KYMRIAH® (tisagenlecleucel) suspension for intravenous infusion

MEDCAC Meeting

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Financial Disclosure

- *I am a paid employee of Novartis*
- *I have no intellectual conflicts of interest to report that may pertain in any way to the subject of this meeting*

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Novartis Urges CMS to Withdraw NCA for CAR T-cell Therapy

- Novartis manufactures KYMRIAH® (tisagenlecleucel), the first FDA-approved Chimeric Antigen Receptor (CAR) T-Cell Therapy

- On 5/16/18, CMS initiated national coverage analysis for CAR T-cell Therapy for Cancers
  - On 8/22/18, CMS will convene Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) meeting to review the available evidence on this topic

- **Mandating patient reported outcomes (PROs) data collection for CAR-T is unnecessary, impractical, and imposes a significant burden on providers and patients**

- **Novartis urges CMS to withdraw the NCA and not pursue Coverage with Evidence Development (CED) as it is inconsistent with past CMS policy, unnecessary, not practical, an administrative burden on providers, and will impact beneficiary access to CAR-T therapy**

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KYMRIAH: First FDA-Approved CAR T-Cell Therapy

- **KYMRIAH is FDA approved for the following indications:**

INDICATIONS	FDA APPROVAL
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 (referred to as “r/r ALL”)	8/30/2017
Treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two 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 (collectively referred to as “r/r DLBCL”); KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma	5/1/2018

KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) via a limited network of certified treatment centers

- **Across both indications, patients received KYMRIAH in both the hospital outpatient and inpatient settings during the clinical trials**
  - 27% of patients in the JULIET study received KYMRIAH in the hospital outpatient setting as described in the physician prescribing information
  - Site of care for patients should be determined by their treating physician
- **KYMRIAH PRO data was collected during clinical trials**
  - Efficacy, safety, and PRO data from KYMRIAH trials established positive benefit risk ratio

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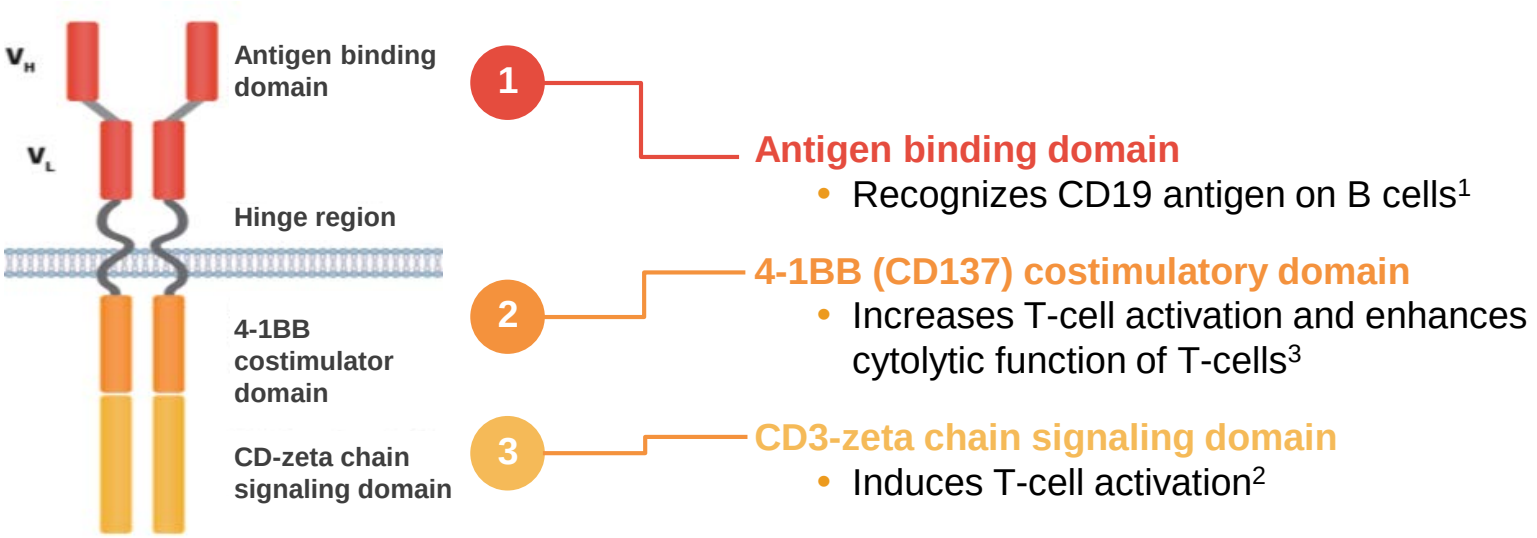
KYMRIAH: A CD19-Targeted Therapy

- **KYMRIAH is a CAR T-cell therapy**
  - Composed of a CD19 antigen-binding domain, a 4-1BB costimulatory domain, and a CD3-ζ signaling domain[1,2]
- **KYMRIAH is specifically manufactured for each individual patient**
  - Produced through the modification of a patient's own T cells with genetic material that encodes a CAR to identify and eliminate CD19-expressing cells



References: 1. Milone MC et al. *Mol Ther.* 2009;17(8):1453-1464. **2.** Kalos M et al. *Sci Transl Med.* 2011;3(95):95ra73. **3.** Zhang H et al. *J Immunol.* 2007;179(7):4910-4918.

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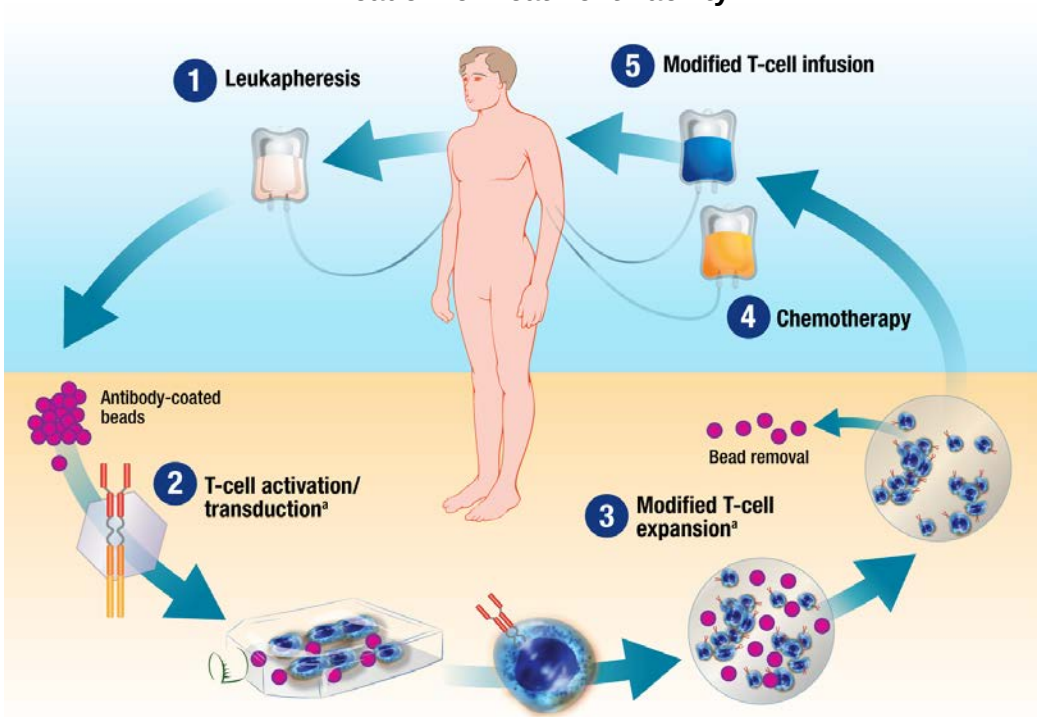
KYMRIAH Treatment Overview

Academic Treatment Facility



Novartis Manufacturing Facility

1. **Leukapheresis:** Patient's T cells are harvested and shipped to Novartis manufacturing facility[1,2]
2. **T cells are activated** and genetically transduced ex vivo with a construct encoding for the anti-CD19 CAR[1-3]
3. **KYMRIAH cells undergo ex vivo expansion** are cryopreserved and shipped back to the treatment facility[1-3]
4. **Chemotherapy:** Patient receives a preparative lymphodepleting regimen before T-cell infusion[1-3]
5. **KYMRIAH cells are infused in the hospital outpatient or inpatient setting**

[a]Cellular reprogramming and ex vivo expansion are conducted at a cell-processing facility.

References: 1. Kalos M et al. *Sci Transl Med.* 2011;3(95):95ra73. **2.** Porter DL et al. *New Engl J Med.* 2011;365(8):725-733. **3.** Porter DL et al. *J Cancer*. 2011;2:331-332.

High Burden of Disease for Patients With R/R ALL and R/R DLBCL

R/R ALL	R/R DLBCL
ALL is diagnosed in ~3000 children in the United States	**DLBCL is diagnosed in ~27,650 patients in the United States**
Despite 80% cure rates after front-line therapy, pALL remains the leading cause of childhood mortality due to malignancy	**~50% to 60% of patients with DLBCL achieve and maintain complete response (CR) after first-line therapy**
R/R ALL population: ~450	**R/R DLBCL population: ~6000**
Median age: 15 years	**Median age: 64 years**
Patient Mix: 11% Medicare, 41% Medicaid, 41% Commercial, 7% Other*	**Patient Mix: 61% Medicare, 30% Commercial, 7% Other*, 2% Medicaid**

- Patients with R/R ALL and R/R DLBCL have a very poor prognosis and limited treatment options
- KYMRIAH offers clinical benefit in these difficult to treat patient populations
- KYMRIAH is available at select treatment centers that comply with the KYMRIAH REMS
- Novartis has a planned a 15-year patient registry to study the safety and long-term effectiveness of patients treated with KYMRIAH in a real-world setting

* Other sources of government insurance, including the US Department of Veterans Affairs (VA), as well as state and local insurance programs, self-pay, and unknown.

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JULIET PIVOTAL STUDY:
Demographics and Baseline Disease Status

Single-arm, open-label, multisite, global Phase II study to determine the safety and efficacy of tisagenlecleucel in adult patients with r/r DLBCL

	Patients (N = 111)
Age, median (range), years	56 (22-76)
≥ 65 years, %	23
ECOG performance status 0/1, %	55/45
Central histology review	
Diffuse large B-cell lymphoma, %	79 [a]
Transformed follicular lymphoma, %	19
Double/triple hits in *CMYC/BCL2/BCL6* genes, %	17
Cell of origin[b]	
Germinal/Nongerminal center B-cell type, %	57/41
Number of prior lines of antineoplastic therapy, %	
2/3/4-6	44/31/21
IPI ≥ 2 at study entry, %	72
Refractory/relapsed to last therapy, %	55/45
Prior auto-SCT, %	49
Bridging chemotherapy, n	**102**
Lymphodepleting chemotherapy, n	**103**

auto-SCT, autologous stem cell transplant;
ECOG, Eastern Cooperative Oncology Group.

[a] *CMYC* + *BCL2*, n = 10; *CMYC* + *BCL2* + *BCL6*, n = 5; *CMYC* + *BCL6*, n = 4.
[b] Determined by the Choi algorithm.

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KYMRIAH Substantially Improves Complete Response Rate

- **Study 1 (JULIET) Primary Endpoint: Best Overall Response Rate (ORR)**
  - ORR: complete response (CR) + partial response (PR)
  - Data are from an updated analysis of the JULIET study that includes 93 patients with at least 3 months of follow-up. The median follow-up for this analysis is 14 months
    - analysis differs from data in the Prescribing Information (PI), which includes a retrospectively identified subgroup of 68 patients who had not received bridging chemotherapy or who had evidence of disease after bridging chemotherapy; median follow-up for data included PI is 9.4 months
- **ORR was consistent across subgroups including a 59% response in patients over age 65**
- **Overall survival at 12 months was 95% and 49% among CR patients and all infused patients, respectively**

Response Rate, %	Best Overall Response Rate (N = 93)
Best Overall Response Rate	52[a]
Complete Response Rate	**40**
Partial Response Rate	11

[a] *P* < .0001; (95% CI, 42%-64%). Null hypothesis of ORR ≤ 20%.

- **Substantially improved complete response rates were observed after KYMRIAH infusion, as compared to SCHOLAR-1 (7%)**

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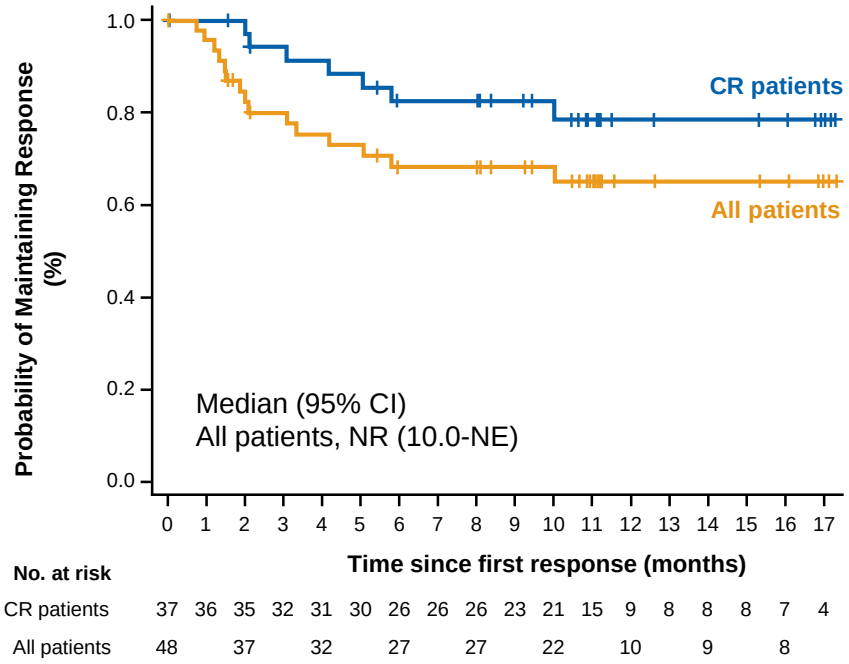
KYMRIAH Substantially Improves Durability of Response

At 14 months median follow-up, median DOR not reached.



CR, complete response; DOR, duration of response; NE, not evaluable; NR, not reached; ORR, overall response rate; PR, partial response; SCT, stem cell transplant.

- **12-month relapse-free survival rate**
  - **78.5% (95% CI, 60%-89%) among CR patients**
  - 65% (95% CI, 49%-78%) among all responders
- **54% (13/24) of patients converted from PR to CR**, including 2 patients 9-12 month after initial response
- Tisagenlecleucel transgene was detected in peripheral blood for up to 2 years in responding patients
- No patients proceeded to transplant while in response

JULIET: AESIs in Adult Patients with R/R DLBCL

	KYMRIAH USPI Analysis[1] Patients (N = 106)	
AESI[a]	**All Grades, %**	**Grade ≥ 3, %**
CRS[b]	74	23
Neurological events	58	18
Prolonged cytopenia[c]		
Thrombocytopenia	—	40
Neutropenia	—	25
Infections[d]	42	25
Febrile neutropenia	17	17
Tumor lysis syndrome	1	1[e]

- The overall safety profile for the updated analysis is consistent with the previously reported AE data; variances in reported prevalence of AEs are due to different definitions of AE terms and approaches to classifying symptoms
  - In an updated analysis (N = 111), the most common AESIs[f] were CRS[b] (58%; 14% grade 3 and 8% grade 4), neurological events (21%, 7% grade 3 and 5% grade 4), prolonged cytopenias[c] (44%; 16% grade 3 and 16% grade 4), infections (34%; 18% grade 3 and 2% grade 4), and febrile neutropenia (15%; 13% grade 3 and 2% grade 4)[2]

[a] Suspected to be KYMRIAH related occurring anytime after tisagenlecleucel infusion. [b] CRS was graded using the Penn scale. [c] Not resolved by day 28. [d] Pathogen unspecified. [e] Novartis data on file. [f] Occurring within 8 weeks of tisagenlecleucel infusion.
AESI, adverse events of special interest; CRS, cytokine release syndrome.
1. KYMRIAH (tisagenlecleucel) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2018. 2. Borchmann P, et al. *Haematologica.* 2018;103(s2) [abstract S799] [oral presentation].

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Registry Data Collection

- Commercial patients prescribed KYMRIAH followed for 15 years on a Registry utilizing information gathered through the CIBMTR
  - 15 years of safety and efficacy data gathered
  - Proven system utilized by the federal government to collect data on cellular therapies

Patient Characteristics

- Age
- Prior chemo/immunotherapy
- Prior transplant (auto/allo)
- Health status

Disease Characteristics

- Pathology
- Site of disease
- Risk factors (genetics, IHC, etc)

Efficacy

- Response (CR, PR, MRD etc)
- Persistence of response (3m, 6m, 1yr-15y)
- Relapse

Acute Safety

- CRS
- Neurologic toxicity
- Infection
- Grade 3-4 AEs in each organ system
- Mortality

Long-term Safety

- B-Cell aplasia/ hypogammaglobulinemia
- New malignancies
- Pregnancy

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NCA Should Be Withdrawn

- **Concerns identified by NCA tracking document are already appropriately managed or are not an issue**
  - FDA adequately manages safety concerns by requiring CAR-T therapies to include REMS with ETASU (Elements to Assure Safe Use) and boxed warnings; real time AE reporting is required by the FDA
  - FDA requires all dispensing hospitals to be certified, and all clinicians using CAR-T therapy to be specifically trained
  - Novartis requires accreditation by Foundation for Accreditation in Cellular Therapy (FACT)
  - Novartis can manufacture only specific doses based on approved indications
  - Physician must indicate diagnosis when placing order; can only be ordered by REMS-certified HCPs, reducing likelihood of off-label use
  - 27% of patients in the JULIET study received KYMRIAH in the hospital outpatient setting as described in the physician prescribing information
- **NCA may negatively impact beneficiary accessing treatment**
  - NCA may lead MACs, and other payers, currently covering therapy to withhold coverage until the scheduled conclusion of the NCA (5/17/19)
  - Could result in access issues for patients with no alternative treatment options and a very short life expectancy if untreated

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CED Should Not Be Pursued

Inconsistent With Past CMS Policy	**CED for CAR-T is inconsistent with past CMS action**	• CED is typically limited to unapproved indications or concerns about broad use of therapy without sufficient clinical criteria • CED has never been used for FDA-approved anticancer therapy • Clinical evidence supports that CAR-T is reasonable and necessary
Unnecessary	**CED not necessary given ongoing data collection (post-approval registry)**	• *"CED will not duplicate or replace the FDA's authority in assuring the safety, efficacy, and security of drugs, biological products, and devices"*[1] • Ongoing outcomes data collected in pivotal clinical study and additional safety and effectiveness data will be reported under registry
Not Practical	**CED not practical given unique data collection tools for each therapy**	• Clinical data supporting FDA approval for therapies will vary by tumor type and indication • Different types of evidence development with individualized data collection tools may be required for each therapy
Administrative Burden on Providers	**CED will impose administrative burden and cost on providers**	• CED will require providers to implement additional administrative processes (e.g., maintenance of registries, collection of data, and patient consents) • Already captured by post-marketing studies and CIBMTR
Beneficiary Access	**CED will impede beneficiary access**	• Delay in access as study is implemented (e.g., IRB approval, site registration); sites may not participate • Delaying access to an FDA-approved and medically accepted non-palliative treatment option for patients with a short life expectancy

[1]CMS Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development, Nov. 20, 2014.

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Summary

- **Patients with r/r ALL and r/r DLBCL have a very poor prognosis and limited treatment options**
- **KYMRIAH offers clinical benefit in difficult to treat DLBCL patient populations, including patients ≥ 65 years of age**
- **Concerns identified by NCA tracking document are already appropriately managed or are not an issue**
- **Patients received KYMRIAH in both the hospital outpatient and inpatient settings during the clinical trials**
- **KYMRIAH PRO data was collected during drug development process**
- **Novartis urges CMS to withdraw the NCA and not pursue CED as it is inconsistent with past CMS policy, unnecessary, not practical, an administrative burden on providers, and will impact beneficiary access to CAR-T therapy**

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