Abstract 6039: 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 (SYNERGY-001/KEYNOTE-184, NCT02521870)

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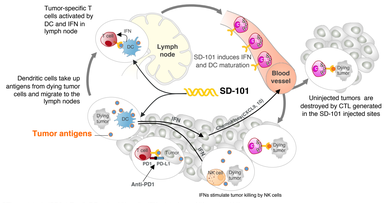
BACKGROUND

- Historically, patients with recurrent unresectable or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) have had a poor prognosis, with limited second-line treatment options (including methotrexate, cetuximab, and paclitaxel) providing an estimated overall response rate (ORR) of 4–14%, a median duration of response (DOR) of 4–7 months, an estimated median progression-free survival (mPFS) of 1.7–3.5 months, and an estimated median overall survival (OS) of less than 7 months.[1]
- KEYTRUDA® (pembrolizumab) is a anti-PD-1 monoclonal antibody (mAb) that received accelerated approval by the FDA to treat patients with R/M HNSCC with disease progression on or after platinum-containing chemotherapy based on results of the KEYNOTE-012 study showing that pembrolizumab monotherapy provided an ORR of 18%.[2,3]
- SD-101 is a synthetic class-C CpG-oligodeoxynucleotide toll-like receptor 9 (TLR9) agonist, which stimulates human plasmacytoid dendritic cells (PDCs) to release interferon-alpha (IFN) and mature into efficient antigen-presenting cells, enhancing both innate and adaptive immune responses (Figure 1).[4]
- 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 un-injected sites.[5]
- In a Phase 1b/2 study of patients with metastatic melanoma, intratumoral injections of SD-101 in combination with pembrolizumab demonstrated clinical responses in both injected and distant lesions.[6]
- Here, we report the results from a phase 2 cohort expansion of patients with R/M HNSCC who were treated with the combination of SD-101 and pembrolizumab. Prior study results were presented at ESMO 2018.[7]

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



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

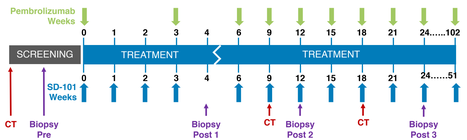
- SD-101 induces PDCs to secrete high levels of interferon-alpha, a potent immunomodulatory cytokine that is able to boost NK cell cytotoxic activity and induce recruitment of T cells. In addition, SD-101 induces DC maturation cross-presentation of tumor associated antigens, inducing CD8+ T cell responses.

METHODS

Phase 2 Expansion Cohort of Phase 1b/2 SYNERGY-001/KEYNOTE-184 Trial

- **Study Treatment:**
  - Investigational Treatment: SD-101 is administered intratumorally 8 mg in 1 lesion or 2 mg in 1–4 lesions
  - Pembrolizumab is administered by I.V. (200 mg)
- **Patients:**
  - Advanced/Metastatic HNSCC
  - ECOG performance status of 0 or 1
  - At least one measurable lesion
  - Anti-PD-1/L1 therapy naïve
- **Primary Endpoint:**
  - Objective response rate in intent-to-treat (ITT) population assessed by RECIST v1.1
- **Secondary Endpoints:**
  - Safety and tolerability, progression-free survival, duration of response, and immunophenotype of the tumor environment

Figure 2. Treatment Schema



CT, Computed Tomography Scan

RESULTS

Table 1. Baseline Patient and Disease Characteristics

Characteristics	2 mg/lesion (N=27)	8 mg/lesion (N=23)
Median age, years; Median (Min, Max)	63 (38, 93)	65 (43, 91)
Sex, (%), Male/female	66.7 / 33.3	91.3 / 8.7
ECOG PS, %, 0/1	18.5 / 81.5	26.1 / 73.9
Primary tumor location, n (%)		
Hypopharyngeal	2 (7.4)	0
Nasopharyngeal	0	3 (13.0)
Oral	13 (48.1)	13 (56.5)
Oropharyngeal	8 (29.6)	2 (8.7)
Laryngeal	3 (11.1)	4 (17.4)
Unknown	0	1 (4.3)
PD-L1 Status, n (%)		
Negative (< 1%)	2 (7.4)	4 (17.4)
Positive (≥ 1%)	9 (33.3)	14 (61.4)
Pending/Missing	16 (59.3)	5 (21.7)
HPV status, n (%)		
Negative	11 (40.7)	7 (30.4)
Positive	9 (33.3)	5 (21.7)
Unknown/pending	7 (25.9)	11 (47.8)
Prior radiotherapy, n (%)	18 (66.7)	19 (82.6)
Prior surgery, n (%)	22 (81.5)	22 (95.7)
0/1/2/≥3 prior lines of therapy, n	9/14/3/1	3/11/6/3
Prior systemic therapy (no anti-PD-1/PD-L1)	20 (74.1)	20 (86.9)
Staging, n (%)		
Local	3 (11.1)	1 (4.3)
Metastatic	16 (59.3)	10 (43.5)
Local/metastatic	7 (25.9)	6 (26.1)
NA	0	1 (4.3)
Organ involvement, n (%)		
Liver	1 (3.7)	1 (4.3)
Lung	7 (25.9)	6 (26.1)
Bone	1 (3.7)	2 (8.7)
Skin/subcutaneous tissue	4 (14.8)	7 (30.4)
Lymph nodes	14 (51.9)	11 (47.8)
Other organs	12 (44.4)	15 (65.2)
Number of target lesions, n (%)		
1	11 (40.7)	6 (26.1)
2	11 (40.7)	5 (21.7)
3+	5 (18.5)	11 (47.8)

ECOG PS = Eastern Cooperative Oncology Group performance status; HPV = human papillomavirus; NA = Not Applicable

Safety

Table 2. Safety Summary

Event, n (%)	2 mg/lesion (N=27)	8 mg/lesion (N = 23)
Subjects with at least one Treatment-Related AE	19 (70.4)	21 (91.3)
Grade 3 & 4	3 (11.1)	8 (34.8)
Immune-related AEs (all grades)	3 (11.1)	4 (17.3)
Hypothyroidism	2 (7.4)	2 (7.4)
Hyperthyroidism	0	1 (4.3)
Pneumonitis	1 (3.7)	0
Colitis	0	1 (4.3)

AE = Adverse events

Efficacy

Table 3. Best Overall Response for ITT Population by RECIST

Best Overall Response Rate (ITT)	2 mg Cohort (N=27)	8 mg cohort (N=23)	Total N (N=50)
Objective response rate, n (%) (95% CI)	6 (22.2) (not mature) (8.6, 42.3)	6 (26.1) (10.2, 48.4)	12 (24.0) (13.1, 38.2)
Disease control rate, n (%)	13 (48)	10 (43.5)	32(44.0)
Best overall response, n (%)			
Complete response	2 (7.4)	0	2 (4.0)
Partial response	4 (14.8)	6 (26.1)	10 (20.0)
Stable disease	7 (25.9)	4 (17.4)	11 (22.0)
Progressive disease	11 (40.7)	10 (43.5)	21 (42.0)
Not evaluable	3 (11.1)	3 (13)	6 (12.0)
Time to response (months)			
Median	2.1	2.1	2.1
Min, max	1.5, 4.1	(2.0, 4.2)	1.5, 4.2
Duration of response			
Median	3.1 (not mature)	5.7	3.8 (not mature)
Min, Max	(2.0, 4.2)	(2.1, 11.1)	(2.0, 11.1)
Progression Free Survival at 9 months (%)	17.7 (4.1, 39.1)	17.4 (5.4, 35.0)	18.2 (8.4, 31.1)
Overall Survival at 9 months (%)	79.9 (57.6, 91.2)	56.9 (31.2, 76.1)	64.3 (44.6, 78.5)

Table 4. Objective Response by PDL1 (CPS Score) and HPV Expression Status (P16 expression) (Pooled 8 mg and 2 mg Per Injection)

Best Overall Response Rate (ITT)	PD-L1 < 1 (N=2)	PD-L1 ≥1 to 20 (N=12)	PD-L1 >20 (N=16)	PD-L1 Unknown (N=20)	HPV Positive (N=14)	HPV Negative (N=19)	HPV Unknown (N=18)
ORR, n (%)	0	4 (33.3)	4 (25.0)	4 (20.0)	5 (35.7)	2 (11.1)	5 (27.8)
(95% CI)					(12.8, 64.9)	(1.4, 34.7)	(9.7. 53.5)
Best overall response, n (%)							
CR	0	0	0	2 (10.0)	1 (7.1)	1 (5.6)	0
PR	0	4 (33.3)	4 (25.0)	2 (10.0)	4 (28.6)	1 (5.6)	5 (27.8)
SD	0	1 (8.3)	3 (18.8)	7 (35.0)	3 (21.4)	5 (27.8)	3 (16.7)
PD	2 (100)	7 (58.3)	9 (56.3)	5 (25.0)	4 (28.6)	9 (50.0)	8 (44.4)
NE	0	0	0	0	2 (14.3)	2 (11.1)	2 (11.1)

Assessed using PDL1 IHC 22C3 PharmDx assay. Combined positive score (CPS) = number of PD-L1+ cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells X 100

Figure 3. Best Percent Change from Baseline in Target Lesion(s)

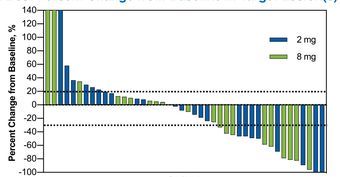


Figure 4. Duration of Follow-up and Patient Status

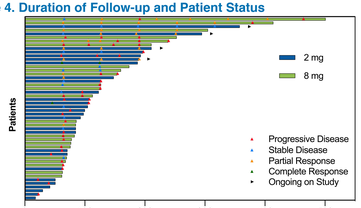
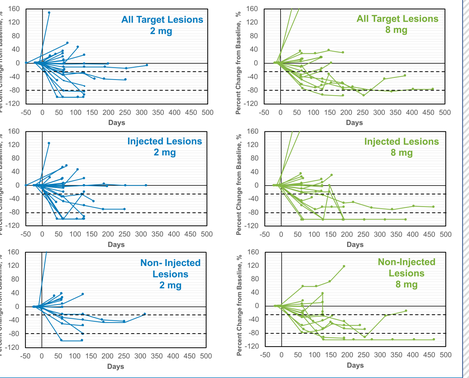
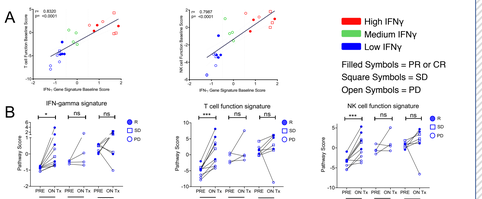


Figure 5. Percent Change From Baseline in Target Lesions



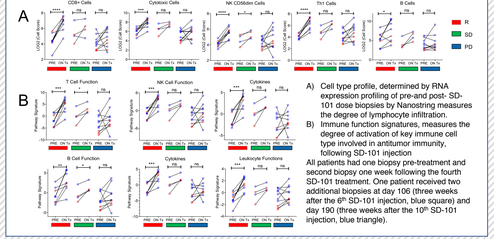
IMMUNE-RELATED BIOMARKERS

Figure 6. Patients Whose Tumors Showed Low IFNγ Signature at Baseline Respond to SD-101 Treatment



A) Patients whose tumors exhibit a low IFNγ signature score at baseline[8] (Blue; score less than -0.5) have low T cell and NK cell function signature scores, consistent with immunologically cold tumors.
B) Patients whose tumors showed low IFNγ at baseline respond to SD-101 and demonstrate immunomodulation of relevant gene signatures and clinical response.

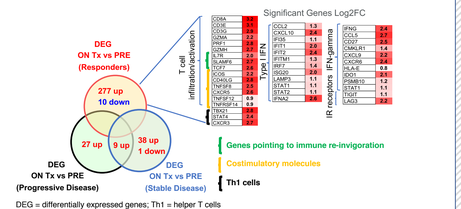
Figure 7. Increase in Infiltration of Immune Cells Correlates with Clinical Response



A) Cell type profile, determined by RNA expression profiling of pre-and post- SD-101 dose biopsies by Nanostring measures the degree of lymphocyte infiltration.
B) Immune function signatures, measures the degree of activation of key immune cell type involved in antitumor immunity, following SD-101 injection

All patients had one biopsy pre-treatment and second biopsy one week following the fourth SD-101 treatment. One patient received two additional biopsies at day 106 (three weeks after the 6th SD-101 injection, blue square) and day 190 (three weeks after the 10th SD-101 injection, blue triangle).

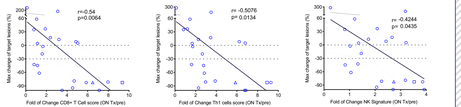
Figure 8. Comparison of Pre-treatment to On-treatment Tumor Biopsies



DEG = differentially expressed genes; Th1 = helper T cells

Analysis of changes in gene expression was performed using nSolver software (Nanostring). Differentially expressed genes (DEG; cut off:LOG2FC≥0.6, p=0.05) in between matched on treatment (ON Tx) and baseline (PRE) biopsies were obtained for patients experiencing response (PR and CR), Progressive Disease (PD) or stable disease (SD). Venn diagram showing the number and overlap of the differentially expressed genes identified in each of the 3 comparisons. Example of DEG pointing to the strong infiltration of activated T cells and to the increase in Type I and II IFNs.

Figure 9. Increase in Density of Immune Cells Correlates with Overall Decrease in Tumor Burden



Fold of changes in lymphocyte infiltration within SD-101 treated lesions was correlated with the maximum percentage change in target lesions from baseline using Pearson correlation coefficient. All patients had one biopsy at baseline and second biopsy one week following the fourth SD-101 treatment. One patient received two additional biopsies at day 106 (three weeks after the 6th SD-101 injection, blue square) and day 190 (three weeks after the 10th SD-101 injection, blue triangle).

CONCLUSIONS

- In this study, SD-101 shows encouraging and comparable therapeutic efficacy at the two dose levels explored: 2 mg per injection and 8 mg for one injection
  - Both dose levels in combination with pembrolizumab appear equivalent in terms of ORR, DOR and PFS
- Responses were observed in SD-101 injected and non-injected lesions
- Responses and disease control were observed in patients with low PD-L1 status at baseline (CPS ≥1–20). An encouraging ORR of 36% was observed in patients with HPV-positive tumors
- Biomarker data are consistent with the mechanism of action of SD-101 and demonstrate strong immunomodulation of the tumor microenvironment including infiltration of activated T cells and upregulation of Type I and Type II IFNs
- Importantly, similarly to what was reported for melanoma naïve patients (ASCO 2019 Abstract 9534), patients whose tumors exhibit an immunologically cold tumor microenvironment at baseline (low IFNγ and T cell signatures) show clinical response during SD-101 plus pembrolizumab treatment
- The combination of SD-101 and pembrolizumab was well-tolerated, consistent with previous reports
  - No evidence of an increased incidence or severity of AEs over pembrolizumab monotherapy
  - No increase in immune-related AEs over pembrolizumab monotherapy
  - AEs associated with SD-101 were mainly mild to moderate injection-site reactions and flu-like symptoms that were manageable with over-the-counter medication

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