A Phase II Study of Venetoclax in Combination With Pomalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma

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Abstract

Venetoclax with pomalidomide and dexamethasone (VenPd) was evaluated in patients with lenalidomide-refractory relapsed/refractory multiple myeloma. Enrollment was limited to 8 patients, and no clear safety or efficacy conclusions can be drawn. The steady-state pharmacokinetic parameters for venetoclax and pomalidomide during coadministration suggested no pharmacokinetic interaction. These preliminary data can be used to guide future combinations of venetoclax with immunomodulatory agents.

Background: Venetoclax is a selective BCL-2 inhibitor with clinical activity in relapsed/refractory multiple myeloma (RRMM). Combinations of venetoclax with agents that have complementary mechanisms of action may improve venetoclax efficacy in RRMM. This study evaluated venetoclax with pomalidomide and dexamethasone (VenPd) in RRMM. **Patients and Methods:** This phase II open label study (NCT03567616) evaluated VenPd in patients with RRMM who had received $\geq$ 1 prior therapy and were refractory to lenalidomide. Venetoclax was administered orally daily for days 1 to 28, pomalidomide was administered orally daily for days 1 to 21, and dexamethasone was administered weekly for each 28-day cycle. The primary objective was to characterize the safety and tolerability of VenPd. The secondary objectives were to evaluate the efficacy and pharmacokinetics. The study was terminated early due to partial clinical hold and decision to pursue biomarker driven strategy. **Results:** Eight patients were enrolled. Patients had a median age of 67.5 years. All patients received 400 mg venetoclax; 4 patients experienced dose-limiting toxicities and the dose was not escalated. All patients had a grade $\geq$ 3 adverse event, and the most common was neutropenia (n = 6); cytopenias were the most prevalent adverse events. Five patients (63%) had a confirmed response, and the median duration of response was 12.9 months. The median progression-free survival was 10.5 months. **Conclusions:** Given the limited enrollment, no clear safety or efficacy conclusions about VenPd can be drawn. Preliminary safety data, particularly the occurrence of cytopenias, can be used to guide dosing strategies for future combinations of venetoclax with immunomodulatory agents.

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Introduction

Multiple myeloma (MM) is a heterogenous malignancy of terminally differentiated plasma cells that is characterized by end-organ damage, bone destruction, anemia, and renal failure.[1] The 5-year survival rate for patients with MM has greatly improved with advances in treatment over the past 2 decades[2]; however, MM remains incurable, and most patients will relapse and eventually become refractory to available therapies.[3-6] MM becomes increasingly aggressive in the relapsed setting, with response durations decreasing with each subsequent line of therapy.[5] There are multiple classes of approved therapies for MM, including proteasome inhibitors, monoclonal antibodies, and immunomodulatory drugs (IMiDs).[7,8] IMiDs are a backbone of MM treatment in the frontline

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and relapsed settings.[8] Regimens that combine IMiDs with agents that have novel, complementary mechanisms of action may improve treatment of relapsed/refractory MM (RRMM).

The BCL-2 family of antiapoptotic proteins, including BCL-2, BCL-X_L, and MCL-1, can drive evasion of apoptosis and resistance to therapy, making BCL-2 a rational therapeutic target for MM.[9,10] Venetoclax is a highly selective, orally bioavailable, small-molecule inhibitor of BCL-2 that induces apoptosis in BCL-2–dependent MM cells.[11] Venetoclax as a monotherapy or in combination has been shown to have meaningful clinical activity against RRMM, particularly in patients with t(11;14).[12-14] BCL-2 dependency varies in MM cells and is higher in MM cells positive for t(11;14).[15-17] Higher BCL-2 dependency is correlated with increased sensitivity to venetoclax treatment.[18] The combination of venetoclax with agents that have complementary mechanisms of action, such as IMiDs, or agents that increase BCL-2 dependency may increase the anti-MM activity of venetoclax.

One such approach is to combine venetoclax with pomalidomide and dexamethasone (VenPd). Pomalidomide is a potent IMiD with antiangiogenic, antiproliferative, and immunomodulatory activity that is currently used in several combinations for the treatment of RRMM.[7] Combination of venetoclax and pomalidomide may enhance immune stimulation, as pomalidomide has been shown to directly stimulate antibody-dependent cytotoxic T-cell responses and increase Th1-type responses, and venetoclax has been shown to lead to enrichment of CD8+ T effector memory cells and reduction of CD4+ and CD8+ naïve T-cells.[19-21] Dexamethasone promotes BCL-2 dependency by increasing expression of BCL-2 and the prodeath protein BIM, promoting binding of BIM to BCL-2, and decreasing expression of the prosurvival protein BCL-X_L.[22] This phase II dose-escalation/dose-expansion study was conducted to evaluate the safety, efficacy, pharmacokinetics, and immune profile of VenPd in patients with RRMM with and without t(11;14).

Patients and Methods

Study Design and Conduct

This phase II, open-label, multicenter, dose-escalation/dose-expansion study enrolled patients with RRMM at 4 centers in the United States, Spain, and the United Kingdom (NCT03567616). Two doses of venetoclax (400 mg and 800 mg) were to be evaluated in the dose-escalation phase, which was based on a Bayesian optimal interval (BOIN) design. Dose-limiting toxicities (DLTs) were evaluated to identify an optimal dose, which was to be expanded in patients with and without t(11;14). The study protocol was approved by the relevant Ethics Committee or Institutional Review Board at each participating institution. The study was performed in accordance with the Declaration of Helsinki and with the current International Conference on harmonisation and Good Clinical Practice guidelines. All patients provided written informed consent.

Patients

Adult patients over 18 years of age with measurable disease and documented evidence of RRMM progression based on International Myeloma Working Group (IMWG) criteria were enrolled. Patients had received at least 1 prior line of therapy, including a proteasome inhibitor and at least 2 consecutive cycles of a lenalidomide-containing regimen, and were refractory to lenalidomide. Patients who received prior treatment with BCL-2 inhibitors or pomalidomide were excluded. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. Positive or negative t(11;14) status was required for enrollment. Patients with known hypersensitivity to IMiDs, known meningeal involvement of MM, or prior allogeneic stem cell transplantation within 6 months or autologous stem cell transplantation within 12 weeks of the first dose of study drug were excluded. Full enrollment criteria are included in the supplementary materials.

Treatment and Assessments

Venetoclax was administered orally at 400 mg daily for days 1 to 28, pomalidomide was administered at 4 mg orally daily for days 1 to 21, and dexamethasone was given at 40 mg weekly (20 mg weekly for patients ≥ 75 years of age) for each 28-day cycle. Treatment continued until documented disease progression, unacceptable toxicity, withdrawn consent, or other criteria for discontinuation were met. Patients could discontinue pomalidomide and dexamethasone and remain on venetoclax monotherapy for up to 2 years following the date of enrollment of the last patient provided they completed VenPd dosing for 1 cycle, continued to tolerate venetoclax, had no evidence of disease progression, and did not meet any criteria for treatment discontinuation. Anti-infective prophylaxis was recommended for management of grade 4 neutropenia. Use of systemic strong or moderate CYP3A inducers or inhibitors or strong CYP1A2 inhibitors were prohibited within 1 week of starting treatment and during cycle 1 of the dose escalation phase; concomitant use of strong or moderate CYP3A inhibitors for cycle 2 and beyond required venetoclax dose reduction. Concomitant use of strong CYP1A2 inhibitors required pomalidomide dose reductions. Prophylaxis for tumor lysis syndrome (TLS) using oral hydration, uric acid reducing agents, and chemistry laboratory monitoring was required for patients with t(11;14) and $> 50\%$ bone marrow infiltration or creatinine clearance of < 50 mL/min and recommended for all other patients.

Presence of t(11;14) was determined at screening by fluorescent in situ hybridization assay per central laboratory testing of a bone marrow aspirate prior to enrollment. Disease assessments were performed by investigators using the 2016 IMWG criteria.[23] Plasmacytoma evaluation and skeletal survey were performed by computed tomography, magnetic resonance imaging, or x-ray (for skeletal survey) at screening and if clinically indicated. Serum and urine assessments required per IMWG criteria were performed at screening and on day 1 of each cycle. Peripheral blood samples were collected on day 1 of cycles 1 to 4 to characterize pharmacodynamic changes in B- and T-cell subpopulations by multicolor flow cytometry (Supplementary Table S1). Blood samples for pharmacokinetic evaluation of venetoclax in dose escalation were collected predose, and 2-, 4-, 6-, 8-, and 24-hours postdose on day 1 and 15 of cycle 1. Blood samples for pharmacokinetic evaluation of pomalidomide in dose escalation were collected predose, and 1-, 2-, 4-, 6-, and 24-hours postdose on day 1 and day 15 of cycle 1. Additional predose blood samples were collected on day 1 of cycles 2, 4, 6, and 8. Treatment-emergent adverse events (TEAEs) were monitored

throughout the study until 30 days following treatment cessation. In the dose-escalation phase, DLTs were evaluated during the first cycle of VenPd. See the supplementary materials for a full definition of DLTs.

Outcomes

The primary objective of the study was to characterize the safety and tolerability of VenPd, and the secondary objectives were to evaluate the efficacy of VenPd and pharmacokinetics of venetoclax and pomalidomide when coadministered. Assessment of the immune response profile post-treatment was a posthoc objective. Efficacy endpoints included overall response rate (ORR, defined as at least partial response [PR]), progression-free survival (PFS), duration of response (DOR), and time to progression (TTP).

Statistical and Pharmacokinetic Analysis

The study was designed to enroll 6 to 12 patients to the dose-escalation part and approximately 50 patients to the dose-expansion part, with approximately 23 patients with t(11;14) and approximately 27 patients without t(11;14). This sample size would allow for 90% statistical power to detect an ORR of 70% with a 1-sided type-1 error rate of 0.025 for patients with t(11;14) and 60% with a 1-sided type-1 error rate of 0.1 for patients without t(11;14), assuming a historical ORR of 35% in each group.[24,25] In March 2019, sponsored studies of venetoclax in MM were placed on partial clinical hold by the United States Food and Drug Administration, and enrollment for this study was not resumed upon lifting of the partial clinical hold for venetoclax in MM. The study was terminated with reduced enrollment. All patients who received at least 1 dose of study drug were included in safety, efficacy, pharmacokinetics, and baseline analyses. Efficacy data were analyzed using point estimates and 95% CIs of ORR using a 1-sided significance level of 0.025 for t(11;14)-positive patients and 0.1 for t(11;14)-negative patients. Adverse events (AEs) were recorded by preferred term using the Medical Dictionary for Regulatory Activities version 23.0 and graded according to the National Cancer Institute Common Terminology Criteria for AEs version 4.03. Pharmacokinetic parameters were determined using noncompartmental methods, including maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), and the area under the plasma concentration versus time curve from 0 to 24 hours (AUC_{0-24}).

Results

Patients

Eight patients were enrolled between November 28, 2018 and February 27, 2019, including 3 with t(11;14) and 5 without t(11;14) (Table 1). Patients were a median age of 67.5 years (range, 60-77) and had received a median of 1.5 (range, 1-5) prior lines of therapy. Six patients (75%) were refractory to lenalidomide, 2 patients (25%) were refractory to a proteasome inhibitor, and 2 patients (25%) were double refractory. Four patients (50%) were refractory to daratumumab. All patients had an ECOG performance status of 1. One patient (13%) had t(14;16), 1 (13%) had del(17p), and 3 (38%) had gain(1q). Six patients (75%) had prior autologous stem cell transplant. All 8 patients received at least 1 dose of VenPd with 400 mg venetoclax. All 8 patients discontinued the study as of the June 18, 2020 data cutoff; the primary reasons for discontinuation were disease progression (n = 4, 50%), patient withdrawal (n = 1, 13%), physician decision (n = 1, 13%), death (n = 1, 13%), and an AE of grade 3 pancreatic neoplasm (n = 1, 13%). The median follow-up was 6.1 months (range, 0.4-15.2).

Safety

Four patients (50%) experienced a DLT, including 1 patient with grade 3 anemia lasting 8 days that was possibly related to venetoclax or pomalidomide; 1 patient with grade 4 neutropenia lasting 14 days that was possibly related to venetoclax or pomalidomide; 1 patient with grade 5 cardio-respiratory arrest that had no possibility of being related to treatment; and 1 patient with grade 3 pneumonia streptococcal lasting 28 days that was possibly related to VenPd. Based on these DLT findings and according to the BOIN design, the venetoclax dose would not be escalated to 800 mg.

All patients had at least 1 TEAE, with the most common (occurring in ≥ 50% of patients) being neutropenia (n = 6, 75%), anemia (n = 4, 50%), fatigue (n = 4, 50%), and hypokalemia (n = 4, 50%; Table 2). Grade ≥ 3 TEAEs occurred in all patients, and the most common (occurring in ≥ 25% of patients) were neutropenia (n = 6, 75%), leukopenia (n = 3, 38%), lymphocyte count decreased (n = 2, 25%), neutrophil count decreased (n = 2, 25%), and white blood cell count decreased (n = 2, 25%; Table 2). TEAEs with a possible relationship to VenPd as assessed by the investigator were reported in all 8 patients, with 8 patients (100%) having TEAEs possibly related to venetoclax, 7 patients (88%) having TEAEs possibly related to pomalidomide, and 5 patients having TEAEs possibly related to dexamethasone. Serious TEAEs were reported in 5 patients (63%), including 3 patients with serious infections (grade 3 pneumococcal infection, grade 3 pneumonia, and grade 3 pneumonia streptococcal; Supplementary Table S2). All of the serious infections were considered possibly related to venetoclax and pomalidomide. Venetoclax was interrupted in all 3 cases, and venetoclax dose was reduced in 1 case; pomalidomide and dexamethasone were interrupted in 2 of the cases. All serious infections resolved following hospitalization. There were no reports of TLS.

TEAEs led to venetoclax dose reduction in 2 patients, including 1 patient with grade 3 streptococcal lower respiratory tract infection, and 1 with grade 3 neutropenia. Three patients had pomalidomide dose reductions from TEAEs, including 1 with grade 3 neutropenia and grade 4 neutropenia, 1 with grade 4 neutropenia, and 1 with grade 2 neutrophil count decreased. Two patients, both with t(11;14), died on study due to TEAEs. One patient discontinued VenPd due to pancreatic neoplasm and died from an AE of cerebrovascular accident, which may have been exacerbated by hypertension 16 days after receiving the last dose of VenPd. The second patient experienced an AE of cardio-respiratory arrest that resulted in death within 11 days of receiving the first dose of VenPd. Neither event was considered to be treatment-related.

Efficacy

Five of 8 patients (63%) had a confirmed response, including 2/8 (25%) with a very good PR (VGPR) and 3/8 (38%) with a PR (Figure 1). Two of 3 patients (67%) with t(11;14) RRMM had a response (1 VGPR and 1 PR). The third patient died 11 days after

Table 1 Patient Demographics and Baseline Characteristics

Characteristic	t(11;14) n = 3	Non-t(11;14) n = 5	All Patients N = 8
Median age, y (range)	68 (67-74)	66 (60-77)	67.5 (60-77)
ECOG performance status, n (%)			
0	0 (0)	0 (0)	0 (0)
1	3 (100)	5 (100)	8 (100)
ISS stage, n (%)			
I	0 (0)	1 (20)	1 (13)
II/III	2 (67)	2 (40)	4 (50)
Not evaluable/unknown	1 (33)	2 (40)	3 (38)
Cytogenetic abnormalities, n (%)			
t(4;14)	0 (0)	0 (0)	0 (0)
t(14;16)	0 (0)	1 (20)	1 (13)
del(17p)	1 (33)	0 (0)	1 (13)
gain(1q) (≥ 3 copies)	1 (33)	2 (40)	3 (38)
No. prior lines of therapy, median (range)	3.0 (1-4)	1.0 (1-5)	1.5 (1-5)
1, n (%)	1 (33)	3 (60)	4 (50)
≥ 2, n (%)	2 (67)	2 (40)	4 (50)
Prior exposure to PI, n (%)	—	—	8 (100)
Refractory to PI	—	—	2 (25)
Prior exposure to lenalidomide, n (%)	—	—	8 (100)
Refractory to lenalidomide	—	—	6 (75)[a]
Prior exposure to daratumumab	—	—	4 (50)
Refractory to daratumumab	—	—	4 (50)
Double refractory[b], n (%)	—	—	2 (25)
Triple refractory[c], n (%)	—	—	2 (25)
Prior autologous stem cell transplantation, n (%)	2 (67)	4 (80)	6 (75)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ISS = International Staging System; PI = proteasome inhibitor.
[a] Two patients who were not refractory to lenalidomide were enrolled due to protocol deviations.
[b] Refractory to both proteasome inhibitors and lenalidomide.
[c] Refractory to proteasome inhibitors, lenalidomide, and daratumumab.

Figure 1 Responses in all patients.
Abbreviations: NE = not estimable; ORR = overall response rate; PR = partial response; SD = stable disease; VGPR = very good partial response

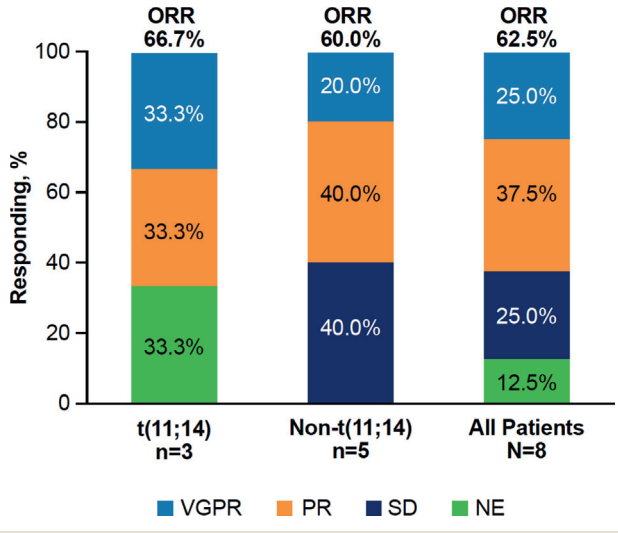


Table 2 Summary of Treatment-Emergent Adverse Events

TEAEs by Preferred Term, n (%)[a]	All Patients N = 8	
	Any Grade	Grade ≥ 3
Any TEAE	8 (100)	8 (100)
Neutropenia	6 (75)	6 (75)
Anemia	4 (50)	1 (13)
Fatigue	4 (50)	0 (0)
Hypokalemia	4 (50)	0 (0)
Dyspnea	3 (38)	0 (0)
Hyperglycemia	3 (38)	0 (0)
Hypophosphatemia	3 (38)	1 (13)
Leukopenia	3 (38)	3 (38)
Thrombocytopenia	3 (38)	1 (13)
Alanine aminotransferase increased	2 (25)	0 (0)
Aspartate aminotransferase increased	2 (25)	1 (13)
Blood creatinine increased	2 (25)	0 (0)
Blood lactate dehydrogenase increased	2 (25)	1 (13)
Constipation	2 (25)	0 (0)
Dizziness	2 (25)	0 (0)
Hypertension	2 (25)	0 (0)
Hyperuricemia	2 (25)	0 (0)
Hypocalcemia	2 (25)	0 (0)
Hypoglycemia	2 (25)	0 (0)
Hypomagnesemia	2 (25)	0 (0)
Hypotension	2 (25)	0 (0)
Insomnia	2 (25)	0 (0)
Lymphocyte count decreased	2 (25)	2 (25)
Lymphopenia	2 (25)	1 (13)
Nasal congestion	2 (25)	0 (0)
Nausea	2 (25)	0 (0)
Neutrophil count decreased	2 (25)	2 (25)
Oropharyngeal pain	2 (25)	0 (0)
Paresthesia	2 (25)	0 (0)
Pyrexia	2 (25)	0 (0)
Vomiting	2 (25)	0 (0)
White blood cell count decreased	2 (25)	2 (25)

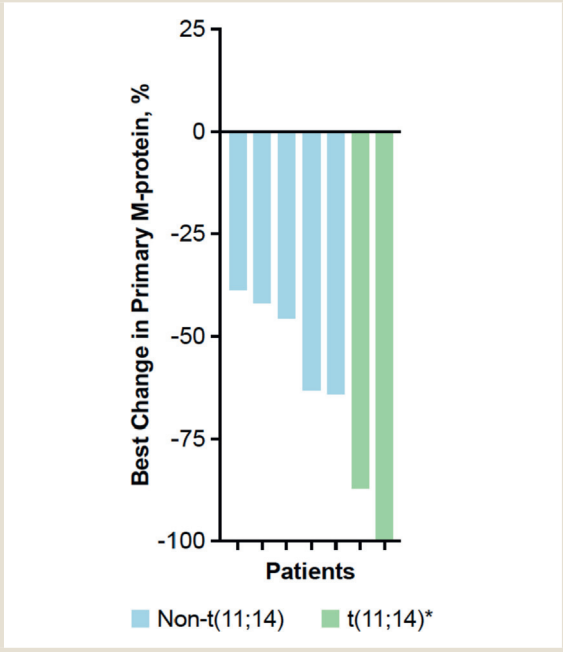
Abbreviation: TEAE = treatment-emergent adverse event.
[a] Occurring in ≥ 2 patients.

receiving the first dose and was not evaluable for response. Three of 5 patients (60%) with non-t(11;14) RRMM had a response (1 VGPR and 2 PR); the other 2 patients had stable disease. Reductions in M-protein ranged from 39% to 100% (Figure 2). Patient responses over time are shown in Figure 3. The median DOR was 12.9 months (95% CI, not estimable [NE]). The median PFS was 10.5 months (95% CI, 0.36-NE) in all patients, 7.2 months (95% CI, 0.36-NE) in those with t(11;14), and not reached (95% CI, 1.87-NE) in those without t(11;14). The Kaplan-Meier estimated PFS at 6 months was 75.0% (95% CI, 31.5-93.1%), 66.7% (95% CI, 5.4-94.5%), and 80.0% (95% CI, 20.4-96.9%), respectively. The median TTP in all patients was 13.8 months (95% CI, 1.87-NE). After a median of 6.1 months of follow-up, 2 patients had died and the median overall survival was not reached (95% CI, 0.4-NE). The Kaplan-Meier estimated overall survival at 6 months was 87.5% (95% CI, 38.7-98.1%%).

Pharmacokinetics

Concentration versus time profiles for venetoclax and pomalidomide are provided in Figure 4. Venetoclax half-life could not be estimated because of limited sampling after T_{max}. On day 15 of cycle 1, the geometric mean C_{max} for venetoclax was 1.97 μg/mL,

Figure 2 Best change in M-protein.
*One patient discontinued the study before the first M-protein assessment.



plasma venetoclax levels peaked at a median of 7 hours postdose, and the geometric mean AUC_{0-24} for venetoclax was 30.5 µg×h/mL. On day 15 of cycle 1, the geometric mean C_{max} for pomalidomide was 61.1 ng/mL, the pomalidomide plasma concentration peaked a median of 3 hours postdose, and the geometric mean AUC_{0-24} for pomalidomide was 862 ng×h/mL. Venetoclax and pomalidomide pharmacokinetic parameter estimates for cycle 1 day 1 and day 15 are provided in Supplementary Table S3.

Immunophenotyping

Immunophenotyping analyses were conducted to identify changes in B-cell and T-cell populations (Supplementary Table S1) after VenPd treatment. Consistent with previous findings that B-cells are highly dependent upon BCL-2 for cell survival,[26,27] VenPd treatment resulted in rapid and sustained reduction in peripheral B-cells (Supplementary Figure S1). In subgroup analyses, naïve B-cells were significantly reduced; however, a trend toward increased plasmablasts was observed in patients treated with VenPd (Supplementary Figure S1).

In contrast to B-cells, no significant change in total T-cells (CD4+ or CD8+) was observed after VenPd treatment (Figure 5). Overall, there were no significant changes in the composition of the T-cell pool (including naïve, central memory, effector memory, and terminally differentiated effector memory T-cells); however, a shift from a Th2 to Th1 phenotype was observed in CD4+ T-cells (Figure 5 and Supplementary Figure S2). By comparison, no change in the Th17 subpopulation was observed in patients treated with VenPd. Finally, no significant change in the percentages of regulatory T-cells was observed with VenPd treatment, including activated, naïve, and memory regulatory T-cell subsets (Supplementary Figure S2).

Discussion

In this study, pharmacokinetics and preliminary safety of VenPd were evaluated and will be useful to guide dosing in future strategies combining venetoclax with IMiDs. An increased risk of death

Figure 3 Patient responses over time.
Abbreviations: PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease; VGPR = very good partial response.

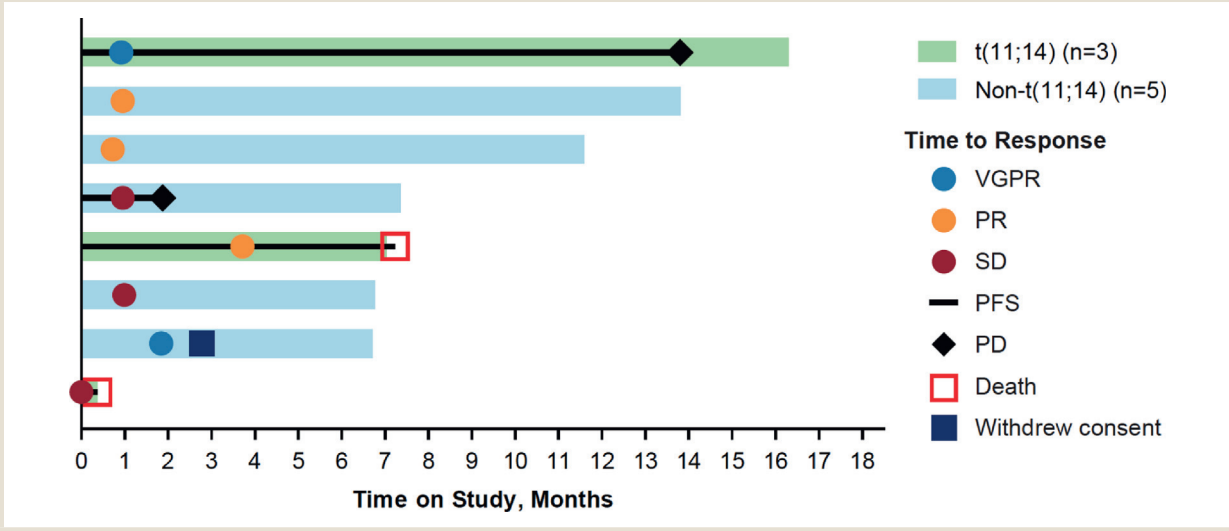
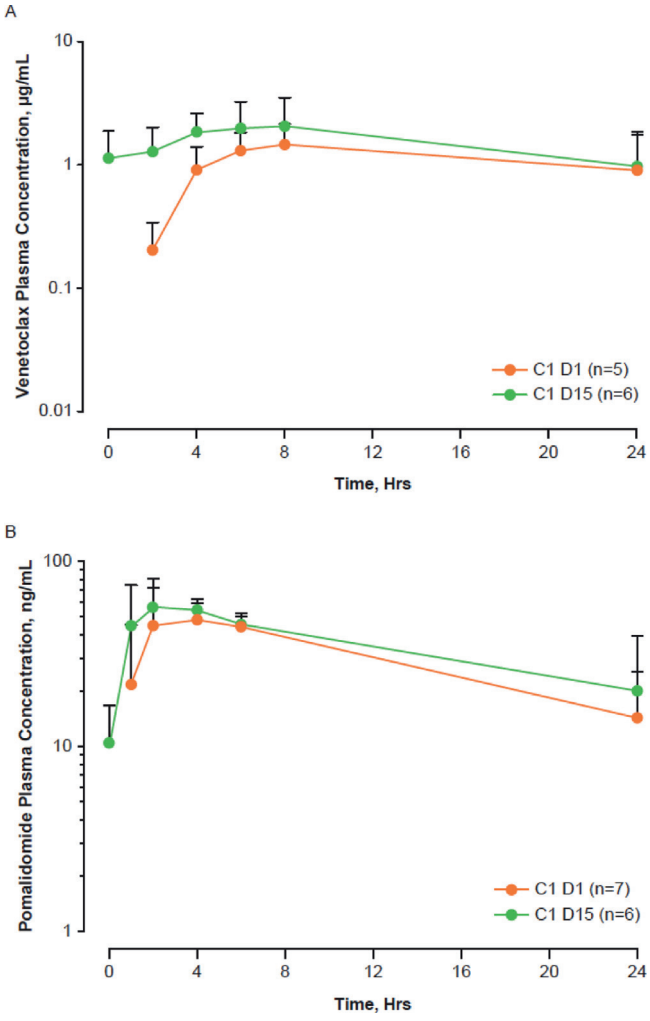


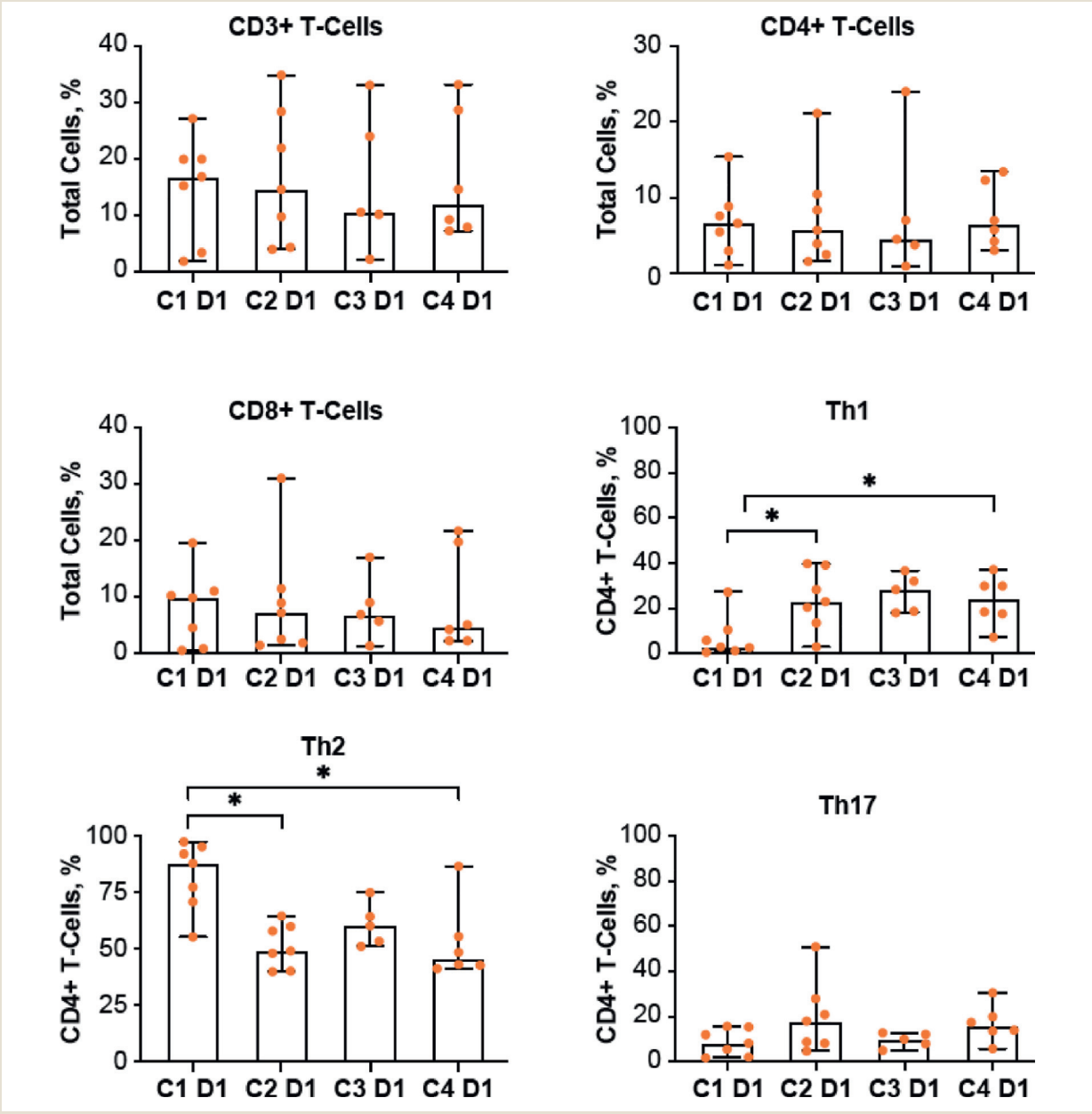
Figure 4 Mean venetoclax and pomalidomide plasma concentration versus time in dose escalation, Concentration-time profiles for venetoclax (A) and pomalidomide (B) are shown for cycle 1, day 1 and day 15 in linear-log scale. Error bars represent standard deviation. Legend shows visit and number of patients evaluated.
Abbreviations: C = cycle; D = day.



due to infections was observed with venetoclax in combination with bortezomib and dexamethasone (VenVd) in the phase III BELLINI trial, primarily in those without t(11;14), which led to a partial clinical hold of all sponsored studies of venetoclax in MM. With a decision to pursue a biomarker-directed approach with venetoclax in MM, enrollment for this study was not re-opened. With only a small number of patients evaluated, safety and efficacy conclusions could not be drawn. In dose escalation, the estimated pharmacokinetic parameters for venetoclax were consistent with those reported in the literature,[13,28] indicating that pomalidomide did not affect venetoclax pharmacokinetics. Additionally, the estimated pharmacokinetic parameters for pomalidomide were consistent with those previously reported,[29] suggesting venetoclax did not affect pomalidomide pharmacokinetics. Comprehensive immunophenotyping studies were conducted to characterize the effects of VenPd treatment on B- and T-cell subsets. On-target reduction in B-cells and a shift from a Th2- to Th1-type response was observed upon VenPd treatment, which is consistent with the expected venetoclax and pomalidomide mechanisms of action, respectively.

The maximum tolerated dose of venetoclax in this combination was not determined, with 4 patients experiencing DLTs at the 400 mg dose level. Three of those patients recovered from the DLTs and resumed treatment. The patient who did not recover had experienced a DLT of grade 5 cardio-respiratory arrest that was deemed unrelated to treatment. Further exploration of dose reductions and granulocyte colony-stimulating factor support may lead to strategies that improve the tolerability of this combination. The majority of grade $\geq$ 3 TEAEs reported in this study were hematological AEs,

Figure 5 Changes in T-cell profiles following VenPd treatment.
Abbreviations: C = cycle; D = day; Th = T-helper; VenPd = venetoclax, pomalidomide, and dexamethasone.



the most common of which was neutropenia in 75% of patients. Three of the 8 patients enrolled reported serious infections, but no deaths from infections were observed, and all infections were manageable with dose interruptions and standard supportive care. Although antibiotic prophylaxis was recommended during the first 90 days of the study, or in the case of grade 4 neutropenia, prophylaxis was not mandated. The reduced enrollment in this trial limited the ability to draw firm conclusions about the safety profile.

Studies have shown promising clinical activity of venetoclax combinations in RRMM, particularly in those with t(11;14).[12-14] In patients with t(11;14) RRMM in the BELLINI trial, VenVd resulted in prolonged PFS (median not reached vs. 9.5 months) and improved response rates (90% vs. 47%) over placebo with Vd.[14] In a phase I trial of patients with t(11;14) RRMM who have been previously exposed to a proteasome inhibitor and an IMiD, venetoclax plus dexamethasone treatment was associated with an ORR of 60%.[12] In this study, 2 of 3 patients (67%) with t(11;14) responded to VenPd treatment, with 1 PR and 1 VGPR. The third patient died prior to a response evaluation.

Patients in this study had received at least 1 prior therapy, including a proteasome inhibitor and lenalidomide, and were refractory to lenalidomide. Because lenalidomide is a preferred frontline treatment for MM, therapeutic options for patients who have been previously exposed to lenalidomide are of interest, and pomalidomide has been utilized in this population.[7,30] Pomalidomide with bortezomib and dexamethasone in a population of patients in which 71% were refractory to lenalidomide elicited an ORR of 82%.[31] The median PFS in the patients with lenalidomide-refractory disease from that study was 9.5 months after 15.9 months of follow-up.[31] The response rate with VenPd in this study, in which 6 patients were refractory to lenalidomide, was 63% with a median PFS of 10.5 months after a median of 6.1 months of follow-up. Median overall survival was not reached. Given the small sample size and limited exposure to VenPd in this study, no clear conclusions regarding the efficacy of this regimen can be drawn.

Conclusion

VenPd was evaluated as a potential combination for the treatment of patients with RRMM following previous treatment with a proteasome inhibitor and lenalidomide. The early termination of this study precludes the ability to draw significant safety or efficacy conclusions about this regimen. Nonetheless, venetoclax combinations are of interest for the treatment of RRMM, and pharmacokinetic and safety findings from this study can be used to guide dosing strategies for future studies evaluating combinations of venetoclax with IMiDs.

Clinical Practice Points

- Current treatment paradigms for RRMM clearly demonstrate that new treatments are needed. Overexpression of BCL-2 is a major contributor to the pathogenesis of MM.
- Venetoclax is a selective, potent BCL-2 inhibitor with demonstrated clinical activity in RRMM. Pomalidomide is a potent IMiD that displays antiangiogenic, antiproliferative, and immunomodulatory activity. Dexamethasone is frequently given in combination with pomalidomide, and it has been shown to promote BCL-2 dependency in MM.
- Venetoclax, pomalidomide, and dexamethasone have all demonstrated significant clinical activity in RRMM. Therefore, VenPd may lead to additive antitumor effects.
- VenPd was evaluated in 8 patients with RRMM. All patients received 400 mg venetoclax. Four patients experienced dose-limiting toxicities, and venetoclax dose was not escalated. Five patients had a confirmed response; the median duration of response was 12.9 months. The median progression-free survival was 10.5 months. The pharmacokinetic parameters of venetoclax and pomalidomide were similar to those reported in literature. Immunoprofiling analyses showed on-target reduction in B-cells and a shift from a Th2- to Th1-type response upon VenPd treatment. Owing to limited enrollment in this study, no clear safety or efficacy conclusions can be drawn.
- IMiDs are a backbone of MM therapy, and combination with agents that have novel complementary mechanisms of action could deepen response rates and response durability. This study provides pharmacokinetic and preliminary safety data in a cohort of patients treated with VenPd that will aid in guiding dosing for future combinations of venetoclax with IMiDs.

Authors' Contributions

Cristina Gasparetto: Study conception, Study methodology, Resources, Investigation, Writing manuscript Kristian M. Bowles: Resources, Investigation, Writing manuscript Al-Ola Abdallah: Resources, Investigation, Writing manuscript Lura Morris: Study methodology, Investigation, Writing manuscript Gudrun Mander: Study methodology, Investigation, Writing manuscript Sheryl Coppola: Investigation, Writing manuscript Jing Wang: Formal data analysis, Writing manuscript Jeremy A. Ross: Study conception, Study methodology, Investigation, Writing manuscript Orlando F. Bueno: Study conception, Study methodology, Investigation, Writing manuscript Emma Arriola: Investigation, Writing manuscript Maria Victoria Mateos: Resources, Investigation, Writing manuscript

Role of the Funding Source

AbbVie sponsored the study and participated in the design, study conduct, analysis, collection, and interpretation of the data, as well as the writing, review, and approval of the publication. All authors had access to the full study data and approved of the decision to submit the manuscript. The corresponding author had final responsibility for the decision to submit.

Data Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan and execution of a Data Sharing Agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.\

Disclosure

C Gasparetto: Participation in boards from Karyopharm, AbbVie, GlaxoSmithKline, Sanofi, and Janssen; speaker for Karyopharm, GlaxoSmithKline, Sanofi, and Oncopeptides; and membership with the Connect Registry (Bristol Myers Squib).

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MV Mateos: Honoraria from lectures and participation in boards from Janssen, Amgen, BMS-Celgene, Takeda, AbbVie, Sanofi, Oncopeptides, GlaxoSmithKline, Pfizer, Regeneron, Karyopharm, Roche, Sea-Gen, and Bluebird Bio.

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Supplementary materials

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