Ofatumumab and Bendamustine Combination Therapy in Patients With Untreated and Relapsed Chronic Lymphocytic Leukemia: Initial Results of the Phase II Study OMB115991

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Introduction

- Ofatumumab is a human monoclonal antibody that targets a membrane-proximal epitope encompassing the small and large loops on CD20 expressed on B cells[1]
- Ofatumumab is currently approved for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab and has shown potential efficacy in treating B-cell non-Hodgkin lymphoma, such as follicular lymphoma, diffuse large B-cell lymphoma, and Waldenström's macroglobulinemia
- In vitro experiments with ofatumumab plus bendamustine, an alkylating agent with additional properties of a purine analogue, have shown significantly improved anti-tumor activity when both agents are used together compared with the individual agents used alone[2]
- Study OMB115991, a phase II, multicenter, single-arm study, was designed to investigate the safety and efficacy of ofatumumab plus bendamustine in 2 populations: patients with untreated CLL who were inappropriate for fludarabine-based therapy (previously untreated population) and patients with relapsed CLL (relapsed population)
- The following primary and secondary objectives were evaluated in the 2 separate patient populations:
  - Primary objective was to evaluate the investigator-assessed overall response rate (ORR)
  - Secondary objectives included:
    - ORR with computed tomography (CT) scan assessment, complete response (CR) rate with and without CT scan assessment, progression-free survival (PFS), overall survival (OS), time to response, duration of response, time to progression, and time to next therapy
    - Safety and tolerability*
    - Disease, prognostic, and biological marker correlation with clinical response

*AEs and SAEs were graded according the National Cancer Institute's (NCI) Common Terminology for Adverse Events (CTCAE) version 4.0, with the exception of hematologic toxicities (platelets, hemoglobin, and ANC), which were graded according to the IWCLL Grading Scale for Hematological Toxicity.

Methods

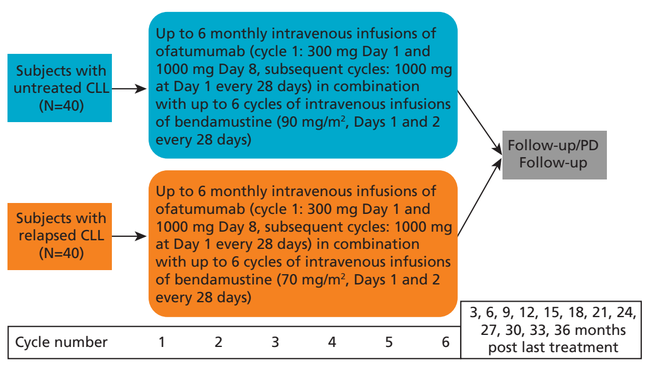
Patient Population

- Inclusion criteria included previously untreated patients considered inappropriate for fludarabine-based therapy, or relapsed patients ≥18 years of age with CLL defined by a circulating B-lymphocyte count ≥5000/μL and flow cytometry confirmation of immunophenotype with CD5, CD19, CD20, CD23, CD79b, and surface Ig, who were indicated for treatment
- Exclusion criteria included refractory disease (in the relapsed population), defined as failing to achieve a complete or partial remission/response lasting at least 6 months to the most recent therapy, an Eastern Cooperative Oncology Group performance status of ≥3, known CLL transformation, known central nervous system involvement of CLL, and known HIV-positivity

Study Design and Treatment

- Phase II, open-label, single-arm, multicenter study of ofatumumab in combination with bendamustine (Figure 1)
- Patients received pre-medications of acetaminophen 1000 mg or equivalent, antihistamine (e.g., diphenhydramine 50 mg or equivalent), and glucocorticoid equivalent to 50 mg prednisolone prior to ofatumumab infusions
- Patients received monthly intravenous infusions of ofatumumab (cycle 1: 300 mg on Day 1 and 1000 mg on Day 8; subsequent cycles 2-6: 1000 mg on Day 1 every 28 days) in combination with bendamustine on Days 1 and 2 every 28 days for up to 6 cycles
  - Patients with previously untreated CLL received a bendamustine starting dose of 90 mg/m^2. Patients with relapsed CLL received a bendamustine starting dose of 70 mg/m^2
  - A dose reduction for bendamustine, but not ofatumumab, was required for toxicity. Previously untreated patients required a bendamustine dose reduction to 60 mg/m^2 and relapsed patients required a bendamustine dose reduction to 50 mg/m^2
- Patients were evaluated for response and safety at the start of each cycle of treatment and at every 3-month follow-up visit until progression, or until 3 years after the last dose of study treatment

Figure 1. Study Schematic



CLL, chronic lymphocytic leukemia; PD, progressive disease

End Point Evaluations

Primary End Point

- ORR as determined by investigator evaluation, according to the 2008 National Cancer Institute-Sponsored Working Group guidelines,[3] measured after 3 cycles, after 6 cycles, and after the last dose of study treatment

Secondary End Points Included

- ORR with CT scan assessment
- Complete response (CR) rate
- PFS
- OS
- Time to response, duration of response, time to progression, and time to next therapy
- Safety and tolerability
- Disease, prognostic, and biological marker correlation

Statistical Analyses

- The study was designed to estimate the ORR for the 2 study populations, i.e., patients with previously untreated CLL and patients with relapsed CLL
- The number of patients expected to be included was approximately 40 for each study population. A sample size of 40 in each study population produced a 95% exact binomial confidence interval of (76%, 97%) and (43%, 75%) when the estimated ORR was 90% for the previously untreated population and 60% for the relapsed population, respectively

Results

- Exposure: 97 patients dosed
  - Previously untreated population: 44 patients enrolled at 21 centers in 8 countries
  - Relapsed population: 53 patients enrolled at 20 centers in 8 countries
- Key baseline patient characteristics are shown in Table 1
- All results are based on a data cutoff date of 28 February 2013

Table 1. Key Baseline Patient Characteristics

Characteristic	Previously Untreated CLL (n=44)	Relapsed CLL (n=53)
Median age, y (range)	62.5 (34-86)	68.0 (37-81)
Modified high-risk Rai stage, %	32	57
Binet stage C, %	27	47
Median serum β_2-microglobulin, mg/L	3.6	4.8
Median lymphocyte count, GI/L	67.6	50.0
17p Deletion, %	5	12
11q Deletion, %	18	29
Unmutated IGHV, %	66	72
ZAP-70 positive, %	82	85
Completed all 6 treatment cycles, %	89	85
Median number of prior therapies (range)	—	1 (1-11)

Efficacy: Previously Untreated Population

- 95% Investigator-assessed ORR (Table 2)
  - 43% Investigator-assessed CR rate
  - 56% Minimal residual disease (MRD) negativity for the subjects who had an investigator-assessed CR and had MRD analysis performed
- With CT evaluation, 82% ORR and 27% CR rate
- Median time to response was 0.95 months
- As of the data cutoff (median duration on study was approximately 8.5 months), time-to-event end points of duration of response, PFS, time to progression, OS, and time to next anti-CLL therapy were not yet mature

Table 2. Summary of Overall Response Rate as Assessed by the Investigator (Previously Untreated Population)

Previously Untreated Population: Ofatumumab + Bendamustine 90 mg/m^2	After 3 Cycles (N=42)[a]	After 6 Cycles (N=39)[b]	Overall Response After Last Dose (N=44)
Overall Response, n (%)			
Complete response (CR)	15 (36)	19 (49)	19 (43)
Complete response w/incomplete bone marrow (CRi)	0	2 (5)	2 (5)
Partial response (PR)	23 (55)	13 (33)	17 (39)
Nodular partial response (nPR)	0	4 (10)	4 (9)
Stable disease	3 (7)	0	1 (2)
Progressive disease	0	0	0
Not evaluable	0	0	0
Missing	1 (2)	1 (3)	1 (2)
Responder, n (%)			
Yes (CR+ CRi + nPR + PR)	38 (90)	38 (97)	42 (95)
No	4 (10)	1 (3)	2 (5)
95% CI for (CR + CRi + nPR + PR)[c]	(77.38, 97.34)	(86.52, 99.94)	(84.53, 99.44)

[a]N is the number of patients who completed study treatment at cycle 1, 2, and 3.
[b]N is the number of patients who completed all 6 cycles of study treatment.
[c]95% exact binomial confidence interval for CR + CRi + nPR + PR.

Safety: Previously Untreated Population

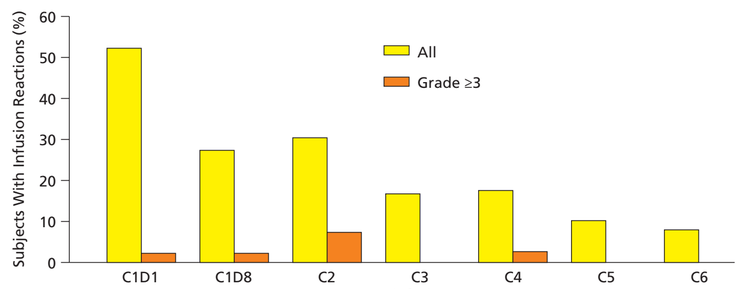
- Exposure: Most patients (89%) received all 6 cycles of study treatment; 2 patients (5%) received fewer than 3 cycles of therapy; 42 patients (95%) received between 3 and 6 cycles
- Adverse events (AEs): Common (≥5%) Grade ≥3 AEs occurring up to 60 days after last infusion are summarized in Table 3

Table 3. Summary of Common (≥5%) Grade 3, 4, or 5 AEs by Preferred Terms Up to 60 Days After Last Dosing (Previously Untreated Population)

Previously Untreated Population: Ofatumumab + Bendamustine 90 mg/m^2 (N=44)	Grade 3	Grade 4	Grade 5
Any Event, n (%)	**15 (34)**	**10 (23)**	**0**
Neutropenia	7 (16)	9 (20)	0
Rash	2 (5)	0	0

- Deaths: none
- Infections
  - The most frequently reported infections were upper respiratory tract infections (9/44 patients, 20%) and lower respiratory tract infections (7/44 patients, 16%)
  - Grade ≥3 infections occurred in 5 patients (11%). No infection led to the permanent discontinuation of study treatment
- Infusion reactions
  - 30 patients (68%) had infusion reactions. Infusion reactions occurred primarily during cycle 1 and 2 and were generally considered mild to moderate (Figure 2)
  - 5 patients (11%) had Grade ≥3 infusion reactions and 2 patients were discontinued from further study treatment due to infusion reactions (delayed type hypersensitivity reaction, anaphylaxis)

Figure 2. Infusion Reactions by Infusion for Ofatumumab in Combination With Bendamustine (Previously Untreated Safety Population)



	C1D1	C1D8	C2	C3	C4	C5	C6
n	44	44	43	42	40	40	39
Count (All)	23	12	13	7	7	4	3
Percent (All)	52%	27%	30%	17%	18%	10%	8%
Count (Grade ≥3)	1	1	3	0	1	0	0
Percent (Grade ≥3)	2%	2%	7%	0%	3%	0%	0%

Efficacy: Relapsed Population

- 74% Investigator-assessed ORR (Table 4)
  - 11% Investigator-assessed CR rate
  - No patients who had an investigator-assessed CR and had MRD analysis performed were MRD negative
- With CT evaluation, 70% ORR and 9% CR
- Median time to response was 0.95 months
- As of the data cutoff (median duration on study was approximately 8.7 months), median time-to-event end points of duration of response, PFS, time to progression, OS, and time to next anti-CLL therapy were either not reached, or were not interpretable due to immaturity of the data

Table 4. Summary of Overall Response Rate as Assessed by the Investigator (Relapsed Population)

Relapsed Population: Ofatumumab + Bendamustine 70 mg/m^2	After 3 Cycles (N=49)[a]	After 6 Cycles (N=45)[b]	Overall Response After Last Dose (N=53)
Overall Response, n (%)			
Complete response (CR)	11 (22)	6 (13)	6 (11)
Complete response w/incomplete bone marrow (CRi)	1 (2)	2 (4)	2 (4)
Partial response (PR)	30 (61)	21 (47)	23 (43)
Nodular partial response (nPR)	0	8 (18)	8 (15)
Stable disease	7 (14)	0	5 (9)
Progressive disease	0	7 (16)	8 (15)
Not evaluable	0	0	0
Missing	0	1 (2)	1 (2)
Responder, n (%)			
Yes (CR+ CRi + nPR + PR)	42 (86)	37 (82)	39 (74)
No	7 (14)	8 (18)	14 (26)
95% CI for (CR + CRi + nPR + PR)[c]	(72.76, 94.06)	(67.95, 92.00)	(59.67, 84.74)

CI, confidence interval
[a]N is the number of patients who completed study treatment at cycle 1, 2, and 3.
[b]N is the number of patients who completed all 6 cycles of study treatment.
[c]95% exact binomial confidence interval for CR + CRi + nPR + PR.

Safety: Relapsed Population

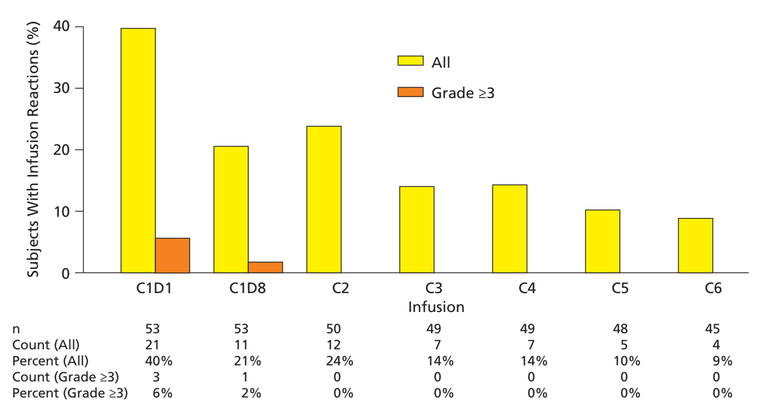
- Exposure: 85% of patients received all 6 cycles of study treatment; 4 patients (8%) received fewer than 3 cycles of therapy; 49 patients (92%) received between 3 and 6 cycles
- AEs: Common (≥5%) Grade ≥3 AEs occurring up to 60 days after last infusion are summarized in Table 5

Table 5. Summary of Common (≥5%) Grade 3, 4 or 5 AEs by Preferred Terms Up to 60 Days After Last Dosing (Previously Untreated Population)

Previously Untreated Population: Ofatumumab + Bendamustine 90 mg/m^2 (N=44)	Grade 3	Grade 4	Grade 5
Any Event, n (%)	**17 (32)**	**18 (34)**	**3 (6)**
Neutropenia	16 (30)	13 (25)	0
Febrile neutropenia	3 (6)	1 (2)	0
Thrombocytopenia	3 (6)	1 (2)	0

- Deaths
  - 4 deaths occurred during the course of the study in the relapsed population
    - 3 patients died ≤60 days after last dose
    - 1 patient died >60 days after last dose
  - Of the 4 deaths, 2 were considered by the investigator to be possibly related to study treatment:
    - 1 patient died of pneumonia and hemolytic anemia 15 days after latest dose of study treatment
    - 1 patient died of sepsis 4 days after latest dose of study treatment
- Infections
  - The most frequently reported infections were upper respiratory tract infections (8/53 patients, 15%) and lower respiratory tract infections (10/53 patients, 19%)
  - Grade ≥3 infections occurred in 8 patients (15%) and 3 patients had fatal SAEs of infection
- Infusion reactions
  - 32 patients (60%) had infusion reactions. Infusion reactions occurred primarily during cycle 1 and 2 and were generally considered mild to moderate (Figure 3)
  - 4 patients (8%) had Grade ≥3 infusion reactions, and no patients were discontinued from study treatment due to infusion reactions

Figure 3. Infusion Reactions by Infusion for Ofatumumab in Combination With Bendamustine (Relapsed Population)



	C1D1	C1D8	C2	C3	C4	C5	C6
n	53	53	50	49	49	48	45
Count (All)	21	11	12	7	7	5	4
Percent (All)	40%	21%	24%	14%	14%	10%	9%
Count (Grade ≥3)	3	1	0	0	0	0	0
Percent (Grade ≥3)	6%	2%	0%	0%	0%	0%	0%

Conclusions

- Results of this phase II, open-label, single-arm, multicenter study demonstrate that ofatumumab in combination with bendamustine is an effective and tolerable therapy, providing high response rates and an acceptable safety profile for patients with either previously untreated CLL who are inappropriate for fludarabine-based therapy, or patients with relapsed CLL
- Investigator-assessed ORR was 95% (CR rate 43%) in the previously untreated population and 74% (CR rate 11%) in the relapsed population. 56% of patients in the in the previously untreated population who had an investigator-assessed CR and had MRD analysis performed were MRD negative at the 3-month follow-up visit
- There were no unexpected AEs or serious AEs with the combination of ofatumumab and bendamustine, suggesting a safety profile consistent with that of an anti-CD20 monoclonal antibody–based chemo-immunotherapeutic regimen
- The most frequent (>5%) investigator-reported Grade 3/4 AEs reported up to 60 days after the end of treatment were neutropenia (36%) and rash (5%) in the previously untreated population and neutropenia (55%), febrile neutropenia (8%), and thrombocytopenia (8%) in the relapsed population
- Infusion reactions occurred primarily during cycle 1 and 2 and were generally considered mild to moderate
- No deaths were reported in the previously untreated population and 4 deaths were reported in the relapsed population: 2 cases of fatal pneumonia, 1 case of fatal sepsis, and 1 death due to CLL progression
- Longer follow-up is required to determine time-to-event end points such as PFS and OS

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Disclosures

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