Immunotherapy of Melanoma

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Disclosures

- Honoraria and travel from BMS, Celldex and Green Peptide for advisory board/data monitoring committee.
- Providence Cancer Center receives institutional support as member of BMS International Immuno-Oncology Network
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- Institutional support in form of a sponsored research agreement between MedImmune and Providence.

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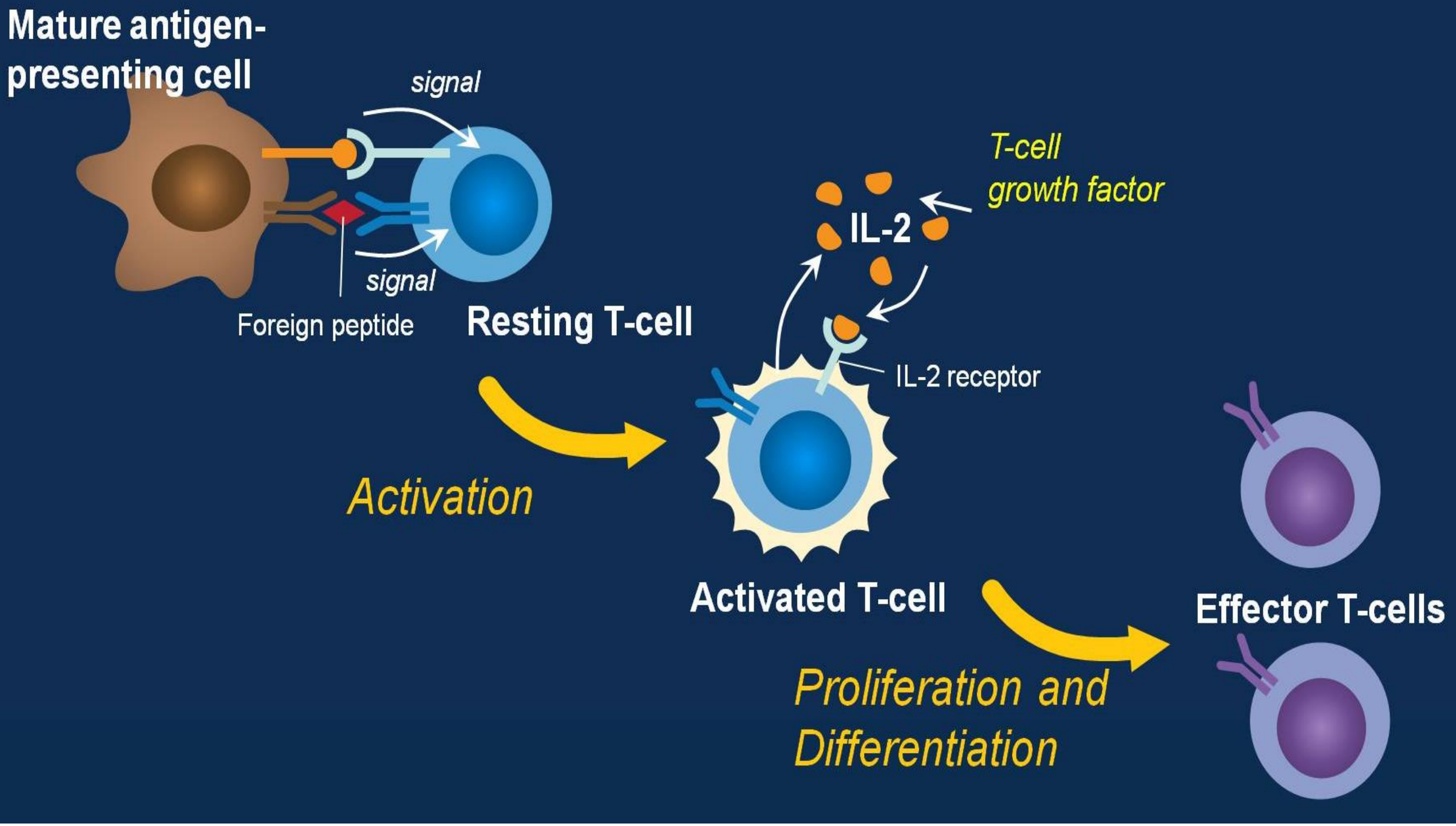
Autocrine Loop: IL-2 Produces More Effector T-cells



Presented By David McDermott at 2016 ASCO Annual Meeting

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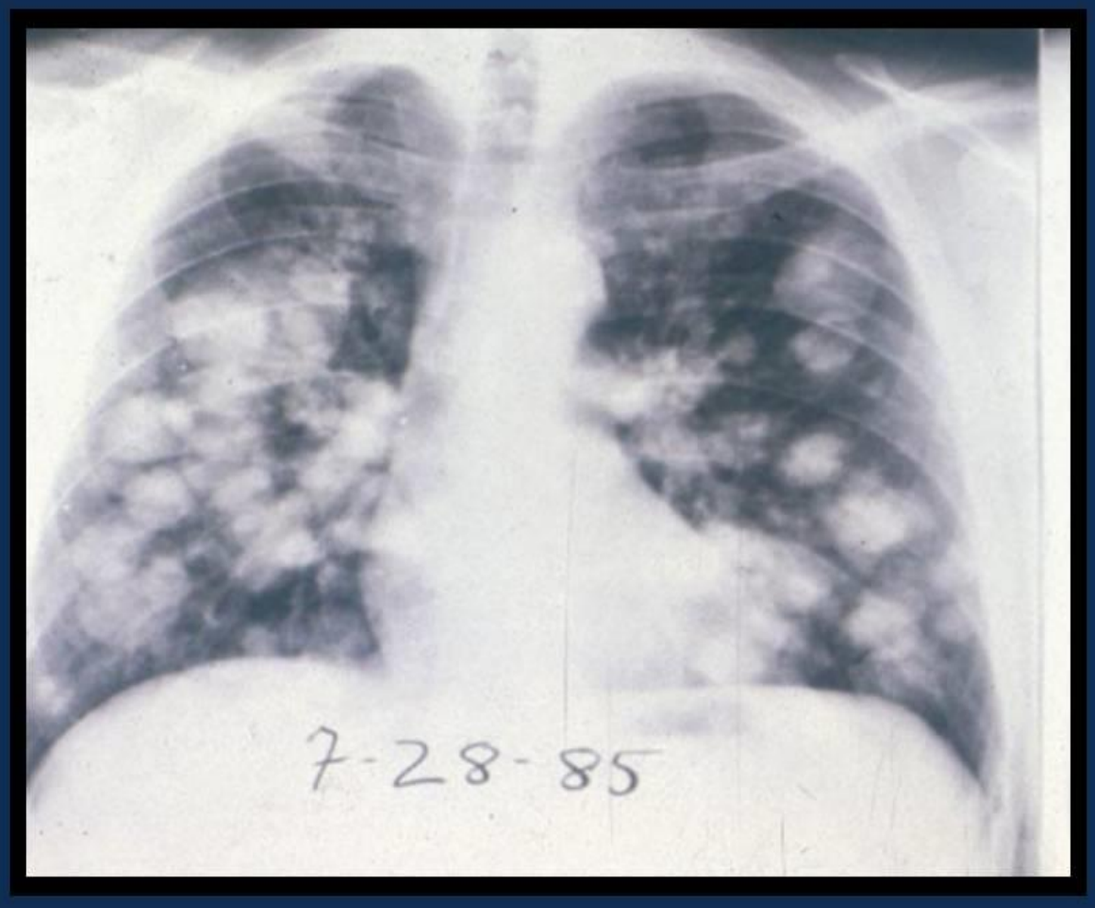
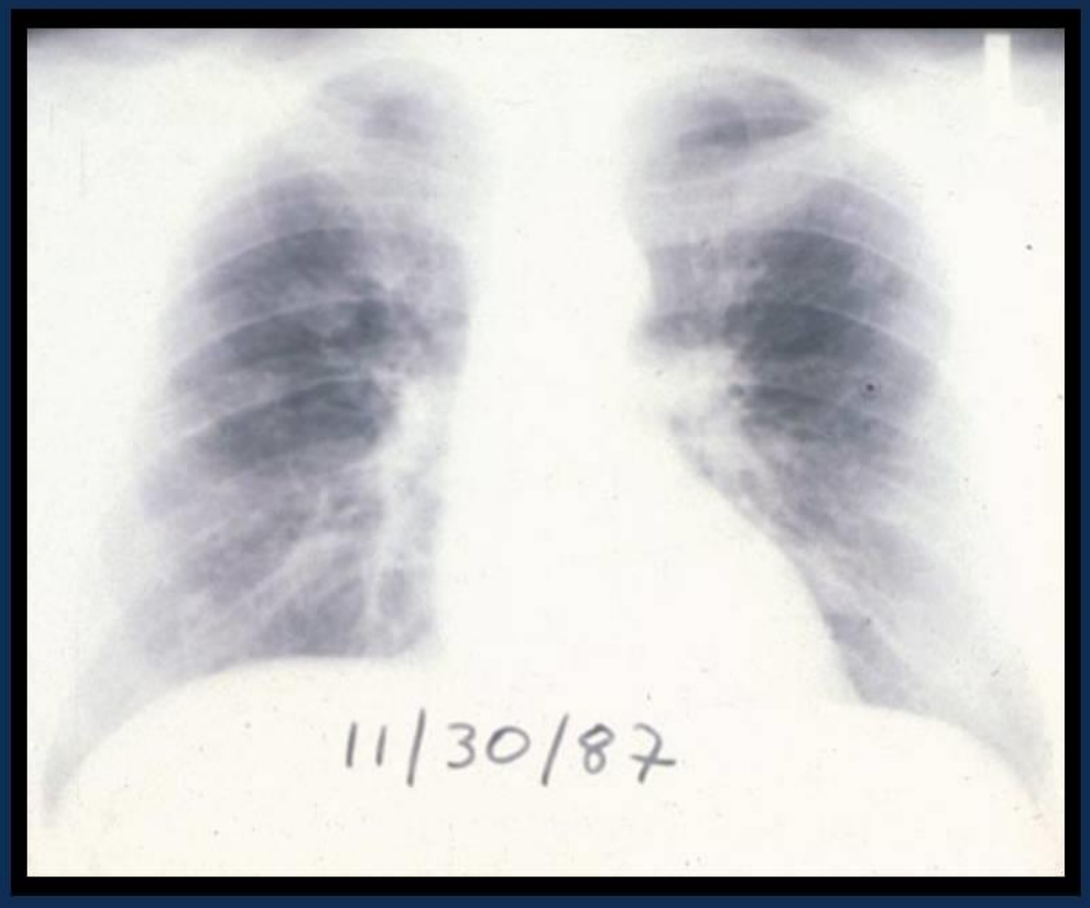
TCGF Therapy for Metastatic Melanoma

T-cell proliferation with HD IL-2



Baseline



After Treatment

Provided by D. Schwartzentruber, MD

Presented By David McDermott at 2016 ASCO Annual Meeting

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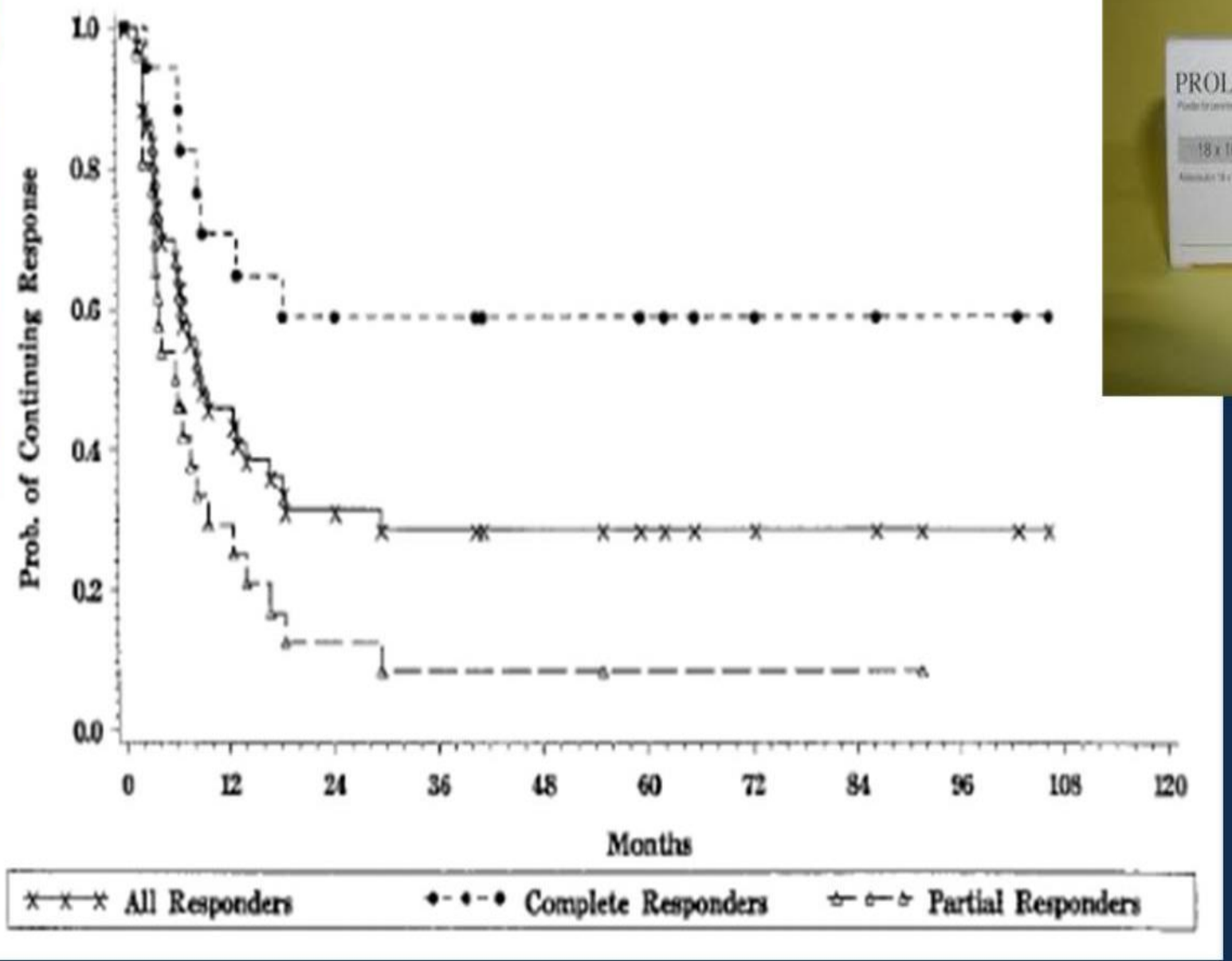
Remission is Possible with TCGFs



Atkins et al. J Clin Oncol. 1999

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Presented By David McDermott at 2016 ASCO Annual Meeting

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IL-2 Clinical Trials

- IL-2 plus stereotactic radiotherapy
- IL-2 plus TIL
- IL-2 plus engineered lymphocytes
- NKTR-214 (pegylated IL-2)

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Checkpoint Inhibitors

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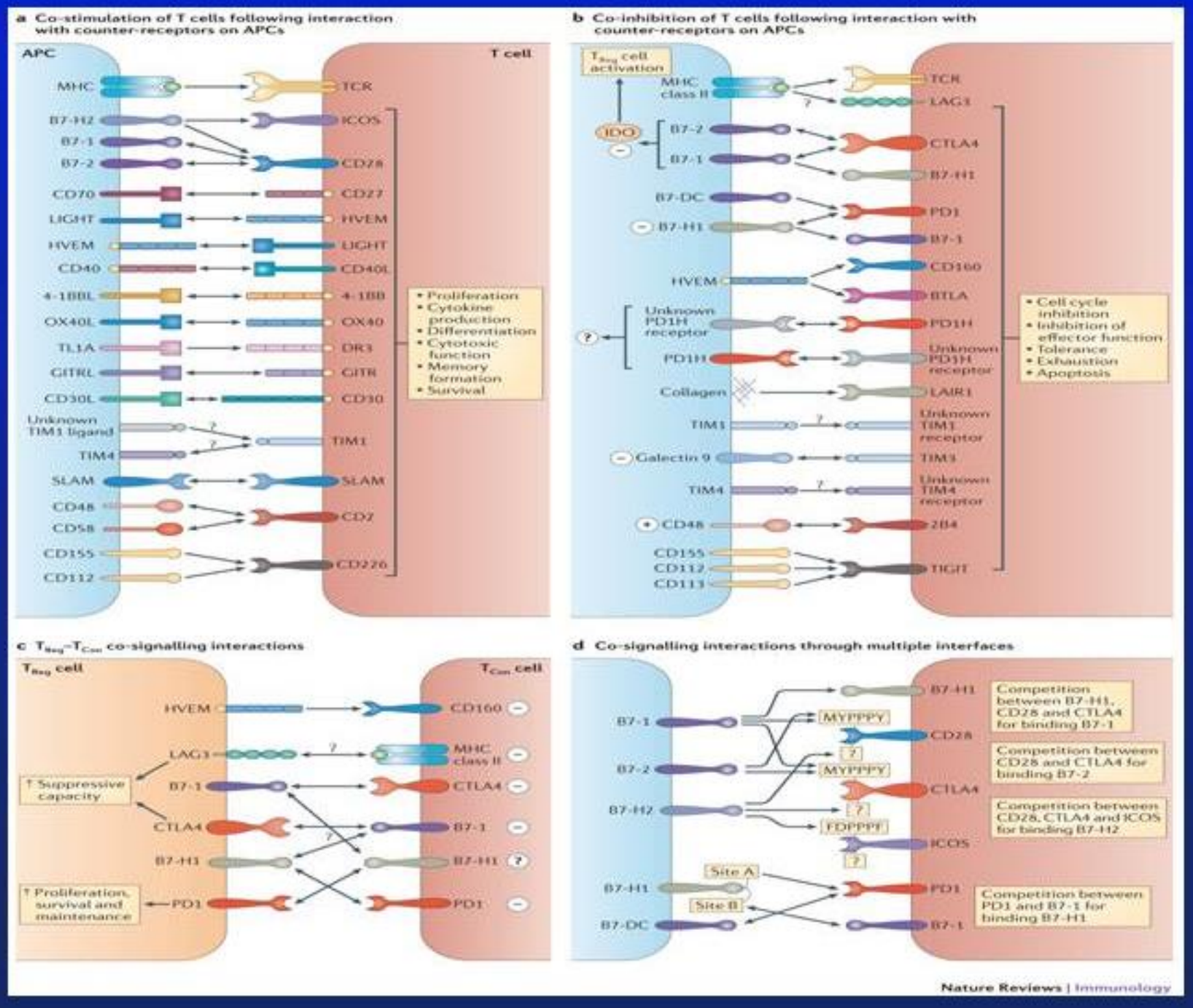
There Are Many "Accelerators" and "Brakes" on T cells within the Tumor Microenvironment



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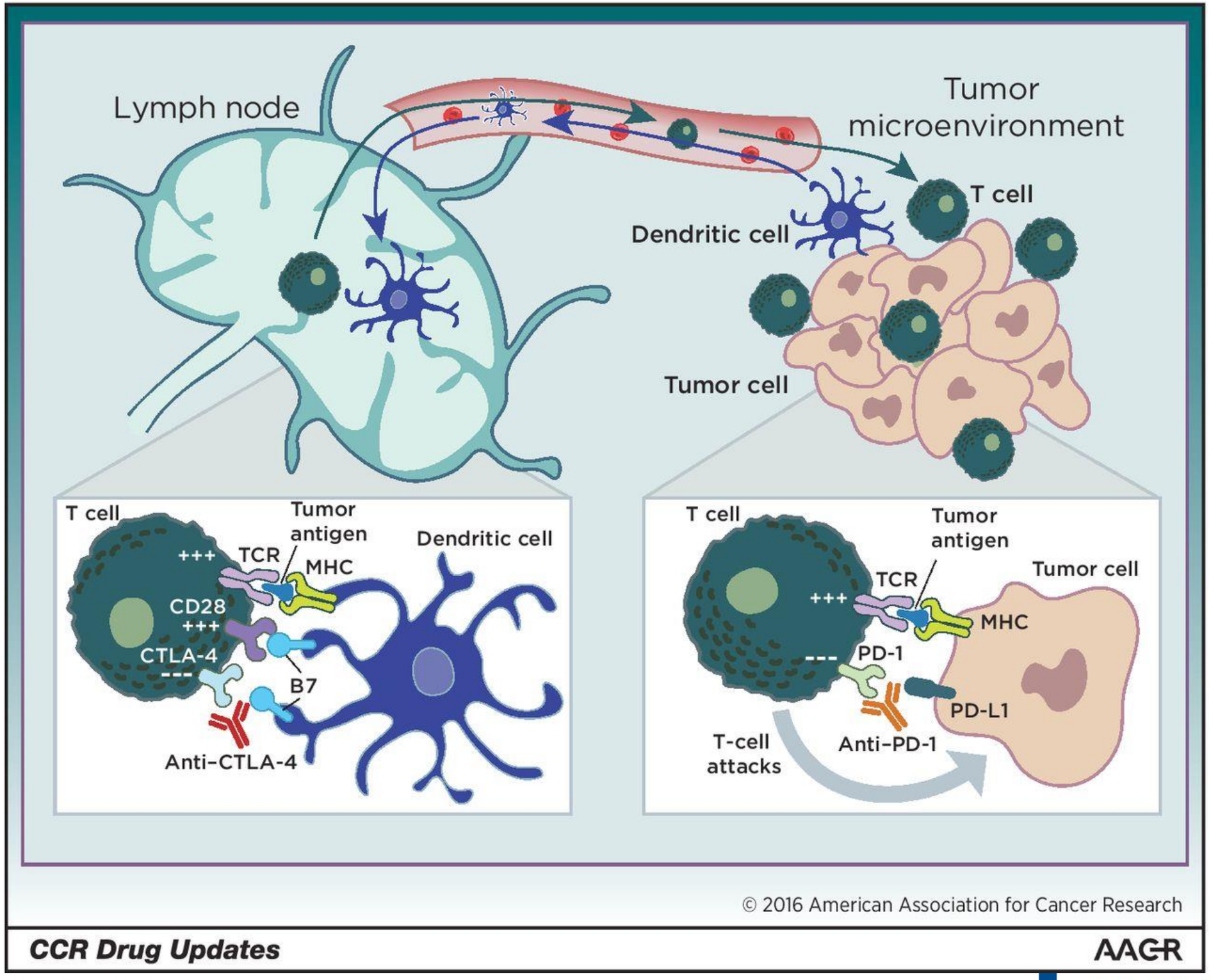
Presented By Jeffrey Weber at 2015 ASCO Annual Meeting

T-cell Activation by Ipilimumab (anti-CTLA-4, site of action in the periphery/lymph nodes) and Nivolumab (anti-PD-1, site of action in the tumor microenvironment)



CCR Drug Updates

AACR

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Matteo S. Carlino, and Georgina V. Long
Clin Cancer Res 2016;22:3992-3998

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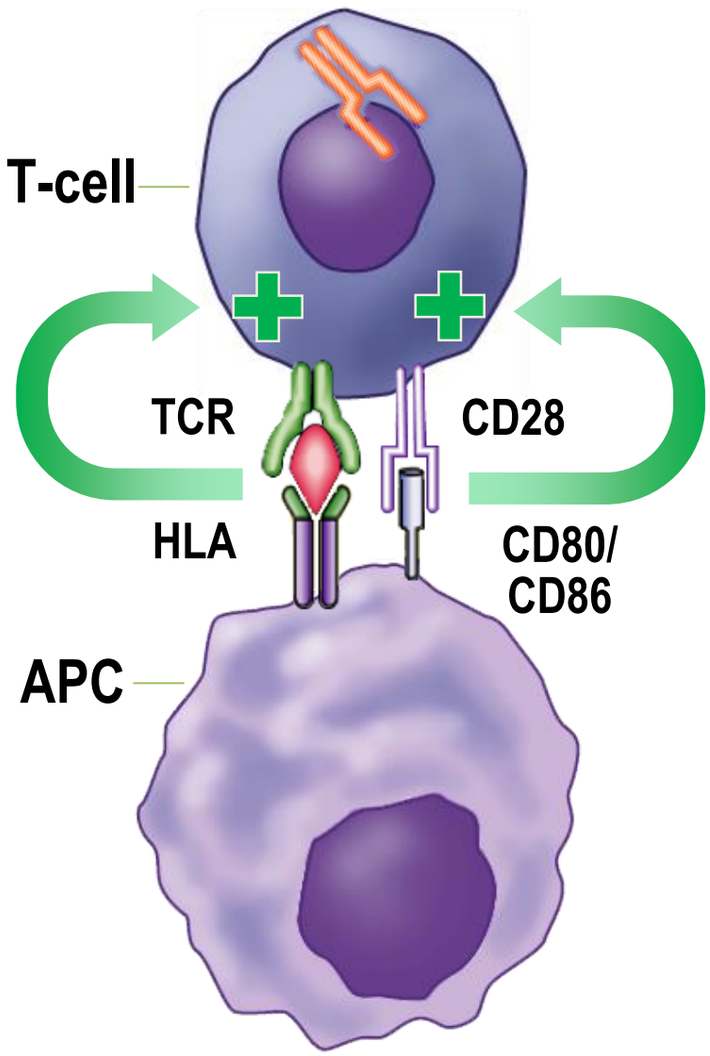
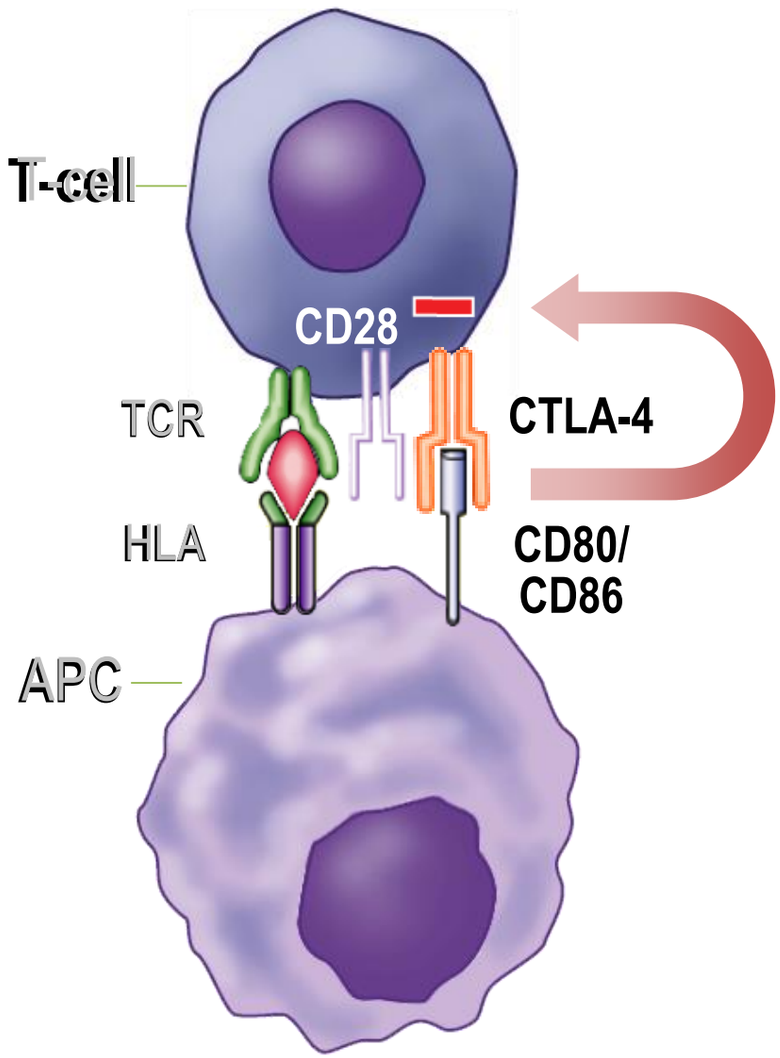
Ipilimumab Augments T-Cell Activation and Proliferation

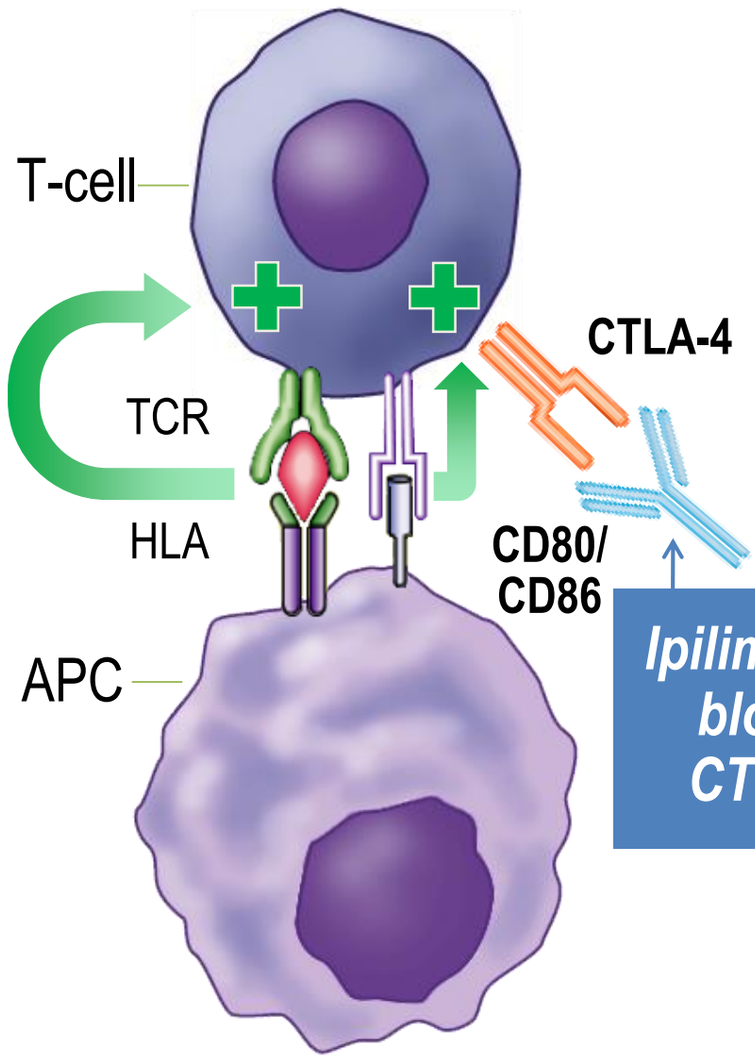
T-cell activation



T-cell inhibition



T-cell remains active



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

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CTLA-4: The Brake on T-Cell Activation

T-cell receptor: antigen/MHC

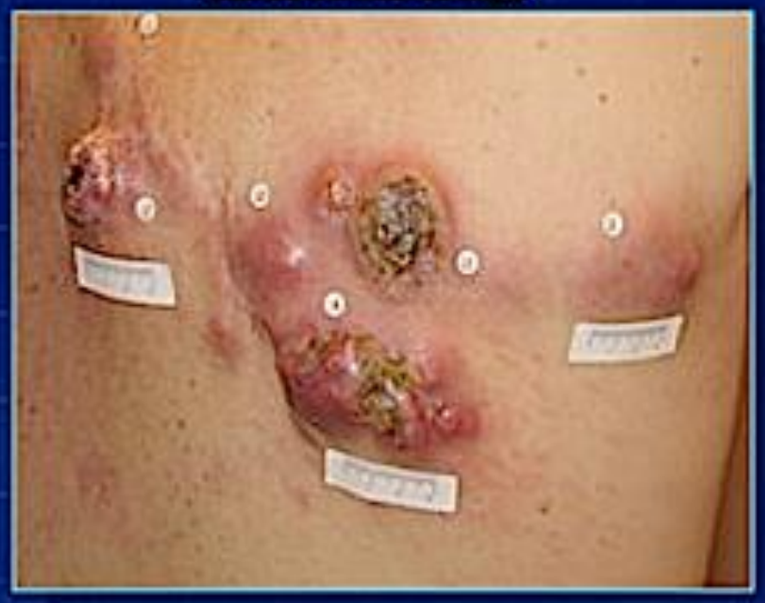
CD28 B7

CTLA-4 B7

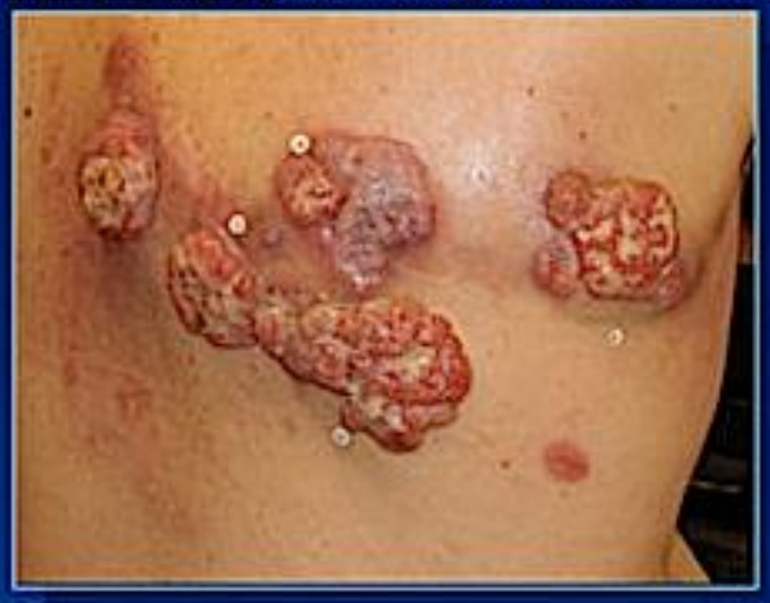
Vaccine?

Ipilimumab: Pattern of Response

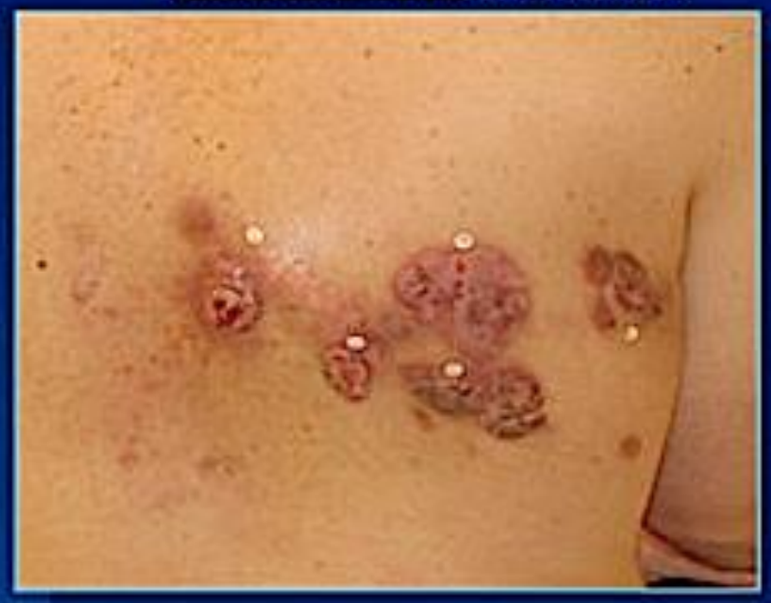
Screening



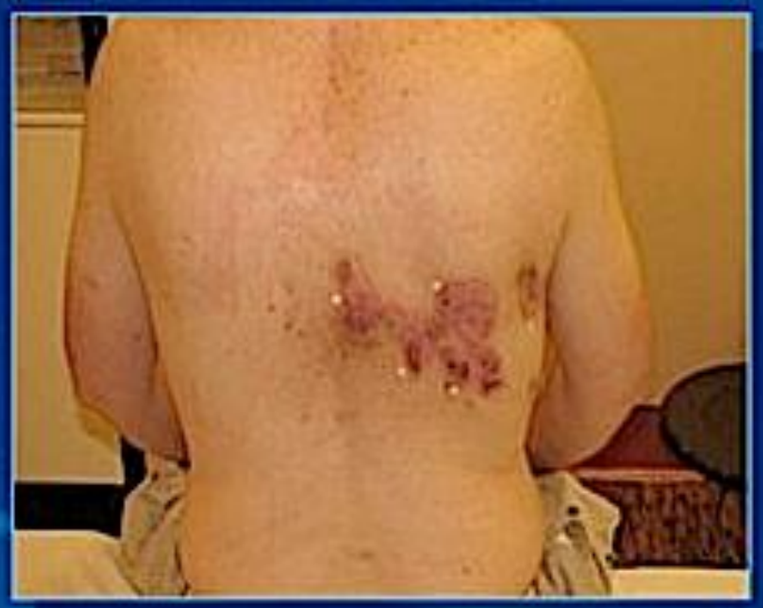
Week 12: swelling & progression



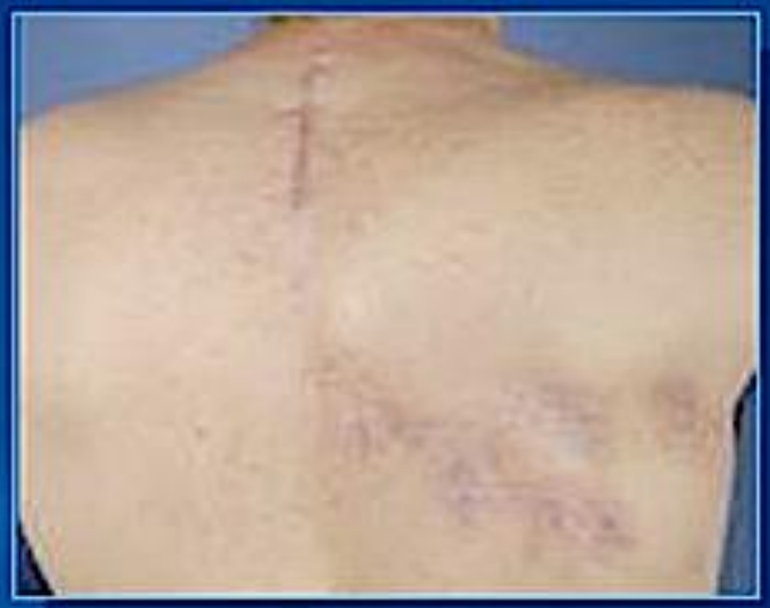
Week 14: improved



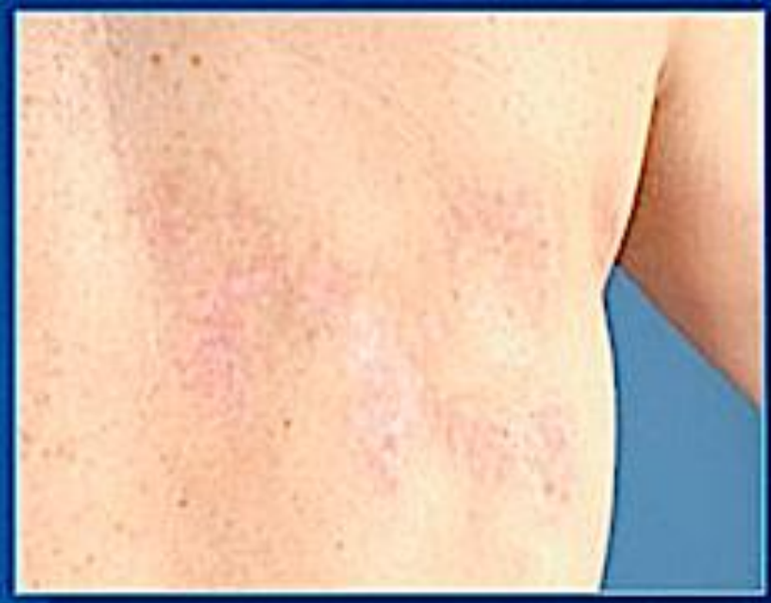
Week 16: continued improvement



Week 72: complete remission



Week 108: complete remission



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Maggon et al, 2011

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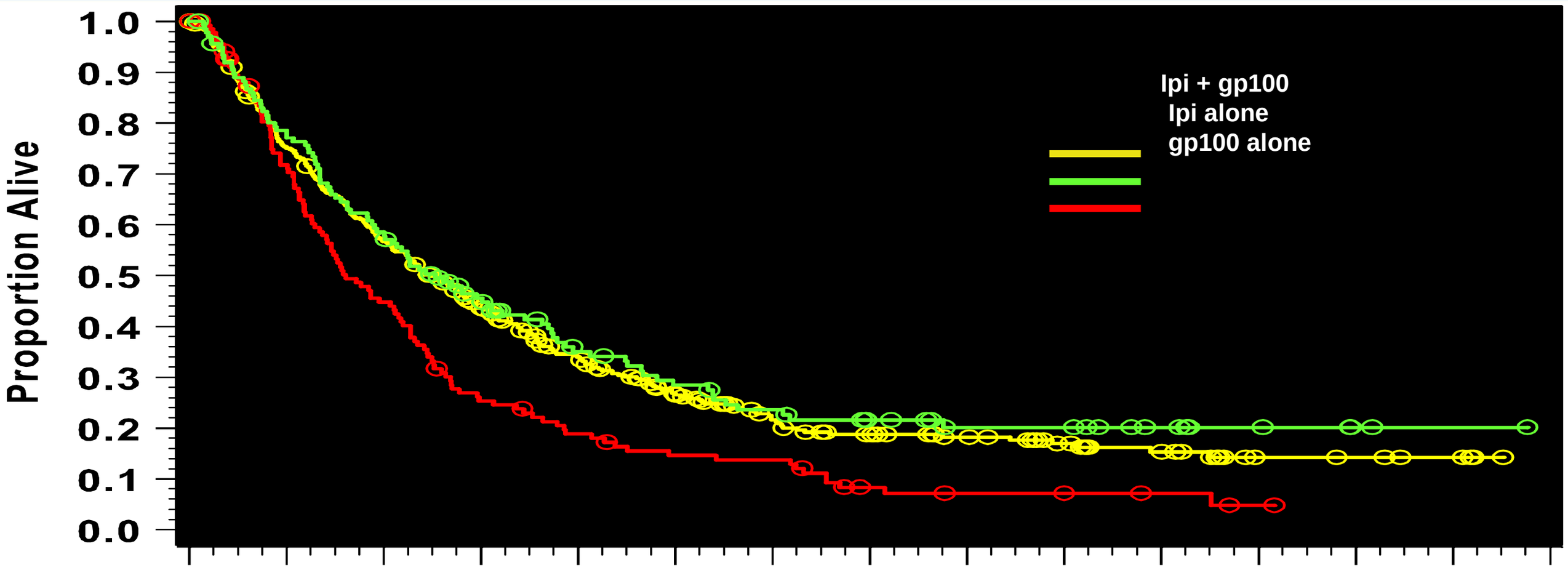
Ipilimumab Analysis of Overall Survival



Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

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Hodi et al, NEJM (August 2010)

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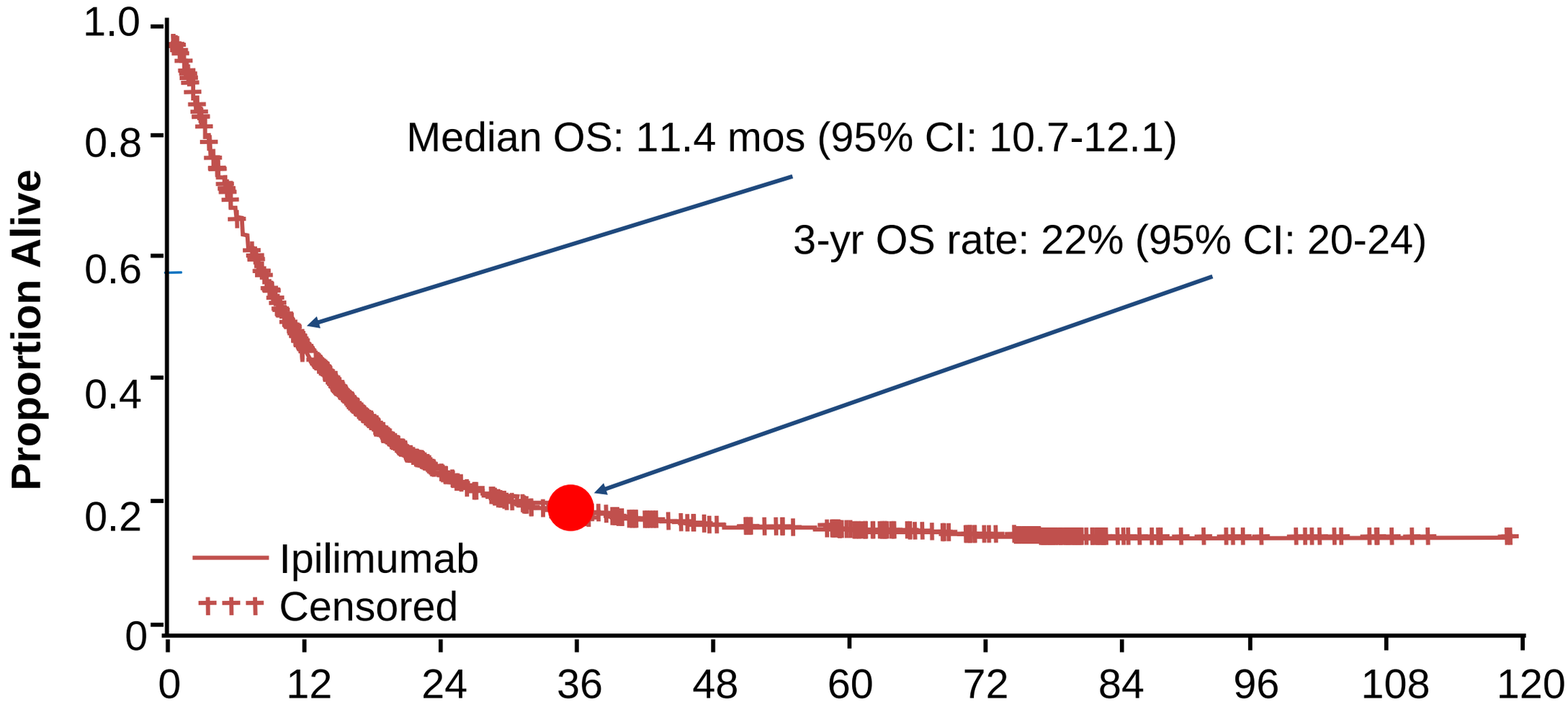
Ipilimumab: Pooled Survival Analysis From Phase II/III Trials in Advanced Melanoma



Pts at Risk, n

Ipilimumab	1861	839	370	254	192	170	120	26	15	5	0

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Hodi S, et al. 2013 European Cancer Congress. Abstract LBA 24. Schadendorf D, et al. J Clin Oncol. 2015;[Epub ahead of print].

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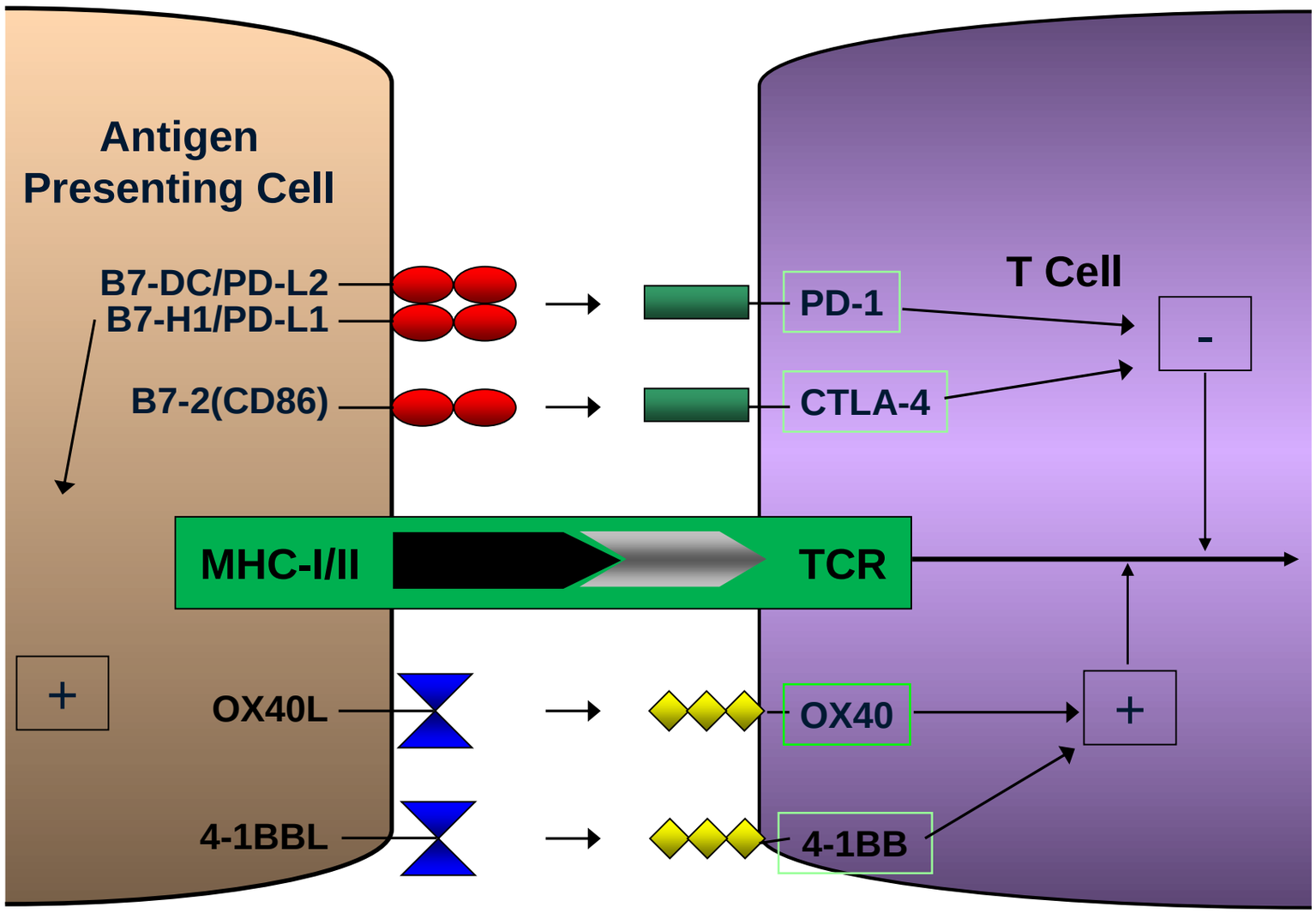
Immune System is the Target for Novel Treatments for Cancer



TNFR family TNF family B7 family CD28 family

Adapted from: Melero et al. *Nature Rev Cancer*. 2007;7:95.

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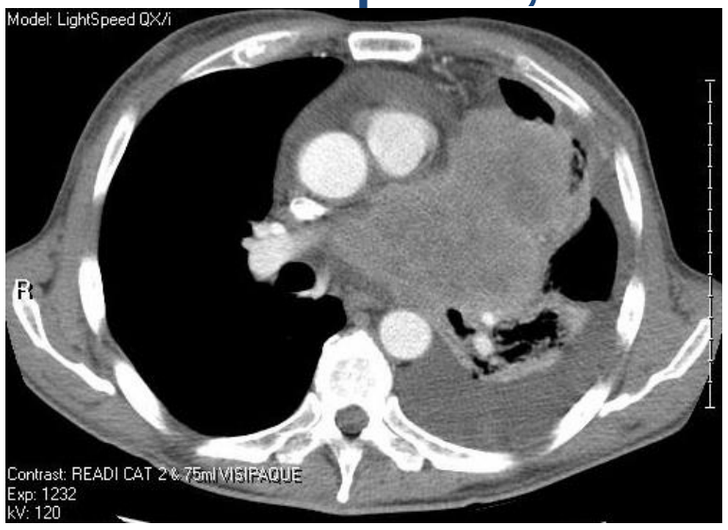
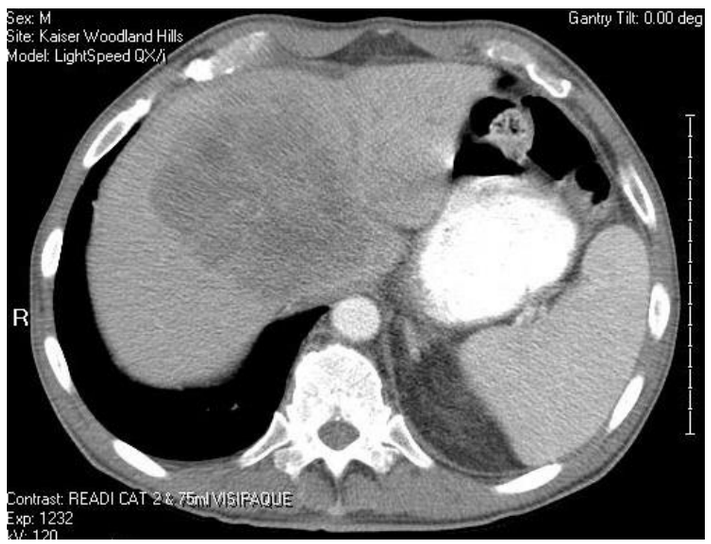
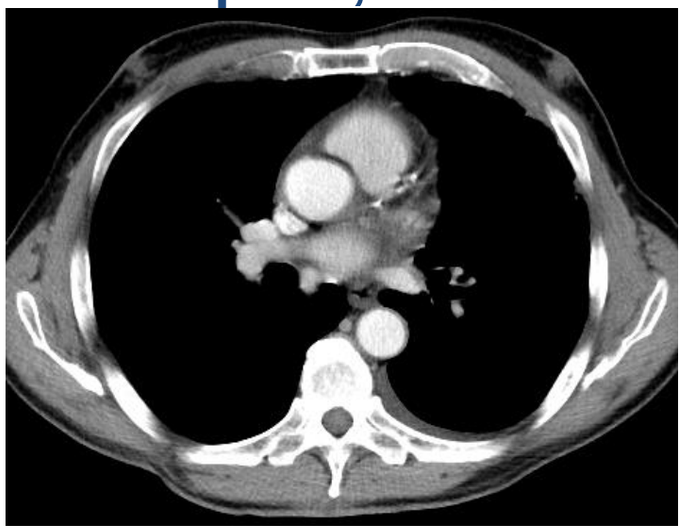
Pembrolizumab for Melanoma

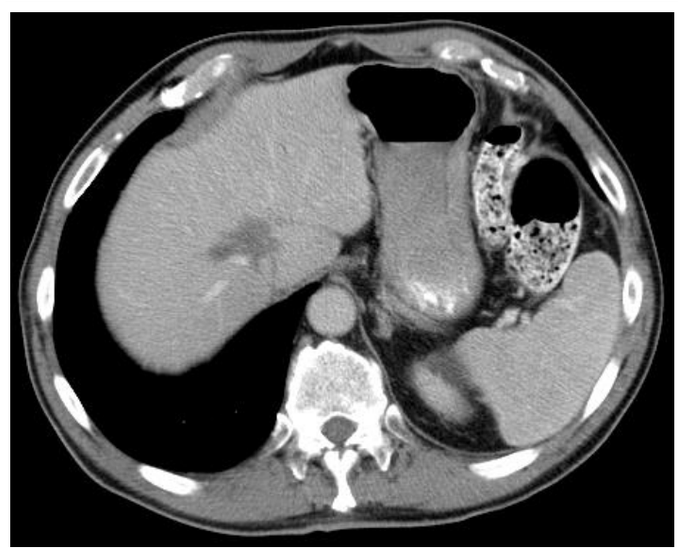
Baseline: April 13, 2012





April 9, 2013





72-yr-old male with symptomatic progression after bio-chemotherapy, HD IL-2, and ipilimumab

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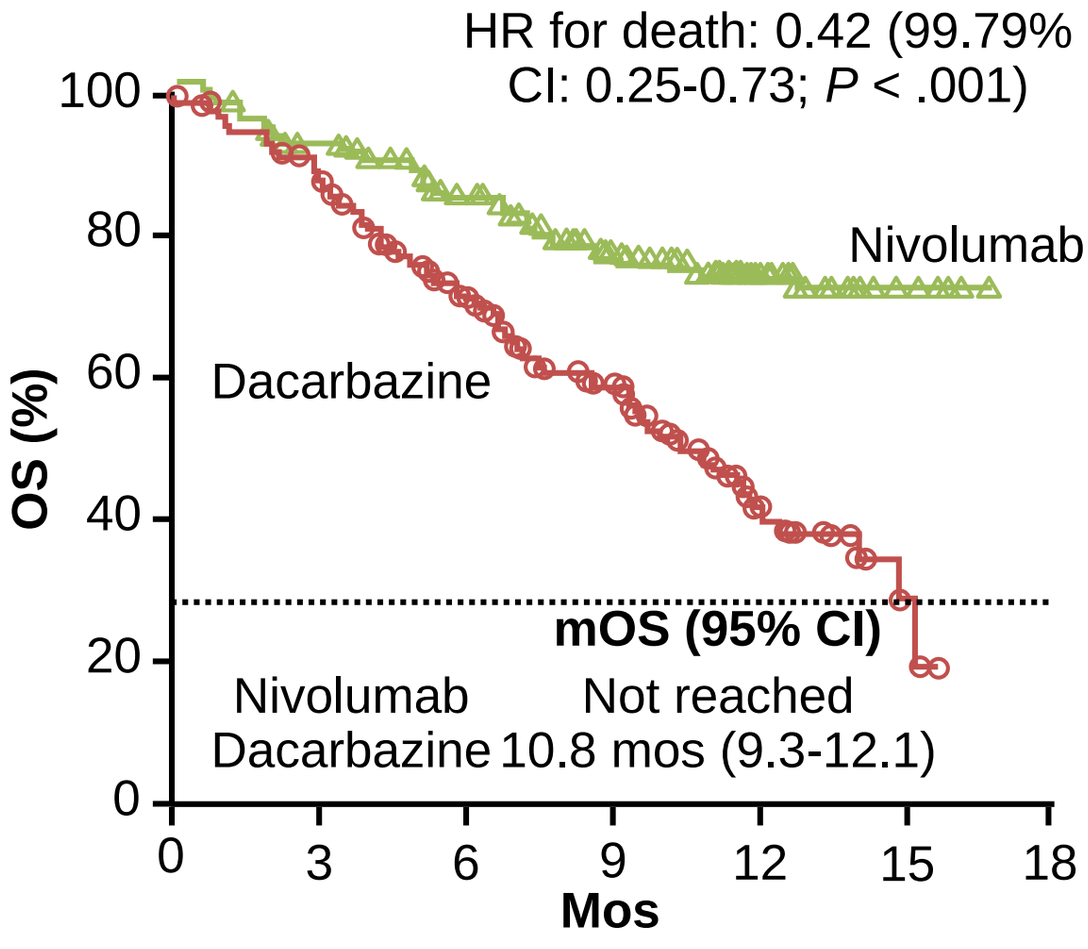
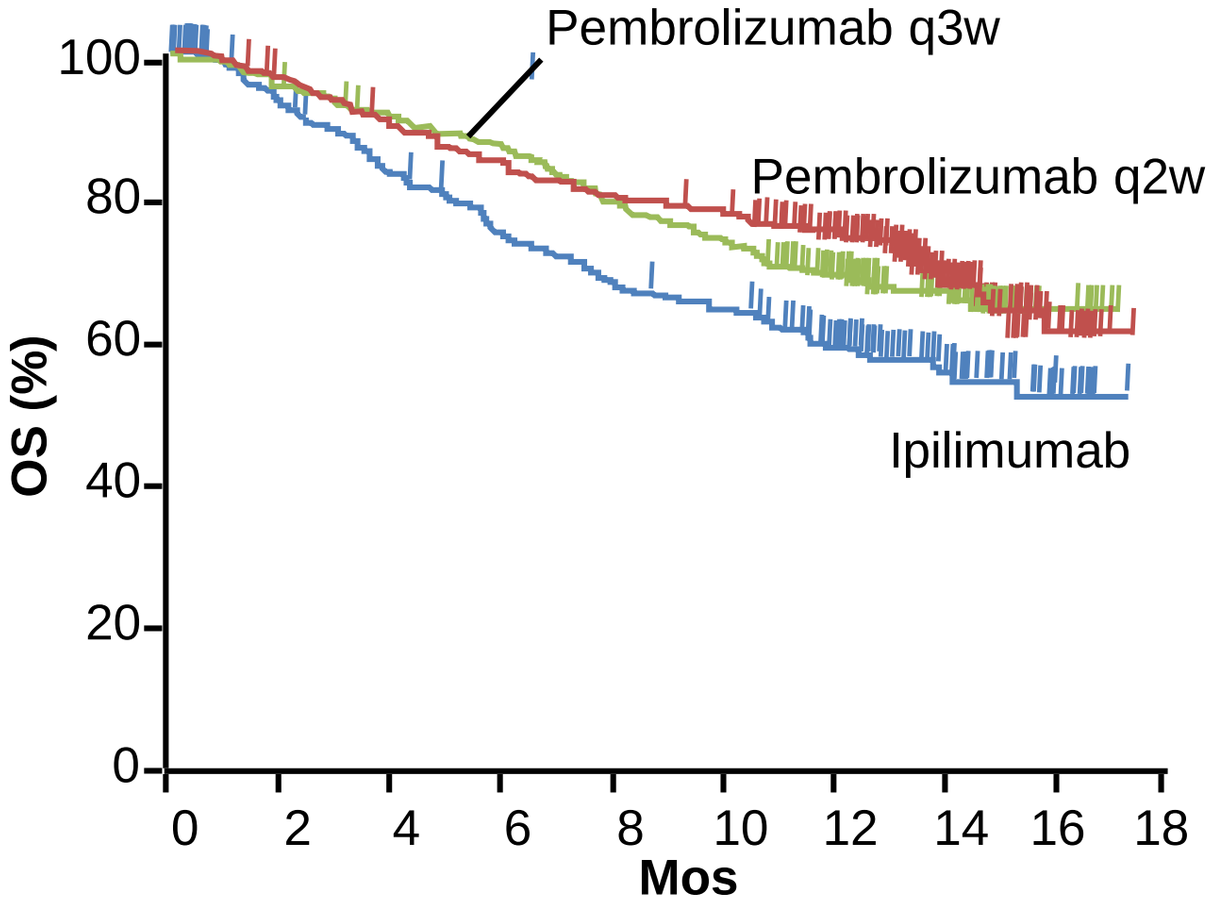
CheckMate 066 and KEYNOTE 006: OS

Nivolumab vs DTIC in *BRAF*-wild type, previously untreated melanoma[1]



Pembrolizumab vs Ipilimumab in Advanced Melanoma[2]



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1. Robert C, et al. N Engl J Med. 2015;372:320-330.
2. Robert C, et al. N Engl J Med. 2015

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Drugs Blocking PD-1/PD-L1 are Active Against Multiple Cancer Types

Durable objective tumor regressions in patients with:

- Melanoma (17-40% of patients responding)
- Lung cancer (10-30%)
- Kidney cancer (12-29%)
- Bladder cancer (25%)
- Ovarian cancer (6-23%)
- Head and neck cancer (14-20%)
- Hodgkin's lymphoma (87%)
- Gastric cancer, breast cancer, mesothelioma, etc……

➢ ***Drugs targeting a single molecular pathway have an unprecedented activity spectrum and provide a "common denominator" for cancer therapy***

Combination Therapy with Checkpoint Inhibitors

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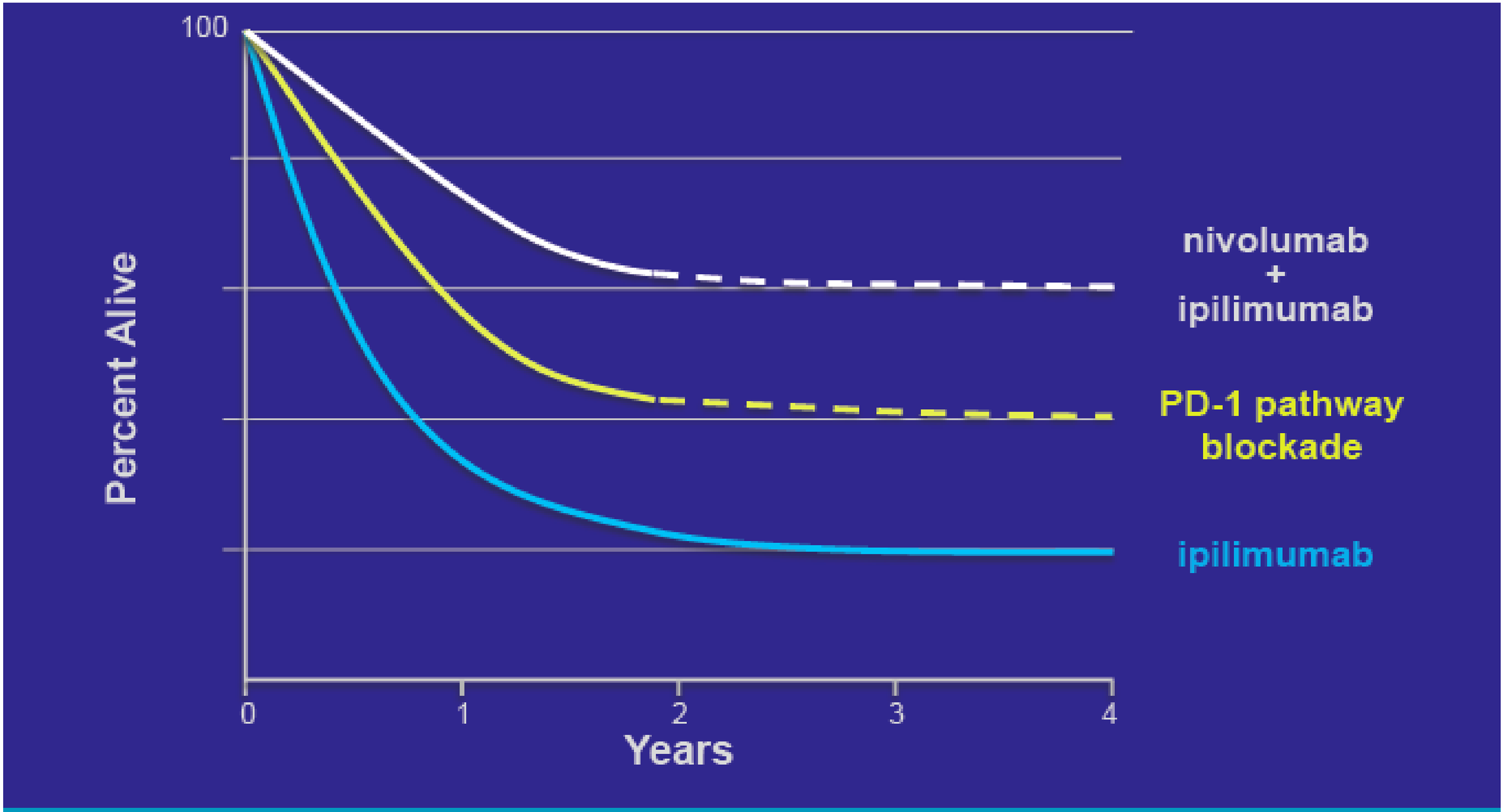
Overall Survival After Checkpoint Blockade



Presented by: Walter J. Urba, MD, PhD

PRESENTED AT: ASCO Annual '13 Meeting

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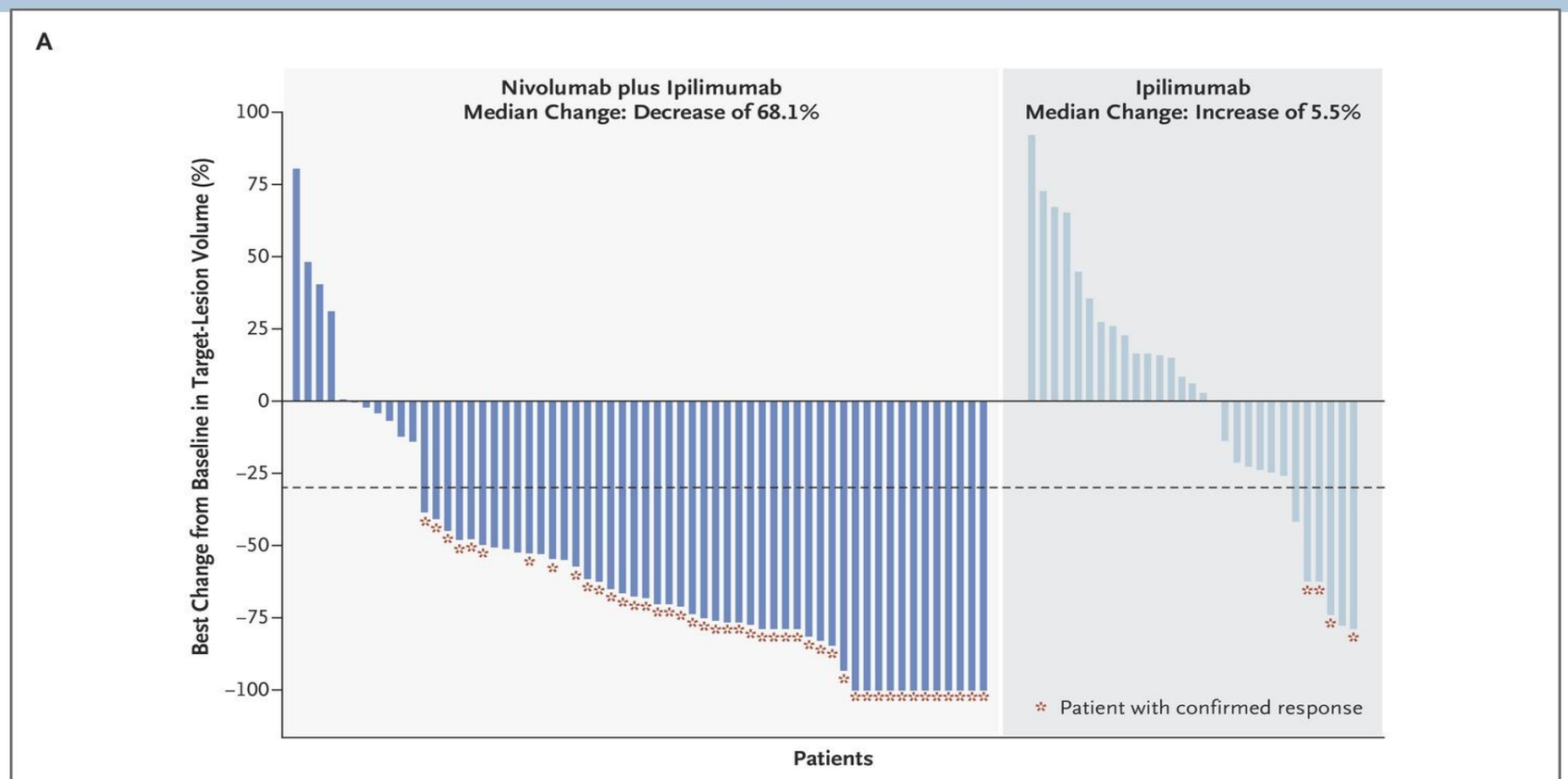
Nivolumab and Ipilimumab versus Ipilimumab



The NEW ENGLAND JOURNAL of MEDICINE

Postow MA, et al. N Engl J Med. 2015;372:2006-2017.

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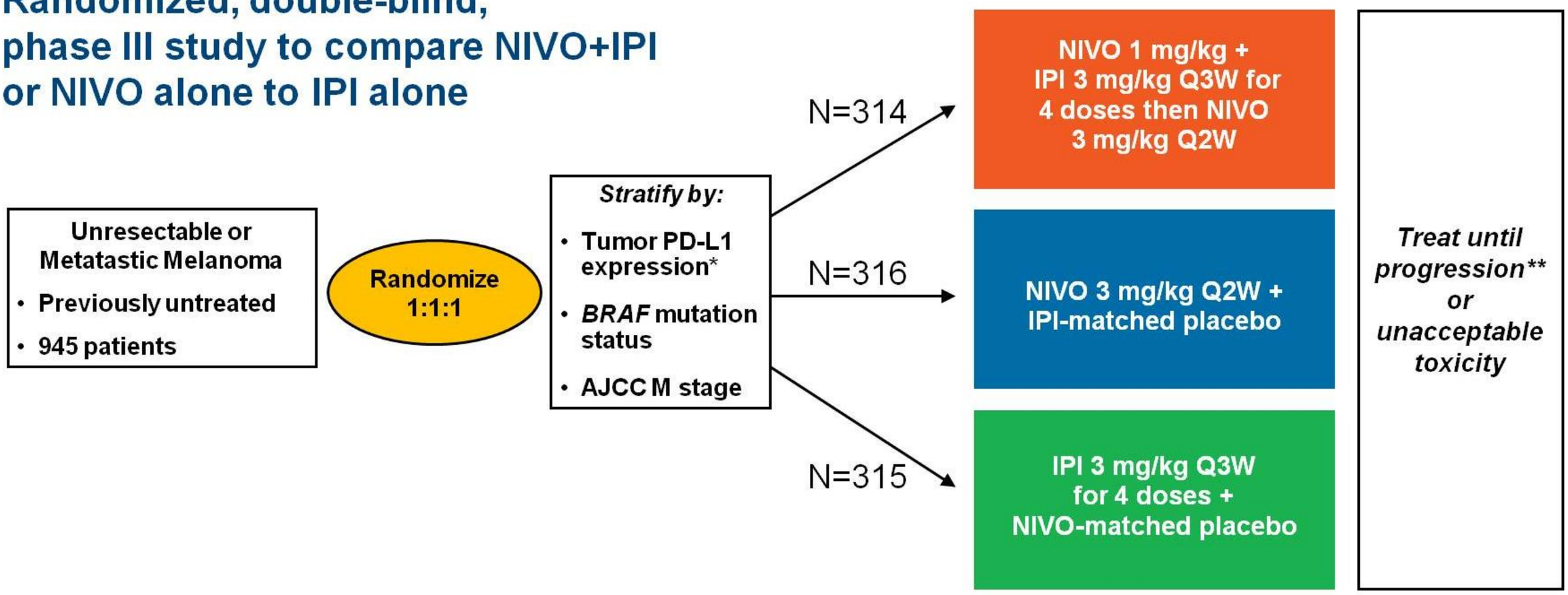
CA209-067: Study Design

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone



*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.

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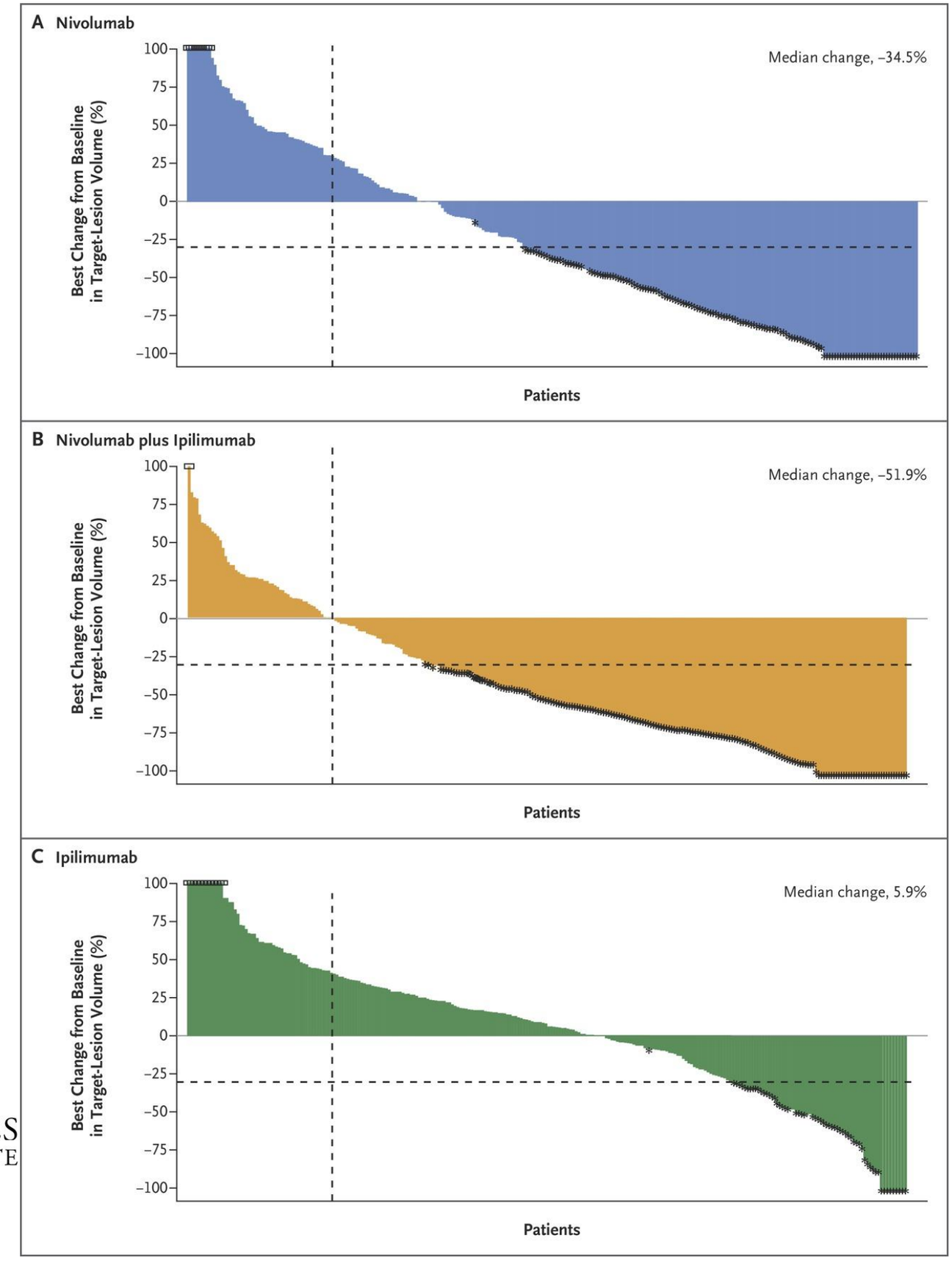
Response in Target Lesions

The NEW ENGLAND JOURNAL of MEDICINE



Nivolumab

Nivolumab/Ipilimumab

BMS:067

Ipilimumab

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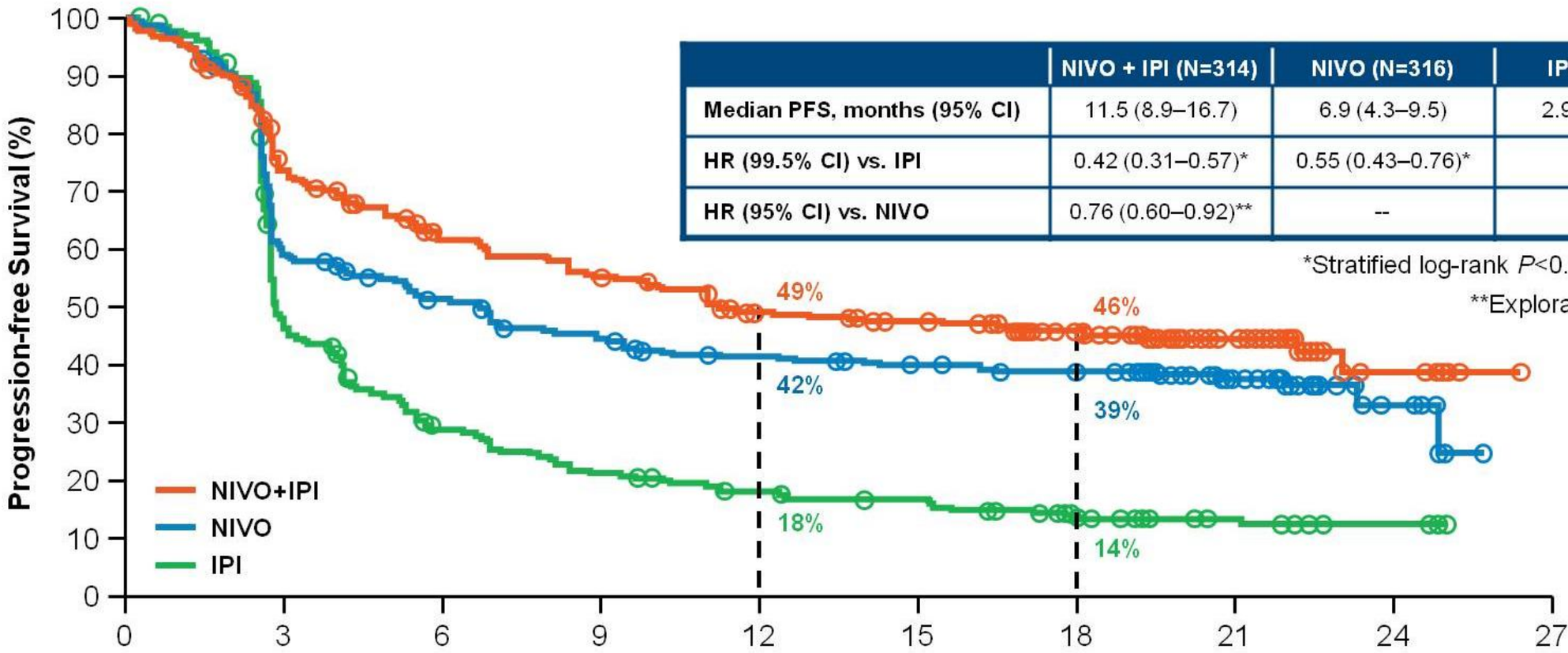
Progression-Free Survival (Intent-to-Treat Population)

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.55 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.76 (0.60–0.92)**	--	--

*Stratified log-rank $P<0.00001$ vs. IPI

**Exploratory endpoint



Number of patients at risk:

Nivolumab + Ipilimumab	314	219	174	156	133	126	103	48	8	0
Nivolumab	316	177	148	127	114	104	94	46	8	0
Ipilimumab	315	137	78	58	46	40	25	15	3	0

Database lock Nov 2015

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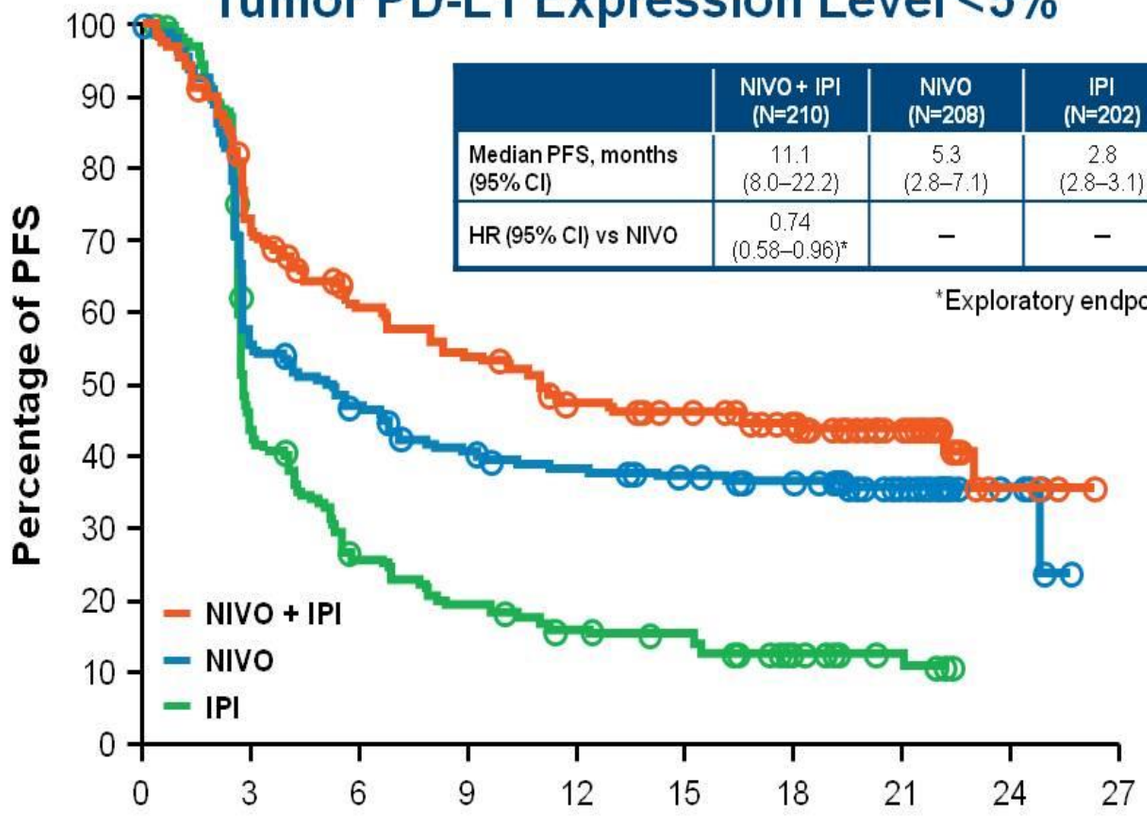
Progression-Free Survival by Tumor PD-L1 Expression

Potential Biomarker

Tumor PD-L1 Expression Level <5%

	NIVO + IPI (N=210)	NIVO (N=208)	IPI (N=202)
Median PFS, months (95% CI)	11.1 (8.0–22.2)	5.3 (2.8–7.1)	2.8 (2.8–3.1)
HR (95% CI) vs NIVO	0.74 (0.58–0.96)*	–	–

*Exploratory endpoint

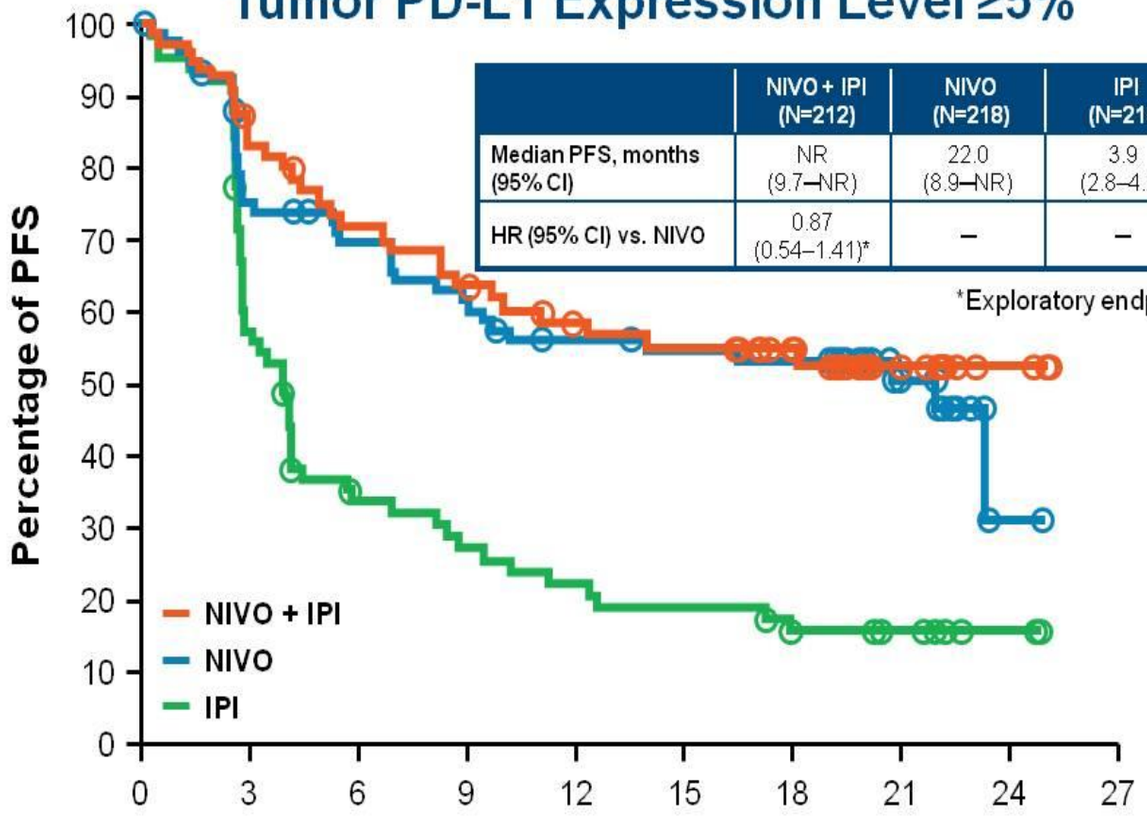


Number of patients at risk:										
NIVO + IPI	210	142	113	101	86	81	69	31	5	0
NIVO	208	108	89	75	69	62	55	29	7	0
IPI	202	82	45	34	26	22	12	7	0	0

Tumor PD-L1 Expression Level ≥5%

	NIVO + IPI (N=212)	NIVO (N=218)	IPI (N=215)
Median PFS, months (95% CI)	NR (9.7–NR)	22.0 (8.9–NR)	3.9 (2.8–4.2)
HR (95% CI) vs. NIVO	0.87 (0.54–1.41)*	–	–

*Exploratory endpoint



Number of patients at risk:										
NIVO + IPI	68	53	44	39	33	31	22	13	3	0
NIVO	80	57	51	45	39	37	36	16	1	0
IPI	75	40	21	17	14	12	8	6	2	0

- For the original PD-L1 PFS analysis, the descriptive hazard ratio comparing NIVO+IPI vs NIVO was 0.96, with a similar median PFS in both groups (14 months)

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Presented By Jedd Wolchok at 2016 ASCO Annual Meeting

Summary of CTLA-4 Blockade Immune-Mediated Toxicities

- Toxicity related to ipilimumab appears to be dose related
- Toxicity-related death occurred in < 1% of cases

Common (> 20%)

- Rash, pruritus
- Fevers, chills, lethargy
- **Diarrhea/colitis**

Occasional (3% to 20%)

- Hepatitis/liver enzyme abnormalities
- Endocrinopathies: hypophysitis, thyroiditis, adrenal insufficiency

Rare (< 2%)

- Episcleritis/uveitis
- Pancreatitis
- Nephritis
- Neuropathies, Guillain-Barré, myasthenia gravis
- Lymphadenopathy (sarcoid)
- Thrombocytopenia
- Toxic epidermal necrolysis, Stevens-Johnson syndrome

Weber JS, et al. J Clin Oncol. 2012;30:2691-2697.
Weber JS, et al. J Clin Oncol. 2015

Summary of PD-1/PD-L1 Blockade Immune-Mediated Toxicities

- Toxicity less common than with anti–CTLA-4 but still can be fatal

Occasional (5% to 20%)

- Fatigue, headache, arthralgia, fevers, chills, lethargy
- Rash: maculopapular, pruritus, vitiligo
  - Topical treatments
- **Diarrhea/colitis**
  - Initiate steroids early, taper slowly
- Hepatitis, liver/pancreatic enzyme abnormalities
- Infusion reactions
- Endocrinopathies: thyroid, adrenal, hypophysitis

Rare (< 5%)

- **Pneumonitis**
  - Grade 3/4 toxicities uncommon
  - Low grade reversible with steroids and discontinuation
- Anemia

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Weber JS, et al. J Clin Oncol. 2012;30:2691-2697. Weber JS, et al. J Clin Oncol. 2015

Less Common Immune-Related Adverse Events

- Hematologic (hemolytic anemia, thrombocytopenia)
- Cardiovascular (myocarditis, pericarditis, vasculitis)
- Ocular (blepharitis, conjunctivitis, iritis, scleritis, uveitis)
- Renal (nephritis)
- Several case reports of rare autoimmune-based toxicities in pts treated with ipilimumab
  - Lupus nephritis
  - Inflammatory enteric neuropathy
  - Tolsosa-Hunt syndrome
  - Myocardial fibrosis
  - Acquired hemophilia A
  - Autoimmune polymyositis

Adverse Events: Combined Therapy

Table 3. Adverse Events.*

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine aminotransferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate aminotransferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

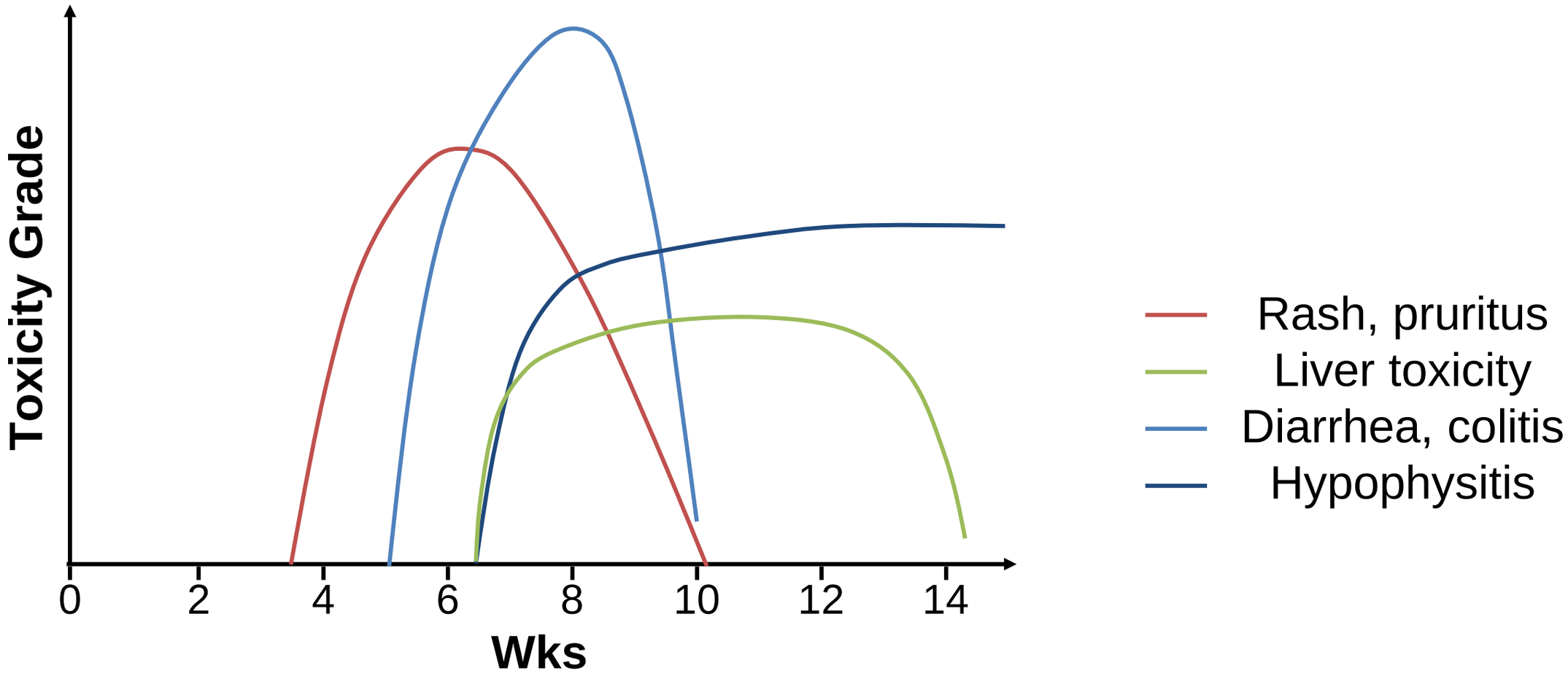
* The safety population included all the patients who received at least one dose of study drug. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

† The treatment-related adverse events listed here were those reported in at least 10% of the patients in any of the three study groups.

The NEW ENGLAND JOURNAL of MEDICINE

Kinetics of Appearance of irAEs with Checkpoint Blockade

- Data from pts receiving anti–PD-1 antibodies q2w for ≥ 3 yrs show most irAEs occur by Wk 24 (6 mos)
- Toxicities with PD-1/PD-L1 agents may take longer to resolve than with ipilimumab, so long-term surveillance is recommended



Weber JS, et al. J Clin Oncol. 2012;30:2691-2697.
Weber JS, et al. J Clin Oncol. 2015

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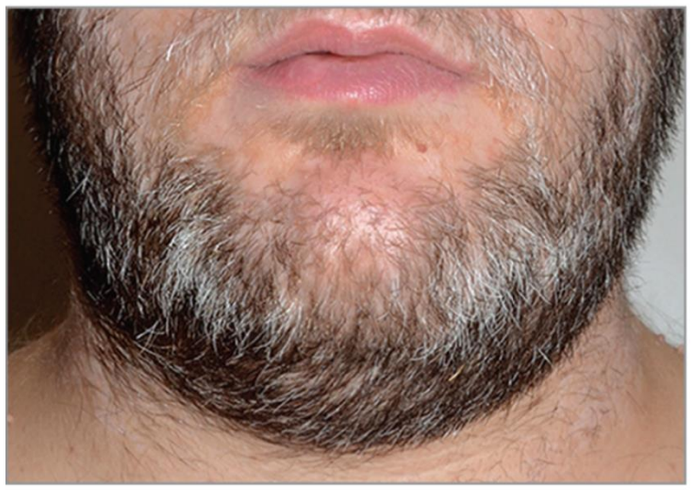
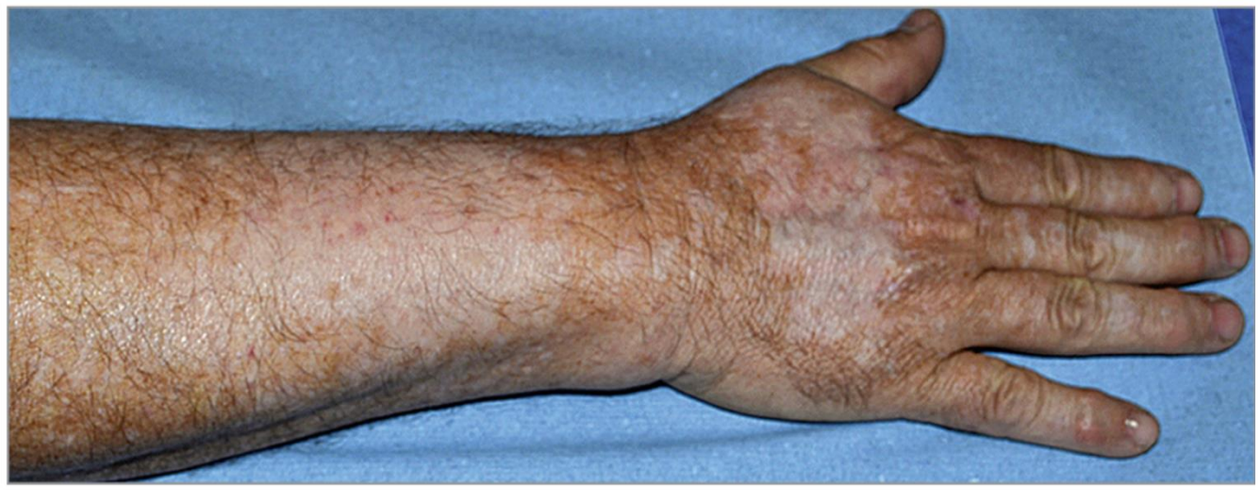
Association of Vitiligo with Tumor Response in Patients with Metastatic Melanoma Treated with Pembrolizumab

Clinical Photographs of a Patient With Vitiligo Occurring During Pembrolizumab Treatment of MelanomaPatient's types of vitiligo. Arrowhead indicates hypomelanotic lesions developed around cutaneous metastases.

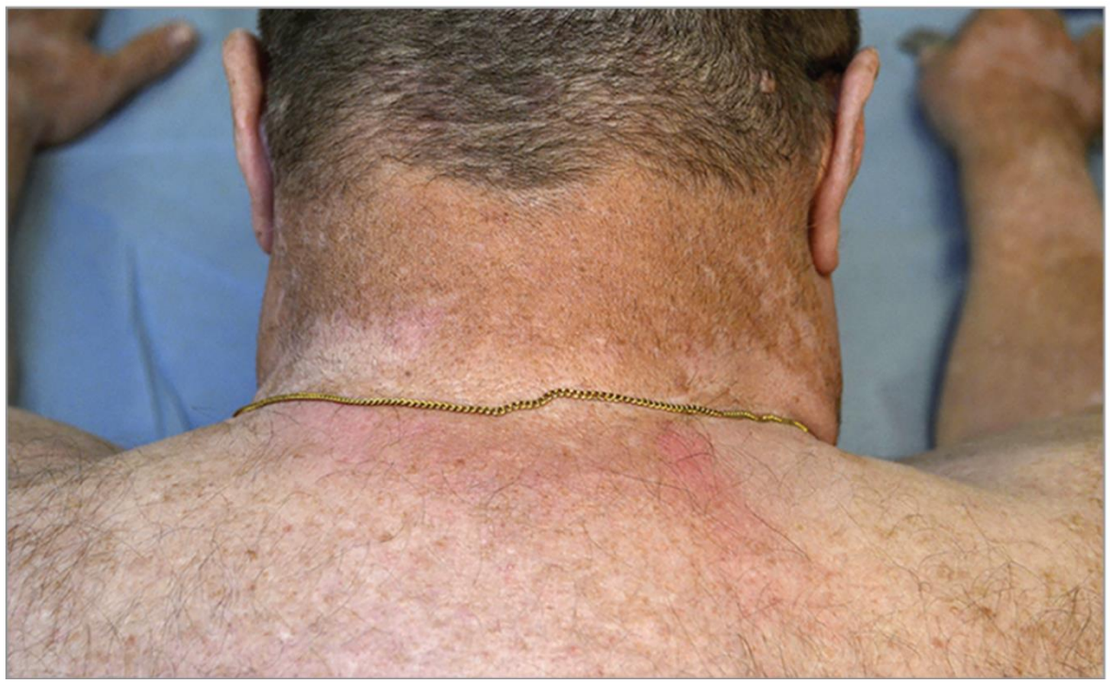
A Acrofacial vitiligo



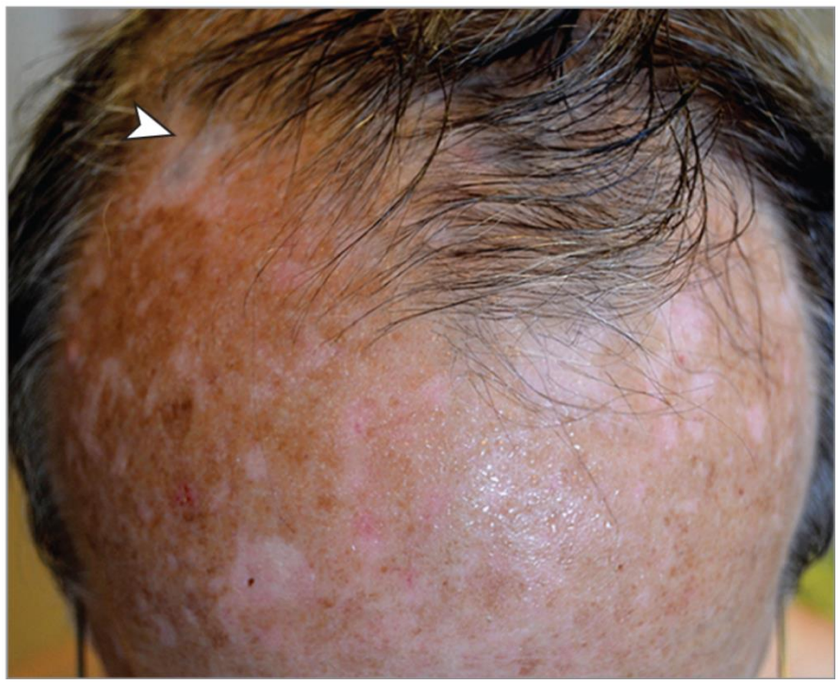
B Vitiligo on the arm and hand



C Generalized vitiligo



A Vitiligo on scalp



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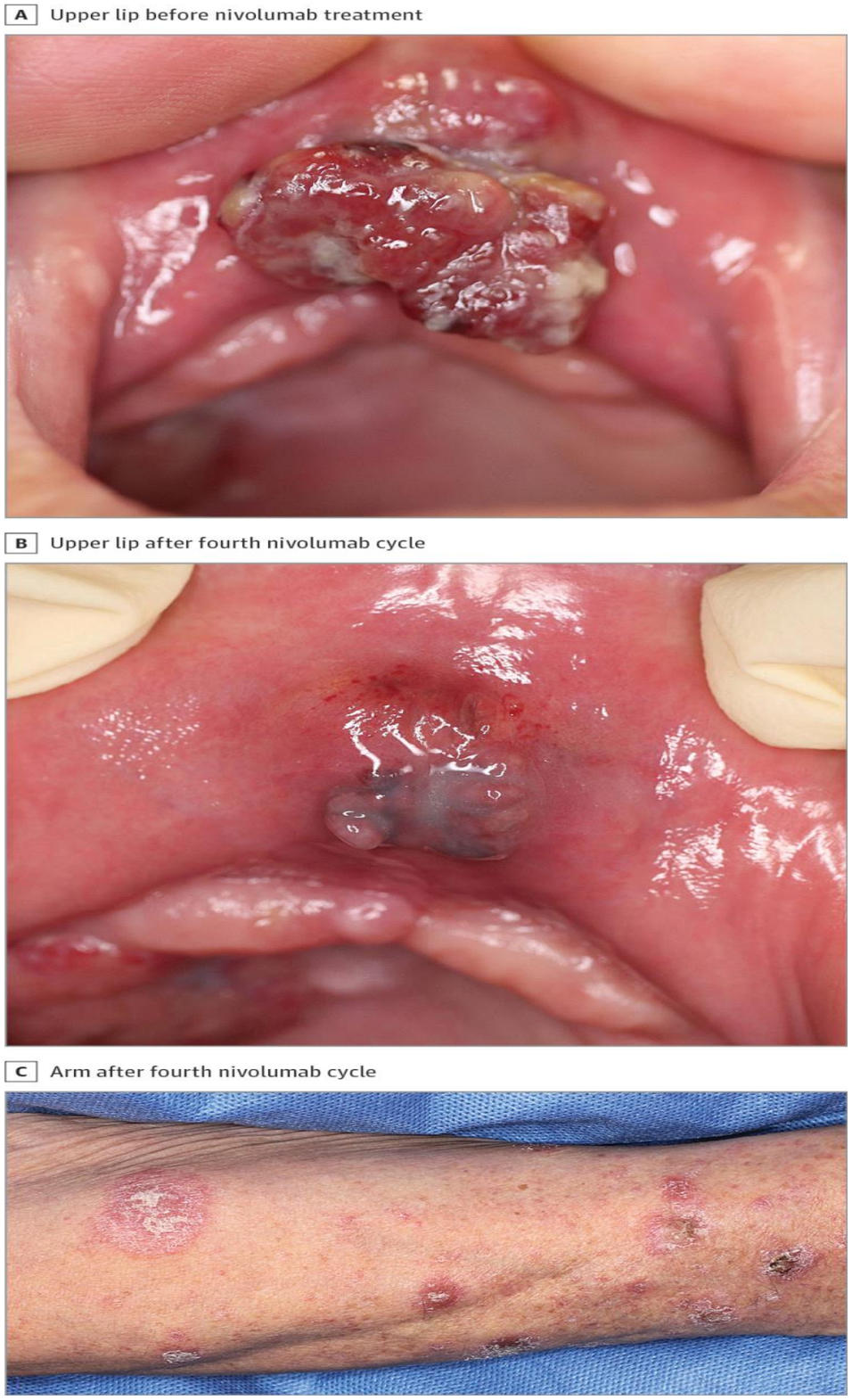
JAMA Dermatol. 2016;152(1):45-51. doi:10.1001/jamadermatol.2015.2707

Occurrence of Psoriasiform Eruption During Nivolumab Therapy for Primary Oral Mucosal Melanoma

A red, partially blackish nodule is present on the upper lip. B, After nivolumab, the nodule on the lip is significantly smaller. C, Well-demarcated, scaly, erythematous plaques are observed on the arm; eruptions show unclear borders or crusts.



JAMA Dermatol. 2015;151(7):797-799. doi:10.1001/jamadermatol.2015.0249

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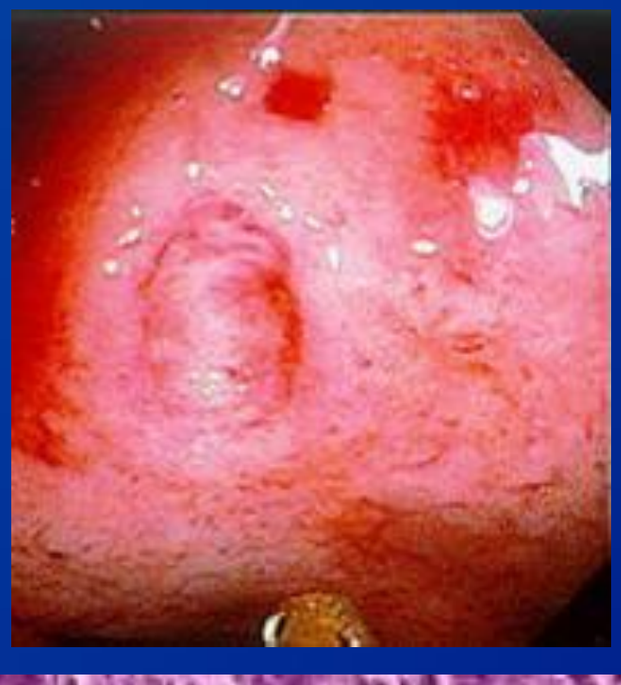
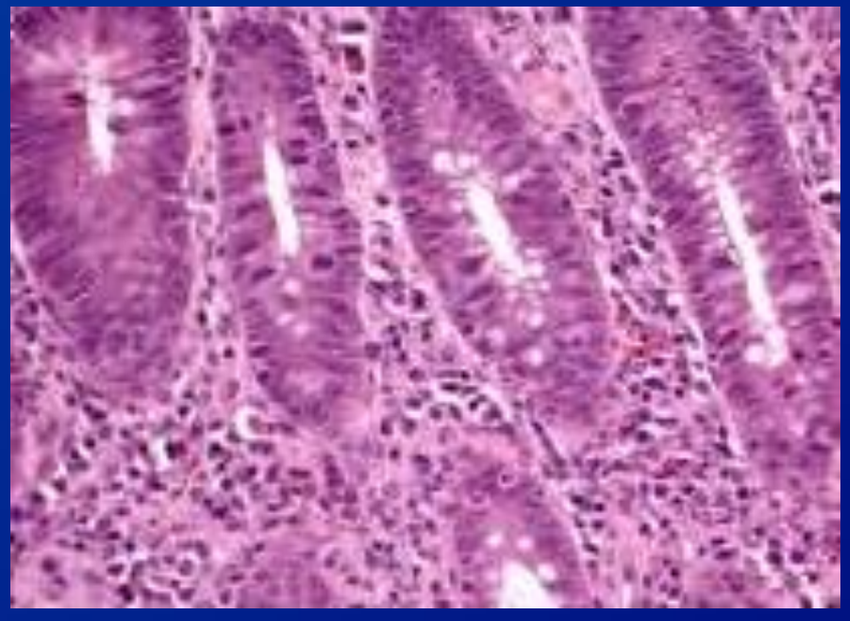
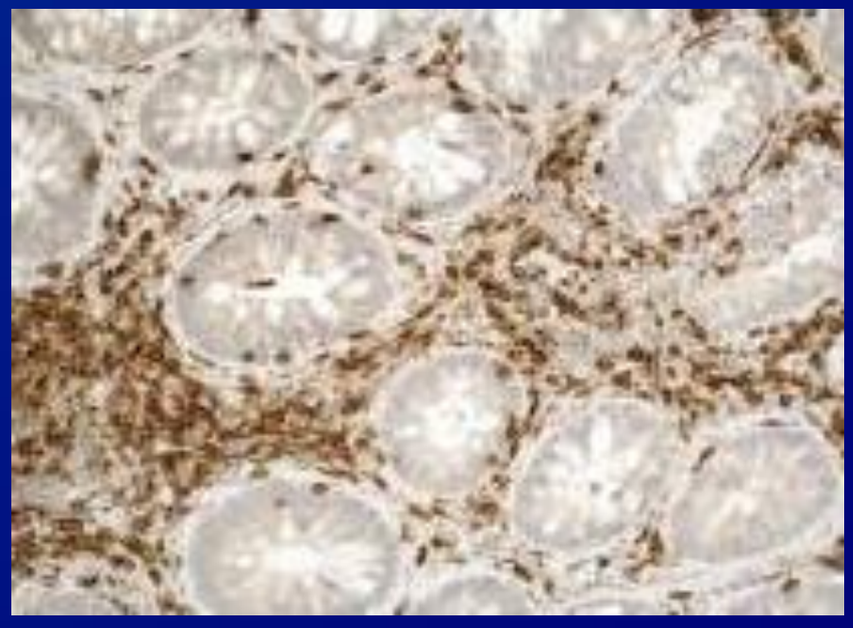
Ipilimumab-Induced Colitis Resembles IBD and Usually Resolves Without Sequelae With Appropriate Therapy







IMER
www.IMERonline.com

Robinson et al, 2004; Phan et al, 2003.

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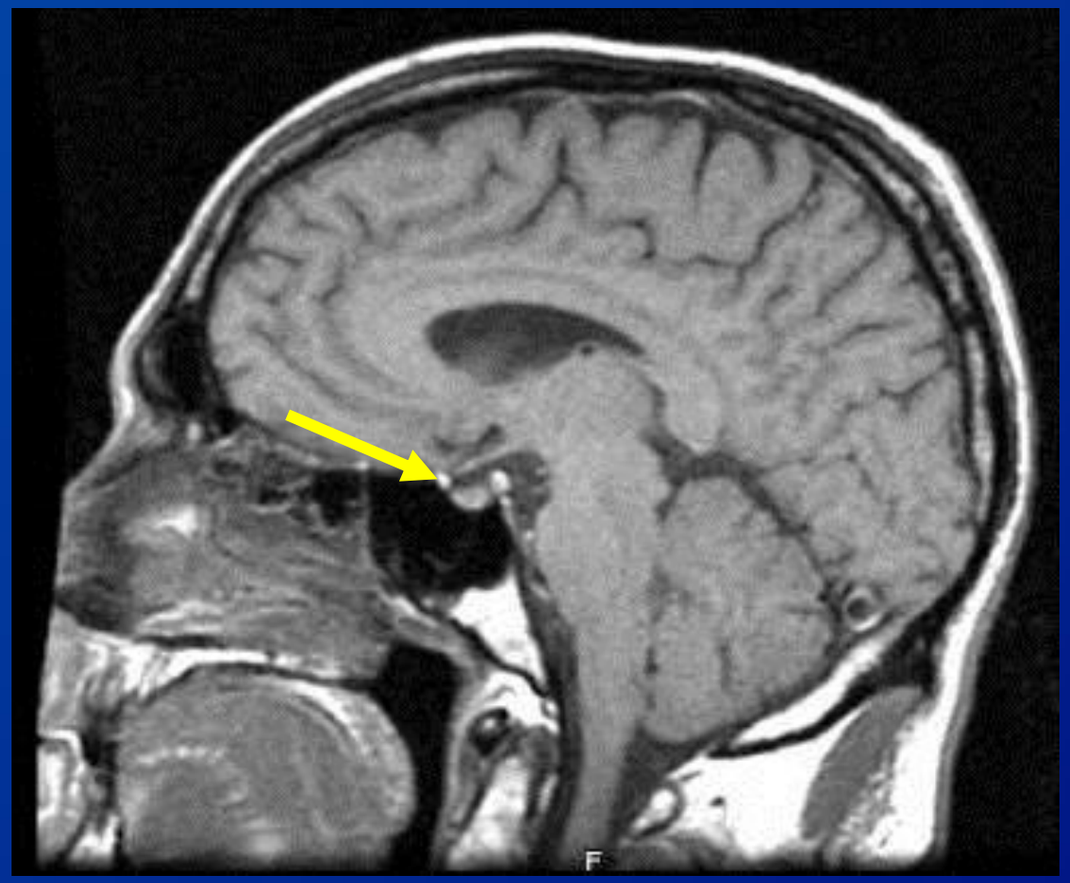
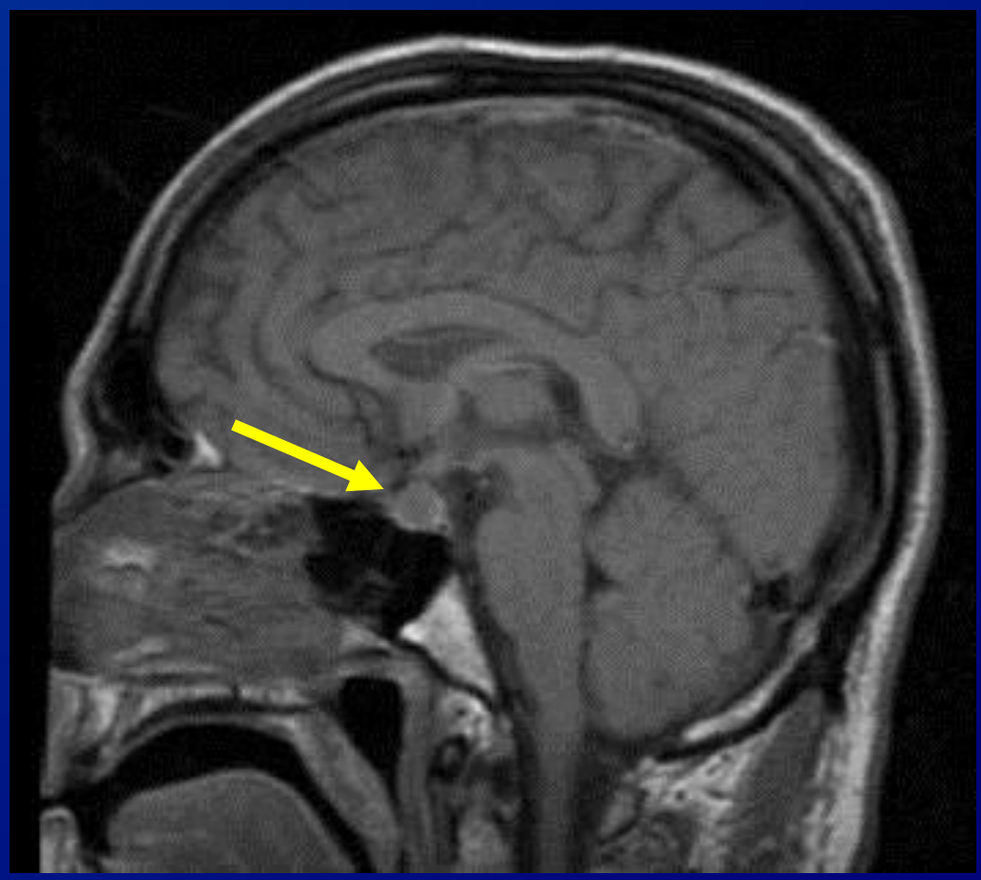
Ipilimumab-Related Pituitary Swelling and Dysfunction



6/30/04 Baseline
(4.5 mm)



12/3/04 Headache/fatigue after 5 doses (10.8 mm)

IMER
www.IMERonline.com

Blansfield et al, 2005.

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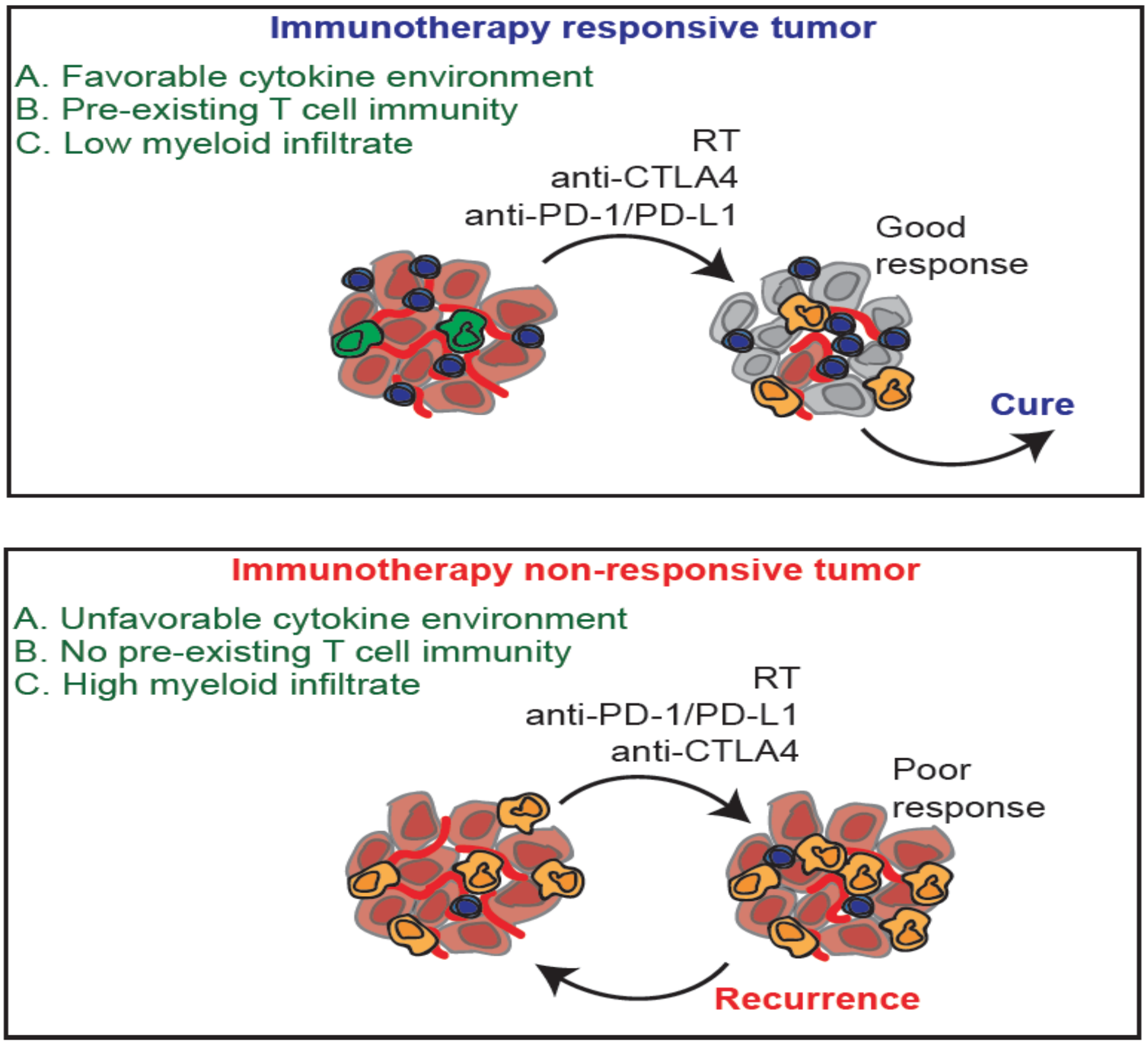
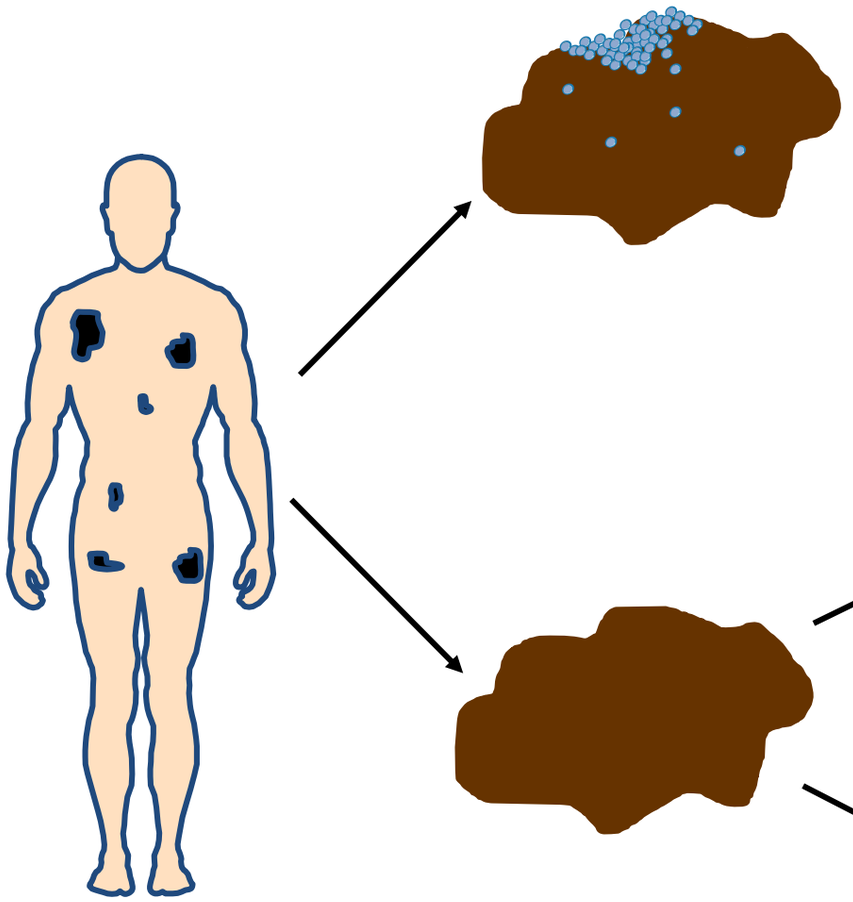
Management of Drug-Related AEs

- The majority of both nivolumab- and ipilimumab-related AEs to date have been reversible and manageable by delaying study drug ± administration of corticosteroids; other immunosuppressants (TNF inhibitors) may also be needed

The Problem


Immunotherapy responsive tumor
A. Favorable cytokine environment
B. Pre-existing T cell immunity
C. Low myeloid infiltrate
RT
anti-CTLA4
anti-PD-1/PD-L1
Good
response
Cure
Immunotherapy non-responsive tumor
A. Unfavorable cytokine environment
B. No pre-existing T cell immunity
C. High myeloid infiltrate
RT
anti-PD-1/PD-L1
anti-CTLA4
Poor
response
Recurrence
M1 Macrophage
M2 Macrophage
T cell
Cancer cell
Dead cancer cell

Management of Cancer in the Post Anti–PD-1/L1



Anti–PD-1/anti–PD-L1

Bring T cells into tumors:

- + Anti–CTLA-4
- + Immune-activating antibodies or cytokines
- + TLR agonists or oncolytic viruses
- + IDO or macrophage inhibitors
- + Targeted therapies

Generate T cells:

- Vaccines
- TIL
- TCR-engineered ACT
- CAR-engineered ACT

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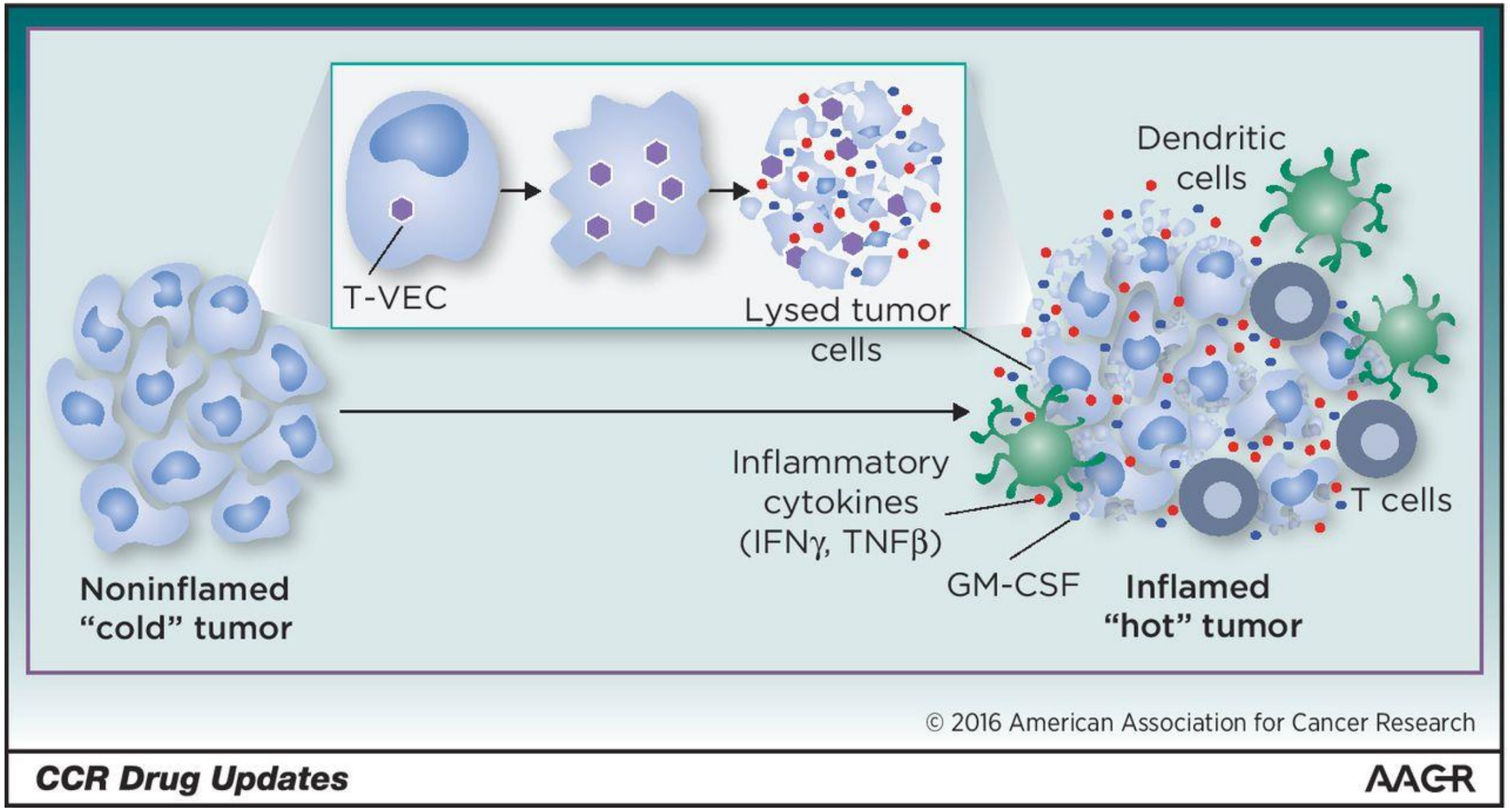
Oncolytic Viruses

In situ vaccination effect of T-VEC, potentially converting a non–T-cell-inflamed tumor to a T-cell–inflamed tumor.



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Patrick A. Ott, and F. Stephen Hodi Clin Cancer Res 2016;22:3127-3131

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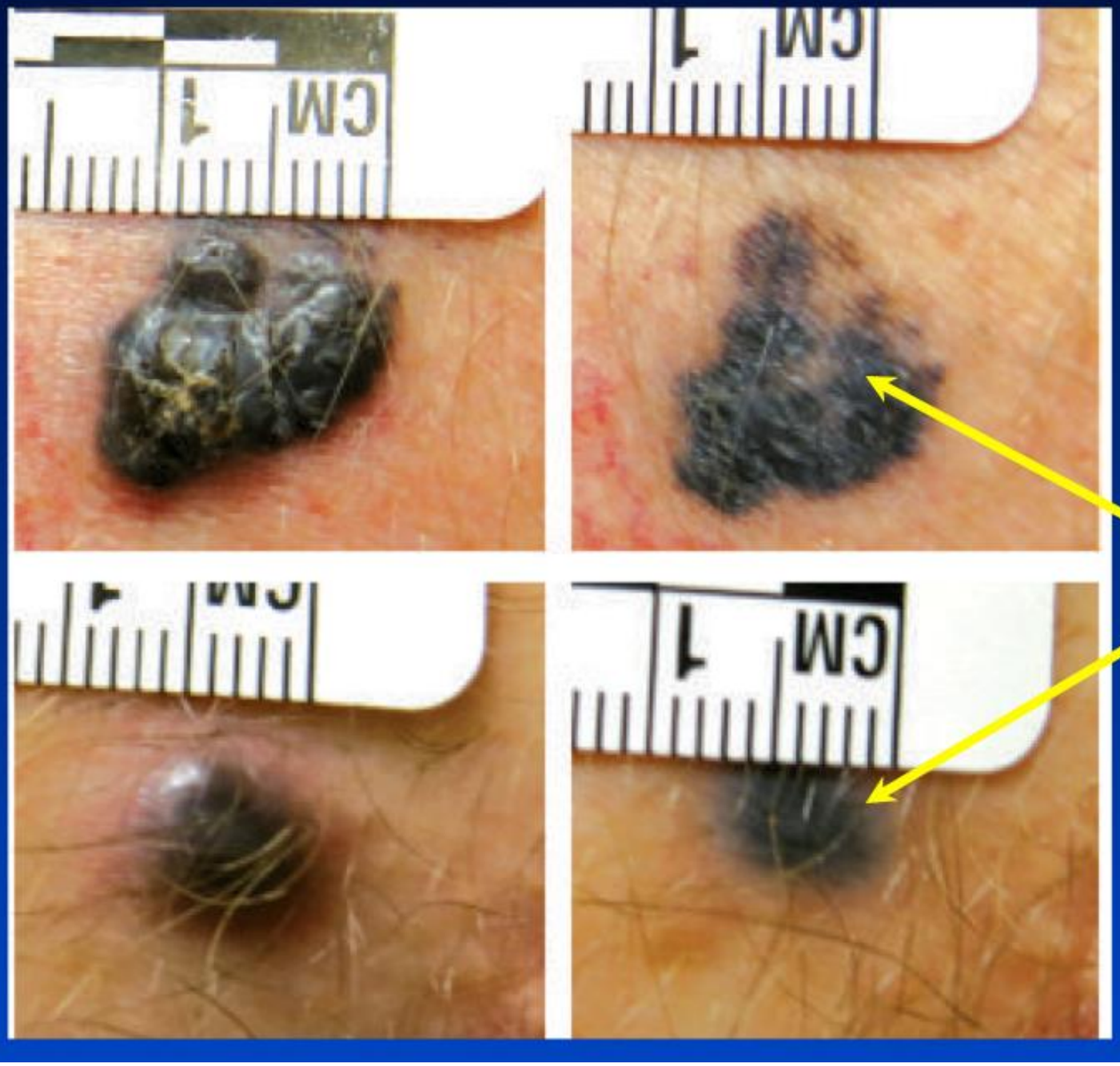
Local Response Anecdote

Baseline

Day 127



Male with cutaneous melanoma on the chest. Injection in chest lesions .

Histopathological analysis confirmed complete melanoma regression

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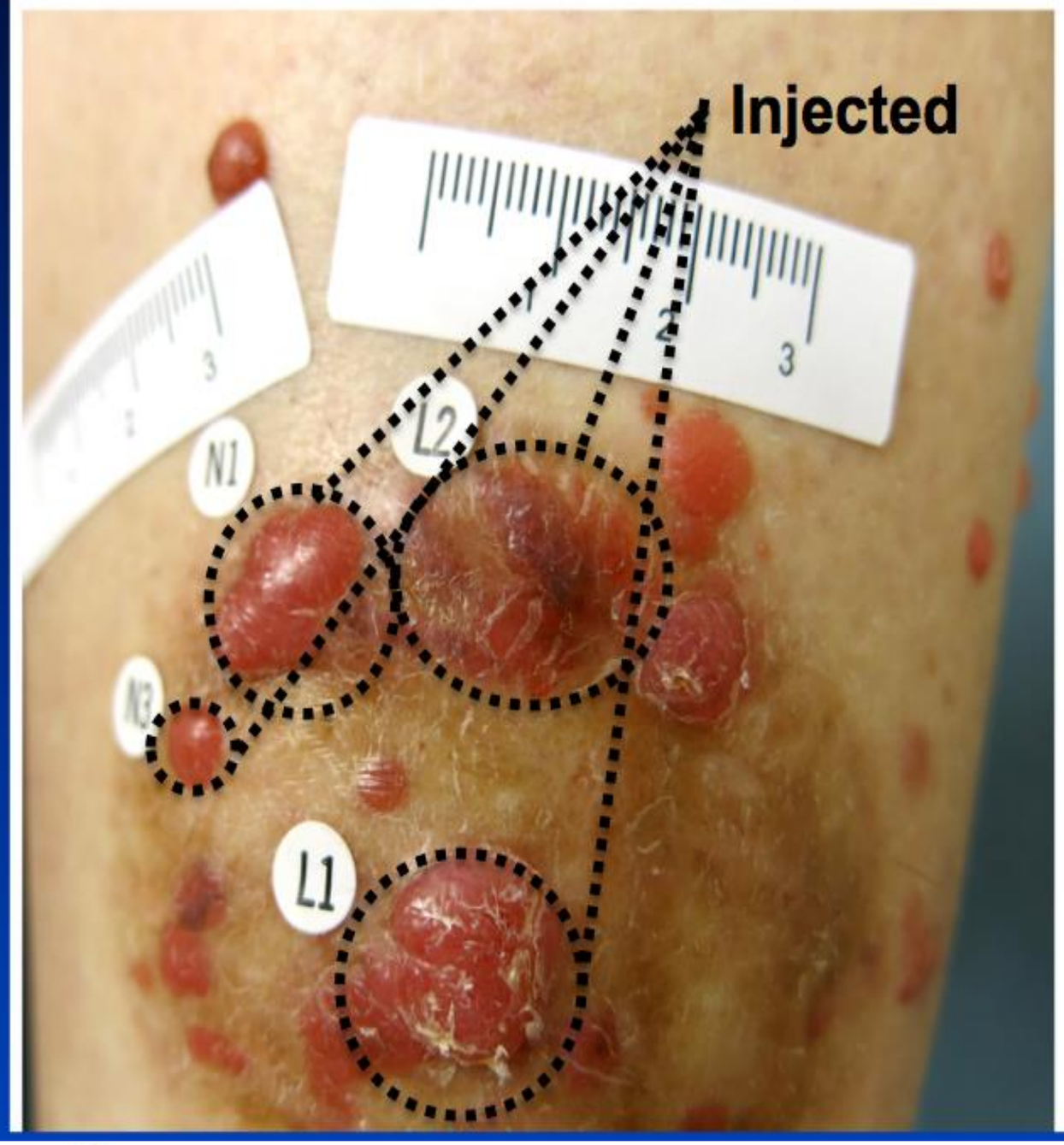
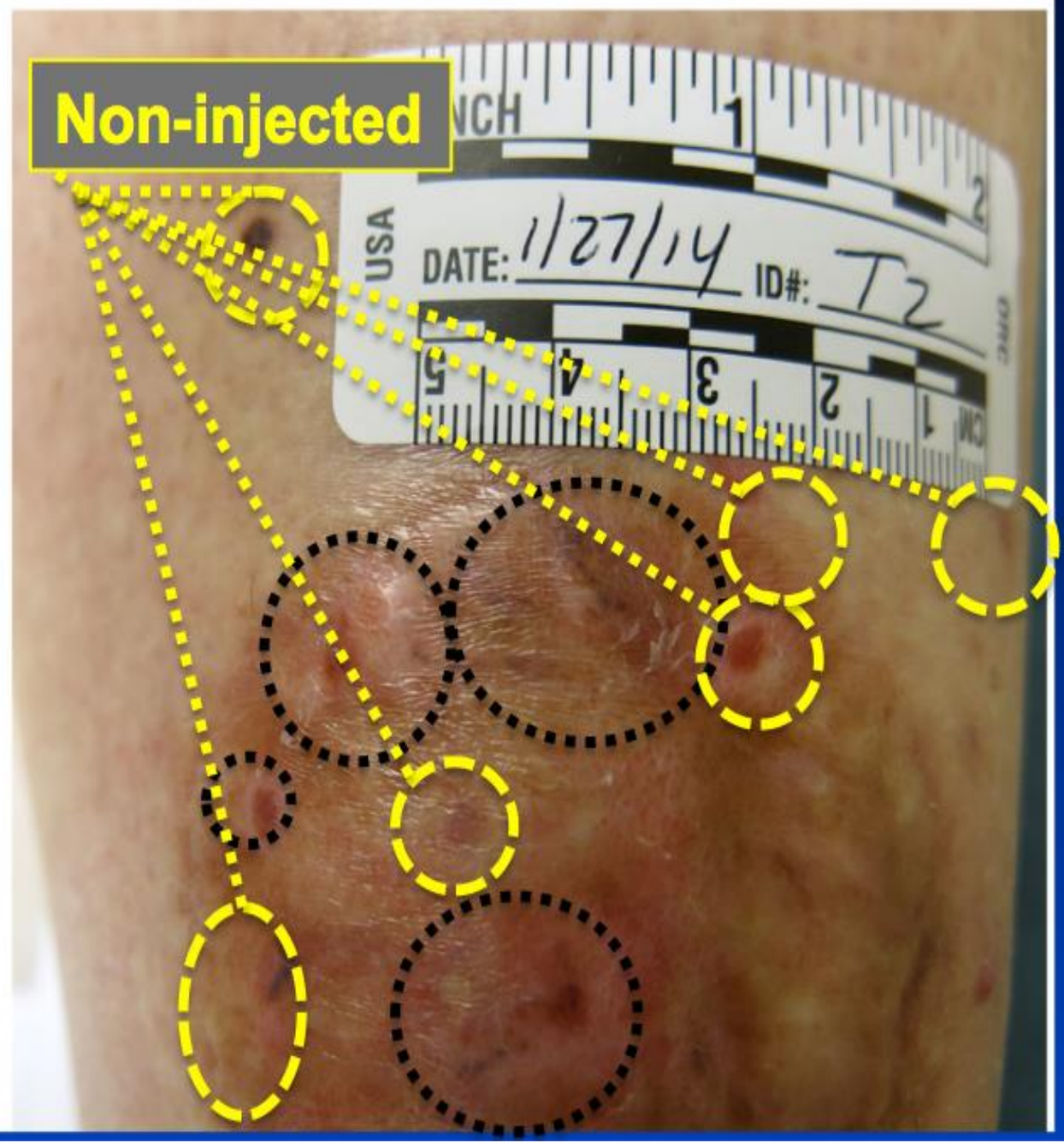
Local Abscopal Effect Anecdote

Baseline



Day 85



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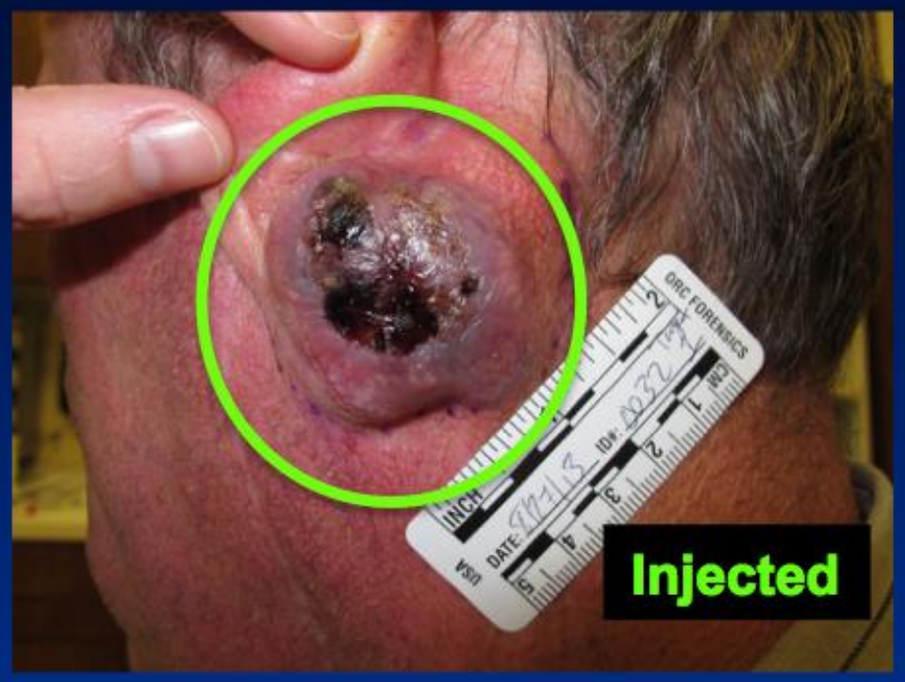
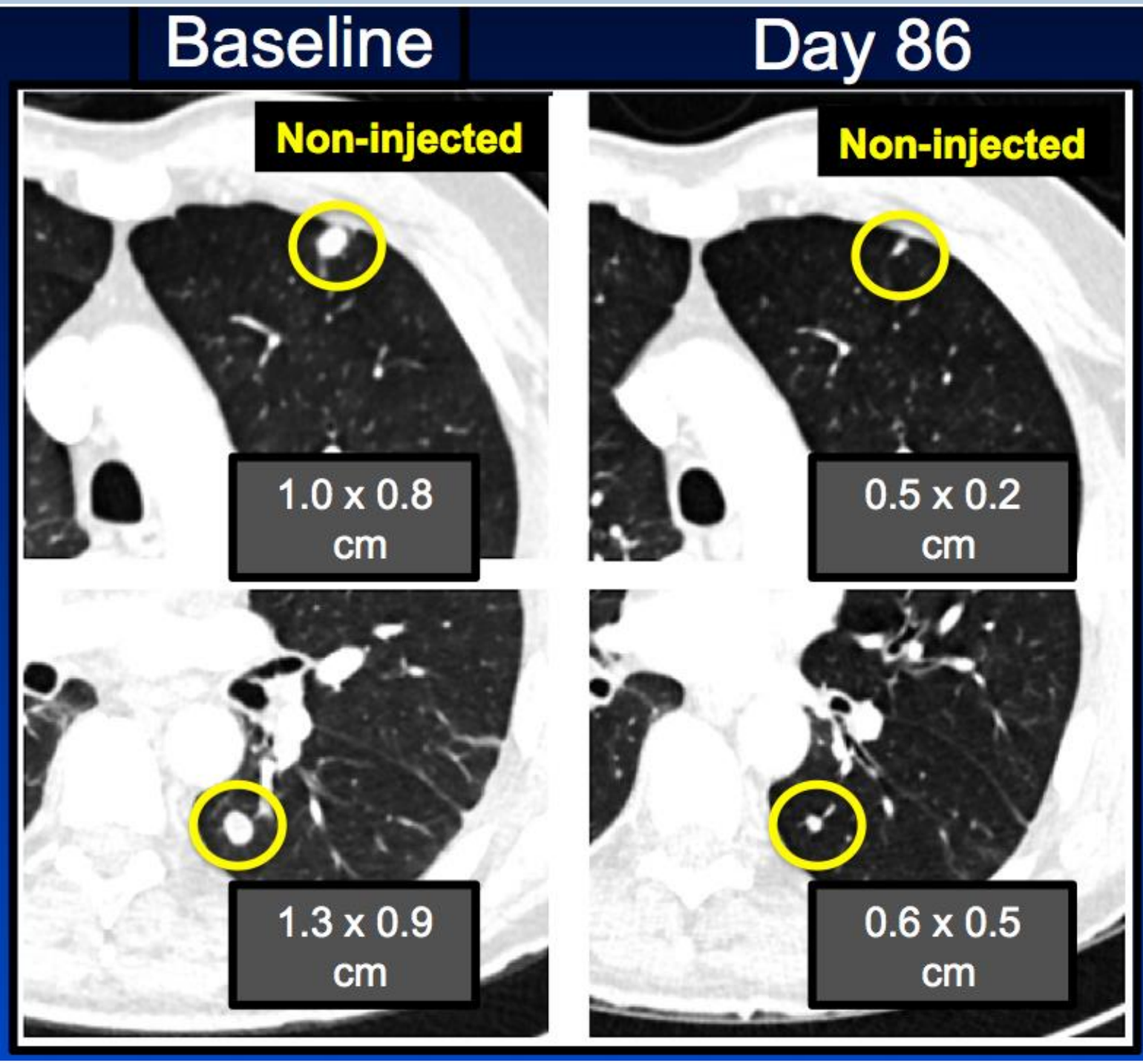
Visceral Abscopal Response Anecdote



Male with metastatic melanoma to left neck and lungs. Injection in left neck.



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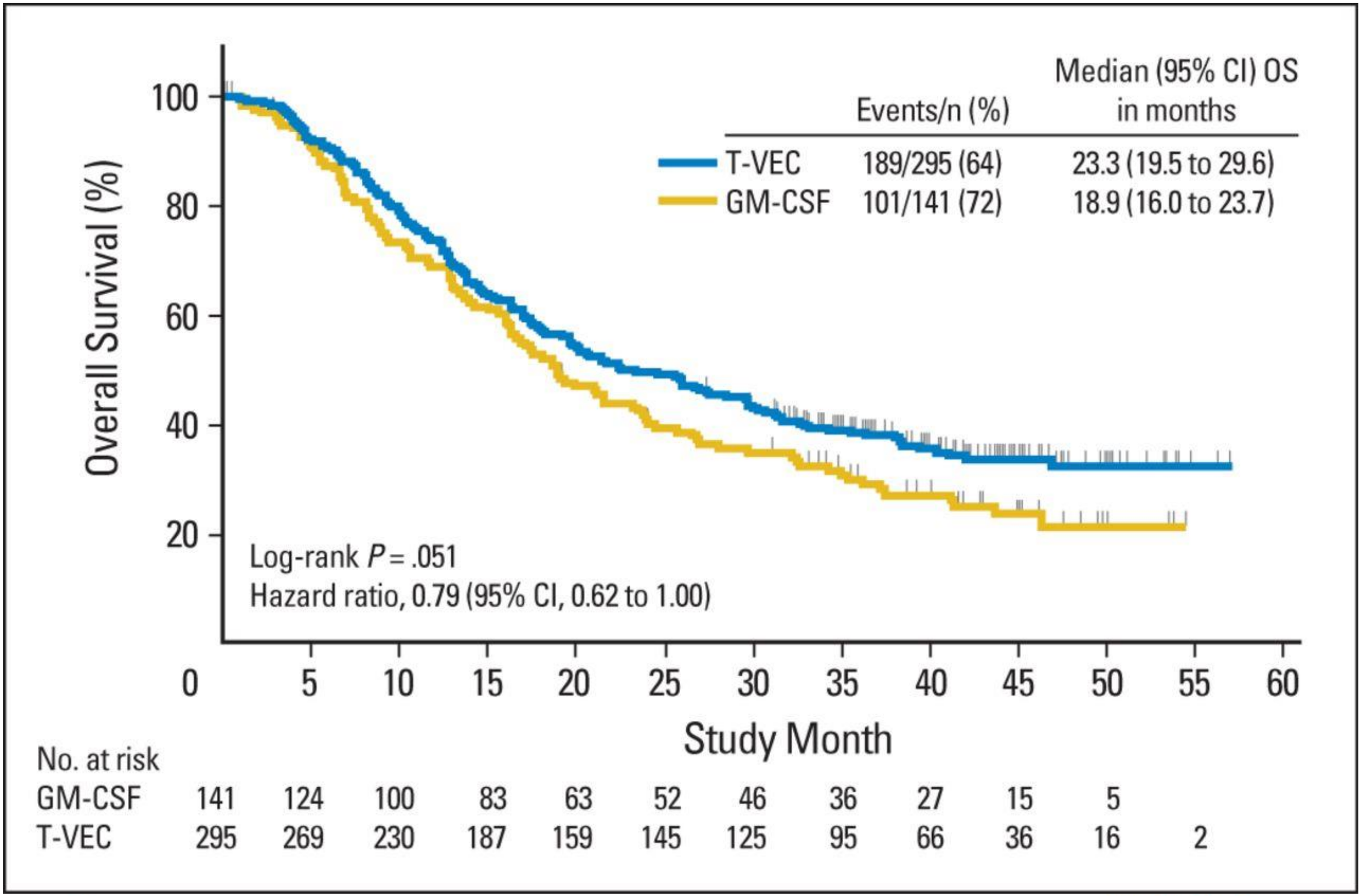
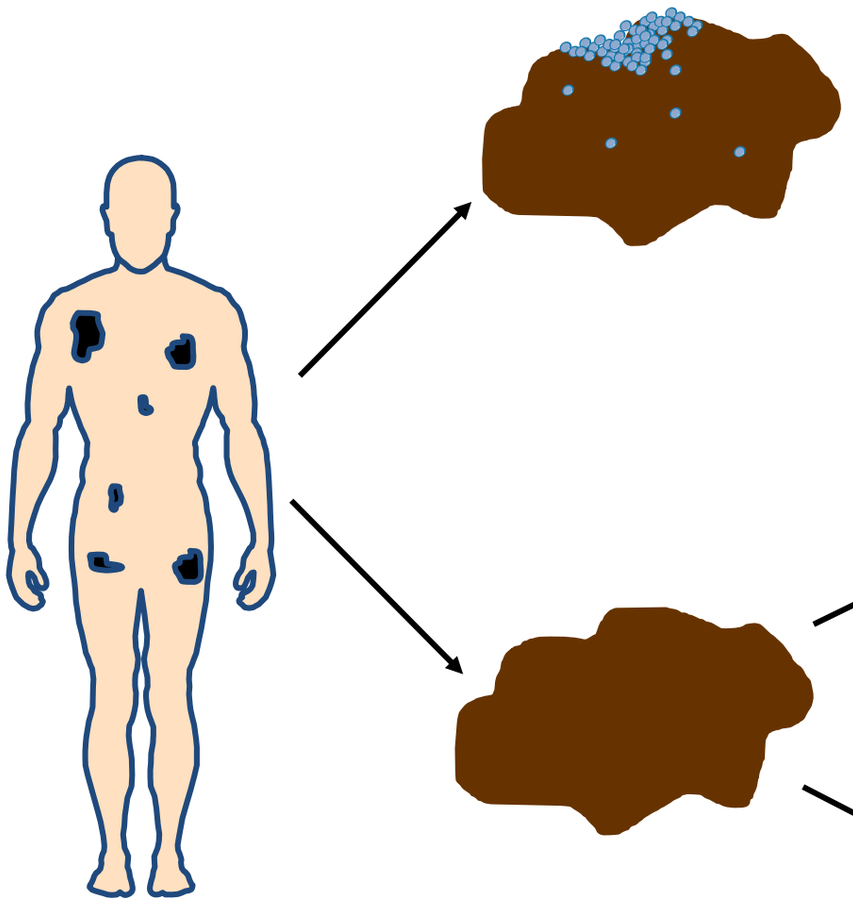
Primary Analysis of Overall Survival (OS) in Intent-to-Treat Population



Robert H.I. Andtbacka et al. JCO 2015;33:2780-2788

JOURNAL of CLINICAL ONCOLOGY ASCO

Management of Cancer in the Post Anti–PD-1/L1



Anti–PD-1/anti–PD-L1

Bring T cells into tumors:

- + Anti–CTLA-4
- + Immune-activating antibodies or cytokines
- + TLR agonists or oncolytic viruses
- + IDO or macrophage inhibitors
- + Targeted therapies

Generate T cells:

- Vaccines
- TIL
- TCR-engineered ACT
- CAR-engineered ACT

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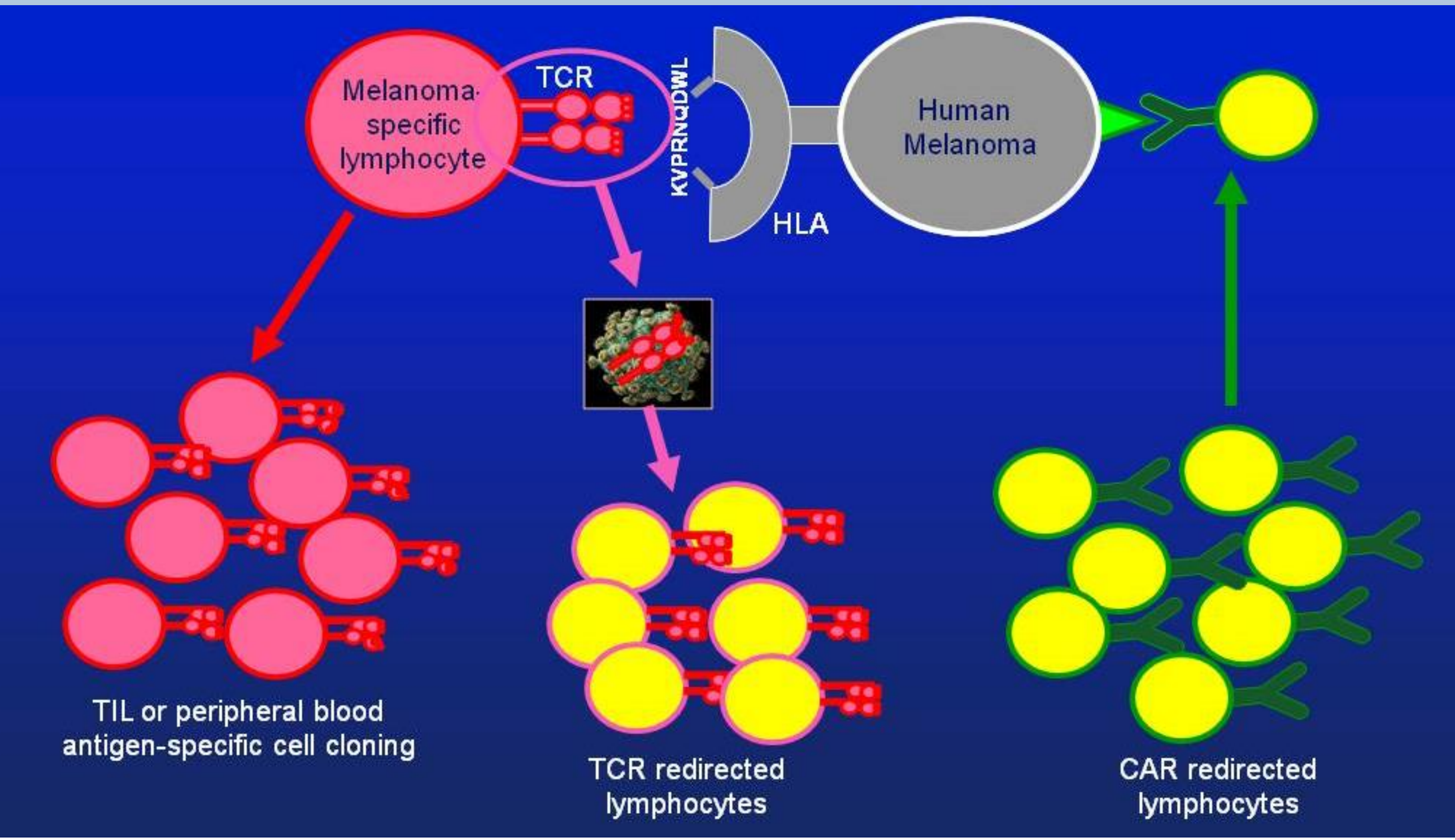
Adoptive Cell Transfer (ACT) Therapies



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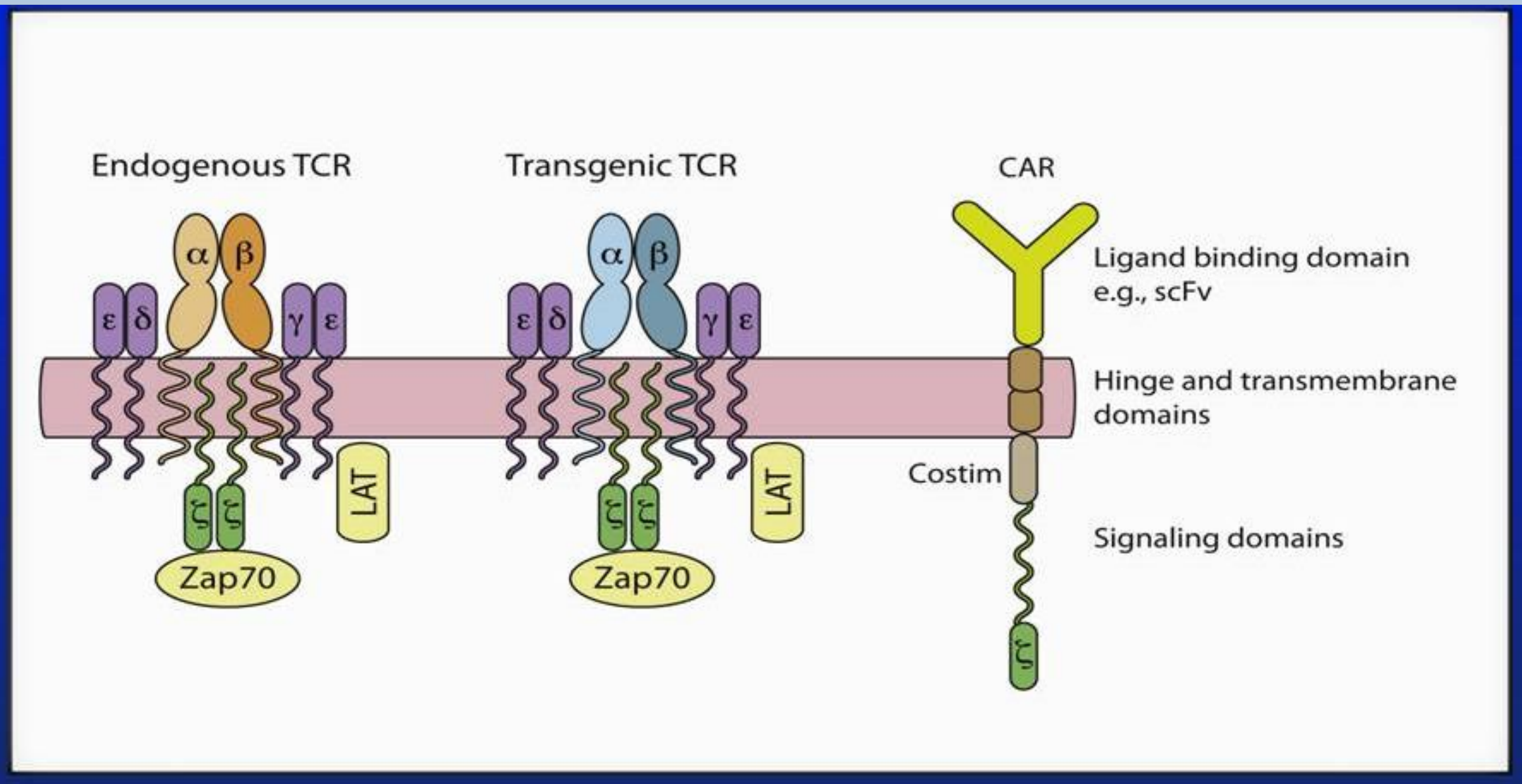
Presented By Jeffrey Weber at 2015 ASCO Annual Meeting

T cells, Transgenic T cells, and CARs



Cell PRESS

Immunity 2013 39, 49-60DOI: (10.1016/j.immuni.2013.07.002)

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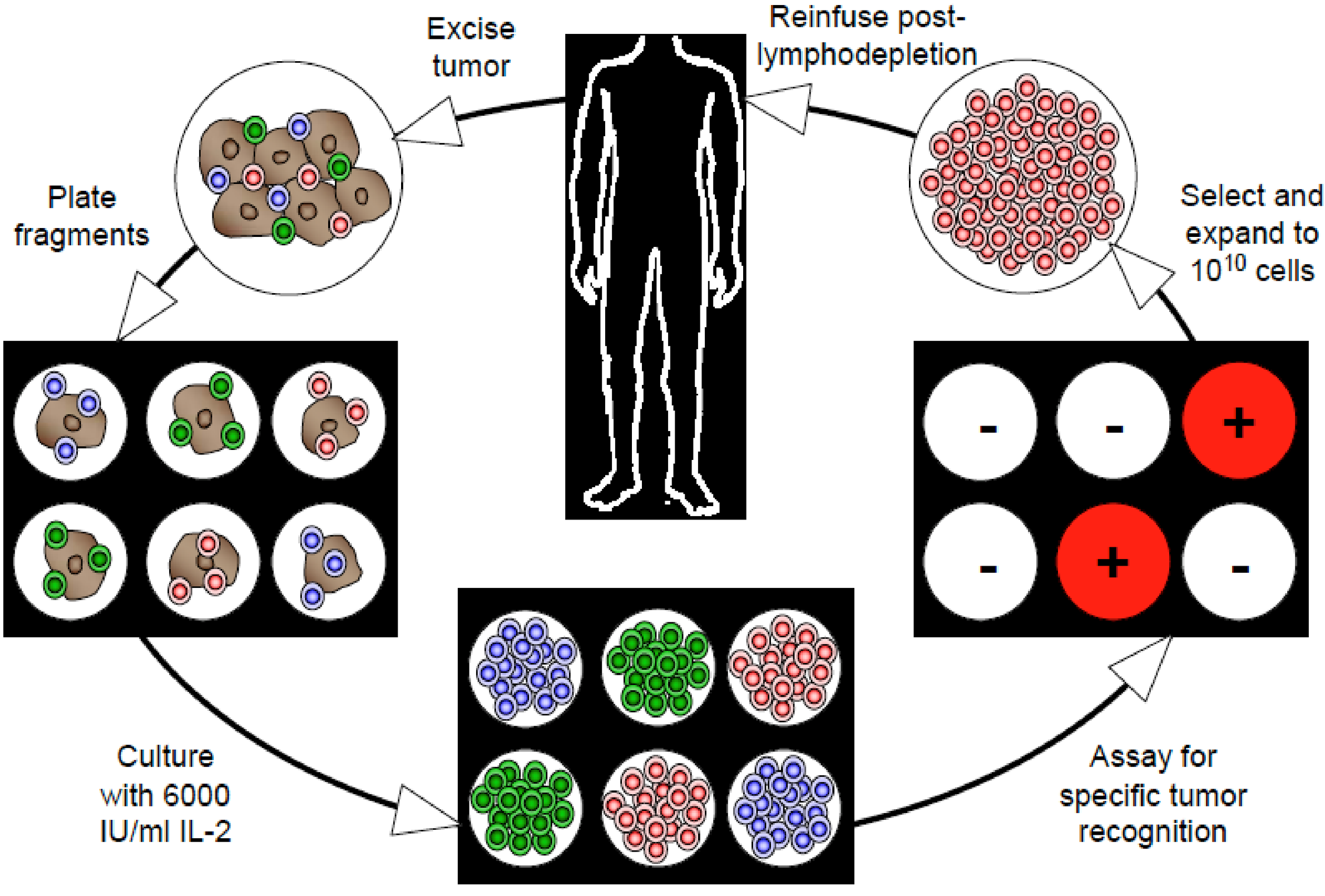
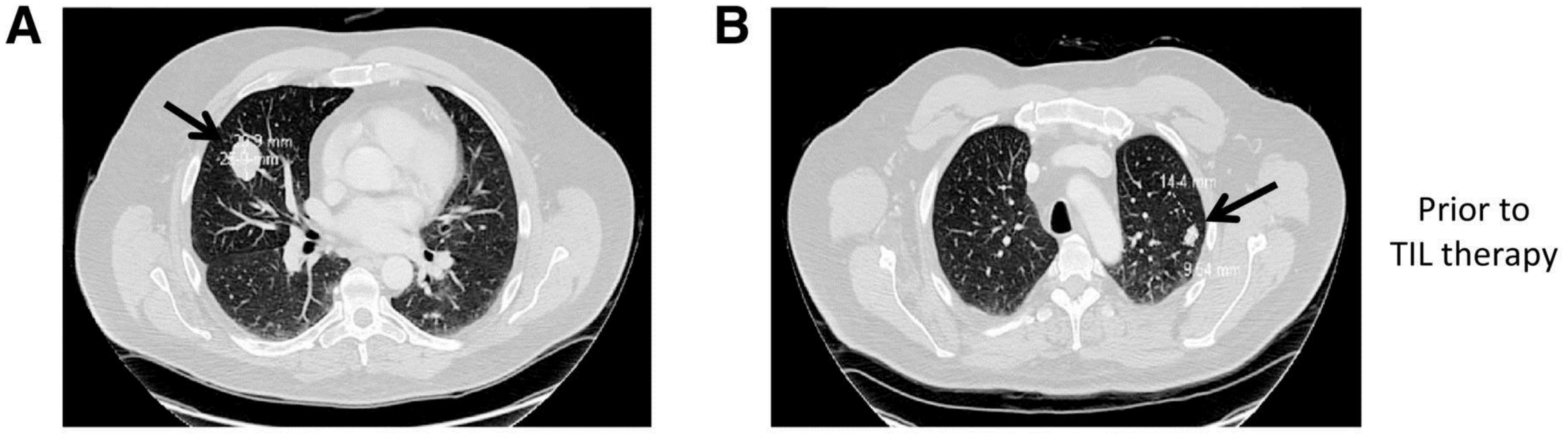
Presented By Jeffrey Weber at 2015 ASCO Annual Meeting

Adoptive Transfer of Tumor Infiltrating Lymphocytes (TIL)



Clinical Response of Patient 3713 After Treatment with Adoptive Cell Therapy

AACR American Association for Cancer Research
Cancer Immunology Research



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Todd D. Prickett et al. Cancer Immunol Res 2016;4:669-678

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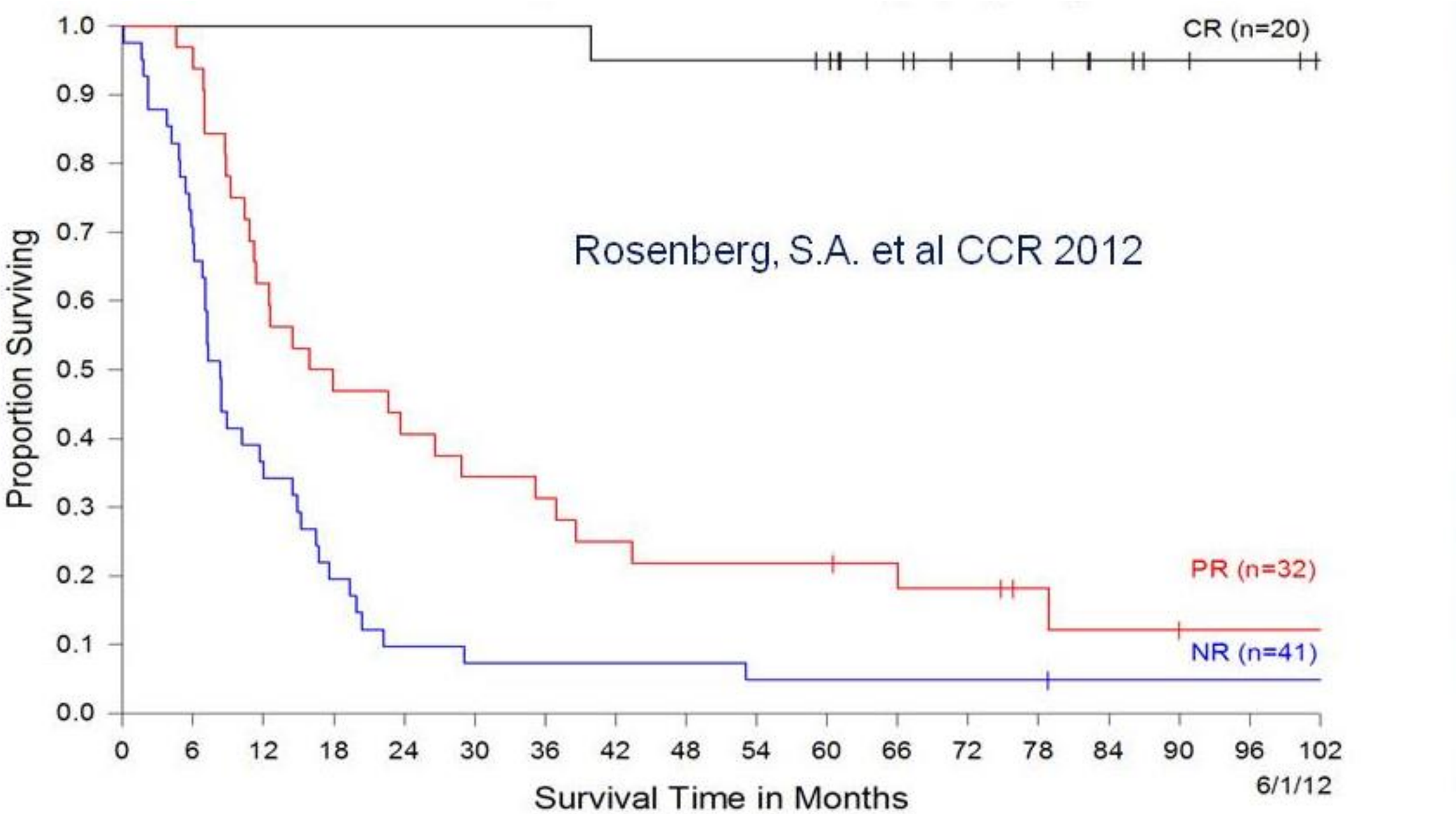
Survival of Patients with Metastatic Melanoma Treated with Autologous Tumor Infiltrating Lymphocytes and IL-2



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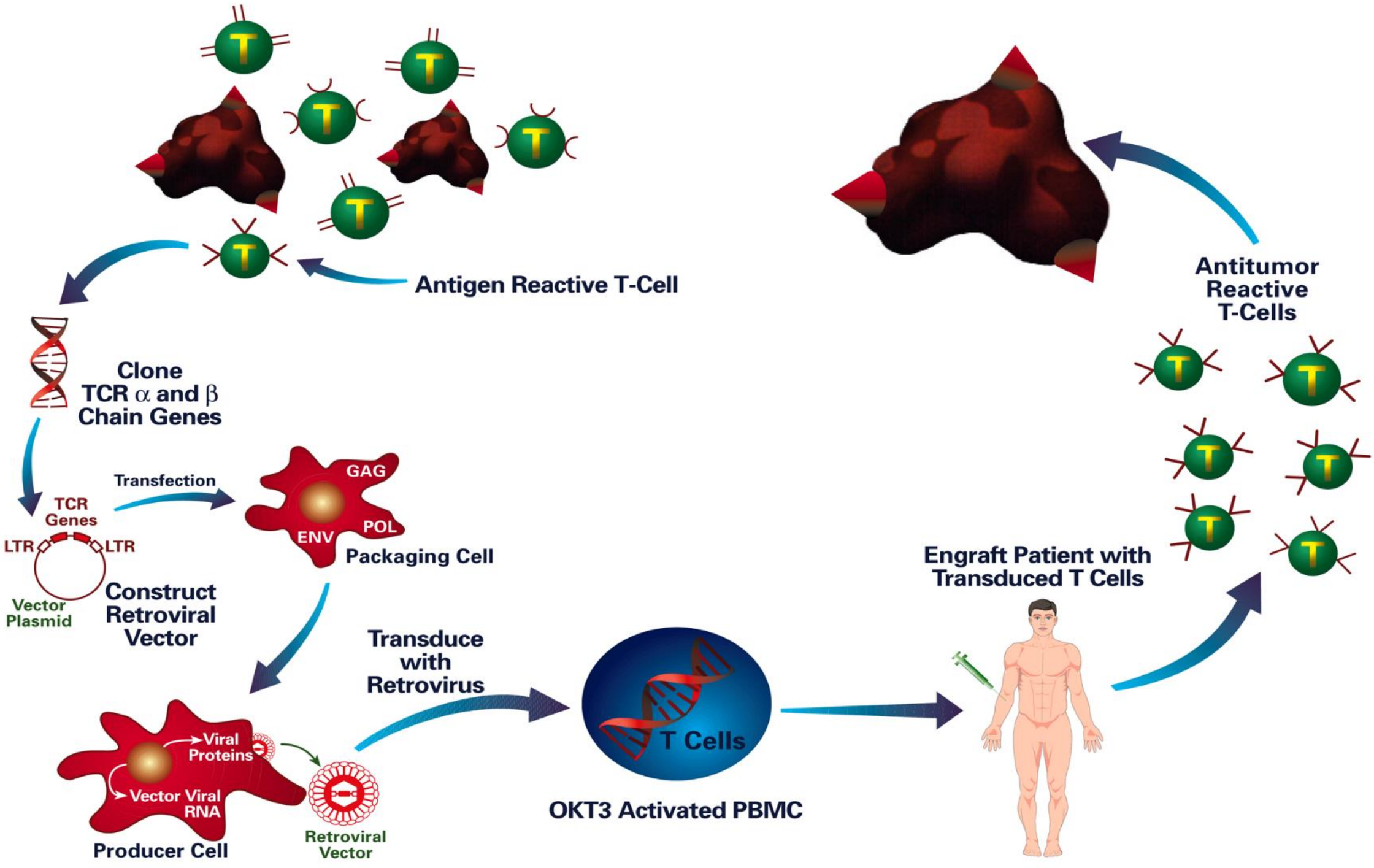
Presented By Jeffrey Weber at 2015 ASCO Annual Meeting

T Cell Receptor Gene Transfer for the Immunotherapy of Cancer



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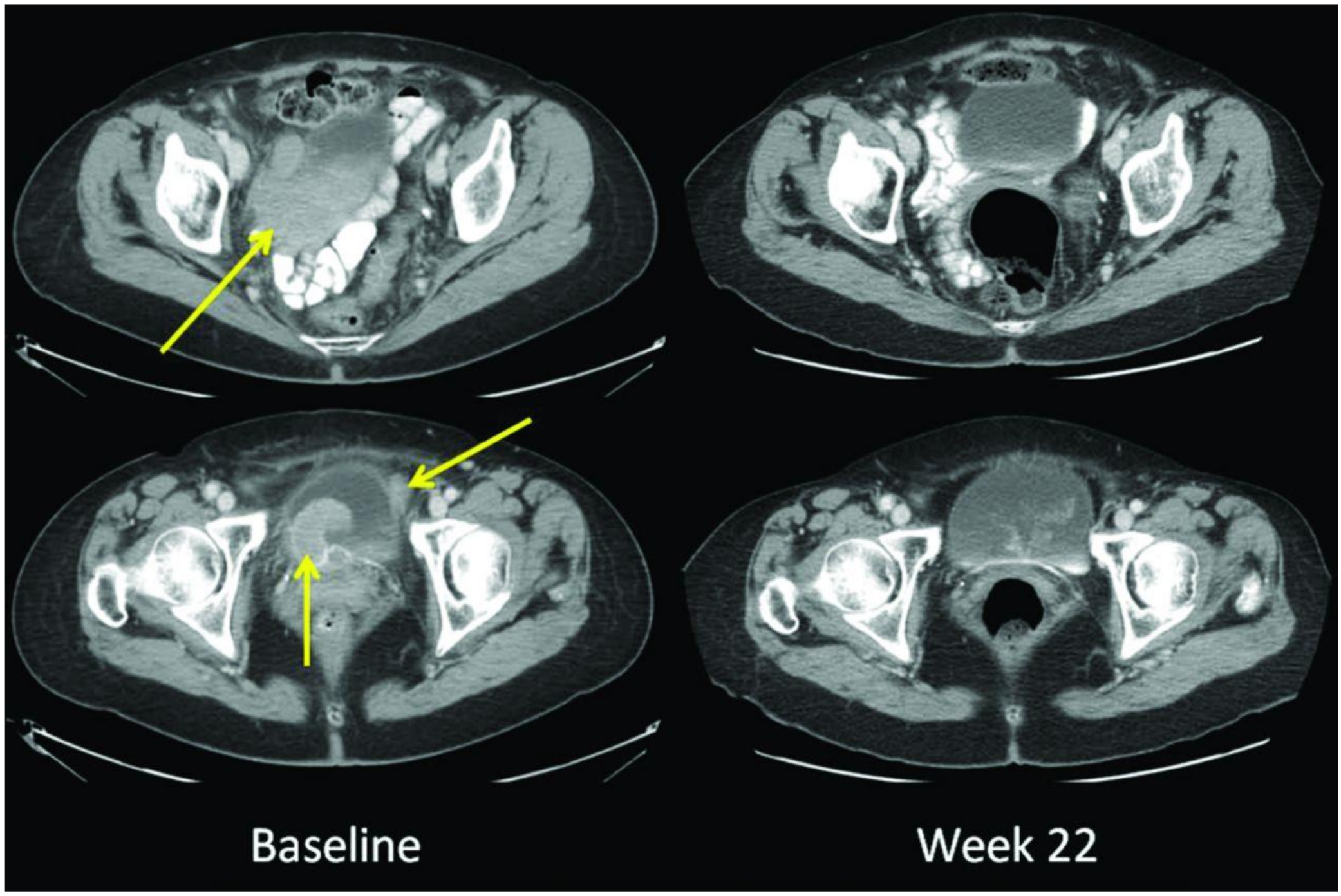
Mucosal Melanoma of the Bladder – Response to Ipilimumab



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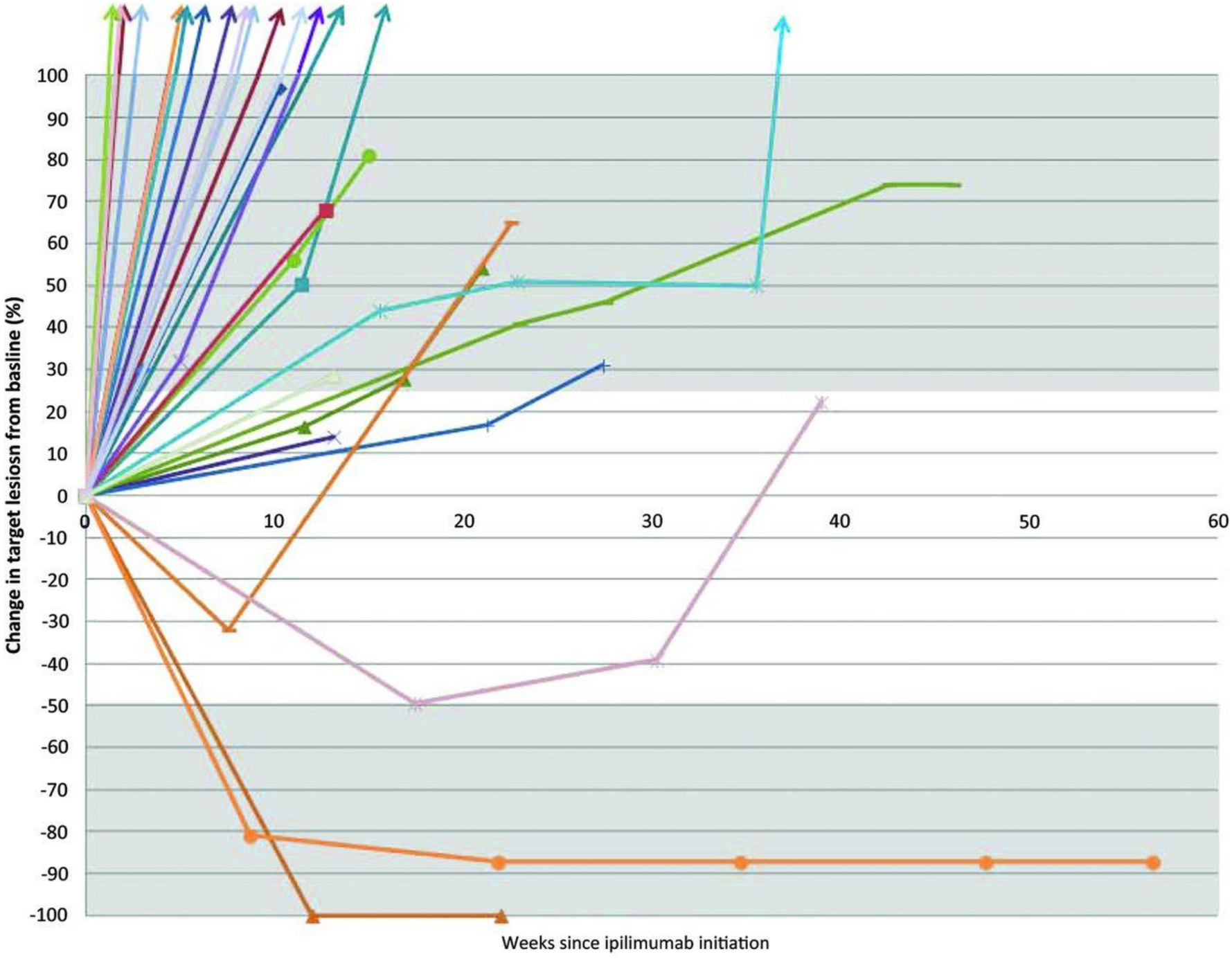
PROVIDENCE Cancer Center

Postow M A et al. The Oncologist 2013;18:726-732

Mucosal Melanoma: Changes in Tumor Burden for 30 Patients



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Postow M A et al. The Oncologist 2013;18:726-732

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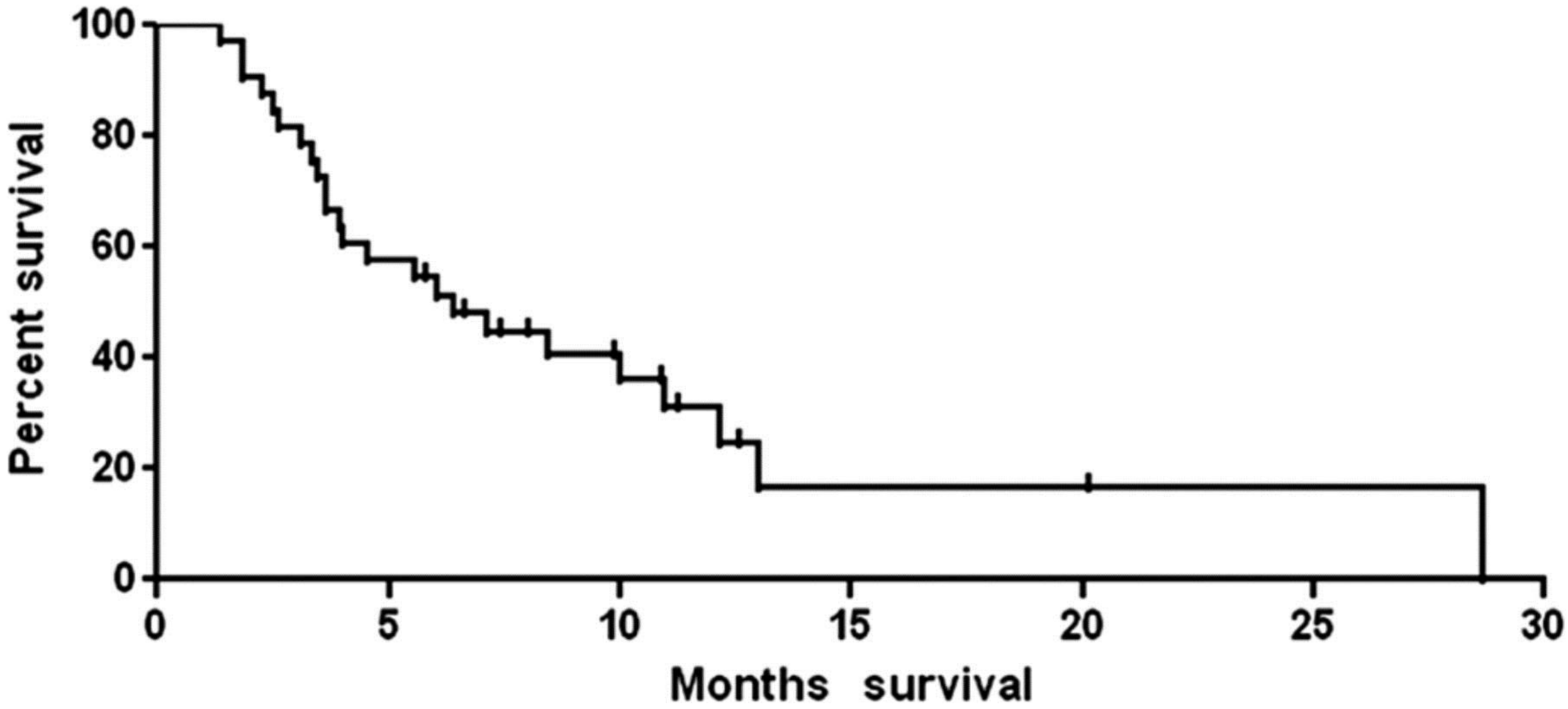
Overall Survival of Mucosal Melanoma Cohort (n = 33)



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Postow M A et al. The Oncologist 2013;18:726-732

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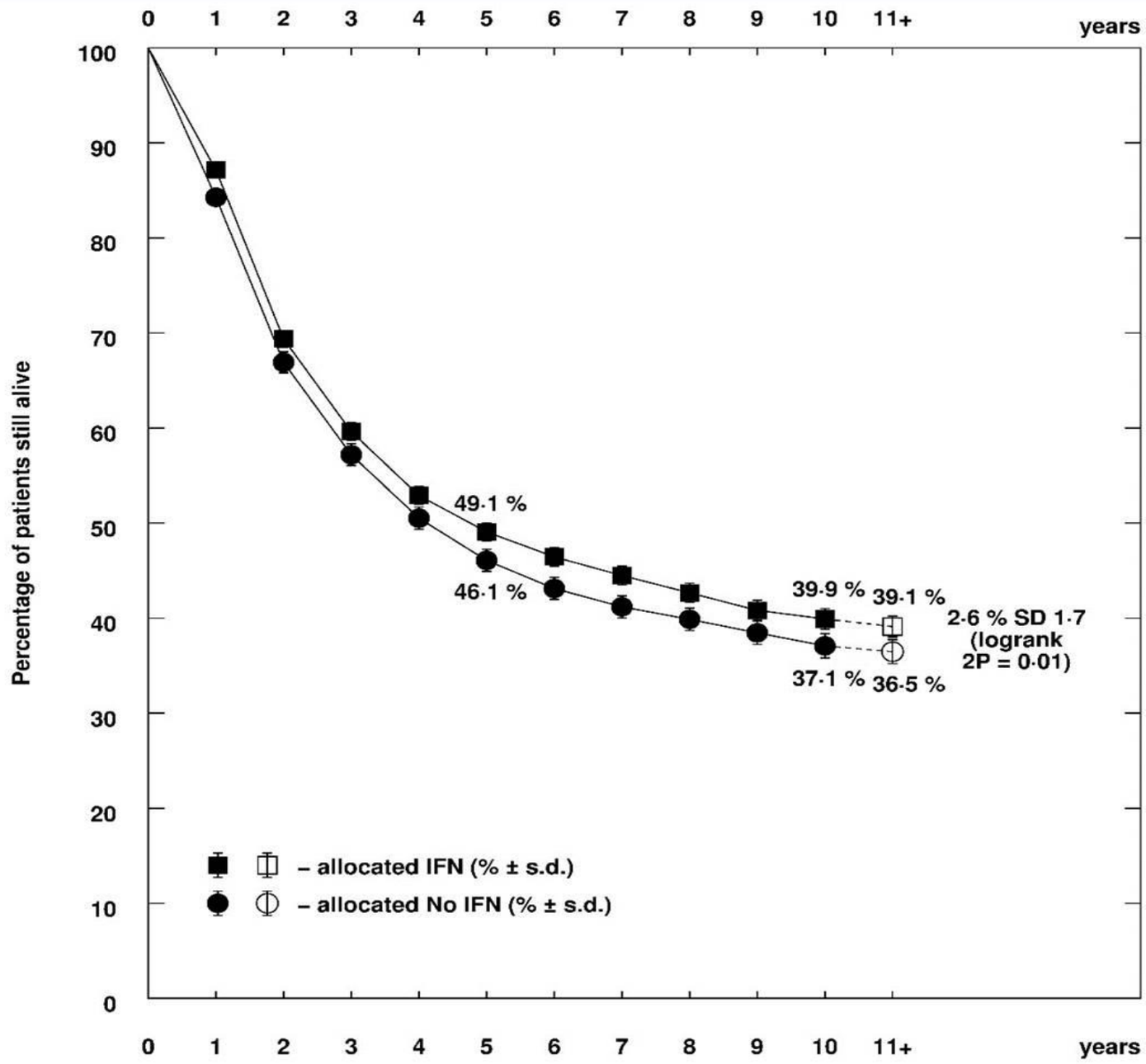
Adjuvant Interferon Alpha

Survival Curve for Overall Survival



Deaths/person–years:											
Treatment											
IFN	453/3260	602/2639	324/2135	203/1733	106/1376	58/1038	34/790	23/581	17/409	7/299	16/812
No IFN	393/2222	403/1743	223/1410	150/1165	89/963	52/770	29/631	15/442	11/288	8/209	11/667

Only includes data from trials providing IPD

Presented By Paul Lorigan at 2016 ASCO Annual Meeting

Recent Adjuvant Trials Results

Trial	No. pts	Experimental arm vs. obs	HR for disease recurrence	HR for OS
AVAST-M	1,343	Bevacizumab vs. observation	0.83 (p=0.03)	0.97 (p=0.76)
DERMA	1,388	MAGE A3 ASCI vs. placebo	*All patients* 1.013 (p=0.86) *Gene signature +ve* 1.11 (p=0.4821)	*All patients* 1.065 (p=0.52)
ECOG 4697	815	GMCSF vs placebo (HLA-A2 positive peptide vs. placebo)	p = 0.131, HR 0.88, 95% CI 0.74-1.04	p = 0.528 (HR 0.95, 95% CI 0.77-1.15)
EORTC 18071	951	Ipilimumab 10mg/kg vs. placebo	0.75 (p=0.0013)	Awaited

MANCHESTER 1824

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The Christie NHS Foundation Trust

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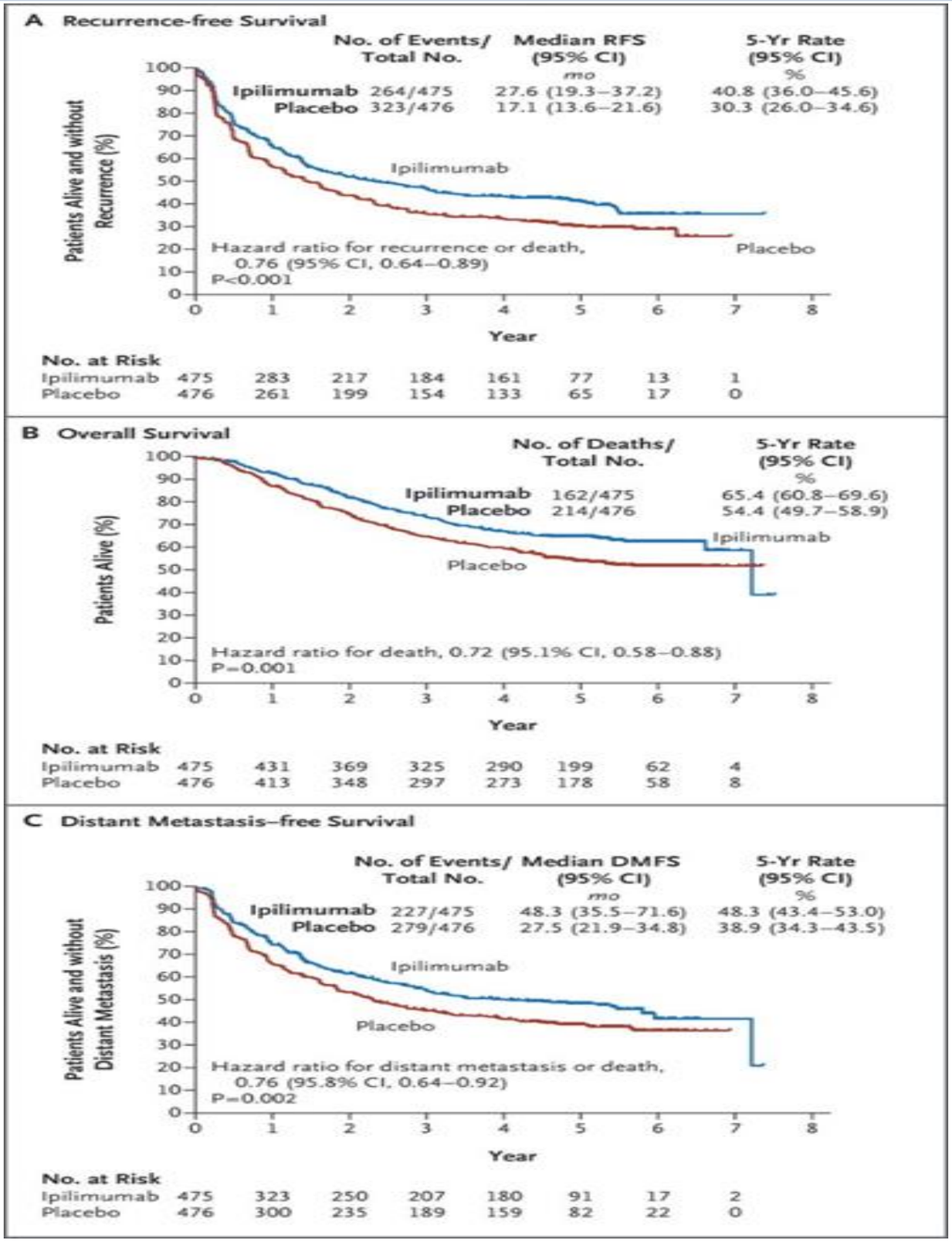
Presented By Paul Lorigan at 2016 ASCO Annual Meeting

Kaplan-Meier Estimates of Recurrence-free Survival (RFS), Overall Survival and Distant Metastasis-free Survival (DMFS).



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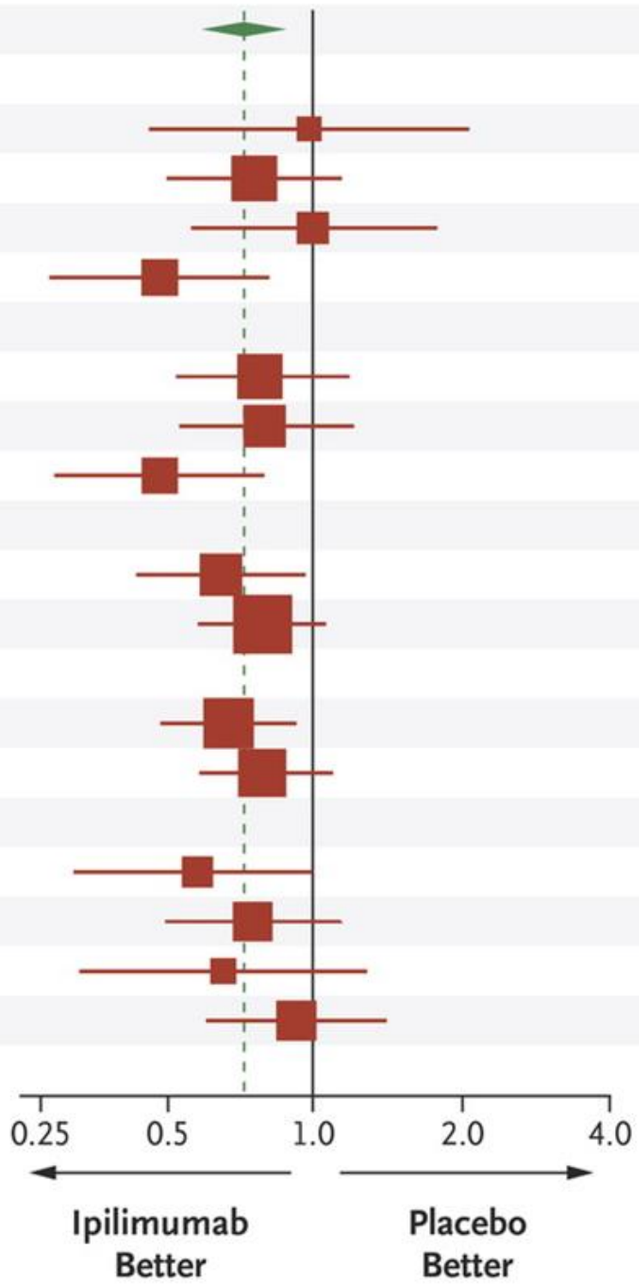
Eggermont AM et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1611299

Forest Plot for Overall Survival

Subgroup	Ipilimumab	Placebo	Hazard Ratio (95% or 99% CI)	P Value
	no. of deaths/total no.			
All patients	162/475	214/476	0.72 (0.59–0.88)	0.001
Disease stage				0.07
IIIA	24/98	22/88	0.98 (0.46–2.09)	
IIIB	68/213	85/207	0.75 (0.50–1.14)	
IIIC with 1–3 positive lymph nodes	34/69	45/83	1.00 (0.56–1.80)	
IIIC with ≥4 positive lymph nodes	36/95	62/98	0.48 (0.28–0.81)	
No. of positive lymph nodes				0.09
1	65/217	82/220	0.79 (0.52–1.21)	
2 or 3	61/163	70/158	0.83 (0.53–1.30)	
≥4	36/95	62/98	0.48 (0.28–0.81)	
Type of positive lymph node				0.21
Microscopic	54/210	76/193	0.61 (0.39–0.96)	
Macroscopic	108/265	138/283	0.80 (0.58–1.11)	
Ulceration				0.29
Yes	73/197	110/203	0.64 (0.44–0.94)	
No	79/257	88/244	0.80 (0.54–1.20)	
Lymph-node and ulceration status				0.35
Microscopic and ulceration	28/99	43/88	0.54 (0.29–0.99)	
Macroscopic and ulceration	45/98	67/115	0.76 (0.46–1.23)	
Microscopic and no ulceration	21/104	29/97	0.62 (0.30–1.29)	
Macroscopic and no ulceration	58/153	59/147	0.90 (0.56–1.45)	



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PROVIDENCE Cancer Center

Eggermont AM et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1611299

Current Intergroup Adjuvant Study for Melanoma

- (SWOG 1404) A Phase III Randomized Trial Comparing Physican/Patient Choice of Either High Dose Interferon or Ipilimumab 10mg/kg to Pembrolizumab 200mg q3w in Patients with High Risk Resected Melanoma

Description:

- To compare overall survival (OS) of patients with resected Stage III and IV melanoma treated with physician/patient choice of either high dose interferon alfa-2b or ipilimumab versus MK-3475 (pembrolizumab).

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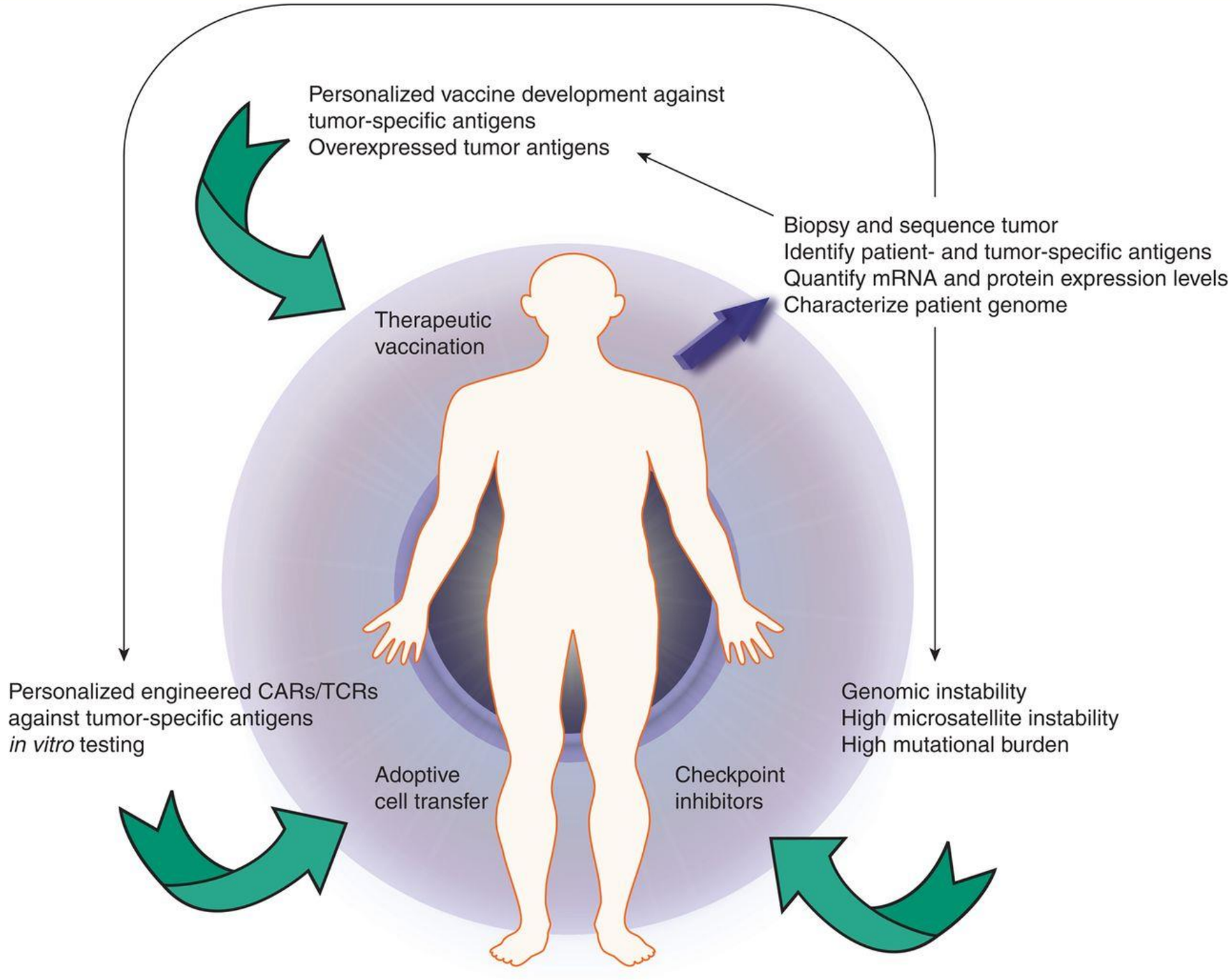
Strategies for Personalized Precision Immunotherapy



Rajarsi Mandal, and Timothy A. Chan Cancer Discov 2016;6:703-713

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