Preliminary Results of the Oral CD73 Inhibitor, ORIC-533, in Relapsed/Refractory Multiple Myeloma (RRMM)

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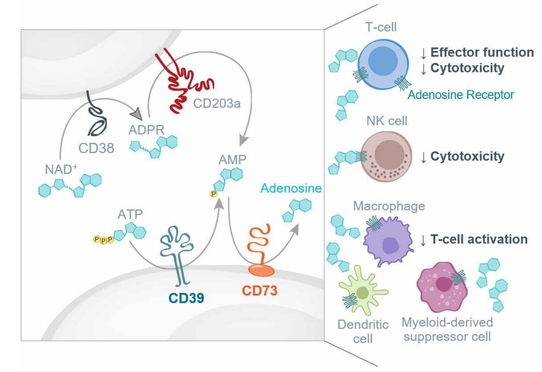
BACKGROUND

Adenosine Pathway Components Are Expressed in Multiple Myeloma



- Immunosuppressive adenosine generation from adenosine monophosphate (AMP) requires the activity of the cell surface ecto-5′-nucleotidase, CD73
- Relapsed/refractory multiple myeloma (RRMM) is adenosine rich
  - Adenosine pathway components are highly expressed on MM cells and on many cell types within the MM niche
  - Adenosine levels in bone marrow are significantly higher in MM patients
  - High CD73 and adenosine are associated with poor prognosis and therapeutic resistance in multiple myeloma
- CD73 inhibition reverses immunosuppression and triggers lysis of RRMM cells in autologous ex vivo assays

Yang R *et al*., J Immunother Cancer 2020; Horenstein A *et al*., Mol Med 2016; Ray A *et al*., Blood 2019; Ray A *et al*., Blood 2021; Ray A *et al*., Clinical Lymphoma Myeloma and Leukemia 2021; Ray *et al*., Blood Cancer J 2022; Junttila *et al*., Blood 2022

STUDY DESIGN

First-in-human, multicenter, dose escalation (Part 1), followed by dose expansion (Part 2)
Phase 1b study (NCT05227144)

PATIENT POPULATION
- Diagnosis of multiple myeloma with relapsed or refractory disease according to IMWG criteria
- Refractory to or not eligible for MM treatment regimens that are known to provide clinical benefit
- Measurable disease
- ECOG 0-2
- Adequate bone marrow, renal, hepatic, pulmonary, and cardiac function

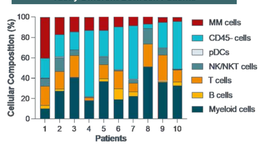
STUDY OBJECTIVES
- Selection of RP2D
- Overall safety and tolerability as a single agent
- Pharmacokinetics
- Antimyeloma activity

Data cutoff Nov 2, 2023 (n=22); PK/PD analyses include data through dose level 4 (1600 mg) (n=19)

BASELINE CHARACTERISTICS

- 22 patients enrolled across 5 dose levels
- Heavily pretreated patient population
  - Median number of prior therapies: 6.5
  - 100% triple-class refractory
  - 96% penta-refractory
  - 59% received prior anti-BCMA/CD3 bispecific or BCMA CAR-T therapy

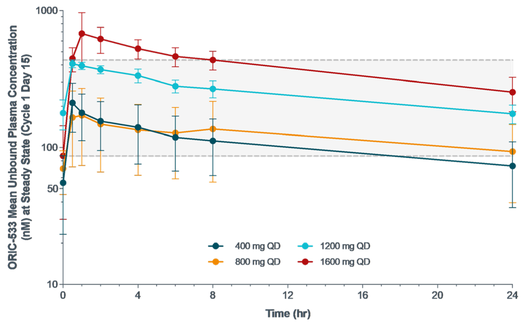
Bone Marrow Milieu at Time of Screening Is Vastly Different Between Patients



	All Patients (N=22)
Age, years, median (range)	67.1 (40, 84)
Females, n (%)	11 (50)
ECOG performance score, n (%)	
0	8 (36)
1	13 (59)
2	1 (5)
Prior lines of therapy, median (range)	6.5 (3 – 16)
Prior therapies, n (%)	
Triple-class refractory disease	22 (100)
Penta-refractory disease	21 (96)
Previous anti-BCMA/CD3 bispecific therapy	7 (32)
Previous BCMA CAR-T therapy	8 (36)
Time since initial diagnosis, years, median (range)	6.5 (1.8, 16.8)
High risk cytogenetics, n (%)	9 (41)
Current status on study	
Ongoing	3 (14)
Disease progression	16 (73)
Adverse event	1 (5)
Noncompliance	1 (5)
Withdrawal of consent	1 (5)

ORIC-533 PHARMACOKINETICS

- Favorable pharmacokinetic profile
  - Increased exposure with higher dose levels
  - Estimated plasma half-life of ~24 hours supports QD dosing
  - Plasma exposure reflects exposure in bone marrow at C2D1 (data not shown)
- Exposures at 1600 mg QD:
  - Correspond to efficacy in ex vivo model systems



Note: The shaded area represents the extrapolated human plasma concentration, adjusted for plasma protein binding, that achieves cytolytic activity against RRMM tumor cells in autologous patient ex vivo experiments

ORIC-533 SAFETY PROFILE

- Well tolerated safety profile with no Grade ≥3 treatment-related toxicities
- No dose-limiting toxicities, dose reductions, or treatment-related serious adverse events

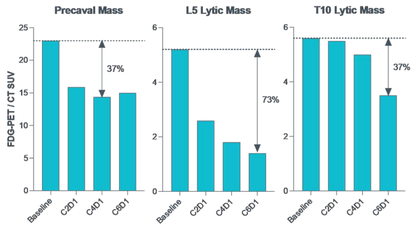
All Treatment-Related Adverse Events (TRAEs)

Dose Level (QD)	400 mg (n=4)		800 mg (n=4)		1200 mg (n=4)		1600 mg (n=7)		2400 mg (n=3)		Total (N=22)	
Preferred Term n (%)	Grade 1/2	Grade ≥3	Grade 1/2	Grade ≥3	Grade 1/2	Grade ≥3	Grade 1/2	Grade ≥3	Grade 1/2	Grade ≥3	Grade 1/2	Grade ≥3
Fatigue	1 (25)	–	–	–	–	–	1 (14)	–	–	–	2 (9)	–
Rash	–	–	–	–	2 (50)	–	–	–	–	–	2 (9)	–
Anemia	1 (25)	–	–	–	–	–	–	–	–	–	1 (5)	–
Diarrhea	–	–	–	–	–	–	1 (14)	–	–	–	1 (5)	–
Dizziness	1 (25)	–	–	–	–	–	–	–	–	–	1 (5)	–
Eye redness	–	–	–	–	1 (25)	–	–	–	–	–	1 (5)	–
Hypophosphatemia	–	–	–	–	1 (25)	–	–	–	–	–	1 (5)	–
Peripheral sensory neuropathy	–	–	–	–	–	–	1 (14)	–	–	–	1 (5)	–
Platelet count decreased	1 (25)	–	–	–	–	–	–	–	–	–	1 (5)	–
WBC count decreased	–	–	–	–	1 (25)	–	–	–	–	–	1 (5)	–

PATIENT VIGNETTES

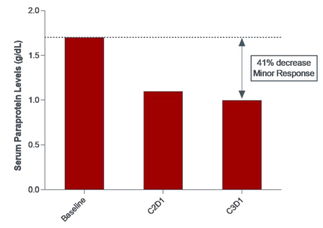
- **History:** 74-year-old male with extramedullary multiple myeloma (initial diagnosis 2015)
- **Prior therapy:** 4 prior lines of therapy, including:
  - Proteosome inhibitor (x2)
  - IMiD (x2)
  - Anti-CD38
  - Autologous transplant
- **ORIC-533 dose:** 1200 mg QD
- **Clinical activity:**
  - Non-secretory myeloma (i.e., no measurable serum or urine paraprotein)
  - FDG-PET/CT of extramedullary plasmacytomas shows
    - Stable disease per RECIST 1.1
    - Decrease in SUV ranging from 37% to 73% across 3 lesions
- **Grade ≥2 TRAEs:** G2 hypo-phosphatemia
- **Duration of treatment:** Completed 7 cycles (6.5 months) followed by disease progression

FDG-PET / CT Standardized Uptake Values (SUV)



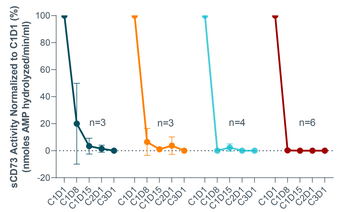
- **History:** 55-year-old female with multiple myeloma (initial diagnosis 2021)
- **Prior therapy:** 4 prior lines of therapy, including:
  - Proteosome inhibitor (x2)
  - IMiD (x2)
  - Anti-CD38
  - Autologous transplant
  - Anti-BCMA/CD3 bispecific MAb (most recent therapy)
- **ORIC-533 dose:** 1600 mg QD
- **Clinical activity:**
  - 41% decrease in serum paraprotein by C3D1
  - Improvement in baseline thrombocytopenia
  - 80% decrease in sBCMA
- **Grade ≥2 TRAEs:** None reported
- **Duration of treatment:** Completed 3 cycles (2.8 months) followed by disease progression

Serum Paraprotein Levels



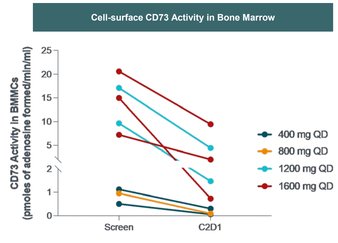
ORIC-533 TARGET ENGAGEMENT

Soluble CD73 Activity in Serum



- ORIC-533 inhibits soluble CD73 enzymatic activity in serum
  - Near complete inhibition by C1D15 in serum of all patients across all dose levels
  - Complete and sustained inhibition by C1D8 in all patients at 1600 mg QD

Cell-surface CD73 Activity in Bone Marrow

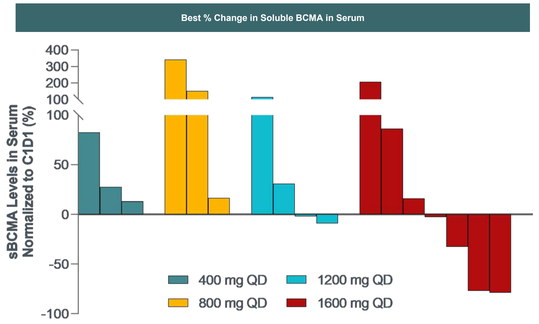


- ORIC-533 inhibits cell-surface CD73 activity on bone marrow mononuclear cells (BMMCs)
  - 50-95% inhibition observed in the bone marrow after one treatment cycle
  - Largest suppression observed at the highest dose level tested (1600 mg QD)

SERUM B-CELL MATURATION ANTIGEN

- Soluble BCMA (sBCMA) reduction has been reported to correlate with clinical response on treatment (Ghermezi *et al*., Haematologica 2017; Burjarski *et al*., Target Oncol 2021; Wiedemann *et al*., Pathol Oncol Res 2023)
- Notable reduction in sBCMA marker observed at the highest dose of 1600 mg QD
  - 70-80% reduction in circulating sBCMA after 2 treatment cycles in 2 patients at 1600 mg QD
  - No or minimal reductions at lower dose levels

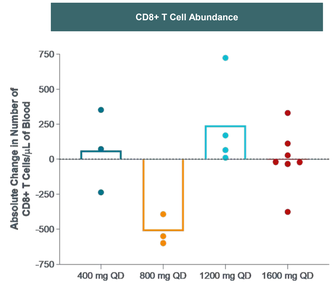
Best % Change in Soluble BCMA in Serum



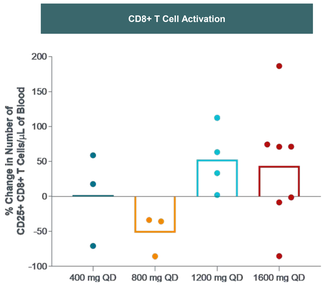
ORIC-533 IMMUNE CELL ACTIVATION (T CELLS)

- Initial evidence of immune activation in the majority of patients treated at 1200 or 1600 mg QD
  - Increased abundance of CD8+ T cells in blood, and/or
  - Enhanced CD8+ T cell activation (CD25+) in blood

CD8+ T Cell Abundance



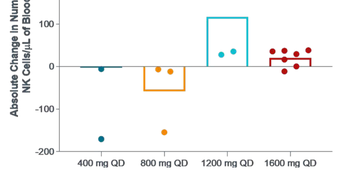
CD8+ T Cell Activation



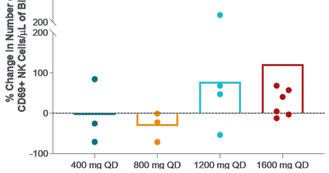
ORIC-533 IMMUNE CELL ACTIVATION (NK CELLS)

- Initial evidence of immune activation in the majority of patients treated at 1200 or 1600 mg QD
  - Increased abundance of NK cells in blood, and/or
  - Enhanced NK cell activation (CD69+) in blood
- Similar immune activation observed with alternate markers CD25 and NKp44 (data not shown)

NK Cell Abundance



NK Cell Activation



CONCLUSIONS

ORIC-533 exhibits potential best-in-class properties and is the first oral CD73 inhibitor to enter clinical development for multiple myeloma

- Highly potent adenosine pathway inhibitor
- Clinical half-life of ~24 hours supports QD dosing
- Well tolerated safety profile with no Grade ≥3 TRAEs
- Complete/substantial inhibition of CD73 activity in serum and BM
- At doses of ≥1200 mg, evidence of immune modulation of CD8+ T cells and NK cells
- At doses of 1600 mg, meaningful reductions in sBCMA levels, suggestive of antimyeloma activity
- Preliminary evidence of clinical antimyeloma activity, including reductions in paraprotein, demonstrated in multiple patients with RRMM

ORIC-533 is an ideal combination candidate with other immune-based antimyeloma therapies, including anti-CD38 antibodies, anti-BCMA/CD3 bispecific antibodies, and BCMA CAR-T therapies

American Society of Hematology, December 9-12, 2023

Thank you to the patients, their families, and caregivers

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