



Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Cancer Immunotherapy in Practice

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#LearnACI

Disclosures

- Advisory Board/Consultant: BMS, Jounce, Iovance, Merck, Immunocore, Regeneron, Replimmune, Sanofi, Novartis, Replimmune, Castle Biosciences
- Data Safety Monitoring Committee: Incyte, AstraZeneca
- Stock ownership: Bellicum, Asensus Surgical, Amarin
- Research support (all to institution): BMS, Merck, Celgene, Novartis, GSK, HUYA, Amgen, Regeneron, Replimmune
- I will not be discussing non-FDA approved indications during my presentation.

CANCER DEATHS IN THE UNITED STATES

Cancer death rates
dropped 27% from
2001 to 2020.

27%



cdc.gov/cancer

WHY DID CANCER DEATH RATES CHANGE FROM 2001 TO 2020?

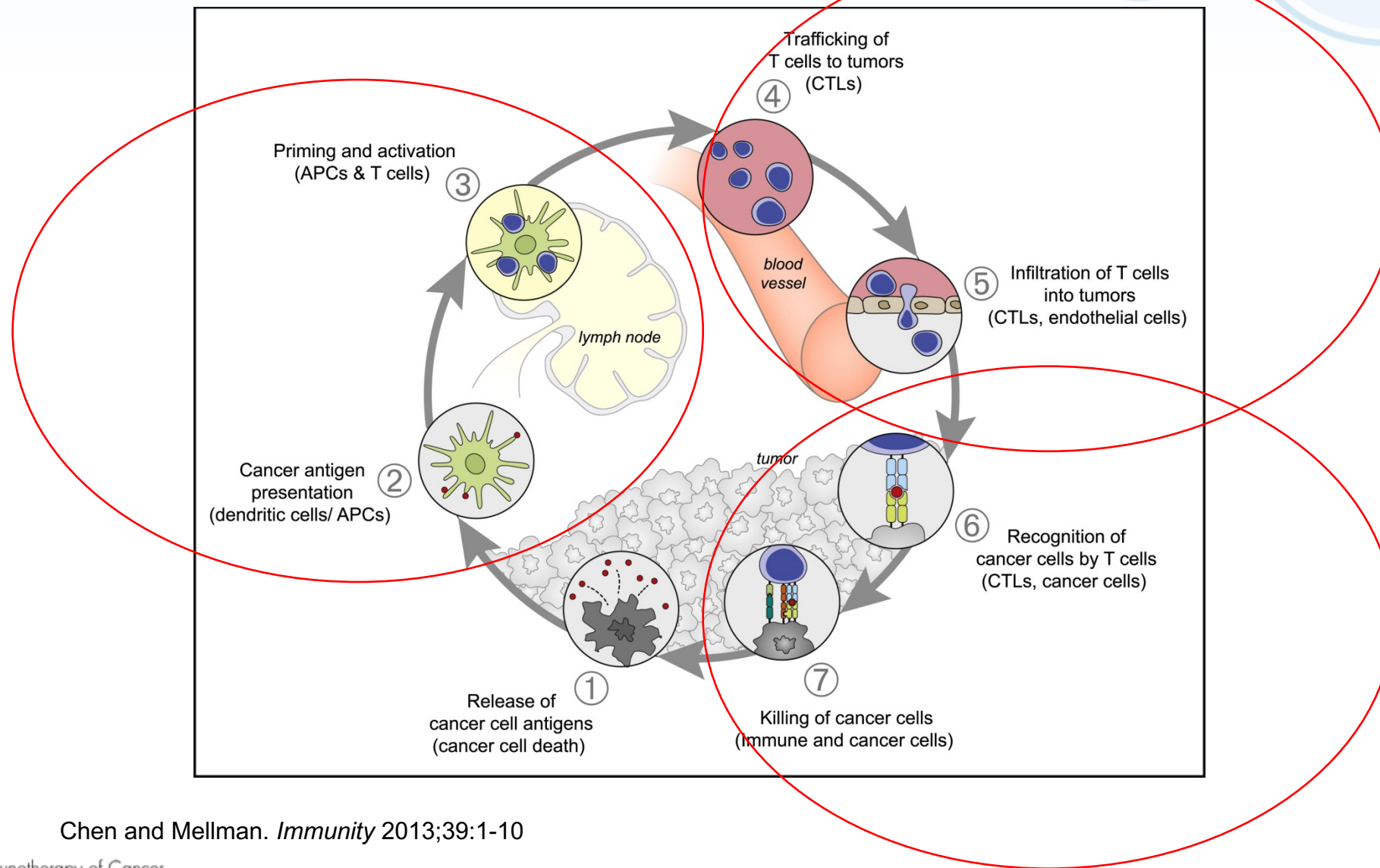
- Educational campaigns to help people quit using tobacco.
- Screening tests that can find cancer early, when treatment is likely to work best.
- Vaccines to prevent viruses that can lead to cancer.
- New cancer treatments and therapies.



cdc.gov/cancer



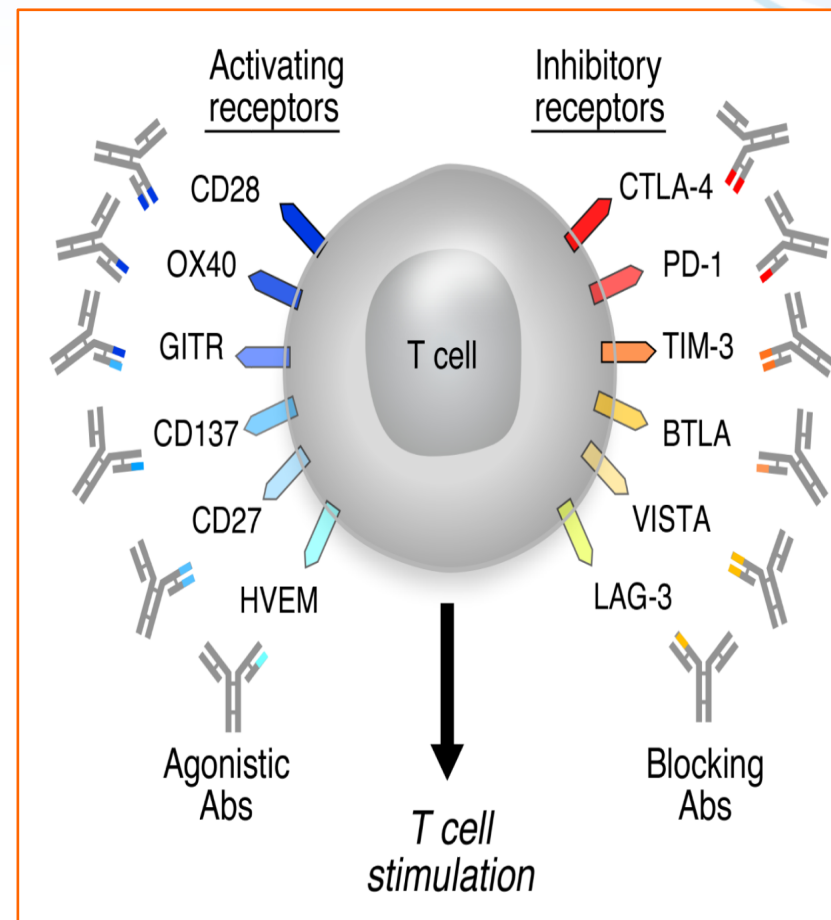
Cancer – Immunity Cycle



T-Cell Targets: A Balancing Act

Treatment by Proxy

- Give a 'new' immune system
 - Allogeneic transplant
 - Adoptive cell therapy (LAK, TIL, CAR-T)
- 'Boost' immune response
 - IL-2, interferon
- **'Block' checkpoints**
 - CTLA4, PD1, LAG3
- *'De novo'* immunization

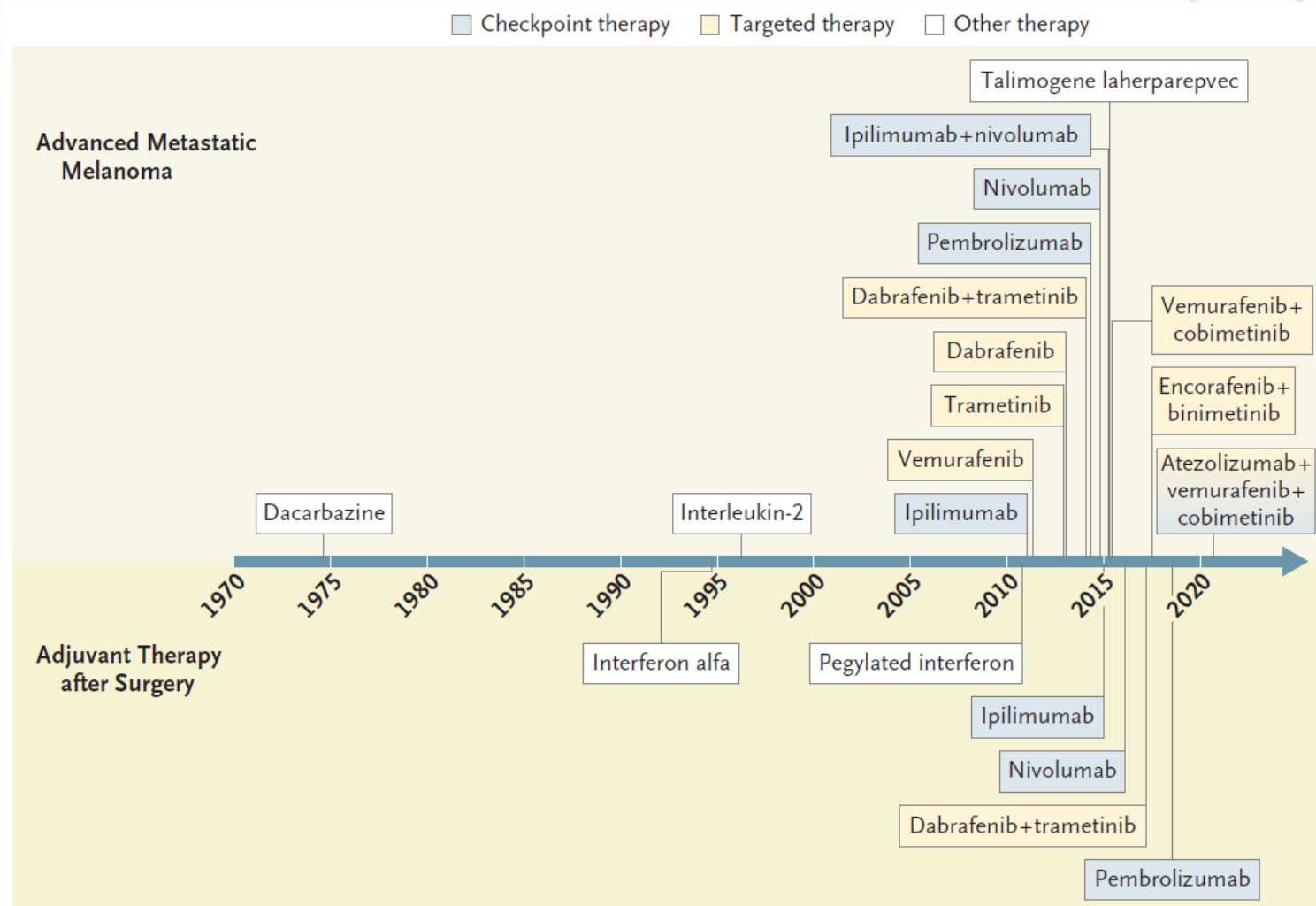


Mellman I, et al. *Nature*. 2011;480:480–489.

Almost ubiquitous use of PD1/PD-L1 AB in 2022

Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab	Avelumab
NSCLC, Melanoma, HCC, RCC, Urothelial, Hodgkin's, MSI-H CRC H/N SCC, Mesothelioma, Esophagus, Gastric/GEJ	Melanoma, NSCLC, HNSCC, Hodgkin's, PMBCL, Gastric, Esophagus, Cervical, Urothelial, MSI-H CRC, Gastric, Esophageal, Cervical, HCC, RCC, TNBC, Endometrial, CSCC, Merkel, TMB-High Cancer. MSI-H Cancer	NSCLC, ES-SCLC, Urothelial, Melanoma, HCC	NSCLC, ES-SCLC	Merkel Urothelial, RCC

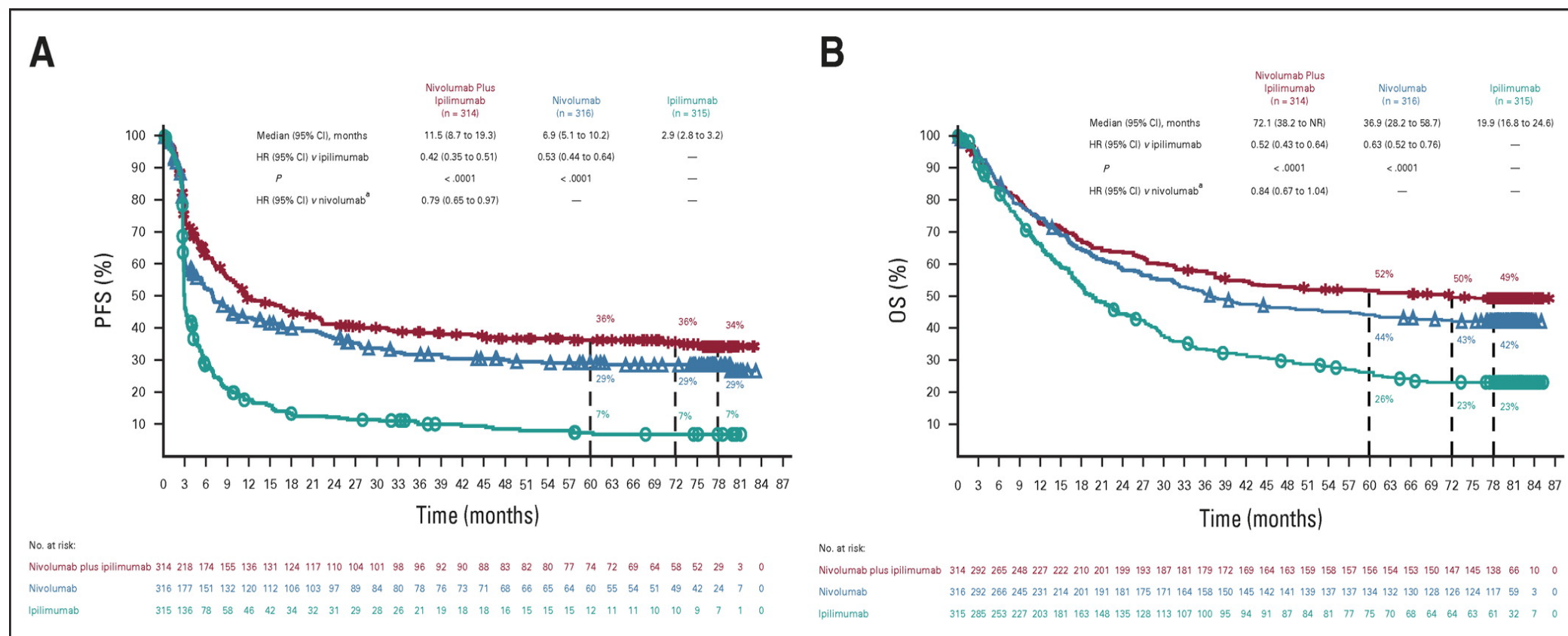
Drug Approvals in Melanoma



Nivolumab +
Relatlimab

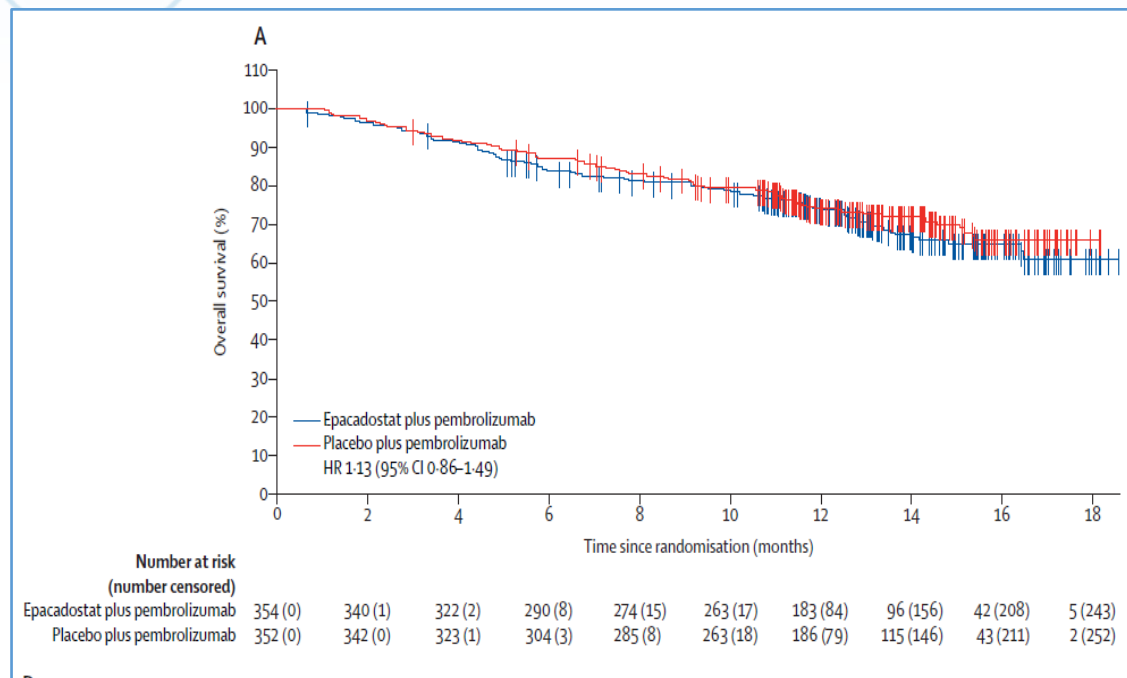
2022

CHECKMATE-067: 6.5-year Survival in Melanoma



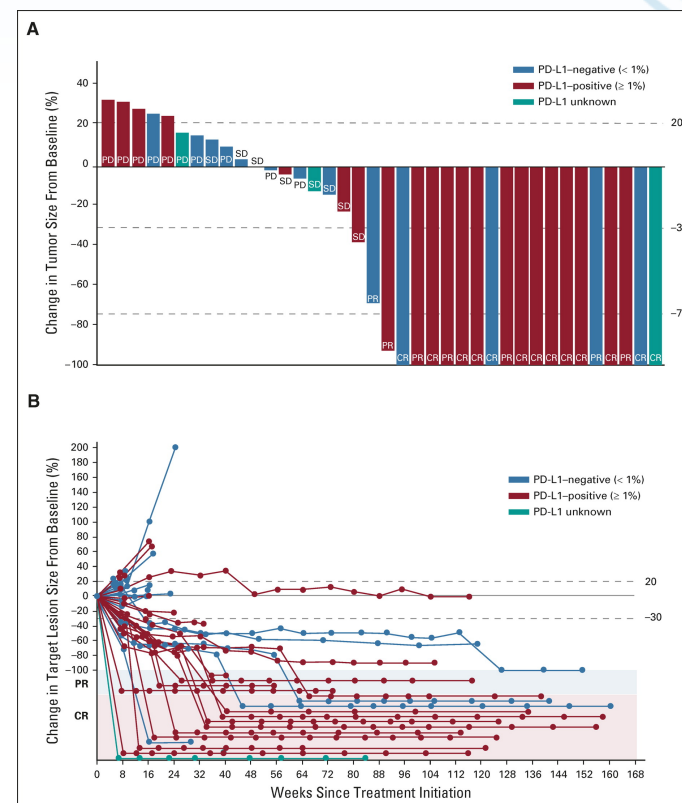
Wolchok et al. *J Clin Oncol* 2022 40:127-137.

But other sobering phase 3 results...



Long et al. *Lancet Oncol* 2019;20:1083.

***Echoes of a failure:
what lessons can we learn?***
Sondak, Khushalani
Lancet Oncol 2019;20:1037

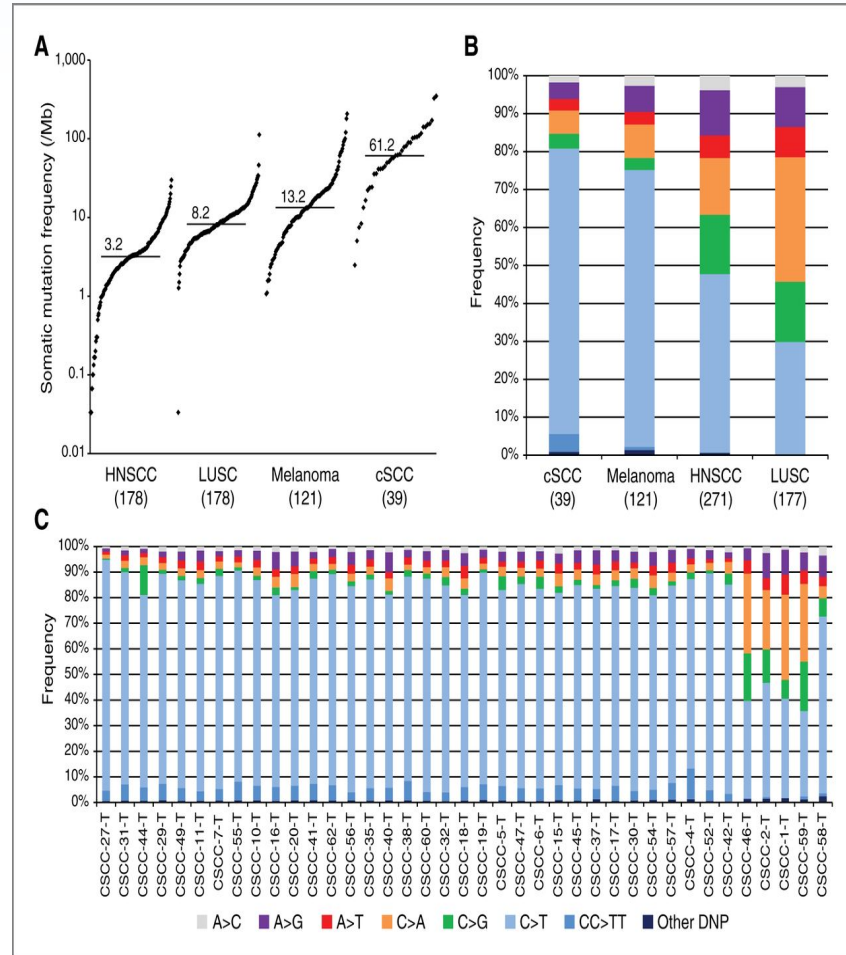


Diab et al. *J Clin Oncol* 2021;39:2914.

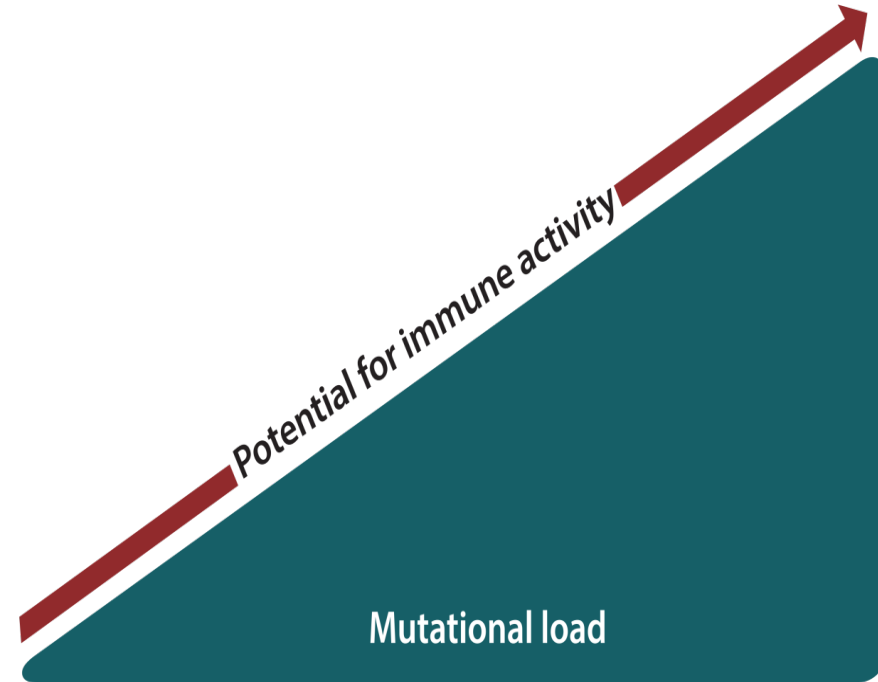
March 14, 2022 – Press Release
Phase 3 PIVOT IO-001

.....study did not meet the primary end-points of progression-free survival and overall response rate by blinded independent central review.....

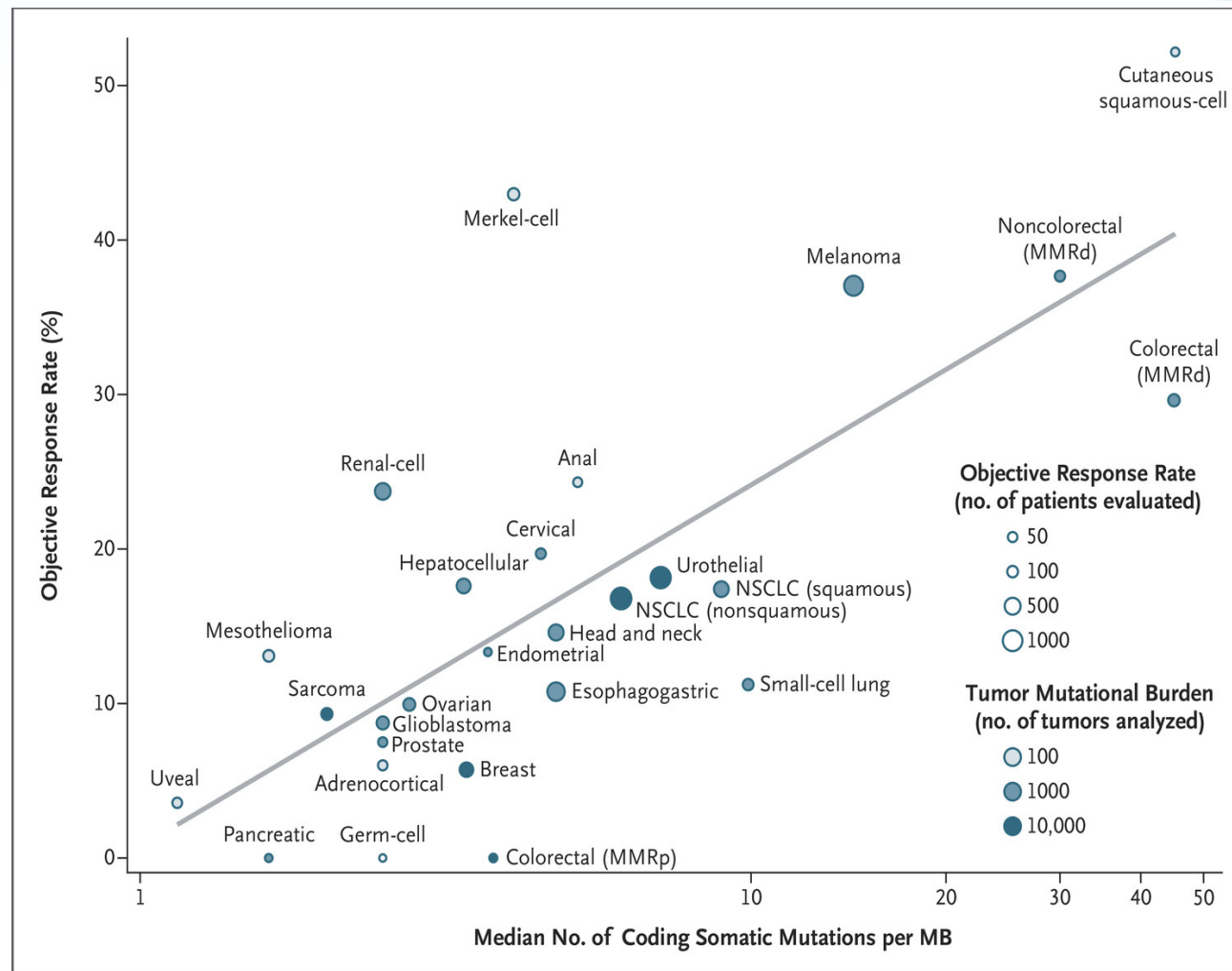
Mutation Frequency in Tumors

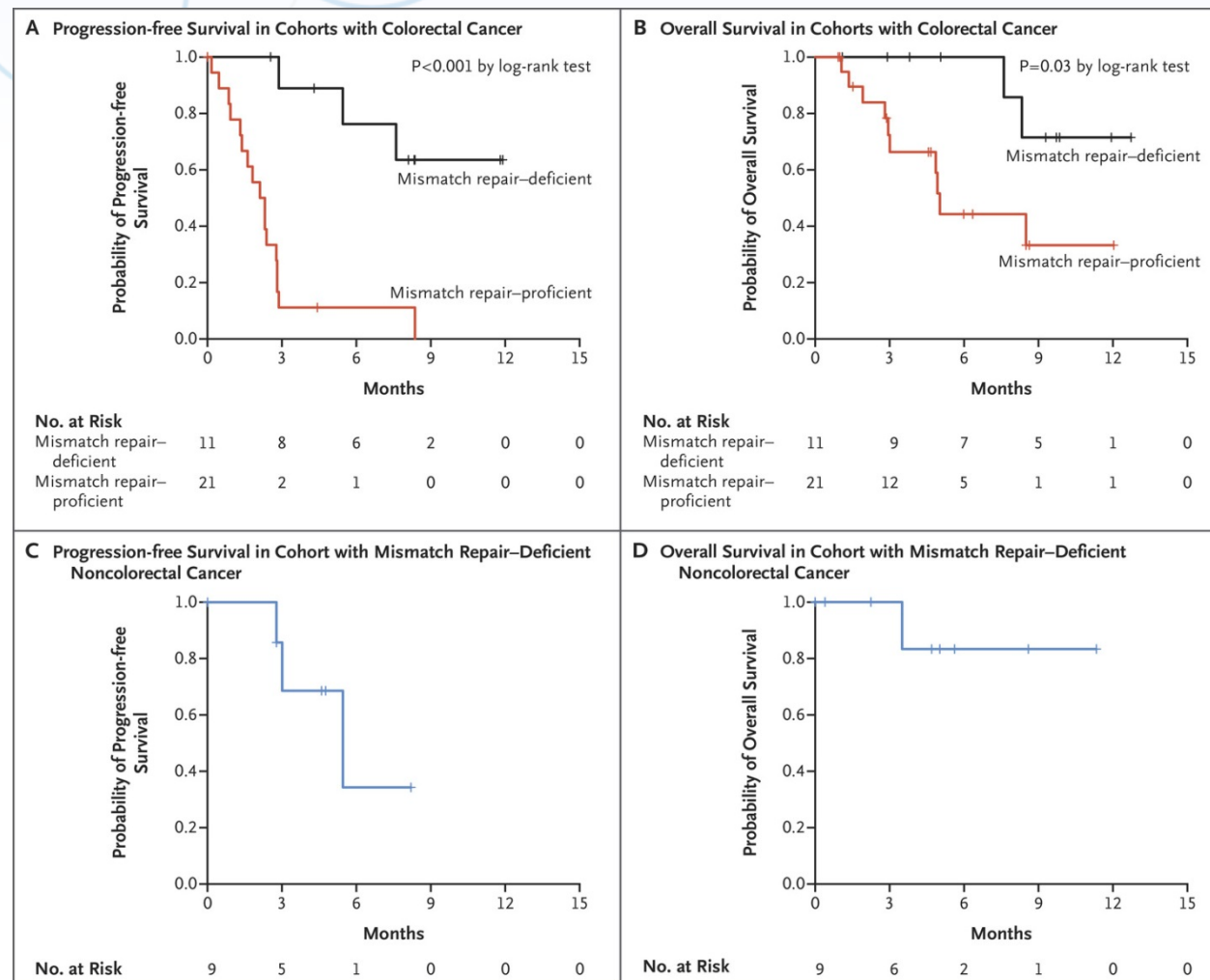


Pickering CR, et al. *Clin Cancer Res.* 2014;20:6582-6592.



TMB and Response to Anti-PD-1/PD-L1 Therapy





- **First tumor agnostic biomarker-based approval (May 23, 2017)**
- **High unmet need**
- **High response rate (40%)**
- **Established safety profile**
- **Extended to pediatric solid tumors**
- **No companion diagnostic to identify MSH-H or dMMR cancers**

Le DT et al. *N Engl J Med* 2015;372:2509-2520.

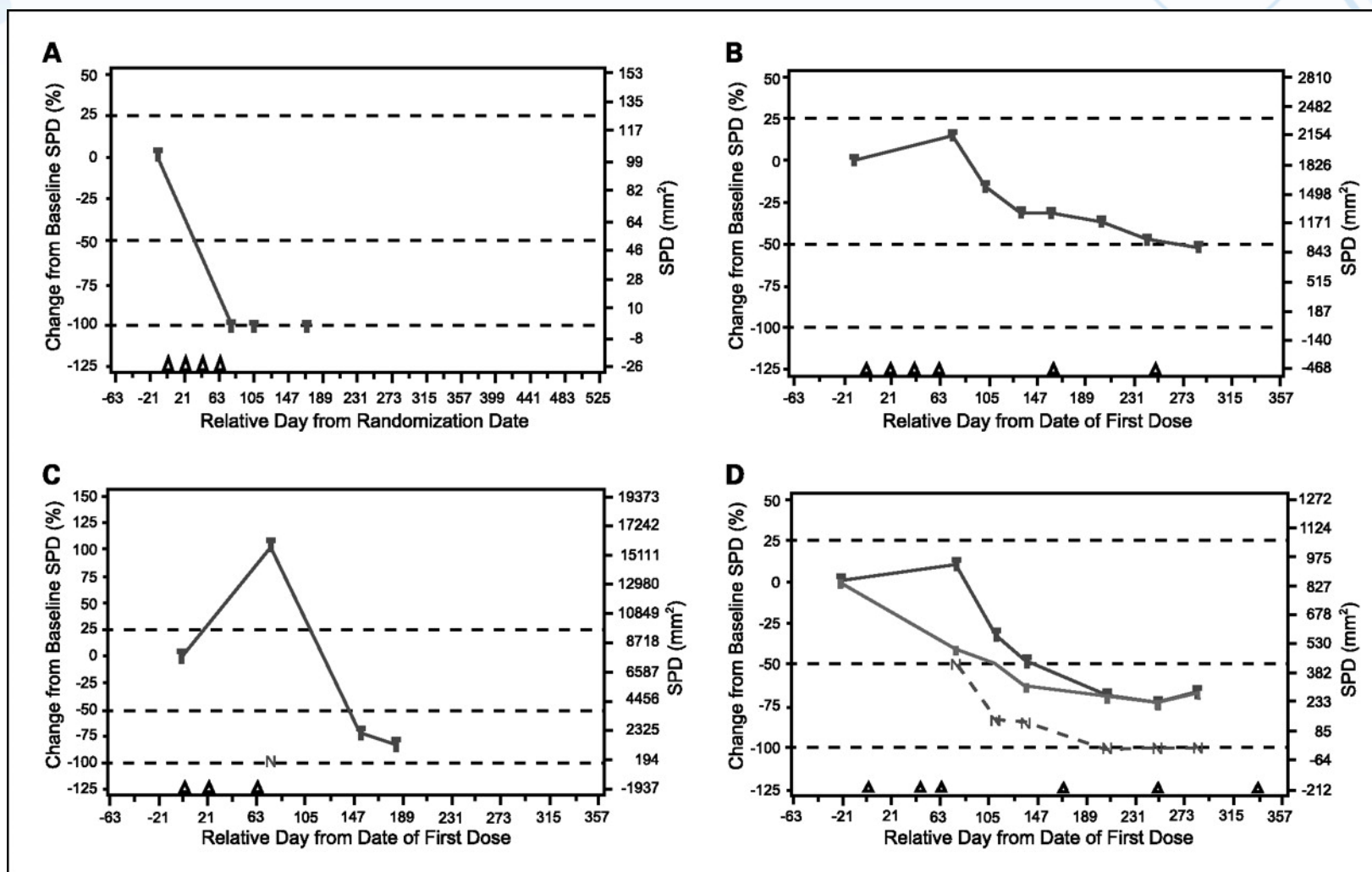
Tips for the Team (I call this *ETA*)

- **E**valuate co-morbidities and potential contra-indications to immune checkpoint inhibition
 - Age is NOT a contra-indication, but tolerance of toxicity needs attention
- **T**hink about goals and duration of treatment
 - Is this predicated on depth of response in a given tumor type?
- **A**nticipate toxicities
 - Almost all toxicity is immune in nature
 - Provider and patient education and communication is key to early recognition and treatment
 - Infusion reactions are uncommon

General Principles of AE Management

- Treat early and treat aggressively
- ≥ grade 3 toxicity
 - Steroids, including intravenous if necessary
 - Slow taper over 4-6 weeks
 - **Interrupt checkpoint inhibitor dosing (This is important!)**
 - Add infliximab if toxicity does not improve within 3-7 days (for hepatitis, use mycophenolate)
- Steroid use not believed to hamper therapeutic effect

Be patient yourself: Patterns of response to ipilimumab



Wolchok JD et al. *Clin Cancer Res* 2009;15:7412-7420



“Not everything that matters can be measured, and not everything that is measured matters”

Albert Einstein

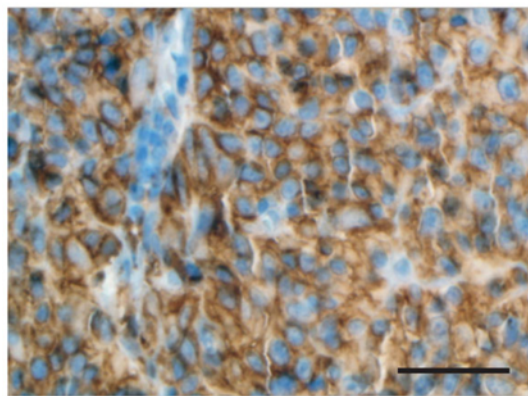
The Need for Biomarkers

- Response to anti-PD1 therapy is not universal
 - Melanoma (40%), NSCLC (20%), RCC (22%)
- Adverse events to IO can range from mild to severe, yet do not necessarily correlate with response
- High drug costs

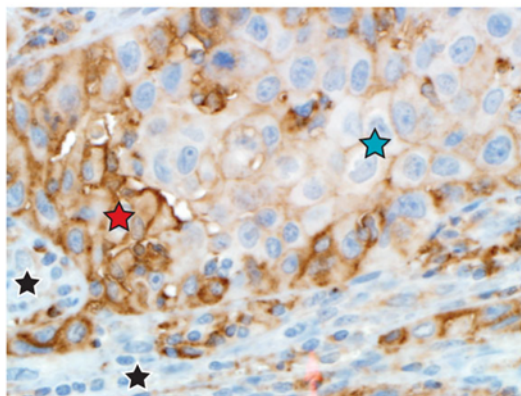
Giving an (expensive) IO drug to a patient who develops severe toxicity, and fails to respond – failure on all fronts

PD-L1 Expression and Response in Different Cancers

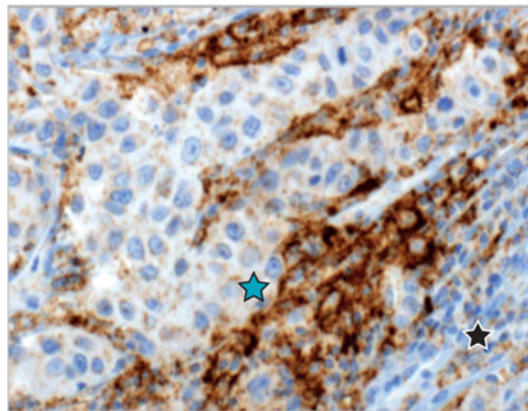
Melanoma



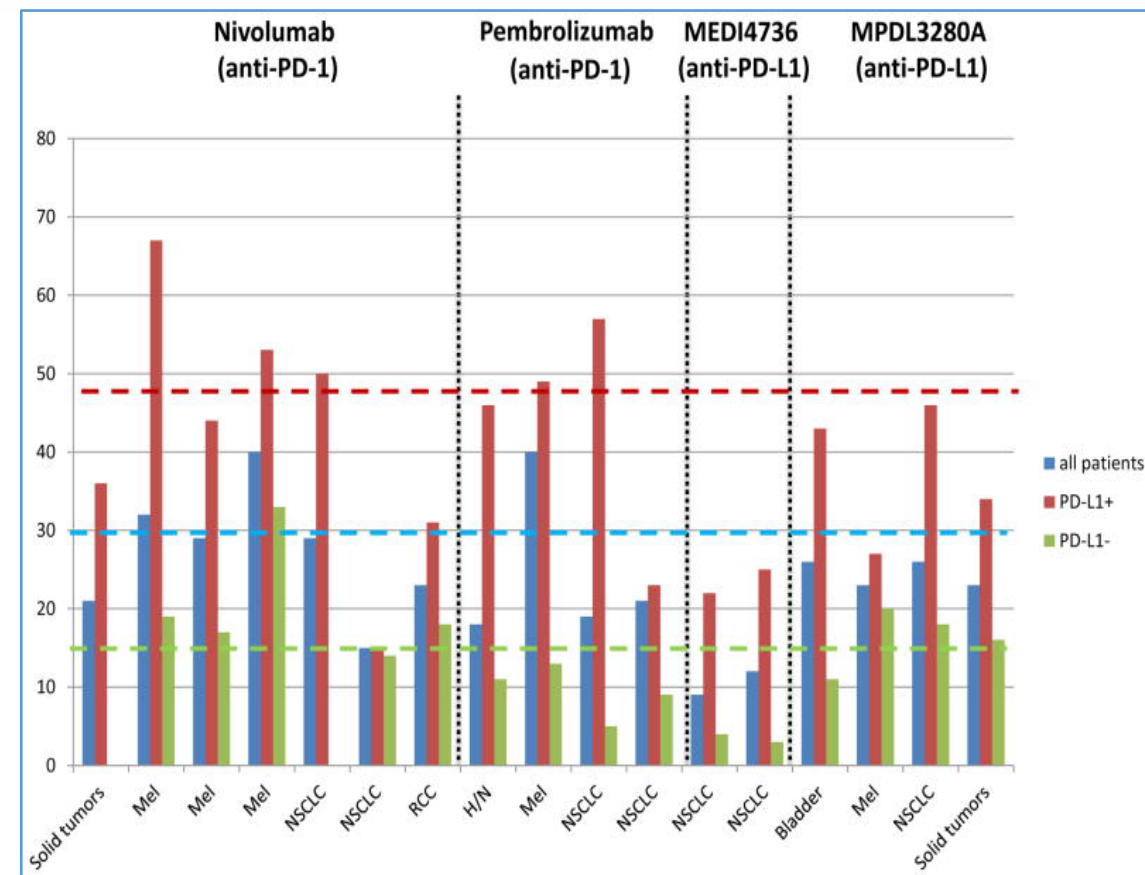
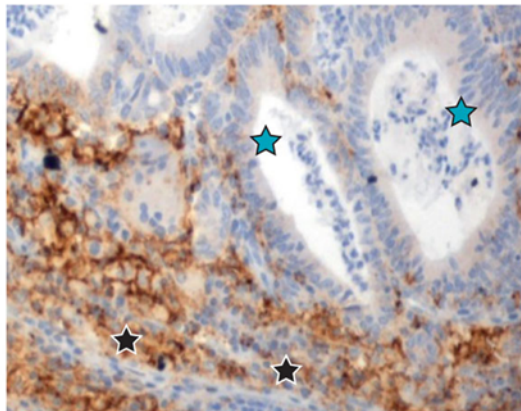
SCCHN



Breast carcinoma



Gastric carcinoma



Topalian et al. *Nat Reviews Cancer*. 2016;16:275

Sunshine J et al. *Curr Opin Pharmacol*. 2015;23:32

Nature Reviews | Cancer

Multi-disciplinary Care



Summary

- Immune checkpoint inhibitor therapy has transformed the landscape of cancer management
- Immunotherapy can be potentially curative in some cancers, yet not all will benefit
- Toxicity management requires anticipation and intervention, sometimes with long term needs
- Biomarker discovery and validation is paramount to realize the goal of 'precision medicine'