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Phase I study of selinexor, ixazomib and low-dose dexamethasone in patients with relapsed or refractory multiple myeloma

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Selinexor, an orally bioavailable, first in class selective inhibitor of nuclear export (XPO1), was FDA approved in combination with dexamethasone for penta-refractory multiple myeloma patients in July 2019. The FDA approval was based on results from 83 patients on the Phase 2b STORM study that showed an ORR of 25% and a median duration of response of 3.8 months [(1)]. Selinexor has been combined with bortezomib [(2)] and carfilzomib [(3)]. Based on early results suggesting possible synergistic activity between selinexor and proteasome inhibitors, we designed a Phase I study to evaluate an all-oral combination therapy using the selective inhibitor of nuclear export (XPO1), selinexor, together with ixazomib and dexamethasone (SId) for patients with relapsed and/or refractory multiple myeloma.

Here, we report our experience with SId. Our study was approved by the Institutional Review Board at MSKCC, and all patients provided written informed consent. Eligible patients were treated on 2 dosing cohorts. Cohort A had bi-weekly dosing of selinexor

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Author Contributions:

M.S. performed research, analyzed data and wrote the paper. N.L. and O.L. designed research, performed research, analyzed data and wrote the paper. D.M., J.S., M.H., N.K., S.M., A.L., H.H., E.S., U.S., V.D., K.W., H.L., O.L., P.D., G.S., D.C., M.S.& S.G. Performed research.

Conflict-of-interest disclosure:

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(given on days 1, 3, 8, 10, 15, and 17 of a 28-day cycle), and we explored 2 dose levels of selinexor (dose level 1: 40mg; dose level 2: 60mg). Cohort B had weekly dosing of selinexor (given on days 1, 8, 15, and 22 of each 28- day cycle), and we explored 2 dose levels of selinexor for this cohort (dose level 1: 80mg; dose level 2: 100mg). Dexamethasone was given the same days as selinexor in both cohorts. Ixazomib 4mg was given on days 1,8 and 15 of each 28-day cycle in both cohorts. All patients were required to take ondansetron 8mg BID or TID through the first cycle after cycle 1 ondansetron was only required on days of study drug and day after. Both cohorts followed a standard 3-by-3 design for dose escalation. Patients were evaluable for safety analysis if they received at least one dose, and all patients who completed one 28-day cycle were evaluable for response. Response was assessed using the International Myeloma Working Group (IMWG) criteria after each cycle. Dose-limiting toxicities (DLTs) were evaluated during the first 28 days of treatment.

Major eligibility criteria for enrollment included a diagnosis of relapsed and/or refractory multiple myeloma following treatment with at least one immunomodulatory drug and at least one proteasome inhibitor. Additionally, patients needed to have adequate hematologic, hepatic, and renal function based on laboratory values within 14 days of study registration. These criteria were defined as ANC ≥ 1,000/mm3, platelets ≥75,000/mm3, total bilirubin ≤ 1.5 mg/dL, AST, and ALT ≤ 3 times the upper limit of normal and calculated or measured creatinine clearance ≥ 30mL/min. Patients were not allowed to receive growth factor support within 14 days of screening and no platelets within 72 hours of screening assessments.

Eighteen patients received treatment with SId; the patients had a median of 5 prior lines of therapy (range 1–11), and 83% (15/18) were PI refractory. Of the total 18 patients,7 patients were enrolled and treated on the bi-weekly dosing schedule (cohort A), and 11 were enrolled and treated on the weekly dosing schedule (cohort B). The initial starting dose for selinexor for cohort A was 40mg. In the initial 3 patients, no DLTs were observed. Therefore, 3 patients were treated at the 60mg dose level. One patient withdrew consent after 1 dose and was replaced. Of the 3 patients who completed dose level 2, no DLTs were observed. Although no DLTs were observed for the bi-weekly cohort A, a clinical decision was made to not proceed further with bi-weekly dosing and instead focus on weekly dosing (cohort B) since it was felt to be better tolerated; therefore, an MTD was not determined for cohort A.

The initial starting dose for the weekly dosing of selinexor (cohort B) was 80mg. In the Initial 3 patients no DLTs were observed. Therefore, the study moved to dose level 2 with 100mg of selinexor weekly. Two patients were enrolled, and both experienced DLTs. Subsequently, the next 3 patients were enrolled at the 80mg dose as 100mg was determined to have exceeded MTD, 3 patients came off study during cycle 1 due to toxicities and were replaced. No DLTs were observed. Thus, a total of 6 patients were treated at the 80mg once-weekly dose, and this was determined to be the MTD. Seven patients required dose reductions, 4 from cohort A (bi-weekly selinexor), and 3 from cohort B (weekly selinexor). Of the 4 patients in cohort A, 2 patients were dose reduced were due to thrombocytopenia and 2 due to syncopal events. All 3 dose reductions in cohort B were due to thrombocytopenia.

There were 4 serious adverse events possibly related to selinexor: 2 grade 3 syncope, 1 grade 3 presyncope & 1 grade 3 abdominal pain/nausea. The most common nonhematologic AEs were gastrointestinal (GI). Most events were grade 1 or 2 and included nausea 50% (grade 3 in 2 patients), vomiting 33% (grade 3 in 2 patients), diarrhea 22% and anorexia 28% (grade 3 in 1 patient). As stated above, patients were required to take prophylactic ondansetron, which limited GI toxicities. Fatigue 56% (Grade 3 in 2 patients), elevated AST 22% and ALT 27%. hyperglycemia 66% (grade 3 in 2 patients), hypophosphatemia 39% (grade 3 in 1 patient), hyperkalemia 21%, hypocalcemia 32%, and hyponatremia 28% were also commonly noted. Hematologic AEs included thrombocytopenia 72% (grade 3 in 6 patients/ grade 4 in 5 patients), anemia 61% (grade 3 in 3 patients) and neutropenia 28% (grade 3 in 2 patients/ grade 4 in 3 patients).

The reason for discontinuation of therapy was due to toxicities in 8 patients and progression of disease in 9 patients. Although cohort B reached MTD, due to the lack of strong clinical activity and the high rate of treatment discontinuation due to GI toxicities, it was decided that the study would not continue with a further expansion cohort as initially planned.

Best responses for all patients were: 2 very good partial response (VGPR), 1 partial response, 7 stable disease, and 4 progression of disease (i.e., overall response rate: 3/14 [22%]). Four patients were not evaluable for response assessment because they withdrew consent before completing 1 full cycle. Three of the 14 patients received 4 or more cycles of SId therapy; these patients had fewer lines of prior therapy (median 4, range 1–6). At the data cut-off for this analysis (June 2019), the longest duration of response was 14 months, with 1 patient still actively receiving treatment in a VGPR. This patient had only received 1 prior line of therapy and was not refractory to proteasome inhibitors.

In summary, the all-oral SId combination therapy in heavily pre-treated patients with RRMM resulted in frequent treatment delays and dose reductions due to thrombocytopenia and GI-related toxicities, which, in turn, resulted in progression of disease. The overall response rate was 22% (3/14), and 3 patients received 4 or more cycles of SId therapy, with the longest duration (VGPR) being 14 months. In our clinical experience, the use once daily low dose (2.5 mg) olanzapine combined with of ondansetron greatly improved the tolerability of selinexor and allowed us to taper a patient off ondansetron without the patient experiencing any significant GI toxicity.

In the setting of optimal management of GI toxicities with prophylactic medications such as olanzapine and/or ondansetron, SId may be an all-oral treatment option for RRMM patients who are less heavily pre-treated (i.e., to avoid significant platelet drops resulting in dose reductions and delays of selinexor). Additional pre-clinical work and predictive biomarkers may identify patients that could potentially derive a benefit.

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Table 1.

Patients' characteristics

Median age, y (range)	66 (44– 78)
Female, n %	8 (45%)
Median prior lines of therapy, n (range)	5 (1–11)
Prior Daratumumab exposure, n %	8 (45%)
Prior ASCT, n %	15 (83%)
Median time (years) since initial diagnosis of MM (range), y (range)	4 (1–9)

Footnote: the number above refer to all 18 patients who received treatment with SId