Memorial Sloan Kettering Cancer Center

Immunologic Checkpoint Blockade: Learnings from Melanoma

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Disclosure Information
Jedd Wolchok, MD, PhD, FASCO

- *Consultant for:* Amgen; Apricity; Arsenal IO; Ascentage Pharma; AstraZeneca; Astellas; Boehringer Ingelheim; Bristol Myers Squibb; Chugai; Dragonfly; F Star; Eli Lilly; Georgimmune; Imvaq; Maverick; Merck; Psioxus, Recepta; Trieza; Trishula; Truvax; Sellas, Werewolf.

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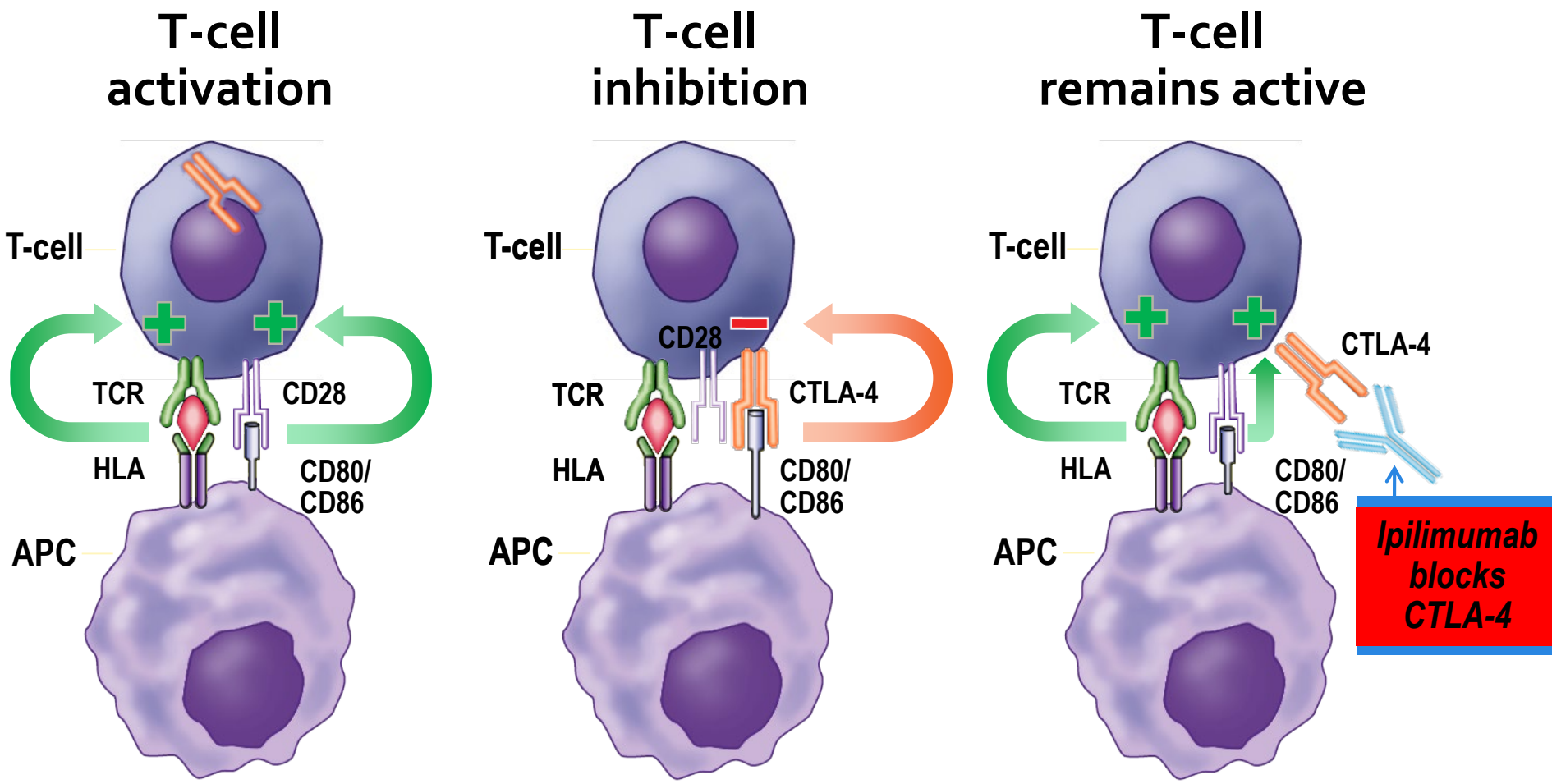
- *Equity in:*
- Tizona Pharmaceuticals; Imvaq; Beigene; Linneaus, Apricity, Arsenal IO; Georgiamune

- *Off Label Discussion:*
- I will not discuss off label use and/or investigational use in my presentation.

Ipilimumab Augments T-Cell Activation and Proliferation



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

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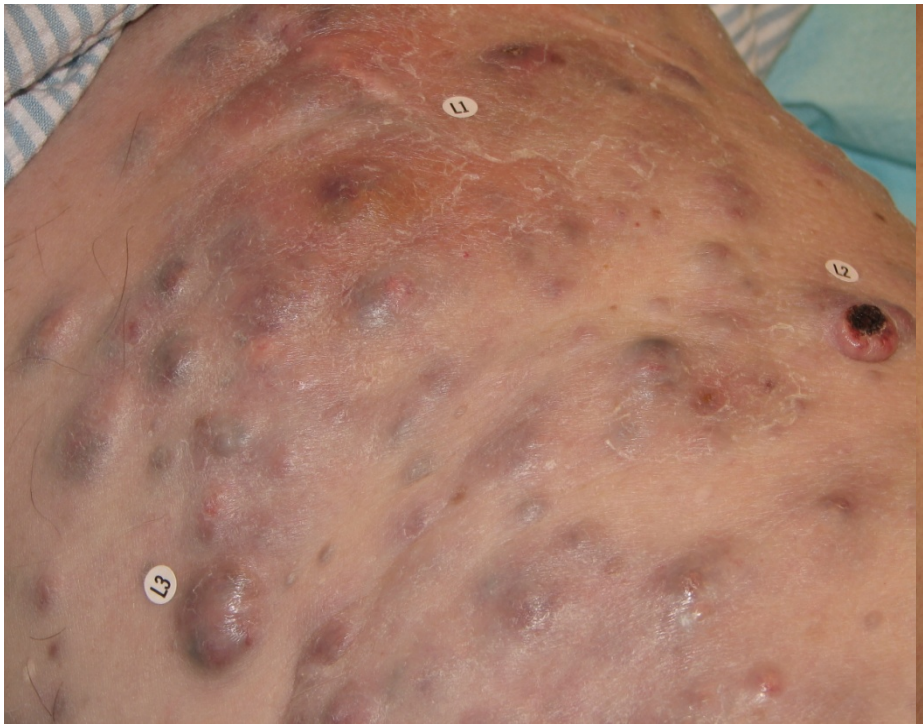
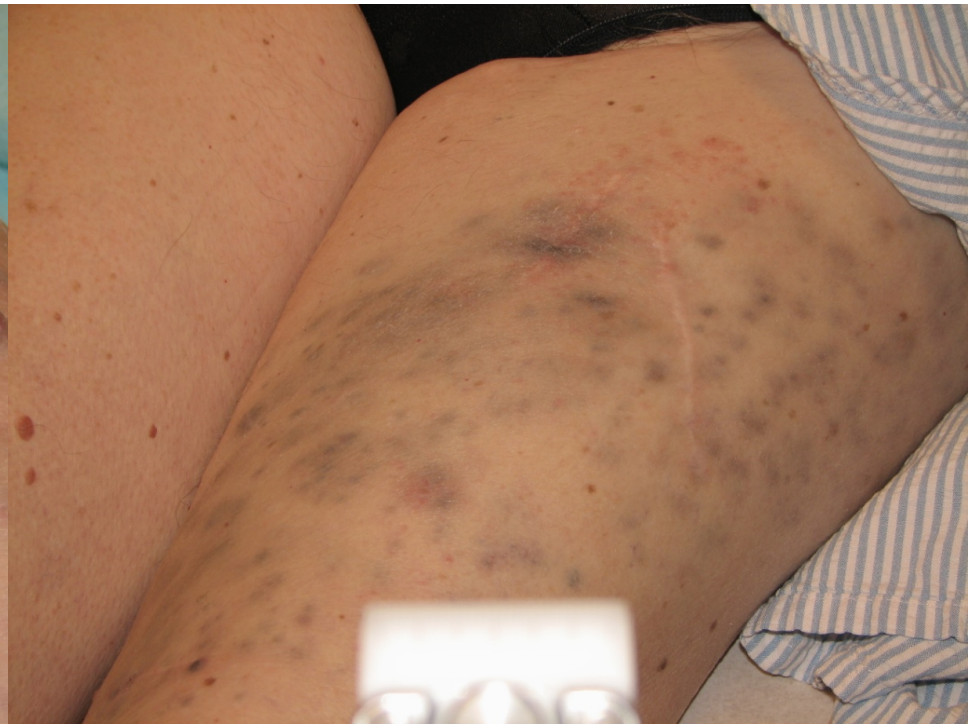
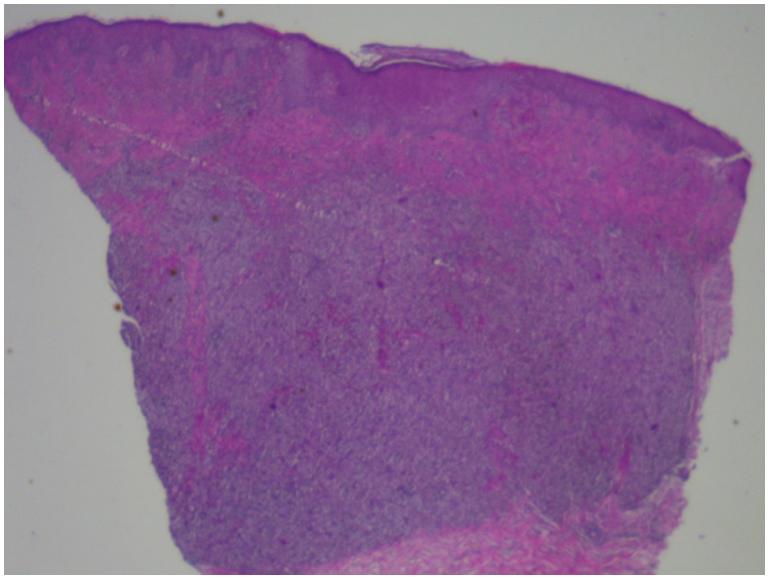
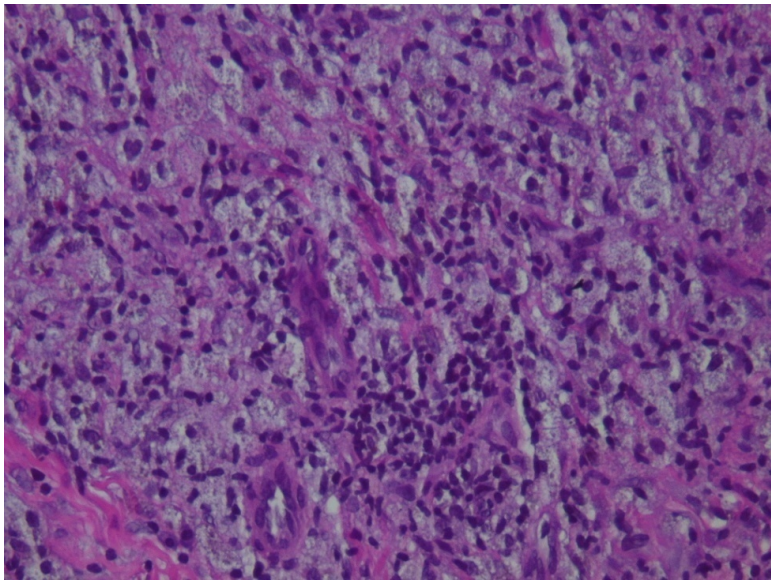


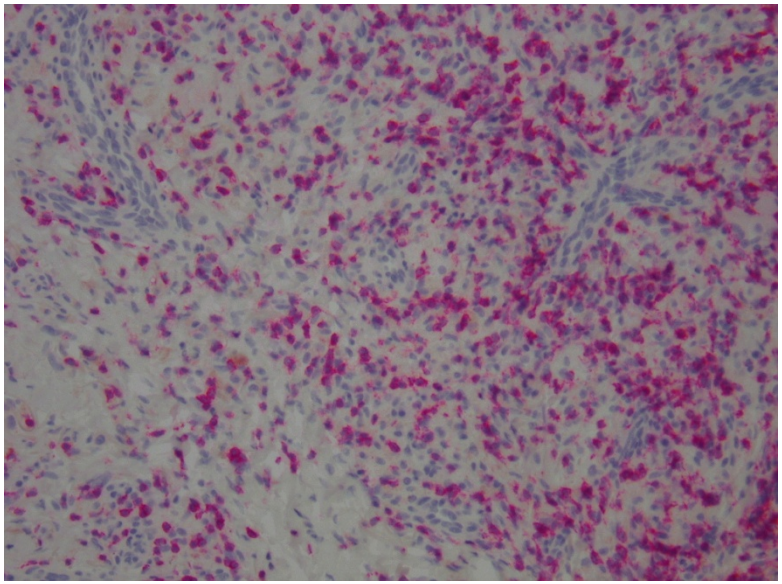




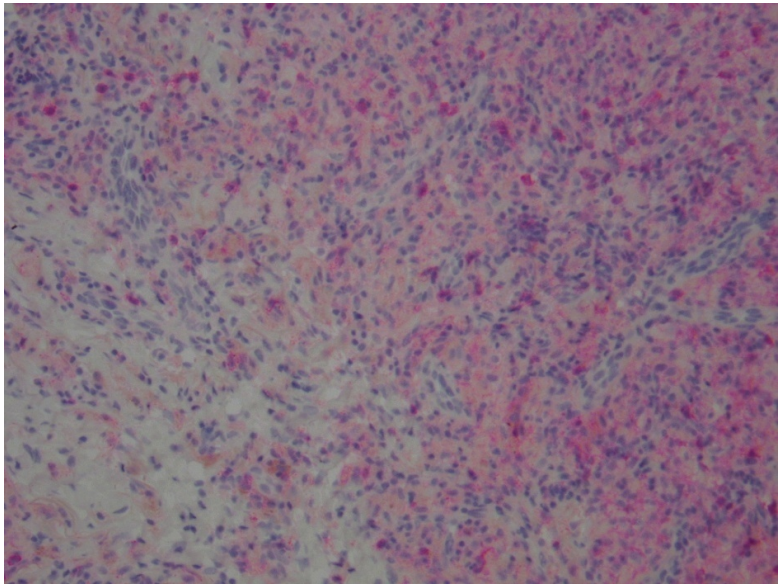
Tumorous nodule with melanin pigment (macrophages and lymphocytes; no melanocytes)



Macrophages and lymphocytes are present, but no tumor cells

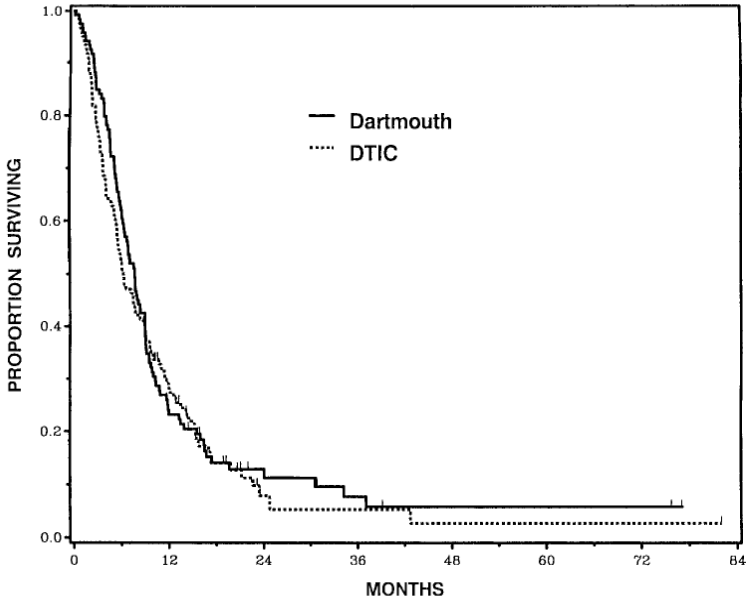


CD8-positive T-cells

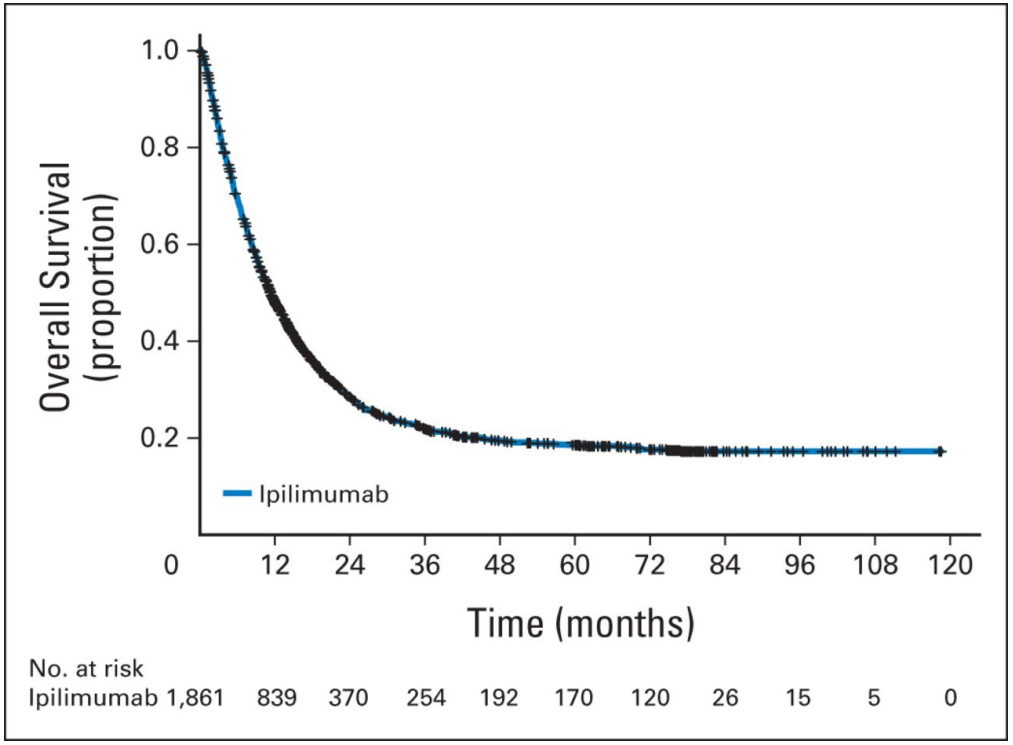


CD4-positive T-cells (macrophages are also weakly pos for CD4)

Ipilimumab Phase II and III data :
Primary analysis of pooled overall survival (OS) data in context of prior standard care



Chapman et al. J Clin Oncol, 1999



Dirk Schadendorf et al. JCO 2015;33:1889-1894

Immune-mediated Adverse Reactions

- Result from increased or excessive immune activity
- Can be severe or life-threatening, affecting various organs

GASTROINTESTINAL

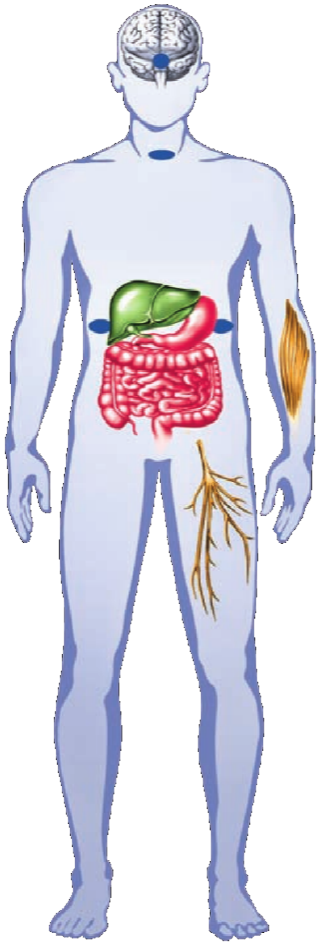
Signs and symptoms such as
- Diarrhea
- Abdominal pain
- Blood or mucus in stool
- Bowel perforation
- Peritoneal signs
- Ileus

LIVER

Signs such as
- Abnormal liver function tests (eg, AST, ALT) or total bilirubin

SKIN

Symptoms such as
- Pruritus
- Rash



NEUROLOGIC

Symptoms such as
- Unilateral or bilateral weakness
- Sensory alterations
- Paresthesia

ENDOCRINE

Signs and symptoms such as
- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries

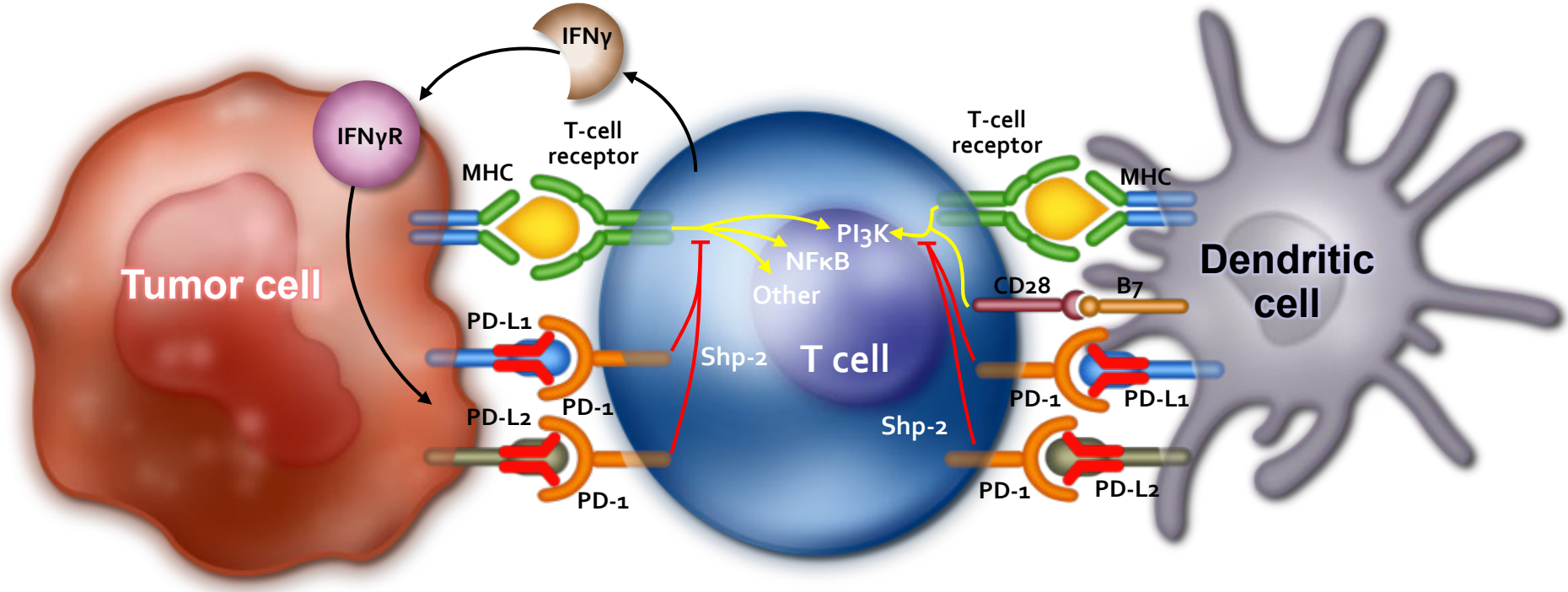
OTHER ADVERSE REACTIONS, including ocular manifestations

Please see each organ system section for related guidance.

Role of PD-1 Pathway in Tumor Immunity

Recognition of tumor by T cell through MHC/antigen interaction mediates IFNγ release and PD-L1/2 up-regulation on tumor

Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells



Nivolumab, Pembrolizumab, Cemiplimab:PD-1 Receptor Blocking Abs
Atezolizumab, Avelumab, Durvalumab: PD-L1 Blocking Abs

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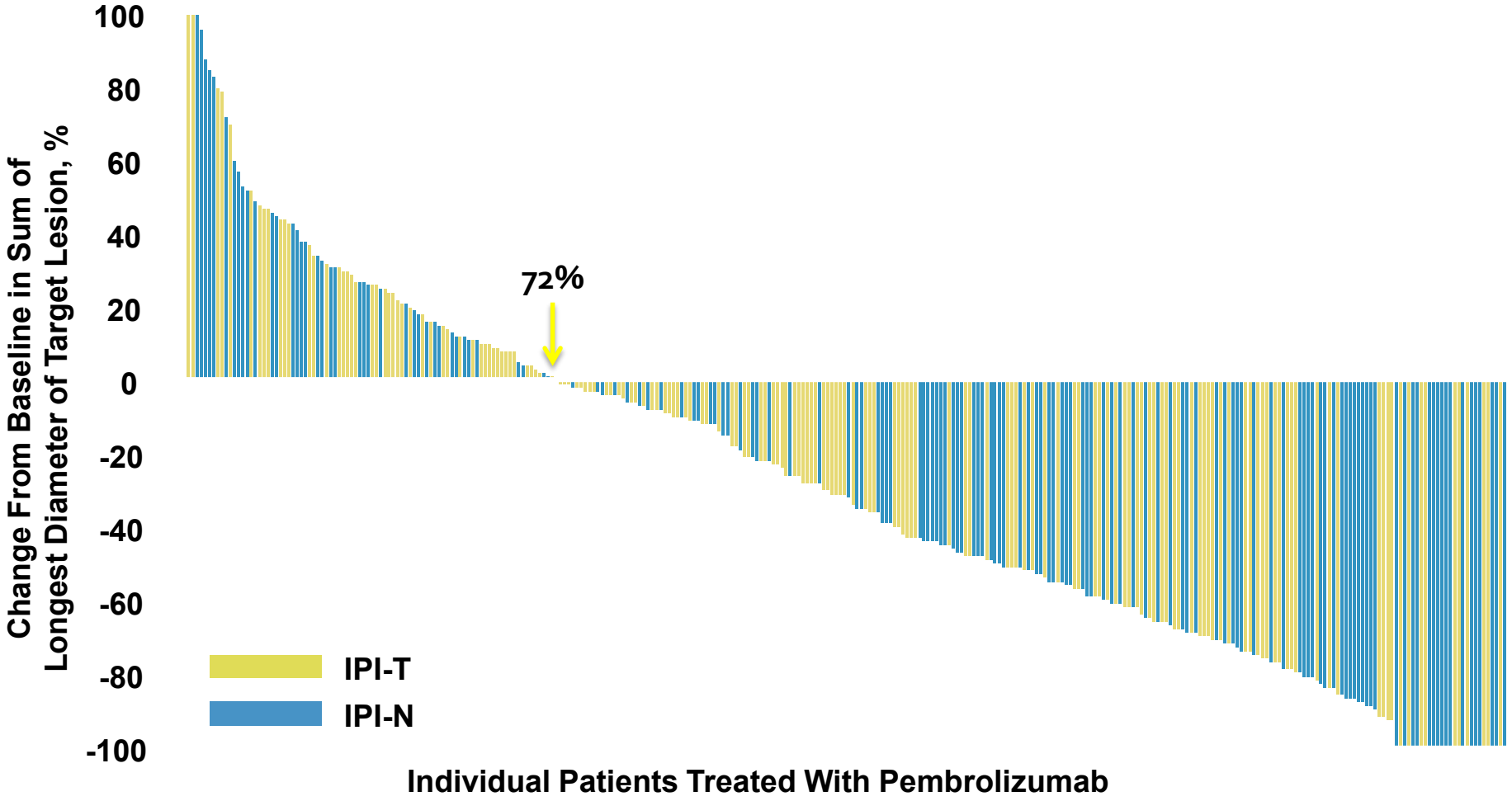
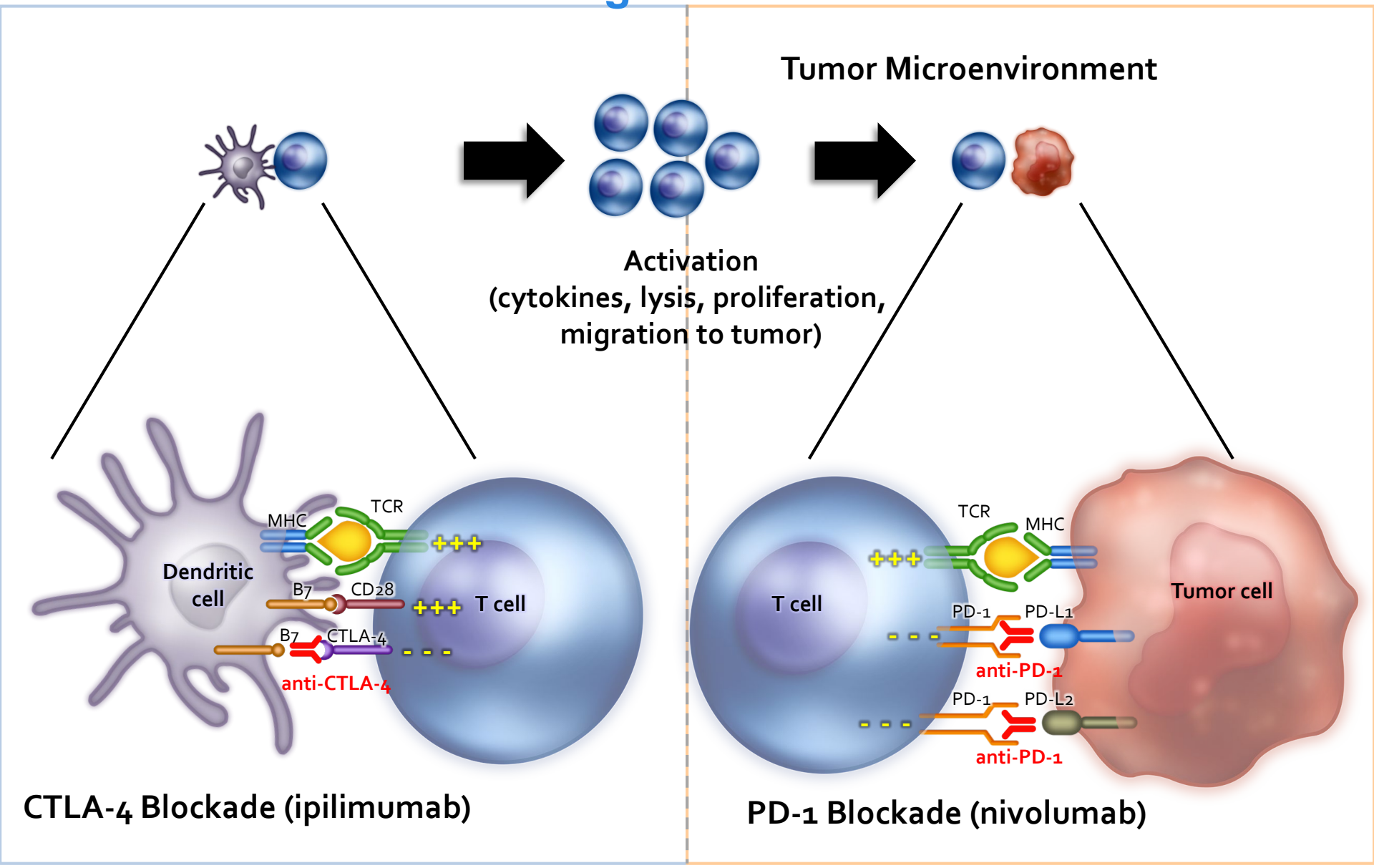
Sznol et al., ASCO, 2013

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



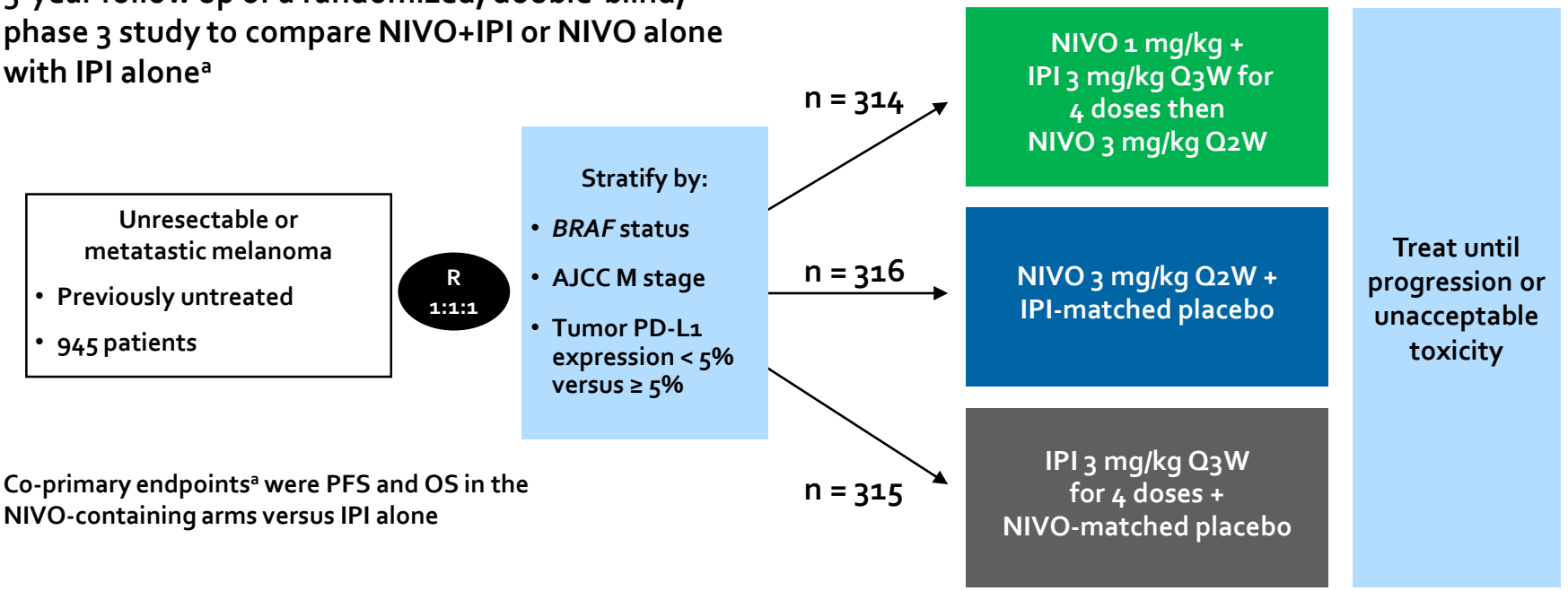
Presented by: Antoni Ribas, ASCO, 2014. Robert et al., Lancet, 2014

Blocking CTLA-4 and PD-1



CheckMate 067: Study Design

5-year follow up of a randomized, double-blind, phase 3 study to compare NIVO+IPI or NIVO alone with IPI alone[a]



Co-primary endpoints[a] were PFS and OS in the NIVO-containing arms versus IPI alone

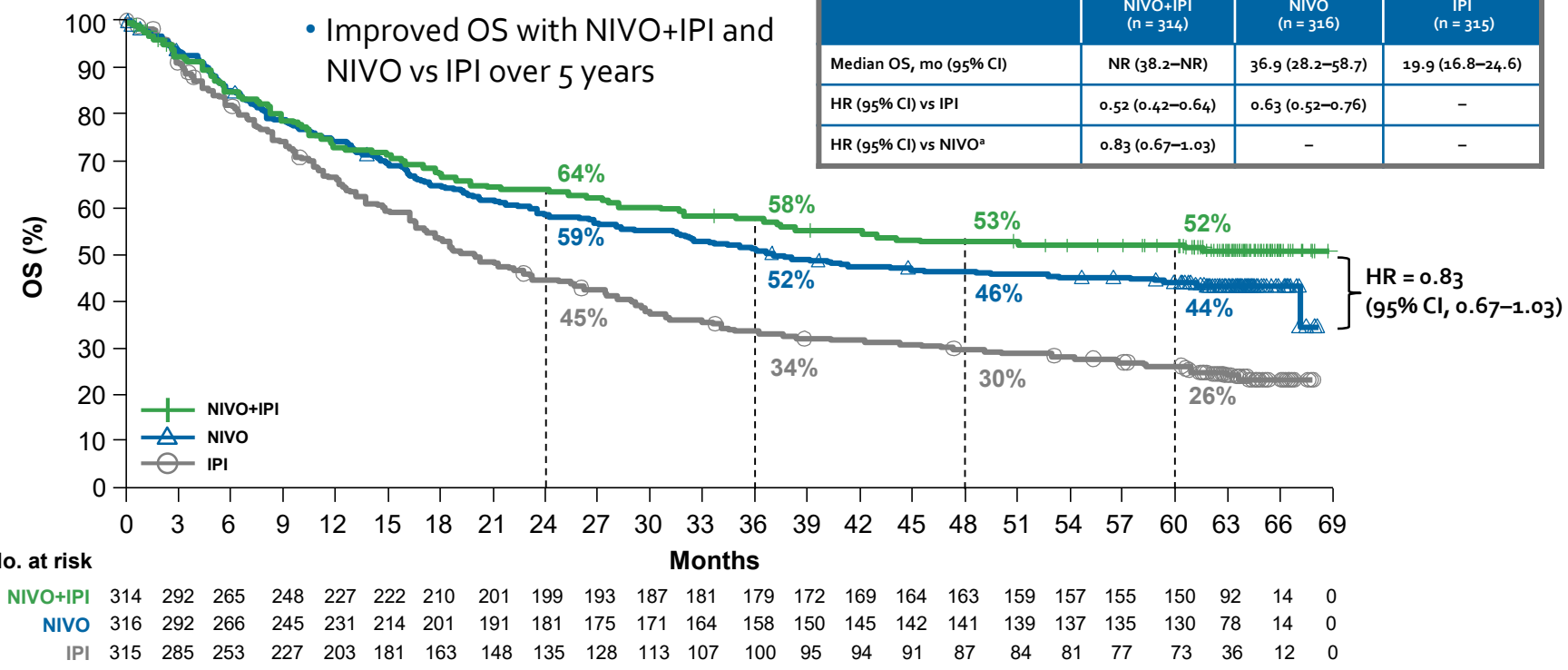
Database lock: July 2, 2019; minimum follow-up of 60 months for all patients

NCT01844505

[a]The study was not powered for a comparison between NIVO+IPI and NIVO.AJCC, American Joint Committee on Cancer.

Overall Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–



[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075; 2. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

Safety Summary

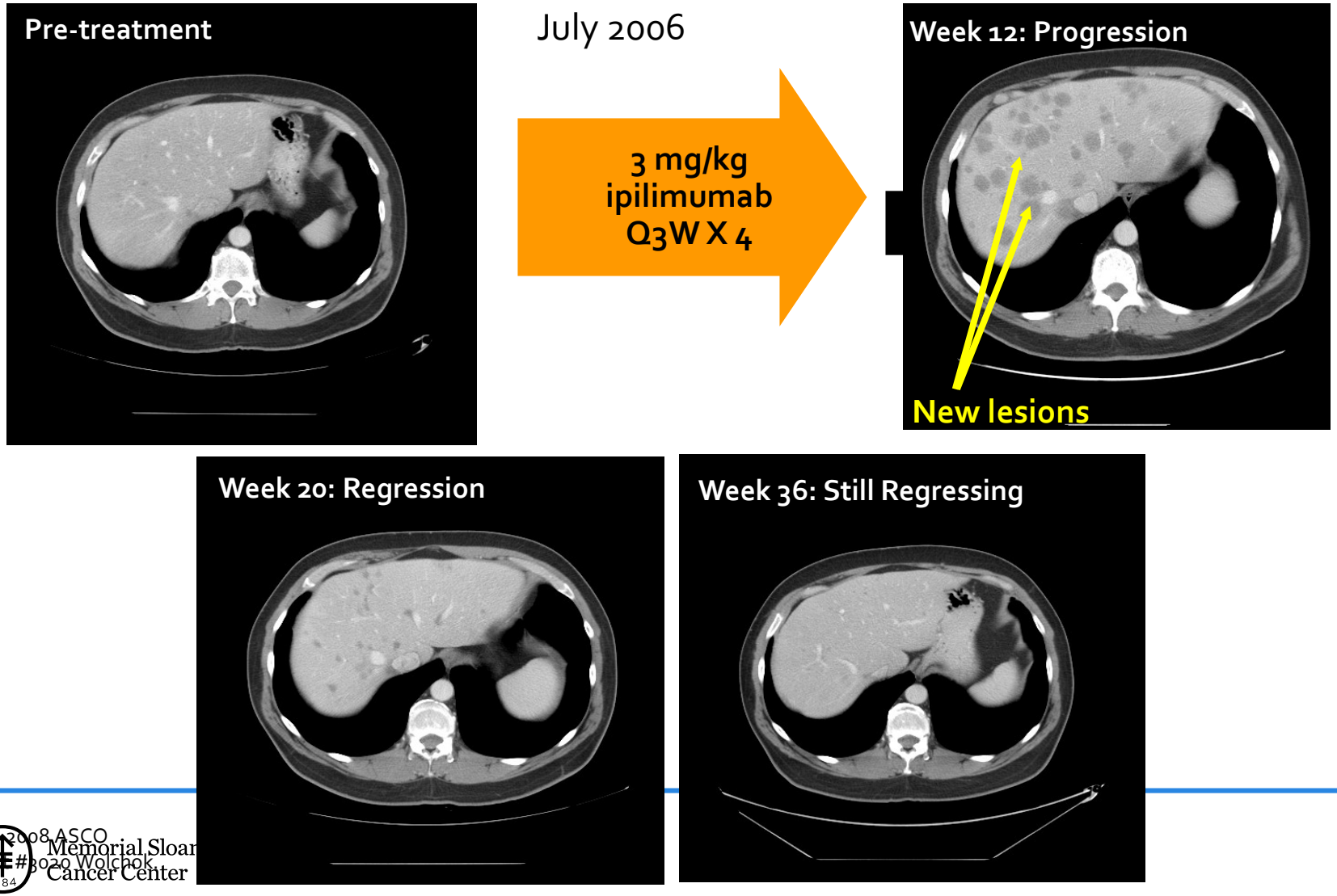
- No new safety signals were observed with the additional follow-up
- No additional deaths due to study drug toxicity were reported since the prior analysis[a]

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
Treatment-related AE, %	96	59	87	23	86	28
Treatment-related AE leading to discontinuation, %	42	31	13	8	15	14
Treatment-related death, n (%)	2 (1)		1 (< 1)		1 (< 1)	

- Survival outcomes were not impacted by discontinuing NIVO+IPI early due to a TRAE[b]
  - Patients who discontinued NIVO+IPI during induction due to a TRAE had 5-year PFS (35%) and OS rates (51%) similar to patients in the overall population (36% and 52%, respectively)

[a]Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO+IPI (n = 1 each; both occurred > 100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1); [b]Post-hoc analysis. TRAE, treatment-related adverse event.

Ipilimumab Pattern of Response: Responses After the Appearance and Subsequent Disappearance of New Lesions

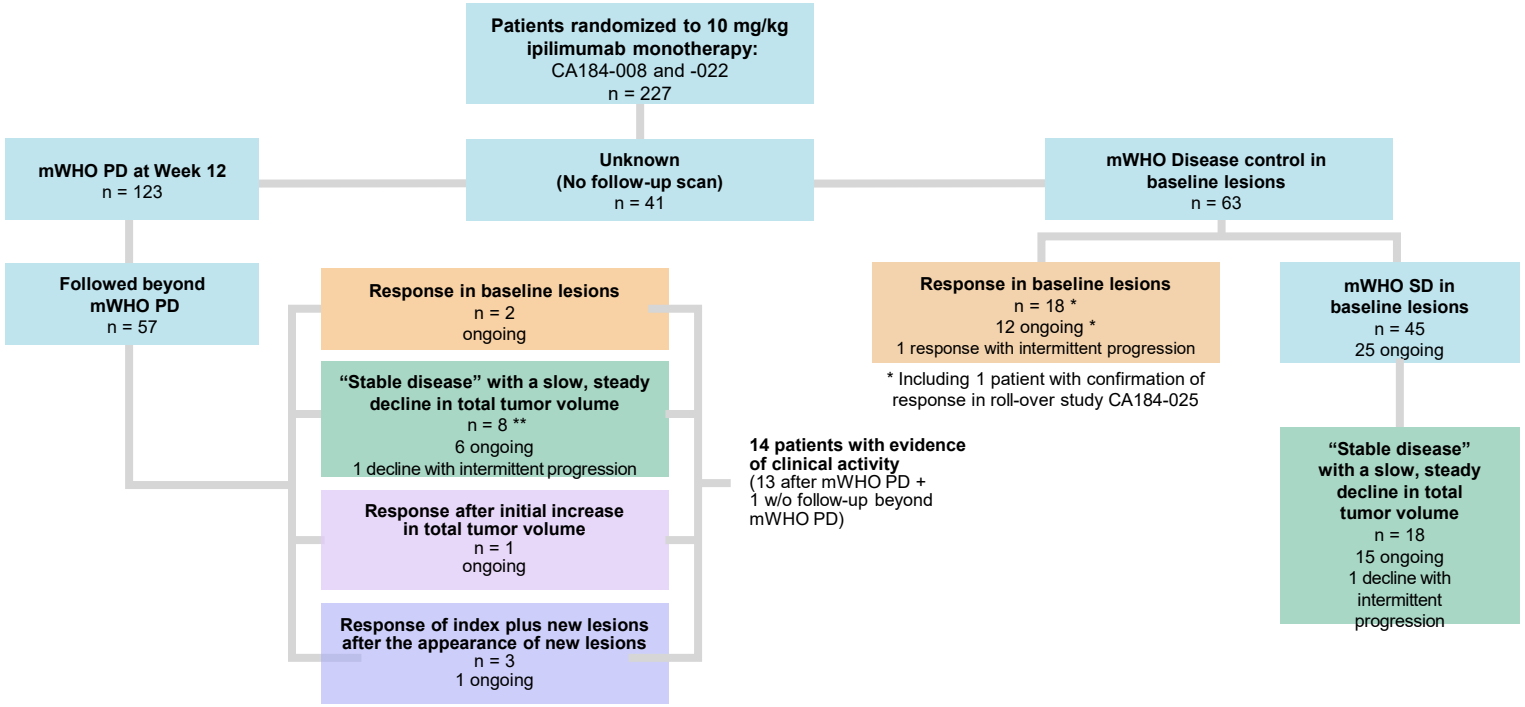


Source: 2008 ASCO Abstract #3020 Wolchok

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

Proportion of Response to Ipilimumab

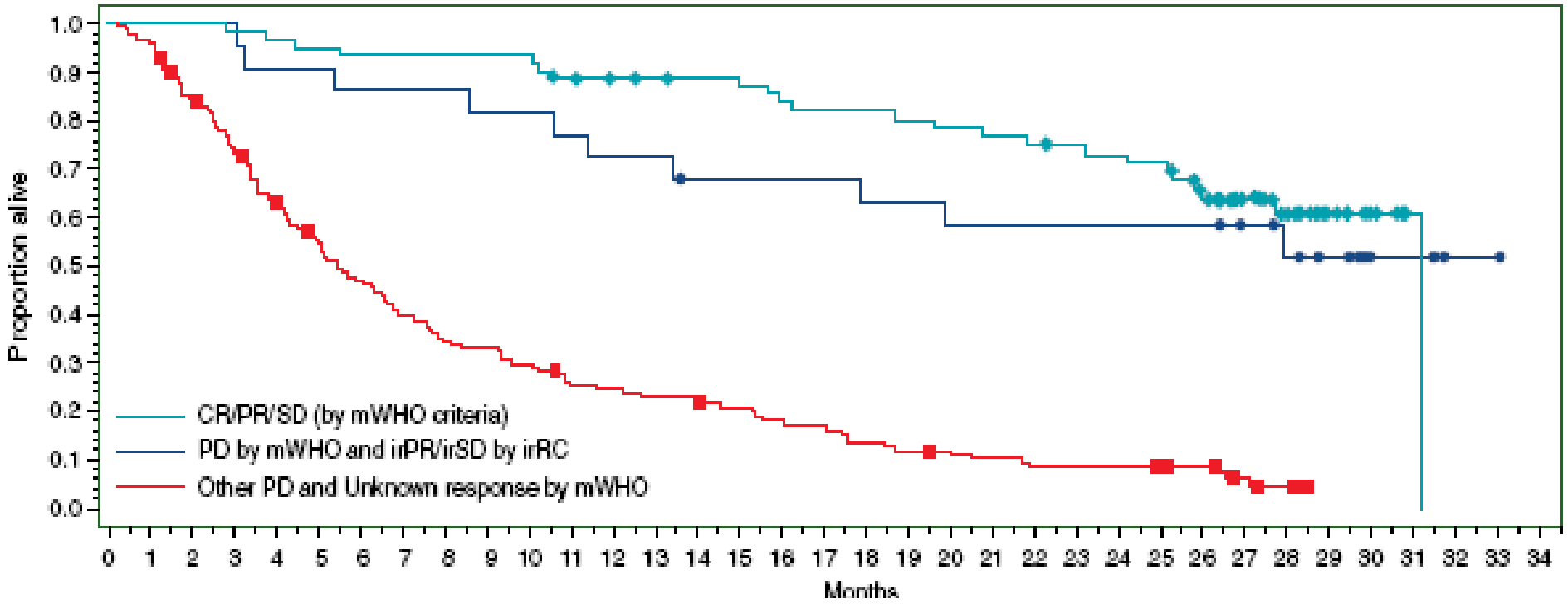


**** 2 of these patients demonstrated SD compared to baseline after initial increase in total tumor volume (both ongoing). One of these had 24% reduction from peak and 2% increase from baseline at the last evaluable tumor assessment.**

Ongoing = response or SD ongoing at the last evaluable tumor assessment (prior to alternate non-ipilimumab therapy) unless patient died. Slow steady decline is defined as a > 25% reduction from baseline in total tumor volume at the last evaluable tumor assessment, unless otherwise noted.

irRC Identifies Survivors in Patients with Progressive Disease by mWHO

Pooled data from phase II studies CA184-008 and CA184-022: ipilimumab monotherapy 10 mg/kg (N=227)



Wolchok et al, *Clin Cancer Res*, 2009

Dose Escalation Subjects: Summary of First-in-Human 89Zr IAB22M2C PET/CT

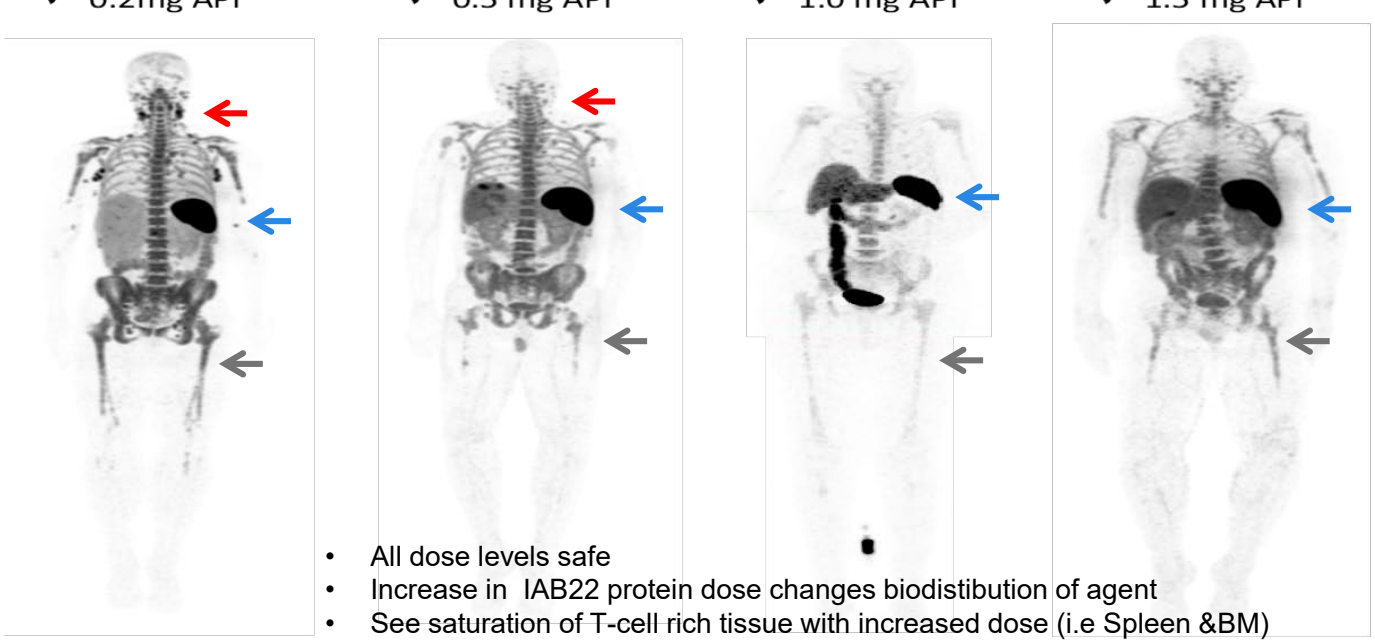
Subject 1
- ✓ Melanoma
- ✓ Long Term CPI
- ✓ 0.2mg API

Subject 2
- ✓ HCC
- ✓ Short Term CPI
- ✓ 0.5 mg API

Subject 3
- ✓ NSCLC
- ✓ Newly Dx
- ✓ 1.0 mg API

Subject 4
- ✓ NSCLC
- ✓ Prior CPI
- ✓ 1.5 mg API

Subject 5
- ✓ NSCLC
- ✓ Prior CPI
- ✓ 5.0 mg API



- All dose levels safe
- Increase in IAB22 protein dose changes biodistibution of agent
- See saturation of T-cell rich tissue with increased dose (i.e Spleen &BM)

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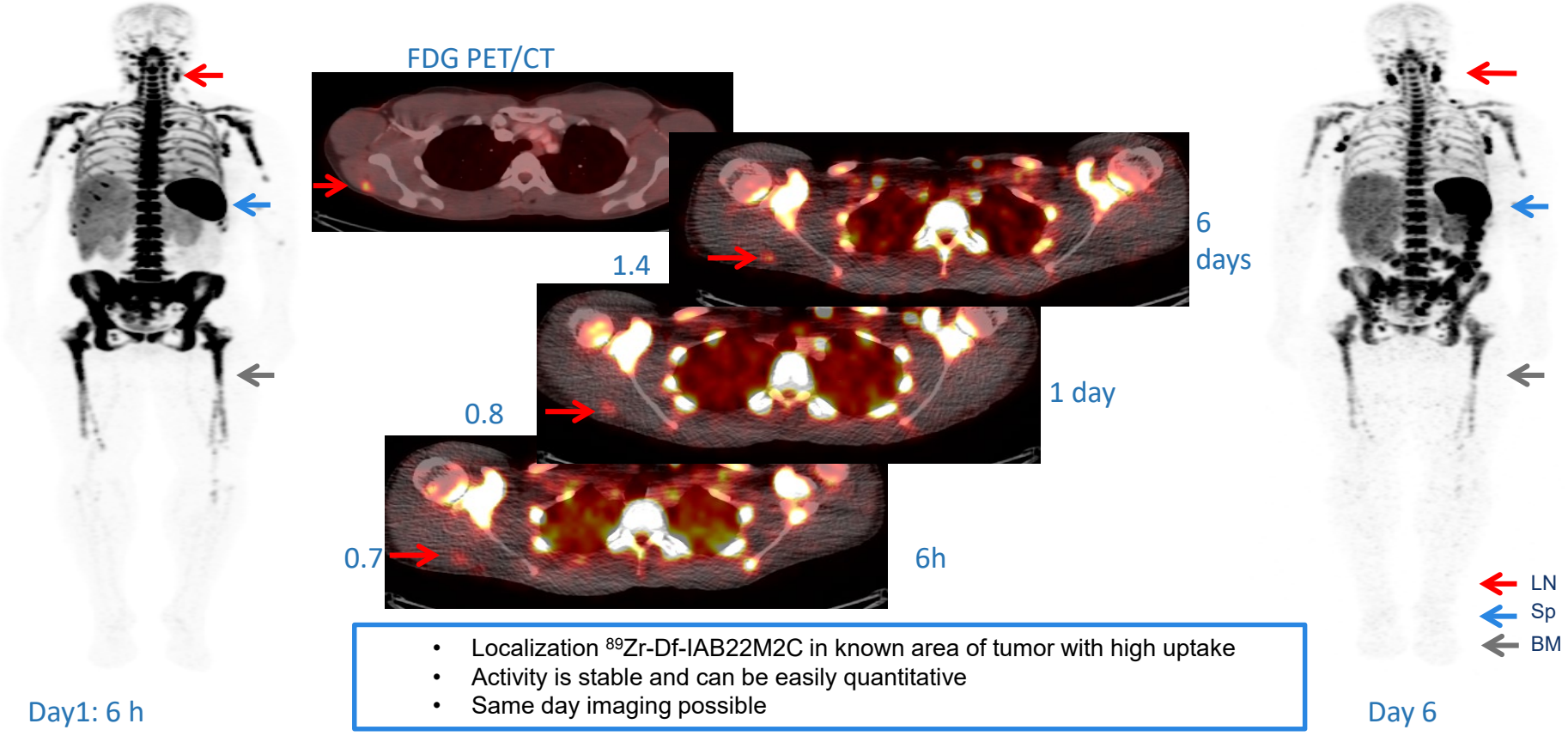
Pandit-Taskar et al., *J Nucl Med*, 2019

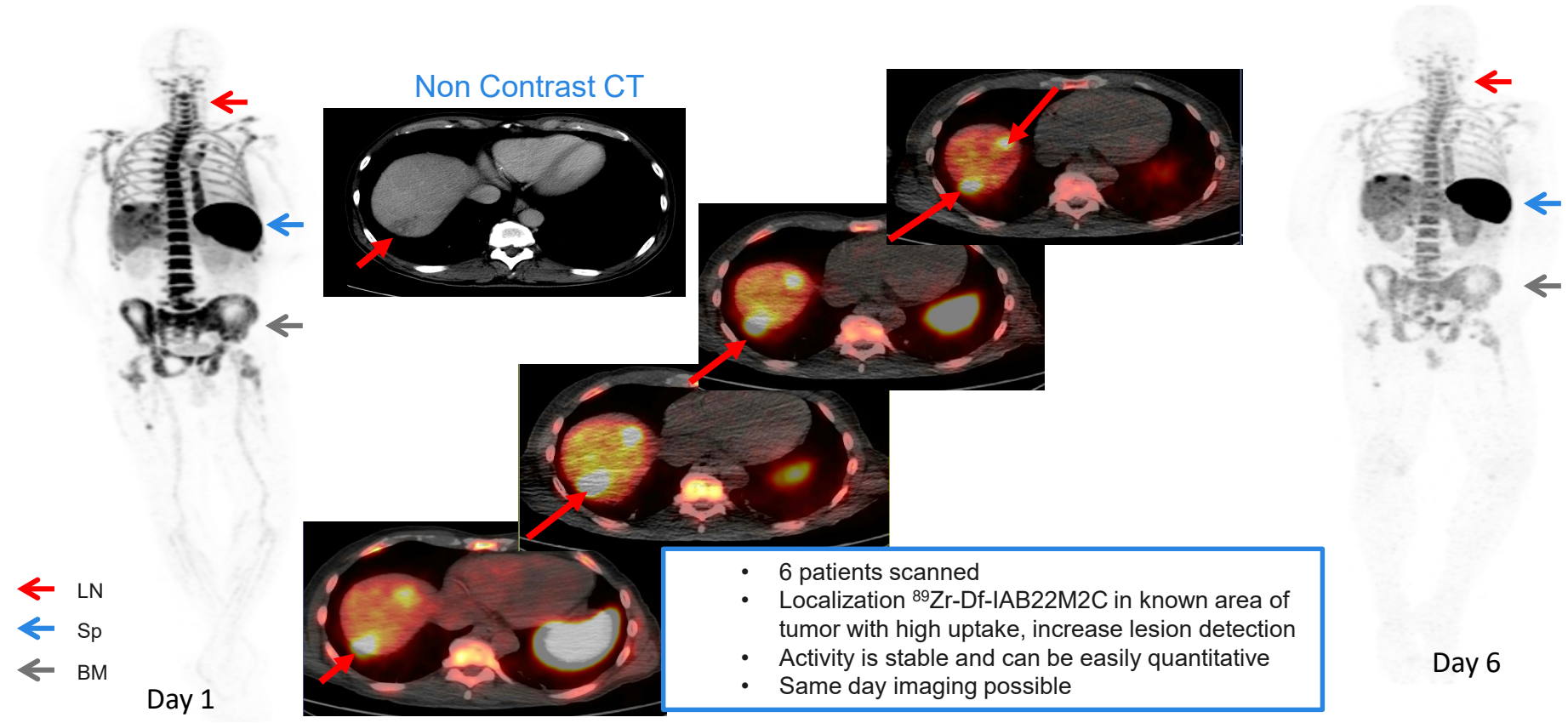
Is a drug hitting its target?
Pharmacodynamic imaging of T cells: Metastatic Melanoma



- Localization ^{89}Zr-Df-IAB22M2C in known area of tumor with high uptake
- Activity is stable and can be easily quantitative
- Same day imaging possible

Pandit-Taskar et al., *J Nucl Med*, 2019

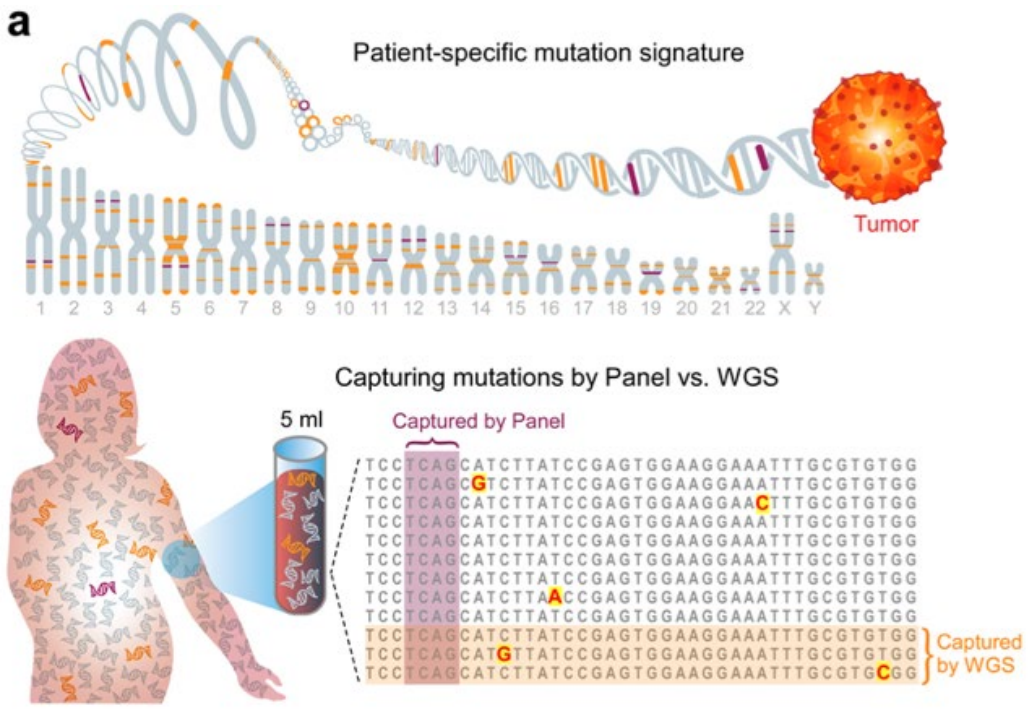
Subject: 64 years old male, Metastatic Hepatocellular Carcinoma, diagnosed May-2017
Treatment history: Nivolumab treatment started 2 weeks prior to scan



- 6 patients scanned
- Localization ^{89}Zr-Df-IAB22M2C in known area of tumor with high uptake, increase lesion detection
- Activity is stable and can be easily quantitative
- Same day imaging possible

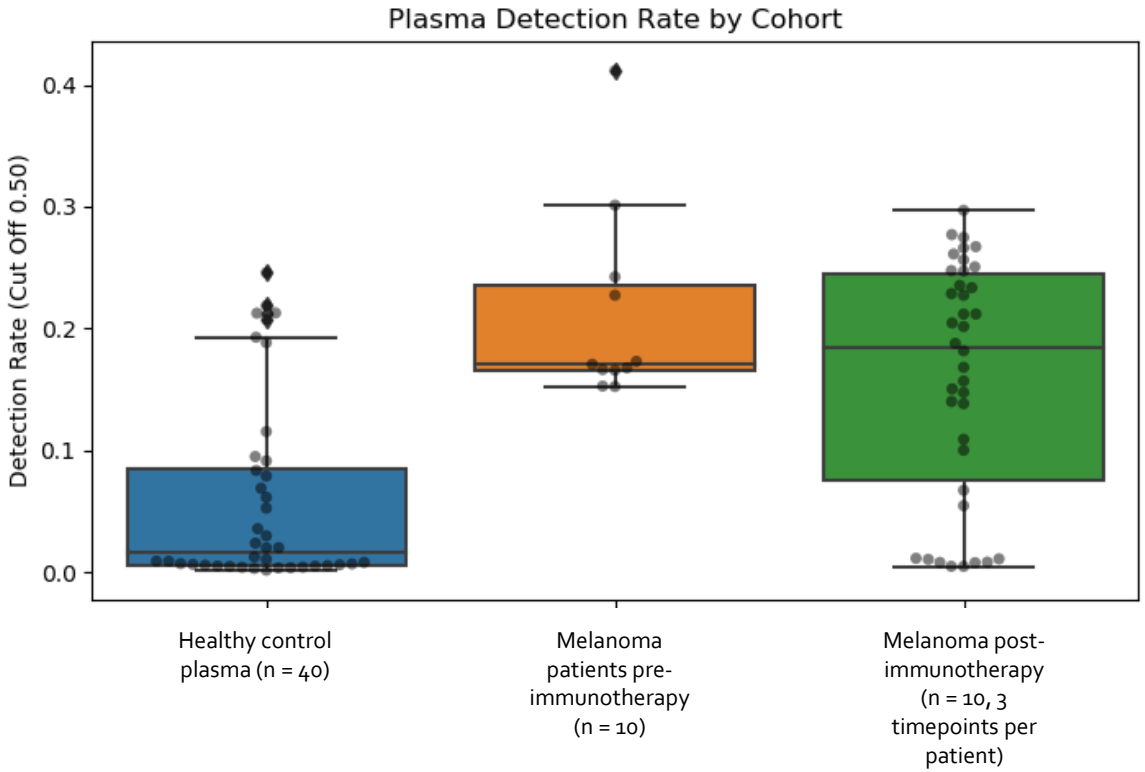
Pandit-Taskar et al., *J Nucl Med*, 2019

Which Patients Need Adjuvant Therapy:
Whole genome mutation integration to overcome input ceiling



Adam Widman & Dan Landau,
MSK, NY Genome Ctr, Weill Cornell Medicine

Deep learning models track response to therapy

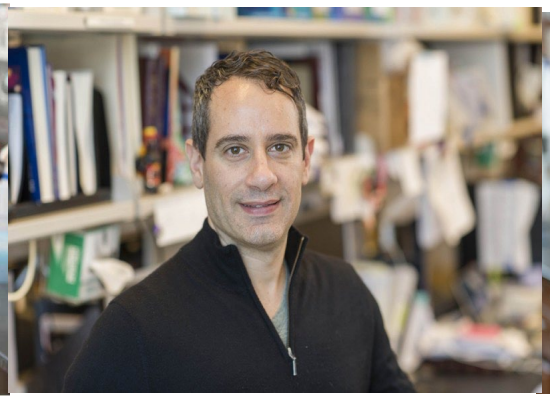


Summary

- Checkpoint blockade is an effective treatment with durable responses and improvement in overall survival in melanoma,
- Combination therapy will be necessary for immunotherapy to achieve full potential (other immune modulators, oncolytic viruses, vaccines, radiation, chemotherapy, targeted therapy, anti-angiogenic therapy).
- New agents are in early clinical development. These include additional antagonists (LAG-3) as well as agonist agents for costimulatory pathways (GITR, OX40, CD40, CD137) and CSF-1R and IDO inhibitors which may be beneficial as part of combinatorial approaches.
- Efforts are under way to study precise mechanisms of primary and acquired resistance to inform future combinations.
- Refinements in cell therapy techniques will improve accessibility and efficacy.
- MRD detection is a priority for optimal use of systemic adjuvant therapy and determining treatment discontinuation strategies.

Taha Merghoub

Roberta Zappasodi



Daniel Hirschhorn

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Melanoma Research Alliance, Ludwig Cancer Research, Parker Institute, NIH, Swim Across America, SU2C, Breast Cancer Research Fdn, Damon Runyon Fdn, ASCO Conquer Cancer Fdn

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