IASO BIOTECHNOLOGY

FUCASO suspension for infusion (Equecabtagene Autoleucel)

Clinical Safety Management Manual

Version 4.0

Cytokine Release Syndrome (CRS) | Neurotoxicity | Secondary malignancies of T-cell origin

FUCASO is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least three prior lines of therapy (including a proteasome inhibitor and an immunomodulatory agent), and have demonstrated disease progression on the last therapy.

This document has been approved by HSA as of 18-Jun-2026

Contents

Introduction

- FUCASO suspension for infusion is a CAR-T product targeting B-cell maturation antigen (BCMA) for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least three prior lines of therapy (including a proteasome inhibitor and an immunomodulatory agent), and have demonstrated disease progression on the last therapy.
- This manual is intended to introduce the management of selected adverse reactions to FUCASO suspension for infusion, with the aim of further improving the clinical safety monitoring and management of patients treated with FUCASO suspension for infusion.
- Please refer to the approved Singapore Package Insert for details.

Safety Monitoring

1 Monitoring Indicators

- A comprehensive understanding of the associated adverse events (AEs) – particularly their grading, monitoring and management – is vital.
- Patients should be monitored in the certified healthcare facility for at least 14 days after infusion of FUCASO. Patients should also be instructed to remain near the healthcare facility for at least 4 weeks post-infusion to receive timely intervention for possible serious adverse reactions.

Monitoring Indicator	Monitoring Purpose & Key Notes
Vital signs (temperature, respiration, heart rate, blood pressure, SpO_2)	Monitor from 15 min before infusion to 1 h after infusion. If vital signs become unstable, closely monitor until all indicators have stabilized. Monitoring of the vital signs facilitates early identification of CRS. An elevated temperature may also indicate an infection.
Patient-reported signs and symptoms	Educate patients to monitor newly-onset / worsening signs and symptoms, especially after discharge. These signs and symptoms include, but are not limited to: • Fever, chills, difficulty breathing, chest tightness, heart palpitation • Headache, dizziness, blurred vision • Nausea / vomiting, muscle and joint pain • Depressed level of consciousness, somnolence, confusion, speech disorders, agitation • Skin bruises, bleeding of the mucous membranes (e.g. nose, gums) or other parts of the body
Peripheral blood cell counts	Monitor blood counts before and after infusion. Patients may exhibit prolonged cytopenias for several weeks following lymphodepletion pretreatment and FUCASO infusion. Prolonged neutropenia has been associated with increased risk of infection.
Plasma gamma immunoglobulin (IgG)	Monitor the level of immunoglobulin after FUCASO infusion. Hypogammaglobulinemia is associated with serious infections.

SpO_2: Blood oxygen saturation

2 Acute Adverse Reactions

- It is recommended that patients remain in hospital for at least 14 days after infusion to closely monitor and intervene any acute adverse reactions.

Adverse Reaction	Incidence/ Onset (FUMANBA-1)	Monitoring & Management
Cytokine Release Syndrome (CRS)	• Incidence: 93.6% (102/109); 0.9% Grade ≥ 3 • Median onset to first occurrence post-infusion: 6.0 days (range 1–13 days) • Median duration: 5.0 days (range 2–30 days)	• Signs and symptoms of CRS include fever at the onset and may also include hypotension, tachycardia, hypoxia, chills • Ensure that corticosteroids and at least two doses per patient of tocilizumab are available for administration prior to FUCASO infusion. The healthcare facility must have access to an additional dose of tocilizumab within 8 hours of each previous dose • Monitor for signs and symptoms of CRS for at least 14 days post-infusion • Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks after infusion and continue to monitor for signs and symptoms of CRS • Please refer to page 3 for adverse event management guidance for CRS
Neurologic Toxicities	• Immune effector cell-associated neurotoxicity syndrome (ICANS) incidence: 1.8% (2/109); no Grade ≥ 3 • Onset: Day 3 and Day 10 (median ~Day 6.5)	• May occur with, after, or without CRS • Signs and symptoms include headache, insomnia, encephalopathy, tremors, dizziness, delirium, confusion, agitation • Monitor for signs and symptoms for at least 14 days post-infusion • Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks after infusion and continue to monitor for signs and symptoms of neurologic toxicities • Please refer to page 6 for adverse event management guidance for neurologic toxicities
Hematologic Toxicities	• Incidence of ≥ Grade 3 blood cell count decreased: 100%	• Monitor blood counts before and after FUCASO infusion • Manage cytopenia with hematopoietic therapy and/or blood transfusion according to local institutional guidelines • Myeloid growth factors, particularly GM-CSF have the potential to worsen CRS symptoms and are not recommended during the first 3 weeks after FUCASO or until CRS has resolved

GM-CSF: Granulocyte-macrophage colony-stimulating factor

Please refer to the Singapore package insert for monitoring and management of other possible adverse reactions.

Adverse Event Management Guidance

1 Cytokine Release Syndrome (CRS)

Definition[2]

- A supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T-cells and/or other immune effector cells.

Symptoms

- In the FUMANBA-1 study, the main CRS symptoms were fever, increased LDH, hypoxia, hypotension, increased AST and vomiting.

Incidence

- In the FUMANBA-1 study, more than 90% of relapsed/refractory multiple myeloma patients experienced CRS, with the majority being Grade 1-2 in severity.

LDH: Lactate dehydrogenase; AST: Aspartate aminotransferase

1.1 Management of CRS

- Monitor patients for signs and symptoms of CRS. Manage and treat as needed based on the CRS grading and management guidelines.

CRS Grading and Management Guidelines

CRS Grading*,[a]	Corticosteroids[d,e]	Anti-IL-6 Therapy[h]	Additional Supportive Treatment
Grade 1 Fever (≥ 38°C)	For early-onset CRS (<72 hours after infusion), consider IV dexamethasone[f] 10mg, every 24 hours	For prolonged CRS (>3 days) in patients or those with significant symptoms, comorbidities and/or are elderly, consider 1 dose of IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg)	• Sepsis screen and empiric broad-spectrum antibiotics, consider G-CSF[i] if neutropenic • Maintenance IV fluid for hydration • Symptomatic management of organ toxicities

CRS Grading and Management Guidelines

CRS Grading*,[a]	Corticosteroids[d,e]	Anti-IL-6 Therapy[h]	Additional Supportive Treatment
Grade 2 Fever (≥ 38°C) with: Hypotension not requiring vasopressors, and/or, Hypoxia requiring low-flow nasal cannula[b] or blow-by, or, Grade 2 organ toxicity[c]	For persistent refractory hypotension after 1–2 doses of anti-IL-6 therapy, consider IV dexamethasone[f] 10 mg every 12–24 hours	IV tocilizumab 8mg/kg over 1 hour (not to exceed 800mg/dose). Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses in total	• IV fluid bolus as needed • For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: Start vasopressors, consider transfer to ICU, consider echocardiogram, and initiate other methods of hemodynamic monitoring. Telemetry, ECG, troponin, and BNP if persistent tachycardia • Manage per Grade 3 if no improvement within 24 hours after starting anti–IL-6 therapy • Symptomatic management of organ toxicities
Grade 3 Fever (≥ 38°C) with: Hypotension requiring a vasopressor with or without vasopressin and/or, Hypoxia requiring high-flow cannula[b], face mask, non-rebreather mask, or Venturi mask, or, Grade 3 organ toxicity or Grade 4 transaminitis	IV dexamethasone[f] 10mg every 6 hours. If refractory, manage as Grade 4	Anti-IL-6 therapy as per Grade 2 if maximum dose not reached within 24-hour period	• Transfer to ICU, obtain ECG, and perform hemodynamic monitoring • Oxygen supplementation • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities
Grade 4 Fever (≥ 38°C) with: Hypotension requiring multiple vasopressors (excluding vasopressin) and/or, Hypoxia requiring positive pressure (e.g., continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, mechanical ventilation), or, Grade 4 organ toxicity (excluding transaminitis)	IV dexamethasone[f] 10mg every 6 hours If refractory, consider 3 doses of IV methylprednisolone 1 g/day If refractory, consider dosing every 12 hours Other lines of therapy may be considered[g]	Anti-IL-6 therapy as per Grade 2 if maximum dose not reached within 24-hour period	• ICU care and hemodynamic monitoring. Mechanical ventilation as needed • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities

G-CSF: Granulocyte Colony-Stimulating Factor; IL-6: Interleukin-6; IV: Intravenous; ICU: Intensive Care Unit; ECG: Electrocardiogram; BNP: B-Type Natriuretic Peptide

*Grading according to the American Society for Transplantation and Cellular Therapy (ASTCT) standard (2019), modified to include organ toxicity and National Comprehensive Cancer Network (NCCN) guidelines (2022. v1) management recommendations. Refer to the latest Singapore Package Insert for FUCASO for details.

a. Fever may not always be present concurrently with hypotension or hypoxia, as it may be masked by interventions such as antipyretics or anti-cytokine therapy (e.g., tocilizumab or steroids). Absence of fever does not impact CRS management decision. In this case, CRS management is driven by hypotension and/or hypoxia and by the more severe symptom not attributable to any other cause.

b. Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.

c. Organ toxicity grading based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

d. After each dose, assess need for subsequent dosing.

e. For patients receiving corticosteroid therapy for CRS, antifungal prophylaxis is strongly recommended.

f. Alternative steroids at an equivalent dose may be considered. For example, methylprednisolone intravenous 1,000 mg/day can be administered for 3 days, followed by a rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days.

g. Other agents such as anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG, antithymocyte globulin (ATG), or extracorporeal cytokine adsorption with continuous renal replacement therapy (CRRT) might be considered. Reported experience with these agents is limited.

h. If there is no improvement after treatment with corticosteroids and IL-6 levels are high, tocilizumab treatment can be considered. After each dose, assess need for subsequent dosing.

i. GM-CSF is not recommended in the setting of CAR-T cell therapy.

2 Neurotoxicity

Definition[3]

- Neurotoxicity, including ICANS, is a disorder characterized by a pathological process affecting the central nervous system following immune effector therapy that results in the activation or deployment of endogenous or infused T cells or other immune effector cells.

Symptom

- In the FUMANBA-1 study, **neurological symptoms** included headache, insomnia, somnolence, dizziness, hypoesthesia and post herpetic neuralgia.
- Neurological events can be concurrent with CRS, following resolution of CRS or in the absence of CRS.

Incidence

- In the FUMANBA-1 study, 14.7% of patients experienced treatment-related **neurological and psychosis disorders**. **ICANS** occurred in 2 patients (1.8%).

ICANS = Immune effector cell-associated neurotoxicity syndrome

2.1 Management of Neurotoxicity

- Closely monitor signs and symptoms suggestive of neurotoxicity (including ICANS) after FUCASO infusion. In case of neurological events, patients should be diagnostically worked up and managed depending on the underlying pathophysiology and in accordance with the local standard of care. Provide intensive care and supportive treatment for severe or life-threatening neurologic toxicities.
- Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any grade of neurologic toxicities.

2.2 Management of ICANS

- Treat promptly with supportive care and/or corticosteroids as needed based on the grading and management guidelines.

Grading and Management of ICANS

Grade*,a	No Concurrent CRS[f]	Additional Therapy if Concurrent CRS
Grade 1 ICE[b] score 7–9 Or depressed level of consciousness[c]: Awakens spontaneously	• Supportive care	• IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg/dose)
Grade 2 ICE score 3–6 Or depressed level of consciousness: Awakens to voice	• Supportive care • 1 dose of IV dexamethasone 10 mg and reassess. May be repeated every 6–12 hours if no improvement[g]	• Anti-IL-6 therapy as per Grade 1[i] • Consider transferring patient to ICU if neurotoxicity associated with Grade ≥ 2 CRS
Grade 3[d] ICE score 0–2 Or depressed level of consciousness: Awakens only to tactile stimulus Or seizure: Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention Or elevated ICP/cerebral edema: Focal/local edema on neuroimaging[e]	• ICU care is recommended • IV dexamethasone 10 mg every 6 hours, or IV methylprednisolone 1 mg/kg every 12 hours • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent Grade ≥ 3 neurotoxicity	• Anti-IL-6 therapy as per Grade 1[i]
Grade 4[d] ICE score 0 (Patient is unconscious and unable to perform ICE) Or depressed level of consciousness: • Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse • Stupor or coma Or seizure: • Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between Or motor findings: • Deep focal motor weakness such as hemiparesis or paraparesis Or elevated ICP/cerebral edema: • Diffuse cerebral edema on neuroimaging; • Decerebrate or decorticate posturing; or • Cranial nerve VI palsy; or • Papilledema; or • Cushing's triad	• ICU care, consider mechanical ventilation for airway protection • High-dose steroids[h] • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent Grade ≥ 3 neurotoxicity • Treat convulsive status epilepticus per institutional guidelines	• Anti-IL-6 therapy as per Grade 1[i]

ICE: Immune Effector Cell Encephalopathy; EEG: Electroencephalogram; IV: Intravenous; IL-6: Interleukin-6; ICU; Intensive Care Unit; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; ECG: Electrocardiogram; ICP: Intracranial Pressure.

*Grading is based on the ASTCT standard (2019). The ICANS grades are determined by the highest level of events listed in the evaluation indicators that cannot be explained by other reasons (ICE score, consciousness level, epilepsy, abnormal motor ability, increased Intracranial pressure/brain edema).

a. Although not used for ICANS grading, other signs or symptoms that may occur and may be related to immune effector cell therapy, such as headache, tremor, myoclonus, inability to maintain fixed posture and hallucination still require attention and treatment.

b. In the ICE score, if one of the following tasks can be completed correctly, a score of 1 point (out of a total of 10 points) will be given: 1) Ability to tell the current year, month, city, and hospital (a total of 4 points); 2) Ability to name 3 objects, for example, a clock, pen, and button (3 points in total); 3) Ability to follow simple commands, for example, extending fingers or closing eyes and sticking out tongue (1 point in total); 4) Ability to write a standard sentence, for example, “The national language of Singapore is Malay” (1 point in total); 5) Count backwards from 100 by 10 (1 point in total).

c. Other reasons (e.g., use of sedatives) for decrease in consciousness level should be ruled out.

d. Patients should undergo assessment for papilledema or other signs of elevated intracranial pressure. If intracranial pressure is excluded, a diagnostic lumbar puncture may be considered for patients with Grade 3 – 4 neurotoxicity.

e. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to the CTCAE v5.0 standard.

f. The use of dexamethasone to prevent CRS may increase the risk of Grade 4 ICANS and persistent neurotoxicity.

g. For patients receiving corticosteroid treatment for CRS and/or neurotoxicity, preventive antifungal therapy is strongly recommended.

h. For example, methylprednisolone IV may be used for 3 days at a dose of 1g/day (which can be considered twice a day), and then quickly decreased to 250mg q12 for 2 days, 125mg q12 for 2 days, and 60mg q12 for 2 days.

i. Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.

3 Secondary Malignancies of T-cell Origin

- Although no secondary tumors have been found in patients receiving treatment with FUCASO, T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19- directed genetically modified autologous T cell immunotherapies.
- Mature T cell malignancies, including CAR positive tumors, may present as soon as weeks following infusion, and may include fatal outcomes.
- Patients must be monitored lifelong for secondary malignancies.
- In the event that a secondary malignancy of T-cell origin occurs, please contact Nanjing IASO Medical Technology Co., Ltd. at PV@iasobio.com to obtain instructions on collection of patient samples for testing.

Reporting of Adverse Reactions

- Reporting suspected adverse reactions is important as it allows continued monitoring of the benefit-risk balance of FUCASO.
- Adverse reactions associated with FUCASO can be reported to Nanjing IASO Medical Technology Co., Ltd. at PV@iasobio.com.
- Healthcare professionals are also encouraged to report adverse reactions to the Vigilance and Compliance Branch, Health Products Regulation Group, Health Sciences Authority online at https://www.hsa.gov.sg/adverse-events.

References

1. Singapore Package Insert for FUCASO suspension for infusion
2. Lee DW, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant 2019;25(4):625-638.
3. Ludwig H, et al. Prevention and management of adverse events during treatment with bispecific antibodies and CAR T cells in multiple myeloma: a consensus report of the European Myeloma Network. Lancet Oncol 2023;24(6): e255-e269.