SITC 2019

Gaylord National Hotel
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Society for Immunotherapy of Cancer

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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): Preliminary Results

Davar D, Karunamurthy A, Hartman D, Ka M, Menna C, Burkette J, Chauvin JM, Zhang S, Ding Q, Pagliano O, Rose A, Sellitto K, Choudry H, Holtzman M, Duvvuri U, Sridharan S, Pingpank J, Najjar Y, Mauro D, Wooldridge J, Labinger B, Krieg A, Kirkwood JM, and Zarour H.

University of Pittsburgh

Disclosure Information
SITC Annual Meeting 2019

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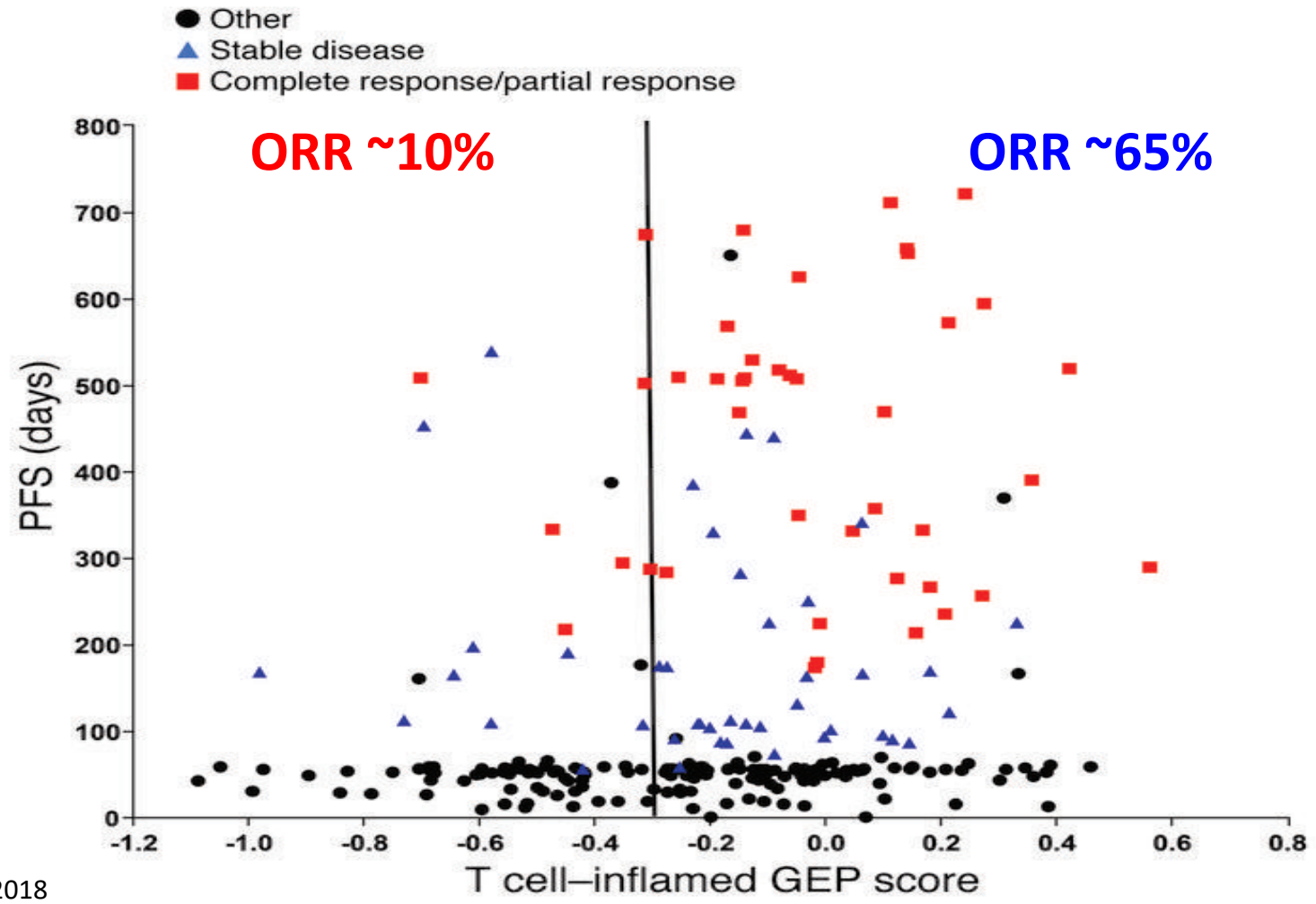
CE Speakers' Bureau: None

Stockholder: None

I will discuss the following investigational agents in my presentation:

Investigational drug CMP-001 in combination with nivolumab in patients with high-risk resectable melanoma.

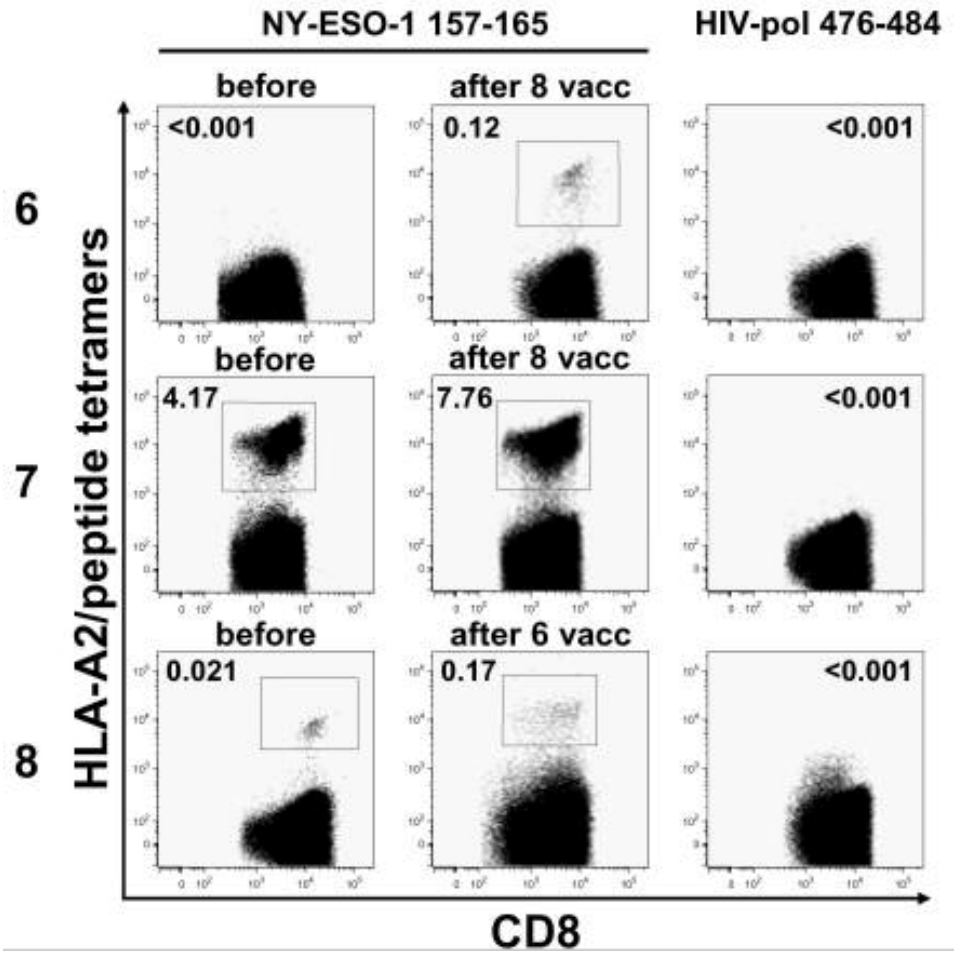
PD-1 Blockade Is Efficacious in Inflamed Tumors



Ayers M, JCI 2017; Critescu R, Science 2018

TLR9 Agonists Make Cold Tumors Hot

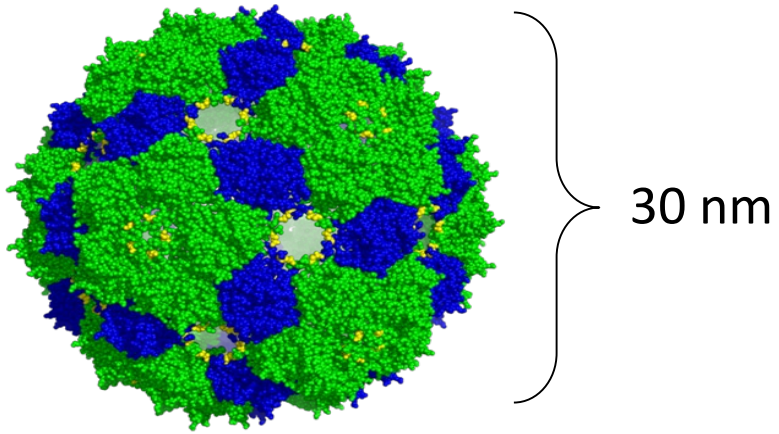
- TLR9 is an endosomal receptor, expressed by B cells and plasmacytoid DCs (pDCs) in humans that can be activated by unmethylated cytosine guanosine oligodeoxynucleotides (CpG ODN)
- TLR9 activation induces Type I IFN production via MyD88 and IRAK4 to activate IRF7 → make tumors hot
- TLR9 agonists have been used in melanoma
  - In combination with cancer vaccines with evidence of immunogenicity[1]
  - In PD-1 naïve[2] and PD-1 R/R melanoma[3] with evidence of response



[1]Fourcade J, J Immunother 2008; [2]Ribas A, Cancer Discov 2018; [3]Kirkwood JM, SITC 2019

CMP-001 – A VLP With Two Components

CMP-001



G10: A CpG-A TLR9 agonist

- GGGGGGGGGGGACGATCGTCGGGGGGGGGG
- Poly G and CpG motifs mimic retroviral, viral DNA, induce systemic T cell responses
- CpG-A is strongest known activator of tumor-associated pDC for IFN, CTL induction[1-4]
- Synthetic native DNA (phosphodiester) drives strongest pDC response[5]
- CpG-A induces pDC differentiation into distinct subset vs. other TLR9 agonists[6]
- Lower induction of inflammatory cytokines vs. other innate immune activators[7]

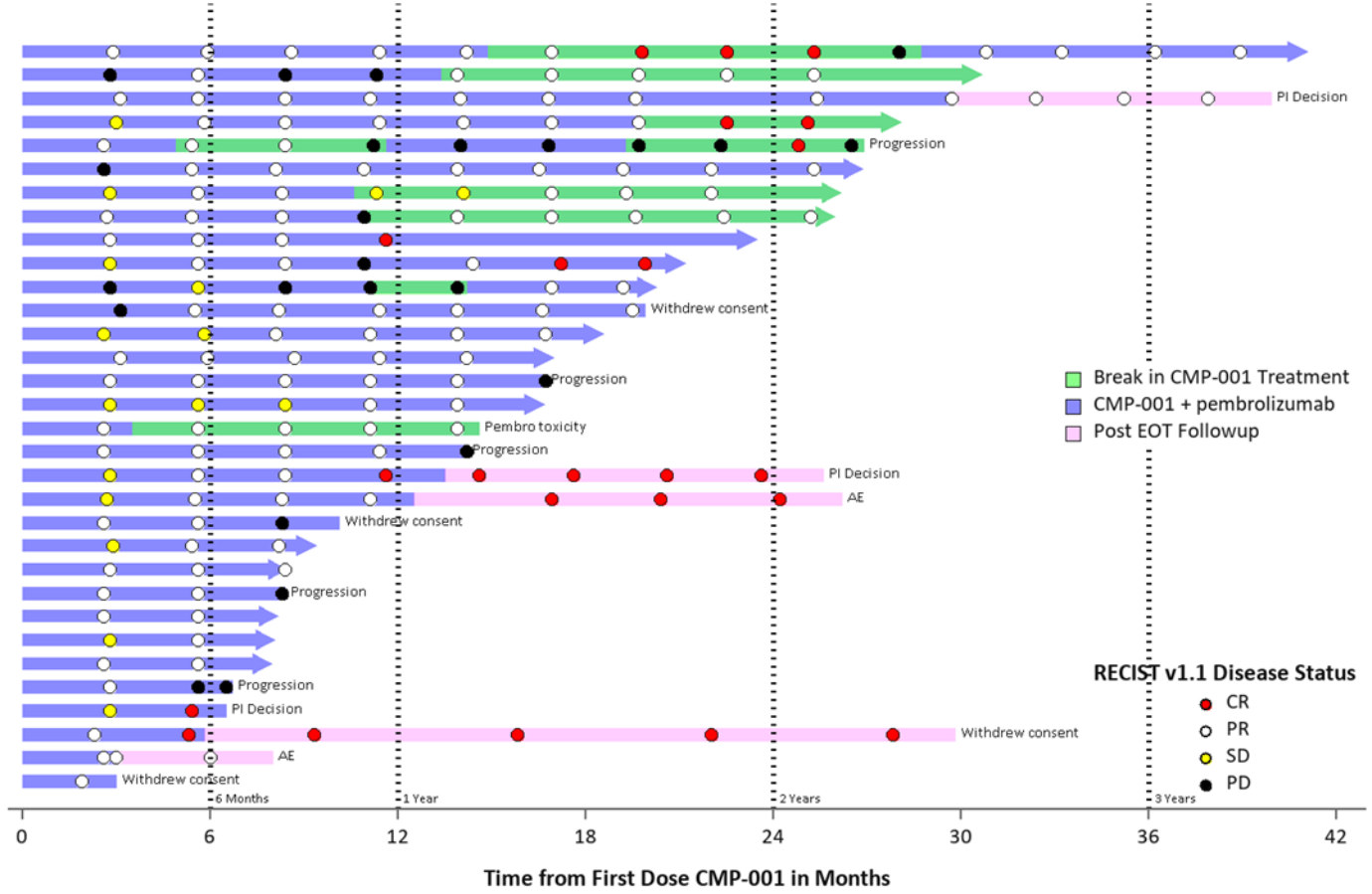
Qb coat protein

- Capsid protein from Qb bacteriophage; 180 subunits form an icosahedral virus-like particle (VLP)
- Protects the G10 inside the VLP from degradation in vivo
- Immunogenic protein induces Ab response after first injection in humans and mice
- Anti-Qb Ab opsonize the VLP, facilitate its uptake into pDC via FcR with enhanced induction of systemic CD8 T cell response[8]

[1]Hartmann E, Cancer Res 2003; [2]Labidi-Galy SI, Cancer Res 2011; [3]Sisirak V, Cancer Res 2012; [4]Rothenfusser S, Blood 2004; [5]Chan et al., Nature Comm. 2015; [6]Alculumbre SG, Nat Immunol 2018; [7]Checkmate, in preparation; [8]Lemke et al., in revision

CMP-001/PD-1 Blockade is Efficacious In PD-1 R/R Melanoma

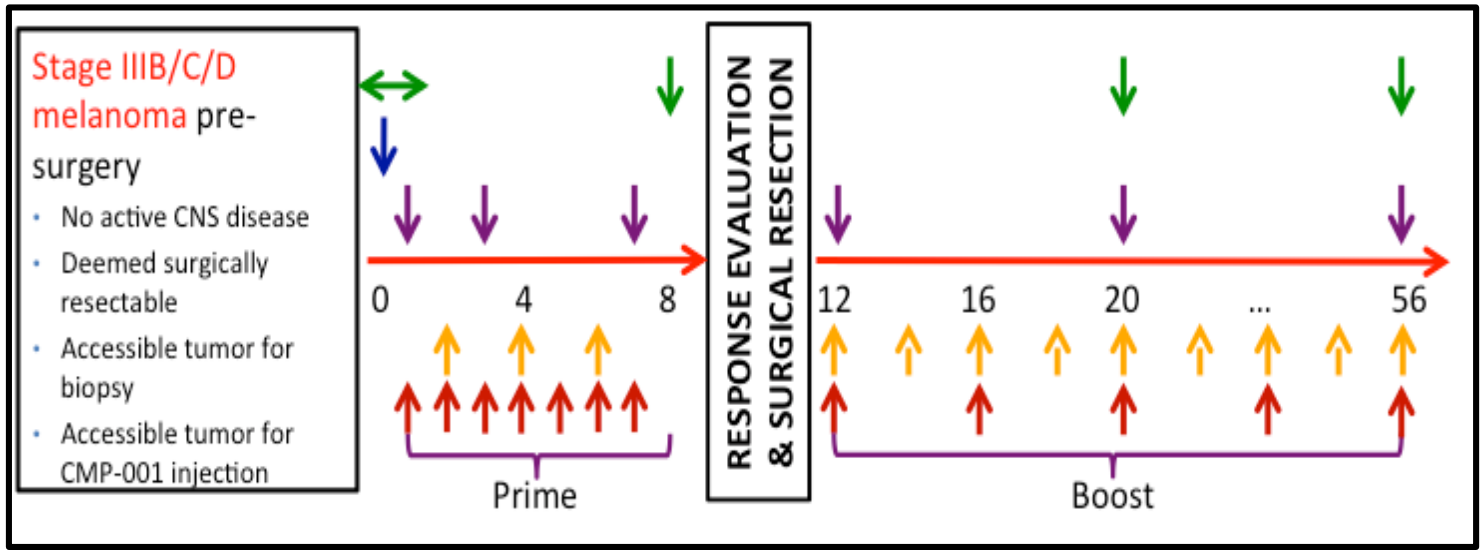
- CMP-001-001
  - Phase IB trial evaluating IT CMP-001 in PD-1 R/R advanced melanoma monotherapy or in combination with pembrolizumab
  - CMP-001 dosed 1-10 mg IT in two dosing schedules (weekly x7 → q3w; or weekly x2 → q3w)
  - ORR: 25% (21/83)
  - Median duration of response has not been reached (16.9+ mos)



Kirkwood JM, SITC 2019

Neoadjuvant CMP-001/Nivolumab

Study Design



Patient Population and Sample Size:

- Stage III B/C/D PD-1 naïve melanoma
- Deemed surgically resectable
- Accessible tumor for biopsy and CMP-001 injection

Intervention:

- Pre-Operative "Prime" Phase:
  - CMP-001: 1st 5mg SC & 2nd – 7th 10mg IT weekly x7
  - Nivolumab: 240mg q2 week x3
- Post-Operative "Boost" Phase:
  - CMP-001 10mg SC q4 week
  - Nivolumab: 480mg q4 week

Endpoint:

- 1^0: Pathologic response assessed by blinded pathologist
- 2^0: RFS, OS

Tumor biopsy
Correlative labs
Scans
CMP-001
Nivolumab

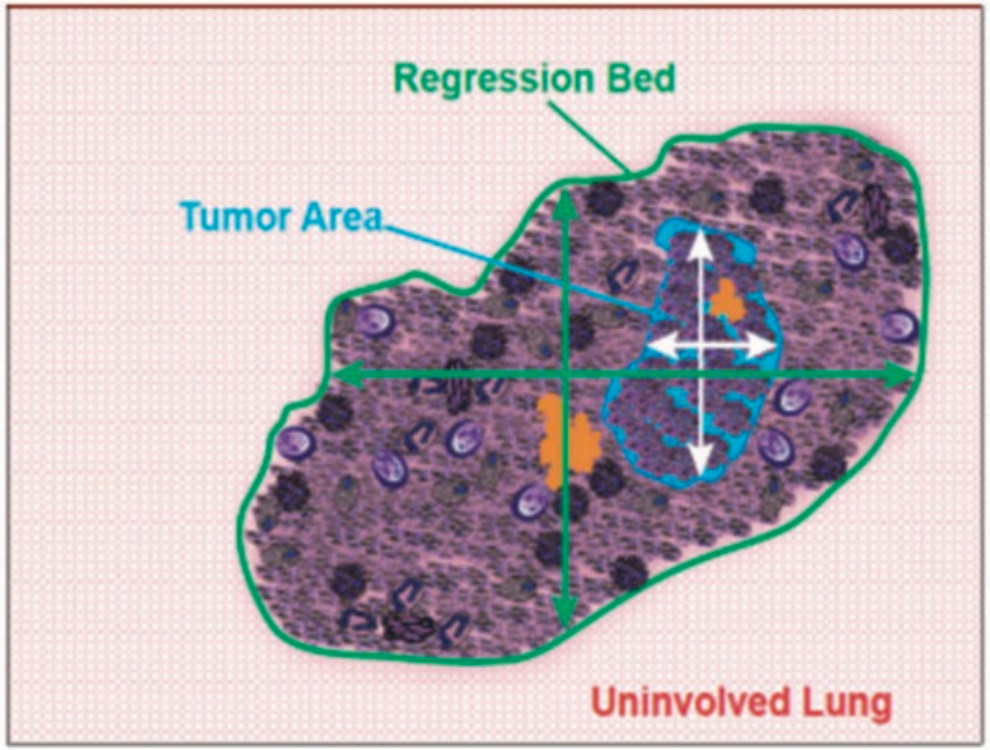
Clinicaltrials.Gov Identifier: NCT03618641

Neoadjuvant CMP-001/Nivolumab

Primary Endpoint

- Primary endpoint:
  - Major pathologic response [defined as ≤10% residual viable tumor (RVT)]; assessed by blinded pathologist using irPRC[1-3]
  - Regression bed and quantity of viable residual tumor were both assessed

- Pathologic response rates from recently reported studies in melanoma:
  - PD-1 monotherapy: 25%-30% complete or near-complete response[4-6]
  - PD-1/CTLA-4 combination: 45%-80% complete or near-complete response[4,7]



[1]Cottrell TR, Ann Oncol 2018; [2]Tetzlaff MT, Ann Oncol 2018; [3]Stein J, Ann Oncol 2019; [4]Amaria RN, Nat Med 2018; [5]Blank CU, Nat Med 2018; [6]Huang AC, Nature 2019; [7]Rozeman EA, Lancet Oncol 2019

Neoadjuvant CMP-001/Nivolumab

Patient Characteristics

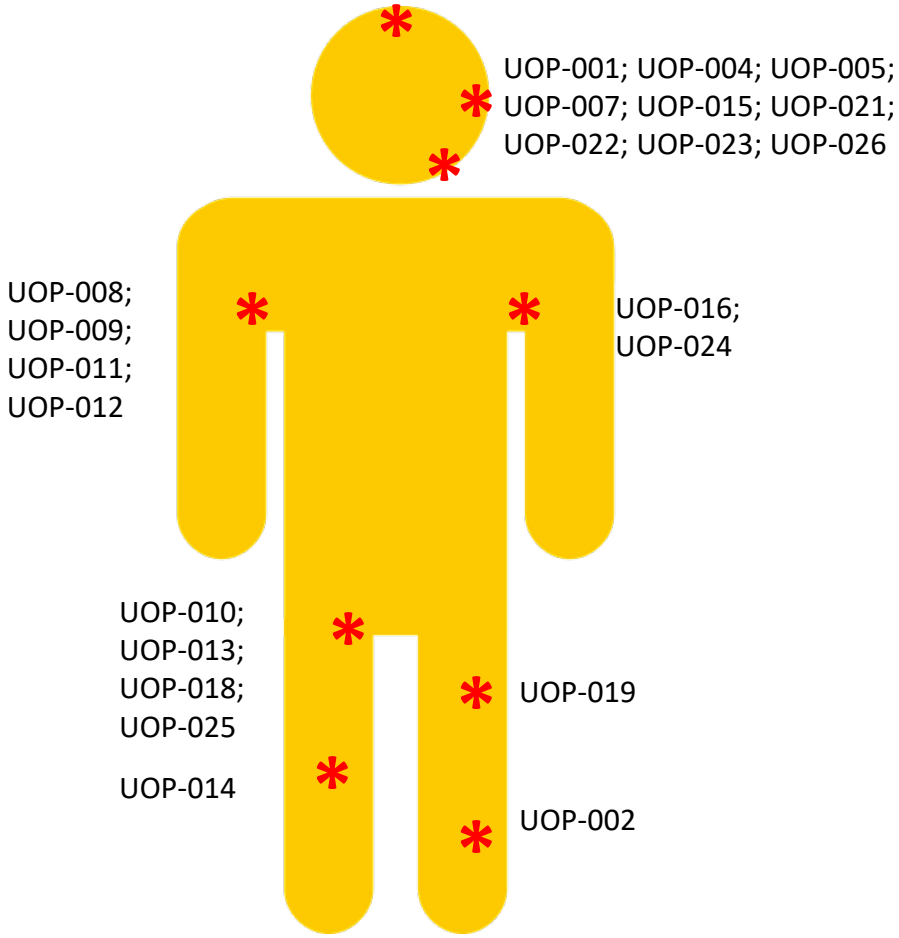
Patient Characteristics	
Enrolled • Evaluable	22 21*
Demographics • Median age • Sex	 60 (range 20-76) 10M, 12F
Prior Therapy • Ipi • BRAF/MEK	 1 (5%) 1 (5%)
AJCC Stage (8th edition) • IIIB • IIIC • IIID	 13 (59%) 6 (27%) 3 (14%)
Mutation Status • BRAF	 4 (18%)

*At data cut-off, 22 patients enrolled. 21 underwent surgery, and evaluable for pathologic response; 1 patient evaluable for imaging and pending surgery.

Data cutoff: 10/1/2019

Neoadjuvant CMP-001/Nivolumab

Patient Characteristics (cont.)



Location (injected/measurable lesion)

- H&N: 9
- Trunk (inguinal/axillary): 10
- Extremity: 3

Nature (injected/measurable lesion)

- LN: 17
- Satellite: 0
- In-transit: 5

Data cutoff: 10/1/2019

Neoadjuvant CMP-001/Nivolumab

Safety and Toxicity

Treatment-related AE (TRAE) Observed

AE Term, N (%)	CMP-001/Nivolumab (N=22)			
	Grade 1	Grade 2	Grade 3	Grade 4-5
Sinus tachycardia	2 (8%)	0	0	0
Colitis	0	0	1 (4%)	0
Diarrhea	2 (8%)	0	0	0
Nausea/vomiting	4 (16%)	2 (8%)	0	0
Chills	5 (21%)	1 (4%)	0	0
Fever	3 (13%)	4 (17%)	0	0
Injection site reaction	0	2 (8%)	0	0
CRS-like syndrome	0	1 (4%)	0	0

No DLTs were observed

Delays and/or surgical complications related to therapy: 0%

Data cutoff: 10/1/2019

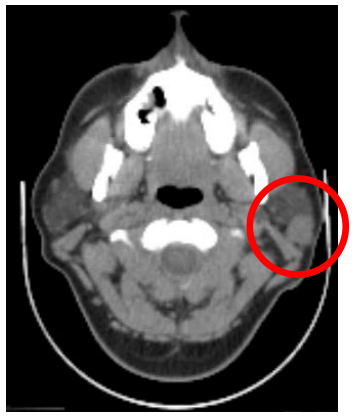
Neoadjuvant CMP-001/Nivolumab

Radiographic Response

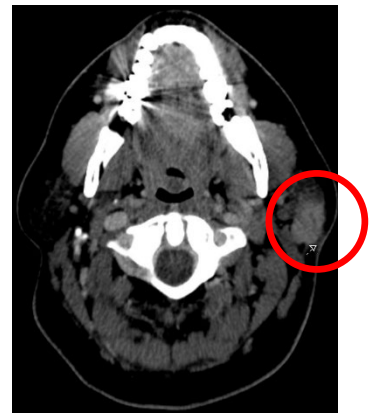
Pre-Treatment

Pre-Surgery

Non-Responder

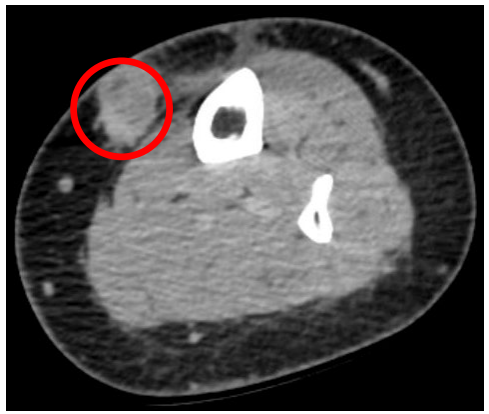


Left intra-parotid
LN 21x15mm

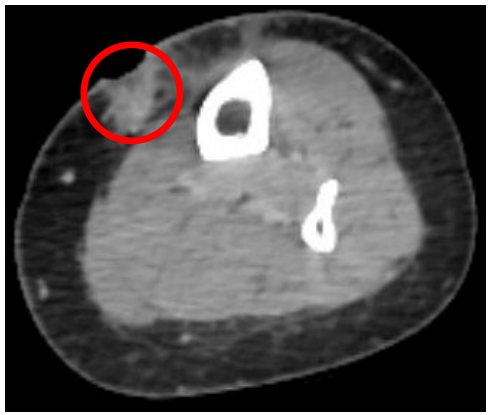


Left intra-parotid
LN 26x22mm

Responder



Left calf soft
tissue nodule
22x17mm



Left calf soft
tissue nodule
11x10mm

Data cutoff: 10/1/2019

Neoadjuvant CMP-001/Nivolumab

Radiographic Response (cont)

Radiographic Response Assessment	
Radiographic Results	22 evaluable
• Response	
• Complete	0
• Partial	11
• Stable disease	7
• Progressive disease	4

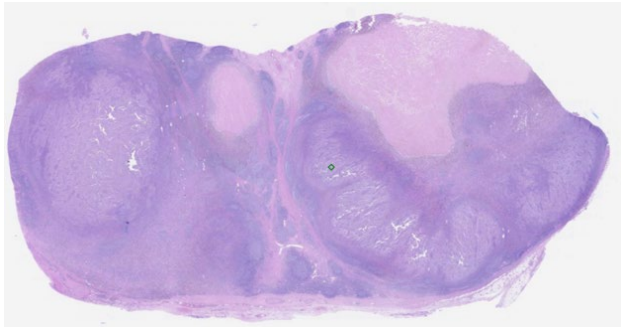
ORR (imaging, RECIST v1.1) = 50%

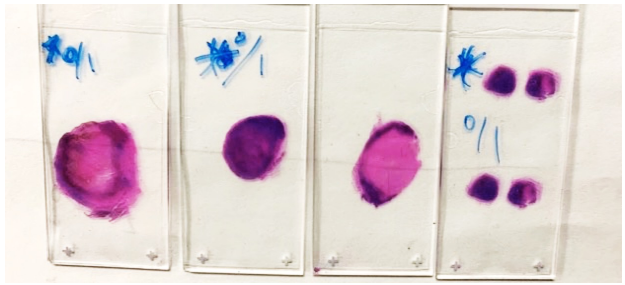
Data cutoff: 10/1/2019

Neoadjuvant CMP-001/Nivolumab

Features of Pathologic Response

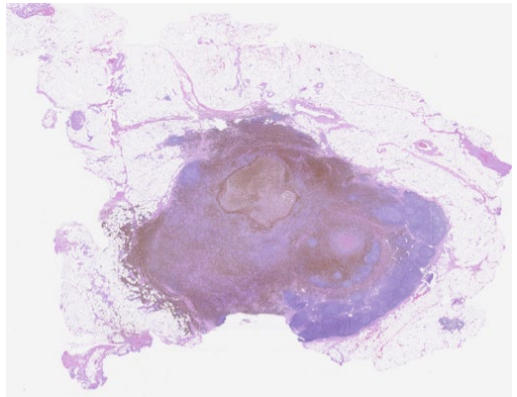
Necrosis



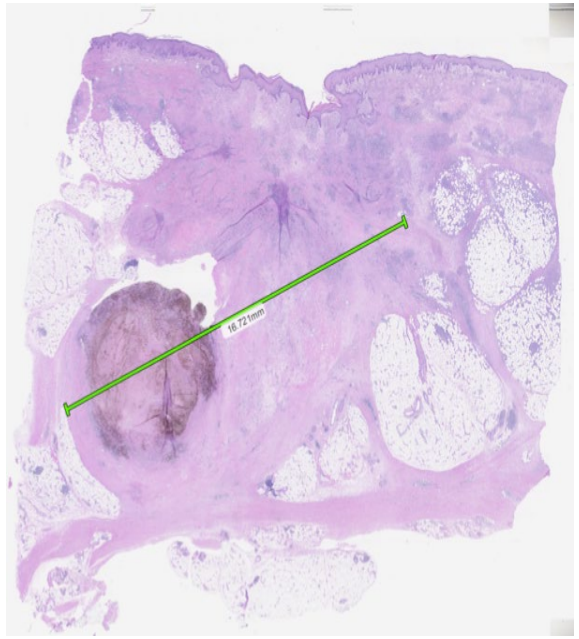


7 involved LN
1 injected (top picture); all 7 LN shown below (bottom picture)

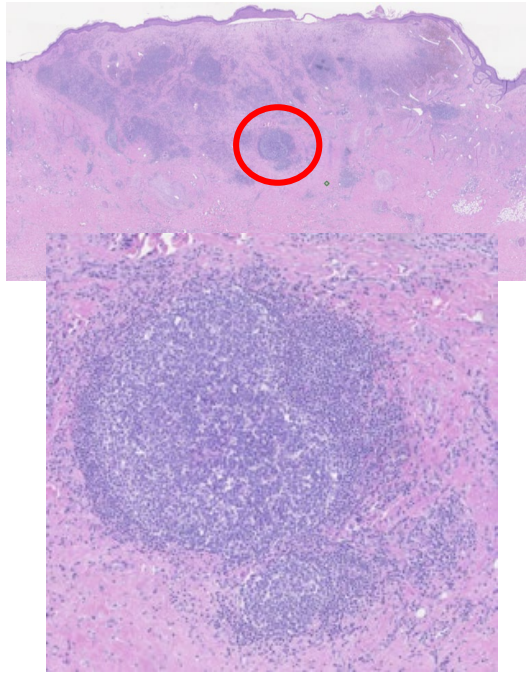
Melanosis



Fibrosis



Germinal center formation



[1]Cottrell TR, Ann Oncol 2018; [2]Tetzlaff MT, Ann Oncol 2018; [3]Stein J, Ann Oncol 2019

Arivarasan Karunamurthy; Asst Prof of Pathology

Neoadjuvant CMP-001/Nivolumab

Blinded Pathologic Response

Residual Viable Tumor (%)			
0% (pCR)	1-10% (pMR)	10-50% (pPR)	>50% (pNR)
13 (62%)	2 (9%)	1 (5%)	5 (24%)

- %RVT calculated using %tumor viable
- Pathologist blinded to clinical and radiographic outcome
- N=21 evaluable

MPR rate (pCR/pMR) = 71%

Arivarasan Karunamurthy; Asst Prof of Pathology

Neoadjuvant CMP-001/Nivolumab

Blinded Pathologic Response

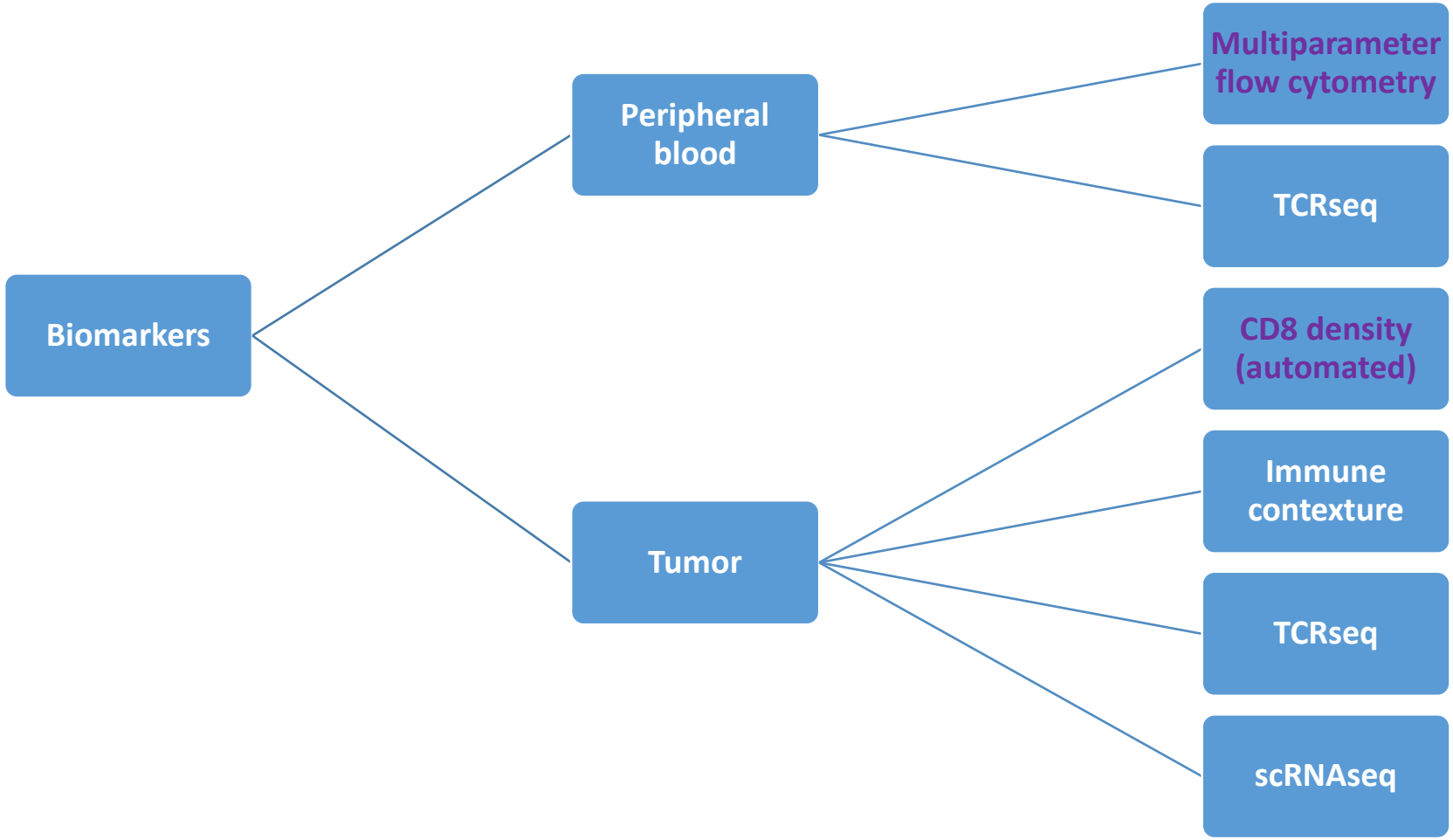
Complete/Near-Complete Responses in Injected and Uninjected Lesions (N=21[#])	
Single lesion (injected)	**Multiple lesions (1 injected)**
12/14	**3/7**

[#]Number of evaluable patients at data cutoff: 21
[*]UOP-014 had 2 treated lesions with pPR (14% - %RVT) in both injected and uninjected lesion

Arivarasan Karunamurthy; Asst Prof of Pathology

Neoadjuvant CMP-001/Nivolumab

Biomarkers of Response



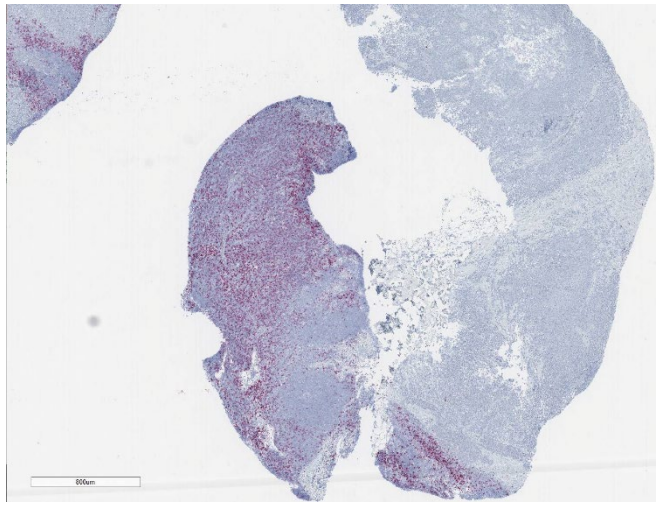
Neoadjuvant CMP-001/Nivolumab

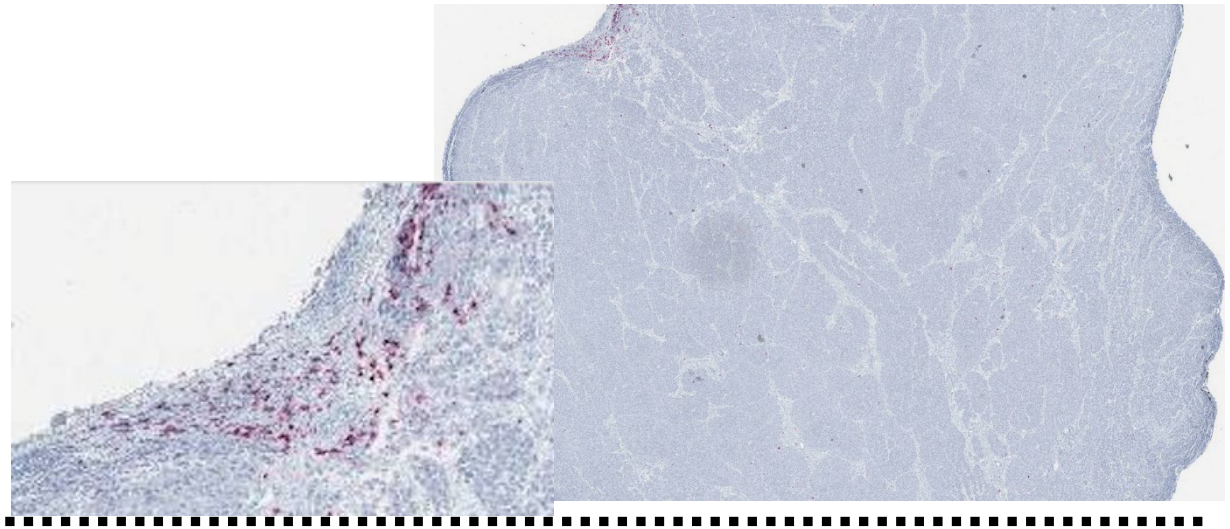
Changes in CD8 Density (cells/mm^2)

Pre-Treatment

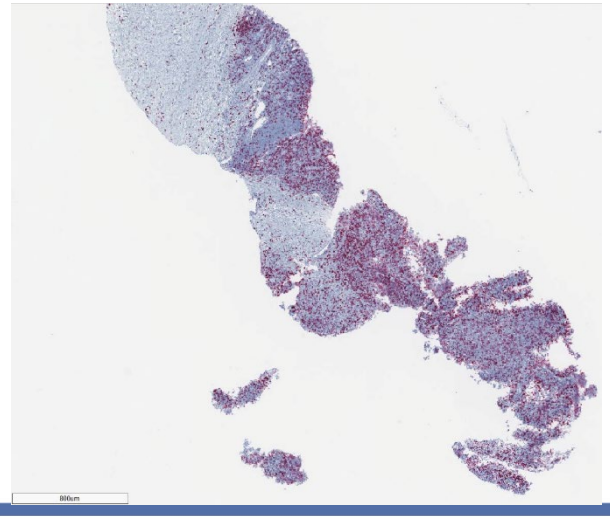
Post-Treatment

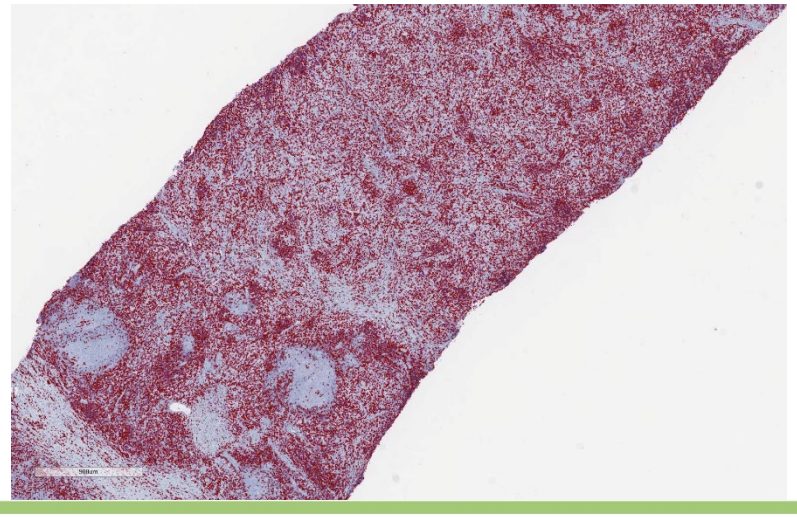
Non-Responder





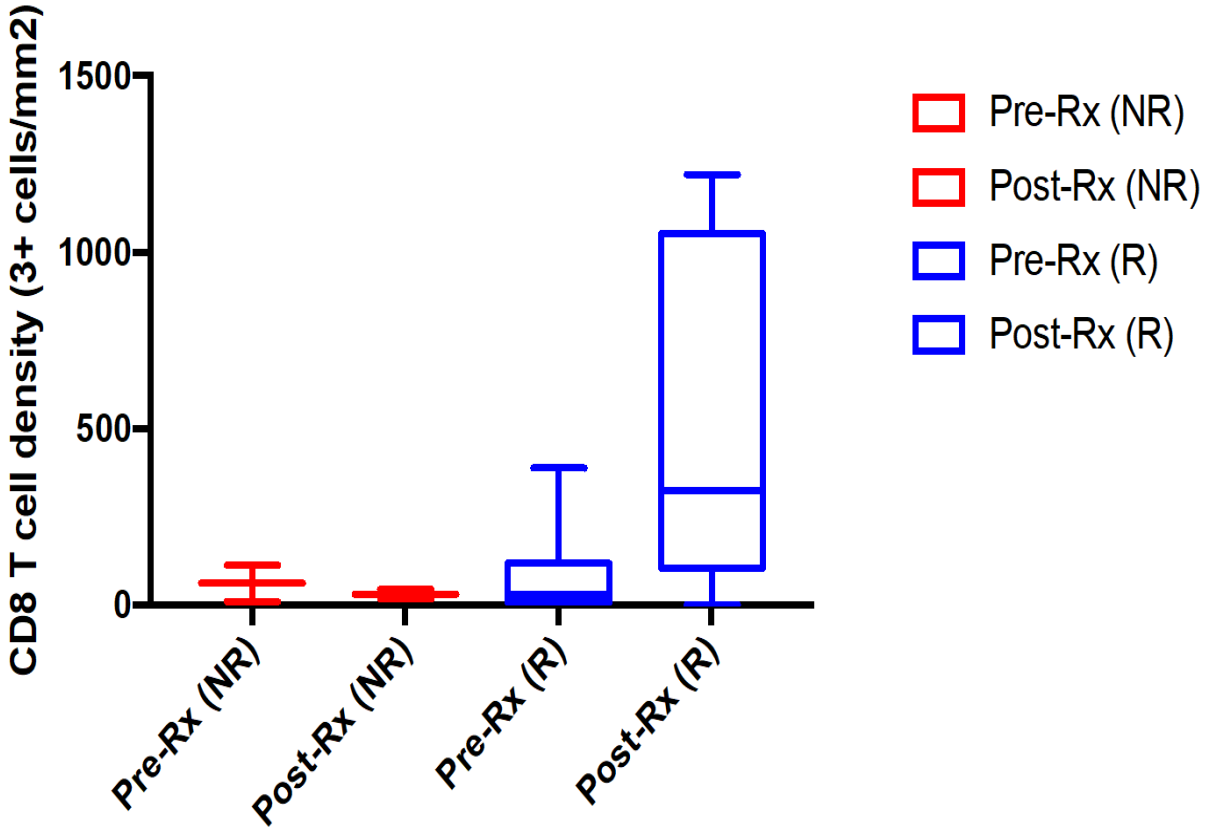
Responder

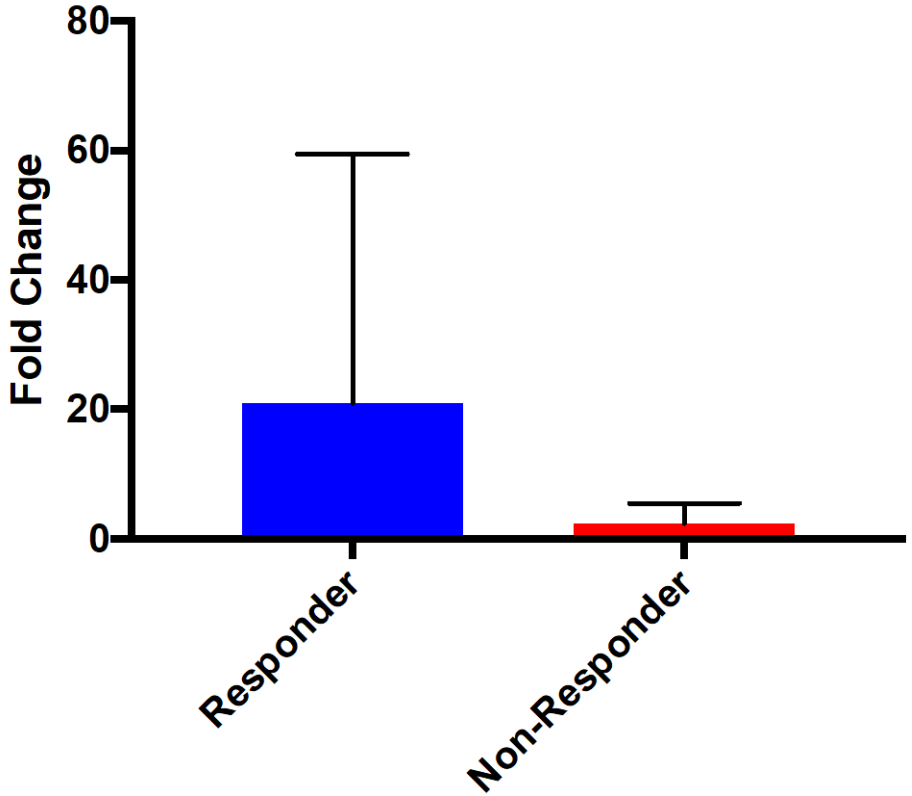




Neoadjuvant CMP-001/Nivolumab

Changes in CD8 Density (cells/mm^2) (cont.)



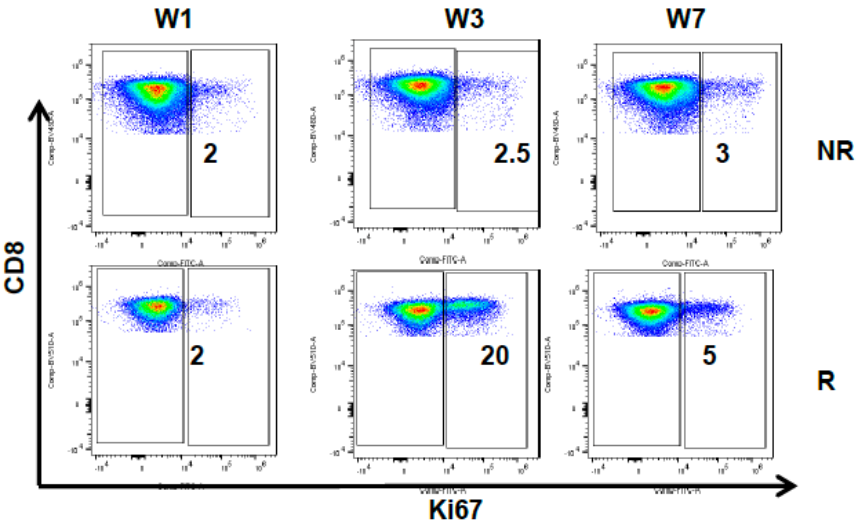


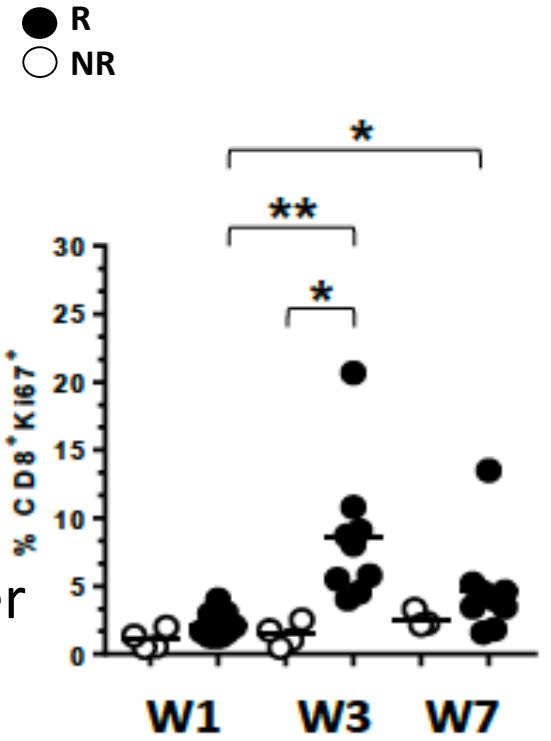
Pathologic responders had greater mean fold change in CD8 T cells on therapy than pathologic non-responders (20.97 vs. 2.37)

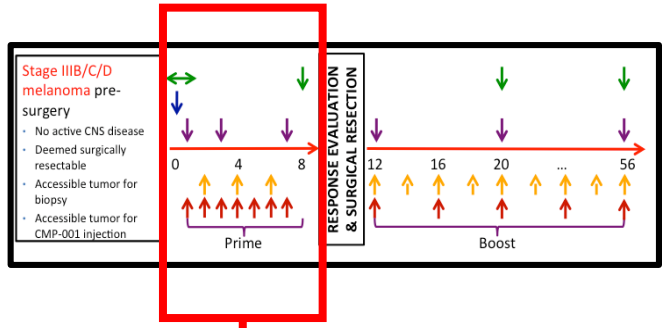
Douglas Hartman; Asst Prof of Pathology

Neoadjuvant CMP-001/Nivolumab

Peripheral Analyses of CD8 Compartment







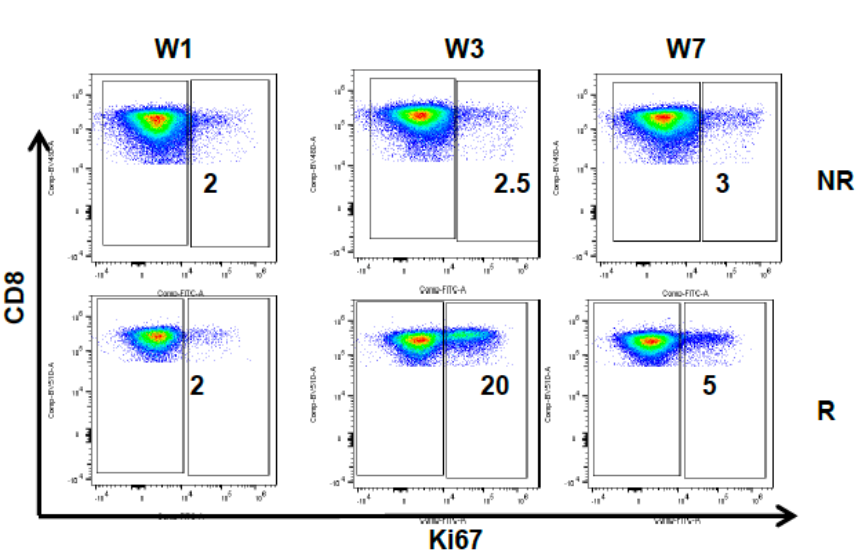
Pathologic responders had significant greater $CD8^+Ki67^+$ T cells detectable peripherally.

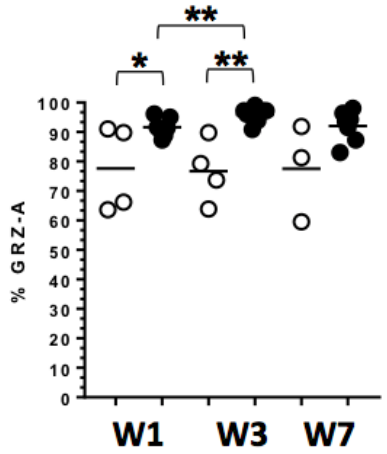
These cells were detectable as early as W3 on therapy.

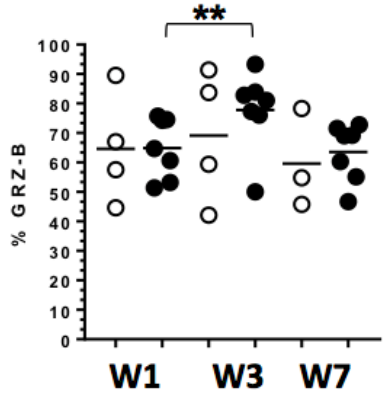
Data from 12 patients (8 R; 4 NR) shown.

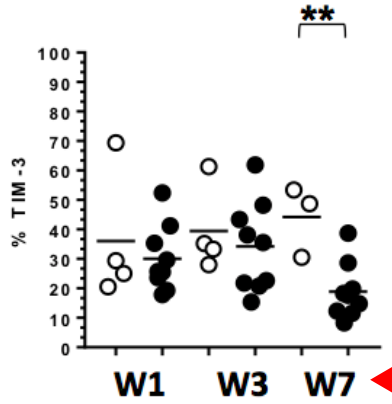
Neoadjuvant CMP-001/Nivolumab

Peripheral Analyses of CD8 Compartment (cont.)









CD8⁺Ki67⁺ T cells were lytic as demonstrated by expression of Granzyme A/B. Levels were greater in pathologic responders (compared to non-responders); and detectable early.

In responders, CD8⁺ T cells expressing TIM-3 were decreased.

Neoadjuvant CMP-001/Nivolumab

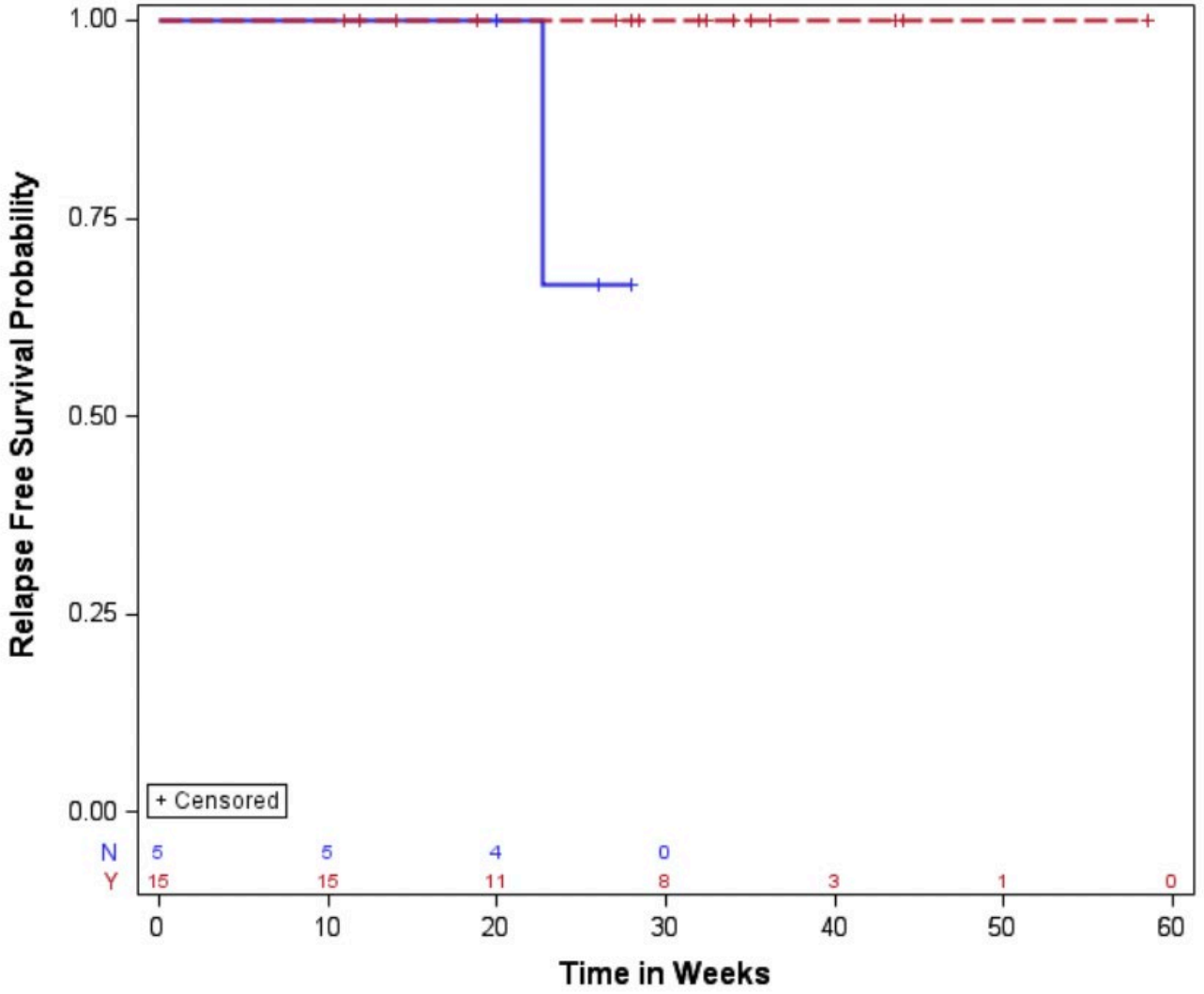
Pathologic Response and RFS

Median follow up:

- All evaluable pts: 6 months

Median RFS:

- Only 1 event
- Median RFS was not reached in either responders (not available) or non-responders (22.71, infinity) (p=0.055)



Data cutoff: 10/1/2019

Neoadjuvant CMP-001/Nivolumab

Conclusions

1. Neoadjuvant CMP-001/nivolumab is associated with high rates of pathologic response: **71% pCR/near pCR.**

2. Neoadjuvant CMP-001/nivolumab was well tolerated with a low incidence of Grade 3 AE. No patient had a delay in surgery as a result of therapy or TRAE.

3. Responders to neoadjuvant CMP-001/nivolumab had increased $CD8^+$ T cells intra-tumorally *and* increased circulating $CD8^+$ $Ki67^+$ T cells peripherally.

4. Responders to neoadjuvant CMP-001/nivolumab have durable RFS.

5. Further enrollment is ongoing.