DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Action Letter

DATE: **November 3, 2023**

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SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for Atezolizumab (MPDL3280A, NSC 783608)

TO: Investigators for CTEP-supported Studies Involving Atezolizumab (MPDL3280A, NSC 783608)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with atezolizumab, and to request all trials with atezolizumab be amended to reflect

1) **new and/or modified risk information** for atezolizumab that are associated with routine assessment of risks for the agent and update of the Comprehensive Adverse Events and Potential Risks (CAEPR) list, and
2) **updated treatment modification guidelines.**

You are receiving this letter because you are conducting a CTEP-sponsored trial that includes atezolizumab. See the accompanying list of CTEP trials with atezolizumab.

In response to the new/modified risk information CTEP is requiring that all trials with atezolizumab be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on November 17, 2023** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Helen Chen (helen.chen@nih.gov). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since atezolizumab is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the Institutional Review Board (IRB) Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/september-29-2008-letter-to-dr-jeffrey-abrams/index.html.

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The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also attached. **Dosing Delays/Dose Modifications guidelines for protocols using atezolizumab (Attachment 3).** Action Letter general instructions as well as instructions regarding amendment preparation (if a CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 4. **You MUST follow the instructions outlined in Attachment 4.**

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SPECIFIC INSTRUCTION

Background

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with atezolizumab.

In addition, CTEP has provided updated dosing delays/dose modifications guidelines for the management of specific AEs that need to be updated in protocols using atezolizumab. The guidelines are provided in attachment 3 of this RRA letter.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) Revise the Section for Dosing Delays/Dose Modifications guidelines for Atezolizumab:

   The industry collaborator for atezolizumab for specific immune related AEs- pericarditis, facial paresis and myelitis. Please amend the relevant sections as follows:

   a. **Under Neurology,** update the guidelines using the text in **Attachment #3**. (yellow highlights indicate changes from previous protocol template**)**

   b. Under Cardiology, add instructions for pericarditis as per **attachment 3.** (yellow highlights indicate changes from previous protocol template**)**

3) Revision of the Protocol CAEPR:

   Protocol Section(s) for Insertion of Revised CAEPR (Version 2.4, September 14, 2023___
   Page Number(s): ____

   - Added New Risk:
     - Rare but Serious: Immune system disorders - Other (hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS)); Nervous system disorders - Other (facial paresis); Nervous system disorders - Other (immune-mediated Myelitis)

   PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.4, and associated risk information for the ICD, to the most recent CAEPR Version 2.3. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.3), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

4) Revision of the ICD as Specified Below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed form. The condensed risk profile is provided as a guide to facilitate the inclusion of all risks listed in the current CAEPR. It should be used as written unless there is a compelling reason to add new language or reformat the list. If changes are made, please state, "The condensed risk profile has been modified" in the cover memo and specify the reasons in the Summary of Changes.

- Added New Risk:
  - Rare, and Serious: Damage to organs in the body when the body produces too many white cells; Abnormal movement of the facial muscles; Swelling of the spinal cord

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to atezolizumab is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

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Attachment 1: Revised Atezolizumab CAEPR – Version 2.4, September 14, 2023

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Atezolizumab (MPDL3280A, NSC 783608)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3097 patients.* Below is the CAEPR for Atezolizumab (MPDL3280A).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, September 14, 2023[1]

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
		Heart failure[2]	
		Myocarditis[2]	
		Pericardial effusion[2]	
		Pericardial tamponade[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
		Adrenal insufficiency[2]	
		Endocrine disorders - Other (diabetes)[2]	
	Hyperthyroidism[2]		
		Hypophysitis[2]	
	Hypothyroidism[2]		
EYE DISORDERS			
		Eye disorders - Other (ocular inflammatory toxicity)[2]	
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis[2]	
	Diarrhea		***Diarrhea (Gr 2)***
	Dysphagia		
	Nausea		***Nausea (Gr 2)***
		Pancreatitis[2]	
	Vomiting		***Vomiting (Gr 2)***

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Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever[3]		
	Flu like symptoms[3]		
HEPATOBILIARY DISORDERS			
		Hepatic failure[2]	
		Hepatobiliary disorders - Other (hepatitis [immune related hepatitis])[2]	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[3]		
		Anaphylaxis[3]	
		Cytokine release syndrome[3]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS))[2]	
		Immune system disorders - Other (systemic immune activation)[2]	
INFECTIONS AND INFESTATIONS			
Infection[4]			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[3]		
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased[2]		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased[2]		
		Creatinine increased	
	GGT increased		
	Lipase increased[*]		
		Platelet count decreased	
	Serum amylase increased[*]		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
		Hyperglycemia[2]	
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		
	Back pain		
		Generalized muscle weakness	
	Myalgia		
		Myositis[2]	
NERVOUS SYSTEM DISORDERS			

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Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
		Ataxia[2]	
		Encephalopathy[2]	
		Guillain-Barre syndrome[2]	
		Myasthenia gravis[2]	
		Nervous system disorders - Other (meningitis non-infective)[2]	
		Nervous system disorders - Other (facial paresis)[2]	
		Nervous system disorders - Other (encephalitis non-infective)[2]	
		Nervous system disorders - Other (immune-mediated Myelitis)[2]	
		Paresthesia[2]	
		Peripheral motor neuropathy[2]	
		Peripheral sensory neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		Renal and urinary disorders - Other (nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
	Hypoxia		
	Nasal congestion		***Nasal congestion (Gr 2)***
		Pleural effusion[2]	
		Pneumonitis[2]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Bullous dermatitis[2]	
		Erythema multiforme[2]	
	Pruritus		
	Rash acneiform		
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (Drug reaction with eosinophilia with systemic symptoms [DRESS])[2]	
		Skin and subcutaneous tissue disorders - Other (Exanthematous pustulosis)[2]	
	Skin and subcutaneous tissue disorders - Other (lichen planus)[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis[2]	

*Denotes adverse events that are <3%.

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Atezolizumab, being a member of a class of agents involved in the inhibition of "immune checkpoints," may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. Immune-mediated adverse reactions have been reported in patients receiving atezolizumab. Adverse events potentially related to atezolizumab may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of atezolizumab, administration of corticosteroids and supportive care.

[3]Infusion reactions, including high-grade hypersensitivity reactions, anaphylaxis, and cytokine release syndrome, which have been observed following administration of atezolizumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of atezolizumab.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on atezolizumab (MPDL3280A) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that atezolizumab (MPDL3280A) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Febrile neutropenia
CARDIAC DISORDERS - Cardiac arrest; Ventricular tachycardia
GASTROINTESTINAL DISORDERS - Constipation; Dry mouth; Ileus
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Portal vein thrombosis
INVESTIGATIONS - Lymphocyte count decreased; Neutrophil count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Muscle cramp: Pain in extremity
NERVOUS SYSTEM DISORDERS - Headache
PSYCHIATRIC DISORDERS - Confusion; Insomnia; Suicide attempt
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Pulmonary hypertension; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin[2]; Hyperhidrosis
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event

Note: Atezolizumab (MPDL3280A) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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Attachment 2: Revised ICD Section(s) for Atezolizumab

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in a "patient-friendly" condensed form. The condensed risk profile is provided as a guide to facilitate the inclusion of all risks listed in the current CAEPR. It should be used as written unless there is a compelling reason to add new language or reformat the list. If changes are made, please state, "The condensed risk profile has been modified" in the cover memo and specify the reasons in the Summary of Changes. Please insert this condensed risk profile as the Table of Possible Side Effects for Atezolizumab in your ICD.

Risk Profile for Atezolizumab (MPDL3280A) (CAEPR Version 2.4, September 14, 2023)

NOTE: The risk list section in the new NCI Consent Form Template (latest version: November 2018) will include the wording below:

"If you choose to take part in this study, there is a risk that the atezolizumab (MPDL3280A) may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The atezolizumab (MPDL3280A) used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Please insert this condensed risk profile as the Table of Possible Side Effects for Atezolizumab (MPDL3280A) in your ICD.

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COMMON, SOME MAY BE SERIOUS

In 100 people receiving atezolizumab (MPDL3280A), more than 20 and up to 100 may have:

- Tiredness
- Infection

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving atezolizumab (MPDL3280A), from 4 to 20 may have:

- Anemia which may require blood transfusion
- Diarrhea, nausea, vomiting
- Difficulty swallowing
- Fever
- Flu-like symptoms including body aches
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Reaction during or following a drug infusion which may cause fever, chills, rash
- Loss of appetite
- Pain in back
- Cough, shortness of breath, stuffy nose
- Itching, acne, rash

Atezolizumab (MPDL3280A) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.
- Pain in belly
- Pain or swelling of the joints
- Rash that develops on skin, nails, scalp and inside of mouth or vagina that may be painful

RARE, AND SERIOUS

In 100 people receiving atezolizumab (MPDL3280A), 3 or fewer may have:

- Bruising, bleeding

Atezolizumab (MPDL3280A) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: shortness of breath, swelling of the ankles and body.
- A condition with high blood sugar which leads to tiredness, frequent urination or excessive thirst.
- Swelling and redness of the eye
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.
- Damage to organs in the body when the body produces too many white cells
- Swelling of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck.
- Abnormal movement of the facial muscles
- Swelling of the spinal cord
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine.
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs.
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Skin: blisters on the skin, including inside the mouth (can be severe), rash with blisters, skin rash developing 1-8 weeks after a drug is given, which may be accompanied by fever, lymph node swelling and organ failure.

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Attachment 3: General AE Management and Dose Modification Guidelines

DOSING DELAYS/DOSE MODIFICATIONS

1. **Immune-mediated Cardiac Events (yellow highlight indicates new changes)**

Immune-mediated myocarditis and pericarditis have been associated with the administration of atezolizumab. Management guidelines for cardiac events are provided in the table below.

- Immune-mediated Myocarditis

  No change

- Immune-mediated Pericardial Disorders

  Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

  Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

  Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

  All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

  Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in the table below. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

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2. **Neurologic Disorders (yellow highlight indicates new changes)**

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders, and specific guidelines for myelitis, are provided in the tables below.

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.

Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a]
	• Investigate etiology and refer patient to neurologist.
	• Initiate treatment as per institutional guidelines.
	• For general immune-mediated neuropathy:
	  ○ If event resolves to Grade 1 or better, resume atezolizumab. [b]
	  ○ If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
	• For facial paresis:
	  ○ If event resolves fully, resume atezolizumab. [b]
	  ○ If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab. [c]

Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Event	**Management**
Immune-mediated myelitis, Grade 1	• Continue atezolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

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Attachment 4: Action Letter GENERAL INSTRUCTIONS

1. **For Lead Organizations, distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For National Clinical Trials Network (NCTN) studies, please follow instructions from your Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.

2. Accrual of new patients must be suspended until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter. This amendment can undergo expedited approval at the discretion of the IRB Chair/designee as explained on the first page of the Action Letter.

3. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.

4. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does <u>not</u> already accompany the Action Letter)

General Instructions on Amendment Preparation:

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. **The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. The condensed risk profile is provided as guide to facilitate the inclusion of all risks listed in the current CAEPR. It should be used as written unless there is a compelling reason to add new language or reformat the list. If changes are made, please state, "The condensed risk profile has been modified" in the cover memo and specify the reasons in the Summary of Changes.**

Specific Instructions on Amendment Preparation Based on Protocol Status:

A. <u>Trials with a current CTEP status of **"Active"**</u>
   - Review and follow **<u>ALL</u>** the instructions outlined in this Action Letter.
   - The information provided in this memo outlines the **<u>ONLY</u>** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy.
   - Suspend accrual of new patients until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter.

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B. Trials with a current status of **"Approved", "Temporarily Closed to Accrual and Treatment",** or **"Temporarily Closed to Accrual"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
- You may include additional non-Action Letter related changes (any type) in your amendment response.

C. Trials with a current CTEP status of **"In Review"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of **"Closed to Accrual"**

If your trial is under a CTEP-held IND:
- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.

If your trial is NOT under a CTEP-held IND:
- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.
  - **If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.**

E. Trials with a current CTEP status of **"Closed to Accrual and Treatment"** or **"Complete"**
- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.