

**DT-9081, A SELECTIVE EP<sub>4</sub> RECEPTOR ANTAGONIST WHICH SYNERGIZES WITH IMMUNE CHECKPOINT INHIBITORS TO INDUCE COMPLETE RESPONSES IN SYNGENEIC MURINE CANCER MODELS**

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**Background** Elevated levels of Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), an eicosanoid synthesized by the cyclooxygenase-2 (COX-2), exert strong immunosuppressive effects in the tumor microenvironment (TME). COX-2-positive solid tumors have the ability to use this pathway as a resistance mechanism, especially to escape from the host immune system, thus limiting the anti-tumor effects of immune checkpoint inhibitors (ICI). These immunosuppressive effects are largely mediated by the EP<sub>4</sub> receptor, expressed on multiple immune cells. DT-9081, a selective EP<sub>4</sub> receptor antagonist, has been designed to counteract the PGE<sub>2</sub>-immunosuppressive effects in the TME and to synergize with ICI.

**Methods** DT-9081 has been evaluated in 2 syngeneic murine cancer models in combination with ICI. DT-9081 was first tested at 30 and 60 mg/kg, as single agent or in combination with anti-CTLA-4 antibody, in the CT26 colorectal cancer model. DT-9081 was then tested at 30 mg/kg as single agent, or at 3, 10 or 30 mg/kg in combination with an anti-PD-1 in the MCA205 sarcoma model. In both studies, tumor growth, survival and type of response were evaluated. Complete responders were additionally submitted to a tumor rechallenge study to evaluate the immune system memory.

**Results** In the CT26 colorectal cancer model, combination of DT-9081 at both doses with anti-CTLA-4 antibody enabled a significant tumor growth inhibition and a noticeable increase in survival as compared to the anti-CTLA-4 antibody treatment alone. Moreover, 3 and 2 complete responses over 10 mice were observed in the groups treated with 30-mg/kg and 60-mg/kg DT-9081 in combination with the anti-CTLA-4 antibody, compared to none in the anti-CTLA-4 antibody treatment alone group.

In the MCA205 sarcoma model, combination of DT-9081 at the 3 tested doses with anti-PD-1 antibody enabled significant tumor growth inhibition and increase in survival, with a maximum anti-tumor efficacy from 10-mg/kg DT-9081. 5, 9 and 10 complete responses over 15 mice were observed in the groups treated with 3-, 10- and 30-mg/kg DT-9081, respectively, in combination with the anti-PD-1 antibody, compared to a single one in the anti-PD-1 antibody treatment alone group.

Complete responders from both studies were additionally assessed to address their response to a new challenge with the corresponding tumor cells. No tumor growth was observed indicating a long lasting tumor immune control.

**Conclusions** DT-9081 demonstrates strong anti-tumor effects in multiple syngeneic mouse tumor models, and synergizes with immune checkpoint inhibitors to induce long lasting complete responses. DT-9081 has completed regulatory development and will enter in clinical development by the end of 2022.

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