Phase 1b/2, Open-Label, Multicenter, Dose-Escalation and Expansion Trial of Intratumoral SD-101 in Combination With Pembrolizumab in Patients with Metastatic Melanoma

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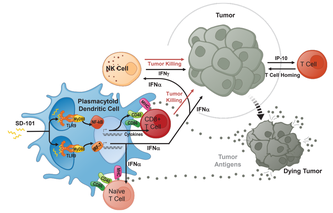
Introduction

- SD-101 is a synthetic Class-C CpG-oligodeoxynucleotide that stimulates plasmacytoid dendritic cells (pDCs) through engagement of Toll-like receptor 9 (TLR9). This stimulation causes pDCs to release interferon-alpha and mature into efficient antigen-presenting cells, thereby strengthening both innate and acquired immune responses (**Figure 1**)[1]
- In patients with low-grade non-Hodgkin's lymphoma, direct injection of SD-101 into tumors, in combination with low dose radiation, not only activated local immune responses, but also induced a systemic (abscopal) effect[2]
- Preclinical studies suggest that the immunostimulatory effects of SD-101 might also boost the activity of PD-1 checkpoint inhibitor therapy. In mouse models, SD-101 converted anti-PD-1 non-responders into responders by increasing the quantity and quality of tumor-specific T cells[3]
- Pembrolizumab is a PD-1 inhibitor that has been approved for treatment of unresectable or metastatic melanoma[a]
- Here, we provide the first interim results from an ongoing clinical study that is assessing the safety, efficacy and pharmacodynamic effect of the combination of SD-101 and pembrolizumab in patients with advanced melanoma

Figure 1. Both Innate and Adaptive Immune Responses Are Increased by Intratumoral Injection of SD-101

SD-101 induces plasmacytoid dendritic cells (pDCs) to secrete high levels of interferon-alpha, a potent immunomodulatory cytokine that is able to boost natural killer cell cytotoxic activity and induce recruitment of T cells. In addition, SD-101 induces pDC maturation and the ability to cross-present tumor associated antigens, promoting CD8+ T-cell responses.



IFNα, interferon-alpha; IFNγ, interferon-gamma; MHC, major histocompatibility complex; MyD, myeloid differentiation; NK, natural killer; TLR, Toll-like receptor.

Methods

- This is an ongoing, Phase 1b/2, open-label, multicenter, dose-escalation and dose expansion study (NCT02521870)
- Eligible patients had histologically- or cytologically-confirmed, unresectable, in-transit (Stage IIIc) or metastatic (Stage IV) melanoma
- Patients also had an ECOG performance status of 0 or 1 with at least one site of measurable disease easily accessible for intratumoral injection
- In the Phase 1b portion of the study (dose escalation), three dose cohorts received SD-101 at 2 mg, 4 mg or 8 mg according to a modified 3 + 3 design. In each dose cohort, SD-101 was administered intratumorally q1 week x 4, followed by q3 weeks x 7
- Patients in all dose cohorts are allowed to receive concomitant pembrolizumab every 3 weeks for up to 2 years
- Safety was assessed by dose-limiting toxicities (until Day 29), adverse events and serious adverse events
- Response was evaluated by the Investigator according to RECIST v1.1.[5] Assessments were based on radiographic images (either CT or MRI) at baseline, every 9 weeks until Day 379, and every 12 weeks thereafter until confirmed progression or initiation of new anti-cancer treatment
- Pharmacodynamic effects were assessed in tumor biopsies using the nCounter® PanCancer Immune Profiling Panel (NanoString Technologies, Inc., Seattle WA). Tumor biopsies were collected pre-dose and on Day 29 and Day 85

Results

Table 1: Demographics and Baseline Characteristics

	SD-101 Dose Cohort			
	2 mg (n=5)	4 mg (n=5)	8 mg (n=6)	Total (n=16)
Male, n (%)	3 (60.0)	3 (60.0)	5 (83.3)	11 (68.8)
Age, mean year (SD)	70.2 (5.76)	58.8 (9.63)	57.7 (14.38)	61.9 (11.65)
Race, n (%)				
White	5 (100)	5 (100)	5 (83.3)	15 (93.8)
Asian	0 (0)	0 (0)	1 (16.7)	1 (6.3)
BMI, mean kg/m^2 (SD)	29.9 (3.05)	26.1 (3.39)	25.7 (4.13)	27.4 (3.86)
Time since diagnosis, median year (range)	8.6 (5.3, 16.7)	2.4 (1.5, 5.3)	3.9 (1.0, 8.6)	5.2 (1.0, 16.7)
ECOG performance status, n (%)				
0	5 (100.0)	3 (60.0)	4 (66.7)	12 (75.0)
1	0 (0)	2 (40.0)	2 (33.3)	4 (25.0)
Stage at study entry, n (%)				
Stage III	0 (0)	1 (20.0)	1 (16.7)	2 (12.5)
Stage IV	5 (100.0)	4 (80.0)	5 (83.3)	14 (87.5)

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

Table 2. Tolerability of SD-101/Pembrolizumab Combination Therapy

	SD-101 Dose Cohort			
	2 mg (n=5)	4 mg (n=5)	8 mg (n=6)	Total (n=16)
Dose-limiting toxicities, n	0	0	0	0
SAEs, n (%)[a]				
Lower gastrointestinal hemorrhage	0 (0)	0 (0)	1 (16.7)	1 (6.3)
Influenza-like illness	0 (0)	0 (0)	1 (16.7)	1 (6.3)
Pyrexia	0 (0)	0 (0)	1 (16.7)	1 (6.3)
Cellulitis	0 (0)	1 (20.0)	0 (0)	1 (6.3)
Sepsis	1 (20.0)	0 (0)	0 (0)	1 (6.3)
Squamous cell carcinoma	1 (20.0)	0 (0)	0 (0)	1 (6.3)
Subjects with at least one event	2 (40.0)	1 (20.0)	1 (16.7)	4 (25.0)

AE, adverse event; SAE, serious adverse event.
[a]Includes all Investigator-assessed events (related and unrelated). No grade 5 AEs were reported in any dosage group.

Figure 2. Induction of Immune Function Signatures (A) and an Immune Cell Infiltrate (B) Following SD-101 and Pembrolizumab Administration

Results are from tumor biopsies prepared from Subject 101005 and analyzed on nCounter® PanCancer Immune Profiling Panels.

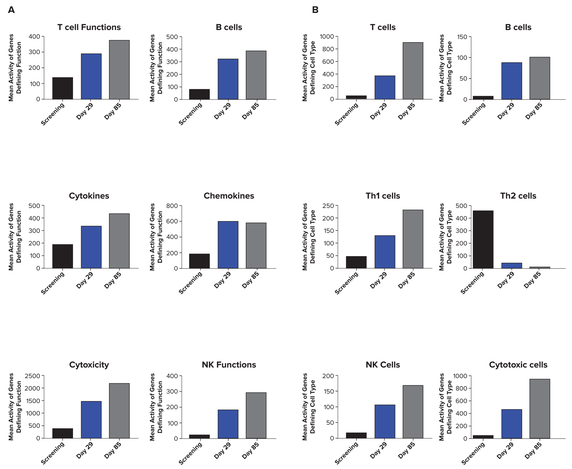


Table 3. Antitumor Response in the SD-101 2-mg Dose Cohort

Best overall response was assessed by the Investigator according to RECIST v1.1. Data cut-off, 12 September 2016.

Patient ID	Anti-PD-1 Naïve or Progressor	Best Overall Response per Investigator
101005	Naïve	CR
101002	Naïve	PR
102004	Naïve	PR
101003	Naïve	PD[a]
101001	Progressor	SD

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Clinical assessment per Investigator without objective documentation via CT or MRI scan.

Conclusions

- In patients with Stage IIIc/IV melanoma, intratumoral injection of SD-101 in combination with pembrolizumab was well tolerated:
  - No dose-limiting toxicities were observed in any SD-101 dose cohort (2, 4 and 8 mg), and a maximum tolerated dose was not identified (**Table 2**)
  - The most common treatment-emergent adverse events were flu-like symptoms, including fever, chills and myalgia, consistent with the engagement of TLR9 and production of interferon-alpha. Most events were grade 1–2, and none were grade 5
  - Four patients (25%) experienced at least one serious adverse event (**Table 2**)
  - One SAE (grade 3 cellulitus) was judged to be possibly related to SD-101 and/or pembrolizumab in a patient in the 4-mg dose cohort. SD-101 was discontinued in this patient and the event resolved
- The preliminary safety profile was consistent with prior SD-101 and pembrolizumab studies. Consequently, there was no evidence that the combination exacerbated treatment-emergent events associated with the individual monotherapies, nor was there evidence of a unique safety signal for the combination
- Treatment with SD-101 and pembolizumab resulted in a broad elevation of immune function signatures, as well as an increase in immune cell infiltrates in the tumor microenvironment (**Figure 2**)
- Early evidence suggests that combination therapy with SD-101 (2 mg) and pembrolizumab may be active in patients with advanced melanoma (**Table 3**)
- Further efficacy analyses in all SD-101 dose cohorts are ongoing

References

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Disclosures

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