Poster# 4010

Selinexor, mezigdomide, and dexamethasone in patients with relapsed/refractory multiple myeloma who relapsed or are ineligible for T-cell redirecting therapy: STOMP Phase 1 preliminary results

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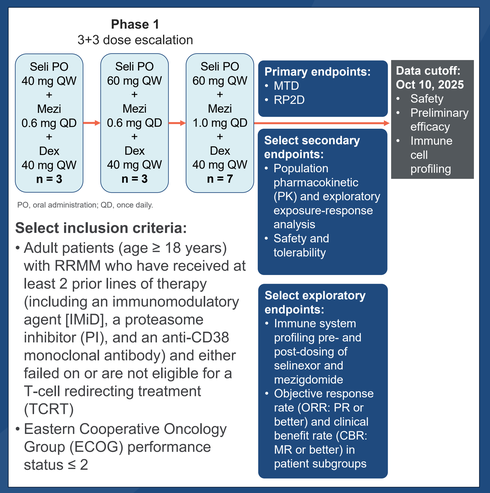
Introduction

- CAR T-cell therapy and anti-B-cell maturation antigen (BCMA) bispecific antibody treatments for relapsed/refractory multiple myeloma (RRMM) show excellent clinical activity, but nearly all patients relapse within 24 months[1]
- Some anti-myeloma therapies such as alkylating chemotherapy may promote T-cell exhaustion and inferior T-cell therapy outcomes[1], leaving an unmet need to identify agents that could be used to either optimize a future CAR-T or bispecific antibody therapy, and/or salvage T-cell redirecting treatment failures
- Both selinexor (seli), an oral exportin 1 (XPO1) inhibitor and mezigdomide (mezi), a novel cereblon E3 ubiquitin ligase modulator (CELMoD), have been shown to have T-cell stimulatory activity in preclinical and clinical studies
  - Selinexor is approved in combination with dexamethasone (dex) in penta-refractory multiple myeloma (MM) and with dexamethasone and bortezomib in RRMM after ≥1 prior therapy[2]
  - Selinexor shown to have anti-inflammatory and T-cell activating properties that may facilitate a favorable immune microenvironment for effector T cells[3–5]
  - Mezigdomide has been shown to reverse T-cell exhaustion and reinvigorate cytokine production pathways, as well as be active and well tolerated in RRMM, including anti-BCMA-exposed and refractory patients[6,7]
- STOMP Arm 12 is investigating whether the all-oral combination of selinexor, mezigdomide, and dexamethasone (SMd) could produce additive or synergistic effects superior to either agent alone in RRMM that has either progressed after or is otherwise ineligible for T-cell redirecting therapy. The Phase 1 results for Arm 12 are presented herein

Methods

STOMP Arm 12: A Phase 1/2 Study of SMd for RRMM (NCT02343042)

- STOMP Arm 12 is multicenter, open-label, clinical study with a 3+3 dose escalation (Phase 1) and expansion (Phase 2) to independently assess the maximum tolerated dose (MTD), efficacy, and safety of SMd in patients with RRMM that has either progressed after or is otherwise ineligible to be treated with a T-cell redirecting therapy
- During the Phase 1 dose escalation phase, selinexor was escalated from 40 mg once weekly (QW) to 60 mg on days 1, 8, 15 (3 weeks on 1 week off), in combination with mezigdomide 0.6 to 1.0 mg daily (QD) on days 1-21 and dexamethasone 40 mg on days 1, 8, 15, and 22 of a 28-day cycle to establish the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D)



Select inclusion criteria:

- Adult patients (age ≥ 18 years) with RRMM who have received at least 2 prior lines of therapy (including an immunomodulatory agent [IMiD], a proteasome inhibitor (PI), and an anti-CD38 monoclonal antibody) and either failed on or are not eligible for a T-cell redirecting treatment (TCRT)
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

Results

Patient Demographics and Baseline Characteristics

- As of Oct 10, 2025, a total of 13 patients have been enrolled
  - 3 in **Cohort 1** seli 40 mg QW/mezi 0.6 mg QD/dex 40 mg QW
  - 3 in **Cohort 2** seli 60 mg QW/mezi 0.6 mg QD/dex 40 mg QW
  - 7 in **Cohort 3** seli 60 mg QW/mezi 1.0 mg QD/dex 40 mg QW

Characteristics	Total (N = 13)
Age (years), median (range)	66 (42–83)
≥ 75 years, n (%)	2 (15)
Sex (male), n (%)	9 (69)
Race, n (%)	
African American	3 (23)
Native Hawaiian or Pacific Islander	1 (8)
White	9 (69)
ECOG performance status, n (%)	
0	8 (62)
1	5 (39)
ISS disease stage, %	
I	9
II	2
III	2
Time since diagnosis (years), median (range)	7.5 (2.7–22.0)
Extramedullary lesions, n (%)	3 (23)
Number of prior lines of therapy, median (range)	5 (2–12)
Exposure to at least one IMiD, n (%)	13 (100)
Exposure to at least one PI, n (%)	13 (100)
Exposure to at least one anti-CD38 antibody, n (%)	13 (100)
Exposure/refractory to T-cell redirecting treatment,† n (%)	3 (23)
Exposure/refractory to belantamab mafodotin, n (%)	3 (23)
Exposure/refractory to to iberdomide, (%)	1 (7)
Autologous stem cell transplant, n (%)	9 (69)
Refractory to at least one IMiD, n (%)	12 (92)
Refractory to at least one PI, n (%)	10 (77)
Refractory to at least one anti-CD38 antibody, n (%)	13 (100)
Refractory to last line of treatment, n (%)	12* (92)

*Data pending; †TCRTs include, CAR T-cell therapy, IgM2644 (CE38xCD3 bispecific), talquetamab (GPRC5DxCD3 bispecific). ISS, International Staging System.

Patient Disposition

Phase 1 Patients enrolled N = 13*

Cohort 1
Seli 40 mg QW + mezi 0.6 mg QD + dex 40 mg QW (n = 3)
Received at least one dose study drug (n = 3)
Discontinued treatment (n = 2)
Adverse event (n = 1)
Disease progression (n = 1)
Withdrawal by patient (n = 0)
Death (n = 0)

Cohort 2
Seli 60 mg QW + mezi 0.6 mg QD + dex 40 mg QW (n = 3)
Received at least one dose study drug (n = 3)
Discontinued treatment (n = 1)
Adverse event (n = 0)
Disease progression (n = 0)
Withdrawal by patient (n = 1)
Death (n = 0)

Cohort 3
Seli 60 mg QW + mezi 1.0 mg QD + dex 40 mg QW (n = 7)
Received at least one dose study drug (n = 7)
Discontinued treatment (n = 4)
Adverse event (n = 0)
Disease progression (n = 1)
Withdrawal by patient (n = 2)
Death (n = 1)

*11 patients were enrolled into the Phase 1 study, and 2 patients from the compassionate use program received at least one dose of selinexor.

TEAEs

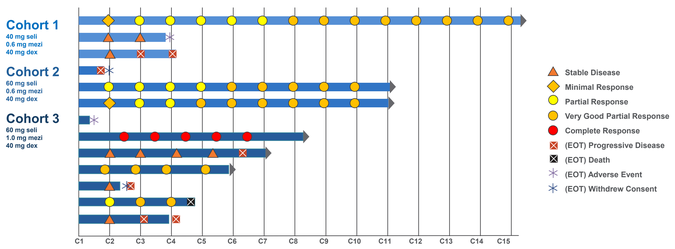
- As of data cutoff (Oct 10, 2025), median duration of treatment was 117 days (range: 15–392)
- The most common treatment-emergent adverse events (TEAEs) in the total population:
  - neutropenia (85%)
  - thrombocytopenia (62%)
  - constipation (54%)
  - leukopenia (54%)
- The most common serious TEAE (Grade 3/4) was neutropenia (54%)
- Dose-limiting toxicities (DLTs)
  - None in cohorts 1 and 2
  - Two DLTs occurred in cohort 3
    - One patient experienced Grade 2 constipation and proctitis (pre-existing) and despite medical intervention withdrew consent prior to completion of Cycle 1, thus being assessed as a DLT per protocol
    - One patient experienced a Grade 4 neutropenia on Cycle 1 Day 15 that did not resolve within 7 days of supportive care and holding all study medication

Recommended Phase 2 Dose

- Seli 60 mg QW + mezi 0.6 mg QD + dex 40 mg QW was selected as the RP2D

TEAE, n (%)	Cohort 1 (n = 3)	Cohort 2 (n = 3)	Cohort 3 (n = 7)	Total (N = 13)
Any Grade	3 (100)	3 (100)	7 (100)	13 (100)
Grade 3/4	3 (100)	1 (33)	4 (57)	8 (62)
Serious TEAE	1 (33)	0 (0)	3 (43)	4 (31)
Leading to dose modification	2 (67)	2 (67)	3 (43)	7 (54)
Leading to dose interruption	2 (67)	1 (33)	2 (29)	5 (39)
Leading to treatment discontinuation	1 (33)	0 (0)	0 (0)	1 (8)
Leading to death	0 (0)	0 (0)	1 (14)	1 (8)
Most common TEAE (≥ 25%), n (%)				
Neutropenia	3 (100)	2 (67)	6 (86)	11 (85)
Thrombocytopenia	2 (67)	2 (67)	4 (57)	8 (62)
Constipation	2 (67)	2 (67)	3 (43)	7 (54)
Leukopenia	1 (33)	2 (67)	4 (57)	7 (54)
Hypocalcemia	1 (33)	2 (67)	4 (57)	7 (54)
Decreased appetite	2 (67)	1 (33)	3 (43)	6 (46)
Anemia	2 (67)	2 (67)	1 (14)	5 (39)
Diarrhea	1 (33)	1 (33)	3 (43)	5 (39)
Fatigue	1 (33)	1 (33)	3 (43)	5 (39)
Nausea	2 (67)	1 (33)	2 (29)	5 (39)
Chills	2 (67)	2 (67)	0 (0)	4 (31)
Dyspnea	0 (0)	1 (33)	3 (43)	4 (31)
Hyperglycemia	1 (33)	1 (33)	2 (29)	4 (31)
Insomnia	0 (0)	3 (100)	1 (14)	4 (31)
Sinus bradycardia	1 (33)	1 (33)	2 (29)	4 (31)
Grade 3/4 TEAE (≥ 25%), n (%)				
Neutropenia	3 (100)	1 (33)	3 (43)	7 (54)

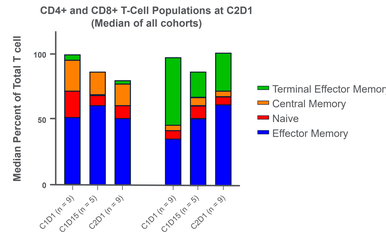
SMd Demonstrated Preliminary Signs of Efficacy

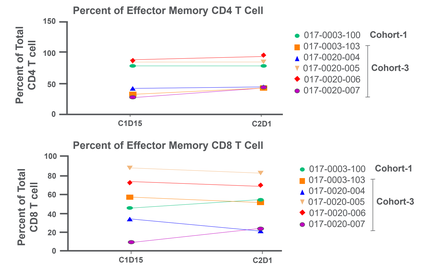


C, cycle; EOT, end of treatment.

- As of Oct 10, 2025, 12 patients have had a response assessment
- The objective response rate (ORR) by investigator was 50% (6/12)
  - Six had a very good partial response (VGPR) or better (50%)
- The clinical benefit rate (CBR) (≥ MR) was 50% (6/12)

SMd Induces a Sustained Effector Phenotype in CD4 and CD8 T-Cell Populations Following Drug Holiday in Primary Patient Samples

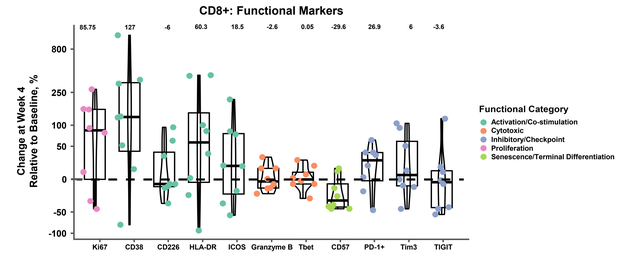




Naive: CD45RA+/ CCR7+ Central Memory: CD45RA-/ CCR7+ Effector Memory: CD45RA-/ CCR7- Terminal effector memory: CD45RA+/ CCR7-

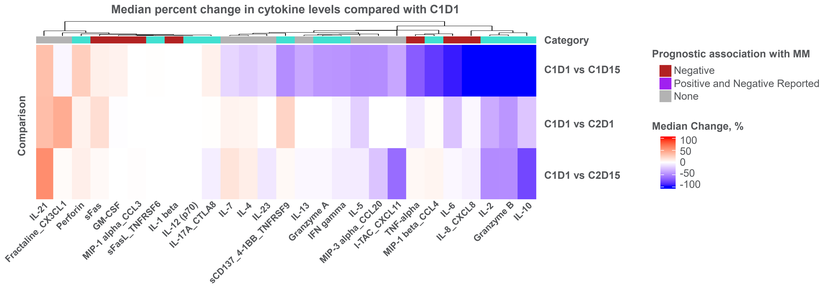
- Median increase in the total number of effector memory CD4 and CD8 T cells were seen after SMd treatment
- The percentage of effector cells was persistent even during dose holiday

SMd Results in CD8+ T-Cell Proliferation and Activation



- Increase in median expression of markers related to CD8 expansion (Ki67, CD38) and MHC-II expression (HLA-DR) and decrease in marker of senescence (CD57) were observed across all dose cohorts
- There were mixed results for change in immune checkpoints and granzyme B

SMd Upregulates T-cell Activation Related Cytokines and Suppresses Pro-inflammatory Cytokines Inversely Associated With Poor MM Prognosis



- Cytokine panel testing in primary patient samples indicated increased T-cell activation signaling (IL-21, Perforin) during on- (C1D15, C2D15) and off-treatment (C2D1) periods
- Pro-inflammatory cytokines and IL-8, IL-6, and TNF-alpha decreased modestly with SMd treatment. These cytokines have also been shown to negatively correlate with MM prognosis[8-10]

Conclusions and Future Directions

- The RP2D of SMd in RRMM is selinexor 60 mg on D1, 8, 15; mezigdomide 0.6 mg on D1-21, and dexamethasone 40mg weekly in a 28-day cycle. Dose limiting toxicities were Grade 2 proctitis and extended Grade 4 neutropenia
- TEAEs were consistent with known selinexor and mezigdomide toxicities, and no new safety signals were detected
- Initial data for this all-oral combination of SMd at dose level 2 demonstrated preliminary signs of efficacy with an overall response rate of 50% in a heavily-pretreated RRMM population that had either failed or was otherwise ineligible to receive a T-cell redirecting therapy. At data cutoff, 5/13 enrolled subjects remained on treatment, with three patients exceeding 11 months of treatment
- Preliminary correlative testing indicated increased T-cell activation and decreases in pro-inflammatory cytokines while on SMd treatment
- Ongoing results support the continued investigation of SMd in patients with RRMM with selinexor 60 mg QW + mezigdomide 0.6 mg QD + dexamethasone 40 mg QW as the RP2D
- Further exploration of 1-mg mezigdomide dosing in combination with selinexor and dexamethasone is anticipated given the DLT based on the Grade 2 proctitis that was pre-existing

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References: **1.** Binder AF, et al. *Front Immunol*. 2023;14:1275329. **2.** Xpovio [package insert]. Newton, MA: Karyopharm Therapeutics, Inc; 2022. **3.** Mehta PH, et al. *Front Immunol*. 2023;12:780442. **4.** Kashyap T, et al. *Antiviral Res*. 2021;192:105115. **5.** Kang Y, et al. *Blood Immunol Cell Ther*. 2025;1(3):100009. **6.** Jeyaraju DV, et al. *Blood*. 2022;140(suppl 1):7070–7071. **7.** Richardson PG, et al. *N Engl J Med*. 2023;389:1009-1022. **8.** Zhang XG, et al. *Blood*. 1989;74:11–13. **9.** Herrero AB, et al. *Am J Path*. 2016;186:2171–2182. **10.** Jourdan M, et al. *Eur Cytokine Netw*. 1999;10:65–70.

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