The Oncologist®

Clinical Trial Results

A Phase II Trial Evaluating the Safety of Rapid Infusion of Ofatumumab in Patients with Previously Treated Chronic Lymphocytic Leukemia

William Donnellan,[a,b] Jesus G. Berdeja,[a,b] Diana Shipley,[a,b] Edward R. Arrowsmith,[a,b] David Wright,[a,c] Scott Lunin,[a,c] Richard Brown,[a,c] James H. Essell,[a,d] Ian W. Flinn[a,b]

[a]Sarah Cannon Research Institute, Nashville, Tennessee, USA; [b]Tennessee Oncology, PLLC, Nashville, Tennessee, USA; [c]Florida Cancer Specialists, Venice, Florida, USA; [d]Oncology Hematology Care, Cincinnati, Ohio, USA

Trial Information

- **ClinicalTrials.gov Identifier**: NCT01848145
- **Sponsor(s)**: Novartis and GlaxoSmithKline
- **Principal Investigator**: Ian W. Flinn
- **IRB Approved**: Yes

Lessons Learned

- Ofatumumab infusion reactions can be diminished by escalating the dose rate in individual patients in sequential infusions.

Abstract

Background. Ofatumumab (OFA) is a fully humanized, anti-CD20 antibody approved for use in chronic lymphocytic leukemia (CLL). The recommended administration requires long infusion times. We evaluated an accelerated infusion regimen of 2 hours.

Methods. The first dose of OFA (300 mg) was given on week 1 day 1 starting at 3.6 mg/hour and doubling every 30 minutes until a rate of 240 mg/hour was reached. If tolerated, the second dose (1,000 mg) was given on week 1 day 3 starting at 50 mg/hour and doubling every 30 minutes until a rate of 800 mg/hour was reached. If tolerated, the third dose (2,000 mg) was given on week 2 day 1 at 800 mg/hour over the first 30 minutes and, if tolerated, at 1,068 mg/hour over the next 90 minutes (goal infusion time: 120 minutes). Subsequent OFA infusions were administered weekly in the same manner for 8 weeks, and then monthly for 4 months.

Results. Thirty-four patients were treated. Most infusion-related reactions occurred during the first and second infusion. Eighty-seven percent (87%) of patients finished the third infusion within 15 minutes of the planned 2 hours and only one had an infusion reaction.

Conclusion. Using this stepped-up dosing regimen, a rapid infusion of OFA is safe and well tolerated. ***The Oncologist*** 2017;22:1156–e111

Discussion

Ofatumumab, obinutuzumab, and rituximab are all effective anti-CD20 monoclonal antibodies that can cause side effects during or after infusion. However, previous studies using rituximab show that infusion-related reactions can be overcome by first starting with a lower dose and then giving a second larger dose within a few days of the initial dose. Such an approach allows for the rapid infusion of rituximab in subsequent doses in patients with CLL. Our completed phase II study of ofatumumab in patients with CLL clearly corroborates the feasibility of reducing the frequency of infusion-related reactions by using this same approach. As shown in Table 1 and Table 2, the number of patients with CLL that experienced infusion-related reactions steadily decreased at each infusion (infusion 1: 62%; infusion 2: 12%, and infusion 3: 3%). These results underscore that our study design was successful and appropriate for the 97% of patients with CLL who completed infusion 3 and, of those, the 87% who completed infusion 3 within the 2-hour treatment plan.

A stepped-up dosing schedule of ofatumumab has implications that go beyond minimizing infusion-related reactions and avoiding wasted medication; it also addresses quality-of-life concerns. The less time that patients spend in the oncologist's office equates to more time that patients can spend doing more pleasurable activities.

Correspondence: Ian W. Flinn, M.D., Ph.D., Sarah Cannon Research Institute, Tennessee Oncology, PLLC, 25th Avenue North, Suite 412, Nashville, Tennessee 37203, USA. Telephone: 615-320-5090; e-mail: iflinn@tnonc.com Received April 13, 2017; accepted for publication May 9, 2017; published Online First on July 7, 2017. http://dx.doi.org/10.1634/theoncologist.2017-0236

Table 1. Summary of ofatumumab infusion times

Infusion times	Infusion 1	Infusion 2	Infusion 3
Started infusion, *n*	34	33	31
Patients who received a full dose infusion, *n* (%)	31 (91%)	31 (94%)	31 (100%)
Patients who completed infusion within 15 minutes of the 2-hour treatment plan, *n* (%)	1 (3%)	24 (73%)	26 (84%)
Patients with infusion-related reactions, *n* (%)	21 (62%)	4 (12%)	1 (3%)
Mean infusion time, minutes (range)	334 (210–475)	193 (130–285)	126 (78–246)

Table 2. Infusion-related toxicities

Infusion 1			
Infusion-related reaction	**Patients, *n* = 21, *n* (%)**	**Grade 1/2**	**Grade 3**
Nausea	2 (10%)	2	—
Itching	3 (14%)	3	—
Fever	1 (5%)	1	—
Shortness of breath	2 (10%)	1	1
Infusion-related reaction	1 (5%)	1	—
Back pain	1 (5%)	1	—
Hypersensitivity reaction	1 (5%)	1	—
Facial flushing, dry/burning eyes	1 (5%)	1	—
Face flushed	1 (5%)	—	1
Hives	3 (14%)	2	1
Rash (infusion reaction)	3 (14%)	3	—
Dry mouth (infusion reaction)	1 (5%)	1	—
Abdominal pain	1 (5%)	1	—
Pruritic rash (back, scalp, forehead, neck)	2 (10%)	2	—
Tickling throat, cough	1 (5%)	1	—
Rigors	1 (5%)	1	—
Sweating on back	1 (5%)	1	—
Ear/throat itching (infusion reaction)	1 (5%)	1	—
Chills	1 (5%)	1	—
Infusion 2			
Infusion-related reaction	**Patients, *n* = 4, *n* (%)**	**Grade 1 /2**	**Grade 3**
Sneezing, eyes swelling, redness or rash	1 (5%)	1	—
Back pain	1 (5%)	1	—
Shortness of breath	1 (5%)	—	1
Flushed feeling (heart racing)	1 (5%)	1	—
Infusion 3			
Infusion-related reaction	**Patients, *n* = 1, *n* (%)**	**Grade 1 /2**	**Grade 3**
Flushing, nausea/vomiting	1 (5%)	1	—

Abbreviation: —, no occurrence.

Trial Information	
Disease	Leukemia – chronic – CLL
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	One prior regimen
Type of Study - 1	Phase II

Type of Study - 2	Single arm
Primary Endpoint	Deliverability
Secondary Endpoint	Safety
Secondary Endpoint	Objective response rate
Secondary Endpoint	Toxicity
Secondary Endpoint	Progression-free survival

Additional Details of Endpoints or Study Design

The primary endpoint was to determine the proportion of patients able to complete rapid infusion 3 within 15 minutes of the planned 2-hour treatment. Ofatumumab has been associated with infusion reactions, which have led to temporary interruption of treatment or withdrawal of treatment. To attenuate infusion-related reactions in our study, patients were premedicated 30 minutes to 2 hours prior to infusion with acetaminophen 1,000 mg p.o., diphenhydramine 50 mg p.o./IV or equivalent, and dexamethasone 10 mg IV. Dose reductions of ofatumumab were not allowed. For grade 1 or 2 infusion reactions, the infusion was temporarily interrupted. Once the patient was stable, the infusion was restarted at half of the infusion rate at the time the infusion was paused. Thereafter, the rate could be increased at the discretion of the investigator. For grade 3 infusion reactions, the infusion was interrupted and the appropriate clinical intervention was implemented. When the event decreased to grade <3, the infusion was restarted at half of the infusion rate at the time the infusion was stopped. Thereafter, the rate could be increased at the discretion of the investigator. If the grade 3 infusion reaction did not resolve or a grade 4 reaction occurred, the patient was permanently discontinued from the study treatment. Of the 21 patients who experienced an infusion reaction during the infusion, 10 patients (48%) had their infusion interrupted (stopped and restarted), 8 patients (38%) had the rate of infusion reduced, 4 patients (19%) stopped the infusion, and 2 patients (10%) had no modification to the infusion in the presence of an infusion-related reaction.

Investigator's Analysis	Active and should be pursued further

Drug Information for Phase II Ofatumumab

Drug 1	
Generic/Working name	Ofatumumab
Trade name	Arzerra
Company name	Novartis and GlaxoSmithKline
Drug type	Antibody
Drug class	CD20
Dose	Infusion 1: 300 mg; infusion 2: 1,000 mg; infusion 3: 2,000 mg milligrams (mg) per flat dose
Route	IV

Schedule of administration

Day 1: 300 mg, starting at 3.6 mg/hour and doubling every 30 minutes until a rate of 240 mg/hour was reached.

Day 3: 1,000 mg, starting at 50 mg/hour and doubling every 30 minutes until a rate of 800 mg/hour was reached.

Day 8: 2,000 mg; if tolerated, the third dose was given on week 2 day 1 at 800 mg/hour over the first 30 minutes and, if tolerated, at 1,068 mg/hour over the next 90 minutes (goal infusion time 120 minutes).

Premedication regimen (30 minutes to 2 hours before treatment): acetaminophen 1,000 mg p.o.; diphenhydramine 50 mg p.o./IV or equivalent; dexamethasone 10 mg IV.

28-day cycle with ofatumumab.

Patient Characteristics for Phase II Ofatumumab

Number of patients, male	17
Number of patients, female	17
Stage	Rai stage 0: 3 (9%) Rai stage 1: 8 (23%) Rai stage 2: 7 (21%) Rai stage 3: 4 (12%) Rai stage 4: 11 (32%) Unknown: 1 (3%)
Age	Median (range): 70 (53–89)
Number of prior systemic therapies	Median (range): 1 (1–5)

IgVH mutation status	
Mutated	9 (26%)
Non-mutated	18 (53%)
Not done	7 (21%)
CD38	
Positive	13 (38%)
Negative	18 (53%)
Not done	3 (9%)
ZAP-70	
Positive	18 (53%)
Negative	5 (15%)
Unknown	11 (32%)
FISH	
Normal	8 (24%)
Abnormal	25 (73%)
11q del	8 (24%)
13q del	15 (44%)
17p del	6 (18%)
Trisomy 12	8 (24%)
Unknown/Not done	1 (3%)
Cancer Types or Histologic Subtypes	Chronic lymphocytic leukemia: 34 Chronic lymphocytic leukemia, poor risk: 13

Primary Assessment Method for Phase II Ofatumumab	
Assessment	
Number of patients enrolled	13
Number of patients evaluable for toxicity	12
Number of patients evaluated for efficacy	12
Evaluation method	International Workshop on CLL Working Group (IWCLL WG) diagnostic criteria
Response assessment CR	$n = 0$ (0%)
Response assessment PR	$n = 0$ (0%)
Response assessment SD	$n = 11$ (92%)
Response assessment PD	$n = 1$ (8%)
Response assessment OTHER	$n = 1$ (8%)
Assessment	
Number of patients screened	34
Number of patients enrolled	34
Number of patients evaluable for toxicity	31
Number of patients evaluated for efficacy	31
Evaluation method	IWCLL WG diagnostic criteria
Response assessment CR	$n = 0$ (0%)
Response assessment PR	$n = 6$ (32%)
Response assessment SD	$n = 11$ (58%)
Response assessment PD	$n = 2$ (10%)
Response assessment OTHER	$n = 2$ (10%)
(Median) duration assessments PFS	9.2485 months, CI: 95%
(Median) duration assessments OS	0 months, CI: 95%

Response Assessment Table

Response assessment	All patients, $n = 31$, n (%)
ORR	6 (19%)
PR	6 (19%)
SD	22 (71%)
PD	3 (10%)
Unevaluable[a]	3 (10%)

[a]Three patients discontinued treatment prior to assessment.
Abbreviations: ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Adverse Events: Phase II Ofatumumab

	All Dose Levels, Cycle 1						
Name	NC/NA	1	2	3	4	5	All Grades
Injection site reaction	94%	0%	0%	6%	0%	0%	6%
Syncope	94%	0%	0%	6%	0%	0%	6%
Cardiac arrest	97%	0%	0%	3%	0%	0%	3%
Hypernatremia	97%	0%	0%	3%	0%	0%	3%
Hypophosphatemia	97%	0%	0%	3%	0%	0%	3%
Febrile neutropenia	97%	0%	0%	3%	0%	0%	3%
Anemia	94%	0%	0%	6%	0%	0%	6%
White blood cell decreased	94%	0%	0%	3%	3%	0%	6%
Platelet count decreased	79%	0%	0%	15%	6%	0%	21%
Neutrophil count decreased	85%	0%	0%	12%	3%	0%	15%
Lymphocyte count decreased	97%	0%	0%	0%	3%	0%	3%
Aspartate aminotransferase increased	97%	0%	0%	3%	0%	0%	3%
Hypertension	97%	0%	0%	3%	0%	0%	3%
Pneumonitis	97%	0%	0%	3%	0%	0%	3%
Urinary tract infection	97%	0%	0%	3%	0%	0%	3%
Generalized muscle weakness	97%	0%	0%	3%	0%	0%	3%

Adverse events account for all 34 patients.
Infusion-related reactions: one patient, grade 3 dyspnea (infusion 1 and infusion 2)/facial flushing (infusion 1); one patient, grade 3 hives (infusion 1).
Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Events

Name	Grade	Attribution
Anemia	3	Possible
Cardiac arrest	5	Unlikely
Urinary tract infection	3	Possible
Loss of consciousness	3	Possible
Pneumonia	3	Possible

Number of treatment related deaths: 0; number of related SAEs: 4.
Total number of patients with related SAEs: 3 (grade 3 SAEs, 1 patient each).
Abbreviation: SAE, serious adverse event.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active and should be pursued further

The anti-CD20 antibodies, either alone or in combination, have become an integral part of the treatment of patients with B-cell lymphomas and chronic lymphocytic leukemia (CLL). However, infusions of the antibodies can be difficult in patients with CLL due to an increase in infusion reactions such as fever and hypotension. The observation with rituximab that these reactions are generally worse on the first infusion than on subsequent doses has led to the development of alternative dosing regimens in CLL.

Ofatumumab (OFA) is a fully human anti-CD20 antibody that induces B-cell lysis primarily through complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity [1]. It recognizes a different epitope of the CD20 molecule than rituximab [2, 3]. Ofatumumab was found to be effective in the pivotal GSK 406 study of 223 patients with CLL [4]. Interestingly, $\geq$90% of patients in the GSK 406 study did not have significant infusion-related reactions following the second OFA dose. Furthermore, the majority of the reported infusion-related reactions were Grade 1 or 2 and the median duration of the third dose was 4.3 hours (range 2.6–21.3). The GSK 406 data suggest that the infusion rate of OFA could be accelerated, which aligns with other trials using the anti-CD20 antibody, rituximab [5–7].

While previous and ongoing studies report that OFA is safe, well tolerated, and has demonstrated significant activity in patients with CLL [4–7], the issue for many patients and physicians is the 4-hour infusion time. The purpose of this study was to evaluate an accelerated infusion regimen that allows the third OFA 2,000 mg infusion to be safely delivered over a 2-hour time period to patients with CLL. We found that 87% of patients could complete the third dose (2,000 mg) within 2 hours, which was the primary endpoint of the study. It is important to note that the second dose of OFA was given 2 days after the first dose rather than the standard approach of giving it a week later. This schedule was chosen based on our previous experience of giving rituximab thrice weekly and the hypothesis that giving anti-CD20 antibodies in close sequence increases tolerability by preventing rebound after the initial infusion [5].

Acknowledgments

The authors thank all participating patients, their families, and site personnel members for their very important contributions to this clinical trial. The authors would also like to thank Candice A. Shaifer, Ph.D. for medical writing assistance and editorial support.

Disclosures

William Donnellan: Pfizer (C/A), Clinical Care Options (H); **Jesus Berdeja:** Takeda, Janssen, Amgen, BMS, Celgene, Bluebird, Constellation, Abbvie, Vivolux, Novartis, Teva, Curis, Acetylon (RF). **Ian W. Flinn:** Novartis, GlaxoSmithKline (RF). The other authors indicated no financial relationships.

(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

References

1. Li B, Zhao L, Guo H et al. Characterization of a rituximab variant with potent antitumor activity against rituximab-resistant B-cell lymphoma. Blood 2009;114:5007–5015.

2. Teeling JL, Mackus WJ, Wiegman LJ et al. The biological acitivity of human CD20 monoclonal antibodies is linked to unique epitopes on CD20. J Immunol 2006;177:362–371.

3. Du J, Yang H, Guo Y et al. Structure of the Fab fragment of therapeutic antibody Ofatumumab provides insights into the recognition mechanism with CD20. Mol Immunol. 2009;46(11-12):2419–2423.

4. Wierda WG, Kipps TJ, Mayer J et al. Ofatumumab as single-agent CD-20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2010;28:1749–1755.

5. Byrd JC, Murphy T, Howard RS et al. Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. J Clin Oncol 2001;19:2153–2164.

6. O'Brien SM, Kantarjian H, Thomas DA et al. Rituximab dose-escalation trial in chronic lymphocytic leukemia. J Clin Oncol 2001;19:2165–2170.

7. Lang D, Prouse J, Barry F et al. Evaluation of the safety and feasibility of rapid rituximab infusion. Asia Pac J Clin Oncol 2012;8:71–75.

Figures and Tables

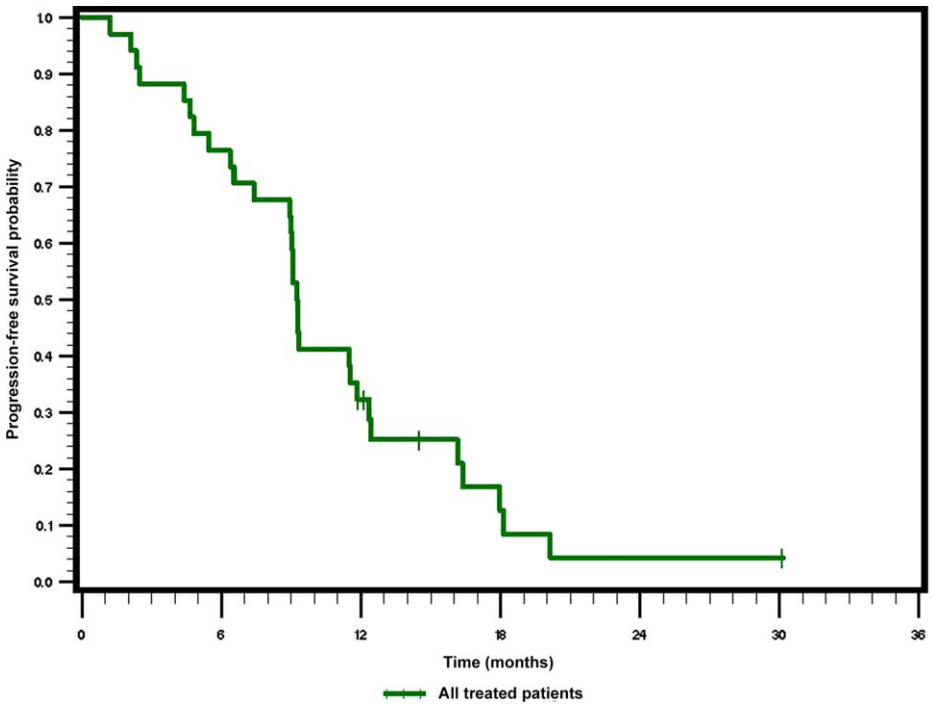

Figure 1. Progression-free survival.

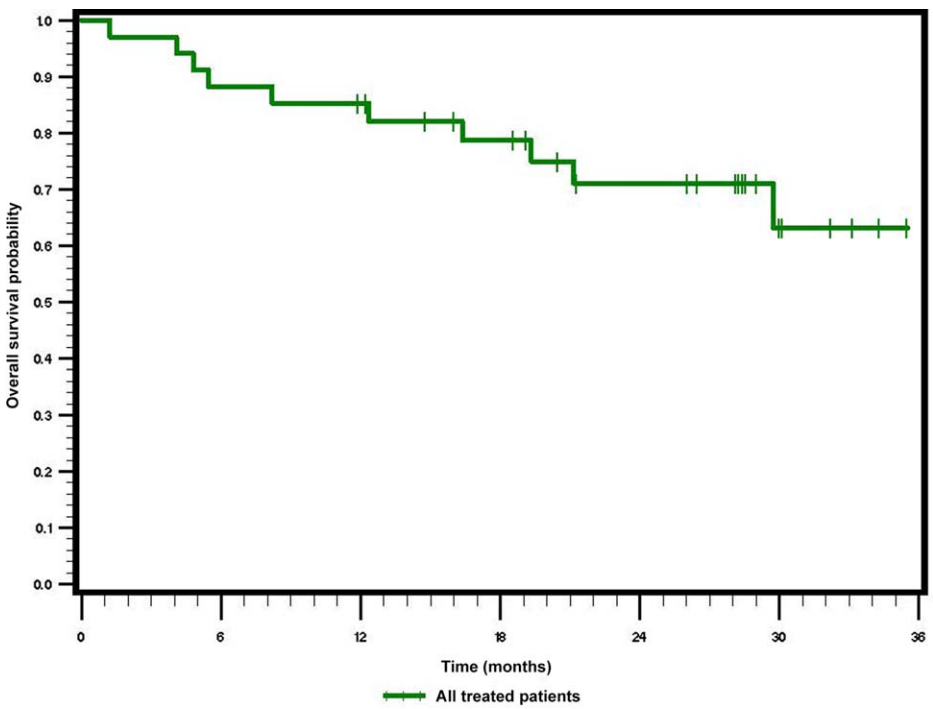

Figure 2. Overall survival.

Table 3. Patient characteristics

Characteristics	Number of patients (%)
Patients enrolled	34
Median age, years (range)	70 (53–89)
Race	
White	33 (97%)
Black	1 (1%)
Sex	
Male	17 (50%)
Female	17 (50%)
Prior anti-CD20+ therapy (rituximab and/or ofatumumab)	31 (91%)
Median β2-microglobin, mcg/mL (range)	3.8 (1.9–26.6)
Median ALC (range)	31 (0.8–131)
Median number of prior therapy regimens (range)	1 (1–5)
Median time from end of prior therapy to start of OFA infusion, approximate weeks (range)	76 (7–599)

Abbreviations: ALC, absolute lymphocytic count; OFA, ofatumumab.