Society for Immunotherapy of Cancer (SITC)

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

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Advances in Cancer Immunotherapy™ - Los Angeles
June 19, 2015

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Society for Immunotherapy of Cancer

Outline

- Basic mechanisms of FDA-approved T cell checkpoint inhibitors
- Indications and clinical data supporting approval
- Clinical work-up prior to treatment
- Side effects
- Management of side effects
- When to stop treatment
- Combination approaches

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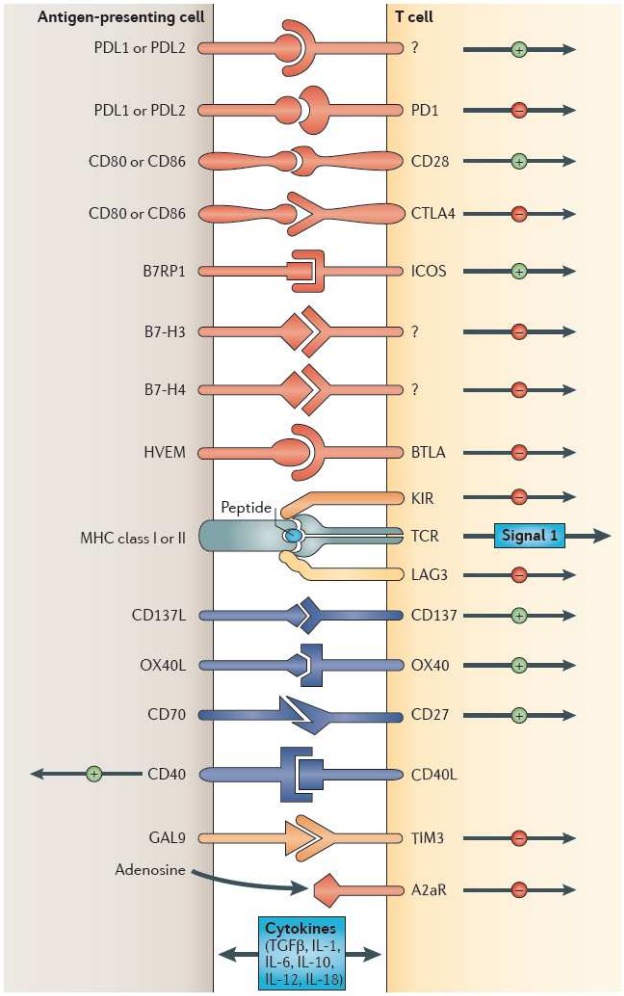
Checkpoint inhibitors

- Pathways that maintain self-tolerance
- Limit immune response



Pardoll *Nature Reviews Cancer* **12**, 252-264 (April 2012)

Checkpoint inhibitors

Antitumor immune response requires breaking immune tolerance

Barriers

- Processing antigens
- Presenting antigens
- Activation of T cells
- Maintenance of response

CTLA4 inhibition and vaccination

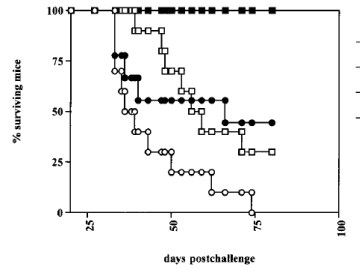


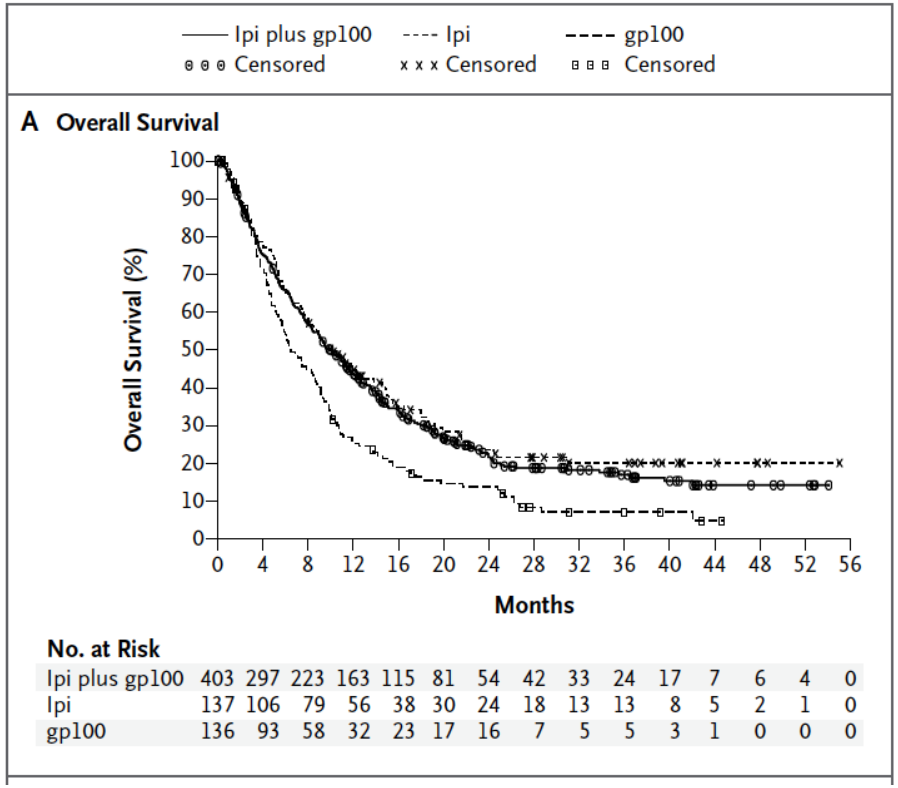
Figure 4. Mice bearing B16-F10 lung metastases show enhanced survival when treated with anti–CTLA-4 and F10/g vaccine. B16-F10 cells (5×10^4 per mouse) were injected into the tail vein and 24 h later, treatment was started using control hamster IgG (10 mice, ○), anti–CTLA-4 antibody 9H10 (9 mice; ●), irradiated F10/g (10^6 subcutaneously) in combination with hamster IgG (10 mice; □) or 9H10 (13 mice; ■) on days 1, 4, and 7, according to the dosing schedule used for subcutaneous tumors (see Fig. 1 legend). Mice were followed for survival, and in some subjects death due to extensive pulmonary metastasis was confirmed by harvesting lungs postmortem.

Figure 6. Rejection of B16-BL6 or B16-F10 as a result of treatment with anti–CTLA-4 and GM-CSF–producing vaccines causes autoimmune skin and hair depigmentation. After successful treatment for B16-BL6 subcutaneously or B16-F10 intravenously, C57Bl/6 mice developed skin and hair depigmentation. (A) Depigmentation of both sites of vaccination and challenge, after rejection of a day 0 tumor. (B) Progressive depigmentation found in a mouse rejecting a B16-BL6 subcutaneous tumor, established 8 d before treatment started. (C) Depigmentation at the site of vaccination of a mouse cured from preestablished B16-F10 lung metastases.

Andrea van Elsas JEM 1999

Checkpoint inhibitors

Ipilimumab (αCTLA4)



- <u>Ipilimumab</u>
  Melanoma 2011
- Improved survival
- Prolonged treatment free survival

Hodi N Engl J Med 2010

Checkpoint inhibitors

Nivolumab (αPD1)

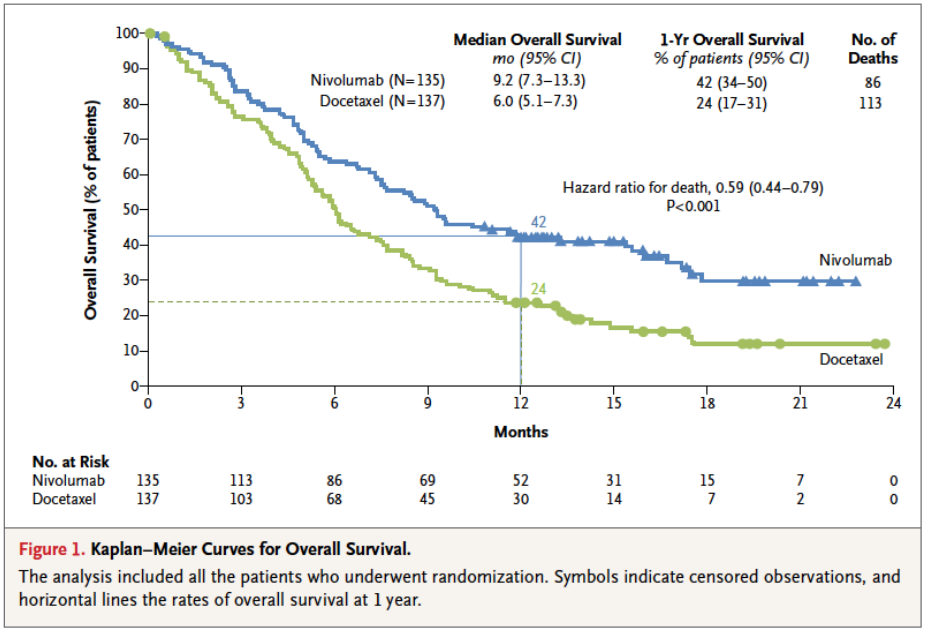


Figure 1. Kaplan–Meier Curves for Overall Survival.
The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

Brahmer N Engl J Med 2015

- Block interaction with PDL1/2 and inhibits T cell anti-tumor response in the TME
- Pembrolizumab *Melanoma 2014*
- Nivolumab *Melanoma 2014* and *Lung 2015*

PD-1 Blockade in Tumors with Mismatch Repair Deficiency

Dung Le, Jennifer Uram, Hao Wang, Bjarne Bartlett, Holly Kemberling, Aleksandra Eyring, Andrew Skora, Brandon Luber, Nilofer Azad, Daniel Laheru, Barbara Biedrzycki, Ross Donehower, Atif Zaheer, George Fisher, Todd Crocenzi, Steven Duffy, James Lee, Richard Goldberg, Albert de la Chapelle, Minori Koshiji, Feriyl Bhaijee, Thomas Huebner, Ralph Hruban, Laura Wood, Nathan Cuka, Drew Pardoll, Nickolas Papadopoulas, Kenneth Kinzler, Shibin Zhou, Toby Cornish, Janis Taube, James Eshleman, Robert Anders, Bert Vogelstein and Luis Diaz Jr.

The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
Providence Cancer Center, Portland, OR
Stanford University School of Medicine, Stanford, CA
Bons Secours Cancer Institute, Richmond, VA
University of Pittsburgh, Pittsburgh, PA
Ohio State University Comprehensive Cancer Center, Columbus, OH
Merck & Co., Inc., Kenilworth, NJ

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Mismatch Repair Deficiency

Microsatellite instability in tumor cells is due to deficient DNA mismatch repair:

- **germline** (Lynch syndrome) and/or **sporadic** mutations (MLH1, MSH2, MSH6, PMS2, EpCAM)
- **epigenetic silencing** (MLH1 hyper-methylation)

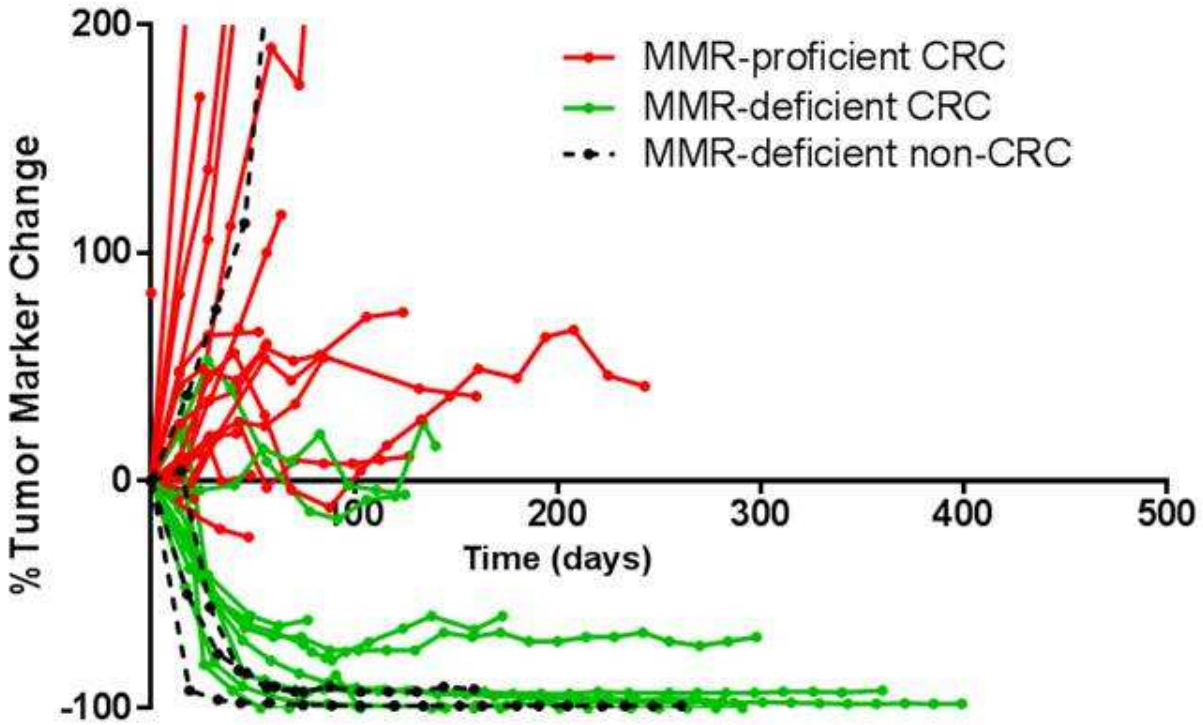
First defined by Papadopoulos and Vogelstein in early 1990s.

Study Design

Colorectal Cancers		Non-Colorectal Cancers
Cohort A **Deficient in Mismatch Repair (n=25)**	Cohort B **Proficient in Mismatch Repair (n=25)**	Cohort C **Deficient in Mismatch Repair (n=21)**

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Primary endpoint: immune-related 20-week PFS rate and response rate
- Mismatch repair testing using standard PCR-based test for detection of microsatellite instability

Biochemical Responses



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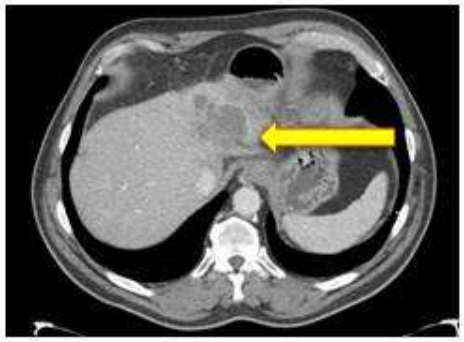
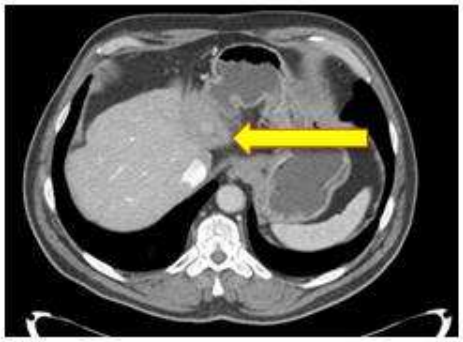
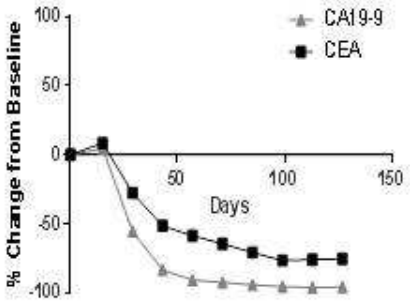
Mismatch repair deficient Cholangiocarcinoma



Baseline



Week 20



Tumor Markers

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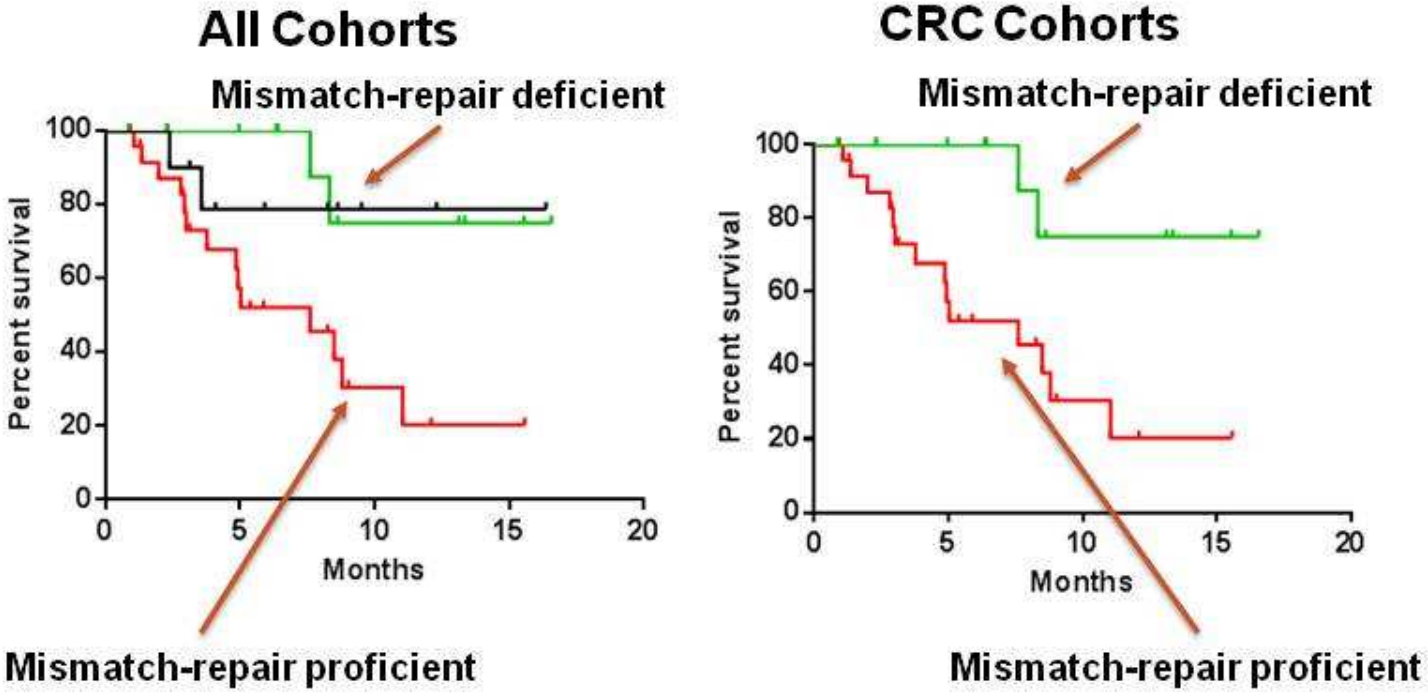
Overall Survival



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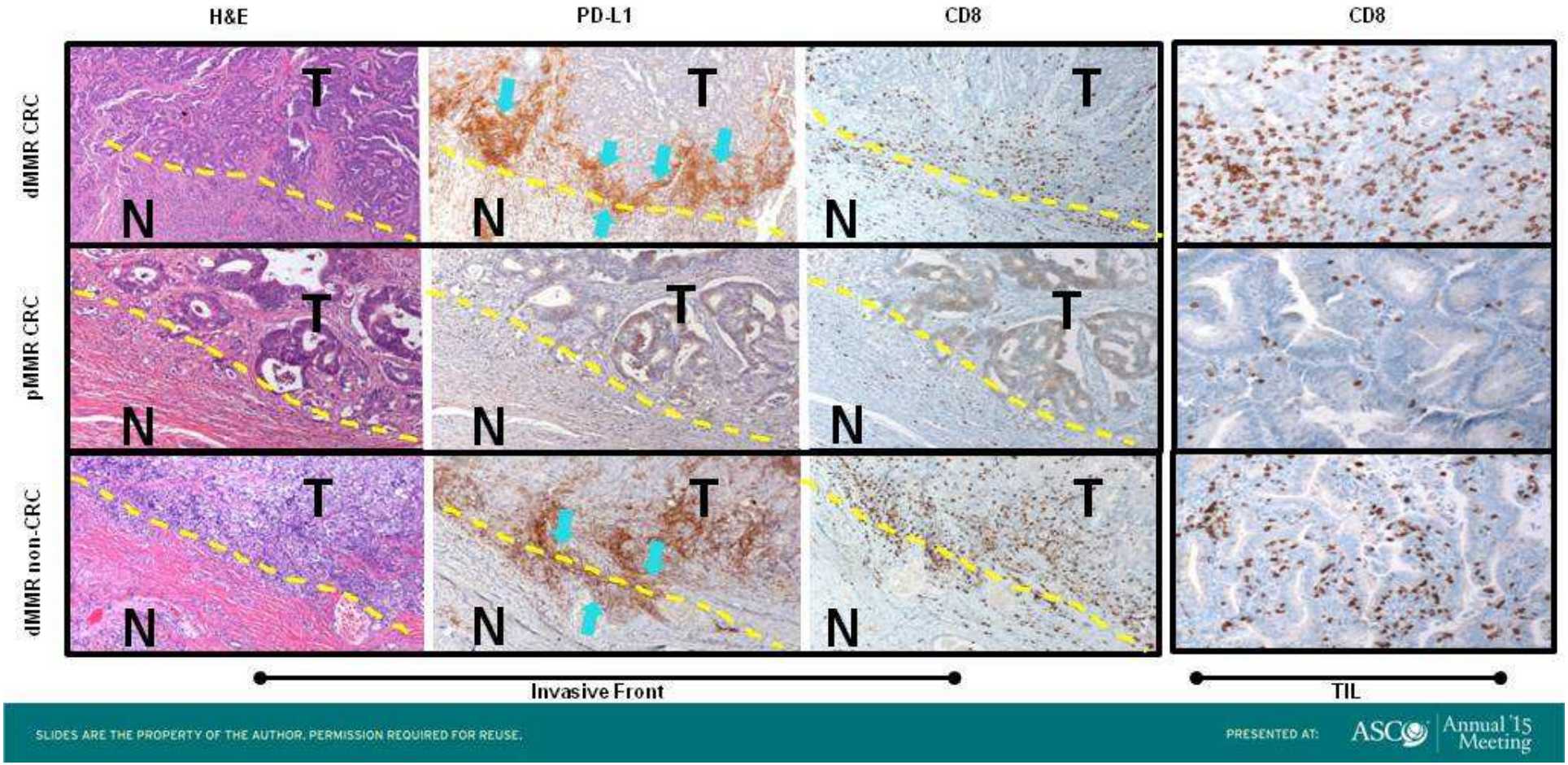
Adverse Events

Event-no. (%)	All Grades N=41
Any	14 (34)
Generalized Symptoms	3 (7)
Pancreatitis	6 (15)
Pneumonitis	1 (2)
Endocrine Disorders	5 (12)
Rash/pruritus	7 (17)
Thrombocytopenia	1 (2)

Up through Jan 2015

Baseline PD-L1 Expression and CD8 T Cell Infiltration



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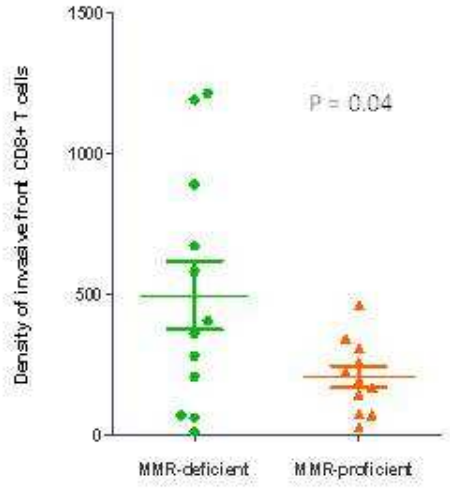
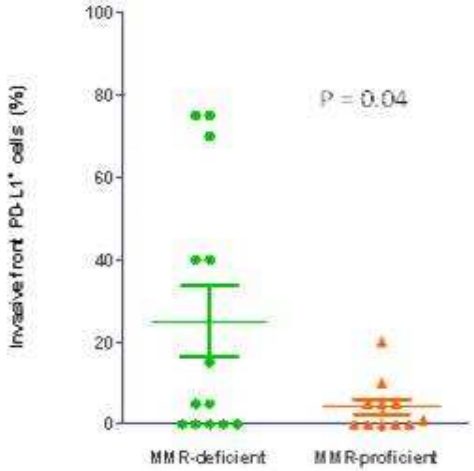
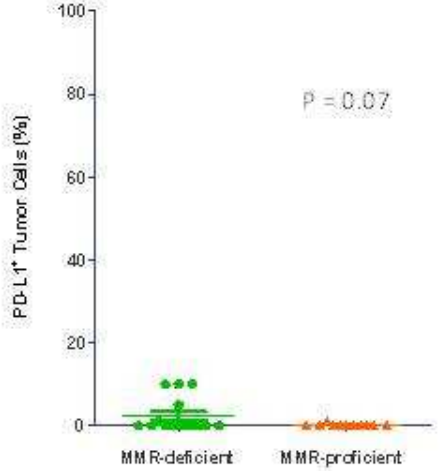
Invasive Front PD-L1 Expression and CD8 T Cell Infiltration



Invasive Front CD8⁺ T cells



Invasive Front PD-L1 Expression



Tumor Front PD-L1 Expression

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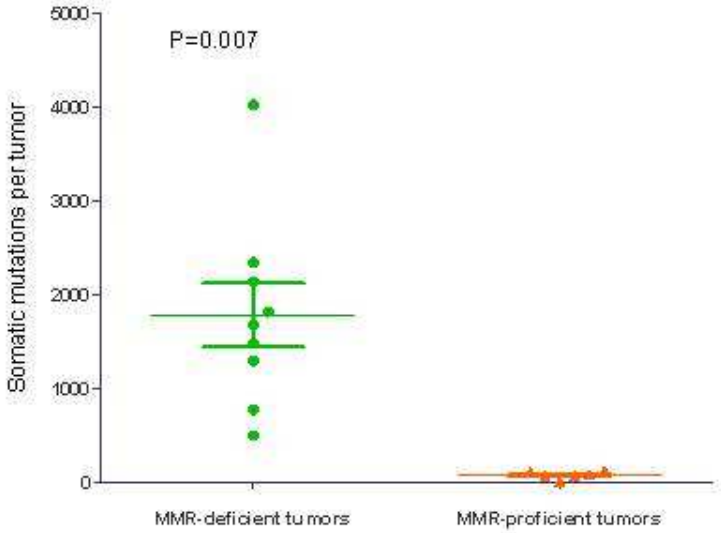
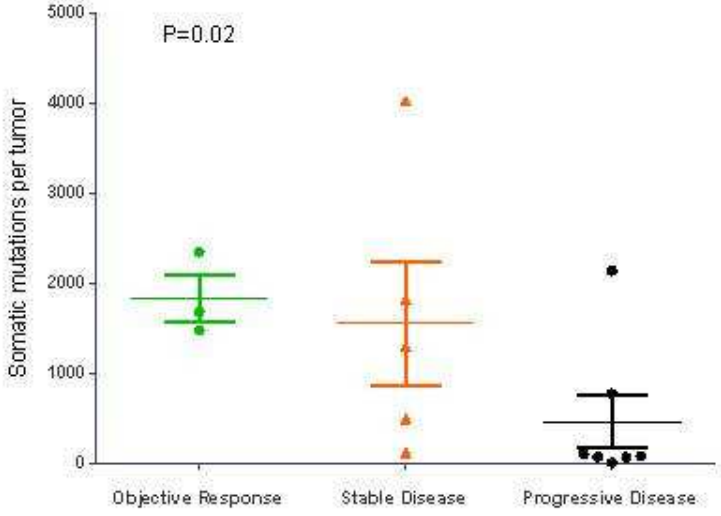
Mutation Burden is Associated with Efficacy





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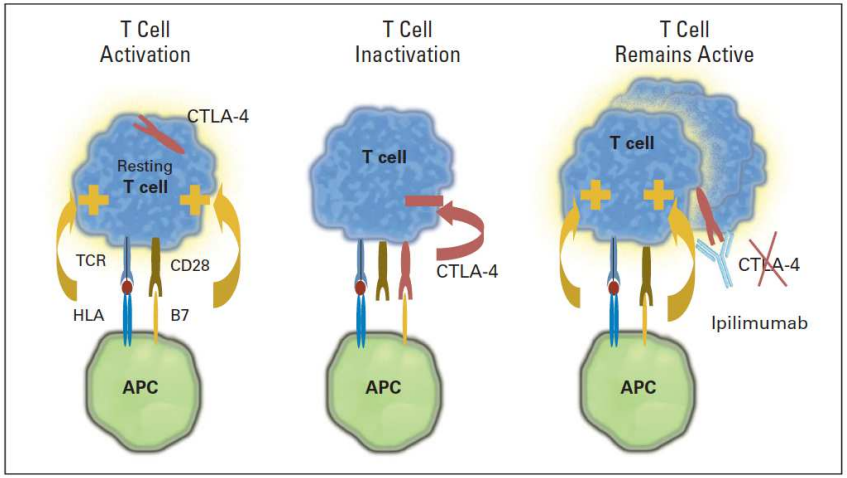
Clinical work-up prior to treatment

- Appropriate for complete staging

- Considerations regarding iAEs
  - Brain metastasis
  - Autoimmune diseases
  - Chronic viral infections
  - Need for immune suppression

Side effects



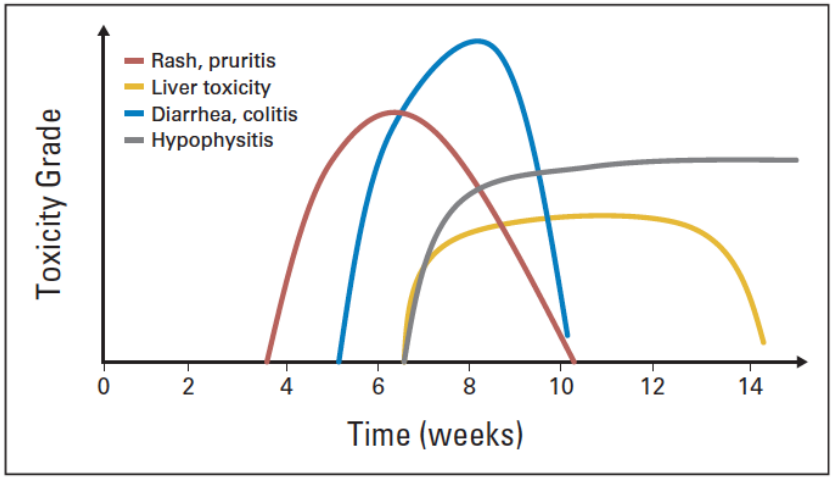


Fig 2. Kinetics of appearance of immune-related adverse event.

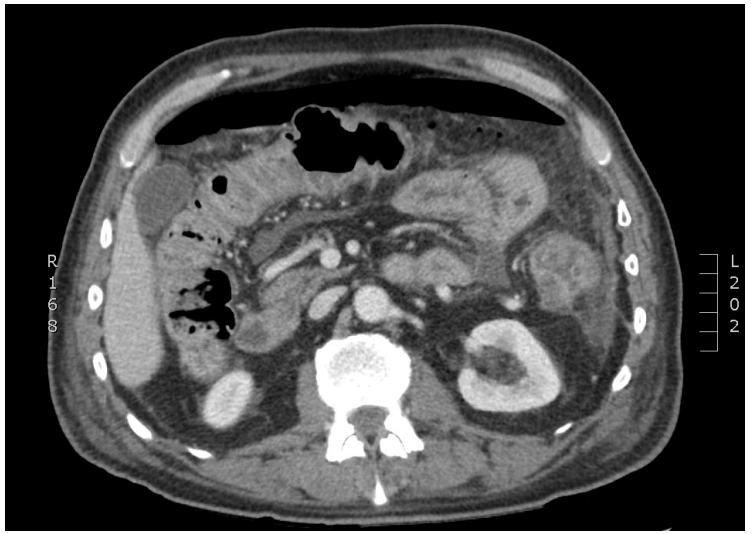
Table 2. Occurrence of Adverse Events With Ipilimumab (10 mg/kg)

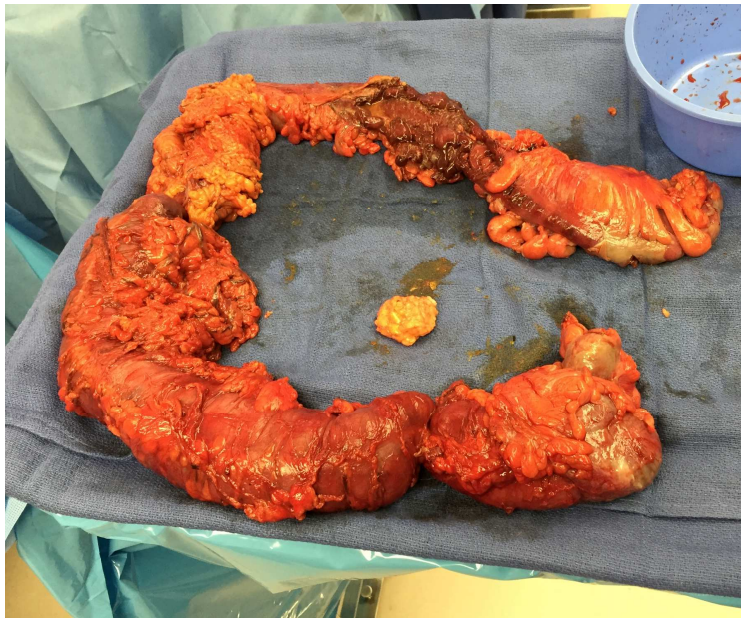
Adverse Event	Any Grade (%)	Grade 3 or 4 (%)
Skin (rash, pruritus)	47-68	0-4
GI (diarrhea, colitis)	31-46	8-23
Hepatitis	3-9	3-7
Hypophysitis	4-6	1-5

Weber JCO 2012

Management of Side Effects

- Sustained T cell activity off target
- Recognition?
- How to turn if off?
  - Steroids
  - Others
  - REMS Ipilimumab





Side effects

- Mechanism of response differs
- Mechanism of irAEs differs
- Evaluate patients appropriate for toxicity

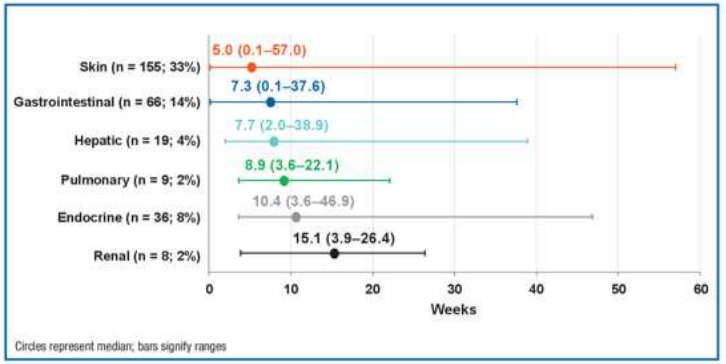
Table 3. Select treatment-related AEs

AE category Pts reporting AE, %	NIVO monotherapy (N = 576)	
	Any grade	Grade 3–4
Any AE	49.0	3.6
Skin	34.0	0.7
Pruritus	17.2	0.2
Rash	12.7	0.3
Vitiligo	7.8	N/A
Gastrointestinal	13.4	1.2
Diarrhea	12.7	0.5
Endocrine	7.8	0.3
Hypothyroidism	4.2	0
Hyperthyroidism	2.1	0.2
Hepatic	4.2	1.0
Aspartate aminotransferase increased	2.8	0.3
Alanine aminotransferase increased	1.9	0.7
Pulmonary	1.9	0
Pneumonitis	1.7	0
Renal	1.4	0.3
Blood creatinine increased	0.5	0

Pts may have had more than one event

- Median time to onset for treatment-related select AEs ranged from 5.0 weeks for skin AEs to 15.1 weeks for renal AEs (**Figure 1**)
- In the 282 pts who experienced new treatment-related select AEs, 85% did so within the first 16 weeks of treatment (**Figure 2**)
- The kinetics of onset and resolution are depicted in Figure 3
- Select AEs generally resolved within several weeks apart from endocrinopathies, as some events were not considered resolved due to the continuing need for hormone replacement therapy

Figure 1. Time to onset of select treatment-related AEs (any grade; N = 474)



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When to stop

- Ipilimumab
  - Induction 4 doses and response assesment
  - May re-induce
- Pembrolizumab or Nivolumab
  - Course often stretches one to two years
  - ?6 months past best response

When to stop treatment

- Each organ system associated with stopping criteria
- General rules
  - Withhold for **moderate iAEs**
    - May use steroids for a few weeks
    - Symptoms better in a week or less
  - Permanently discontinue for **severe iAEs**
    - Need for prolonged steroids or other immune modulators
    - Inability to reduce steroids to <7.5mg per day

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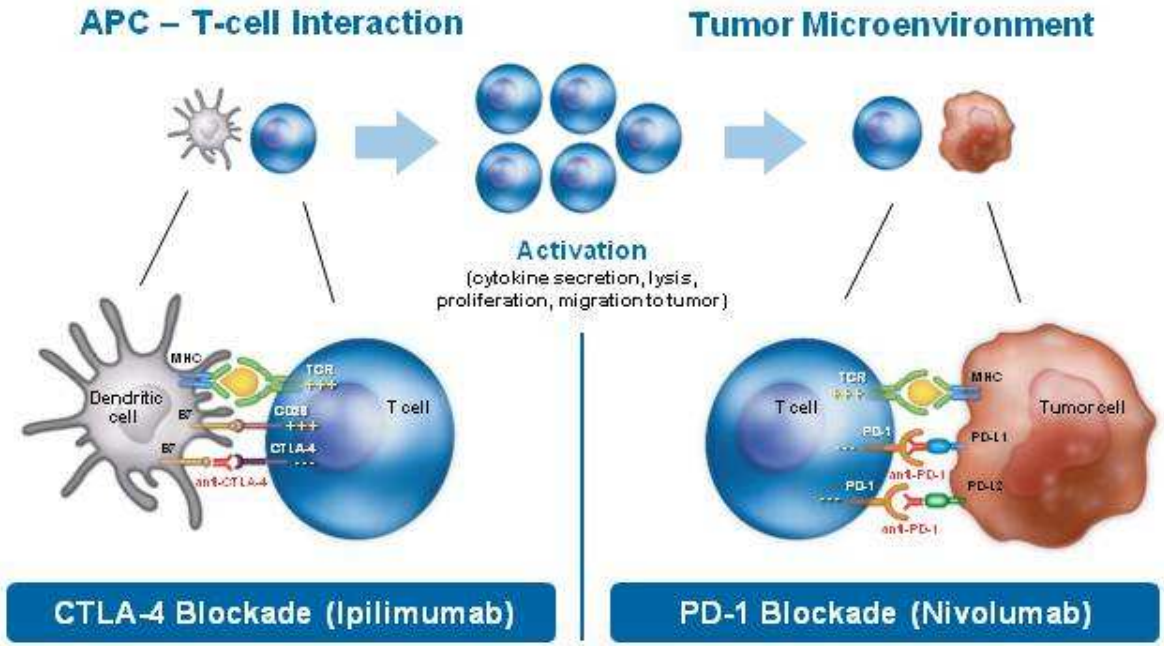
Biologic Rationale for Combined PD-1 and CTLA-4 Blockade

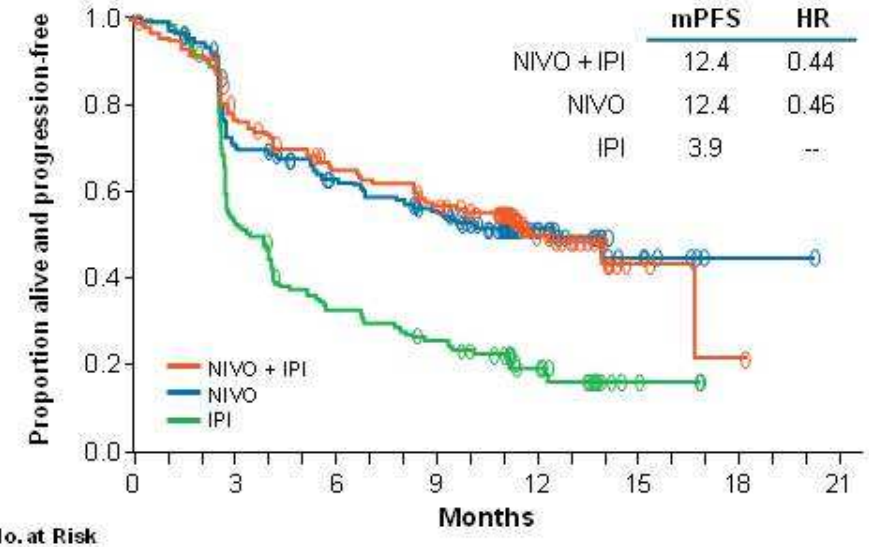
- Ipilimumab (IPI) monotherapy in melanoma improves OS (~20% of treated patients alive ≥3 years)[1]
- Phase III studies of nivolumab (NIVO) monotherapy in advanced melanoma:[2,3]
  - 1-year OS rate of 73% and ORR of 40% in untreated melanoma (BRAF wild-type)
  - ORR of 32% after progression on IPI, or IPI and a BRAF inhibitor if BRAF mutation-positive



1. Schadendorf et al. *J Clin Oncol* 2015 Feb 9 [Epub ahead of print]; 2. Robert et al. *N Engl J Med* 2015;372:320-330; 3. Weber et al. *Lancet Oncol* 2015;16:375-384.

PFS by PD-L1 Expression Level (1%)

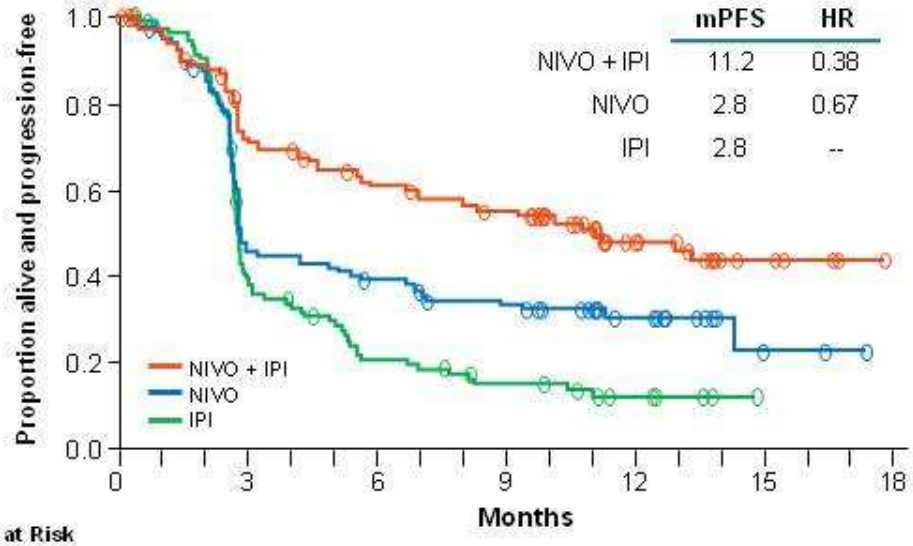
PD-L1 ≥1%*



	mPFS	HR
NIVO + IPI	12.4	0.44
NIVO	12.4	0.46
IPI	3.9	--

No. at Risk								
NIVO + IPI	155	113	91	78	32	4	1	
NIVO	171	115	97	83	34	7	1	0
IPI	164	83	47	36	16	3		

PD-L1 <1%*



	mPFS	HR
NIVO + IPI	11.2	0.38
NIVO	2.8	0.67
IPI	2.8	--

No. at Risk							
NIVO + IPI	123	82	65	57	26	6	0
NIVO	117	50	42	34	13	2	0
IPI	113	39	19	12	5	0	

*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

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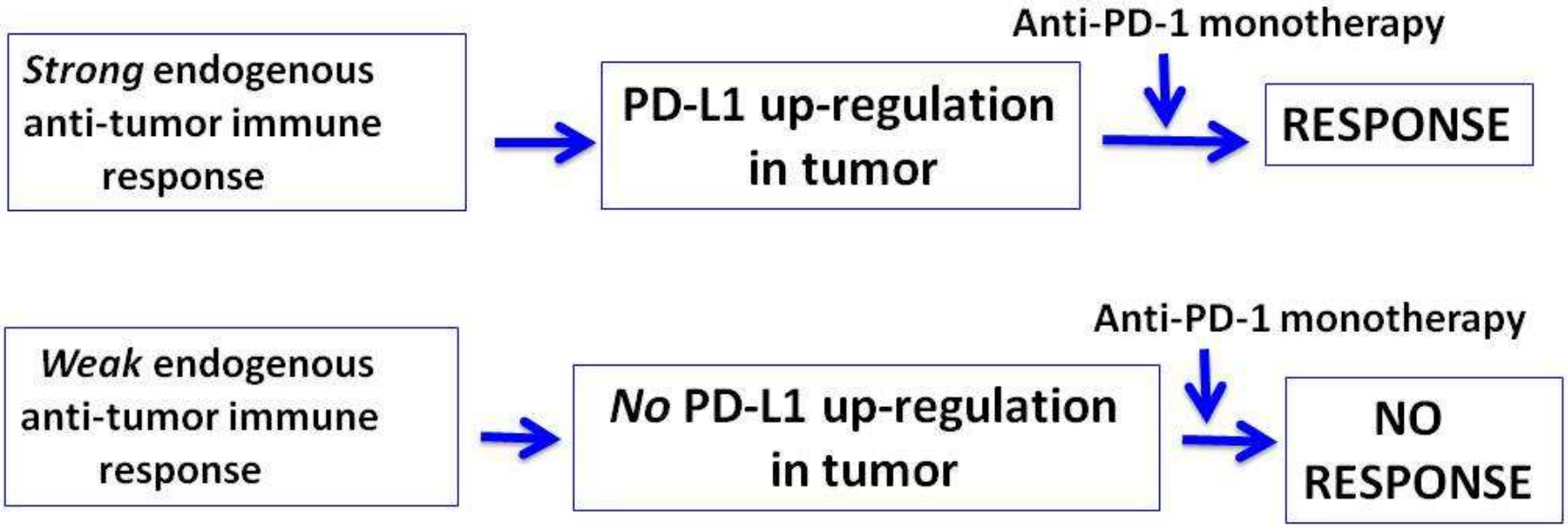
Treatment-Related Select AEs Reported in ≥10% of Patients

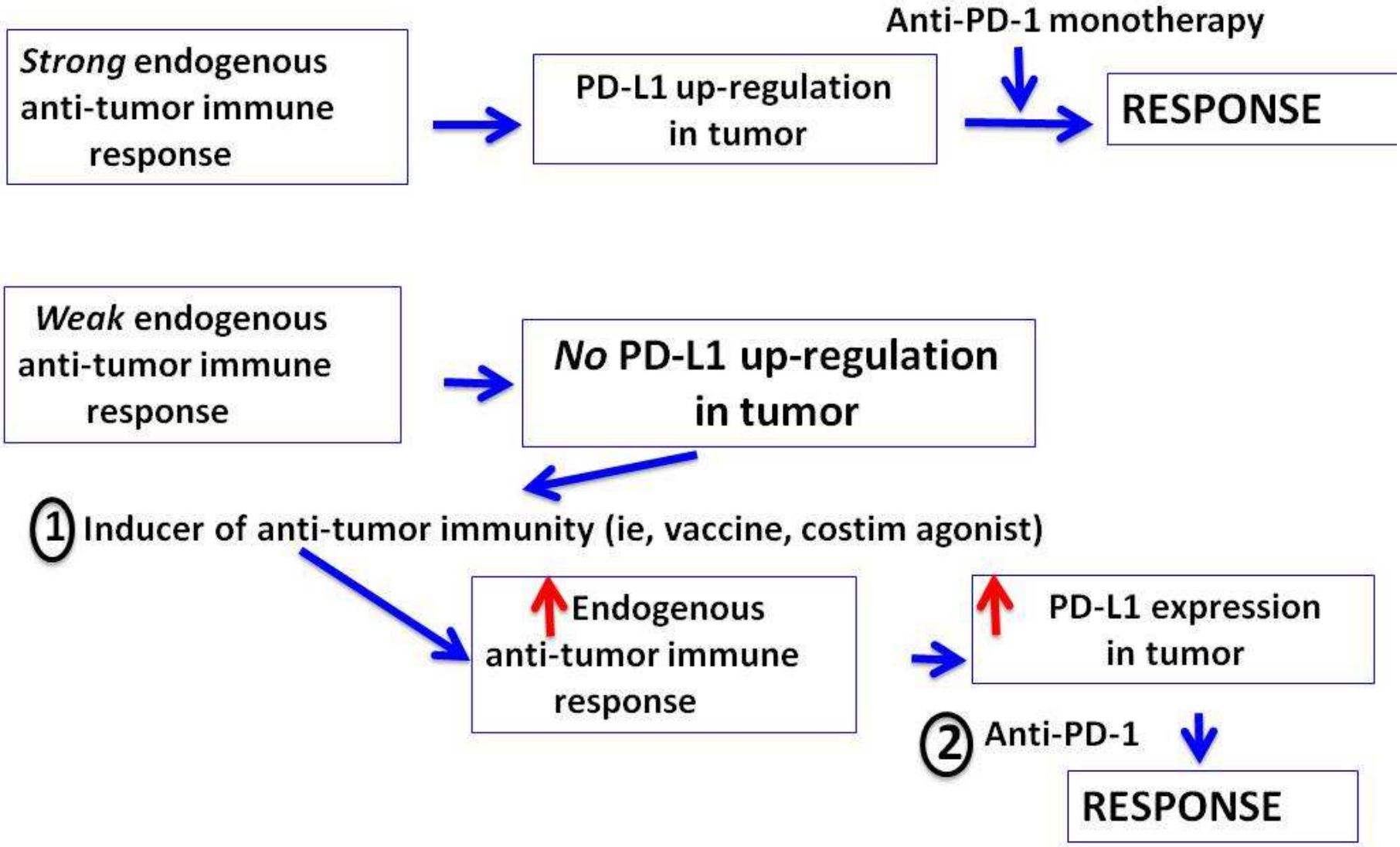
Patients Reporting Event, %	NIVO + IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Skin	59.1	5.8	41.9	1.6	54.0	2.9
Pruritus	33.2	1.9	18.8	0	35.4	0.3
Rash	28.4	2.9	21.7	0.3	20.9	1.6
Rash maculo-papular	11.8	1.9	4.2	0.3	11.9	0.3
Gastrointestinal	46.3	14.7	19.5	2.2	36.7	11.6
Diarrhea	44.1	9.3	19.2	2.2	33.1	6.1
Colitis	11.8	7.7	1.3	0.6	11.6	8.7
Hepatic	30.0	18.8	6.4	2.6	7.1	1.6
Increase in alanine aminotransferase	17.6	8.3	3.8	1.3	3.9	1.6
Increase in aspartate aminotransferase	15.3	6.1	3.8	1.0	3.5	0.6
Endocrine	30.0	4.8	14.4	0.6	10.9	2.3
Hypothyroidism	15.0	0.3	8.6	0	4.2	0

- With immune modulatory agents, resolution rates for the majority of grade 3–4 select AEs were: 85-100% for NIVO + IPI, 50-100% for NIVO, and 83-100% for IPI
- As observed in prior studies, most endocrine events did not resolve

Implications of adaptive resistance for combinatorial immunotherapy



Implications of adaptive resistance for combinatorial immunotherapy



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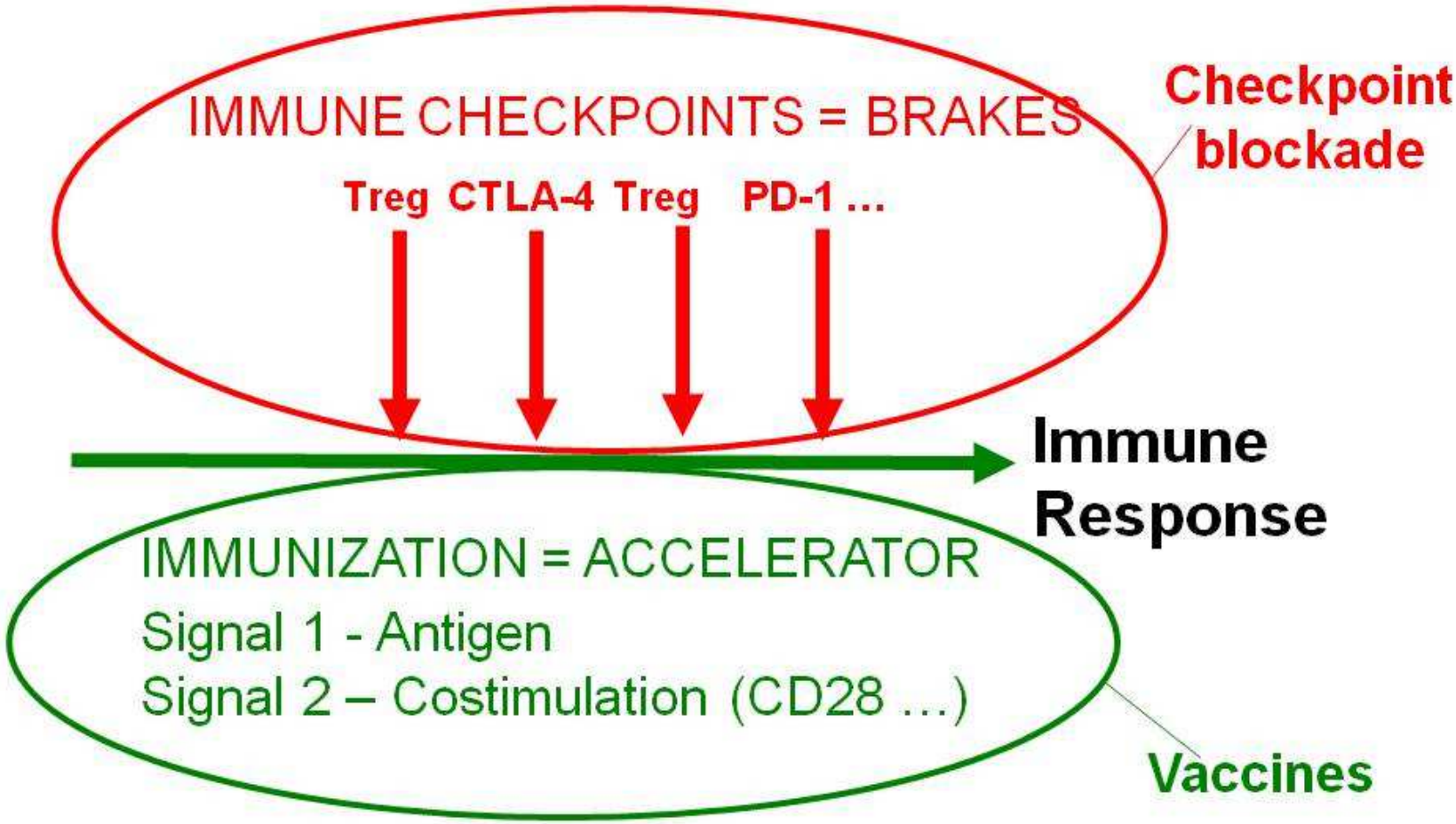
The amplitude of immune responses is determined by a balance of positive signals (antigen+costimulation) and negative forces (immune checkpoints)



Take Home Messages

- Breaking immune tolerance induces both anti-tumor and immune related adverse events
- Understanding what checkpoints are employed for an individual patient will allow for single agent approaches or rational combinations that can minimize risk

Thank you

Questions?