# High Impact Clinical Trials

# Disclosure

- Advisory Board: PDS Biotechnology, Merus, NewLink, MEI Biologics, Bioline Therapeutics, Syndax, IO Biotech, Northwest Therapeutics, Boullett Biotech, UbiVax
- Board Member: Advaxis Immunetherpies
- KOL/Consultant: J&J, AstraZenica, NewLink Genetics, Medimmune, Lycera, Berringer Engelheim
- Unrestricted preclinical Research funding: MedImmune, AstraZenica, NewLink Genetics, Advaxis Immunetherapies, PDS, Gilead, Bioline Therapeutics, Lycera, IO Biotech, Syndax, Biotechnologies, AmpImmune, CureTech

# High Impact Clinical Trials

- Pooled 3-Year Overall Survival Data from Phase II and Phase III Trials of Nivolumab (NIVO) Combined with Ipilimumab (IPI) in Advanced Melanoma
  Stephen Hodi, MD – Dana-Farber Cancer Institute

- Nivolumab + Ipilimumab (N+I) vs Sunitinib (S) for Treatment-Naïve Advanced or Metastatic Renal Cell Carcinoma (aRCC): Results From CheckMate 214, including Overall Survival by Subgroups Robert J. Motzer, MD – Memorial Sloan Kettering Cancer Center

- Immune and Tumor Responses to Human IL-10 (AM0010, Pegilodecakin) Alone or in Combination with Immune Checkpoint Blockade Martin Oft, MD – ARMO BioScience

- A Phase 1 Study of TSR-022, an Anti-TIM-3 Monoclonal Antibody, in Patients (pts) with Advanced Solid Tumors Glen J. Weiss, MD – Western Regional Medical Center Inc.

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Hodi, et al – Dana-Farber Cancer Institute

NIVO+IPI as first-line therapy resulted in a longer treatment-free interval and a higher rate of treatment-free survival than either NIVO or IPI alone

# High Impact Clinical Trials

Nivolumab + Ipilimumab (N+I) vs Sunitinib (S) for Treatment-Naïve Advanced or Metastatic Renal Cell Carcinoma (aRCC): Results From CheckMate 214, including Overall Survival by Subgroups

Motzer, et al – Memorial Sloan Kettering Cancer Center

CheckMate 214 demonstrated superior OS and ORR with NIVO + IPI versus SUN in intermediate/poor risk treatment-naïve aRCC

# High Impact Clinical Trials

Immune and Tumor Responses to Human IL-10 (AM0010, Pegilodecakin) Alone or in Combination with Immune Checkpoint Blockade

Martin Oft, MD – ARMO BioScience

Combination IL-10 + antiPD1:

Tolerated with no significant increase in AE profile over either agent in monotherapy

ORR in RCC 44% (15 of 34 pts (2 CRs), 2x expected RR)

ORR in NSCLC 41% (11 of 27 pts, 2x expected RR)

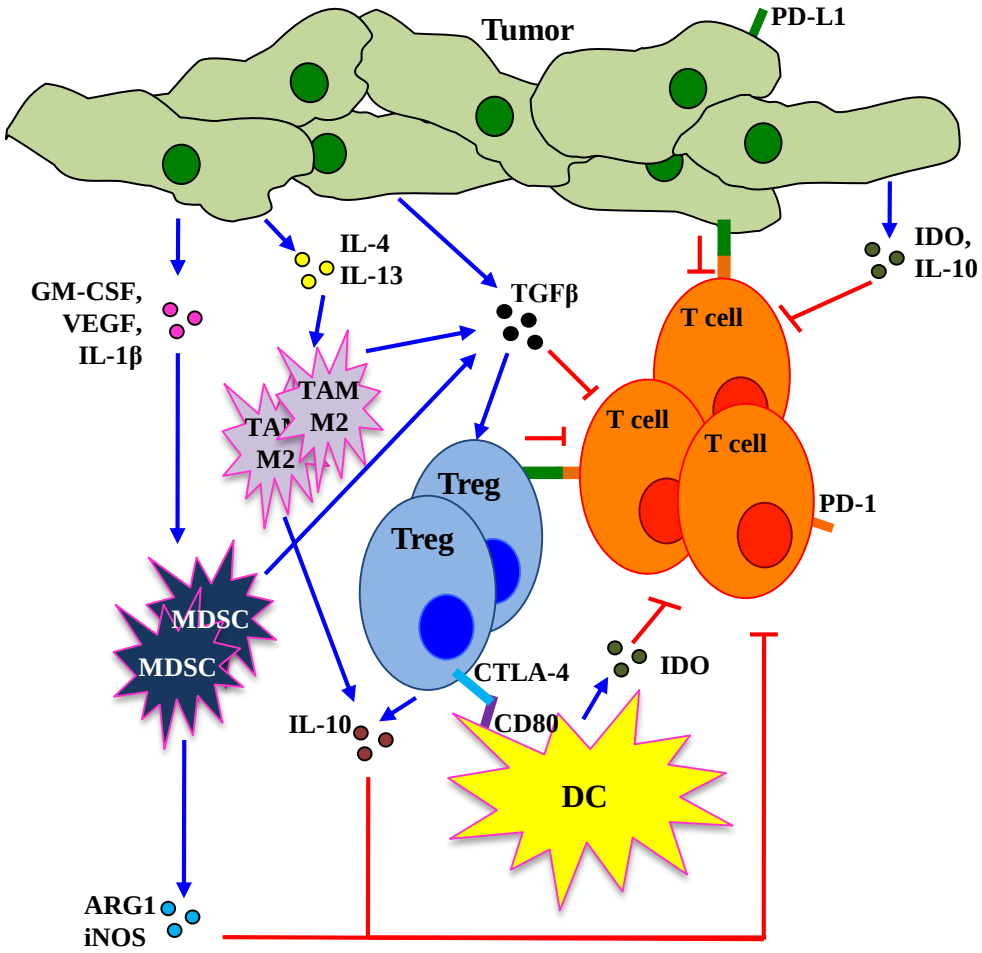
# High Impact Clinical Trials

## A Phase 1 Study of TSR-022, an Anti-TIM-3 Monoclonal Antibody, in Patients (pts) with Advanced Solid Tumors

Weiss, et al, Western Regional Medical Center Inc.

TSR-022 monotherapy is well tolerated across multiple dose levels, consistent with the safety profiles of other checkpoint inhibitors.

# Tumor-Immune Interaction



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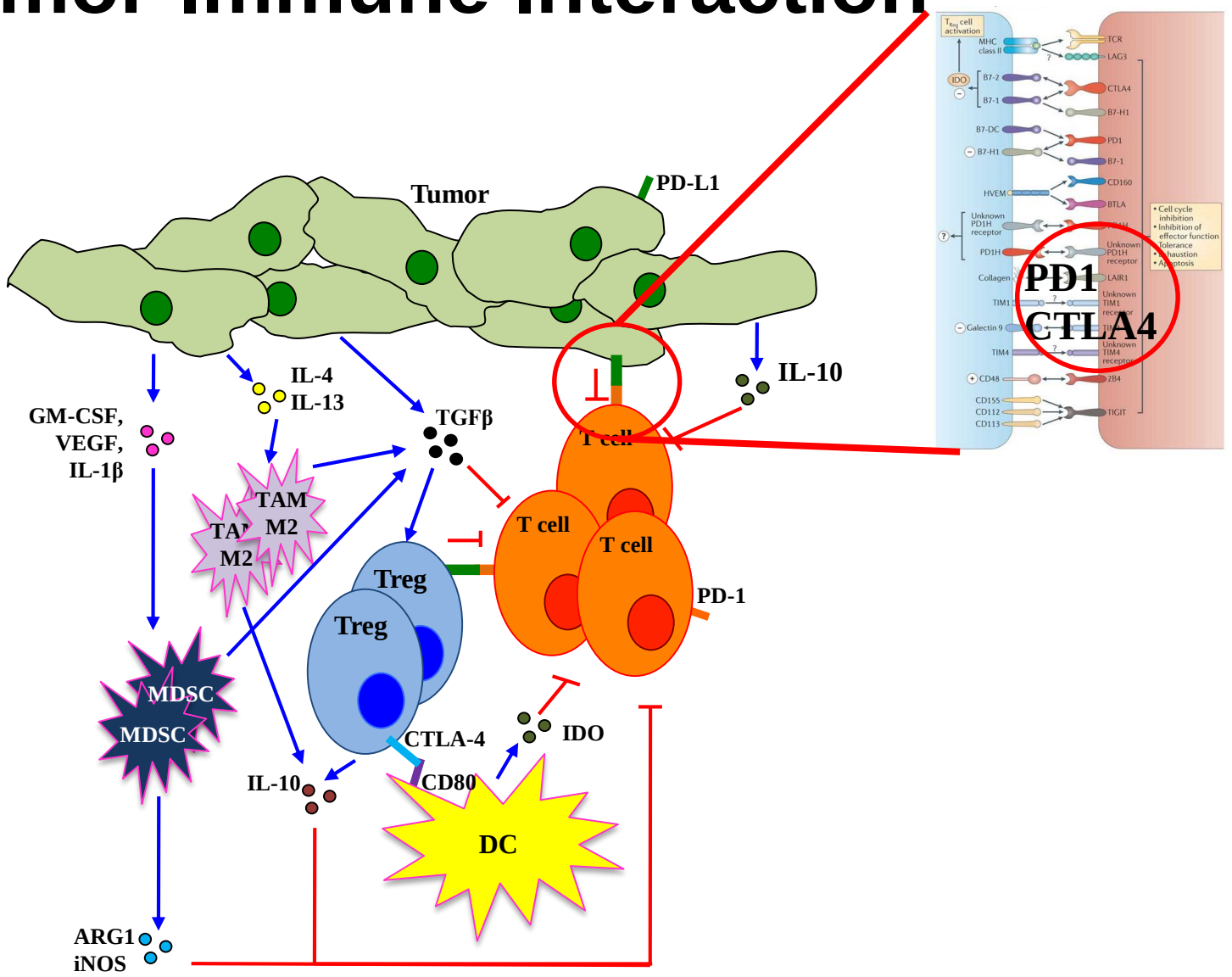

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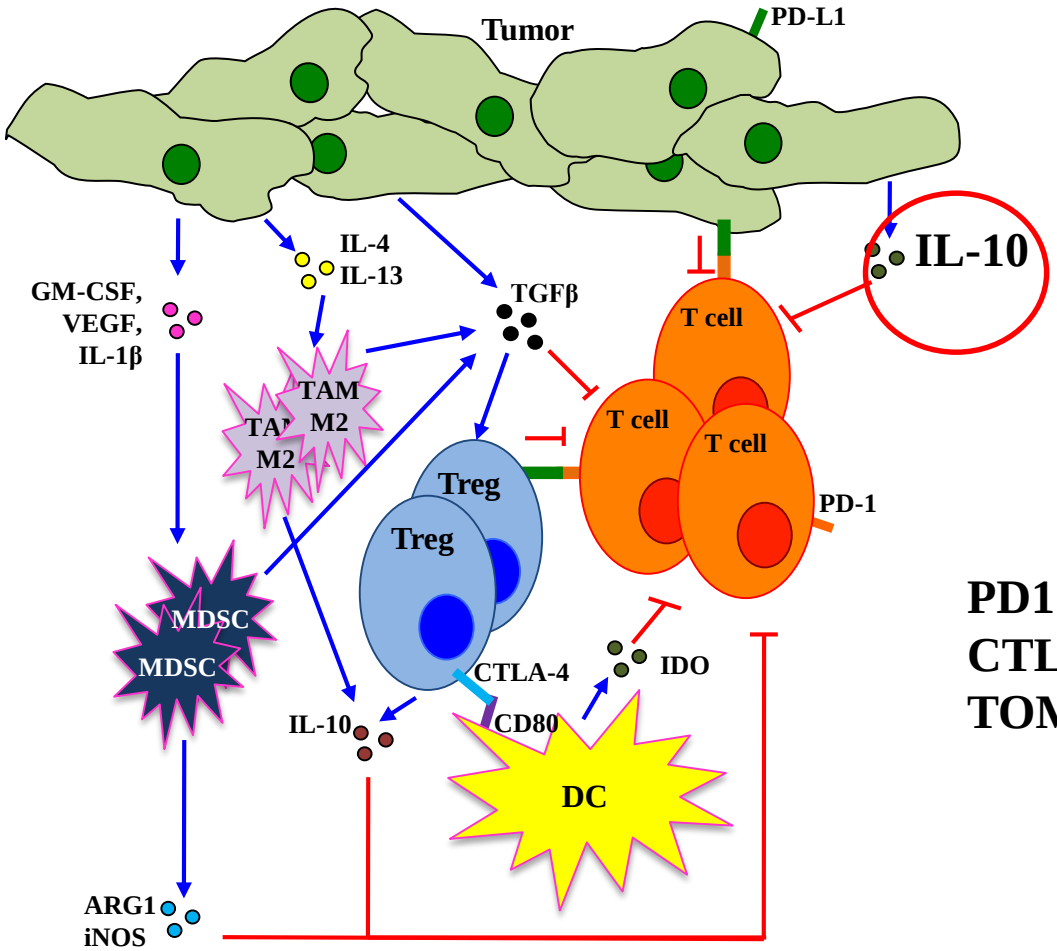


**PD1**
**CTLA4**
**TOM3**

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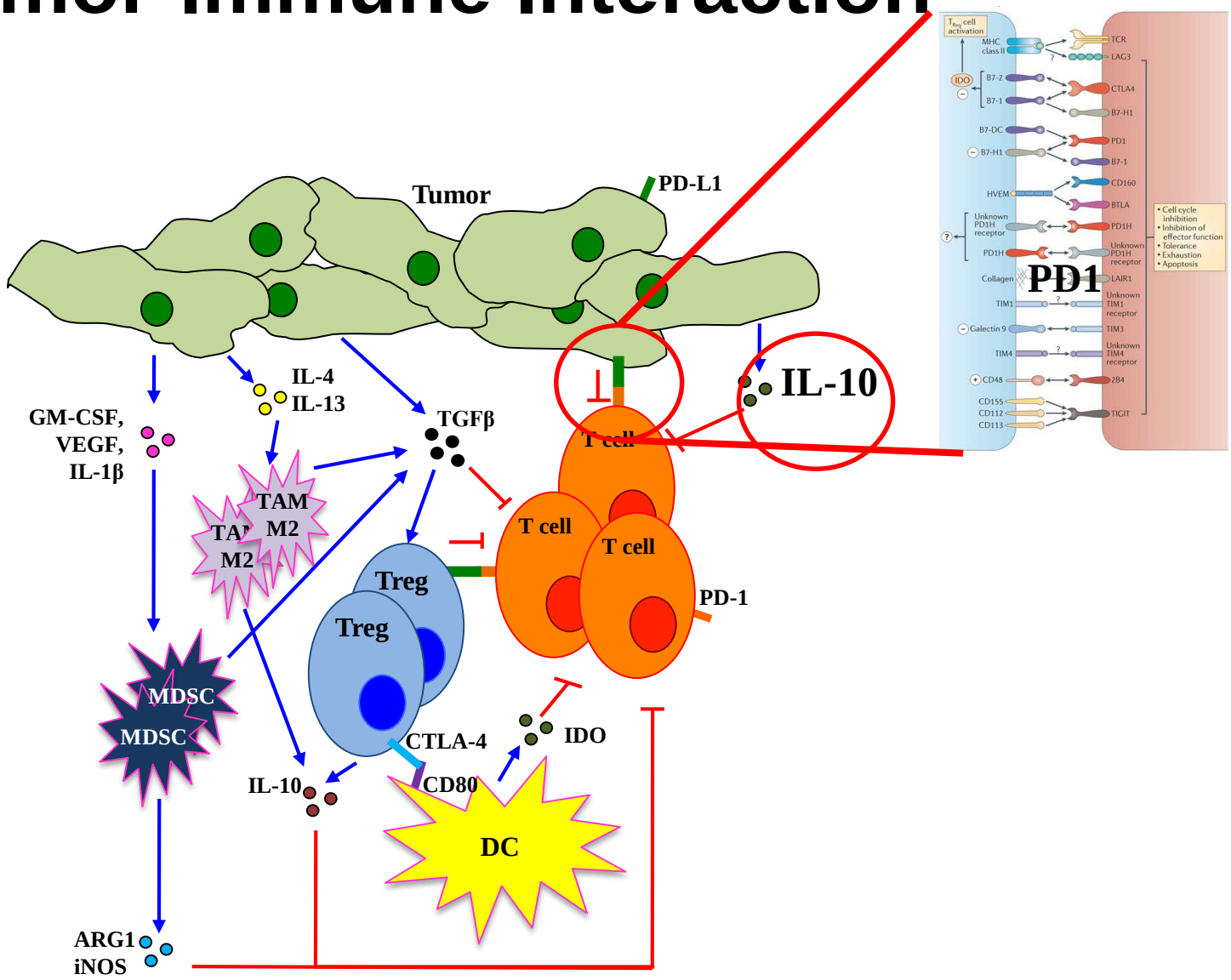

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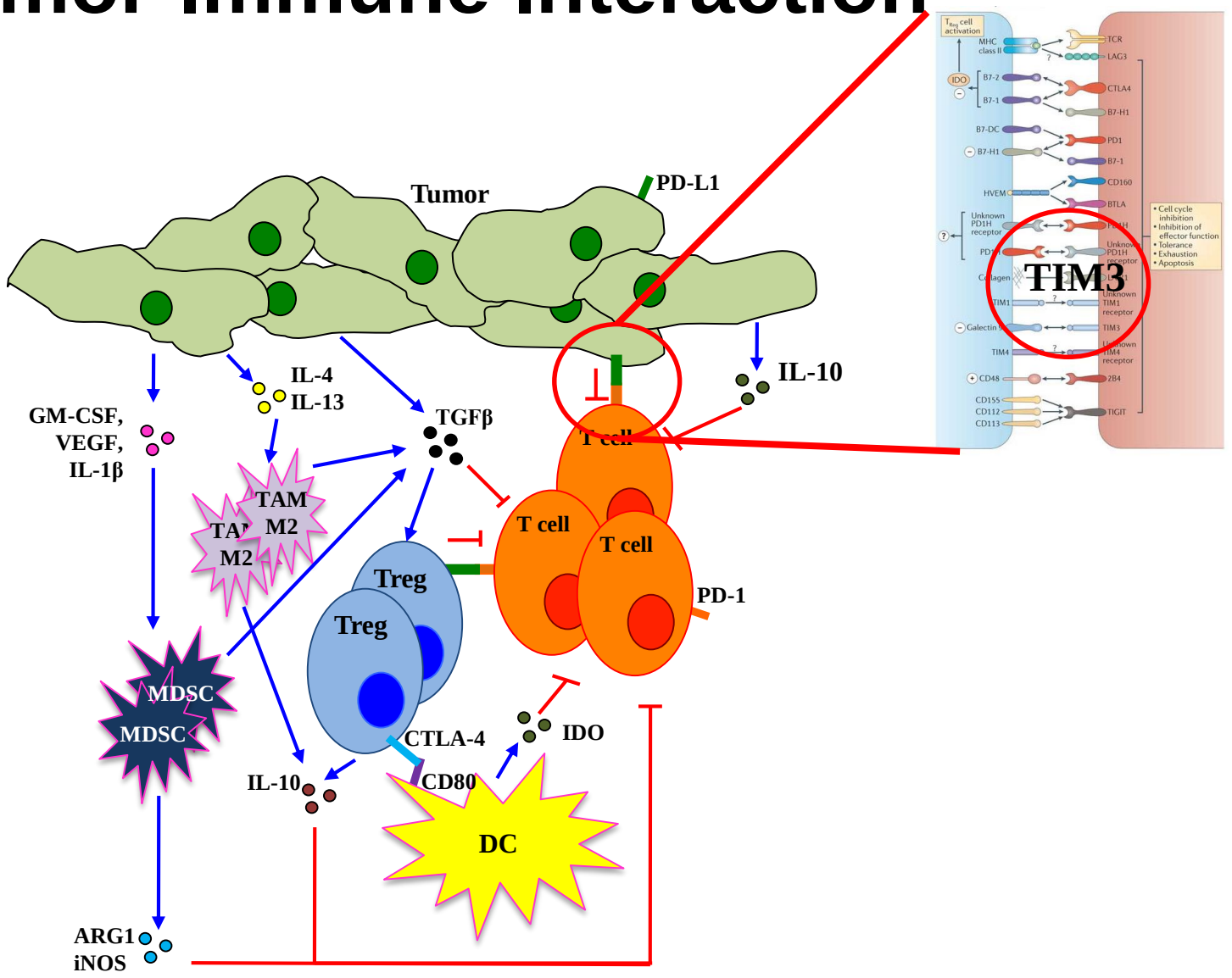

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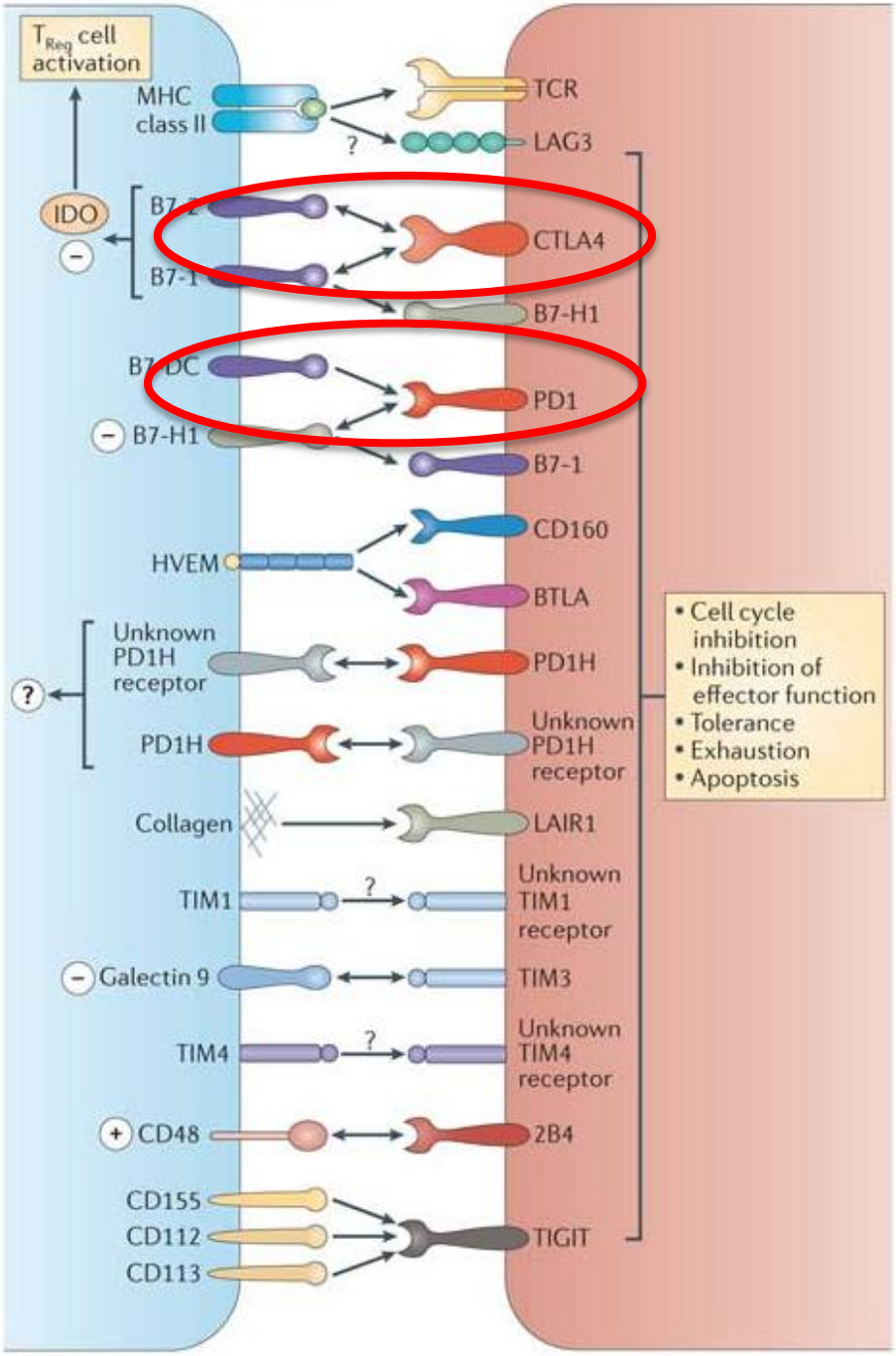
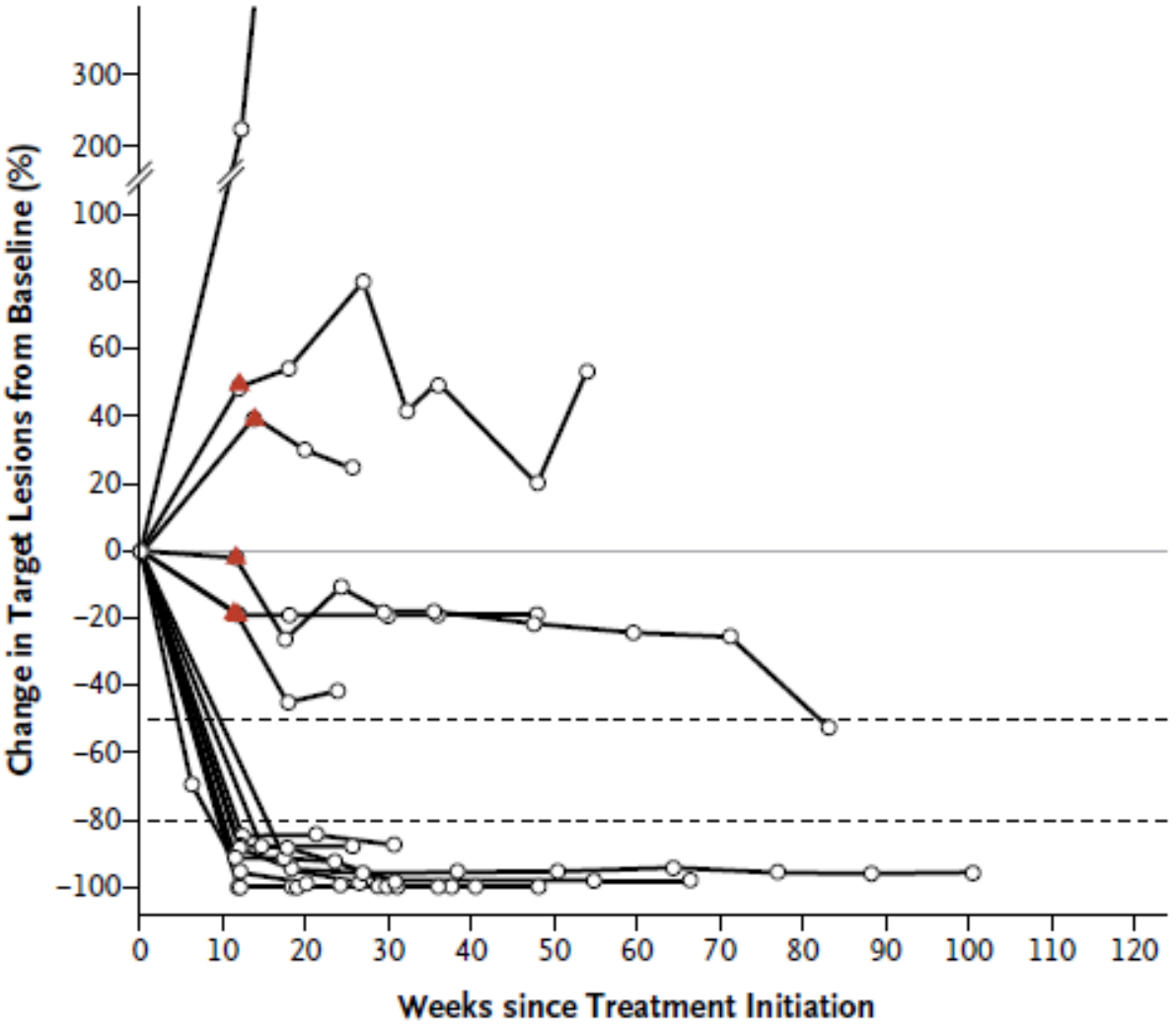
# High Impact Clinical Trials

Combination

# Co-inhibitory Molecules

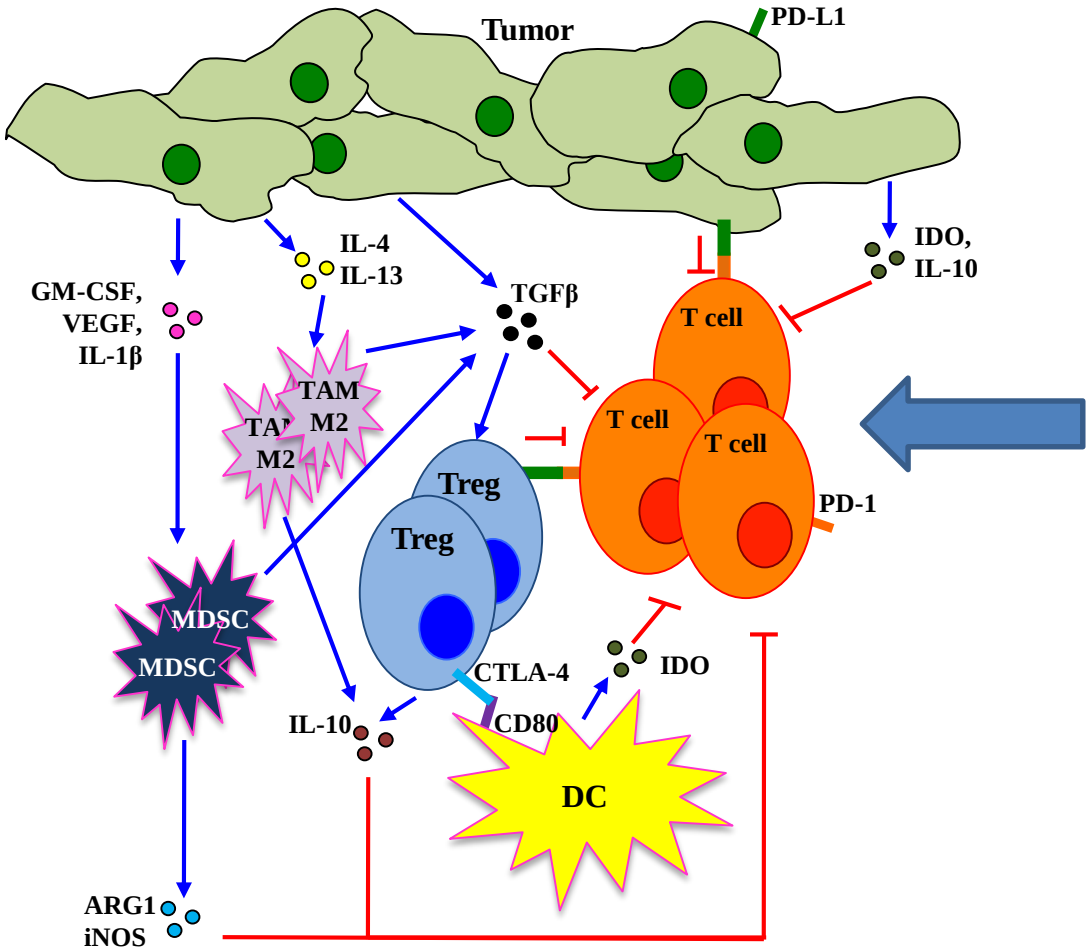


# Nivolumab plus ipilimumab in advanced melanoma

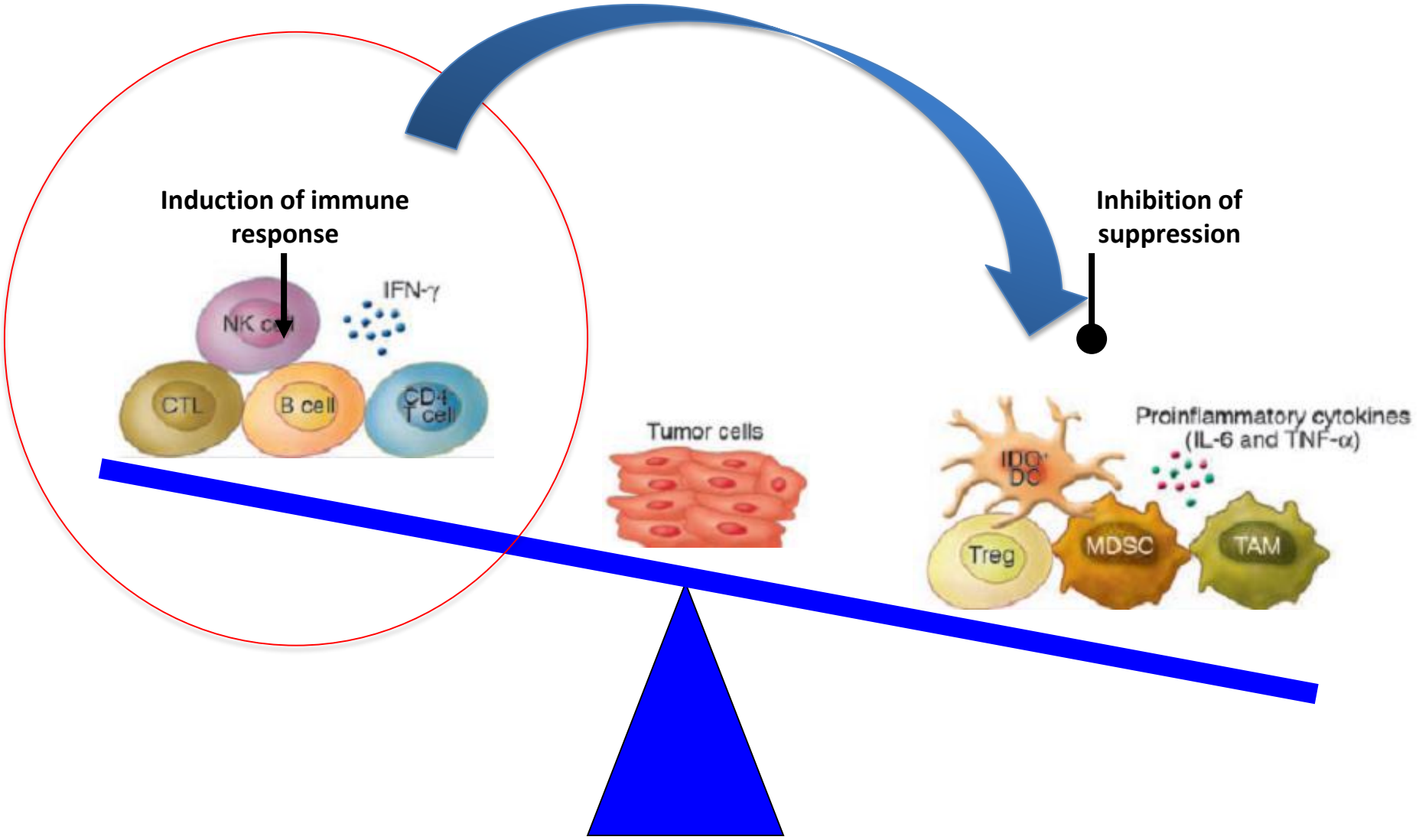



Wolchok JD et al. *The New England journal of medicine* 369(2), 122-133 (2013).

# Combinational Immunotherapy



# Effective Therapeutic immunebalance



# Combinational Immunotherapy

- Vaccines

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- Vaccines
- Immune Modulators
  - Immune Agonists
    - Stimulatory cytokines (IL-2, IL-12, IL-15, TLR etc..)
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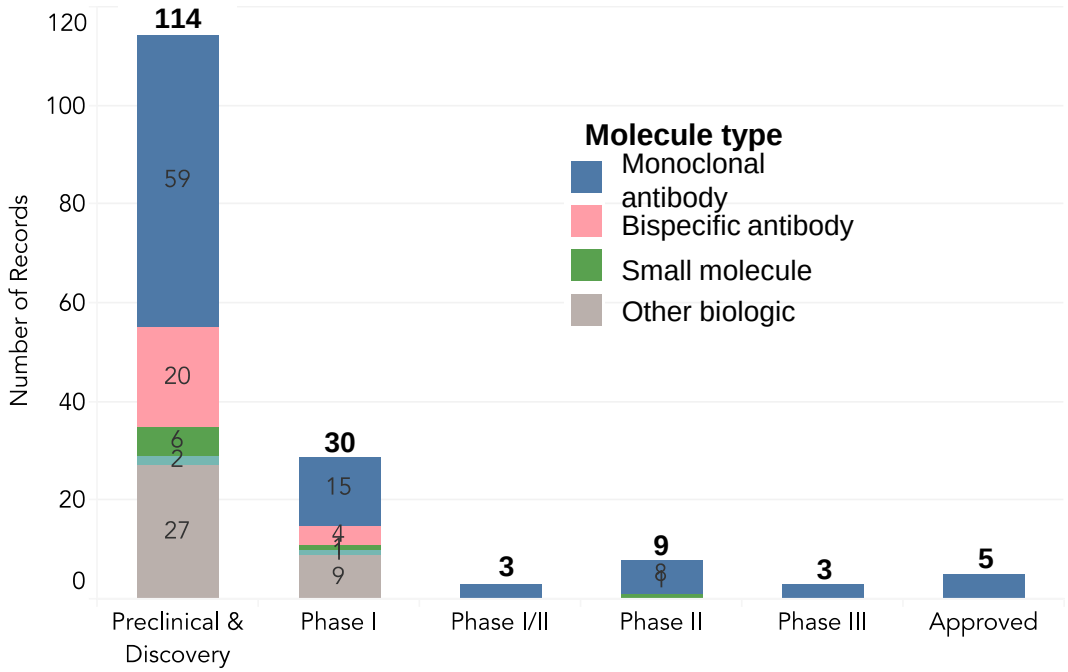
  - Chemotherapy
  - Radiation Therapy
- Small Molecules
- CARS

# 164 PD-1/L1-TARGETED AGENTS, 50 IN CLINICAL DEVELOPMENT




- **164 Agents (clinical+ preclin)**

Tang, Shalabi, Lucey (submitted)



Email: *ClinicalAcceleratorIO@cancerresearch.org*

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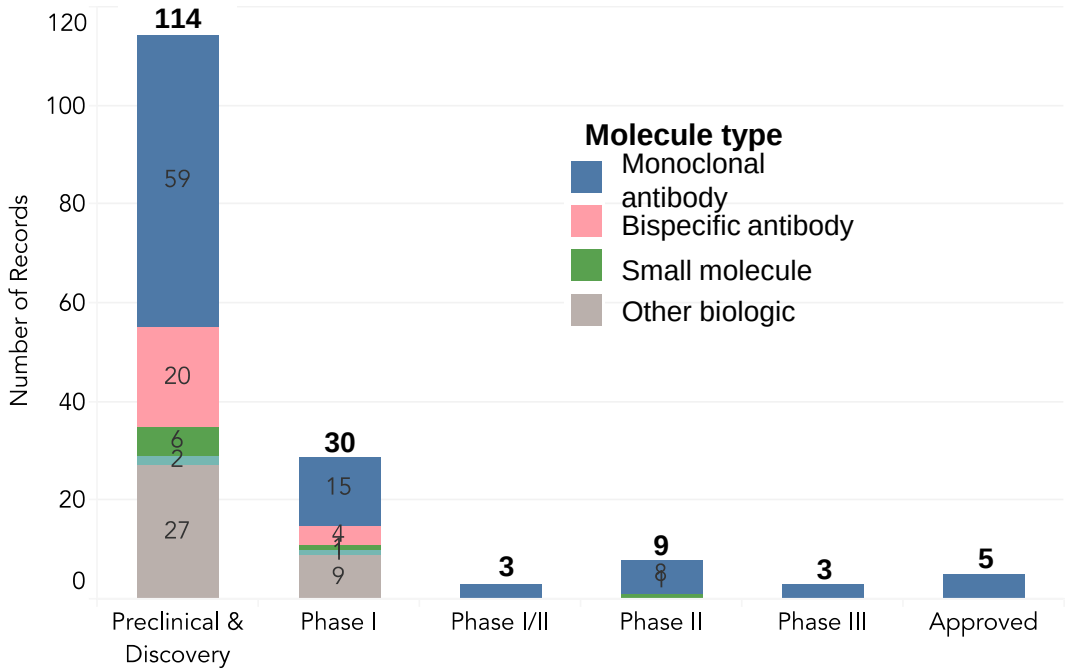


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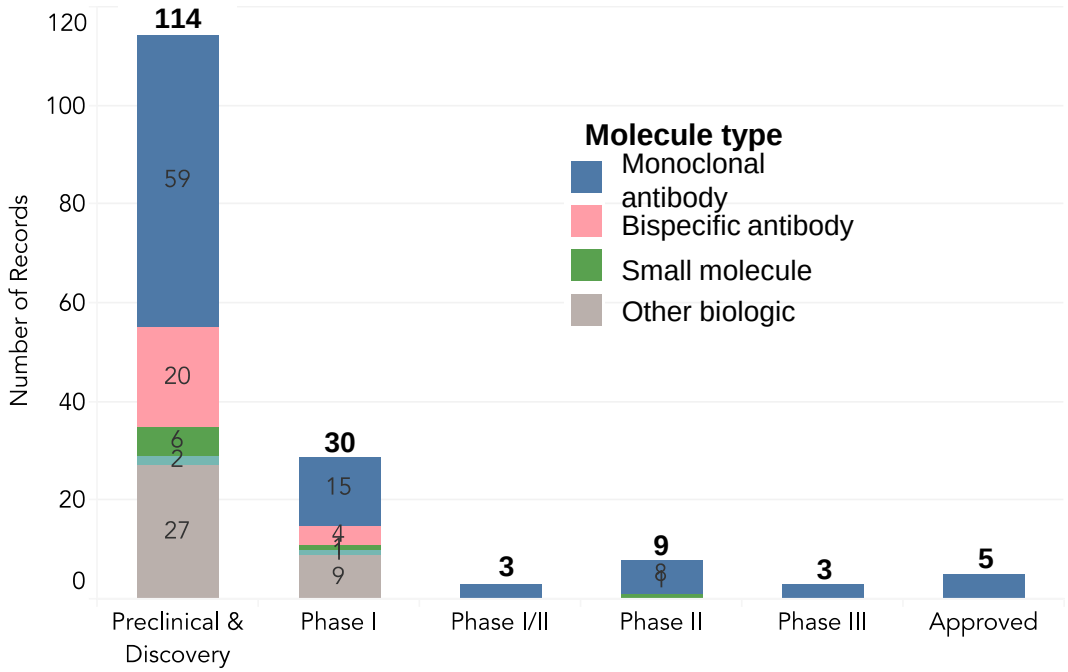


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- **34 MoAb Clinical Development**

Tang, Shalabi, Lucey (submitted)

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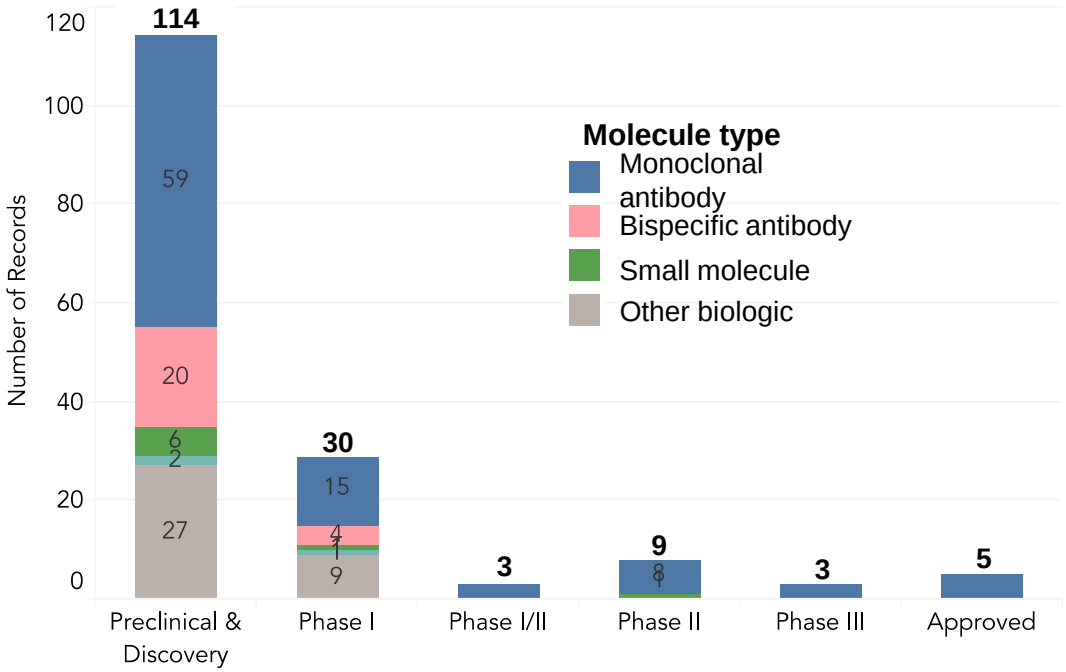



- **Clinical Trials: 1,502**
- **Combos CT: 1,105**

Tang, Shalabi, Lucey (submitted)

# Combinational Immunotherapy

940 different IO agents in clinical stage

Source: Aman Shalabi CIR

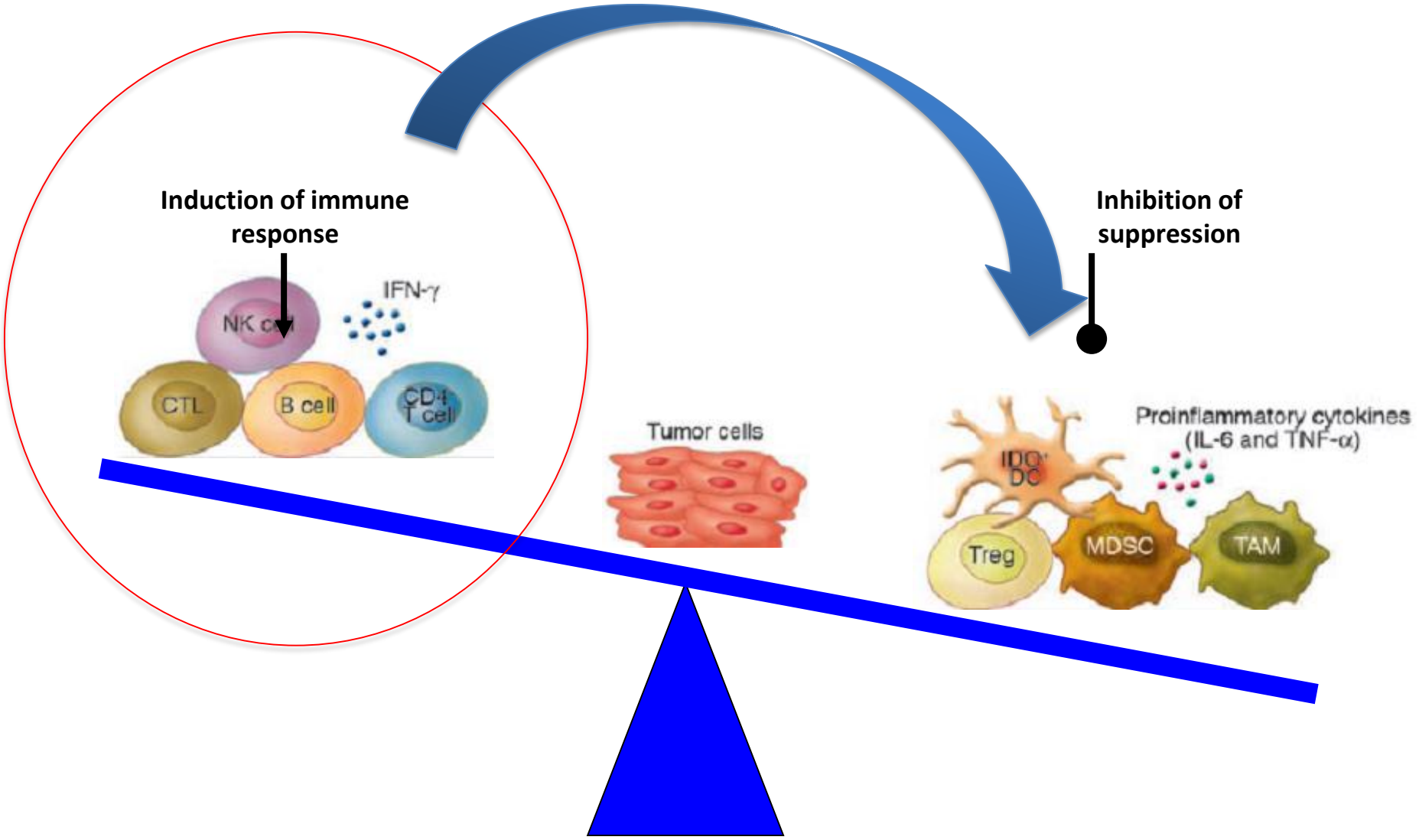
# High Impact Clinical Trials

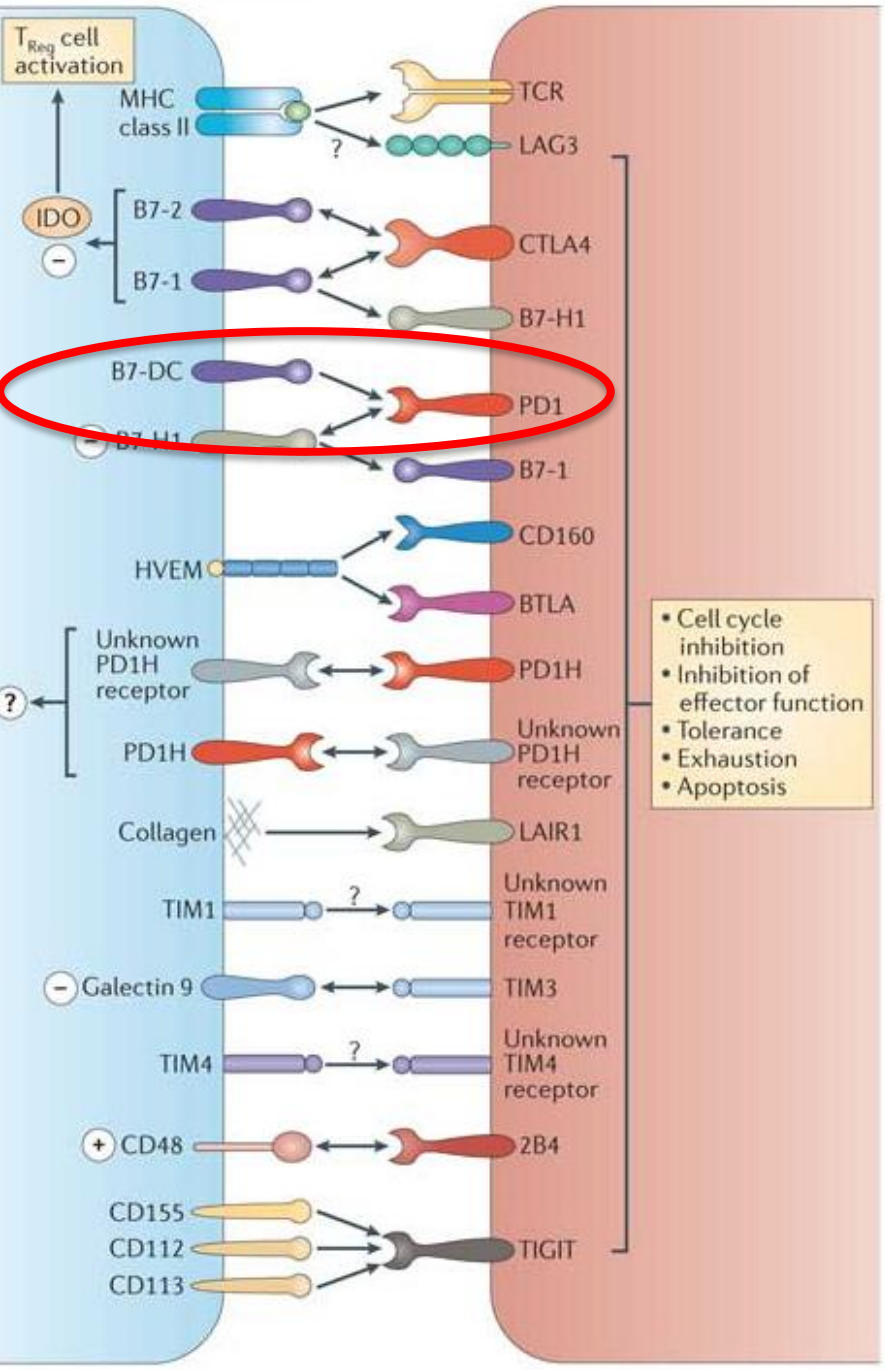
?? Combination

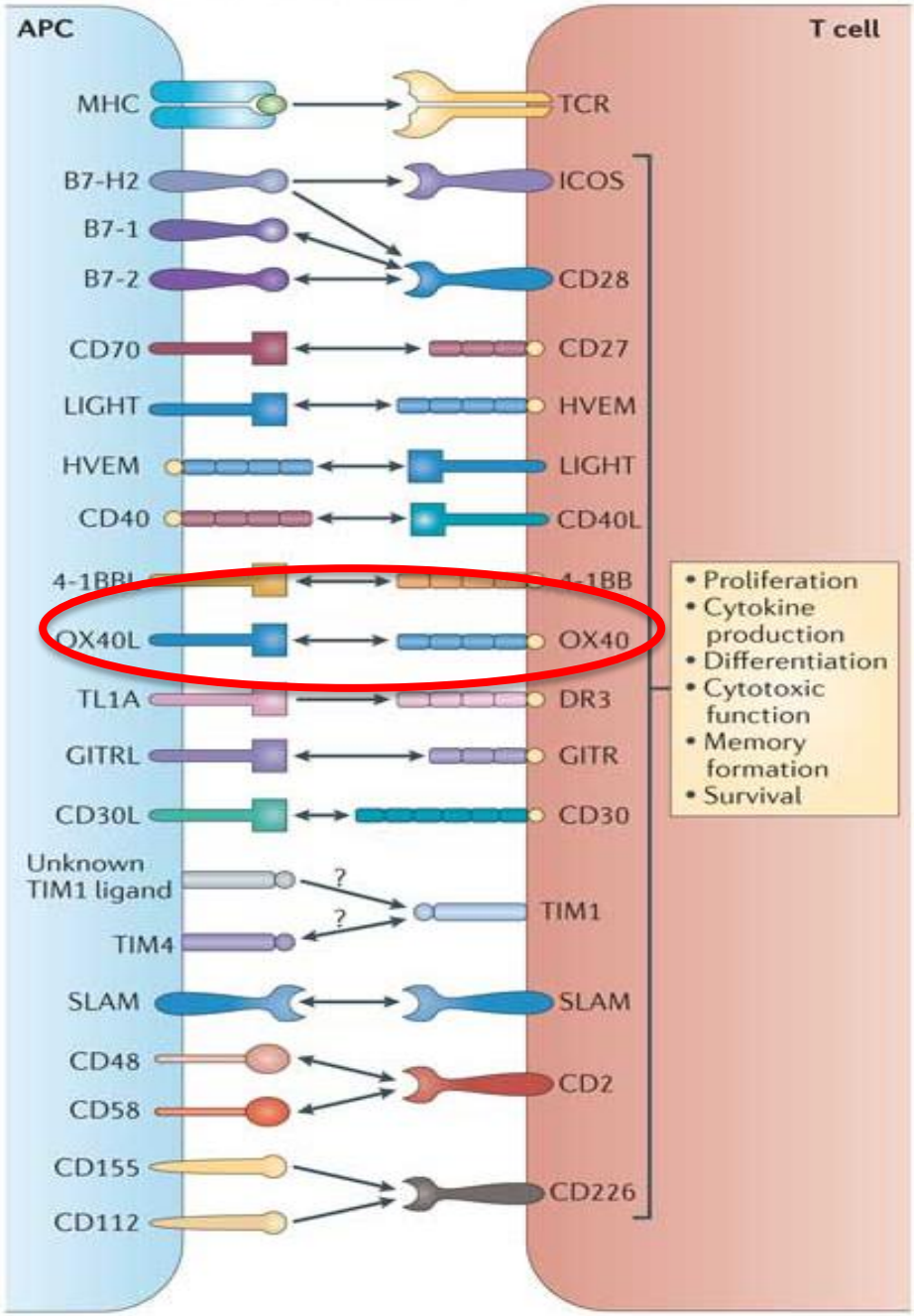
# High Impact Clinical Trials

Rational combination is
not logic but science

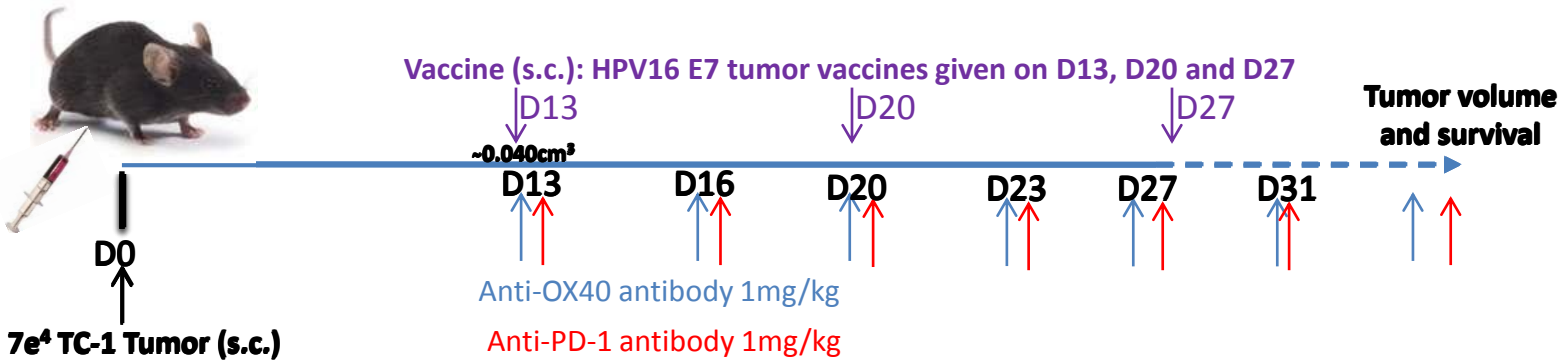
# Effective Therapeutic immunebalance




$T_{Reg}$ cell activation
MHC class II
TCR
?
LAG3
IDO
B7-2
B7-1
CTLA4
B7-H1
B7-DC
PD1
B7-H1
B7-1
CD160
HVEM
BTLA
Unknown PD1H receptor
PD1H
?
PD1H
Unknown PD1H receptor
Collagen
LAIR1
TIM1
?
Unknown TIM1 receptor
Galectin 9
TIM3
TIM4
?
Unknown TIM4 receptor
CD48
2B4
CD155
CD112
CD113
TIGIT
• Cell cycle inhibition
• Inhibition of effector function
• Tolerance
• Exhaustion
• Apoptosis


APC
T cell
MHC
TCR
B7-H2
ICOS
B7-1
B7-2
CD28
CD70
CD27
LIGHT
HVEM
HVEM
LIGHT
CD40
CD40L
4-1BBL
4-1BB
OX40L
OX40
TL1A
DR3
GITRL
GITR
CD30L
CD30
Unknown TIM1 ligand
?
?
TIM1
TIM4
SLAM
SLAM
CD48
CD2
CD58
CD155
CD226
CD112
• Proliferation
• Cytokine production
• Differentiation
• Cytotoxic function
• Memory formation
• Survival

# Adding α-PD1 to α-OX40 and E7 vaccine negates the effect of α-OX40 and Vaccine combination



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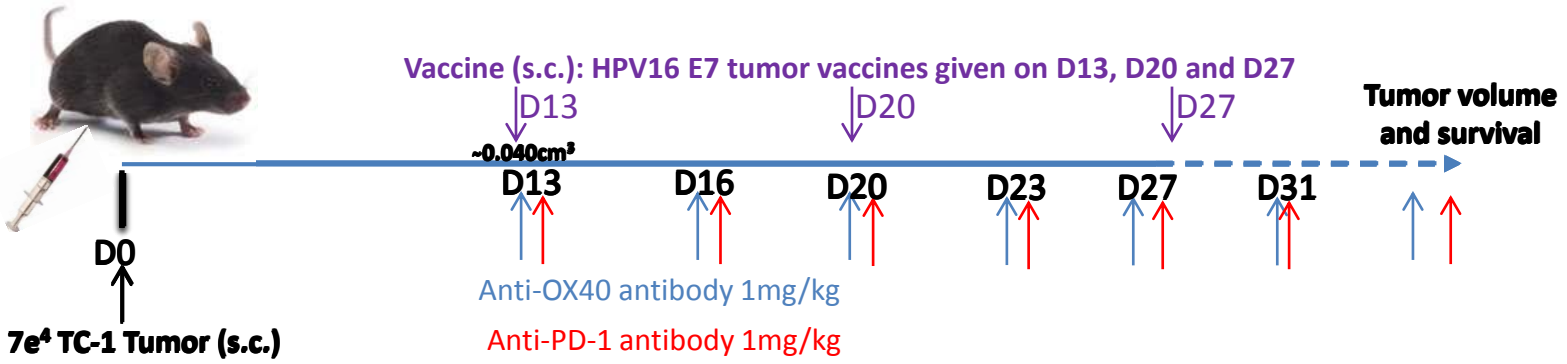


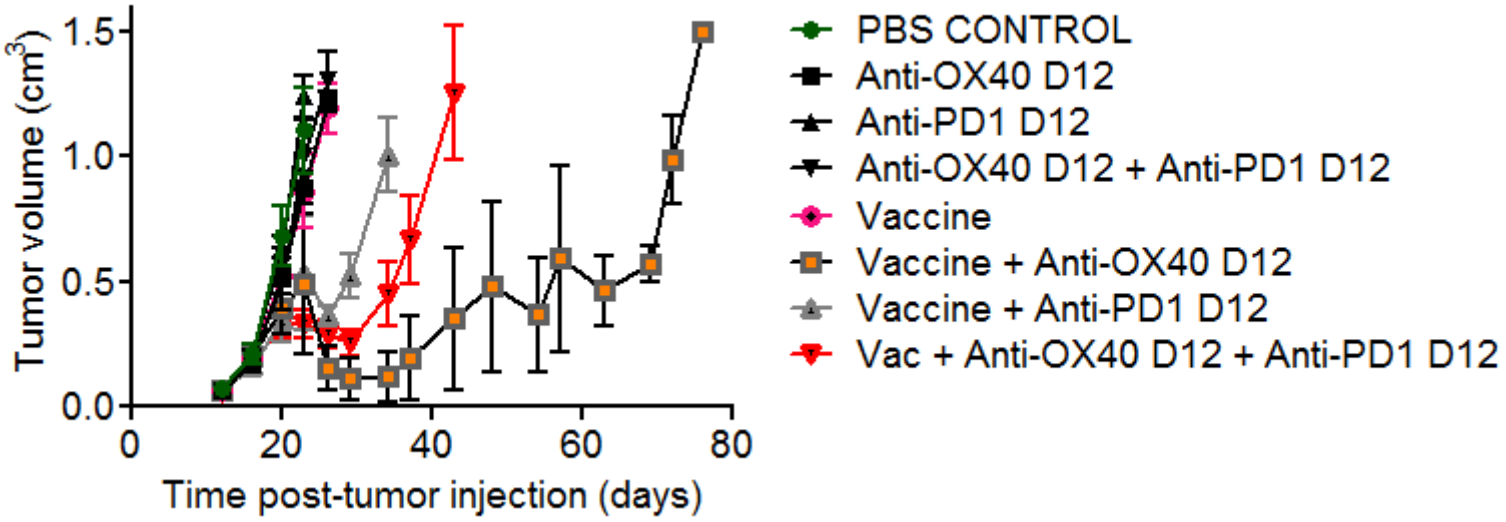


Shrimali, et al. 2017

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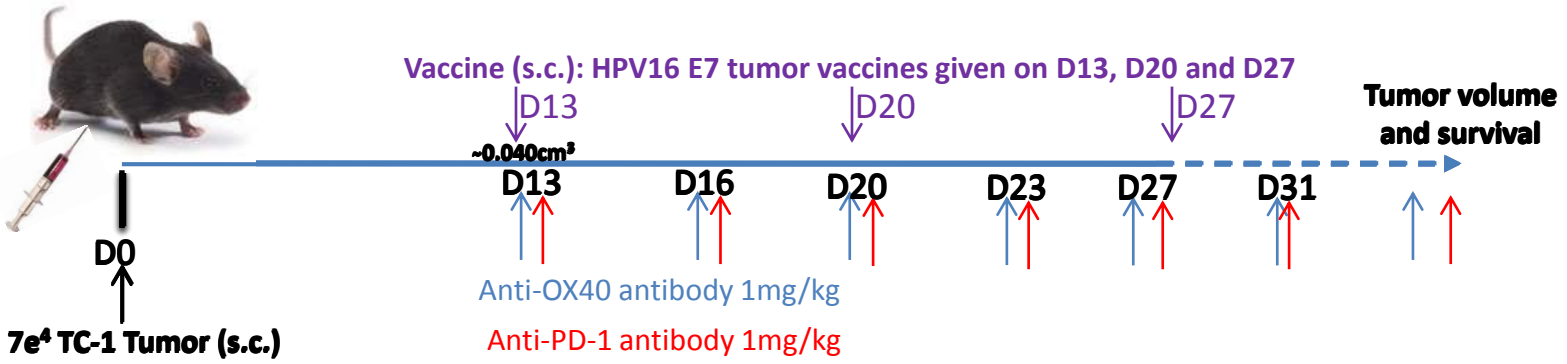
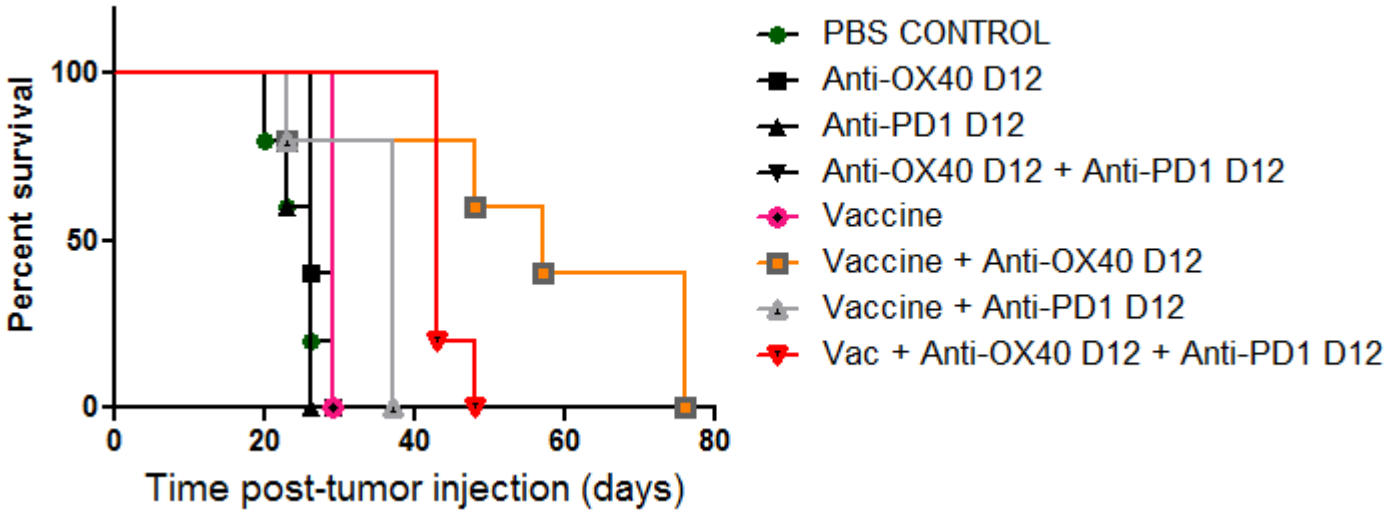
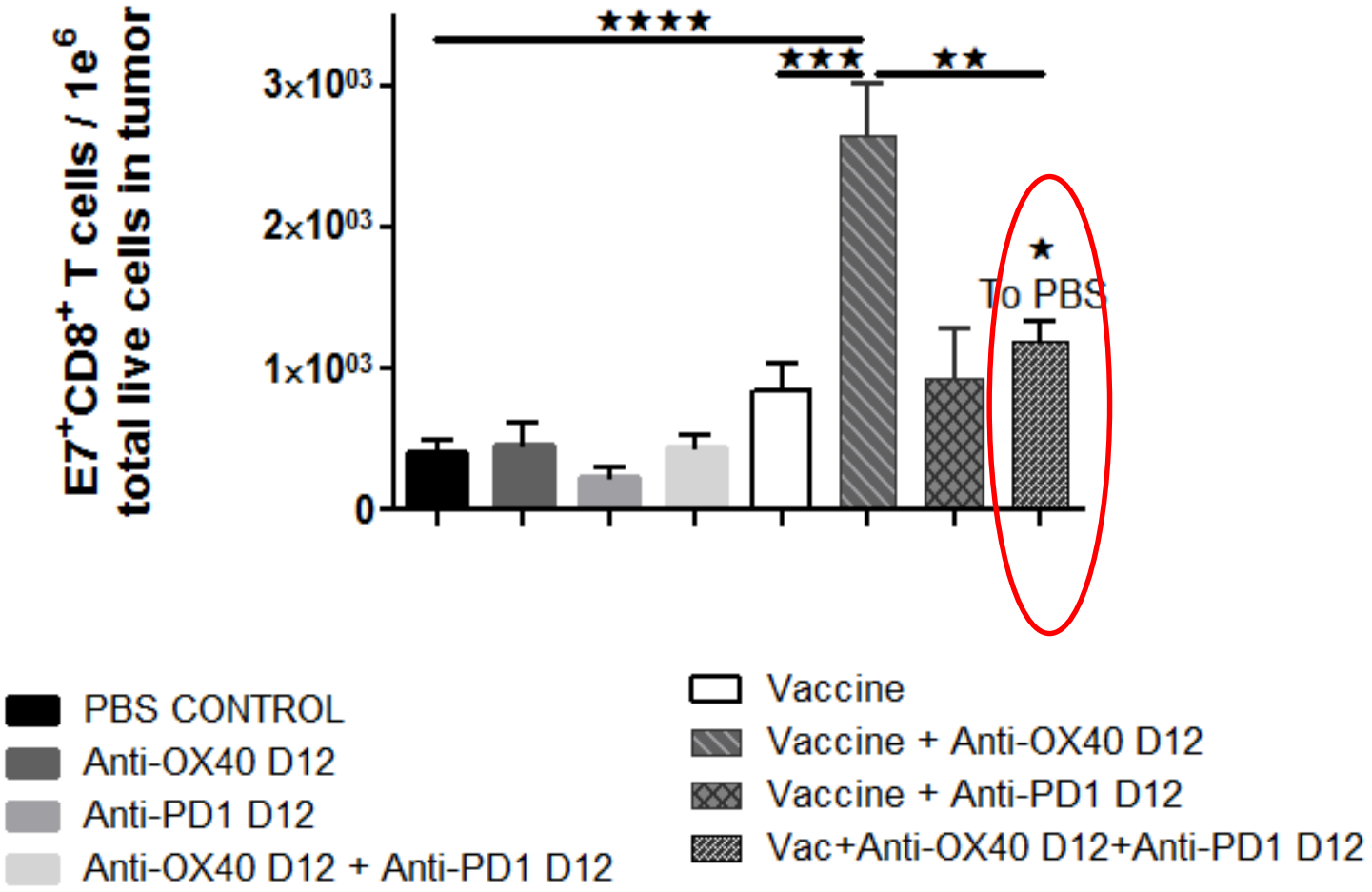



Shrimali, et al. 2017

# Tumor infiltration of CD8$^+$ T cells and antigen specific CD8$^+$ T cells

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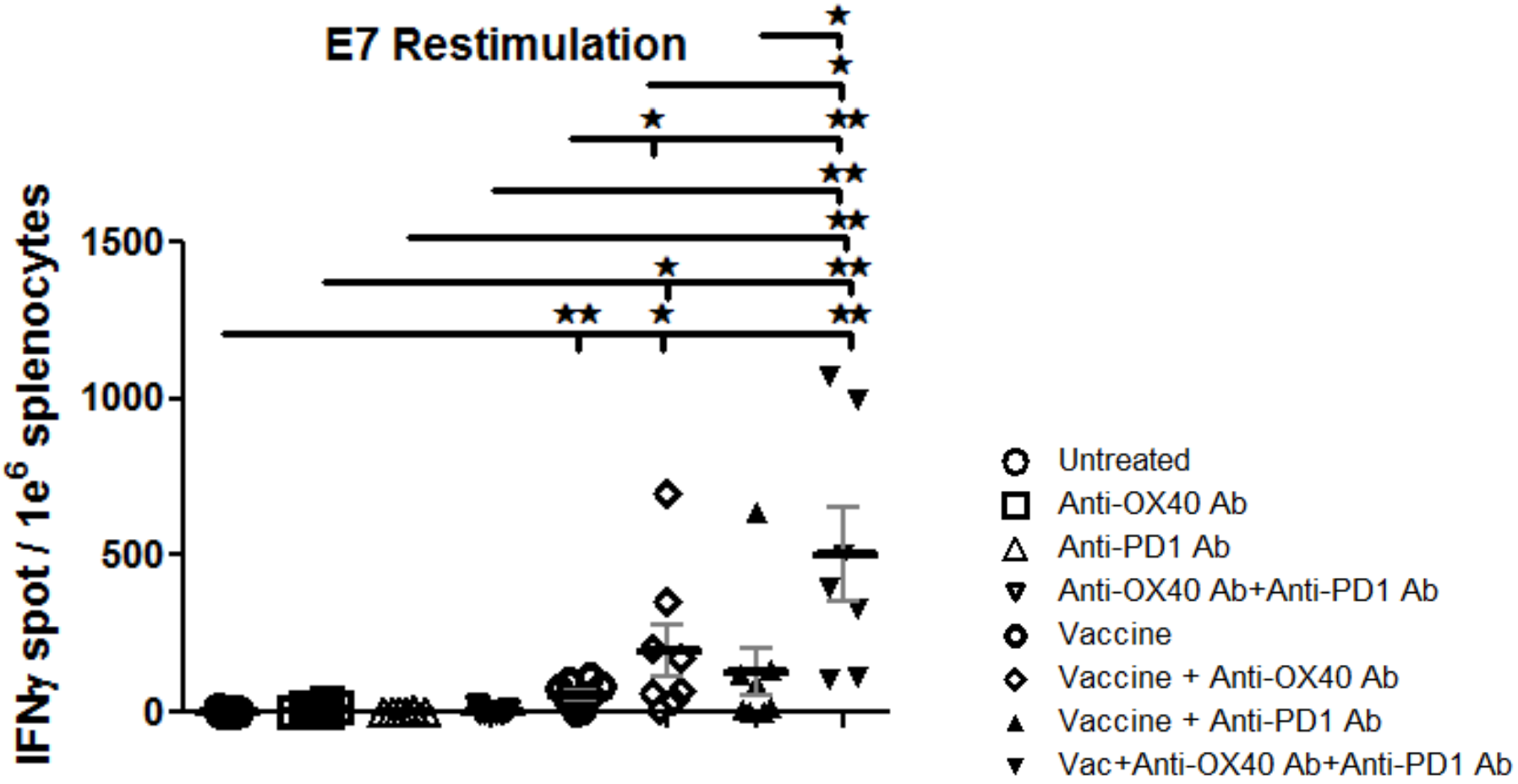


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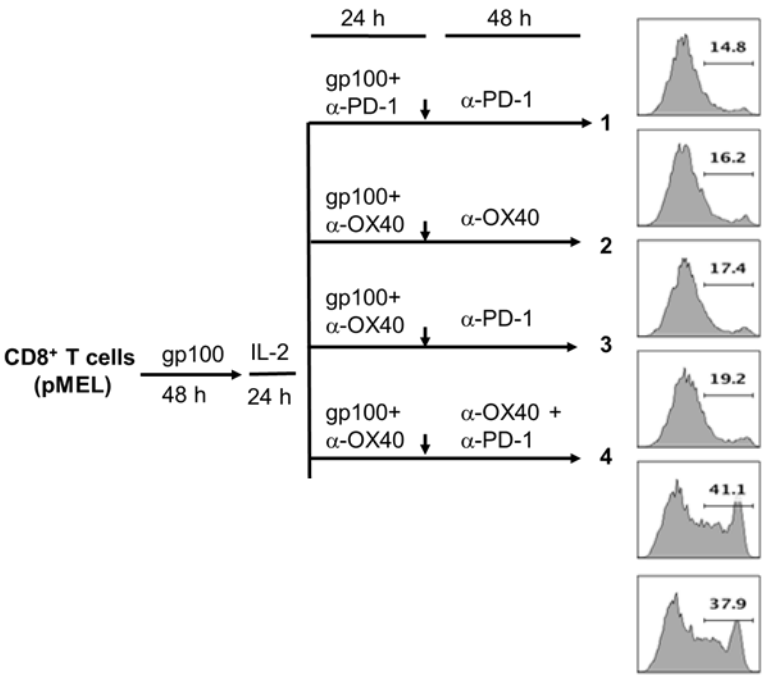
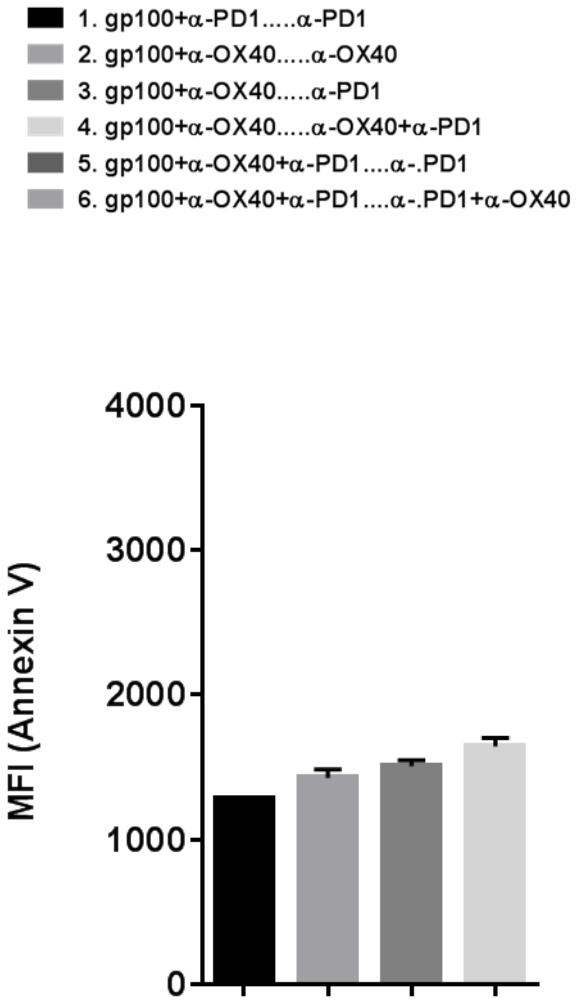
# Adding α-PD1 to α-OX40 in antigen primed cells induces apoptosis in vitro

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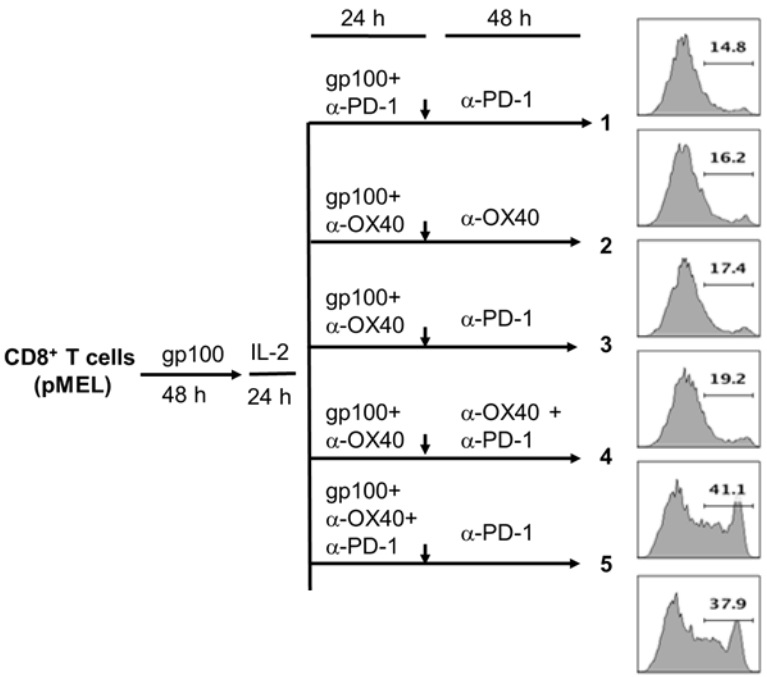


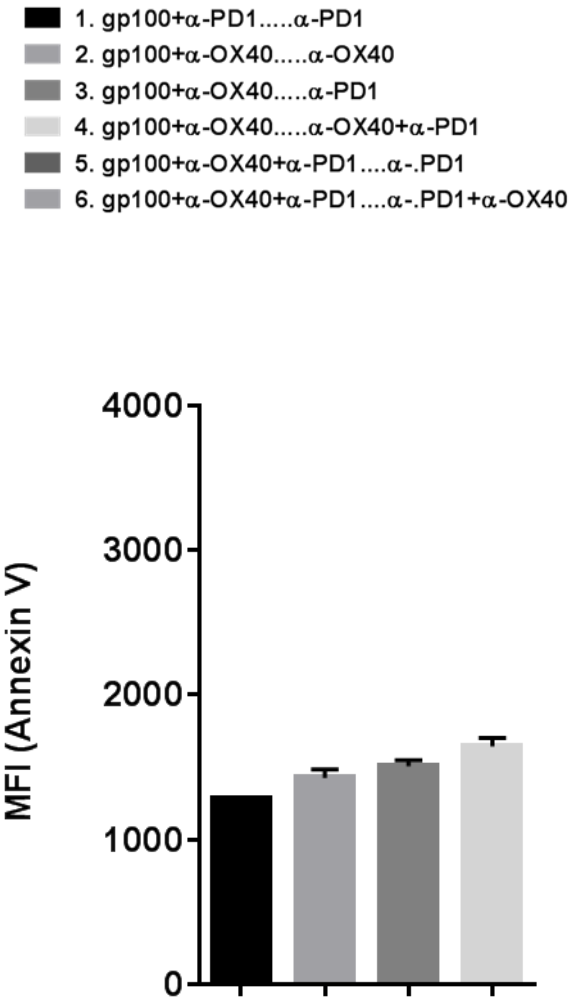


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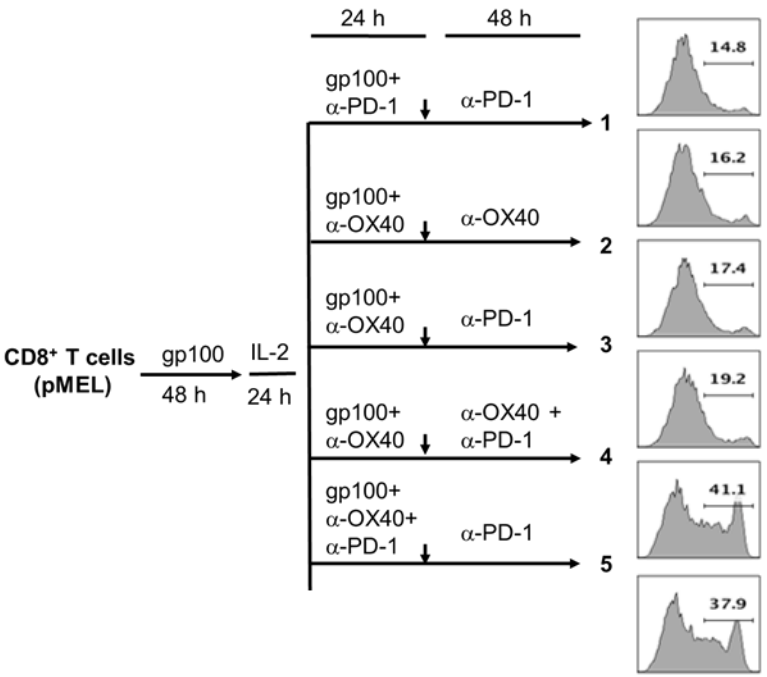


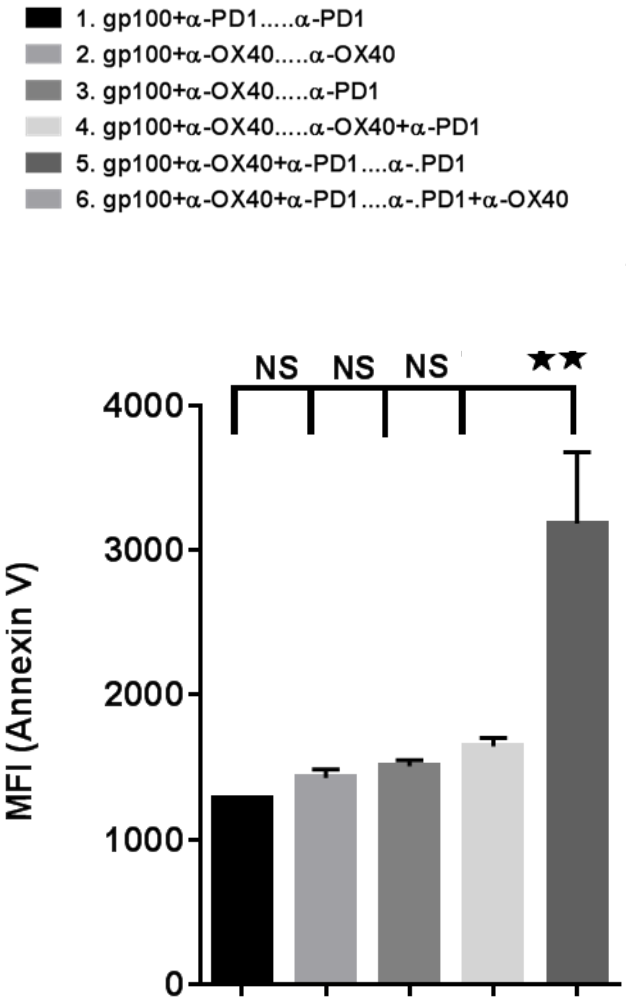


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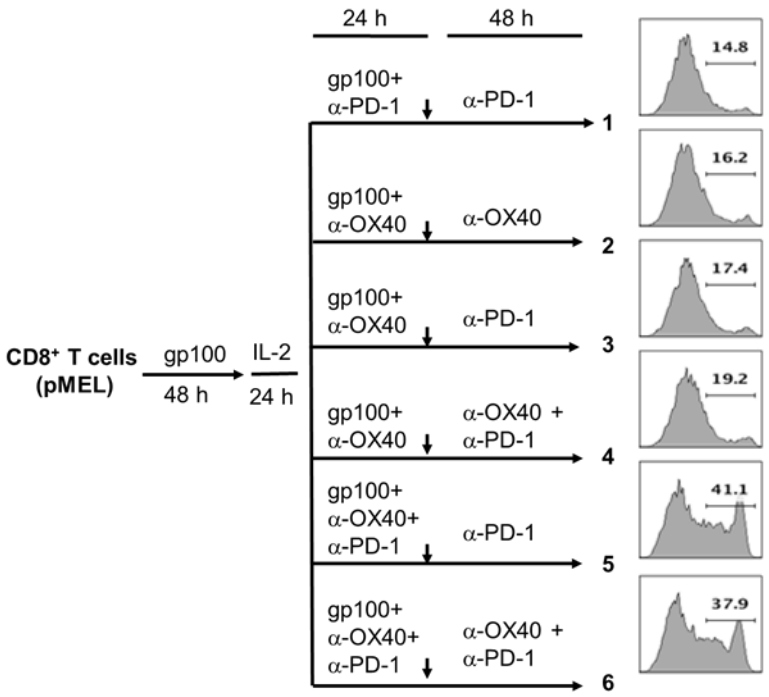


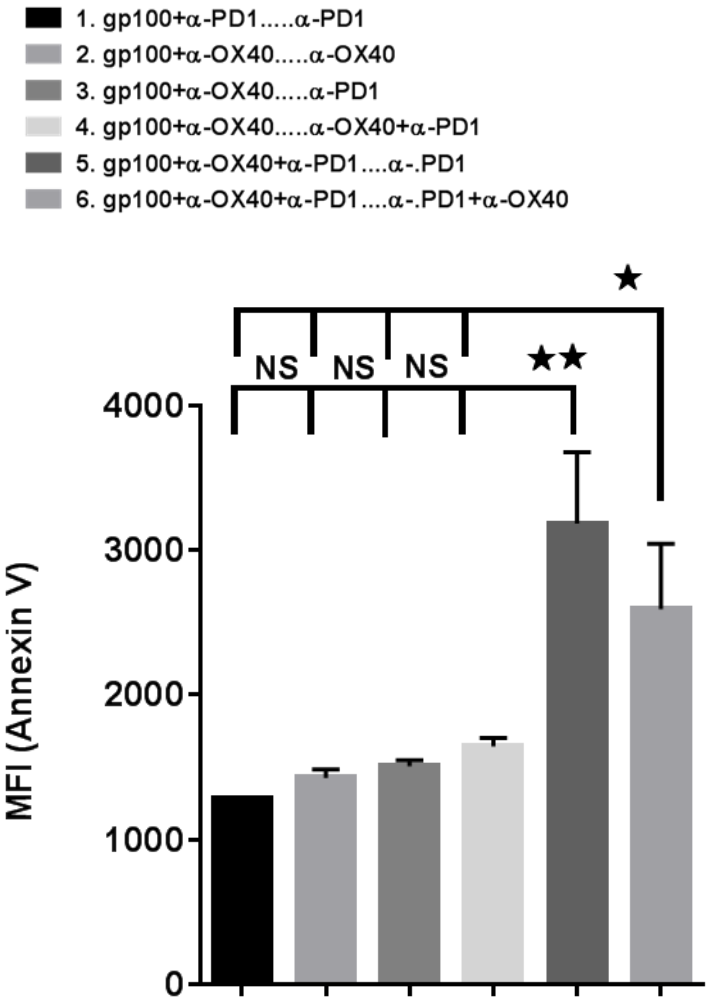


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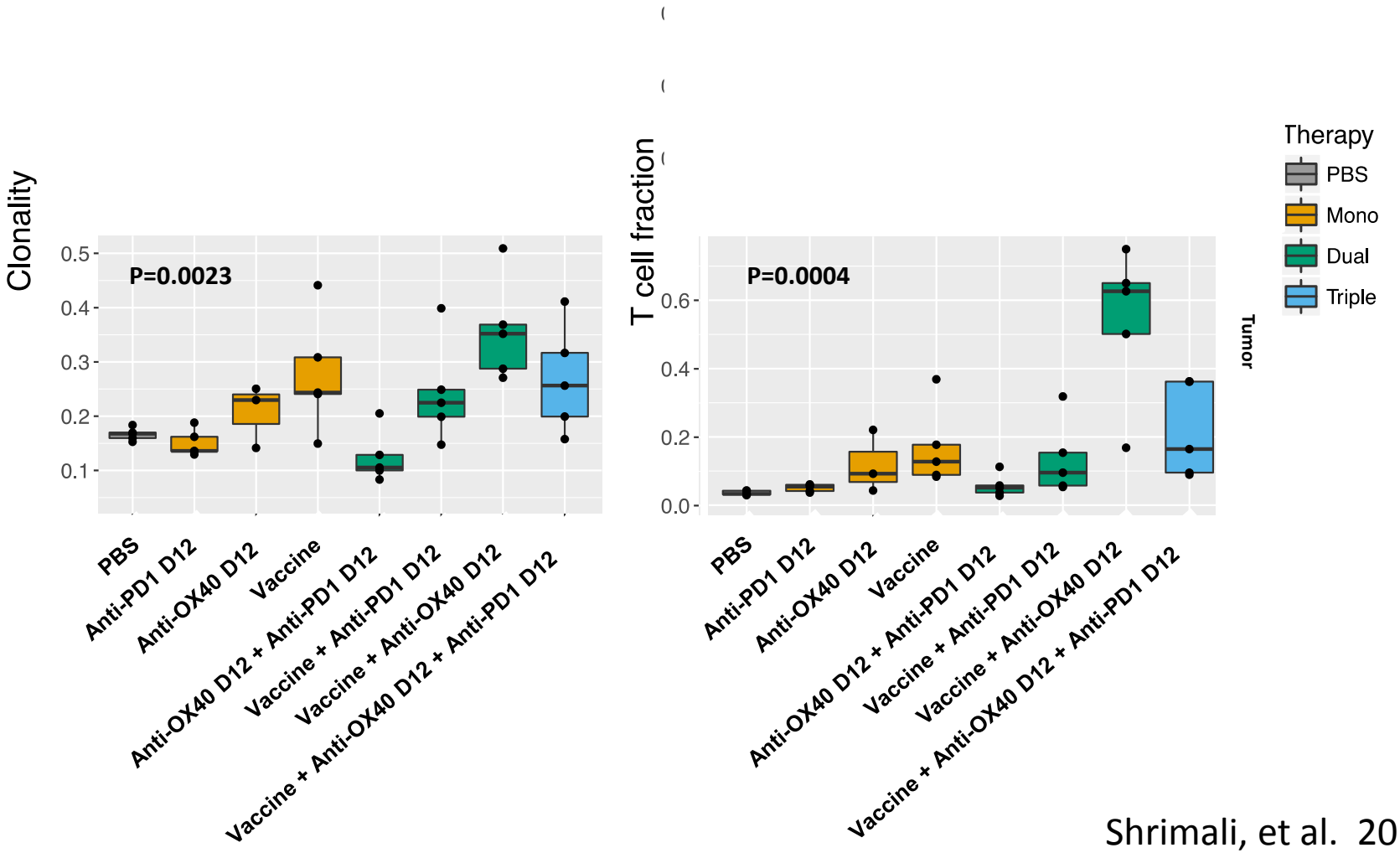
# Adding α-PD1 to α-OX40 and E7 vaccine reduces clonality and T cell fraction

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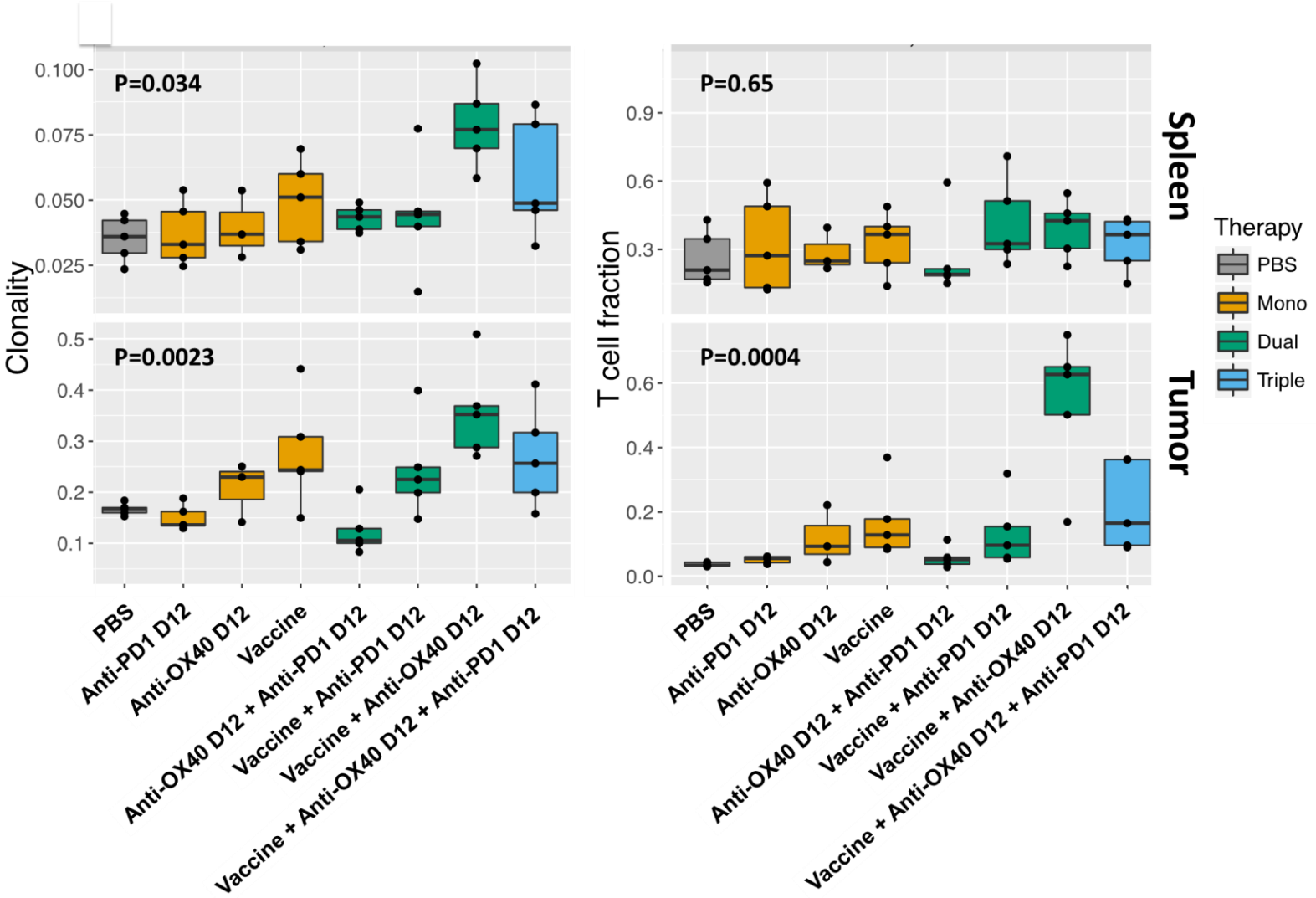


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# Timing of PD-1 Blockade Is Critical to Effective Combination Immunotherapy with Anti-OX40

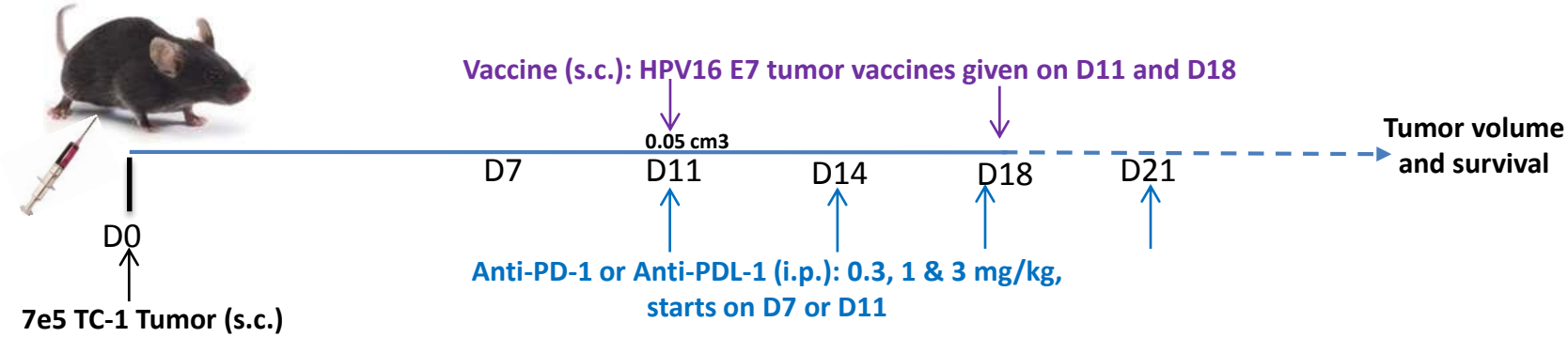
David J. Messenheimer[1,2], Shawn M. Jensen[1], Michael E. Afentoulis[1], Keith W. Wegmann[1], Zipei Feng[1,3], David J. Friedman[1], Michael J. Gough[1], Walter J. Urba[1], and Bernard A. Fox[1,2,3,4]

# Combination of Ani-PD1

## 300 trials - CIR

- Vaccine-- neoantigens
- XRT
- Chemo
- Etc…

# Experimental protocol: Therapeutic study




Verma et at, Submitted

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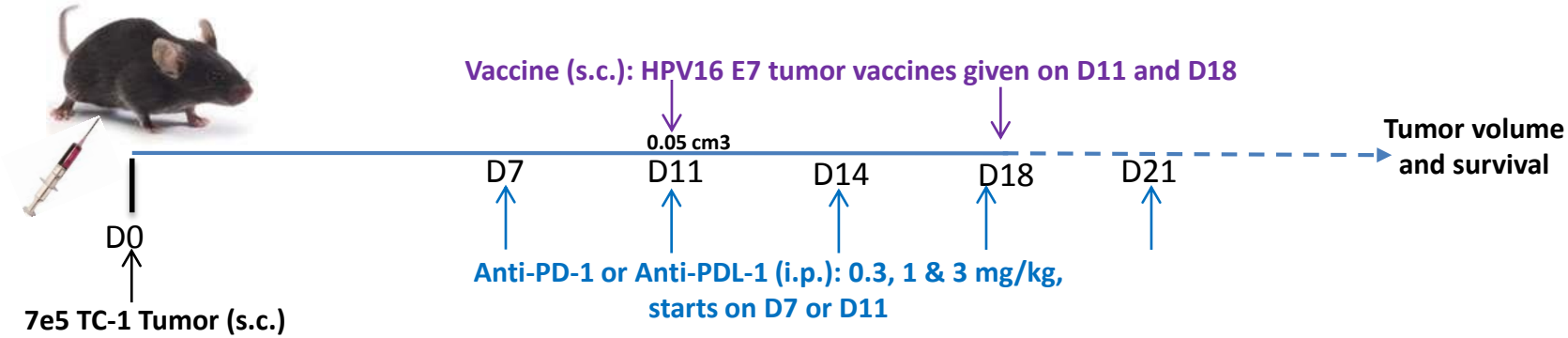
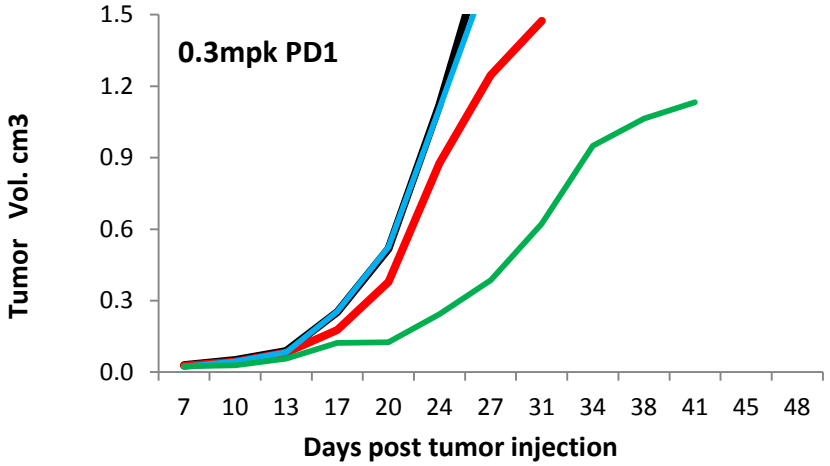
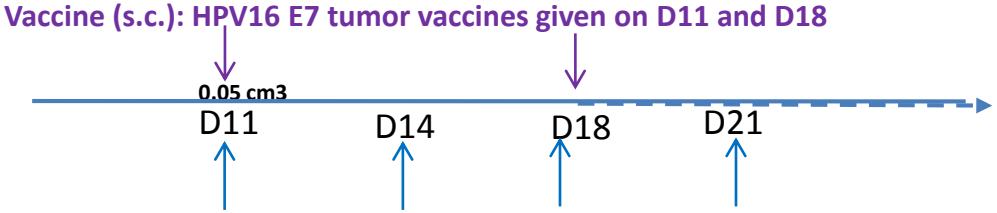


# PD1 combination with priming agent

**Tumor growth**
**Group average**




PBS control
Vaccine control
Antibody alone
Ab D7 Vac D11
Ab D11 Vac D11




Verma et at,

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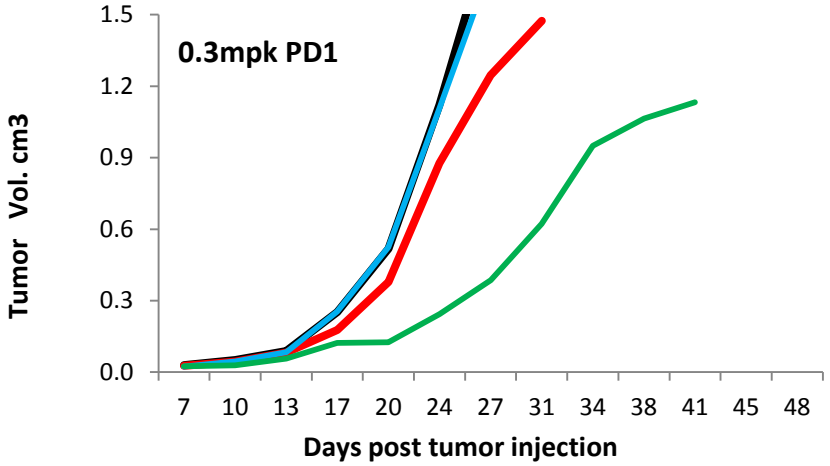
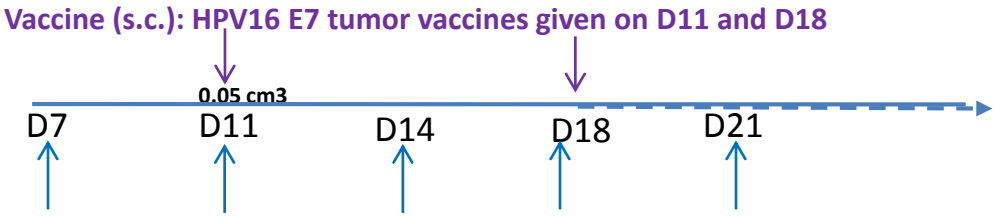
**Tumor growth**
**Group average**



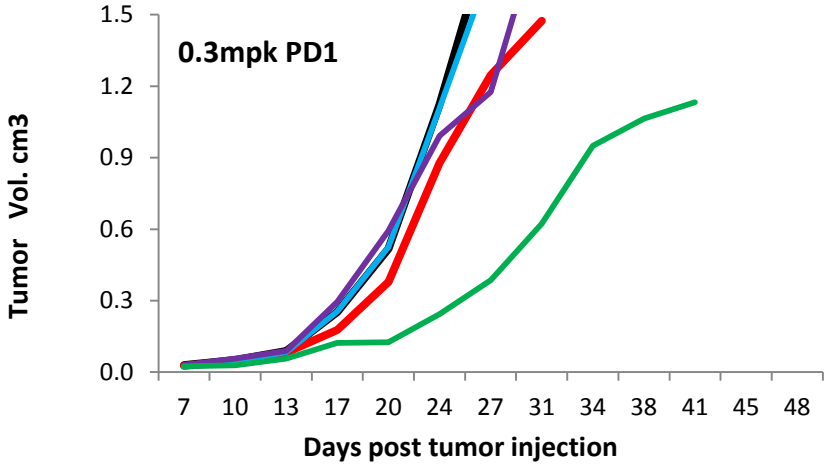

PBS control
Vaccine control
Antibody alone
Ab D7 Vac D11
Ab D11 Vac D11



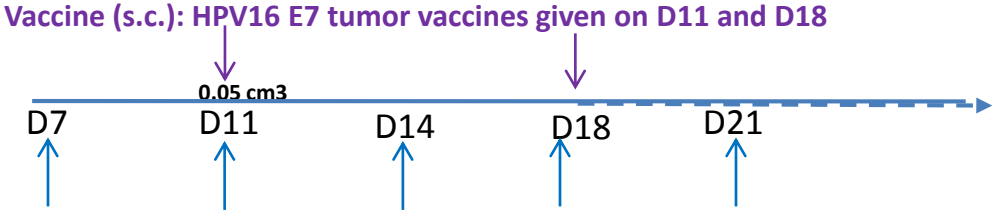

Verma et at,

# PD1 combination with priming agent

**Tumor growth**
**Group average**

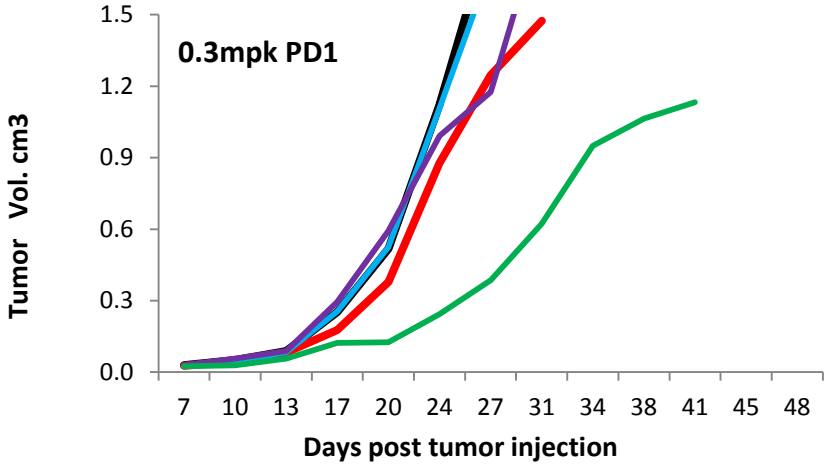



PBS control
Vaccine control
Antibody alone
Ab D7 Vac D11
Ab D11 Vac D11

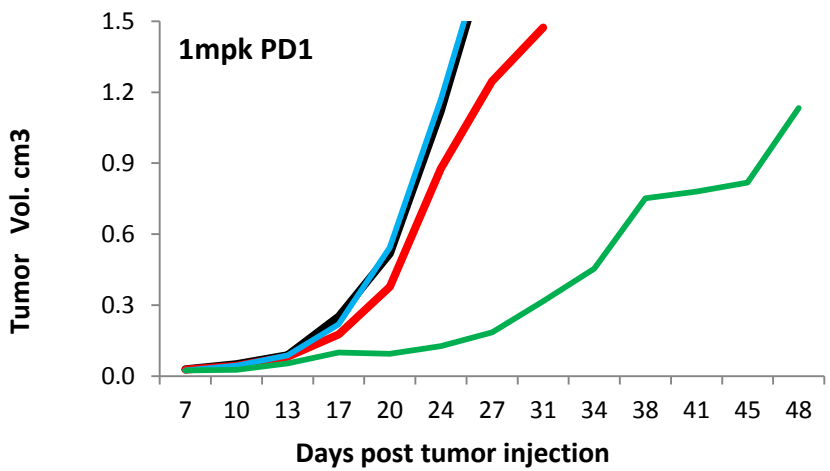


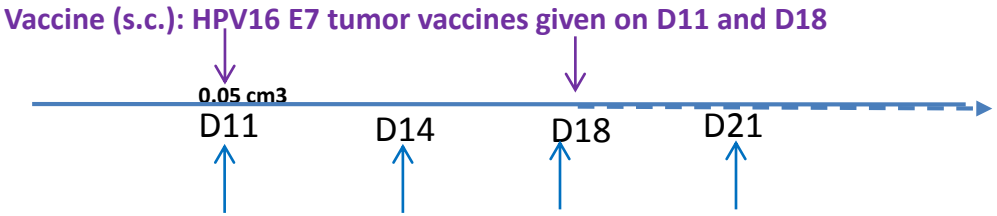

Verma et at,

# PD1 combination with priming agent




**Tumor growth**
**Group average**




- PBS control
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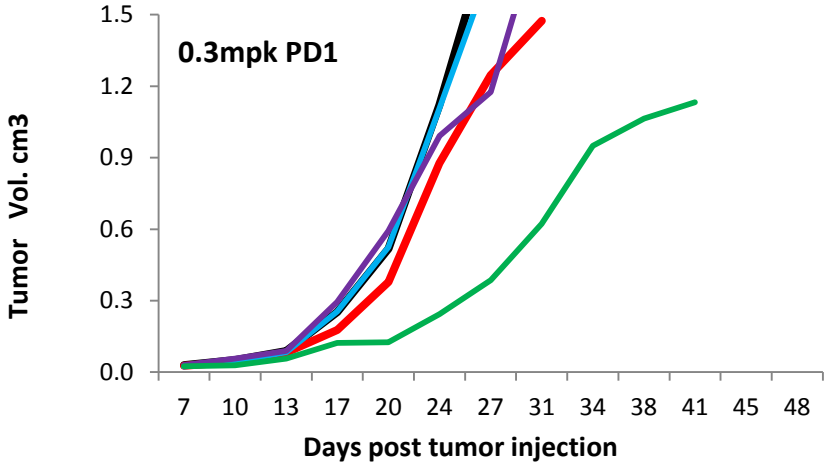
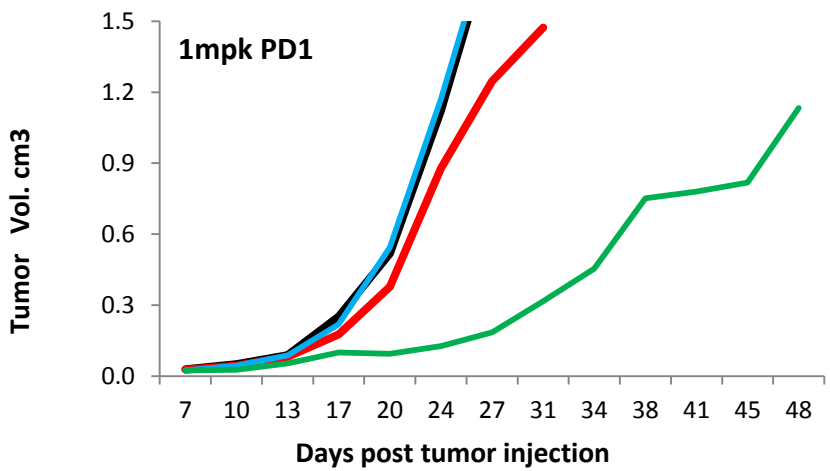
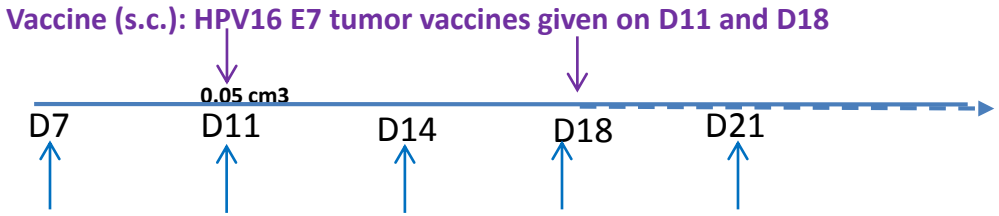
Verma et at,

# PD1 combination with priming agent




**Tumor growth**
**Group average**

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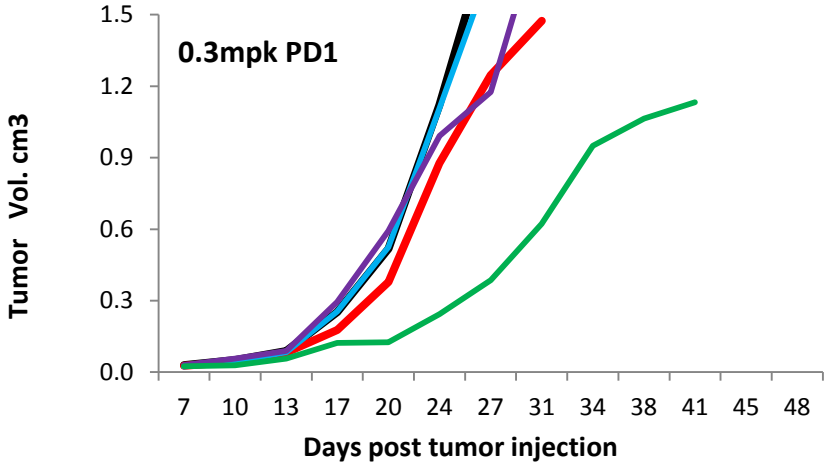
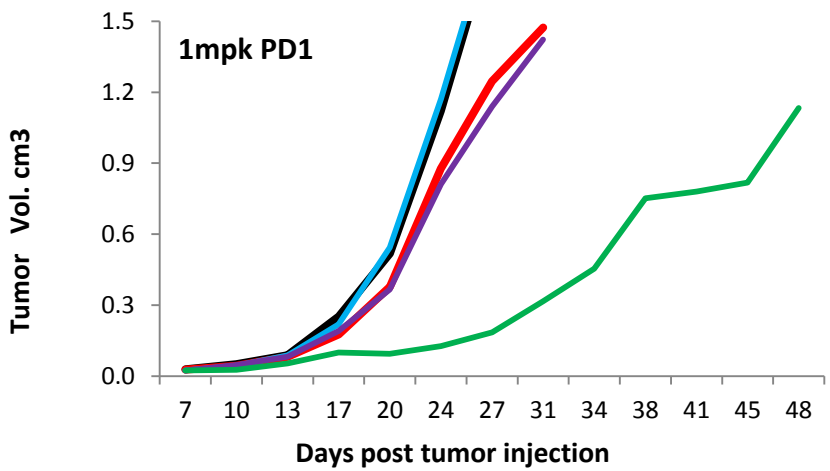
Verma et at,

# PD1 combination with priming agent




**Tumor growth**
**Group average**

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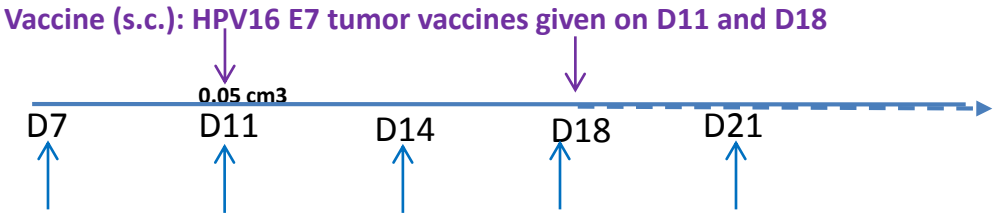
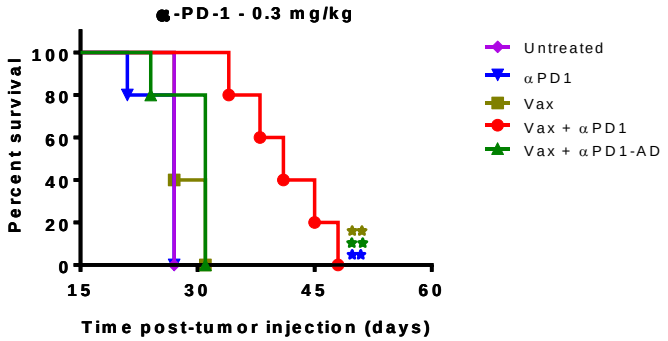
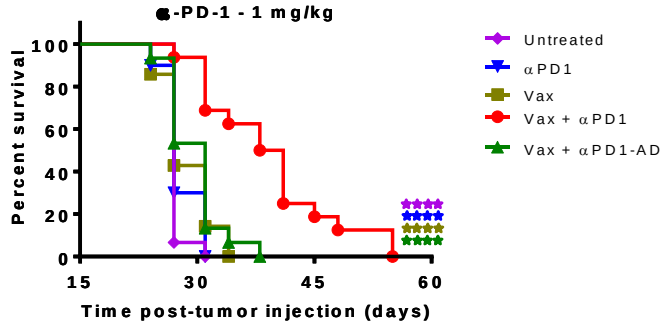
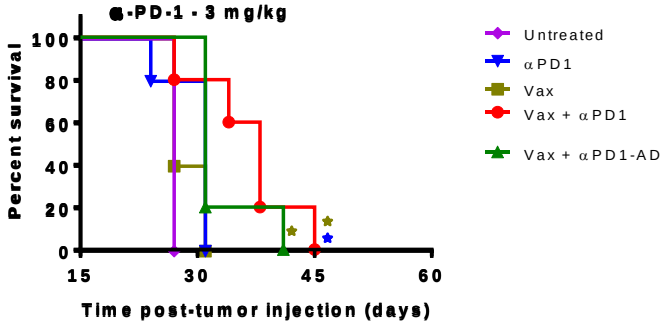



Verma et at,

# PD1 combination with priming agent




Verma et at,

# High Impact Clinical Trials

Not every combination is a potential HIGH IMPACT

# Combinational Immunotherapy

- What to combine ?
- When to combine ?
- How to combine ?

# Combinational Immunotherapy

- What to combine ?
- When to combine ?
- How to combine ?

….Then combine

# Acknowledgments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