

Toxicity Management Guidelines (TMGs)

Drug Substance Rilvegostomig (AZD2936)

TMG Version Version 7.0: 5 February 2026

ANNEX TO CLINICAL STUDY PROTOCOL

**Dosing Modification and Toxicity Management Guidelines
(TMGs) for Rilvegostomig (AZD2936) Monotherapy or
Combination Therapy**

Note: Annex is to be used in any Clinical Study Protocol within which patients are treated with rilvegostomig (AZD2936) monotherapy or rilvegostomig (AZD2936) plus combination therapy.

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VERSION HISTORY

Section name	Description of change	Brief rationale	Date/Version
General consideration for imAEs	Clarified dose hold duration and no dose reduction and added additional reference to list	Clarification and alignment with consensus guidelines.	Version 7/ February 2026
imAEs not otherwise specified	Minor updates to toxicity management text	Clarification	Version 7/ February 2026
Pneumonitis/ILD	Minor updates to toxicity management text (IV methylprednisolone dose) updated to align with current ESMO and NCCN guidelines.	Alignment with consensus guidelines.	Version 7/ February 2026
Diarrhea/colitis	Minor clarification to toxicity management text	Clarification	Version 7/ February 2026
Nephritis/renal dysfunction	Minor clarification to toxicity management text	Clarification	Version 7/ February 2026
Cutaneous events	Clarification for Table 6 (Blistering Rash [Bullous Pemphigoid, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis]) for Grade 2 treatment & toxicity management for grade 3 events	Clarification and alignment with consensus guidelines.	Version 7/ February 2026
Endocrinopathies	Minor clarification of toxicity management related to restarting study treatment	Clarification	Version 7/ February 2026
Nervous System Disorders	Table 16 Encephalitis: Grade 2 has been removed in line with CTCAE grading. Table 20 Clarification for study treatment restart for grade 1 events	Grade 2 encephalitis is not in CTCAE v.5.0. Clarification	Version 7/ February 2026
Increase in Troponin (Including Asymptomatic and Symptomatic Elevation), Including Myocarditis	<u>Clarification that all elevations in troponin should be investigated</u> Increase in troponin: Clarification of restart criteria and diagnostic testing required to rule out myocarditis in asymptomatic troponin elevation Myocarditis: Minor updates to toxicity management text for simplification	Clarification	Version 7/ February 2026

Section name	Description of change	Brief rationale	Date/Version
General Guidelines: Hepatitis (Elevated LFTs) and Isolated Hyperbilirubinemia (with Normal or Abnormal AST/ALT)	Minor updates including clarification of the guidance on steps to take when ALT/AST is elevated due to a different cause	Clarification and alignment with consensus guidelines.	Version 7/ February 2026
Subcutaneous Injection Site Reactions	New section added due to addition of a new subcutaneous formulation in some studies	To support new formulation	Version 7/ February 2026

ALT, alanine aminotransferase; ASCO, American Society of Clinical Oncology; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; ESMO, European Society for Medical Oncology; ILD, interstitial lung disease; LFT, liver function test; NCCN, National Comprehensive Cancer Network; TMGs, toxicity management guidelines.

INTRODUCTION

Toxicity Management Guidelines (TMGs) have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune checkpoint inhibitor rilvegostomig (programmed cell death protein 1 [PD-1]/ T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory [TIGIT] motif bispecific inhibitor).

These TMGs are applicable to the management of participants receiving rilvegostomig as monotherapy or in combination with other anti-cancer drugs (eg, antineoplastic chemotherapy, targeted agents) administered concurrently or sequentially as part of a Clinical Study Protocol (CSP)-specific treatment regimen. The TMGs provide information for the management of immune-mediated adverse events (imAEs), infusion-related reactions (IRRs), and non-imAEs that may be observed in participants receiving rilvegostomig monotherapy or in combination with other anti-cancers drugs, with specific instructions for rilvegostomig-specific dose modifications (including discontinuation) and treatment interventions.

Investigators are advised to use CSP-specified guidelines for the management of toxicities observed with other anti-cancer treatment given in combination with rilvegostomig. In the absence of detailed CSP guidance, investigators may follow local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment given in combination with rilvegostomig.

The TMGs should be used in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version as specified in the CSP. The instructions for dose delays or discontinuations must be followed as CSP-specific recommendations, and deviation from these instructions will be considered protocol deviations. The recommendations regarding the evaluation and treatment of individual toxicities are guidelines that should be followed (however, investigators are able to exercise discretion on what is clinically appropriate for each patient). Not following these guidelines will not be considered a protocol deviation, unless otherwise specified.

Dosing modification (dose delay and/or permanent discontinuation) and toxicity management for immune-mediated, infusion-related, and non-imAEs associated with the use of rilvegostomig should therefore be performed in accordance with this Annex to the CSP, which for the purposes of submission and approval of substantial updates is maintained as a standalone document.

Although the TMG versioning is independent of the CSP, the TMG Annex to the CSP should be read in conjunction with the CSP.

1 IMMUNE-MEDIATED ADVERSE EVENTS

1.1 General Considerations Regarding Immune-mediated Adverse Events (imAEs)

1.1.1 Rilvegostomig Dose Hold/Delay

Unless otherwise specified in the CSP, the maximum duration of dose hold/delay for managing adverse events (AEs) should be 12 weeks from the last dose. No dose reductions are permitted for rilvegostomig.

1.1.2 Concurrent Adverse Events

If a patient experiences multiple concurrent AEs for which the individual dose modification and TMGs provides different approaches, generally the most conservative approach should be followed, but clinical judgment should be exercised to select the most appropriate approach, to achieve effective toxicity management. This may include implementing a dose delay, even if not specifically mandated in the guidance for each of the individual toxicities, if considered clinically appropriate, according to the nature and severity of the concurrent events. Investigators may also contact the Study Clinical Lead or designee to discuss potential dose hold, or permanent discontinuation, as applicable per CSP.

1.1.3 General Guidance for imAEs

These guidelines are provided as a recommendation to support investigators in the management of potential imAEs.

Immune-mediated events can occur in nearly any organ or tissue; therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (eg, National Comprehensive Cancer Network [NCCN], American Society of Clinical Oncology [ASCO], European Society for Medical Oncology [ESMO]) in the management of these events (Section 1.1.4). Refer to Section 1.2 for general guidance on imAEs not noted in the “Specific Immune-mediated Adverse Events” section (Section 1.3).

Early identification and management of imAEs are essential to ensure safe use of rilvegostomig. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying imAEs. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (eg, disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold investigational drug(s) for severe (Grade 3) imAEs. Permanently discontinue investigational drug(s) for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive

treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Based on the severity of the imAE, rilvegostomig should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1 , corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents such as tumor necrosis factor (TNF) inhibitors (eg, infliximab) (following a negative tuberculosis screen) should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines. **With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii pneumonia* (PJP, formerly known as *Pneumocystis carinii pneumonia*) prophylaxis, gastrointestinal protection, osteoporosis (measures for prevention and mitigation of osteoporosis), and glucose monitoring.**

1.1.4 Relevant Society Guidelines for Management of imAEs

These society guidelines are provided as references to serve in support of best clinical practice and the TMGs. Note, these were the current versions of these guidelines at the time of updating the TMGs. Refer to the most up to date version of these guidelines:

- [Brahmer et al 2021](#)
Brahmer JR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer. 2021;9(6):e002435.
- [Haanen et al 2022](#)
Haanen J, et al. ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow up. Ann Oncol. 2022;33(12):1217-38.
- [Salem et al 2023](#)
Salem JE, et al. Abatacept/Ruxolitinib and Screening for Concomitant Respiratory Muscle Failure to Mitigate Fatality of Immune-Checkpoint Inhibitor Myocarditis. Cancer Discov. 2023;13(5):1100-15.
- [Sangro et al 2020](#)
Sangro B, et al. Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma. J Hepatol. 2020;72(2):320-41.
- [Schneider et al 2022](#)
Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO Guideline Update. J Clin Oncol. 2021;39(36), 4073-4126. Erratum in: J Clin Oncol. 2022;40(3):315.
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Management of immunotherapy-related toxicities version 1.2026 Available from: <https://www.nccn.org/guidelines/guidelines-detail?category=3&id=1486>.

1.2 Immune-mediated Adverse Events Not Otherwise Specified

Table 1 Immune-mediated Adverse Events Not Otherwise Specified

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any grade (refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	Note: It is possible that events with an inflammatory or immune-mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (eg, immune thrombocytopenia, hemolytic anemia, uveitis, vasculitis).	- The study physician may be contacted for immune-mediated reactions not listed in the “specific immune-mediated reactions” section. - Thorough evaluation to rule out any alternative etiology (eg, disease progression, concomitant medications, and infections) - Consultation with relevant specialist. - Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Monitor as clinically indicated
Grade 2	- Hold rilvegostomig until resolution to Grade ≤ 1 or baseline. - If toxicity worsens, then treat as Grade 3 or Grade 4. - Rilvegostomig can be resumed once event stabilizes to Grade ≤ 1 after completion of steroid taper to equivalent of prednisone ≤ 10 mg/day. - Consider whether rilvegostomig should be permanently discontinued or toxicity management should be escalated in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade < 1 upon treatment with systemic steroids and following full taper to equivalent of prednisone ≤ 10 mg/day.	For Grade 2, 3, or 4 Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (eg, NCCN, ESMO)
Grade 3	- For Grade 3 events with low likelihood for morbidity and mortality, hold rilvegostomig. - In Grade 3 events with high likelihood for morbidity and mortality, permanently discontinue rilvegostomig.	
Grade 4	Permanently discontinue rilvegostomig.	

CTCAE, Common Terminology Criteria for Adverse Events; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; NCI, National Cancer Institute.

1.3 Specific Immune-mediated Adverse Events

1.3.1 Pneumonitis/Interstitial Lung Disease (ILD)

Table 2 **Pneumonitis/ILD**

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance	- Patients should be thoroughly evaluated to rule out any alternative etiology with similar clinical presentation (eg, infection, pulmonary embolism, progressive disease). - Monitor patients for signs (eg, tachypnea) and symptoms of pneumonitis or ILD (new-onset or worsening shortness of breath or cough). Evaluate patients with imaging and PFTs, including other diagnostic procedures as described below. - Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease related etiologies excluded, and managed as described below. - Initial work-up should include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up (including clinically relevant culture specimens to rule out infection), and HRCT scan, as clinically appropriate. - Consultation with Pulmonary and Infectious Diseases specialist is advised.
Grade 1	No dose modifications required. However, consider holding rilvegostomig as clinically appropriate and during diagnostic work-up for other etiologies.	Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up, and then as clinically indicated.
Grade 2	- Hold rilvegostomig until Grade 2 resolution to Grade ≤ 1. - If toxicity worsens, then treat as Grade 3 or Grade 4. - If toxicity improves to Grade ≤ 1, then the decision to reinstitute rilvegostomig will be	- Monitor symptoms daily and consider hospitalization. - Consultation with Pulmonary and Infectious Diseases specialist is advised. - Promptly start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent). ^a - Reimage as clinically indicated, consider HRCT or chest CT with contrast and repeat in 3 to 4 weeks. - If no improvement within 2 to 3 days, additional work-up should be considered and prompt treatment with IV methylprednisolone 1 to 2 mg/kg/day started. ^a - If no improvement within 2 to 3 days despite IV methylprednisolone ^a at 1 to 2 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). ^a Caution: Rule out sepsis

Table 2 Pneumonitis/ILD

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
	based upon treating physician's clinical judgment and after completion of steroid taper to equivalent of prednisone $\leq$ 10 mg/day.	and refer to infliximab label for general guidance before using infliximab; refer to labels of other drugs before use.
Grade 3 or 4	Permanently discontinue rilvegostomig.	• Hospitalize the patient. • Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.^a • Consult Pulmonary and Infectious Diseases specialist. • Consider nasal swab for potential viral pathogens, sputum culture (including bacterial, fungal, and AFB), blood culture, and urine antigen test (<i>Pneumococcus</i>, <i>Legionella</i>). • Consider cardiac evaluation to exclude cardiac causes for clinical presentation. Invasive evaluation bronchoscopy with BAL, if feasible, to rule out infection and malignant lung infiltration and consider transbronchial lung biopsy, if feasible, and clinically indicated. • Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded. • Provide supportive care (eg, oxygen). • If no improvement within 2 to 3 days, additional work-up should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider)^a. Caution: Rule out sepsis and refer to infliximab label for general guidance before using infliximab; refer to labels of other drugs before use..

^a Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

AFB, acid-fast bacilli; BAL, bronchoalveolar lavage; CSP, Clinical Study Protocol; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IV, intravenous; NCI, National Cancer Institute; PFT, pulmonary function test; PO, by mouth; TNF, tumor necrosis factor.

1.3.2 Diarrhea/Colitis

Table 3 Diarrhea/Colitis

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance PERMANENTLY DISCONTINUE RILVEGOSTOMIG FOR ANY GRADE OF INTESTINAL PERFORATION.	- Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). - Consider further evaluation with imaging study with contrast or lower GI endoscopy/sigmoidoscopy, if clinically appropriate. - Consult GI specialist for consideration of further work-up. WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY - Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections), including testing for <i>Clostridium difficile</i> toxin, CMV, other viral etiology, ova, and parasites, if appropriate). - Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade events, including intestinal perforation. - Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
Grade 1	No dose modifications.	- Monitor closely for worsening symptoms. - Symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), loperamide, or diphenoxylate/atropine for 2 to 3 days as an adjunct for symptom relief, and other supportive care measures are advised. - If symptoms persist, check lactoferrin and/or calprotectin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management and consider adding mesalamine and/or cholestyramine as needed.
Grade 2	- Hold rilvegostomig until resolution to Grade $\leq$ 1 - If toxicity worsens, then treat as Grade 3 or Grade 4. - If toxicity improves to Grade $\leq$ 1, then rilvegostomig can be resumed after completion of steroid taper to equivalent of prednisone $\leq$ 10 mg/day.	- Symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide (9 mg daily prior to systemic steroid for pathologically confirmed microscopic colitis) is advised. - Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. ^a

Table 3 **Diarrhea/Colitis**

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
		If no improvement within 3 days despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, re-consult GI specialist and if indicated, promptly start further immunosuppressives (eg, infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating physician or relevant practice guidelines; consider vedolizumab, if refractory). Consider tofacitinib or ustekinumab if infliximab and/or vedolizumab-refractory colitis ^a Caution: it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab; refer to labels of other drugs before use. Consider, as necessary, discussing with study physician if no resolution to Grade ≤ 1 in 3 to 4 days.
Grade 3	- Hold rilvegostomig until resolution to Grade ≤ 1. - If clinical or endoscopic evidence of moderate/severe colitis, permanently discontinue rilvegostomig - Rilvegostomig can only be resumed if all of the following conditions are met: - Absence of clinical or endoscopic evidence of moderate/severe colitis. - Toxicity improves to Grade ≤ 1. - Completion of steroid taper to equivalent of prednisone ≤ 10 mg/day. - Permanently discontinue rilvegostomig for Grade 3 if toxicity does not improve to Grade ≤ 1 within 14 days.	- Urgent consultation with GI specialist and imaging and/or colonoscopy, as appropriate. - Consider inpatient care for provision of supportive care. - Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. ^a - Monitor stool frequency and volume and maintain hydration. - If still no improvement within 2 days, promptly add further immunosuppressants (eg, infliximab at 5 mg/kg IV or vedolizumab). Consider tofacitinib or ustekinumab for infliximab and/or vedolizumab-refractory colitis (infliximab may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). ^a Caution: Ensure consultation with GI specialist to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab; refer to labels of other drugs before use. - If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.
Grade 4	Permanently discontinue rilvegostomig.	Manage as per Grade 3 (above).

^a Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

CMV, cytomegalovirus; CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal; IV, intravenous; NCCN, National Comprehensive Cancer Network; NCI, National Cancer Institute; PO, by mouth.

1.3.3 Nephritis or Renal Dysfunction

Table 4 Nephritis or Renal Dysfunction

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance	• Consultation with a nephrologist is advised. • Consider imaging studies without IV contrast to rule out any alternative etiology. • Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decreased urine output, or proteinuria). • Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, infections, recent IV contrast, nephrotoxic medications, fluid status). • Follow urine protein/creatinine ratio every 3 to 7 days.
Grade 1	No dose modifications.	• Monitor serum creatinine weekly and any accompanying symptoms and more frequently if clinically indicated. ◦ If creatinine returns to baseline, resume its regular monitoring per CSP. • Hydration, electrolyte replacement, and diuretics, are advised as clinically indicated. • Consultation with nephrologist is advised if not resolved within 14 days, or earlier, as clinically indicated.
Grade 2	• Hold rilvegostomig until resolution to Grade $\leq$ 1 or baseline. • If toxicity improves to Grade $\leq$ 1 or baseline, then resume rilvegostomig after completion of steroid taper to equivalent of prednisone $\leq$ 10 mg/day.	• Hydration, electrolyte replacement, and diuretics, are advised as clinically indicated. • Follow urine protein/creatinine ratio every 3 to 7 days. • . • Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. • Consult nephrologist and consider renal biopsy if clinically indicated. • Start prednisone 0.5 to 1 mg/kg/day if other causes are ruled out. ^a • If event is persistent beyond 3 to 5 days or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. ^a • If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional work-up. ^a • When event returns to baseline, resume routine serum creatinine monitoring per CSP.

Table 4 Nephritis or Renal Dysfunction

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Grade 3 or 4	Permanently discontinue rilvegostomig.	- Carefully monitor serum creatinine daily. - Follow urine protein/creatinine ratio every 3 to 7 days. - Consult nephrologist and consider renal biopsy if clinically indicated. - Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.^a - If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional work-up and prompt treatment with an immunosuppressant in consultation with a nephrologist.^a - Consider adding one of the following if kidney injury remains Grade ≥ 2 after 4 to 6 weeks of steroids or if creatinine increases during steroid taper (or one off steroids) (eg, infliximab, azathioprine, mycophenolate).^a

^a Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

BUN, blood urea nitrogen; CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous; NCI, National Cancer Institute; PO, by mouth.

1.3.4 Cutaneous Adverse Events

1.3.4.1 Non-blistering Rash (Maculopapular, Eczematous, Psoriasiform, Lichenoid) or Pruritus

Table 5 Non-blistering Rash (Maculopapular, Eczematous, Psoriasiform, Lichenoid) or Pruritus

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance	- Monitor for signs and symptoms of dermatitis (dry skin, rash, and pruritus). - Advise sun protection and avoidance of skin irritants. - Encourage emollient use (moisturizing creams or ointments).
Grade 1	No dose modifications.	- Topical treatment to affected areas is indicated: - Low potency topical steroid (eg, hydrocortisone 2.5% cream) to rash/itch on face and high potency topical steroid (eg, clobetasol propionate 0.05%, halobetasol propionate 0.05%) to rash/itch on body BID. - Consider oral antihistamines (hydroxyzine, diphenhydramine). - For lichenoid rash: narrow-band UVB phototherapy, if available and feasible. If not responsive, treat as Grade 3 management.
Grade 2	- For persistent (> 1 week) Grade 2 events, hold scheduled rilvegostomig until resolution to Grade ≤ 1 or baseline. - If toxicity improves to Grade ≤ 1 or baseline, rilvegostomig can be resumed after completion of steroid taper to equivalent of prednisone ≤ 10 mg/day.	- Consider dermatology consultation, skin biopsy, and laboratory evaluation of the rash (eg, CBC with differential, renal and hepatic function, IgE, IL-5, TNF-α IL-6 when available) as indicated. - Topical treatment to affected areas is indicated: - Low potency topical steroid (eg, hydrocortisone 2.5% cream) to rash/itch on face and high potency topical steroid (eg, clobetasol propionate 0.05%, halobetasol propionate 0.05%) to rash/itch on body BID. - Systemic therapy may be indicated: - Consider oral antipruritic (eg, hydroxyzine, diphenhydramine, pregabalin, gabapentin). Increase/titrate dose to itch response. - Consider the addition of a steroid-sparing biologic as needed to target morphology, biomarker, and/or histologic presentation. - For pruritus, eczema, maculopapular rash: - Consider dupilumab, omalizumab, or benralizumab.

Table 5 Non-blistering Rash (Maculopapular, Eczematous, Psoriasiform, Lichenoid) or Pruritus

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
		◦ For psoriasiform rash: Consider inhibitors of IL-23 (eg, risankizumab, guselkumab) or IL-17 (eg, ixekizumab, secukinumab) or topical vitamin D analogues. ◦ For lichenoid rash: Consider dupilumab, omalizumab, benralizumab, acitretin, or tacrolimus 0.1%. • In case this Grade 2 rash/pruritus becomes intolerable or does not show improvement within 1 week, follow toxicity management guidance for Grade 3, described below.

Table 5 Non-blistering Rash (Maculopapular, Eczematous, Psoriasiform, Lichenoid) or Pruritus

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Grade 3	- Hold rilvegostomig until resolution to Grade ≤ 1 or baseline. - If toxicity improves to Grade ≤ 1 or baseline, then rilvegostomig can be resumed after completion of steroid taper to equivalent of prednisone ≤ 10 mg/day.	- Consult dermatology, perform skin biopsy, and laboratory evaluation of the rash (eg, CBC with differential, renal and hepatic function, IgE, IL-5, TNF-α, IL-6 when available) as indicated. - Topical treatment to affected areas is indicated: - Low potency topical steroid (eg, hydrocortisone 2.5% cream) to rash/itch on face and high potency topical steroid (eg, clobetasol propionate 0.05%, halobetasol propionate 0.05%) to rash/itch on body BID. - Systemic therapy is indicated: - Consider oral antipruritic (eg, hydroxyzine, diphenhydramine, pregabalin, gabapentin). Increase/titrate dose to itch response. - Promptly initiate empiric IV/PO methylprednisolone 1 mg/kg/day or equivalent until rash/itch resolves to Grade ≤ 1. - If systemic steroid-refractory, steroid-dependent, or flares with steroid taper, consider addition of steroid-sparing biologic to target morphology, biomarker, and/or histologic presentation. - For pruritus, eczema, maculopapular rash: Consider dupilumab, omalizumab, or benralizumab. - For psoriasiform rash: Consider inhibitors of IL-23 (eg, risankizumab, guselkumab) or IL-17 (eg, ixekizumab, secukinumab). - For lichenoid rash: Consider dupilumab, omalizumab, benralizumab, or acitretin. - Consider hospitalization. - Monitor extent of rash (Rule of Nines).
Grade 4	Permanently discontinue rilvegostomig.	

BID, twice daily; CBC, complete blood count; CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; IgE, immunoglobulin E; IL-5/6/17/23, interleukin 5/6/17/23; IV, intravenous; NCI, National Cancer Institute; PO, by mouth; TNF- α , tumor necrosis factor alpha; UVB, ultraviolet B.

1.3.4.2 Blistering Rash (Bullous Pemphigoid, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis)

Table 6 Blistering Rash (Bullous Pemphigoid, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis)

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance HOLD RILVEGOSTOMIG IF GRADE 3 PEMPHIGOID OR SCAR ^a IS SUSPECTED. PERMANENTLY DISCONTINUE RILVEGOSTOMIG IF SCAR OR GRADE 3 PEMPHIGOID IS CONFIRMED.	- Monitor for signs and symptoms of dermatitis (dry skin, rash, and pruritus). - Advise sun protection and avoidance of skin irritants. - Encourage emollient use (moisturizing creams or ointments).
Grade 1 Bullous pemphigoid	Consider holding rilvegostomig.	- Consult dermatology, perform skin biopsy, and laboratory evaluation of the rash (eg, CBC with differential, renal and hepatic function, IgE, IL-5, bullous pemphigoid antibodies, IL-6, TNF-αwhen available) as indicated. - Topical treatment to affected areas is indicated: - Low potency topical steroid (eg, hydrocortisone 2.5% cream) to rash/itch on face and high potency topical steroid (eg, clobetasol propionate 0.05%, halobetasol propionate 0.05%) to rash/itch on body BID. - Systemic therapy may be indicated: - Consider oral antipruritic (eg, hydroxyzine, diphenhydramine, pregabalin, gabapentin). Increase/titrate dose to itch response. - Consider dupilumab, rituximab or omalizumab.
Grade 2 Bullous pemphigoid	- Hold rilvegostomig until resolution to Grade $\leq$ 1 or baseline. - If toxicity improves to Grade $\leq$ 1 or baseline, then rilvegostomig can be resumed after completion of steroid taper to equivalent of prednisone $\leq$ 10 mg/day.	- Consult dermatology, perform skin biopsy (H&E and direct immunofluorescence), and laboratory evaluation of the rash (eg, CBC with differential, renal and hepatic function, IgE, IL-5, bullous pemphigoid antibodies, IL-6, TNF-αwhen available) as indicated. - Topical treatment to affected areas is indicated: - Low potency topical steroid (eg, hydrocortisone 2.5% cream) to rash/itch on face and high potency topical steroid (eg, clobetasol propionate 0.05%, halobetasol propionate 0.05%) to rash/itch on body BID.

Table 6 Blistering Rash (Bullous Pemphigoid, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis)

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
		- Systemic therapy is indicated: - Consider oral antipruritic (eg, hydroxyzine, diphenhydramine, pregabalin, gabapentin). Increase/titrate dose to itch response. - Consider prednisone 0.5 to 1 mg/kg/day PO/IV as a bridge therapy until steroid-sparing biologic is effective. - In case this Grade 2 rash/pruritus becomes intolerable or does not show improvement within 1 week, follow toxicity management guidance for Grade 3 as described below.
Grade 3 Bullous pemphigoid or SJS/TEN	Permanently discontinue rilvegostomig.	- Urgent dermatology consult, perform urgent skin biopsy (H&E and direct immunofluorescence), and laboratory evaluation of the rash (eg, CBC with differential, renal and hepatic function, IgE, IL-5, bullous pemphigoid antibodies, IL-6, TNF-α when available) as indicated. - Hospitalize the patient; inpatient care required. - Monitor extent of rash (Rule of Nines). - Supportive wound care required. <u>For Bullous Pemphigoid:</u> - Topical treatment to affected areas is indicated: - Low potency topical steroid (eg, hydrocortisone 2.5% cream) to rash/itch on face and high potency topical steroid (eg, clobetasol propionate 0.05%, halobetasol propionate 0.05%) to rash/itch on body BID. - Systemic therapy is indicated: - Consider oral antipruritic (eg, hydroxyzine, diphenhydramine, pregabalin, gabapentin). Increase/titrate dose to itch response. - Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.^b - Consider initiating the combination of IVIG (1 g/kg/day $\times$ 2 days then repeat monthly until clear) + rituximab (weekly $\times$ 4 weeks) to enable successful steroid taper; continue until clear.
Grade 4 Bullous pemphigoid or SJS/TEN		

Table 6 Blistering Rash (Bullous Pemphigoid, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis)

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
		◦ Consider dupilumab or omalizumab. <u>For SJS/TEN:</u> • Advise intensive care unit admission. • Additional urgent ophthalmology, urology, gynecology, or otorhinolaryngology (ENT) consultations depending on management of mucosal surfaces. • Systemic therapy is indicated: ◦ Promptly initiate empiric etanercept or IV cyclosporine, or IV methylprednisolone 1 to 2 mg/kg/day. ^b ◦ Consider IVIG 1g/kg/day x 2 days. or per local label.

^a SCAR terms include SJS, TEN, Erythema Multiforme, Acute Generalized Exanthematous Pustulosis, DRESS and Drug-induced hypersensitivity syndrome.

^b Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

BID, twice daily; CBC, complete blood count; CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; DRESS, Drug Reaction with Eosinophilia and Systemic Symptoms; ENT, ear, nose, and throat; H&E, hematoxylin and eosin; IgE, immunoglobulin E; IL-5/6, interleukin 5/6; IVIG, intravenous immunoglobulin; IV, intravenous; NCI, National Cancer Institute; PO, by mouth; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson Syndrome; TEN, toxic epidermal necrolysis; TNF- α , tumor necrosis factor alpha.

1.3.5 Endocrinopathies

1.3.5.1 Thyroid Events

Table 7 Thyroid Events

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance	- Consider consultation with endocrinologist for endocrine events. - Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms of hyperthyroidism may include profuse sweating, tremors, tachycardia, palpitations, unintentional weight loss and generalized weakness. Non-specific symptoms of hypothyroidism may include fatigue, cold intolerance, behavior changes, mental status changes (eg, apathy), unusual bowel habits (eg, constipation), and unusual hair loss. - Thyroiditis is usually transient and resolves in a couple of weeks to primary hypothyroidism or normal function. - Graves' disease is generally persistent and is due to increased thyroid hormone production that can be treated with anti-thyroid medical therapy. - Physical examination findings of ophthalmopathy or thyroid bruit are diagnostic of Graves' disease and should prompt early endocrine referral. - Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections). - Monitor and evaluate thyroid function tests (eg, TSH, free T3 and free T4, anti-thyroid antibodies), and if clinically indicated, thyroid ultrasound evaluation. - If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis), the investigator should send a blood sample for appropriate autoimmune antibody testing. - Investigators should ask patients with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.

AE, adverse event; CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

Table 8 Hyperthyroidism

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Grade 1 (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	No dose modifications.	- Continue rilvegostomig and follow closely with TSH and free T4 every 2 to 3 weeks, or more frequently as clinically indicated, to see if the patient develops persistent hyperthyroidism or hypothyroidism. - Monitor patient with appropriate endocrine function tests. - If TSH < 0.5 × LLN, or TSH > 2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation with endocrinologist.
Grade 2	- Hold rilvegostomig until patient is clinically stable. - Rilvegostomig can be resumed under the following conditions: - After resolution to Grade ≤ 1 or baseline or stabilizes and is controlled on endocrine replacement therapy. - The patient is clinically stable as per investigator or treating physician's clinical judgment. - Prednisone equivalent dose is ≤ 10 mg/day.^a	- Consult endocrinologist. - Hydration and supportive care. - Non-selective beta-blocker for symptomatic relief (eg, propranolol or atenolol). - Consider anti-thyroid drugs (eg, methimazole or propylthiouracil). - Corticosteroids are not usually required to shorten duration.
Grade 3 or 4	- Hold rilvegostomig until patient is clinically stable. - Rilvegostomig can be resumed if all the following conditions are met: - After resolution to Grade ≤ 1 or baseline or stabilizes and is controlled on endocrine replacement therapy. - The patient is clinically stable as per investigator or treating physician's clinical judgment. - Prednisone equivalent dose is ≤ 10 mg/day.^a	- Hospitalization is advised. - Consult endocrinologist. - Hydration and supportive care. - Non-selective beta-blocker for symptomatic relief (eg, propranolol or atenolol). - If severe or suspected thyroid storm or thyrotoxic crisis, hospitalize patient and start prednisone 1 to 2 mg/kg/day or equivalent and taper over 1 to 2 weeks.^a - Consider anti-thyroid drugs (eg, methimazole or propylthiouracil) or potassium iodide.

^a Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; LLN, lower limit of normal; NCI, National Cancer Institute; T4, thyroxine; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

Table 9 Hypothyroidism

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance	- For patients without risk factors, full thyroid hormone replacement can be estimated with an ideal body weight-based dose of approximately 1.6 µg/kg/day. - For elderly or frail patients with multiple comorbidities, consider titrating up from low dose, starting at 25 to 50 µg. - Adrenal dysfunction, if present, must always be replaced before thyroid hormone therapy is initiated.
Grade 1	No dose modifications.	Continue rilvegostomig and follow closely with TSH and free T4 every 2 to 3 weeks, or sooner, as clinically indicated.
Grade 2	No dose modifications.	- Consider consultation with endocrinologist, if necessary. - Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels > 10 mIU/L that persist (measured 3 to 4 weeks apart).
Grade 3 or 4	No dose modifications.	- Consult endocrinologist. - Prescribe thyroid hormone supplementation. - Consider hospitalization for IV thyroid hormone supplementation therapy if signs of myxedema (bradycardia, hypothermia).

CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous; NCI, National Cancer Institute; T4, thyroxine; TSH, thyroid-stimulating hormone.

1.3.5.2 Adrenal Insufficiency

Table 10 Adrenal Insufficiency

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance	• Diagnosis: Adrenal gland failure may lead to low morning cortisol, high morning ACTH, as well as hyponatremia and hyperkalemia with orthostasis and volume depletion due to loss of aldosterone. • Consultation with endocrinologist is advised and consult endocrinologist prior to surgery or any procedure for stress-dose planning. • Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including adrenal hemorrhage or metastases, or infections). • Monitor and evaluate relevant labs such as ACTH (morning), cortisol level (morning) and basic metabolic panel (including sodium, potassium, carbon dioxide, and glucose). • Consider ACTH stimulation test for indeterminate results. • If a patient experiences adrenal insufficiency that is thought to be possibly of autoimmune nature, the investigator should send a blood sample for appropriate autoimmune antibody testing. • Primary and secondary adrenal insufficiency can be distinguished by the relationship between ACTH and cortisol. If the ACTH is low with low cortisol, then management is as per hypophysitis (Table 11). • Patients on corticosteroids for management of other conditions will have low morning cortisol as a result of iatrogenic, secondary adrenal insufficiency. ACTH will also be low in these patients. A diagnosis of adrenal insufficiency is challenging to make in these situations (see hypophysitis, Table 11). • In case of life-threatening cases for someone with suspected adrenal insufficiency, dexamethasone use is advised as a stimulation test can still be performed for confirmation of diagnosis. If the diagnosis is already confirmed, hydrocortisone 100 mg can be used. • All patients need education on stress dosing and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by emergency personnel.
Grade 1	• Hold rilvegostomig until patient is clinically stable. • Rilvegostomig can be resumed if all the following conditions are met:	• Consider consultation with endocrinologist. • Monitor patient with appropriate laboratory tests.

Table 10 Adrenal Insufficiency

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
	- After resolution to Grade $\leq$ 1 or baseline or stabilizes and is controlled on endocrine replacement therapy. - The patient is clinically stable as per investigator or treating physician's clinical judgment on replacement hormone therapy.	- Replacement therapy with prednisone (5 to 10 mg/day) or hydrocortisone (10 to 20 mg orally every morning, 5 to 10 mg orally in early afternoon). ^a - Assess if patient requires fludrocortisone (0.1 mg/day) for mineralocorticoid replacement in primary adrenal insufficiency. - Titrate steroid dose up or down as symptoms dictate.
Grade 2	- Hold rilvegostomig until patient is clinically stable. - Rilvegostomig can be resumed if all the following conditions are met: - After resolution to Grade $\leq$ 1 or baseline or stabilizes and is controlled on endocrine replacement therapy. - The patient is clinically stable as per investigator or treating physician's clinical judgment on replacement hormone therapy.	- Consult endocrinologist. - Monitor patient with appropriate laboratory tests. - Initiate outpatient treatment at 2 to 3 times maintenance (if prednisone, 20 mg daily; if hydrocortisone, 20 to 30 mg in the morning, and 10 to 20 mg in the afternoon) to manage acute symptoms. ^a - Maintenance therapy as in Grade 1. - Assess if patient requires fludrocortisone (0.1 mg/day) for mineralocorticoid replacement in primary adrenal insufficiency. ^a - Titrate steroid dose up or down as symptoms dictate.
Grade 3 or 4	- Hold rilvegostomig until patient is clinically stable. - Rilvegostomig can be resumed if all the following conditions are met: - After resolution to Grade $\leq$ 1 or baseline or stabilizes and is controlled on endocrine replacement therapy. - The patient is clinically stable as per investigator or treating physician's clinical judgment on replacement hormone therapy.	- Consult endocrinologist. - Hospitalization is advised. - Initiate high-dose IV stress-dose steroids (hydrocortisone 100 mg or dexamethasone 4 mg IV Q8h) and aggressive hydration (at least 2 L normal saline). ^a - Taper stress-dose corticosteroids down to maintenance doses over 7 to 14 days after discharge. - Maintenance therapy as in Grade 1. - Assess if patient requires fludrocortisone (0.1 mg/day) for mineralocorticoid replacement in primary adrenal insufficiency. - Titrate steroid dose up or down as symptoms dictate. - For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity.

^a Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

ACTH, adrenocorticotrophic hormone; CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous; NCI, National Cancer Institute; Q8h, every 8 hours.

1.3.5.3 Hypophysitis/Hypopituitarism

Table 11 Hypophysitis/Hypopituitarism

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance	• Diagnosis: Low ACTH with low cortisol. Low or normal TSH with a low free T4. Hypernatremia and volume depletion with diabetes insipidus. Low testosterone or estradiol with low LH and FSH. Consultation with endocrinologist is advised. • Most commonly presenting with primary adrenal insufficiency; may also include central hypothyroidism, hypogonadism, diabetes insipidus (rare). • Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections). • Evaluate ACTH (morning), cortisol (morning), TSH, free T4, electrolytes. • Evaluate LH, FSH, and testosterone levels in males or estrogen in premenopausal females with fatigue, loss of libido, and mood changes. • An MRI of the brain with or without contrast with pituitary/sellar cuts in patients with multiple endocrine abnormalities, new severe headaches or complaints of visual disturbances is advised. • If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing. • When multiple hormone deficiencies are present, always replace corticosteroids first when planning hormone replacement therapy to avoid precipitating adrenal crisis. • If secondary adrenal insufficiency present educate on stress dosing and a medical alert bracelet for adrenal insufficiency to trigger stress-dose corticosteroids by emergency personnel.
Grade 1	• Hold rilvegostomig until patient is clinically stable. • Rilvegostomig can be resumed if all the following conditions are met:	• Monitor patient with appropriate endocrine function tests. • Consultation with endocrinologist is advised. • Hormonal supplementation as needed, using dosing as above for primary hypothyroidism and adrenal insufficiency (eg, hydrocortisone 10 to 20 mg orally in the morning, 5 to 10 mg orally in early afternoon; levothyroxine by weight).

Table 11 Hypophysitis/Hypopituitarism

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
	- After resolution to Grade ≤ 1 or baseline or stabilizes and is controlled on endocrine replacement therapy. - The patient is clinically stable as per investigator or treating physician's clinical judgment on replacement hormone therapy.	- Testosterone or estrogen therapy as needed in those without contraindications. - Follow free T4 for thyroid hormone replacement titration (TSH is not accurate in central hypothyroidism).
Grade 2	- Hold rilvegostomig until patient is clinically stable. - Rilvegostomig can be resumed if all the following conditions are met: - After resolution to Grade ≤ 1 or baseline or stabilizes and is controlled on endocrine replacement therapy. - The patient is clinically stable as per investigator or treating physician's clinical judgment on replacement hormone therapy.	- Consult endocrinologist. - As clinically indicated, consider pituitary scan. - Toxicity management per Grade 1.
Grade 3 or 4	- Hold rilvegostomig until patient is clinically stable. - Rilvegostomig if all the following conditions are met: - After resolution to Grade ≤ 1 or baseline or stabilizes and is controlled on endocrine replacement therapy.	- Consult endocrinologist. - Pituitary scan is advised. - Hospitalization is advised. - Consider initial pulse dose steroids (prednisone 1 to 2 mg/kg/day, tapered over 1 to 2 weeks).^a - Toxicity management per guidelines for Grade 3 or 4 toxicity in sections on specific hormonal deficiencies noted above.

Table 11 Hypophysitis/Hypopituitarism

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
	The patient is clinically stable as per investigator or treating physician's clinical judgment on replacement hormone therapy.	

^a Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

ACTH, adrenocorticotrophic hormone; AE, adverse event; CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MRI, magnetic resonance imaging; NCI, National Cancer Institute; T4, thyroxine; TSH, thyroid-stimulating hormone.

1.3.5.4 Type 1 Diabetes Mellitus

Table 12 Type 1 Diabetes Mellitus

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance	- Consultation with endocrinologist is advised. - Monitor patients for signs and symptoms of polydipsia, polyuria, profound dehydration, and weakness. - Laboratory work-up should include HbA1c, blood glucose and electrolytes to detect anion gap and urine ketone levels; insulin and C-peptide levels can be useful; if autoimmune diabetes is suspected, the following antibodies are highly specific: anti-glutamic acid decarboxylase antibodies, anti-islet cell antibodies, anti-insulin antibodies. - If a patient experiences an AE that is thought to be possibly of autoimmune nature, the investigator should send a blood sample for appropriate autoimmune antibody testing. - Additional considerations regarding insulin therapy: - Insulin therapy can be used as the default in any case with hyperglycemia.

Table 12 Type 1 Diabetes Mellitus

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
		◦ Long-acting therapy alone is not usually sufficient for type 1 diabetes mellitus where half of daily requirements are usually given in divided doses as prandial coverage and half as long acting. ◦ Insulin doses will be lower in type 1 diabetes mellitus because of preserved sensitivity (total daily requirement can be estimated at 0.3 to 0.4 units/kg/day).
Grade 1	No dose modifications.	• Monitor patient with appropriate endocrine function tests. • Screen for type 1 diabetes mellitus if appropriate, for example, acute onset with prior normal values or clinical concern for ketosis. • If type 1 diabetes mellitus is diagnosed, initiate insulin therapy, titrate for adequate glucose control.
Grade 2	• Hold rilvegostomig until patient is clinically stable (eg, glucose control obtained) and the toxicity improves to Grade $\leq$ 1. • Rilvegostomig can be resumed if all the following conditions are met: ◦ After resolution to Grade $\leq$ 1 or baseline or stabilizes and is controlled on endocrine replacement therapy. ◦ The patient is clinically stable as per investigator or treating physician's clinical judgment.	• Monitor patient with appropriate endocrine function tests. • Administer and titrate insulin for type 1 diabetes mellitus (or as default therapy if there is confusion about type). • Urgent consultation with endocrinologist for any patient with new-onset type 1 diabetes mellitus; in the absence of endocrinology, internal medicine may suffice. • Consider hospitalization for type 1 diabetes mellitus if early outpatient evaluation is not available or signs of ketoacidosis are present.
Grade 3 or 4	• Hold rilvegostomig until patient is clinically stable (eg, glucose control is obtained). • Rilvegostomig can be resumed if all the following conditions are met:	• Urgent consultation with endocrinologist for all patients. • Initiate insulin therapy for all patients. • Hospitalize the patient if: ◦ Concerns for developing diabetic ketoacidosis.

Table 12 **Type 1 Diabetes Mellitus**

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
	- After resolution to Grade $\leq$ 1 or baseline or stabilizes and is controlled on endocrine replacement therapy. - The patient is clinically stable as per investigator or treating physician's clinical judgment.	- Symptomatic patients regardless of diabetes type. - New-onset type 1 diabetes mellitus unable to see endocrinology.

AE, adverse event; CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; HbA1c, glycated hemoglobin; NCI, National Cancer Institute.

1.3.6 Increases in Amylase and/or Lipase, or Pancreatitis

Table 13 **Increases in Amylase and/or Lipase**

Severity grade of the event (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Grade 1	No dose modifications.	- If no signs or symptoms of pancreatitis, corticosteroid treatment is not indicated. - Consider appropriate diagnostic testing if applicable (eg, abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT). - If clinical evidence of pancreatitis, manage according to pancreatitis recommendations (Table 14).
Grade 2, 3, or 4	- If symptomatic or clinical signs are observed, hold rilvegostomig and review TMGs (in column to the right). - No dose modifications required if asymptomatic or biochemical changes only.	

CSP, Clinical Study Protocol; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; MRCP, magnetic resonance cholangiopancreatography; NCI, National Cancer Institute.

Table 14 Pancreatitis

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance	- Gastroenterology referral is advised. - Monitor patients for signs and symptoms of pancreatitis. Non-specific symptoms may include abdominal pain, nausea, and vomiting. - Patients should be thoroughly evaluated to rule out any alternative etiology. - Monitor and evaluate relevant labs including blood counts, calcium, LDH, and albumin. - If exocrine pancreatitis is thought to be autoimmune in nature, the investigator should consider sending a blood sample for appropriate autoimmune antibody testing.
Grade 2	- Hold rilvegostomig until resolution to Grade ≤ 1. - If toxicity improves to Grade ≤ 1, then rilvegostomig can be resumed after completion of steroid taper to equivalent of prednisone ≤ 10 mg/day.	- IV hydration. - Supportive care (eg, medication for pain, nausea).
Grade 3	- Hold rilvegostomig until resolution to Grade ≤ 1. - If toxicity improves to Grade ≤ 1, then rilvegostomig may be resumed after completion of steroid taper to equivalent of prednisone ≤ 10 mg/day.	Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.^a
Grade 4	Permanently discontinue rilvegostomig.	

^a Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

CSP, Clinical Study Protocol; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous; LDH, lactate dehydrogenase; NCI, National Cancer Institute; PO, by mouth.

1.3.7 Nervous System Disorders

1.3.7.1 Aseptic Meningitis

Table 15 Aseptic Meningitis

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance Permanently discontinue rilvegostomig.	- Symptoms may include headache, photophobia, neck stiffness, and nausea/vomiting which may resemble an infectious meningitis. - Patients may be febrile. - Mental status should be normal. - Consultation with neurologist is advised. - An MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis is advised. - Exclude bacterial and viral infections. (eg, HSV). - Start IV acyclovir until polymerase chain reaction results are available. - Hospitalization is advised. - Once infection has been ruled out, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day, or equivalent. ^a

^a Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; HSV, herpes simplex virus; IV, intravenous; MRI, magnetic resonance imaging; NCI, National Cancer Institute.

1.3.7.2 Encephalitis

Table 16 Encephalitis

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	Permanently discontinue rilvegostomig.	- Symptoms may include confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality. - Consultation with neurologist is advised. - Testing, including MRI of the brain (with and without contrast), lumbar puncture, EEG (to evaluate for subclinical seizures), ESR, CRP, ANCA (if vasculitis suspected), and thyroid panel (including TPO and thyroglobulin, and additional autoantibodies to rule out paraneoplastic disorders) is advised. - Exclude bacterial and viral infections. (ie, HSV). - Start IV acyclovir until polymerase chain reactions are available.
Grade 3 or 4	Permanently discontinue rilvegostomig.	- Hospitalization is advised. - Once infection is ruled out, start methylprednisolone 1 g IV daily for 3 to 5 days for progressive symptoms. Consider adding IV Ig or plasmapheresis. ^a

^a Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

ANCA, antineutrophil cytoplasmic antibody; CRP, C-reactive protein; CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; EEG, electroencephalogram; ESR, erythrocyte sedimentation rate; HSV, herpes simplex virus; Ig, immunoglobulin; IV, intravenous; MRI, magnetic resonance imaging; NCI, National Cancer Institute; TPO, thyroid peroxidase.

1.3.7.3 Demyelinating Disease (Optic Neuritis, Transverse Myelitis, Acute Disseminated Encephalomyelitis [ADEM])

Table 17 Demyelinating Disease (Optic Neuritis, Transverse Myelitis, ADEM)

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	Permanently discontinue rilvegostomig.	- An MRI of the spine and brain is recommended. - Once imaging is complete, consider lumbar puncture. - Testing to rule out additional etiologies: Vitamin B12, copper, HIV, RPR, ANA, anti-Ro/La antibodies, aquaporin-4 IgG, MOG IgG, paraneoplastic panel is advised. - Hospitalize the patient. - Consultation with neurologist is advised. - Promptly initiate high methylprednisolone pulse dosing (1 g IV daily for 3 to 5 days, then taper over 4 weeks). ^a - Strongly consider early initiation of IV Ig or plasmapheresis.

^a Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

ADEM, acute disseminated encephalomyelitis; ANA, antinuclear antibody; CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; HIV, human immunodeficiency virus; Ig, immunoglobulin; IgG, immunoglobulin G; IV, intravenous; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; NCI, National Cancer Institute; RPR, rapid plasma reagin.

1.3.7.4 Peripheral Neuropathy

Table 18 Peripheral Neuropathy

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance	- Patients should be evaluated to rule out any alternative etiology for neuropathy (eg, disease progression, infections, metabolic syndromes, or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a consultation with neurologist. - Consultation with neurologist is advised. - Neurophysiologic diagnostic testing is advised (eg, electromyogram and nerve conduction). Investigations are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.
Grade 1	No dose modifications.	Monitor symptoms for interference with ADLS, gait difficulties, imbalance, or autonomic dysfunction.
Grade 2	- Hold rilvegostomig until resolution to Grade ≤ 1. - Permanently discontinue rilvegostomig if the event does not resolve to Grade ≤ 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. - If toxicity improves to Grade ≤ 1 within 30 days, then rilvegostomig can be resumed after completion of steroid taper to equivalent of prednisone ≤ 10 mg/day.	- Consultation with neurologist is advised. - Consider EMG/NCS. - Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. - Observation for additional symptoms or consider initiating prednisone 0.5 to 1 mg/kg orally. ^a - If progression, initiate methylprednisolone 2 to 4 mg/kg/day and treat as GBS (Table 19). ^a - Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine).
Grade 3 or 4	Permanently discontinue rilvegostomig.	- Hospitalization is advised. - Monitor symptoms and obtain neurology consult. - Treat per GBS recommendations.

^a Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

ADLS, activities of daily living; CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; EMG, electromyogram; GBS, Guillain-Barré syndrome; NCI, National Cancer Institute; NCS, nerve conduction test.

1.3.7.5 Guillain-Barré Syndrome

Table 19 Guillain-Barré Syndrome

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	Permanently discontinue rilvegostomig.	• Urgent hospitalization is advised. • Consult with neurologist. • Obtain MRI of spine to rule out compression lesion. • Obtain lumbar puncture. • Obtain antibody tests for GBS variants. • Obtain PFTs. • Obtain EMG and nerve conduction studies. • Frequently monitor PFTs and neurologic evaluations. • Monitor for concurrent autonomic dysfunction. • Initiate medication as needed for neuropathic pain.
Grade 1	Permanently discontinue rilvegostomig.	Care should be taken to monitor patients for potential decompensation.
Grade 2, 3, or 4	Permanently discontinue rilvegostomig	Promptly start IVIg or plasmapheresis and methylprednisolone 1g IV daily for 5 days, then taper over 4 weeks. ^a

^a Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; EMG, electromyogram; GBS, Guillain-Barré syndrome; Ig, immunoglobulin; IV, intravenous; MRI, magnetic resonance imaging; NCI, National Cancer Institute; PFT, pulmonary function tests.

1.3.7.6 Myasthenia Gravis

Table 20 Myasthenia Gravis

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance	- Consult neurologist. - Hospitalization is advised. - Obtain PFTs. - Obtain labs: ESR, CRP, CPK, aldolase, and anti-striational antibodies. - Consider cardiac exam, ECG, troponin, transthoracic ECHO for possible concomitant myocarditis (Table 22). - Obtain EMG and nerve conduction studies. - Consider MRI of brain/spine to rule out CNS involvement by disease. - Avoid medications that might exacerbate MG (eg, beta blockers, some antibiotics, IV magnesium).
Grade 1	- Hold rilvegostomig until resolution of symptoms. - If symptoms progress to $\geq$ Grade 2 or do not resolve, permanently discontinue rilvegostomig. - Rilvegostomig can be resumed once, and only if symptoms resolve completely (as confirmed by neurologist).	Care should be taken to monitor patients for signs of potential decompensation such as respiratory insufficiency or autonomic instability.
Grade 2	Permanently discontinue rilvegostomig	- Pyridostigmine 30 mg three times daily and gradually increase based on symptoms (maximum dose 120 mg four times daily) is advised. - Starting low dose prednisone 20 mg daily and increase every 3 to 5 days is advised. (Target dose 1 mg/kg/day. Maximum dose is 100 mg daily). ^a
Grade 3 or 4	Permanently discontinue rilvegostomig	- Start methylprednisolone 1 to 2 mg/kg/day. Taper steroids based on symptom improvement. ^a - Start plasmapheresis or IV Ig. - Rituximab use is advised, if refractory to plasmapheresis or IV Ig. - Frequent PFT assessments. - Daily neurologic evaluations.

^a Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

CNS, central nervous system; CPK, creatine phosphokinase; CRP, C-reactive protein; CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; ECHO, echocardiogram; EMG, electromyogram; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; IV, intravenous; MG, myasthenia gravis; MRI, magnetic resonance imaging; NCI, National Cancer Institute; PFT, pulmonary function test.

1.3.8 Increase in Troponin (Including Asymptomatic and Symptomatic Elevation), Including Myocarditis

Patients who present with treatment emergent troponin elevations must be evaluated to rule out ICI-related myocarditis in addition to other cardiopulmonary AE(s), even if asymptomatic.

- In certain instances, ICI-related myocarditis has been observed in patients with treatment-emergent elevations in troponin above the baseline value, but <ULN. Therefore, it is important to evaluate any trends observed in serial troponin values, and repeat troponin testing or further cardiac assessment should be considered
- For treatment emergent elevations in troponin that are above the upper limit of normal, please refer to the toxicity management guidance table below. ([Table 21](#)).

Table 21 Increase in Troponin

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance • Hold rilvegostomig during diagnostic work-up. • Permanently discontinue rilvegostomig if myocarditis is confirmed	• Early consultation with cardiologist to promptly assess if and when to complete a cardiac biopsy, cardiac MRI, and any other diagnostic procedures is advised. • The prompt diagnosis of immune-mediated myocarditis is very important in all patients, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. • Monitor patients for signs (new or changing ECG and laboratory findings) and symptoms of myocarditis (new-onset or worsening fatigue, ankle swelling, chest pain, palpitations, shortness of breath). As some symptoms can overlap with other cardiopulmonary toxicities, simultaneously evaluate for and rule out other cardiopulmonary toxicity (pericarditis, pneumonitis [Table 2]) as well as other causes (eg, acute coronary syndrome, pulmonary embolism, congestive heart failure, malignant pericardial effusion). • Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections, especially viral, acute coronary syndrome).
Grade 1 (Levels above the ULN and below the level of myocardial infarction as defined by the assay manufacturer)	• Hold rilvegostomig during diagnostic work-up. • Assessment of whether rilvegostomig can be restarted should be undertaken by the	• Initial work-up should include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), repeat serial troponin (e.g. at 6 and 12 hours) to evaluate for acute coronary syndrome, NT-proBNP or BNP, CPK, CKMB, and ECG. • Monitor and closely follow up in 24 to 48 hours with repeat NT-proBNP, CPK, CKMB, troponin, ECG, and other work-up as clinically indicated.

Table 21 Increase in Troponin

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Grade 3 (Levels consistent with myocardial infarction as defined by the manufacturer)	- investigator in consultation with a cardiologist - Rilvegostomig can only be restarted if: (1) the diagnostic work up (per the "Toxicity Management" section) is complete and negative, AND (2) the asymptomatic troponin elevation is considered (a) not clinically significant and (b) not related to rilvegostomig - Otherwise, rilvegostomig must be permanently discontinued.	- Additional evaluation should include ECHO, and additional laboratory work-up, as indicated. - Consider cardiac MRI with T1/T2 mapping to assess for the presence of myocardial edema, and/or endomyocardial biopsy to make an accurate diagnosis when it is possible and the clinical condition of the patient allows.

BNP, brain natriuretic peptide; CKMB, creatine kinase MB; CPK, creatine phosphokinase; CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; ECHO, echocardiogram; ICI, immune checkpoint inhibitor; MRI, magnetic resonance imaging; NCI, National Cancer Institute; NT-proBNP, N-terminal-pro hormone BNP; ULN, upper limit of normal.

Table 22 Myocarditis

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	- Note: See text at start of this section (1.3.8) for guidance on the management of asymptomatic troponin elevation. - Hold rilvegostomig during diagnostic work-up.	- Early consultation with cardiologist to promptly assess if and when to complete a cardiac biopsy, cardiac MRI, and any other diagnostic procedures is advised. - The prompt diagnosis (eg, using ESC diagnostic criteria) of immune-mediated myocarditis is very important in all patients, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. - Consider discussing with Study Clinical Lead or designee, as needed.

Table 22 Myocarditis

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
	Permanently discontinue rilvegostomig for any grade of myocarditis.	- Monitor patients for signs (new or changing ECG and laboratory findings) and symptoms of myocarditis (new-onset or worsening swollen ankles, fatigue, chest pain, palpitations, shortness of breath). As some symptoms can overlap with other cardiopulmonary toxicities, simultaneously evaluate for and rule out other cardiopulmonary toxicity (pericarditis, pneumonitis [Table 2]) as well as other causes (eg, acute coronary syndrome, pulmonary embolism, congestive heart failure, malignant pericardial effusion). - Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections, especially viral). - Abatacept with ruxolitinib may be used in concomitant myositis and myocarditis Salem et al, 2023).
Grade 2	Permanently discontinue rilvegostomig.	- Monitor symptoms daily, hospitalize the patient. - Supportive care (eg, oxygen). - Consultation with cardiologist is advised to determine if and when to complete a cardiac biopsy, cardiac MRI, and any other diagnostic procedures. - Initial work-up MUST include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), repeat serial troponin (at 6 and 12 hours) to evaluate for acute coronary syndrome, NT-proBNP or BNP, CPK, CKMB, and ECG. - Monitor and closely follow up in 24 to 48 hours with repeat NT-proBNP, CPK, CKMB, troponin, ECG, and other work-up as clinically indicated. - Additional evaluation may include ECHO, and additional laboratory work-up as indicated. - Promptly start high-dose pulse IV methylprednisolone 1 g/day for 3 days and then 2 mg/kg prednisone daily. ^a - If no improvement within 2 to 3 days despite IV methylprednisolone at 1 g/day, promptly start additional immunosuppressives (eg, tacrolimus, mycophenolate mofetil, or TNF inhibitors such as infliximab at 5 mg/kg IV which may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure. ^a

Table 22 Myocarditis

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
		• Close monitoring for worsening symptoms or signs of myocarditis needs to be performed before and during the tapering of corticosteroid or other immunosuppressive.
Grade 3 or 4	Permanently discontinue rilvegostomig.	• Monitor symptoms daily, hospitalize the patient. • Supportive intensive care (eg, oxygen, circulatory support including hemodynamic, temporary pacing, arrhythmia treatment, as needed). • Laboratory work-up and imaging, as described under general guidance for all grades of myocarditis, is advised. • An urgent consultation with cardiologist is advised to determine if and when to complete diagnostic procedures, including a cardiac biopsy. • Promptly start high-dose pulse high-dose IV methylprednisolone 1 g/day for 3 days and then 2 mg/kg prednisone daily. Consider initiation ACE inhibitors or ARBs for LV dysfunction, if clinically appropriate. ^a • If no improvement within 3 to 5 days despite IV methylprednisolone, consider starting additional immunosuppressives such as tacrolimus or mycophenolate mofetil. In unstable patients who do not respond to corticosteroids, consider antithymocyte globulin or IV Ig. • Close monitoring for worsening symptoms or signs of myocarditis needs to be performed before and during the tapering of corticosteroid or other immunosuppressive.

^a Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CKMB, creatine kinase MB; CPK, creatine phosphokinase; CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; ECHO, echocardiogram; ESC, European Society of Cardiology; ICI, immune checkpoint inhibitor; Ig, immunoglobulin; IV, intravenous; LV, left ventricular; MRI, magnetic resonance imaging; NCI, National Cancer Institute; NT-proBNP, N-terminal-pro hormone BNP; TNF, tumor necrosis factor.

1.3.9 Myositis/Polymyositis

Table 23 Myositis/Polymyositis

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance	- Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections). - Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back. Also, difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. As some symptoms can overlap with other toxicities, simultaneously evaluate for and rule out alternate etiologies (eg, breathing difficulty in pneumonitis [Table 2]). - If polymyositis/myositis is suspected, a neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. - If breathing complications, refer also to guidance under pneumonitis/ILD (Table 2). - Given possibility of a pre-existing (but previously unknown) autoimmune disorder, consider consultation with rheumatologist. Myocarditis may co-occur with polymyositis/myositis and myasthenia gravis (3 M's); also refer to guidance for these events (Table 22 and Table 20). - Consider that patients may present with or progress to rhabdomyolysis. Treat signs and symptoms as per institutional protocol or local clinical practice. - Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, ESR or CRP level, urine myoglobin, electrolytes (including potassium), and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (ie, consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, ANA, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider barium swallow for evaluation of dysphagia or dysphonia.

Table 23 Myositis/Polymyositis

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Grade 1	No dose modifications.	- Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. - Consultation with neurologist is advised.
Grade 2	- Hold rilvegostomig until resolution to Grade ≤ 1. - Permanently discontinue rilvegostomig if the event does not resolve to Grade ≤ 1 within 30 days or if there are signs of respiratory insufficiency. - If toxicity improves to Grade ≤ 1, then rilvegostomig can be resumed after completion of steroid taper to equivalent of prednisone ≤ 10 mg/day.	- Monitor symptoms daily and consider hospitalization. - Consultation with rheumatologist or neurologist is advised, and initiate evaluation. - If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids <u>along with receiving input</u> from neurology consultant.^a - If clinical course is <i>not</i> rapidly progressive, start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work-up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day.^a - If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 days, consider starting another immunosuppressive such as TNF inhibitors (eg, infliximab), IV Ig or plasmapheresis, or other therapies based on the discretion of the treating specialist consultant or relevant practice guideline. Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab; refer to labels of other drugs before use.^a
Grade 3	- Hold rilvegostomig until resolution to Grade ≤ 1. - If there are signs of respiratory insufficiency permanently discontinue rilvegostomig. - Rilvegostomig can be resumed once, and only if event improves to Grade ≤ 1 and after completion of steroid taper to equivalent of prednisone ≤ 10 mg/day within 30 days. Otherwise permanently discontinue rilvegostomig.	- Monitor symptoms closely; hospitalization is advised. - Consult rheumatologist or neurologist. - Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids <u>along with receiving input</u> from neurology consultant.^a - If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 days, consider starting another immunosuppressive such as TNF inhibitors (eg, infliximab) IV Ig or plasmapheresis, or other therapies based on the discretion of the treating specialist consultant or relevant practice guideline. Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab; refer to labels of other drugs before use.^a

Table 23 Myositis/Polymyositis

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Grade 4	Permanently discontinue rilvegostomig.	

^a Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

ANA, antinuclear antibody; BUN, blood urea nitrogen; CRP, C-reactive protein; CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; ESR, erythrocyte sedimentation rate; ILD, interstitial lung disease; Ig, immunoglobulin; IV, intravenous; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NCI, National Cancer Institute; PO, by mouth; TNF, tumor necrosis factor.

1.3.10 General Guidelines: Hepatitis (Elevated Liver Function Tests [LFTs]) and Isolated Hyperbilirubinemia (with Normal Aspartate Aminotransferase [AST] / Alanine Aminotransferase [ALT])

CAUTION: Infliximab should not be used for management of immune-related hepatitis unless under the specific direction of a hepatologist.

NOTE: Dose modification and TMGs for elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin are provided based on the degree of the elevation and not based on CTCAE grading.

See specific sections immediately below this section to find guidance for management of hepatitis (elevated liver function tests [LFTs]):

- Where baseline levels of ALT and/or AST are normal (Section [1.3.10.1](#))
- Where baseline levels of ALT and/or AST are abnormal (Section [1.3.10.2](#))

Hyperbilirubinemia with or without alkaline phosphatase (ALP) elevations (with normal/mildly elevated AST/ALT) may also be a presentation of immune-mediated liver injury. For clinically significant changes in bilirubin and/or ALP consider holding rilvegostomig and work-up to evaluate the cause and manage with immunosuppressants as per institutional guidance.

Table 24 Hepatitis (Elevated LFTs; General Guidance)

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any elevations in AST, ALT, or TBL as described below	General guidance	• Monitor and evaluate LFT: AST, ALT, ALP, and TBL. • Evaluate for alternative etiologies (eg, viral hepatitis, disease progression [hepatobiliary imaging; ERCP or MRCP for cholestatic picture], cholestatic DILI, concomitant medications [urine toxicology screen, acetaminophen levels], alcohol use [CD-transferrin, urinary ethyl-glucuronide and ethyl-sulfate if history of alcohol use in past 3 to 5 days, or serum phosphatidylethanol if alcohol use in past 3 weeks], autoimmune hepatitis related to autoantibodies [ANA, anti-LKM, ASMA], portal vein thrombosis, Wilson's disease [serum copper, blood ceruloplasmin, slit-lamp examination for Kayser-Fleischer rings, genetic testing], etc). • If ALT/ AST elevations is due to an alternative etiology, levels should improve to $\leq 3.0 \times \text{ULN}$ before reintroduction of rilvegostomig.

Table 24 Hepatitis (Elevated LFTs; General Guidance)

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
		- Consider checking CPK and aldolase (to rule out myositis, especially when the AST is disproportionally elevated relative to ALT). - For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg. - For HCV+ patients: evaluate quantitative HCV viral load. - Consultation with hepatologist/infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load > 2000 IU/mL, is advised. - Consultation with hepatologist/infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥ 2-fold, is advised. - For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; anti-LKM, anti-liver/kidney microsomal antibodies; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; CD-transferrin, carbohydrate-deficient transferrin; CPK, creatine phosphokinase; DILI, drug-induced liver injury; ERCP, endoscopic retrograde cholangiopancreatography; HBcAB, hepatitis B core antibody; HBeAg, hepatitis B “e” antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; LFT, liver function test; MRCP, magnetic resonance cholangiopancreatography; TBL, total bilirubin; ULN, upper limit of normal.

1.3.10.1 Elevated LFTs With Normal or Near Normal Baseline Levels of AST and/or ALT (Defined As ALT/AST < 1.5 × ULN)

CAUTION: Infliximab should not be used for management of immune-related hepatitis unless under the specific direction of a hepatologist.

Hyperbilirubinemia with or without ALP elevations (with normal/mildly elevated AST/ALT) may also be a presentation of immune-mediated liver injury. For clinically significant changes in bilirubin and/or ALP, consider holding rilvegostomig and work-up to evaluate the cause and manage with immunosuppressants as per institutional guidance.

Table 25 Treatment-emergent Elevated LFTs with Normal Baseline Levels of AST and/or ALT ^a

Treatment emergent ALT/AST elevations	TBL ^b values at time of treatment emergent ALT elevation	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
$\leq 3.0 \times \text{ULN}$	Normal (if abnormal, follow hyperbilirubinemia guidance above this table).	No dose modifications.	Repeat blood tests (eg, ALT, AST, ALP, GGT, TBL) within 7 days.
$> 3.0 \times \text{ULN}$ and $\leq 5.0 \times \text{ULN}$	- TBL $< 2 \times \text{ULN}$. - Patients with Gilbert's syndrome: No change or increase to $< 2 \times$ baseline DBL.	- Hold rilvegostomig. - If AST and ALT improve to $\leq 3.0 \times \text{ULN}$ (and resolution is sustained), rilvegostomig can be resumed after completion of steroid taper to equivalent of prednisone $\leq 10 \text{ mg/day}$, with close liver test monitoring.	- Consultation with hepatologist is advised. - Initiate close monitoring and evaluation. Repeat blood tests (eg, ALT, AST, ALP, GGT, TBL, DBL, CPK, INR) within 2 to 3 days. - Frequency of subsequent monitoring may be adjusted based on clinical scenario and severity of injury. Monitoring should continue until ALT/AST levels return to $\leq 3 \times \text{ULN}$, regardless of whether or not rilvegostomig had been discontinued. - If rising ALT/AST on re-check, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. - If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, perform additional work-up, and increase IV methylprednisolone 2 to 4 mg/kg/day while concomitantly initiating additional immunosuppressives (ie, mycophenolate mofetil at 1 g PO BID). ^c - Discuss with Study Clinical Lead or designee if mycophenolate mofetil is not available. Infliximab should NOT be used unless under the specific direction of a hepatologist.. - Once ALT/AST return to $\leq 3 \times \text{ULN}$, corticosteroids can be tapered over ≥ 28 days.
	- TBL $\geq 2 \times \text{ULN}$. - Patients with Gilbert's syndrome: DBL $\geq 2 \times$ the baseline value	Hold rilvegostomig to evaluate for Potential Hy's law.	- Consultation with hepatologist is advised. - Initiate close monitoring and evaluation. - Repeat blood tests (eg, ALT, AST, ALP, GGT, TBL, DBL, CPK, INR) within 2 to 3 days. Frequency of monitoring may be adjusted based on

Table 25 Treatment-emergent Elevated LFTs with Normal Baseline Levels of AST and/or ALT ^a

Treatment emergent ALT/AST elevations	TBL ^b values at time of treatment emergent ALT elevation	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
		- Permanently discontinue rilvegostomig in the absence of any alternative cause. - Where abnormality was due to an alternative cause that is treated, rilvegostomig can be resumed when ALT, AST <3xULN, TBL ≤ 2xULN (<2x DBL for Gilbert's) if clinically appropriate	clinical scenario and severity of injury. Monitoring should continue until ALT/AST levels return to $\leq 3 \times \text{ULN}$, regardless of whether or not rilvegostomig had been discontinued. - Promptly start IV methylprednisolone 1 to 4 mg/kg/day or equivalent; if no improvement in 3 to 5 days, initiate additional immunosuppressives (ie, mycophenolate mofetil at 1 g PO BID). ^c Discuss with Study Clinical Lead or designee if mycophenolate mofetil is not available. Infliximab should NOT be used unless under the specific direction of a hepatologist.. - Once ALT/AST return to $\leq 3 \times \text{ULN}$, corticosteroids can be tapered over ≥ 28 days. - If rilvegostomig is restarted after a hold and completion of steroid taper, perform LFTs twice weekly until response to restart is known. - Refer to the CSP for more details regarding reporting and evaluation of Potential Hy's Law.
> $5.0 \times \text{ULN}$ and $\leq 8.0 \times \text{ULN}$	- TBL < $2 \times \text{ULN}$. - Patients with Gilbert's syndrome: No change or increase to < $2 \times$ baseline DBL.	- Hold rilvegostomig. - Do not restart rilvegostomig if clinical symptoms or signs of liver failure (based on elevated serum levels of DBL, prolonged PT or INR [INR > 1.5], hepatic encephalopathy, or ascites caused by impaired hepatic function). - If elevations downgrade to AST and ALT $\leq 3.0 \times \text{ULN}$ (and resolution is sustained) within 21 days, rilvegostomig can be resumed after completion of steroid taper to equivalent of prednisone ≤ 10 mg/day.	- Consultation with hepatologist is advised. - Initiate close monitoring and evaluation. - Repeat blood tests (eg, ALT, AST, ALP, GGT, TBL, DBL, CPK, INR) within 2 to 3 days. - Frequency of subsequent monitoring may be adjusted based on clinical scenario and severity of injury. Monitoring should continue until ALT/AST levels return to $\leq 3 \times \text{ULN}$, regardless of whether or not rilvegostomig had been discontinued. - Promptly start IV methylprednisolone 1 to 4 mg/kg/day or equivalent; if no improvement in 3 to 5 days, initiate additional immunosuppressives (ie, mycophenolate mofetil at 1 g PO BID). ^c Discuss with Study Clinical Lead or designee if mycophenolate mofetil is not available. Infliximab should NOT be used unless under the specific direction of a hepatologist.

Table 25 Treatment-emergent Elevated LFTs with Normal Baseline Levels of AST and/or ALT ^a

Treatment emergent ALT/AST elevations	TBL ^b values at time of treatment emergent ALT elevation	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
		Otherwise, permanently discontinue rilvegostomig.	- If rilvegostomig is restarted after a hold and completion of steroid taper, perform LFTs twice weekly until response to restart is known. - Once ALT/AST return to $\leq 3 \times \text{ULN}$, corticosteroids can be tapered over ≥ 28 days.
	TBL $\geq 2 \times \text{ULN}$. Patients with Gilbert's syndrome: DBL $\geq 2 \times$ the baseline value	- Hold rilvegostomig to evaluate for Potential Hy's law. - Permanently discontinue rilvegostomig in the absence of any alternative cause.	- Consultation with hepatologist is advised. - Repeat blood tests (eg, ALT, AST, ALP, GGT, TBL, DBL, CPK, INR) within 2 to 3 days. Frequency of monitoring may be adjusted based on clinical scenario and severity of injury. Monitoring should continue until ALT/AST levels return to $\leq 3 \times \text{ULN}$, regardless of whether or not rilvegostomig had been discontinued. - Promptly start IV methylprednisolone 1 to 4 mg/kg/day or equivalent; if no improvement in 3 to 5 days, initiate additional immunosuppressives (ie, mycophenolate mofetil at 1 g PO BID).^c Discuss with Study Clinical Lead or designee if mycophenolate mofetil is not available. Infliximab should NOT be used unless under the specific direction of a hepatologist.. - Once ALT/AST return to $\leq 3 \times \text{ULN}$, corticosteroids can be tapered over ≥ 28 days. - If rilvegostomig is restarted after a hold and completion of steroid taper, perform LFTs twice weekly until response to restart is known. - Refer to the CSP for more details regarding reporting and evaluation of Potential Hy's Law.
$> 8.0 \times \text{ULN}$	- Normal or elevated. - Patients with Gilbert's syndrome: No change or change in baseline DBL.	Permanently discontinue rilvegostomig.	- Consultation with hepatologist is advised. - Repeat blood tests (eg, ALT, AST, ALP, GGT, TBL, DBL, CPK, INR) within 2 to 3 days. Frequency of monitoring may be adjusted based on clinical scenario and severity of injury. Monitoring should continue until

Table 25 Treatment-emergent Elevated LFTs with Normal Baseline Levels of AST and/or ALT ^a

Treatment emergent ALT/AST elevations	TBL ^b values at time of treatment emergent ALT elevation	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
			ALT/AST levels return to $\leq 3 \times \text{ULN}$, regardless of whether or not rilvegostomig had been discontinued. - Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent; if no improvement in 3 to 5 days, initiate additional immunosuppressives (ie, mycophenolate mofetil at 1 g PO BID). ^c Discuss with Study Clinical Lead or designee if mycophenolate mofetil is not available. Infliximab should NOT be used unless under the specific direction of a hepatologist.. - Once ALT/AST return to $\leq 3 \times \text{ULN}$, corticosteroids can be tapered over ≥ 28 days. - Refer to the CSP for more details regarding reporting and evaluation of Potential Hy's Law.

^a ALP is not included in this table as isolated ALP elevation is often related to the underlying malignancy and uncommonly related to ILICI. Furthermore, there are limited published data regarding management of ILICI in patients who develop isolated ALP elevation during ICI treatment.

^b Measurement of total and conjugated (or direct) bilirubin is recommended to help identify patients with indirect hyperbilirubinemia due to Gilbert's syndrome or hemolysis versus liver injury.

^c Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

Adapted from: [Regev et al 2020](#).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CPK, creatine phosphokinase; CSP, Clinical Study Protocol; DBL, direct bilirubin; GGT, gamma glutamyl transferase; ICI, immune checkpoint inhibitor; ILICI, immune-mediated liver injury caused by checkpoint inhibitors; INR, international normalized ratio; IV, intravenous; LFT, liver function test; PO, by mouth; PT, prothrombin time; TBL, total bilirubin; ULN, upper limit of normal.

1.3.10.2 Elevated LFTs with Abnormal Baseline

CAUTION: Infliximab should not be used for management of immune-related hepatitis unless under the specific direction of a hepatologist.

Hyperbilirubinemia with or without ALP elevations (with normal/mildly elevated AST/ALT) may also be a presentation of immune-mediated liver injury. For clinically significant changes in bilirubin and/or ALP, consider holding rilvegostomig and work-up to evaluate the cause and manage with steroids as per institutional guidance.

Table 26 Elevated LFTs with Abnormal Baseline Levels of AST and/or ALT ^a

Treatment emergent ALT/AST elevations	TBL ^b values at time of treatment emergent ALT elevation	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
> baseline and $\leq 1.5 \times$ baseline	Normal (if abnormal, follow hyperbilirubinemia guidance above this table).	No dose modifications.	Repeat blood tests (eg, ALT, AST, ALP, GGT, TBL) within 7 days.
> $1.5 \times$ baseline and $\leq 3 \times$ baseline	- TBL < $2 \times$ ULN. - Patients with Gilbert's syndrome: No change or increase to < $2 \times$ baseline DBL.	- Hold rilvegostomig. - If toxicity improves to AST and ALT $\leq 1.5 \times$ baseline (and resolution is sustained), rilvegostomig can be resumed after completion of steroid taper to equivalent of prednisone ≤ 10 mg/day, with close liver test monitoring. - If AST/ALT > $10 \times$ ULN, permanently discontinue rilvegostomig.	- Initiate close monitoring and evaluation. Repeat blood tests (eg, ALT, AST, ALP, GGT, TBL, DBL, CPK, INR) within 2 to 3 days. - Frequency of monitoring may be adjusted based on clinical scenario and severity of injury. Monitoring should continue until ALT/AST levels return to $\leq 1.5 \times$ baseline, regardless of whether or not rilvegostomig had been discontinued. - Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. - If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work-up, increase IV methylprednisolone 2 to 4 mg/kg/day, and concomitantly start additional immunosuppressives (ie, mycophenolate mofetil at 1 g PO BID).^c - Discuss with Study Clinical Lead or designee if mycophenolate mofetil is not available. Infliximab should NOT be used unless under the specific direction of a hepatologist. - Once ALT/AST return to $\leq 1.5 \times$ baseline, corticosteroids can be tapered over ≥ 28 days. - Consultation with hepatologist is advised.

Table 26 **Elevated LFTs with Abnormal Baseline Levels of AST and/or ALT ^a**

Treatment emergent ALT/AST elevations	TBL ^b values at time of treatment emergent ALT elevation	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
	- TBL $\geq 2 \times$ ULN. - Patients with Gilbert's syndrome: DBL $\geq 2 \times$ the baseline value	- Hold rilvegostomig to evaluate for Potential Hy's law. - Permanently discontinue rilvegostomig in the absence of any alternative cause. - If AST/ALT $> 10 \times$ ULN, permanently discontinue rilvegostomig.	- Repeat blood tests (eg, ALT, AST, ALP, GGT, TBL, DBL, CPK, INR) within 2 to 3 days. Frequency of monitoring may be adjusted based on clinical scenario and severity of injury. Monitoring should continue until ALT/AST levels return to $\leq 1.5 \times$ baseline, regardless of whether or not rilvegostomig had been discontinued. - Promptly start IV methylprednisolone 1 to 4 mg/kg/day or equivalent; if no improvement in 3 to 5 days, initiate additional immunosuppressives (ie, mycophenolate mofetil at 1 g PO BID). ^c Discuss with Study Clinical Lead or designee if mycophenolate mofetil is not available. Infliximab should NOT be used unless under the specific direction of a hepatologist. - Once ALT/AST return to $\leq 1.5 \times$ baseline, corticosteroids can be tapered over ≥ 28 days. - If rilvegostomig is restarted after a hold and completion of steroid taper, perform LFTs twice weekly until response to restart is known. - Consultation with hepatologist is advised. - Refer to the CSP for more details regarding reporting and evaluation of Potential Hy's Law.

Table 26 **Elevated LFTs with Abnormal Baseline Levels of AST and/or ALT ^a**

Treatment emergent ALT/AST elevations	TBL ^b values at time of treatment emergent ALT elevation	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
> 3.0 × baseline and ≤ 5 × baseline	- TBL < 2 × ULN. - Patients with Gilbert's syndrome: No change or increase to < 2 × baseline DBL.	- Hold rilvegostomig. - If elevations downgrade to ≤ 1.5 × baseline (and resolution is sustained) within 21 days, rilvegostomig can be resumed after completion of steroid taper to equivalent of prednisone ≤ 10 mg/day. Otherwise, permanently discontinue rilvegostomig. - If AST/ALT > 10 × ULN, permanently discontinue rilvegostomig.	- Initiate close monitoring and evaluation. Repeat blood tests (eg, ALT, AST, ALP, GGT, TBL, DBL, CPK, INR) within 2 to 3 days. - Frequency of monitoring may be adjusted based on clinical scenario and severity of injury. Monitoring should continue until ALT/AST levels return to ≤ 1.5 × baseline, regardless of whether or not rilvegostomig had been discontinued. - Promptly start IV methylprednisolone 1 to 4 mg/kg/day or equivalent; if no improvement in 3 to 5 days initiate additional immunosuppressives (ie, mycophenolate mofetil at 1 g PO BID).^c Discuss with Study Clinical Lead or designee if mycophenolate mofetil is not available. Infliximab should NOT be used unless under the specific direction of a hepatologist. - Consultation with hepatologist is advised. - If rilvegostomig is restarted after a hold and completion of steroid taper, perform LFTs twice weekly until response to restart is known.
	- TBL ≥ 2 × ULN. - Patients with Gilbert's syndrome: DBL ≥ 2 × the baseline value	- Hold rilvegostomig to evaluate for Potential Hy's law. - Permanently discontinue rilvegostomig in the absence of any alternative cause. - Follow guidance above if alternative cause (e.g. Gilbert's syndrome) for TBL elevation is identified. - If AST/ALT > 10 × ULN, permanently discontinue rilvegostomig.	- Repeat blood tests (eg, ALT, AST, ALP, GGT, TBL, DBL, CPK, INR) within 2 to 3 days. Frequency of monitoring may be adjusted based on clinical scenario and severity of injury. Monitoring should continue until ALT/AST levels return to ≤ 1.5 × baseline, regardless of whether or not rilvegostomig had been discontinued. - Promptly start IV methylprednisolone 1 to 4 mg/kg/day or equivalent; if no improvement in 3 to 5 days initiate additional immunosuppressives (ie, mycophenolate mofetil at 1 g PO BID).^c Discuss with Study Clinical Lead or designee if mycophenolate mofetil is not available. Infliximab should NOT be used unless under the specific direction of a hepatologist. - Once ALT/AST returns to ≤ 1.5 × baseline, corticosteroids can be tapered over ≥ 28 days. - Consultation with hepatologist is advised.

Table 26 **Elevated LFTs with Abnormal Baseline Levels of AST and/or ALT ^a**

Treatment emergent ALT/AST elevations	TBL ^b values at time of treatment emergent ALT elevation	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
			- If rilvegostomig is restarted after a hold and completion of steroid taper, perform LFTs twice weekly until response to restart is known. - Refer to the CSP for more details regarding reporting and evaluation of Potential Hy's Law.
$> 5.0 \times \text{baseline}$ <u>or</u> $> 10 \times \text{ULN}$	- Normal or elevated. - Patients with Gilbert's syndrome: No change or change in baseline DBL.	Permanently discontinue rilvegostomig. If $\text{TBL} > 2 \times \text{ULN}$, evaluate for Potential Hy's law.	- Repeat blood tests (eg, ALT, AST, ALP, GGT, TBL, DBL, CPK, INR) within 2 to 3 days. Frequency of monitoring may be adjusted based on clinical scenario and severity of injury. Monitoring should continue until ALT/AST levels return to $\leq 1.5 \times \text{baseline}$, regardless of whether or not rilvegostomig had been discontinued. - Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent; if no improvement in 3 to 5 days initiate additional immunosuppressives (ie, mycophenolate mofetil at 1 g PO BID). ^c Discuss with Study Clinical Lead or designee if mycophenolate mofetil is not available. Infliximab should NOT be used unless under the specific direction of a hepatologist. - Once ALT/AST return to $\leq 1.5 \times \text{baseline}$, corticosteroids can be tapered over ≥ 28 days. - Consultation with hepatologist is advised. - Refer to the CSP for more details regarding reporting and evaluation of Potential Hy's Law.

^a ALP is not included in this table as isolated ALP elevation is often related to the underlying malignancy and uncommonly related to ILICI. Furthermore, there are limited published data regarding management of ILICI in patients who develop isolated ALP elevation during ICI treatment.

^b Measurement of total and conjugated (or direct) bilirubin is recommended to help identify patients with indirect hyperbilirubinemia due to Gilbert's syndrome or hemolysis versus cholestatic liver injury.

^c Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

Adapted from: [Regev et al 2020](#).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CPK, creatine phosphokinase; CSP, Clinical Study Protocol; DBL, direct bilirubin; GGT, gamma glutamyl transferase; ICI, immune checkpoint inhibitor; ILICI, immune-mediated liver injury caused by checkpoint inhibitors; INR, international normalized ratio; IV, intravenous; LFT, liver function test; PO, by mouth; TBL, total bilirubin; ULN, upper limit of normal.

1.3.11 Cytokine Release Syndrome (CRS)

NOTE: Grading of CRS events, along with dose modification and TMGs per grade, are provided based on American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading by [Lee et al 2019](#).

Table 27 Cytokine Release Syndrome

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade CRS grading is based on the ASTCT criteria (Lee et al 2019)	General guidance	- CRS is a systemic inflammatory response caused by the release of cytokines, chemokines, and IFN-inducible genes that are expected to induce both innate and adaptive immunity. Clinically, CRS consists of a constellation of symptoms that may include fever (defined as temperature > 38°C not attributable to any other cause), nausea, headaches, flushing, flu-like symptoms, tachypnea, hypoxemia, tachycardia, hypotension, confusion, etc, along with possible laboratory changes in the CBC, LFTs, CRP, and ferritin. Because these symptoms can progress quickly to become potentially life-threatening, suggested guidelines for the management of CRS are provided below. These general guidelines are to assist the investigator in the diagnosis and management of the potential immune-mediated/CRS events and are not meant to supplant discussions with the Study Clinical Lead or designee. - Prompt and urgent intervention to prevent progression of CRS is required; however, other causes of systemic inflammatory response should be ruled out, including infection and malignancy progression.
Grade 1 Fever ($\geq 100^{\circ}\text{F}$ or $\geq 38^{\circ}\text{C}$) ^a not attributable to any other cause	No dose modifications.	- Patients should be thoroughly evaluated to rule out any alternative etiology. - Symptomatic treatment (eg, fluids, antipyretics). - Close monitoring of the vital parameters and of biologic laboratory tests (including CBC, LFTs, CRP, and ferritin) should be performed until resolution of symptoms.

Table 27 Cytokine Release Syndrome

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Grade 2 Fever ($\geq 100^{\circ}\text{F}$ or $\geq 38^{\circ}\text{C}$) ^a with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula or blow-by oxygen	- Hold rilvegostomig until resolution to Grade ≤ 1. - If toxicity does not improve to Grade ≤ 1 within 48 hours, then permanently discontinue rilvegostomig. - If toxicity improves to Grade ≤ 1 within 48 hours, then rilvegostomig can be resumed if all the following conditions are met: - The event stabilizes and is controlled. - The patient is clinically stable as per investigator or treating physician's clinical judgment. - Prednisone equivalent dose is ≤ 10 mg/day.	- Recommend hospitalization for management and observation until recovery. - Close monitoring of the vital parameters and of biologic laboratory tests including CBC, LFTs, CRP, and ferritin should be performed until the resolution of the symptoms. - Aggressive supportive care including fluid and electrolyte replacement. - Systemic corticosteroids (1 to 2 mg/kg/day of methylprednisolone IV) should be considered.^b - Tocilizumab may be considered per the investigator's institutional SOPs. - If the symptoms do not improve within 48 hours despite appropriate medical management, proceed with measures applicable to Grade 3.
Grade 3 Fever ($\geq 100^{\circ}\text{F}$ or $\geq 38^{\circ}\text{C}$) ^a with hypotension requiring one vasopressor with or without vasopressin and/or hypoxia requiring high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask not attributable to any other cause	Permanently discontinue rilvegostomig.	- Proceed with the CRS management as per Grade 2. - Consider higher dose corticosteroids of 1 to 2 mg/kg every 12 hours of methylprednisolone IV (ie, 2 to 4 mg/kg/day).^b

Table 27 Cytokine Release Syndrome

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Grade 4 Fever (≥ 100 °F or $\geq 38^{\circ}\text{C}$) ^a with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation) not attributable to any other cause	Permanently discontinue rilvegostomig.	Proceed with the CRS management as per Grade 3.

^a In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

^b Refer to the local Prescribing Information for infliximab, mycophenolate mofetil, and steroids.

ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CBC, complete blood count; CPAP, continuous positive airway pressure; CRP, C-reactive protein; CRS, cytokine release syndrome; IFN, interferon; IV, intravenous; LFT, liver function test; SOP, standard operating procedure.

1.3.12 Subcutaneous Injection Site Reactions

Table 28 Subcutaneous Injection Site Reactions

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any Grade (Refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance	- Monitor patients for signs and symptoms of worsening cutaneous adverse events - Use digital photography for event monitoring as available, refer to the clinical study protocol for specific requirements. - Rotate the injection site at subsequent IP administrations

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Grade 1 or 2	No dose modifications	• Provide supportive care (including, but not limited to oral analgesics, topical treatments/antihistamines, cold compress) • Other supportive care should be administered per institutional standard at the discretion of the investigator. • Treat other signs/symptoms accordingly per institutional guidelines
Grade 3 or 4	Permanently Discontinue	• Dermatology consult recommended • Treat per institutional guidelines • Hospitalize as required, per investigator discretion.

Adapted from Zhi, L., Liu, D. & Shameem, M. Injection site reactions of biologics and mitigation strategies. *AAPS Open* **11**, 5 (2025). [https://doi.org/10.1186/s41120-025-00108-](https://doi.org/10.1186/s41120-025-00108-4)

4

2 INFUSION-RELATED REACTIONS (IRRs)

Table 29 Infusion-related Reactions (Including Hypersensitivity Reactions)

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any grade (refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	General guidance	- Manage per institutional standard at the discretion of investigator. - Monitor patients for signs and symptoms of IRRs (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	- The infusion rate of rilvegostomig may be decreased by 50% or temporarily interrupted until resolution of the event. - For Grade 2: - The infusion rate of rilvegostomig may be decreased 50% or temporarily interrupted until resolution of the event. - Subsequent infusions may be given at 50% of the initial infusion rate.	- Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. - Investigators are recommended to prescribe premedication for prevention of IRRs in patients who have Grade 2 or recurrent Grade 1 IRRs related to rilvegostomig. - Premedication such as a combination of acetaminophen, H1 blocker (eg, diphenhydramine, chlorpheniramine) and H2 blocker (eg, famotidine), is advised. - If necessary, a steroid premedication may be added. - Steroids should not be used for routine premedication of Grade ≤ 2 infusion reactions.
Grade 3 or 4	Permanently discontinue rilvegostomig.	Manage severe IRRs per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and famotidine, and IV glucocorticoid).

CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; IM, intramuscular; IRR, infusion-related reaction; IV, intravenous; NCI, National Cancer Institute.

3 NON-IMMUNE-MEDIATED ADVERSE EVENTS

Table 30 Non-immune-mediated Adverse Events

Severity grade of the event	Dose modifications (dose delay and/or permanent discontinuation)	Toxicity management
Any grade (refer to NCI CTCAE applicable version in CSP for defining the CTCAE grade/severity)	Note: Dose modifications are not required for AEs not deemed to be related to rilvegostomig (ie, events due to underlying disease) unless continuation of treatment could interfere with recovery from the event, or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold rilvegostomig until resolution to Grade $\leq$ 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	- Hold rilvegostomig until resolution to Grade $\leq$ 1 or baseline. - For AEs that downgrade to Grade $\leq$ 2 within 7 days or resolve to Grade $\leq$ 1 or baseline within 14 days, resume rilvegostomig administration. Otherwise, discontinue study rilvegostomig. - At the discretion of the investigator, rilvegostomig may be permanently discontinued.	Treat accordingly, as per institutional standard.
Grade 4	Permanently discontinue rilvegostomig. Note: For Grade 4 laboratory values without other AEs, decision to discontinue should be based on accompanying clinical signs/symptoms, the investigator's clinical judgment, and consultation with the Sponsor.	Treat accordingly, as per institutional standard.

AE, adverse event; CSP, Clinical Study Protocol; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute.

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