Bendamustine Combined with Rituximab for Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

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Abstract

Background:

Diffuse Large B Cell Lymphoma (DLBCL) accounts for 35% of all non-Hodgkins lymphomas in western society. Current front-line chemoimmunotherapies are highly effective, curing 50-90% of patients based on stage and prognostic factors. Relapsed/refractory patients typically receive salvage chemotherapy and, if responsive and medically fit, autologous stem cell transplant. Patients ineligible for transplant or who relapse after transplant, generally have a poor prognosis. Many salvage regimens for DLBCL are poorly tolerated and may require hospitalization. Bendamustine has shown single-agent and combination activity in indolent lymphomas, however, data about its utility in aggressive lymphomas such as DLBCL are limited. The favorable toxicity profile of bendamustine and demonstrated synergy with rituximab make it worthy of investigation in DLBCL. Below are initial results of a phase II clinical trial of bendamustine rituximab (BR) for subjects with relapsed/ refractory DLBCL.

Methods:

This open label, single arm trial will enroll up to 54 patients whom have failed at least one prior therapy and have at least one measurable lesion with response assessed by the Revised Response Criteria for Malignant Lymphoma. Study treatment is given in six 28-day cycles, with bendamustine (120 mg/m2) given on days 1 and 2, rituximab (375 mg/m2) given on day 1. Safety is assessed weekly, and disease status is evaluated at completion of every two cycles. A two-stage Simon design is used to initially confirm response.

Results:

An ORR of 60%, required by the study design, was achieved in the first 15 subjects. Currently, the intent-to-treat population includes 25 subjects, (median age 75, range, 62-90) with ECOG status at baseline of 0 (n=10, 40%), 1 (n=13, 52%), and 2 (n=2, 8%). 76 cycles have been administered to the modified intent-to-treat population (23 subjects, median 3 cycles per subject). Current efficacy data received for 17 evaluable subjects results in ORR of 53% (CR 12%, PR 41%), with SD (18%) and PD (29%). Treatment related adverse events include one grade 4 neutropenia.

Conclusions:

Thus far, the data suggests that BR is active and well-tolerated. This study is ongoing, data regarding response and toxicity will be updated upon completion.

Background: Diffuse Large B-Cell Lymphoma

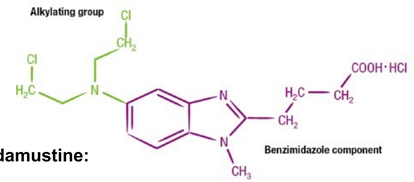
Diffuse Large B-Cell Lymphoma (DLBCL):

- Most common form of non-Hodgkin's lymphoma (NHL)
- Fast-growing, aggressive form
- Accounts for 35% of NHL population
- U.S. yearly incidence is 7 in 100,000
- Average age at diagnosis is 64
- 40% of cases develop outside the lymphatic system

Relapsed / Refractory DLBCL:

- 40-60% of patients who achieve complete remission ultimately relapse
- 50% of R/R patients do not respond to initial rituximab therapy
- 60% of prior rituximab responding patients show no benefit from re-treatment

Background: Study Treatment



Bendamustine:

- Bifunctional alkylating agent with a purine-like benzimidazole ring
- Study Dose: 120 mg/m^2 IV, Days 1, 2 of Cycles 1-6

Rituximab:

- Chimeric human/murine antibody directed against CD20
- Study Dose: 375 mg/m^2 IV, Day 1 of Cycles 1-6

Methods: Study Design / Objectives

Study Design / Objectives:

- Single-arm, phase II, open-label, two-stage Simon design (response assessed after first 15 patients; if ≥ 8 patients respond, study continued)
- Primary Objective: Overall Response Rate
- Secondary Objective(s): Duration of Response, Time to Progression, Progression-Free Survival, Safety Profile

Methods: Major Inclusion / Exclusion Criteria

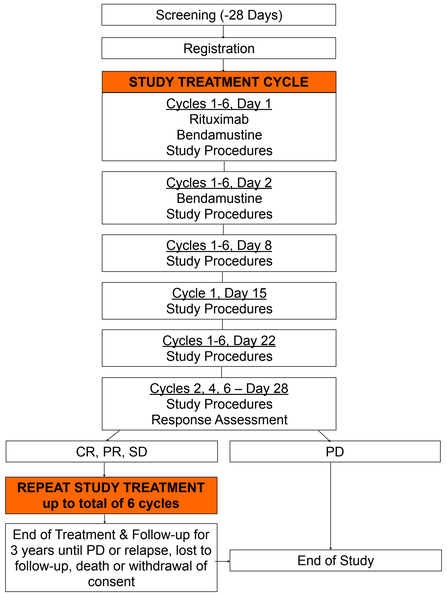
Major Inclusion Criteria:

- Confirmed diagnosis of CD20-positive DLBCL
- At least 1 measurable lesion > 1.5 cm
- ECOG performance status 0-2
- LVEF within institutional levels of normal
- Relapsed or Refractory (progression or non-response within last 60 days) to at least 1 prior therapeutic treatment

Major Exclusion Criteria:

- Any active CNS metastases
- Prior treatment with bendamustine
- Known anaphylaxis or resistance to rituximab
- Active or seropostitive for HIV, HBV or HCB infection
- Thyroid function unmaintained within normal range
- Other cancer except non-melanoma skin cancer or *in situ* of cervix or breast

Methods: Study Schema



Results: Demography

*Intent-to-treat Population (N=25)

Age	Median	75
	Range	62-90
Gender	Male	12 (48%)
	Female	13 (52%)
ECOG	0	10 (40%)
	1	13 (52%)
	2	2 (8%)
Bone Marrow Involvement at Baseline	Positive	2 (8%)
	Negative	21 (84%)
	Unknown	2 (8%)
Baseline RIPI (Revised International Prognostic Index Score)	0	0
	1	1 (4%)
	2	8 (32%)
	3	10 (40%)
	4	6 (24%)
	5	0
Previous Lines of Chemotherapy Treatment	1	19 (76%)
	2	1 (4%)
	3	2 (8%)
	4	2 (8%)
	5	1 (4%)
Previous Other Treatments	Allogenic Stem Cell Transplant	0
	Autologous Stem Cell Transplant	2 (8%)
	Oncologic Surgery	0
	Radiotherapy	7 (28%)
	Radioimmunotherapy	1 (4%)

Results: Best Response by Baseline RIPI Score

*Modified Intent-to-treat Population (N=17)

	RIPI Score					
	0	**1**	**2**	**3**	**4**	**5**
CR	0	0	1	1	0	0
PR	0	0	3	2	2	0
SD	0	0	1	2	0	0
PD	0	0	0	3	2	0

Results: Responses by Cycle

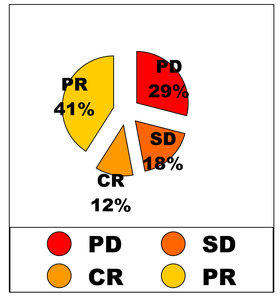
*Modified Intent-to-treat Population (N=17)

	Grade 2 (n=17)		Grade 4 (n=9)		Grade 6 (n=4)	
	n	%	n	%	n	%
CR	1	6	1	11	2	50
PR	8	47	3	33	2	50
SD	3	18	2	23	0	0
PD	5	29	3	33	0	0

Results: Objective Response Rate

*Modified Intent-to-treat Population (N=17)

	n	%
Objective Response Rate (CR + PR)	9	53
Complete Remission (CR)	2	12
Partial Remission (PR)	7	41
Stable Disease (SD)	3	18
Progressive Disease (PD)	5	29



Results: Treatment Related Grade 3 / 4 Adverse Events

*Safety Population (N=23)

MedDRA LLT	Grade 3	Grade 4
Neutrophil Count Decreased	3	1
White Blood Cell Count Decreased	3	0
Hemoglobin Decreased	2	0
Platelet Count Decreased	1	0

Results: Patient Discontinuation

*Intent-to-treat Population (N=25)

End of Study Reason	(n=11)
Progressive Disease	8
Patient Withdrew Consent	3

Conclusions

This study is designed to evaluate the combination therapy BR (bendamustine, a bifunctional alkylating agent, with rituximab, an anti-CD20 antibody) as a treatment option for patients with relapsed or refractory, CD20 positive diffuse large B-cell lymphoma. Stage 1 of the two-stage Simon design has been completed, and the criteria for continuation has been met. Overall, the data thus far suggests that BR is active and well-tolerated.