Atezolizumab (Tecentriq®) as adjuvant treatment following complete resection and platinum-based chemotherapy for patients with non-small cell lung cancer (NSCLC)

General information

Drug description	Indication [1]
Atezolizumab (Tecentriq®) is a PD-L1 inhibitor.	Atezolizumab (Tecentriq®) as monotherapy is indicated 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 non-small cell lung cancer (NSCLC).

Current treatment [2]

- Patients with NSCLC are offered the following chemotherapy drugs, in combination with cisplatin or carboplatin:
  - Vinorelbine
  - Gemcitabine
  - Paclitaxel
  - Docetaxel
  - Etoposide
  - Pemetrexed

Regulatory status

EMA [1]

Approval status for this indication: On 22 April 2022, 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:

- Early-stage NSCLC:
  - Tecentriq® as monotherapy is indicated 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 TC** and who do not have EGFR mutant or ALK-positive NSCLC.

Other indications: Tecentriq® is indicated:

- Urothelial carcinoma (UC):
  - as monotherapy for the treatment of adult patients with locally advanced or metastatic UC:
    - after prior platinum-containing chemotherapy, or
    - who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%.
- Metastatic 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.

FDA [3, 4]

Approval status for this indication: On 15 October 2021, the FDA approved atezolizumab (Tecentriq®) for adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II to IIIA NSCLC whose tumours have **PD-L1 expression on ≥ 1% of TC**, as determined by an FDA-approved test.

- ✓ Priority review
- ✓ The FDA also approved the VENTANA PD-L1 (SP263) Assay (Ventana Medical Systems, Inc.) as a companion diagnostic device to select patients with NSCLC for adjuvant treatment with Tecentriq®.

Other indications: Tecentriq® is indicated:

- UC
  - for the treatment of adult patients with locally advanced or metastatic UC who:
    - are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 (PD-L1 stained tumour-infiltrating IC covering ≥ 5% of the tumour area), as determined by an FDA-approved test, or
    - are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status
  - This indication is approved under accelerated approval based on tumour response rate and duration of response.
- NSCLC
  - 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

- 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®.

❖ Small cell lung cancer (SCLC)
- in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

❖ Triple-negative breast cancer (TNBC)
- in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.

❖ Hepatocellular carcinoma (HCC)
- in combination with bevacizumab, for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy.

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®.
- 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 tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving Tecentriq®.

❖ SCLC
- in combination with carboplatin and etoposide, for the first-line treatment of adult patients with ES-SCLC.

❖ HCC
- in combination with bevacizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy.

❖ Melanoma
- in combination with cobimetinib and vemurafenib for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Costs

Tecentriq® concentrate for solution for infusion 1200 mg/ml = **€ 4,799.20** (ex-factory price) [5].

Warnings and precautions [3]

❖ **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 dermatologic adverse reactions, immune-mediated nephritis and renal dysfunction, and solid organ transplant rejection.
- 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 based on severity of infusion reactions.

❖ **Complications of allogeneic HSCT**
- Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody.

❖ **Embryo-foetal toxicity:**
- Can cause foetal harm. Advise females of reproductive potential of the potential risk to a foetus and use of effective contraception.

Study characteristics [6-8]

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

IMpower010 GO29527 NCT02486718	1005[1]	adjuvant atezolizumab 1200 mg every 21 days (for 16 cycles or 1 year)	best supportive care[2]	disease-free survival (investigator-assessed)	**ongoing**[3], randomised, multicentre, open-label, phase 3 study	PD-L1	F Hoffmann-La Roche and Genentech	[7]

Efficacy (I vs. C): primary data (interim analysis)	**Safety** (I vs. C): primary data (interim analysis), safety population n=990
Patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells **Median duration of follow-up at the data cutoff** (21 Jan, 2021): 32.8 months (IQR 27.6–39.0) **Disease-free survival events**: 35% vs. 46%; stratified HR for disease-free survival 0.66 (95% CI 0.50–0.88; p=0.0039) **3-year disease-free survival rates**: 60.0 % vs. 48.2% **Patients in the stage II–IIIA population:** **Median duration of follow-up at the data cutoff** (21 Jan, 2021): 32.2 months (27.4–38.3) **Disease-free survival events**: 39% vs. 45%; HR for disease-free survival 0.79, 0.64–0.96; p=0.020 **3-year disease-free survival rates**: 56% vs. 49% **OS**: stratified HR 0.77 (0.51–1.17) **ITT population**: **Median duration of follow-up at the data cutoff** (21 Jan, 2021): 32.2 months (27.5–38.4) **Disease-free survival**: 37% vs. 43%; boundary for statistical significance for disease-free survival was not crossed (HR of 0.81, 0.67–0.99; p=0.040) **3-year disease-free survival**: 58% vs. 53% **OS**: stratified HR 1.07 (95% CI 0.80–1.42) **Patients in the stage II–IIIA population whose tumours expressed PD-L1 on 50% or more of tumour cells** **Disease-free survival** (secondary endpoint): unstratified HR was 0.43 (95% CI 0.27–0.68) **OS**: stratified HR 0.99 (0.73–1.33) **UPDATE: Interim analysis of the Impower010 trial[4]; median follow up 46 months** [9]: Median OS in patients with PD-L1 expression of 1% or more: not reached in either group; HR 0.71; 95% CI, 0.49-1.03 OS rates at 36 months and 60 months: 82.1% and 76.8% vs. 78.9% and 67.5% Median OS (in all patients who were randomised to treatment): not reached in either group; OS events in: 26.0% vs. 26.4% of patients in each respective group	**AEs of any grade**: 459/495 (93%) vs. 350/495 (71%) **AEs of grade 3 or 4:** 108/495 (22%) vs. 57/495 (12%) **AEs of grade 5**: 8/495 (2%) vs. 3/495 (1%) **SAEs:** 87/495 (18%) vs. 42/495 (8%) **Treatment-related AEs**: 335/495 (68%) **Treatment-related AEs of grade 3 or 4:** 53/495 (11%) **Treatment-related SAEs**: 37/495 (7%) **Atezolizumab-related AEs of grade 5**: 4/495 patients (1%)[5] **Atezolizumab discontinuation due to AEs**: 90 patients/495 (18%) **Immune-mediated AEs**: 256/495 (52%) vs. 47/495 patients (9%)

[1] 507 patients were assigned to receive atezolizumab and 498 were assigned to receive best supportive care, making up the ITT population; 882 patients who were randomly assigned had stage II–IIIA disease, and of these, **476 had tumours expressing PD-L1 on 1% or more of tumour cells per SP263 assay**; these groups formed the 3 primary efficacy populations.

[2] Observation and regular scans for disease recurrence after adjuvant platinum-based chemotherapy (1-4 cycles).

[3] The IMpower010 trial is currently ongoing; estimated study completion date is 12/2027.

[4] Presented at the 2022 World Conference on Lung Cancer.

[5] Myocarditis, interstitial lung disease, multiple organ dysfunction syndrome, and acute myeloid leukaemia.

Median OS (in the ITT population): not reached in either group; HR 0.995; 95% CI, 0.78-1.28; p= .9661; OS events were reported in 25.0% and 24.9% of patients in each group, respectively.											
ESMO-MCBS version 1.1 [10] for FDA indication: patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells											
Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	adjuvant	1	-	3-year DFS: +12%	0.66 (0.50–0.88)	Improvement in DFS alone (HR <0.65) without mature survival data	A	-	-	-	A
Adapted	adjuvant	1	-	3-year DFS: +12%	0.66 (0.50–0.88)	Improvement in DFS alone (HR 0.65-0.80) without mature survival data	B	-	-	-	B

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	-	no, open-label	unclear[6]	yes[7]	unclear

First published: 05/2022
Last updated: 09/2022

Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, 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, HCC=hepatocellular carcinoma, HR=hazard ratio, HSCT=haematopoietic stem cell transplantation, I=intervention, IC=immune cells, Int.=intention, ITT=intention-to-treat, IQR=interquartile range, MG=median gain, n=number of patients, NSCLC=non-small cell lung cancer, OS=overall survival, PD-L1=programmed-death-ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, SCLC=small cell lung cancer, ST=standard treatment, TC=tumour cells, TNBC=triple-negative breast cancer, UC=urothelial carcinoma

References:

1. European Medicines Agency (EMA). Medicines. Tecentriq [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/tecentriq-4].
2. National Institute for Health Research (NIHR). Atezolizumab for resected non-small cell lung cancer - adjuvant. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/12762-Atezolizumab-for-NSCLC-V1.0-AUG2020-NON-CONF.pdf].
3. U.S. Food and Drug Administration (FDA). Tecentriq. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761034s043lbl.pdf].
4. U.S. Food and Drug Administration (FDA). FDA approves atezolizumab as adjuvant treatment for non-small cell lung cancer. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-adjuvant-treatment-non-small-cell-lung-cancer].
5. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
6. Supplement to: Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet 2021; published online Sept 20.

[6] The Impower010 trial is ongoing; currently, only primary analysis data is available.

[7] The funder 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. All authors contributed to drafting the manuscript with editorial and writing assistance funded by the sponsor, had access to all the data in the study, provided final approval to publish, and agreed to be accountable for all aspects of the manuscript.

7. Felip E, Altorki N, Zhou C, et al, for the IMpower010 Investigators. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet 2021; 398: 1344–57 Published Online September 20, 2021. [Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673621020985].
8. U.S. National Library of Medicine, ClinicalTrials.gov. Study to Assess Safety and Efficacy of Atezolizumab (MPDL3280A) Compared to Best Supportive Care Following Chemotherapy in Patients With Lung Cancer [IMpower010]. [Available from: https://clinicaltrials.gov/ct2/show/NCT02486718].
9. Virgil H, CancerNetwork. IMpower010 Trial Highlights Trend Towards OS Benefit With Atezolizumab in Resected NSCLC. [Available from: https://www.cancernetwork.com/view/impower010-trial-highlights-trend-towards-os-benefit-with-atezolizumab-in-resected-nsclc].
10. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. . Annals of Oncology 28: 2340–2366, 2017.
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].