

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO 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**

Bortezomib (NSC #681239, IND #58443) will be supplied by NCI/PMB.

Ofatumumab will be supplied by GlaxoSmithKline.

Bendamustine will be supplied by Cephalon.

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| <input checked="" type="checkbox"/> Update: | <input type="checkbox"/> Status Change: |
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| <input checked="" type="checkbox"/> Other: Bortezomib CAEPR update | |

The changes included in this update to CALGB 50904 have been made in response to the NCI Action Letter from Dr. John J. Wright, dated XX/XX2017. This Action Letter is posted on the CALGB 50904 study page on the Alliance web site. A revised CAEPR for bortezomib with new risk information has been added to the protocol. Therefore, the model consent form has been revised to incorporate these new risks, consistent with the NCI Model Consent Template instructions. There are no changes to the risk/benefit ratio.

*IRB approval (or disapproval) is required within 90 days. Expedited review is allowed.
Please follow your IRB of record guidelines.*

UPDATES TO THE PROTOCOL:

Section 17.3 (CAEPR for Bortezomib [Velcade, NSC 681239])

This section has been revised to include the updated bortezomib CAEPR (Version 2.6, May 25, 2017) provided by CTEP. Changes from Version 2.5 to Version 2.6 include the following:

- The SPEER grades have been updated.
- Increase in Risk Attribution:
 - Changed to Rare but Serious from Also Reported on Bortezomib Trials But With Insufficient Evidence for Attribution: Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; GGT increased; INR increased; Investigations - Other (albumin); Hepatic failure; Hepatobiliary disorders - Other (hepatitis); Tumor lysis syndrome
- Provided Further Clarification:
 - A new footnote #4 has been added: “Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include hepatitis, increases in liver enzymes, and hyperbilirubinemia.”
 - Footnote #4 has been added to: Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; GGT increased; INR increased; Investigations - Other (albumin); Hepatic failure; Hepatobiliary disorders - Other (hepatitis).
- Additional Changes:

In previous versions of the protocol, the footnotes were inadvertently left out of the CAEPR. Therefore, in addition to the new footnote #4 described above, the following footnotes have been added back to the protocol CAEPR with this update:

- Footnote #1: “This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.”
 - Footnote #2: “Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.”
 - Footnote #3: “Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.”
 - Footnote #5: “Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.”
-

UPDATES TO THE MODEL CONSENT:

What side effects or risks can I expect from being in the study?

Based on the updated bortezomib CAEPR described above, the following changes have been made to the NCI condensed risk profile for bortezomib (found under “Risks and side effects related to GROUP B treatment”):

- Increase in Risk Attribution:
 - Changed to Rare from Also Reported on Bortezomib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): “Liver damage which may cause yellowing of eyes and skin, swelling”
- Provided Further Clarification:
 - “Kidney damage which may cause swelling, may require dialysis” (under Rare) is now reported as “Kidney damage which may require dialysis” (under Rare).
 - “Damage to organs which may cause shortness of breath, or changes in thinking” (under Rare) is now reported as “Damage to organs (brain, lungs, blood vessel in lungs, others) which may cause changes in thinking, or shortness of breath” (under Rare).

**Replacement protocol and model consent documents have been issued.
This study remains closed to new patient accrual.**

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

CALGB 50904

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BORTEZOMIB (NSC #681239, IND #58443) AND BENDAMUSTINE IN PATIENTS WITH UNTREATED
FOLLICULAR LYMPHOMA**

Clinicaltrials.gov Identifier: NCT01286272

*Bortezomib (NSC #681239, IND #58443) will be supplied by NCI/PMB.
Ofatumumab will be supplied by GlaxoSmithKline.
Bendamustine will be supplied by Cephalon.*

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	For patient enrollments:	Submit study data:
<p>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206</p> <p>Email: CTSURegulatory@ctsu.coccc.org (for submitting regulatory documents only)</p>	<p>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.</p> <p>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.</p>	<p>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.</p>
<p>The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members’ website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.</p>		
<p><u>For clinical questions (i.e. patient eligibility or treatment-related)</u> contact the Alliance Study Chair.</p>		
<p><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p><u>For detailed information on the regulatory and monitoring procedures for CTSU sites</u> please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members’ website https://www.ctsu.org > education and resources tab > CTSU Operations Information > <u>CTSU Regulatory and Monitoring Policy</u></p>		
<p>The CTSU Web site is located at https://www.ctsu.org.</p>		

A RANDOMIZED PHASE II TRIAL OF OFATUMUMAB AND BENDAMUSTINE VS. OFATUMUMAB, BORTEZOMIB (NSC #681239, IND #58443) AND BENDAMUSTINE IN PATIENTS WITH UNTREATED FOLLICULAR LYMPHOMA

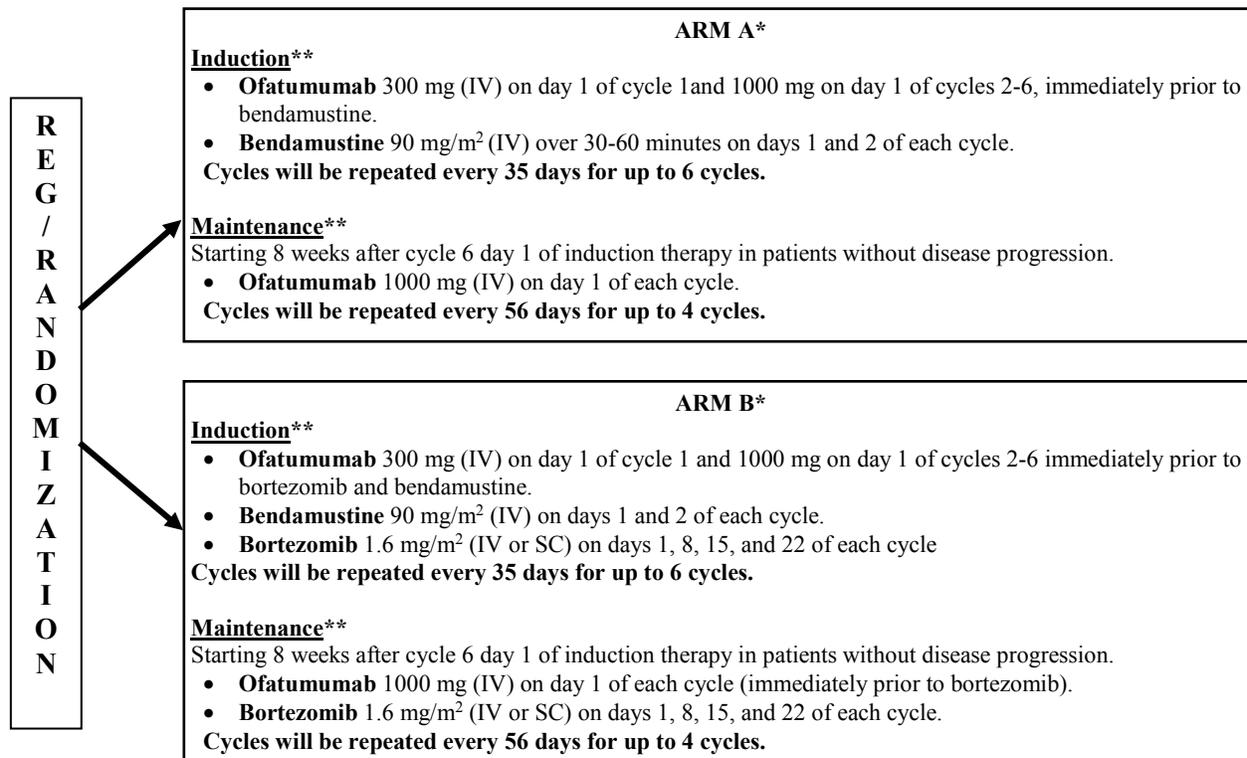
Schema Page 1 of 1

Eligibility Criteria

- Histologically confirmed follicular non-Hodgkin lymphoma, WHO classification grade 1, 2, or 3a (> 15 centroblasts per high power field with centrocytes present)
- Follicular Lymphoma International Prognostic Index (FLIPI) score ≥ 3 (see [Section 4.1.2](#)) or FLIPI score of 2 with at least 1 tumor mass/lymph node > 6 cm
- No prior treatment (see [Section 4.2](#))
- No prior cytotoxic chemotherapy, radiotherapy, immunotherapy or radioimmunotherapy
- No corticosteroids are permitted, except for maintenance therapy for a non-malignant disease
- Age ≥ 18 years
- ECOG performance status 0-2
- Measurable disease (see [Section 4.3](#))
- No known CNS involvement by lymphoma
- Non-pregnant and non-nursing
- Patients with HIV infection are eligible provided they meet the parameters in [Section 4.8](#)
- No active hepatitis B or C infection (see [Section 4.9](#))

Required Laboratory Values

- Granulocytes: $\geq 1,000/\mu\text{l}$
- Platelet Count: $\geq 75,000/\mu\text{l}$
- Creatinine: ≤ 2.0 mg/dL
- AST and ALT: ≤ 2.5 x ULN
- Bilirubin: ≤ 2 x ULN



* 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 [8.1.1](#), [8.1.2](#), [8.2.1](#), and [8.2.2](#) for induction and maintenance premedication.

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1.0 INTRODUCTION

1.1 Prognosis and treatment options in follicular lymphoma

The follicular lymphoma international prognostic index (FLIPI) identifies three prognostic groups in patients with follicular non-Hodgkin lymphoma (NHL) on the basis of the presence of 5 different risk factors: age > 60 years of age, stage III-IV disease, hemoglobin < 12 g/dL, elevated LDH, or involvement of 4 or more nodal sites. For those patients with 3 or more of these adverse risk factors, predicted overall survival (OS) is 52% at 5 years and 35% at 10 years, compared to a 10 year OS of 70% in the low risk group [1]. More recently, a second prognostic index, FLIPI 2, has been developed and may be more accurate than the original FLIPI. FLIPI2 identifies age > 60 years, bone marrow involvement, hemoglobin < 12 g/dL, elevated β 2-microglobulin, or bulky disease > 6 cm as adverse prognostic factors associated with PFS and OS [2]. Newer therapies and treatment paradigms need to be developed for these patients with a high-risk FLIPI 1 and FLIPI 2 scores at diagnosis in order to improve responses and most importantly, prolong response duration.

As front-line therapy for patients with follicular non-Hodgkin lymphoma, rituximab, cyclophosphamide, vincristine, and prednisone (RCHOP) results in an overall response rate (ORR) of 100%, with 87% of patients obtaining a complete response (CR) or complete response unconfirmed (CRu) [3]. With this regimen, the median time to disease progression is 82.3 months [3]. However, in those patients with poor risk FLIPI scores, the median time to progression following RCHOP is significantly shorter, at only 30.05 months, compared to 83.5 and 51.95 months for patients with 0-1 or 2 adverse risk factors, respectively [3].

Recently, several studies have demonstrated that rituximab in combination with the unique alkylating agent, bendamustine, has similar efficacy and an improved toxicity profile in comparison to CHOP in the treatment of patients with newly diagnosed and relapsed indolent NHL [4-7]. In the relapsed setting, response rates of 77-92%, complete responses of 15-60%, and progression-free survivals of 6.7-24 months have been noted [4, 5, 7]. Toxicities have been minimal consisting of grade 3-4 myelosuppression in 16-54% in relapsed patients, with increased toxicity at the 120 mg/m² dose level of bendamustine (120 mg/m² on days 1 and 2) compared to the 90 mg/m² dose [4, 5, 7]. In a randomized phase III trial of rituximab-bendamustine vs. RCHOP in patients with untreated indolent NHL, including 55% follicular lymphoma patients, the overall response rate was similar between the rituximab-bendamustine and RCHOP treatment arms at 93.8% and 93.5%, respectively [7]. However, toxicity was significantly less in the rituximab-bendamustine arm with only 15% alopecia, a 36.5% rate of infection, and 10.7% risk of grade 3-4 neutropenia, compared to 62%, 47.8%, and 46.5 % alopecia, infection, and neutropenia rates with RCHOP [7]. The median PFS with R-bendamustine was 54 months compared to 34.8 months with R-CHOP (p=0.0002). Therefore, although RCHOP and R-bendamustine have similar response rates in untreated patients with follicular lymphoma, the toxicity profile and prolonged PFS significantly favors the use of R-bendamustine in this population.

1.2 Ofatumumab in follicular lymphoma

One possible approach to improve remission duration and increase molecular responses in these high-risk follicular lymphoma patients is to consider the use of novel monoclonal antibody therapy in combination with chemotherapy regimens such as CHOP or bendamustine. Ofatumumab is fully humanized anti-CD20 monoclonal antibody that targets a novel epitope of the CD20 molecule and releases much more slowly from the antigen than rituximab. Compared with rituximab, ofatumumab appears to have more

potent complement-dependent cytotoxicity and is able to induce lysis in B-cell lymphoma cell lines that are resistant to rituximab [8, 9]. There is also increased NK-cell mediated ADCC potency with ofatumumab, when compared to rituximab [10]. In a phase 1/2 clinical trial of ofatumumab in patients with relapsed or refractory follicular lymphoma, responses were observed at doses ranging from 300-1000 mg of ofatumumab given once a week for 4 weekly doses [11]. The response rate did not appear to be dose dependent, with responses across all dose levels and adjusted for body surface area. Therefore, a fixed dose of 1000 mg has been selected for future phase II trials. In addition, toxicity consists primarily of infusion reactions, and sustained B-cell depletion occurs from 6-10 months after ofatumumab dosing.

Some responses have also been noted in patients who are refractory to rituximab [12]. In a phase II study of ofatumumab at doses of 500 - 1000 mg in 116 patients with relapsed follicular NHL that was refractory to rituximab (defined as failure to achieve a PR, disease progression during rituximab treatment, or disease progression within 6 months of a rituximab-containing treatment), the ORR was 11% in all patients, and was 22% in patients who were refractory to rituximab containing monotherapy [12]. Although this ORR was low, what is encouraging is that 47% of patients on this study had high-risk follicular NHL, with FLIPI scores of 3 or higher, and responses were observed in refractory patients including at least 1 CR. In addition, toxicity was mild and consisted of grade 3-4 infusion reactions in only 3 patients. Furthermore, additional studies have suggested that combination therapy with chemotherapy and ofatumumab is well-tolerated. In patients with previously untreated CLL, combination therapy with ofatumumab, fludarabine, and cyclophosphamide is well-tolerated without grade 3-4 infusion toxicity and with no unexpected increase in myelosuppression or infectious toxicity [13]. In addition, a higher CR was observed in patients receiving 1000 mg of ofatumumab compared to 500 mg when combined with fludarabine and cyclophosphamide [13]. Although additional comparative studies between rituximab and ofatumumab are needed, it currently appears that combination therapy with ofatumumab and nucleoside analogues is feasible and that ofatumumab has efficacy in patients with high-risk follicular lymphoma who are refractory to rituximab.

1.3 Vertical regimen in follicular lymphoma

In a multi-center phase I study, 16 patients with relapsed follicular lymphoma and a median of 3 prior therapies (including 31% who were previously transplanted) received rituximab 375 mg/m² IV on days 1, 8, 15, and 22 of cycle 1 and then on day 1 of cycles 2-5, bortezomib 1.6 mg/m² on days 1, 8, 15, and 22, and bendamustine 60-90 mg/m² on days 1-2 of a 35 day cycle [14]. Doses up to 90-mg/m² bendamustine were well tolerated. Toxicities consisted of grade 3-4 neutropenia in 25% of patients and grade 4 thrombocytopenia in 6% of patients. Other events included grade 3 diarrhea (31%), fatigue (25%), vomiting (13%), and nausea (13%).

In a subsequent phase II trial with this regimen, the ORR in 49 patients with relapsed and refractory follicular NHL was 84%, and 35% of these patients had high-risk FLIPI scores at the time of study enrollment. Grade 3-4 toxicities were uncommon and included neutropenia in 25% of patients, thrombocytopenia in 6%, peripheral neuropathy in 6%, febrile neutropenia in 5%, and herpes zoster in 1 patient [15]. Therefore, the vertical regimen combining rituximab, bortezomib, and bendamustine appears well-tolerated with preliminary efficacy in patients with relapsed follicular lymphoma and should be explored as front-line therapy.

1.4 Maintenance therapy in follicular lymphoma

Another approach to improve remission duration and improve response rate in high-risk follicular lymphoma patients is to consider the addition of maintenance therapy to chemotherapy combination regimens. In newly diagnosed and relapsed patients, maintenance rituximab following either single agent rituximab or combination chemotherapy improves response duration, progression-free survival (PFS), and OS [16-19]. Following initial therapy with 4 weekly doses of rituximab, rituximab maintenance at least doubles event-free and progression-free survival from ranges of 7.4-12 months to 23-31 months [17, 18]. Following RCHOP in the relapsed setting, those patients receiving maintenance rituximab had an improvement in 3 year OS from 77% to 85% [19]. Although a variety of rituximab maintenance schedules exist, every 2 month dosing proposed by Ghielmini et al. reflects known rituximab pharmacokinetic data, where it has been observed that the consistent antibody concentrations in the blood correlate with patient response, and that continuous drug exposure may be more crucial than achieving maximal serum levels [17]. To date, maintenance therapy with the novel CD20 monoclonal antibody ofatumumab has not been explored, and little data is available regarding the outcomes of maintenance therapy in patients with high-risk follicular lymphoma.

1.5 FDG-PET Imaging

Preliminary studies with FDG-PET in follicular lymphoma indicate that FDG-PET detects disease in 95-98% of untreated and relapsed follicular lymphoma patients [20, 21], and that persistent PET positivity after chemotherapy correlates with progression-free survival [20, 22]. In a retrospective analysis of 31 patients with follicular grade 1-2 NHL, PET was both specific (88%) and sensitive (95%) [20]. Bishu et al. reported that in 2 of 16 patients who remained PET positive after completion of chemotherapy, PFS was 5.8 months, compared to 29.5 months for their PET negative counterparts [20]. Similarly, Zinzani et al. noted that 2-year PFS for previously untreated patients with follicular lymphoma receiving CHOP or a fludarabine-containing induction was 20% in 6 of 45 patients who were PET positive at the completion of therapy, compared to 90% in the PET negative group [22]. Therefore, as in diffuse large cell lymphoma and Hodgkin lymphoma, it appears that PET positivity at the completion of therapy does correlate with outcomes; however, these studies are currently small. We propose evaluating FDG-PET at baseline, after 2 cycles and at the end of induction chemotherapy (6-8 weeks after cycle 6 day 1) as part of this trial to determine prospectively in a large subset of uniformly treated patients with follicular lymphoma if PET positivity correlates with PFS.

1.6 Study Rationale

On the basis of the considerable success of rituximab-bendamustine in the front-line treatment of follicular NHL, the improvements in toxicity with bendamustine-containing therapy, the tolerability and efficacy of the vertical regimen in patients with untreated follicular lymphoma, and the potential improvement in efficacy with the novel monoclonal antibody ofatumumab, we propose a randomized phase II study of ofatumumab-bendamustine compared to ofatumumab-bortezomib-bendamustine in patients with untreated, high-risk follicular NHL. The primary endpoint is to determine the complete response rate with ofatumumab-bendamustine and ofatumumab, bortezomib, and bendamustine in patients with high-risk follicular lymphoma in order to generate prospective data of expected outcomes in this population with bulky disease or adverse FLIPI risk factors. Although it is known in the high-risk FLIPI patients that RCHOP leads to a median PFS of 30 months [3], it is unclear if similar outcomes will be observed in untreated follicular lymphoma patients with adverse risk factors receiving ofatumumab and

bendamustine front-line. In addition, with the preliminary efficacy of the vertical regimen in patients with relapsed follicular lymphoma [14], the addition of bortezomib to ofatumumab and bendamustine may further improve complete response rate, overall response rate and progression-free survival in high-risk, previously untreated patients.

We propose examining ofatumumab and bendamustine (ARM A) and ofatumumab, bortezomib, and bendamustine (ARM B) to determine the optimal front-line therapeutic approach in high-risk follicular lymphoma. We postulate that intensifying therapy with the addition of bortezomib to the ofatumumab-bendamustine regimen in patients with high-risk follicular lymphoma will improve complete response rates and ultimately progression-free survival. For ARM B, we have elected to follow the previously published rituximab, bortezomib, and bendamustine schedule in untreated indolent lymphoma as previously described in the vertical study [14], although only 1 dose of ofatumumab will be given during cycle 1 (as opposed to 4 doses of rituximab) in order to ensure that total doses of ofatumumab are similar between ARMS A and B. For ARMs A and B, we will use the previously published 1000 mg dose of ofatumumab in combination with bendamustine, that has been shown to be tolerable in CLL and follicular lymphoma and in combination with chemotherapy [11-13], and is associated with a higher CR-rate in patients with CLL [13]. In addition, with the proven efficacy of maintenance rituximab in prolonging progression-free survival in patients with untreated and relapsed follicular lymphoma [16-19], we will also explore the role of maintenance ofatumumab (ARM A) or maintenance ofatumumab and bortezomib (ARM B) in patients who respond to induction therapy.

1.7 Inclusion of Women and Minorities

It is the intent of CALGB/the Alliance to enroll patients regardless of gender or race. Both men and women of all races and ethnic groups are eligible for this study. In the development of this protocol, the possibility of inherent gender or racial/ethnic differences in treatment response has been considered.

Accrual Targets					
Ethnic Category	Sex/Gender				
	Females		Males		Total
Hispanic or Latino	2	+	2	=	4
Not Hispanic or Latino	59	+	67	=	126
Ethnic Category: Total of all subjects	61 (A1)	+	69 (B1)	=	130 (C1)
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	2	+	2	=	4
Black or African American	3	+	3	=	6
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	56	+	64	=	120
Racial Category: Total of all subjects	61 (A2)	+	68 (B2)	=	130 (C2)

(A1 = A2)

(B1 = B2)

(C1 = C2)

2.0 OBJECTIVES

2.1 Primary Objective

To determine the complete response (CR) rate in newly diagnosed untreated follicular lymphoma patients receiving 6 cycles of ofatumumab-bendamustine (ARM A) and 6 cycles of ofatumumab, bortezomib, and bendamustine (ARM B) using International Harmonization Project Response Criteria [23].

2.2 Secondary Objectives

- 2.2.1** To determine progression-free survival (PFS) in patients with untreated follicular lymphoma after 6 cycles of ofatumumab-bendamustine (ARM A) followed by maintenance ofatumumab and after 6 cycles of ofatumumab, bortezomib, and bendamustine followed by maintenance ofatumumab and bortezomib (ARM B)
- 2.2.2** To determine the toxicity profile of ofatumumab and bendamustine and ofatumumab, bortezomib, and bendamustine in patients with untreated high-risk follicular lymphoma
- 2.2.3** To determine if changes in both qualitative and semi-quantitative FDG-PET findings at baseline, after cycle 2 (day 32-35), and at end of therapy (6-8 weeks after the last cycle of induction chemotherapy but prior to maintenance therapy) with ofatumumab-bendamustine and ofatumumab, bortezomib, and bendamustine correlate with response and PFS in patients with high-risk follicular lymphoma
- 2.2.4** To assess if a combinatorial approach using both qualitative and semi-quantitative changes in FDG-PET and CT or MRI studies at baseline, after cycle 2 (day 32-35), and at end of therapy (6-8 weeks after the last cycle of induction chemotherapy prior to maintenance therapy) would result in a higher predictive value for response and PFS in patients with high-risk follicular lymphoma
- 2.2.5** To correlate all molecular parameters with FDG-PET parameters in determination of response and PFS
- 2.2.6** To correlate pre-treatment single nucleotide polymorphisms with response and PFS following ofatumumab-bendamustine and ofatumumab, bortezomib, and bendamustine therapy in patients with untreated high-risk follicular lymphoma
- 2.2.7** To correlate CD-68, bcl-2, Ki-67, FOXP3, activated cytotoxic T-cells, lymphoma associated macrophages (LAM), MUM1, CD10, nuclear p65 and cREL subunits of NFkB, and selected genetic translocations by FISH analysis (such as Bcl-2 and Bcl-6) with response and PFS in patients receiving initial therapy for high-risk follicular lymphoma
- 2.2.8** To determine whether immune gene signatures previously identified as prognostic factors in follicular lymphoma can be applied to paraffin embedded tissues in ofatumumab and bendamustine or ofatumumab, bendamustine, and bortezomib treated patients; evaluate microRNA signatures associated with these gene signatures and outcome

3.0 ON-STUDY GUIDELINES

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate. Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness that would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection, uncontrolled diabetes mellitus or cardiac disease, which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.

- Patients with a “currently active” second malignancy other than non-melanoma skin cancers. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are free of disease for ≥ 3 years.

4.0 ELIGIBILITY CRITERIA

All questions regarding eligibility criteria should be directed to the Study Chair. Please note that the Study Chair cannot grant waivers to eligibility requirements.

4.1 Documentation of Disease:

4.1.1 Histologic Documentation:

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.

4.1.2 Patients must have at least one of the following indicators of poor risk disease:

≥ 3 risk factors by the Follicular Lymphoma International Prognostic Index, or
 2 risk factors by the Follicular Lymphoma International Prognostic Index and at least one bulky mass or lymph node > 6 cm in size

Follicular Lymphoma International Prognostic Index (FLIPI score) [1, 23]:

1. Age > 60 years
2. Involvement of > 4 nodal sites
3. Stage III-IV disease
4. Hemoglobin < 12.0 g/dL
5. LDH $>$ Upper limit of normal (ULN)

0-1 of the above risk factors:	Low Risk
2 risk factors:	Intermediate Risk
≥ 3 risk factors:	Poor Risk

4.2 Prior Treatment

4.2.1 No prior cytotoxic chemotherapy, radiotherapy, immunotherapy, or radioimmunotherapy.

4.2.2 No corticosteroids are permitted, except for maintenance therapy for a non-malignant disease or to prevent treatment-related ofatumumab reactions. (Maintenance therapy dose must not exceed 20 mg/day prednisone or equivalent).

4.3 Measurable Disease

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)

4.4 CNS Involvement

Patients must have no known CNS involvement by lymphoma.

4.5 Age Requirement

Patients must be ≥ 18 years of age.

4.6 ECOG Performance Status

Patients must have ECOG performance status of 0-2.

4.7 Pregnancy and Nursing Status

Patients must be 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 within 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).

4.8 HIV Status

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 $> 400/\mu\text{l}$; 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 zidvudine or stavudine are allowed owing to overlapping toxicity with chemotherapy.

4.9 Hepatitis B or C

Patients must have 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 10.0](#)).

4.10 Required Initial Laboratory Values

Granulocytes	$\geq 1,000/\mu\text{l}$
Platelet count	$\geq 75,000/\mu\text{l}$
Creatinine	≤ 2.0 mg/dL
AST and ALT	≤ 2.5 x upper limits of normal (ULN)
Bilirubin	≤ 2 x ULN

5.0 REGISTRATION/RANDOMIZATION

5.1 Registration Requirements

Informed Consent: The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form is required.

Monthly Conference Call Participation: One representative from each institution with a patient enrolled in this protocol must participate in a monthly (once a month) conference call to discuss toxicity (see [Section 16.3](#) Adverse Event Monitoring). This will occur for the first 40 patients enrolled on the study (20 in ARM A and 20 in ARM B). Institutions with patients enrolled on this protocol that do not participate in the conference calls may be denied future registrations to this trial.

5.1.1 CTSU Registration Requirements

This study is supported by the NCI Cancer Trials Support Unit (CTSU). Study documents and forms can be accessed on the Alliance website: www.allianceforclinicaltrialsinoncology.org.

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed **Statement of Investigator Form** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed Supplemental Investigator Data Form (IDF)
- a completed **Financial Disclosure Form** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm. For questions, please contact the **CTEP Investigator Registration Help Desk** by email at pmbregpend@ctep.nci.nih.gov.

5.1.2 CTEP Associate Registration Procedures/CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the *CTEP Associate Registration Help Desk* by email at <ctepreghelp@ctep.nci.nih.gov>.

5.1.3 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at <https://www.ctsu.org>. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the CALGB 50904 protocol page located on the CTSU members' website. Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password

- Click on the Protocols tab in the upper left of your screen
- Under RSS Browser, select 'Regulatory and Roster Forms and Resources' to expand this menu, then select the 'Printable CTSU Forms' folder
- Download the required CTSU Site Registration forms

Requirements For CALGB 50904 Site Registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval and Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office

1818 Market Street, Suite 1100

Philadelphia, PA 19103

Phone: 1-866-651-2878

Fax: 215-569-0206

E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password

- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

5.1.4 Patient Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < <https://eapps-ctep.nci.nih.gov/iam/index.jsp> >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data *and upon enrollment, initializes the patient in the Rave database.* OPEN can be accessed at <https://open.ctsu.org> or from the OPEN tab on the CTSU members' side of the website at <https://www.ctsu.org>.

5.1.5 Additional Required Regulatory Documentation

The following documentation is required and should be submitted at the time of IRB approval. Participation and drug shipment (bendamustine, ofatumumab) are contingent upon the receipt of the following documentation by the Regulatory Support System (RSS):

- Documentation of IRB approval of the protocol and informed consent document
- Copy of IRB approved consent form
- Pharmacy license with the address for drug shipment
- CV of investigator(s)

5.1.6 Registration to Correlative Study

There is one correlative study within CALGB 50904 (CALGB 151005). This correlative science study must be offered to all patients enrolled on CALGB 50904, although patients may opt not to participate. The three components of this correlative study are:

- Single Nucleotide Polymorphism Analysis ([Section 12.1](#)).
- Immunohistochemical Markers ([Section 12.2](#)).
- Validation of Gene Signatures in Lymphoma ([Section 12.3](#)).
- If a patient answers “yes” to model consent questions #1 and/or #2, then the patient should be registered to CALGB 151005 at the same time that s/he is registered to the treatment trial (50904) with samples submitted per [Section 6.4](#).

6.0 DATA SUBMISSION, HISTOLOGY REVIEW, AND CORRELATIVE SCIENCE SPECIMEN SUBMISSION

6.1 Data Submission

Forms should be submitted to the Alliance Statistics and Data Center in compliance with the Data Submission schedule below. Forms that use the Teleform barcode and cornerstones should be submitted electronically using the “Submit to CALGB” button located at the bottom of the last page of each form. Original forms should **not** be submitted by fax or mail.

Amended forms and supporting documentation (e.g., reports or flow sheets) should be submitted by mail to:

Alliance Statistics and Data Center
Attn: Andy Johnson
RO FF-3-24-CC/NW Clinic
200 First Street SW
Rochester, MN 55905

For the most up-to-date forms for this study, please refer to the Alliance Web site at <https://www.allianceforclinicaltrialsinoncology.org/>.

Form*	Submission Schedule
<i>Baseline</i>	
C-2024 50904 On-Study Form	Submit within one month of registration.
C-2028 50904 Lymphoma Measurement Form	
C-2029 50904 FDG-PET Adjunctive Data Sheet	
Report Imaging and Pathology reports	
<i>Treatment</i>	
C-2025 50904 Treatment Summary Form	Submit at the completion of each cycle during Induction and Maintenance.
C-2027 50904 Adverse Event Form**	
C-2026 50904 Follow-up Form	Submit following cycle 2 (FDG-PET and CT/MRI), cycle 4 (CT/MRI only), and cycle 6 (FDG-PET and CT/MRI) during induction.
C-2028 50904 Lymphoma Measurement Form	
C-2029 50904 FDG-PET Adjunctive Data Sheet	
Report Imaging and Pathology reports	
C-2026 50904 Follow-up Form	Submit every 4 months during Maintenance.
C-2028 50904 Lymphoma Measurement Form	
Report Imaging and Pathology reports	
<i>Follow-up (Post-treatment)</i>	
C-2026 50904 Follow-up Form	Submit every 4 months for 2 years, then every 6 months until disease progression or for a maximum of 10 years from study entry.
C-2028 50904 Lymphoma Measurement Form	
Report Imaging and Pathology reports	
<i>Other</i>	
C-300 Off Treatment Form	Submit at end of all protocol treatment.
C-113 Notification of Death	Submit at time of death.
C-1001 New Malignancy Form	Submit at time of diagnosis of new malignancy.
C-1820 Adverse Events Addendum Form	Complete if additional space is needed to report other adverse events. See form for instructions.

- * Use CALGB Remarks Addenda (C-260) if additional comments are necessary or additional writing space is needed.
- † If patient never starts treatment and is not randomized, then the patient will be cancelled. No data submission is required. If the patient never starts treatment, but has been randomized, then submit all Baseline forms, Post-Treatment Follow-up forms, and other forms.
- ** Submit AE form until all protocol treatment related events have resolved or until non-protocol treatment begins. If patient death is reported via CTEP-AERS, report a Grade 5 event on the AE form even if the patient is off protocol treatment.

Common Terminology Criteria for Adverse Events (CTCAE): This study will utilize the Common Terminology Criteria for Adverse Events version 4.0 for toxicity and adverse event reporting.

6.2 Alliance Biospecimen Management System Instructions

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: <http://bioms.wustl.edu/bioms>, using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS. For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS.

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

6.3 Histologic Review

Submission of a tissue block is critical for confirmation of lymphoma diagnosis. High quality hematoxylin and eosin-stained sections and any required confirmatory studies (such as immunohistochemistry and in situ hybridization) may be done most efficiently from the tissue block in laboratories of the Alliance Biorepository at Ohio State University (OSU).

Within 60 days of registration, send a formalin-fixed, paraffin-embedded block of well-fixed lymphoma tissue containing adequate material for histologic confirmation of diagnosis. A block at least 1 cm x 1 cm x 2 mm is preferable, although smaller is acceptable if no other block is suitable. If only one block exists, and the tissue is sufficiently large, it is acceptable to split the block into two and submit one. Contact Dr. Eric Hsi (216-444-5230) with questions.

Samples should be logged and shipped via the Biospecimen Management System see [Section 6.2](#) for instructions. The requested tissue block should be labeled with the protocol number (50904), institutional surgical pathology number, study patient ID, institution, date of acquisition, and tissue source. A copy of the BioMS shipping manifest must be printed and placed in the shipment with the specimens. In addition to the pathology specimen and the shipping manifest, send a copy of the pathology report (include consultative pathology reports, if available) to OSU.

Failure to submit pathology materials **within 60 days** of patient registration will be considered a major protocol violation.

If a patient has consented to participate in the research studies proposed (model consent question #2), only one tissue block need be submitted to accommodate both histologic confirmation of diagnosis and correlative science studies (see [Section 6.4.2](#)).

The CALGB/Alliance has instituted special considerations for the small percentage of institutions whose policies prohibit release of any blocks. If, due to institutional policy, a block cannot be sent, please call 614-293-7073 to obtain a protocol for submission of representative tissue from your institution.

6.4 Specimen Submission for Correlative Studies

All participating institutions must ask patients for their consent to participate in the correlative substudy (CALGB 151005) planned for CALGB 50904, although patient participation is optional. Single nucleotide polymorphism analysis, immunohistochemical

staining, and validation of gene signatures will be performed. Rationale and methods for the scientific components of these studies are described in [Section 12.0](#). For patients who consent to participate, specimens will be collected at the following time points for these studies:

Sample Type	Time Points		Ship to:
	Prior to Treatment	Progression or Relapse	
Whole Blood (lavender top)	1 x 10 mL ¹		OSU
FFPE tissue	1 block ²	1 block ³	OSU

- 1 For patients who consent (Question #1) to companion study 151005, described in [Section 12.1](#).
- 2 Diagnostic tissue block is required for all patients registered to CALGB 50904. For patients who consent (Question #2) to companion study 151005, only one tissue block need be submitted to accommodate both histologic confirmations of diagnosis and correlative science studies as described in [Sections 12.2](#) and [12.3](#).
- 3 If biopsy has been performed, for patients who consent (Question #3 and/or #4).

6.4.1 Whole Blood Submission

For patients who consent to participate (model consent question #1), whole blood will be used for the single nucleotide polymorphism analysis described in [Section 12.1](#).

Whole blood will be collected prior to initiation of therapy only. Collect 10 mL of whole blood in lavender top tube. The tube should be inverted 8-10 times to mix the tube additive, and then refrigerated until shipped. Samples should be packaged to prevent breakage and shipped on a cold pack for processing and cell cryopreservation for later DNA extraction.

Specimens should be logged and shipped via the Biospecimen Management System (BioMS), see [Section 6.2](#) for instructions. A copy of the shipping manifest produced by BioMS must be printed and placed in the shipment with the specimens. All submitted specimens must be labeled with the protocol number (50904), study patient ID, patient's initials, date and time of specimen collection and type of specimen collected (e.g., whole blood).

Ship samples by overnight courier the same day they are collected. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery." Do not ship specimens on Saturdays. Ship specimens to the OSU:

Alliance Biorepository at Ohio State University
 Innovation Center
 2001 Polaris Parkway
 Columbus, OH 43240
 Tel: 614-293-7073
 Fax: 614-293-7967
 path.calgb@osumc.edu

6.4.2 Paraffin-Embedded Tissue Block Submission

Paraffin embedded tissue will be used for immunohistochemical evaluation of markers of angiogenesis, cell of origin, lymphoma associated macrophages, and tumor infiltrating T-cells (Tregs), and validation of gene signatures in lymphoma.

Furthermore, the CALGB/Alliance Lymphoma Committee is committed to conducting correlative science studies utilizing tissue from consenting patients enrolled on treatment trials, and has chosen tissue microarrays (TMAs) as the method of archiving tissue. TMAs are constructed by removing two 1 mm diameter tissue cores from the lymphoma tissue block using a specially designed instrument (Beecher Instruments, Sun Prairie, WI). The resulting tissue array can contain 100 cases in a single tissue block, and allows rapid, high throughput analysis of markers by immunohistochemistry or in situ hybridization. The original tissue block remains intact with only a small amount of tissue removed with no significant distortion. The original block may then be returned to the submitting institution.

Samples should be logged and shipped via the Biospecimen Management System (BioMS), see [Section 6.2](#) for instructions. A copy of the shipping manifest produced by BioMS must be printed and placed in the shipment with the specimens. All submitted specimens must be labeled with the protocol number (50904), study patient ID, patient's initials, date and time of specimen collection and type of specimen collected (e.g., FFPE block).

Please be sure to use a method of shipping that is secure and traceable. Ship specimens Monday through Thursday by overnight service to assure receipt. Do not ship specimens on Fridays or Saturdays.

For patients who consent to participate (model consent question #2), send a formalin-fixed, paraffin-embedded block of well-fixed lymphoma tissue to OSU:

Alliance Biorepository at Ohio State University
 Innovation Center
 2001 Polaris Parkway
 Columbus, OH 43240
 Tel: 614-293-7073
 Fax: 614-293-7967
 path.calgb@osumc.edu

If a patient has consented to participate (model consent question #2), only one tissue block need be submitted to accommodate both histologic confirmation of diagnosis and correlative science studies (see [Section 6.4](#)).

6.4.3 Progression or Relapse Specimen Submission

Samples should be logged and shipped via the Biospecimen Management System (BioMS), see [Section 6.2](#) for instructions. A copy of the shipping manifest produced by BioMS must be printed and placed in the shipment with the specimens. All submitted specimens must be labeled with the protocol number (50904), study patient ID, patient's initials, date and time of specimen collection and type of specimen collected (e.g., FFPE).

Please be sure to use a method of shipping that is secure and traceable. Ship specimens Monday through Thursday by overnight service to assure receipt. Do not ship specimens on Fridays or Saturdays.

At the time of progression or relapse, if a patient has consented to allow tissue to be kept for future research (model consent question # 3 and/or 4), and if a biopsy has been performed, please submit a formalin-fixed, paraffin-embedded block of well-fixed lymphoma tissue for pathology review and future correlative science to OSU:

CALGB 50904

Alliance Biorepository at Ohio State University
Innovation Center
2001 Polaris Parkway
Columbus, OH 43240
Tel: 614-293-7073
Fax: 614-293-7967
path.calgb@osumc.edu

7.0 REQUIRED DATA

Guidelines for Pre-Study Testing

To be completed within 16 DAYS before registration:

- All blood work***
- History and physical

To be completed within 28 DAYS before registration:

- Any radiologic exam, scan of any type (e.g., PET, CT or MRI) or ultrasound, which is utilized for tumor measurement

To be completed within 42 DAYS before registration:

- Any baseline exams used for screening,
- Any radiologic exam, scan of any type or ultrasound of uninvolved organs that is not utilized for tumor measurement
- Bone marrow aspirate & biopsy (bilateral preferred)

Tests & Observations	Prior to Registration	Day 1 of each induction cycle	Day 1 of each maintenance cycle	Time of Restaging*	Post Treatment Follow up**
History and Progress notes	X	X	X		X
Physical Examination (physician visit)	X	X	X		X
Pulse, Blood Pressure	X	X	X		
Height	X				
Weight/Body Surface Area†	X	X†	X†		
Performance Status	X	X	X		X
Tumor Measurements	X	A	A	A	A
Drug Toxicity Assessment		X	X		X
Laboratory Studies					
CBC, Differential, Platelets	X	B	B		X
Serum Creatinine, BUN	X	X	X		X
Serum Electrolytes, Ca ⁺⁺		X	X		X
AST, ALT, ALK Phos, Bilirubin	X	X	X		X
Uric Acid, LDH	X	H	H		H
β2 microglobulin	X				
Serum or urine βHCG	X***				
HBsAg, HBsAB, HB core antibody	C				
HBV DNA testing	D	D	D		D
HCV testing	X				
HIV (if required, see Section 4.9)	X				
Staging					
CT scan/MRI (chest/abd/pelvis)	X			X††	X
CT scan/MRI neck	E			E	E
FDG-PET/CT scan	F ¹			F ²	
Bone Marrow Asp & Bx (bilateral preferred)	X			G	G
Histologic Review	X				

* Restage after cycles 2, 4, and 6 during induction and then every 4 months during maintenance therapy.

** At least every 4 months for 2 years, then every 6 months until disease progression or for a maximum of 10 years from study entry.

- *** Within 14 days prior to registration for females of childbearing potential.
- † Although doses are recalculated prior to each treatment, the actual dose given need not be changed unless the difference is $\geq 10\%$.
- †† Repeat CT of the chest/abdomen/pelvis or MRI scan after cycle 2, cycle 4, cycle 6 and every 4 months during maintenance therapy.
- A As indicated to follow measurable disease.
- B Obtain on day 1 of each cycle for patients in ARM A; Obtain on days 1 and 15 of each cycle for patients in ARM B.
- C All patients must be screened for hepatitis B before starting treatment. Carriers of hepatitis B should be carefully monitored, including HBV DNA testing, for evidence of active HBV infection every 2 months for at least 6 months after ofatumumab treatment ends. For patients with evidence of prior HBV infection, i.e. HBsAg positive, lamuvidine or other HBV suppressive therapy is required (see [Section 10.0](#)).
- D HBV DNA testing should be performed at baseline, at the start of each induction and maintenance cycle, and then every 2 months for up to 6 months from the last ofatumumab dose for patients who are carriers of hepatitis B or who have had prior HBV infection.
- E Perform if nodes are palpable prior to treatment.
- F¹ Perform PET/CT at baseline, within 4 weeks of treatment initiation (see [Section 11.0](#)).
- F² Restage with PET/CT after cycle 2 (perform between days 32-35) and cycle 6 (perform 6-8 weeks after the start of cycle 6). PET/CT is not required during maintenance therapy or post-treatment follow-up (see [Section 11.0](#)).
- G If initially positive, repeat only in patients who are demonstrated to be in CR by all other criteria.
- H LDH only. Uric acid is only required at baseline (prior to registration).

8.0 TREATMENT PLAN

Protocol treatment is to begin within 7 days of registration (unless otherwise specified by Study Chair). Questions regarding treatment should be directed to the Study Chair.

All dosing is to be determined by actual weight. Please see [Section 9.0](#) for dose modifications, [Section 10.0](#) for ancillary therapy, and [Section 13.0](#) for drug formulation, availability and preparation.

8.1 Induction

Eligible patients will be randomized to receive either 6 cycles of ofatumumab with bendamustine (ARM A) or 6 cycles of ofatumumab, bendamustine, and bortezomib (ARM B). Response will be assessed by CT or MRI and/or FDG-PET/CT scan according to International Harmonization Criteria [23] after 2 (CT/MRI and FDG-PET/CT), 4 (CT/MRI only) and 6 (CT/MRI and FDG-PET/CT) cycles of ofatumumab-bendamustine (ARM A) or ofatumumab, bortezomib, and bendamustine (ARM B). Patients without evidence of disease progression by CT scan after 2 and 4 cycles will continue for a maximum of 6 cycles.

8.1.1 ARM A: Ofatumumab and Bendamustine Induction

Premedication: Acetaminophen (or equivalent) 650 mg orally and diphenhydramine (or equivalent) 50-100 mg orally or by IV 30-60 minutes prior to each ofatumumab infusion. On day 1 of cycle 1 only, administer 20 mg IV dexamethasone (or acceptable equivalent steroid). Additional acetaminophen, diphenhydramine, and glucocorticoids may be provided at the treating physician's discretion for the management of ofatumumab-related infusion reactions.

Ofatumumab 300 mg IV on day 1 of cycle 1, and then 1000 mg IV on day 1 of cycles 2-6 (immediately prior to bendamustine).

The initial rate during the first cycle should be 25 mL/hr during the first hour. The rate may be increased, if tolerated, by 50 mL/hr increments every 30 minutes to a maximum of 400 mL/hr. If administration is well-tolerated during the first cycle, the initial rate during subsequent cycles of therapy may be increased to 50 mL/hr for the first hour. If tolerated, the rate may be increased by 100 mL/hr increments every 30 minutes to a maximum rate of 400 mL/hr.

Note: The plan for rate escalation is based on mL/hr and not mg/hr.

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 a total of 6 cycles. To begin a cycle the ANC > 1000/μL and platelets > 75,000/μL. Remove the patient from the protocol for treatment delays exceeding 3 weeks.

See [Section 9.0](#) for dose modifications and management of toxicity. See [Section 10.0](#) for ancillary therapy.

8.1.2 ARM B: Ofatumumab, Bortezomib, and Bendamustine Induction

Premedication: Acetaminophen (or equivalent) 650 mg orally and diphenhydramine (or equivalent) 50-100 mg orally or by IV 30-60 minutes prior to each ofatumumab infusion. On day 1 of cycle 1 only, administer 20 mg IV dexamethasone (or acceptable equivalent steroid). Additional acetaminophen, diphenhydramine, and glucocorticoids may be provided at the treating physician's discretion for the management of ofatumumab-related infusion reactions.

Ofatumumab 300 mg IV on day 1 of cycle 1, and 1000 mg IV on day 1 of cycles 2-6 (immediately prior to bortezomib and bendamustine).

The initial rate during the first cycle should be 25 mL/hr during the first hour. The rate may be increased, if tolerated, by 50 mL/hr increments every 30 minutes to a maximum of 400 mL/hr. If administration is well-tolerated during the first cycle, the initial rate during subsequent cycles of therapy may be increased to 50 mL/hr for the first hour. If tolerated, the rate may be increased by 100 mL/hr increments every 30 minutes to a maximum rate of 400 mL/hr.

Note: The plan for rate escalation is based on mL/hr and not mg/hr.

Bendamustine 90 mg/m² IV over 30-60 minutes on days 1 and 2 of each cycle.

Bortezomib 1.6 mg/m² by IV over 3-5 seconds or by subcutaneous injection on days 1, 8, 15, and 22 of each cycle.

Cycles will be repeated every 35 days for a total of 6 cycles. To begin a cycle the ANC \geq 1000/ μ L and platelets \geq 75,000/ μ L. Remove the patient from the protocol for treatment delays exceeding 3 weeks.

See [Section 9.0](#) for dose modifications and management of toxicity. See [Section 10.0](#) for ancillary therapy.

8.2 Maintenance therapy

Patients without evidence of disease progression after 6 cycles of ofatumumab with bendamustine (ARM A) or 6 cycles of ofatumumab, bendamustine, and bortezomib (ARM B) may continue to receive either ofatumumab alone (ARM A) or ofatumumab and bortezomib maintenance therapy (ARM B). Maintenance therapy will start 2 months (8 weeks) after cycle 6 day 1 of induction therapy. Maintenance therapy will be administered every 2 months for a total of 4 cycles. Response will be assessed by CT or MRI scans according to International Harmonization Criteria[23] every 4 months during maintenance therapy. Patients without evidence of disease progression will continue for a maximum of 4 cycles (8 months) of maintenance therapy.

8.2.1 ARM A: Ofatumumab Maintenance

Premedication: Acetaminophen (or equivalent) 650 mg orally and diphenhydramine (or equivalent) 50-100 mg orally or by IV 30-60 minutes prior to each ofatumumab infusion. Additional acetaminophen, diphenhydramine, and glucocorticoids may be provided at the treating physician's discretion for the management of ofatumumab-related infusion reactions.

Ofatumumab 1000 mg IV on day 1 of each cycle.

The infusion rate can start at 50 mL/hr. If tolerated, the rate may be increased by 100 mL/hr increments every 30 minutes to a maximum rate of 400 mL/hr.

Note: The plan for rate escalation is based on mL/hr and not mg/hr. The administration schedule and rates of infusion in this study are different from those described in the package literature.

Cycles will be repeated every 56 days (2 months) for a total of 4 cycles. To begin a cycle the ANC must be \geq 1000/ μ L and platelets must be \geq 75,000/ μ L. Remove the patient from the protocol for treatment delays exceeding 3 weeks.

See [Section 9.0](#) for dose modifications and management of toxicity. See [Section 10.0](#) for ancillary therapy.

8.2.2 ARM B: Ofatumumab and Bortezomib Maintenance

Premedication: Acetaminophen (or equivalent) 650 mg orally and diphenhydramine (or equivalent) 50-100 mg orally or by IV 30-60 minutes prior to each ofatumumab infusion. Additional acetaminophen, diphenhydramine, and glucocorticoids may be provided at the treating physician's discretion for the management of ofatumumab related infusion reactions.

Ofatumumab 1000 mg IV on day 1 of each cycle (immediately prior to bortezomib). The infusion rate can start at 50 mL/hr. If tolerated, the rate may be increased by 100 mL/hr increments every 30 minutes to a maximum rate of 400 mL/hr.

Note: The plan for rate escalation is based on mL/hr and not mg/hr. The administration schedule and rates of infusion in this study are different from those described in the package literature.

Bortezomib 1.6 mg/m² by IV over 3-5 seconds or by subcutaneous injection on days 1, 8, 15, and 22 of each cycle.

Cycles will be repeated every 56 days (2 months) for a total of 4 cycles. To begin a cycle the ANC must be $\geq 1000/\mu\text{L}$ and platelets must be $\geq 75,000/\mu\text{L}$. Remove the patient from the protocol for treatment delays exceeding 3 weeks.

See [Section 9.0](#) for dose modifications and management of toxicity. See [Section 10.0](#) for ancillary therapy.

9.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

Dose Levels			
	Starting Dose	Dose Level -1	Dose Level -2
Ofatumumab (Arms A and B)	1000 mg	1000 mg	1000 mg
Bendamustine (Arms A and B)	90 mg/m ²	60 mg/m ²	45 mg/m ²
Bortezomib (Arm B only)	1.6 mg/m ²	1.3 mg/m ²	1 mg/m ²

9.1 Dose Modification for Hematologic Toxicity

Patients with treatment delays greater than 3 weeks should be removed from protocol therapy.

The following dose modifications should be made for febrile neutropenia and blood counts obtained within 2 days prior to each cycle. If more than one of these applies, use the most stringent (i.e., the greatest dose reduction.)

9.1.1 Neutropenia

For ANC < 1000 on Day 1 (or within 48 hours of day 1) of **induction** therapy, delay treatment until ANC ≥ 1000 .

If **induction** treatment is delayed for ANC < 1000 on day 1, administer filgrastim or pegfilgrastim beginning on day 3 (Arm A) or day 23 (Arm B) of all subsequent **induction** cycles.

For recurrent ANC < 1000 during **induction** therapy, despite a colony stimulating factor, decrease dose of bendamustine (Arms A and B) by one dose level for all subsequent **induction** cycles, and decrease the dose of bortezomib (Arm B) by one dose level for all subsequent **induction** cycles.

For ANC < 1000 on Day 1 (or within 48 hours of day 1) of **maintenance** therapy, delay treatment until ANC ≥ 1000 .

If **maintenance** treatment is delayed for ANC < 1000 on day 1, decrease the dose of bortezomib (Arm B) by one dose level for all subsequent **maintenance** cycles.

Use of pegfilgrastim or filgrastim is not permitted during **maintenance**, except in the event of serious infection per ASCO guidelines.

During **induction or maintenance**, there are no dose reductions below dose level -2 if dose reduction below dose level -2 is required for neutropenia, discontinue all protocol therapy.

During induction or maintenance, remove the patient from the protocol for delays exceeding 3 weeks.

9.1.2 Thrombocytopenia

For platelets < 75,000 on Day 1 of **induction or maintenance** therapy, delay treatment until platelets \geq 75,000.

Resume treatment when thrombocytopenia improves to \geq 75,000 with one dose level reduction of bendamustine (Arm A and B, **induction only**) and one dose level reduction of bortezomib (Arm B, **induction and maintenance**) for all subsequent cycles.

During **induction or maintenance**, there are no dose reductions below dose level -2. If dose reduction below dose level -2 is required for thrombocytopenia, discontinue all protocol therapy.

During induction or maintenance, remove the patient from the protocol for delays exceeding 3 weeks.

9.1.3 Febrile Neutropenia

For febrile neutropenia (defined as temperature \geq 38.5° C [101° F] sustained for more than one hour concomitant with an ANC < 500/ μ L) during **induction**, hold therapy until resolution.

Administer filgrastim or pegfilgrastim starting on day 3 (Arm A) or day 23 (Arm B) of all subsequent **induction** cycles.

For recurrent febrile neutropenia despite filgrastim or pegfilgrastim support during **induction**, reduce the dose of bendamustine (Arms A and B) by one dose level for all subsequent induction cycles, and decrease the dose of bortezomib (Arm B) by one dose level for all subsequent induction cycles.

For febrile neutropenia (defined as temperature \geq 38.5° C [101° F] sustained for more than one hour concomitant with an ANC < 500/ μ L) during **maintenance**, hold therapy until resolution.

After resolution of the febrile neutropenia, reduce the dose of bortezomib (Arm B) by one dose level for all subsequent **maintenance** cycles.

Use of pegfilgrastim or filgrastim is not permitted during **maintenance**, except in the event of serious infection per ASCO guidelines.

During **induction or maintenance**, there are no dose reductions below dose level -2. If dose reductions below dose level -2 are required, discontinue all protocol therapy.

During induction or maintenance, remove the patient from the protocol for delays exceeding 3 weeks.

9.2 Grade 2-4 Peripheral Neuropathy

For grade 2 peripheral neuropathy during **induction or maintenance**, decrease bortezomib by one dose level for all subsequent cycles.

For grade 3 peripheral neuropathy during **induction or maintenance**, hold protocol therapy until the toxicity resolves to grade 1 or less. Delay cycle up to 2 weeks for resolution of the adverse event. Contact the study chair for delays exceeding 2 weeks. When toxicity resolves to grade 1 or less, resume protocol therapy and reduce the bortezomib (Arm B) by one dose level for all subsequent cycles. Remove the patient from protocol for treatment delays exceeding 3 weeks.

For grade 4 peripheral neuropathy during **induction or maintenance**, discontinue bortezomib. Therapy with ofatumumab and bendamustine may continue.

During **induction or maintenance**, there are no dose reductions below dose level -2. If dose reduction below dose level -2 is required for neurotoxicity, discontinue bortezomib.

9.3 Ofatumumab Infusion and Hypersensitivity Reactions

Ofatumumab infusions must be interrupted if any infusion reactions (fever, chills, dyspnea, rash, etc.) \geq grade 1 occur. Appropriate supportive care including acetaminophen, diphenhydramine, albuterol, and glucocorticoids may be administered according to institutional infusion reaction protocols. When the symptoms have resolved completely, the infusion may be restarted at half the previous rate. If tolerated, ofatumumab may be gradually re-escalated to the initial infusion rate. If the patient experiences a second infusion reaction, the ofatumumab infusion should be stopped. At the investigator's discretion, patients unable to complete the full dose of ofatumumab may resume the incomplete treatment on the same or following day after dexamethasone 20 mg orally or IV (or equivalent) is given 30-60 minutes prior to re-treatment.

9.4 Dermatologic Toxicity or Hepatitis B Reactivation

In the instance of \geq grade 3 erythema multiforme or hepatitis B re-activation (i.e., detectable HBV DNA), remove the patient from all protocol therapy.

9.5 Other Grade 3-4 Non-Hematologic Toxicity

For other grade 3-4 non-hematologic toxicity that occurs during **induction or maintenance** considered at least possibly related to bendamustine or bortezomib, hold bortezomib (Arm B) and bendamustine (Arm A and B) until toxicity improves to grade 1 or less. Delay cycle up to 2 weeks for resolution of the adverse event. Contact the study chair for delays exceeding 2 weeks.

Once the toxicity has resolved to grade 1 or less, resume treatment with one dose level reduction for bendamustine (Arms A and B), and one dose level reduction for bortezomib for all subsequent **induction and maintenance** cycles.

During **induction or maintenance**, there are no dose levels below dose level -2. If dose reduction below dose level -2 is required for other grade 3 or 4 toxicity, discontinue all protocol therapy.

During induction or maintenance, remove the patient from the protocol for delays exceeding 3 weeks.

9.6 Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification. This will eliminate the risk of calculation

error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation

9.7 HBV Reactivation

Discontinue ofatumumab in patients with prior HBV infection if HBV DNA testing reveals evidence of reactivation.

10.0 ANCILLARY THERAPY

Patients should receive full supportive care, including transfusions of blood and blood products, erythropoietin, antibiotics, antiemetics (non-steroidal), etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on CALGB Remarks Addenda (form C-260).

Treatment with hormones or other chemotherapeutic agents may not be administered.

Prophylaxis against herpes zoster reactivation according to institutional guidelines is recommended for patients in arm A. Due to high risk of herpes zoster with bortezomib use, prophylaxis against herpes zoster reactivation utilizing valacyclovir, acyclovir, or famciclovir is required for patients in Arm B for up to 6 months after final bortezomib dose.

Hepatitis B surface antigen positive patients will receive lamivudine 100 mg/day orally (or acceptable alternative) until 6 months after the last ofatumumab dose. HBV DNA testing will occur at the start of each induction and maintenance cycle and then will continue every 2 months until 6 months after the last ofatumumab dose.

Anti-emetic prophylaxis (non-steroidal) may be provided prior to bortezomib and bendamustine infusions. Supportive care with anti-emetics, anti-diarrheals, and stool softeners is permitted for the treatment of gastrointestinal adverse events.

10.1 CALGB Policy Concerning the Use of Growth Factors

The use of an erythropoiesis-stimulating agent (ESA) is allowed. If an ESA is used, it should be within the context of the most current guidelines.

The use of filgrastim or pegfilgrastim in CALGB 50904 is described in [Sections 9.1.1](#) and [9.1.3](#).

11.0 FDG-PET IMAGING, INTERPRETATION, QUALITATIVE AND SEMI-QUANTITATIVE ANALYSES

11.1 Institution Credentialing Procedures for FDG-PET/CT Imaging

Prior to enrollment of patients, institutions must be credentialed to participate in the trial by the Alliance Imaging Core Laboratory (ICL) at the Ohio State University Medical Center if they have not previously been credentialed for any other CALGB trials. The Imaging Core Lab will provide a site manual that outlines all of the details as they relate to the image acquisition and reconstruction.

11.1.1 FDG-PET/CT Requirements for Participation

- 1) The participating center must have, or have access to, a facility with an integrated positron-emission tomography and computed tomography (PET/CT) scanner.
- 2) The participating center must have the ability to submit PET and CT studies electronically to the ICL in digital DICOM format (other formats: BITMAP, JPG). Hardcopy or scanned files are not acceptable.

- 3) Participating sites must be credentialed by the ICL so that the performance characteristics and infrastructure requirements are met:

If a site has been credentialed by either the ICL, or ACRIN, or ACR CQIE, only a protocol refresher will be needed for participating in CALGB 50904.

If a site has never been credentialed by any of the above institutions, however they either participated in other CALGB PET/CT trials or successfully completed certain protocol refresher processes (i.e., CALGB 50604, CALGB 50801) by the ICL, a protocol refresher (and/or WebEx Site Visit, if necessary) is required for 50904 participation.

If an institution has never been credentialed by the ICL or any of the above institutions, and has not participated in a CALGB trial with a PET/CT component, the ICL will adhere to the ACRIN criteria for PET imaging approval procedures. In order for an institution to be approved to participate in this study, they are required to submit the following for technical and quality review by the ICL:

- i) Two test patient studies (for all PET/CT instruments utilized)

Images of two unidentified patients shall consist of three volume or multislice files as follows: a) Whole body CT from PET/CT scanner; b) Whole body (torso) emission with attenuation correction (A/C); and c) Whole body (torso) emission without A/C.

- ii) Uniform phantom data with the SUV measurement of the phantom (for all PET/CT instruments utilized):

Water-fillable uniform phantom: The phantom must be filled with water, and a known amount of F-18 (either as fluoride or as FDG) should be injected into the phantom. The activity injected should be determined by measurement of the syringe before and after the injection in a properly calibrated dose calibrator. The injected activity should be chosen to result in an activity concentration similar to that encountered in clinical FDG imaging (i.e., 1-1.5 mCi of F-18 should be added to the 6,283 mL phantom: 2 mCi for the 9.293 mL phantom). After thoroughly mixing the phantom, the phantom must be scanned with the same protocol used for the patient imaging. The images also must be reconstructed with the same algorithm and filters used for patient imaging. A circular or elliptical region of interest (ROI) covering most of the interior of the phantom must be drawn over all slices, and the average SUV and standard deviation must be measured and reported in the PET/CT Instrument Technical Specifications Form (Appendix II). The expected SUV for the uniform phantom is 1.0 and the acceptable range is 0.9 to 1.1.

(Alternatively) Ge-68/Ga-68 calibration phantom: This phantom can readily be scanned with the same protocol used for patient imaging. The assay date and activity from the calibration certificate of this phantom must be reported on the PET/CT Instrument Technical Specifications Form (Appendix II). The images must be reconstructed with the same algorithm and filters used for patient imaging. A circular or elliptical ROI covering most of the interior of the phantom must be drawn over all slices, and the average SUV and standard deviation must be measured and reported in the PET Instrument Technical Specification form. The expected SUV for the uniform phantom is 1.0 and the acceptable range is 0.9 to 1.1.

- iii) Appendix II: PET/CT Instrument Technical Specifications Form (for all PET/CT instruments utilized)

iv) Appendix III: Imaging Site Personnel Form

11.2 FDG-PET/CT Imaging

A PET/CT scan will be obtained pre-treatment (baseline), after cycle 2 (day 32-35), and at the end of therapy (6-8 weeks after cycle 6, day 1 after the last cycle of induction chemotherapy).

As several series do support the utility of FDG-PET in assessing residual disease and predicting PFS in follicular NHL [20, 22], these 3 PET scans will be considered standard of care.

Semi-quantitative and qualitative PET analysis will be performed by the Alliance Imaging Committee using absolute values of and changes in SUVs, as well as various reading schemes using various references such as mediastinal blood pool and the liver. PET/CT results at the completion of induction therapy will be correlated with response and PFS with maintenance therapy. PET results will also be evaluated in combination with changes seen on dedicated CT or MRI studies between baseline and after 2 cycles, 6 cycles, and end of therapy to assess if a combinatorial approach using both metabolic and morphologic changes would result in a higher predictive value for response and PFS.

All PET scans should be obtained on integrated PET/CT machines.

The following PET/CT images will be collected digitally for archival use:

- Baseline (within 4 weeks of treatment initiation)
- After cycle 2 (day 32-35)
- End of treatment (6-8 weeks after cycle 6, day 1)

11.2.1 FDG-PET/CT Imaging Procedures**11.2.1.1 Patient Preparation**

Patients must fast for at least four hours before the PET/CT scan. Oral hydration is strongly encouraged prior to and during injection of ^{18}F -FDG (250-500 mL water can be given PO during the uptake period) and during the uptake period after administration of ^{18}F -FDG. IV furosemide (10 mg) may be administered (but is not mandatory) to increase urinary elimination of the tracer and minimize image artifacts caused by urinary stasis in the abdomen and pelvis. Intravenous fluids containing dextrose or parenteral feeding should be withheld for at least 6 hours prior to the injection of ^{18}F -FDG. **No steroid administration is allowed for at least 7 days prior to FDG-PET imaging.** Active exercise should be discouraged for at least 24 hours prior to the study. Muscle stress, tension, chewing, and movement during the uptake period should be minimized to decrease muscle uptake. Patients should not speak during the injection and uptake period. Interviews with the patient should be withheld until after completion of the imaging study.

The blood glucose level should be checked before ^{18}F -FDG injection. Blood sugar (measured by glucometer) must be less than 200 mg/dL at the time of the FDG-PET/CT study. If the blood glucose level is greater than 200 mg/dL, the FDG-PET/CT imaging should be rescheduled. If the blood glucose level still exceeds 200 mg/dL on the following scheduled day for PET scanning, the patient will not be included in the trial. Insulin administration immediately before the PET/CT study to reduce the glucose levels is not allowed. Patients with diabetes should continue to adhere to their oral agents or insulin routines. These medications should

not be administered near the ^{18}F -FDG injection time. In insulin-dependent patients, insulin should be administered at least 5 hours prior to the ^{18}F -FDG injection. Patients with diabetes who are on diabetic medication should take their medication 4-5 hours prior to the test. If blood sugar exceeds 150 mg/dL (but less than 200 mg/dL), a note should be made in on the case report form.

Metallic objects should be removed from the patients whenever possible. Patients should be kept in a warm waiting room prior to ^{18}F -FDG injection to avoid brown adipose tissue uptake. In anxious and claustrophobic patients, administration of oral diazepam (0.06-0.10 mg/kg) is recommended 30-40 minutes prior to the initiation of the imaging study.

Weight (kg), height (cm), blood glucose (mg/dL), and the date and time of chemotherapy and colony stimulating administration (e.g., GCSF, GMCSF) will be recorded prior to the injection of ^{18}F -FDG.

10-20 mCi of ^{18}F -FDG will be administered IV, depending on the manufacturer's recommendation. A 10-20 mL saline flush is recommended in reducing the venous retention of ^{18}F -FDG. The patient must wait for at least 60 minutes prior to the initiation of the PET/CT acquisition for all PET/CT scans (both pre-and post-therapy scans). The wait period should be kept with a minimal variation of **10 minutes** among patients. The wait period must not exceed 75 minutes at baseline. **It is NOT acceptable to start imaging with wait periods of less than 60 minutes and longer than 75 minutes.** The time difference between baseline and other PET studies (after cycles 2 and 6) should **not** be > 10 minutes. A time difference of > 15 minutes between PET/CT studies is **NOT** acceptable.

The imaging will start after voiding the bladder. 150-200 mL of water must be given to the patient immediately prior to the study acquisition before they are positioned on the table to distend stomach and avoid physiologic stomach uptake.

11.2.1.2 FDG Dosing and Administration

The administered activity of FDG should be based on the PET/CT scanner manufacturer's recommendation. The recommended FDG dose is 0.14-0.21 mCi/kg. The actual FDG dose should be a bolus of 10-20 mCi, followed by a saline flush (per institutional procedure). A dose at the higher end of the range is recommended, if feasible, with appropriate reduction in the per kilogram dose for heavier patients (in accordance with the manufacturer's recommendation). The effective FDG dose injected and time of injection should be documented on CALGB form C-2029 (50904 FDG-PET Adjunctive Data Sheet).

11.2.2 FDG-PET/CT Image Acquisition

Patients will be positioned on the table in a headfirst, supine position with arms elevated above the abdomen to reduce beam-hardening artifacts at the level of the liver. A separate head and neck imaging will be pursued for those whose primary disease site is in the neck with the arms positioned along the side. The use of IV and oral contrast is at the discretion of each facility. However, IV-contrast CT acquisition should follow PET imaging acquired with non-contrast CT to avoid variations in FDG uptake in the blood pool and the tumor that is caused by the

contrast agent. If IV contrast is not used, CT should be acquired using a current of not less than 120 mA/second to allow for sufficient resolution for definition of anatomic structures. Immediately after CT scanning, a PET emission scan will be obtained.

Six to seven contiguous volumes will be chosen, depending on the patient's height, to ensure data acquisition of the entire region of interest (ROI), the level of the skull base to the 1/3 proximal femurs. The time/bed position should be in accordance with the manufacturer's recommendations for optimal imaging. Adjacent fields of view should share overlapping slices.

It is critical that follow-up emission scans be performed in an identical way to the baseline scan, with the same scanner, same scan direction (skull to thighs or thighs to skull), and consistent arm positioning (arms up or arms down).

It is NOT acceptable to start imaging with wait periods of less than 60 minutes and longer than 75 minutes. The time difference between baseline and other PET studies (after cycles 2 and 6) should **not** be > 10 minutes. A time difference of > 15 minutes between PET/CT studies is **NOT** acceptable.

11.2.3 Qualitative PET Analysis

Semi-quantitative and qualitative PET analysis will be performed by the Alliance Imaging Committee.

Tumor selection: Up to 6 lesions (target lesions) demonstrating highest (or relatively higher compared to other lesions) FDG uptake will be selected for analyses at baseline. Their locations and size (length and width) will be defined. Tumor #1 will be the tumor site with highest FDG uptake; the others will be selected in descending order of uptake. On the integrated PET/CT scan, the location and dimensions of the index tumors will be determined at the baseline scan and at all subsequent studies. For all reading scales, the interpreter's degree of suspicion for an abnormality will be recorded with the use of a 5-point ordinal categoric scale.

The evaluation will be performed using the three different sets of criteria as follows:

- using mediastinum blood pool (MBP) as the reference organ [24].
- using liver as the reference organ [25].
- measurements of SUVmax normalized to body weight

Mediastinum blood pool (MBP) is evaluated at the aortic arch level. Negative post-therapy PET scan (metabolic responders): Upon qualitative evaluation, tumor FDG uptake that is less than or equal to the MBP in target tumors, regardless of uptake in non-target tumors (if any), will be considered negative for the presence of residual lymphoma. Positive post-therapy PET scan: Upon qualitative evaluation, diffuse or focal uptake in target tumors exceeding that seen in the MBP will be considered positive for residual tumor.

Liver uptake will be evaluated on axial slices.

Negative and positive post-therapy PET scans with respective criteria set are defined as follows.

The following criteria will be used for the 5-point ordinal scale:

MBP-based Assessment (IHP criteria)

- 1) No uptake visible for assessed lesion
- 2) Increased lesion uptake, but < MBP uptake
- 3) Increased lesion uptake, but equal to MBP uptake
- 4) Lesion uptake moderately increased compared with MBP
- 5) Lesion uptake markedly increased compared with MBP

Liver-based Assessment (London criteria)

- 1) No uptake
- 2) Increased lesion uptake \leq MBP
- 3) Increased lesion uptake $>$ MBP and \leq liver
- 4) Lesion uptake moderately increased compared with liver
- 5) Lesion uptake markedly increased compared with liver

Interpretation of ultimate positivity/negativity: Negative is scores of 0-3; Positive is scores of 4-5. Additionally, after therapy if any residual uptake is observed in non-target lesions, these lesions will be evaluated in the same fashion as the target organs.

SUV Assessment: Circular or volumetric regions of interest (ROI) will be placed over the target lesions, in mid-segment of the liver and MBP. When circular ROI are used, care must be taken that the ROI is drawn on the slice with the highest FDG uptake. When volumetric ROI are used, care must be taken that the region is confined to the lesion and does not include adjacent structures with high physiologic FDG uptake (e.g., renal collecting system, bone marrow after GCSF). Percent change between baseline and after therapy at all points as well as absolute SUVs will be determined at all points.

11.2.4 FDG-PET/CT and CT/MRI Data Archiving, Storage, and Submission

Once the image acquisition has been completed, the entire study (complete PET/CT data in digital DICOM format), along with CALGB form C-2029 (50904 FDG-PET Adjunctive Data Sheet) and CALGB form C-2028 (50904 Lymphoma Measurement Form), must be submitted to the Imaging Core Laboratory **within no more than 3 business days**. Institutions must also send CALGB forms C-2029 and C-2028 to the Alliance Statistical Center, Data Operations at Duke University.

The complete PET/CT and CT/MRI scans will be submitted to the Imaging Core Lab in digital DICOM format. BMP files, JPG files, or hard copies (films) are not acceptable. The raw data of the entire study should be saved until the scan is accepted by the Imaging Core Lab. De-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the study patient ID number and protocol number. The de-identified digital images may be burned to a CD or transferred to a PC-based system. The following datasets must be sent:

- Transmission CT data
- Emission data with CT attenuation correction
- Emission data without CT attenuation correction

Data may be transferred by **1) Web Transfer; 2) FTP transfer; 3) Shipment/Mail Transfer**. Once the data submission is complete, you must send an e-mail to the Imaging Core Lab at CALGB50904@imagingcorelab.com to

inform them that the images have been sent from your institution. Please include the study patient ID number and the date of the scan.

1) Web Transfer:

Any PCs with Internet access and web browser (e.g., Internet Explorer, Mozilla Firefox) can be used to web transfer DICOM images and other required files to the Imaging Core Lab. The standard Web Transfer information will be provided separately through the specific trial e-mail *CALGB50904@ImagingCoreLab.com*, per the request by participating sites before their first data submission.

2) FTP Transfer:

Any FTP software can be used to initiate access to the secure FTP Server of the Imaging Core Laboratory. The standard FTP access information will be provided separately through the specific trial e-mail *CALGB50904@ImagingCoreLab.com*, per the request by participating sites before their first data submission.

3) Shipment/Mail Transfer:

If FTP data transfers cannot be achieved, the de-identified images in digital DICOM format should be burned to a CD and mailed to the Imaging Core Lab. Please submit only one patient's images per CD, with the patient's study patient ID number, study type (i.e., PET baseline, after cycle 2 or end of treatment), date of scans, date of first study treatment, and name of submitting institution.

Submit these data to:

Alliance Imaging Core Lab
 Attn: CALGB50904
 The Ohio State University
 395 W. 12th Avenue, Suite 414
 Columbus, Ohio, 43210
 Tel: 614-293-9151
 Fax: 614/293-9275
 CALGB50904@imagingcorelab.com

If there are any difficulties or questions concerning the FDG-PET and CT/MRI data submission, please contact the Imaging Core Lab.

The Alliance Imaging Core Lab will acknowledge receipt of the imaging data via email confirmation to the institution **within 1 business day** of receipt. The data will be reviewed for quality. After completion of the quality check, another e-mail assessing the protocol compliance will be sent to the institution **within 3 business days**.

12.0 CORRELATIVE SCIENCE COMPANION STUDY (CALGB 151005)

There are three components to the CALGB 151005 correlative science companion study that must be presented to all patients, though patients may opt not to participate. The first component will be to evaluate Fc receptor polymorphisms and to correlate clinical outcomes in patients with previously untreated, high-risk follicular NHL treated with ofatumumab and bendamustine or ofatumumab, bendamustine, and bortezomib. The second component will be to correlate CD-68, bcl-2, Ki-67, FOXP3, Granzyme B, activated cytotoxic T-cells, lymphoma-associated macrophages (LAM), MUM1, CD10, and selected genetic translocations by FISH analysis (including Bcl-2 and Bcl-6) with response and progression-free survival following RCHOP and maintenance therapy in previously untreated patients with high-risk follicular lymphoma. The third component will be to determine whether immune gene signatures previously identified as

prognostic factors in follicular lymphoma can be applied to paraffin-embedded tissues in patients treated with either ofatumumab and bendamustine or ofatumumab, bendamustine, and bortezomib.

12.1 Single Nucleotide Polymorphism Analysis

12.1.1 Background

This study will correlate single nucleotide polymorphisms (SNPs) in the Fc gamma receptors 2A and 3A with response to ofatumumab-bendamustine (ARM A) or ofatumumab, bortezomib, and bendamustine (ARM B) and subsequent maintenance therapy in patients with previously untreated follicular NHL.

12.1.2 Objective

To correlate pre-treatment single nucleotide polymorphisms with response and PFS following ofatumumab-bendamustine and ofatumumab, bortezomib, and bendamustine therapy in patients with untreated high-risk follicular lymphoma.

12.1.3 Methods

SNP analysis will be performed at The Ohio State University in the laboratory of Dr. John Byrd, M.D., according to published protocols [26, 27]. Briefly, genomic DNA will be extracted and quantified, and 250 ng will be amplified in a standard polymerase chain reaction (PCR). PCR products will then be digested using restriction enzymes, and products will be analyzed by agarose gel electrophoresis. Results are compared to published data.

12.2 Immunohistochemical Markers

12.2.1 Background

Recent data have also suggested that the host immune response may affect the clinical course and survival of patients with follicular lymphoma. Dave et al. used gene-expression profiling in a series of follicular lymphomas, and found that a survival-predictor score could be generated using expression of immune response genes [28]. Genes associated with a favorable prognosis (termed “immune response 1”) included many genes expressed by T cells and macrophages, while genes associated with a poor prognosis (“immune response 2”) included many expressed by macrophages and dendritic cells. The combination of both immune response signatures was highly predictive of survival [28]. A subsequent study using a different group of patients demonstrated that lymphoma associated macrophages (LAMs) as recognized by expression of CD68 correlated with a poor prognosis, while expression of the T-cell antigens CD3, CD4, and CD8 did not correlate with clinical outcome [29]. Presence of immune modulating T-cells, regulatory T-cells (Tregs) as determined by FOXP3 expression, has also been studied with variable results, possibly related to patient populations and different methods of assessment of FOXP3. In one study, FOXP3 expression pattern has been suggested to be associated with poor outcome [30], while in others the number or pattern of FOXP3+ cells has been associated with favorable outcome [31]. Another subset of immune modulating T-cells (TFH) cells, recognized by PD-1, have also been shown to correlate with favorable survival [32]. These cellular components of the inflammatory infiltrate have not been examined together in the setting of a multi-institutional trial, and are of particular interest in CALGB phase II rituximab and immunotherapy based studies in which treatment-naïve patient response to biologic therapies is monitored by PET.

With regard to the tumor cells themselves, MUM1 expression in follicular lymphoma (FL) cells has recently been demonstrated. This post-germinal center/activated B-cell markers has not been previously known to be expressed to any degree in FL. Correlates of MUM1 have been suggested such as higher cytologic grade, lack of CD10, BCL6 amplification, and Ki67 [30, 33]; however, the clinical significance of MUM1+ FL has not been characterized. We have data to suggest a more aggressive clinical course as evidenced by the need to treat at diagnosis, as opposed to watchful waiting [21]. Furthermore, our preliminary data derived from SWOG cohorts suggests that MUM1+ FL (>20% of cells) has a poor OS compared to MUM1- FL in newly diagnosed patients receiving CHOP with monoclonal antibody [34]. Thus, this CALGB patient population is of particular interest to follow-up and confirm this observation in an independent data set.

12.2.2 Objective

To correlate CD-68, bcl-2, Ki-67, FOXP3, activated cytotoxic T-cells, lymphoma associated macrophages (LAM), MUM1, CD10, nuclear p65 and cREL subunits of NFkB, and selected genetic translocations by FISH analysis (such as Bcl-2 and Bcl-6) with response and PFS in patients receiving initial therapy for high-risk follicular lymphoma.

12.2.3 Methods

In patients who consent, tissue microarrays (TMA) will be constructed from paraffin-embedded tissue collected prior to initiation of therapy. Immunohistochemistry for FOXP3 (22510, Abcam), granzyme B (GrB7, Accurate Chemical), and CD68 (PGM1, Dako) will be performed using an automated immunostainer (Ventana Medical Systems, Tucson, AZ), with tonsil used as a positive control tissue. Pattern of FOXP3 (perifollicular versus other) and number of FOXP3/1000x high power field (average of five fields) will be scored using a “hotspot” counting method. Granzyme B will be quantitated in a similar manner. Ki-67 will be analyzed by image analysis (Aperio) within follicles. BCL2, MUM1, CD10 will also be performed using automated stainers (Ventana) and scored in tumor cells as negative (5%), weakly positive (6-20%), or strongly positive (> 20%). In an attempt to standardize analysis, we will also perform image analysis to quantitate the number of positive cells. FISH analysis will be performed with specific break-apart probes (Vysis) on TMAs according to standard procedures with cutoffs (positive, negative, and aneuploid) set by the central laboratory. Only those cells demonstrating nuclear staining will be counted.

Pre-treatment levels of NFkB activity will be assessed by evaluation of nuclear (active) p65 and cREL subunits of NFkB by automated immunohistochemistry using TMAs in the laboratory of Dr. Hsi. Nuclear staining will be scored via image analysis (Aperio) in the laboratory of Dr. Said (lymphoma pathology cadre) and correlated with outcome.

12.3 Validation of Gene Signatures in Lymphoma

12.3.1 Background

Specific expression profiles have been discovered and have been proven useful in subclassification and outcome prediction in lymphoma, including follicular lymphoma [28, 35-38]. However, these signatures have yet to be validated in independent patient cohorts from routinely processed tissues in modern (anti

CD20-containing) regimens. Such validation is of interest in this study. In addition to these established signatures, there is emerging evidence that expression of micro-RNAs are of pathogenetic importance in lymphoma. These micro-RNAs, which regulate gene expression, are differentially expressed in lymphocytes subsets, lymphoma subtypes, and may also be useful biomarkers [39-45]. Indeed a comprehensive profile of normal B-cell micro-RNA profiles has been established [45]. In order to further explore micro-RNA expression profiles and relationships with established gene signatures and outcome, we will also interrogate microRNA signatures that may correlate with these key gene signatures in this study.

12.3.2 Objectives

To determine whether immune gene signatures previously identified as prognostic factors in FL can be applied to paraffin embedded tissues in ofatumumab and bendamustine or in ofatumumab, bendamustine, and bortezomib treated patients; to evaluate microRNA signatures associated with these gene signatures and outcome.

12.3.3 Methods

Published gene signatures will be validated, focusing on immune response that have been associated with outcome in follicular lymphoma [28], on the paraffin embedded tissue collected on this trial.

Microarrays, quantitative real-time PCR, serial analysis of gene expression (SAGE) or similar methods will be used to generate gene expression profiles of tumors. Additional correlative studies may be done in conjunction with molecular profiling to assess genomic and protein changes using additional standard methods such as sequencing, polymerase chain reaction (PCR), immunophenotyping, Southern, Northern and Western Blot.

13.0 DRUG FORMULATION, AVAILABILITY AND PREPARATION

Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

It is not necessary to change the doses of ofatumumab, bendamustine, or bortezomib due to changes in weight unless the calculated dose changes by $\geq 10\%$.

13.1 Ofatumumab

Please review the ofatumumab prescribing information.

AVAILABILITY

Ofatumumab will be supplied by GlaxoSmithKline and distributed by Biologics. It may be ordered using the Drug Order Form on the CALGB 50904 study page, on the Alliance web site. Ofatumumab will be supplied in vials containing 100 mg or 1000 mg, at a concentration of 20 mg/mL. Please refer to the agent's package insert for additional information.

STORAGE & STABILITY

Intact vials of ofatumumab should be stored under refrigeration. Vials do not contain a preservative and are intended for single use. Diluted solutions should also be stored under refrigeration if they are not used immediately after preparation.

At the end of the study, institutions should provide a copy of the local drug destruction policies to the Alliance protocol office, and then destroy all unused drug onsite.

PREPARATION

For the 300 mg dose, withdraw and discard 15 mL from 1000 mL of 0.9% NaCl. Then add 300 mg to the 1000 mL bag, for IV infusion. For the 1000 mg dose, withdraw and discard 50 mL from 1000 mL of 0.9% NaCl. Then add 1000 mg to the 1000 mL bag, for IV infusion.

ADMINISTRATION

In this study, ofatumumab will be administered as an IV infusion, at the rate(s) specified in [Section 8.0](#). Maintenance doses should begin at the initial rate of 50 mL/hr followed by rate increase by 50 mL/hr every 30 minutes until a maximum rate of 400 mL/hr, because of the time elapsed between doses.

TOXICITIES

In the published reports of Phase I/II studies, the most commonly occurring adverse events (AEs) were infusion-related AEs. In these studies, infusion-related AEs were defined as those events occurring on the day of drug administration. Infusion-related AEs (e.g., hypersensitivity reactions, cytokine release syndrome) include fever, chills, fatigue, dyspnea, pharyngolaryngeal pain, cough, pruritus, rash and urticaria. The majority of these events were of grade 1 and 2 severity. Other reported AEs include headache, hypotension and nausea. Most AEs were noted on the day of ofatumumab administration; infusion-related AEs were generally seen within the first few hours of the start of the ofatumumab infusion. The number of AEs reported decreased with each subsequent dose.

As with rituximab, serious infections have been reported infrequently with ofatumumab. Exacerbation or reactivation of viral infections (e.g., JC virus reactivation leading to progressive multifocal leukoencephalopathy [PML], hepatitis B reactivation) have been reported in patients with CLL or follicular lymphoma, and less so in patients with rheumatoid arthritis. Patients presenting with new neurologic findings (e.g., major changes in vision, unusual eye movements, loss of balance or coordination, confusion) should be evaluated for PML.

Tumor lysis syndrome and small bowel obstruction have also been reported. Tumor lysis syndrome may be more likely in patients with high numbers of circulating malignant cells, as has been seen with rituximab.

Cardiac toxicity, including heart failure and myocardial infarction, were reported rarely in patients with CLL who received ofatumumab.

13.2 Bendamustine

Please review the bendamustine prescribing information.

AVAILABILITY

Bendamustine will be supplied and distributed by Cephalon. It may be ordered using the Drug Order Form on the CALGB 50904 study page, on the Alliance web site. Bendamustine will be supplied in vials containing 100 mg as a lyophilized powder. Please refer to the agent's package insert for additional information.

STORAGE AND STABILITY

Intact vials should be stored at room temperature and protected from light. Once reconstituted or further diluted for infusion, bendamustine is stable for 24 hours when stored refrigerated (2-8°C or 36-47°C) or for 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light.

At the end of the study, institutions should provide a copy of the local drug destruction policies to the Alliance protocol office, and then destroy all unused drug onsite.

PREPARATION

Add 5 mL of sterile water for injection to a 25 mg vial or 20 mL of sterile water for injection in a 100 mg vial to yield a concentration of 5 mg/mL. The desired volume should be withdrawn from the vial, and injected into 500 mL of 0.9% NaCl or 2.5% dextrose/0.45%NaCl for IV infusion.

ADMINISTRATION

In this study, bendamustine will be administered as an IV infusion over 30-60 minutes, following ofatumumab (Arm A) or bortezomib (Arm B).

TOXICITIES

The most common adverse events reported with bendamustine include myelosuppression, GI toxicity, fatigue, fever and chills, and infection. Grade 3 or 4 neutropenia is reported in 60% of patients but febrile neutropenia is less common. Grade 3 or 4 thrombocytopenia is reported in 25% of patients. Dose delays due to myelosuppression were common in a study of bendamustine given every 21 days to patients with rituximab refractory NHL. Nausea and vomiting are seen in approximately 77% and 40% of patients, respectively. Most of these events are grade 1 or 2. Infusion reactions during or shortly after bendamustine administration have been reported in as many as 15% of patients. Reactions consist of fever and chills, and less frequently, shortness of breath, hypotension or anaphylactic/anaphylactoid reactions. Pre-medication with steroids following mild infusion reactions may prevent further reactions with subsequent doses. Fatigue has been reported in 57% of patients. Less commonly, severe skin reactions (e.g. TEN, SJS) and second malignancies have been seen. In some cases, skin reactions have been seen in patients who also received other medications associated with severe skin toxicity (e.g., allopurinol). In addition, extravasation reactions including erythema, swelling and pain have been described.

As in the case with other alkylators, secondary malignancies including MDS and AML have also been reported.

13.3 Bortezomib (NSC #681239, IND #58443)*AVAILABILITY*

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead

investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (<https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jsp>). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (<https://eapps-ctep.nci.nih.gov/iam/>) and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

PREPARATION

IV preparation: Each vial should be reconstituted with 3.5 mL normal (0.9%) saline, resulting in a bortezomib solution of 1 mg/mL.

SC preparation: Each vial should be reconstituted with 1.4 mL normal (0.9%) saline, resulting in a bortezomib solution of 2.5 mg/mL.

STORAGE AND STABILITY

Intact vials should be stored at room temperature and protected from light. Solutions reconstituted as instructed are stable for at least 8 hours at room temperature.

At the end of the study, all unused (including expired) drug should be returned to the PMB.

ADMINISTRATION

IV administration: The desired volume of bortezomib reconstituted solution is administered as a rapid IV injection over 3 to 5 seconds.

SC administration: The desired volume of bortezomib reconstituted solution is administered as a subcutaneous injection in the thigh or abdomen. Rotate sites at least 1 inch away from old sites.

TOXICITIES

The most frequently reported adverse events associated with bortezomib to date include gastrointestinal events, fatigue, and thrombocytopenia. Gastrointestinal events include nausea, vomiting, anorexia, diarrhea, and constipation. Most GI events have been grade 1 or 2 and they occurred early in treatment, persisting for several cycles. Occasional grade 4 vomiting and diarrhea have been noted. Prophylaxis against GI events is not thought to be necessary with the first cycle of treatment. Ileus and abdominal pain/cramping have also been reported. Fatigue is also predominantly of grade 1 or 2 severity and has onset early in treatment (i.e. during the first and second cycles). Thrombocytopenia, although occurring in 38% of patients in phase II studies, is reported to be transient (resolution during the rest period in each cycle) and uncomplicated. Thrombocytopenia of grade 3 severity was seen in 25% of patients.

Peripheral neuropathy was noted in 35% of patients in phase II studies (grade 3 in 13% and grade 4 in < 1%). Peripheral neuropathy is primarily sensory and appears to be more severe in patients with pre-existing sensory signs or symptoms. It does not seem to be related to cumulative dose, in that new onset or worsening of existing neuropathy was noted throughout the cycles of treatment. Recently motor neuropathy has also been described. Peripheral neuropathy may or may not be completely reversible.

Grade 3 neutropenia was described in 10% of patients in phase II studies. Febrile neutropenia occurred in 4%. Clinically significant infections (distinct from neutropenia) were reported in 13%. Fever was reported in 36% of patients; severity of grades 3 or 4 in 4%.

Hypotension, the mechanism of which is unknown, was reported in 11% of patients in

phase II studies. Most patients were orthostatic. Hypotension required pharmacologic treatment and a small number of patients had syncopal events. Orthostatic hypotension was not acutely related to bolus injection of bortezomib.

Other reported adverse events and potential risks include anemia, rash/desquamation, vasculitis, headache, lymphopenia, granulocytopenia, dyspnea, constipation, edema, and pruritis.

Also reported on bortezomib trials but with the relationship to bortezomib still undetermined: hyponatremia, hypokalemia, hyperkalemia, hypertension, tachycardia, bradycardia, atrial flutter, myalgia, and instances of various pain, clotting abnormalities, renal dysfunction, abnormal liver function tests and certain central nervous system abnormalities (confusion and altered mentation status).

For a comprehensive adverse events and potential risks list (CAEPR), see [Section 17.3](#).

14.0 CRITERIA FOR RESPONSE, PROGRESSION AND RELAPSE

For the purposes of this study, patients will be restaged using CT or MRI scan and/or FDG-PET/CT according to [Section 7.0](#) after cycles 2, 4, and 6 of induction therapy, every 4 months during maintenance therapy, every 4 months for 2 years after completion of therapy, and then every 6 months until disease progression or for a maximum of 10 years from study entry.

14.1 Definitions of Response [23]

14.1.1 Complete Response (CR):

Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

In patients with no pre-treatment PET scan, or if the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET-negative.

The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry, but that demonstrates a small population of clonal lymphocytes by flow cytometry, will be considered a CR until data become available demonstrating a clear difference in patient outcome.

14.1.2 Partial Response (PR):

At least a 50% decrease in the sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected prior to initiation of therapy according to all of the following: a) they should be clearly measurable in at least two perpendicular dimensions; b) if possible, they should be from disparate regions of the body; and c) they should

include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

No increase should be observed in the size of other nodes, liver, or spleen.

Splenic and hepatic nodules must regress by $\geq 50\%$ in their SPD, or, for single nodules, in the greatest transverse diameter.

With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement, will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

No new sites of disease should be observed.

For patients with no pre-treatment PET scan, or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

14.1.3 Stable Disease (SD)

Stable disease is defined as patient fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see below). The PET should be positive at prior sites of disease, with no new areas of involvement on the post-treatment CT or PET.

14.1.4 Progression (PD) or Relapse:

Lymph nodes should be considered abnormal if the long axis is > 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is > 1.0 . Lymph nodes ≤ 1.0 cm by ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.

Appearance of any new lesion > 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of < 1.0 cm must increase by $\geq 50\%$ and to a size of 1.5 x 1.5 cm, or > 1.5 cm in the long axis.

At least a 50% increase in the longest diameter of any single previously identified node > 1.0 cm in its short axis.

Lesions should be PET-positive if a typical FDG-avid lymphoma or the lesion was PET-positive prior to therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

14.2 Guidelines for Evaluation of Measurable Disease

Clinical Lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes).

Chest X-ray: Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis. Head & neck and extremities usually require specific protocols.

Ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible when the primary endpoint of the study is objective response evaluation. It is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

15.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

15.1 Duration of Treatment

Remove patients from protocol therapy who have disease progression after cycles 2, 4, or 6 of induction therapy. During maintenance therapy, patients may remain on study therapy for the planned duration of protocol treatment provided there is no evidence of disease progression or unacceptable toxicity. Remove from all protocol therapy any patient with rapid or documented disease progression.

15.2 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Notify the Study Chair.
- Document the reason(s) for discontinuation of therapy in patient records and CALGB form C-300 (Off Treatment Form).
- Follow the patient for relapse, progression, survival, and secondary malignancy or new primaries.

16.0 STATISTICAL CONSIDERATIONS

16.1 Randomization

One hundred thirty (65 per arm) newly diagnosed high-risk follicular lymphoma patients will be randomized between

Arm A: 6 cycles of ofatumumab-bendamustine

Arm B: 6 cycles of ofatumumab, bortezomib, and bendamustine

16.2 Primary Endpoint

The primary endpoint of this trial is to determine the CR rate in newly diagnosed high-risk follicular lymphoma patients. Arm A (control) has not been rigorously investigated in this high-risk patient population, so that we employ a randomized phase II trial design. In the

up-front setting, the CR rate with R-bendamustine in a subset of patients with high-risk untreated follicular NHL (FLIPI > 2) was estimated as 41% [6]. Therefore, based on available CR and ORR data with rituximab-bendamustine in front-line therapy for patients with intermediate to high-risk FLIPI scores, we anticipate a CR rate following induction therapy of about 40% for patients in Arm A. Improvement in CR rate to 60% with combined ofatumumab, bortezomib, and bendamustine (Arm B) would be of interest for further study of this therapy in follicular lymphoma.

Let PA and PB denote the CR rates of Arms A and B, respectively. Following a two-stage design with one-sided $\alpha=15\%$ for $H_0: PA=PB$ vs. $H_1: PA<PB$ requires $N=122$ eligible patients (61 patients per arm) for 84% power under $H_1: PA=40\%, PB=60\%$. This design is based on the two-stage Fisher's exact test [45].

Stage 1: Thirty patients will be randomized to each arm. Let X1 and Y1 denote the number of complete responders from Arms A and B, respectively. If $Y_1 - X_1$ is larger than or equal to 0, then the study will proceed to the second stage. Otherwise, the study will be stopped.

Stage 2: An additional 31 patients will be randomized to each arm. Let X and Y denote the number of complete responders among the cumulative 61 patients of Arms A and B, respectively. If $Y - X$ is larger than or equal to the critical value a , then Arm B will be accepted for further investigation. The critical value a for $Y - X$ after the 2nd stage will be determined based on the total number of complete responders (CR) from the two arms for 15% of one-sided α reflecting the two-stage testing. Note that the Fisher's exact test is valid (i.e. accurately control the type I error) even when PA is different from 40% since it tests on the odds ratio between PA and PB. The specification of PA and PB is required only to calculate the sample sizes.

16.3 Adverse Event Monitoring

Monthly conference calls to monitor toxicity will be held until the first 40 patients (20 per arm) have completed the induction therapy. As far as the monthly conference calls continue, we will monitor all toxicity data available from the patients.

We will closely monitor grade 3-4 infusion reactions and peripheral neuropathy in addition to all other types of toxicities. Four statistical interim looks will be when the first 5, 10, 15 and 20 patients complete the protocol therapy for each arm.

Infusion Reactions: Expected rate of grade 3-4 reactions is only about 20-30% as a single agent but may be a bit higher in previously untreated patients. As a result, a rate of 50% of grade 3-4 reactions will be considered acceptable while 75% or above will be considered unacceptable for each arm. Grade 3-4 reactions will be evaluated independently for each arm. We will consider stopping the study for amendment if 5 of the first 5, 8 or more of the first 10, 12 or more of the first 15, or 14 or more of the first 20, patients experience grade 3-4 reactions for either arm. This monitoring rule has 10%, 48%, 66% and 82% probability to stop the trial if an arm has 50%, 65%, 70% and 75% grade 3-4 reaction rate, respectively.

Peripheral Neuropathy: Grade 3-4 peripheral neuropathy will be monitored for each arm.

Arm A: The expected rate of grade 3-4 peripheral neuropathy in the control arm is about 5%. We will consider stopping the study for amendment if 2 or more of the first 5, 3 or more of the first 10, 3 or more of the first 15, or 3 or more of the first 20 patients experience grade 3-4 peripheral neuropathy for arm A. This monitoring rule has 8.5%, 34%, 61% and 80% probability to stop the trial if arm A has 5%, 10%, 15% and 20% grade 3-4 peripheral neuropathy rate, respectively.

Arm B: The expected rate of grade 3-4 peripheral neuropathy in arm B is about 20%. We will consider stopping the study for amendment if 3 or more of the first 5, 5 or more of the

first 10, 7 or more of the first 15, or 8 or more of the first 20 patients experience grade 3-4 peripheral neuropathy for arm B. This monitoring rule has 10%, 33%, 66% and 90% probability to stop the trial if arm A has 20%, 30%, 40% and 50% grade 3-4 peripheral neuropathy rate, respectively.

16.4 Secondary Endpoints

PFS: Kaplan-Meier curves of PFS and OS will be generated for the two arms. The p-values of the log-rank test will be calculated to compare PFS and OS between the two arms.

Toxicity: The toxicity profile of the two arms will be summarized using frequency tables. The chi-squared test will be conducted to compare the toxicity rate of grade 3 or higher between the two arms.

Pre-treatment single nucleotide polymorphisms (SNP): The PFS will be compared among the three genotype groups of each SNP using the log-rank tests. A max-type test will be used by taking the maximum value of the log-rank tests under dominant, recessive, and proportional hazard model. The critical value (or p-value) of the max test will be obtained by a permutation method. No multiple testing adjustment may be applied because of the small sample size.

Immunohistochemical (IHC) Markers: The IHC markers will be correlated with response (using the two-sample t-test) and PFS (using the Cox regression method) data. No multiple testing adjustment will be applied because of the small sample size.

Predictive value of FDG-PET: In analysis, the ratio between the SUVmax after cycle 2 and the SUVmax at baseline will be used as the observation for each patient. (A ratio smaller than 1 means decrease in post-therapy SUVmax from the baseline). The ratio will be correlated with response (using the two-sample t-test) and PFS (using the Cox regression method) data. In addition, FDG-PET ratios between baseline and after 2 cycles will be evaluated in combination with changes obtained from dedicated CT or MRI studies to determine if a combinatorial approach using both metabolic and morphologic changes would result in a higher predictive value for response and PFS. We will regress response on FDG-PET (or CT or MRI), treatment arm and their interaction using the logistic regression method. We will conduct an analysis on the pooled data if the treatment effect and the interaction between treatment are not significant. The association of the imaging data with PFS will be similarly analyzed using Cox regression method.

We will compare the predictive values between FDG-PET and FDG-PET plus CT or MRI. For some patients the MRI may be positive but CT or MRI may be negative, and vice versa. These patients will contribute only one data point to the analysis. However those patients with positivity (negativity) for both FDG-PET and MRI/CT will contribute paired data points to the analysis of positive (negative) predictive value. In order to handle the partially correlated binary data, we will use a GEE-type approach in the statistical testing.

Qualitative analyses using various reading schemes will also be performed to determine changes in FDG-PET positivity or negativity. Similar analyses will be conducted using FDG-PET data after cycle 6 and at the end of therapy. A transformation (such as logarithm) of the FDG-PET outcomes may be considered to improve the normality of error terms and/or linearity of the time trajectory.

In another set of data analysis, the change rate (slope) of the time trajectory of FDG-PET findings will be calculated for each patient and correlated with response (using two-sample t-test) and PFS (using Cox regression method). Similar analyses will be conducted with PET findings combined with CT or MRI.

Dave et al. discovered gene signature associated with overall survival from 191 patients. The gene signature will be validated with respect to CR rate, progression-free survival

(PFS) and overall survival (OS). In order to test for the association of the gene expression signatures with response to treatment, we will median-center and divide our patients into high and low expressors of the gene expression signature. We will test the association between the gene signature and the response in this study by chi-squared test for a 2x2 table. Based on our experience from 150711 (59 of 60 patients participated), we expect that most of n=122 eligible patients will participate in this correlative study. If the CR rate for the high- and low-risk groups are 35% and 65%, respectively, then we are going to have 91% power to validate the association with a two-sided alpha=5%. The log-rank test will be used to compare the PFS between high and low-risk groups as defined by the gene signature. The association with OS will be validated similarly. This validation will also be conducted within each arm.

16.5 Accrual and Follow-up

Accounting for possible dropouts and ineligible patients, we will accrue a total of 130 patients to this study. Ineligible patients will be excluded in the final analysis. With an expected accrual of 3 patients per month, it will take about 44 months to complete the accrual. For analyzing PFS OS, each patient will be followed until disease progression or death, or for a maximum of 10 years from study entry.

16.6 Safety Considerations

Toxicity will be assessed according to NCI criteria for adverse events, version 4.0. As there are no phase I data available regarding the combination of ofatumumab with bendamustine or bortezomib, monthly conference calls will be conducted among participating investigators, the study chair, and the study statistician to monitor adverse events in the first 40 patients enrolled (20 enrolled on Arm A and Arm B).

16.7 CDUS Reposting

The Alliance Statistical Center at Duke University will submit quarterly reports to CTEP by electronic means using the Clinical Data Update System (CDUS).

17.0 ADVERSE EVENT REPORTING (AER)

Investigators are required by Federal Regulations to report serious adverse events as defined below. Investigators are required to notify the Investigational Drug Branch, the Alliance Central Protocol Operations Program Office, the Study Chair, and their Institutional Review Board (IRB) if a patient has an adverse event requiring expedited reporting. All such events must be reported in an expedited manner using the CTEP Adverse Event Expedited Reporting System (CTEP-AERS). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting.

All treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).

The Alliance requires investigators to route all expedited adverse event reports (AERs) through the Central Protocol Operations Program Office for CALGB or Alliance-coordinated studies.

Note: Please be sure to read this entire protocol section, as requirements are described in both the table below and the bullet points following the table. Note that the table and the additional instructions or exclusions are protocol-specific, and in the case of a conflict, the additional instructions or exclusions supersede the table.

17.1 CALGB 50904 Reporting Requirements

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND within 30 Days of the Last Day of Treatment

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

Expedited AE reporting timelines are defined as:

- “24-Hour; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

¹Serious adverse events that occur more than 30 days after the last day of treatment require reporting as follows: **Expedited 24-hour notification followed by complete report within 5 calendar days for:**

- All Grade 4, and Grade 5 AEs that are at least possibly related to treatment
- Expedited 10 calendar day reports for:**
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization and that are at least possibly related to treatment
 - Grade 3 adverse events that are at least possibly related to treatment

Effective Date: May 5, 2011

17.2 Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND:

- CALGB 50904 uses a drug under a CTEP IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all agents (any arm) in this trial.
- Treatment expected adverse events include those listed in [Section 9.0](#) and in the package inserts for ofatumumab, bendamustine and in the CAEPR (see below) for bortezomib. Note: the ASAE column of the bortezomib CAEPR has been replaced with the specific protocol exceptions to expedited reporting (SPEER) list. This list now includes "expected" severity grades in addition to event terms.

- Grade 3/4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but must be reported as part of study results.
- Febrile neutropenia and hospitalization resulting from such do not require CTEP-AERS, but must be reported as part of study results.
- Grade 3 nausea or grade 3/4 vomiting and hospitalization resulting from such do not require CTEP-AERS, but must be reported as part of study results.
- Grade 3/4 peripheral neuropathy and hospitalization resulting from such do not require CTEP-AERS, but must be reported as part of study results.
- Grade 3/4 infusion reactions or hypersensitivity reactions and hospitalization from such do not require CTEP-AERS, but must be reported as part of study results.
- Grade 3 fatigue and hospitalization resulting from such do not require CTEP-AERS, but must be reported as part of study results.
- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB, according to local IRB policy
- Deaths clearly due to progressive disease do not require CTEP-AERS, but must be reported as part of study results via routine reporting

17.3 CAEPR for Bortezomib (Velcade, NSC 681239)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2084 patients.* Below is the CAEPR for bortezomib (Velcade).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, May 25, 2017¹

Adverse Events with Possible Relationship to Bortezomib (Velcade) (CTCAE 4.0 Term) [n= 2084]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			<i>Anemia (Gr 3)</i>
CARDIAC DISORDERS			
		Heart failure	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		<i>Abdominal pain (Gr 3)</i>
Constipation			<i>Constipation (Gr 3)</i>
Diarrhea			<i>Diarrhea (Gr 3)</i>
	Dyspepsia		<i>Dyspepsia (Gr 2)</i>
	Gastrointestinal hemorrhage ²		
		Gastrointestinal perforation ³	

Adverse Events with Possible Relationship to Bortezomib (Velcade) (CTCAE 4.0 Term) [n= 2084]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Ileus		<i>Ileus (Gr 3)</i>
Nausea			<i>Nausea (Gr 3)</i>
Vomiting			<i>Vomiting (Gr 3)</i>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		<i>Chills (Gr 2)</i>
	Edema limbs		<i>Edema limbs (Gr 3)</i>
Fatigue			<i>Fatigue (Gr 3)</i>
Fever			<i>Fever (Gr 3)</i>
HEPATOBIILIARY DISORDERS			
		Hepatic failure ⁴	
		Hepatobiliary disorders - Other (hepatitis) ⁴	
INFECTIIONS AND INFESTATIONS			
Infection ⁵			<i>Infection⁵ (Gr 4)</i>
INVESTIGATIONS			
		Alanine aminotransferase increased ⁴	
		Alkaline phosphatase increased ⁴	
		Aspartate aminotransferase increased ⁴	
		Blood bilirubin increased ⁴	
		GGT increased ⁴	
		INR increased ⁴	
		Investigations - Other (albumin) ⁴	
	Neutrophil count decreased		<i>Neutrophil count decreased (Gr 4)</i>
Platelet count decreased			<i>Platelet count decreased (Gr 4)</i>
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			<i>Anorexia (Gr 3)</i>
	Dehydration		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		<i>Arthralgia (Gr 3)</i>
	Back pain		<i>Back pain (Gr 3)</i>
	Bone pain		<i>Bone pain (Gr 2)</i>
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)		
	Myalgia		<i>Myalgia (Gr 3)</i>
	Pain in extremity		<i>Pain in extremity (Gr 3)</i>
NERVOUS SYSTEM DISORDERS			
	Dizziness		<i>Dizziness (Gr 3)</i>
	Headache		<i>Headache (Gr 3)</i>
		Leukoencephalopathy	

Adverse Events with Possible Relationship to Bortezomib (Velcade) (CTCAE 4.0 Term) [n= 2084]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Neuralgia		<i>Neuralgia (Gr 3)</i>
	Paresthesia		
Peripheral motor neuropathy			<i>Peripheral motor neuropathy (Gr 3)</i>
Peripheral sensory neuropathy			<i>Peripheral sensory neuropathy (Gr 3)</i>
		Reversible posterior leukoencephalopathy syndrome	
PSYCHIATRIC DISORDERS			
	Anxiety		
	Insomnia		<i>Insomnia (Gr 2)</i>
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Adult respiratory distress syndrome	
	Cough		<i>Cough (Gr 2)</i>
	Dyspnea		<i>Dyspnea (Gr 3)</i>
	Pharyngeal mucositis		<i>Pharyngeal mucositis (Gr 2)</i>
		Pulmonary hypertension	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		<i>Rash maculo-papular (Gr 3)</i>
VASCULAR DISORDERS			
	Hypotension		<i>Hypotension (Gr 4)</i>

¹This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

²Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

³Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

⁴Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include hepatitis, increases in liver enzymes, and hyperbilirubinemia.

⁵Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on bortezomib (Velcade) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that bortezomib (Velcade) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (hematocrit low); Blood and lymphatic system disorders - Other (lymphadenopathy); Disseminated intravascular coagulation; Febrile neutropenia; Hemolytic uremic syndrome; Leukocytosis

CARDIAC DISORDERS - Acute coronary syndrome; Asystole; Atrial fibrillation; Atrial flutter; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (cardiac amyloidosis); Cardiac disorders - Other (cardiomegaly); Chest pain - cardiac; Left ventricular systolic dysfunction; Mobitz type I; Myocardial infarction; Palpitations; Pericardial effusion; Pericardial tamponade; Pericarditis; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular arrhythmia; Ventricular fibrillation; Ventricular tachycardia

EAR AND LABYRINTH DISORDERS - External ear inflammation; Hearing impaired; Tinnitus

ENDOCRINE DISORDERS - Hypothyroidism

EYE DISORDERS - Blurred vision; Conjunctivitis; Dry eye; Extraocular muscle paresis; Eye disorders - Other (chalazion); Eye disorders - Other (choroidal effusion); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (retinal hemorrhage with bilateral vision impairment); Keratitis; Watery eyes

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Bloating; Colitis; Dry mouth; Duodenal ulcer; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (colonic wall thickening); Gastrointestinal disorders - Other (early satiety); Gastrointestinal disorders - Other (eructation); Gastrointestinal disorders - Other (ileitis); Gastrointestinal disorders - Other (ischemic bowel); Gastrointestinal disorders - Other (mouth/tongue ulceration); Gastrointestinal disorders - Other (retching); Gastrointestinal pain; Gingival pain; Hemorrhoids; Mucositis oral; Oral pain; Pancreatitis; Small intestinal obstruction; Typhlitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (catheter related complication); General disorders and administration site conditions - Other (hepato-renal syndrome); Hypothermia; Injection site reaction; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS

HEPATOBIILIARY DISORDERS - Hepatobiliary disorders - Other (portal vein thrombosis); Hepatobiliary disorders - Other (VOD)

IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Cytokine release syndrome

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fall; Fracture; Vascular access complication

INVESTIGATIONS - Activated partial thromboplastin time prolonged; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Creatinine increased; Ejection fraction decreased; Investigations - Other (BUN); Investigations - Other (low chloride); Investigations - Other (pancytopenia); Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Avascular necrosis; Buttock pain; Chest wall pain; Generalized muscle weakness; Joint range of motion decreased; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (cramping); Osteonecrosis of jaw

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Acoustic nerve disorder NOS; Akathisia; Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Edema cerebral; Encephalopathy; Facial muscle weakness; Facial nerve disorder; Hypersomnia; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Memory impairment; Nervous system disorders - Other (autonomic neuropathy); Nervous system disorders - Other (Bell's palsy); Nervous system disorders - Other (cranial palsy); Nervous system disorders - Other (dysautonomia); Nervous system disorders - Other (L sided facial droop); Nervous system disorders - Other (paralysis); Nervous system disorders - Other (polyneuropathy); Nervous system disorders - Other (spinal cord compression); Nervous system disorders - Other (tongue paralysis); Presyncope; Seizure; Somnolence; Stroke; Syncope; Tremor; Vasovagal reaction

PSYCHIATRIC DISORDERS - Agitation; Confusion; Delirium; Depression; Personality change; Psychosis

RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Hematuria; Proteinuria; Renal and urinary disorders - Other (bilateral hydronephrosis); Renal and urinary disorders - Other (calculus renal); Renal and urinary disorders - Other (glomerular nephritis proliferative); Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Aspiration; Atelectasis; Bronchopulmonary hemorrhage; Bronchospasm; Epistaxis; Hiccups; Hypoxia; Laryngeal edema; Mediastinal hemorrhage; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumonitis; Postnasal drip; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (obstructive airways disease); Respiratory, thoracic and mediastinal disorders - Other (pleurisy); Respiratory, thoracic and mediastinal disorders - Other (respiratory distress); Respiratory, thoracic and mediastinal disorders - Other (tachypnea); Tracheal mucositis; Tracheal stenosis; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Bullous dermatitis; Dry skin; Erythema multiforme; Erythroderma; Hyperhidrosis; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (angioedema); Skin and subcutaneous tissue disorders - Other (leukoclastic vasculitis); Skin and subcutaneous tissue disorders - Other (skin lesion NOS); Urticaria

VASCULAR DISORDERS - Capillary leak syndrome; Flushing; Hematoma; Hypertension; Thromboembolic event; Vascular disorders - Other (trach site); Vasculitis

Note: Bortezomib (Velcade) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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APPENDIX I COLLABORATIVE AGREEMENT PROVISIONS

The agent supplied by CTEP, DCTD, NCI used in this protocol (bortezomib) is provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between Millennium Pharmaceuticals, Inc. (hereinafter referred to as Collaborator) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator” (<http://ctep.cancer.gov/industry/ipo.html>) contained within the terms of the award, apply to the use of the Agents in this study:

1. Agent may not be used for any purpose outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator’s data for Agent are confidential and proprietary to Collaborator and Provider and should be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or a patient’s family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from <http://ctep.cancer.gov>.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different agreements, the access to and use of data by Collaborator shall be as follows: (data pertaining to such combination use shall hereinafter be referred to as “Multi-Party Data.”)
 - a. NCI will provide Collaborator with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict the NCI’s participation in the proposed combination protocol.
 - b. Each Collaborator shall agree to permit the use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational Agent.
 - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for the development, regulatory approval, and commercialization of its own investigational agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator, the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used, and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator’s wish to contact them.
5. Any data provided to Collaborator for phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial should be provided to CTEP by the Group Office for Cooperative Group Studies or by the investigator for non-Cooperative

Group Studies for immediate delivery to Collaborator for advisory review and comment prior to submission for publication. Collaborator will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's intellectual property rights, are protected. Copies of abstracts should be provided CTEP for forwarding to Collaborator for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, Maryland 20892
Fax: 301-402-1584
Email: anshers@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator. No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

APPENDIX II CALGB 50904 PET/CT INSTRUMENT

Technical Specifications Form
(From ACRIN Credentialing Application, 2005)

Page 1 of 5

Institution:	Date:
Institution Address:	
Institution Contact Name and Telephone Number:	
E-mail:	Fax:
PET Center Name:	
Date:	
PET Center Address:	
PET Center Contact Name and Telephone Number:	
E-mail:	Fax:
Type of Scanner: <i>(e.g., GE Discovery ST, Siemens Biograph, Philips Gemini, GE Advance, Siemens/CTI ECAT, etc.)</i>	
Transmission Source: <i>(e.g., ⁶⁸GE-rods, ¹³⁷Cs-point, CT)</i>	
Method of Attenuation Correction: <i>(e.g., segmentation, subtraction of emission contribution to transmission scan, CTAC)</i>	
<u>Routine QC Testing Performed</u>	
Daily:	
Monthly:	
Quarterly:	
Yearly:	
Other:	

CALGB 50904 PET/CT INSTRUMENT TECHNICAL SPECIFICATIONS FORM
(From ACRIN Credentialing Application, 2005)

UNIFORM PHANTOM SCAN INFORMATION			
Phantom Length:	Phantom Diameter:		
Phantom Volume:			
Radionuclide:			
Scan Date:	Scan Time:	Scan Duration:	
<u>For Water-Fillable Phantoms, Provide the Following Data:</u>			
Assayed Activity in Syringe <u>before</u> injection:	mCi	Time:	
Assayed Activity in Syringe <u>after</u> injection:	mCi	Time:	
<u>For Ge-68/Ga-68 Calibration Phantoms, Provide the Following Data:</u>			
Calibration Date:	Time:		
Calibration Activity:	mCi	Time:	
Number of Pixels in ROI:	Slice #	Average SUV in ROI¹	Std Dev of SUV (if available)
	1	_____	_____
	2	_____	_____
	3	_____	_____
	4	_____	_____
	5	_____	_____
	6	_____	_____
	7	_____	_____
	8	_____	_____
Report info for <u>EVERY</u>	9	_____	_____
slice of the phantom	10	_____	_____
	11	_____	_____
	12	_____	_____
	13	_____	_____
	14	_____	_____
	15	_____	_____
	16	_____	_____
	17	_____	_____
	18	_____	_____
	19	_____	_____
	20	_____	_____
¹ A circular or elliptical region of interest (ROI) covering most of the interior of the phantom.			

CALGB 50904 PET/CT INSTRUMENT TECHNICAL SPECIFICATIONS FORM
(From ACRIN Credentialing Application, 2005)

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FOR IMAGING CORE LABORATORY USE ONLY:

Phantom Images Review:

Date:

Comments:

Approved

Disapproved

Signature

Date

CALGB 50904 PET/CT INSTRUMENT TECHNICAL SPECIFICATIONS FORM

(From ACRIN Credentialing Application, 2005)

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WHOLE BODY FDG-PET TEST PATIENT #1:

File Name: _____ **Patient Height:** _____ **Patient Weight:** _____

FDG Dose (mCi): _____ **Dose Assay Time:** _____

Blood glucose prior to FDG administration (mg/dL): _____

Injection Time: _____ **Start Time of Emission Scan:** _____

ACQUISITION No. of Bed Positions: _____

EMISSION TIME (MIN/BED): _____ **TRANSMISSION TIME (MIN/BED):** _____

RECONSTRUCTION ALGORITHM: (e.g., 2D FBP, 2D OSEM, 3D FORE/OSEM, 3D RAMLA)	PIXEL SIZE (mm)
	X-Y:
	Z:

Scatter Correction Applied: Yes No

(Include algorithm type, e.g., model-based, tail-fit, Bergstrom):

Randoms Correction Applied: Online Smoothed Randoms (offline) None

FOR IMAGING CORE LABORTORY USE ONLY:

Test Patient #1 Review:

Date: _____

Comments:

Approved

Disapproved

Signature

Date

CALGB 50904 PET/CT INSTRUMENT TECHNICAL SPECIFICATIONS FORM

(From ACRIN Credentialing Application, 2005)

Page 5 of 5

WHOLE BODY FDG-PET TEST PATIENT #2:

File Name: _____ **Patient Height:** _____ **Patient Weight:** _____

FDG Dose (mCi): _____ **Dose Assay Time:** _____

Blood glucose prior to FDG administration (mg/dL): _____

Injection Time: _____ **Start Time of Emission Scan:** _____

ACQUISITION No. of Bed Positions: _____

EMISSION TIME (MIN/BED): _____ **TRANSMISSION TIME (MIN/BED):** _____

RECONSTRUCTION ALGORITHM:	PIXEL SIZE (mm)
(e.g., 2D FBP, 2D OSEM, 3D FORE/OSEM, 3D RAMLA)	X-Y: Z:

Scatter Correction Applied: Yes No

(Include algorithm type, e.g., model-based, tail-fit, Bergstrom):

Randoms Correction Applied: Online Smoothed Randoms (offline) None

FOR IMAGING CORE LABORTORY USE ONLY:

Test Patient #2 Review:

Date: _____

Comments:

Approved

Disapproved

Signature

Date

APPENDIX III CALGB 50904 IMAGING SITE PERSONNEL FORM

Responsible CRA Contact Complete Address E-mail Phone Number Fax Number	Radiology Department Contact Complete Address E-mail Phone Number Fax Number

Please provide the information requested above. Provide the middle initial for individuals who commonly use them. Also, please add or correct the degree/title as necessary. This information will be retained by the Imaging Core Laboratory.

Once completed, you may **send this form to:**

Alliance Imaging Core Laboratory
Attn: CALGB 50604
Wright Center of Innovation
The Ohio State University
395 West 12th Avenue, Room 414
Columbus, OH 43210
Fax: 614-293-9275

Call the Imaging Core Laboratory at 614-293-2929 or 614-366-0807 with any questions. Thank you for your assistance.