A phase 3, two-stage, randomized study of mezigdomide, bortezomib, and dexamethasone versus pomalidomide, bortezomib, and dexamethasone in relapsed/refractory multiple myeloma: SUCCESSOR-1

MM-372

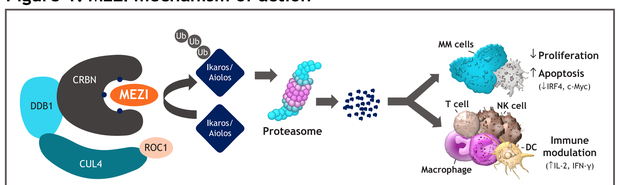
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Introduction

- Mezigdomide (MEZI; CC-92480) is a novel, potent, oral cereblon (CRBN) E3 ligase modulator (CELMoD™) that has been specifically optimized to achieve rapid and deep degradation of the key hematopoietic transcription factors Ikaros and Aiolos[1,2] (**Figure 1**)
  - Preclinical and translational data suggest a differentiated profile of MEZI from immunomodulatory drugs (IMiDs®), including unique CRBN-binding interactions[3-5]
- MEZI demonstrates superior tumoricidal and immune-modulatory effects compared with IMiD agents, and has shown promising results in combination with proteasome inhibitors (PIs)[1]
  - Preclinically, MEZI in combination with a PI and dexamethasone (DEX) displays more potent tumoricidal activity than pomalidomide (POM) plus a PI and DEX[6]
  - Preliminary phase 1/2 trial results have demonstrated promising efficacy and safety of MEZI in combination with bortezomib (BORT) and DEX (Vd) in patients with relapsed/refractory multiple myeloma (RRMM)[7]

Figure 1. MEZI mechanism of action



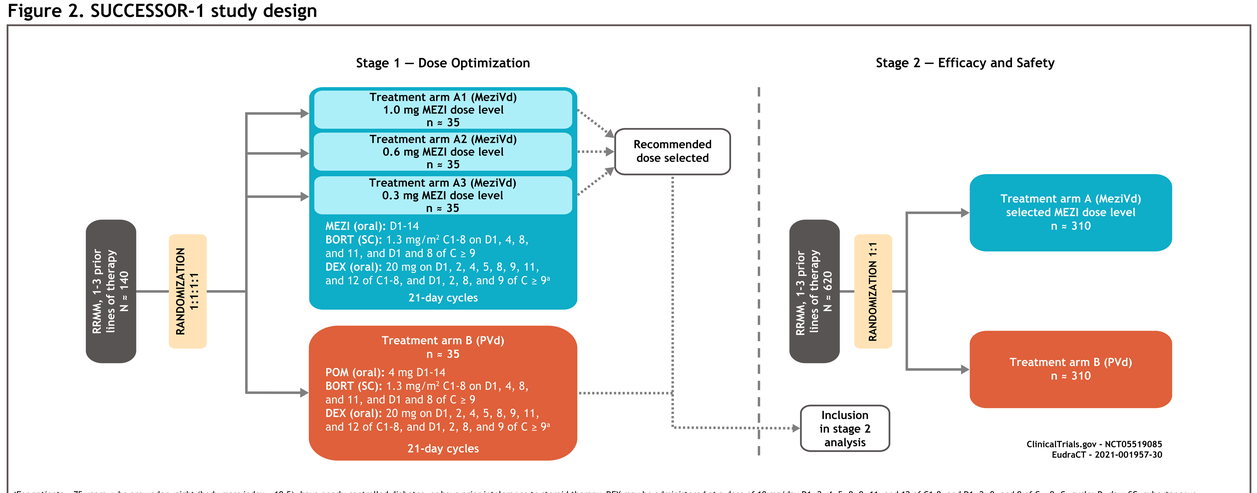
c-Myc, cellular Myc; CUL4, cullin 4; DC, dendritic cell; DDB1, DNA damage-binding protein 1; IFN, interferon; IL, interleukin; IRF4, interferon regulatory factor 4; MM, multiple myeloma; NK, natural killer; ROC1, regulator of cullins-1; Ub, ubiquitin.

Objective

- To describe SUCCESSOR-1, a two-stage, multicenter, randomized, open-label, phase 3 trial comparing the efficacy and safety of MEZI, BORT, and DEX (MeziVd) versus POM, BORT, and DEX (PVd) in patients with RRMM and prior lenalidomide (LEN) exposure (NCT05519085)

Methods

Figure 2. SUCCESSOR-1 study design



[a]For patients > 75 years, who are underweight (body mass index < 18.5), have poorly controlled diabetes, or have prior intolerance to steroid therapy, DEX may be administered at a dose of 10 mg/day D1, 2, 4, 5, 8, 9, 11, and 12 of C1-8, and D1, 2, 8, and 9 of C ≥ 9. C, cycle; D, day; SC, subcutaneous.

Table 1. Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years • ECOG PS 0-2 • Measurable disease per IMWG criteria • 1–3 prior lines of therapy • ≥ MR achieved with ≥ 1 prior lines of therapy • Prior LEN tx • Progression ≤ 60 days of last dose of BORT maintenance (Q2W or less) are not excluded • PD during or after last regimen	• Prior tx with MEZI or POM • PD < 60 days of last PI dose • PI refractoriness (except to BORT maintenance dosed Q2W or less) • Prior BORT tx with best response < MR, or BORT discontinuation due to toxicity • Prior investigational agents < 28 days • Plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome, or clinically significant light-chain amyloidosis • MM with central nervous system involvement • Peripheral neuropathy ≥ grade 2

ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; MR, minimal response; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes; Q2W, every 2 weeks; tx, treatment.

Table 2. Study endpoints

Primary endpoint	
• PFS: time from randomization to PD or death, whichever occurs first	
Secondary endpoints	
• Determination of recommended MEZI dose in combination with Vd (part 1 only)	
• Overall survival	• PFS2
• Duration of response	• MRD negativity rate
• Overall response rate	• Safety
• Time to progression	• Health-related quality of life
• Time to response	• PK analyses
• Time to next treatment	• Biomarker analyses

MRD, measurable residual disease; PFS2, time from randomization to progression on second-line therapy; PK, pharmacokinetics.

Study design

- Global, multicenter, open-label phase 3 study to be conducted in 2 stages to compare the efficacy and safety of MeziVd versus PVd in patients with RRMM (**Figure 2**)
  - The purpose of stage 1 is to identify the optimal MEZI dose in combination with Vd based on Project Optimus by the United States Food and Drug Administration and on activity noted at all tested dose levels
  - In stage 2, the selected dose of MEZI with Vd will continue to enroll along with the control arm (PVd)
- Key eligibility criteria are shown in **Table 1** and study endpoints are shown in **Table 2**
- Progression-free survival (PFS) will be compared between treatment arms stratified by baseline stratification factors used in the randomization
  - Randomization stratification factors:
    - Prior lines of therapy (1 vs > 1)
    - Age (≤ 70 vs > 70 years)
    - International Staging System stage at screening (I vs II vs III)
- Treatment continues until confirmed disease progression (PD) or unacceptable toxicity

Conclusions

- Preclinical evidence has shown that MEZI displays more potent tumoricidal activity than POM when combined with DEX and a PI, and in a phase 1/2 trial, MeziVd demonstrated encouraging efficacy and safety in RRMM[6,7]
- SUCCESSOR-1 is a head-to-head phase 3 study comparing the efficacy and safety of MeziVd with PVd in patients with RRMM and prior LEN exposure
- Enrollment began in September 2022 and is ongoing

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