FIRST-IN-HUMAN PHASE 1 STUDY OF THE NOVEL CELMOD AGENT CC-92480 COMBINED WITH DEXAMETHASONE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

Author(s): Paul G. Richardson, Annette J. Vangsted, Karthik Ramasamy, Suzanne Trudel, Joaquín Martínez, María-Victoria Mateos, Paula Rodríguez-Otero, Sagar Lonial, Rakesh Popat, Albert Oriol, Chatchada Karanes, Robert Z. Orlowski, Jesus G. Berdeja, Pekka Anttila, Martin Kaiser, C. Ola Landgren, Lilly Wong, Chenyang Shi, Manisha Lamba, Evelyn Barnett, Alix Harding, Zariana Nikolova, Daniel W. Pierce, Michael Pourdehnad, Nizar J. Bahlis

Background

CC-92480 is a novel cereblon E3 ligase modulator (CELMoD) agent designed for rapid, maximal degradation of Ikaros and Aiolos. In vitro, it has enhanced antiproliferative and tumoricidal activity in multiple myeloma (MM) cell lines, including those resistant to lenalidomide (LEN) and pomalidomide (POM), with strong immune stimulatory activity.

Aims

This phase 1, multicenter, dose-escalation study (NCT03374085) evaluated the maximum tolerated dose (MTD), recommended phase 2 dose, safety, tolerability, and pharmacokinetics of CC-92480 + dexamethasone (DEX) in heavily pretreated patients with relapsed/refractory MM (RRMM).

Methods

Eligible patients had disease progression on or within 60 days of their last MM therapy and were either resistant or intolerant to, or not otherwise candidates for, currently available therapies. Several treatment schedules evaluated escalating doses of CC-92480 + DEX (40 mg, or 20 mg if ≥ 75 years of age).

Results

As of December 24, 2019, 66 patients had received CC-92480 + DEX. Median age was 67 years (range 40–78), and median number of prior regimens was 6 (range 2–13). Prior therapies included stem cell transplantation (67%), bortezomib (92%), LEN (89%), POM (83%), and anti-CD38 antibodies (78%). CC-92480 doses and schedules explored included 0.1–1.0 mg once daily (QD) (10/14 days), 0.8–1.0 mg QD (21/28 days), 0.2–0.8 mg twice daily (3/14 days), and 1.6–2.0 mg QD (7/14 days). The MTD was 1.0 mg for both 10/14 days and 21/28 days schedules.

Grade 3–4 treatment-emergent adverse events (TEAEs) were reported in 58 (88%) patients. Most frequent grade 3–4 TEAEs included neutropenia (53%), infections (30%), anemia (29%), and thrombocytopenia (17%), with 9% grade 3 fatigue. Among the different cohorts, 10 patients had dose-limiting toxicities, the majority of which were related to neutropenia.

The overall response rate (ORR) was 21% (9 very good partial responses [VGPRs]; 5 partial responses [PRs]). Efficacy was dose- and schedule-dependent; across two 1.0 mg QD schedules

(10/14 days and 21/28 days), 10 of 21 (48%) patients responded (7 VGPRs and 3 PRs), with response independent of refractoriness to prior immunomodulatory drugs (IMiDs).

Plasma exposure and peripheral blood Ikaros and Aiolos degradation were dose-dependent. CC-92480 significantly decreased Ikaros and Aiolos in bone marrow plasma cells, including those of LEN- and POM-refractory patients.

Conclusion

TEAEs associated with CC-92480 were related mainly to myelosuppression in heavily pretreated, including triple-class-refractory (refractory to at least one IMiD drug, one proteasome inhibitor, and one anti-CD38 antibody), patients with RRMM. Promising activity with 48% ORR at therapeutic doses was observed. The study is ongoing to further optimize the dose and schedule, with combination studies underway and dose-expansion cohorts planned.

Session topic: 14. Myeloma and other monoclonal gammopathies – Clinical

Keyword(s): Ikaros, Multiple myeloma, Phase I/II, Refractory