A phase IIb study of selinexor in combination with daratumumab in patients with daratumumab-refractory multiple myeloma

Multiple myeloma (MM) is the second most common hematologic malignancy with a 5-year survival of only 61%.[1,2] The use of autologous stem cell transplantation (ASCT), immunomodulatory agents, proteasome inhibitors, anti-CD38 monoclonal antibodies, and cellular therapy have significantly improved outcomes in MM patients, yet most patients develop highly resistant MM and eventually succumb to the disease. There is an unmet need to develop anticancer agents with novel mechanisms to treat relapsed or refractory MM (RRMM) and to prolong durability of response to approved agents. Selinexor is an oral, selective inhibitor of nuclear export compound that blocks exportin 1, leading to retention of tumor suppressor proteins and apoptosis in malignant cells. Preclinical studies suggest synergistic activity when selinexor is combined with other MM treatments, and that daratumumab resistance could be associated with selinexor sensitivity.[3-6] Phase I clinical trials have determined the recommended dose of selinexor in combination with carfilzomib (CFZ), pomalidomide (POM), and daratumumab (DARA).[7,8] We hypothesize that the addition of selinexor can prolong response in patients who are relapsing on their current CFZ-, POM-, elranatamab-, or DARA-based regimens. Herein, we report the results of the exploratory arm of an ongoing investigator-initiated, four-arm, phase II, multicenter study whereby patients were treated with combination selinexor, DARA, and dexamethasone (DEX) after being refractory or relapsing on their current DARA-containing regimen (clinicaltrials.gov NCT04661137). This analysis showed promising efficacy with the potential of selinexor to prolong response duration to DARA with a manageable safety profile in heavily pretreated, DARA-refractory MM patients.

Patients with histologically confirmed MM were included in this trial provided that they were in relapse or refractory to a CFZ-, POM-, elranatamab-, or DARA-containing regimen. Evidence of disease progression or refractory disease on the current regimen was defined as achieving stable disease (SD) or less for ≥1 cycle during treatment for <25% response. Subjects detailed in this report were enrolled between April 2021 and April 2024 to the exploratory arm if their most recent line of therapy contained DARA and they developed relapsing or refractory disease to their current regimen. The primary endpoint was overall response rate (ORR) for treatment with selinexor, DARA and DEX utilizing International Myeloma Working Group (IMWG) response criteria.[9] Secondary endpoints include: duration of response (DOR), clinical benefit rate (CBR), disease control rate (DCR), progression-free survival (PFS), time to progression (TTP), time to next treatment (TTNT), overall survival (OS), and safety. Patients were asked to complete the Functional Assessment of Cancer Therapy-Multiple Myeloma (FACT-MM) questionnaire at screening and day 1 of each cycle starting with cycle 2. This study received approval from the ethics committees of the institutes involved and from regulatory authorities. It was conducted according to the principles of the Declaration of Helsinki, the International Conference on Harmonization, and the Guidelines for Good Clinical Practice. All patients provided written informed consent prior to entering the study.

In this exploratory analysis, patients were enrolled on the DARA arm and received selinexor, DARA, and DEX in 28-day cycles. Oral selinexor (100 mg or 5x20 mg tablets) was given on days 1, 8, 15, and 22. Intravenous (i.v.) DARA (16 mg/kg) or subcutaneous (s.q.) DARA (1,800 mg) was administered on days 1, 8, 15, and 22 for the first 2 cycles, days 1 and 15 for cycles 3-6, and day 1 for cycle 7 and cycles thereafter. DARA was continued at the same dosing schedule as the patient's prior regimen. Oral or i.v. DEX (40 mg or 20 mg if patient ≥75 years of age) was given on days 1, 8, 15, and 22. Baseline characteristics and adverse events (AE) were descriptively summarized. The ORR was reported as the proportion of responders along with the corresponding two-sided 95% Clopper-Pearson exact confidence interval (CI). Kaplan-Meier procedures were used for time-to-event analyses, and rate endpoints were summarized using two-sided 95% Clopper-Pearson exact CI. A two-sided *P* value <0.05 was considered statistically significant. All analyses were conducted using R software (v.4.3; R Core Team, Vienna, Austria).[10]

Ten patients were enrolled onto the DARA, selinexor, and DEX treatment arm. Median age was 67 years (range 61-82), 60% female, 50% White, 30% Black, 10% Asian, and 10% Hispanic or Latino. Patients presented with the following disease characteristics: 30% International Staging System (ISS) stage III MM, 70% high-risk cytogenetics, 20% extramedullary disease, 100% refractory to the last line of therapy (LOT), 100% prior ASCT, 60% triple-refractory, and 30% quadruple-refractory (Table 1). Four unique patients had high-risk cytogenetics, including 3 patients with 1q21 duplication (in combination with a second high-risk feature), 3 with t(4;14), and one with *TP53* mutation; 3 patients had 2 or more high-risk

features. Patients completed a median of 5 cycles (range 0-11), with a median treatment duration of 4.5 months (range 0-10). Seven patients discontinued treatment, 5 due to disease progression and 2 withdrew consent due to treatment-related AE. No treatment-related deaths occurred. There was one death on-study; this was not drug-related, as the patient developed sepsis approximately ten months after discontinuing study treatment. There were 9 patients evaluable for response; one withdrew before response evaluation. ORR was 50% (95% CI: 24-76%), CR 10% (1/10, 95% CI: 1-46%), VGPR 10% (1/10, 95% CI: 1-46%), and PR 30% (3/10, 95% CI: 8-65%) (*Online Supplementary Table S1*). CBR was 60% (95% CI: 27-86%), and DCR was 80% (95% CI: 44-96%). In patients (N=4) with high-risk cytogenetic features, ORR was 25% whereas in patients without these features (N=6) the ORR was 67%. At data cutoff (April 26, 2024), 5 patients remained on-study. At a median follow-up of 14 months, median DOR was 5.06 months (95% CI: 4.76, NA), median TTP was 6.6 months (95% CI: 5.75, NA), and TTNT was 6.24 months (95% CI: 6.21, NA) (Figure 1A-C). Median PFS was 6.87 months (95% CI: 5.75, NA), and median OS was 29.3 months (95% CI: 16.5, NA) (Figure 2A, B).

All (10/10) patients experienced any grade (G) AE (*Online Supplementary Table S2*). The most common hematologic G1-2 AE during treatment were anemia (40%), thrombocytopenia (40%; G3 10%), and neutropenia (10%; G3 10%). The most common non-hematologic G1-2 AE during treatment were fatigue / malaise / weakness (90%), hyponatremia (90%), respiratory tract infections (80%), nausea / vomiting (50%), diarrhea (40%), anorexia (30%), dyspepsia / gastroesophageal reflux disease (GERD) (30%), musculoskeletal / bone cramps / pain (30%), transaminitis (30%), increased blood urea nitrogen (BUN) values / creatinine (30%), and hypomagnesemia (30%). There were 5 unique patients who experienced severe AE (SAE), of which 3 patients experienced SAE related to study treatment: hyponatremia, sepsis and pneumonia, and acute hypoxic respiratory failure from parainfluenza A-1. The 2 SAE unrelated to study treatment included sepsis associated with infected hardware of the right humerus, and a head injury after a mechanical fall (without loss of consciousness) and subarachnoid hemorrhage.

There were 5 patients who answered the FACT-MM questionnaire up through cycle 4, and they demonstrated improvement in patient-reported symptoms but no change in family support, daily activities, or patient-reported outlook (*Online Supplementary Figure S1*). Over the course of 9 cycles, one experienced an improvement in reported symptoms, ability to carry out daily activities, and negative outlook, while positive outlook and family support remained consistent. In contrast to this, over the course of 11 cycles, another patient experienced an increase in symptoms reported at cycle 7 that appeared to improve in later cycles, yet positive outlook seemed to worsen despite generally consistent ability for daily activities and family / peer support.

In this population of heavily-pretreated, high-risk, and multiple-refractory MM patients, results of the present

Table 1. Baseline patient and multiple myeloma characteristics.

Characteristics	Patients N=10 N (%)
Age in years	
Median (range)	67 (61-82)
≤64	5 (50)
65-74	3 (30)
≥75	2 (20)
Sex	
Male	4 (40)
Female	6 (60)
Race/ethnicity	
Asian	1 (10)
Hispanic or Latino	1 (10)
Non-Hispanic Black	3 (30)
Non-Hispanic White	5 (50)
ECOG Performance Status Score	
0	4 (40)
1-2	6 (60)
International Staging System	
I	5 (50)
II	2 (20)
III	3 (30)
High-risk cytogenetics	4 (40)
t(4;14)	3 (30)
t(14;16)	0 (0)
del(17p)	0 (0)
1q21	3 (30)
MYC	0 (0)
TP53	1 (10)
Double hit or more of high-risk cytogenetic features	3 (30)
Median N of prior LOT (range)	3 (2-6)
Prior treatment history	
Bortezomib	5 (50)
Carfilzomib	7 (70)
Daratumumab	10 (100)
Pomalidomide	7 (70)
Lenalidomide	9 (90)
Prior transplant history	
Autologous stem cell transplant	10 (100)
Allogeneic stem cell transplant	0 (0)
Refractory disease	
To last line of therapy	10 (100)
Triple refractory	6 (60)
Quadruple refractory	3 (30)
Penta-refractory	0 (0)
Immunomodulatory agents	6 (60)
Proteasome inhibitors	6 (60)
Anti-CD38 monoclonal antibody	10 (100)

ECOG: Eastern Cooperative Oncology Group; ISS: International Staging System; LOT: lines of therapy; N: number.

analysis indicate that DARA-sensitivity can be prolonged using the triplet combination of selinexor, DARA, and DEX in those refractory to their current DARA-based regimen. In a small number of patients, triplet combination therapy resulted in an ORR of 50%, CBR of 60%, median PFS of 6.87 months, and median OS of 29.3 months. These results indicate a meaningful clinical benefit for this population who had previously shown resistance to DARA-containing regimens, especially as more MM patients are developing CD38-refractory disease earlier in the disease course with the widespread use of anti-CD38 monoclonal antibodies in the upfront setting. In the MAMMOTH study, patients with MM refractory to anti-CD38 monoclonal antibodies were found to have an ORR of 31% to their next LOT (25% in patients receiving DARA in their next LOT), highlighting how difficult it is to treat a CD38-exposed or refractory population.[11] In addition, our data are consistent with results of the STOMP and BOSTON studies in patients who were anti-CD38 monoclonal antibody refractory.[12,13] However, these patients had a regimen change that included two new agents, whereas in the present study the effects of selinexor are isolated, as patients received only one new agent while continuing on DARA and DEX. Furthermore, the safety profile of the combination in our study was consistent with previous studies, with no G4 AE observed.

In conclusion, the combination of selinexor, DARA, and DEX showed promising efficacy and a manageable safety profile in heavily-pretreated, DARA-refractory MM patients. Selinexor has the potential to prolong response duration to DARA with acceptable tolerability. It is possible that synergy exists between DARA and selinexor, even in a DARA-refractory patient, as the expected ORR to single-agent selinexor is <30%. Future studies should

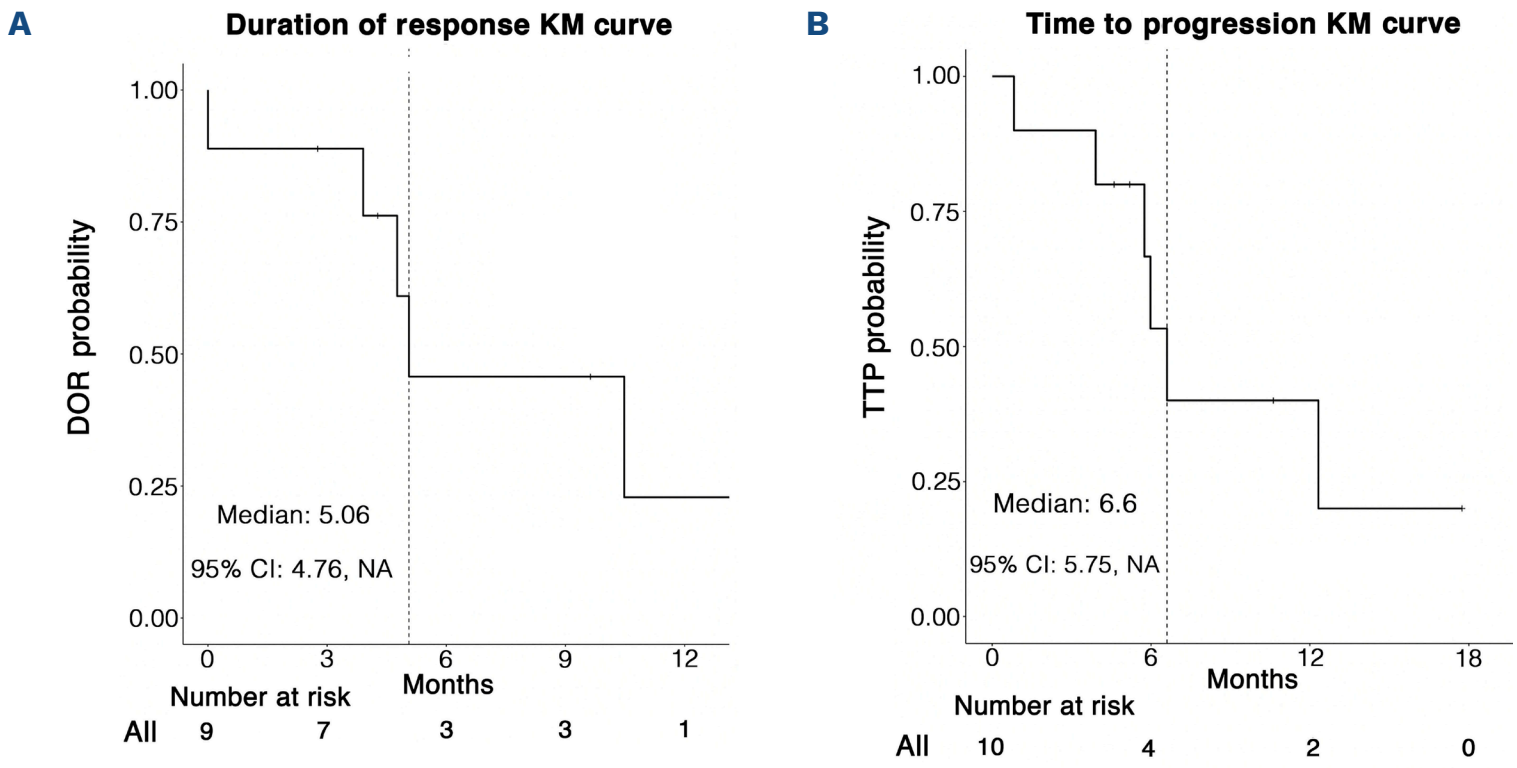

Figure 1. Duration of response, time to progression, and time to next treatment in patients with relapsed or refractory multiple myeloma receiving treatment with selinexor, daratumumab, and dexamethasone. (A) Duration of response (DOR). (B) Time to progression (TTP). (C) Time to next treatment (TTNT). NA: Not able to estimate.

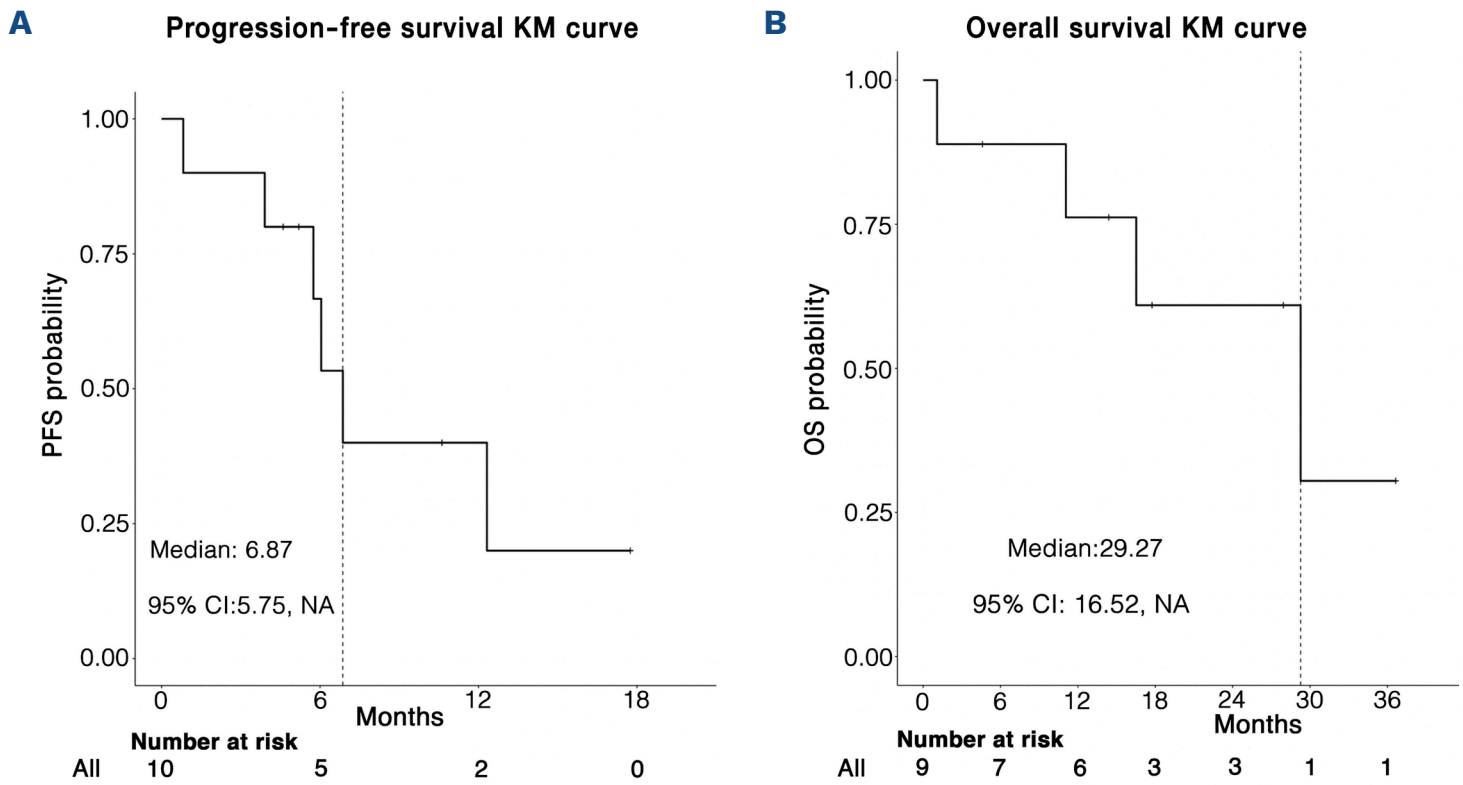

Figure 2. Progression-free survival and overall survival in patients with relapsed or refractory multiple myeloma receiving treatment with selinexor, daratumumab, and dexamethasone. (A) Progression-free survival (PFS). (B) Overall survival (OS). NA: Not able to estimate.

explore the combination's potential in broader patient populations and assess long-term survival outcomes.

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Data-sharing statement

Deidentified individual participant data that underlie the reported results will be made available three months after publication for a period of five years after the publication date. Proposals for access should be sent to Noa.Biran@hmhn.org.

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