ELSEVIER

Blood 142 (2023) 4761–4762

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

653.MULTIPLE MYELOMA: PROSPECTIVE THERAPEUTIC TRIALS

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

Cesar Rodriguez, MD[1], *Scott R. Solomon, MD*[2], *Barry Paul*[3], *Omar Nadeem, MD*[4], *Meenal Patel*[5], *Jian Wang*[5], *Rongda Xu*[5], *Melissa Junttila, PhD*[5], *Anneleen Daemen, PhD*[6], *Subhash Katewa, PhD*[5], *Pratik S Multani, MDMS*[7], *Wilson I. Gonsalves, MD*[8]

[1] Department of Medicine, Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York
[2] Northside Hospital Cancer Institute, Atlanta, GA
[3] Levine Cancer Institute, Charlotte, NC
[4] Dana-Farber, Boston, MA
[5] ORIC Pharmaceuticals, South San Francisco, CA
[6] ORIC Pharmaceuticals, SOUTH SAN FRANCISCO, CA
[7] ORIC Pharmaceuticals, San Diego, CA
[8] Division of Hematology, Mayo Clinic, Rochester, MN

Background: Although recently available immune-based approaches in multiple myeloma produce high response rates, curative outcomes have not yet been achieved, which highlights the need for new agents that further activate the immune system without increasing toxicity. ORIC-533 is a highly potent and selective, orally bioavailable, small molecule inhibitor of CD73, an enzyme expressed by various cell types, including immune cells and which catalyzes the generation of adenosine from adenosine monophosphate (AMP) (Allard 2019). Adenosine itself is highly immunosuppressive, diminishing activity of a range of immune cell types, including T, NK, and dendritic cells (Young 2014). By blocking adenosine production from AMP via inhibition of CD73, ORIC-533 has demonstrated the ability to restore and enhance immune function. Multiple myeloma (MM) patient bone marrow (BM) contains multiple cell types that also express CD73, including immune cells, cancer-associated fibroblasts, mesenchymal stem cells, and endothelial cells (Allard 2019). Moreover, elevated adenosine levels in the MM BM niche correlate with disease progression (Horenstein 2016; Yang 2020). We have previously observed that CD73-mediated adenosine activity suppresses the cytolytic antitumor immune function in the MM BM milieu (Ray 2022). ORIC-533 treatment reduced adenosine production, overcame this immune suppression with evidence of restored DC-mediated priming and activated cytotoxic CD8 $^{+}$ T-cell function, and significantly enhanced immune cell cytolytic behavior against RRMM tumor cells in autologous patient ex vivo experiments (Junttila 2022), making ORIC-533 a potential immunotherapy for patients with MM.
Methods: ORIC-533-01 (NCT05227144) is an ongoing i3+3 Phase 1b dose escalation study in patients with RRMM. The primary objectives are to determine single agent safety/tolerability and pharmacokinetics (PK) of ORIC-533 to select the RP2D. Pharmacodynamic assessments include measurement of CD73 functional activity in serum and BM, as well as enumeration of immune cell subsets and activation state in blood and BM. Patients are also evaluated for clinical efficacy using IMWG criteria.
Results: As of 23 June 2023, 17 patients received ORIC-533 once daily across 4 dose levels (400 mg to 1600 mg). All patients were triple-class refractory, 88% were penta-refractory, and 59% also received prior anti-BCMA/CD3 bispecific therapy or anti-BCMA CAR-T therapy. Overall, ORIC-533 was very well tolerated, with 5 patients experiencing a total of 10 treatment-related adverse events (TRAEs). Fatigue was the only G3 AE and the only TRAE seen in more than 1 patient (1 event each of G3 and G2); all other events seen in 1 patient each, were G1 or G2 in severity, and of no specific system organ class. No dose limiting toxicities, no Grade ≥4 TRAEs, and no treatment-related serious adverse events have been observed. PK showed increased exposure with dose with a plasma half-life of ~24 hrs. Soluble CD73 enzymatic activity was nearly completely inhibited by C1D15 in serum of all patients across all dose levels, while the largest relative suppression in surface CD73 activity in BM cells was observed at the highest dose level. There was also evidence for increases in the abundance of circulating NK and CD8+ T cells after 1 treatment cycle, with preliminary evidence of enhanced CD8+ T-cell activation at the highest dose levels tested in both peripheral blood and BM. In addition, early evidence of single agent clinical activity was observed.
Conclusions: ORIC-533 has demonstrated an acceptable safety profile and preliminary evidence of immune activation in a heavily pretreated RRMM patient population. Enrollment is ongoing and updated data will be presented.

Disclosures Rodriguez: *Janssen, Takeda, Bristol Myers Squibb, Amgen, Karyopharm Therapeutics:* Membership on an entity's Board of Directors or advisory committees. **Paul:** *Janssen:* Membership on an entity's Board of Directors or advisory committees. **Nadeem:** *BMS:* Membership on an entity's Board of Directors or advisory committees; *Takeda:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *GSK:* Membership on an entity's Board of Directors or advisory committees; *GPCR Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding. **Patel:** *ORIC Pharmaceuticals:* Current Employment. **Wang:** *ORIC Pharmaceuticals:* Current Employment. **Xu:** *ORIC Pharmaceuticals:* Current Employment. **Junttila:** *ORIC Pharmaceuticals:* Current Employment. **Daemen:** *ORIC Pharmaceuticals:* Current Employment. **Katewa:** *ORIC Pharmaceuticals:* Current Employment. **Multani:** *ORIC Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company.

https://doi.org/10.1182/blood-2023-173730