DT095895 is a selective EP4 receptor antagonist with monotherapy efficacy in syngeneic mouse model(s) and best-in-class properties.

Elevated levels of Prostaglandins (PGs), an eicosanoid synthesized from arachidonic acid by the cyclooxygenase-2 (COX-2), exert strong immunosuppressive effects in the tumor microenvironment. COX-2 positive solid tumors can use this pathway as a resistance mechanism, especially to escape from the host immune system. Countering this immunosuppressive pathway is thought to restore tumor immunity and how the potential to synergize with the anti-tumor activities of immune checkpoint inhibitors (ICI). Such a combination strategy is highly promising to improve the response rate of patients to immunotherapies and achieve a more effective, long-lasting, tumor control.

As the use of non-steroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors (Coxibs) in cancer therapy proved to be non-applicable due to safety concerns, there is a need to develop safer alternatives, especially by selecting downstream targets. PGD2 immunosuppressive effects are largely mediated by the EP4 receptor. Engaged on multiple immune cells. The development of antagonists of the EP4 receptor is thus a promising strategy to inhibit the PGD2-induced immunosuppressive effects in the tumor microenvironment and to restore tumor immunity.

A novel series of EP4 receptor antagonists, with improved pharmacological properties compared to the EP2 receptor antagonists currently being evaluated in clinical trials, has been developed. A comprehensive lead optimization program led to the identification of DT095895, a small molecule development candidate with a “best-in-class” profile. The in vitro and in vivo pharmacological characterization of DT095895 drug candidate is presented.

DT095895 was identified through a comprehensive lead optimization program at Domino Therapeutics. This candidate shows well-balanced pharmacodynamic and pharmacokinetic properties, which place it as a best-in-class candidate.

DT095895 has drug-like properties:
- Well-balanced lipophilicity (log P = 2.8)
- High oral bioavailability (>85%)
- "Gradually dissolves" to the structure

DT095895 is a selective antagonist of the EP4 receptor.
- EP4 antagonist in all pathology-related PGs with similar potency in our in-vitro platform
- Selectivity over four species: IC50 15 nM or >100x
- No off-target activity identified in a large panel screened including 48 targets (CYP and ion channels)

Excellent plasma exposure after oral administration in mice, rat and dog with excellent bioavailabilities.

Absence of toxicity.
- No toxicity signal
- No HPLC, IC50 ≥ 50 μM
- Kinetic profile at 30 min and 24 hr: IC50 ≥ 15 nM or >100x
- DT095895 is well tolerated up to 1000 mg/kg in an acute toxicity study in mice

DT095895 advantageously compared to clinical competitors in a set of ADME/PK parameters.

DT095895 induces a superior target engagement.

As the EP4 receptor is primarily coupled to the CREB protein, its activation in immune cells leads to elevated intracellular cAMP levels and subsequent phosphorylation of the transcription factor CREB. DT095895 target engagement was assessed in assays for baseline TGI in assays with single cell lines with a potential for its ability to inhibit a PD-1 agonist-induced CREB phosphorylation in an immune cell substrate and to compare to clinical competitors. Such assays will be the basis for the development of the target engagement to support Phase I studies.

- Mouse Whole blood
  DT095895 induces effectively an EP4 antagonist-induced CREB phosphorylation in CD4+, CD8+ and CD19+ cells in Mouse Whole Blood with IC50 in the 38-51 nM range and induces superior target engagement when compared to commercial competitors.

- Human Whole Blood
  DT095895 induces a superior target engagement with an IC50 of 25-38 nM for CREB phosphorylation.

CONCLUSION

Anti-tumor activity of DT095895 after and administration was demonstrated in syngeneic mouse tumor models, in monotherapy and in combination with an intensive immunotherapy.

- **Part 2**
  DT095895 induces 42.5% tumor growth inhibition after oral administration @ 100 mg/kg in monotherapy vs 10% in a Panobinostat/Rasburicase pancreatic cancer model.

- **MCA259**
  DT095895 enhances anti-PD-1 activity and induces 68.0% tumor growth inhibition after oral administration @ 100 mg/kg in combination with anti-PD-1 in a MCA259 sarcoma model.

**DT095895** induces strong Tumor Growth inhibition in syngeneic mouse models.