3271 Preclinical Development of Triptolide Derivative MRx102 as a Therapeutic Agent for Acute Myeloid Leukemia

Program: Oral and Poster Abstracts
Session: Acute Myeloid Leukemia - Therapy, excluding Transplantation: Poster III
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Acute Myeloid Leukemia (AML) is the most common form of adult acute leukemia and the second most common childhood leukemia. AML has the lowest survival rate among leukemias, and the frequency is increasing as the population ages. Current therapies are inadequate, and a need exists for better therapeutic agents to treat AML, both as initial treatment for newly diagnosed patients and for those who have failed current therapy and relapsed. Natural products, such as taxol, have shown activities in a variety of disease states, including cancer. Triptolide is a natural product diterpenoid derived from *Tripterygium wilfordii* Hook f, and has shown anti-cancer activity in a broad range of solid tumors in preclinical models. It induces apoptosis in various leukemic cell lines and primary AML blasts (Carter, B *et al*, *Blood* 2006). Derivatives of triptolide with improved pharmacokinetics and bioavailability offer the opportunity to optimize the activity of triptolide for clinical application in AML. MRx102 is a triptolide derivative that is more hydrophobic than triptolide. It has potent in vitro cytotoxic activity with human tumor and leukemia cell lines, an unusual result for triptolide derivatives because they are usually much less active in vitro than the parent compound. Designed as a prodrug, MRx102 exerts cytotoxic activity with human AML cell lines and other human leukemia cell lines without pre-incubation with plasma esterases (IC_{50} of 51.0 and 37.1 nM with MV4-11 AML cells at 48 and 72 hours, respectively, ~55% and ~36% of the activity of triptolide, respectively). MRx102 decreases the viable CD34+ blasts of AML patient samples (a mean of 79.8 ± 8.8% specific apoptosis at 100 nM, n=3), and overcomes the apoptosis protection by co-cultivated stromal cells (with a similar mean of 74.1 ± 8.5%). MRx102 shows dose-dependent anti-tumor activity with the MV4-11 cell line in nude mouse human AML tumor xenografts. After 42 days of MRx102 dosing at 1.35 mg/kg/day i.p., tumor volume was inhibited by 99.7%. Tumors removed from several mice

appeared to be Matrigel pellets rather than vascularized tumors, suggesting that many of the tumors were completely eliminated. In studies with the OCI-AML3 human AML cell line xenograft model, the group receiving MRx102 at 1.35 mg/kg/day i.p. showed similar high activity, with mean tumor volume reduced by as much as 99.2% on day 23 compared to the vehicle control group. Tumors of 7 of 10 mice were smaller than the day 0 volumes at the day 28 end of the study. As part of drug development, toxicology testing with MRx102 was initiated with an acute single dose rat toxicology study with no deaths and no adverse signs up to the top dose of 3.0 mg/kg MRx102 in DMSO/PBS administered i.v. The maximum tolerated dose (MTD) is greater than 3 mg/kg of MRx102, and the no observable adverse effect level (NOAEL) is at least 3 mg/kg. A 7-day subacute rat toxicology study of MRx102 showed no deaths and no adverse signs up to the top dose of 1.5 mg/kg/day MRx102 in DMSO/PBS administered daily i.v. for 7 days. The histopatholgy report shows no findings related to administration of the test article. The MRx102 MTD is greater than 1.5 mg/kg/day, and the NOAEL is at least 1.5 mg/kg/day. Previously observed NOAELs for related compounds have been less than 0.1 mg/kg/day. The current studies show potent anti-tumor activity as well as an unusually positive safety profile for MRx102 when compared to triptolide and other triptolide derivatives. Further MRx102 drug development is underway, with the intention of submitting an Investigational New Drug application to the Food and Drug Administration leading to clinical evaluation of MRx102 in AML patients. Updated results on current drug development activities will be presented at the meeting. This work is supported in part by NCI SBIR Contract HHSN261200900061C to MyeloRx LLC.

Disclosures: Fidler: *MyeloRx LLC:* Employment, Equity Ownership, PI for an NCI Contract to MyeloRx LLC, Patents & Royalties. **An:** *MyeloRx LLC:* Employment, Equity Ownership, participant in research under an NCI SBIR Contract to MyeloRx LLC. **Musser:** *MyeloRx LLC:* Employment, Equity Ownership, Patents & Royalties, participant in research under an NCI SBIR Contract to MyeloRx LLC. **Mak:** *MyeloRx LLC:* participant in research under an NCI SBIR Contract to MyeloRx LLC. **Carter:** *MyeloRx LLC:* participant in research under an NCI SBIR Contract to MyeloRx LLC. **Andreeff:** *MyeloRx LLC:* Consultancy, participant in research under an NCI SBIR Contract to MyeloRx LLC.

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