Abstract 3781: Phase 1b/2, Open-Label, Multicenter Study of Intratumoral SD-101 in Combination With Pembrolizumab in Patients With Advanced Melanoma Resistant/Refractory to Anti-PD-1/PD-L1 Therapy (SYNERGY-001/KEYNOTE-184, NCT02521870)

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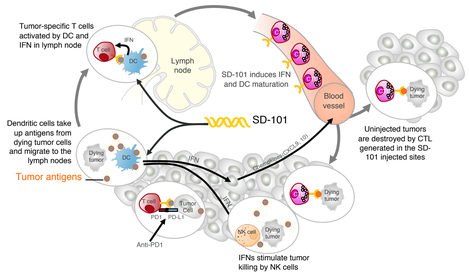
BACKGROUND

- PD-1 blockade has significantly improved outcomes in advanced melanoma, yet durable responses are elicited in less than half of the patients, therefore this remains an area of unmet need.[1]
- KEYTRUDA® (pembrolizumab) is an anti-PD-1 monoclonal antibody (mAb) that is approved by the FDA to treat patients with unresectable or metastatic melanoma.[1]
- 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).[2]
- Preclinical studies of anti-PD-1 non-responder mouse tumor models 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.[3]
- In the phase 1b portion of this study, intratumoral injections of SD-101 in combination with pembrolizumab demonstrated clinical responses in both injected and distant lesions of patients with metastatic melanoma.[4]
- Here, we report the results from a phase 2 expansion cohort of patients with advanced melanoma resistant/refractory (R/R) to anti-PD-1/PD-L1 therapy who were treated with the combination of SD-101 and pembrolizumab. Preliminary results from the phase 1b portion of this study were presented at AACR 2018 (Abstract: CT139) and published in Cancer Discovery (2018): Ribas, A., et al.[5,6]

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.

STUDY OBJECTIVE

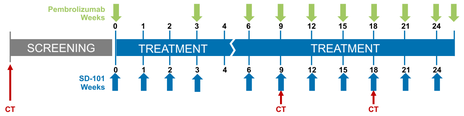
- To confirm the safety profile and assess the efficacy of SD-101 and pembrolizumab combination therapy in patients with advanced melanoma who were R/R to anti-PD-1 therapy.

METHODS

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

- **Patients:**
  - Stage IIIC, Stage IV Metastatic Melanoma
  - Resistant or refractory to prior anti-PD-1/PD-L1 therapy
  - ECOG performance status of 0 or 1
  - At least 2 lesions that qualify as a target lesion per RECIST v1.1, and 1 of the qualifying lesions must be easily accessible and amenable to multiple intratumoral injections. The target lesion should be of sufficient size such that the required tumor biopsies do not significantly affect tumor assessment per RECIST v1.1.
- **Study Treatment:**
  - SD-101 was administered intratumorally in one target lesion, 8 mg Weekly x 4 doses then Q3W x 7 doses*
  - 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
- Secondary Endpoints: Safety and tolerability, duration of response, and immunophenotype of the tumor environment

*Out of 38 patients, 4 patients treated with 4 mg per injection and 4 patients treated with up to 2 mg per injection in other cohorts were excluded; 30 patients have been treated with 8 mg per injection.

RESULTS

Table 1. Demographics and Baseline Characteristics

Characteristics	N = 30
Median age, years (Min, Max)	64 (53, 76)
Male, n (%)	23 (76.7)
ECOG PS 0/1, n (%)	30 (100)
Baseline LDH, mean (SD)	223 (3.0, 1886.0)
≤ULN, n (%)	17 (55%)
>1 to ≤2 ULN, n (%)	9 (29%)
>2 ULN, n (%)	4 (13%)
Stage at Screening, n (%)	
IIIC	10 (33.3)
IV	19 (63.3)
Missing	1 (3.3)
Metastases involving:	
Skin/Subcutaneous tissue	20 (66.7)
Lymph Nodes	15 (50)
Liver	9 (30)
Lung	6 (20)
Bones	3 (10)
Other	13 (43.3)
PD-L1 expression, n (%)*	
Positive (≥1%)	4 (13.3)
Negative (<1%)	13 (43.3)
Pending	13 (43.3)

ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; SD = standard deviation; ULN = upper limit of normal; * Expression determined using Dako 22C3 antibody

Table 2. Baseline Disease Characteristics

Characteristics, n (%)	N = 30
Prior radiotherapy	6 (20)
Prior surgery	28 (93.3)
Prior lines of therapy, 1/2/≥3	11/8/11
PD1/PD-L1 therapy	
Resistant*	18 (60)
Refractory**	12 (40)
Prior CTLA-4 therapy	12 (40)

* Resistant: progressive disease after at least 3 months on treatment and initial objective response or stable disease. A disease with a relapse while on adjuvant treatment or within 6 months after the end of an adjuvant treatment is also considered resistant.
**Refractory: tumor initially resistant, best confirmed response is progressive disease while on treatment.

Efficacy

Table 3. Best Overall Response in mITT by RECIST

Best ORR, n (%)	N = 29 (mITT*)
Objective response rate	6 (21.4)
Complete response	1 (3.4)
Partial response	5 (17.2)
Duration of response (months), median (min, max)	2.1 (1.0, 6.1)
Stable disease	5 (17.2)
Disease Control Rate	11 (38.0)
Progressive disease	11 (37.9)

Note: Patients receiving 1 and 2 mg dosing were excluded (1 of 4 patients who received 1 or 2 mg dosing experienced a partial response)
*mITT: excluding patients on treatment but did not yet have their first CT scan and tumor assessment

Figure 3. Best Percent Change from Baseline in Target Lesions

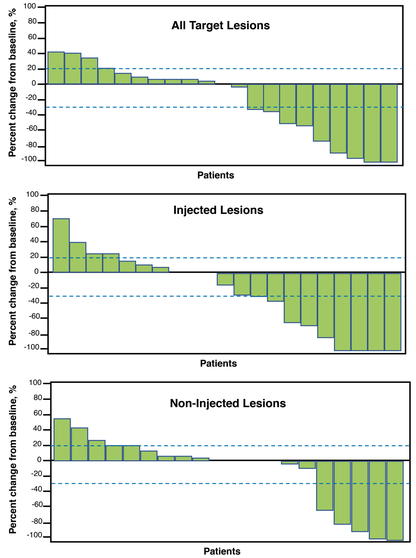


Figure 4. Percent Change from Baseline Over Time

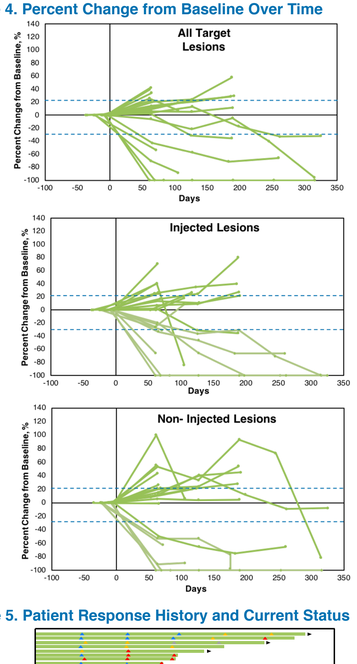


Figure 5. Patient Response History and Current Status

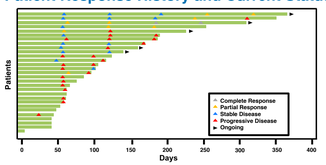


Table 4. PD-L1 Expression Levels and Efficacy

Patient	Best Response	TPS	
1	PR	0	PD-L1 negative
2	SD	0	
3	SD	0	
4	PD	0	
5	PD	0	
6	PD	0	
7	PR	<1	
8	SD	<1	
9	PD	<1	
10	SD	1	PD-L1 positive
11	SD	1	
12	PD	1	
13	PD	1	
14	CR	3	
15	PR	10	
16	PR	10	
17	PD	90	

TPS: tumor proportion score; PD-L1 expression data are pending for 13 patients

CONCLUSIONS

- The combination of SD-101 and pembrolizumab was well tolerated, consistent with previous reports:
  - AEs associated with SD-101 were transient, mild to moderate injection-site reactions and flu-like symptoms that were manageable with over-the-counter medications
  - Low incidence of immune-related AEs
- Preliminary data showed encouraging efficacy, with an ORR of 21.4%
  - Responses were observed in both SD-101 injected and non-injected lesions; however, it is too early to determine the durability of responses
  - Responses and disease control were observed in PD-L1 positive and negative tumors
  - The addition of SD-101 to pembrolizumab appears to restore tumor sensitivity to PD-1 inhibitor in patients who are R/R to anti-PD1/PD-L1 therapy
- Based on results from the phase 2 study in PD-1/PD-L1 naive patients demonstrating higher efficacy of multiple 2mg injections (up to 4 injections) compared to 1 injection of 8 mg, a phase 2 study with the new dosing of 2 mg per injection is ongoing

SAFETY

Table 5. Safety Summary

Event, N (%)	N = 30
Any Treatment-related AE	24 (80)
Grade 3-4	12 (40)
Chills	1 (3.3)
Myalgia	2 (6.6)
Injection-site pain	1 (3.3)
Fatigue	2 (6.6)
Headache	0
Malaise	2 (6.6)
Vomiting	3 (10)
Any irAEs	4 (13.3)
Grade 3-4	2 (6.6)
AEs leading to d/c of either or both drug	4 (13.3)
SAEs	3 (10)
Death**	1 (3.3)

irAE = immune-related adverse event; d/c = discontinuation; SAE = serious adverse event
**Death not related to study treatment

Table 6. Immune-Related Adverse Events

Event, n (%)	N = 30
irAEs all grades	4 (13.3)
Hypothyroidism	1 (3.3)
Pneumonitis	1 (3.3)
Autoimmune hepatitis	1 (3.3)
Pancreatitis	1 (3.3)

REFERENCES

1. Keytruda (pembrolizumab) for injection, for intravenous use [package insert]. Merck Sharp & Dohme Corp, Whitehouse Station, NJ USA. 2014.
2. Guiducci C, et al. J Exp Med 2006;203:1999-2008.
3. Wang S, et al. Proc Natl Acad Sci U S A, 2016. 113(46):E7240-e7249.
4. Leung ACF, et al. Journal of Clinical Oncology 2017;35:15 (suppl):9550.
5. Ribas A, et al. Cancer Res 2018;78 (13 Supplement):CT139.
6. Ribas A, et al. Cancer Discovery 2018; DOI: 10.1158/2159-8290.CD-18-0280.

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