Cancer Research Consortium of West Michigan
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FAST FACTS

S1608: RANDOMIZED PHASE II TRIAL IN EARLY RELAPSING OR REFRACTORY FOLLICULAR LYMPHOMA

Eligibility Criteria

Disease Related Criteria

1. Patients must have follicular lymphoma (Grade I, II or IIIa) confirmed at initial diagnosis and at relapse with identifiable FDG avid disease on PET/CT. Patients that have involvement with large cell lymphoma are not eligible.
2. Patients must not have clinical evidence of central nervous system involvement by lymphoma, since the proposed treatment strategies are not designed to address CNS involvement adequately. If performed, any laboratory or radiographic tests performed to assess CNS involvement must be negative.
3. Patients must have a whole body or limited whole body PET/CT scan performed within 42 days prior to registration.
4. Patients must have bone marrow biopsy performed within 42 days prior to registration.

All disease must be assessed and documented on the **S1608** FDG-PET/CT Assessment Form.

Prior/Concurrent Therapy Criteria

A. The intent is to enroll patients with FL relapsed within 2 years of completing their first course of chemotherapy (CHOP or bendamustine based therapy) + anti-CD20 therapy. Patient is still eligible if he/she received radiation therapy or anti-CD20 therapy prior to chemoimmunotherapy or if maintenance anti-CD20 therapy was administered after chemoimmunotherapy.

- Patients must have either failed to achieve a complete remission, or must have relapsed within 2 years after completing CHOP or bendamustine-containing chemoimmunotherapy (including an anti-CD20 monoclonal antibody), as measured from the last dose of CHOP or bendamustine. Relapsed patients must not have received any intervening chemotherapy.
- Patients must have received only 1 course of chemotherapy, containing at least 3 cycles of CHOP or bendamustine. (Note that no minimum dose is required.)
- Patients who received any anti-CD20 antibody therapy prior to CHOP or bendamustine are eligible.
- Patients who additionally received any maintenance anti-CD20 antibody therapy or consolidative radioimmunotherapy within 2 years of the last dose of the CHOP or bendamustine therapy are eligible.
- Involved field or involved site radiation is not considered a line of therapy.
- Examples of eligible prior treatment regimens (note this list is not all inclusive):
- 1st line Rituximab treatment followed years later by bendamustine rituximab
- Bendamustine rituximab x 4 cycles
- 1st line rituximab treatment, 2nd line ibrutumomab tiuxetan, followed by bendamustine bortezomib rituximab x 6 cycles followed by rituximab maintenance
- Bendamustine obinutuzumab x 3 cycles
- CHOP rituximab x 6 cycles followed by rituximab maintenance

B. For all forms of systemic therapy, patients must have completed therapy at least 21 days prior to registration. Patients must have completed any radioimmunotherapy at least 84 days prior to registration. Patients must have recovered from all treatment related toxicities from these therapies prior to registration.

C. Patients must not have any prior treatment with any PI3K inhibitor, or lenalidomide.

Specimen Submission Criteria
Patients must have tissue specimens collected prior to registration as outlined in Section 15.1. Patients must be offered participation in biobanking of residual specimens, as outlined in Section 15.1e. With patient consent, residuals from the mandatory submission(s) will be banked for future research.

Note: See Section 15.1d for information regarding pre-ordering of blood specimen kits for pre-treatment samples.

Clinical/Laboratory Criteria

1. Patients must be ≥ 18 years of age.
2. All patients must have a Zubrod performance status of 0, 1 or 2 (see Section 10.4).
3. Patients must have adequate bone marrow function as evidenced by ANC ≥ 1,500/mcL and platelets ≥ 75,000/mcL within 28 days prior to registration.
4. Patients must have adequate renal function as documented by a calculated creatinine clearance ≥ 60 mL/min, within 28 days prior to registration.

   $$\text{Estimated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{serum or plasma creatinine (mg/dl)}}$$

5. Patients must have adequate hepatic function obtained within 28 days prior to registration and documented by all of the following:
   - Total bilirubin ≤ 1.5 x IULN (≤ 5 x IULN if secondary to lymphoma, Gilbert's syndrome, or medication related [e.g., indinavir, tenofovir, atazanavir])
   - Direct bilirubin ≤ 1.5 x IUL10N (≤ 5 x IULN if secondary to lymphoma)
   - AST and ALT ≤ 2.5 x IULN (≤ 5 x IULN secondary to lymphoma)
6. Patients must have an echocardiogram (ECHO) or MUGA scan within 42 days prior to registration with a cardiac ejection fraction ≥ 45%.
7. Patients with Hepatitis B Virus infection must have undetectable HBV on suppressive therapy and no evidence of HBV-related hepatic damage.
   Patients with Hepatitis C virus infection are eligible if complete eradication therapy has been successfully completed, and there is no detectable HVC or related hepatic damage.
   Patients with known HIV infection are eligible if they meet all of the following criteria in addition to the other protocol eligibility criteria:
   - Patient must have no history of AIDS-related complications, other than a history of low CD4+ T-cell count (< 200/mm3) prior to initiation of combination antiretroviral therapy. On study CD4+ T-cell count may not be informative due to leukemia and should not be used as an exclusion criterion if low.
   - Patient must be healthy on the basis of HIV disease with high likelihood of near normal life span were it not for the leukemia.
   - Patient must have serum HIV viral load of < 200 copies/mm3
   - Patient must be on combination antiretroviral therapy with minimal pharmacokinetic interactions with study therapy and minimal overlapping clinical toxicity with protocol therapy. (Recommend a regimen of the integrase inhibitor dolutegravir combined with either disoproxil fumarate/emtricitabine or dolutegravir combined with tenofovir alafenamide/emtricitabine.)
   - Protease inhibitors and once daily formulations containing cobicistat are NOT allowed due to potential pharmacokinetic interactions with leukemia therapy.

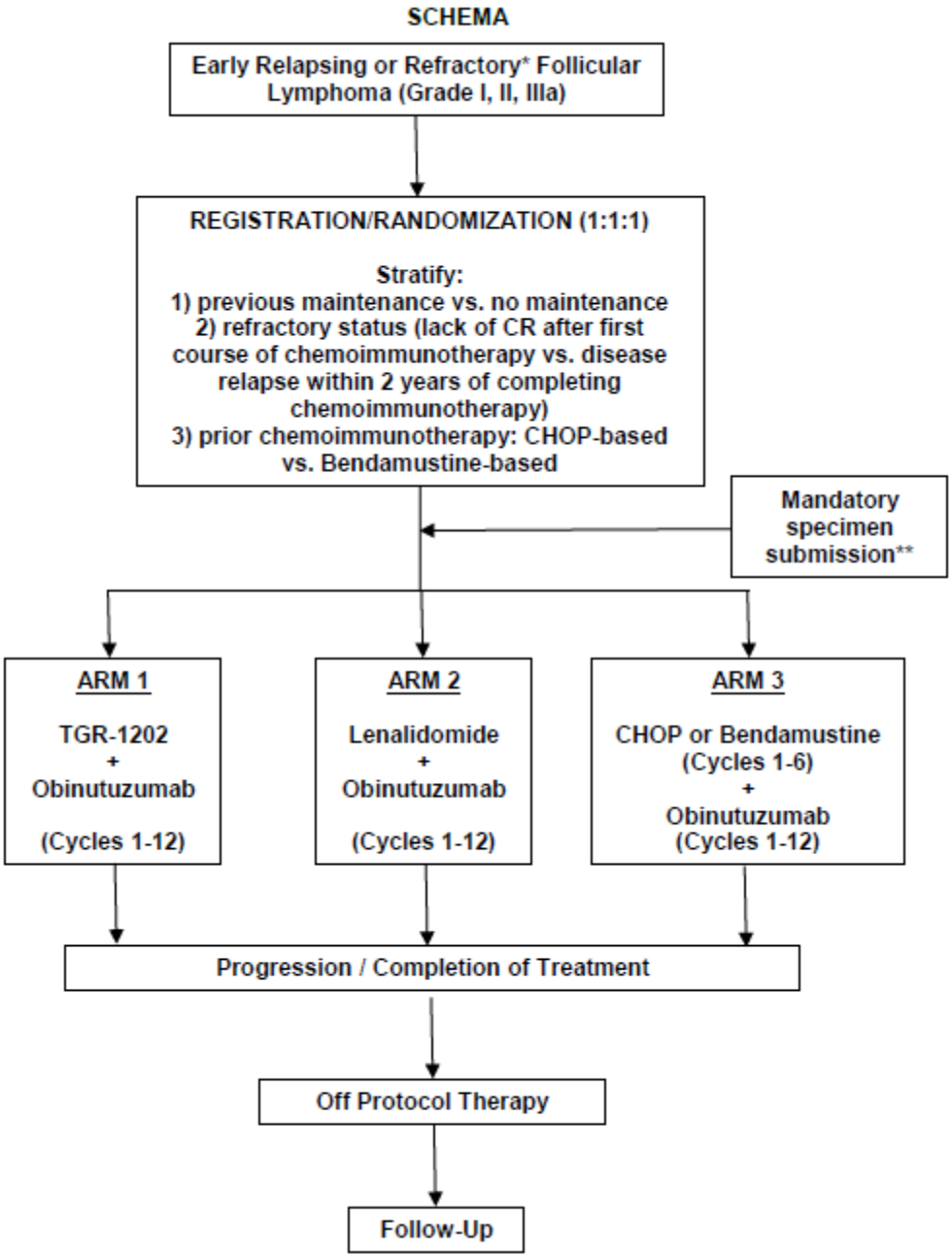
- Stavudine and zidovudine are NOT allowed because of overlapping toxicity with protocol therapy.

8. Patients must be able and willing to receive prophylaxis with daily aspirin, low molecular weight heparin, factor X inhibitors or Warfarin if randomized to lenalidomide. Patients must also be willing to receive pneumocysitis jirovecii prophylaxis with sulfamethoxazole/trimethoprim, dapsone, atovaquone or inhaled pentamadine, in the event that they are randomized to TGR-1202. Patients unable or unwilling to take any listed prophylaxis are NOT eligible.
9. Patients must be able to discontinue CYP2C9 substrates with a narrow therapeutic index (e.g. warfarin, phenytoin), if randomized to TGR-1202. Patients must discontinue such agents at least 1 week or 5 half-lives prior to beginning protocol therapy (whichever is longer). A list of 2C9 substrates is available at http://medicine.iupui.edu/clinpharm/ddis/main-table/. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently updated medical reference.
10. No second prior malignancy is allowed except for adequately treated basal (or squamous cell) skin cancer, in situ cervical cancer or other cancer for which the patient has been disease free for three years.
11. Patients must have a complete history and physical examination within 28 days prior to registration.
12. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days and again within 24 hours prior to starting Cycle 1 of lenalidomide. Further, they must either commit to complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual intercourse or begin TWO acceptable methods of birth control: one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before starting lenalidomide, while taking lenalidomide, during dose interruptions, and for at least 28 days after the last dose of lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP, even if they have had a successful vasectomy. A FCBP is female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). All patients must be counseled by a trained counselor every 28 days about pregnancy precautions and risks of fetal exposure. (See Appendix 18.1: Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, and also Appendix 18.2: Lenalidomide Education and Counseling Guidance Document).

    NOTE: Patients not randomized to receive lenalidomide will not be required to undergo serial pregnancy testing or lenalidomide counseling after registration.

13. Patients must have LDH and beta-2-microglobulin collected within 28 days prior to registration.

SCHEMA


Early Relapsing or Refractory* Follicular Lymphoma (Grade I, II, IIIa)
REGISTRATION/RANDOMIZATION (1:1:1)
Stratify:
1) previous maintenance vs. no maintenance
2) refractory status (lack of CR after first course of chemoimmunotherapy vs. disease relapse within 2 years of completing chemoimmunotherapy)
3) prior chemoimmunotherapy: CHOP-based vs. Bendamustine-based
Mandatory specimen submission**
ARM 1
TGR-1202
+
Obinutuzumab
(Cycles 1-12)
ARM 2
Lenalidomide
+
Obinutuzumab
(Cycles 1-12)
ARM 3
CHOP or Bendamustine
(Cycles 1-6)
+
Obinutuzumab
(Cycles 1-12)
Progression / Completion of Treatment
Off Protocol Therapy
Follow-Up