CT098

Phase 1b/2, Open-Label, Multicenter Study of Intratumoral SD-101 in Combination With Pembrolizumab in Anti-PD-1 Treatment-Naïve Patients With Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

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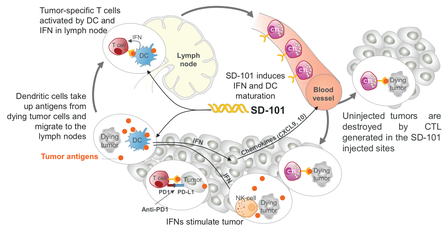
BACKGROUND

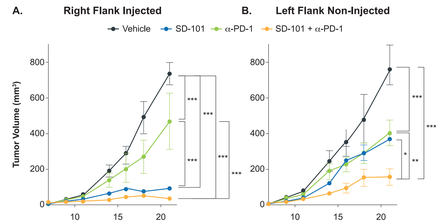
- Head and neck squamous cell carcinoma (HNSCC) patients with recurrent unresectable or metastatic disease have a poor prognosis, with an approximate median progression-free survival (PFS) of 2.0 months and median overall survival (OS) of 8.0 months with current treatment options, including cetuximab, platinum, fluorouracil, methotrexate, anti-CTLA4 (ipilimumab) and anti-PD-1 (nivolumab and pembrolizumab) therapies.
- SD-101 is a synthetic Class-C CpG-oligodeoxynucleotide agonist of Toll-like receptor 9 (TLR9).
- SD-101 stimulates plasmacytoid dendritic cells (pDCs) to release interferon-alpha and mature into efficient antigen-presenting cells, enhancing both innate and adaptive immune responses (**Figure 1**).[1]
- Preclinical mouse models of head and neck tumors demonstrated that intratumoral injection of SD-101, in combination with PD-1 blockade, suppressed the growth of tumors not only at the injected site, but also at distant uninjected sites (**Figure 2**).[2]
- Direct injection of SD-101 into tumors of metastatic melanoma patients in combination with pembrolizumab also demonstrated responses in both the injected and distant lesions.[3]
- Pembrolizumab is a PD-1 inhibitor that has been approved under accelerated approval for the treatment of patients with recurrent unresectable or metastatic HNSCC.[4]
- Here, we provide results from a cohort of patients with advanced unresectable or metastatic HNSCC who are naïve to prior anti-PD-1/L1 therapy. This cohort was part of an ongoing Phase 2 clinical study assessing the safety, efficacy and pharmacodynamic activity of the combination of SD-101 and pembrolizumab.

Figure 1. Both Innate and Adaptive Immune Responses Are Increased by Intratumoral Injection of SD-101. SD-101 engages TLR9 on 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 to the tumor microenvironment. In addition, SD-101 induces DC maturation and the ability to cross-present tumor associated antigens, inducing CD8+ T-cell responses.



CTL = cytotoxic (CD8+) T cell; DC = dendritic cells; IFN = interferon; NK = natural killer

Figure 2. Combination Therapy with Intratumoral Administration of SD-101 Agonists and Systemic Anti-PD-1 Antibody Inhibited Tumor Growth at Both Primary and Distant Sites in Head and Neck Cancer Models. Mice were implanted in both flanks with head and neck HPV-negative tumors cells (SCC7). Tumor-bearing mice (n=7–8/group) received SD-101 (50 µg/injection) intratumorally (i.t.) in right flank on days 7, 11, 14, and 18. Anti PD-1 antibody (250 µg/injection) was given i.p. on day 4, 6, 11, 14, and 18. Tumor growth at injected (A) and uninjected (B) sites was monitored. Data (means ± SEM) are pooled from 2–3 independent experiments showing similar results.

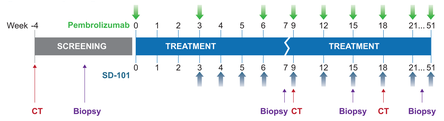


*P<0.05, **P<0.01, ***P<0.001 (two-way repeated measures ANOVA with Bonferroni post hoc test)

METHODS

- Ongoing phase 2 open-label, multicenter study enrolling anti-PD1/L1 treatment naïve HNSCC (NCT02521870; DV3-MEL-01/Keynote-184).
- Eligible patients have recurrent or metastatic HNSCC with at least 1 target lesion per RECIST v1.1, which must be accessible for intratumoral injection, an ECOG performance status of 0 or 1, and no prior anti-PD-1/L1 therapy.
- Patients receive 200 mg pembrolizumab q3 weeks up to 2 years. SD-101 (8 mg/lesion) is administered i.t. in a single lesion in two cycles: q1 week × 4 starting at week 3, followed by q3 weeks concomitantly with pembrolizumab until week 27; then another cycle starting at week 36 until week 60 (**Figure 3**).

Figure 3. Study Design



CT, computed tomography scan.

- The primary endpoint was objective response rate (ORR; irRECIST) both locally and systemically; secondary endpoints included safety and tolerability, time to response, and duration of response (DOR).
- Safety was assessed by adverse events, including immune related-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.
- To assess pharmacodynamic effects, biopsies of the injected tumor were collected at screening (prior to dosing) and post-dosing on Days 50, 106 and 190 (data from screening and Day 50 are presented here). RNA expression profiles were determined using the nCounter® PanCancer Immune Profiling Panel (NanoString Technologies, Inc., Seattle WA) to evaluate the immunophenotype of the tumor environment. Nanostring data were analyzed using the nSolver™ Analysis Software.

RESULTS

Table 1. Demographics and Baseline Characteristics

Characteristic	Total (N=22)
Age (years)	
Median (Min, Max)	65 (43, 91)
Sex, n (%)	
Male/female	20 (91)/2 (9)
ECOG PS, n (%)	
0/1	6 (27)/15 (68)
Baseline LDH (U/L), mean (SD)	206 (100)
≤ULN, n (%)	16 (73)
>1ULN to ≤2ULN, n (%)	3 (14)
>2ULN, n (%)	1 (5)
HPV status, n (%)	
Negative	5 (23)
Positive	6 (27)
Unknown or missing**	12 (50)
Time since diagnosis (years)	
Median (min, max)	2.1 (0.3, 6.1)
Stage at screening, n (%)	
Locally recurrent	3 (14)
Locally recurrent and metastatic	3 (14)
Metastatic	9 (41)
Missing**	7 (32)
Primary tumor location, n (%)	
Hypopharynx	3 (14)
Nasopharynx	2 (9)
Oral	7 (32)
Oropharynx	3 (14)
Missing**	7 (32)
Injected site irradiated prior to study, n (%)	
No	7 (32)
Yes	8 (36)
Missing**	7 (32)
Prior radiotherapy, n (%)	13 (59)
Prior surgery, n (%)	17 (77)
0/1/2/≥3 prior lines of therapy, n	7/8/4/3
Organ involvement, n (%)*	
Liver	2 (9)
Lung	6 (27)
Bone	2 (9)
Skin/subcutaneous tissue	6 (27)
Lymph nodes	9 (41)
Other organs	11 (50)

ECOG PS = Eastern Cooperative Oncology Group performance status; SD = standard deviation; ULN = upper limit of normal.
*Patients may have >1 site of organ involvement; **Collection in progress.

Safety

Table 2. Overview of Treatment-Emergent Adverse Events

Subjects with Event, n (%)	Total (N=22)
All TEAEs	18 (82)
Grade 3–4	11 (50)
Potential irAEs*	3 (14)
Related TEAEs	20 (74)
Grade 3–4	7 (26)
TEAEs leading to discontinuation of either or both drugs	2 (9)
SAEs	5 (23)
TEAEs leading to death	0

irAE = immune-related adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
*Potential irAEs: 1 Grade 3 colitis, 1 Grade 1 hyperthyroidism, and 1 Grade 1 thyroid disorder.

Table 3. Treatment-Related ≥ Grade 3 Adverse Events

Subjects with Event, n (%)	Total (N=22)
Fatigue	2 (9.1)
Injection site pain	2 (9.1)
Injection site swelling	2 (9.1)
Myalgia	2 (9.1)
Atrial fibrillation	1 (4.5)
Colitis	1 (4.5)
Dehydration	1 (4.5)
Headache	1 (4.5)
Influenza-like illness	1 (4.5)
Injection-site erythema	1 (4.5)
Malaise	1 (4.5)
Pain	1 (4.5)

Efficacy

Table 4. Objective Response Rate

Response Rate	n (%)
Evaluable patients*	N=18
Objective response rate, n (%)	6 (33)
95% confidence interval	(16, 56)
Best overall response, n (%)	
Complete response	0
Partial response	6 (33)
Stable disease	4 (22)
Progressive disease†	8 (44)
All enrolled patients	N=22
Not evaluable**	4 (18)
Time to response (days)	
Median	64
Min, max	(62, 128)

*Includes all patients who had a tumor assessment and patients who discontinued the study prior to a scan. Response was assessed by the investigator according to RECIST v1.1. Cut-off date, 27 March 2018. Among patients who had a scan, ORR = 38%. Duration of response data are too immature to assess.
†Two patients had clinical disease progression, including one death, prior to a scan on study.
**Four patients on study have not yet had a tumor assessment.

Figure 4. Best Percent Change From Baseline in Target Lesions

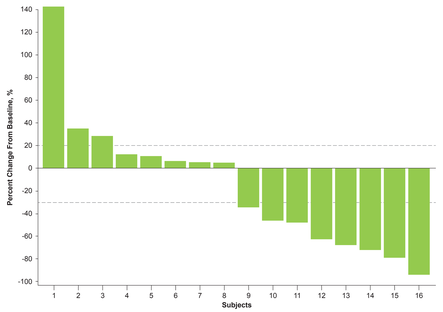


Figure 5. Percent Change From Baseline Over Time in All Target Lesions and Injected and Non-injected Target Lesions

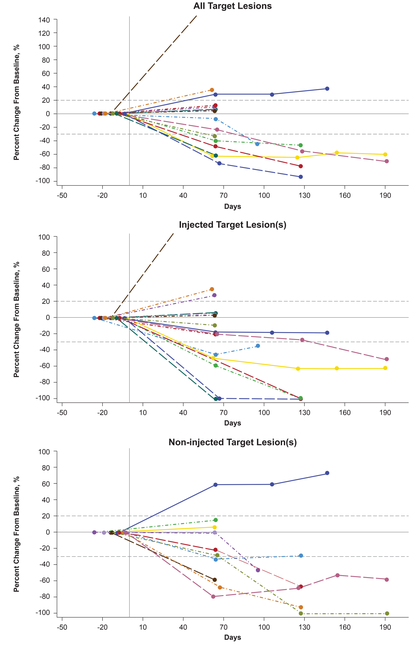
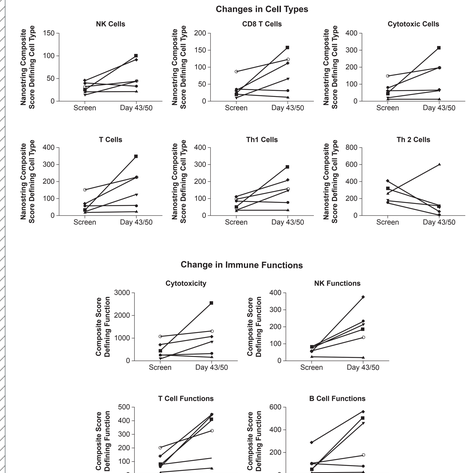


Figure 6. Case Study: Response to Therapy in a Non-Injected Liver Lesion in a Patient With PD. Shown is a CT scan from a 63-year-old male HNSCC patient with Stage IV disease metastatic to the liver at baseline. The patient had a PD-L1-negative tumor and had not previously received anti-PD-1/L1 treatment. On Day 64 the patient had stable disease in target lesions and PD in non-target lesions involving right hepatic lobe and right piriform sinus plus 6 new liver lesions. He continued on treatment, receiving a total of 6 doses of SD-101 and 5 doses pembrolizumab. One month later, the Day 94 scan showed partial response (PR, 45% decrease from baseline) in target lesions (left and right hepatic lobes [shown below] and right neck, level 2 LN) and a decrease in the non-target lesion of the right hepatic lobe, as well as the 6 liver lesions seen on D64. Note, though, the right piriform sinus lesion continued to increase in size. The patient continued on pembrolizumab monotherapy, achieving subsequently a CR in the liver on D248.

Biomarker Analyses

Figure 7. The Combination of SD-101 and Pembrolizumab Induces Broad Immune Activity and a Th1 Response in the Tumor Microenvironment. Immune activity and cellularity of the tumor environment was evaluated using a Nanostring gene expression PanCancer Immune Profiling Panel. Change (N=6) in the profile of immune cells and functions in the tumor microenvironment prior to dosing (screen) and after 3 doses of pembrolizumab and 4 doses of SD-101 (Day 43/50).



CONCLUSIONS

- Intratumoral injection of SD-101 in combination with pembrolizumab was well tolerated.
  - The most common adverse events related to SD-101 treatment were transient, mild-to-moderate flu-like symptoms (fatigue, malaise, chills) and injection-site pain (**Tables 2 and 3**).
  - The combination of SD-101 and pembrolizumab did not increase the frequency or severity of treatment-emergent adverse events observed in prior clinical studies with the individual monotherapies, nor was there evidence of a unique safety signal for the combination.
- Antitumor responses resulted from the combination of SD-101 and pembrolizumab.
  - Preliminary data in evaluable patients showed promising efficacy, with an ORR of 33% (38% among patients who had a scan) (**Table 4, Figures 4, 5, 6**).
  - Pembrolizumab alone had a reported ORR of 15% (ITT population) in KEYNOTE-040.[6]
  - Importantly, responses were observed not only in the SD-101 injected lesion(s), but also in non-injected lesion(s) (**Figure 6**).
    - This included a delayed CR in the liver of a PD-L1 negative patient.
- Biomarker analyses showed the combination induced broad immune activity and a Th1 response in the tumor microenvironment, consistent with findings in another solid tumor studied to date, i.e., melanoma (**Figure 7**).
- In conclusion, SD-101 and pembrolizumab demonstrated promising antitumor activity with an acceptable safety profile in anti-PD-1/L1 naïve recurrent unresectable or metastatic HNSCC. Combining an intratumoral TLR9 innate immune stimulant with PD-1 blockade can potentially increase clinical efficacy with minimal additional toxicity relative to PD-1 blockade alone.

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