Tecentriq®▼(atezolizumab)

Important Safety Information to Minimise the Risks of Immune-Related Adverse Reactions

For Healthcare Professionals

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Reporting forms and information can be found at www.medicinesauthority.gov.mt/adrportal. Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or calling +44 (0)1707 367554.

As Tecentriq is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number.

Tecentriq is a biological medicine and should be prescribed by both non-proprietary and brand name. The brand name and batch number of the dispensed product should be recorded on the patient's prescription, case record and other appropriate clinical systems.

This educational material is provided by Roche Products Limited and mandatory as a condition of the Marketing Authorisation in order to further minimise important selected risks.

RXUKATEZ00125k
Date of preparation: October 2018
v3.0.0

Indications

Urothelial Carcinoma

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (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

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving Tecentriq.

Important Safety Information

This guide is intended to provide information about the management of certain important identified risks when prescribing atezolizumab for UC and NSCLC, including immune-related pneumonitis, hepatitis, colitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, meningoencephalitis, pancreatitis, myocarditis and infusion-related reactions.

All patients receiving treatment with atezolizumab must be given a Patient Alert Card by their healthcare professional to educate them about the symptoms of immune-related adverse reactions and the need to report them to their treating doctor immediately. Treating doctors should also advise their patients to keep the Patient Alert Card with them at all times and show it to any healthcare professional who may treat them.

To obtain copies of the Patient Alert Card, please contact the Roche Medical Information department (tel: +44 (0)1707 361010 or email: medinfo.uk@roche.com) or download via the Medicines Authority of Malta website (http://www.medicinesauthority.gov.mt/rmm).

For more information, please refer to atezolizumab Summary of Product Characteristics at: www.medicines.org.uk/emc.

Explore the Following Sections to Learn More About Managing Immune-Related Adverse Reactions:

What is Atezolizumab?

Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells suppresses cytotoxic T-cell activity through the inhibition of T-cell proliferation and cytokine production. PD-L1 may be expressed on tumour cells and tumour-infiltrating immune cells, and can contribute to the inhibition of the antitumour immune response in the microenvironment.

Atezolizumab is an Fc-engineered humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and blocks interactions with the PD-1 and B7.1 receptors, releasing PD-L1 / PD-1 pathway-mediated inhibition of the immune response, including reactivation of the antitumour immune response.

Common Adverse Reactions

The most common adverse reactions were fatigue (34.3%), decreased appetite (26.2%), nausea (22.9%), dyspnoea (20.6%), rash (18.7%), diarrhoea (19.3%), pyrexia (19.4%), asthenia (15.0%), vomiting (14.6%), arthralgia (13.6%), and pruritus (11.8%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Recognise and Manage Immune-Related Adverse Reactions Associated With Therapy

Atezolizumab is associated with immune-related adverse reactions.

- Early identification and timely intervention can help to reduce the severity and duration of immune-related adverse reactions.
- Other aetiologies for adverse events should be considered.

For suspected immune-related adverse reactions, ensure adequate evaluation to confirm aetiology or exclude other causes. Based on the severity of the adverse reactions:

- Withhold atezolizumab and administer corticosteroids. Upon improvement to Grade ≤1, initiate corticosteroid taper and continue to taper over at least 1 month.
  - Rapid tapering may lead to worsening of adverse reaction.
- Consider restarting atezolizumab within 12 weeks after adverse reaction onset date if the adverse reaction improves to and remains at Grade ≤1 and corticosteroid dose is ≤10 mg prednisone or equivalent per day.
- Permanently discontinue atezolizumab if any Grade ≥3 toxicity occurs a second time and for any Grade 4 immune-related adverse reaction, except for endocrinopathies that are controlled with replacement hormones.
- Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.

If immunosuppression with corticosteroids is used to treat an immune-related adverse reaction, a taper of at least 1 month duration should be initiated upon improvement to ≤Grade 1.

- Rapid tapering may lead to worsening of adverse reaction.

Atezolizumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids[1] or other immunosuppressants.

Atezolizumab should also be permanently discontinued for immune-related adverse reactions that persist despite treatment modifications (described in this guide) or if a reduction of corticosteroid dose to ≤10 mg oral prednisone or equivalent per day cannot be achieved within 12 weeks of adverse reaction onset date. Please see the next section for detailed information regarding individual immune-related adverse reactions and management recommendations.

[1]*Immunosuppressive doses of corticosteroids are defined by prednisone >10 mg daily PO, or equivalent.*

Immune-Related Pneumonitis

- Cases of pneumonitis, including fatal cases, have been observed with atezolizumab treatment.
- Monitor patients for signs and symptoms of pneumonitis (see below).

Pneumonitis

Signs and symptoms

- Breathing difficulties or cough
- Radiographic changes (e.g. focal ground glass opacities, patchy infiltrates)
- Dyspnoea
- Hypoxia

Rule out infectious and disease-related aetiologies.

Pneumonitis occurred in 2.9% (75/2619) of patients who received atezolizumab. Of the 75 patients, one experienced a fatal event. The median time to onset was 3.5 months (range 3 days to 20.5 months). The median duration was 1.5 months (range 1+ day to 15.1+ months; + denotes a censored value). Pneumonitis led to discontinuation of atezolizumab in 10 (0.4%) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.5% (39/2619) of patients receiving atezolizumab.

Immune-Related Pneumonitis

Managing Immune-Related Pneumonitis

NCI CTCAE v4	**Pneumonitis Grade 2** (Symptomatic; medical intervention indicated; worsens from baseline)	**Pneumonitis Grade 3–4** (Severe symptoms; O_2 indicated. G4: life threatening; urgent intervention indicated)
Atezolizumab treatment	**Withhold atezolizumab**	**Permanently discontinue atezolizumab**
Corticosteroids	Prednisone 1–2 mg/kg or equivalent per day	Prednisone 1–2 mg/kg or equivalent per day
Follow-up	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month; treatment with atezolizumab may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of oral prednisone 10 mg daily or less	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month
	If no improvement, worsens or recurs: Treat as Grade 3/4	**If no improvement:** Consider adding additional immunosuppressive medication

Immune-Related Hepatitis

- Cases of hepatitis, including fatal cases, have been observed with atezolizumab treatment.
- Monitor patients for signs and symptoms of hepatitis (see below).
- Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin should be monitored prior to initiation of treatment, periodically during treatment and as indicated based on clinical evaluation.

Hepatitis

Signs and symptoms

- Elevations in transaminases
- Total bilirubin elevations
- Jaundice
- Right sided abdominal pain
- Tiredness

Rule out infectious and disease-related aetiologies.

Hepatitis occurred in 1.8% (47/2619) of patients who received atezolizumab. Of the 47 patients, one experienced a fatal event. The median time to onset was 1.4 months (range 8 days to 18.8 months). The median duration was 1.3 months (range 1+ day to 19.7+ months; + denotes a censored value). Hepatitis led to discontinuation of atezolizumab in 5 (0.2%) patients. Hepatitis requiring the use of corticosteroids occurred in 0.4% (10/2619) of patients receiving atezolizumab.

Immune-Related Hepatitis

Managing Immune-Related Hepatitis

NCI CTCAE v4	**Hepatitis Grade 2** (AST/ALT >3.0–5.0 × ULN or bilirubin >1.5–3.0 × ULN)	**Hepatitis Grade 3–4** (G3: AST/ALT >5.0–20.0 × ULN or bilirubin >3.0–10.0 × ULN; G4: AST/ALT >20.0 × ULN or bilirubin >10.0 × ULN)
Atezolizumab treatment	**Withhold atezolizumab if persists >5–7 days**	**Permanently discontinue atezolizumab**
Corticosteroids	Prednisone 1–2 mg/kg or equivalent per day, if atezolizumab withheld	Prednisone 1–2 mg/kg or equivalent per day
Follow-up	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month; atezolizumab may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of oral prednisone 10 mg daily or less	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month
	If no improvement, worsens or recurs: Treat as Grade 3/4	**If no improvement:** Consider adding additional immunosuppressive medication

ALT: alanine aminotransaminase; AST: aspartate aminotransaminase; ULN: upper limit of normal.

Immune-Related Colitis

- Colitis has been observed with atezolizumab treatment.
- Monitor patients for diarrhoea and additional symptoms of colitis (see below).

Colitis

Signs and symptoms

- Watery, loose or soft stools; increase in bowel movements or stool frequency
- Abdominal pain
- Mucus or blood in stool

Rule out infectious and disease-related aetiologies.

Colitis occurred in 1.2% (31/2619) of patients who received atezolizumab. The median time to onset was 4.2 months (range 15 days to 17.2 months). The median duration was 1.2 months (range 1+ day to 17.8+ months; + denotes a censored value). Colitis led to discontinuation of atezolizumab in 7 (0.3%) patients. Colitis requiring the use of corticosteroids occurred in 0.6% (16/2619) of patients receiving atezolizumab.

Immune-Related Colitis

Managing Immune-Related Colitis

NCI CTCAE v4	**Diarrhoea / Colitis Grade 2** (Increase of 4–6 stools / day or moderate increase in ostomy output compared to baseline); or abdominal pain, mucus or blood in the stool	**Diarrhoea / Colitis Grade 3** (Increase of ≥7 stools / day or severe increase in ostomy output compared to baseline, incontinence, limiting self care ADL, hospitalisation indicated); or severe abdominal pain; peritoneal signs	**Diarrhoea / Colitis Grade 4** (Life-threatening consequences; urgent intervention indicated)
Atezolizumab treatment/ other therapy	**Withhold atezolizumab; symptomatic therapy**	**Withhold atezolizumab; symptomatic therapy**	**Permanently discontinue atezolizumab; symptomatic therapy**
Corticosteroids	Prednisone 1–2 mg/kg or equivalent per day, if symptoms persists >5 days or recur	Treat with IV steroids (methylprednisolone 1–2 mg/kg or equivalent per day) and convert to oral corticosteroids (prednisone 1–2 mg/kg or equivalent per day) once improvement	Treat with IV steroids (methylprednisolone 1–2 mg/kg or equivalent per day) and convert to oral corticosteroids (prednisone 1–2 mg/kg or equivalent per day) once improvement
Follow-up	**If improves to ≤Grade 1:** Taper steroids over at least 1 month; atezolizumab may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of oral prednisone 10 mg daily or less	**If improves to ≤Grade 1:** Taper steroids over at least 1 month; atezolizumab may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of oral prednisone 10 mg daily or less	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month
	If no improvement, worsens or recurs: Treat as Grade 3 or 4	**If no improvement, worsens or recurs:** Treat as Grade 4	**If no improvement:** Consider adding additional immunosuppressive medication

ADL: activities of daily living.

Immune-Related Endocrinopathies

- Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency, type 1 diabetes mellitus including diabetic ketoacidosis, and hypophysitis have been observed with atezolizumab treatment.
- Monitor patients for signs and symptoms of endocrinopathies (see below). Thyroid function should be monitored prior to and periodically during treatment with atezolizumab. Appropriate management of patients with abnormal thyroid function tests at baseline should be considered. Asymptomatic patients with abnormal thyroid function tests can receive atezolizumab.
- Blood and urine glucose and ketones should be tested, and fasting glucose sampled to confirm hyperglycaemia.
- Monitor patients for signs and symptoms of immune-related diabetes mellitus, including diabetic ketoacidosis.
- Pituitary hormone levels and function tests and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Endocrinopathies

Signs and symptoms

- Fatigue
- Headache
- Mental status change
- Heat or cold intolerance
- Tachycardia or bradycardia
- Unusual bowel habits
- Weight change
- Polyuria / polydipsia
- Blurred vision

Unless an alternate aetiology has been identified, signs and symptoms of endocrinopathies should be conservatively considered immune-related.

Immune-Related Endocrinopathies

Hypothyroidism occurred in 4.7% (122/2619) of patients who received atezolizumab. The median time to onset was 5.1 months (range 1 day to 31.3 months). Hyperthyroidism occurred in 1.0% (25/2619) of patients who received atezolizumab. The median time to onset was 2.6 months (range 24 days to 15.7 months). Adrenal insufficiency occurred in 0.3% (8/2619) of patients who received atezolizumab. The median time to onset was 5.5 months (range 2 days to 19 months). The median duration was 16.8 months (range 1 day to 16.8 months). Adrenal insufficiency requiring the use of corticosteroids occurred in 0.2% (6/2619) of patients receiving atezolizumab. Diabetes mellitus occurred in 0.3% (8/2619) of patients who received atezolizumab. The median time to onset was 3.6 months (range 2 days to 9.9 months). Diabetes mellitus led to the discontinuation of atezolizumab in 3 (<0.1%) patients. Hypophysitis occurred in <0.1% (1/2619) of patients who received atezolizumab. The time to onset for this patient was 13.7 months.

Immune-Related Endocrinopathies

Managing Immune-Related Endocrinopathies

	Symptomatic Hypothyroidism	Symptomatic Hyperthyroidism	Symptomatic Adrenal Insufficiency (Patients with unexplained symptoms should be investigated for the presence of pituitary or adrenal endocrinopathies)	Hyperglycemia (Grade 3–4) or DKA (G3: Fasting glucose value >250–500 mg/dL or >13.9–27.8 mmol/L; hospitalisation indicated; G4: Fasting glucose value >500 mg/dL or >27.8 mmol/L with life-threatening consequences)
Atezolizumab treatment/ other therapy	**Withhold atezolizumab; initiate thyroid replacement therapy as needed**	**Withhold atezolizumab; initiate symptomatic therapy including antithyroid medicinal product as needed**	**Withhold atezolizumab; initiate hormone replacement therapy as needed**	**Withhold atezolizumab;** Start insulin replacement and management per local guidelines
Corticosteroids	Isolated hypothyroidism may be managed with replacement therapy and without corticosteroids.		Treat with an initial dose of IV methylprednisolone 1–2 mg/kg per day followed by oral prednisone 1–2 mg/kg per day, when symptoms improve	
Follow-up	**If improves:** Restart atezolizumab when symptoms are controlled by thyroid replacement and TSH levels are decreasing	**If improves:** Restart atezolizumab when symptoms are controlled by antithyroid medicinal product and thyroid function is improving	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month; Treatment may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤10 mg oral prednisone per day and patient is stable on replacement therapy (if required)	**Treatment with atezolizumab may be resumed if metabolic control is achieved on insulin replacement therapy**
	If no improvement or worsens: Permanently discontinue atezolizumab	**If no improvement or worsens: Permanently discontinue atezolizumab**	**If worsens or symptomatic adrenal insufficiency recurs: Permanently discontinue atezolizumab**	**If no improvement or worsens despite appropriate diabetes management: Permanently discontinue atezolizumab**

DKA: diabetic ketoacidosis; TSH: thyroid stimulating hormone.

Immune-Related Endocrinopathies

Managing Immune-Related Endocrinopathies

	Hypophysitis (pan-hypopituitarism) Grade 2–3 (G2: Moderate; minimal intervention indicated; or limiting age appropriate instrumental ADL; G3: Severe or medically significant, but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; or limiting self care ADLs)	**Hypophysitis (pan-hypopituitarism) Grade 4** (G4: Life-threatening consequences or urgent intervention indicated)
Atezolizumab treatment/ other therapy	**Withhold atezolizumab and initiate hormone replacement therapy as needed**	**Permanently discontinue atezolizumab and initiate hormone replacement therapy**
Corticosteroids	Treat with IV steroids (methylprednisolone 1–2 mg/kg or equivalent per day) and convert to oral corticosteroids (prednisone 1–2 mg/kg or equivalent per day) once improvement	Treat with IV steroids (methylprednisolone 1–2 mg/kg or equivalent per day) and convert to oral corticosteroids (prednisone 1–2 mg/kg or equivalent per day) once improvement
Follow-up	**If improves ≤Grade 1:** Taper corticosteroids over at least 1 month; Treatment may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤10 mg oral prednisone per day and patient is stable on replacement therapy (if required)	**If improves ≤Grade 1:** Taper corticosteroids over at least 1 month
	If worsens or recurs: Treat as Grade 4	**If no improvement or worsens:** Consider adding additional immunosuppressive medication

ADL: activities of daily living.

Immune-Related Meningoencephalitis

- Meningoencephalitis has been observed with atezolizumab treatment.
- Monitor patients for signs and symptoms of meningitis or encephalitis (see below).

Meningoencephalitis

Signs and symptoms

- Headache
- Mental status change, confusion, altered or depressed level of consciousness
- Photophobia
- Seizure
- Motor or sensory dysfunction
- Meningeal irritability, nuchal rigidity

Rule out infectious and disease-related aetiologies.

Meningitis occurred in 0.1% (3/2619) of patients who received atezolizumab. The time to onset ranged from 15 to 16 days. The duration ranged from 14 days to 3.4 months. All three patients required the use of corticosteroids and discontinued atezolizumab. Encephalitis occurred in <0.1% (2/2619) of patients who received atezolizumab. The time to onset was 14 and 16 days. One of these patients required the use of corticosteroids. Encephalitis led to discontinuation of atezolizumab in 1 (<0.1%) patient.

Managing Immune-Related Meningoencephalitis

Atezolizumab treatment	**Permanently discontinue atezolizumab**
Corticosteroids	Treat with IV corticosteroids (methylprednisolone 1–2 mg/kg or equivalent per day) followed by oral corticosteroids (prednisone 1–2 mg/kg or equivalent per day) after improvement
Follow-up	**If improves to ≤Grade 1:** Taper steroids over at least 1 month
	If not improving or worsening: Consider adding additional immunosuppressive medication

Immune-Related Neuropathies

- Myasthenic syndrome/myasthenia gravis and Guillain-Barré syndrome have been observed with atezolizumab treatment.
- Monitor patients for signs and symptoms of immune-mediated neuropathies (below).

Motor and Sensory Nerve Disorders

Signs and symptoms

- Muscle weakness (including ocular muscles)
- Fatigability
- Difficulty swallowing
- Paraesthesia or altered sensation
- Ascending or progressive paralysis
- Respiratory muscle weakness
- Meningeal irritability, nuchal rigidity

Rule out infectious and disease-related aetiologies.

Neuropathies, including Guillain-Barré syndrome and demyelinating polyneuropathy occurred in 0.2% (5/2619) of patients who received atezolizumab. The median time to onset was 7 months (range 20 days to 8.1 months). The median duration was 4.6 months (1+ day to 8.3+ months; + denotes a censored value). Guillain-Barré syndrome led to the discontinuation of atezolizumab in 1 (<0.1%) patient. Guillain-Barré syndrome requiring the use of corticosteroids occurred in <0.1% (2/2619) patients. Myasthenia gravis occurred in <0.1% (4/6000) of patients who received atezolizumab in clinical trials for multiple tumour types. The time to onset ranged from 20 days to 4 months. All four patients discontinued atezolizumab. Myasthenic syndrome/myasthenia gravis requiring the use of corticosteroids occurred in <0.1% (3/6000) patients.

Immune-Related Neuropathies

Managing Immune-Related Neuropathies

	Myasthenia gravis, Myasthenic syndrome, Guillain-Barré syndrome (Patients should be investigated for a thymoma and presence of paraneoplastic syndromes that may present with motor and sensory nerve disorders)
Atezolizumab treatment/ other therapy	**Permanently discontinue atezolizumab; treat as per institutional guidelines**
Corticosteroids	**Initiation of systemic corticosteroids (at a dose of 1 to 2mg/kg/day of prednisone or equivalent) should be considered**
Follow-up	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month (if corticosteroids started)
	If no improvement: Consider adding additional immunosuppressive medication

Immune-Related Pancreatitis

- Cases of immune-related pancreatitis and increases in serum amylase and lipase levels, have been observed with atezolizumab treatment.
- Patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis.

Pancreatitis and elevations in serum amylase and lipase occurred in 0.6% (15/2619) of patients who received atezolizumab. The median time to onset was 5.5 months (range 9 days to 16.9 months). The median duration was 27 days (range 1+ day to 11.2+ months; + denotes a censored value). Pancreatitis led to the discontinuation of atezolizumab in 1 (<0.1%) patient. Pancreatitis requiring the use of corticosteroids occurred in 0.1% (3/2619) of patients receiving atezolizumab.

Managing Immune-Related Pancreatitis

NCI CTCAE v4	**Amylase or Lipase elevation Grade 3–4** (G3: amylase/lipase >2.0–5.0 × ULN; G4: amylase/lipase >5.0 × ULN)	**Pancreatitis Grade 2 or 3** (G2: enzyme elevation or radiologic findings only; G3: severe pain; vomiting)	**Pancreatitis Grade 4** (Life-threatening consequences; urgent intervention indicated)
Atezolizumab treatment/ other therapy	**Withhold atezolizumab**	**Withhold atezolizumab**	**Permanently discontinue atezolizumab**
Corticosteroids	Methylprednisolone 1–2 mg/kg IV daily or equivalent and convert to 1–2 mg/kg oral prednisone or equivalent per day (once symptoms improve)	Methylprednisolone 1–2 mg/kg IV daily or equivalent and convert to 1–2 mg/kg oral prednisone or equivalent per day (once symptoms improve)	Methylprednisolone 1–2 mg/kg IV daily or equivalent and convert to 1–2 mg/kg oral prednisone or equivalent per day (once symptoms improve)
Follow-up	**If improves to ≤Grade 1:** Treatment with atezolizumab may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤10 mg oral prednisone or equivalent per day	**If improves to ≤Grade 1:** Treatment with atezolizumab 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 oral prednisone or equivalent per day	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month
	If recurs: Treat as Grade 3 or 4 elevation, unless signs/ symptoms of pancreatitis	**If recurs: Permanently discontinue atezolizumab**	**If worsens: Consider additional immunosuppressive medications**

ULN: upper limit of normal

Immune-Related Myocarditis

- Cases of immune-related myocarditis have been observed with atezolizumab treatment.
- Patients should be closely monitored for signs and symptoms that are suggestive of acute myocarditis.

Immune-Related Myocarditis

Signs and symptoms

- Shortness of breath
- Decreased exercise tolerance
- Fatigability
- Chest pain
- Swelling of ankles or legs
- Irregular heart beat
- Fainting

Rule out infectious and disease-related aetiologies.

Myocarditis occurred in <0.1% (2/8000) of patients who received atezolizumab in clinical trials for multiple tumour types. The time to onset was 18 and 33 days. Both patients required corticosteroids and discontinued atezolizumab.

Immune-Related Myocarditis

Managing Immune-Related Myocarditis

NCI CTCAE v4	**Myocarditis Grade 1** (Asymptomatic with laboratory [e.g. BNP] or cardiac imaging abnormalities)	**Myocarditis Grade 2** (Symptoms with mild to moderate activity or exertion)	**Myocarditis Grade 3–4** (G3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; G4: Life-threatening consequences; urgent intervention indicated [e.g. continuous IV therapy or mechanical haemodynamic support])
Atezolizumab treatment/ other therapy	**Initiate treatment as per institutional guidelines**	**Withhold atezolizumab**	**Permanently discontinue atezolizumab**
Corticosteroids		Methylprednisolone 1-2 mg/kg IV daily or equivalent and convert to 1-2 mg/kg oral prednisone or equivalent per day (once symptoms improve)	Methylprednisolone 1-2 mg/kg IV daily or equivalent and convert to 1-2 mg/kg oral prednisone or equivalent per day (once symptoms improve)
Follow-up		**If improves to ≤Grade 1:** Treatment with atezolizumab may be resumed when myocarditis improves to Grade 0 or Grade 1 within 12 weeks, or symptoms of myocarditis have resolved, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day **If recurs: Permanently discontinue atezolizumab**	**If improves to ≤Grade 1:** Taper corticosteroids over at least 1 month **If worsens:** Consider additional immunosuppressive medications

BNP: B-Natriuretic Peptide.

Atezolizumab Infusion-Related Reactions (IRR)

NCI CTCAE v4	**IRR Grade 2** (Infusion interruption indicated but responds promptly to symptomatic treatment)	**IRR Grade 3–4** G3: (Prolonged; recurrence of symptoms following initial improvement; hospitalisation indicated) G4: (Life-threatening consequences; urgent intervention indicated)
Atezolizumab treatment/ other therapy	**The rate of infusion should be reduced or treatment should be interrupted**	**Stop infusion of atezolizumab**
Monitoring (acute event)	Per local Infusion Centre IRR protocol	Per local Infusion Centre IRR protocol; Evaluation in Emergency Department or Hospital
Corticosteroids		As per local medical management of IRR
Follow-up	Reassess per local Infusion Centre protocols and at the end of infusion	Evaluate in Emergency Department or Hospital
	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	**Permanently discontinue atezolizumab**
	If no improvement, worsens or recurs: Treat as Grade 3/4	

IRR: infusion-related reaction.

Notes

Notes

Notes

Notes

Notes