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Phase II Trial of Neoadjuvant Nivolumab (Nivo) and Intra-Tumoral (IT) CMP-001 in High-Risk Resectable Melanoma (Neo-C-Nivo): Final Results

Davar D, Karunamurthy A, Hartman D, Chauvin JM, Deblasio R, Menna C, Ding Q, Zidi B, Zhang S, Pagliano O, Rose A, Choudry H, Holtzman M, Duvvuri U, Sridharan S, Pingpank J, Najjar Y, Wooldridge JE, Krieg AM, Kirkwood JM, and Zarour H.

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Background

- Patients with clinically occult disease with 5-year MSS rates of 76% (N1b), 71% (N2b) and 64% (N3b)[1;] and the standard of care herein is upfront surgery followed by adjuvant therapy either with anti-PD-1 (BRAF mutant or WT) or dabrafenib/trametinib (if BRAF mutant) based pivotal phase III studies.[2-4]

- Neoadjuvant immunotherapy enhances systemic T-cell response to tumor antigens, resulting in enhanced detection and killing of micrometastatic tumor disseminated beyond resected tumor, hypothesized to etiology of postsurgical relapse.[5]

- Neoadjuvant immunotherapy with anti-PD-1 monotherapy produces pathologic response rates (PRR) of 18-25% of patients;[6-7] while anti-PD-1/anti-CTLA-4 combination results in PRR of 65-78%.[6,8-10]

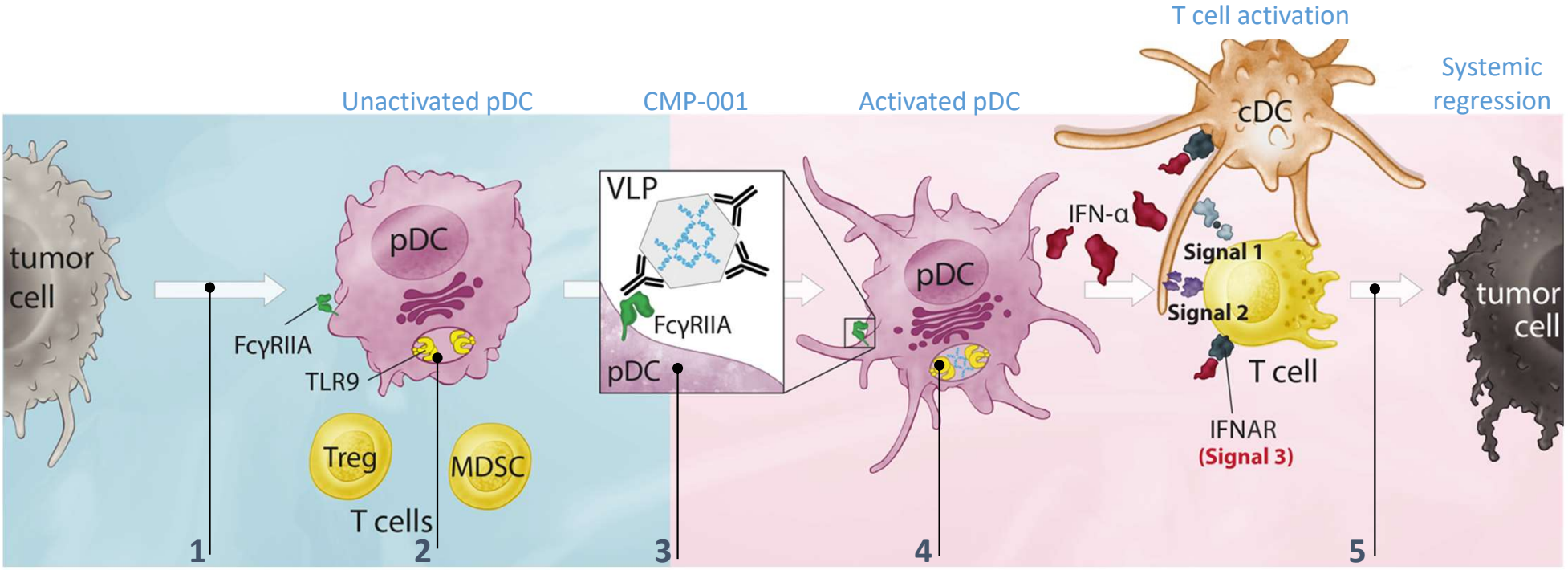
- TLR9 is an endosomal receptor, expressed by B cells and plasmacytoid DCs (pDCs) in humans that can be activated by unmethylated cytosine guanosine oligodeoxynucleotides (CpG ODN). TLR9 activation induces Type I IFN production via MyD88 and IRAK4 to activate IRF7.[11]

- CMP-001 is a type A CpG that activates pDC and stimulates IFNa production.[12] In studies in PD-1 refractory melanoma, intra-tumoral (IT) CMP-001 produced responses both singly and in combination with pembrolizumab.[13]

- To evaluate the benefit of neoadjuvant IT CMP-001, we designed a phase II study to evaluate the effects of neoadjuvant IT CMP-001 and nivolumab in high-risk resectable melanoma.

[1]Gershenwald JE, CA Cancer J Clin 2017. [2]Long GV, NEJM 2017. [3]Weber JS, NEJM 2018. [4]Eggermont AMM, NEJM 2019. [5]Liu J, Cancer Discov 2016. [6]Amaria RN, Nat Med 2018. [7]Huang AC, Nat Med 2019. [8]Blank CU, Nat Med 2018. [9]Blank CU, Ann Oncol 2019. [10]Rozeman EA, Lancet Oncol 2019. [11]Krieg AM, Nat Rev Drug Discov 2006. [12]Lemke-Miltner CD, J Immunol 2020. [13]Kirkwood JM, J Immunother Cancer 2019.

CMP-001 – Mechanism of Action



1 Tumor recruits resting pDC

2 Supports Immuno-suppressive TME

3 Antibody-bound CMP-001 activates TLR9

4 Type I IFN enhances T cell activation

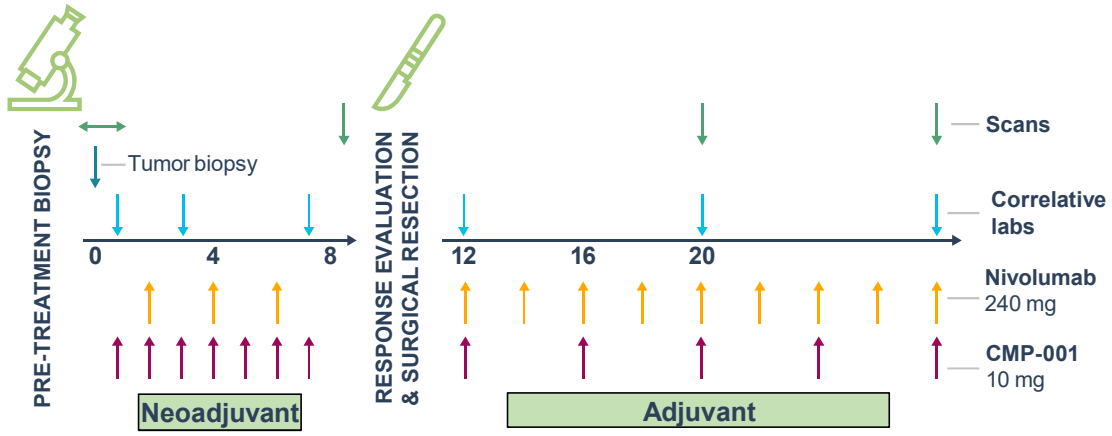
5 Neoantigen-specific T cells mediate systemic tumor regression

TME: tumor microenvironment, Treg: regulatory T cell, MDSC: myeloid derived suppressor cells

Neoadjuvant CMP-001 & Nivolumab: Study Design

Stage III B/C/D melanoma pre-surgery

- No active CNS disease
- Deemed surgically resectable
- Accessible tumor for biopsy
- Accessible tumor for CMP-001 injection
- Planned sample size: 28-32 evaluable patients



Primary endpoint: Major pathologic response (MPR) rate by irPRC[1-3]

Secondary endpoints: Relapse-free survival and overall survival

Pathologic Response[1-3]	%RVT
Complete Response (pCR)	**0%**
Major Response (pMR)	**≤10%**
Partial Response (pPR)	**10%> and ≤50%**
Non-response (pNR)	<50%
RVT, residual viable tumor	

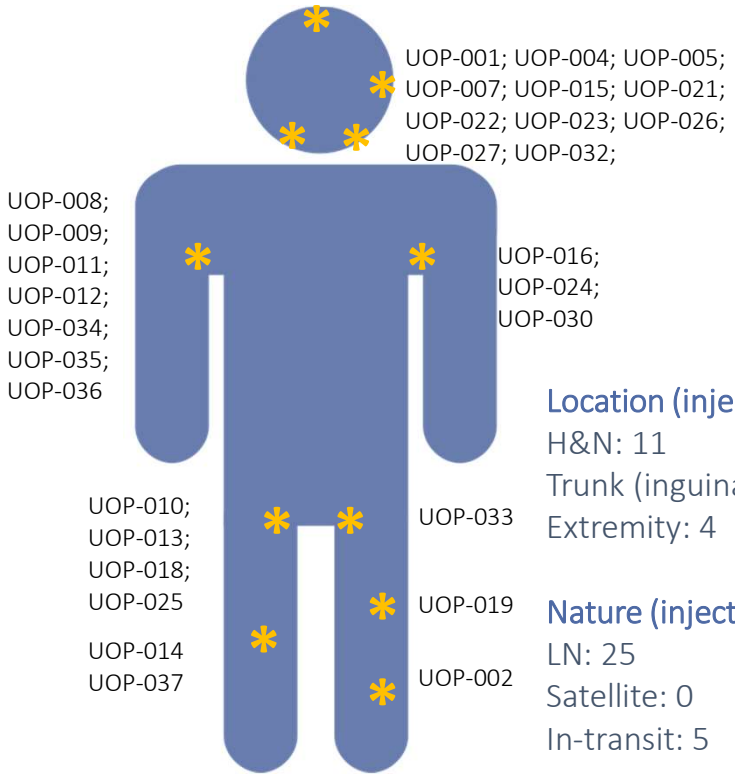
PRR — MPR

Reference Path Response Rates	
Therapy	**PRR[1-3]**
Pembro x1	19% pCR; 30% PRR[4]
Nivo 3mg/kg x 4 vs. Ipi/Nivo x3	45% pCR[5]
Ipi/Nivo (Ipi→Nivo; Ipi-1/Nivo-3; Ipi-3/Nivo-1)	65-80% PRR[6]
Ipi/Nivo (Ipi-1/Nivo-1)	50% pCR; 71% PRR[7]

[1]Cottrell TR, Ann Oncol 2018; [2]Tetzlaff MT, Ann Oncol 2018; [3]Stein JE, CCR 2020;
[4]Huang AC. Nat Med 2019; [5]Amaria RN, Nat Med 2019; [6]Roseman EA, Lancet Oncol 2019; [7]Blank CU, ASCO 2020

Patient Characteristics

Neoadjuvant CMP-001 & Nivolumab



Location (injected/measurable lesion)

H&N: 11

Trunk (inguinal/axillary): 15

Extremity: 4

Nature (injected/measurable lesion)

LN: 25

Satellite: 0

In-transit: 5

Patient Characteristics	
Enrolled	
• Safety Evaluable	31
• Efficacy Evaluable	30*
Demographics	
• Median age	61 (range 19-93)
• Sex	16M, 14F
Prior Therapy	
• Ipi	1 (5%)
• BRAF/MEK	1 (5%)
AJCC Stage (8th edition)	
• IIIB	17 (57%)
• IIIC	11 (37%)
• IIID	2 (6%)
Mutation Status	
• BRAF	5 (17%)

*At data cut-off: 1 patient with systemic progression prior to surgery evaluable for safety but not response

Safety and Toxicity

Neoadjuvant CMP-001 & Nivolumab

- No DLTs or G4/5 TRAE were observed.
- 8 G3 TRAE in total were observed in 7 patients, only 3 of which required medical intervention. Commonest G3 toxicity was hypertension, requiring intervention in only 1 instance. 1 instance of G3 irAE-colitis was observed
- Majority of TRAE were of G1-2 severity and consistent with the MOA of agents. Incidence of CRS was low, possibly due to prophylaxis used.
- No TRAE resulted in delays in planned surgery.
- 1 patient with G4 skin infection deemed *unrelated to* CMP and nivolumab had a delay in surgery although disease remained resectable at the time of surgery.

Treatment-Related Adverse Events (TRAE) (N=31)

	Grade 1 (n/%)	Grade 2 (n/%)	Grade 3 (n/%)
Constitutional			
- Arthalgia, myalgia	7 (22.6)	6 (19.4)	1 (3.2)
- Fever	14 (45.2)	5 (16.1)	0 (0.0)
- Flu-like symptoms	14 (45.2)	8 (25.8)	0 (0.0)
- Fatigue	14 (45.2)	3 (9.7)	0 (0.0)
- CRS-like reaction* (ECI)	2 (6.5)	3 (9.7)	0 (0.0)
irAE			
- Colitis	0 (0.0)	0 (0.0)	1 (3.2)
Cardiac			
- Hypertension	2 (6.4)	5 (16.1)	3 (9.7)
Electrolyte			
- Hyponatremia	19 (61.3)	0 (0.0)	0 (0.0)
- Hypophosphatemia	12 (38.7)	12 (38.7)	1 (3.2)
Gastrointestinal			
- Nausea/vomiting	4 (12.9)	5 (16.1)	0 (0.0)
Hematologic			
- Anemia	9 (29.0)	1 (3.2)	0 (0.0)
- Thrombocytopenia	10 (32.3)	0 (0.0)	0 (0.0)
Other			
- Injection site reaction	9 (6.5)	4 (12.9)	0 (0.0)
- Injection site infection	3 (9.7)	3 (9.7)	1 (3.2)

Data cutoff: 10/1/2020

Blinded Pathologic Response

Neoadjuvant CMP-001 & Nivolumab

Pathologic responses[1,2]	% RVT	N	%
Complete response (pCR)	0%	15	50%
Major response (pMR)	1-10%	3	10%
Partial response (pPR)	11-50%	3	10%
Non-response (pNR)	> 50%	9	30%
Total Evaluable		30	

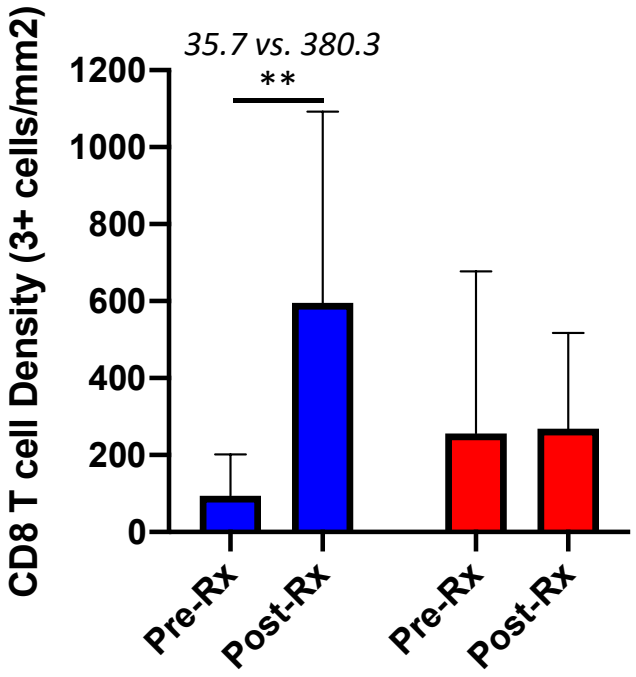
Pathological Response = 70%

Major Pathological Response = 60%

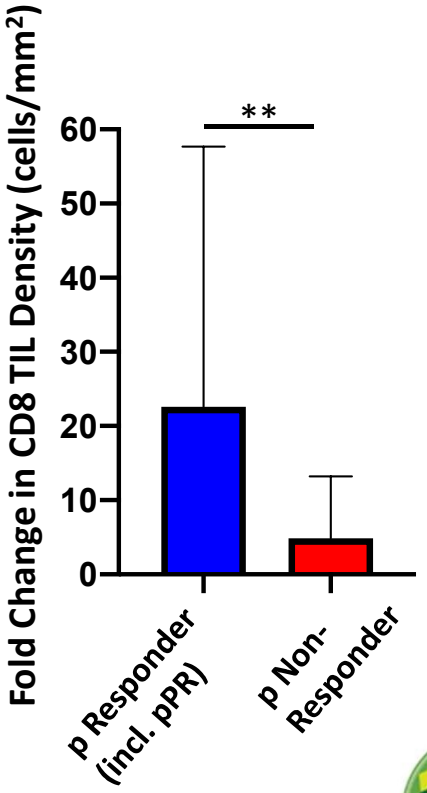
- %RVT calculated using %tumor viable
- Pathologist blinded to clinical and radiographic outcome
- N=30 evaluable

Changes in CD8 TIL Density (cells/mm2)

Neoadjuvant CMP-001 & Nivolumab



Pathologic responders had median greater fold change in CD8 T cells (10.3 vs. 0.8; N = 26 incl 17 R and 9 NR with paired samples)

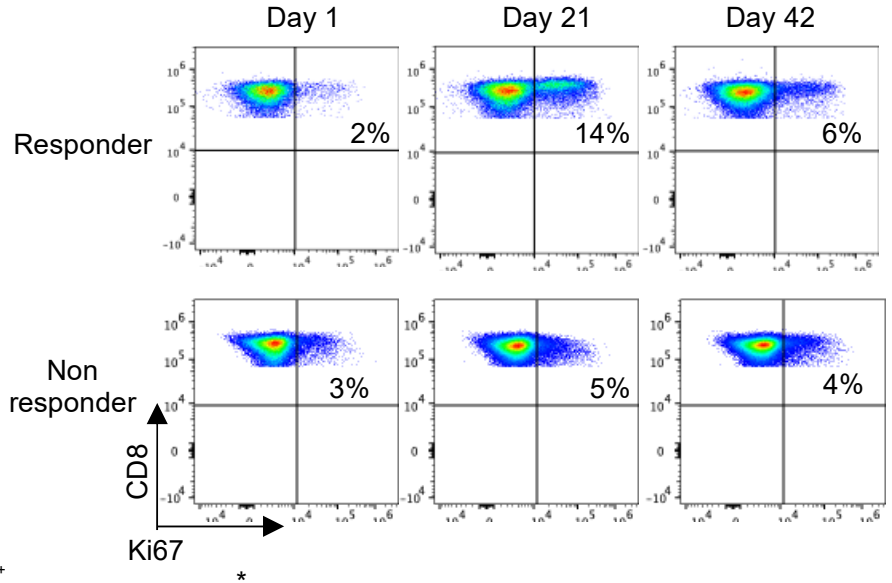


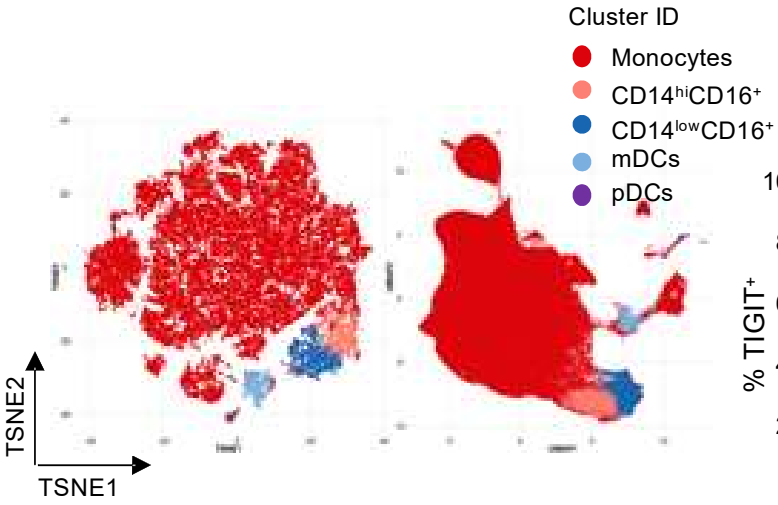
Peripheral Immune Kinetics

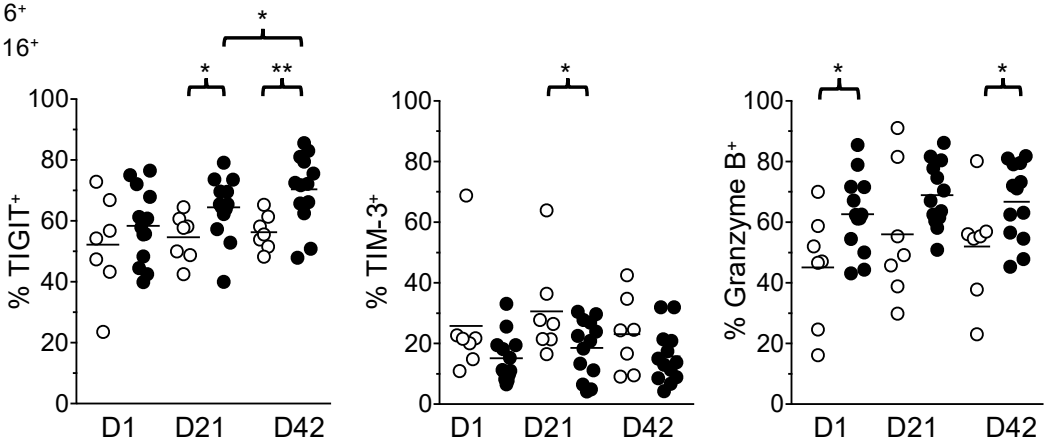
Neoadjuvant CMP-001 & Nivolumab

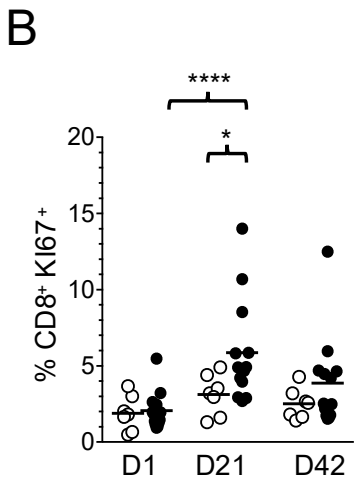
Responders had evidence of activated CD8⁺ T cells peripherally.

Tim-3 upregulation was noted on CD8⁺ T cells in non-responders.







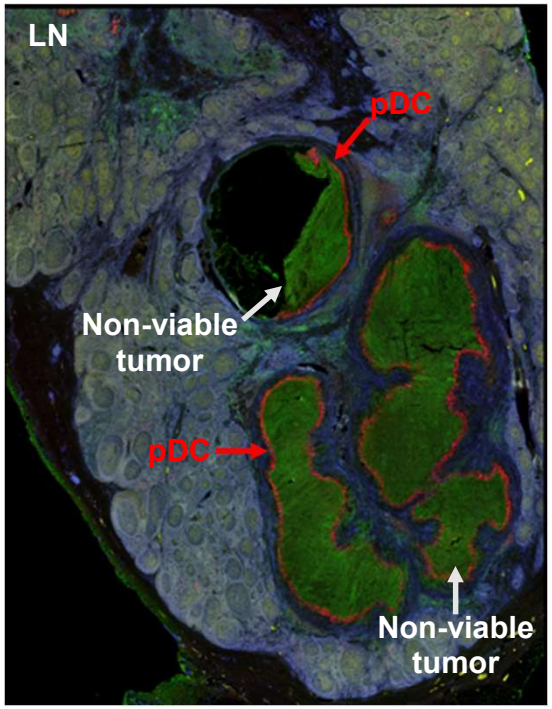


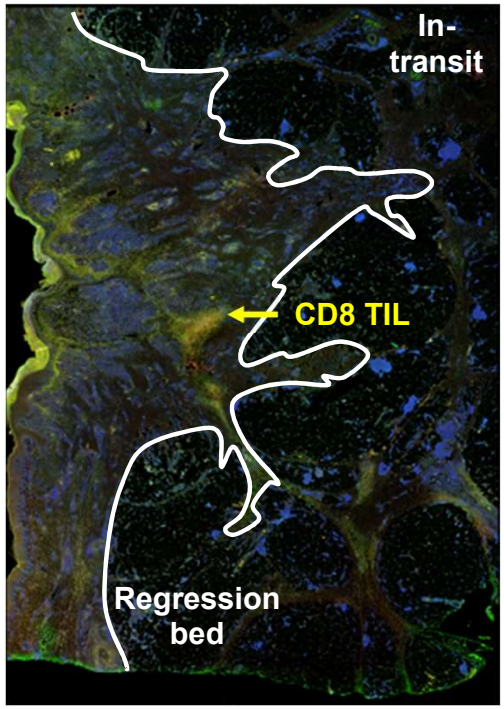
Digital Spatial Profiling (DSP, GeoMx) Revealed Distinct Patterns of Pathologic Response

Neoadjuvant CMP-001 & Nivolumab

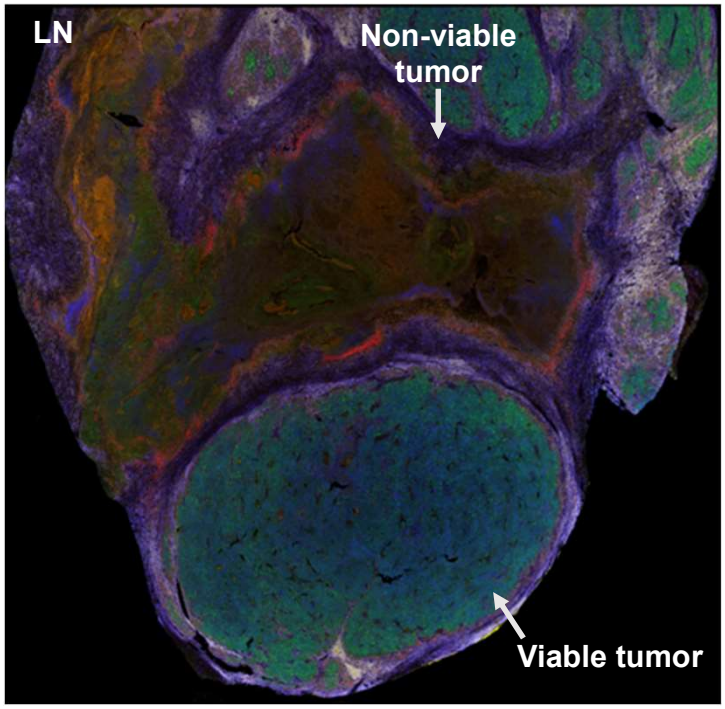
CD303
CD45
S100B
DNA

Major Pathologic Response





Pathologic Non-Response



Slide 11

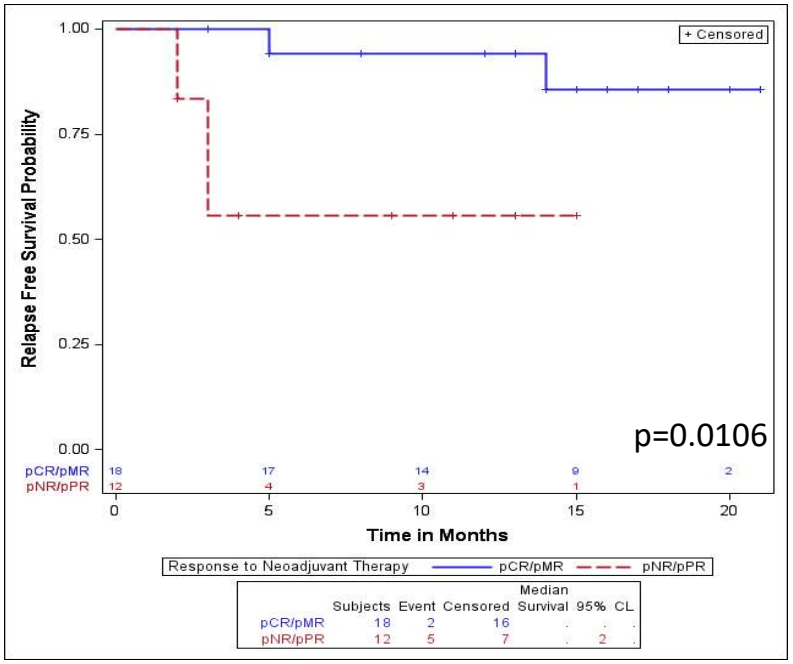
JW7 Consider spelling out or define in a footnote

James Wooldridge, 11/1/2020

Pathological Response is Associated with Durable RFS

Neoadjuvant CMP-001 & Nivolumab

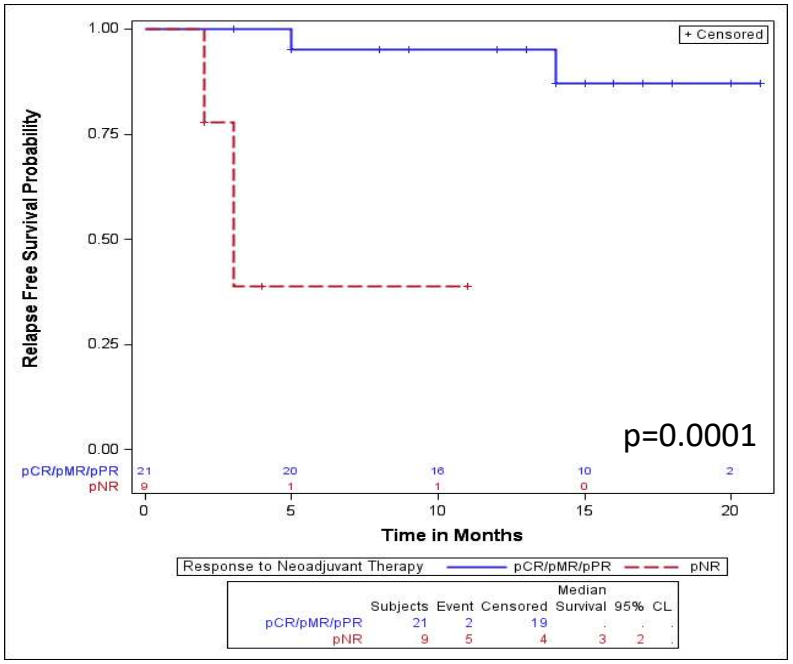
RFS in major pathologic responders



Median RFS: not reached in R (17, ∞) vs. not reached (5, ∞)

Landmark 1-year RFS:
89% (pCR + pMR)
90% (pCR/pMR + pPR)

RFS in all pathologic responders



Median RFS: not reached in R (not available) vs. 5 (4, ∞)

Conclusions

Neoadjuvant CMP-001 & Nivolumab

1. Neoadjuvant CMP and nivolumab was well-tolerated with a low incidence of Grade 3 TRAE. No Grade 4/5 TRAEs were reported.

2. Neoadjuvant CMP and nivolumab produced a high rate of pathologic response: 60% major pathologic response (%RVT ≤ 10%), and up to 70% if pPR (%RVT <10% to ≤50%) included.

3. Neoadjuvant CMP and nivolumab produced compelling evidence of immune activation peripherally and intra-tumorally; with clear evidence of pDC presence within TME in responders.

4. Pathologic response was associated with durable RFS.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