Pressure-enabled intravascular delivery of SD-101 into the liver with systemic or subcutaneous checkpoint inhibitor for control of liver metastases in a murine model

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Background: Myeloid-derived suppressive cells (MDSCs) blunt the activity of immunotherapy through the promotion of an immunosuppressive tumor microenvironment (TME) in the setting of liver metastases (LM). Ongoing clinical trials are evaluating intravenous checkpoint inhibitors (CPIs) in combination with the class C TLR9 agonist SD-101 via intravascular Pressure Enabled Drug Delivery™ (PEDD™) for multiple intrahepatic tumor indications (NCT04935229, NCT05220722). We delivered SD-101 in a murine model of PEDD in combination with an anti-PD-1 antibody administered either intraperitoneally (IP) or subcutaneously (SQ) to evaluate whether the route of CPI administration impacts the ability of intrahepatic TLR9 stimulation to control LM.

Methods: To develop LM, C57/BL6 mice were challenged with MC38-Luc tumor cells via the intra-splenic route followed by splenectomy. After a week, mice were treated with 10µg SD-101 via PEDD and twice weekly anti-PD-1 antibody delivered either IP or SQ. Tumor burden was monitored by IVIS and on D10 liver was harvested to isolate $CD45^+$ cells. Flow cytometry (FC) analysis was performed to quantify MDSCs ($CD11b^+Gr1^+$), B cells (B220), T ($CD3^+$) cells, M1($F4/80^+CD38^+Egr2^-$), and M2 ($F4/80^+CD38^-Egr2^+$) macrophages in the TME.

Results: SD-101 delivered via PEDD in combination with anti-PD-1 antibody delivered either via SQ or IP significantly ($p< 0.0001$) reduced LM progression (fold over D0) compared to control (Veh:87.46 vs. SD-101: 13.90 vs. SQ: 0.002 vs. IP: 0.04). FC analysis of $CD45^+$ cells isolated from the tumor-bearing livers revealed that CPI in combination with SD-101 significantly reduced liver MDSCs (Veh: 37.57% vs. SQ: 7.18% vs. IP: 10.18%; $p<0.05$). The percentage of B cells (Veh: 8.32% vs. SQ: 18.09% vs. IP: 15.65%: $p<0.05$); T cells (Veh: 7.14% vs. SD-101: 15.18% vs. SQ: 17.81% vs. IP: 19.13%: $p<0.05$) and the ratio of M1/M2 macrophages (Veh: 2.25 vs. SD-101: 12.8 vs. SQ: 12.99 vs. IP: 12.90: $p<0.05$) increased significantly as compared to Veh. There were no significant differences between SQ and IP CPI delivery in controlling tumor progression or modulation of the TME.

Conclusion: SD-101 administered via PEDD in combination with CPI that was delivered IP or SQ provided control of LM, with intrahepatic TLR9 stimulation enabling CPI via either route equally. PEDD of a class C TLR9 agonist has the potential to prime the TME to reduce immunosuppression in LM which may improve the anti-tumor efficacy of CPIs irrespective of the route of administration.