Atezolizumab (Tecentriq®) plus bevacizumab for the treatment of advanced or unresectable hepatocellular carcinoma (HCC)

General information

Drug description [1]	Indication [2]
Atezolizumab selectively targets programmed death ligand-1 (PD-L1) to prevent interaction with receptors PD-1 and B7-1, thus reversing T-cell suppression.	Atezolizumb in combination with bevacizumab is indicated for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy.

Current treatment [3]

- For people with advanced HCC that have not received previous treatment, NICE recommends treatment with lenvatinib only for people with Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1.
- Sorafenib is recommended as an option for treating advanced HCC only for people with Child-Pugh grade A liver impairment.

Regulatory status

EMA [2]

Approval status for this indication: On 17 September 2020, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Tecentriq®. The CHMP adopted a new indication:

- Atezolizumab, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy.

Other indications: Atezolizumab is indicated in:

- 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%
- Non-small cell lung cancer (NSCLC):
  - in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.
  - 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 atezolizumab.
  - 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.
- Breast cancer: in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.

FDA

Approval status for this indication: On 29 May 2020, the FDA approved atezolizumab in combination with bevacizumab for patients with unresectable or metastatic HCC who have not received prior systemic therapy [4].

Other indications: Atezolizumab is indicated in:

- UC:
  - for the treatment of adult patients with locally advanced or metastatic UC who:
    - are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating IC covering ≥ 5% of the tumor area), as determined by an FDA-approved test, or
    - are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or
    - have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy (accelerated approval).
- NSCLC:
  - for the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of TC ≥ 50% or PD-L1 stained tumor-infiltrating IC covering ≥ 10% of the tumor area, IC ≥ 10), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor 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 tumor 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 tumor aberrations
  - as a single-agent, 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 atezolizumab.
- TNBC:
  - in combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating IC of any intensity covering ≥ 1% of the tumor area), as determined by an FDA approved test (accelerated approval)
- SCLC:
  - in combination with carboplatin and etoposide, for the first-line treatment of adult patients with ES-SCLC
- Melanoma:

❖ 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). ✓ **Medicine under additional monitoring**	• in combination with cobimetinib and vemurafenib, for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma [5].

Costs

Tecentriq® concentrate for solution for infusion 1200 mg = **€ 4,703.22** (ex-factory price) [6]

Study characteristics [1, 5]

Trial name	*n*	Intervention (I)	Comparator (C)	PEs (co-primary)	Characteristics	Biomarker	Funding	Publication(s)
IMbrave150 NCT03434379	501	Atezolizumab (1200 mg) + bevacizumab (15 mg/kg), every 3 weeks	Sorafenib (400 mg orally twice daily)	OS + PFS in the ITT population	Global, multicentre, open-label, phase 3 randomised trial	-	F. Hoffmann–La Roche/Genentech	Link

Efficacy (I vs. C)

OS: at the time of the primary analysis HR for death was 0.58 (95% CI, 0.42-0.79; p<0.001)
OS at 12 months: 67.2% (95% CI, 61.3-73.1) vs. 54.6% (95% CI, 45.2-64.0)
Median OS (95% CI): NE-13.2, HR 0.58 (95% CI 0.42-0.79), p=0.0006
Median PFS: 6.8 months (95% CI, 5.7-8.3) vs. 4.3 months (95% CI, 4.0-5.6), HR for disease progression or death 0.59 (95% CI, 0.47-0.76; p<0.001).
ORR: 27.3% (95% CI, 22.5-32.5) vs. 11.9% (95% CI, 7.4-18.0) with sorafenib, according to independent assessment with RECIST 1.1 (p<0.001), and 33.2% (95% CI, 28.1-38.6) vs.13.3% (95% CI, 8.4-19.6) according to hepatocellular carcinoma–specific mRECIST (p<0.001).
CR: 5.5% vs. 0
Disease control rate (objective response plus stable disease): 73.6% vs. 55.3%
DOR longer than 6 months: 87.6% vs. 59.1%
Median duration of response: NE-6.3 months
QoL: Treatment with atezolizumab–bevacizumab delayed deterioration of patient-reported QoL (median time to deterioration, 11.2 vs. 3.6 months with sorafenib; HR 0.63; 95% CI, 0.46-0.85, physical functioning (median time to deterioration, 13.1 vs. 4.9 months; HR 0.53; 95% CI, 0.39-0.73), and role functioning (median time to deterioration, 9.1 vs. 3.6 months; HR 0.62; 95% CI, 0.46-0.84).

Safety (I vs. C)

Grade ≥3 AEs: n=186/329 (56.5%) vs. n=86/156 (55.1%)
SAEs: n=125/239 (38.0%) vs. n=48/156 (30.8)
Death[1]: n=15/329 (4.6%) vs. 9/156 (5.8%)
Discontinuation[2]: n=51/329 (15.5%) vs. n=16/156 (10.3%)
Withdrawal from atezolizumab-bevacizumab: n=23/329 (7.0%)

ESMO-MCBS version 1.1

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2b	≤6 m	PFS: +2.5 m	PFS: 0.59 (0.47-0.76)	HR≤0.65 AND Gain ≥1.5 m	3	-	impr. QoL	+1	4
Adapted	NC	2b	≤6 m	PFS: +2.5 m	PFS: 0.59 (0.47-0.76)	HR≤0.65 AND Gain ≥1.5 m	3	+1.4% grade ≥3 AEs, +7.2% SAEs, +5.2% discontinuation	impr. QoL	+1	4

Risk of bias (study level)

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	no, open-label	unclear[3]	yes[4]	high

First published: 10/2020
Last updated: 01/2021

[1] death due to AE(s)
[2] of any treatment component due to AEs
[3] Primary analysis data; IMbrave150 is currently ongoing (until 30 June, 2022)
[4] The sponsor provided the trial drugs, and collaborated with an academic steering committee on the trial design and on the collection, analysis, and interpretation of the data. Drafts of the manuscript were prepared by the authors, with editorial assistance funded by the sponsor.

Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, DOR=duration of response, 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, HCC=hepatocellular carcinoma, HR=hazard ratio, I=intervention, impr.=improved, IC=immune cells, Int.=intention, m=months, 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, QoL=quality of life, RECIST=Response Evaluation Criteria In Solid Tumors, SAE=serious adverse event, SCLC=small cell lung cancer, ST=standard treatment, TC=tumour cells, TNBC= triple-negative breast cancer, UC=urothelial carcinoma

References:

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