CALGB 50904: A Randomized Phase II Trial of Ofatumumab and Bendamustine vs. Ofatumumab, Bortezomib (NSC #681239, IND #58443) and Bendamustine in Patients with Untreated Follicular Lymphoma

Fast Facts

Ofatumumab, Bendamustine, Bortezomib provided
CTCAE v.4

Documentation of Disease
1) Histologically confirmed follicular non-Hodgkin lymphoma, WHO classification grade 1, 2, or 3a (>15 centroblasts per high power field with centrocytes present). Bone marrow biopsies as the sole means of diagnosis are not acceptable, but they may be submitted in conjunction with nodal biopsies. **Fine needle aspirates are not acceptable.** Failure to submit pathology within 60 days of patient registration will be considered a major protocol violation.
2) Patients must have at least one of the following indicators of poor risk disease:
   i. ≥ 3 risk factors by the Follicular Lymphoma International Prognostic Index (FLIPI) OR 2 risk factors by the Follicular Lymphoma International Prognostic Index (FLIPI) and at least one bulky mass or lymph node > 6 cm in size

Follicular Lymphoma International Prognostic Index (FLIPI):
- Age ≥ 60 years
- Involvement of ≥ 4 nodal sites
- Stage III-IV disease
- Hemoglobin < 12.0 mg/dL
- LDH > Upper limit of normal (ULN)

Prior Treatment
1) No prior cytotoxic chemotherapy, radiotherapy, immunotherapy, or radioimmunotherapy.
2) No corticosteroids are permitted, except for maintenance therapy for a nonmalignant disease or to prevent treatment-related ofatumumab reactions. (Maintenance therapy dose must not exceed 20 mg/day prednisone or equivalent).

Measurable Disease
1) Measurable disease must be present either on physical examination or imaging studies. Non-measurable disease alone is not acceptable. Any tumor mass > 1 cm is acceptable. Lesions that are considered non-measurable include the following:
   - Bone lesions
   - Leptomeningeal disease
   - Ascites
   - Pleural/pericardial effusion
   - Inflammatory breast disease
   - Lymphangitis cutis/pulmonis
   - Bone marrow involvement (involvement by non-Hodgkin lymphoma should be noted)
2) No known CNS involvement by lymphoma.
3) Age ≥ 18 years of age
4) ECOG Performance Status 0-2
5) Non-pregnant and non-nursing. Due to the unknown teratogenic potential of this regimen, pregnant or nursing patients may not be enrolled. Women of childbearing potential must have a negative serum or urine pregnancy test 10-14 days prior to registration. In addition, women and men of childbearing potential must commit to use an effective form of contraception throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives (Norplant), or double barrier method (diaphragm plus condom).
6) Patients with HIV infection are eligible. Patients with HIV infection must meet the following: no evidence of co-infection with hepatitis B or C; CD4+ count > 400/μl; no evidence of resistant strains of HIV; on anti-HIV therapy with an HIV viral load < 50 copies HIV RNA/mL; no history of AIDS-defining conditions. No safety data are available regarding HIV positive individuals treated with ofatumumab. No zidovudine or stavudine are allowed owing to overlapping toxicity with chemotherapy.
7) No evidence of active hepatitis B or C infection (i.e., no positive serology for anti-HBc or anti-HCV antibodies). HBV seropositive patients (HBsAg +) are eligible if HBV DNA is undetectable at baseline and they are closely monitored for evidence of active HBV infection by HBV DNA testing at each treatment cycle. After completing treatment, HBsAg + patients must be monitored by HBV DNA testing every 2 months for 6 months post-treatment, while continuing lamivudine (see Section 9.4).

8) Required Initial Laboratory Values:
   - Granulocytes ≥ 1,000/μl
   - Platelet count ≥ 75,000/μl
   - Creatinine ≤ 2.0 mg/dL
   - AST and ALT ≤ 2.5 x upper limits of normal (ULN)
   - Bilirubin ≤ 2 x ULN

Pre-study Parameters
1) History and physical including pulse, performance status, blood pressure, height and weight/BSA
2) Labs including CBC with differential and platelets, serum creatinine, BUN, serum electrolytes, Ca++, ALT, AST, Alk Phos, bilirubin, LDH, Uric Acid, β-2 microglobulin, serum or urine βHCG (if required), HBsAg, HBsAb, HB core antibody, HBV DNA testing, HCV testing virus antibody, HIV (if required)
3) CT or MRI chest, abdomen and pelvis; CT or MRI neck, FDG-PET/CT Scan
4) Bone marrow biopsy and aspirate (bilateral preferred)

Treatment

**ARM A**

**Induction**
- Ofsatumumab 300 mg (IV) on day 1 of cycle 1 and 1000 mg on day 1 of cycles 2-6, immediately prior to bendamustine.
- Bendamustine 90 mg/m² (IV) over 30-60 minutes on days 1 and 2 of each cycle.
Cycles will be repeated every 35 days for up to 6 cycles.

**Maintenance**
- Ofsatumumab 1000 mg (IV) on day 1 of each cycle.
- Cycles will be repeated every 56 days for up to 4 cycles.

**ARM B**

**Induction**
- Ofsatumumab 300 mg (IV) on day 1 of cycle 1 and 1000 mg on day 1 of cycles 2-6 immediately prior to bortezomib and bendamustine.
- Bortezomib 1.6 mg/m² (IV) on days 1, 8, 15, and 22 of each cycle.
Cycles will be repeated every 35 days for up to 6 cycles.

**Maintenance**
- Ofsatumumab 1000 mg (IV) on day 1 of each cycle (immediately prior to bortezomib).
- Bortezomib 1.6 mg/m² (IV) on days 1, 8, 15, and 22 of each cycle.
Cycles will be repeated every 56 days for up to 4 cycles.

* In Arms A and B, restage patients with CT or MRI of the chest, abdomen, and pelvis and FDG-PET/CT after cycles 2 and 6 of induction therapy. Additionally, in Arms A and B, restaging with CT or MRI of the chest, abdomen, and pelvis is performed after 4 cycles of induction. During maintenance therapy, restage every 4 months with CT or MRI of chest, abdomen, and pelvis. After the completion of therapy, restage every 4 months with CT or MRI of the chest, abdomen, and pelvis for two years and then every 6 months until disease progression or for a maximum of 10 years from study entry.

** See Sections 7.1.1, 7.1.2, 7.2.1, and 7.2.2 for induction and maintenance premedication.