Chimeric Antigen Receptor (CAR) T-Cell Therapy and Patient Reported Outcomes

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Disclosure

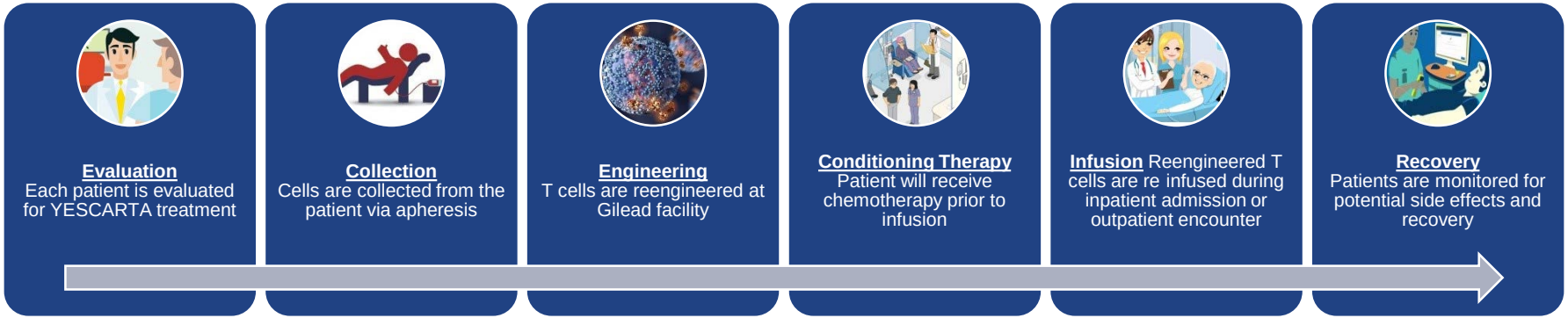
- Full-time, salaried employee of Kite, a Gilead Company.

A Commitment to Patients with Unmet Medical Needs

- Kite, a Gilead company, is a research-based company that is committed to discovering, developing, and commercializing innovative therapies in areas of unmet medical need
- We applaud the focus of CMS and FDA on patient reported outcomes (PROs) and recognize the importance of incorporating PROs into our own drug development process, as well as into our overall assessment of the efficacy and value of our therapies for patients, including Medicare beneficiaries
- While Kite recognizes the importance of PRO measurement in clinical trials, the science behind where these instruments are most appropriate for CAR T is still evolving
- Our CAR T therapy, YESCARTA®, is currently approved for patients who have exhausted treatment options and have poor survival rates

YESCARTA Clinical Overview

- YESCARTA is a CD19-directed genetically modified autologous T-cell immunotherapy administered one time
  - FDA approval in October 2017 for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
  - One-time infusion limited to certified healthcare facilities
  - FDA-approved label is site-of-service neutral
  - YESCARTA is manufactured and prescribed to label



ZUMA-1 (Cohort 1 and 2 Pivotal Trial): Objective Response

	Phase 2 Primary Analysis N = 101		Phase 1 and 2 Updated Analysis N = 108	
Median follow-up, mo	8.7		15.4	
	ORR	**CR**	**ORR**	**CR**
Best objective response, %	82	54	82	58
Ongoing, %	44	39	42	40

- 57% of patients in phase 1 obtained a CR
- In the updated analysis, 23/60 patients with either a PR (11/35) or SD (12/25) at the first tumor assessment (1 mo. post–axi-cel) subsequently achieved CR up to 15 months post-infusion without additional therapy
- Median (range) time to conversion from PR to CR = 64 (49 – 424) days

Neelapu et al, ASH 2017 #578
Response was evaluated by investigator assessment.
CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.

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ZUMA-1: Summary of Adverse Events

AE, n (%)	Primary Analysis N = 108	Updated Analysis N = 108
Grade ≥ 3 AE	103 (95)	105 (97)
Grade ≥ 3 SAE	48 (44)	50 (46)
Grade ≥ 3 CRS	14 (13)	13 (12)
Grade ≥ 3 NE	32 (30)	33 (31)
Grade 5 AE	4 (4)[a]	4 (4)[b]

- Since the primary analysis with ≥ 6 months of follow-up, there have been no new axi-cel–related CRS, NE, or Grade 5 AEs
- Median duration of hospitalization: 14 days
  - CRS and NE generally self limited and reversible; all CRS events resolved except for 1 HLH and 1 cardiac arrest
  - All NE events resolved except for 1 grade1 memory impairment (Locke et al ASCO 2017 7512)
- Most patients experienced hypogammaglobulinemia and B cell aplasia; 8% had IVIG support at any point on study

[a]Grade 5 AEs occurred in 4 patients. Axi-cel–related, 2 (2%; HLH and cardiac arrest resulting in anoxic brain injury); axi-cel–unrelated, 2 (2%; pulmonary embolism and intracranial hemorrhage). [b]There were no new grade 5 AEs at the updated analysis. AE, adverse event; SAE, serious adverse event; CRS, cytokine release syndrome; NE, neurologic event

Patients Aged ≥ 65 Years of Age: Sub-group Analysis

Characteristic	Phase 1 and 2 N = 108
Median (range) age, y	58 (23 – 76)
≥ 65 y, n (%)	27 (25)

- Medicare-age patients treated in ZUMA-1 ranged from 65 – 76 years of age
- **Observed overall response rates are similar in patients ≥ 65 years of age compared to the overall ZUMA-1 population**
  - **For patients aged ≥65,**
    - **Objective response rate was 89% vs 82% in all ZUMA-1**
    - **Complete response rate was 70% vs 58% in all ZUMA-1**
    - **Durable remission rate was 48% vs 42% in all ZUMA-1**
- **Compared with subjects < 65 years of age, subjects ≥ 65 years of age had a lower incidence of SAEs (33% vs. 62%), a lower incidence of Grade 3 or higher infections (19% vs. 30%), and a higher incidence of Grade 3 or higher neurologic events (41% vs. 27%)**
  - The higher incidence of neurologic events in subjects ≥ 65 years of age was driven by events that would be expected to occur more frequently in the ≥ 65 years age group (delirium, agitation, and disturbance in attention)

ORR, objective response rate; CI, confidence interval; SAE, serious adverse event

CIBMTR Cell Therapy Registry Tracks and Analyzes Long-Term Outcomes Data for YESCARTA

- The Center for International Blood & Marrow Transplant Research (CIBMTR) has launched a cell therapy registry for current approved therapies and potential future therapies
- The registry objectives are:
  - To study therapies using cellular products for indications other than hematopoietic replacement or recovery; and
  - To provide an infrastructure to allow long-term follow-up of patients treated with cellular therapy product.
- CIBMTR is conducting training with certified institutions on the registry and how to use it
- The registry may include data from other countries and is modular
- An analysis of data from the registry data will be overseen by a Steering Committee
  - Steering committee is made up of representatives of key certified sites and manufacturers

Data Elements Collected in Registry: Efficacy and Safety

Efficacy	Data
Demographics	Age, gender, height, weight, center
Information on the malignancy	Documented diagnosis using a standard terminology (e.g., ICD)
	Date of diagnosis
	Disease burden / stage at cellular therapy treatment
Functional status / prognostic info	Performance status
Prior therapy for the malignancy	Lines of therapies
CAR-T cell administration	Product and dose
CAR-T cell early response: efficacy measures & assessment	Treatments for side effects (e.g. CRS)
	Response: ORR, duration of response, relapse free survival, event free survival
Later response: efficacy events	Response: yearly assessment (ORR, duration of response, relapse free survival, event free survival)
Follow up: efficacy	Is the patient still alive? (Y/N) If no, specify date of death and cause
	Last known alive date
	New morbidity or malignancy diagnoses - date, type
	Next malignancy treatment (type), if any, including stem cell transplant
	Relapse free survival, event free survival

Safety	Data
Early Response-Safety	Drug-related adverse events: neurological events (incl. cerebral oedema), CRS/MAS, cytopenias (bone marrow recovery), TLS, certain infections
	Drug-related (grade 3-4) adverse events: skin; respiratory, cardiovascular, hepatic, renal, gastrointestinal, other system events; duration of B-cell aplasia/ hypogammaglobulinemia
	Treatments for any of the above
Follow up	Is the patient still alive? (Y/N) If no, specify date of death and cause of death
	Last known alive date
Later events - Safety	Pregnancies and outcomes, CAR T cells in neonate, B cell aplasia in neonate
Late Response - Safety	Safety assessment: months 3, 6, 12 and then yearly
	New malignancy; Insertional mutagenesis; New incidence or exacerbation of pre-existing neurological disorder; hematological disorder; hep B reactivation

ICD, International Classification of Diseases; CRS, cytokine release syndrome; ORR, objective response rate; MAS, macrophage activation syndrome; TLS, tumor lysis syndrome

YESCARTA Registry Update

- The CIBMTR CAR T registry has been enrolling patients as of March 27, 2018
- All 61 certified sites are also registered as CIBMTR centers
- As of July 6, 2018, there are:
  - ~220 cell orders shipped since registry enrollment
  - 82 YESCARTA recipients reported in the registry
- Patients can be enrolled up to three months post YESCARTA infusion
- Patient enrollment is expected to be 90% based on previous registry experience

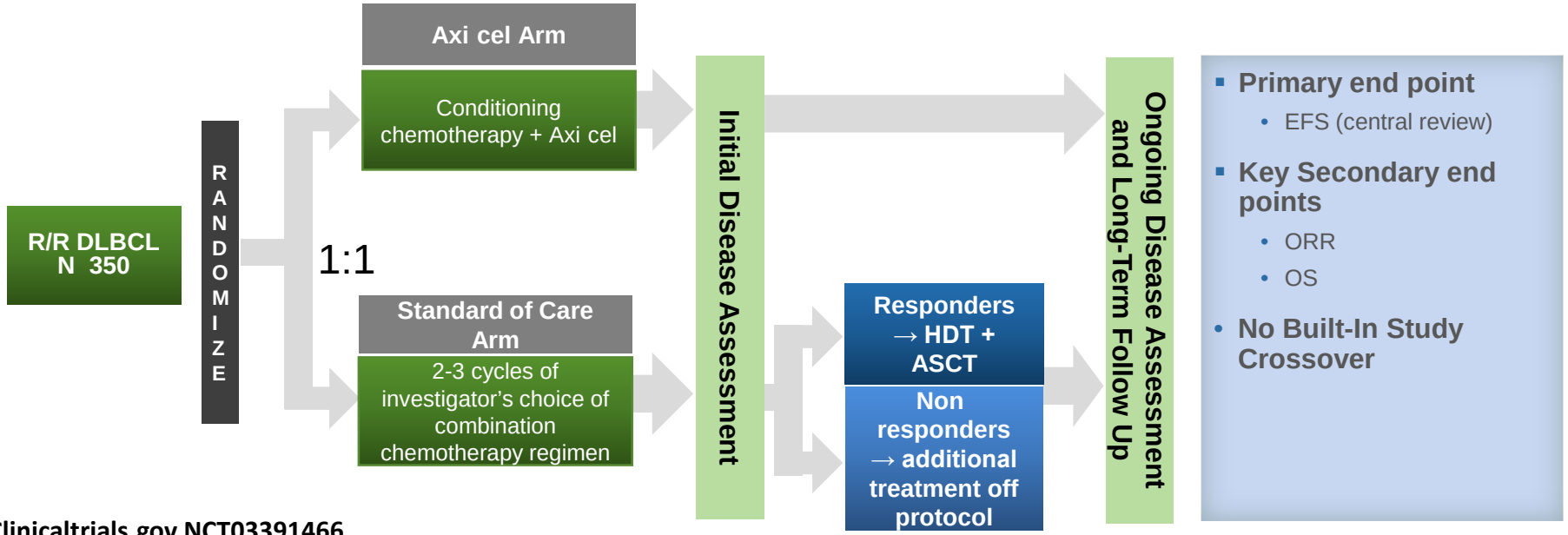
- CIBMTR, Center for International Blood & Marrow Transplant Research

Kite Uses PROs to Understand The Balance of Efficacy and Safety from a Humanistic Perspective

- PRO tools are variable
  - They may be global, disease-specific, and/or designed to measure AEs
- Kite collects PROs via tools that assess overall QoL; some are disease agnostic
- These instruments are being used to collect PROs in ZUMA-7; EQ-5D is also being used in ZUMA-1 (cohorts 3 and 4)
  - ZUMA-7 is a randomized, head-to-head comparison of YESCARTA and stem cell transplant
  - ZUMA-1 cohort 3 examines the effect of prophylactic tocilizumab on CRS
  - ZUMA-1 cohort 4 examines the effect of steroidal intervention on patients with prolonged Grade 1 neurotoxicity

PRO, patient reported outcome; AEs, adverse events; QoL, quality of life; CIBMTR, Center for International Blood & Marrow Transplant Research

ZUMA-7 Axi-cel vs. Second-Line SOC Therapy in Adult R/R DLBCL: Study Schema and End Points



Clinicaltrials.gov NCT03391466

ASCT, autologous stem cell transplantation; axi-cel, axicabtagene ciloleucel; CR, complete response; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; HDT, high dose therapy; ORR, objective response rate; PROs, patient reported outcomes; R/R, relapsed/refractory.

[a]Patients will receive a 3-day conditioning regimen consisting of fludarabine 30 mg/m^2/d + cyclophosphamide 500 mg/m^2/d (days −5 to −3) followed by 2 rest days (day −2 and day −1). On day 0, patients will receive a single infusion of axi-cel administered intravenously at 2 × 10^6 anti-CD19 CAR T cells/kg.

[b]Patients will receive 2-3 cycles of investigator's choice of salvage combination chemotherapy regimen (R-ICE, R-DHAP, R-ESHAP, or R-GDP) administered every 2-3 weeks.

[c]Defined as death, disease progression, or new lymphoma therapy.

Kite Experience with PROs To Date

- Kite generally uses PRO tools in Phase 3 trials (e.g., ZUMA-7)
  - For example, in ZUMA-7, we used three PRO tools to assess the incremental patient benefit of YESCARTA over SOC
  - In some cases, we use PRO tools in Phase 2 trials; these are more exploratory to inform Phase 3 design
- PRO tools used in ZUMA-7 were selected for their ability to achieve various study goals
  - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC—QLQ-C30) to evaluate key domains and fatigue
  - EuroQol 5D 5-level Version (EQ-5D-5L) to evaluate general well-being
    - Also used in ZUMA-1 (cohorts 3 and 4) because it was premature to evaluate other PROs
  - Work Productivity and Activity Impairment (WPAI) Questionnaire v2.0 to measure work productivity and absenteeism

PRO, patient reported outcome; SOC, standard of care