Abstract C105

Pediatric Preclinical Testing Program (PPTP) Stage 1 Evaluation of the CD56-Targeting Antibody-Drug Conjugate Lorvotuzumab Mertansine (IMGN901)

Lorvotuzumab Mertansine (IMG901) is an antibody-drug conjugate composed of the following:
- The cytotoxic maytansinoid, DM1, a potent antimitotic agent that inhibits tubulin polymerization.
- The humanized monoclonal antibody lorvotuzumab (hu901), which selectively binds to CD56 (NCAM1, neural cell adhesion molecule).
- A disulfide linker covalently joining DM1 to lorvotuzumab (1-D-DM1 linked per antibody molecule).
- LM shows high level preclinical activity against CD56-expressing adult cancer xenografts.
- LM is currently in clinical trials for patients with CD56-positive cancers (e.g., small-cell lung cancer (SCLC), multiple myeloma, and Merkel cell carcinoma).
- The activity of LM was evaluated against the Pediatric Preclinical Testing Program (PPTP) in vitro panel and against selected CD56-expressing xenografts from the PPTP in vivo panel.

**Methods**

**In vitro**: in vitro testing was performed using DMS3CAN, a high-throughput immunohistochemical fluorescence-based digital image microscopy system (Keshelava, et al. Methods Mol Med. 110:139-153, 2005). LM and its cytotoxic moiety L-DM1-SMe were tested at clinical relevant concentrations. The PPTP consists of 80 childhood cancer xenografts with a standard 96 hour exposure period. Relative IC50 values were calculated using a model of the potency of LM and L-DM1-SMe against the PPTP cell lines.

**Immunohistochemistry for NCAM (CD56)**: Standard IHC methods were employed using DAKO Envision+ (Carpinteria, CA) and DAKO Rabbit Anti-CD56. Staining intensity was scored (0= negative, 1=weak, 2=moderate, 3=strong) and uniformity of staining was scored (<2% of cells stained = focal, 25% to 75% of cells stained = heterogeneous, and >75% of cells stained = homogeneous).

**In vivo**: Standard PPTP methods for in vivo testing were employed. For each xenograft line, 10 mice bearing SC tumors initiated treatment when the tumors were between 0.3-0.5 cm3. Treatment was initiated by the intravenous route using a weekly 3 schedule with a total treated tumor xenografts and cell lines. Molecular characterization of the PPTP models is in Neale, et al. (Clin Cancer Res 2006).

**Results**

**In vivo Results Summary & Conclusions**

- Lorvotuzumab Mertansine (LM) induced significant differences in EFS distribution compared to control in 15 of 17 (93%) of the evaluate solid tumor xenografts, including all 7 neuroblastoma xenografts.
- Objective responses were observed in 8 of 17 (47%) solid tumor xenografts (2 complete responses (CR) and 4 maintained CR (MCR)):
  - 3 of 7 neuroblastoma xenografts
  - 2 of 5 rhabdomyosarcoma xenografts
  - One Wilms tumor xenograft
- Each of the 6 xenografts achieving CR or MCR had homogeneous staining by IHC for NCAM (CD56) with expression levels of 3 or 3+.
- Comparison of LM in vivo activity to that previously described for vinblastine showed that neuroblastoma xenografts with data for both agents were more responsive to LM than to vinblastine.
- LM demonstrated target-directed activity in vitro and promising activity in vivo against CD56-expressing childhood cancers.

Lorvotuzumab Mertansine was provided for testing by Immunogen, Inc. Testing was supported by NCI NO1CM22226. The PPTP expression values are the expression index for the tumor to the median expression value for all PPTP xenografts and cell lines. Molecular characterization of the PPTP models is in Neale, et al. (Clin Cancer Res 2006).