Immunotherapy and the Future of Cancer Therapy

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Disclosure

- Consulting:
  Agenus, Dendreon, NexImmune, ImmunExcite, Janssen, Lilly, Merck, Pierre Fabre, Roche / Genentech

- Patents
  AZ Medimmune, BMS, Janssen

- Stockholder
  Compugen, NexImmune, Potenza, Tizona

- Sponsored Research Agreement
  BMS, Janssen, Aduro Biotech

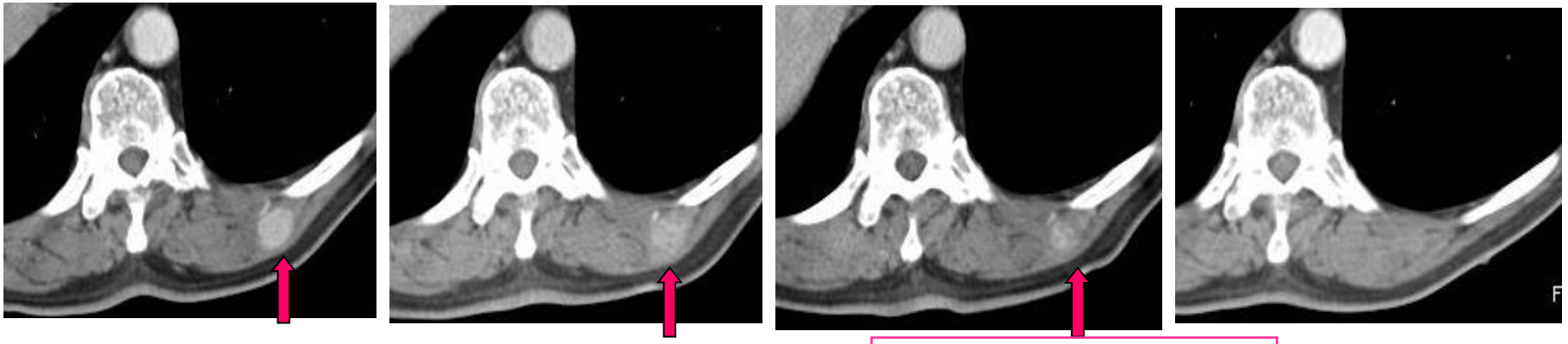
Case Presentation

- 66 year old man with recurrent RCC
- s/p nephrectomy 6 years prior to visit
- Relapsed 4 years prior to visit with multiple pulmonary nodules
- Rx with on clinical trials of sorafenib, HDAC inhibitor, etc
- CT: Multiple metastatic lesions in lungs, bone (R scapula), soft tissue
- Labs WNL

Continued ….

- Enrolled on first Phase I of MDX-1106 (now Nivolumab)
- Received 3 on study treatments
- Side Effects = hypothyroidism, GI disturbance
- Discontinued due to stable partial response
- Last seen 10/**2015**, CT Scan = Complete Response

01/15/08 (pre-Rx) **03/25/08** **04/22/08** **07/22/08**



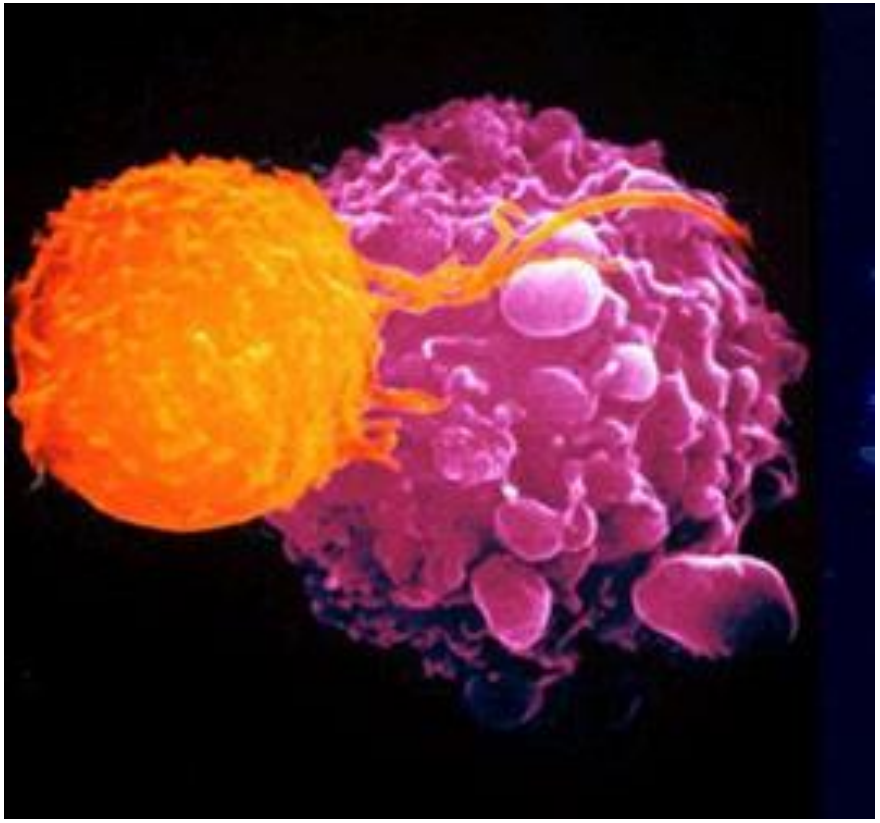
US-guided biopsy: No viable tumor

Outline

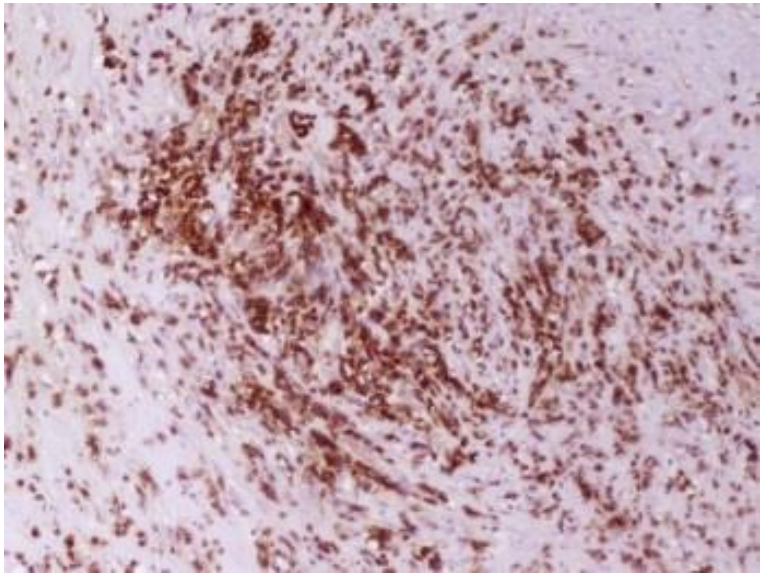
- How does current immunotherapy “work”?
- How often does immunotherapy work?
- Can we select patients for immunotherapy?
- Can immunotherapy be improved?
  - Combining 2 checkpoint blocking agents
  - Combining a cancer vaccine with immunotherapy

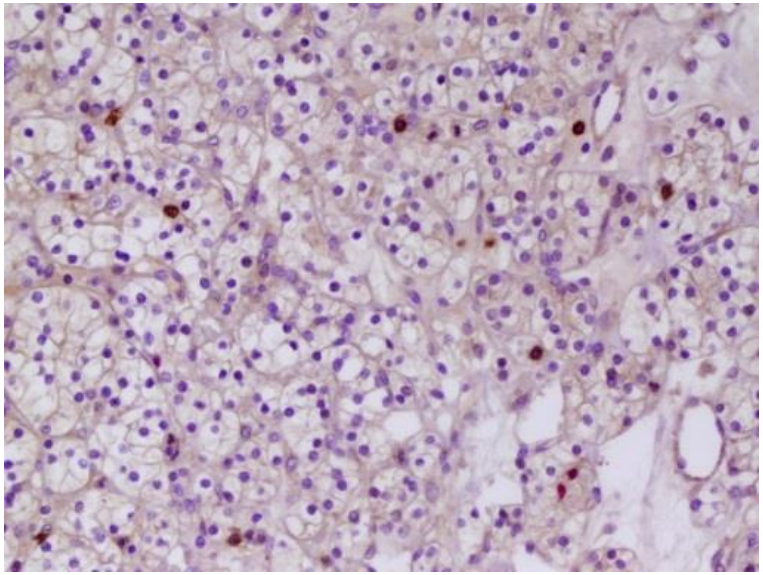
Biology of Immune Checkpoint Blockade

CD8 T Cells Are
“Born to Kill”



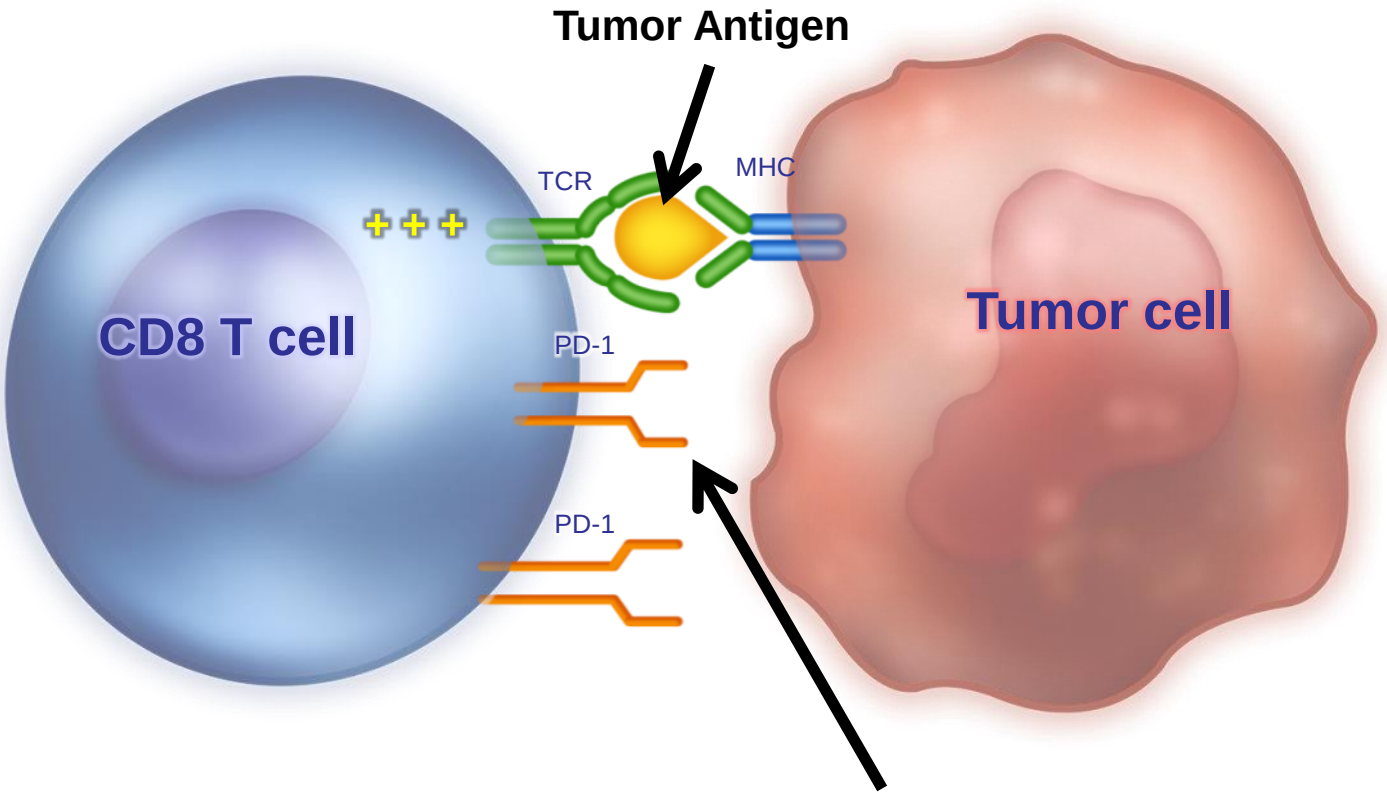
Some Tumors are Heavily Infiltrated with Killer CD8 T Cells





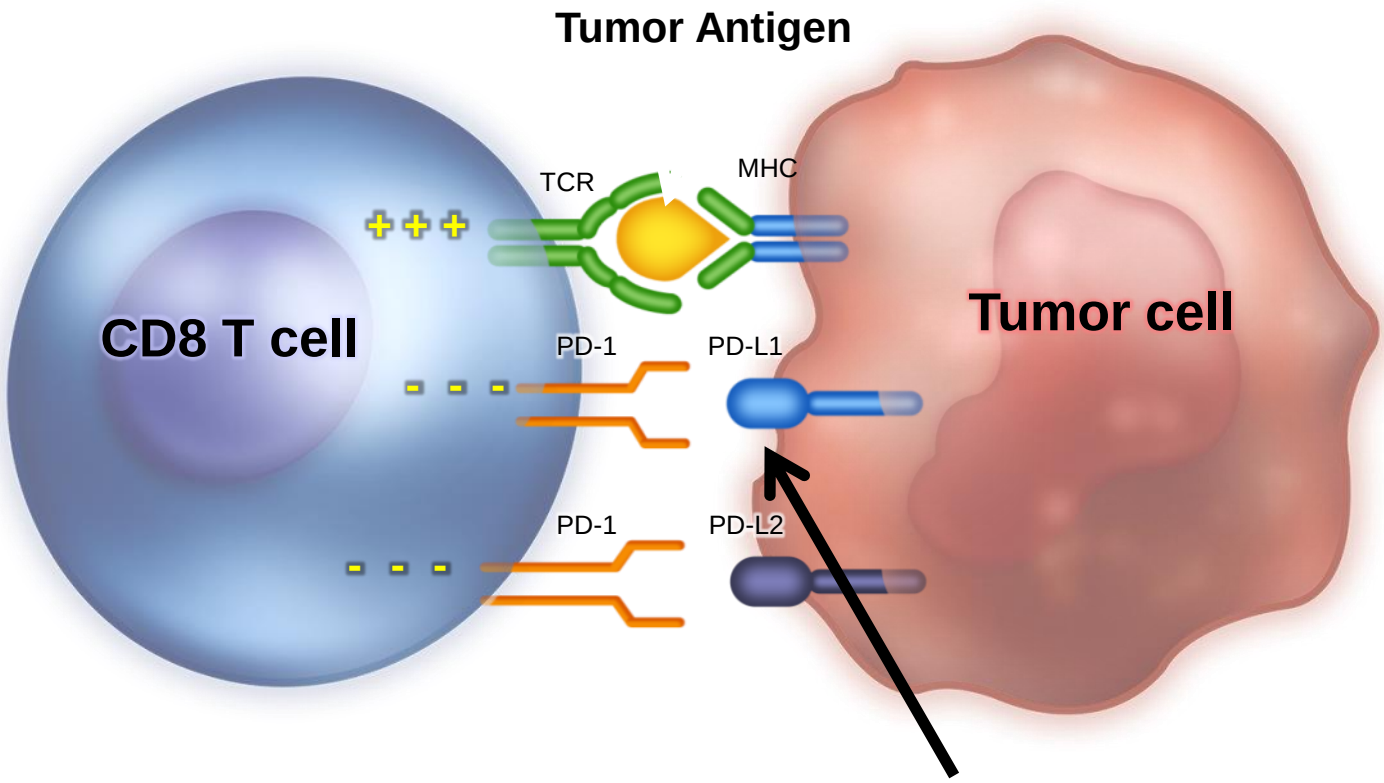
Brown Staining = CD8

Why Aren't CD8 Killer T Cells in Tumors Functional?



PD-1 is UP-Regulated in Tumor Infiltrating CD8 T Cells and IS CAPABLE Of Sending a "NO GO" Signal

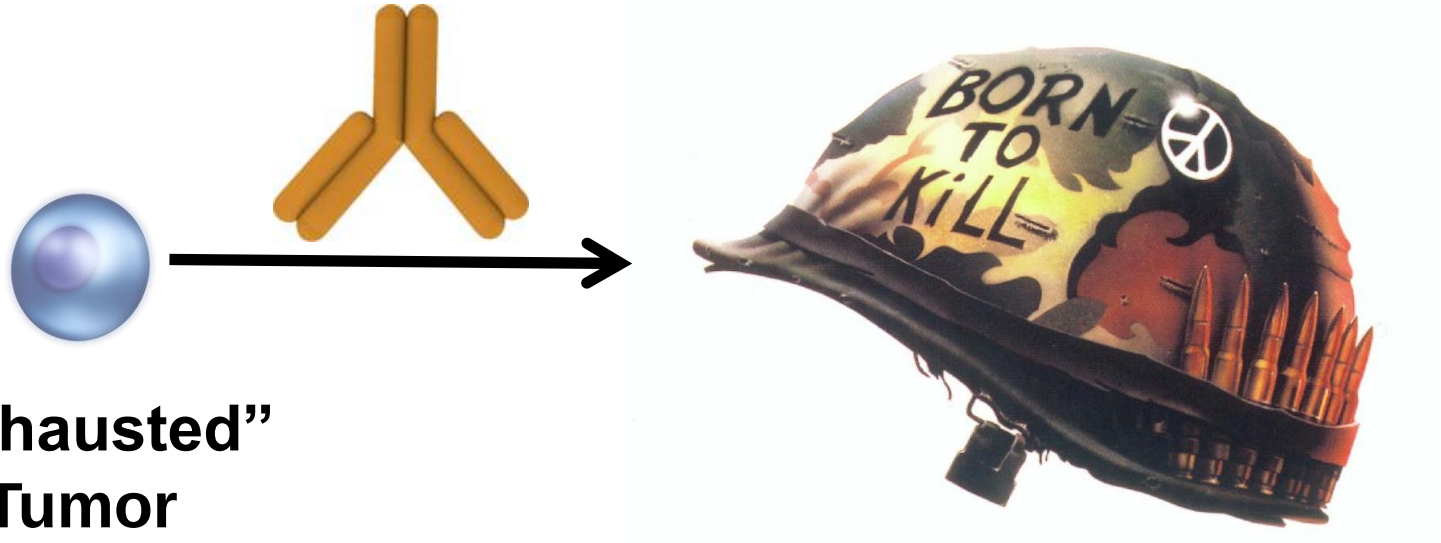
PD-L1 Engages PD-1 to Send the “NO GO” Signal: PD-L1 (or L2) is the ‘Foot on the Brake’



PD-L1 Expression on Tumor Cells OR
Myeloid Cells SENDS that Negative Signal

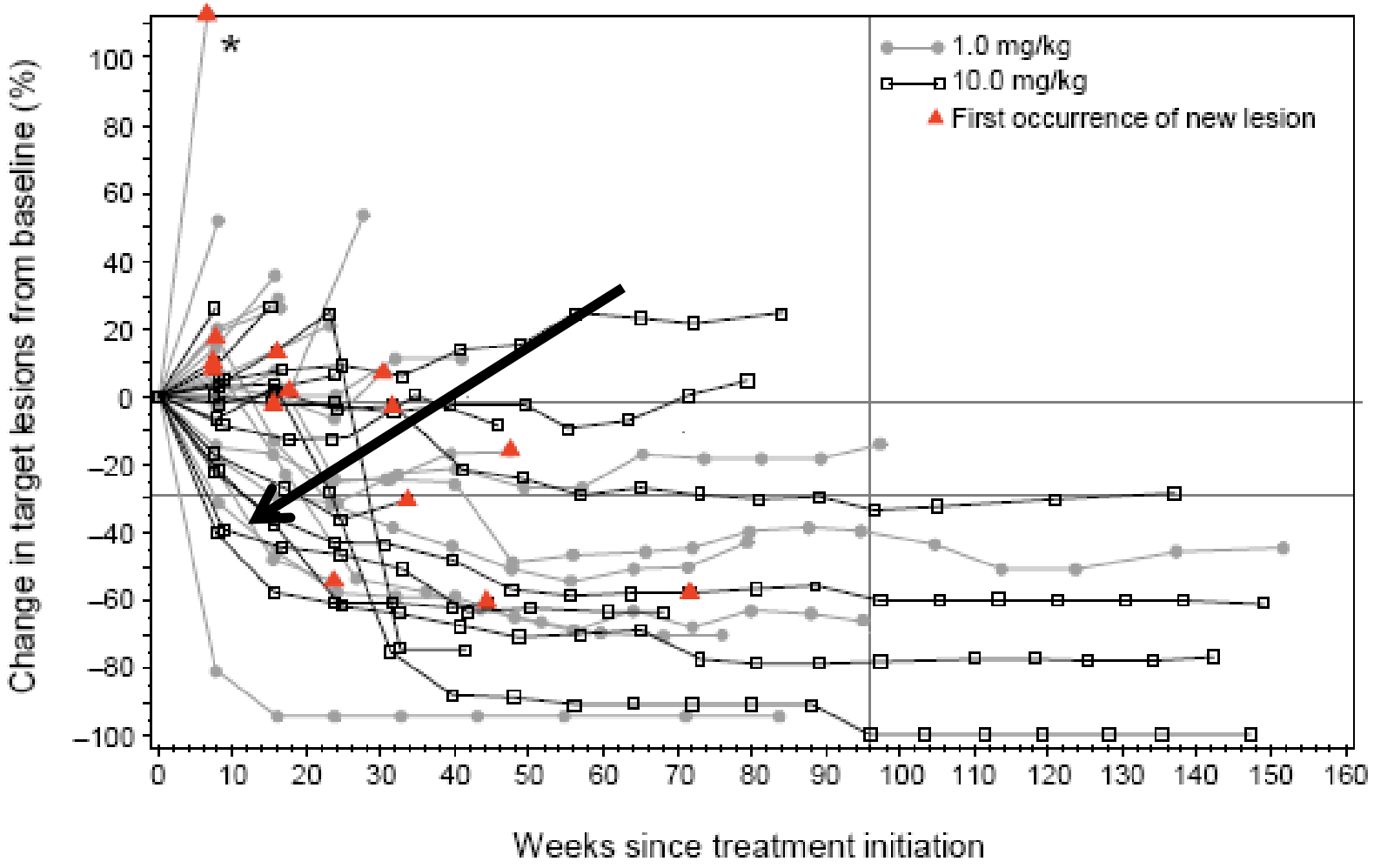
Blocking PD-1 or PD-L1
Allows CD8 T Cells to Regain the Capacity to Kill

Anti-PD-1 or
Anti-PD-L1



“Exhausted”
Tumor
Infiltrating
T Cell

Objective Responses: Evidence of CD8 T Cell Killing



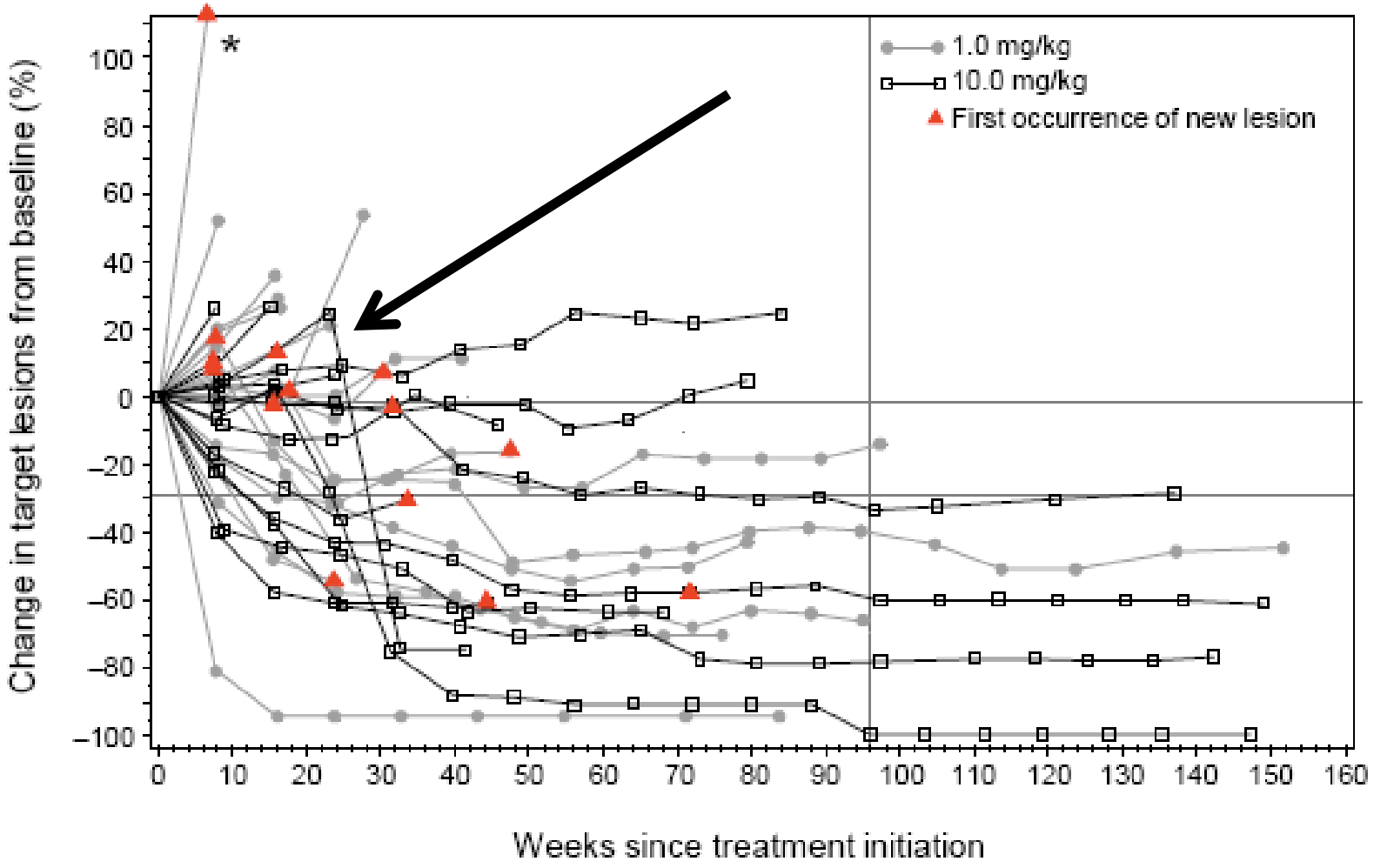
Drake CG et al Journal of Clinical Oncology, 2013 ASCO Annual Meeting Abstracts.
Vol 31, No 15_suppl (May 20 Supplement), 2013: 4514 ASCO 2013

PD-1 Blockade Drives
CD8 T Cell Proliferation

Anti-PD-1 or
Anti-PD-L1

“Exhausted”
Tumor
Infiltrating
T Cell

CD8 T Cell Proliferation
May Lead to "Pseudo-Progression"

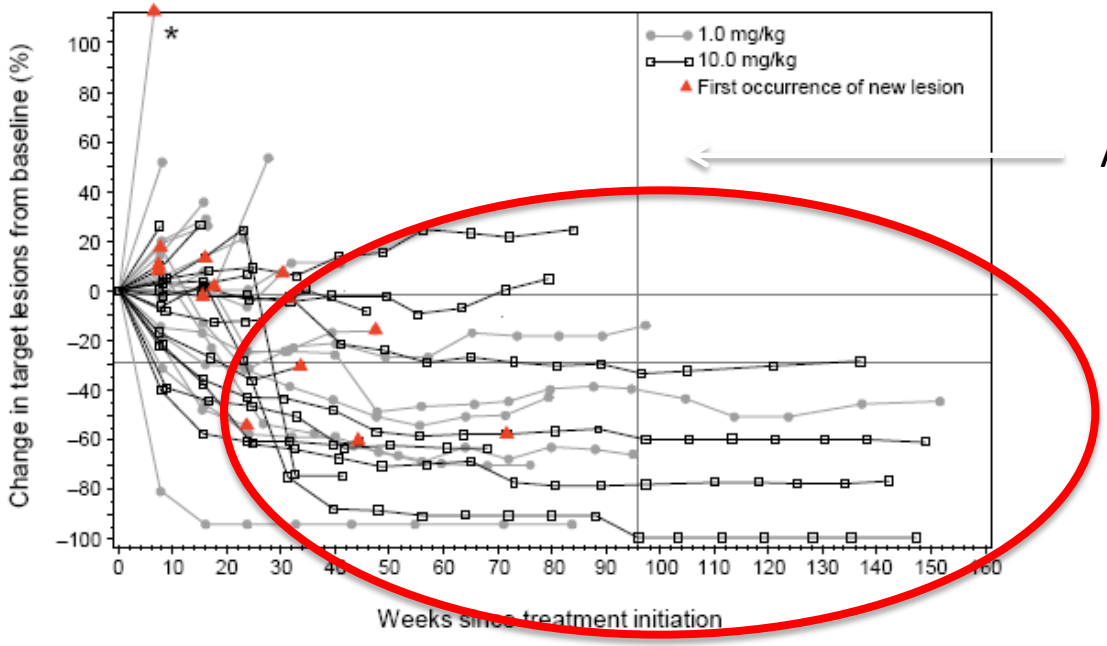


Drake CG et al Journal of Clinical Oncology, 2013 ASCO Annual Meeting Abstracts.
Vol 31, No 15_suppl (May 20 Supplement), 2013: 4514 ASCO 2013

Durable Response Off Treatment
Is this Immune Memory?

- Generally tolerable: fatigue, rash, pruritus, diarrhea
  - 3 deaths: pneumonitis (non-RCC)

- Preliminary efficacy in heavily pre-treated patients:
  - **29% objective responses**
  - Median PFS 7.3 months



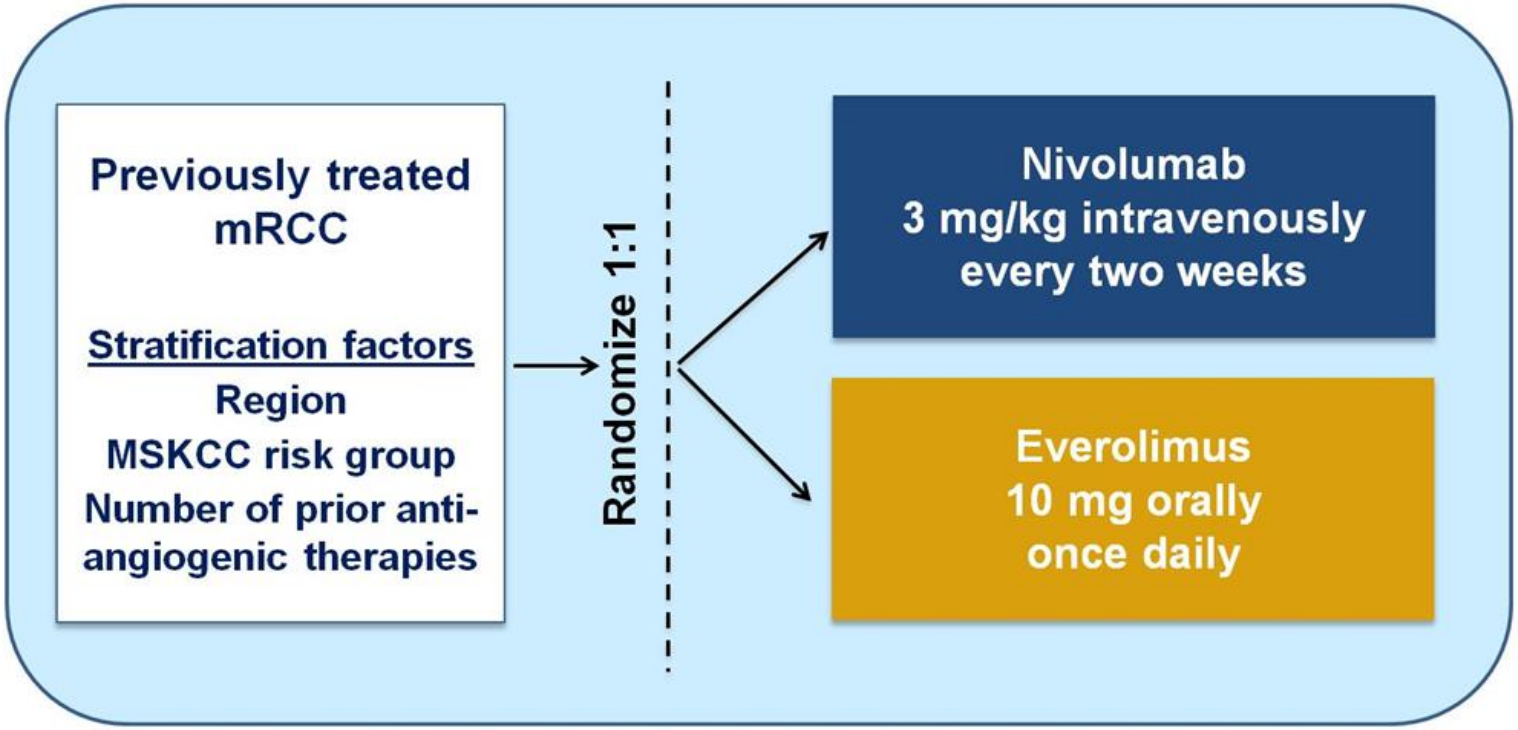
All stopped therapy

Durability of Response Even Off Drug

Drake CG et al Journal of Clinical Oncology, 2013 ASCO Annual Meeting Abstracts. Vol 31, No 15_suppl (May 20 Supplement), 2013: 4514 ASCO 2013

Clinical Data on Immune Checkpoint Blockade

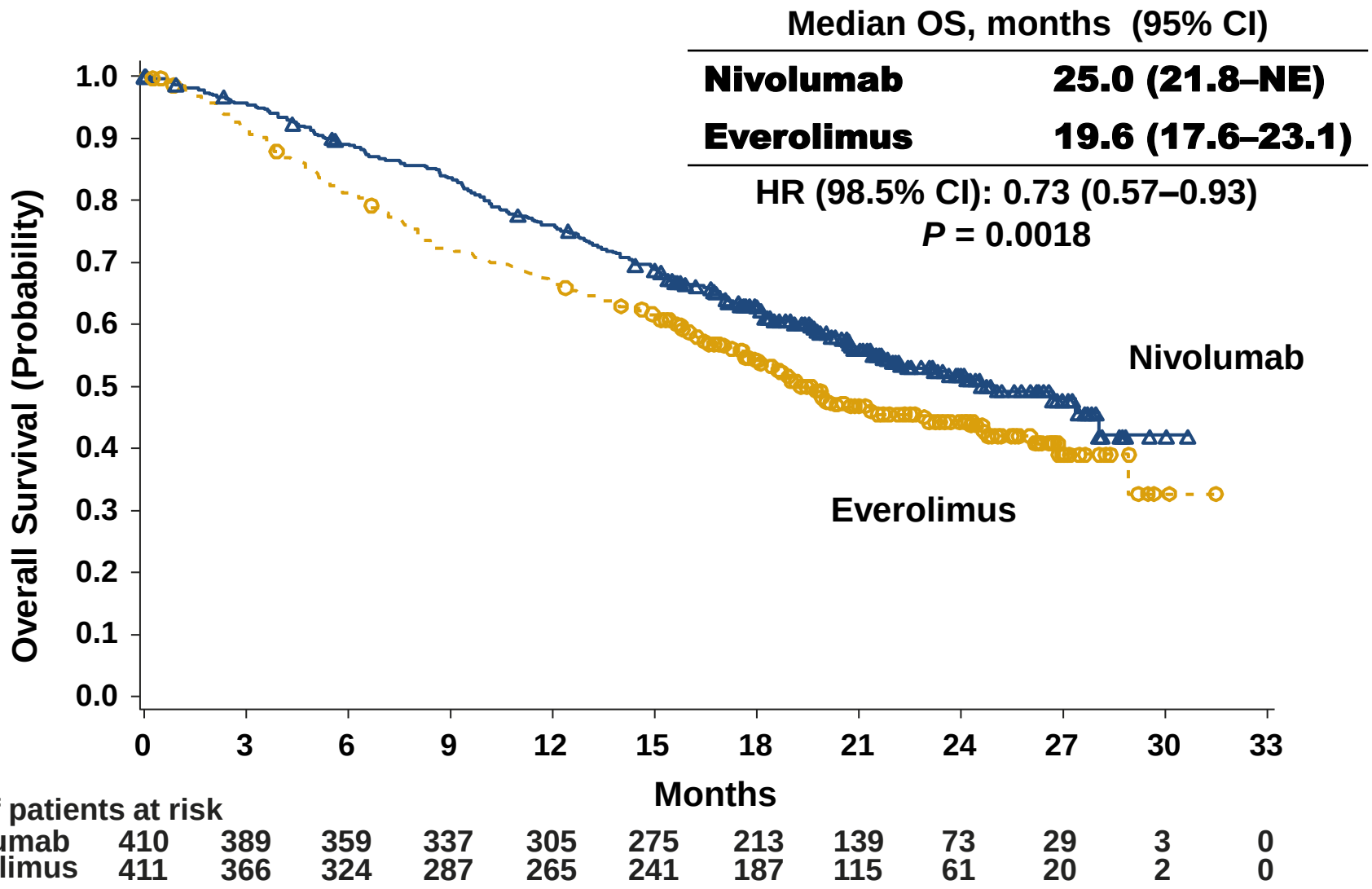
Pivotal Trial of PD-1 Blockade in RCC: Nivolumab vs SOC



- Patients were treated until progression or intolerable toxicity occurred
- Treatment beyond progression was permitted if drug was tolerated and clinical benefit was noted

Presented by Sharma et al at the European Cancer Congress, Vienna, 26 September 2015

The Pivotal Trial: Phase III Trial of Anti-PD-1 (Nivolumab) in Refractory RCC



Sharma et al, NEJM 2015

Treatment-related AEs in ≥10% of patients

	Nivolumab N = 406			Everolimus N = 397		
	Any grade	Grade 3	Grade 4[a]	Any grade	Grade 3	Grade 4[b]
Treatment-related AEs, %	79	18	1	88	33	4
Fatigue	33	2	0	34	3	0
Nausea	14	<1	0	17	1	0
Pruritus	14	0	0	10	0	0
Diarrhea	12	1	0	21	1	0
Decreased appetite	12	<1	0	21	1	0
Rash	10	<1	0	20	1	0
Cough	9	0	0	19	0	0
Anemia	8	2	0	24	8	<1
Dyspnea	7	1	0	13	<1	0
Edema peripheral	4	0	0	14	<1	0
Pneumonitis	4	1	<1	15	3	0
Mucosal inflammation	3	0	0	19	3	0
Dysgeusia	3	0	0	13	0	0
Hyperglycemia	2	1	<1	12	3	<1
Stomatitis	2	0	0	29	4	0
Hypertriglyceridemia	1	0	0	16	4	1
Epistaxis	1	0	0	10	0	0

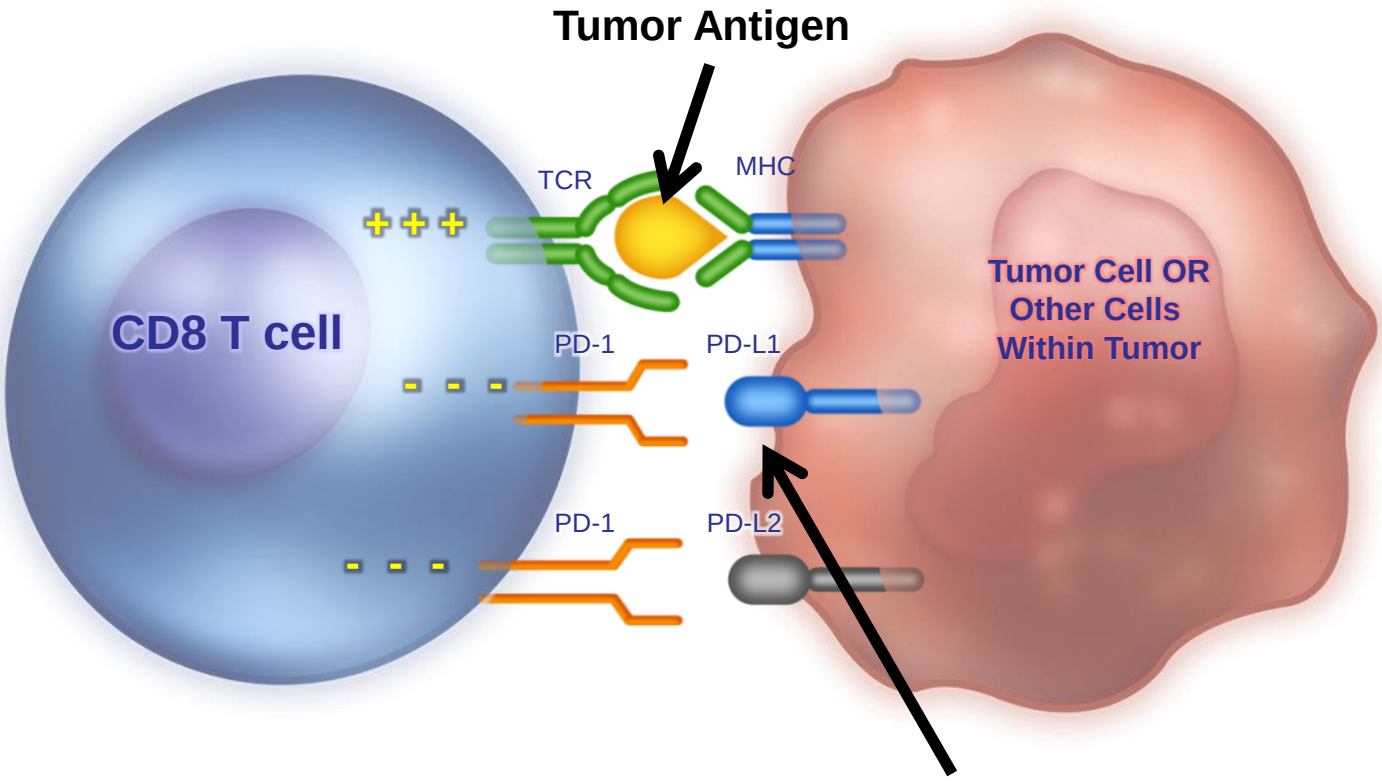
[a] Grade 4 AEs not listed in table: increased blood creatinine (1), acute kidney injury (1), anaphylactic reaction (1).
[b] Grade 4 AEs not listed in table: increased blood triglycerides (2), acute kidney injury (1), sepsis (1), chronic obstructive pulmonary disorder (1), increased blood cholesterol (1), neutropenia (1), pneumonia (1).

PD-1 / PD-L1 Blocking Antibodies: Partial list of FDA Approvals

- Pembrolizumab in melanoma
- Nivolumab in melanoma
- Nivolumab in NSCLC (squamous)
- Nivolumab in NSCLC (non-squamous)
- Pembrolizumab in NSCLC
- Nivolumab in Kidney Cancer

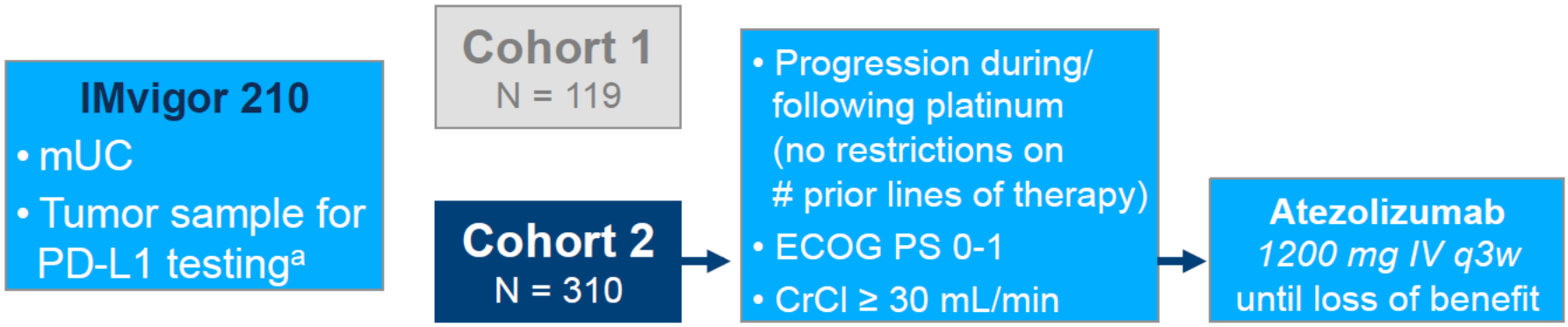
- ? Next – Atezolizumab in Bladder Cancer

Can PD-L1 Expression in the Tumor / Tumor Microenvironment Predict Response?



CD8 T Cells are Being Held in Check
WHEN PD-L1 is Expressed

Anti-PD-L1 In Bladder Cancer
Imvigor 210 (Phase II)



- Co-primary endpoints: (1) ORR per confirmed RECIST v1.1 and central IRF
  (2) ORR per investigator-assessed modified RECIST
- Key secondary endpoints: DOR, PFS, OS, safety

Hoffman-Centis, ASCO GU 2016

Anti-PD-L1 In Bladder Cancer Results

	All (N = 310)
ORR (95% CI) per confirmed IRF RECIST v1.1	15% (11, 19)
ORR (95% CI) per investigator mRECIST	19% (15, 24)
Complete response (CR) per confirmed IRF RECIST v1.1	5%

Hoffman-Centis, ASCO GU 2016

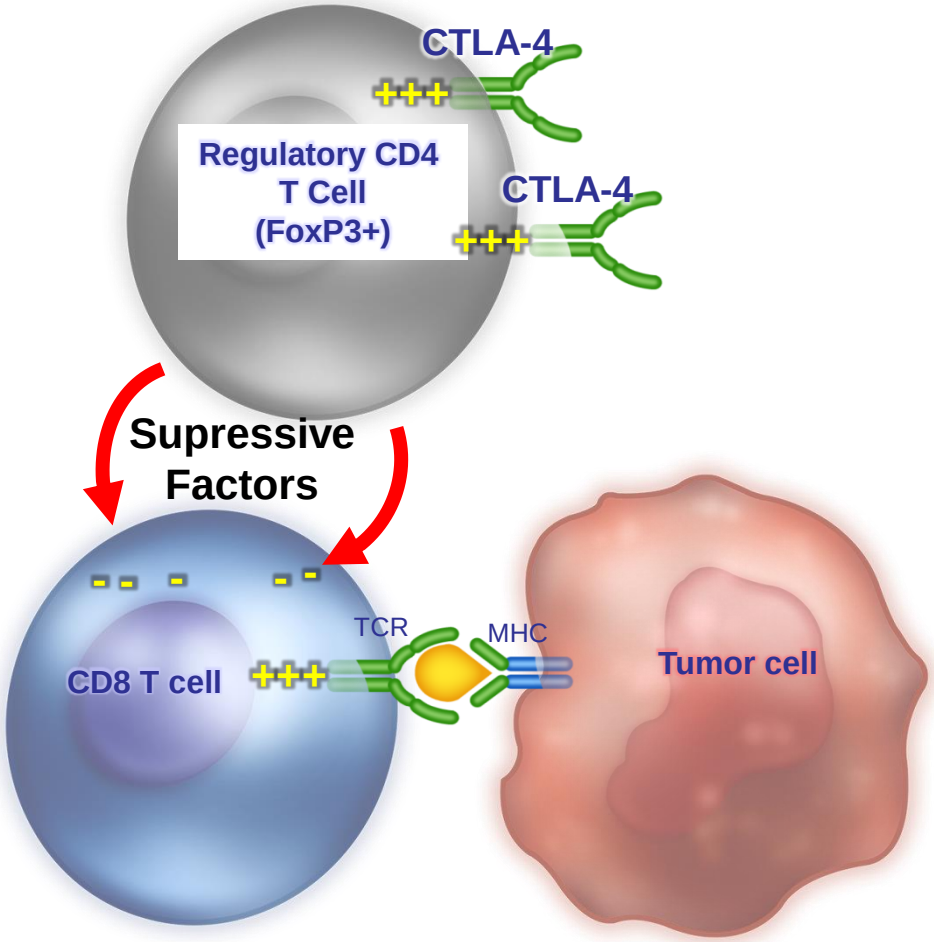
PD-L1 Expression on Myeloid Cells Is (Weakly) Associated with Response

	IC2/3 (n = 100)	IC1/2/3 (n = 207)	All (N = 310)	IC1 (n = 107)	IC0 (n = 103)
ORR (95% CI) per confirmed IRF RECIST v1.1	26% (18, 36)	18% (13, 24)	15% (11, 19)	10% (5, 18)	8% (3, 15)
ORR (95% CI) per investigator mRECIST	27% (19, 37)	22% (16, 28)	19% (15, 24)	17% (10, 25)	13% (7, 21)
Complete response (CR) per confirmed IRF RECIST v1.1	11%	6%	5%	2%	2%

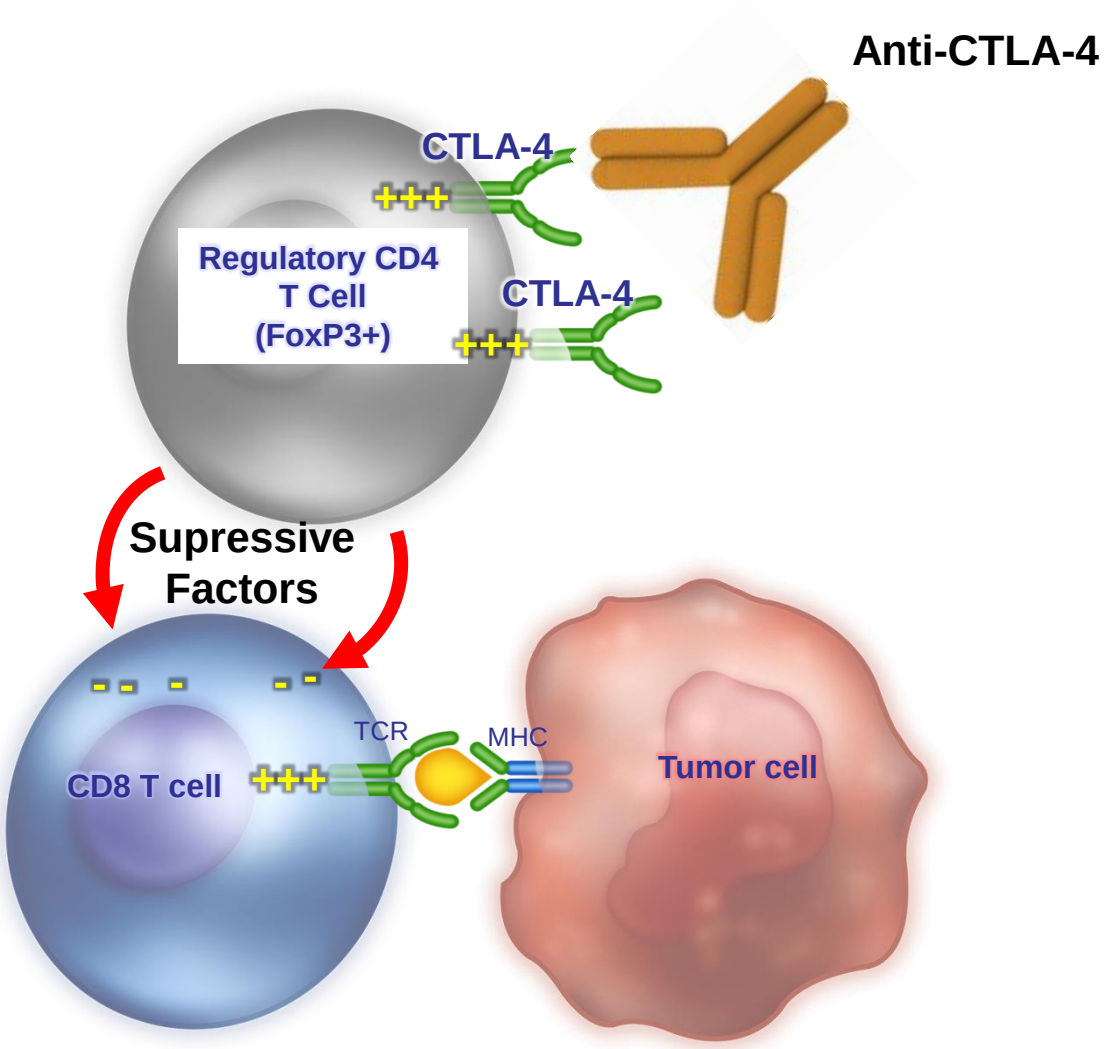
Hoffman-Centis, ASCO GU 2016

Immunotherapy Combination Regimens

CTLA-4 is Expressed on CD4 T Cells (Treg) that Turn off CD8 Killer T Cells



Anti-CTLA-4 **May** Deplete the Suppressive Regulatory T Cells



High Rate of Immune-Related Adverse Events when Anti-CTLA-4 is Combined with Anti-PD-1

Table 2. Highest Grade of Selected Treatment-Related Adverse Events That Occurred in at Least One of the Patients Who Received the Concurrent Regimen.*

Event	Cohort 1 (N=14)		Cohort 2 (N=17)		Cohort 2a (N=16)		Cohort 3 (N=6)		All Patients in Concurrent-Regimen Group (N=53)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	number of patients (percent)									
Pneumonitis	1 (7)	0	2 (12)	1 (6)	0	0	0	0	3 (6)	1 (2)
Endocrinopathy	1 (7)	0	3 (18)	0	1 (6)	0	2 (33)	1 (17)	7 (13)	1 (2)
Hypothyroidism	0	0	2 (12)	0	0	0	0	0	2 (4)	0
Hypophysitis	0	0	1 (6)	0	0	0	1 (17)	1 (17)	2 (4)	1 (2)
Thyroiditis	0	0	1 (6)	0	1 (6)	0	1 (17)	0	3 (6)	0
Adrenal insufficiency	0	0	2 (12)	0	0	0	0	0	2 (4)	0
Hyperthyroidism	0	0	1 (6)	0	0	0	1 (17)†		2 (4)†	0
Thyroid-function results abnormal	1 (7)	0	0	0	0	0	0	0	1 (2)	0
Hepatic disorder	4 (29)	3 (21)	5 (29)	3 (18)	2 (12)	1 (6)	1 (17)	1 (17)	12 (23)	8 (15)
Aspartate aminotransferase increased	4 (29)	3 (21)	4 (24)	2 (12)	2 (12)	1 (6)	1 (17)	1 (17)	11 (21)	7 (13)
Alanine aminotransferase increased	3 (21)	2 (14)	5 (29)	3 (18)	2 (12)	0	1 (17)	1 (17)	11 (21)	6 (11)
Gastrointestinal disorder	5 (36)	1 (7)	6 (35)	2 (12)	6 (38)	2 (13)	3 (50)	0	20 (38)	5 (9)
Diarrhea	5 (36)	0	5 (29)	1 (6)	5 (31)	2 (13)	3 (50)	0	18 (34)	3 (6)
Colitis	1 (7)	1 (7)	2 (12)	1 (6)	1 (6)	0	1 (17)	0	5 (9)	2 (4)
Renal disorder	1 (7)	1 (7)	1 (6)	1 (6)	1 (6)	1 (6)	0	0	3 (6)	3 (6)
Blood creatinine increased	1 (7)	1 (7)	1 (6)	1 (6)	1 (6)	1 (6)	0	0	3 (6)	3 (6)
Acute renal failure	0	0	1 (6)	1 (6)	1 (6)	1 (6)	0	0	2 (4)	2 (4)
Renal failure	0	0	1 (6)	1 (6)	0	0	0	0	1 (2)	1 (2)
Tubulointerstitial nephritis	1 (7)	0	0	0	0	0	0	0	1 (2)	0
Skin disorder	10 (71)	1 (7)	14 (82)	0	10 (62)	1 (6)	3 (50)	0	37 (70)	2 (4)
Rash	8 (57)	1 (7)	11 (65)	0	7 (44)	1 (6)	3 (50)	0	29 (55)	2 (4)
Pruritus	6 (43)	0	11 (65)	0	7 (44)	0	1 (17)	0	25 (47)	0
Urticaria	0	0	0	0	1 (6)	0	0	0	1 (2)	0
Blister	0	0	1 (6)	0	0	0	0	0	1 (2)	0
Infusion-related reaction	0	0	1 (6)	0	0	0	0	0	1 (2)	0

* Only the highest grade of event was counted for each patient. Adverse events that require more frequent monitoring or intervention with immune suppression or hormone replacement are listed, according to a prespecified list of terms from the *Medical Dictionary for Regulatory Activities*, version 15.1. The dose levels in the cohorts were as follows: cohort 1 received 0.3 mg of nivolumab per kilogram of body weight and 3 mg of ipilimumab per kilogram, cohort 2 received 1 mg of nivolumab per kilogram and 3 mg of ipilimumab per kilogram, cohort 2a received 3 mg of nivolumab per kilogram and 1 mg of ipilimumab per kilogram, and cohort 3 received 3 mg of nivolumab per kilogram and 3 mg of ipilimumab per kilogram. The doses in cohort 3 exceeded the maximum doses that were associated with an acceptable level of adverse events, and the doses in cohort 2 were identified as the maximum doses that were associated with an acceptable level of adverse events. The numbers reported for the specific adverse events within an organ category may be greater than the total number reported for the organ category because patients who had more than one adverse event were counted for each event but were counted only once for the organ category.

† Data include one patient with an event of unknown grade.

Hepatitis

Colitis

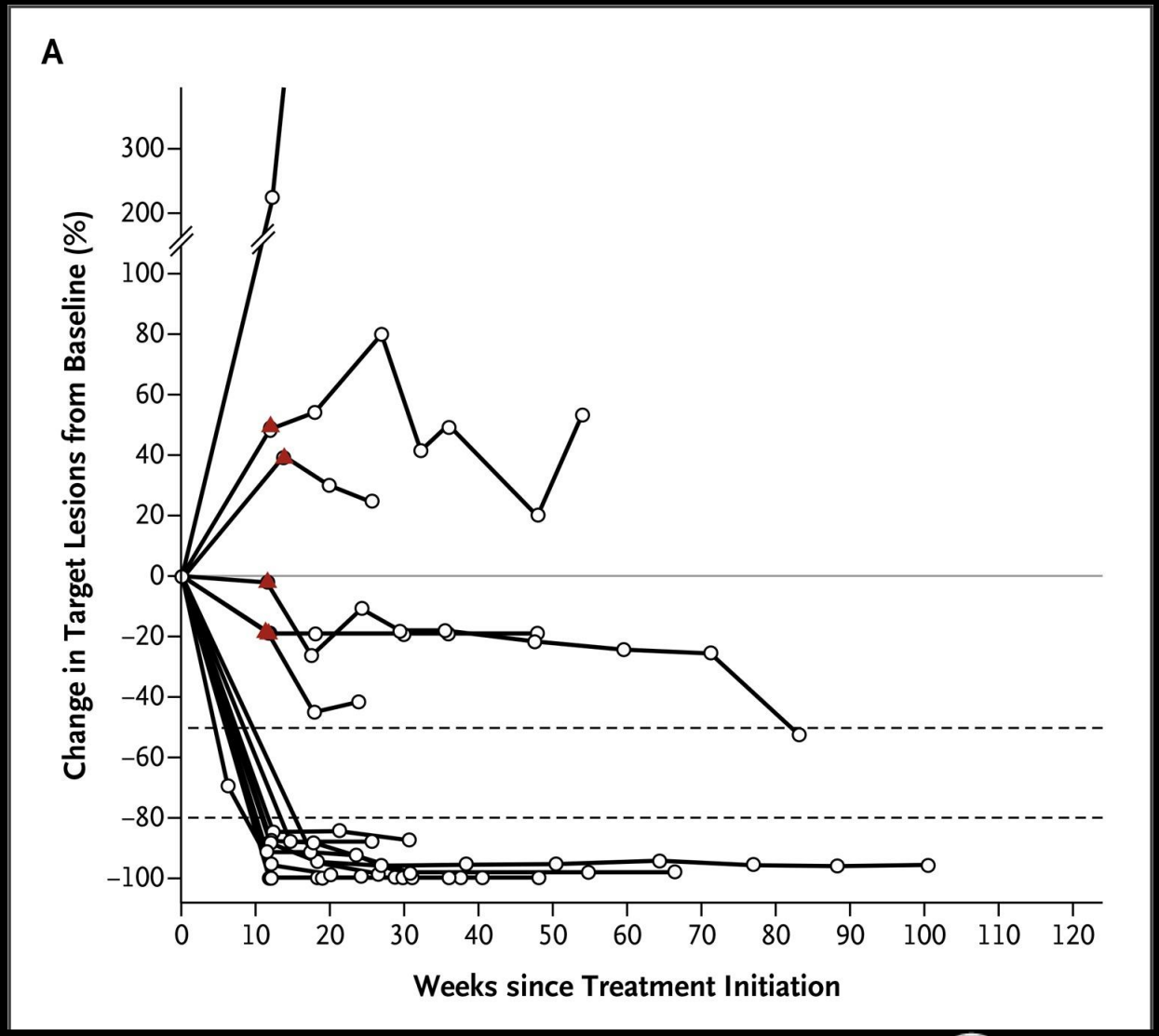
Nephritis

Dermatitis

The NEW ENGLAND JOURNAL of MEDICINE

Wolchok JD et al. N Engl J Med 2013;369:122-133

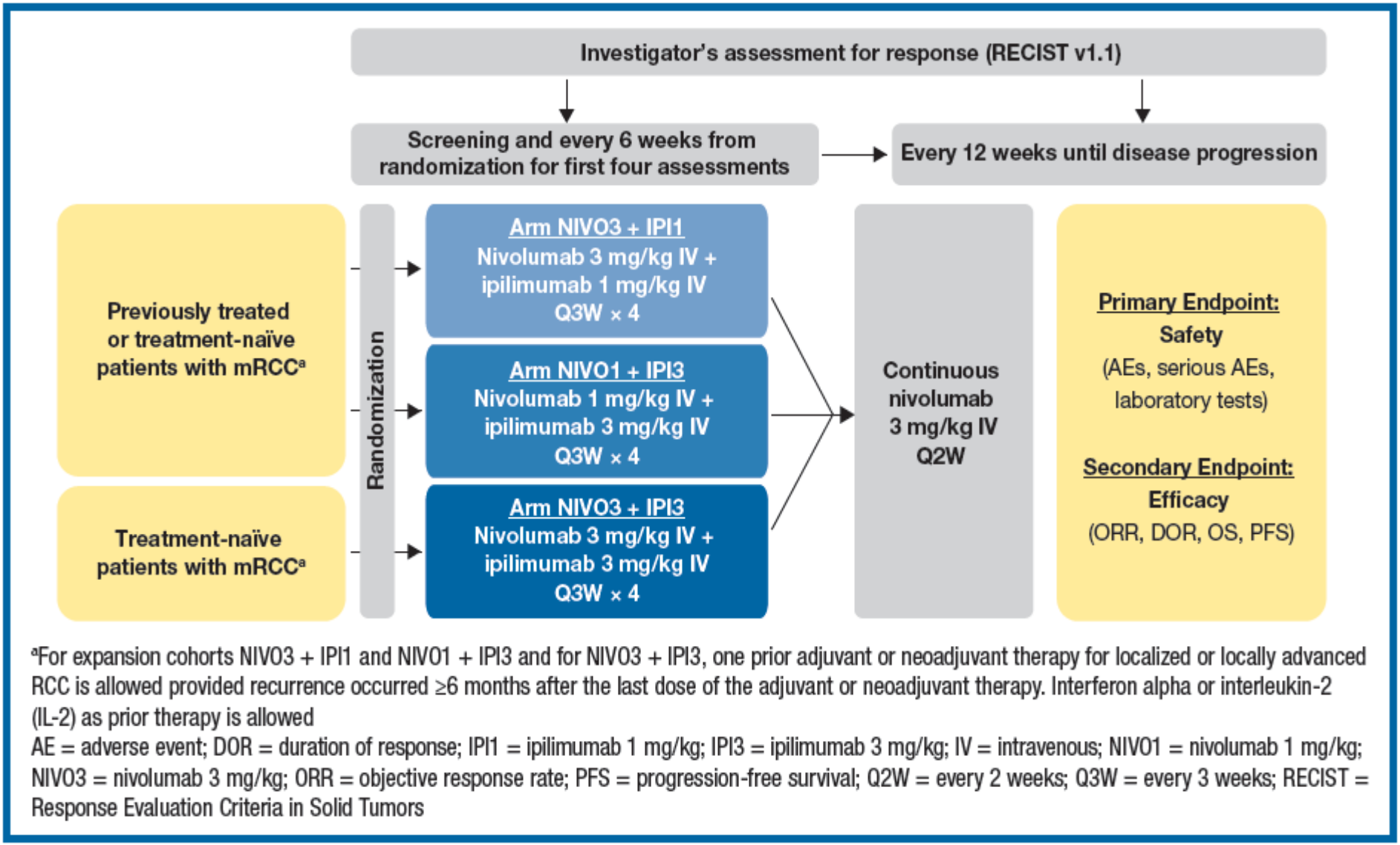
Blocking BOTH PD-1 and CTLA-4 (ipilimumab and nivolumab in advanced melanoma)



Wolchok JD et al. N Engl J Med 2013;369:122-133

The NEW ENGLAND JOURNAL of MEDICINE

Combined Checkpoint Blockade in Kidney Cancer



[a]For expansion cohorts NIVO3 + IPI1 and NIVO1 + IPI3 and for NIVO3 + IPI3, one prior adjuvant or neoadjuvant therapy for localized or locally advanced RCC is allowed provided recurrence occurred ≥6 months after the last dose of the adjuvant or neoadjuvant therapy. Interferon alpha or interleukin-2 (IL-2) as prior therapy is allowed

AE = adverse event; DOR = duration of response; IPI1 = ipilimumab 1 mg/kg; IPI3 = ipilimumab 3 mg/kg; IV = intravenous; NIVO1 = nivolumab 1 mg/kg; NIVO3 = nivolumab 3 mg/kg; ORR = objective response rate; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors

Motzer et al al ASCO 2015

Increased Response Rate with Combination Treatment

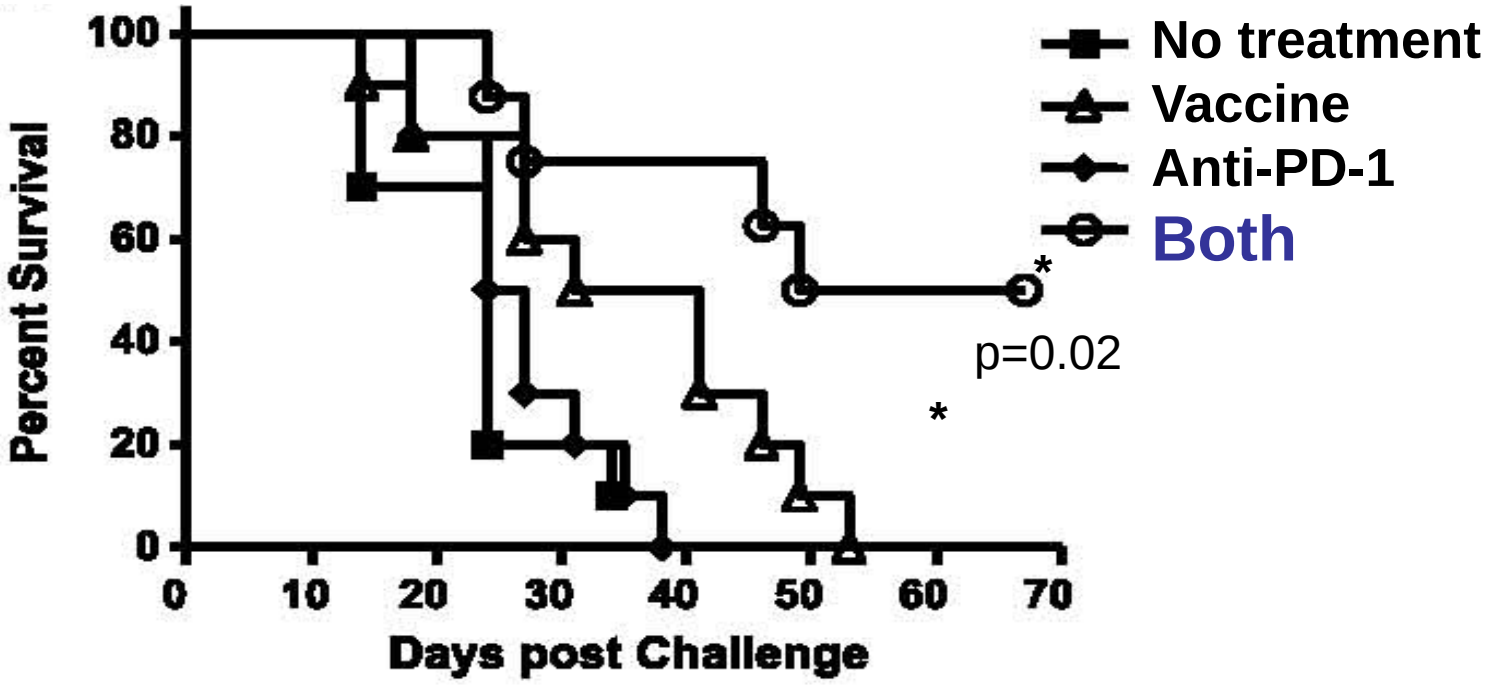
	NIVO3 + IPI1	NIVO1 + IPI3	NIVO3 + IPI3
	N = 47	N =47	N = 6
Confirmed ORR[a], n (%) 95% CI	18 (**38.3**) 24.5–53.6	19 (**40.4**) 26.4–55.7	0
Best overall response[b], n (%) Complete response Partial response Stable disease Progressive disease	 **4 (8.5)** 14 (29.8) 17 (36.2) 10 (21.3)	 1 (2.1) 18 (38.3) 17 (36.2) 7 (14.9)	 0 0 5 (83.3) 1 (16.7)

Increased Toxicity with Combination Treatment

	NIVO3 + IPI1		NIVO1 + IPI3	
	N = 47		N = 47	
Preferred term, n (%)	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Total patients with an event	**39 (83.0)**	**16 (34.0)**	**44 (93.6)**	**30 (63.8)**

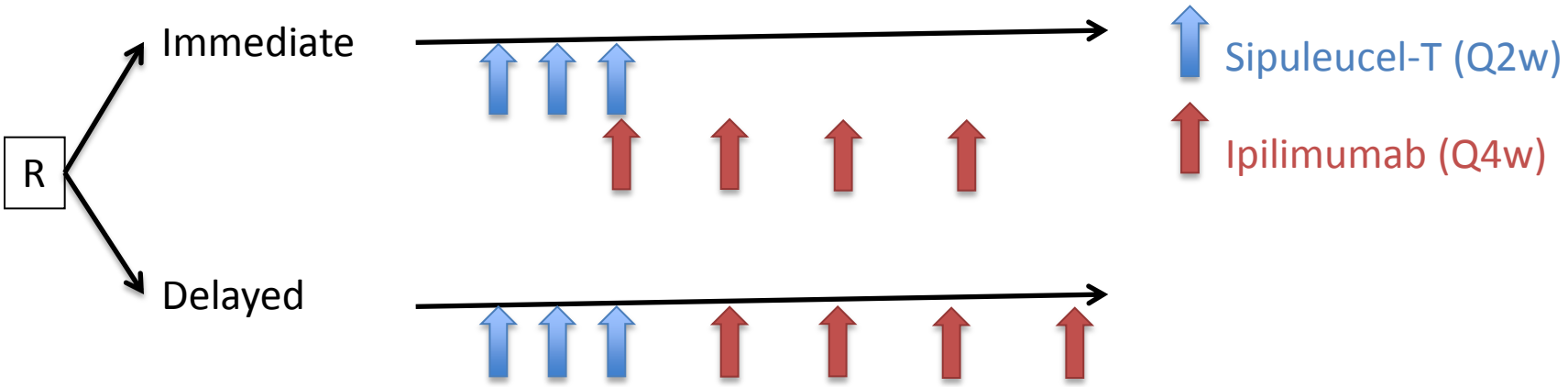
Combining a Cancer Vaccine With Checkpoint Blockade

(In Mice)



Li and Jooss: ***Clinical Cancer Research***

Combining Sipuleucel-T With CTLA-4 Blockade



Larry Fong UCSF and Pam Sharma MDACC

UCSF
University of California
San Francisco

Outstanding Clinical Questions

1. What are mechanisms of progression after initial response ?
    1. **Loss of tumor antigen**
    2. Loss of Class I MHC on Target Cells
    3. Emerging suppressive cells

2. What are mechanisms of resistance to immunotherapy?
    1. **Lack of T cell infiltrate**
    2. Other immune checkpoint molecules
    3. Suppressive cells (T cells and others)
    4. Suppressive cytokines (TGF-beta, IL-10)

3. What are optimal combination regimens?
    1. Anti-PD-1 / PD-L1 plus anti-CTLA-4
    2. Anti-PD-1 / PD-L1 plus a VEGF-targeted therapy
    3. Combining checkpoint blockade with an agonist (OX40, CD40, 41BB)

4. What is optimal treatment regimen?
    1. Fixed time period then stop
    2. Continuous i.e. lifelong
    3. Treat to maximal response than stop
    4. What is the rate of response to re-treatment

5. Why has prostate cancer not been as responsive to PD-1 or CTLA-4 blockade?

Summary

1. Immune Checkpoint Blockade Expanding Role in Cancer Treatment
    1. Well-tolerated
    2. Good response rate
    3. Some responses maintained long-term off-treatment
    4. Outstanding questions
        1. Optimal regimen
        2. Predictive biomarkers for response

2. Why are the Non-Responsive Tumors Non-Responsive?

3. Combination Approaches = Next Step Forward
    1. + Chemotherapy
    2. + Radiation Therapy
    3. + Cancer Vaccines
    4. Combining multiple checkpoint blocking agents