

Prioritisation of potential immunotherapy combination studies

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ITOC 3



Activities & Links of Interest

- **Principal Investigator & Co-Investigator in Clinical Trials**

Anti-PD-1, anti-PD-L1, anti-CTLA-4, anti-CSF1-R, anti-GITR, anti-OX40, EP4 inhibitor, Oncolytic Peptide

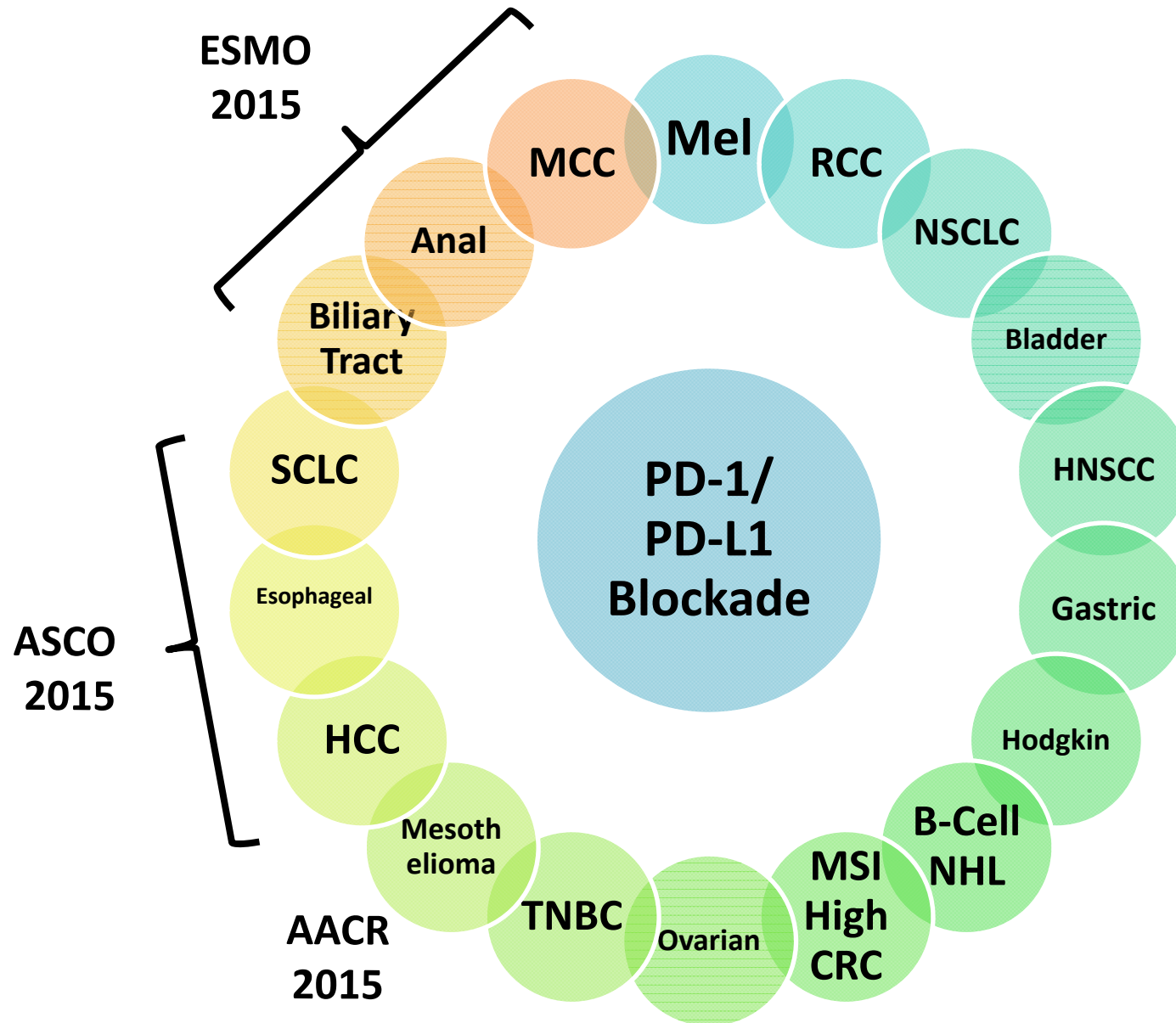
MSD, BMS, Roche/Genentech, Amgen, Astra Zeneca/Medimmune, GSK, Eisai, Lytix Biopharma

- **Consultancy & Advisory Boards**

MSD, BMS, Roche/Genentech, Amgen, Novartis, Pfizer, Lytix Biopharma, Rigontec

I will be partial and biased !

2010-2015: the PD-Lomas





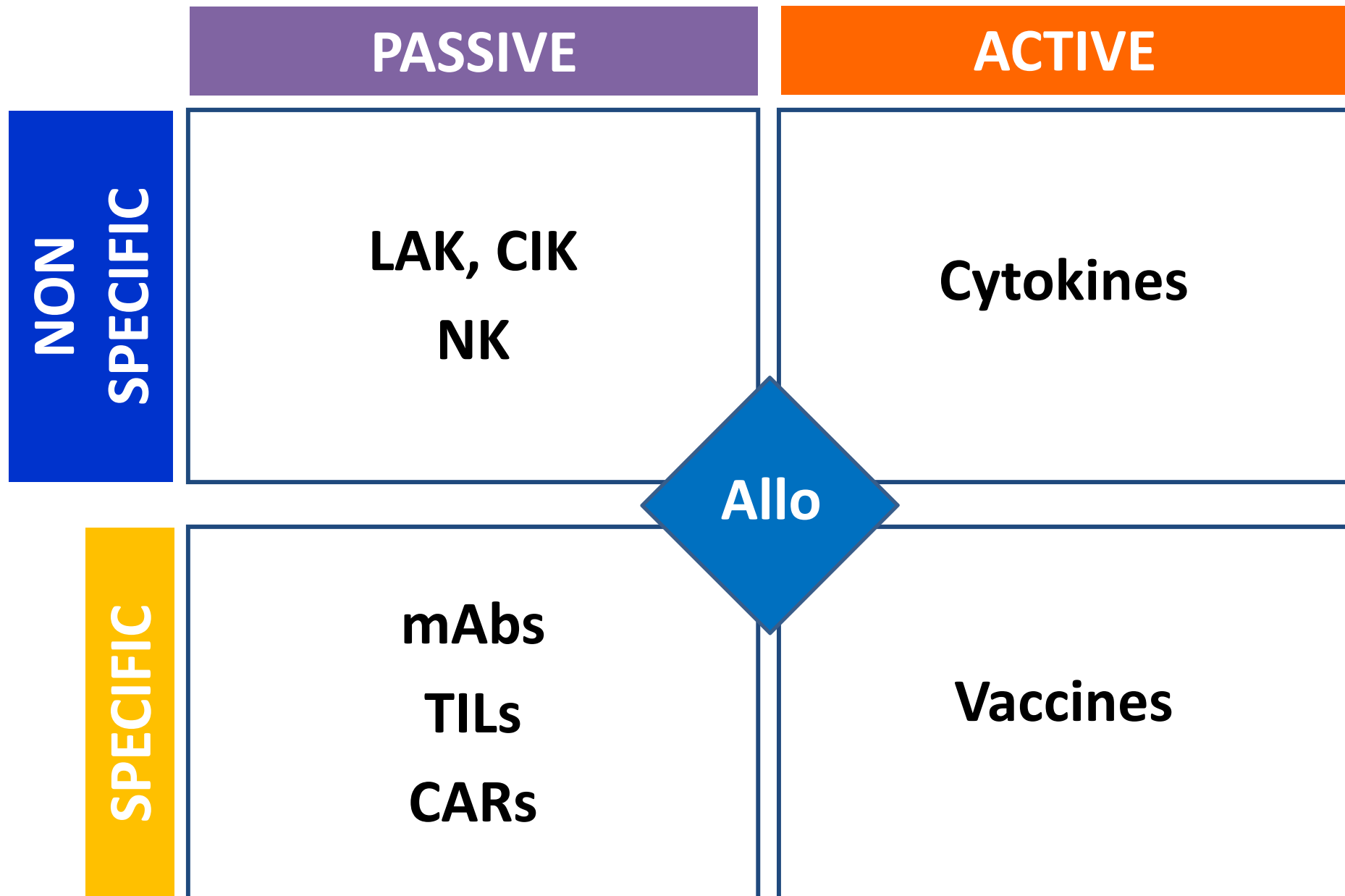
How can we prioritize immunotherapy combinations ? 

Recherche Google

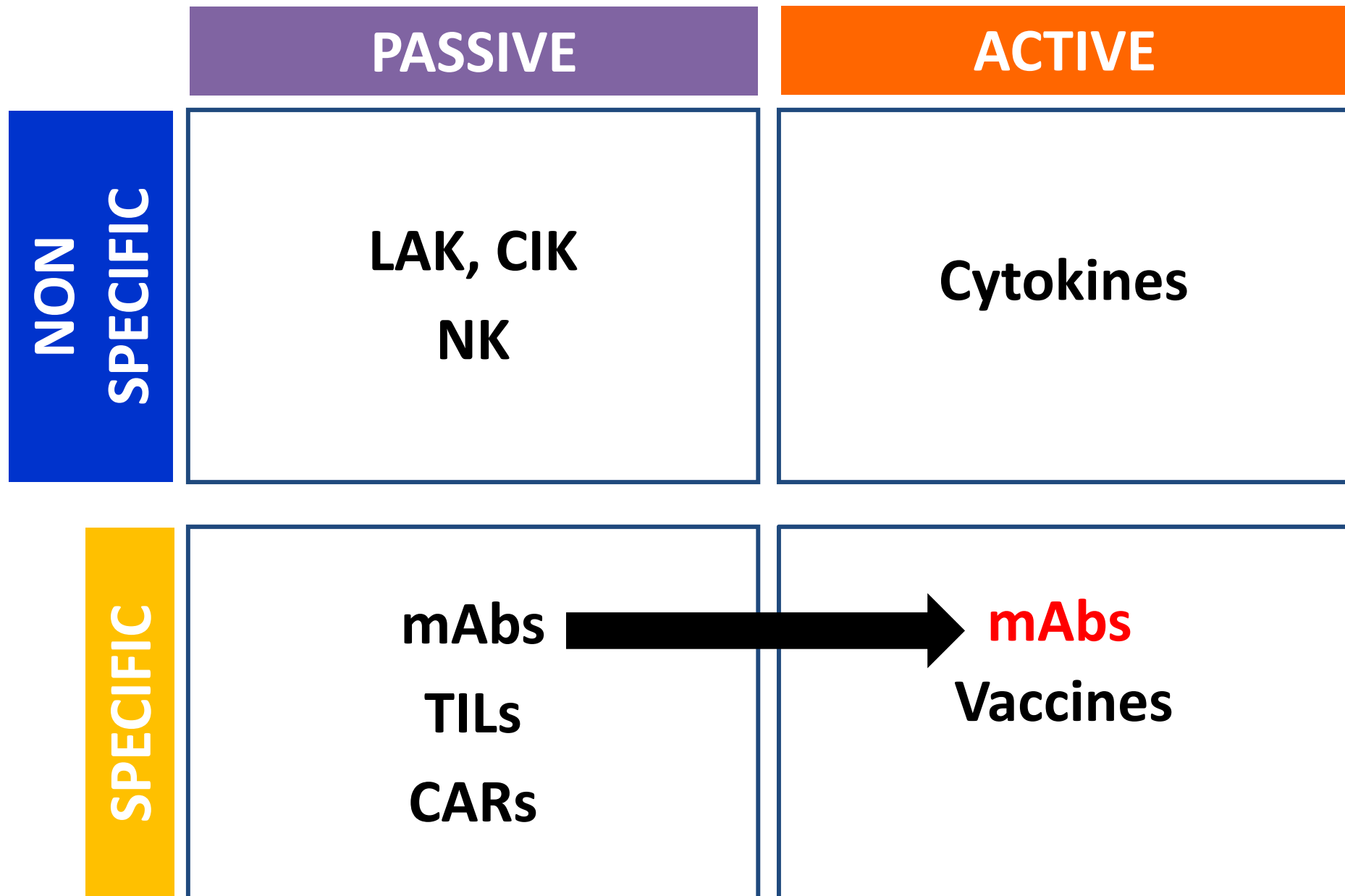
J'ai de la chance

***All immunotherapies
are not created equal***

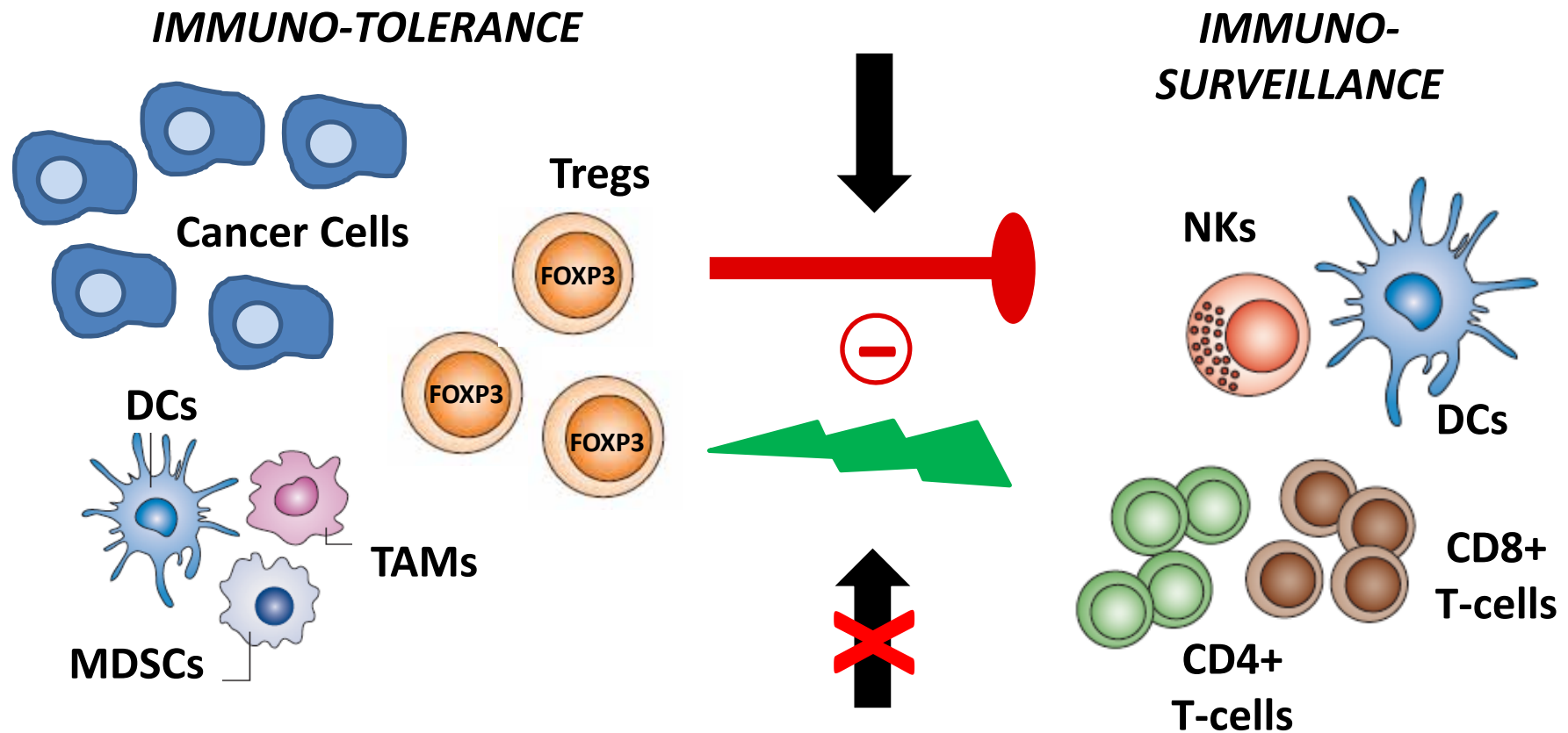
Cancer Immunotherapies



Cancer Immunotherapies

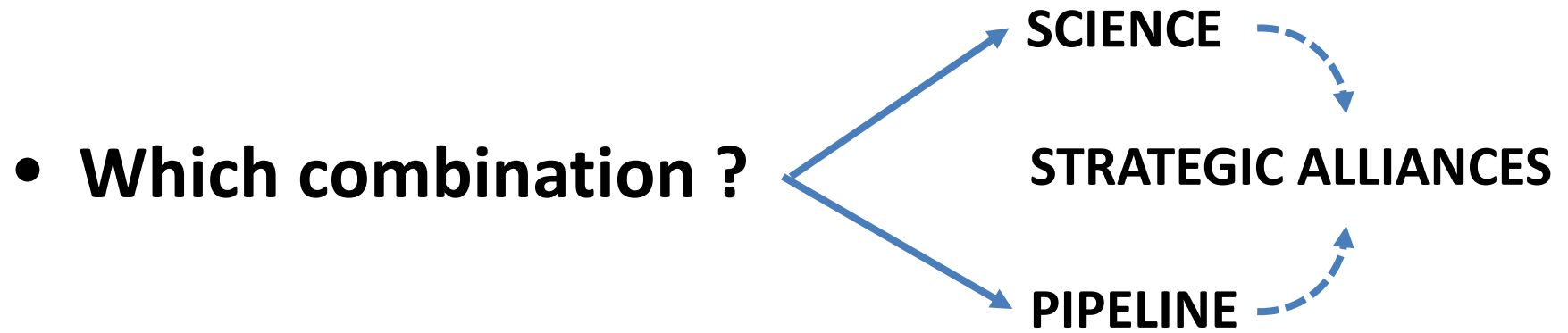


Inhibit the inhibitors rather than stimulate the stimulators



Adapted from Colombo MP, et al Nat Rev Cancer. 2007 Nov;7(11):880-7.

Prioritization of (CTLA4/PD-1) Combinations



PRE-CLINICAL RATIONALE

EX VIVO

- tumor >>> blood, DLN
- IHC & Flow Cytometry
- Functional Assay > Descriptive Experiment

PRE-CLINICAL RATIONALE

EX VIVO

- tumor >>> blood, DLN
- IHC & Flow Cytometry
- Functional Assay > Descriptive Experiment

IN VIVO

- Immunocompetent >>> Xenograft
- Transplantable & Spontaneous
- Established Tumors+++

Prioritization of Combinations

- Which combination ?

- Which cancer ?



MEDICAL NEED

INCIDENCE

REGISTRATION PATH

RATIONALE

Prioritization of Combinations

- Which combination ?

- Which cancer ?

MEDICAL NEED

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REGISTRATION PATH

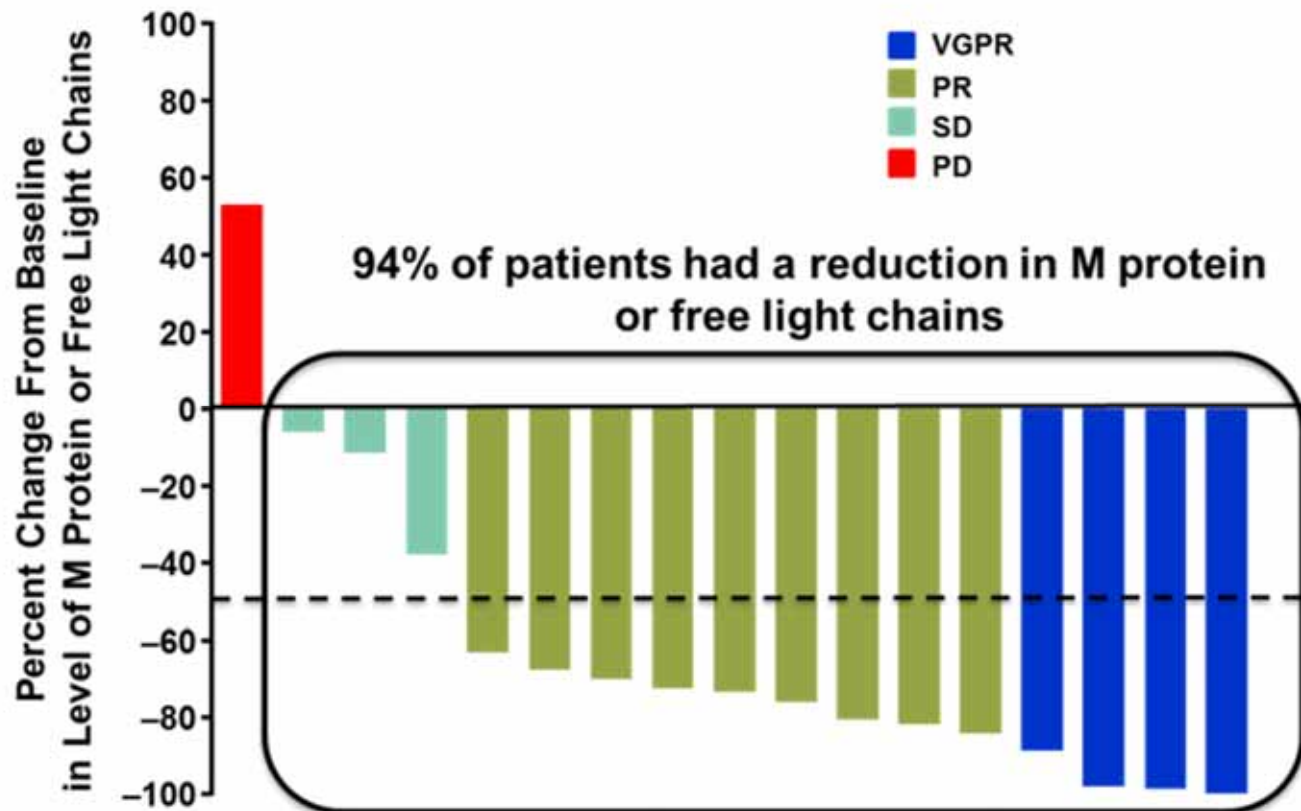
RATIONALE

→ Only PD-Lomas ?

Multiple Myeloma

> α PD-1 alone **ORR = 0% (0/27)**

> Lenalidomide + α PD-1 + Dexamethasone **ORR = 76% (13/17)**



San Miguel et al, ASH 2015

Prioritization of Combinations

- Which combination ?

- Which cancer ?

MEDICAL NEED

INCIDENCE


REGISTRATION PATH

RATIONALE

~~→ Only PD-Lomas ?~~

→ Only in PD-L1+ ?

- **α CTLA4 + α PD-1**
- **chemotherapy + α PD-L1**
- **α VEGF + α PD-L1**
- **...**



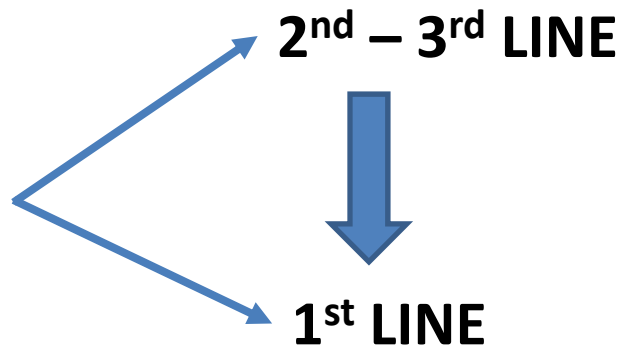
**No
Predictive Value
of PD-L1
in Combinations**

Prioritization of Combinations

- Which combination ?

- Which cancer ?

- Which line ?

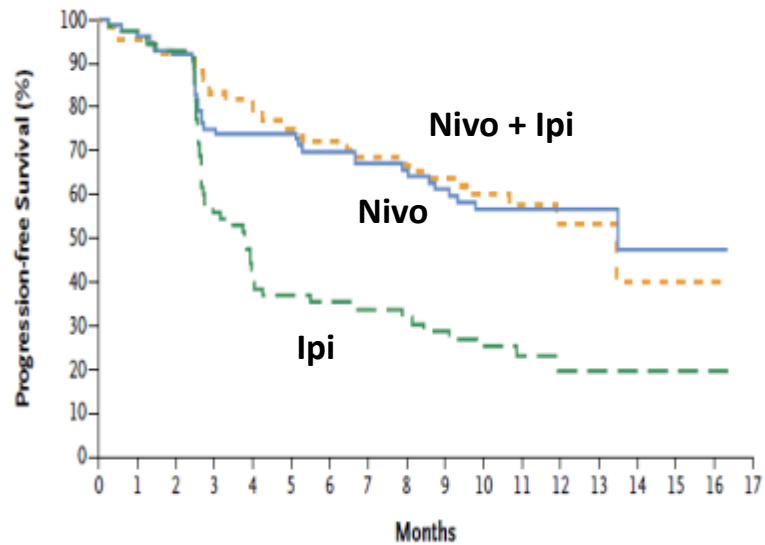


Prioritization of Combinations

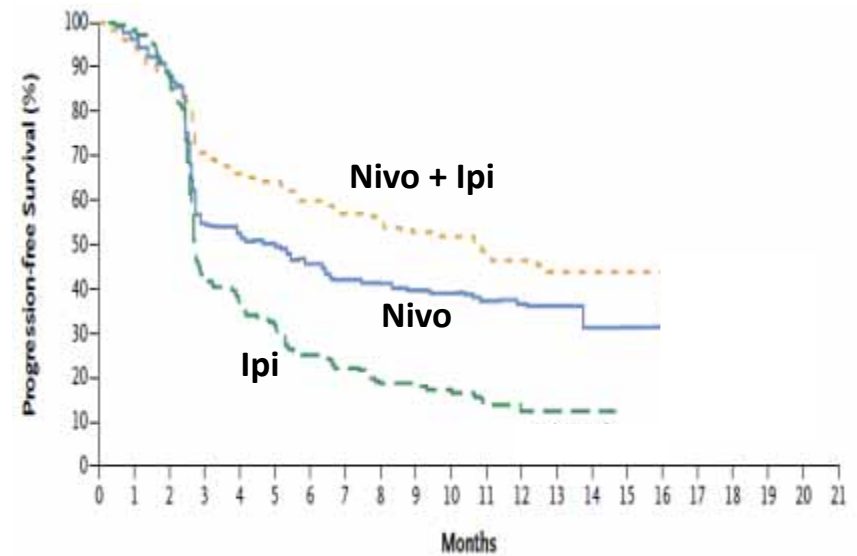
- Which endpoint ?
 - PD Marker
 - ORR
 - PFS
 - OS

Anti-CTLA4 only in PD-L1^{neg} patients?

PD-L1^{pos} Patients

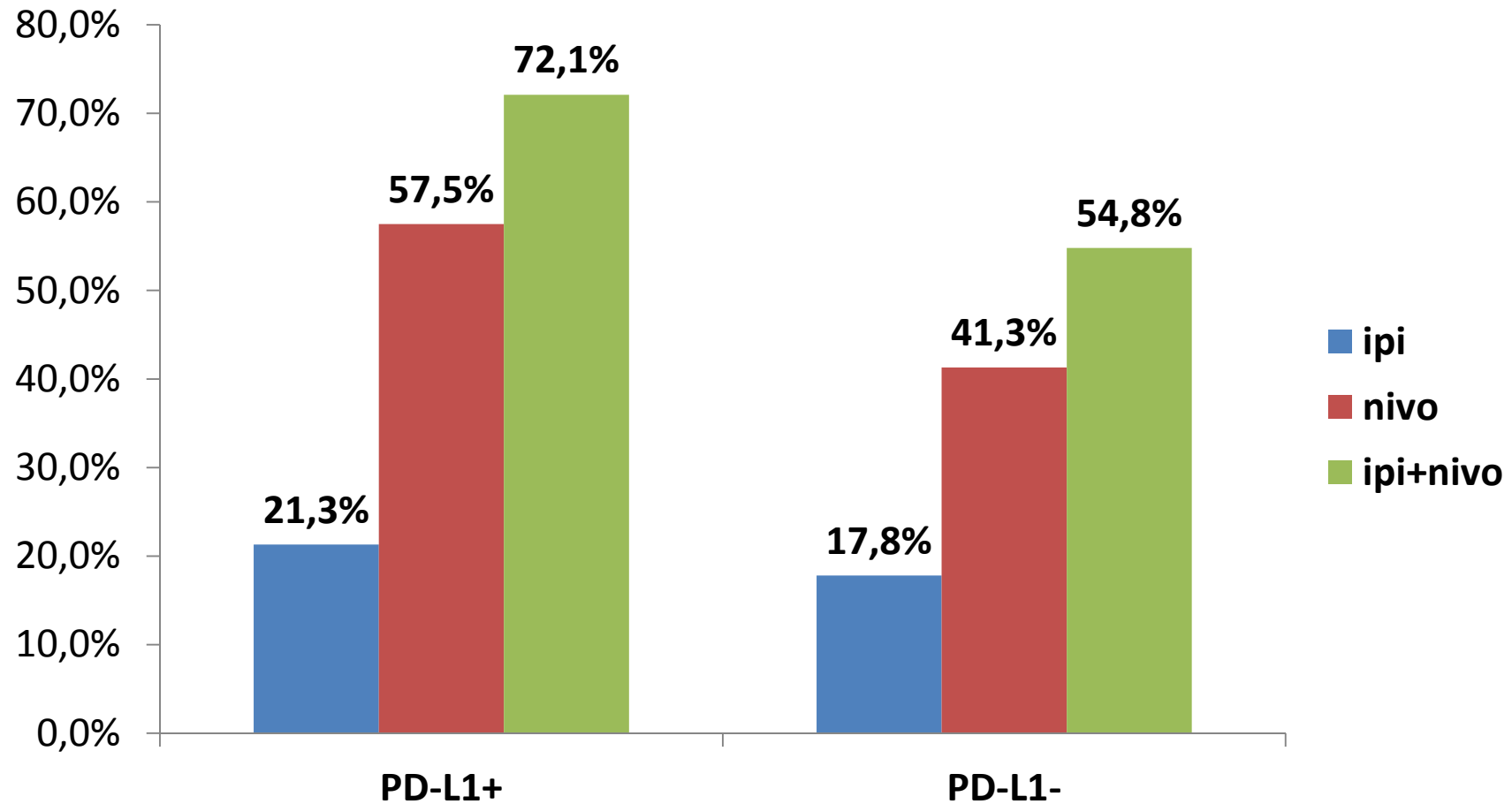


PD-L1^{neg} Patients



Larkin J et al. N Engl J Med 2015.

ORR of nivo+ipi > nivo in PD-L1^{neg}



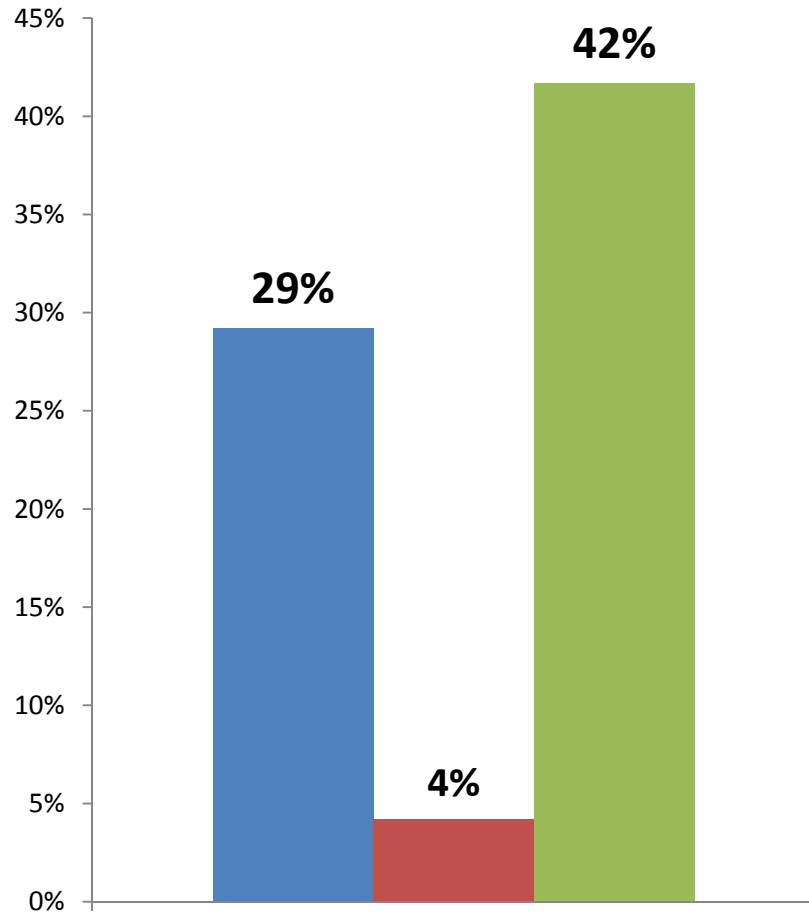
First line, Unresectable MM, Randomized Phase III study, RECIST 1.1

Larkin J, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med* 2015.

ORR or DCR?

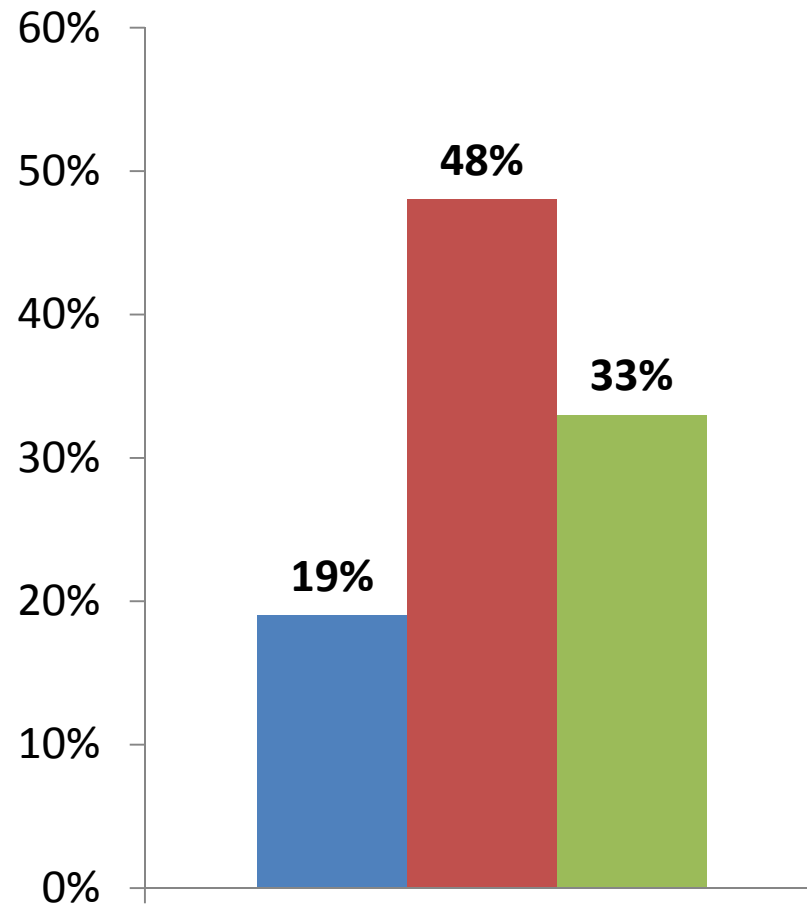
■ PD ■ SD ■ CR + PR

SCLC



Ott, Pembrolizumab, WCLC 2015

HCC



El-Khoueiry, Nivolumab, ASCO 2015

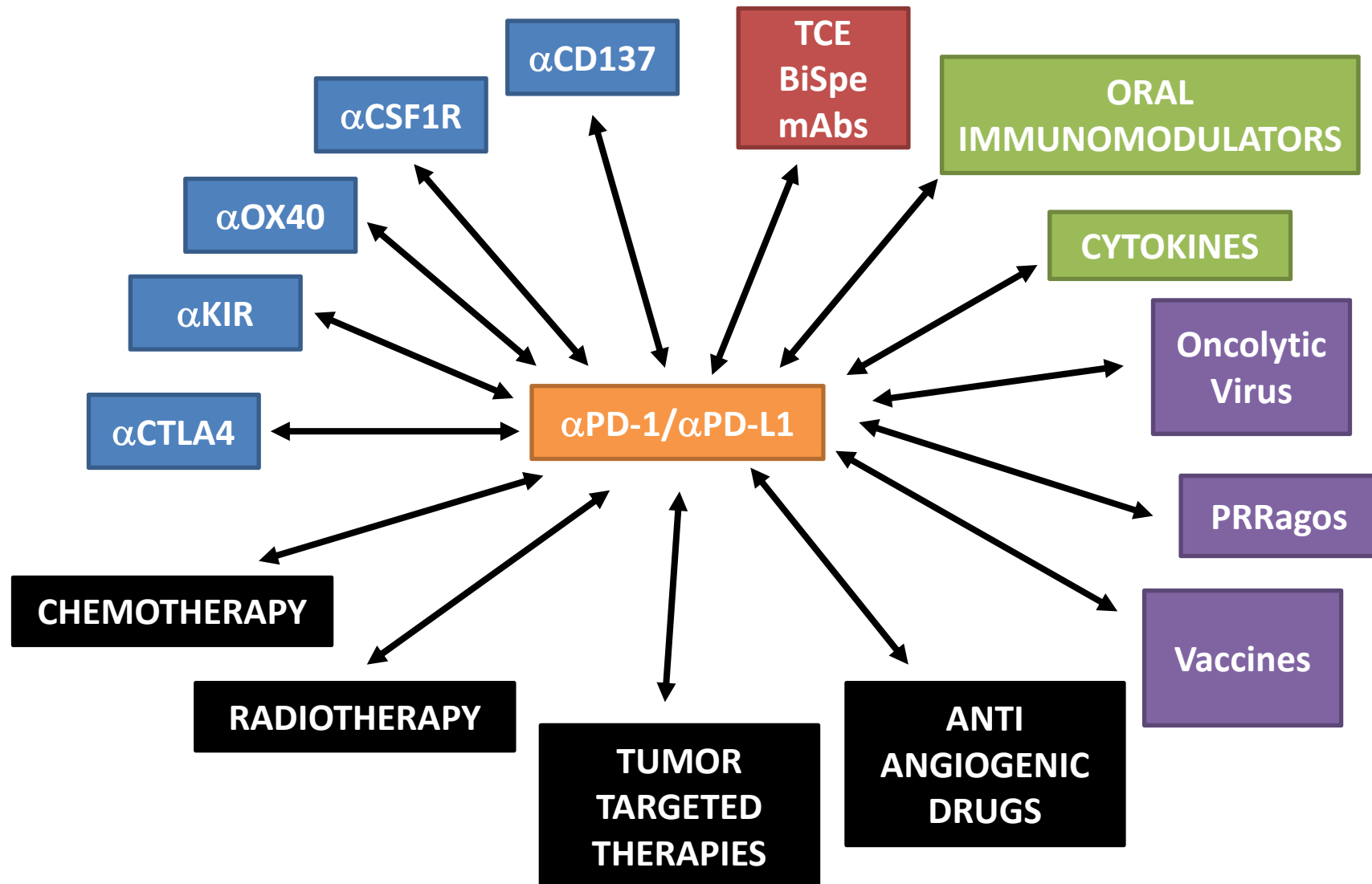
Prioritization of Combinations

- Which endpoint ?
- Which trial design ?
 - Dose Escalation
 - Expansion Cohorts
 - Randomize

Prioritization of Combinations

- **Which endpoint ?**
- **Which trial design ?**
- **Which strategy ?**

2016: We are already there !



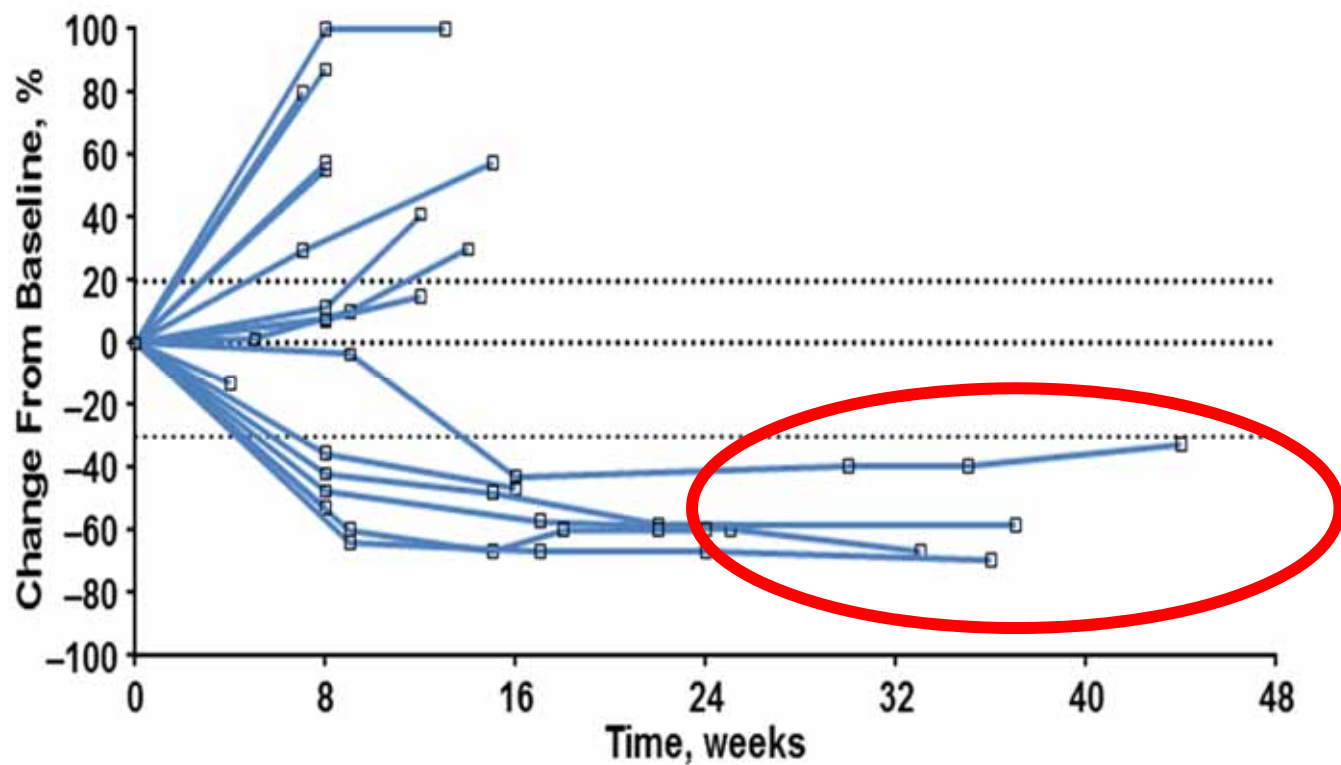
STATEMENT #1

Clinic Will Rule
(not science)

STATEMENT #2

***Many Combinations
will be Synergistic***

Criteria#1: Durability of responses

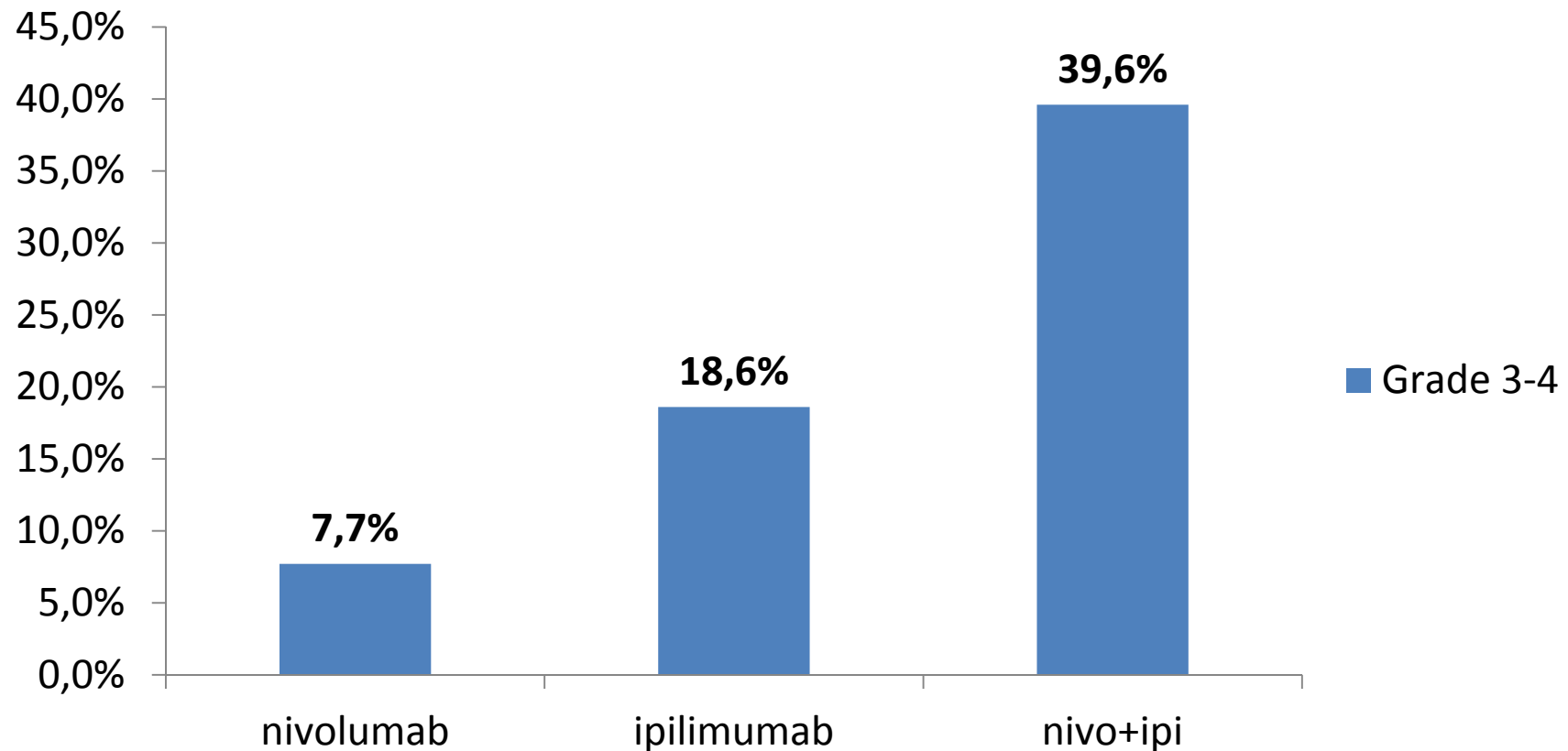


Ott et al. Pembrolizumab in SCLC. WCLC 2015

Criteria#2:

Toxicity of the Combination for Pts?

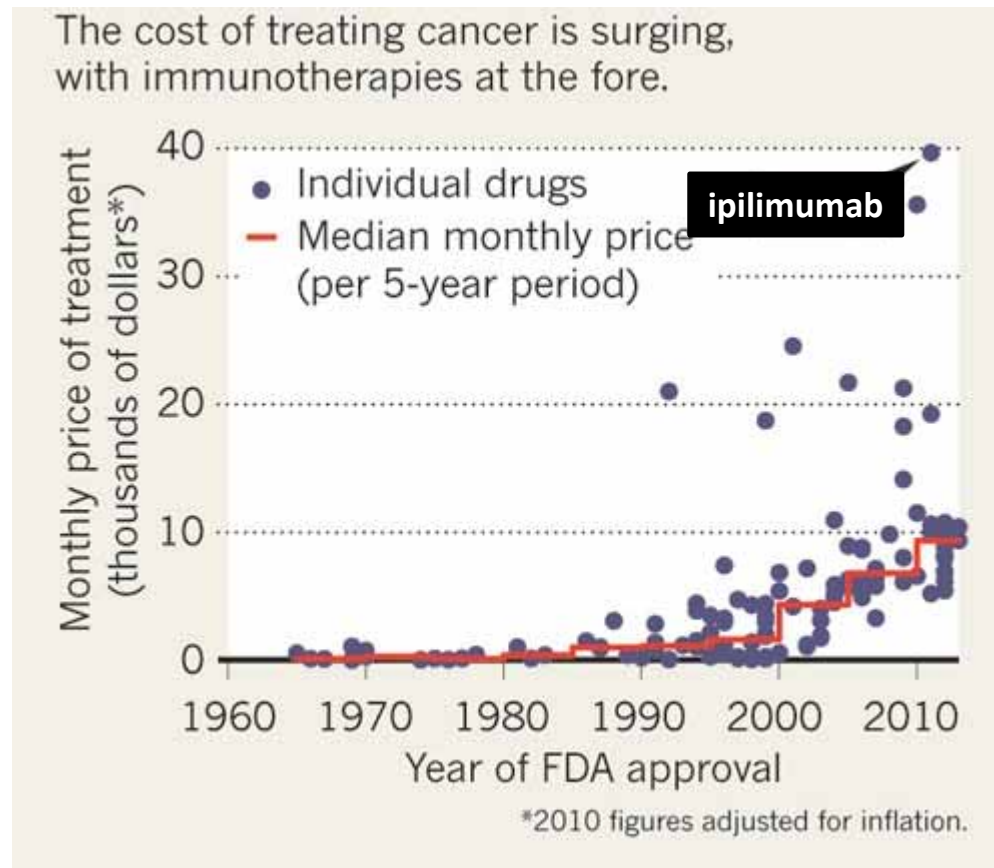
Grade 3-4 Adverse Events with anti-CTLA4 + anti-PD-1



Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015.

Criteria #3:

Toxicity of the combo for the health system?



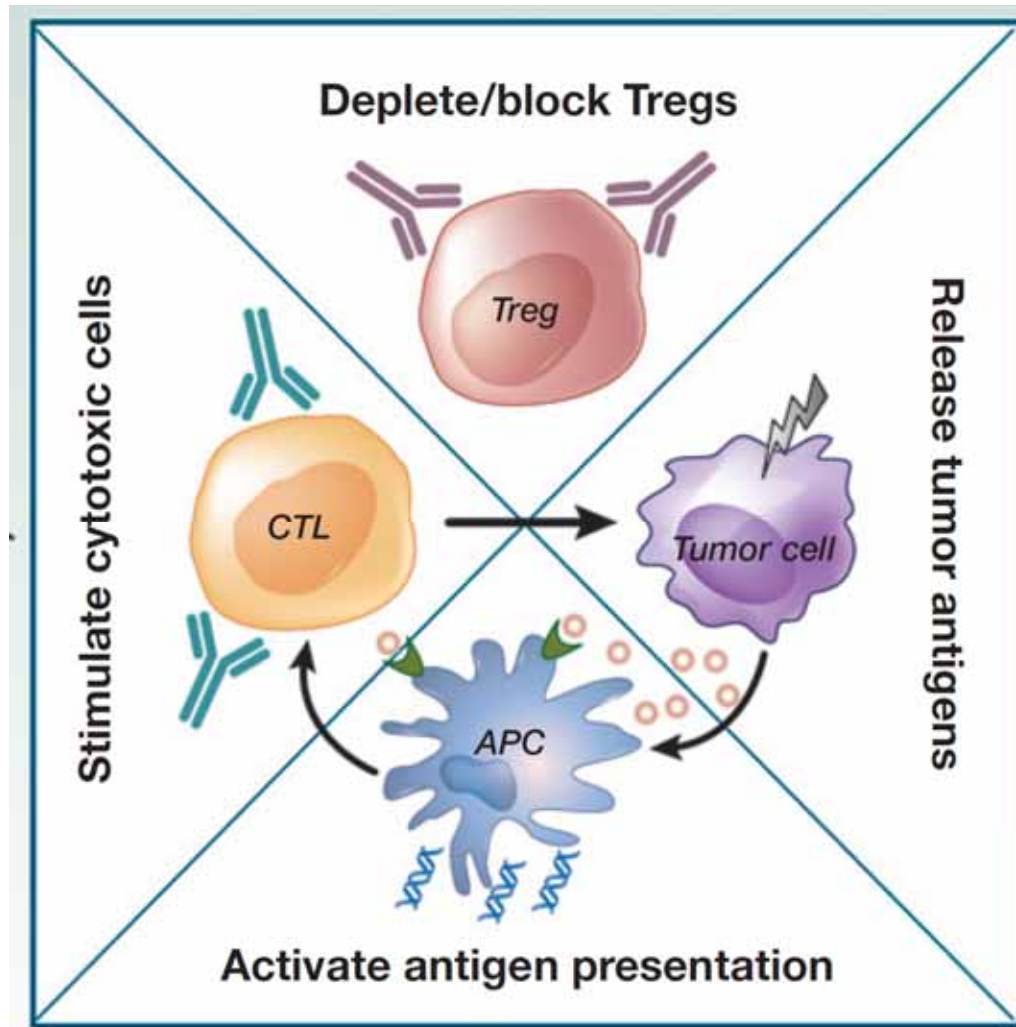
[Nature](#). 2013 May 30;497(7451)

Immunotherapy's cancer remit widens. Ledford H.

STATEMENT #3

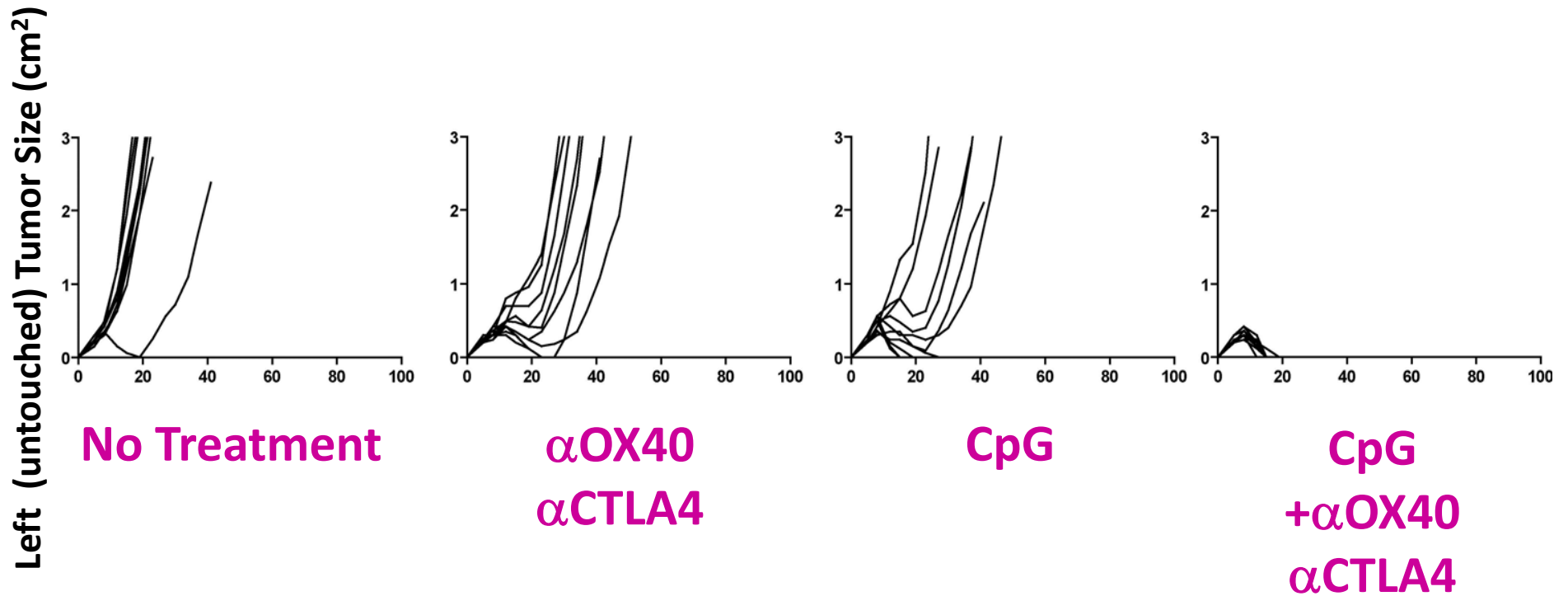
***Pattern Recognition Receptors
will be the next
Immune Checkpoints to Target***

Address Myeloid Cells Phenotype



Marabelle A, Clin Cancer Res 2014;20:1747–56.

Overcome Immune Checkpoint Blockade Resistance with combinations of TLR agonists



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