2016 ASCPT Annual Meeting

Session - Rational Development of Combination Cancer Immunotherapy
Friday, March 11, 2016 1:00 PM - 2:30 PM

Biomarkers for Immuno-Oncology and Combination Development

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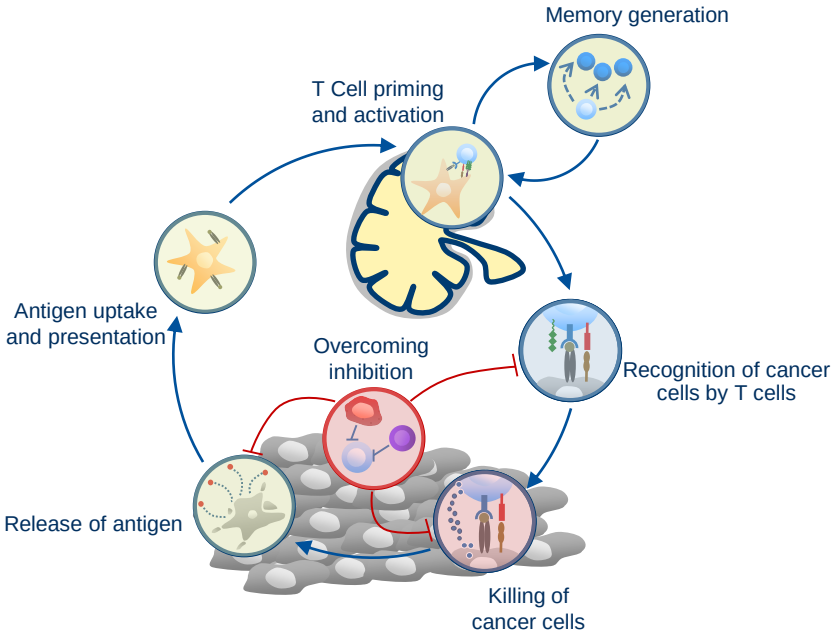
Antitumor Immunity Cycle and Mechanisms of Escape



Tumor Escape from Immune Recognition
Antigen loss leads to tumor cell variant growth
Low MHC/Peptide presentation
Tumor-induced physical barrier – T cells can't get in
Tumor treated as 'Self' due to T cell tolerization
Immune suppression by tumor and other cells

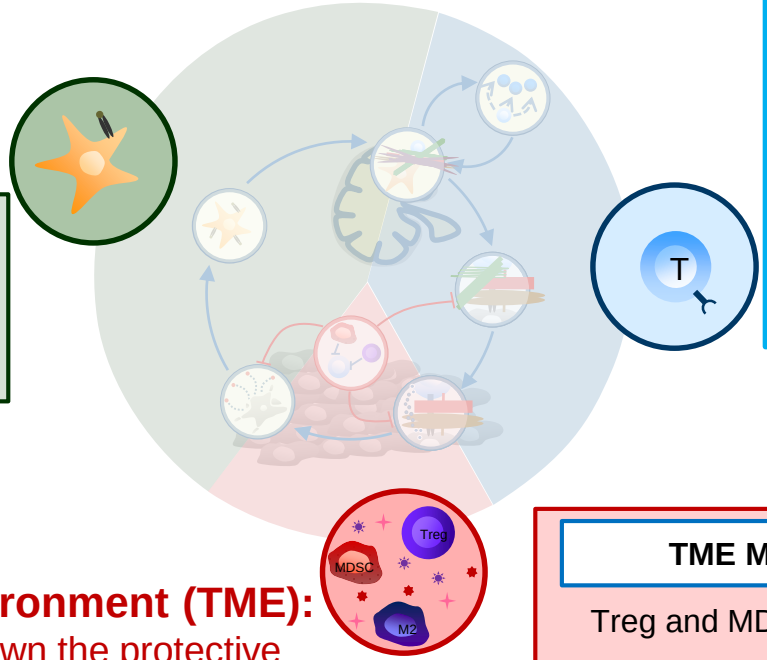
Chen and Mellman (2013). Immunity. 39: 1.

Antitumor Activity can be Promoted by Targeting Critical Phases in the Immune Cycle

Antigen Presentation:
Making tumors visible to the immune system

AP Increasers

Oncolytic virus; Small Molecule
Radiation; Chemotherapy
NK cell activators



T-Cell Activation:
Turning resting / inactive immune cells into killer cells

T Cell (Re)Activators

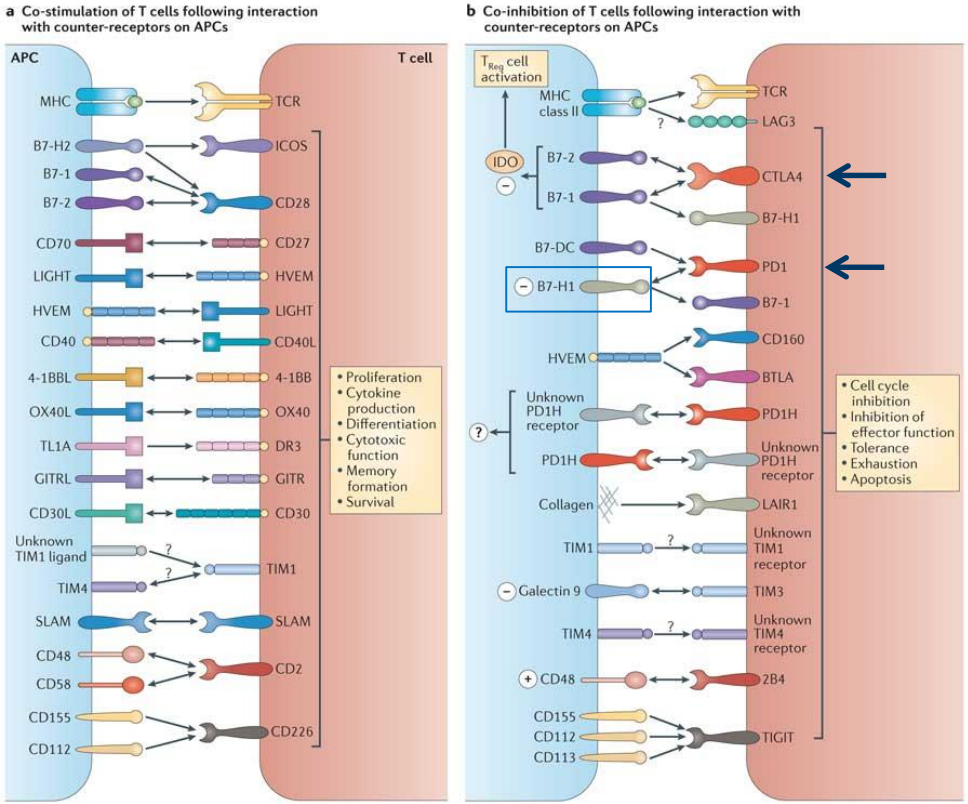
Checkpoint Inhibitors
Agonists of CoStimulators

Tumor Microenvironment (TME):
Breaking down the protective shield around tumor cells

TME Modifiers

Treg and MDSC Depleters

APC Co-stimulation vs. Co-inhibition of T cells



- By targeting co-stimulatory or -inhibitory pathways we may amplify immune activity

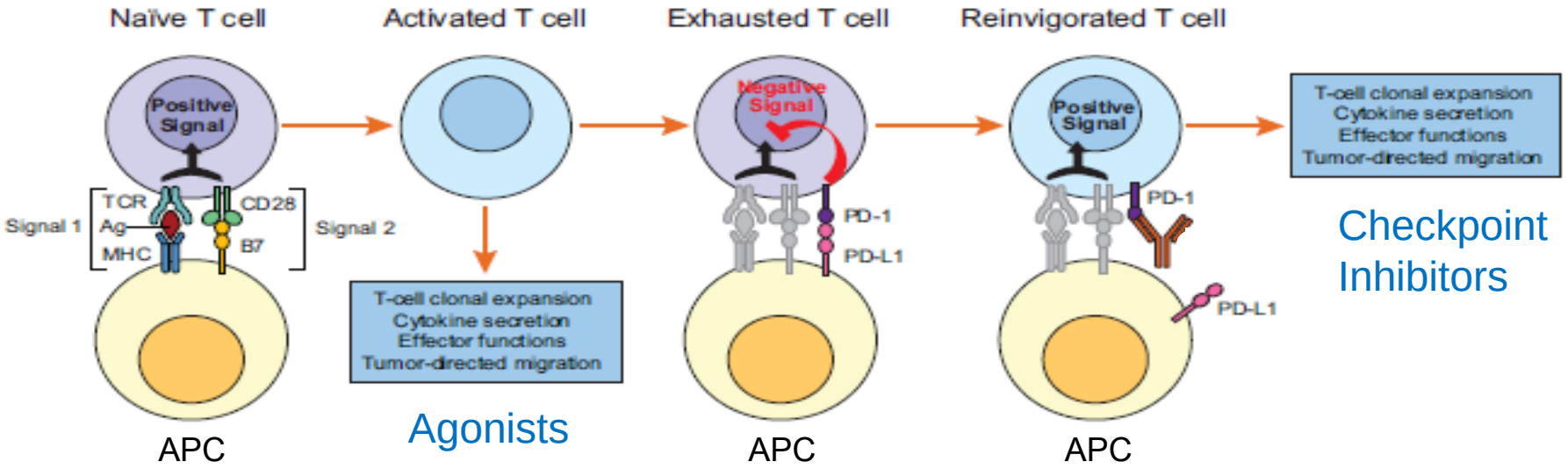
Block inhibitory signals = ‘Release the brakes’
Pathway agonism = ‘Press the Gas’

- Many current combination strategies focus on blockade of multiple inhibitory pathways (e.g. anti-CTLA-4 / PD-1) or mixed targeting of stimulatory and inhibitory pathways (e.g. anti-4-1BB / PD-1)

- Biomarker strategies will focus on understanding expression of these proteins

Chen and Flies (2013). Nature Rev Immunology. 13: 227.

Goals of Pre-Clinical and Clinical Biomarker Studies



Biomarker studies aim to understand

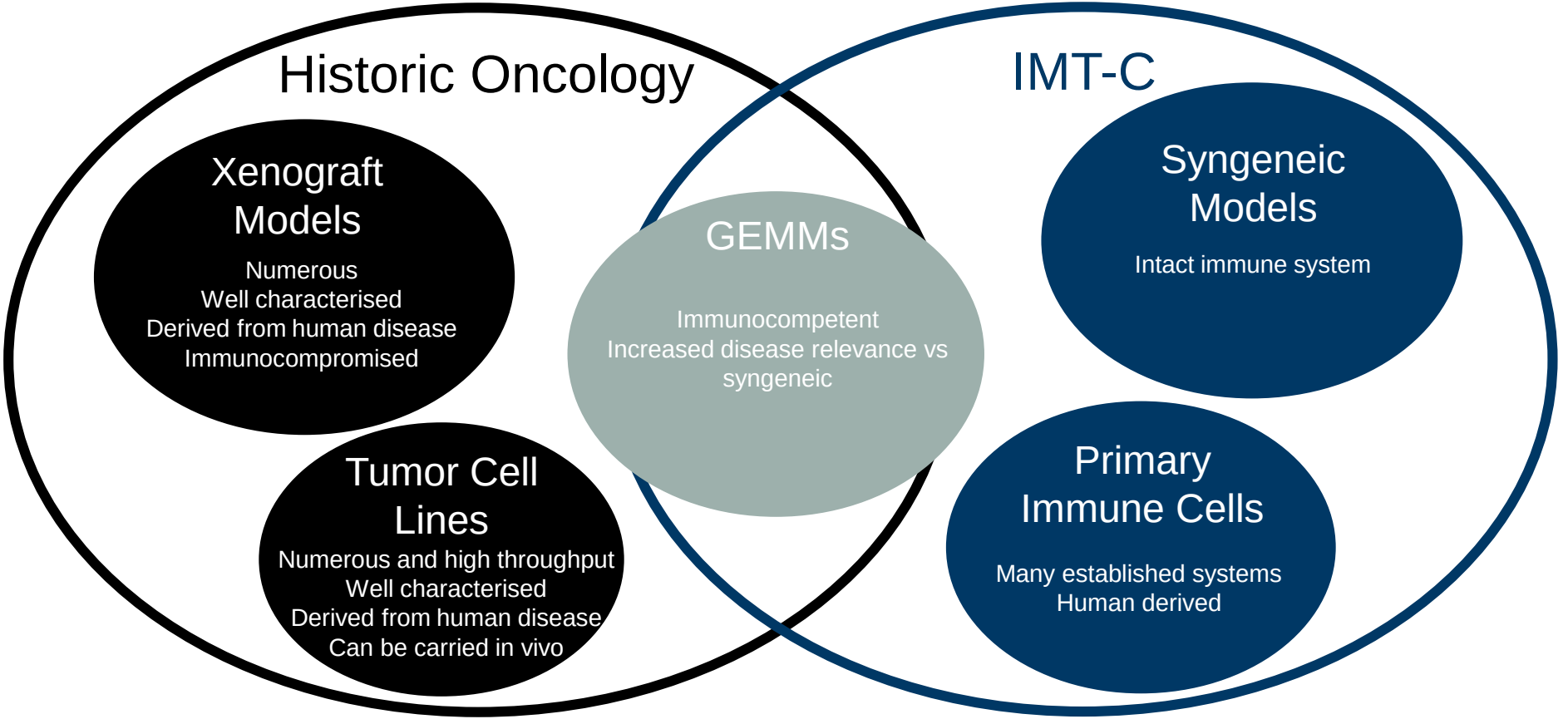
- Change over time
- Baseline predictive value
- Change with response

Immunotherapy (IMT) studies have sought

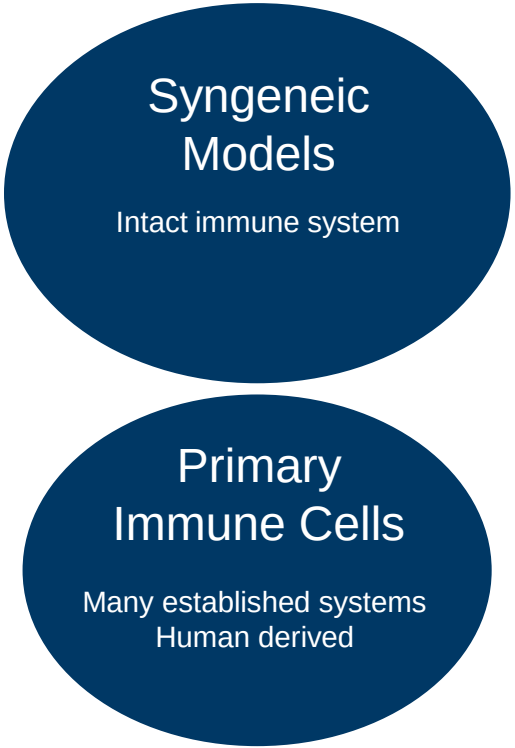
- T cell proliferation
- Cytokine production
- Cytotoxic function

Inman (2013) European Urology. 63: 881.

Preclinical Strategy for IMT vs Traditional Oncology



Model Systems Have Established Basic Principles of Antitumor Immune Activity



Associated with Therapy-Induced Tumor Rejection
Acute, peripheral T cell activation and proliferation Ki67+ T cells expressing activation markers (e.g. ICOS)
Increases in plasma / serum cytokines Critical are Th1-biased responses - Produce IFNγ, IL-2 and TNF-beta, evoking cell-mediated immunity and phagocyte-dependent inflammation
Chemokines expressed in the TME (Attract T cells to site) IFNγ-induced chemokines CXCL9 and CXCL10 may be critical as they recruit effector T cells
Migration of CD8+ Cytotoxic T cells (that can overcome immunosuppressive signals in the TME)

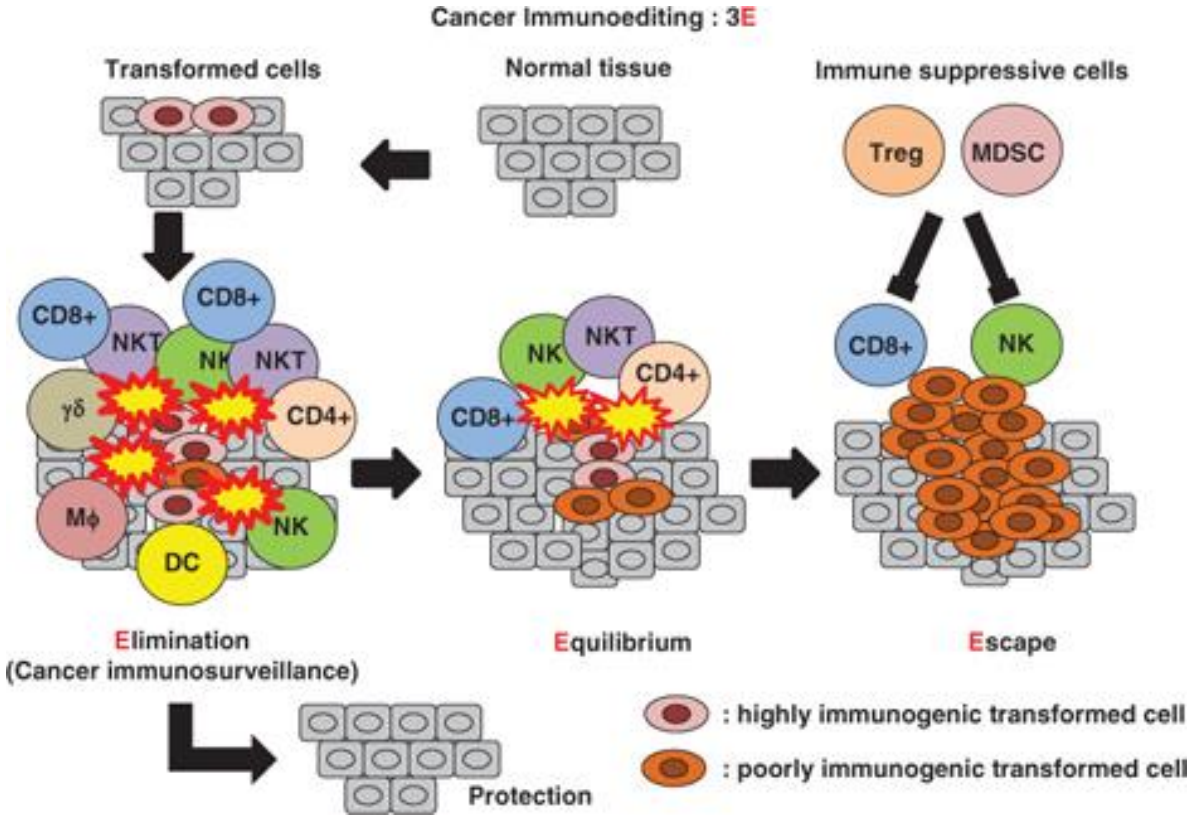
However Model Systems Have Limitations

Limitations of Syngeneic Models
Primarily models of acute inflammation and tumour initiation
Variability in response within groups
Limited window for intervention
Rely on mouse cross reactivity or surrogate reagents
Direct correlation to human disease may be limited

Combination studies may be challenging in Syngeneics and GEMMs may be limiting

- Insights from pre-clinical models are only useful if they relate to human disease
- *Essential* to build an understanding of the human tumor microenvironment

Tumors in the Clinic – Immunoediting Concepts

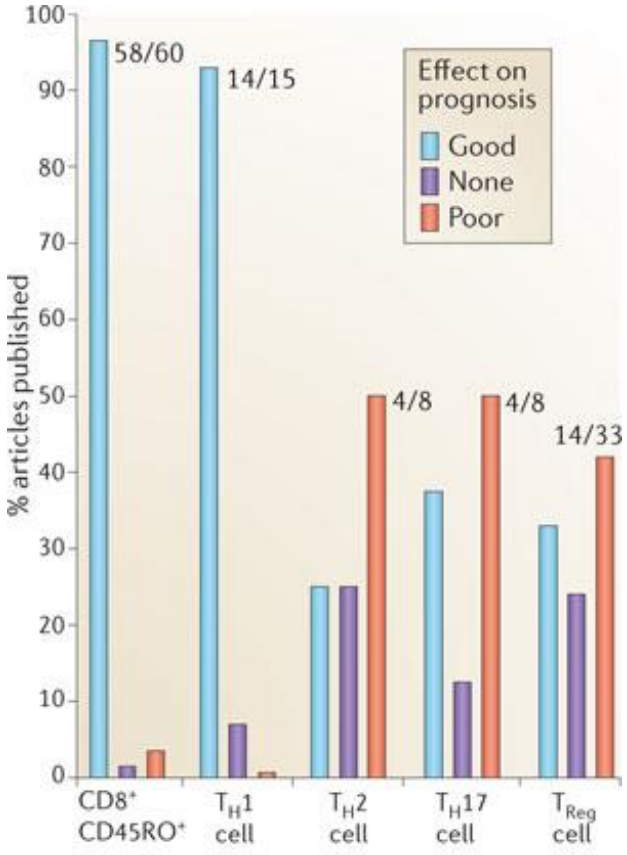


Cancer immunoediting concepts predict that many tumors will be characterized by immunosuppressive cells and/or by a lack of cytotoxic T cells

Assessed by tumor tissue IHC to determine *Prognostic* roles of different resident cell types

Reviewed in Sakakura (2013). Adv in Cell and Mol Otolaryngology. 1: 21809.

Immune Contexture is Prognostic



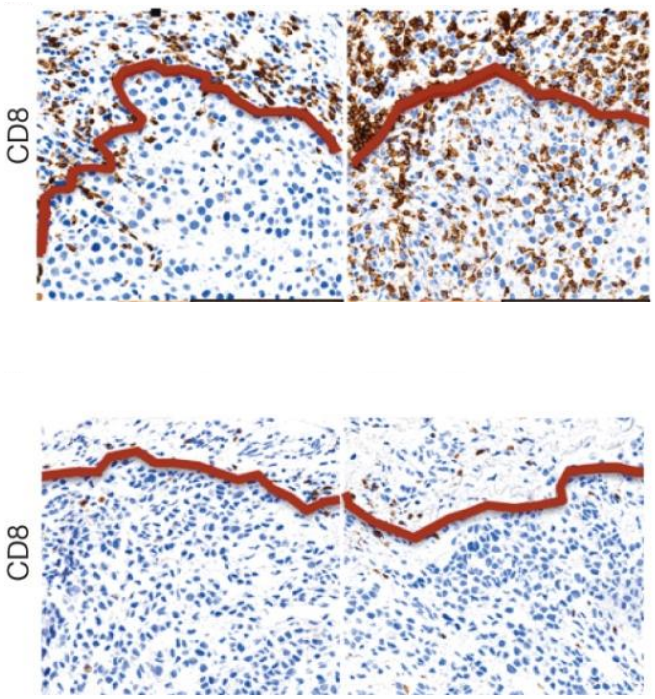
- CD8+ cells and Th1-biased immune responses tend to be associated with good prognosis

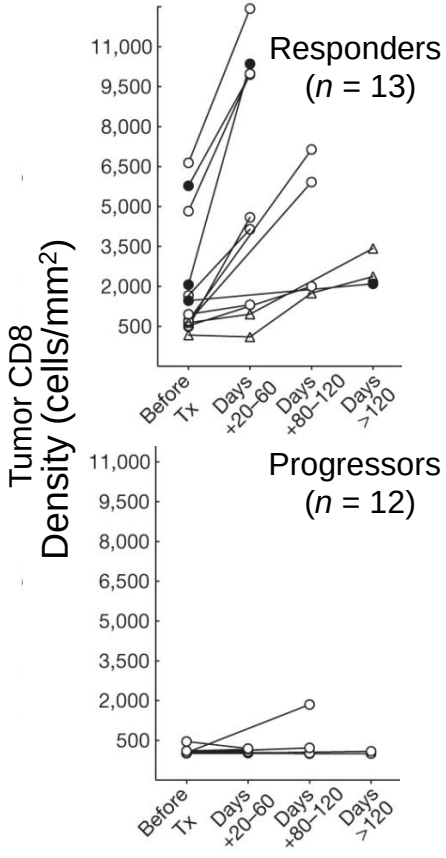
- Treg, Th17, and Th2-biased immune responses tend to be associated with poor prognosis

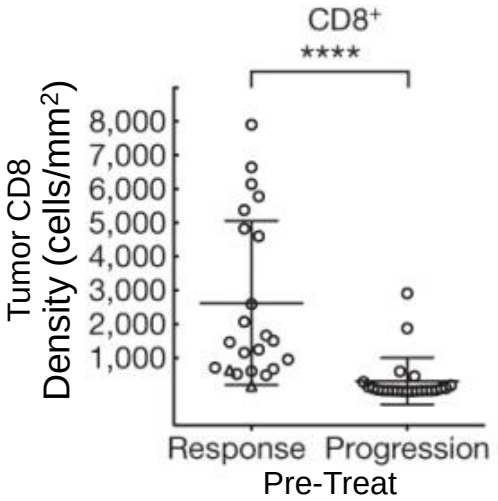
This underscores the role of the immune system in cancer and suggests the possibility that similar measures may be predictive of response to IMT

Reviewed in Fridman (2012). Nature Reviews Cancer. 12: 298.

Response to IMT in the Clinic: CD8+ Cells in the TME



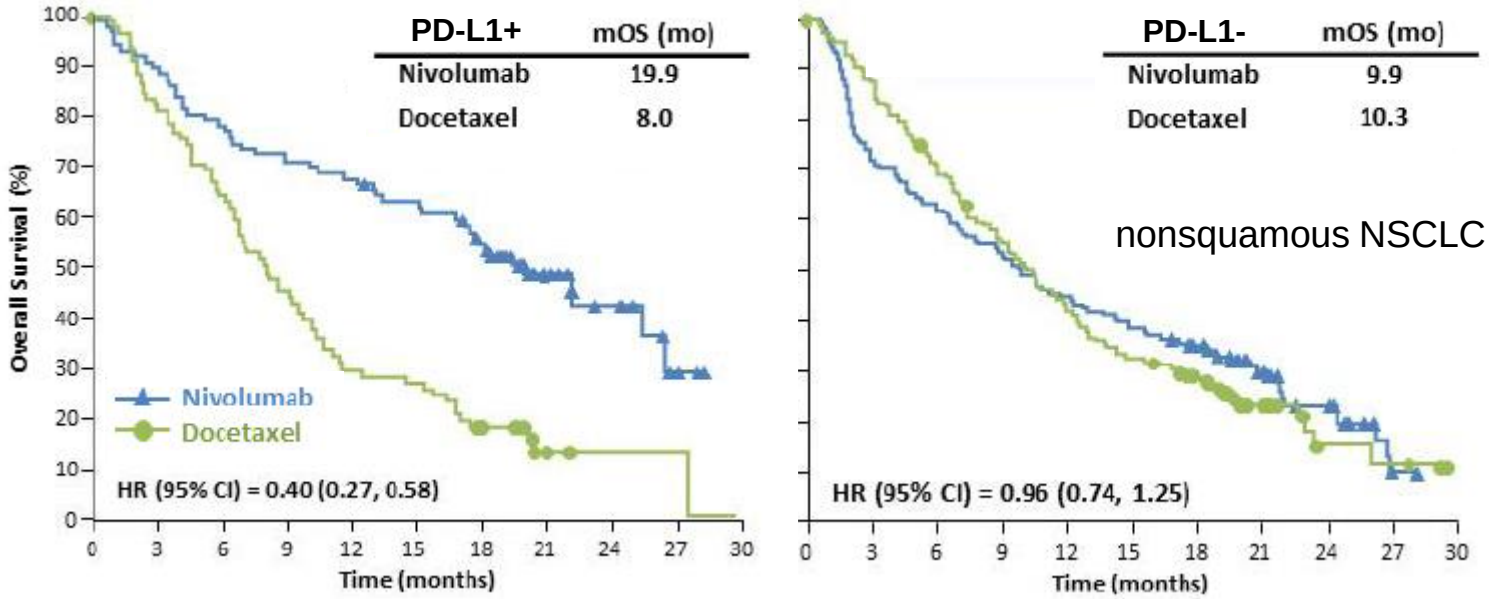




pembrolizumab - Tumeh. Nature (2014). 515: 568.

PD-L1: Lead Predictive Marker for Anti-PD-1 Pathway Agents

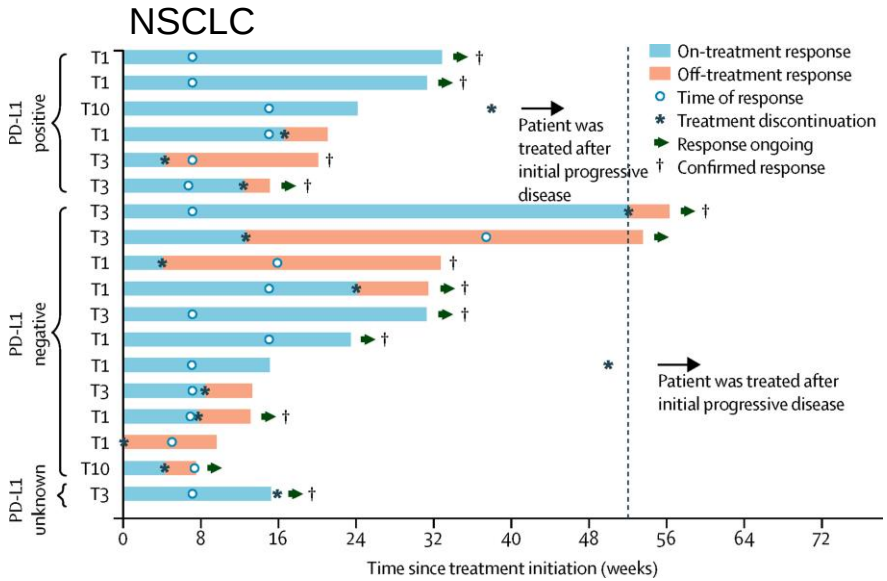
- Baseline, tumor PD-L1 expression predicts likelihood of response / benefit
  - Tumors use PD-L1 to evade T cell activity
  - PD-L1 expression is a beacon for ongoing, cellular immune responses that may be reinvigorated



nivolumab was approved in all-comers because of improved safety vs. docetaxel

nivolumab - Borghaei. NEJM (2015). 373:1627.

Anti-CTLA-4 / PD-L1: Responses in PD-L1- NSCLC



	Durvalumab 10–20 mg/kg every 2 weeks or 4 weeks plus tremelimumab 1 mg/kg*	Durvalumab 10–20 mg/kg every 2 weeks or 4 weeks plus tremelimumab 3 mg/kg	Durvalumab 15 mg/kg every 4 weeks plus tremelimumab 10 mg/kg
All evaluable patients with ≥24 weeks of follow-up			
Objective response	6/26 (23% [9–44])	5/25 (20% [7–41])	0/9 (0% [0–34])
Disease control	9/26 (35% [17–56])	8/25 (32% [15–54])	1/9 (11% [0–48])
PD-L1-positive (≥25%)			
Objective response	2/9 (22% [3–60])	2/5 (40% [5–85])	0/4 (0% [0–60])
Disease control	3/9 (33% [8–70])	2/5 (40% [5–85])	1/4 (25% [1–81])
PD-L1-negative (<25%)			
Objective response	4/14 (29% [8–58])	2/17 (12% [2–36])	0/4 (0% [0–60])
Disease control	6/14 (43% [18–71])	5/17 (29% [10–56])	0/4 (0% [0–60])
PD-L1-negative (0%)			
Objective response	4/10 (40% [12–74])	1/10 (10% [0–45])	0/3 (0% [0–71])
Disease control	5/10 (50% [19–81])	3/10 (30% [7–65])	0/3 (0% [0–71])
PD-L1 status unknown			
Objective response	0/3 (0% [0–71])	1/3 (33% [1–91])	0/1 (0% [0–98])
Disease control	0/3 (0% [0–71])	1/3 (33% [1–91])	0/1 (0% [0–98])

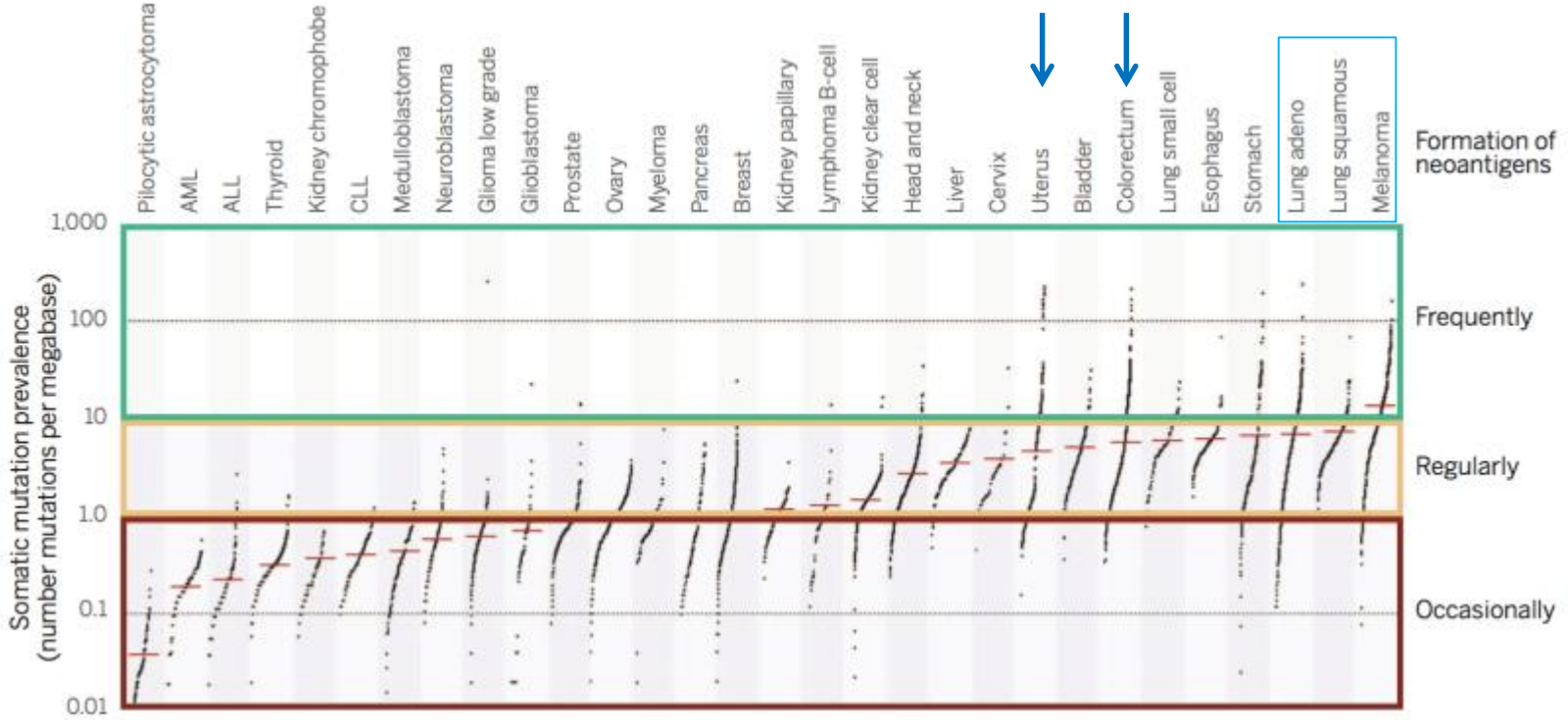
Data are number of patients/total number of patients (% [95% CI]). Objective response includes all confirmed complete and partial responses. Disease control comprises all confirmed complete and partial responses, and stable disease for 24 weeks or longer. Table includes patients with measurable disease at baseline with one or more follow-up scans, and patients who discontinued because of progressive disease or death without any follow-up scan. All patients were treated 24 weeks or more before the cutoff date. * Three patients who received durvalumab 3 mg/kg every 4 weeks and tremelimumab 1 mg/kg are excluded because this regimen was judged subtherapeutic.

Table 3: **Antitumour activity in combined cohorts and by PD-L1 status**

Suggests PD-L1 status may be used also to ID patients for combo regimens

durvalumab + tremelimumab - Antonia. Lancet (2016). Online, Feb.5, 2016

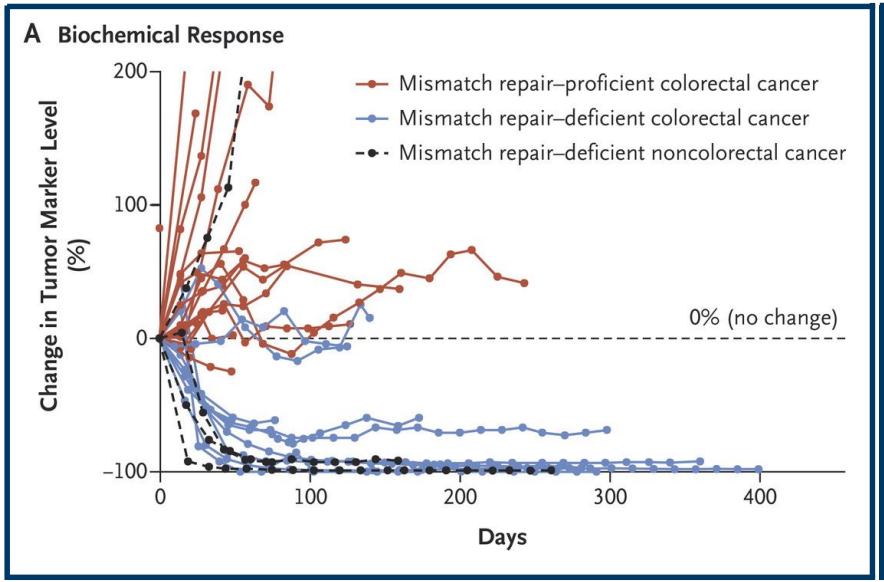
Emerging Data - Mutation (and MSI)

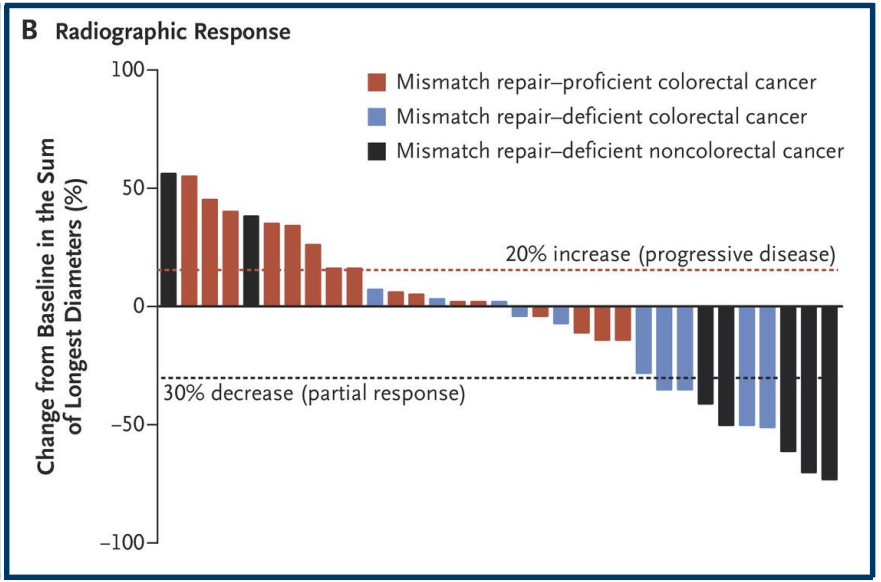


- Mutation load appears to be proportional to neoantigen formation
- Such tumors may be most ‘visible’ to the immune system

Reviewed in Schumacher and Schreiber (2015). Science. 348: 69

MMR-Deficient CRC





Demonstrates clinical activity is greater in MMR-deficient vs. -proficient CRC

pembrolizumab - Le (2015). NEJM. 372: 2509

Selection of IMT for the Right Patients May Rely on Multiple Biomarker Measures

- Current Biomarker Landscape:

  Individual positive selection measures that enrich for response to PD-1 monotherapy and may include –

  - PD-L1: Companion Dx currently on the market
  - MSI-H: Routinely measured clinically (for CRC)

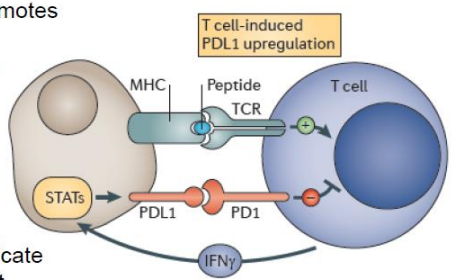
However, negative PD-L1 status may not preclude response / benefit and MSI is found only in a limited percentage of patients

Is there a set of factors that together identify patients for receiving monotherapy versus receiving combination therapy by default?

One example of a combined approach – PD-L1 / IFNγ

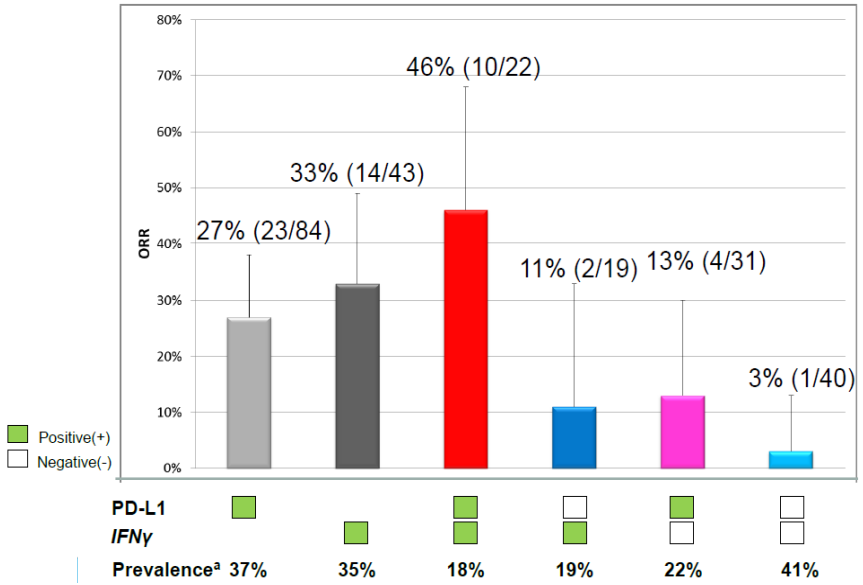
Biology of IFNγ and relationship with tumoral PD-L1

- IFNγ is a Th1 and NK cytokine that promotes cancer cell cytotoxicity:
  - Recruits tumor-infiltrating macrophages
  - Induces nitric oxide production
  - Increases cytotoxic T-cell proliferation
- IFNγ can induce expression of PD-L1
- High *IFNγ* mRNA expression might indicate immune active tumor microenvironment
  - Potentially identifies responders to durvalumab



Pardoll, Nature Reviews 2012

Durvalumab-treated NSCLC patient ORR by pretreatment *IFNγ* mRNA and/or PD-L1 status



Suggests multiple measures may improve both positive and negative selection

durvalumab - Presented by Higgs, ECCO / ESMO Annual Meeting 2015

Composite Biomarker Status to Inform Combo Decisions?

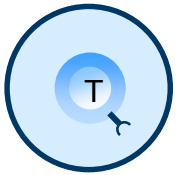
- Measures like CD8, IFNγ/PD-L1, and MSI are converging as means to identify *inflamed tumors* which may respond to current IMT; however, how these measures provide predictive value together is not fully understood

- Depending on the TME contexture, additional agents may be necessary for current IMT agents to be effective – likely to rely on:
  - i) Treg and/or MDSC depletion
  - ii) Blockade of other co-inhibitory pathways
  - iii) Agonism of co-stimulatory pathways

  AND Methods to detect the presence of immuno-modulating pathways

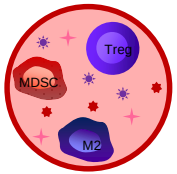
- If tumors are not T cell-inflamed, agents that kick-start the immune reaction will likely be necessary (e.g. agents that increase **Antigen Presentation**)

What may be monitored to ID patients for Therapy?



T-Cell Activation

- PD-L1
- Co-activators, Co-repressors
  e.g. Tim3, Lag3, TNFRSF Proteins
- Measures of T cell activity – Gene Signatures



Tumor Microenvironment

- Treg (FoxP3+)
- Myeloid Derived Suppressor Cells (MDSC)
- Pathologic features -
  Digital Imaging (with other T cell measures above)

Antigen Presentation

- Mutation / MSI (and neoantigens)
- Hallmarks of DNA damage repair deficiency
- MHC and peptide antigens
- Antigen-directed T cell measures
- Markers of ‘immunogenic cell death’

Summary

- Efforts to phenotype the tumor microenvironment before and after treatment are providing a better understanding of immune processes that lead to tumor killing
- In parallel to the initial IMT approvals, the first wave of prognostic and selective marker(s) are being established
- As new combination regimens are evaluated, TME phenotyping (and peripheral measures) may identify additional markers or sets of markers associated with patients likely (or unlikely) to receive benefit
- Though classic Companion Dx strategies have typically relied on a single measure to identify patients for therapy, IMT may rely on composite biomarker information and/or a ‘Biomarker Decision Tree’ to aid in choice of therapy or therapies