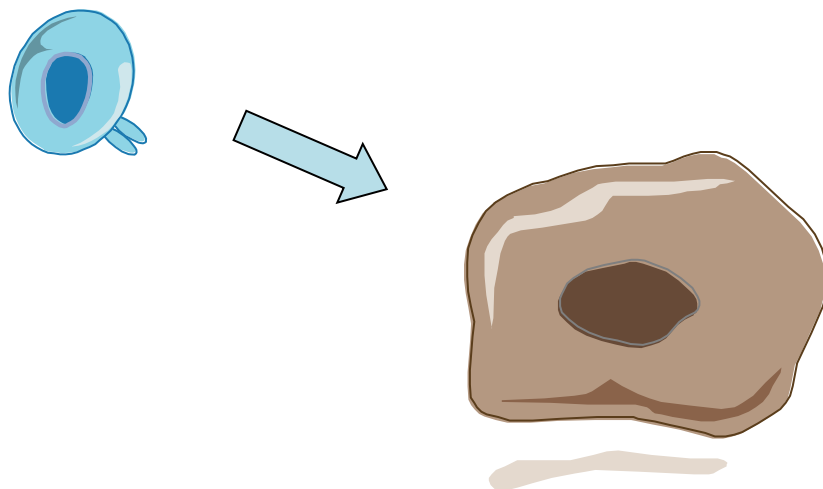


# The science behind combinations with immunotherapy in melanoma

## - Combining Immunotherapies -

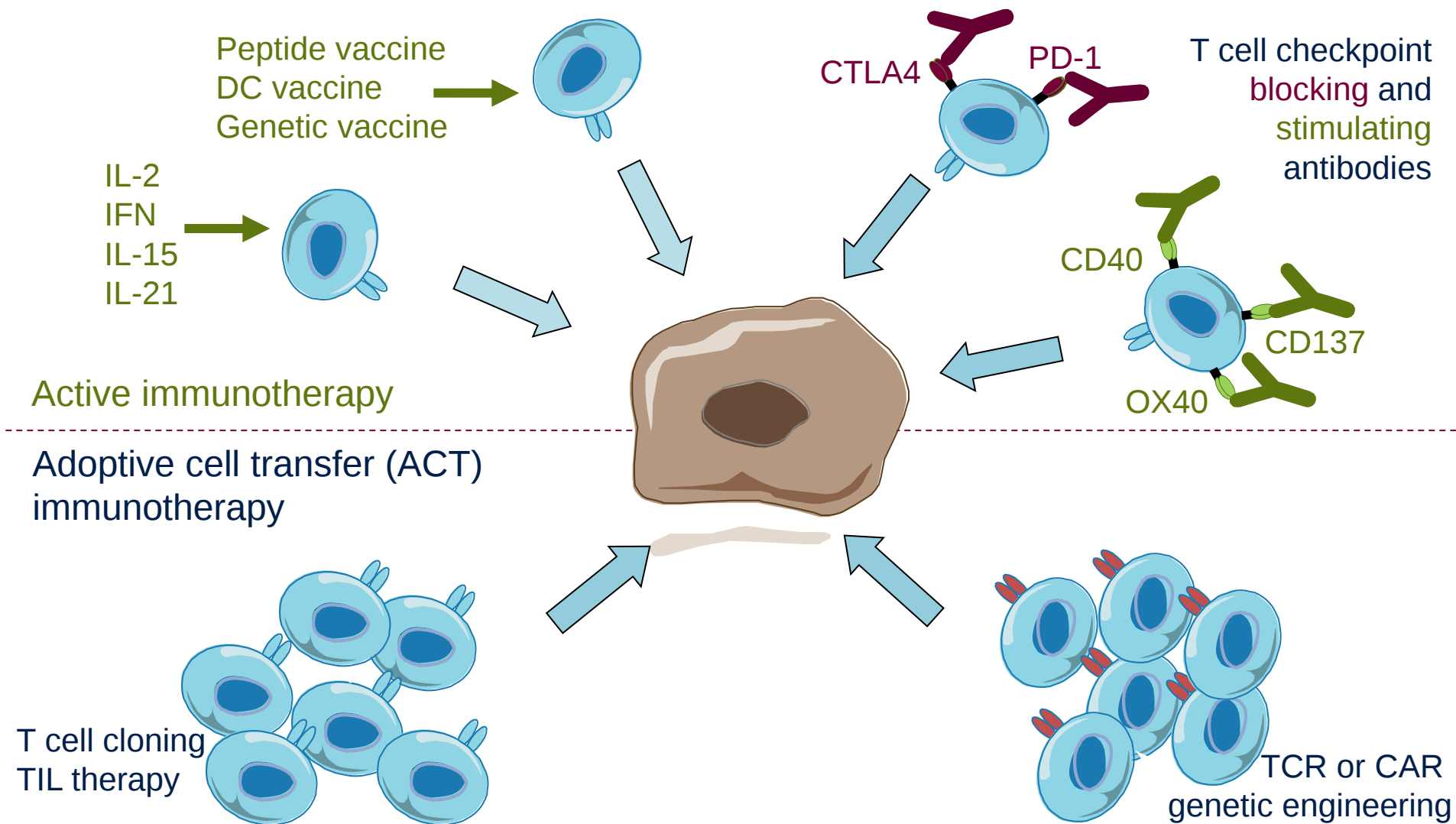
Christian Blank  
The Netherlands Cancer Institute

# Immunotherapy in melanoma



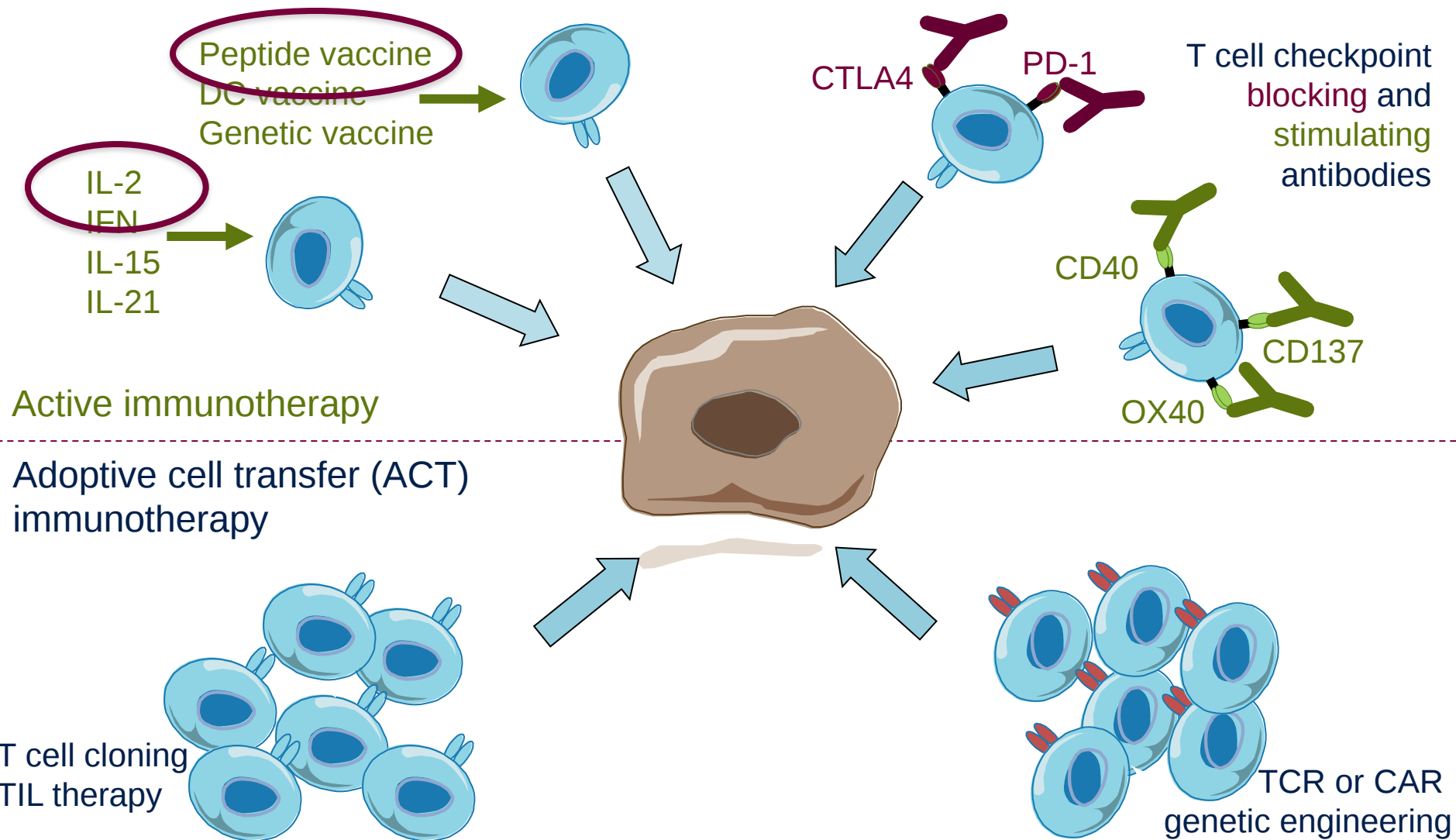
kindly provided by Toni Ribas

# Immunotherapy in melanoma

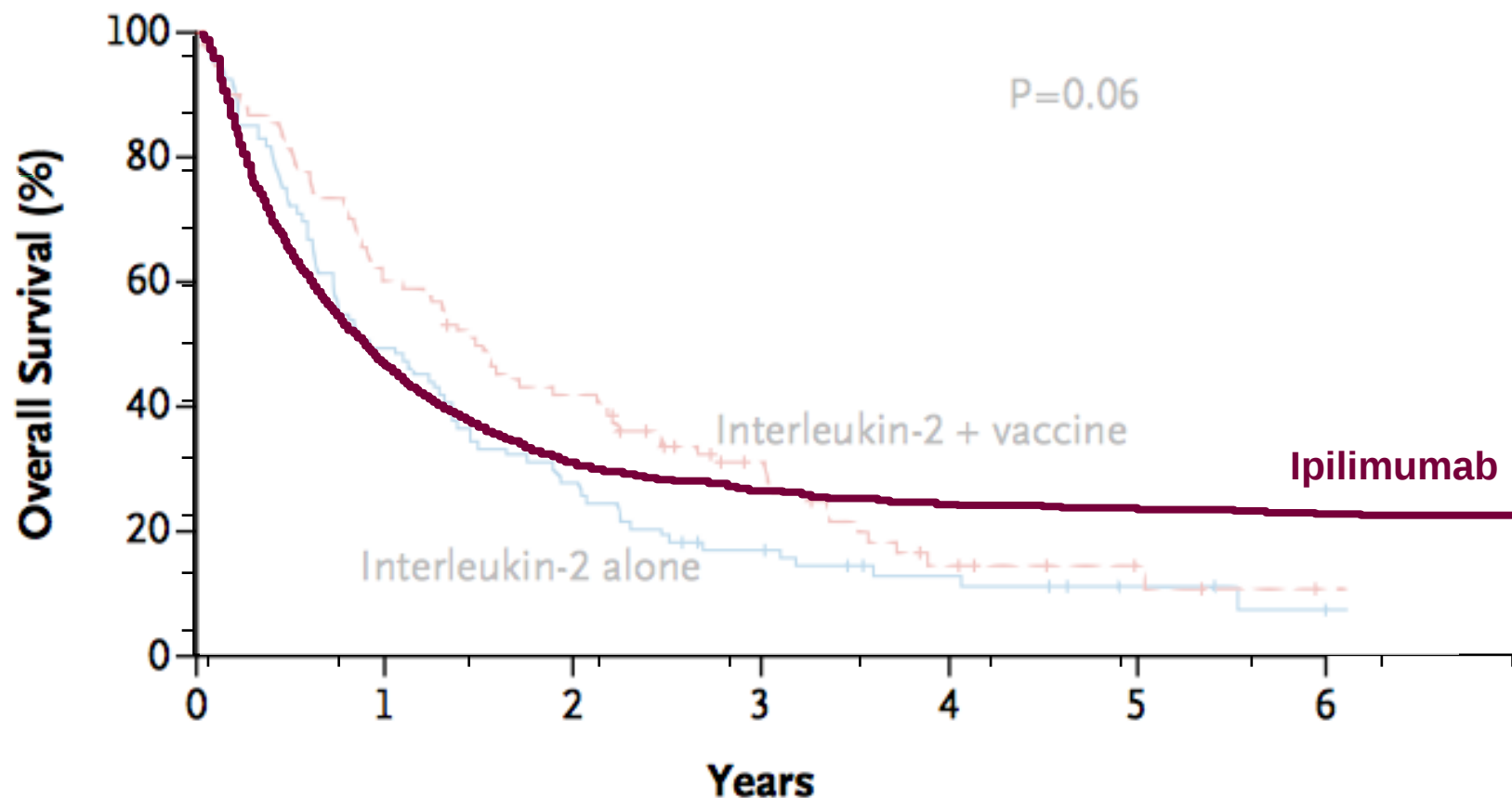


kindly provided by Toni Ribas

# Combining Immunotherapies



# Interleukin-2 and gp100 Peptide Vaccine



Schwartzentruber et al., NEJM  
20110

# Combining Immunotherapies

Peptide vaccine  
DC vaccine  
Genetic vaccine

IL-2  
IFN  
IL-15  
IL-21

CTLA4  
PD-1

T cell checkpoint  
blocking and  
stimulating  
antibodies

CD40

CD137

OX40

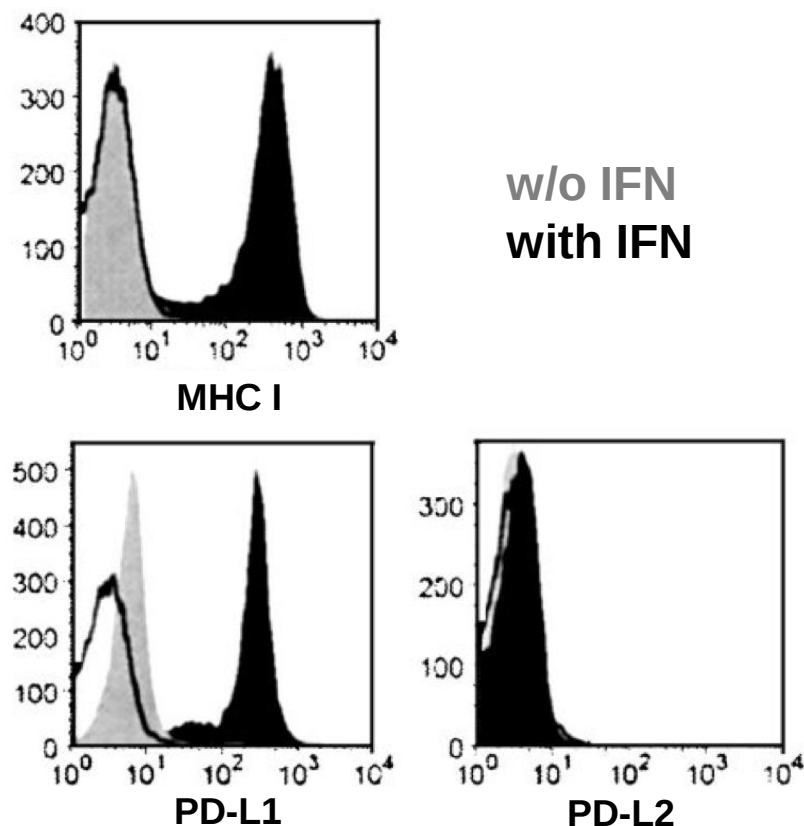
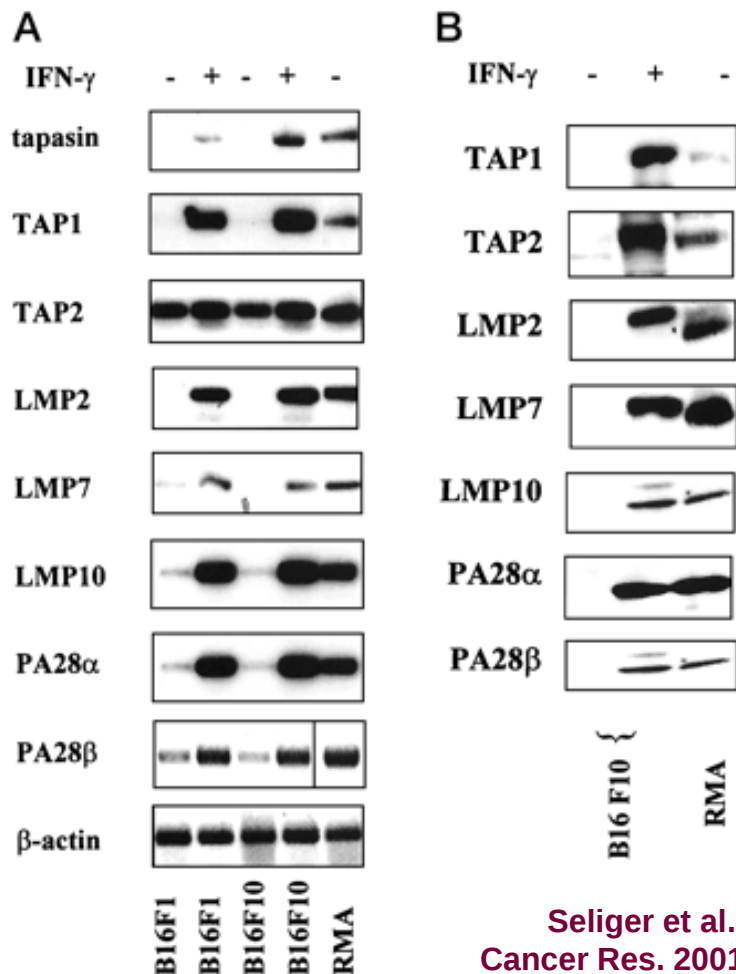
Active immunotherapy

Adoptive cell transfer (ACT)  
immunotherapy

T cell cloning  
TIL therapy

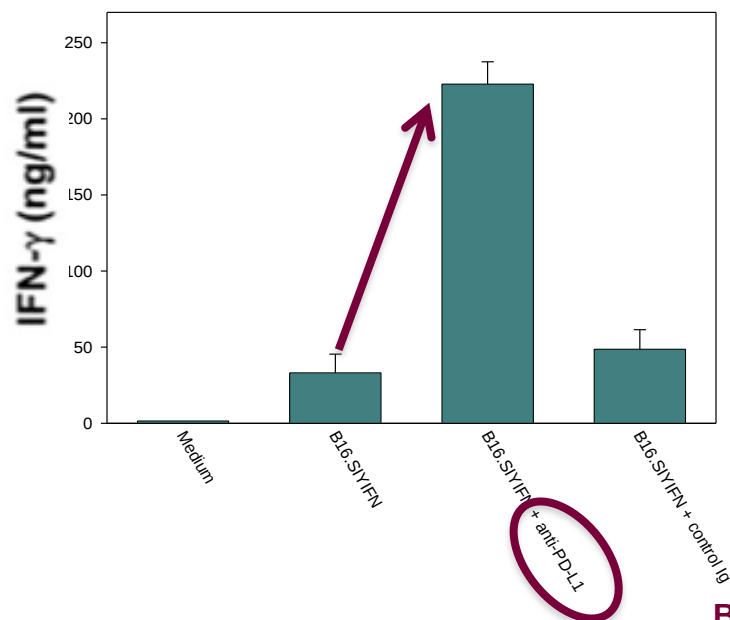
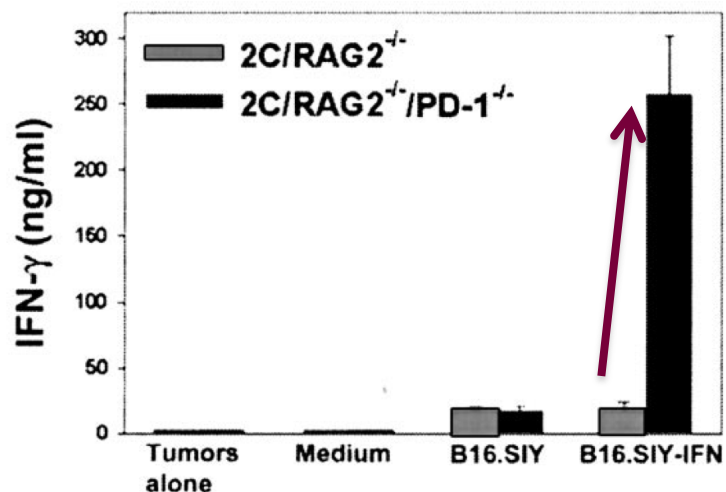
TCR or CAR  
genetic engineering

# Interferon Induces MHC and PD-L1 Upregulation

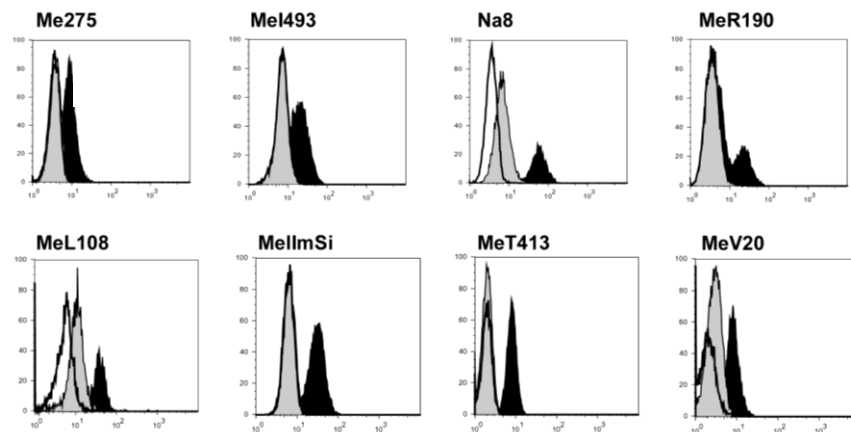


Blank,  
Gajewski, et al.  
Cancer Res 2004

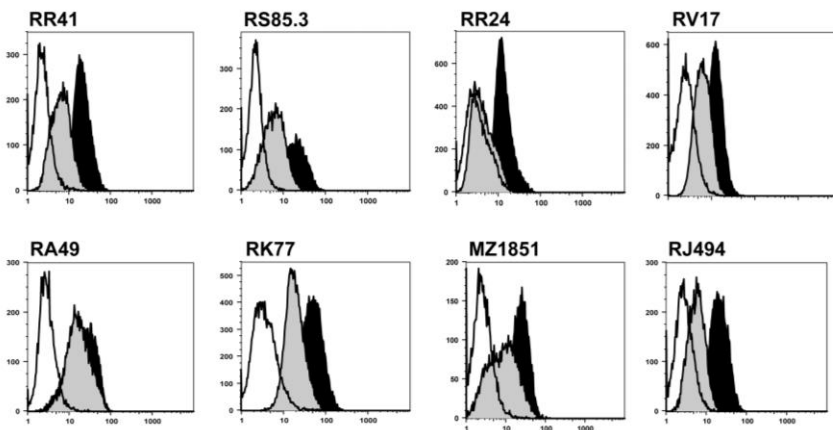
# Synergy Between Interferon and PD-L1 Blockade



## Melanoma cell lines



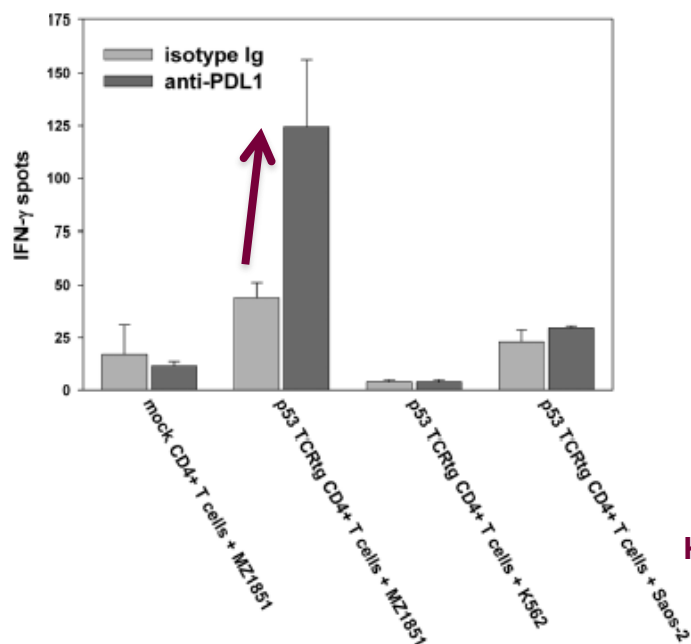
## RCC cell lines



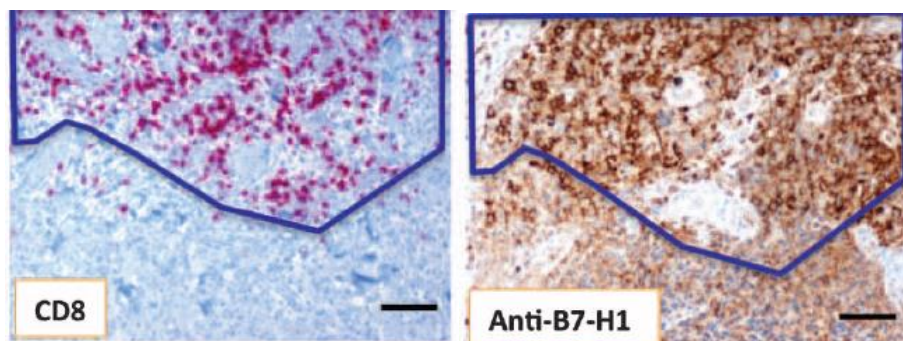
30 September 2014, Madrid, Spain

Blank,  
Gajewski, et al.  
Cancer Res 2004

Blank, Kuball, et al.  
Int J Cancer 2006



Blank,  
Kuball, et al.  
Int J Cancer  
2006

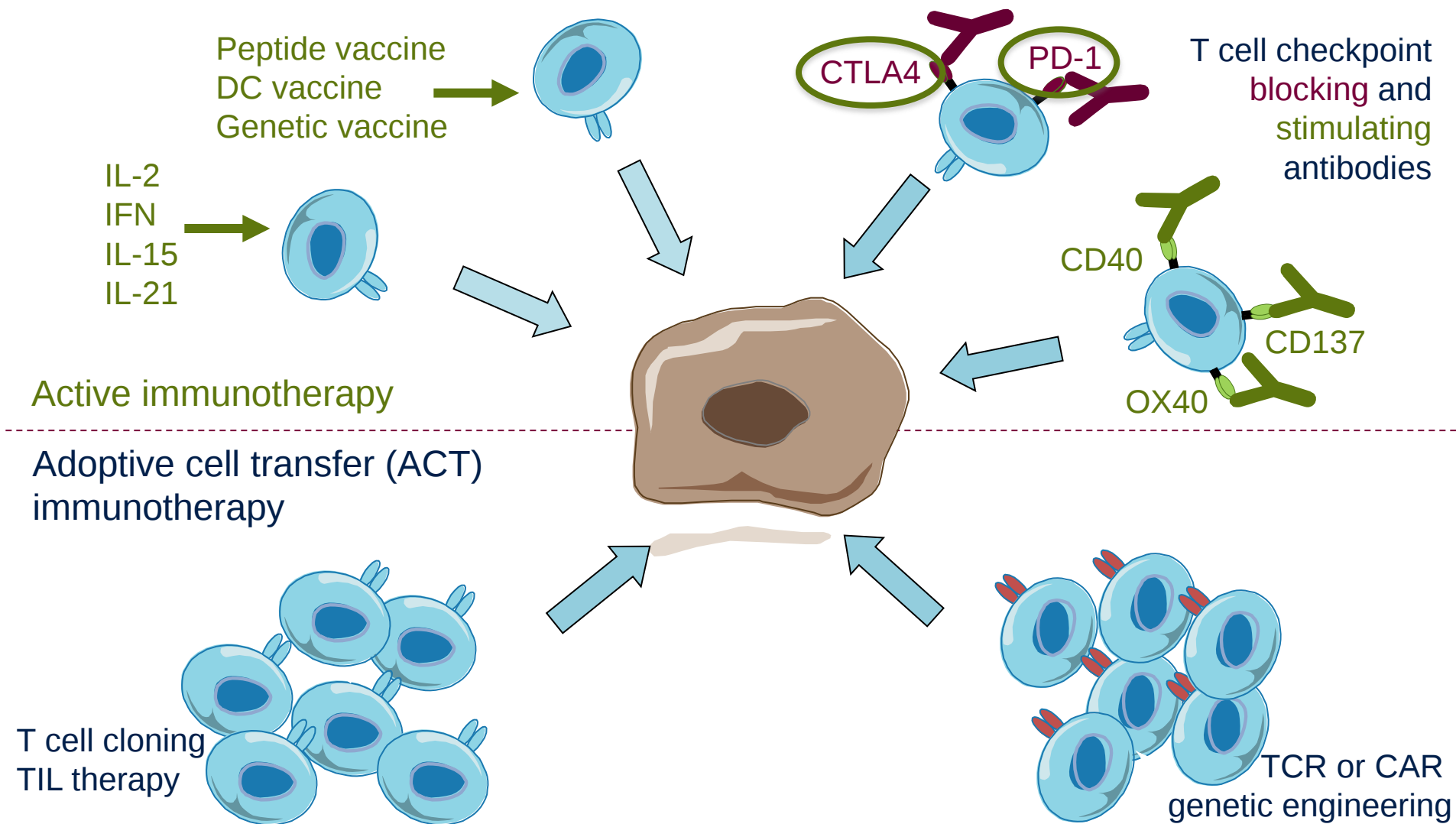


Taube,  
Topalian et al.  
STM 2012

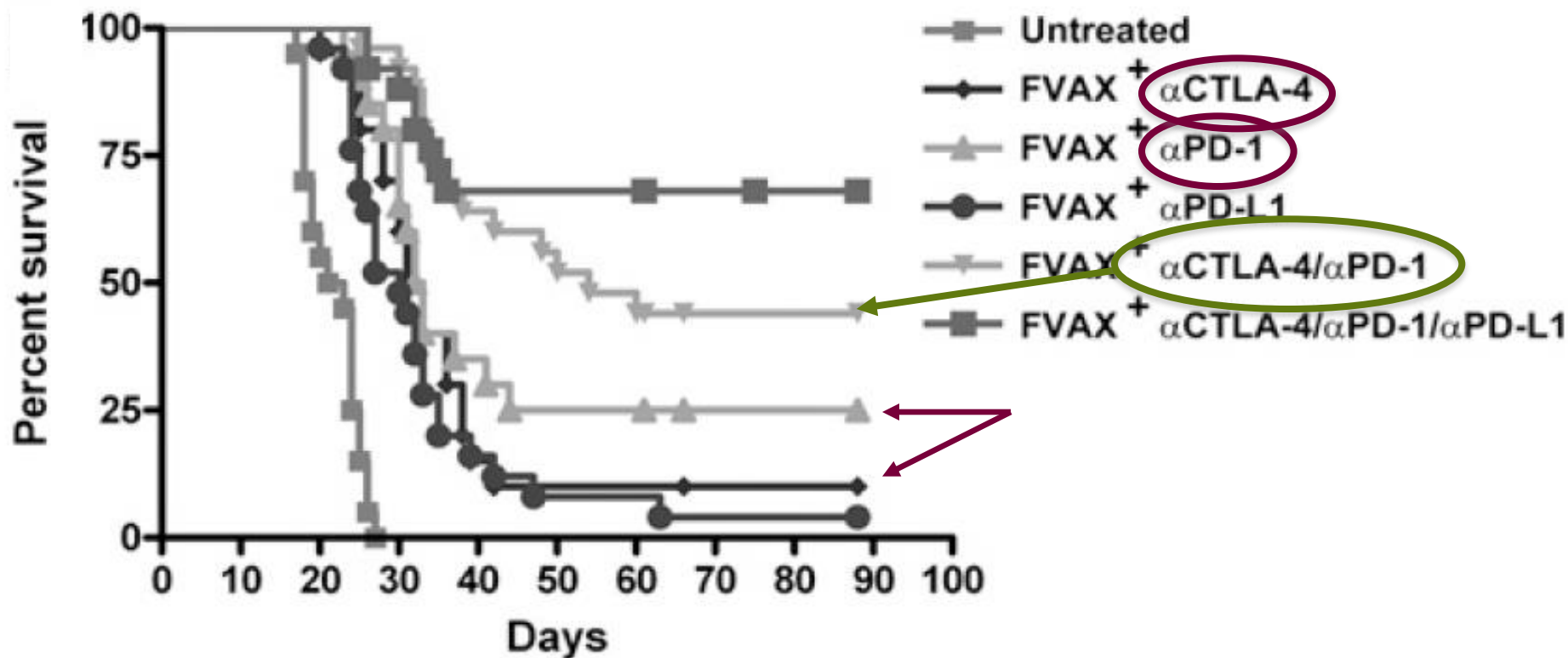
## Treatment of Advanced Melanoma With MK-3475 and Peginterferon (Phase 1) NCT02112032

A Study to Assess the Safety and Tolerability of MPDL3280A in Combination With Other Immune-modulating Therapies in Patients With Locally Advanced or Metastatic Solid Tumors (Phase 1, combinations with ipilimumab or interferon-alpha2b)  
NCT02174172

# Combining Immunotherapies

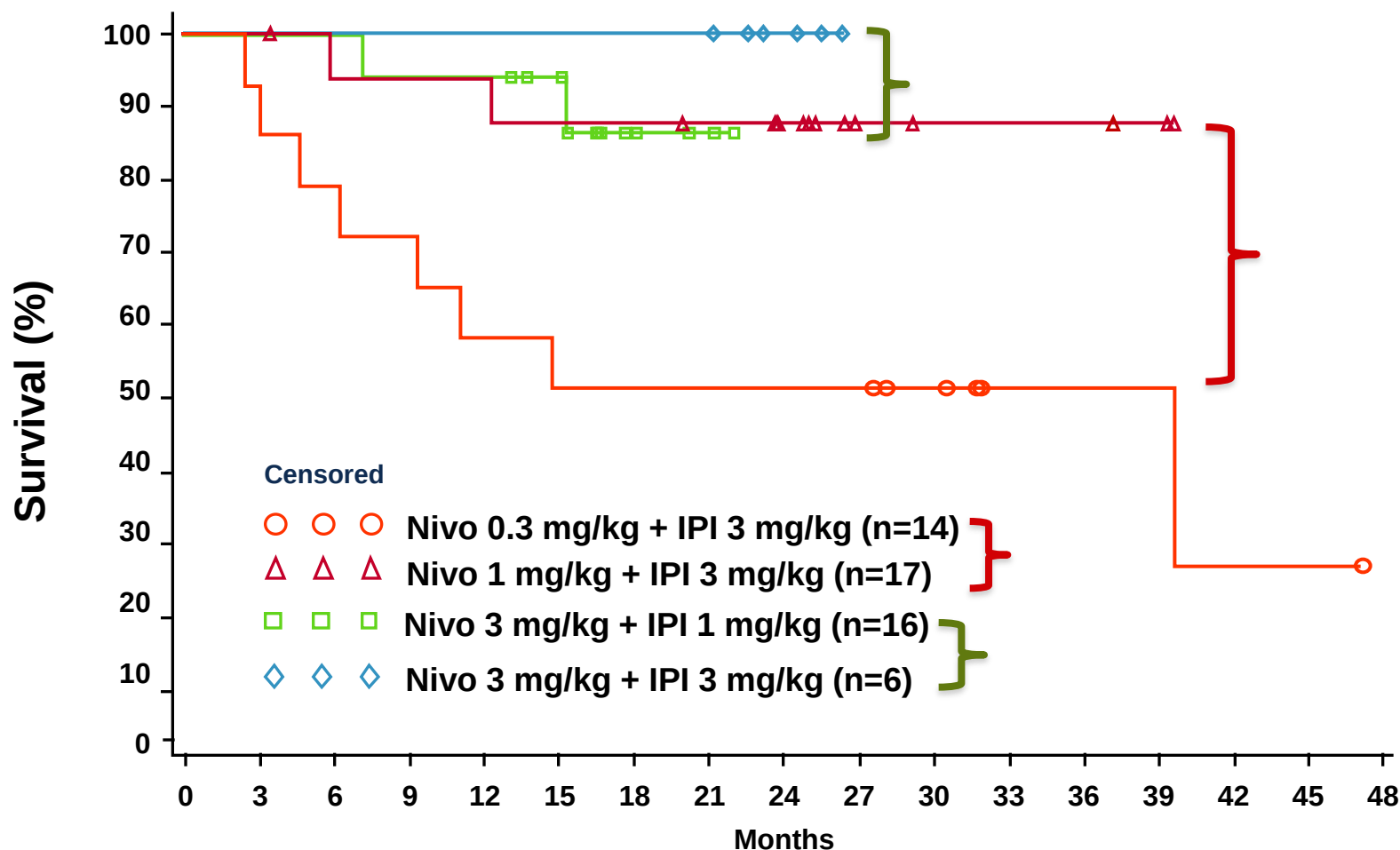


# PD-1/PD-L1 blockade synergizes with aCTLA-4



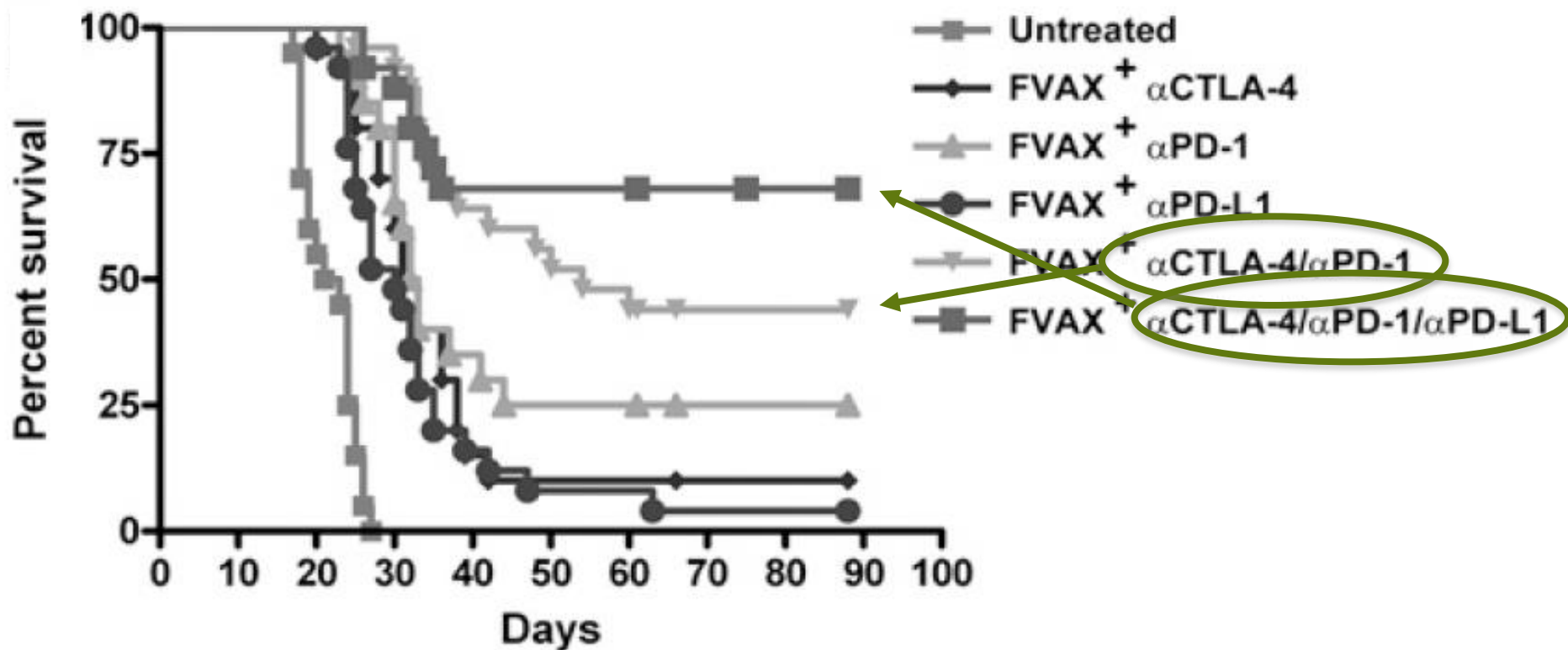
Curran et al., PNAS 2010

# Nivolumab is Probably Synergistic with Ipilimumab



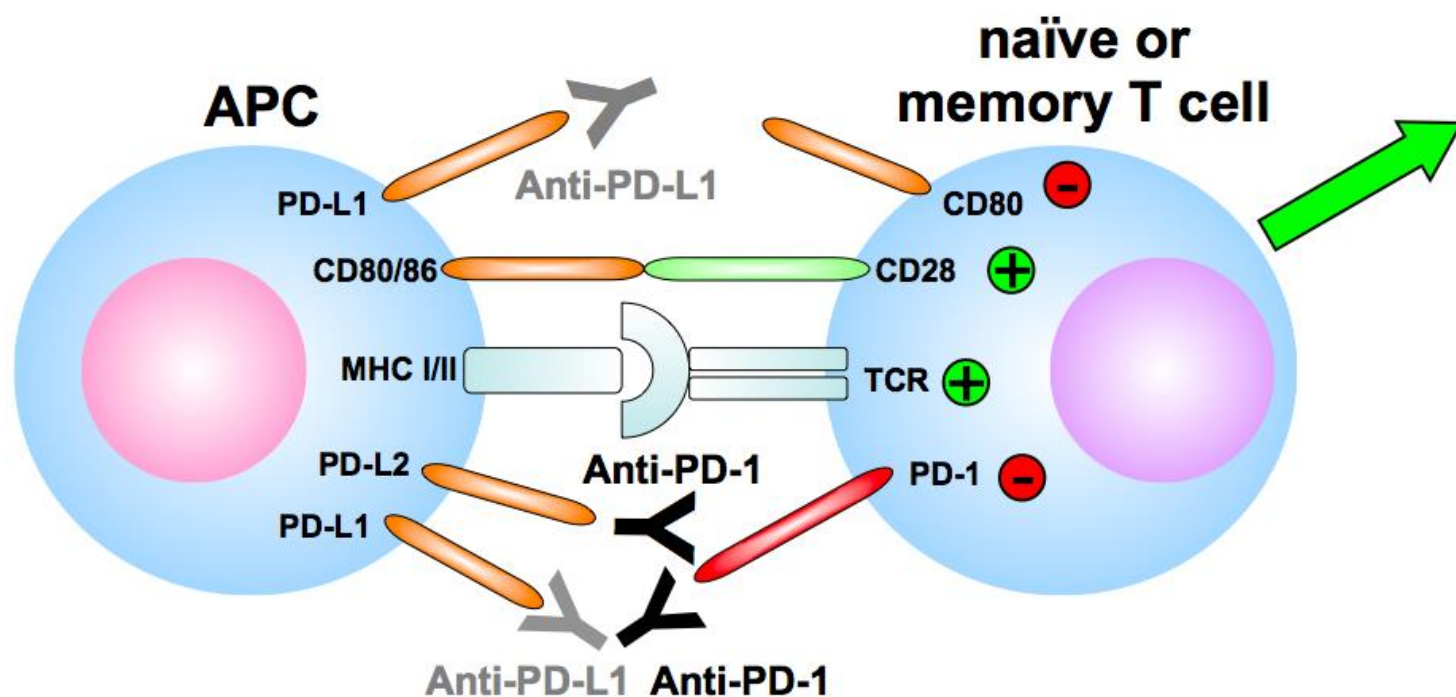
Sznol et al., ASCO 2014, LBA9003

# PD-1 plus PD-L1 blockade synergizes with aCTLA-4



Curran et al., PNAS 2010

# Blocking PD-1 and PD-L1 in Combination with CTLA-4 Blockade

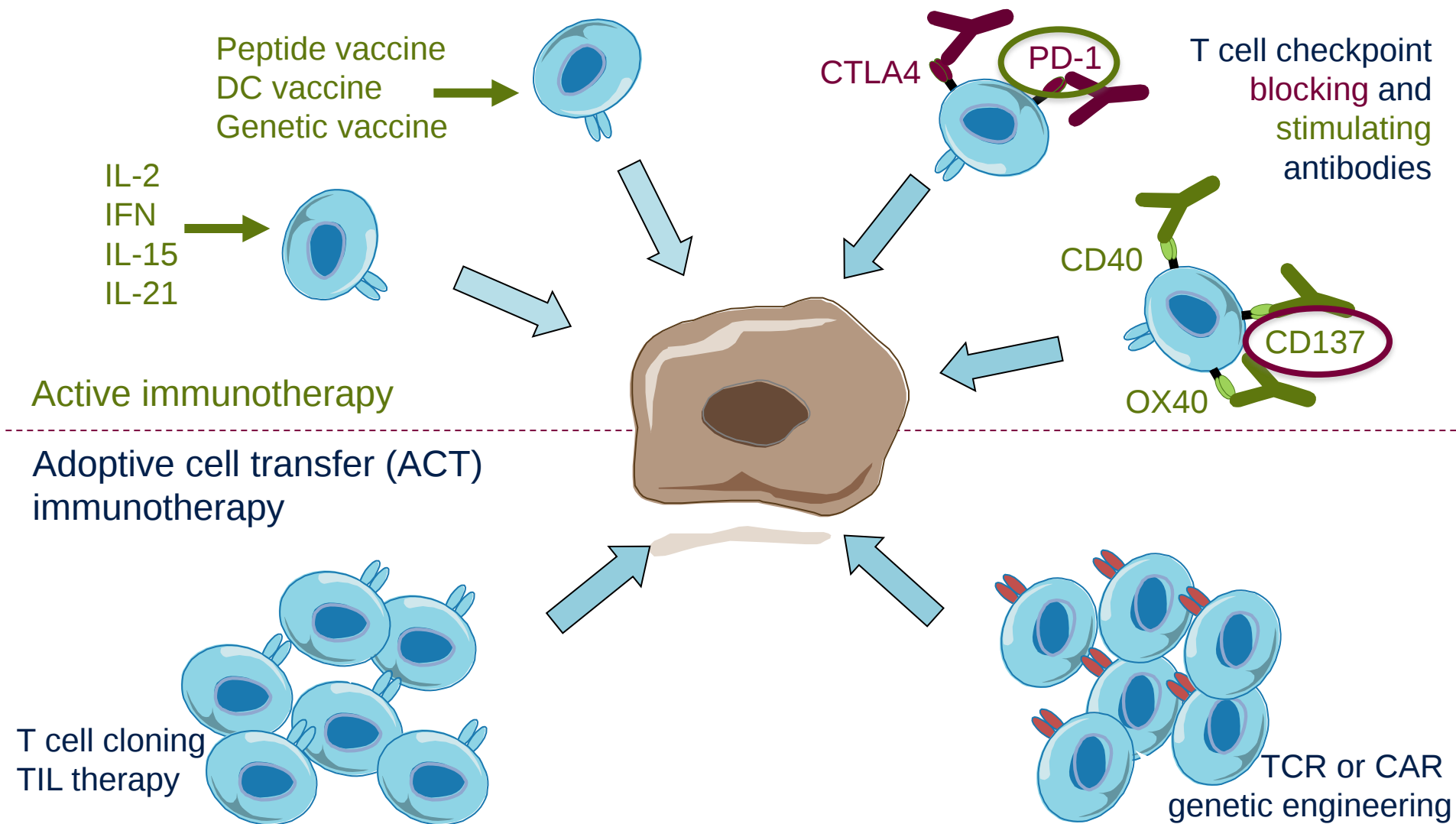


Blank, Curr Opin Oncol, 2014  
based on work from  
G. Freeman and A. Sharpe

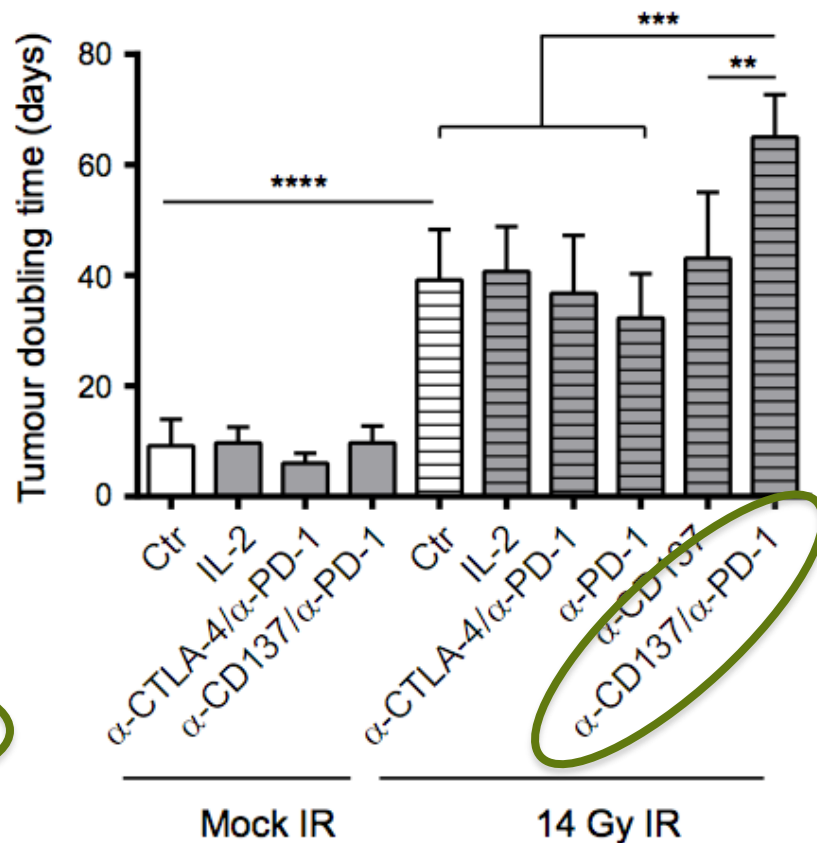
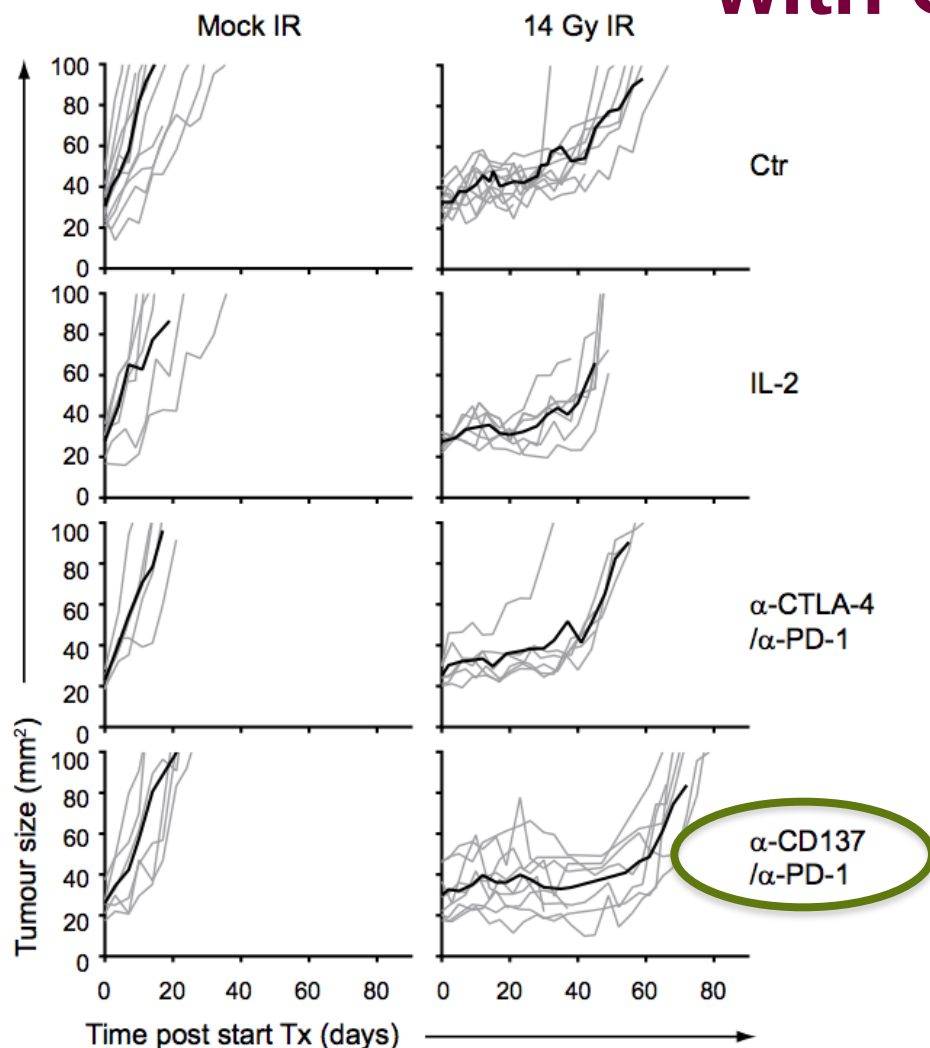
# Combining Immunotherapies loose the brake and push the throttle



# Combining Immunotherapies



# PD-1 blockade Synergizes with CD137 Co-stimulation



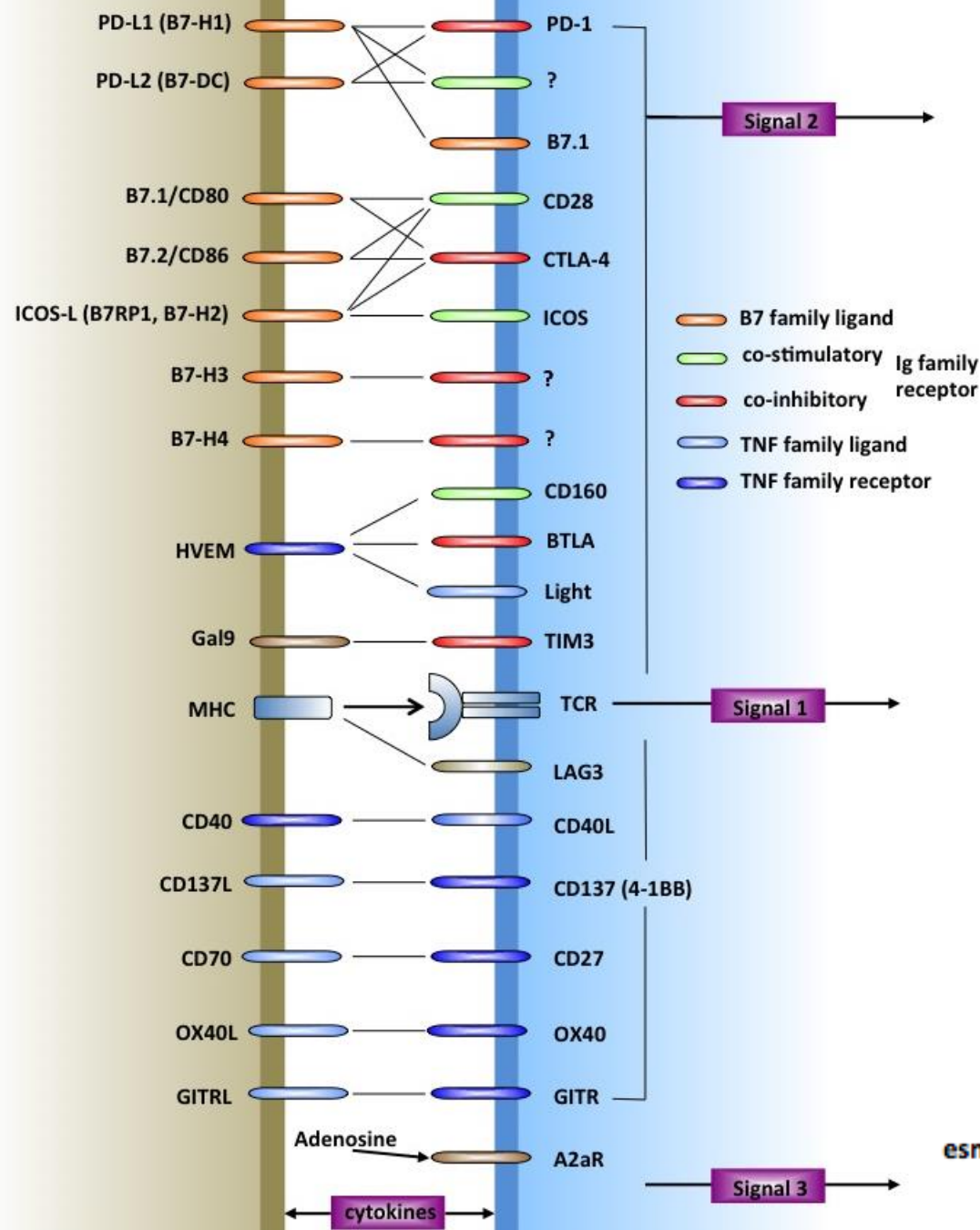
Verbrugge, Blank, et al., submitted

MADRID  
2014

ESMO congress

# Peripheral cells or APC

# T cell

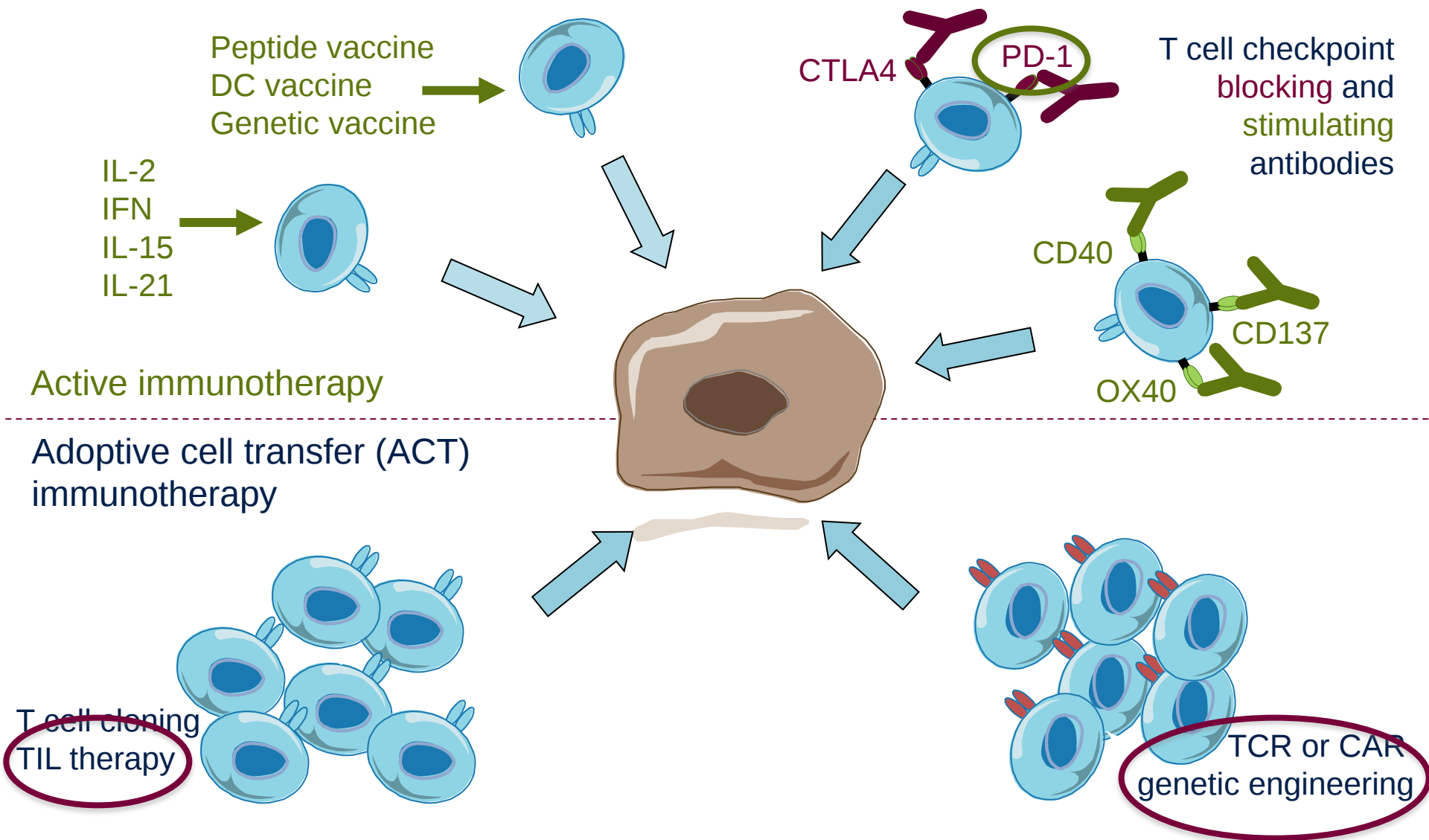


Blank, Curr Opin Oncol, 2014

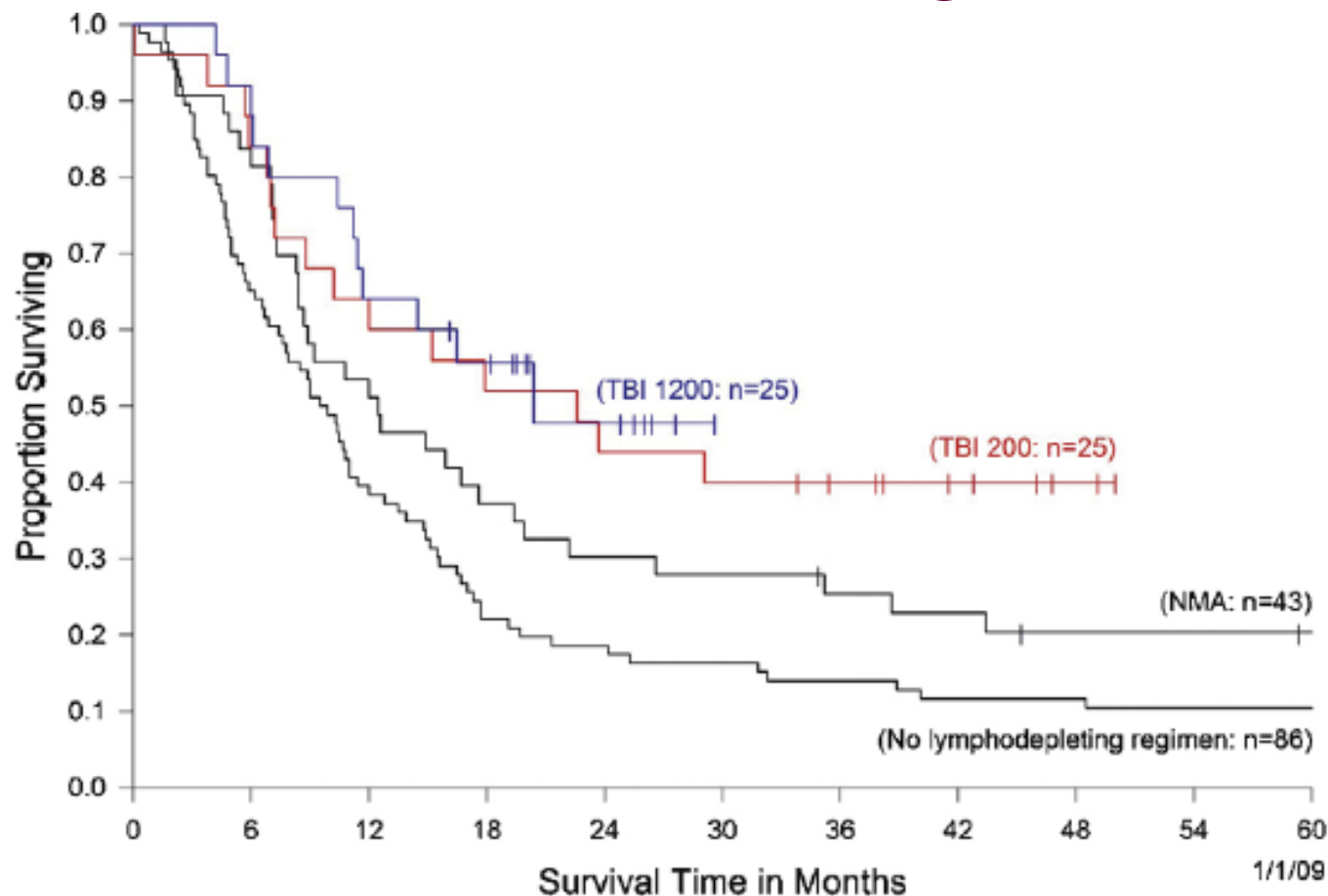
26-30 September 2014, Madrid, Spain

esmo.org

# Combining Immunotherapies

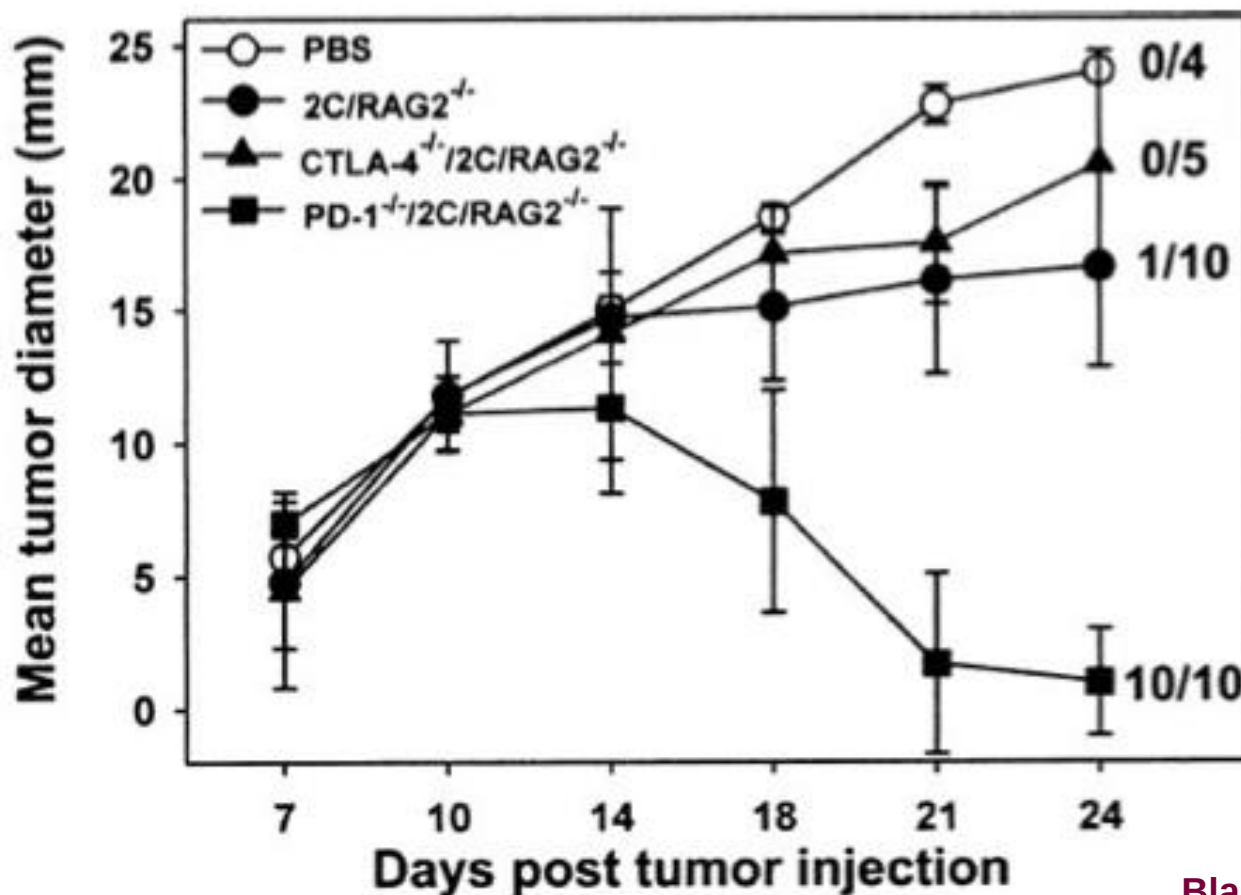


# TIL Therapy Can Induce Long-Time Survival



Rosenberg and Dudley Curr Opin Immunol 2009

# PD-1 Deficient TCRtg T cells Are Superior in Melanoma Control



Blank, Gajewski, et al.  
Cancer Res 2004

# Promising Immunotherapy Combinations

- IFN + PD-1/PD-L1 blockade
- PD-1 / PD-L1 / CTLA-4 blockade
- PD-1 blockade with CD137 co-stimulation
- TIM-3, LAG-3, OX40, CD40, ICOS, CD27, CD160
- PD-1 k.o. TIL or TCR/CAR engineered T cells
- Modulation of the immune regulatory cell compartments (Treg, MDSC)

# Tumor Immunotherapy

