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Preliminary safety and efficacy of TH-302, an investigational hypoxia-targeted drug, and dexamethasone (dex) in patients (pts) with relapsed/refractory multiple myeloma (RR MM)

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Background: While alkylators, IMiDs and proteasome inhibitors are current standard treatment for pts with MM, the presence of hypoxia in the diseased bone marrow (Colla, *Leukemia* 2010) presents a new therapeutic target for MM. TH-302 is a novel 2-nitroimidazole prodrug of the DNA alkylator bromo-isophosphoramide mustard that is selectively activated under hypoxia. Synergistic induction of apoptosis in MM cells by TH-302 and bortezomib was shown in MM models *in vivo* and *in vitro* (Hu et al, *Mol Cancer Ther* 2013). An ongoing Phase 1/2 study investigates TH-302 with dex in RR MM. In the dose-escalation stage of the study, the maximum tolerated dose (MTD) of biweekly TH-302 was established at 340 mg/m^2 and preliminary activity was reported based on the modified IMWG guidelines (Ghobrial et al., ASH 2013). The 340 mg/m² plus dex expansion arm is ongoing.

Methods: The Phase 1/2 open-label multicenter study investigates IV TH-302 (240-480 mg/m²) plus PO dex (40 mg) on Days 1, 4, 8 and 11 of a 21-day cycle. At the MTD, a Simon two-stage minimax design was implemented to pursue a regimen with ≥25% response rate or discontinue if ≤5% (90% power, 10% alpha).

Results: 16 pts (11 male, 5 female) were enrolled through completion of the initial stage of the Simon design, including 9 at the MTD. Median prior therapies was 6 (3 – 11) and median age 60 years (53 – 86). All had previously received both bortezomib and lenalidomide/thalidomide containing regimens and an alkylating agent. The most common ≥Gr 3 AEs were thrombocytopenia (44%) and leukopenia (38%). Dose limiting Gr 3 stomatitis was only reported in the 480 mg/m^2 cohort. 7 pts had SAEs, 6 of which were related to TH-302, including 3 pts with pneumonia. The pre-specified target for response for the initial 9-pt Simon stage at the MTD was achieved with 1 PR, 2 MRs, 4 SDs, 1 PD and 1 NA. To date, 15 of 24 pts have been enrolled to evaluate safety and efficacy at the MTD.

Conclusions: TH-302 can be administered at 340 mg/m^2 biweekly with dex. Preliminary clinical activity has been noted in pts with heavily pre-treated RR MM. Data from pts in the Simon two-stage treated at the MTD will be updated and presented at the meeting.