Preclinical Studies of SB 11285, a Novel STING agonist for Immuno-oncology

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Background: The activation of innate and adaptive immunity via Stimulator of Interferon Genes (STING) signaling is a potentially transformative immuno-therapeutic strategy in cancer. We report here the in vivo efficacy and safety studies of SB 11285.

Methods: **(1) Tumor Growth Inhibition (TGI) and Tumor Growth Delay (TGD) studies** in syngeneic mouse models were initiated when mean tumor volume (MTV) reached 100mm^3: **(i) A20 Lymphoma: (10 animals/Group);** (**A**) Saline; (**B**) 100µg SB 11285, intratumoral (i.t.), days 3,4,6,8,10; (**C**) 100mg/kg Cyclophosphamide, intraperitoneal (i.p), days 1,2; and (**D**) combination of cyclophosphamide+SB 11285. **(ii) CT26 Colon Carcinoma** experimental design is shown in **Table**. **(2) Re-challenge study** was initiated in tumor-free animals in A20 lymphoma model on day 73, and monitored for an additional 45 days. **(3) Presence of activated immune cells** in tumor tissues was evaluated by immuno-histochemistry. **(4) Cytokine response** was evaluated in serum after a single i.p. injection of SB 11285 at 10mg/kg. **(5) Maximum Tolerated Dose (MTD)** in mice was determined by daily i.p. injection of SB 11285 for 10 days.

Results: **(i) A20 model**. % TGI in the treatment groups were: **A**, 0; **B**, 86; **C**, 98, and **D**, 93; % TGD, day 70: **A**, 0; **B**, 64; **C**, 156; **D**, 288. In **D**, day 73, 90% of animals remained tumor-free. **(ii) CT26 model**. Table 1 shows MTV on day 19 and %TGD on day 43; **(iii) Re-challenge study**. All animals from the SB 11285-treated groups remained completely tumor-free on day 45 compared to control group (MTV,1666 mm^3); **(iv) Immuno-histochemistry** of SB 11285-treated groups, revealed the infiltration of CD8$^+$T and NK cells into tumor and surrounding tissues; **(v)** Cytokine analysis did not show systemic inflammatory response; **(vi) MTD** of i.p. SB 11285 was 16 mg/kg/day.

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Conclusion: SB 11285, a novel STING agonist, showed very potent, and highly durable immune response-mediated anti-tumor activity. SB 11285 was well tolerated, safe, and is being advanced to IND-enabling studies.

Group (10 mice/group)	Dose	Days	Route	MTV mm^3, day 19	% TGD, day 43
Saline	50µg	1,4,7,10,17	i.t.	2335	-
SB 11285	50µg	1,4,7,10,17	i.t.	589	91
Anti-CTLA ab	5mg/kg (then 2.5mg/kg)	1,(4,7)	i.p.	1684	17
Anti-CTLA ab+SB 11285	5mg/kg (then 2.5mg/kg) +[50µg]	1,(4,7)+[1,4,7,10,17]	i.p.+[i.t.]	176	176