Abstract #TPS3162

A Phase 1a/1b Dose-escalation Study of Intravenously Administered SB 11285 Alone and in Combination with Nivolumab in Patients with Advanced Solid Tumors

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BACKGROUND

Immunotherapy has emerged as a transformative approach for the treatment of cancer. However, a significant percentage of patients are nonresponsive to these immunotherapies or experience disease relapse which highlights the need for new therapies. Recent work has highlighted a major role for Stimulator of Interferon Genes (**STING**) agonists in immunotherapy.

Conceptually, the activation of the STING pathway in immune cells in the tumor microenvironment and tumor cells could result in the induction of innate and adaptive immunity and subsequent activation of cytotoxic T cells and NK cells for durable anti-tumor responses.

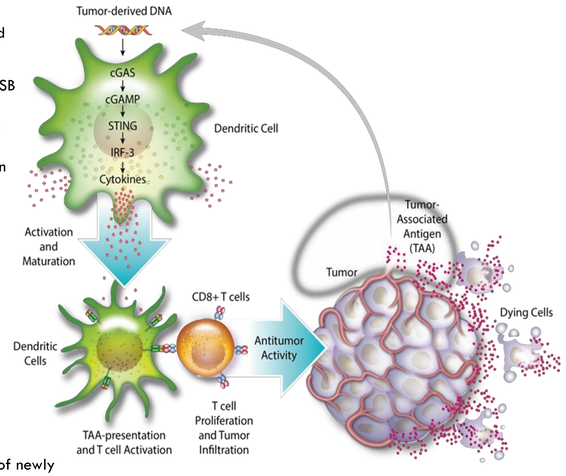
MECHANISM OF ACTION

SB 11285 is a novel agonist of STING pathway leading to the activation of tumor-resident Antigen Presenting Cells (APCs) and trafficking of CD8+ T cells to the tumor.

In our preclinical studies using multiple tumor-derived cell lines, SB 11285 has been observed to cause the induction of cytokines consistent with engagement of the STING target, as well as cell death by STING-mediated apoptosis.
SB 11285 caused long-lasting and complete tumor regression in majority of animals, with induction of immune memory and abscopal effect when administered intravenously, intraperitoneally and intratumorally.

ACTIVATION OF STING

- Increases Type I Interferon production
- Induces the recruitment of CD8-positive T cells against tumor antigens
- Systemic Delivery enables targeting a range of tumors

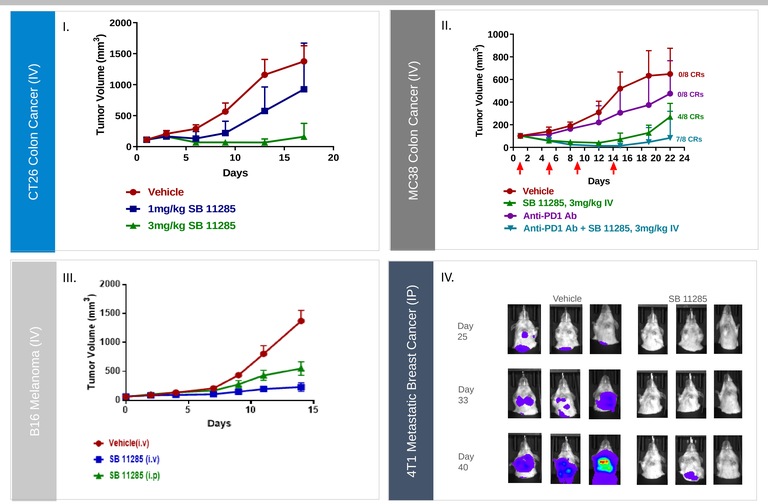


Kai, L. et. al., (2017). International Journal of Molecular Sciences. 18. 404. 10.3390/ijms18020404.

Systemic administration could additionally facilitate trafficking of newly activated CD8+T cells from periphery into the tumor site.

In addition, preclinical models indicate that survival and local tumor shrinkage were significantly enhanced when SB 11285 was administered with anti-CTLA antibody or anti-PD-1 antibody, suggesting synergistic activity with concomitant STING activation.

IN VIVO ACTIVITY



I. IV Dose responsive tumor growth inhibition in CT26 colon cancer model with SB 11285

II. IV Dose responsive tumor growth inhibition in B16 melanoma model with SB 11285

III. IV SB 11285 activity is synergistic with anti-PD1 antibody in MC38 colon cancer model

IV. IP SB 11285 inhibits tumor metastasis in 4T1 breast cancer model

Bridging the Gap between Innate and Adaptive Immunity with **Stimulator of Interferon Genes (STING)** Agonist

IV administered STING Agonist shows no Dose Limiting Toxicities (DLTs) or Study Drug Related Serious Adverse Events (SAEs) to date

Clinical Trial NCT04096638 is in recruitment phase at multiple sites in USA

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TRIAL DESIGN

- Phase 1, first in human, open-label, multicenter dose escalation Phase 1a/1b study to determine Dose Limiting Toxicities (DLTs), Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D)
- Part 1 Dose Escalation study evaluates ascending doses of intravenously administered SB 11285 as monotherapy (1a) and in combination with nivolumab (1b). Combination Dose escalation opens once the 2nd dose level of Monotherapy is declared to be safe by Safety Review Committee (SRC)
- Part 2 has three Combination Expansion Cohorts at RP2D: Melanoma, HNSCC, tumors naïve or Relapsed/Refractory to anti PD-1/PD-L1
- Patients are treated over 28 days dosing cycles (total of 12 cycles) until unacceptable toxicity or progressive disease

Part 1a: Monotherapy Dose Escalation 3+3
SB 11285 Monotherapy
Patients = 15 - 30

→ **Part 1b:** Combination Dose Escalation 3+3
SB 11285 plus Nivolumab
Patients = 9 - 18

→ RP2D

Part 2: Combination Expansion Cohorts

- **COHORT A: Melanoma** Patients = 21
- **COHORT B: Head & Neck** Patients =21
- **COHORT C: Tumors not in Cohort A & B Naïve or Relapsed / Refractory to anti PD-1/PD-L1** Patients = 20

OBJECTIVES

PRIMARY OBJECTIVES

Part 1 – Dose-Escalation Cohorts:
- Determine the MTD, and RP2D of IV SB 11285 as monotherapy and in combination with nivolumab
- To evaluate the safety and tolerability of IV SB 11285 as monotherapy and in combination with nivolumab

Part 2 – Dose Expansion Cohorts:
- Evaluate preliminary antitumor activity of IV SB 11285 in combination with nivolumab in terms of Objective Response Rate (ORR) using RECIST v1.1
- Confirm the RP2D and schedule of IV SB 11285 in combination nivolumab
- Further evaluate the safety and tolerability of IV SB 11285 in combination with nivolumab

SECONDARY OBJECTIVES (Dose Escalation and Dose Expansion Cohorts)
- Characterize the whole blood Pharmacokinetics (PK) of IV SB 11285 as monotherapy and in combination with nivolumab
- Evaluate additional measure of clinical benefit including: ORR (Part 1 only), Duration of Response (DOR), Progression Free Survival (PFS) by RECIST and Overall Survival

EXPLORATORY OBJECTIVES (Dose Escalation and Dose Expansion Cohorts)
- Evaluate the Pharmacodynamics (PD) of IV SB 11285 as monotherapy and in combination with nivolumab
- Assess the biological effects of IV SB 11285 demonstrated by changes in immune cells, immune cell markers, serum cytokines (such as TNF-α , IFN-α, IFN-β and others consistent with engagement of the STING target) and gene expression patterns

KEY INCLUSION CRITERIA

- Male or Female patients ≥ 18 years of age with locally advanced or metastatic or unresectable solid tumors in both Part 1 & 2 with additional tumor specific criteria for Part 2 Expansion Cohorts of Melanoma, HNSCC
- ECOG Performance status ≤ 1
- Estimated life expectancy ≥ 3 months
- Measurable disease according to RECIST 1.1 criteria
- Intact Hematologic and Organ Function: ANC ≥ 1500 mm^3, Platelets ≥ 100,000/mm^3, Hemoglobin ≥ 9 g/dL, Serum creatinine ≤1.5 mg/dL, ALT and AST ≤ 3.0 times the upper limit of normal

KEY EXCLUSION CRITERIA

- Women who are pregnant or lactating
- Active autoimmune disease
- QT/QTc prolongation ≥ 470 msec Female, ≥ 450 msec Male
- Ongoing infection requiring systemic antibiotic therapy or with active EB, Hep B/C virus or HIV
- Clinically significant pulmonary disease, chronic or recurrent renal or urinary tract disease, liver disease, endocrine disorder
- Active heart disease including MI within 3 months
- Major surgery within the last 4 weeks
- Recent anticancer therapy or investigational therapy; "Check-point inhibitors" within 28 days (except Part 2 Cohort C)

STUDY STATUS

- 4 out of 5 sites for Part 1 are active and open for enrollment
- Currently patients are at 2nd dose level of Part 1a (Monotherapy Dose Escalation)
- No drug related Serious Adverse Events (SAEs), AEs indicating Cytokine Release Syndrome or DLTs have been reported
- Pursuant to the collaboration with Roche, a Protocol Amendment to replace Nivolumab with Atezolizumab in Part 1b and Part 2 of the Phase 1 trial has been submitted to and is currently under review by the FDA