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

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TRIAL INFORMATION

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

LESIONS 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/m² 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 regimens [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].
Ofatumumab is a 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.

### 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)     |
| Un evaluable                      | 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.

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### 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 (m²) |
| 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

| 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 | 0 | 0 | 20 |
| Anemia | 76 | 14 | 5 | 5 | 0 | 0 | 24 |
| Event                                      | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Grade 6 | Grade 7 |
|--------------------------------------------|---------|---------|---------|---------|---------|---------|---------|
| 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      |
| Hypertension                               | 90      | 0       | 10      | 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                       | 90      | 0       | 0       | 5       | 0       | 0       | 10      |
| Abdominal infection                        | 95      | 0       | 0       | 5       | 0       | 0       | 10      |
| 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 0 5
Psychiatric disorders - Hallucination 95 5 0 0 0 0 0 5
Hearing impaired 95 0 5 0 0 0 0 5
Herpes zoster 95 0 5 0 0 0 0 5
Blood bilirubin increased 95 5 0 0 0 0 0 5
Hypercalcemia 95 0 0 5 0 0 0 5
Hyperuricemia 95 0 0 0 5 0 0 5
Hypoalbuminemia 95 0 5 0 0 0 0 5
Hypocalcemia 95 0 0 5 0 0 0 5
Hyponatremia 95 5 0 0 0 0 0 5
Mitral valve prolapse 95 0 0 5 0 0 0 5
Mucositis 95 5 0 0 0 0 0 5
Nasal congestion 95 0 5 0 0 0 0 5
Necrosis 95 0 0 0 0 0 5 5
Neuropathy 95 5 0 0 0 0 0 5
Paresthesia 95 5 0 0 0 0 0 5
Peripheral neuropathy 95 5 0 0 0 0 0 5
Pleural effusion 95 0 5 0 0 0 0 5
Pneumonitis 95 0 0 5 0 0 0 5
Sepsis 95 0 0 0 5 0 0 5
Sinusitis 95 0 5 0 0 0 0 5
Skin reaction 95 5 0 0 0 0 0 5
Syncope 95 0 5 0 0 0 0 5
Thromboembolic event 95 0 0 0 5 0 0 5
Tremor 95 0 5 0 0 0 0 5
Tumor lysis syndrome 95 0 0 5 0 0 0 5
Upper respiratory infection 95 0 5 0 0 0 0 5
Upper respiratory symptoms 95 5 0 0 0 0 0 5

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

Assessment, Analysis, and Discussion

Completion

Investigator’s Assessment Study completed
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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### 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)               | 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)                    |
| Urticaria         | 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.
Figure 1. Progression-free survival (n = 21).
Abbreviations: CI, confidence interval; PFS, progression-free survival.

| Sample Size | All Patients |
|-------------|--------------|
| Median PFS (90% CI) | 8.6 months (4.6, 10.6) |
| 12-month PFS probability (90% CI) | 31.7% (15.5%, 48.8%) |

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

| Sample Size | All Patients |
|-------------|--------------|
| Median TTP (90% CI) | 10.5 months (6.5, not reached) |
| 12-month TTP probability (90% CI) | 40.1% (15.1%, 60.4%) |

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

| Sample Size | All Patients |
|-------------|--------------|
| Median OS (90% CI) | 12.0 months (9.9, 30.8) |
| 12-month OS probability (90% CI) | 52.4% (33.4%, 68.3%) |

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