**Phase I/ib study of the novel CD20-targeted immunotoxin MT-3724 in relapsed/refractory non-Hodgkin’s B-cell lymphoma**

Michelle A. Fanale1, Paul A. Hamlin, Jr., Catherine S. Gierga1, Steven I. Park2, David J. Valacis4, Jack P. Higgins2, Anas Younes2

1Department of Pathology and Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; 2Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; 3Department of Medicine, University of North Carolina, Chapel Hill, NC; 4Department of Pharmaceutical Sciences, School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC.

**Background**

- In 2016 an estimated 72,000 new cases and 23,153 deaths attributable to non-Hodgkin’s B-cell lymphoma (NHL) will occur in the US (2016 American Cancer Society Cures). Most cases are incurable.
- Anti-CD20 monoclonal antibody (mAb) therapy is widely used for the treatment of NHL, but development of refractory disease to CD20 mAbs has been reported.
- There are several mechanisms by which disease may become refractory to CD20 MAb including increased MAb metabolism, initial development of CD20 MAb-resistant subclones with lower-affinity CD20 expression, resistance to MAb effector mechanisms and impaired immune cell function (Smith NH. Malignant lymphomas of action and resistance). 2003. J Clin Oncol 21:4163-4170.
- MT-3724 potently destroys a different mechanism of action (MAb), antigenic and immunoreactive immunotoxin, compared to currently available NHL therapies
- MT-3724 is the first successful immunotoxin to lend and interconvert against CD20 (a non-receptor interacting epitope).

**Mechanism of Action**

MT-3724’s mechanism of action is differentiated from currently available oncology therapeutics

MT-3724 inhibits protein translation by irreversibly and stereospecifically inactivating ribosomes, leading to ribotoxic stress, caspase activation, and apoptosis.

MT-3724 specifically targets and potently kills CD20 expressing cells, and demonstrates similar cytotoxicity on cells that lack CD20 surface expression.

**Preclinical Data Overview**

- MT-3724 demonstrates potent and specific activity against CD20+ B lymphocytes.
- MT-3724 exposure at day 12 due to anti-CD20 mAb.
- MT-3724 targets via CD20.
- MT-3724 (NHP) peripheral B cells.

**Pharmacodynamic & Pharmacodynamics**

- MT-3724 exposure demonstrates dose proportional increase.
- Increased levels of circulating NT cell (CD19+) resulted in lower MT-3724 serum half-life due to higher anti-CD20 mAb levels (CD19+).
- MT-3724 serum half-life (~1.3 h) comparable to other immunoconjugates.
- MT-3724 achieves significant reduction in peripheral B cells to be dose dependent.

**Pharmacokinetics & Pharmacodynamics**

- Table 2: Cycle 1 Day 1 Pharmacokinetic Parameters & Baseline B-cell Levels

**Safety**

- Table 3: Adverse Events (AEs)

**Efficacy**

- Table 4: Best Responses to MT-3724 Treatment

**Conclusions**

- MT-3724 appears well-tolerated up to 10 mg/kg/dose over repeated cycles of treatment.
- Clinical activity in dose as low as 5 mg/kg in a heavily pre-treated NHL population.
- Two responses observed in DLBCL – MDA may be a gatekeeping variable, NHL.
- Maximum tolerated dose exceeded at 100 mg/kg.
- CD20 MAb exposure appears to impact MT-3724.
- Week 12 period extended to 12-week for anti-CD20 Mab and enrollment continues.
- Further studies in refractory and induction settings are planned for MT-3724.