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ADVANCES IN Cancer IMMUNOTHERAPY™

What's Next for Cancer Immunotherapy?

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Disclosures

- Consultant: Bristol-Myers Squibb, Novartis, EMD Serono, Array BioPharma, Macrogenics, Merck
- Research grants: Bristol-Myers Squibb, Merck

- I will be discussing non-FDA approved indications during my presentation.

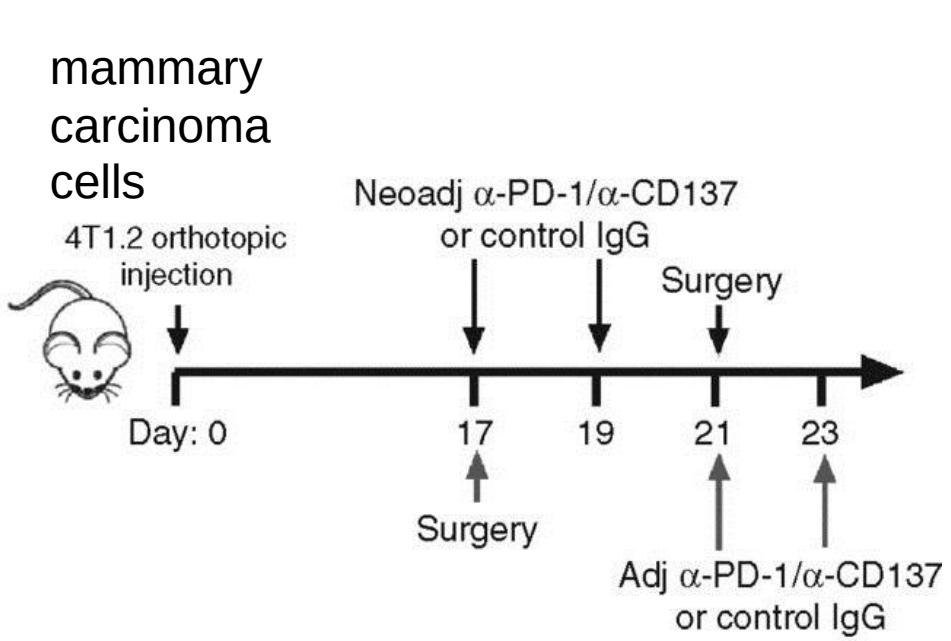
What's Next? Widening the net.

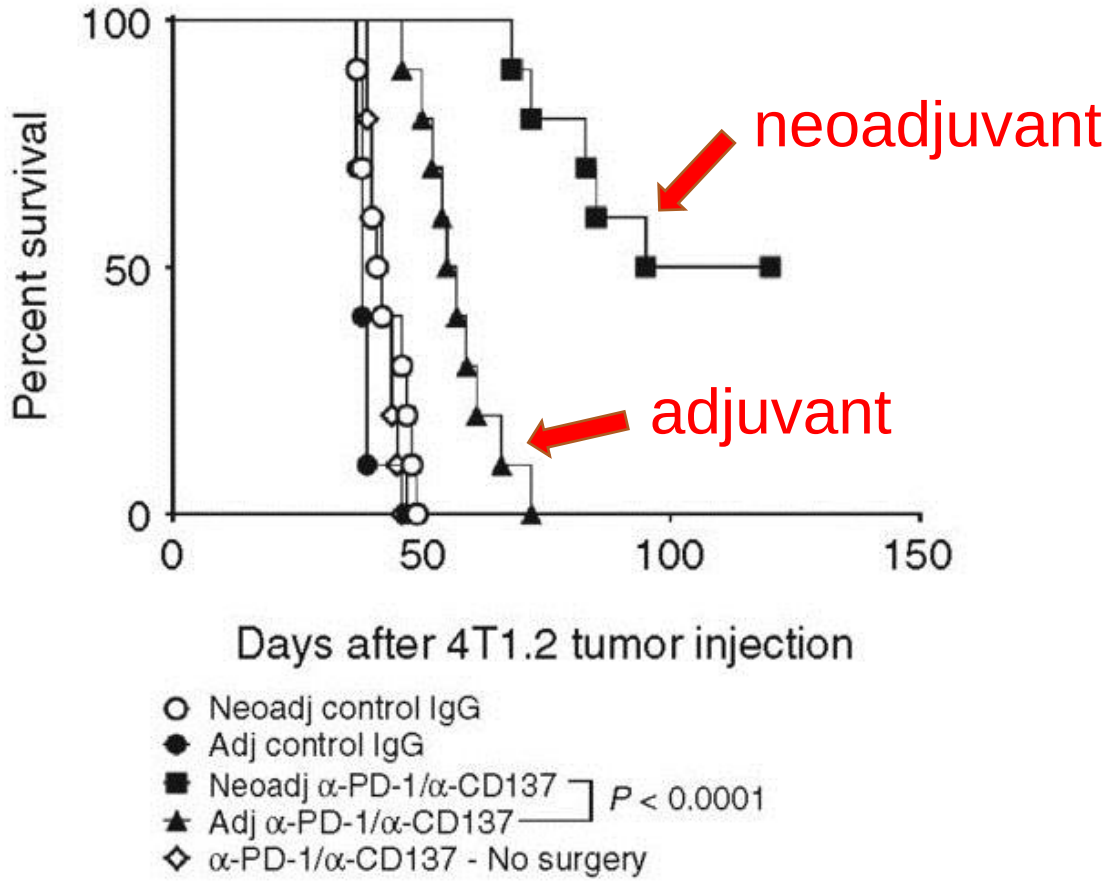
1. Expanding the settings (e.g., neoadjuvant) in which cancer immunotherapy is administered

2. Testing immune checkpoint blocking therapy in
   - patients with a larger variety of tumor types
   - patient populations previously excluded from clinical trial participation

3. Combining anti-PD-1 with novel immunomodulatory drugs

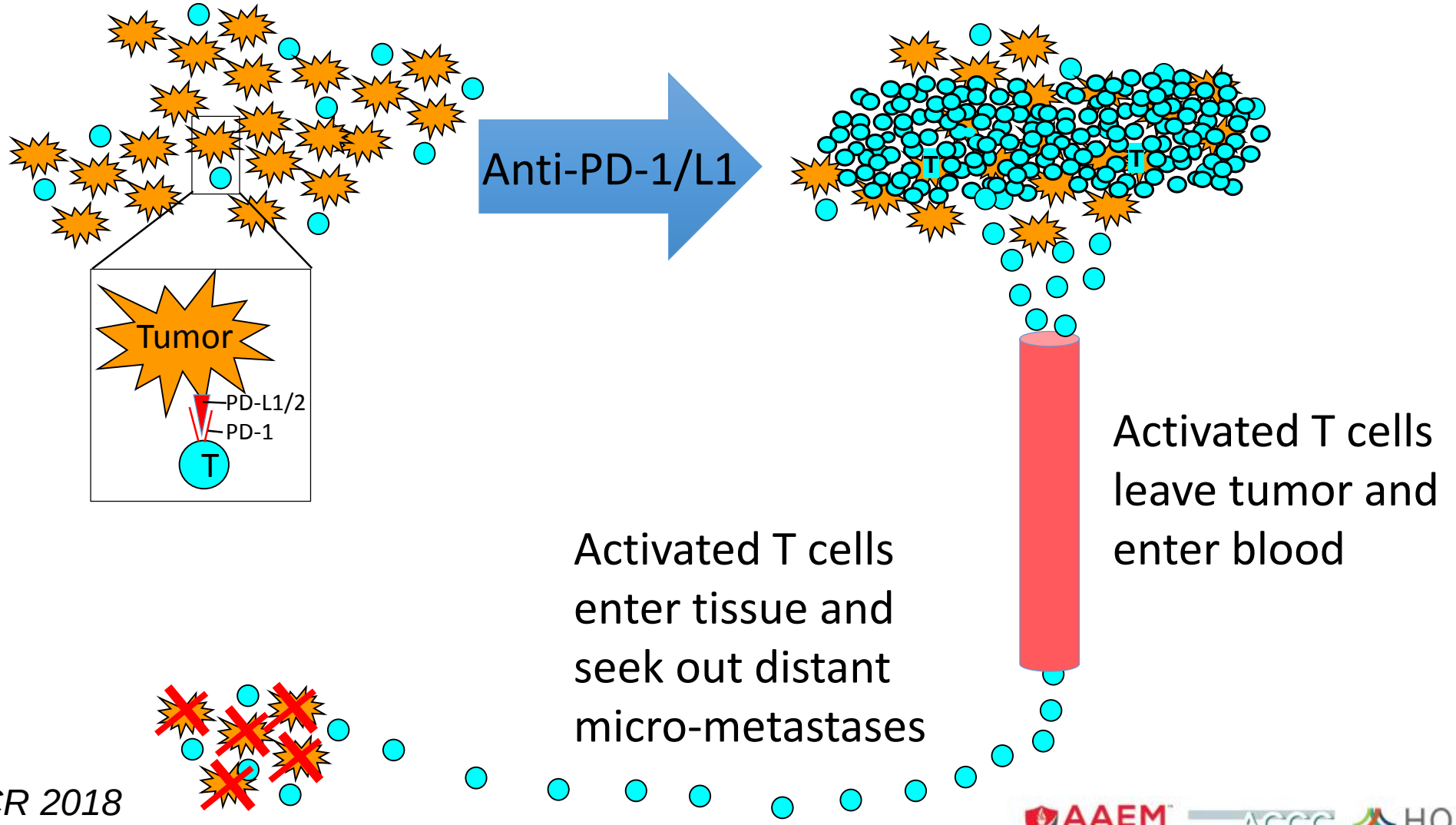
Neoadjuvant compared with adjuvant anti-PD-1 + anti-CD137 therapy is more efficacious in eradicating metastatic disease in mice.





Liu et al., Cancer Discov 2016

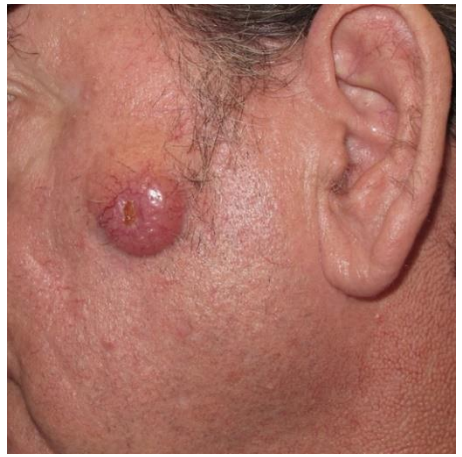
Neoadjuvant checkpoint blockade as a primer for systemic anti-tumor T cell responses



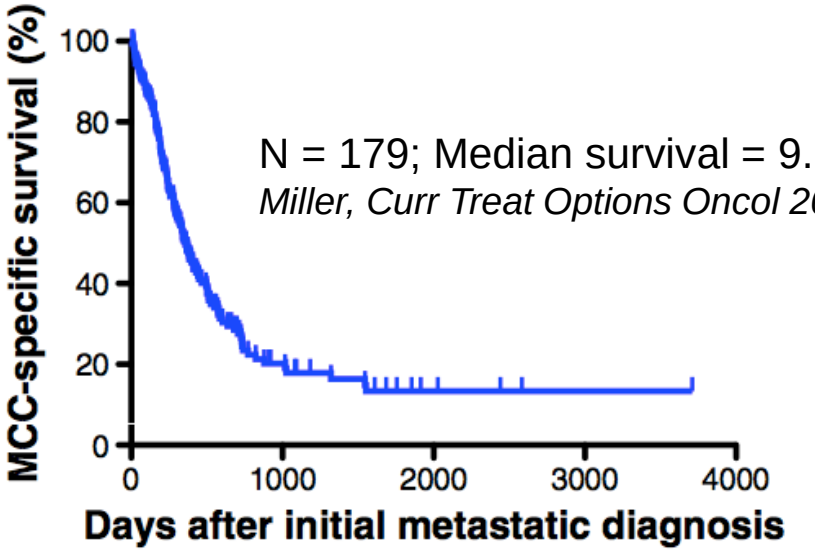
Pardoll, AACR 2018

Into the clinic: Merkel cell carcinoma

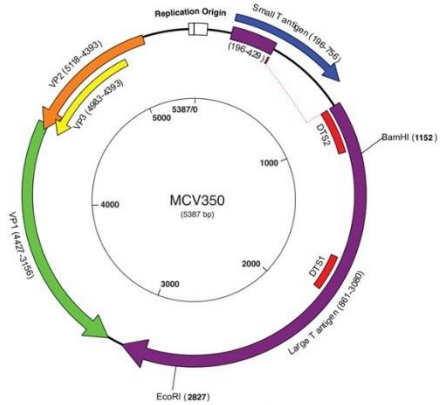
- ~ 2500 cases/year in the US
- Risk factors: age >50y, immune suppression
- Objective response to anti-PD-(L)1 in 32-64% of pts with advanced disease
- Merkel cell polyomavirus (MCPyV) present in ~80% of cases
- ***> 40% of MCC patients develop advanced disease***



Nghiem et al., AACR 2016

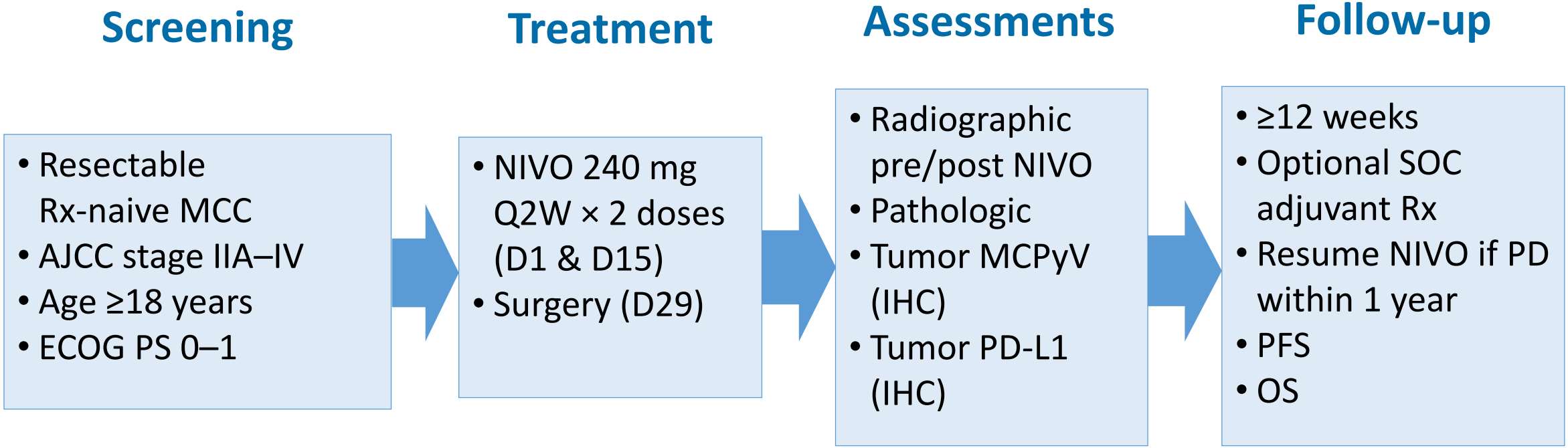


N = 179; Median survival = 9.5 mo
Miller, Curr Treat Options Oncol 2013



Feng et al., Science 2008

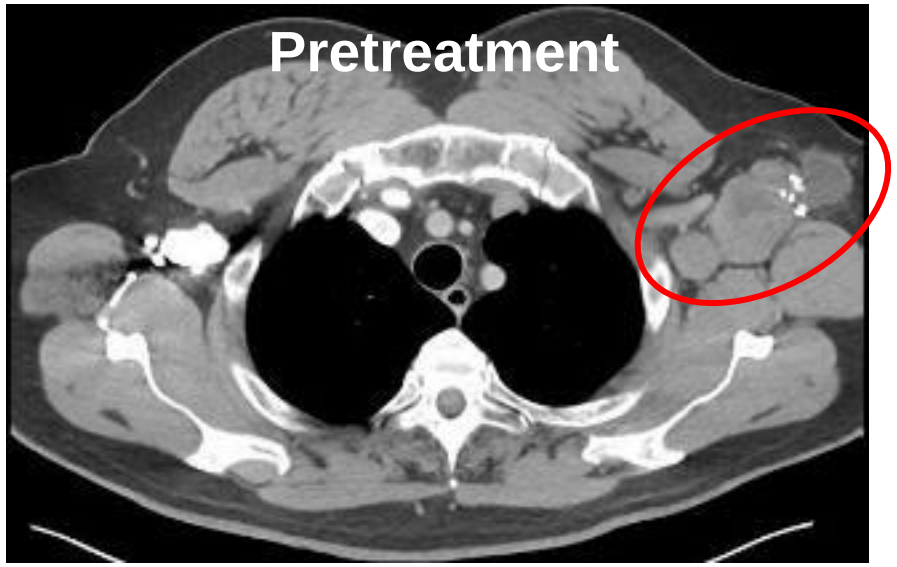
Nivolumab as Neoadjuvant Therapy in Patients With Resectable Merkel Cell Carcinoma (CheckMate 358)

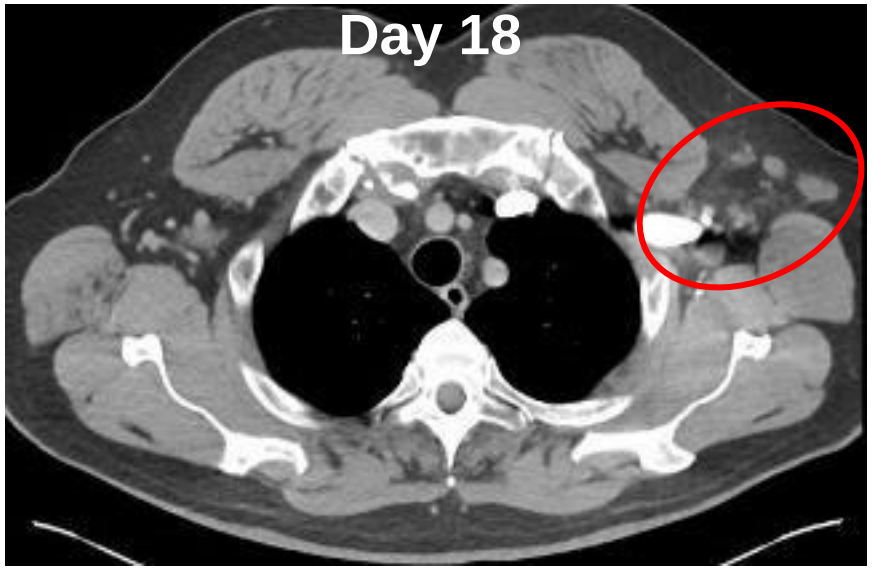


Topalian et al, ASCO 2018

Response of MCC to neoadjuvant nivolumab

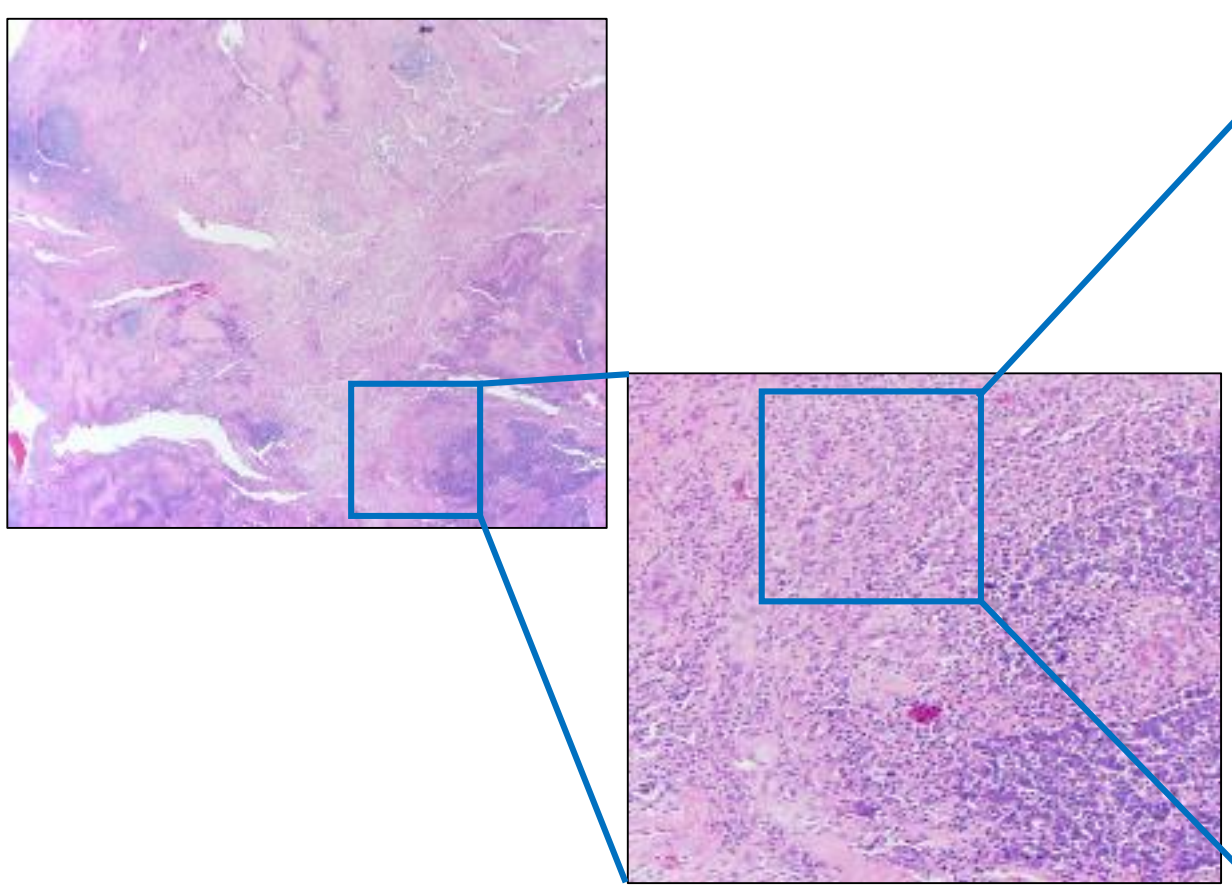
- 67-year-old male with stage III MCC, primary site unknown
- Tumor MCPyV-, PD-L1 <1%
- Received 2 doses of NIVO (D1 & D15)
- Underwent surgery on D23 (complete left axillary lymph node dissection)
- Major pathologic response
- No postoperative therapy
- No evidence of disease 18 months post-op

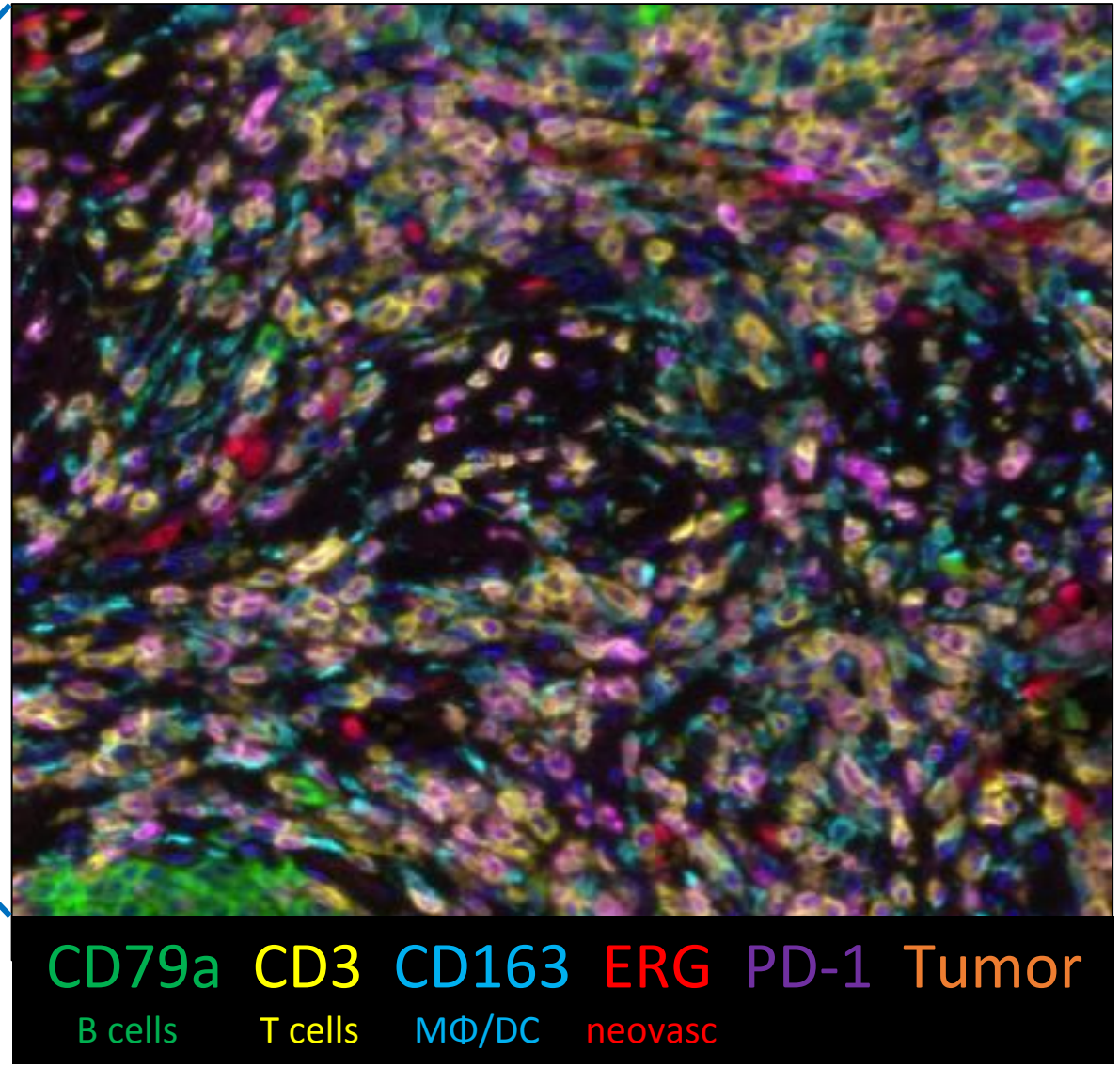




Topalian et al, ASCO 2018

Major pathologic response of MCC lymph node metastases to neoadjuvant nivolumab (D23)

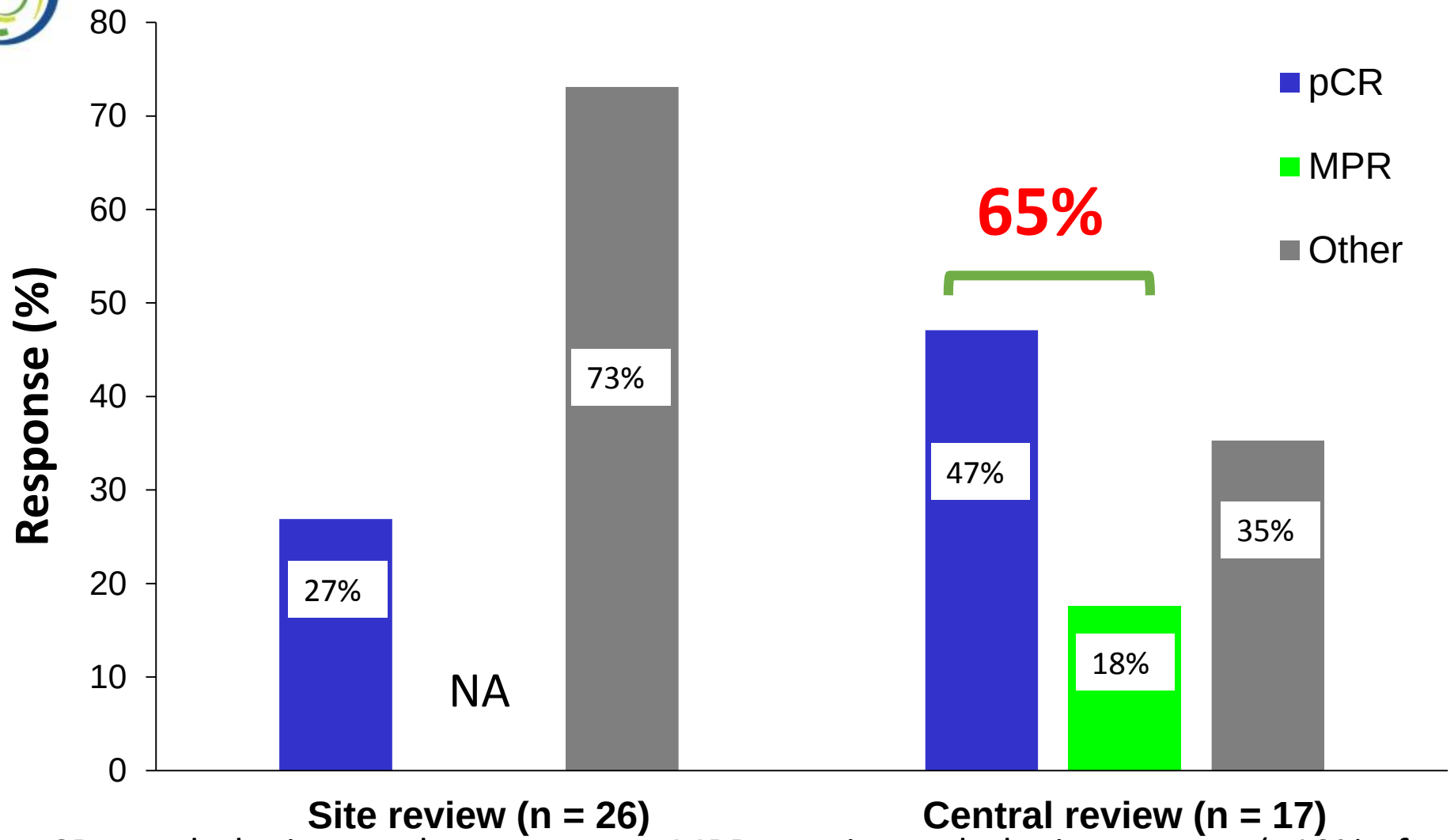




Tissue volumes support extensive correlative analyses

Topalian et al, ASCO 2018

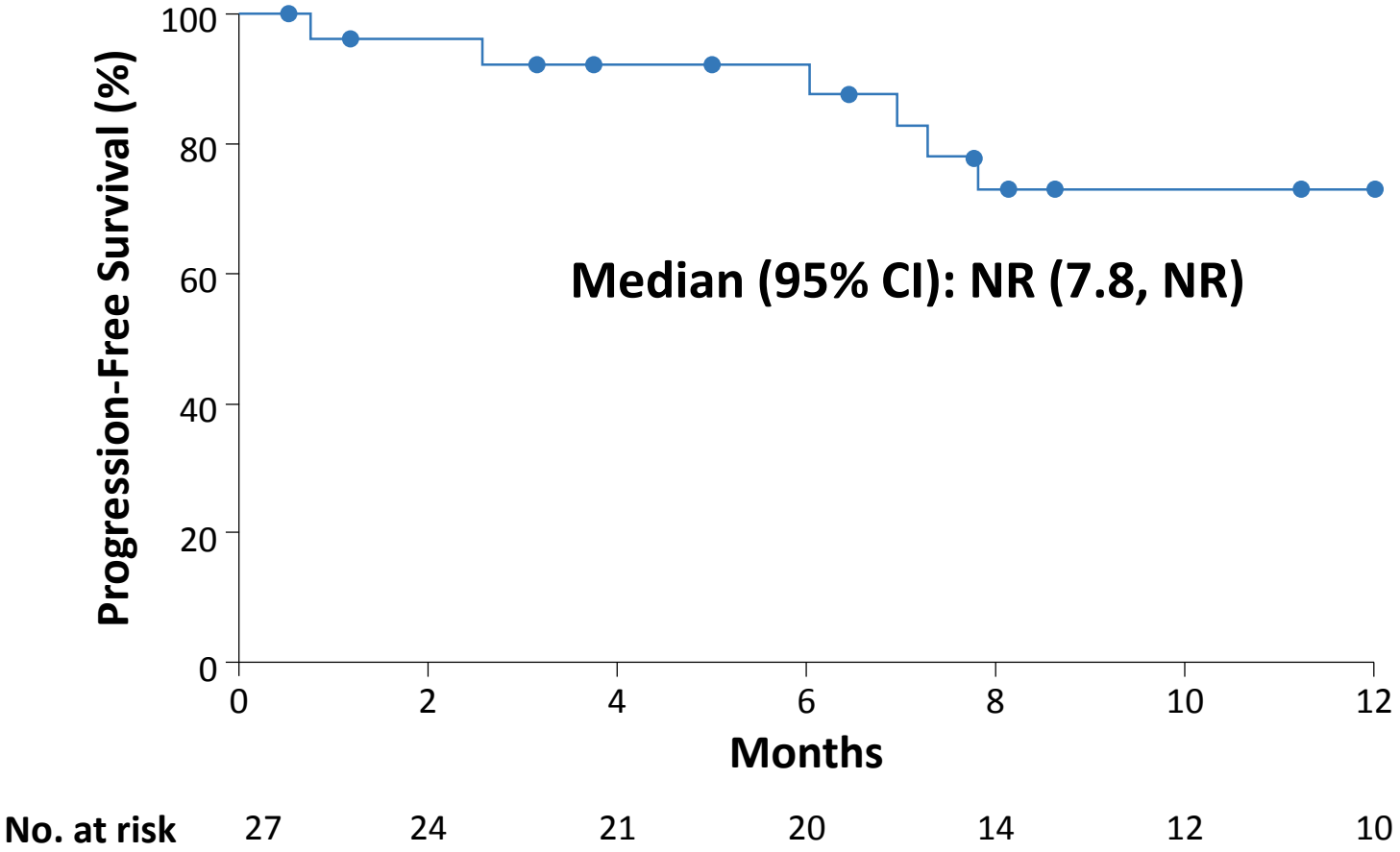
Pathologic Response



Topalian et al, ASCO 2018

pCR = pathologic complete response; MPR = major pathologic response (≤10% of residual viable tumor); NA = not assessed.

Progression-Free Survival



At ASCO 2018, among 15 patients with pCR or MPR by site and/or central review, none had relapsed after surgery, with a median follow-up of 12 months.

NR = not reached

Topalian et al, ASCO 2018

What's Next? Widening the net.

1. Expanding the settings in which cancer immunotherapy is administered

2. Testing immune checkpoint blocking therapy in
   - patients with a larger variety of tumor types
   - patient populations previously excluded from clinical trial participation

3. Combining anti-PD-1 with novel immunomodulatory drugs

Durable responses to PD-(L)1 pathway blockers in multiple cancer types

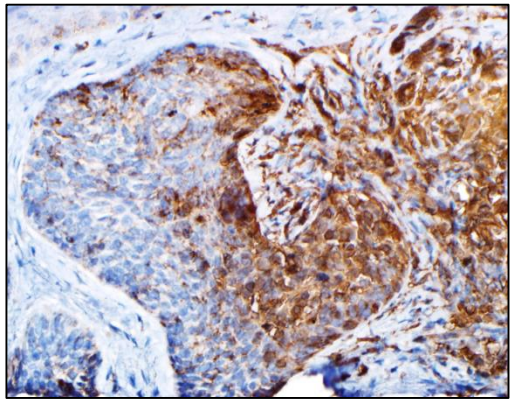
- Melanoma (17-50% of patients responding)
- Lung cancer (10-30%)
- Kidney cancer (12-29%)
- Bladder cancer (15-30%)
- Head and neck cancer (20-25%)
- Hodgkin lymphoma (65-87%)
- Merkel cell Ca (32-64%)
- MSI-hi solid tumors (~50%)
- Hepatocellular Ca (~15%)
- Gastric Ca (13-25%)
- Cervical Ca (14%)
- Primary mediastinal large B-cell lymphoma (45%)
- Small cell lung cancer (12-33%)
- Cutaneous squamous cell Ca (47%)
- TNBC (with chemo, 56%)

What's next:

Profiling of other tumor types in order to build a rationale for development of immunotherapies

Expanding the reach of cancer immunotherapy: Advanced basal cell carcinoma

- Locally-advanced unresectable or metastatic BCC is rare (<10,000 cases per year in the US).
- Standard therapy with hedgehog pathway inhibitors is often poorly tolerated, response duration suboptimal.
- BCC is characterized by genetic and immunologic markers associated with response to anti-PD-1 therapy in some other cancers.
  - Mutational burden among the highest reported in any human cancer type[1]
  - PD-L1 expression in ~80-100% of specimens [2,3]

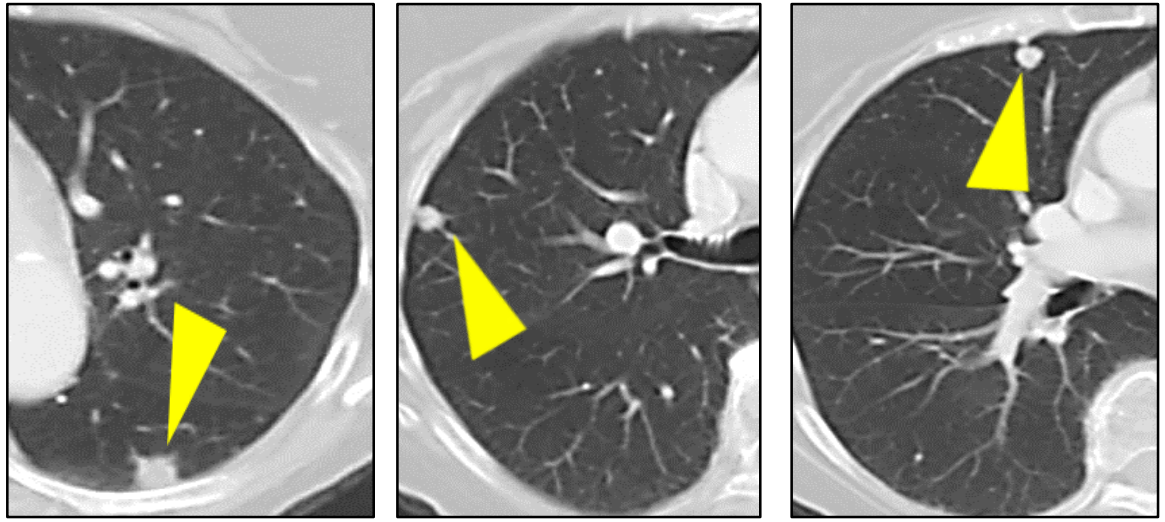


PD-L1 expressed by tumor cells and infiltrating immune cells in an archival BCC specimen. Immunohistochemistry, magnification 200X.

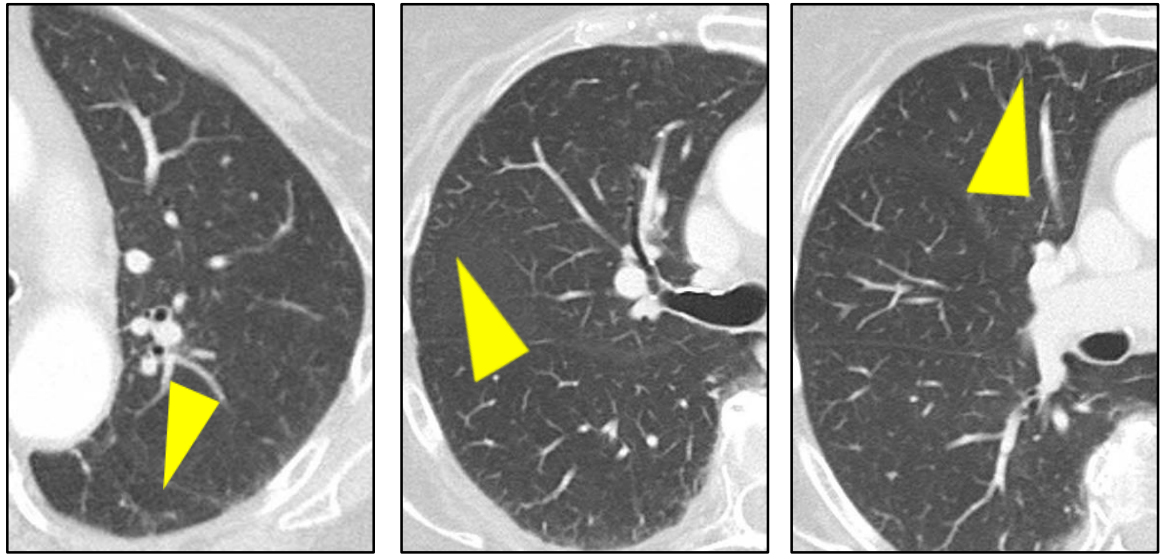
1. Jayaraman et al, J Invest Dermatol, 2014.
2. Lipson et al, JITC, 2017.
3. Soni et al, Amer Soc of Dermatopath Ann Mtg, 2018.

Durable complete response of metastatic BCC to anti-PD-1

Pre-Rx

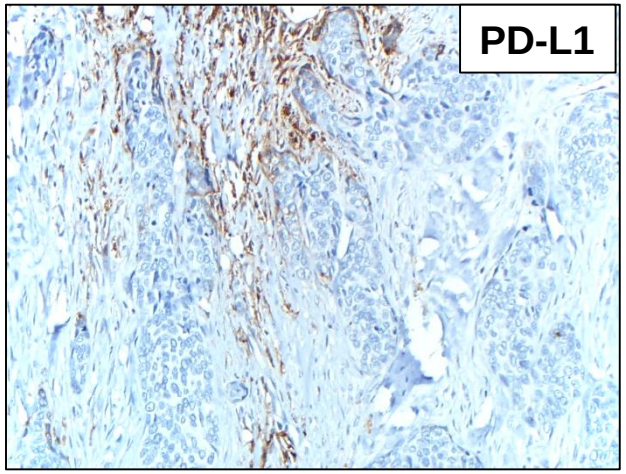


40 mo



81 y.o. F with metastatic BCC

- Progressed after therapy with hedgehog inhibitor, MEK inhibitor, IGF-1R mAb, radiation
- 2015: started pembro (~2 yrs)
- CR ongoing at 3.5+ yrs

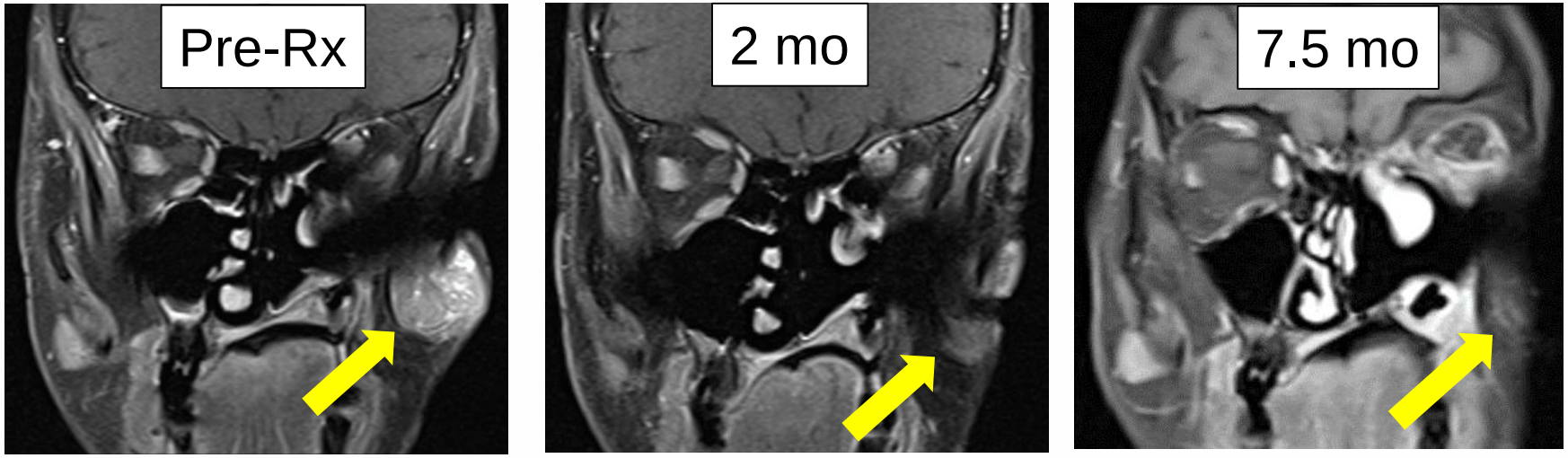


Adapted from Lipson et al., JITC, 2017

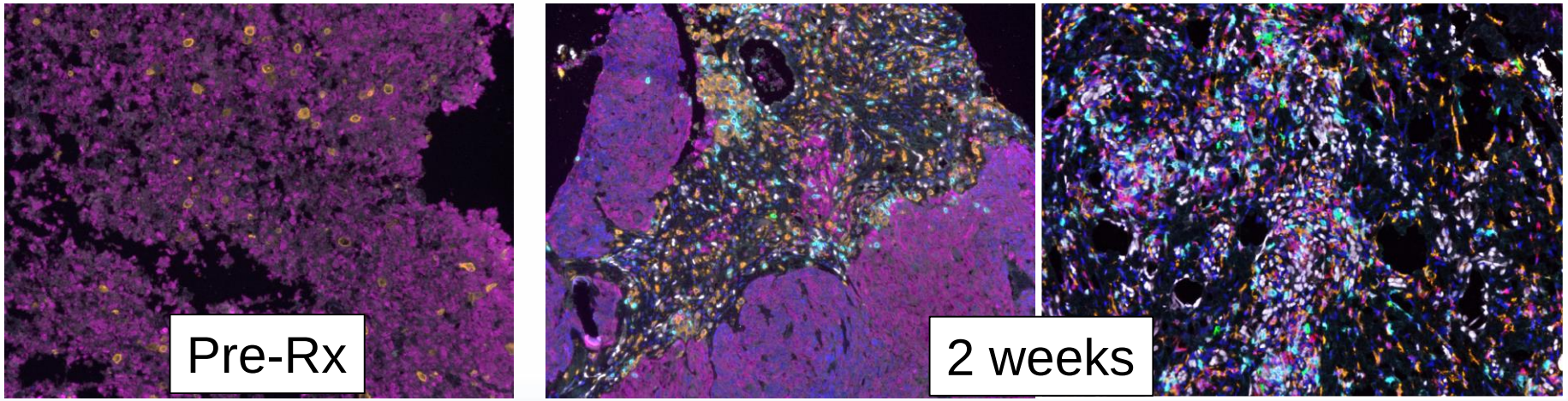
Nivolumab alone or plus ipilimumab for patients with locally-advanced unresectable or metastatic basal cell carcinoma (NCT03521830)

- Investigator-initiated phase 2 study
- Enroll 19 patients with locally-advanced or metastatic BCC, 1st-line or previously treated.
- Treat with nivolumab 480 mg q4w, add ipilimumab 1 mg/kg if PD after 16 weeks.
- Endpoints
  - Primary: objective response rate (CR + PR)
  - Secondary: disease control rate (CR + PR + SD ≥26 weeks), duration of response, progression-free survival, overall survival
  - Exploratory: interrogation of tumor immune microenvironment in pre- and on-therapy biopsies

Study patient with partial response to nivolumab, ongoing at 8+ months



History: 61 y.o. F with 20-year history of neglected L eyelid BCC, eroding through nose and orbit. Hedgehog inhibitor therapy started 10/2016, tumor regression followed by enlargement of L cheek mass. Biopsy-proven BCC.



Multispectral immunofluorescence imaging illustrates rapid influx of a mixed population of immune cells and remodeling of the TME consistent with immune-mediated tumor regression.

Green: B cells; Red: T cells; Orange: macrophages; Teal: PD-1; Purple: tumor; White: neovasculature

What's Next? Widening the net.

1. Expanding the settings in which cancer immunotherapy is administered

2. Testing immune checkpoint blocking therapy in
   - patients with a larger variety of tumor types
   - patient populations previously excluded from clinical trial participation (i.e., "difficult-to-treat")

3. Combining anti-PD-1 with novel immunomodulatory drugs

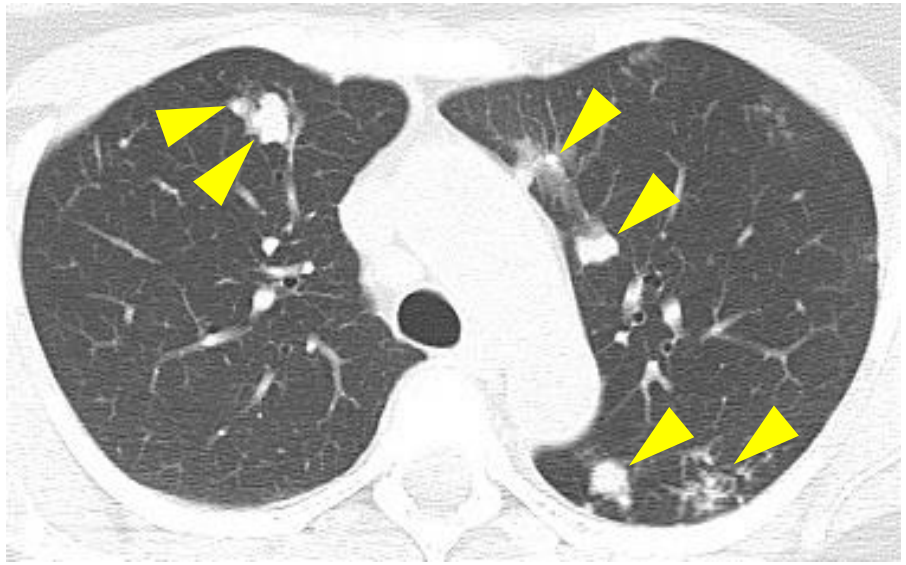
Testing ICI in difficult-to-treat patient populations

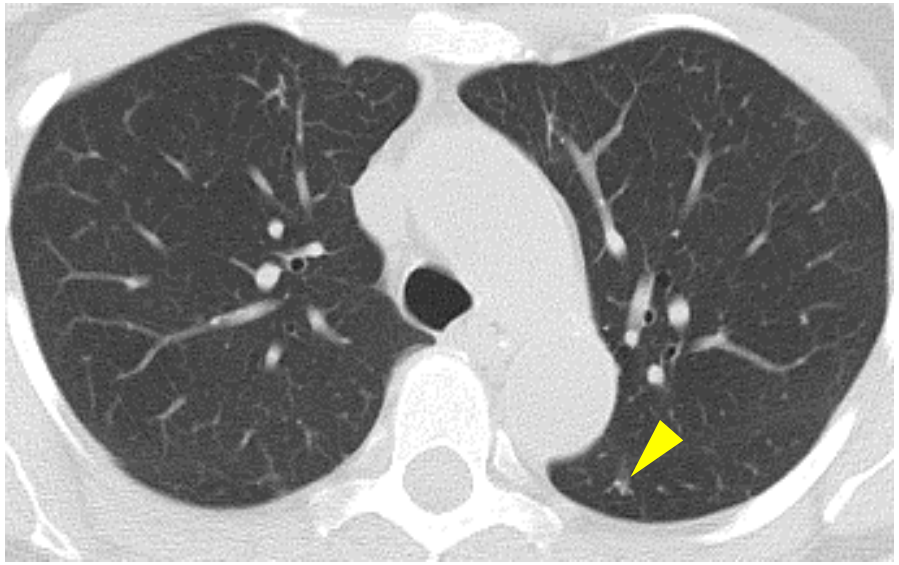
- Solid organ transplant recipients are at substantially increased risk for developing skin cancers.[1-3]
  - ~ 50x risk for cutaneous squamous cell carcinoma
  - ~ 25x risk for Merkel cell carcinoma

- These patients have generally been excluded from previous clinical trials testing ICIs in cancer.

1. Vajdic, Int'l J of Cancer, 2009; 2. Wimmer, Kidney Int'l, 2007; 3. Clarke, J Natl Cancer Inst, 2015

Durable response of metastatic cutaneous SCC to anti-PD-1 therapy in a kidney transplant recipient





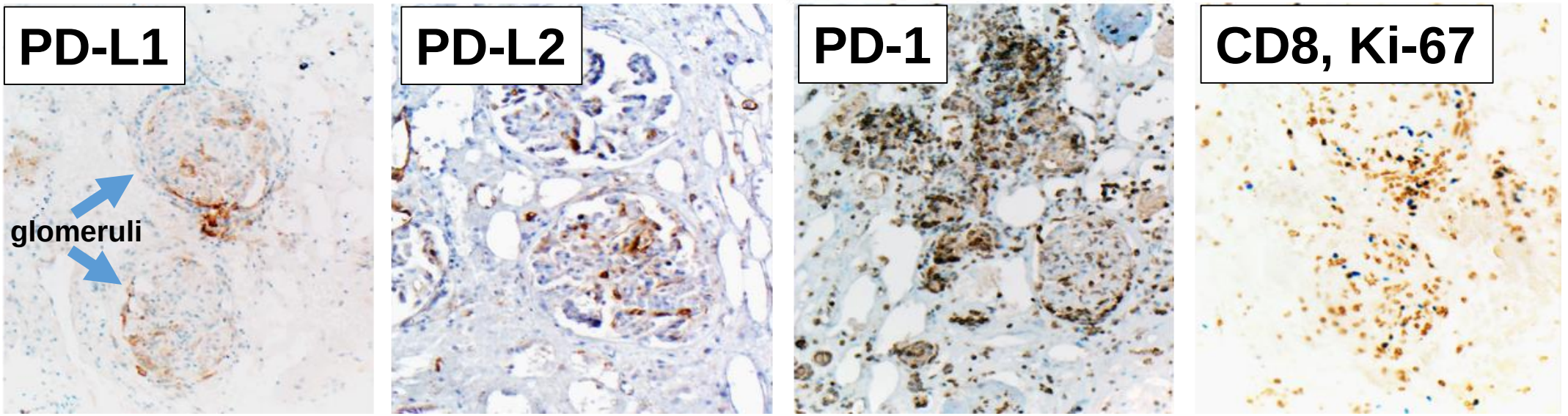
Lipson et al., NEJM 2016

Pre-Rx

8 mo

- 57 y.o. kidney transplant recipient maintained on various immunosuppressants ~25 yrs.
- Early 2014, presented with metastatic cSCC, resistant to cetuximab and MEK inhibitor.
- Anti-PD-1 started late 2014 led to tumor regression, but allograft rejected at ~8 wks
- No evidence of cSCC at ~5 years.

T cell-mediated allograft rejection



Lipson et al., NEJM 2016

- The PD-1 pathway plays an important role in allograft tolerance.
- Tumors arising in chronically immunosuppressed patients may contain immune-reactive TMEs and should be considered for anti-PD-1 therapy.

Designing a trial of ICI in solid organ transplant recipients

- ~100 literature reports of ICI for various advanced cancers (melanoma, cSCC, HCC, etc.) in liver or kidney transplant recipients
  - Different ICI regimens and graft preservation regimens administered
  - Tumor “control rate” (PR + CR + SD) ~35%
  - Graft rejection rate ~40%
  - Allograft loss appears less likely with dual agent immunosuppression (e.g., prednisone and tacrolimus [calcineurin inhibitor]) vs prednisone alone

- **Goal: devise a safe and effective immunotherapy regimen against cancers arising in kidney transplant recipients (CR/PR/SD in 40% of patients, with allograft preservation)**

Nivolumab, tacrolimus and prednisone for selected advanced cancers in kidney transplant recipients (NCT03816332)

- Experimental Therapeutics Clinical Trials Network (ETCTN): Collaborative NCI-funded network spanning the US

- Lead clinical trial site: Johns Hopkins

- Participating sites:
  - Harvard
  - Northwestern
  - Ohio State
  - University of Pittsburgh
  - Yale

Trial design: Nivolumab, tacrolimus and prednisone for selected advanced cancers in kidney transplant recipients

- Enroll 9-16 kidney transplant recipients with advanced melanoma, BCC, MCC, cSCC, or MSI-high cancers refractory to standard (non-immunologic) therapies
- Treat cancer with nivolumab (480 mg q4w) for ≤16 wks, add ipilimumab if tumor progression; preserve graft with tacrolimus (serum trough 2-5 ng/ml) + prednisone (5 mg daily)
- Endpoints
  - Primary: proportion of patients experiencing CR/PR/SD without allograft loss at 16 wks.
  - Secondary: ORR, PFS, OS, rate of allograft loss.
- Exploratory studies: characterize immunologic changes in TME and allograft pre/post therapy.

What's Next? Widening the net.

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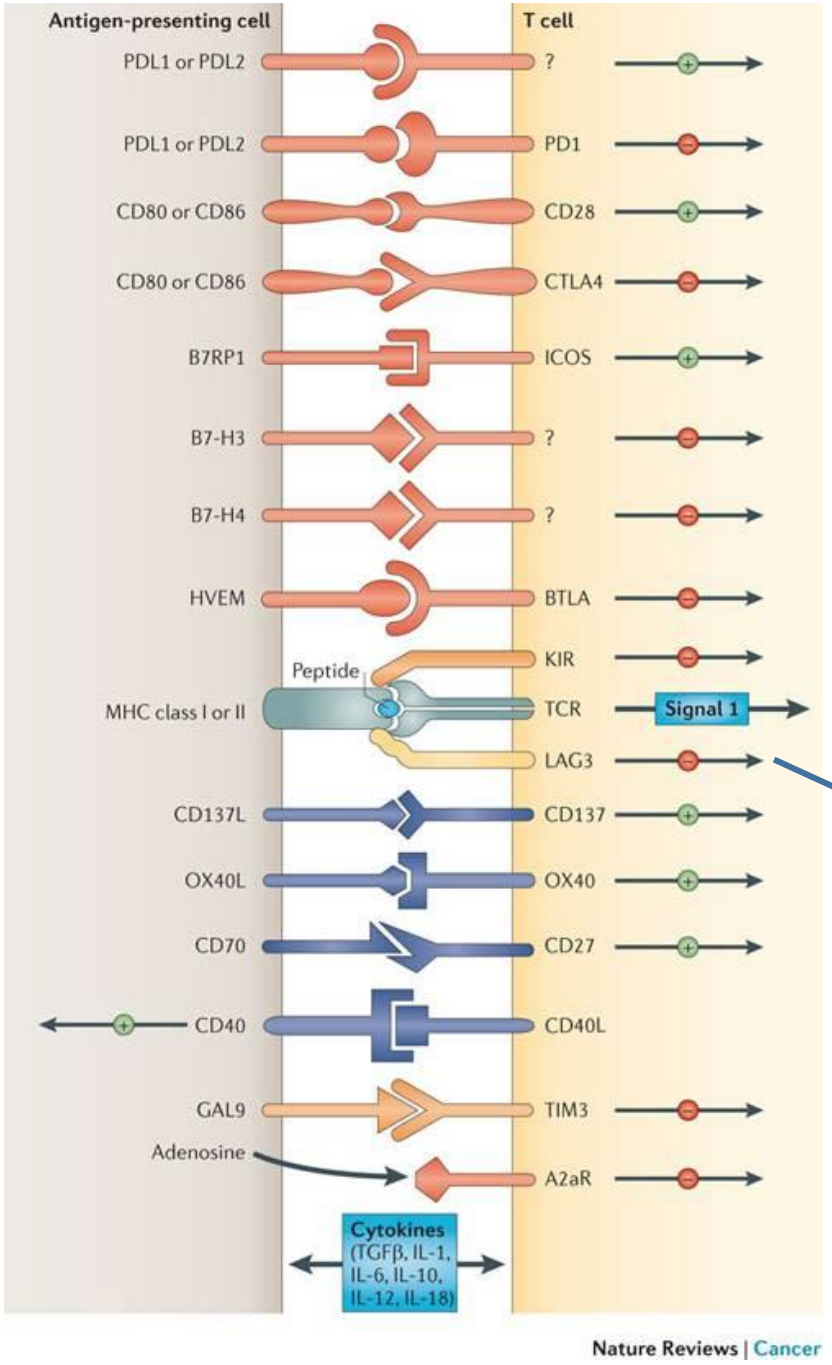


Numerous checkpoints, countless combinations

Lymphocyte-activation gene 3 (LAG-3)

Pardoll, Nat Reviews 2015

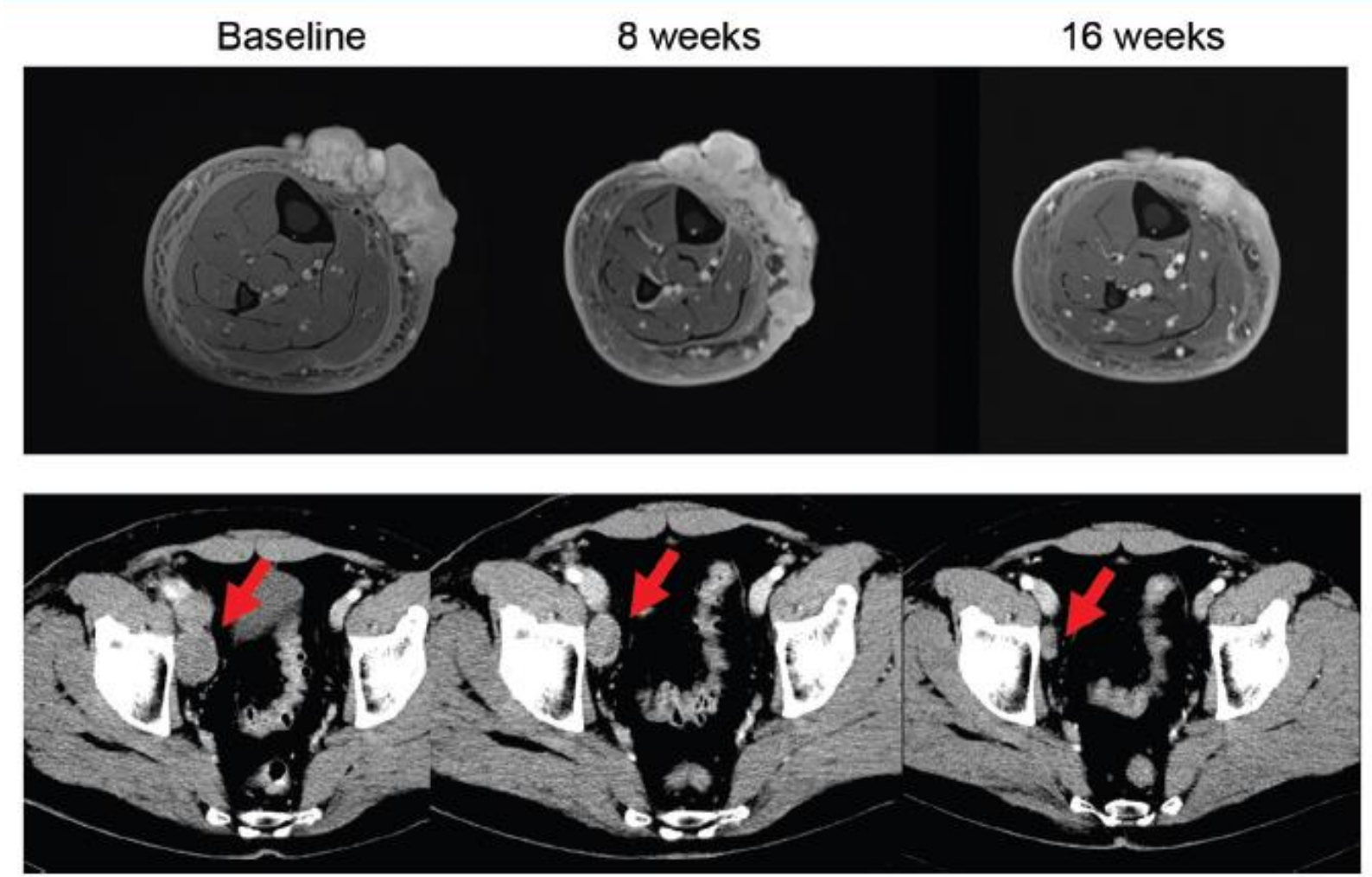
Role of LAG-3 in T-cell exhaustion and anti–PD-1 resistance

- LAG-3 regulates a checkpoint pathway that limits the activity of T cells
- In therapy-naïve patients, constitutive LAG-3 expression may limit the anti-tumor activity of PD-1 pathway blockade
- In patients exposed to PD-1 pathway blockade, adaptive upregulation of LAG-3 expression may lead to treatment resistance and tumor progression
- Hypothesis: Anti-LAG-3 combined with anti-PD-1 may restore T-cell activation and anti-tumor response in tumors that express LAG-3

Refs: Grosso JF et al. J Clin Invest. 2007. Wherry EJ. Nat Immunol. 2011. Koyama S et al. Nat Commun. 2016.

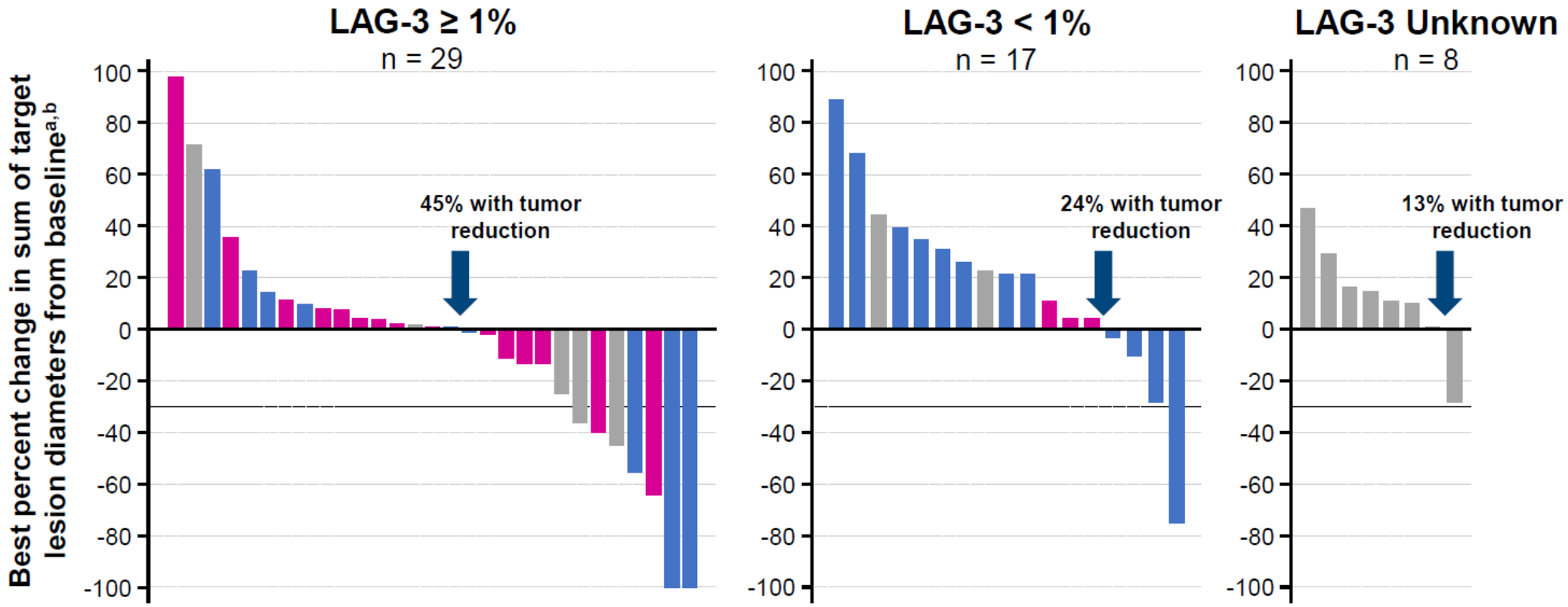
Anti–LAG-3 + Nivolumab in anti-PD-1–Refractory Melanoma (NCT01968109)

- 51 y.o. M w/ advanced BRAF-WT melanoma, refractory to first-line nivolumab (anti-PD-1)
- Trial Rx: relatlimab (anti-LAG-3) + nivolumab
- Cutaneous and nodal tumor regressions



Lipson et al, SITC 2016

LAG-3 tumor expression enriches for anti-tumor response



Pink: PD-L1 ≥ 1% **Blue**: PD-L1 < 1% **Gray**: PD-L1 unknown

Ascierto et al, ESMO 2017

What's Next for Cancer Immunotherapy?

1. Expanding the settings in which cancer immunotherapy is administered: neoadjuvant, adjuvant high / moderate risk

2. Testing immune checkpoint blocking therapy in
   - patients with a larger variety of tumor types (rare cancers)
   - patient populations previously excluded from clinical trial participation (autoimmune diseases, >1 cancer type)

3. Combining anti-PD-1 with novel immunomodulatory drugs (biomarker-driven trials, perhaps informed by correlative studies performed on neoadjuvant tumor specimens)