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Evaluating Efficacy and Safety of Tisagenlecleucel Reinfusion Following Loss of B-Cell Aplasia in Pediatric and Young Adult Patients With Acute Lymphoblastic Leukemia: HESTER Phase II Study

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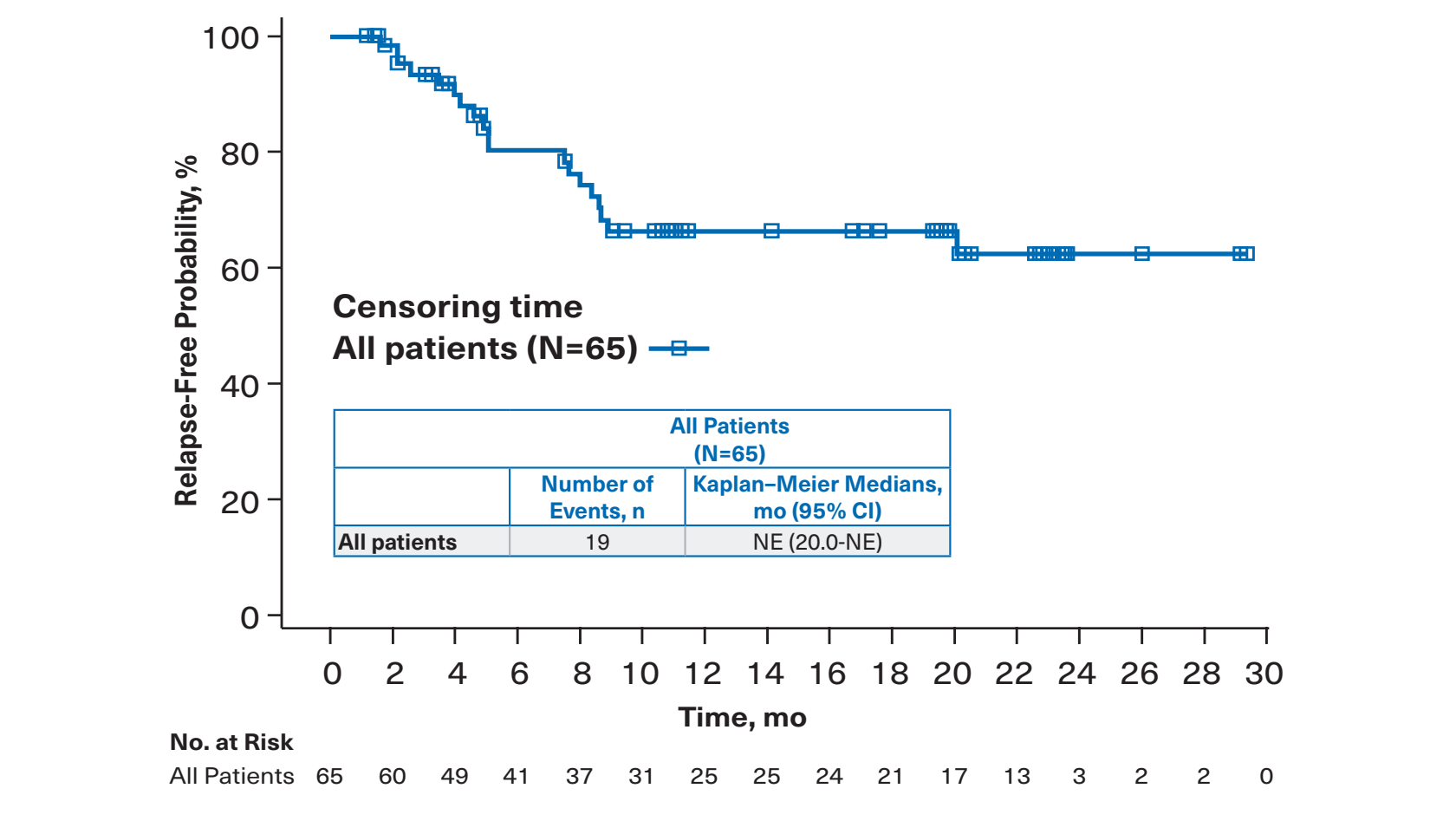
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INTRODUCTION

Tisagenlecleucel in Patients With r/r B-ALL

- Tisagenlecleucel is an anti-CD19 CAR-T cell therapy approved for certain pediatric and young adult patients with relapsed or refractory (r/r) B-cell acute lymphoblastic leukemia (B-ALL) and certain adult patients with r/r diffuse large B-cell lymphoma (DLBCL)
- In the pivotal ELIANA trial, patients with r/r B-ALL were infused with tisagenlecleucel and demonstrated an overall remission rate of 82% with **relapse-free probability of 62% at 24 months** along with a manageable safety profile (**Figure 1**)¹
- Sustained remissions were associated with B-cell aplasia**, an expected on-target effect and pharmacodynamic marker of tisagenlecleucel persistence

Figure 1. ELIANA: Relapse-Free Survival in Pediatric and Young Adult Patients With r/r B-ALL



Reprinted from Grupp SA, et al. ASH 2018; Abstract 895. B-ALL, B-cell acute lymphoblastic leukemia; CI, confidence interval; NE, not estimable; r/r, relapsed or refractory.

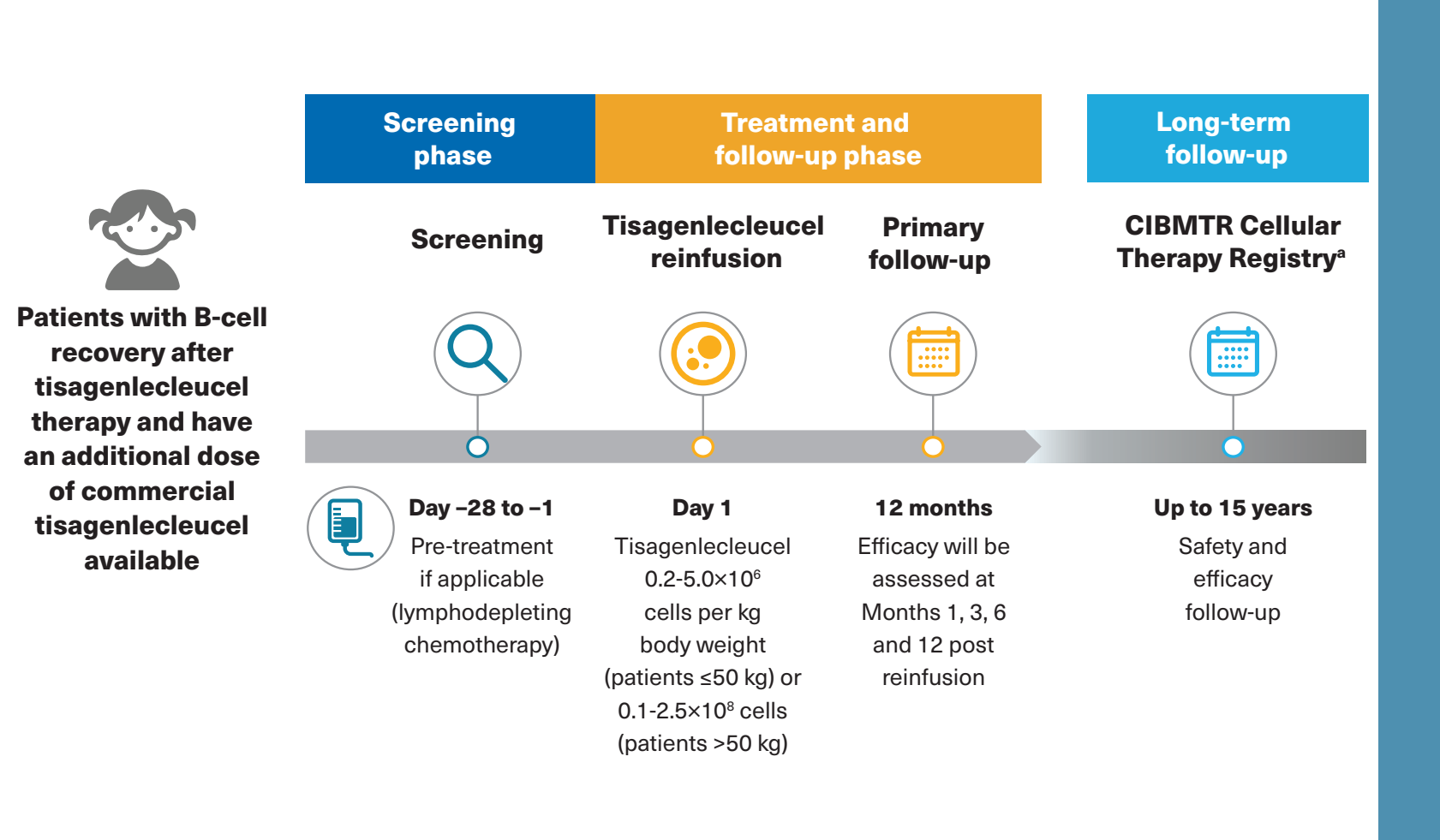
Rationale for Tisagenlecleucel Reinfusion

- Early B-cell recovery is associated with higher risk of relapse²
- Reinfusion with 1 or more additional doses of tisagenlecleucel** may restore B-cell aplasia in some patients³
- Among a subset of patients reinfused with tisagenlecleucel, **one third achieved remission**³
- Reinfusion may prolong tisagenlecleucel activity and immunosurveillance, which may result in **prolonged durable remission**

Study Design

- HESTER (NCT04225676) is a Phase II, open-label, multicenter trial that will determine the efficacy and safety of tisagenlecleucel reinfusion in pediatric and young adult patients with B-ALL experiencing loss of B-cell aplasia (**Figure 2**)

Figure 2. HESTER Study Design



*For patients who do not provide consent for participation for the registry, adverse events will need to be reported per the Safety Reporting guidelines of 15 years or until the patient enrolls in the CIBMTR Cellular Therapy registry. CIBMTR, Center for International Blood and Marrow Transplant Research.

PATIENT ELIGIBILITY

Table 1. Key Inclusion Criteria

Additional dose of commercial tisagenlecleucel (unexpired) available
Age ≤25 years at time of ICF signature
Patients with CD19+ leukemia
Karnofsky (age ≥16 years) or Lansky (age <16 years) performance status ≥50 at screening
Patients previously treated with commercial tisagenlecleucel and present evidence of B-cell recovery defined by either of the following criteria: • PB absolute B-lymphocyte count ≥50/μL OR • PB B lymphocyte ≥10% of the total lymphocytes
Patients must meet the following hematological values without transfusion at screening: • ANC ≥1000/mm³ • ALC >300/mm³ • Absolute number of CD3+ T cells >150/mm³ • Platelets ≥50,000/mm³ • Hemoglobin ≥8.01 g/dL
Serum creatinine of ≤1.5 times ULN or eGFR ≥60 mL/min/1.73 m ²
Adequate pulmonary function, defined as • No or mild dyspnea (grade ≤1) • Oxygen saturation measured by pulse oximetry >90% on room air
Liver function including ALT and AST ≤5 times the ULN or total bilirubin <2 mg/dL ^a

Note: Nonhematologic toxicity from prior treatment must be resolved to CTCAE grade 1 or better. The use of hydroxyurea is permitted for temporary control of WBC elevations in patients with aggressive disease both prior to and during the first 7 days after enrollment. The use of corticosteroids within 1 week prior to enrollment is also allowed. ^aPatients with Gilbert's syndrome may be included if their total bilirubin is <4 mg/dL. ALC, absolute lymphocyte count; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CD, cluster of differentiation; CTCAE, Common Terminology Criteria for Adverse Events; eGFR, estimated glomerular filtration rate; ICF, informed consent form; PB, peripheral blood; ULN, upper limit of normal; WBC, white blood cell.

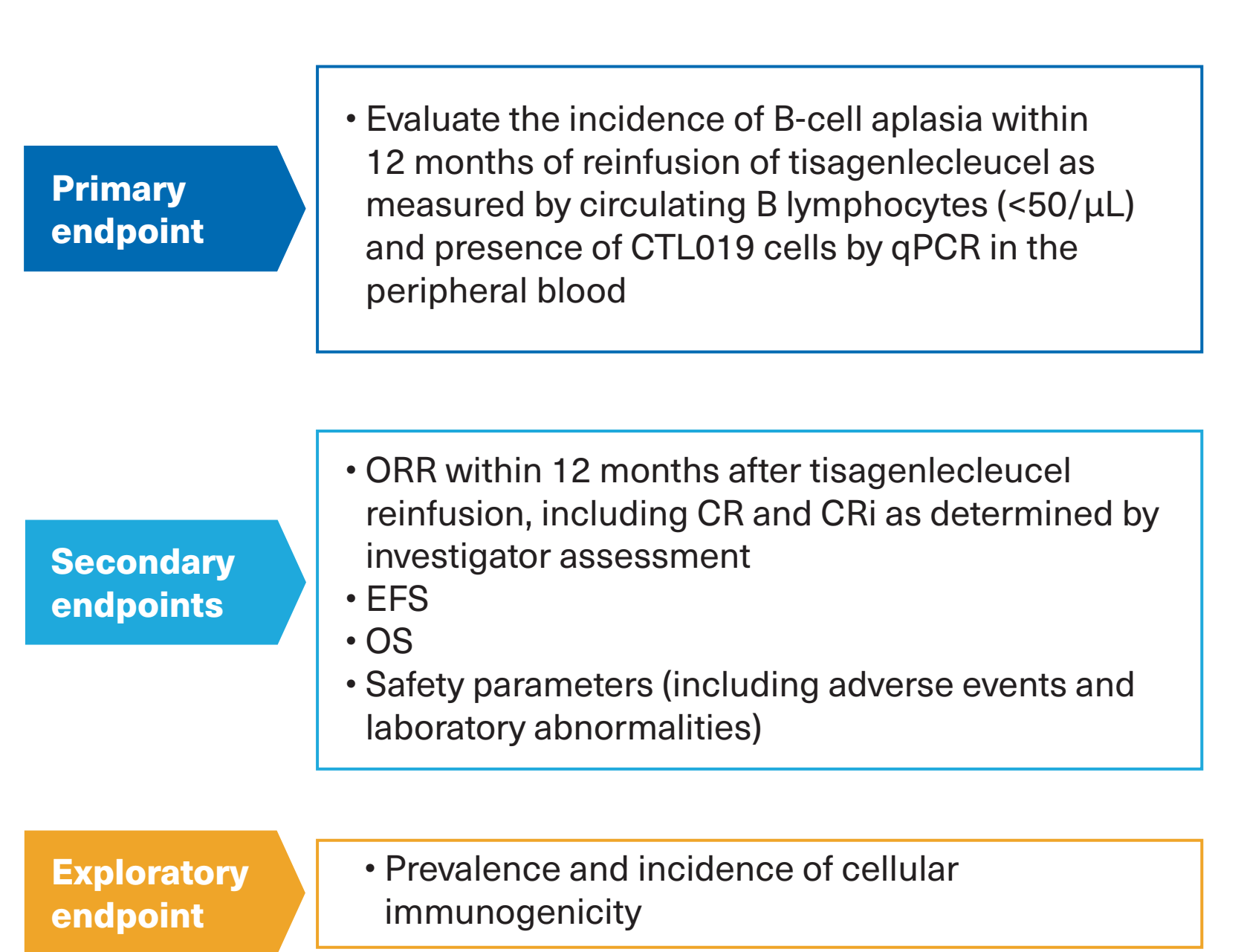
Table 2. Key Exclusion Criteria

Prior gene therapy or adoptive T-cell therapy other than tisagenlecleucel
Active CNS involvement by malignancy
Presence of active or prior hepatitis B or C and/or HIV positive indicated by serology ^a
Systemic chemotherapy/radiotherapy and TKIs ≤2 and ≤1 week prior to enrollment, respectively
Known hypersensitivity to tisagenlecleucel or any product given in the study protocol
Any study procedure is a contraindication to participation in the study
Cardiac disorder including • Unstable angina and/or MI, unstable angina pectoris, CABG <6 months prior to screening • Clinically significant cardiac arrhythmias, complete left bundle branch block, high-grade AV block • LVEF <45% as determined by ECHO, MRA, or MUGA • NYHA functional class III or IV
Clinically significant acute infection confirmed by clinical evidence, imaging, or positive lab tests (blood cultures, PCR) within 72 hours prior to tisagenlecleucel infusion
Previous or concurrent malignancy except for curatively treated non-melanoma skin cancers, in situ carcinoma, and cancers in complete remission for ≤3 years without evidence of recurrence

Note: Nonhematologic toxicity from prior treatment must be resolved to CTCAE grade 1 or better. The use of hydroxyurea is permitted for temporary control of WBC elevations in patients with aggressive disease both prior to and during the first 7 days after enrollment. The use of corticosteroids within 1 week prior to enrollment is also allowed. ^aSerology must be repeated if the time between testing at screening and tisagenlecleucel infusion is >6 weeks. AV, atrioventricular; CABG, coronary artery bypass graft; CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; ECHO, echocardiogram; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, magnetic resonance angiography; MUGA, multiple uptake gated acquisition; NYHA, New York Heart Association; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor; WBC, white blood cell.

STUDY ENDPOINTS

Figure 3. Primary, Secondary, and Exploratory Endpoints



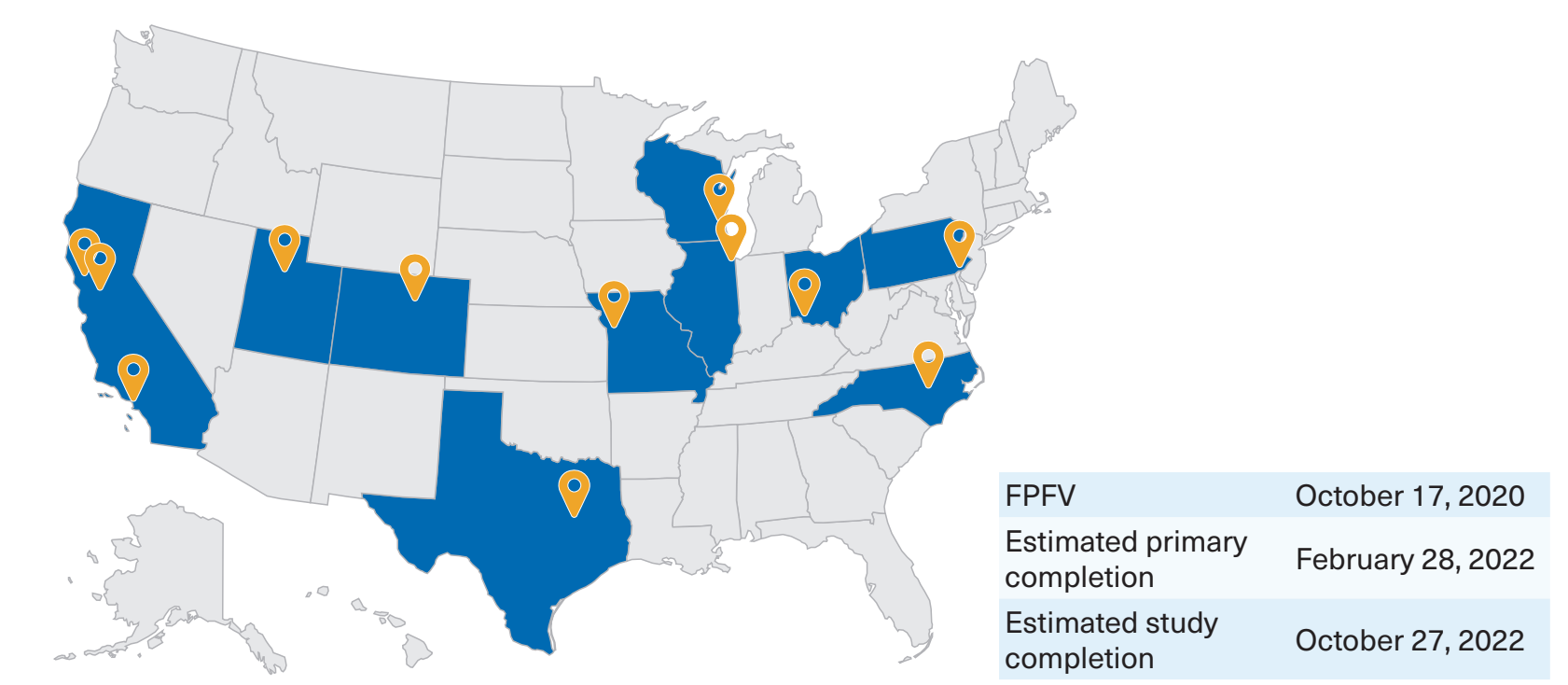
CR, complete remission; CRi, CR with incomplete blood count recovery; EFS, event-free survival; ORR, overall remission rate; OS, overall survival; qPCR, quantitative polymerase chain reaction.

- This is an exploratory study to evaluate the incidence of B-cell aplasia after reinfusion of tisagenlecleucel
- All secondary and exploratory variables will be summarized descriptively

ENROLLMENT AND STUDY DATES

- Estimated enrollment is **54 patients**^a
- 12 participating sites** in the United States (**Figure 4**):
 - Children's Mercy Hospital
 - Cincinnati Children's Hospital
 - University of California San Francisco
 - Children's Hospital of Philadelphia
 - University of Texas Southwestern Medical Center
 - Ann and Robert H. Lurie Children's
 - Hospital of Chicago
 - Children's Hospital Los Angeles
 - Stanford
 - University of Utah
 - Children's Hospital Colorado
 - Medical College of Wisconsin
 - Duke University

Figure 4. Participating Sites



^aA minimum of 49 evaluable patients will be required for the study; considering a dropout rate of 10%, a total of approximately 54 patients will be enrolled into the study. PPFV, first patient first visit.

References

- Grupp SA, et al. ASH 2018; Abstract 895.
- Maude SL, et al. *N Engl J Med*. 2018;378(5):439-448.
- Maude SL, et al. ASCO 2016; Abstract 3007.

Disclosures

Michael W. Boyer reports consultancy for Thunder Biotech, Inc. **Stephan A. Grupp** reports consultancy for Novartis, Roche, GlaxoSmithKline, Cure Genetics, Humanigen, Inc., CBMG, Janssen/J&J; research funding from Novartis, Kite, and Servier; and is on advisory committees for Jazz, Adaptimmune, TCR2, Eureka, Cellectis, Juno, and Allogene. **Michelle Hermiston** is on advisory committees for Sobi and Novartis. **G. Doug Myers** reports consultancy, honoraria, and speakers bureau for Novartis. **Michael A. Pulsipher** reports research funding from Miltenyi Biotec and Adaptive and honoraria from Novartis, Mesoblast, Miltenyi Biotec, Adaptive, Jasper Therapeutics, and Bellicum. **Christine L. Phillips** is on advisory committees for Novartis. **Christina Kovacs** and **Jennifer Willert** are employees at Novartis. All other authors had nothing to disclose.

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