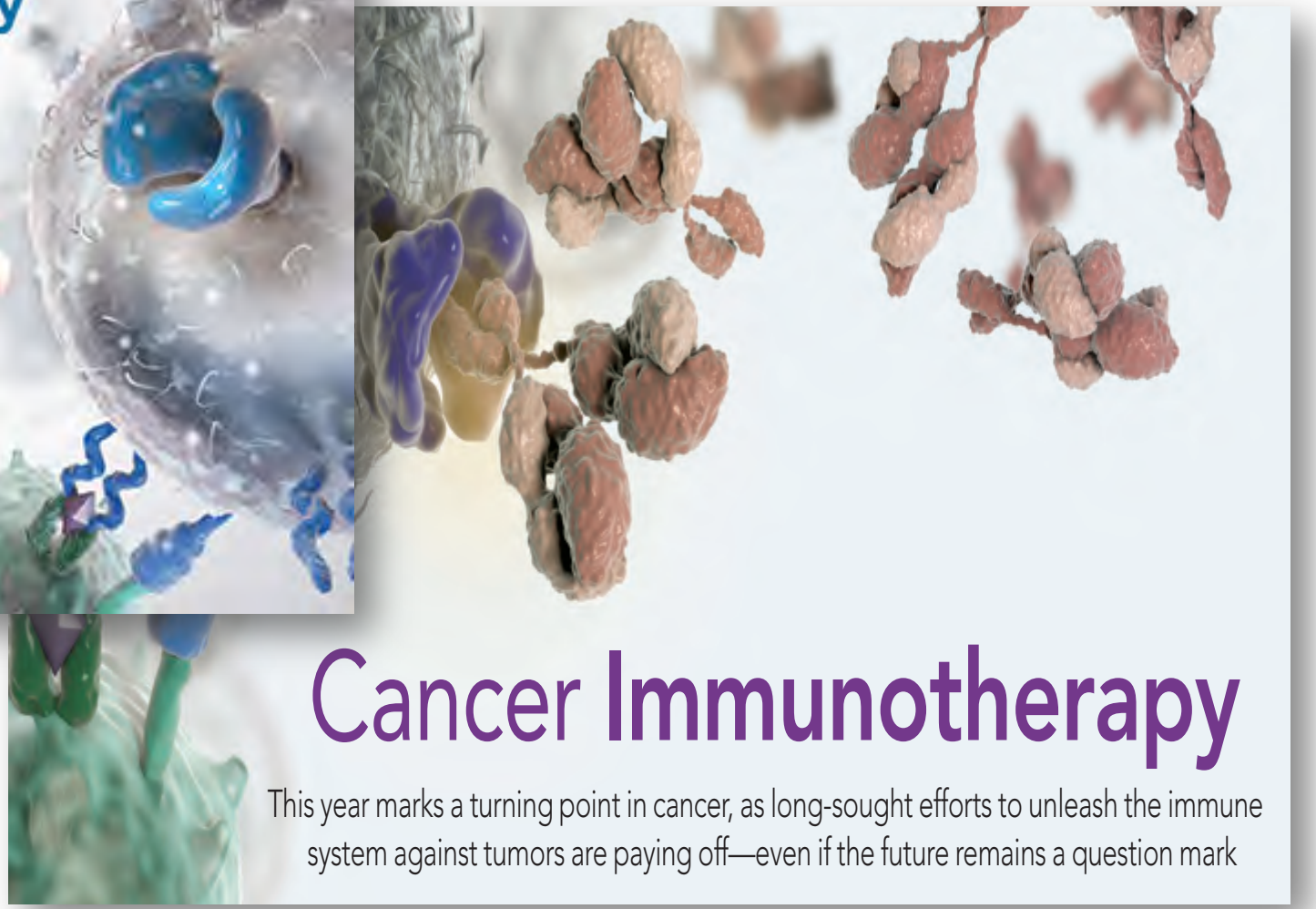
Immunology and Cancer

George A. Fisher MD PhD



Cancer **Immunotherapy**

This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumors are paying off—even if the future remains a question mark

Immunology: What we used to know…

- B cells make antibodies which bind to antigens
  - Antibodies: molecules that “target” (bind) specific proteins
- T cells can kill cells recognized as “foreign” or diseased
  - T cells have antibody like receptors on their cell surface
  - Designed to kill virus infected cells or potentially cancer cells
- Dendritic cells (DCs) educate the T cells
  - DCs “process” antigens and “present” them to T cells in lymph nodes
- Macrophages are the garbage trucks of the immune system
  - They “eat” dead or dying cells and dispose of remains

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T cells: What we know now…

- Different types of T cells

  -Killer T cells: capable to killing cancer cells

  -Suppressor T cells (T_{reg}): inhibit activation of Killer T cells

- "Checkpoint" proteins can stimulate or block T cells

  -Checkpoint proteins on some normal tissues, tumor cells and on macrophages, T_{reg} cells and Killer T cells

  -Antibodies made in the laboratory can bind to and block function of checkpoint proteins

- T cells can be genetically engineered to attack cells with any specific antigen

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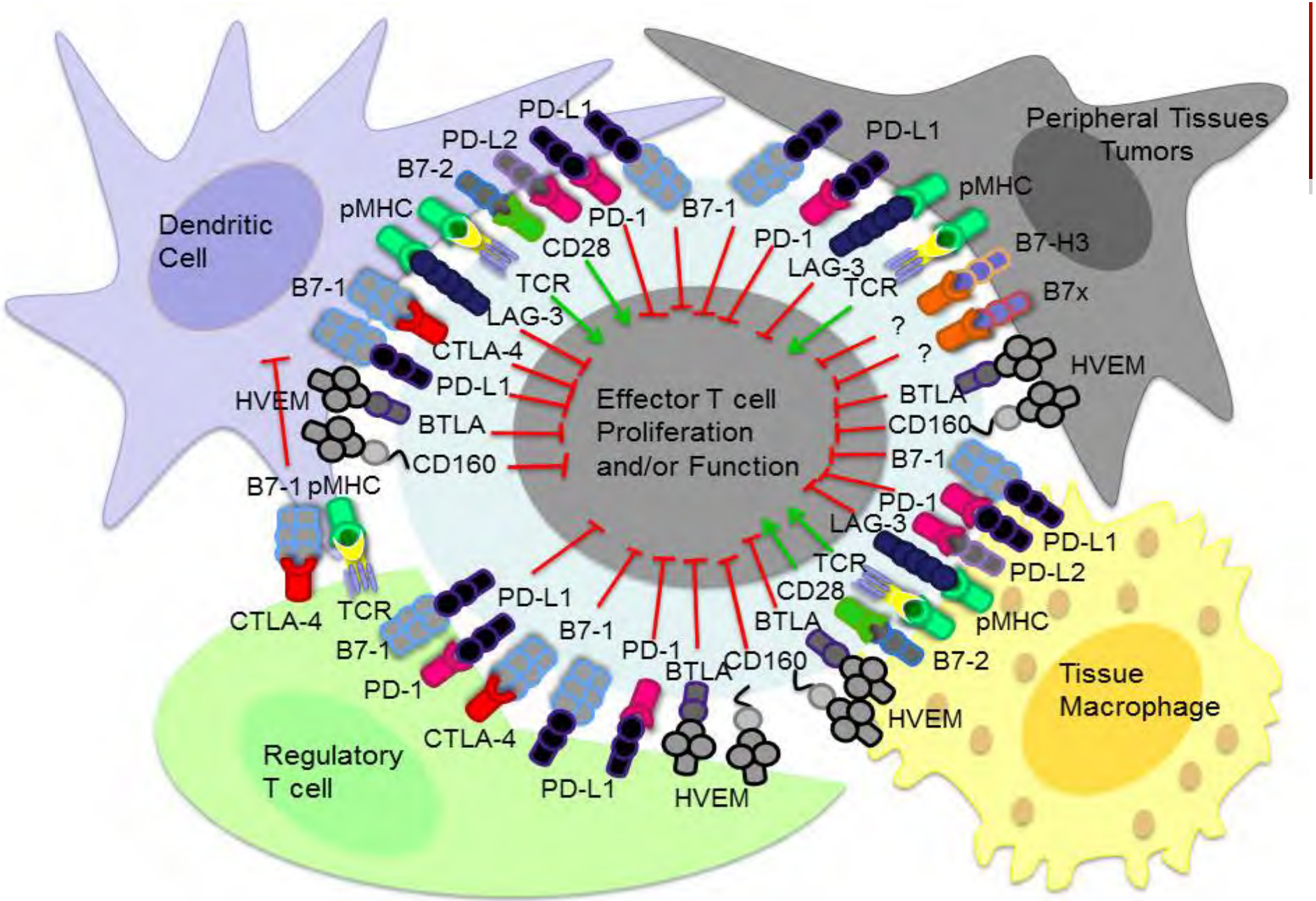
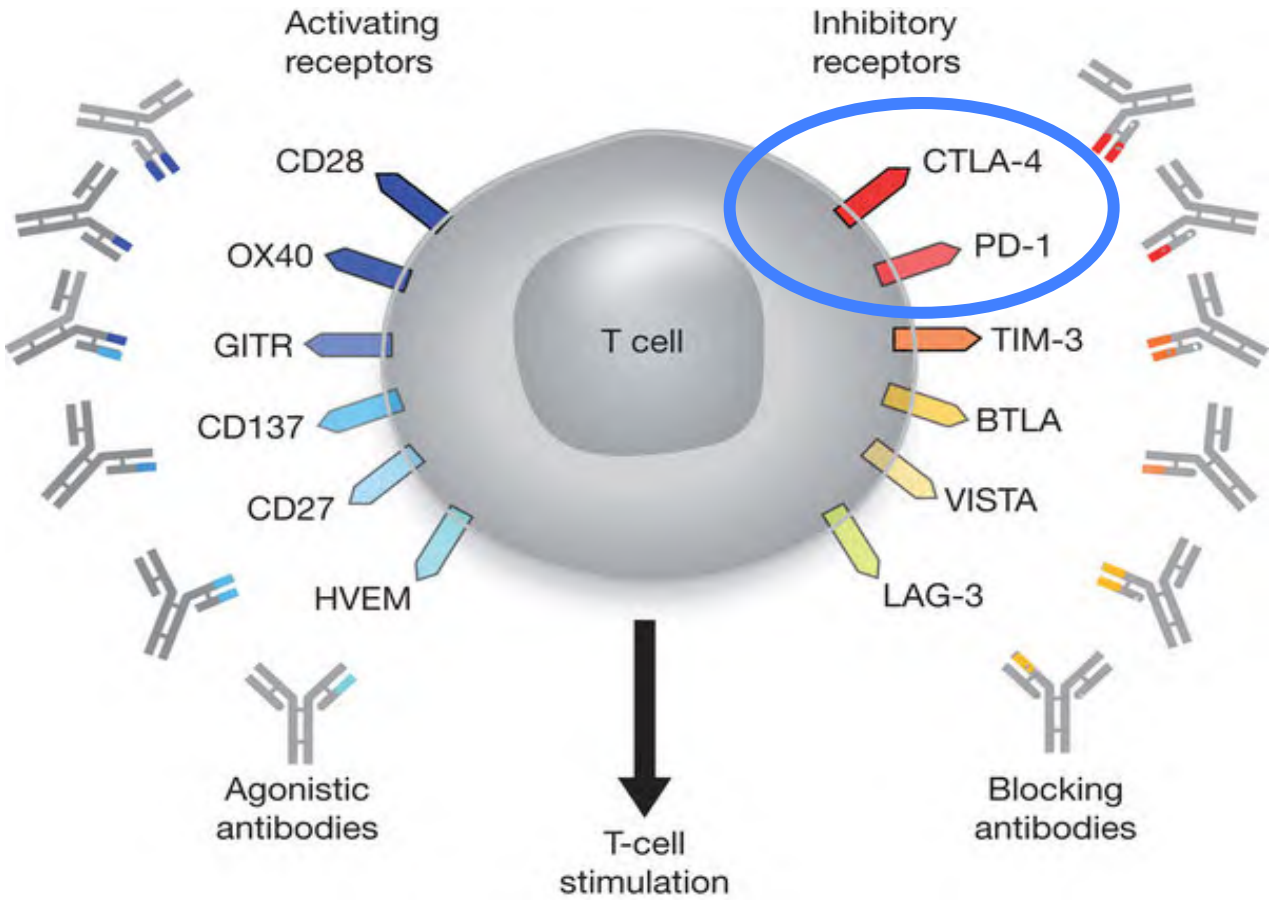

Dendritic Cell
PD-L1
PD-L2
B7-2
pMHC
PD-1
CD28
TCR
LAG-3
B7-1
CTLA-4
PD-L1
BTLA
CD160
HVEM
B7-1 pMHC
CTLA-4
TCR
B7-1
PD-1
PD-L1
CTLA-4
Regulatory T cell
PD-L1
B7-1
PD-1
BTLA
CD160
HVEM
Effector T cell Proliferation and/or Function
Peripheral Tissues Tumors
PD-L1
pMHC
PD-1
B7-1
LAG-3
TCR
B7-H3
B7x
?
?
HVEM
BTLA
CD160
B7-1
PD-1
LAG-3
PD-L1
PD-L2
TCR
CD28
pMHC
BTLA
B7-2
CD160
HVEM
Tissue Macrophage

Controlling the immune system: Gas Pedals and Brakes



Turning up The Activating

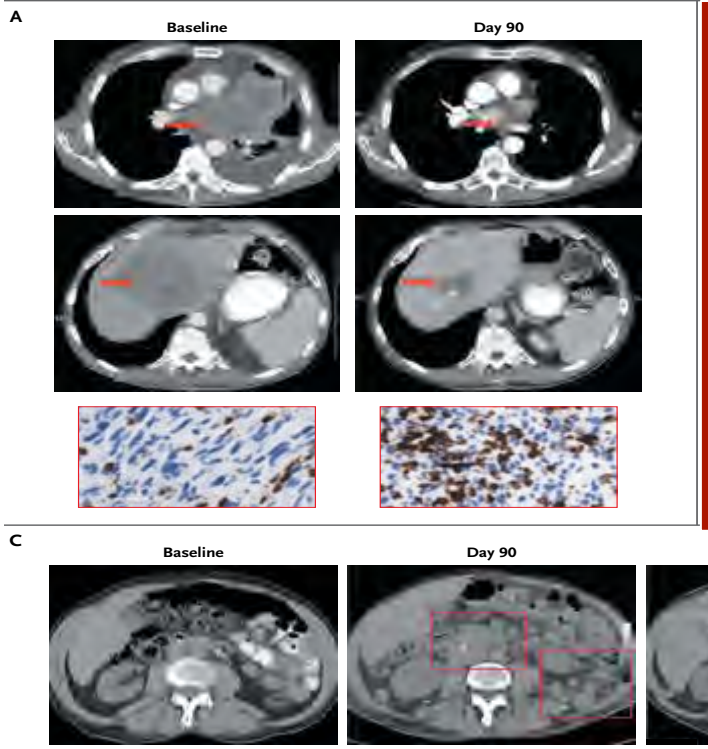
Blocking the Inhibiting

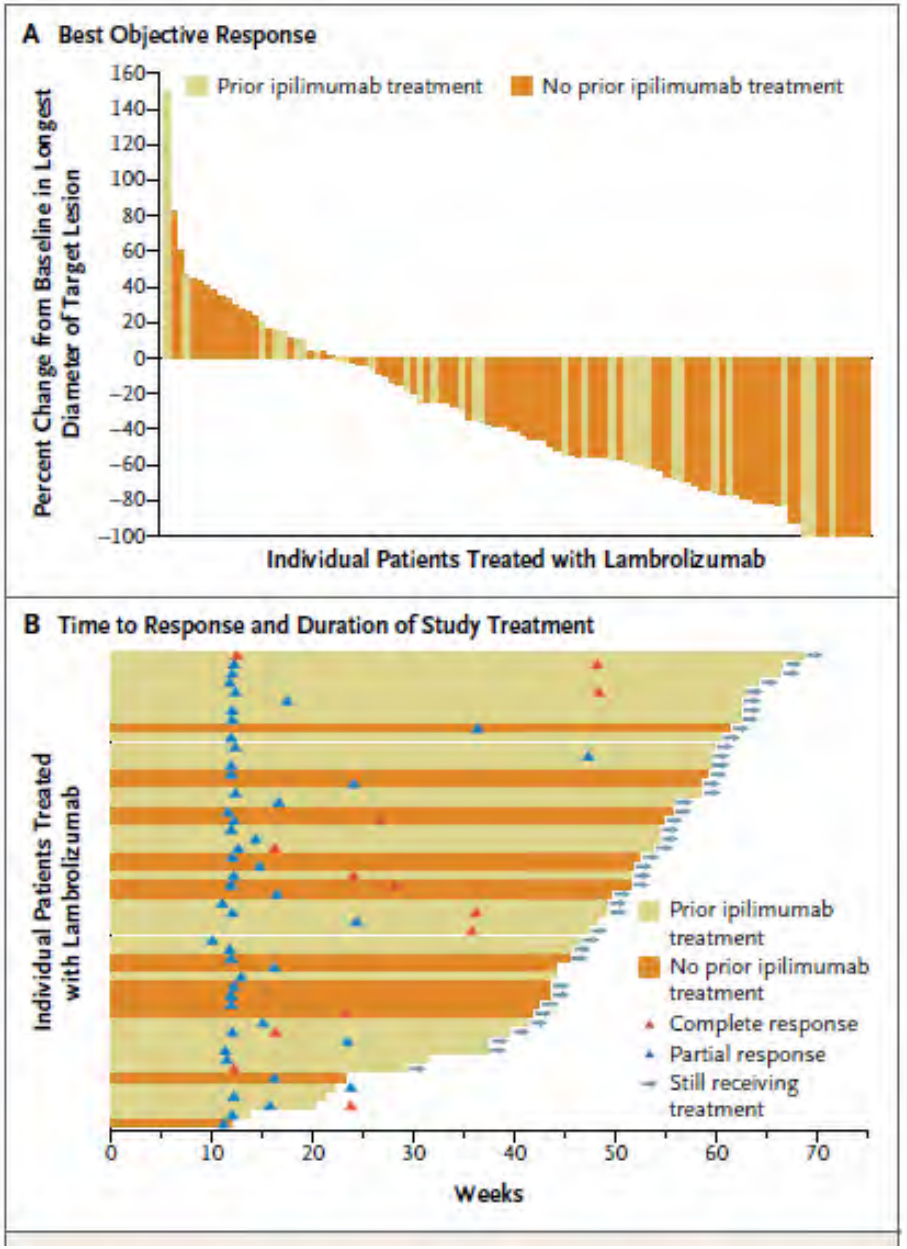
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma

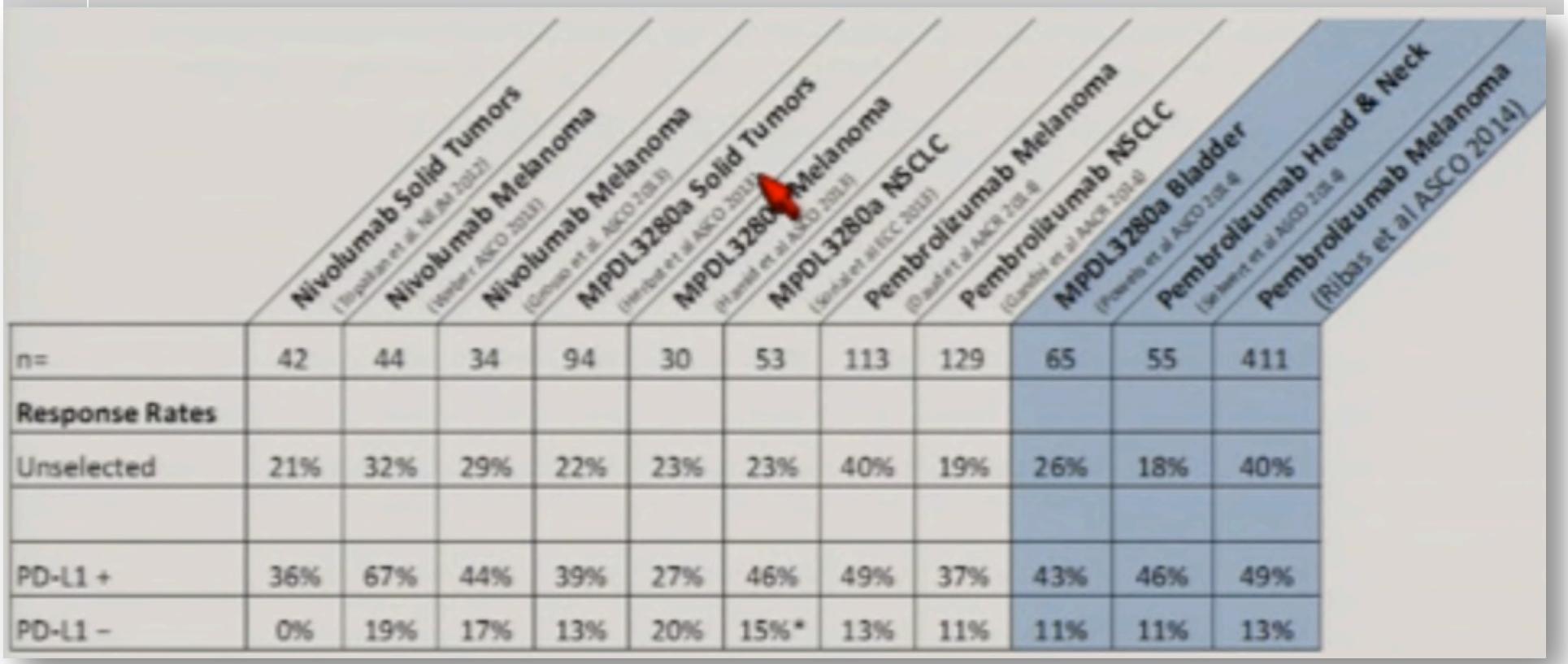
Omid Hamid, M.D., Caroline Robert, M.D., Ph.D., Adil Daud, M.D., F. Stephen Hodi, M.D., Wen-Jen Hwu, M.D., Ph.D., Richard Kefford, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Richard W. Joseph, M.D., Jeffrey S. Weber, M.D., Ph.D., Roxana Dronca, M.D., Tara C. Gangadhar, M.D., Amita Patnaik, M.D., Hassane Zarour, M.D., Anthony M. Joshua, M.B., B.S., Ph.D., Kevin Gergich, M.A., Jeroen Elassaiss-Schaap, Ph.D., Alain Algazi, M.D., Christine Mateus, M.D., Peter Boasberg, M.D., Paul C. Tumeh, M.D., Bartosz Chmielowski, M.D., Ph.D., Scot W. Ebbinghaus, M.D., Xiaoyun Nicole Li, Ph.D., S. Peter Kang, M.D., and Antoni Ribas, M.D., Ph.D.





Ribas *et al*. ASCO 2013

Presence of PD-L1 correlates with improved response to PD1 targeted drugs

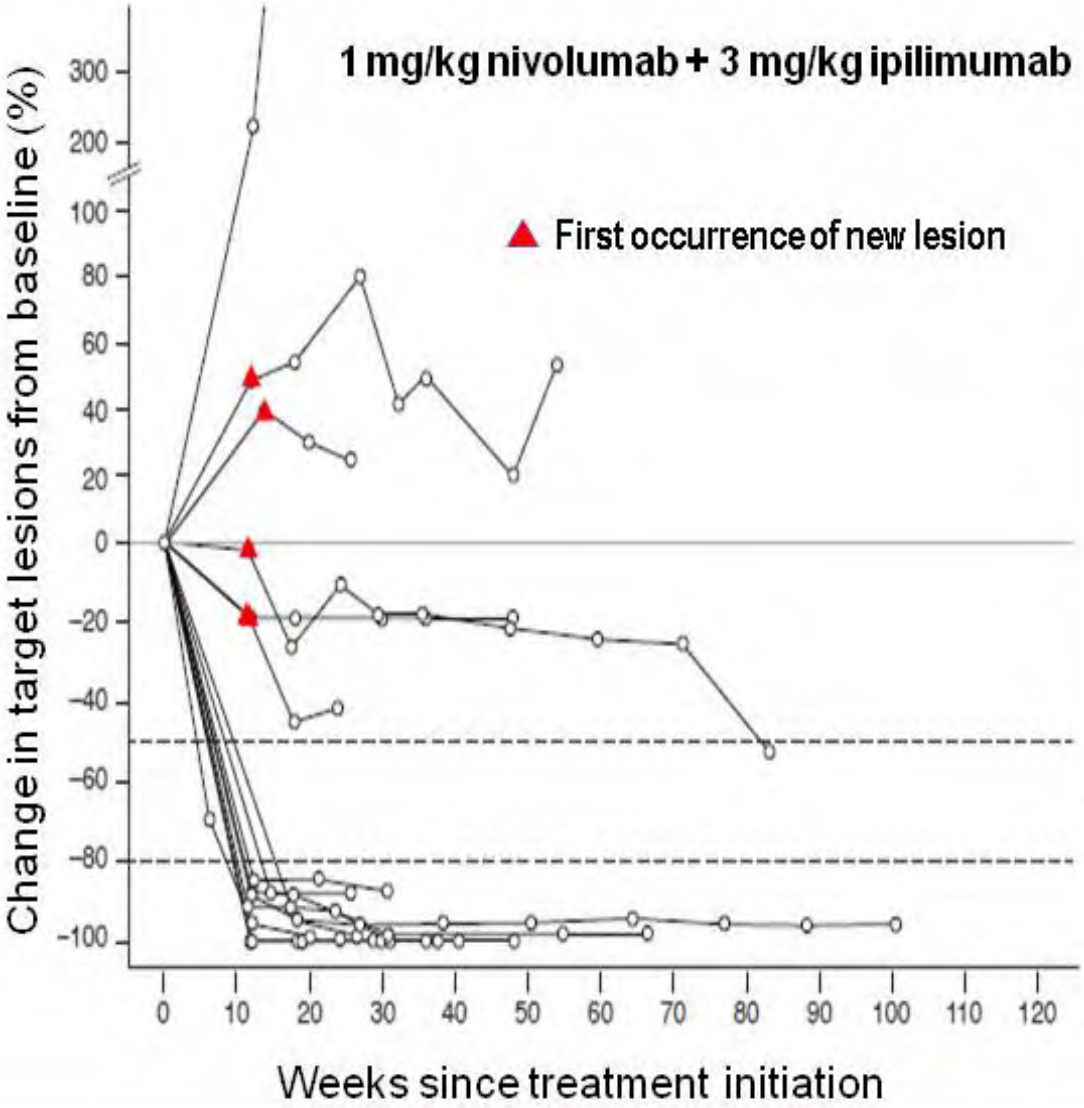


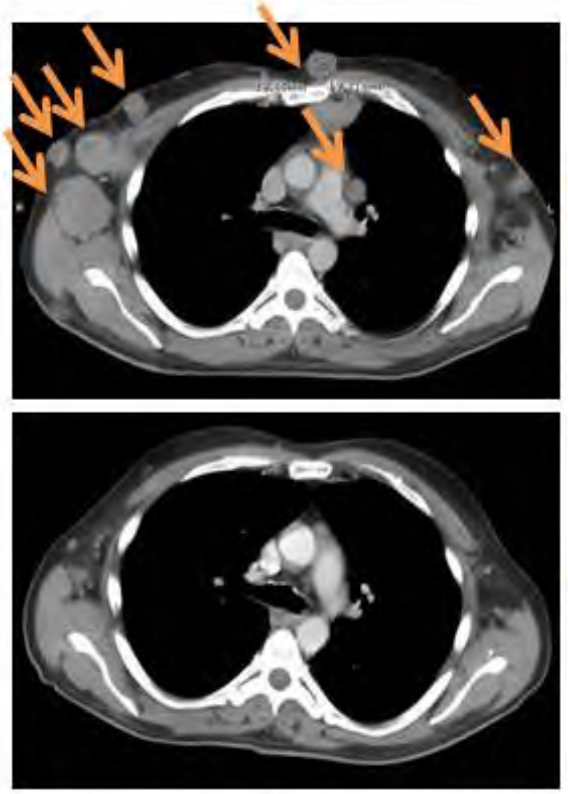
	Nivolumab Solid Tumors	Nivolumab Melanoma	Nivolumab Melanoma	MPDL3280a Solid Tumors	MPDL3280a Melanoma	MPDL3280a NSCLC	Pembrolizumab Melanoma	Pembrolizumab NSCLC	MPDL3280a Bladder	Pembrolizumab Head & Neck	Pembrolizumab Melanoma (Ribas et al ASCO 2014)
n=	42	44	34	94	30	53	113	129	65	55	411
Response Rates											
Unselected	21%	32%	29%	22%	23%	23%	40%	19%	26%	18%	40%
PD-L1 +	36%	67%	44%	39%	27%	46%	49%	37%	43%	46%	49%
PD-L1 –	0%	19%	17%	13%	20%	15%*	13%	11%	11%	11%	13%

PD-1: Nivolumumab (Bristol): Approved for melanoma (dec ‘14)
Pembrolizumab (Merck): Approved for melanoma (sept ‘14)
Pidilizumab (Curetech)
PD-L1: MPDL328a (Genentech)
BMS-936559; MEDI4736; MSB0010718C

Rapid and Durable Changes in Target Lesions

Wolchok et al, ASCO 2013





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

Evaluating PD-L1 status as a putative biomarker

Therapy	PD-L1 Status	ORR
Nivolumab monotherapy (melanoma) (0.1-10 mg/kg) Grosso et al. ASCO 2013	+	**41%** (7/17)
	-	**14%** (3/21)
Concurrent ipilimumab + nivolumab	+	**46%** (6/13)
	-	**41%** (9/22)
Sequenced nivolumab (after ipilimumab)	+	**50%** (4/8)
	-	**8%** (1/13)

PD-L1 Positivity rate = 45% (17/38, monotherapy), 37% (13/35, combination therapy), and 38% (8/21, sequenced therapy)

Wolchok et al, ASCO 2013

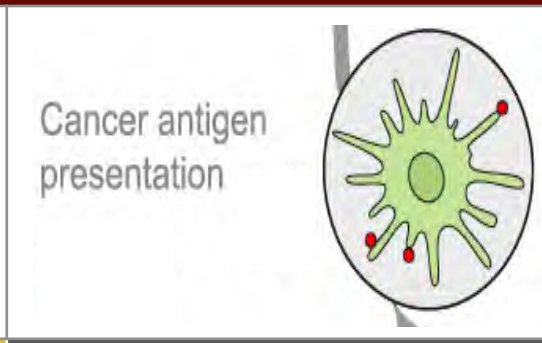
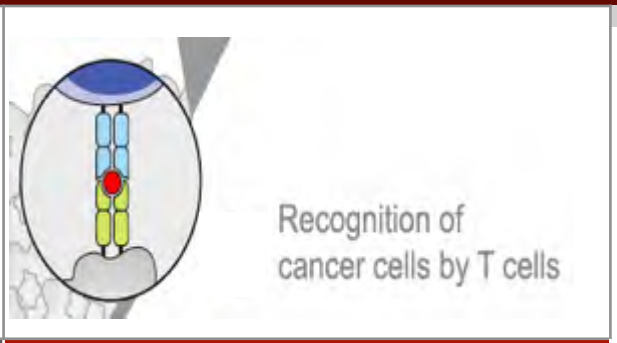
Linking the dots (or leaps of faith?)

- PD1/PD-L1 drugs “may” work better with a drug that targets CTLA-4 (ipilumumab) especially in tumors with low PD-L1 expression

- But, combination associated with higher risk of autoimmune complications (e.g. colitis causing diarrhea)

- Might injecting ipilumumab directly into a tumor (rather than intravenously) and combining with PD1 or PD-L1 agent be an effective strategy??

Cancer Immunotherapy Approaches

		
Checkpoint Modulators	**Vaccines**	**Cell-based Therapies**
Promote T cell activation or inhibit suppressors	Activate tumor-specific T cells to induce an antitumor immune response.	Manipulate autologous immune cell subsets ex vivo
• Anti PD-1 • Anti PD-L1 • Anti CTLA-4 • Anti CD137 • And many others..	• Peptide-derived • Manipulated tumor cells • Viral vectors	• TILs • Dendritic cells • CAR-T cells

Figures adapted from Chen and Mellman, *Immunity* 2013.

“It’s tough to make predictions, especially about the future” Yogi Berra