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 therapeudic 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...
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 ant myeloma 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 ≥0.5 g/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 × 109/L and a platelet count ≥50 × 109/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 Weill 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 sulfura 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). 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 Staging System (R-ISS) as the presence of del17p, t(4;14), or t(14;16) determined by FISH at any percentage level. 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; the presence of adverse cytogenetics; lenalidomide-, bortezomib-, or double-refractory status, and R-ISS stage. All analyses were performed in Stata version 10.1 (Stata Corporation, College Station, TX).

Efficacy

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 (8.4-14.6)|
| Albumin, median (range)        | 3.5 (0.7-4.5)|
| B2M, 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-k                          | 44 (37) |
| IgG-λ                          | 27 (23) |
| IgA-k                          | 14 (12) |
| IgA-λ                          | 13 (11) |
| Free-k                         | 14 (12) |
| Free-λ                         | 5 (4)   |
| IgD-k                          | 2 (2)   |
| IgM-k                          | 1 (1)   |

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.

Statistical analysis

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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.

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 3. Best response to ClaPD (IMWG criteria)

| Characteristic          | 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 (26)         | 23 (23)                          | 24 (26)                      | 20 (25)                  |
| PD                      | 10 (9)          | 10 (10)                          | 8 (9)                        | 8 (10)                   |

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

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 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.
MR, MR, MR, PR, sCR, VGPR, PR, VGPR, CR, CR, PR, VGPR, sCR, CR, PR

CI, 13.2-27.8 months), 19.0 months (95% CI, 0.9-62.7 months),
therapy just prior to ClaPd had a median OS of 21.6 months (95%
other studies of the Pom-dex combination. The median PFS with Pom-
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 doublet in RRMM patient population with significant prior lenalidomide and
demonstrated the increased activity achieved by adding clari-
in the setting of newly diagnosed MM.18,25 This study of ClaPd
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
hypergycemia (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. Dexam-
ethasone dose reduction occurred in 68 patients (57%) and was
discontinued in 5 patients (4%) in the majority of cases for
hypergycemia 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 descrip-
tion 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 clari-
thromycin 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,
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
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intensity for dexamethasone in ClaPd was 61%.

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 lenalido-
mide, 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),
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.\textsuperscript{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 antmyeloma 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\%.\textsuperscript{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.\textsuperscript{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 hematologic. The MM-003 study reported rates of grade $\geq$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 $\geq$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 $\geq$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. Clarithromycin is a CYP3A4 inhibitor and in this capacity does impact dexamethasone metabolism.\textsuperscript{27,28} The potentially increased dexamethasone 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

| Prognostic variable | Univariate | Multivariate |
|---------------------|------------|-------------|
|                     | HR 95% CI  | P           | HR 95% CI  | P           |
| R-ISS $>$ 1          | 2.75 1.48-5.13 .001* | 2.75 1.09-7.38 .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 .70-1.58 .815 |
| 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.
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. 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

### Table 5. Adverse events

| Adverse event* | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Any grade | Grade ≥3 |
|----------------|--------|--------|--------|--------|--------|-----------|---------|
| 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 (%)** | | | | | | | |

| Adverse event† | Grade | Any grade | Grade ≥3 |
|----------------|-------|-----------|---------|

- 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.
significant improvement in disease control and therapeutic activity that results
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
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.

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**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
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