BREAKFREE
FROM THE CYCLE

A SINGLE INFUSION. A CHANCE AT LASTING REMISSION.

Indication

KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of systemic therapy.

This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

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, 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**
- **T cell malignancies have occurred following treatment of hematological malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including KYMRIAH**
- **KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS**

KYMRIAH® (tisagenlecleucel) Suspension for IV infusion

Please see additional Important Safety Information on pages 5-6.

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

KYMRIAH is a single infusion that delivered strong efficacy with durable responses in adult patients with r/r FL[1,2]

KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) after two or more lines of systemic therapy.[1]

This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).[1]

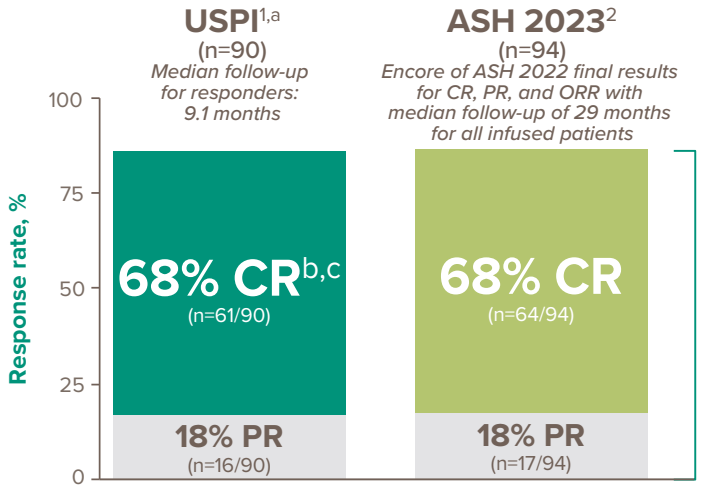
ELARA is an open-label, single-arm, global, phase 2 trial of tisagenlecleucel in 97 adults with r/r FL after ≥2 treatment lines or who relapsed after autologous stem-cell transplant[1,2]

Primary end point

- CRR based on best response by IRC (Lugano 2014 classification)

Secondary end points

- ORR, DOR, PFS, OS, safety, cellular kinetics

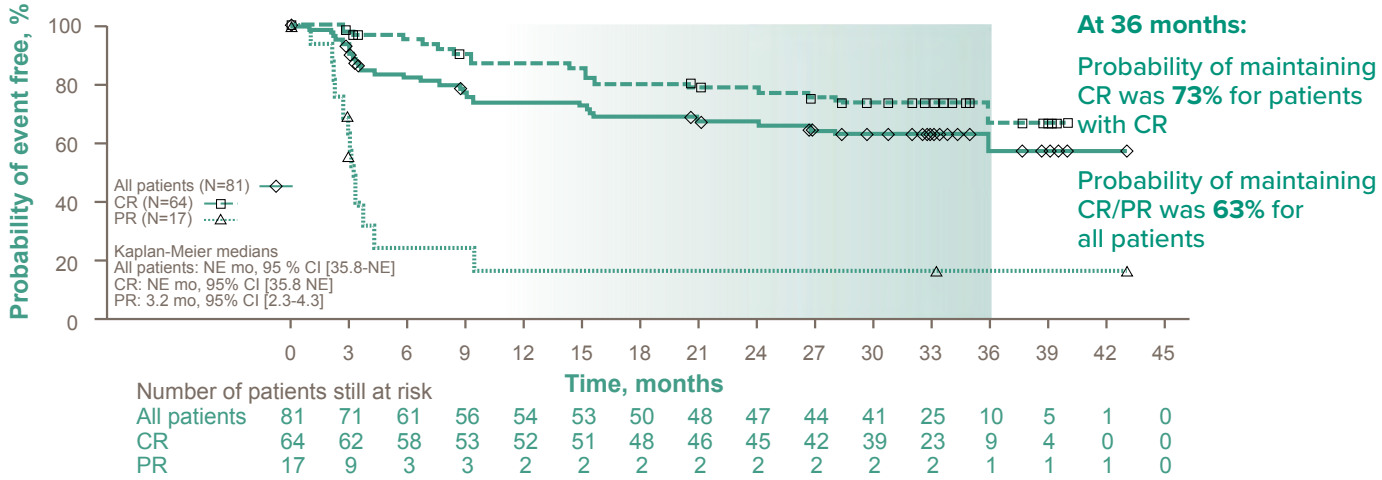


ASH, American Society of Hematology; CR, complete response; CRR, complete response rate; CRS, cytokine release syndrome; DOR, duration of response; FL, follicular lymphoma; IRC, Independent Review Committee; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; r/r, relapsed/refractory; USPI, US Prescribing Information.

[a]This included the first 90 patients with measurable disease who received KYMRIAH consecutively and had at least 9 months' follow-up from first objective response or discontinued earlier.[1] [b]Two patients with best overall response of CR had their disease relapse more than 6 months after the last line of therapy.[1] [c]Of the 30 patients who initially achieved a PR, 14 patients (47%) converted to a CR, including 10 patients at the next subsequent visit and within 6 months post infusion.[1]

KYMRIAH is a durable treatment, with an estimated 73% of patients with a CR still in response at 3 years[2]

Duration of Response (N=81)



Number of patients still at risk

All patients	81	71	61	56	54	53	50	48	47	44	41	25	10	5	1	0
CR	64	62	58	53	52	51	48	46	45	42	39	23	9	4	0	0
PR	17	9	3	3	2	2	2	2	2	2	2	2	1	1	1	0

ELARA Study (ASH 2023)

- 54% of patients were still in response at data cutoff with a median follow-up of 41 months[2]
- In the USPI with 9.1 months of follow-up for responders in ELARA, median DOR was not reached[1,*]

*The first disease assessment was scheduled to be performed at Month 3 post infusion. The median follow-up is the time from first objective response to last disease assessment.[1]

Please see Important Safety Information on pages 5-6.
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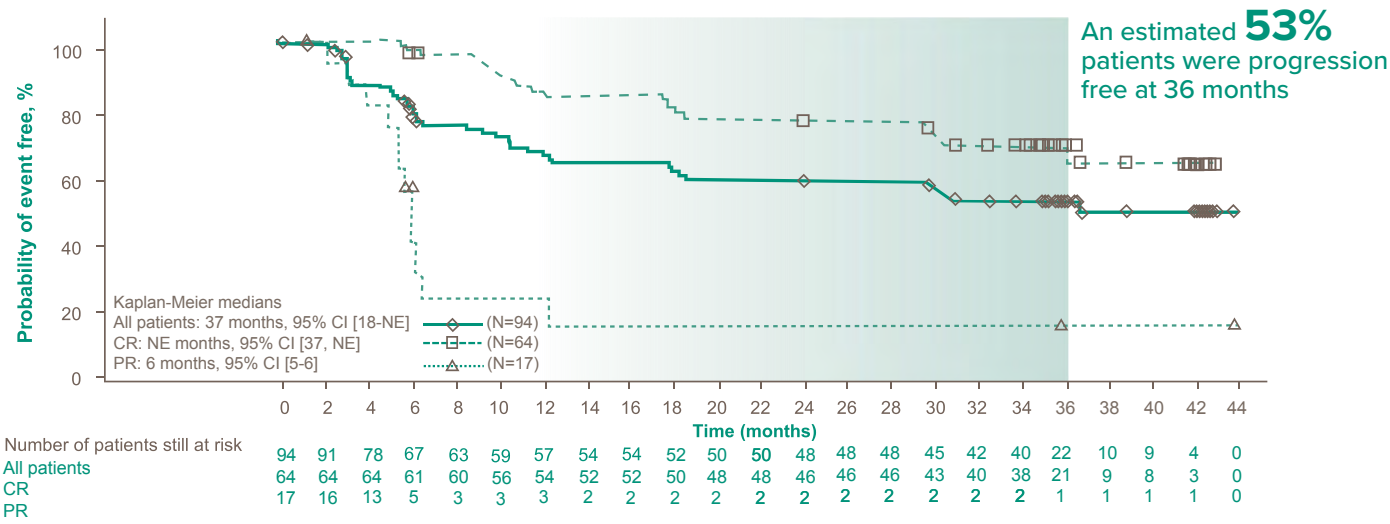
KYMRIAH is a single infusion that delivered strong efficacy with durable responses in adult patients with r/r FL[1,2] (continued)

An estimated 53% of patients treated with KYMRIAH were progression free at 36 months[2]

Progression-Free Survival (N=94)



ELARA Study (ASH 2023)

Overall Survival (N=94)

An estimated 82% of patients treated with KYMRIAH were still alive 36 months after infusion[2]

Time to Next Anti-Lymphoma Treatment (N=94)

65% probability of patients having not started a new anti-lymphoma therapy 36 months after infusion[2]

With a median follow-up of 41 months, median OS and median time to start of next anti-lymphoma treatment were not reached.[2]

PFS and OS data should be interpreted with caution in a single-arm trial as the statistical significance is unknown.

Time to next anti-lymphoma treatment was an exploratory end point in the ELARA trial and should be interpreted with caution.[4]

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KYMRIAH demonstrated a well-characterized safety profile[1,2]

Nearly all CRS events observed in the ELARA study occurred within the first 8 weeks post infusion[3]

The most common adverse reactions (incidence >20%) were CRS, infections-pathogens unspecified, fatigue, musculoskeletal pain, headache, and diarrhea[1]

Cytokine Release Syndrome[1,2]

ELARA[1,2] — **Lee Grading Scale**[1,2]

Data cut:		All grades, %	Grade ≥3, %
ASH 2023: 41 months[2]	N=97	**50**	**1**
USPI: 21 months[1,5]	N=97	**53**	**0**

USPI: 21 months[1] — N=97

4 days — Median time to onset (range, 1-14)

4 days — Median time to resolution (range, 1-13)

Ensure that at least 2 doses of tocilizumab are available on site prior to infusion of KYMRIAH[1]

Of the 51 patients who had CRS[1]

- 15 (29%) received systemic tocilizumab
- 2 (4%) received corticosteroids in addition to tocilizumab

Key manifestations of CRS[1]

May include:

- Fever
- Hypoxia
- Hypotension
- Tachycardia

May be associated with:

- Hepatic, renal, and cardiac dysfunction
- Coagulopathy

CRS management in ELARA allowed for the use of tocilizumab and corticosteroids as early as grade 2[1,6]

- In ELARA, all CRS events resolved with appropriate management[4,7]

Rates of NEs in ELARA were mainly grade 1 or 2[1,3]

Neurological Events[1,3]

ELARA[1,3]

Data cut:		All grades, %	Grade ≥3, %
ASH 2022*: 29 months[3]	N=97	**8**	**2**
USPI: 21 months[1,5]	N=97	**43**	**6**

USPI: 21 months[1] — N=97

8 days — Median time to first event (range, 1-345)

5 days — Median duration (range, NR)

The most common NE observed with KYMRIAH was headache (25%)[1]

The reported rates of NEs vary between the ASH 2022 analysis and the USPI due to differences in the criteria and clinical manifestations by which they are defined

***The 29-month analysis (ASH 2022) reported the rate of serious NEs. These NEs included: encephalopathy, dyskinesia, muscular weakness, and tremor, but excluded headache[3]**

Onset of NEs can be concurrent with CRS, following resolution of CRS, or in the absence of CRS[1]

Key manifestations of NEs may include[1]:

- Headache
- Encephalopathy
- Delirium
- Anxiety
- Sleep disorders
- Dizziness
- Tremor
- Peripheral neuropathy
- Seizures
- Aphasia

The majority of the NEs related to KYMRIAH required no specific protocol-defined intervention other than supportive care[4]

- All NEs resolved with appropriate management[6]

ASH, American Society of Hematology; CAR, chimeric antigen receptor; CCR, C-C chemokine receptor; CD, cluster of differentiation; C_{max}, peak transgene concentration; CR, complete response; CRR, complete response rate; CRS, cytokine release syndrome; CV%, coefficient of variation percentage; DOR, duration of response; FL, follicular lymphoma; IRC, Independent Review Committee; NE, not estimable; NEs, neurological events; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POD24, progression of disease within 2 years of frontline systemic therapy; PR, partial response; r/r, relapsed/refractory; T_{max}, time to peak transgene concentration; USPI, US Prescribing Information.

References: 1. Kymriah Prescribing information. Novartis Pharmaceuticals Corp. **2.** Schuster SJ et al. Presented at: 65th American Society of Hematology Annual Meeting; December 9-12, 2023; San Diego, CA. Abstract 601. **3.** Dreyling M et al. Presented at: 64th American Society of Hematology Annual Meeting; December 10-13, 2022; New Orleans, LA. Abstract 608. **4.** Data on file CCTL019E2202. Novartis Pharmaceuticals Corp; July 2021. **5.** Data on File. Internal Communication 2022. Novartis Pharmaceuticals Corp. **6.** Lee DW et al. *Blood.* 2014;124(2)188-195. **7.** Schuster SJ et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 4-8, 2021; Chicago, IL. Abstract 7508.

Please see Important Safety Information on pages 5-6.

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Important Safety Information (continued)

Warnings and Precautions

Cytokine Release Syndrome: CRS, including fatal or life-threatening reactions, occurred following treatment with KYMRIAH. CRS occurred in 51 (53%) of the 97 adult patients with r/r FL receiving KYMRIAH. The median times to onset and resolution of CRS were 4 days (range: 1-14) and 4 days (range: 1-13), respectively. Of the 51 patients with CRS, 15 (29%) received systemic anticytokine treatment with tocilizumab. Three (6%) patients required 3 doses of tocilizumab, 4 (8%) patients required 2 doses, and 8 (16%) patients required a single dose of tocilizumab. Two (4%) patients received corticosteroids in addition to tocilizumab.

Among patients with r/r FL with CRS, key manifestations included fever (92%), hypotension (40%), hypoxia (19%), and tachycardia (2%). 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.

Ensure that a minimum of 2 doses of tocilizumab are available on-site prior to infusion of KYMRIAH. Monitor patients 2 to 3 times during the first week following KYMRIAH infusion at the REMS-certified health care facility for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for at least 4 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.

Neurological Toxicities: Neurological toxicities, including severe or life-threatening reactions, occurred following treatment with KYMRIAH. Neurological toxicities occurred in 42 (43%) of the 97 patients with r/r FL, including ≥ grade 3 in 6%. The median times to the first event and duration were 8 days (range: 1-345) and 5 days, respectively.

Among KYMRIAH patients who had a neurological toxicity, 84% occurred within 8 weeks following KYMRIAH infusion. Resolution occurred within 3 weeks in 74% of patients with r/r FL.

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.

The most common neurological toxicities observed in patients with r/r FL included headache (25%), encephalopathy (3%), delirium (1%), anxiety (2%), sleep disorders (6%), dizziness (8%), tremor (3%), and peripheral neuropathy (7%). Other manifestations included seizures and aphasia.

Monitor patients 2 to 3 times during the first week following KYMRIAH infusion at the REMS-certified health care facility 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 4 weeks after infusion and treat promptly. Neurological toxicity should be managed with supportive care and/or corticosteroids as needed.

Counsel patients to seek immediate medical attention should signs or symptoms of neurological toxicity occur at any time.

KYMRIAH REMS to Mitigate CRS 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. The required components of the KYMRIAH REMS are:

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

Further information is available at www.kymriah-rems.com or 1-844-4KYMRIAH (1-844-459-6742).

Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS): HLH/MAS, which can be life-threatening or fatal, has occurred following treatment with KYMRIAH. One patient (1%) with r/r FL developed HLH with a fatal outcome > 1 year after receiving KYMRIAH. The patient did not have CRS during or immediately preceding HLH. Treatment of HLH should be administered as per institutional standards.

Hypersensitivity Reactions: Allergic 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 the infusion.

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

Important Safety Information (continued)

Serious Infections: Infections, including life-threatening or fatal infections, occurred in 50 (52%) of the 97 patients with r/r FL; 20 patients (21%) 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 13% of patients with r/r FL 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.

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.

Prolonged Cytopenias: Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and KYMRIAH infusion. In patients with r/r FL, ≥ grade 3 cytopenias not resolved by Day 28 following KYMRIAH treatment included thrombocytopenia (17%) and neutropenia (16%) among 97 treated patients. Prolonged neutropenia has been associated with increased risk of infection. 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.

Hypogammaglobulinemia: Hypogammaglobulinemia and agammaglobulinemia related to B-cell aplasia can occur in patients after KYMRIAH infusion. Hypogammaglobulinemia was reported in 18% of patients with r/r FL. 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 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.

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.

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 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.

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.

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.

Adverse Reactions

The most common adverse reactions (>20%) reported in patients with r/r FL were CRS, infections-pathogen unspecified, fatigue, musculoskeletal pain, headache, and diarrhea.

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

NOVARTIS

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