LBA45: Phase 1b/2, Open Label, Multicenter, Study of the Combination of SD-101 and Pembrolizumab in Patients with Advanced Melanoma Who Are Naïve to Anti-PD-1/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, agonist of toll-like receptor 9 (TLR9). SD-101 stimulates human plasmacytoid dendritic cells to release interferon-alpha and mature into efficient antigen-presenting cells, enhancing both innate and adaptive immune responses.[2]
- Preclinical studies in multiple 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 non-injected sites.[3]
- In a previous phase 1b/2 study of patients with indolent non-Hodgkin's lymphoma, treatment of a single lesion with low dose radiation and intratumoral SD-101 induced abscopal tumor shrinkage in 83% of patients.[4]
- Here, we report the latest results from the phase 1b dose escalation and phase 2 expansion cohort of patients with advanced melanoma naïve to anti-PD-1/L1 therapy who were treated with the combination of SD-101 and pembrolizumab. (Updates data presented at ASCO 2018 (Abstract 9513)[5]. Results of the phase 1b portion of this study were published in Ribas, A., et al., Cancer Discovery (2018).[6]

METHODS

Phase 1b/2 Trial (SYNERGY-001/KEYNOTE-184)

Phase 1b Dose Escalation*

- SD-101 **2 mg** i.t. + Pembrolizumab 200 mg i.v.
- SD-101 **4 mg** i.t. + Pembrolizumab 200 mg i.v.
- SD-101 **8 mg** i.t. + Pembrolizumab 200 mg i.v.
- SD-101 **1 mg** i.t.† + Pembrolizumab 200 mg i.v.

Phase 2 Dose Expansion

SD-101 **2 mg i.t. in up to 4 lesions** + Pembrolizumab **200 mg** i.v.

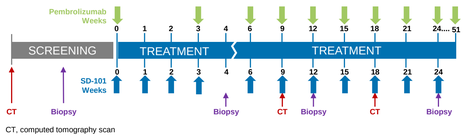
OR

SD-101 **8 mg i.t. in one lesion** + Pembrolizumab **200 mg** i.v.

*DLT period 29 days; †3 patients received 1 mg/lesion; i.t.= intratumoral; i.v. = intravenous. Data Cutoff: September 21, 2018

- **Patients:**
  - Unresectable Stage IIIC, Stage IV Metastatic Melanoma
  - ECOG performance status of 0 or 1
  - No prior anti-PD-1/L1 therapy
  - At least one injectable lesion

Figure 1. Study Design



CT, computed tomography scan

- **Primary Endpoint:** Objective response rate assessed by RECIST v1.1
- **Secondary Endpoints:** Safety and tolerability, progression-free survival, duration of response, and immunophenotype of the tumor environment

RESULTS

Table 1. Demographics and Baseline Characteristics (Phase 1b/2)

Characteristics	2 mg/lesion n = 47	8 mg/lesion n = 40
Median age, years (Min, Max)	66 (36, 85)	66 (33, 89)
> 65 years, n (%)	30 (64)	23 (58)
Male, n (%)	33 (70)	26 (65)
ECOG PS 0, n (%)	30 (64)	30 (75)
Baseline LDH, median (Q1, Q3)	193 (162, 234)	195 (177, 238)
> ULN, n (%)	8 (17)	10 (25)
Stage at Screening, n (%)		
IIIC	10 (21)	8 (20)
IV	37 (79)	32 (80)
M1a	16 (34)	11 (28)
M1b	9 (19)	9 (23)
M1c	12 (26)	12 (30)
PD-L1 Expression, n (%)*		
Positive (≥1%)	19 (40)	13 (33)
Negative (<1%)	15 (32)	15 (38)
Pending	13 (28)	12 (30)
Prior lines of therapy, 0 / 1 / 2 / ≥3. n (%)	34 / 11 / 2 / 0 (72 / 23 / 4 / 0)	28 / 11 / 0 / 1 (70 / 28 / 0 / 3)

ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; Q1 = first quartile; Q3 = third quartile; ULN = upper limit of normal; * Expression determined by tumor proportion score using Dako 22C3 antibody

Safety

Table 2. Safety Summary

Event, N (%)	2 mg/lesion n = 47	8 mg/lesion n = 40	Total N = 87
Any Treatment-related AE	43 (91)	37 (93)	80 (92)
Grade 3-4	12 (26)	16 (40)	28 (32)
Chills	4 (9)	1 (3)	5 (6)
Myalgia	5 (11)	0	5 (6)
Fatigue	2 (4)	3 (8)	5 (6)
Headache	4 (9)	2 (5)	6 (7)
Malaise	3 (6)	2 (5)	5 (6)
Any irAEs	10 (21)	6 (15)	16 (18)
Grade 3-4	3 (6)	1 (3)	4 (5)
AEs leading to d/c of either or both drug	7 (15)	13 (33)	20 (23)
SAEs	14 (30)	15 (38)	29 (33)
Death	0	1 (3)	1 (1)

irAE = immune-related adverse event; d/c = discontinuation; SAE = serious adverse event.
Note: death was considered not related to drug

Table 3. Immune-Related Adverse Events

Event	2 mg/lesion n = 47	8 mg/lesion n = 40	Total N = 87
irAEs all grades, n (%)			
Hypothyroidism	7 (15)	3 (8)	10 (12)
Pneumonitis	2 (4)	1 (3)	3 (3)
Myositis	1 (2)	1 (3)	2 (2)
Autoimmune retinopathy	0	1 (3)	1 (1)
Autoimmune hepatitis	0	1 (3)	1 (1)
Myasthenia gravis	0	1 (3)	1 (1)
Colitis	1 (2)	0	1 (1)
Autoimmune colitis	1 (2)	0	1 (1)
Hypophysitis	2 (4)	0	2 (2)
Hyperthyroidism	1 (2)	0	1 (1)
Autoimmune myocarditis	0	1 (3)	1 (1)
Optic neuritis	0	1 (3)	1 (1)

Efficacy

Table 4. Best Overall Response by RECIST v1.1 (ITT Population)

	2 mg/lesion n = 47	8 mg/lesion n = 40
Objective response rate, n (%) [95% CI]	**33 (70) [56, 81]**	**19 (48) [33, 63]**
Complete response	5 (11)	2 (5)
Partial response	28 (60)	17 (43)
Time to response, median (months)	2.1	2.3
Duration of response, median (months) (95% CI)	**Not reached (9.0, NE)**	**Not reached (8.2, NE)**
Stable disease, n (%)	4 (9)	8 (20)
Disease Control Rate, n (%)	37 (79)	27 (68)
Progressive disease, n (%)	6 (13)	9 (23)
Non-evaluable*, n (%)	4 (9)	4 (10)

*Patients discontinued prior to first scan: 2 mg—clinical progression (n=2), irAE (n=1), withdrew consent (n=1); 8 mg—clinical progression (n=1), unrelated AE/death (n=1); irAE (n=1), withdrew consent (n=1). CI = confidence interval; ITT= Intention to treat; NE=not estimable
NOTE: Two patients in the 2 mg group with recently reported PRs are not reflected in the figures

Table 5. Responses in Both PD-L1 Negative and Positive Tumors

PD-L1 Expression	2 mg/lesion N	2 mg/lesion ORR (%)	8 mg/lesion N	8 mg/lesion ORR (%)
≥1%	19	79	13	62
<1 %	15	80	15	33
Pending/missing	13	46	12	50

ORR= objective response rate; PD-L1 expression based on tumor proportion score (Dako 22C3 antibody)

Figure 2. Best Percent Change From Baseline in All Target Lesions

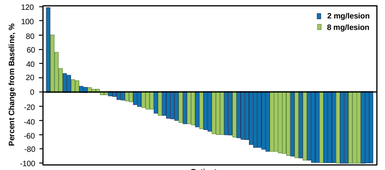


Figure 3. Duration of Follow Up and Patient Status

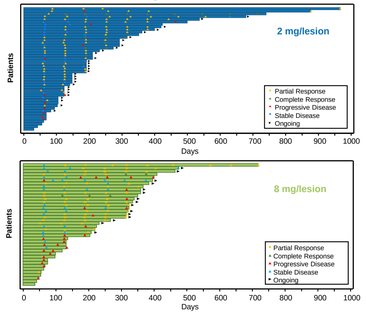


Figure 4. Responses in Two Non-injected Liver Lesions in a Patient with PD-L1 Expression of 1% who Received 2 mg of SD-101 in a Single Lesion

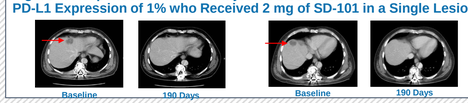
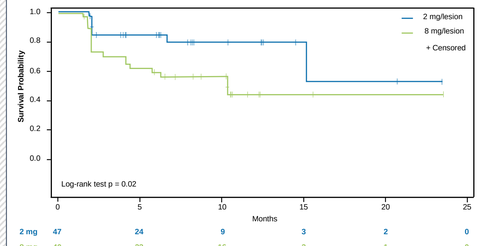


Figure 5. Progression-free Survival (ITT Population)



2 mg	47	24	9	3	2	0	
8 mg	40	23	16	2	1	0	

Table 6. Progression-free Survival (ITT Population)

	2 mg/lesion	8 mg/lesion
PFS (Kaplan-Meier method)		
6-month rate (95% CI)	85% (70, 93)	60% (42, 73)
Median (months) (95% CI)	not reached (15.2, NE)	10.4 (4.2, NE)
Follow-up, median (months)	5.9	6.9

. CI = confidence interval; ITT = intention to treat; NE=not estimable; PFS = progression-free survival

Figure 6. Percent Change From Baseline Over Time for Target Lesions in Patients Who Received 2 mg or 8 mg SD-101 Per Lesion

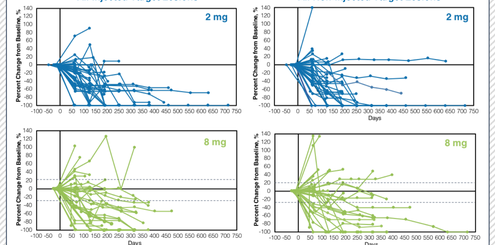
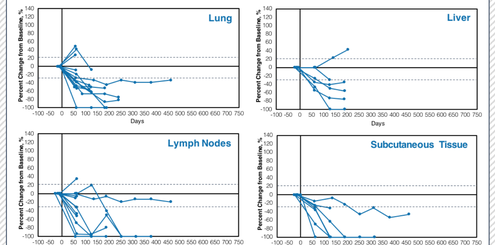


Figure 7. Percent Change From Baseline Over Time in Non-injected Target Lesions by Organ System (2 mg SD-101 Per Lesion)

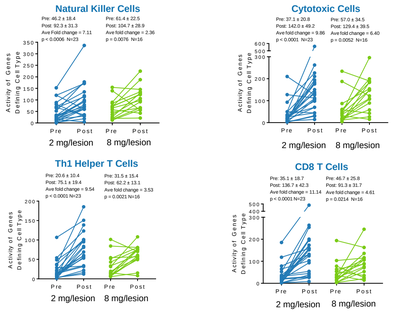


CONCLUSIONS

- The addition of 2 mg/lesion of SD-101 to pembrolizumab appears to increase immune activity in the tumor microenvironment and efficacy compared with 8 mg/lesion in similar patient populations
  - The ORR in the 2 mg/lesion SD-101 group (70%) was higher than in the 8 mg/lesion SD-101 group (48%)
  - The median PFS in the 2 mg/lesion group (15.2+ months) was significantly longer than in the 8 mg/lesion group (10.4 months)
  - The median DOR in both groups has not been reached
  - Responses occurred in patients with PD-L1 negative tumors and PD-L1 positive tumors
  - Tumor shrinkage occurred in injected lesions, and non-injected visceral lesions including in the liver and lung
- The combination of SD-101 and pembrolizumab was well tolerated, consistent with previous reports
  - AEs associated with SD-101 were transient, mild to moderate flu-like symptoms that were manageable with over-the-counter medications
  - No increase in immune-related AEs over pembrolizumab monotherapy was observed[7,8]
- Clinical responses were supported by immunologic data consistent with the mechanism of SD-101
  - Increases in CD8+ cells, NK cells, cytotoxic cells and Th1 cells in the tumor microenvironment were observed in both SD-101 dose groups but were higher in the 2 mg group and appeared to correlate with enhanced clinical efficacy
- SD-101 is also being investigated in patients with anti-PD-1/L1 resistant/refractory advanced melanoma
  - The addition of SD-101 (8 mg/lesion) to pembrolizumab appears to restore tumor sensitivity to a PD-1 inhibitor in a significant percentage of these patients with an ORR of 21.4% (see ESMO Abstract 3781)

Immune-Related Biomarkers

Figure 8. Changes in Immune Activity in the Tumor Microenvironment



Values above the graphs represent the means and 95% confidence intervals. Methods: biopsies of the injected tumor were collected at screening (prior to dosing) and post-dose. Biopsies were analyzed by 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

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