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A phase I/II study of twice-weekly ixazomib plus pomalidomide and dexamethasone in relapsed and refractory multiple myeloma

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Access to anonymized clinical data might be granted upon reasonable request to the corresponding author.

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Contributions

ON and PGR designed the study; ON, PMB, TJB, JPL, GB, CCM, JLR, SM, AS, YL, MAH-B, MPC, TN, AD, ER, AMVH, AJD, RG (as CRC), NCM, KM, IMG, and KCA enrolled and treated patients; ON, RAR, MPC, TN, EJB, ER, AMVH, AJD, RG (as CRC), KM, AL (as CRC), and RP oversaw the study and collected data; ON, RAR, EJB, and PGR analyzed study data; ON, RAR, EJB, KCA, and PGR interpreted study data; ON, RAR, EJB, and PGR wrote the original draft of the manuscript; ON, RAR, PMB, TJB, JPL, GB, CCM, JLR, SM, AS, YL, MAH-B, MPC, TN, EJB, AD, ER, AMVH, AJD, RG, KM, AL, RP, NCM, KCA, IMG, and PGR critically reviewed and revised the draft manuscript; and all authors approved the final manuscript for submission.

Abstract

Triplets incorporating proteasome inhibitors, immunomodulatory drugs, and dexamethasone are active regimens for patients with relapsed/refractory multiple myeloma (RRMM). All-oral regimens may offer greater real-world feasibility and convenience than other options. This phase I/II dose-escalation and expansion study evaluated the oral proteasome inhibitor ixazomib at a dose of 3 or 4 mg on a twice-weekly schedule (days 1, 4, 8, and 11) in 21-day cycles, plus pomalidomide at a dose of 2, 3, or 4 mg (days 1–14) and dexamethasone 12 or 8 mg (days of/after ixazomib), in 50 patients with RRMM. Patients had received a median of 2 prior lines, with 98.0% and 88.0% having received prior lenalidomide and bortezomib, respectively. The highest dose level investigated (ixazomib 4 mg, pomalidomide 4 mg) was the recommended phase II dose (RP2D). Patients received a median of 11 cycles. Common toxicities were neutropenia (76.0%; grade 3/4 22.0%/4.0%), thrombocytopenia (70.0%; 8.0%/8.0%), leukopenia (68.0%; 22.0%/0%), fatigue (52.0%; 4.0%/0%), and anemia (46.0%; 2.0%/0%). During dose escalation, two dose-limiting toxicities (grade 3 upper respiratory tract infection; grade 3 neutropenia) were reported. The overall response rate was 60.0% (24.0% ≥very good partial response [VGPR]) in all 50 patients and 65.8% (28.9% ≥VGPR) in the 38 patients who received the RP2D; the median duration of response was 18.0 and 19.3 months, median progression-free survival was 13.9 and 17.8 months, and 3-year overall survival rates were 85.2% and 80.3%, respectively. Twice-weekly ixazomib plus pomalidomide-dexamethasone is a well-tolerated, efficacious all-oral regimen with real-world utility in RRMM.

Introduction

Outcomes have improved substantially over the past two decades for patients with multiple myeloma (MM), with median overall survival (OS) in excess of 10 years in transplant-eligible patients with newly diagnosed MM (NDMM)[1] and increasing OS in the setting of relapsed/refractory MM (RRMM).[2] These improvements have been associated with a rapidly expanding therapeutic armamentarium, with multiple novel agents and regimens becoming available to clinicians, particularly in the past 10 years.[3,4] Nevertheless, despite these treatment advances, the majority of patients with MM experience relapse and progressively shorter outcomes[5] and become refractory to multiple therapies. Furthermore, MM patients and their disease characteristics are highly heterogeneous,[6] resulting in differing treatment approaches, preferences, and outcomes.[2,7-9] These factors underscore the ongoing need for additional effective and well-tolerated treatment options for patients with RRMM.

In the current treatment algorithm, proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and CD38 monoclonal antibodies (mAbs) are the backbones of therapy, with quadruplet regimens comprising bortezomib or carfilzomib, lenalidomide, and daratumumab or isatuximab, plus dexamethasone, the standards of care in the NDMM setting.[3,4] For patients with RRMM, triplet/quadruplet regimens comprising these agents are among the key standard-of-care options, along with therapies incorporating different PIs and IMiDs versus those used in first-line treatment, as well as novel immune-based approaches with the antibody–drug conjugate belantamab mafodotin, chimeric antigen receptor (CAR) T-cell therapies, and bispecific antibodies.[3,4] However, although there is this wealth of treatment options, clinicians must take into account numerous real-world factors when considering options for patients with RRMM, who may be primarily being treated in the community setting rather than at academic or specialist centers.[10] Such factors may include challenges associated with geography (distance to treatment center), convenience of therapy, patient preferences for their treatment, issues associated with immune status, and other criteria that may restrict eligibility for certain options.[7-9,11,12] Accessibility of some treatments, notably CAR T-cell therapies, may also present challenges.[13] Treatment options that remain viable in this real-world context are thus important, such as active all-oral combination regimens.

Ixazomib is the only oral PI available for the treatment of RRMM; it is approved in the US in combination with lenalidomide-dexamethasone (Rd) for patients with MM who have received ≥1 prior therapy[14] based on the findings of the TOURMALINE-MM1 study, which demonstrated superior progression-free survival (PFS) with weekly ixazomib plus lenalidomide-dexamethasone (Rd) versus Rd alone.[15-17] Ixazomib was initially evaluated as a single agent in patients with RRMM using both twice-weekly[18] and weekly[19] dosing

schedules, and twice-weekly[20] and weekly[21-23] dosing of ixazomib has also been evaluated in combination with Rd for patients with NDMM.

Combinations incorporating the IMiD pomalidomide are among the standards of care for RRMM. Many patients receive lenalidomide-based therapy until disease progression as part of first-line therapy; they are thus lenalidomide-exposed or lenalidomide-refractory in the RRMM setting and require alternative options such as regimens including a different IMiD. Pomalidomide is a highly potent IMiD that, in combination with dexamethasone, has demonstrated activity in patients with RRMM who are lenalidomide-exposed/refractory.[24] In the US, it is approved in combination with dexamethasone for patients with MM who have received ≥2 prior therapies including lenalidomide and a PI and have demonstrated disease progression on or within 60 days of completing their last therapy.[25]

Triplet combinations of a PI plus pomalidomide-dexamethasone (Pom-dex) have demonstrated substantial efficacy, with improved PFS, in RRMM,[26-29] including in patients with lenalidomide-refractory disease as in the OPTIMISMM phase III trial of bortezomib-Pom-dex versus bortezomib-dexamethasone.[28,29] Weekly ixazomib plus Pom-dex has also shown notable activity in the RRMM setting,[30-33] including in lenalidomide-refractory patients in the Alliance A061202 study.[32,33] Based on the promising activity seen with twice-weekly ixazomib-Rd in NDMM[20] and the twice-weekly bortezomib dosing regimen used in combination with Pom-dex in OPTIMISMM,[28,29] and in the context of the potential utility of a twice-weekly regimen in patients with high-risk features requiring more intensive therapy for rapid disease control, we conducted this phase I/II open-label, single-arm study to evaluate twice-weekly ixazomib plus Pom-dex in patients with RRMM.

Methods

Study design and patients

The study comprised a dose-escalation phase and an expansion phase at the maximum tolerated dose (MTD)/recommended phase II dose (RP2D). The study protocol and all amendments (DF/HCC Protocol #19-291; Takeda Protocol: X16117) were approved by institutional review boards or ethics committees at all participating sites. The study was conducted in accordance with the Declaration of Helsinki and per International Council for Harmonization Good Clinical Practice guidelines and all applicable laws and regulations. Eligible patients had MM with measurable disease, per International Myeloma Working Group (IMWG) criteria,[34] and required further treatment following disease progression (PD) on ≥2 prior therapies (or PD on/within 60 days of last therapy, after having received an IMiD

plus a PI as first-line therapy). Patients were excluded if they had prior ixazomib exposure, were pomalidomide-refractory, or had received IMiDs or PIs within 14 days. Other eligibility criteria are listed in **Supplementary Methods**. Written informed consent was provided by all patients prior to study participation.

Study treatment

Patients received treatment in 21-day cycles comprising ixazomib 3 or 4 mg on days 1, 4, 8, and 11, pomalidomide 2, 3, or 4 mg on days 1–14, and dexamethasone 12 mg (8 mg for patients aged ≥75 years) on the days of and after ixazomib dosing. Dose-escalation levels are shown in **Table 1**. Dose escalation proceeded per a standard 3+3 design, with 3–6 patients treated at each dose level; the MTD was the highest dose level at which <2 of 6 patients had a dose-limiting toxicity (DLT) during cycle 1 of treatment. DLTs are defined in **Supplementary Methods**.

Concomitant medications are detailed in **Supplementary Methods**. Treatment continued until PD, occurrence of unacceptable adverse events (AEs), patient withdrawal, or other reasons such as intercurrent illness that prevented further treatment. Patients who discontinued treatment for reasons other than PD were followed every 4 weeks until PD or initiation of subsequent therapy. Following PD, patients were followed every 3 months for 2 years for OS.

Objectives and assessments

The primary objectives were to determine the MTD in the dose-escalation phase I component, determine overall response rate (ORR; ≥partial response) and clinical benefit rate (CBR; ≥minimal response) in phase II, and evaluate safety in both phases. Disease response/progression was assessed using the 2011/2016 IMWG criteria.[35,36] AEs were assessed throughout treatment and until 30 days after last dose of study drug. Secondary objectives and assessment details are provided in **Supplementary Methods**.

Statistical analysis

Up to 24 patients were to be enrolled in the dose-escalation phase, and in phase II, at the MTD/RP2D, additional patients were to be enrolled to give a total of 37 treated at the MTD/RP2D across both phases. The phase II component used a Simon optimal two-stage design, with 19 patients enrolled in the first stage; with a null hypothesis of a 40% ORR and an alternative hypothesis of a 60% ORR, the study had 85% overall power with an alpha of 0.093. Analysis populations and additional statistical analysis details are provided in **Supplementary Methods**.

Results

Patient characteristics and disposition

Between September 26, 2019, and June 18, 2024, a total of 51 patients were enrolled at four study sites in the United States. One patient was a screen failure and was not treated; the other 50 patients were treated and were evaluable for safety and efficacy.

Patient demographics and disease characteristics in the overall population, by study phase and cohort, and in patients who received the RP2D are summarized in **Table 2**. Among all 50 patients, the median age was 68 years, with 60% of patients aged ≥65 years. Adverse prognostic characteristics included International Staging System (ISS) disease stage III in 26.0% of patients, high-risk cytogenetics in 42.0% (with del(17p) in 16.0% and gain 1q in 30.0%), and refractory disease in 60.0%. Patients had received a median of 2 prior lines of treatment, including lenalidomide in 98.0% and bortezomib in 88.0%, as well as stem cell transplantation in 32.0%. Overall, 56.0% and 20.0% of patients were refractory to lenalidomide and bortezomib, respectively.

At data cut-off (September 15, 2025), 5 (10.0%) patients were ongoing on study treatment and a further 10 (20.0%) remained on study in follow-up. Reasons for discontinuing study treatment included PD in 31 patients (62.0%), toxicity or side-effects in 5 (10.0%), physician or patient decision in 4 (8.0%), consent withdrawal in 1 (2.0%), death in 1 (2.0%, following sudden cardiac arrest during dialysis), and other reasons in 3 (6.0%; cardiac comorbidities, adenocarcinoma, clinical deterioration). Median follow-up, determined based on inverse Kaplan–Meier analysis of OS, was 30.8 months (95% CI 28.4–36.3).

Dose escalation and recommended phase II dose

During the dose-escalation phase, there were no DLTs reported in 3 patients treated in cohort 0 (ixazomib 3 mg, pomalidomide 2 mg) or in 3 patients treated in cohort 1 (ixazomib 3 mg, pomalidomide 3 mg). In cohort 2 (ixazomib 3 mg, pomalidomide 4 mg), one of the first 3 patients enrolled experienced a DLT of grade 3 upper respiratory tract infection, which was considered probably related to dexamethasone and was also a serious AE (SAE). No dose reduction was required. A further 3 patients were enrolled to cohort 2; no other DLTs were reported, and dose escalation proceeded to cohort 3. In cohort 3 (ixazomib 4 mg, pomalidomide 4 mg), one of the first 3 patients experienced a DLT of grade 3 neutropenia, which was considered probably related to ixazomib and pomalidomide and possibly related to dexamethasone. No dose reduction was required. A further 3 patients were enrolled to

cohort 3; no other DLTs were reported. As further dose escalation was not planned per protocol, the cohort 3 dose level was determined to be the MTD/RP2D.

Treatment exposure and safety

At data cut-off, patients had received a median of 13 cycles of treatment (range 1–79); 20 patients (40.0%) had received ≥18 cycles (~1 year) of treatment, including the 5 patients ongoing on study treatment. The safety profile is summarized in the overall population, in the phase I dose-escalation cohort (patients who received <RP2D), and in patients who received the RP2D (Cohort 3 in phase I, plus phase II cohort) in **Table 3**, together with the relative dose intensity of each agent. All patients reported at least one AE of any grade and at least one treatment-related AE (TRAE), with 78.0% and 64.0% having at least one grade 3/4 AE or grade 3/4 TRAE, respectively. The proportions of patients who had grade 3/4 AEs and grade 3/4 TRAEs were numerically higher in the RP2D cohort than in the phase I (<RP2D) cohort (81.6% and 66.7%; 73.7% and 33.3%, respectively), but the differences between cohorts in AE/TRAE maximum severity grades were not nominally significant (test for trend in proportions, *P*=0.60 and *P*=0.11, respectively).

The most common AEs (unrelated or related), reported in at least 20% of the total population, are summarized by severity grade in **Figure 1A**, with the corresponding rates of these events in patients who received the RP2D shown in **Figure 1B**. The most common AEs overall were neutropenia (76.0%), thrombocytopenia (70.0%), leukopenia (68.0%), fatigue (52.0%), and anemia (46.0%). The most common grade 3/4 AEs were neutropenia (22.0%/4.0%), leukopenia (22.0%/0%), and thrombocytopenia (8.0%/8.0%). In addition to those shown in **Figure 1A**, grade 3 AEs included syncope in 3 patients (6.0%), glucose intolerance and lung infection each in 2 patients (4.0%), and atrial fibrillation, catheter-related infection, dehydration, fall, fever, generalized muscle weakness, heart failure, hypertension, hyponatremia, localized edema, lymphopenia, non-cardiac chest pain, pneumonitis, sinusitis, thromboembolic event, treatment-related secondary malignancy, urinary tract infection, and vascular disorders – other each in 1 patient (2.0%). There were no other grade 4 AEs reported on treatment; 1 patient (2.0%) had a grade 4 cardiac arrest while on study but off treatment. Peripheral sensory neuropathy was seen in 32.0% of patients overall, with 1 patient (2.0%) having a grade 3 event.

The incidence of SAEs was numerically lower in the RP2D cohort than in the phase I (<RP2D) cohort (28.9% and 50.0%, respectively; Cochran-Armitage test *P*=0.32), whereas the incidence of dose reductions due to AEs was numerically higher (86.8% and 58.3%; Cochran-Armitage test *P*=0.11). Overall, 5 patients (10.0%), all of whom were treated at the

RP2D (5/38, 13.2%), discontinued treatment due to AEs (peripheral sensory neuropathy within pain, N=2, peripheral sensory neuropathy, N=1) or reported side effects ("significant side effects", N=1, "edema", N=1).

Efficacy

In all 50 patients, the ORR (partial response or better) was 60.0% (95% CI: 45.2–73.6), with 24.0% (95% CI: 13.1–38.2) having a very good partial response or better (≥VGPR; **Figure 2**). In the phase II/RP2D cohort (N=38), the ORR was 65.8% (95% CI: 48.6–80.4; N=25 responding patients), with 11 patients (28.9%; 95% CI: 15.4–45.9) having ≥VGPR (**Figure 2**). CBR in all 50 patients and the phase II/RP2D cohort was 62.0% (95% CI: 47.2–75.3) and 68.4% (95% CI: 51.3–82.5), respectively. In patients who received lenalidomide in their most recent prior therapy (N=40), the ORR was 55.0%, and among the 17 and 23 patients who received full-dose and maintenance lenalidomide, respectively, in their most recent prior therapy, the ORRs were 47.1% and 60.9%. In lenalidomide-refractory (N=28) and bortezomib-refractory (N=10) patients, the ORRs were 57.1% and 50.0%, respectively. A total of 6 patients had samples taken to confirm achievement of complete response and for minimal residual disease (MRD) analysis; one patient was not evaluable due to lack of a clonality samples, and analysis is being explored for the other five.

The median duration of response (DOR) in all 30 responding patients was 18.0 months (95% CI: 12.3–46.0) and in the 19 responding patients treated at the RP2D was 19.3 months (95% CI: 11.6–not evaluable [NE]) (**Figure 3A**). DOR appeared similar between responding patients with refractory or relapsed disease status (N=19 and 11, median 19.3 and 22.5 months, respectively, *P*=0.38), with lenalidomide-refractory and lenalidomide-non-refractory disease (N=16 and 14, median 18.0 and 22.5 months, respectively, *P*=0.37), and with or without 1q amp (N=9 and 13, median 12.6 months and not reached, *P*=0.20), but shorter in responding patients who were bortezomib-refractory compared with those who were not (N=5 and 25, median 12.6 and 22.5 months, *P*=0.0082). Comparisons of DOR in other subgroup pairs were limited by small numbers of responding patients in one of the subgroups (N<5).

At data cut-off, PFS events had occurred in 30 patients (60.0%), including 27 who had PD and 3 who had died in the absence of PD. The median PFS in all 50 patients was 13.9 months (95% CI: 11.6–20.6) and in patients treated at the RP2D was 17.8 months (95% CI: 12.2–24.5) (**Figure 3B**), with respective 2-year PFS rates of 28.3% (95% CI: 14.3–44.0) and 33.6% (95% CI: 16.1–52.1). PFS in select patient subgroups is shown in **Figure 4**. PFS appeared similar between patients with refractory or relapsed disease status (**Figure 4A**),

patients who were lenalidomide-refractory or non-refractory (**Figure 4B**), and those with high-risk and standard-risk cytogenetics (**Figure 4D**), including patients with/without del(17p) (**Figure 4E**) and patients with/without 1q amp (**Figure 4F**). Patients who were bortezomib-refractory (N=10) had shorter PFS than those who were not (N=40), with median PFS of 9.7 and 16.4 months, respectively (**Figure 4C**). Patients who had a response of ≥VGPR (N=12) had longer PFS than those who had <VGPR (N=38), with medians of 29.7 and 12.4 months, respectively (**Figure 4G**).

The median time to progression (TTP) in all 50 patients was 13.9 months (95% CI: 11.6–20.6) and in patients treated at the RP2D was 17.8 months (95% CI: 12.2–46.8), with respective 2-year TTP rates of 27.6% (95% CI: 13.2–44.2) and 33.2% (95% CI: 14.7–53.0). With 10 patients (20.0%) having died in total, median OS was not reached in all 50 patients or in patients treated at the RP2D (**Figure 3C**); 3-year OS rates were 85.2% and 80.3%, respectively.

Discussion

This phase I/II, multicenter study, which incorporated community sites and thereby reflected real-world treatment practice within the rigor of a clinical study, demonstrated the real-world feasibility, safety, and efficacy of the all-oral triplet regimen of twice-weekly ixazomib plus Pom-dex. The regimen was well tolerated in an elderly RRMM patient population (60% aged ≥65 years; albeit that 98% had Eastern Cooperative Oncology Group performance status 0 or 1, and all required creatinine clearance ≥45 mL/min) with substantial prior exposure to lenalidomide and bortezomib and in which more than half of the patients were lenalidomide-refractory, with a lengthy median duration of treatment and a limited rate of discontinuation due to toxicity. The MTD/RP2D reflected the approved doses of ixazomib (4.0 mg) and pomalidomide (4.0 mg) in other regimens; common toxicities reflected the known safety profiles of the agents in the triplet regimen,[15,18-20,22-24,29,37] with no new or unexpected AEs. The triplet regimen was efficacious, with an ORR of 65.8% at the RP2D, including 28.9% of patients with ≥VGPR, and notable long-term outcomes including durable responses and a median PFS of 17.8 months.

Together with other studies in RRMM and real-world analyses, the findings of our study demonstrate the efficacy/effectiveness of triplet therapy with ixazomib-Pom-dex. Our data specifically support the feasibility and activity of using twice-weekly ixazomib dosing in combination with Pom-dex in patients with RRMM, without appearing to substantively increase toxicity relative to previously published data with once-weekly ixazomib in

combination with Pom-dex,[32] and suggest an additional ixazomib dosing schedule option for this regimen. Furthermore, these findings also suggest the feasibility of utilizing twice-weekly ixazomib in other combination regimens, such as with daratumumab-dexamethasone,[38] selinexor-dexamethasone,[39] or iberdomide-dexamethasone.[40]

Weekly ixazomib plus Pom-dex has shown substantial activity in RRMM in a number of other studies. The Alliance A061202 phase I/II randomized trial in lenalidomide-refractory patients at first relapse showed that ixazomib-Pom-dex significantly improved PFS versus Pom-dex alone (median 20.3 versus 7.5 months, hazard ratio 0.437) and resulted in a higher ORR (63.2% *vs.* 43.6%) and ≥VGPR rate (28.9% versus 5.1%).[32,33] These improvements were also seen in patients with high-risk cytogenetics,[32] reflecting the benefit seen in our study in terms of DOR and PFS in patients with 1q amp and del(17p). Direct cross-trial comparisons are confounded by differences in the patient populations receiving twice-weekly ixazomib in our study and weekly ixazomib in the Alliance trial, such as the higher proportion of patients with ISS stage III disease in our study and their greater exposure to prior therapies but lower rate of lenalidomide-refractory status.[32] Nonetheless, efficacy data at the RP2D in our study suggested similar ORR, ≥VGPR rate, median DOR, and median PFS with twice-weekly compared to weekly ixazomib[32] despite a population with somewhat more advanced-stage disease. A study of weekly ixazomib-Pom-dex plus clarithromycin in 32 PI- and lenalidomide-exposed patients with RRMM resulted in an ORR of 75% and a lengthy median PFS of 22.2 months, with similar outcomes in patients with high-risk features such as del(17p).[41] Additionally, an all-oral quadruplet regimen comprising weekly ixazomib-Pom-dex plus selinexor has shown promising preliminary activity in functionally high-risk patients with MM.[42]

Twice-weekly ixazomib dosing, as used in our study, may have specific utility in settings in which greater therapeutic intensity is required, such as in patients with high-risk features associated with more aggressive and rapidly progressive disease, who require rapid and maintained disease control. Such features may include specific high-risk cytogenetic abnormalities such as del(17p), t(4;14), and amp/gain 1q, more advanced disease stage with greater disease burden, and functional high-risk features such as early relapse[43] (potentially associated with high-risk gene-expression profiles and/or molecular features[44]). This is supported by findings from the IFM 2014-01 study, in which twice-weekly ixazomib 3.0 mg plus pomalidomide 4.0 mg and dexamethasone resulted in a >3-fold improvement in median TTP (10.2 months) compared to Pom-dex alone (3.0 months, IFM 2010-02 study) in high-risk patients with adverse cytogenetics [del(17p) and/or t(4;14)] who were refractory to lenalidomide.[45] Our subgroup data are also supportive in this regard, indicating no or limited

differences in PFS in the presence or absence of high-risk features. Furthermore, the twice-weekly regimen with 21-day treatment cycles used in our study may also be beneficial for patients in whom it would be preferable to limit the duration of continuous pomalidomide exposure (i.e. 14 days instead of 21 days in a standard 28-day cycle), such as those at potentially increased risk of pomalidomide-associated toxicities.

As noted, our study demonstrates the real-world feasibility and effectiveness of an all-oral triplet regimen of twice-weekly ixazomib plus Pom-dex. Promising findings with weekly ixazomib plus Pom-dex have also been reported from a multicenter study in China that included 30 real-world and 20 clinical trial patients with RRMM after 1–3 prior lines; an ORR of 70% and a median time to next therapy of 9.5 months were reported.[31] These findings reflect the real-world feasibility and activity seen with the all-oral triplet combination of ixazomib-Rd in patients with RRMM,[46-48] which represents a convenient, active option in this setting.[17] For example, although carfilzomib-Rd appears to offer somewhat better efficacy than ixazomib-Rd in clinical trials, the Korean KMM2004 study – a retrospective, real-world, multicenter analysis – showed similar response rates with the regimens and prolonged outcomes with the all-oral triplet.[49] Additionally, another retrospective cohort study utilizing the TriNetX platform and real-world electronic health records showed a significantly lower risk of cardiac toxicities with ixazomib-Rd.[50]

It should be acknowledged that other triplet and quadruplet regimens incorporating a different PI, with or without a mAb, plus Pom-dex provide notable efficacy in the lenalidomide-refractory RRMM setting[26,27] that may potentially exceed that achieved with ixazomib-Pom-dex. However, convenience, tolerability, and other real-world issues may impact the feasibility and effectiveness of such regimens relative to an all-oral treatment option.

Indirect comparison of the safety profile of twice-weekly and weekly ixazomib dosing in combination with Pom-dex is confounded by differences in the patient population between our study and the Alliance trial,[32] as well as in the median number of doses of ixazomib and pomalidomide received (median 11 3-week cycles, compared to 9.5 4-week cycles[32]) and in the dexamethasone dosing schedule. Rates of hematologic toxicities showed no consistent pattern between our study (at the RP2D) and the Alliance trial,[32] with grade 2–4 neutropenia in 60.5% and 71.1%, thrombocytopenia in 28.9% and 13.2%, leukopenia in 52.6% and 42.1%, and anemia in 10.5% and 34.2% of patients, respectively. Gastrointestinal toxicities of grade 2–4 constipation (10.5% and 7.9%) and diarrhea (29.0% and 21.1%) were broadly similar, as were the rates of grade 2–4 peripheral sensory neuropathy (26.3% and 23.7%).

These findings reflect the broadly similar safety profiles reported with twice-weekly ixazomib (MTD 2.0 mg/m^2)[18] and weekly ixazomib (MTD 2.97 mg/m^2)[19] in phase I monotherapy studies in heavily pretreated patients with RRMM; however, safety data for twice-weekly[20] and weekly ixazomib[22] plus Rd in patients with NDMM suggested greater toxicity with the more intensive regimen. Careful monitoring for key side effects is therefore important to ensure the tolerability of twice-weekly ixazomib plus Pom-dex.

Limitations of our study include the single-arm, non-comparative design, preventing direct evaluation of efficacy and safety against other regimens, and the small numbers of patients in some subgroup analyses, precluding interpretation of similar/differential efficacy. Our study also enrolled a limited number of patients with previous exposure to daratumumab, which may affect the broader representativeness of these findings in the context of widespread first-line use of CD38 monoclonal antibodies.[3,4] Nevertheless, in this context it is interesting to note that weekly ixazomib in combination with the cereblon E3 ligase modulator iberdomide and dexamethasone has shown promising activity in elderly patients with RRMM at first relapse, including patients refractory to lenalidomide and daratumumab.[40]

In conclusion, our study has demonstrated the feasibility, tolerability, and efficacy of an all-oral triplet regimen of twice-weekly ixazomib plus Pom-dex in patients with RRMM. These findings suggest the utility of twice-weekly ixazomib dosing in this combination regimen, including its tolerability in an elderly population and its potential for use in patients with high-risk features. The results also indicate that the triplet may therefore represent a valuable real-world treatment option in this setting, and, taken together, our findings suggest it may have a high likelihood of translation from these promising clinical trials results to practice, not least given its outpatient use and all-oral administration, which in turn can further improve patient outcome.[7,11]

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Tables

Table 1. Planned dose levels and study enrolment in phase I and phase II.

Cohort/dose level	Ixazomib dose, mg	Pomalidomide dose, mg	Phase I enrolment, n	Phase II enrolment, n	Total
–1	2.3	2	0	0	0
0	3	2	3	0	3
1	3	3	3	0	3
2	3	4	6	0	6
3 (RP2D)	4	4	6	32	38
Total	–	–	18	32	50

RP2D: recommended phase II dose

Table 2. Patient demographics and disease characteristics, overall, in the phase I dose-escalation cohort, including in individual cohorts, in the phase II cohort, and at the RP2D.

Characteristic	All (N=50)	Phase I					Phase II (N=32)	RP2D (N=38)
		All (N=18)	Cohort 0 (N=3)	Cohort 1 (N=3)	Cohort 2 (N=6)	Cohort 3 (N=6)		
Age								
Median (range), years	68 (49–83)	68 (57–83)	71 (57–76)	61 (58–70)	70 (59–74)	64 (57–83)	68 (49–80)	67 (49–83)
≥65 years, *n* (%)	30 (60.0)	11 (61.1)	2 (66.7)	1 (33.3)	5 (83.3)	3 (50.0)	19 (59.4)	22 (57.9)
Sex, N (%)								
Male	26 (52.0)	9 (50.0)	2 (66.7)	2 (66.7)	3 (50.0)	2 (33.3)	17 (53.1)	19 (50.0)
Female	24 (48.0)	9 (50.0)	1 (33.3)	1 (33.3)	3 (50.0)	4 (66.7)	15 (46.9)	19 (50.0)
Race, N (%)								
White	39 (78.0)	15 (83.3)	3 (100)	3 (100)	4 (66.7)	5 (83.3)	24 (75.0)	29 (76.3)
Asian	4 (8.0)	2 (11.1)	0	0	2 (33.3)	0	2 (6.3)	2 (5.3)
African American	1 (2.0)	0	0	0	0	0	1 (3.1)	1 (2.6)
Other	6 (12.0)	1 (5.6)	0	0	0	1 (16.7)	5 (15.6)	6 (15.8)
ECOG PS, N (%)								
0	17 (34.0)	6 (33.3)	0	1 (33.3)	3 (50.0)	2 (33.3)	11 (34.4)	13 (34.2)
1	32 (64.0)	12 (66.7)	3 (100)	2 (66.7)	3 (50.0)	4 (66.7)	20 (62.5)	24 (63.2)
2	1 (2.0)	0	0	0	0	0	1 (3.1)	1 (2.6)
ISS disease stage, N (%)								
I	17 (34.0)	4 (38.9)	0	1 (33.3)	1 (16.7)	2 (33.3)	13 (40.6)	15 (39.5)
II	18 (36.0)	8 (44.4)	2 (66.7)	1 (33.3)	3 (50.0)	2 (33.3)	10 (31.3)	12 (31.6)
III	13 (26.0)	5 (27.8)	1 (33.3)	0	2 (33.3)	2 (33.3)	8 (25.0)	10 (26.3)
Missing	2 (4.0)	1 (5.6)	0	1 (33.3)	0	0	1 (3.1)	1 (2.6)
Cytogenetic risk, N (%)								
High risk	21 (42.0)	8 (44.4)	1 (33.3)	0	4 (66.7)	3 (50.0)	13 (40.6)	16 (42.1)
t(4;14)	1 (2.0)	1 (5.6)	0	0	0	1 (16.7)	0	0
del(17p)	8 (16.0)	1 (5.6)	0	0	1 (16.7)	0	7 (21.9)	7 (18.4)
t(14;16)	5 (10.0)	2 (11.1)	0	0	0	2 (33.3)	3 (9.4)	5 (13.2)
Gain 1q	15 (30.0)	8 (44.4)	1 (33.3)	0	4 (66.7)	3 (50.0)	7 (21.9)	20 (52.6)
Standard risk	18 (36.0)	3 (16.7)	0	1 (33.3)	2 (33.3)	0	15 (46.9)	15 (39.5)
Missing	11 (22.0)	7 (38.9)	2 (66.7)	2 (66.7)	0	3 (50.0)	4 (12.5)	7 (18.4)
Hyperdiploidy	11 (22.0)	3 (16.7)	1 (33.3)	1 (33.3)	1 (16.7)	0	8 (25.0)	8 (21.1)
Disease status, N (%)								
Refractory	30 (60.0)	9 (50.0)	3 (100)	3 (100)	3 (50.0)	0	21 (65.6)	21 (55.3)
Relapsed	20 (40.0)	9 (50.0)	0	0	3 (50.0)	6 (100)	11 (34.4)	17 (44.7)
Median prior lines (range), N	2 (1–6)	2 (1–4)	2 (1–3)	2 (1–2)	2 (1–3)	2 (1–4)	2 (1–6)	2 (1–6)
Prior therapies, N (%)								
SCT	16 (32.0)	11 (61.1)	2 (66.7)	2 (66.7)	3 (50.0)	4 (66.7)	5 (15.6)	9 (23.7)
Lenalidomide*	49 (98.0)	18 (100)	3 (100)	3 (100)	6 (100)	6 (100)	31 (96.9)	37 (97.4)
Refractory	28 (56.0)	8 (44.4)	1 (33.3)	1 (33.3)	3 (50.0)	3 (50.0)	20 (62.5)	23 (60.5)
Bortezomib	44 (88.0)	17 (94.4)	3 (100)	2 (66.7)	6 (100)	6 (100)	27 (84.4)	33 (86.8)
Refractory	10 (20.0)	5 (27.8)	1 (33.3)	0	2 (33.3)	2 (33.3)	5 (15.6)	7 (18.4)
Daratumumab	6 (12.0)	1 (5.6)	0	0	0	1 (16.7)	5 (15.6)	6 (15.8)
Refractory	2 (4.0)	0	0	0	0	0	2 (6.3)	2 (5.3)

*Of the 49 patients who had prior lenalidomide, 17 and 23 received full-dose and maintenance lenalidomide, respectively, as part of their most recent prior therapy. ECOG PS: Eastern Cooperative Oncology Group performance status; ISS: International Staging System; RP2D: recommended phase II dose; SCT: stem cell transplantation.

Table 3. Summary of safety profile and dose intensity overall, in the phase I dose-escalation cohort, and at the RP2D.

AEs, N (%)	All (N=50)	Phase I (<RP2D) (N=12)	Phase II/RP2D (N=38)
Any AE	50 (100)	12 (100)	38 (100)
Max grade 1	1 (2.0)	0	1 (2.6)
Max grade 2	10 (20.0)	4 (33.3)	6 (15.8)
Max grade 3	31 (62.0)	7 (58.3)	24 (63.2)
Max grade 4	8 (16.0)	1 (8.3)	7 (18.4)
Any related AE	50 (100)	12 (100)	38 (100)
Max grade 1	3 (6.0)	1 (8.3)	2 (5.3)
Max grade 2	15 (30.0)	7 (58.3)	8 (21.1)
Max grade 3	27 (54.0)	4 (33.3)	23 (60.5)
Max grade 4	5 (10.0)	0	5 (13.2)
Any SAE	17 (34.0)	6 (50.0)	11 (28.9)
Discontinuation due to AEs	5 (10.0)	0	5 (13.2)
Dose reduction (any drug) due to AEs	40 (80.0)	7 (58.3)	33 (86.8)
Ixazomib*	27 (54.0)	2 (16.7)	25 (65.8)
Pomalidomide†	26 (52.0)	4 (33.3)	22 (57.9)
Dexamethasone‡	35 (70.0)	6 (50.0)	29 (76.3)
Median relative dose intensity (range), %#			
Ixazomib	94 (32–100)	100 (44–100)	89 (32–100)
Pomalidomide	96 (54–100)	100 (76–100)	92 (54–100)
Dexamethasone	76 (36–100)	95 (39–100)	70 (36–100)

*Protocol-specified ixazomib dose reductions were from 4.0 to 3.0 to 2.3 mg, twice-weekly, and then to 2.3 mg once-weekly. Overall, 5 patients (10%) switched to weekly dosing of ixazomib.

†Protocol-specified pomalidomide dose reductions were from 4 to 3 to 2 to 1 mg.

‡Protocol-specified dexamethasone dose reductions were from 12 to 8 to 4 mg for patients aged <75 years and from 8 to 4 mg and then to 4 mg on the day of ixazomib dosing only.

#Relative dose intensity calculated as the actual dose received in each cycle (accounting for dose reductions) relative to the assigned dose, averaged over all cycles, x 100.

AE: adverse event; RP2D: recommended phase II dose; SAE: serious adverse event.

Figure captions

Figure 1. Most common toxicities reported on treatment with twice-weekly ixazomib plus pomalidomide and dexamethasone. Figures show all AEs reported in ≥20% of patients in (A) the overall population, N=50, and (B) those treated at the RP2D (N=38). ALT: alanine aminotransferase; PSN: peripheral sensory neuropathy; RP2D: recommended phase II dose; URTI: upper respiratory tract infection.

Figure 2. Best responses to twice-weekly ixazomib plus pomalidomide and dexamethasone. Best response to study treatment in (A) the overall population, N=50, and (B) those treated at the RP2D, N=38. CR: complete response; MR: minimal response; NE: not evaluable; ORR: overall response rate; PR: partial response; RP2D: recommended phase II dose; sCR: stringent complete response; SD: stable disease; VGPR: very good partial response.

Figure 3. Kaplan–Meier analyses of time-to-event outcomes. (A) Duration of response in all responding patients, N=30, and in responding patients treated at the RP2D, N=25. (B) Progression-free survival and (C) overall survival in the overall population, N=50, and in those treated at the RP2D, N=38. CI: confidence interval; NE: not evaluable; NR: not reached; RP2D: recommended phase II dose.

Figure 4. Kaplan–Meier analyses of progression-free survival in patient subgroups. Progression-free survival in patient subgroups defined by (A) baseline disease status (relapsed or refractory), (B) lenalidomide refractoriness, (C) bortezomib refractoriness, (D) cytogenetics risk, (E) presence of del(17p), (F) presence of 1q amp, and (G) best response to treatment. CI: confidence interval; HR: high-risk; NE: not evaluable; PFS: progression-free survival; refract: refractory; RP2D: recommended phase II dose; SR: standard-risk; V: bortezomib; VGPR: very good partial response.

Figure 1

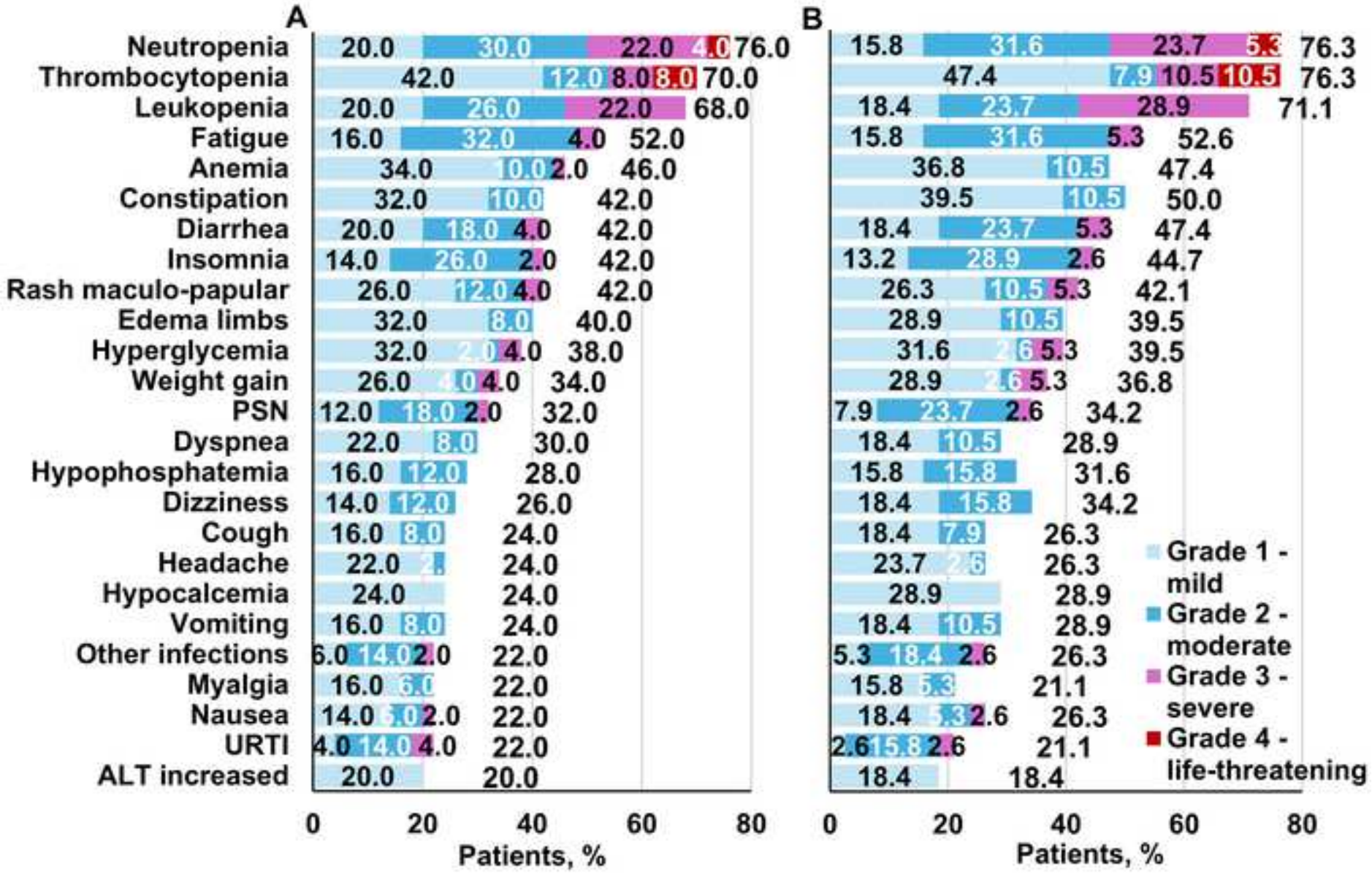

Figure 2

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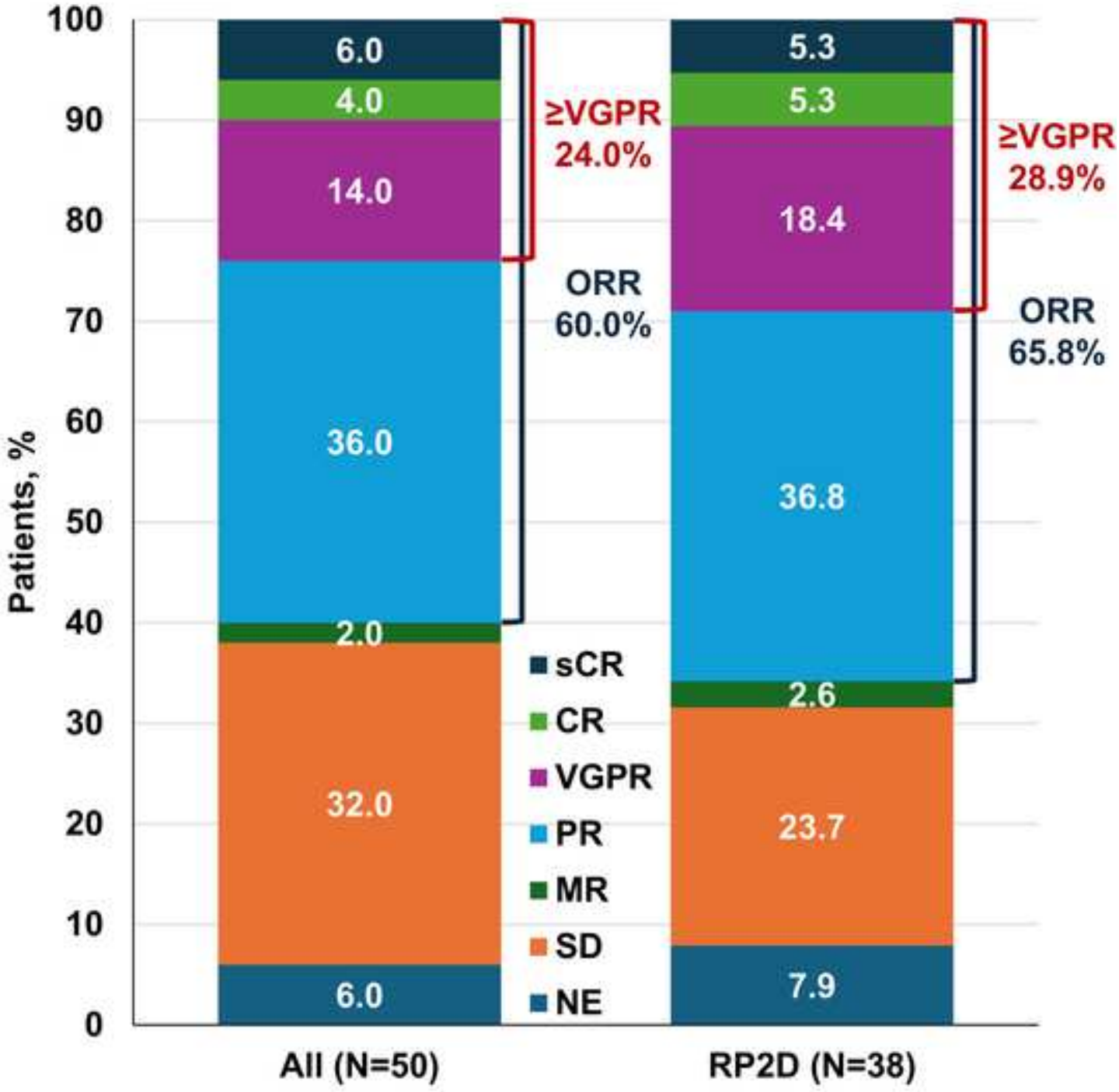

Figure 3

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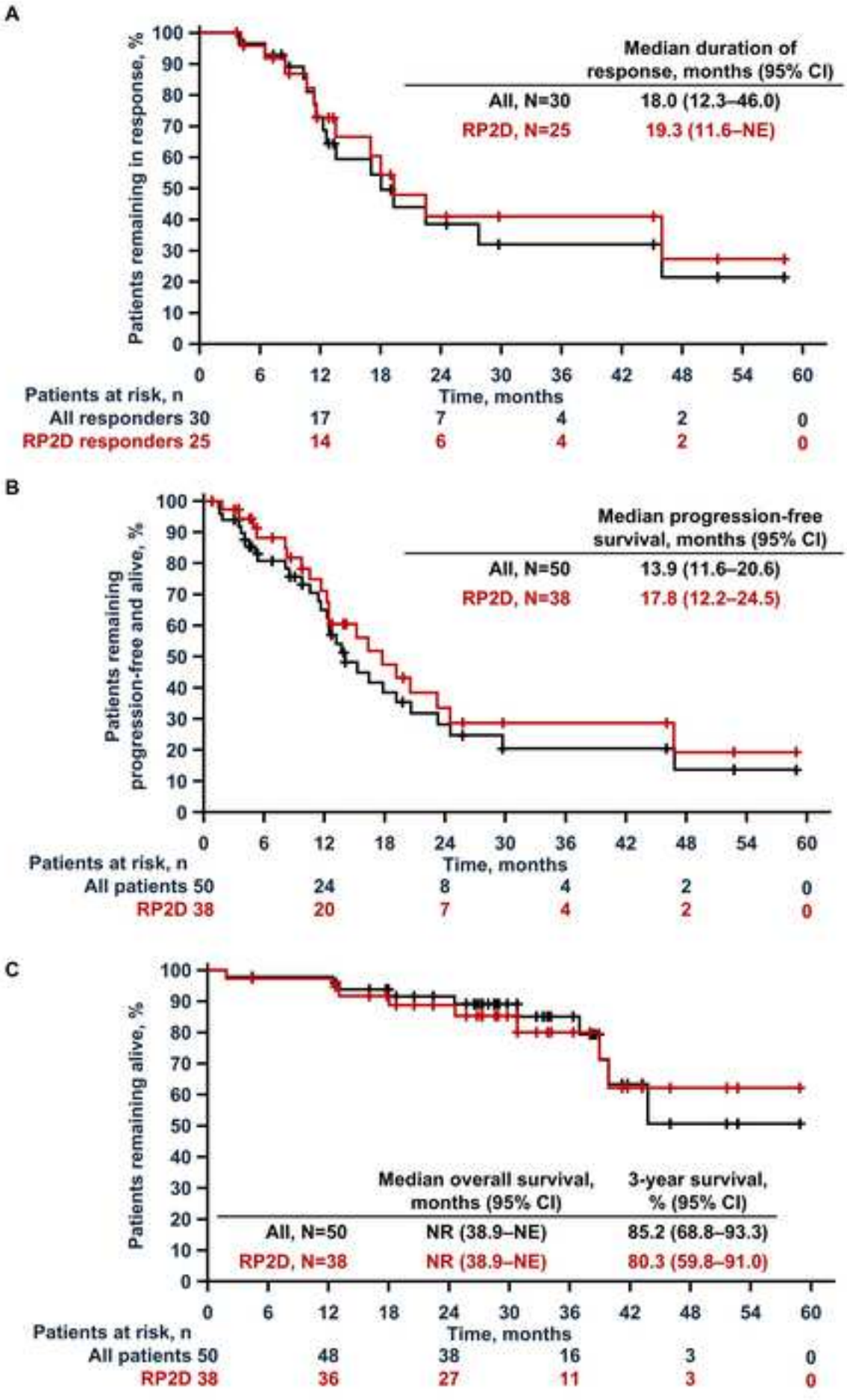

Figure 4

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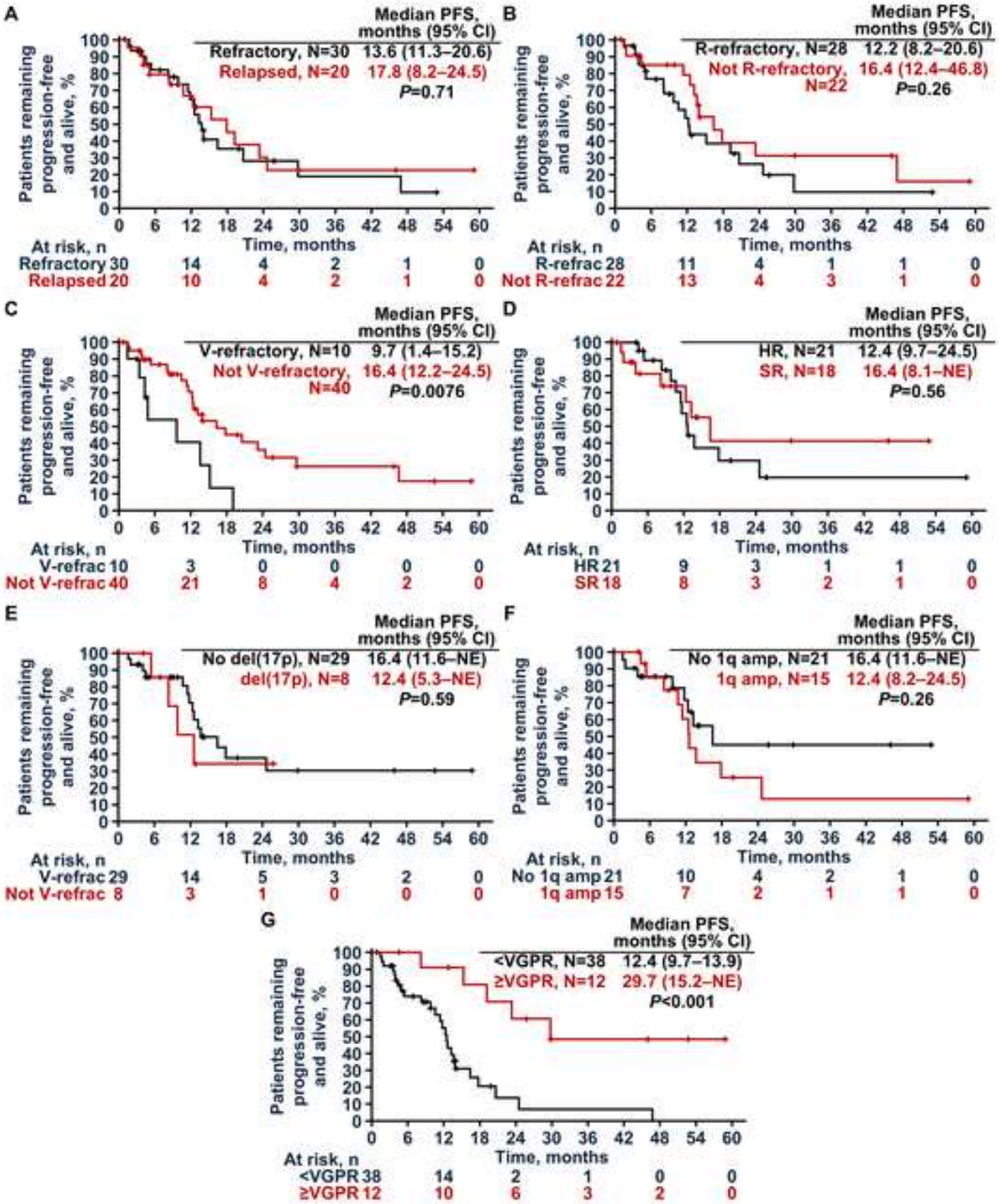

Supplementary Information

Supplementary Methods

Additional eligibility criteria

Patients required adequate hematologic (absolute neutrophil count ≥1 x 10^9/L; platelets ≥75 x 10^9/L, without transfusion requirement within 14 days prior to therapy; hemoglobin ≥8.0 g/dL), hepatic (total bilirubin ≤1.5 x upper limit of normal [ULN], or <3.0 x ULN if patient had Gilbert Syndrome; alanine aminotransferase and aspartate aminotransferase ≤1.5 x ULN), and renal (calculated creatinine clearance ≥45 mL/min) function and an Eastern Cooperative Oncology Group performance status of 0–2. Patients had to have been registered into and in compliance with the mandatory POMALYST REMS® program.

Patients were excluded if they: had prior ixazomib exposure; were pomalidomide-refractory; or had received IMiDs or PIs within 14 days, cytotoxic therapies for MM within 21 days, other investigational therapies and/or mAbs within 4 weeks, live vaccines within 30 days, prior peripheral stem cell transplant (SCT) within 12 weeks, or prior allogeneic SCT with active graft-versus-host disease prior to first dose of study treatment. Additional exclusion criteria included: known gastrointestinal disease or procedure that could interfere with oral absorption/tolerance of treatment; known central nervous system involvement; systemic treatment with strong CYP3A inhibitors or inducers or strong CYP1A2 inhibitors within 14 days; major surgery or radiotherapy within 14 days; any active or uncontrolled cardiovascular conditions; concurrent systemic amyloidosis or plasma cell leukemia, or POEMS syndrome; any serious infection within 14 days; or known seropositivity for HIV, hepatitis B, or hepatitis C.

Definition of dose-limiting toxicity (DLT)

DLTs were defined as: grade ≥3 non-hematologic toxicity not related to disease progression; thrombocytopenia of grade 4 (>1 occurrence, not attributable to underlying disease), grade 3 or ≥2 with bleeding; grade 4 neutropenia for >5 days and/or febrile neutropenia; any grade 5 events unless due to progressive disease (PD); inability to receive treatment on day 1 of cycle 2 due to possibly treatment-related toxicity.

Concomitant medications

Patients were required to receive prophylactic anti-thrombotic therapy. Additionally prophylactic anti-emetics prior to ixazomib, antimicrobial and antiviral (pneumocystis carinii pneumonia) prophylaxis, and prophylactic acyclovir or valacyclovir were recommended.

Objectives and Assessments

Secondary objectives were to assess duration of response (DOR), time to progression (TTP), PFS, and OS, and to determine the minimal residual disease (MRD)-negative response rate in patients achieving a complete response (CR).

Disease response and progression was assessed using the 2011/2016 IMWG criteria[1,2] on day 1 of each treatment cycle and at follow-up visits prior to PD. Bone marrow aspiration and biopsy was done at screening for cytogenetics assessment and subsequently as required to confirm CR and assess MRD status. MRD was to be evaluated using the clonoSEQ Assay (Adaptive Biotechnologies, Inc., Seattle, WA, USA) employing multiplex polymerase chain reaction and next-generation sequencing. MRD status was determined based on a sensitivity threshold of 10^{-5}. Extramedullary plasmacytomas were assessed at screening, as clinically indicated, and to confirm response or progression using a consistent method (computerized tomography, magnetic resonance imaging, or positron emission tomography).

AEs were assessed throughout treatment and until 30 days after last dose of study drug; serious AEs (SAEs) and possibly treatment-related AEs were followed until resolution or stabilization. If required due to AEs, protocol-specified ixazomib dose reductions were from 4.0 to 3.0 to 2.3 mg, twice-weekly, and then to 2.3 mg once-weekly, pomalidomide dose reductions were from 4 to 3 to 2 to 1 mg, and dexamethasone dose reductions were from 12 to 8 to 4 mg for patients aged <75 years and from 8 to 4 mg and then to 4 mg on the day of ixazomib dosing only.

Toxicity and accrual data were monitored and reviewed up to four times a year by the Dana-Farber/Harvard Cancer Center Data and Safety Monitoring Committee.

Statistical analysis

The safety analysis set comprised all patients who received at least one dose of any study drug and was used for evaluation of exposure, outcomes, and safety. The DLT analysis set comprised all patients in phase I who completed cycle 1 or discontinued during cycle 1 due to a DLT. The efficacy analysis set for the evaluation of the primary efficacy endpoint, ORR, comprised all patients who receive at least one cycle, had a baseline disease assessment, and had at least 1 post-baseline disease assessment (≥28 days after first dose). Response rates are reported as proportions with 95% exact binomial confidence intervals (CIs).

DOR (time from response to disease progression or death), TTP (time from first dose to disease progression), PFS (time from first dose to disease progression or death, and OS

(time from first dose to death) were estimated using Kaplan–Meier methodology, with patients who had not progressed or died censored at the date last known to be progression-free or alive (according to endpoint); 95% CIs for medians and landmark rates were calculated using Greenwood's method to estimate variance. Median follow-up was calculated using the reverse Kaplan–Meier method. Statistical analyses were performed using R version 4.4.2 (October 31, 2024).

Supplementary references

1. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-4695.
2. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e346.

DF/HCC Protocol #: 19-291
Takeda Protocol: X16117

TITLE: A Phase I/II Study of Twice Weekly Ixazomib Plus Pomalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma

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DF/HCC Project Manager:
Emily Benjamin
Dana-Farber Cancer Institute
[redacted]

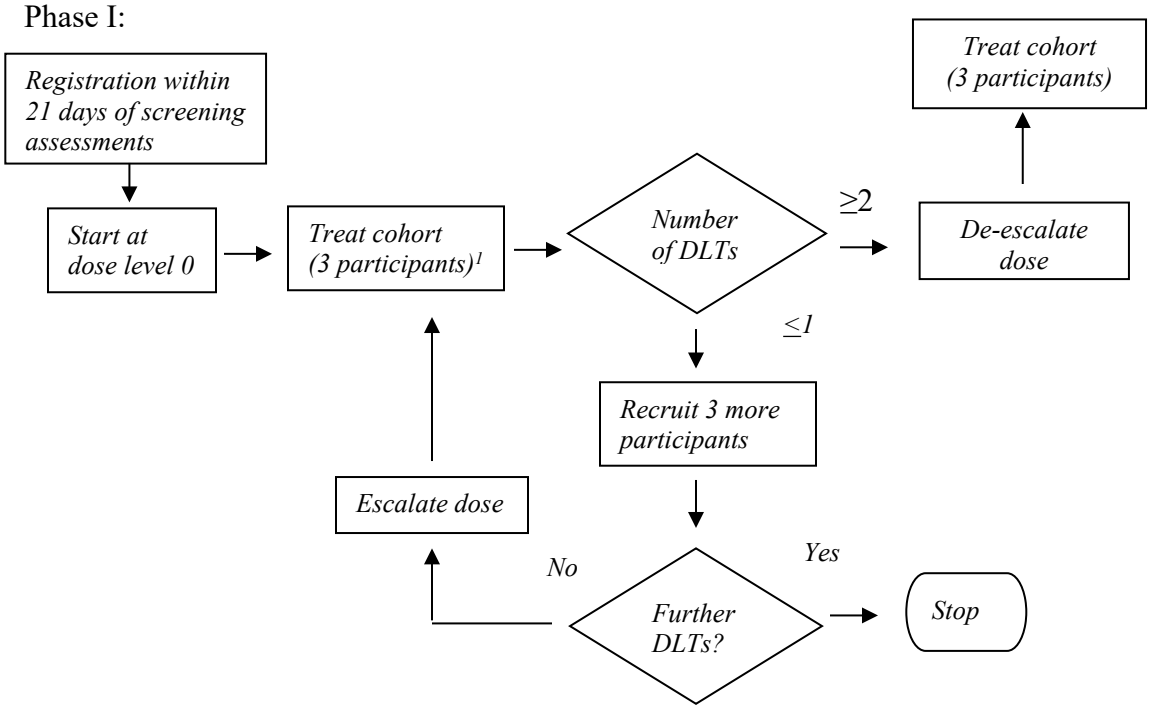
Agent(s): Ixazomib, Takeda
Pomalidomide, commercial
Dexamethasone, commercial

IND #: 143660
IND Sponsor: Omar Nadeem, MD

Protocol Type: Phase I/II / Version #8 Version Date: 04Apr2024

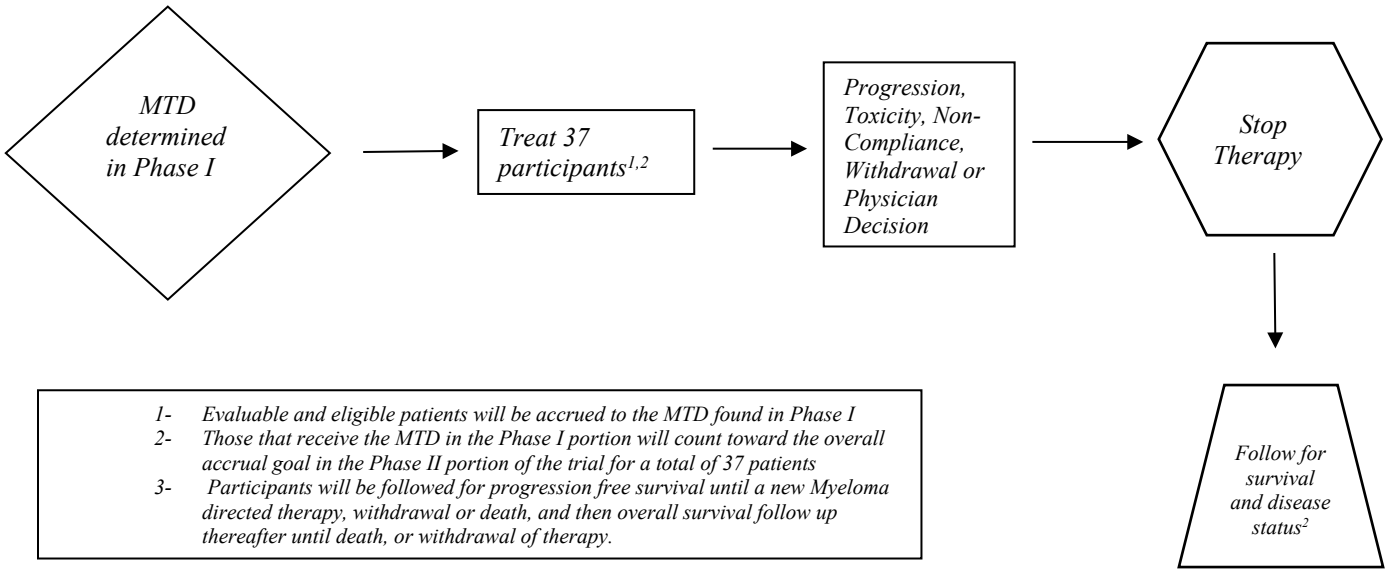
SCHEMA

Phase I:



1-Minimum of 3 and maximum of 6 eligible patients will be enrolled to each dose cohort

Phase II: Treatment at the MTD determined in Phase I



1- *Evaluable and eligible patients will be accrued to the MTD found in Phase I*
2- *Those that receive the MTD in the Phase I portion will count toward the overall accrual goal in the Phase II portion of the trial for a total of 37 patients*
3- *Participants will be followed for progression free survival until a new Myeloma directed therapy, withdrawal or death, and then overall survival follow up thereafter until death, or withdrawal of therapy.*

TABLE OF CONTENTS

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1. OBJECTIVES

1.1 Study Design

This is a Phase I/II study using the combination of twice weekly ixazomib plus pomalidomide and dexamethasone in relapsed and or refractory multiple myeloma (RRMM) patients.

1.2 Primary Objectives

- To determine the maximum tolerated dose of this combination in the dose escalation Phase I portion
- To determine the overall response rate and clinical benefit rate in the Phase II portion of the study
- To evaluate the safety of this combination in patients with multiple myeloma

1.3 Secondary Objectives

- To assess time to progression
- To assess the progression free survival
- To assess duration of response
- To assess overall survival
- To determine minimal residual disease (MRD) rate in those who achieve CR by IMWG criteria at any time during treatment

1.4 Correlative Study Objective

- To characterize somatic aberrations present in cell free DNA (cfDNA) and circulating tumor cells (CTCs) as biomarkers of response/ resistance to ixazomib/pom/dex.
- To define markers of the permissive bone marrow microenvironment that characterize risks of progression in MM.
- To define the immune-oncogenomic landscape of MM in response to therapy

2. BACKGROUND

2.1 Study Disease(s)

MM is a B-cell neoplasm characterized by the proliferation of clonal plasma cells and associated with a variety of clinical manifestations such as lytic bone lesions, hypercalcemia, renal impairment, and anemia. It accounts for 10-15% of hematologic malignancies and 20% of deaths related to cancers of the blood and bone marrow (McKenna, 2008). The pathogenesis of MM is driven by interactions between MM cells and the bone marrow microenvironment, which is composed of extracellular matrix (ECM) proteins such as fibronectin, collagen, and laminin, along with cellular elements such as hematopoietic stem cells, immune cells, bone marrow endothelial cells, and bone marrow stromal cells (BMSCs). Adhesion of MM cells to ECM proteins and accessory cells leads to increased expression of factors such as IL-6, insulin-like growth factor (IGF-1), and vascular endothelial growth factor (VEGF), which in turn further stimulates growth and survival of the malignant clone (Chauhan, 1995).

2.2 Pomalidomide Background

Pomalidomide, an analogue of thalidomide, is an immunomodulator (IMiD) with antineoplastic activity that displays similar anti-angiogenic activity, but far greater anti-proliferative and immunomodulatory activity compared to the parent drug (Payvandi et al, 2004, Celgene). In in-vitro cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibited the proliferation of lenalidomide-resistant MM cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhanced T cell- and natural killer (NK) cell-mediated immunity and inhibited production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes (Quach et al, 2009).

Pomalidomide is indicated for patients with MM who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.

The approval of pomalidomide was based on a Phase III multi-center, randomized, open-label trial (MM-003) that compared pomalidomide + low-dose dexamethasone to high-dose dexamethasone in adult patients with relapsed refractory multiple myeloma (RRMM) (FDA Pomalyst prescribing information 2013, San Miguel et al, 2013). The trial enrolled patients who had received at least two prior treatment regimens, including lenalidomide and bortezomib, and demonstrated disease progression on or within 60 days of the last therapy. A total of 455 patients were enrolled in the trial: 302 in the pomalidomide + low-dose dexamethasone arm and 153 in the high-dose dexamethasone arm.

The trial demonstrated that treatment with pomalidomide in combination with low-dose dexamethasone was superior to high-dose dexamethasone in patients with primary refractory MM and RRMM. A statistically significant difference in favor of the experimental treatment was shown for the primary analysis of progression free survival (PFS) based on Independent review and adjudication committee assessed data (median 3.6 months versus 1.8 months, with a median follow-up of 4.2 months). The HR was 0.45 (95% CI: 0.35-0.59 $p < 0.001$) (FDA Pomalyst prescribing information 2013). The median PFS was subsequently reported to be 4.0 months versus. 1.9 months at a median of 10 months' follow-up, based on investigator assessed data (San Miguel et al, 2013). The overall response rate (ORR) 23.5% of the pomalidomide + low-dose dexamethasone arm was higher than the 3.9% in the high-dose dexamethasone arm. In addition, median overall survival (OS) was significantly longer with pomalidomide + low-dose dexamethasone than high-dose dexamethasone: HR 0.70 (95% CI: 0.54-0.92 $p = 0.009$) (FDA Pomalyst prescribing information 2013). Additional details regarding pomalidomide can be found in the US prescribing information.

Although pomalidomide-dexamethasone represents an important therapeutic advance for the treatment of patients with RRMM. Nonetheless, patients with lenalidomide and bortezomib (double) refractory disease have a median progression-free survival of only 4.0 months with the combination, thus highlighting the need for further progress.

2.3 Ixazomib Background

Ixazomib, a novel oral, reversible, and specific 20S proteasome inhibitor, has pharmacodynamic properties that may allow for improved proteasome inhibition at the tumoral level and has synergistic activity in combination with IMiDs in preclinical MM models (Chauhan et al, 2011,

Kumar et al, 2014). Clinical studies have demonstrated activity as a single agent in relapsed/refractory MM and in combination with lenalidomide-dexamethasone in newly diagnosed patients. Ixazomib has been approved in the US in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received at least 1 prior therapy (Moreau et al, 2016, FDA Ninlaro Prescribing Information 2015).

The pivotal Phase III Study C16010 was the basis for the approval, involving 722 patients with RRMM (Moreau et al, 2016). The primary endpoint of PFS was met in the ITT population at the primary analysis, with a significant PFS benefit for patients receiving ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone (HR=0.742, p=0.012; median PFS 20.6 vs 14.7 months). The PFS benefit in the ixazomib regimen was supported by improvements versus the placebo regimen in other efficacy data: ORR (78% vs 72%), time to progression (TTP) (median, 21.4 vs 15.7 months), and duration of response (median, 20.5 vs 15.0 months) at the primary analysis. At a median follow-up of approximately 23 months, the median OS had not been reached in either regimen; nevertheless, the 2-year OS rate was 77.5%, which is one of the largest achieved to date in Phase III studies of RRMM. Additional details regarding ixazomib can be found in the US prescribing information.

2.4 Study Rationale

The IMiDs, thalidomide, lenalidomide, and the most potent analog, pomalidomide, are currently Food and Drug Administration (FDA) approved for the treatment of newly-diagnosed and/or relapsed multiple myeloma and have played a central role in the improved survival of myeloma patients over the last decade.

Results from two Phase I studies of single agent ixazomib administered on a weekly or twice weekly schedule for patients with relapsed and relapsed/refractory multiple myeloma have been published (Kumar et al, 2014, Richardson et al, 2014). In the twice-weekly dosing study, escalating doses of ixazomib were administered on days 1, 4, 8 and 11 of a 21-day cycle. Sixty patients had enrolled on the study and 26 to the dose escalation cohorts. The median time from diagnosis was 4.8 years and patients had received a median of 4 prior lines of therapy (range 1 – 28). The MTD was 2.0 mg/m^2. Of 55 patients evaluable for response, 6 had achieved ≥ PRs, 1 had achieved an MR, and 33 patients achieved stable disease (SD), thus yielding a disease control rate (DCR, or ≥ SD rate) of 76%.

The triplet regimen of ixazomib, lenalidomide and dexamethasone has also been studied in NDMM using a twice weekly ixazomib dosing schedule. The recommended Phase 2 dose of ixazomib was 3.0 mg in a 21day cycle with lenalidomide on days 1 – 14, which is a less intense schedule for lenalidomide and dexamethasone. This dose and schedule achieved a high ORR of 95% in NDMM but with a slightly higher rate of dose reductions and discontinuations due to toxicity than once weekly ixazomib.

A Phase I/II study of pomalidomide, ixazomib and dexamethasone has also been completed in patients with lenalidomide and proteasome inhibitor (PI) refractory MM (Voorhees et al, 2015). Out of 22 evaluable patients, the median age was 65 (range 47 - 77) and the median time from diagnosis 5.2 years (range 0.5 – 12.0). The median number of prior therapies was 3 (2 – 10) and 100% had received prior Len, bortezomib and Dex and 77% prior autologous stem cell transplant. Dose limiting toxicity was hematologic and the MTD was established with 4 mg of

pomalidomide and 4 mg of ixazomib. This study was once weekly. Our study will explore twice weekly dosing.

Given the synergy between IMiDs and proteasome inhibitors in pre-clinical models of multiple myeloma; well-established clinical efficacy of existing IMiD/proteasome inhibitor-based combinations in newly-diagnosed and relapsed and relapsed/refractory multiple myeloma; well documented clinical activity of pomalidomide and dexamethasone in patients with lenalidomide- and bortezomib-refractory disease; improved PK and PD characteristics of ixazomib compared with bortezomib; superior pre-clinical anti-tumor efficacy of ixazomib compared to bortezomib; and promising early clinical activity of ixazomib as a single agent and in combination therapy with lenalidomide and dexamethasone, we hypothesize that the addition of ixazomib to pomalidomide and dexamethasone therapy will further improve outcomes for patients with lenalidomide-and proteasome inhibitor-refractory multiple myeloma.

In addition, we believe the twice-weekly schedule of ixazomib will improve patient outcomes and lead to deeper responses in this patient population.

2.5 Correlative Studies Background

DNA and RNA sequencing of tumor cells from the bone marrow

The "clonal evolution" model of cancer emerged amid ongoing advances in technology, especially in recent years during which next generation sequencing has provided ever higher resolution pictures of the genetic changes in cancer cells and heterogeneity in tumors where tumor progression proceeds in a branching rather than in a linear manner, leading to substantial clonal diversity and coexistence of wide genetic heterogeneity[49,50]. The genomic complexity in MM was recently corroborated by massive parallel-sequencing studies displaying the lack of a universal driving mutation[35]. Recent studies have shown intraclonal heterogeneity that occurs at different stages of MM[36,37]. Most recently, exome sequencing confirmed that the heterogeneity observed in MM and how it is likely to be an essential feature of clonal evolution and disease progression[51,52]. Although treatment is very effective in MM patients nowadays; however, new resistant clones may arise in certain patients causing disease relapse and resistance to maintenance treatment. Moreover, the recent advances in RNA sequencing technologies, like single cell RNA(ScRNA) sequencing is now enabling us to better understand the composition and state of the tumor microenvironment including immune cells and stromal cells. ScRNA sequencing coupled with bulk RNA sequencing will allow us to accurately identify expression levels of CD38 and other proteins on both tumor and immune cells at different time points, and how this would affect treatment response and disease course.

Circulating cell-free DNA (cfDNA) and tumor cells (CTCs) are considered emerging and promising approaches to capture the genomic landscape and heterogeneity of the tumor cells in bone marrow, but from blood samples. We published a proof of concept study in Nature Communication on how blood biopsies were good surrogates for the mutational profile in bone marrow. We plan to expand on this by studying serial samples from patients throughout treatment as a tool for detecting minimal residual disease and new mutations that can rise during treatment.

We plan to perform exome sequencing and RNA sequencing studies on tumor cells obtained at the time of screening as well as from subsequent bone marrow biopsy samples to examine clonal heterogeneity, resistant clones at best response and at time of end of study or at disease progression.

The tumor research samples will be collected at the time of scheduled bone marrow biopsies. From these samples, high quality DNA and RNA for both exome sequencing and RNA sequencing of tumor cells will be obtained. In brief, BM aspirates will be obtained after informed consent. The tumor cells will be collected using CD138+ bead selection (over 90% purity based on prior publications)[35,36]. For samples that have a small fraction of plasma cells, we will use flow sorting for CD138/CD38/CD56 and CD19-ve to obtain a pure malignant plasma cell population based on prior published markers of malignant plasma cells[55]. Germline DNA will also be obtained from a buccal swab from all patients.

A- WES of tumor and germline DNA: WES will be performed on all samples pre and post-treatment on the clinical trial to study clonal evolution of malignant cells. DNA will be isolated and libraries will be hybridized to Illumina human whole exome capture kit as previously described. All sequencing studies will be performed at the Genomic Platform of the Broad Institute. Samples will be multiplexed and sequenced on Illumina Novaseq to obtain an average depth of coverage of 175x for tumors and 70x for germlines to have enough sensitivity for mutation detection [41].

B- WGS of tumor and germline DNA: Considering the emerging importance of structural variants like, jumping translocations involving important oncogenes, Chromothripsis, and Chromoplexy in MM, we will use an innovative approach to study translocations in MM by low pass WGS (12x mean coverage). Libraries will be prepared using new HiseqX technology (Illumina®) which offers long range phased (i.e. barcoded) reads which enable much more accurate structural characterization. Libraries will be sequenced on a HiSeq X Ten sequencer available at the Broad Institute. This will be performed on the same samples of WES.

C- Targeted deep sequencing: To be able to analyze small sub-clones, we will design a specific hybrid capture targeted panel of baits to detect the main MM drivers by deep sequencing. This panel includes exons of significantly mutated genes in MM as well as those identified in WES of our samples, baits on the main CNA regions (17p, 1q, 13q) and baits on the IGH, IGL, IGK and *MYC* loci, enabling us to detect somatic mutations, CNAs and translocations. The total size of the bait set is 2Mb. This will be used for samples at the time of best response and in those samples that do not have enough DNA for WES or WGS. Libraries will be prepared using Agilent's SureSelect XT library prep kit and hybridized to a customized targeted bait set. Samples will be multiplexed and sequenced on Illumina Novaseq with the goal of an average depth of coverage of 1500x to have enough sensitivity for mutation detection at low allelic fraction (1%)[41].

D- Computational analysis and expected outcome. All bioinformatics and statistical analyses will be performed with guidance of the biostatistics and bioinformatics Core B. Briefly, BAM files aligned to the hg19 human genome will be produced using Illumina sequencing reads and the Picard pipeline[42]. SNVs will be determined using the MuTect2 algorithm[43], in single mode for targeted sequencing with additional filters for mutation call such as 1000 genome and COSMIC mutations. Indels and translocations will be determined by the algorithms IndelLocator[37] and dRanger, respectively. Focal as well as arm-level copy number variations will be determined based on WES and subsequent application of the GISTIC[44] algorithm. We will use MutSigCV[45] to detect candidate cancer genes using three signals of positive selection: (i) increased mutation burden as

compared to a background model; (ii) clustering of mutations along the gene; and (iii) enrichment of mutations at likely functional sites. The output of MutSigCV consists of a list of the most significantly genomic events across samples. False-discovery rates (q values) ≤ 0.1 will be considered as significantly mutated. All candidate SNVs/indels/CNVs will be reviewed in the IGV[46].

E- RNA sequencing of tumor cells. For RNA Sequencing, poly-A selection and cDNA synthesis will be performed, followed by library preparation, sequencing (76bp or 101bp paired reads), and sample identification with quality control. Details of experimental design are described in[62,63-65]. We will perform library construction using a non-strand specific Illumina TruSeq Protocol and sequence coverage to 100M total reads. Analysis will be performed as described in the preliminary data and in previous studies[63-65].

F- Single-cell sequencing of the tumor microenvironment. Single-cell RNA sequencing (RNA-seq) of the tumor microenvironment can define genotypic and phenotypic states of tumor cells and surrounding microenvironment, and that the microenvironment affected the gene expression program of tumor cells and their resistance to therapy. We will apply 10X genomics in this study to evaluate the tumor microenvironment and assess specific changes in cell type and transcriptional signature of BM niche cells that correlate with tumor progression or resistance to therapy. Given how expensive single cell sequencing is, we expect to only perform this on patients with deep responses or those with complete resistance and lack of responses.

G- cfDNA and circulating tumor cells (CTCs) from the peripheral blood. cfDNA sequencing can be challenging because of the small fragment size of DNA in the peripheral blood (average of 166bp), the low yield of DNA and the usual low allelic fraction of tumor-derived DNA among the cfDNA. Therefore, we developed two different approaches to sequence cfDNA. The first approach applies WES and is performed by the Blood Biopsy Group at the Broad Institute. After high-speed centrifugation of frozen samples to eliminate residual cells from plasma, cfDNA was extracted using the Qiagen circulating nucleic acid kit. As little as 5ng of cfDNA was then subjected to library preparation using the Kapa HyperPlus kit, which enables us to prepare libraries from small DNA fragments and minimal DNA yield. CfDNA libraries were initially qualified for further sequencing using ultra-low-pass whole genome sequencing (ULP-WGS). The ULP-WGS is a low-cost approach developed by the Blood Biopsy Group to nominate samples containing sufficient tumor fraction in cfDNA samples for WES. Large numbers of cfDNA libraries were multiplexed and sequenced to an average of 0.1X genome-wide sequencing coverage.

H- Whole-exome sequencing of cfDNA and CTCs: These studies will be performed at the Blood Biopsy Group at the Broad Institute in collaboration. As described in the preliminary data, cfDNA and CTCs will be subjected to library preparation using the Kapa HyperPlus kit and initially qualified for WES by ULP-WGS. The ULP-WGS will be used to nominate samples containing sufficient fraction of tumor-derived DNA for WES. Qualified matched samples will be hybridized to the Agilent XT v5 enrichment kit, with additional baits on MYC, IGH, IGL and IGK loci. For both cfDNA and CTCs, the coverage goal will be increased to 200x, which enables us to accurately call mutations even with low allelic fraction samples.
All analyses concerning the ULP-WGS will be performed by the bioinformatics team of the Getz

Lab and Blood Biopsy Group at the Broad Institute. WES analyses will be performed through the FireCloud, including MuTect[43], IndelLocator[37], dRanger, GISTIC2.0[44] and ABSOLUTE[18] algorithms to evaluate SNVs, Indels, translocations, CNVs and mutated cancer fractions. We will further study the correlation of mutated cancer fractions between matched cfDNA, CTCs and BM tumor cells for each patient to characterize the mutational spectrum in the 3 compartments; thus identify their overlapping landscape as well as their potential specificities. Based on our preliminary data, we expect to identify in cfDNA and CTCs more than 80% of the somatic mutations present in BM

3. PARTICIPANT SELECTION

Patients with relapsed and relapsed refractory myeloma may be eligible for this trial of they meet all the following entry criteria.

3.1 Inclusion Criteria

3.1.1 Previously diagnosed with MM based on standard IMWG criteria and currently requires treatment.

3.1.2 Patient has given voluntary written informed consent before performance of any study-related procedures not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to their future medical care

3.1.3 Patient has received at least two previous therapies who now demonstrate progression

OR who have received an IMiD plus a proteasome inhibitor as their first line of therapy and has demonstrated disease progression on or within 60 days of completion of the last therapy

3.1.4 Patient has measurable disease defined as at least one of the following according to Standard Diagnostic Criteria (Rajkumar 2014):

- Serum IgG, IgA, or IgM M-protein ≥ 0.5 g/dL, or
- Serum IgD M-protein ≥ 0.05 g/dL, or
- Urine M protein ≥200 mg/24 hours or
- Serum free light chain (FLC) assay: Involved FLC assay ≥10 mg/dL (≥100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65)

3.1.5 Screening Laboratory evaluations within the following parameters

- Absolute neutrophil count (ANC) ≥ 1,000 cells/dL (1.0 x 109/L) (Growth factors cannot be used more recently than 14 days prior to initiation of therapy)
- Platelet count ≥ 75,000 cells/dL (75 x 10^9/L) (without transfusions required during the 14 days prior to initiation of therapy)
- Hemoglobin ≥ 8.0 g/dl (RBC transfusions are permitted)
- Total Bilirubin ≤ 1.5 X upper limit of normal (ULN) (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
- AST (SGOT) and ALT (SGPT) ≤ 3.0 x ULN

- Calculated creatinine clearance ≥ 45 mL/min

3.1.6 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A)

3.1.7 All study participants must be registered into the mandatory POMALYST REMS® program, and be willing and able to comply with the requirements of the POMALYST REMS® program.

3.1.8 Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the POMALYST REMS® program.

3.1.9 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Prior exposure to ixazomib OR is refractory to pomalidomide

- Patients that have previously been treated with ixazomib, or participated in a study with ixazomib,whether treated with the agent or not, are also excluded

3.2.2 Participation in other clinical trials, including those with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial.

- Participants on prior clinical trials with agents that are already FDA approved for use in multiple myeloma need only have a washout appropriate for the drug(s) class as outlined in section 3.2.9
- Investigational agents for indications other than for their disease under study may be approved after review and approval by the Sponsor-Investigator

3.2.3 Diagnosed or treated for another malignancy within 3 years prior to enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low risk prostate cancer after curative therapy.

3.2.4 Known GI disease or is in need of, or has had a previous GI procedure that could interfere with the oral absorption or tolerance of ixazomib or pomalidomide including difficulty swallowing.

3.2.5 Known central nervous system involvement.

3.2.6 Systemic treatment, within 14 days before the first dose of treatment, with strong CYP3A or inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of St. John's wort OR systemic treatment within 14 days of the first dose of treatment with a strong inhibitor of CYP1A2 (ciprofloxacin, fluvoxamine, cimetidine, enoxacin, ethynyl estradiol, mexiletine)

3.2.7 Any medical or psychiatric illness/social situation that in the Investigator's opinion, would impose excessive risk to the patient, would adversely affect his/her participating in this study or would limit compliance with study requirements.

3.2.8 Any active, or uncontrolled cardiovascular conditions, including but not limited to uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, grade 3 thromboembolic event or myocardial infarction within the past 6 months.

3.2.9 The following therapies within the stated time frames prior to initiation of therapy:

- Previous cytotoxic therapies, including cytotoxic investigational agents, for multiple myeloma within 21 days (42 days for nitrosoureas).
- The use of live vaccines within 30 days.
- ImiDs or proteasome inhibitors within 14 days.
- Other investigational therapies and/or monoclonal antibodies within 4 weeks.
- Prior peripheral stem cell transplant within 12 weeks.
- Prior allogeneic stem cell transplantation with active graft-versus-host-disease.

3.2.10 Currently active graft versus host disease of any stage or grade after allogeneic stem cell transplantation

3.2.11 Prior major surgical procedure or radiation therapy within 14 days of initiation of therapy.

- Those who require a limited course of radiation for management of bone pain more than 14 days out from initiation of therapy are not excluded
- If the involved field is small, 7 days will be considered a sufficient interval between radiotherapy and administration of the ixazomib.

3.2.12 Daily requirement for corticosteroids (equivalent to > 10 mg/day prednisone, though >10mg/day is acceptable if physiological levels require, so long as the dose is stable for at least 7 days prior to initiation of therapy. Inhalation corticosteroids are exempt from this criterion.

- Lower amounts of corticosteroids that are not part of a daily requirement within 14 days prior to initiating therapy

3.2.13 Concurrent symptomatic amyloidosis or plasma cell leukemia

3.2.14 POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes)

3.2.15 Infection requiring systemic antibiotic therapy or other serious infection within 14 days of starting therapy.

- Those who are on prophylactic antibiotics only, or on antibiotics and have confirmation of resolution of active infection are eligible.

3.2.16 Known seropositive for active viral infection with human immunodeficiency virus (HIV) hepatitis B (HBV) or hepatitis C viral (HCV). Those who are seropositive because of hepatitis B vaccine are eligible. Patients who are positive for HBV core antibody or HBV surface antigen must have a negative polymerase chain reaction (PCR) result prior to enrollment. Those who are PCR positive will be excluded

3.2.17 Female patients who are lactating or have a positive serum pregnancy test during the screening period

3.2.18 Participants who are receiving any other investigational agents for any indication

3.2.19 History of erythema multiforme or severe hypersensitivity to prior IMiD's® or those who have a known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.

3.2.20 Inability to tolerate thromboprophylaxis

3.2.21 Failure to have fully recovered (≤ Grade 1 according to CTCAE v 5) from the reversible effects of prior chemotherapy

- Peripheral neuropathy must have resolved to ≤ Grade 1 toxicity or peripheral neuropathy grade 2 with no pain to be eligible
- Alopecia of any grade is eligible

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 Registration Process for Other Investigative Sites

All sites should call or email the lead site project manager, or lead research coordinator to verify dose level and or slot availabilities. The required forms will be provided by the lead site institution.

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.
2. Complete the ODQ protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.

To register a participant, the following documents should be completed by the research nurse or applicable personnel and e-mailed to the lead site project manager at DFCI:

- Copy of all screening tests and procedures
- Signed participant consent form
- HIPAA authorization form
- Completed eligibility checklist

To complete the registration process, the designee at DFCI will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled Subject Protocol Registration (SOP #: REGIST-101) and register the participant on the protocol. Following the registration, the designee at DFCI will send an e-mail to the participating site confirming the subject is on study. A participant cannot initiate study treatment until the Participating Institution receives and e-mail confirming patient registration.

Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution. Following registration, participants should begin protocol therapy within 5 days or as soon as feasible. If there are delays in treatment being initiated, the lead site must be notified.

Issues that would cause treatment delays should be discussed with the Sponsor-Investigator. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The lead site research coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

The study drugs will be administered within a 21-day cycle. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Phase I will follow a standard "3 +3" dose escalation design: Starting with the first cohort, 3 to 6 patients will be treated at this and each subsequent dose level.

The MTD is defined as the highest dose level where at most 1 patient (of the 6 treated) develops a DLT, and 2 or more of the 3 to 6 patients developed a DLT at the next higher dose level unless the MTD is identified as dose level 3. Approximately 3-24 patients will be enrolled in Phase I.

The Phase II portion of the study will be a single-arm open-label enrollment with dosing based on the MTD determination in the Phase I portion of the study. All evaluable participants that receive the MTD in Phase I will be counted toward the 37 total patients accrued in the in the Phase II portion. For example, if 6 participants were treated at the MTD, 31 additional participants would be enrolled in the Phase II portion of the study.

5.1 Treatment Regimen

5.1.1 Phase I Treatment Regimen

Table 5-1 Ixazomib, Pomalidomide and Dexamethasone Treatment Regimen

Agent	Dose	Route	Schedule	Cycle Length
Ixazomib	2.3, 3 or 4 mg	Oral	Days 1, 4, 8, 11	21 days
Pomalidomide	2, 3, or 4 mg/day	Oral	Days 1-14	
Dexamethasone	12 mg	Oral	Days* 1, 2, 4, 5, 8, 9, 11, 12	

*The dosing for dexamethasone will be 8 mg on the days listed for patients ≥ 75 years of age.

5.1.2 Phase I Dose Escalation Cohorts

Three dose levels of ixazomib and three dose levels of pomalidomide may be evaluated according to the following dose escalation cohorts in Table 5-2 starting with Cohort 0.

Table 5-2 Dose Escalation Cohorts

Dose level 0 will be the starting point of the trial, with the design to escalate or de-escalate depending on DLTs experienced during the first cycle as described in section 5.7.

Cohort	Ixazomib (mg)	Pomalidomide (mg)
-1	2.3	2
0	3	2
1	3	3
2	3	4
3	4	4

5.2 Phase II Treatment Regimen

Table 5-3 Phase II Treatment Regimen

Phase II Ixazomib/ Pomalidomide/ Dexamethasone Treatment Regimen				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
Ixazomib	4 mg	Oral	Days 1, 4, 8, 11	21 days
Pomalidomide	4 mg	Oral	Days 1-14	
Dexamethasone	12 mg	Oral	Days* 1, 2, 4, 5, 8, 9, 11, 12	

*Those who are <75 at enrollment will receive dexamethasone at 12mg on the days listed, whereas those ≥ 75 at enrollment will receive 8mg- Participants who turn 75 years of age during treatment may receive the lower dose of dexamethasone at the investigator's discretion. Please refer to 6.3 for details on dose reduction and toxicity management of dexamethasone.

NOTE: The participant will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each cycle.

5.3 Phase I Dose Escalation Schema

The first cohort of patients (3 - 6) enrolled in the Phase I portion of the study will receive dose level 0. A full safety evaluation will be conducted when the planned number of safety evaluable patients have completed the first cycle of therapy with DLT assessment. Subsequent patients will be enrolled in the dose level based on the dose escalation schema in Table 5-2. The optimal dose of therapy will be defined as the highest dose that results in ≤ 1/6 patients with DLT during the first cycle of combination therapy. Patients who discontinue treatment for reasons other than study drug related toxicity and/or are considered non-evaluable for DLT assessment may be replaced at the discretion of the Principal Investigator (PI)/DSMC (Section 5.8).

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined in section 5.7.

Table 5-4 Dose Escalation Criteria

Number of Participants with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 participants at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter at least 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended Phase II dose. At least 6 participants must be entered at the recommended Phase II dose.

At least 6 participants must be entered at the MTD. If ≤ 1 of these 6 patients encountered DLT, then this dose level will be taken forward to Phase II. The 6 patients treated in Phase I with the dose taken forward to Phase II will be the first 6 patients of the Phase II component of the study.

Patients who discontinue treatment with any drug in the regimen (excluding dexamethasone) for any reason may continue treatment with the other drug in the regimen at the investigator discretion if in the patients' best interest.

5.4 Safety Rules and Data Safety and Monitoring Trigger for Enrollment Pause

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Sponsor-Investigator and study team. This information can also be found in Appendix E addressed in more detail.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

If a DLT (according to the criteria stated in section 5.8) occurs in 5 or more of the first 15 patients enrolled in the Phase II portion in this protocol, we will pause enrollment and the DSMC will review and monitor toxicity from this study to provide guidance regarding whether to continue enrollment or terminate the study.

At approximately half way through accrual in the Phase II portion of the study (~patient 19 enrolled to Phase II), the Sponsor-Investigator and statistician will review toxicity data for all participants beginning with Cycle 1 through their current or final treatment cycle to further assess the toxicity profile of the combination beyond the Cycle 1 DLT window.

If any deaths occur on study that cannot be directly related to disease progression or extraneous causes, we will pause enrollment and the DSMC will review and monitor toxicity from this study to provide guidance regarding whether to continue enrollment or terminate the study.

5.5 Pre-Treatment Criteria

Patients must meet the hematologic and chemistry inclusion/exclusion criteria prior to initiation of therapy. Refer to Section 10 Study Calendar for all pre-treatment study procedures.

Pre-treatment concomitant medications and procedures that are required and or recommended and those to be avoided are detailed in Section 5.9: General Concomitant medications and Supportive Care Guidelines

All study participants taking pomalidomide must be registered into the mandatory POMALYST REMS™ program, and be willing and able to comply with the requirements of the POMALYST REMS™ program.

5.5.1 Cycle 1 Day 1- Criteria to Treat

Prior to initiation of therapy, patients must continue to meet eligibility criteria including ECOG performance status of ≤ 2 and the Cycle 1 Day 1 laboratory results must also meet the entry criteria as follows:

- ANC ≥ 1,000 cells/ mm^3 (1.0 x 10^9/L) (Growth factors cannot be used within 10 days [14 days for pegfilgrastim] of initiation of therapy)
- Platelet count ≥ 75,000 cells/ mm^3 (75 x 10^9/L)
- Hemoglobin ≥ 8.0 g/dl –
    - RBC transfusions are permitted to achieve this
- Renal function: Estimated glomerular filtration rate by Cockcroft-Gault formula ≥ 45 mL/min
- Negative pregnancy test for females of child bearing potential
- All study participants must be registered into the mandatory POMALYST REMS® program, and be willing and able to comply with the requirements of the POMALYST REMS® program.

5.5.2 Criteria to start subsequent cycles of treatment:

All patients should be evaluated for adverse events prior to continuation of therapy beyond Cycle 1, Day 1 including intra-cycle dosing and initiation of subsequent cycles. Dose modifications and guidelines are outlined in Section 6.

- ANC must be ≥ 1000 cell/mm^3 (1.0 x10^9/L)
- Platelet count must be ≥ 75,000 cell/mm^3 (75 x 10^9/L)
- All non-hematologic toxicities must be ≤ Grade 1 or returned to baseline (except alopecia and fatigue ≤ Grade 2)

If these criteria are not met on the scheduled Day 1, the new cycle should be held and patients should be re-evaluated weekly or more frequently. A new cycle can only be initiated when the criteria are met. If criteria to resume one of the study drugs is not met on day 1 of subsequent cycle, patient may still start a new cycle with approval from PI and resume the other study drugs.

5.6 Agent Administration

5.6.1 Pomalidomide administration

Starting on Cycle 1 Day 1, pomalidomide is to be taken orally from Day 1 to Day 14 of each 21-day cycle.

Instruct patient as follows:

- Pomalidomide may be taken with water and should be swallowed whole. Do not break, chew or open the capsules. Pomalidomide can be taken with or without food preferably

at the same time every day.

- If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for more than 12 hours, it should not be taken, rather the patient should wait for the next scheduled time point.

5.6.2 Ixazomib Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub investigator(s). Patients should be monitored for toxicity, as necessary, and doses of ixazomib should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of ixazomib dose (see Section 6.3). Capsules of ixazomib will also be referred to as study drug. Study drug will be supplied by Millennium as capsules of 2.3, 3, and 4mg ixazomib.

Starting on Cycle 1 Day 1 ixazomib is to be taken orally on Days 1, 4, 8, and 11 of each 21-day cycle.

Instruct the patient as follows:

- Take ixazomib at approximately the same time each day on an empty stomach. **Ixazomib should be taken on an empty stomach (at least 1 hour before or at least 2 hours after food)**. Water is allowed during this time.
- Each capsule should be swallowed with water. Do not to break, chew, or open the capsules. A total of approximately 240 mL (about 1 cup/8 oz) of water should be taken with the capsules.
- Missed doses can be taken as soon as the patient remembers as long as the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. Patients who vomit a dose after ingestion will not receive an additional dose, but should resume dosing at the time of the next scheduled dose.

5.6.3 Dexamethasone Administration

Starting with Cycle 1 Day 1, dexamethasone 12 mg should be administered orally on Days 1, 2, 4, 5, 8, 9, 11, 12, of each 21-day cycle for patients < 75 years of age

For those ≥ 75 years of age, 8mg should be administered orally on days 1, 2, 4, 5, 8, 9, 11, 12, of each 21-day cycle.

If a participant turns 75 years of age during treatment (after enrollment), they may have the option of switching to the 8mg dose at the investigator's discretion.

Please refer to section 6.3 for details on dose reduction of and toxicity management due to dexamethasone.

5.7 Patient Diary

Patients should be instructed to document all oral study drug administration on a patient diary and return unused capsules and packaging for review of compliance at the end of each cycle. Sites are responsible to maintain the diary as source documentation and record administration and patient compliance regarding study drug dosing in the eCRF.

5.8 Definition of Dose-Limiting Toxicity (DLT)

Toxicity will be graded according to the National Cancer Institute – Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE 5.0). The following criteria will apply to each cohort to be evaluated in Phase I, Cycle 1 only. Each cohort will be assessed by the PI/DSMC prior to changes in cohort assignment. Patients need to have received 2 doses at a particular dose level to be evaluable for a DLT. Patients who discontinue therapy during cycle 1 for reasons other the study drug related toxicity and are considered non-evaluable for DLT assessment may be replaced at the discretion of the PI/DSMC

Management and dose modifications associated with the above adverse events are outlined in Section 6.

5.8.1 DLT Criteria

- Grade ≥3 non-hematologic toxicity that cannot be clearly related to disease progression
- Grade 4 thrombocytopenia (platelet count < 25,000 cells/ mm^3) on more than one occasion that cannot be attributed to underlying disease
- Grade 3 thrombocytopenia or Grade ≥ 2 with bleeding
- Grade 4 neutropenia (ANC < 500 cells/mm^3) lasting for >5 days and/or, febrile neutropenia of any duration
- Inability to receive Day 1 dose of Cycle 2 due to a toxicity that is thought to be at least possibly related to the drug combination
- Any Grade 5 event, unless due to progressive disease
- Any event in the Sponsor-Investigator's opinion that warrants additional exploration/expansion of that dose level

5.9 General Concomitant Medication and Supportive Care Guidelines

5.9.1 Required Concomitant Therapy

- Contraceptive measures: Males and females of child bearing potential shall be required to use 2 effective contraceptive methods (or abstinence) according to the POMALYST REMS™ program. The best method should be in compliance with the REMS™ program and be determined in consultation with the Investigator. Because of the increased risk of venous thromboembolism in patients with MM taking pomalidomide and dexamethasone, combined oral contraceptive pills, although not contraindicated, are not recommended.
- Anticoagulation: Pomalidomide increases the risk of thromboembolism. Anti-coagulation prophylaxis is required after an assessment of each patient's underlying risk factors. Unless there is an excess risk of bleeding, all patients should receive prophylactic anti-thrombotic treatment, unless contraindicated. The use of aspirin is an acceptable anti-

thrombotic therapy. If aspirin is contraindicated, patients should receive another form of anti-thrombotic therapy according to hospital guidelines or physician preference.

5.9.2 Recommended Concomitant Therapy

- Antiemetics: Prophylactic treatment with anti-emetic(s) prior to ixazomib administration is recommended. Subsequent anti-emetic drugs including 5-hydroxytryptamine 3 serotonin receptor antagonists drugs against delayed emesis if it occurs should be administered at the discretion of the investigator. Dexamethasone should not be administered as an anti-emetic. Fluid deficit should be corrected before initiation of study drug and during treatment.
- Antidiarrheals: Prophylactic antidiarrheals will not be used in this protocol. However, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals such as loperamide once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).
  - In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.
  - If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalized for intravenous hydration and correction of electrolyte imbalances.
- Antimicrobial (including anti-fungal) or antiviral prophylaxis: It is recommended that participants receive pneumocystis carinii pneumonia (PCP) prophylaxis using appropriate therapy according to institutional guidelines and at the discretion of the investigator.
- Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Prophylaxis with acyclovir (400 mg PO BID) or valacyclovir (500 mgs twice daily) or equivalent antiviral therapy is recommended while on study therapy and for 1 month beyond the end of therapy per institutional guidelines and at the discretion of the site investigator, unless the participant develops a hypersensitivity to the agents.
- Blood products including RBC transfusions (packed RBC or whole blood), single donor or pooled donor platelet transfusions should be utilized as clinically warranted and following institutional policies and recommendations. Platelet transfusions are not permitted to render the patient eligible for trial participation except as noted in Section 3.1.5.
- The use of growth factors is not permitted to render the patient eligible except as noted in Section 3.1.5. Growth factors are not permitted during Cycle 1 of Phase I unless the patient experiences a DLT. Use of Growth factors should follow published guidelines of the Journal of Clinical Oncology, Vol 24, No 18 (June 20), 2006: pp. 2932-2947. erythropoiesis stimulating agents (ESA)s, if indicated permitted (according to the package insert and institutional guidelines or American Society of Clinical Oncology Guidelines (Rizzo, 2010). The use of myeloid growth fact or (granulocyte-colony

stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]) may be given to support subjects who have developed Grade 4 neutropenia or Grade 3 neutropenia with fever and/or infection

- Fluid deficit should be corrected before initiation of therapy and as needed during treatment to avoid dehydration.
- Supportive care may be used per standard institutional practice and as deemed necessary by the investigator. In addition to those mentioned above, supportive care includes, but is not limited to prophylactic analgesics, antipyretics, and nutritional support, H2 blockers, or proton pump inhibitors, bowel regimen oral or parenteral electrolyte supplementation and prophylactic treatment for tumor lysis syndrome when appropriate.
- The use of chronic low-dose steroids (equivalent to ≤ 10 mg/day prednisone) to treat an underlying medical condition that is not a malignancy is permitted during the course of study treatment.
- Bisphosphonates: Bisphosphonates therapy iv or p.o. should be administered if indicated in accordance with institutional guidelines.

5.9.3 Prohibited or Restricted Concomitant Medications

- Other investigative agents must not be used during the study.
- The use of live vaccines is prohibited during the study and for 30 days after last dose of study drug
- Radiation therapy is not permitted while on study for new bone disease indicative of progressive disease, however palliative radiation to pre-existing bone disease (present prior to enrollment) is allowable.
- Concomitant administration of ixazomib with strong CYP3A inducers (such as rifampin, phenytoin, carbamazepine). Extra caution should be exercised when using these medications concomitantly and incidence of any side effects should be carefully monitored.
- Avoid co-administration of strong inhibitors of CYP1A2 in combination with pomalidomide. (e.g. ciprofloxacin, enoxacin, fluvoxamine)

5.10 Criteria for Taking a Participant Off Protocol Therapy

5.10.1 Treatment discontinuation

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. Patients may be withdrawn from the treatment if any of the following occur:

- Disease progression, unless the participant is exhibiting clinical benefit and then, only after discussion with the Sponsor-Investigator
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant

unacceptable for further treatment in the judgment of the treating investigator

- Major violation of the study protocol (i.e., unable to adhere to study schedule) that in the opinion of the investigator, puts the participant at undue risk.
- Confirmed pregnancy.
- Lost to follow-up

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant. Safety monitoring and follow-up assessments should continue as appropriate according to the study schedule, unless the patient has withdrawn consent for study participation. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the PI.

5.11 Duration of Follow Up

Progression free follow up (PFS-FU) and Overall survival follow (OS-FU) up assessments should be completed on all patients unless due to death, lost to follow-up or the patient specifically has withdrawn consent for follow-up. Discontinuation from treatment does not preclude the need to complete follow-up assessments.

5.11.1 PFS-FU

Patients who discontinue therapy for reasons other than disease progression should continue to have monthly disease assessments done for PFS-FU until progression or initiation of subsequent therapy. Schedule the first assessment 4 weeks after the EOT visit. The date and regimen of the first subsequent therapy should be recorded in the eCRF if it occurs during PFS-FU.

5.11.2 OS-FU

Following confirmed disease progression, patients will be followed for OS-FU, follow-up for overall survival status, second primary malignancies and first subsequent therapy will take place every three months +/- 7 days for 24 months. OS-FU may be completed by phone contact. Death information from public sources, (e.g. death registry, obituary listing, etc.), can also be used when it is available and verifiable. The date and regimen of the first subsequent therapy should be recorded in the eCRF if it occurs during OS - FU.

5.12 Criteria for Taking a Participant Off Study

Patients may be withdrawn **from the study** if any of the following occur:

- Withdrawal of consent for study participation.
- Death.
- Lost to follow-up.
- Discontinuation of the study by DFCI

- Completed OS follow up as per protocol

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated throughout this section. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

If multiple adverse events are seen, dose modifications should be based on the worst preceding toxicity. AE should be attributed to a specific drug, if possible, so that the dose modifications can be made accordingly. Reduction of one agent and not the other(s) is appropriate if toxicity is related primarily to one of the agents. For toxicities attributable to pomalidomide and ixazomib, only one of the drugs must be reduced for each incidence of toxicity severe enough to necessitate dose reduction. However, both drugs may be reduced at the investigators discretion. No dose escalations are permitted in any given patient once a dose level has been reduced.

The dose modification guidelines should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. Reductions are based on toxicity noted within a cycle and may contribute to the dose level for the subsequent cycle.

Administration of the study treatment should be discontinued in the event of a treatment emergent AE (TEAE) that persists despite appropriate dose modifications or any other AE that, in the opinion of the investigator, warrants discontinuation.

All delays or changes to study treatment administration must be recorded in the eCRF. The maximum amount of time for which treatment may be held due to drug related toxicity is 28 days from a scheduled Day 1 (Day 57). If study drug is held for more than 28 days due to drug related toxicity, the patient will be removed from the study treatment and enter progression free survival follow-up (PFS-FU). If, however the patient was clearly benefitting from therapy, the patient may be able to continue treatment at the Investigator discretion and in consultation with the PI, after resolution of the AE.

For the start of the new cycle all drugs should be held until the criteria to start a new cycle are met. (See Section 6.6)

Treatment delays for reasons other than toxicity or other co-morbid condition (vacation, elective surgery etc.) may occur for a maximum of 14 days. If there is a need to hold study treatment for longer, a discussion with the Sponsor-Investigator must occur to obtain approval for the participant to remain on study.

6.1 Dose Reduction Steps

Table 6-1 Dose Reduction Steps for Pomalidomide

Starting dose of Pomalidomide	1ST Dose Reduction	2ND Dose Reduction	3RD Dose Reduction
4 mg	3 mg	2 mg	1 mg
3 mg	2 mg	1 mg	discontinue
2 mg	1 mg	discontinue	-----
1 mg	discontinue	-----	-----

6.2 Dose Reduction Steps for Ixazomib

If a dose reduction is made to 2.3 mg weekly, the participant will take Ixazomib on days 1 and 8.

Table 6-2 Dose Reduction Steps of Ixazomib

Starting dose of Ixazomib	1ST Dose Reduction	2ND Dose Reduction	3rd Dose Reduction	4th Dose Reduction
4 mg	3 mg	2.3 mg	2.3 mg Weekly	Discontinue
3 mg	2.3 mg	2.3 mg Weekly	Discontinue	N/A
2.3 mg	2.3 mg Weekly	Discontinue	N/A	N/A

6.3 Dose Reduction Steps for Dexamethasone

Table 6-3 Dose Reduction Steps for Dexamethasone

Dose levels reflect dosing to be given per the schedule in section 5.2 Treatment Plan- That includes dosing on the day of and the day after each ixazomib dose unless otherwise noted.

For Those <75

Starting Dose	Dose reduction Step - 1	Dose reduction Step - 2	Dose reduction Step - 3
12mg	8mg	4 mg	discontinue

For Those ≥75

Starting Dose	Dose reduction Step - 1	Dose reduction Step - 2	Dose reduction Step - 3
8mg	4 mg	4mg (day of ixazomib only)	discontinue

*Alternative dexamethasone dosing schedule may be administered at the investigator's discretion after discussion with the Sponsor-Investigator.

6.4 Dose Modification Guidelines

Each Adverse Event should be attributed to a specific study drug if possible so that dose modifications can be made accordingly. Further clarification can be obtained in consultation with the study PI. If multiple toxicities are noted, the dose adjustment should be made according to the most severe toxicity guidelines.

Table 6-4 Dose Modifications during a Cycle of Therapy.

<table>
<tr><th colspan="3">Dose Modification
During a cycle of therapy</th></tr>
<tr><th>Toxicity</th><th>Pomalidomide</th><th>Ixazomib</th></tr>
<tr><td rowspan="3">Neutropenia
ANC < 0.5 x 10^9/l or Febrile neutropenia (fever ≥38.5°C and ANC <1 x 10^9/l)</td><td>Hold, follow CBC weekly if ANC return to ≥1 x 10^9/l (and fever resolves) prior to day 21 resume pomalidomide with one level dose reduction* and complete the cycle.</td><td>Hold, follow CBC weekly when ANC return to ≥1 x 10^9/l (and fever resolves) prior to day 21 Resume ixazomib with one level dose reduction*</td></tr>
<tr><td colspan="2">* First occurrence, reduce pomalidomide subsequent occurrence reduce Ixazomib. Alternate drug dose reductions if feasible to avoid excessive reduction of any one or both drugs.</td></tr>
<tr><td colspan="2">*If neutropenia is the only toxicity requiring dose reduction, use of G-CSF may be considered in conjunction with dose reduction at the investigator's discretion.</td></tr>
<tr><td rowspan="2">Thrombocytopenia
Platelet count <25 x 10^9/l</td><td>Hold pomalidomide and anticoagulation and follow CBC per standard of care and at minimum, weekly. If platelet count return to ≥50 x 10^9/l prior to day 21, resume pomalidomide with one level dose reduction*and complete the cycle.</td><td>Ixazomib dose should be withheld. Complete blood count (CBC) should be repeated at minimum, weekly – It is recommended that CBC re- check occur every other day until platelet counts have exceeded 30 x10^9/l on at least 2 occasions.
Upon recovery, ixazomib may be reinitiated with 1 dose level reduction. If platelet count return to ≥50 x 10^9/l prior to day 21, resume ixazomib with one level dose reduction* of any one or both drugs.</td></tr>
<tr><td colspan="2">*First occurrence, reduce pomalidomide subsequent occurrence reduce Ixazomib.</td></tr>
</table>

Dose Modification **During a cycle of therapy**			
Toxicity		**Pomalidomide**	**Ixazomib**
		Alternate drug dose reductions if feasible to avoid excessive reduction of any one or both drugs.	
		If thrombocytopenia is the only toxicity requiring dose reduction, use of platelet transfusions may be considered in conjunction with a dose reduction at the investigator's discretion.	
Non-Hematologic Toxicity **Assess attribution if feasible and reduce appropriate drug** **Hold ixazomib or pomalidomide or both depending on the attribution to either or both drugs, until resolution to Grade ≤1 or baseline**			
Toxicity	**Grade**	**Pomalidomide**	**Ixazomib**
Peripheral Neuropathy	New onset grade 1 with pain or Grade 2	No change	Hold study drug until resolution to Grade ≤ 1 or baseline
	Grade 2 with pain or Grade 3	No dose reduction required but may be considered following reduction of ixazomib.	Hold study drug until resolution to Grade ≤ 1 or baseline Reduce study drug to next lower dose upon recovery
	Grade 4	Discontinue pomalidomide	Discontinue ixazomib
Skin Rash	Rash, maculopapular, ≥Grade 2 or 3	*Hold pomalidomide dose; follow weekly If the toxicity resolves to ≤Grade 1 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle through Day 21	*No dose reduction required but may be considered following reduction of pomalidomide
	Any rash Grade 4	Discontinue therapy	Discontinue therapy
		*Both pomalidomide and ixazomib may cause rash attempt to identify causative agent if possible and reduce appropriate drug (s). Alternative approached from above may be considered.	
Thromboembolic event ≥ Grade 3		Hold Pomalidomide dose and start anticoagulation Restart at investigator's discretion (maintain dose level)	No change in dose required
Hyperthyroidism or Hypothyroidism ≥ Grade 2		Hold pomalidomide for remainder of cycle, evaluate etiology, and initiate	No change in dose required

Dose Modification During a cycle of therapy		
Toxicity	**Pomalidomide**	**Ixazomib**
	appropriate therapy. Maintain dose level when dosing restarted at next cycle at discretion of treating physician. See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level	
Any ≥ Grade 3 drug related adverse event. Assess attribution to each dug if feasible so dose modifications can be made accordingly.	Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle*.	Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle*.
	*Reduction of one agent and not the other(s) is appropriate if toxicity is related primarily to one of the agents. For toxicities attributable to ixazomib and pomalidomide, only one of the drugs is *required* to be reduced for each incidence of toxicity severe enough to necessitate dose reduction.	
Grade 4 drug related non-hematologic toxicity	Discontinue therapy	Discontinue therapy

- Though these guidelines should generally be followed, an alternative delay/hold/reduction plan may be implemented with the approval of the Sponsor-Investigator.

6.5 Dose Modifications of Dexamethasone

Multiple dose reductions are permitted. If a patient is unable to tolerate dexamethasone due to dexamethasone related toxicity, dexamethasone may be further reduced or discontinued following consultation with the medical monitor. However, the patient may continue on treatment with pomalidomide and ixazomib, at the investigators discretion.

Table 6-5 Dexamethasone Dose Reduction Guidelines

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenalulcer, gastritis Grade 1–2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.

Body System	Symptom	Recommended Action
Gastrointestinal	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone and do not resume
Cardiovascular	Edema ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurology	Confusion or Mood alteration ≥ Grade 2 (interfering with function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart with one dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness ≥ Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease dexamethasone dose by one dose level. If weakness persists despite above measures, decrease dose by one additional dose level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia ≥ Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory.

6.6 Initiation of a New Cycle of Therapy

Patients should be assessed at the beginning of each cycle according to the tests and evaluations outlined on Day 1 of each cycle in Table 10-1 Schedule of Events. To begin a new cycle of treatment the following criteria must be met:

- ANC must be ≥ 1000 cell/mm^3 (1.0 x10^9/L)
- Platelet count must be ≥ 75,000 cell/mm^3 (75.0 x 10^9/L)
- All non-hematologic toxicities must be ≤ Grade 1 or returned to baseline (except alopecia and fatigue ≤ Grade 2)

If these criteria are not met on the scheduled Day 1, the new cycle should be held and patients should be re-evaluated weekly. A new cycle can only be initiated when the criteria are met.

6.7 Guidelines for Restarting Pomalidomide or Ixazomib

If there are dose modifications or delays of pomalidomide or ixazomib in the previous cycle, these guidelines should be followed for the initiation of a new cycle.

- If there are no other toxicities that require a dose reduction of pomalidomide/ixazomib and thrombocytopenia and/or neutropenia can be managed by the use of platelet transfusions or G-CSF, no dose reductions are required but may be made at the investigator's discretion.
- If pomalidomide/ixazomib was held during the previous cycle and restarted at a reduced dose level within the cycle, without interruption for the remainder of the cycle, then this reduced dose level will be initiated on Day 1 of the new cycle. Note, if treatment is held during the cycle and then resumed, the treatment days remain unchanged.
- If pomalidomide/ixazomib dosing was omitted for the remainder of the previous cycle or if a new cycle is delayed due to pomalidomide/ixazomib-related toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with one-level dose reduction.

The maximum amount of time for which the cycle may be held due to drug related toxicity is 28 days from a scheduled Day 1 (Day 57). If study drug is held for more than 28 days due to drug related toxicity the patient will be removed from the study treatment and enter progression free survival follow-up (PFS-UP). If, however the patient was clearly benefiting from therapy, the patient may be able to continue treatment at the Investigator discretion and in consultation with the medical monitor, after resolution of the AE.

No dose re-escalation is permitted once a dose reduction has been implemented.

6.8 Treatment Duration

Patients will receive treatment until there is documented disease progression, according to the IMWG-URC guidelines (Rajkumar et al. 2011, Section 11), to be confirmed on two consecutive assessments, unacceptable toxicity or the patient/treating physician determines it is not in the patient's best interest to continue.

Participants may remain on treatment if experiencing clinical benefit after discussion and subsequent approval with the Sponsor-Investigator.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Adverse Events List(s)

7.1.1 Adverse Event List for Ixazomib

Refer to the Package Labeling for full details on the side effects of ixazomib. The following adverse reactions are described in detail in the Package Labeling for ixazomib.

- Thrombocytopenia
- Gastrointestinal Toxicities
- Peripheral Neuropathy
- Peripheral Edema

- Cutaneous Reactions
- Hepatotoxicity

7.1.2 Adverse Event List for Pomalidomide

Refer to the Package Labeling for full details on the side effects of pomalidomide. The following adverse reactions are described in detail in the Package Labeling for pomalidomide:

- Fetal Risk
- Venous Thromboembolism
- Hematologic Toxicity
- Hypersensitivity Reactions
- Dizziness and Confusional State
- Neuropathy
- Risk of Second Primary Malignancies

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5. A copy of the CTCAE version 5 can be downloaded from the internet:

  https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.
- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Investigators **must** report to the Sponsor-Investigator any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.2 External Site Serious Adverse Event Reporting Obligations

For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution must abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and all grade 5 (death) regardless of study phase or attribution.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Sponsor-Investigator within the timeframes detailed in the table below.

7.3.3 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy after notifying the lead site of the event.

7.3.4 In the event of an unanticipated problem or life-threatening complications, treating investigators must immediately notify the Sponsor-Investigator.

7.3.5 Adverse Event Reporting Guidelines

The following adverse events must be reported to the DFCI IRB according to the expedited reporting guidelines:

- **CTCAE Grade 2 and Grade 3 Events** – that are *Unexpected* and there is a *Reasonable Possibility* that the *Adverse Event* is related to the study Intervention.

  CTCAE Grade 4 Events – Report all events that are Unexpected. Events that are Expected and listed within the protocol and/or current consent form do not need to be reported to the DFCI IRB.

  Please note, an event that presents at a higher severity than what is currently listed within the protocol and/or current consent as expected would be considered unexpected and reportable.

- **ALL CTCAE Grade 5 Events.**

  The Sponsor-Investigator/lead site study team will submit SAE reports from outside institutions to the DFCI OHRS on behalf of the reporting institution according to DFCI IRB policies and procedures in reporting adverse events after review for clarity and completion.

SAEs must be reported on each participant up to 30 days after the last dose of study drug has been administered.

7.4 Expedited Reporting to the Food and Drug Administration (FDA)

The Sponsor-Investigator will be responsible for all communications with the FDA. The Sponsor-Investigator will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Sponsor-Investigator on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

Adverse events thought at least possibly related to the study treatment should be followed until resolution, stabilization, or until the participant is removed from study and can no longer be feasibly followed.

7.6 Definitions

7.6.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

7.6.2 Adverse Drug Reaction

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. This includes adverse reactions which arise from: use of a medicinal product within the terms of the marketing authorization; use outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors; and occupational exposure*.

* This corresponds to the exposure to a medicinal product for human use as a result of one's occupation, such as nurses who may handle products routinely in their occupational setting.

7.6.3 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache).

This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

7.7 Procedures for Reporting Serious Adverse Events to Takeda/Millennium

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common

underlying pathology should be noted as one comprehensive event. For serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from the first dose of study drug through 30 days after administration of the last dose of ixazomib. Any SAE that occurs at any time after completion of ixazomib treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium Pharmacovigilance (or designee). In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Millennium Pharmacovigilance (or designee).

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Since this is an investigator-initiated study, the principal investigator, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported in English to Millennium Pharmacovigilance (or designee):

> **Fatal and Life Threatening SAEs** within 24 hours of the sponsor-investigator's observation or awareness of the event
>
> **All other serious (non-fatal/non-life threatening) events** within 4 calendar days of the sponsor-investigator's observation or awareness of the event

The SAE report must include at minimum:

- **Event term(s)**
- **Serious criteria**
- **Intensity of the event(s):** Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- **Causality of the event(s):** Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Millennium.

Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version used at your institution, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

The lead site will submit SAE reports to Takeda/Millennium on behalf of the reporting site to ensure proper completion, tracking, and adherence to submission timelines.

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

SAE and Pregnancy Reporting Contact Information
US & Canada
Toll-Free Fax Number: [redacted]

Suggested Reporting Form:

- SAE Report Form (provided by Millennium/Takeda)
- US FDA MedWatch 3500A **(preferred)**
- Any other form deemed appropriate by the sponsor-investigator

7.8 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study or within 90 days after the last dose, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 7.7). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation, or within 90 days of discontinuing treatment in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:

- Pregnancy Report Form (a template will be provided to participating institutions by the lead site)

8. PHARMACEUTICAL INFORMATION

8.1 Ixazomib

8.1.1 Description

Ixazomib citrate, a prodrug, rapidly hydrolyzes under physiological conditions to its biologically active form, ixazomib. The chemical name of ixazomib citrate is 1,3,2-dioxaborolane-4,4-diacetic acid, 2-[(1R)-1-[[2-[(2,5 dichlorobenzoyl)amino]acetyl]amino]-3-methylbutyl]-5-oxo- and the structural formula is: The molecular formula for ixazomib citrate is C20H23BCl2N2O9 and its molecular weight is 517.12. Ixazomib citrate has one chiral center and is the R-stereoisomer. The solubility of ixazomib citrate in 0.1N HCl (pH 1.2) at 37°C is 0.61 mg/mL (reported as ixazomib). The solubility increases as the pH increases.

8.1.2 Form

The ixazomib capsule formulation consists of the drug substance (ixazomib citrate), microcrystalline cellulose, talc, and magnesium stearate. Ixazomib is available in the following capsule strengths:

- 4 mg: Light orange gelatin capsule imprinted with “Takeda” on the cap and “4.0 mg” on the body in black ink. NINLARO 4 mg capsules contain 4 mg of ixazomib equivalent to 5.7 mg of ixazomib citrate.
- 3 mg: Light grey gelatin capsule imprinted with “Takeda” on the cap and “3.0 mg” on the body in black ink. NINLARO 3 mg capsules contain 3 mg of ixazomib equivalent to 4.3 mg of ixazomib citrate.
- 2.3 mg: Light pink gelatin capsule imprinted with “Takeda” on the cap and “2.3 mg” on the body in black ink. NINLARO 2.3 mg capsules contain 2.3 mg of ixazomib equivalent to 3.3 mg of ixazomib citrate.

8.1.3 Storage and Stability

On receipt at the investigative site, ixazomib should remain in the blister and carton provided until use or dispensation. Store at room temperature, do not store above 86°F (30°C). Do not freeze Ixazomib. Store capsules in original packaging until immediately prior to use. Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication at room temperature, below 86°F (30°C), for the duration of each cycle . Patients should be instructed to return their empty blister packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature at the site should be reported to Takeda as an excursion and should be dealt with on a case-by-case basis.

8.1.4 Drug-Drug Interaction Information

Avoid concomitant administration of ixazomib with strong CYP3A inducers (such as rifampin, phenytoin, carbamazepine, and St. John's Wort).

8.1.5 Handling

Ixazomib is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised during handling. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during clean-up and during return of broken capsules and powder to minimize skin contact. The area should be ventilated and the site washed with soap and water after material pick up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations. In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Patients are to be instructed on proper storage, accountability, and administration of ixazomib, including that study drug is to be taken as intact capsules. Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.6 Availability

Ixazomib capsules will be supplied by the sponsor as single capsules at 3 different dose strengths, containing 4.0, 3.0, and 2.3 mg of ixazomib. Ixazomib will be provided by Millennium.

8.1.7 Preparation

Ixazomib is dispensed in blisters in a child-resistant carton. For the 2.3, 3.0, 4.0 mg capsule strengths, there are 3 capsules in each wallet/carton. Ixazomib is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised during handling.

8.1.8 Administration

Starting on Cycle 1 Day 1xazomib is to be taken orally on Days 1, 4, 8, and 11 of each 21-day cycle.

Instruct the patient as follows:

- Take ixazomib at approximately the same time each day on an empty stomach. Ixazomib should be taken at least 1 hour before or at least 2 hours after food. Water is allowed during this time.
- Each capsule should be swallowed separately with water. Do not to break, chew, or open the capsules. A total of approximately 240 mL (about 1 cup/8 oz) of water should be taken with the capsules.
- Missed doses can be taken as soon as the patient remembers as long as the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a

missed dose. Patients who vomit a dose after ingestion will not receive an additional dose, but should resume dosing at the time of the next scheduled dose.

It is recommended that dexamethasone be taken at least 2 hours before the ixazomib dose on the ixazomib dosing days

8.1.9 Ordering

Ixazomib will be provided free of charge by Takeda. Takeda Medical Affairs internal study number is X16117. A study specific drug order form will be provided to each participating institution by the lead site once all required regulatory documents and procedures are in place.

8.1.10 Accountability

All study drug must be stored by the sites in a secure facility with limited access. The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment supplied to the site in a drug accountability log. At study close-out, and as appropriate during the course of the study, all unused study drug packaging and any associated supplies should be discarded according to the site drug destruction policy.

Patients should be instructed to document all oral study drug administration on a patient diary and return unused capsules and packaging for review of compliance at the end of each cycle. Sites are responsible to maintain the diary as source documentation and record administration and patient compliance regarding study drug dosing in the eCRF.

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

8.1.11 Destruction

Patients should be instructed to return their empty or partially used cartons to the investigative site, rather than discarding them at home. Unused ixazomib may be destroyed at the site according to the drug destruction policy.

8.1.12 Product Complaints- Ixazomib

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Millennium (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

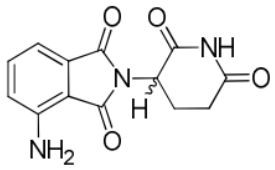
For Product Complaints
Phone: 1-844-617-6468 **Hours: Mon-Fri, 9a.m-7 p.m. ET**
Email: [redacted]
Fax: [redacted]

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance

8.2 Pomalidomide

8.2.1 Description

POMALYST is an immunomodulatory antineoplastic agent. The chemical name is (RS)-4-Amino-2-(2,6-dioxopiperidin-3-yl)-isoindoline-1,3-dione and it has the following chemical structure:



The empirical formula for pomalidomide is C13H11N3O4 and the gram molecular weight is 273.24. Pomalidomide is a yellow solid powder. It has limited to low solubility into organic solvents and it has low solubility in all pH solutions (about 0.01 mg/mL). Pomalidomide has a chiral carbon atom which exists as a racemic mixture of the R(+) and S(-) enantiomers. POMALYST is available in 1-mg, 2-mg, 3-mg, and 4-mg capsules for oral administration. Each capsule contains pomalidomide as the active ingredient and the following inactive ingredients: mannitol, pregelatinized starch, and sodium stearyl fumarate. The 1-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, white ink, and black ink. The 2-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, FD&C red 3, and white ink. The 3-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, and white ink. The 4-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 1, FD&C blue 2, and white ink.

8.2.2 Form

Pomalidomide is available in capsules of 1 mg, 2 mg, 3 mg and 4 mg for oral administration.

- 1 mg: Dark blue opaque cap and yellow opaque body, imprinted “POML” on the cap in white ink and “1 mg” on the body in black ink
- 2 mg: Dark blue opaque cap and orange opaque body, imprinted “POML” on the cap and “2 mg” on the body in white ink
- 3 mg: Dark blue opaque cap and green opaque body, imprinted “POML” on the cap and “3 mg” on the body in white ink
- 4 mg: Dark blue opaque cap and blue opaque body, imprinted “POML” on the cap and “4 mg” on the body in white ink

8.2.3 Storage and stability

Store at 20°C-25°C (68°F-77°F) away from direct sunlight and protected from excessive heat and cold. Excursions permitted to 15°C-30°C (59°F-86°F).

8.2.4 Drug-Drug Interaction Information

Strong CYP1A2 Inhibitors: Avoid concomitant use of strong CYP1A2 inhibitors.

8.2.5 Handling

Female caregivers of childbearing potential should not handle or administer pomalidomide unless they are wearing gloves. Care should be exercised in handling of pomalidomide. pomalidomide capsules should not be opened or crushed.

If powder from pomalidomide contacts the skin, wash the skin immediately and thoroughly with soap and water. If pomalidomide contacts the mucous membranes, flush thoroughly with water.

Follow local and federal procedures for proper handling and disposal of anticancer drugs.

8.2.6 Availability

Pomalidomide is being supplied via the POMALYST REMS® Program and will be shipped by Biologics LLC. Biologics is open Monday through Friday from 9:00am EST to 6:00pm EST. Biologics ships via FedEx Priority Overnight for next business day delivery according to the REMS® guidelines.

Pomalidomide will procured through the participant's insurance, via commercial supply.

Orders processed on Friday will be received on Monday.
The Patient, the Prescriber and the Pharmacist must be enrolled in the REMS® program: www.CelgeneRiskManagement.com.

8.2.7 POMALYST REMS® Program

Pomalidomide will be provided in accordance with the Celgene Corporation's POMALYST REMS® program. Per the standard POMALYST REMS® program requirements, all physicians who prescribe pomalidomide for patients enrolled into this trial, and all patients enrolled into this trial, must be registered in and must comply with all requirements of the POMALYST REMS® program as required by the US FDA. Patients will receive enough pomalidomide for 28 days. Study drug is to be handed back to the patient to return per POMALYST REMS® policy.

8.2.8 Preparation

Pomalidomide is an oral drug, and does not require specific preparation details.

8.2.9 Administration

- Pomalidomide may be taken with water and should be swallowed whole. Do not break, chew or open the capsules. Pomalidomide can be taken with or without food preferably at the same time every day.
- If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for more than12 hours, it should not be taken, rather the patient

should wait for the next scheduled time point.

- If a dose of Pomalidomide is vomited, it should not be retaken.

8.2.10 Ordering

Pomalidomide will be ordered in accordance with the Pomalyst REMS program through Biologics LLC. Per the standard POMALYST REMS™ program requirements, all physicians who prescribe pomalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the POMALYST REMS™ program

8.2.11 Accountability

Pomalidomide is commercially available therefore, no drug accountability records are required. The investigator is responsible for monitoring patient compliance by monitoring the patient diary.

8.3 Dexamethasone

8.3.1 Description

Dexamethasone is a synthetic adrenocortical steroid. Corticosteroids are naturally occurring chemicals produced by the adrenal glands located above the kidneys. Corticosteroids affect the function of many cells within the body and suppress the immune system. Corticosteroids also block inflammation and are used in a wide variety of inflammatory diseases affecting many organs.

The molecular weight for dexamethasone is 392.47. It is designated chemically as 9- fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione. Dexamethasone is stable in air and almost insoluble in water.

8.3.2 Form

Dexamethasone is a white to practically white, odorless, crystalline powder. It is available in 2 or 4 mg tablets (commercially) for oral administration. Each tablet contains dexamethasone as the active ingredient, and the following inactive ingredients: calcium phosphate, lactose, magnesium stearate, and starch. The tablet shell may contain the following: D&C Yellow 10, FD&C Yellow 6, and/or FD&C Blue 1.

8.3.3 Storage and Stability

Dexamethasone should be stored at controlled room temperature, 68-77◦F (20-25◦C) and not frozen, and according to label requirements.

8.3.4 Handling

Dexamethasone should be handled by trained pharmacy staff. The use of gloves and other appropriate protective clothing is recommended as necessary.

8.3.5 Availability

Dexamethasone supply will be obtained through commercial supply and billed to study participants' insurance.

8.3.6 Preparation

Dexamethasone is an oral drug, and does not require specific preparation details.

8.3.7 Administration

Participants will receive 12mg of dexamethasone on, Days 1, 2, 4, 5, 8, 9, 11, 12. If the participant is over 75 years of age at enrollment, they will receive 8mg of dexamethasone on Days 1, 2, 4, 5, 8, 9, 11, 12. Alternative dosing scheduled, and dose reductions are allowed per section Table 6_3

- Keep capsules in the bottle(s) provided and do not transfer them to any other container. Store at room temperature.
- Dexamethasone should be taken whole, by mouth on the day of and the day after the ixazomib dose. Tablets must be swallowed whole and taken with food at the same time each day. It is recommended that dexamethasone be taken at least 2 hours before the ixazomib dose on the ixazomib dosing days
- If a participant vomits dexamethasone, they should not take another dose to make up it up.
- If a participant misses a dose of dexamethasone, they should take it as soon as they remember on the same day. If a participant misses taking dexamethasone for the entire day, they should take their regular dose the next scheduled day.

8.3.8 Ordering

The investigator or designee will order drug supply from commercial supply.

8.3.9 Accountability

As drug is from commercial supply, no drug accountability records are required for dexamethasone for this study.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

This trial will provide saliva, blood and bone marrow aspirate samples of relapsed and or refractory myeloma patients treated with ixazomib, pomalidomide and dexamethasone to further characterize the MM genome and immune cell function and define molecular events driving progression of MM.

We will attempt to obtain samples on all patients at the time points specified in the table in this section. It is anticipated that approximately 90% of samples collected will be adequate for studies proposed. Samples will be kept until exhausted.

The tumor cells will be collected as described below. From these samples, high quality DNA (for tumor cells) and RNA (for tumor cells and immune cells) for both exome sequencing and RNA sequencing will be obtained. Germline DNA will be also obtained from a buccal swab (saliva) from all patients at any time point of the study

Proteomic analysis will be used to identify and characterize proteins involved in the pathogenesis of multiple myeloma. We also aim to characterize somatic aberrations present in cell free DNA (cfDNA) and circulating tumor cells (CTCs) as biomarkers of response/resistance. We wish to further define markers of the permissive bone marrow microenvironment that characterize risks of progression in MM. Lastly, we expect to further define the immune-oncogenomic landscape of MM in response to therapy.

9.1 Exome Sequencing of tumor cells

Whole-exome capture libraries will be constructed from 100ng of tumor and normal DNA followed by shearing, end repair, phosphorylation and ligation to barcoded sequencing adapters. The DNA will be size-selected to exonic hybrid capture using SureSelect v2 Exome bait (Agilent, CA). Samples will be multiplexed and sequenced on Illumina HiSeq flowcells with the goal of an average depth of coverage of 100x. The resulting data will be analyzed with the current Illumina pipeline, which generates data files (BAM files). The details of the current analysis pipeline are published elsewhere. Briefly, somatic single nucleotide variants are determined using the MuTect algorithm. Indels and translocations are determined by the algorithms IndelLocator and dRanger, respectively. The MutSig algorithm identifies genes in which the observed mutations are inconsistent with what would be expected at random[58]. To accurately assess the significance of mutations, MutSig takes into account several covariates, which influence the background mutation model. These include the expression level of genes (for which published gene expression data of MM samples can be used), and other gene characteristics observed empirically to co-vary with mutation rate: local relative replication time, and open vs. closed chromatin status. Focal as well as arm-level copy number variations will be determined based on whole exome sequencing and subsequent application of the GISTIC algorithm[61].

For RNA Sequencing, poly-A selection and cDNA synthesis will be performed, followed by library preparation, sequencing (76bp or 101bp paired reads), and sample identification with quality control. Details of experimental design are described in. We will perform library

construction using a non-strand specific Illumina TruSeq Protocol and sequence coverage to 100M total reads. Analysis will be performed as described in the preliminary data and in previous studies.

The DNA and or RNA library will be prepared at the Ghobrial Lab, and then sequencing will be done at the following external lab:
Broad Institute Genomics Services
320 Charles Street
Cambridge, MA 02141

Sequencing data will then be provided back to Ghobrial lab in the form of BAM file. The samples that are sent for analysis are exhausted during the process, and thus not able to be returned.

9.2 Immune cell characterization in peripheral blood and bone marrow

Peripheral blood and bone marrow derived mononuclear cells will undergo immunologic assessments to assess the impact of therapy on general measures of cellular immunity. We will determine the number of immune cells (T-regs, CD4 effector T cells, CD8 T-regs, CD8 effector T cells, NK, NKT, B cells, MSCs, M1 and M2 macrophages, Dendritic cells and MDSCs at screening and during therapy. These cells will be quantified using CyTOF at DFCI. Each cell type will be defined by unique combinations of antibodies based on previous publications[66,67]. Regulatory T cells will be defined as CD4/CD25/FOXP3+ cells. Levels of naïve, effector and central memory cells will be quantified as CD45RA, CD45RO/CD62L-/CD27- and CD45RO/CD62L+/CD27+ cells, respectively. NK cells will be quantified by expression of CD56+ subsets. MDSCs will be quantified by CD33+/lineage-/DR- and CD11b/lineage-/DR- cells. CD38 expression in these immune cell subpopulations will be examined, and the CD38+ groups will be evaluated for response to daratumumab. We will also examine the percent expression of checkpoint regulators and how they are modulated with therapy. These checkpoint regulators include PD-1, Lag-3, Tim-3 and CTLA-4

Mass cytometry uses a time-of-flight ICP-MS instrument (CyTOF system, Fluidigm) that can detect dozens of markers simultaneously at a high mass-spectrum acquisition frequency on the timescale of high-frequency laser ablation. We will use the DFCI core facilities to develop CyTOF panels. The LMA CyTOF Core currently houses two mass cytometers operating on CyTOF2 platforms. Core staff members are available to support researchers in various aspects of mass cytometry technology procedure from initial consultation to data interpretation. Expert technical assistance regarding experimental design, acquisition, interpretation, troubleshooting, primary analysis and advanced data analysis are provided. The in-house antibody resource at the Brigham and Women's Hospital offers comprehensive mouse and human CyTOF antibody catalogues. Fluidigm Metal Conjugated Antibodies are currently representing over 300 pre-conjugated antibodies that are available for human and mouse from Fluidigm, Inc. Analysis pipelines include Cytobank, FlowJo and FCS Express that can be used to visualize Mass Cytometry data with traditional bivariates, histogram overlays, and heat maps. Cytobank (cloud based cytometry data analysis) can be used for traditional data visualization as well as visualization of high dimensionality data by SPADE and ViSNE. Other high dimensionality visualizations, such as ACCENSE, Wanderlust, and PCA are available for visualization by R and Matlab.

All human samples will be processed from viably frozen or fresh bone marrow aspirates or peripheral blood cells. Bone marrow aspirates/PB cells will be lysed and CD138+ve cells fractions will be separated by bead selection. The CD138-negative populations will be thawed, washed, fixed with fixation buffer (Fluidgm Sciences Inc.) and barcoded using the Cell-ID™ 20-Plex Pd *Barcoding* Kit enabling *barcoding* of up to 20 samples. After barcoding, cells will be incubated with the human surface marker antibodies as a single multiplexed sample. Next, cells will be fixed, permeabilized and incubated with antibodies against intracellular proteins. After a subsequent wash, cells will be resuspended at the concentration of $1x10^6$ cells/mL and acquired on a on a CyTOF Helios mass cytometer (Fluidgm Sciences Inc.). Downstream analysis of the individual component samples will be performed after running the debarcoding application.

Immunomodulatory drugs function through CRL4CRBN mediated degradation of multiple factors including the core lymphoid transcription factors Ikaros and Aiolos. Levels of both the E3 ubiquitin ligase substrate adaptor, CRBN, and the substrate proteins have been proposed to modulate sensitivity to IMiDs. In order to better understand the determinants of resistance and response to therapy we aim to study the expression of CRBN, IKZF1, IKZF3 and other substrates at both the RNA and protein level using RNA sequencing and targeted proteomics. Further secondary transcriptional effects resulting from the depletion of these transcription factors will be explored provided sufficient sample collection and resources, including research time and adequate funding.

9.3 Minimal Residual Disease (MRD)

Bone marrow and blood samples will be collected per the collection time described in the table of sample collection below. Depending on sample funding and availability, additional testing may also be performed at Adaptive Biotechnologies in Seattle, WA for MRD testing by their NGS platform known as ClonoSEQ. Peripheral blood and/or bone marrow samples will be collected, processed and stored at Dana-Farber Cancer Institute for possible future analysis at Adaptive. If funding allows, the samples will be sent on those who achieve a CR or are suspected of achieving a CR during treatment or during progression free follow-up. The samples will be prepared in the Ghobrial lab and sent for testing in bulk by Adaptive at an undetermined time during the study for analysis.

The clonoSEQ Assay is an in vitro diagnostic that uses multiplex polymerase chain reaction (PCR) and next-generation sequencing (NGS) to identify and quantify rearranged IgH (VDJ), IgH (DJ), IgK, and IgL receptor gene sequences, as well as translocated BCL1/IgH (J) and BCL2/IgH (J) sequences in DNA extracted from bone marrow from patients with B-Cell acute lymphoblastic leukemia (ALL) or multiple myeloma (MM). Rearranged immunoreceptor loci from genomic DNA will be extracted, amplified, and sequenced using V and J segment primers for each immunoreceptor gene. Tumor-specific clonotypes will be identified for each patient based on their high prevalence in bone marrow. Sequences will be analyzed using standardized algorithms for clonotype determination.

Adaptive MRD levels will be quantified using spiked-in reference sequences. Adaptive Inc. will hold the samples for up to 6 months after they have been analyzed, and then will subsequently destroy the samples after exhaustion of the DNA.

Adaptive Biotechnologies
151 Eastlake Ave E, Ste 200
Seattle, WA 098102

9.4 Correlative Sample Collection Table

Sample Time Point[3]	Recipient	Sample Type	Shipping Method	Container[1]
Baseline (Pre Treatment)	DFCI	Peripheral Blood	Fridge pack same day	3x 10mL Purple Top 1x6ml Red Top
		Bone Marrow Aspirate		2x10mL Purple Top 1x3ml Purple Top
		Buccal Swab[2]	Ambient same day	2x Buccal Swab
Each Day 1 of a Cycle (Pre- Dose)	DFCI	Peripheral Blood	Fridge pack same day	2x10mL Purple Top 1x6ml Red Top[3]
Confirm Response[4]	DFCI	Peripheral Blood	Fridge pack same day	3x 10mL Purple Top 1x6ml Red Top
		Bone Marrow Aspirate		2x10mL Purple Top 1x3ml Purple Top
End of Treatment and/or Disease Progression	DFCI	Peripheral Blood	Fridge pack same day	3 x 10mL Purple Top 1 x 6ml Red Top
		Bone Marrow Aspirate		2 x10mL Purple Top 1 x 3mL Purple Top
Progression Free Survival Follow-up[5]	DFCI	Peripheral Blood	Fridge pack same day Same day	3 x 10mL Purple Top 1 x 6ml Red Top
Clinically Indicated	DFCI	Bone Marrow Aspirate	Fridge pack same day	2x10mL Purple Top 1 x 3mL Purple Top

[1] Purple Top= K2EDTA Tube; Red Top= No Additive
[2] Buccal swabs can be collected at any point while on the study- Two swabs may be taken to ensure collection of cells
[3] Samples at all time points are voluntary, and do not exclude patients from treatment
[4] CR- For definition of Complete Response, please refer to section 11- This sample should be drawn the day that the bone marrow biopsy is performed to confirm CR
[5] If participants are coming to the main research facility for progression free survival follow up, samples will be requested. If disease assessment labs are done at an outside facility, no samples are expected to be collected.

9.5 Sample Collection and Shipment Information

Collection of peripheral blood specimens, bone marrow aspirate and saliva for exploratory analysis is voluntary for this trial. Please see the correlative sample table for a list of timepoints and collection instructions. These collections will be taken at the time of routine blood/bone marrow aspirate collection timepoints required for this study. Specimens will be shipped (or delivered by hand or courier) according to instructions below to Dana-Farber Cancer Institute. Once the shipment is received, samples will be subsequently processed, analyzed, and stored at Dana-Farber

Cancer Institute indefinitely.

9.5.1 Specimens Required

- 3 x 10 mL Purple Top Tubes (K2EDTA) and 1 x 6mL Red Top tube of venous or peripheral blood will be collected and shipped Mondays to Thursdays for same-day shipment by trackable carrier (Fed Ex or UPS) or, if DF/HCC site, hand delivery or delivery by local courier is also acceptable
- 2 x 10ml Purple Top Tubes (K2EDTA) and 1x3ml Purple Top tube of bone marrow aspirate will be collected and shipped Mondays to Thursdays for same-day shipment by trackable carrier (Fed Ex or UPS) or, if DF/HCC site, hand delivery or delivery by local courier is also acceptable
- 2 buccal swabs will be collected at any time during the study (though preferred at time of screening for logistics purposes) will be collected and shipped Mondays to Thursdays for same-day shipment by trackable carrier (Fed Ex or UPS) or, if DF/HCC site, hand delivery or delivery by local courier is also acceptable

9.5.2 Shipping Information

- Label all specimens with the following:
    - Subject initials, Subject study number, DFCI designated protocol number, visit at which sample was drawn (screening, C2, response or relapse/progression etc), date the sample was drawn (mm/dd/yyyy), and the type of sample (blood, aspirate, or saliva)

9.5.3 Shipping Instructions**:**

Shipments must be sent on the day of collection and cannot be batch shipped.

9.5.4 Processing Information:

Once collected, the vacutainers will be refrigerated and stored according to instructions below. There is no required processing for purple or red top tubes at each participating site prior to shipment.

Package tubes at room temperature and wrap in a liberal amount of paper towel around the tubes to ensure adequate insulation of the specimen(s) and absorption in the event of a breakage. Place wrapped specimen in a biohazard labeled Ziploc bag with a fridge pack and zip close. Wrap bubble wrap around the bag and place in a cardboard box. If space remains in the box, stuff with extra paper towel to reduce shifting of samples. Complete the shipping requisition form provided to you by the lead site, and ship to the address listed below. Prepare the package for shipping, applying

packing tape as needed. Ship the package using FedEx or UPS next day or overnight delivery the same day the sample was collected.

With each shipment, please include the following:

1. An inventory sheet including a complete list of samples shipped (patient number, timepoint, study #) must accompany each shipment. Please sign and date the form, and retain a copy for site record maintenance. **A sample requisition form will be provided by the lead site for use to accompany shipment.**

2. An electronic copy (Word or Excel) of the sample requisition form must also be sent via email and include the tracking number of the package. The listing must also include a contact name, address and phone number of the person who is responsible for the shipment.

3. Please email the lead site project manager or contact to notify of an incoming shipment.

4. Please ship Monday to Thursday as shipments cannot be received on weekends and/or on holidays.

5. Once drawn, samples may be shipped **via priority overnight air to:**

   Irene Ghobrial, MD,
   Dana-Farber Cancer Institute
   390 Longwood Avenue
   LC 8116
   Boston, MA 02215
   Phone: (617) 582-9857

   Please retain a copy of both the requisition form, and the shipping waybill/receipt for site record maintenance.

10. STUDY CALENDAR

All assessments including scans and bone marrow biopsies must be done within 28 days of registration. If screening labs (heme, chem, and m-protein evaluations) are completed within 7 days of starting treatment, they need not be repeated for C1D1. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted.

Each cycle is defined as 21 days

Table 10-1 Schedule of Events

Evaluation	Screening Within -28 Days of Registration	All Cycles[t]					End of Treatment[q]	PFS - FU[r]	OS-FU[s]
		Day 1	Day 4	Day 8	Day 11	Day 15[g]			
Informed consent [a]	X								
Inclusion/exclusion criteria	X	X							
Medical and disease history [b]	X								
Physical examination/symptom assessment[c]	X	X					X		
Overall Survival Contact[s]									X
Vital signs[d]	X	X					X		
ECOG performance status	X	X					X		
Pregnancy test [e]	X	X		(X)		(X)	X		
Pomalidomide REMS™/PPP counseling [e]	X	X							
Electrocardiogram[f]	X						X		
Chest X-ray[m]	X								
Hematology[g,]	X	X				(X)	X		
Coagulation [h]	X	(X)							
Comprehensive chemistries [i]	X	X					X	(X) [r]	
Hepatitis B screening (HBsAg, Anti-HBs, Anti-HBc)	X								
Thyroid function tests (TSH/ free T4)	X								
Bone marrow aspiration and core biopsy [j]	X	(X)					X	(X)[r]	
M protein assessments (SPEP/UPEP, IFE, SFLC) [k]	X[k]	X					X	X[r]	
Disease Response evaluation		X					X	(X)	
Serum β2-microglobulin	X								
Assessment of extramedullary plasmacytoma[l]	X	(X)					(X)	(X)[r]	
Skeletal survey [m]	X	(X)					(X)	(X)[r]	
Correlative samples[n, j]	X	X					X	(X)	
Dexamethasone administration[o]		Day 1 and 2	Day 4 and 5	Day 8 and 9	Days 11 and 12				

Ixazomib administration [o]		X	X	X	X				
Pomalidomide administration[o]		Daily days 1 –14							
Concomitant medications [p]	X	→					X →		
AE monitoring[v]		→					X →		

(X) Only if indicated

a) All patients must sign an (IRB/IEC/REB)-approved informed consent document prior to enrollment and prior to any study related procedures.

b) Medical History including demographics, prior and current medical illness and conditions, prior surgical procedures. Disease history includes date of initial diagnosis, ISS and cytogenetics at diagnosis (if previously evaluated). Prior surgery and/or radiation and anticancer therapy, including start and stop dates, documentation of best response, date of progressive disease and relapsed or refractory status (Appendix C).

c) A complete physical exam, including height (screening only) and weight, neurologic assessment and assessment for extramedullary myeloma (if present on PE) will be conducted at screening, Day 1 of each cycle and End of Treatment visit. A symptom directed physical examination will be conducted as needed during a cycle. Plasmacytomas that can be followed by physical exam are to be evaluated on Day 1 of each cycle. Baseline symptoms and residual toxicity from previous therapy is to be assessed within 28 days prior to registration.

d) Vital signs including blood pressure, pulse, respiration rate, temperature. To be assessed at screening and on Day 1 of each cycle.

e) All FCBP must have a negative pregnancy test (serum) documented ≤ 14 days prior to start of therapy, then a repeat pregnancy test (urine or serum) within 24 hours of Day 1 of each treatment cycle, and at End of Treatment visit. Note: Additional pregnancy testing is required as a condition of the POMALYST REMS™ program prior to and while on treatment and following last dose of pomalidomide. A FCBP is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing POMALYST therapy and then weekly during the first month, then monthly thereafter in females with regular menstrual cycles, or every 2 weeks in females with irregular menstrual cycles

f) A 12-lead ECG (on a local machine) assessment will be performed on all patients at screening and End of Treatment visit and as clinically indicated.

g) Hematology: CBC with differential, and platelet count. Hematology labs need only be performed on Day 15 during cycles 1-3 only.

h) Coagulation: prothrombin time (PT), or international normalized ratio (INR). activated partial thromboplastin time (aPTT), and fibrinogen. Evaluation should be performed at screening visit and may be repeated at the Investigator's discretion, if medically indicated. If patient is receiving coumadin or other anticoagulant therapy, then coagulation parameters should be monitored more frequently, per investigator's discretion

i) Comprehensive chemistry: sodium, chloride, potassium, magnesium, phosphate, uric acid, BUN (urea), glucose (fasting preferred at baseline), ALT/AST (SGPT/SGOT), alkaline phosphatase, total protein, total bilirubin, albumin, serum creatinine, and estimated creatinine clearance by Cockroft-Gault Equations (Appendix B) calcium and lactate dehydrogenase (LDH).

j) Bone marrow aspiration and biopsy at screening to be evaluated for morphology and for cytogenetics by standard banding and FISH, including marrow karyotype if possible. Suggested probes include, at a minimum del 13q14, t(4:14), t(11;14), t(14:16), and del 17p. After Baseline, bone marrow sampling for plasma cell count is required to qualify CR and to assess MRD status. Bone marrow for correlative studies will be collected at screening, time of response and progression and at any time a clinically indicated marrow is performed.

k) Serum or urine protein electrophoresis (SPEP, UPEP), serum and urine immunofixation (IFE) and serum free light chain (SFLC) assay. To be conducted prior to the start of each cycle. For cycles delayed ≤ 7 days, repeat evaluations are not required. If the start of a new cycle is delayed > 7 days a repeat disease evaluation must be performed prior to the subsequent cycle. UPEP is required in all participants to confirm CR

- 24 h urine collection for Urine M-protein (U-PEP) +/- Urine Immunofixation (IF) is required on day 1 of every cycle- After C1D1 patients may stop UPEP measurement if the subject is not followed by their UPEP (that is, the subject does not have light chain myeloma with a urine M-spike of >200 mg/24 hours at baseline or C1D1), and either there has been no measurable disease by UPEP for 2 consecutive cycles, or the subject is in a complete response. A urine sample to measure UPEP should be obtained at suspected disease progression and to confirm PD

l) Known or suspected extramedullary plasmacytomas are to be assessed at screening, as clinically indicated and to confirm response or progression. The same method of evaluation should be used throughout the study (eg. Computerized tomography [CT]/ magnetic resonance imaging [MRI]/ positron emission tomography [PET]).

m) Skeletal survey includes lateral radiograph of the skull, and anterioposterior views of femur and humeri, anterioposterior and lateral views of the spine, and anterioposterior views of the pelvis and ribs. Low dose PET/CT scan may be used in addition or in place of conventional X-ray)-The same technique should be used with each evaluation for consistency. Required if previous survey > 6 weeks from start of therapy and at any time when clinically indicated. Limited X-rays may be performed as clinically indicated to confirm PD. If a radiologist interpreting the skeletal survey is able to comment on the chest cavity, a separate chest X-ray need not be performed for screening purposes.

n) Correlative Samples. Collection of blood, bone marrow aspirate, and/or saliva samples for correlative samples to be obtained at baseline and on Day 1 of each cycle, at end of treatment, to confirm complete response/best response, and any time that a clinically indicated bone marrow biopsy procedure is performed. For full schedule of correlative samples, please refer to section 9.4. For patients that get their progression free survival follow up labs done at an outside facility and not the main research center, no correlative samples are expected to be collected.

o) See Section 6 in the protocol for complete details on study drug administration, dose modifications and start of a new cycle of therapy and study drug compliance.

p) Concomitant medications and procedures: - all blood products and medications within 21 days prior to first dose until the End of Treatment Visit.

q) End of Treatment visit should be scheduled 30 days (accepted time window ±3 days) after last dose of study drug or as soon as possible if the decision to remove patient from therapy occurs later than 30 days after last dose (such as in the case of unresolved toxicity), with evaluation of safety variables including recording of new and ongoing AEs, review of concomitant medications. If a new treatment for MM is to be introduced sooner than 30 days after last dose of study drug, the EoT visit should occur as close as possible before the first dose of the new drug.

r) Progression Free Survival Follow-Up (PFS-FU): Patients who discontinue therapy for reasons other than disease progression should continue to have disease assessments monthly (every 28 days +/- 7 days) until documented progression (confirmed on 2 consecutive assessments) or initiation of subsequent therapy.

s) Overall Survival Follow-up (OS-FU): Following confirmed disease progression or initiation of subsequent therapy, follow-up for overall survival status and second primary malignancies will take place every three months (84 days) +/- 14 days for 24 months. Follow-up may be completed by phone contact, clinic visit, or other method of data collection. Death information from public sources, e.g. death registry, obituary listing, etc. can also be used when it is available and verifiable.

t) +/- 3 day window permitted (except Cycle 1 Day 1 and PFS/ OS-FU) for holidays/administrative reasons.

u) A disease response assessment is required every cycle based on Day 1 disease evaluation labs beginning with Cycle 2 Day 1 and every Cycle Day 1 thereafter, at EOT, and at each PFS follow up visit

v) SAEs must be recorded for up to 30 days after the last dose of study drug or until resolution or stabilization- AEs that are deemed at least possibly related to the study drug(s) must be followed until resolution or stabilization with no expected resolution.

11. MEASUREMENT OF EFFECT

11.1.1 Response Criteria

Disease response will be assessed using the updated International Myeloma Working Group Response Criteria (IMWG) (Rajkumar 2011).

Table 11-1 International Myeloma Working Group Response Criteria

Response	IMWG criteria
sCR	CR as defined below plus: • normal FLC ratio and • absence of clonal cells in bone marrow by immunohistochemistry or 2 – 4 color flow cytometry
CR	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow. • In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required.
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h. • In patients with only FLC disease, >90% decrease in the difference between involved and uninvolved FLC levels is required.
PR	• 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h • If the serum and urine M-protein are unmeasurable,[3] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Stable Disease	• Not meeting criteria for CR, VGPR, PR or progressive disease
Progressive disease	Increase of ≥ 25% from lowest response value in any one of the following: • Serum M-component (the absolute increase must be ≥ 0.5 g/dL)[4] and/or • Urine M-component (the absolute increase must be ≥ 200 mg/24 h) and/or • Only in patients without measurable serum and urine M-protein, the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL

	• Only in patients without measurable serum and urine M-protein and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

All response categories (CR, sCR, VGPR, nad PD) require two consecutive assessments made at any time before the institution of any new therapy; complete response and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable in serum, urine both or either. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥ I gm/dl are sufficient to define response if starting M-component is ≥ 5 g/dl.

11.1.2 Duration of Response

Duration of overall response: The duration of overall response is measured as the time from initiation of first response to first documentation of disease progression or death. Patients who have not progressed or died are censored at the date last known progression-free.

Duration of overall complete response: The duration of overall CR is measured as the time from initiation of CR to first documentation of disease progression or death. Patients who have not progressed or died are censored at the date last known progression-free.

11.1.3 Progression-Free Survival

Progression-Free Survival (PFS): PFS is defined as the time from start of therapy to the disease progression or death from any cause. Patients who have not progressed or died are censored at the date last known progression-free.

11.1.4 Overall Survival

Overall Survival: Overall Survival (OS) is defined as the time from or registration to death due to any cause, or censored at date last known alive.

Time to Progression: Time to Progression (TTP) is defined as the time from registration to progression, or censored at date of last disease evaluation for those without progression reported.

11.1.5 Response Review

Central review of disease response assessments is not planned for this trial. Disease response assessments will be performed locally on the following disease response measures: M-protein quantification and immunofixation from serum and a 24-hour urine collection, and serum FreeLiteTM testing.

11.2 Other Response Parameters

This section is not applicable to this study.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (Adverse Events:

List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality in accordance with DF/HCC SOPs.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Sponsor-Investigator and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Sponsor-Investigator, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix E.

The Sponsor-Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.
- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

12.4 Collaborative Agreements Language

Not Applicable

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 Phase I:

The Phase I portion of this trial is designed to assess tolerability and toxicity profiles for the combination therapy of Pomalidomide, Dexamethasone and Ixazomib. As such, it will follow a standard “3+3” dose

escalation design: Starting with the first cohort, 3 to 6 patients will be treated at this and each subsequent dose level.

The MTD is defined as the highest dose level where at most 1 patient (of the 6 treated) develops a DLT, and 2 or more of the 3 to 6 patients developed a DLT at the next higher dose level unless the MTD is identified as dose level 4.

The following table presents the probability of escalating doses for various true but unknown rates of DLTs.

Table 13-1 3+3 Dose Escalation

True rate of DLT (%)	Probability of dose-escalation
10	0.91
20	0.71
30	0.49
40	0.31
50	0.17
60	0.08

With four dose levels explored, approximately 3-24 patients will be enrolled in Phase I.

13.1.2 Phase II:

The Phase II portion of the study will be a single-arm open-label enrollment with dosing based on the MTD determination in the Phase I portion of the study. Once the RP2D from the Phase I study has been established, a Phase II study will begin at this dose level to assess efficacy. The primary endpoint of the Phase II portion will be overall response rate (ORR) defined as achieving a partial response or better.

Response will be evaluated using a Simon optimal two-stage design. An ORR of 60% or more will be considered worthy of further study; an ORR of 40% or lower will be considered unpromising.

The study will enroll 19 patients to the first stage. If eight or fewer patients respond to treatment, then the study will stop early for lack of efficacy.

If nine or more from the first stage respond to treatment, then an additional 18 patients will be enrolled to the second stage. If at least 19 of 37 total patients respond (partial response or better), then the study will be considered successful and the treatment considered worthy of further exploration.

This design has an overall power of 85% and type I error of 0.093. Under the null hypothesis of a 40% response rate, the study will stop after the first stage due to lack of efficacy with probability 0.67. Under the alternative hypothesis of a 60% response rate, the study will stop after the first stage with probability 0.088.

13.2 Sample Size, Accrual Rate and Study Duration

Phase I: A total of approximately 3 - 24 safety evaluable patients will be enrolled in up to 4 dose levels of ixazomib, pomalidomide and dexamethasone.

Phase II: A total of 37 evaluable participants will be accrued within 36 months.

In accordance with the NIH guidelines on the inclusion of women and minorities as participants in clinical research. The accrual targets in Table 13-2 reflect the expected accrual over the life of the study.

Table 13-2 Minority Accrual Targets

Accrual Targets						
Ethnic Category	**Sex/Gender**					
	Females		**Males**		**Total**	
Hispanic or Latino	1	+	1	=	2	
Not Hispanic or Latino	21	+	22	=	43	
Ethnic Category: Total of all subjects	22 (A1)	+	23 (B1)	=	45	(C1)
Racial Category						
American Indian or Alaskan Native	0	+	0	=	0	
Asian	0	+	1	=	1	
Black or African American	1	+	1	=	2	
Native Hawaiian or other Pacific Islander	0	+	0	=	0	
White	21	+	21	=	42	
Racial Category: Total of all subjects	22 (A2)	+	(B2) 23	=	45	(C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)	

13.3 Interim Monitoring Plan

Phase I: Starting with the first cohort, 3 to 6 patients will be treated at this and each subsequent dose level. Following completion of cycle for each patient, the cohort will be evaluated for safety and occurrence of DLT. The MTD is defined as the highest dose level where at most 1 patient (of the 6 treated) develops a DLT, and 2 or more of the 3 to 6 patients developed a DLT at the next higher dose level unless the MTD is identified as dose level 4.

Phase II: The study will enroll 19 subjects to the first stage. If eight or fewer subjects respond to treatment, then the study will stop early for lack of efficacy.

If nine or more from the first stage respond to treatment, then an additional 18 subjects will be enrolled to the second stage. If at least 19 of 37 total subjects respond, then the study will be considered successful and the treatment considered worthy of further study.

13.4 Analysis of Primary Endpoints

This design has an overall power of 85% and type I error of 0.093. Under the null hypothesis of a 40% response rate, the study will stop after the first stage due to lack of efficacy with probability 0.67. Under the alternative hypothesis of a 60% response rate, the study will stop after the first stage with probability 0.088.

13.5 Analysis of Secondary Endpoints

The time to event secondary endpoints are defined as follows:

- Time to progression: time from first dose of study drug to progression, censored at date last known progression-free for those who have not progressed
- Progression-free survival: time from first dose of study drug to the disease progression or death from any cause, censored at date last known progression-free for those who have not progressed or died

- Duration of response: time from response to disease progression or death, or date last known progression-free and alive for those who have not progressed or died
- Overall survival: time from first dose of study drug to death or date last known alive

Overall survival, time to progression, progression free survival and the duration of response will be estimated using the method of Kaplan-Meier.

13.6 Reporting and Exclusions

13.6.1 Evaluation of Toxicity

Safety Analysis set: The Safety analysis set is defined as all patients who received at least one dose of ixazomib, pomalidomide or dexamethasone. The Safety analysis set will be the primary population for the summaries of all exposure and safety data. The analysis (PFS) will be performed using the Safety analysis set.

DLT Analysis set: The DLT analysis set is defined as all patients in Phase I that complete Cycle 1 of therapy or are discontinued due to a DLT event defined in Section 5.8.

13.6.2 Evaluation of the Primary Efficacy Endpoint

Efficacy Analysis set: The efficacy analysis set will be comprised of all patients who receive at least one cycle of therapy, had a baseline disease assessment, and had at least 1 post-baseline disease assessment (≥28 days after first dose). Those that are not evaluable for efficacy will be replaced, however, those participants would not be censored in the evaluation of toxicity.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

Grade	Description
0	Normal activity, fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but fully ambulatory, restricted in physically strenuous but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

(Oken et al. 1982)

APPENDIX B COCKCROFT-GAULT FORMULA

Cockcroft-Gault formula

For males:

$$\text{Creatinine Clearance} = \frac{(140-\text{age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \text{ OR } \frac{(140-\text{age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[µmol/L]})}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85\ (140-\text{age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \text{ OR } \frac{0.85\ (140-\text{age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[µmol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

APPENDIX C DEFINITION OF RELAPSED REFRACTORY DISEASE

This study will use the IMWG definitions:

Refractory Myeloma:

Refractory myeloma is defined as disease that is non-responsive (failure to achieve minimal response or develops PD while on therapy) while on primary or salvage therapy, or progresses within 60 days of last therapy. There are 2 categories of refractory myeloma.

- Relapsed and refractory myeloma: Relapsed and refractory myeloma is defined as disease that is non-responsive while on salvage therapy or progresses within 60 days of last therapy in patients who have achieved minimal response or better at some point previously to then progressing in their disease course.
- Primary refractory myeloma: refractory myeloma is defined as disease that is non-responsive in patients who have never achieved minimal response or better with any therapy. It includes patients who never achieve MR or better in whom there is no significant change in M protein and no evidence of clinical progression; as well as primary refractory, progressive disease where patients meet criteria for true progressive disease.

Relapsed myeloma:

Relapsed myeloma is defined as previously treated myeloma, which progresses and requires the initiation of salvage therapy but does not meet the criteria for either primary refractory myeloma or relapsed and refractory myeloma (Rajkumar et al. 2011).

APPENDIX D NCI CTCAE VERSION 5.0

Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) v5.0

Publish Date: (v5.0:November 27th, 2017)

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

APPENDIX E **MULTICENTER GUIDELINES**

DFCI IRB Protocol #: 19-291

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

TABLE OF CONTENTS

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. FDA). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and

safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Research Informatics for Operations (RIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Paul Richardson, MD will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with the FDA
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).

- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting pPolicy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB of record.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that

requires a full revised consent form.

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

To register a participant, the following documents should be completed by the Participating Institution and faxed or e-mailed to the Coordinating Center lead project manager

- Copy of required laboratory tests and documents that support all aspects of the eligibility checklist
- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)
- Completed Eligibility Checklist

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.

Treatment or other protocol-specific interventions may not begin without confirmation from the Coordinating Center that the participant has been registered.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures

from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated therapy will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical

examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7.

Participating Institutions must report the SAEs to the DF/HCC Sponsor/Coordinating Center following the DFCI IRB Adverse Event Reporting Policy of the IRB of record.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review/submit to the IRB according to their institutional policies and procedures.

3.10 Data Management

DF/HCC RIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC RIO provides a web based training for all eCRF users.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol under investigational agent ordering.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring on a periodic basis. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center. A study specific monitoring plan will be shared with each participating site during the site initiation visit.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

When participating institutions are activated for this study, they will be required to participate in monthly Coordinating Center initiated teleconferences. These teleconferences will occur regularly until completion of accrual. After completion of accrual, phone calls will occur every other month until study treatment ceases for all participants. Minutes of these meetings should be kept and referenced when needed.

At least one member of the study team should be able to join the teleconference each time one is held, and at minimum provide updates about the site's patients if they are unable to join.

Participating Institutions will be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification as required by the Coordinating Center Monitor.

On-Site Monitoring will occur according to the study specific monitoring plan. Source documentation verification (SDV) will be conducted by having access to participants' complete medical record and source documents. A letter outlining what will be reviewed will be sent prior to each visit.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

The following **minimum** accrual requirements are recommended:

1) Phase I: 2 per site/annually
2) Note: Diseases that are extremely rare may have accrual expectations of 0-1 accruals/year.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Policies, and the Code of Federal Regulations (CFR).

6.1 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced

by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

APPENDIX F **STUDY DRUG DIARY**

PHASE I/II STUDY OF TWICE WEEKLY IXAZOMIB PLUS POMALIDOMIDE AND DEXAMETHASONE IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA

SELF-ADMINISTERED DRUG DIARY

PATIENT INSTRUCTIONS:

Take your medications exactly as prescribed by your doctor. See the next page for specific doses for each medication that you are taking on this study.

- Keep capsules in the bottle(s) provided and do not transfer them to any other container. Store at room temperature.
- Pomalidomide should be taken by mouth once per day for 14 days. Capsules must be swallowed whole with water at approximately the same time each day and can be taken with or without food.
- Ixazomib capsules should be taken whole from the blister package, and at approximately at the same time each day on an empty stomach. It should be taken at least one hour before or 2 hours after food with about 1cup (8oz) of water
- Dexamethasone should be taken whole, by mouth on the day of and the day after your ixazomib dose. Tablets must be swallowed whole and taken with food at the same time each day. It is recommended that dexamethasone be taken at least 2 hours before the ixazomib dose on the ixazomib dosing days
- Patients who vomit a dose after Ixazomib ingestion will not receive an additional dose but should resume dosing at the time of the next scheduled dose.
- If you vomit after taking pomalidomide or dexamethasone, do NOT take another dose. Please note any vomiting in the **Comments** section of the diary on the next page.
- If you miss a dose of pomalidomide and it has been less than 12 hours since the missed dose, take it as soon as you remember on the same day. If it has been more than 12 hours since missing a pomalidomide dose, you should not take the dose on that day, but take the next dose at the normal time on the following day.
- Missed doses of ixazomib should be taken as soon as you remember, as long as the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose.
- If you miss a dose of dexamethasone, take it as soon as you remember on the same day. If you miss taking dexamethasone for the entire day, take your regular dose the next scheduled day (do NOT take double your regular dose to make up for the missed dose).
- If you miss a dose, please record "0" for **Number Taken** on the next page.
- Please bring any unused pomalidomide and ixazomib and all empty containers and diary to your next visit.
- **If you take more than the prescribed dose of pomalidomide or ixazomib, seek emergency medical care immediately and contact the study team**

TREATMENT STUDY PARTICIPANT SELF-ADMINISTERED DIARY

Participant Identifier: _____Cycle #: _____

Cohort:_____

Your MD _____

Phone _____

	Date	Number Taken			Comments
		Pomalidomide	Dexamethasone	Ixazomib	
Ex:	6/1/2009	1	1	1	Vomited hour later
Day 1					
Day 2					
Day 3					
Day 4					
Day 5					
Day 6					
Day 7					
Day 8					
Day 9					
Day 10					
Day 11					
Day 12					
Day 13					
Day 14					
Day 15					
Day 16					
Day 17					
Day 18					
Day 19					
Day 20					
Day 21					

Your RN _____

Phone _____

STUDY DRUG INSTRUCTIONS:

Take the following medications as indicated below.

Record the dose of each medication on the chart to the right after taking each day.

If you take more than the prescribed dose of pomalidomide or ixazomib, seek emergency medical care immediately and contact the study team.

Pomalidomide:
☐ All Cycles: ___ mg by mouth on Days 1-14

Ixazomib:
☐ All Cycles: ___ mg by mouth on Days 1, 4, 8, 11

Dexamethasone:
☐ All Cycles: ____ mg by mouth on Days 1,2,4,5,8,9,11,12

Patient Signature: _____Date: _____

Delegated Staff
Signature:_____Date:_____