An open-label, phase Ib study of obinutuzumab plus lenalidomide in relapsed/refractory follicular B-cell lymphoma

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Key points:

- Oral lenalidomide plus obinutuzumab is well tolerated and effective in patients with relapsed or refractory follicular B-cell lymphoma
- The recommended dose of lenalidomide in combination with obinutuzumab 1000 mg was established as 20 mg

Abstract

Obinutuzumab is a type II anti-CD20 monoclonal antibody that enhances antibody-dependent cellular cytotoxicity better than rituximab. Given promising results with lenalidomide and rituximab, this phase 1b study assessed the safety and efficacy of lenalidomide combined with obinutuzumab (GALEN). Patients aged ≥18 years with relapsed or refractory FL after rituximab-containing therapy received escalating doses (10 [n=7], 15 [n=3], 20 [n=6], and 25 mg [n=3]) of daily oral lenalidomide on days 1-21 of cycle 1 and on days 2-22 of cycles 2-6 (28-day cycles). Obinutuzumab 1000 mg IV was given on days 8, 15, and 22 (cycle 1) and on day 1 (cycles 2-6). Dose was escalated in a 3+3 design based on dose-limiting toxicity (DLT) during cycle 1 to establish the maximum tolerated dose (MTD). We observed 164 adverse events (AEs), of which 139 events were grade 1/2. The most common AEs were constipation (52.6%), neutropenia (47.4%), and asthenia (36.8%); 64.3% (9/14) of the grade 3/4 AEs were neutropenia/neutrophil decrease, but without any febrile neutropenia. Four DLTs occurred in 2 patients, both deemed unrelated to treatment. MTD was not reached. Twelve patients (63.2%) responded: 8 complete, 3 unconfirmed complete, and one partial response. Oral lenalidomide plus obinutuzumab is well tolerated and effective in relapsed or refractory FL. The recommended dose of lenalidomide was established at 20 mg based on the risk of grade 3/4 neutropenia from cycle 2. This trial was registered at www.clinicaltrials.gov as #NCT01582776.

Introduction

Some of the most recent advances for the treatment of non-Hodgkin lymphoma (NHL) involve chemotherapy-free combinations as alternatives to immunochemotherapeutic regimens. Lenalidomide exerts direct immunomodulatory activity on lymphoma cells, enhances the function of T cells and natural killer (NK) cells, and improves antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).[1] The actions of lenalidomide combined with the CD20 type I antibody rituximab have been shown to be synergistic in preclinical lymphoma models,[2-5] and effective in patients with various types of NHL,[6-11] in first-line[6-8] or relapsed or refractory (R/R) NHL.[9-11]

Obinutuzumab is a glycoengineered type II anti-CD20 monoclonal antibody (binding to a CD20 extracellular domain epitope overlapping with rituximab binding[12]) that enhances ADCC/ADCP and induces direct B-cell killing effects better than rituximab in preclinical models,[13,14] and has shown efficacy in NHL.[15-18] We recently demonstrated that lenalidomide also triggered NK cell activation *in vivo* and that this effect was further improved upon subsequent obinutuzumab infusion thereby enhancing directly and indirectly the efficacy of obinutuzumab.[19] Thus, combining obinutuzumab with lenalidomide may be even more effective than rituximab plus lenalidomide. In 2012, a phase 1b/2 study was initiated to assess the safety and efficacy of obinutuzumab combined with lenalidomide (GALEN) for patients with R/R lymphoma.

Here, we report results of the phase 1b study, in which the primary objectives were to establish the recommended phase 2 dose of lenalidomide in combination with a fixed dose of obinutuzumab, and to investigate the combination's safety, tolerability, and preliminary antitumor activity in patients with R/R follicular lymphoma (FL). Of note, the treatment schedule

included 1 week of lenalidomide alone before the first obinutuzumab infusion, allowing separate evaluation of T cell activation and CD20 modulation induced by lenalidomide from those related to the combination.

Patients and methods

Study design and patients

We performed a phase 1b, multicenter, open-label study sponsored by the Lymphoma Study Association (LYSA) using a 3 + 3 dose-escalation design to establish the maximum tolerated dose (MTD) of lenalidomide combined with obinutuzumab for patients with relapsed/refractory FL. Patients were enrolled from 7 centers in France affiliated with the LYSA. The central Independent Ethics Committee and the Agence Nationale de Sécurité du Médicament et des Produits de Santé approved the protocol, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory requirements. All patients gave written informed consent. The study was registered with ClinicalTrials.gov (GALEN trial; NCT01582776).

Eligible patients were ≥18 years of age with a histopathologically confirmed diagnosis of CD20-positive FL (World Health Organization grade 1, 2, or 3a) who had relapsed or refractory disease after ≥1 systemic treatment containing rituximab and life expectancy ≥3 months. Additional inclusion criteria were an Eastern Cooperative Oncology Group Performance Status score of 0–2; adequate bone marrow, liver, and kidney function; and at least 1 bidimensionally measurable lesion on computed tomography (CT) scan (greatest transverse diameter >15 mm and short axis ≥10 mm). All patients were required to fulfill the lenalidomide requirements for pregnancy prevention.

The main exclusion criteria were central nervous system or leptomeningeal involvement by lymphoma, prior treatment with obinutuzumab or lenalidomide, and known CD20-negative status at relapse/progression. Patients were excluded if they had known infection with HIV, positive serology for hepatitis B or C, any serious active disease or comorbid medical condition (eg, severe cardiac disease), or any laboratory abnormalities not due to underlying lymphoma (eg, absolute neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, aspartate aminotransferase or alanine aminotransferase ≥3.0 times upper limit of normal, serum total bilirubin >34 μmol/L, or calculated creatinine clearance <50 mL/min). Patients were excluded if they had a history of other malignancies within 5 years (except for nonmelanoma skin tumors), any anticancer drug therapy within 28 days of initiation, or any corticosteroids within 4 weeks (except ≤10 mg/day prednisone).

Treatments

To identify the recommended phase 2 dose of lenalidomide, 4 patient cohorts received escalating doses (10, 15, 20, and 25 mg) of daily oral lenalidomide (on days 1-21 of the first 28-day cycle, and on days 2-22 of 28-day cycles 2 to 6) in combination with IV infusions of obinutuzumab at a fixed dose of 1000 mg (on days 8, 15, and 22 of the first cycle and on day 1 of cycles 2 to 6; total of 8 infusions; Figure 1). Steroid premedication was mandatory before the first obinutuzumab infusion. All patients were required to take daily aspirin (100 mg) for prophylaxis against deep vein thrombosis (DVT) during the study period. Patients who could not tolerate aspirin, had a history of DVT, or had high risk of DVT received low-molecular-weight heparin or warfarin. Growth factors were allowed in the study and recommended for up to 3 days if grade 4 neutropenia occurred, but were not prophylactically administered.

The lenalidomide dose was escalated in a 3+3 design based on the dose-limiting toxicity (DLT) assessment during cycle 1. The MTD was defined as the dose level prior to that which resulted in 2 or more out of 6 patients experiencing DLTs. The recommended phase 2 dose was to be the MTD, but if the MTD was not reached, then the recommended dose was to be defined by all investigators according to the overall safety profile, approved by the data safety monitoring committee, and validated in 6 patients.

Objectives and outcomes

The primary objective was to establish the recommended phase 2 dose of lenalidomide in combination with a fixed dose of obinutuzumab. Secondary objectives included safety and efficacy of the therapeutic combination. Efficacy variables included complete response (CR), complete response unconfirmed (CRu), partial response (PR), overall response rate (ORR, or CR/CRu/PR), complete response rate (CRR, or CR/CRu), best overall response rate, progression-free survival, response duration, and overall survival after 3 and 6 cycles according to the International Working Group (IWG) 1999 and IWG 2007).[20,21] Patient response was assessed by the principal investigator.

Safety. Safety evaluations included all adverse events (AEs) according to system organ class preferred term, clinical laboratory tests, vital sign measurements, physical examinations, electrocardiograms, and Eastern Cooperative Oncology Group Performance Status score. The National Cancer Institute-Common Terminology Criteria for Adverse Events (version 4.03) were used to grade toxicity. Hematologic DLT was defined as grade ≥3 neutropenia or thrombocytopenia lasting ≥7 days, grade 4 neutropenia or thrombocytopenia lasting >3 days, and

no recovery of absolute neutrophil count ≥1.5 x 10^9/L or platelet count ≥100 x 10^9/L by 8 weeks after the start of the previous cycle. Nonhematologic toxicity was defined as grade 3 blistering rash or grade 3 rash that does not resolve within 7 days following standard treatment, or grade 4 rash; venous thrombosis/embolism grade 3 despite adequate prevention; any grade 4 infusion-related reaction (IRR) during or within 24 hours after start of the first obinutuzumab infusion, or any grade 3 IRR that does not resolve to grade 2 despite interventions (reduced infusion rate, temporary stop, supportive care, and/or corticosteroids); tumor flare reaction of grade 3, or of grade 3 that does not resolve within 5 days following standard medical treatment; and any other grade ≥3 nonhematologic toxicity. Patients who experienced a DLT during the first cycle were not replaced. Patients who discontinued the first cycle without experiencing safety problems were replaced to ensure 3 safety-evaluable patients per dose cohort.

***Efficacy*.** Patients were evaluated using CT scans with IV contrast of the neck, chest, abdomen, and pelvis, and with whole-body positron emission tomography (PET) scans. Disease response was assessed by the Revised Response Criteria for Malignant Lymphoma (International Working Group [IWG] 1999 and IWG 2007).[20,21] Tumor assessments (clinical examination, laboratory tests, abdominal and chest CT scan, PET scan, and bone marrow examination) were done at baseline, after cycle 3, and 4 weeks after cycle 6 (except bone marrow examination if negative at baseline). During follow-up, clinical and neurologic examination and laboratory tests were repeated every 3 months, and imaging studies (CT; optional PET) every 6 months.

Exploratory endpoints. The study included a pilot exploration of some specific aspects of the biologic impact of the treatment strategy on malignant cells and immune response. Heparinized

blood was drawn at various time points to perform a thorough analysis of peripheral blood immune-cell subsets (phenotyping of T cells, malignant and normal B cells, NK cells, and myeloid cells) by flow cytometry before and 1 week after lenalidomide treatment, shortly after the first obinutuzumab infusion, and at the end of 1 and 6 cycles of treatment.

Statistical analysis

The sample size estimate for this phase 1b study was based on a 3+3 escalation rule with 4 dose levels, and therefore needed to include between 3 and 24 patients. Safety evaluations were summarized descriptively. The treated population consisted of all patients who received ≥1 dose of the study drug. This population was used for all safety and efficacy analyses. Response rate 95% confidence intervals (CIs) were calculated according to the Exact Pearson-Clopper method. Survival functions were estimated using Kaplan-Meier methodology with appropriate 95% CIs. Immune parameters measured as continuous values were compared by Wilcoxon matched-pairs signed-rank test using GraphPad Prism 5.0 software.

Results

Patient disposition and demographics

Twenty patients with FL were enrolled between October 2012 and January 2014. Patients were to receive daily lenalidomide 10 mg (n=7), 15 mg (n=3), 20 mg (n=6), or 25 mg (n=4). One patient enrolled at 25 mg was withdrawn before receiving any treatment because of neutropenia occurring at baseline screening, leaving 19 patients evaluable for safety and efficacy. A patient taking 10 mg was not evaluable for DLT and was replaced since she missed one infusion of obinutuzumab during the first cycle due to fortuitous concomitant diagnosis of breast cancer at

day 4 on microbiopsies of breast lesions that were presumed to be lymphomatous (n=18 for DLT assessment). Two patients permanently discontinued the study because of AEs, including cardiac arrest at cycle 1 (n=1), ischemic stroke at cycle 3 (n=1), two from disease progression, and 1 from study treatment toxicity. Median number of treatment cycles was 6 (range, 1–6). The median percentage of planned doses (total dose taken [mg]*100/total dose expected [mg]) taken for both lenalidomide and obinutuzumab was ≥90%.

Half of the enrolled patients were male and the mean age of all the patients was 61.5 years (Table 1). Patients mostly had Ann Arbor stage IV disease (70%) and had received 1 to 5 prior systemic therapies (median=2). Four patients were refractory to their last lymphoma therapy and 8 were refractory to rituximab (Table 1).

Dose-limiting toxicity

Four DLTs occurred in 2 of the 18 evaluable patients during cycle 1: 1 death due to cardiac arrest at 10 mg in the presence of grade 3 worsening pleural effusion, and another patient treated at 20 mg who had grade 3 pulmonary infection with grade 3 hypokalemia; both cases were deemed unrelated to study treatment. While the MTD was not reached; the toxicity review committee suggested a recommended phase 2 dose (RP2D) of 20 mg lenalidomide instead of 25 mg in view of the incidence of grade 3 and 4 neutropenia from cycle 2 at 25 mg (Table 2), which may have clinical relevance or an impact on treatment exposure during phase 2. An additional 3 patients were enrolled in the 20-mg cohort confirming the tolerability of this dosage. The suggested RP2D was validated by the data safety monitoring committee.

Safety

All 19 patients (100%) experienced at least 1 adverse event (AE); the total number of AEs was 164 (Table 2). The most common AEs (all grades, ≥20% of patients) were constipation (52.6%), neutropenia/neutrophil count decreased (47.4%), asthenia (36.8%), cough (26.3%), muscle spasms (26.3%), diarrhea (21.1%), and pyrexia (21.1%). Grade 1 (50.6%) or 2 (34.1%) was the most common grade of AEs regardless of causality; AEs of worst grade 3, 4, and 5 represented 11.0%, 3.0%, and 1.2% of all AEs, respectively (Table 2).

Thirteen AEs (7.9%) were deemed related only to obinutuzumab, 54 (32.9%) were related only to lenalidomide, and 32 (19.5%) were related to the combination of both. Neutropenia was the only drug-related grade 3 or 4 AE occurring in >2 patients (Table 2), and none of these were febrile neutropenia. Other drug-related AEs of special interest including IRRs (n=3), rash (n=3), and TFR (n=1) were rare and mild (worst grade was 2).

A total of 9 serious AEs (SAEs) were recorded in 7 patients (36.8%), including 3 (33.3%) second primary malignancies, and 4 (44.4%) occurring during cycle 1. Four SAEs were deemed related only to lenalidomide, including cerebral ischemic stroke at cycle 2, acute monocytic leukemia (WHO), pulmonary embolism, and pancreatic carcinoma (n=1 each). The other 5 SAEs were deemed unrelated to either study treatment, and included pulmonary infection, cardiac arrest, costal fracture, worsening pleural effusion, and breast cancer (n=1 each).

Six of 19 patients (31.6%) died during the study. Three patients died of lymphoma, including a 70-year-old man at cycle 4 and 2 women during the follow-up period (39 years old and 43 years old). A fourth patient had an unexplained death at day 14 of cycle 1. This 73-year-old man had worsening pleural effusion due to FL; he died of cardiac arrest presumably due to pulmonary embolism or cardiac dysrhythmia, which was considered not related to either treatment. The fifth patient was a 60-year-old man who died of metastatic pancreatic carcinoma

diagnosed 20 months after initiation of study treatment while still having a CR of FL; he had received 4 prior regimens including first-line consolidation with BEAM (carmustine, etoposide, cytarabine, and melphalan) followed by autologous stem cell transplantation in 1992 and second-line therapy with fludarabine/mitoxantrone in 1998. The sixth patient was a 64-year-old man who died of bilateral pneumopathy in the context of acute monocytic leukemia diagnosed 3 years after initiation of study treatment; he had received 4 prior therapies including R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) and involved-field radiotherapy twice.

Efficacy

The 19 patients included in the safety set were evaluated for efficacy (patients with missing assessments were considered nonresponders). The ORR and CRR after 3 cycles (intermediate assessment) and 6 cycles (end of treatment) according to IWG 1999 and 2007 are summarized in Table 3. Overall, after 6 cycles in the total safety set, ORR (CR/CRu/PR) was achieved by 12 patients (63.2%; 95% CI, 38.4-83.7) according to both IWG 1999 and IWG 2007. Rates of CRR (CR/CRu) at the end of treatment were 11 patients (57.9%; 95% CI, 33.5-79.7). Seven patients progressed (n=4) or relapsed (n=3) during the study.

Median follow-up for the final analysis was 38.1 months (95% CI, 35.0-41.6). At 3 years, progression-free survival was 52.1% (95% CI, 28.0-71.6), duration of response was 68.4% (95% CI, 35.9-86.8), and overall survival was 73.3% (95% CI, 47.2-87.9), illustrated in Figure 2A-C.

Biological evaluation

As soon as 1 week after lenalidomide dosing, T lymphocytes were strongly activated in peripheral blood, as exemplified by the increase in the percentage of these cells expressing high levels of HLA-DR (HLA-DR^{bright}, Figure 3A). Of note, HLA-DR^{bright} T cells further increased 2 hours after obinutuzumab infusion. This activation was transient, as HLA-DR expression returned to the basal level at the end of cycle 1 of treatment; that is, after a 1-week washout of lenalidomide. Nevertheless, some of the activated T cells persisted over time during treatment courses, as HLA-DR expression remained significantly higher after 6 cycles (end of induction; Figure 3A). In parallel, we analyzed whether the obinutuzumab target was altered by concomitant lenalidomide. CD20 surface expression was not modulated in normal B cells. Moreover, 9 patients displaying detectable circulating malignant B cells (99% [range, 14–100] of blood B cells) also revealed a lack of downregulation of CD20 on tumor cells (Figure 3B).

Discussion

In this first clinical study of combined obinutuzumab and lenalidomide (GALEN) given for 6 months, an acceptable safety and tolerability profile was found in patients with R/R FL. Four DLTs were reported, the MTD was not reached, and most of the drug-related AEs were grade 1 or 2. Grade 3 or 4 hematopoietic AEs (primarily neutropenia/neutrophil count decreased) were observed as laboratory findings (without any cases of grade 3 or 4 febrile neutropenia) in 11 patients. There was no signal of increased incidence or more severe infusion-related reactions, thromboembolic events, or thrombocytopenia. While 2 secondary primary malignancies were deemed possibly related, both patients had received heavy prior therapy that could have contributed to their emergence. The 20-mg dose was selected as the RP2D based on the safety

profile, in particular, the increasing incidence of grade 3 and 4 neutropenia at 25 mg after cycle 1.

In the small group of patients reported here, of whom 40% where rituximab refractory and 20% refractory to last prior therapy, the GALEN regimen showed promising efficacy compared with a report of lenalidomide plus rituximab.[9] We found here an ORR (CR) of 63.2% (57.9%) at the end of the 6 cycles and progression-free survival, duration of response, and overall survival of 52.1%, 68.4% and 73.3%, respectively, after 3 years. The 52.1% 3-year progression-free survival achieved with 6 cycles of lenalidomide and 8 infusions of obinutuzumab appears promising compared to the 52% 2-year time to progression seen in relapsed but not refractory FL patients who received 12 cycles of lenalidomide but only 4 infusions of rituximab.[9] Our data are consistent with the preliminary report of another phase 1 study that combined obinutuzumab and lenalidomide using a slightly different initial treatment schedule (no 8 days of lenalidomide prophase and a longer induction period of 12 months); no DLTs were observed at the highest dose of 20 mg, which was selected as the RP2D.[22]

Correlation of pharmacodynamic and biomarker studies is essential to decipher signaling mechanisms and to ensure optimal efficacy with a manageable toxicity profile. Lenalidomide has been proposed to reduce CD20 expression on malignant B cells from chronic lymphocytic leukemia (CLL), suggesting a potential antagonism between lenalidomide and anti-CD20 therapy in CLL.[23] To our knowledge, this finding has not been explored in B-cell NHL. Here, we show that there appears to be no pharmacodynamic antagonism between obinutuzumab and lenalidomide since CD20 expression remained unaffected by lenalidomide (Figure 3). Functional experiments on GALEN patients' samples are underway to determine whether lenalidomide is able restore in vivo the capacity of circulating T cells to mount an efficient immune synapse with

malignant B cells, and whether NK cell-related ADCC and phagocytosis of opsonized lymphoma cells by macrophages are modulated by the combination.

In conclusion, oral lenalidomide plus obinutuzumab is well tolerated and effective in patients with R/R FL. The recommended phase 2 dose of lenalidomide was established at 20 mg based on the increased incidence of grade 3/4 neutropenia from cycle 2 at 25 mg. To further explore the optimal duration of this combination, the phase 2 part of this study is currently assessing efficacy of the GALEN regimen with a lenalidomide dose of 20 mg during 6 months and 2 years of maintenance (lenalidomide at a lower dose of 10 mg on days 2-22 of each cycle for a maximum of 12 cycles to mitigate hematological toxicity, combined with obinutuzumab 1000 mg on day 1 every 2 cycles, then one additional year of obinutuzumab as a single agent every 2 cycles) in 3 separate populations of 90-100 patients: R/R aggressive lymphoma (cohort 1: diffuse large B-cell lymphoma and mantle cell lymphoma), relapsed/refractory FL (cohort 2), and first-line FL with Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria (cohort 3).

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Authorship contribution: F.M. and R.H. designed the study; all authors participated in the collection and assembly of data; F.M., R.H., C.M., and K.T. provided data analysis and interpretation; F.M. was primarily involved in the manuscript writing; all authors participated in the manuscript development process and provided final approval of the manuscript for submission.

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Table 1. Demographic and Disease Characteristics in the Enrolled Set

Characteristic	Enrolled Set (N=20)
Age (yr)	
Mean (SD)	61.5 (12.5)
Range	39-80
Sex, n (%)	
Male	10 (50)
Female	10 (50)
Initial histology (local)	
CD20+ FL grade 1	9 (45)
CD20+ FL grade2	7 (35)
CD20+ FL grade 3a	1 (5)
CD20+ FL (grade unknown)	3 (15)
Number of prior treatments	
Median	2.0
Range	1-5
Ann Arbor stage	
1 and 2	3 (15)
3 and 4	17 (85)
Performance status (ECOG)	
0	16 (80)
1	4 (20)
Bone marrow involvement	
N	15
Involved	6 (40)
LDH (IU/L)	
Normal	13 (65)
>Upper limit of normal	7 (35)
Bulk >5 cm	
No	15 (75)
Yes	5 (25)
Calculated FLIPI score	
0	2 (10)
1	3 (15)
2	6 (30)
3	7 (35)
4	1 (5)
5	1 (5)
Refractory to rituximab	
No	12 (60)
Yes	8 (40)
Refractory to prior lymphoma therapy	
No	16 (80)
Yes	4 (20)

ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; LDH = lactic dehydrogenase.

Table 2. Adverse Events Occurring in ≥10% of Patient and All AEs of Grade 3 or 4 in the Treated Set by Dosage Group

	Lenalidomide Dose				
Adverse Event*	10 mg (n=7)	15 mg (n=3)	20 mg (n=6)	25 mg (n=3)	Treated Set (N=19)
Total with ≥1 AE (all grades)	**7 (100)**	**3 (100)**	**6 (100)**	**3 (100)**	**19 (100)**
Constipation	3 (42.9)	1 (33.3)	5 (83.3)	1 (33.3)	10 (52.6)
Neutropenia/neutrophil count decreased	1 (14.3)	1 (33.3)	4 (66.7)	3 (100)	9 (47.4)
Asthenia	1 (14.3)	2 (66.7)	2 (33.3)	2 (66.7)	7 (36.8)
Cough	1 (14.3)	2 (66.7)	1 (16.7)	1 (33.3)	5 (26.3)
Muscle spasms	1 (14.3)	0 (0.0)	3 (50.0)	1 (33.3)	5 (26.3)
Diarrhea	1 (14.3)	1 (33.3)	1 (16.7)	1 (33.3)	4 (21.1)
Pyrexia	2 (28.6)	1 (33.3)	1(16.7)	0 (0.0)	4 (21.1)
Infusion-related reaction	0 (0.0)	1 (33.3)	1 (16.7)	1 (33.3)	3 (15.8)
Nausea	1 (14.3)	1 (33.3)	1 (16.7)	0 (0.0)	3 (15.8)
Rash	1 (14.3)	1 (33.3)	1 (16.7)	0 (0.0)	3 (15.8)
Rhinitis, allergic	0 (0.0)	1 (33.3)	1 (16.7)	1 (33.3)	3 (15.8)
Weight increase	1 (14.3)	1 (33.3)	0 (0.0)	1 (33.3)	3 (15.8)
Weight loss	2 (28.6)	0 (0.0)	1 (16.7)	0 (0.0)	3 (15.8)
Bronchitis	1 (14.3)	1 (33.3)	0 (0.0)	0 (0.0)	2 (10.5)
Dry skin	0 (0.0)	1 (33.3)	1 (16.7)	0 (0.0)	2 (10.5)
Fatigue	1 (14.3)	0 (0.0)	0 (0.0)	1 (33.3)	2 (10.5)
Headache	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	2 (10.5)
Rhinitis	0 (0.0)	0 (0.0)	1 (16.7)	1 (33.3)	2 (10.5)
Sinusitis	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	2 (10.5)
Upper abdominal pain	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)
Urinary tract infection	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	2 (10.5)
Total with ≥1 grade 3/4 AE	**4 (57.1)**	**2 (66.7)**	**5 (83.3)**	**3 (100)**	**14 (73.7)**
Neutropenia/neutrophil count decreased	1 (14.3)	1 (33.3)	4 (66.7)	3 (100)	9 (47.4)
Anemia	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (5.3)
Acute myeloid leukemia	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (5.3)
Breast cancer	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Hypertension	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Hypokalemia	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (5.3)
Ischemic stroke	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (5.3)
Lung infection	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (5.3)
Pleural effusion	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (5.3)

AE = adverse event.

* Data are presented as n (%).

Table 3. Response Rates by International Working Group 1999 and 2007 Criteria at Intermediate and Final Assessments (Response-Evaluable Patient Population*)

Assessment time	Lenalidomide dose				Total
	10 mg (n=7)	15 mg (n=3)	20 mg (n=6)	25 mg (n=3)	(N=19)
IWG 1999[20]					
Intermediate (3 mo)					
CR	0	1 (33.3)	2 (33.3)	1 (33.3)	4 (21.1)
CRu	1 (14.3)	0	0	0	1 (5.3)
PR	2 (28.6)	2 (66.7)	2 (33.3)	2 (66.7)	8 (42.1)
SD	3 (42.9)	0	0	0	3 (15.8)
PD	0	0	1 (16.7)	0	1 (5.3)
Not evaluated	1 (14.3)	0	1 (16.7)	0	2 (10.5)
CRR (CR/CRu)	1 (14.3)	1 (33.3)	2 (33.3)	1 (33.3)	5 (26.3)
(95% CI)					(9.1-51.2)
ORR (CR/CRu/PR)	3 (42.9)	3 (100.0)	4 (66.7)	3 (100.0)	13 (68.4)
(95% CI)					(43.4-87.4)
End of treatment					
CR	1 (14.3)	2 (66.7)	3 (50.0)	2 (66.7)	8 (42.1)
CRu	2 (28.6)	1 (33.3)	0	0	3 (15.8)
PR	0	0	0	1 (33.3)	1 (5.3)
SD	0	0	0	0	0
PD	3 (42.9)	0	2 (33.3)	0	5 (26.3)
Not evaluated	1 (14.3)	0	1 (16.7)	0	2 (10.5)
CRR (CR/Cru)	3 (42.9)	3 (100.0)	3 (50.0)	2 (66.7)	11 (57.9)
(95% CI)					(33.5-79.7)
ORR (CR/CRu/PR)	3 (42.9)	3 (100.0)	3 (50.0)	3 (100.0)	12 (63.2)
(95% CI)					(38.4-83.7)
IWG 2007[21]					
Intermediate (3 mo)					
CR	1 (14.3)	1 (33.3)	2 (33.3)	2 (66.7)	6 (31.6)
PR	2 (28.6)	2 (66.7)	3 (50.0)	1 (33.3)	8 (42.1)
SD	2 (28.6)	0	0	0	2 (10.5)
PD	1 (14.3)	0	1 (16.7)	0	2 (10.5)
Not evaluated	1 (14.3)	0	0	0	1 (5.3)
CRR (CR/Cru)	1 (14.3)	1 (33.3)	2 (33.3)	2 (66.7)	6 (31.6)
(95% CI)					(12.6-56.6)
ORR (CR/CRu/PR)	3 (42.9)	3 (100.0)	5 (83.3)	3 (100.0)	14 (73.7)
(95% CI)					(48.8-90.9)
End of treatment					
CR	3 (42.9)	3 (100.0)	2 (33.3)	3 (100.0)	11 (57.9)
PR	0	0	1 (16.7)	0	1 (5.3)
SD	0	0	0	0	0
PD	2 (28.6)	0	2 (33.3)	0	4 (21.1)
Not evaluated	2 (28.6)	0	1 (16.7)	0	3 (15.8)
CRR (CR/Cru)	3 (42.9)	3 (100.0)	2 (33.3)	3 (100.0)	11 (57.9)
(95% CI)					(33.5-79.7)
ORR (CR/CRu/PR)	3 (42.9)	3 (100.0)	3 (50.0)	3 (100.0)	12 (63.2)
(95% CI)					(38.4-83.7)

CR = complete response; CRR = complete response rate; CRu = complete response unconfirmed; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease.

*Data are presented as n (%). Patients who received at least 1 dose of the study treatment, and had baseline and at least 1 post-treatment tumor assessment. Patients with missing assessments are considered nonresponders.

Figure Legends

Figure 1. Treatment Schedule. Escalating doses of oral lenalidomide (10 mg, 15 mg, 20 mg, or 25 mg) were given to 4 patient cohorts (n=3 to 6) from days 1 to 21 in cycle 1 and from day 2 to day 22 in cycles 2 through 6. Obinutuzumab (1000 mg) was given IV on days 8, 15, and 22 of cycle 1, and on day 1 of cycles 2 through 6 (total of 8 infusions). Cycles are 28 days in length.

Figure 2. Progression-free survival (A), duration of response (B), and overall survival (C) in the treated set.

Figure 3. Lenalidomide activates T cells in vivo and does not alter CD20 expression. A) HLA-DR expression was measured by flow cytometry in peripheral blood on CD4 and CD8 T cells at various time points. B) CD20 expression was measured by flow cytometry on circulating normal and/or malignant B cells. C1D1 = first day of the first treatment cycle (before lenalidomide intake); C1D8 = eighth day of the first cycle (before or after obinutuzumab [GA101] infusion); C2D1 = first day of the second cycle (before lenalidomide intake); end of induction = 28th day of the sixth cycle of treatment. Median value is depicted as a black bar. MFI = mean fluorescence intensity; ns = not significant. *$P \leq 0.05$ ***$P \leq 0.001$.

Figure 1

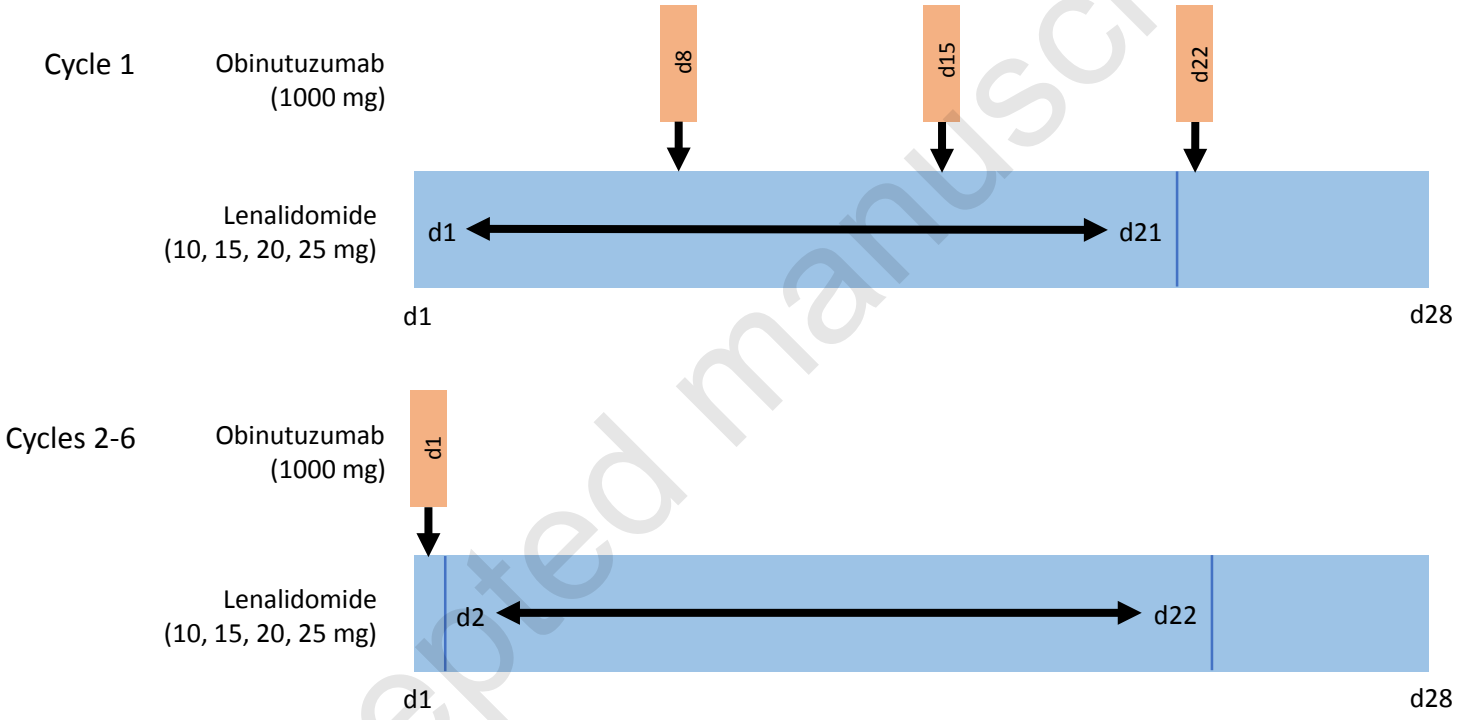

Figure 2

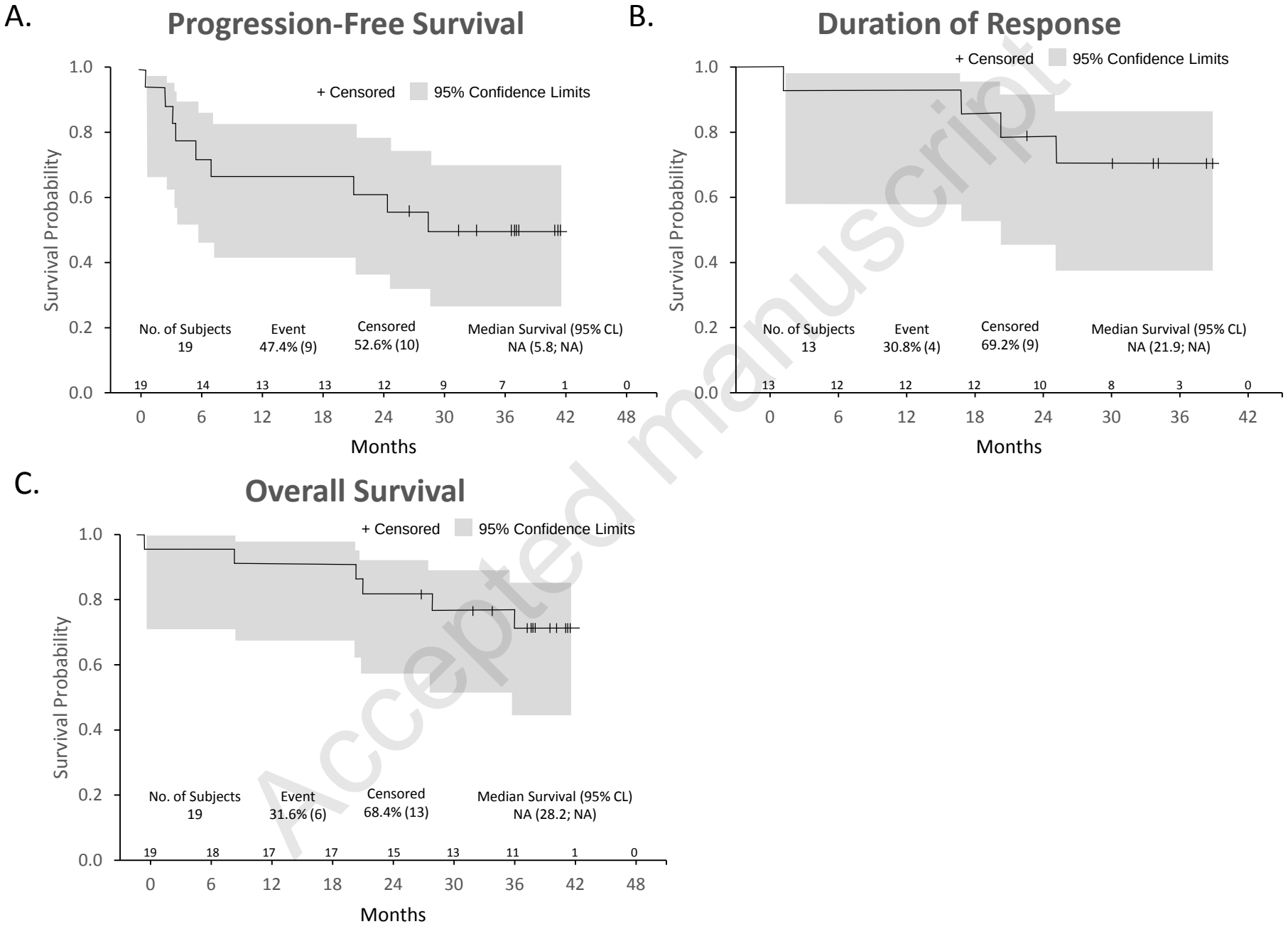

Figure 3