Abstract 9555: Phase 1b/2, Open Label, Multicenter, Study of the Combination of SD-101 and Pembrolizumab in Patients with Advanced/Metastatic Melanoma Resistant to Anti-PD-1/PD-L1 Therapy (SYNERGY-001/KEYNOTE-184, NCT02521870)

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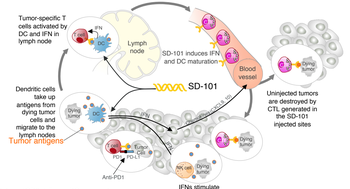
BACKGROUND

- 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 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 (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]
- There remains a high unmet need for effective therapy in the previously treated, PD-1/PD-L1 inhibitor resistant/refractory metastatic melanoma population, 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 previously presented by Ribas *et al* at AACR 2018 (Abstract: CT139) and published in *Cancer Discovery (2018)*.[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

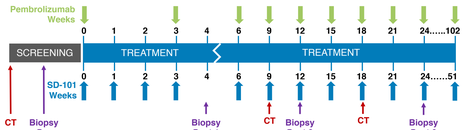
- SD-101 induces PDCs to secrete high levels of interferon-alpha, a potent immunomodulatory cytokine that is able to boost NK cell cytotoxic activity and induce recruitment of T cells. In addition, SD-101 induces DC maturation cross-presentation of tumor associated antigens, inducing CD8+ T cell responses.

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) every three weeks
- **Patients:**
  - Advanced/metastatic melanoma
  - Prior anti PD-1/PD-L1 exposure
  - ECOG performance status of 0 or 1
  - At least one injectable lesion

Figure 2. Treatment Schema



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, Immunophenotype of the tumor environment

RESULTS

Table 1. Baseline Patient and Disease Characteristics

Characteristics	2 mg (N = 31)	8 mg (N = 30)
Median age, years (range)	67 (24, 90)	62.5 (33, 88)
Sex, %		
Male / female	67.7 / 32.3	76.7/ 23.3
ECOG PS, %		
0 / 1	61.3 / 38.7	53.3 / 46.7
BRAF V600E Mutation Status, n (%)		
Mutant	8 (25.8)	15 (50.0)
Wild-type	21 (67.7)	14 (46.7)
Unknown	2 (6.5)	1 (3.3)
Stage at screening		
IIIC	5 (16.1)	9 (30.0)
Metastatic	26 (83.9)	21 (70.0)
Number of Target Lesions, n (%)		
1	0	3 (10.0)
2	11 (35.5)	8 (26.7)
≥ 3	20 (64.5)	19 (63.3)
Organ Involvement, n (%)		
Liver	4 (12.9)	10 (33.3)
Lung	11 (35.5)	7 (23.3)
Bone	3 (9.7)	3 (10.0)
Skin/subcutaneous tissue	22 (71.0)	21 (70.0)
Lymph nodes	20 (64.5)	15 (50.0)
Other organs	11 (35.5)	13 (43.3)
Prior radiotherapy, n (%)	8 (25.8)	6 (20.0)
Prior surgery, n (%)	29 (93.5)	28 (93.3)
1 / 2 / ≥3 prior lines of therapy, n	13 / 9 / 9	10 / 8 / 12
Prior CTLA-4 therapy	13 (41.9)	12 (40.0)

ECOG PS = Eastern Cooperative Oncology Group performance status;

Safety

Table 2. Safety Summary

Event, n (%)	2 mg (N = 31)	8 mg (N = 30)
Subjects with at least one Treatment-Related AE	26 (83.9)	26 (86.7)
Subjects with Grade 3 & 4 Treatment related AE	5 (16.1)	7 (23.3)
Immune Related AEs All grades*	0	1 (3.3)
Hyperthyroidism	0	1 (3.3)

*Hypothyroidism, pneumonitis, myositis, hepatitis and colitis were not seen in 2 or 8 mg groups

Efficacy

Figure 3. Duration of Follow Up and Patient Status

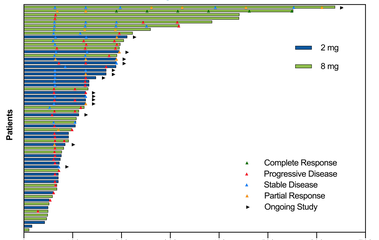


Table 3. Best Overall Response for ITT Population by RECIST v1.1

Best Overall Response Rate (ITT)	2 mg (N = 31)	8 mg (N = 30)
Objective response rate, n (%) (95% CI)	6 (19.4) (7.5, 37.5)	4 (13.3) (3.8, 30.7)
Best overall response, n (%)		
Complete response	0	1 (3.3)
Partial response	6 (19.4)	3 (10.0)
Stable disease	9 (29.0)	9 (30.0)
Progressive disease	12 (38.7)	10 (33.3)
Not evaluable*	4 (12.9)	7 (23.3)
Time to response (months)		
Median	4.2	3.2
Min, Max	(2.1, 6.4)	(2.3, 8.6)
Duration of response		
Median	0.03 (not mature)	6.8
Min, Max	(0.03, 4.1)	(0.95, 15.8)
Duration of follow up		
Median	3.5	3.9
Min, Max	(0.6, 7.0)	(0.6, 21.1)

* Patients discontinued prior to first scan; ITT = Intent to treat

Table 4. Objective Response by BRAF Expression Status

Best Overall Response Rate (ITT)	BRAF Mutant (N = 22)	BRAF Wild Type (N = 36)	BRAF Unknown (N = 3)
ORR, n (%)	3 (13.6)	6 (16.7)	1 (33.3)
(95% CI)	(2.9, 34.9)	(6.4, 32.8)	(0.8, 90.6)
BOR, n (%)			
CR	0	1 (2.8)	0
PR	3 (13.6)	5 (13.9)	1 (33.3)
SD	6 (27.3)	10 (27.8)	2 (66.7)
PD	10 (45.5)	12 (33.3)	0
NE	3 (13.6)	8 (22.2)	0

ORR = Objective response rate; BOR = Best overall response; CR = complete response; PR = partial response; SD = stable disease; PD = Progressive disease; NE = not evaluable

Data is combination of 2 mg and 8 mg arms

Figure 4. Best Percent Change from Baseline in Lesion(s)

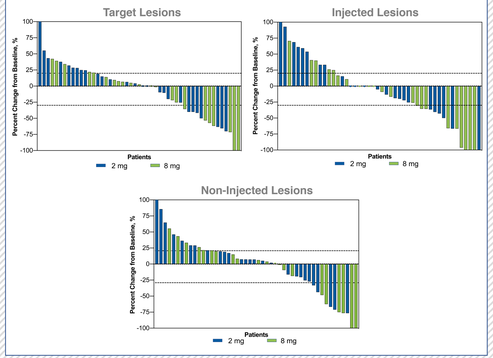
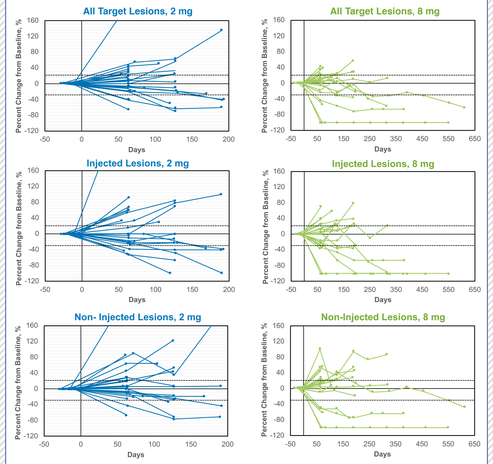
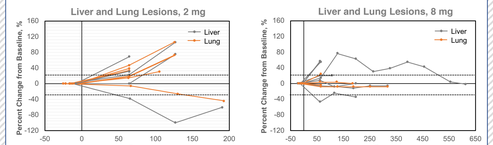


Figure 5. Percent Change From Baseline in Lesion(s)

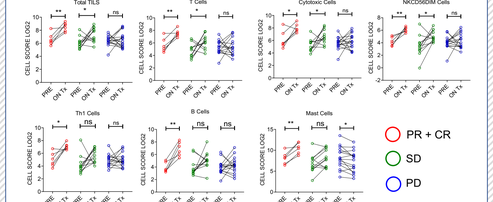


Organ-Specific Percent Change from Baseline in Target Lesions



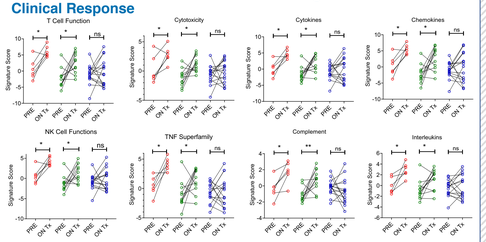
IMMUNE-RELATED BIOMARKERS

Figure 6. Increase in Infiltration of Immune Cells Correlates with Clinical Response



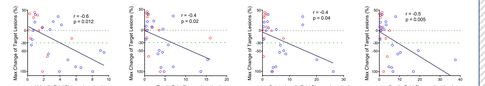
Cell type profile determined by RNA expression profiling at baseline and on treatment biopsies by Nanostring measures the degree of lymphocyte infiltration. All patients had biopsies at baseline and one week after the fourth SD-101 treatment (ON Tx).

Figure 7. Upregulation of Immune Related Signature Correlates with Clinical Response



Immune profiling determined by RNA expression by Nanostring measures changes in the tumor microenvironment after initiation of SD-101 treatment. All patients had biopsies at baseline and one week after the fourth SD-101 treatment (ON Tx).

Figure 8. Increased Density of Immune Cells in SD-101 Treated Lesions Correlates with an Overall Decrease in Tumor Burden



Fold of changes in lymphocytes infiltration in SD-101 treated lesions was correlated with the maximum percentage change in target lesions from baseline using Pearson correlation coefficient. Red: ≤2 mg; Blue: 8 mg

CONCLUSIONS

- In a population of confirmed PD-1 resistant or refractory patients SD-101 in combination with pembrolizumab showed efficacy at both dose levels tested
- Responses were observed in SD-101 injected and non-injected lesions (including liver and lung metastases)
- Responses and disease control were observed in BRAF mutant or wild type tumors
- Biomarker data demonstrate that SD-101 added to pembrolizumab significantly changes the tumor microenvironment of patients that previously failed PD-1 blockade including the infiltration of activated T cells, NK cells, and B cells
- 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 medications

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