26G-ISMS40 **Lenvatinib Mesilate (LEN) Enhanced Antitumor Activity of a PD-1 Blockade Agent by Potentiating Th1 Immune Response**

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Lenvatinib (LEN) selectively inhibits the kinase activities of VEGFR1-3, FGFR1-4, KIT, PDGFRα, and RET, which are involved in tumor angiogenesis and tumor cell proliferation in several cancer types. Currently, Phase 1b/2 clinical trials of the combination of LEN and pembrolizumab (a monoclonal antibody [mAb] that blocks the interaction between PD-1 and its ligands) are ongoing for selected types of cancer including renal cell carcinoma, melanoma and non-small cell lung carcinoma, etc. In this study, we will report that tumor associated macrophage and regulatory T cell population were downregulated by treatment of LEN, and combination of LEN with PD-1 mAb showed more potent antitumor activity in CT26 mice tumor syngenic model compared with either single treatment alone. Notably, complete tumor regressions were detected in some mice with combination treatment in the H22 mice tumor syngenic model. Re-inoculation of fresh H22 cells into these cured mice was rejected. BioMap analysis showed that PD-1 mAb increased both Th1 and Th2 cytokines, LEN decreased Th2 cytokines, and combination treatment increased Th1 cytokines but decreased Th2 cytokines.
The results indicate that the combination of LEN with PD-1 mAb was more effective than single-agent treatment in multiple syngeneic tumor models and was accompanied with a potent antitumor immune response.