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	ODMS 01/03/2021
Treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are considered cisplatin ineligible and whose tumours have a PD-L1 expression ≥5%	C67	00544c	ODMS 01/07/2021
As monotherapy for the first-line treatment of adult patients with metastatic non-small cell lung cancer (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	C34	00544d	ODMS 01/10/2021

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.					

ELIGIBILITY:

- Indications as above
- ECOG 0-1
- Adequate haematological and organ function
- **Non Small Cell Lung Cancer: Second Line**
  - Locally advanced or metastatic (Stage IIIB, Stage IV, or recurrent) NSCLC
  - Prior treatment with ≥1 platinum based combination chemotherapy regimen
  - Patients with EGFR mutations or an ALK fusion oncogene are required to have received previous tyrosine kinase inhibitor therapy.

- **Non Small Cell Lung Cancer: First Line**
  - Histologically or cytologically confirmed stage IV non-squamous or squamous NSCLC with no sensitizing EGFR mutations or ALK translocations.
  - No prior treatment for Stage IV non-squamous or squamous NSCLC.
  - Confirmation of PD-L1 tumour proportion score of ≥ 50% or PD-L1 stained tumour-infiltrating immune cells (IC) tumour area (IC ≥ 10%) by a validated test
  - Patients who have received prior neo-adjuvant, adjuvant chemotherapy or chemoradiotherapy for non-metastatic disease must have experienced a treatment-free interval of at least 6 months since the last chemotherapy or chemoradiotherapy cycle.

- **Urothelial Carcinoma: Second Line**
  - Locally advanced or metastatic urothelial carcinoma that shows predominantly transitional-cell features on histologic testing
  - Prior treatment with ≥1 platinum based combination chemotherapy regimen

- **Urothelial Carcinoma: First Line**
  - Locally advanced or metastatic urothelial carcinoma that shows predominantly transitional-cell features on histologic testing
  - PD-L1 expression ≥5% as demonstrated by a validated test method

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.

Non Small Cell Lung Cancer: First Line

- Known sensitizing mutation in the EGFR gene or ALK fusion oncogene

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
- 1L Urothelial Cancer and 1L Non Small Cell Lung Cancer: PD-L1 expression using a validated test method

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

Immune related adverse reaction	Treatment modification
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 anti-thyroid 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
Rash/Severe cutaneous adverse reaction Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1] Grade 4 or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1]	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

Immune related adverse reaction	Treatment modification
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 or above	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 Permanently discontinue atezolizumab
Other immune-related adverse reactions Grade 2 or Grade 3 Grade 4 or recurrent Grade 3	Withhold until adverse reaction 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.).	
[1]Regardless of severity	

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

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal (**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:** These 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.
- **Immune-related severe cutaneous adverse reactions (SCARs):** Immune-related severe cutaneous adverse reactions (SCARs), including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients treated with atezolizumab. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. In case a SCAR is suspected, atezolizumab should be withheld and patients should be referred to a specialist in SCARs for diagnosis and treatment. If SJS or TEN is confirmed, and for any grade 4 rash/SCAR, treatment with atezolizumab should be permanently discontinued. Caution is recommended when considering the use of atezolizumab in patients with previous history of a severe or life-threatening SCAR with other immune-stimulatory cancer medicines.(7)

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.

COMPANY SUPPORT RESOURCES/Useful Links:

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

Patient Alert Card

https://www.hpra.ie/img/uploaded/swedocuments/53ca611d-f634-4438-83db-4da11cebd0c6.pdf

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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
5	19/08/2020	Updated emetogenic potential	Prof Maccon Keane
6	01/03/2021	Updated reimbursement status	Prof Maccon Keane
7	30/03/2021	Updated adverse effects with respect to HPRA safety update and risk of SCARS.	Prof Maccon Keane
8	01/07/2021	Addition of new indication for urothelial carcinoma. Updated company support resources.	Prof Maccon Keane
9	09/09/2021	Reviewed. Updated Table 1 (Rash/SCAR, myositis), amended dose modification in hepatic impairment.	Prof Maccon Keane
10	01/10/2021	Addition of new indication: first line treatment of metastatic non small cell lung cancer	Prof Maccon Keane
11	16/12/2022	Amended dose modifications table	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.