Atezolizumab 1680mg Monotherapy – 28 Day

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of adult patients with locally advanced or metastatic non-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>small cell lung cancer (NSCLC) after prior chemotherapy.</td>
<td>C34</td>
<td>00593a</td>
<td>ODMS 01/03/2019</td>
</tr>
<tr>
<td>Treatment of adult patients with locally advanced or metastatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>urothelial carcinoma (mUC) after prior platinum-containing chemotherapy</td>
<td>C67</td>
<td>00593b</td>
<td>Reimbursement not approved</td>
</tr>
</tbody>
</table>

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 patient's individual clinical circumstances.

Atezolizumab is administered once every 28 days until disease progression or unacceptable toxicity develops.

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

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Atezolizum</td>
<td>1680mg</td>
<td>IV infusion</td>
<td>250ml 0.9% NaCl over 60 minutes</td>
<td>Every 28 days</td>
</tr>
</tbody>
</table>

*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
- 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.
## NCCP Chemotherapy Regimen

### Table 1: Guidelines for withholding or discontinuation of atezolizumab

<table>
<thead>
<tr>
<th>Immune related adverse reaction</th>
<th>Treatment modification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pneumonitis</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>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</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>Permanently discontinue atezolizumab</td>
</tr>
<tr>
<td><strong>Hepatitis</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 2: (ALT or AST &gt; 3 to 5 x upper limit of normal [ULN] or blood bilirubin &gt; 1.5 to 3 x ULN)</td>
<td>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</td>
</tr>
<tr>
<td>Grade 3 or 4: (ALT or AST &gt; 5 x ULN or blood bilirubin &gt; 3 x ULN)</td>
<td>Permanently discontinue atezolizumab</td>
</tr>
<tr>
<td><strong>Colitis</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) or Symptomatic Colitis</td>
<td>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</td>
</tr>
<tr>
<td>Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)</td>
<td>Permanently discontinue atezolizumab</td>
</tr>
<tr>
<td><strong>Hypothyroidism or hyperthyroidism</strong></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>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</td>
</tr>
<tr>
<td><strong>Adrenal insufficiency</strong></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>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</td>
</tr>
<tr>
<td><strong>Hypophysitis</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 2 or 3</td>
<td>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</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue atezolizumab</td>
</tr>
<tr>
<td><strong>Type 1 diabetes mellitus</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4 hyperglycaemia (fasting glucose &gt;250 mg/dL or 13.9 mmol/L)</td>
<td>Withhold atezolizumab. Treatment may be resumed when metabolic control is achieved on insulin replacement therapy</td>
</tr>
<tr>
<td><strong>Infusion-related reactions</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 1 or 2</td>
<td>Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved.</td>
</tr>
</tbody>
</table>

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### NCCP Chemotherapy Regimen

<table>
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<th>Immune related adverse reaction</th>
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</thead>
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<tr>
<td><strong>Grade 3 or 4</strong></td>
<td>Permanently discontinue atezolizumab</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>Withhold atezolizumab. Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Permanently discontinue atezolizumab</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue atezolizumab</td>
</tr>
<tr>
<td><strong>Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis</strong></td>
<td>Permanently discontinue atezolizumab</td>
</tr>
<tr>
<td>All grades</td>
<td>Permanently discontinue atezolizumab</td>
</tr>
<tr>
<td><strong>Pancreatitis</strong></td>
<td>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</td>
</tr>
<tr>
<td>Grade 3 or 4 serum amylase or lipase levels increased (&gt; 2 x ULN) or Grade 2 or 3 pancreatitis</td>
<td>Permanently discontinue atezolizumab</td>
</tr>
<tr>
<td>Grade 4 or any grade of recurrent pancreatitis</td>
<td>Permanently discontinue atezolizumab</td>
</tr>
<tr>
<td><strong>Myocarditis</strong></td>
<td>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</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Permanently discontinue atezolizumab</td>
</tr>
<tr>
<td>Grade 3 and 4</td>
<td>Permanently discontinue atezolizumab</td>
</tr>
<tr>
<td><strong>Nephritis</strong></td>
<td>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</td>
</tr>
<tr>
<td>Grade 2: (creatinine level &gt; 1.5 to 3.0 x baseline or &gt; 1.5 to 3.0 x ULN)</td>
<td>Permanently discontinue atezolizumab</td>
</tr>
<tr>
<td>Grade 3 or 4: (creatinine level &gt; 3.0 x baseline or &gt; 3.0 x ULN)</td>
<td>Permanently discontinue atezolizumab</td>
</tr>
<tr>
<td><strong>Myositis</strong></td>
<td>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</td>
</tr>
<tr>
<td>Grade 2 or 3</td>
<td>Permanently discontinue Atezolizumab</td>
</tr>
<tr>
<td>Grade 4 or recurrent Grade 3</td>
<td>Permanently discontinue Atezolizumab</td>
</tr>
<tr>
<td><strong>Other immune-related adverse reactions</strong></td>
<td>Withhold until adverse reactions recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10mg prednisolone or equivalent per day.</td>
</tr>
<tr>
<td>Grade 2 or Grade 3</td>
<td>Permanently discontinue atezolizumab (except endocrinopathies controlled with replacement hormones)</td>
</tr>
<tr>
<td>Grade 4 or recurrent Grade 3</td>
<td>Permanently discontinue atezolizumab</td>
</tr>
</tbody>
</table>

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<tbody>
<tr>
<td>Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Event Version 4.0 (NCI-CTCAE v.4).</td>
<td></td>
</tr>
</tbody>
</table>

Renal and Hepatic Impairment:

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

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/Moderate</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>Severe</td>
<td>Data too limited to draw conclusions</td>
</tr>
<tr>
<td></td>
<td>Moderate/Severe</td>
</tr>
<tr>
<td></td>
<td>Has not been studied</td>
</tr>
</tbody>
</table>

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

REFERENCES:

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>09/04/2020</td>
<td></td>
<td>Prof Maccon Keane</td>
</tr>
</tbody>
</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.
NCCP Chemotherapy Regimen

1 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