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# Phase 2 study of clarithromycin, pomalidomide, and dexamethasone in relapsed or refractory multiple myeloma

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**Key Points**

- ClaPd yields high response rates and extended PFS in relapsed MM.

- ClaPd is an effective, well-tolerated, all-oral regimen for patients with relapsed MM.

The addition of clarithromycin enhances the efficacy of lenalidomide plus dexamethasone in treatment-naive multiple myeloma (MM). We conducted a phase 2 trial to evaluate the safety and efficacy of clarithromycin, pomalidomide, and dexamethasone (ClaPd) in relapsed or refractory multiple myeloma (RRMM) with prior lenalidomide exposure. One hundred twenty patients with a median of 5 prior lines of therapy received clarithromycin 500 mg orally twice daily, pomalidomide 4 mg orally on days 1 to 21, and dexamethasone 40 mg orally on days 1, 8, 15, and 22 of a 28-day cycle. The overall response rate (ORR) was 60% with 23% achieving at least a very good partial response. There was no statistical difference in response rates for patients who were refractory to lenalidomide (ORR, 58%), bortezomib (ORR, 55%), or both lenalidomide and bortezomib (ORR, 54%). Median progression-free survival (PFS) for the cohort was 7.7 months and median overall survival (OS) was 19.2 months. A history of dual-refractoriness to lenalidomide and bortezomib did not significantly impact either PFS or OS. The most common toxicities were neutropenia (83%), lymphopenia (74%), and thrombocytopenia (71%). The most common grade ≥3 toxicities included neutropenia (58%), thrombocytopenia (31%), and anemia (28%). ClaPd is an effective combination in RRMM with response and survival outcomes that are independent of lenalidomide- or bortezomib-refractory status. Toxicities are manageable with low rates of nonhematologic or high-grade events. ClaPd is a convenient, all-oral option in RRMM with comparable efficacy to other highly active, 3-drug, pomalidomide-based combinations. This trial was registered at www.clinicaltrials.gov as #NCT01159574.

## Introduction

Despite therapeutic improvements in the treatment of multiple myeloma (MM), the clinical course for most patients is marked by progression events and the need for sequential therapeutic interventions.[1] Additionally, the relapsed and refractory MM (RRMM) setting is characterized by patient heterogeneity and increasing frailty due to cumulative treatment toxicities and comorbidities. Treatment options for RRMM with significant efficacy and manageable toxicity profiles remain a critical need.

Pomalidomide is a second-generation immunomodulatory agent approved for use in patients with RRMM who have received 2 prior therapies including lenalidomide and bortezomib.[2] The activity of pomalidomide and dexamethasone (Pom-dex) was demonstrated in the landmark phase 3 MM-003 study.[3] In this trial, patients who had received a median of 5 prior therapies randomized to Pom-dex

The full-text version of this article contains a data supplement.

achieved a median progression-free survival (PFS) of 4 months and median overall survival (OS) of 12.7 months, both significantly longer than the control arm of high-dose dexamethasone. The PFS and OS benefit was maintained even in study patients refractory to prior lenalidomide. The overall response rate (ORR) achieved was 30% with a median duration of response of 7 months. The results with the Pom-dex doublet prompted studies of adding additional agents, such as daratumumab, elotuzumab, carfilzomib, cyclophosphamide, and ixazomib, to enhance response and survival outcomes.[4-8] These studies have generally shown enhancement of ORR, PFS, and OS. For example, in June 2017, the combination of pomalidomide and daratumumab was approved for patients with MM who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor. This approval was based on phase 1b trial results (EQUULEUS; MMY1001 study) where patients with RRMM and a median of 4 prior lines of therapy achieved an ORR of 60% with a PFS and OS of 8.8 and 17.5 months, respectively.[4]

Clarithromycin is a macrolide antibiotic that has been shown to increase antimyeloma activity when administered with thalidomide and immunomodulatory agents in preclinical studies.[9] There are protean potential mechanisms of action for macrolide antibiotics in myeloma. Preclinical studies have shown that clarithromycin has immunomodulatory properties mediated in part by suppression of interleukin-6, interleukin-1, and tumor necrosis factor α.[10-12] Other studies have demonstrated that clarithromycin inhibits autophagy, increasing the cytotoxic effect of immunomodulatory drugs on MM cells.[13] Another purported mechanism of clarithromycin efficacy in myeloma is through modulation of corticosteroid dosing by inhibiting the CYP3A4 isozyme.[14] The plasma cell–bone marrow stroma connection has been shown to be critical in sustaining MM growth and is also thought to be 1 of the targets of the immunomodulatory drugs.[15] Macrolides have also been shown to alter the expression of cell adhesion molecules, such as ICAM-1, lymphocyte function-associated antigen (LFA), and VCAM1, thus interrupting these myeloma-sustaining interactions.[16]

Prior evaluation of the addition of clarithromycin to lenalidomide and dexamethasone, the BiRD regimen, showed significant activity in patients with newly diagnosed MM.[17,18] The ORR achieved with this regimen was 93% with 68% of patients achieving a very good partial response (VGPR) or better. After long-term follow-up, the median PFS with BiRD was 49 months. A matched case-control analysis of patients treated with BiRD compared with lenalidomide and dexamethasone alone demonstrated increased efficacy of BiRD at all response levels, including an increase in the rate of complete response (CR) at 45.8% vs 13.9% and a near doubling of PFS at 48.3 vs 27.5 months.

The significant increase in clinical benefit resulting from the addition of clarithromycin to an immunomodulatory agent–based regimen in the upfront setting was the rationale for conducting a phase 2 study of clarithromycin with Pom-dex, the ClaPd regimen, in patients with RRMM and prior lenalidomide exposure. The objectives of the study were to determine ORR, PFS, and regimen tolerability.

## Patients and methods

### Patient selection

Patients were required to have a histologically confirmed diagnosis of MM that was relapsed after prior therapy or refractory to the most recently received therapy, as per current International Myeloma Working Group (IMWG) definitions.[19] All patients must have received at least 3 prior lines of therapy, which must have included lenalidomide, and been subsequently determined to be refractory, resistant, or relapsed to lenalidomide. A prior line of therapy was defined as a predetermined course of treatment according to IMWG definition.[19] Patients were required to have measurable disease either with a monoclonal protein ≥0.5g/dL, serum free light chain ≥10 mg/dL, urinary m-protein ≥200 mg per 24 hours, or measurable plasmacytoma(s). Key inclusion criteria included: age ≥18 years; Karnofsky performance status ≥60; anticipated life expectancy of at least 3 months; adequate hepatic function with a bilirubin <1.5× upper limit of normal (ULN), aspartate aminotransferase <2.0× the ULN, and alanine aminotransferase <3.0× the ULN; serum creatinine <2.5× the ULN; adequate bone marrow reserve as evidenced by an absolute neutrophil count ≥0.75 × $10^9$/L and a platelet count ≥50 × $10^9$/L; and no absolute contraindication to prophylactic aspirin or alternative anticoagulation. Exclusion criteria included a prior history of malignancy within the previous 5 years (excluding nonmelanoma skin cancer or in situ carcinoma of breast or cervix); known HIV infection; known active hepatitis B or C infection; active infection or coexisting medical problem that would preclude study therapy; congestive heart failure (New York Heart Association class III-IV); conduction system abnormalities uncontrolled by conventional intervention; evidence of acute cardiac ischemia, thromboembolic event, or acute myocardial infarction within the prior 6 months; known hypersensitivity to thalidomide or lenalidomide; or need for concurrent use of any strong CYP3A4 inhibitors.

All patients signed written informed consent prior to study enrollment. Patients had to commit to standard contraceptive guidelines during pomalidomide therapy. The Institutional Review Board of the Weill Medical College of Cornell University, NewYork-Presbyterian Hospital–Cornell Medical Center, approved the study in accordance with federal regulations and the Declaration of Helsinki. All patients provided written informed consent.

### Study design

This was a single-institution, single-arm, open-label, phase 2 study. The study was conducted at Weil Cornell Medical College/NewYork-Presbyterian hospital. The primary objective was to evaluate the response to the combination of ClaPd for patients with RRMM who had received at least 3 prior lines of therapy and were relapsed or refractory to prior lenalidomide exposure. Secondary objectives were to evaluate the safety and tolerability of ClaPd; the time to maximum response; duration of response; and time to progression or treatment failure.

### Treatment

Following enrollment, patients initiated therapy with ClaPd. Patients took pomalidomide 4 mg orally daily on days 1 to 21 of a 28-day cycle, clarithromycin 500 mg orally twice daily on days 1 to 28, and dexamethasone 40 mg orally on days 1, 8, 15, and 22. Patients received prophylaxis against thromboembolism with aspirin 81 mg daily and pneumocystis jiroveci with trimethoprim-sulfamethoxazole or suitable alternative in case of sulfa allergy. ClaPd were continued until disease progression or intolerance to therapy.

## Assessments

Response assessments were conducted after each cycle including serum and urine protein electrophoresis and immunofixation, serum free light chain, and quantitative immunoglobulin-level measurements. Responses were based on independent assessment by 3 study investigators and were classified according to IMWG Uniform Response Criteria with categories for stringent CR (sCR), CR, VGPR, partial response (PR), minor response (MR), stable disease (SD), and progression of disease (PD).[19] Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria of Adverse Events (version 4.0). Cytogenetic testing with karyotyping and fluorescence in situ hybridization (FISH) was performed on CD138-selected cells. High-risk cytogenetics were defined as per the IMWG and used in the Revised International Stating System (R-ISS) as the presence of del17p, t(4;14), or t(14;16) determined by FISH at any percentage level.[20] Additional cytogenetic abnormalities of gain(1q), del(1p), t(14;20), and karyotypic del(13q) were also analyzed for effect on survival outcomes.

## Statistical analysis

The primary end point of the study was to determine ORR to the ClaPd regimen. Secondary end points included PFS and OS. Patients who had received at least 1 dose of ClaPd were eligible for response evaluation. Survival outcomes were determined for each enrolled subject on intent-to-treat basis. PFS and OS were estimated according to the Kaplan-Meier method. A Cox proportional hazards regression model was used to evaluate the impact of tumor and patient characteristics on survival outcomes. Specific patient characteristics analyzed for impact on survival outcomes included age; lactate dehydrogenase; sex; percentage of bone marrow plasmacytosis; number of prior lines of therapy; and plasma cell proliferation as measured by the ratio of immunohistochemical Ki67/CD138 staining[21]; the presence of adverse cytogenetics; lenalidomide-, bortezomib-, or double-refractory status, and R-ISS stage. All $P$ values are 2-sided with statistical significance evaluated at the .05 $\alpha$ level. All analyses were performed in Stata version 10.1 (Stata Corporation, College Station, TX).

# Results

## Patients and treatment

Between 2010 and 2013, 120 patients with RRMM at the Weill Cornell Medicine–NewYork-Presbyterian Hospital were enrolled and 117 were treated with ClaPd. Of the 3 untreated patients, 2 expired prior to study drug dosing (1 from progressive myeloma, the other from an unrelated intracranial hemorrhage), and 1 withdrew to pursue alternate treatment. Patient characteristics are listed in Table 1 and treatment history in Table 2. Patients were heavily pretreated with a median of 5 prior lines of therapy (range, 3-15). All had prior lenalidomide exposure and 84% were lenalidomide refractory as per IMWG definition. One hundred nineteen of 120 patients had received prior bortezomib and 78% were bortezomib refractory. Sixty-eight percent (81 of 120) were double refractory to both lenalidomide and bortezomib. Seventy-four percent had previously undergone autologous stem cell transplant. High-risk cytogenetic features as defined by IMWG were identified in 35% of patients, notably 25% with del(17p). There were 29 patients identified with the additional cytogenetic abnormalities of gain(1q), del(1p), t(14;20), and karyotypic del(13q) without other IMWG defined high-risk cytogenetic abnormalities.

**Table 1. Patient characteristics**

| Characteristic | N = 120 |
|---|---|
| Male, n (%) | 58 (48.3) |
| Age, median (range), y | 63 (42-87) |
| Creatinine, median (range) | 0.9 (0.44-2.5) |
| LDH, median (range) | 170.5 (79-1353) |
| Hemoglobin, median (range) | 10.4 (6.4-14.6) |
| Albumin, median (range) | 3.5 (0.7-4.5) |
| B2M, n = 105, median (range) | 3.5 (1.2-40.4) |
| % Ki67/CD138, n = 88, median (range) | 7.5 (0-85) |
| Calcium, median (range) | 9.1 (7.8-12.3) |
| % BM plasmacytosis, n = 111, median (range) | 62.5 (0-100) |
| Prior MGUS, n (%) | 9 (7.5) |
| Prior smoldering myeloma, n (%) | 18 (15) |
| **Cytogenetics, n = 113, n (%)*** | |
| High risk (R-ISS defining) | 39 (35) |
| Del 17p or loss of P53 | 28 (25) |
| t(4;14) | 11 (10) |
| t(14;16) | 6 (5) |
| Additional high-risk markers | |
| t(14;20) | 1 (1) |
| Gain (1q) | 47 (42) |
| Loss (1p) | 16 (14) |
| Karyotype del 13q | 13 (2) |
| **Stage** | |
| R-ISS, n = 100, % | |
| 1 | 18 |
| 2 | 64 |
| 3 | 18 |
| ISS, n = 105, n (%) | |
| 1 | 42 (40) |
| 2 | 37 (35) |
| 3 | 26 (25) |
| **M-protein isotype, n (%)** | |
| IgG-κ | 44 (37) |
| IgG-λ | 27 (23) |
| IgA-κ | 14 (12) |
| IgA-λ | 13 (11) |
| Free κ | 14 (12) |
| Free λ | 5 (4) |
| IgD-κ | 2 (2) |
| IgM-κ | 1 (1) |

B2M, β2-microglobulin; BM, bone marrow; ISS, International Staging System; LDH, lactate dehydrogenase; MGUS, monoclonal gammopathy of undetermined significance.
*Patients with multiple high-risk abnormalities were included with each abnormality.

## Efficacy

One hundred seventeen patients received at least 1 dose of ClaPd treatment and were evaluable for response. Responses are summarized in Table 3. The ORR was 60% (70 of 117) with 23%

**Table 2. Prior myeloma treatment history**

| Characteristic | N = 120 |
|---|---|
| Years since diagnosis, median (range) | 4.6 (0.8-21.2) |
| Prior lines of therapy, median (range) | 5 (3-15) |
| **Prior therapy, n (%)** | |
| Lenalidomide | 120 (100) |
|   Relapsed | 19 (16) |
|   Refractory | 101 (84) |
|   Lenalidomide as last therapy prior to ClaPD* | 36 (30) |
|     Treatment† | 26 (22) |
|     Maintenance‡ | 10 (8) |
| Bortezomib | 119 (99) |
|   Relapsed | 25 (22) |
|   Refractory | 94 (78) |
| Double refractory | 81 (68) |
| Autologous stem cell transplant | 89 (74) |
| Thalidomide | 74 (62) |
| Cyclophosphamide | 72 (60) |
| Doxorubicin | 53 (43) |
| Carfilzomib | 31 (25) |
| Cisplatin | 26 (22) |
| Bendamustine | 21 (18) |

*Patients who received lenalidomide as part of last line of therapy prior to start of ClaPD.
†Treatment dosing: lenalidomide in combination with corticosteroid at 25 mg per day or renal-adjusted dose.
‡Maintenance lenalidomide: lenalidomide monotherapy after achievement of maximum response on prior regimen, dosing not exceeding 10 mg per day.

achieving at least VGPR. The maximum response achieved was stringent CR in 5% of patients, CR in 1%, VGPR in 17%, PR in 37%, MR in 7%, SD in 25%, and PD in 9%. The median length of follow-up was 20.3 months, ranging from 0.3 to 92.7 months. The median time on study was 7.2 months (range, 0.3-57.2 months). The median time to PR was 1 cycle (range, 1-7) and the median duration of response (DOR) was 9.3 months. Patients, regardless of prior lenalidomide- or bortezomib-refractory status had deepening responses to continued ClaPd over time as shown in Figure 1. The

median PFS for the full cohort was 7.7 months (95% confidence interval [CI], 5.6, 9.5 months) (Figure 2A). Median OS was 19.2 months (95% CI, 14.2, 26.7 months) (Figure 2B).

Multivariable analysis of factors associated with response, PFS, and OS was performed (Table 4). There was no statistically significant difference in response rates for patients who were lenalidomide (ORR, 58%), bortezomib (ORR, 55%), or double refractory (ORR, 54%) (P = .918). Similarly, neither high-risk cytogenetics nor R-ISS influenced ORR.

PFS was significantly shorter for those patients with IMWG-defined high-risk cytogenetics and those with R-ISS > 1. The inclusion of the additional cytogenetic abnormalities of gain(1q), del(1p), t(14;20), and karyotypic del(13q) into the definition of high-risk cytogenetics did not significantly influence PFS outcome. The median PFS for patients with high- vs standard-risk cytogenetics was 5.8 months (95% CI, 3.6, 8.7 months) vs 8.4 months (95% CI, 5.7, 12.1 months) (log-rank P = .0366). The median PFS for R-ISS 1 vs R-ISS > 1 patients was 14 months (95% CI, 6.6, 21 months) vs 5.8 months (95% CI, 3.9, 8.3 months) (P = .0125). Double-refractory status to lenalidomide and bortezomib had a trend toward shorter PFS that was not statistically significant with median PFS for double vs non-double-refractory patients at 6.5 months (95% CI, 4.7, 9.1 months) vs 8.3 months (95% CI, 4.0, 12.1 months) (log-rank P = .268) (supplemental Figure 1). PFS for patients on full-dose lenalidomide, maintenance lenalidomide, and no lenalidomide as part of therapy just prior to ClaPd had a median PFS of 7.67 months (95% CI, 5.13-10.2 months), 4.67 months (95% CI, 1.87-14.03 months), and 8.4 months (95% CI, 2.77-14.93 months), respectively. A trend is seen for shorter PFS in those treated with full-dose lenalidomide just prior to ClaPd, however, this was a relatively small group (n = 10) and no statistical difference between the groups for PFS (log-rank P = .882) was seen.

Median OS was also significantly shorter in those patients with high-risk cytogenetics and R-ISS > 1. Median OS for high- vs standard-risk patients was 14.2 months (95% CI, 8, 25.7 months) vs 25 months (95% CI, 16.9, 31.6) (log-rank P = .0237). Loss of 17p was significantly associated with shorter OS, at 12.4 months (95% CI, 6.2, 16.8 months) vs 27.1 months (95% CI, 16.9, 33.2 months) (log-rank P = .0006). Presence of the t(4;14) abnormality on FISH had a trend toward shortened OS at 13.6 vs 23.8 months but did not reach statistical significance (P = .46). Gain(1q), del(1p), t(14;20), and karyotypic del(13q) did not significantly influence OS.

**Table 3. Best response to ClaPD (IMWG criteria)**

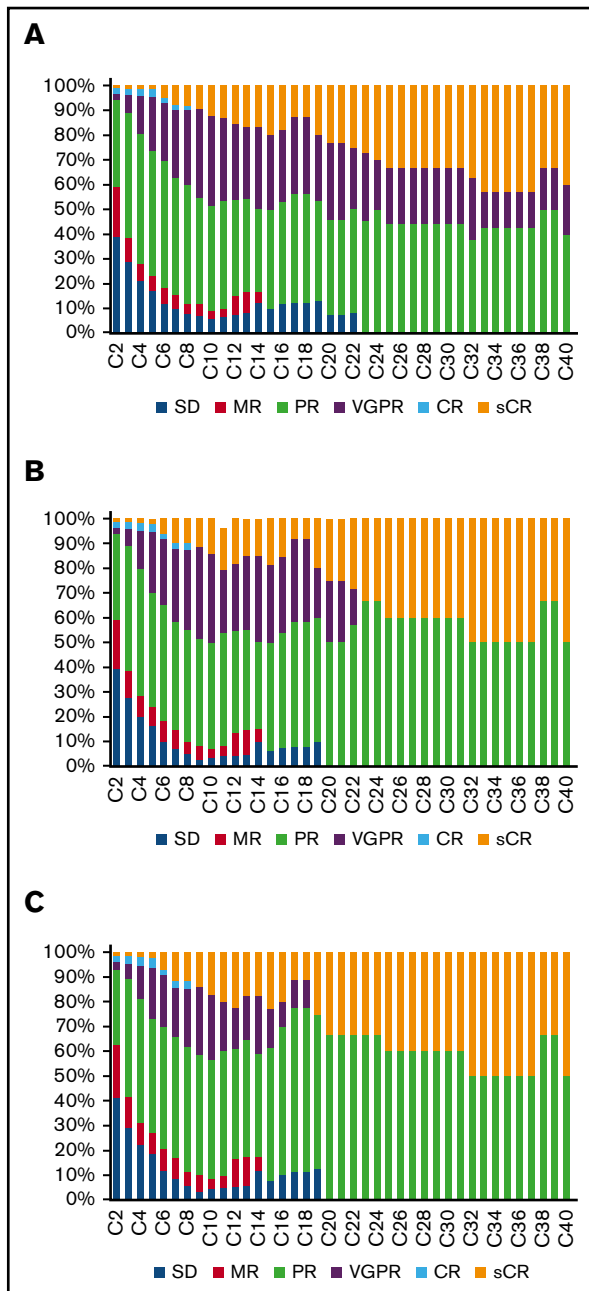| | Overall, N = 117 | Lenalidomide refractory, N = 101 | Bortezomib refractory, N = 94 | Double refractory, N = 81 |
|---|---|---|---|---|
| ORR (≥PR) | 70 (60) | 59 (58) | 52 (55) | 44 (54) |
| CBR (≥MR) | 78 (67) | 66 (65) | 59 (63) | 51 (63) |
| sCR | 6 (5) | 6 (6) | 5 (5) | 5 (6) |
| CR | 1 (1) | 1 (1) | 1 (1) | 1 (1) |
| VGPR | 20 (17) | 15 (15) | 14 (15) | 9 (11) |
| PR | 43 (37) | 37 (37) | 32 (34) | 29 (36) |
| MR | 8 (7) | 7 (7) | 7 (7) | 7 (9) |
| SD | 29 (25) | 23 (23) | 24 (26) | 20 (25) |
| PD | 10 (9) | 10 (10) | 8 (9) | 8 (10) |

All values are n (%).
CBR, clinical benefit rate.

**Figure 1. Responses over time to ClaPD.** Responses by treatment cycle in patients who were lenalidomide refractory (A), bortezomib refractory (B), and refractory to both lenalidomide and bortezomib (double refractory) (C).

Median OS for R-ISS 1 vs R-ISS > 1 patients was 46.9 months (95% CI, 24.3, 84 months) vs 15 months (95% CI, 1.35, 12.8 months) (log-rank $P = .0009$). Similar to PFS, double-refractory status had no impact on OS with median PFS for double vs non-double-refractory patients at 25.7 months (95% CI, 13.1, 33.2 months) vs 16.8 months (95% CI, 13.2, 25 months) (log-rank $P = .281$) (supplemental Figure 2). OS for patients on full-dose lenalidomide, maintenance lenalidomide, and no lenalidomide as part of therapy just prior to ClaPd had a median OS of 21.6 months (95% CI, 13.2-27.8 months), 19.0 months (95% CI, 0.9-62.7 months),

and 16.8 months (95% CI, 6.27-29.4 months), respectively. There was no statistical difference by log-rank testing between the groups for OS (log-rank $P = .887$).

### Safety

Regimen toxicities are listed in Table 5. The most common toxicities were hematologic. Neutropenia was observed in 83% of patients with 58% grade 3/4. A significant proportion of patients required interruption of either all medications (44%, 53 of 120) or pomalidomide alone (15%, 18 of 120) to allow recovery from neutropenia. Febrile neutropenia occurred in 4% of patients (5 of 120). Anemia and thrombocytopenia were observed in 62% and 71% of patients, respectively, with 28% and 31% grade 3/4. The most common nonhematologic toxicities included fatigue, electrolyte abnormalities, and low-grade gastrointestinal toxicities, primarily diarrhea and constipation. The most common nonhematologic grade 3 or higher toxicities included fatigue (15%), pulmonary infection (13%), and hyperglycemia (15%). Pomalidomide dose reduction for any toxicity occurred in 33% of patients (39 of 120), most commonly for hematologic toxicities. No patients discontinued pomalidomide for toxicity. The overall relative dose intensity (dose received/intended dose) for pomalidomide was 89%. Clarithromycin was dose reduced for toxicity in 6 patients (5%) and was discontinued in 34 patients (28%), with an overall dose intensity of 61%. Clarithromycin dose reductions were primarily for gastrointestinal adverse effects. Dexamethasone dose reduction occurred in 68 patients (57%) and was discontinued in 5 patients (4%) in the majority of cases for hyperglycemia and psychomotor adverse effects. Overall dose intensity for dexamethasone in ClaPd was 61%.

### Discussion

Pomalidomide with low-dose dexamethasone (Pom-dex) has been shown in multiple studies including MM-003, the phase 3b STRATUS, and the phase 2 MM-002 and IFM-2009-02 trials to have activity in the setting of relapsed and refractory MM.[3,22-24] From these studies, there has emerged a well-defined description of the activity and safety of Pom-dex in a heavily pretreated RRMM patient population with significant prior lenalidomide and bortezomib exposure (supplemental Table 1). We have previously demonstrated the increased activity achieved by adding clarithromycin to lenalidomide and dexamethasone, the BiRD regimen, in the setting of newly diagnosed MM.[18,25] This study of ClaPd therapy verifies that the addition of clarithromycin to Pom-dex in the RRMM setting can lead to increased clinical activity on Pom-dex while maintaining an entirely oral regimen.

The ORR observed of 60% with the ClaPd regimen represents a marked increase from what has been described in previous studies evaluating the Pom-dex doublet in RRMM. The ORR observed from patients treated with Pom-dex in the MM-002 study was 32.7%, in MM-003 it was 31.4%, in STRATUS it was 32.6%, and in IFM-2009-02 it was 34.5%. The ORR results for ClaPd are especially impactful in light of the cohort having an identical pretreatment history as the studies above with a median of 5 prior lines of therapy. The median PFS in patients treated with ClaPd was 7.7 months, which also is significantly longer that what has been observed with other studies of the Pom-dex combination. The median PFS with Pom-dex was 4.2 months in MM-002, 4.0 months in MM-003, 4.6 months in STRATUS, and 4.6 months in IFM-2009-02. Median OS data with Pom-dex across studies is significantly more heterogenous, possibly
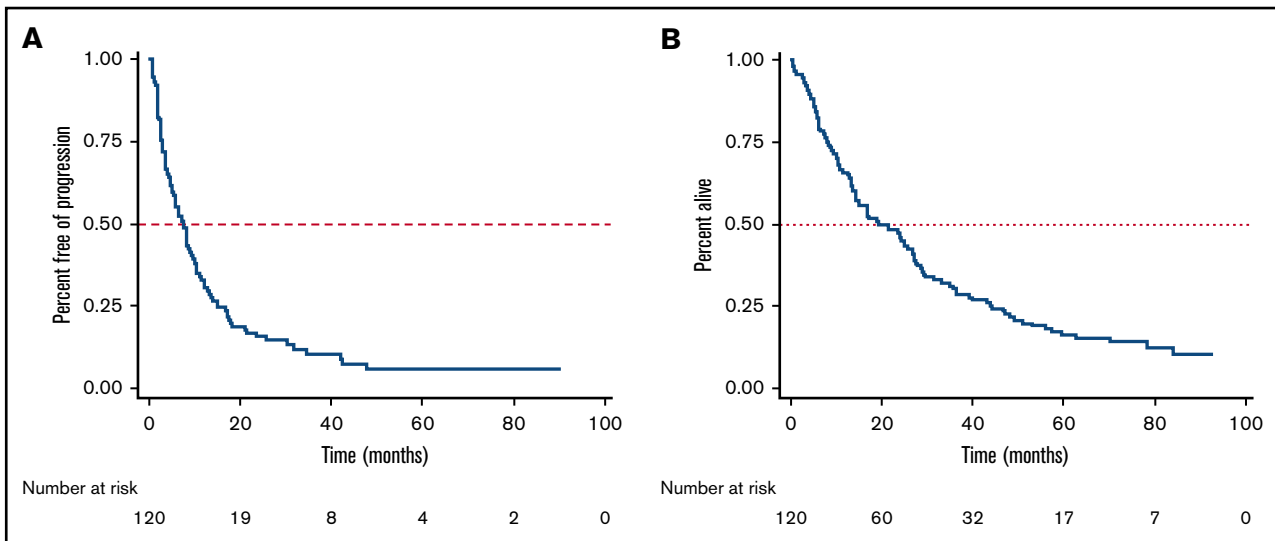
**Figure 2. Survival outcomes.** (A) PFS. Median PFS was 7.67 months (95% CI, 5.6, 9.5). (B) OS. Median OS was 19.2 months (95% CI, 14.2, 26.7).

representing subsequent treatment availability in different settings and obfuscates comparison, with MM-003 at 12.7 months, STRATUS at 11.9 months, and IFM-2009-02 at 14.9 months. An updated IMWG analysis of survival outcomes for those patients who have received at least 3 prior lines of chemotherapy, are double refractory to an immunomodulatory drug and proteasome inhibitor, and have been exposed to an alkylating agent has shown an expected median survival of 13 months.[26] The median OS of 19.2 months seen with ClaPd compares favorably to the Pom-dex studies above and is particularly notable in a population with a median of 5 prior lines of therapy with most patients double-refractory to lenalidomide and bortezomib.

The ORR and PFS observed with ClaPd also compares favorably to other 3 drug pomalidomide-based combinations incorporating additional agents widely considered to be highly active in RRMM. Results and patient characteristics from these studies are summarized in supplemental Table 2. Although we acknowledge that cross-trial comparisons are not ideal for determination of the superiority of particular antimyeloma regimens, they can be informative and serve to spur further phase 3 studies. The ORR of 60% seen with ClaPd is similar to the reported ORRs from studies of daratumumab, Pom-dex (DPD) at 60%; elotuzumab, lenalidomide, and dexamethasone (EloPD) at 53%; carfilzomib, Pom-dex (KPD) at 50%; and cyclophosphamide, Pom-dex (CPD) at 65%.[4-7] A recently reported phase 1/2 study of ixazomib, pomalidomide, dexamethasone (IPD) found an ORR of 48% at the phase 2 dose of 4 mg of ixazomib weekly, 4 mg of pomalidomide days 1 to 21, 40 mg of dexamethasone weekly for a 28-day cycle.[8] Additionally, the 7.7-month median PFS for ClaPd is comparable to 8.8 months reported for DPD, 10.3 months for EloPD, 7.2 months for KPD, 9.5 months for CPD, and 8.6 months for IPD.

The toxicity profile observed during treatment with ClaPd is analogous to what has been described in other studies with Pom-dex in RRMM. The most notable toxicities were primarily hemato-logic. The MM-003 study reported rates of grade ≥3 neutropenia of 48%, anemia of 33%, thrombocytopenia of 22%, febrile

neutropenia of 10%, and compiled infection of 30%. The STRATUS study described rates of grade ≥3 neutropenia of 49%, anemia of 33%, thrombocytopenia of 24%, febrile neutropenia of 5.3%, and compiled infection of 28%. The rates of these grade ≥3 events observed with the ClaPd combination were 58% for neutropenia, 28% for anemia, 31% for thrombocytopenia, with 5% of patients experiencing febrile neutropenia; 35% compiled infection. Clari-thromycin is a CYP3A4 inhibitor and in this capacity does impact dexamethasone metabolism.[27,28] The potentially increased dexameth-asone exposure in patients receiving ClaPd may explain the increase in the steroid-related side effects seen such as hyperglycemia or psychomotor agitation. Similarly, there could be potential flare of pomalidomide toxicity when CYP1A2 inhibitors are used, such as ciprofloxacin. The authors suggest remaining mindful of these potential drug interactions. Other toxicities seen with ClaPd were primarily low grade and consistent with those routinely observed in the RRMM setting.

**Table 4. Univariate and multivariate analysis of prognostic markers as predictors of overall survival**

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| **Prognostic variable** | **HR** | **95% CI** | **P** | **HR** | **95% CI** | **P** |
| R-ISS > 1 | 2.75 | 1.48-5.13 | .001* | 2.75 | 1.03-7.38 | .044* |
| Ki67/CD138† ≥ 5% | 2.48 | 1.53-4.03 | <.001* | 1.84 | 1.06-3.18 | .030* |
| Prior lines of therapy >3 | 1.97 | 1.22-3.19 | .012* | 1.38 | .751-2.56 | .302 |
| Marrow plasmacytosis >60% | 1.89 | 1.24-2.88 | .003* | 1.26 | .744-2.12 | .394 |
| High risk cytogenetics (R-ISS) | 1.62 | 1.06-2.48 | .025* | 1.04 | .625-1.73 | .874 |
| Bortezomib refractory | 1.27 | .78-2.04 | .337 | | | |
| Double refractory | 1.26 | .83-1.91 | .282 | | | |
| Age >65 y | 1.03 | .70-3.28 | 1.514 | | | |
| Lenalidomide refractory | 0.94 | .56-1.58 | .815 | | | |

HR, hazard ratio.
*Statistically significant.
†Ki67/CD138: percentage of CD138^{+} cells that stain positively for Ki67 on immunohistochemistry.

**Table 5. Adverse events**

| Adverse event* | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Any grade | Grade ≥3 |
|---|---|---|---|---|---|---|---|
| **Hematologic, n (%)** | | | | | | | |
| Neutropenia | 9 (8) | 20 (17) | 50 (42) | 20 (17) | — | 99 (83) | 70 (58) |
| Lymphopenia | 8 (7) | 9 (8) | 57 (48) | 15 (13) | — | 89 (74) | 72 (60) |
| Leukopenia | 13 (11) | 32 (27) | 32 (27) | 9 (8) | — | 86 (72) | 41 (34) |
| Thrombocytopenia | 27 (23) | 21 (18) | 14 (12) | 23 (19) | — | 85 (71) | 37 (31) |
| Anemia | 5 (4) | 36 (30) | 27 (23) | 6 (5) | — | 74 (62) | 33 (28) |
| **Nonhematologic, n (%)** | | | | | | | |
| Fatigue | 24 (20) | 43 (36) | 15 (13) | 3 (3) | — | 85 (71) | 18 (15) |
| Hyperglycemia | 28 (23) | 31 (26) | 15 (13) | 3 (3) | — | 77 (64) | 18 (15) |
| Hypoglycemia | 46 (38) | 17 (14) | 5 (4) | 5 (4) | — | 73 (61) | 10 (8) |
| Hypoalbuminemia | 28 (23) | 39 (33) | 3 (3) | — | — | 70 (58) | 3 (3) |
| Hypocalcemia | 36 (30) | 24 (20) | 5 (4) | 1 (1) | — | 66 (55) | 6 (5) |
| Hyponatremia | 52 (43) | 5 (4) | 5 (4) | — | — | 62 (52) | 5 (4) |
| Hypomagnesemia | 45 (38) | 6 (5) | — | — | — | 51 (43) | — |
| Increased creatinine | 28 (23) | 13 (11) | 4 (3) | 1 (1) | — | 46 (38) | 5 (4) |
| Diarrhea | 29 (24) | 9 (8) | 6 (5) | — | — | 44 (37) | 6 (5) |
| Back pain | 20 (17) | 14 (12) | 5 (4) | — | — | 39 (33) | 5 (4) |
| Edema | 26 (22) | 12 (10) | — | — | — | 38 (32) | — |
| Dysgeusia | 26 (22) | 10 (8) | 1 (1) | — | — | 37 (31) | 1 (1) |
| Peripheral neuropathy | 21 (18) | 15 (13) | 1 (1) | — | — | 37 (31) | 1 (1) |
| Elevated ALT | 30 (25) | 4 (3) | 2 (2) | — | — | 36 (30) | 2 (2) |
| Elevated ALK | 33 (28) | 2 (2) | 1 (1) | — | — | 36 (30) | 1 (1) |
| Insomnia | 28 (23) | 7 (6) | 1 (1) | — | — | 36 (30) | 1 (1) |
| Muscle weakness | 15 (13) | 9 (8) | 9 (8) | — | — | 33 (28) | 9 (8) |
| Constipation | 29 (24) | 3 (3) | — | — | — | 32 (27) | — |
| Hypophosphatemia | 8 (7) | 6 (5) | 17 (14) | — | — | 31 (26) | 17 (14) |
| Dyspnea | 20 (17) | 8 (7) | 2 (2) | — | — | 30 (25) | 2 (2) |
| Tremor | 24 (10) | 4 (3) | 1 (1) | — | — | 29 (24) | 1 (1) |
| URI | 7 (6) | 20 (17) | — | — | — | 27 (23) | — |
| Dizziness | 17 (14) | 6 (5) | 2 (2) | — | — | 25 (21) | 2 (2) |
| Cough | 22 (18) | 2 (2) | — | — | — | 24 (20) | — |
| Nausea | 15 (13) | 6 (5) | 2 (2) | — | — | 23 (19) | 2 (2) |
| Infection, other† | 9 (8) | 8 (7) | 3 (3) | — | — | 20 (17) | 3 (3) |
| Elevated AST | 15 (13) | 3 (3) | 1 (1) | — | — | 19 (16) | 1 (1) |
| Lung infection | 1 (1) | 3 (3) | 14 (12) | — | 1 (1) | 19 (16) | 15 (13) |
| Rash | 10 (8) | 5 (4) | — | — | — | 15 (13) | — |
| Generalized weakness | 5 (4) | 4 (3) | 4 (3) | — | — | 13 (11) | 4 (3) |
| Deep vein thrombosis | 1 (1) | 6 (5) | — | — | — | 7 (6) | — |
| Febrile neutropenia | 1 (1) | — | 3 (3) | 1 (1) | — | 5 (4) | 4 (3) |
| Atrial fibrillation | — | 1 (1) | 1 (1) | — | — | 2 (2) | 1 (1) |

ALK, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; URI, upper respiratory infection.

*If an adverse event occurred in the same patient more than once, the most severe grade of the adverse event is reported.

†Includes mucosal, skin, eye, bronchial, cellulitis, ear, fungal, sinus, and tooth infections.

Several of the previously discussed studies have demonstrated that the activity of Pom-dex is not impacted by refractoriness to lenalidomide, bortezomib, both agents, or the sequence of prior exposures.[3] Our findings were consistent with this for the ClaPd combination, which showed no statistically significant difference in response rates in patients who were lenalidomide-, bortezomib, or double-refractory. The IFM-2010-02 study attempted to evaluate the ability for pomalidomide to overcome the negative impact of adverse cytogenetic risk factors focusing on t(4:14) and del(17p). They found that, in a cohort of 50 patients, time to progression and DOR were

significantly increased in patients with del(17p) compared with t(4;14) (time to progression, 7.3 vs 2.8 months; DOR 8.3 vs 2.4 months). However, in the DPD study, the PFS for patients with high-risk cytogenetics was 3.9 months, which is comparable to the 5.8 months seen in the ClaPd trial. In our study, the median OS was significantly impacted by the presence of high-risk cytogenetics as well. With ClaPd, the detection of either del(17p) and t(4;14) on FISH appeared to shorten OS by ~50%, (del17p, 12.4 vs 27.1 months; t(4;14), 13.6 vs 23.8 months); however, this finding reached statistical significance only in the del17p population, perhaps due to the relatively low number (9%) of t(4;14) patients in this study. A loss of del17p in at least 20% to 60% of tested cells has been considered as a minimum threshold for negative prognostic impact in myeloma, although further analysis of this hypothesis is pending.[29] Using the conservative approach of including any percentage signal for del17p as high risk in this clinical trial, we may have diluted the negative prognostic impact of a large percentage del17p clones in the study cohort and thus the effect of del17p on PFS and OS may have been even more profound.

Mature data from the MM-003 trial have indicated that patients who achieved at least a minimal response with Pom-dex had longer median OS than those who failed to (17.2 vs 7.5 months) and that this benefit was further increased by achieving a partial response (19.9 months).[30] This highlights the importance of increasing the proportion of patients who achieve at least a PR in the RRMM treatment setting. However, given the heterogeneity of RRMM, the need to achieve this with a manageable toxicity profile remains critical, particularly in multiply relapsed, frail, or elderly patients. The improvement in disease control and therapeutic activity that results from adding clarithromycin to Pom-dex is associated with limited additional toxicity. Although clarithromycin appears to augment efficacy with an acceptable safety profile in combination with immunomodulatory agents, this may not be the case when used with proteasome inhibitors. A recent randomized phase 2 study combining clarithromycin with cyclophosphamide, bortezomib, and dexamethasone (CyBorD) in newly diagnosed MM was stopped prematurely due to increased gastrointestinal and neurologic toxicity concerns in the clarithromycin arm.[31] Of note, bortezomib is metabolized hepatically largely via CYP3A4, and given clarithromycin's known inhibition of this enzyme's activity, its concurrent use may increase bortezomib exposure and associated toxicities.

In this analysis, clarithromycin appears to add a similar clinical benefit to Pom-dex as other partners including daratumumab, carfilzomib, cyclophophasmide, and ixazomib in an entirely oral combination. The ClaPd combination thus represents a convenient, comparatively low-cost alternative that spares other active agents for use in other lines of therapy. Using 2018 pricing data from the Center for Medicare & Medicaid Services (CMS) for injectables, and US average wholesale pricing for oral drugs, 6 months of DPD, EloPD, IxaPD would cost $214 370.80, $204 047.60, and $184 227.60, respectively. The cost for 6 months of ClaPd would be substantially lower at $132 387.60. Further analysis using Markov modeling would be necessary to further elucidate the potential cost savings of using clarithromycin.

Clarithromycin is a significant yet often underutilized component of the myeloma therapeutic armamentarium. In this report, we have described the effectiveness and tolerability of ClaPd. The ClaPd regimen demonstrated high rates of overall response and significant duration of disease control in a heavily pretreated RRMM population while maintaining a toxicity profile similar to Pom-dex alone (Table 5). The clinical efficacy advantage of adding clarithromycin to Pom-dex should be explored further in a phase 3 clinical trial.

## Acknowledgments

## Authorship

Contribution: T.M.M., A.C.R., R.N.P., M.C., and R.N. conceived and designed the study; T.M.M., A.C.R., R.N.P., K.A.P., A.P., A.B., L.T., D.J., and R.N. collected and assembled the data; T.M.M., P.A.F., and R.N. analyzed and interpreted the data; and all authors wrote and provided final approval for the manuscript.

Conflict-of-interest disclosure: T.M.M. provided consultation services for Amgen Inc, Takeda Inc, Celgene Inc, and Janssen. A.C.R. received honoraria for speakers' bureau activities from Celgene Inc. K.A.P. and A.P. received honoraria for speakers' bureau activities from Celgene Inc and Takeda Inc. M.C. received honoraria for speakers' bureau activities from, was an advisory board member for, and received research funding from Celgene Inc and Takeda Inc. R.N. received honoraria for speakers' bureau activities from, was an advisory board member for, and received research funding from Celgene Inc, Takeda Inc, and Onyx Inc. The remaining authors declare no competing financial interests.

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