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# Ofatumumab in Combination with Glucocorticoids for Primary Therapy of Chronic Graft-versus-Host Disease: Phase I Trial Results

Joseph Pidala [1,2,*], Jongphil Kim [2,3], Brian C. Betts [1,2], Melissa Alsina [1,2], Ernesto Ayala [1,2], Hugo F. Fernandez [1,2], Teresa Field [1,2], Mohamed A. Kharfan-Dabaja [1,2], Frederick L. Locke [1,2], Asmita Mishra [1,2], Taiga Nishihori [1,2], Leonel Ochoa-Bayona [1,2], Lia Perez [1,2], Marcie Riches [1,2], Claudio Anasetti [1,2]

[1] *Blood and Marrow Transplantation, Moffitt Cancer Center, Tampa, Florida*
[2] *Oncologic Sciences, College of Medicine at University of South Florida, Tampa, Florida*
[3] *Biostatistics, Moffitt Cancer Center, Tampa, Florida*

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A B S T R A C T

Standard primary therapy for chronic graft-versus-host disease (GVHD) is incompletely effective. Based on biologic insights implicating pathogenic B cells, we conducted a phase I trial examining the combination of standard (1 mg/kg/day prednisone) glucocorticoid therapy with ofatumumab, a humanized anti-CD20 monoclonal antibody, for primary chronic GVHD therapy. Patients ages ≥ 18 with National Institutes of Health Consensus moderate-to-severe chronic GVHD newly requiring 1 mg/kg/day prednisone were treated at 3 escalating dose levels (300 mg, 700 mg, and 1000 mg) of i.v. ofatumumab on days 1 and 14 of initial glucocorticoid therapy. Dose-limiting toxicity (DLT) was defined by grade 4 infusion reactions, related grade 4 constitutional symptoms, related grade ≥ 3 organ toxicities, or grade 4 neutropenia lasting > 14 days. A total of 12 patients (median age 54; range, 25 to 72) were treated (dose level 1: n = 3; level 2: n = 3; level 3: n = 6). At enrollment, overall chronic GVHD was moderate (n = 7) or severe (n = 5), with diverse organ involvement (skin: n = 8; mouth: n = 8; eye: n = 8; lung: n = 4; gastrointestinal: n = 3; liver: n = 5; genital: n = 2; joint/fascia: n = 5). Infusion of ofatumumab was well tolerated, and no DLT was observed. From the total number of adverse events (n = 29), possibly related adverse events (n = 4) included grade 1 fatigue, grade 1 transaminitis, and 2 infusion reactions (grades 2 and 3). Infectious complications were expected, and there were no cases of hepatitis B reactivation or progressive multifocal leukoencephalopathy. Ofatumumab in combination with prednisone is safe and a phase II examination of efficacy is ongoing.



## INTRODUCTION

Chronic graft-versus-host disease (GVHD), a major late complication of allogeneic hematopoietic cell transplantation (HCT), is associated with mortality, disability, infectious complications, prolonged immune suppression, and impaired quality of life [1–8]. Accepted standard primary therapy for chronic GVHD includes ≥ 1 mg/kg/day of prednisone with or without a calcineurin inhibitor [9,10] as combination therapy with other broadly immune suppressive agents has not demonstrated consistent benefit over prednisone alone in controlled trials [11–13]. Only 30% of patients will experience complete resolution of chronic GVHD by 6 to 9 months of primary steroid therapy and another 30% will achieve only a partial response [11–14]. *Failure-free survival*, defined by absence of second-line immune suppressive treatment, nonrelapse mortality (NRM), and recurrent malignancy after initial systemic treatment for chronic GVHD is only 68% at 6 months and 54% at 12 months [15].

Multiple observations support a role for B lymphocytes in human chronic GVHD pathogenesis: B cell–activating factor (BAFF) and the BAFF/B cell ratio have been associated with

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* Correspondence and reprint requests: Joseph Pidala, MD, PhD, Blood and Marrow Transplantation, Moffitt Cancer Center, 12902 Magnolia Drive, FOB 3308, Tampa, FL 33612.
*E-mail address:* joseph.pidala@moffitt.org (J. Pidala).

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risk for subsequent chronic GVHD development [16]. In the setting of established chronic GVHD, investigators have detected anti–H-Y in the setting of sex mismatched HCT [17,18] and activating anti-platelet-derived growth factor receptor (PDGFR) antibodies in the context of cutaneous sclerosis [19]. Active chronic GVHD has been shown to correlate with BAFF levels [20,21], BAFF/B cell ratio [22], as well as various B cell subpopulations [22–27]. Interestingly, several associations have also been detected with chronic GVHD severity [26], phenotype [19,21,26], and response to therapy [21,25,28]. Alongside these observations, anti-CD20 therapy in chronic GVHD has proven successful: rituximab has demonstrated activity as a single-agent in steroid refractory chronic GVHD [29]. As well, 2 independent trials testing varied schedules of rituximab for chronic GVHD prophylaxis after HCT have suggested improvements over expected chronic GVHD rates [30,31].

Ofatumumab is a fully humanized IgG1kappa monoclonal antibody (mAb) targeting a unique epitope on the CD20 molecule expressed on human B cells. As a type I CD20 mAb, like rituximab, potent complement-dependent cytotoxicity is dependent on ability to translocate CD20 into lipid rafts. In contrast to rituximab, it has increased binding affinity to CD20, prolonged dissociation rate, and increased cell kill (including B cells with low-density CD20 expression) due to greater complement-dependent cytotoxicity [32–34]. Compared with rituximab and obinutuzumab, ofatumumab demonstrates greater complement activation, independent of CD20 density, and elicits the greatest monocyte-derived macrophage mediated Ab-dependent cellular phagocytosis [35]. Ofatumumab was approved for advanced chronic lymphocytic leukemia therapy in 2009 and has also demonstrated activity in multiple lymphoid malignancies and autoimmune conditions. Given experimental evidence of increased potency, observations supporting activity in the setting of prior rituximab exposure or rituximab resistance [36–46] and evidence of chronic GVHD development after rituximab prophylaxis [30,31], ofatumumab holds promise as a novel chronic GVHD intervention.

The primary objective of the phase I component of this phase I/II trial was to examine the safety of ofatumumab in combination with 1 mg/kg/day prednisone as primary therapy of chronic GVHD.

## METHODS

### *Overview of Trial Design*

The overall trial is a phase I/II trial to examine the safety and efficacy of prednisone and escalating dose of ofatumumab for primary therapy of chronic GVHD (NCT01680965). Here we report the phase I trial results. Phase II accrual is ongoing. Prednisone is uniformly initiated at 1 mg/kg/day and the phase I component examined escalating dose of ofatumumab at dose level cohorts of 300 mg, 700 mg, and 1000 mg given on days 0 and 14 of study. In the phase II component, patients are followed for 24 months (baseline, study therapy day 0 and day 14, and months 1, 3, 6, 12, 18, and 24 after therapy). The primary efficacy endpoint for the phase II trial is 6-month clinician-reported overall response (composite of complete and partial response). Additional endpoints include other therapeutic response metrics, utilization of second-line systemic immune suppressive therapy, additional clinical and patient-reported outcomes, and allied biologic correlative studies.

### *Included Patients*

Adults ages $\geq$ 18 with chronic GVHD newly requiring systemic glucocorticoid therapy were included. Chronic GVHD diagnosis and severity scoring adhered to the National Institutes of Health (NIH) Consensus Criteria on Diagnosis and Staging of Chronic GVHD [47]. In the phase I component of this trial, only those with overall moderate-to-severe chronic GVHD were eligible. Patients had to begin ofatumumab therapy within 14 days from initiation of 1 mg/kg/day of prednisone therapy for chronic GVHD. The following were study exclusion criteria: relapsed malignancy after HCT, previous systemic glucocorticoid therapy at $\geq$1 mg/kg/day prednisone or equivalent for chronic GVHD, current hepatic/biliary disease (with exception of that due to chronic GVHD), treatment with experimental non–Food and Drug Administration–approved therapy within 5 terminal half-lives or 4 weeks before enrollment, other solid tumor within past 5 years (except completely resected nonmelanoma skin cancer), prior treatment with any anti-CD20 monoclonal antibody or alemtuzumab within 3 months, uncontrolled infectious complications, significant cerebrovascular disease in past 6 months, human immunodeficiency virus positivity, uncontrolled significant cardiac or other medical conditions, clinically active hepatitis B defined as positive HBsAg or positive HBcAb with detectable hepatitis B viral load, active hepatitis C confirmed by viral load, pregnancy or lactation, women and men unable or unwilling to use adequate contraceptive methods through 1 year after completion of protocol therapy, absolute neutrophil count $< 1.0 \times 10^9$/L; creatinine $> 2 \times$ upper limit of normal (ULN), total bilirubin $> 1.5 \times$ ULN, transaminase $> 2 \times$ ULN, or alkaline phosphatase $> 2.5 \times$ ULN (except for that due to chronic GVHD).

### *Treatment Plan*

Prednisone was started at 1 mg/kg actual body weight per day. The duration of prednisone therapy and tapering schedule were not mandated by the protocol. In the setting of increased chronic GVHD activity, prednisone could be increased with upper limit of 1 to 2 mg/kg/day; doses higher than this were considered a separate line of additional systemic immune suppressive therapy. As no cases had discontinued all systemic immune suppression (both initial GVHD prophylaxis agents and any therapy delivered for acute GVHD) by the time of chronic GVHD onset, these agents were continued alongside the new addition of study therapy (1 mg/kg/day prednisone + ofatumumab). Taper of other systemic agents and use of topical agents (eg, ocular drops, mouth rinses, topical steroid creams) were not regulated by the trial. Ofatumumab was administered by i.v. infusion; preparation and infusion conditions were per standard procedures. Dose level cohorts in this phase I trial included the following: cohort 1, 300 mg; cohort 2, 700 mg; and cohort 3, 1000 mg (all delivered once on day 0 and again on day 14 of therapy). This dose/schedule was modeled after a prior trial conducted in rheumatoid arthritis that demonstrated safety, sustained depletion of peripheral blood $CD19^+$ B cells (persistent for 48 weeks), and efficacy with association between increasing dose and clinical response [48]. A dose level −1 of 100 mg was prespecified in the event excess dose-limiting toxicity (DLT) occurred at dose level 1. Premedication was uniformly delivered within 30 minutes before each infusion: acetaminophen 1000 mg, diphenhydramine 50 mg, and methylprednisolone i.v. 50 mg. Vital signs were monitored every 30 ($\pm$5) minutes during infusion or more frequently as needed. The initial infusion rate, timing of sequential infusion rate escalation, and rules surrounding response to observed infusion reactions were enforced. If grade 4 infusion reactions occurred, no further ofatumumab therapy was to be given; lesser grade infusion reactions were managed with supportive care including i.v. fluids, antihistamines, and steroids. Supportive antimicrobial prophylaxis followed institutional standards. Immunoglobulin replacement was delivered per discretion of the treating physician, not mandated per protocol.

### *Phase I Trial Characteristics*

The phase I trial followed a traditional (3 + 3) escalation design. Successive dose level cohorts were enrolled and monitored for DLT. The minimum DLT observation period was 46 days after completion of ofatumumab therapy for the last patient on each dose level. DLT was defined by the occurrence of any of the following within 46 days of the last ofatumumab therapy: grade 4 infusion reactions, grade 4 constitutional symptoms at least possibly due to ofatumumab, $\geq$ grade 3 organ toxicities at least possibly due to ofatumumab, and grade 4 neutropenia lasting more than 14 days. The following were criteria for patient termination from the study: patient withdrawal, death, relapsed malignancy, and completion of study follow-up. Patients in the maximally tolerated dose (MTD) cohort are carried forward in the phase II component and will complete all planned phase II follow-up (24 months), whereas those at lower non-MTD cohorts complete an abbreviated study follow-up with clinical assessment measures and biologic studies only at the 6- and 12-month time points.

### *Statistical Methods*

The occurrence of DLT attributable to ofatumumab in $\leq$17% served as the boundary for the MTD of ofatumumab in this phase I trial. Escalation to each higher dose level was permitted when 0 of 3 or no more than 1 of 6 (number treated per level was increased to 6 if 1 of 3 experienced a DLT) in a dose level cohort experienced a DLT. Dose de-escalation was indicated if a greater proportion experienced a DLT at any dose level. A total of 6 patients were enrolled at the MTD cohort.