Abstract 3560: 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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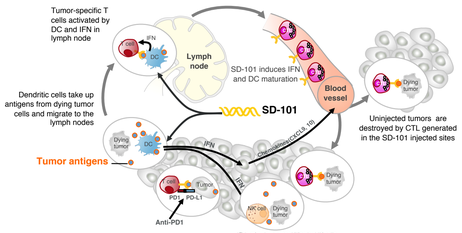
BACKGROUND

- 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% with 85% of those responses lasting ≥6 months.[2,3]
- SD-101 is a synthetic Class-C CpG-oligodeoxynucleotide toll-like receptor nine (TLR9) agonist, which stimulates human plasmacytoid dendritic cells (PDCs) to release interferon-alpha 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.

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

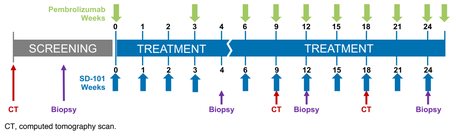
- SD-101 induces PDCs to secrete high levels of interferon-alpha, a potent immunomodulatory cytokine that is able to boost NK cell cytotoxic activity and induce recruitment of T cells. In addition, SD-101 induces DC maturation cross-presentation of tumor associated antigens, inducing CD8+ T cell responses.

METHODS

Ongoing Phase 1b/2, Open-label, Multicenter, Expansion Study of Intratumoral SD-101 in Combination With Pembrolizumab (NCT02521870, SYNERGY-001 DV3-MEL-01/Keynote-184)

- **Patients:**
  - Advanced/metastatic head and neck squamous cell carcinoma
  - Prior anti-PD-1/PD-L1 naïve
  - ECOG performance status of 0 or 1
  - At least one injectable lesion
- **Study Treatment:**
  - Two dose levels were assessed: **8 mg one lesion** and **2 mg per lesion up to 4 lesions**
  - Pembrolizumab was administered IV (200 mg Q3W)

Figure 2. Study Design



CT, computed tomography scan.

- **Primary Endpoint:** Overall response rate assessed by RECIST v1.1 and reported for the modified intent-to-treat (mITT) population that excludes patients on study who have not yet reached the first CT scan.
- **Secondary Endpoints:** Safety and tolerability, DOR, time to relapse, pharmacodynamics, immunophenotype of the tumor environment
- **Data cutoff date**: August 16, 2018

RESULTS

Table 1. Demographics and Baseline Characteristics

Characteristics	8 mg (n=23)	2 mg (n=10)
Median age, years (Min, Max)	65 (43, 91)	60 (38, 84)
Male/female sex, %	91/9	50/50
ECOG PS 0 or 1, %	100	100
Primary tumor location, n (%)		
Hypopharyngeal	1 (4.3)	1 (10.0)
Nasopharyngeal	1 (4.3)	0
Oral	10 (43.4)	4 (40.0)
Oropharyngeal	5 (21.7)	2 (20.0)
Laryngeal	3 (13.0)	1 (10.0)
Unknown	3 (13.0)	2 (20.0)
HPV status, n (%)		
Negative	6 (26.0)	5 (50.0)
Positive	3 (13.0)	2 (20.0)
Unknown	14 (60.8)	3 (30.0)

ECOG PS = Eastern Cooperative Oncology Group performance status; HPV = human papillomavirus

Table 2. Baseline Disease Characteristics: SD-101 8 mg or 2 mg/Injection

Characteristics	8 mg (n=23)	2 mg (n=10)
Prior radiotherapy, n (%)	18 (78.3)	5 (50.0)
Prior surgery, n (%)	21 (91.3)	8 (80.0)
0/1/2/≥3 prior lines of therapy, n	4/11/5/3	4/6/0/0
Prior systemic therapy*	19 (82.6)	6 (60.0)
Organ involvement, n (%)		
Liver	1 (4.3)	0
Lung	6 (26.1)	3 (30.0)
Bone	2 (8.7)	0
Skin/subcutaneous tissue	7 (30.4)	1 (10.0)
Lymph nodes	11 (47.8)	2 (20.0)
Other organs	15 (65.2)	2 (20.0)
Number of Target Lesions:		
1	6 (26.1)	4 (40.0)
2	5 (21.7)	3 (30.0)
3	8 (34.8)	0
4	1 (4.3)	1 (10.0)
5	2 (8.7)	0

* No patients received prior PD-1/PD-L1/CTLA-4 therapy

Efficacy

Table 3. Objective Response Rate: SD-101 8 mg or 2 mg/injection

	8 mg	2 mg
mITT patients, n*	22	2
Objective response rate, n (%)	6 (27.3)	
95% confidence interval	(16, 56)	
Best overall response, n (%)		
Complete response	0	
Partial response	6 (27.3)	
Stable disease	4 (18.2)	2 (100)
Progressive disease	10 (45.5)	
Time to response (months)		
Median	2.1	
Min, max	(2.0, 4.2)	
Duration of response (months)		
Median	3.6+	
Min, Max	(0.0, 6.9)	

* mITT = excluding patients on treatment but did not yet have their first CT scan and tumor assessment

Figure 3. Percent Change From Baseline for Target Lesions: SD-101 8 mg

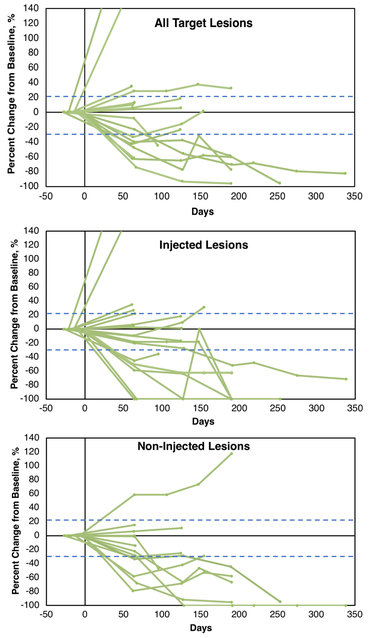


Figure 4. Current Patient Status with SD-101 8 mg

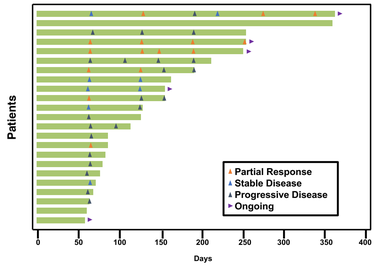


Table 4. PD-L1 Expression Data and Efficacy: SD-101 8 mg

Subject	Best Response	TPS	
1	PD	0	PD-L1 negative
2	PD	0	
3	PR	<1	
4	SD	2	PD-L1 positive
5	PD	5	
6	PD	10	
7	PD	10	
8	PD	15	
9	PR	30	
10	PR	40	
11	PD	60	
12	PR	90	
13	PD	95	

TPS: tumor proportion score; additional PD-L1 expression data pending

Safety

Table 5. Safety Summary: SD-101 8 mg or 2 mg/Injection*

Event, n (%)	8 mg (n=23)	2 mg (n=7)
Any Treatment-related AE	19 (82.6)	2 (28.6)
Grade 3-4	8 (34.8)	0
Chills	0	0
Myalgia	2 (8.7)	0
Influenza-like synd.	1 (4.3)	0
Injection-site pain	2 (8.7)	0
Fatigue	4 (17.4)	0
Headache	1 (4.3)	0
Malaise	1 (4.3)	0
Cellulitis	1 (4.3)	0
AEs leading to d/c of either or both drugs	5 (21.7)	1 (14.3)
SAEs	6 (26.1)	1 (14.3)
Treatment-related SAEs	2 (8.7)	0
Death (treatment-related)	0	0

d/c = discontinuation; SAE = Serious adverse event
* Three patients in the 2 mg cohort have insufficient follow-up for safety assessment

Table 6. Immune-Related Adverse Events: 8 mg and 2 mg/Injection*

Event, n (%)	8 mg (n=23)	2 mg (n=7)
irAEs All grades	7 (30.4)	0
Hypothyroidism	1 (4.3)	0
Pneumonitis	1 (4.3)	0
Myositis	2 (8.6)	0
Hepatitis	2 (8.6)	0
Colitis	1 (4.3)	0

irAE = immune-related adverse event
* Three patients in the 2 mg cohort have insufficient follow-up for safety assessment

CONCLUSIONS

- 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 transient, mainly mild to moderate injection-site reactions and flu-like symptoms that were manageable with over-the-counter medications
- The combination therapy showed promising efficacy in patients with HNSCC, with an ORR of 27.3%
  - Responses were observed in both SD-101 injected and non-injected lesions
  - Responses were observed in both PD-L1 negative and positive tumors

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This study was sponsored by Dynavax Technologies Corporation in collaboration with Merck & Co., Inc., Kenilworth, NJ USA. We thank the patients and their families and caregivers for participating in the study; the participating study teams and Albert Candia, Brit Harvey, Kavya Kazipeta and Tripta Dahiya for contributions to the analysis of the data (Dynavax Technologies Corporation). Copies of this poster obtained through QR (Quick Response) and/or text key codes are for personal use only and may not be reproduced without written permission of the authors.

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