TG-1701 is a novel, orally available and covalently bound BTK inhibitor

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**Background**

- **Targeting BTK**: BTK is a tyrosine kinase (BTK), an essential component of the BCR signaling pathway, has been demonstrated to be an effective treatment option for B-cell malignancies and autoimmune diseases. However, new BTK inhibitors are needed to allow for better safety and efficacy as a single agent and in combination with other agents.

- **Aims**: We present TG-1701, a novel, orally available and covalently bound BTK inhibitor that exhibits unique pharmacologic properties compared to prior BTK inhibitors.

**Methods**

- **In vitro pharmacodynamic activity of TG-1701**: The selectivity, kinase selectivity, and in vitro kinase activity of TG-1701 were assessed.

- **In vivo pharmacodynamic activity of TG-1701**: The selectivity, kinase selectivity, and in vivo kinase activity of TG-1701 were assessed.

- **Occupancy assay**: In vitro occupancy was determined using a gamma receptor occupancy assay.

- **Kinase selectivity**: Kinase selectivity was determined using an enzyme activity assay.

- **In vitro and in vivo Pharmacology**: In vitro and in vivo pharmacology data are provided.

- **Clinical perspective**: Potential for TG-1701 Use in Combination with other agents.

**In vitro selectivity**

- **Kinase selectivity (IC50)**
  - BTK: 0.22 nM
  - ABL: > 3000 nM
  - Erk: 0.8 nM
  - JNK: 147 nM
  - JAK2: 250 nM
  - FGFR1: 200 nM
  - PDGFR: 72 nM
  - Erk1/2: 30 nM
  - PLC-γ: 2 nM

**Pathway inhibition**

- **BTK inhibition**: BTK inhibition was determined in a cell-based assay using a phospho-specific antibody.

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**In vivo pharmacodynamic activity of TG-1701**

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**Clinical perspective**

- **Potential for TG-1701 Use in Combination with other agents.**

**Conclusions**

1. TG-1701 is a novel, specific and covalent BTK inhibitor, more selective than Brutinib toward a panel of kinases including EGFR.
2. Occupancy assay in vitro and in vivo suggest that 0% occupancy can be reached using 100 mg/kg dose in human dose escalation clinical trial.
3. TG-1701 reduced the phosphorylation of BTK and other kinases downstream the BTK pathway, demonstrating a strong growth inhibitory activity against a set of lymphoma cell lines (data not shown) and inhibits PLC-γ-dependent calcium release.
4. TG-1701 demonstrated similar antitumor efficacy to Brutinib and acalabrutinib.
5. PK profile allows for a once-a-day dosing, TG-1701 is not a CYP inhibitor, and possesses a favorable profile for combination (data not shown).
6. In vivo, a 10 mg/kg dose escalation has started in China.
7. TG-1701 will be tested in combination with several TKIs including ibrutinib and umbralisib.