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Society for Immunotherapy of Cancer

Durable responses in anti-PD-1 refractory melanoma following intratumoral injection of Toll-like receptor 9 (TLR9) agonist CMP-001, in combination with pembrolizumab

On Behalf of the CMP-001-001 Study Team:

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Disclosure Information
SITC Annual Meeting 2019

John M. Kirkwood, MD

Financial relationships to disclose:

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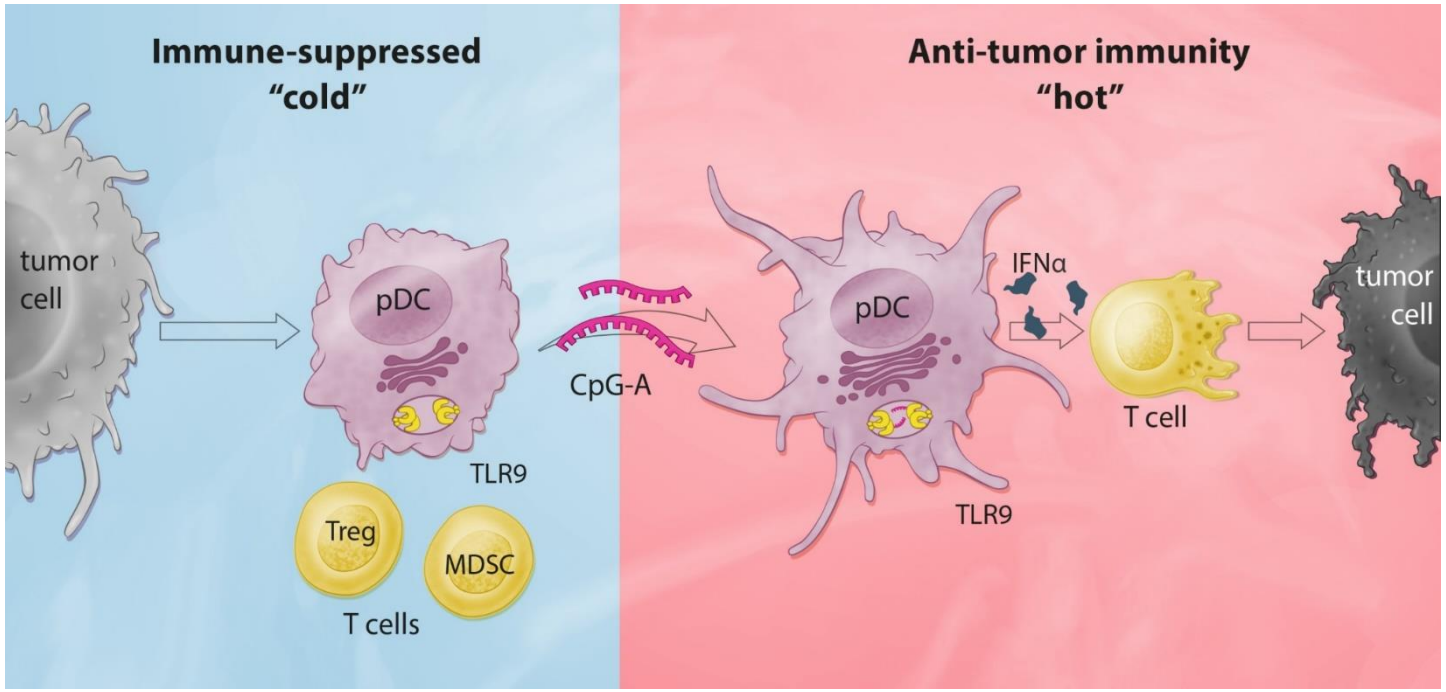
I will discuss the following investigational use in my presentation:

Investigational drug CMP-001 in combination with
pembrolizumab in patients with advanced melanoma

CMP-001 (CpG-A) Activates Tumor-associated pDC and Induces Systemic Tumor-Specific CTL

CMP-001 is a CpG-A DNA TLR9 agonist packaged in a virus-like particle for enhanced systemic anti-tumor T cell response



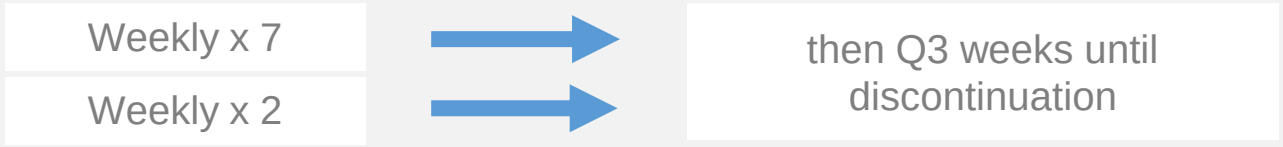
- pDC - plasmacytoid dendritic cell | TLR9 - Toll-like receptor 9 | MDSC - Myeloid-derived suppressor cell
- Swiecki, M., and M. Colonna. *Nature Reviews Immunology* 15.8 (2015): 471. Hartmann, E., et al. *Cancer research* 63.19 (2003): 6478-6487

Phase 1B Study of Intratumoral CMP-001 +/- Pembrolizumab in Anti-PD-1 Refractory Melanoma (NCT02680184)

Key Elements of Study Design

- 3+3 Dose Escalation (1, 3, 5, 7.5, 10mg; n=44) / Expansion (5, 10mg; n=100, ongoing)
- CMP-001 intratumoral/pembrolizumab IV

Two schedules of escalation with CMP-001 evaluated:



- Q12 week scans. RECIST v1.1 assessment per investigator
- Parallel Monotherapy Cohort (n=24, ongoing)

Two different formulations of CMP-001 were used during the trial:

1. 0.01% polysorbate 20 (PS20), n=83 including the 44 dose escalation patients, and 39 expansion patients
2. 0.00167% PS20 (n=61 expansion patients)

Study Objectives

- Safety
- Dose and schedule selection
- Anti-tumor activity
- Pharmacodynamics

Phase 1B Study of Intratumoral CMP-001 + Pembrolizumab in Anti-PD-1 Refractory Melanoma

- Key Inclusion Criteria
  - Metastatic or unresectable melanoma
    - Dose Escalation: Best prior response to anti-PD-1-based therapy of PD or SD*
    - Dose Expansion: Progression on anti-PD-1-based therapy, regardless of best prior response to anti-PD-1
  - No restriction on number of prior lines of therapy, including prior TLR9 agonist (CpG-C)
- Key Exclusion Criteria
  - Anti-CTLA-4 antibody or investigational therapy within 30 days
  - Requirement of > 10 mg/d prednisone (systemically)
  - Grade 4 autoimmune toxicity on prior immunotherapy
  - Active (i.e., symptomatic or growing) CNS metastases

*SD > 12 weeks; no minimum duration of anti-PD-1 was required if the patient was PD per PI

CMP-001 + Pembrolizumab in Anti-PD-1 Refractory Melanoma: Baseline Characteristics

Baseline Characteristic	N = 144 (%)
ECOG	
0	94 (65.3%)
1	50 (34.7%)
BRAF mutation	47 (32.6%)
LDH >ULN	57 (39.6%)
Baseline liver/CNS/bone mets	44 (30.6%)
Prior PD-1 Best Response of CR/PR	24 (16.7%)
Prior PD-1 Last Response of PD	134 (93.1%)
Prior Cancer Therapies*:	
Anti-PD-1 Therapy	144 (100%)
Monotherapy	108 (75.0%)
Combination therapy	72 (50.0%)
Ipilimumab	69 (47.9%)
Monotherapy	32 (22.2%)
Combination therapy	39 (27.1%)

* Some patients had both monotherapy and combination prior cancer therapies

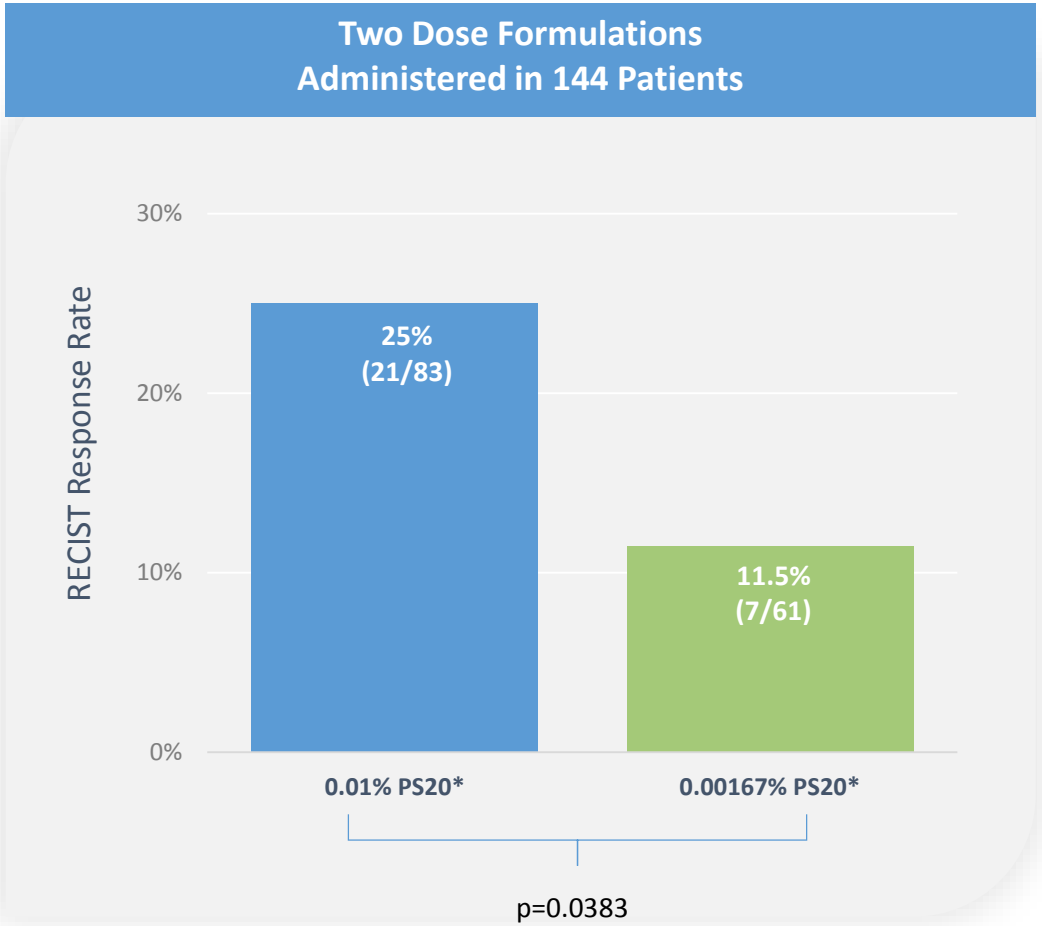
CMP-001 + Pembrolizumab Treatment-Related Adverse Events

Adverse Event		N=144*		
		All Grades	Grade 3	Grade 4
Flu-like Symptoms	Chills	103 (72%)	4 (3%)	0
	Pyrexia	80 (56%)	4 (3%)	0
	Fatigue	73 (51%)	2 (1%)	0
	Nausea	65 (45%)	0	0
	Vomiting	42 (29%)	0	0
	Headache	40 (28%)	0	0
Injection Site Pain		40 (28%)	0	0
Hypotension		26 (18%)	9 (6%)	1 (0.7%)
Back pain		23 (16%)	4 (3%)	0
Arthralgia		22 (15%)	3 (2%)	0
Hypertension		13 (9%)	7 (5%)	0
AST increased		10 (7%)	3 (2%)	1 (0.7%)
ALT increased		9 (6%)	2 (1.4%)	1 (0.7%)
Anemia		9 (6%)	3 (2%)	0
Hypophosphatemia		5 (4%)	3 (2%)	0

*Includes treatment-related TEAEs reported in >20% of patients or Grade 3/4 treatment-related TEAEs reported in 3 or more patients.
- No Grade 5 treatment-related TEAEs were reported.
- Six patients (4%) discontinued due to TEAEs.

CMP-001 + Pembrolizumab in PD-1 Refractory Melanoma

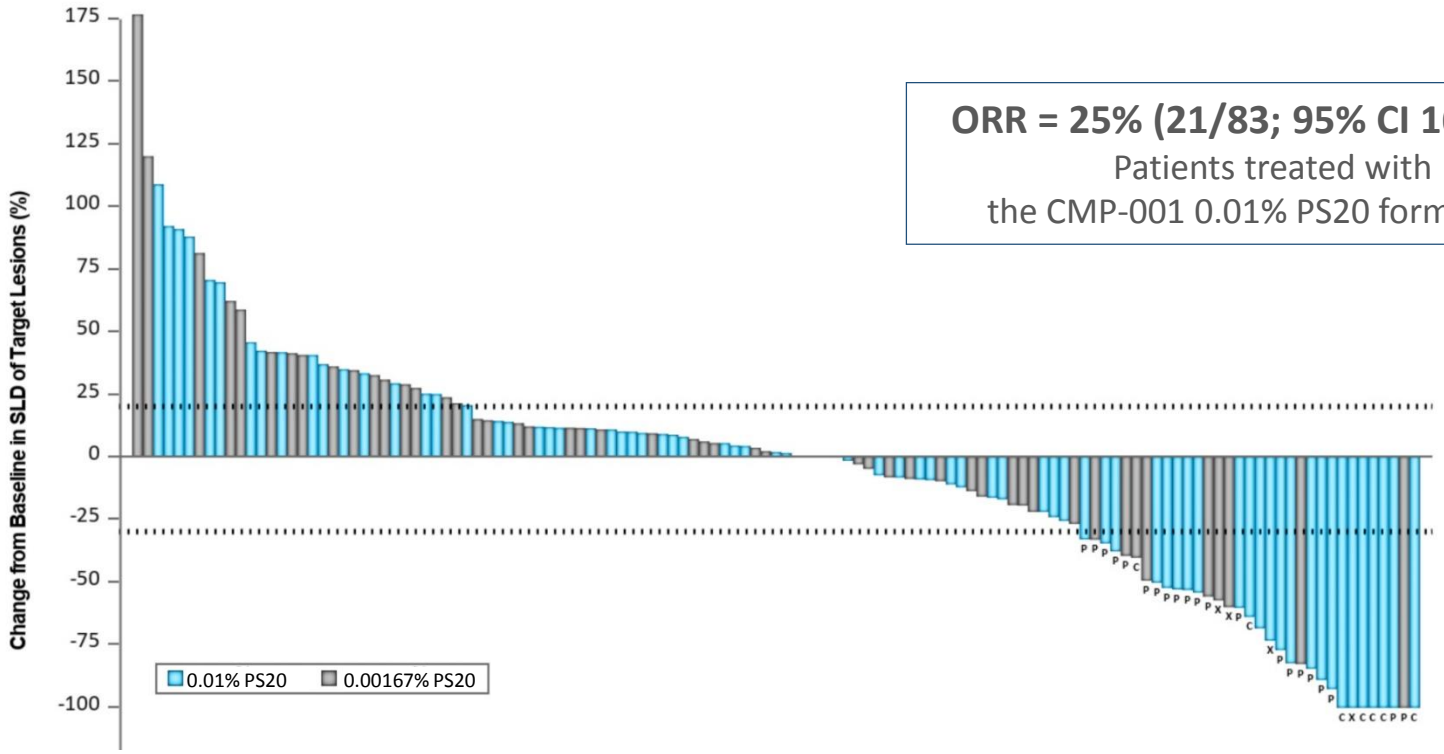
Impact of Formulation on Anti-tumor Activity (RECIST v1.1 Responders)



*Starting formulation

CMP-001 + Pembrolizumab in Anti-PD-1 Refractory Melanoma

Best Tumor Response (ITT, RECIST v1.1, All Patients [N=144])

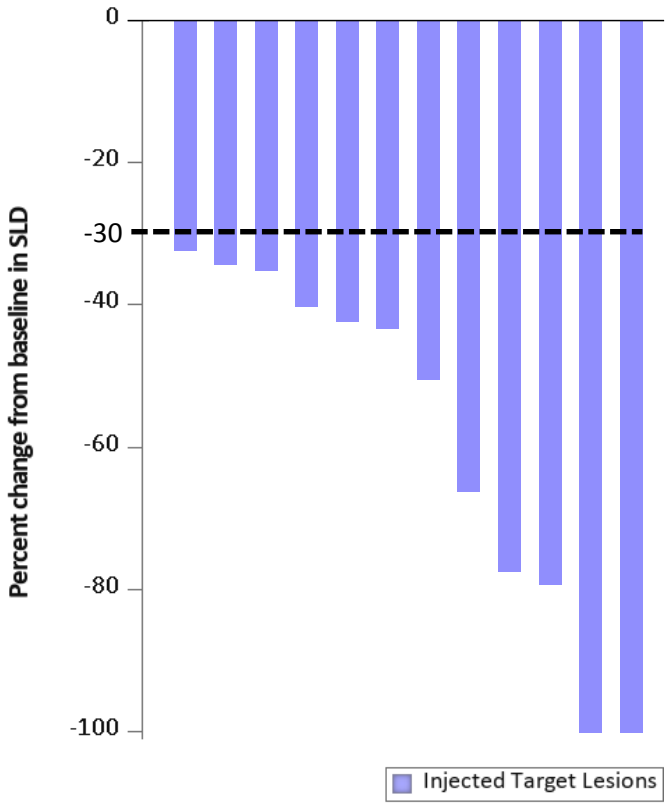


ORR = 25% (21/83; 95% CI 16%-36%)
Patients treated with
the CMP-001 0.01% PS20 formulation

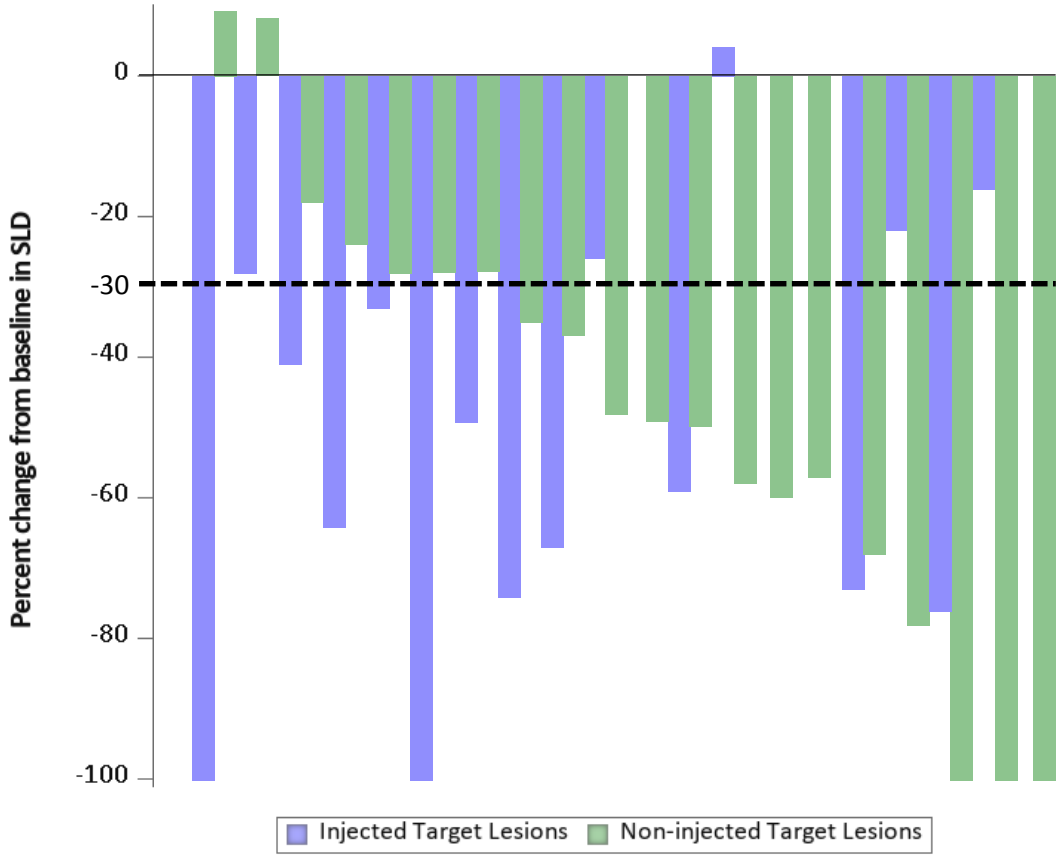
- Waterfall Plot includes all patients with post-baseline scans (N = 125)
- C=Complete response, P=Partial response. Patients with partial response after progression noted as 'X'

CMP-001 + Pembrolizumab in Anti-PD-1 Refractory Melanoma

Similar Responses in Injected vs. Non-Injected Lesions of Responders (N= 32, including 28 RECIST & 4 iRECIST)



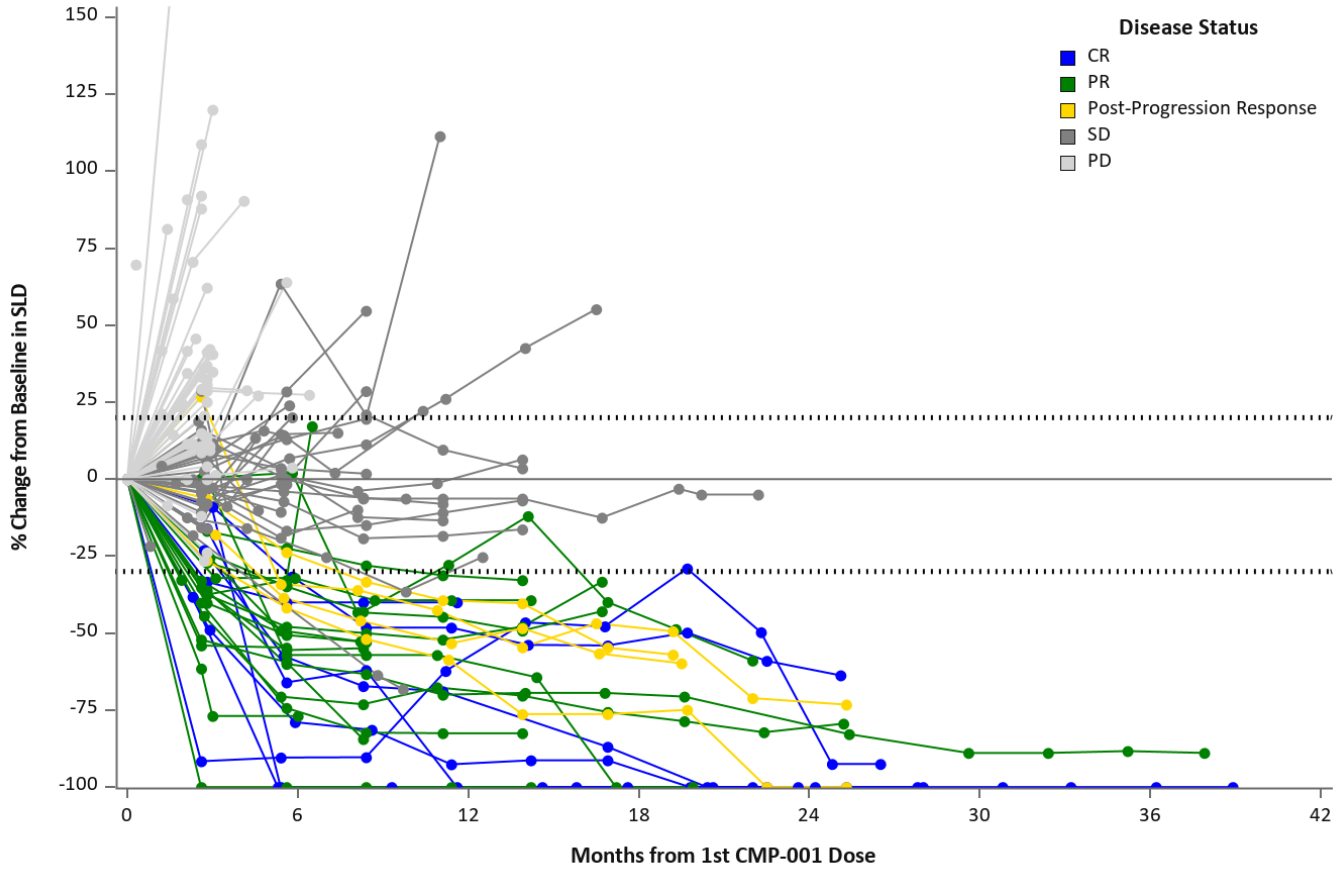
Patients with injected target lesions only (N=12)



Patients with non-injected target lesions (N=20)

CMP-001 + Pembrolizumab in Anti-PD-1 Refractory Melanoma

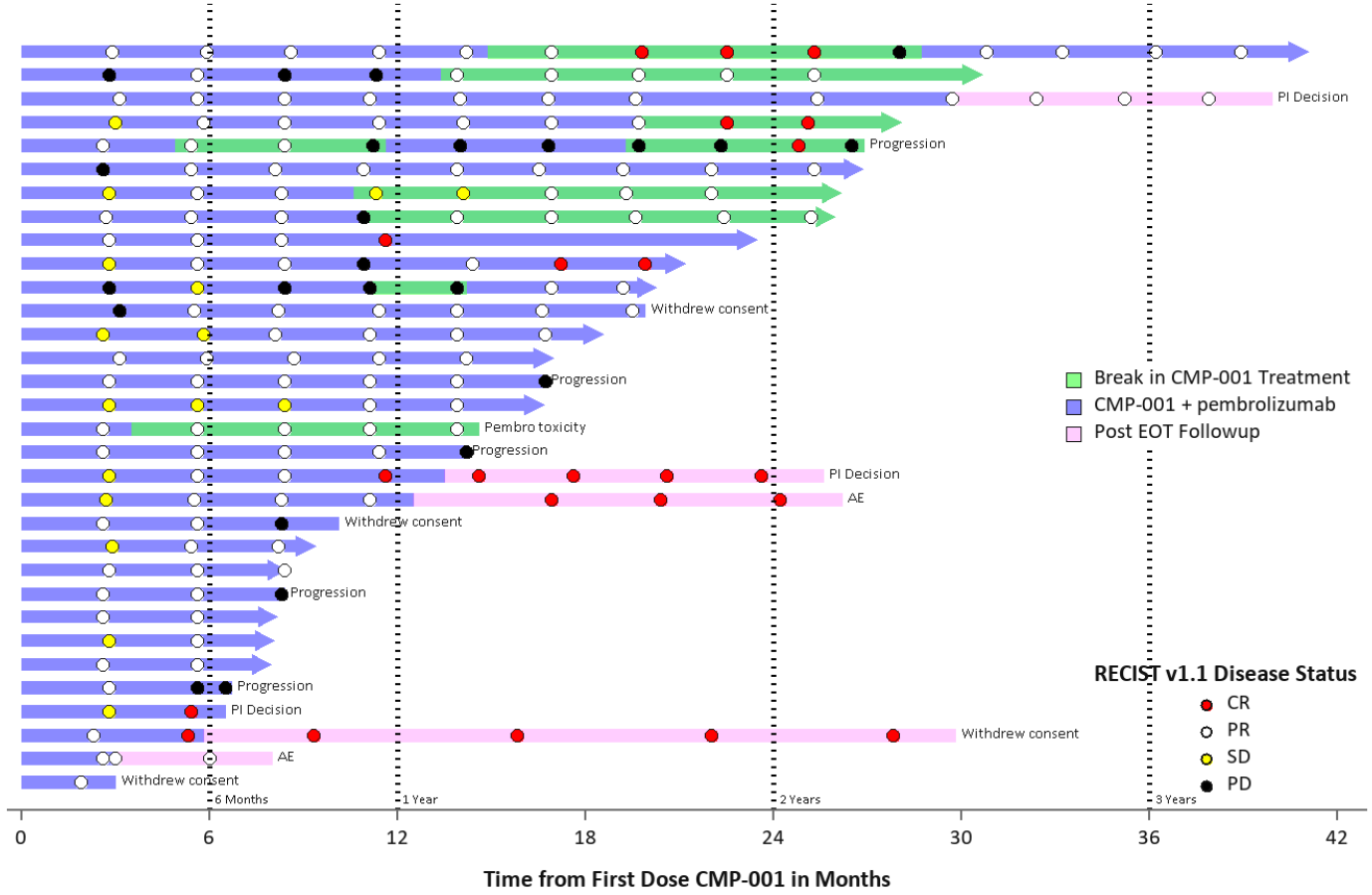
Percent Change from Baseline in Target Lesions Sum of Longest Diameters (All Patients (N=144)



- Spider Plot includes all patients with post-baseline scans (N = 125)

CMP-001 + Pembrolizumab in Anti-PD-1 Refractory Melanoma

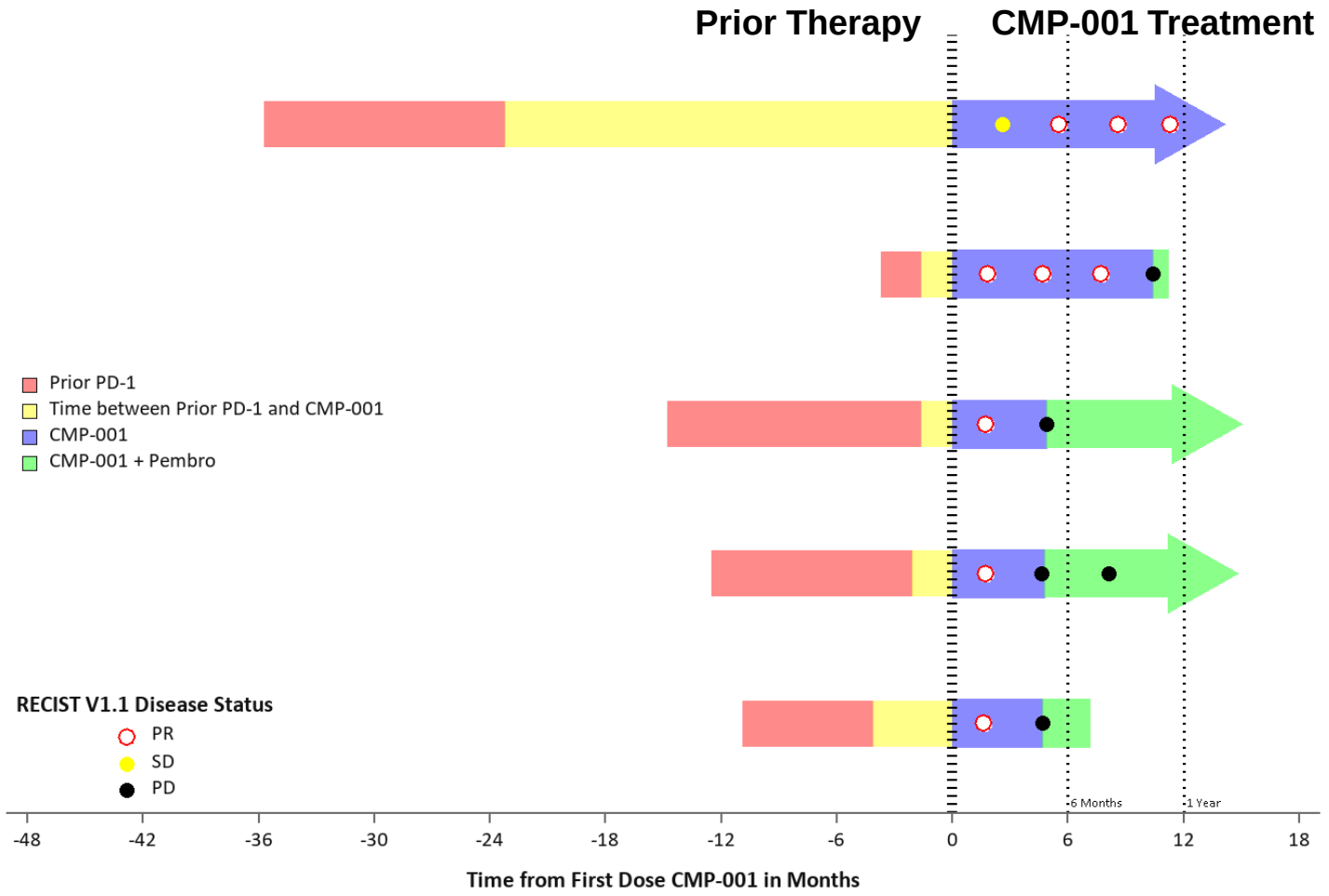
Duration of CMP-001 Treatment and Disease Status over Time for CMP-001 + Pembrolizumab Responders (N=32, including 28 RECIST & 4 iRECIST)



Median duration of response has not been reached (16.9+ mos)

CMP-001 Monotherapy in PD-1 Refractory Melanoma

Duration of CMP-001 Treatment and Disease Status over Time for Responders (N=5)



Conclusions

- Intratumoral CMP-001 reversed resistance to anti-PD-1 in melanoma patients who progressed on prior anti-PD-1 therapy.
- CMP-001 in combination with pembrolizumab was well tolerated; no apparent increase in autoimmune disorders related to study treatment.
- CMP-001 monotherapy was active and induced systemic anti-tumor responses, but responses tended to be less durable than combination therapy.
- IHC, RNA-Seq, and serum chemokine analyses were consistent with pDC activation through TLR9 as the mechanism of action in responding patients.
- These data support further clinical development of CMP-001 in melanoma and other tumor types.
    - Clinical investigation in neoadjuvant melanoma is in progress (abstract # O34, to be presented at 6:15 PM on Nov. 9)

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