BROAD ANTI-TUMOR ACTIVITY OF A POTENT AND SELECTIVE SMALL MOLECULE ANTAGONIST OF PD-L1 ABSK043 IN COMBINATION WITH OTHER AGENTS IN PRECLINICAL MODELS

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Background Immunotherapy has revolutionized cancer treatment in the last decade. Several monoclonal PD-1 and PD-L1 antibodies have been approved for various cancers. Unlike antibodies, small molecules may offer potential advantages in oral dosing, adjustable control of drug exposure, improved tumor penetration and many other aspects. Therefore, small molecule antagonist which can efficiently abolish interaction of PD-1 and PD-L1 may render a novel and alternative treatment approach with potentially improved clinical benefits. ABSK043, an oral small molecule antagonist of PD-L1 discovered by us, has entered into clinical Phase I in 2021. Preclinically, ABSK043 has shown significant tumor growth inhibition as a single agent in multiple models. To explore potential synergy of ABSK043 with other therapeutic agents, in vivo combination experiments were conducted.

Methods For in vivo studies, the tumor (MC38-human PDL1 knock in)-bearing syngeneic mice were treated with ABSK043 and other agents. In addition, we also developed a humanized bladder cancer model using the RT112/84 cell line. Mice were injected intravenously with human PBMC from healthy volunteer, and injected subcutaneously into flank with cancer cells.

Results ABSK043 demonstrated strong in vivo synergy with several therapeutic agents such as carboplatin, a key component of the widely used CRC standard-of care chemotherapy treatment regimen, as well as other target therapy or immune-oncology agents.

Conclusions Taken together, these data for the first time demonstrated broad combination synergy of a small molecule PD-L1 antagonist with other agents and provided basis for potential clinical evaluation of these combination treatment for cancer patients.