
SITC
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Gaylord National Hotel
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Society for Immunotherapy of Cancer

SITC 2017

On the Horizon: Immuno-Oncology (I-O) Combinations

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Society for Immunotherapy of Cancer

Presenter Disclosure Information

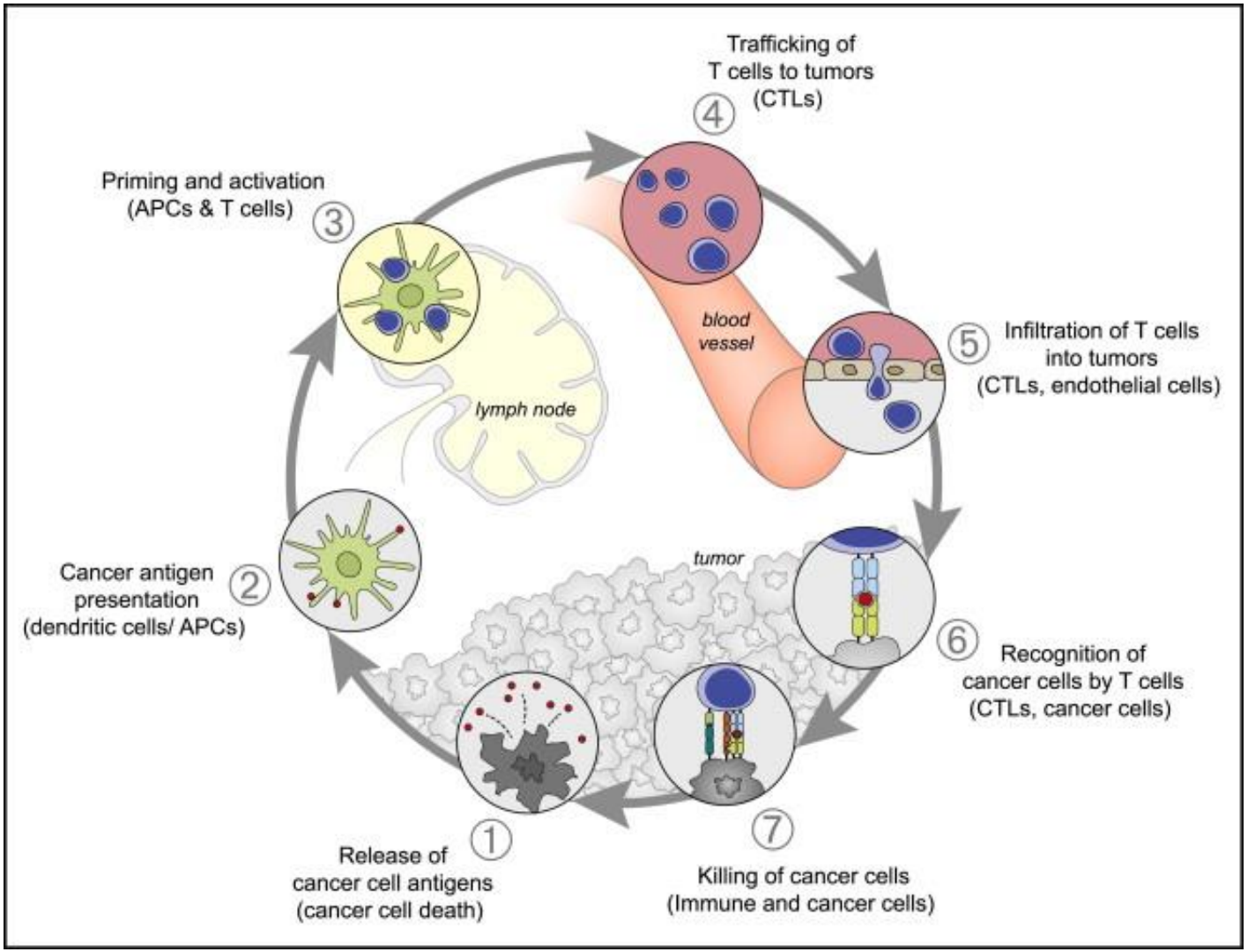
Jeffrey A. Sosman

- Advisory Boards: BMS, Incyte, Array, Novartis
- Research funding: BMS, Amgen

Overview of Talk

- What's required for effective Cancer Immunotherapy
- Options for Combination Therapy
  - Examples
    - Vaccines
    - IDOi
    - Anti-LAG-3
    - Adoptive Cell Therapy
- Improving Patient Selection
    - Biomarker Development
    - Use to select most effective and least toxic

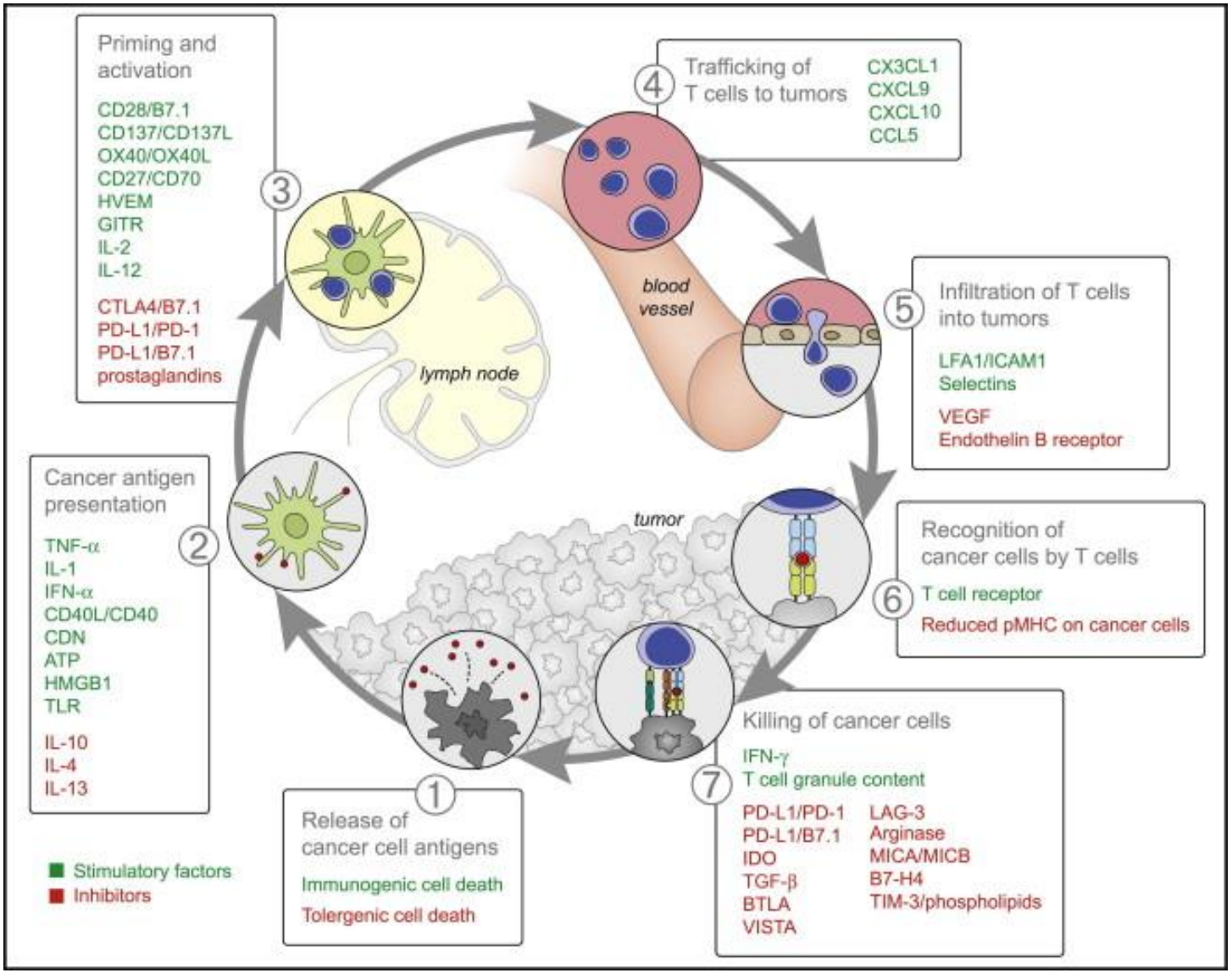
The Cancer–Immunity Cycle



Daniel S. Chen , Ira Mellman

Immunity, Volume 39, Issue 1, 2013, 1 - 10

The Cancer–Immunity Cycle



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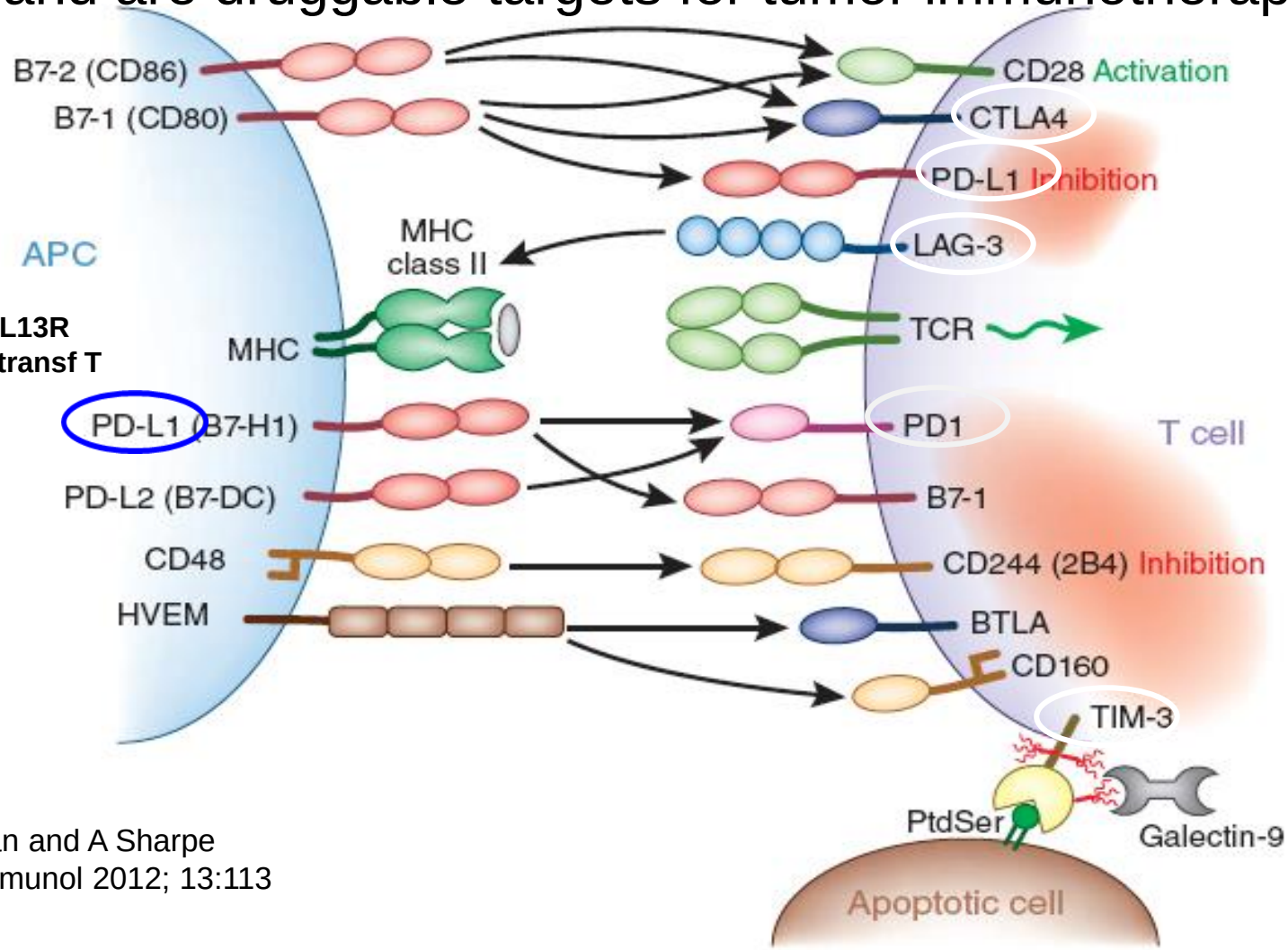
Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle Each step of the Cancer-Immunity Cycle requires the coordination of numerous factors, both stimulatory and inhibitory in nature. Stimulatory factors shown in green promote immunity, ...

Where will Improvements come from?

- **Combinations:**
  - **Based on Template: anti-PD-1/PD-L1 or with anti-PD-1/anti-CTLA-4**
    - **Block other co-inhibitory: LAG3, TIM3, KIR, VISTA**
    - **Activate co-stimulatory: 4-1BB, OX-40, GITR, CD27, ICOS**
    - **Block inhibitory molecules- IDOi, TGFbi, CSF1Ri, anti-IL-6 or anti- IL-10**
    - **Effect trafficking- anti-VEGF, CCL5, CXCR4i**
    - **Vaccines- TVEC- oncolytic virus, Neoantigen, other cellular**
    - **Adoptive Cellular therapy- TIL, CAR-T cells, TCR T-cells**

T cells in Tumors Express Multiple Immunoinhibitory Receptors

These regulate the balance between T cell activation and tolerance and are druggable targets for tumor immunotherapy



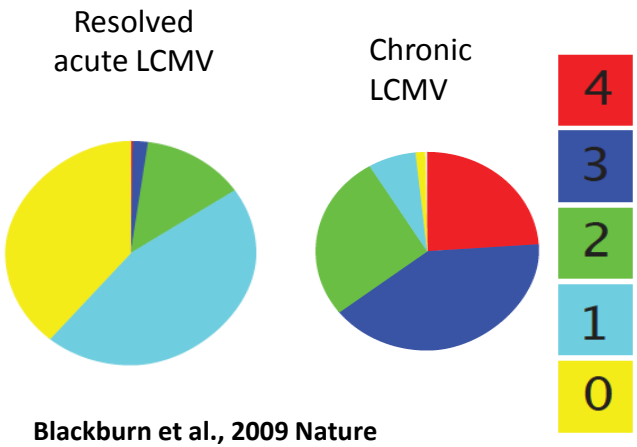
CAR-T cell
CD19, CD38, IL13R
TCR ag spec-transf T cell
TIL

CD137
OX40
GITR
TIGIT
CD40
VISTA
CD73
(Adenosine R)
NKG2D
IL2v- FAP or CEA-CD3
TCR CD3
ICOS

TLR agonist
IODi
CSF1R ab or sm
CXCR2
CXCR4
STAT3i
PI3Kd
ANG2
Anti-VEGF

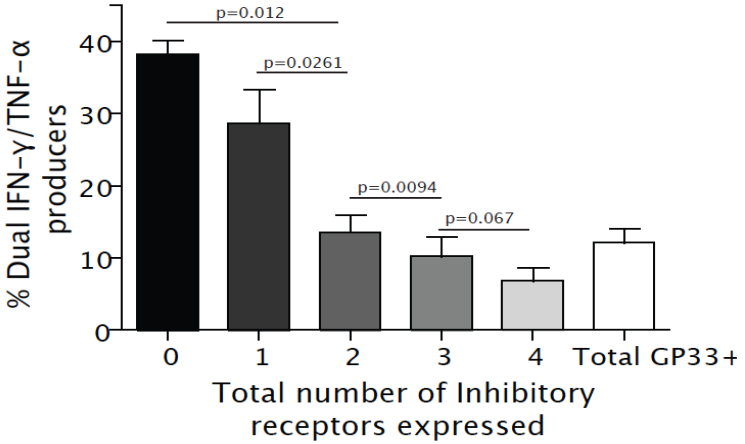
G Freeman and A Sharpe
Nature Immunol 2012; 13:113

T cells can coexpress multiple inhibitory receptors



Blackburn et al., 2009 Nature Immunology 10: 29-37

Degree of dysfunction



Co-blockade enables better rescue of exhausted T cells and therapeutic efficacy than blockade of a single inhibitory pathway, but ONLY anti-PD-1 monotherapy has substantial effects

Where will Improvements come from?

- **Combinations:**
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    - **Signal Inhibition, BRAF directed (BRAFi+MEKi), MEKi, PI3K inhibition (PTEN effects)**
    - **Cytokines- IL-2, IFN a,b,g,, Directed cytokines (FAP-IL-2v or CEA-IL-2v)**
    - **Epigenetic modulation- gene expression and EVR expression**
    - **Microbiome modification- fecal transplants**
    - **Chemotherapy other cytotoxics**
    - **Localized Irradiation SBRT, SRS**

PD-1/PD-L1 Combinations in Development

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Triplets Immune checkpoint inhibitors

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- Anti-PD-1 + Anti-LAG-3 + IDOi
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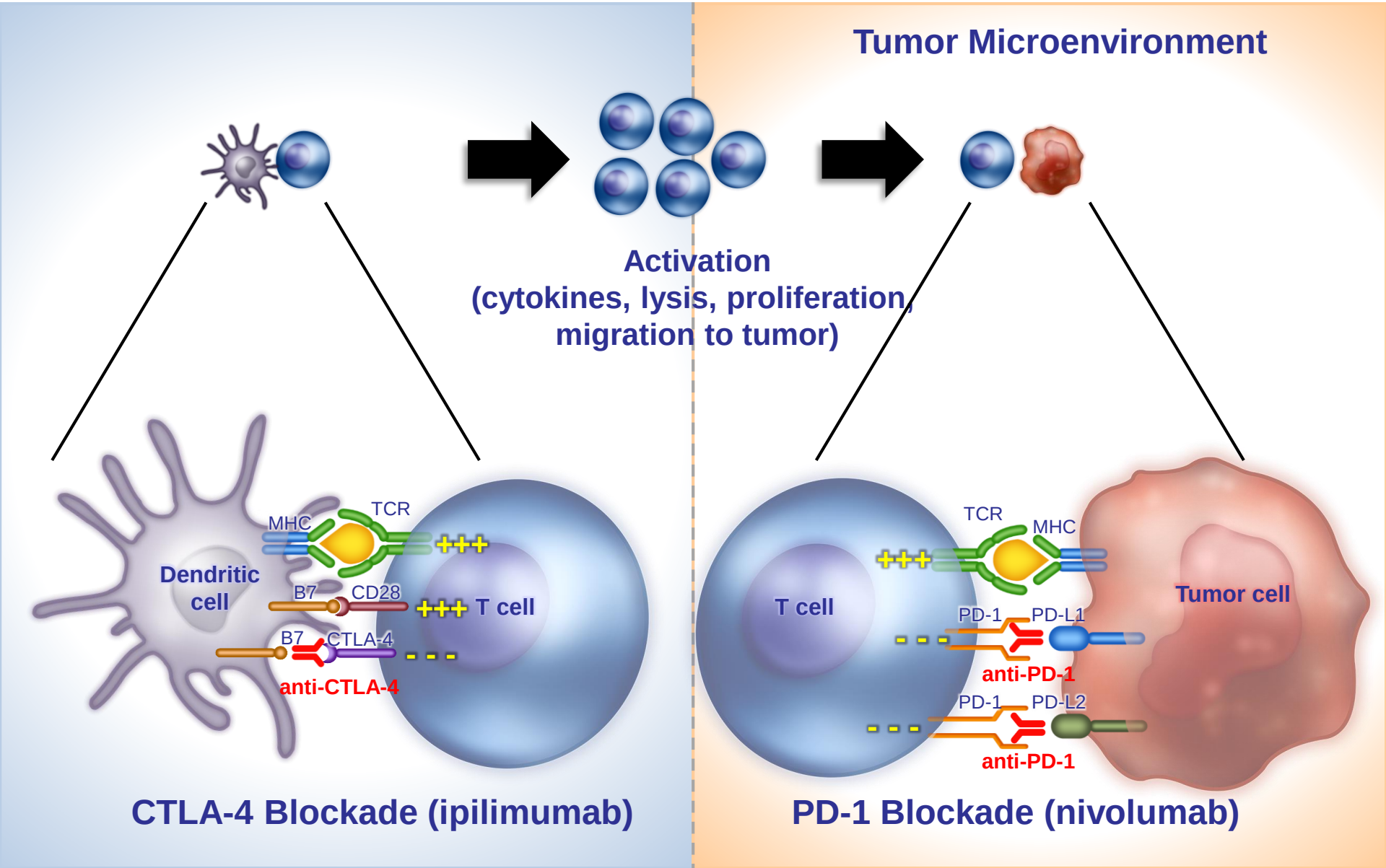
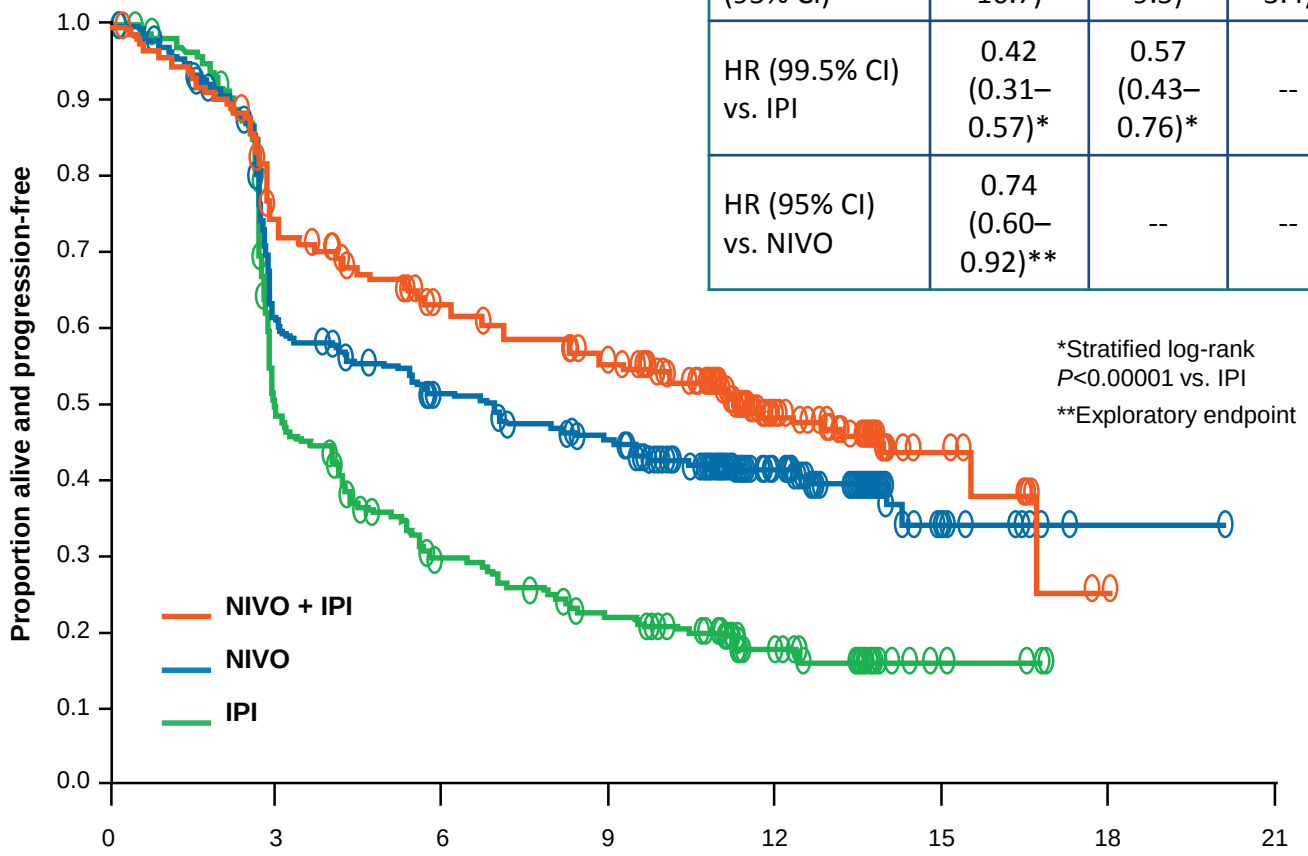
Blocking CTLA-4 and PD-1

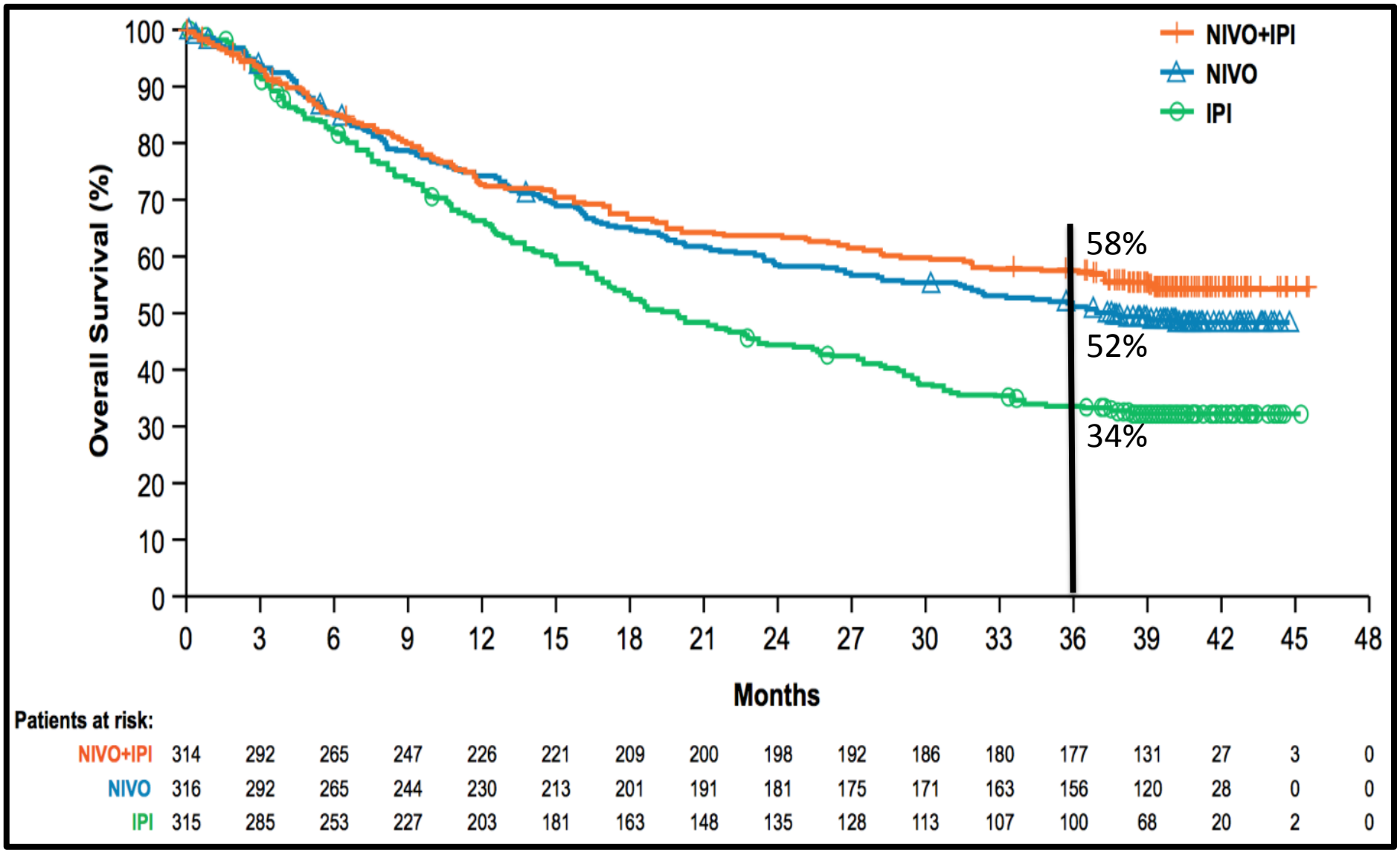


CA-067 Ipi+Nivo vs Nivo vs Ipi Progression-Free Survival

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--



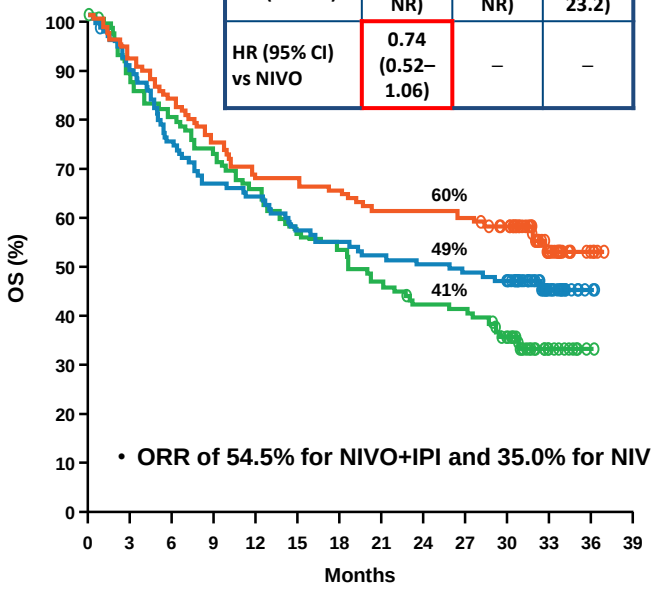
Overall Survival in All Randomized Melanoma Patients : 067 Ipi+ Nivo vs Nivo vs Ipi



Outcomes Observed at a 1% Cutoff

PD-L1 Expression Level <1%

<1% PD-L1	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR (26.5–NR)	23.5 (13.0–NR)	18.6 (13.7–23.2)
HR (95% CI) vs NIVO	0.74 (0.52–1.06)	–	–



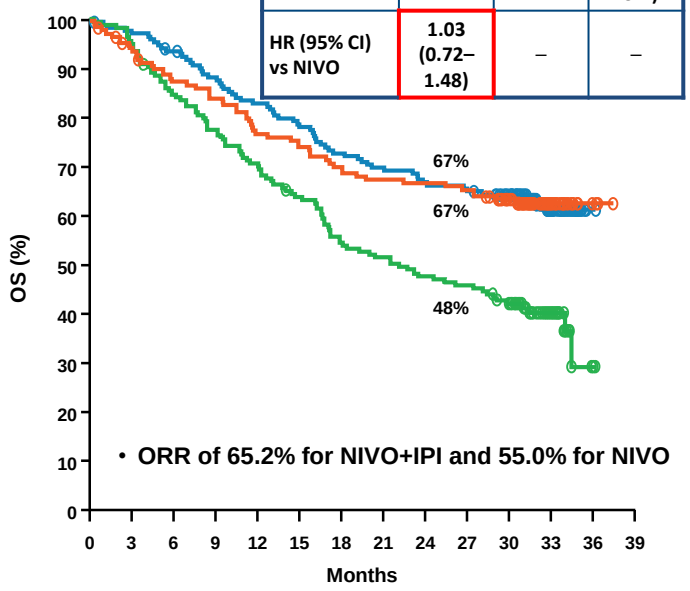
- ORR of 54.5% for NIVO+IPI and 35.0% for NIVO

Patients at risk:

NIVO+IPI	123	113	102	91	82	82	79	74	74	72	66	18	4	0
NIVO	117	103	86	76	73	65	62	59	57	55	50	16	2	0
IPI	113	96	87	79	71	61	57	50	44	43	32	10	1	0

PD-L1 Expression Level ≥1%

≥1% PD-L1	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR	NR	22.1 (17.1–29.7)
HR (95% CI) vs NIVO	1.03 (0.72–1.48)	–	–

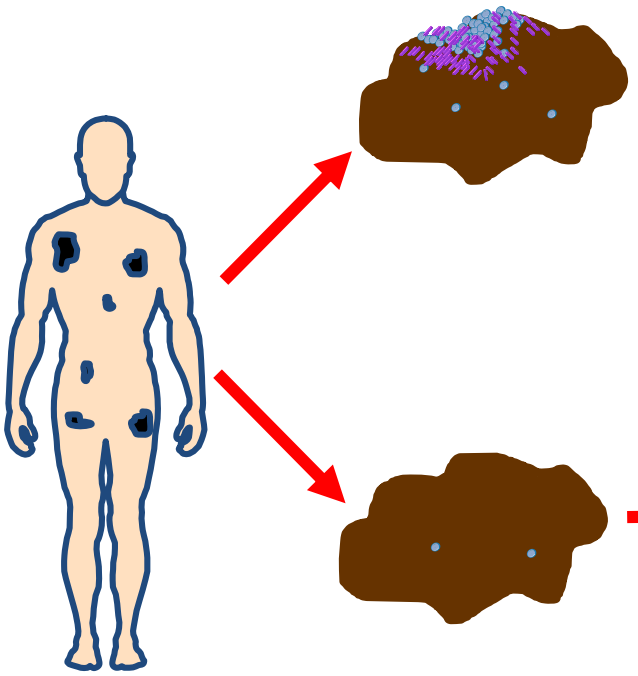


- ORR of 65.2% for NIVO+IPI and 55.0% for NIVO

Patients at risk:

NIVO+IPI	155	144	132	127	116	112	105	102	101	99	85	27	3	0
NIVO	171	165	158	148	139	131	122	117	112	109	98	36	1	0
IPI	164	155	138	126	115	102	89	83	77	74	64	21	2	0

Enhancing Efficacy of anti-PD-1/L1



Anti-PD-1/anti-PD-L1

Bring T cells into tumors:

+ anti-CTLA4
+ TLR agonists or oncolytic viruses
+ IDO or macrophage inhibitors

Modified from Ribas, Cancer Discovery 2016

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Triplets Immune checkpoint inhibitors

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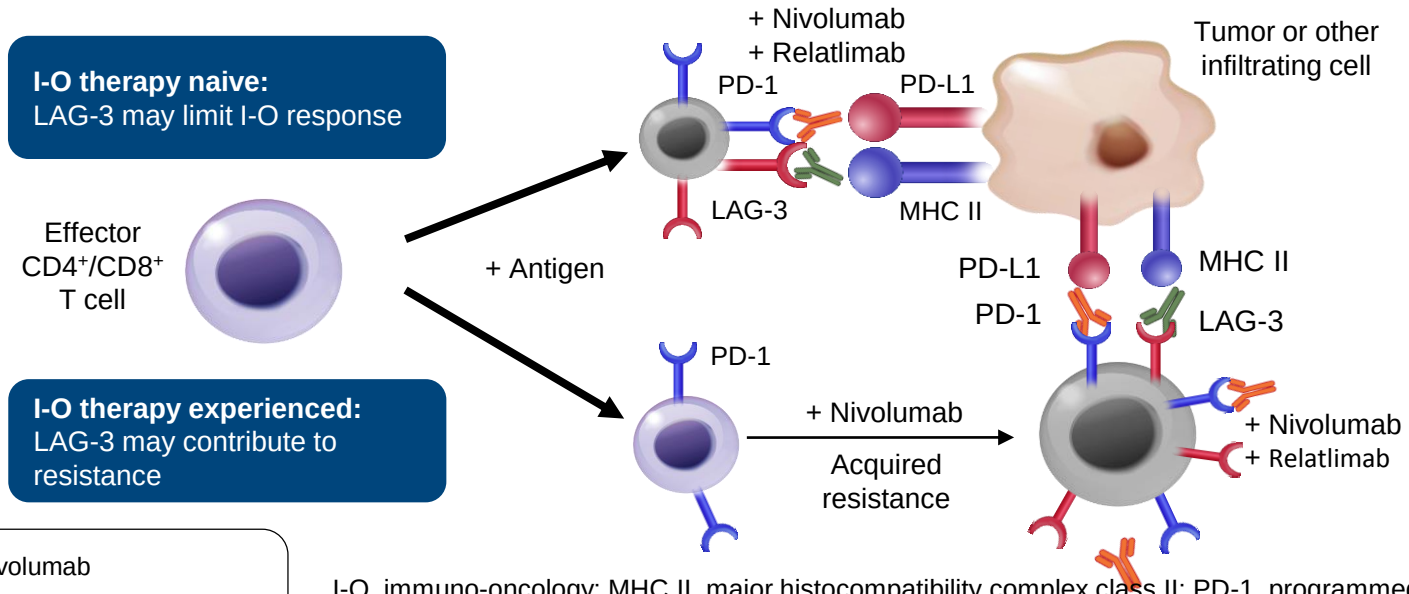
- Anti-PD-1 + Anti-LAG-3 + IDOi
- Anti-PD-1 + Anti- CTLA-4 + Anti-LAG3

Potential Role of LAG-3 in T-Cell Exhaustion and Anti–PD-1 Resistance

- **LAG-3 regulates a checkpoint pathway that limits the activity of T cells[1]**
- **LAG-3 and PD-1 receptors are overexpressed and/or co-expressed on tumor-infiltrating lymphocytes in melanoma[2,3]**



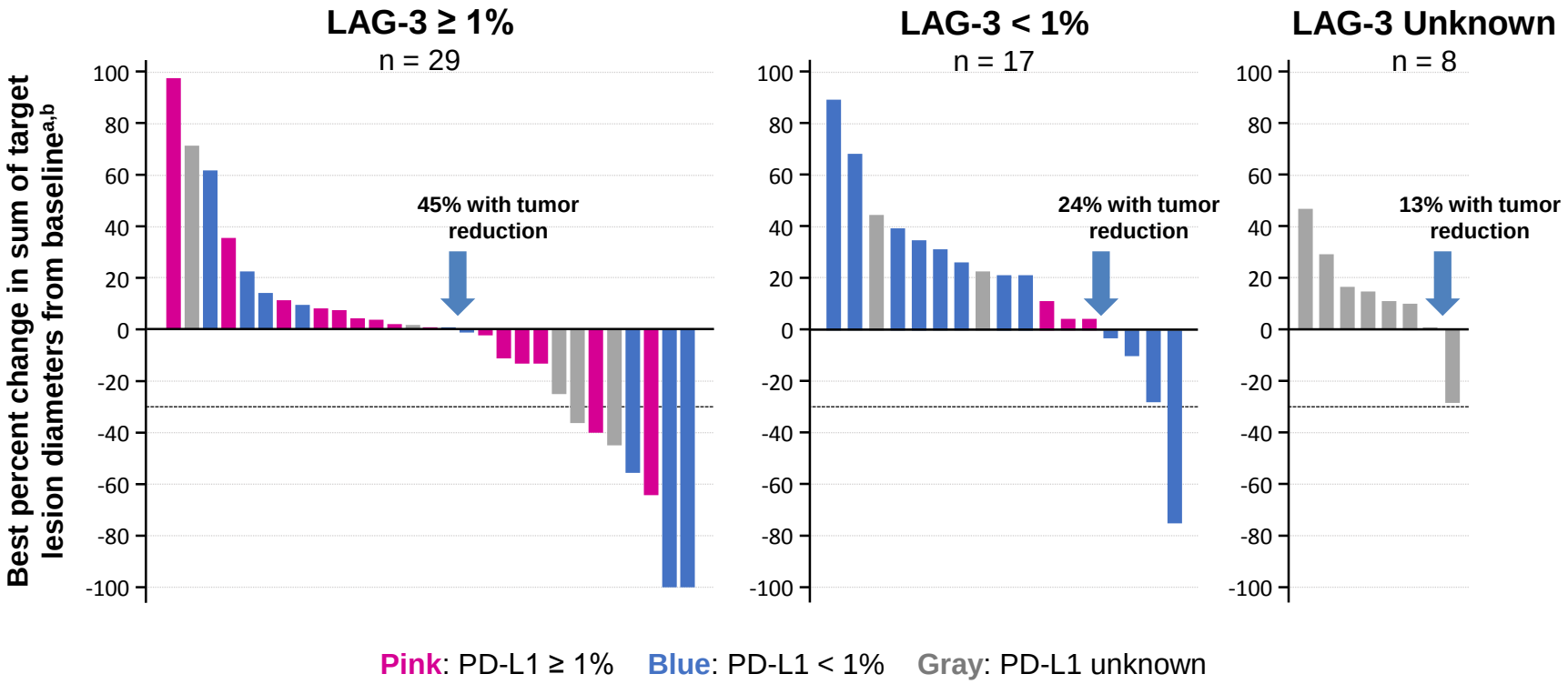
I-O, immuno-oncology; MHC II, major histocompatibility complex class II; PD-1, programmed death-1; PD-L1, programmed death ligand 1.

1. Grosso JF et al. *J Clin Invest*. 2007;117:3383–3392. 2. Goding SR et al. *J Immunol*. 2013;190:4899–4909. 3. Taube JM et al. *Clin Cancer Res*. 2015;21:3969–3976.

Ascierto P etal, ESMO 2017

Antitumor Activity of Relatlimab (anti-LAG3) + Nivolumab

Change in Tumor Size by LAG-3 Expression



[a]Six patients with clinical progression prior to their first scan and 1 with PD due to a new symptomatic brain metastasis prior to getting full scans were not included.
[b]One patient with best change from baseline > 30% had a best response of SD.

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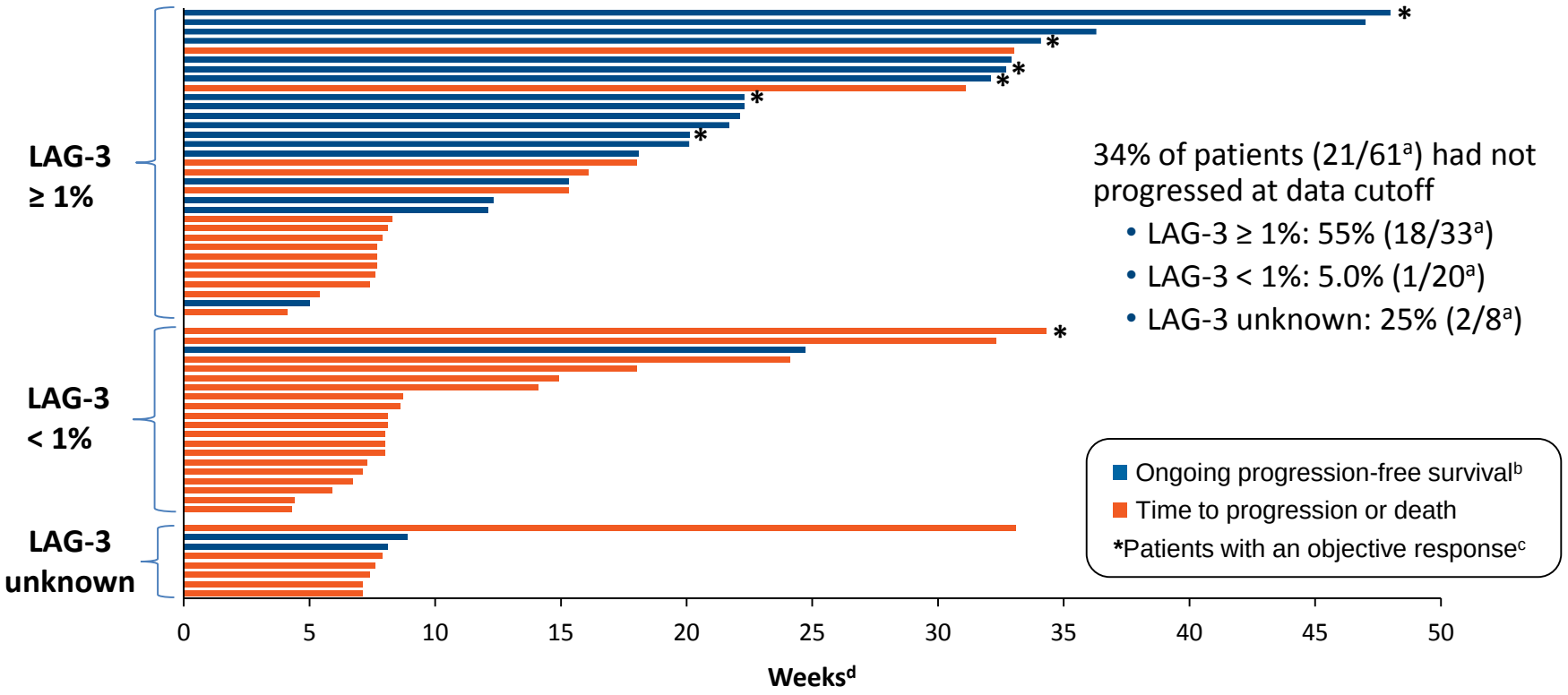
Ongoing Clinical Follow-Up



[a]Response-evaluable patients; all progressed during prior anti–PD-1/PD-L1 therapy. [b]Censored on last visit. [c]One response was unconfirmed. [d]Evaluations are planned for every 8 weeks.

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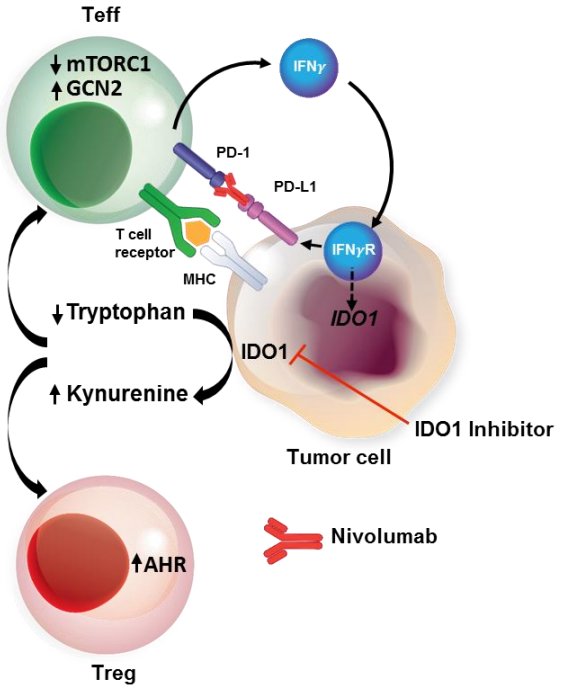
Rationale for IDO1 Inhibitor Plus Anti–PD-1 Combination Therapy

- IDO1 enzyme inhibits T-cell function through local depletion of tryptophan and production of immunosuppressive kynurenine and downstream metabolites[1]
- High IDO1 expression is associated with a decrease in immune cell tumor infiltration and an increase in regulatory T cells[1,2]
- IDO1 expression in tumors has also been associated with poor prognosis, increased progression, and reduced survival[1,2]
- Anti–PD-1 treatment upregulates *IDO1* expression in patients[3,4]



Adapted from Moon YW et al. *J Immunother Cancer*. 2015;3:51. Published under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

IFNγR, interferon gamma receptor; MHC, major histocompatibility complex; PD-L1, programmed death-1 ligand. 1. Moon YW et al. *J Immunother Cancer.* 2015;3:51. 2. Godin-Ethier J et al. *Clin Cancer Res.* 2011;17:6985–6991. 3. Urba WJ et al. Presented at the AACR 2015 Annual Meeting; April 18–22, 2015: Philadelphia, Pennsylvania [oral 4886]. 4. Choueiri TK et al. Presented at the AACR 2015 Annual Meeting; April 18–22, 2015: Philadelphia, Pennsylvania [poster 5].

Recent Results of anti-PD-1 + IDOi

- Phase I/II results from the KEYNOTE-37 trial, the combination Pembrolizumab and Epecadostat induced objective responses in 29 of 53 (55%) treatment-naïve patients, including seven CRs
- 22 of 38 evaluable patients (58%) responded to the recommended phase II dose of epacadostat (100 mg).

- Median progression-free survival (PFS) of 22.8 months in the treatment-naïve pts, and NR in the patients who received the phase II dose of epacadostat

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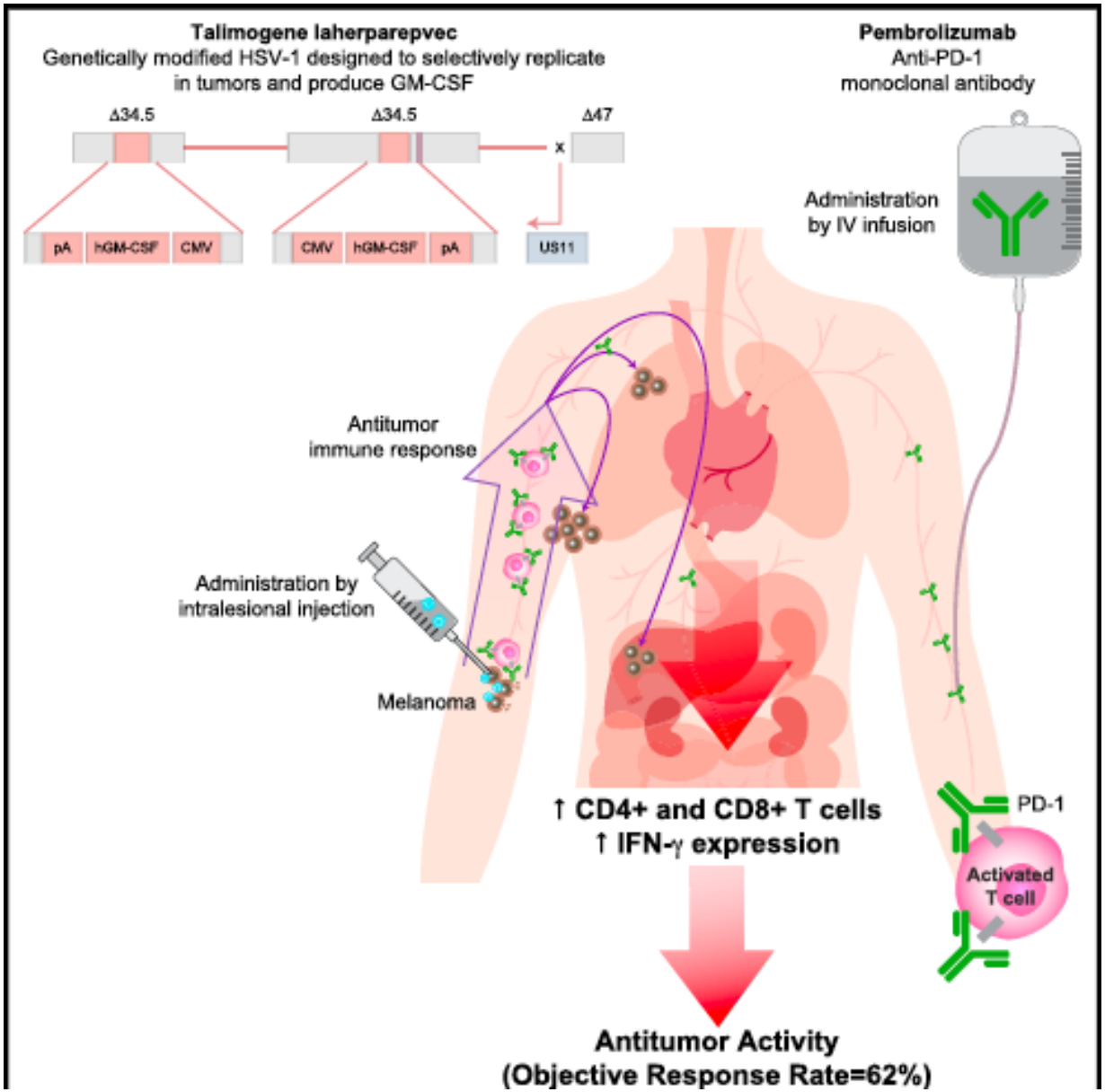
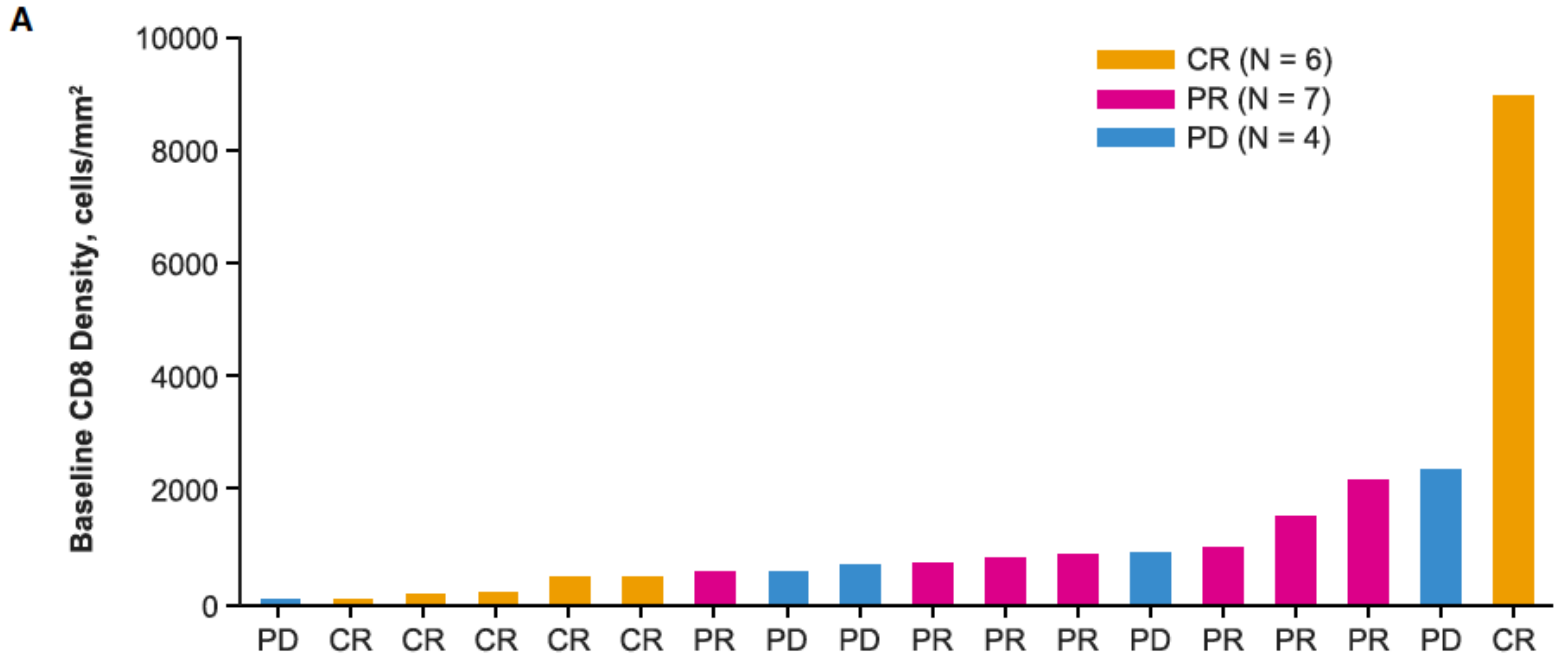
Oncolytic Virus Injection Promotes Intratumoral T Cell Infiltration to Improve Anti-PD-1 Immunotherapy



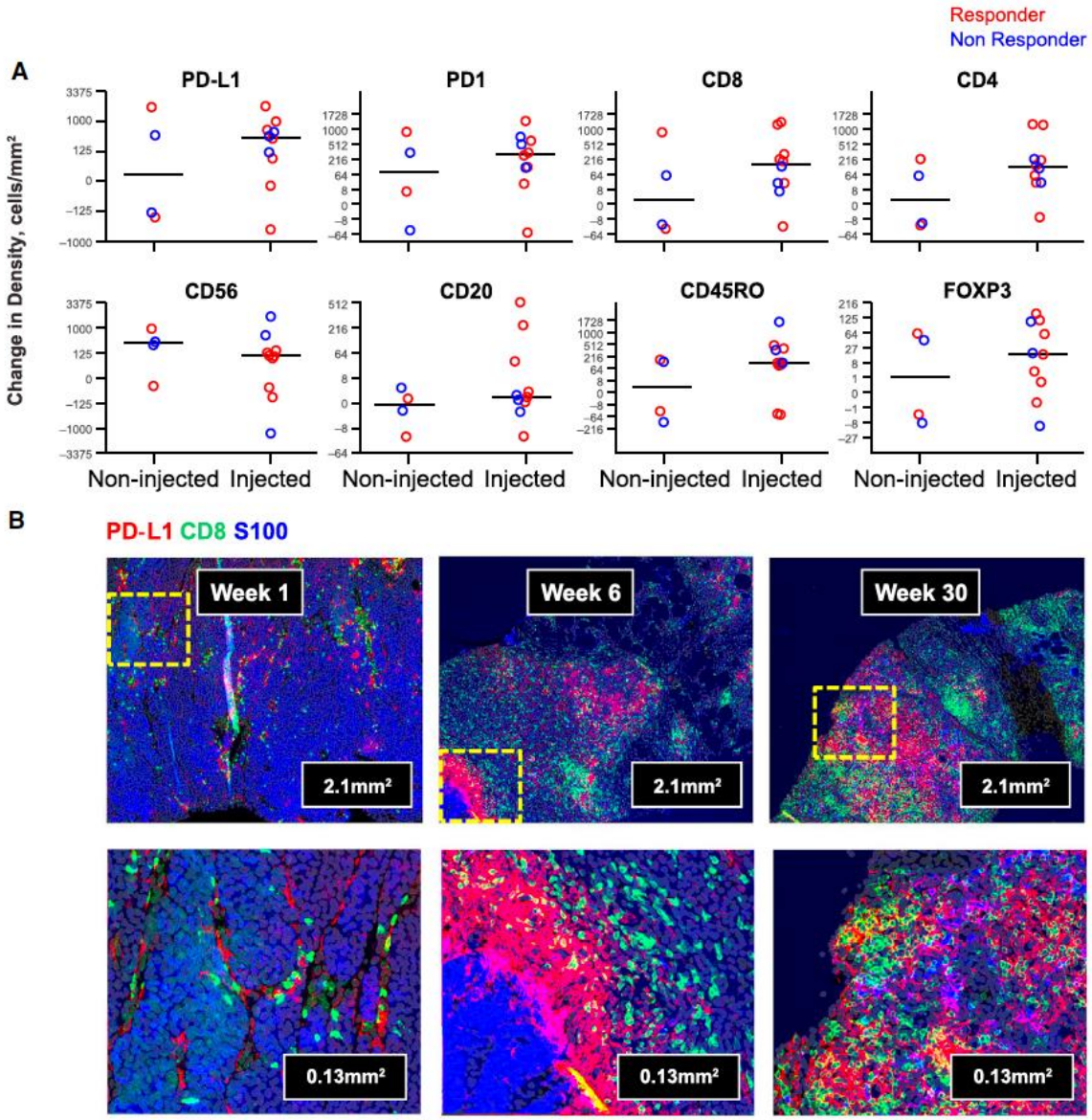
Ribas etal, CELL 2017

Combination of Talimogene Laherparepvec and Pembrolizumab Is Effective in Patients with Low Tumor CD8+ Density



Ribas etal, CELL 2017

Talimogene Laherparepvec Increases Tumor-Infiltrating Lymphocyte Density and PD-L1 Expression in Tumors



Ribas etal, CELL 2017

Combination Therapy Base on Tumor Sequencing

- **Tumor Genome sequencing:**

  MSI, PD-L1/2 amplification, viral genomes ➔ PD-1 therapy
  Identify which oncogenes are drug targets?
  Identify which mutations are immunogenic?

Sequence the tumor to identify mutations

- PD-1 blockade + personalized cancer vaccine
- PD-1 blockade + CAR-T cells
- PD-1 blockade + kinase inhibitors

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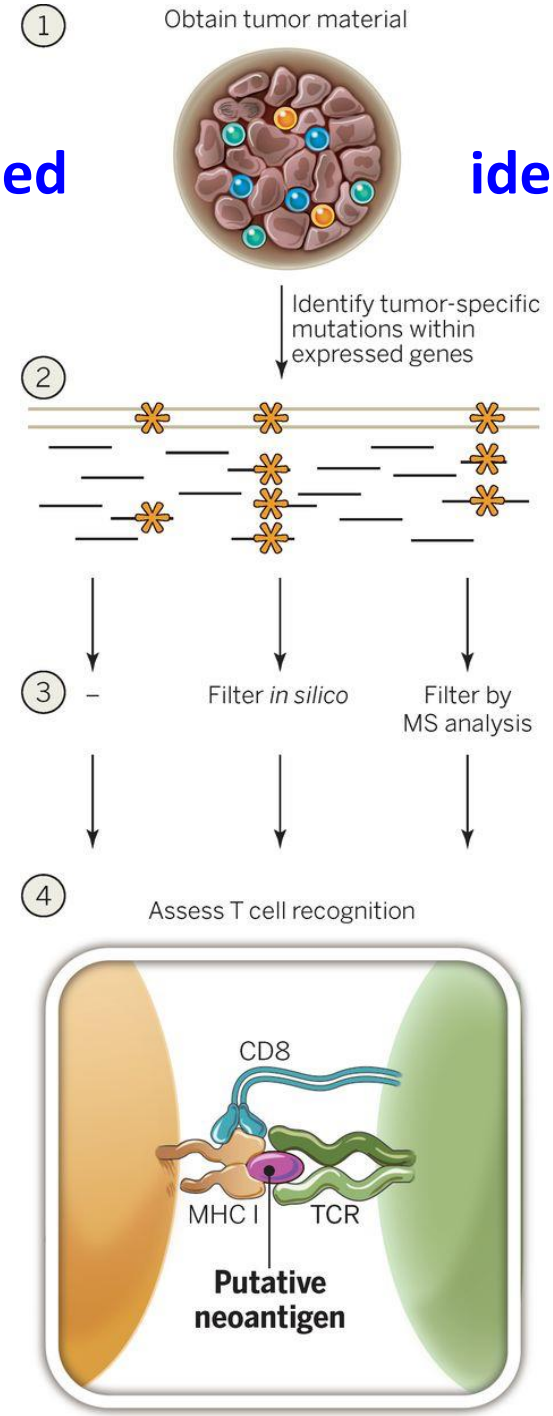
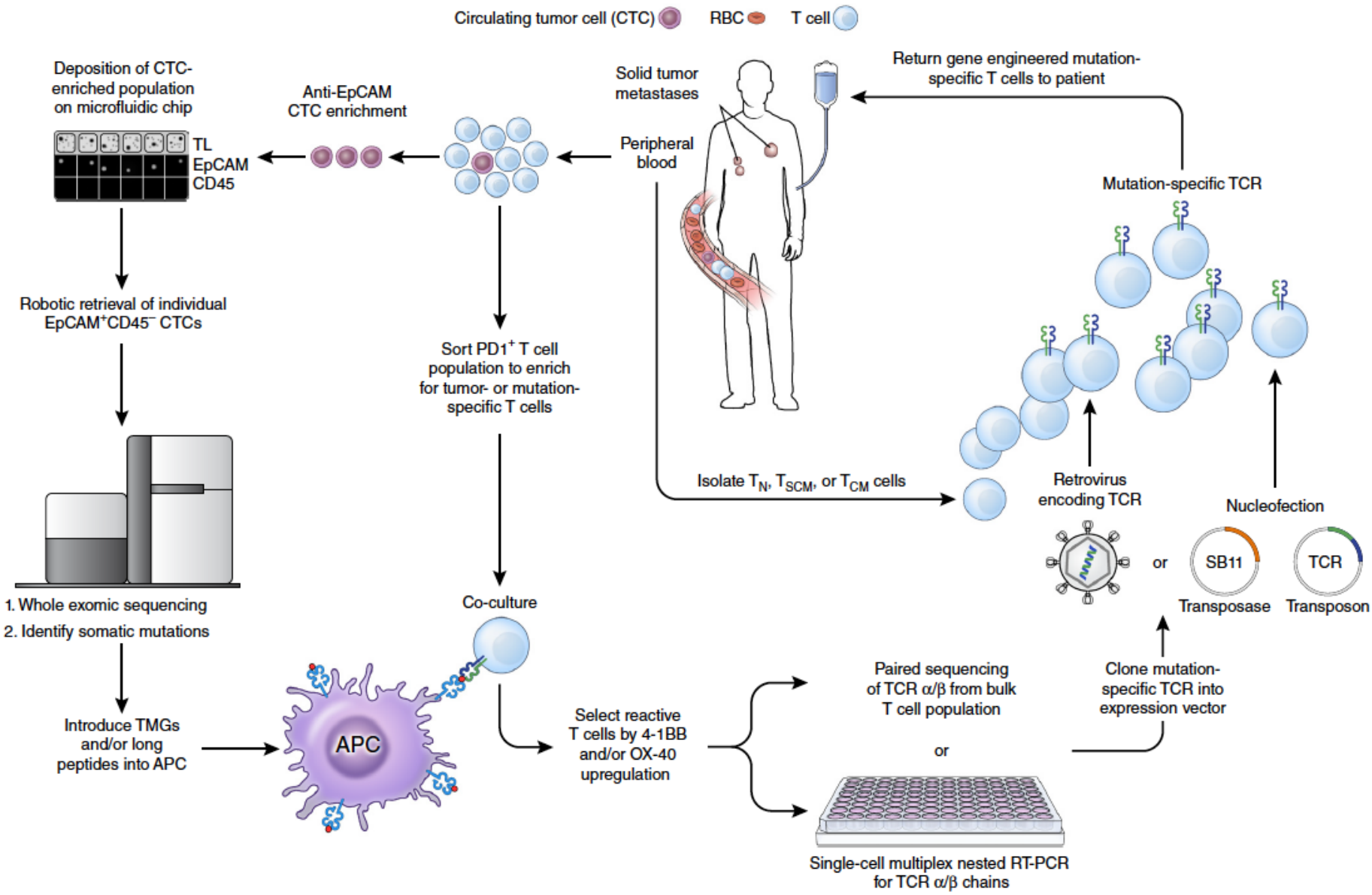
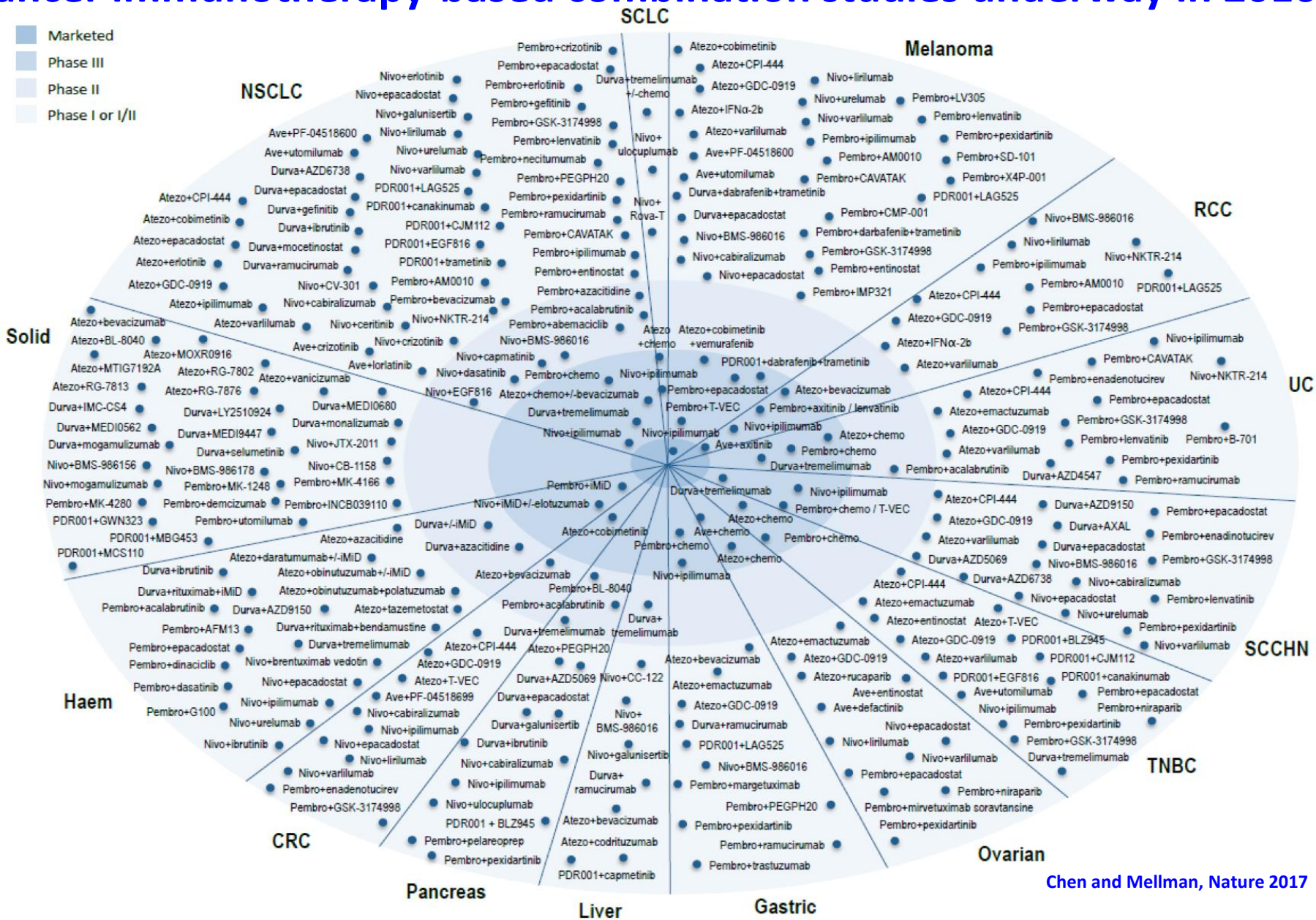
Cancer exome–based identification of neoantigens.



A pathway for generating autologous TCR gene therapies targeting neoantigens for patients with advanced epithelial cancers.



Cancer immunotherapy-based combination studies underway in 2016



Chen and Mellman, Nature 2017

A dramatic and unprecedented increase in clinical cancer immunotherapy combination studies (across Phase I, II and III trials) has occurred in recent years. The studies in this figure represent many of the current studies that include a PD-L1/PD-1 pathway inhibitor in combination with other immune modulators, targeted therapy, chemotherapy and/or radiation therapy. These studies are designed to characterize the efficacy, safety and biology related to combinability, synergy or antagonism associated with these combinations. Adapted from Vanessa Lucey of the Cancer Research Institute.

How to move forward

- **Targeting specific clinical settings**
  - Adjuvant therapy, Neoadjuvant therapy
  - Make immune-resistant tumor sensitive
  - Brain metastases
- **Biomarkers: predicting a response, predicting toxicity, pharmacodynamic changes, changes at progression**
  - Define who is likely to respond or;
  - Who will require additional therapy?
  - What is the best therapy to add?
  - Pretreatment; following therapy; at progression
  - PD-L1, IHC multiplex, MTB, neoepitopes (MANAs), RNA signature (inflammation, Y-IFN, T cell), CTLA-4/PD-1 T cells
- **Biopsies, Biopsies, Biopsies**
  - Try to develop situations to make biopsies easier- neoadjuvant
  - Find alternative sources of tissue- blood etc- cfDNA, WES, etc

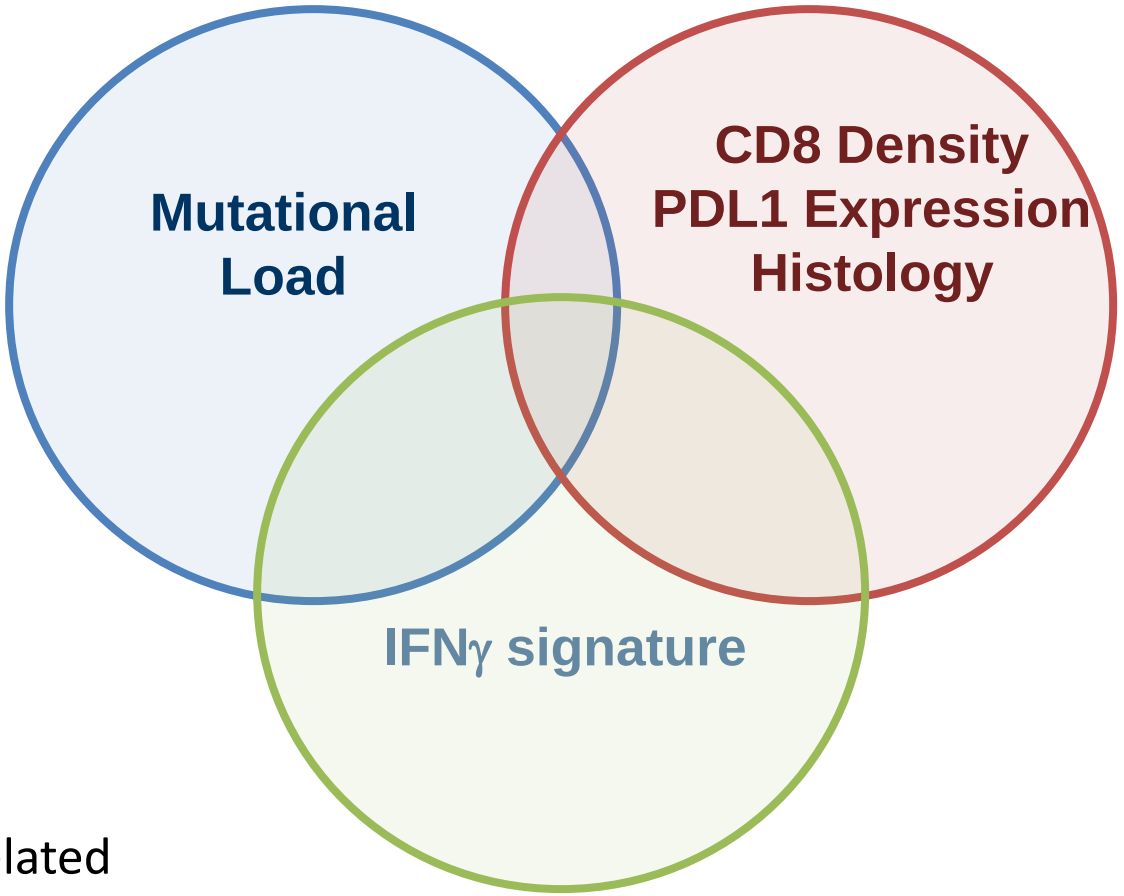
Summary

- What's required for effective Cancer Immunotherapy
- Combination Therapy –
  - Underway in full gear
  - Rationale for many combinations- selection
    - IDOi
    - Anti-LAG-3
    - Vaccines
    - Adoptive Cell Therapy
- Improving Patient Selection
    - Biomarker Development- **Too many**- how to simplify
    - Use to select the most effective
    - Use to select the least toxic

Cancer-immune phenotypes.

Chen and Mellman, Nature 2017

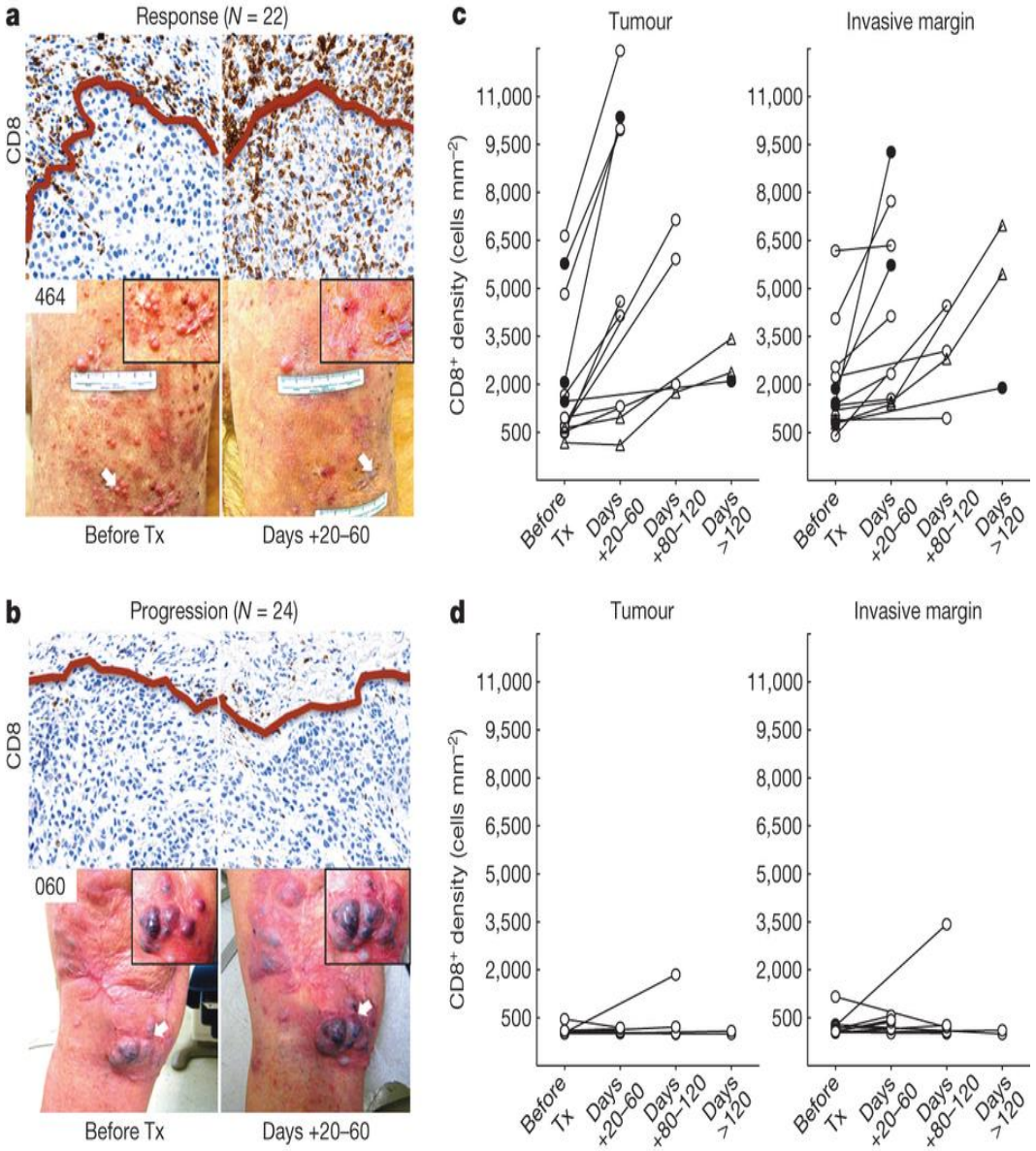
Biomarker Model



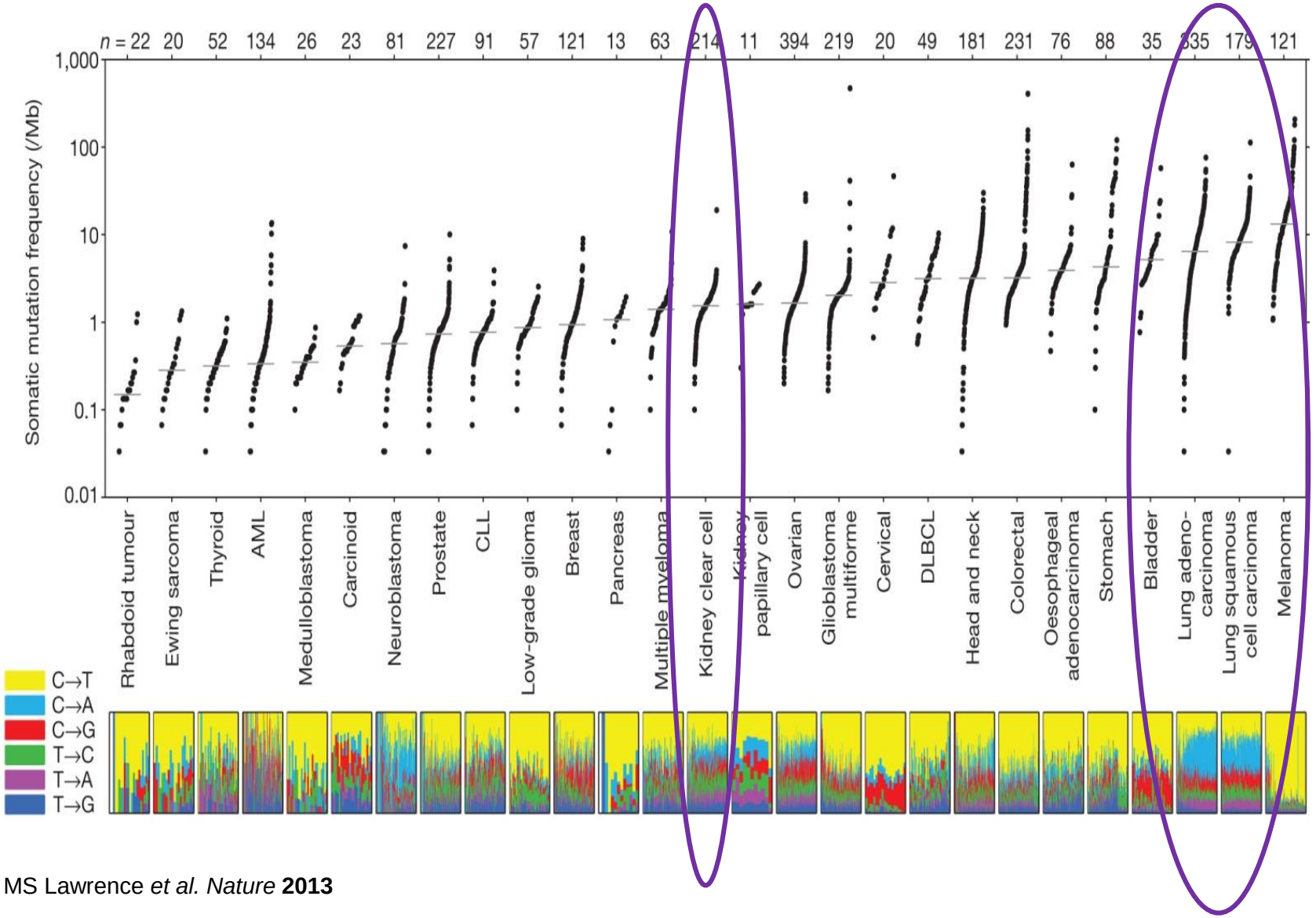
- All inter-related
- Some tumors may have a larger sweet spot

M Atkins with permission.

CD8+T cell Density within the Tumor and at Invasive Margin Importance



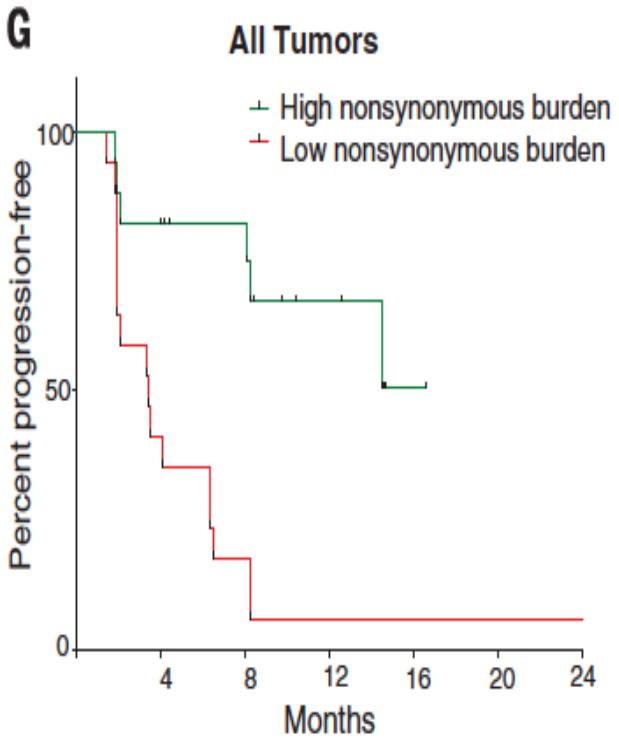
Somatic mutations by tumor type



MS Lawrence *et al. Nature* **2013**

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

Naiyer A. Rizvi,[1,2*†] Matthew D. Hellmann,[1,2*] Alexandra Snyder,[1,2,3*] Pia Kvistborg,[4] Vladimir Makarov,[3] Jonathan J. Havel,[3] William Lee,[5] Jianda Yuan,[6] Phillip Wong,[6] Teresa S. Ho,[6] Martin L. Miller,[7] Natasha Rekhtman,[8] Andre L. Moreira,[8] Fawzia Ibrahim,[1] Cameron Bruggeman,[9] Billel Gasmi,[10] Roberta Zappasodi,[10] Yuka Maeda,[10] Chris Sander,[7] Edward B. Garon,[11] Taha Merghoub,[1,10] Jedd D. Wolchok,[1,2,10] Ton N. Schumacher,[4] Timothy A. Chan[2,3,5‡]



3 APRIL 2015 • VOL 348 ISSUE 6230

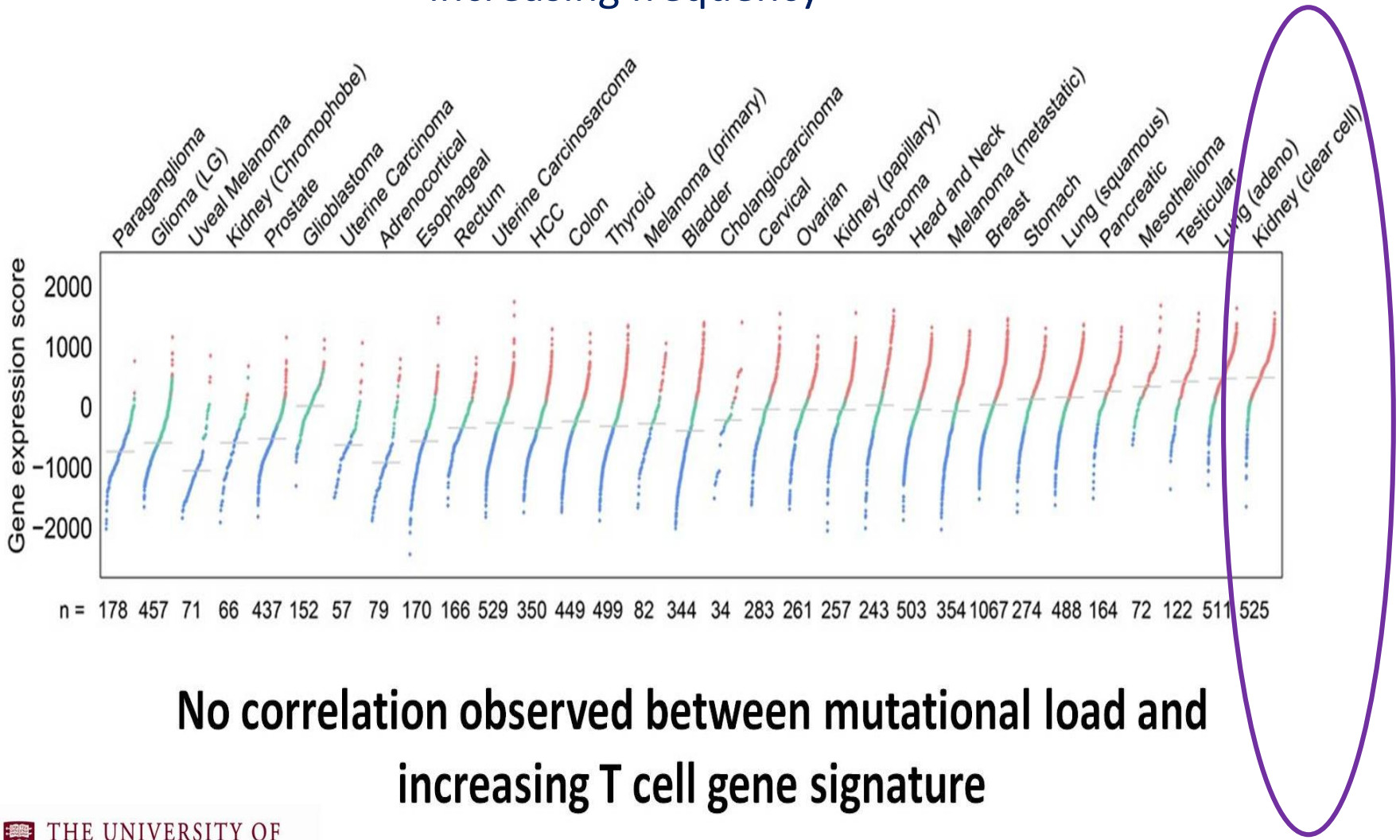
Hypothesis:
PD-1 Blockade works in patients with most “mutated” / “immunogenic” cancers.

This data supports hypothesis

B Fox CFDA

Science
AAAS

T cell-inflamed tumor microenvironment by tumor type in increasing frequency



No correlation observed between mutational load and increasing T cell gene signature

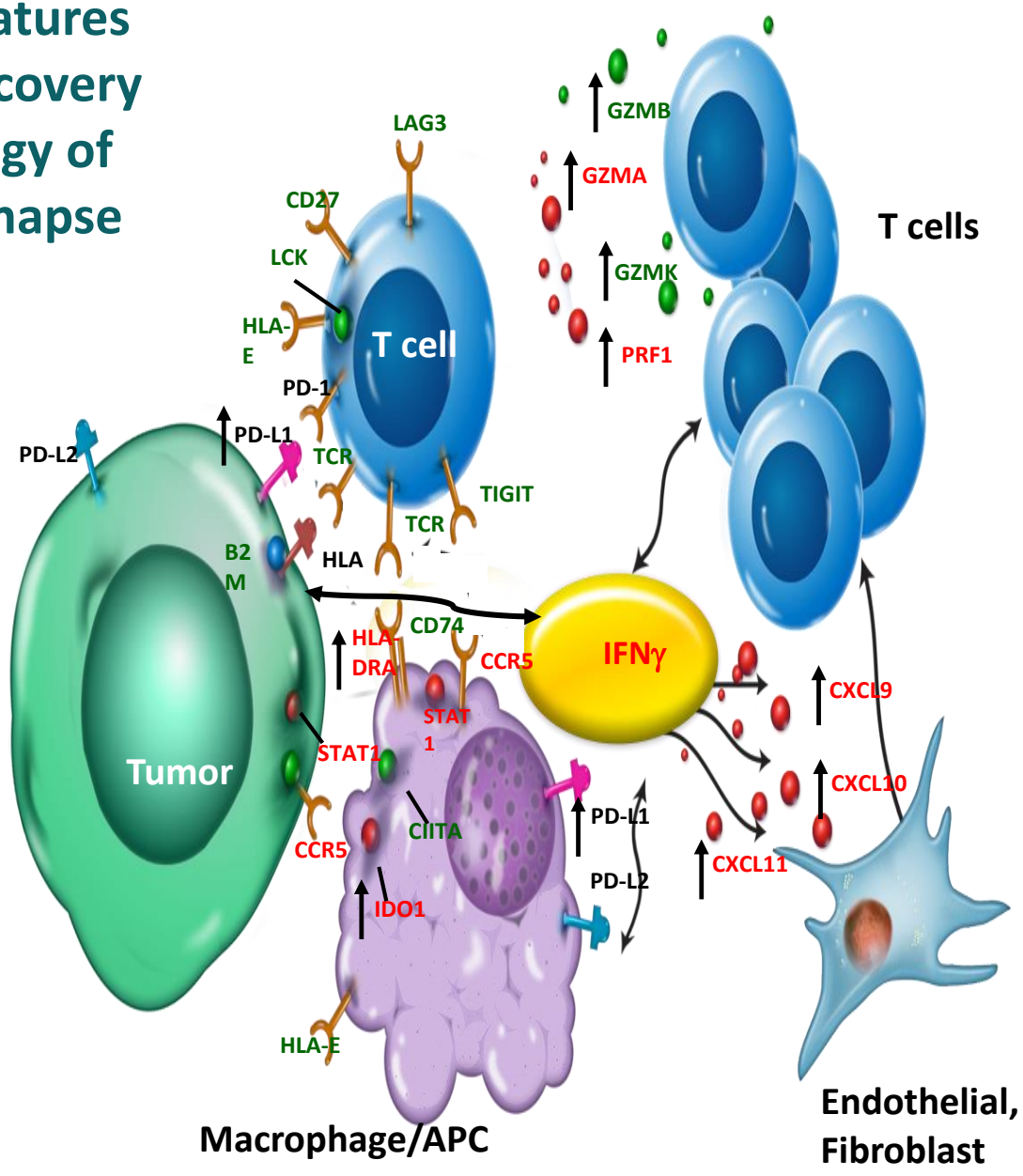
THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Presented By Jason Luke at 2016 ASCO Annual Meeting

Expanded Gene Signatures Identified During Discovery Analysis Reveal Biology of Complex Immune Synapse

Discovery analysis of entire NanoString melanoma data set led to identification of new genes:

- **IFNγ signaling**
- **MHC class I and II antigen presentation machinery**
- **T-cell activation markers**



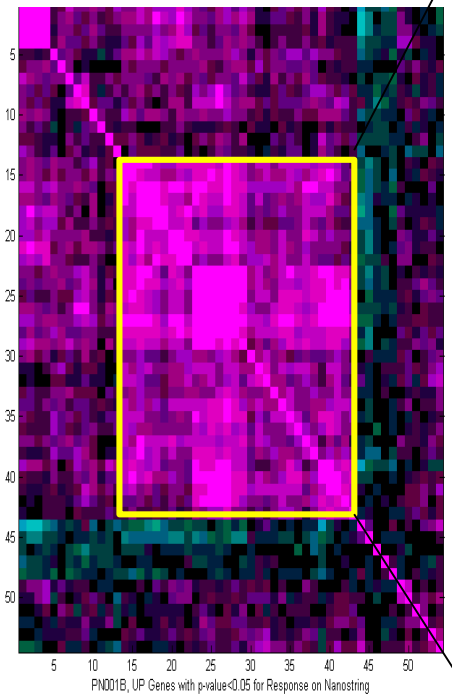
Signature Expanded in Validation Set
(While Blinded to Clinical Outcome)

Melanoma Discovery Set

19 Patients

Melanoma Validation Set

62 Patients Independent Data Set

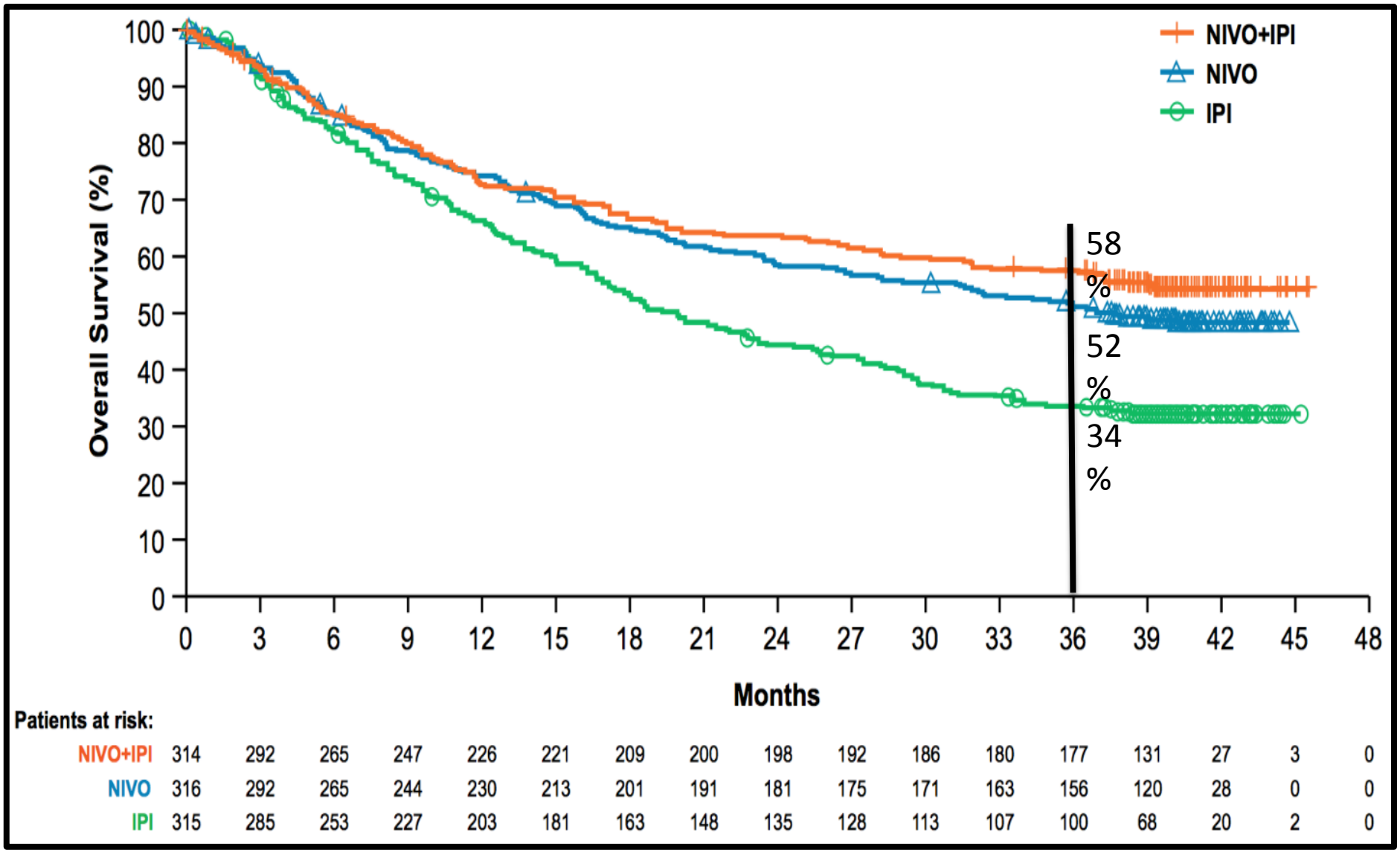


Correlation Matrix of Top Significant Genes in the Discovery Set Evaluated in the Validation Set

IL2Rg
CXCR6
CD3d
CD2
ITGAL
TAGAP
CIITA
HLA-DRA
PTPRC
CXCL9
CCL5
NKG7
GZMA
PRF1
CCR5
CD3e
GZMK
IFNγ
HLA-E
GZMB
PDCD1
SLAMF6
CXCL13
CXCL10
IDO1
LAG3
STAT1
CXCL11

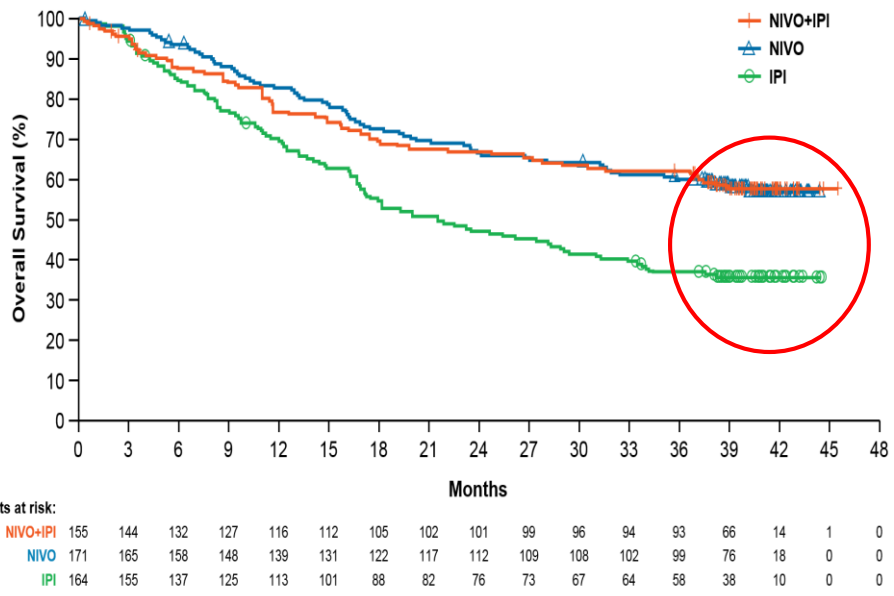
"Preliminary Expanded Immune" (28-gene) signature: coherent set correlated with the 10-gene "Preliminary IFNγ" signature genes (in red)

Overall Survival in All Randomized Patients : 067 Ipi+ Nivo vs Nivo vs Ipi

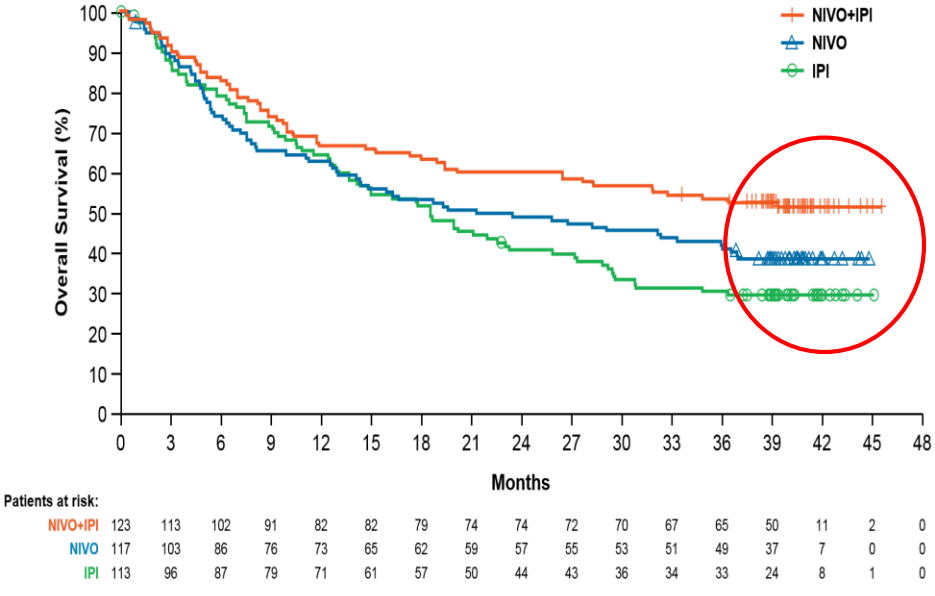


Can PD-L1 IHC Determine Cohort that Benefits from Combination Therapy vs Single agent Therapy?

PD-L1 expression level ≥1%



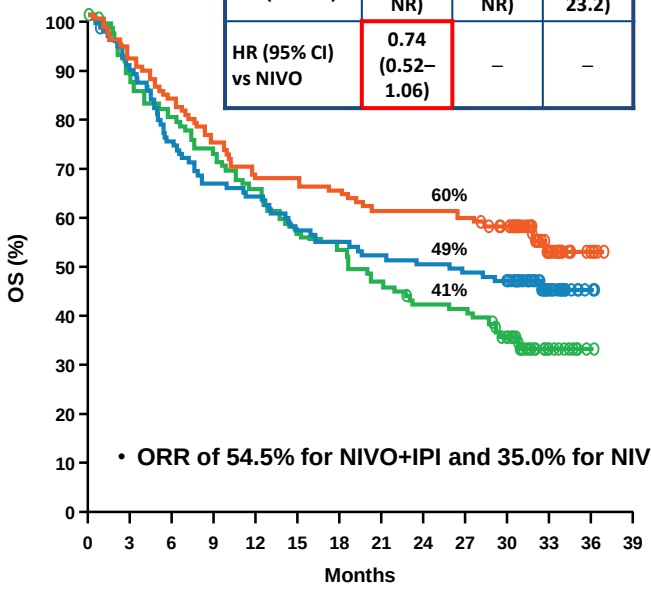
PD-L1 expression level <1%



Outcomes Observed at a 1% Cutoff

PD-L1 Expression Level <1%

<1% PD-L1	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR (26.5–NR)	23.5 (13.0–NR)	18.6 (13.7–23.2)
HR (95% CI) vs NIVO	0.74 (0.52–1.06)	–	–



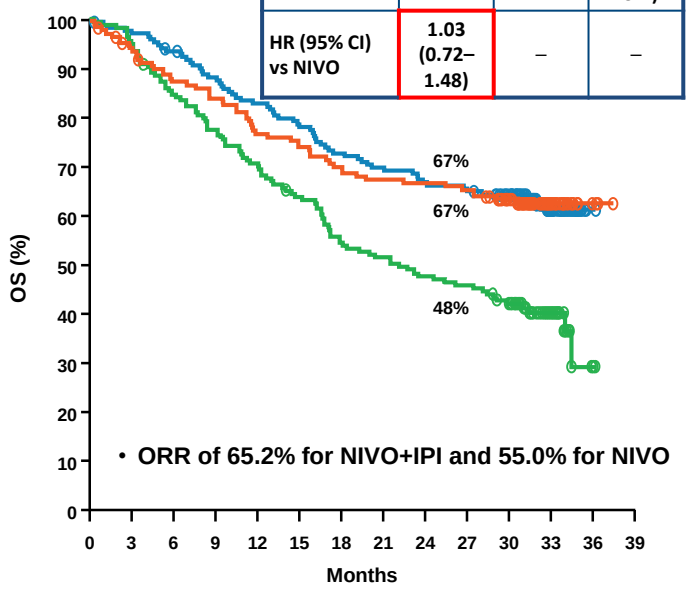
- ORR of 54.5% for NIVO+IPI and 35.0% for NIVO

Patients at risk:

NIVO+IPI	123	113	102	91	82	82	79	74	74	72	66	18	4	0
NIVO	117	103	86	76	73	65	62	59	57	55	50	16	2	0
IPI	113	96	87	79	71	61	57	50	44	43	32	10	1	0

PD-L1 Expression Level ≥1%

≥1% PD-L1	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR	NR	22.1 (17.1–29.7)
HR (95% CI) vs NIVO	1.03 (0.72–1.48)	–	–



- ORR of 65.2% for NIVO+IPI and 55.0% for NIVO

Patients at risk:

NIVO+IPI	155	144	132	127	116	112	105	102	101	99	85	27	3	0
NIVO	171	165	158	148	139	131	122	117	112	109	98	36	1	0
IPI	164	155	138	126	115	102	89	83	77	74	64	21	2	0

Tumor Type

ICOS

PD-L1

Intratumoral FOXP3 & IDO

Treg

TCR Clonality

Intratumoral CD8+/FOXP3+

Mutation Burden

Microbiota

NY-ESO-1

IL-17 CD4+ cells

Absolute lymphocyte count

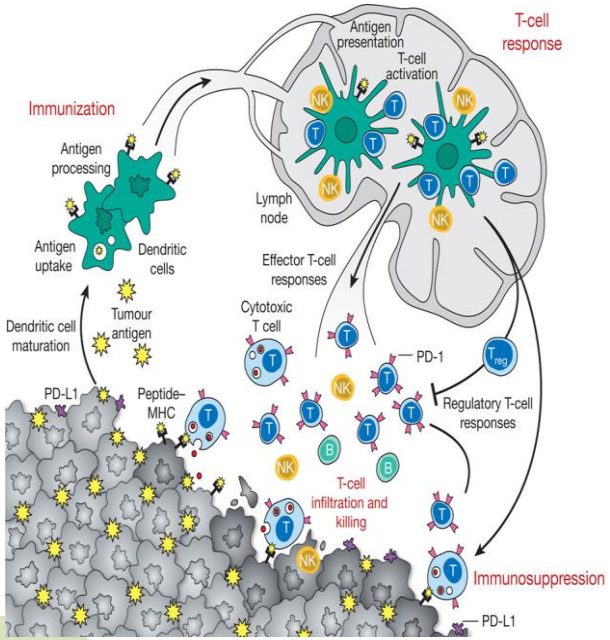
Prior Therapies?

"Inflamed" microenvironment

MDSC

CD45RO

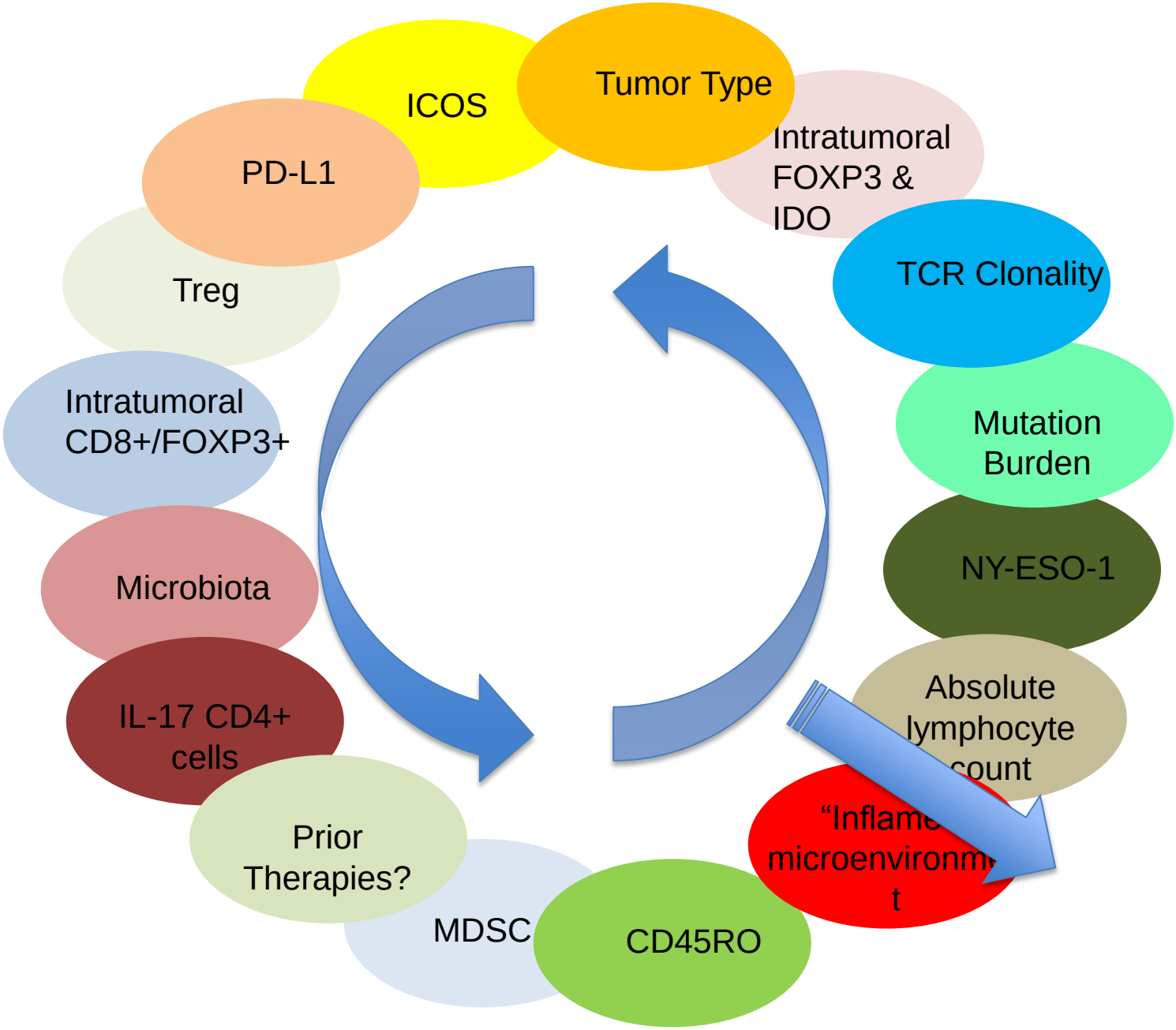
Mellman et al. Nature 2011



Yuan et al, PNAS 2011;
DiGiacom lo et al Cancer Immunol Immunother 2013;
Queirolog et al,Cancer Invest 2013;
Wolchok et al,Cancer Immun 2010;
Tumeh et al Nature 2105;
Snyder et al NEJM 2014;
Rizvi et al Science 2015;
Van Allen et al Science 2105;
Sivan et al Science 2015;
Vetizou et al Science 2015;
Rosenberg et al Lancet 2016

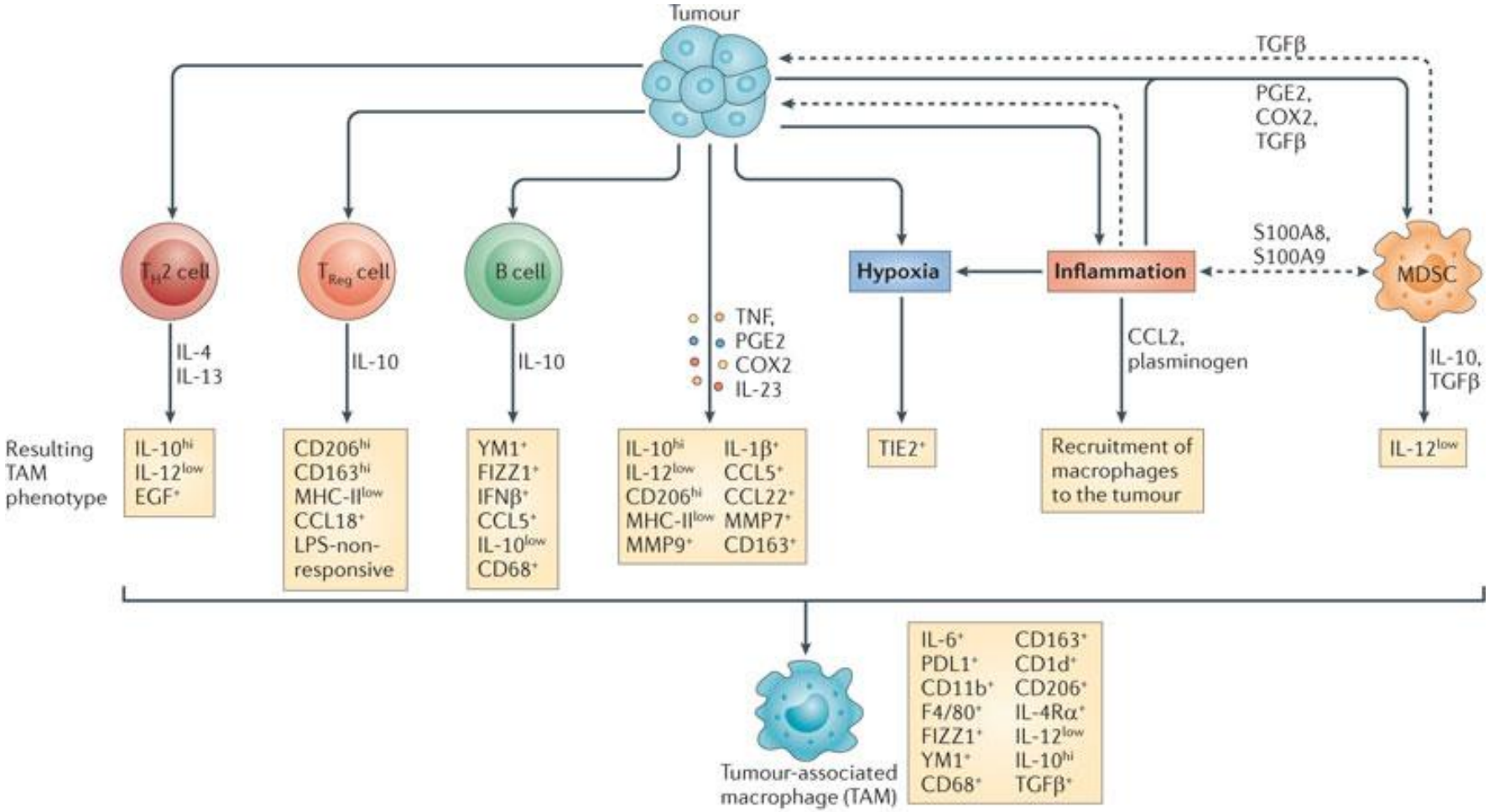
Ku et al Cancer 2010;
Menard et al Clin Cancer Res 2008;
Weber et al JCO 2009;
Hodi et al PNAS 2008;
Hamid et al JCO 2009;
Ng et al Cancer Immuno Res 2013;
Tarhini et al PLoS One 2014;
Kitano et al Cancer Immunol Res 2013;
Spranger et al Sci Transl Med 2013;
Kitano et al Cancer Immunol Res 2014;
Ji RR et al, Cancer Immunol Immunother 2012;

Presented by: Alexandra Snyder, M.D.



Presented by: Alexandra Snyder, M.D.

Tumor Interactions to Suppress the Immune System



Nature Reviews | Immunology

Overcome Tumor -Induced Immune Suppression

The Barriers

- Cell Populations
- Soluble Factors
- Immune checkpoints
- Loss of Tumor Antigens