ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Melanoma

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MUSC Hollings Cancer Center

Association of Community Cancer Centers

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Disclosures

- No Disclosures

-I will be discussing non-FDA approved indications during my presentation.

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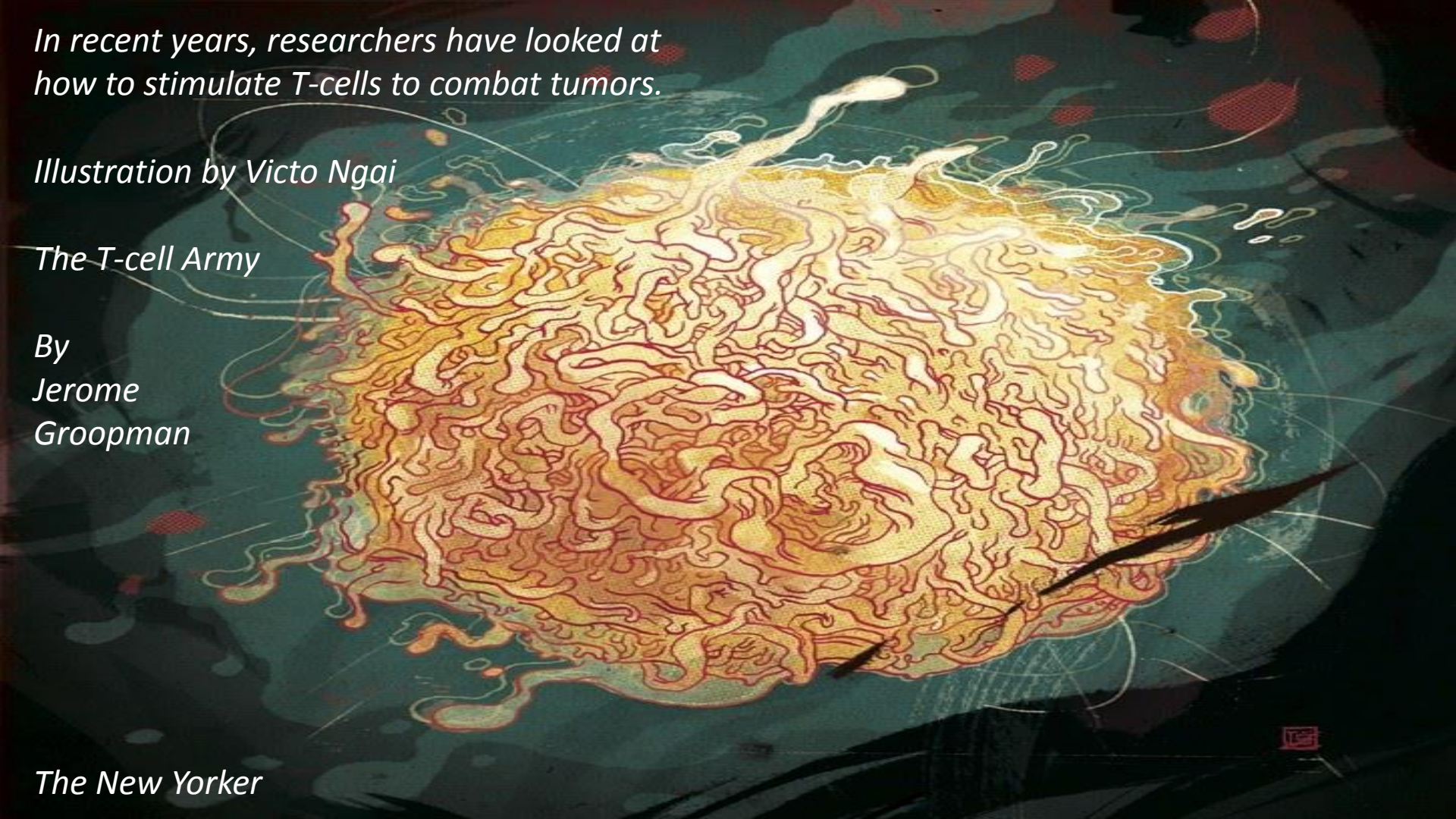
In recent years, researchers have looked at how to stimulate T-cells to combat tumors.

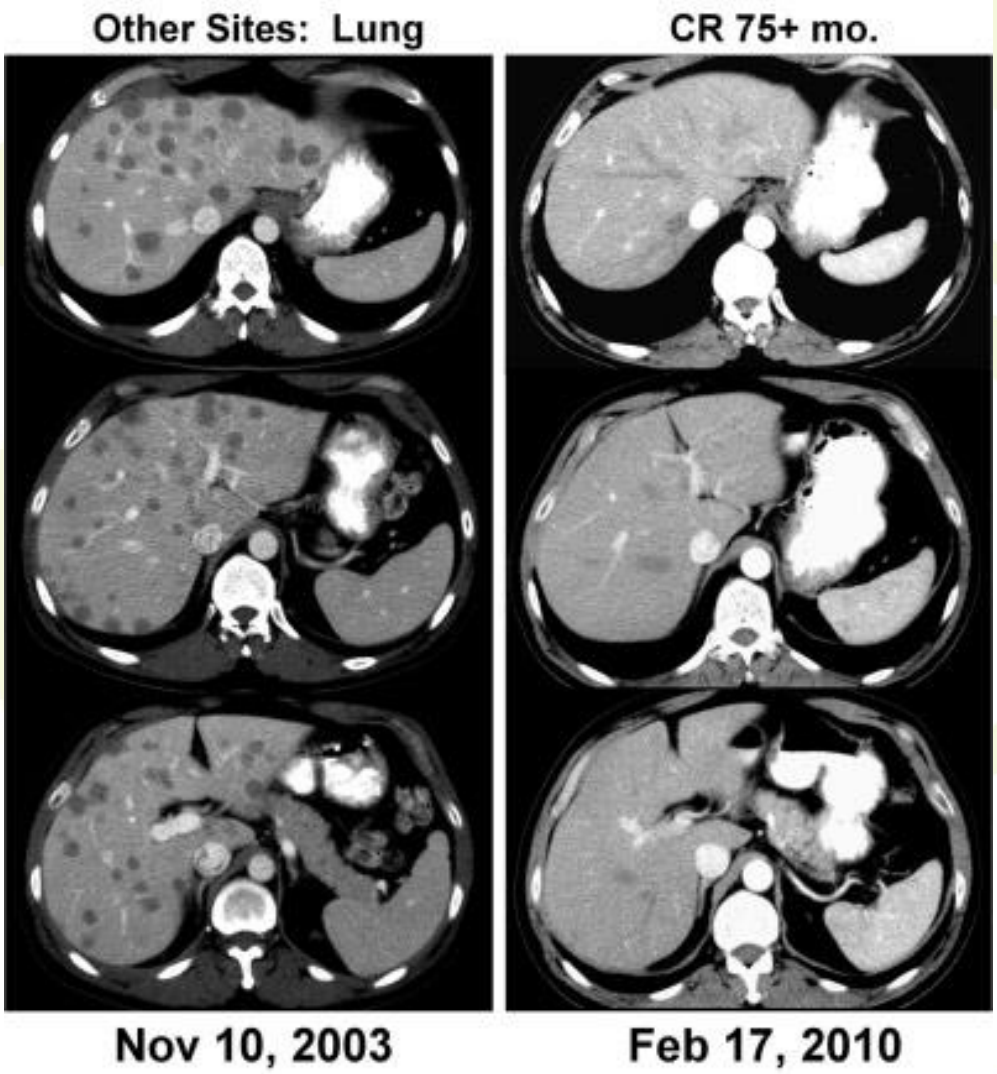
Illustration by Victo Ngai

The T-cell Army

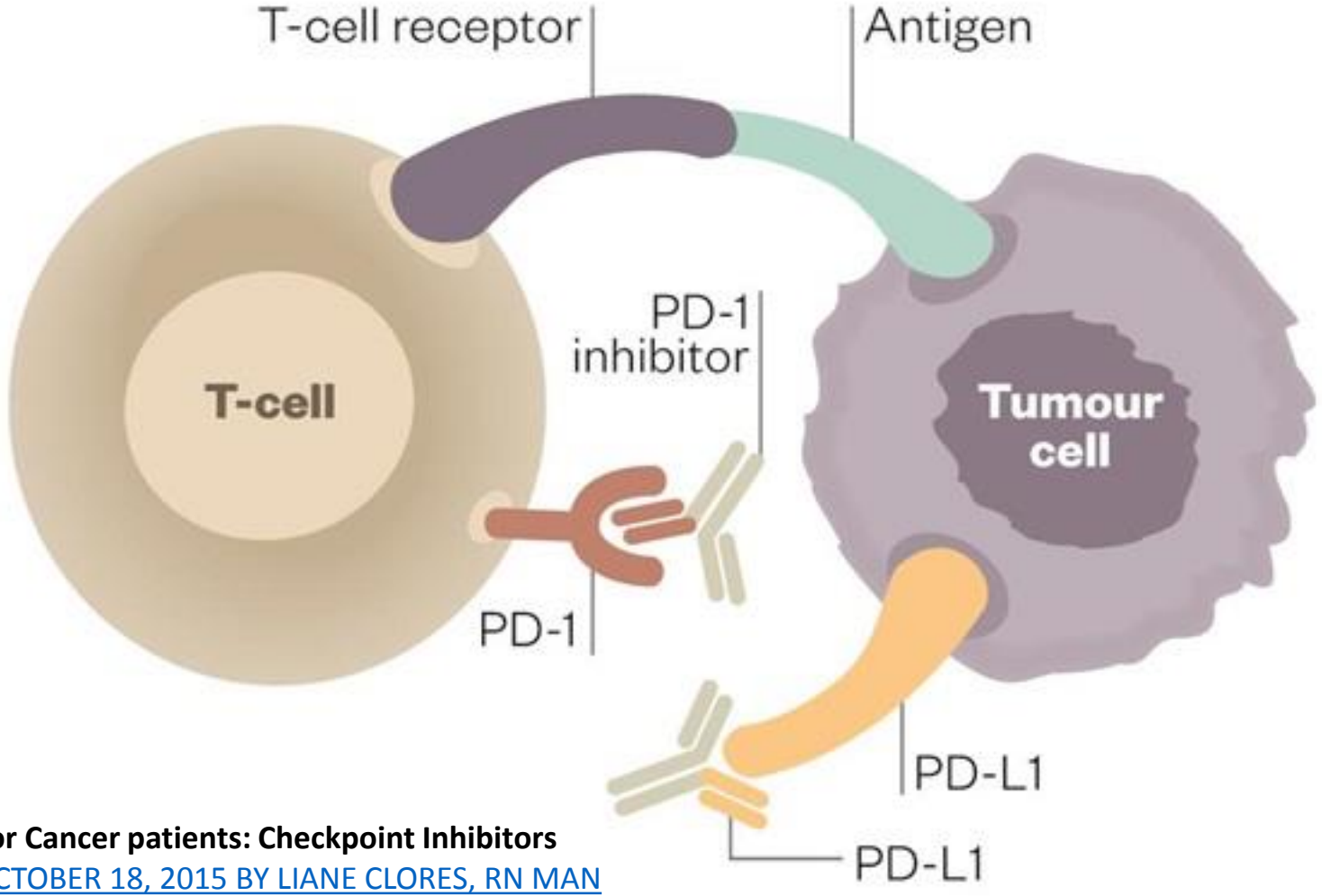
By
Jerome
Groopman



The New Yorker



https://home.ccr.cancer.gov/connections/2014/vol8_no1/intheclinic.asp



Giving hope for Cancer patients: Checkpoint Inhibitors
POSTED ON OCTOBER 18, 2015 BY LIANE CLORES, RN MAN

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Types of Immunotherapies for Melanoma

- Cytokines
  - Interferon-α 2b- Adjuvant therapy
  - Interleukin-2- Stage IV
- Oncolytic Virus
  - Modified Herpes Virus (Talimogene Laharparepvec; TVEC)
- Checkpoint antibodies
  - Anti-CTLA4 (ipilimumab)
  - Anti-PD1 (pembrolizumab, nivolumab)
    - (Avelumab for Merkel cell carcinoma – March 2017)
- *Adoptive T cell Transfer Therapy and Neoantigen Vaccines*

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Adjuvant Therapy

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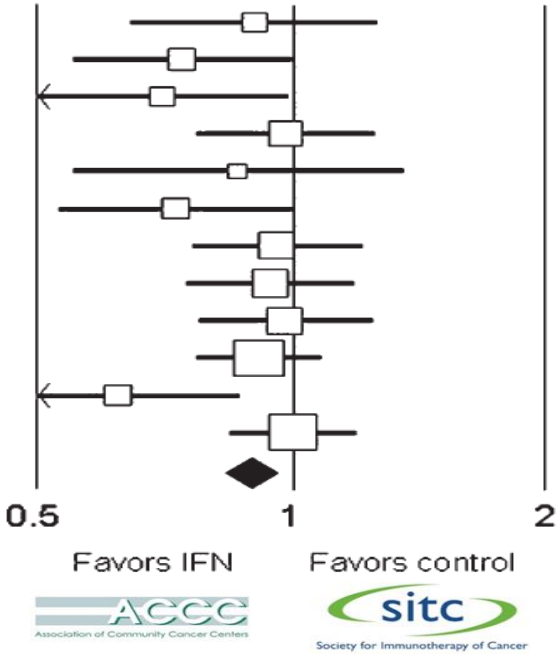
Adjuvant Treatment of High-Risk Melanoma

	HR	LL	UL	SE	Patients	Events (IFN/control)
NCCTG (Creagan, 1995)	0.90	0.64	1.25	0.17	264	68/72
E1684 (Kirkwood, 1996)	0.73	0.54	0.99	0.15	287	81/90
FCGM (Grob, 1998)	0.70	0.49	0.98	0.17	499	59/76
E1690 (Kirkwood, 2000)	0.98	0.76	1.24	0.12	642	194/186
SMG (Cameron, 2001)	0.86	0.54	1.35	0.23	96	31/36
E1694 (Kirkwood, 2001)	0.72	0.52	0.99	0.16	880	52/81
WHO (Cascinelli, 2001)	0.95	0.76	1.20	0.12	444	146/138
UKCCCR (Hancock, 2004)	0.94	0.74	1.17	0.12	674	151/156
EORTC18871 (Kleeberg, 2004)	0.98	0.77	1.23	0.12	484	137/202
EORTC18952 (Eggermont, 2005)	0.91	0.76	1.07	0.09	1388	534/292
DeCOG (Garbe, 2008)	0.62	0.44	0.86	0.17	296	65/88
EORTC18991 (Eggermont, 2008)	1.00	0.84	1.18	0.09	1256	256/257
	0.89	0.83	0.96	0.04		



Mocellin et al. JNCI. 2010

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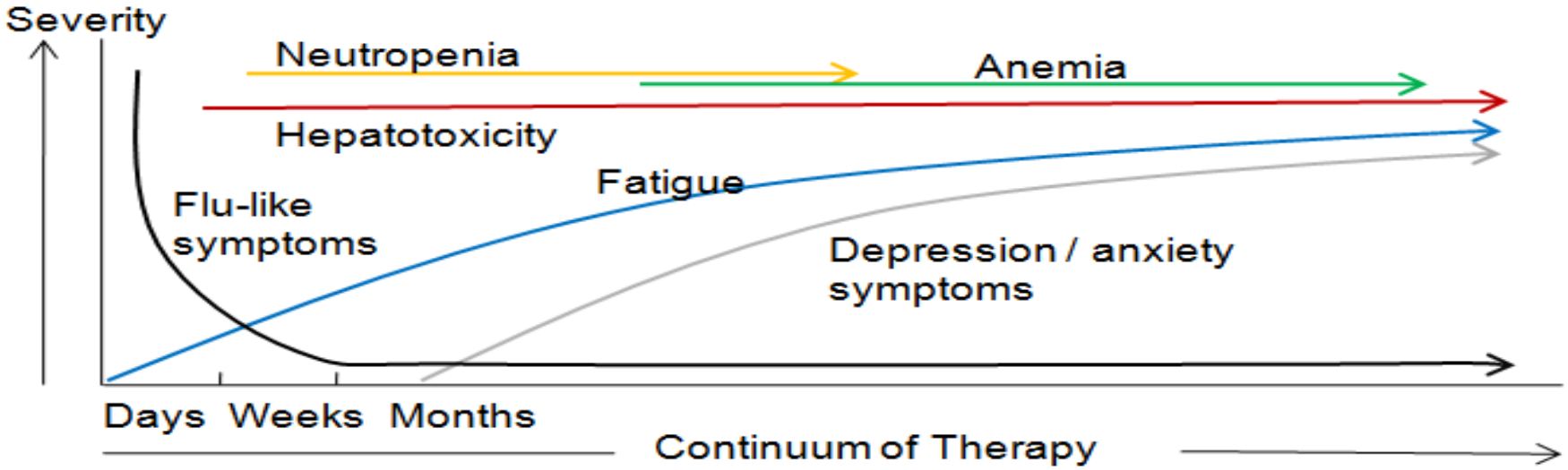
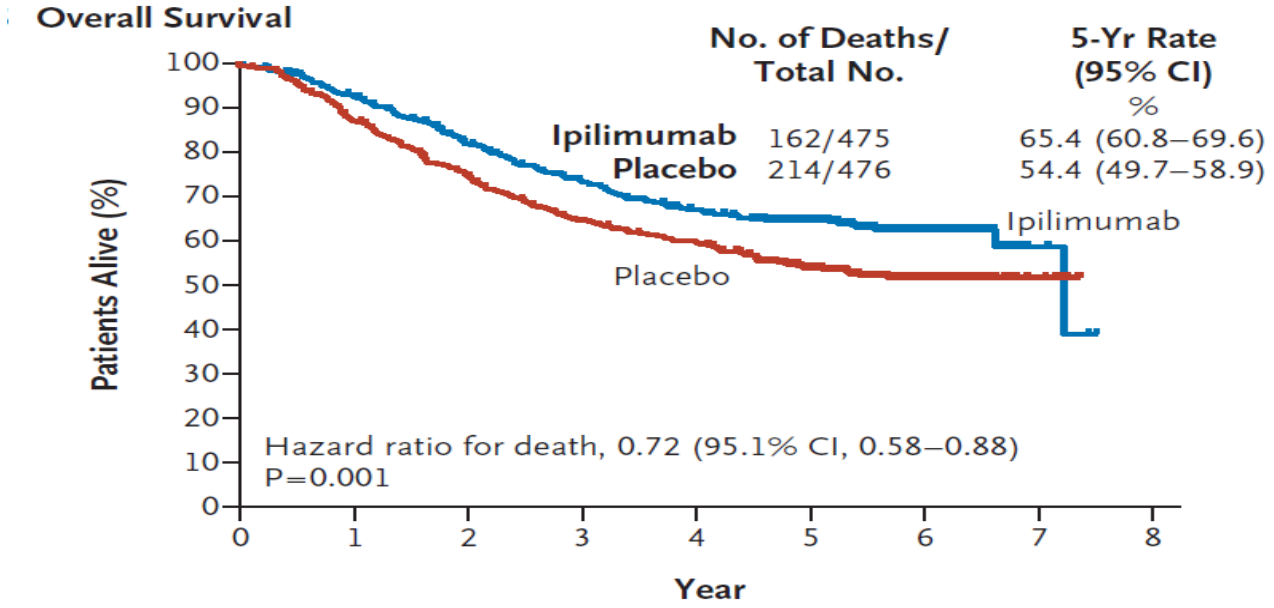
Toxicity of Adjuvant Interferon-α



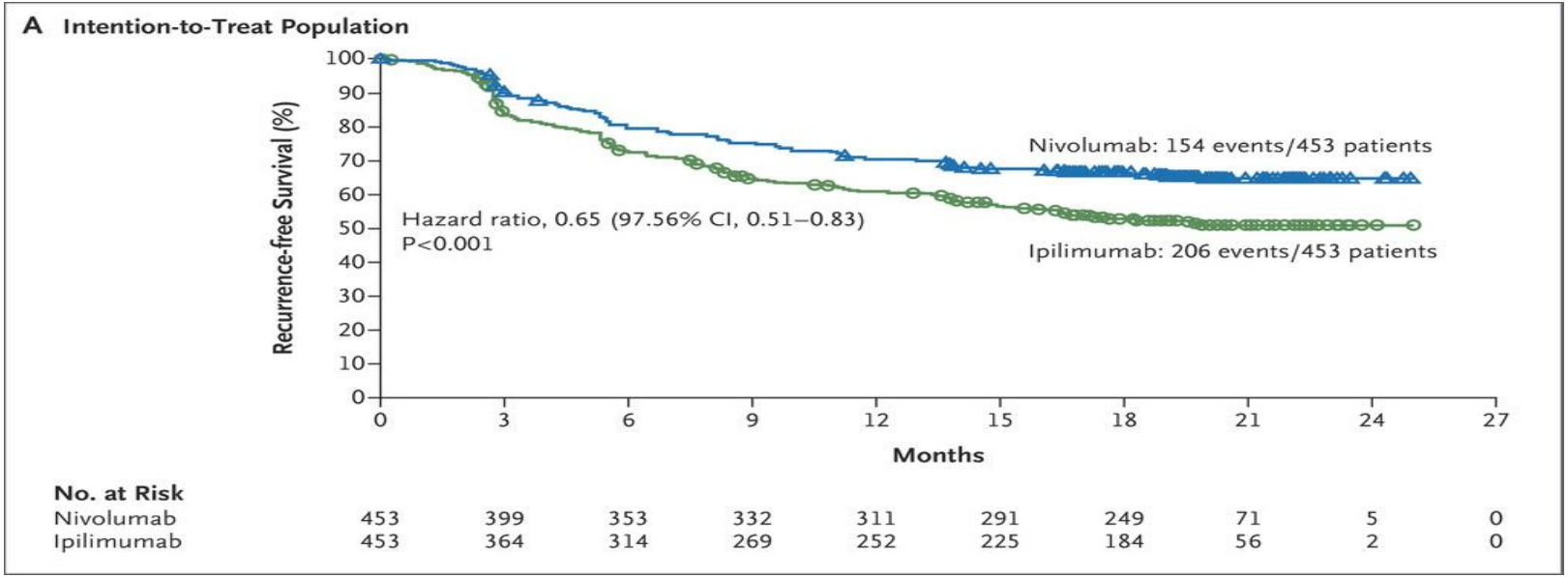
http://www.sinobiological.com/Interferon-Side-Effects-a-6085.html

Adjuvant Ipilimumab in High-Risk Melanoma



Eggermont *et al*. NEJM 2016

Adjuvant nivolumab vs ipilimumab in High-Risk Melanoma



Weber *et al*. NEJM 2017

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Systemic Therapy/Injectables

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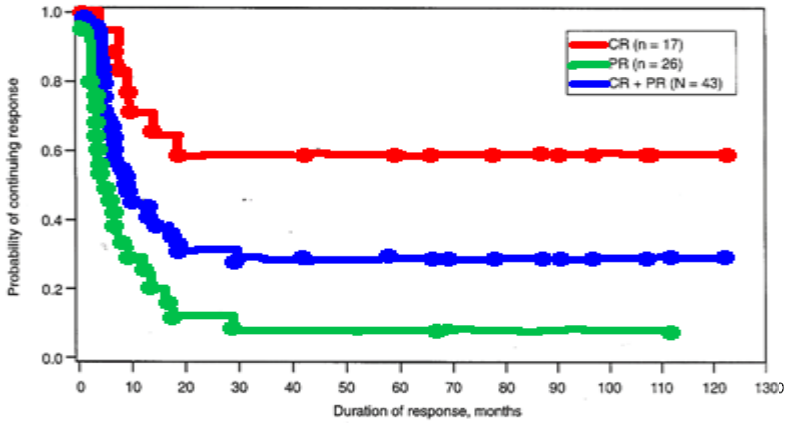
High Dose Interleukin-2 Therapy (HD IL-2) : Durable Responses

- HD IL-2 produces durable responses in 6%-10% of patients with advanced melanoma
- Few relapses in patients responding for over 2.5 years (cured?)
- FDA approval for melanoma in 1998
- High toxicity



Atkins et al. J Clin Oncol. 1999

Atkins et al. J Clin Oncol. 1999

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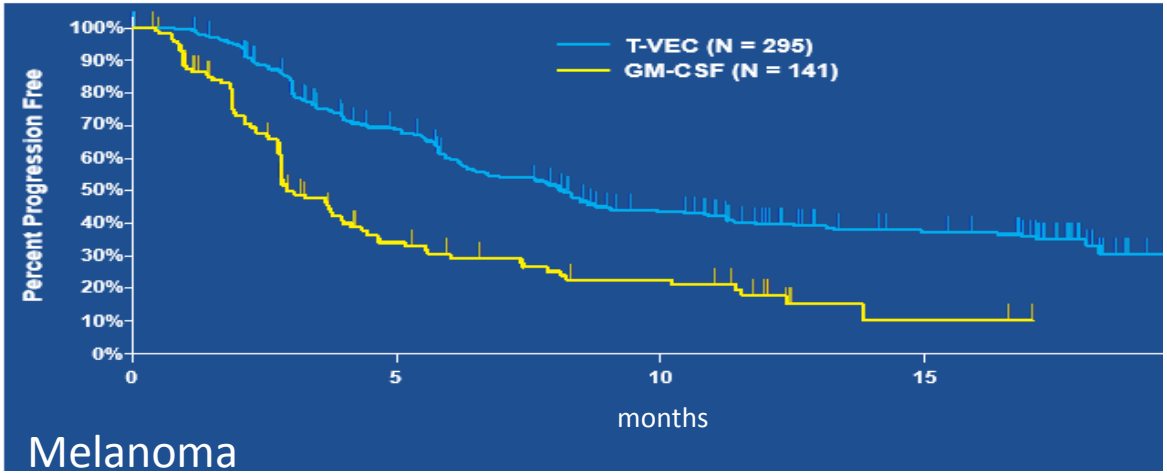
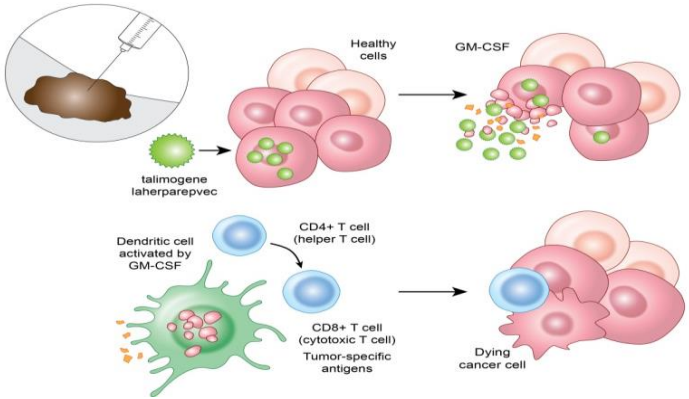
Phase III Trial of T-VEC vs GM-CSF PFS per Investigator



Melanoma



Andtbacks et al. ASCO 2013; LBA9008

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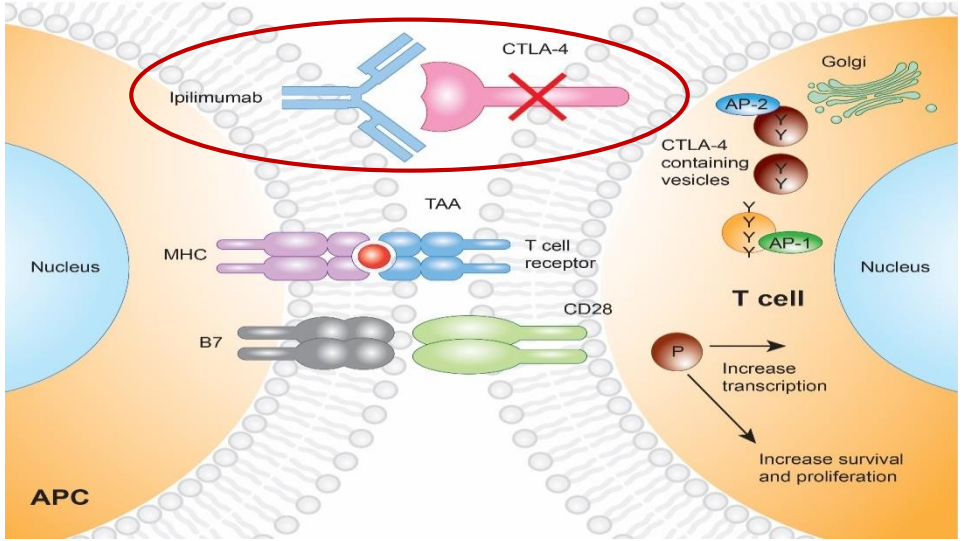
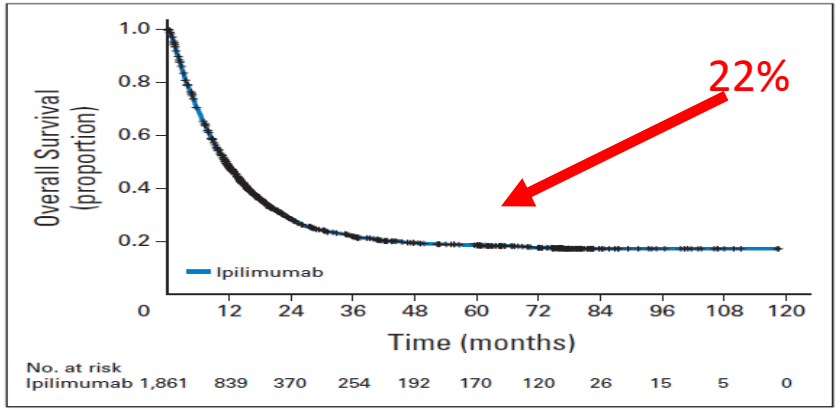
Ipilimumab & Immune Check-Point Blockade





Luke et al, Oncologist 2013
Schadendorf et al, J Clin Oncol 2015

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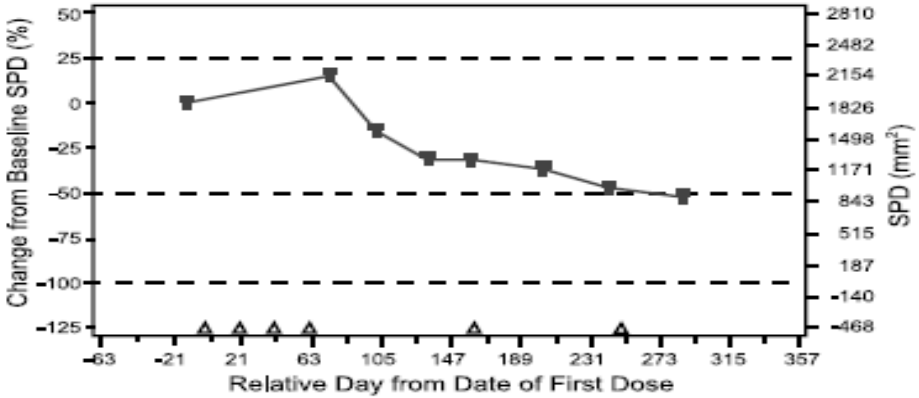
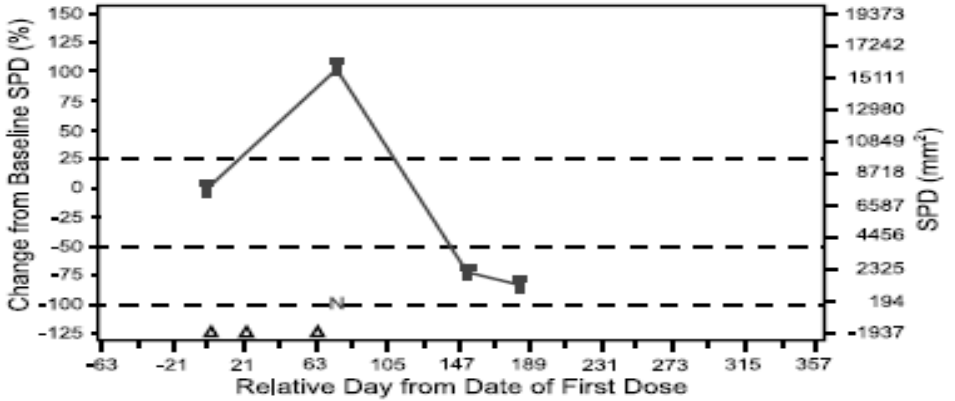
Immune Related Response Criteria





Wolchok et al. Clin Can Res 2009

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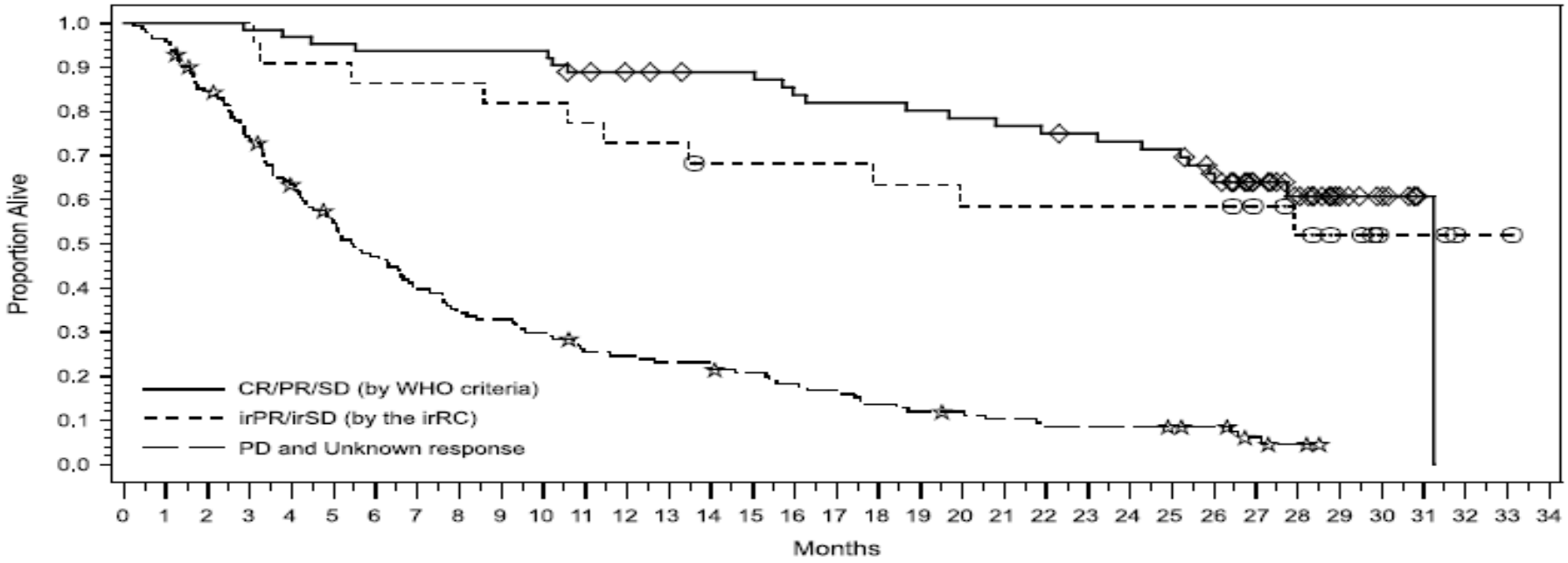
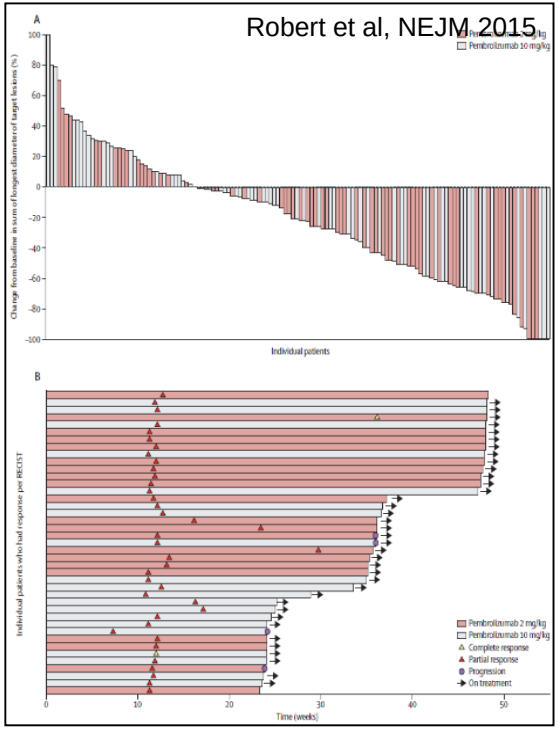
Immune Related Response Criteria



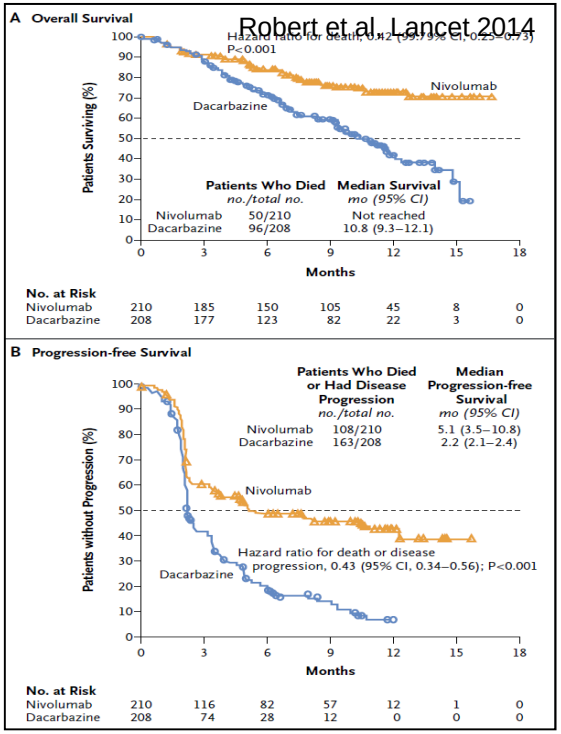
Wolchok et al. Clin Can Res 2009

Anti-PD1 in Melanoma

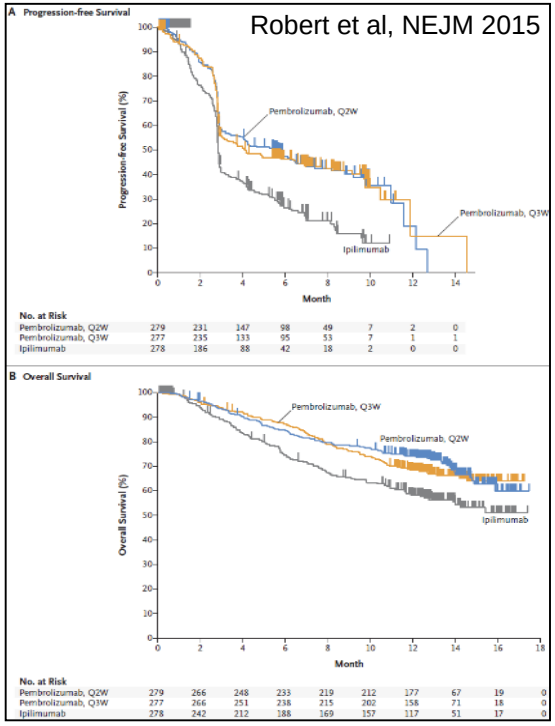
Anti-PD1 (pembrolizumab) *after* ipilimumab



Front-line anti-PD1 (nivolumab) vs. DTIC in Melanoma(BRAF WT)



Front-line anti-PD1 (pembrolizumab) vs. ipilimumab



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Case #1: stage III→stage IV-M1a

TL, male patient in 30s

- Therapeutic lymph node dissection of left inguinal node on 1/2017 revealed 3+ stage III melanoma of unknown primary origin
  - Randomized to pembrolizumab on SWOG-1404 adjuvant trial
  - 6 cycles: no significant irAEs
- Relapse in L neck and R back soft tissue

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Case #1: stage IV-M1a Oligometastatic M1a BRAFwt on adjuvant pembrolizumab

- Systemic therapy
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab 3 mg/kg x 4
  - Nivolumab plus Ipilimumab
  - Targeted Rx based on next-generation sequencing
  - High-dose IL-2
- Lesional therapy
  - Talimogene laherparepvec
  - Radiotherapy

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Best Therapies → Clinical Trials

- Tumor-infiltrating lymphocytes (TILs)
- Neoantigen vaccines
- Oncolytic virotherapy
- New/improved immune checkpoint blockers w/immunomodulators
  - of resistance (indoleamine dioxygenase inhibitors)
  - agonistic costimulatory antibodies (CD137, ICOS, OX40)
  - hypofractionated or stereotactic radiotherapy
- Molecularly-focused treatment paradigms—all immunomodulatory
  - Metabolic reprogramming
  - Next generation sequencing→molecular drivers and/or modifiers

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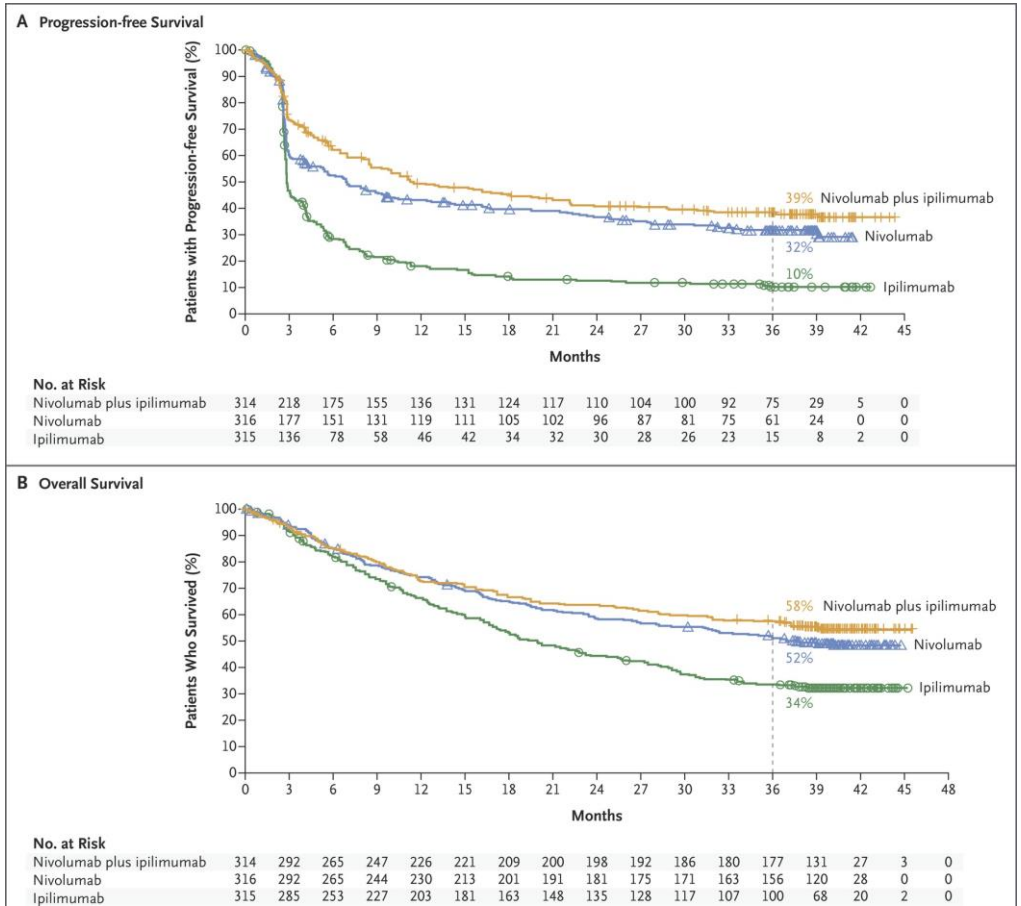
Ipilumamab: CTLA-4

Nivolumab: PD-1

Ipi+Nivo vs. Ipi or Nivo in Melanoma



Wolchok et al. NEJM, 2017

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Nivo/Ipi combo active brain mets!

The combination of Nivo and Ipi showed an intracranial response rate of 46% for assymptomatic patients with melanoma brain mets who didn't receive prior local Therapy to the brain according to updated findings for a phase II ABC trial presented at the 2017 World Congress of Melanoma in Brisbane, Australia.

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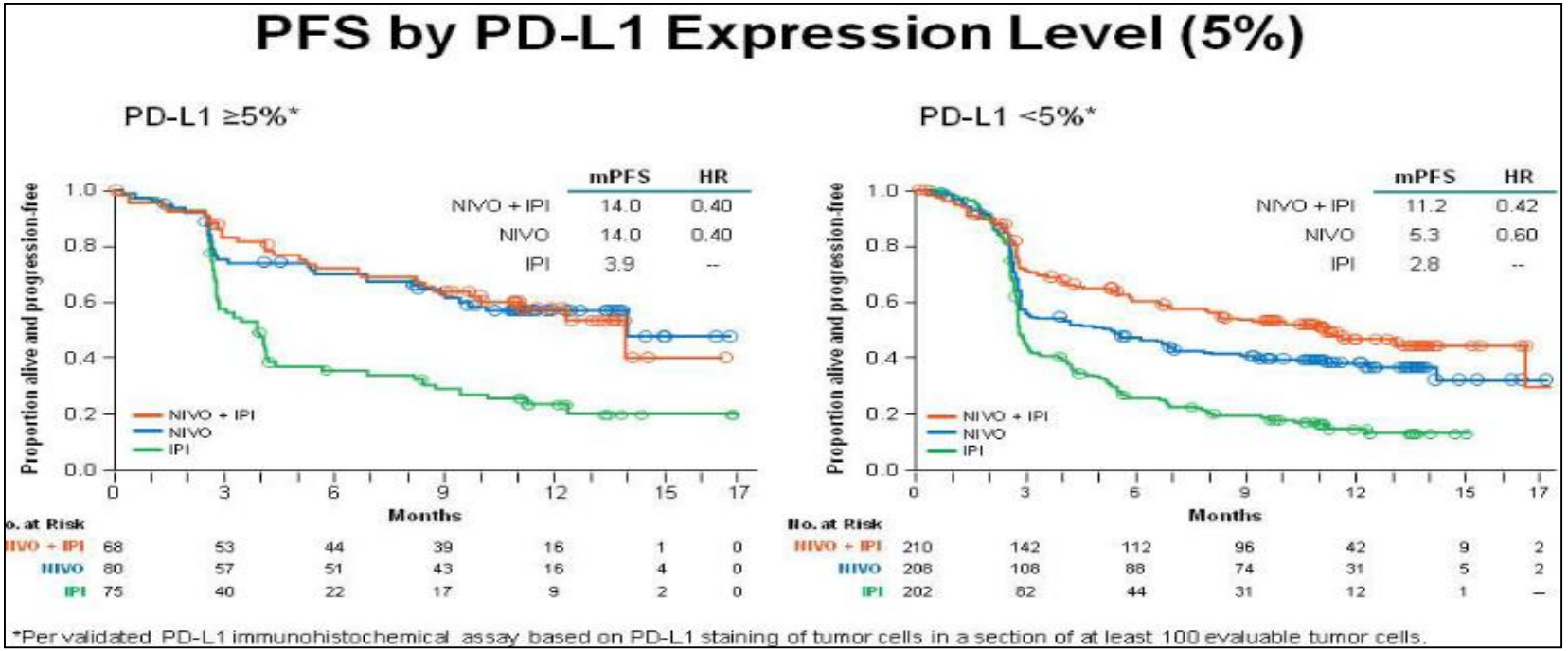
Ipilumamab: CTLA-4

Nivolumab: PD-1

Ipi+Nivo vs. Ipi or Nivo vs. Ipi in Melanoma



Presented by Jedd Wolchok at ASCO 2015 - Wolchok et al. J Clin Oncol 33, 2015 (suppl; abstr LBA1)

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Ipilumamab: CTLA-4

Nivolumab: PD-1

Ipi+Nivo vs. Ipi or Nivo vs. Ipi in Melanoma

Safety Summary

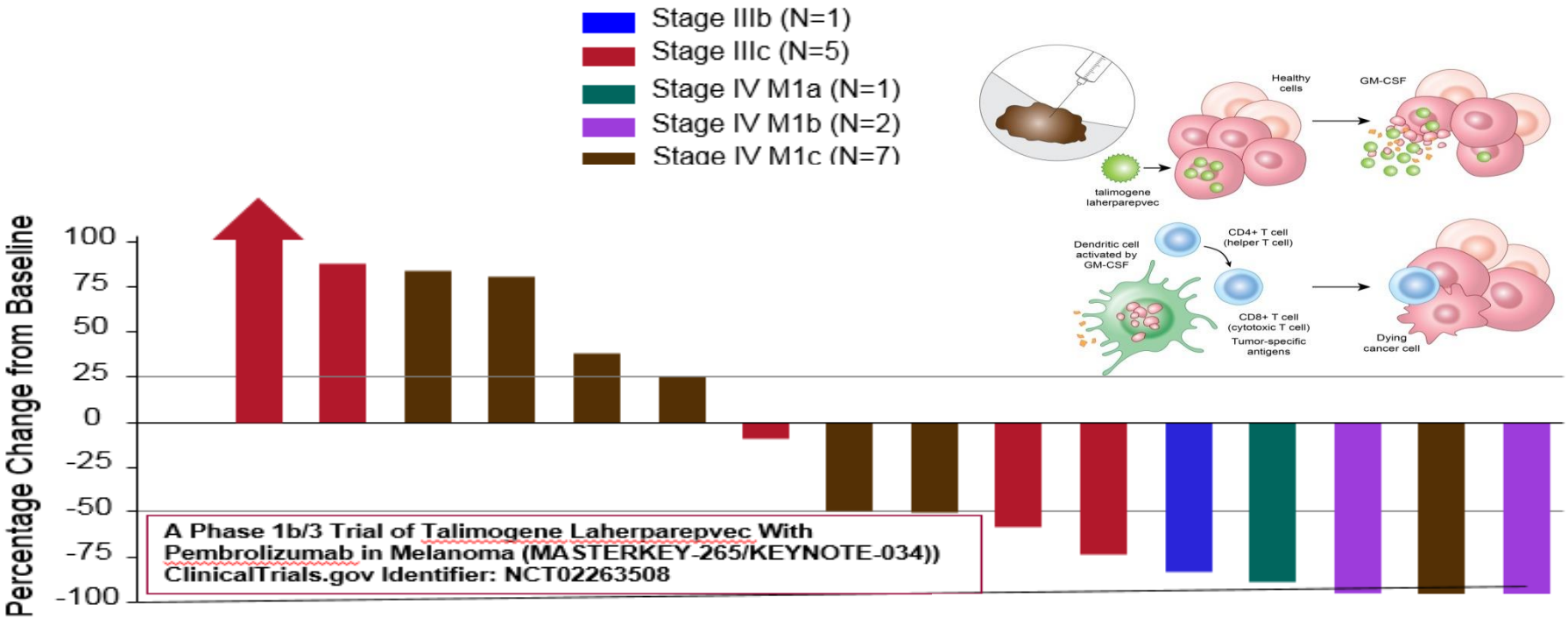
Patients Reporting Event, %	NIVO + IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse event (AE)	95.5	55.0	82.1	16.3	86.2	27.3
Treatment-related AE leading to discontinuation	36.4	29.4	7.7	5.1	14.8	13.2
Treatment-related death*	0		0.3		0.3	

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response

Presented by Jedd Wolchok at ASCO 2015 - Wolchok et al. J Clin Oncol 33, 2015 (suppl; abstr LBA1)

T-Vec + Pembrolizumab in Stage IIIB-IV Melanoma



RECIST response = 46%, no increase in toxicity from pembrolizumab alone

Long et al. SMR 2015

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On-Going Phase III Trials in Melanoma

- BRAFi + MEKi + anti PD-(L)1
- MEKi + anti PD-(L)1
- Indolamine Dioxygenase inhibitors (IDOi) + anti PD-(L)1
- Talimogene laharparepvec (TVEC) + anti PD(L)1
- And many more

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Conclusions

- Immunotherapy is standard of care in melanoma
- Likely first and second line in most patients
- Understanding mechanisms of action important
- Manage side effects, understand long-term benefit
- Immunotherapy combination is the future for melanoma and likely all cancers!

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