TG-1601 is a novel BET inhibitor with strong binding affinity and long-lasting effect in preclinical models

**Background**

- BET ( bromodomain and extra-terminal) protein complex binds to acetylated histones on chromatin and participates in the regulation of gene transcription. Inhibition of BET protein binding to chromatin with small molecules selectively suppresses the transcription of sets of oncogenes, including MYC and BCL-2.

- TG-1601 (also CI-120) is a novel, selective and potent small molecule inhibitor of BET bromodomains. TG-1601 binds to the first and second bromodomains (BD1, BD2) of the BET family protein, BRD2, BRD3, BRD4, and HDAC with IC50 values ranging from 0.6 to 2 nM. MYC protein expression is strongly inhibited in the Mv-16-13 cancer cell line with an EC50 of 5 nM, as compared to the BD1 and BD2 YM in a variety of leukemia and myeloma cancer cell lines, indicating potent inhibition of cell proliferation.

**Time course and dose-response studies conducted in vitro bearing the Mv-16-13 xenograft showed that MYC protein expression was undetectable 3 hours following a single 25 mg/kg dose, with a TG-1601 tumor concentration of 5 nM achieved. Interestingly, at 24 h post-dose, while TG-1601 is cleared from the tumor, MYC protein levels remain below 40% of the initial level, indicating a long-lasting effect. Pharmacodynamic activity of TG-1601, potentially attributable to BET binding affinity compared to earlier generation molecules.

**In-vivo**

In-vivo efficacy in the long-lasting effect, efficacy studies in Mv-16-13 tumor-bearing mice, dosed with a 20 mg/kg/day PO regimen beginning before drug holidays, showed that drug holidays of 2, 3 and 4 days per week only modestly affected efficacy (25%, 11% and 5% TGI, respectively), suggesting discontinuous dosing of TG-1601 in mice may not significantly impact efficacy.

**In vitro cytotoxic activity**

**In vitro pharmacodynamic activity of TG-1601**

- In vitro pharmacodynamic activity of TG-1601

**In vivo anti-tumor activity in MM1-s multiple myeloma model**

- In vivo anti-tumor activity in MM1-s multiple myeloma model

**Pharmacodynamic markers**

- In vivo and ex vivo validation of CCRI and IL1RN

**Conclusions**

- TG-1601 is a novel and potent BET inhibitor that specifically inhibits the binding of the BET subfamily of bromodomains containing proteins.

- TG-1601 potently inhibits cell growth of various multiple myeloma and leukemia cell lines in vitro, but does not affect the growth of normal transformed cell lines.

- TG-1601 inhibits tumor growth.

- TG-1601 inhibits tumor growth and drug holidays do not alter its antitumor efficacy. TG-1601 and its metabolites are detected in tumor tissue.

- TG-1601 shows costimulatory effects in an in vivo model with anti-CD163 antibody. Clinical trials will be focused on potential synergies between TG-1601 and other drugs in the TG pipeline (e.g., anti-HER2, anti-angiogenic agents).

- As an important part of the phase I drug development, surrogate markers (e.g. EDU and OTX) will be tested to define the pharmacodynamic activity.