MADRID 2017 ESMO congress

ESMO COLLOQUIA

RATIONALE FOR CHEMO-IMMUNOTHERAPY COMBINATION TREATMENT IN SOLID TUMOURS

GRANADA AUDITORIUM
HALL 9
MADRID SPAIN

MONDAY, 11 SEPTEMBER 2017
13:00-14:30

Co-Chairs
Jaafar Bennouna, France

13:00	Introduction *Jaafar Bennouna, Nantes, France*
13:05	Optimizing immunotherapy: Rationale for a combination therapy approach *Elisa Giovannetti, Amsterdam, Netherlands*

Elisa Giovannetti, MD, PhD

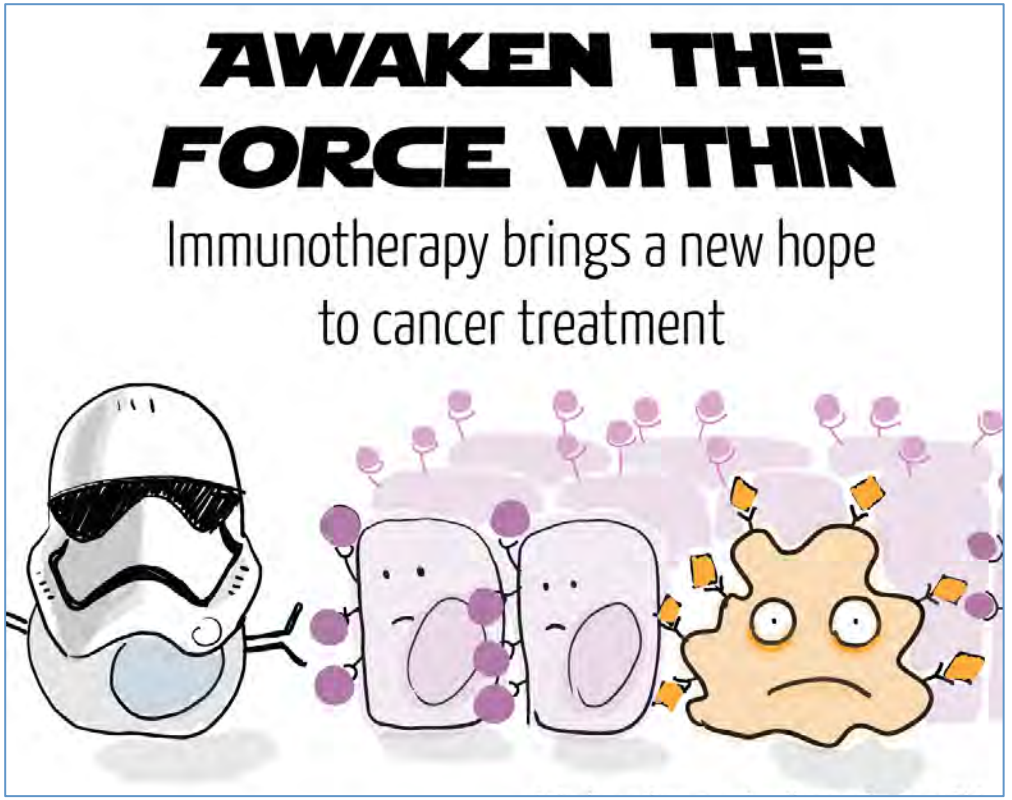
VUmc Cancer Center Amsterdam
The Netherlands

Cancer Pharmacology Lab
AIRC Start-up Unit Pisa (IT)

key objectives

- Provide an overview of the current pharmacological approaches for harnessing the immune system to attack cancer
- Describe mechanisms by which chemotherapy can increase tumor immunity
- Introduce the concept of priming to maximize efficacy of immune checkpoint blockade, particularly in tumors with low immunogenicity

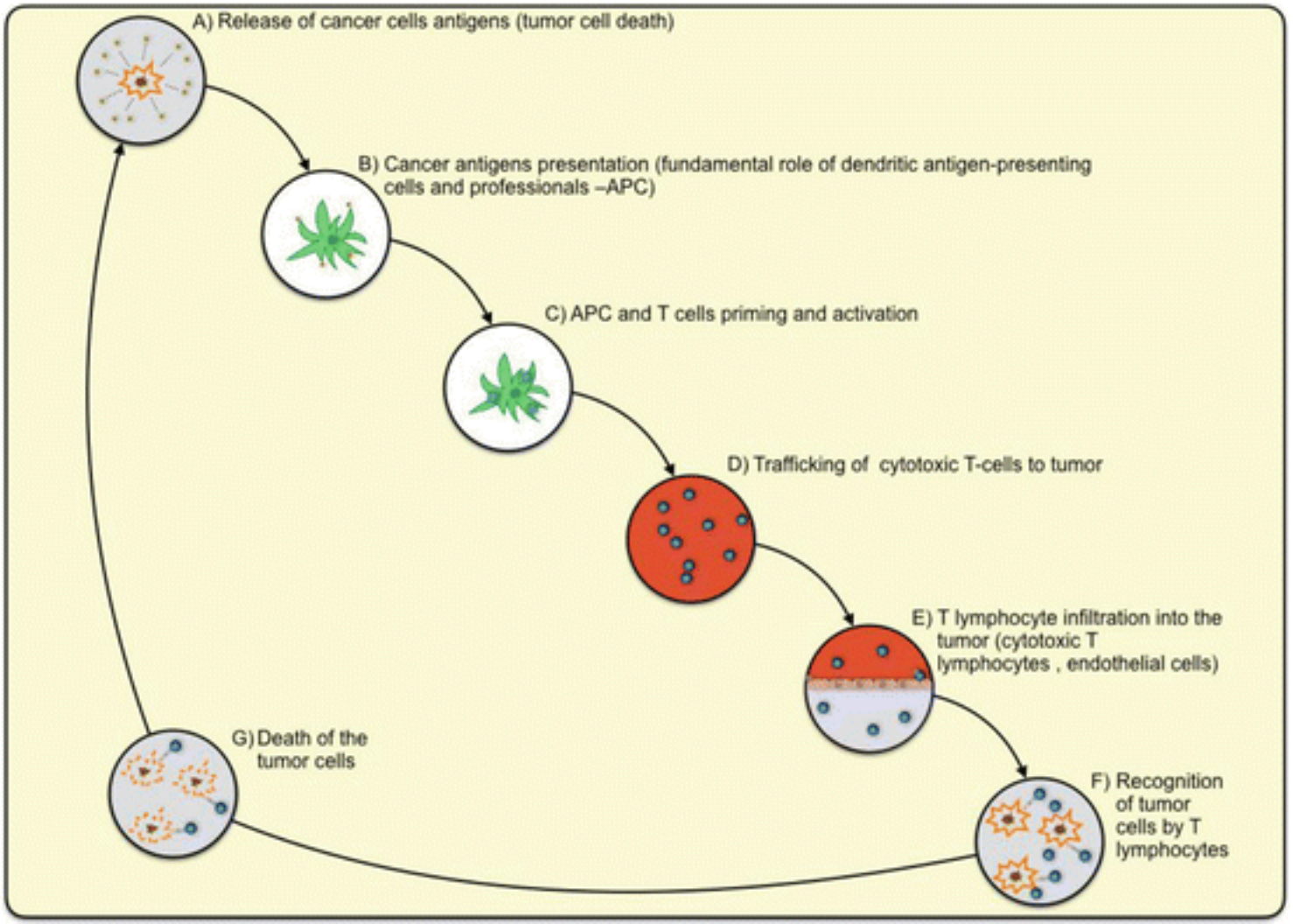
… over the last years, there has been a wave of successes with immunotherapy …



Immune evasion is an emerging hallmark of cancer

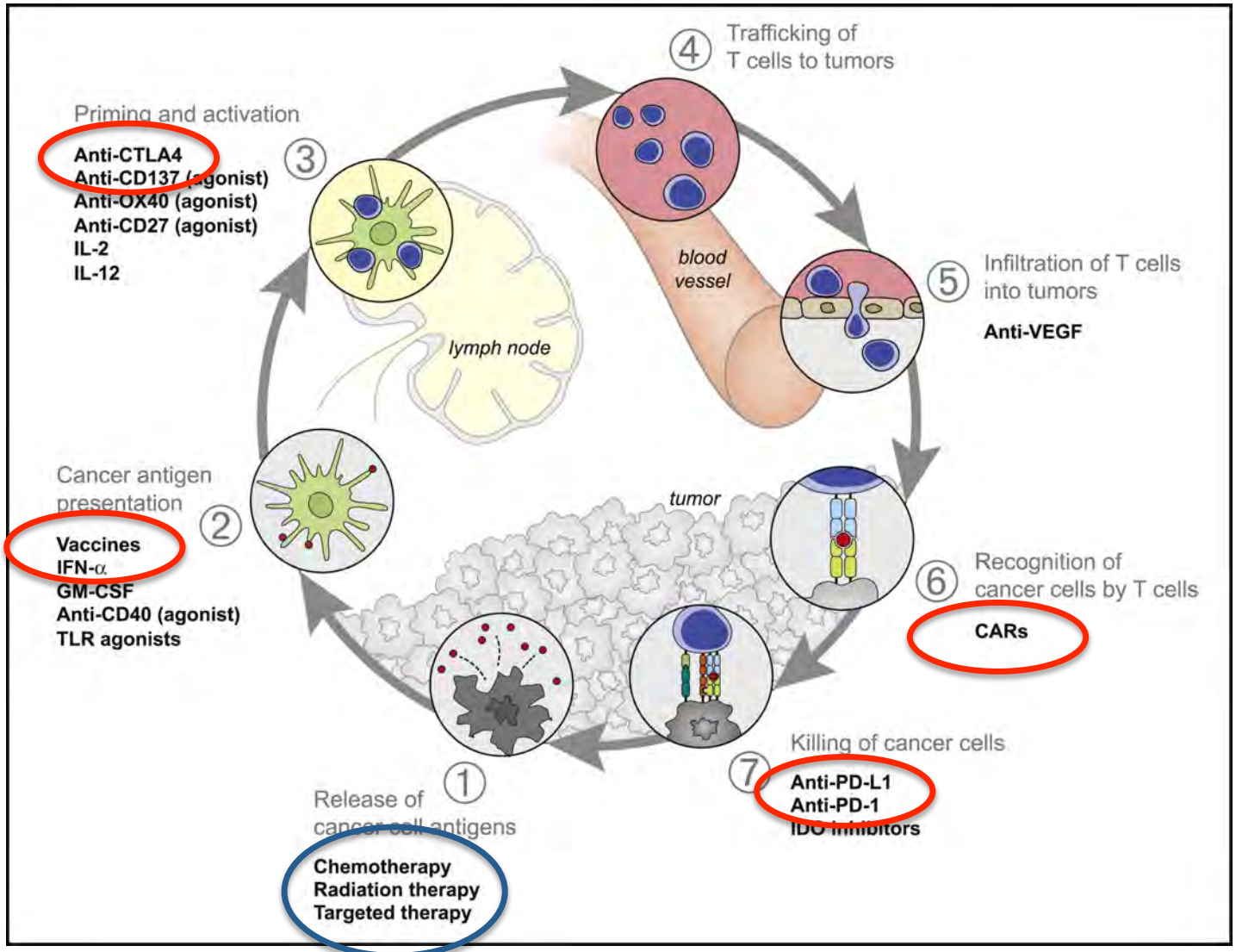
Hanahan and Weinberg, Cell 2011

The cancer - immunity cycle



Rolfo et al. Immunotherapy. Advances in Experimental Medicine and Biology. Springer 2017

Therapies that target the cancer-immunity cycle



Chen and Mellman, Cell 2013

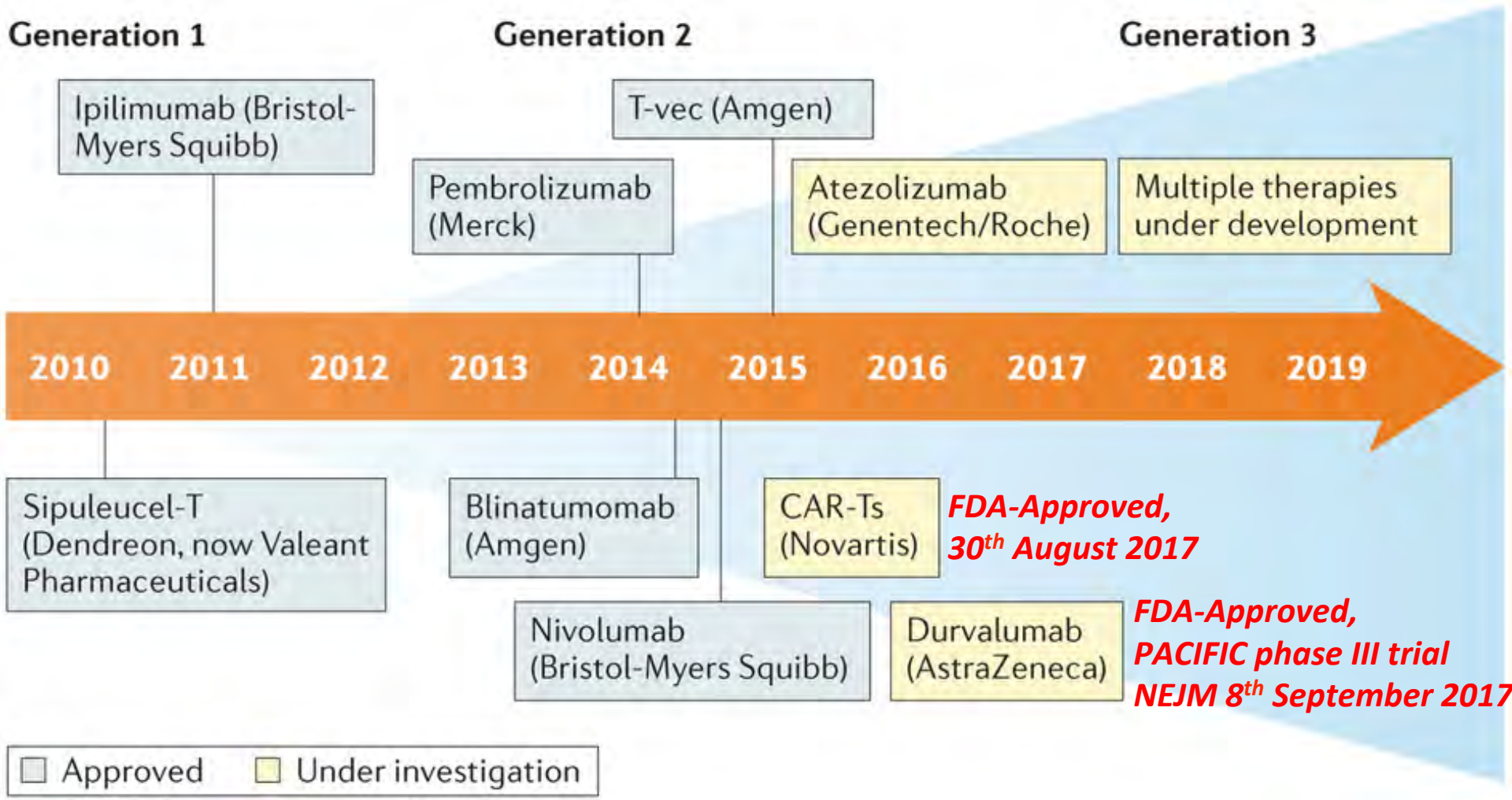
Characteristics of immuno-oncology modalities

Modality	Status	Pre-clinical findings	Pharmacokinetics	Pharmacodynamics	Clinical	
					Efficacy	Safety
Cytokines	IL-2 and IFNα approved but uncommonly used owing to high toxicity and low efficacy	Moderate effects	Clear kinetics	Multiple effects, MoA is complex and hard to attribute to one mechanism	Low	High unspecific toxicity (for example, whole body oedema)
Cellular therapies (CAR-Ts and TCR-Ts)	Multiple CAR-Ts and TCR-Ts in clinical trials; high complexity of manufacture and supply chain; strong target dependency; and few clinically effective targets (for example, CD19 and NY-ESO-1)	Moderate-to-strong effects	*In vivo* tracing and longevity of infused cells	Clear MoA; target-dependent effects	High response rates depending on the target (up to 90% for CD19, 50–60% for NY-ESO-1)[129]	Cytokine release syndrome; target-dependent cross-reactivity with healthy tissue
Vaccines	Many types of cancer vaccines in clinical trials (including peptides, proteins, viruses and cells)	Clear effects in mice, but these do not directly translate to humans	No direct pharmacokinetics for peptide- or protein-based vaccines	Measurable immune responses	Minimal as monotherapy; combinations to be explored	Minimal toxicity
Checkpoint-modulatory antibodies	Ipilimumab (targeting CTLA4), pembrolizumab (targeting PD1) and nivolumab (targeting PD1) approved; many compounds (including PDL1 blockers) in clinical investigation	Moderate effects	Clear kinetics	Universal mechanism not bound to histology, specific mutations or cancer antigens; multiple downstream effects after target engagement	Strong effects on survival with long-term survival in a subset of patients	Distinct irAEs; manageable with treatment algorithms

Hoos, Nat Rev Drug Discov 2016

Immunotherapy drug-development milestones

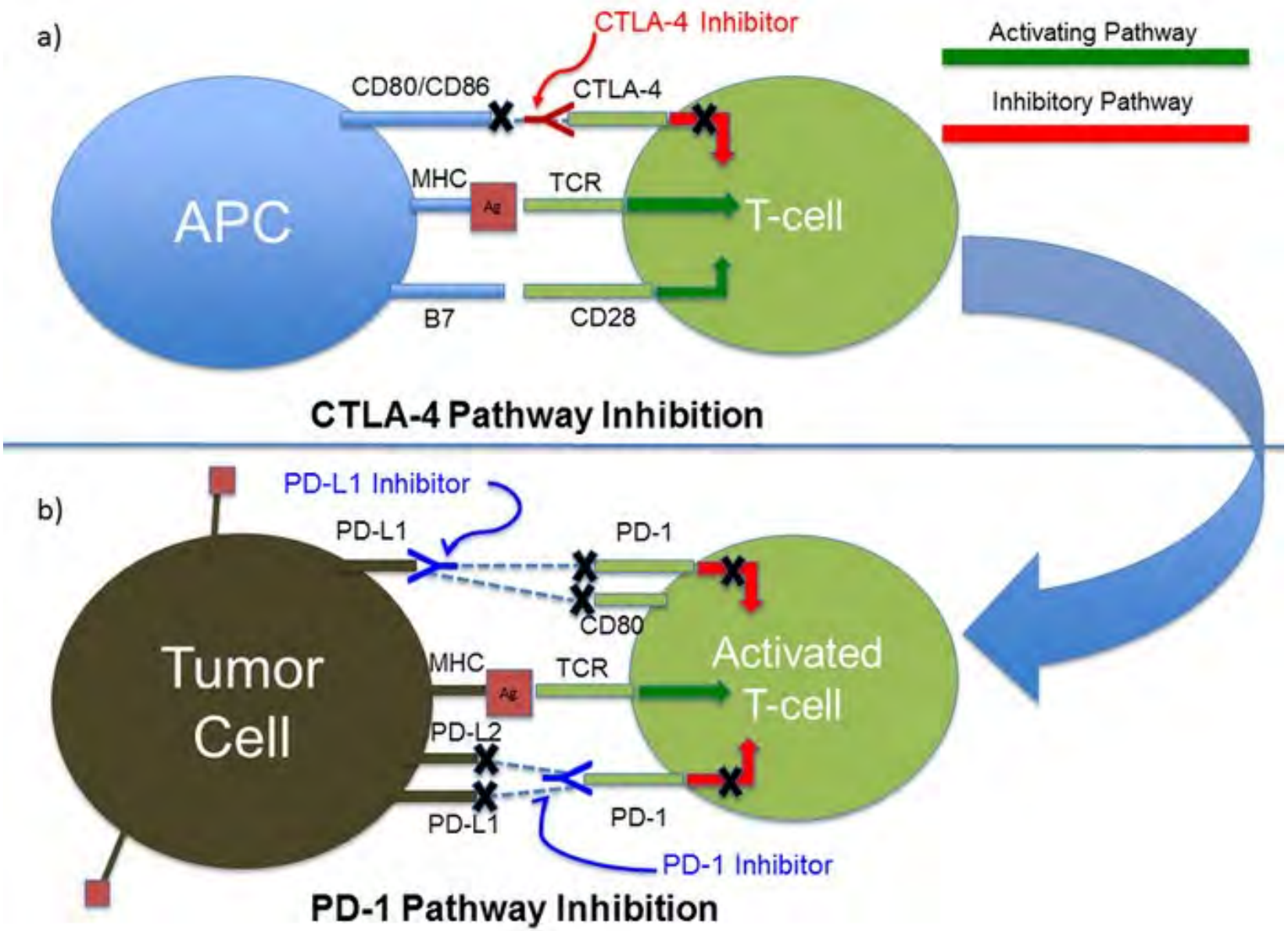
(…from 6 months ago, but already outdated)



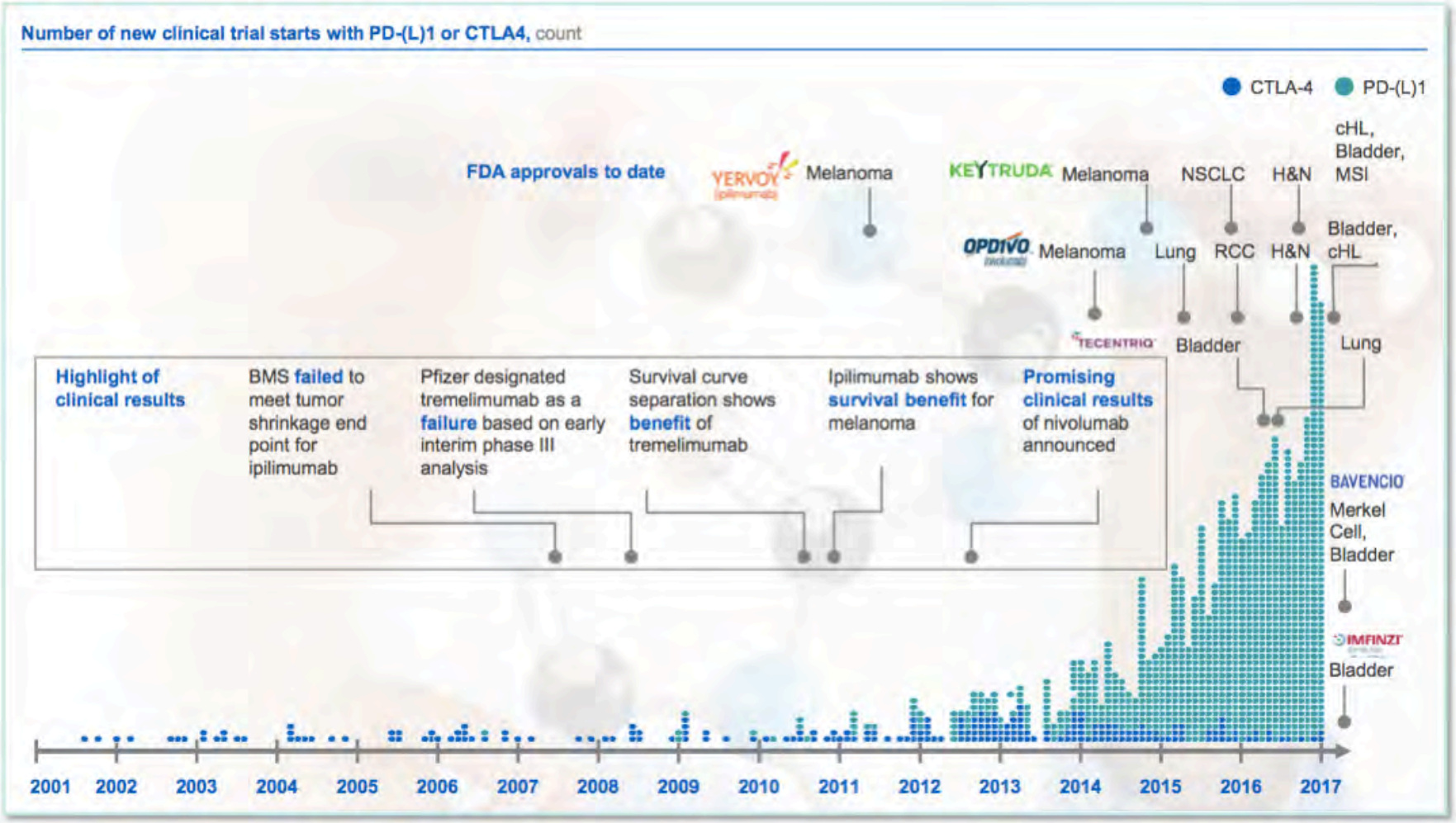
Hoos, 2016

Nature Reviews | Drug Discovery

Check-point inhibition

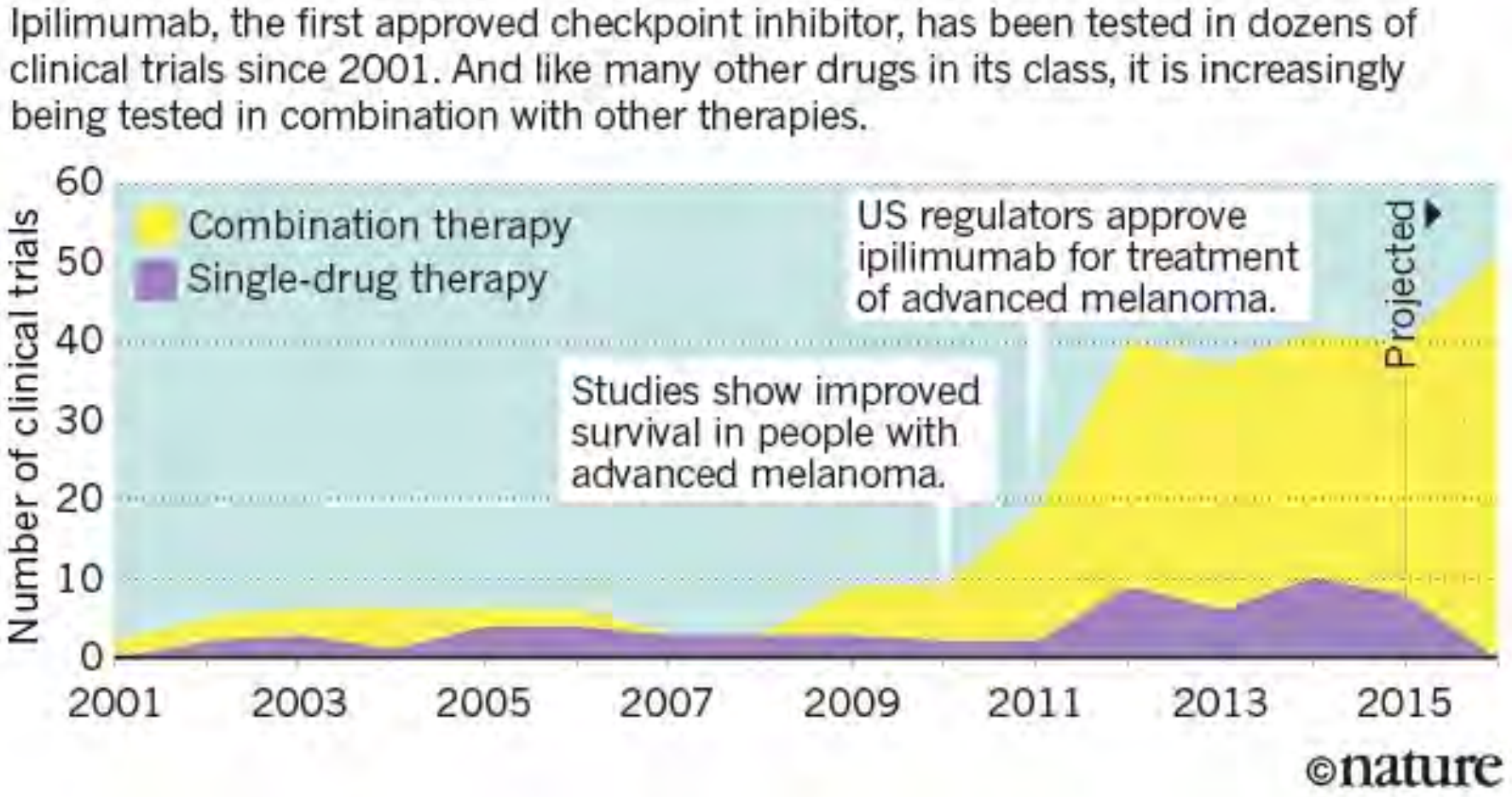


Immuno-oncology has driven recent volume of clinical activity (focus on checkpoint inhibitors)



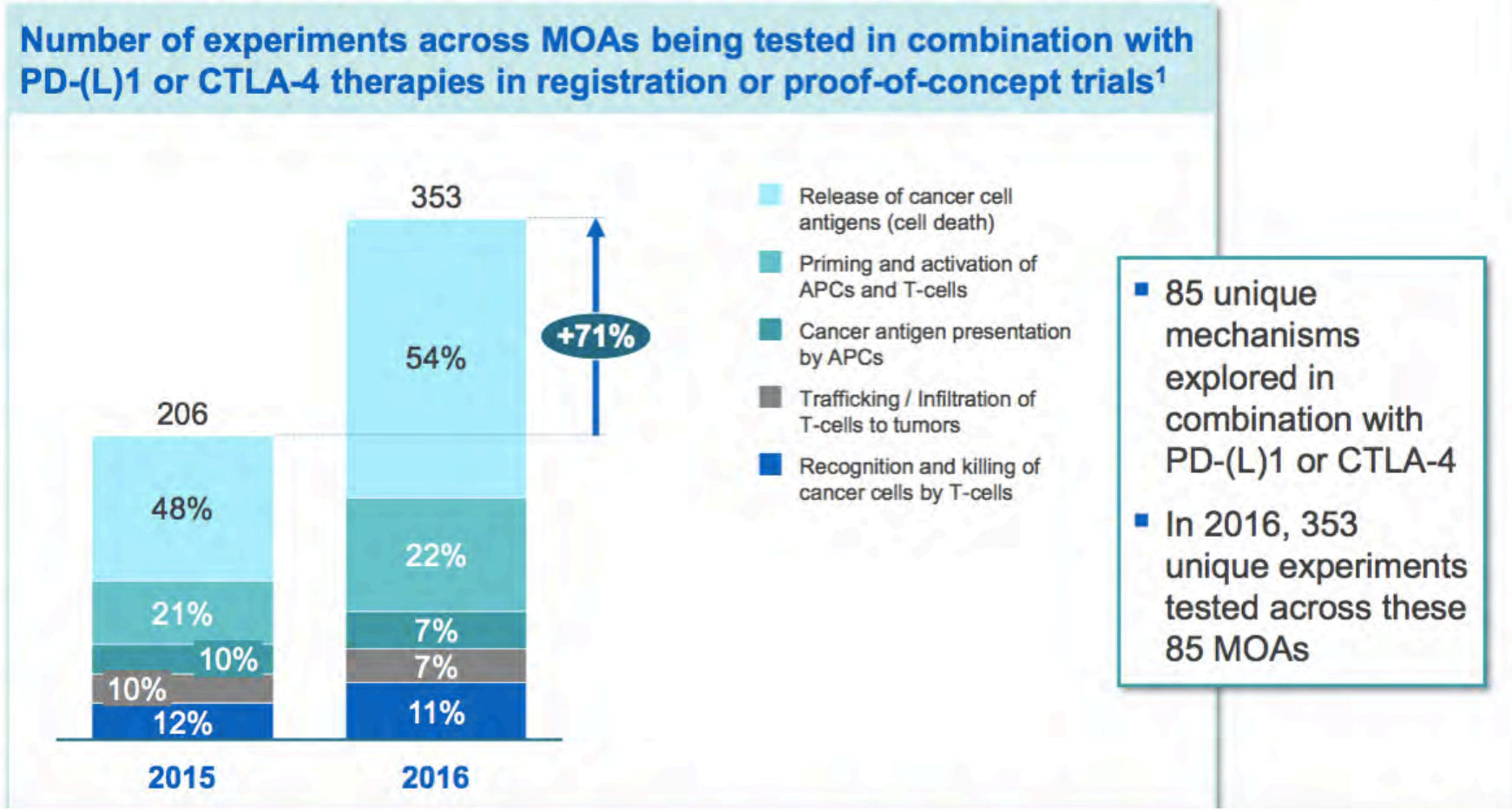
SOURCE: McKinsey MIOSS, clinicaltrials.gov as of 6/30/2017, FDA, ACSO

A “combinatorial explosion”



Ledford, Nature 2016

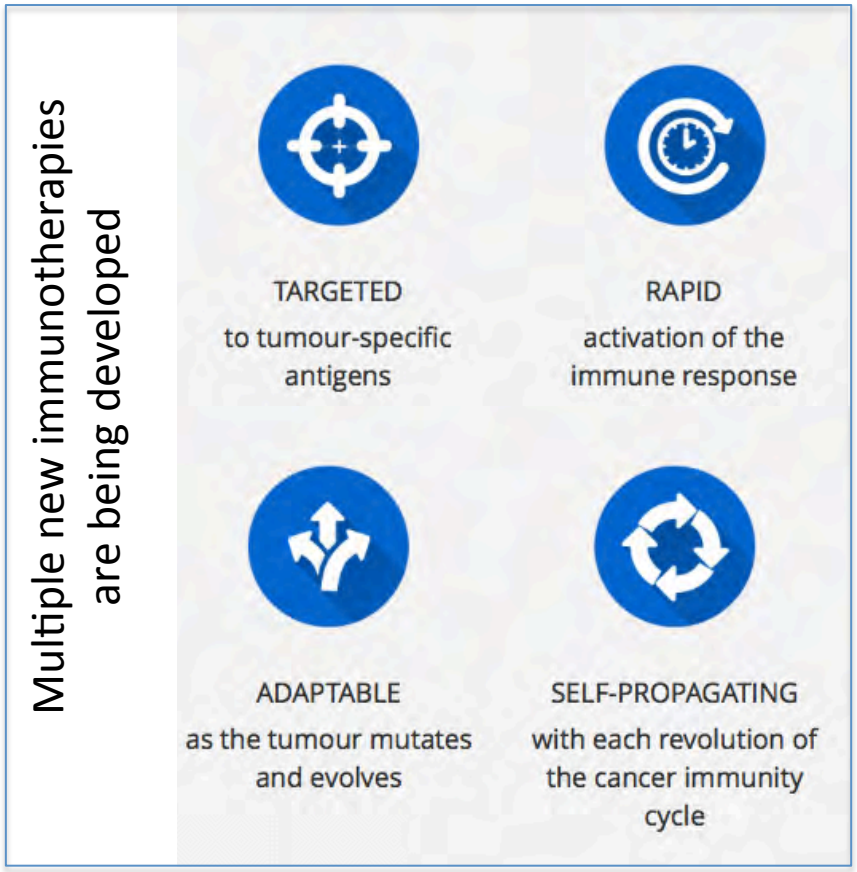
Increasing role of combination therapies

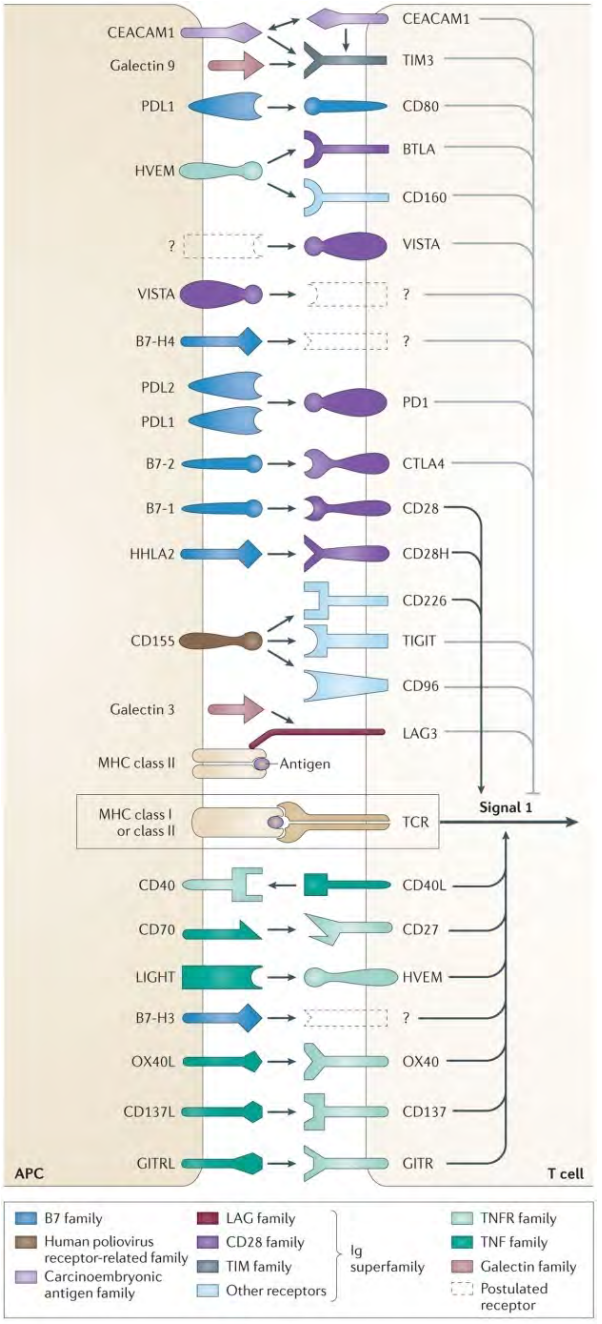


SOURCE: McKinsey Center for Asset Optimization MIOSS; Data as of 1/31/2017

NEW DRUGS for a more complex picture:

multiple co-stimulatory and inhibitory interactions regulate T cell responses

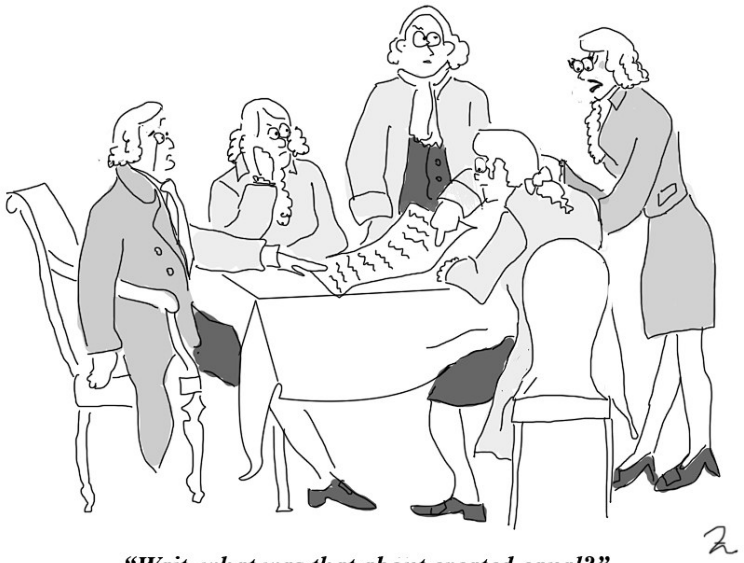




Pardoll, 2012

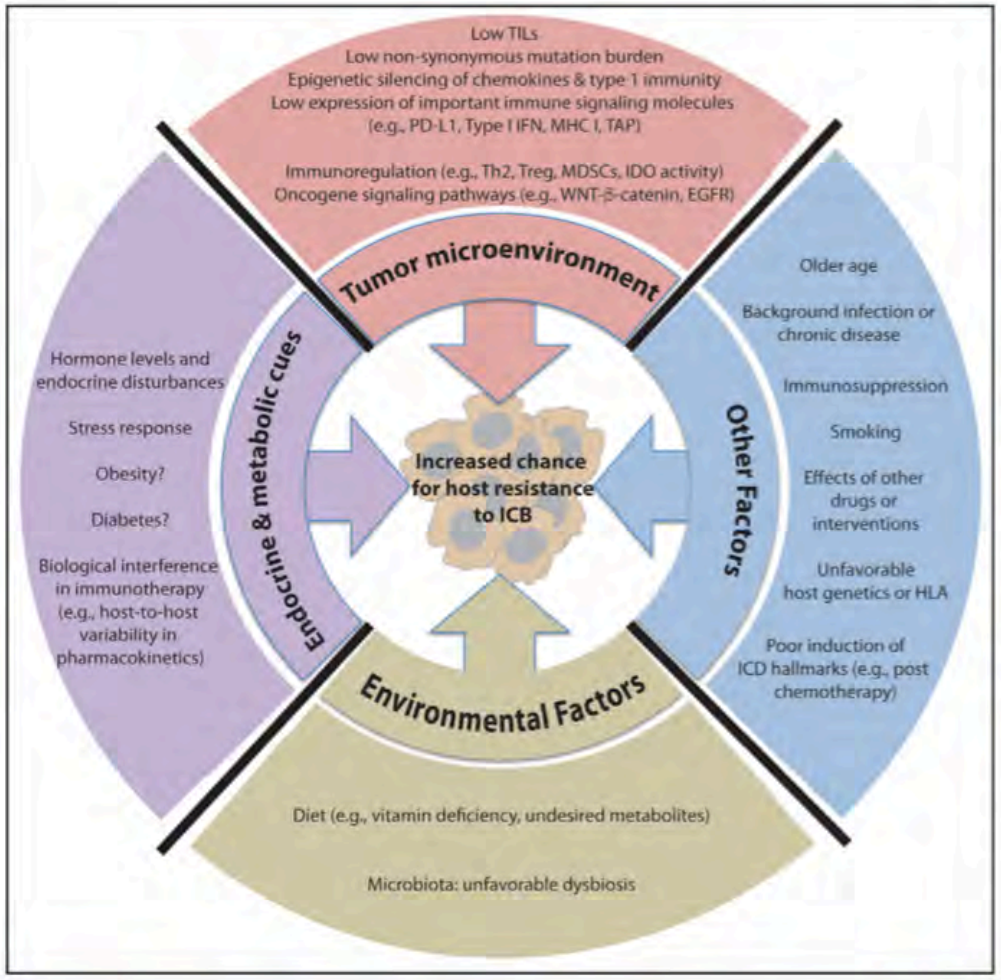
Nature Reviews | Cancer

…but not all cancers are created equal



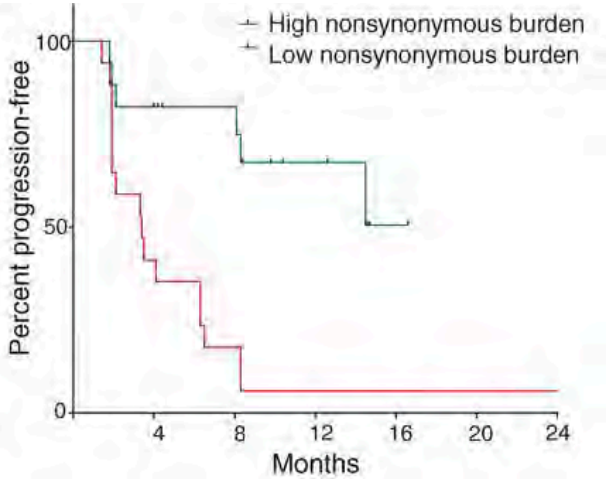
"Wait, what was that about created equal?"

Resistance to Immune-Checkpoint Blockade



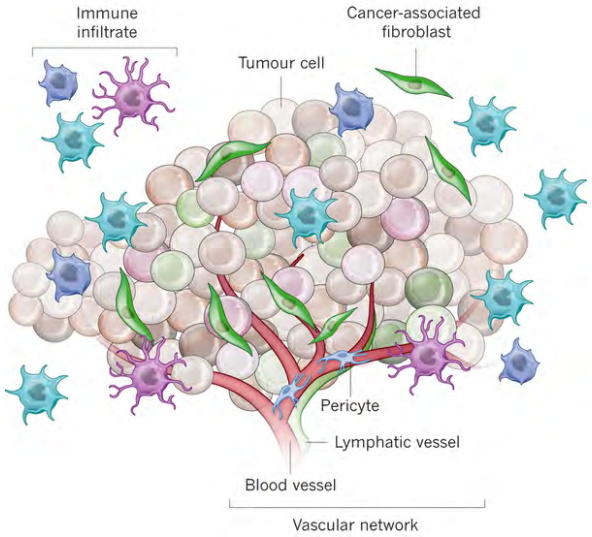
Pitt et al. Cell 2016

Mutational landscape and sensitivity to PD-1 blockade



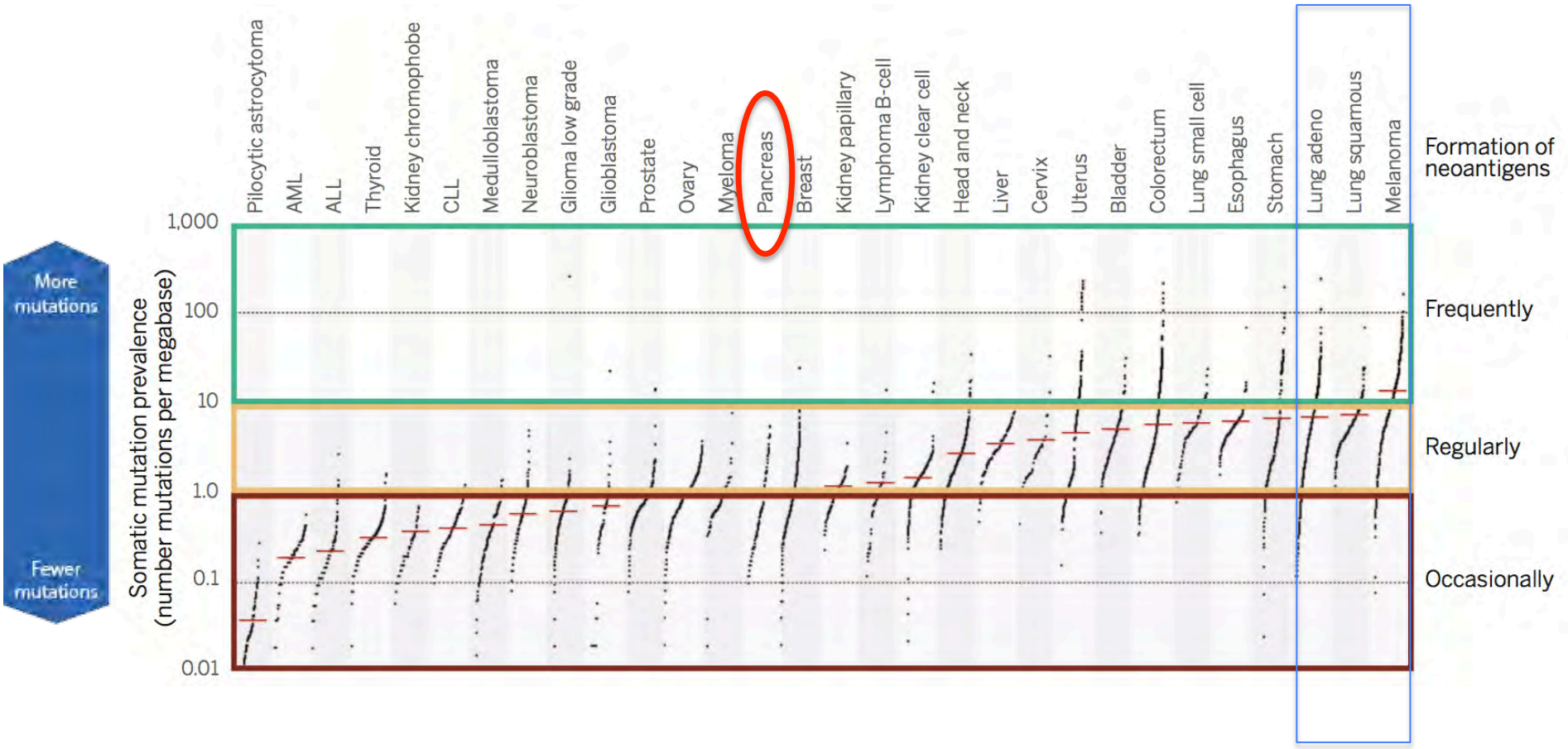
Rizvi et al. Science 2015

Tumor microenvironment



Junttila & de Sauvage, Nature 2013

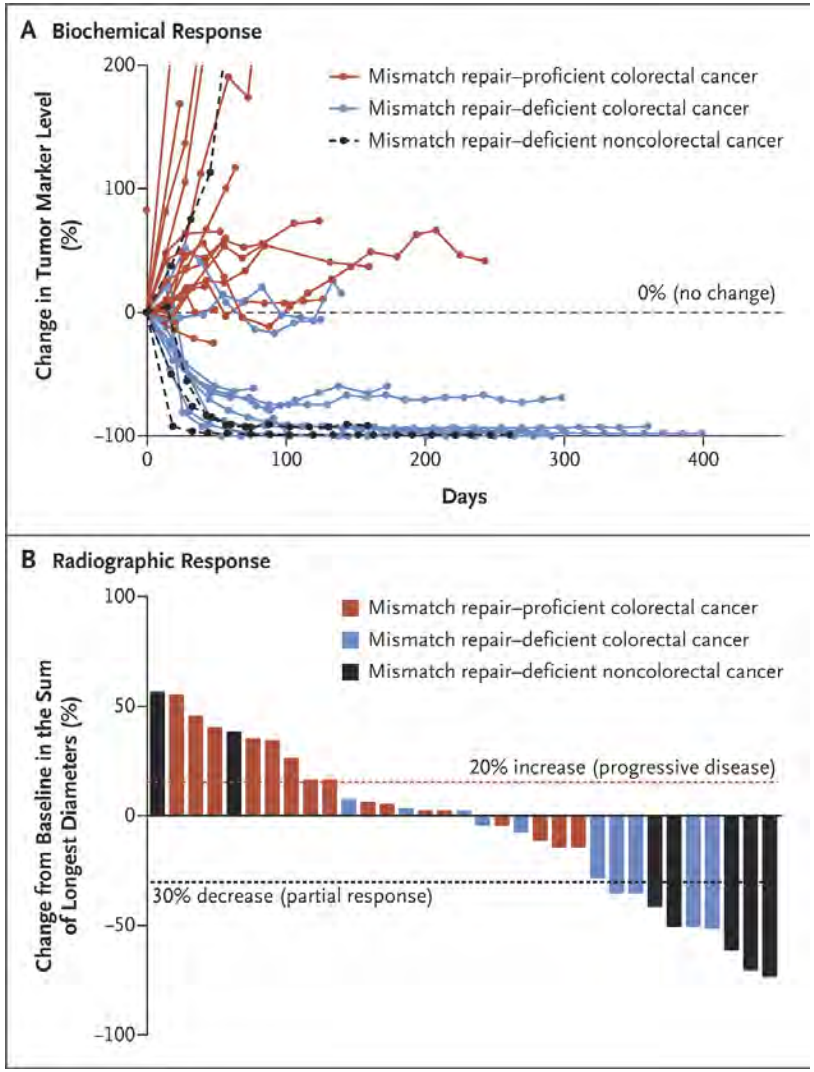
Tumor immunogenicity and mutation load

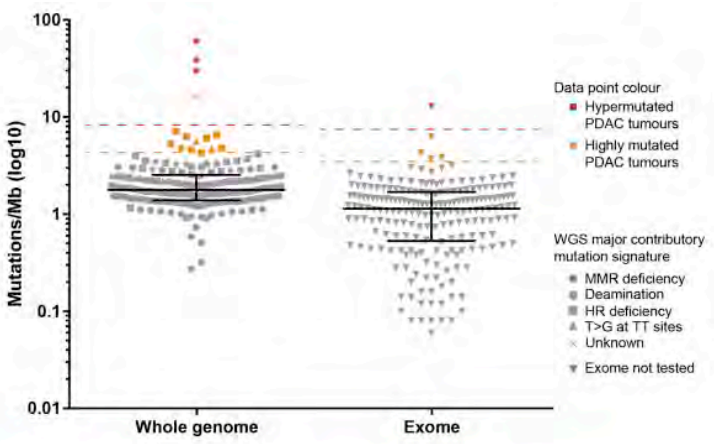


Tumor with best outcome to immunotherapeutic approaches

Alexandrov et al. Nature 2013

Tumor immunogenicity and mismatch repair



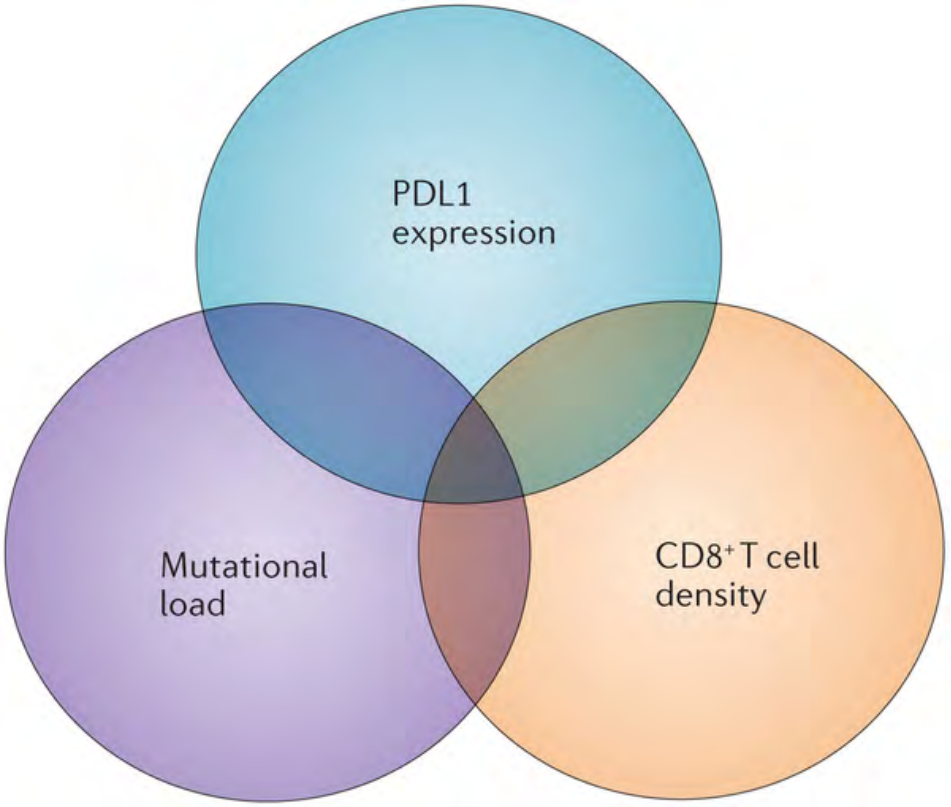


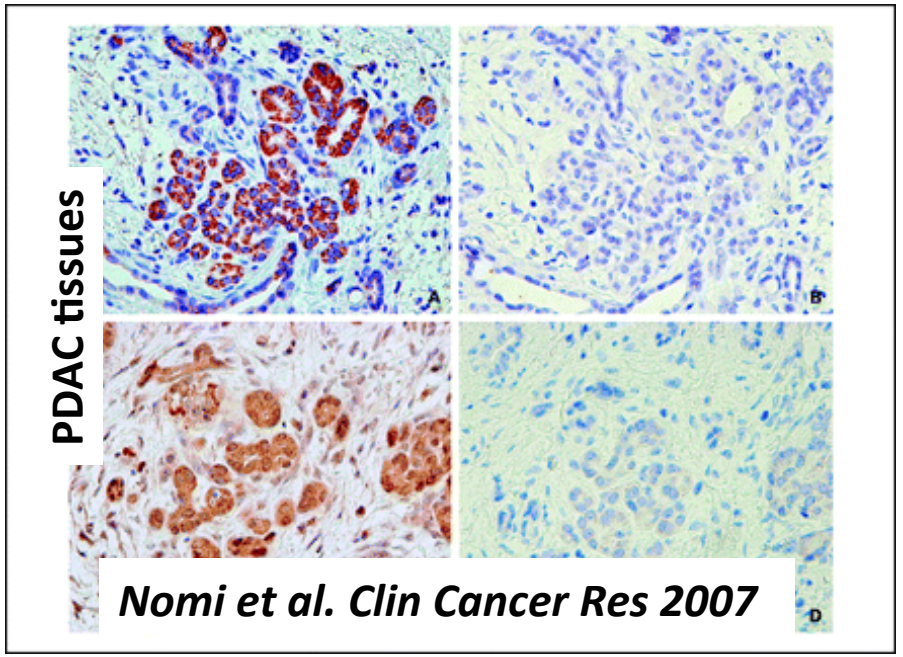
- Sequencing of 385 unselected sporadic pancreas cancers defined a mean mutation load of 1.1-1.8 mutation/Mb
- 5 extreme outliers were classified as hypermutated as they contained ≥12 mutations/Mb
- IHC for mismatch repair proteins (MSH2, MSH6, MLH1, and PMS2) identified 4 MMR-deficient tumors, all hypermutated

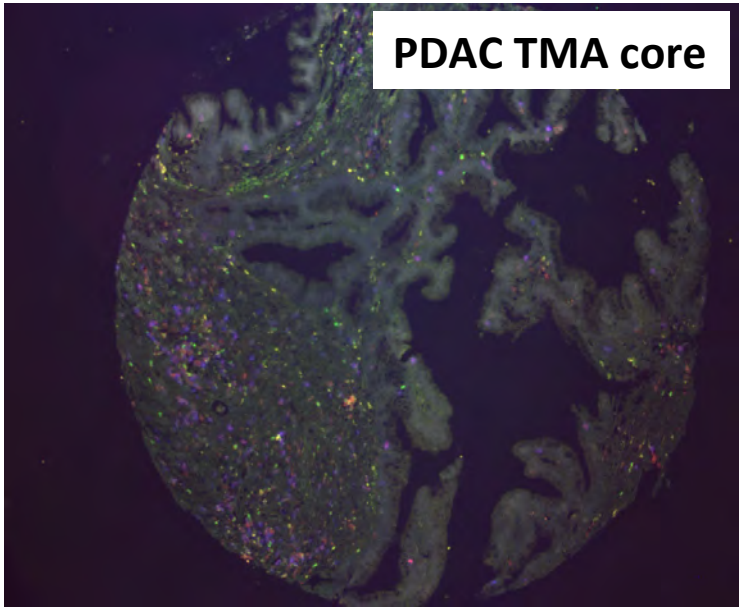
Le et al. NEJM 2015

Humpris et al. Gastroenterology 2017

Multifactorial biomarkers of clinical response to PD1 pathway blockade



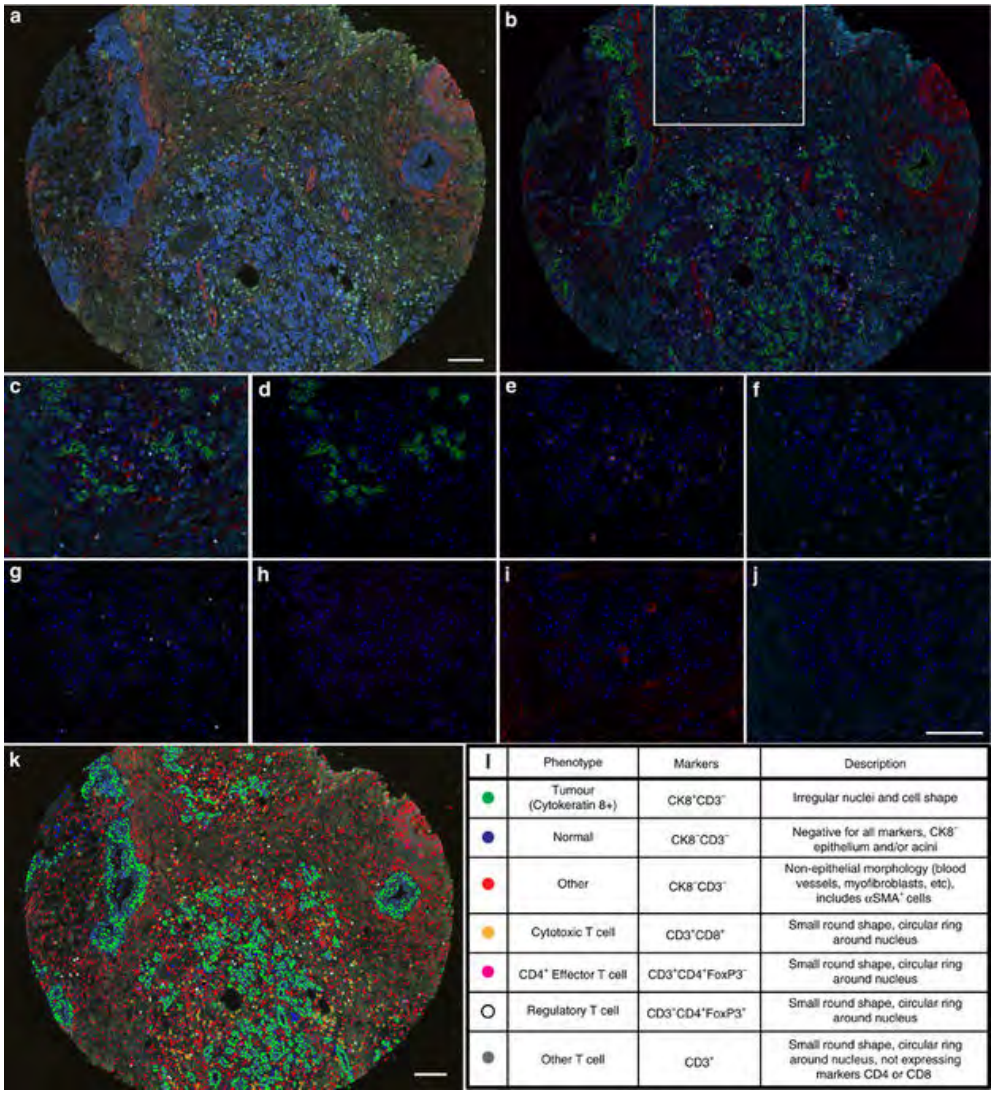




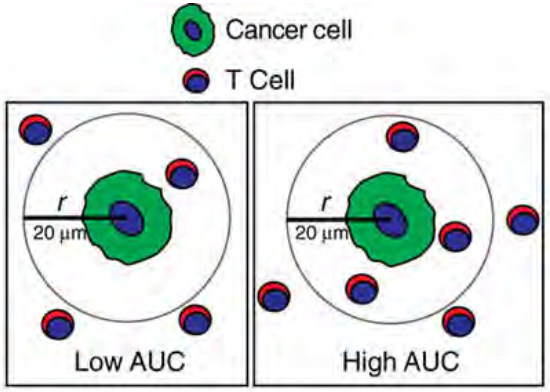
CD3, CD8 and FoxP3 IF
Jordanova,
Giovannetti et al.
Unpublished data

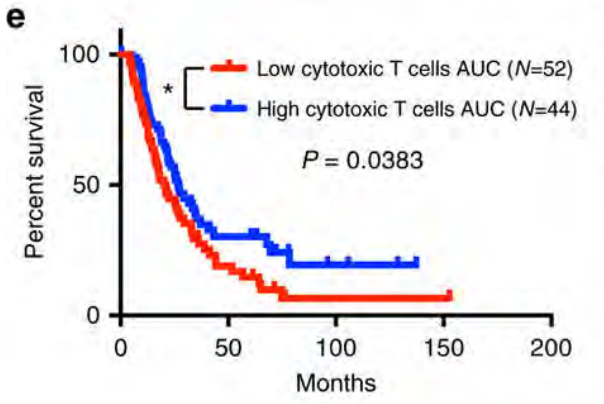
Topalian et al. Nature 2016

Spatial computation of intratumoral cytotoxic T cells correlates with survival of patients with pancreatic cancer



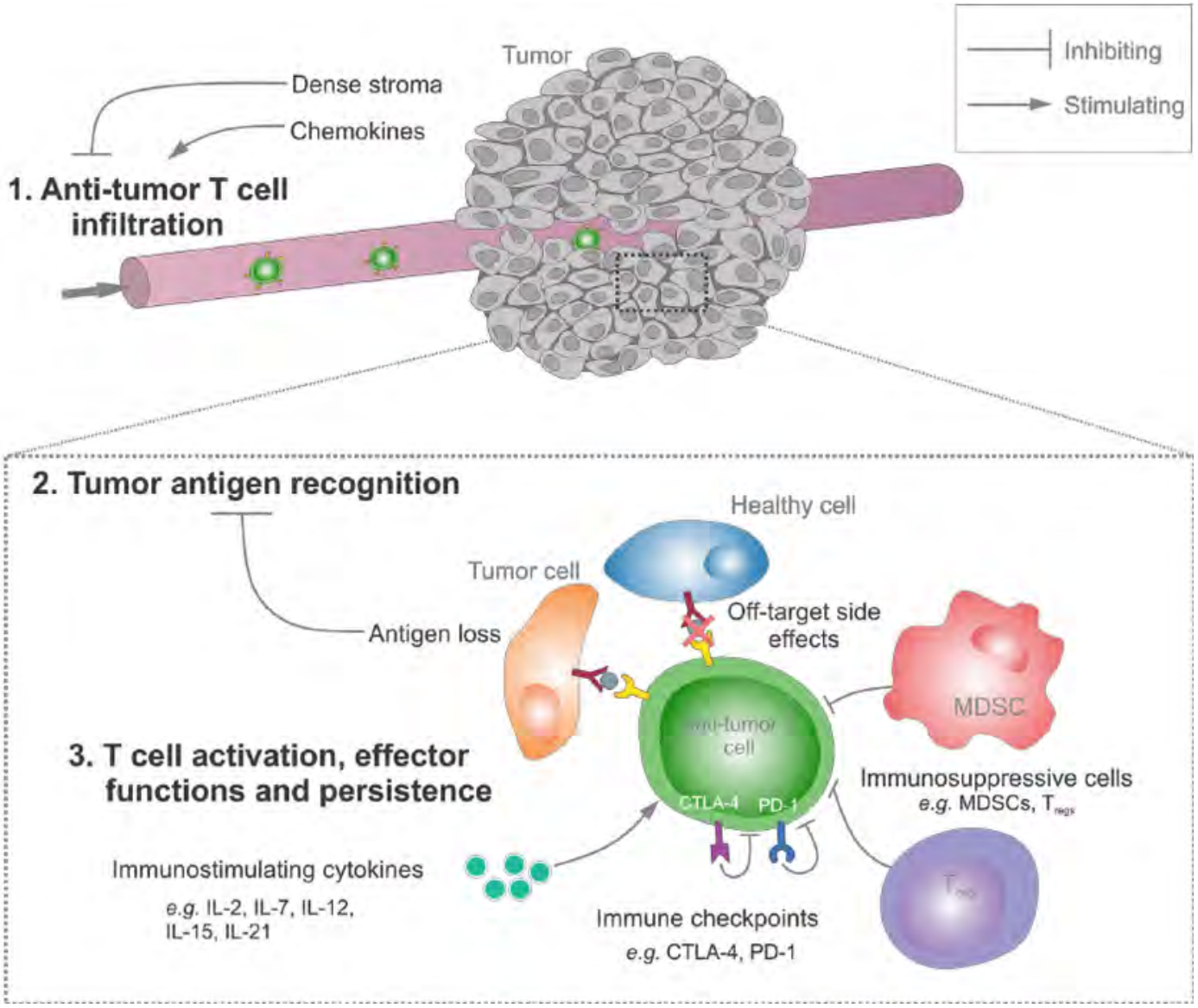
	Phenotype	Markers	Description
●	Tumour (Cytokeratin 8+)	$CK8^+CD3^-$	Irregular nuclei and cell shape
●	Normal	$CK8^-CD3^-$	Negative for all markers, $CK8^-$ epithelium and/or acini
●	Other	$CK8^-CD3^-$	Non-epithelial morphology (blood vessels, myofibroblasts, etc), includes αSMA^+ cells
●	Cytotoxic T cell	$CD3^+CD8^+$	Small round shape, circular ring around nucleus
●	$CD4^+$ Effector T cell	$CD3^+CD4^+FoxP3^-$	Small round shape, circular ring around nucleus
○	Regulatory T cell	$CD3^+CD4^+FoxP3^+$	Small round shape, circular ring around nucleus
●	Other T cell	$CD3^+$	Small round shape, circular ring around nucleus, not expressing markers CD4 or CD8





Carstens et al. Nat Commun 2017

The stromal component

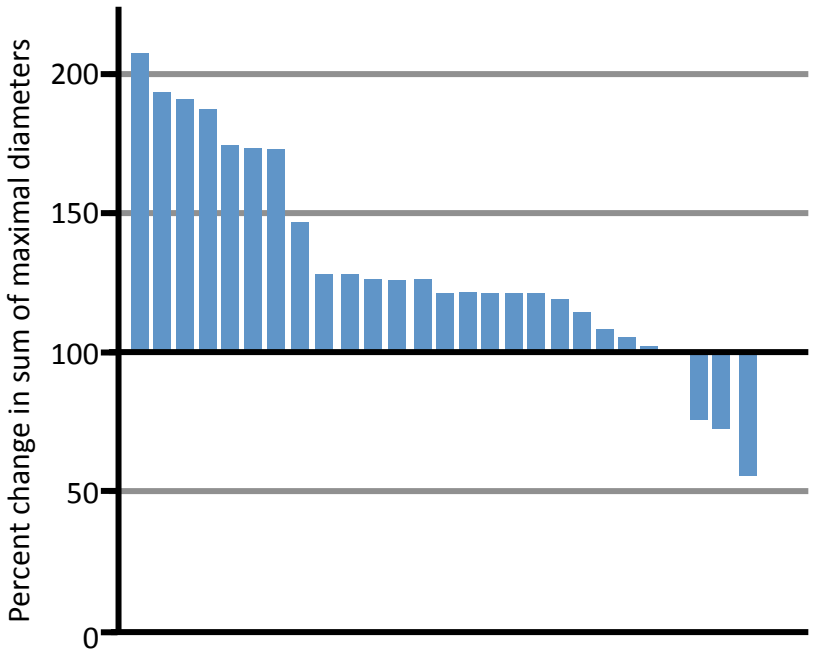


Wayteck et al. Cancer Letters 2013

Lack of efficacy of check-points inhibitors in pancreatic cancer

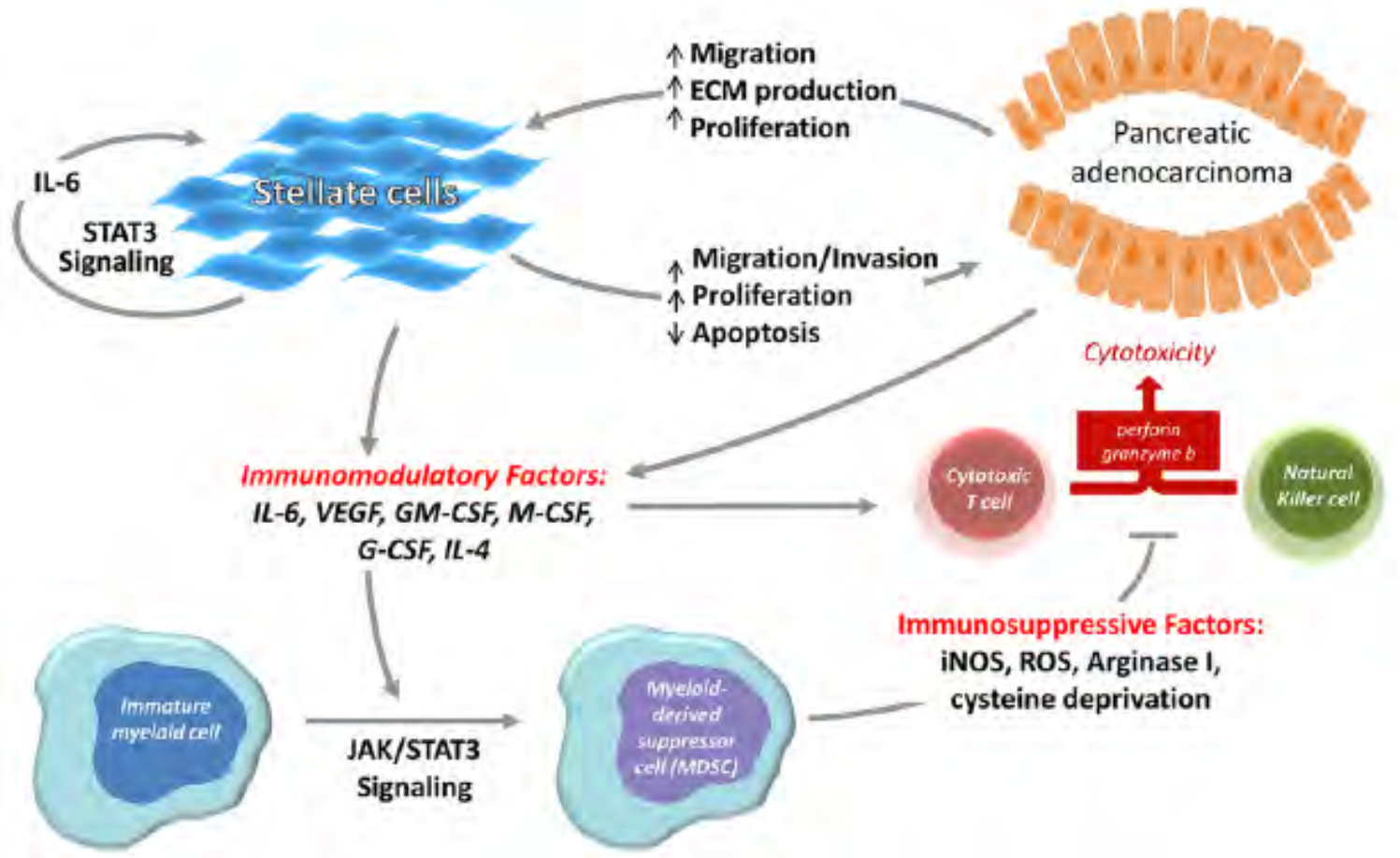
- In a Phase I trial, 207 patients with solid tumours, including 14 with pancreatic cancer, were treated with the anti-PD-L1 antibody, nivolumab[1]
  - Objective responses seen in NSCLC, RCC, ovarian cancer and melanoma
  - No response seen in pancreatic cancer
- In a Phase 2 trial, 27 patients with advanced/metastatic pancreatic cancer were treated with the anti-CTLA4 antibody, ipilumumab (3 mg/kg)[2]
  - No objective responses reported
  - 1 delayed response after PD observed
  - Unclear if sub-optimal dosing contributed to the poor efficacy

Disappointing tumour response to ipilumumab in patients with advanced pancreatic cancer[2]



1.Brahmer et al. NEJM 2012
2. Royal et al. J Immunother 2010

Targeting pancreatic cancer associated fibroblasts: A viable target to reduce immunosuppression?

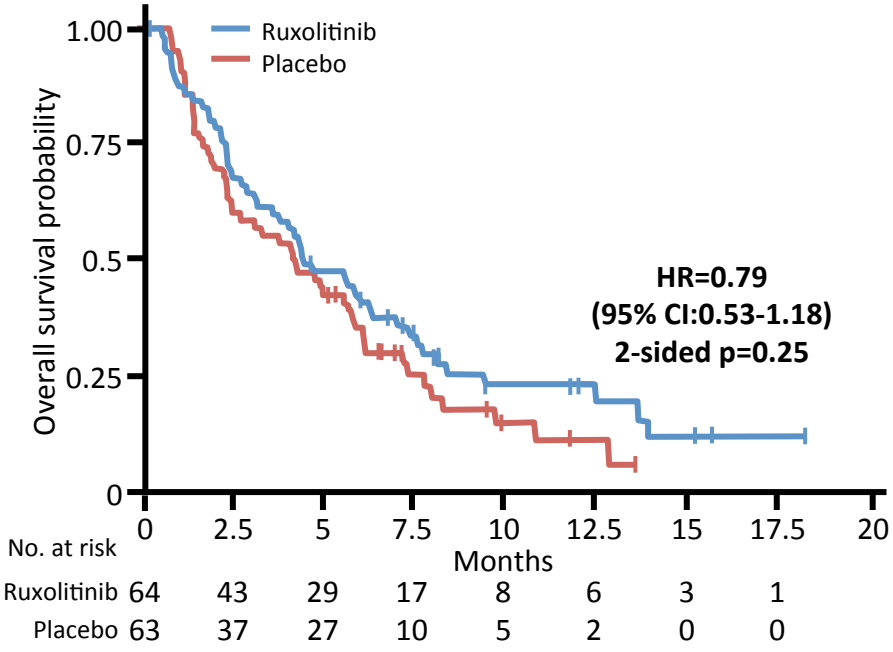


Mace et al. OncoImmunology 2013

Enhanced efficacy with JAK1/2 inhibition in ‘inflammatory’ pancreatic cancer

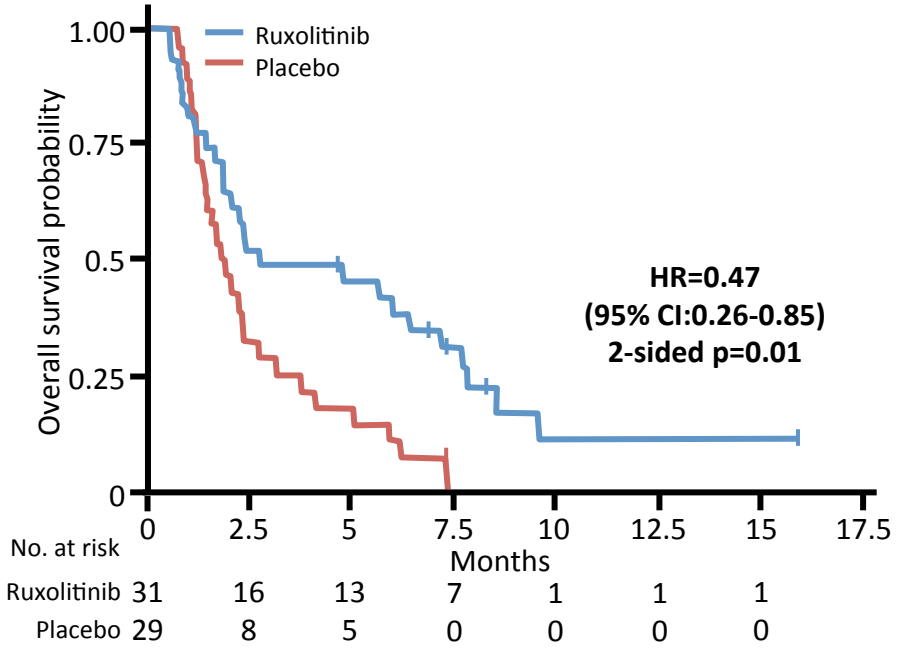
Overall survival (ITT)

	Ruxolitinib + cape (n=54)	Placebo + cape (n=63)
Median OS, days	137	130
Survival rate, %		
3 months	64	58
6 months	42	35
12 months	22	11



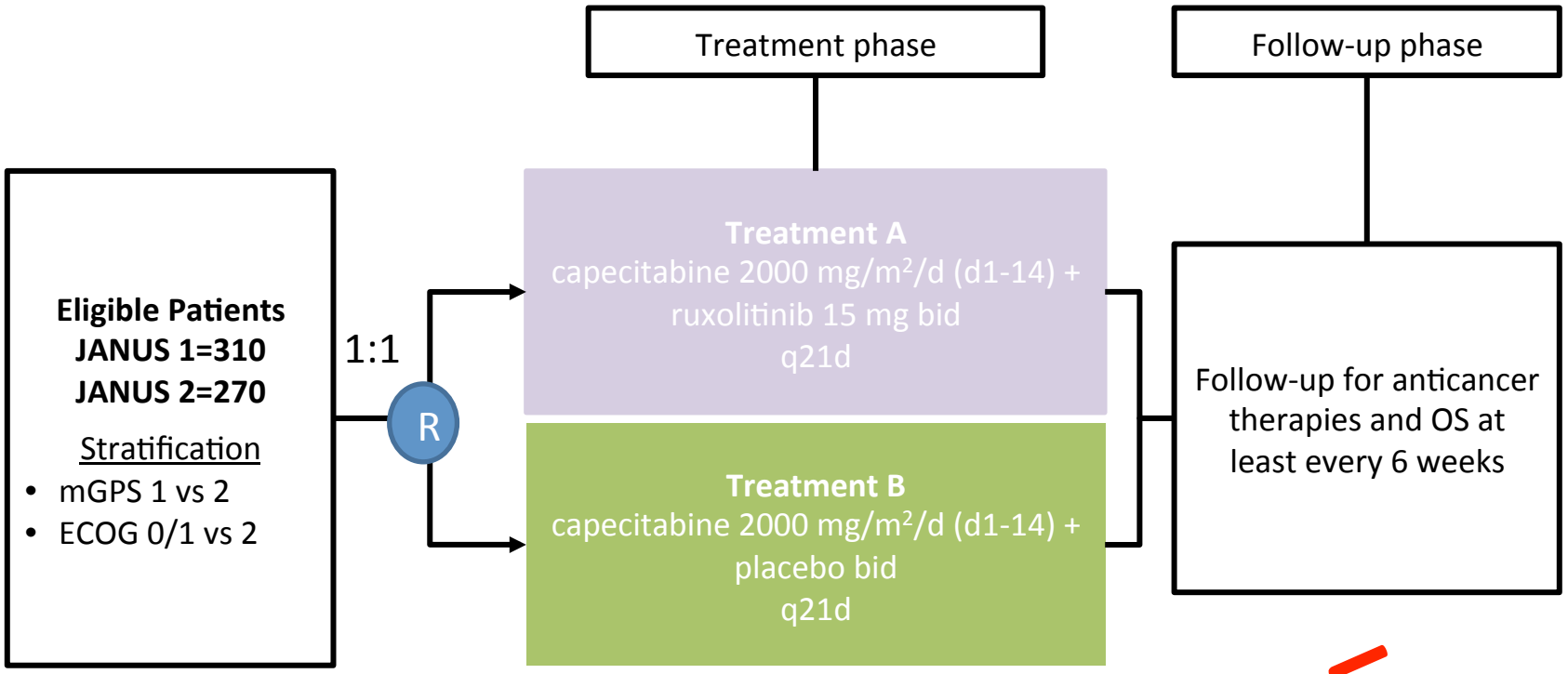
Overall survival in patients with CRP >13 mg/L

	Ruxolitinib + cape (n=31)	Placebo + cape (n=29)
Median OS, days	83	55
Survival rate, %		
3 months	48	29
6 months	42	11
12 months	11	0



Hurwitz et al. JCO 2015

Phase 3 trials of 2nd line ruxolitinib + capecitabine in MPC with evidence of a systemic inflammatory response (JANUS 1 & 2)



Modified Glasgow Prognostic Score (mGPS)

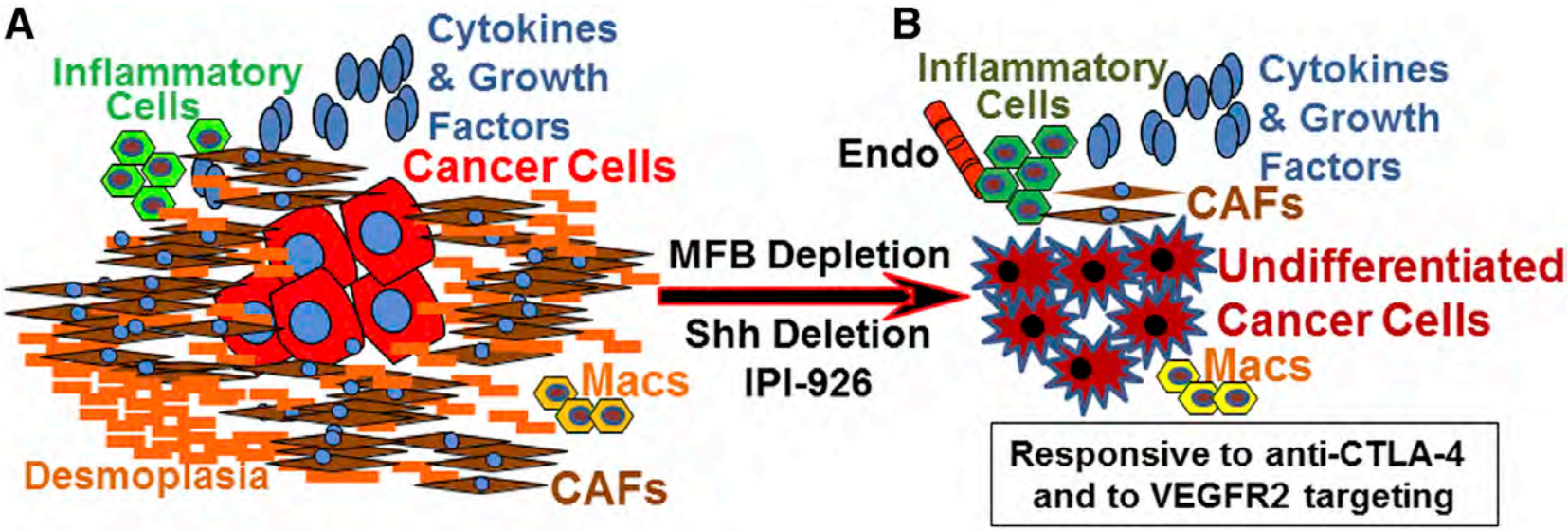
CRP or Albumin Value	Score
CRP ≤ 10 mg/L	0
CRP >10 mg/L and albumin ≥35 g/dL	1
CRP >10 mg/L and albumin <35 g/dL	2

Primary endpoint: OS
Secondary endpoints: PFS, RR, DoR

NEGATIVE

O'Reilly ASCO 2015 abstract TPS4146
Hurwitz ASCO 2015 abstract TPS4147

Pancreatic Cancer Stroma: Friend or Foe?

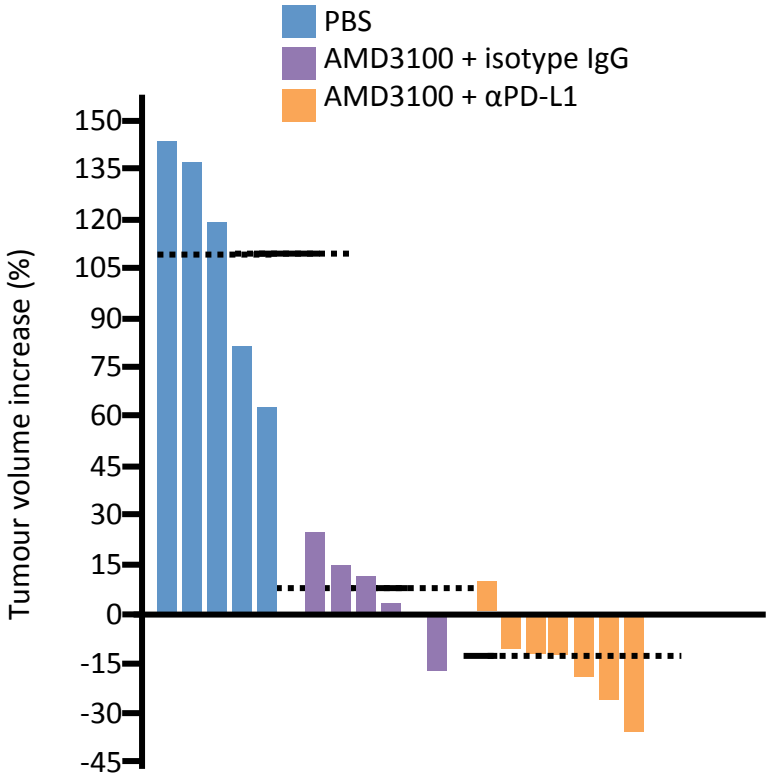


Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival

Gore and Korc, Cancer Cell 2014
Özdemir et al. Cancer Cell 2014

Targeting CXCL12 from FAP-expressing carcinoma associated fibroblasts synergizes with anti-PD-L1

- In murine models, depleting FAP+ CAFs restored (1) immune control of PDAC growth and (2) antitumor effects of α-CTLA-4 and α-PD-L1
- Chemokine ligand 12 (CXCL12) may be responsible for immunosuppression by FAP+ cells:
  - Cancer cells were coated with CXCL12
  - FAP+ CAF was the principal source of CXCL12 in the tumour
- **AMD3100**, a CXCL12 receptor chemokine (C-X-C motif) inhibitor, induced rapid T-cell accumulation among cancer cells and acted synergistically with α-PD-L1



CAF, carcinoma-associated fibroblast; FAP, fibroblast activation protein

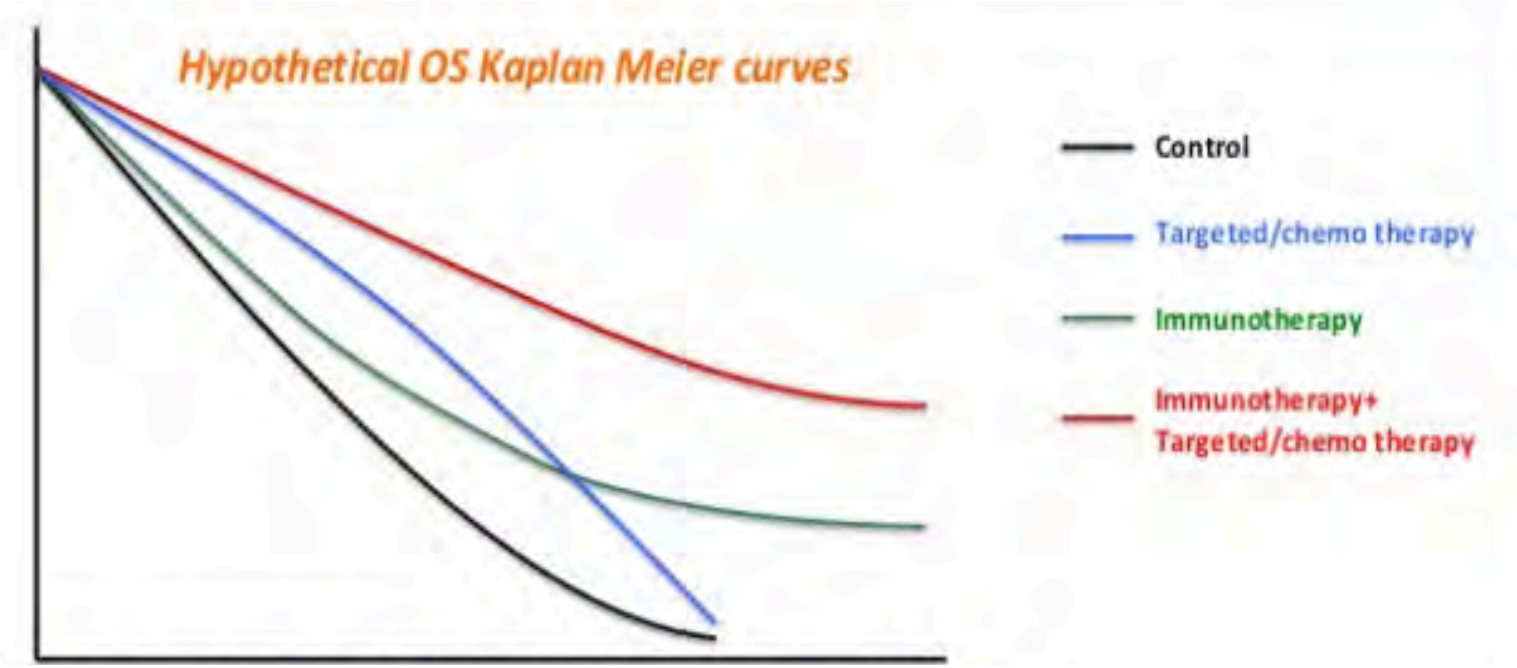
Feig et al. PNAS 2013

Emerging evidence for combination strategies with immune checkpoint inhibitors

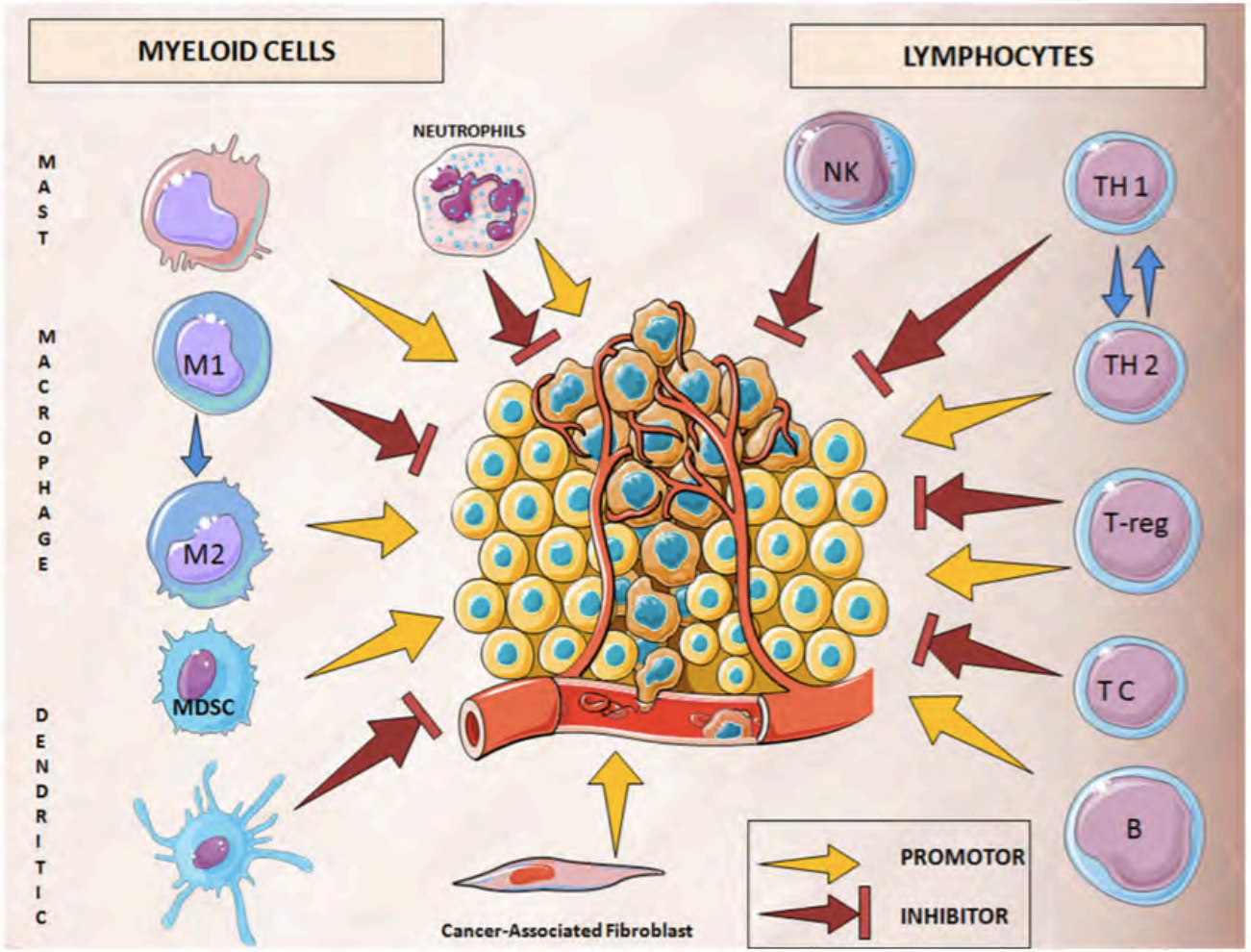
- Despite the **recent "misstep" with the MYSTIC** trial (…and waiting for the final data from the CHECK MATE trials)

- Various combinations with immune checkpoint inhibitors are being explored, including:
  - CXCL12 receptor chemokine inhibitors
  - Vaccines
  - CD40 agonists
  - Chemotherapy (already with a very successful story: KEYNOTE-021g trial)

Combination of immunotherapy with chemo- and targeted therapy



Chemotherapy and targeted therapy modulate the key players in the immune regulation of tumor growth

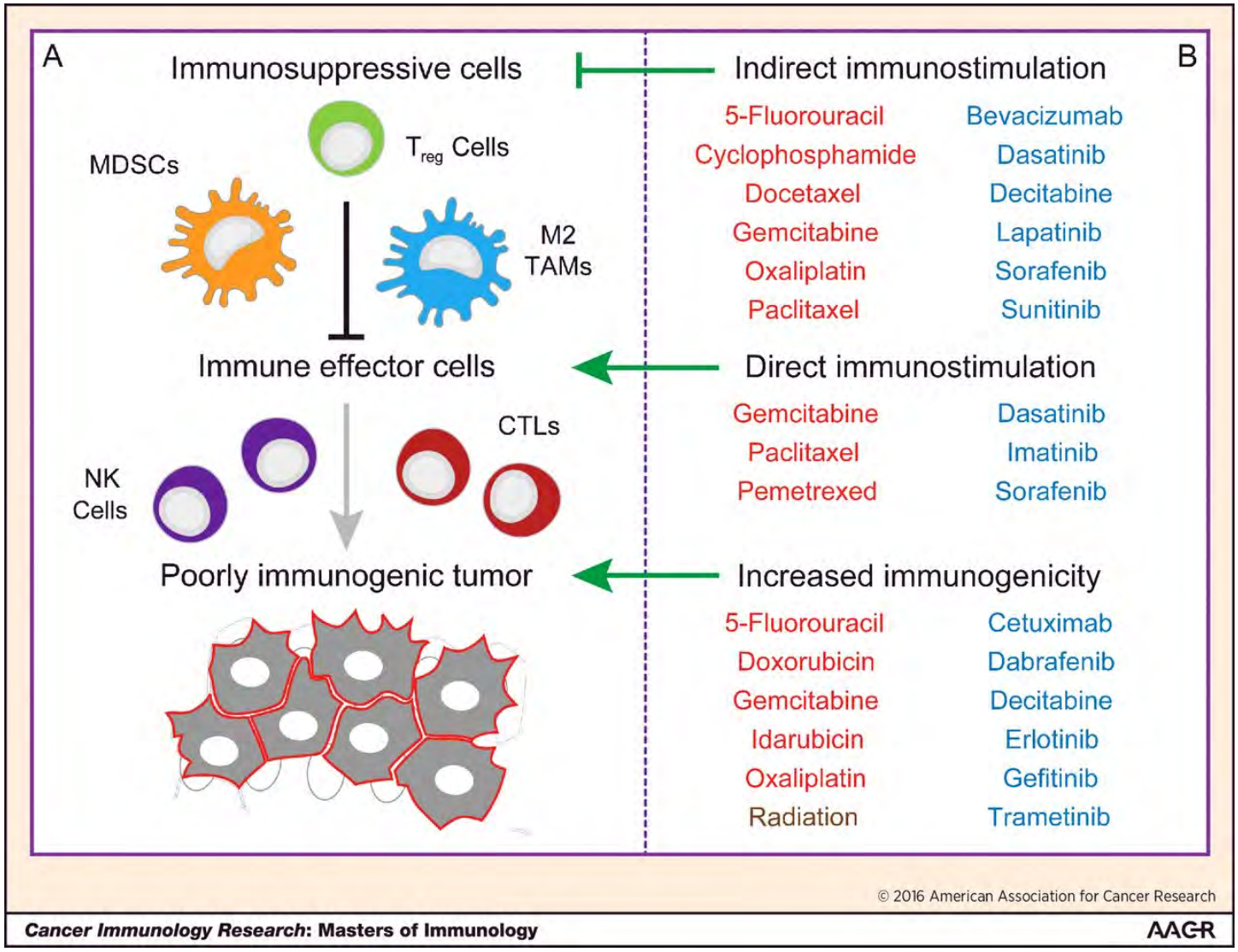


Immune regulation of tumor growth with myeloid and lymphoid cells promoting or suppressing tumor growth.

Abbreviations: M1, macrophage M1; M2, macrophage M2; MDSC, myeloid-derived-suppressor cells; NK, natural killer cell; TH, T helper; Treg, regulatory T cell; TC, lymphocyte T cytotoxic; B, B cell.

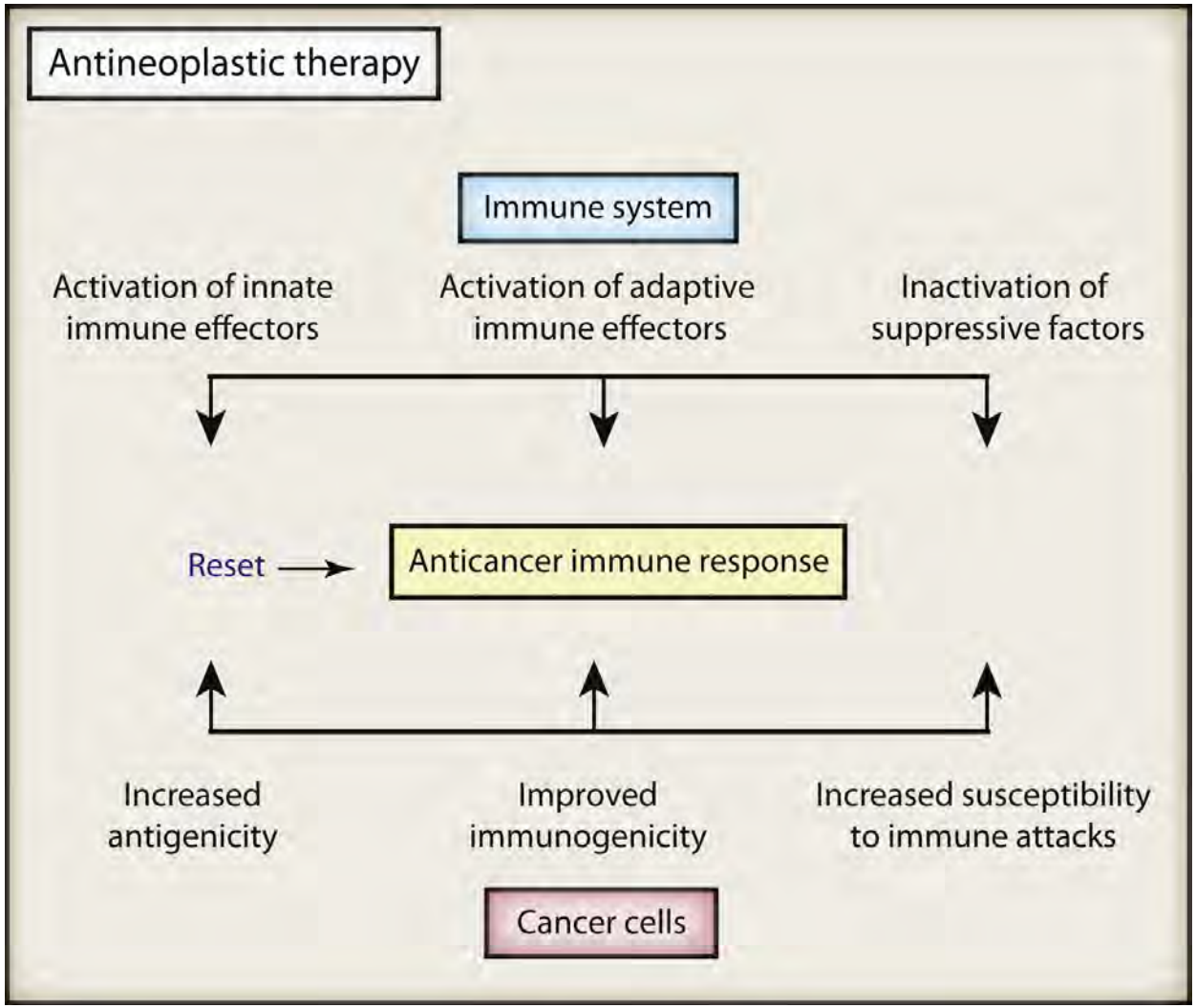
Goubran et al. Cancer Growth Metastasis 2014

Immunological effects of anticancer therapies



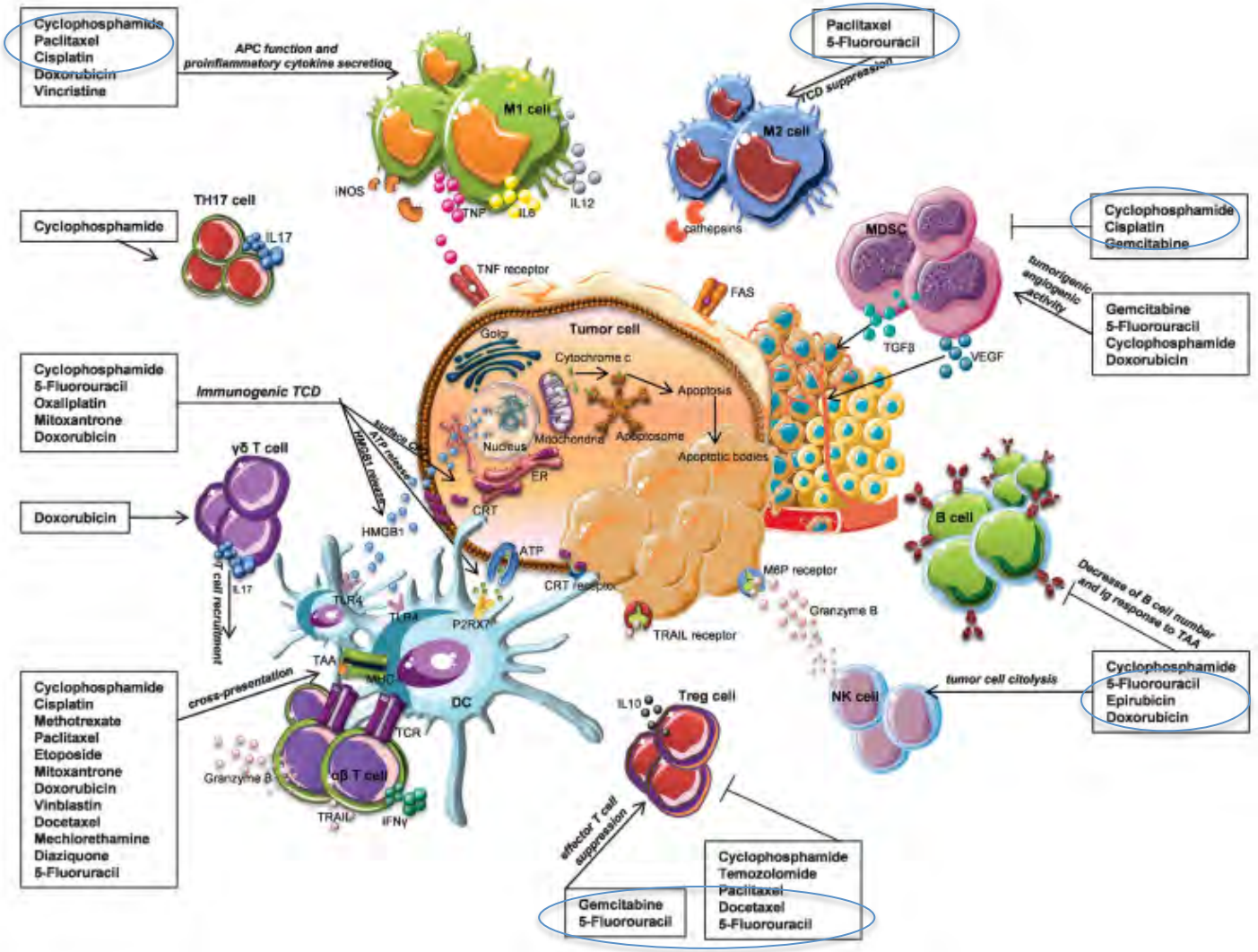
Galluzzi et al. 2017

Effects of chemotherapy on tumor-specific immune response



Zitvogel et al. Immunity 2013

Chemotherapy stimulates immune-based anti-cancer activity through multiple mechanisms



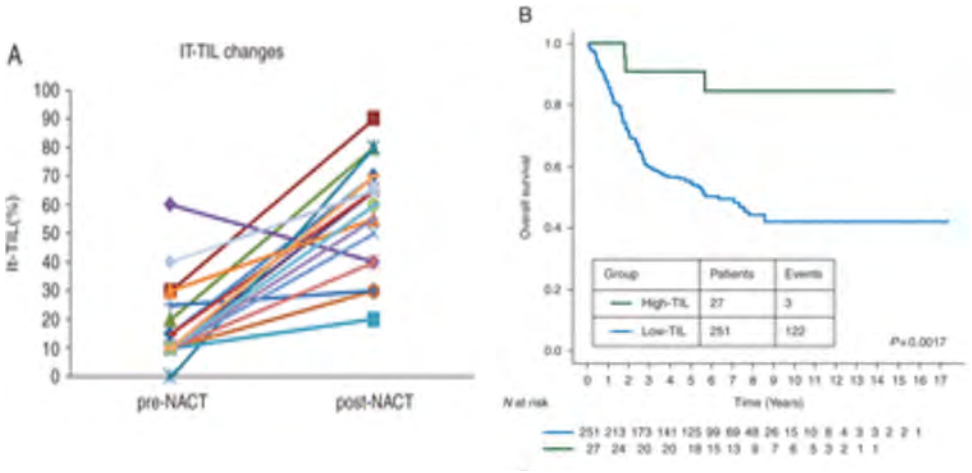
Bracci et al. Cell Death Differ 2014

Chemotherapy mediated activation of anticancer immune responses

- Chemotherapy may stimulate the immune system by:
  - Lysing tumor cells to create an endogenous cancer vaccine[1,2]
  - Activating dendritic cells[3]
  - Depleting immunosuppressive Tregs at low doses[4]
  - Increasing tumor-infiltrating lymphocytes (TILs)[5]

- Chemotherapy increased TIL number following neoadjuvant therapy in 278 patients with TNBC[5]
  - Higher numbers of TILs were significantly associated with longer 5-year survival rates[5]

1. ***Bracci et al. Cell Death Differ 2014***
2. ***Mellman et al. Nature 2011***
3. ***Tanaka et al. Cancer Res 2009***
4. ***Banissi et al. Cancer Imm Immunother 2009***
5. ***Dieci et al. Ann Oncol 2014***



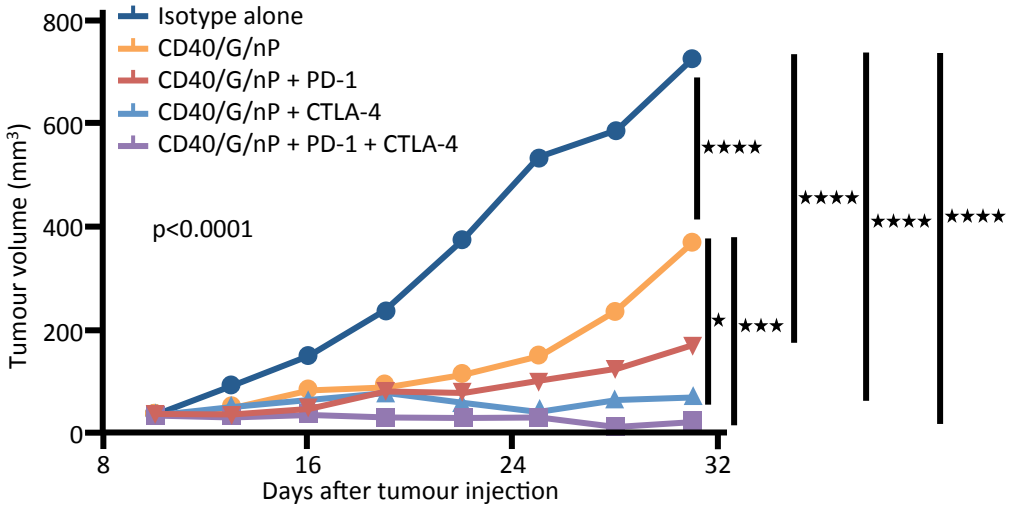
Immune response and chemotherapy: an example of a potentially successful combination strategy

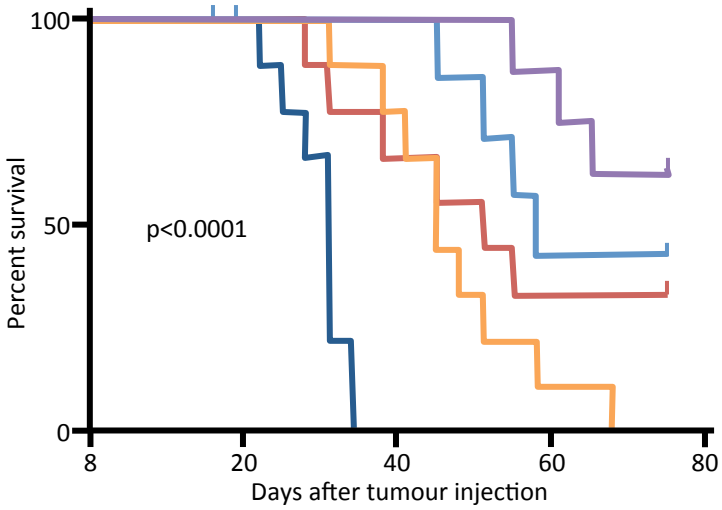
Drug	Effect on immune system
Taxanes	• Enhances T cell and NK cell function • Increases recruitment of TIL • Increase efficacy of immuno-stimulatory agents
Doxorubicin	• Induces immunogenic cell death • Increases proliferation of CD8 T cells • Stimulates antigen presentation by DCs • Stimulates MCP1 and M6PR
Cyclophosphamide	• Induces immunogenic cell death • Suppresses Treg inhibitory functions and restores the proliferative capacity of effector T cells and NK cell cytotoxicity
Gemcitabine	• Reduces the number of myeloid suppressor cells • Increases the antitumor activity of CD8(+) T cells and activated NK cells
Oxaliplatin	• Induces immunogenic cell death • Increases MHC I complex • Inhibits PD-L2

Kono et al. Cell Death and Disease 2013

Checkpoint inhibition + CD40 agonist + nab-paclitaxel/gemcitabine: Preclinical data

- T cell stimulation with CD40 agonist mAB + nab-paclitaxel/gemcitabine renders PDAC highly sensitive to immune checkpoint blockade
- CD40/nab-paclitaxel/gemcitabine/PD-1/CTLA-4 leads to complete tumour rejection and long-term tumour-free survival in a KPC mouse model
  - PD-1/CTLA-4: **5% long-term survivors**
  - CD40/nab-paclitaxel/gemcitabine: **12% long-term survivors**
  - CD40/nab-paclitaxel/gemcitabine/PD-1/CTLA-4: **39% long-term survivors**





Winograd et al. Cancer Immunol Res 2015

Combining DNA damaging therapeutics with immunotherapy: more haste, less speed

- Choice of agent. DNA damaging agents are not equally immunogenic

- **Dose.** Carefully designed trials need to consider testing whether maximal tumor cell death (at the MTD) should be compromised in an effort to spare immunoreactive T-cell populations

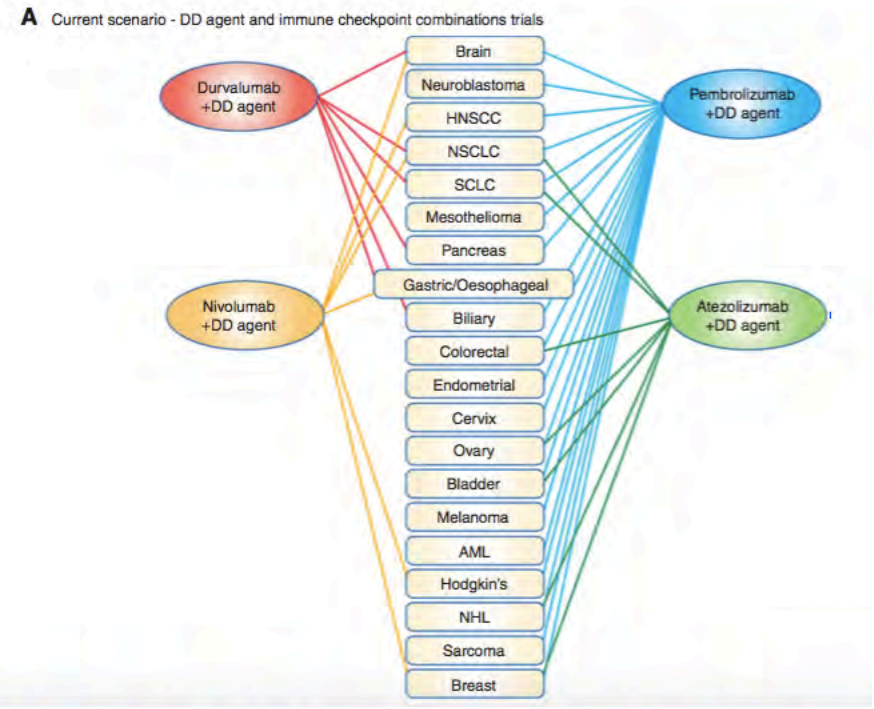
- **Scheduling and sequencing of combinations.** It might be advantageous to prime the immune system, administering DNA damaging agents up front, followed by a period of concurrent treatment

- **Toxicity.** Most toxicities do not overlap, but many DNA damaging chemotherapy regimens incorporate significant doses of corticosteroids, whose immuno-suppressive effects have the potential to attenuate the effects of the immune checkpoint inhibitors

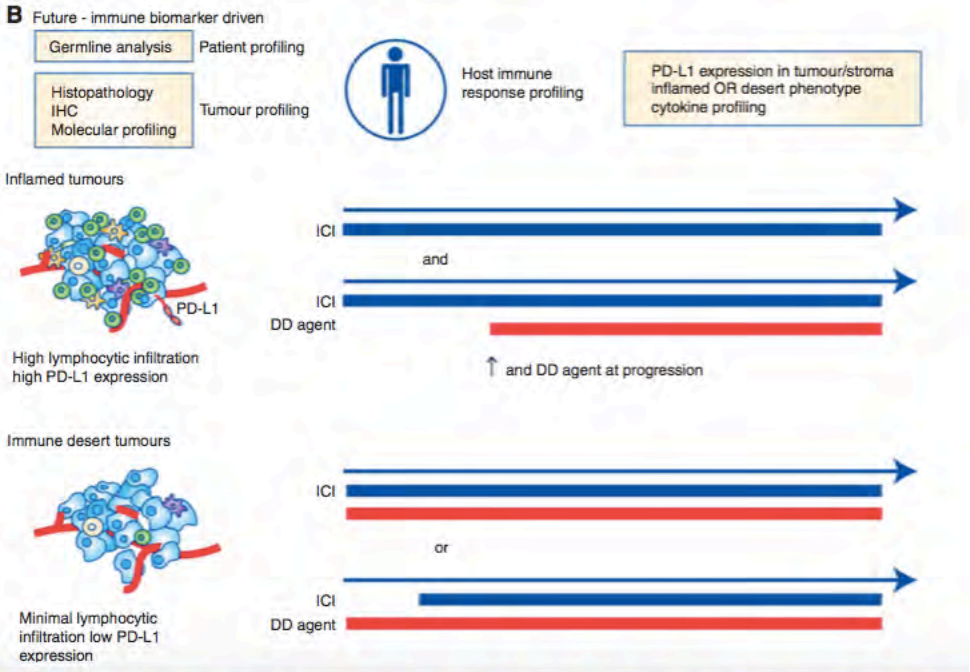
- **Biomarkers.** Utilizing PD biomarkers should be a compulsory component of early-phase combination studies in order to determine optimal doses and scheduling

Brown et al. Br J Cancer 2018

Current and future scenario



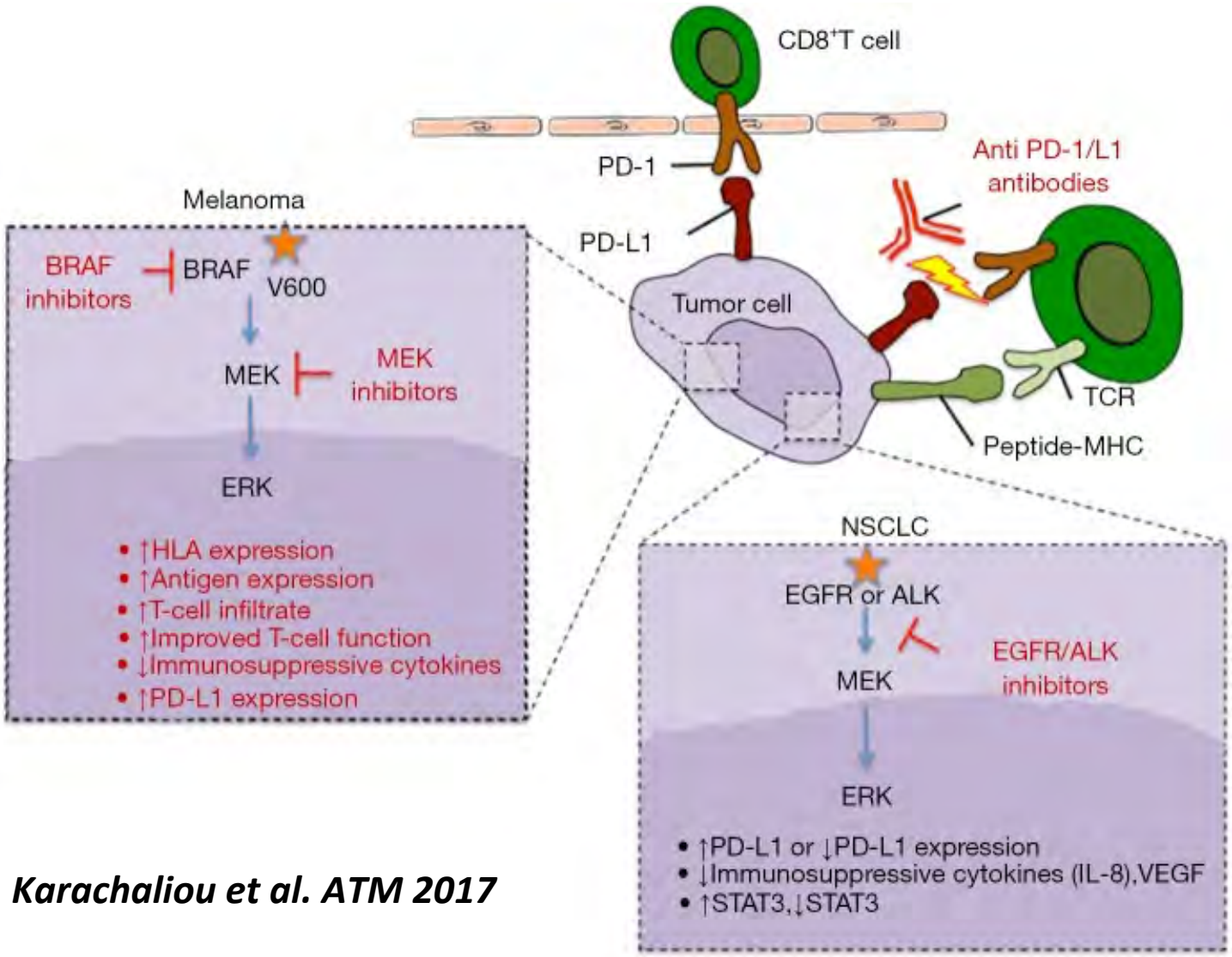
Chemotherapy combination trials with current PD-1 and PD-L1 checkpoint inhibitors are actually testing every standard of care chemotherapy regimen in every tumour type, as registered with www.clinicaltrials.gov



Inflamed tumors might demonstrate high levels of effector T cells (green), APCs (orange) and MDSCs (purple), with low PD-L1 expression and may respond to immune **checkpoint inhibitor (ICI) monotherapy**, requiring combination treatment with DNA damaging (DD) agents on progression only

Conversely immune desert tumors that may require **priming with DD agents** followed by concurrent treatment with an ICI

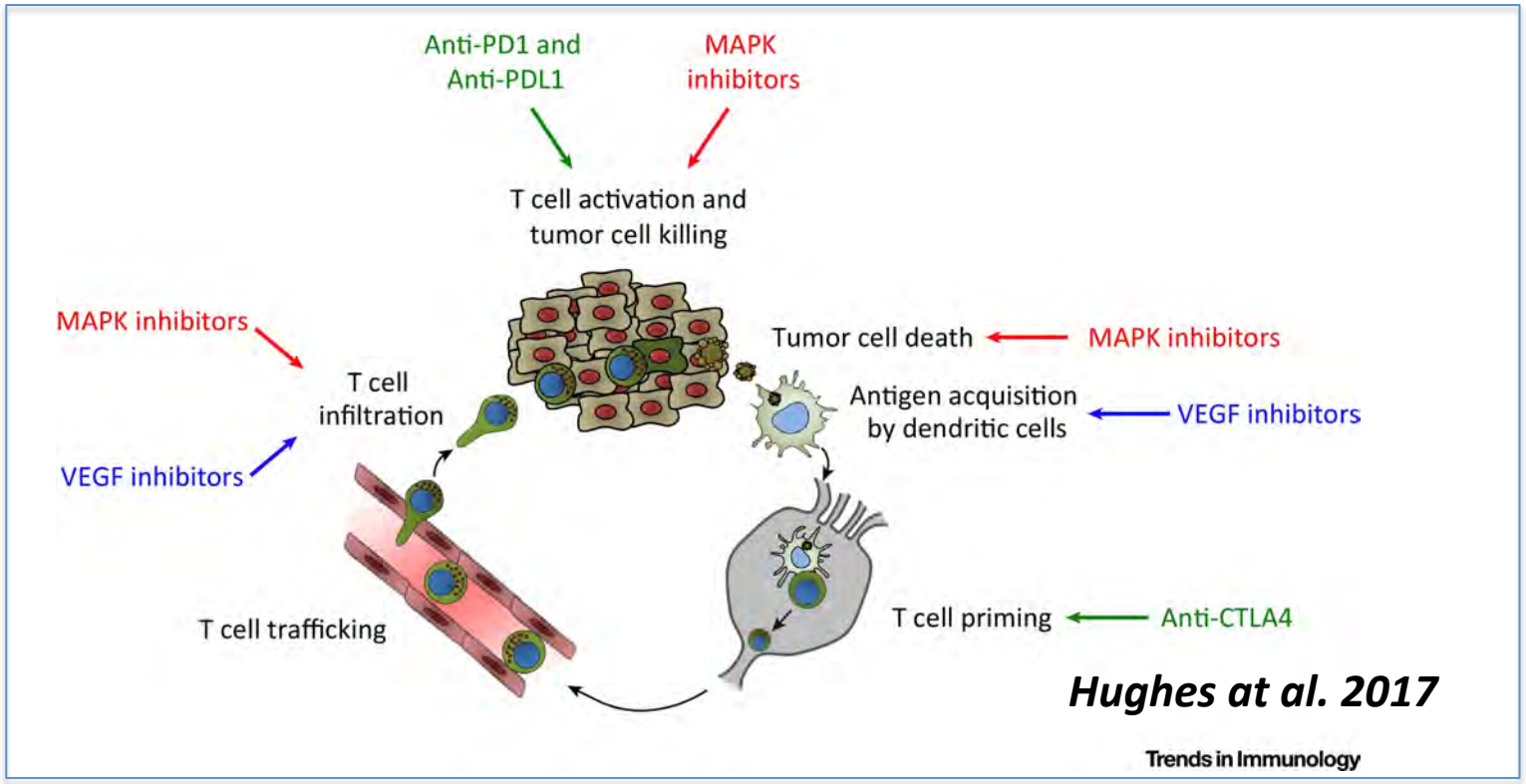
Biological rationale behind combining immunecheckpoint blockade with targeted therapies in melanoma and NSCLC



Karachaliou et al. ATM 2017

MAPK inhibitors complement T cell checkpoint therapies by enhancing tumor antigen expression, immunogenic tumor cell death, and T cell infiltration into tumors

VEGF inhibitors complement T cell checkpoint therapies by enhancing dendritic cell maturation and activity, as well as T cell infiltration into tumors



A thorough preclinical assessment of the mechanism of action and risks associated with each potential combination of targeted therapy and immunotherapy may help limit the **severity and incidence of toxicities** in the clinic, as well as inform **dose-sequencing** and **clinical-monitoring paradigms**

Microenvironment and Immunology

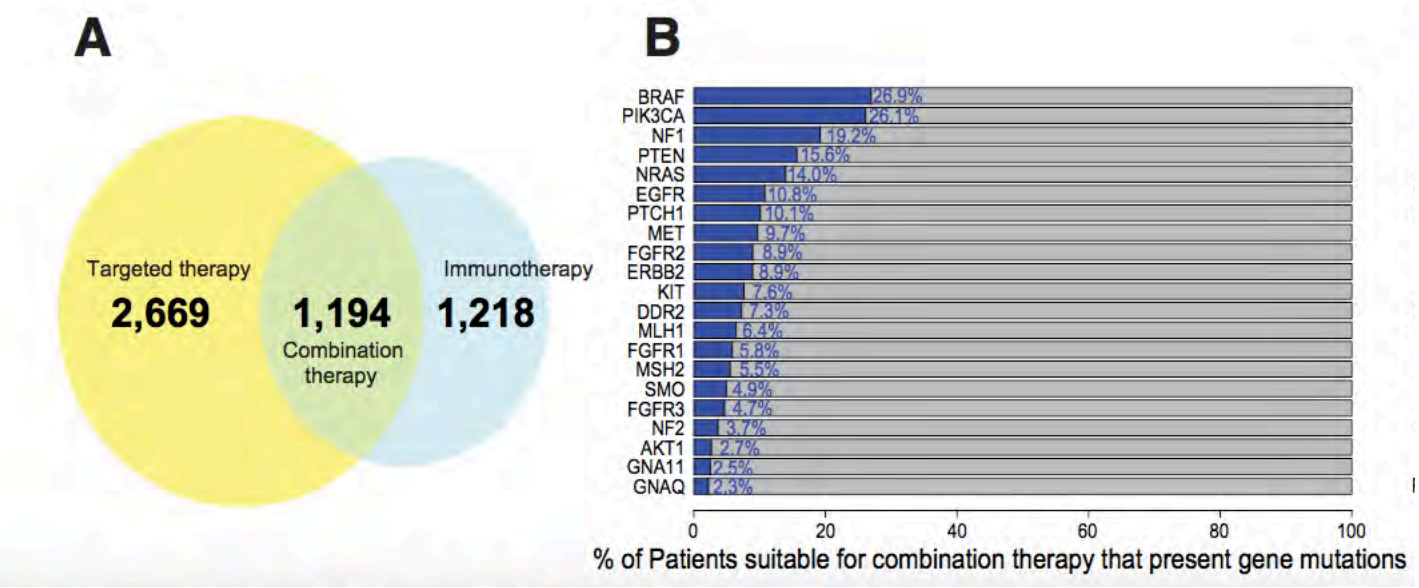
Cancer Research

77(13), 2017

Landscape of Combination Immunotherapy and Targeted Therapy to Improve Cancer Management

Leandro M. Colli[1], Mitchell J. Machiela[1], Han Zhang[1], Timothy A. Myers[1], Lea Jessop[1], Olivier Delattre[2], Kai Yu[1], and Stephen J. Chanock[1]

A survey of **13,349 genomic profiles** from public databases for cases with specific mutations targeted by current agents or a burden of exome-wide nonsynonymous mutations (NsM) that exceed a proposed threshold for response to checkpoint inhibitors

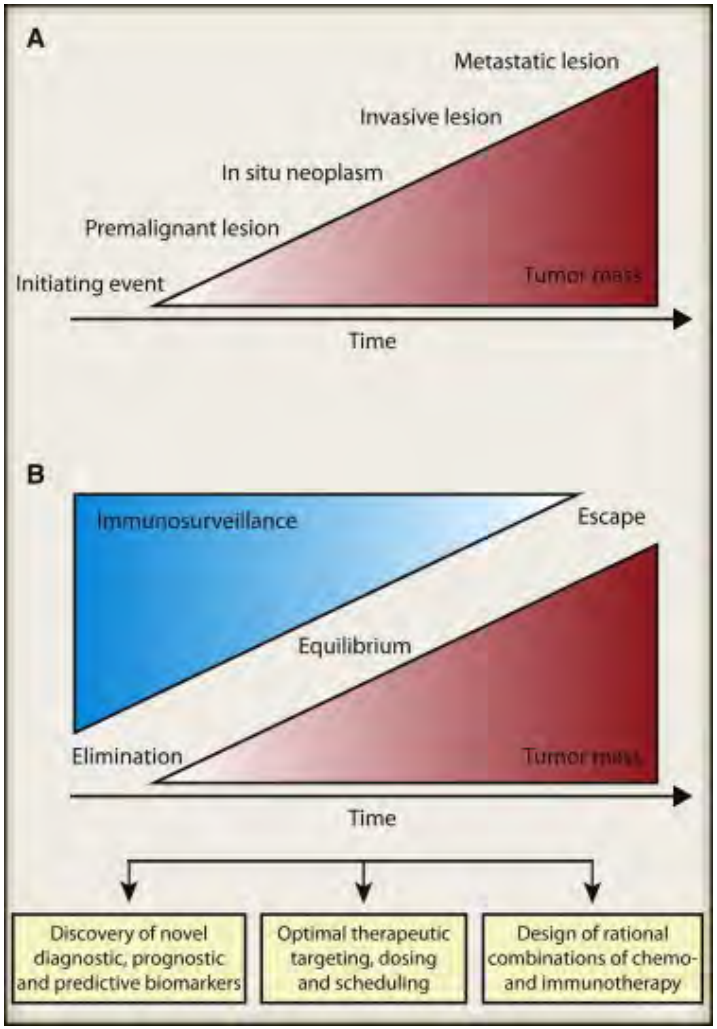


Future prospects: rationally designed combinations and biomarkers

The approval of several immunotherapies has engendered a new-found awareness of the potential antitumour activity of a patient's endogenous immune system once the 'brakes' elicited by the immune system have been released (***Pardoll, Nat Rev Cancer 2012***)

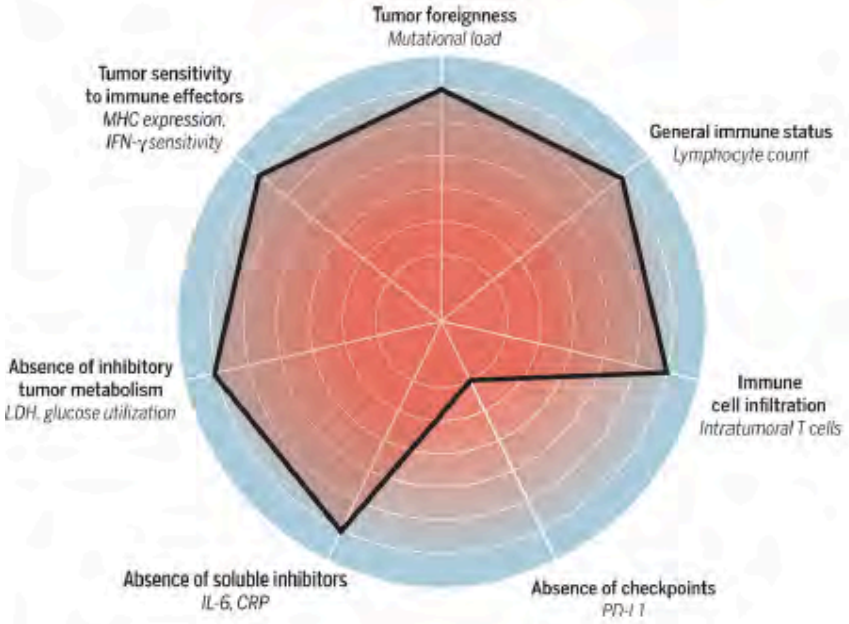
Immune checkpoints are a tiny fraction of the receptors/ligands that inhibit immune responses at various levels. The opportunities to explore the plethora of potential immuno-therapy targets brings forth 2 challenges:

1) the clinical development (based on strong preclinical studies) of optimal **pharmacological** targeting and combinatorial approaches
2) the definition of **potential biomarkers** that can guide the therapeutic choice

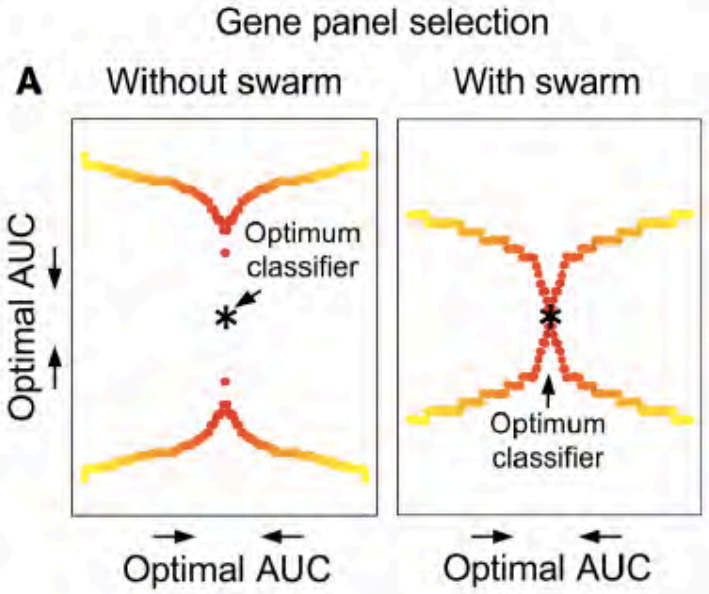


Zitvogel et al. Immunity 2013

New biomarkers for mono-/combination therapies:
1) the cancer immunogram
2) Swarm intelligence-enhanced algorithm of RNA-seq data using blood-based liquid biopsies



Blank et al. Science 2016



Best et al. Cancer Cell 2017

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