Masonic Cancer Center, University of Minnesota
Blood and Marrow Transplantation Program

Chimeric Antigen Receptor (CAR)-T Cell Therapy for Patients with B-cell Hematologic Malignancies

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Revision History

Revision #	Version Date	Detail of Changes	Consent change? (Y/N)
	6/06/2018	Original for review	
	07/10/2018	Updated per CPRC Stipulations: clarified objectives and endpoints and statistics for Arms A and C; edited wording and punctuation of eligibility criteria for clarity; additional minor edits throughout for consistency	NA
	05/23/2019	Updated study committee Updated Event Reporting Guidelines Minor edits to eligibility criteria and study calendar to align with current SOPs Section 6.5 clarified patient evaluation may be performed by a designated health care provider Corrected spelling and grammatical errors	No
	10/07/2020	Updated Study committee Clarified Eligibility Criteria Deleted eligibility checklists from protocol – eligibility checklists are now kept in Oncore Arm C – Added bendamustine back as alternative lymphodepleting regimen Throughout protocol added Tecartus CAR-T product for MCL (Arm D) Removed recommended collection target dose Increased window around Yescarta infusion timing Updated management of expected AEs to current literature Added 9 month clinical care follow up visit	Yes
	11/13/2020	Minor edits to synopsis, section 3.0 and section 11 per CPRC Stipulations	Yes (redated)
	02/11/2021	Schema – removed recommendation for 7 days inpatient monitoring, as decision will be made by clinical team Section 4 minor edits to inclusion/ exclusion criteria per current institutional guidelines; edited typographical errors Section 6.1 and 6.2 removed concomitant medications – replaced by new appendix VI Tisagenlecleucel washout instructions Section 6.4 removed infusion dose guidelines. Dose will be determined by will be based on data at the time of infusion. Section 8. Updated clinical care activities to current institutional guidelines Throughout document fixed numbering on headers, appendices, corrected typographical errors	No
	05/26/2021	Updated study committee Throughout protocol (synopsis, schema, section 1.1, section 1.2, section 2,section 3, section 4.5, section 4.6, section 6, section 9.3	Yes

Revision #	Version Date	Detail of Changes	Consent change? (Y/N)
		section 11) – added arms (eligibility, treatment, and statistics) for newly approved CAR-T products Arm E Breyanzi and Arm F Abecma. Rationale – these CAR-T products have received FDA approval. This protocol was designed to be amended as new CAR-T products are approved. Synopsis, section 4.2, section 2, added follicular lymphoma to Arm B, rationale - recent FDA approval for this indication Synopsis, section 1.2, Section 11 – clarified that secondary endpoints for large cell lymphoma and follicular lymphoma will be evaluated separately. Rationale – to keep datapoints separate for different indications Section 4.0 – minor edits to eligibility criteria for clarity and consistency Section 4.8 – updated contraception methods from "highly effective" to "effective." Rationale: guidance from current product package inserts Section 6 – clarified that the washout guidance for Tisagenlecleucel is applicable to all CAR-T products. Rationale – to avoid confusion Section 6 – removed prohibited medications table – this was replaced by Appendix VI in previous amendment. Rationale – table mistakenly not removed in prior amendment Section 6.2 – updated leukapheresis instructions to conform to current SOPs Section 6.4 – updated Peds Kymriah dosing per current manufacturer instructions – clarification New section 6.8 – added language on follow-up to include guidance for patients who are withdrawn from treatment. Rationale – clarification per coordinator request Section 7.0 – Updated Expected toxicities. Rationale – per new study product package inserts Section 8 – Updated clinical care activities calendar. Rationale – to conform to current BMT program order sets and SOPs	
	11/03/2021	Updated study committee Updated protocol title to clarify that product is for B-cell malignancies Throughout protocol (synopsis, schema, section 1.1, section 1.2, section 2,section 3, section 4.5, section 4.6, section 6, section 9.3 section 11) – added arms (eligibility, treatment, and statistics) for newly approved indication Arm G Tecartus for B-Cell ALL. Rationale – these CAR-T products have received FDA approval. This protocol was designed to be amended as new CAR-T products and indications are approved. Synopsis, section 1.2, Section 11 – clarified which objectives and endpoints are for which indications and products. Rationale – to clarify datapoints for different indications Synopsis, Section 11 – updated enrollment goal. Rationale – to account for new approvals and indications	Y (updated study title)

Revision #	Version Date	Detail of Changes	Consent change? (Y/N)
		Section 2 – Updated background to include new research results Section 4.0 – minor edits to eligibility criteria for clarity and consistency Section 6.5 – Updated product infusion instructions to current standard of care Section 7.13 – Updated HLH/ MAS risk per new package insert Section 8 – Updated clinical care activities calendar. Rationale – to conform to current BMT program order sets and SOPs Section 9.2 – Specified that CARTOX screening assessments will be performed through at least day 14. Rationale – in order to standardize procedure and reduce protocol deviations	
	12/14/2021	Section 11.4 Edited typographical error per CPRC Stipulation	No
	06/30/2023	Title page – updated collaborators Study synopisis, - Section 4.1.1. – removed 'pediatric' from diagnosis per admin memo 3/30/2022, Section 4.1.3, section 4.2.3, section 4.4.3, section 4.4.3, section 4.5.3, section 4 6.3 and section 4.7.3 - updated acceptable platelet parameter to >30,000 to better reflect current clinical practice Section 4.1.5, section 4.2.5, section 4.3.5, section 4.4.5, section 4.5.5, section 4.6.5 - removed CNS disease as an exclusion criteria to better reflect current clinical practice Appendix I, II, V, VI, VII, VIII – removed package insert information per admin memo 3/30/2022 Throughout protocol: updated references to CAR-T product package inserts in appendixes to simply refer to package inserts Appendix III – renumbered to Appendix I Appendix IV – renumbered to Appendix II	Y (per continuing review updated contact information per most recent template)

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Abbreviations

AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine Aminotransferase/Glutamic Pyruvic Transaminase/SGPT
AST	Aspartate Aminotransferase/Glutamic Oxaloacetic Transaminase/SGOT
ATG	Anti-thymocyte globulin
B-ALL	B-cell precursor acute lymphoblastic leukemia
BM	Bone Marrow
BMT	Bone Marrow Transplantation
CAR	Chimeric Antigen Receptor
CBC	Complete Blood Count
CD137	4-1BB costimulatory molecule
CNS	Central Nervous System
CR	Complete remission
CRF	Case Report/Record Form
CRi	Complete remission with incomplete blood count recovery
CRS	Cytokine Release Syndrome
CSF	Cerebral Spinal Fluid
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL019 cells	CD 19 redirected autologous T cells (also called CART19 T cells)
DLI	Donor Lymphocyte Infusion
DLBCL	Diffuse Large B Cell Lymphoma
DOR	Duration of Remission
ECG	Electrocardiogram
ECHO	Echocardiogram
EDC	Electronic Data Capture
EFS	Event Free Survival
FAB	Fragment Antigen Binding
FDA	Food and Drug Administration
FISH	Fluorescent *in situ* hybridization
G-CSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
GVHD	Graft versus Host Disease
HIV	Human Immunodeficiency Virus
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine Device
LDH	Lactate Dehydrogenase

LFT	Liver Function Test
LP	Lumbar Puncture
LVEF	Left Ventricular Ejection Fraction
MCL	Mantle Cell Lymphoma
MRD	Minimal Residual Disease
MUGA	Multiple Uptake Gated Acquisition
MYC	A regulator gene located on chromosome 8 that is disregulated via translocations in Burkitt's lymphoma/leukemia
NCCN	National Comprehensive Cancer Network
NE	Norepinephrine Equivalent
NHL	non-Hodgkin's lymphomas
O2	Oxygen
ORR	Overall Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PHI	Personal Health Information
PI	Principal Investigator
PML	Progressive Multifocal Leukoencephalopathy
PR	Partial Remission
aPTT	Activated Partial Thromboplastin Time
r/r	Relapsed or refractory
RCL	Replication Competent Lentivirus
RFS	Relapse Free Survival
SAE	Serious Adverse Event
scFv	Single chain Fv fragment of an antibody
SCID	Severe Combined Immunodeficiency
SCT	Stem Cell Transplantation
sIg	Surface Immunoglobulin
SNP	Single Nucleic Polymorphisms
TCR-zeta	Signaling domain found in the intracellular region of the TCR zeta, gamma and epsilon chains
TKI	Tyrosine Kinase Inhibitor
TLS	Tumor Lysis Syndrome
ULN	Upper Limit of Normal
VSV-G	Vesicular Stomatitis Virus, Glycoprotein

Study Synopsis

MT2017-45 Chimeric Antigen Receptor (CAR)-T Cell Therapy for Patients with Hematologic B-Cell Malignancies

Study Design:	This is a phase II study of FDA-approved CAR-T products for patients with hematologic malignancies. The study provides criteria for consistent treatment and management according to FDA labelling of CAR-T products and does not contain experimental components. Patients will be assigned to Arms based on age, diagnosis and treating physician CAR-T product preference. Overall remission rate, safety events and other endpoints will be calculated for each Arm separately.
Primary Objective:	The primary objective for Arm A (Kymriah ALL,) is to estimate the complete remission (CR) and CRi (without count recovery) rate at day 28 as a composite endpoint The primary objective for Arm B (Yescarta) is to estimate the Overall Response Rate (complete response + Partial response by Lugano) (ORR) separately for DBLBC and FL. The primary objective for Arm C (Kymriah Lymphoma) is to estimate the Overall Response Rate (complete response + Partial response by Lugano) (ORR). The Primary objective for Arm D (Tecartus for relapsed or refractory mantle cell lymphoma) is the Overall Response Rate (complete response + Partial response by Lugano) (ORR). The Primary objective for Arm E (Breyanzi) is the Overall Response Rate (complete response + Partial response by Lugano) (ORR). The Primary objective for Arm F (Abecma) is to estimate the Overall Response Rate (complete response + Partial response by IMWG criteria) (ORR). The Primary objective for Arm G (Tecartus for relapsed or refractory B-cell precursor acute lymphoblastic leukemia (B-ALL)) is to estimate the complete remission (CR) and CRi (without count recovery) rate at day 28 as a composite endpoint.
Secondary Objectives:	Secondary treatment related objectives for Arm A and Arm G include the following: • Evaluate the proportion of patients with MRD-negative CR (or CRi). Secondary treatment related objectives for all arms include the following: • Evaluate the treatment related mortality (in absence of disease relapse/progression) at day 28, day 100 and 1 year. • Evaluate the Relapse-free Survival (RFS) as evaluated by the time of achievement of complete remission to relapse or death. • Evaluate the event-free survival (EFS) from the date of the CAR-T infusion through 1 year post treatment.

- Evaluate the overall Survival (OS) from the date of the CAR-T infusion through the date of patient death for any reason.
- Evaluate the proportion of patients developing grade 3, 4 targeted toxicity of CRS and/or neurotoxicity.

Eligible Diseases:	Arm A: Relapsed or refractory pediatric CD19+ B-cell Acute Lymphoblastic Leukemia; age 0 to ≤ 25 years at the time of infusion receiving Kymriah "Tisagenlecleucel" product. Arm B: Adults (≥18 years) with relapsed or refractory large B-cell lymphoma and follicular lymphoma after two or more lines of systemic chemotherapy receiving Yescarta (" axicabtagene ciloleucel" product. Arm C: Adults (≥18 years) with relapsed or refractory diffuse large B cell lymphoma receiving Kymriah "Tisagenlecleucel" product. Arm D: Adults (≥18 years) with relapsed or refractory mantle cell lymphoma receiving Tecartus product ("Brexucabtagene Autoleucel") Arm E: Adults (≥18 years) with relapsed or refractory large B-cell lymphoma receiving Breyanzi product ("lisocabtagene maraleucel") Arm F: Adults (≥18 years) with for relapsed or refractory multiple myeloma receiving Abecma product ("Idecabtagene Vicleucel") Arm G: Adults (≥18 years) with relapsed/refractory B-ALL receiving Tecartus product ("Brexucabtagene Autoleucel")
Key Inclusion Criteria	Adequate organ function as defined in section 4.0; not pregnant; no evidence of uncontrolled infection
Enrollment:	Approximately 340 patients over 5 years

Study Schema

			
3-4 weeks prior to planned CAR-T Infusion CAR-T cells manufacturing	2-14 days prior to planned CAR-T Infusion	Day 0 CAR-T infusion	30 days intensive monitoring

 T- Cells collected via Leukapheresis

 lymphodepleting chemotherapy (suggested regimens in section 6.0)

 CAR-T infusion

*Need for and the length of inpatient stay may vary. For adults treated with Yescarta, Kymriah, Tecartus, Breyanzi, or Abecma

Eligibility Glossary	
Arm A Kymriah B-ALL	Section 4.1
Arm B Yescarta DLBCL/FL	Section 4.2
Arm C Kymriah Lymphoma	Section 4.3
Arm D Tecartus for MCL	Section 4.4
Arm E Breyanzi DLBCL	Section 4.5
Arm F Abecma MM	Section 4.6
Arm G: Tecartus B-ALL	Section 4.7

1 Study Objectives

1.1 Primary Objective

The primary objective for Arm A is to estimate the composite rate of complete remission (CR) and CRi (without count recovery) rate at day 28.

The primary objective for Arm B is to estimate the Overall Response Rate (complete response + Partial response by Lugano) (ORR) separately for DBLBC and FL.

The primary objective for Arm C is to estimate the Overall Response Rate (complete response + Partial response by Lugano) (ORR).

The primary object for Arm D is the Overall Response Rate (complete response + Partial response by Lugano) (ORR).

The primary object for Arm E is the Overall Response Rate (complete response + Partial response by Lugano) (ORR).

The primary object for Arm F is to estimate the Overall Response Rate (complete response + Partial response by IMWG criteria) (ORR).

The Primary objective for Arm G (Tecartus for B-ALL) is to estimate the complete remission (CR) and CRi (without count recovery) rate at day 28.

1.2 Secondary Objectives

Secondary treatment related objectives for Arm A include the following:

- Evaluate the proportion of patients with MRD-negative CR (or CRi).

Secondary treatment related objectives for all Arms include the following:

- Evaluate the treatment related mortality (in absence of disease relapse/progression) at day 28, day 100 and 1 year.
- Evaluate the Relapse-free Survival (RFS) as evaluated by the time of achievement of complete remission to relapse or death.
- Evaluate the event-free survival (EFS) from the date of the CAR-T infusion through 1 year post treatment.
- Evaluate the overall Survival (OS) from the date of the CAR-T infusion through the date of patient death for any reason.

- Evaluate the proportion of patients developing grade 3, 4 targeted toxicity of CRS and/or neurotoxicity.

1.3 Correlative Objective

- Patients may be co-enrolled to an independent protocol for research blood and product collection.

2 Background and Rationale

A recent discovery in immunotherapy includes development of genetically modified autologous T cells to express epitopes recognizing various antigens on tumor cells.

Mechanism of Action of all autologous CAR-T products

CAR-T19 is a CD19-directed genetically modified autologous T cell immunotherapy which involves reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing malignant and normal cells. The CAR is comprised of a murine single-chain antibody fragment which recognizes CD19 and is fused to intracellular signaling domains. The costimulatory domain is CAR-T product specific.

The CD3 zeta component is critical for initiating T-cell activation and antitumor activity, while co-stimulatory enhances the expansion and persistence of CAR-T. Upon binding to CD19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of the CAR-T cells.

KYMRIAH

KYMRIAH (tisagenlecleucel) is an FDA approved CD19-directed genetically modified autologous T cell immunotherapy comprised of autologous T cells that are genetically modified using a lentiviral vector to encode an anti-CD19 chimeric antigen receptor (CAR). The CAR is comprised of a murine single-chain antibody fragment (scFv) specific for CD19, followed by a CD8 hinge and transmembrane region that is fused to the intracellular signaling domains for 4-1BB (CD137) and CD3 zeta.

KYMRIAH is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells, then transduced with the lentiviral vector containing the anti-CD19 CAR transgene, and activated with anti-CD3/CD28 antibody coated beads. The transduced T cells are expanded in cell culture, washed, and formulated into a suspension, which then is cryopreserved.

CLINICAL STUDIES

Relapsed or Refractory (R/R) B-cell Acute Lymphoblastic Leukemia (ALL)

In a single-center phase 1-2a study recently reported by Maude et al (2018) the anti-CD19 chimeric antigen receptor (CAR) T-cell therapy tisagenlecleucel (Kymriah) produced high rates of complete remission and was associated with serious but mainly reversible toxic effects in children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL). A phase 2, single-cohort, 25-center, global study of tisagenlecleucel in pediatric and young adult patients with CD19+ relapsed or refractory B-cell ALL. The primary end point was the overall remission rate (the rate of complete remission or complete remission with incomplete hematologic recovery) within 3 months. For this planned analysis, 75 patients received an infusion of tisagenlecleucel and could be evaluated for efficacy. The overall remission rate within 3 months was 81%, with all patients who had a response to treatment found to be negative for minimal residual disease, as assessed by means of flow cytometry. The rates of event-free survival and overall survival were 73% (95% confidence interval [CI], 60 to 82) and 90% (95% CI, 81 to 95), respectively, at 6 months and 50% (95% CI, 35 to 64) and 76% (95% CI, 63 to 86) at 12 months. The median duration of remission was not reached. Persistence of tisagenlecleucel in the blood was observed for as long as 20 months. Grade 3 or 4 adverse events that were suspected to be related to tisagenlecleucel occurred in 73% of patients. The cytokine release syndrome occurred in 77% of patients, 48% of whom received tocilizumab. Neurologic events occurred in 40% of patients and were managed with supportive care, and no cerebral edema was reported. Kymriah was FDA approved in August of 2017 for patients up to age 25 with second or greater relapse or refractory.

Adult Relapsed or Refractory (r/r) Diffuse Large B-cell Lymphoma (DLBCL)

The efficacy and safety of KYMRIAH was evaluated in an open-label, multicenter, single-arm trial (JULIET; NCT02445248). Eligible patients were ≥ 18 years of age with relapsed or refractory DLBCL, who received ≥ 2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous hematopoietic stem cell transplantation (HSCT). The study excluded patients with active central nervous system malignancy, prior allogenic HSCT, an ECOG performance status ≥ 2, a creatinine clearance < 60, alanine aminotransferase > 5 times normal, cardiac ejection fraction < 45%, or absolute lymphocyte concentration less than 300/µL.

Following 2 to 11 days after completion of lymphodepleting (LD) chemotherapy consisting of either fludarabine (25 mg/m2 i.v. daily for 3 days) and cyclophosphamide (250 mg/m2 i.v. daily for 3 days starting with the first dose of fludarabine) or bendamustine (90 mg/m2 i.v. daily for 2 days), KYMRIAH was administered as a single intravenous infusion. Bridging chemotherapy between leukapheresis and LD chemotherapy was permitted to control disease burden. LD chemotherapy could be omitted if the white blood cell count was < 1000

cells/µL. The major efficacy outcome measures were objective response rate per Lugano criteria [2014] as assessed by an independent review committee and duration of response.

Of the 160 patients enrolled, 106 patients received tisagenlecleucel, including 92 patients who received product manufactured in the U.S. and were followed for at least 3 months or discontinued earlier. Eleven out of 160 patients enrolled did not receive tisagenlecleucel due to manufacturing failure. Thirty-eight other patients did not receive tisagenlecleucel, primarily due to death (n = 16), physician decision (n = 16), and adverse events (n = 3).

Of the 92 patients receiving KYMRIAH, 90% received physician's choice of bridging chemotherapy in the interval between start of screening and KYMRIAH infusion, among whom the median number of bridging chemotherapy regimens was 1 (range: 1 to 5) with 83% of patients receiving ≤ 2 regimens. A retrospectively identified sub-group of 68 patients was evaluable for the major efficacy outcome measures. Patients included in this sub-group had either had no bridging chemotherapy, or had imaging that showed measurable disease after completion of bridging chemotherapy, prior to KYMRIAH infusion. Of the 24 patients not included, 8 had no evidence of disease at baseline prior to KYMRIAH infusion, 15 did not have baseline imaging following bridging chemotherapy, and 1 was excluded because of initial misclassification of a neuroendocrine tumor as DLBCL.

Among the efficacy evaluable population of 68 patients, the baseline characteristics were: median age 56 years (range: 22 to 74 years); 71% male; 90% White, 4% Asian, and 3% Black or African American; 78% had primary DLBCL not otherwise specified (NOS) and 22% had DLBCL following transformation from follicular lymphoma, of whom 17% were identified as high grade; and 44% had undergone prior autologous HSCT. The median number of prior therapies was 3 (range: 1 to 6), 56% had refractory disease and 44% relapsed after their last therapy. Ninety percent of patients received lymphodepleting chemotherapy (66% of patients received fludarabine and 24% received bendamustine) and 10% did not receive any LD chemotherapy. The median time from leukapheresis and cryopreservation to KYMRIAH infusion was 113 days (range: 47 to 196 days). The median dose was 3.5×10^8 CAR-positive viable T cells (range: 1.0 to 5.2×10^8 cells). Seventy-three percent of patients received KYMRIAH in the inpatient setting.

Efficacy was established on the basis of complete response (CR) rate and duration of response (DOR), as determined by an independent review committee:

N = 68

Overall Response Rate (ORR) (CR+PR). n (%) (95% CI): n= 34 (50 %) (37.6%, 62.4%)

Complete Response Rate n (%) (95% CI): n= 22 (32%) (21.5%, 44.8%)

Partial Response Rate n (%) (95% CI) : n=12 (18%) (9.5%, 28.8%)

The median time to first response to KYMRIAH (CR or PR) was 0.9 months (range: 0.7 to 3.3 months). The median duration of response was not reached. Response durations were longer in patients who achieved CR, as compared to patients with a best response of partial response (PR). Of the 22 patients who experienced a CR, 9 achieved this status by 1 month, 12 more by month 3, and the last by month 6 after KYMRIAH infusion.

YESCARTA

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy using chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 and CD3-zeta co-stimulatory domains. The anti-CD19 CAR T cells are expanded and infused back into the patient, where they can recognize and eliminate CD19-expressing target cells.

YESCARTA is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells and activated with anti-CD3 antibody in the presence of IL-2, then transduced with the replication incompetent retroviral vector containing the anti-CD19 CAR transgene. The transduced T cells are expanded in cell culture, washed, formulated into a suspension, and cryopreserved.

CLINICAL STUDIES

Relapsed or Refractory Large B-Cell Lymphoma

A single-arm, open-label, multicenter trial ZUMA-1 evaluated the efficacy of a single infusion of (axicabtagene ciloleucel) YESCARTA in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. Eligible patients had refractory disease to the most recent therapy or relapse within 1 year after autologous hematopoietic stem cell transplantation (HSCT). The study excluded patients with prior allogeneic HSCT, any history of central nervous system lymphoma, ECOG performance status of 2 or greater, absolute lymphocyte count less than 100/µL, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the upper limit of normal, cardiac ejection fraction less than 50%, or active serious infection. Following lymphodepleting chemotherapy, Yescarta was administered in a single intravenous infusion at target dose of 0.5-2 x 10^6 CAR positive viable T cells/kg. Maximum permitted dose was 2x 10^8.

Lymphodepleting chemotherapy was administered on day -5,-4 and -3 before YESCARTA. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not

permitted. All patients were hospitalized for YESCARTA infusion and for a minimum of 7 days afterward.

Of 111 patients who underwent leukapheresis, 101 received YESCARTA. Of the patients treated, the median age was 58 years (range: 23 to 76), 67% were male, and 89% were white. Most (76%) had DLBCL, 16% had transformed follicular lymphoma, and 8% had primary mediastinal large B-cell lymphoma. The median number of prior therapies was 3 (range: 1 to 10), 77% of the patients had refractory disease to a second or greater line of therapy, and 21% had relapsed within 1 year of autologous HSCT.

One out of 111 patients did not receive the product due to manufacturing failure. Nine other patients were not treated, primarily due to progressive disease or serious adverse reactions following leukapheresis.

Efficacy was established on the basis of complete remission (CR) rate and duration of response (DOR), as determined by an independent review committee (Table 5 and Table 6). The median time to response was 0.9 months (range: 0.8 to 6.2 months). Response durations were longer in patients who achieved CR, as compared to patients with a best response of partial remission (PR) (Table 6). Of the 52 patients who achieved CR, 14 initially had stable disease (7 patients) or PR (7 patients), with a median time to improvement of 2.1 months (range: 1.6 to 5.3 months).

Follicular lymphoma

On March 5, 2021, the Food and Drug Administration granted accelerated approval to axicabtagene ciloleucel (Yescarta, Kite Pharma, Inc.) for adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Approval in FL was based on a single-arm, open-label, multicenter trial[11] that evaluated axicabtagene ciloleucel, a CD19-directed chimeric antigen receptor (CAR) T cell therapy, in adult patients with relapsed or refractory FL after two or more lines of systemic therapy, including the combination of an anti-CD20 monoclonal antibody and an alkylating agent. Following lymphodepleting chemotherapy, axicabtagene ciloleucel was administered as a single intravenous infusion.

The main efficacy measures were objective response rate (ORR) and duration of response (DOR) as determined by an independent review committee. Among 81 patients in the primary efficacy analysis, the ORR was 91% (95% CI: 83, 96) with a complete remission (CR) rate of 60% and a median time-to-response of 1 month. The median DOR was not reached, and the 1-year rate of continued remission was 76.2% (95% CI: 63.9, 84.7). For all leukapheresed patients in this trial (n=123), the ORR was 89% (95% CI: 83, 94) with a CR rate of 62%.

TECARTUS (Brexucabtagene Autoleucel)

TECARTUS is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

Mechanism of Action

TECARTUS, a CD19-directed genetically modified autologous T cell immunotherapy, containing CD28 and CD3-zeta co-stimulatory domains.

Clinical Studies

A single-arm, open-label, multicenter trial (ZUMA-2; NCT02601313) evaluated the efficacy and safety of a single infusion of TECARTUS in adult patients with relapsed or refractory mantle cell lymphoma (MCL) who had previously received anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a Bruton tyrosine kinase inhibitor (BTKi; ibrutinib or acalabrutinib).[8] Eligible patients also had disease progression after their last regimen or refractory disease to their most recent therapy. The study excluded patients with active or serious infections, prior allogeneic hematopoietic stem cell transplant (HSCT), detectable cerebrospinal fluid malignant cells or brain metastases, and any history of central nervous system (CNS) lymphoma or CNS disorders.

Seventy-four patients were leukapheresed, five (7%) of whom did not begin conditioning chemotherapy or receive TECARTUS: three (4%) experienced manufacturing failure, one (1%) died of progressive disease, and one (1%) withdrew from the study. One patient (1%) received lymphodepleting chemotherapy but did not receive TECARTUS due to ongoing active atrial fibrillation. Sixty-eight of the patients who were leukapheresed received a single infusion of TECARTUS, and 60 of these patients were followed for at least six months after their first objective disease response, qualifying them as efficacy-evaluable. Among the 60 efficacy-evaluable patients, 2×10^6 CAR-positive viable T cells/kg were administered to 54 (90%). The remaining six (10%) patients received doses of 1.0, 1.6, 1.8, 1.8, 1.9, and 1.9×10^6 CAR-positive viable T cells/kg.

Of the 60 efficacy-evaluable patients, the median age was 65 years (range: 38 to 79 years), 51 (85%) were male, and 56 (93%) were white. Most (50 patients; 83%) had stage IV disease. Twenty patients (33% of 60) had baseline bone marrow examinations performed per protocol; of these, ten (50%) were negative, eight (40%) were positive, and two (10%) were indeterminate. The median number of prior therapies among all 60 efficacy-evaluable patients was three (range: two to five). Twenty-six (43%) of the patients had relapsed after or were refractory to autologous HSCT. Twenty-one (35%) had relapsed after their last

therapy for MCL, while 36 (60%) were refractory to their last therapy for MCL. Among the 60 efficacy-evaluable patients, 14 (23%) had blastoid MCL. Following leukapheuresis and prior to administration of TECARTUS, 21 (35%) of the 60 patients received bridging therapy. Sixteen (27%) were treated with a BTKi, 9 (15%) with a corticosteroid, and 4 (7%) with both a BTKi and a corticosteroid.

Among the 60 efficacy-evaluable patients, the median time from leukapheresis to product delivery was 15 days (range: 11 to 28 days), and the median time from leukapheresis to product infusion was 27 days (range: 19 to 63 days). The protocol-defined lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m2 intravenously, both given on each of the fifth, fourth, and third days before TECARTUS infusion, was administered to 53 (88%) of the 60 efficacy-evaluable patients. The remaining seven patients (12%) either received lymphodepletion over four or more days or received TECARTUS four or more days after completing lymphodepletion. All treated patients received TECARTUS infusion on Day 0 and were hospitalized until at least Day 7.

The primary endpoint of objective response rate (ORR) per the Lugano Classification (2014) in 60 evaluable patients was 87%, CR rate 62% and PR rate 25%. The median time to response was 28 days (range: 24 to 92 days). DOR for CR patients not reached; range (1.9- 29.2 months). The median time to response was 28 days (range: 24 to 92 days) with a median follow-up time for DOR of 8.6 months.

TECARTUS for B-ALL

The efficacy of TECARTUS was evaluated in ZUMA-3 (NCT02614066), an open-label, single-arm, multicenter trial in adult patients with relapsed or refractory B-cell precursor ALL. Eligible patients were adults with primary refractory ALL, first relapse following a remission lasting ≤ 12 months, relapsed or refractory ALL after second-line or higher therapy, or relapsed or refractory ALL at least 100 days after allogeneic stem cell transplantation (HSCT). The study excluded patients with active or serious infections, active graft-vs-host disease or taking immunosuppressive medications within 4 weeks prior to enrollment, and any history of CNS disorders, including CNS-2 disease with neurologic changes and CNS-3 disease irrespective of neurological changes. Treatment consisted of lymphodepleting chemotherapy (fludarabine 25 mg/m2 iv daily on Days -4, -3 and -2; cyclophosphamide 900 mg/m2 iv on Day -2) followed by a single intravenous infusion of TECARTUS at a target dose of 1 × 106 anti-CD19 CAR T cells/kg (maximum 1 × 108 cells) on Day 0. All treated patients were hospitalized until at least Day 7.

Seventy-one patients were enrolled and leukapheresed; six of these patients did not receive TECARTUS due to manufacturing failure, eight patients were not treated primarily due to

adverse events following leukapheresis, two patients underwent leukapheresis and received lymphodepleting chemotherapy but were not treated with TECARTUS, and one patient treated with TECARTUS was inevaluable for efficacy. Among the remaining 54 efficacy-evaluable patients, the median time from leukapheresis to product delivery was 16 days (range: 11 to 39 days) and the median time from leukapheresis to TECARTUS infusion was 29 days (range: 20 to 60 days).

Of the 54 patients who were efficacy evaluable, the median age was 40 years (range: 19 to 84 years), 61% were male, and 67% were White, 6% were Asian, 2% were Black or African American, and 2% were American Indian or Alaska Native. At enrollment, 46% had refractory relapse, 26% had primary refractory disease, 20% had untreated second or later relapse, and 7% had first untreated relapse. Among prior therapies, 43% of patients were previously treated with allo-SCT, 46% with blinatumomab, and 22% with inotuzumab. Twenty-six percent of patients were Philadelphia chromosome positive (Ph+). Fifty (93%) patients had received bridging therapy between leukapheresis and lymphodepleting chemotherapy to control disease burden.

The efficacy of TECARTUS was established on the basis of complete remission (CR) within 3 months after infusion and the duration of CR (DOCR). Twenty-eight (51.9%) of the 54 evaluable patients achieved CR, and with a median follow-up for responders of 7.1 months, the median DOCR was not reached (Table 8). The median time to CR was 56 days (range: 25 to 86 days). All efficacy evaluable patients had potential follow-up for ≥ 10 months with a median actual follow-up time of 12.3 months (range: 0.3 to 22.1 months).

Breyanzi "lisocabtagene maraleucel"

BREYANZI is a CD19-directed genetically modified autologous T cell immunotherapy indicated 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 (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.[9]

Mechanism of Action

BREYANZI is a CD19-directed genetically modified autologous cell immunotherapy administered as a defined composition to reduce variability in CD8-positive and CD4-positive T cell dose. The CAR is comprised of an FMC63 monoclonal antibody derived single chain variable fragment (scFv), IgG4 hinge region, CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and CD3 zeta activation domain. CD3 zeta signaling is critical for initiating activation and antitumor activity, while 4-1BB (CD137) signaling enhances the expansion T cell and persistence of BREYANZI.

Clinical Studies

The efficacy of BREYANZI was evaluated in an open-label, multicenter, single-arm trial[12] in adult patients with relapsed or refractory large B-cell non-Hodgkin lymphoma after at least 2 lines of therapy. The study included patients with ECOG performance status ≤ 2, prior autologous and/or allogeneic hematopoietic stem cell transplant (HSCT), and secondary CNS lymphoma involvement. The study excluded patients with a creatinine clearance of less than 30 mL/min, alanine aminotransferase > 5 times the upper limit of normal, or left ventricular ejection fraction < 40%. There was no prespecified threshold for blood counts; patients were eligible to enroll if they were assessed by the investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy. Bridging therapy for disease control was permitted between apheresis and the start of lymphodepleting chemotherapy, including intrathecal chemotherapy or radiation therapy for treatment of CNS involvement with lymphoma.

Efficacy was based on complete response (CR) rate and duration of response (DOR), as determined by an independent review committee (IRC) using 2014 Lugano criteria. The median time to first response (CR or partial response [PR]) was 1.0 month (range: 0.7 to 8.9 months). The median time to first CR was 1.0 month (range 0.8 to 12.5 months). Of the 104 patients who achieved CR, 23 initially had stable disease (6 patients) or PR (17 patients), with a median time to improvement of 2.2 months (range: 0.7 to 11.6 months).

Response durations were longer in patients who achieved a CR, as compared to patients with a best response of PR (Table 6). Of the 104 patients who achieved CR, 68 (65%) had remission lasting at least 6 months and 64 (62%) had remission lasting at least 9 months.

Of the 287 patients who underwent leukapheresis and had radiographically evaluable disease, 27 additional patients achieved a respons. The IRC-assessed overall response rate in the leukapheresed population (n=287) was 59% (95% CI: 53, 64), with a CR rate of 43% (95% CI: 37, 49) and PR rate of 15% (95% CI: 11, 20). These efficacy results include responses that may have been contributed solely by bridging therapy, responses after receipt of product outside of the intended dose range, and responses to product that did not meet release specifications.[9]

Abecma "Idecabtagene Vicleucel"

ABECMA is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.[10]

Mechanism of Action

ABECMA is a chimeric antigen receptor (CAR)-positive T cell therapy targeting B-cell maturation antigen (BCMA), which is expressed on the surface of normal and malignant plasma cells. The CAR construct includes an anti-BCMA scFv-targeting domain for antigen specificity, a transmembrane domain, a CD3-zeta T cell activation domain, and a 4-1BB costimulatory domain.[10]

Clinical Studies

Efficacy of ABECMA was evaluated in KarMMa[13], an open-label, single-arm, multicenter study in adult patients with relapsed and refractory multiple myeloma who had received at least 3 prior lines of antimyeloma therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. The study included patients with ECOG performance status of 0 or 1. The study excluded patients with a creatinine clearance of less than or equal to 45 mL/minute, alanine aminotransferase >2.5 times upper limit of normal and left ventricular ejection fraction <45%. Patients were also excluded if absolute neutrophil count <1000 cells/mm3 and platelet count <50,000/mm3. Patients had measurable disease by International Myeloma Working Group (IMWG) 2016 criteria at enrollment. Bridging therapy with alkylating agents, corticosteroids, immunomodulatory agents, proteasome inhibitors, and/or anti-CD38 monoclonal antibodies to which patients were previously exposed was permitted for disease control between apheresis and until 14 days before the start of lymphodepleting chemotherapy.

Response durations were longer in patients who achieved a stringent CR as compared to patients with a PR or VGPR. Of the 28 patients who achieved a stringent CR, it is estimated that 65% (95% CI: 42%, 81%) had a remission lasting at least 12 months.

The median duration of response for VGPR patients (n=25) was 11.1 months (95% CI: 8.7, 11.3).

The median duration of response for PR patients (n=19) was 4.0 months (95% CI: 2.7, 7.2).

Within the recommended dose of 300 to 460 x 10^6 CAR-positive T cells, a dose-response relationship was observed with higher ORR and sCR rate in patients who received 440 to 460 x 106 compared to 300 to 340 x 10^6 CAR-positive T cells. Overall response rate of 79% (95% CI: 65%, 90%) and sCR rate of 31% (95% CI: 19%, 46%) was observed with 440 to 460 x 10^6 CAR-positive T cells. Overall response rate of 65% (95% CI: 51%, 78%) with sCR rate of 25% (95% CI: 14%, 39%) was observed in 300 to 340 x 106 CAR-positive T cells.

One hundred and thirty-five patients underwent leukapheresis. Fifteen out of the 23 patients who received treatment outside of the recommended dose range of 300 to 460 x 10^6 CAR-positive T cells experienced a response in addition to the responses noted in Table 6. The IRC assessed overall response in the leukapheresis population (n=135) was 64% (95% CI: 56%, 72%) with stringent CR rate of 24% (95% CI: 17%, 32%), VGPR rate of 21% (95% CI: 14%, 29%) and PR rate of 20% (95% CI: 14%, 28%).

3 Study Design

This is a phase II study of FDA-approved CAR-T products for patients with hematologic malignancies. The study provides criteria for consistent treatment and management according to FDA labelling of CAR-T products and does not contain experimental components. There are no experimental components related to eligibility, treatment and management of CAR-T therapies.

This study will have multiple treatment arms based on disease and choice of CAR-T product. For the patients who are eligible for more than one Arm, Arm choice additionally may depend upon treating physician preference, insurance company prior authorization, or drug availability:

- ARM A: Relapsed or refractory pediatric CD19+ B-cell Acute Lymphoblastic Leukemia treated with Kymriah
- ARM B: Relapsed or refractory large B-cell lymphoma or Follicular lymphoma treated with Yescarta
- Arm C: Adult patients with relapsed and refractory diffuse large B cell lymphoma treated with Kymriah.
- Arm D: Adults (≥18 years) with relapsed or refractory mantle cell lymphoma receiving Tecartus product (Brexucabtagene Autoleucel)
- Arm E: Adults (≥18 years) with relapsed or refractory large B-cell lymphoma receiving Breyanzi product ("lisocabtagene maraleucel")
- Arm F: Adults (≥18 years) with for relapsed or refractory multiple myeloma receiving Abecma product ("Idecabtagene Vicleucel")
- Arm G: Adults (≥18 years) with B-ALL receiving Tecartus product (Brexucabtagene Autoleucel)

  Lymphodepleting chemotherapy options are summarized in "Lymphodepleting chemotherapy guidelines" to provide the treating physician with individual patient flexibility.

4 Patient Selection

Study entry is open to persons of any age regardless of gender, race or ethnic background. While there will be every effort to seek out and include females and minority patients, the patient population is expected to be no different than that of similar studies at the University of Minnesota.

4.1 ARM A (Kymriah) and Arm G (Tecartus) :Refractory/relapsed B-cell acute lymphoblastic leukemia expressing CD19

4.1.1 Age and Disease Status

- Must be age 0- ≤ 25 years (for Arm A Kymriah) or >18 years (Arm G Tecartus)
- Disease status: Relapsed and refractory B-cell ALL defined by one of these:
  - Primary induction failure with no complete remission after ≥2 cycles of induction chemotherapy, or
  - Patients with persistent minimal residual disease (MRD >0.01% by flow cytometry or persistent by cytogenetic or molecular assays) after ≥2 cycles of consolidation chemotherapy, or
  - First relapse following remission lasting <12 months
  - Patients in 2nd or greater relapse of B-ALL or
  - Down Syndrome or other congenital diseases assuming that they fit the criteria for second or greater relapse or refractory leukemia, or
  - Patients with Ph+ ALL who have failed or are intolerant to two lines of TKI assuming they fit the criteria for second or greater relapse or are considered refractory.
  - Relapsed or refractory ALL after allogeneic stem cell transplantation and off immunosupression

4.1.2 Performance Status

- Arm A: Karnofsky (age ≥16 years) or Lansky (age < 16 years) performance status ≥ 50% at screening; Arm G: ECOG 0, 1 or 2

4.1.3 Organ Function

- Renal function defined as:
  - A serum creatinine of ≤1.5 x ULN OR
  - eGFR ≥ 40 mL/min/1.73 m^2
- Liver function defined as:

- ALT ≤ 5 times the ULN for age (unless due to disease)
- Bilirubin ≤ 2.0 mg/dl with the exception of patients with Gilbert syndrome; may be included if their total bilirubin is ≤ 3.0 x ULN and direct bilirubin ≤ 1.5 x ULN

- Must have a minimum level of pulmonary reserve defined as ≤ Grade 1 dyspnea and pulse oxygenation SpO2 > 88% on room air
- Hemodynamically stable and LVEF ≥ 40% confirmed by echocardiogram or MUGA

4.1.4 Other Inclusion Criteria

- Life expectancy ≥12 weeks
- Women of child bearing potential and sexually active males with partners of child bearing potential must agree to use adequate birth control for the duration of treatment. See section 4.7 for definitions of child bearing potential and section 4.8 for definitions of adequate birth control.
- Written voluntary consent (adults) or parental/guardian consent (minors or adults with diminished capacity) prior to the performance of any research related tests or procedures.
- See sections 4.7 and 4.8 for additional criteria involving pregnancy and contraception.

4.1.5 Exclusion Criteria

- Pregnant or breastfeeding - Females of childbearing potential must have a blood test or urine study within 14 days prior to registration to rule out pregnancy.
- Patients with Burkitt's lymphoma/leukemia (i.e. patients with mature B-cell ALL, leukemia with B-cell [sIg positive and kappa or lambda restricted positivity] ALL, with FAB L3 morphology and /or a MYC translocation)
- Presence of Grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD). All GVHD medication must be stopped 1 week prior to apheresis.
- Uncontrolled active hepatitis B or hepatitis C
- Active HIV infection
- Uncontrolled acute life threatening bacterial, viral or fungal infection (e.g. blood culture positive ≤ 72 hours prior to infusion)
- Unstable angina and/or myocardial infarction within 1 month prior to CAR-T infusion

- Investigational medicinal product within the last 7 days prior to apheresis or CAR-T infusion
- Intolerance to the excipients of the CAR-T cell product
- Patient has taken one of the prohibited concomitant medications within the timeframe outlined in package insert.

4.2 ARM B: Yescarta for Relapsed or Refractory diffuse large B cell lymphoma and Follicular lymphoma

4.2.1 Age and Disease Status

- Adult patients (age ≥ 18 years)
- One of the following histologies and expression of CD19 by tumor cells:
  - diffuse large B-cell lymphoma (DLBCL) not otherwise specified, or
  - primary mediastinal large B-cell lymphoma, or
  - high grade B-cell lymphoma, or
  - DLBCL arising from follicular lymphoma
  - Follicular lymphoma any grade
- Disease status:
  - Chemotherapy refractory disease after ≥2 lines of chemotherapy, or
  - Relapsed with no remission after ≥1 lines of salvage chemotherapy, or
  - Relapsed following autologous HCT (and failed at least 2 prior lines of therapy including high dose chemotherapy). If salvage therapy is given post autoHCT, the subject must have no complete response, or relapse after the last line of therapy
- Measurable disease at time of apheresis :
  - Nodal lesions or extranodal lesion

4.2.2 Performance Status

- ECOG performance status 0-1 (ECOG 2 permissible for FL)

4.2.3 Organ Function

- Renal function defined as:

- A serum creatinine of ≤1.5 x ULN OR
- eGFR ≥ 40 mL/min/1.73 m2

- Liver function defined as:

  - ALT ≤ 5 times the ULN for age (unless due to disease)
  - Bilirubin ≤ 2.0 mg/dl with the exception of patients with Gilbert syndrome; may be included if their total bilirubin is ≤ 3.0 x ULN and direct bilirubin ≤ 1.5 x ULN
- Must have a minimum level of pulmonary reserve defined as ≤ Grade 1 dyspnea and pulse oxygenation SpO2 > 91% on room air
- Hemodynamically stable and LVEF ≥ 45% confirmed by echocardiogram or MUGA
- Adequate bone marrow reserve (unless marrow infiltrated by disease) defined as :

  - Absolute neutrophil count (ANC) > 1,000/mm3 (only for NHL)
  - Platelets ≥ 30,000/mm3 (transfusion support can be provided)
  - Hemoglobin >8.0 mg/dl (transfusion support can be provided)

4.2.4 Other Inclusion Criteria

- Life expectancy ≥12 weeks
- Women of child bearing potential and sexually active males with partners of child bearing potential must agree to use adequate birth control for the duration of treatment. See section 4.7 for definitions of child bearing potential and section 4.8 for definitions of adequate birth control.
- Written voluntary consent (adults) or parental/guardian consent (minors or adults with diminished capacity) prior to the performance of any research related tests or procedures.
- See sections 4.7 and 4.8 for additional criteria involving pregnancy and contraception.

4.2.5 Exclusion Criteria

- Pregnant or breastfeeding - Females of childbearing potential must have a blood test or urine study within 14 days prior to registration to rule out pregnancy.
- Presence of Grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD). All GVHD medication must be stopped 1 week prior to apheresis.

- Uncontrolled active hepatitis B or hepatitis C
- Active HIV infection (controlled HIV is permissible)
- Uncontrolled acute life threatening bacterial, viral or fungal infection (e.g. blood culture positive ≤ 72 hours prior to infusion)
- Unstable angina and/or myocardial infarction within 1 month prior to CAR-T infusion
- Investigational medicinal product within the last 7 days prior to apheresis or CAR-T infusion
- Intolerance to the excipients of the CAR-T cell product
- Any immunosuppressive medication must be stopped ≥ 2 weeks prior to apheresis (steroids must be stopped >72 hours prior to apheresis).
- Patient has taken one of the prohibited concomitant medications within the timeframe outlined in the package insert.

4.3 ARM C: Kymriah for relapsed or refractory diffuse large B cell lymphoma Inclusion Criteria

4.3.1 Age and Disease Status

- Adult patients (age ≥ 18 years)
- with relapsed or refractory (r/r) large B-cell lymphoma, including
  - diffuse large B-cell lymphoma (DLBCL) not otherwise specified,
  - high grade B-cell lymphoma
  - DLBCL arising from follicular lymphoma.
- Disease status:
  - after two or more lines of systemic therapy or
  - relapse after autologous HCT

4.3.2 Performance Status

- ECOG performance status 0-2

4.3.3 Organ Function

- Renal function defined as:
  - A serum creatinine of ≤1.5 x ULN OR
  - eGFR ≥ 30 mL/min/1.73 m2
- Liver function defined as:
  - ALT ≤ 5 times the ULN for age (unless due to disease)

- Bilirubin ≤ 2.0 mg/dl with the exception of patients with Gilbert syndrome; may be included if their total bilirubin is ≤ 3.0 x ULN and direct bilirubin ≤ 1.5 x ULN

- Must have a minimum level of pulmonary reserve defined as ≤ Grade 1 dyspnea and pulse oxygenation SpO2 > 91% on room air
- Hemodynamically stable and LVEF ≥ 40% confirmed by echocardiogram or MUGA
- Adequate bone marrow reserve (unless marrow infiltrated by disease) defined as :

  - Absolute neutrophil count (ANC) > 1,000/mm3 (only for NHL)
  - Platelets ≥ 30,000/mm3 (transfusion support can be provided)
  - Hemoglobin >8.0 mg/dl (transfusion support can be provided)

4.3.4 Other Inclusion Criteria

- Life expectancy ≥12 weeks
- Women of child bearing potential and sexually active males with partners of child bearing potential must agree to use adequate birth control for the duration of treatment. See section 4.7 for definitions of child bearing potential and section 4.8 for definitions of adequate birth control.
- Written voluntary consent (adults) or parental/guardian consent (minors or adults with diminished capacity) prior to the performance of any research related tests or procedures.
- See sections 4.7 and 4.8 for additional criteria involving pregnancy and contraception.

4.3.5 Exclusion Criteria

- Pregnant or breastfeeding - Females of childbearing potential must have a blood test or urine study within 14 days prior to registration to rule out pregnancy.
- Presence of Grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD). All GVHD medication must be stopped 2 weeks prior to apheresis.
- Uncontrolled active hepatitis B or hepatitis C
- Active HIV infection
- Uncontrolled acute life threatening bacterial, viral or fungal infection (e.g. blood culture positive ≤ 72 hours prior to infusion)

- Unstable angina and/or myocardial infarction within 1 month prior to CAR-T infusion
- Investigational medicinal product within the last 7 days prior to apheresis or CAR-T infusion
- Intolerance to the excipients of the CAR-T cell product
- Any immunosuppressive medication must be stopped ≥ 2 weeks prior to apheresis (steroids must be stopped >72 hours prior to apheresis).
- Patient has taken one of the prohibited concomitant medications within the timeframe outlined in package insert

4.4 ARM D: Tecartus (Brexucabtagene Autoleucel) for relapsed or refractory mantle cell lymphoma

4.4.1 Age and Disease Status

- Adult patients (age ≥ 18 years)
- with relapsed or refractory (r/r) mantle cell lymphoma, including
  - prior 1st line therapy (containing anthracycline or Bendamustine or cytarabine or other)
  - prior Rituximab or other CD20 directed antibody (or inability to treat with CD20 MoAb)
  - not a candidate or relapse after autologous HCT
  - active disease at enrollment

4.4.2 Performance Status

- ECOG performance status 0-1

4.4.3 Organ Function

- Renal function defined as:
  - A serum creatinine of ≤1.5 x ULN OR
  - eGFR ≥ 50 mL/min/1.73 m2
- Liver function defined as:
  - ALT ≤ 5 times the ULN for age (unless due to disease)
  - Bilirubin ≤ 2.0 mg/dl with the exception of patients with Gilbert syndrome; may be included if their total bilirubin is ≤ 3.0 x ULN and direct bilirubin ≤ 1.5 x ULN
- Must have a minimum level of pulmonary reserve defined as ≤ Grade 1 dyspnea and pulse oxygenation SpO2 > 91% on room air

- Hemodynamically stable and LVEF ≥ 45% confirmed by echocardiogram or MUGA
- Adequate bone marrow reserve (unless marrow infiltrated by disease) defined as :

    - Absolute neutrophil count (ANC) > 1,000/mm3 (only for NHL)
    - Platelets ≥ 30,000/mm3 (transfusion support can be provided)
    - Hemoglobin >8.0 mg/dl (transfusion support can be provided)

4.4.4 Other Inclusion Criteria

- Life expectancy ≥12 weeks
- Women of child bearing potential and sexually active males with partners of child bearing potential must agree to use adequate birth control for the duration of treatment. See section 4.7 for definitions of child bearing potential and section 4.8 for definitions of adequate birth control.
- Written voluntary consent (adults) or parental/guardian consent (minors or adults with diminished capacity) prior to the performance of any research related tests or procedures.
- See sections 4.7 and 4.8 for additional criteria involving pregnancy and contraception.

4.4.5 Exclusion Criteria

- Pregnant or breastfeeding - Females of childbearing potential must have a blood test or urine study within 14 days prior to registration to rule out pregnancy.
- Presence of Grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD). All GVHD medication must be stopped 2 weeks prior to apheresis.
- Uncontrolled active hepatitis B or hepatitis C
- Active HIV infection
- Uncontrolled acute life threatening bacterial, viral or fungal infection (e.g. blood culture positive ≤ 72 hours prior to infusion)
- Unstable angina and/or myocardial infarction within 1 month prior to CAR-T infusion
- Investigational medicinal product within the last 7 days prior to apheresis or CAR-T infusion
- Intolerance to the excipients of the CAR-T cell product

- Any immunosuppressive medication must be stopped ≥ 2 weeks prior to apheresis (steroids must be stopped >72 hours prior to apheresis).
- Patient has taken one of the prohibited concomitant medications within the timeframe outlined in the package insert

4.5 ARM E: Breyanzi "lisocabtagene maraleucel" for relapsed or refractory large B-cell lymphoma

4.5.1 Age and Disease Status

- Adult patients (age ≥ 18 years)
- with relapsed or refractory disease after two or more lines of systemic therapy, including
  - diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma),
  - high-grade B-cell lymphoma,
  - primary mediastinal large B-cell lymphoma,
  - follicular lymphoma grade 3B

4.5.2 Performance Status

- ECOG performance status 0-2

4.5.3 Organ Function

- Renal function defined as:
  - A serum creatinine of ≤1.5 x ULN OR
  - eGFR ≥ 30 mL/min/1.73 m2
- Liver function defined as:
  - ALT ≤ 5 times the ULN for age (unless due to disease)
  - Bilirubin ≤ 2.0 mg/dl with the exception of patients with Gilbert syndrome; may be included if their total bilirubin is ≤ 3.0 x ULN and direct bilirubin ≤ 1.5 x ULN
- Must have a minimum level of pulmonary reserve defined as ≤ Grade 1 dyspnea and pulse oxygenation SpO2 > 91% on room air
- Hemodynamically stable and LVEF ≥ 40% confirmed by echocardiogram or MUGA
- Adequate bone marrow reserve (unless marrow infiltrated by disease) defined as :
  - Absolute neutrophil count (ANC) > 1,000/mm3 (only for NHL)

- Platelets ≥ 30,000/mm3 (transfusion support can be provided)
- Hemoglobin >8.0 mg/dl (transfusion support can be provided)

4.5.4 Other Inclusion Criteria

- Life expectancy ≥12 weeks
- Women of child bearing potential and sexually active males with partners of child bearing potential must agree to use adequate birth control for the duration of treatment. See section 4.7 for definitions of child bearing potential and section 4.8 for definitions of adequate birth control.
- Written voluntary consent (adults) or parental/guardian consent (minors or adults with diminished capacity) prior to the performance of any research related tests or procedures.
- See sections 4.7 and 4.8 for additional criteria involving pregnancy and contraception.

4.5.5 Exclusion Criteria

- Pregnant or breastfeeding - Females of childbearing potential must have a blood test or urine study within 14 days prior to registration to rule out pregnancy.
- Presence of Grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD). All GVHD medication must be stopped 2 weeks prior to apheresis.
- Uncontrolled active hepatitis B or hepatitis C
- Active HIV infection
- Uncontrolled acute life threatening bacterial, viral or fungal infection (e.g. blood culture positive ≤ 72 hours prior to infusion)
- Unstable angina and/or myocardial infarction within 1 month prior to CAR-T infusion
- Investigational medicinal product within the last 7 days prior to apheresis or CAR-T infusion
- Intolerance to the excipients of the CAR-T cell product
- Any immunosuppressive medication must be stopped ≥ 2 weeks prior to apheresis (steroids must be stopped >72 hours prior to apheresis).
- Patient has taken one of the prohibited concomitant medications within the timeframe outlined in the package insert

4.6 ARM F: Abecma "Idecabtagene Vicleucel" for relapsed or refractory multiple myeloma

4.6.1 Age and Disease Status

- Adult patients (age ≥ 18 years)
    - Relapsed (progression after prior partial or complete remission) or refractory multiple myeloma
    - Evidence of active disease (medullary or extramedullary)
    - Prior therapy (Failure or intolerance to) with an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody

4.6.2 Performance Status ECOG 0-1 (2 is permitted if due to effects of myeloma)

4.6.3 Organ Function

- Renal function defined as:
    - A serum creatinine of ≤2 x ULN or
    - eGFR ≥ 50 mL/min/1.73 m^2
- Liver Function as defined as :
    - ALT ≤ 5 times the ULN for age (unless due to disease)
    - Bilirubin ≤ 2.0 mg/dl with the exception of patients with Gilbert syndrome; may be included if their total bilirubin is ≤ 3.0 x ULN and direct bilirubin ≤ 1.5 x ULN
- Must have a minimum level of pulmonary reserve defined as ≤ Grade 1 dyspnea and pulse oxygenation SpO2 > 91% on room air
- Hemodynamically stable and LVEF ≥ 45% confirmed by echocardiogram or MUGA
- Adequate bone marrow reserve (unless marrow infiltrated by disease) defined as :
    - Platelets ≥ 30,000/mm3 (transfusion support can be provided)
    - Hemoglobin >8.0 mg/dl (transfusion support can be provided)

4.6.4 Other Inclusion Criteria

- Life expectancy ≥12 weeks
- Women of child bearing potential and sexually active males with partners of child bearing potential must agree to use adequate birth

control for the duration of treatment. See section 4.7 for definitions of child bearing potential and section 4.8 for definitions of adequate birth control.

- Written voluntary consent (adults) or parental/guardian consent (minors or adults with diminished capacity) prior to the performance of any research related tests or procedures.
- See sections 4.7 and 4.8 for additional criteria involving pregnancy and contraception.

4.6.5 Exclusion Criteria

- Pregnant or breastfeeding - Females of childbearing potential must have a blood test or urine study within 14 days prior to registration to rule out pregnancy.
- Presence of Grade 2 to 4 acute or extensive chronic graft-versus-host disease (GVHD). All GVHD medication must be stopped 2 weeks prior to apheresis.
- Uncontrolled active hepatitis B or hepatitis C
- Active HIV infection
- Uncontrolled acute life threatening bacterial, viral or fungal infection (e.g. blood culture positive ≤ 72 hours prior to infusion)
- Unstable angina and/or myocardial infarction within 1 month prior to CAR-T infusion
- Investigational medicinal product within the last 7 days prior to apheresis or CAR-T infusion
- Intolerance to the excipients of the CAR-T cell product
- Any immunosuppressive medication must be stopped ≥ 2 weeks prior to apheresis (steroids must be stopped >72 hours prior to apheresis).
- Patient has taken one of the prohibited concomitant medications within the timeframe outlined in package insert

4.7 Criteria for Females

Women who are not of reproductive potential (defined as either <11 years of age, Tanner Stage 1, post-menopausal for at least 24 consecutive months (i.e. have had no menses) or have undergone hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy) are eligible without requiring the use of contraception. Women who are not yet of reproductive potential are to agree to use acceptable forms of contraception when they reach reproductive potential if within 1 year of CAR-T infusion. Acceptable documentation includes written or oral

documentation communicated by clinician or clinician's staff of one of the following:

- Demographics show age <11
- Physical examination indicates Tanner Stage 1
- Physician report/letter
- Operative report or other source documentation in the patient record
- Discharge summary
- Follicle stimulating hormone measurement elevated into the menopausal range

4.8 Methods of contraception

Women of child-bearing potential (defined as all women physiologically capable of becoming pregnant) and all male participants, must agree to use effective methods of contraception for the duration of treatment and a period of 1 year after the CAR-T infusion. According to the World Health Organization and the United States Center for Disease Control and Prevention, the most effective forms of birth control include complete abstinence, surgical sterilization (both male and female), intrauterine devices (IUDs), and the contraceptive implant. The next most effective forms of birth control include injectables, oral contraceptive pills, the contraceptive ring, or the contraceptive patch. Acceptable, but least effective, methods of birth control include male condoms (with or without spermicide) and female condoms.

5 Patient Registration In OnCore

Registration will occur after the patient/parent/guardian has signed the subject consent and eligibility is confirmed. To be eligible for registration to this study, the patient must meet each criteria listed on the eligibility checklist based on the eligibility assessment documented in the patient's medical record. A copy of the eligibility checklist is under attachments within the study in OnCore.

Patients will be registered in OnCore by the Masonic Cancer Center's Clinical Data Associates (CDA's). Each patient will be assigned to a study treatment arm based on diagnosis.

6 Treatment Plan (as per package insert for FDA approved agents)

In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care drug therapy (i.e. acetaminophen, diphenhydramine, antimicrobials, etc.).

All treatment will be given per current institutional guidelines with individual patient modifications as clinically indicated. All drugs are commercially available.

Details of the treatment plan are found in the following sections:

Prohibited Concomitant Medications and Therapy	section 6.1
Leukapheresis	section 6.2
Lymphodepleting chemotherapy	section 6.3
CAR-T Infusion Eligibility	section 6.4
CAR-T Infusion	section 6.5
Supportive Care Guidelines	section 6.6
Post CAR-T Reactions	section 6.7

6.1 Prohibited Concomitant Medications and Therapy

The following guidelines should be followed during the study:

- Granulocyte macrophage-colony stimulating factor (GM-CSF) should be avoided due to the potential to worsen CRS symptoms.
- Granulocyte colony stimulating factor (G-CSF) should not be given within 72 hours of CAR-T infusion and long acting G-CSF should not be given within 10 days of CAR-T infusion.
- Steroids or other immunosuppressant drugs should NOT be used as pre-medication for CAR-T therapy or following CAR-T infusion, except as required for physiological glucocorticoid replacement therapy,
- Use of steroids with blood product administration should be eliminated just prior to and following CAR-T if possible or at least minimized.

The following medications are not allowed: please refer to the most recent Washout Guidance Prior to Tisagenlecleucel in package insert.
NOTE: the washout guidance for Tisagenlecleucel is applicable to all CAR-T products, with exceptions for myeloma noted in section 6.2. Ibrutinib and radiation therapy is permitted during apheresis for all Arms.

6.2 Leukapheresis

Patients will undergo leukapheresis to collect autologous T-cells, which will be used to manufacture the CAR-T autologous cellular immunotherapy product. Please refer to the most recent Washout Guidance Prior to CAR-T therapy in package insert.

- **Confirm Leukapheresis Eligibility (Eligibility Checklist kept in Oncore)**
- Patient has to be eligible for CAR-T therapy per FDA label **(Eligibility Checklists for each arm kept in Oncore)**
- Collect CBC (CDC/diff and T cell subset (LAB 3245) at least 24 hours prior apheresis)
- Review absolute lymphocyte count (ALC) (preferred to be >100 but not required)
- Use standard Apheresis order set
- Collect daily CBC/differential on day of collection
- Add T cell subsets (LAB3245) for product to Apheresis Order Set
- **Suggested target yield (not routinely calculated in real time) : CD3+ lymphocyte count >/= 1.0 x 10^9 cells *AND* target total nucleated cell dose (TNC) count >/= 2.0 x 10^9**
- One collection is typically planned.
- Leukapheresis material will be then shipped to the CAR-T manufacturer by MCT facility using SOP.
- Recommendations prior to apheresis:
    - IMiDs -lenalidomide/pomalidomide and Ibrutinib (and other BTK inhibitors) can be continued during apheresis (all Arms)
    - radiotherapy can be continued up to apheresis as long as ALC is at least 100 (all Arms)
    - all other medication should stop at least 1 week prior to apheresis

Apheresis product for Kymriah is shipped frozen. Cryopreservation must be initiated within 24 hours for the end of leukapheresis procedure.

Apheresis product for Yescarta and Tecartus is shipped fresh within 48 hours after apheresis

Apheresis product for Breyanzi is shipped fresh.

Apheresis product for ABECMA is shipped fresh.

CAR-T products are manufactured in FDA approved manufacturing facilities

6.3 Lymphodepleting chemotherapy

Prior to CAR-T cell infusion, all patients will receive one cycle of lymphodepleting chemotherapy as outlined below. The purpose of this chemotherapy is to induce lymphopenia in order to facilitate homeostatic expansion of CAR-T cells.

The **recommended** lymphodepleting regimens are:

ARM A – Kymriah (Tisagenlecleucel) for ALL treatment

Primary regimen:

-Fludarabine 30 mg/m^2 IV daily for 4 days, plus

-Cyclophosphamide 500 mg/m^2 IV daily for 2 days starting with the first dose of fludarabine

Alternative regimen:

(For patients with severe hemorrhagic cystitis with prior cyclophosphamide)

-Cytarabine 500 mg/m^2 IV daily for 2 days, plus

-Etoposide 150 mg/m^2 IV daily x 3 days starting with the 1st dose of cytarabine

Infuse Kymriah 2-14 days after completing chemotherapy

ARM B – Yescarta (Axicabtagene) for DLBCL and FL treatment

Primary regimen:

-Fludarabine 30 mg/m^2 IV daily for 3 days, plus

-Cyclophosphamide 500 mg/m^2 IV daily for 3 days starting with the first dose of fludarabine

Alternative regimen:

None identified.

Infuse Yescarta 2-4 days after completing chemotherapy

ARM C – Kymriah (Tisagenlecleucel) for DLBCL treatment

Primary regimen:

-Fludarabine 25 mg/m^2 IV daily for 3 days, plus

-Cyclophosphamide 250 mg/m^2 IV daily for 3 days starting with the first dose of fludarabine

Alternative regimen:

(For patients with severe hemorrhagic cystitis with prior cyclophosphamide or resistance to a previous cyclophosphamide regimen)

-Bendamustine 90 mg/m2 IV daily for 2 days

Infuse Kymriah 2-11 days after completing chemotherapy

ARM D – Tecartus (Brexucabtagene Autoleucel) for relapsed or refractory Mantle cell lymphoma

Primary regimen:

- Cyclophosphamide 500 mg/m^2 IV on the fifth, fourth, and third days before infusion of TECARTUS.
- Fludarabine 30 mg/m^2 IV on the fifth, fourth, and third days before infusion of TECARTUS.

Alternative regimen:

None identified.

Arm E: Breyanzi (lisocabtagene maraleucel) for relapsed or refractory large B-cell lymphoma

Primary Regimen:

-Fludarabine 30 mg/m^2 intravenously (IV) for 3 days, plus

-Cyclophosphamide 300 mg/m^2 IV for 3 days **starting with the first dose of fludarabine**

Infuse BREYANZI 2 to 7 days after completion of lymphodepleting chemotherapy.

Alternative Regimen

None Identified

ARM F: Abecma (Idecabtagene Vicleucel) for relapsed or refractory multiple myeloma

Primary Regimen

-Fludarabine 30 mg/m^2 IV daily for 3 days, plus

-Cyclophosphamide 300 mg/m^2 IV daily for 3 days starting with the first dose of fludarabine

Infuse ABECMA 2 days after completion of lymphodepleting chemotherapy. May delay up to 7 days for certain conditions (see ABECMA package insert)

Alternative Regimen

None identified

ARM G – Tecartus (Brexucabtagene Autoleucel) B-ALL

Primary regimen:

Administer a lymphodepleting chemotherapy regimen of:

- fludarabine 25 mg/m2 intravenously over 30 minutes on the fourth, third, and second day before infusion of TECARTUS

-administer cyclophosphamide 900 mg/m2 over 60 minutes on the second day before infusion of TECARTUS

Alternative regimen:

None identified.

ALL=Acute Lymphoblastic Leukemia, DLBCL=diffuse large B-cell lymphoma, FL follicular lymphoma, MM=Multiple Myeloma, B-ALL= B-cell precursor acute lymphoblastic leukemia

Treating investigators should consult with a member of the study team if they wish to use an alternative regimen from the above. The dose modification is permitted.

6.4 CAR-T Infusion Eligibility

Prior to CAR-T infusion, eligibility must be reconfirmed and documented in the CAR-T Epic Order set. The following criteria must be met:

6.4.1 DO NOT INFUSE CAR-T CELLS IF (instead delay until the event has resolved):

- 6.4.1.1 There is a significant change in patient status.
- 6.4.1.2 SpO2 sats <91% on RA or using supplemental O2.
- 6.4.1.3 New uncontrolled cardiac arrhythmia.
- 6.4.1.4 Hypotension requiring vasopressor support.
- 6.4.1.5 Uncontrolled, active infection with + culture within 72 hours.
- 6.4.1.6 Rapidly progressing malignancy

6.4.2 **Influenza Testing:** All patients will undergo a rapid influenza diagnostic test during the months of October through May within 10 days prior to the planned CAR-T infusion. If the patient is positive for influenza, he/she should complete a full course of oseltamivir phosphate or zanamivir and become asymptomatic.

6.4.3 **Performance Status:** Patient should not experience a significant change in clinical or performance status compared to initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse events associated with experimental cell infusion.

6.4.4 **Laboratory Abnormalities:** Patients experiencing laboratory abnormalities after enrollment, that in the opinion of the treating investigator or PI may impact subject safety or the subjects' ability to receive the CAR-T infusion, may have their infusion delayed until it is determined to be clinically appropriate to proceed with the CAR-T infusion.

6.4.5 **Leukemia Disease Status:** Prior to CAR-T infusion and following lymphodepleting (LD) chemotherapy patients must not have accelerating disease, as this will put them at unacceptable risk for severe CRS. Patients should not receive CAR-T infusion if they exhibit significant progression of

disease during or following LD chemotherapy as evidenced by: significant and increasing circulating blasts, significant increases in organomegaly.

6.4.6 **Lymphoma Disease Status:** Patients should not receive CAR-T infusion if they exhibit significant progression of disease during or following LD chemotherapy as evidenced by: significant increase in nodal disease, significant increases in extranodal areas, occurrence of new lymphoma manifestations, or evidenced by significant increase in lymphoma cells in blood.

6.4.7 **Infection:** CAR-T infusion must be delayed if there is an uncontrolled active infection, as evidenced by positive blood cultures for bacteria, fungus, or PCR positivity for new viral DNA within 72 hours of CAR-T cell infusion, or clinical or radiographic evidence of active infection. Following the treatment of a recent infection, significant improvement must be established either clinically and/or radiographically, prior to CAR-T infusion.

6.4.8 **GVHD Status:** Patients should not be infused if they develop Grade 2-4 acute or extensive chronic GVHD since the time of screening.

6.4.9 **Chemotherapy Toxicity:** Patients experiencing toxicities from their preceding lymphodepleting chemotherapy will have their infusion schedule delayed until these toxicities have been resolved (to Grade 1 or baseline). See section 8.8 for specific prohibited concomitant therapies. The specific toxicities warranting delay of CAR-T cell infusion include:

- Pulmonary: Requirement for supplemental oxygen to keep saturation greater than 91% or presence of progressive radiographic abnormalities on chest x-ray
- Cardiac: New cardiac arrhythmia not controlled with medical management. Prior to infusion ECG also required
- Hypotension: requiring vasopressor support

6.4.10 **Prohibited concomitant medications:** If patients are taking any of the medications listed in package insert, their infusion must be delayed until the medications have been stopped.

6.5 CAR-T Infusion

- **All cell doses are independent of patient weight, except for r/r B-Cell ALL patients ≤50 kg (KYMRIAH recipients only)**
- **Two doses of tocilizumab should be on site prior to CAR-T infusion.**

- **An attending physician or designated health care provider MUST evaluate the patient just prior to CAR-T infusion to ensure the patients meets CAR-T infusion criteria.**
- Do NOT use a leukocyte-depleting filter.
    - - Infuse all contents of the infusion bag.
    - - Rinse the infusion bag with 10 mL normal saline while maintaining a closed tubing system to assure as many cells as possible are infused into the patient.

CAR-T product contains human cells genetically modified with a lentivirus/retrovirus. Follow local biosafety universal guidelines applicable for handling and disposal of such products to avoid potential transmission of infectious diseases when handling the product.

Premedication:

All patients should be pre-medicated with acetaminophen and diphenhydramine. May repeated every 4-6 hours as needed.

Steroids should NOT be used for premedication. Therapeutic steroids must be stopped >72 hours prior to CAR-T infusion. (Physiological replacement doses are allowed: > 6-12mg /m2/day). **No** systemic corticosteroids other than physiologic replacement of hydrocortisone.

Cell thawing and infusion of CAR-T product:

For detailed instructions on the storage, handling, preparation and administration of the CAR-T cell product, refer to the KYMRIAH and YESCARTA and TECARTUS and Breyanzi and Abecma package Inserts and UM MCT SOP. All used infusion supplies, including the infusion bag(s) and tubing, will be disposed of according to the specific guidance provided in the Procedure Manual.

<u>After cell thawing, CAR-T cell product should NOT be washed prior to infusion, and all contents will be infused.</u>

KYMRIAH is provided in a single-dose unit containing chimeric antigen receptor (CAR)-positive viable T cells based on the patient weight reported at the time of leukapheresis. The entire manufactured product is administered to the patient and will be based on data at the time of infusion.

Adult r/r DLBCL: A single dose of KYMRIAH may contain 0.6 to 6.0 x 10^8 CAR-positive viable T cells provided in one or more patient-specific infusion bag(s).

Pediatric r/r B-Cell ALL ≤50 kg: A single dose of KYMRIAH may contain 0.2-5.0 x 10^6 CAR-positive T cells per kg body weight provided in a single patient-specific infusion bag.

Pediatric r/r B-cell ALL >50 kg: A single dose of KYMRIAH may contain 0.1-2.5 x 10^8 CAR-positive T cells provided in a single patient-specific infusion bag.

The actual number of CAR-positive T cells in the product is reported on the Certificate of Analysis (CoA) that is shipped with KYMRIAH. The volume of CAR-positive viable T cells in an infusion bag ranges from 10 mL to 50 mL.

YESCARTA is supplied in an infusion bag (NDC 71287-119-01) containing approximately 68 mL of frozen suspension of genetically modified autologous T cells in 5% DMSO and 2.5% albumin (human).

Each bag contains suspension of dose 2 x 10^6cells CAR positive viable T cells with maximum 2x 10^8 CAR positive viable T-cells.

Tecartus (Brexucabtagene Autoleucel)

TECARTUS is supplied in an infusion bag containing approximately 68 mL of frozen suspension of genetically modified autologous T cells in 5% DMSO and human serum albumin. Each TECARTUS infusion bag is individually packed in a metal cassette. TECARTUS is stored in the vapor phase of liquid nitrogen and supplied in a liquid nitrogen dry shipper.

	Infusion Bag NDC number	Metal Cassette NDC number
MCL	71287-219-01	71287-219-02
ALL	71287-220-01	71287-220-02

Recommended Dosage for MCL

The target dose is 2 × 10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2 × 10^8 CAR-positive viable T cells.

Recommended Dosage for B-ALL

The target dose is 1 × 10^6 CAR-positive viable T cells per kg body weight, with a maximum of 1 × 10^8 CAR-positive viable T cells.

Breyanzi “lisocabtagene maraleucel”

BREYANZI consists of genetically modified autologous T cells, supplied in vials as separate frozen suspensions of each CD8 component (NDC 73153-901-08) and CD4 component (NDC 73153-902-04). Each CD8 or CD4 component is packed in a carton containing up to 4 vials, depending upon the concentration of the cryopreserved drug product CAR-positive viable T cells. The cartons for each CD8 component and CD4 component are in an outer carton (NDC 73153-900-01). BREYANZI is shipped directly to the cell lab or clinical pharmacy associated with the infusion center in the vapor phase of a liquid nitrogen shipper.

A single dose of BREYANZI contains 50 to 110 × 10^6 CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components), with each component supplied separately in one to four single-dose 5 mL vials. Each mL contains 1.5 × 10^6 to 70 × 10^6 CAR-positive viable T cells.

Abecma "Idecabtagene Vicleucel"

ABECMA is supplied in one or more infusion bag(s) (see below) containing a frozen suspension of genetically modified autologous T cells in 5% DMSO. A single dose of ABECMA contains a cell suspension of 300 to 460 x10^6 CAR-positive T cells in one or more infusion bags

Each infusion bag of ABECMA is individually packed in a metal cassette. ABECMA is stored in the vapor phase of liquid nitrogen and supplied in a liquid nitrogen dry vapor shipper.

•50 mL infusion bag and metal cassette (NDC 59572-515-01)

•250 mL infusion bag and metal cassette (NDC 59572-515-02)

•500 mL infusion bag and metal cassette (NDC 59572-515-03)

Breyanzi:

Once the vials of CAR-positive viable T cells (CD8 component and CD4 component) are removed from frozen storage, the thaw must be carried to completion and the cells administered within 2 hours.

- **Administration (use CAR-T infusion order set)**
- Confirm the patient's identity with the patient identifiers on the infusion bag.
- Thaw before using

- Infusion will be completed within 30 minutes of thawing the cryopreserved product in order to preserve maximum cell viability. Use Package Insert for an individual product for safe cell infusion.
- Vital signs (temperature, respiration rate, pulse, pulse oximetry, and blood pressure) will be taken prior to, during and immediately after the infusion.
    - - Prime the tubing prior to infusion with normal saline.
- Administer CAR-T as an intravenous infusion at 10 mL to 20 mL per minute, adjusted as appropriate for smaller children and smaller volumes. The volume in the infusion bag ranges from 10 mL to 50 mL. For BREYANZI administer CD8 component first followed by CD4 component. Use package insert for detail.
- **Following CAR-T infusion:**

Should emergency treatment be required in the event of life- threatening hypersensitivity or other acute infusion-related reaction, supportive therapy such as oxygen, bronchodilators, epinephrine, antihistamines, and corticosteroids should be given according to local institutional guidelines. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

Adhere to CAR-T logistics guidelines (Fairview Intranet) for details re pre and post CAR-T infusion care.

6.6 Supportive Care Guidelines

All patients should receive prophylactic allopurinol, or a non-allopurinol alternative (e.g. febuxostat), use rasburicase as medically indicated. The risk of tumor lysis syndrome (TLS) is dependent on disease burden. Patients will be closely monitored both before and after lymphodepleting chemotherapy and CAR-T infusions including blood tests for potassium and uric acid.

Infection prophylaxis should follow local guidelines and is mainly dictated by the preceding lymphodepleting chemotherapy.

Infection prophylaxis following CAR-T infusion should follow local guidelines for neutropenia.

All blood products administered 6 months following CAR-T should be irradiated.

Immunosuppressive medications, including steroids, should not be administered unless life threatening circumstances arise.

- **Monitoring**

- Monitor patients at least daily for 14 days at the certified healthcare facility following CAR-T cell infusions for signs and symptoms of CRS and neurologic toxicities. (Refer to Appendix II for management guidelines)
- Instruct patients to remain within proximity of the certified healthcare facility (within 45 minutes drive) for up to 4 weeks following infusion.
- Patients should be advised not to drive or operate the machinery for 2 months.
- Providers will provide patients and caregivers with a Patient Wallet Card (required for Yescarta and Kymriah and Tecartus) prior to CAR-T infusion. Patient will be informed they need to carry PWC at all times and to share it with any Health Care Profession involved in patient's care.

Due to the potential for neurologic events, including altered mental status or seizures, patients receiving CAR-T19 are at risk for altered or decreased consciousness or coordination in the 8 weeks following CAR-T 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.

6.7 Post CAR-T Adverse Reactions

The following adverse reactions have been observed in patients treated with KYMRIAH and YESCARTA and Tecartus and Breyanzi and Abecma and are detailed in package inserts:

- Cytokine Release Syndrome
- Neurologic Toxicities (ICANS Immune Effectors Associated Neurotoxicity Syndrome)
- Hypersensitivity Reactions
- Serious Infections
- Prolonged Cytopenias
- Hypogammaglobulinemia
- Secondary malignancies

Because of risk of CRS and neurologic toxicities, CAR-T cell products are available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) called KYMRIAH REMS and YESCARTA & Tecartus and Breyanzi and Abecma REMS. REMS program to manage known or potential serious risks associated with a drug product is required by the FDA to ensure that the benefits of the drug outweigh its risks. The REMS documents are available: https://kymriahrems.com/ and www.YescartaTecartusREMS.com or 1-844-

454-KITE (5483); or https://www.breyanzirems.com/ or 1-888-423-5436; or https://www.abecmarems.com/ or 1-888-423-5436 .

The required components are:

1. Healthcare facilities that administer CAR-T must be enrolled and comply with REMS program
2. Healthcare facilities must have on-site 2 doses tocilizumab for each patient treated
3. Health care providers who prescribe, dispense and administer CAR-T must be trained about the management of CRS and neurologic toxicities
4. Patients and caregivers are provided for Patient Wallet Card (required for Yescarta and Kymriah)

More detail in package inserts (Appendices I, II, V, VII and VIII).

6.8 Follow Up

This protocol outlines recommended treatment guidelines for patients undergoing CAR-T cell therapies. In the event of disease relapse, disease progression, or other events which may require alternative treatment, treating physician discretion will be used in determining additional treatment, transfer to another study, or hospice care. Patients will continued to be followed in the BMT database for standard transplant related endpoint data.

7 Management of Selected Expected Toxicities (guided by package insert and not considered investigational)

This study will conform to the Risk Evaluation and Mitigation Strategy (REMS) program to manage known or potential serious risks associated with a drug product. This program is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. The FDA has required a REMS for YESCARTA™ (axicabtagene ciloleucel) and Kymriah™ (tisagenlecleucel) and TECARTUS (Brexucabtagene Autoleucel).

The REMS documents are available:
www.YescartaTecartusREMS.com
http://www.kymriah-rems.com/
https://www.breyanzirems.com/
https://www.abecmarems.com/

Additional Guidance on Management of CAR-T related toxicities can be found in Appendix II

7.1 Acute Infusion reaction

Acetaminophen/paracetamol and diphenhydramine/H1 antihistamine may be repeated every 4-6 hours as needed. A course of non-steroidal anti-inflammatory medication may be prescribed if the patient continues to have fever not relieved by acetaminophen/paracetamol. It is recommended that patients not receive corticosteroids at any time, except those already on physiologic replacement therapy, or in the case of a life threatening emergency, since this may have an adverse effect on CAR-T cells.

7.2 Febrile reaction

In the event of febrile reaction, an evaluation for infection should be initiated, and patients managed appropriately with antibiotics, fluids and other supportive care. Inpatient treatment is recommended initially. In the event that the patient develops sepsis or systemic bacteremia following CAR-T cell infusion, appropriate cultures and medical management should be initiated. If a contaminated CAR-T cell product is suspected, the product can be retested for sterility using archived samples that are stored at the manufacturing site. Consideration of a cytokine release syndrome (see below) should be given.

7.3 Cytokine Release Syndrome (CRS) / Macrophage Activation Syndrome (MAS)

Cytokine Release Syndrome (CRS) / Macrophage Activation Syndrome (MAS) are expected toxicities of CAR-T therapies. They are reported to present as spectrum ranging from grade 1-4. Deaths due to CRS were reported with CAR-T therapies.

Data from CAR-T treated patients experiencing CRS show marked elevations in IL-6 and IFN-g. The symptoms generally occur 1-14 days after cell infusion in patients with ALL and may include high fevers, rigors, myalgia/arthralgias, nausea/vomiting/anorexia, fatigue, headache, encephalopathy, hypotension, dyspnea, tachypnea and hypoxia. Renal failure/renal injury, hyperbilirubinemia and increased ALT or AST can also occur. Supportive care and anti-cytokine therapy have been used for effective management of CRS. Prompt responses to tocilizumab have been seen in most patients. Several patients with a suboptimal response to the first dose of tocilizumab have received a second or third dose of tocilizumab with CRS resolution.

A detailed treatment algorithm has been established and approved by FDA with clear criteria for CRS management and guidance on when to administer tocilizumab and is presented in Appendix II. This guideline was designed to avoid life-threatening toxicities, while attempting to allow the CAR-T cells to establish a proliferative phase which appears to correlate with tumor response.

The management of CRS is based solely upon clinical parameters as described in Appendix II. Serum cytokine and inflammatory marker levels could aid clinical management decisions of CRS.

Cases of transient left ventricular dysfunction, as assessed by cardiac ECHO, have been reported in some patients with severe CRS (grade 4). Therefore, consideration should be given to monitoring cardiac function by cardiac ECHO, during severe CRS, especially in cases with prolonged severe hemodynamic instability, delayed response to high dose vasopressors, and/or severe fluid overload.

Clinically significant coagulopathy is often seen with moderate to severe CRS (Grade 3 and 4) and may continue as CRS is beginning to clinically resolve. Coagulation parameters (PT, aPTT, and fibrinogen) should be more frequently monitored in this setting. CAR-T associated coagulopathy with or without clinical bleeding and hypofibrinogenemia is strongly recommended to be managed with cryoprecipitate or fibrinogen concentrate in addition to routine blood product support. CAR-T related CRS can be associated with neurologic events (Immune Effectors Associated Neurologic Syndrome). 10 point ICANS score should be assigned to each patient daily at least for 14 days post CAR-T infusion.
Two types of neurologic events with respect to timing of onset have been observed. Onset of neurologic events can be concurrent with high fevers during the development and maximal grade of CRS. Delayed onset of neurologic events can also occur as CRS is resolving or after CRS has completely resolved. Consideration should be given to monitoring for ICANS during and after resolution of CRS.

A modification of the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 ASTCT CRS and ICANS grading scale is summarized in Appendix II

7.4 Neurologic Toxicities (Immune Effectors Associated Neurotoxicity Syndrome (ICANS)

Neurologic toxicities, which may be severe or life-threatening, occurred following treatment with CAR-T, including concurrently with CRS, after CRS resolution, or in the absence of CRS.

CAR T cell-associated neurotoxicity, occurred in 28% (36/127) of patients receiving ABECMA, including Grade 3 in 4% (5/127) of patients. One patient had ongoing Grade 2 neurotoxicity at the time of death. Two patients had ongoing Grade 1 tremor at the time of data cutoff. The median time to onset of neurotoxicity was 2 days (range: 1 to 42 days). CAR T cell-associated neurotoxicity resolved in 33 of 36 (92%); For patients who experienced neurotoxicity including three patients with ongoing neurotoxicity, the median duration of CAR T cell-associated neurotoxicity was 6 days (range: 1 to 578 days). Neurotoxicity resolved in 33 patients and median time to resolution was 5 days (range 1 to 61 days). Thirty-four patients with neurotoxicity had CRS. The onset of neurotoxicity during CRS was observed in 29 patients, before the onset of CRS in three patients, and after the CRS event in two patients.

The rate of Grade 3 neurotoxicity was 8% in 450 x 10^6CAR-positive T cells dose cohort and 1.4% in the 300 x 10^6CAR-positive T cells dose cohort. The most frequent (greater than or equal to 5%) manifestations of CAR T cell-associated neurotoxicity include encephalopathy (20%), tremor (9%), aphasia (7%), and delirium (6%).
Grade 4 neurotoxicity and cerebral edema have been associated with ABECMA in a patient in another study in multiple myeloma. Grade 3 myelitis and Grade 3 parkinsonism have occurred after treatment with ABECMA in another study in multiple myeloma.

Monitor patients at least daily for 7 days following ABECMA infusion at the REMS-certified healthcare facility for signs and symptoms of neurologic toxicities. Rule out other causes of neurologic symptoms. Monitor patients for signs or symptoms of neurologic toxicities for at least 2 weeks after infusion and treat promptly. Neurologic toxicity should be managed with supportive care and/or corticosteroids as needed

7.5 Tumor lysis syndrome

Close monitoring for TLS before and after chemotherapy and CAR-T infusions, including blood tests (potassium, uric acid, etc.) will be done as per standard of care.

7.6 Graft-Versus-Host Disease (GVHD)

The chance of GVHD occurring is low, but it is a potential risk with CAR-T therapy. GVHD is an immune-mediated disorder that may occur following allogeneic SCT. Manifestations include scleroderma, dry eyes, dry mouth, lichenoid oral changes, bronchiolitis obliterans, vanishing bile ducts, or weight loss.

7.7 Infection

CAR-T should not be administered to patients with active infections or inflammatory disorders. Severe, life-threatening, or fatal infections occurred in patients after CAR-T infusion. Infections (all grades) occurred in 70% of patients treated with ABECMA. Grade 3 or 4 infections occurred in 23% of patients. Grade 3 or 4 infections with an unspecified pathogen occurred in 15%, viral infections in 9%, bacterial infections in 3.9%, and fungal infections in 0.8% of patients. Overall, four patients had Grade 5 infections (3%); two patients (1.6%) had Grade 5 events of pneumonia, 1 patient (0.8%) had Grade 5 bronchopulmonary aspergillosis, and 1 patient (0.8%) had cytomegalovirus (CMV) pneumonia associated with Pneumocystis jirovecii. Monitor patients for signs and symptoms of infection before and after CAR-T infusion and treat appropriately. Administer prophylactic, pre-emptive, and/or therapeutic antimicrobials according to standard institutional guidelines.

Febrile neutropenia (was observed in 16% (20/127) of patients after ABECMA 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

7.8 B cell depletion

Transient or permanent B cell depletion is a complication with CAR19-T therapy, since normal B cells express CD19. This is expected to resolve if and when the CAR19-T cells are cleared. CAR19-T related hypogammaglobulinemia is typically managed with immunoglobulin replacement therapy dependent upon age specific, disease specific and local institutional guidelines. Other potential complications of B cell aplasia include progressive multifocal leukoencephalopathy (PML) and reactivation of hepatitis B virus.

- **Progressive Multifocal Leukoencephalopathy (PML)**

  PML is rare but well described with antibody therapies causing B cell aplasia. It is a demyelinating disease of the central nervous system, resulting from infection of oligodendrocytes and astrocytes, mostly with JC virus.

- **CMV Reactivation**

Cytomegalovirus (CMV) infection resulting in pneumonia and death has occurred following CAR19-T administration. Monitor and treat for CMV reactivation in accordance with clinical guidelines.

- **Hepatitis B reactivation**

Reactivation of hepatitis B refers to the abrupt increase in hepatitis B virus (HBV) replication in a patient with inactive or resolved hepatitis B. Reactivation can occur spontaneously, but more typically is triggered by immunosuppressive therapy of cancer, autoimmune disease, or organ transplantation. Patients with evidence of reactivated hepatitis B should initiate either tenofovir or entecavir, and pursue appropriate consultation.

In general, the risk of hepatitis B reactivation is increased in patients with B cell depletion. Patients with latent or active hepatitis B are typically excluded from CAR-T treatment protocols; however infection could potentially occur following the treatment trial completion or early withdrawal. Therefore, patients with a history of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection. Standard guidelines should be followed for the treatment of active/reactivated hepatitis B.

7.9 New or secondary malignancies

There is a theoretical concern that transduction of a patient's T-cells with CD19 CAR lentiviral/retroviral vector could result in an oncogenic effect within these T-cells that could result in a T-cell leukemia or lymphoma.

7.10 Replication-competent lentivirus (RCL) testing

An RCL may be generated during CAR-T manufacturing or subsequently after introduction of vector transduced cells into the patient. However, an RCL resulting from manufacturing is highly unlikely since elements are incorporated in the design of the vector system that minimize vector recombination and generation of RCL. Furthermore, the vector used to transduce the product undergoes sensitive assays for detection of RCL before it can be released to a patient. Thus patients will only receive cell products that meet RCL release criteria (as detected by Vesicular Stomatitis Virus/Glycoprotein (VSV-G) qPCR, for example).

7.11 Clonality and insertional oncogenesis

Four of nine treated patients in a gene therapy trial for X-linked Severe Combined Immunodeficiency (SCID) developed T cell leukemia 31-68 months post-treatment. The T cell leukemias were attributable to clonal expansion conferred by gammaretroviral vector integration sites in the CD34+ bone marrow stem cell modification (Hacein-Bey-Abina et al 2008). This represents the most severe adverse event caused by vector integration. However, there is also evidence for retroviral vector integration site dominance in a gene therapy trial of ß-thalasaemia without malignancy (Cavazzana-Calvo et al 2010). The lentiviral vector used for Kymriah manufacturing is part of a vector class that may have a lower risk for integration in or near oncogenic regions than onco-retroviral vectors (Montini E et al 2009). As of February 2018, none of the patients treated with Kymriah have developed a new malignancy, T cell or otherwise, related to lentiviral vector integration. Subjects should be monitored for malignancy by complete blood count (CBC).

7.12 Liver safety monitoring

Following CAR-T infusion, transient and reversible changes in ALT, AST, and total bilirubin (TBIL) are typically observed in parallel with the course of cytokine release syndrome (CRS). These LFT abnormalities should be followed until return to baseline values. If these LFT abnormalities are observed within the first 8 weeks following Kymriah infusion and are explicable by CRS, further diagnostic work up is typically not warranted.

7.13 Hemophagocytic Lymphohistiocytosis (HLH)/ Macrophage activation syndrome (MAS)

HLH/MAS occurred in 4% (5/127) of patients receiving ABECMA and lower incidence is reported with other CAR19-T cells. One patient treated in the 300 x10^6CAR-positive T cells dose cohort developed fatal multi-organ HLH/MAS with CRS. In another patient with fatal bronchopulmonary aspergillosis, HLH/MAS was contributory to the fatal outcome. Three cases of Grade 2 HLH/MAS resolved.

The rate of HLH/MAS was 8% in the 450 x10^6CAR-positive T cells dose cohort and 1% in the 300 x10^6CAR-positive T cells dose cohort. All events of HLH/MAS had onset within 10 days of receiving ABECMA, with a median onset of 7 days (range: 4 to 9 days) and occurred in the setting of ongoing or worsening CRS. Two patients with HLH/MAS had overlapping neurotoxicity.

HLH/MAS, including life-threatening reactions, occurred following treatment with TECARTUS. HLH/MAS occurred in 4% (3/78) of patients with ALL. Two patients experienced Grade 3 events and 1 patient experienced a Grade 4 event. The median time to onset for HLH/MAS was 8 days (range: 6 to 9 days) with a median duration of 5 days (range: 2 to 8 days). All three patients with HLH/MAS had concurrent CRS symptoms and neurologic events after TECARTUS infusion.

The manifestations of HLH/MAS include hypotension, hypoxia, multiple organ dysfunction, renal dysfunction and cytopenia.

HLH/MAS is a potentially life-threatening condition with a high mortality rate if not recognized early and treated. Treatment of HLH/MAS should be administered per institutional standards.

7.14 Effects on Ability to Drive and Use Machines

Due to the potential for neurologic events, including altered mental status or seizures, patients receiving CAR-T are at risk for altered or decreased consciousness or coordination in the 8 weeks following ABECMA 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.

7.15 Side Effects of CAR-T

Very Common >30%	Common 10-30%	Rare 1 -10%
• Cytokine release syndrome • Cytokine release syndrome, grades 1-2 • ICANS/Neurotoxicity grades 1-2 • Hypogammaglobulinemia • Infection, unspecified pathogen • Pyrexia • Prolonged neutropenia • Decreased appetite • Headache • Encephalopathy	• CRS and ICANS grade 3-4 • Increased AST, grades 3-4 • Hypokalemia, grades 3-4 • Prolonged thrombocytopenia • Viral infection • Tachycardia • Nausea • Diarrhea • Vomiting • Hypoxia • Fatigue • Acute kidney injury • Hypotension, grades 3-4 • Increased ALT, grades 3-4	• Face edema • Peripheral edema • Chills • Fluid overload • Back pain • Pleural effusion • Nasal congestion • Pulmonary edema, grades 3-4 • Encephalopathy, grades 3-4 • Fungal infection, grades 3-4 • Blood and lymphatic system disorders: DIC histiocytosis lymphocytic

Very Common >30%	Common 10-30%	Rare 1 -10%
• Hypotension	• Increased bilirubin, grades 3-4 • Delirium • Hypophosphatemia, grades 3-4 • Hypertension • Bacterial infection • Cough • Constipation • Viral infection, grades 3-4 • Hypoxia, grades 3-4 • Prolonged neutropenia, Day 56 • Infection, unspecified pathogen, grades 3-4 • Hypofibrinogenemia with grades 3-4 CRS • Abdominal pain • Pain in extremity • Pulmonary edema • Decreased appetite, grades 3-4 • Pyrexia, grades 3-4 • Myalgia • Fungal infection • Anxiety • Bacterial infection, grades 3-4 • Acute kidney injury, grades 3-4 • Prolonged thrombocytopenia, Day 56 • Arthralgia • Tachypnea	hemophagocytosis, coagulopathy • Investigations: Blood creatinine increased, aPTT prolonged • Respiratory, thoracic, and mediastinal disorders: Respiratory distress, respiratory failure, acute RDS • Cardiac disorders: Cardiac arrest, cardiac failure • Metabolism and nutrition disorders: Tumor lysis syndrome • Vascular disorders: Capillary leak syndrome • General disorders and administration site conditions: Multiple organ dysfunction syndrome • Nervous System: Intracranial hemorrhage, seizure • Gastrointestinal disorders: Abdominal compartment syndrome • Immune system disorders: GVHD • CMV re-activation • PC pneumonia

8 Clinical Care Activities

Scheduled evaluations after screening and until day 28 may be performed +/-3 days from the targeted date; assessments performed after day 28 and through 3 months may be done +/-14 days of the targeted date. After 3 month assessments may be done +/- 28 days of the targeted date. In addition, targeted days may be altered as clinically appropriate. Any modifications or omissions to the clinical care activities will not be considered protocol deviations.

	Screening (week -16 to week -12)	Prior to Chemo (Day -14 to -2)	Prior to CAR-T	Infusion (Day 0)	D 4	D 7	D 11[ŦŦ]	D 14	D 17[ŦŦ]	D 21	D 28	D 60	3 Month	6 month	9 months	12 month	18 Month	Yearly through 15 years
Obtain Informed Consent	x																	
Obtain written acknowledgment of "MEDICATION GUIDE"for Yescarta only[ǂǂ]	x																	
Patient history	x																	
Demographics	x																	
Inclusion/exclusion criteria	x																	
Confirm CD19 expression on bx for lymphoma /leukemia	x																	
Medical History	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x		
Annual Survival Data as required by FDA																x		x
Prior antineoplastic therapy	x																	
Donor chimerism (prior allogeneic SCT patients only)	x																	
Physical examination	x	x	x	x	x	x	x	x	x	x	x		x	x		x		
Performance status	x	x		x							x		x	x		x		
Height	x													x		x		
Weight	x	x	x[ᴐ]	x[ᴐ]	x[ᴐ]	x[ᴐ]	x[ᴐ]	x[ᴐ]	x[ᴐ]	x[ᴐ]	x	x[ᴐ]	x	x	x[ᴐ]	x		x[ᴐ]
Vital signs	x	x		x	x	x	x	x	x	x	x		x	x		x		
Pulse oximetry	x			x														
Intervention																		
Lymphodepleting Chemotherapy		X																
CAR-T cell infusion				X														

	Screening (week -16 to week -12)	Prior to Chemo (Day -14 to -2)	Prior to CAR-T	Infusion (Day 0)	D 4	D 7	D 11 ǂ	D 14	D 17ǂ	D 21	D 28	D 60	3 month	6 month	9 month	12 month	18 month	Yearly through 15 years
Laboratory assessments																		
Hematology (CBC/diff)	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	2 years
Chemistry (CMP)	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	2 years
(ferritin, LDH, CRP)		X		X	X	X	X	X	X	X	X							
Serum pregnancy test	X																	
HIV test	X																	
Hepatitis B and C serology	X																	
Influenza PCR		Within 10 days of infusion																
Coagulation factors (PT, aPTT, INR, fibrinogen, D-dimer)	X			X	x	x	x	x	x	x	x							
Serum immunoglobulin levels (IgG)	x			X							x	x	x	x	x	x	X	X
CMV Ag				X		X		X			X	X	X					
ECHO	x																	
Electrocardiogram (ECG)	x																	
T Cell Subset Extended Profile (includes CD4 and CD19 B-cells l)				x							x	x	x	x		x		
Uric Acid	X			x	x	x	x	x	x	x	x							
Clonoseq Adaptive *	X (ID)										X							
Additional Laboratory assessments for Kymriah (PEDS only)																		
T Cell Subset Extended Profile (includes B-cell lymphocyte subset)	X			x							x	Monthly Through 2 years						
Hematology (CBC/diff)	X	X		X	X	X	X	X	X	X	X	Monthly Through 2 years						2 years
Serum immunoglobulin levels (IgG)	x			X							x	Monthly Through 2 years						x

	Screening (week -16 to week -12)	Prior to Chemo (Day -14 to -2)	Prior to CAR-T	Infusion (Day 0)	D 4	D 7	D 11[Ŧ]	D 14	D 17[Ŧ]	D 21	D 28	D 60	3 Month	6 month	9 month	12 month	18 month	Yearly through 15 years
Disease Assessments for ALL																		
Bone marrow biopsy: morphology, flow cytometry (leukemia/ lymphoma evaluation), FISH, cytogenetics & MRD tracking through NGS	x (anytime prior to car-t infusion)										x	X	x	x	X[ʊ]	x	X	2 years
Lumbar puncture: WBC/diff, total protein, glucose, RBC, leukemia/lymphology evaluation, and cytology	X (if symptoms)	X (if symptoms)									x	X[ʊ]	x[¥, ʊ]	x[¥, ʊ]	X[ʊ]	x	X	2 years
Disease Assessments for Lymphoma																		
PET/CT[ß] or CT or PET[ß] Whole Body (lymphoma only)	x (anytime prior to car-t infusion)	x									X (PET only)[ß]		X (PET/ CT)[ß]	X (CT)	X (CT)	x (CT)	X(CT)	2 years (CT)
Disease Assessments for Myeloma Only																		
SPEP, UPEP, Kappa/Lambda light chains, Immunofixation, LDH, B2 microglobulin	x										X	X	X	X	X	X		2 years
Bone marrow biopsy	X (ok after apheresis)												X	X		X		2 years
PET	X (ok after apheresis)												X			X		2 years

Ŧ Optional, per Treating physician recommendation

¥ Adults, only if history of CNS disease

ß(If PET denied by insurance, a CT CAP+neck with IV contrast can be done)

ʊ Peds only regardless of CNS disease history

& - If PET CT denied by insurance, a skeletal survey can be done

⇈ All Medication Guides can be found in the drug package inserts

*Adaptive testing is optional for NHL and ALL (logistics TBD)

8.1 Optional Research Samples

Subjects will be given the option to co-enroll on study MT2017-12, "Monitoring of Immune and Microbial Reconstitution in Hematopoietic Cell Transplantation (HCT) and Novel Immunotherapies" to provide research sample collection.

9 Adverse Event Monitoring, Documentation, and Reporting

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 5.0 (CTCAE) and reported on the schedule below. A copy of the CTCAE can be downloaded from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50.

Treatment related outcomes and events will be recorded in the Blood and Marrow Transplantation (BMT) database and CIBMTR.

9.1 Event Monitoring

Event monitoring will be performed by the patient's clinical care team.

9.2 Event Documentation

Targeted toxicity may be documented as CARTOX note at every visit in EMR by a clinical team, or in the daily notes. CARTOX screening assessments will be performed through at least day 14.

Treatment related outcomes and events will be recorded in the Blood and Marrow Transplantation (BMT) database.

Events requiring prompt reporting to the University of Minnesota Institutional Review Board (IRB), early stopping rule events (treatment related mortality before day 100), and protocol deviations will be documented in OnCore. Refer to section 9.3 for reporting requirements.

9.3 Event Reporting

Agency	Criteria for reporting	Timeframe	Form to Use	Submission address/ fax numbers
U of MN IRB	Events requiring prompt reporting including, but not limited to unanticipated death of a locally enrolled subject(s); new or increased risk; any adverse event that require a change to the protocol or consent form or any protocol deviation that resulting in harm For a complete list refer to http://www.research.umn.edu/irb/guidance/ae.html#.VC7xraI0-sh	Within 5 business days of event discovery	Report Form	ETHOS Portal
Masonic Cancer Center SAE Coordinator	Events that impact the early study stopping rules – treatment related morality before day 100 (section 11.4).	At time of reporting	Event Form	SAE Coordinator mcc-saes@umn.edu
CIBMTR	Required: • CRS (all grade) • Neurologic Toxicities (all grades) Encouraged: • AEs and SAEs	BMT Database will report per CIBMTR SOP	CIBMTR Form	Online into FormsNet3 (CIBMTR's EDC)
FDA for Novartis product	•Patient death •Unexpected SAEs	At time of reporting	**MedWatch website www.fda.gov/medwatch**	**Report to the FDA directly by calling 1-800-FDA-1088**
	• As part of REMS CAR-T requires reporting of known AE's of CRS and Neurotoxicities: CIBMTR Summary forms (sent back to center from CIBMTR)	Every 3 months	**CIBMTR summary**	**CIBMTR will Report to Novartis** **Site may report to Novartis by calling 1-888-669-6682**
FDA for Kite products (Yescarta & Tecartus)	•Patient death •Unexpected SAEs	At time of reporting	**MedWatch website www.fda.gov/medwatch**	**Report to the FDA directly by calling 1-800-FDA-1088**
	• CIBMTR Summary forms (sent back to center from CIBMTR)	Every 3 months	**CIBMTR summary**	**CIBMTR will report to Kite** **Site may report to Kite by calling 1-844-454-KITE**
FDA for Bristol Meyer Squibb products	• Patient death • Unexpected SAEs • CIBMTR Summary forms (sent back to center from CIBMTR)		**www.fda.gov/medwatch.**	**To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-888-805-4555 or FDA at 1-800-FDA-1088**

(Breyanzi and Abecma)				
Kymriah for ALL (Outcomes based contract agreement in place)	No remission on day 28 bone marrow biopsy (determined by PI or designee)	Between day 38-35 after Kymriah infusion	**Kymriah Care Hub**	**Report to Novartis by calling 1-888-669-6682**

All stem cell transplant/therapy patients co-enroll on standard data-collection and long term data storage protocols.

The SAE Coordinator will provide the Masonic Cancer Center's Data and Safety Monitoring Council (DSMC) with the SAE in an appropriate format depending on the individual SAE (as reported or in a summary format).

10 Study Data Collection and Monitoring

10.1 Data Collection

This study will track events requiring prompt reporting to the IRB, stopping rule events, and clinical deviations using University of Minnesota CTSI's instance of OnCore® (Online Enterprise Research Management Environment).

The Oncore database resides on dedicated secure and PHI compliant hardware consisting of 3 physical servers: dev, DR, and production. The dev server is located in the University of Minnesota (UMN) datacenter (WBOB) and houses six database instances (test, train, sandbox, mcc reports, oncdm, and vendor) that are backed up locally because the data is refreshed from Oncore production data. The production server is located in the UMN datacenter (WBOB). All the data servers are managed by the Academic Health Center – Information Systems (AHC-IS) virtual servers which utilize clustered infrastructure to provide real-time failover of virtual servers. This real-time clustering is physically limited to the UMN data center. All relevant AHC IS procedures related for PHI compliant servers (as required by the Center of Excellence for HIPAA Data) apply to Oncore databases.

The integrated data will be stored in PHI compliant servers managed by AHC IS with access given to those authorized users in the Clinical and Translation Science Institute Informatics team (CTSI BPIC and MCC CISS). The data will be integrated and extracted to researchers through the CTSI Informatics team and will be

delivered through secure and compliant mechanisms (e.g. AHC IE data shelter, BOX, sftp, etc). If data de-identification is needed, then compliant AHC IE data de-identification tools will be used. The informatics team will grant the IRB approved study team members access to data.

Key study personnel are trained on the use of OnCore and will comply with protocol specific instructions embedded within the OnCore.

All treatment related outcomes and complications will be recorded in the Blood and Marrow Transplantation (BMT) database.

10.2 Data and Safety Monitoring

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at http://z.umn.edu/dmsp.

For the purposes of data and safety monitoring, this phase II study is classified as moderate risk. Therefore the following requirements will be fulfilled:

- The Masonic Cancer Center Data and Safety Monitoring Council (DSMC) will review the trial's progress twice yearly
- The PI will comply with at least twice yearly monitoring of the project by the Masonic Cancer Center monitoring services.
- The PI will oversee the submission of all reportable adverse events per the definition of reportable in section 9.3 to the Masonic Cancer Center's SAE Coordinator and the University of Minnesota IRB.

In addition, at the time of the continuing review with the University of Minnesota IRB, a copy of the report with any attachments will be submitted to the Cancer Protocol Review Committee (CPRC).

10.3 Study Related Monitoring

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University of Minnesota compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

10.4 Record Retention

The investigator will retain study records for at 6 years after the study file is closed with the IRB and FDA.

In addition, the Clinical Trials Office (CTO) will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient.

Please contact the CTO before destroying any study related records.

11 Statistical Consideration

This is a phase II study using FDA-approved CAR-T products for patients with hematologic malignancies. Patient will be assigned to Arms (A B, C, D, E,F and G) based on age, CAR-T product and diagnosis. Overall remission rate, safety events and other endpoints will be calculated for Arm A, B, C D, E, E and G separately.

Arm A: Relapsed or refractory pediatric CD19+ B-cell Acute Lymphoblastic Leukemia; age 0 to ≤ 25 years at the time of infusion and Kymriah product.

Arm B: Adults (≥18 years) with relapsed or refractory large B-cell lymphoma and follicular lymphoma after two or more lines of systemic chemotherapy and Yescarta product

Arm C: Adult patients (≥18 years) with Refractory diffuse large B cell lymphoma and Kymriah product

Arm D: Adults (≥18 years) with relapsed or refractory mantle cell lymphoma receiving Tecartus product

Arm E: Adults (≥18 years) with relapsed or refractory large B-cell lymphoma receiving Breyanzi “lisocabtagene maraleucel”

Arm F: Adults (≥18 years) with relapsed or refractory multiple myeloma receiving Abecma “Idecabtagene Vicleucel”

Arm G: Adults (≥18 years) with B-ALL receiving Tecartus product (Brexucabtagene Autoleucel)

11.1 Primary Endpoint

The primary endpoint for Arm A is the composite rate of complete remission (CR) and CRi (without count recovery) rate at day 28.

The primary endpoint for Arm B is the Overall Response Rate (complete response + Partial response by Lugano) (ORR) separately for DLBCL and FL.

The primary endpoint for Arm C is the Overall Response Rate (complete response + Partial response by Lugano) (ORR).

The primary endpoint for Arm D is the Overall Response Rate (complete response + Partial response by Lugano) (ORR).

The primary endpoint for Arm E is the Overall Response Rate (complete response + Partial response by Lugano) (ORR).

The Primary objective for Arm F is to estimate the Overall Response Rate (complete response + Partial response by IMWG criteria) (ORR).

The Primary objective for Arm G is the composite rate of complete remission (CR) and CRi (without count recovery) rate at day 28.

11.2 Secondary Endpoints

Secondary endpoints for Arm A and G include the following:

- The proportion of patients with MRD-negative CR (or CRi).

Secondary endpoints for all Arms include the following:

- Treatment related mortality (in absence of disease relapse/progression) at day 28, day 100 and 1 year.
- The Relapse-free Survival (RFS) as evaluated by the time of achievement of complete remission to relapse or death.
- The event-free survival (EFS) from the date of the CAR-T infusion through 1 year post treatment.
- Overall Survival (OS) from the date of the CAR-T infusion through the date of patient death for any reason.

- The proportion of patients developing grade 3, 4 targeted toxicity of CRS and/or neurotoxicity.

11.3 Analysis of Primary and Secondary Endpoints

The analysis will be done for Arm A, B, C, D, E, F and G separately. The binary endpoints such as CR, CRi rate, composite rate of CR and CRi rate, MRD-negative CR, ORR, Complete Remission rate by Lugano criteria and proportion of patients who are alive but not in remission at day 28, summary statistics including proportions and their 95% confidence intervals will be calculated. Safety of CAR-T therapy assessments including grade 3 and 4 targeted toxicity of CRS and/or neurotoxicity will be presented in the data listings and summarized with descriptive statistics.

Kaplan-Meier curves will be used to estimate event free survival (EFS), overall survival (OS) and relapse-free survival (evaluated by the time of achievement of CR/PR to relapse or death) with 95% confidence interval. Treatment related mortality at day 28, 100 and 1 year, will be estimated with 95% confidence interval by competing risk analysis treating relapse, disease relapse/progression as the competing risk.

All analyses will be conducted using SAS software (SAS Institute Inc., Cary, NC). Results will be deemed statistically significant at the 0.05 significance level unless otherwise specified.

11.4 Sample Justification and Accrual

For Arm A, sixty patients will achieve 99.9% power to detect a difference of overall remission rate (ORR) between null hypothesis (ORR) of 40% and alternative hypothesized rate of 70%. For Arm B, sixty patients will achieve 88.5% power to detect a difference of overall remission rate (ORR) between null hypothesis (ORR) of 40% and alternative hypothesized rate of 60%. For Arm C, sixty patients will achieve 89.2% power to detect a difference of overall remission rate (ORR) between null hypothesis (ORR) of 35% and alternative hypothesized rate of 55%. For Arm D, sixty patients will achieve 99.9% power to detect a difference of overall remission rate (ORR) between null hypothesis (ORR) of 40% and alternative hypothesized rate of 75%. For Arm E, sixty patients will achieve 90% power to detect a difference of overall remission rate (ORR) between null hypothesis (ORR) of 30% and alternative hypothesized rate of 50%. For Arm F, sixty patients will achieve 89% power to detect a difference of overall remission rate (ORR) between null hypothesis (ORR) of 50% and alternative hypothesized rate of 70%. For Arm G, sixty patients will achieve 88.5% power to detect a difference of overall remission rate (ORR) between null hypothesis (ORR) of 40% and alternative hypothesized rate of 60%. The power calculations were based on two-sided exact test with a significance level of 0.05 (PASS15, NCSS, LLC).

Based on prior enrollment, we expect to accrue approximately 15 patients per arm B,C,D,E, F and about 10 patient per arm A and G per year.

11.5 Early Stopping Rule for Excessive Toxicity during Expansion Component

Stopping rules will be employed to monitor excess toxicity for the seven arms separately. The stopping rule was developed using Pocock stopping boundaries. [1]

Excess toxicity will be defined as TRM by day 100 post infusion. The goal is to construct a boundary based on toxicity such that the probability of early stopping is at most 10% if the toxicity rate is equal to 20%. Given these parameters, the upper stopping boundary for toxicity is 3 out of 3, 4 out of 6, 5 out of 9, 6 out of 12, 7 out of 16, 8 out of 19, 9 out of 22, 10 out of 26, 11 out of 30, 12 out of 33, 13 out of 37, 14 out of 41, 15 out of 45, 16 out of 49, 17 out of 53, 18 out of 57, and 19 at any time. If the true toxicity rate is as high as 40% then chance of early stopping is 96% and the expected sample size is 4.2.

12 Conduct of the Study

12.1 Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

12.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

12.3 Informed Consent

All potential participants will be given a copy of the IRB-approved Consent to review. The investigator or designee will explain all aspects of the treatment in lay language and answer all questions regarding the treatment. If the participant decides to participate, he/she will be asked to sign and date the Consent

document. Patients who refuse to participate or who withdraw will be treated without prejudice.

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APPENDIX I - Performance Status Scales

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Ref: Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group.*Am J Clin Oncol.* 1982;5:649-655.

Karnofsky Performance Status Scale (≥ 16 years)

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Lansky Score (children < 16 years)

Lansky Score	Performance Status
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

APPENDIX II - Management Of Adverse Events

Steps to diagnose and manage CRS, CRES and related toxicities can be found at the following link:

http://intranet.fairview.org/fv/groups/intranet/documents/bmtprotocol/s_148596.pdf