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ADVANCES IN Cancer IMMUNOTHERAPY™

What's Next for Cancer Immunotherapy?

Justin M. Balko, PharmD, PhD

Associate Professor of Medicine and Pathology, Microbiology and Immunology

Vanderbilt University Medical Center

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

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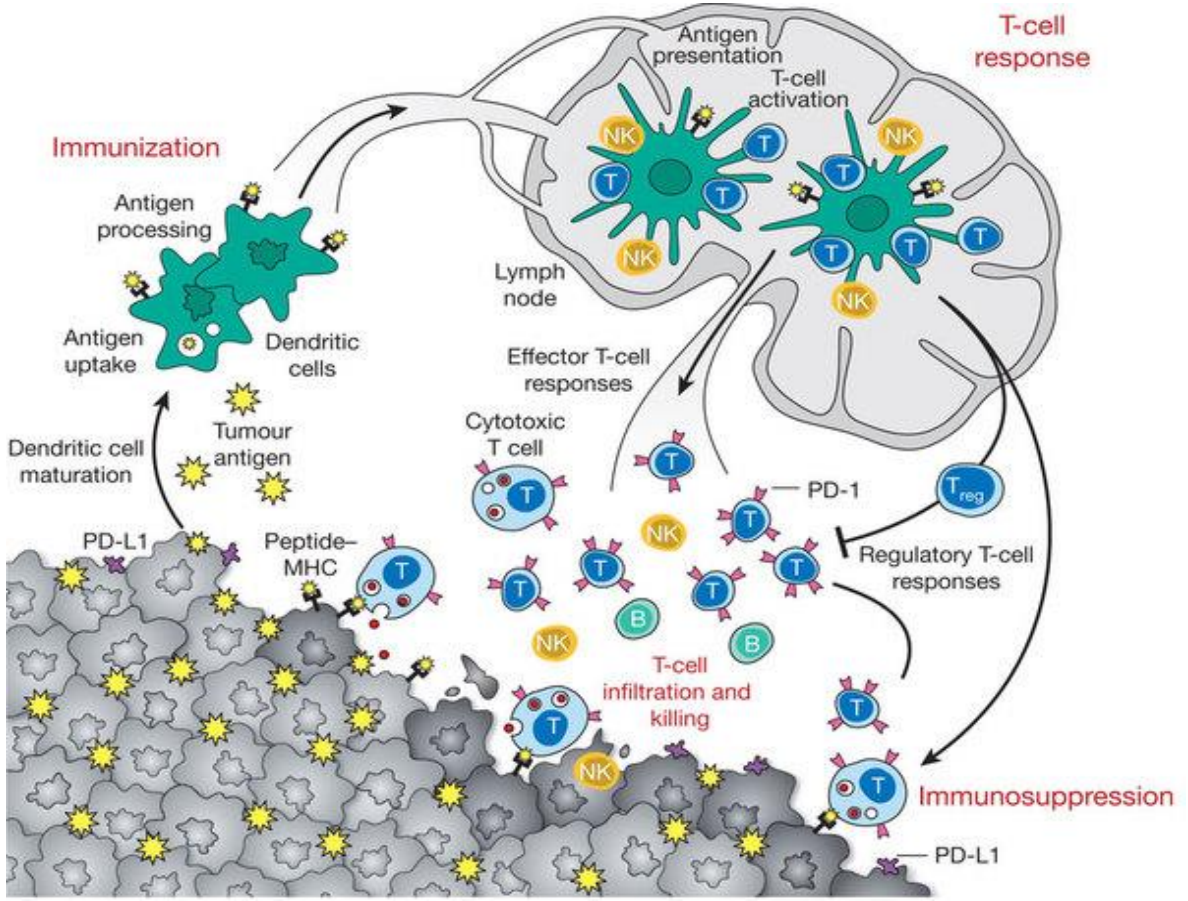
- **Provisional patentholder**
  - Immunotherapy targets and biomarkers in cancer.
- ***I will be discussing non-FDA approved indications during my presentation.***

What's been done?

- Transformation of cancer therapy
- Immune checkpoint inhibitors have the highest potential for wide therapeutic adoption
  - mABs targeting PD-1/L1 and CTLA-4 axes
- Healthcare costs, widely variable response rates, and unpredictable toxicities hinder usage



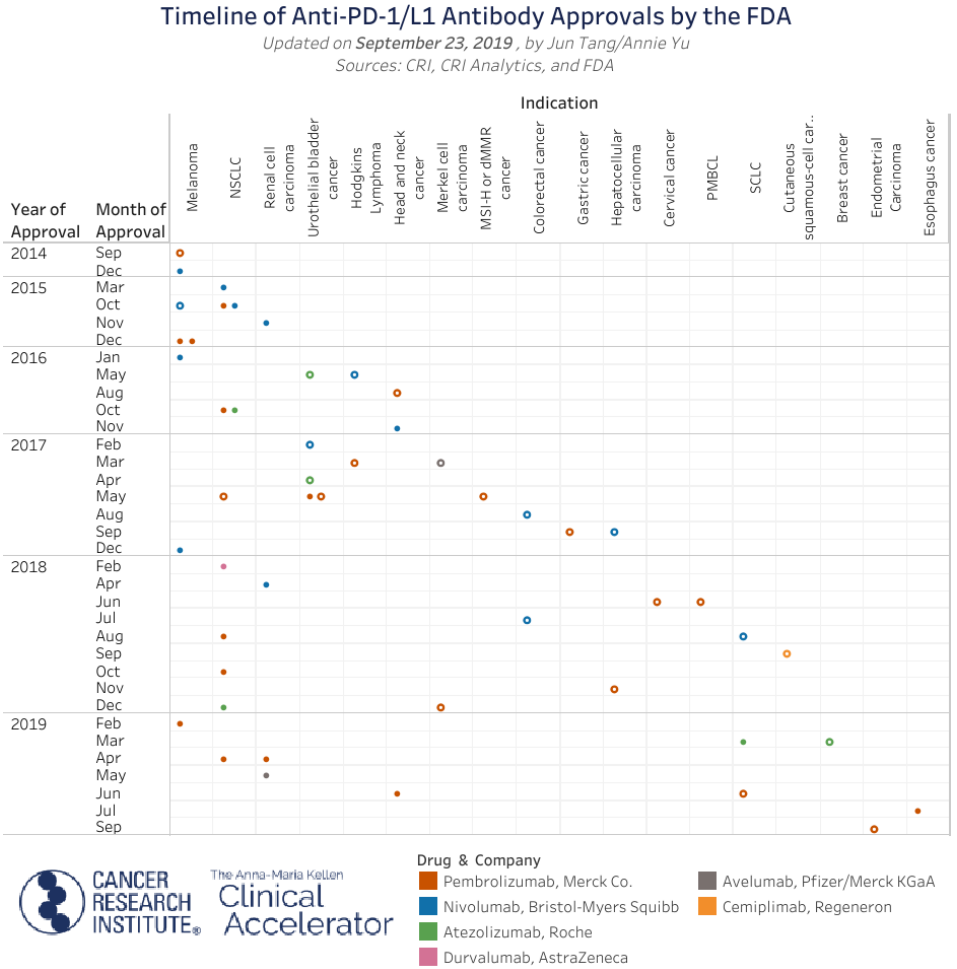
Mellman et al Nature 2011

Klapper et al. Cancer 2008

Expansion of indications for PD-1/L1 targeted ICI therapy

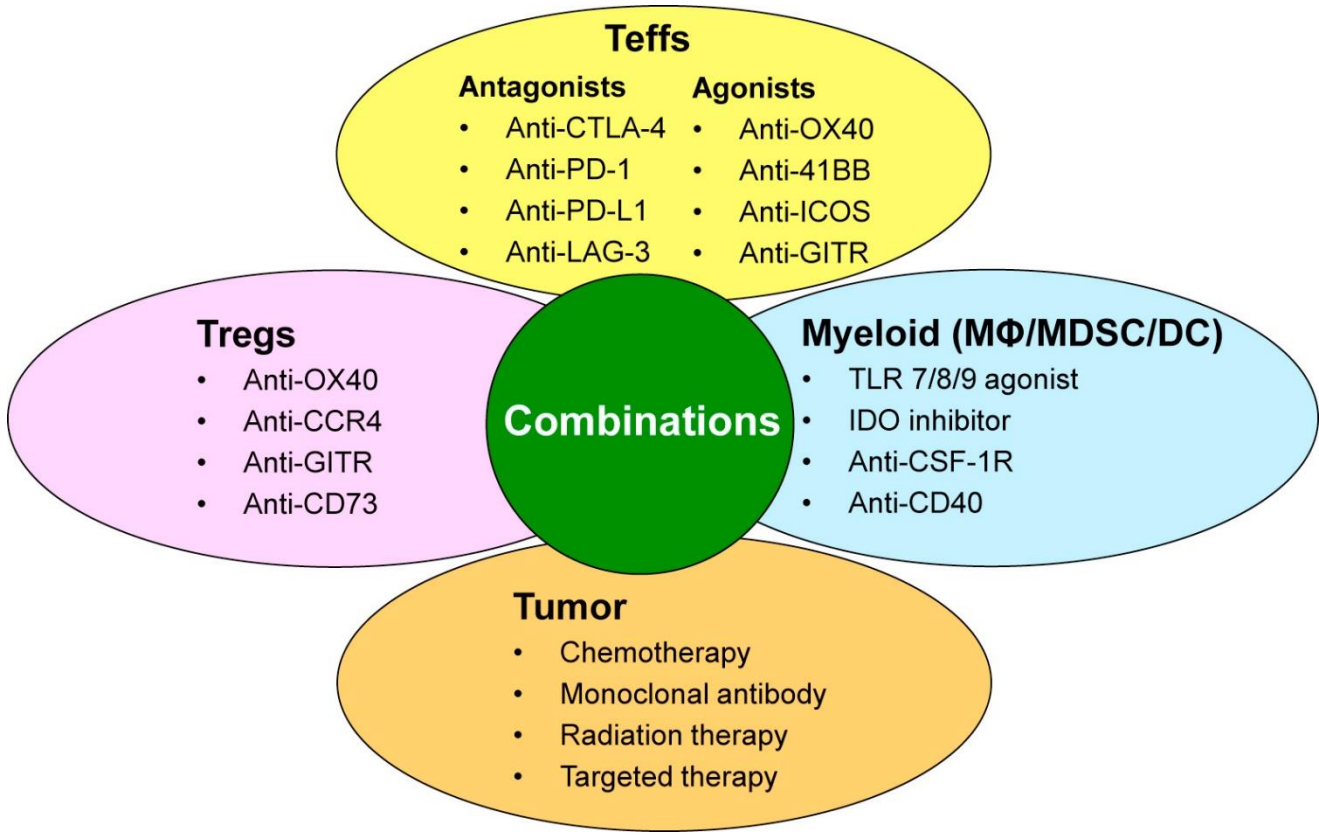
- Indications are rapidly expanding – nearly monthly
- A wide variety of solid and hematologic malignancies
- Estimations are nearly $1M per patient treated (all healthcare, combination immunotherapy)
  - $150-300K/QALY quality-adjusted life-years[1]
- Non-complex biomarkers that maximize benefiting patients can improve cost-effectiveness

[1]Verma et al, JITC. 2018



What are the next steps?

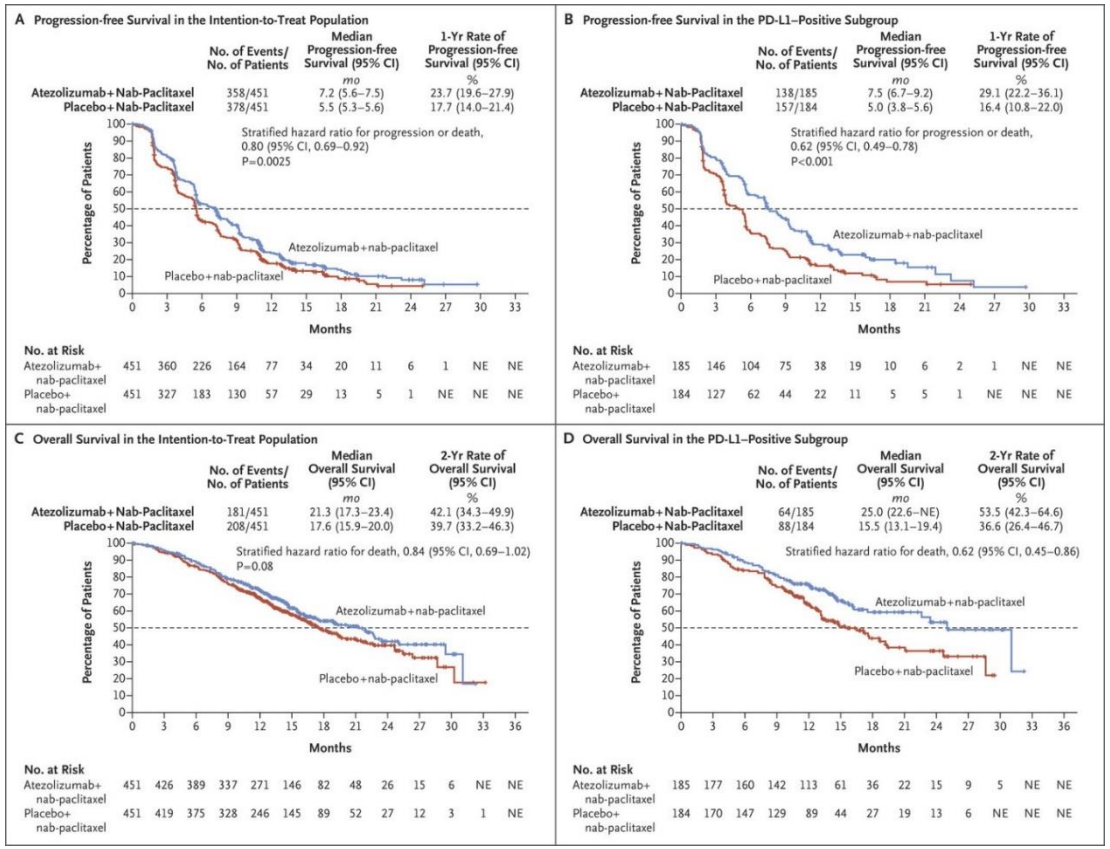
- Novel immunotherapies and combinations
  - 100s of active clinical trials in this area
- Goals are to identify therapeutic strategies that enhance tumor inflammation, driving response to agents like anti-PD-1/L1



Sathyanarayanan et al, Molecular Oncology 2015

IMpassion130 – first approval of immunotherapy combination in TNBC

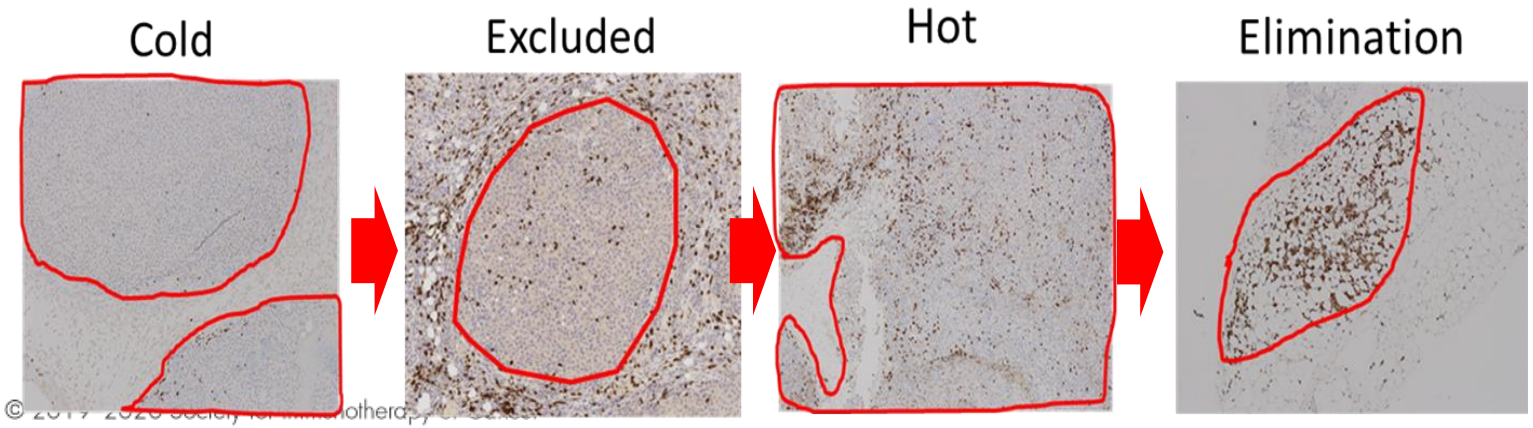
- Recent FDA-approval in PD-L1+ mTNBC in combination with nAb-paclitaxel
- Open question in mTNBC:
  - PD-L1 is a challenging biomarker
    - Tumor vs. stroma
    - Antibody variability
  - How to improve patient selection

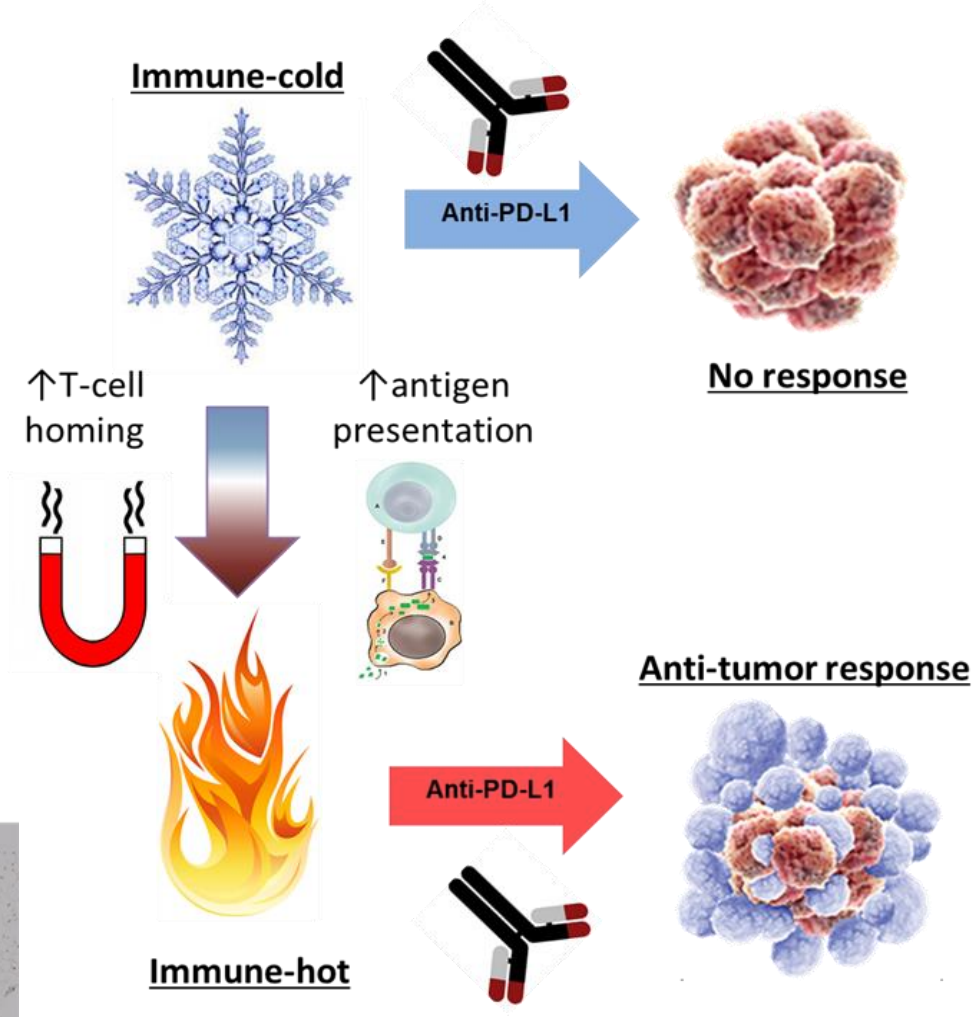


P Schmid et al. N Engl J Med 2018.

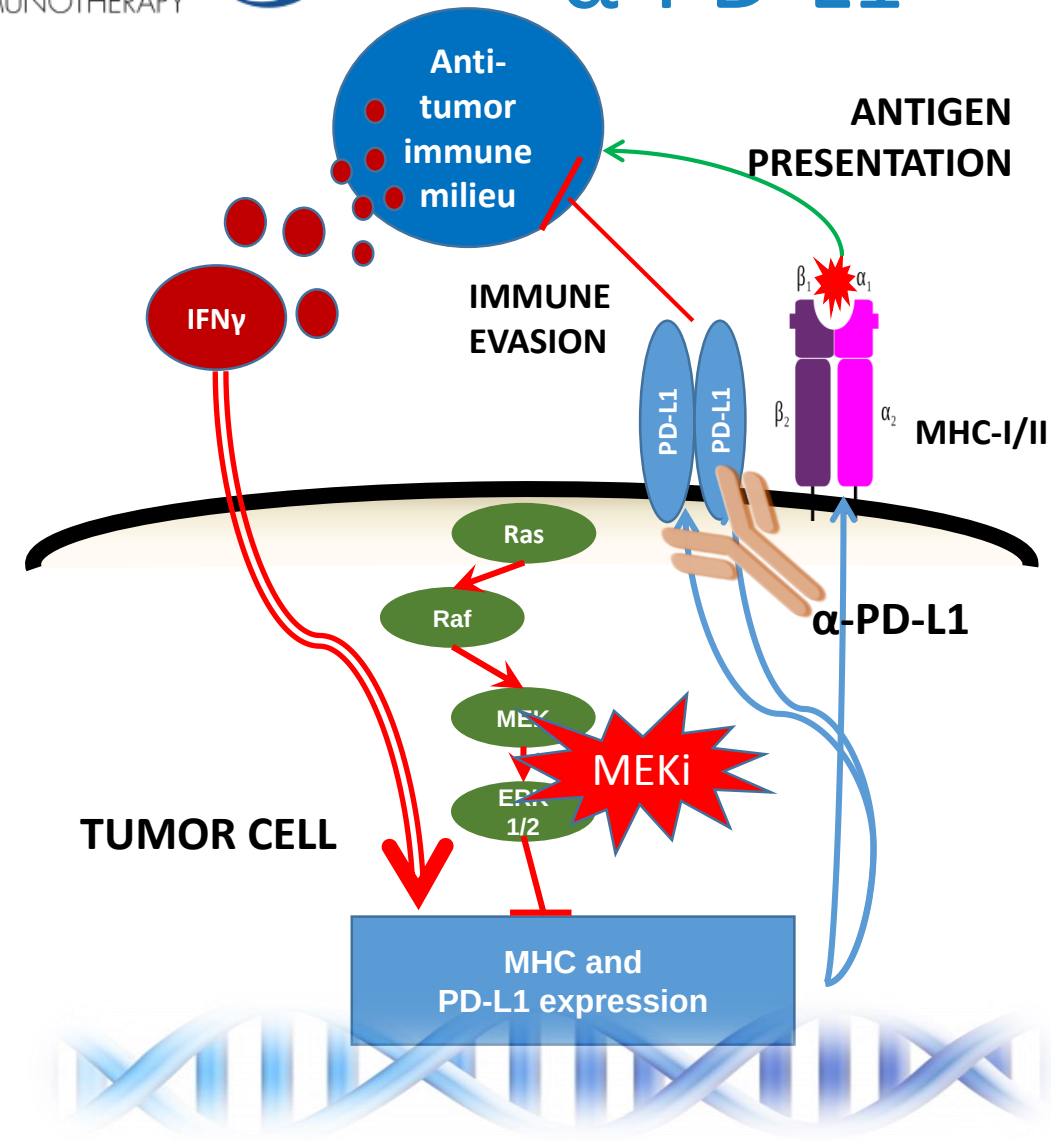
Strategies for enhancing anti-PD-1/L1 response

- Immune-hot or excluded
  - Deepen response/enhance rates
    - Agonize T cells
    - Enhance antigen presentation
    - Inhibit additional/alternative checkpoints
    - Target regulatory phenotypes (e.g. Treg/MDSCs)
- Immune cold/desert
  - Enhance response rates
    - Prime T cells
    - Recruit T cells
    - Enhance antigen presentation





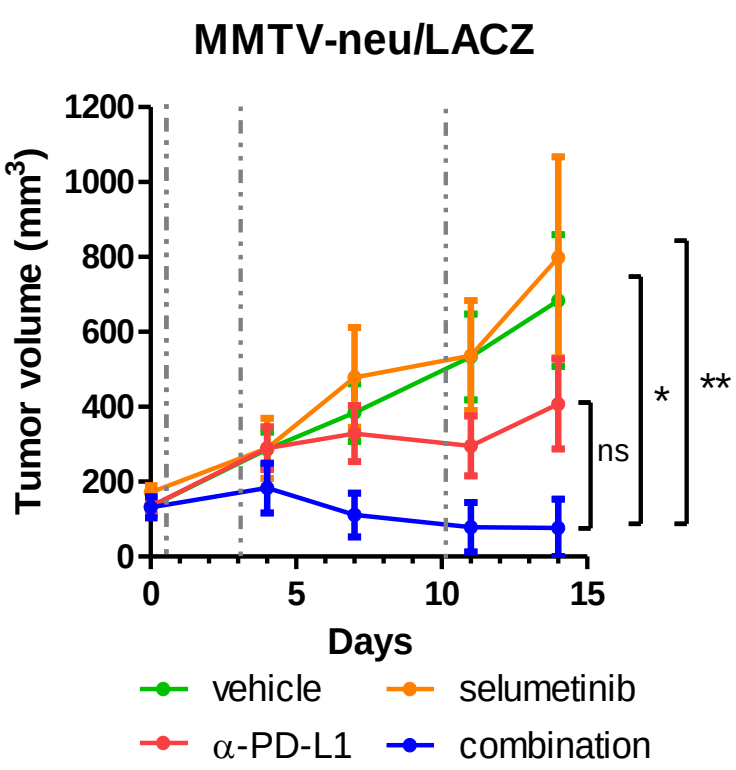
Potential for synergistic activity of MEKi + α-PD-L1

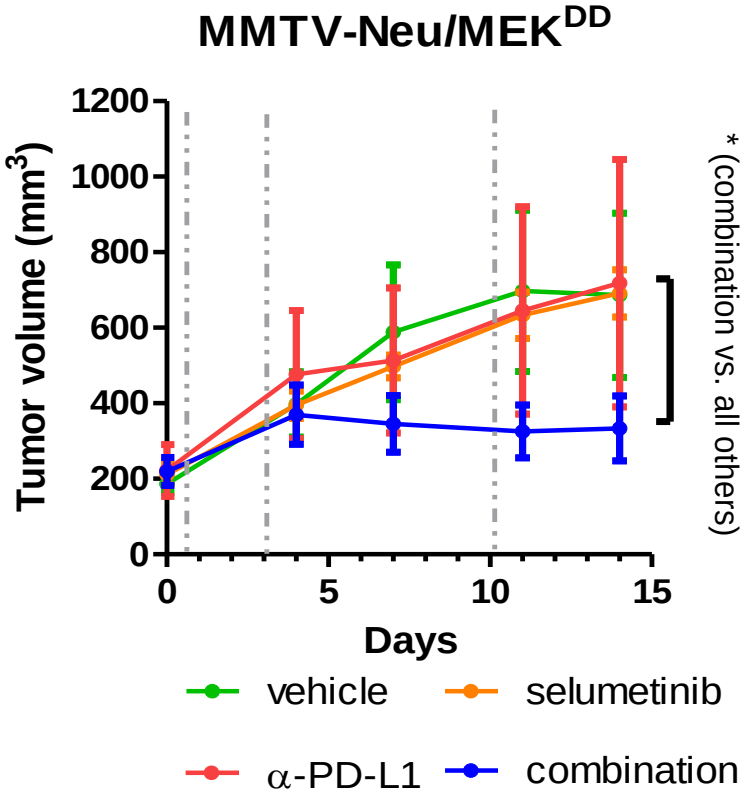


- Interferon upregulates MHC and PD-L1, which is decreased by MEK activation.
- PD-L1 reduces the immune response while MHC expression increases it
- Co-treatment with MEK inhibitors and PD-L1 mABs may synergize

Loi and Balko, CCR 2016

MEKi + anti-PD-L1 potentiates CD8 T cell mediated tumor elimination

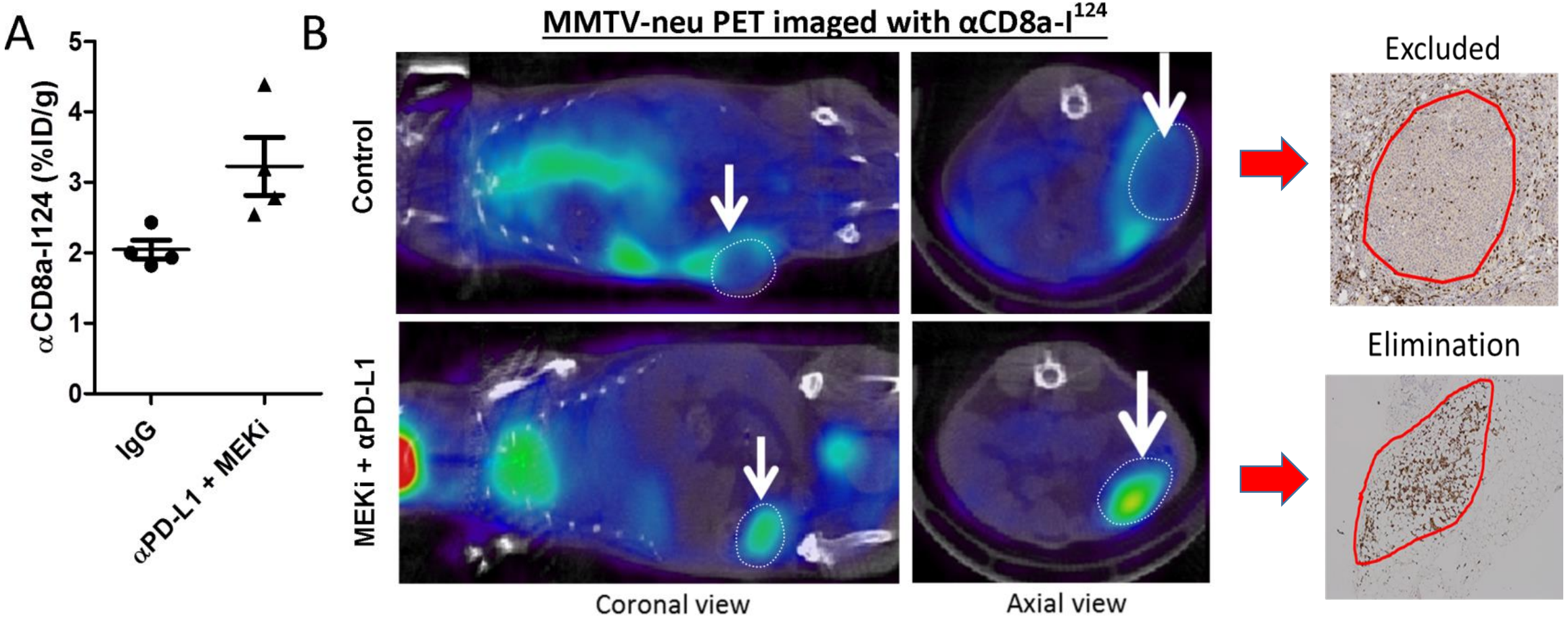




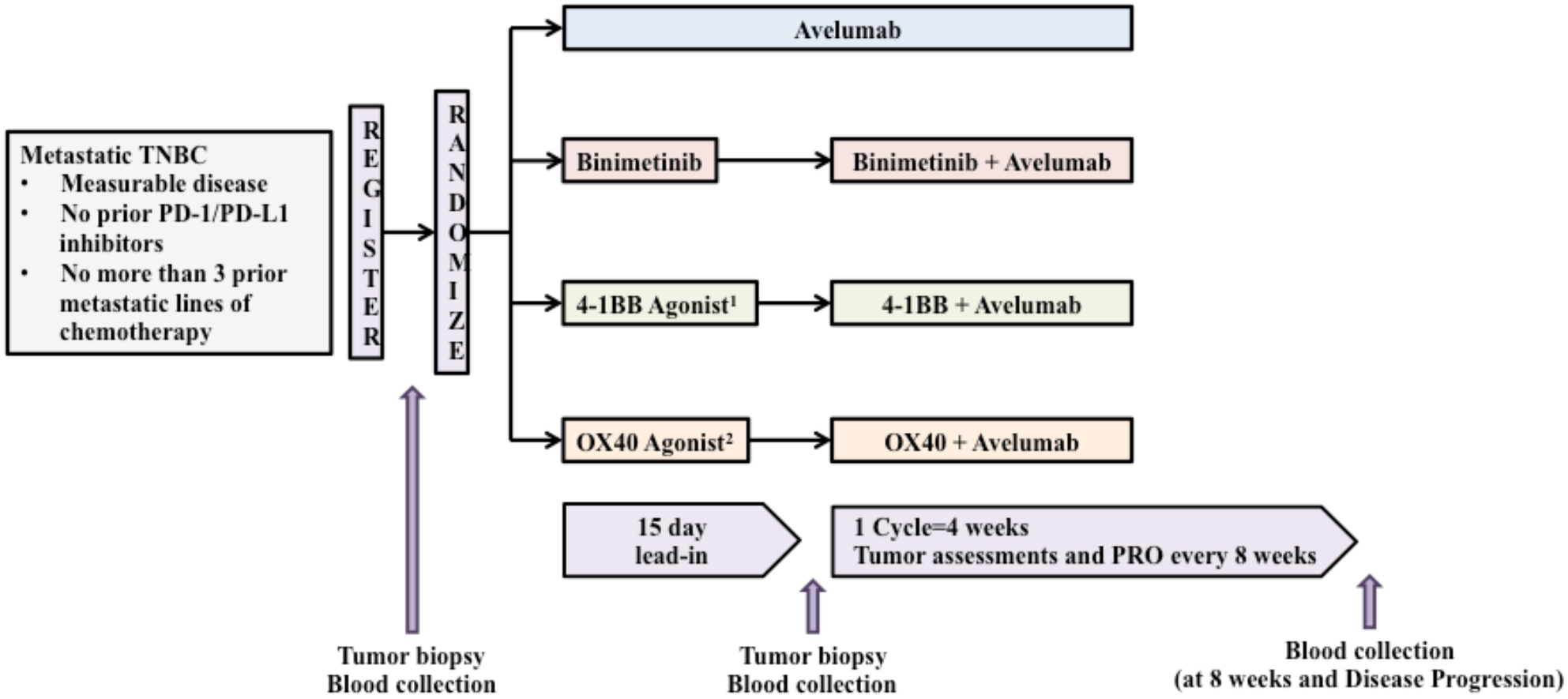
Without MEK activation

With MEK activation

MEKi + anti-PD-L1 potentiates CD8 T cell mediated tumor elimination



InCITe: Innovative Combination Immunotherapy for mTNeBC

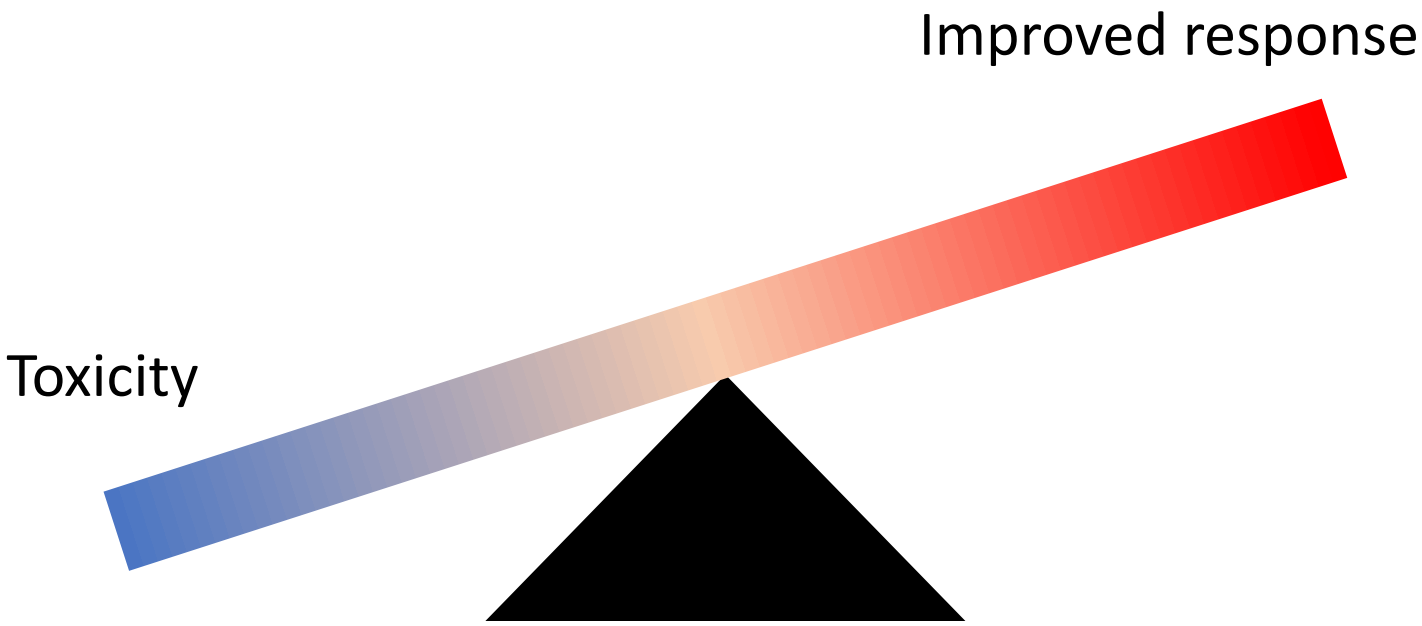


Goga, Liu, Rugo, Perou, Balko, Mayer et al

What are the next steps?

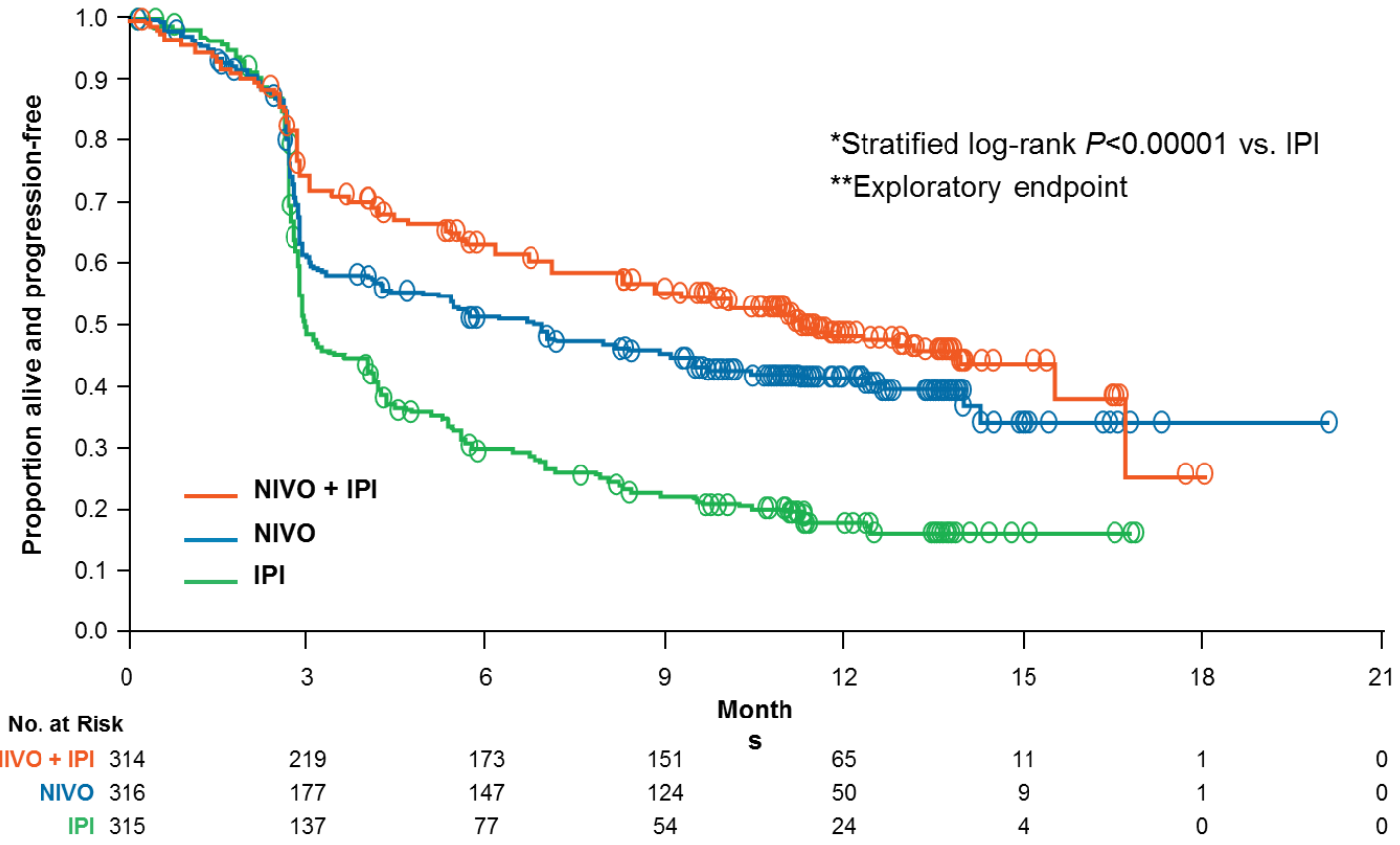
- Managing risk/benefit
  - Predictive markers of toxicity
  - Prioritizing patients for optimal benefit
  - Precision medicine approach

Combination therapy



Personalized ICI therapy in melanoma

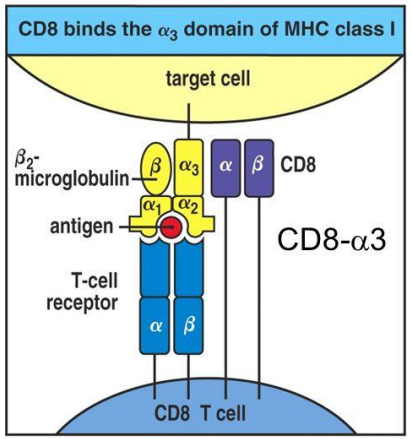
- Goals:
  - Predict responders
  - Prioritize therapy
  - Prioritize combinations
  - Predict and mitigate toxicities
- Current biomarkers:
  - Mutation load (NGS)
  - Inflammation gene signatures (RNAseq/gene panel)
  - PD-L1 (IHC, mixed efficacy)



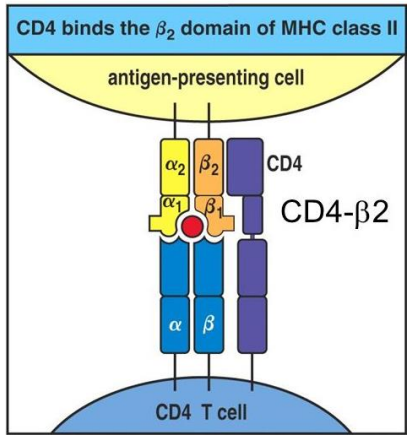
Adapted from Wolchok J, ASCO 2015

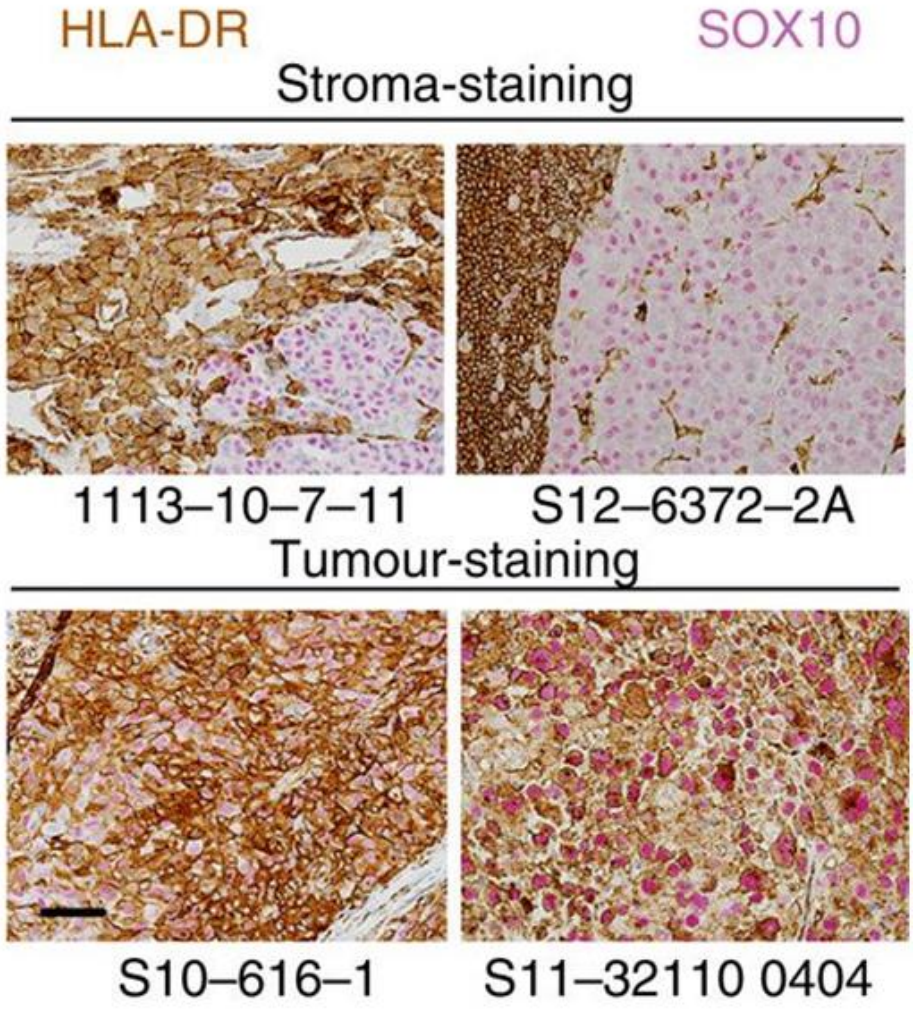
Tumor specific MHC-II as a predictor of anti-PD-1 outcomes

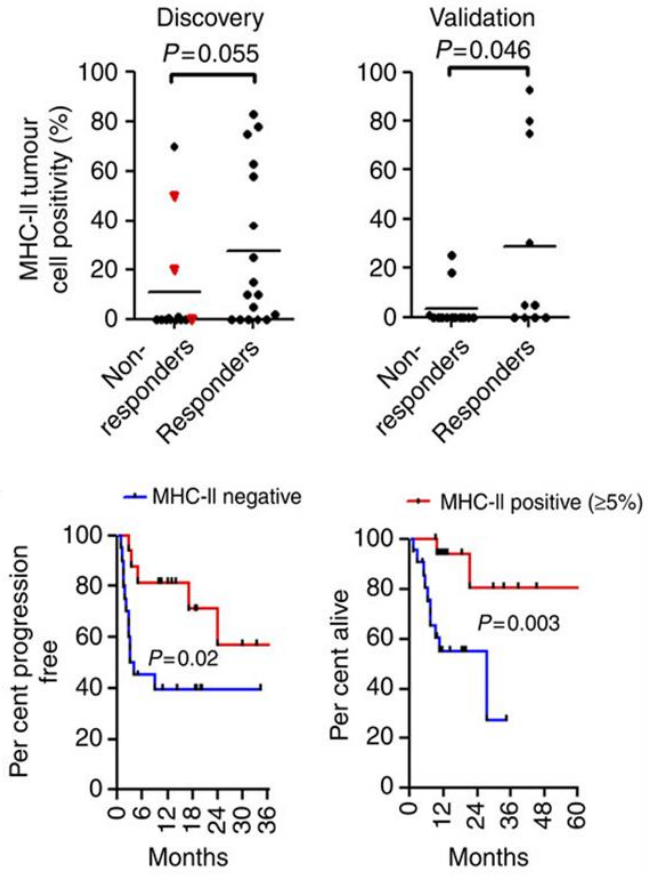
CD8-MHC I



CD4-MHC II





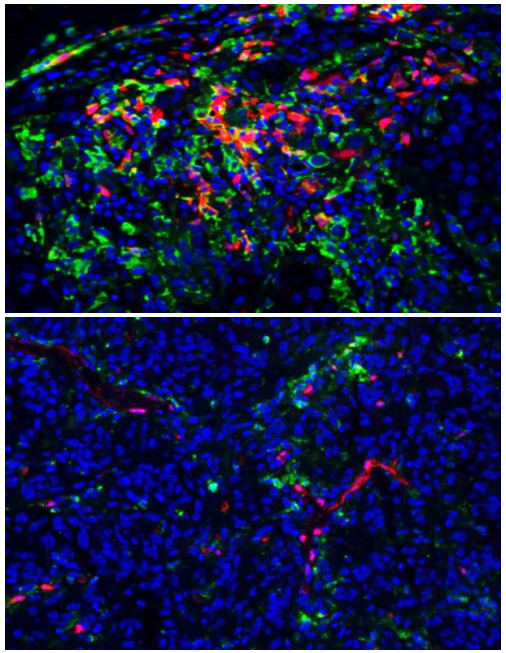


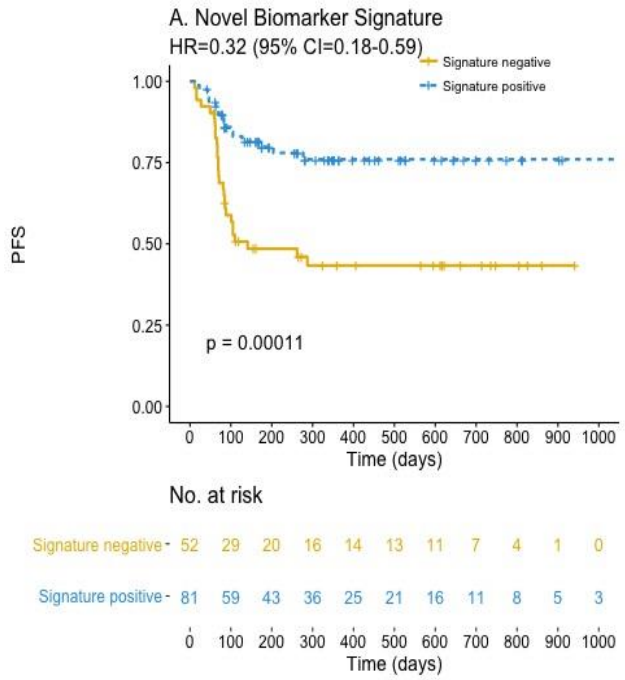
Johnson and Balko, Nature Comm 2016

Tumor specific MHC-II as a predictor of anti-PD-1 outcomes

- MHC-II + PD-1/L1 interaction signature in a series of melanoma patients (n=141)

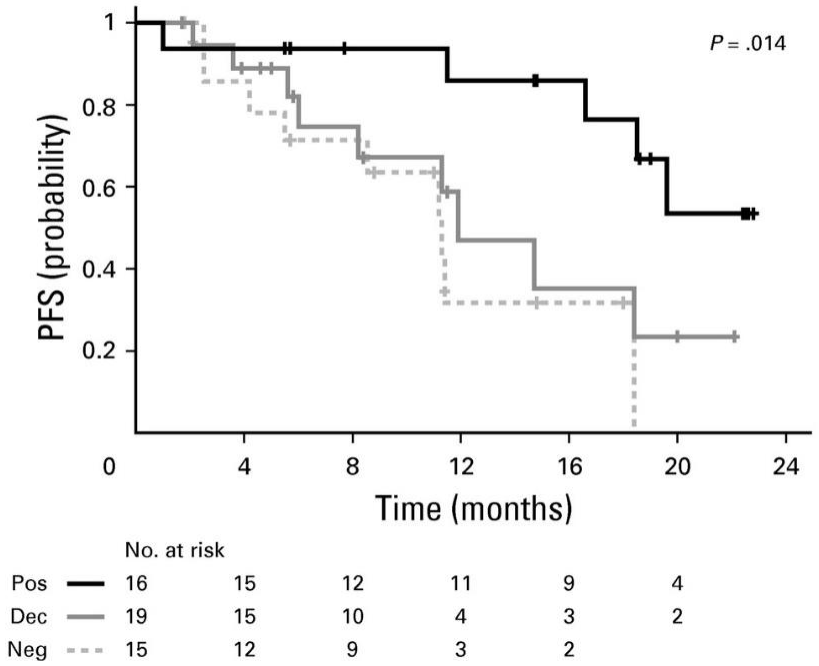
PD-1 PD-L1 DAPI





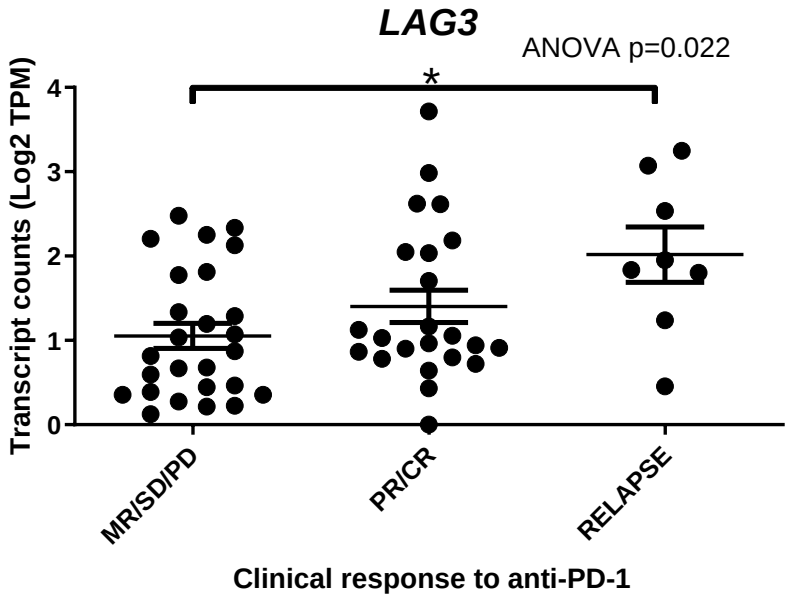
Johnson and Balko et al, CCR, 2018

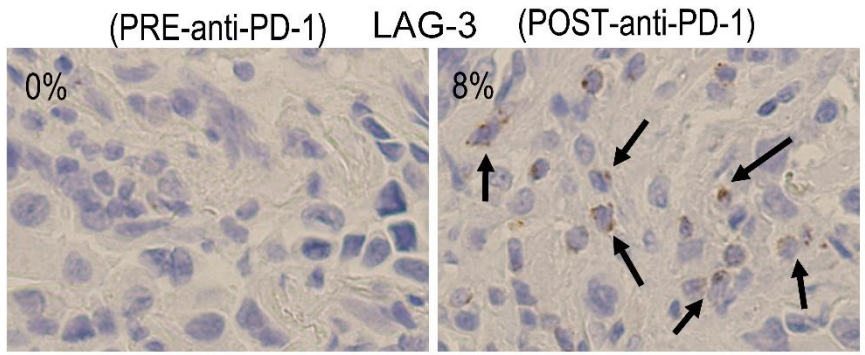
- MHC-II in RS cells of Hodgkin's Lymphoma predicts anti-PD-1 benefit

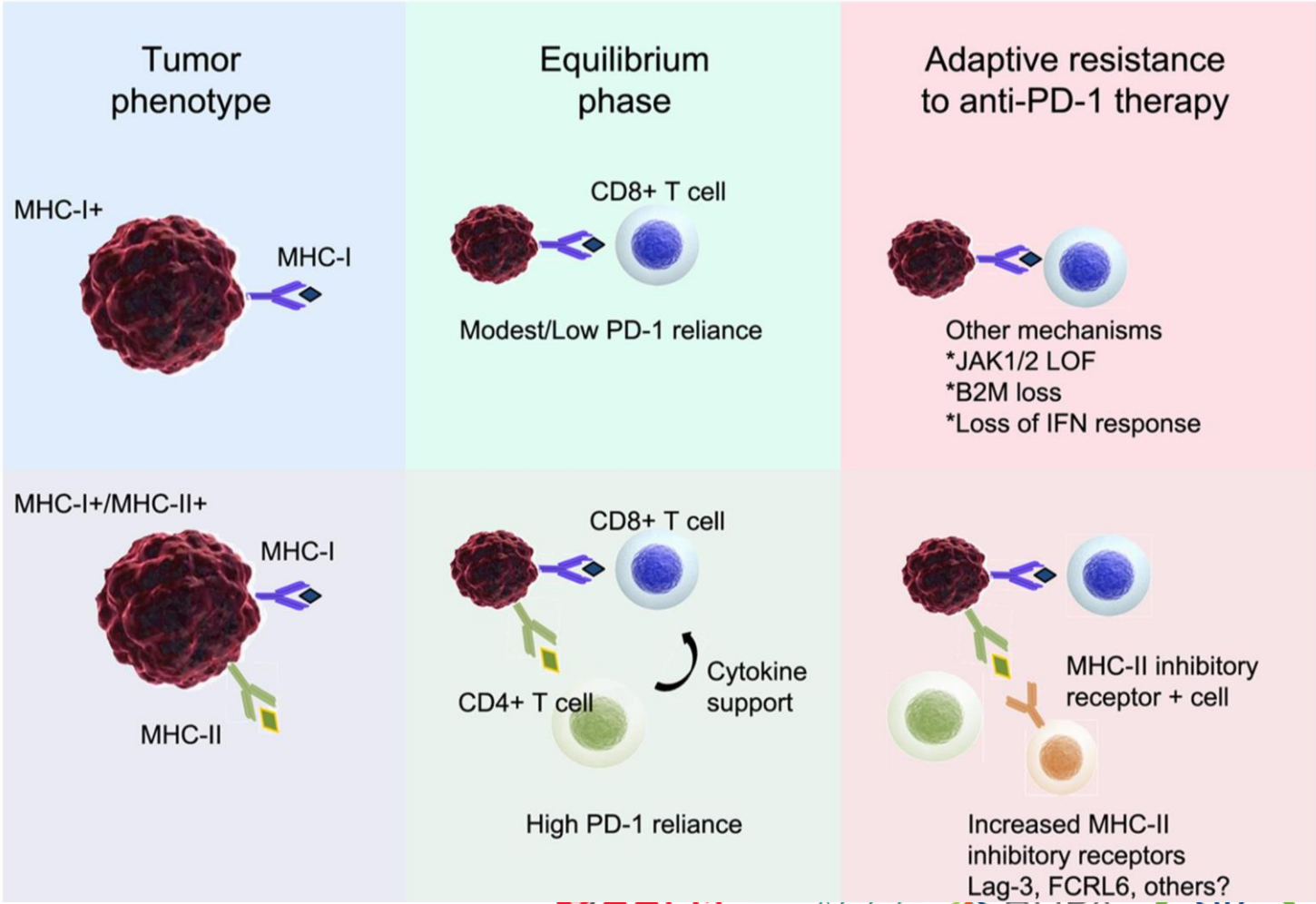


Roemer et al, JCO, 2018

LAG-3: an alternative checkpoint with specificity for MHC-II

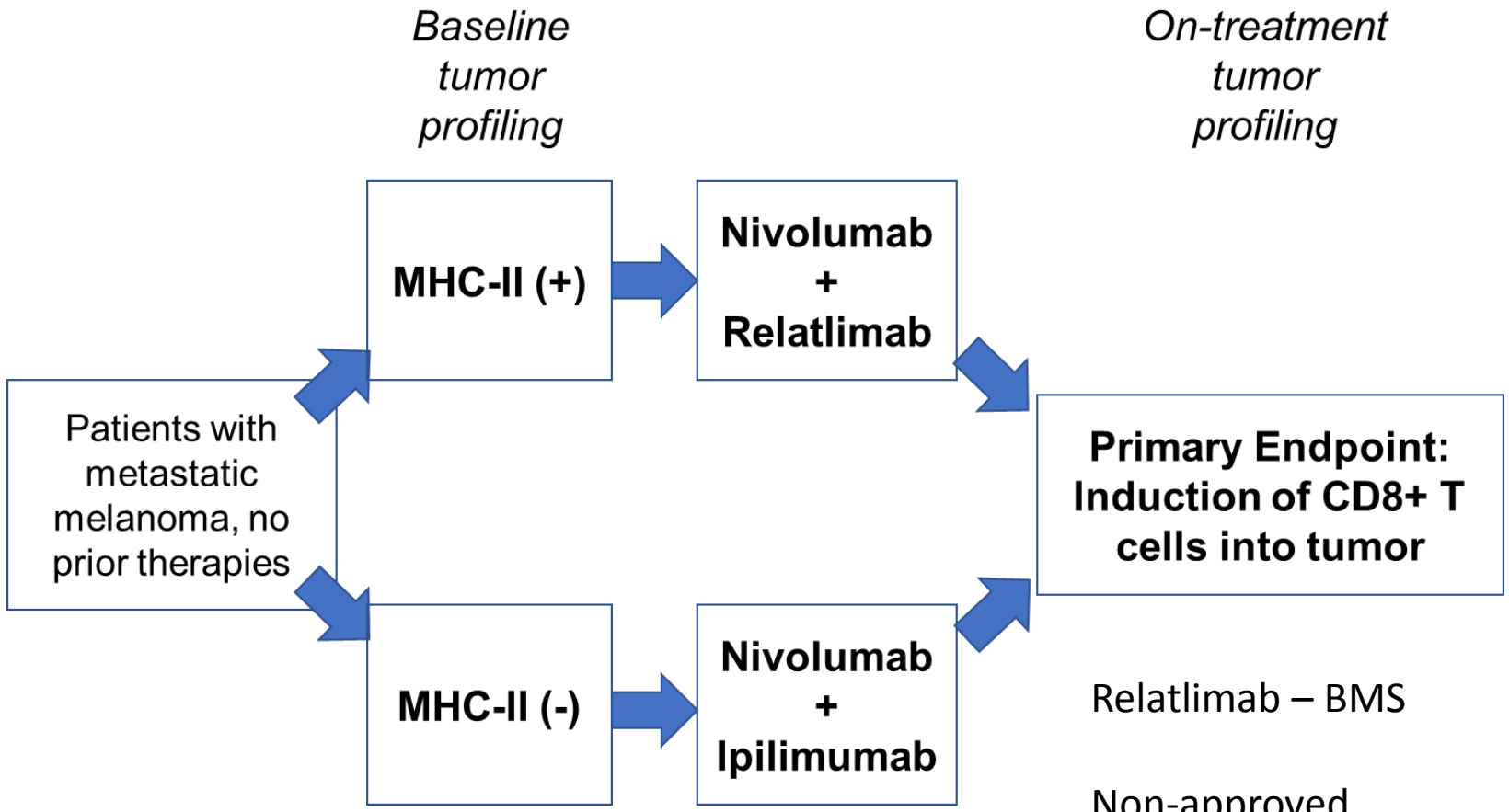






Johnson and Balko, JCI Insight, 2018

A personalized medicine approach for immunotherapy



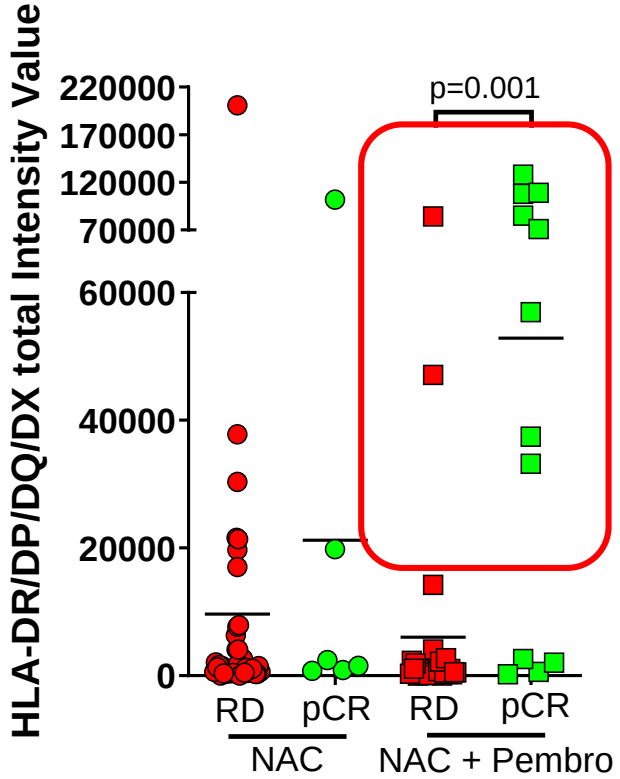
Relatlimab – BMS

Non-approved indication

- Allocate MHC-II+ patients to anti-PD-1+ anti-LAG3
  - High response rate to PD-1
  - Address resistance up front
- Allocate MHC-II- patients to anti-PD-1+ anti-CTLA-4
  - Low response rate to single-agent PD-1
  - Low CD4+ T cells

Tumor-specific MHC-II predicts benefit to anti-PD-1 + NAC in HER2- breast cancer

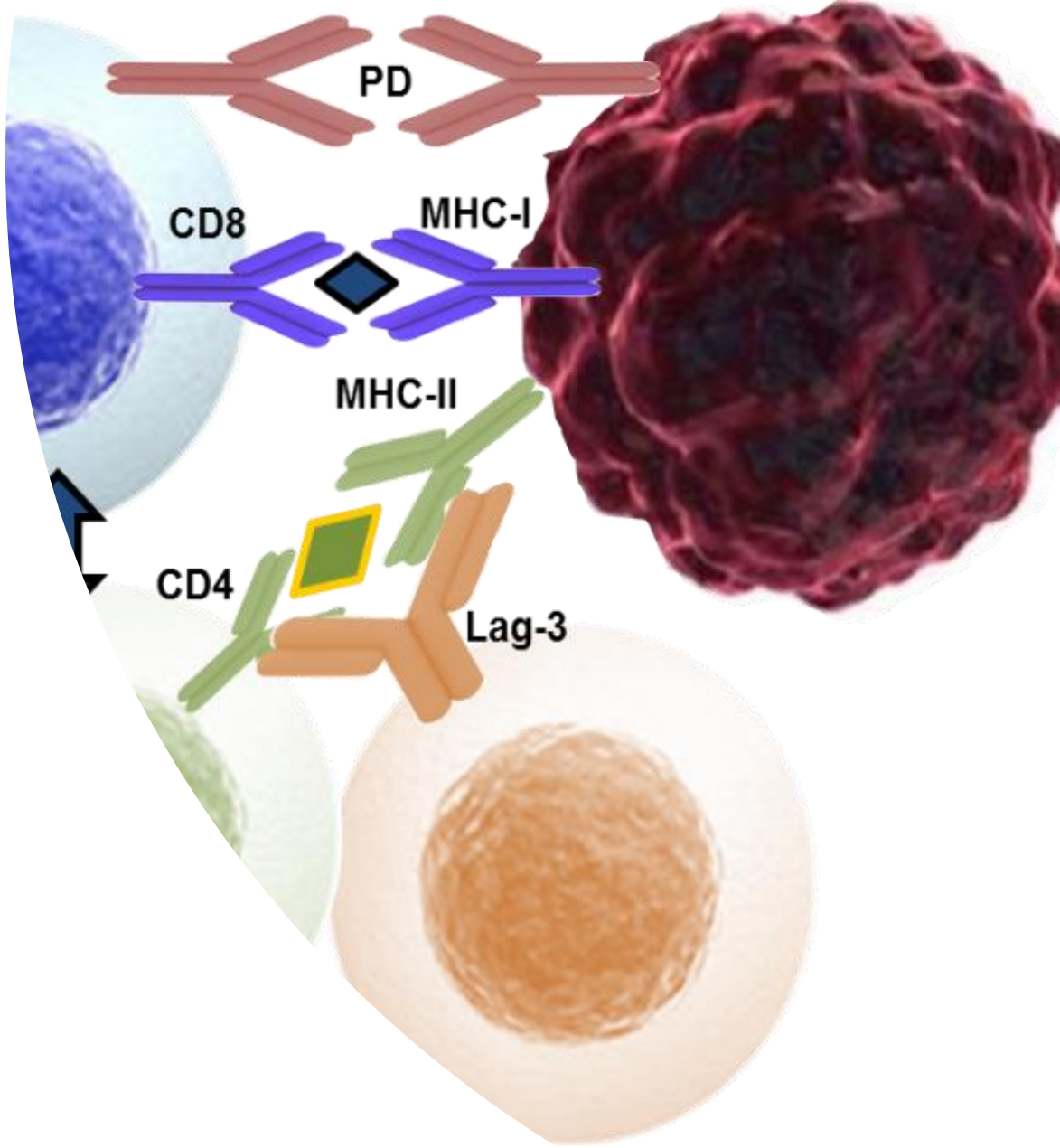
- KEYNOTE-522
  - Anti-PD-1 + NAC will likely be approved in primary TNBC
- I-SPY2 trial arm
  - Investigators identified MHC-II on tumor cells (RPPA) as a powerful biomarker of outcome
    - 8/12 (66%) pCRs had high tsMHC-II
    - 8/10 (80%) high tsMHC-II had pCR
- Can tsMHC-II be a pan-cancer biomarker of anti-PD-1 benefit?



Data courtesy of Emmanuel Petricoin and I-SPY2 team

Conclusions

- The current cost-effectiveness of immunotherapy ***hinges*** on patient selection
- MHC-II- tumors
  - ↑~↓ CD8+ T cells; ↓ CD4+ T cells
  - Better response to anti-CTLA-4 (expansion of tumor reactive CD4 helper cells) with anti-PD-1
- MHC-II+ tumors
  - ↑ CD8+ and ↑ CD4+ T cells
  - Exceptional response rates to anti-PD-1 alone
  - Lag-3 is a possible mechanism of adaptive resistance
- MHC-II may be a pan-cancer biomarker to help precision oncology with immunotherapy
- Efforts to identify risk factors for toxicity (severe irAEs) are underway
  - Managing risk/benefit



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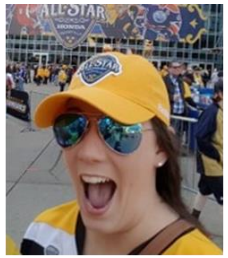
Mellissa Nixon, PhD


Na Luo, PhD

Collaborators

Ingrid Mayer

Sherene Loi

Roberto Salgado

Paula Gonzalez Ericsson

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