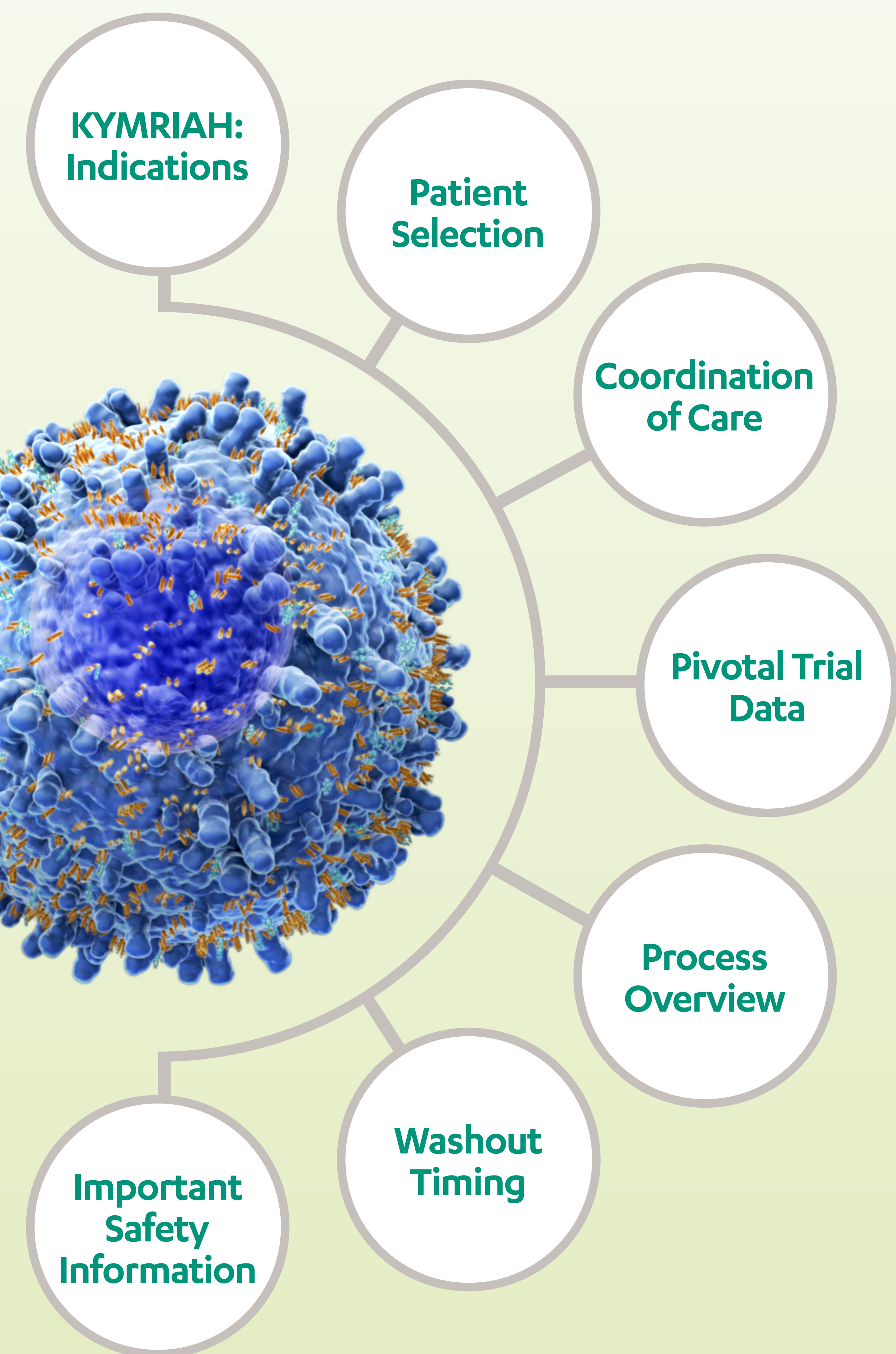


# KYMRIAH<sup>®</sup> (tisagenlecleucel) Reference Guide

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

Tap or click each topic to learn more



Please see Important Safety Information on [pages 2](#) and [14-27](#).

[Click here](#) for full Prescribing Information, including Boxed WARNING, and Medication Guide.





# 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, 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

NEXT



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

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## Patient Selection



**KYMRIAH may be appropriate for adults with relapsed or refractory DLBCL who<sup>1</sup>:**

- 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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Please see additional Important Safety Information on [pages 2](#) and [14-27](#).

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# Coordination of Care for KYMRIA<sup>®</sup>H



## Timely Collaboration

Certain therapies may impact the overall quality of your patient's T cells, which are used to manufacture KYMRIA<sup>®</sup>H.<sup>2</sup> As soon as you consider KYMRIA<sup>®</sup>H for eligible patients, reach out to a treatment center to:

- 🔹 Determine treatment eligibility
- 🔹 Initiate treatment planning

[Click here to find a certified  
KYMRIA<sup>®</sup>H Treatment Center](#)



## Settings of Care

KYMRIA<sup>®</sup>H is FDA approved to be administered in both outpatient and inpatient settings<sup>1</sup>



## Monitoring

After getting KYMRIA<sup>®</sup>H, patients should plan to stay within 2 hours of the location where they receive their treatment for at least 4 weeks<sup>1</sup>

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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<sup>1,3,4</sup>
- 27 sites in 10 countries across Europe, North America, Australia, and Asia

### Patient Demographics (9.4-month analysis)

- Aged 22-76 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<sup>1,3,4</sup>**

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%.<sup>1</sup>

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DLBCL Pivotal Trial Data

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Please see additional Important Safety Information on [pages 2 and 14-27](#).

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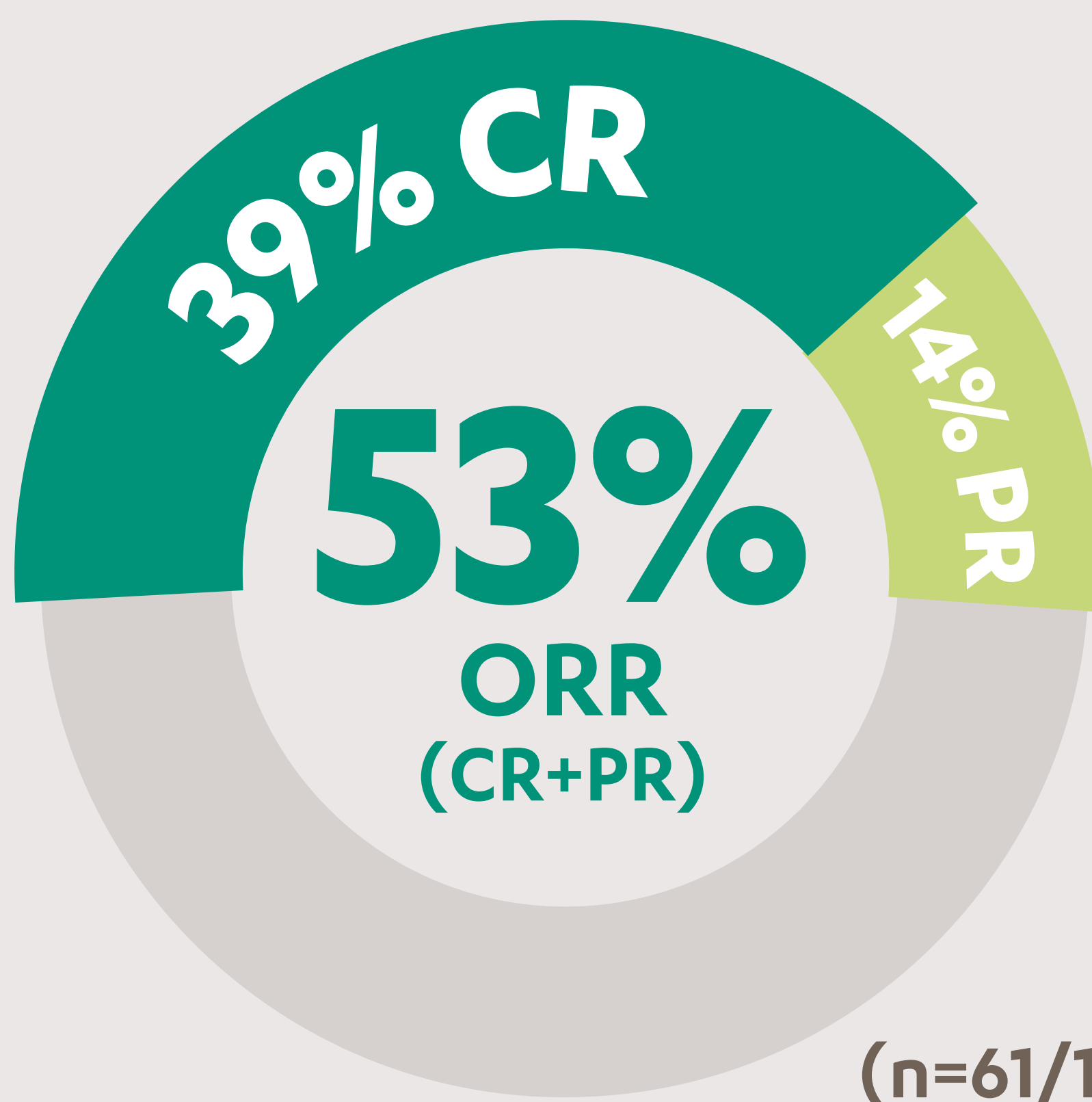
## Primary End Point - Pivotal Trial



### Overall Response Rates

KYMRIAH is a single infusion that delivers **strong efficacy with durable responses** in patients with relapsed or refractory DLBCL<sup>5</sup>

The majority of patients responded in the **JULIET 40.3-month** updated analysis<sup>5</sup>



● Complete Response (CR)

● Partial Response (PR)

● + ● Overall Response Rate (ORR)

### JULIET 9.4-Month Prescribing Information Data<sup>1</sup>:

**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 KYMRIA<sup>®</sup> (n=37) were **progression-free at 3 years<sup>5</sup>**

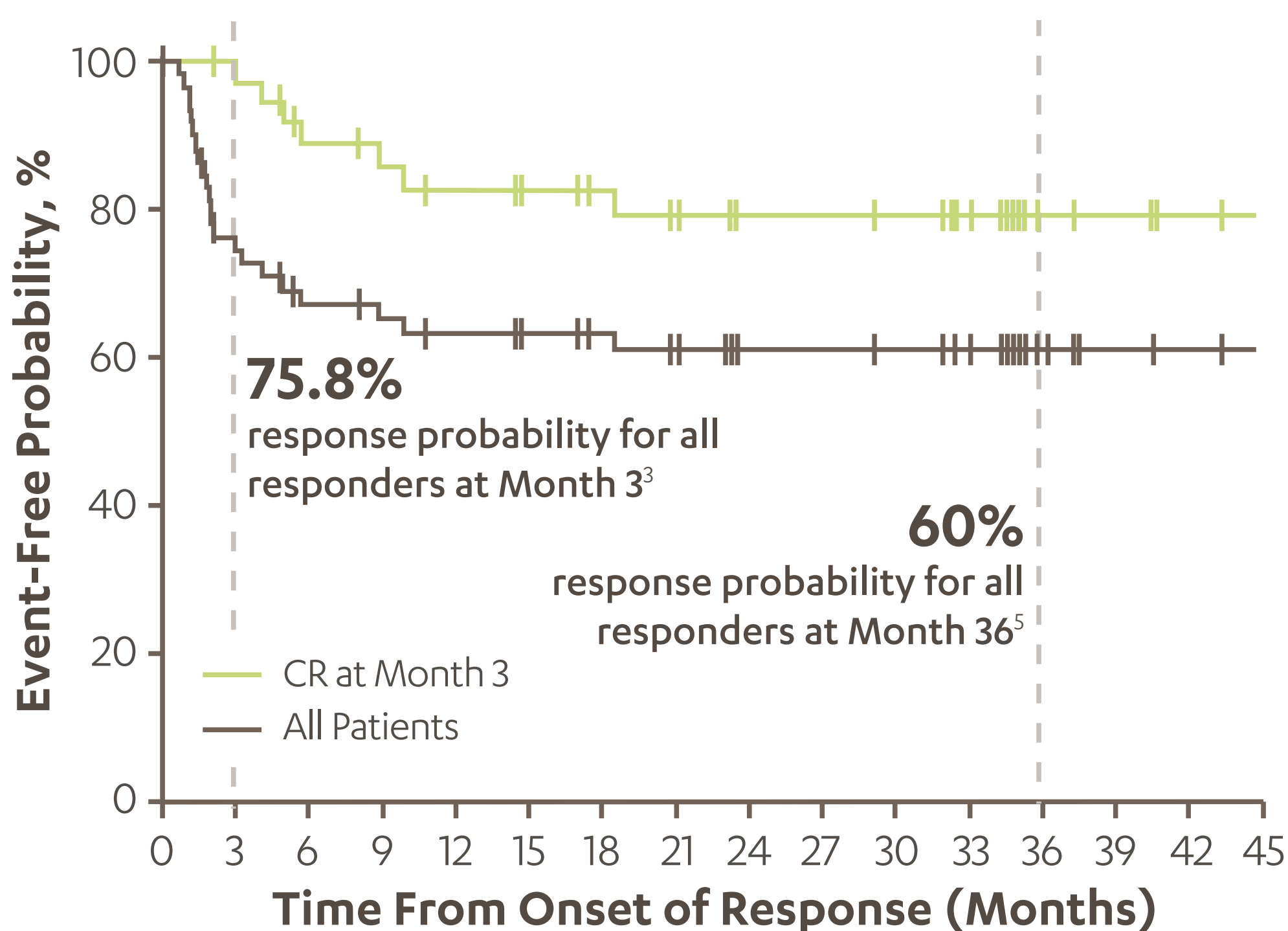
- Median overall survival (OS) was not reached for patients in CR in the 40.3-month analysis<sup>5</sup>
- PFS and OS data should be interpreted with caution in a single-arm trial, as the statistical significance is unknown



### Duration of Response (DOR)

KYMRIA<sup>®</sup> is a durable treatment with **60% of responding patients** still in response at 40.3 months<sup>5</sup>

## JULIET 40.3 MONTHS<sup>3,5</sup>



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<sup>1,\*</sup>

\*DOR for patients who achieved a PR was 3.4 months.<sup>1</sup>



DLBCL Pivotal Trial Data  
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Please see additional Important Safety Information on [pages 2 and 14-27](#).

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STUDY DESIGN

## Safety - Pivotal Trial



### Cytokine Release Syndrome<sup>a-c</sup>

Longer-term data, 32.6 months (N=115)<sup>3</sup>

Median time to onset

3 days

Median time to resolution

7 days

RESPONSE RATES

Longer-term data, 32.6 months (N=115)<sup>3</sup>

Prescribing Information data, 26 months (N=115)<sup>1,d</sup>

All Grades

57%

74%

Grades ≥3

23%

23%

PROGRESSION-FREE SURVIVAL AND DURATION OF RESPONSE

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

CYTOKINE RELEASE SYNDROME



### Key Signs and Symptoms<sup>1</sup>



Fever 85%



Hypoxia 35%



Hypotension 45%  
Tachycardia 13%

NEUROLOGICAL EVENTS

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

SAFETY PROFILE

<sup>a</sup>Cytokine release syndrome in JULIET was graded using the Penn Scale.<sup>1</sup>

<sup>b</sup>Ensure that at least two doses of tocilizumab are available on-site prior to infusion of KYMRIA.<sup>1</sup>

<sup>c</sup>After getting KYMRIA, patients should plan to stay within 2 hours of the location where they receive their treatment for at least 4 weeks<sup>1</sup>

<sup>d</sup>Median time from infusion to data cutoff of December 2018.<sup>1</sup>



DLBCL Pivotal Trial Data

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## Safety - Pivotal Trial (continued)



### Neurological Events<sup>a</sup>

Longer-term data,  
32.6 months (N=115)<sup>3</sup>

Median time  
to first event

6  
days

Median  
duration

13  
days

RESPONSE  
RATES

Longer-term data,  
32.6 months (N=115)<sup>3</sup>

Prescribing Information data,  
26 months (N=115)<sup>1</sup>

All Grades

Grades ≥3

20%

11%

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<sup>3</sup>

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

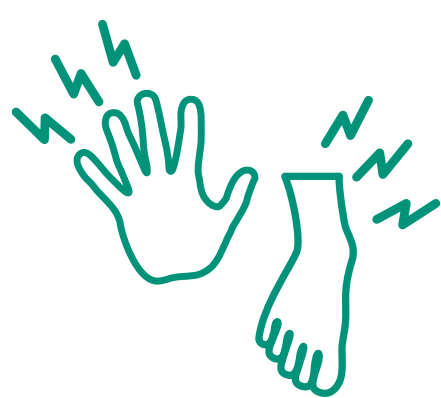
PROGRESSION-FREE SURVIVAL  
AND DURATION OF RESPONSE



### Key Signs and Symptoms<sup>1,\*</sup>



Headache 21%  
Encephalopathy 16%



Peripheral  
neuropathy 12%



Dizziness 12%

CYTOKINE RELEASE  
SYNDROME

NEUROLOGICAL  
EVENTS

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

<sup>a</sup>Neurological events were graded in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.<sup>1,6</sup>

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

SAFETY  
PROFILE



DLBCL Pivotal Trial Data

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Please see additional Important Safety Information on [pages 2 and 14-27](#).

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## Safety - Pivotal Trial (continued)



### Safety Profile From the JULIET Trial

Selected adverse reactions anytime after infusion reported in  $\geq 10\%$  following treatment with KYMRIA<sup>®</sup> in adult r/r DLBCL<sup>1</sup>

Adverse Reaction	USPI: 26 Months (N=115) <sup>1</sup>		
	All grades, %	Grades $\geq 3$ , %	
Blood And Lymphatic System Disorders	Febrile neutropenia	17	17
Cardiac Disorders	Tachycardia <sup>a</sup>	13	3
	Arrhythmia <sup>b</sup>	10	5
Gastrointestinal Disorders	Diarrhea	31	1
	Nausea	29	1
	Constipation	17	1
	Abdominal pain <sup>c</sup>	10	2
General Disorders And Administration Site Conditions	Fever	35	5
	Fatigue <sup>d</sup>	27	6
	Edema <sup>e</sup>	27	3
	Pain <sup>f</sup>	14	3
	Chills	12	0
Immune System Disorders	Cytokine release syndrome	74	23
	Hypogammaglobulinemia <sup>g</sup>	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 <sup>h</sup>	13	1
Nervous System Disorders	Headache <sup>i</sup>	21	1
	Encephalopathy <sup>j</sup>	16	11
	Peripheral neuropathy <sup>k</sup>	12	3
	Dizziness <sup>l</sup>	12	2
Psychiatric disorders	Anxiety	10	1
	Sleep disorder <sup>m</sup>	10	0
Renal and Urinary Disorders	Acute kidney injury <sup>n</sup>	17	6
Respiratory, Thoracic, and Mediastinal Disorders	Dyspnea <sup>o</sup>	21	6
	Cough <sup>p</sup>	17	0
Skin and Subcutaneous Tissue Disorders	Rash <sup>q</sup>	11	0
Vascular Disorders	Hypotension <sup>r</sup>	25	9
	Hemorrhages	22	8

<sup>a</sup>Tachycardia includes sinus tachycardia and tachycardia. <sup>b</sup>Arrhythmia includes atrial fibrillation, cardiac arrest, supraventricular, tachycardia, and ventricular extrasystoles. <sup>c</sup>Abdominal pain includes abdominal discomfort, abdominal pain, and abdominal pain upper. <sup>d</sup>Fatigue includes fatigue and malaise. <sup>e</sup>Edema includes face edema, fluid overload, fluid retention, generalized edema, localized edema, edema peripheral, peripheral swelling. <sup>f</sup>Pain includes pain and pain in extremity. <sup>g</sup>Hypogammaglobulinemia includes blood immunoglobulin G decreased, immunodeficiency, immunoglobulins decreased and hypogammaglobulinemia. <sup>h</sup>Musculoskeletal pain includes back pain, flank pain, musculoskeletal chest pain, neck pain, and non-cardiac chest pain. <sup>i</sup>Headache includes headache and migraine. <sup>j</sup>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. <sup>k</sup>Peripheral neuropathy includes paraesthesia, hypoesthesia, hyperaesthesia, peripheral sensory neuropathy, neuropathy peripheral, cranial nerve paralysis, demyelinating polyneuropathy, Horner's syndrome, polyneuropathy, and sciatica. <sup>l</sup>Dizziness includes dizziness, presyncope, and syncope. <sup>m</sup>Sleep disorder includes insomnia and sleep disorder. <sup>n</sup>Acute kidney injury includes acute kidney injury, blood creatinine abnormal, and blood creatinine increased. <sup>o</sup>Dyspnea includes dyspnea, dyspnea exertional, respiratory distress, and respiratory failure. <sup>p</sup>Cough includes cough, productive cough, and upper-airway cough syndrome. <sup>q</sup>Rash includes dermatitis, dermatitis acneiform, dermatitis contact, rash, rash maculo-papular, rash papular, and rash pruritic. <sup>r</sup>Hypotension includes hypotension and orthostatic hypotension. <sup>s</sup>Hemorrhage includes anal hemorrhage, blood urine present, cerebral hemorrhage, contusion, cystitis hemorrhagic, disseminated intravascular coagulation, duodenal ulcer hemorrhage, epistaxis, eye contusion, gastrointestinal hemorrhage, hematemesis, hematochezia, hematuria, large intestinal hemorrhage, melena, mouth hemorrhage, petechiae, pharyngeal hemorrhage, post procedural hemorrhage, pulmonary hemorrhage, purpura, retinal hemorrhage, traumatic hematoma, tumor hemorrhage, upper gastrointestinal hemorrhage.

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DLBCL Pivotal Trial Data

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# KYMRIAH: Process Overview<sup>1,7,8</sup>

## PATIENT SELECTION

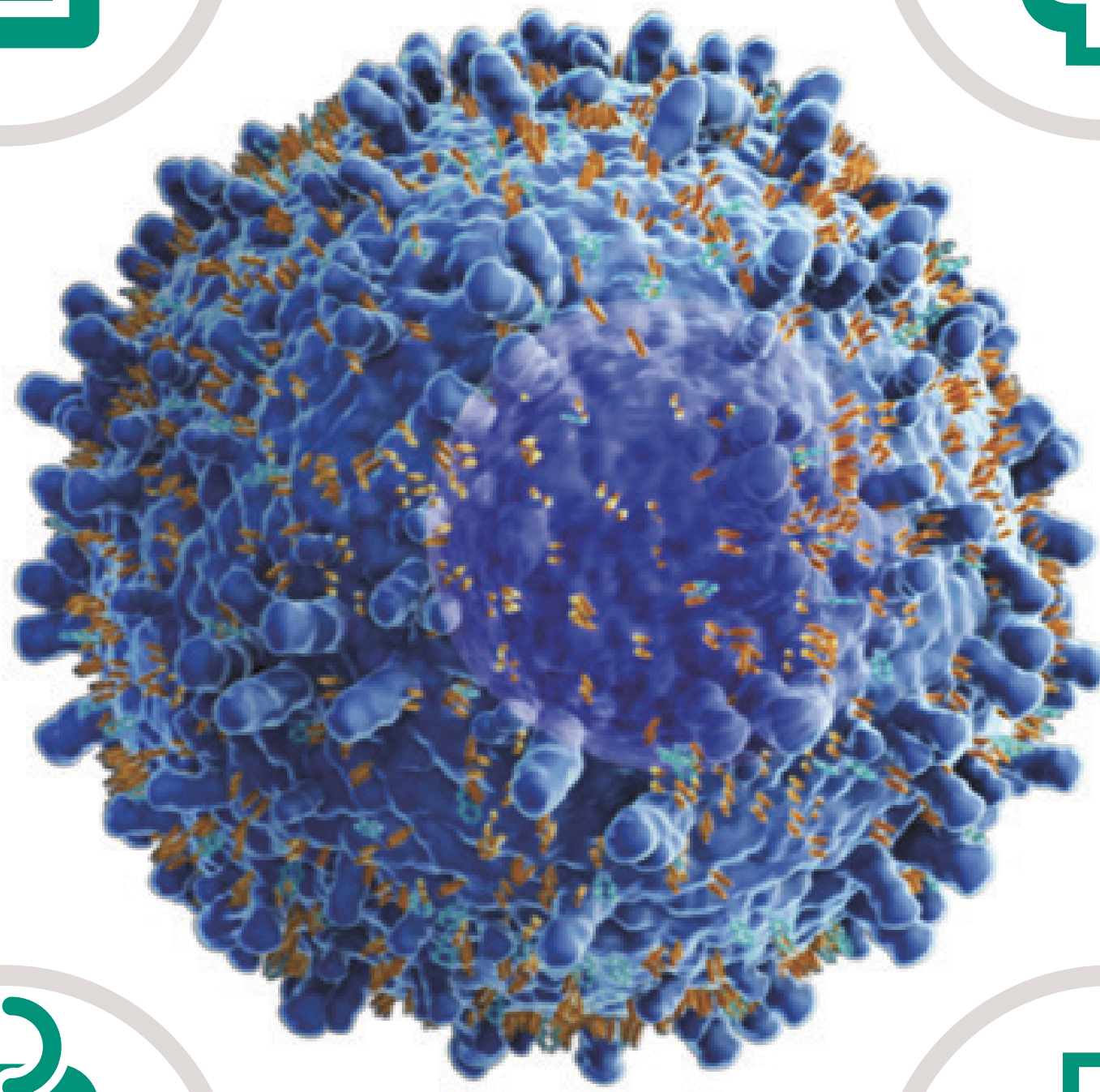


## COORDINATION OF CARE



MONITORING

LEUKAPHERESIS AND  
CRYOPRESERVATION



INFUSION

MANUFACTURING

INPATIENT OR OUTPATIENT

~21 DAYS

BACK

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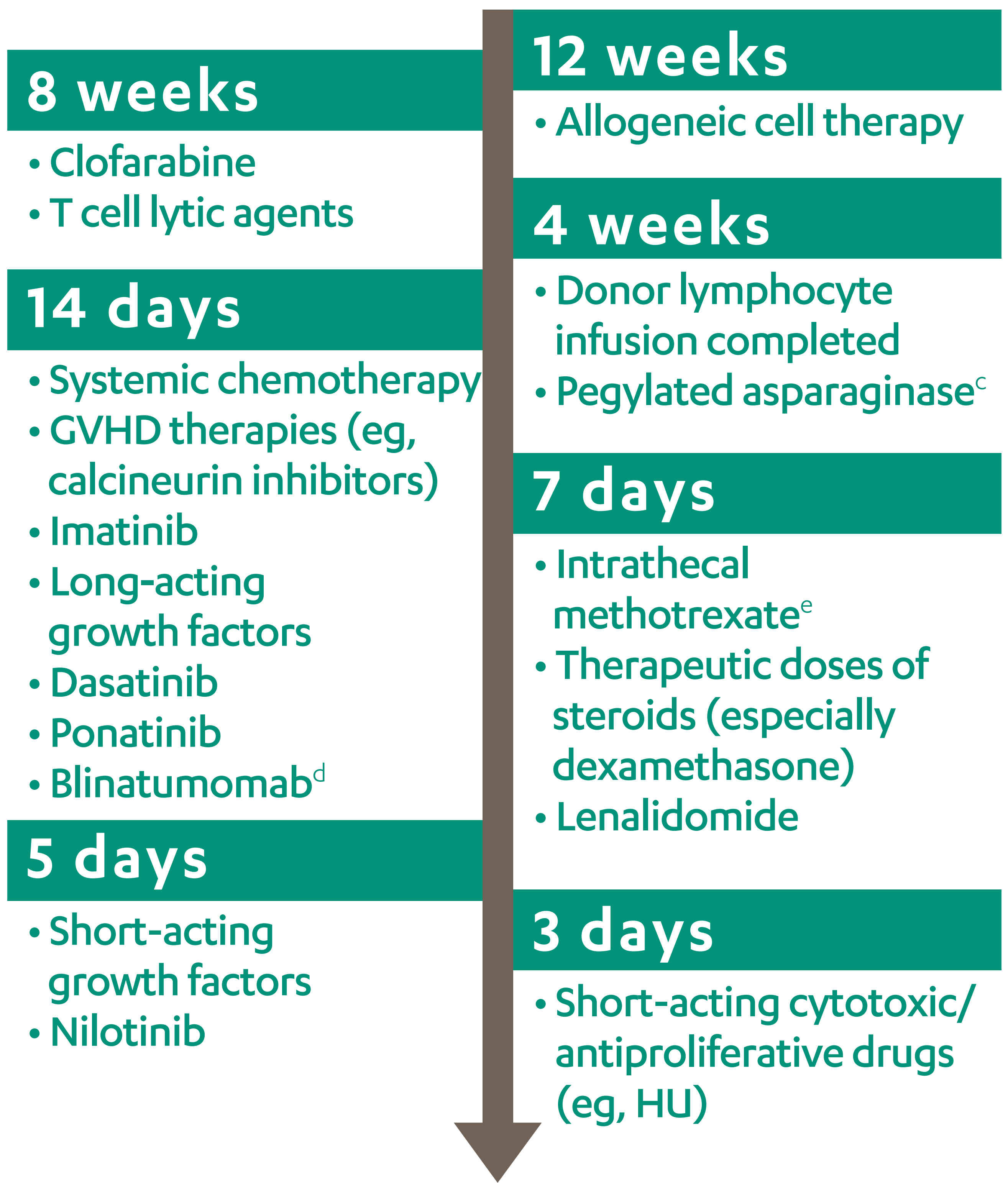
# Guidance on Washout Timing<sup>9</sup>

IF PATIENT'S CONDITION AND DISEASE STATUS ALLOW



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

- Alemtuzumab and ATG: Washout  $\geq 6$  months<sup>a</sup>
- Bendamustine and fludarabine: Washout  $\geq 12$  weeks<sup>b</sup>



**Leukapheresis and Cryopreservation**



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# Guidance on Washout Timing<sup>9</sup> (continued)

## Vaccination with Live Vaccine<sup>1,9</sup>

Vaccination with live vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during KYMRIA<sup>®</sup> treatment, and until immune recovery following treatment with KYMRIA<sup>®</sup>

## 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.

<sup>a</sup>Alemtuzumab and ATG (T cell lytic agents): Allow adequate washout and avoid use for  $\geq 6$  months prior to leukapheresis and consider the potential prolonged effects on T cells.

<sup>b</sup>For bendamustine and fludarabine, allow adequate washout and avoid use for  $\geq 12$  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.

<sup>c</sup>In the CASSIOPEIA trial (NCT03876769) for pALL, the recommended washout period is 14 days.

<sup>d</sup>Although blinatumomab half-life is short ( $\sim 2$  hours), it is recommended to washout 1 to 2 weeks prior to leukapheresis.

<sup>e</sup>If indicated, intrathecal cytarabine can be given up to a day prior to leukapheresis. For an intravenous cytarabine dose  $< 100$  mg/m<sup>2</sup>, a washout of 7 days is recommended; for a dose  $\geq 100$  mg/m<sup>2</sup>, 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 KYMRIA<sup>®</sup>.**



WASHOUT  
2 OF 2

**NEXT**



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CYTOKINE RELEASE SYNDROME

PROLONGED CYTOPENIAS

# Important Safety Information for KYMRIA<sup>®</sup> (tisagenlecleucel)

## Warnings and Precautions

### Cytokine Release Syndrome (CRS)

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

- CRS occurred in 61 (77%) of the 79 pediatric and young adult patients with r/r ALL, including  $\geq$  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 (eg, methylprednisolone)
- CRS occurred in 85 (74%) of the 115 adult patients with r/r DLBCL receiving KYMRIA, including  $\geq$  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

NEUROLOGICAL TOXICITIES

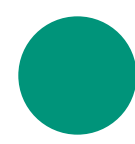
HYPOGAMMAGLOBULINEMIA

REMS PROGRAM AND HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

SECONDARY MALIGNANCIES, DRIVING & DRUG INTERACTIONS

HYPERSENSITIVITY AND SERIOUS INFECTIONS

PREGNANCY AND ADVERSE REACTIONS



CRS  
1 OF 3

Please see additional Important Safety Information on [pages 2](#) and [14-27](#).

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CYTOKINE RELEASE SYNDROME

PROLONGED CYTOPENIAS

# Important Safety Information for KYMRIA<sup>®</sup> (tisagenlecleucel)

## Cytokine Release Syndrome (continued)

- Five deaths occurred within 30 days of KYMRIA<sup>®</sup> 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 KYMRIA<sup>®</sup> 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

NEUROLOGICAL TOXICITIES

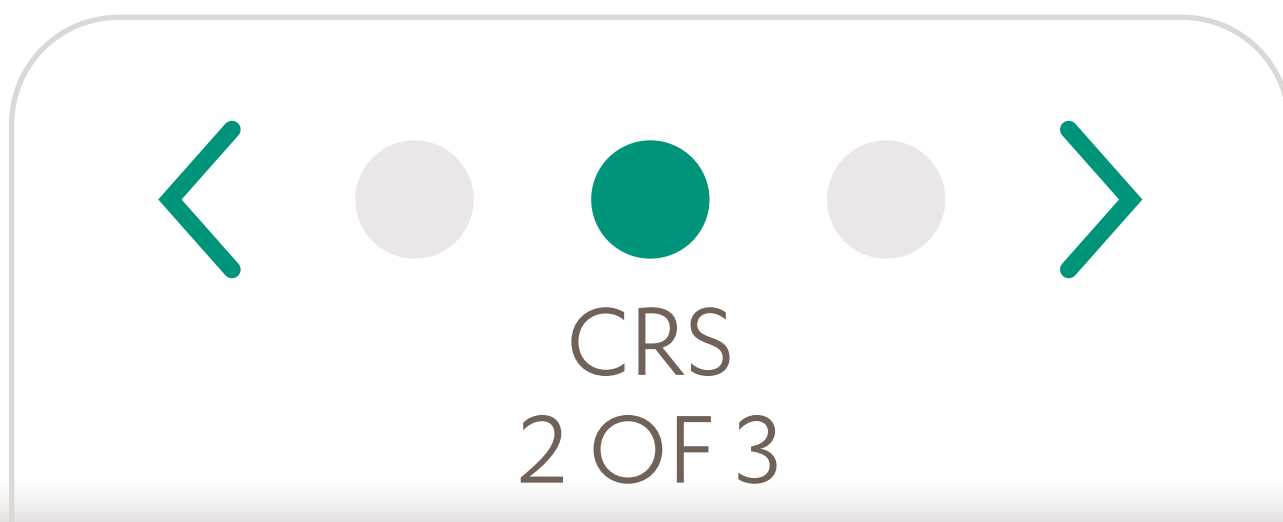
HYPOGAMMAGLOBULINEMIA

REMS PROGRAM AND HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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CYTOKINE RELEASE SYNDROME

PROLONGED CYTOPENIAS

# Important Safety Information for KYMRIA<sup>®</sup> (tisagenlecleucel)

## Cytokine Release Syndrome (continued)

- Ensure that a minimum of 2 doses of tocilizumab are available on-site prior to infusion of KYMRIA. Monitor patients 2 to 3 times during the first week following KYMRIA 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 KYMRIA
- 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

HYPOGAMMAGLOBULINEMIA

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CRS  
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CYTOKINE RELEASE SYNDROME

PROLONGED CYTOPENIAS

NEUROLOGICAL TOXICITIES

HYOGAMMAGLOBULINEMIA

REMS PROGRAM AND HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

SECONDARY MALIGNANCIES, DRIVING & DRUG INTERACTIONS

HYPERSENSITIVITY AND SERIOUS INFECTIONS

PREGNANCY AND ADVERSE REACTIONS

# Important Safety Information for KYMRIA<sup>®</sup> (tisagenlecleucel) Neurological Toxicities (NTs)

- 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 KYMRIA, including  $\geq$  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 KYMRIA 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 KYMRIA<sup>®</sup> (tisagenlecleucel) Neurological Toxicities (continued)

- The most common neurological toxicities observed with KYMRIA 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 2 to 3 times during the first week following KYMRIA 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



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# Important Safety Information for KYMRIA<sup>®</sup> (tisagenlecleucel)

## KYMRIA<sup>®</sup> Risk Evaluation and Mitigation Strategy (REMS)

### KYMRIA<sup>®</sup> REMS to Mitigate CRS and Neurological Toxicities

- Because of the risk of CRS and neurological toxicities, KYMRIA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIA REMS. The required components of the KYMRIA REMS are:
- Health care facilities that dispense and administer KYMRIA 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 KYMRIA infusion, if needed for treatment of CRS
- Further information is available at [www.kymriah-rem.com](http://www.kymriah-rem.com) or 1-844-4KYMRIA (1-844-459-6742)

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

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

- 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



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## Hypersensitivity Reactions

- Allergic reactions may occur with KYMRIA
- Serious hypersensitivity reactions, including anaphylaxis, may be due to dimethyl sulfoxide or dextran 40 in KYMRIA
- Observe patients for hypersensitivity reactions during the infusion

## Serious Infections

### Infection

- 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%)

### Infection Prevention and Management

- Prior to KYMRIA infusion, infection prophylaxis should follow local guidelines
- Patients with active uncontrolled infection should not start KYMRIA treatment until the infection is resolved
- Monitor patients for signs and symptoms of infection after treatment with KYMRIA and treat appropriately

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# Important Safety Information for KYMRIA<sup>®</sup> (tisagenlecleucel)

## Serious Infections (continued)

### Febrile Neutropenia

- Febrile neutropenia ( $\geq$  grade 3) was also observed in 34% of patients with r/r ALL and 17% of patients with r/r DLBCL after KYMRIA<sup>®</sup> 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
- There is no experience with manufacturing KYMRIA<sup>®</sup> 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<sup>8,a,b</sup>

Test Type	Results				
HBsAG	+	-	-	-	-
HBcAB	Any	+	+	-	-
HBsAB	Any	-	+	+	-
<b>Manufacturing Eligibility</b>	Not eligible	Not eligible	Eligible	Eligible	Eligible

<sup>a</sup>Follow institutional procedures for testing and retesting; NAT is an appropriate confirmatory test.

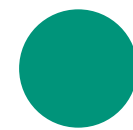
<sup>b</sup>Novartis considers NAT results as confirmatory. Negative NAT results would supersede any serologic test results, and leukapheresis would be eligible for manufacturing.

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# Important Safety Information for KYMRIA<sup>®</sup> (tisagenlecleucel)

## Prolonged Cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and KYMRIA<sup>®</sup> infusion

	 <b>JULIET</b> N=115 (%)	 <b>ELIANA<sup>a</sup></b> N=52 (%)	
<b>Grade <math>\geq 3</math></b>	<b>Day 28</b>	<b>Day 28</b>	<b>Day 56</b>
Prolonged neutropenia	<b>25</b>	<b>40</b>	<b>17</b>
Prolonged thrombocytopenia	<b>39</b>	<b>27</b>	<b>12</b>

- ⚠ Prolonged neutropenia has been associated with increased risk of infection
- ⚠ Cytopenia: A deficiency or lack of cellular elements in the circulating blood<sup>10</sup>

### 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 KYMRIA<sup>®</sup> infusion or until CRS has resolved

<sup>a</sup>ELIANA is the pivotal, global, Phase 2 trial of KYMRIA<sup>®</sup> in patients with relapsed or refractory ALL up to 25 years of age.<sup>1</sup>

  
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# Important Safety Information for KYMRIAHA® (tisagenlecleucel)

## Hypogammaglobulinemia

Hypogammaglobulinemia and agammaglobulinemia related to B-cell aplasia can occur in patients after KYMRIAHA 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 KYMRIAHA and manage using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement standard guidelines

### B-cell Aplasia<sup>10</sup>

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

### Immunization with Live Vaccine

- The safety of immunization with live vaccines during or following KYMRIAHA 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 KYMRIAHA treatment, and until immune recovery following treatment with KYMRIAHA
- Pregnant women who have received KYMRIAHA may have hypogammaglobulinemia. Assess immunoglobulin levels in newborns of mothers treated with KYMRIAHA

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# Important Safety Information for KYMRIA<sup>®</sup> (tisagenlecleucel)

## Secondary Malignancies

- Patients treated with KYMRIA 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 KYMRIA. 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 1-844-4KYMRIA 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 KYMRIA 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

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# Important Safety Information for KYMRIA<sup>®</sup> (tisagenlecleucel) Drug Interactions

- HIV and the lentivirus used to make KYMRIA<sup>®</sup> 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 KYMRIA<sup>®</sup>

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# Pregnancy, Lactation, Females and Males of Reproductive Potential

- No data are available of KYMRIA<sup>®</sup> use in pregnant or lactating women. Therefore, KYMRIA<sup>®</sup> is not recommended for women who are pregnant or breastfeeding. A risk to the breastfed infant cannot be excluded
- Pregnancy after KYMRIA<sup>®</sup> 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 KYMRIA<sup>®</sup>
- Report pregnancies to Novartis Pharmaceuticals Corporation at 1-888-669-6682

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# Important Safety Information for KYMRIA<sup>®</sup> (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 KYMRIA, including Boxed WARNING, and Medication Guide.

For more information, go to [www.KYMRIA-hcp.com](http://www.KYMRIA-hcp.com) or call 1-844-4KYMRIA (1-844-459-6742)




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