STARTING YOUR PATIENTS ON

KYMRIAH™
(tisagenlecleucel) Suspension for IV infusion

The first FDA-approved CAR-T cell therapy for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

This guide will walk you through how to start your appropriate patients on KYMRIAH™ (tisagenlecleucel), so that you can begin coordinating care with a KYMRIAH Treatment Center.

IMPORTANT SAFETY INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

• Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab [see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.1)].

• Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed [see Warnings and Precautions (5.2)].

• KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS [see Warnings and Precautions (5.3)].

Please see additional Important Safety Information throughout. Please see full Prescribing Information for KYMRIAH, including Boxed WARNING, and Medication Guide.
Think KYMRIAH at the First Sign of Second Relapse

KYMRIAH is a prescription medication indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Consider KYMRIAH for pediatric and young adult patients with any of the following clinical characteristics:

- Have not gone into remission following frontline treatment (primary refractory)
- Have had relapse following second or subsequent complete remissions (post-chemotherapy)
- Have had relapse following hematopoietic stem cell transplant (HSCT)
- Have refractory disease or experienced a second or later relapse and are ineligible or not a candidate for HSCT

With KYMRIAH:

- Patients do not need to be in complete remission to receive treatment
- No donor is required

If you are considering a patient for KYMRIAH, contact a treatment center right away to discuss eligibility, current treatments, and next steps, as ongoing chemotherapy can lead to T-cell depletion, which may affect the quality of the final cell product.

The KYMRIAH Treatment Process

1. **Patient identification**
2. **Collection**
3. **Manufacturing**
4. **Lymphodepleting chemotherapy**
5. **Infusion**
6. **Short-term monitoring**
7. **Long-term monitoring**

KYMRIAH therapy is available at select treatment centers. Call KYMRIAH CARES or visit KYMRIAH-hcp.com for more information about KYMRIAH Treatment Centers, the ordering process, product information, and patient support. Contact the treatment center to discuss next steps such as insurance approval.

**Call or visit**

1-844-4KYMRIAH (1-844-459-6742)

KYMRIAH-hcp.com

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INDICATION

KYMRIAH is a CD19-directed genetically-modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

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• Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed [see Warnings and Precautions (5.2)].

• KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS [see Warnings and Precautions (5.3)].

Warnings and Precautions:

• Cytokine Release Syndrome: Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with KYMRIAH. In Study 1, CRS occurred in 79% (54/68) of patients receiving KYMRIAH, including Grade 3 or 4 (Penn grading system) CRS in 49% (33/68) patients. The median time to onset of CRS was 3 days (range: 1-22 days). Of the 54 patients with CRS, 27 (50%) received tocilizumab; 7 (13%) patients received two doses of tocilizumab, 3 (6%) patients received three doses of tocilizumab and 14 (26%) patients received addition of corticosteroids (e.g. methylprednisolone). The median time to resolution of CRS was 8 days (range: 1-36 days).

Key manifestations of CRS include high fever, lower than normal blood pressure, difficulty breathing, and may be associated with hepatic, renal, and cardiac dysfunction, and coagulopathy.

Risk factors for severe CRS are high pre-infusion tumor burden (greater than 50% blasts in bone marrow), uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy, active infections, and/or inflammatory processes.

Delay the infusion of KYMRIAH after lymphodepleting chemotherapy if the patient has unresolved serious adverse reactions from preceding chemotherapies (including pulmonary toxicity, cardiac toxicity, or hypotension), active uncontrolled infection, active graft versus host disease (GVHD), or worsening of leukemia burden [see Dosage and Administration (2.2)].

Ensure that tocilizumab is available on site prior to infusion of KYMRIAH. Monitor patients for signs or symptoms of CRS for at least 4 weeks after treatment with KYMRIAH. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time [see Patient Counseling Information (17)]. At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care, tocilizumab and/or corticosteroids as indicated [see Dosage and Administration (2.3)].

• Neurological Toxicities: Neurological toxicities, which may be severe or life-threatening can occur following treatment with KYMRIAH. The majority of neurological toxicities occurred within 8 weeks following KYMRIAH infusion. In Study 1, neurological toxicities within 8 weeks after KYMRIAH infusion occurred in 65% of patients, including Grade 3 or 4 neurological toxicities in 18% of patients, and 75% of events resolved within 12 days. The most common neurological toxicities were headache (37%), encephalopathy (34%), delirium (21%), anxiety (13%), and tremor (9%). Other manifestations of neurological toxicities included disturbances in consciousness,
disorientation, confusion, agitation, seizures, mutism and aphasia. Onset of neurological toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS.

Monitor patients for neurological events and exclude other causes for neurological symptoms. Provide supportive care as needed for KYMRIAH-associated neurological events.

**KYMRIAH REMS to Mitigate Cytokine Release Syndrome and Neurological Toxicities:** Because of the risk of CRS and neurological toxicities, KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS [see Boxed Warning and Warnings and Precautions (5.1, 5.2)]. The required components of the KYMRIAH REMS are:

— Healthcare facilities that dispense and administer KYMRIAH must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for administration within 2 hours after KYMRIAH infusion, if needed for treatment of CRS.

— Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer KYMRIAH are trained about the management of CRS and neurological toxicities.

Further information is available at www.kymriahtms.com or 1-844-4KYMRIAH.

**Hypersensitivity Reactions:** Allergic reactions may occur with infusion of KYMRIAH. Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO) or dextran 40 in KYMRIAH.

**Serious Infections:** Serious infections, including life-threatening or fatal infections, occurred in patients after KYMRIAH infusion. In Study 1, infections (all Grades) after KYMRIAH infusion occurred in 40 patients (59%), including 24 patients (35%) with Grade 3-4 infections and 2 patients (3%) with fatal infections. Infections with an unknown pathogen occurred in 41% of patients, viral infections in 26%, bacterial infections in 19%, and fungal infections in 13%. Prior to KYMRIAH infusion, infection prophylaxis should follow local guidelines. Monitor patients for signs and symptoms of infection after treatment with KYMRIAH and treat appropriately [see Dosage and Administration (2.3)].

Febrile neutropenia (Grade 3 or 4) was also observed in 37% of patients after KYMRIAH infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated.

**Viral Reactivation**
Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Hepatitis cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive, and also in patients who are HBsAg-negative but hepatitis B core antibody (anti-HBc) positive. HBV reactivation has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg-negative, anti-HBc-positive and hepatitis B surface antibody [anti-HBs] positive).

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur.

Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

**Prolonged Cytopenias:** Patients may exhibit cytopenias for several weeks following lymphodepleting
chemotherapy and KYMRIAH infusion. Grade 3 and 4 cytopenias not resolved by Day 28 following KYMRIAH treatment included neutropenia (40%) and thrombocytopenia (27%) among 52 responding patients. At 56 days following KYMRIAH, 17% and 12% of responding patients had grade 3 and 4 neutropenia or thrombocytopenia respectively. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly GM-CSF, are not recommended during the first 3 weeks after KYMRIAH infusion or until CRS has resolved.

• Hypogammaglobulinemia: Hypogammaglobulinemia and agammaglobulinemia (IgG) can occur in patients with a complete remission after KYMRIAH infusion. In Study 1, 43% of patients had hypogammaglobulinemia. B-cell aplasia is an on-target effect of KYMRIAH and therefore a patient may experience hypogammaglobulinemia for as long as KYMRIAH persists [see Clinical Pharmacology (12.3)].

Monitor immunoglobulin levels after treatment with KYMRIAH and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement standard guidelines.

The safety of immunization with live viral vaccines during or following KYMRIAH treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of lymphodepleting chemotherapy, during KYMRIAH treatment, and until immune recovery following treatment with KYMRIAH.

Pregnant women who have received KYMRIAH may have hypogammaglobulinemia. Assess immunoglobulin levels in newborns of mothers treated with KYMRIAH.

• Secondary Malignancies: Patients treated with KYMRIAH may develop secondary malignancies or recurrence of their leukemia. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Novartis Pharmaceuticals Corporation at 1-844-4KYMRIAH to obtain instructions on patient samples to collect for testing.

• Effects on Ability to Drive and Use Machines: Due to the potential for neurological events, including altered mental status or seizures, patients receiving KYMRIAH are at risk for altered or decreased consciousness or coordination in the 8 weeks following KYMRIAH infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

Adverse Reactions
The most common adverse reactions (incidence greater than 20%) are cytokine release syndrome, hypogammaglobulinemia, infections-pathogen unspecified, pyrexia, decreased appetite, headache, encephalopathy, bleeding, hypotension, tachycardia, nausea, diarrhea, vomiting, viral infection disorders, hypoxia, fatigue, acute kidney injury, and delirium [see Adverse Reactions (6)].

Drug Interactions
HIV and the lentivirus used to make KYMRIAH have limited short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid test (NAT) tests may yield false positive results in patients who have received KYMRIAH.

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