Combinations in oncohematology

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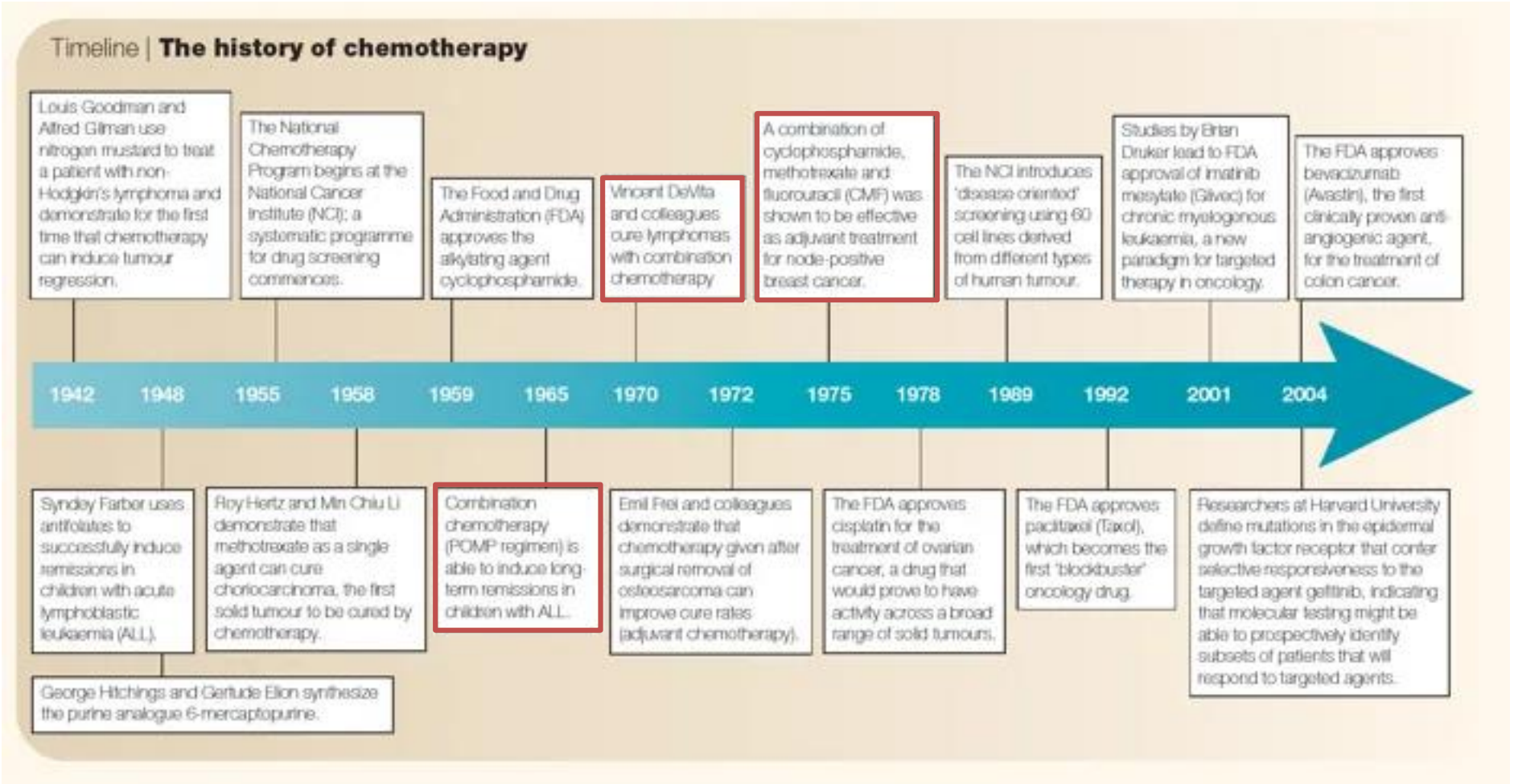
Timeline | The history of chemotherapy
Louis Goodman and Alfred Gilman use nitrogen mustard to treat a patient with non-Hodgkin's lymphoma and demonstrate for the first time that chemotherapy can induce tumour regression.
The National Chemotherapy Program begins at the National Cancer Institute (NCI); a systematic programme for drug screening commences.
The Food and Drug Administration (FDA) approves the alkylating agent cyclophosphamide.
Vincent DeVita and colleagues cure lymphomas with combination chemotherapy
A combination of cyclophosphamide, methotrexate and fluorouracil (CMF) was shown to be effective as adjuvant treatment for node-positive breast cancer.
The NCI introduces 'disease oriented' screening using 60 cell lines derived from different types of human tumour.
Studies by Brian Druker lead to FDA approval of imatinib mesylate (Gleevec) for chronic myelogenous leukaemia, a new paradigm for targeted therapy in oncology.
The FDA approves bevacizumab (Avastin), the first clinically proven anti-angiogenic agent, for the treatment of colon cancer.
1942
1948
1955
1958
1959
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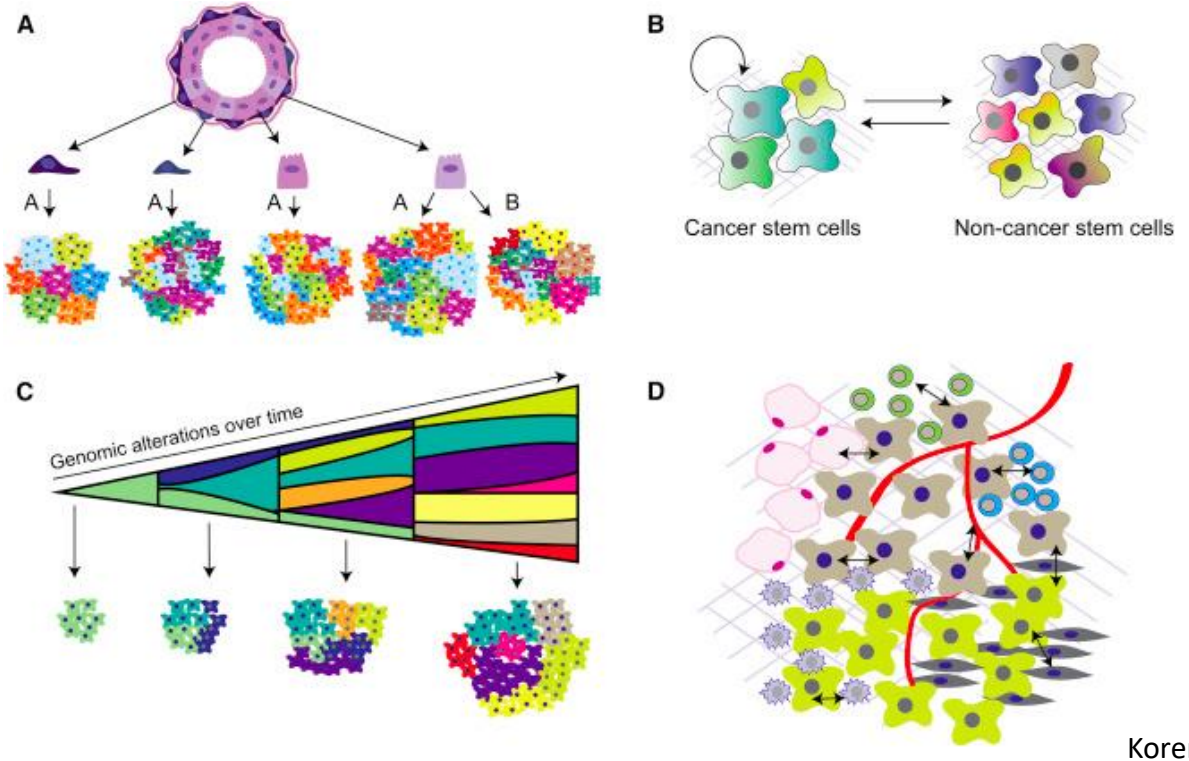
2001
2004
Syndey Farber uses antifolates to successfully induce remissions in children with acute lymphoblastic leukaemia (ALL).
George Hitchings and Gertude Elion synthesize the purine analogue 6-mercaptopurine.
Roy Hertz and Min Chiu Li demonstrate that methotrexate as a single agent can cure choriocarcinoma, the first solid tumour to be cured by chemotherapy.
Combination chemotherapy (POMP regimen) is able to induce long-term remissions in children with ALL.
Emil Frei and colleagues demonstrate that chemotherapy given after surgical removal of osteosarcoma can improve cure rates (adjuvant chemotherapy).
The FDA approves cisplatin for the treatment of ovarian cancer, a drug that would prove to have activity across a broad range of solid tumours.
The FDA approves paclitaxel (Taxol), which becomes the first 'blockbuster' oncology drug.
Researchers at Harvard University define mutations in the epidermal growth factor receptor that confer selective responsiveness to the targeted agent gefitinib, indicating that molecular testing might be able to prospectively identify subsets of patients that will respond to targeted agents.

The rationale for combination: tumor heterogeneity



Koren and Bentjres-Ali, Mol Cell 2015

How to design combinations?

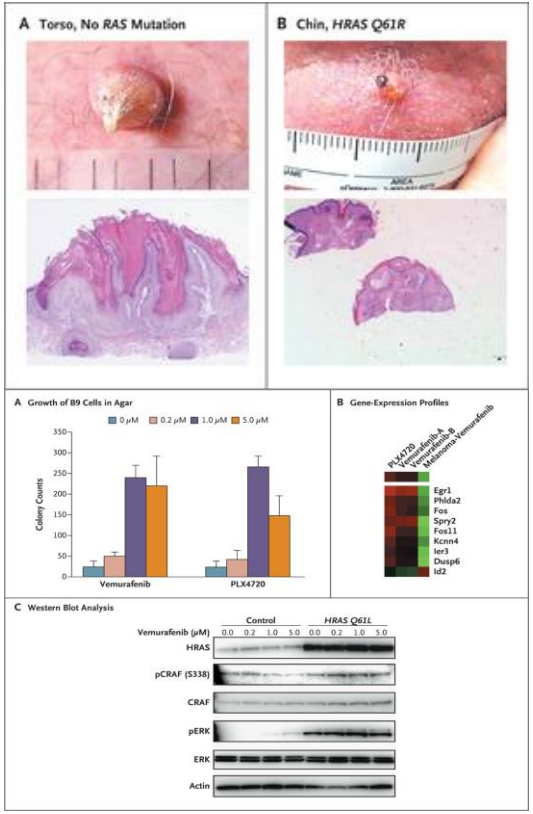
“Two is meglio che one”

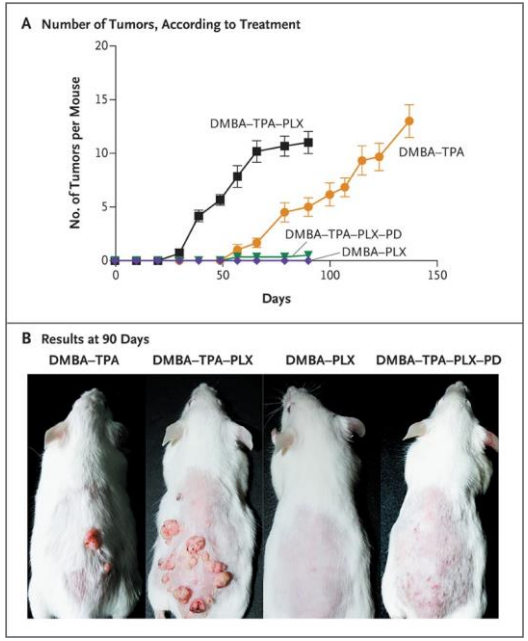
More or less random

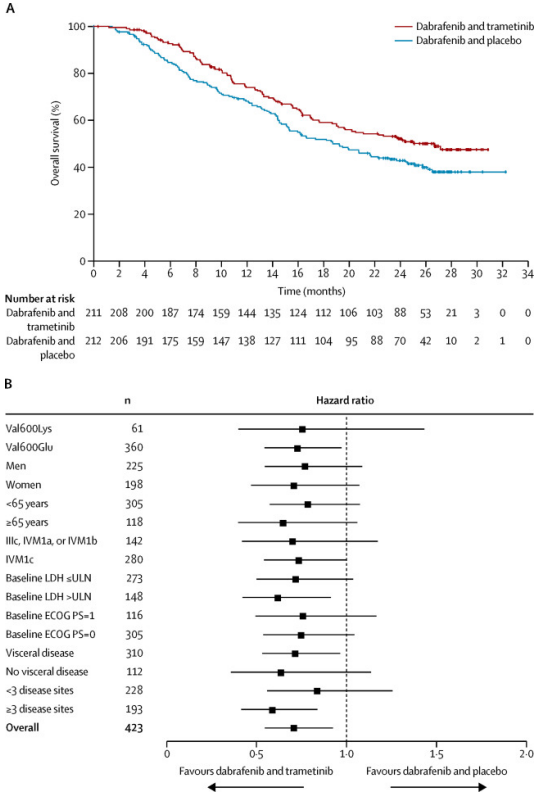
“Perfect match”

More or less rational

BRAF+MEK inhibition: a very rational combination

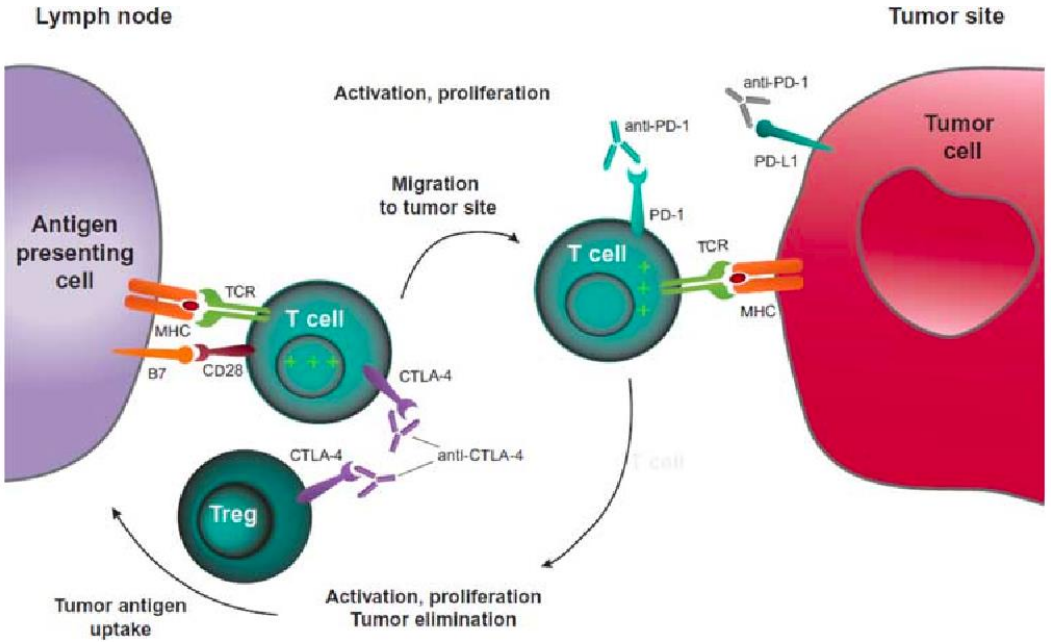






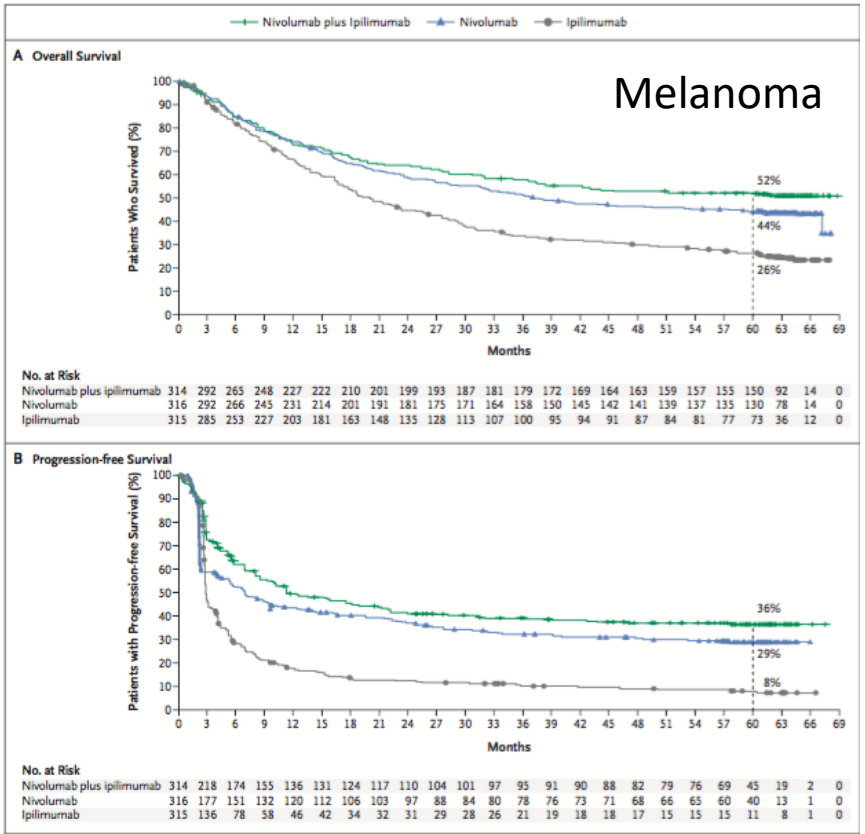
Su et al NEJM 2015
Long et al Lancet 2015

The mother of all immuno combinations: CTLA4+PD1



Buchbinder et al Am JCO 2016

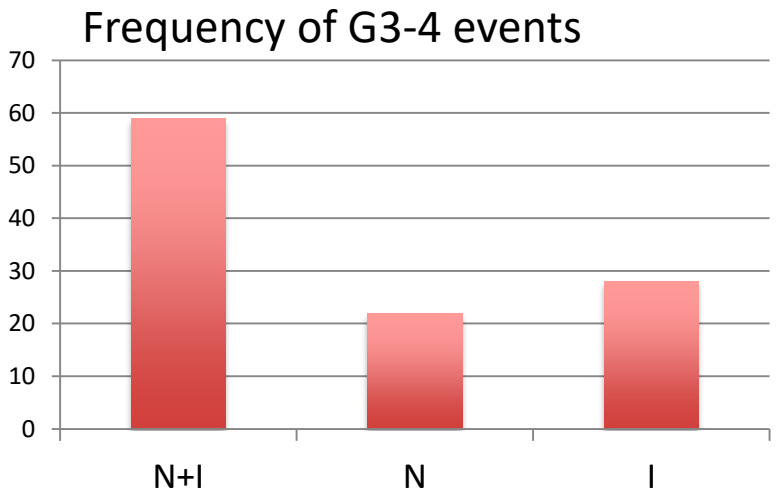
The mother of all immuno combinations: CTLA4+PD1

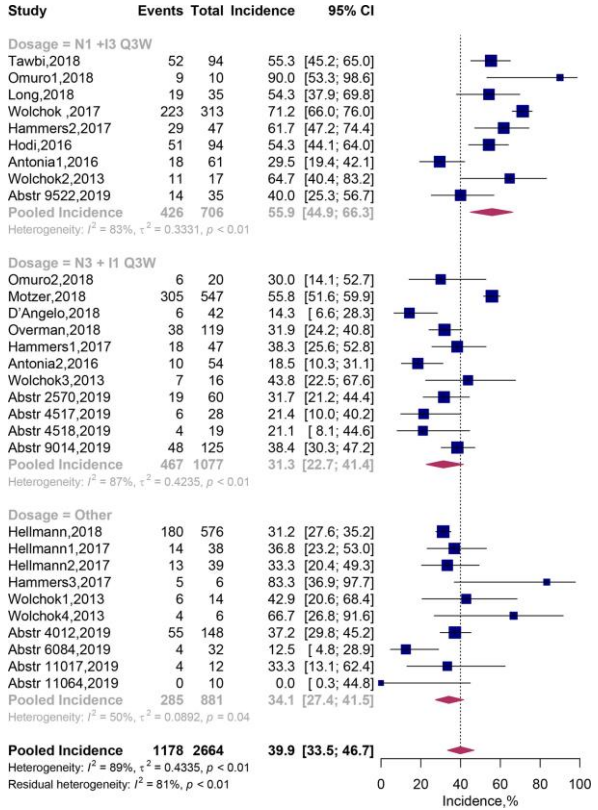


- Other tumors:
- NSCLC
- Colorectal
- Kidney

Larkin NEJM 2019

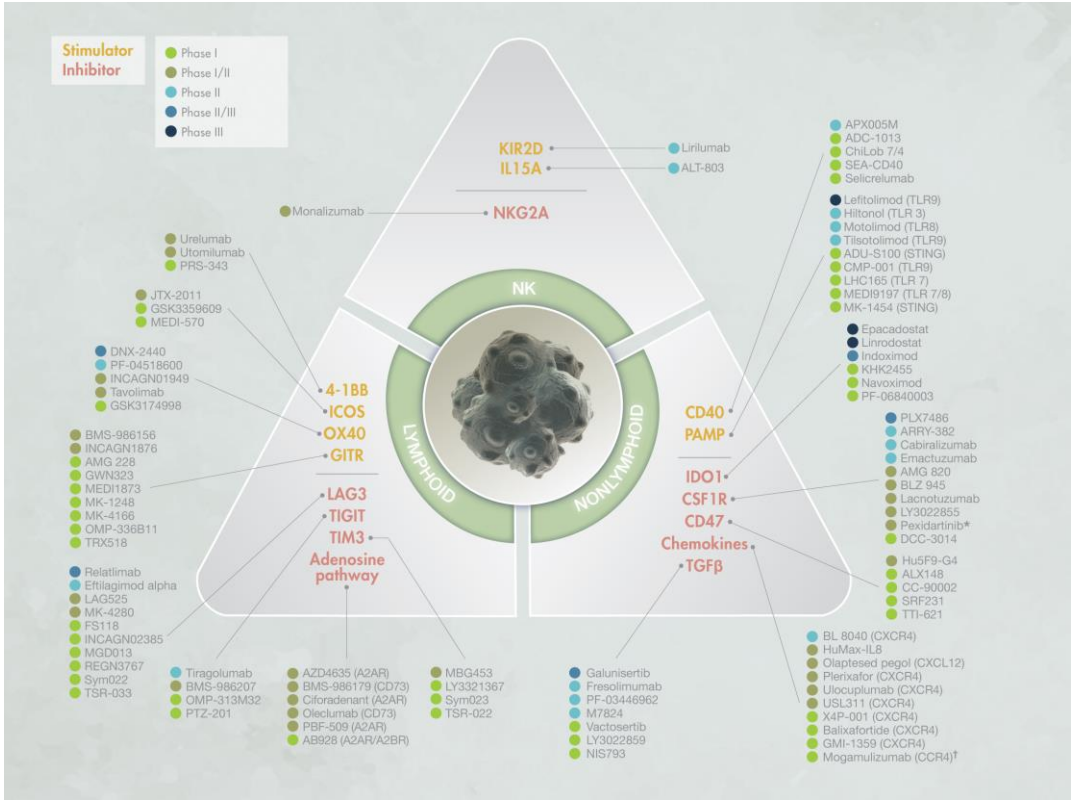
More efficacy, more toxicity





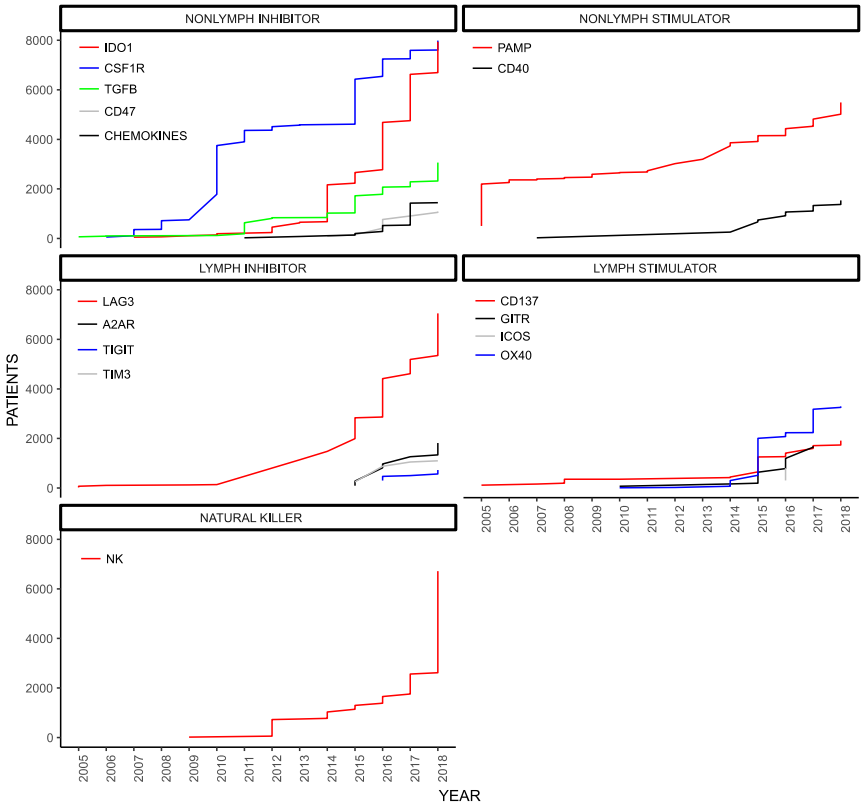
Xu et al Front Pharmacol 2019

The evolving landscape of "Next Generation" Immune Modulators



Mazzarella et al Eur J Canc 2019

The evolving landscape of "Next Generation" Immune Modulators



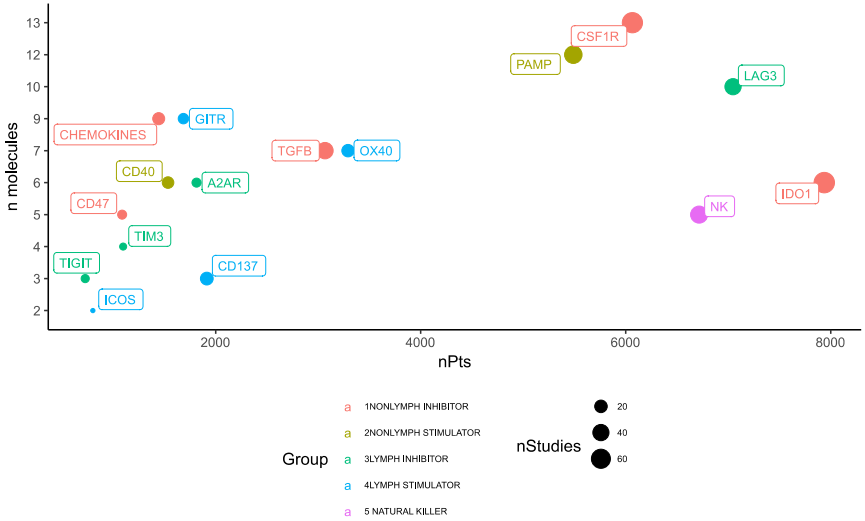
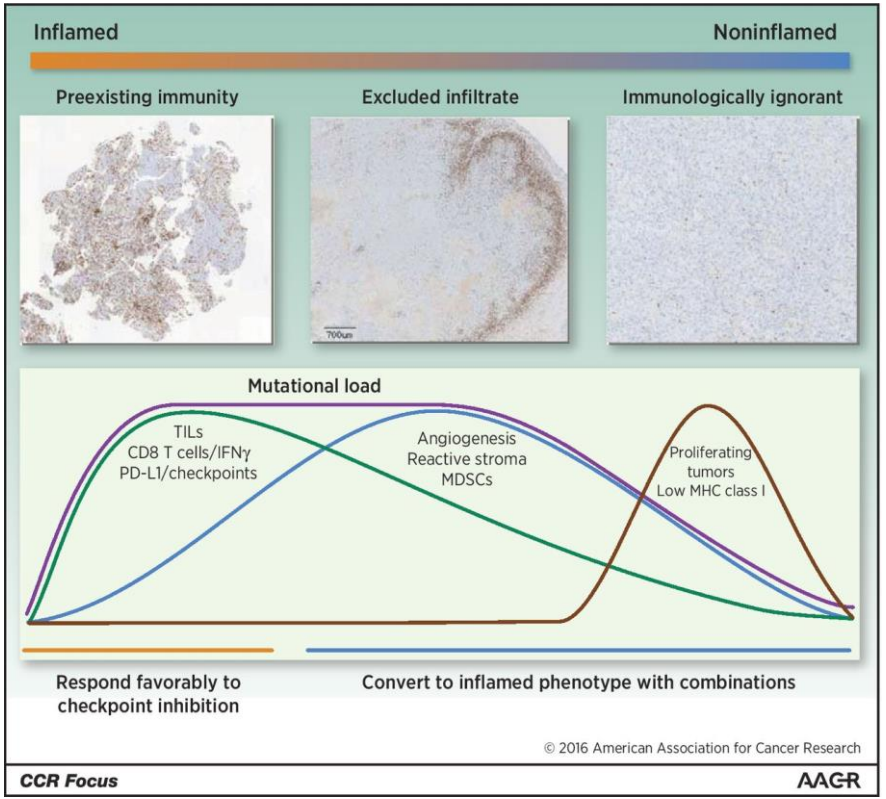


Figure 4

Mazzarella et al Eur J Canc 2019

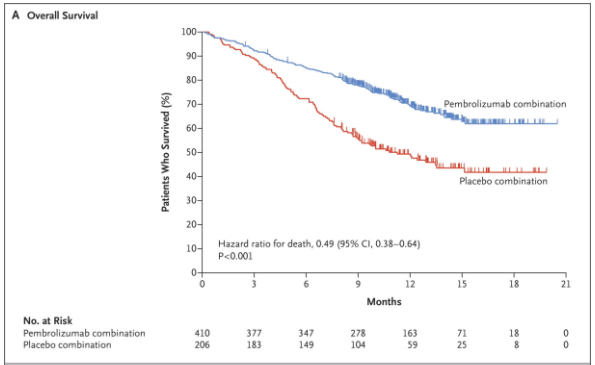
General principle of immuno-oncology combinations: turn cold into hot

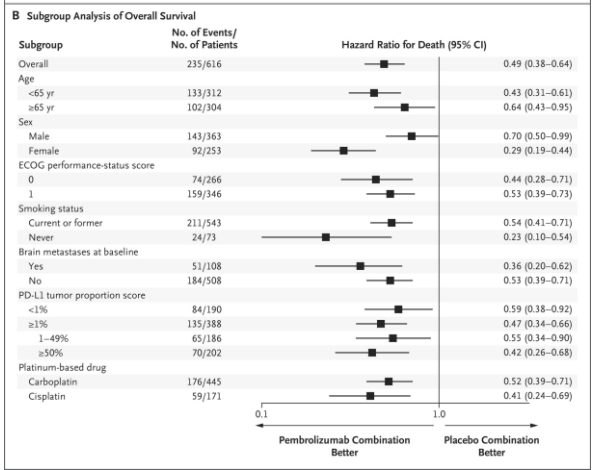
- Chemo
- Targeted therapy
- Radio
- Intralesional/vaccine/oncolytic
- CAR-T



Other combinations

- Chemo
- Targeted therapy
- Radio
- Intralesional/vaccine/oncolytic
- CAR-T



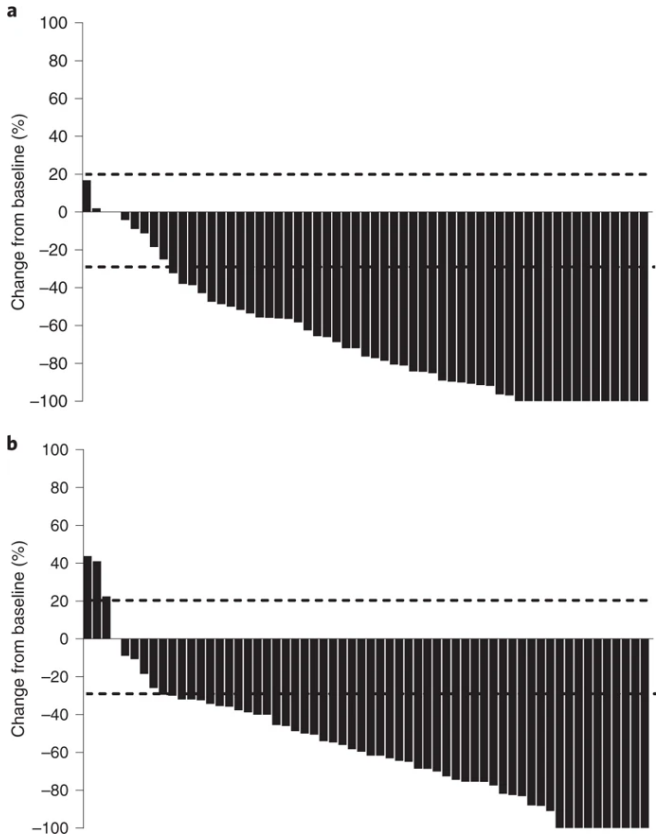


Lung cancer

Gandhi NEJM 2018

Other combinations

- Chemo
- Targeted therapy
- Radio
- Intralesional/vaccine/oncolytic
- CAR-T

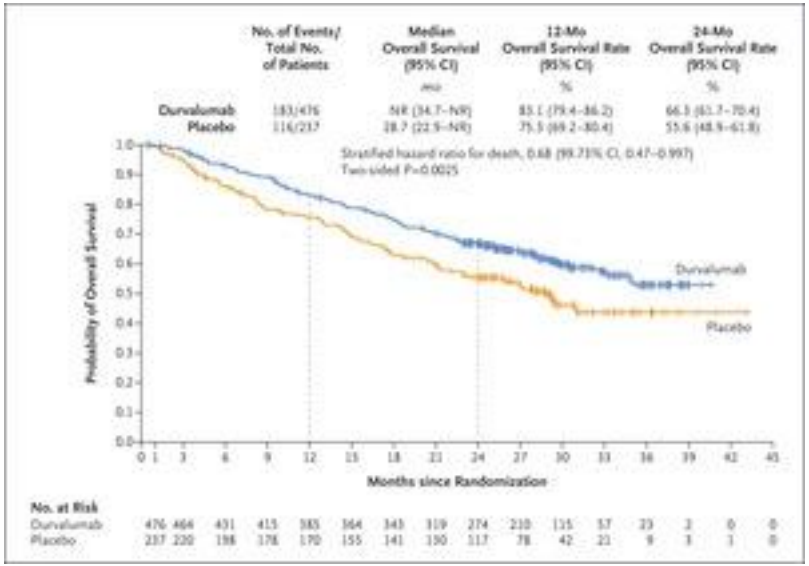


BRAFi+
MEKi+
PD1 in
Melanoma

Ascierto, Ferrucci et al Nat Med 2019

Other combinations

- Chemo
- Targeted therapy
- Radio
- Intralesional/vaccine/oncolytic
- CAR-T

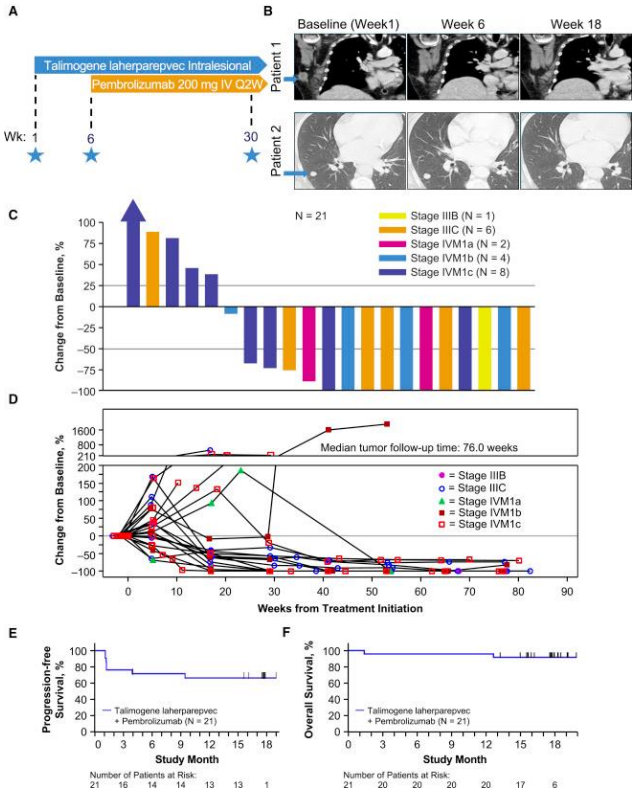


Lung cancer
PACIFIC

Scott et al NEJM 2018

Other combinations

- Chemo
- Targeted therapy
- Radio
- Intralesional/vaccine/oncolytic
- CAR-T

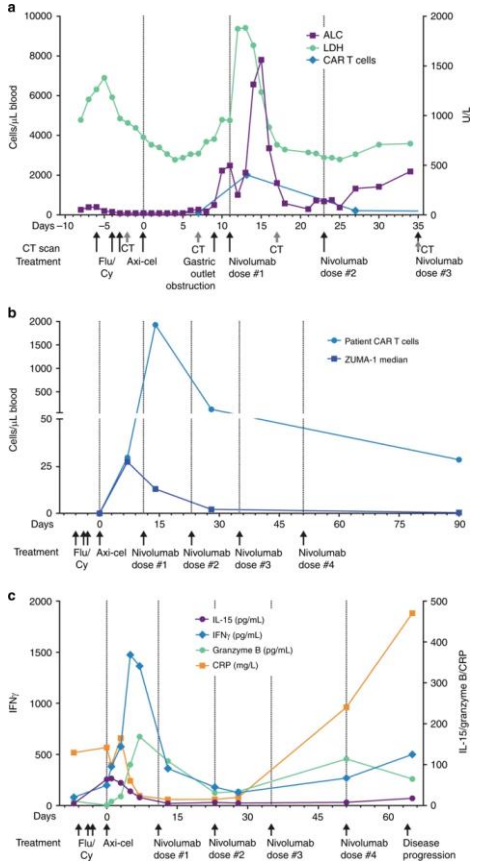


Oncolytic virus (T-VEC)+ PD1

Ribas et al Cell 2017

Other combinations

- Chemo
- Targeted therapy
- Radio
- Intralesional/vaccine/oncolytic
- CAR-T



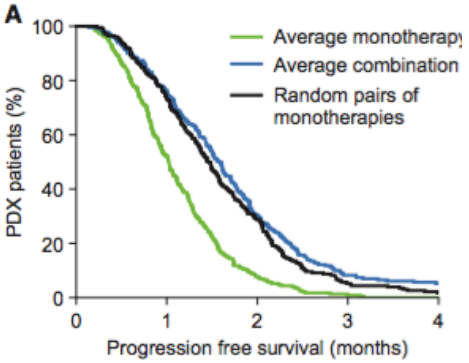
Lymphoma,
CD19 CART+
Pembro

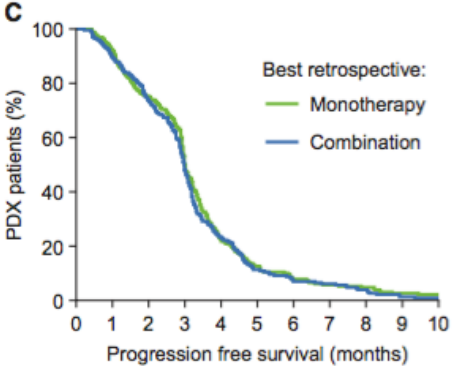
Hill et all Bone Marr transp 2019

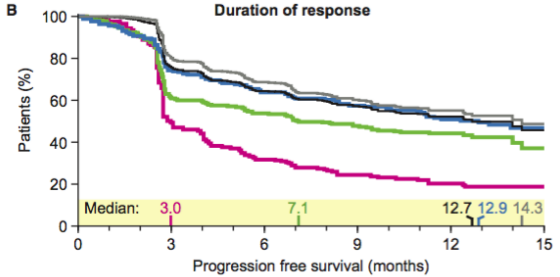
A WORD OF CAUTION

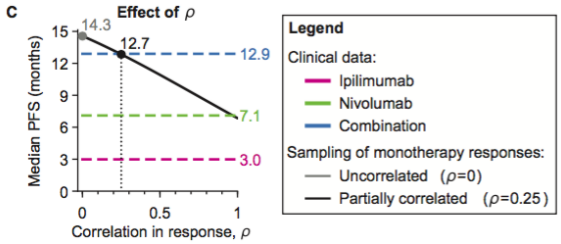
Cell

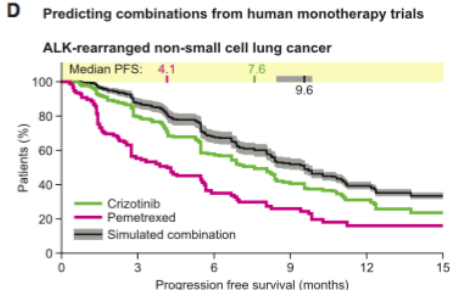
Combination Cancer Therapy Can Confer Benefit via Patient-to-Patient Variability without Drug Additivity or Synergy





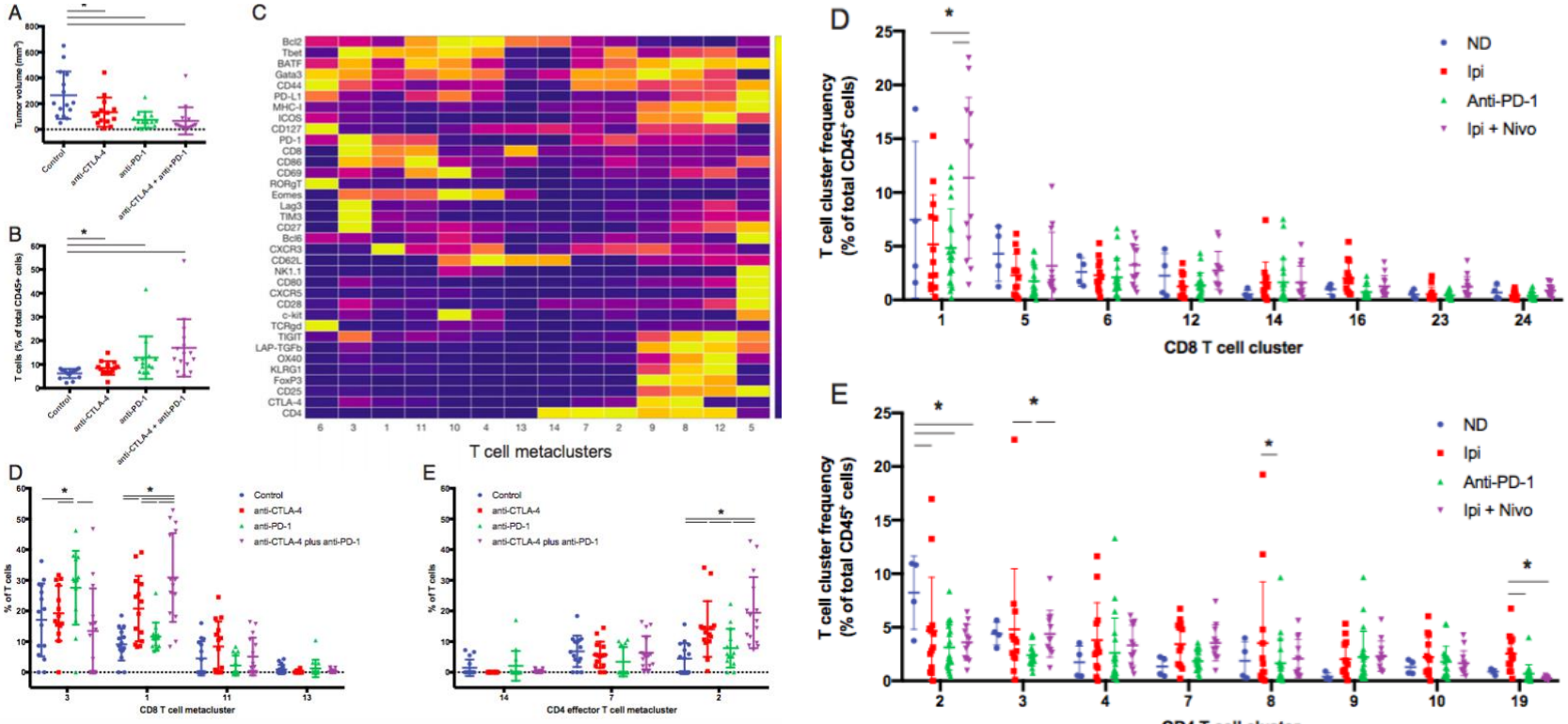






Combination anti–CTLA-4 plus anti–PD-1 checkpoint blockade utilizes cellular mechanisms partially distinct from monotherapies

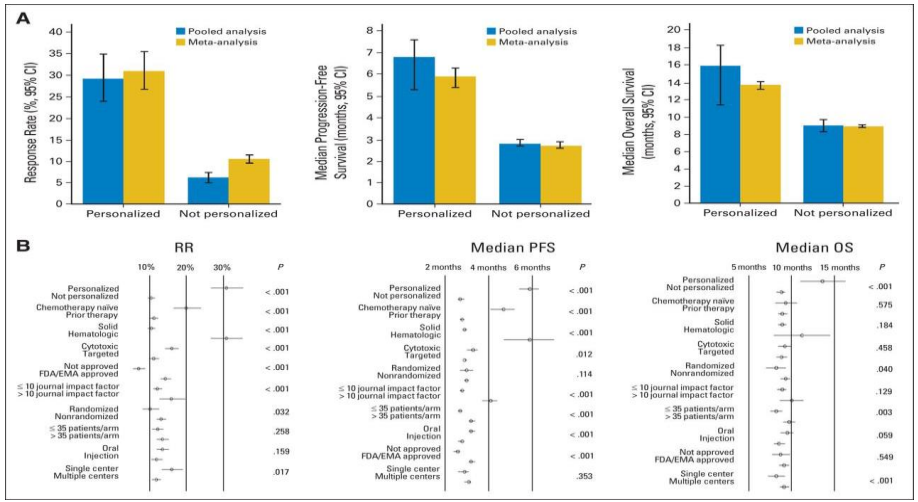
Spencer C. Wei[a], Nana-Ama A. S. Anang[a], Roshan Sharma[b,c], Miles C. Andrews[d], Alexandre Reuben[d], Jacob H. Levine[b], Alexandria P. Cogdill[a,d], James J. Mancuso[a], Jennifer A. Wargo[c,d,e], Dana Pe'er[b,f], and James P. Allison[a,g,1]



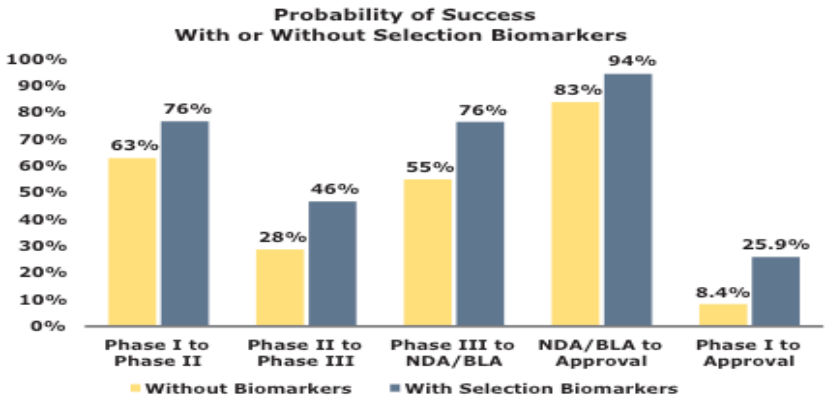
BIOMARKERS!!!!!

Targeting therapy improves efficacy

Benefit for patients

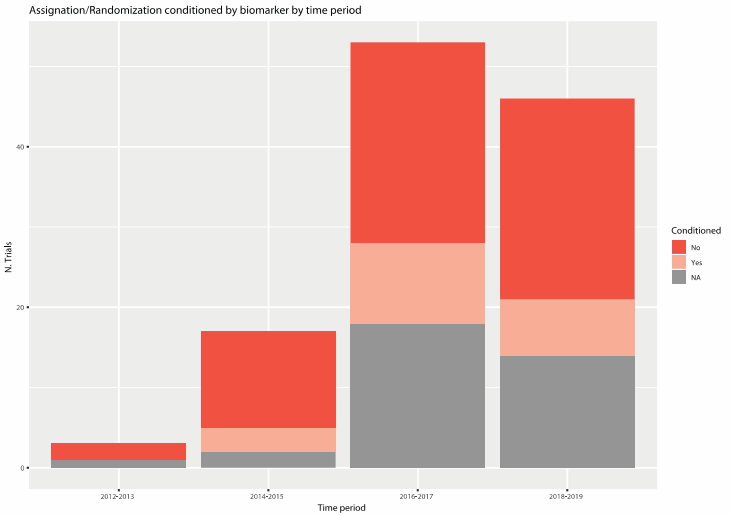


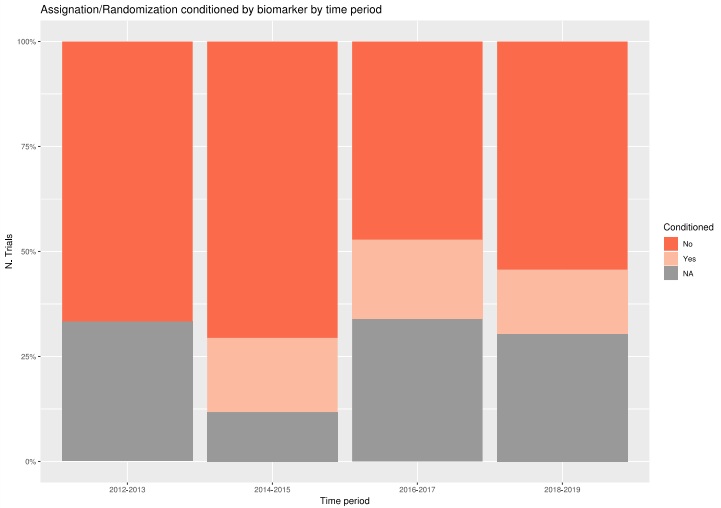
Benefit for drug development



Published in: Maria Schwaederle; Melissa Zhao; J. Jack Lee; Alexander M. Eggermont; Richard L. Schilsky; John Mendelsohn; Vladimir Lazar; Razelle Kurzrock; *JCO* **2015,** 33, 3817-3825.
DOI: 10.1200/JCO.2015.61.5997

Increasing use of biomarkers in immuno-oncology trials

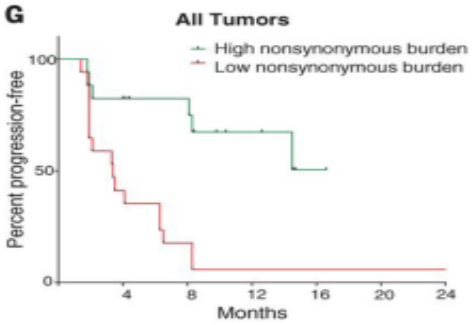




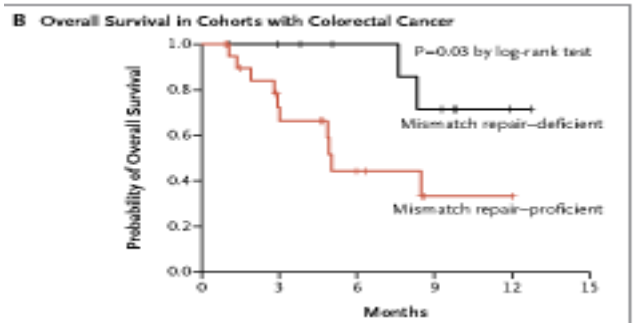
Mazzarella et al under review 2019

Immunotherapy biomarkers. Mutational load

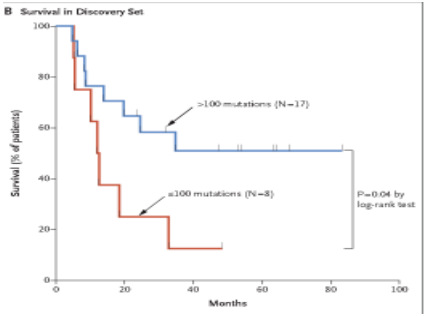
In NSCLC with Pembrolizumab
(Rizvi et al 2015)



In colorectal with Pembrolizumab
MSI-Hi vs MSI-Lo
(Le NEJM 2015)

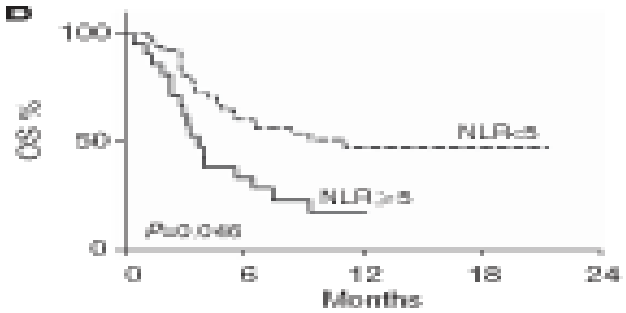


In Melanoma with Ipilimumab
(Snyder NEJM 2014)

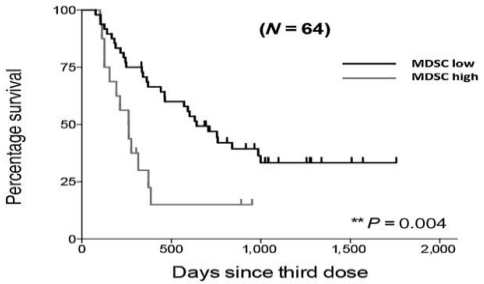


Immunotherapy biomarkers. Host immune status

Neutrophil-to-Lymphocyte ratio
In Melanoma treated w Ipilimumab
(Ferrucci BJC 2015)



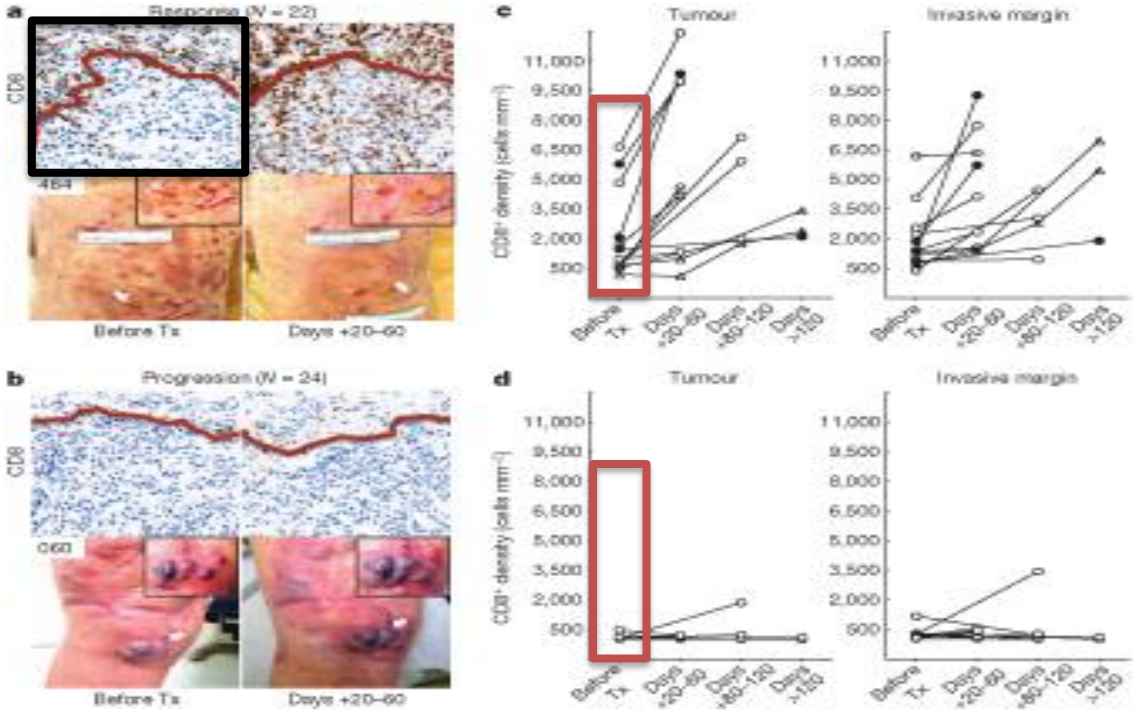
MDSC in Melanoma treated w Ipilimumab
(Kitano Canc Imm Res 2014)



Immunotherapy biomarkers. Immune cell infiltration

CD8 Infiltrate
Present at diagnosis
In responders

CD8 Infiltrate
Absent at diagnosis
In non-responders



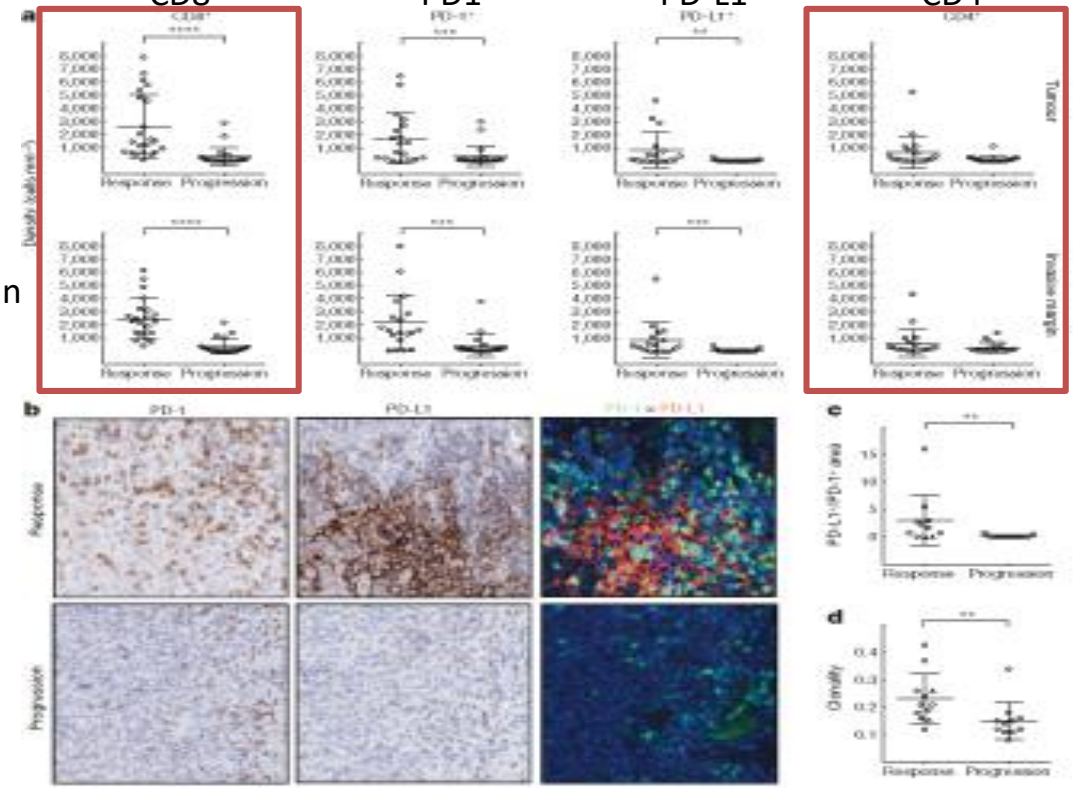
Pembrolizumab in melanoma, Tumeh Nature 2014

Immune cell infiltration

CD8 PD1 PD-L1 CD4

Intra-tumor

Invasive margin



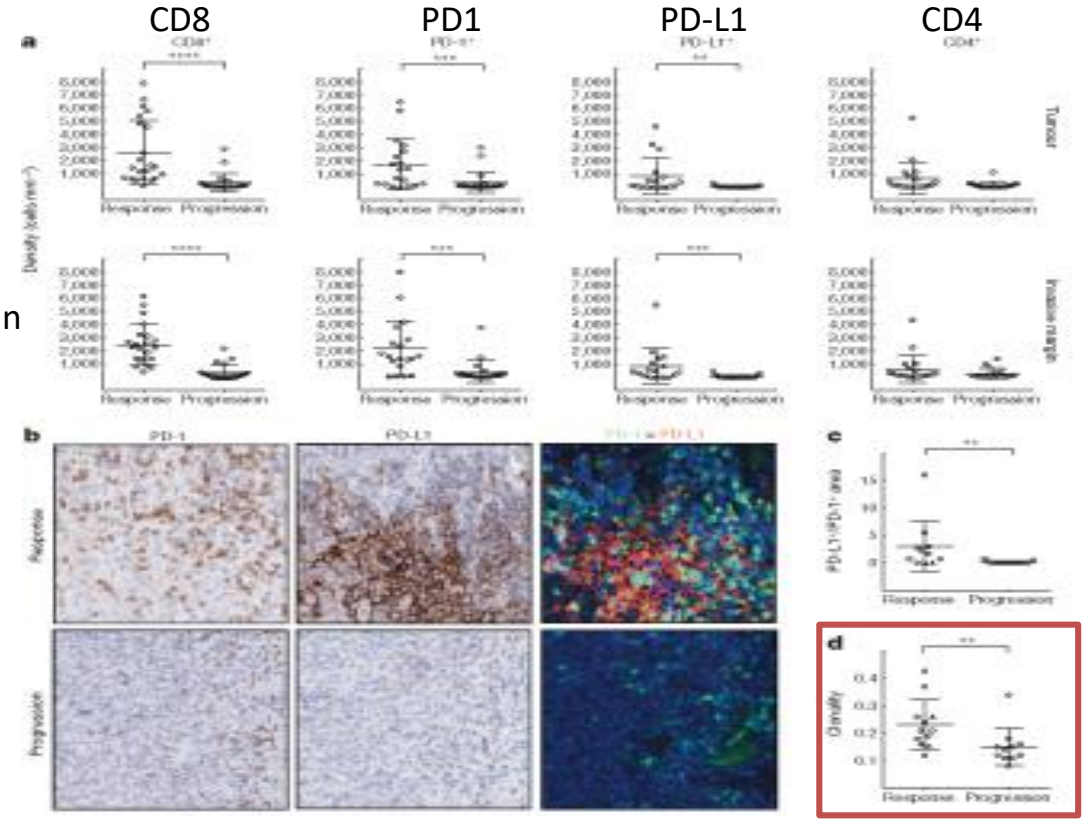
CD8 but not CD4 infiltrate
Correlates with response

Pembrolizumab in melanoma, Tumeh Nature 2014

Immune cell infiltration and clonality

Intra-tumor

Invasive margin

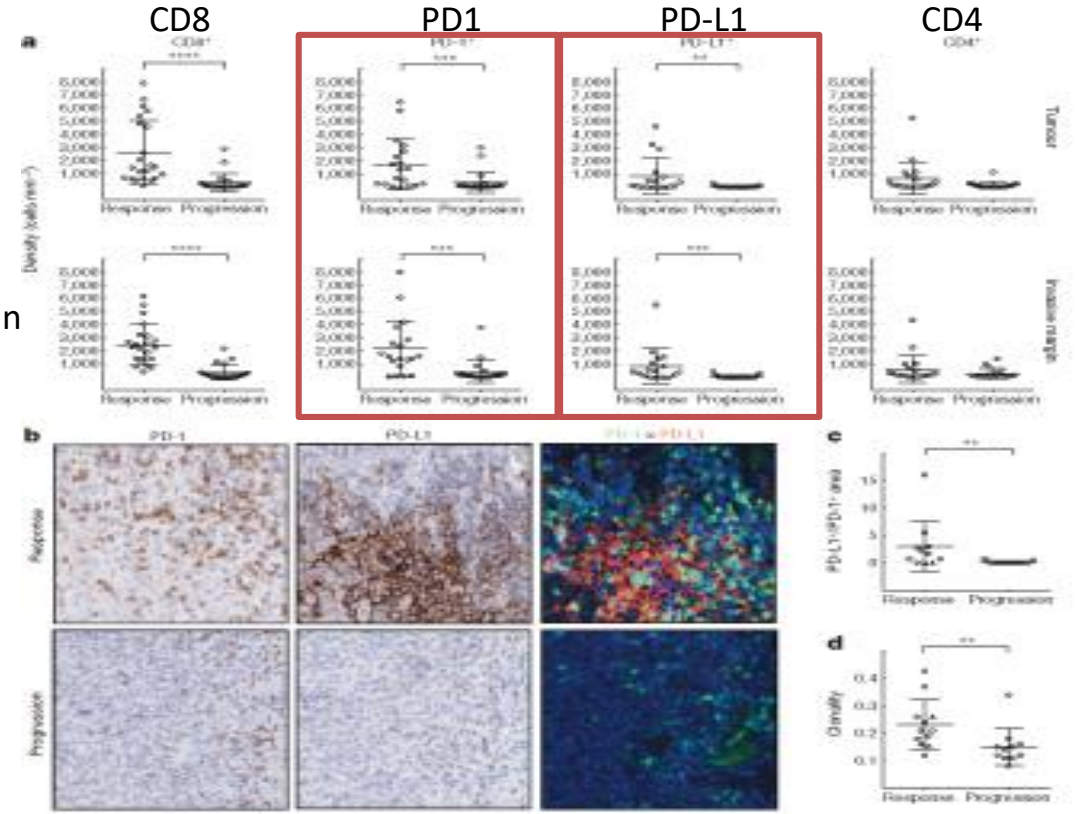


CD8 but not CD4 infiltrate
Correlates with response

T cell clonality
Correlates with response

Pembrolizumab in melanoma, Tumeh Nature 2014

Immunotherapy biomarkers. Checkpoint expression



CD8 but not CD4 infiltrate
Correlates with response

T cell clonality
Correlates with response

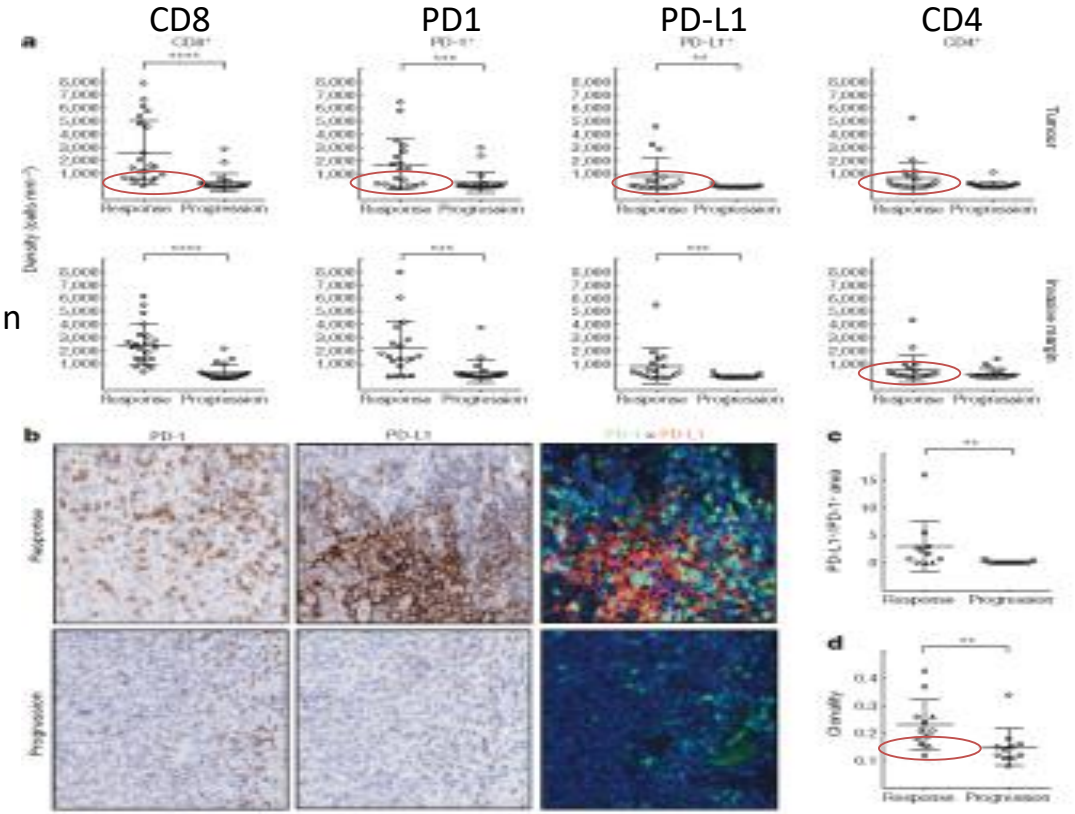
PD1 / PD-L1 expression
Correlates with response

Pembrolizumab in melanoma, Tumeh Nature 2014

No single parameter is perfect

Intra-tumor

Invasive margin



CD8 but not CD4 infiltrate
Correlates with response

T cell clonality
Correlates with response

PD1 / PD-L1 expression
Correlates with response

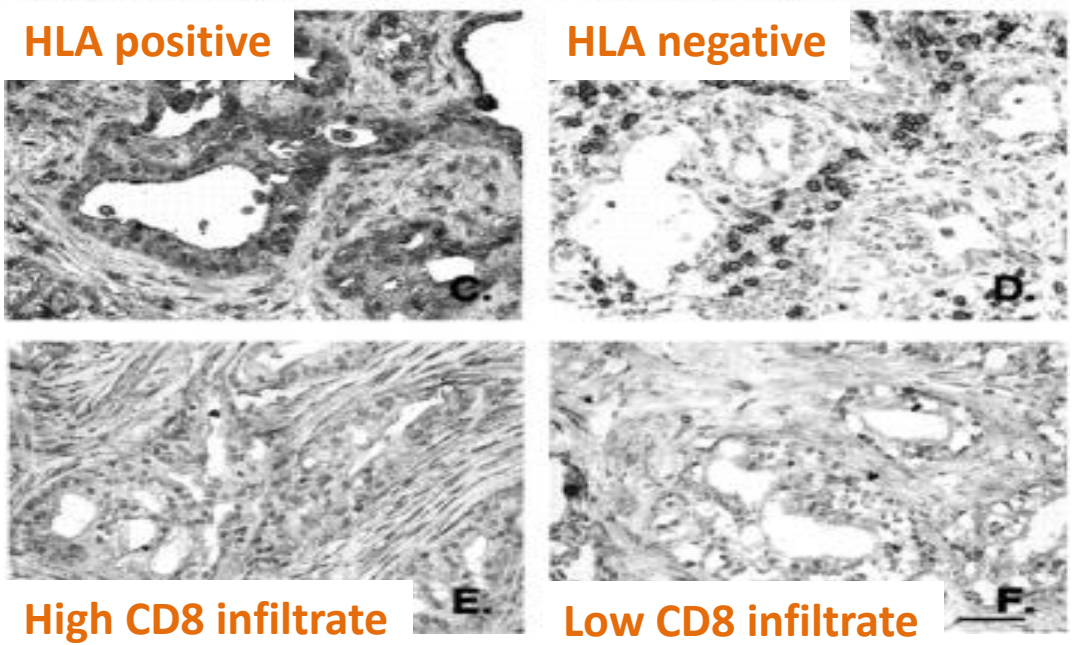
No single parameter perfectly discriminates responders from non-responders

Pembrolizumab in melanoma, Tumeh Nature 2014

Immunotherapy biomarkers. HLA loss

HLA expression

CD8 expression

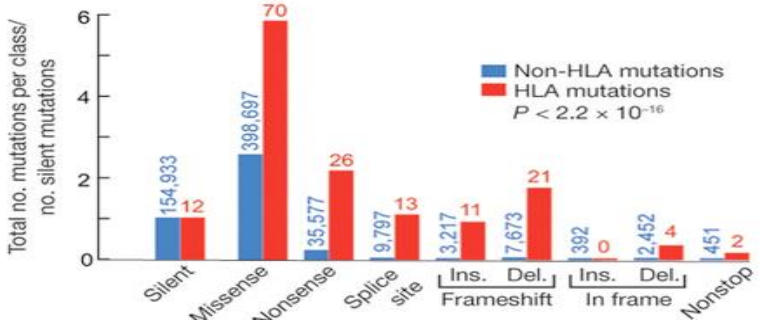


Low HLA expression in 61% pancreatic tumors

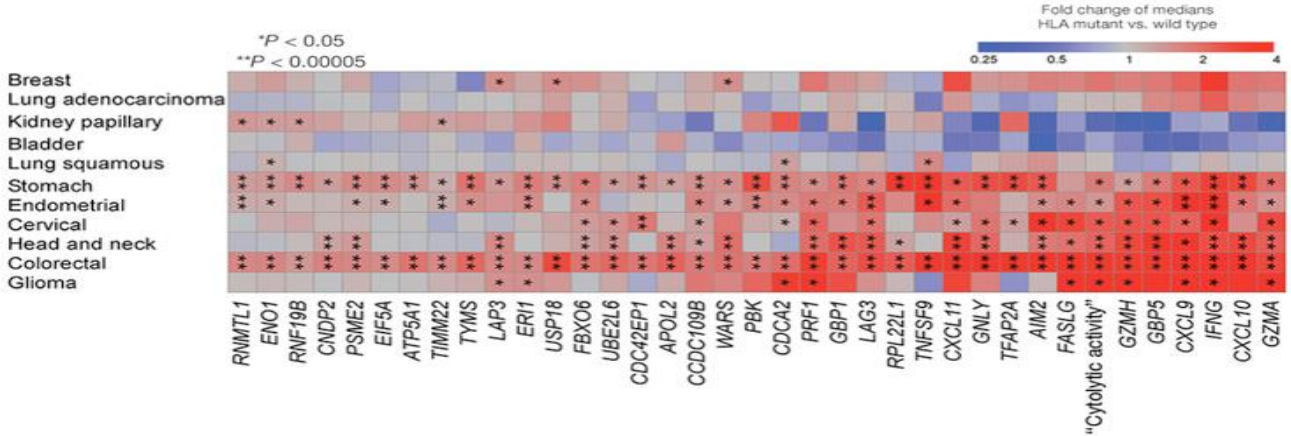
Correlates with low CD8 infiltrate

Ryschich Clin Can Res 2005

Immunotherapy biomarkers. HLA mutations



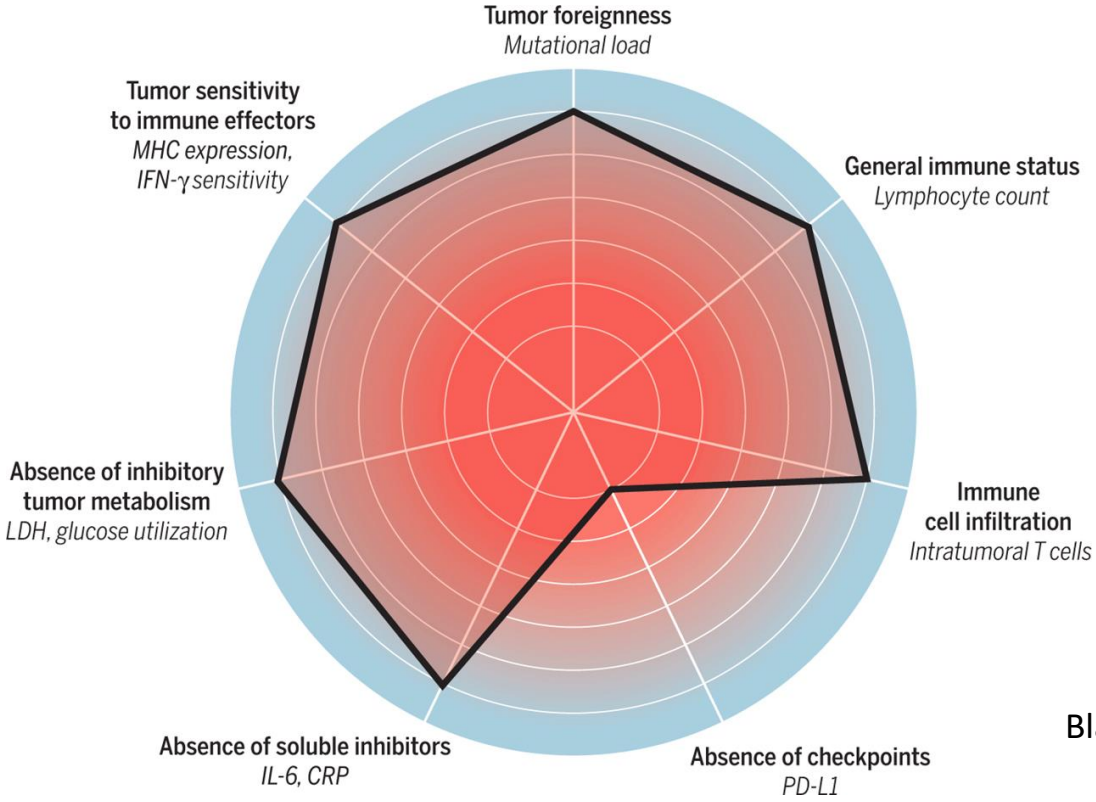
Spectrum of mutations is different than non-HLA muts



HLA-mutated tumors are associated with NK transcriptional signature

Shukla Nat Biotech 2015

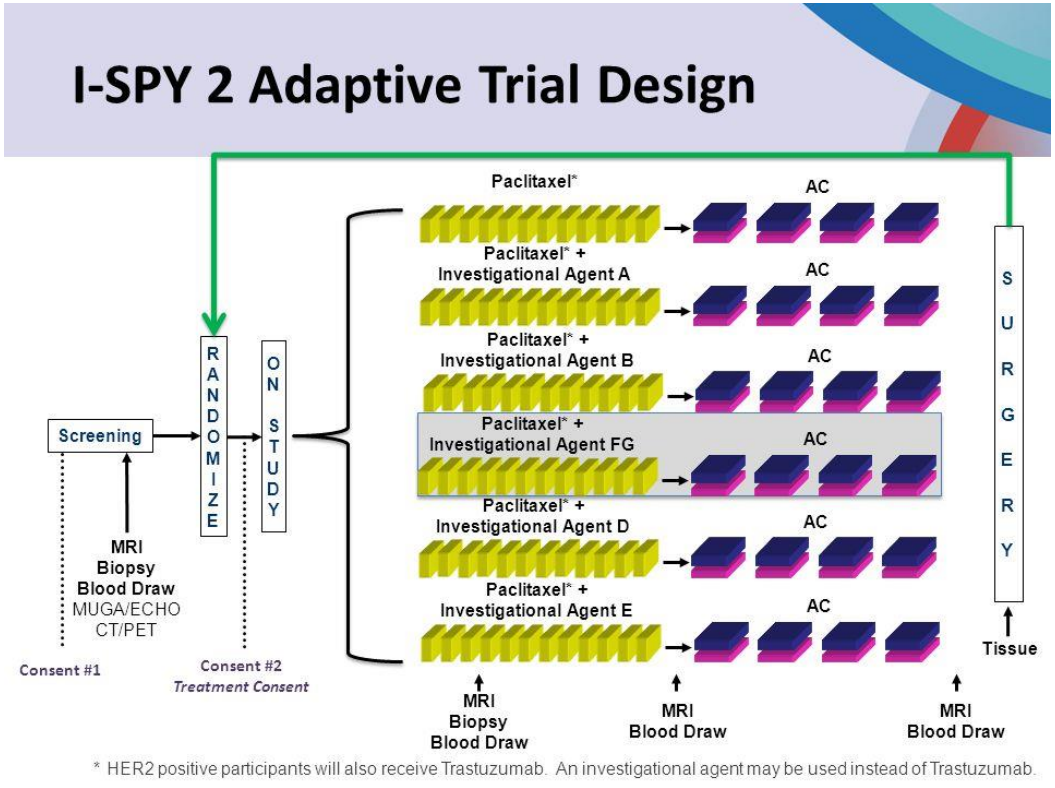
The cancer immunogram: nice but still far from real-life application

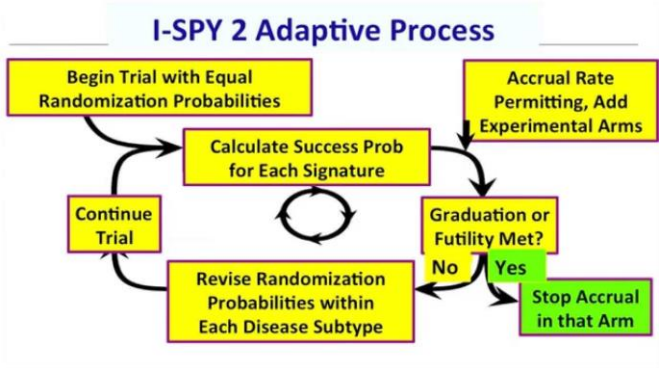


Blank et al Science 2016

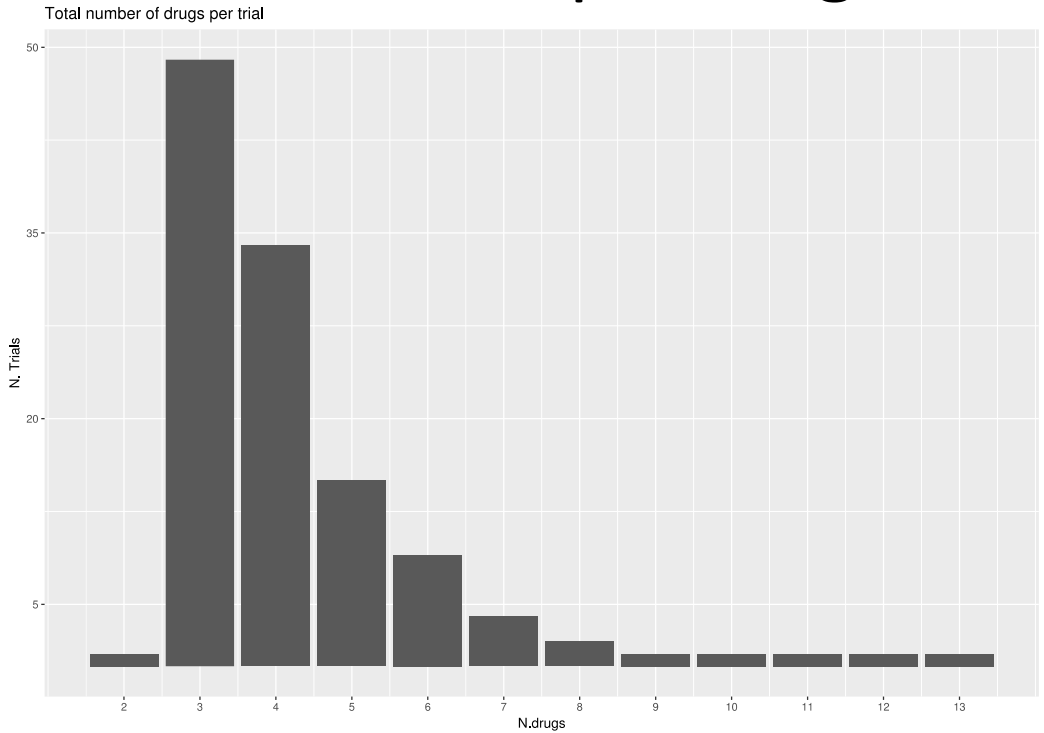
HOW TO INCORPORATE ALL THIS INFO IN DRUG DEV?

Master protocols and adaptive designs to accelerate development





Immuno combo trials are increasingly conducted with multiple drugs



Mazzarella et al under review 2019

Take home messages

- Combo design should be based on **specific rationale**, but this is not always possible
- Ways to accelerate:
  - Enhance **translational and preclinical** research to identify putative biomarkers
  - Incorporate **biomarkers early** in development, possibly phase 1
  - Use **adaptive designs** to accelerate early development
  - Use **master protocols** with fixed backbone if multiple combos are hypothesized
  - Carefully look at **toxicity**

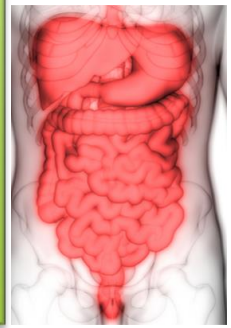
Intro 1

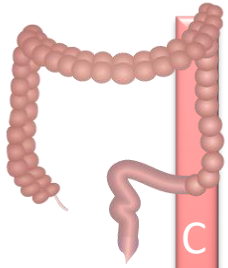
Diarrhea and Colitis: the US NIH NCI Perspective

The CTCAE v.5 of IMDC

DIARRHEA

- **G1**
  - Increase of **<4** stools per day over baseline
- **G2**
  - **4-6** stools over baseline
  - Limits instrumental ADL
- **G3**
  - **>6** stools over baseline
  - Hospitalization indicated
  - Limits self care ADL
- **G4**
  - Life- threatening
  - Urgent interventions

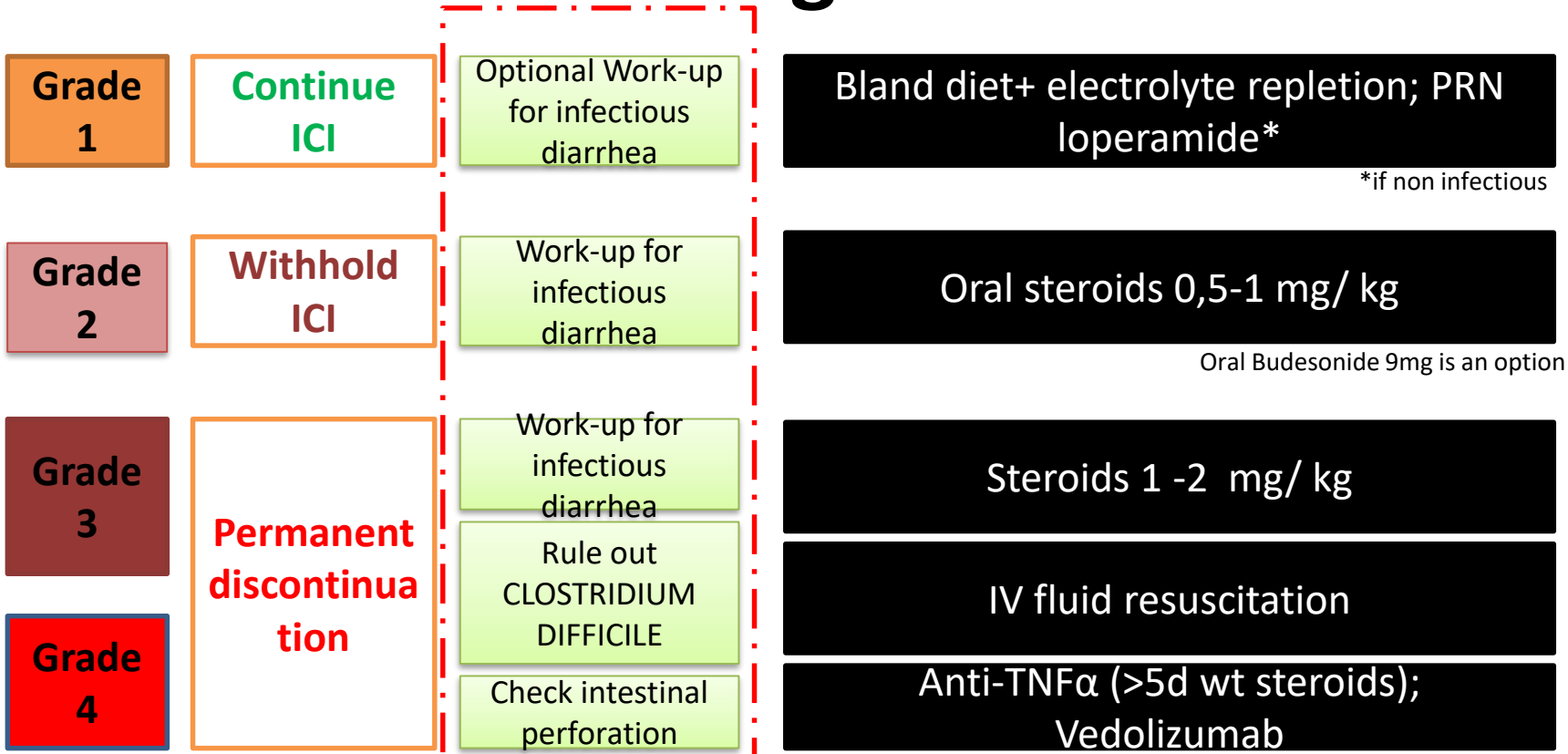




COLITIS

- **G1**
  - Asymptomatic (**clinical or instrumental observation**)
- **G2**
  - Abdominal pain, **mucus, blood** in the stool
- **G3**
  - Severe abdominal **pain**; peritoneal signs
- **G4**
  - Life- threatening
  - Urgent interventions

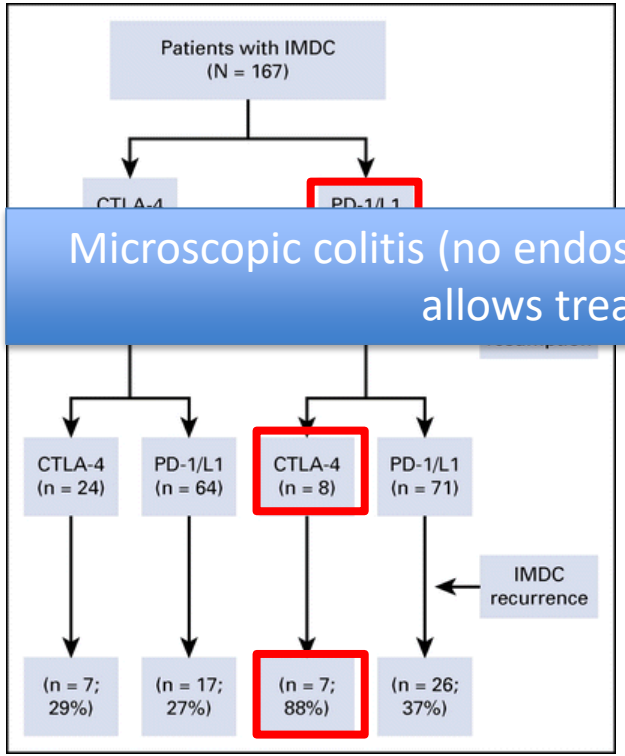
The current management of IMDC



***REDUCTIO AD UNUM* DOES NOT APPLY**

Som A, World J Clin Cases. 2019

Results: who has an increased risk?



Microscopic colitis (no endoscopic signs) can be cured with topical budesonide and allows treatment contnuation!!! (unpublished)

Covariate	Odds Ratio	95% CI	*P*
Initial ICI type			
Anti–CTLA-4		Reference	
Anti–PD-1/L1	3.45	1.59 to 7.69	.002
Anti–PD-1/L1	0.30	0.11 to 0.81	.019
Grade of initial diarrhea*			
1		Reference	
2	1.19	0.37 to 3.80	.775
3-4	2.19	0.66 to 7.29	.202
Required immunosuppressive therapy initially	3.22	1.08 to 9.62	.019
Duration of initial IMDC symptoms	1.01	1.00 to 1.03	.031

Abu-Sbeih H et al, J Clin Oncol 2019

Thank you

Looking for postdocs

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