Preclinical Characterization of a Novel Non-Cyclic Dinucleotide Small Molecule STING Agonist with Potent Anti-Tumor Activity in Mice

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**Key Points**

- **STING** (stimulator of interferon genes) has emerged as an attractive cancer immunotherapy target due to its key role in induction of type I interferons (IFNs) and other pro-inflammatory cytokines that promote tumor-specific antigen cross-presentation and effective T cell priming.

- Currently, all known STING agonists in clinical trials are based on cyclic dinucleotide (CDN) scaffolds, however, these high molecular weight synthetic CDNs often display limited potency, cellular permeability, stability, and short tumor retention time.

- In this study we present TTI-10001, a novel non-CDN small molecule STING agonist with favorable drug properties and potent anti-tumor activity in mice.

**TTI-10001 is a Potent, Cell Permeable, Small Molecule Pan-STING Agonist**

- Key drug properties of TTI-1001:
  - Non-CDN-based
  - MW: 470 Da
  - LogD: 4.6
  - Solubility: 1 mg/mL in water
  - Permeability (Caco2 assay): 100% (high)

**TTI-10001 Exhibits a Favorable Safety Profile and is Well Tolerated in Mice**

- In vivo ADME:
  - Human STING K75E
  - Rat STING K75E
  - Human STING WT
  - Human STING K75E

- Mouse body weight after intratumoral (IT) or intravenous (IV) administration

- No deaths, body weight loss, or overt morbidity observed at the indicated doses

**TTI-10001 Activates the STING Signaling Pathway**

- A) STING signaling pathway
- B) TTI-10001 increases phosphorylation of STING/IRF3

**TTI-10001 Achieves High In Vivo Exposure and Durable Tumor Retention**

- A) TTI-10001 in vivo drug levels
- B) PK parameters at TTI-1001

- C) Mouse IPN induction by TTI-10001
- D) Human IPN induction by TTI-10001

**TTI-10001 Induces Pro-Inflammatory Cytokine Expression and Promotes T Cell Activation In Vivo**

- A) Cytokine induction by TTI-10001 in MC38 injected tumors
- B) Activation of CD3+ CD8+ CD69+ T cells in tumor draining lymph node (Splenocytes) in spleens

**TTI-10001 induces Tumor Regression in Two Immunocompetent Mouse Models**

- A) MC38 (colorectal adenocarcinoma) model
- B) 4T1 (breast cancer model) model

**Conclusions**

- TTI-10001 is a novel, non-CDN, potent, small molecule pan-STING agonist
- TTI-10001 exhibits favorable potency, cell permeability, and tumor retention properties that enable to potentially overcome the common limitations of current CDN-derived STING agonists
- TTI-10001 is well tolerated in mice at relevant doses after IV or IV administration
- TTI-10001 induced durable complete regressions in both injected and distal tumors
- These data support further evaluation of TTI-10001 as a potential first-in-class small molecule STING agonist for cancer immunotherapy