Atezolizumab 1200mg Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.	C34	00544a	ODMS 01/03/2019
Treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC) after prior platinum-containing chemotherapy	C67	00544b	Reimbursement not approved[i]

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Atezolizumab is administered once every 21 days until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when atezolizumab is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Atezolizumab	1200mg	IV infusion	250ml 0.9% NaCl over 60 minutes[a]	Every 21 days
[a]Initial dose must be given over 60 minutes; subsequent doses may be given over 30 minutes if tolerated					
If a planned dose of atezolizumab is missed, it should be administered as soon as possible; it is recommended not to wait until the next planned dose. The schedule of administration must be adjusted to maintain a 3-week interval between doses					

ELIGIBILTY:

- Indications as above
- ECOG 0-1
- Prior treatment with ≥1 platinum based combination chemotherapy regimen
- Adequate haematological and organ function
- **Non Small Cell Lung Cancer:**
  - Locally advanced or metastatic (Stage IIIB, Stage IV, or recurrent) NSCLC
  - Patients with EGFR mutations or an ALK fusion oncogene are required to have received previous tyrosine kinase inhibitor therapy.
- **Urothelial carcinoma mUC:**
  - Locally advanced or metastatic urothelial carcinoma that shows predominantly transitional-cell features on histologic testing

CAUTION:

Use with caution in:

- Patients with clinically significant autoimmune disease

EXCLUSIONS:

- Hypersensitivity to atezolizumab or any of the excipients.
- Symptomatic central nervous system (CNS) metastases
- Any medical condition that requires immunosuppressive doses of systemic corticosteroids or other immunosuppressive medication(s) (defined as >10mg prednisolone/daily (or steroid equivalent, excluding inhaled or topical steroids)
- Symptomatic interstitial lung disease
- Any active clinically significant infection requiring therapy
- Prior treatment with, anti-CTLA4, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway-targeting agents.

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Glucose
- TFTs
- Virology Screen:Hepatitis B (HBsAg, HBcoreAb) and Hepatitis C

Regular tests:

- FBC, renal,liver profile and glucose prior to each cycle
- TFTs every 3 to 6 weeks

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Dose reduction of atezolizumab is not recommended.
- Guidelines for withholding of doses or permanent discontinuation are described below in Table 1.

Table 1: Guidelines for withholding or discontinuation of atezolizumab

Immune related adverse reaction	Treatment modification
Pneumonitis Grade 2 Grade 3 or 4	Withhold atezolizumab Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day Permanently discontinue atezolizumab
Hepatitis Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN] or blood bilirubin > 1.5 to 3 x ULN) Grade 3 or 4: (ALT or AST > 5 x ULN or blood bilirubin > 3 x ULN)	Withhold atezolizumab. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day Permanently discontinue atezolizumab
Colitis Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) or Symptomatic Colitis Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)	Withhold atezolizumab. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone equivalent per day Permanently discontinue atezolizumab
Hypothyroidism or hyperthyroidism Symptomatic	Withhold atezolizumab Hypothyroidism: Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing Hyperthyroidism: Treatment may be resumed when symptoms are controlled by antithyroid medicinal product and thyroid function is improving
Adrenal insufficiency Symptomatic	Withhold atezolizumab Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day and patient is stable on replacement therapy
Hypophysitis Grade 2 or 3 Grade 4	Withhold atezolizumab Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day and patient is stable on replacement therapy Permanently discontinue atezolizumab
Type 1 diabetes mellitus Grade 3 or 4 hyperglycaemia (fasting glucose >250 mg/dL or 13.9 mmol/L)	Withhold atezolizumab Treatment may be resumed when metabolic control is achieved on insulin replacement therapy
Infusion-related reactions Grade 1 or 2 Grade 3 or 4	Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved. Permanently discontinue atezolizumab

Immune related adverse reaction	Treatment modification
Rash Grade 3 Grade 4	Withhold atezolizumab Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day Permanently discontinue atezolizumab
Myasthenic syndrome/ myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis All grades	Permanently discontinue atezolizumab
Pancreatitis Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis Grade 4 or any grade of recurrent pancreatitis	Withhold Atezolizumab Treatment may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day Permanently discontinue atezolizumab
Myocarditis Grade 2 Grade 3 and 4	Withhold atezolizumab Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day Permanently discontinue atezolizumab
Nephritis Grade 2: (creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 3.0 x ULN) Grade 3 or 4: (creatinine level > 3.0 x baseline or > 3.0 x ULN)	Withhold atezolizumab Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day Permanently discontinue atezolizumab
Myositis Grade 2 or 3 Grade 4 or recurrent Grade 3	Withhold Atezolizumab Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day Permanently discontinue Atezolizumab

Immune related adverse reaction	Treatment modification
Other immune-related adverse reactions Grade 2 or Grade 3 Grade 4 or recurrent Grade 3	Withhold until adverse reactions recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10mg prednisolone or equivalent per day. Permanently discontinue atezolizumab (except endocrinopathies controlled with replacement hormones)
Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Event Version 4.0 (NCI-CTCAE v.4.).	

Renal and Hepatic Impairment:

Table 2: Dose modification of atezolizumab in renal and hepatic impairment

Renal Impairment		Hepatic Impairment	
Mild/Moderate	No dose adjustment required	**Mild**	No dose adjustment required
Severe	Data too limited to draw conclusions	**Moderate/Severe**	Has not been studied

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low (**Refer to local policy).**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE: Not usually required

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Immune-mediated adverse reactions:** Most immune-related adverse reactions occurring during treatment with atezolizumab were reversible with interruptions of atezolizumab and initiation of corticosteroids and/or supportive care. Immune-related adverse reactions affecting more than one body system have been observed. Immune-related adverse reactions with atezolizumab may occur after the last dose of atezolizumab. For suspected immune-related 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 studies in patients whose immune-related 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-related adverse reaction that recurs and for any

Grade 4 immune-related adverse reactions, except for endocrinopathies that are controlled with replacement hormones.

- **Infusion related reactions:** have been observed in clinical trials 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.

DRUG INTERACTIONS:

- No formal pharmacokinetic drug interaction studies have been conducted with atezolizumab. Since atezolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.
- The use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting atezolizumab
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Atezolizumab L01XC32

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

HCP Guide

https://www.hpra.ie/img/uploaded/swedocuments/2c7d7f7e-c3b2-4544-8ce5-23faa51909c7.pdf

Patient Alert Card

http://www.hpra.ie/img/uploaded/swedocuments/fa95ee3c-5d21-4587-b365-f96da68fce06.pdf

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1. Fehrenbacher L et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre,open-label, phase 2 randomised controlled trial Lancet 2016; 387: 1837–46
2. Rittmeyer A, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial *Lancet* 2017; 389: 255–65
3. Gutzmer, R. et al. Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmunity or ipilimumab-triggered autoimmunity. European Journal of Cancer; 2017, 75, 24–32. https://doi.org/10.1016/j.ejca.2016.12.038
4. Powles, T et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2018 Feb 24;391(10122):748-757
5. Tecentriq® Summary of Product characteristics accessed July 2019 available at https://www.ema.europa.eu/en/documents/product-information/tecentriq-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	01/03/2019		Dr Richard Bambury
2	11/03/2019	Updated immune related adverse reactions regarding nephritis	Dr Richard Bambury
3	24/07/2019	Addition of new indication for urothelial carcinoma Inclusion of caution for use in patients with history of serious auto-immune disease Updated immune related adverse reactions regarding myositis	Prof Maccon Keane
4	24/09/2019	Clarification of eligibility criteria and baseline testing	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] Post 2012 indication. Not reimbursed through the ODMS or Community Drug Schemes (including the High Tech arrangements of the PCRS community drug schemes). Please check https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/new.html for the most up to date reimbursement approvals.

ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes