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Phase 1 Study of Tabalumab, a Human Anti-B-Cell Activating Factor Antibody, and Bortezomib in Patients with Relapsed/Refractory Multiple Myeloma

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Abstract

Purpose: Tabalumab, a human mAb that neutralizes B-cell–activating factor (BAFF), demonstrated antitumor activity in xenograft models of multiple myeloma. Here we report on a phase I study of relapsed/refractory multiple myeloma patients in which the primary objective was to identify a tolerable and potentially efficacious dose of tabalumab when combined with bortezomib.

Experimental Design: Forty-eight patients were enrolled; 20 to the dose-escalation cohort, and 28 to cohort expansion in which a dose of 100 mg of tabalumab was evaluated. All patients had received either prior bortezomib or an immunomodulatory drug; the median number of prior therapies was 3. Bortezomib was administered intravenously on days 1, 4, 8, and 11 of a 21-day schedule. Tabalumab was given every 21 days for 3 cycles, then every 42 days thereafter.

Results: The most common grade 3/4 toxicities included thrombocytopenia, neutropenia, pneumonia, and peripheral sensory neuropathy. There were no dose-limiting toxicities, and the maximum tolerated dose was not reached. Pharmacokinetic data suggested serum exposure increased in a greater than dose-proportional manner up to a dose of 100 mg. Out of 46 evaluable patients, 20 had confirmed responses. The median time to progression (9 patients censored) was 4.8 months, and the median response duration (4 patients censored) was 7.2 months.

Conclusions: A dose of 100 mg tabalumab in combination with bortezomib was well tolerated and active and is currently under further investigation. *Clin Cancer Res; 22(23); 5688–95. ©2016 AACR.*

Introduction

B-cell–activating factor (BAFF) is a member of the TNFα superfamily and, along with a proliferating inducing ligand (APRIL), has been implicated as one of the main survival factors for immature, naïve, activated B cells and plasma cells (1). Multiple myeloma is a B-cell malignancy with associated proliferation and growth of clonal plasma cells. It is a stromally dependent cancer with expansion predominantly in the bone marrow niche. The roles of ligands such as BAFF and APRIL have been previously studied (2–5). These stromally derived cytokines have demonstrated their ability to confer a survival advantage on myeloma cells (2, 3, 6, 7). Moreover, BAFF has been reported to induce antiapoptotic proteins such as Bcl-2 and Bcl-Xl and to reduce proapoptotic proteins such as Bak (8).

We previously demonstrated elevated levels of serum BAFF in patients with multiple myeloma (4). Using a neutralizing antibody against soluble and membrane-bound BAFF in an *in vivo* model, we demonstrated anti-multiple myeloma activity and improved survival, compared with an isotype control (4). Our data suggested that BAFF was produced by the stromal compartment, specifically the osteoclast compartment, and that treatment with an anti-BAFF antibody resulted in antitumor activity and decreased osteoclast numbers (4). Others have shown that elevated BAFF and APRIL levels are associated with poorer outcome and more aggressive disease (9, 10). This association of elevated BAFF levels with poorer outcomes, along with the role of BAFF in the survival of multiple myeloma cells, provided the rationale for targeting BAFF in relapsed/refractory multiple myeloma.

Although the single-agent activity of tabalumab is unknown, the lack of direct toxicity to multiple myeloma cells (4) prompted the investigation of this antibody in combination. Therefore, we

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Multiple myeloma is a B-cell malignancy with associated proliferation and growth of clonal plasma cells. It is a stromally dependent cancer with expansion predominantly in the bone marrow niche. The stromally derived cytokine B-cell–activating factor (BAFF) has been demonstrated to confer a survival advantage on myeloma cells. In addition, it has been shown that BAFF levels are associated with more aggressive disease and poorer outcomes. Tabalumab is a neutralizing antibody against soluble and membrane-bound BAFF. This is the first clinical report of targeting BAFF with tabalumab in multiple myeloma. The purpose of this study was to identify a tabalumab dose to test in future studies. In combination with bortezomib, tabalumab was well tolerated, and the combination demonstrated efficacy even in patients previously treated with bortezomib.

conducted a phase I dose-escalation study of tabalumab (anti-BAFF antibody) combined with bortezomib in patients with relapsed or refractory multiple myeloma. The rationale for combining tabalumab and bortezomib was based on preclinical data demonstrating that BAFF neutralization decreased osteoclast numbers and led to indirect anti-multiple myeloma activity (4) and that bortezomib, in addition to its potent anti-multiple myeloma activity and effects on the bone compartment, increases osteoblast number and function (11). Moreover, preclinical data suggest inhibition of BAFF by bortezomib (12–13).The purpose of the study was to determine a potentially efficacious dose of tabalumab for further evaluation in combination with bortezomib.

Materials and Methods

Study design

This study was a nonrandomized, open-label, multicenter, dose-escalation study of intravenous tabalumab in combination with bortezomib in patients with relapsed or refractory multiple myeloma and is registered at ClinicalTrials.gov as NCT00689507. The primary objective of the study was to identify a recommended phase II dose of tabalumab with bortezomib for patients with relapsed or refractory multiple myeloma. Secondary objectives for studying tabalumab in combination with bortezomib included characterizing the associated safety and toxicity profile, assessing the associated changes in pharmacokinetics and pharmacodynamics, describing the response rate (RR), duration of response (DOR), and time to progression (TTP), and exploring a potential drug–drug interaction between tabalumab and bortezomib. This study also aimed to characterize the safety, toxicity, pharmacokinetics, pharmacodynamics, and preliminary efficacy of tabalumab in combination with bortezomib and dexamethasone.

The study consisted of two parts: part A, dose-escalation, and Part B (B1, B2, and B3), cohort expansion; each cycle was 21 days in length (Fig. 1). In part A (dose escalation), cohorts consisting of 3 to 6 patients received tabalumab dose levels between 1 mg and 300 mg along with bortezomib. Bortezomib was administered intravenously for all patients (as the study was designed prior to the approval of subcutaneous administration; ref. 14). Cohorts were expanded to a maximum of 6 patients if 1 patient at any dose level experienced a dose-limiting toxicity (DLT). If 2 patients experienced a DLT at a specific dose level, that cohort would be closed. Part B1 was designed to allow determination of the pharmacokinetics for bortezomib without tabalumab, to detect potential drug–drug interactions. Thus, for cycle 1, patients were treated with bortezomib on day 1 and tabalumab on day 2. Subsequent cycles in part B1 were carried out according to the schedule in part A. In part B2, patients were assigned to receive tabalumab and bortezomib. During the clinical trial, an amendment to the study was made (part B3) and patients received dexamethasone in addition to tabalumab and bortezomib (according to the schedule in part B2) to assess the safety of the three-drug combination (Fig. 1).

After completion of the planned 8 cycles (endpoint) of study treatment containing bortezomib, patients could, at the investigator's discretion and contingent upon study drug availability, discontinue study treatment and enter observation, receive additional

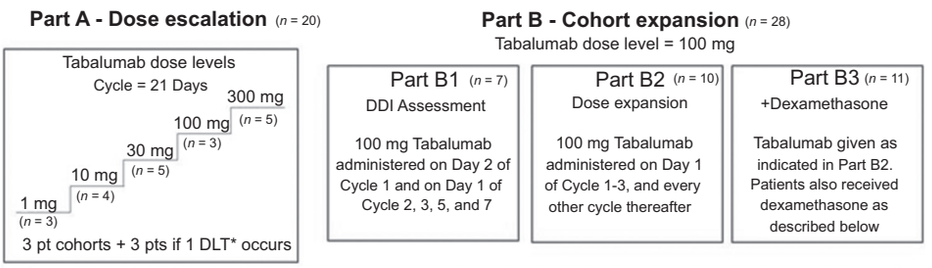

Figure 1.
Design for phase 1 study of tabalumab and bortezomib.
* any of: ≥grade 3 nonhematologic toxicity; thrombocytopenia with platelets <10,000/μL on ≥2 occasions despite transfusion support; grade 4 neutropenia lasting >5 days +/or neutropenic fever ≥101°F; or >7-day delay in ability to receive day 1 dose for cycle 2 due to toxicity. DDI, drug–drug interaction; DLT, dose-limiting toxicity.

Therapy administration and schedule

Therapy	Administration	Cycle number (cycle = 21 days) 1	2	3	4	5	6	7	8	Days of indicated cycles
Bortezomib	1.3 mg/m^2 3-5 sec bolus injection	X	X	X	X	X	X	X	X	Days 1, 4, 8 and 11
Tabalumab	30 min infusion	X	X	X		X		X		Day 1 (on Day 2 in Part B1 for DDI assessment)
Dexamethasone	20 mg po	X	X	X	X	X	X	X	X	Days 1, 2, 4, 5, 8, 9, 11, and 12

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cycles of tabalumab plus bortezomib, and dexamethasone (for patients in part B3), or receive additional cycles of tabalumab alone, until any criteria for discontinuation were met.

Ethical considerations

This study was conducted according to the principles of the Declaration of Helsinki, and protocol approval was obtained from institutional/ethics review boards. Patients provided written informed consent before participation in the trial.

Study population

Consenting adults with relapsed or refractory multiple myeloma, an Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$2, and who had been treated with at least 1 prior anti-multiple myeloma regimen were eligible for the study. Prior therapy with bortezomib was allowed provided that there was no relapse or progression $\leq$3 months from the last dose. Patients were required to be bortezomib-sensitive so that this study could be used to interpret a planned phase II study in which bortezomib would be a comparator. This protocol-specific definition was established prior to the now commonly utilized International Myeloma Working Group (IMWG) definition for treatment of refractory multiple myeloma. Patients had to have measurable disease according to 1 or more of the following criteria: monoclonal protein in the serum of $\geq$10 g/L, monoclonal light chain in the urine protein electrophoresis $\geq$200 mg/24 hours, and involvement of serum-free light chain (SFLC) level $\geq$100 mg/L provided the SFLC ratio was abnormal, and/or measurable plasmacytoma. Adequate organ function was also required, including an absolute neutrophil count $\geq$1,000/μL, platelet count $\geq$50,000/μL, hemoglobin $\geq$8 g/dL, total bilirubin $\leq$1.5 times the upper limit of normal (ULN), aspartate transaminase $\leq$3 times ULN, and creatinine $\leq$3.0 mg/dL. Patients also must have discontinued prior cancer therapies at least 2 weeks prior to study enrollment (6 weeks for mitomycin-C or nitrosoureas) and have a life expectancy of $\geq$16 weeks.

Response criteria

Response was assessed according to the International Uniform Response Criteria (IURC) for multiple myeloma established by the IMWG (15). Monoclonal protein was measured in both serum and urine at baseline, at cycle 2 and at each cycle thereafter. In addition, bone marrow assessment was performed at baseline and when necessary to establish a complete response (CR). An optional bone marrow assessment occurred at the end of cycle 2, for exploratory pharmacodynamic biomarkers. Reassessment of bone marrow and soft tissue plasmacytomas were required to confirm responses.

Time to progression (TTP) was defined as the time from study enrollment to the first objectively determined disease progression. The DOR was defined as the time from the first observation of a CR, very good partial response (VGPR), or partial response (PR) to the first objectively determined disease progression. For both TTP and DOR, patients without observed progression as of the data cut-off date, including those who received anticancer therapy other than study treatment or died prior to progression, were censored as of the date of the last complete objective disease assessment.

Pharmacokinetic assessment

Pharmacokinetic blood samples were collected to measure serum concentration levels of tabalumab at the following times: 0, 2, 6, 24, 72, 168, 240, and 504 hours after the first infusion, and 0, 2, 6, 24, 72, 168, 240, and 720 hours after the fifth infusion (cycle 7). In addition, blood samples were collected to measure bortezomib plasma concentration levels at 0.5, 1, 2, 4, 6, and 24 hours postdose on day 1 of cycle 1. Noncompartmental analyses were used to estimate pharmacokinetic parameters for both compounds (WinNonLin/Phoenix, version 6.3). Observations below the limit of quantitation of the assay were excluded from the analysis.

Table 1. Patient demographics and prior therapies

Demographics and patient characteristics	All patients $N = 48$
Sex, n (%)	
Male	21 (44)
Female	27 (56)
Age, years, median (range)	65.7 (41–84)
Race, *n* (%)	
White	38 (79)
Black	7 (15)
Asian	2 (4)
Other	1 (2)
ECOG, *n* (%)	
0	13 (27)
1	34 (71)
2	1 (2)
Prior therapies	
Any prior therapy, *n* (%)	48 (100)
Transplant, *n* (%)	25 (52)
Bortezomib, *n* (%)	37 (77)
IMiD, *n* (%)	42 (88)
Bortezomib or IMiD, *n* (%)	48 (100)
Prior treatments, median (range)	3 (1–10)
Multiple myeloma status, *n* (%)	
Progressive disease	36 (75)
Refractory	12 (25)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory drug.

Assessment of B cells, immunoglobulins, and BAFF levels

Total $CD19^+$ B-lymphocyte counts were enumerated from whole blood samples using flow cytometry at Esoterix, Inc. (LabCorp). Levels of immunoglobulin (Ig) A, IgG, and IgM (g/L) were enumerated from serum samples using Nephelometry at Covance, Inc. The B-cell ($CD19^+$) count and immunoglobulin levels were measured at baseline and postbaseline. BAFF protein levels were measured from baseline serum samples using an analytically validated ELISA at Pacific Biomarkers. Exploratory descriptive analyses were performed for biomarkers. For patients with multiple baseline measurements for BAFF, the average value was calculated. For immunoglobulins and B cells ($CD19^+$), the percent changes from baseline (PCB) were calculated. Patients who had IgG, IgA, or IgM subtypes of multiple myeloma were excluded from the corresponding immunoglobulin analyses.

Results

Patient enrollment, demographics, and prior therapies

Of 62 patients who were screened, 48 met the inclusion criteria and received study treatment. The median age of patients in the study was 65.7 years (range 41–84 years), 56% were female, and the majority (98%) had an ECOG performance status of 0 or 1 (Table 1). All 48 patients had received either prior bortezomib (77%) or immunomodulatory drugs (IMiD; 88%), 52% had received a transplant prior to enrollment in the study, and the median number of prior therapies for all patients was 3 (range, 1–10; Table 1).

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Table 2. Summary of treatment-emergent adverse events

	Grade ≥3[b]		All grades	
TEAEs[a] (preferred term)	***n***	**%**	***N***	**%**
Peripheral sensory neuropathy	6	13	30	63
Fatigue	3	6	28	58
Diarrhea	4	8	27	54
Musculoskeletal pain	3	6	24	50
Nausea	1	2	23	48
Thrombocytopenia	15	31	16	33
Abdominal pain	1	2	16	33
Vomiting	1	2	16	33
Headache	0	0	16	33
Decreased appetite	0	0	14	29
Upper respiratory tract infections	1	2	13	27
Pyrexia	1	2	11	23
Constipation	0	0	11	23
Anemia	3	6	11	23
Cough	1	2	10	21
Chills	0	0	10	21
Edema peripheral	0	0	10	21
Neutropenia	7	15	8	17
Pneumonia	6	13	6	13
Neuralgia	2	4	6	13
Hypokalemia	4	8	5	10
Renal failure	4	8	5	10
Gastrointestinal hemorrhage	2	4	2	4

Abbreviation: TEAE, treatment-emergent adverse event (regardless of relatedness to study drug).

[a]Listing includes TEAEs ≥ grade 3 that were experienced by 2 or more patients and TEAEs of grade 1/2 that were experienced by at least 20% of patients.

[b]No grade 5 events occurred for the TEAEs listed.

Cycles of treatment received and adverse events

The median number of cycles of treatment received in the study was 5.5 (range: 1–28); 10 (21%) patients completed at least 8 cycles of therapy. Most patients ($n = 35$, 73%) discontinued treatment due to progressive disease. The most common treatment-emergent adverse events (TEAE) of any grade were peripheral sensory neuropathy (63%), fatigue (58%), diarrhea (54%), musculoskeletal pain (50%), and nausea (48%; Table 2). Grade 3/4 TEAEs most commonly experienced were thrombocytopenia (31%), neutropenia (15%), pneumonia (13%), and peripheral sensory neuropathy (13%; Table 2). The toxicity profile was consistent with what is typically seen with bortezomib in this patient population.

Four patients experienced 1 or more serious adverse events (SAE) considered possibly related to the study drug. These included nausea ($n = 1$), acute respiratory distress syndrome (ARDS; $n = 1$), pancreatitis ($n = 1$), hypovolemia ($n = 1$), vomiting ($n = 1$), diarrhea ($n = 1$), and *C. difficile* colitis ($n = 1$). Two deaths occurred on study. One death due to ARDS and deemed possibly related to the study drug occurred in part B2 (no dexamethasone) of the study; this patient received 3 cycles of treatment and also had progressive disease and respiratory illness complicated by ARDS. The other death occurred in a patient who received 18 cycles of treatment in the 100 mg cohort; death was deemed due to progressive disease.

Summary of responses and TTP

Of 48 patients entered, 46 had response assessments and could be evaluated for a confirmed IURC (13) response (Fig. 2A). Twenty patients (42%) had confirmed PRs or better; of these, 3 patients achieved a CR, 2 had a VGPR, and 15 had a PR (Fig. 2A). Monoclonal protein responses were measured for 48 patients; 31 of these patients had response assessments in serum and 27 had assessments in urine (Fig. 2B). A decrease in monoclonal protein levels in the serum or urine compared with baseline was observed in the majority of patients on at least 1 assessment (Fig. 2B). The median DOR, with 4 patients censored, was 7.2 months [95% confidence interval (CI): 3.7–13.8 months], and the median TTP, with 9 patients censored, was 4.8 months (95% CI, 4.0–7.1 months; Fig. 2C and D). In part A ($n = 20$), there were no dose–response trends for any response categories, including CR (2 patients; 1 each at 10 mg and 300 mg), VGPR (2 patients), or PR (6 patients).

Pharmacokinetics

During the dose-escalation phase (part A), 20 patients were treated at 1 of 5 dose levels (1, 10, 30, 100, or 300 mg) as described in Fig. 1. Serum concentration data for tabalumab were available for analysis from a total of 48 patients across a total dose range of 1 mg to 300 mg. However, pharmacokinetic data after repeated intravenous dosing were only available from 20 patients, allowing the calculation of mean pharmacokinetic parameters only for the 30 and 100-mg groups.

After a single intravenous administration (Fig. 3A; Supplementary Table S1), the time course of tabalumab in serum showed a dose-proportional increase in the maximum serum concentration (C_{max}), whereas dose proportionality could not be established for the area under the concentration–time curve from time 0 to time of the last measurable concentration ($AUC_{0-tlast}$) or time 0 to infinity (AUC_{0-inf}). Correspondingly, the mean systemic clearance decreased with dose between 1 and 100 mg to stabilize at a value of approximately 0.0076 to 0.0085 L/hour (0.18 to 0.20 L/day) at 100 mg and above. The elimination half-life ($t_{1/2}$) increased from approximately 37 hours (1.6 day) at 1 mg to 466 to 498 hours (19–21 days) at 100 and 300 mg. The same was observed after repeated intravenous dosing (Fig. 3B; Supplementary Table S1), where systemic clearance decreased with dose to stabilize at mean values of approximately 0.0064 and 0.0062 L/hour (0.15 L/day) at 30 mg and 100 mg, respectively. These findings suggest that the dose of 100 mg provides full target neutralization both after a single dose and at steady state. These data provided the rationale to select 100 mg as the dose for the cohort expansion phase (part B), further suggesting that higher doses and identification of a MTD was not necessary. The combination with dexamethasone did not seem to impact the disposition of tabalumab at the dose of 100 mg, either after a single dose or after repeated administration.

Bortezomib plasma concentration data after a single intravenous dose were available from 46 patients. One patient was deemed a statistical outlier and was excluded from the summary statistics. Twenty-eight patients had bortezomib administered at the same time as tabalumab alone, 6 had bortezomib administered alone, and 11 had bortezomib administered in the presence of both tabalumab and dexamethasone. The pharmacokinetic parameters for bortezomib administered in the presence of tabalumab were similar to values previously published in the literature (Supplementary Table S2; refs. 14, 16–18). There was no apparent difference in the pharmacokinetics of bortezomib depending on the dose of tabalumab coadministered (Fig. 3C; Supplementary Table S2). Likewise, there was no apparent difference in the disposition of bortezomib in patients who received bortezomib in the presence or absence of tabalumab (Fig. 3D; Supplementary Table S3). No difference in the disposition of bortezomib was

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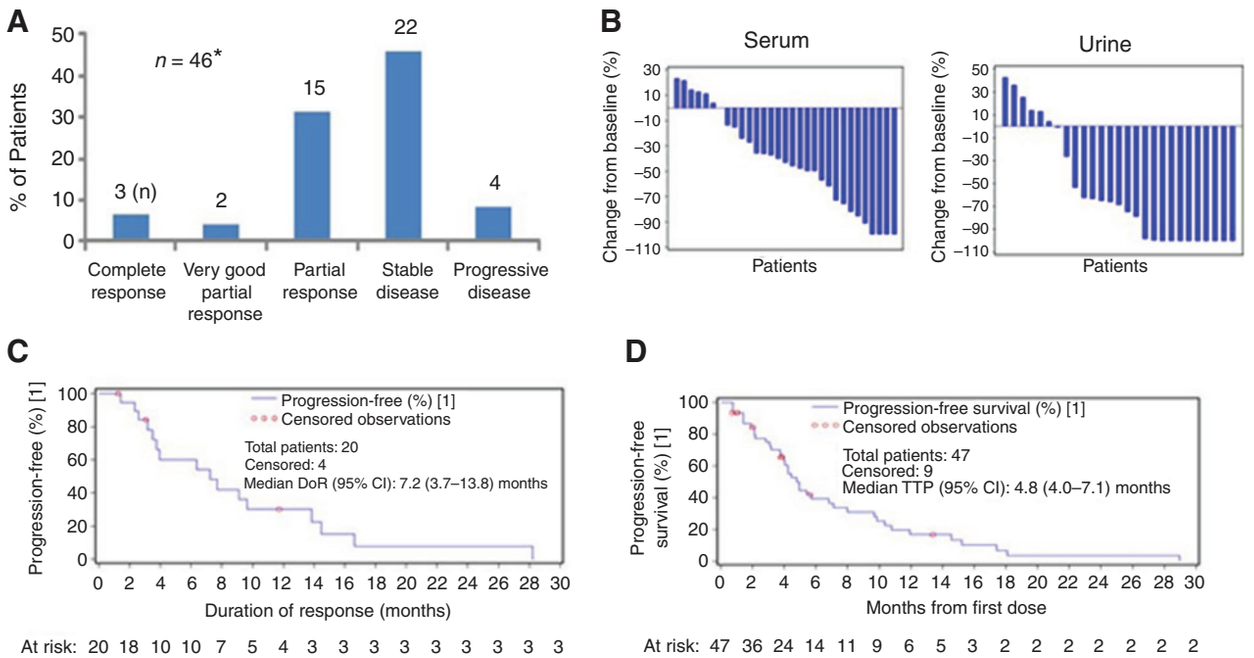

Figure 2.

Summary of responses and time to progression in multiple myeloma patients. **A,** Bar graph showing number of patients with each best confirmed International Uniform Response Criteria (IURC) response; the asterisk (*) denotes that 2 patients did not have response assessments and thus were not evaluable. **B,** Monoclonal protein best response in serum (left) and urine (right). Patients on the *x*-axes are sorted by best response from baseline for serum or urine monoclonal protein in descending order. Graphs show the subset of total patients ($n = 48$) who had response assessments: serum ($n = 31$), urine ($n = 27$). **C,** Duration of response was measured for the 20 patients in **A**) who had confirmed responses (4 patients were censored). Nonresponders are excluded. [1], based on Kaplan–Meier estimates of time to first progression. Time is measured from date of first response (partial, very good partial, or complete response). Censoring occurs at last progression-free visit. **D,** TTP was measured for 47 patients (9 patients were censored). [1], based on Kaplan–Meier estimates of time to first progression. Time is measured from the date of the first dose. Censoring occurs at last progression-free visit. DLT, dose-limiting toxicity; DoR, duration of response.

observed following the combination with tabalumab and dexamethasone.

Percentage change from baseline for B cells and immunoglobulins

The percent changes from baseline for B cells ($CD19^+$) and immunoglobulins are shown in Supplementary Fig. S1. The median B-cell count declined by 62% after cycle 4, and a similar level of B-cell decrease was observed throughout the remainder of the study (Supplementary Fig. S1A). For uninvolved serum IgG levels, the maximum median decrease (14%) was observed near the end of cycle 2 and during cycle 3 (Supplementary Fig. S1B). A maximum median decrease was observed during cycle 4 for IgA levels (Supplementary Fig. S1C), while the median levels of uninvolved IgM did not change with regard to baseline measurements (Supplementary Fig. S1D).

Baseline BAFF expression

BAFF expression levels were measured at baseline for 46 patients in the study, 19 who had a best overall response of PR or better (Fig. 4). BAFF levels ranged from 97 pg/mL to 11,368 pg/mL. No responses were observed in the 9 patients who had BAFF levels >1,500 pg/mL, while 19 of the 37 patients with baseline BAFF <1,500 pg/mL had an observed response (Fig. 4). Of these 9 nonresponders with the highest BAFF levels, 7 received a tabalumab dose of 100 mg and 2 received 300 mg of tabalumab.

Discussion

mAb-based therapies hold great promise in multiple myeloma (19). Among these, the signaling lymphocyte activation molecule family 7 (SLAM F7)-directed mAb, elotuzumab, has shown efficacy when combined with lenalidomide (20, 21). Others targeting tumor cell–related target proteins include mAbs directed against CD38, including daratumumab (22), which has shown great promise as a single agent in relapsed/refractory multiple myeloma, and SAR650984, which is now entering later phase trials (23–28). Previous attempts to target the cytokine milieu, such as IL6-directed strategies using siltuximab, have shown mixed results (29–30). This is the first report of an IgG4 antibody, tabalumab, directed against both membrane-bound and soluble BAFF, in patients with previously treated multiple myeloma. Given that tabalumab is an IgG4 antibody lacking immune mechanisms, there was less rationale for combination with the immunomodulatory drugs.

The TNF alpha superfamily cytokines BAFF and APRIL have been previously studied in the context of other autoimmune diseases, including systemic lupus erythematosus (SLE) and rheumatoid arthritis (31–33). Their roles in B-cell malignancies other than multiple myeloma have also been reported (34–36). BAFF signals through 3 receptors, including the BAFF receptor, transmembrane activator, and calcium-modulating ligand interactor (TACI), and B-cell maturation antigen (BCMA; ref. 1). This

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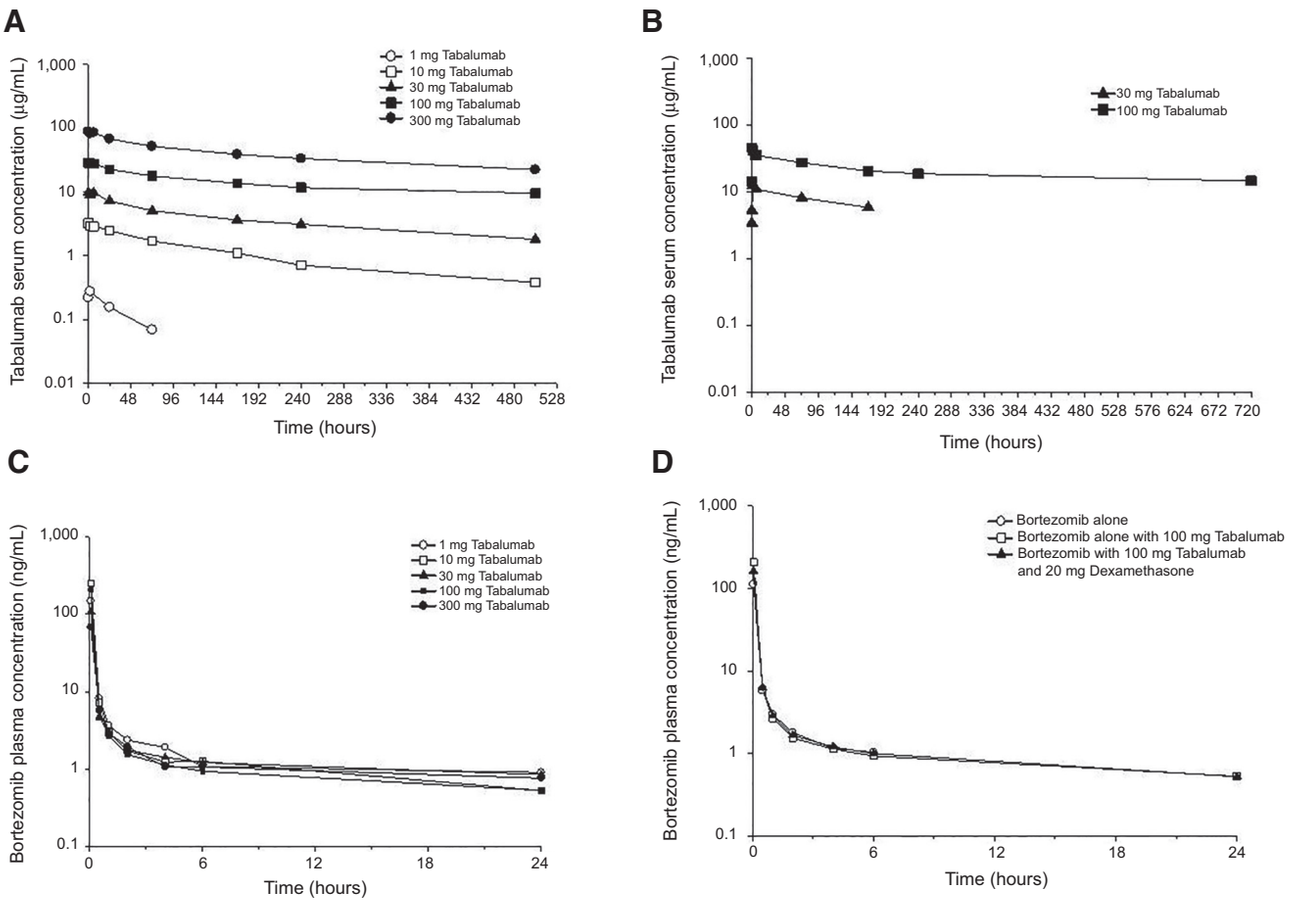

Figure 3.

Mean serum/plasma concentration–time profiles for tabalumab and bortezomib in multiple myeloma patients. **A,** Geometric mean time course of tabalumab serum concentration following a single intravenous infusion of varying doses of tabalumab combined with 1.3 mg/m^2 bortezomib and with/without 20 mg oral dexamethasone. **B,** Geometric mean time course of tabalumab serum concentration following multiple intravenous infusions of 30 or 100 mg tabalumab combined with 1.3 mg/m^2 bortezomib and with/without 20 mg oral dexamethasone. **C,** Geometric mean time course of bortezomib plasma concentration following a single 1.3 mg/m^2 intravenous bolus administration in the presence of 1, 10, 30, 100, or 300 mg tabalumab. **D,** Geometric mean time course of bortezomib plasma concentration following a single 1.3 mg/m^2 intravenous bolus administration in the absence of tabalumab, in the presence of 100 mg tabalumab, or in the presence of 100 mg tabalumab and 20 mg oral dexamethasone.

axis is therefore being intensively studied for clinical development. A BAFF-directed antibody belimumab was recently approved for the treatment of SLE (37). Other BAFF antagonists, such as atacicept and blisibimod, are also undergoing clinical investigation (33).

In this phase I study, tabalumab and bortezomib were well-tolerated, and no DLTs were observed. Full target neutralization was obtained at a dose of 100 mg, which was selected as the dose for the cohort expansion phase of this study. Overall, the toxicities noted paralleled those that were expected for patients with multiple myeloma, especially those receiving bortezomib with or without dexamethasone treatment. Given that BAFF-directed strategies affect B-cell immunity and antibody production, we evaluated B-cell subsets and effects on uninvolved immunoglobulin production. We observed a decrease in baseline CD19$^+$ cells and immunoglobulin production, consistent with the mechanism of action of tabalumab, bortezomib, and dexamethasone. Six (13%) patients experienced grade 3/4 pneumonia in the study, 4 who were in the cohort that received dexamethasone. Importantly, there were no infusion-related toxicities and, with the exception of part B3, in which dexamethasone was added to the treatment regimen, tabalumab was administered without premedications, underscoring its favorable tolerability profile. The study was initiated without dexamethasone with the intent to assess the activity of tabalumab and bortezomib as a steroid-free regimen. However, we modified the protocol and incorporated steroids in the later part of the study based on the improved efficacy and widespread use of steroids as part of standard of care with bortezomib. The addition of steroids did not impact either pharmacokinetics or efficacy.

In this phase I dose-finding study, we also observed encouraging anti-myeloma activity, with 20 of 48 patients (42%) showing a PR or better in these heavily pretreated patients, all of whom had received either bortezomib (77%) or an IMiD (88%). The median DOR was 7.2 months, and the median TTP was 4.8 months. In a recent meta-analysis, the observed RR to bortezomib

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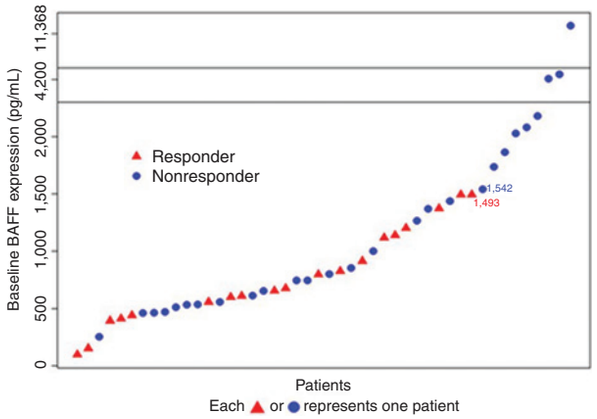

Figure 4.

BAFF expression at baseline. BAFF serum protein levels were measured at baseline and plotted for each individual patient on the *y*-axis in increasing order. Red triangles represent responders (includes partial responses, very good partial responses, and complete responses) and blue circles represent nonresponders (includes stable disease and progressive disease). For patients with multiple measurements in the same day, the average of these measurements is presented.

re-treatment in patients with relapsed/refractory multiple myeloma was 39% (38), which is comparable with other studies of bortezomib combination treatments in similar patients (39–41). More recently, Petrucci and colleagues (42) observed a RR of 40% with bortezomib retreatment in multiple myeloma patients. In the current study, patients with very high BAFF levels, generally considered to have a poor prognosis, were among the nonresponders. Whether this patient population would have had an improved outcome with the higher dose of tabalumab is being prospectively studied in a randomized phase II trial (NCT01602224).

There are several limitations of the current study which should be acknowledged. First, this study was not designed to provide information about the single-agent activity of tabalumab. The safety profile of tabalumab alone has been well-established in rheumatologic diseases (43–44) and as it targets predominantly the nontumor compartment, treating relapsed/refractory patients with single-agent tabalumab was unlikely to produce responses. Therefore, the true contribution of tabalumab to the efficacy seen in this study cannot be evaluated. An ongoing randomized phase II study of bortezomib and dexamethasone, with or without tabalumab, will provide a more definitive assessment of the relative efficacy of tabalumab in combination with bortezomib and dexamethasone. Finally, it is important to note that the current study included only patients who were previously sensitive to bortezomib, but utilized a protocol-specific definition that was more liberal than the current definition recommended by the IMWG. Therefore, it is not possible to speculate, based on the results of this study, whether tabalumab reversed bortezomib resistance. This question deserves exploration whether tabalumab improves outcomes in bortezomib-sensitive disease.

Finally, there are other potentially relevant molecules in the BAFF signaling pathway, including APRIL, the BAFF receptor, TACI, and BCMA. There is evidence that APRIL may play a significant role in plasma cell survival, suggesting that agents with activity against both BAFF and APRIL, such as atacicept may be more relevant in this context. Strategies to target BCMA are in development and may allow further dissection of the relevance of these targets in multiple myeloma. Despite these complexities, it remains important to determine whether targeting BAFF alone is sufficient in multiple myeloma, and the final results of a randomized phase II trial with tabalumab (NCT01602224) are awaited to answer this question.

Disclosure of Potential Conflicts of Interest

N. Raje is a consultant/advisory board member for Takeda. E. Faber reports receiving speakers bureau honoraria from Celgene and Sanofi Aventis and is a consultant/advisory board member for CTI BioPharma, Gilead, and Seattle Genetics. G. Schiller reports receiving a commercial research grant from Eli Lilly & Company. A.D. Cohen is a consultant/advisory board member for Bristol-Meyers Squibb, Celgene, and Janssen. T.S. Nguyen, C. Kaiser, DM. Cronier, and J.E. Wooldridge have ownership interest (including patents) in Eli Lilly & Company. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

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Phase 1 Study of Tabalumab, a Human Anti-B-Cell Activating Factor Antibody, and Bortezomib in Patients with Relapsed/Refractory Multiple Myeloma

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