Merkel Cell Carcinoma: Viral Antigens as Tumor Rejection Antigens

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Disclosures

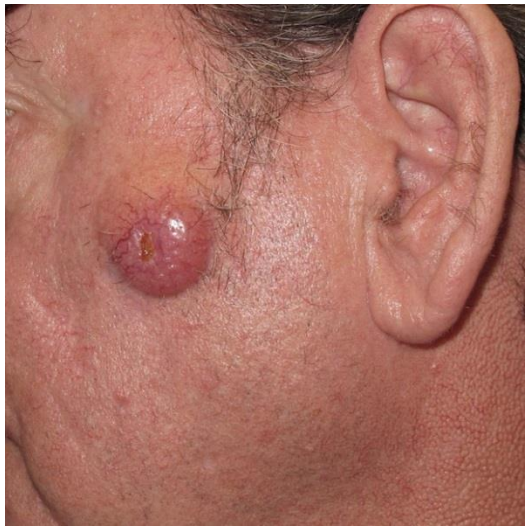
- Consultant for: Dragonfly Therapeutics, Five Prime Therapeutics, Immunocore, Merck; and (spouse) Amgen, Compugen, Janssen, MedImmune/AZ, Merck, Potenza
- Grant/Research support from: Bristol-Myers Squibb; and (spouse) Compugen, Potenza
- Stock/stock options: Dragonfly Therapeutics, Five Prime Therapeutics; and (spouse) Compugen, Potenza Therapeutics, Tizona, Trieza
- Royalties through institution (spouse): BMS, Immunomic Therapeutics, Potenza

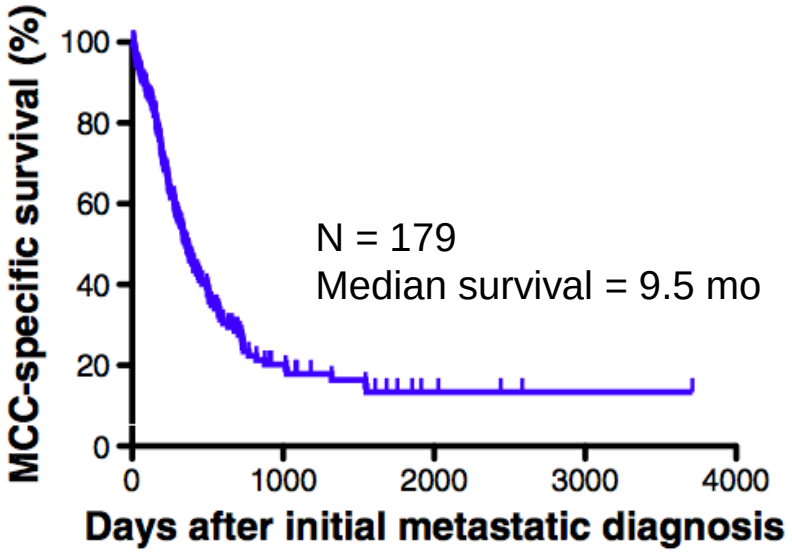
- and -

- I will discuss investigational uses for anti-PD-(L)1 drugs in my presentation.

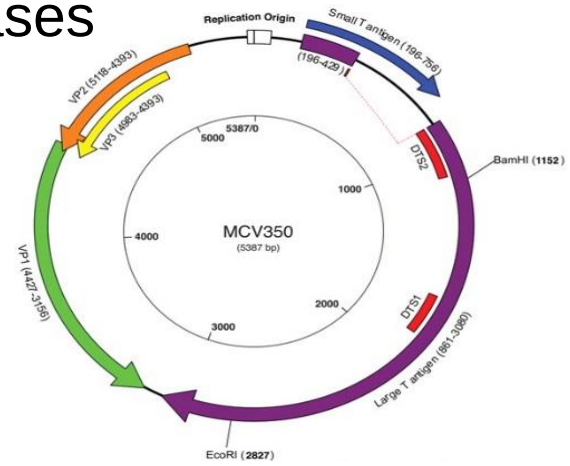
Merkel cell carcinoma

- ~ 2500 cases/year in the US
- Age >50, immune suppression
- Merkel cell polyomavirus (MCPyV) present in ~60-80% of cases
- ***> 40% of patients with MCC develop advanced disease***





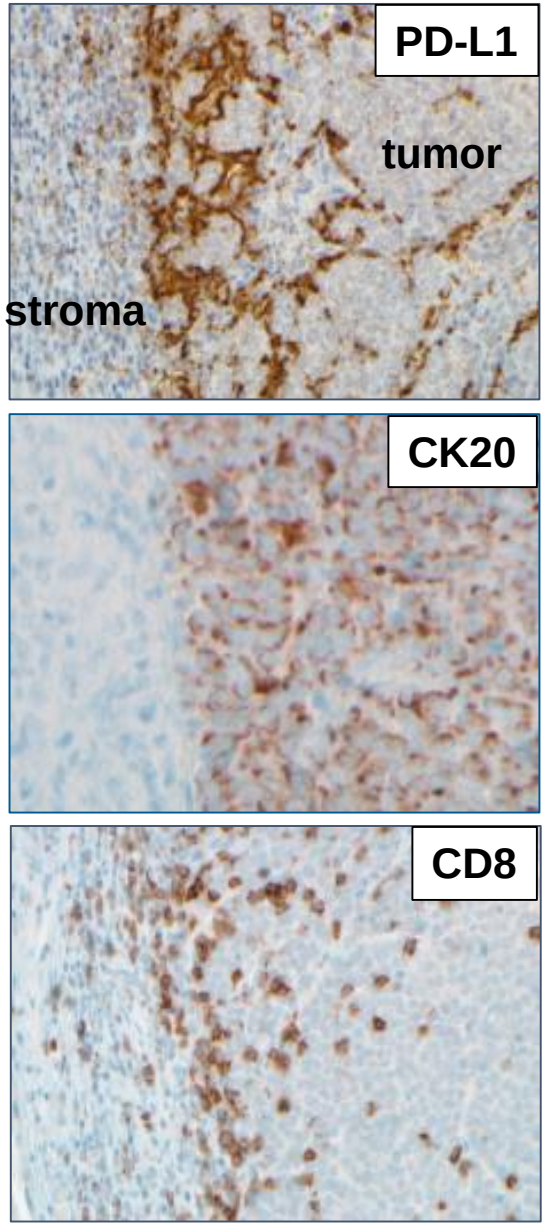
Miller, Curr Treat Options Oncol 2013

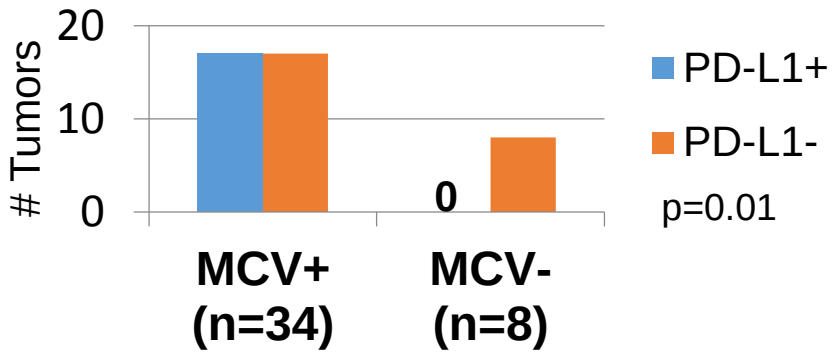


Feng et al., Science 2008

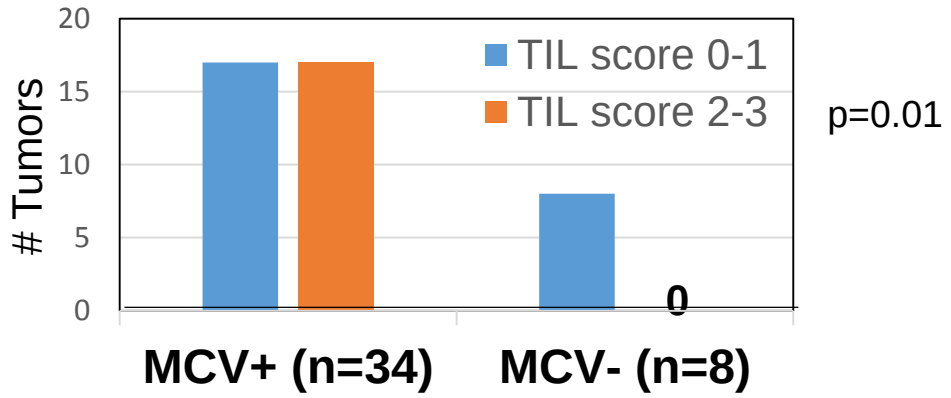
Adapted from Nghiem et al., AACR 2016

Association of MCPyV with tumor cell PD-L1 expression and intensity of immune infiltrates in MCC



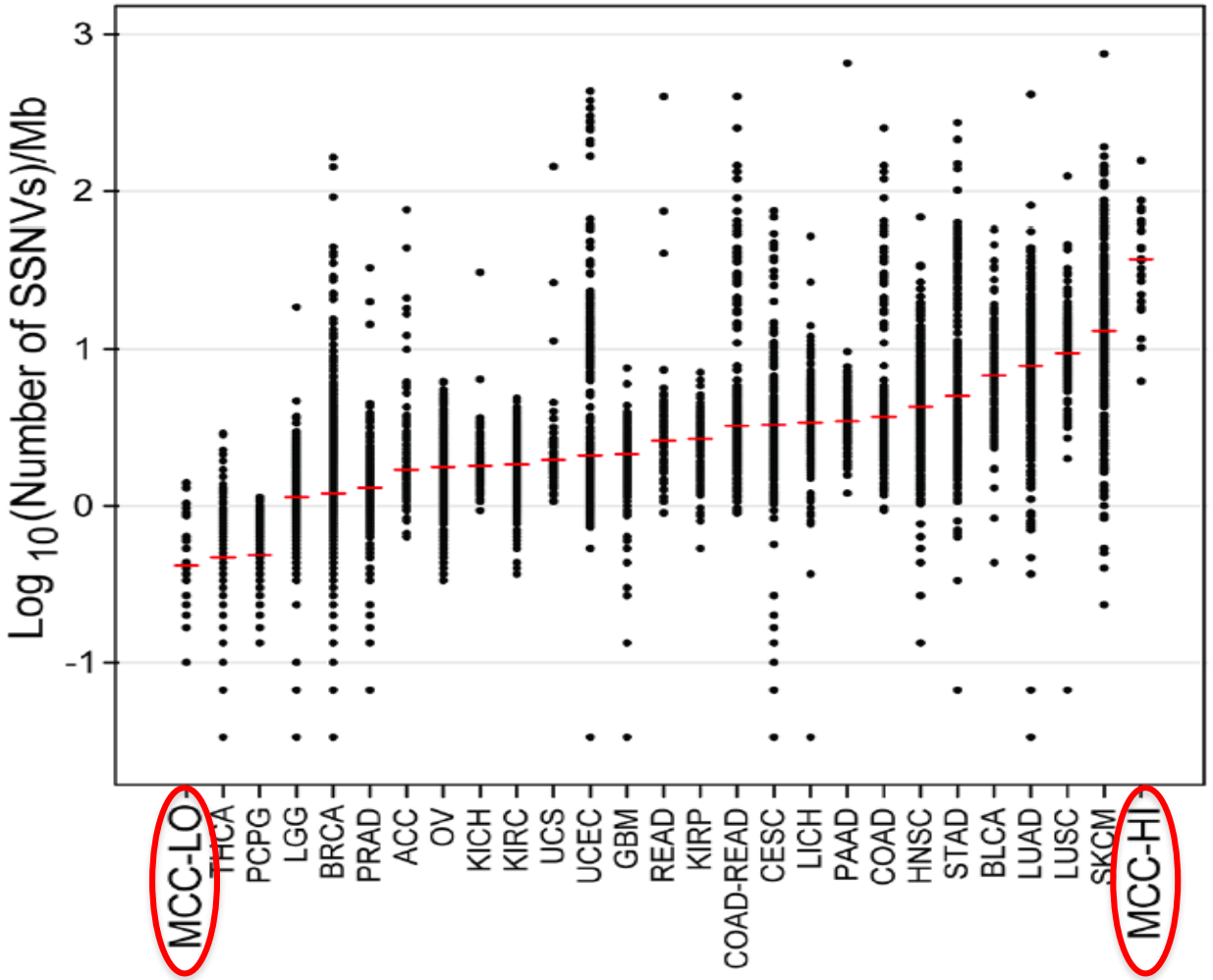


"PD-L1+": ≥5% tumor cells expressing PD-L1 with IHC



Lipson et al., Cancer Immunol Res 2013

Virus(+) vs. virus(-) MCC:
at the extremes of mutational density compared to TCGA data from other cancers



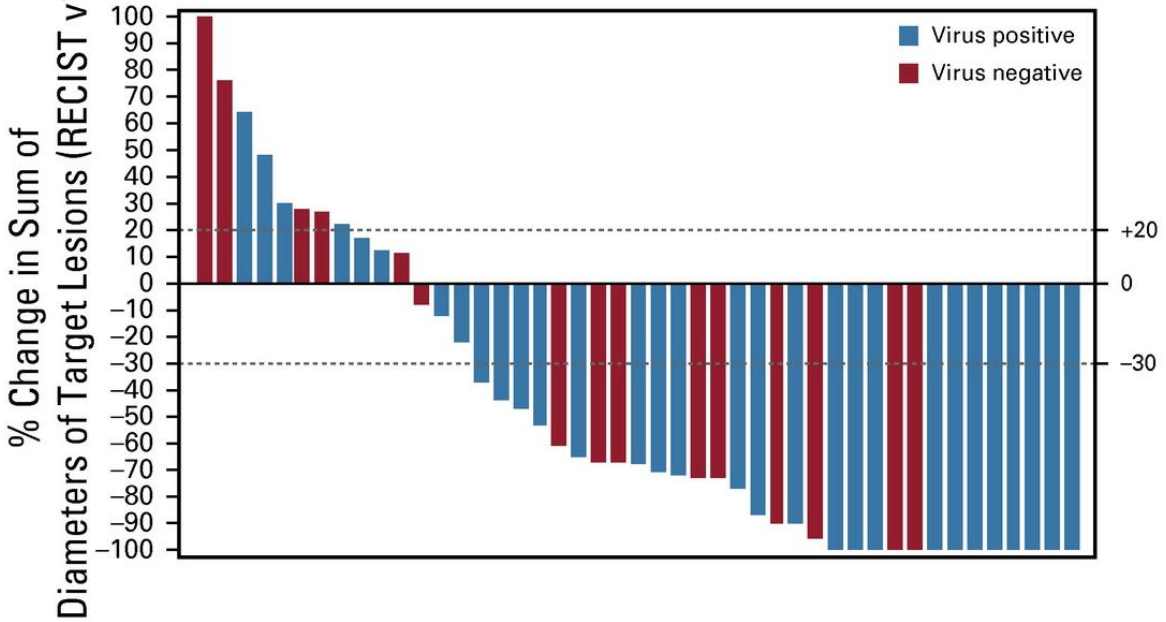
Virus Positive ← → Virus Negative

Merkel cell carcinoma

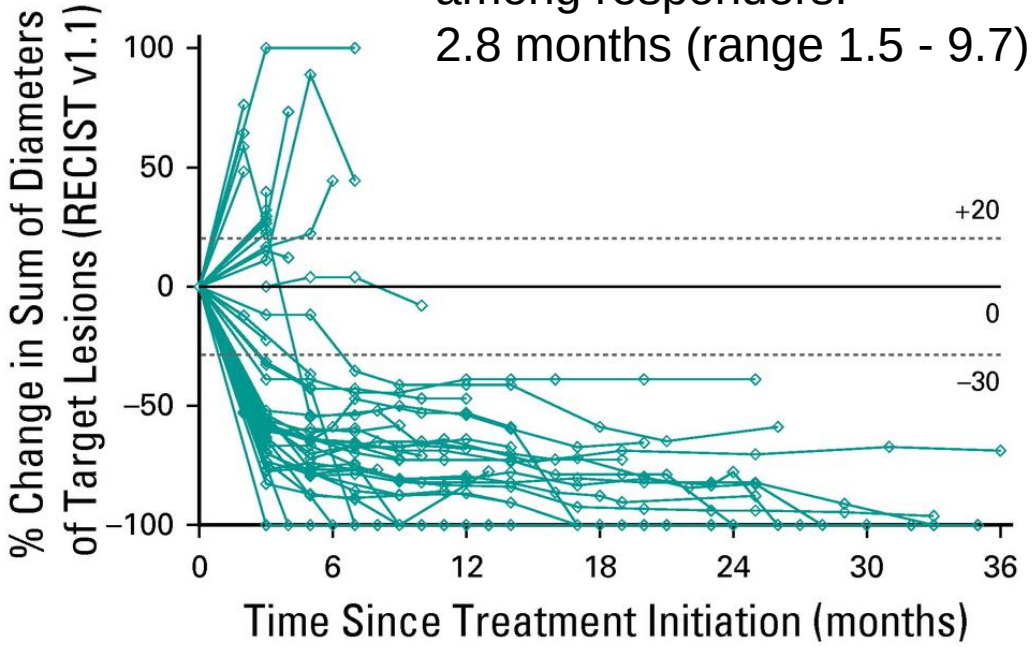
Goh et al., Oncotarget 2015

Quality vs quantity of tumor antigens: regardless of tumor viral status, advanced MCC responds rapidly and durably to first-line anti-PD-1 therapy (pembrolizumab)

ORR = 56%

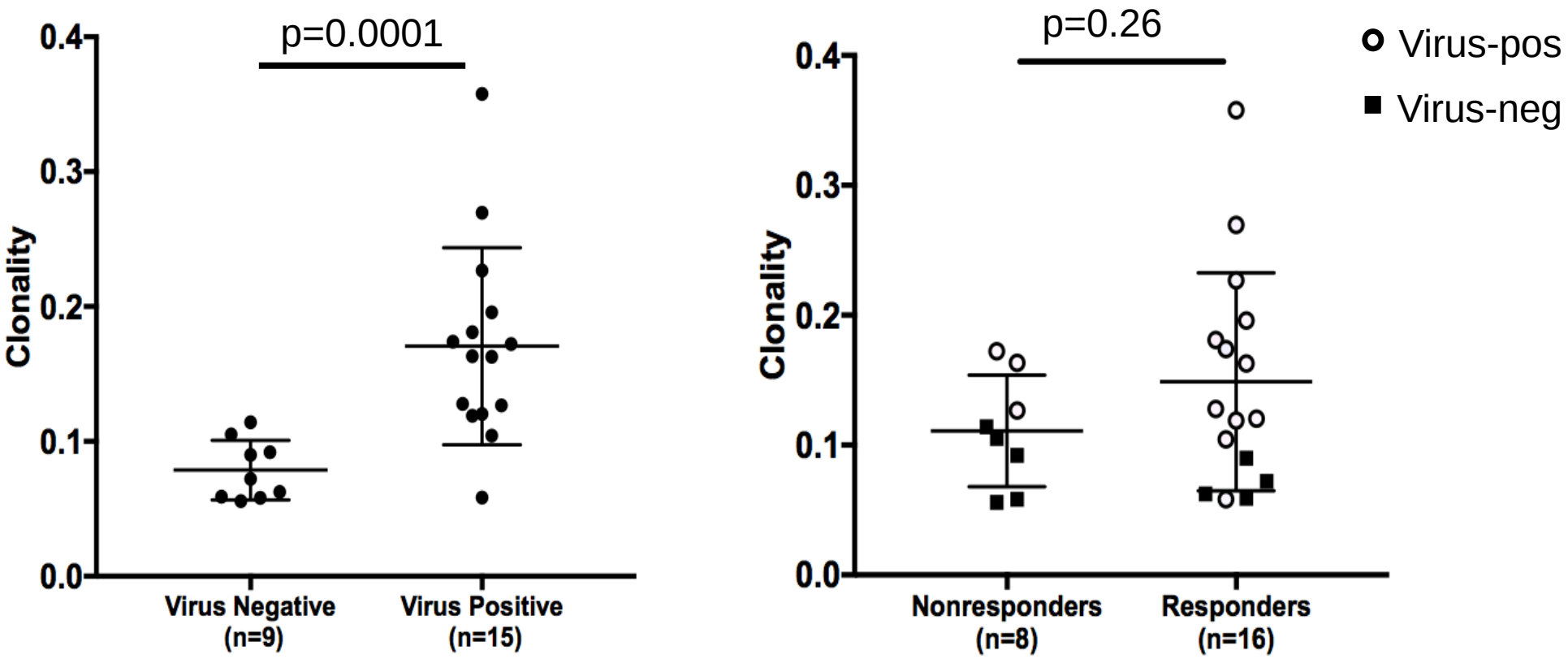


Median time to response among responders:
2.8 months (range 1.5 - 9.7)



Nghiem et al., J Clin Oncol 2019

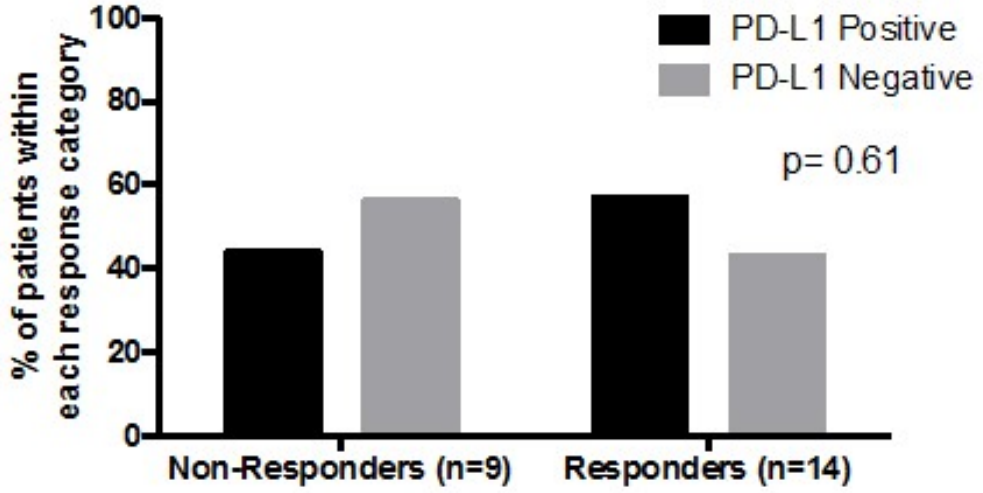
TCR clonality in MCC TILs correlates with tumor viral status but *not* with response to anti-PD-1



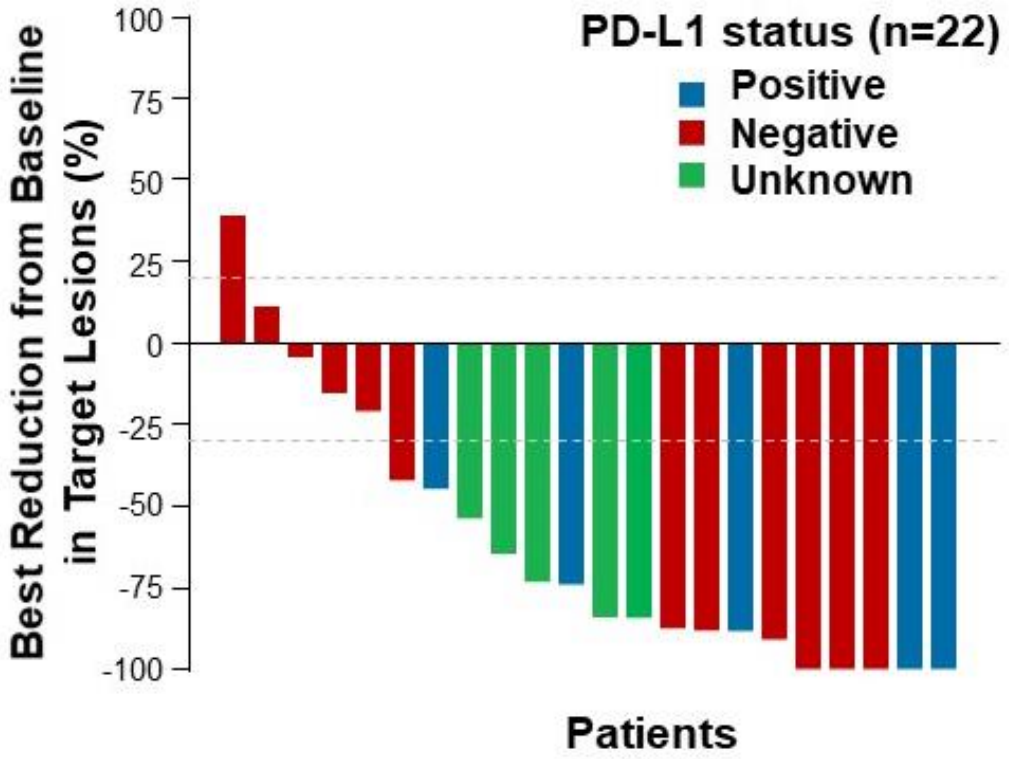
Miller, Nghiem, et al., JITC 2018

Precision immunotherapy for MCC: can we find a biomarker predicting treatment response?

Tumor PD-L1 expression does *not* correlate with MCC response to anti-PD-1



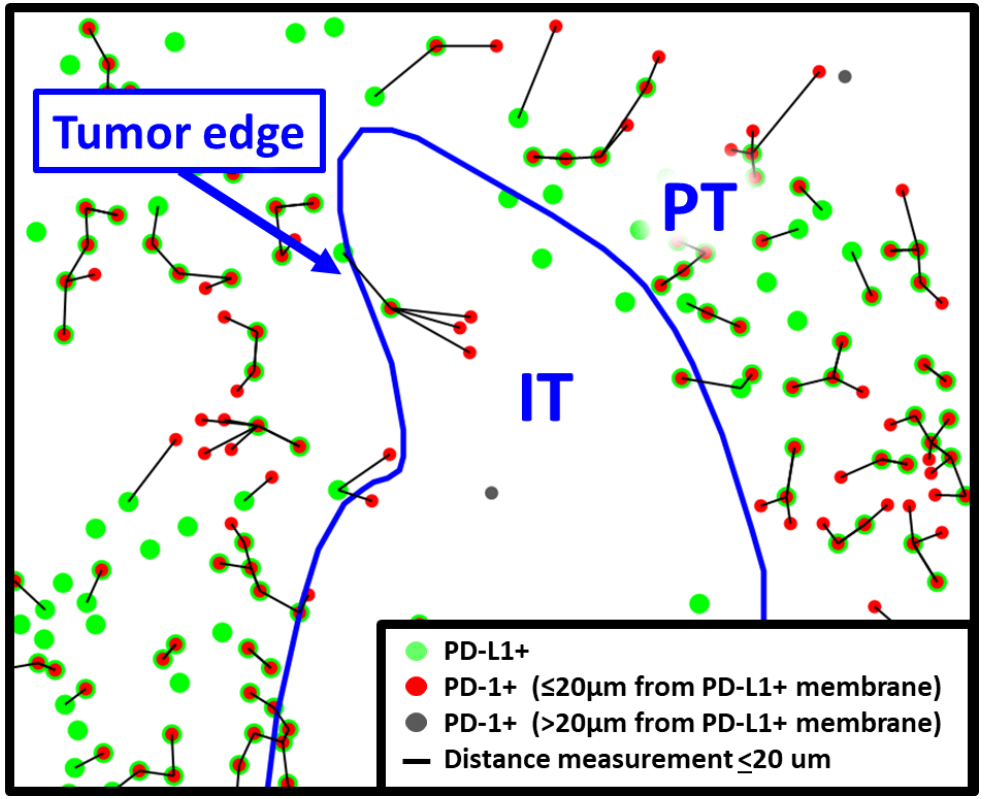
Pembrolizumab, 25 pts first line
Nghiem et al., NEJM 2016

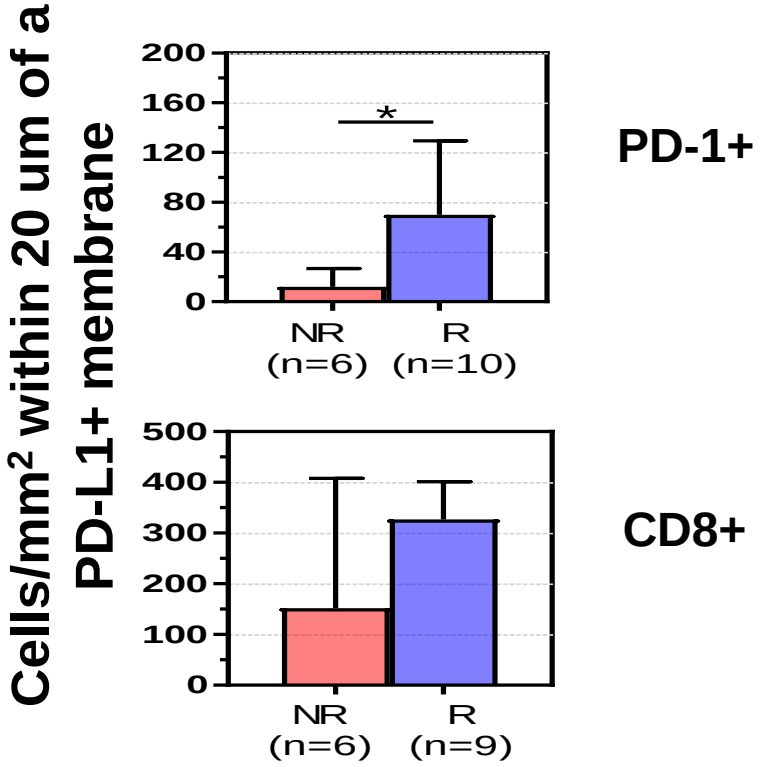


Nivolumab, 22 pts first/second line
Topalian et al., AACR 2017

Multiplex biomarkers: “nearest neighbor” analysis

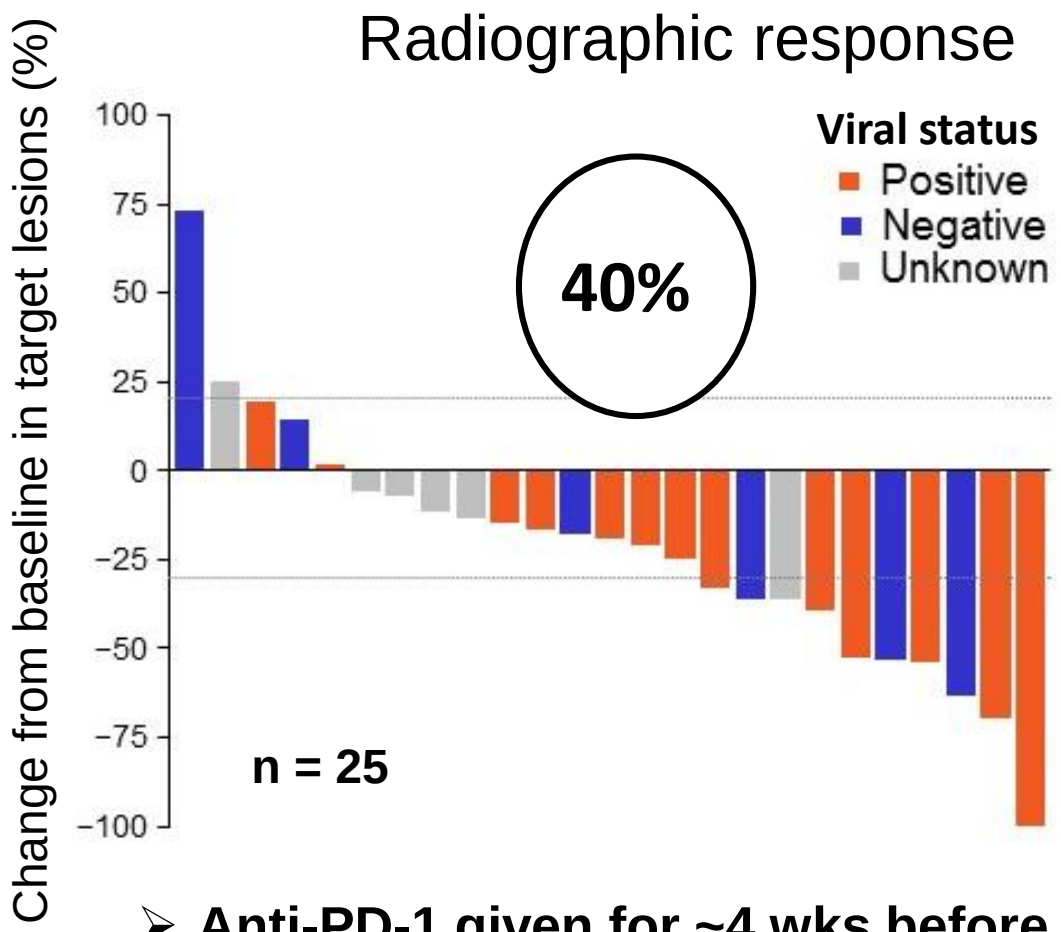
Density of interacting PD-1+:PD-L1+ cells correlates with MCC response to anti-PD-1 (pembro)

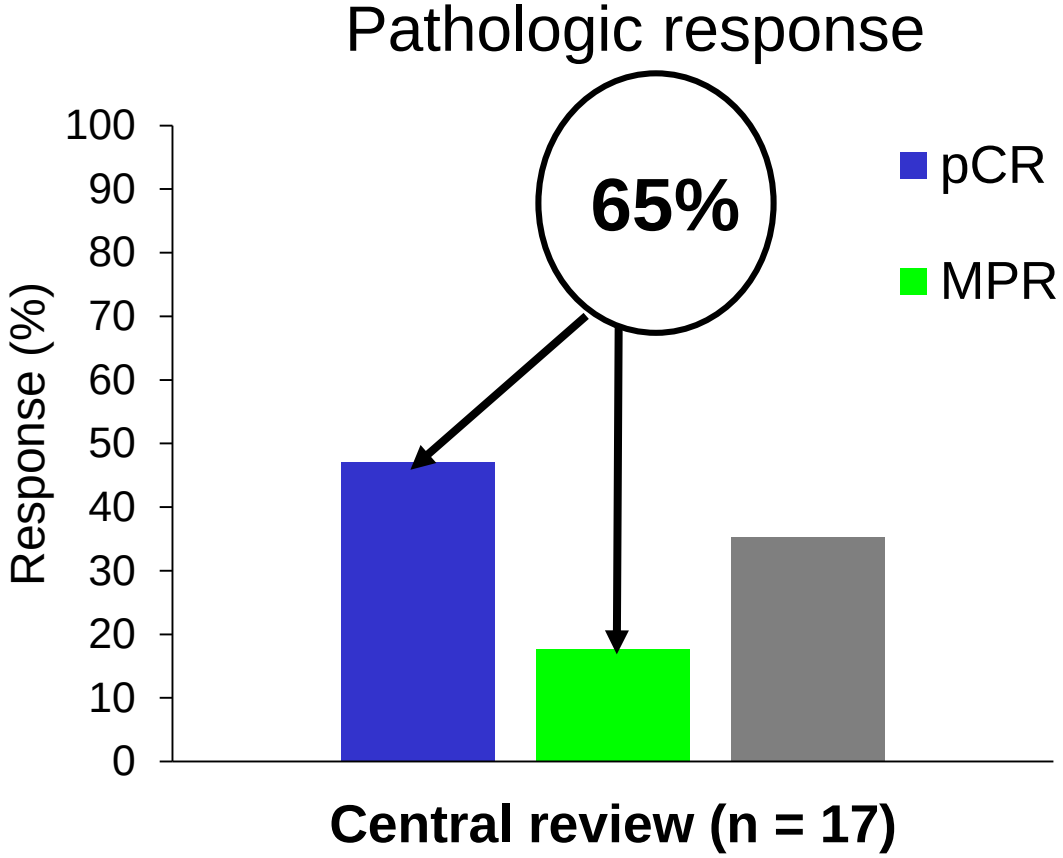




Giraldo, Taube, et al., J Immunother Cancer 2018

Neoadjuvant anti-PD-1 (nivolumab) in resectable MCC: pathologic response as a potential marker for clinical outcomes



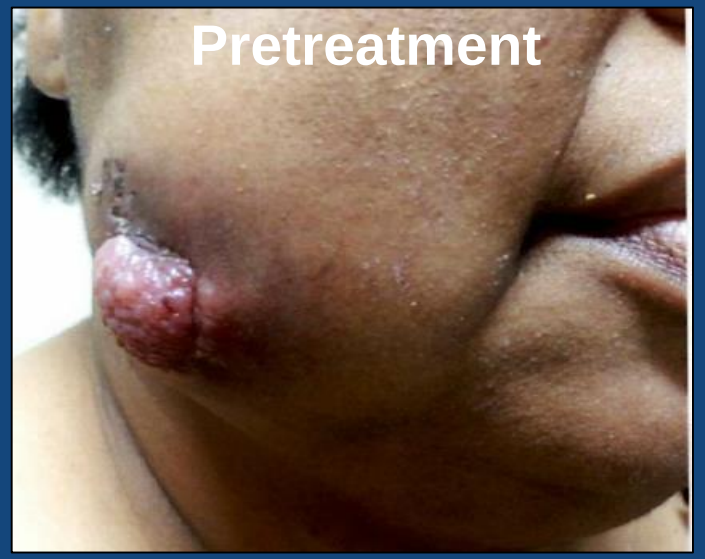


- **Anti-PD-1 given for ~4 wks before surgery**

Adapted from Topalian et al., ASCO 2018

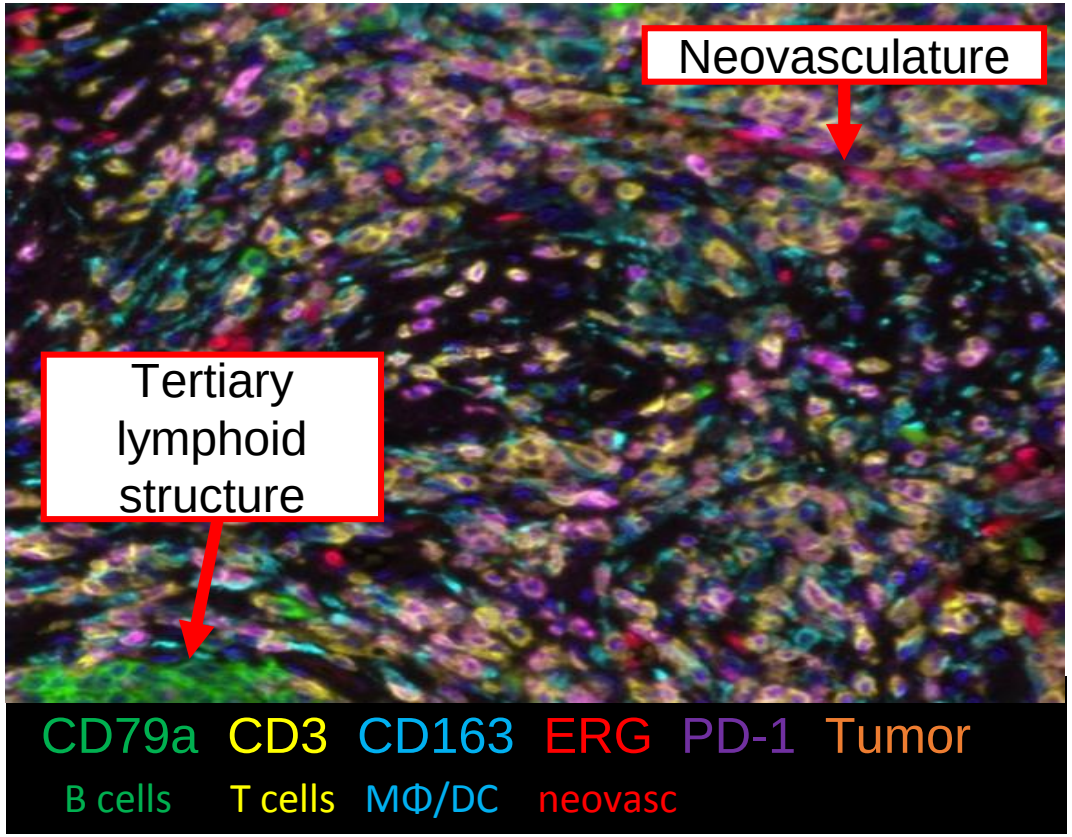
Response of metastatic MCC to neoadjuvant anti-PD-1 (nivolumab)

- 53-year-old female with MCC T3N1
- Merkel cell polyomavirus+, PD-L1 <1%
- Received 2 doses of nivolumab (D1 & D15)
- Underwent surgery on D20 (radical cheek resection, parotidectomy, cervical LN dissection)
- Pathologic CR
- Postoperative radiotherapy to primary site
- No evidence of disease 19 months post-op



Courtesy Dr. Asim Amin, Atrium Health

Exploring multiplex biomarkers for neoadjuvant immunotherapies: correlations with response and survival



MCC regressing after neoadjuvant nivolumab
(Topalian, Taube et al., ASCO 2018)

Evidence emerging from neoadjuvant immunotherapy trials shows that hallmarks of tumor regression resemble wound healing.

- Lymphoid infiltrates, prominent plasma cells
- Tertiary lymphoid structures
- Proliferative fibrosis
- Neovasculature

NSCLC: Cottrell, Taube et al., Ann Oncol 2018;
Melanoma: Tetzlaff et al., Ann Oncol 2018.

➢ ***Such analyses are expected to provide a deeper understanding of MOA for immune checkpoint blockade, enabling the next wave of therapeutic development.***

Conclusions

- In virus+ MCC, the presence of a limited number of strong viral antigens can compensate for low tumor mutational burden in eliciting robust antitumor immunity.
- Neoadjuvant application of anti-PD-(L)1 in early-stage MCC may reduce tumor burden and prime systemic antitumor immunity.
- A deeper understanding of MOA for immune checkpoint blockers in MCC will guide the design of more effective immunotherapies.

Acknowledgements

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