Phase 1b/2, Open-Label, Multicenter, Dose Escalation and Expansion Trial of Intratumoral SD-101 in Combination With Pembrolizumab in Patients With Metastatic Melanoma

(DV3-MEL-01/KEYNOTE-184)

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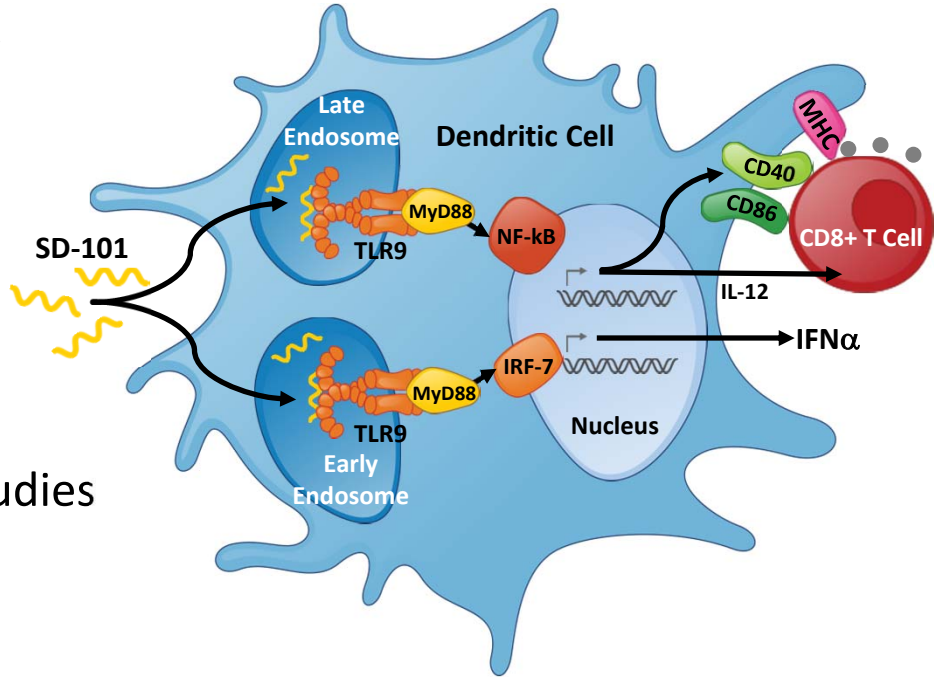
SD-101: TLR9 Agonist Optimized for Immuno-oncology

- SD-101 is a oligonucleotide with immunostimulatory CpG motifs that activate plasmacytoid dendritic cells via Toll-like receptor-9
- SD-101 activates 2 key pathways leading to functional maturation of dendritic cells and substantial production of IFNα
- Intratumoral SD-101 injection focuses these activities on the tumor and draining lymph nodes
- Leads to activation of cytotoxic T cells specific for multiple tumor antigens
- Strong synergy observed between SD-101 and anti-PD1 on preclinical studies



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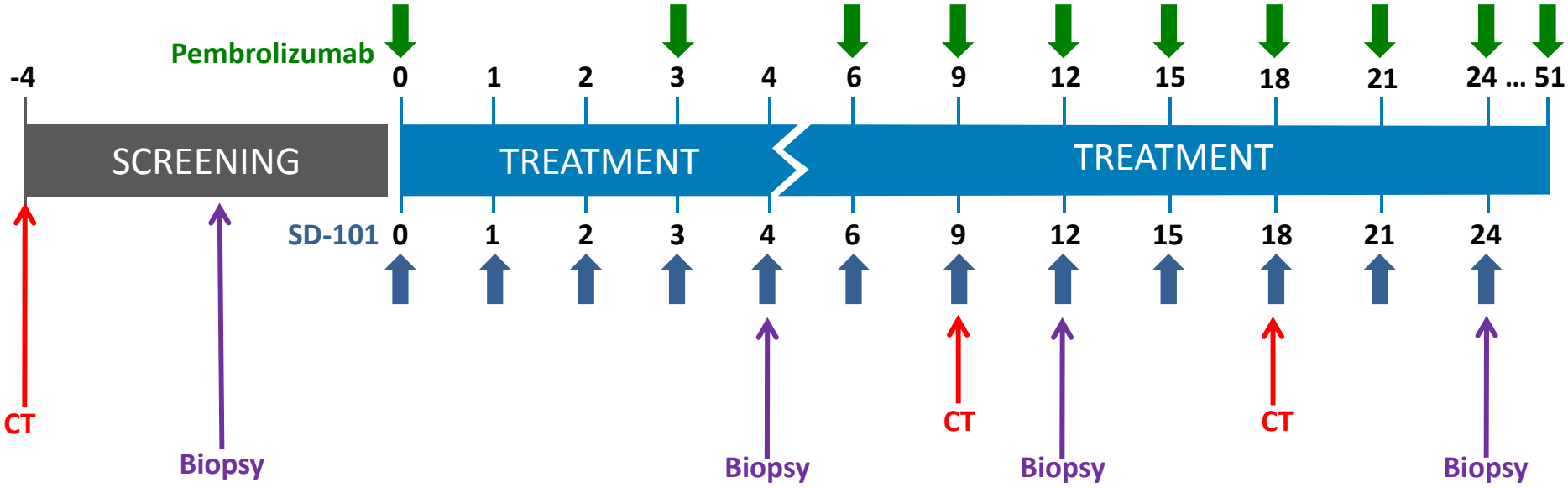
Patients, Study Design and Treatment

Patients	Dose Escalation**
▸ Stage IIIc or Stage IV metastatic melanoma*	SD101 **2mg** QW + Pembrolizumab 200 mg/Q3W
▸ ECOG performance status of 0 or 1	↓
▸ At least one injectable site	SD101 **4mg** QW + Pembrolizumab 200 mg/Q3W
▸ Response by RECIST v1.1	↓
▸ Prior anti-PD1 or anti-PD1 naive	SD101 **8mg** QW + Pembrolizumab 200 mg/Q3W



*Histologically confirmed
**DLT Period 29 days

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Baseline Characteristics

Characteristics	Anti-PD-1 Naïve Subjects (N=8)	Anti-PD-1 Experienced (N=11)	All (N=19)
Median age, yrs (range)	68.5 (49, 78)	61 (34, 73)	64 (34, 78)
Male, %	6 (75.0%)	8 (72.7%)	14 (73.4%)
White, %	7 (87.5%)	10 (90.9%)	17 (89.5%)
ECOG PS, %			
0	6 (75.0%)	8 (72.7%)	14 (73.7%)
1	2 (25.0%)	3 (27.3%)	5 (26.3%)
Stage at screening			
IIIc	0	2 (18.2%)	2 (10.5%)
IV	8 (100.0%)	8 (72.7%)	16 (84.2%)
Organs involved (target and non-target)			
Liver	2 (25.0%)	6 (54.6%)	8 (42.1%)
Lung	5 (62.5%)	4 (36.4%)	9 (47.4%)
Lymph nodes	5 (62.5%)	6 (54.5%)	11 (57.9%)
Skin/subcutaneous tissue	5 (62.5%)	9 (81.8%)	14 (73.7%)
0/1/2/≥ 3 prior lines of therapy, %	4/3/1/0	0/1/3/7	4/4/4/7

Best Overall Response

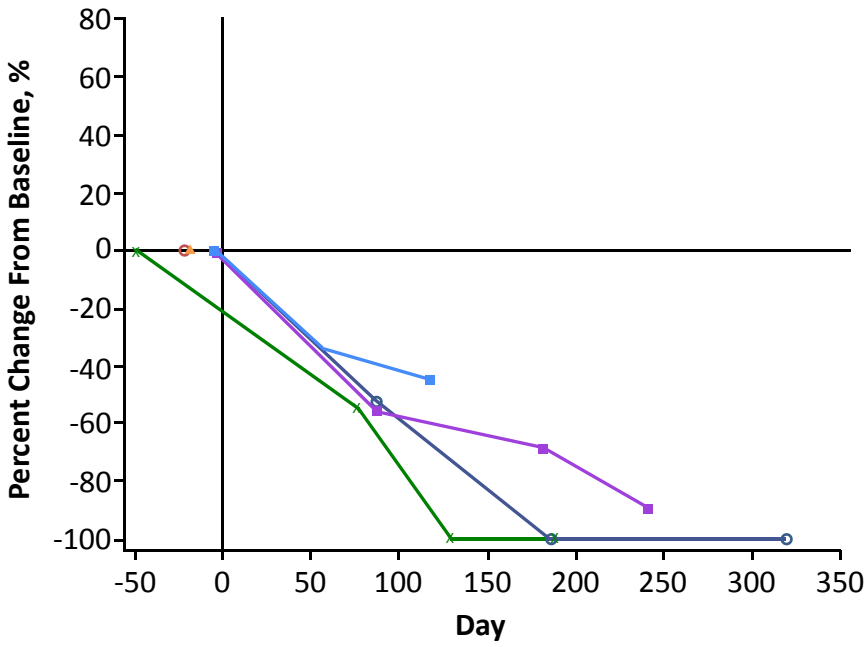
Best OR*, %	Anti PD-1 Naïve (Evaluable N=5)	Anti PD-1 Experienced (Evaluable N=8)
CR	1 (20.0%)	0
PR	3 (60.0%)	0
SD	0	4 (50.0%)
PD	1 (20.0%)	4 (50.0%)
PR+CR	4 (80.0%)	0

- Median follow-up for anti PD-1-naïve patients is 188 days (1,319)
- Median follow-up for anti PD-1 experienced is 81 days (61,169)

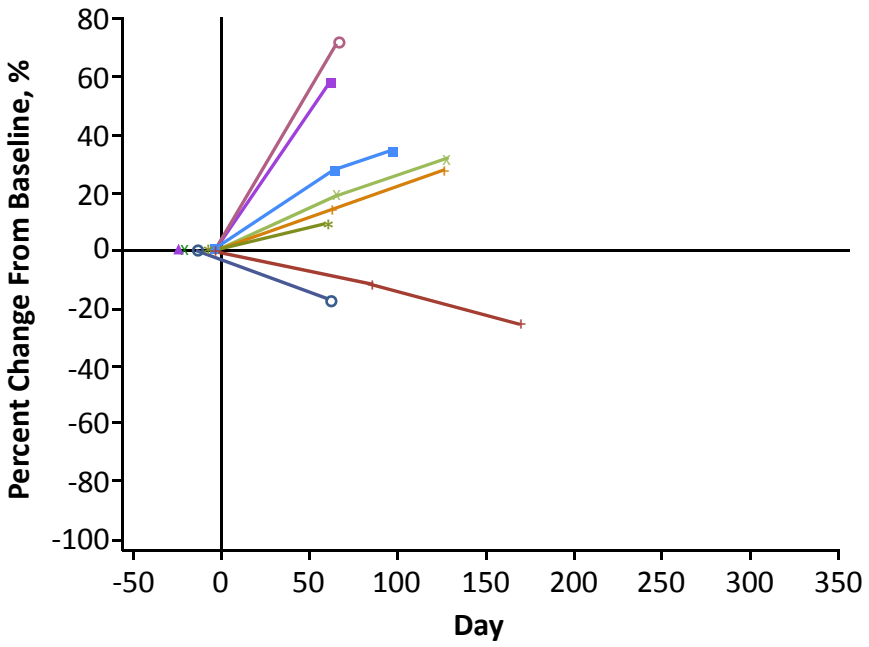
* Investigator assessed using RECIST v1.1

Percent Change in Tumor Burden

Anti-PD1 Naïve Patients



Anti-PD1 Experienced Patients



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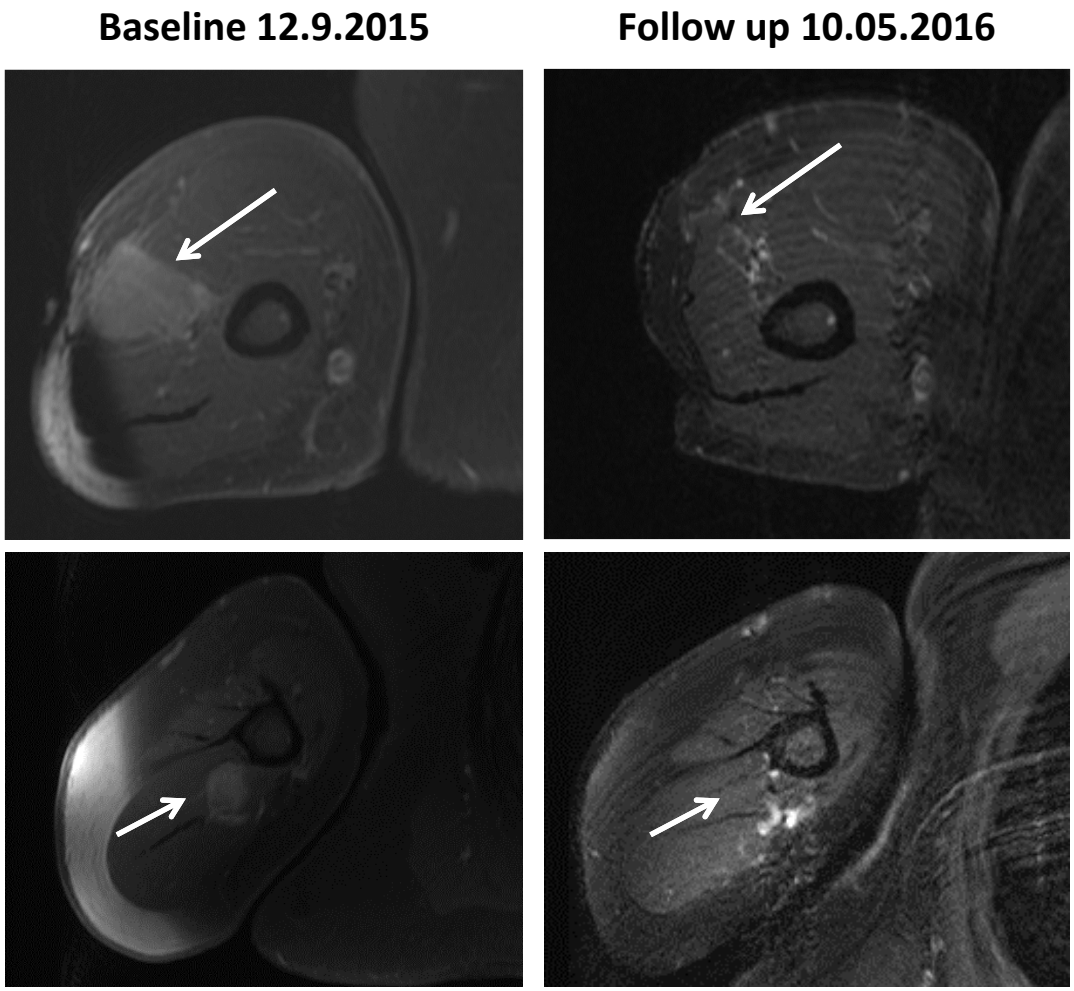
Response to Therapy in Injected and Non-injected Lesions



Subject 101005, CR
78 year old, white male Stage IV at screening
No prior treatment; anti-PD1 naïve

Induction of Immune Signatures in Tumor Biopsies Following SD-101 and Pembrolizumab Treatment

Subject 101005, CR

Biopsy from injected lesion

↓

RNA isolation

↓

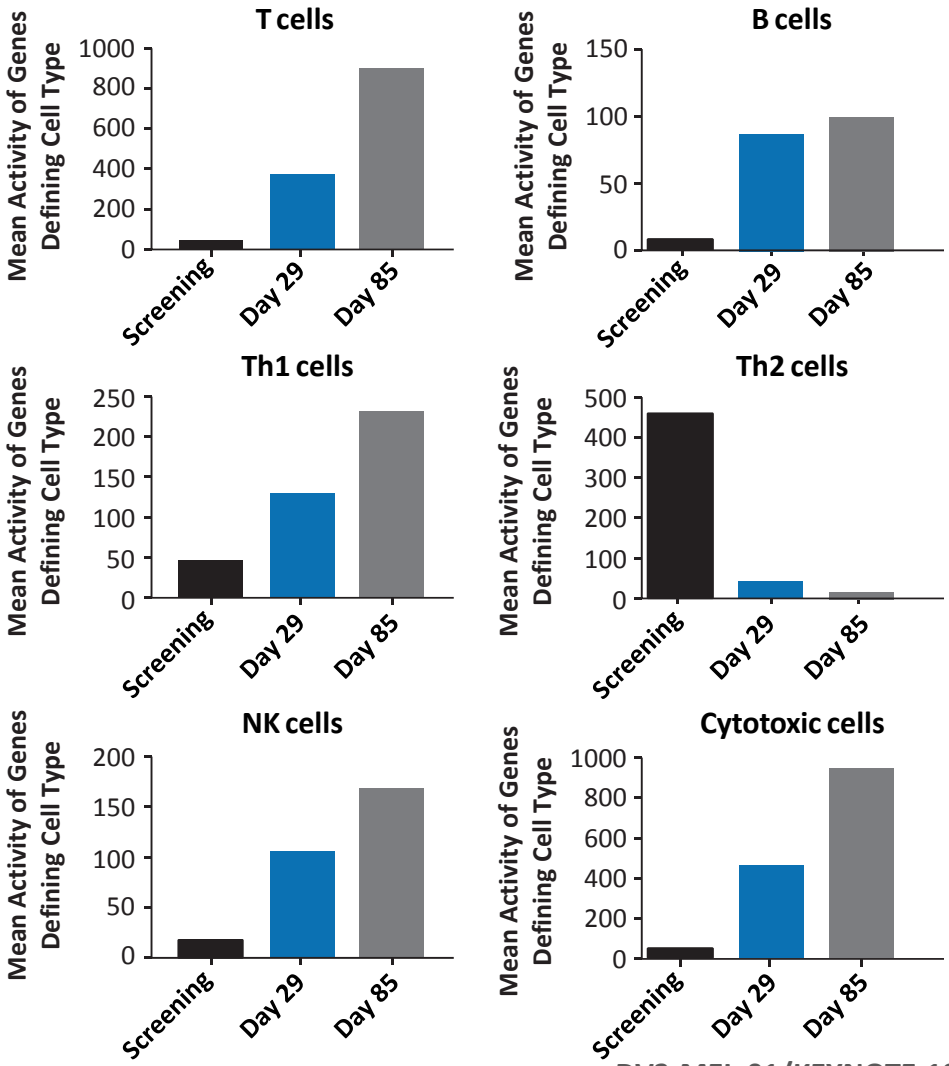
Quantitative gene expression measurement by Nanostring

↓

Nanostring's PanCancer Immune Profiling Panel of 600 genes defining immune cell types and functions

↓

Data expressed as the mean expression of genes clustered by cell type



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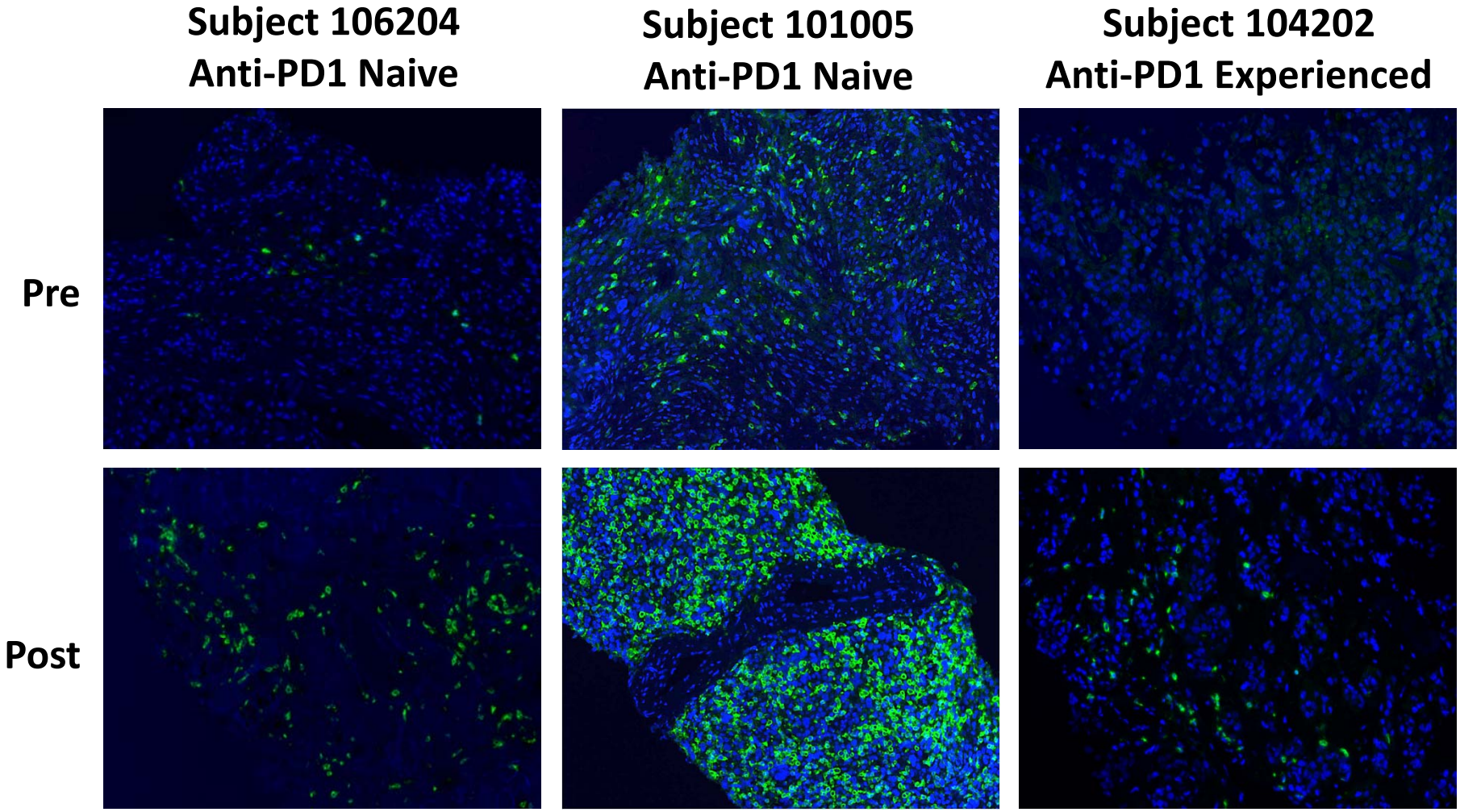
CD8 T Cell Tumor Infiltrate Following SD-101 and Pembrolizumab Treatment as Demonstrated by Multiplex IHC*



*Acteris Inc., South San Francisco, CA

Overview of Safety

Subjects With at Least 1 Event, N (%)	1 mg (N=3)	2 mg (N=5)	4 mg (N=5)	8 mg (N=6)	Total (N=19)
All AEs	3 (100)	5 (100)	5 (100)	6 (100)	19 (100)
Grade 3-4*	0	4 (80)	2 (40)	3 (50)	9 (47.4)
SAEs	0	3 (60)	1 (20)	3 (50)	7 (36.8)
AEs related to SD-101	3 (100)	5 (100)	5 (100)	5 (83.3)	18 (94.7)
Grade 3-4	0	0	2 (40)	0	2 (10.5)
AEs related to pembrolizumab	3 (100)	5 (100)	5 (100)	5 (83.3)	18 (94.7)
Grade 3-4	0	1 (20)	1 (20)	0	2 (10.5)
AEs leading to d/c of SD-101	0	0	1 (20)	1 (16.7)	2 (10.5)
AEs leading to d/c of pembrolizumab	0	0	0	1 (16.7)	1 (5.3)
AEs leading to death	0	0	0	0	0
Dose limiting toxicities	0	0	0	0	0

*Anemia, febrile neutropenia, lower GI hemorrhage, injection site erythema, injection site pain, sepsis, failure to thrive, basal cell carcinoma, squamous cell carcinoma

Frequent AEs (>20%)

	1 mg (N=3)	2 mg (N=5)	4 mg (N=5)	8 mg (N=6)	Total (N=19)
Anemia	2 (66.7)	2 (40)	0	0	4 (21.1)
Chills	2 (66.7)	3 (60)	1 (20)	4 (66.7)	10 (53.6)
Fatigue	3 (100)	3 (60)	2 (40)	6 (100)	14 (73.7)
Influenza-like illness	0	0	4 (80)	1 (16.7)	5 (26.3)
Injection site erythema	1 (33.3)	1 (20)	3 (60)	2 (33.3)	7 (36.8)
Injection site pain	1 (33.3)	0	2 (40)	1 (16.7)	4 (21.1)
Malaise	1 (33.3)	3 (60)	1 (20)	2 (33.3)	7 (36.8)
Pyrexia	1 (33.3)	3 (60)	1 (20)	2 (33.3)	7 (36.8)
Myalgia	1 (33.3)	4 (80)	3 (60)	3 (50)	11 (57.9)
Headache	1 (33.3)	3 (60)	1 (20)	3 (50)	8 (42.1)

Conclusions

- In patients with Stage IIIc/IV melanoma, intratumoral SD-101 in combination with pembrolizumab was well tolerated
  - No dose-limiting toxicities were observed in any SD-101 dose cohort
- The most common treatment-emergent adverse events were flu-like symptoms (fever, chills and myalgia)
  - Consistent with engagement of TLR9 and production of IFN-alpha
- Preliminary data suggest that combination therapy with SD-101 and pembrolizumab appears to show activity in both treatment-naïve and in anti-PD1 failures in patients with advanced melanoma
- SD-101 and pembrolizumab resulted in elevation of immune function as evidenced by
  - Increases in immune function signatures
  - Increase in immune cell infiltrates in the tumor microenvironment

Acknowledgements

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