Poster 9513

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 Therapy (SYNERGY-001)

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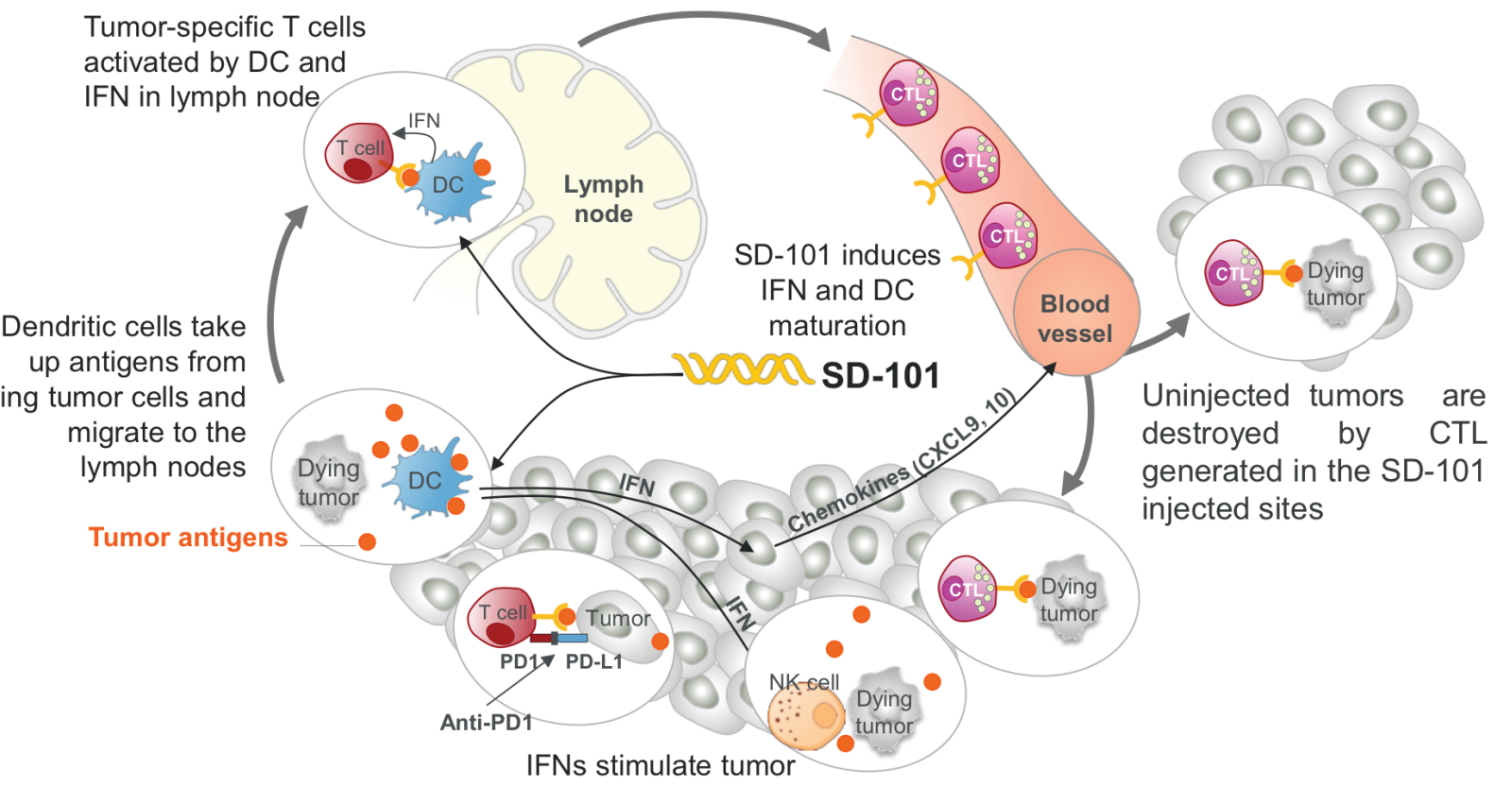
BACKGROUND

- SD-101 is a synthetic Class-C CpG-oligodeoxynucleotide that stimulates plasmacytoid dendritic cells (pDCs) through engagement of Toll-like receptor 9 (TLR9). This stimulation causes pDCs to release interferon-alpha and mature into efficient antigen-presenting cells, strengthening both innate and acquired immune responses (**Figure 1**).[1]
- Pembrolizumab is a PD-1 inhibitor that has been approved for treatment of unresectable or metastatic melanoma.[2]
- SD-101 in combination with pembrolizumab induced a 33% ORR in 18 patients with head and neck squamous cell carcinoma.[3]
- Previously, we presented the best overall response in evaluable patients naïve to anti-PD-1 therapy (ASCO 2017)[4] and durability data from the Phase 1b portion of this study (AACR 2018)[5]:
  - ORR in evaluable patients=78% (ITT, 2 CR, 5 PR, 2 not evaluable)
  - Landmark 12-month PFS rate=88% (ITT), with 86% of responses ongoing (median follow up of 18 months).
- Results from dose-finding in the Phase 1b and Phase 2 portions of the study are presented here.

Figure 1. Both Innate and Adaptive Immune Responses Are Increased by Intratumoral Injection of SD-101. SD-101 engages TLR9 on plasmacytoid dendritic cells (pDCs) to secrete high levels of interferon-alpha, a potent immunomodulatory cytokine that is able to boost natural killer cell cytotoxic activity and induce recruitment of T cells to the TME. In addition, SD-101 induces DC maturation and the ability to cross-present tumor associated antigens, inducing CD8+ T cell responses (CTL).



CTL = CD8+ T cell; DC = dendritic cell; IFN = interferon; NK = natural killer; TLR = Toll-like receptor.

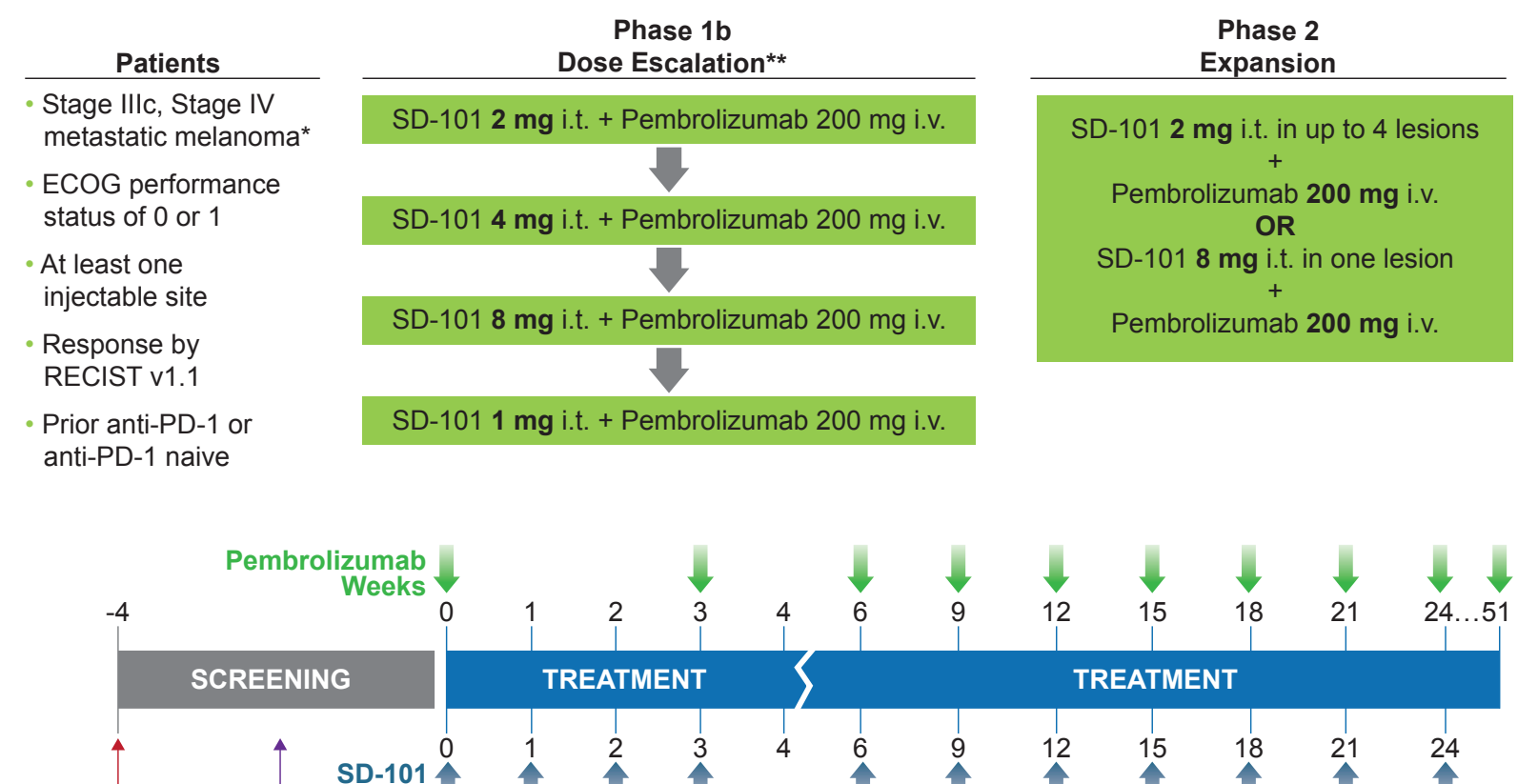
OBJECTIVES

- To confirm the safety profile and assess the efficacy of SD-101 / pembrolizumab combination therapy in patients with advanced melanoma who were naïve to anti-PD-1 therapy
- To assess different doses of SD-101 and compare outcomes following injection of an 8 mg dose into one lesion versus ≤ 2 mg in up to 4 lesions

METHODS

- This is an ongoing, Phase 2, open-label, multicenter, dose-expansion/dose-finding study (NCT02521870) (**Figure 2**). Data are as of May 9, 2018.
- In order to qualify for the study, patients had to have Stage IIIC or Stage IV advanced melanoma, ECOG performance status scores of 0 or 1, and at least one injectable lesion. There was no stratification or enrichment by any patient characteristic.
- Safety was assessed by adverse events, immune related adverse events, and serious adverse events.
- Response was evaluated by the investigator according to RECIST v1.1.[6] Assessments were based on radiographic images (either CT or MRI) at baseline, every 9 weeks until Day 379, and every 12 weeks thereafter until confirmed progression or initiation of new anti-cancer treatment.
- To assess pharmacodynamic effects, biopsies of the injected tumor were collected at screening (prior to dosing) and post-dosing on Day 29. 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
- Baseline PD-L1 expression was measured with a validated assay using the Dako 22C3 antibody.
- Multiplex fluorescent immunohistochemistry was conducted with serial application of primary and secondary antibodies using automated slide stainers and tyramide signal amplification reagents. Images of stained samples were captured by Vectra 2 Image Acquisition platform (Perkin Elmer).

Figure 2. Study Design



Patients
- Stage IIIc, Stage IV metastatic melanoma*
- ECOG performance status of 0 or 1
- At least one injectable site
- Response by RECIST v1.1
- Prior anti-PD-1 or anti-PD-1 naive

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 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.

*Histologically confirmed
**DLT period 29 days
i.t. = intratumoral; i.v. = intravenous.

- In the Phase Ib portion of the study (dose escalation), 3 patients received 1 mg in one lesion and are included in the ≤ 2 mg group. One patient received 4 mg in one lesion and had a complete response. That patient is not included in these analyses.

RESULTS

Table 1. Demographic and Baseline Characteristics of Patients by Dose Group (ITT Population)

Characteristics	≤ 2 mg* (N=37)	8 mg (N=39)
Age (years)		
Median (Min, Max)	67 (37, 81)	66 (33, 89)
Sex, n (%)		
Male	25 (68)	26 (67)
Female	12 (32)	13 (33)
ECOG PS, n (%)		
0	24 (65)	30 (77)
1	13 (35)	9 (23)
Baseline LDH (U/L), mean (SD)	292 (362)	216 (79)
≤ ULN, n (%)	29 (78)	31 (79)
> ULN	8 (22)	8 (21)
Time Since Diagnosis (years)		
Median (Min, Max)	1.3 (0, 17)	1.0 (0, 16)
Stage at Screening, n (%)		
IIIC	15 (41)	9 (23)
IVM1a	8 (22)	6 (15)
IVM1b	2 (5)	6 (15)
IVM1c	9 (24)	16 (41)
Missing	3 (8)	2 (5)
Organ Involvement, n (%)		
Lung	9 (24)	19 (49)
Liver	4 (11)	2 (5)
Lymph nodes	18 (49)	23 (59)
Skin/ Subcutaneous	21 (57)	14 (36)
Bone	3 (8)	2 (5)
Other	12 (32)	15 (38)
PD-L1 Expression, n (%)		
Positive (≥ 1%)	8 (22)	11 (28)
Negative (< 1%)	10 (27)	13 (33)
Pending	19 (51)	15 (38)
Prior Systemic Therapy, n (%)	10 (27)	10 (26)
Prior anti-CTLA4 therapy	6 (16)	4 (10)
Prior lines of therapy, n (%)		
0	27 (73)	29 (74)
1	8 (22)	9 (23)
2	2 (5)	0
3 or more	0	1 (3)

ECOG PS = Eastern Cooperative Oncology Group performance status; NA = not applicable; SD = standard deviation; ULN = upper limit of normal.
*3 patients received 1 mg/lesion of SD-101.

Table 2. Overview of Safety (Safety Population)

Event, n (%)	≤ 2 mg (N=37) n (%)	8 mg (N=39) n (%)	Total (N=76) n (%)
Any Treatment-related AE	28 (76)	36 (92)	64 (84)
Grade 3–4	8 (22)	14 (36)	22 (29)
Chills	3 (8)	1 (3)	4 (5)
Myalgias	6 (16)	1 (3)	7 (9)
Injection-site pain	2 (5)	0	2 (3)
Fatigue	2 (5)	4 (10)	6 (8)
Headache	3 (8)	2 (5)	5 (7)
Malaise	2 (5)	3 (8)	5 (7)
Any irAEs	6 (16)	4 (10)	10 (13)
Grade 3–4	3 (8)	2 (5)	5 (7)
irAEs (preferred term) All grades			
Hypothyroidism	4 (11)	2 (5)	6 (8)
Pneumonitis	1 (3)	1 (3)	2 (3)
Myositis	0	1 (3)	1 (1)
Autoimmune retinopathy	0	1 (3)	1 (1)
Autoimmune hepatitis	0	1 (3)	1 (1)
Myasthenia gravis	0	1 (3)	1 (1)
Colitis	1 (3)	0	1 (1)
Autoimmune colitis	1 (3)	0	1 (1)
Hypophysitis	1 (3)	0	1 (1)
Autoimmune myocarditis	0	1 (3)	1 (1)
Optic neuritis	0	1 (3)	1 (1)
AEs leading to d/c of either or both drugs	4 (11)	10 (26)	14 (18)
SAEs	9 (24)	12 (31)	21 (28)
Death	0	1 (3)	1 (1)

d/c = discontinuation; irAE = immune-related adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Figure 3. Best Percent Change From Baseline in All Target Lesions

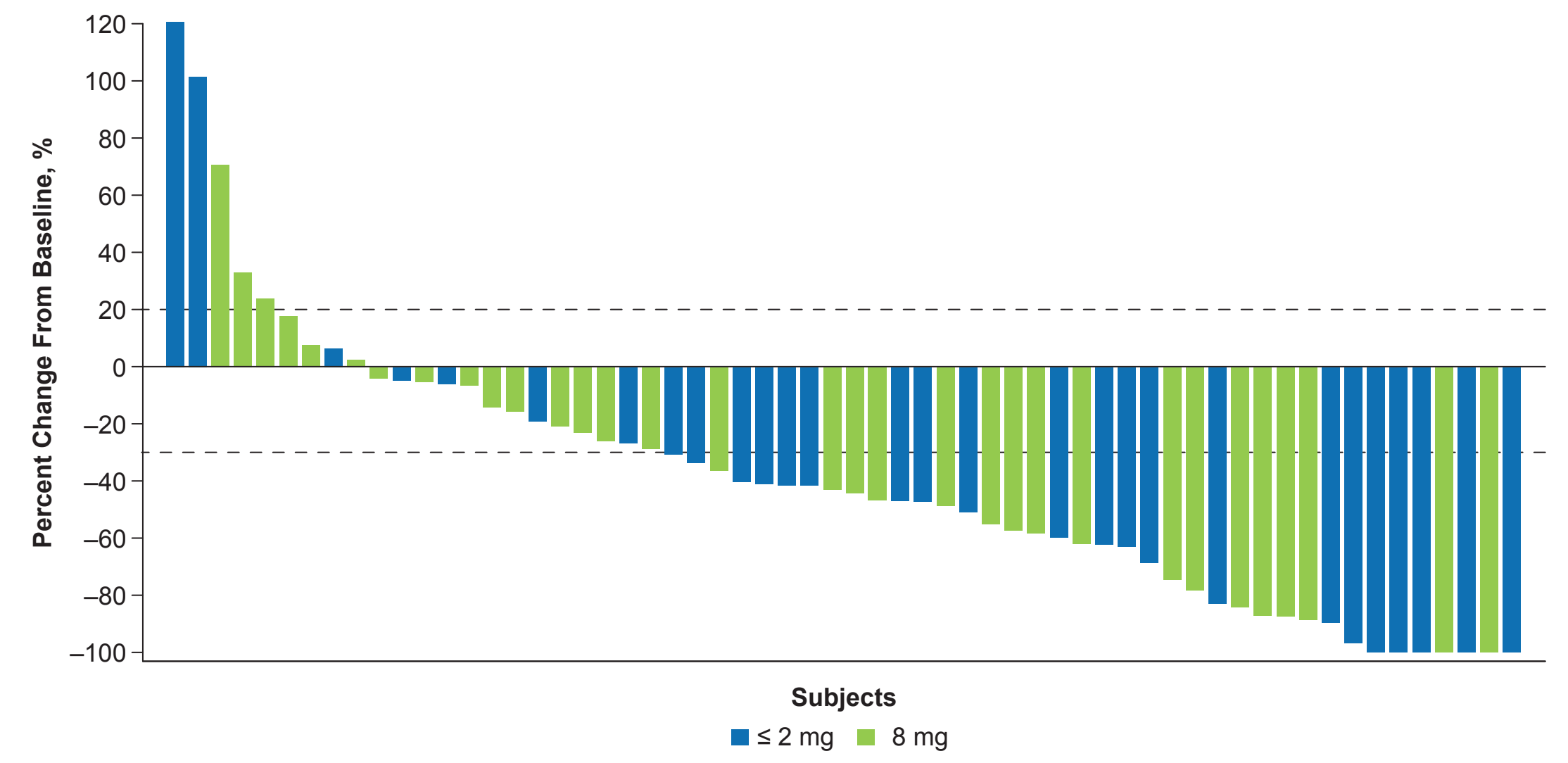


Table 3. Best Overall Response by Investigator Using RECIST v1.1

Response Rate	≤ 2 mg	8 mg
mITT*	N=30	N=39
Overall Response Rate, n (%) (95% CI)	21 (70) (52, 83)	15 (38) (25, 54)
CR	5 (17)	1 (3)
PR	16 (53)	14 (36)
SD	3 (10)	10 (26)
PD	4 (13)	7 (18)
Not evaluable†	2 (7)	7 (18)
All enrolled patients	N=37	N=39
Not evaluable**	7 (19)	0 (0)

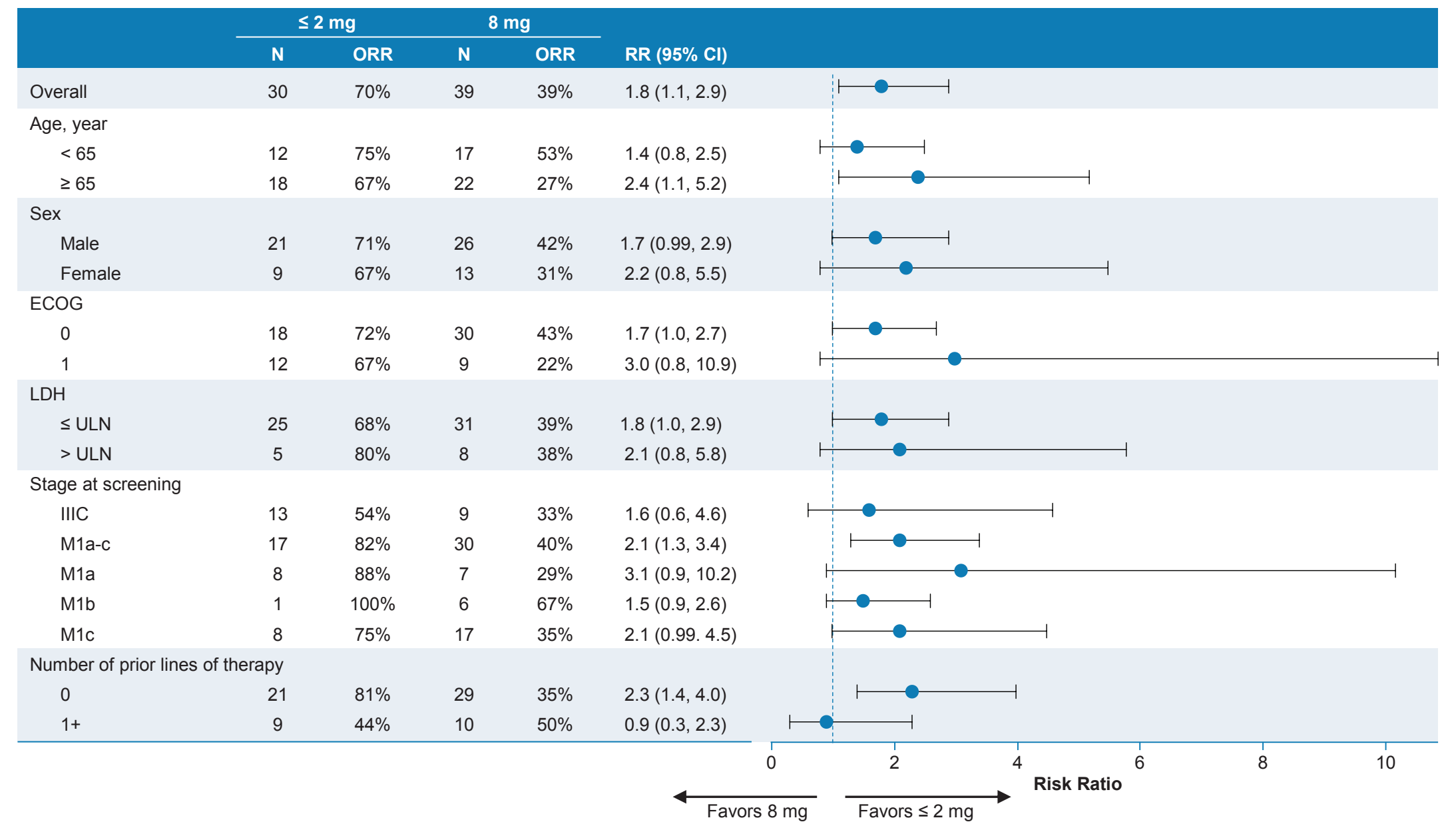
*mITT = ITT excluding patients on study who have not yet had time to reach a first scan. †Patients discontinued prior to first scan: 1 or 2 mg—clinical progression (n=1), irAE (n=1); 8 mg—clinical progression (n=2), AE/death (n=1); irAE (n=3), withdrew consent (n=1). **Patients on study who have not yet had a scan.

Table 4. Durability of Responses

	≤ 2 mg	8 mg
PFS		
6-month rate	76% (16/21)	41% (14/34)
Median (months)	Not reached	4.2
Median DOR (months)	4.7+ (not reached)	2.1+ (not reached)
Median follow up (months)	6.0	4.9

- In subgroup analyses by baseline characteristics, the ORR in the 2 mg group was higher than in the 8 mg group (see **Figure 4**).

Figure 4. Subgroup Analyses Favor ≤ 2 mg Dose Over 8 mg Dose



	≤ 2 mg N	≤ 2 mg ORR	8 mg N	8 mg ORR	RR (95% CI)
Overall	30	70%	39	39%	1.8 (1.1, 2.9)
Age, year					
< 65	12	75%	17	53%	1.4 (0.8, 2.5)
≥ 65	18	67%	22	27%	2.4 (1.1, 5.2)
Sex					
Male	21	71%	26	42%	1.7 (0.99, 2.9)
Female	9	67%	13	31%	2.2 (0.8, 5.5)
ECOG					
0	18	72%	30	43%	1.7 (1.0, 2.7)
1	12	67%	9	22%	3.0 (0.8, 10.9)
LDH					
≤ ULN	25	68%	31	39%	1.8 (1.0, 2.9)
> ULN	5	80%	8	38%	2.1 (0.8, 5.8)
Stage at screening					
IIIC	13	54%	9	33%	1.6 (0.6, 4.6)
M1a-c	17	82%	30	40%	2.1 (1.3, 3.4)
M1a	8	88%	7	29%	3.1 (0.9, 10.2)
M1b	1	100%	6	67%	1.5 (0.9, 2.6)
M1c	8	75%	17	35%	2.1 (0.99. 4.5)
Number of prior lines of therapy					
0	21	81%	29	35%	2.3 (1.4, 4.0)
1+	9	44%	10	50%	0.9 (0.3, 2.3)

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; ORR = overall response rate; RR = risk ratio; ULN = upper limit of normal.

Figure 5. Percent Change From Baseline Over Time in All Target Lesions for Patients Who Received ≤ 2 mg Versus 8 mg SD-101 Per Lesion

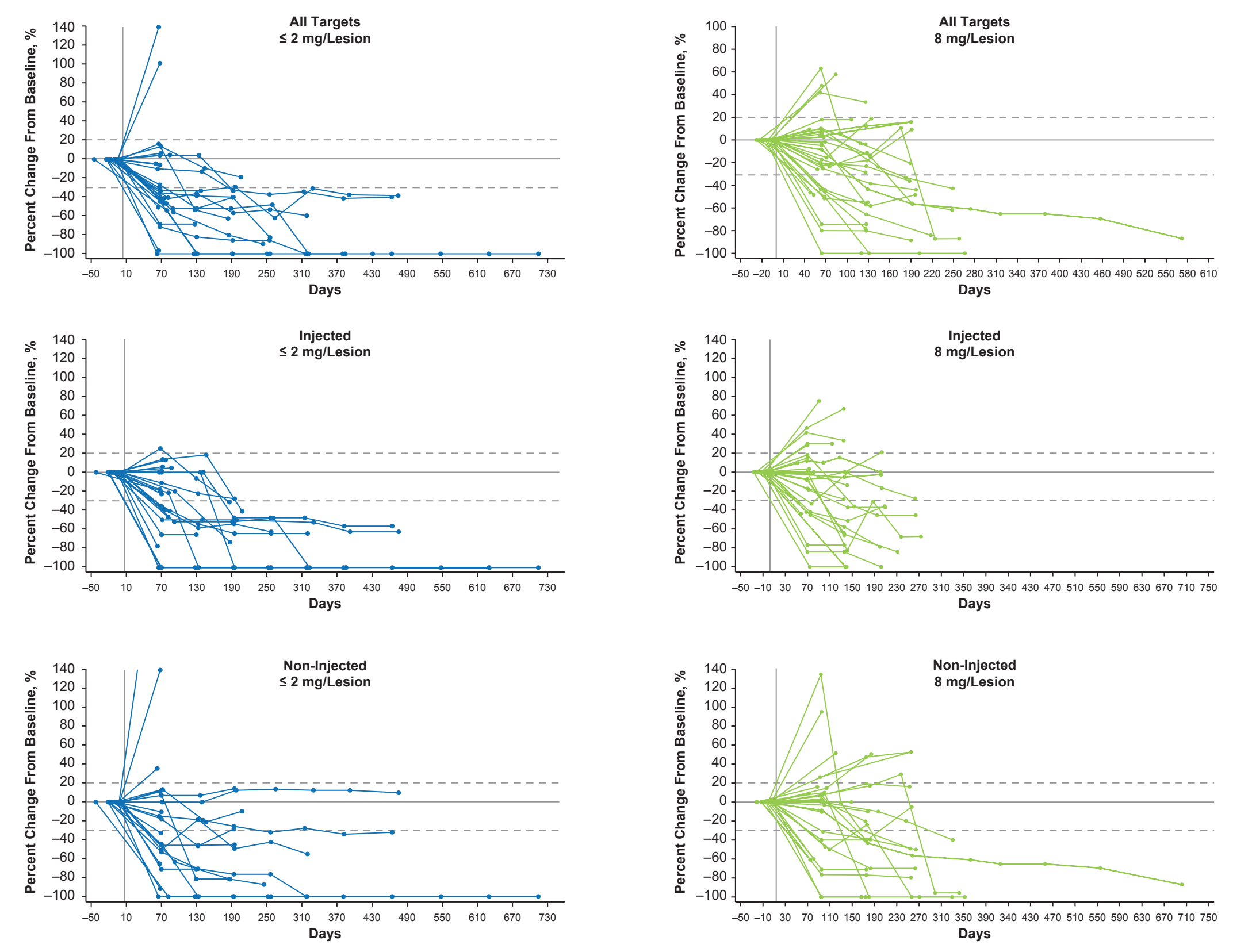


Figure 6. Percent Change From Baseline in Target Lesions by Organ System Among Patients Who Received ≤ 2 mg SD-101 Per Lesion

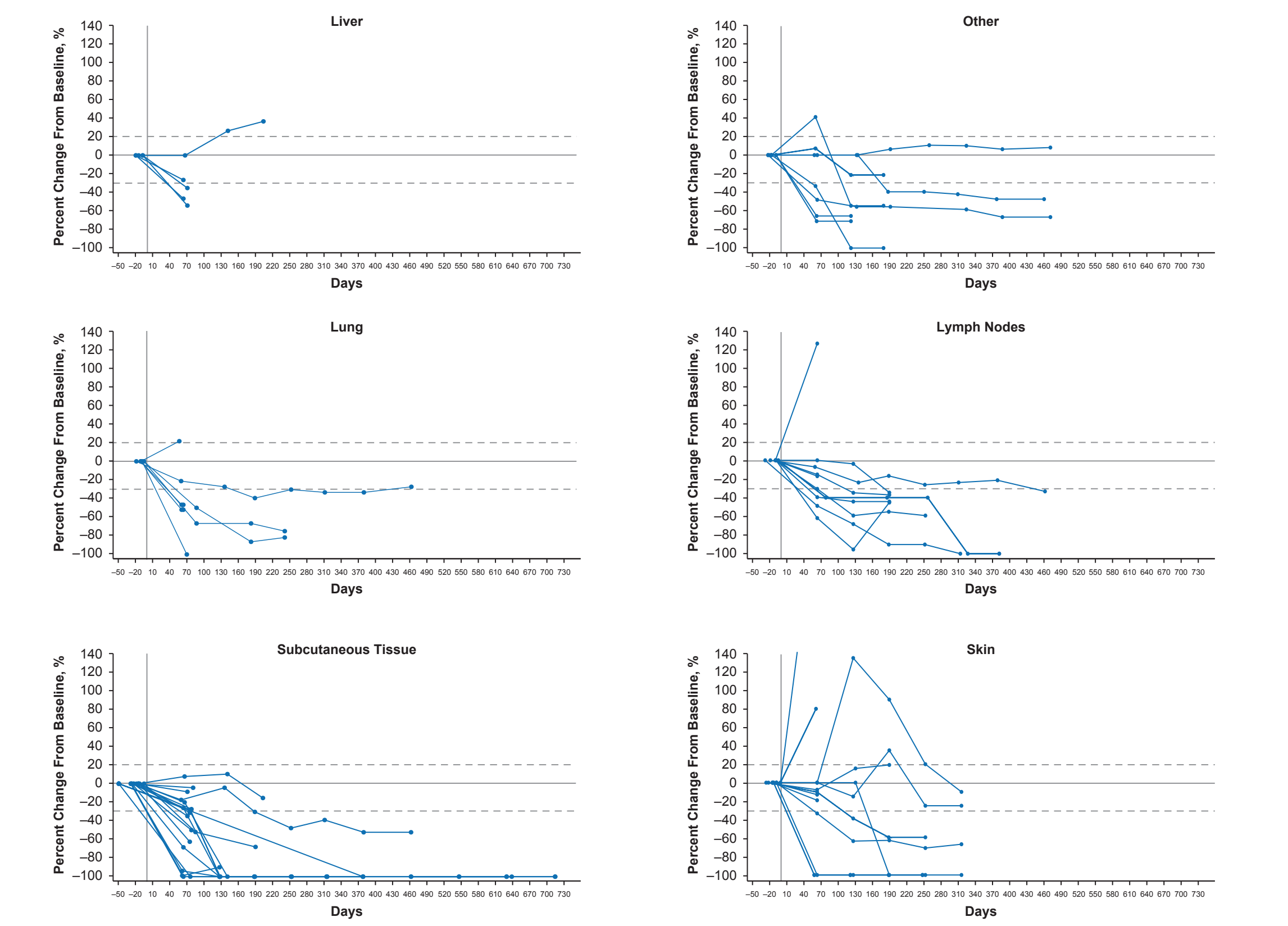
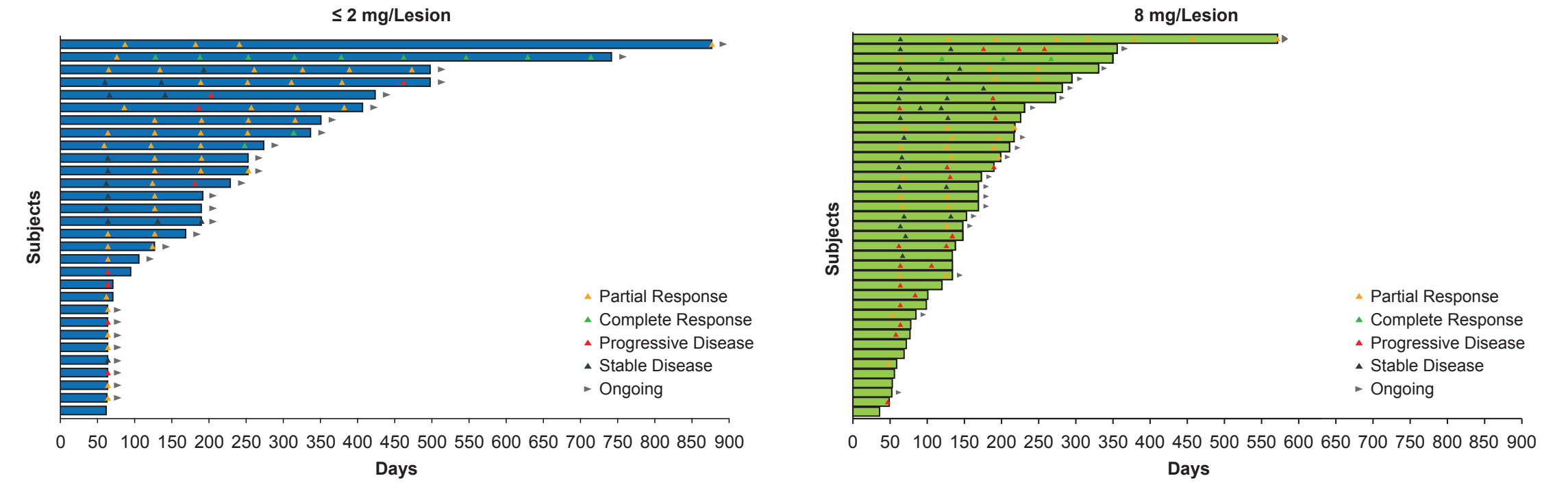


Figure 7. Duration of Follow Up and Subject Status by Dosage



- Only 1 patient with a response discontinued due to progressive disease.

Figure 8. SD-101 in Combination With Pembrolizumab Leads to Antitumor Activity in Patients With Positive or Negative PD-L1 Expression at Baseline. A. Patients receiving a ≤ 2 mg dose. B. Patients receiving an 8 mg dose. Data sorted by PD-L1 expression. PD-L1 expression was assessed by immunohistochemistry using a validated assay with the DAKO 22C3 antibody.

A.

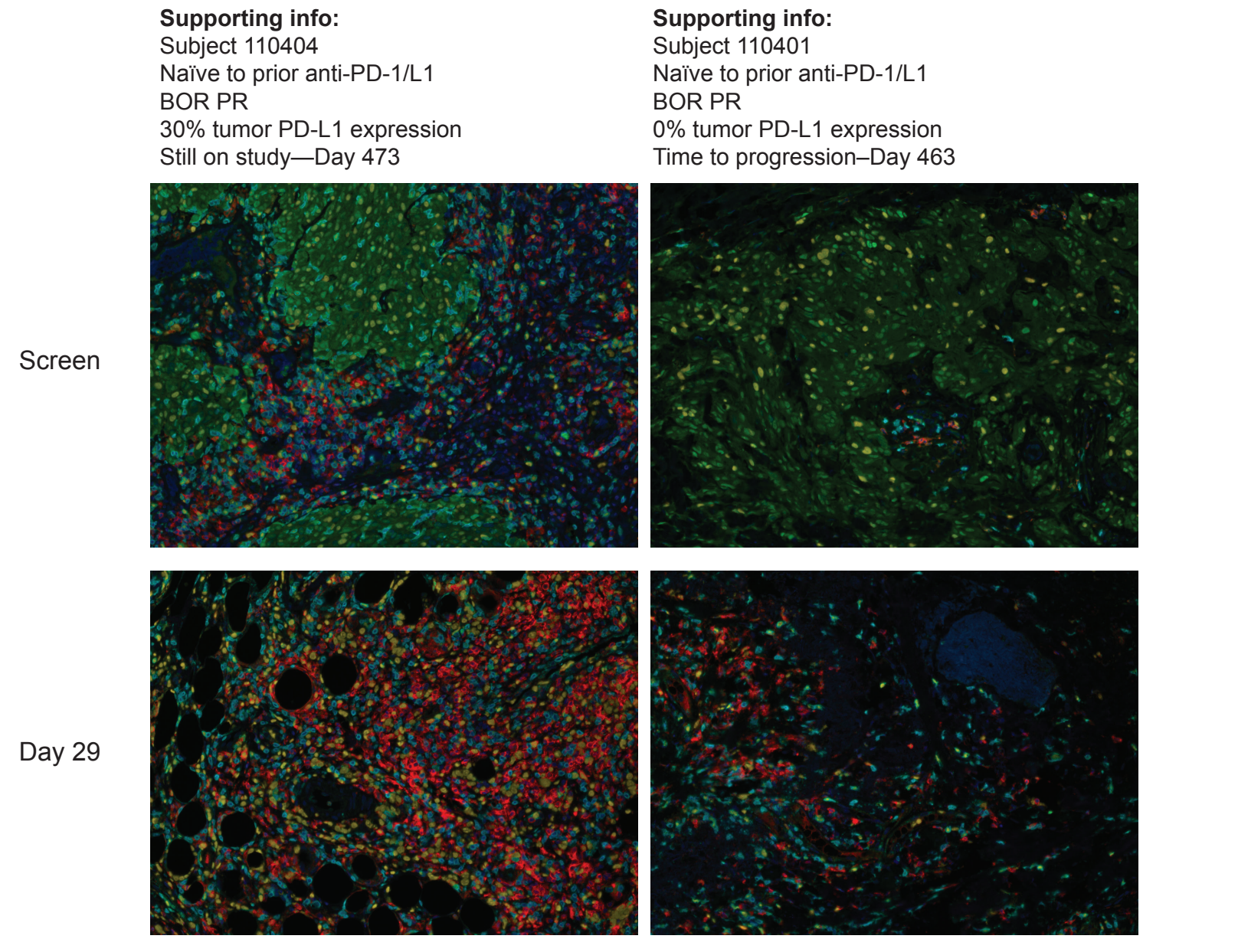
Patients received ≤ 2 mg		
Patient ID	PD-L1 Expression (%TPS)	BOR
101005	0	CR
305551	0	CR
110401	0	PR
115538	0	PR
101518	0	PR
305565	0	PR
102004	0	PR
108569	0	SD
101003	0	Clinical PD
110501	<1	PR
104530	1	PR
113523	3	PR
126525	3	SD
305545	3	PD
110404	30	PR
101002	30	PR
101539	50	PR
115572	80	PR

B.

Patients received 8 mg		
Patient ID	PD-L1 Expression (%TPS)	BOR
110508	0	PR
101553	0	PR
105504	0	SD
112507	0	SD
123528	0	SD
110511	0	PD
133547	0	PD
140550	0	PD
110522	0	WC
130560	0	Death AE
126542	<1	PR
135519	<1	PD
123524	<1	PD
123555	1	PD
123552	2	PR
133510	5	CR
134515	10	SD
110512	25	PR
133566	30	PR
134532	30	SD
109513	30	PD
104520	80	SD
110503	90	CR
123533	90	PR

Data presented here represent currently available samples. Analysis with other samples is ongoing.
TPS = Tumor Proportion Score; BOR = Best Overall Response; WC = withdrew consent

Figure 9. Administration of SD-101 and Pembrolizumab Results in an Increase in Infiltrating CD4 and CD8 Lymphocytes

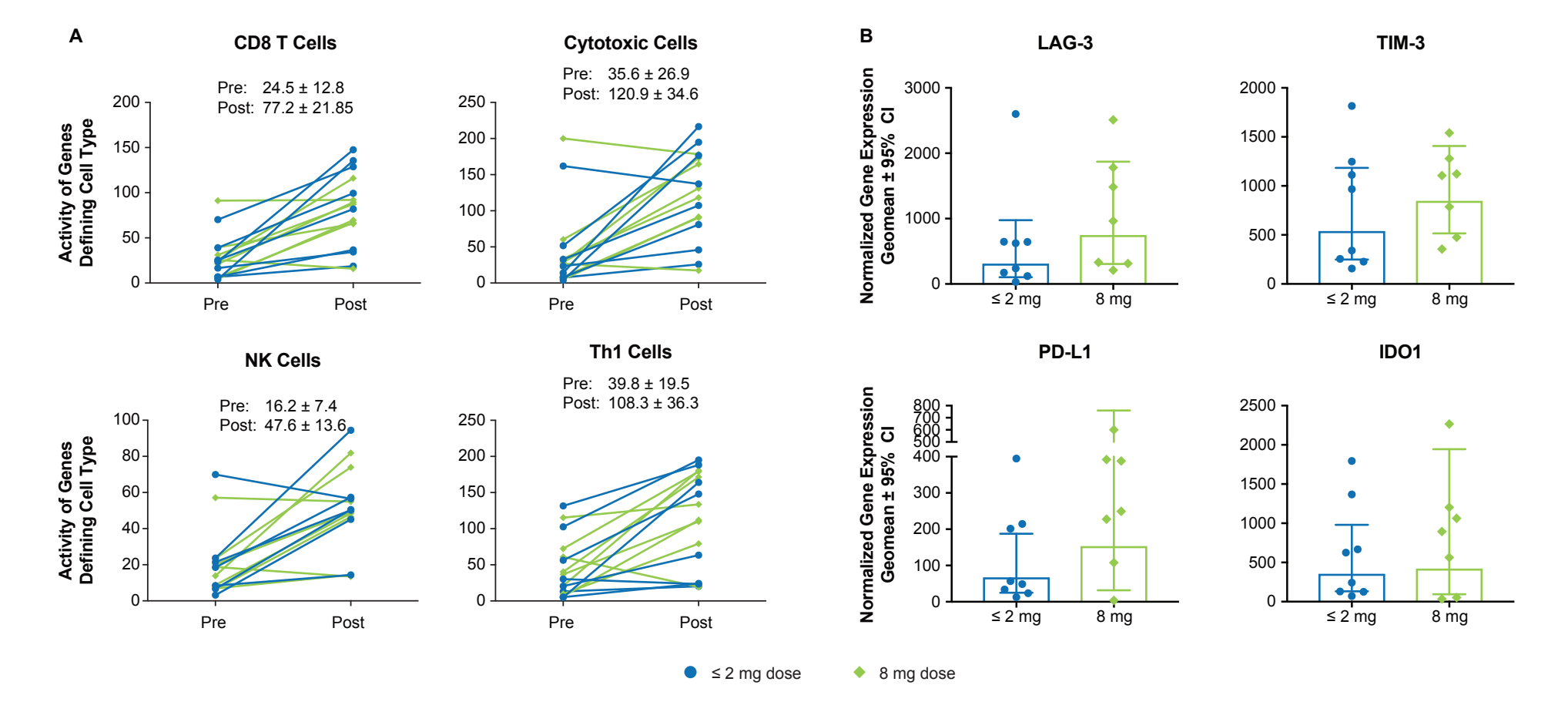


Supporting info:
Subject 110404
Naïve to prior anti-PD-1/L1
BOR PR
30% tumor PD-L1 expression
Still on study—Day 473

Supporting info:
Subject 110401
Naïve to prior anti-PD-1/L1
BOR PR
0% tumor PD-L1 expression
Time to progression–Day 463

Red = CD4 T cells; Cyan = CD8 T cells; Yellow = Ki67; Green = S100; Dark blue = DAPI.
Subject 110404 was devoid of CD4 T cells but not CD8 T cells at screening. Subject 110401 appeared to be devoid of CD4 and CD8 T cells at screening.

Figure 10. The Combination of SD-101 and Pembrolizumab Induces Broad Immune Activity and Checkpoint Gene Expression in the Tumor Microenvironment. A. Postdose biopsies show a significant increase ($P<0.02$) in a variety of immune cells. Values above the graphs represent the means and 95% confidence intervals. B. Higher levels of checkpoint gene activity in post-dose biopsies are consistently observed at 8 mg.



CONCLUSIONS

In this non-randomized single-arm study, all patients had injectable lesions and were enrolled contemporaneously by the same investigators. The comparison of two different dose groups was prespecified to support the selection of a dose for phase 3. While not a randomized study, the 8 mg group can potentially serve as an appropriate active-control group.

SAFETY: 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 monotherapy.
- No increase in immune-related AEs over pembrolizumab monotherapy.[7,8]
- 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.
- The combination of SD-101 and pembrolizumab appears to be much less toxic than the combination of nivolumab and ipilimumab.

EFFICACY: The addition of SD-101 to pembrolizumab appears to improve pembrolizumab responses; ≤ 2 mg of SD-101 per lesion induced a much higher (ORR 70%) and more durable response rate than pembrolizumab with 8 mg of SD-101 (ORR 38%).

- In the ≤ 2 mg group, the median PFS has not been reached, the 6-month PFS rate is 76%, and the median DOR is 4.7+ months. In the 8 mg group, the median PFS is 4 months, the 6-month PFS rate is 41%, and the median DOR is 2.1+ months.
- Overall responses were higher in the ≤ 2 mg group than in the 8 mg group in every disease stage.
- Tumor shrinkage has been observed in both injected lesions and non-injected visceral lesions, including in the liver and lung.
- Preliminary data suggest that SD-101 may improve the immune response to PD-L1-negative tumors over pembrolizumab monotherapy. Multiple patients with negative PD-L1 expression at baseline had tumor responses.

BIOMARKERS: Clinical responses were supported by immunologic data consistent with the mechanism of SD-101.[1]

- Increases in CD4+ cells, CD8+ cells, NK cells, cytotoxic cells and Th1 cells in the tumor microenvironment were observed.
- Immune checkpoints are elevated by treatment in a higher proportion of patients who received 8 mg than in patients who received ≤ 2 mg.

The combination of SD-101 and pembrolizumab was well tolerated and induced durable tumor responses. The SD-101 dose going forward in this patient population will be 2 mg.

ACKNOWLEDGMENTS

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