Atezolizumab (Tecentriq®) as monotherapy for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC)

General information

Drug description	Indication [1]
Atezolizumab is an anti-programmed death-ligand 1 (PD-L1) monoclonal antibody.	Atezolizumab as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% tumour cells (TC) or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC.

Current treatment [2]

- The following are recommended for first-line treatment of patients with advanced non-squamous (stages IIIB and IV) NSCLC, and no specific modifications to the EGFR or ALK genes:
  - PD-L1 under 50% (no gene mutation, fusion protein or biomarker):
    - Atezolizumab plus bevacizumab, carboplatin and paclitaxel
    - Pembrolizumab, with pemetrexed and platinum chemotherapy
    - Pemetrexed in combination with cisplatin.
  - PD-L1 50% or over (no gene mutation, fusion protein or biomarker):
    - Pembrolizumab, with pemetrexed and platinum chemotherapy
    - Pembrolizumab.
- For treatment of squamous NSCLC, NICE recommends platinum-based chemotherapy (that is, cisplatin or carboplatin and either docetaxel, gemcitabine, paclitaxel, or vinorelbine) as an option for people with previously untreated stage III or IV NSCLC and good performance status.
- Pembrolizumab monotherapy is also recommended as an option for untreated PD-L1-positive metastatic NSCLC if the tumour expresses PD-L1 with at least 50% tumour proportion score and has no EGFR- or ALK-positive mutations.

Regulatory status

EMA [1]

Approval status for this indication: On 25 March 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Tecentriq®.

The full indication will be as follows:

- Tecentriq® as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating IC and who do not have EGFR mutant or ALK-positive NSCLC.

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

- <u>Urothelial carcinoma (UC)</u>
  - 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%.
- <u>NSCLC</u>
  - 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 18 May 2020, the FDA approved atezolizumab (Tecentriq®) 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%), with no EGFR or ALK genomic tumour aberrations.

Other indications: Tecentriq® is indicated:

- <u>UC</u>
  - 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 (accelerated approval).
- <u>NSCLC</u>
  - 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

- 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 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®.

❖ 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.

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

❖ 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.

✓ **Medicine under additional monitoring**

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

❖ TNBC
- in combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumours express PD-L1 (PD-L1 stained tumour-infiltrating IC of any intensity covering ≥ 1% of the tumour area), as determined by an FDA approved test (accelerated approval).
- Limitations of Use: Tecentriq® is not indicated for use in combination with paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic TNBC.

❖ Small Cell Lung Cancer (SCLC)
- in combination with carboplatin and etoposide, for the first-line treatment of adult patients with ES-SCLC.

❖ Hepatocellular Carcinoma (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 = **€ 4,799.20** (ex-factory price) [5]

Impower110 patients (atezolizumab group) received atezolizumab at a dose of 1200 mg IV once every 3 weeks; the median treatment duration for atezolizumab was 5.3 months [6].

Warnings and precautions [4]

❖ **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 the 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 [6-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
Impower110, GO29431, NCT02409342	572	atezolizumab 1200 mg IV once every 3 weeks	platinum-based chemotherapy (4 or 6 cycles) once every 3 weeks	OS	randomised, open-label, phase 3 trial	PD-L1	F. Hoffmann–La Roche/ Genentech	[6]

Efficacy (I vs. C)[1]	Safety (I vs. C)[2]
Interim analysis of OS In the specified population, **49.3%** of patients who had high PD-L1 expression, **47.0%** of patients who had high or intermediate PD-L1 expression, and **45.7%** of patients who had any PD-L1 expression had died. **Median OS** among patients with **EGFR and ALK wt + high PD-L1 expression:** 20.2 months vs. 13.1 months; HR 0.59; 95% CI, 0.40-0.89; p=0.01 **Median OS** among patients with **EGFR and ALK wt + high/intermediate PD-L1 expression:** 18.2 months vs. 14.9 months; HR 0.72; 95% CI, 0.52-0.99; p=0.04 **Median OS** among patients with **EGFR and ALK wt + any PD-L1 expression:** 17.5 months vs. 14.1 months; HR 0.83; 95% CI, 0.65-1.07 Patients receiving subsequent chemotherapy (among patients with EGFR and ALK wt + high PD-L1 expression): 1.9% vs. 29.6% **Analysis of PFS** **PFS:** 8.1 months vs. 5.0 months; stratified HR for disease progression or death 0.63; 95% CI, 0.45-0.88 **PFS** among patients with **EGFR and ALK wt + high/intermediate PD-L1 expression:** 7.2 months vs. 5.5 months; HR 0.67; 95% CI, 0.52-0.88 **Occurrence and Duration of Response** **Confirmed response:** 38.3% vs. 28.6% **Confirmed ongoing responses:** 68.3% vs. 35.7% **Investigator-assessed confirmed response** among patients with **EGFR and ALK wt + high/intermediate PD-L1 expression:** 30.7% vs. 32.1%, with confirmed responses ongoing in 70.6% vs. 34.6% **investigator-assessed confirmed response** among patients with **EGFR and ALK wt + any PD-L1 expression:** 29.2% vs. 31.8%, confirmed responses ongoing in 70.4% vs. 33.0% **PD-L1 immunohistochemical analyses** **Median OS** among patients with **high PD-L1 expression as assessed by the SP142 assay:** 20.2 months vs. 13.1 months; HR 0.59; 95% CI, 0.40-0.89 **OS in patients with a tumour proportion score of ≥50% on the 22C3 Assay:** 20.2 months vs. 11.0 months; HR 0.60; 95% CI, 0.42-0.86 **OS in patients with PD-L1 expression on ≥50% of tumour cells on the SP263 assay:** 19.5 months vs. 16.1 months; HR 0.71; 95% CI, 0.50-1.00 **Median OS** in the population of patients who could be evaluated for **biomarker levels** who were **PD-L1–positive as assessed by the SP142 assay:** 17.5 months vs. 14.1 months; HR 0.83; 95% CI, 0.65-1.07 **Median OS** in patients who had a **tumour proportion score of at least 1% on the 22C3 assay:** 17.8 months vs.14.0 months; HR 0.73; 95% CI, 0.55 to 0.97 **Median OS** in patients who had **PD-L1 expression on at least 1% of tumour cells on the SP263 assay:** 17.8 months vs.14.0 months; HR 0.77; 95% CI, 0.58-1.02 **Median OS** among patients who had **intermediate/low PD-L1 expression assessed by the SP142 assay:** 12.9 months vs. 14.9 months; HR 1.04; 95% CI, 0.76-1.44 **OS in patients with a tumour proportion score of 1 to 49% on the 22C3 assay:** 16.5 months vs. 15.7 months; HR 1.00; 95% CI, 0.63-1.58 **OS in patients with PD-L1 expression on 1 to 49% of tumour cells on the SP263 assay:** 13.3 months vs.10.6 months; HR 0.94; 95% CI, 0.58-1.53 **Analyses of blood-based tumour mutational burden** A total of 22.4% of the patients with EGFR and ALK wt tumours ad a blood-based tumour mutational burden score of at least 16, and this burden level appeared to identify a distinct population as compared with the population identified as having high PD-L1 expression on the SP142 or 22C3 immunohistochemical assay. **Median OS among patients with a blood-based tumour mutational burden score of at least 16:** 13.9 months vs. 8.5 months; HR 0.75; 95% CI, 0.41-1.35 **Median PFS among patients with a blood-based tumour mutational burden score of at least 16:** 6.8 months vs. 4.4 months; HR 0.55; 95% CI, 0.33-0.92	**Grade ≥3 AEs**: n=86/286 (30.1%) vs. n=138/263 (52.5%) **Related grade 3-4 AEs:** n=37/286 (12.9%) vs. n=116/263 (44.1%) **Serious AEs**: n=81/286 (28.3%) vs. n=75/263 (28.5%) **Related serious AEs**: n=24 (8.4%) vs. n=41(15.6%) **Grade 5 AEs**: n=11 (3.8%) vs. n=11 (4.2%) **Related grade 5 AEs**: n=0 vs. n=1 (0.4%) **Immune-mediated AEs**: n=115 (40.2%) vs. n=44 (16.7%) **Grade 3-4 immune-mediated AEs:** n=19 (6.6%) vs. n=4 (1.5%) **Immune-mediated AE requiring use of corticosteroids**: n=30 (10.5%) vs. n=3 (1.1%) **AEs leading to any treatment withdrawal**: n=18 (6.3%) vs. n=43 (16.3%)

[1] Interim analysis data.

[2] Safety analysis was performed in all the patients who received a trial agent, including patients who received any amount of atezolizumab (n=286) and those who received chemotherapy only (n=263).

Patient-reported outcomes [8]

- **Completion rates were high** in both arms for the QLC-C30 and the QLC-LC13 at baseline and most study visits.
- Mean baseline scores for global health status, physical functioning, and role functioning were moderate, symptom burden was low, and all were similar in both arms.
- **No differences in TTD** were seen between arms for **cough** (HR 0.98; 95% CI, 0.48-2.03)**, chest pain (**HR 1.02; 95% CI, 0.47-2.22)**, dyspnoea** (HR 0.96, 95% CI, 0.57-1.60)**, and 3-symptom composite score** (HR 0.92; 95% CI, 0.59-1.44).
- Mean change in **physical function** from baseline to week 42 was modestly improved with atezolizumab and greater than or similar to chemotherapy.
- No clinically meaningful worsening in **dyspnoea, cough or chest pain** was seen with atezolizumab vs. chemotherapy.
- Mean change in cough and chest pain from baseline numerically improved immediately after the start of treatment and was maintained to week 48 with atezolizumab**.**
- **Fatigue and nausea/vomiting scores** numerically improved immediately with atezolizumab and were maintained to week 48.

Exploratory analysis with longer follow up (median: 31.3 months) in patients with high PD-L1 expression ≥ 50% TC or ≥ 10% IC [10]:

Overall Survival

Median time to events (months): 20.2 (95% CI, 17.2-27.9) vs.14.7 (17.2-27.9); stratified HR 0.76 (95% CI, 0.54-1.09)

12-month OS (%): 66.1 vs. 52.3

Secondary endpoints

Investigator-assessed PFS (RECIST v1.1)

Median duration of PFS (months): 8.2 (95% CI, 6.8-11.4) vs. 5.0 (4.2-5.7); stratified HR 0.59 (95%CI ,0.43-0.81)

12-month PFS (%): 39.2 vs. 19.2

Investigator-assessed ORR (RECIST 1.1)

Complete response: 0.9% vs. 2.0%

Partial response: 39.3% vs. 26.5%

Investigator-assessed DOR (RECIST 1.1)

Median in months: 38.9 (95% CI, 16.1-NE) vs. 8.3 (5.6-11.0)

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	-	OS: +7.1 months	0.59 (0.40-0.89)	HR ≤ 0.70 AND gain ≥5 months	4	-22.4% AEs ≥grade 3	Improvements with atezolizumab in physical function, fatigue and nausea/vomiting scores	+1	5
Adapted	NC	2a	-	OS: +7.1 months	0.59 (0.40-0.89)	HR ≤ 0.70 AND gain ≥5 months	4	-22.4% AEs ≥grade 3; -10% AEs leading to any treatment withdrawal	Improvements with atezolizumab in physical function, fatigue and nausea/vomiting scores	+1	5

Risk of bias (study level) [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	-	no, open-label	unclear[3]	yes[4]	unclear

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[3] IMpower110 trial is ongoing until 05/2021. Interim analysis data available.

[4] Industry-funded; the sponsor funded the trial, provided the trial treatments, and collaborated with the academic authors on the design of the trial and the collection, analysis, and interpretation of the data. Earlier versions of the manuscript were developed by the authors, with editorial and writing assistance funded by the sponsor.

Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, DOR=duration of response, 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, IV=intravenous, MG=median gain, n=number of patients, NE=not estimable, NICE=National Institute for Health and Care Excellence, NSCLC=non-small cell lung cancer, ORR=objective response rate, OS=overall survival, PD-L1= programmed death ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QLQ-C30=Quality of Life Questionnaire Core 30, QLQ-LC13=Quality of Life Questionnaire lung cancer module, QoL=quality of life, SAE=serious adverse event, SCLC=small cell lung cancer, ST=standard treatment, TC=tumour cells, TNBC=triple-negative breast cancer, TTD=time to confirmed deterioration, UC=urothelial carcinoma, wt=wild-type.

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