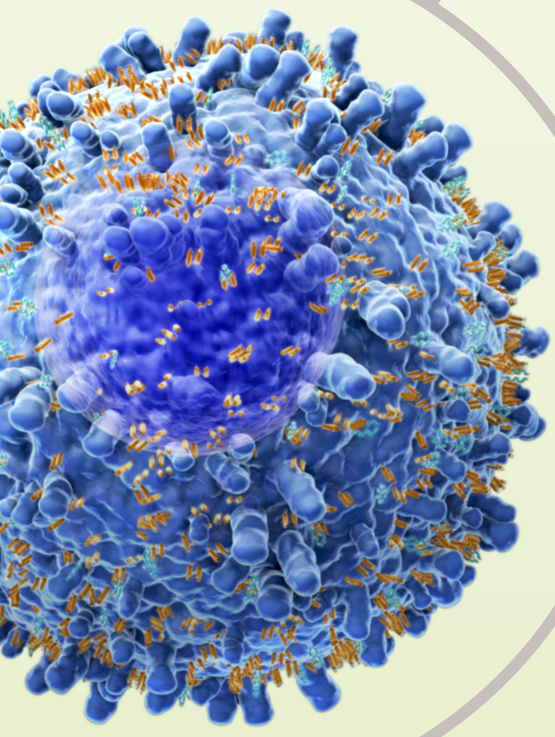
KYMRIAH® (tisagenlecleucel) Reference Guide

KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy

Tap or click each topic to learn more



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Please see Important Safety Information on pages 2 and 14-26.

Click here for full Prescribing Information, including Boxed WARNING, and Medication Guide.

KYMRIAH® (tisagenlecleucel) Suspension for IV infusion

KYMRIAH: Indications

The **first and only** CAR-T cell therapy with adult and pediatric FDA-approved indications

DLBCL

Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after 2 or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma

Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma

ALL

Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

Important Safety Information for KYMRIAH® (tisagenlecleucel)

WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGICAL TOXICITIES, and SECONDARY HEMATOLOGICAL MALIGNANCIES

- **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 or tocilizumab and corticosteroids**
- **Neurological toxicities, including severe or life-threatening reactions, occurred following treatment with KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. Provide supportive care and/or corticosteroids as needed**
- **T cell malignancies have occurred following treatment of hematological malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including KYMRIAH**

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CAR, chimeric antigen receptor; FDA, Food and Drug Administration.

Please see additional Important Safety Information on pages 14-26.
Click here for full Prescribing Information, including Boxed WARNING, and Medication Guide.

Patient Selection

KYMRIAH may be appropriate for adults with relapsed or refractory DLBCL who[1]:

- Have not gone into remission (refractory after second line of therapy)
- Have relapsed (after second line of chemotherapy or following autologous stem cell transplant [ASCT])
- Have challenges with stem cell collection after salvage chemotherapy
- Are ineligible or not a candidate for ASCT owing to inability to achieve complete response (CR) or are unlikely to achieve CR after salvage therapy

Note: Patients do not need to be in remission to receive KYMRIAH.

Click here for the DLBCL website for KYMRIAH

Information contained within this guide focuses on DLBCL. For information about ALL, please see the following website:

Click here for the ALL website for KYMRIAH

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Coordination of Care for KYMRIAH

Timely Collaboration

Certain therapies may impact the overall quality of your patient's T cells, which are used to manufacture KYMRIAH.[2] As soon as you consider KYMRIAH for eligible patients, reach out to a treatment center to:

- **Determine treatment eligibility**
- **Initiate treatment planning**

Click here to find a certified KYMRIAH Treatment Center

Settings of Care

KYMRIAH is FDA approved to be administered in both outpatient and inpatient settings[1]

Monitoring

Monitor patients daily during the first week following KYMRIAH infusion for signs and symptoms of CRS and neurologic toxicities

- Instruct patients to remain within proximity of a health care facility for at least 2 weeks following infusion
- Advise patients to avoid driving for at least 2 weeks following infusion

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Pivotal Trial Data

JULIET Study Design

A Pivotal Global Phase 2 Trial in r/r DLBCL

- JULIET is an open-label, multicenter, single-arm global trial[1,3,4]
- 27 sites in 10 countries across Europe, North America, Australia, and Asia

Patient Demographics (9.4-month analysis)

- Aged 22 to 76 years (median, 56 years)
- Progressive disease after ASCT or ineligible for transplant (49% underwent ASCT)

Key Inclusion/Exclusion Criteria

- Histologically confirmed DLBCL (78% DLBCL NOS, 22% tFL)
- ≥2 prior lines of therapy (median, 3)
- No prior anti-CD19 therapy or active CNS involvement

End Points:

- Primary: best ORR (CR+PR)*
- Key Secondary: DOR, PFS, OS, safety

Patient baseline characteristics were consistent across the Prescribing Information and updated analyses[1,3,4]

CNS, central nervous system; DOR, duration of response; IRC, independent review committee; NOS, not otherwise specified; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; tFL, transformed follicular lymphoma.

*IRC, response based on the Lugano Classification with a null hypothesis of ORR ≤20%.[1]

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DLBCL Pivotal Trial Data
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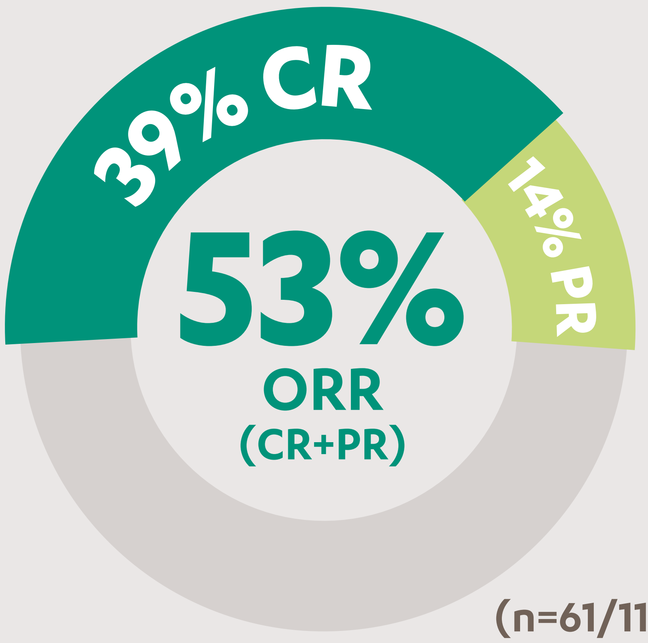
Primary End Point – Pivotal Trial

Overall Response Rates

KYMRIAH is a single infusion that delivers **strong efficacy with durable responses** in patients with relapsed or refractory DLBCL[5]

The majority of patients responded in the **JULIET 40.3-month** updated analysis[5]



(n=61/115)

Complete Response (CR) | Partial Response (PR) | Overall Response Rate (ORR)

JULIET 9.4-Month Prescribing Information Data[1]:

50% Overall Response Rate (n=34/68)
32% Complete Response (n=22/68)
18% Partial Response (n=12/68)

DLBCL Pivotal Trial Data
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Secondary End Points – Pivotal Trial

Progression-Free Survival (PFS)

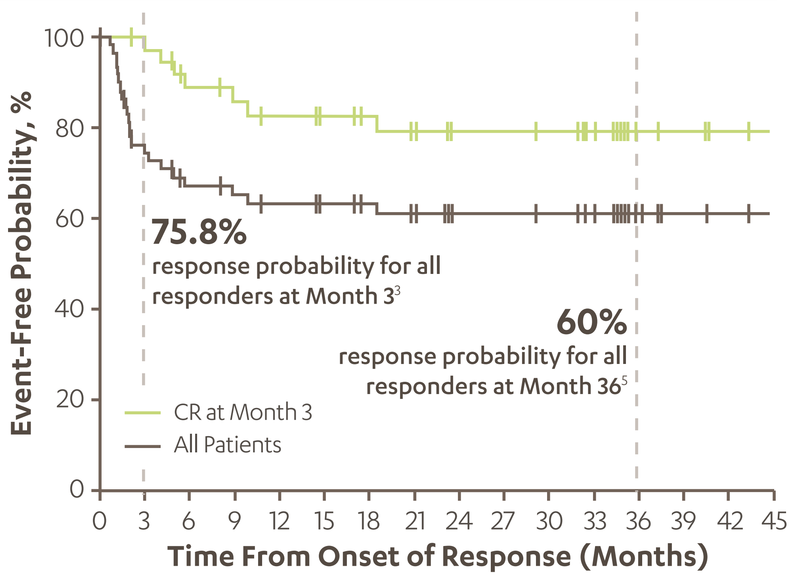
More than 60% of Patients who reached a complete response by Month 3 with KYMRIAH (n=37) were **progression-free at 3 years**[5]

- Median overall survival (OS) was not reached for patients in CR in the 40.3-month analysis[5]
- PFS and OS data should be interpreted with caution in a single-arm trial, as the statistical significance is unknown

Duration of Response (DOR)

KYMRIAH is a durable treatment with **60% of responding patients** still in response at 40.3 months[5]

JULIET 40.3 MONTHS[3,5]



No. of patients at risk

CR at Month 3	37	36	30	29	26	24	22	20	17	17	16	14	3	2	1	0
All Patients	61	42	35	34	31	29	27	25	21	21	20	18	5	2	1	0

- Median DOR was not reached in the 9.4-month Prescribing Information analysis[1,*]

*DOR for patients who achieved a PR was 3.4 months.[1]

Safety – Pivotal Trial

Cytokine Release Syndrome[a-c]

Longer-term data, 32.6 months (N=115)[3]

Median time to onset **3 days**

Median time to resolution **7 days**

	All Grades	Grades ≥3
Longer-term data, 32.6 months (N=115)[3]	**57%**	**23%**
Prescribing Information data, 26 months (N=115)[1,d]	74%	23%

The reported rates of cytokine release syndrome vary between the 32.6-month analysis and the USPI due to differences in the criteria and clinical manifestations by which they are defined

Key Signs and Symptoms[1]

Fever 85%

Hypoxia 35%

Hypotension 45%
Tachycardia 13%

Cytokine release syndrome may be associated with hepatic, renal, and cardiac dysfunction, and coagulopathy

[a]Cytokine release syndrome in JULIET was graded using the Penn Scale.[1]
[b]Confirm that at least two doses of tocilizumab are available on-site prior to infusion of KYMRIAH.[1]
[c]After getting KYMRIAH, patients should plan to stay close to a health care facility for at least 2 weeks[1]
[d]Median time from infusion to data cutoff of December 2018.[1]

Please see additional Important Safety Information on pages 2 and 14-26.
Click here for full Prescribing Information, including Boxed WARNING, and Medication Guide.

Safety – Pivotal Trial (continued)

Neurological Events[a]

Longer-term data, 32.6 months (N=115)[3]

Median time to first event: 6 days

Median duration: 13 days

	All Grades	Grades ≥3
Longer-term data, 32.6 months (N=115)[3]	**20%**	**11%**
Prescribing Information data, 26 months (N=115)[1]	60%	19%

After 32.6 months of follow-up, there were no deaths attributed to neurological events, and no fatal cases of cerebral edema have occurred[3]

The reported rates of neurological events vary between the 32.6-month analysis and the USPI due to differences in the criteria and clinical manifestations by which they are defined

Key Signs and Symptoms[1,*]

Headache 21%
Encephalopathy 16%

Peripheral neuropathy 12%

Dizziness 12%

Other neurological manifestations include anxiety, sleep disorders, tremor, peripheral neuropathy, seizures, mutism, and aphasia

[a]Neurological events were graded in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.[1,6]

*The most common neurological events observed in greater than 10% of patients.

Please see additional Important Safety Information on pages 2 and 14-26.
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Safety – Pivotal Trial (continued)

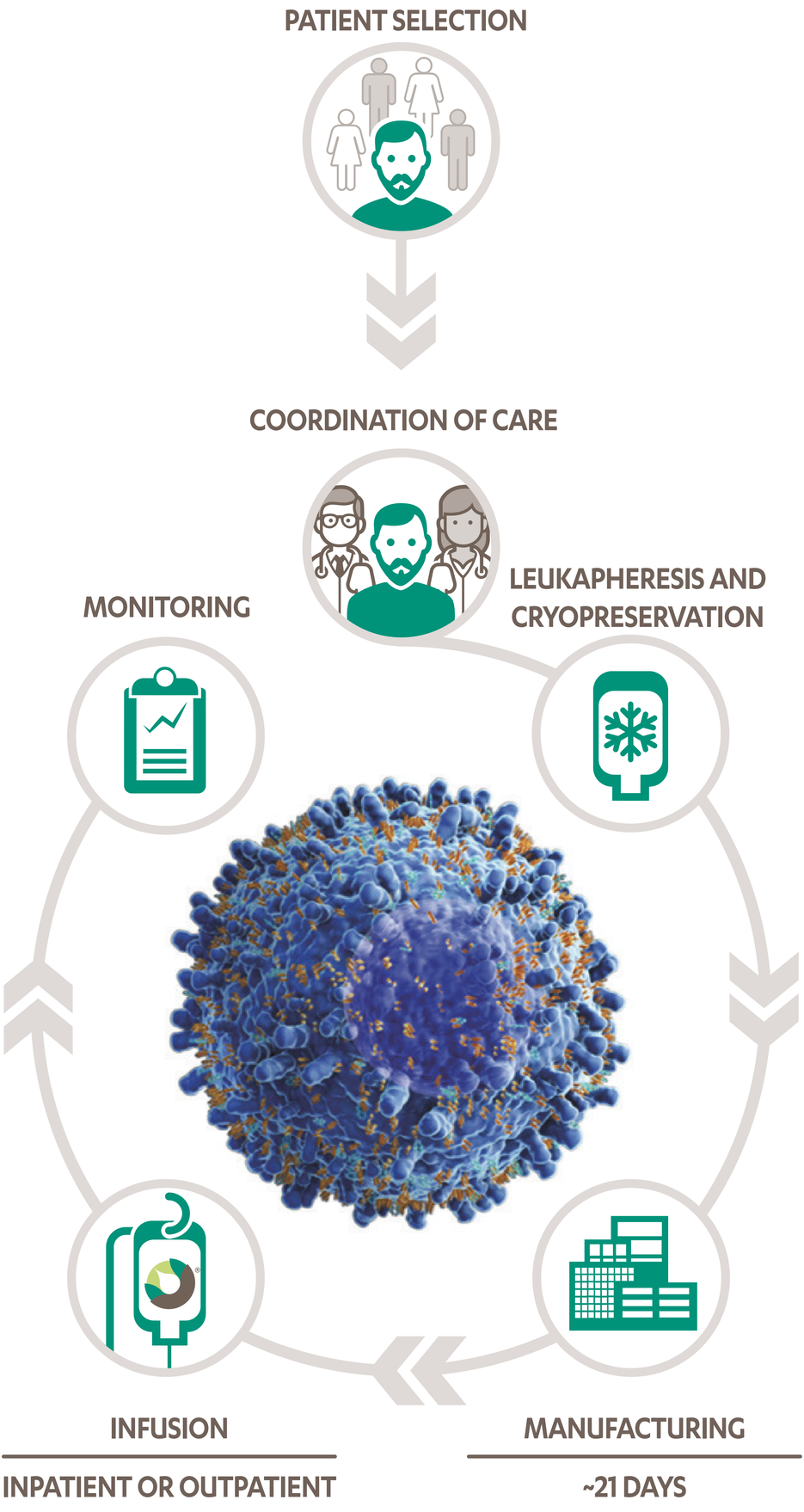
Safety Profile From the JULIET Trial

Adverse Reactions Reported in ≥10% of Adult Patients with r/r DLBCL[1]

Adverse Reaction		USPI: 26 Months (N=115)[1]	
		All grades, %	Grades ≥3, %
Blood and Lymphatic System Disorders	Febrile neutropenia	17	17
Cardiac Disorders	Tachycardia[a]	13	3
	Arrhythmia[a]	10	5
Gastrointestinal Disorders	Diarrhea	31	1
	Nausea	29	1
	Constipation	17	1
	Abdominal pain[a]	10	2
General Disorders and Administration Site Conditions	Fever	35	5
	Fatigue[a]	27	6
	Edema[a]	27	3
	Pain[a]	14	3
	Chills	12	0
Immune System Disorders	Cytokine release syndrome	74	23
	Hypogammaglobulinemia[a]	17	6
Infections and Infestations	Infections—pathogen unspecified	48	26
	Bacterial infectious disorders	17	8
	Fungal infectious disorders	11	5
	Viral infectious disorders	11	2
Investigations	Weight decreased	12	4
Metabolism and Nutrition Disorders	Decreased appetite	14	4
Musculoskeletal and Connective Tissue Disorders	Arthralgia	14	0
	Musculoskeletal pain[a]	13	1
Nervous System Disorders	Headache[a]	21	1
	Encephalopathy[b]	16	11
	Peripheral neuropathy[c]	12	3
	Dizziness[d]	12	2
Psychiatric Disorders	Anxiety	10	1
	Sleep disorder[a]	10	0
Renal and Urinary Disorders	Acute kidney injury[a]	17	6
Respiratory, Thoracic, and Mediastinal Disorders	Dyspnea[e]	21	6
	Cough[a]	17	0
Skin and Subcutaneous Tissue Disorders	Rash[a]	11	0
Vascular Disorders	Hypotension[a]	25	9
	Hemorrhages[a]	22	8

[a] Includes multiple related composite terms. [b] Encephalopathy includes cognitive disorder, confusional state, disturbance in attention, lethargy, mental status changes, somnolence, memory impairment, metabolic encephalopathy, and thinking abnormal. Encephalopathy is a dominant feature of immune effector cell–associated neurotoxicity syndrome (ICANS), along with other symptoms. [c] Peripheral neuropathy includes paraesthesia, hypoaesthesia, hyperaesthesia, peripheral sensory neuropathy, neuropathy peripheral, cranial nerve paralysis, demyelinating polyneuropathy, Horner's syndrome, polyneuropathy, and sciatica. [d] Dizziness includes dizziness, presyncope, and syncope. [e] Dyspnea includes dyspnea, dyspnea exertional, respiratory distress, and respiratory failure.

KYMRIAH: Process Overview[1,7,8]



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Guidance on Washout Timing[9]

IF PATIENT'S CONDITION AND DISEASE STATUS ALLOW

Recommendations for stopping these therapies at the following time points before leukapheresis:

- Alemtuzumab and ATG: Washout ≥6 months[a]
- Bendamustine and fludarabine: Washout ≥12 weeks[b]

8 weeks

- Clofarabine
- T cell lytic agents

14 days

- Systemic chemotherapy
- GVHD therapies (eg, calcineurin inhibitors)
- Imatinib
- Long-acting growth factors
- Dasatinib
- Ponatinib
- Blinatumomab[d]

5 days

- Short-acting growth factors
- Nilotinib

12 weeks

- Allogeneic cell therapy

4 weeks

- Donor lymphocyte infusion completed
- Pegylated asparaginase[c]

7 days

- Intrathecal methotrexate[e]
- Therapeutic doses of steroids (especially dexamethasone)
- Lenalidomide

3 days

- Short-acting cytotoxic/ antiproliferative drugs (eg, HU)

Leukapheresis and Cryopreservation

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WASHOUT
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Guidance on Washout Timing[9] (continued)

Vaccination with Live Vaccine[1,9]

Vaccination with live vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during KYMRIAH treatment, and until immune recovery following treatment with KYMRIAH

General Considerations

1. Adequate ALC and/or CD3+ count in peripheral blood prior to leukapheresis is recommended to avoid failure of T cell collection for CAR-T production
2. Washout of 5 half-lives is adequate for drug clearance, but effects of some drugs on T cells may persist after drug clearance
3. Effect of the drug/agent on T cell fitness and/or CD19 expression
4. Recommended drug washouts prior to leukapheresis are guidance only; patient's condition and disease status should also be considered when determining the washout timing

ALC, absolute lymphocyte count; ATG, anti-thymocyte globulin; GVHD, graft-versus-host disease; HU, hydroxyurea.

[a]Alemtuzumab and ATG (T cell lytic agents): Allow adequate washout and avoid use for ≥6 months prior to leukapheresis and consider the potential prolonged effects on T cells.
[b]For bendamustine and fludarabine, allow adequate washout and avoid use for ≥12 weeks prior to leukapheresis due to the potential long-term effects on T cells; however, there are limited data in the context of CAR-T cell therapy for these agents.
[c]In the CASSIOPEIA trial (NCT03876769) for pALL, the recommended washout period is 14 days.
[d]Although blinatumomab half-life is short (~2 hours), it is recommended to washout 1 to 2 weeks prior to leukapheresis.
[e]If indicated, intrathecal cytarabine can be given up to a day prior to leukapheresis. For an intravenous cytarabine dose <100 mg/m^2, a washout of 7 days is recommended; for a dose ≥100 mg/m^2, a washout of 14 days is recommended.

Please speak with your Novartis contact for the latest washout guidance and recommendations when determining patient readiness for KYMRIAH.

Important Safety Information for KYMRIAH® (tisagenlecleucel)

Warnings and Precautions

Cytokine Release Syndrome (CRS)

CRS, including fatal or life-threatening reactions, occurred following treatment with KYMRIAH.

- CRS occurred in 61 (77%) of the 79 pediatric and young adult patients with r/r ALL, including ≥ grade 3 (Penn Grading System) in 48% of patients. The median times to onset and resolution of CRS were 3 days (range: 1-22; 1 patient with onset after Day 10) and 8 days (range: 1-36), respectively. Of the 61 patients with CRS, 31 (51%) received tocilizumab. Ten (16%) patients received 2 doses of tocilizumab and 3 (5%) patients received 3 doses of tocilizumab; 17 (28%) patients received addition of corticosteroids (e.g., methylprednisolone).
- CRS occurred in 85 (74%) of the 115 adult patients with r/r DLBCL receiving KYMRIAH, including ≥ grade 3 (Penn Grading System) in 23% of patients. The median times to onset and resolution of CRS were 3 days (range: 1-51; 1 patient with onset after Day 10) and 7 days (range: 2-30), respectively. Of the 85 patients with CRS, 19 (22%) received systemic tocilizumab or corticosteroids. Seven (8%) patients received a single dose of tocilizumab and 11 (13%) patients received 2 doses of tocilizumab; 11 (13%) patients received corticosteroids in addition to tocilizumab. One patient received corticosteroids for CRS without concomitant tocilizumab, and 2 patients received corticosteroids for persistent neurotoxicity after resolution of CRS.

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Please see additional Important Safety Information on pages 2 and 14-26.
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Important Safety Information for KYMRIAH® (tisagenlecleucel)

Cytokine Release Syndrome (continued)

- Five deaths occurred within 30 days of KYMRIAH infusion.
- One patient with r/r ALL died with CRS and progressive leukemia, and 1 patient had resolving CRS with abdominal compartment syndrome, coagulopathy, and renal failure when an intracranial hemorrhage occurred.
- Of the 3 patients with r/r DLBCL who died within 30 days of infusion, all had a history of CRS in the setting of stable to progressive underlying disease, 1 of whom developed bowel necrosis.
- Among patients with CRS, key manifestations included fever (93% r/r ALL; 85% r/r DLBCL), hypotension (69% r/r ALL; 45% r/r DLBCL), hypoxia (57% r/r ALL; 35% r/r DLBCL), and tachycardia (26% r/r ALL; 13% r/r DLBCL). CRS may be associated with hepatic, renal, and cardiac dysfunction; and coagulopathy.
- Delay KYMRIAH infusion after lymphodepleting chemotherapy if patient has unresolved serious adverse reactions from preceding chemotherapies, active uncontrolled infection, active graft vs host disease, or worsening of leukemia burden.
- Risk factors for severe CRS in the r/r ALL population are high pre-infusion tumor burden (>50% blasts in bone marrow), uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy, active infections, and/or inflammatory processes.

CRS
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Please see additional Important Safety Information on pages 2 and 14-26.
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Important Safety Information for KYMRIAH® (tisagenlecleucel)

Cytokine Release Syndrome (continued)

- Confirm that a minimum of 2 doses of tocilizumab are available on-site prior to infusion of KYMRIAH. Monitor patients daily during the first week following KYMRIAH infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for at least 2 weeks after treatment with KYMRIAH.
- At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care, tocilizumab, and/or corticosteroids as indicated.
- Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time.

Please see additional Important Safety Information on pages 2 and 14-26.
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Important Safety Information for KYMRIAH® (tisagenlecleucel)

Neurological Toxicities

- Neurological toxicities, including severe or life-threatening reactions, occurred in 56 (71%) of the 79 patients with r/r ALL and 69 (60%) of the 115 patients with r/r DLBCL following treatment with KYMRIAH, including ≥ grade 3 in 22% of patients with r/r ALL and 19% of patients with r/r DLBCL.
- Among patients who had a neurological toxicity, 84% occurred within 8 weeks following KYMRIAH infusion.
- Median time to the first event was 6 days from infusion (range: 1-301) for patients with r/r ALL and 5 days (range: 1-368) for patients with r/r DLBCL. The median duration was 7 days for patients with r/r ALL and 17 days for patients with r/r DLBCL. Resolution occurred within 3 weeks in 71% of patients with r/r ALL and 50% of patients with r/r DLBCL.
- Encephalopathy lasting up to 70 days was noted. The onset of neurological toxicity can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

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Important Safety Information for KYMRIAH® (tisagenlecleucel)

Neurological Toxicities (continued)

- The most common neurological toxicities observed with KYMRIAH included headache (35% r/r ALL; 21% r/r DLBCL), encephalopathy (30% r/r ALL; 16% r/r DLBCL), delirium (19% r/r ALL; 5% r/r DLBCL), anxiety (16% r/r ALL; 10% r/r DLBCL), sleep disorders (11% r/r ALL; 10% r/r DLBCL), dizziness (5% r/r ALL; 12% r/r DLBCL), tremor (8% r/r ALL; 6% r/r DLBCL), and peripheral neuropathy (4% r/r ALL; 12% r/r DLBCL). Other manifestations included seizures and aphasia.
- Monitor patients daily during the first week following KYMRIAH infusion for signs and symptoms of neurological toxicities. Rule out other causes of neurological symptoms. Monitor patients for signs or symptoms of neurological toxicities for at least 2 weeks after infusion and treat promptly. Neurological toxicity should be managed with supportive care and/or corticosteroids as needed. Advise patients to avoid driving for at least 2 weeks following infusion.
- Counsel patients to seek immediate medical attention should signs or symptoms of neurological toxicity occur at any time.

Please see additional Important Safety Information on pages 2 and 14-26.
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Important Safety Information for KYMRIAH® (tisagenlecleucel)

Hemophagocytic Lymphohistiocytosis (HLH)/ Macrophage Activation Syndrome (MAS)

HLH/MAS, which can be life-threatening or fatal, has occurred following treatment with KYMRIAH.

- HLH was reported in 6% (5/79) of patients with r/r ALL (time to onset ranged from 3 to 18 days) and 2% (2/115) of patients with r/r DLBCL (times to onset were Day 7 and Day 10); all HLH events occurred during ongoing CRS and resolved.
- Treatment of HLH should be administered per institutional standards.

Hypersensitivity Reactions

Hypersensitivity reactions may occur with KYMRIAH.

- Serious hypersensitivity reactions, including anaphylaxis, may be due to dimethyl sulfoxide or dextran 40 in KYMRIAH.
- Observe patients for hypersensitivity reactions during and after the infusion.

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Important Safety Information for KYMRIAH® (tisagenlecleucel)

Serious Infections

Infections, including life-threatening or fatal infections, occurred in 57 (72%) of the 79 patients with r/r ALL:

- 38 patients (48%) experienced ≥ grade 3 infections, including fatal infections in 2 patients (3%) and in 67 (58%) of the 115 patients with r/r DLBCL.
- 38 patients (33%) experienced ≥ grade 3 infections, including fatal infection in 1 patient (1%).
- Prior to KYMRIAH infusion, infection prophylaxis should follow local guidelines.
- Patients with active uncontrolled infection should not start KYMRIAH treatment until the infection is resolved.
- Monitor patients for signs and symptoms of infection after treatment with KYMRIAH and treat appropriately.
- Febrile neutropenia (≥ grade 3) was also observed in 34% of patients with r/r ALL and 17% of patients with r/r DLBCL 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.

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Please see additional Important Safety Information on pages 2 and 14-26.
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Important Safety Information for KYMRIAH® (tisagenlecleucel)

Serious Infections (continued)

- In immunosuppressed patients, opportunistic fatal infections of the central nervous system including progressive multifocal leukoencephalopathy due to John Cunningham virus reactivation have occurred after KYMRIAH administration. Perform appropriate diagnostic evaluations in patients with neurological adverse events.
- 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.
- There is no experience with manufacturing KYMRIAH for patients with a positive test for HIV or with active HBV or active hepatitis C virus (HCV).

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

Summary of HBV Testing and Eligibility for Manufacturing[8,a,b]

Test Type	Results				
HBsAG	+	–	–	–	–
HBcAB	Any	+	+	–	–
HBsAB	Any	–	+	+	–
Manufacturing Eligibility	Not eligible	Not eligible	Eligible	Eligible	Eligible

NAT, nucleic acid test.

[a]Follow institutional procedures for testing and retesting; NAT is an appropriate confirmatory test.
[b]Novartis considers NAT results as confirmatory. Negative NAT results would supersede any serologic test results, and leukapheresis would be eligible for manufacturing.

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Important Safety Information for KYMRIAH® (tisagenlecleucel)

Prolonged Cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and KYMRIAH infusion. In patients with r/r ALL, ≥ grade 3 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 neutropenia or thrombocytopenia, respectively. In patients with r/r DLBCL, ≥ grade 3 cytopenias not resolved by Day 28 following KYMRIAH treatment included thrombocytopenia (39%) and neutropenia (25%) among 115 treated patients.

- Prolonged neutropenia has been associated with increased risk of infection.

	JULIET N=115 (%)	ELIANA[a] N=52 (%)	
Grade ≥3	**Day 28**	**Day 28**	**Day 56**
Prolonged neutropenia	25	40	17
Prolonged thrombocytopenia	39	27	12

- Cytopenia: A deficiency or lack of cellular elements in the circulating blood.[10]

Cytopenias Should Be Managed per Local Guidelines

Myeloid growth factors, particularly granulocyte-macrophage colony-stimulating factor, are not recommended during the first 3 weeks after KYMRIAH infusion or until CRS has resolved.

[a]ELIANA is the pivotal global, phase 2 trial of KYMRIAH in patients up to 25 years of age with relapsed or refractory ALL.[1]

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Important Safety Information for KYMRIAH® (tisagenlecleucel)

Hypogammaglobulinemia

Hypogammaglobulinemia and agammaglobulinemia related to B-cell aplasia can occur in patients after KYMRIAH infusion.

- Hypogammaglobulinemia was reported in 53% of patients with r/r ALL and 17% of patients with r/r DLBCL.
- Monitor immunoglobulin levels after treatment with KYMRIAH and manage using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement standard guidelines.

B-Cell Aplasia[10]

B cells produce antibodies or immunoglobulins. B-cell aplasia, a decrease in the number of or the absence of B cells, results in:

- Hypogammaglobulinemia
  Decreased quantity of immunoglobulins
- Agammaglobulinemia
  Absence or extremely low levels of immunoglobulins

- The safety of immunization with live vaccines during or following KYMRIAH treatment has not been studied.
- Vaccination with live vaccines is not recommended for at least 6 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.

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Important Safety Information for KYMRIAH® (tisagenlecleucel)

Secondary Malignancies

- Patients treated with KYMRIAH may develop secondary malignancies or recurrence of their cancer. T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including KYMRIAH. Mature T cell malignancies, including CAR-positive tumors, may present as soon as weeks following infusion and may include fatal outcomes.
- 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.

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 tests may yield false positive results in patients who have received KYMRIAH.

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Important Safety Information for KYMRIAH® (tisagenlecleucel)

Pregnancy, Lactation, Females and Males of Reproductive Potential

- No data are available of KYMRIAH use in pregnant or lactating women. Therefore, KYMRIAH is not recommended for women who are pregnant or breastfeeding. A risk to the breastfed infant cannot be excluded.
- Pregnancy after KYMRIAH administration should be discussed with the treating physician. Pregnancy status of females of reproductive potential should be verified with a pregnancy test prior to starting treatment with KYMRIAH.
- Report pregnancies to Novartis Pharmaceuticals Corporation at 1-888-669-6682.

BACK

PREGNANCY AND ADVERSE REACTIONS 1 OF 2

Please see additional Important Safety Information on pages 2 and 14-26.
Click here for full Prescribing Information, including Boxed WARNING, and Medication Guide.

Important Safety Information for KYMRIAH® (tisagenlecleucel)

Adverse Reactions

- The most common adverse reactions (>20%) reported in patients with r/r ALL were CRS, infections-pathogen unspecified, hypogammaglobulinemia, fever, decreased appetite, viral infectious disorders, headache, febrile neutropenia, hemorrhage, musculoskeletal pain, vomiting, encephalopathy, diarrhea, hypotension, cough, nausea, bacterial infectious disorders, pain, hypoxia, tachycardia, edema, fatigue, and acute kidney injury.
- The most common adverse reactions (>20%) reported in patients with r/r DLBCL were CRS, infections-pathogen unspecified, fever, diarrhea, nausea, fatigue, hypotension, edema, hemorrhage, dyspnea, and headache.

Click here for full Prescribing Information for KYMRIAH, including Boxed WARNING, and Medication Guide.

For more information, go to www.KYMRIAH-hcp.com or call 1-844-4KYMRIAH (1-844-459-6742)

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