SWOG 2308: RANDOMIZED PHASE III STUDY OF MOSUNETUZUMAB VS. RITUXIMAB FOR LOW TUMOR BURDEN FOLLICULAR LYMPHOMA

ELIGIBILITY CRITERIA

5.1. Disease Related Criteria

a. Participants must have a histologically confirmed diagnosis of Classic Follicular Lymphoma (cFL). cFL was previously categorized as Grade 1-3A per WHO-HAEM4R, but grading of classic FL is no longer mandatory. Please refer to Section 4.1 regarding classification.
NOTE: Participants with Follicular Lymphoma with uncommon features (uFL) are eligible, including FL with diffuse growth pattern (dFL). Diagnosis is as per local pathology. Lymphoma FISH is not required. Molecular testing is not required.

b. Participants must not have Follicular Lymphoma with "blastoid" or "large centrocyte" cytological features, or Follicular large B-cell lymphoma (FLBL) (Previously categorized as follicular lymphoma grade 3B).

c. Participants must have low-tumor burden follicular lymphoma defined as:

1. Nodal or extra-nodal tumor mass with diameter less than 7 cm in its greater diameter
2. Involvement of no more than 3 nodal or extra nodal sites with diameter greater than 3 cm.
3. Absence of B symptoms
4. No symptomatic splenomegaly
5. No compression syndrome (ureteral, orbital, gastrointestinal)
6. No pleural or peritoneal serous effusion related to follicular lymphoma

Participants must have Ann Arbor stage II, III, or IV follicular lymphoma. Participants with Stage I disease may be included if they do not wish to undergo radiation or are not candidates for radiation. Please refer to Section 4.2 regarding staging classification.

d. Participants must either be experiencing distress due to their disease or would prefer active management of their disease rather than a watch and wait approach.

e. Participants must have staging imaging performed within 49 days prior to registration, as follows. PET-CT baseline scans are preferred. If a baseline PET-CT scan cannot be obtained, CT scans of the chest, abdomen, and pelvis, along with a bone marrow biopsy, are acceptable. If CT scans are used for staging at baseline, a CT scan of the neck is recommended. All measurable dominant lesions must be assessed within 49 days prior to registration (see Section 10.1a.). Tests to assess non-measurable disease must be performed within 49 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form.
NOTE: if the initial evaluation is insufficient to detect measurable disease, treating investigators may obtain a CT scan with contrast.

f. Participants must have bi-dimensionally measurable disease (at least one lesion with longest diameter >1.5 cm).

5.2. Prior/Concurrent Therapy Criteria

a. Participants must not have had prior systemic therapy for follicular lymphoma. Radiation therapy for a previous diagnosis of early-stage follicular lymphoma is allowed.

5.3. Clinical/Laboratory Criteria

a. Participant must be ≥ 18 years of age at the time of registration.

b. Participant must have Zubrod Performance Status of 0-2 (see Section 10.4).

c. Participant must have a complete medical history and physical exam within 28 days prior to registration.

d. Participants must have adequate organ and marrow function as defined below within 28 days prior to registration:

- leukocytes ≥3 x 10^3/uL
- hemoglobin >9.0 g/dL
- absolute neutrophil count ≥1.5 x 10^3/uL
- platelets ≥100 x 10^3/uL
- total bilirubin ≤ 2x institutional upper limit of normal (ULN) unless history of Gilbert's disease. Participants with history of Gilbert's disease must have total bilirubin ≤ 5 x institutional ULN.
- AST/ALT ≤ 3 × institutional ULN
- LDH < institutional ULN

e. Participants must have a calculated creatinine clearance ≥ 30 mL/min using the following Cockcroft-Gault Formula. This specimen must have been collected and processed within 28 days prior to registration:

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

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 creatinine value with a minimum of 0.7 mg/dL.

f. Participants must not have an active or uncontrolled infection before initiation of study treatment in the opinion of the treating investigators.

g. Participants must not have uncontrolled diabetes within 14 days prior to registration in the opinion of the treating investigators.

h. Participants must not have uncontrolled blood pressure and hypertension within 14 days prior to registration in the opinion of the treating investigators.

i. Participants with known human immunodeficiency virus (HIV)-infection must be on effective anti-retroviral therapy at registration and have undetectable viral load test on the most recent test results obtained within 6 months prior to registration.

j. Participants with evidence of chronic hepatitis B virus (HBV) infection must have undetectable HBV viral load while on suppressive therapy on the most recent test results obtained within 6 months prior to registration, if indicated. Participants with a positive total Hep B core antibody and negative HBsAg at screening are at high risk for reactivation and should receive prophylactic antivirals (e.g., entecavir) before and throughout the treatment.

k. Participants must not have active autoimmune disease requiring systemic therapy.

l. Participants must not have had undergone organ transplants requiring ongoing systemic immunosuppressive therapy.

m. Participants with a history of hepatitis C virus (HCV) infection must have been treated and cured. Participants currently being treated for HCV infection must have undetectable HCV viral load test on the most recent test results obtained within 6 months prior to registration, if indicated.

n. Participants must not have known chronic active Epstein Barr Virus infection (CAEBV); testing in asymptomatic participants is not required.

o. Participants must not have a positive test result for COVID-19 within seven (7) days prior to registration.

p. Participants must not have a prior or concurrent malignancy whose natural history or treatment (in the opinion of the treating physician) has the potential to interfere with the safety or efficacy assessment of the investigational regimen.

q. Participants must not have a history of confirmed progressive multifocal leukoencephalopathy (PML).

r. Participants must not have received allogeneic stem cell transplantation.

s. Participants must not have a history of macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis (HLH).

t. Participants with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, must have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification (see Section 18.2). Participant must not have significant cardiovascular disease such as Class III or IV cardiac disease, myocardial infarction within 6 months prior to registration. Participants with unstable arrhythmias, or unstable angina, should be excluded.

u. Participants must not be pregnant or nursing (nursing includes breast milk fed to an infant by any means, including from the breast, milk expressed by hand, or pumped). 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.

5.4. Additional Criteria

a. Participants must be offered the opportunity to participate in specimen banking as outlined in Section 15.3. With participant consent, specimens must be collected and submitted via the SWOG Specimen Tracking System as outlined in Section 15.2.

6.0 STRATIFICATION FACTORS

Participants will be randomized on a 1:1 ratio using a dynamic balancing (*20*) algorithm with stratification based on:

1) Follicular lymphoma international prognostic index. FLIPI score 0-2 vs. ≥ 3.
2) Receipt of prior radiation therapy for follicular lymphoma: yes vs. no.
3) Age: ≤ 80 years vs > 80 years.