# A Phase I Study of Ruxolitinib, Lenalidomide, and Steroids for Patients with Relapsed/Refractory Multiple Myeloma

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## ABSTRACT

**Purpose:** Ruxolitinib with lenalidomide and dexamethasone shows antimyeloma effects *in vitro* and *in vivo*. MUC1 leads to lenalidomide resistance in multiple myeloma cells, and ruxolitinib blocks its expression. Thus, ruxolitinib may restore sensitivity to lenalidomide. Therefore, a phase I trial was conducted to determine the safety and efficacy of ruxolitinib with lenalidomide and methylprednisolone for patients with relapsed/refractory multiple myeloma (RRMM) who had been treated with lenalidomide/steroids and a proteasome inhibitor and showed progressive disease at study entry.

**Patients and Methods:** A traditional 3+3 dose escalation design was used to enroll subjects in four cohorts with planned total enrollment of 28 patients. Subjects received ruxolitinib twice daily, lenalidomide daily on days 1–21 of a 28-day cycle, and methylprednisolone orally every other day. Primary endpoints were safety, clinical benefit rate (CBR), and overall response rate (ORR).

**Results:** Twenty-eight patients were enrolled. The median age was 67 years and received a median of six prior treatments including lenalidomide and steroids to which 93% were refractory. No dose-limiting toxicities occurred. The CBR and ORR were 46% and 38%, respectively. All 12 responding patients were refractory to lenalidomide. Grade 3 or grade 4 adverse events (AE) included anemia (18%), thrombocytopenia (14%), and lymphopenia (14%). Most common serious AEs included sepsis (11%) and pneumonia (11%).

**Conclusions:** This phase I trial demonstrates that a JAK inhibitor, ruxolitinib, can overcome refractoriness to lenalidomide and steroids for patients with RRMM. These results represent a promising novel therapeutic approach for treating multiple myeloma (ClinicalTrials.gov number, NCT03110822).

## Introduction

Multiple myeloma is the most common primary malignancy of the bone marrow (1, 2). The etiology of myeloma is largely unknown, although genetic predisposition and environmental factors have been speculated. Multiple myeloma arises from malignant plasma cells that clonally expand and accumulate in the bone marrow (3). These clonal plasma cells produce high levels of monoclonal immunoglobulins (4). Plasma cell dyscrasias are classified as monoclonal gammopathy of undetermined significance, solitary plasmacytoma, smoldering myeloma, active myeloma, extra-medullary myeloma, and plasma cell leukemia (4).

In 2019, The American Cancer Society estimates that 32,110 adults (18,130 men and 13,980 women) will be diagnosed with multiple myeloma and 12,960 deaths (6,990 men and 5,970 women) from this disease will occur in the United States (5). Currently, there is not yet an established curative treatment available for patients diagnosed with multiple myeloma. However, in recent years, new and more effective drugs have become available for the treatment of multiple myeloma. Many newer drugs have been evaluated together and in combination with older agents, rapidly increasing the number of therapeutic options available to patients with multiple myeloma and resulting in deeper and durable treatment responses in a large proportion of patients. Among the drugs that have been FDA approved specifically for myeloma are immunomodulatory agents including thalidomide, and its newer analogs lenalidomide and pomalidomide.

Immunomodulatory agents exert their antineoplastic action by affecting various cancer cell functions and the microenvironment, including leading to changes in cytokine production, immune cell function, and in some instances, inflammation, cell proliferation, and tumor cell death (6). Recent studies have identified the key role of cereblon in producing the anti–multiple myeloma efficacy of these drugs (7, 8). Thalidomide has been found to be effective as an anti-multiple myeloma agent in one-third of patients with myeloma; notably, higher response rates have been observed when combined with steroids (1, 2). Lenalidomide is an analog of thalidomide that has shown more potent anti–multiple myeloma activity than thalidomide in preclinical studies and has been FDA approved for the treatment of previously untreated as well as relapsed or refractory multiple myeloma (RRMM) in combination with dexamethasone (9). Recently, an analog of thalidomide and lenalidomide, pomalidomide, has also been approved for patients with RRMM. Unfortunately, responses to immunomodulatory agents even in combination with other active multiple myeloma agents are transient, and thus, therapeutic approaches to help overcome resistance to these drugs are necessary.

Recently, the JAK family, including JAK1 and JAK2, has been shown to play a role in the pathogenesis of multiple myeloma. Specifically,

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

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## Translational Relevance

This phase I trial evaluated the safety and efficacy of a novel, all-oral combination consisting of the JAK 1/2 inhibitor ruxolitinib, lenalidomide, and steroids for treating patients with relapsed/refractory multiple myeloma. Many newer drugs have been evaluated together and in combination with older agents for these patients, but the responses to these regimens including those containing immunomodulatory agents are transient; thus, new therapeutic approaches to help overcome resistance to immunomodulatory agents are needed. The results from this trial are promising, especially given that the benefits were observed among patients who were refractory to lenalidomide and steroids with the addition of ruxolitinib. Thus, this study provides the basis for studying the addition of JAK inhibitors to improve the efficacy of immunomodulatory agents with steroids for treating patients with myeloma, but perhaps can also be expanded for treating patients with other cancers that are refractory to this class of drugs.

cytokines in the bone marrow of patients with multiple myeloma have been shown to activate the JAK/STAT signaling pathways in tumor cells and promote tumor growth, survival, and drug resistance (10). JAK kinases play a major role in the transmission of signals from cytokine and growth factor receptors into the nucleus (11).

The JAK1/2 inhibitor, INCB16562, has been shown to be a potent inhibitor of multiple myeloma. Specifically, this agent reduces the growth of myeloma xenografts in mice and enhances the anti–multiple myeloma activity of other active multiple myeloma agents in combination with other active anti–multiple myeloma drugs (10). Our laboratory has shown that another selective JAK1 inhibitor (INCB052793) alone and in combination with active multiple myeloma agents has also demonstrated anti–multiple myeloma effects in cell lines *in vitro* and xenografts growing in immunodeficient mice (12).

JAK2 is an intracytoplasmic tyrosine kinase whose abnormal activation has also been implicated in several hematologic disorders and malignances. Occurrence of events such as mutations, gene translocations, or cytokines released by bone marrow stromal cells, was reported to result in aberrant JAK2 activation (13). For example, the activation of JAK2 with V617F mutation results in uncontrolled cytokine and growth factor signaling and is believed to play a key role in the pathophysiology of myeloproliferative neoplasms. Enhanced JAK2 activity is believed to contribute to the development of leukemia, lymphoma, and multiple myeloma. In multiple myeloma, elevated levels of specific cytokines and growth factors have been shown to contribute to enhanced JAK activation (13, 14). Among these cytokines is IL6, known as a growth and survival factor for myeloma cells (14). Binding of IL6 to the IL6 receptor activates JAK2, which in turn can phosphorylate the IL6 receptor, thereby augmenting its downstream signaling effects. Thus, pharmacologic inhibition of JAK1, JAK2, or both kinases may be a promising therapeutic strategy for treatment of multiple myeloma. The treatment of multiple myeloma cell lines and patient-derived primary multiple myeloma cells with various JAK1, JAK2, and JAK1/JAK2 pan-specific inhibitors (e.g., INCB052793, INCB16562, TG101209, and CYT387/momelotinib) inhibited cell proliferation (12, 15–17). Specifically, JAK inhibitors have demonstrated synergistic activity with established anti–multiple myeloma therapies such as melphalan and bortezomib (CYT387) or melphalan, bortezomib, and dexamethasone (INCB16562), in both multiple myeloma cell lines and patient-derived primary multiple myeloma cells (16). In addition, sensitization of multiple myeloma cells to dexamethasone in response to JAK inhibitors occurs through cross-talk between the JAK/STAT pathway and glucocorticoids (17). In this regard, dexamethasone treatment has been shown to increase STAT3 and the prosurvival factor PI3K levels in melanoma cells resulting in an increase in STAT3 levels (18). Prolonged exposure to dexamethasone results in resistance (18), which could be overcome, at least in part, through JAK/STAT inhibition.

Ruxolitinib is an oral, selective inhibitor of JAK1 and JAK2, and is the only JAK1/2 inhibitor approved by the FDA for the treatment of intermediate- and high-risk myelofibrosis and hydroxyurea-refractory or intolerant polycythemia vera (19, 20).

There is increasing preclinical evidence from our laboratory and others suggesting that ruxolitinib may be effective for treating patients with multiple myeloma. Specifically, ruxolitinib in combination with lenalidomide and dexamethasone reduced the proliferation of the multiple myeloma cell lines U266 and RPMI8226 and primary tumor cells derived from patients with multiple myeloma, and this inhibition was greater when these drugs were combined compared with single agents (21). Enhanced antitumor activity was observed when ruxolitinib, lenalidomide, and dexamethasone were administered together to SCID mice bearing human multiple myeloma tumors (12, 21). Interestingly, ruxolitinib as a single agent showed no anti–multiple myeloma effects, whereas the combination of this drug with dexamethasone showed enhanced anti–multiple myeloma effects compared with steroid treatment alone (12, 21). Furthermore, one of the mechanisms of action appears to be via inhibition of MUC1 (mucin-1) expression in multiple myeloma cells and, as a result, this leads to a decrease in lenalidomide resistance (22, 23). Tribbles 1 is responsible for polarization of macrophages to the M2 phenotype, which are tumor stimulatory, and ruxolitinib results in downregulation of its expression, which is upregulated in multiple myeloma bone marrow (22, 23). The checkpoint proteins PD-L1 and PD-L2 (ligand 1 and 2 of programmed-death receptor) are increased in multiple myeloma bone marrow, and ruxolitinib reduces their expression augmenting the anti–multiple myeloma effects of T cells *in vitro* (24, 25).

Taken together, these results suggest that ruxolitinib may help overcome lenalidomide and steroid resistance for patients with RRMM that are failing therapy from lenalidomide-based therapy. Here, we report the results of the first phase I, all oral combination clinical trial evaluating the safety and efficacy of ruxolitinib in combination with methylprednisolone and lenalidomide for treatment of RRMM.

## Patients and Methods

### Patients

Study patients with measurable disease (M-protein or free light chain) according to International Myeloma Working Group (IMWG) criteria (26) that were relapsed or refractory to at least three or more lines of therapy, including a proteasome inhibitor and lenalidomide, were eligible for this study. All patients had Eastern Cooperative Oncology Group (ECOG) performance score of $\leq$2 and a life expectancy of >3 months. Eligible patients also met the following laboratory criteria: an absolute neutrophil count $\geq 1.5 \times 10^9$ per liter, platelet count $\geq 75 \times 10^9$ per liter, hemoglobin $\geq$ 8.0 g per deciliter, calculated or measured creatinine clearance $\geq$ 60 mL per minute as calculated by Cockcroft–Gault method, total bilirubin levels $\leq$ 2.0 mg per deciliter, aspartate aminotransferase and alanine aminotransferase $\leq$2 times the upper limit normal, serum potassium within the normal range, and corrected serum calcium < 12 mg per deciliter. For subjects with extensively infiltrated bone marrow ($\geq$70% plasma cells), absolute

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neutrophil count had to be $\geq 1.0 \times 10^9$ per liter and platelet count $\geq 50 \times 10^9$ per liter. Key exclusion criteria included POEMS syndrome, plasma cell leukemia, primary amyloidosis, other nonmalignancy hematologic malignancy, impaired cardiac function, known positivity for human immunodeficiency virus, hepatitis B or C, and tuberculosis. Other inclusion and exclusion criteria are provided in Supplementary Data (Supplementary Table S4).

### Study design

This was an open-label, multi-center phase I study conducted in two parts: dose escalation (part 1) and dose expansion (part 2). The study protocol and statistical plan were approved by the institutional review board or independent ethic committee at each investigational site. All patients provided written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines.

### Study treatments

In part 1 of the study, subjects were enrolled in four cohorts using standard 3+3 dose escalation design. If a dose-limiting toxicity (DLT; Supplementary Data; Supplementary Table S1) occurred in one participant in the cohort, another 3 patients were treated at the same dose level. The MTD was defined as one dose level below the dose in which DLTs were observed in 33% or more of participants.

All subjects received ruxolitinib twice daily orally (day 1–28), lenalidomide once daily orally (day 1–21), and methylprednisolone orally every other day (day 1–28). At dose level 0, subjects received 5 mg ruxolitinib, 5 mg lenalidomide, and 40 mg methylprednisolone. At dose levels +1 and +2, ruxolitinib dose was escalated to 10 mg and 15 mg, respectively, whereas the lenalidomide and methylprednisolone doses remained unchanged. At dose level +3, subjects received 15 mg ruxolitinib, 10 mg lenalidomide, and 40 mg methylprednisolone. In part 2 of the study, subjects received treatment at the MTD or maximum administered dose (MAD).

Treatment cycles of 28 days continued until disease progression or intolerable toxicity. An H2 blocker was administered prior to each ruxolitinib dose for peptic ulcer disease prophylaxis. Subjects received medications for herpes zoster and deep vein thrombosis prophylaxis.

This article includes data from patients enrolled from February 2, 2017, to clinical cut-off date of September 1, 2018.

### Sample size considerations

The sample size estimate was calculated assuming that, with 3+3 design, up to 3 patients would enroll in each of the four dose levels pending tolerability data at the current dose level. Under these assumptions, up to 24 subjects would be sufficient to determine the MTD. Taking into consideration an attrition rate of 15%, the trial will require a total of up to 28 enrolled patients.

Our secondary objective for this study was to determine overall response rate (ORR) and clinical benefit rate (CBR), showing it to be significantly greater than that of a trivial baseline response rate. Estimating that the study will continue to enroll subjects at the MTD until 28 patients are enrolled, efficacy will be calculated assuming an exact binomial test with effect size (g) = 0.18, alpha = 0.05, and power = 0.80 (two-tailed). Under these assumptions, 28 subjects are sufficient to detect a response rate significantly different from baseline.

### End points and assessments

Safety and MTD determination were primary end points of this study. Safety was determined by the frequencies and severities of adverse events (AEs) for all 28 patients. AEs were assessed at every study visit. Terminology Criteria for Adverse Events were used for safety assessments as described in Common Terminology Criteria for Adverse Events version 4.03. Safety assessments also included assessment of clinical laboratory tests, vital signs, physical examination, and electrocardiogram. MTD was defined by the number of DLT occurrences per dose level. Definition of DLTs can be found in Supplementary Table S1. Because no DLTs in the dose escalation part of the study were observed and MTD could not be determined, the MAD was used for part 2 of the study.

Efficacy was assessed for 26 patients; 2 patients did not complete one full cycle of treatment and therefore were excluded from this analysis. Secondary end points were ORR, CBR, progression-free survival (PFS), time to response, duration of response (DOR), and overall survival (OS). PFS was assessed for 23 of 26 patients; 3 patients did not have disease progression, however were taken off the study due to clinical deterioration.

Disease assessments were performed every 28 days (within a 2-day window before or after) until progression. Definitions of these efficacy end points are provided in Supplementary Table S2. Responses were assessed according to the IMWG (Supplementary Table S3) uniform response criteria for myeloma.

### Study oversight

This investigator-sponsored study was funded by Incyte Corporation and performed by Oncotherapeutics (clinical research organization). The investigator was responsible for the study design and statistical analysis plan. The data were collected by the appointed personnel of participating clinic centers, and compiled, maintained, and analyzed by Oncotherapeutics. All investigators had full access to the data and were not restricted by confidentiality agreements. A professional medical writer helped prepare the article. All authors reviewed, revised, and approved this article for submission. The investigators vouched for the accuracy and completeness of the data, analyses, and for the fidelity of the study to the protocol.

### Statistical analysis

Responses were evaluated in accordance with the IMWG uniform response criteria (Supplementary Table S3). PFS and DOR were analyzed using the Kaplan–Meier method. Data for PFS and DOR were censored at the last disease assessment before the onset of new anticancer therapy, or at the last disease assessment before the time of data cutoff. OS was censored at the last follow-up visit before the onset of a new anticancer therapy, or at the study visit before the time of data cutoff. Patients were not followed-up once they began a new anticancer therapy.

## Results

### Patients and treatment

As of clinical data cut-off date (September 1, 2018), a total of 28 patients with multiple myeloma were enrolled into the study. Of the 28 patients, 9 patients were enrolled in the three lower-dose level cohorts (dose levels 0, +1, and +2; 3 patients per each cohort) and 19 patients were enrolled at the highest planned dose (dose level +3). No DLTs were observed in the dose-escalation part of the study. The baseline characteristics of the patients are described in **Table 1**. The median age was 67 years (range, 49-81) and the median time since initial diagnosis was 58 months.

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**Table 1.** Baseline demographic and clinical characteristics of all patients.

| Characteristics | All patients ($N = 28$) |
|---|---|
| Median age (range), years | 67 (49–81) |
| Sex, no. (%) | |
| Male | 17 (61) |
| Female | 11 (39) |
| Race, no. (%) | |
| White | 25 (89) |
| Hispanic/Latino | 2 (7) |
| African American/Black | 1 (4) |
| Ig Isotypes, no. (%) | |
| IgG lambda, IgG kappa | 6 (21), 9 (32) |
| IgA lambda, IgA kappa | 4 (15), 2 (7) |
| Free kappa, free lambda | 1 (4), 6 (21) |
| ECOG performance status score, no. (%) | |
| 0 | 20 (71) |
| 1 | 8 (29) |
| 2 | 0 |
| Number of prior lines of therapy, no. | |
| Median | 6 |
| Prior therapy, no. (%) | |
| Lenalidomide | 28 (100) |
| Pomalidomide | 26 (93) |
| Bortezomib | 25 (89) |
| Carfilzomib | 17 (61) |
| Ixazomib | 11 (39) |
| Doxorubicin | 15 (54) |
| Elotuzumab | 14 (50) |
| Daratumumab | 8 (29) |
| Cyclophosphamide | 6 (21) |
| Autologous stem cell transplant | 3 (11) |
| Median time since diagnosis (range), months | 58 (15–131) |

The patient population in this study consisted of heavily pretreated subjects, 17 (61%) male, with a median of six prior regimens. All patients had previously received lenalidomide-containing therapy. In addition, 25 (89%) were exposed to bortezomib, 17 (61%) to carfilzomib, and 26 (93%) to pomalidomide. A smaller proportion of patients were exposed to antibody-based agents [elotuzumab, 14 (50%) and daratumumab, 8 (29%); **Table 1**].

Notably, 26 (93%) were refractory to their last lenalidomide-containing regimen, where refractoriness was defined as progression while receiving lenalidomide-containing treatment or within 8 weeks of the last dose of lenalidomide. The following is the breakdown of the lenalidomide doses for 26 patients that were refractory to lenalidomide-containing treatment prior to receiving ruxolitinib-containing therapy: 4 patients (25 mg every day), 1 patient (15 mg every day), 13 patients (10 mg every day), 5 patients (5 mg every day), and 3 patients (2.5 mg every day). Of 26 patients, 18 (69%) were treated with $\geq$10 mg of lenalidomide-containing regimen with the response rates of 29% ORR and 41% CBR. Also, of these 18 patients, 13 (72%) were treated with lenalidomide-containing regimen immediately prior to ruxolitinib-containing therapy. Responses of these 13 patients were 1 complete response (CR), 1 very good partial response (VGPR), 3 partial response (PR), 1 minimal response (MR), and 7 stable disease (SD).

As of September 1, 2018, 3 patients were still receiving treatments and 25 patients had discontinued. Of the 25 discontinued patients, 20 (80%) were taken off this study due to disease progression, 4 (16%) discontinued treatment due to clinical deterioration or worsening of the disease, and 1 patient (4%) withdrew from the study by choice.

**Table 2.** Treatment emergent AEs occurring in $\geq$10% of patients.

| AE | All grades ($N = 28$) | Grade 3 or higher ($N = 28$) |
|---|---|---|
| Patients with AE, *n* (%) | 28 (100%) | 15 (54%) |
| Blood and lymphatic system disorders | | |
| Anemia | 16 (57%) | 5 (18%) |
| Gastrointestinal disorders | | |
| Diarrhea | 10 (36%) | 1 (4%) |
| Nausea | 6 (21%) | 1 (4%) |
| Vomiting | 4 (14%) | 1 (4%) |
| Constipation | 4 (14%) | 0 (0%) |
| Hematochezia | 3 (11%) | 1 (4%) |
| Dyspepsia | 3 (11%) | 0 (0%) |
| General disorders and administration site conditions | | |
| Fatigue | 11 (39%) | 0 (0%) |
| Pyrexia | 10 (36%) | 0 (0%) |
| Chills | 7 (25%) | 0 (0%) |
| Asthenia | 5 (18%) | 0 (0%) |
| Edema, peripheral | 5 (18%) | 1 (4%) |
| Influenza-like illness | 3 (11%) | 0 (0%) |
| Noncardiac chest pain | 3 (11%) | 0 (0%) |
| Infections and infestations | | |
| Upper respiratory tract infection | 8 (29%) | 0 (0%) |
| Pneumonia | 6 (21%) | 3 (11%) |
| Nasopharyngitis | 5 (18%) | 0 (0%) |
| Sepsis | 3 (11%) | 3 (11%) |
| Bronchitis | 3 (11%) | 0 (0%) |
| Urinary tract infection | 3 (11%) | 0 (0%) |
| Injury, poisoning, and procedural complications | | |
| Contusion | 4 (14%) | 0 (0%) |
| Fall | 3 (11%) | 0 (0%) |
| Investigations | | |
| Lymphocyte count decreased | 8 (29%) | 4 (14%) |
| Platelet count decreased | 8 (29%) | 4 (14%) |
| Neutrophil count decreased | 5 (18%) | 4 (14%) |
| White blood cell count decreased | 5 (18%) | 3 (11%) |
| Alanine aminotransferase increased | 5 (18%) | 0 (0%) |
| Aspartate aminotransferase increased | 4 (14%) | 0 (0%) |
| Metabolism and nutrition disorders | | |
| Hypokalemia | 9 (32%) | 0 (0%) |
| Hypophosphatemia | 6 (21%) | 2 (7%) |
| Hypomagnesemia | 4 (14%) | 0 (0%) |
| Hyperglycemia | 3 (11%) | 1 (4%) |
| Decreased appetite | 3 (11%) | 0 (0%) |
| Hyponatremia | 3 (11%) | 0 (0%) |
| Musculoskeletal and connective tissue disorders | | |
| Pain in extremity | 4 (14%) | 0 (0%) |
| Back pain | 4 (14%) | 0 (0%) |
| Muscle spasms | 4 (14%) | 0 (0%) |
| Musculoskeletal pain | 3 (11%) | 1 (4%) |
| Musculoskeletal chest pain | 3 (11%) | 0 (0%) |
| Arthralgia | 3 (11%) | 0 (0%) |
| Nervous system disorders | | |
| Dizziness | 6 (21%) | 1 (4%) |
| Psychiatric disorders | | |
| Insomnia | 5 (18%) | 0 (0%) |
| Irritability | 4 (14%) | 0 (0%) |
| Depression | 3 (11%) | 0 (0%) |
| Respiratory, thoracic, and mediastinal disorders | | |

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**Table 2.** Treatment emergent AEs occurring in ≥10% of patients. (Cont'd)

| AE | All grades ($N = 28$) | Grade 3 or higher ($N = 28$) |
|---|---|---|
| Dyspnea | 10 (36%) | 1 (4%) |
| Cough | 8 (29%) | 0 (0%) |
| Oropharyngeal pain | 4 (14%) | 0 (0%) |
| Productive cough | 4 (14%) | 0 (0%) |
| Epistaxis | 3 (11%) | 0 (0%) |
| Sinus congestion | 3 (11%) | 0 (0%) |
| Skin and subcutaneous tissue disorders | | |
| Hyperhidrosis | 4 (14%) | 0 (0%) |
| Vascular disorders | | |
| Hypotension | 5 (18%) | 1 (4%) |

## Safety

In the dose-escalation part of the study, no DLTs were observed; and, therefore, an MTD could not be determined. Thus, enrollment was expanded at the MAD, the highest planned dosing cohort consisting of 15 mg ruxolitinib, 10 mg lenalidomide, and 40 mg methylprednisolone. Overall of total all grades AEs, 53% were possibly related to ruxolitinib, 62% attributed to lenalidomide, and 46% to methylprednisolone. The most common AEs (all grades) reported were anemia (occurred in 57% of patients), fatigue (39%), dyspnea (36%), pyrexia (36%), diarrhea (36%), hypokalemia (32%), cough (29%), thrombocytopenia (29%), lymphopenia (29%), upper respiratory tract infections (29%), chills (25%), dizziness (21%), hypophosphatemia (21%), pneumonia (21%), and nausea (21%; **Table 2**). Grade 3 or 4 AEs were observed in 54% of the patients (**Table 2**). Grade 3 or 4 AEs that occurred in 2 or more patients were anemia (18%), thrombocytopenia (14%), lymphopenia (14%), neutropenia (14%), pneumonia (11%), leukopenia (11%), sepsis (11%), and hypophosphatemia (7%; **Table 2**).

Of 28 evaluable subjects, 10 (36%) experienced serious AEs (SAE; **Table 3**). The most frequent SAEs were sepsis (11%), pneumonia (11%), cellulitis (7%), and gastrointestinal bleeding (7%). The rate of infection of grade ≥3 was 18% (5/28 patients) and is compatible with the grade 3 or higher infection rates that have been previously reported among patients with multiple myeloma treated with lenalidomide (**Table 3**; refs. 27–29). One patient died because of disease progression (**Table 3**). Among all treated patients, 54% (15) had dose interruption or modification due to AEs. The AEs that resulted in dose interruption or modification in 2 or more patients were anemia (21%), pneumonia (14%), irritability (14%), sepsis (11%), thrombocytopenia (11%), insomnia (11%), contusion (11%), leukopenia (7%), weight increase (7%), neutropenia (7%), fatigue (7%), and diarrhea (7%).

**Table 3.** SAEs.

| SAE | Frequency ($N = 28$) |
|---|---|
| Patients with a SAE, *n* (%) | 10 (36%) |
| Blood and lymphatic system disorders | |
| Anemia | 1 (4%) |
| Cardiac disorders | |
| Acute myocardial infarction | 1 (4%) |
| Angina pectoris | 1 (4%) |
| Atrial fibrillation | 1 (4%) |
| Gastrointestinal disorders | |
| Gastrointestinal hemorrhage | 2 (7%) |
| Abdominal pain | 1 (4%) |
| Enterocolitis | 1 (4%) |
| General disorders and administration site conditions | |
| Pyrexia | 1 (4%) |
| Infections and infestations | |
| Pneumonia | 3 (11%) |
| Sepsis | 3 (11%) |
| Cellulitis | 2 (7%) |
| Neutropenic sepsis | 1 (4%) |
| Injury, poisoning, and procedural complications | |
| Humeral fracture | 1 (4%) |
| Nervous system disorders | |
| Cerebrovascular accident | 1 (4%) |
| Psychiatric disorders | |
| Confusional state | 1 (4%) |
| Renal and urinary disorders | |
| Acute kidney injury | 1 (4%) |
| Renal failure | 1 (4%) |
| Respiratory, thoracic, and mediastinal disorders | |
| Dyspnea | 1 (4%) |
| Hypoxia | 1 (4%) |

**Table 4.** Response to treatment of all evaluable patients ($N = 26$).

| | *N* (%) |
|---|---|
| Best response status: | |
| CR | 1 (4) |
| VGPR | 2 (8) |
| PR | 7 (26) |
| MR | 2 (8) |
| SD | 12 (46) |
| Progressive disease | 2 (8) |
| ORR: | |
| CR+VGPR+PR | 10 (38) |
| CBR: | |
| CR+VGPR+PR+MR | 12 (46)[a] |

[a]All 12 responding patients were refractory to lenalidomide, and thus progressed while on or within 8 weeks of the last lenalidomide dose.

## Efficacy

Twenty-six patients were evaluated for the secondary end points; 2 patients that did not complete one full cycle of treatment were

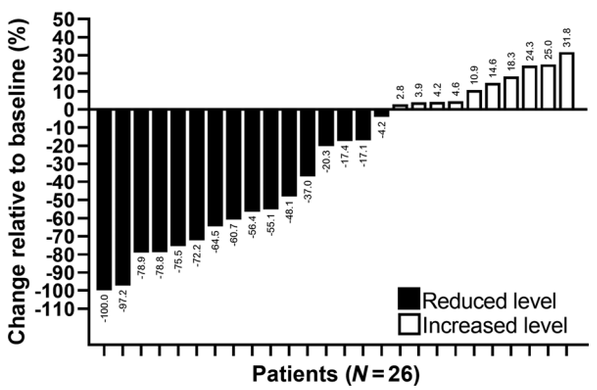


**Figure 1.**
Summary of best responses among all evaluable patients. The waterfall plot illustrates the best overall responses among 26 patients with RRMM. *Y*-axis reflects percentage change in levels of serum or urine monoclonal protein and/or Ig from baseline levels.

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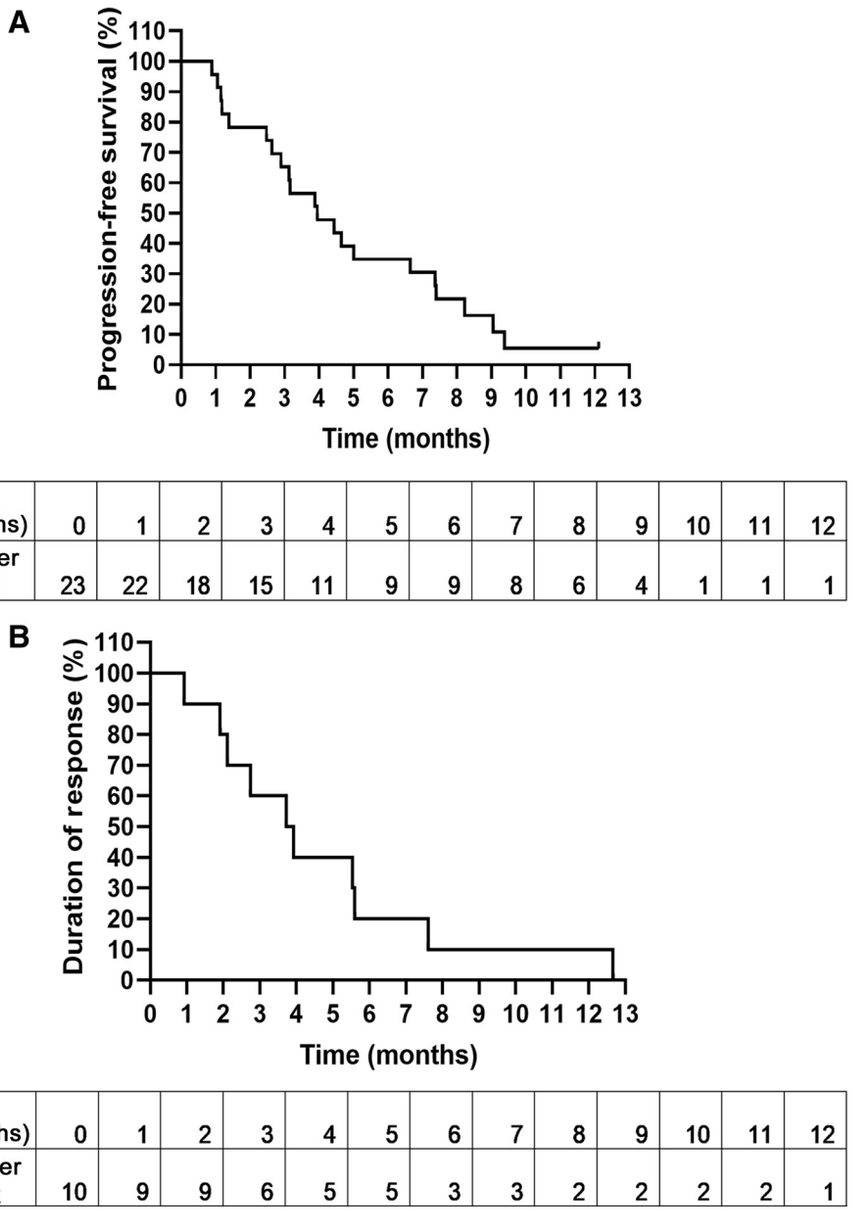


**Figure 2.**
Kaplan–Meier estimates of PFS and DOR. **A,** Median PFS for 23 evaluable patients is 4 months. **B,** DOR for 10 patients achieving PR or better with the median DOR of 3.8 months. The number of patients at risk is shown in the table immediately below the Kaplan–Meier curves.

excluded from this analysis (**Table 4**). Overall, the CBR and ORR were 46% and 38%, respectively (**Table 4**). Notably, all 12 responding patients were refractory to previous treatment with a lenalidomide- and steroid-containing combination. According to adjusted IMWG uniform response criteria (Supplementary Table S3), 1 patient had a CR, 2 had VGPR, 7 had PR, and 2 achieved a MR. Twelve patients showed SD and 2 patients showed progressive disease (**Table 4**; **Fig. 1**). The ORR for the 17 patients that were treated at the dose level +3 (15 mg ruxolitinib, 10 mg lenalidomide, and 40 mg methylprednisolone) was 40%. The median PFS for all evaluable patients ($N = 23$) was 4.0 months (**Fig. 2A**) and the median DOR for 12 patients with MR or greater was 4.0 months. Among these latter 12 patients, 10 responded with PR or better; their median DOR was 3.8 months (**Fig. 2B**). The median duration of observation time for patients in all dose levels was 3.7 months (range, 0.2–13.3 months).

## Discussion

The results of this phase I trial show that the addition of ruxolitinib to lenalidomide and steroids can overcome resistance to these latter two drugs and is well tolerated for the treatment of heavily pretreated RRMM patients with a median of six prior lines of therapy.

This is the first report demonstrating that a JAK inhibitor has clinical activity for treating patients with cancer. While ruxolitinib is the only FDA-approved agent for the treatment of patients with myelofibrosis (19, 20), the use was not effective for treatment of several types of cancers, including colorectal and pancreatic carcinomas (30, 31). The first published preclinical study exploring antimyeloma effects of ruxolitinib combined with bortezomib in multiple myeloma showed that the *JAK1* and *JAK2* genes are overexpressed in tumor samples collected from patients with multiple myeloma (32). In addition, significant increases in cell death were achieved in multiple

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myeloma cell lines treated with the combination of ruxolitinib and bortezomib (32), suggesting that targeting the JAK/STAT signaling pathway could be a new therapeutic approach for patients with multiple myeloma. Using human multiple myeloma xenograft models, ruxolitinib as a single agent showed no anti-myeloma effects, whereas the combination of ruxolitinib, lenalidomide, and dexamethasone produced a marked reduction in tumor size and growth *in vivo* (32).

Consistent with the results of these preclinical studies, this clinical trial shows that adding low-dose ruxolitinib to lenalidomide and steroids may overcome resistance to these latter two agents, which are frequently used to treat patients with multiple myeloma. Specifically, nearly half (46%) of patients achieved at least an MR and all were refractory to lenalidomide (**Table 4**). Of 12 responding patients, most ($N = 10$) patients achieved a PR or better with the median DOR of 3.8 months (**Fig. 2B**). Despite a relatively short median observation time of 3.7 months, the median PFS for all evaluable patients ($N = 23$) was 4 months.

Ruxolitinib in combination with lenalidomide and steroids produced clinically manageable AEs that were consistent with the previously known toxic effects of the combination of lenalidomide and steroids for the treatment of patients with RRMM (33, 34), and potential adverse reactions associated with ruxolitinib (20). The most common grade 3 or higher AEs were anemia (18%), thrombocytopenia (14%), lymphopenia (14%), neutropenia (14%), pneumonia (11%), leukopenia (11%), sepsis (11%), and hypophosphatemia (7%; **Table 2**) with the rate of anemia and neutropenia being lower than the rates reported of 20% and 37%, respectively, in another clinical trial involving patients with RRMM receiving lenalidomide and steroids (27). The rate of infection of grade $\geq$3 was 18% and is lower than those rates that have been reported in previously published trials for patients with RRMM that were treated with a two-drug combination of an immunomodulatory agent with dexamethasone (22.8%, 22%, and 28.1%; refs. 27–29). The results of this phase I trial are promising both in terms of efficacy and safety and it is particularly encouraging that benefits were observed in heavily pretreated multiple myeloma patients that were refractory to lenalidomide and steroids. Notably, the combination of ruxolitinib, lenalidomide, and steroids is an all-oral regimen, and thus offers a convenient, effective therapeutic option for patients with multiple myeloma.

Presumably, the underlining mechanism for the ability of ruxolitinib to overcome resistance to lenalidomide is via inhibition of MUC1 through regulation of the WNT/β-catenin/CD44 pathway (22, 23). In support of this, a recent preclinical study by Yin and colleagues has demonstrated that in multiple myeloma cells, inhibition of the oncoprotein MUC1 together with lenalidomide produced synergistic suppression of β-catenin and downregulation of CD44 (22). More importantly, both events were effective at reversing resistance of multiple myeloma cells to lenalidomide. In addition, experiments carried out in our laboratory have recently shown that ruxolitinib reduces MUC1 and CD44 expression in bone marrow from patients with RRMM (25). Interestingly, ruxolitinib also reduced expression of the checkpoint genes *PD-L1* and *PD-L2* and also led to a marked reduction in tumor stimulatory M2 macrophage polarization in bone marrow from patients with multiple myeloma (25, 35). Recently, it has been shown that anti–PD-L1 treatment leads to a reduction in M2 macrophage polarization (35, 36), consistent with our findings regarding ruxolitinib. Together, these preclinical results and this clinical study provide support for further exploring the clinical use of JAK inhibitors in combination with immunomodulatory agents for treating patients with RRMM. It also provides the basis for studying the addition of JAK inhibitors to improve the efficacy of immunomodulatory agents with steroids for treating patients with other cancers.

## Disclosure of Potential Conflicts of Interest

J.R. Berenson is an employee/paid consultant for, reports receiving other commercial research support from, and reports receiving speakers bureau honoraria from Incyte, and holds ownership interest (including patents) in OncoTracker. R.A. Moss reports receiving commercial research grants from Oncotherapeutics, Millenium, Bristol-Myers Squibb, and Parexel. S. Lim is an employee/paid consultant for Novartis Pharmaceuticals Corporation. No potential conflicts of interest were disclosed by the other authors.

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**Other (partial study management and data collection):** C. Turner
**Other (data collection, pharmacy-related assistance, drug preparation, and storage for treatments):** B.M. Eades

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## References

1. Smith ML, Newland AC. Treatment of myeloma. QJM 1999;92:11–4.
2. Morgan GJ. Advances in the biology and treatment of myeloma. Br J Haematol 1999;105:4–6.
3. Kastrinakis NG, Gorgoulis VG, Foukas PG, Dimopoulos MA, Kittas C. Molecular aspects of multiple myeloma. Ann Oncol 2000;11:1217–28.
4. Me M. Myeloma and lymphoma. Semin Musculoskelet Radiol 2000;4:8.
5. American Cancer Society. Cancer facts and figures. American Cancer Society; 2019. Available from: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2019.html.
6. Lacy MQ, McCurdy AR. Pomalidomide. Blood 2013;122:2305–9.
7. Rasco DW, Papadopoulos KP, Pourdehnad M, Gandhi AK, Hagner PR, Li Y, et al. A First-in-human study of novel cereblon modulator avadomide (CC-122) in advanced malignancies. Clin Cancer Res 2019;25:90–8.
8. Zheng J, Sha Y, Roof L, Foreman O, Lazarchick J, Venkta JK, et al. Pan-PIM kinase inhibitors enhance lenalidomide's anti-myeloma activity via cereblon-IKZF1/3 cascade. Cancer Lett 2019;440–441:1–10.
9. Hideshima T, Raje N, Richardson PG, Anderson KC. A review of lenalidomide in combination with dexamethasone for the treatment of multiple myeloma. Ther Clin Risk Manag 2008;4:129–36.

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10. Li J, Favata M, Kelley JA, Caulder E, Thomas B, Wen X, et al. INCB16562, a JAK1/2 selective inhibitor, is efficacious against multiple myeloma cells and reverses the protective effects of cytokine and stromal cell support. Neoplasia 2010;12:28–38.
11. Baker SJ, Rane SG, Reddy EP. Hematopoietic cytokine receptor signaling. Oncogene 2007;26:6724–37.
12. Sanchez E, Li M, Patil S, Soof CM, Nosrati JD, Schlossberg RE, et al. The anti-myeloma effects of the selective JAK1 inhibitor (INCB052793) alone and in combination in vitro and *in vivo*. Ann Hematol 2019;98:691–703.
13. Furqan M, Mukhi N, Lee B, Liu D. Dysregulation of JAK-STAT pathway in hematological malignancies and JAK inhibitors for clinical application. Biomark Res 2013;1:5.
14. Podar K, Chauhan D, Anderson KC. Bone marrow microenvironment and the identification of new targets for myeloma therapy. Leukemia 2009;23:10–24.
15. Ramakrishnan V, Kimlinger T, Haug J, Timm M, Wellik L, Halling T, et al. TG101209, a novel JAK2 inhibitor, has significant in vitro activity in multiple myeloma and displays preferential cytotoxicity for CD45+ myeloma cells. Am J Hematol 2010;85:675–86.
16. Monaghan KA, Khong T, Burns CJ, Spencer A. The novel JAK inhibitor CYT387 suppresses multiple signalling pathways, prevents proliferation and induces apoptosis in phenotypically diverse myeloma cells. Leukemia 2011;25:1891–9.
17. Gupta N, Mayer D. Interaction of JAK with steroid receptor function. JAKSTAT. 2013;2:e24911.
18. Krasil'nikov M, Shatskaya V. Signal transducer and activator of transcription-3 and phosphatidylinositol-3 kinase as coordinate regulators of melanoma cell response to glucocorticoid hormones. J Steroid Biochem Mol Biol 2002;82:369–76.
19. Rosenthal A, Mesa RA. Janus kinase inhibitors for the treatment of myeloproliferative neoplasms. Expert Opin Pharmacother 2014;15:1265–76.
20. Mascarenhas J, Coltoff A. The role of JAK2 inhibition in polycythemia vera. Target Oncol [Internet]. 2018 Aug 21. Available from: https://www.targetedonc.com/publications/targeted-therapies-cancer/2018/2018-august/the-role-of-jak2-inhibition-in-polycythemia-vera.
21. Haiming C, Sanchez E, Li M, Wang C, Gillespie A, Shvartsur A, et al. Increased M2 macrophages in multiple myeloma patients with progressive disease and down-regulated polarization with the JAK2 inhibitor ruxolitinib. Blood 2014;124:4106.
22. Yin L, Tagde A, Gali R, Tai YT, Hideshima T, Anderson K, et al. MUC1-C is a target in lenalidomide resistant multiple myeloma. Br J Haematol 2017;178:914–26.
23. Chen H, Li M, Sanchez E, Soof CM, Bujarski S, Ng N, et al. Jak1/2 pathway inhibition suppresses M2 polarization and overcomes resistance of myeloma to lenalidomide by reducing TRIB1, MUC1, CD44, CXCL12, and CXCR4 expression. Br J Haematol 2020;188:283–94.
24. Tai YT, Lin L, Xing L, Cho SF, Yu T, Acharya C, et al. APRIL signaling via TACI mediates immunosuppression by T regulatory cells in multiple myeloma: therapeutic implications. Leukemia 2019;33:426–38.
25. Chen H, Li M, Sanchez E, Soof CM, Bujarski S, Ng N, et al. The JAK inhibitor blocks PD-L1, PD-L2 and CD44 expression in multiple myeloma (MM) and sensitizes MM cells to lenalidomide and steroids. Blood 2018;132:1910.
26. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467–73.
27. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016;375:1319–31.
28. Dimopoulos MA, Dytfeld D, Grosicki S, Moreau P, Takezako N, Hori M, et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. N Engl J Med 2018;379:1811–22.
29. Dimopoulos MA, Palumbo A, Corradini P, Cavo M, Delforge M, Di Raimondo F, et al. Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS (MM-010): a phase 3b study in refractory multiple myeloma. Blood 2016;128:497–503.
30. Wang SW, Sun YM. The IL-6/JAK/STAT3 pathway: potential therapeutic strategies in treating colorectal cancer (review). Int J Oncol 2014;44:1032–40.
31. Garrido-Laguna I. JAK inhibitors used as anti-inflammatory therapeutics for pancreatic cancer. Contemporary Oncology [Internet]. 2015 Aug 23. Available from: https://www.onclive.com/publications/contemporary-oncology/2015/august-2015/jak-inhibitors-used-as-anti-inflammatory-therapeutics-for-pancreatic-cancer.
32. de Oliveira MB, Fook-Alves VL, Eugenio AIP, Fernando RC, Sanson LFG, de Carvalho MF, et al. Anti-myeloma effects of ruxolitinib combined with bortezomib and lenalidomide: a rationale for JAK/STAT pathway inhibition in myeloma patients. Cancer Lett 2017;403:206–15.
33. Chen H, Sanchez E, Li M, Wang C, Gillespie A, Shvartsur A, et al. . Anti-myeloma activity by the combination of the JAK2 inhibitor ruxolitinib with lenalidomide and corticosteroids. Blood 2014;124:2114.
34. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Spicka I, Oriol A, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015;372:142–52.
35. Jelinek T, Paiva B, Hajek R. Update on PD-1/PD-L1 inhibitors in multiple myeloma. Front Immunol 2018;9:2431.
36. Xiong H, Mittman S, Rodriguez R, Moskalenko M, Pacheco-Sanchez P, Yang Y, et al. Anti-PD-L1 treatment results in functional remodeling of the macrophage compartment. Cancer Res 2019;79:1493–506.


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