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***Melanoma: The poster child for
immunotherapy***

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SITC Immunotherapy CME - June 23rd, 2016

Disclosures

- Consultancy:
 - Amgen
 - Array
- Research Grant Support to Institution:
 - Bristol-Myers Squibb
- Clinical Trial Support to Institution:
 - Novartis, MedImmune, Bristol-Myers Squibb, Pharmacyclics, Merck, BBI Therapeutics, Five Prime Therapeutics, Genentech, Corvus Pharmaceuticals, Delcath, Abbvie, Celldex, EMD Serono, Incyte
- I will discuss the investigational use of pembrolizumab and TVEC



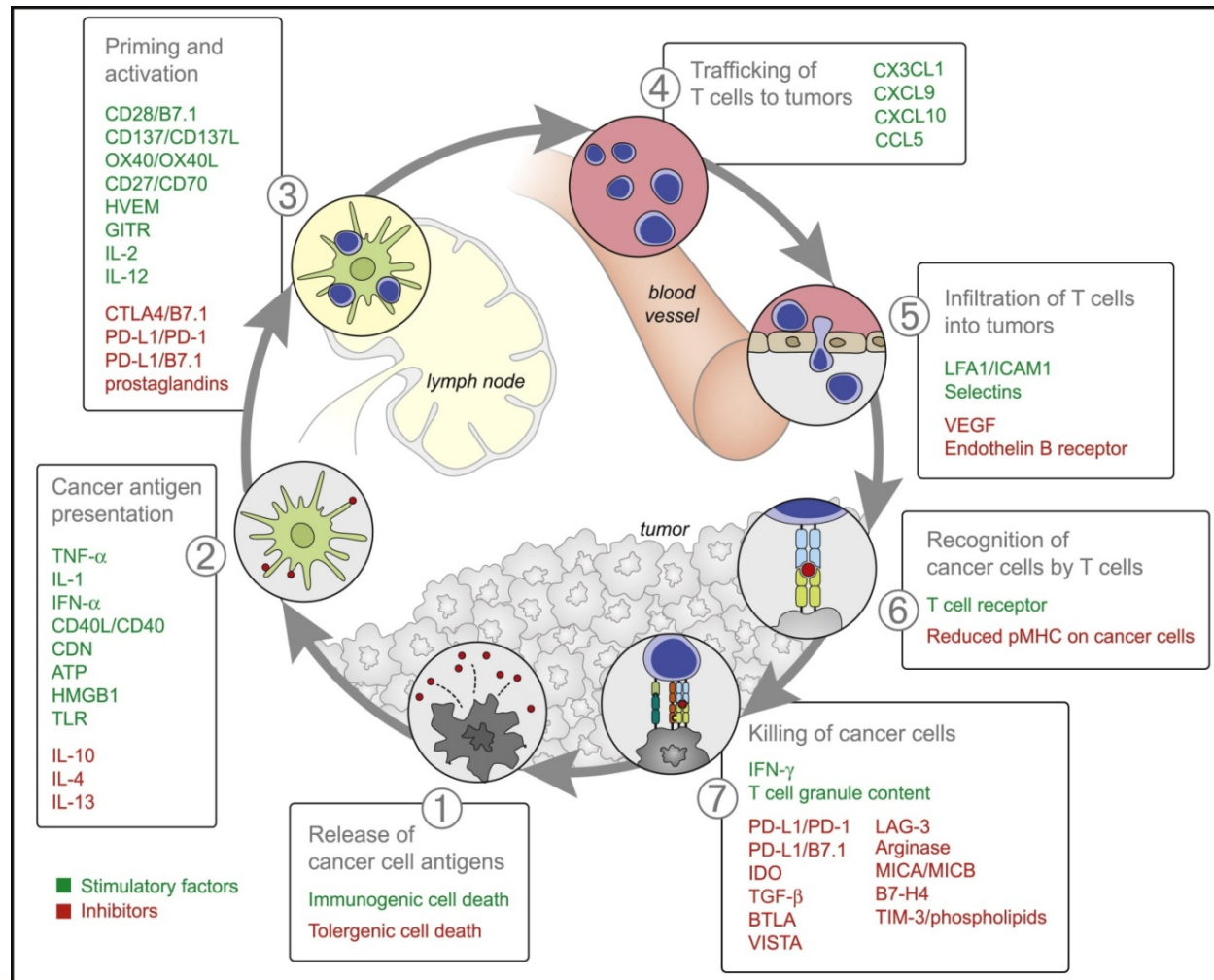
Learning objectives

- To describe the available forms of immunotherapy for melanoma
- To describe mechanism of action and management of adverse events with immune-checkpoint immunotherapy
- To discuss the future of immunotherapy for melanoma and all cancer

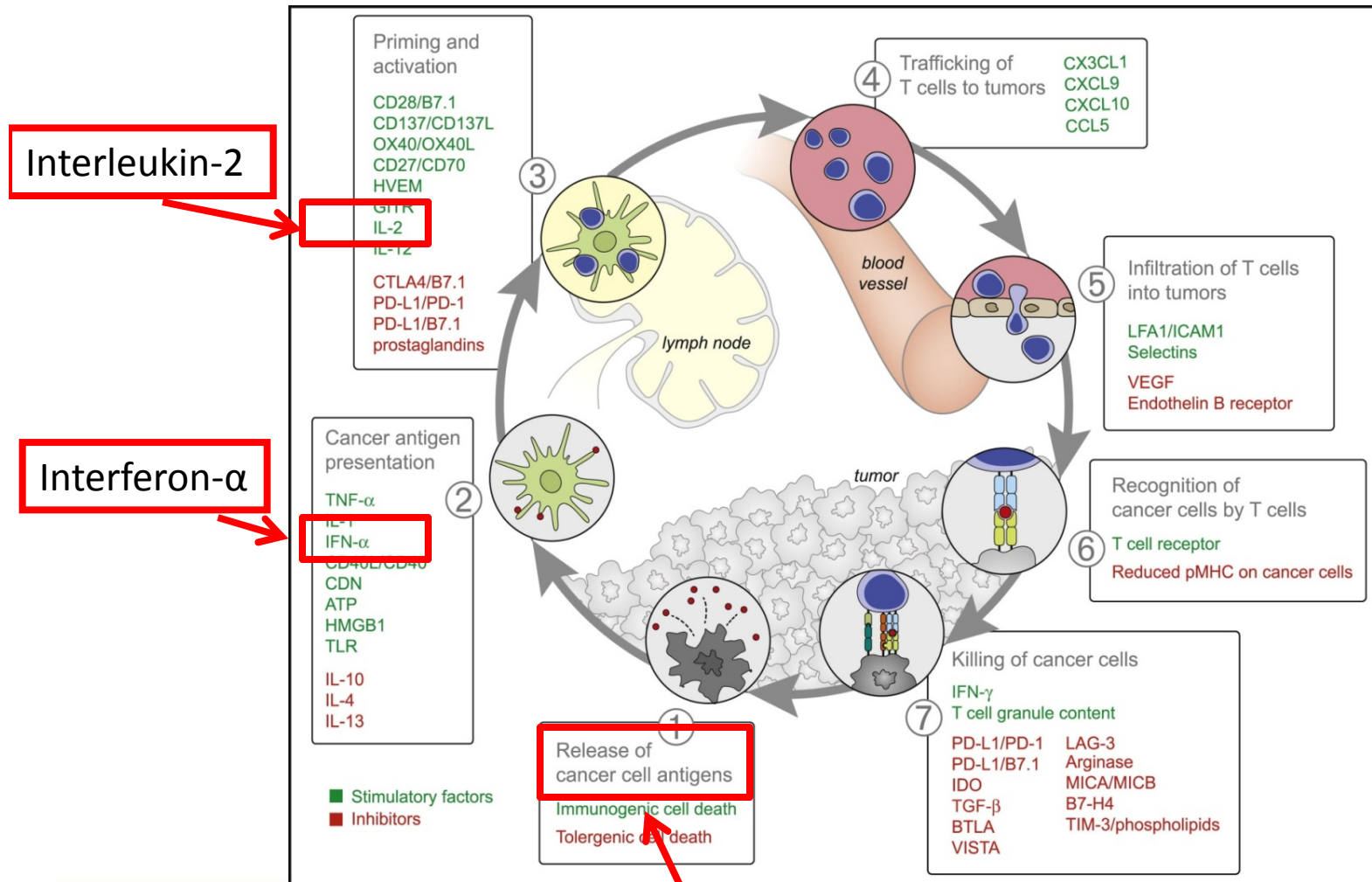


What are immunotherapy treatments?

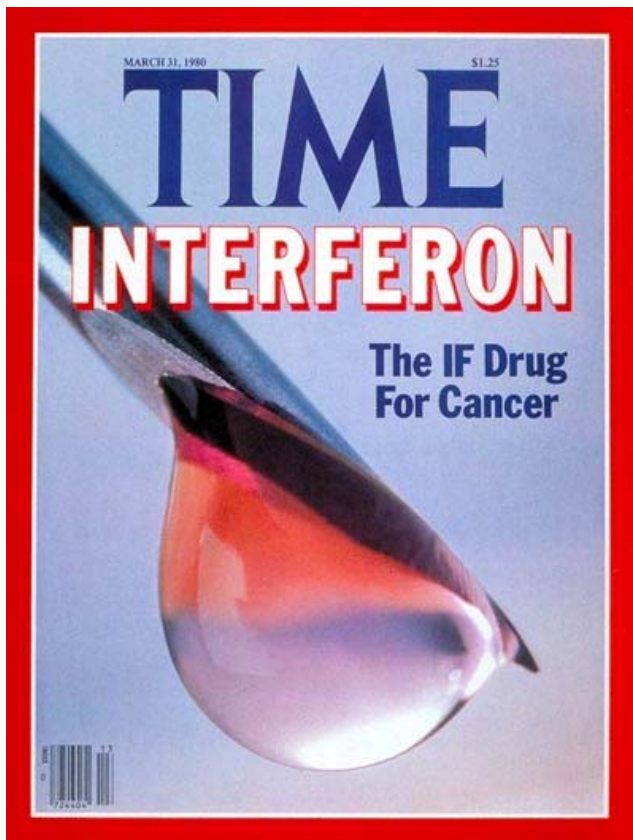
The “Cancer Immunity Cycle”



Cytokines and Oncolytic Viruses

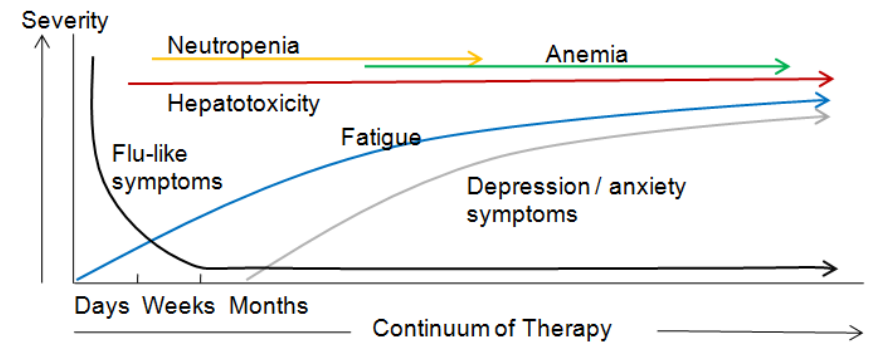
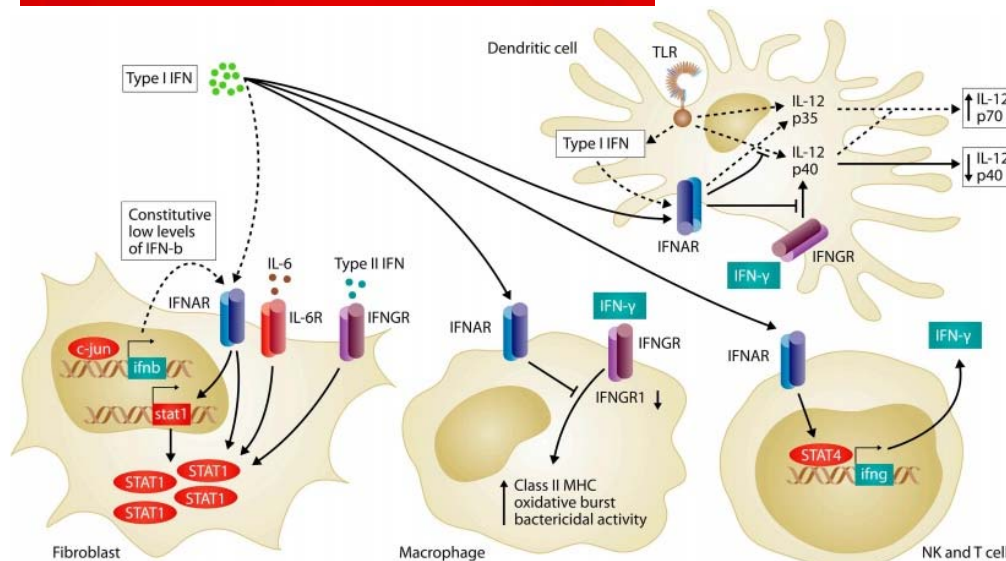
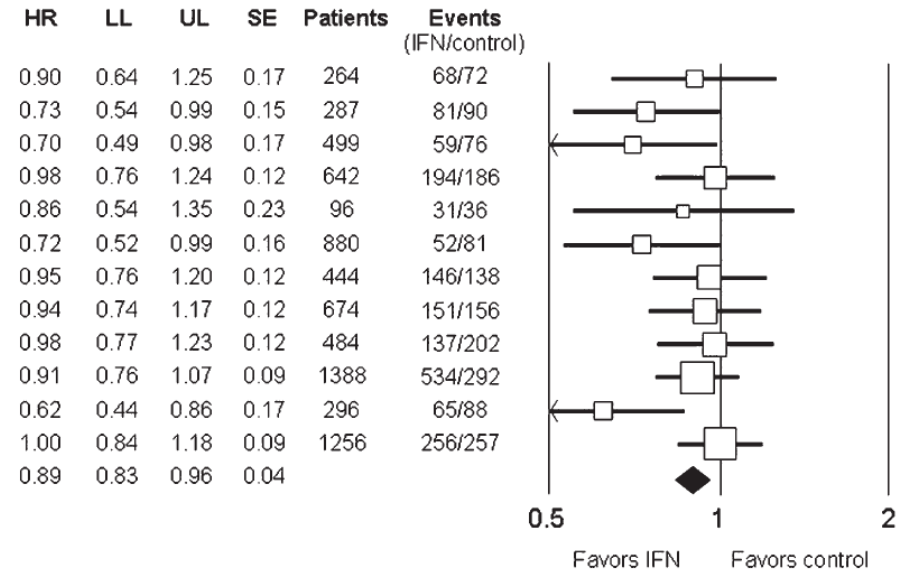


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Adjuvant Interferon- α

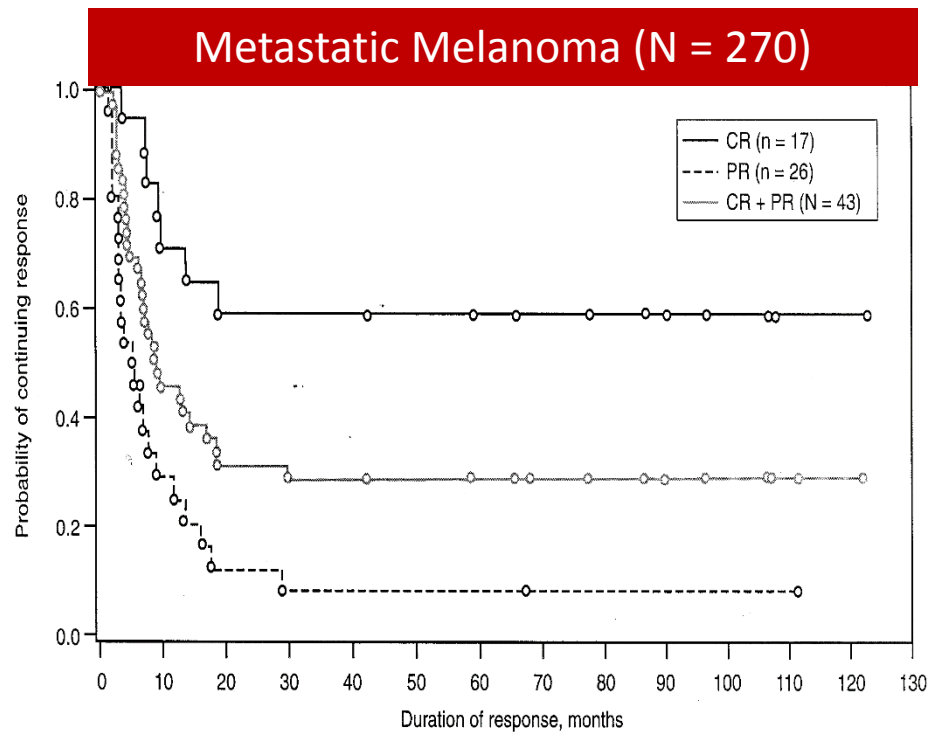
NCCTG (Creagan, 1995)	0.90	0.64	1.25	0.17	264	68/72
E1684 (Kirkwood, 1996)	0.73	0.54	0.99	0.15	287	81/90
FCGM (Grob, 1998)	0.70	0.49	0.98	0.17	499	59/76
E1690 (Kirkwood, 2000)	0.98	0.76	1.24	0.12	642	194/186
SMG (Cameron, 2001)	0.86	0.54	1.35	0.23	96	31/36
E1694 (Kirkwood, 2001)	0.72	0.52	0.99	0.16	880	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



Time Magazine, March 31st, 1980
Trinchieri, J Exp Med. 2010
Mocellin et al. JNCI. 2010
<http://www.sinobiological.com/Interferon-Side-Effects-a-6085.html>

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 1997

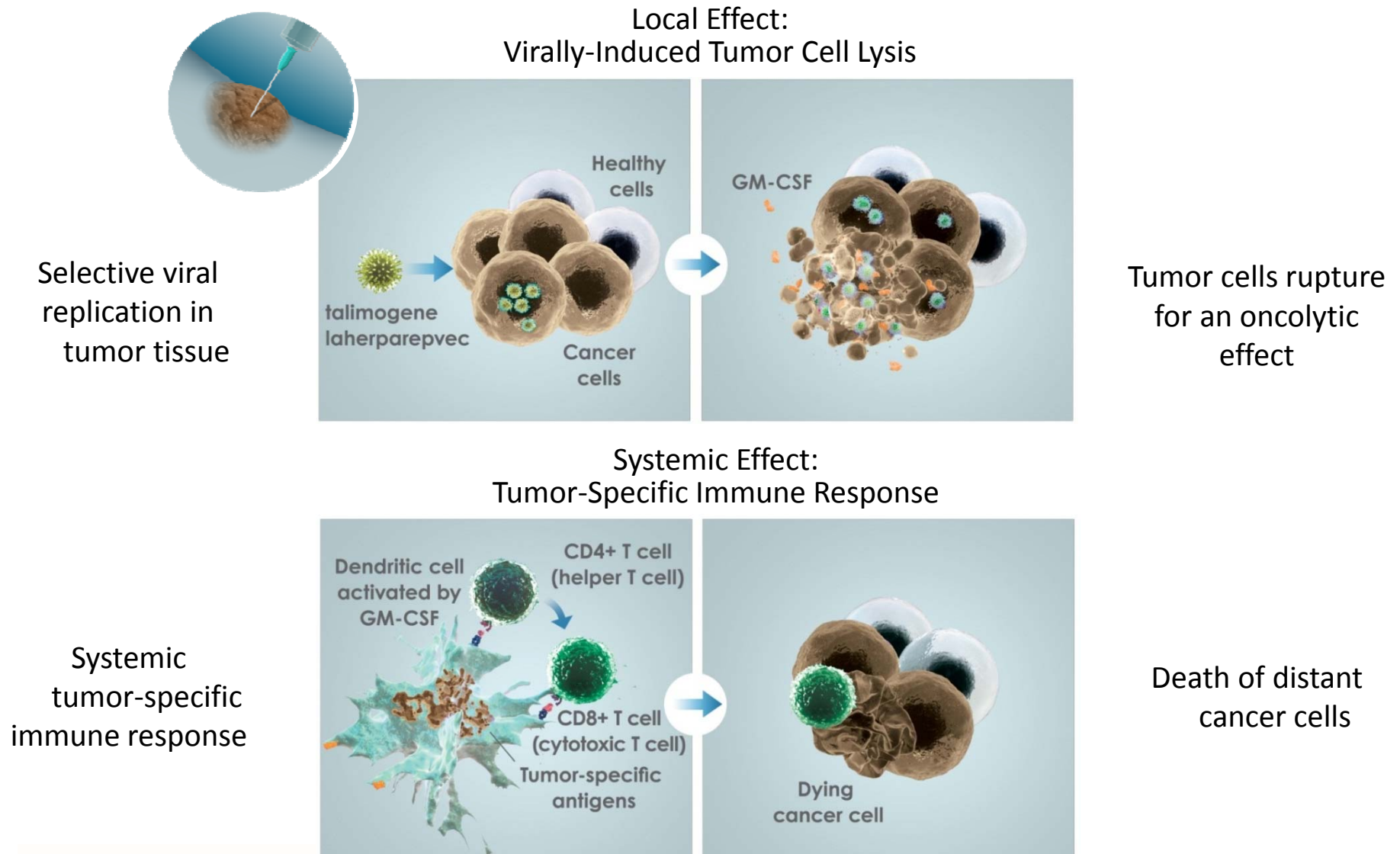


HD IL-2 Therapy in Melanoma

- High-dose IL-2 benefits some patients **BUT**
 - Toxic
 - Expensive
 - Inpatient procedure
- Use limited to well-selected patients at experienced centers
- Efforts to better select patients who might benefit from HD IL-2 therapy have not been particularly successful (NRAS?)



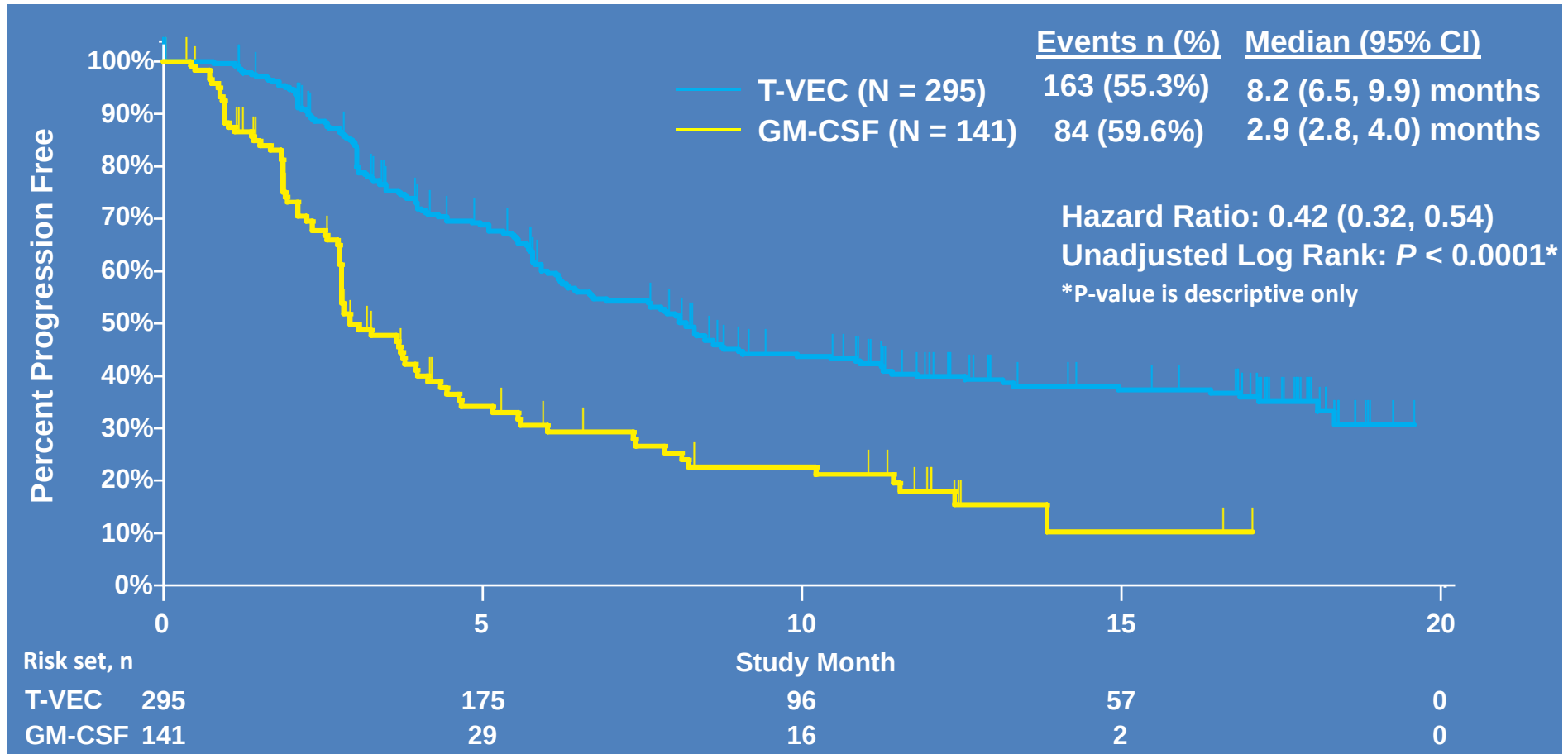
T-VEC: An HSV-1-Derived Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects



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Phase III trial of T-VEC vs GM-CSF

PFS Per Investigator

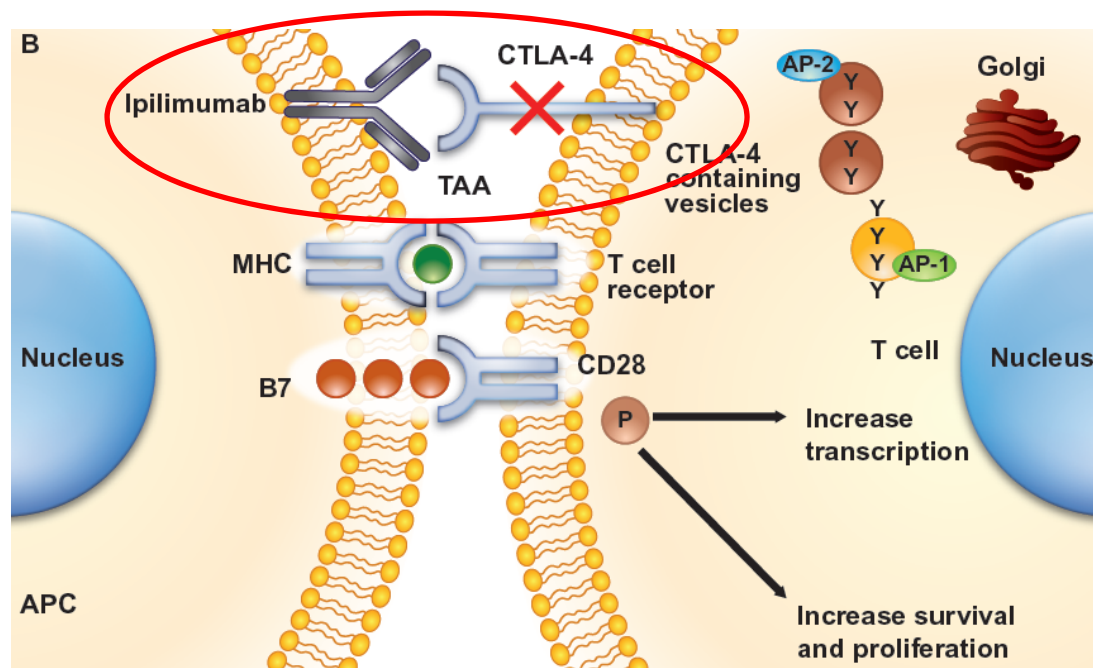


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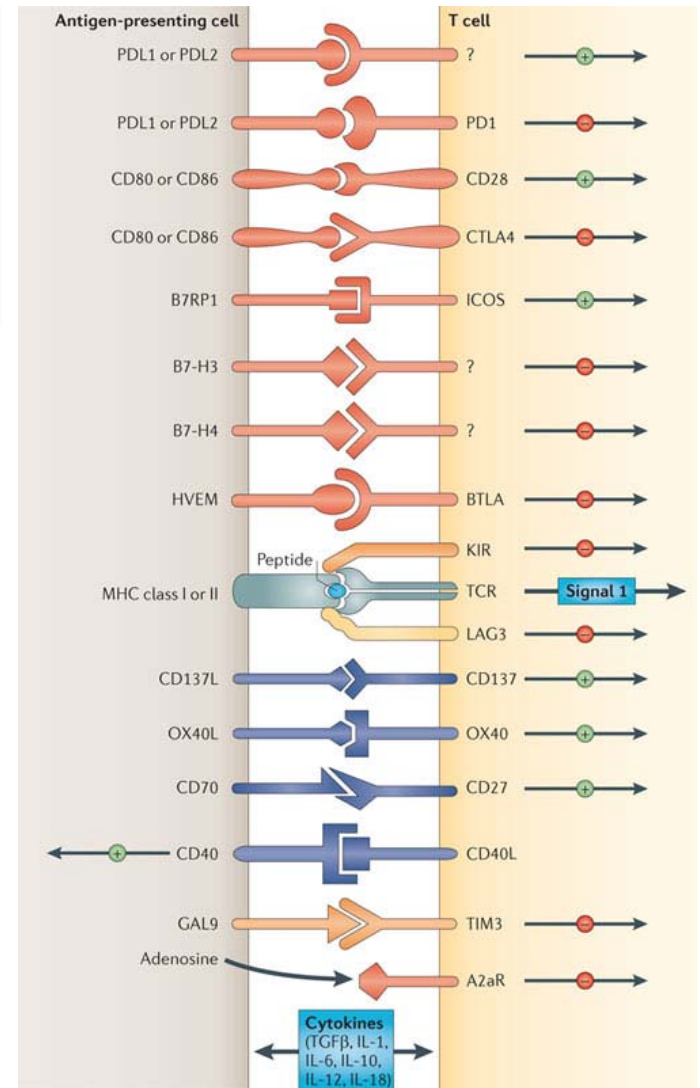


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Ipilimumab and Immune Check-Point Blockade



Luke et al, Oncologist 2013



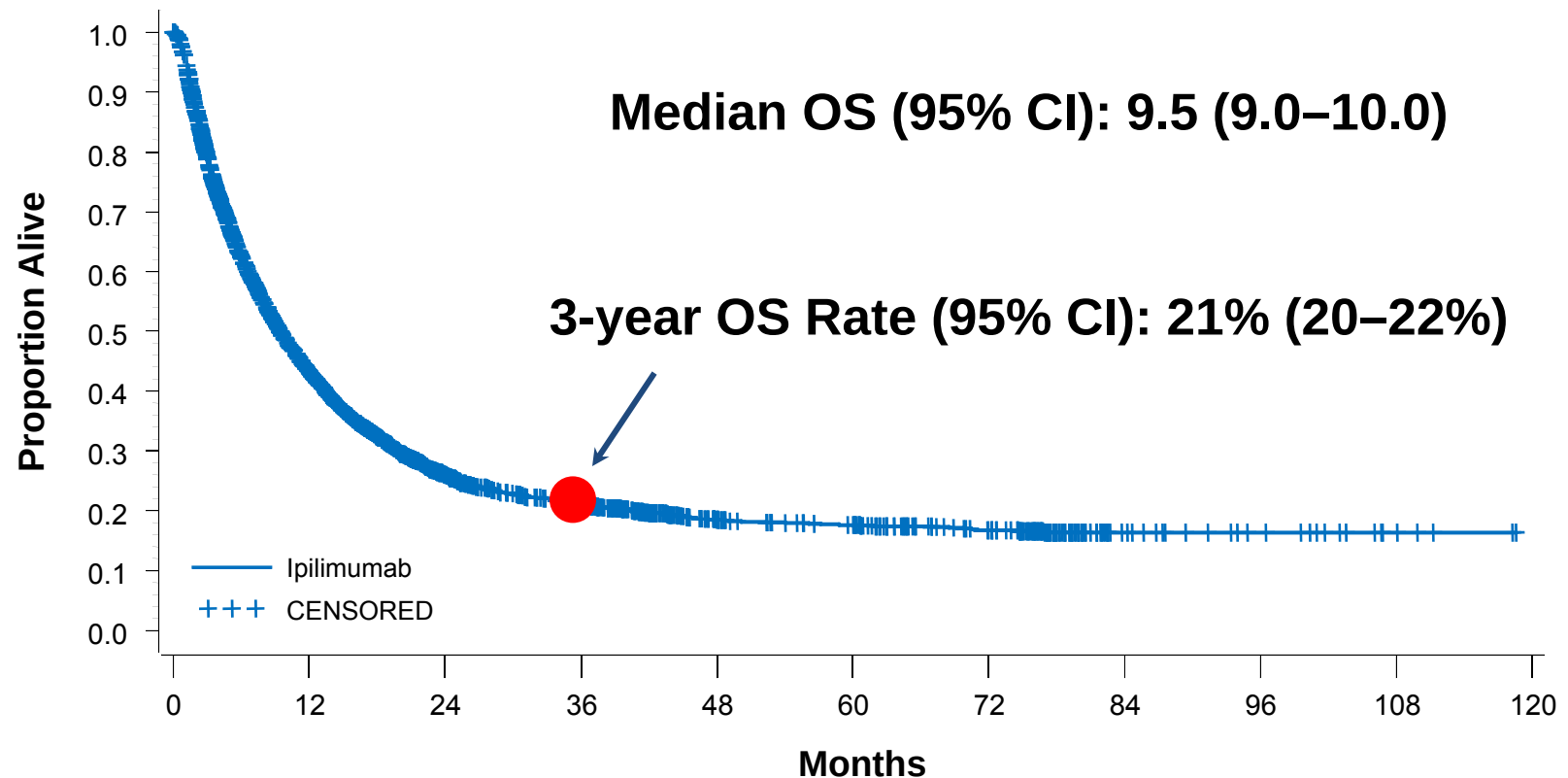
Nature Reviews | Cancer

Pardoll, Nat Rev Can 2012



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Pooled Overall Survival Analysis of 4846 Patients treated with ipilimumab



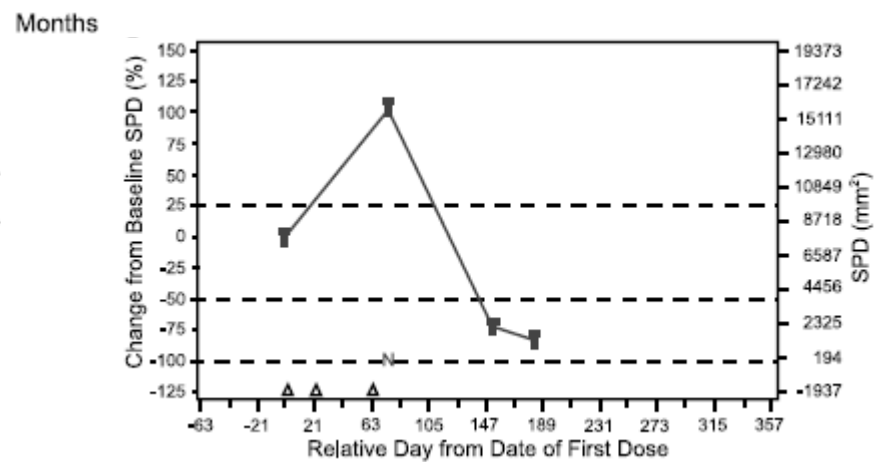
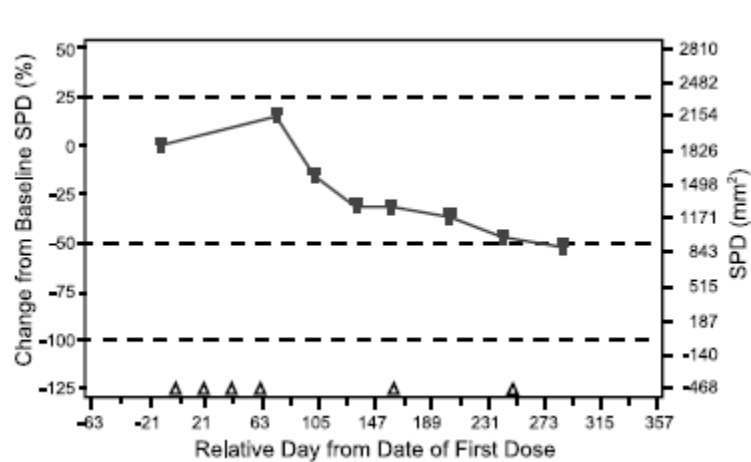
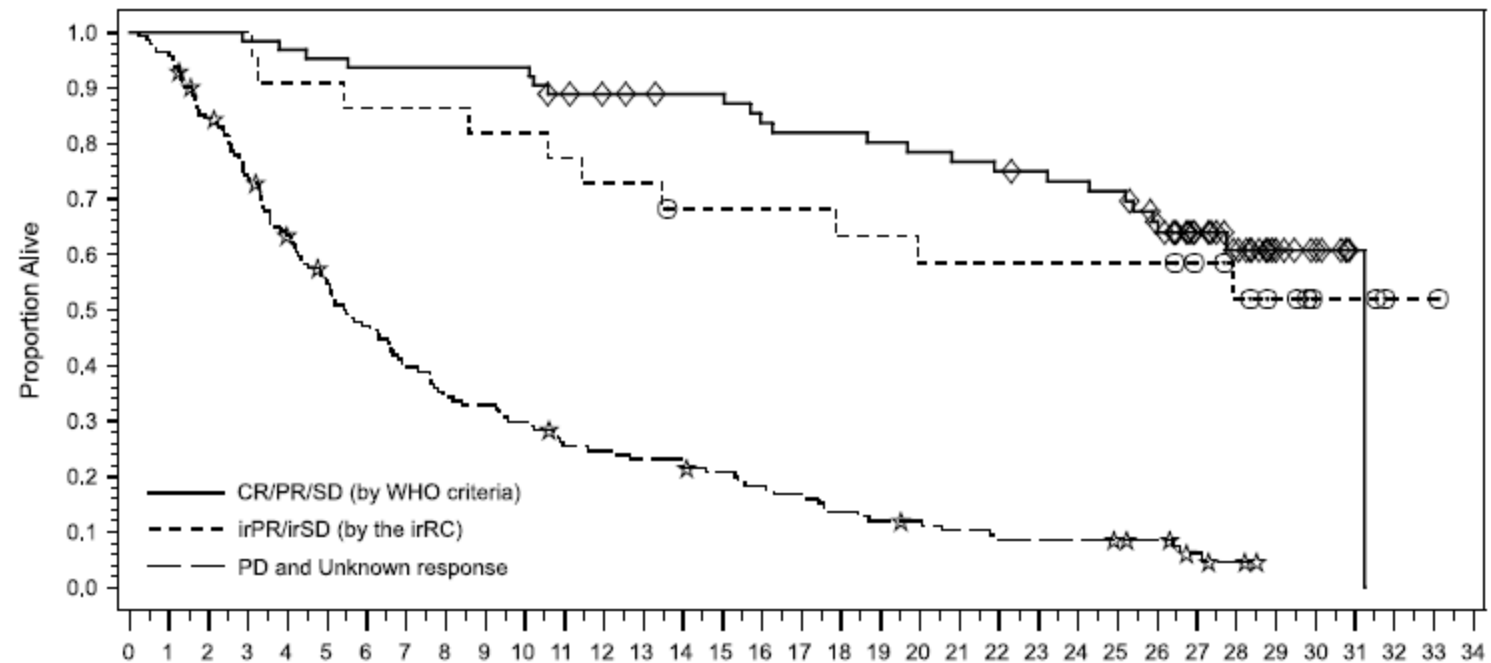
Patients at Risk

Months	0	12	24	36	48	60	72	84	96	108	120
Ipilimumab	4846	1786	612	392	200	170	120	26	15	5	0



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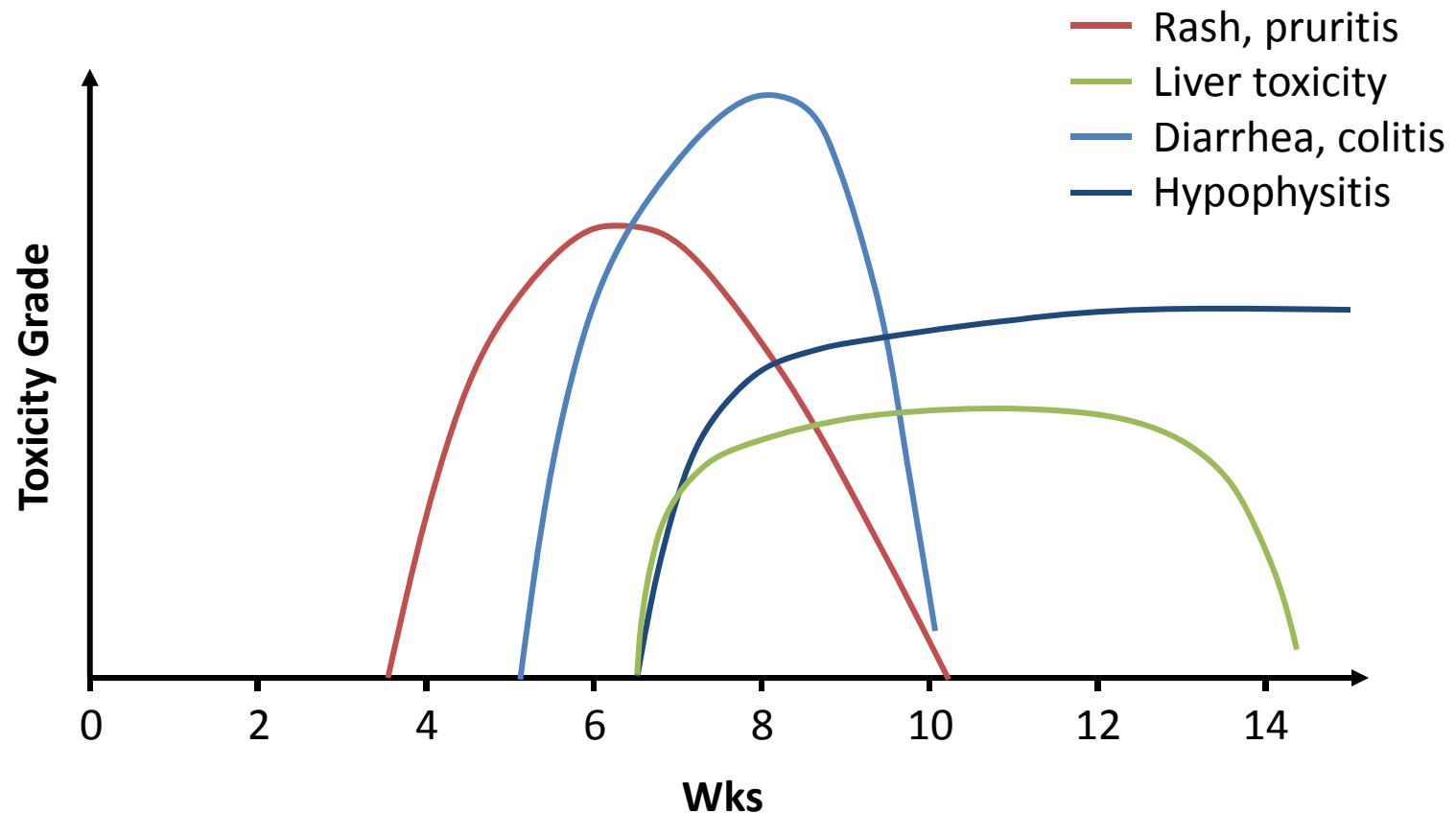
Immune Related Response Criteria



Ipilimumab Immune-Related Adverse Events From Phase III Trial

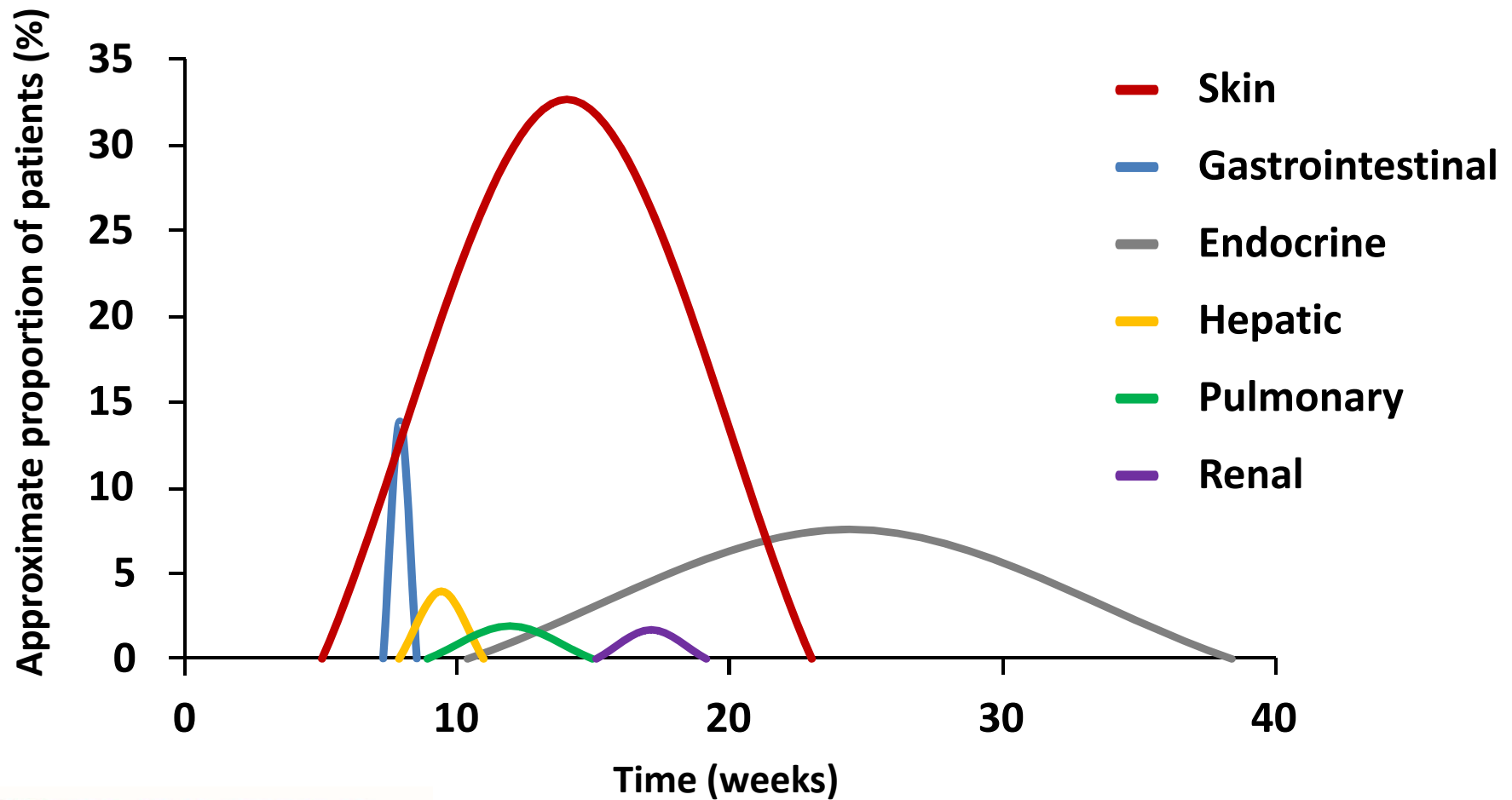
irAE, %	All grades (Gr 3/4)		
	Ipi + gp100 N=380	Ipi +pbo N=131	gp100 + pbo N=132
Any	57 (9.7/0.5)	60 (12.2/2.3)	32 (3.0/0)
Dermatologic	39 (2.1/0.3)	42 (1.5/0)	17 (0/0)
GI	31 (5.3/0.5)	28 (7.6/0)	14 (0.8/0)
Endocrine	3 (1.1/0)	8 (2.3/1.5)	2 (0/0)
Hepatic	2 (1.1/0)	3 (0/0)	4 (2.3/0)

Kinetics of Appearance of irAEs with Ipilimumab



PD-1 Blockade With Nivolumab

Kinetics of irAEs in Melanoma



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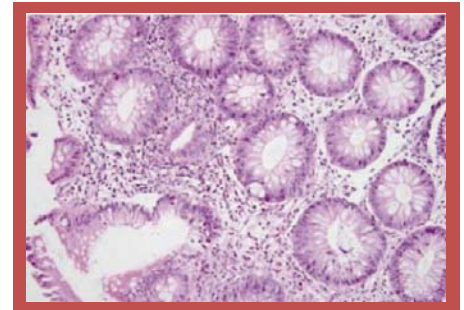
Gastrointestinal Inflammation

- Patterns: Minor irritation to Colitis to Perforation
- Evaluation
 - Calculate frequency and volume of diarrhea
 - Stool sample to rule-out infection (*C. difficile*, *O/P* etc.)
 - Abdominal ultrasound or CT scan
 - Colonoscopy (+/- biopsy)
 - Rule out other causes: perforation, peritonitis with pain, fever

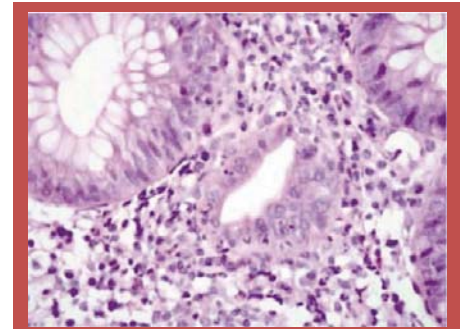
Ulceration in Descending Colon



Focal Active Colitis



Alterations in Crypt Epithelium



Grade	Management
Mild/grade 1: ≤ 4 stools/day above baseline	▪ Manage symptomatically (bland diet, PPI, antidiarrheal) ▪ Consider delaying tx until symptoms improve
Moderate/grade 2: increase of 4-6 stools/day above baseline (persistent)	▪ Colonoscopy and steroids ▪ Low-dose steroids may be sufficient ▪ Hold treatment
Severe/grade ≥ 3 : ≥ 7 stools/day above baseline	▪ Initiate high-dose steroids ▪ Discontinue treatment
Prevention	▪ No known methods

Dermatitis

- Symptoms: Onset 3-4 weeks
- Distribution on trunk, hands and feet
 - May be intense and widespread
- Stevens-Johnson syndrome, toxic epidermal necrolysis or mucosal/oral lesions very rare

Severity	Management
Mild/moderate (rash/pruritus)	▪ Topical nonsteroidal cream, antihistamine, oatmeal baths ▪ Skin care, moisturize, sunscreen, avoid sun
Persistent (> 1 wk) or interferes with ADLs	▪ Moderate-potency steroid creams or ▪ Moderate-dose parenteral steroids ▪ Dermatology referral
Severe	▪ Discontinue treatment ▪ High-dose steroids ▪ Avoid rapid steroid taper



Ocular Inflammation/Uveitis

- Pattern
 - Uveitis/ Iritis- inflammation of the colored portion of eye
 - Conjunctivitis: inflammation of conjunctiva
- Symptoms: painful, itchy watery eyes, decreased visual acuity, dry eyes
- Diagnosis:
 - Referral to ophthalmologist
 - Slit lamp evaluation
- Treatment: Corticosteroid eye drops

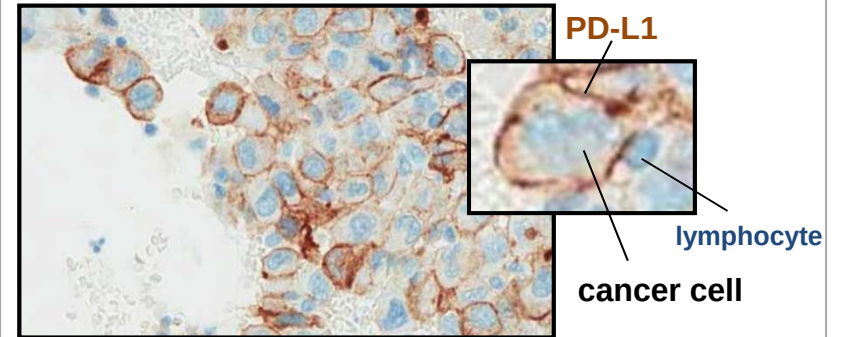
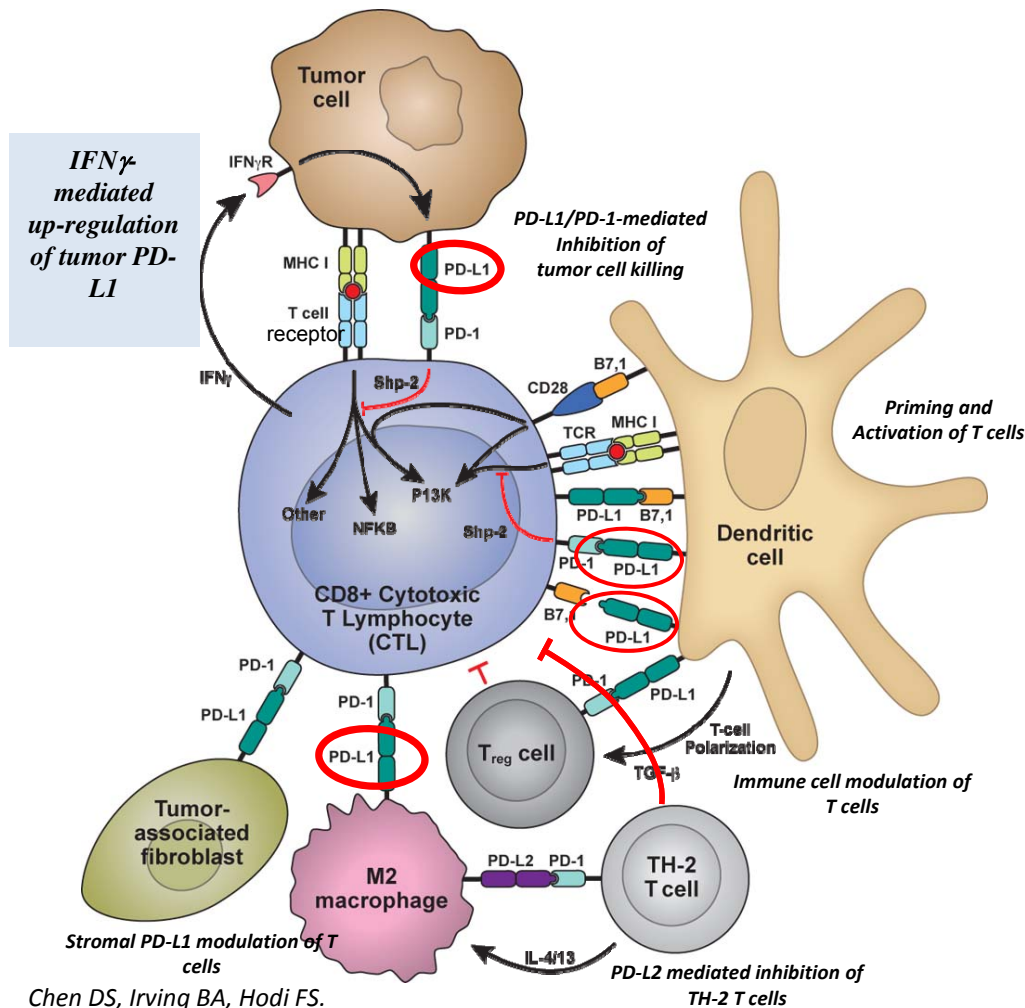


Ipilimumab and immune-checkpoint blockade: Managing irAEs

System	Symptoms	Management
GI tract	Diarrhea Abdominal pain Dark, bloody stools	Moderate enterocolitis: hold ipilimumab, administer antidiarrheal. Persistent diarrhea (> 1 wk): systemic corticosteroids. 7+ stools/day: start methylprednisone, permanently discontinue ipilimumab.
Skin	Principles of Managing irAEs: - Hold ipilimumab - Initiate steroids therapy (1–2 mg/kg of prednisone or equivalent daily) - Consider infliximab (if gastrointestinal toxicity) or mycophenolate (if hepatotoxicity) if steroids do not resolve symptoms	
Liver		
CNS		
Endocrine	Headaches Fatigue Behavior/mood changes Menstruation changes Dizziness/light-headedness	Moderate endocrinopathy: hold ipilimumab, start corticosteroids. Endocrine abnormalities can be difficult to detect, due to nonspecific symptoms. Consider having an endocrinologist follow the pt.
Eyes	Vision problems Irritation	Monitor for redness suggesting uveitis; treat with topical steroidal eye drops.



PD-L1 dampens the anti-tumor immune response



Presence of intratumoral T-cells may lead to adaptive immune resistance

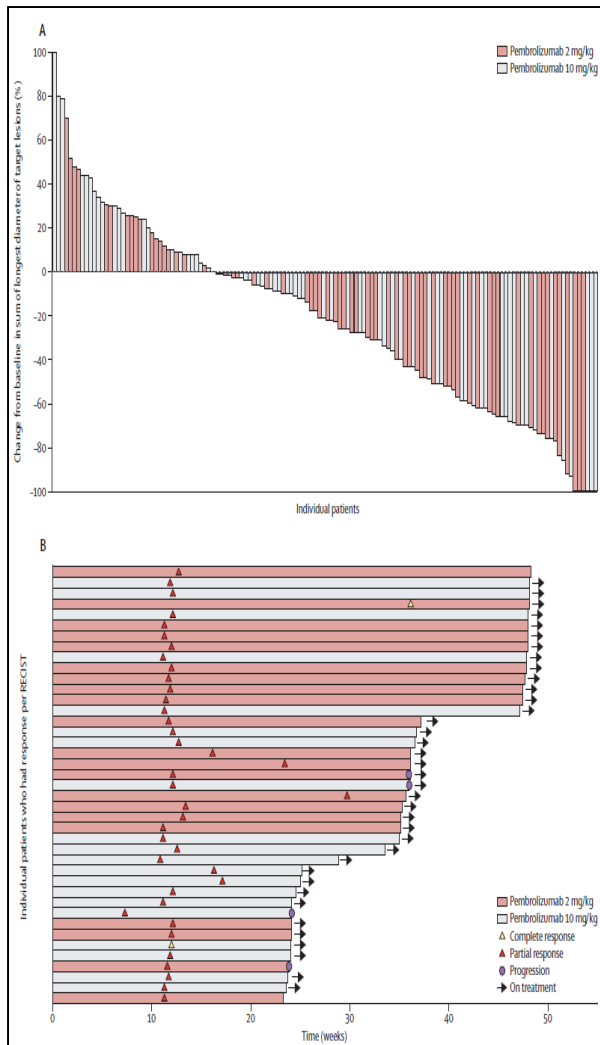
PD-L1 expression in the tumor microenvironment can inhibit anti-tumor T cell activity:

1. PD-L1 expression by tumor infiltrating **immune cells**
2. PD-L1 expression by **cancer cells**



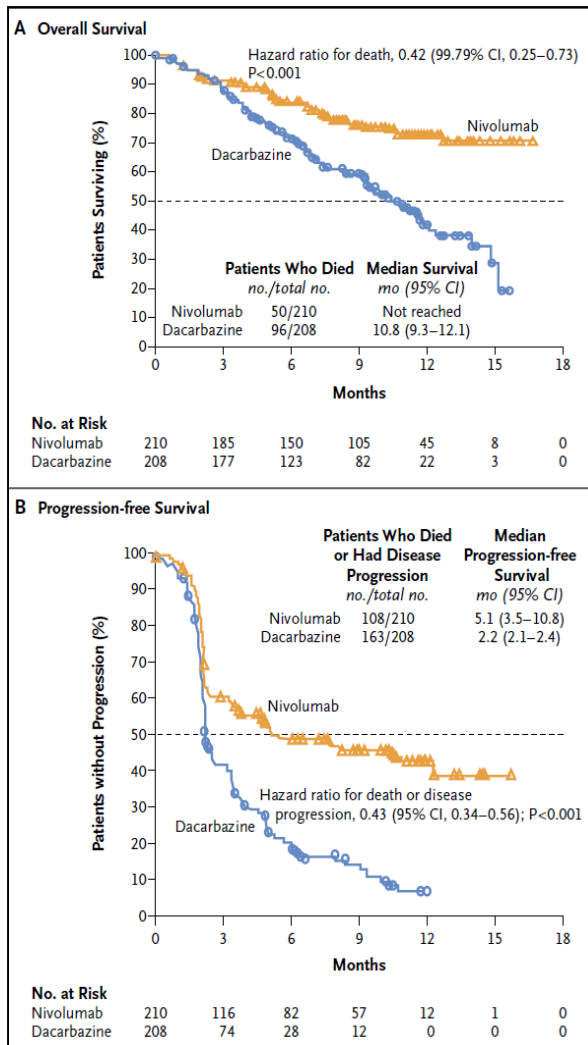
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Anti-PD1 (pembrolizumab) *after* ipilimumab in Melanoma



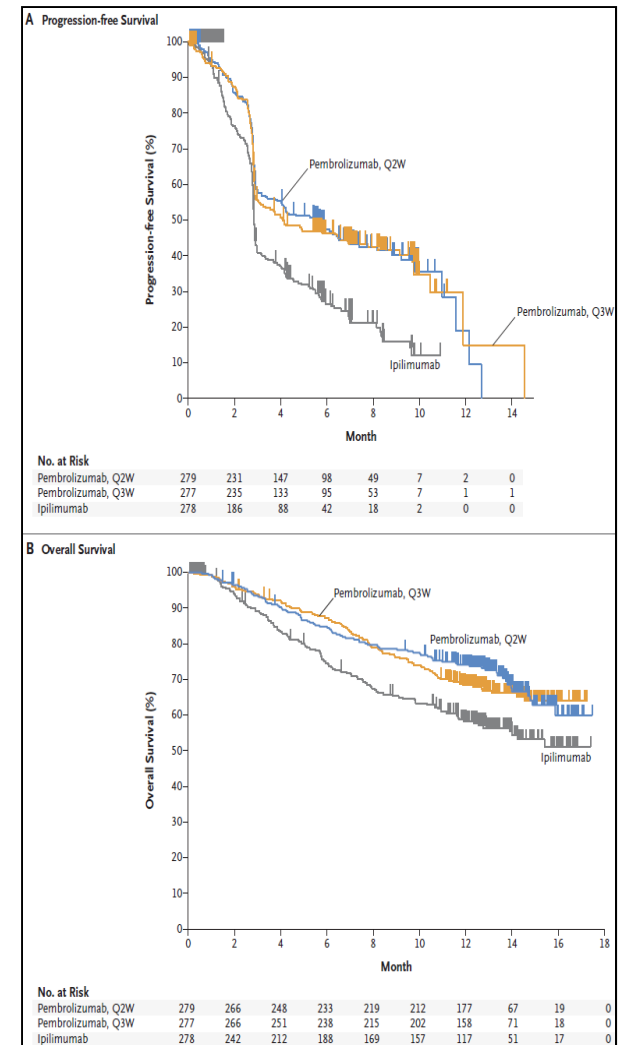
Robert et al, NEJM 2015

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



Robert et al, Lancet 2014

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



Robert et al, NEJM 2015

Pembrolizumab-Related Adverse Events

Adverse Event	All Grades, n (%)	Grade 3-4, n (%)
Any	107 (79.3)	17 (12.6)
Fatigue	41 (30.4)	2 (1.5)
Rash	28 (20.7)	3 (2.2)
Pruritus	28 (20.7)	1 (0.7)
Diarrhea	27 (20.0)	1 (0.7)
Myalgia	16 (11.9)	0
Headache	14 (10.4)	0
Increased AST	13 (9.6)	2 (1.5)
Asthenia	13 (9.6)	0
Nausea	13 (9.6)	0
Vitiligo	12 (8.9)	0
Hypothyroidism	11 (8.1)	1 (0.7)
Increased ALT	11 (8.1)	0
Cough	11 (8.1)	0
Pyrexia	10 (7.4)	0
Chills	9 (6.7)	0
Abdominal pain	7 (5.2)	1 (0.7)



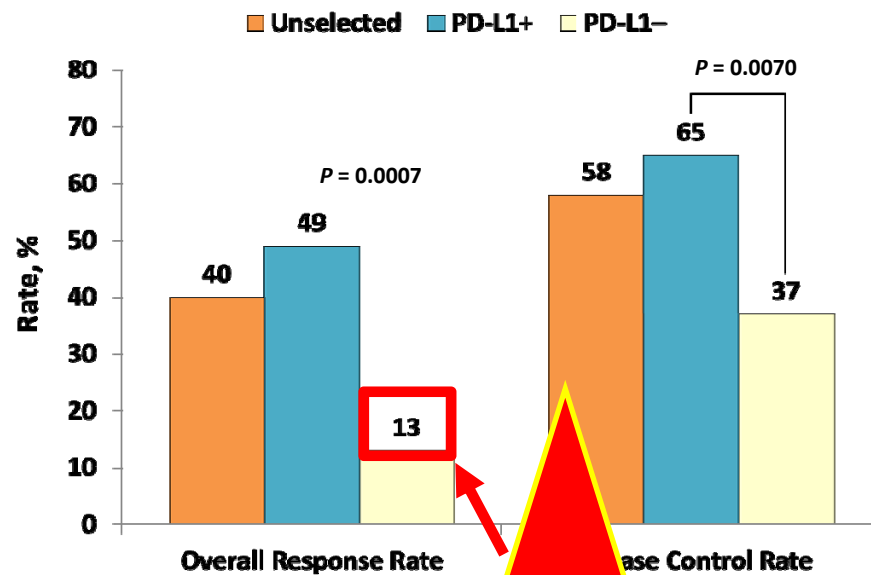
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Observed in >5% of Patients (N = 135)

Ribas A, et al. ASCO 2013. Abstract 9009.

Value of PD-L1 IHC as a Biomarker?

Response to Pembrolizumab by PD-L1



13% response
rate in PD-L1
negative
melanoma is
higher than
chemotherapy or
ipilimumab

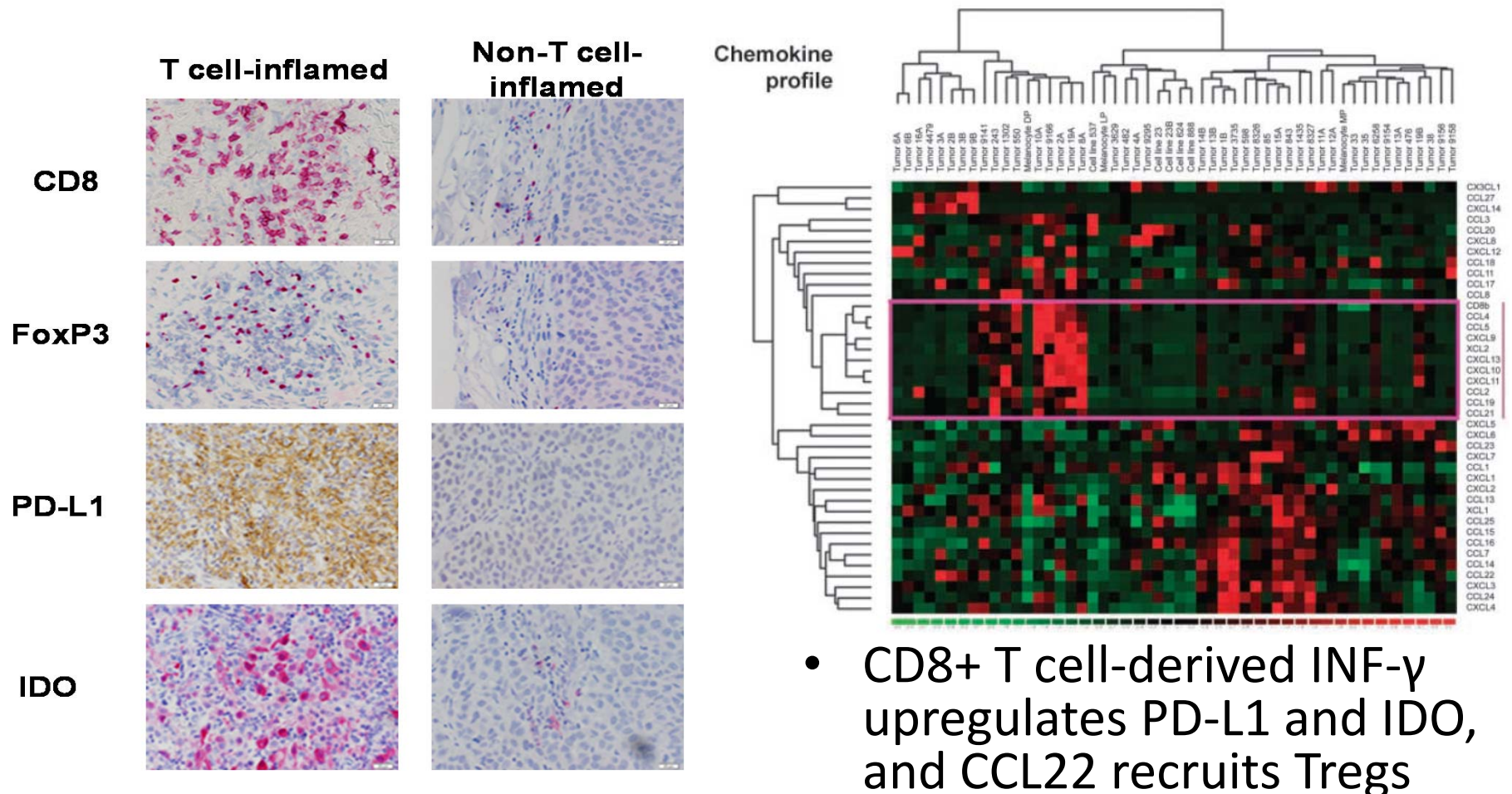
PD-L1 Immunohistochemistry assays from industry

	1	2	3	4	5
Antibody Clone	5H1 Yale	28-8 Dako - BMS	22C3 Dako - Merck	SP142 Ventana - Genentech	SP263 Ventana - MedImmune
Automated	No	Yes	Yes	Yes	Yes
Staining location scored	Membrane	Membrane	Membrane	Membrane	Membrane
Cell type(s) scored	Tumor cells	Tumor cells	Tumor and/or infiltrating immune cells	Infiltrating immune cells	Infiltrating immune cells
"Positive" cut-point	≥5%	≥5%	≥1%	≥1% to ≥10% ("IHC 1-2-3")	≥1% to ≥10% ("IHC 1-2-3")

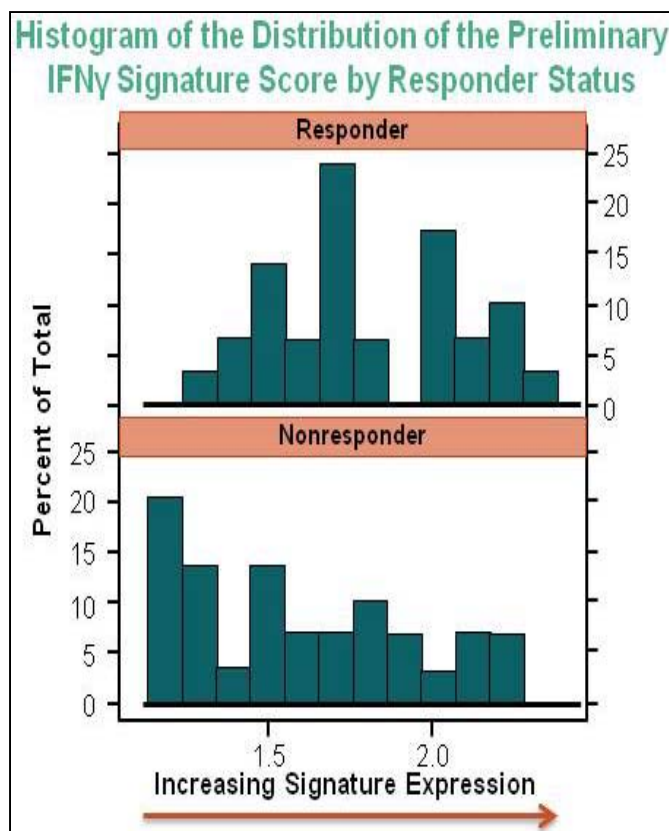


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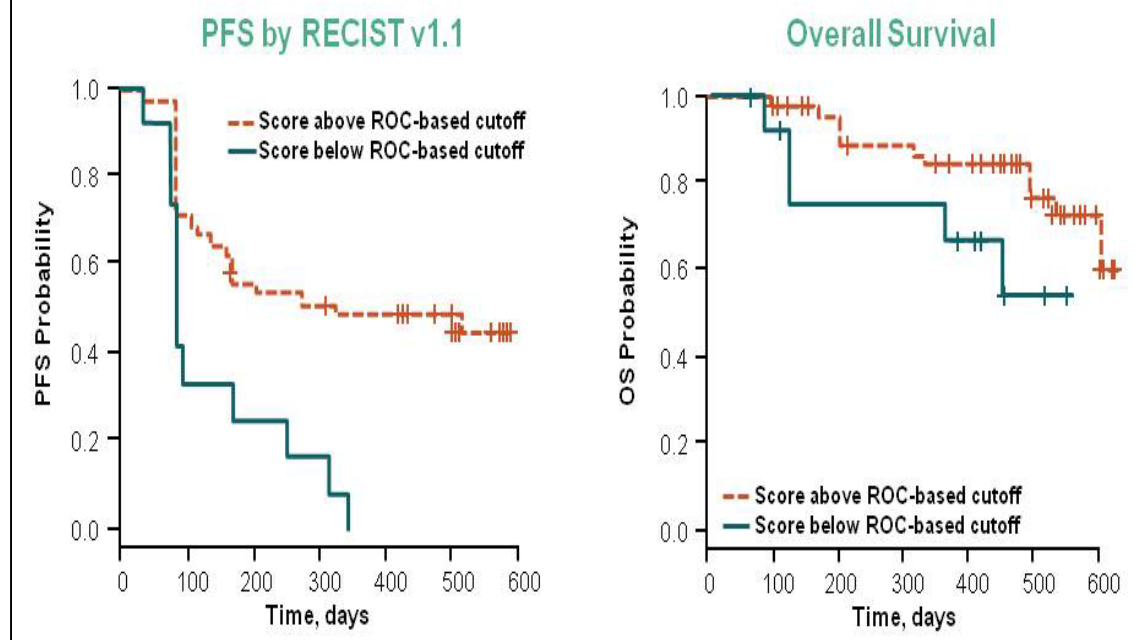
The T cell-inflamed tumor microenvironment is characterized by high expression of immune-inhibitory pathways, including FoxP3+ Tregs, PD-L1, and IDO.



Interferon- γ gene expression signature (Melanoma, Gastric, HNSCC, Urothelial)



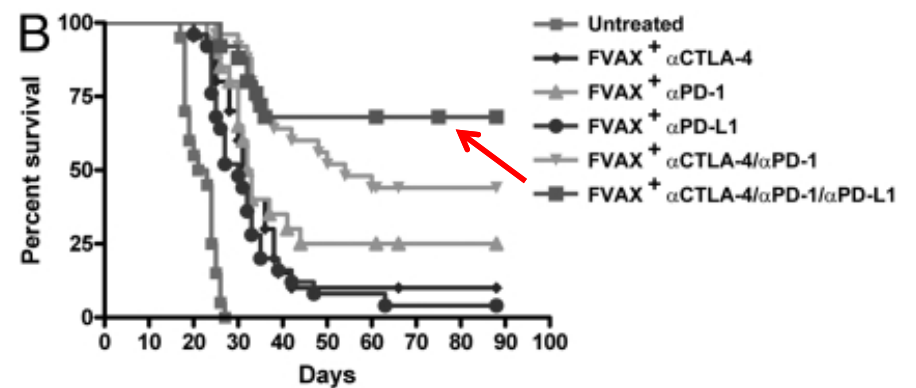
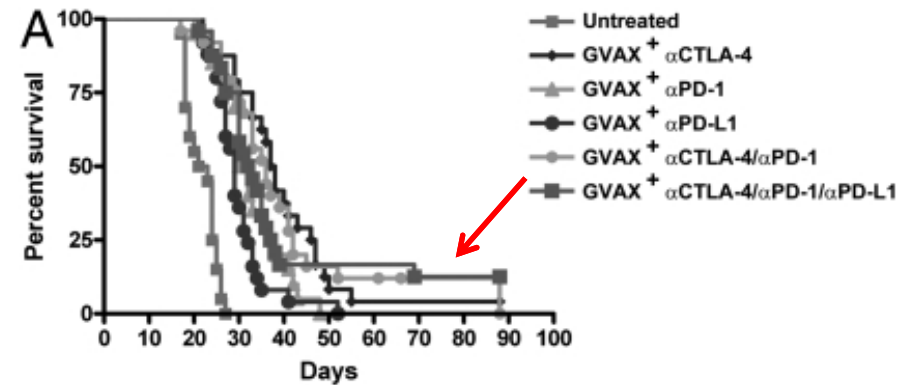
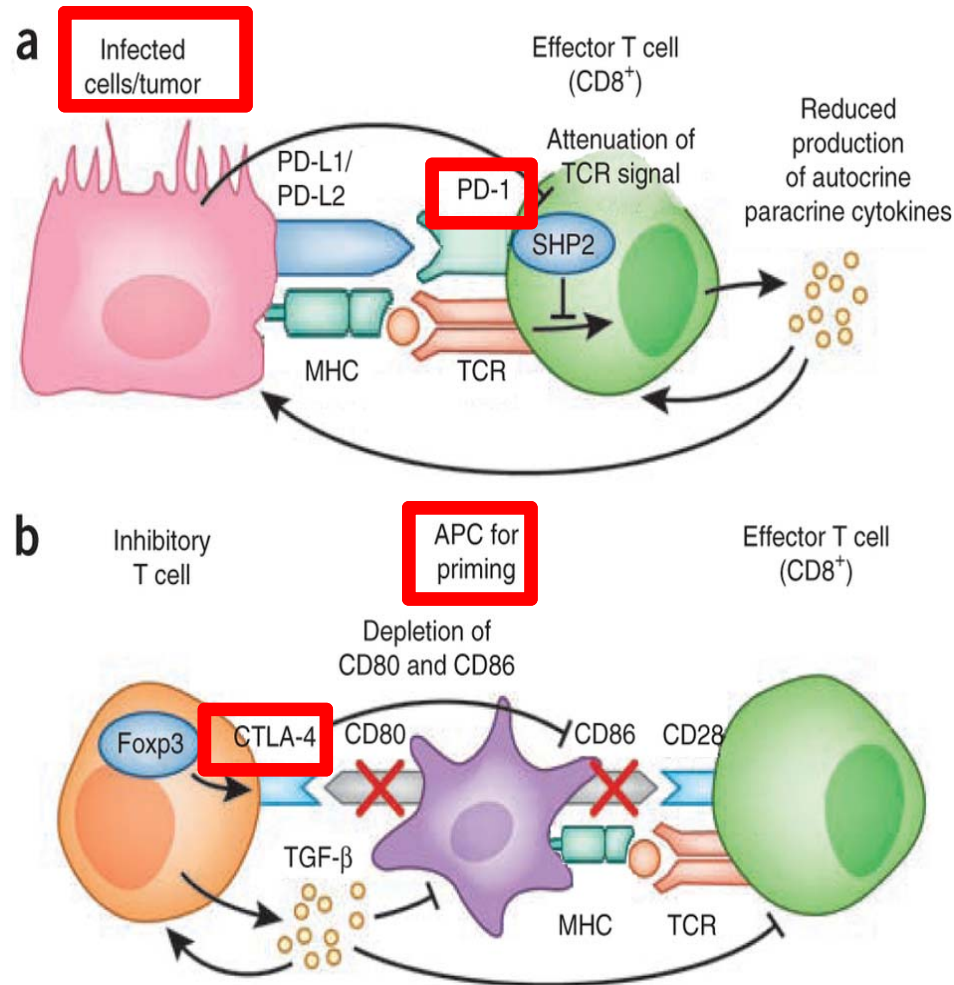
PFS and OS in Patients With Melanoma and IFN γ Signature Score Above and Below the Cutoff



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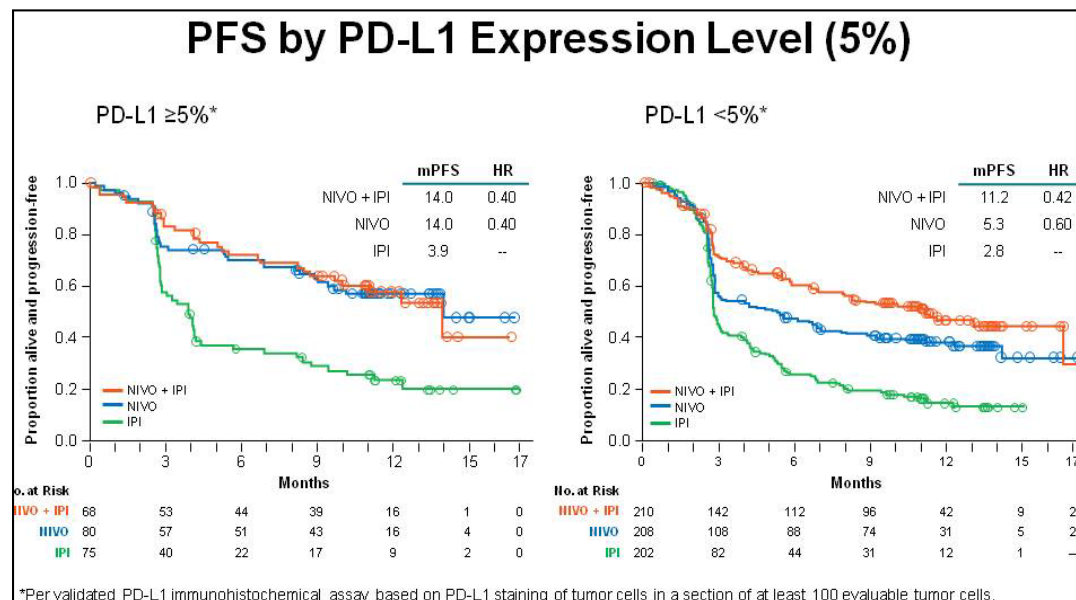
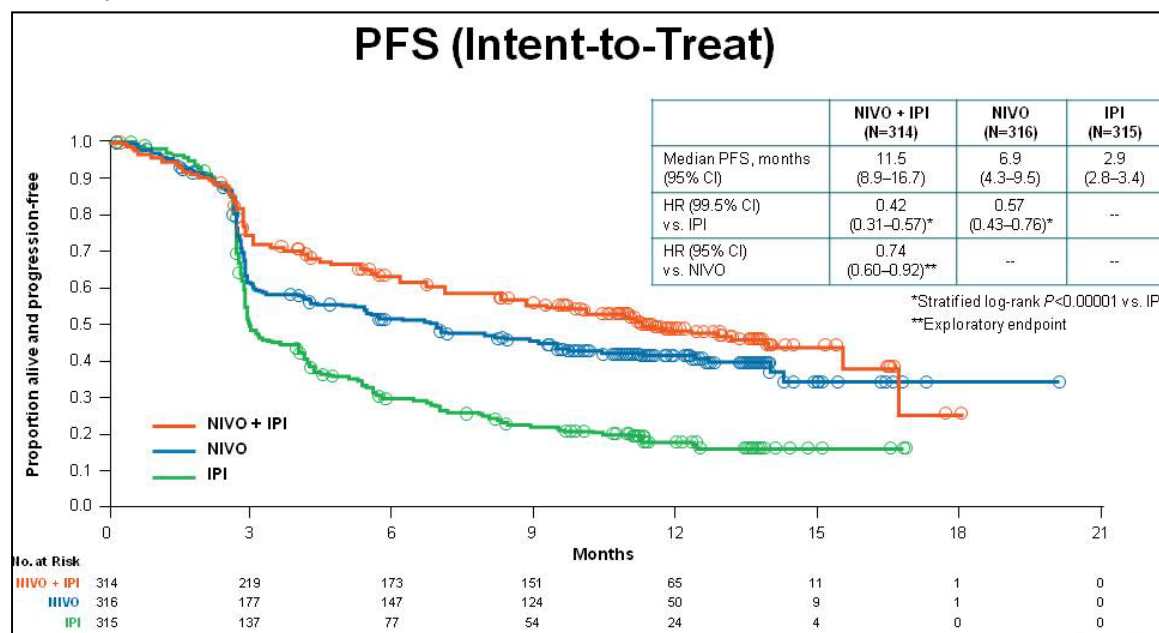
Presented By Antoni Ribas at 2015 ASCO Annual Meeting - J Clin Oncol 33, 2015 (suppl; abstr 3001)

Combining Anti-CTLA4 and Anti-PD1 Antibodies



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)



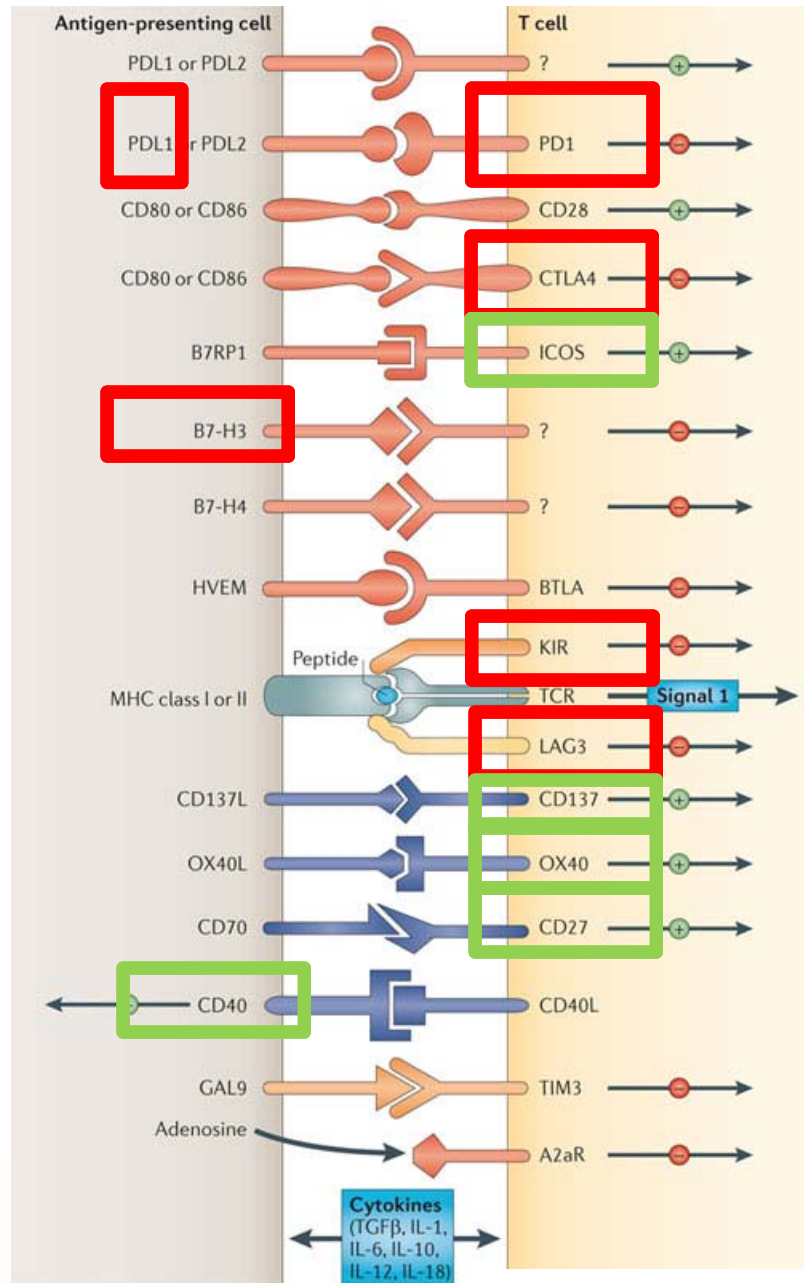
Safety Summary

	NIVO + IPI (N=313)	NIVO (N=313)	IPI (N=311)
Patients Reporting Event, %			
	Any Grade	Grade 3–4	Any Grade
	Any Grade	Grade 3–4	Any Grade
Treatment-related adverse event (AE)	95.5	55.0	82.1
Treatment-related AE leading to discontinuation	36.4	29.4	7.7
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

What is the future: **COMBINATIONS!**

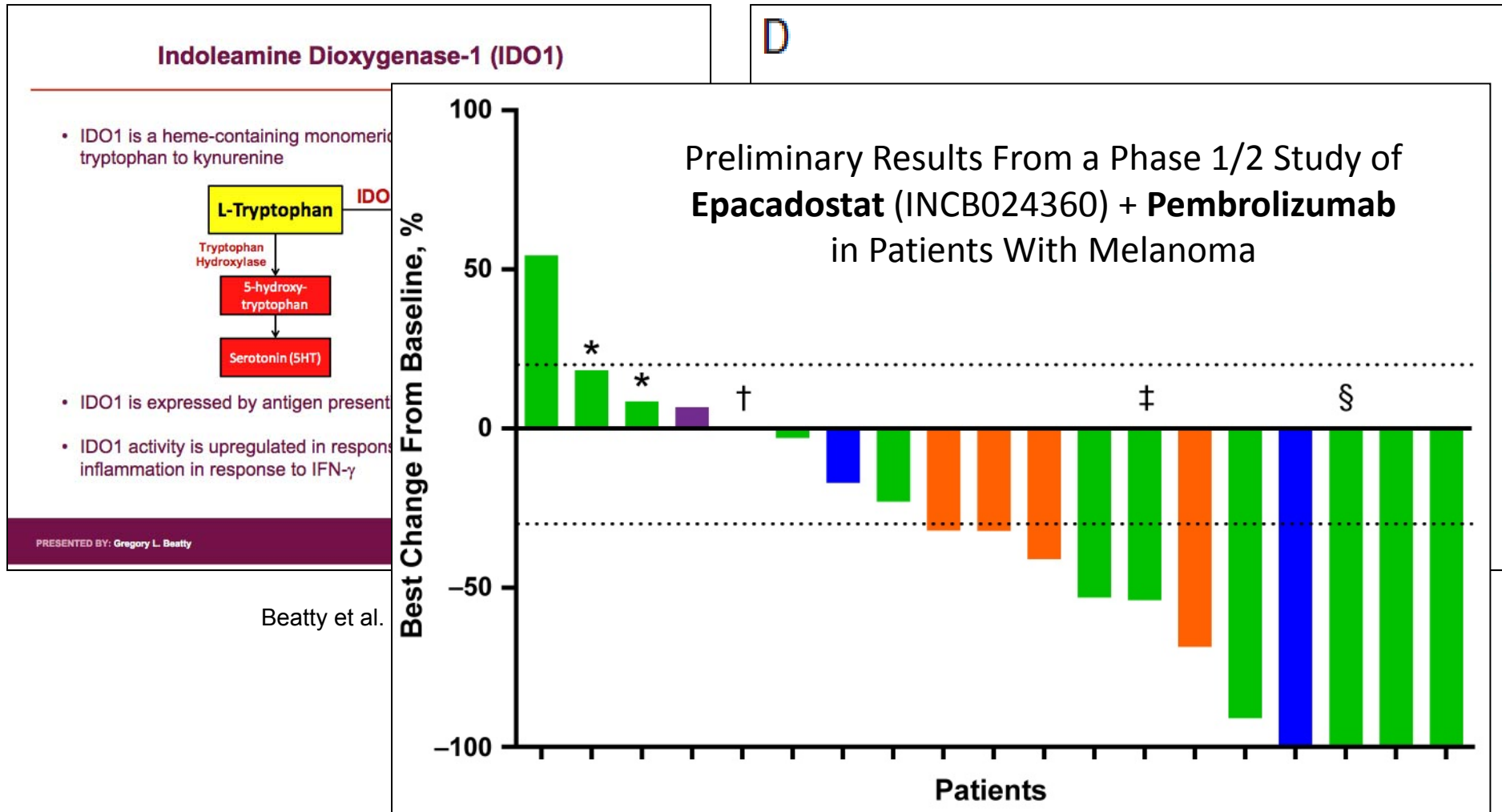


Pardoll, Nat Rev Can 2012

Other interesting immune approaches

- **Metabolic**
 - IDO inhibitor
- **Cytokines**
 - IL-2, IL-12 etc
- **Oncolytic Viruses**
 - TVEC
- **Targeted therapy**
 - BRAF, VEGF etc.
- **Chemotherapy**
 - Gemcitabine, Cisplatin
- **Radiation**

IDO inhibitor epacadostat + pembrolizumab

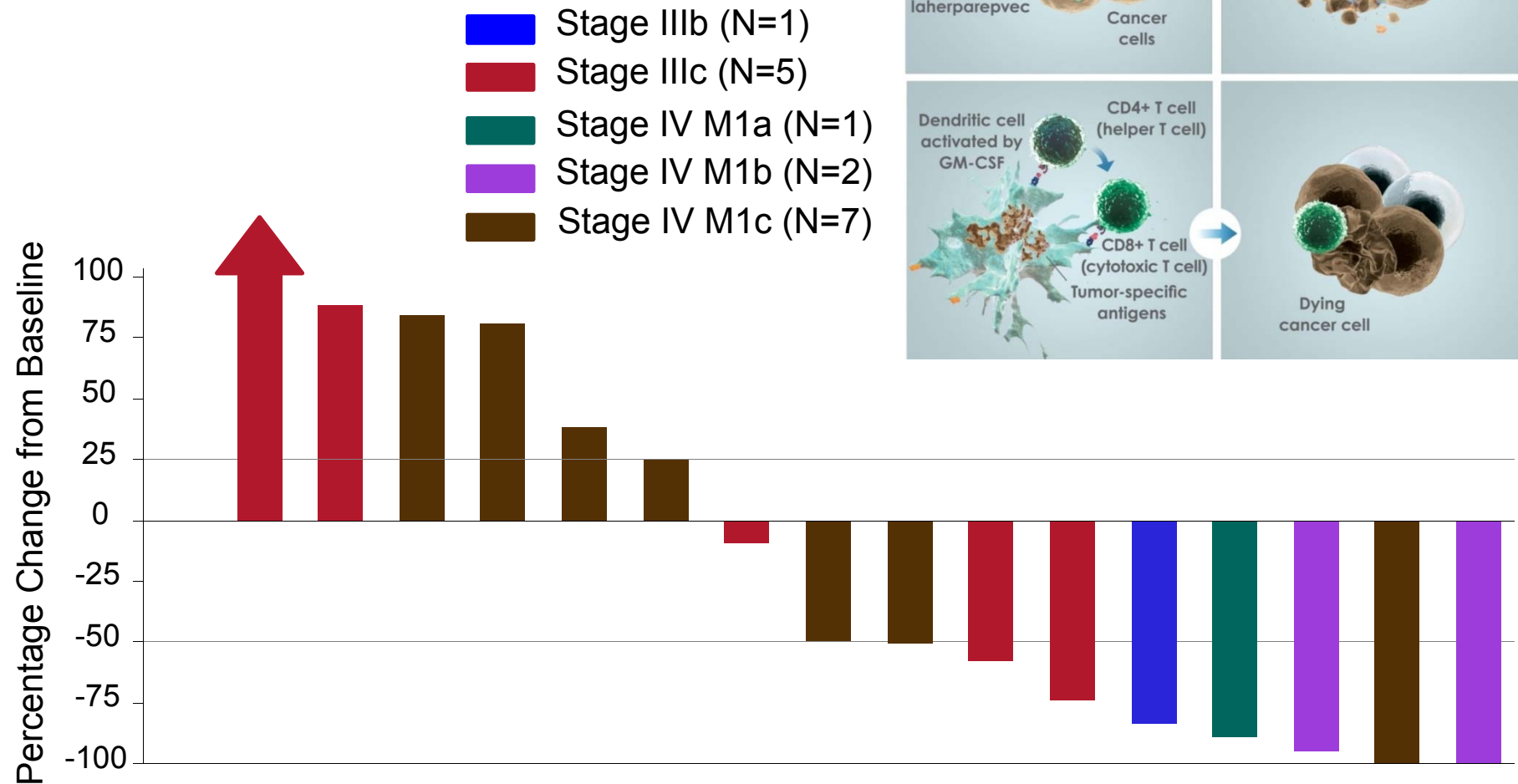
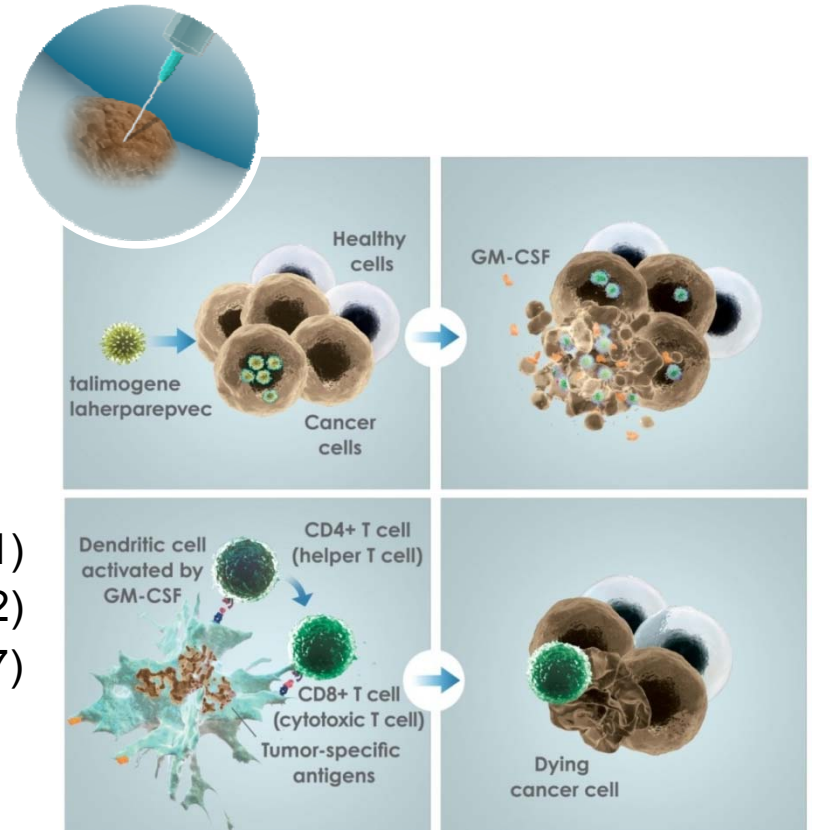


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RECIST response = 55%, no increase in toxicity from pembrolizumab alone

Hamid et al. SMR 2015

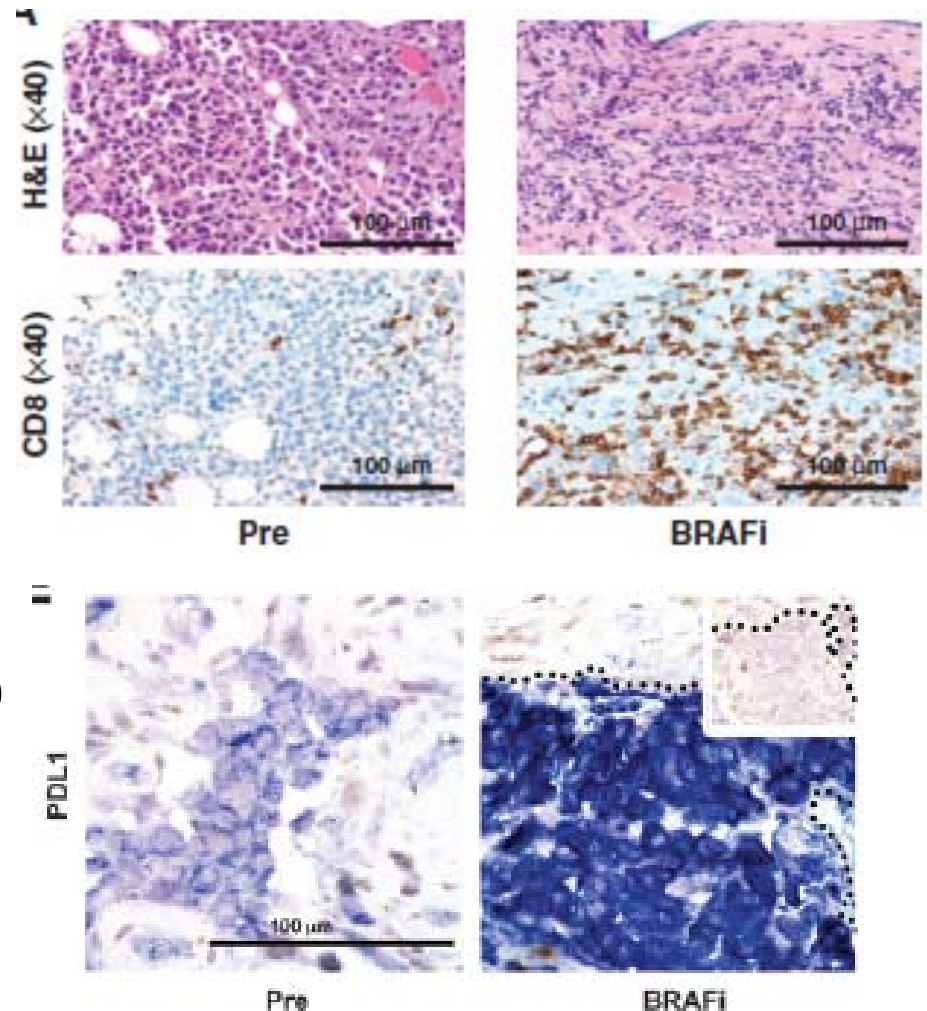
T-Vec + Pembrolizumab in Stage IIIB-IV Melanoma



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

What about Targeted Therapy – Immunotherapy Combos?

- BRAF inhibitor associated with increase CD8+ T-cell infiltrate
- Resistance to BRAF inhibitors leads to up regulation of PD-L1



What about Targeted Therapy – Immunotherapy Combos?

- Phase I ipilimumab + vemurafenib
 - **Stopped for hepatic toxicity**
- Phase I ipilimumab + dabrafenib + trametinib
 - **Stopped for colitis/perforation toxicity**
- On-going studies of BRAF and MEK inhibitors with anti-PD1/L1 antibodies
 - **First report suggests no gain in response rate and substantial toxicity with combo**



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 combinations are likely the future
 - For melanoma and likely all cancers!

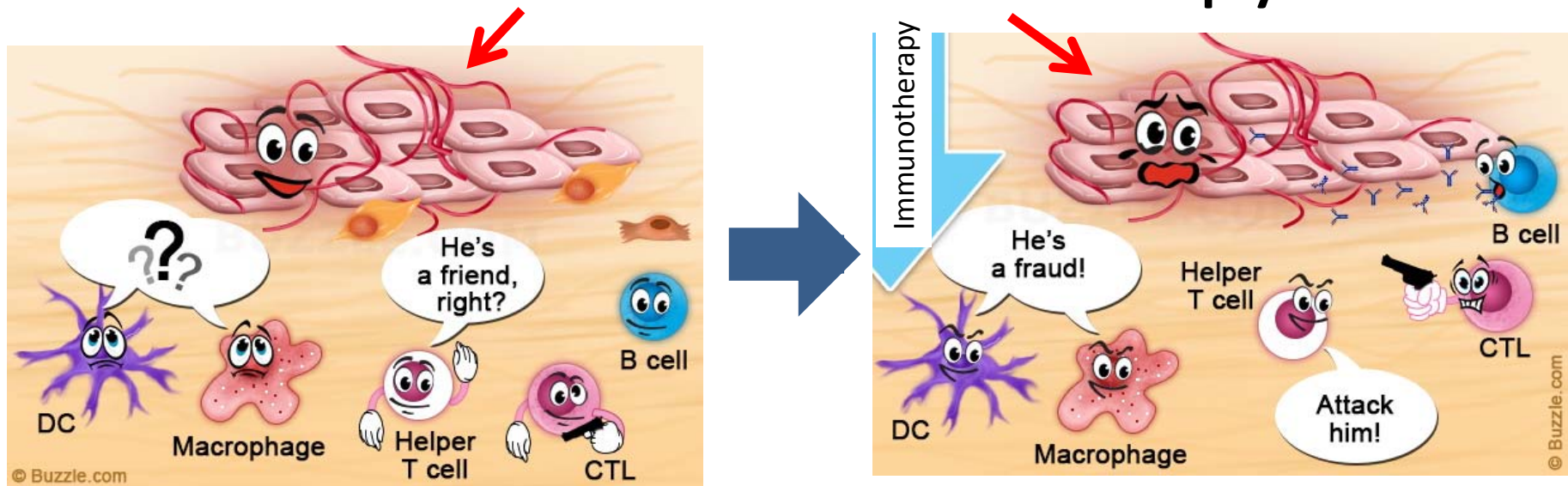


Thanks!



- Q's?
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Cancer Immunotherapy



@jasonlukemd



@UCCancerCenter



<http://goldenprague.us/strategies-for-cancer-vaccine-development/>