Abstract 9534: 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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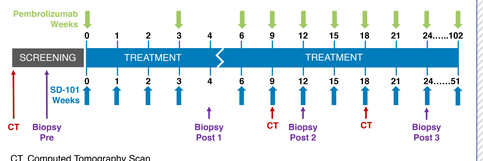
BACKGROUND

- PD-1 blockade has significantly improved outcomes in advanced melanoma, yet durable responses are elicited in fewer than half of 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 in combination with intratumoral SD-101 induced abscopal tumor shrinkage in 83% of patients.[4]
- Here, we report the latest results from patients with advanced melanoma who were naïve to anti-PD-1/L1 therapy and were treated with the combination of SD-101 and pembrolizumab. Prior study results were presented at ASCO 2018 and ESMO 2018.[5,6] Results of the phase 1b portion of this study were previously published by Ribas et al in *Cancer Discovery*.[7]

METHODS

- **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:**
  - Unresectable Stage IIIC, Stage IV Metastatic Melanoma
  - ECOG performance status of 0 or 1
  - At least one measurable lesion
  - Anti-PD-1/L1 treatment naïve

Figure 1. Treatment Schema



CT, Computed Tomography Scan

- **Primary Endpoint:**
  - Objective response rate assessed by assessed by investigators using RECIST v1.1
- **Secondary Endpoints:**
  - Safety and tolerability
  - Progression-free survival
  - Duration of response
- **Exploratory Endpoint:**
  - Immunophenotype of the tumor environment

RESULTS

Table 1. Baseline Patient and Disease Characteristics

Characteristics	2 mg/lesion (N=45)	8 mg/lesion (N = 41)
Median age, years (range)	70 (36, 85)	66 (33, 89)
Male, n (%)	32 (71)	27(66)
ECOG PS = 0, n (%)	28 (62)	30 (73)
Baseline LDH, Median (Q1, Q3) ≤ ULN	195 (163, 240) 34 (76)	195 (181, 246) 27 (66)
Stage at screening, n (%)		
IIIC	10 (22)	8 (20)
IV	35 (78)	33 (80)
M1a	14 (31)	11 (27)
M1b	9 (20)	9 (23)
M1c	12 (27)	12 (30)
BRAF V600E Mutation, n (%)		
Wild-type	21 (47)	21 (51)
Mutant	18 (40)	12 (29)
Unknown	6 (13)	8 (17)
PD-L1 Expression (Dako 22C3), n (%)		
Positive (≥ 1%)	20 (44)	13 (32)
Negative (< 1%)	14 (31)	15 (37)
Pending/Missing	11 (24)	13 (32)
0/1/2/≥3 prior lines of therapy, n (%)	34/9/2/0 (76/20/4/0)	29/11/0/1 (71/27/0/2)

ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = Lactate Dehydrogenase; ULN = upper limit of normal; mm= Millimeter

Safety

Table 2. Safety Summary

Event, n (%)	2 mg/lesion (N=45)	8 mg/lesion (N = 41)	Total (N=86)
Any Treatment-related AE	45 (100)	39 (95)	84 (98)
Grade 3–4	14 (31)	18 (44)	32 (37)
Any irAEs*	12 (27)	6 (15)	18 (17)
Grade 3–4	2 (4)	2 (5)	4 (5)
AEs leading to d/c of either or both drugs	11 (24)	17 (42)	28 (34)
Treatment-related SAEs	4 (9)	12 (29)	16 (19)
Death (Unrelated to drug)	0	0	0

*10 patients in the 2 mg group had hypothyroidism
d/c = discontinuation; irAE = Immune-related adverse event; SAE = Serious adverse event

Efficacy

Table 3. Best Overall Response for ITT Population by RECIST v1.1

Best Overall Response Rate (ITT)	2 mg/lesion (N=45)	8 mg/lesion (N = 41)
Objective response rate (ORR), n (%) (95% CI)	**34 (76)** (61, 87)	**20 (49)** (33, 65)
Complete response	8 (18)	4 (10)
Partial response	26 (58)	16 (39)
Stable disease	2 (4)	7 (17)
Progressive disease	5 (11)	9 (22)
Not evaluable†	4 (9)	5 (12)
Time to response, median (months)	2.2	2.3
Duration of response (DOR), median (months) (95%CI)	not reached (NE, NE)	not reached (14.2, NE)

† Patients discontinued prior to first scan: 2 mg—clinical progression (n=3), consent withdrawn (n=1); 8 mg—clinical progression (n=2), irAE/AE (n=2), withdrew consent (n=1). NE, not estimable; ITT, intent to treat

Note: The concordance between blinded central assessment and investigator assessment on a subset of the 2 mg group (n=38) was 89%

- ORR in patients with BRAF mutant tumors who received 2 mg/lesion (n=18) was 61%
- ORR in patients with PD-L1 negative tumors who received 2 mg/lesion (n=14) was 79%

Figure 2. Best Percent Change From Baseline by PD-L1 Status (2 mg/Lesion)

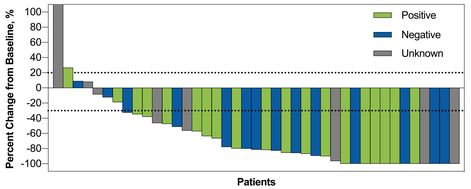


Figure 3. Percent Change From Baseline Over Time in Target Lesions (2 mg/Lesion)

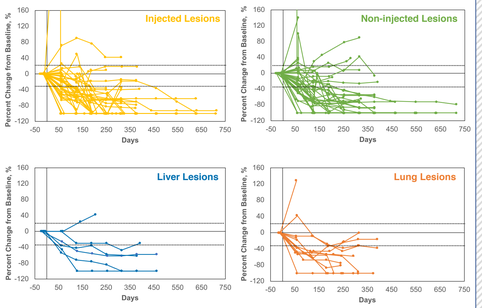


Figure 4. Duration of Follow Up and Patient Status (2 mg/Lesion)

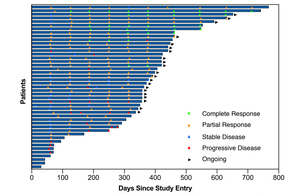


Figure 5. Progression-free Survival (PFS) in ITT Population

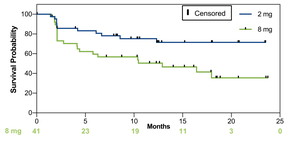
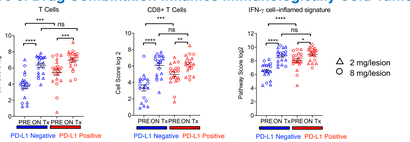


Table 4. Progression-free and Overall Survival Outcomes

	2 mg/lesion	8 mg/lesion
Progression-free Survival (95% CI)		
12-month rate	75% (59, 86)	51% (33, 65)
18-month rate	72% (54, 83)	36% (18, 54)
Median, months	NE (NE, NE)	12.9 (4.2, NE)
Overall Survival (95% CI)		
12-month rate	98% (85, 99.7)	92% (78, 98)
Median, months	NE (17.8, NE)	NE (NE, NE)
Follow-up, median, months	10.4	8.7

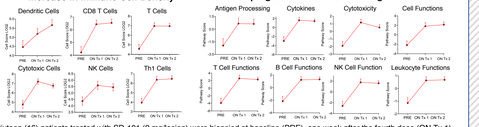
IMMUNE-RELATED BIOMARKERS

Figure 6. Drug Combination Inflames Immunologically Cold Tumors



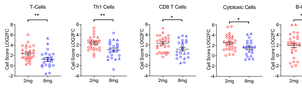
Patients were biopsied during screening (PRE) and one week after the fourth dose of SD-101 (ON Tx). Biopsies were scored for both PD-L1 status by IHC (PDL1 IHC 22C3 PharmDx assay) and assessed for gene expression using Nanostring (nCounter® PanCancer Immune Profiling Panel). Patients with PD-L1 negative tumors compared with those with PD-L1 positive tumors at baseline had significantly fewer infiltrating cells and lower levels of a IFNγ signature, which is based on the geometric mean of 15/18 genes in the gene expression profile developed by Merck.[8]

Figure 7. Longitudinal Data on Tumor Biopsies Demonstrates Sustained Immune Response



Sixteen (16) patients treated with SD-101 (2 mg/lesion) were biopsied at baseline (PRE), one week after the fourth dose (ON Tx 1), and three weeks after the ninth dose (ON Tx 2).

Figure 8. Significantly More Pronounced Modulation of the Tumor Microenvironment for 2 mg/Lesion vs. 8 mg/Lesion



Patients were biopsied at the start of the trial (PRE) and one week after the 4th dose of SD-101 (POST1). Biopsies were assessed using Nanostring. Graphs shows the Log2 fold change from baseline (POST1/PRE) of cell density score, comparing 2 mg and 8 mg doses.

CONCLUSIONS

- The addition of 2 mg/lesion SD-101 plus pembrolizumab improves efficacy compared with 8 mg/lesion of SD-101 plus pembrolizumab, in similar patient populations
  - The ORR in the SD-101 2 mg/lesion group (76%) was higher than in the SD-101 8 mg/lesion group (49%)
  - The median DOR in both groups has not been reached, with the lower bound of the 95% confidence interval of at least 14 months
  - The 18-month PFS rate in the SD-101 2 mg/lesion group (72%) was higher than in the SD-101 8 mg/lesion group (36%)
  - Similar rates of responses occurred in patients with PD-L1 negative tumors and PD-L1 positive tumors
  - Tumor shrinkage has been observed in both injected and non-injected lesions, including visceral lesions such as the liver and lung
- Immunologically cold tumors are a therapeutic challenge for anti-PD-1 therapy; the ability of SD-101 with pembrolizumab to convert cold tumors (PD-L1 negative, low IFNγ and T cell signature at baseline) into T cell rich tumors is demonstrated by biomarker data in the samples tested
  - This ability to convert cold into inflamed tumors is consistent with similar effects in HNSCC (ASCO 2019, Abstract 6039)
- The superior induction of infiltrating effector immune cells in lesions treated with the 2 mg/lesion dose compared with 8 mg/lesion is consistent with the increased response observed
- 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
  - No increase in immune-related AEs over pembrolizumab monotherapy were observed[9,10]

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This study was sponsored by Dynavax Technologies Corporation in collaboration with Merck Sharpe & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA. We thank the patients and their families and caregivers for participating in the study and the teams involved in conducting the study. Copies of this poster are for personal use only and may not be reproduced without written permission of the authors.

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