The Oncologist®

Clinical Trial Results

Phase II Study of Bendamustine and Ofatumumab in Elderly Patients with Newly Diagnosed Diffuse Large B-Cell Lymphoma Who Are Poor Candidates for R-CHOP Chemotherapy

Ian W. Flinn,[a,b] Jack Erter,[a,b] Davey B. Daniel,[a,b] Joseph R. Mace,[c] Jesus G. Berdeja[a,b]

[a]Sarah Cannon Research Institute, Nashville, Tennessee, USA; [b]Tennessee Oncology, PLLC, Nashville, Tennesse, USA; [c]Florida Cancer Specialists, St. Petersburg, Florida, USA

Trial Information

- **ClinicalTrials.gov Identifier:** NCT01626352
- **Sponsor:** Sarah Cannon Research Institute
- **Principal Investigator:** Ian W. Flinn
- **IRB Approved:** Yes

Lessons Learned

- The combination of ofatumumab and bendamustine in elderly patients with diffuse large B-cell lymphoma demonstrated modest efficacy compared with standard of care.
- The poor response may have been due to patient age and the high rate of treatment discontinuation.

Abstract

Background. This phase II trial evaluated the efficacy of bendamustine and ofatumumab in elderly patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) who were not candidates for rituximab cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

Methods. Patients received IV 90 mg/m^2 bendamustine on days 1 and 2 of cycles 1 through 6 and IV 1,000 mg ofatumumab on days 1 and 8 of cycle 1 and on day 1 of cycles 2 through 6. Both drugs were administered at the U.S. Food and Drug Administration-approved dose for combination therapy. All patients received premedications before each infusion of ofatumumab and hematopoietic growth factors. Treatment was administered in 21-day cycles, with restaging after cycle 3 and cycle 6. The primary endpoint was complete response rate (CRR).

Results. Twelve of 21 enrolled patients completed treatment; median age was 83 years. The most common reasons for treatment discontinuation were disease progression (three patients), intercurrent illness (two patients), and death (one patient due to drug-related sepsis and bowel necrosis and one patient due to unknown cause). Thrombocytopenia (14%), neutropenia (10%), diarrhea (10%), vomiting (10%), and dehydration (10%) were the most common grade ≥3 treatment-related adverse events. The overall response rate was 90.5% and the CRR was 33.3%. Median progression-free survival (PFS) and overall survival (OS) were 8.6 and 12.0 months, respectively.

Conclusion. The combination of ofatumumab and bendamustine is feasible in elderly patients with DLBCL. ***The Oncologist*** 2019;24:1035–e623

Discussion

The R-CHOP combination is considered standard of care for patients with DLBCL [1], although there is concern about increased toxicity in the elderly population [2]. Older patients with DLBCL have been shown to have a worse outcome than corresponding younger patients on the same treatment regimen [3]. A lower tolerance to treatment, comorbidities, and an inferior immunosurveillance have been analyzed and reviewed as important causes for the differences in outcome between young and older patients with DLBCL [2]. For this reason, alternative effective treatment modalities with less toxicity are required in the elderly population.

Bendamustine is an alkylating agent that causes intra- and interstrand cross-links between DNA bases [4]. Studies of the combination of bendamustine and rituximab in elderly patients have demonstrated a complete response rate of approximately 50%, and the combination was associated with lower rates of grade ≥3 hematologic toxicities than R-CHOP [5–7].

Correspondence: Ian W. Flinn, M.D., Ph.D., Sarah Cannon Research Institute, 25th Ave. North, Suite 412, Nashville, Tennessee 37203, USA. Telephone: 615-320-5090; e-mail: iflinn@tnonc.com Received November 7, 2018; accepted for publication April 6, 2019; published Online First on May 9, 2019. http://dx.doi.org/10.1634/theoncologist.2019-0286

Table 1. Treatment response (n = 21)

Assessment	Results
Overall response rate, *n* (%)	19 (90.5)
Complete response	7 (33.3)
Partial response	12 (57.1)
Stable disease	1 (4.8)
Progressive disease	1 (4.8)
Unevaluable	0
PFS, median (90% CI), months	8.6 (4.6–10.6)
TTP, median (90% CI), months	10.5 (4.5, not reached)
OS, median (90% CI), months	12.0 (5.9–30.8)

Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

Ofatumumab is fully human anti-CD20 antibody, well tolerated by elderly patients, that induces B-cell lysis primarily through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity [8]. The antibody recognizes a different epitope of the CD20 molecule than rituximab [9, 10].

In this study, we evaluated the safety and efficacy of ofatumumab plus bendamustine for the treatment of DLBCL in the elderly population. The drug combination is safe, but efficacy was modest. At 33.3% (Table 1), the complete response rate was lower than the historic CRRs of approximately 50% in elderly patients treated with bendamustine plus rituximab [5–7]. However, it should be noted that the median PFS and median OS in this study, at 8.6 months and 12 months respectively, were generally consistent with those observed in similar populations treated with bendamustine plus rituximab [5–7]. The poor response rate seen here may have been due, in part, to patient age and general health. The inclusion criteria for this study required patients to be ≥70 years old and also to be considered poor candidates for R-CHOP therapy. Elderly patients unable to tolerate R-CHOP treatment may still derive some benefit from this treatment regimen. Further studies are needed to better identify less toxic, but more efficacious, therapies for DLBCL for patients too frail to receive R-CHOP.

Trial Information	
Disease	Lymphoma – non-Hodgkins
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study – 1	Phase II
Type of Study – 2	Single arm
Primary Endpoint	Complete response rate
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Overall response rate
Secondary Endpoint	Overall survival
Investigator's Analysis	Level of activity did not meet planned endpoint

Drug Information	
Drug 1	
Generic/Working Name	Bendamustine
Trade Name	Treanda
Company Name	Cephalon, Inc.
Drug Type	Antineoplastic/cytotoxic
Drug Class	Alkylating agent
Dose	90 milligrams (mg) per squared meter (m^2)
Route	IV
Schedule of Administration	Days 1 and 2 of cycles 1 through 6
Drug 2	
Generic/Working Name	Ofatumumab
Trade Name	Arzerra
Company Name	GlaxoSmithKline
Drug Type	Antibody
Drug Class	CD20
Dose	1000 milligrams (mg) per flat dose

Route	IV
Schedule of Administration	Days 1 and 8 during cycle 1 only and on day 1 of cycles 2 through 6

Patient Characteristics	
Characteristic	**(*n* = 21), *n* (%)**
Median age, years (range)	83 (73–88)
Sex	
Male	9 (42.9)
Female	12 (57.1)
Race	
White	20 (95.2)
American Indian/Alaskan Native	1 (4.8)
Modified Ann Arbor stage at diagnosis	
Stage III	14 (66.7)
Stage IV	7 (33.3)
Median B2-microglobin (range)	3 (0–7)
B2-microglobin normality	
Abnormal	18 (85.7)
Normal	3 (14.3)
Cancer Types or Histologic Subtypes	DLBCL, 21

Primary Assessment Method	
Title	Complete Response (CR)
Number of patients screened	21
Number of patients enrolled	21
Number of patients evaluable for toxicity	21
Number of patients evaluated for efficacy	21
Evaluation method	International Working Group for Response Categories
Response Assessment CR	*n* = 7 (33.3%)
Response Assessment PR	*n* = 12 (57.1%)
Response Assessment SD	*n* = 1 (4.8%)
Response Assessment PD	*n* = 1 (4.8%)
Response Assessment Other	*n* = 0 (0%)
(Median) Duration Assessments PFS	8.6 months, CI: 90%
(Median) Duration Assessments TTP	10.5 months, CI: 90%
(Median) Duration Assessments OS	12.0 months, CI: 90%

Adverse Events

All Cycles

Name	NC/NA, %	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5, %	All grades, %
Platelet count decreased	81	0	5	14	0	0	19
White blood cell decreased	95	0	0	0	5	0	5
Neutrophil count decreased	80	5	5	5	5	0	20
Anemia	76	14	5	5	0	0	24

Lymphocyte count decreased	95	0	0	5	0	0	5
Vomiting	85	5	0	10	0	0	15
Fatigue	48	33	19	0	0	0	52
Nausea	56	29	10	5	0	0	44
Cough	71	19	10	0	0	0	29
Anorexia	76	5	14	5	0	0	24
Diarrhea	75	10	5	10	0	0	25
Constipation	81	19	0	0	0	0	19
Edema	80	10	10	0	0	0	20
Infusion-related reaction	80	10	10	0	0	0	20
Pruritus	81	0	19	0	0	0	19
Weight loss	80	10	10	0	0	0	20
Allergic rhinitis	90	10	0	0	0	0	10
Back pain	90	5	5	0	0	0	10
Chest pain	90	5	5	0	0	0	10
Dehydration	90	0	0	10	0	0	10
Dyspnea	90	0	5	5	0	0	10
Headache	90	10	0	0	0	0	10
Hyperglycemia	90	5	5	0	0	0	10
Hypoglycemia	90	5	5	0	0	0	10
Hypokalemia	90	0	5	5	0	0	10
Hypomagnesemia	90	0	5	0	5	0	10
Hypotension	90	0	10	0	0	0	10
Insomnia	90	5	5	0	0	0	10
Urinary frequency	90	5	5	0	0	0	10
Urinary tract infection	90	0	5	5	0	0	10
Urticaria	90	0	5	5	0	0	10
Abdominal distension	95	0	0	5	0	0	5
Abdominal infection	95	0	0	5	0	0	5
Abdominal pain	95	0	5	0	0	0	5
Alkaline phosphatase increased	95	5	0	0	0	0	5
Allergic reaction	95	5	0	0	0	0	5
Animal bite	95	5	0	0	0	0	5
Arthralgia	95	0	5	0	0	0	5
Ascites	95	0	5	0	0	0	5
Aspartate aminotransferase increased	95	5	0	0	0	0	5
Asthenia	95	5	0	0	0	0	5
Pain	95	5	0	0	0	0	5
Bladder infection	95	0	0	5	0	0	5
Bone pain	95	0	0	5	0	0	5
Chills	95	5	0	0	0	0	5
Creatinine increased	95	0	5	0	0	0	5
Depression	95	0	5	0	0	0	5
Dry skin	95	5	0	0	0	0	5
Dysgeusia	95	0	5	0	0	0	5
Dyspepsia	95	5	0	0	0	0	5
Ear pain	95	0	5	0	0	0	5
Erythema multiforme	95	0	5	0	0	0	5
Fall	95	0	5	0	0	0	5

Fever	95	5	0	0	0	0	5
Upper gastrointestinal hemorrhage	95	0	0	5	0	0	5
Psychiatric disorders - Hallucination	95	5	0	0	0	0	5
Hearing impaired	95	0	5	0	0	0	5
Herpes zoster	95	0	5	0	0	0	5
Blood bilirubin increased	95	5	0	0	0	0	5
Hypercalcemia	95	0	0	5	0	0	5
Hyperuricemia	95	0	0	0	5	0	5
Hypoalbuminemia	95	0	5	0	0	0	5
Hypocalcemia	95	0	0	5	0	0	5
Hyponatremia	95	5	0	0	0	0	5
Mitral valve prolapse	95	0	0	5	0	0	5
Mucositis	95	5	0	0	0	0	5
Nasal congestion	95	0	5	0	0	0	5
Necrosis	95	0	0	0	0	5	5
Neuropathy	95	5	0	0	0	0	5
Paresthesia	95	5	0	0	0	0	5
Peripheral neuropathy	95	5	0	0	0	0	5
Pleural effusion	95	0	5	0	0	0	5
Pneumonitis	95	0	0	5	0	0	5
Sepsis	95	0	0	0	5	0	5
Sinusitis	95	0	5	0	0	0	5
Skin reaction	95	5	0	0	0	0	5
Syncope	95	0	0	5	0	0	5
Thromboembolic event	95	0	0	0	5	0	5
Tremor	95	0	5	0	0	0	5
Tumor lysis syndrome	95	0	0	5	0	0	5
Upper respiratory infection	95	0	5	0	0	0	5
Upper respiratory symptoms	95	5	0	0	0	0	5

Abbreviations: NC/NA, no change from baseline/no adverse event.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Level of activity did not meet planned endpoint

Over 50% of patients with diffuse large B-cell lymphoma (DLBCL) are 65 years of age or older [5], and older patients with DLBCL have been shown to have a worse outcome than younger patients [6]. In this study, we evaluated the safety and efficacy of bendamustine plus the anti-CD20 monoclonal antibody ofatumumab for the treatment of DLBCL in older patients who were not good candidates for rituximab cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy. Treatment summary is shown in Table 2. The most common grade ≥3 AEs were thrombocytopenia (14%), neutropenia (10%), diarrhea (10%), vomiting (10%), and dehydration (10%; Table 3). The overall response rate was 90.5%, and the complete response (CR) rate was 33.3%. Median progression-free survival (PFS) was 8.6 months (Fig. 1), median time to progression was 10.5 months (Fig. 2), and median overall survival was 12.0 months (Fig. 3). The study was closed early because of low accrual. This study demonstrated the safety of the bendamustine plus ofatumumab combination for the treatment of DLBCL in this patient population. However, with a CR rate of 33.3%, this drug combination showed modest efficacy compared with standard of care, but median survival was comparable to bendamustine plus rituximab.

The study was discontinued early because of low enrollment rates. The low CR rate for patients on this study regimen may have dampened enthusiasm for later patient enrollment. In addition, the common use of other treatment regimens such as rituximab plus bendamustine may have resulted in fewer patients entering the study. The combination of rituximab plus bendamustine treatment regimens has demonstrated some efficacy in older patients with DLBCL [5–7], but there remains a critical need for safer and more effective therapies.

Although the efficacy of ofatumumab plus bendamustine as first-line treatment for DLBCL in older patients was modest,

elderly patients unable to tolerate R-CHOP treatment may still derive some benefit from this treatment regimen. The drug combination was safe in the study population, and both PFS and overall survival were similar to those seen in patients treated with rituximab and bendamustine [5–7]. There may also be some use for ofatumumab in treating rituximab-refractory patients. Ofatumumab targets a different epitope on the CD20 molecule [9, 10] than rituximab, and the drug has been shown to be active in patients with rituximab-refractory follicular lymphoma [11]. Similarly, it may have efficacy in the treatment of rituximab-refractory DLBCL.

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Disclosures

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figures and Tables

Table 2. Treatment summary (*n* = 21)

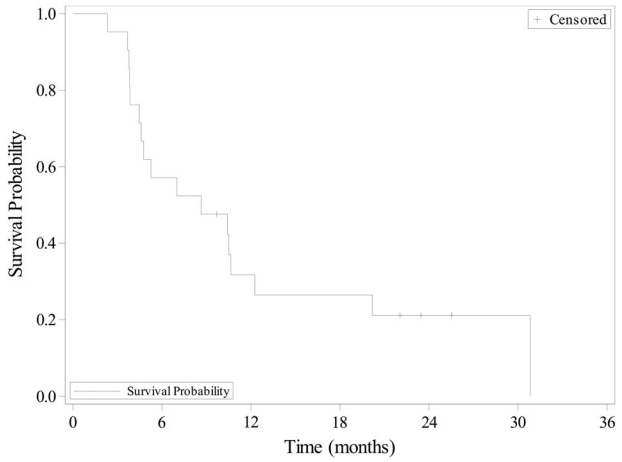
Treatment factor	*n* (%)
Patients off treatment	21 (100)
Completed treatment	12 (57.1)
Disease progression	3 (14.3)
Intercurrent event/illness[a]	2 (9.5)
Death[b]	2 (9.5)
Patient request	1 (4.8)
Noncompliance	1 (4.8)
Cause of death – all deaths (includes EOS and follow-up)	14 (66.7)
Death due to AE (bowel necrosis)	1 (4.8)
Death due to disease	6 (28.6)
Death due to intercurrent illness	1 (4.8)
Death cause unknown	6 (28.6)
Median follow-up, month (range)	9.9 (2.3–50.4)

[a]One patient with poor posthospitalization status, including G3/2 unrelated diarrhea; one patient, both physician/patient decision (due to valvular heart disease).
[b]Causes of death: One patient, treatment-related sepsis and bowel necrosis; one patient, cause unknown, unrelated.
Abbreviations: AE, adverse event; EOS, end of study.

Table 3. Toxicities grade ≥3 (*n* = 21)

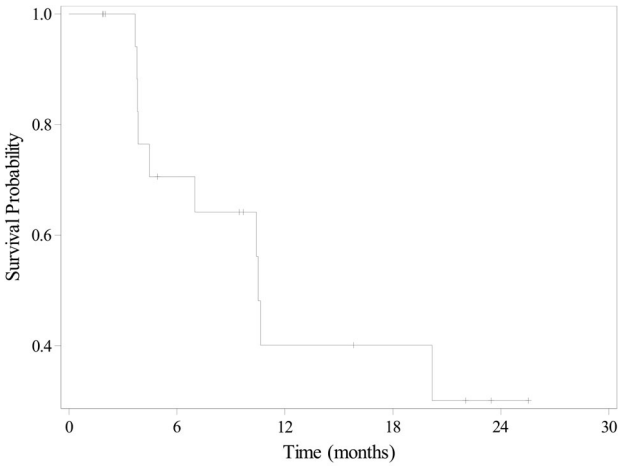
Toxicity	Grade 3, *n* (%)	Grade 4, *n* (%)	Grade 5, *n* (%)	Total (G3–G5), *n* (%)
Hematologic[a]				
Thrombocytopenia	3 (14)	0	0	3 (14)
Neutropenia	1 (5)	1 (5)	0	2 (10)
Leukopenia		1 (5)	0	1 (5)
Anemia	1 (5)	0	0	1 (5)
Lymphopenia	1 (5)	0	0	1 (5)
Nonhematologic[b]				
Vomiting	2 (10)	0	0	2 (10)
Necrosis	0	0	1 (5)	1 (5)
Hypomagnesemia	0	1 (5)	0	1 (5)
Hyperuricemia	0	1 (5)	0	1 (5)
Sepsis	0	1 (5)	0	1 (5)
Anorexia	1 (5)	0	0	1 (5)
Diarrhea	1 (5)	0	0	1 (5)
Uticaria	1 (5)	0	0	1 (5)
Fatigue	1 (5)	0	0	1 (5)
Pneumonia	1 (5)	0	0	1 (5)
Dehydration	1 (5)	0	0	1 (5)
Hypocalcemia	1 (5)	0	0	1 (5)
Hypokalemia	1 (5)	0	0	1 (5)
Tumor lysis syndrome	1 (5)	0	0	1 (5)

[a]All hematologic toxicities reported, regardless of causality.
[b]Only related nonhematologic toxicities are reported.



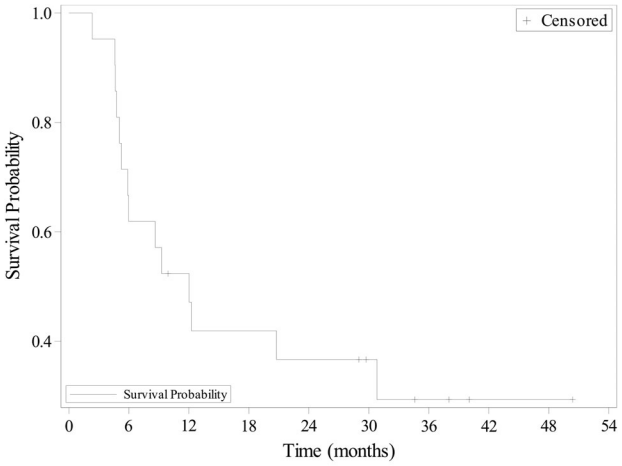
	All Patients
Sample Size	21
Median PFS (90% CI)	8.6 months (4.6, 10.6)
12-month PFS probability (90% CI)	31.7% (15.9%, 48.8%)

Figure 1. Progression-free survival (n = 21).
Abbreviations: CI, confidence interval; PFS, progression-free survival.



	All Patients
Sample Size	21
Median TTP (90% CI)	10.5 months (4.5, not reached)
12-month TTP probability (90% CI)	40.1% (19.1%, 60.4%)

Figure 2. Time to progression (n = 21).
Abbreviations: CI, confidence interval; TTP, time to progression.



	All Patients
Sample Size	21
Median OS (90% CI)	12.0 months (5.9, 30.8)
12-month OS probability (90% CI)	52.4% (33.4%, 68.3%)

Figure 3. Overall survival (n = 21).
Abbreviations: CI, confidence interval; OS, overall survival.