Society for Immunotherapy of Cancer (SITC)

Understanding Checkpoint Inhibitors: Approved Agents, Drugs in Development and Combination Strategies

Jeffrey A. Sosman
Vanderbilt-Ingram Cancer Center

Advances in Cancer Immunotherapy™ - Nashville
October 2, 2015

Society for Immunotherapy of Cancer

Disclosures

Consulting Fees:

- Merck & Co.
- Genentech

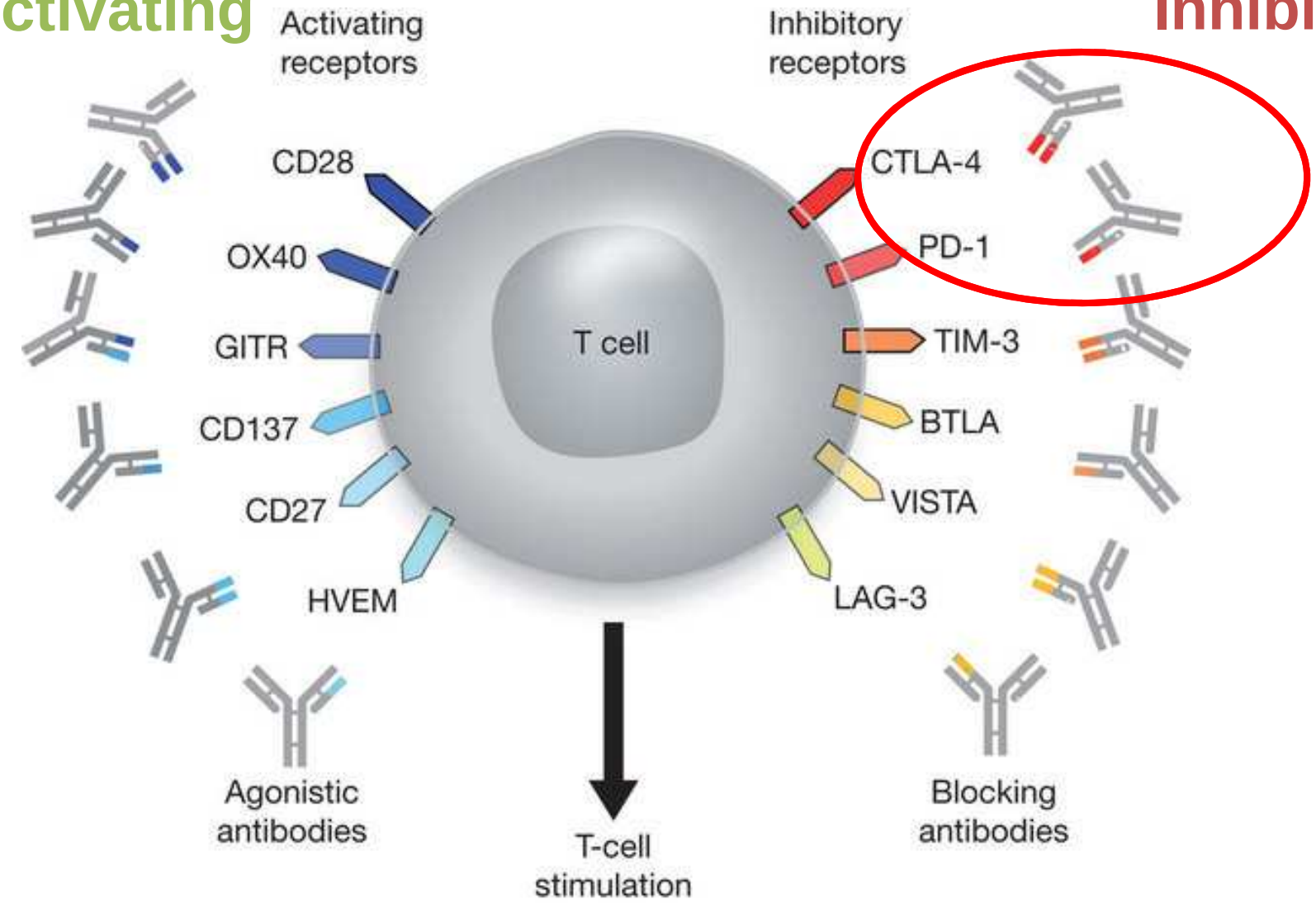
Research Support

- Glaxo Smith Kline
- Bristol Myers Squibb

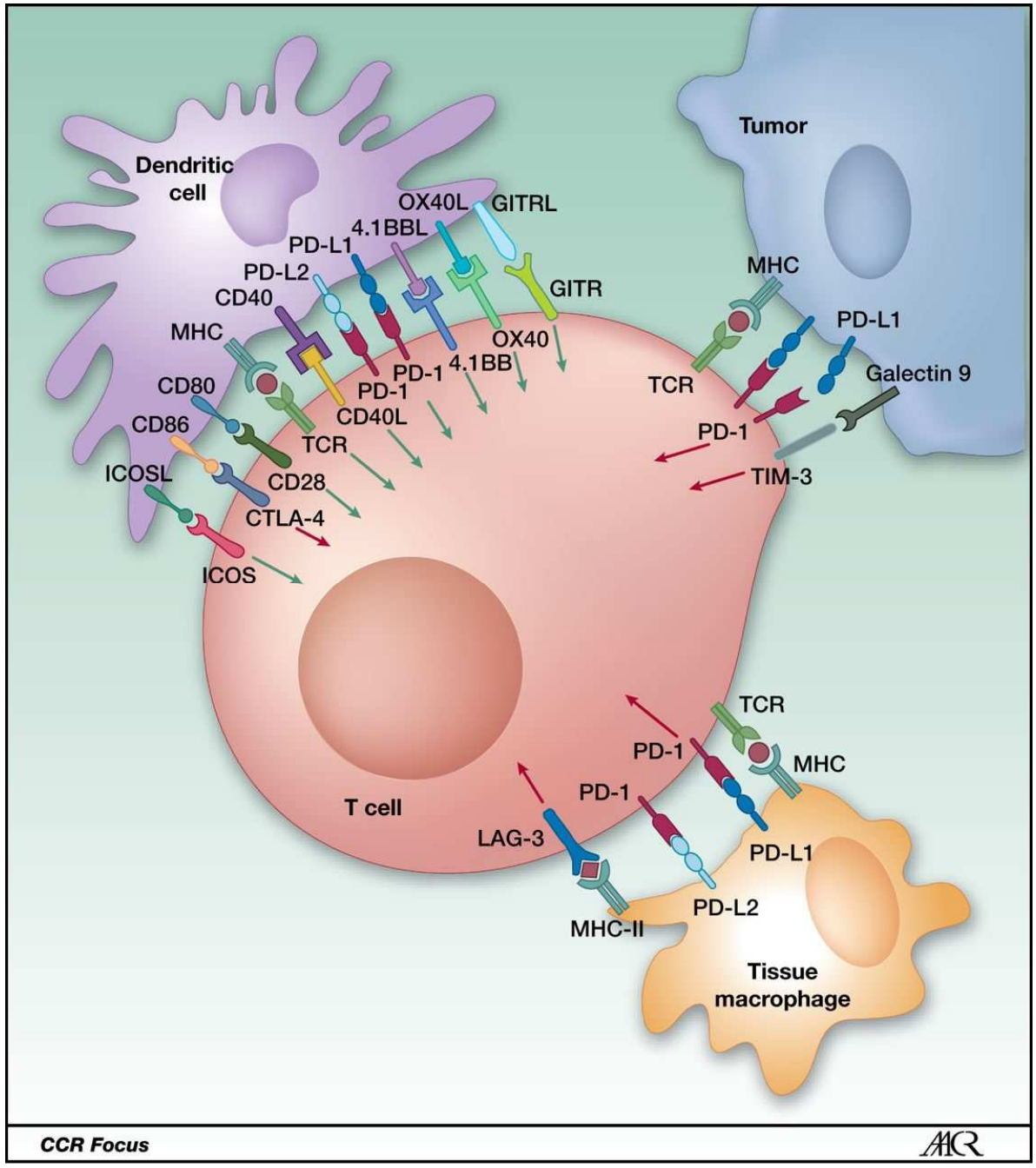
I will be discussing the use of products for non-FDA approved indications

Checkpoint Receptors

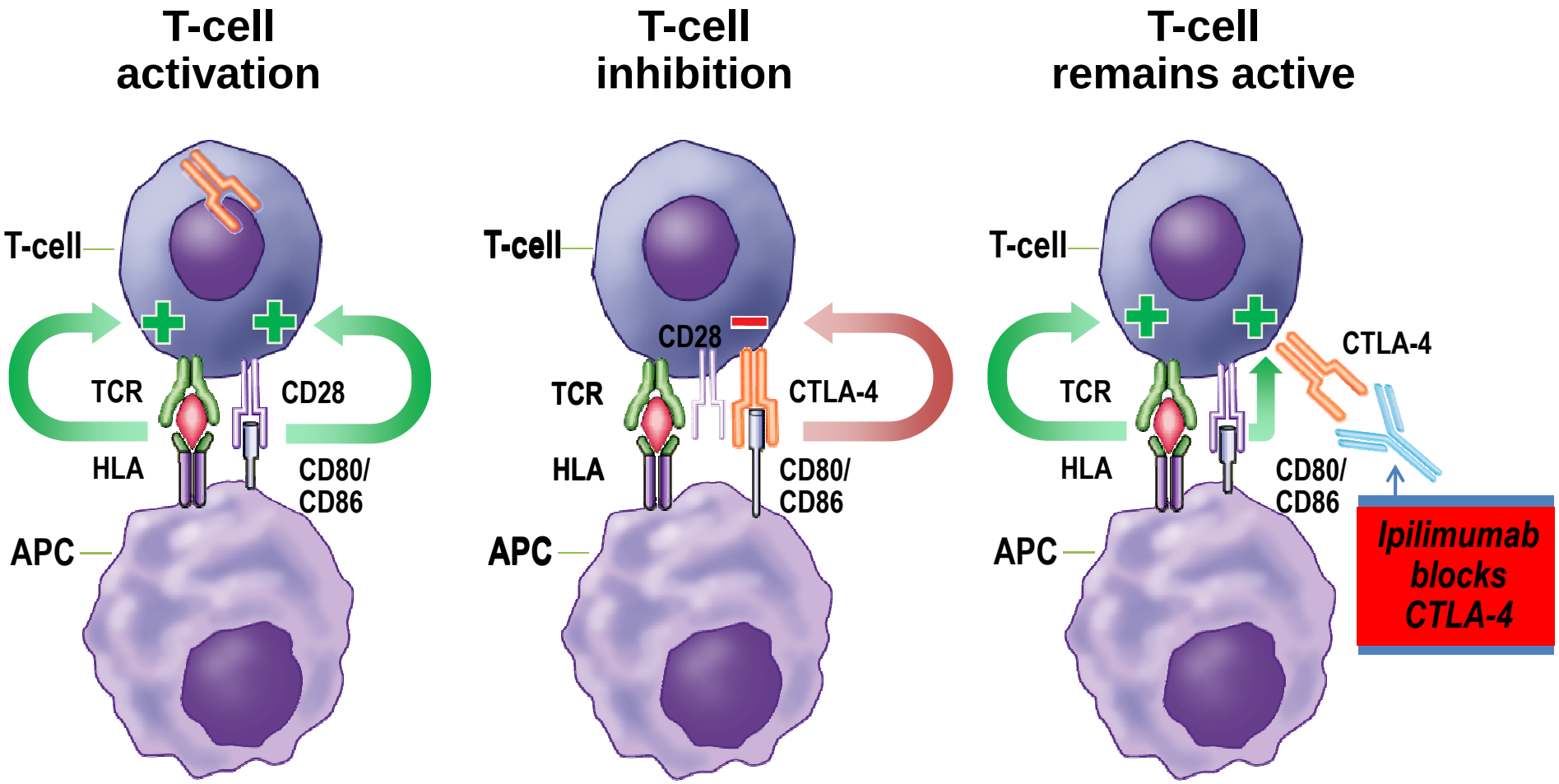
Activating **Inhibiting**



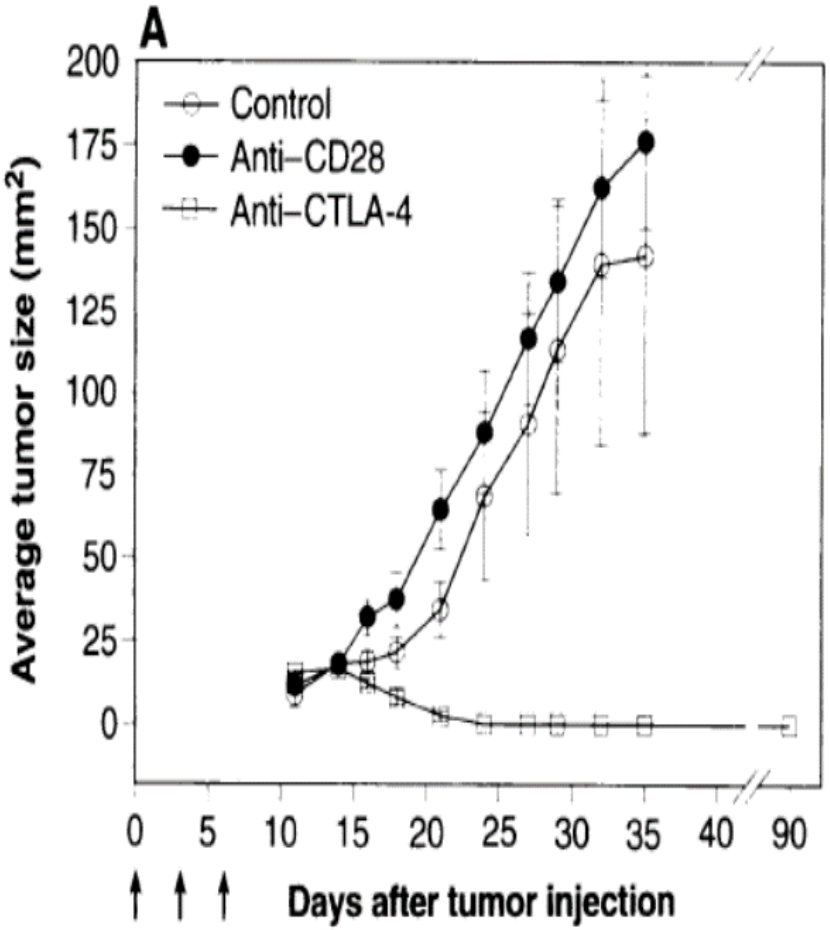
Mellman, Nature, 2011


Dendritic cell
Tumor
OX40L
GITRL
4.1BBL
PD-L1
PD-L2
CD40
MHC
GITR
OX40
4.1BB
PD-1
CD80
CD40L
CD86
TCR
ICOSL
CD28
CTLA-4
ICOS
MHC
PD-L1
Galectin 9
TCR
PD-1
TIM-3
T cell
TCR
PD-1
MHC
PD-1
LAG-3
PD-L1
PD-L2
MHC-II
Tissue macrophage

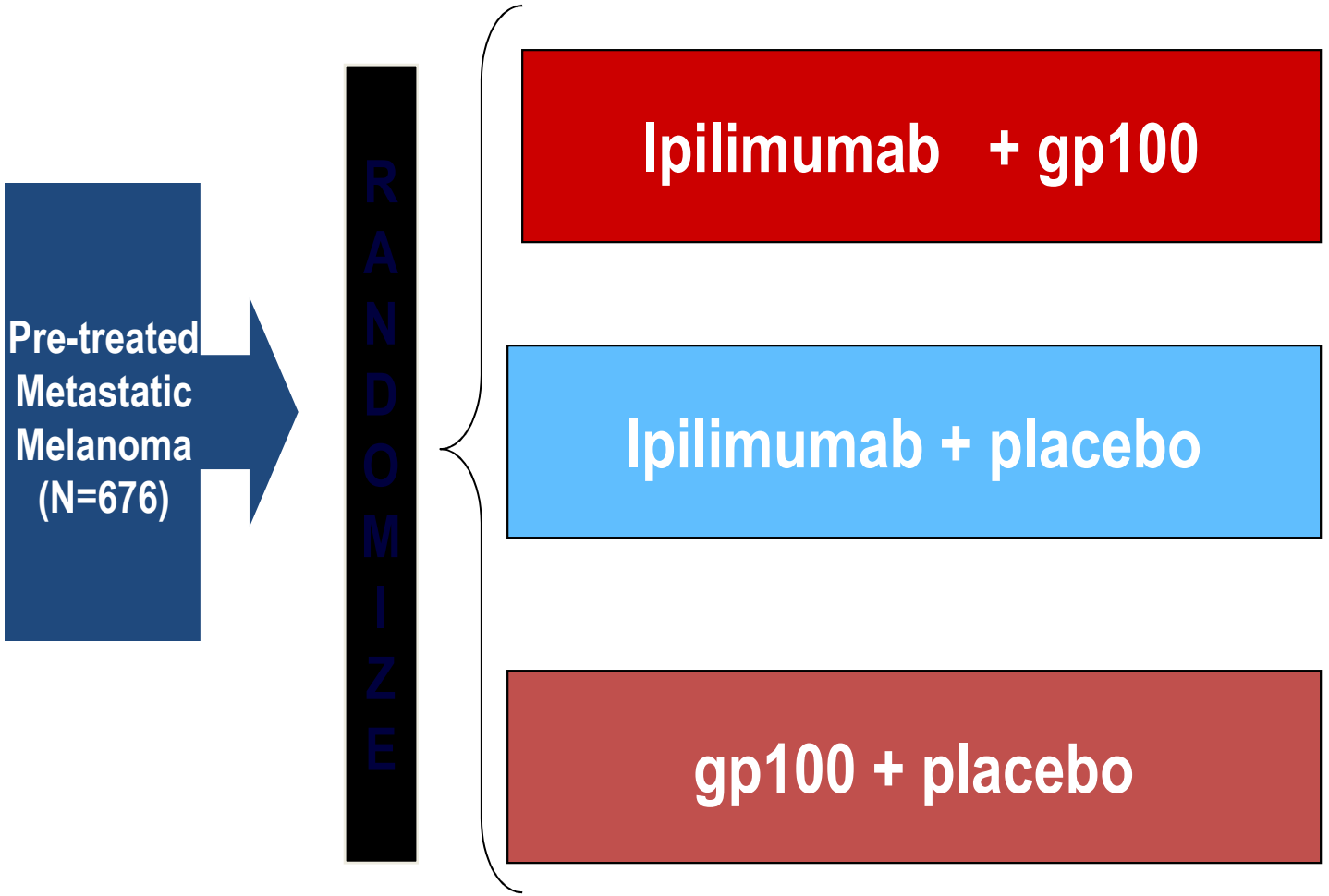
Ipilimumab Augments T-Cell Activation and Proliferation

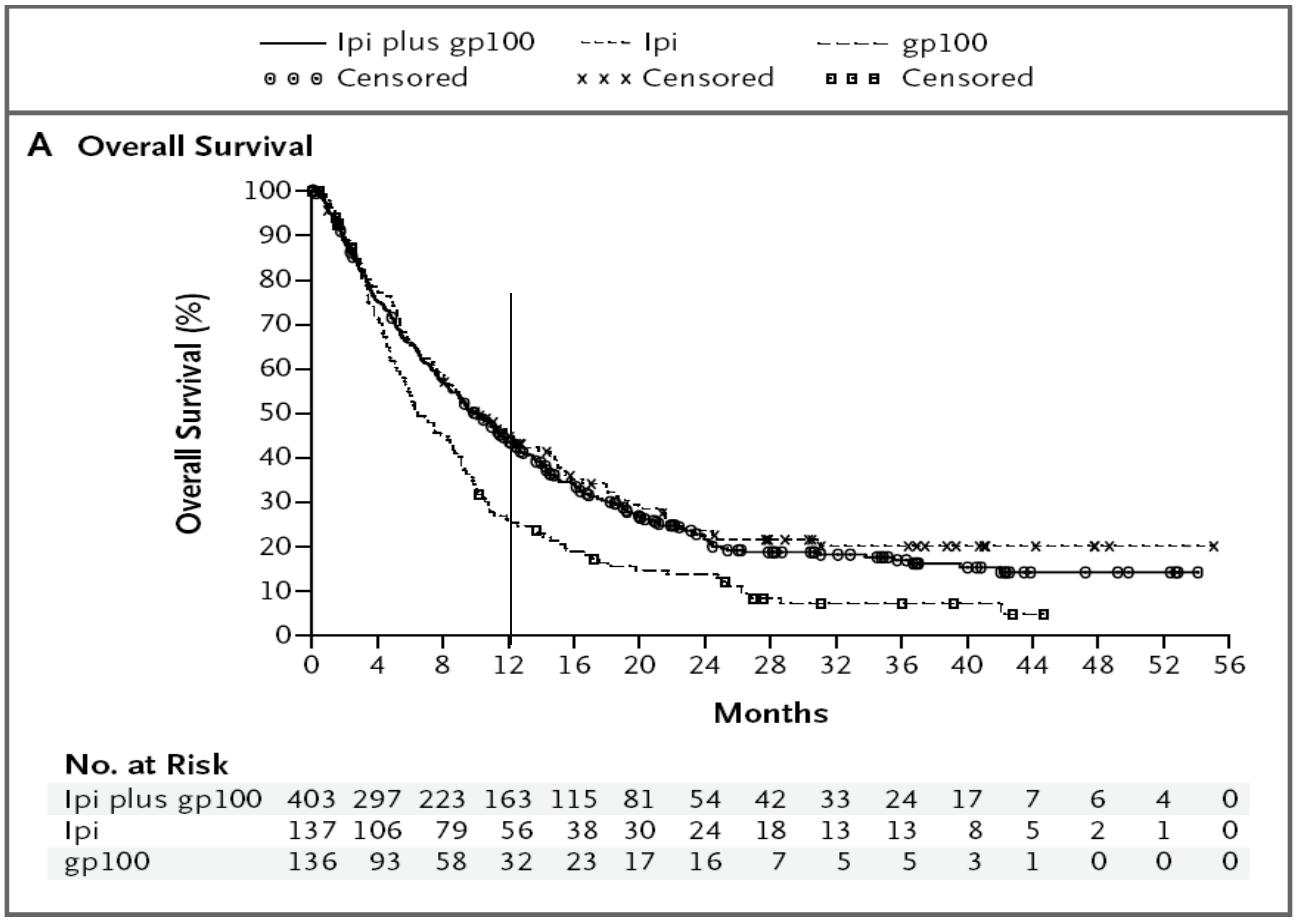


Adapted from O'Day et al. Plenary session presentation, abstract #4, ASCO 2010.


A
Control
Anti–CD28
Anti–CTLA-4
Average tumor size (mm²)
200
175
150
125
100
75
50
25
0
0
5
10
15
20
25
30
35
40
90
Days after tumor injection

Pivotal 2nd Line Phase III Trial Study Design





Survival Rate	Ipilimumab + gp100	Ipilimumab alone	gp100 alone
1-yr	44%	46%	25%
2-yr	22%	24%	14%

N ENGL J MED 363;8 NEJM.ORG AUGUST 19, 2010

Immune-Related Adverse Events

- Rash (approx 20%)
- Colitis/enteritis (approx 15%)
- Elevated AST/ALT (approx 10%)
- Endocrinopathies: Thyroiditis, Hypophysitis, Adrenal insufficiency(2-5%)

Severity is inversely related to vigilance of surveillance.
If detected early, most are easily treated and reversible.

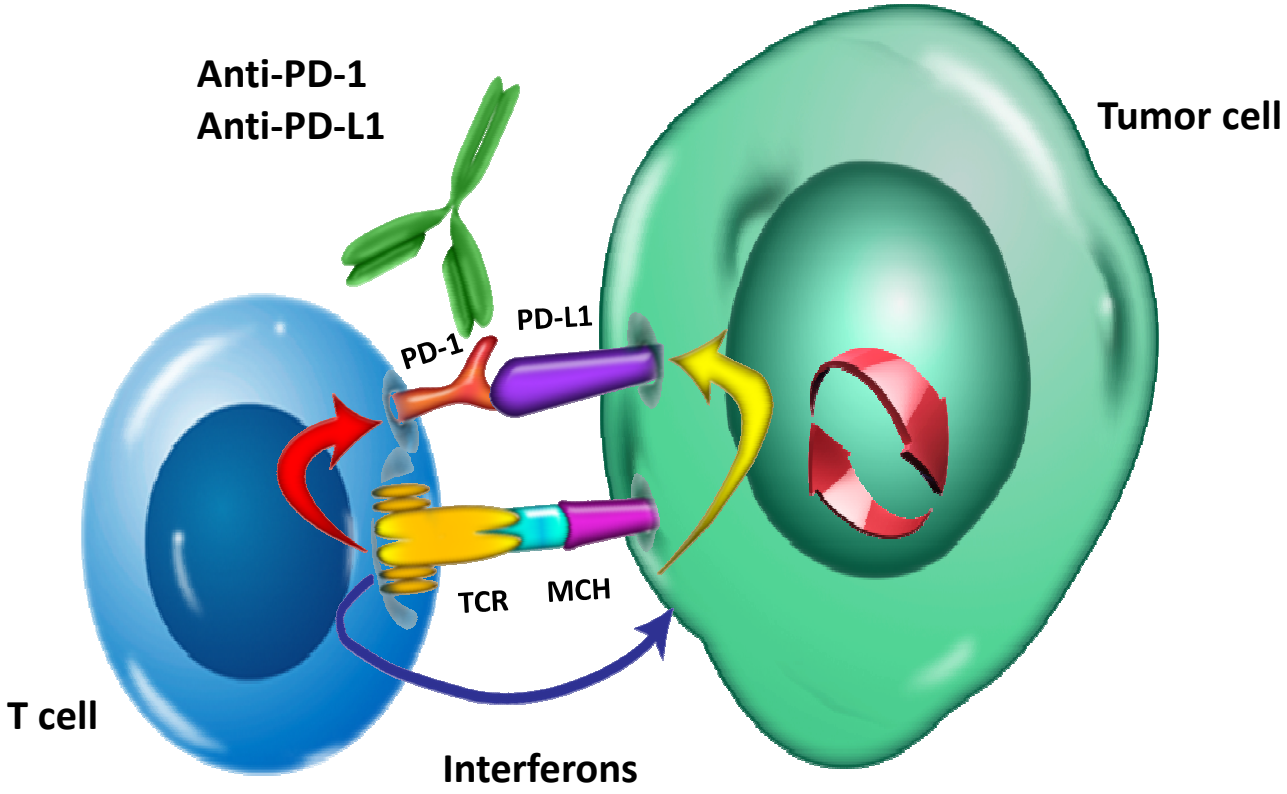
Four Patterns of Response to Ipilimumab Therapy Observed

- 2 conventional:
  - Response in baseline lesions
  - ‘Stable disease’ with slow, steady decline in total tumor volume
- 2 novel:
  - Response after initial increase in total tumor volume
  - Response in index plus new lesions at or after the appearance of new lesions

Overall Response Criteria using the irRC

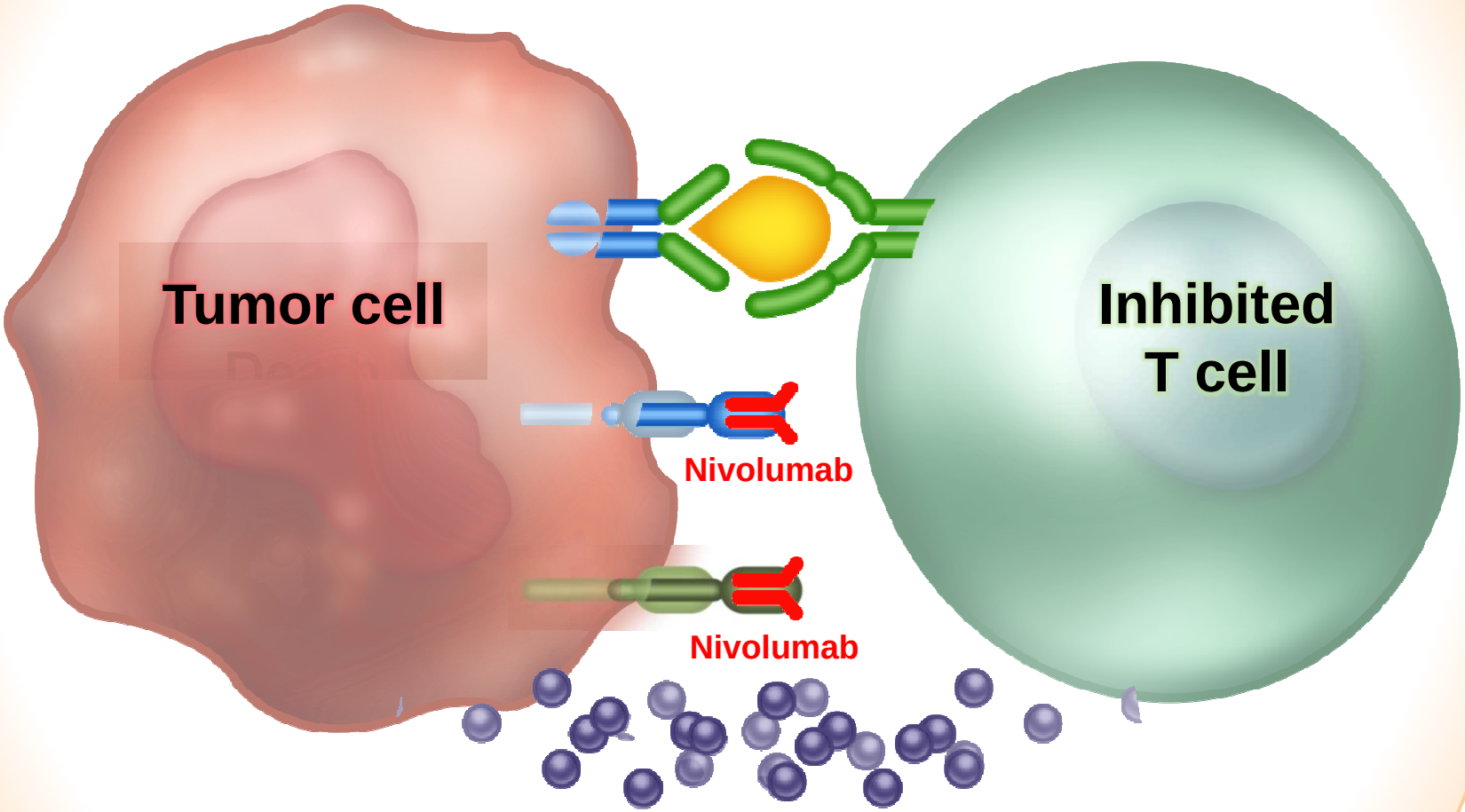
- At the baseline tumor assessment, the sum of the **products of the two largest perpendicular diameters (SPD)** of all index lesions
- The overall response according to the irRC is derived from time-point response assessments (based on tumor burden) as follows:
- irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions)
  - confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented
- irPR, decrease **in tumor burden ≥50% relative to baseline**
  - confirmed by a consecutive assessment at least 4 wk after first documentation
- irSD, not meeting criteria for irCR or irPR, in absence of irPD
- **irPD, increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden)**
  - **confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented**

Mechanism of Action of Anti–PD-1 Therapy: Inhibition of Adaptive Immune Resistance



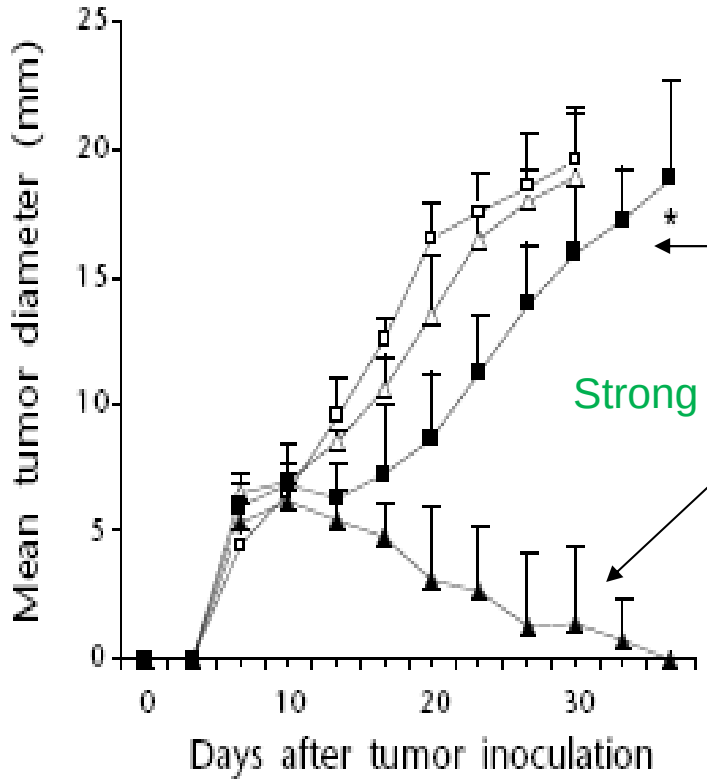
Pardoll DM et al. *Nat Rev Cancer*. 2012;12:252-64; Taube JM et al. *Sci Transl Med*. 2012;4:127ra37; Tumeh P et al. *Nature*. 2014;515:568-71.

PD-1/PD-L1/L2 MOA



Tumor Microenvironment

B7-H1 (PD-L1) negates positive co-stimulation in tumor cells



Expression of checkpoint blocks effect of strong co-stimulation

+ B7.1
and B7-H1

Strong co-stimulation → tumor regression

+B7.1

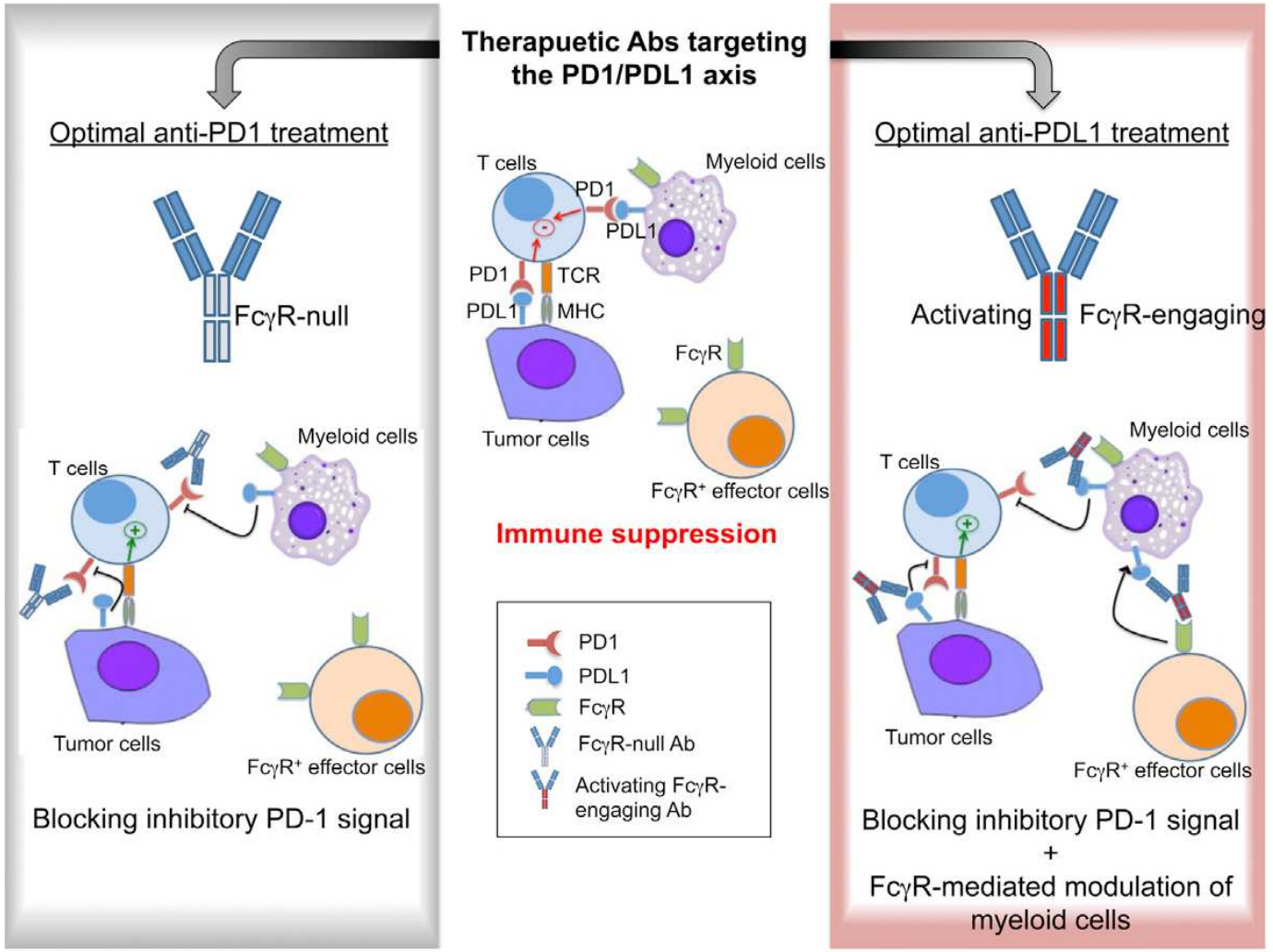
22/22 human melanomas expressed B7-H1,

17/22 at 2-3+ intensity

Open triangle – P815
Rectangles – P815/B7-H1
Closed triangle – P815/B7-1
Closed squares – P815/B7-1/B7-H1

Dong et al, Nat Med, 2002

FcγRs Modulate the Anti-tumor Activity of Antibodies Targeting the PD-1/PD-L1 Axis by Different Mechanisms for anti-PD1 and anti-PDL1



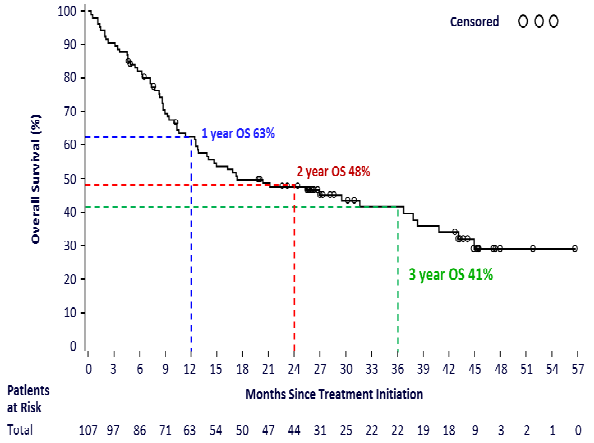
Dahan R etal, Cancer Cell 2015

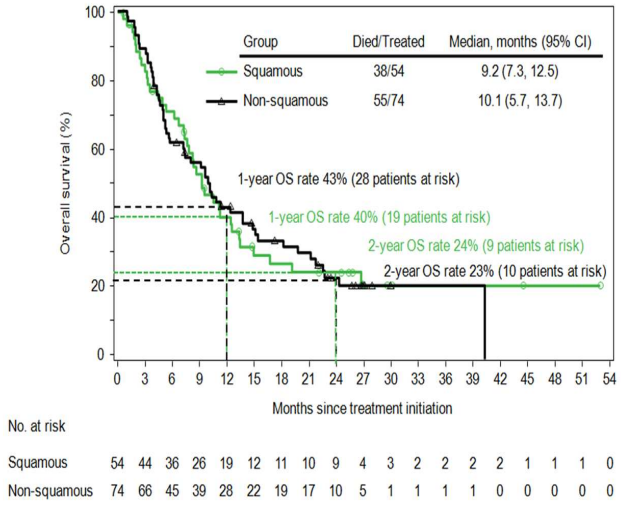
Clinical Activity of Nivolumab (anti-PD-1) (Phase 1 Multi-Dose Trial)

Dose mg/kg	ORR % (n/N)	Estimated Median DOR Weeks (Range)	Stable Disease Rate ≥24 Wks % (n/N)	Median PFS Months (95% CI)
NSCLC	17 (22/129)	74 (6+, 134+)	10 (13/129)	2 (2, 4)
MEL[a]	31 (33/107)	104 (18, 117+)	7 (7/107)	4 (13, 44)
RCC[a]	29 (10/34)	56 (37, 127+)	27 (9/34)	7 (4, 13)

CI = confidence interval; DOR = duration of response; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

[a]1 CR was noted in MEL and 1 CR was noted in RCC.

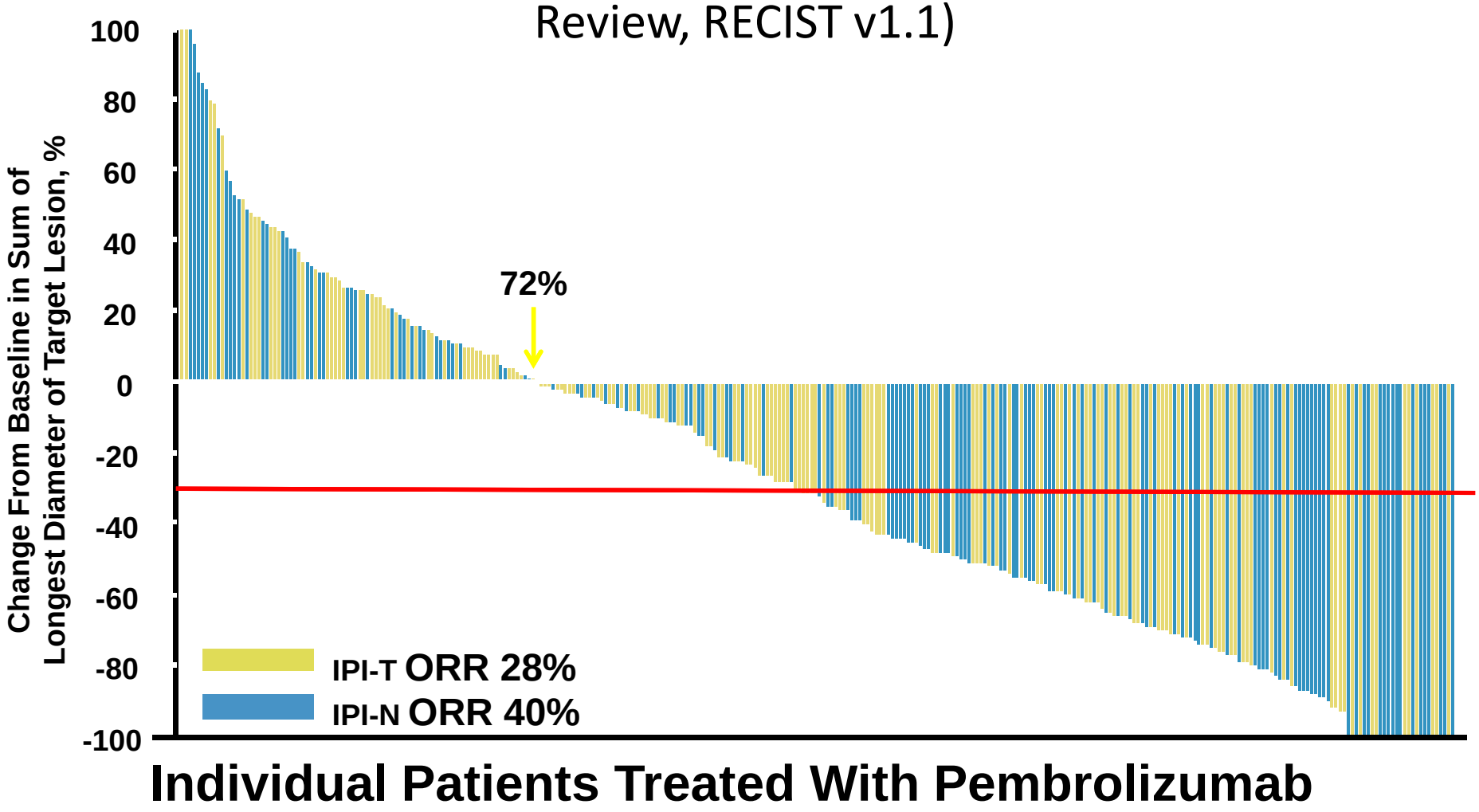




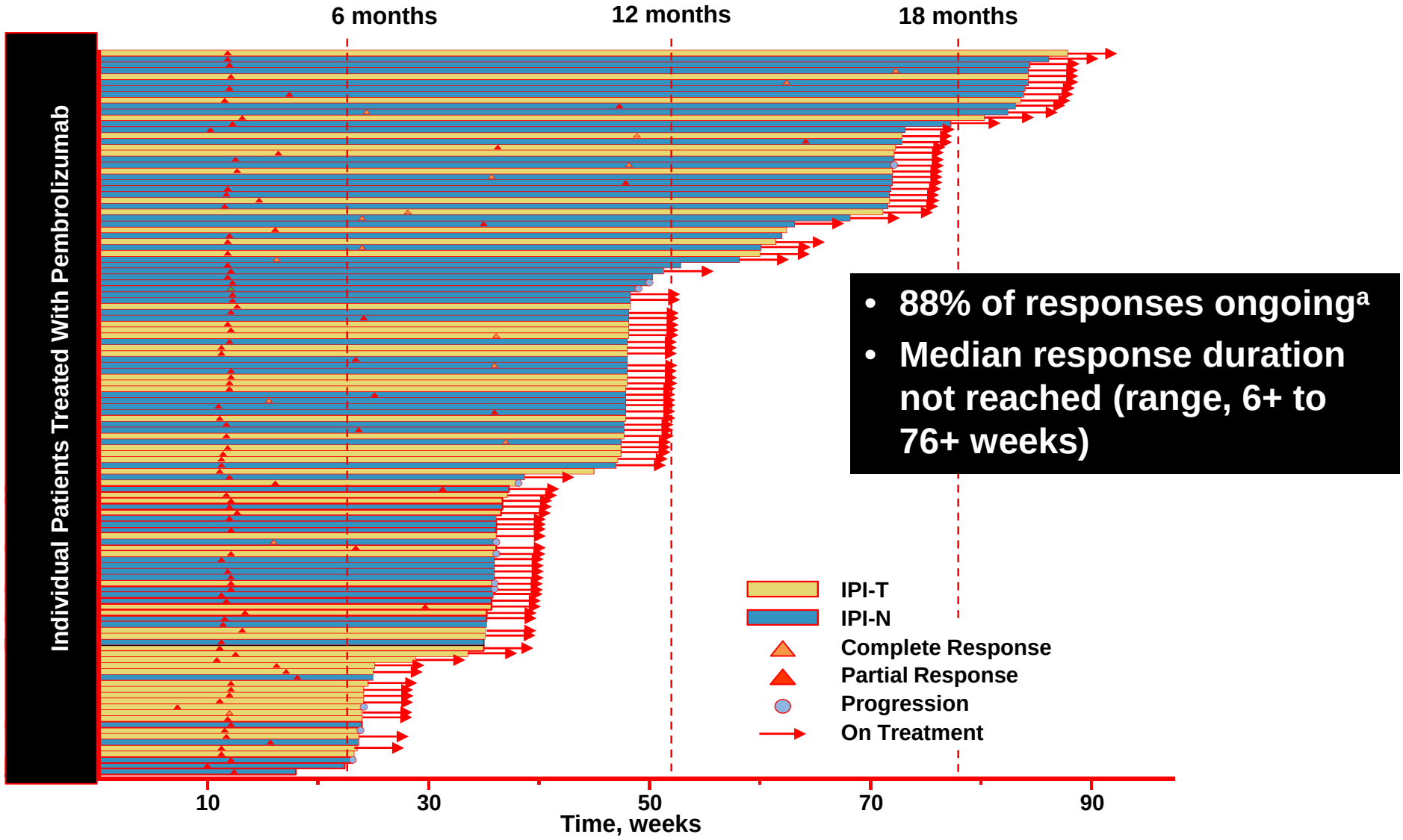
- 30/65 (46%) responses were evident at first tumor evaluation (8 weeks)
- 42/65 (65%) responses were ongoing >1 year
- No OR in CRPC or CRC

Phase I Trial of Pembrolizumab (Keynote 1)

Maximum Percent Change from Baseline in Tumor Size[a] (Central Review, RECIST v1.1)



Time to and Durability of Response (Central Review, RECIST v1.1)



[a]Ongoing response defined as alive, progression free, and without new anticancer therapy.
Analysis cut-off date: October 18, 2013.

Pembrolizumab

Presented by: Omid Hamid

Anti-PD1 Trials with both Nivolumab and Pembrolizumab

- Phase I does not demonstrate a real dose response effect (0.1-10mg/kg for Nivolumab)
- Response rates in the range of 30-40%
- Responses are durable with median duration of nearly 2 years
- Toxicity is considerably less than with Ipilimumab (anti-CTLA-4), though similar types of toxicities but less frequent

Spectrum of PD-1/PD-L1 Antagonist Activity

Active

- **Melanoma**
- **Renal cancer (clear cell and non-clear cell)**
- **NSCLC – adenocarcinoma and Squamous cell**
- Small cell lung cancer
- Head and neck cancer
- Gastric and GE junction
- **Mismatch repair deficient tumors (colon, cholangiocarcinoma)**
- Bladder
- Triple negative breast cancer
- Ovarian
- Glioblastoma
- Hepatocellular carcinoma
- Thymoma
- Mesothelioma
- Cervical
- **Hodgkin Lymphoma** Follicular lymphoma
- T-cell lymphoma (CTCL, PTCL)
- Diffuse large cell lymphoma
- **Merkel Cell**

Minimal to no activity:

- Prostate cancer
- MMR+ Colon cancer
- Myeloma
- Pancreatic Cancer

Major PD-1/PD-L1 antagonists

- Nivolumab (anti-PD-1)
- Pembrolizumab (anti-PD-1)
- Atezolizumab (MPDL3280, anti-PD-L1)
- MEDI-4736 (anti-PD-L1)

Will these tumors respond better to Nivo + Ipi?

NAME
Nivolumab and pembrolizumab

APPROVED FOR
Metastatic melanoma (both) and non-small cell lung cancer (nivolumab)

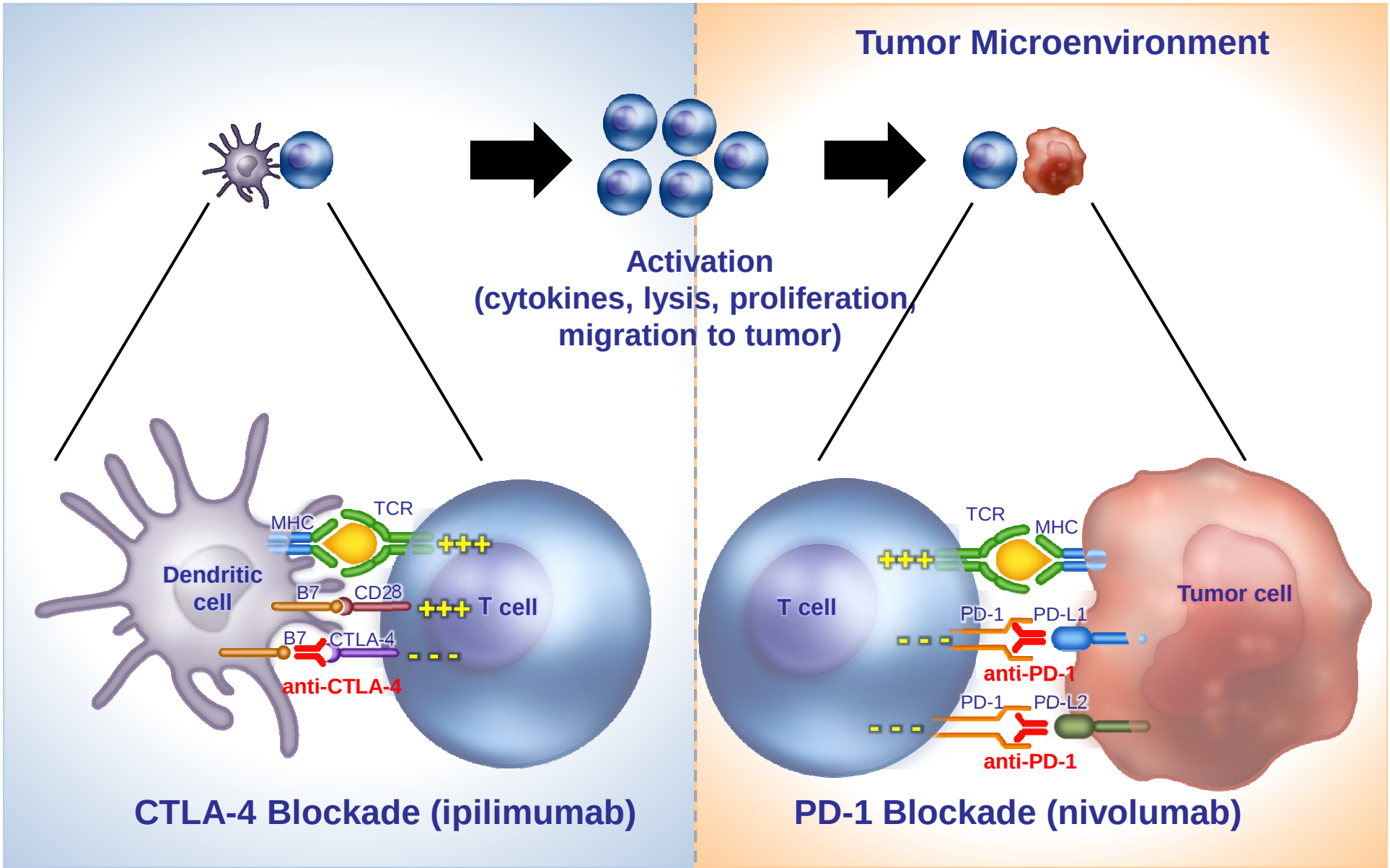
TYPE
Nivolumab | a fully human IgG4 monoclonal antibody
Pembrolizumab | a humanized IgG4 monoclonal antibody

MOLECULAR TARGETS
PD-1, a surface protein of the immunoglobulin superfamily

CELLULAR TARGETS
PD-1 is present on T cells, B cells, and macrophages. It is induced after T cell activation and plays a co-inhibitory role to negatively regulate immune responses upon binding to one of its two ligands, PD-L1 or PD-L2.

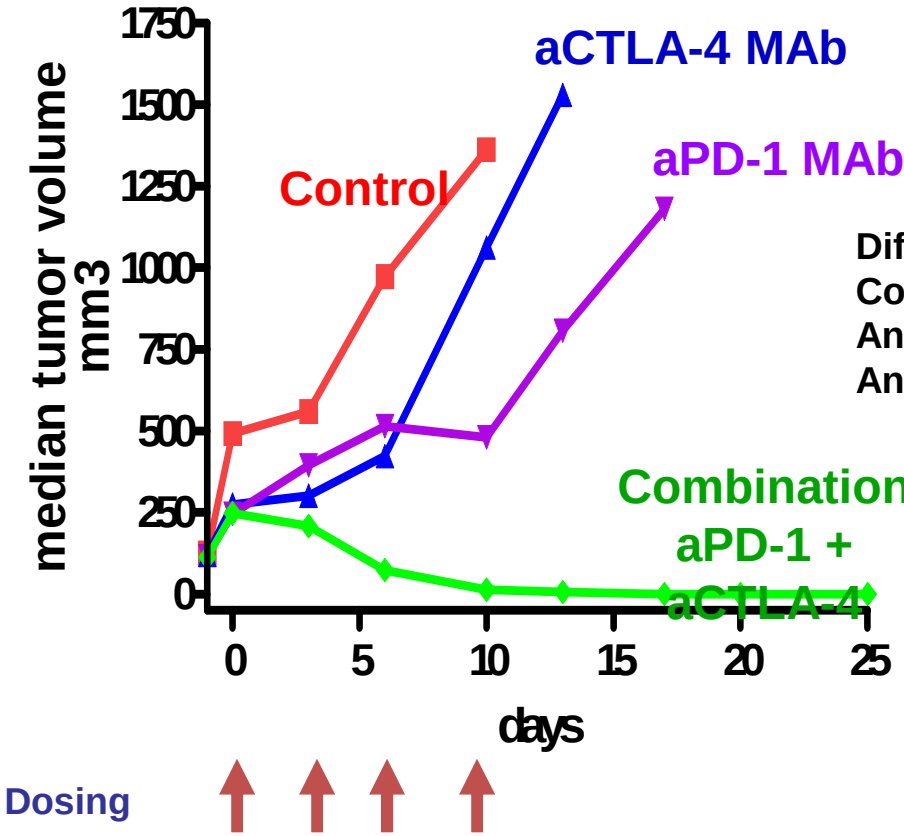
EFFECTS ON TARGETS
PD-1 blockade is thought to prevent PD-L1 expressed on tumor cells, stromal cells, and antigen-presenting cells (APC) from engaging PD-1 expressed on T cells, leading to more robust T cell activity.

Blocking CTLA-4 and PD-1



Synergistic Activity with Anti-PD-1 and Anti-CTLA-4 Antibodies

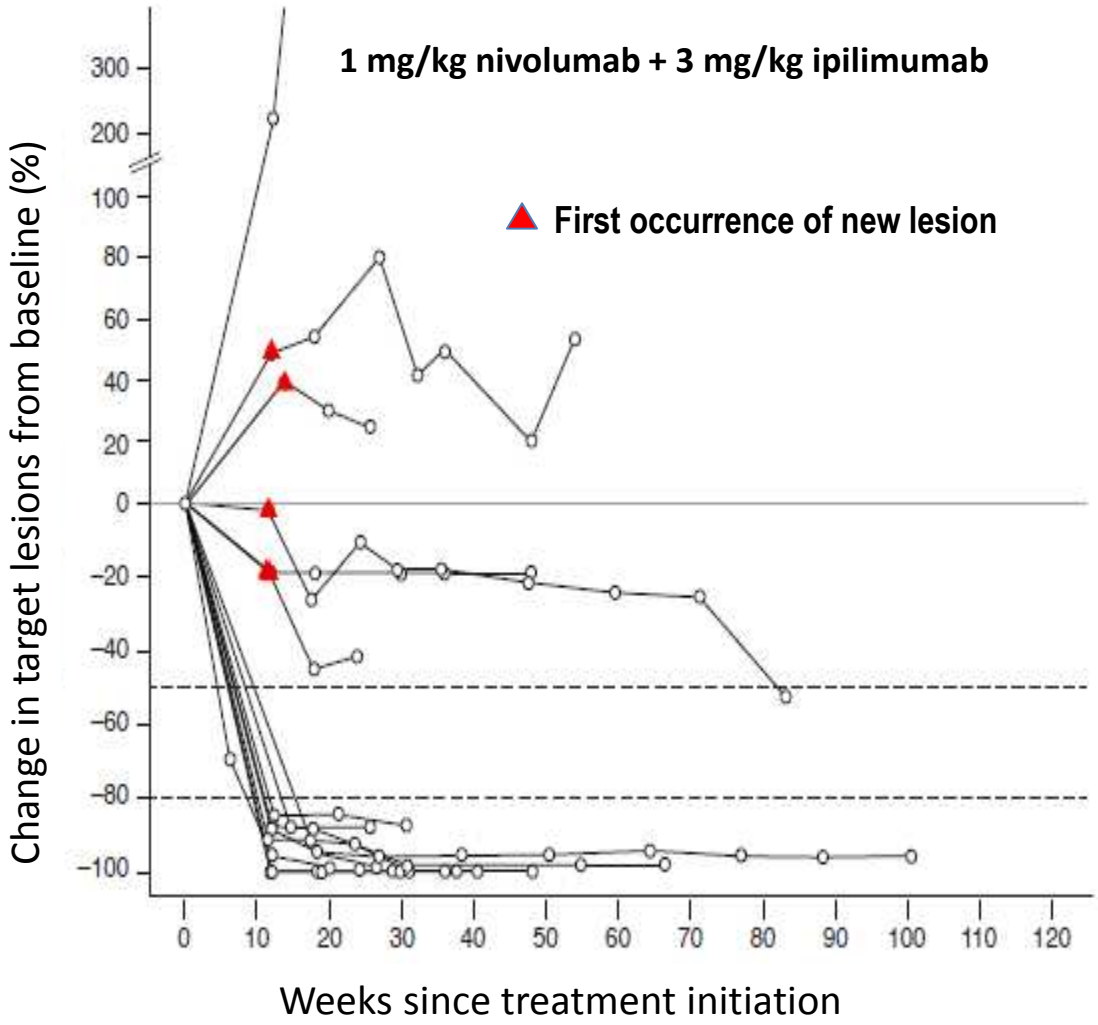
Combination of Non-Efficacious Doses of anti-PD1 and anti-CTLA-4 Antibodies is Efficacious in Mouse Model

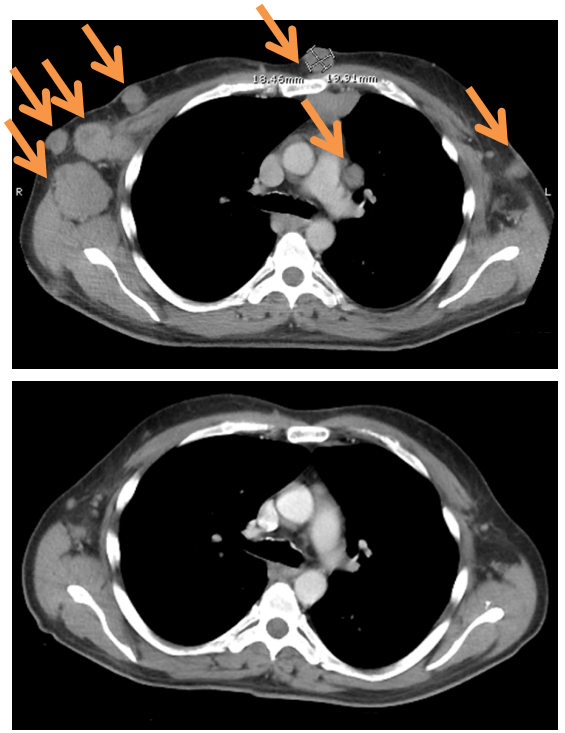


Different roles in T cell Differentiation-
Compensatory upregulation
Anti-CTLA4 elimination of tumor Treg
Anti-CTLA4 induced tumor T cell infiltration

Provided by Alan Korman, BMS

Rapid and Durable Changes in Target Lesions





Pre-treatment

12 weeks

- A 52-year-old patient presented with extensive nodal and visceral disease
- Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting
- Within 4 wk, LDH normalized and symptoms resolved
- At 12 wk, there was marked reduction in all areas of disease as shown

Wolchok et al., NEJM, 2013

Adverse Events from Immune Checkpoint Inhibitors

- Generally do not induce cytokine like effects
- Autoimmunity can affect any organ system
  - But skin, GI, liver, and endocrine organs most common
  - Multiple organ systems can be affected (concurrently or serially)
- Incidence/severity anti-CTLA-4 > PD-1/PD-L1 antagonists
- Dose-relationship for anti-CTLA-4; not evident for active range of anti-PD-1/PD-L1
- Re-challenge with same agent often (but not always) leads to recurrent toxicity
- High grade AE to one class does not preclude safe administration of the other class
- Vast majority of events (except endocrine) completely reversible over time

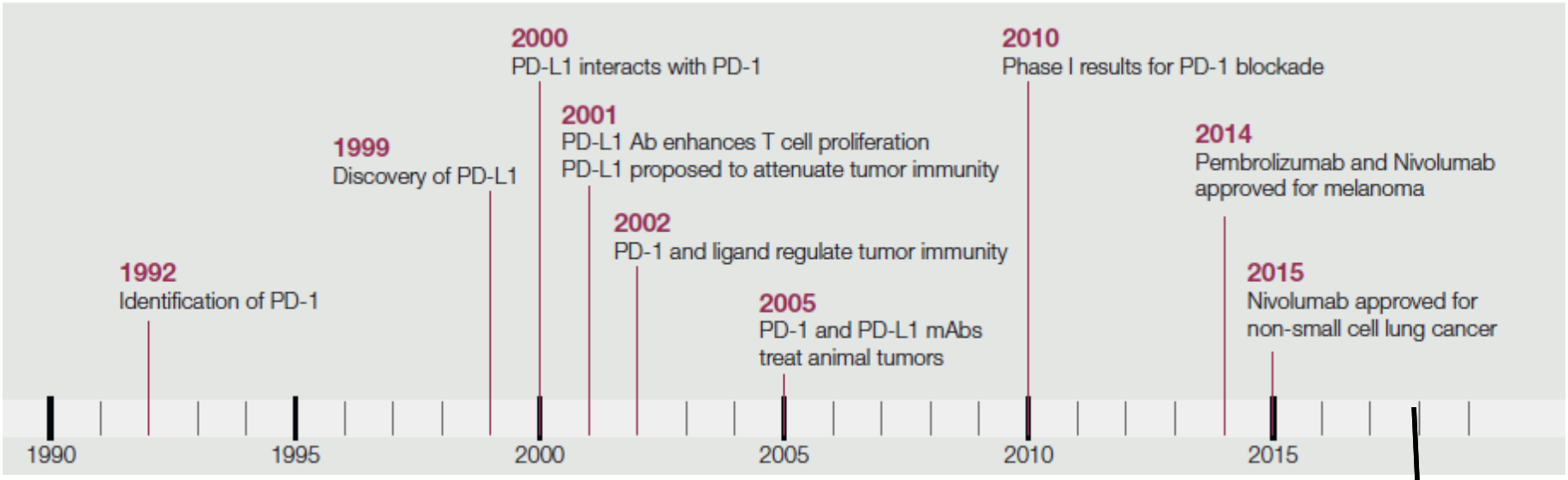
Unusual Immune Checkpoint Adverse Events

- Systemic inflammatory syndrome (first dose)
- Severe arthritis
- Myositis
- Pneumonitis
- Nephritis
- Bowel perforation
- Meningitis
- Myasthenia Gravis
- Ascending polyneuropathy (Guillan-Barre)
- Uveitis
- Thrombocytopenia (ITP)
- Dry eye syndrome
- Lichen planus
- Alopecia areata
- Insulin-dependent diabetes mellitus

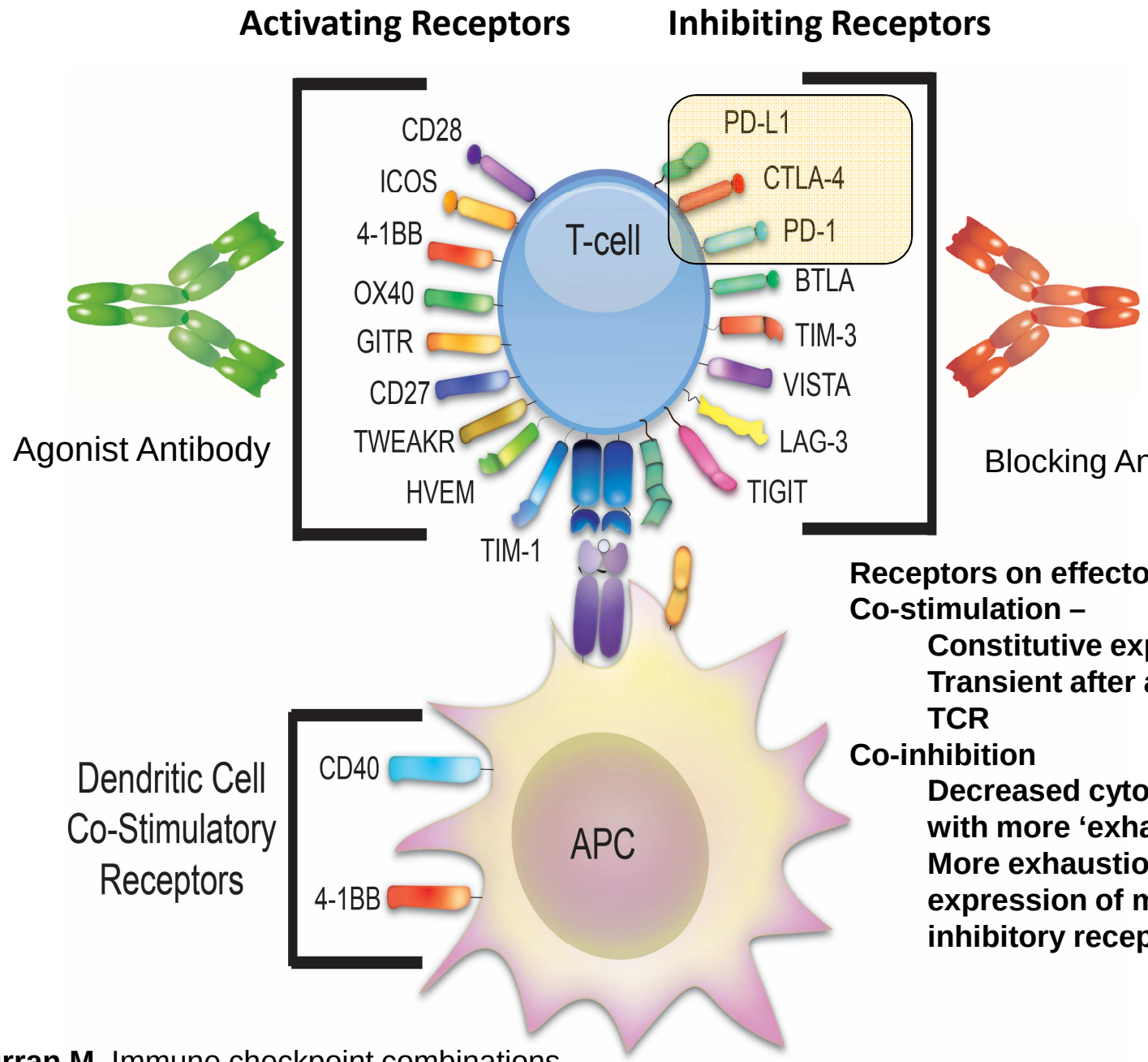
Principles of AE Management

- Onset of adverse effects not predictable for individuals
- Close follow-up of patients, and timely management necessary to minimize morbidity
- Set of basic clinical decisions
  - Autoimmune or other cause?
  - Hold or continue treatment?
  - When to start steroids?
  - Dose? Duration?
  - PO or IV?
  - Inpatient versus outpatient?
  - When to start second-line immune suppressive?

Time Line for anti-PD1 from Discovery to Now



Nivolumab+ Ipilimumab as a combination approved for melanoma



Receptors on effector T, Treg, NK cells
Co-stimulation –
- **Constitutive expression or**
- **Transient after activation through TCR**

Co-inhibition
- **Decreased cytokine production with more 'exhaustion'**
- **More exhaustion associated with expression of multiple co-inhibitory receptors**

Ai M., **Curran M.** Immune checkpoint combinations from mouse to man. *Cancer Immunology Immunotherapy*, 2015.

PD-1/PD-L1 Combinations in Development

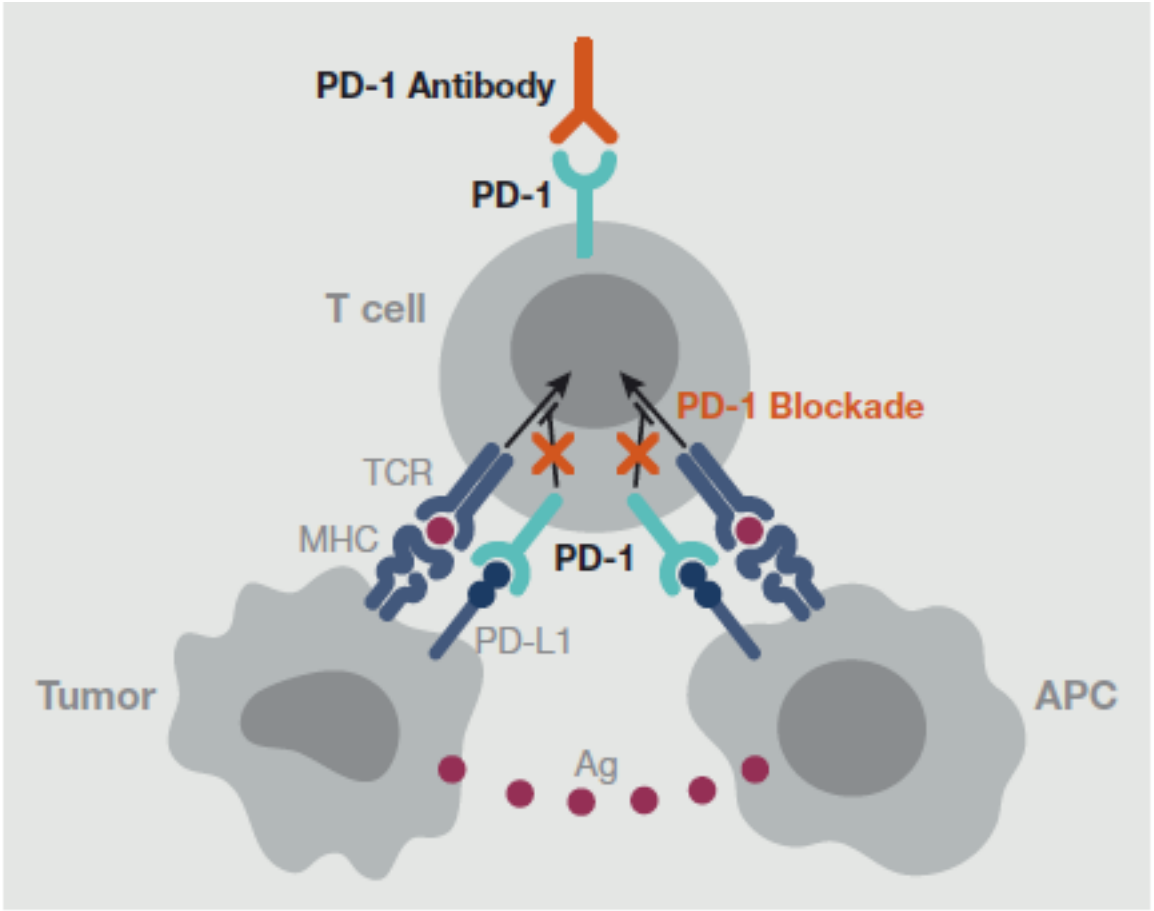
- Ipilimumab (anti-CTLA-4)
- Tremelimumab (anti-CTLA-4)
- Bevacizumab
- IFNs – RCC/melanoma
- IL-21 – terminated?
- IL-2 (proposed)
- anti-LAG3
- anti-KIR
- peptide vaccines
- Oncolytic viruses (Tvec)
- Anti-OX40 (proposed)
- Anti-CD27
- Anti-CD137
- Treg inhibitors – mogamulizumab
- IDOi
- Adoptive Cell Therapy
- Dabrafenib +/- Trametinib
- Vemurafenib +/-Cobimetinib
- RT
- HDACi
- CSF1-R antagonists
- CD3 or IL-2-bispecifics

CTLA-4 Combinations in Development

- IL-2
- Interferon
- GM-CSF
- Anti-CD27
- IDOi
- Bevacizumab
- Sunitinib
- Dabrafenib+-trametinib
- Tvec
- ACT
- IL-21
- Anti-PD-1/Anti-PD-L1
- Chemotherapy
- RT
- Vaccines
- Rituximab, Signaling Ab

Conclusions

- Single agent checkpoint inhibitors are effective in subsets of many different malignancies (anti-PD-1/anti-PD-L1 > anti-CTLA-4)
- Combinations should be addressed to underlying immunobiology of tumor-host relationship
  - But no reliable method to assess
  - Multiple combinations possible
- Ipilimumab-nivolumab provides proof of concept of potential increased activity of combination therapy
- Combinations may produce increased autoimmunity but should be manageable in most patients
- For a subset of patients, a single agent appears to be sufficient for durable response
  - But no reliable method to identify this subset



Nivolumab and pembrolizumab are monoclonal antibodies that block the programmed death-1 receptor (PD-1, CD279), resulting in dis-inhibition of tumor-specific immune responses. Both are recently approved for use in the treatment of metastatic melanoma, and nivolumab as well for non-small cell lung cancer.