Atezolizumab

COMMON TRADE NAME(S): Tecentriq™

B - Mechanism of Action and Pharmacokinetics

Atezolizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to programmed cell death-ligand 1 (PD-L1) and blocks interactions with the PD-1 and B7.1 receptors on activated T cells. It releases PD-L1/PD-1 pathway-mediated inhibition of the immune response, leading to activation of an anti-tumour immune response.

Distribution

Two-compartment disposition model for the dose range of 1 - 20 mg/kg. Steady state is reached after 6-9 weeks of repeat dosing (2 to 3 cycles).

Metabolism

Antibodies are primarily cleared by catabolism.

Elimination

Half-life 27 days

C - Indications and Status

Health Canada Approvals:

- For the treatment of adult patients with locally advanced or metastatic non-small cell lung
cancer (NSCLC) with progression on or after platinum-based chemotherapy.

- Patients with EGFR or ALK aberrations should have progressed on therapy for these aberrations prior to receiving atezolizumab.

Health Canada Conditional Approvals
(pending the result of studies to verify the drug’s clinical benefit. Patients should be advised of the nature of the marketing authorization granted.)

For the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Note: Conditional approval is based on tumour response rate and durability of response. An improvement in survival or disease-related symptoms has not been established.

D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: None

Adverse reactions listed below are based on a large phase III study in NSCLC patients receiving atezolizumab 1200 mg IV every 3 weeks. Severe adverse effects from other studies are also included.

<table>
<thead>
<tr>
<th>ORGAN SITE</th>
<th>SIDE EFFECT* (%)</th>
<th>ONSET**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Hypotension (3%)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Myocarditis (rare; may be severe)</td>
<td>E D</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Rash, pruritus (17%) (may be severe)</td>
<td>E D</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal pain (3%)</td>
<td>E D</td>
</tr>
<tr>
<td></td>
<td>Anorexia (24%)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Constipation (18%)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Diarrhea (15%) (may be severe; colitis - 1%)</td>
<td>E D</td>
</tr>
<tr>
<td></td>
<td>Nausea, vomiting (18%)</td>
<td>I E</td>
</tr>
</tbody>
</table>
The most common side effects for atezolizumab include fatigue, anorexia, dyspnea, constipation, fever, chills, nausea, vomiting, rash, pruritus, diarrhea, musculoskeletal pain and myelosuppression ± infection.

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions of immune-related toxicities and their management.

* "Incidence" may refer to an absolute value or the higher value from a reported range.
* "Rare" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = immediate (onset in hours to days)  E = early (days to weeks)
D = delayed (weeks to months)  L = late (months to years)
Immune-related pneumonitis, colitis, hepatitis, pancreatitis, nephritis, endocrinopathies, meningoencephalitis, and neuropathies were reported in patients who received atezolizumab for advanced urothelial carcinoma or NSCLC (n= 2160) and may be severe.

- **Pneumonitis** occurred in 3% of patients with median time to onset of 3.5 months (range: 3 days to 20.5 months).
- **Colitis** occurred in 1-2% of patients with median time to onset of 4 months (range: 15 days to 15 months).
- **Hepatitis** has been reported across tumour sites and may be fatal. In advanced urothelial cancer or NSCLC, hepatitis occurred in 7 patients with onset of 9 days to 8 months.
- **Pancreatitis**, including increased amylase and lipase, occurred in 10 patients with advanced urothelial cancer or NSCLC. The time to onset was 1 week to 17 months.
- **Nephritis** has been reported post-marketing in patients receiving atezolizumab for urothelial carcinoma or NSCLC. Patients recovered with corticosteroid treatment.
- **Endocrinopathies**: Hypothyroidism occurred in 5% of patients. The median time to onset was 5.5 months (range: 15 days to 2.5 years). Hyperthyroidism occurred in 2% of patients. The median time to onset was 3.5 months (range: 21 days to 19 months). Diabetes mellitus occurred in 4% of patients. The median time to onset was 3 months (range 3 weeks to 15.3 months). Adrenal insufficiency has also been reported.
- **Meningoencephalitis** has been reported in patients with metastatic urothelial carcinoma or NSCLC. Meningitis occurred in 3 patients and encephalitis in 2 patients. The time to onset was 14 -16 days.
- **Neuropathies** including Guillain-Barré syndrome and demyelinating polyneuropathy have been reported in 5 patients and were mostly grade 3. The median time to onset was 7 months (range: 18 days to 8 months).

**Infusion-related reactions** with dyspnea, pyrexia, chills, and hypotension, occurred in > 1% of patients and all were ≤ grade 2.

**Infection** occurred in 42% of patients (10% ≥ grade 3, fatal in < 1%). Urinary tract infections were the most common type of grade 3 or higher infection.

**E - Dosing**

Refer to protocol by which patient is being treated.

**Pre-medications (prophylaxis for infusion reaction)**

- Consider antipyretic and H1-receptor antagonist.

**Adults:**
Intravenous: 1200 mg Every 3 weeks

until confirmed disease progression or unacceptable toxicity.

Dosage with Toxicity:

- Healthcare professionals should also consult the most recent atezolizumab product monograph for additional information.

Summary of Principles of Management

- Immune-related adverse effects (irAEs) are different in their presentation, onset and duration compared to conventional chemotherapy. Patient and provider education is essential.

- Initial irAE presentation can occur months after completion of treatment and affect multiple organs.

- Dose escalation or reduction is not recommended.

- If no other cause can be identified (such as infection), any new symptom should be considered immune-related and prompt treatment initiated.

- Organ-specific system-based toxicity management is recommended.

- Refer to CCO’s Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions of Immune-related toxicities and their management.

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
<th>Re-challenge</th>
</tr>
</thead>
</table>
| 1 or 2 | - Stop or slow the infusion rate.  
         - Manage the symptoms.  
         **Restart:**  
         - No specific recommendations can be made at this time. | - Re-challenge with close monitoring. Consider pre-medication with antipyretic and H1-receptor antagonists. |
3 or 4
- Stop treatment.
- Aggressively manage symptoms.
- Permanently discontinue (do not re-challenge).

**Dosage with Hepatic Impairment:**

Refer to CCO's *Immune Checkpoint Inhibitor Toxicity Management Guideline* for management of immune-related hepatic toxicities

<table>
<thead>
<tr>
<th>Hepatic impairment</th>
<th>Atezolizumab dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (bilirubin ≤ 1-1.5 x ULN and any AST OR AST &gt; ULN)</td>
<td>No change</td>
</tr>
<tr>
<td>Moderate (bilirubin 1.5-3 x ULN and any AST)</td>
<td>No data</td>
</tr>
<tr>
<td>Severe (bilirubin &gt; 3 x ULN and any AST)</td>
<td>No data</td>
</tr>
</tbody>
</table>

**Dosage with Renal Impairment:**

Refer to CCO's *Immune Checkpoint Inhibitor Toxicity Management Guideline* for management of immune-related renal toxicities

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Atezolizumab dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl ≥ 30 mL/min</td>
<td>No change</td>
</tr>
<tr>
<td>CrCl &lt; 30 mL/min</td>
<td>No data</td>
</tr>
</tbody>
</table>

**Dosage in the elderly:**

- No dose adjustment needed. No differences in safety or efficacy between patients ≥ 65 years of age and younger patients observed.
Children:

- The safety and efficacy in children and adolescents below 18 years of age have not been established.

F - Administration Guidelines

- Withdraw 20 mL of liquid concentrate from the vial and dilute to the required administration volume with 0.9% sodium chloride solution. Mix by gentle inversion; do not shake.
- Dilute with 0.9% Sodium Chloride Injection only into a polyvinyl chloride (PVC), polyethylene (PE) or polyolefin (PO) infusion bag.
- The initial dose must be administered over 60 minutes. If the first infusion is tolerated all subsequent infusions may be administered over 30 minutes.
- If a planned dose is missed, it should be administered as soon as possible; do not wait until the next planned dose. The schedule of administration should be adjusted to maintain a 3-week interval between doses.
- Store vials at 2-8°; do not freeze. Protect from light.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Atezolizumab may cause serious immune-mediated reactions affecting multiple organ systems, including GI, hepatic, cardiac, respiratory, endocrine and others. Use with caution and monitor closely in patients with pre-existing conditions such as colitis, hepatic impairment, respiratory or endocrine disorders, such as hypo or hyperthyroidism or diabetes mellitus.
- Severe infections have been observed in clinical trials.

Other Drug Properties:

- Carcinogenicity: Unknown
Pregnancy and Lactation:

- Fetotoxicity: Probable
- Embryotoxicity: Probable
  Atezolizumab is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 5 months after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Likely

H - Interactions

- Atezolizumab is not expected to have pharmacokinetic drug-drug interactions as it is not metabolized by drug metabolizing enzymes. No pharmacokinetic drug interaction studies have been performed.
- Use of systemic corticosteroids or immunosuppressants should be avoided prior to starting atezolizumab because of potential interference with efficacy. They can be used to treat immune-mediated reactions after starting the drug.

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph

Recommended Clinical Monitoring

<table>
<thead>
<tr>
<th>Monitor Type</th>
<th>Monitor Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver function tests (AST, ALT, bilirubin)</td>
<td>Baseline, prior to each treatment and as clinically indicated; frequent with severe toxicity</td>
</tr>
<tr>
<td>Renal function tests, including electrolytes</td>
<td>Baseline, prior to each treatment, and as clinically indicated; frequent with severe toxicity</td>
</tr>
<tr>
<td>Thyroid function tests</td>
<td>Baseline, periodic, and as clinically indicated</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>Baseline, periodic, and as clinically indicated</td>
</tr>
</tbody>
</table>
Clinical toxicity assessment for infection, infusion-related and immune-mediated reactions, ocular, endocrine, skin, GI, cardiac and respiratory toxicity

At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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**J - Supplementary Public Funding**

**New Drug Funding Program (NDFP Website)**
- Atezolizumab – Advanced or Metastatic Non-Small Cell Lung Cancer

**K - References**


Atezolizumab (TECENTRIQ™) product monograph, Hoffmann-La Roche Limited, April 6, 2018.

**February 2020** Added NDFP form

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**L - Disclaimer**

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.
The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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