ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Melanoma

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Duke Cancer Institute

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

Disclosures

- Research Funding:
  - Merck & Co
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- Consultant: FujiFilm Pharmaceuticals
- Scientific Advisory Board: G1 Therapeutics

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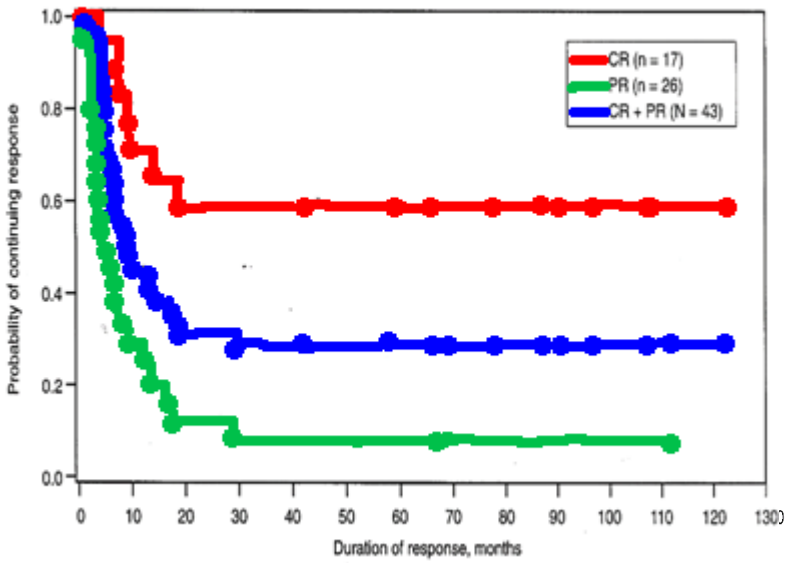
Types of Immunotherapies for Melanoma

- Cytokines
  - Interferon-α 2b
  - Interleukin-2
- Checkpoint antibodies
  - Anti-CTLA4 (ipilimumab)
  - Anti-PD1 (pembrolizumab, nivolumab)
- Oncolytic Virus
  - Modified Herpes Virus (Talimogene Laharparepvec; TVEC)
- Adjuvant Immunotherapy
- Novel Combination Immunotherapy Regimens

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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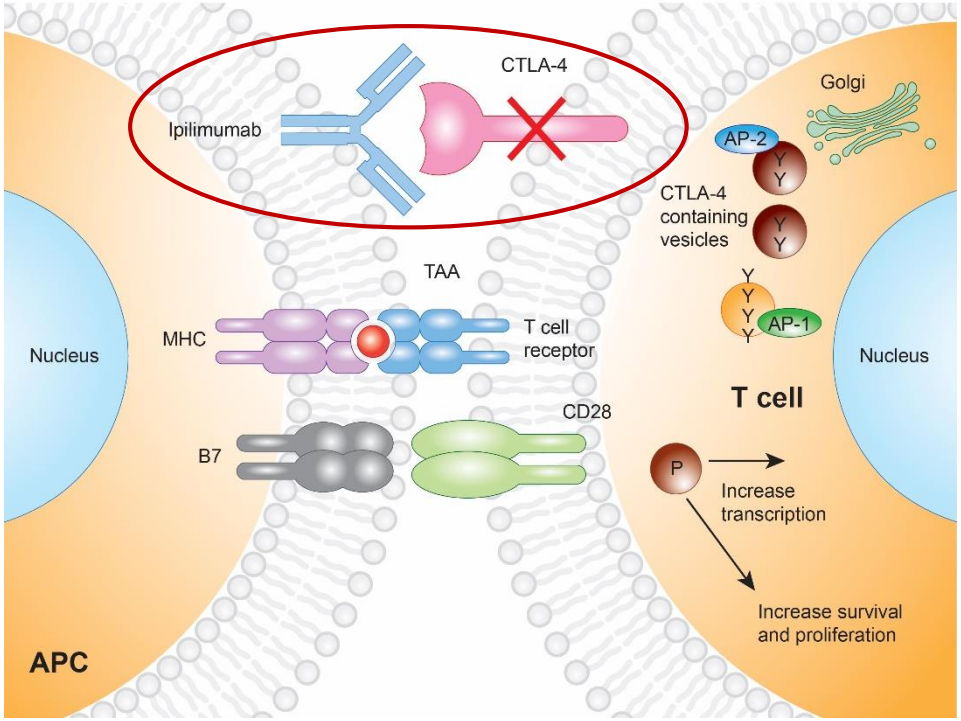
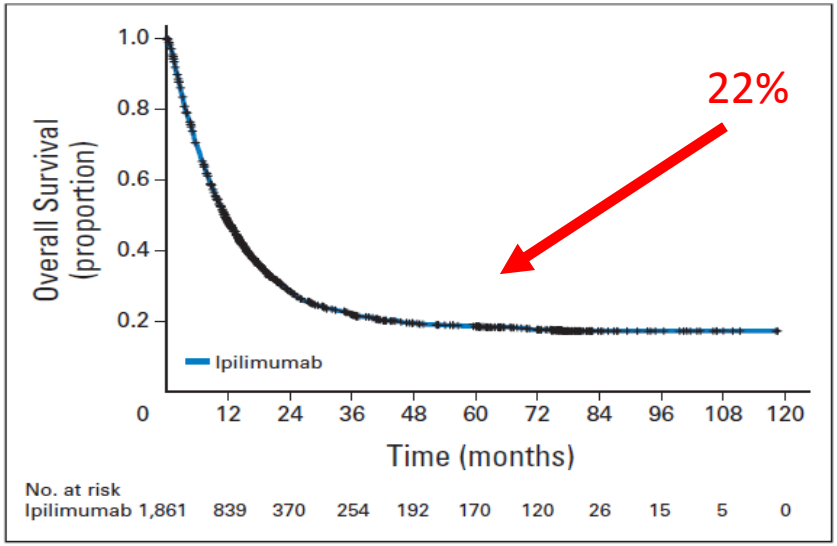
Ipilimumab (Anti-CTLA-4 Antibody Therapy)





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

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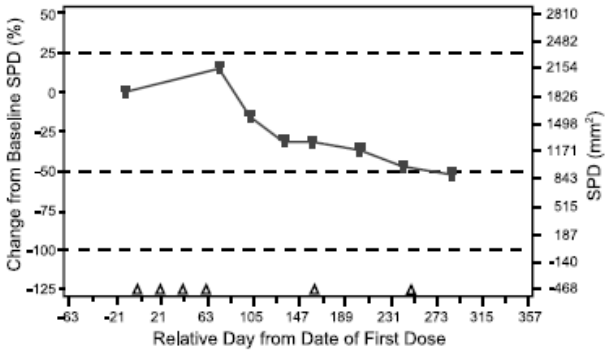
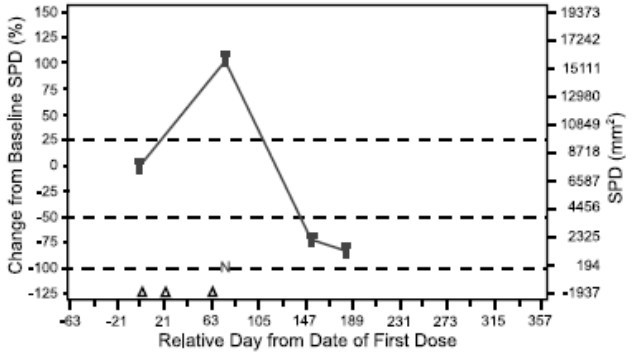
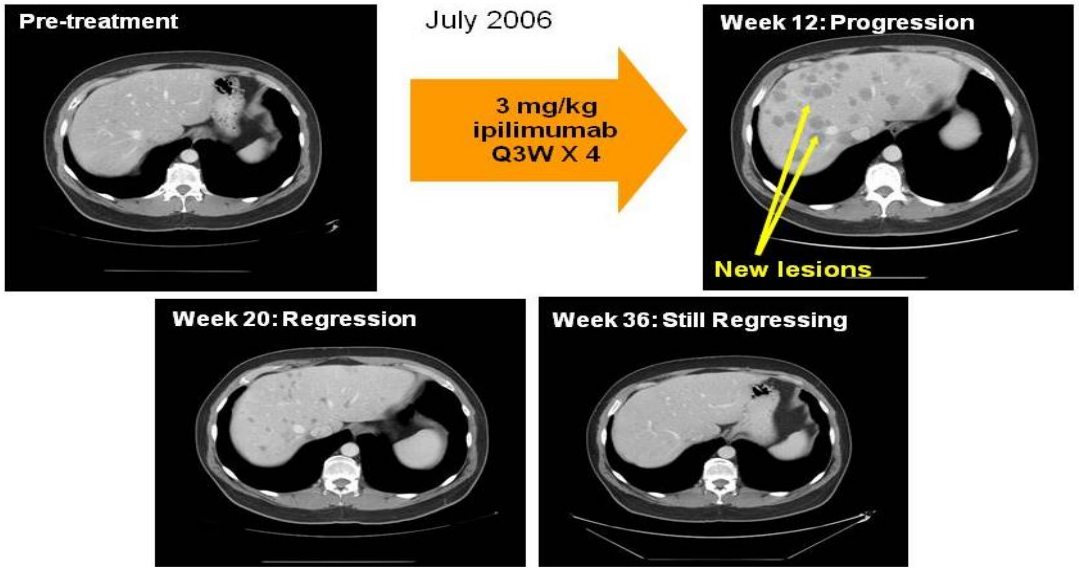
Pseudo-Progression and Immune Related Response Criteria





- Use of traditional RECIST may lead to premature discontinuation of therapy



- Immune-related response criteria:
  - Requires calculation of total tumor burden
  - Requires repeat scan 4 weeks later

Jedd Wolchok, 2008 Annual ASCO Meeting.

Wolchok et al. Clin Can Res 2009

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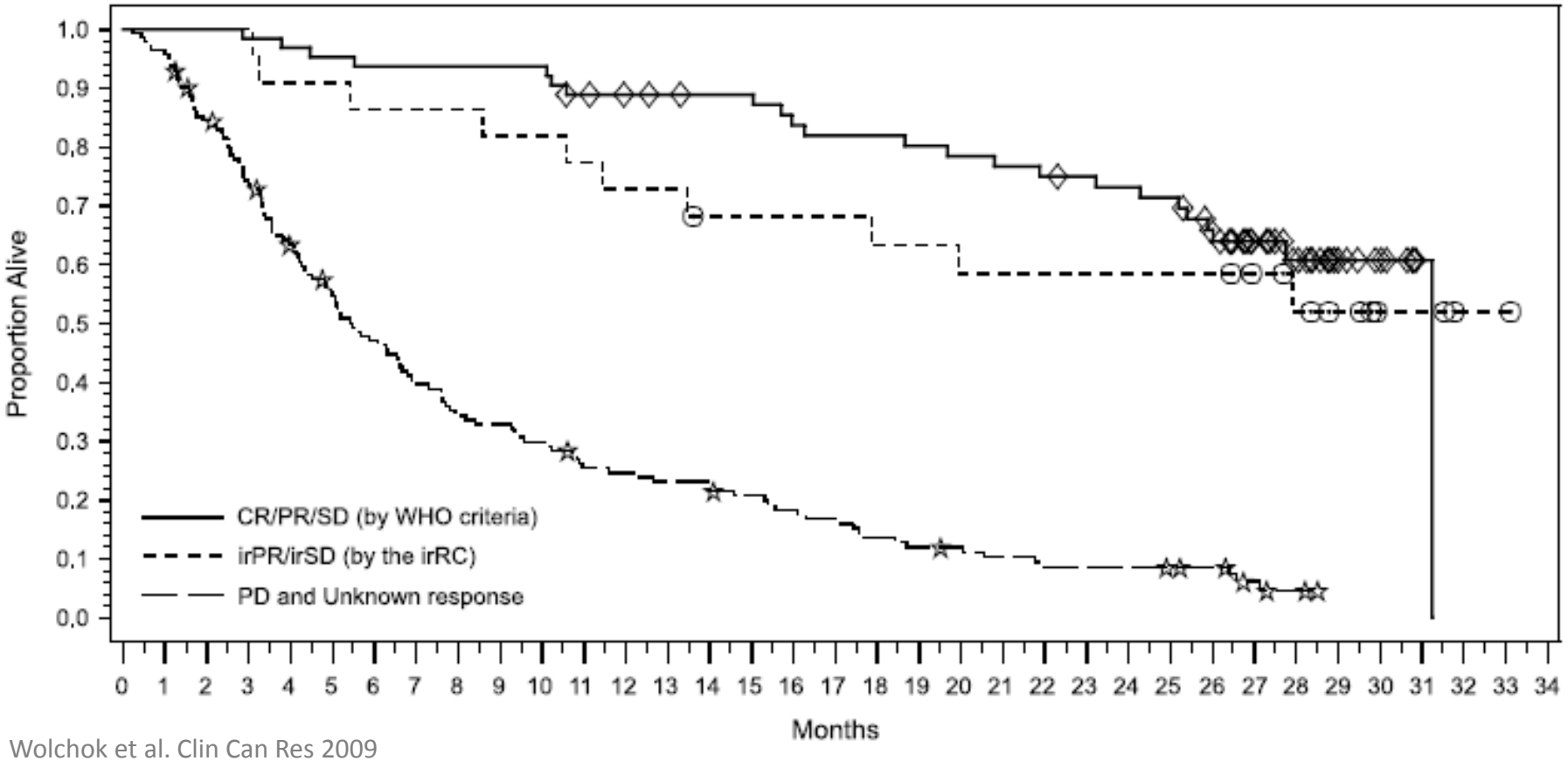
Immune Related Response Criteria



Wolchok et al. Clin Can Res 2009

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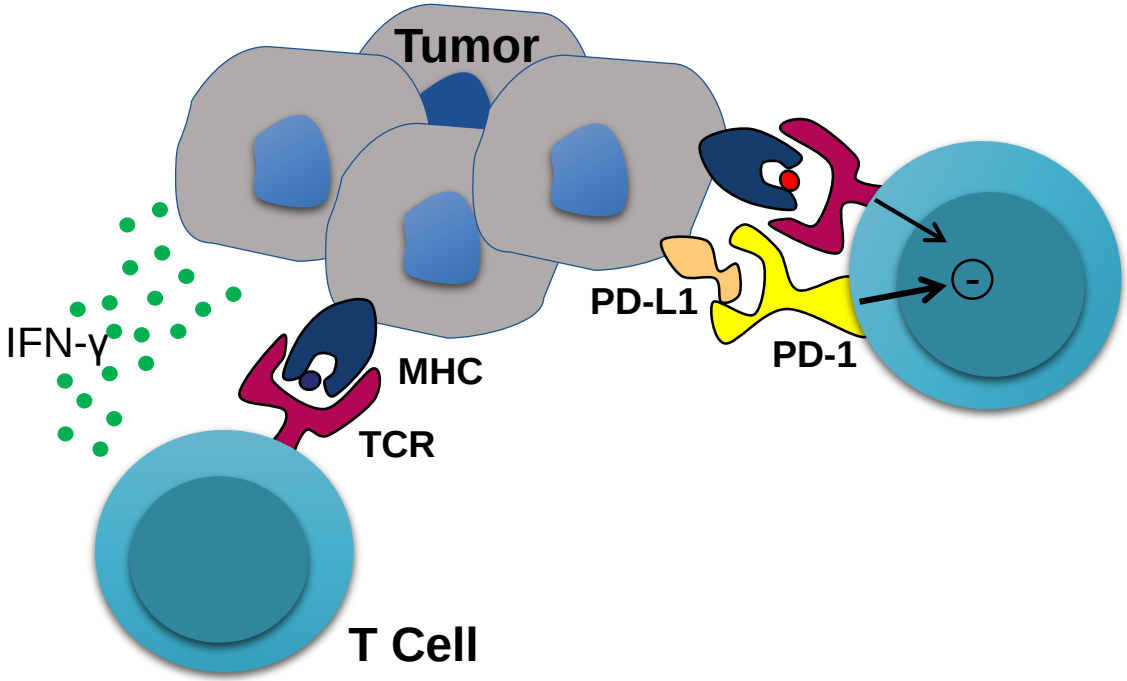
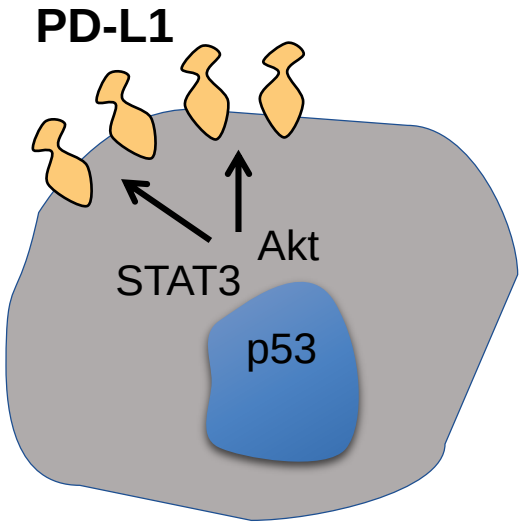
Pembrolizumab/Nivolumab (Anti-PD-1 Antibody Tx)

- PD-1 signaling promotes T cell tolerization by inhibiting downstream activation signals
- PD-1 expression is upregulated by activated and exhausted T cell populations
- Tumor PD-L1 expression is regulated via two general mechanisms:
  1. Adaptive immune resistance: upregulated by IFN-γ in peripheral tissues
  2. Innate immune resistance: oncogenic signaling pathways





Francisco, L. et al. *Immunol Rev.* 2010. 236: 219. Pardoll, D.M. *Nat Rev Cancer*. 2012. 12: 252.

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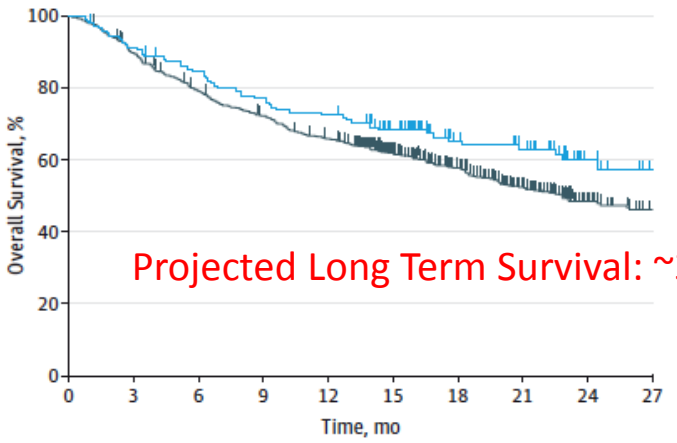
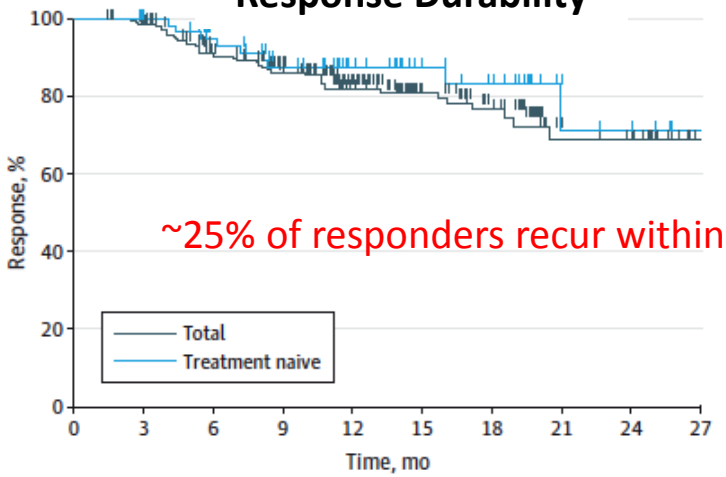
Pembrolizumab/Nivolumab (Anti-PD-1 Antibody Tx)

Overall Survival



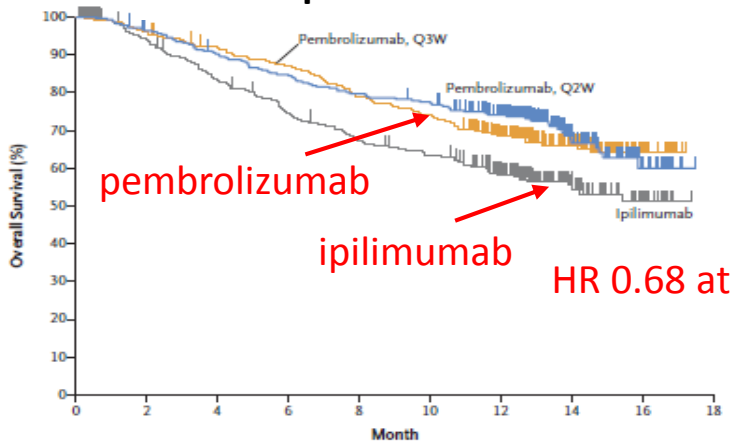
Projected Long Term Survival: ~35%

Response Durability



~25% of responders recur within 2 years

Vs. Ipilimumab



pembrolizumab

ipilimumab

HR 0.68 at 26 months

- ORRs: 30-40%
- Reduction in Risk of Death Relative to Ipilimumab: 31-37%

Ribas, A. et al. *JAMA* . 2916. 315(15): 1600.
Robert, C. et al. *NEJM*. 2015.

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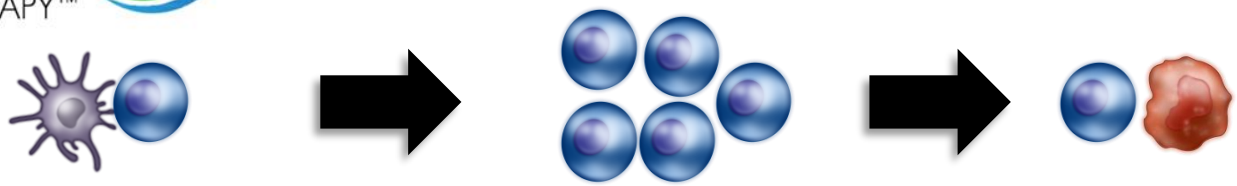
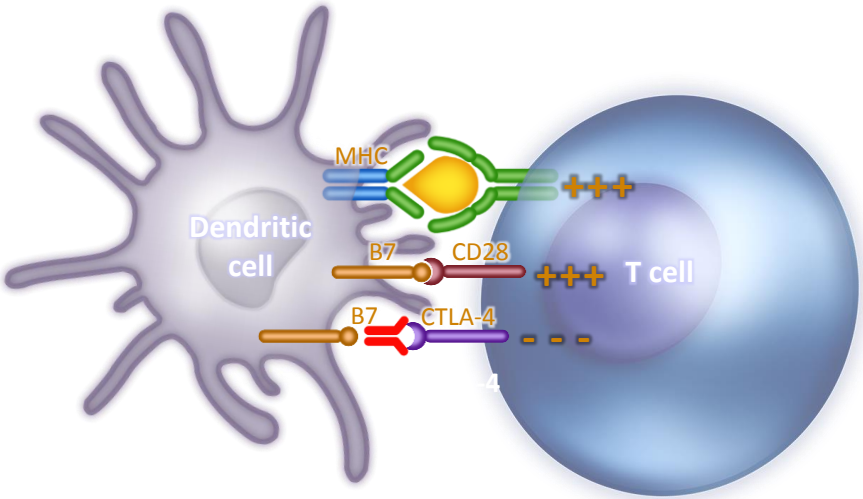


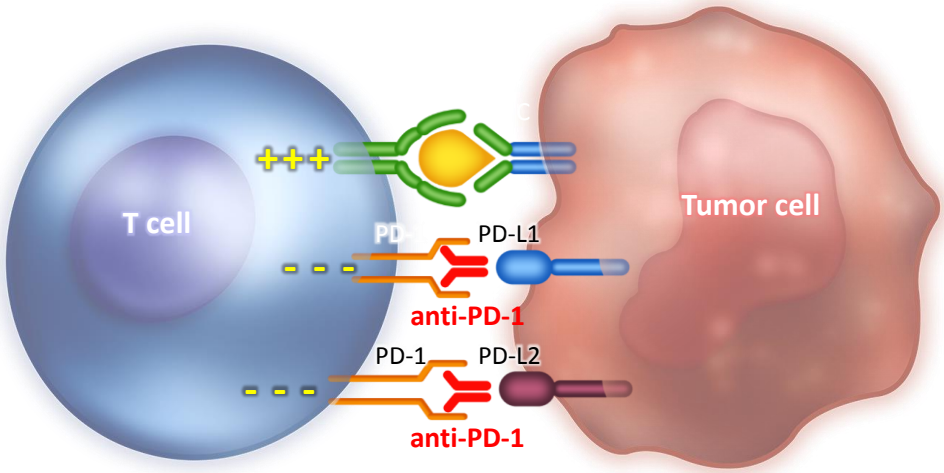
Activation
(cytokines, lysis, proliferation, migration to tumor)

Lymph Node Microenvironment



CTLA-4 Blockade

Tumor Microenvironment



PD-1 Blockade

Jedd Wolchok, 2013 Annual ASCO Meeting.

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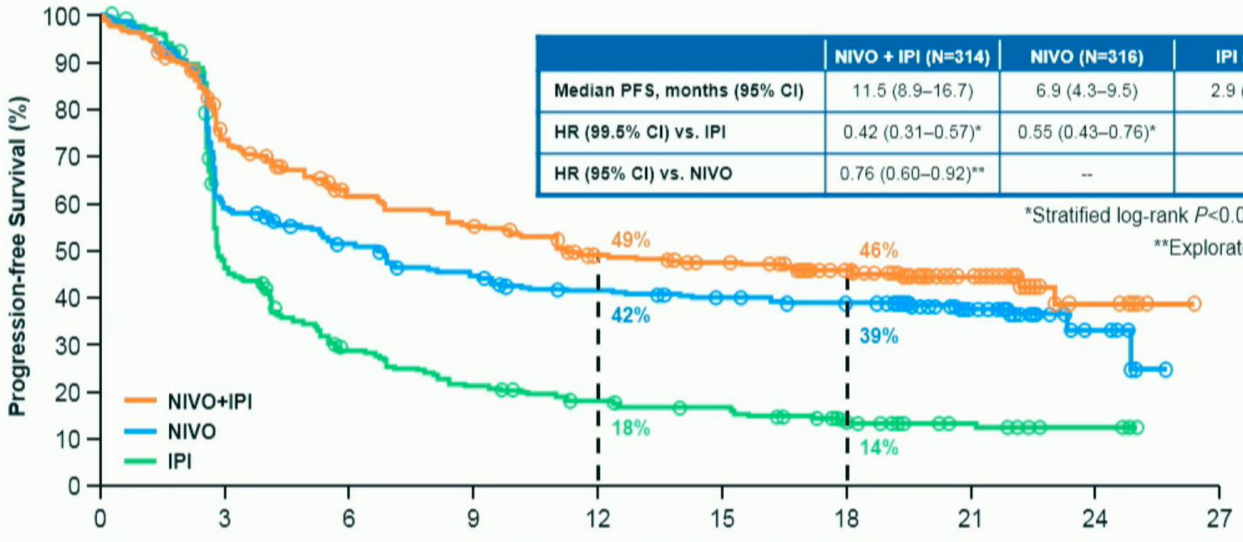
Ipilumamab: CTLA-4

Nivolumab: PD-1

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

Phase III – Checkmate 067

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

ORR

Ipi/Nivo 57.6%

Nivo 43.7%

Ipi 19.0%

Jedd Wolchok, 2016 Annual ASCO Meeting.

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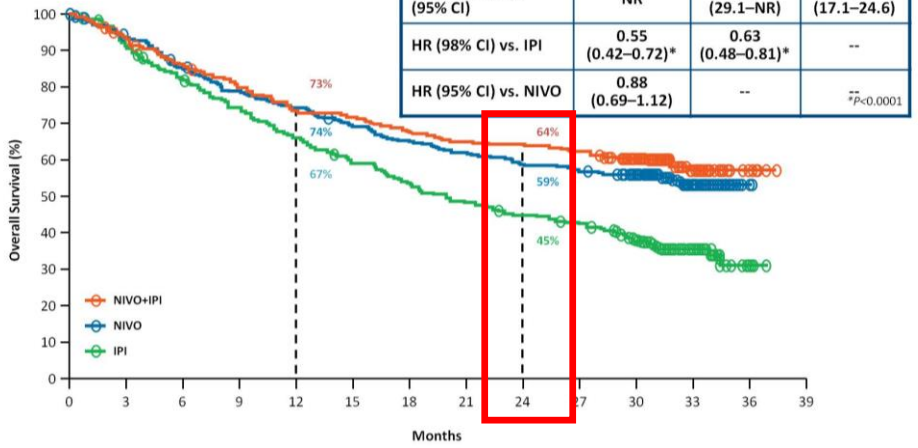
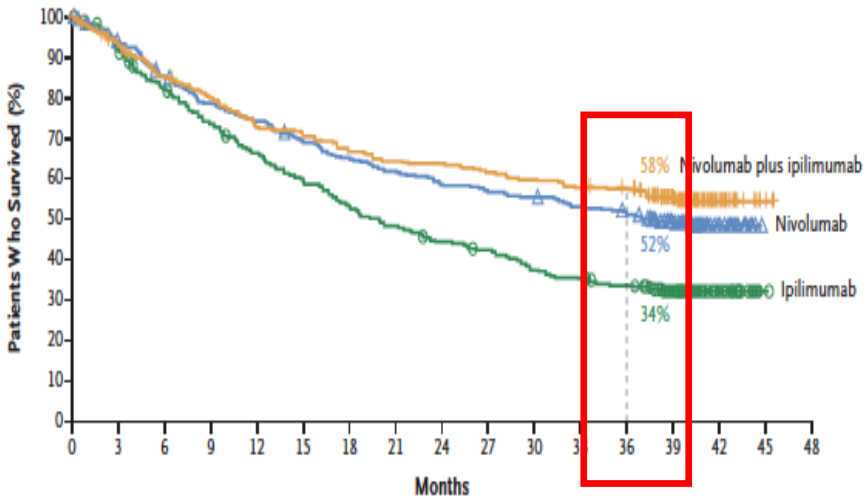
Ipi+Nivo vs. Ipi or Nivo vs. Ipi in Melanoma

2 year Follow-Up

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, mo (95% CI)	NR	NR (29.1–NR)	20.0 (17.1–24.6)
HR (98% CI) vs. IPI	0.55 (0.42–0.72)*	0.63 (0.48–0.81)*	--
HR (95% CI) vs. NIVO	0.88 (0.69–1.12)	--	-- *P<0.0001



3 year Follow-Up



Median Overall Survival

Ipi/Nivo NR
Nivo 37.6 months
Ipi 19.9 months

HR for Death

Ipi/Nivo vs Ipi 0.55 (95% CI 0.45 – 0.69)
Nivo vs Ipi 0.65 (95% CI 0.53 – 0.80)
Ipi/Nivo vs Nivo 0.85 (95% CI 0.68 – 1.07)

J. Larkin. 2017 AACR Annual Meeting.
Wolchok, J. et al. *NEJM.* 2017. 377: 1345.

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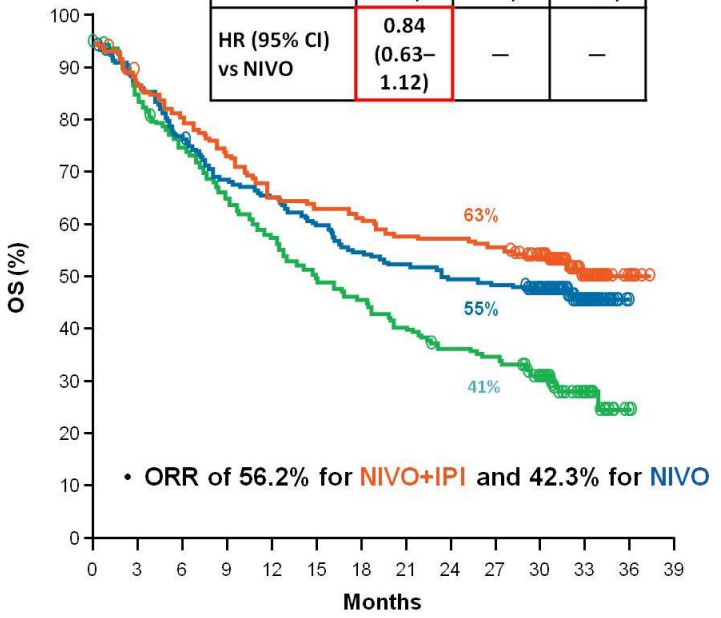
Ipilumamab: CTLA-4

Nivolumab: PD-1

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

PD-L1 Expression Level <5%

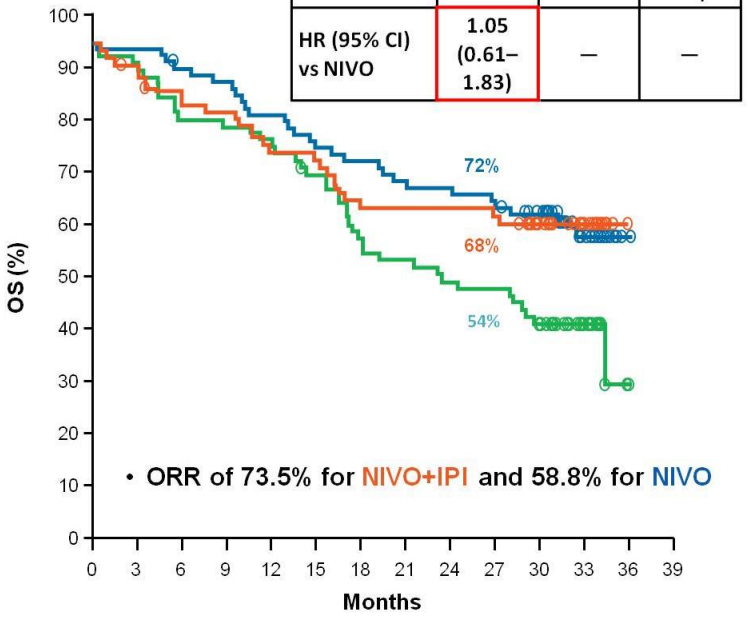
	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR (31.8–NR)	NR (23.1–NR)	18.5 (13.7–22.5)
HR (95% CI) vs NIVO	0.84 (0.63–1.12)	—	—



• ORR of 56.2% for NIVO+IPI and 42.3% for NIVO

PD-L1 Expression Level ≥5%

	NIVO+IPI	NIVO	IPI
Median OS, mo (95% CI)	NR	NR	28.9 (18.1–NR)
HR (95% CI) vs NIVO	1.05 (0.61–1.83)	—	—



• ORR of 73.5% for NIVO+IPI and 58.8% for NIVO

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J. Larkin. 2017 Annual AACR Meeting.

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Ipilumamab: CTLA-4

Nivolumab: PD-1

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

Safety Summary

- Updated safety information with 9 additional months of follow-up were consistent with the initial report

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	56.5	84.0	19.8	85.9	27.0
Treatment-related AE leading to discontinuation	38.7	30.7	10.5	7.3	15.4	13.5
Treatment-related death*	0		0.3		0.3	

- 68.8% of patients who discontinued NIVO+IPI due to treatment-related AEs achieved a response

*One reported in the NIVO group (neutropenia) and one in the IPI group (colon perforation)

Database lock Nov 2015

J. Wolchok. 2016 Annual ASCO Meeting

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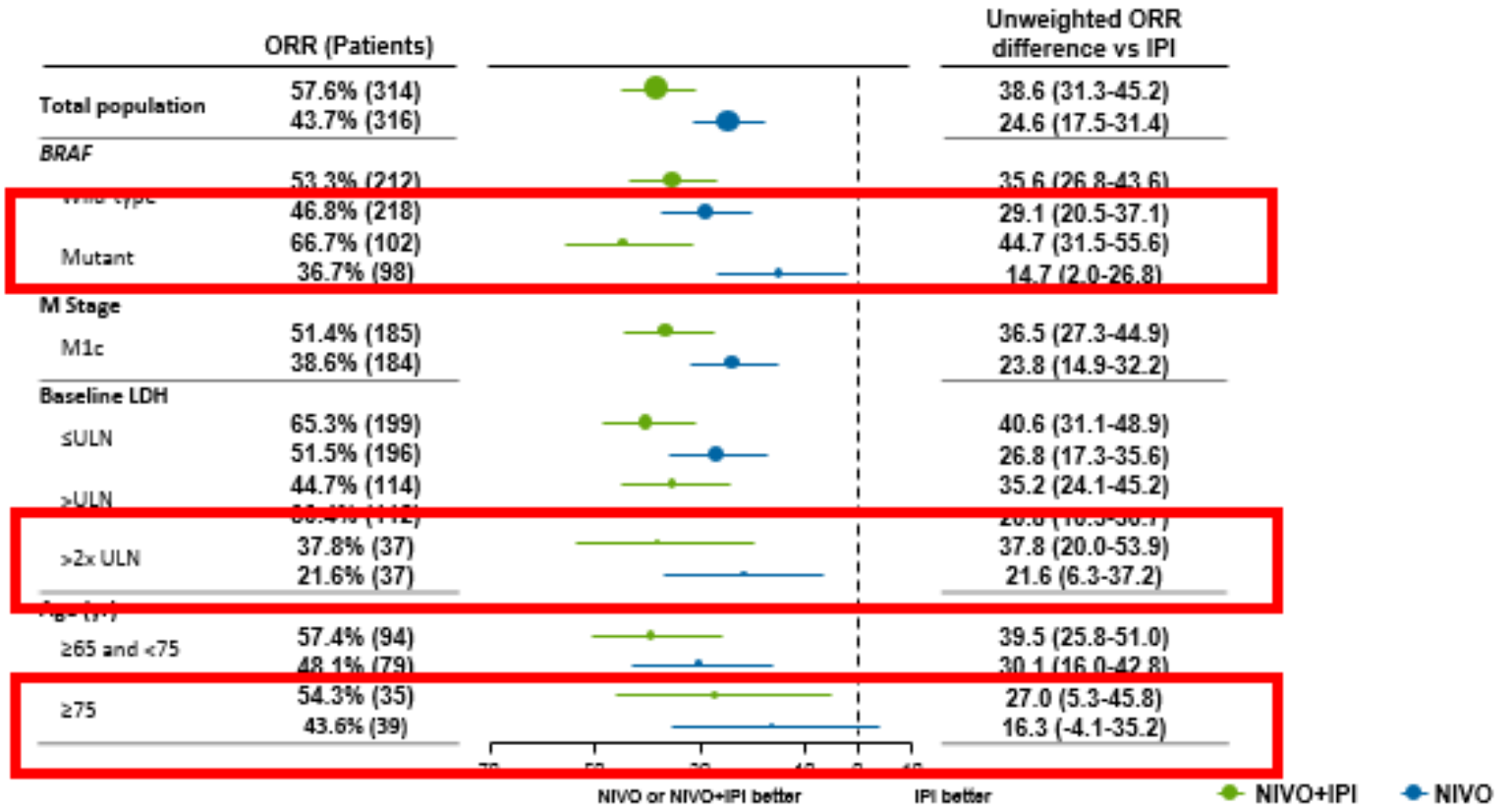
Ipi-Nivo vs Nivo Overall Response Rate in Patient Subgroups



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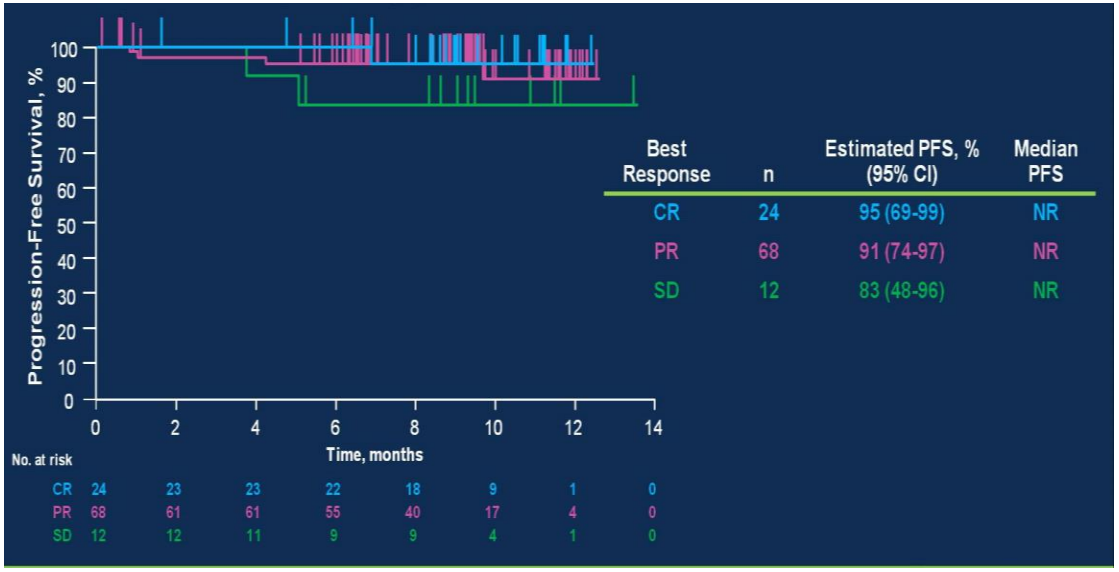
Anti-PD-1 Antibody Discontinuation



Best Response	n	Estimated PFS, % (95% CI)	Median PFS
CR	24	95 (69-99)	NR
PR	68	91 (74-97)	NR
SD	12	83 (48-96)	NR

- Keynote-001 Study: After a CR while receiving two years of pembrolizumab therapy, 97% of patients maintain a CR after one year of follow-up

- Keynote-006 Study: 95% of CR patients, 91% of PR patients, and 83% of SD patients were either disease-free or stable within one year of follow-up after discontinuing therapy

Caroline Robert. 2017 Annual ASCO Meeting. Chicago, IL.

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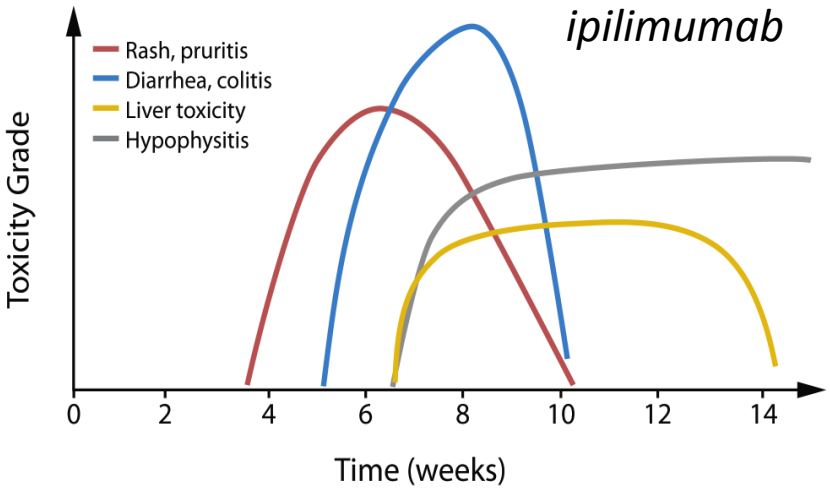
Immunotherapy Toxicity

Organ	Symptoms
Skin (dermatitis, mucositis)	rash, itching, dry eyes, dry mouth
Colon (colitis)	loose stools, stomach cramping, fatigue
Thyroid (thyroiditis)	rapid heart rate, sweating, heat intolerance, fatigue
Pituitary (hypophysitis)	fatigue, headache, muscle cramping, nausea
Liver (hepatitis)	Fatigue, nausea, fever, nightsweats



Mellman, I. et al. *Nature*. 2011. 480: 480.

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Immunotherapy Toxicity

- Steroid therapy for ipilimumab-induced side-effects is not associated with inferior outcome
- Meta-analysis of 4 independent anti-PD-1 antibody studies → 24% received steroid therapy for side-effects; no significant difference in the response rate (30% vs 32%)

Figure 4. Steroids and ipilimumab-induced responses by mWHO criteria

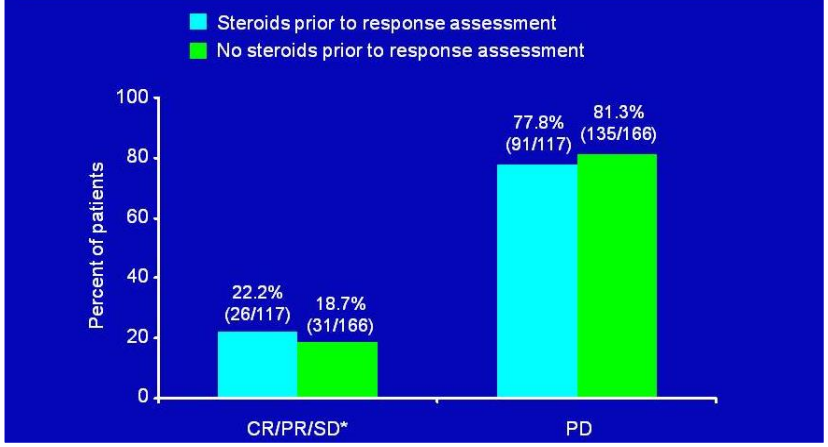
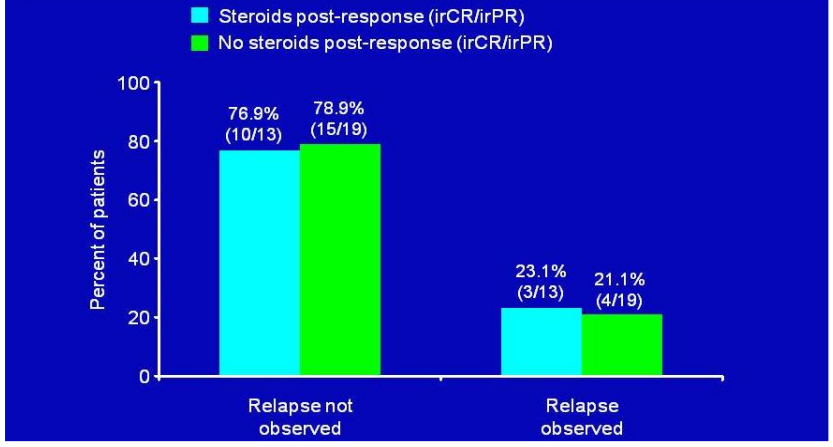


Figure 7. Steroids and maintenance of response by irRC criteria



Weber, J. et al. *Clin Cancer Res.* 2009. 15: 5591-5598.
Amin, A. *Proc. ASCO* 2009. Abstract 9037.
Weber, J. et al. *J Clin Oncol.* 2017. 35: 785.

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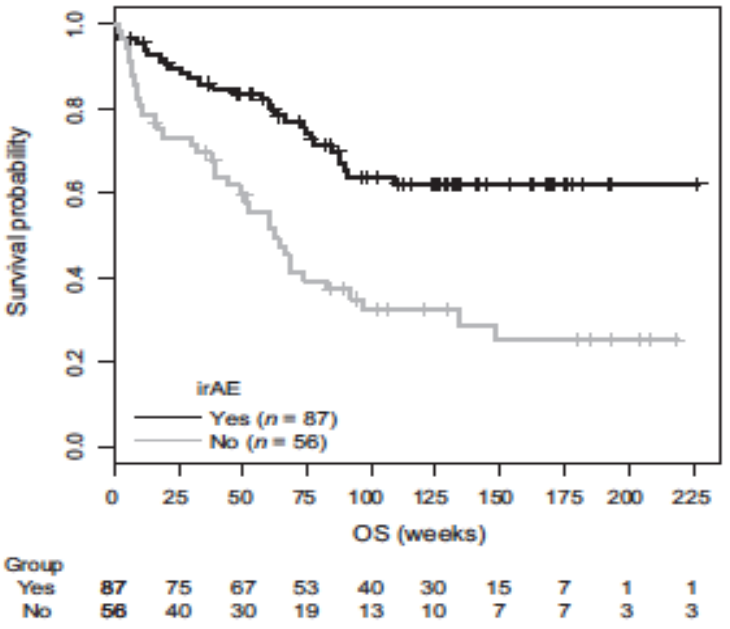
Immunotherapy Toxicity

Single Agent Nivolumab

# of Side-Effects	Response Rate
0	18%
1-2	47%
⩾ 3	85%

Overall Survival



- Immune-related toxicities correlate with response rate and overall survival

Freeman-Keller, M. et al. *Clin Cancer Res*. 2015.
Weber, J. et al. *J Clin Oncol.* 2017. 35: 785.

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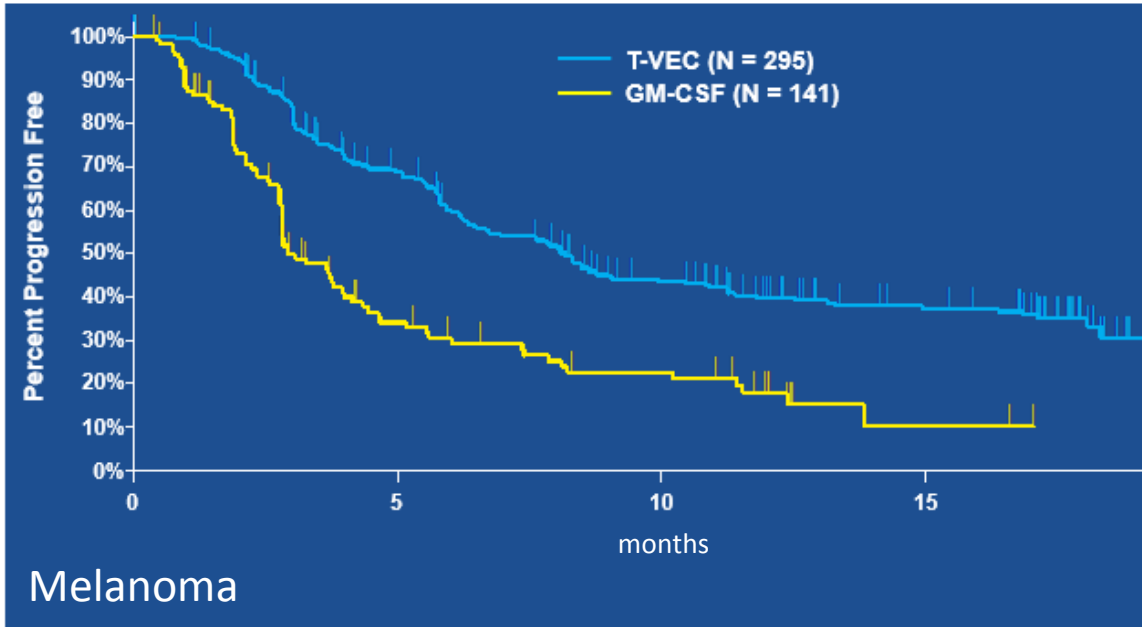
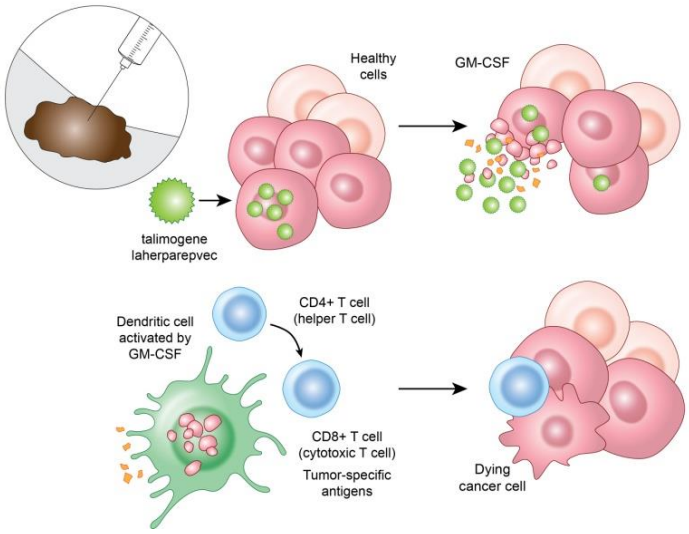
Phase III Trial of T-VEC vs GM-CSF





- Durable Response Rate: TVEC (16.3%) vs GM-CSF (2.1%)
- Most effective for patients with stage IIIB, IIIC, and IV (M1a) disease
- Overall, well tolerated with transient side-effects (inflammation, fever, HA)

Andtbacka, R. et al. *JCO.* 2015. 33: 2780.
Andtbacka et al. ASCO 2013; LBA9008

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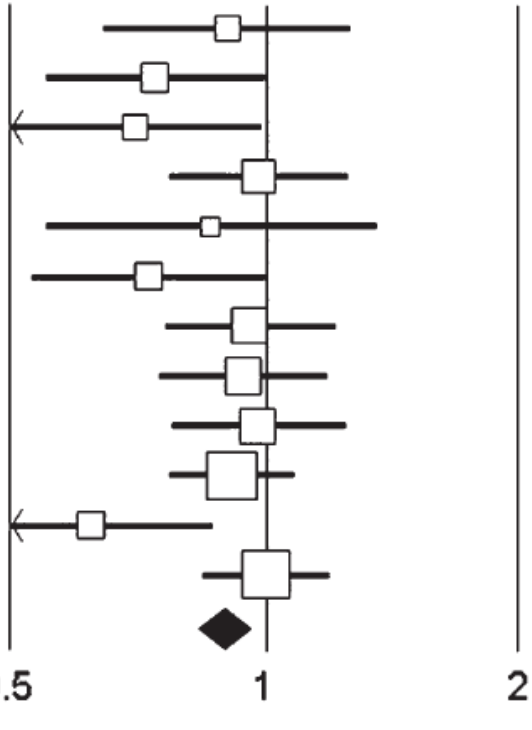
Adjuvant IFN-α High-Risk Melanoma

	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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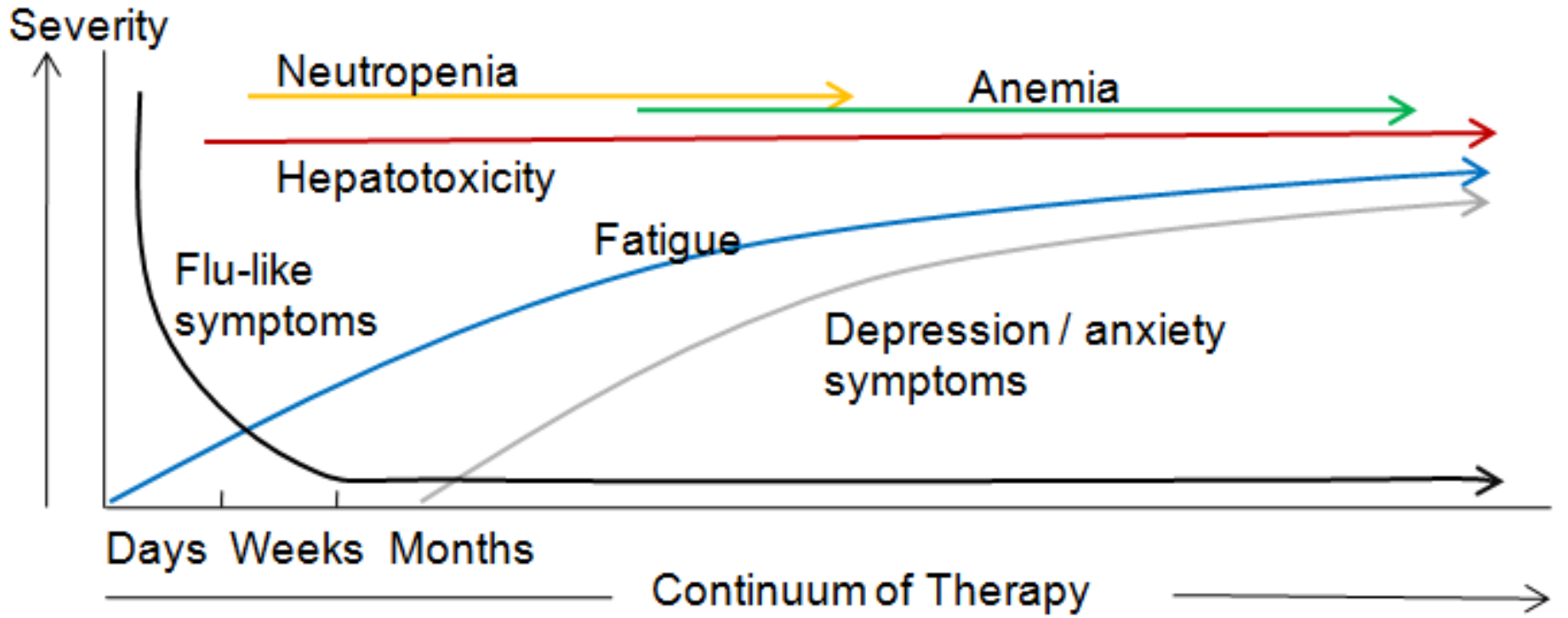
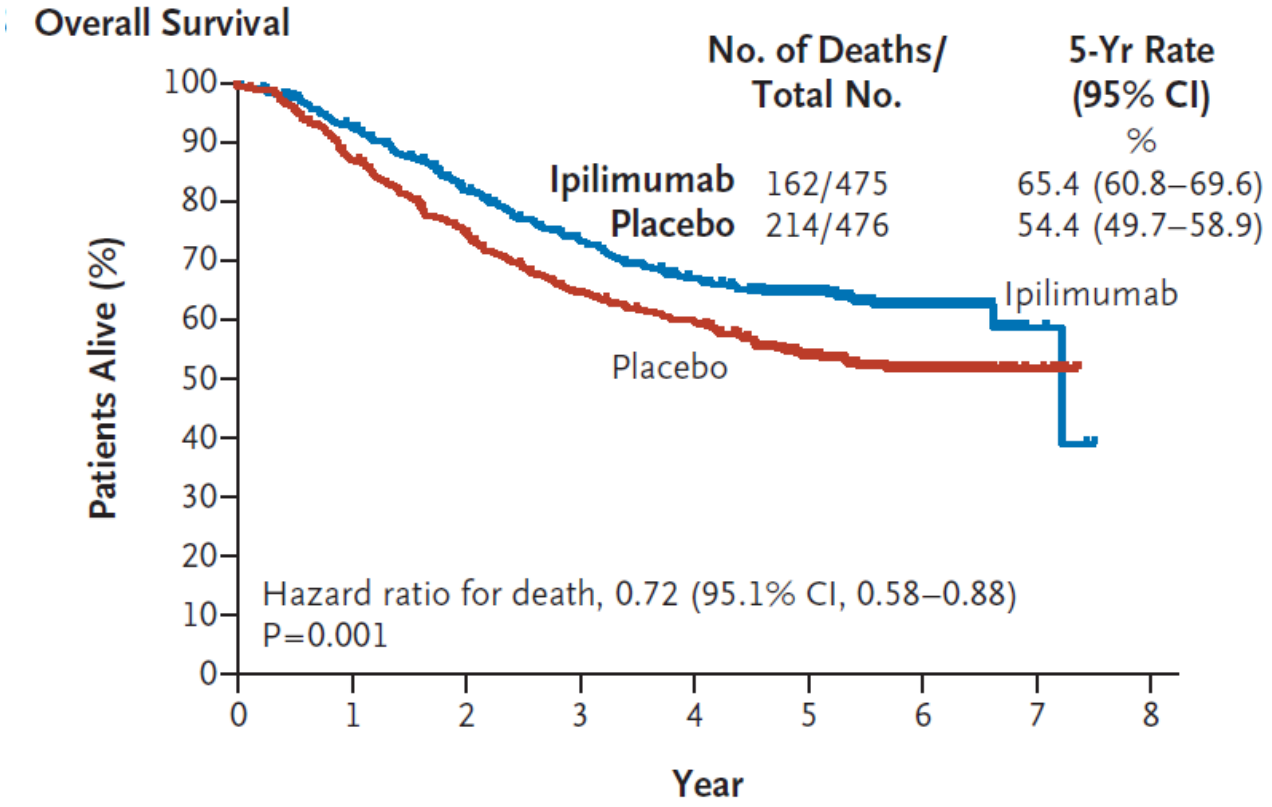
Toxicity of Adjuvant IFN-α



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

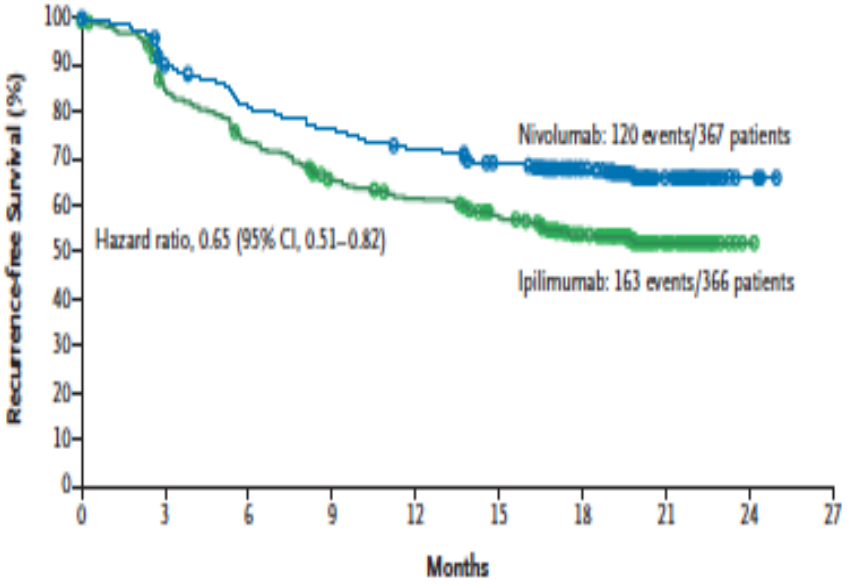
Adjuvant Ipilimumab in High-Risk Melanoma



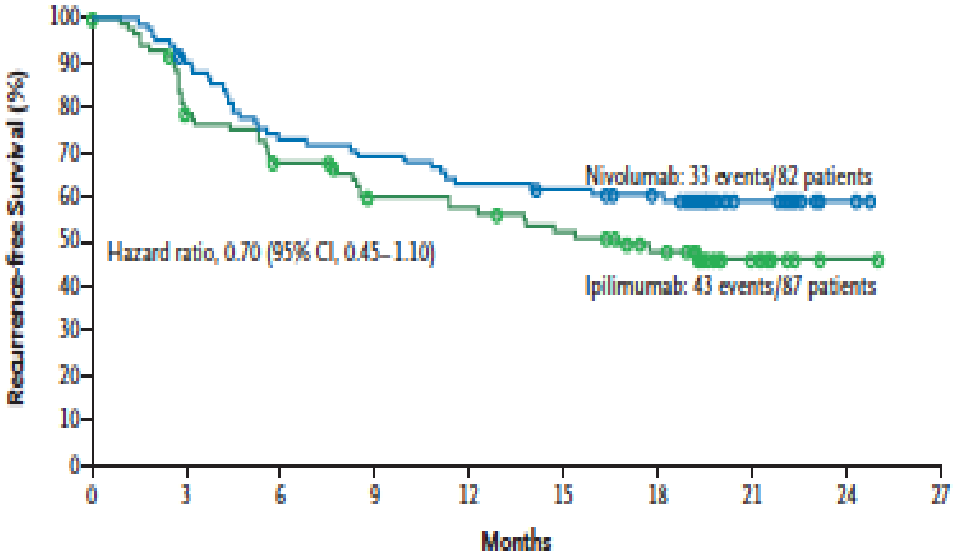
Eggermont *et al*. NEJM 2016

Adjuvant Nivolumab in Resected Stage IIIB-IV Melanoma

Stage IIIB and IIIC



Stage IV



- Approved by the FDA on December 20, 2017
- Management of patients with recurrence after adjuvant anti-PD-1 antibody immunotherapy will become an important issue in the field

Weber, J. et al. *NEJM*. 2017.

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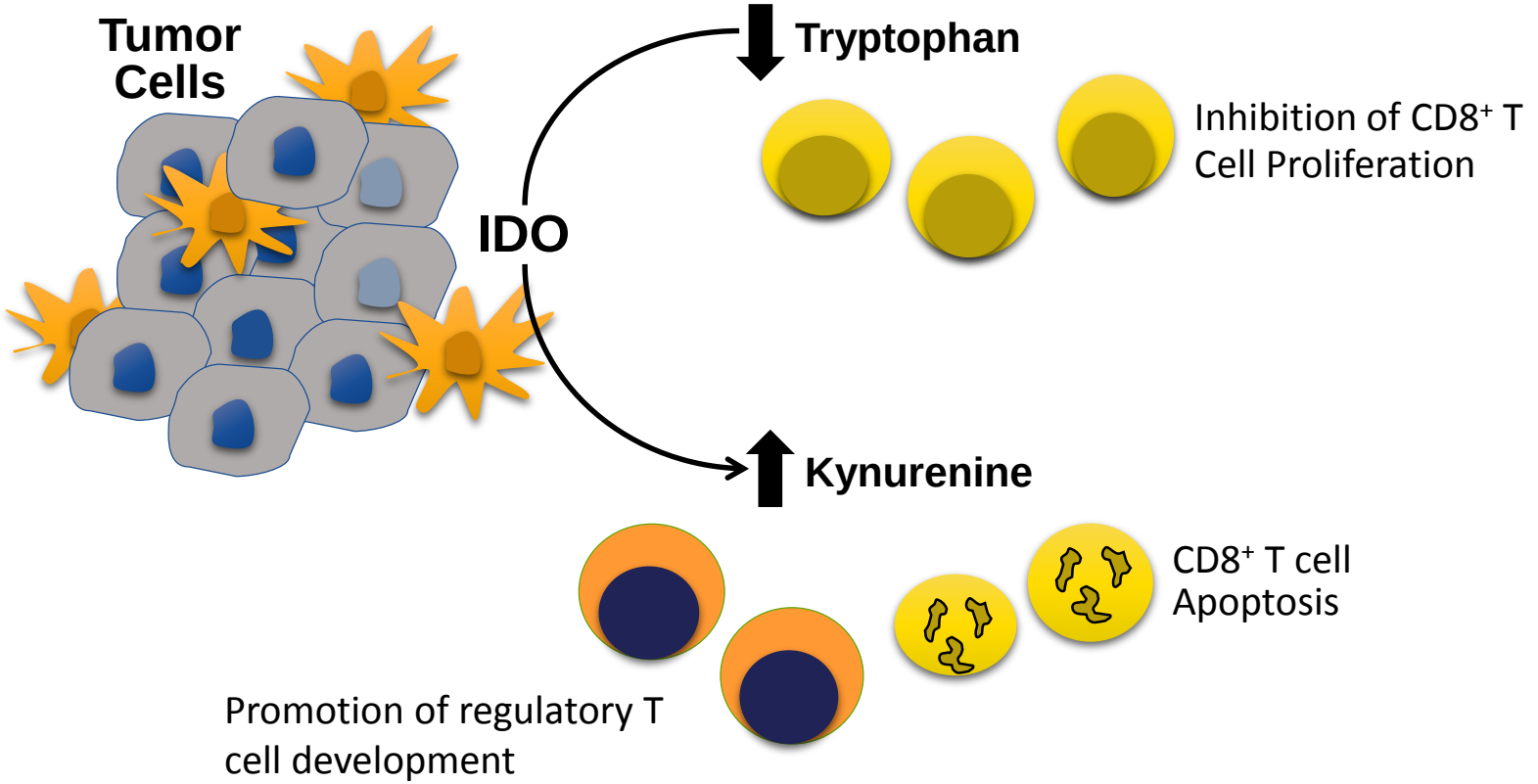
Indoleamine 2,3-dioxygenase (IDO)



Hanks, B. 2015 SITC-ACI Presentation

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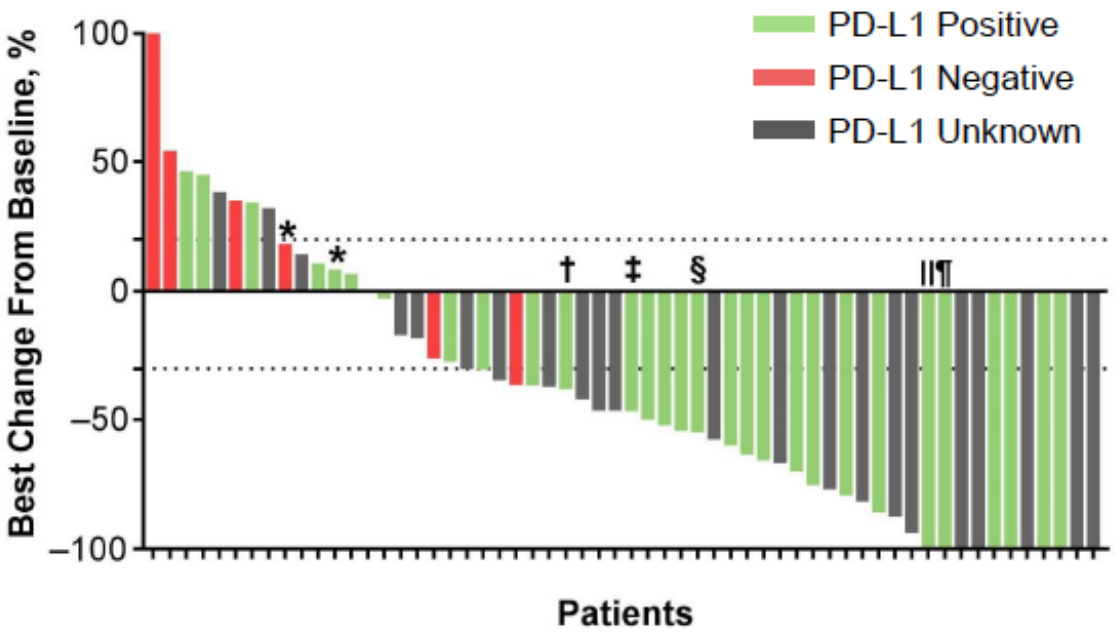
IDO Inhibitor Epacadostat + Pembrolizumab



- ORR 56%
- 33/40 patients PD-L1+
  - PD-L1+ 52% ORR
  - PD-L1- 14% ORR
- mPFS 12.4 months compared with ipi/nivo at 11.7 months
- 17% Grade 3/4 side-effects noted; 7% treatment discontinuation rate

- Phase 2 Study: epacadostat 100 mg po bid + pembrolizumab 200 mg IV every 3 weeks

Omid, H. et al. ESMO 2017.

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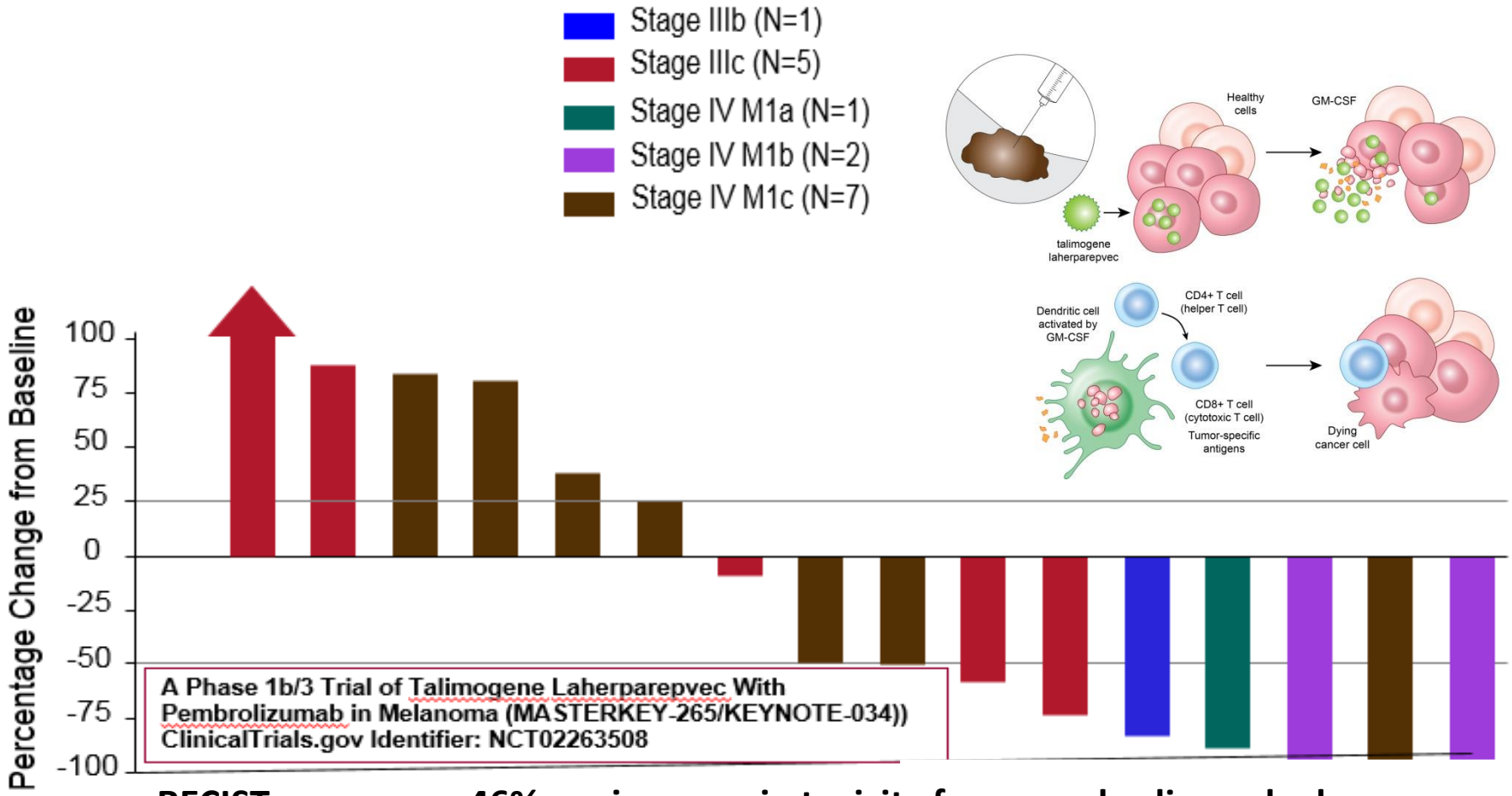
T-Vec + Pembrolizumab in Stage IIIB-IV Melanoma



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

Long et al. SMR 2015

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Conclusions

- Checkpoint inhibitor immunotherapy has revolutionized the management of metastatic melanoma, improving 1 yr survival from 25% to >70% in a span of 6 years
- Immunotherapy strategies represent the preferred 1st line treatment options in advanced melanoma patients
- Significant percentage of melanoma patients still do not benefit from currently available treatments
  - ~50% of melanoma patients fail to respond to combination checkpoint inhibitor immunotherapy
  - 25% of those patients that do respond to checkpoint inhibitor immunotherapy recur within 2 years
- Understanding immunotherapy resistance will drive the future of Melanoma immunotherapy
  - Development of predictive biomarkers
  - Development of synergistic immunotherapy combinations

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