibitor: atezolizumab (independent of PD-L1 expression), nivolumab (independent of PD-L1 expression), pembrolizumab (only in TPS >1%); evidence of efficacy is not established in patients, who have been pre-treated with an immune checkpoint inhibitor in first-line therapy;*