Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

What's Next for Cancer Immunotherapy?

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Sidney Kimmel Cancer Center
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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

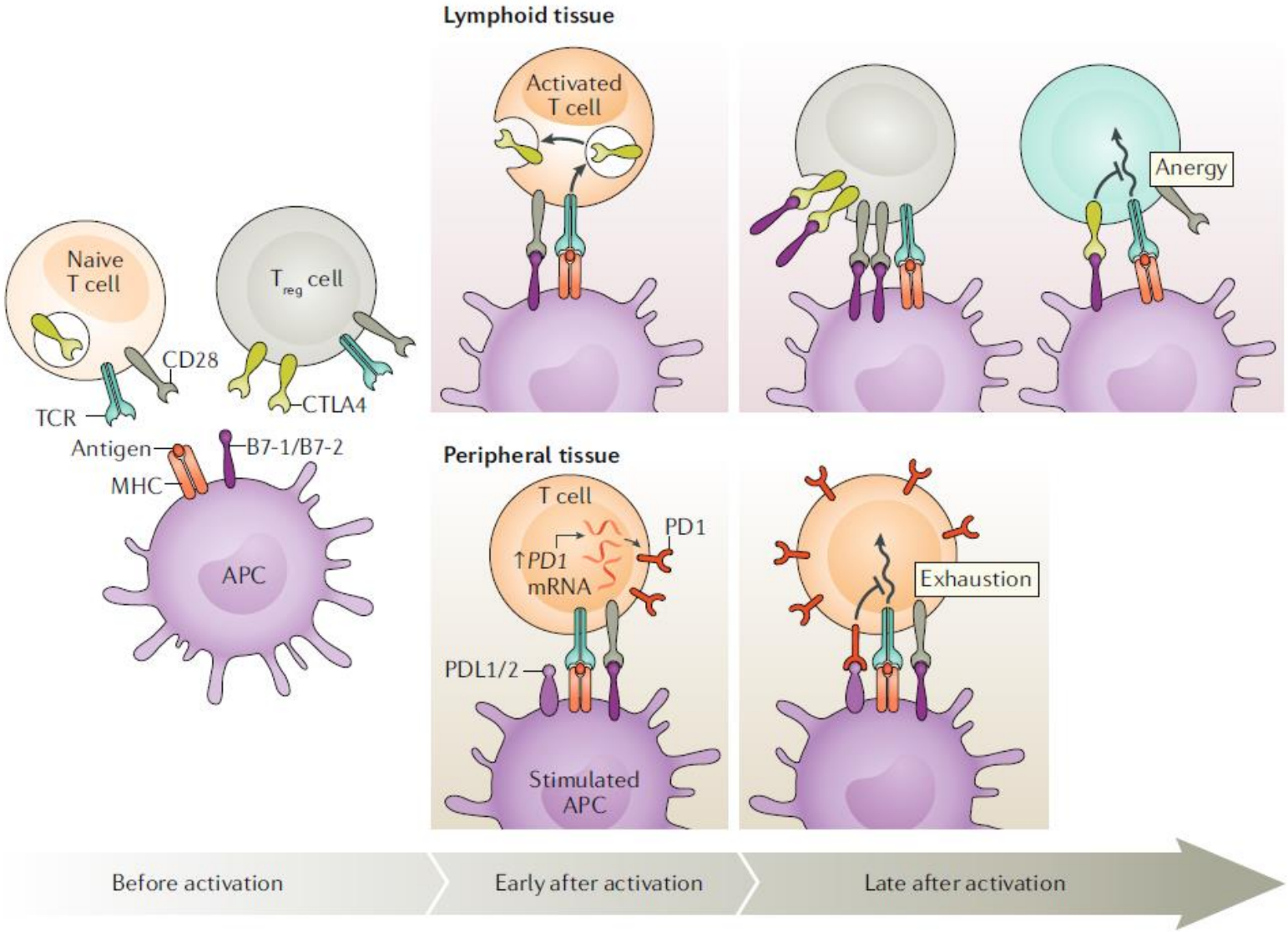
HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

Disclosures

- None

What we have learned: The “two-signal” model



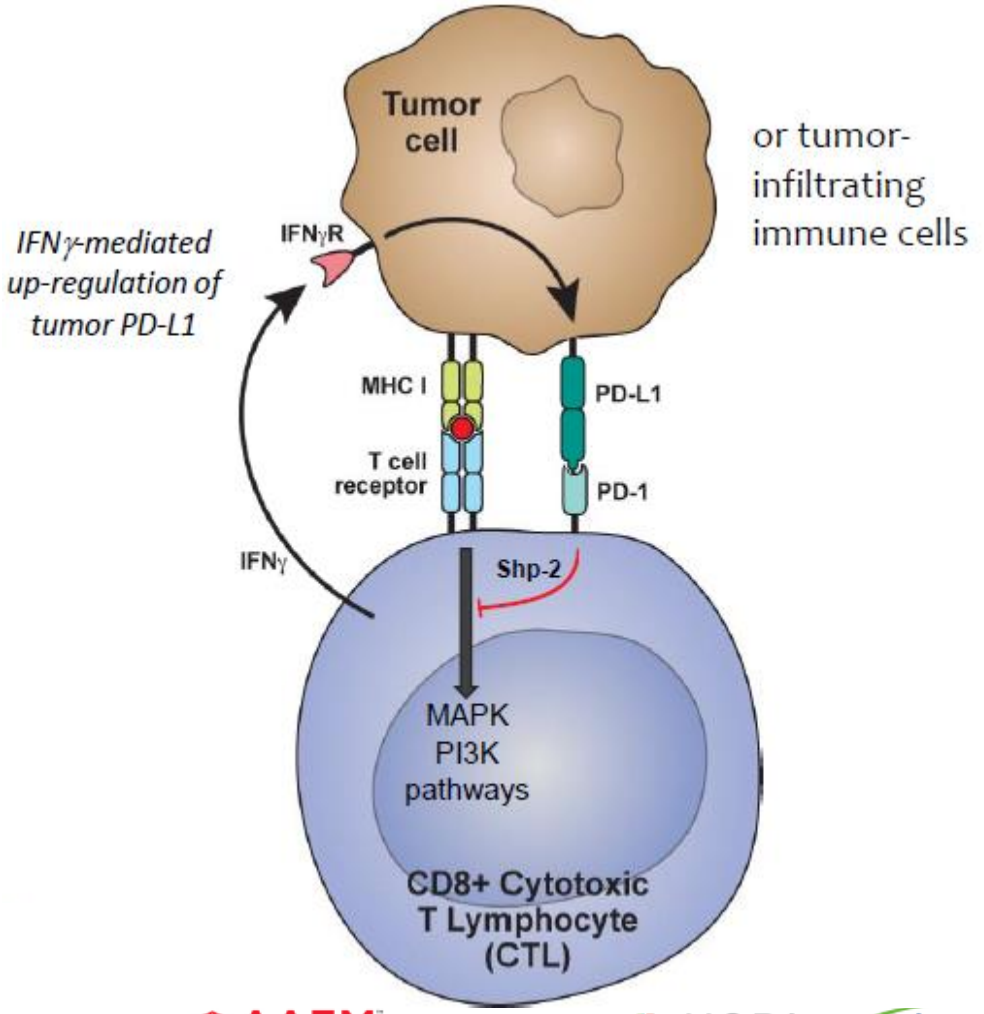
Waldman et al., Nature Reviews Immunology 2020

Blocking the PD-L1/PD-1 axis restores or prevents loss of T cell activity

- PD-L1/PD-1 interaction inhibits T cell activation, attenuates effector function

- Tumors & surrounding cells upregulate PD-L1 in response to T cell activity

- **Blocking PD-L1/PD-1 restores or prevents loss of T effector function**



T Cell Therapy: From Development to Approval

1987 — Development of first CAR-T (Gross et al, PNAS 1989)

1992 — Discovery of CTLA-4 (Brunet et al, Nature 1987)

1992 — Discovery of PD-1 (Ishida et al, EMBO 1992)

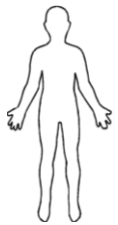
1996 — Anti-CTLA-4 leads to tumor rejection in mice (Leach et al, Science 1996)

2000 — Discovery of PD-L1/PD-L2 (Freeman et al, JEM 2000; Latchman et al, Nat Immunol 2001)

2002 — Preclinical Testing of CAR-T cells (Brentjens et al, Science Nature Medicine 2003)

2003 — Blockade of PD-1/PD-L-1 leads to anti-tumor response in mice (Brunet et al, Nature 2002)

2003 — 1st human trial and response with anti-CTLA-4 (melanoma) (Hodi et al, PNAS 2003)



2011 — **1st FDA approval Ipilimumab** for unresectable and stage IV melanoma

2012 — 1st human trial and response with anti-PD-1 (Brahmer et al, NEJM 2012)

2014 — **FDA approval Nivolumab and Pembrolizumab (anti-PD-1)** for unresectable and stage IV melanoma (2nd line)

2017 — **1st FDA approval for CAR-T** for pediatric B cell ALL

2018 — FDA approval for adult relapsed or refractory lymphoma

2015 to Present: Over 40 FDA approvals for anti-PD-1, PD-L1, CTLA-4 antibodies in multiple tumor types (melanoma, non-small cell lung cancer, small cell lung cancer, gastric, microsatellite-instability solid tumors, merkel cell carcinoma, head and neck, bladder, renal cell, cervical, triple negative breast cancer)

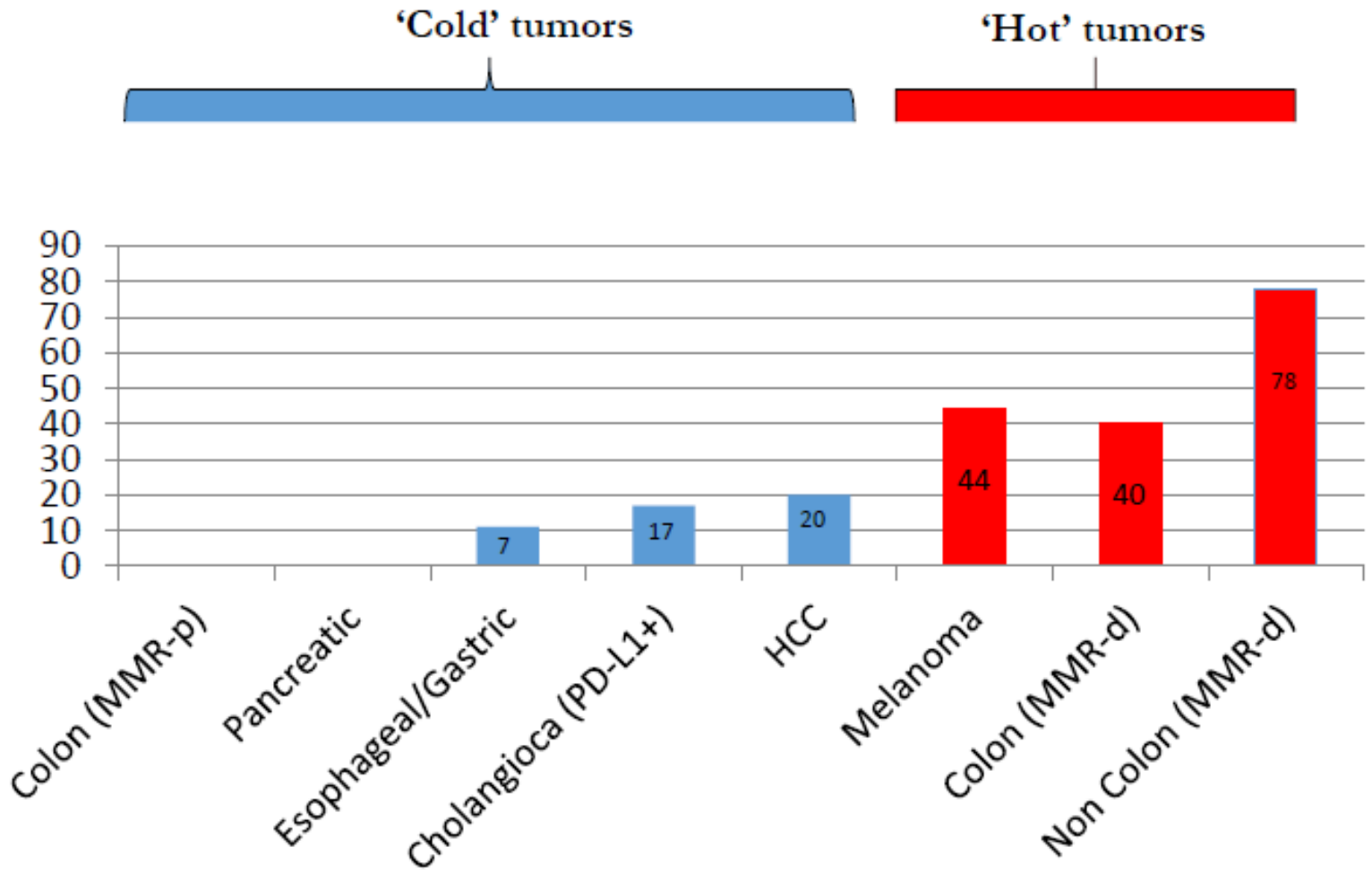
Preclinical Development

Clinical Development

FDA Approval

Modified from Zaidi N.

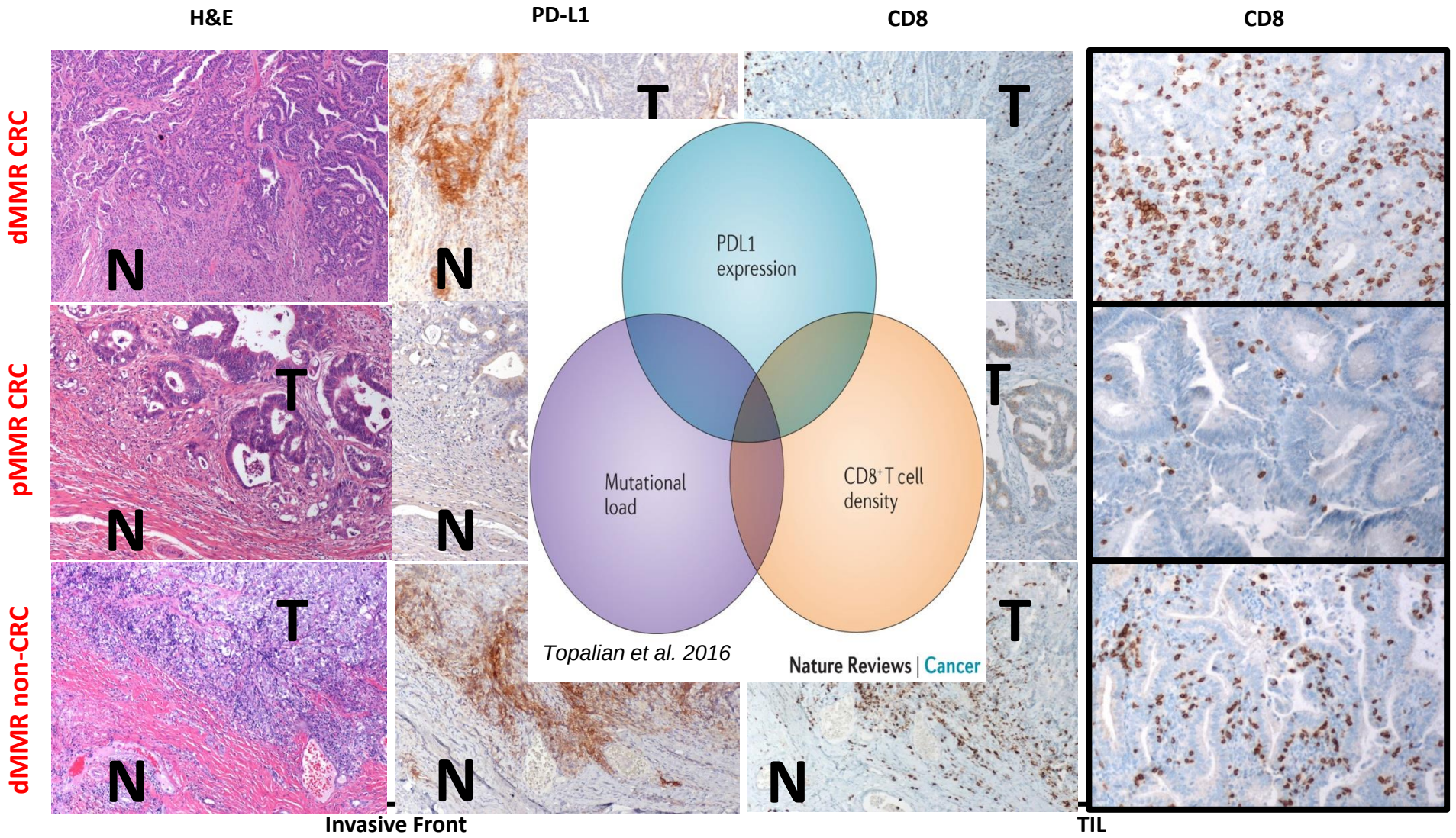
Low Response Rate to Single Agent Anti-PD-1



Cancer Immunotherapy: what is next?

- **Identify (and enrich) patients** most likely to respond to αPD-L1/PD-1
- Identify combinations that extend the depth and breadth of response to αPD-L1/PD-1
- Investigate new targets to overcome immunosuppression and enhance T cell expansion

Diagnostic biomarkers to enrich responders to PD-L1/PD-1



Courtesy of Dr Laheru and Dr Anders

Diagnostic biomarkers to enrich responders to PD-L1/PD-1

Tumor Mutational Burden (TMB) correlates with response to checkpoint inhibitors

Increased mutational burden

↓

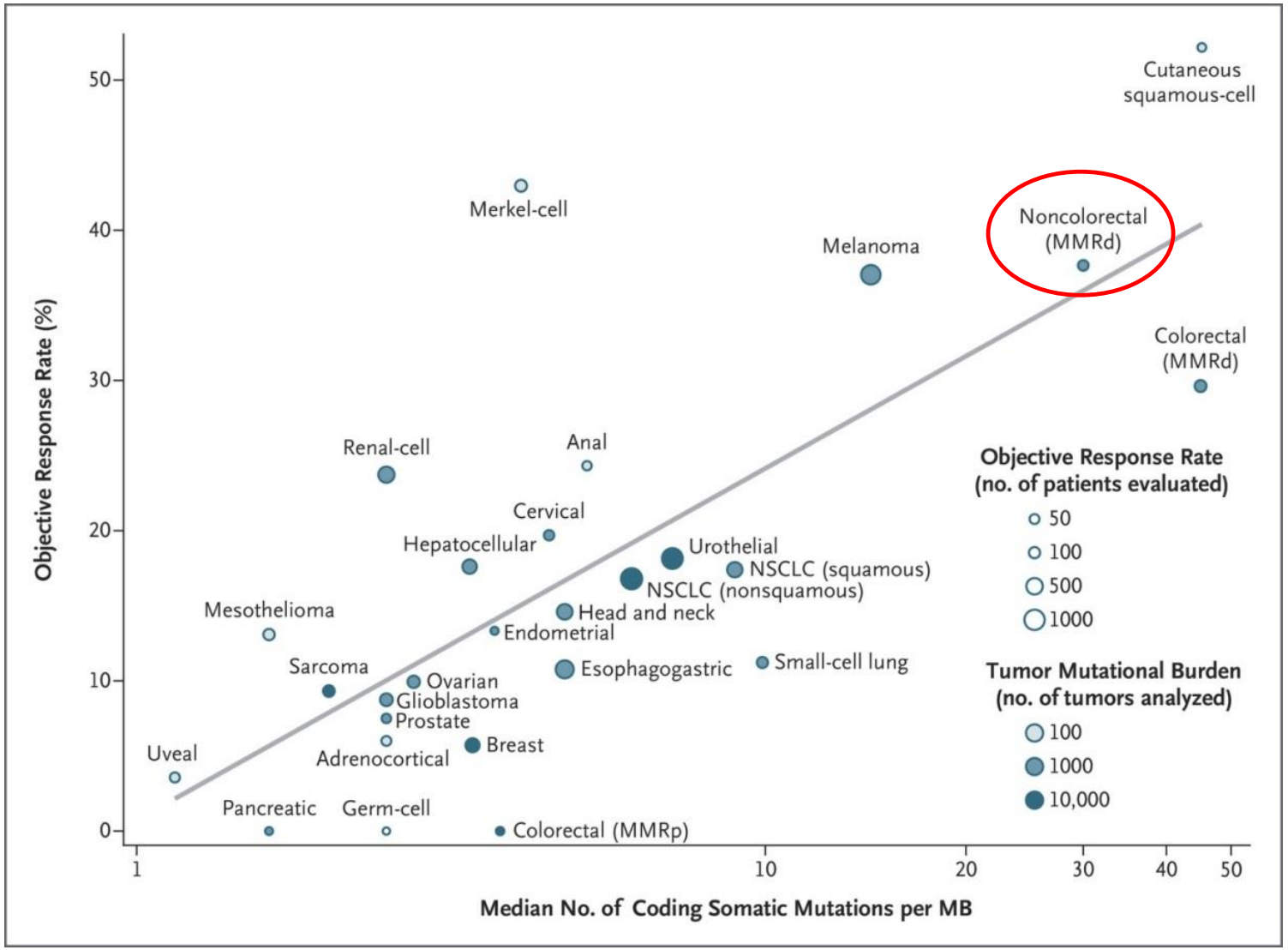
Higher number of neoantigens

↓

Greater number of TILs

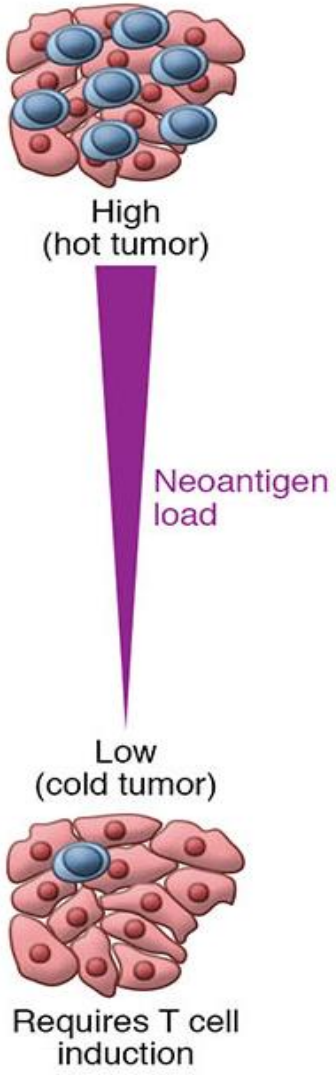
↓

Better response to immunotherapy



Yarchoan, Hopkins. Jaffee, *NEJM*, 2017

Diagnostic biomarkers to enrich responders to PD-L1/PD-1



Hot Tumors

- ❑ Example: Melanoma
- ❑ **High numbers of infiltrating T effector cells**
- ❑ More responsive to checkpoint inhibitor

Key Challenge

Heat Up Immunologically "Cold" Tumors

Cold Tumors

- ❑ Example: Pancreatic cancer (~60 neoantigens per tumor)
- ❑ **Low numbers of infiltrating T effector cells**
- ❑ Not responsive to checkpoint inhibitor
- ❑ Immunosuppressive signals in tumor

Popovic, Jaffee, Zaidi, JCI, 2018

Cancer Immunotherapy: present and future focus

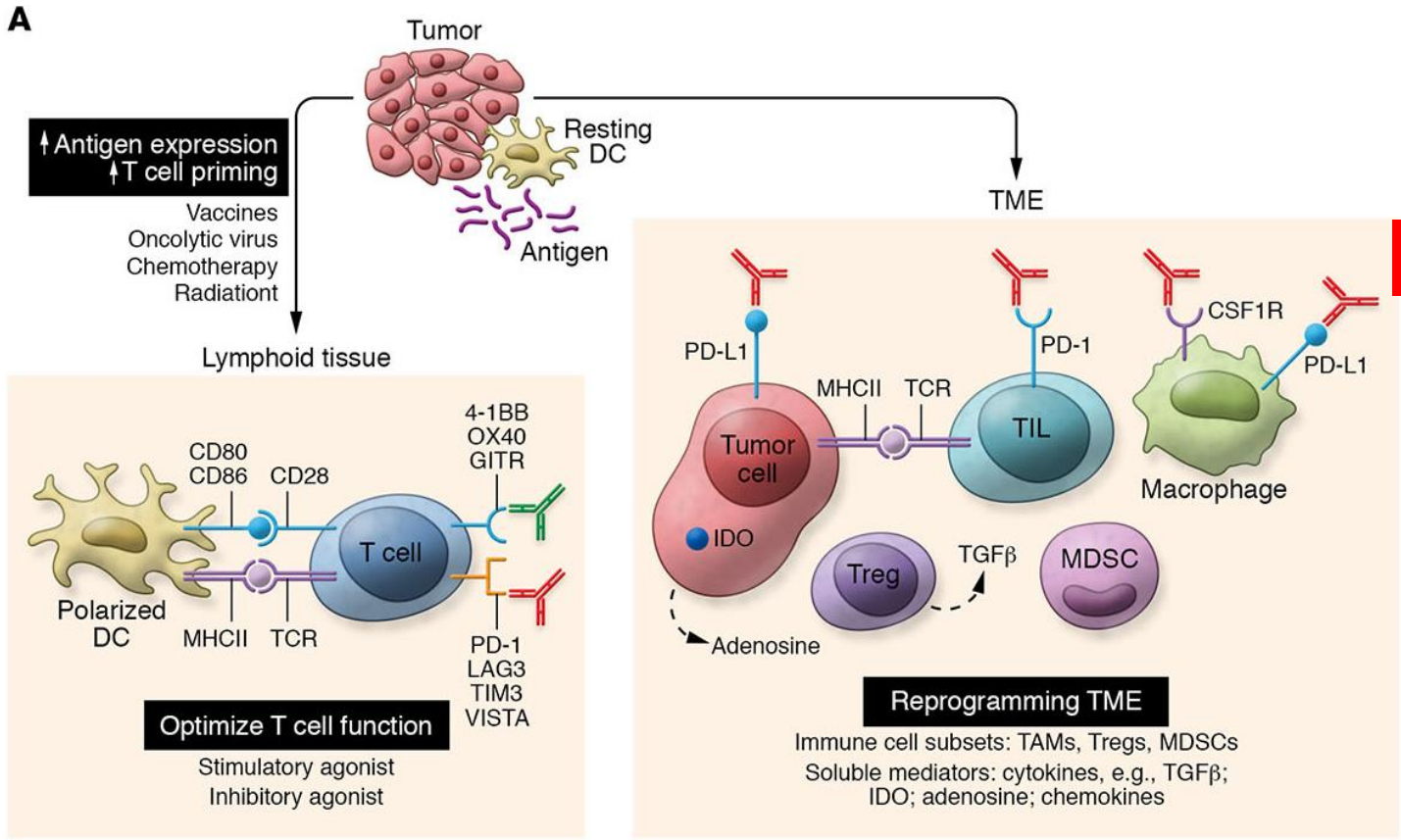
- Identify (and enrich) patients most likely to respond to αPD-L1/PD-1
- **Identify combinations** that extend the depth and breadth of response to αPD-L1/PD-1
- **Investigate new targets** to overcome immunosuppression and enhance T cell expansion

Non immunogenic cancer requires a multi- steps process to reprogram the TME and optimize immunotherapy

STEP 1

Induce T Cells

- ❑ Vaccines
- ❑ Chemotherapy/Radiation
- ❑ Oncolytic viruses
- ❑ Adoptive T cell therapy
  - Chimeric antigen receptor (CAR)-modified T cells
  - *Ex vivo* expansion of TILs



STEP 2

Reprogramming TME

- ❑ Epigenetic modifiers

STEP 3

Optimize T cell Function and Quality

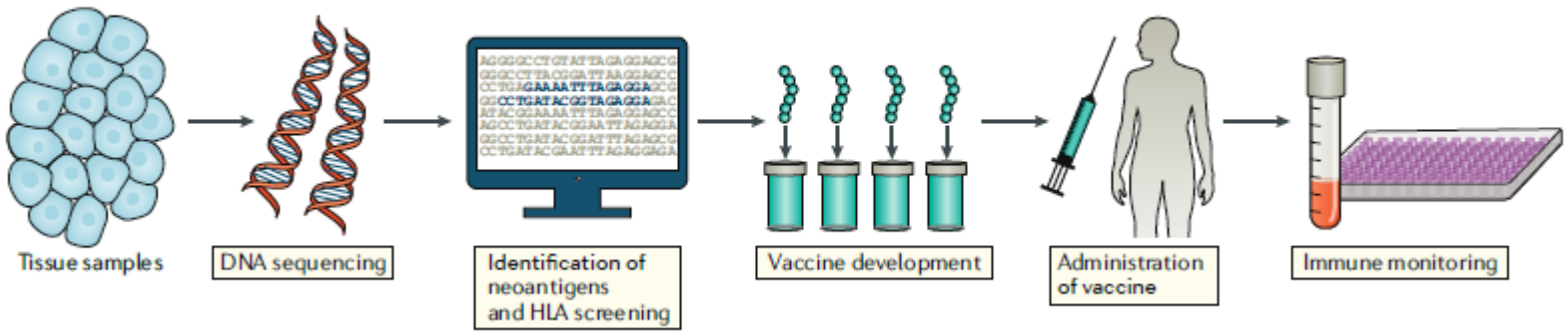
- ❑ Checkpoint agonist and antagonist

Popovic, Jaffee, Zaidi, JCI, 2018

Cutting–Edge Immunotherapies: Cancer Vaccines

Vaccine

- Induce high quality T cells into the tumor in otherwise T cell poor tumors
- Multiple trials are underway testing many vaccine strategies
  - Cell-based vaccines (Sipuleucel-T)
  - Peptide loaded dendritic cell vaccines
  - Protein/peptide vaccines
  - Personalized neoantigen cancer vaccines



Cutting–Edge Immunotherapies: Cancer Vaccines

Targeting Neoantigens To Harness an Immune Response

DNA alterations that tumor cells accumulate can lead to the formation of novel stretches of amino acid (neoepitopes) that have the potential to bind to MHC molecules

- Absent in normal tissues; specific to tumor cells
- Targeting neoantigens results in less off–site toxicity in normal tissue
- Quality of T cell repertoire less likely to be affected by central T cell tolerance (normally eliminates high-affinity T cells specific for self–antigens in thymus)

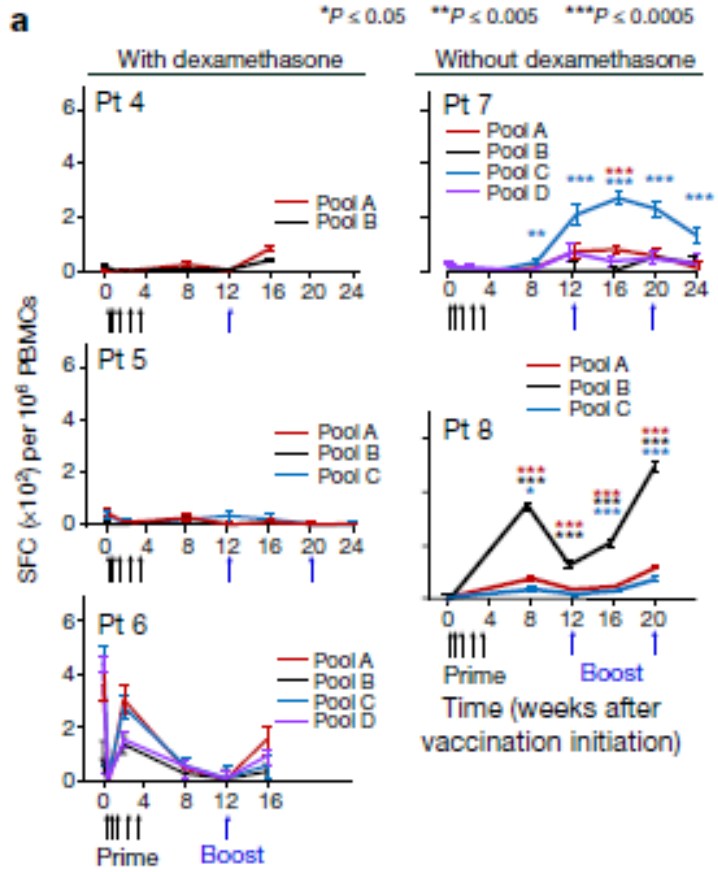
Modified from Neeha Zaidi, JHH

Cutting–Edge Immunotherapies: Cancer Vaccines

Proof–of–Concept in Immunologically Cold Tumor

Neoantigen vaccine generates intratumoral T cell responses in phase Ib glioblastoma trial

Actively personalized vaccination trial for newly diagnosed glioblastoma



- Patients elicited neoantigen–specific T cells in peripheral blood
- One patient had cancer re–resected when it recurred, with T cells within the tumor showing upregulated multiple exhaustion markers
- Only a small fraction of predicted neoepitopes used for vaccine development induce an immune response

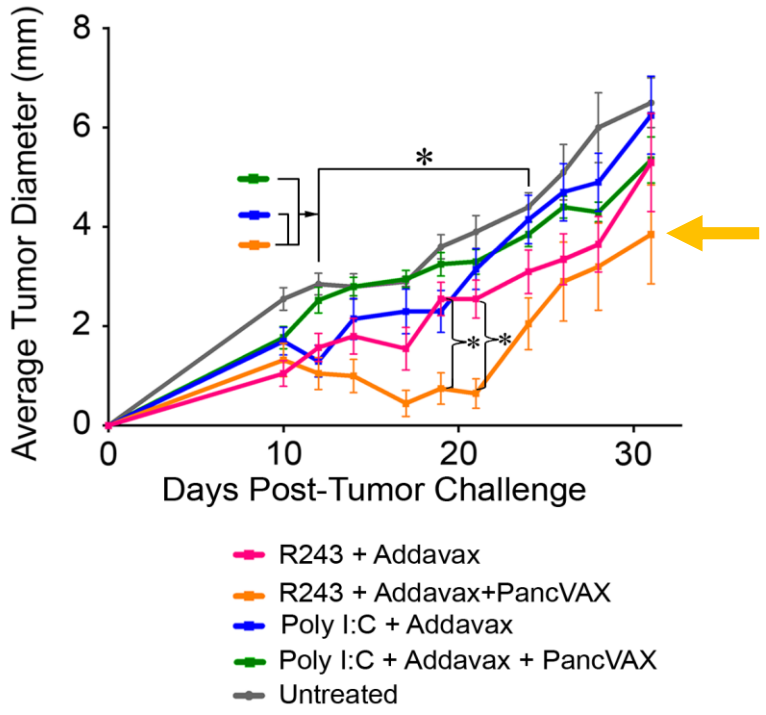
Keskin et al., Nature, 2018; Hilf et al., Nature 2019

Cutting–Edge Immunotherapies: Cancer Vaccines

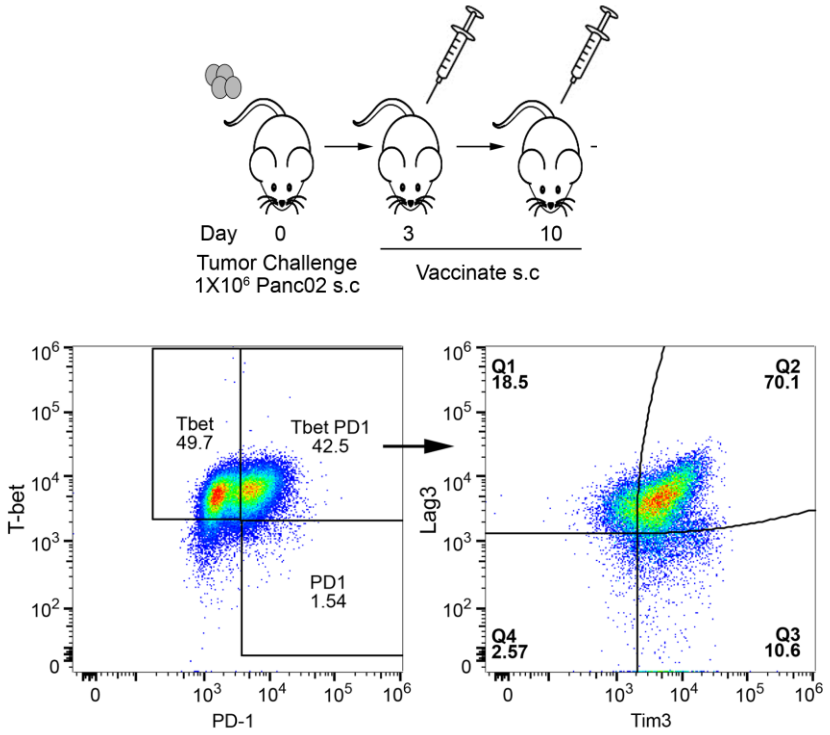
Vaccine Alone ➡ Transient Tumor Regression

➡ Upregulation of Multiple Inhibitor Checkpoints

- STING–targeted vaccine yields transient tumor regression



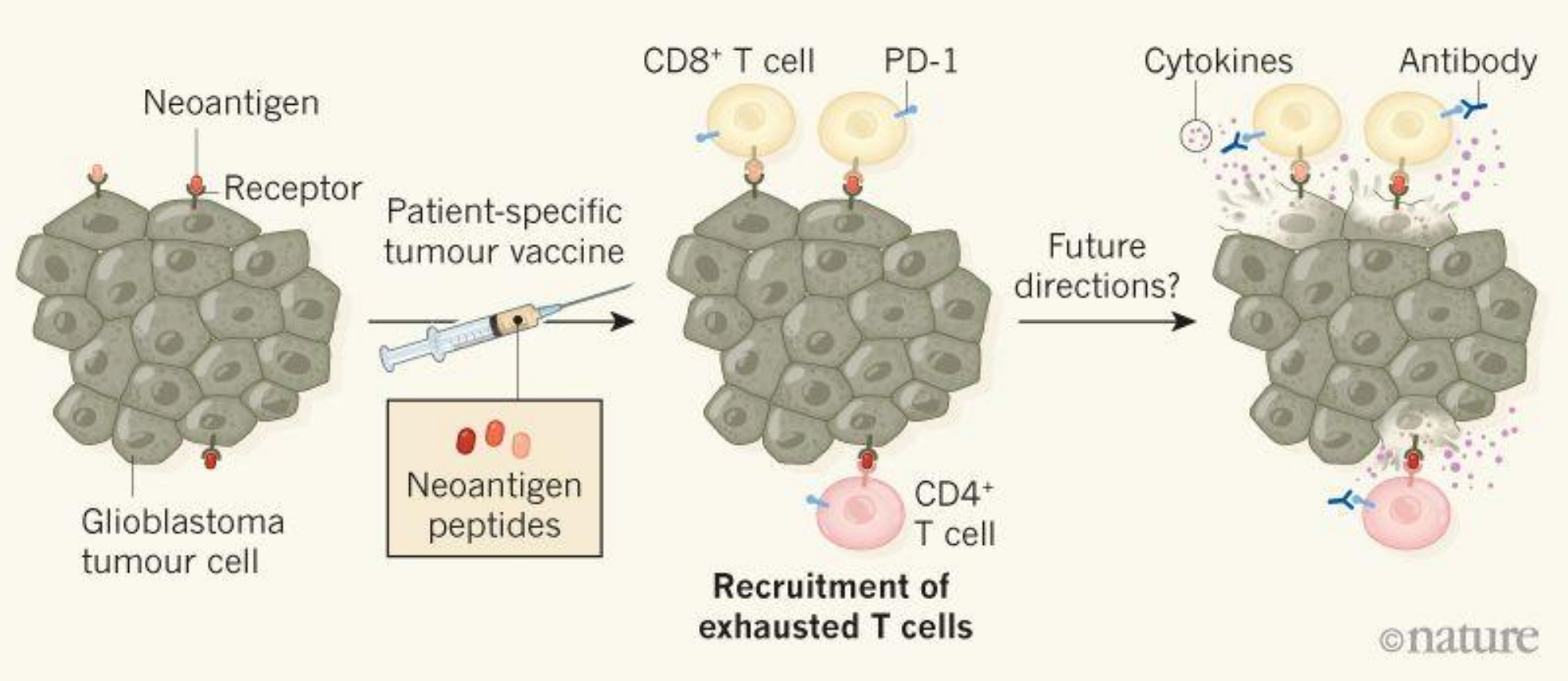
- STING–targeted vaccine leads to upregulation of inhibitory checkpoints (T Cell Exhaustion)



Kinkead et al. JCI Insight, 2018

Cutting–Edge Immunotherapies: Cancer Vaccines

T Cells Can be Induced in Immunologically "Cold" Tumors, But Require Activation



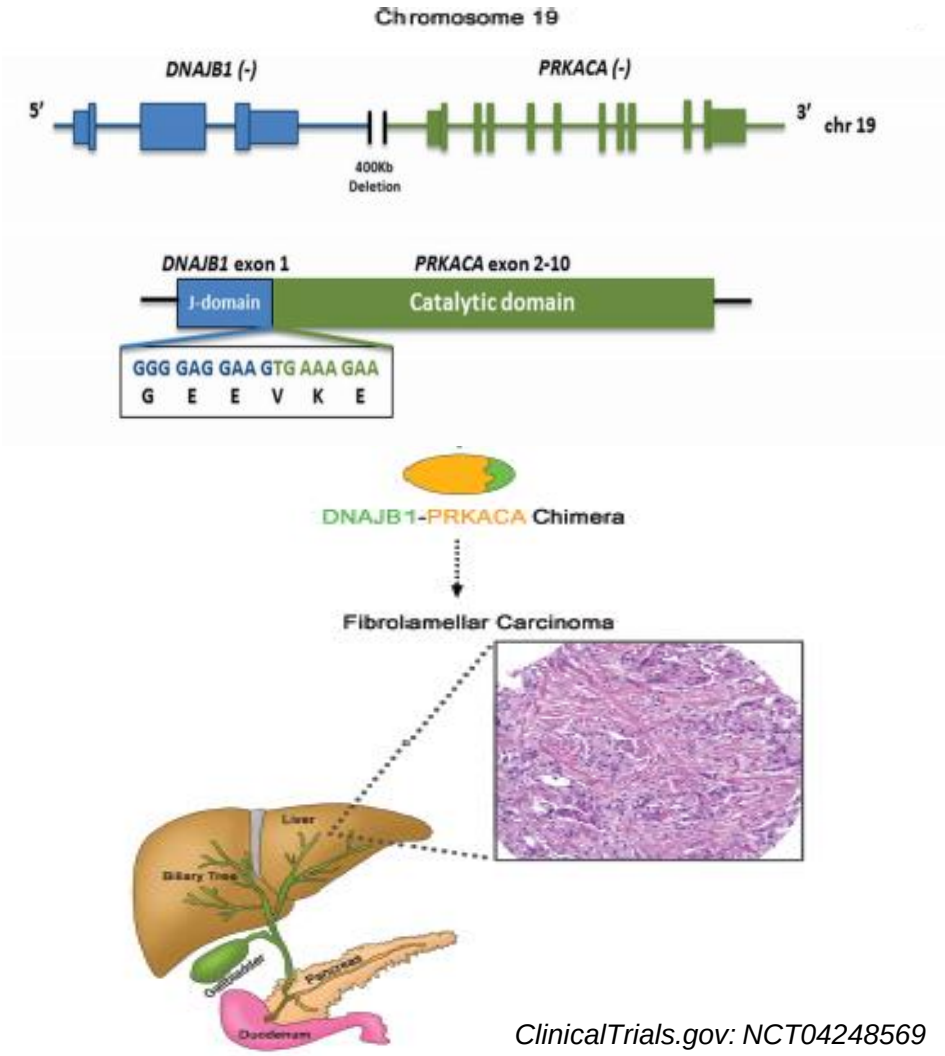
Potential Alternatives Strategies
Vaccines + Checkpoint/TME Modulators

Zaidi N, Jaffee EM, Nature 2019

A pilot study of a DNAJB1-PRKACA fusion kinase vaccine combined with nivolumab and ipilimumab for patients with fibrolamellar hepatocellular carcinoma (FLC)

FLC is a rare form of liver cancer, affecting young adults (age 14-33) without underlying liver disease.

- Low incidence
- Patients with advanced disease have mOS of ~12 months
- There is no standard systemic therapy

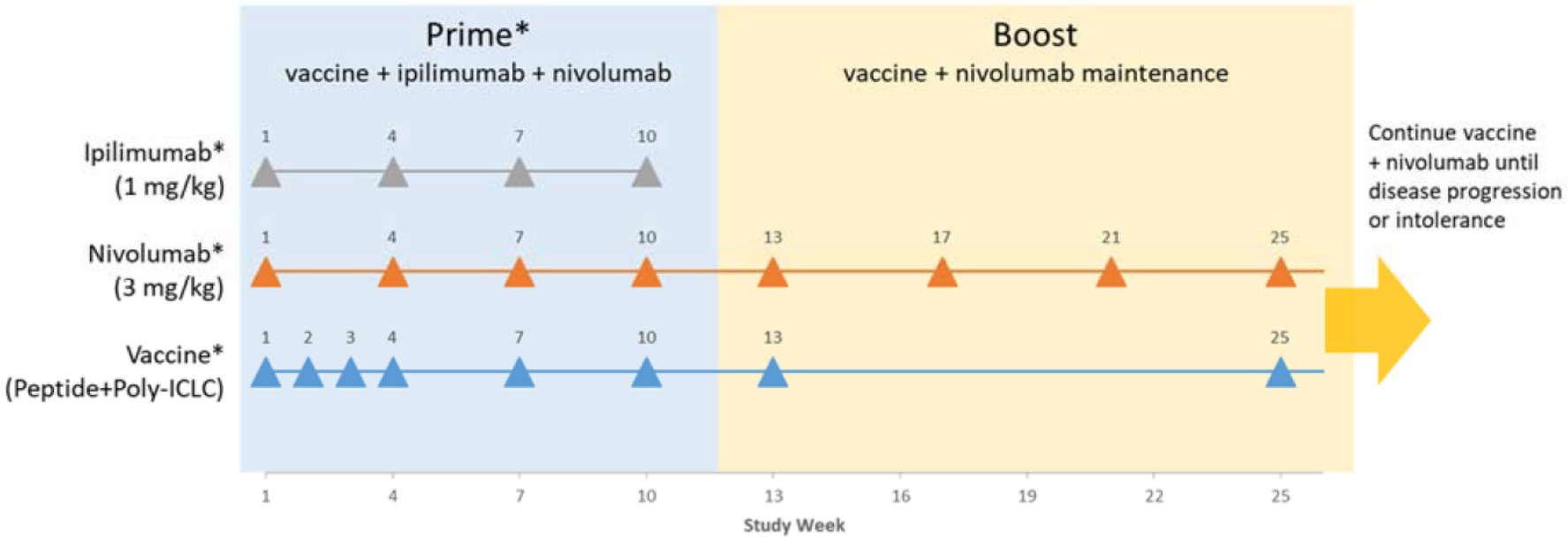


*The recurrent **DNAJB1-PRKACA chimeric transcript** in FLC is shared from patient to patient: ⟹ a single "off the shelf" vaccine can be used to treat multiple different patients*

ClinicalTrials.gov: NCT04248569

A pilot study of a DNAJB1-PRKACA fusion kinase vaccine combined with nivolumab and ipilimumab for patients with fibrolamellar hepatocellular carcinoma (FLC)

We are conducting a trial of a **vaccine targeting the DNAJB1-PRKACA chimeric transcript**, in combination with nivolumab and ipilimumab for the treatment of unresectable fibrolamellar hepatocellular carcinoma



ClinicalTrials.gov: NCT04248569

Non immunogenic cancer requires a multi- steps process to reprogram the TME and optimize immunotherapy

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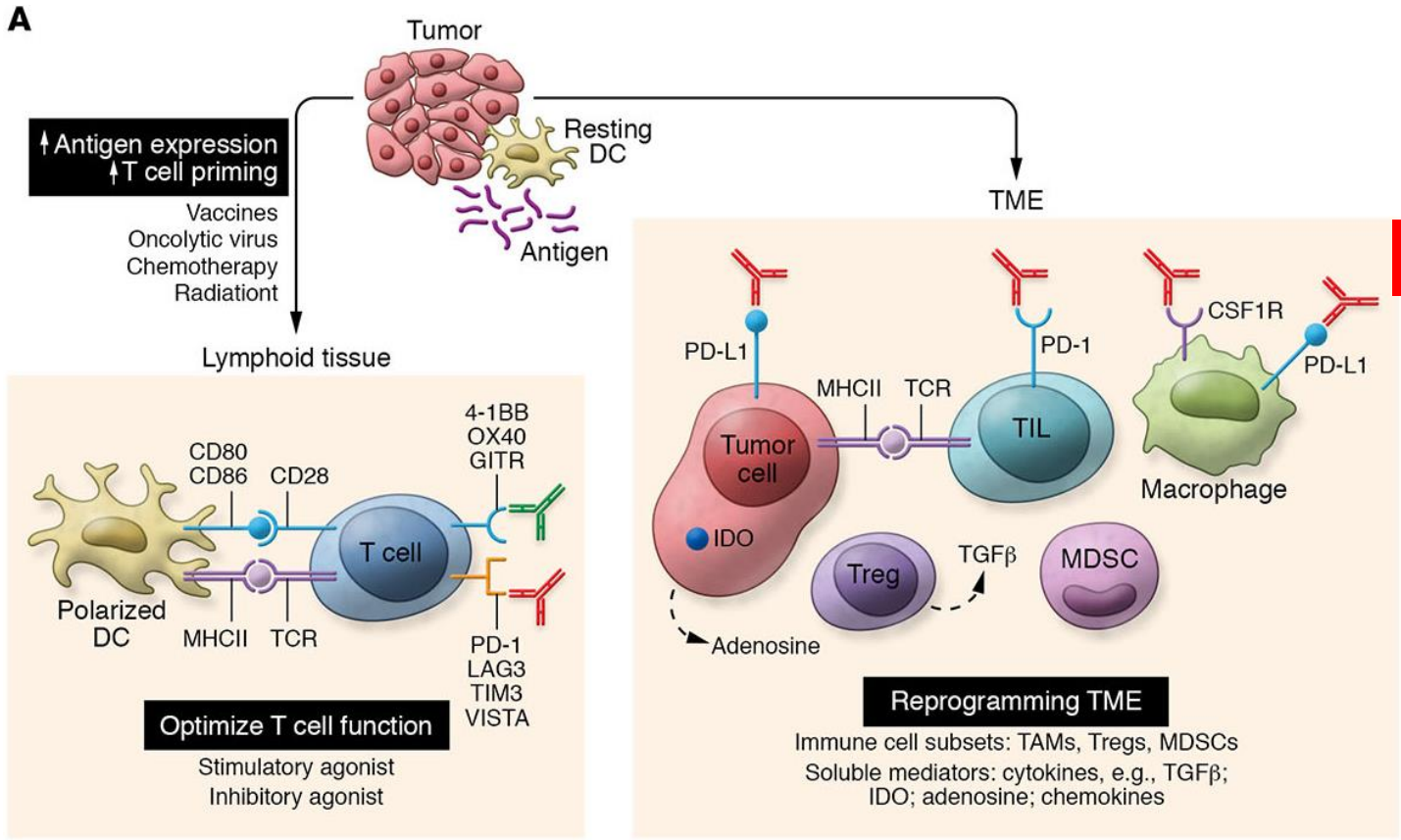


STEP 2

Reprogramming TME

- ❑ Epigenetic modifiers

STEP 3

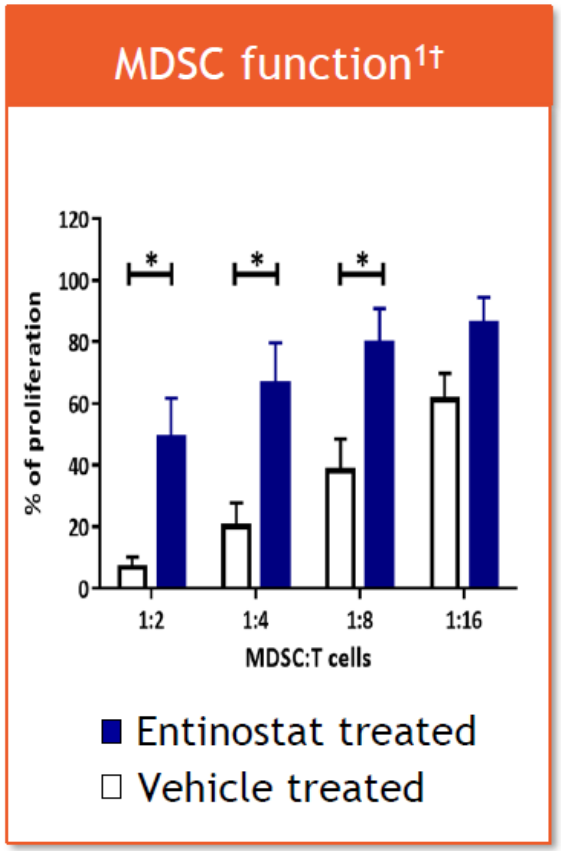
Optimize T cell Function and Quality

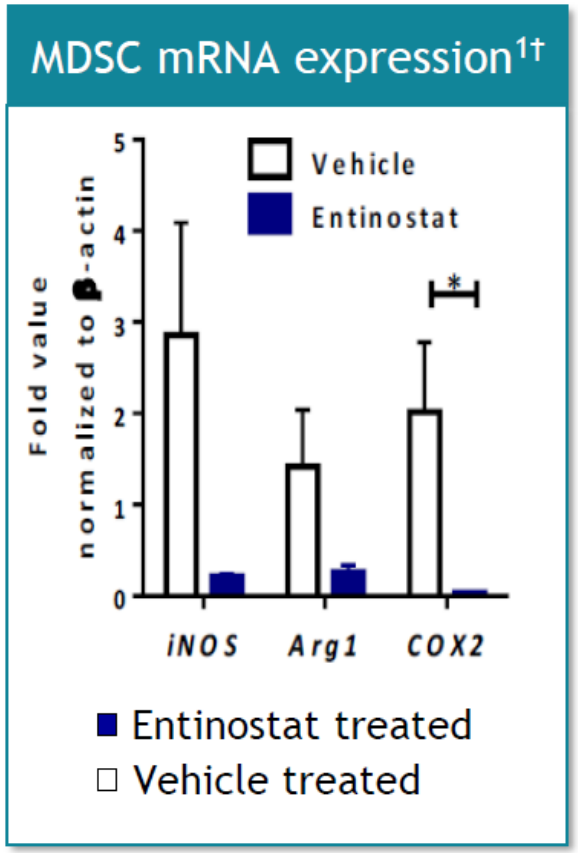
- ❑ Checkpoint agonist and antagonist

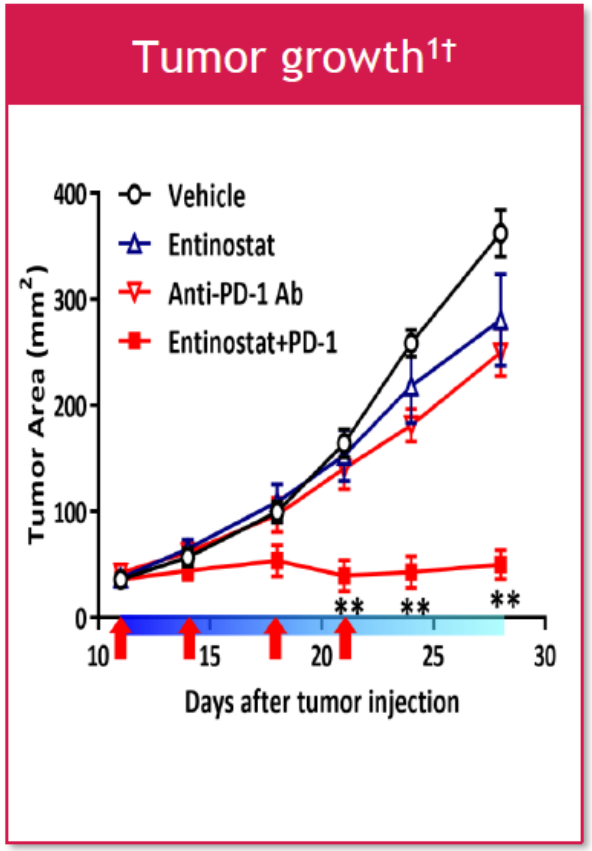
Popovic, Jaffee, Zaidi, JCI, 2018

Cancer Immunotherapy: what is next? Epigenetic modifiers

- Entinostat is an oral class-1 selective histone deacetylase
- Entinostat lead to downregulation of immunosuppressive cell types in the TME
- Synergy with anti-PD-1 in preclinical model



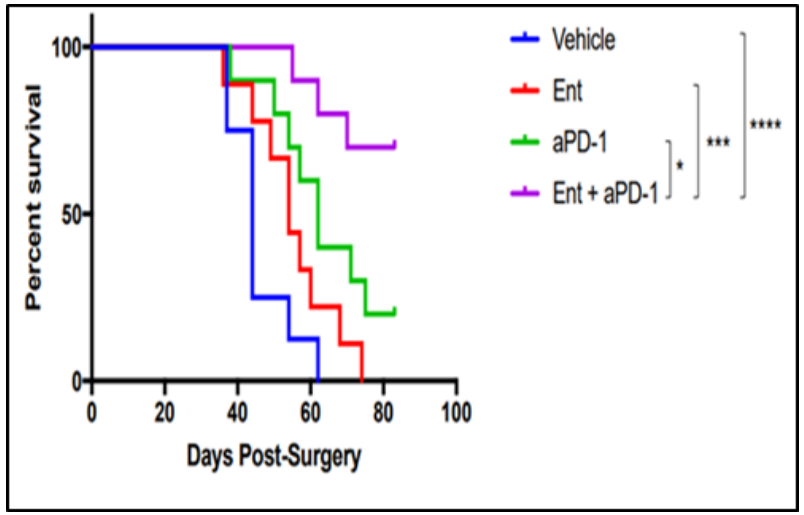




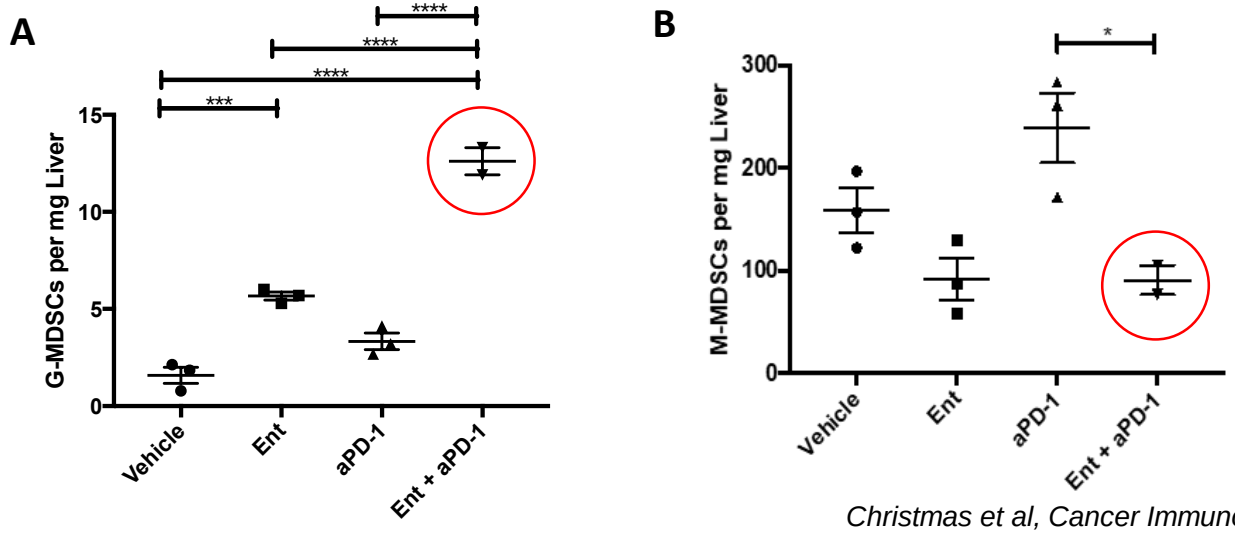
Orillion et al. Clin Cancer Res. 2017

Epigenetic Modulation of the Tumor Microenvironment Enhances Immune Checkpoint Efficacy in a Murine Model of Pancreatic Cancer

Significantly improved survival in combination treated mice



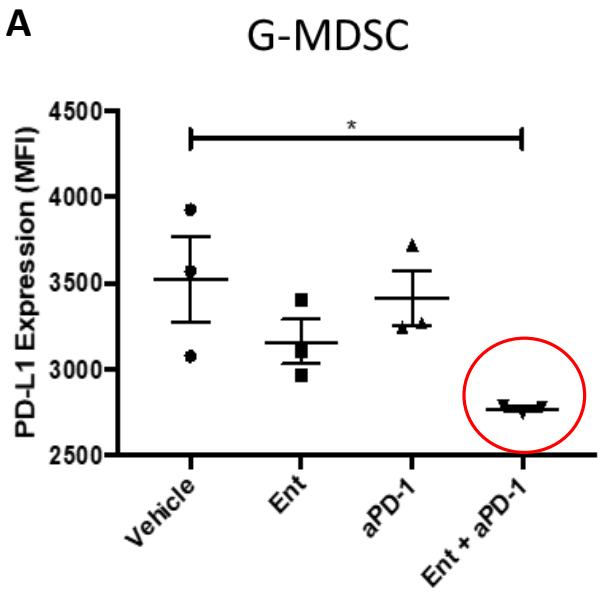
Significant increase in G-MDSC in combination treated mice

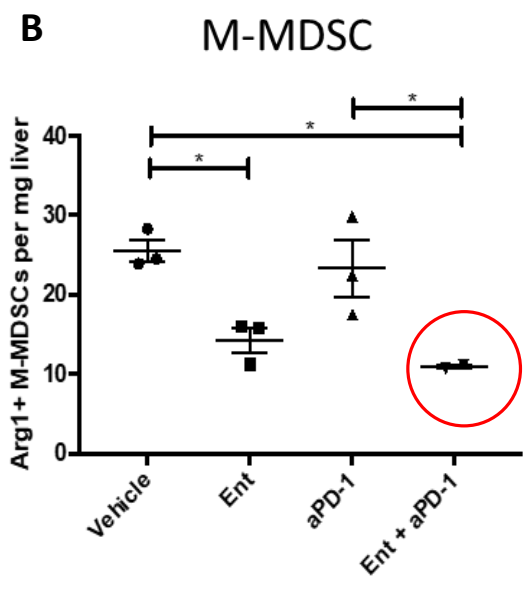


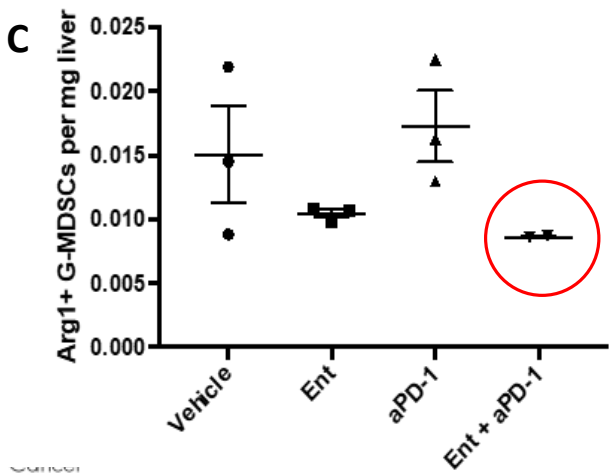
Christmas et al, Cancer Immunology Research 2018

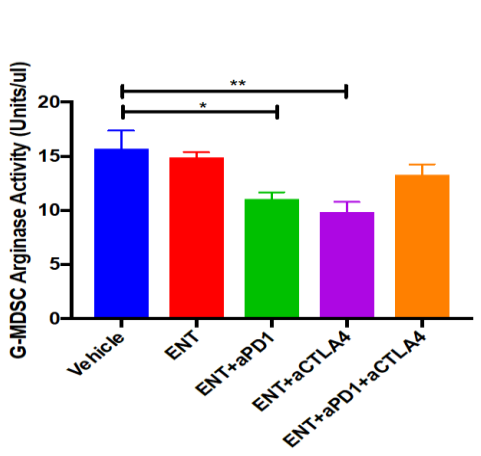
Epigenetic Modulation of the Tumor Microenvironment Enhances Immune Checkpoint Efficacy in a Murine Model of Pancreatic Cancer

Significant decrease in PD-L1 expression and Arg-1 activity in MDSCs in combination treated mice

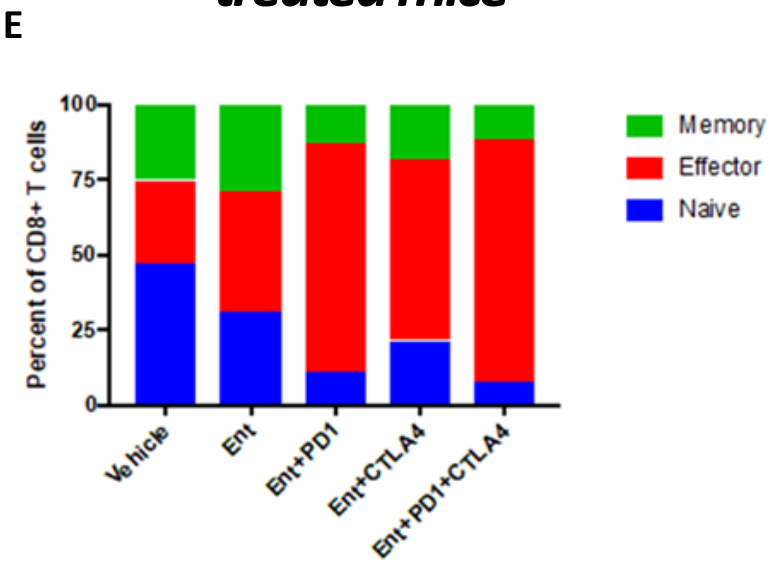








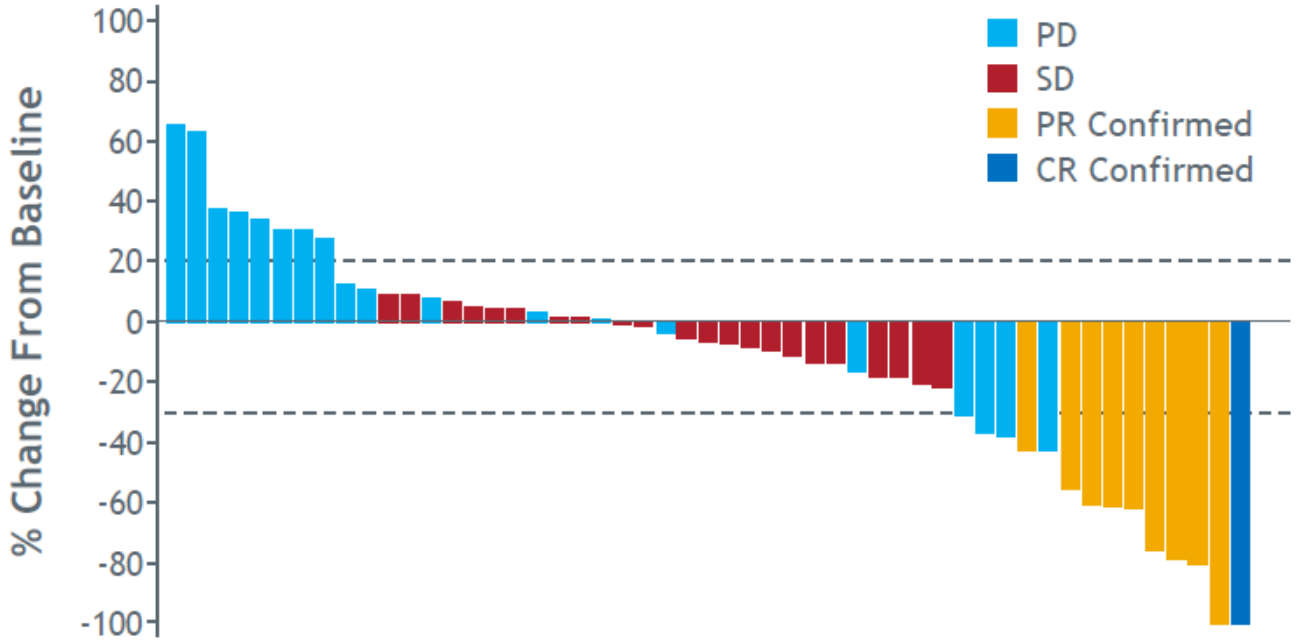
Significant increase in CD8+ effector T cells in combination treated mice



Christmas et al, Cancer Immunology Research 2018

Cancer Immunotherapy: what is next? Epigenetic modifiers

- ENCORE 601: entinostat and pembrolizumab in patients with non–small cell lung cancer, melanoma, and MMR-p colorectal cancer
  - 10 confirmed responses of 53 treated [19% ORR (95% CI: 9%-32%)]
    - 1 CR, 9 PR
  - Median duration of response: 13 months (range 3-20)
    - 4 responders ongoing
  - An additional 9 patients have had SD for > 5 months
    - 36% CBR (95% CI: 235-50%)



- Entinostat in combination with nivolumab for patients with advanced cholangiocarcinoma and pancreatic adenocarcinoma (NCT03250273)

Sullivan et al, Abstract CT 027, JCO; Baretti et al. Abstract TPS4151, JCO

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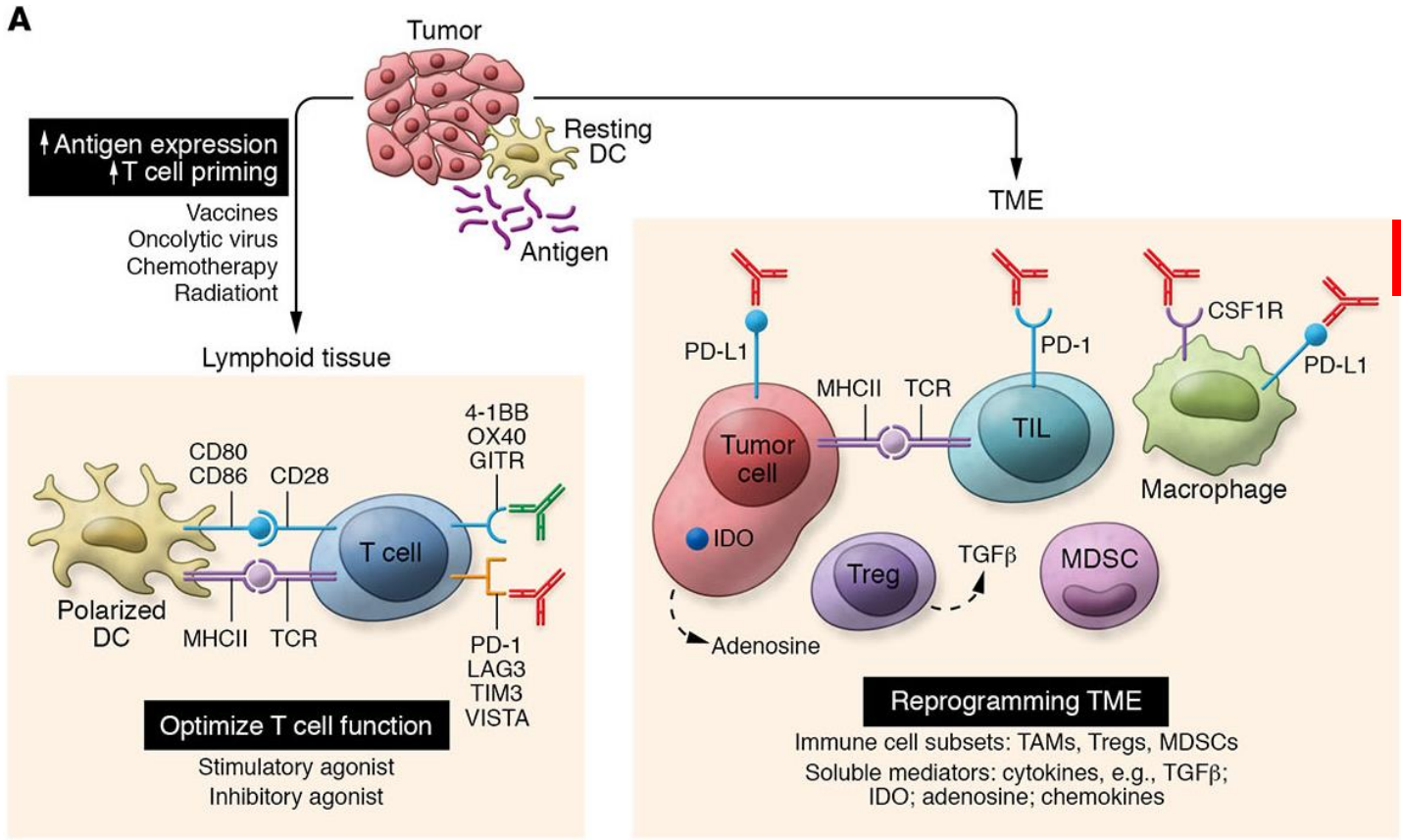

STEP 2

Reprogramming TME

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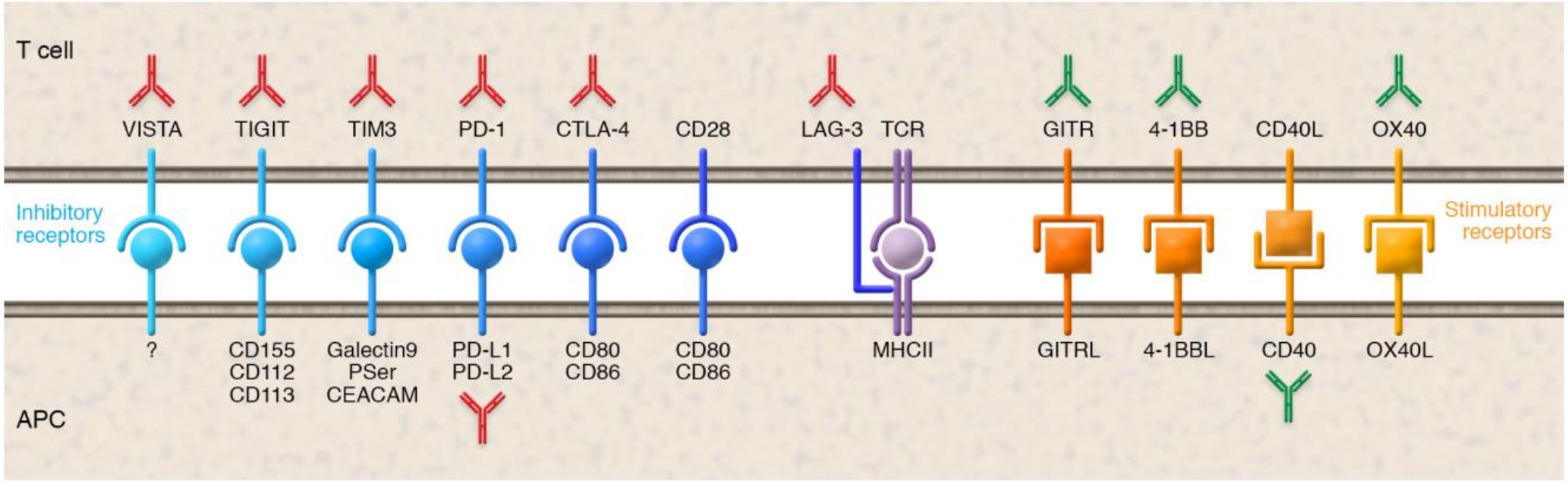
Popovic, Jaffee, Zaidi, JCI, 2018

Cancer Immunotherapy: looking for next generation targets

Antagonists of negative regulators

Agonists to costimulators



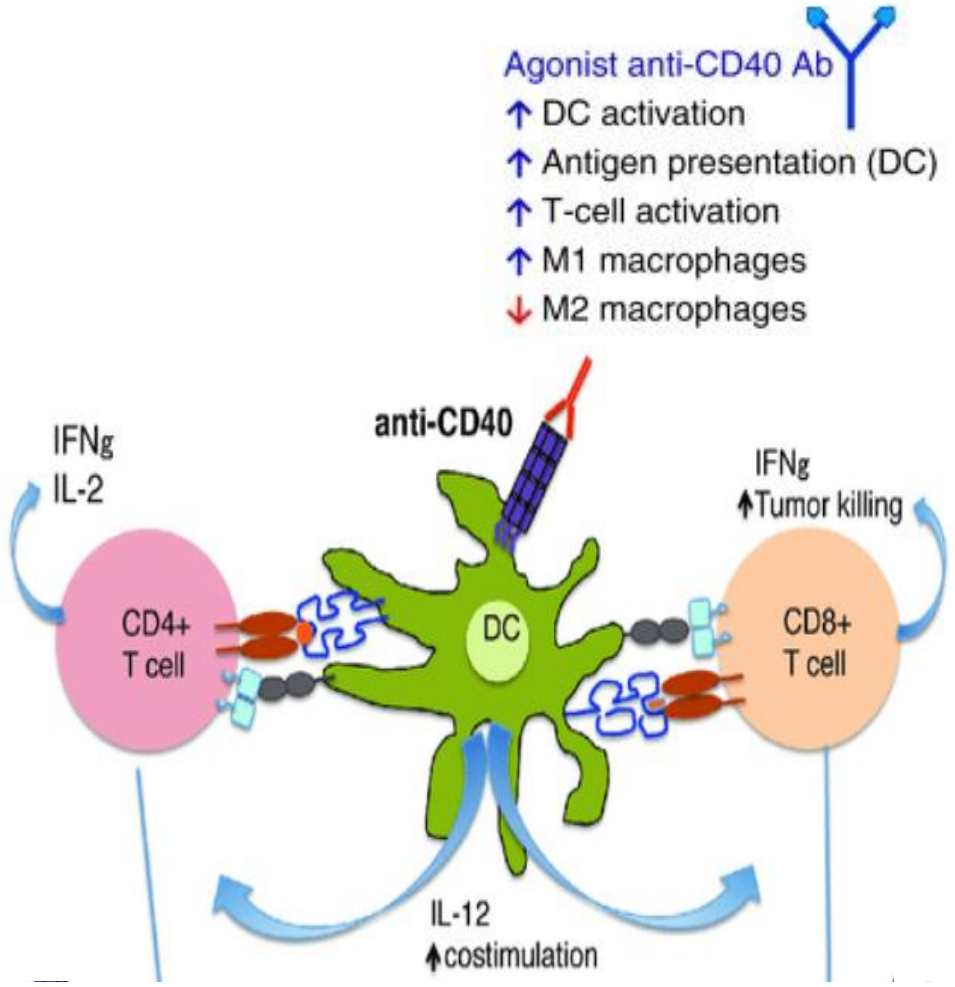
Key Points

- Biologic roles are not redundant
- Differential upregulation in different tumor types
- Either antagonist or agonist antibodies are currently under clinical testing based on promising preclinical data

Popovic, Jaffee, Zaidi, JCI, 2018

Anti-CD40: A Promising Immune Checkpoint Agonist

- **Preclinical Studies**: Using PDAC murine models, CD40 mAb has shown robust antitumor activity in combination with chemotherapy, checkpoint inhibitors, and other immune modulators
- **Interim Analysis of Phase Ib**: Evaluating the CD40 mAb APX005M in combination with gemcitabine and nab-paclitaxel with or without nivo in untreated patients with metastatic PDAC (O'Hara *et al*, *JCO* 2019)
  - **Response:** Of 30 patients enrolled, 14 (58%) PRs (11 confirmed, 3 unconfirmed) and 8 (33%) stable disease. 1 patient (4%) had progressive disease, and 1 (4%) had no treatment evaluation
  - **Immune profiling of PBMCs at baseline and on-treatment by mass cytometry**: Revealed remodeling of the myeloid compartment in response to treatment, with rapid activation of dendritic cells in most patients.



The cancer-immunity cycle and strategies for cancer immunotherapy

Pan et al. Journal of Hematology & Oncology, 2020

Conclusions and Perspectives

- We are at the beginning of an exciting journey for patients and for scientific investigation
- Need to expand focus to include targeting stroma and to understand host **genetics and epigenetics**, the **microbiome**, and **the environment**
- Better **laboratory models** to study the immune response and tumor microenvironment
- Much excitement in the field as new studies are open to address contemporary questions
- We now have more sophisticated tools to spatially assess what is going in the tumor immunologically + we can also look at more markers at the same time
- Capitalizing on the potential of **revers translation** strategies to maximize our efforts in both the lab and the clinic to bring benefit to an ever greater number of patients

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Questions?