FAST FACTS

S2114 - A RANDOMIZED PHASE II TRIAL OF CONSOLIDATION THERAPY FOLLOWING CD19 CAR T-CELL TREATMENT FOR RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA OR GRADE IIIB FOLLICULAR LYMPHOMA

ELIGIBILITY CRITERIA

STEP 1: REGISTRATION

a. Disease Related Criteria
    1. Participants must have a histologically confirmed diagnosis of diffuse large B-cell lymphoma or follicular lymphoma grade 3b or PMBCL. Please refer to Section 4.2 regarding eligible DLBCL subtypes.
    2. Participants with transformed DLBCL must have transformed DLBCL from follicular or marginal zone lymphoma.
    3. Participant must have bi-dimensionally measurable systemic disease (at least one lesion with longest diameter > 1.5 cm)
    4. Participants with secondary CNS lymphoma (parenchymal, spinal cord, meningeal, cerebrospinal fluid involvement) must be asymptomatic from their CNS disease.
    5. Participants must not have a history of CLL/SLL, a diagnosis of Richter's transformation, or a diagnosis of mantle cell lymphoma.
b. Prior/Concurrent Therapy
    1. Participants must be registered for Step 1 after they have signed institutional consent for CAR T-cell leukapheresis but prior to the start of lymphodepleting (LD) chemotherapy for commercial CAR T-cell product.
    2. In the opinion of the enrolling physician, participants must be felt to be a candidate for CAR T-cell therapy with plans to be treated with FDA approved commercially available CD19 CAR T-cell construct.
        a. Participants must qualify for commercially approved CD19 CAR T-cell therapy per FDA package insert.
        b. If the CAR T-cell product does not meet parameters to be given as an FDA approved product (i.e. does not meet specification criteria mandated by FDA and is infused under an expanded access protocol (EAP) or single participant investigational new drug (IND)) the participant will be taken off of study and no longer be eligible for Step 2 Randomization.
    3. Participants are permitted to receive or have received 'bridging therapy' after CAR T-cell leukapheresis. However, participants must not receive polatuzumab vedotin, and/or mosunetuzumab as part of bridging therapy.
        a. Bridging therapy is defined as lymphoma directed therapy administered between leukapheresis and the start of LD chemotherapy. This includes cytotoxic chemotherapy (e.g.: BR,R-gem/ox), radiation, corticosteroids, as well as novel therapies such as BTK inhibitors (e.g.: Ibrutinib), immunomodulators (e.g.: lenalidomide), monoclonal antibodies (e.g.: rituximab, obinutuzumab, tafasitamab) antibody drug conjugates (e.g:loncastuximab), checkpoint inhibitors (e.g.: pembrolizumab, nivolumab), clinical trial treatments, etc.
        b. If a participant receives polatuzumab vedotin or mosunetuzumab as bridging they will ineligible to continue on Step 1 Registration portion of the study and be ineligible for Step 2 Randomization.
    4. PET-CT scan must be planned for completion within 60 days prior to the start of LD chemotherapy.
        a. All pre-CAR T-cell therapy disease must be assessed and documented on the Baseline/Pre-Registration Tumor Assessment Form.
        b. If receiving bridging therapy, participants must have a PET-CT scan upon completion of all planned bridging therapy. If the PETCT scan after completion of bridging therapy is onsistent

with complete remission per Lugano criteria as determined by enrolling physician, that participant will be ineligible for Step 2 Randomization.

c. Participants are permitted to receive corticosteroids after leukapheresis without the need to repeat a PET-CT scan. If steroids are used, they must be planned to stop no later than 3 days before CAR -T cell infusion. Recommend dose no greater than Dexamethasone 40 mg (or equivalent) for < 7 days.

d. If response assessment by central review cannot be completed (I.e., poor quality of PET-CT scan, PET-CT, performed out of window, etc.) this would be recorded as 'inadequate assessment' and patient would not be eligible for randomization.

5. Participants that have previously been treated with polatuzumab vedotin or mosunetuzumab prior to CAR T-cell leukapheresis for either indolent or aggressive NHL are eligible as long as the participant did not have refractory disease or progression/relapse within 6 months of the last infusion with either agent.
6. Participants must be planning to receive CAR T-cell infusion no earlier than 2 days and no later than 14 days after completion of the last day of lymphodepleting chemotherapy. Any participant receiving CAR T-cell infusion outside of this window will be ineligible for Step 2 Randomization.
7. LD chemotherapy prior to CAR T-cell infusion must be planned to start within 60 days after Step 1 Registration.
8. Participants must not have received prior CAR T-cell infusion previous to Step 1 Registration.

C. Clinical/Laboratory Criteria

1. Participants must be ≥ 18 years of age at the time of registration.
2. Participants must have Zubrod PS of 0, 1, or 2.
3. Participants must have adequate hepatic function within 14 days prior to registration, evidenced by the following*
   a. Total bilirubin us ≤ 1.5 x ULN and *Unless due to Gilbert's disease or lymphomatous involvement of liver
   b. AST and ALT≤ 3 institutional ULN.
4. Participants must have adequate renal function as evidence by below:
   a. Creatinine clearance ≥40 mL/min, as estimated by the Cockcroft and Gault formula. The creatinine value used in the calculation must have been obtained within 14 days prior to registration.

      Estimated creatinine clearance is based on actual body weight.

      $$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{weight in kg}) \dagger}{72 \times \text{serum creatinine} *}$$

      Multiply this number by 0.85 if the participant is a female.

      The kilogram weight is the participant weight with an upper limit of 140% of the IBW.

      * Actual lab serum creatinine value with a minimum of 0.7 mg/dL.
5. Participants must have an echocardiogram (ECHO) or MUGA within 60 days prior to registration with a cardiac ejection fraction ≥ 40%.
   a. Participants with current symptoms of cardiac disease must have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, participants must be class 2B or better. (Section 18.2)
   b. Participants must not have documented myocardial infarction and percutaneous coronary intervention (PCI) within 6 months prior to registration or myocardial infarction without PCI within 3 months of registration, or unstable angina.

6. Participants with peripheral neuropathy must have < grade 2.
7. Participants must not be pregnant or nursing. Individuals who are of reproductive potential must have agreed to use an effective contraceptive method with details provided as a part of the consent process. A person who has had menses at any time in the preceding 12 consecutive months or who has semen likely to contain sperm is considered to be of "reproductive potential." In addition to routine contraceptive methods, "effective contraception" also includes refraining from sexual activity that might result in pregnancy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) including hysterectomy, bilateral oophorectomy, bilateral tubal ligation/occlusion, and vasectomy with testing showing no sperm in the semen.
8. Participants with hepatitis B virus infection must have undetectable viral load within 14 days prior to registration, be on suppressive therapy and have no evidence of HBV related hepatic damage.
9. Participants with Hepatitis C infection must have eradication therapy completed, have no evidence of HCV related damage and have undetectable viral load within 14 days prior to registration.
10. Participants with known human immunodeficiency virus (HIV)-infection must be on effective anti-retroviral therapy at time of registration and have undetectable viral load test on the most recent test results obtained within 6 months prior to registration.
11. Participants must not have a prior or concurrent malignancy whose natural history or treatment have the potential to interfere with the safety or efficacy assessment of the investigational regimen.
12. Participants must not have any evidence of serious intracranial hemorrhage and/or edema within 6 months prior to registration.
13. Participants must not have evidence of acute or chronic Graft vs Host Disease from allogeneic stem cell transplant unless it is either grade 1 involvement of the skin requiring topical therapy or not requiring systemic immunosuppression.
14. Participants must not have known or suspected hypersensitivity to any of the study agents.
15. Participants must not have active autoimmune disease requiring systemic treatment in the last 2 years.

d. Specimen Submission Criteria

1. Participants must be offered the opportunity to participate in banking for planned translational medicine and future research, as outlined in Section 15.2. With participant consent, any residuals from the mandatory tissue submission will also be banked for future research.
   Note: Streck tubes must be ordered in advance, as indicated in Section 15.2c. Please allow 5-7 days for shipment of the collection kits.

e. Regulatory Criteria

NOTE: As a part of the OPEN registration process (see Section 13.5 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

1. Participants must be informed of the investigational nature of this study and must sign and give informed consent in accordance with institutional and federal guidelines.
   • For participants with impaired decision-making capabilities, legally authorized representatives may sign and give informed consent on behalf of study participants in accordance with applicable federal, local, and CIRB regulations.

STEP 2: RANDOMIZATION

a. Disease Related Criteria

1. Participants must have met all eligibility criteria for Step 1 Registration.
2. Participant's CAR T-cell product must have met specification parameters to be given as an FDA approved commercial product.
3. Participants must have a PET-CT scan between days 25-40 after CAR T-cell infusion and determined to have a response consistent with stable disease or partial remission by central review compared to most recent Pre-LD chemo/CAR T-cell PET-CT scan.
   Note: Patients with delayed enrollment > 21 days after 'Day +30' PETCT scan will necessitate a repeat PET-CT scan if concerning signs or symptoms of lymphoma progression develop.

Note: If response assessment by central review cannot be completed (I.e., poor quality of PET-CT scan, PET-CT performed out of window, etc.) this would be recorded as 'inadequate assessment' and patient would not be eligible for randomization.

4. Eligible participants must be randomized no later than 60 days after CAR -T infusion.
5. Participants must not have received CAR T-cell products given via expanded access protocol (EAP) or under single participant investigational new drug (IND).
6. Participants must not have clinical evidence of active CNS lymphoma involvement. This includes parenchymal, spinal cord, meningeal, or cerebrospinal fluid involvement.
   Note: Participants that had cerebrospinal fluid involvement at Step 1 Registration must submit documentation illustrating remission as assessed by CSF evaluation within 28 days prior to registration.

   Note: Participants with history of parenchymal, spinal cord, or meningeal CNS involvement at Step 1 Registration must submit documentation illustrating remission as assessed by contrast-enhanced MRI imaging within 28 days prior to registration.

b. Prior/Concurrent Therapy
   1. Participants must have started LD chemotherapy within 60 days of signing consent for Step 1 Registration.
   2. Participants must have received an FDA approved CD19 CAR T-cell construct no earlier than 2 days and no later than 14 days after completion of the last day of lymphodepleting chemotherapy.
   3. Participants must have S2114 CAR T-cell Therapy form submitted to SWOG prior to Step 2 Randomization.
   4. Participants must have had a PET-CT scan upon completion of all planned bridging therapy if received, with the exception of up to 7 days of corticosteroids. If the PET-CT scan after completion of bridging therapy was consistent with complete remission per Lugano criteria as determined by enrolling physician, that participant will be ineligible for Step 2 Randomization.
      a. If response assessment by central review cannot be completed (I.e., poor quality of PET-CT scan, PET-CT performed out of window, etc.) this would be recorded as 'inadequate assessment' and patient would not be eligible for randomization.
   5. Participants must not have received radiation or chemotherapy since CAR T-cell infusion and there must be no intention to send the participant for receipt of radiation therapy after randomization.
   6. Participant must not have received polatuzumab vedotin or mosunetuzumab as bridging therapy.

c. Clinical/Laboratory Criteria
   1. Participants must have Zubrod PS of 0, 1, or 2
   2. Participants must have adequate bone marrow within 7 days prior to Step 2 Randomization evidenced by the following:
      a. ANC ≥ 1.0 x 103/uL and participants must not have received myeloid growth factor within 72 hours prior to this lab being drawn
      b. platelets ≥ 75 x 103/uL and participants must not have received platelet transfusion within 72 hours prior to this lab being drawn
   3. Participants must have adequate hepatic function, within 7 days prior to Step 2 Randomization evidenced by the following
      a. Total bilirubin ≤ 1.5 x institutional ULN, and *Unless due to Gilbert's disease or lymphomatous involvement of liver
      b. AST and ALT ≤ 3 x institutional ULN
   4. Participants must have adequate renal function within 7 days prior to Step 2 Randomization as evidence by below:

a. Creatinine clearance ≥ 40 mL/min, as estimated by the Cockcroft and Gault formula. The creatinine value used in the calculation must have been obtained within 7 days prior to Step 2 Randomization. Estimated creatinine clearance is based on actual body weight.
b. Calculated Creatinine Clearance = $\frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine}}$ †

Multiply this number by 0.85 if the participant is a female.

† The kilogram weight is the participant weight with an upper limit of 140% of the IBW.

*Actual lab serum creatinine value with a minimum of 0.7 mg/dL.

5. Participants with peripheral neuropathy must have < grade 2.
6. Participants with current symptoms of cardiac disease must have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, participants must be class 2B or better. (Section 18.2)
7. Participants with history of hepatitis B viral infection must have undetectable viral load within 14 days prior to Step 2 Randomization and on suppressive therapy.
8. Participants with history of hepatitis C viral infection must have undetectable viral load within 14 days prior to Step 2 Randomization.
9. Participants with known human immunodeficiency virus (HIV)-infection must be continuing to receive anti-retroviral therapy and have an undetectable viral load test within 14 days prior to Step 2 Randomization.
10. Participants must not have documented myocardial infarction or unstable angina since Step 1 Registration.
11. Participants must not have any evidence of Cytokine Release Syndrome (CRS) by ASTCT guidelines within 7 days prior to Step 2 Randomization. Corticosteroid doses for treatment of CRS no higher than 10 mg of prednisone (or equivalent) are allowed if deemed to be part of a taper or replacement therapy (i.e. adrenal insufficiency or pituitary insufficiency) by the investigator. See also Section 18.4.
12. Participants must not have evidence of I-CANS by ASTCT guidelines within 7 days prior to Step 2 Randomization. Corticosteroid doses for treatment of I-CANS no higher than 10 mg of prednisone (or equivalent) are allowed if deemed to be part of a taper or replacement therapy (i.e. adrenal insufficiency or pituitary insufficiency) by the investigator.
13. Participants must not have any evidence of serious intracranial hemorrhage and/or edema since Step 1 Registration.
14. Participants must not have uncontrolled systemic fungal, bacterial or viral infection.
15. Participants must not have known or suspected chronic active Epstein-Barr virus (EBV) infection.
16. Participants must not have known or suspected history of hemophagocytic lymphohistiocytosis (HLH).
17. Participants must not have history of progressive multifocal leukoencephalopathy (PML).
18. Participants must not have active autoimmune disease requiring systemic treatment since enrollment to Step 1 Registration.

STEP 3: CROSSOVER REGISTRATION (Arm 4 Only)

Participants randomized to Arm 4 (observation) who subsequently have lymphoma progression within 12 months of CAR T-cell infusion will be eligible to cross over to Arm 3 to receive mosunetuzumab and polatuzumab vedotin combination as described in Section 7.6c.
Participants must meet the following criteria in order to qualify for cross-over.

a. Prior/Concurrent Therapy

1. Participants must have documented disease progression as defined in Section 10.1b while on Arm 4 (observation) on this protocol. The Followup Tumor Assessment Form documenting disease progression must be submitted to SWOG prior to Step 3 Crossover Registration.
2. Participants must be registered within 28 days of the date of progression.
3. Participants must have imaging that clearly demonstrates progression compared to day +30 PET-CT scan.
   Note: These scans should be performed as standard of care and only performed between scheduled response assessments required for study if symptoms arise that are concerning for progression.
4. Participants must not have received any lymphoma directed therapy (systemic therapy, radiation) after progression and prior to Step 3 Crossover Registration.

b. Clinical/Laboratory Criteria

1. Participants must have Zubrod PS of 0, 1, or 2
2. Participants must have adequate bone marrow within 14 days prior to Step 3 Crossover Registration evidenced by the following:
   a. ANC ≥ 1.0 x 103/uL and participants must not have received myeloid growth factor within 72 hours prior to this lab being drawn
   b. platelets ≥ 75 x 103/uL and participants must not have received platelet transfusion within 72 hours prior to this lab being drawn
3. Participants must have adequate hepatic function, within 14 days prior to Step 3 Crossover Registration evidenced by the following
   a. Total bilirubin ≤ 1.5 x institutional ULN, and *unless due to Gilbert's disease or lymphomatous involvement of liver
   b. AST and ALT ≤ 3 x institutional ULN
4. Participants must have adequate renal function within 14 days prior to Step 3 Crossover Registration as evidence by below:
   a. Creatinine clearance ≥ 40 mL/min, as estimated by the Cockcroft and Gault formula. The creatinine value used in the calculation must have been obtained within days prior to Step 3 Crossover Registration. Estimated creatinine clearance is based on actual body weight.

   $$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{weight in kg})\ \dagger}{72 \times \text{serum creatinine}\ *}$$

   Multiply this number by 0.85 if the participant is a female.
   † The kilogram weight is the participant weight with an upper limit of 140% of the IBW.
   *Actual lab serum creatinine value with a minimum of 0.7 mg/dL.
5. Participants with peripheral neuropathy must have < grade 2.
6. Participants with current symptoms of cardiac disease must have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, participants must be class 2B or better. (Section 18.2)
7. Participants with history of hepatitis B viral infection must have undetectable viral load within 14 days prior to Step 3 Crossover Registration and on suppressive therapy.
8. Participants with history of hepatitis C viral infection must have undetectable viral load within 14 days prior to Step 3 Crossover Registration.
9. Participants with known human immunodeficiency virus (HIV)-infection must be continuing to receive anti-retroviral therapy and have an undetectable viral load test within 14 days prior to Step 3 Crossover Registration.
10. Participants must not have documented myocardial infarction or unstable angina since Step 2 Randomization.

11. Participants must not have any evidence of serious intracranial hemorrhage and/or edema since Step 2 Randomization.
12. Participants must not have uncontrolled systemic fungal, bacterial or viral infection.

SCHEMA