

ADVANCES IN
Cancer
IMMUNOTHERAPY™



Immunotherapy for the Treatment of Melanoma

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Society for Immunotherapy of Cancer

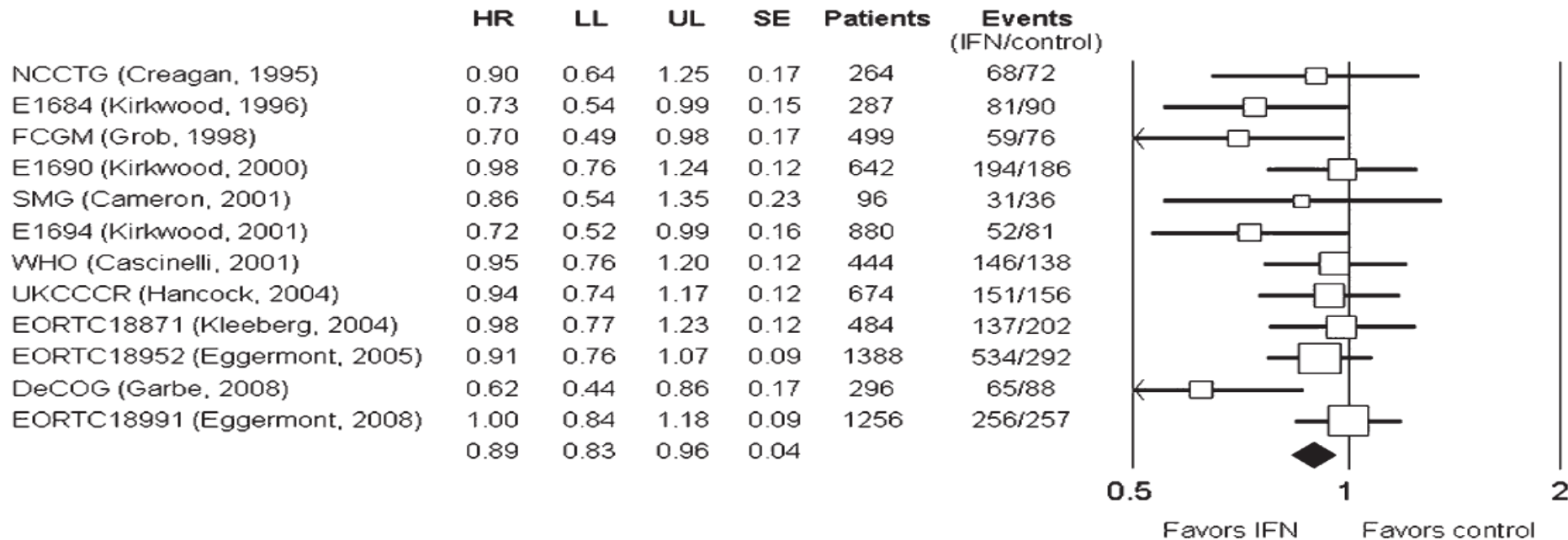
Disclosures

- No relevant financial relationships to disclose
- I not will be discussing non-FDA approved indications during my presentation.

Types of Immunotherapies for Melanoma

- Cytokines
 - Interferon- α 2b
 - Interleukin-2
- Oncolytic Virus
 - Modified Herpes Virus (Talimogene Laharparepvec; TVEC)
- Checkpoint antibodies
 - Anti-CTLA4 (ipilimumab)
 - Anti-PD1 (pembrolizumab, nivolumab)
 - (Avelumab for Merkel cell carcinoma – March 2017)

Adjuvant Treatment of High-Risk Melanoma

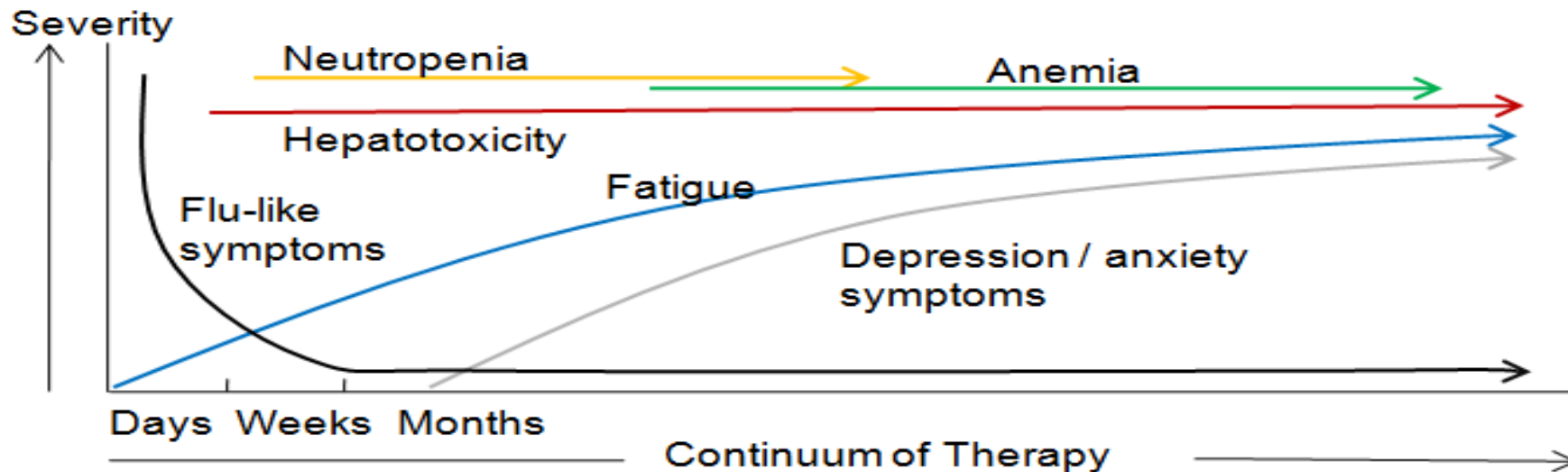


Mocellin et al. JNCI. 2010





Toxicity of Adjuvant Interferon- α

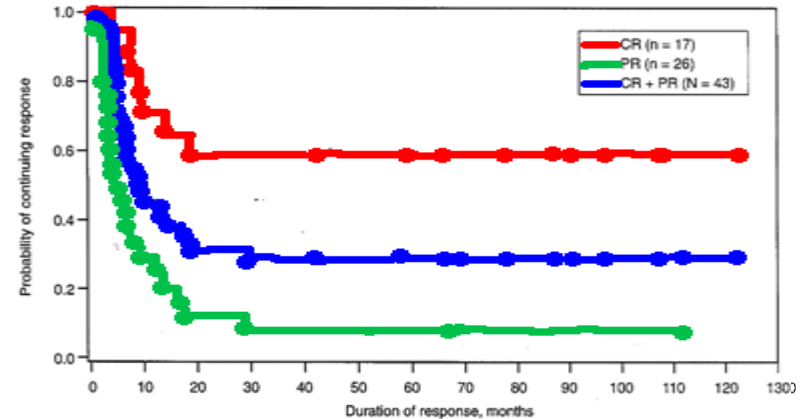


<http://www.sinobiological.com/Interferon-Side-Effects-a-6085.html>



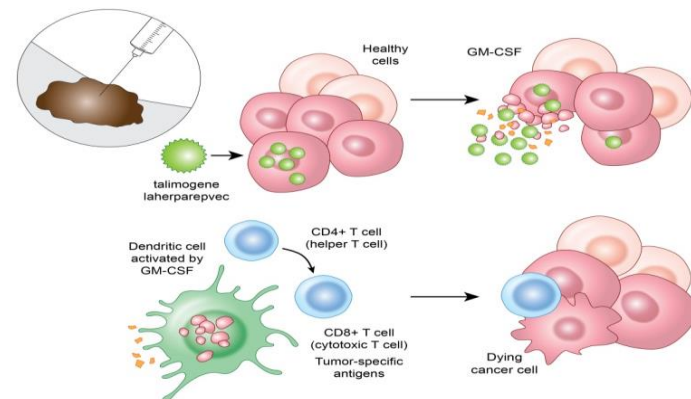
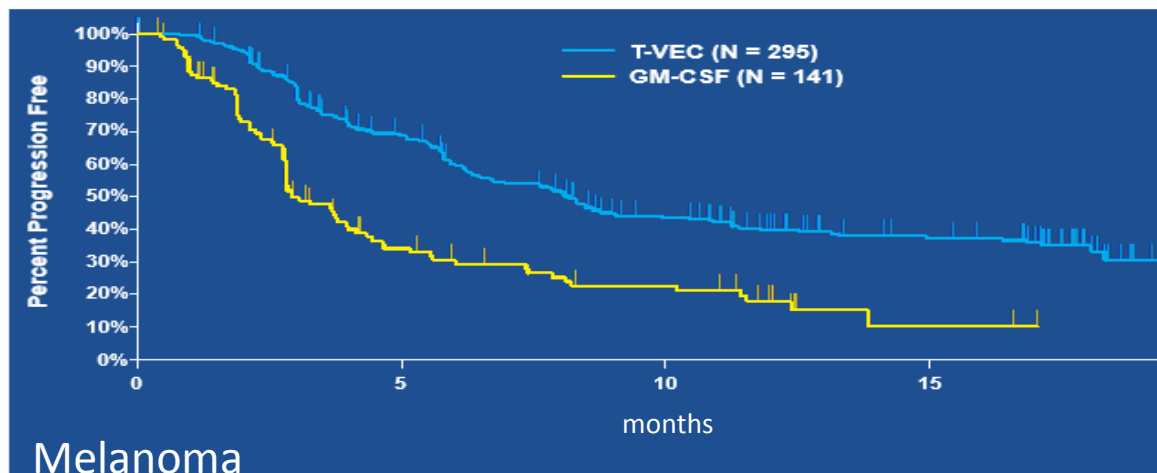
High Dose Interleukin-2 Therapy (HD IL-2) : Durable Responses

- 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 1998
- High toxicity

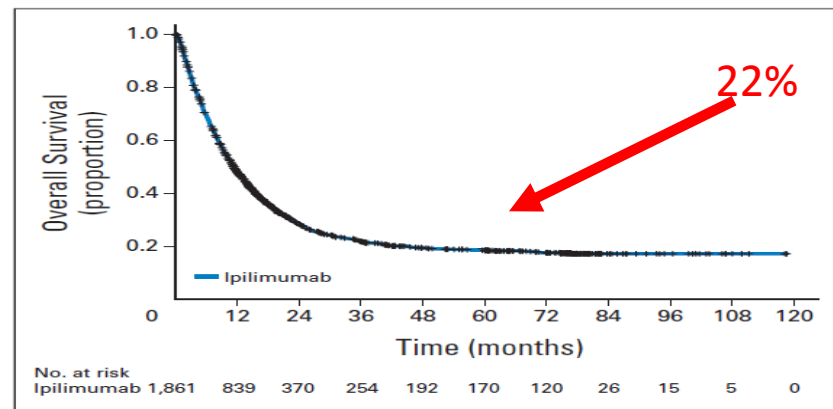
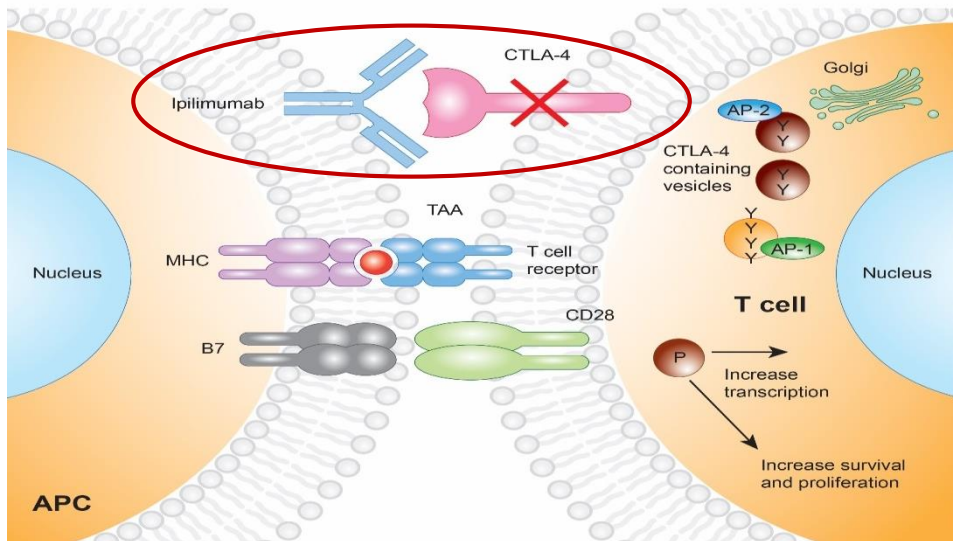


Atkins et al. J Clin Oncol. 1999

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



Ipilimumab & Immune Check-Point Blockade



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



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

- Systemic therapy

- Nivolumab
- High-dose IL-2
- Nivolumab plus ipilimumab
- Targeted Rx based on next-generation sequencing
- Ipilimumab 10 mg/kg x 4 then maintenance
- Ipilimumab 3 mg/kg x 4
- IFN- α (PEG- or unmodified)

- Lesional therapy

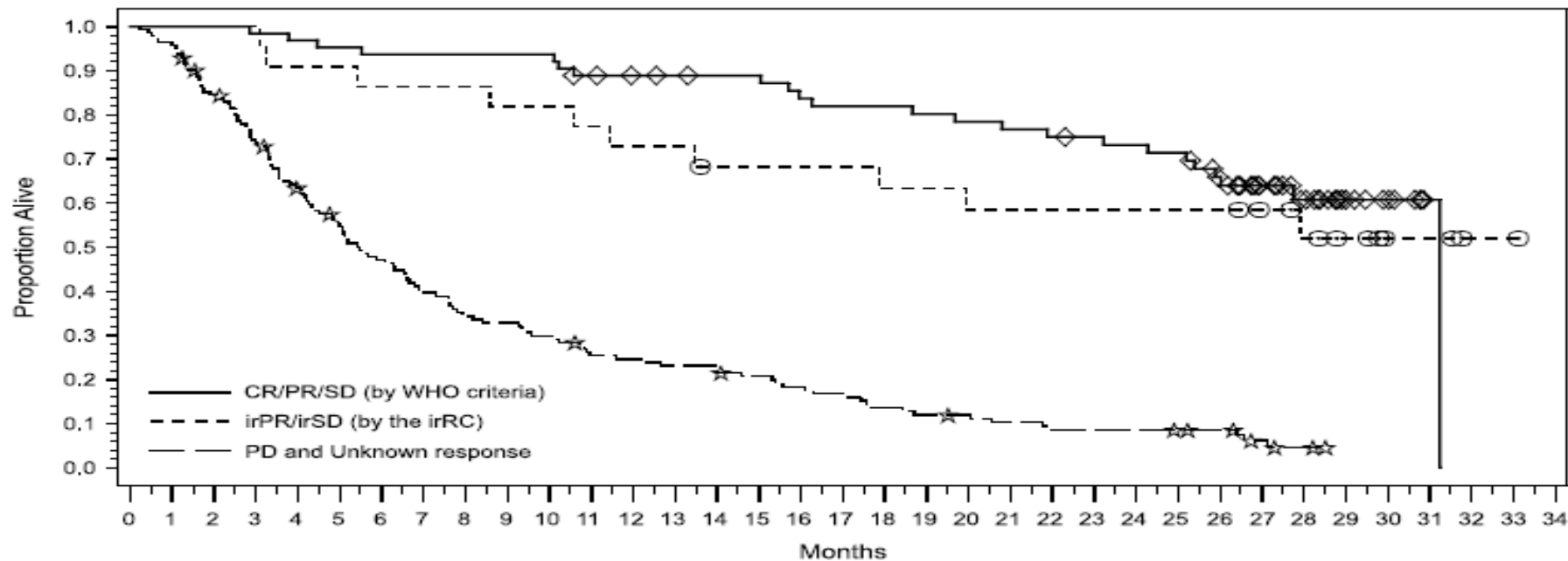
- Talimogene laherparepvec
- Radiotherapy
- Intralesional IL-2
- Intralesional GM-CSF

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, OX40)
 - hypofractionated or stereotactic radiotherapy
- Molecularly-focused treatment paradigms—all immunomodulatory
 - Metabolic reprogramming
 - Next generation sequencing→molecular drivers and/or modifiers



Immune Related Response Criteria

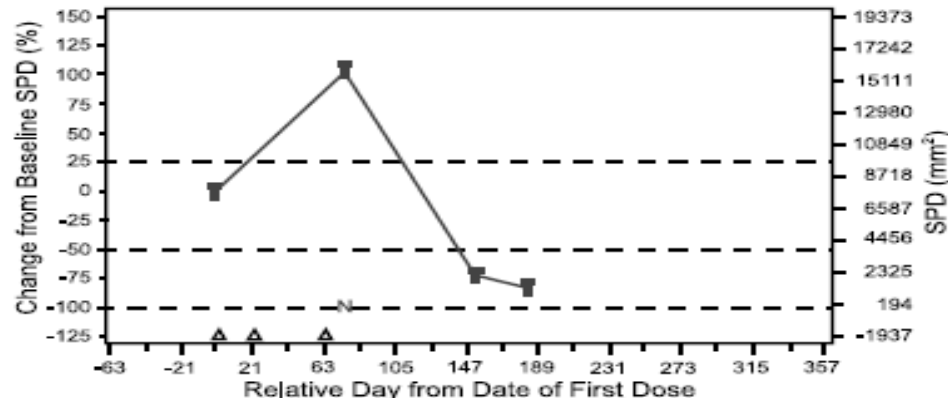
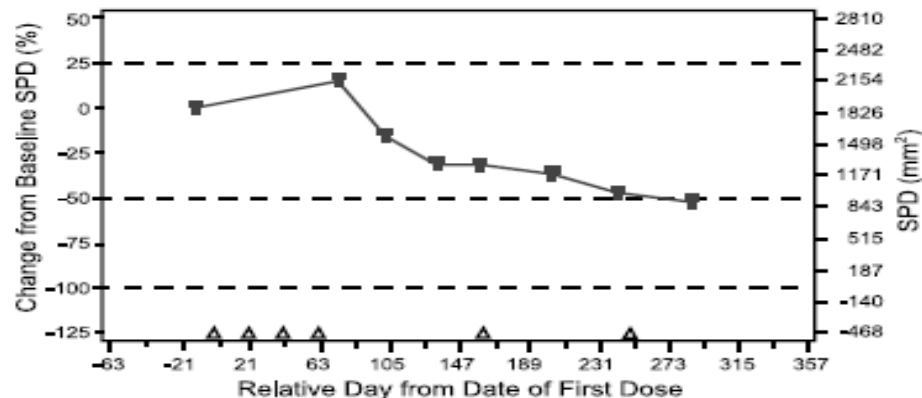


Wolchok et al. Clin Can Res 2009





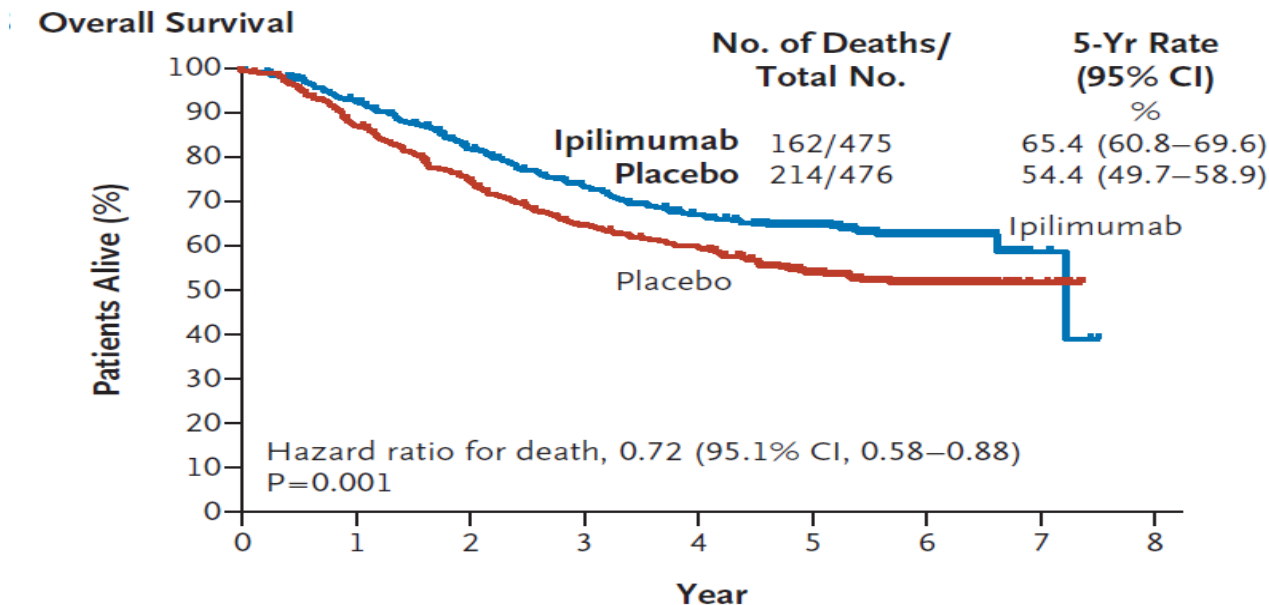
Immune Related Response Criteria



Wolchok et al. Clin Can Res 2009



Adjuvant Ipilimumab in High-Risk Melanoma



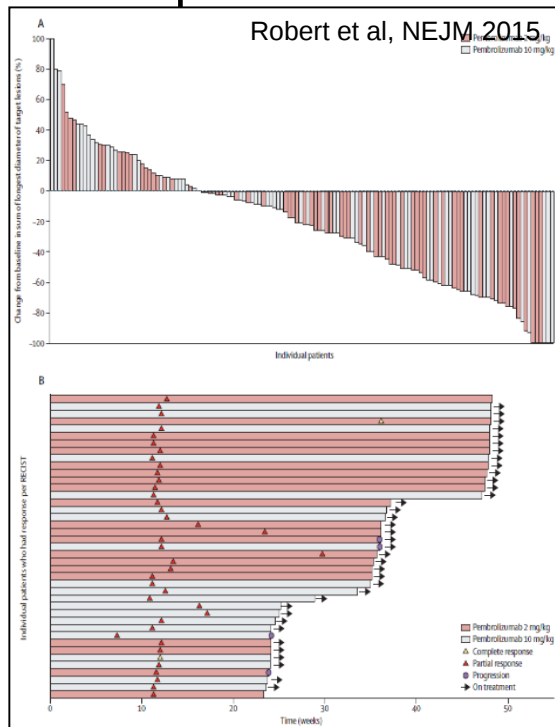
No. at Risk

Ipilimumab	475	431	369	325	290	199	62	4
Placebo	476	413	348	297	273	178	58	8



Anti-PD1 (pembrolizumab) *after* ipilimumab

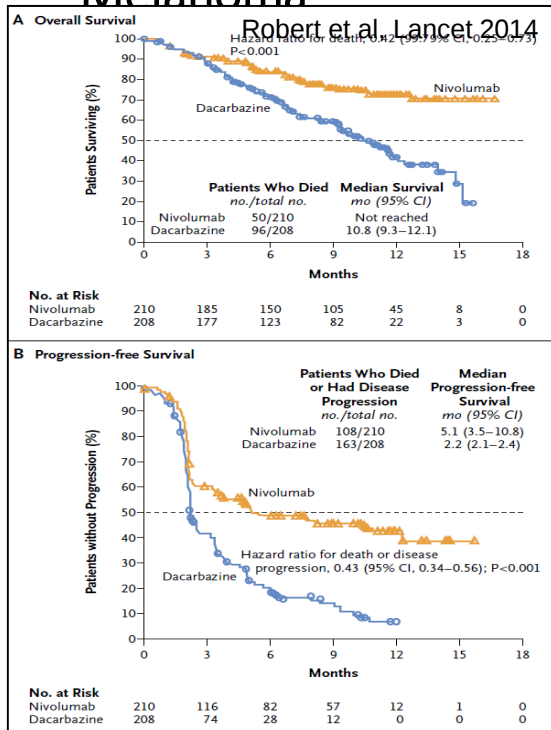
Robert et al, NEJM 2015



Anti-PD1 in Melanoma

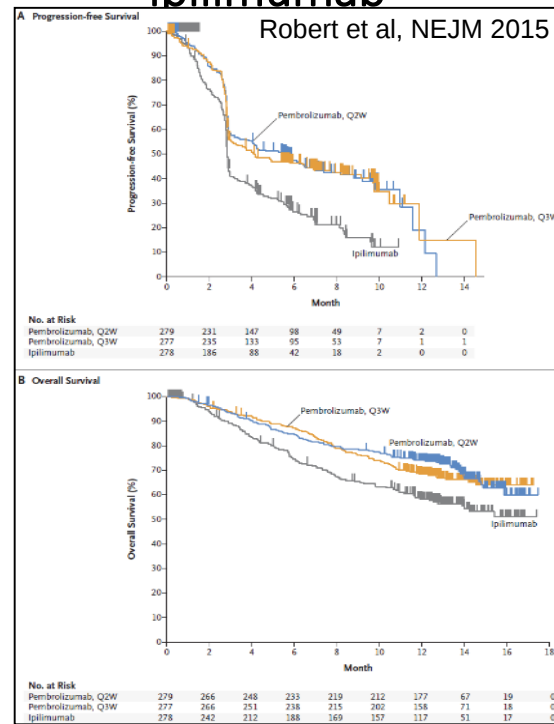
Front-line anti-PD1 (nivolumab) vs. DTIC in Melanoma^(BRAF WT)

Robert et al, Lancet 2014



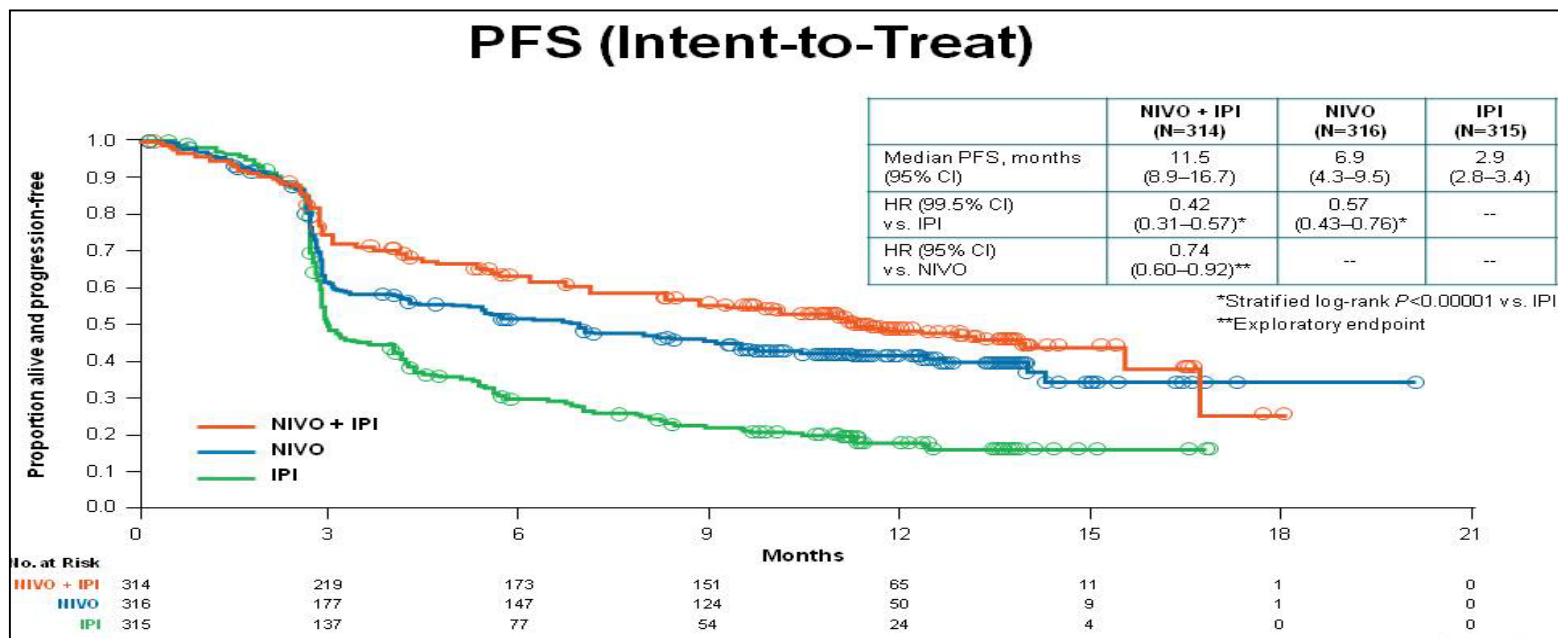
Front-line anti-PD1 (pembrolizumab) vs. ipilimumab

Robert et al, NEJM 2015

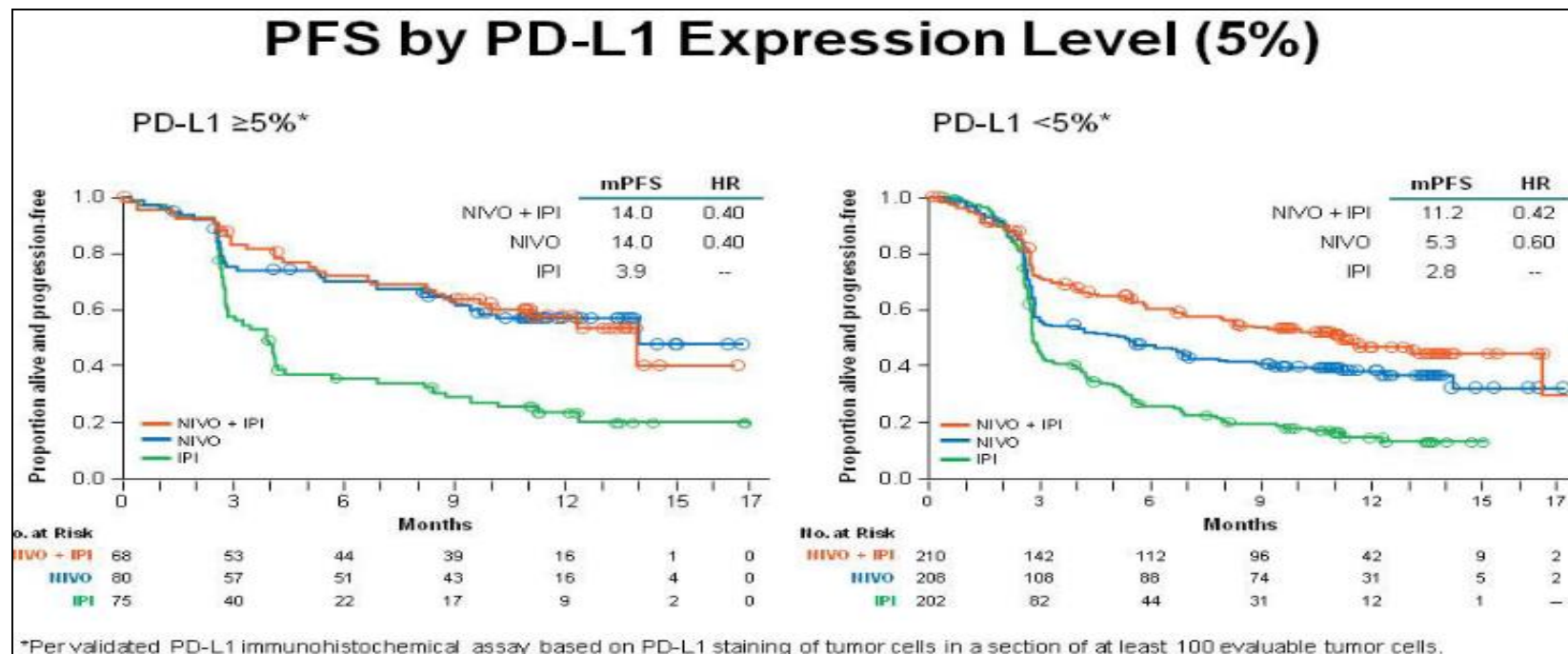




Ipi+Nivo vs. Ipi or Nivo vs. Ipi in Melanoma



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



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



Case #2: same as #1, but BRAF^{V600}

Additional decision needed: MAPK inhibitor timing and choice

How I treated patient:

- Resected, sent tumor for research studies of tumor microenvironment
- Margins + at muscle—did not send for resection
- Ipilimumab at “adjuvant” dose of 10mg/kg with maintenance



Case #2: metastatic melanoma BRAFm from unknown primary

RN, male patient in 50s

- Presented 8/2015 with pleuropulmonary disease symptoms and large R adrenal BRAF^{V600E} metastasis
- Initial Therapy:
 - dabrafenib and trametinib
 - Near CR x 18 months
 - Tolerated therapy with minimal side effects—mainly peripheral edema

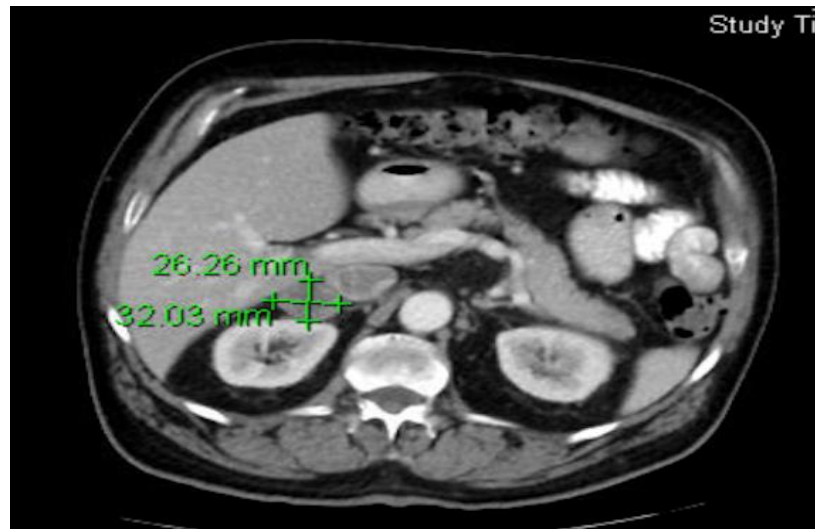
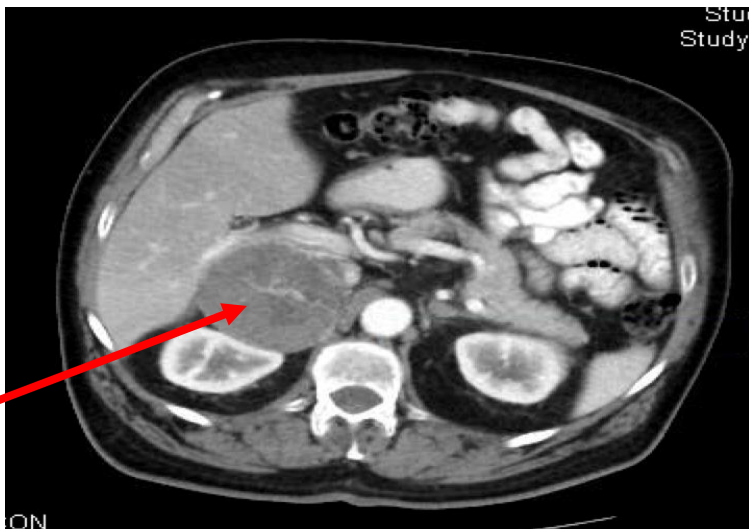
Progression in R adrenal but controlled in lung; new small asymptomatic brain metastasis

- Checkmate 209204
 - nivolumab plus ipilimumab for metastatic melanoma to brain



Therapeutic effect—representative images (also had small brain metastasis→ CR)

Adrenal
metastasis



Case #2: Questions raised

1. Was it appropriate to start with MAPKi? YES
2. Should he have received combination with immunotherapy NO
3. Is it best to switch to immunotherapy early, or at best response to MAPKi? UNKNOWN
4. Why did he have such a sustained response to MAPKi? Immunomodulation?
5. Is nivolumab plus ipilimumab the optimal immunotherapy in June 2017? PROBABLY
6. Should PD-L1 expression have been checked? Maybe...but many issues remain
7. How long to continue Rx? UNKNOWN/1 yr?



Toxicity management issues

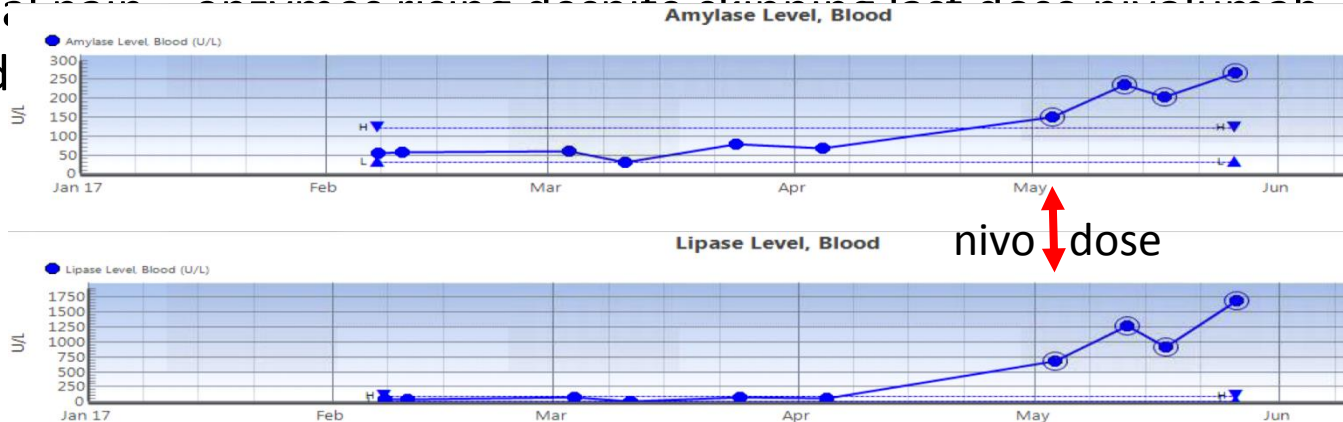
Diarrhea from ipilimumab/nivolumab combination responded to steroid;
Ipilimumab dropped after 2 cycles, in part because pt was traveling to Poland (QoL)

Nivolumab dosed at 1 mg/kg in cycles 3 and 4—should it have been increased?

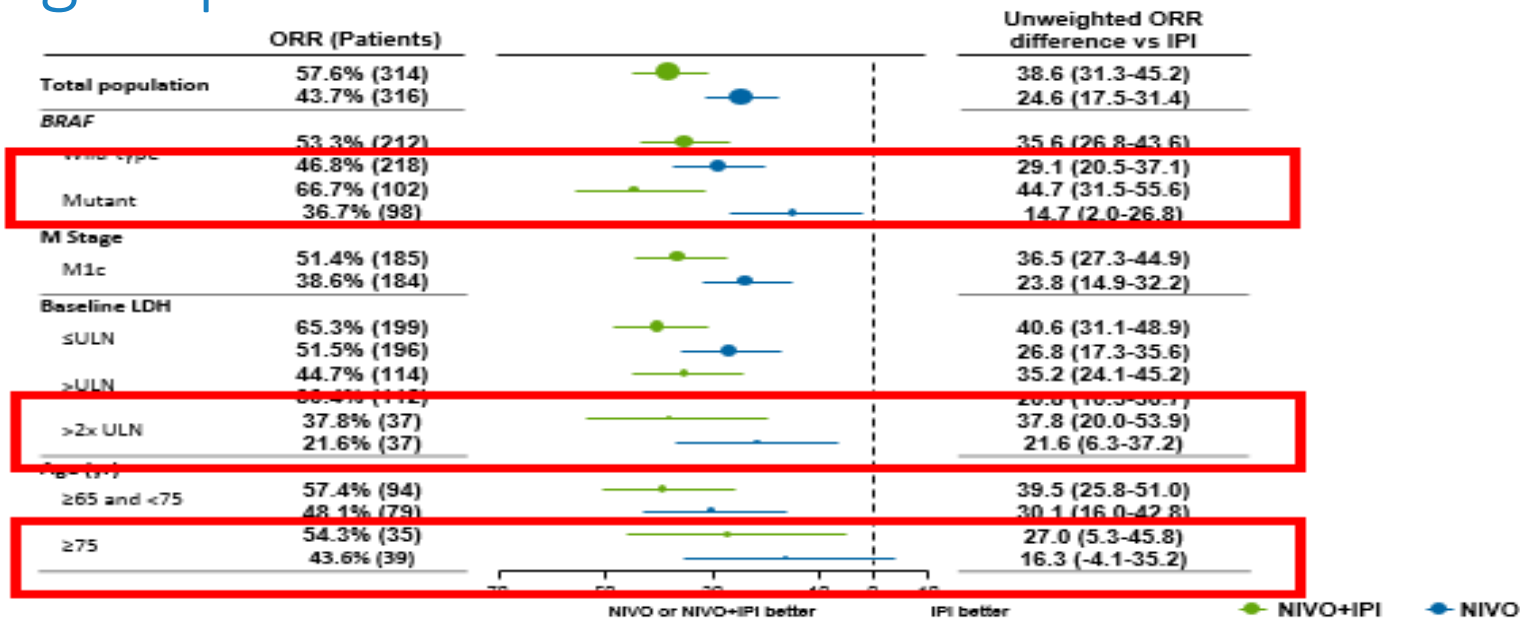
Pt developed chemical pancreatitis, initially without Sx, now with mild abdominal pain, nausea, vomiting, decreased appetite, weight loss, decreased energy → steroid?

[US not d

DLs normally



Ipi-Nivo vs Nivo Overall Response Rate in Patient Subgroups



On-Going Phase III Trials in Melanoma

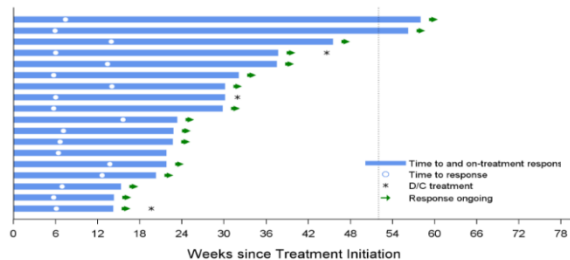
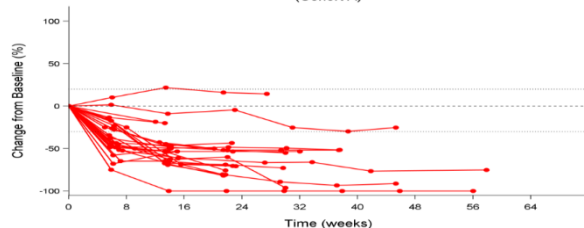
- BRAFi + MEKi + anti PD-(L)1
- MEKi + anti PD-(L)1
- Indolamine Dioxygenase inhibitors (IDOi)
+ anti PD-(L)1
- Talimogene laharparepvec (TVEC) + anti
PD(L)1

Target-Immuno Triplets: BRAF + MEK + PD1/L1

Dabrafenib+Trametinib+

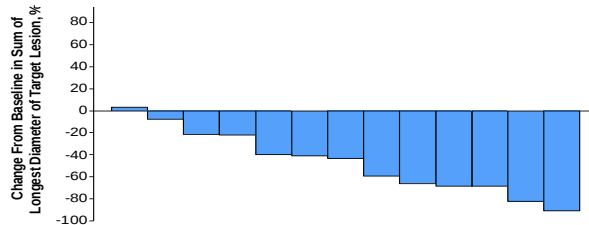
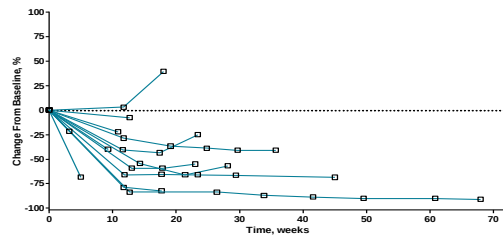
Nirvalumab

Tumor Size Change from Baseline
(Cohort A)



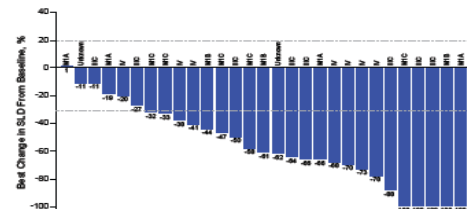
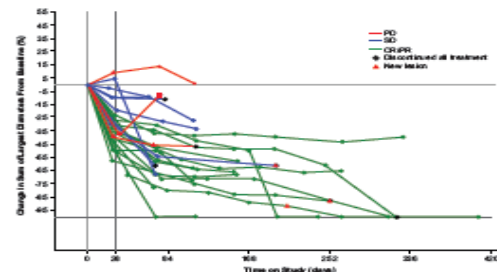
Dabrafenib+Trametinib+

Pembrolizumab



Vemurafenib+Cobimetinib+

Atezolizumab



Target-Immuno Triplets: BRAF + MEK + PD1/L1

Dabrafenib+Trametinib+

Nirvalumab

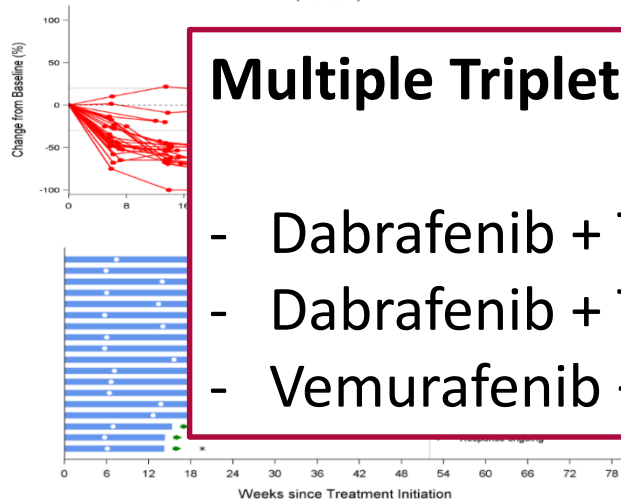
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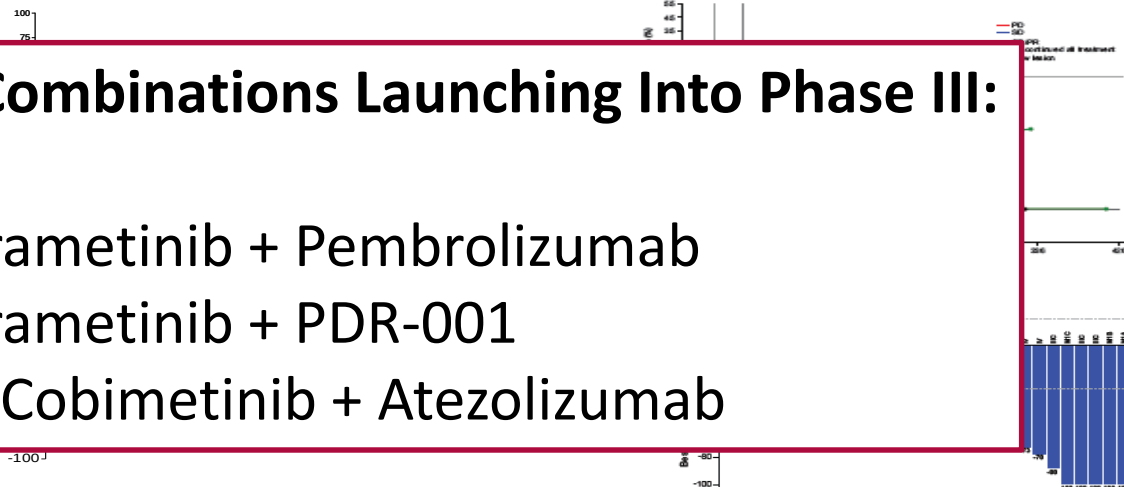
Vemurafenib+Cobimetinib+

Atezolizumab



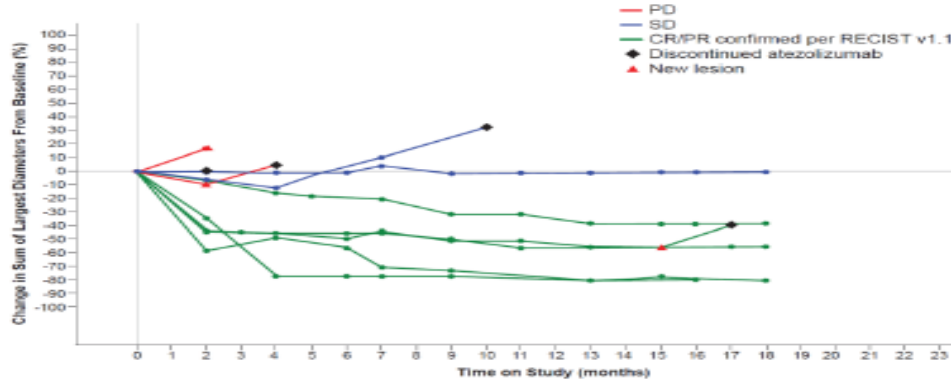
Multiple Triplet Combinations Launching Into Phase III:

- Dabrafenib + Trametinib + Pembrolizumab
- Dabrafenib + Trametinib + PDR-001
- Vemurafenib + Cobimetinib + Atezolizumab



MEK inhibitor + PDL-1 for BRAFwt Melanoma Phase I Cobimetinib + Atezolizumab

BRAF WT (n = 10)



**Phase III Study of Cobimetinib +
Atezolizumab versus Pembrolizumab in
Patients with Untreated BRAFV600
Wild-Type Melanoma**

PROTOCOL NUMBER: CO39722

	N = 22, n (%)
Median safety follow-up, mo (range)	14.0 mo (2.4-20.2)
All grade treatment-related AEs	22 (100%)
Grade 3-4 treatment-related AEs	13 (59%)
Grade 3-4 atezolizumab-related AEs	8 (36%)
Grade 3-4 cobimetinib-related AEs	10 (45%)
AEs leading to treatment dose modification/interruption	14 (64%)
Treatment-related SAEs ^a	4 (18%)
Treatment discontinuation ^b	3 (14%)
Cobimetinib discontinuation	3 (14%)
All treatment discontinuation	1 (5%)

Atezolizumab:
 PD-L1

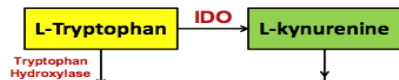
Pembrolizumab :
 PD-1



IDO inhibitor epacadostat + pembrolizumab

Indoleamine Dioxygenase-1 (IDO1)

- IDO1 is a heme-containing monomeric oxidoreductase that metabolizes tryptophan to kynurenine

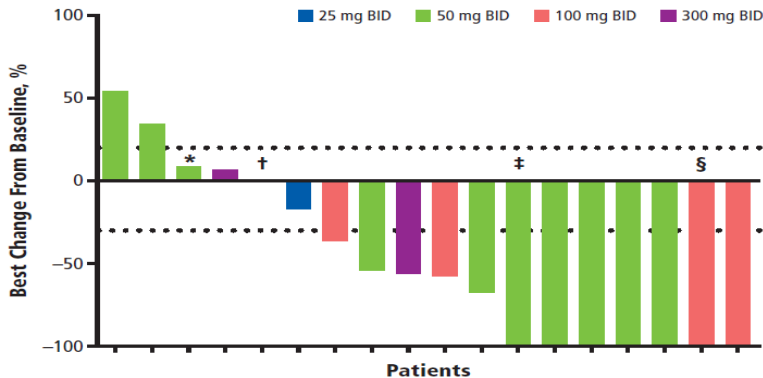


A Phase 3 Study of Pembrolizumab + Epacadostat or Placebo in Subjects With Unresectable or Metastatic Melanoma (Keynote-252 / ECHO-301)
ClinicalTrials.gov Identifier: NCT02752074

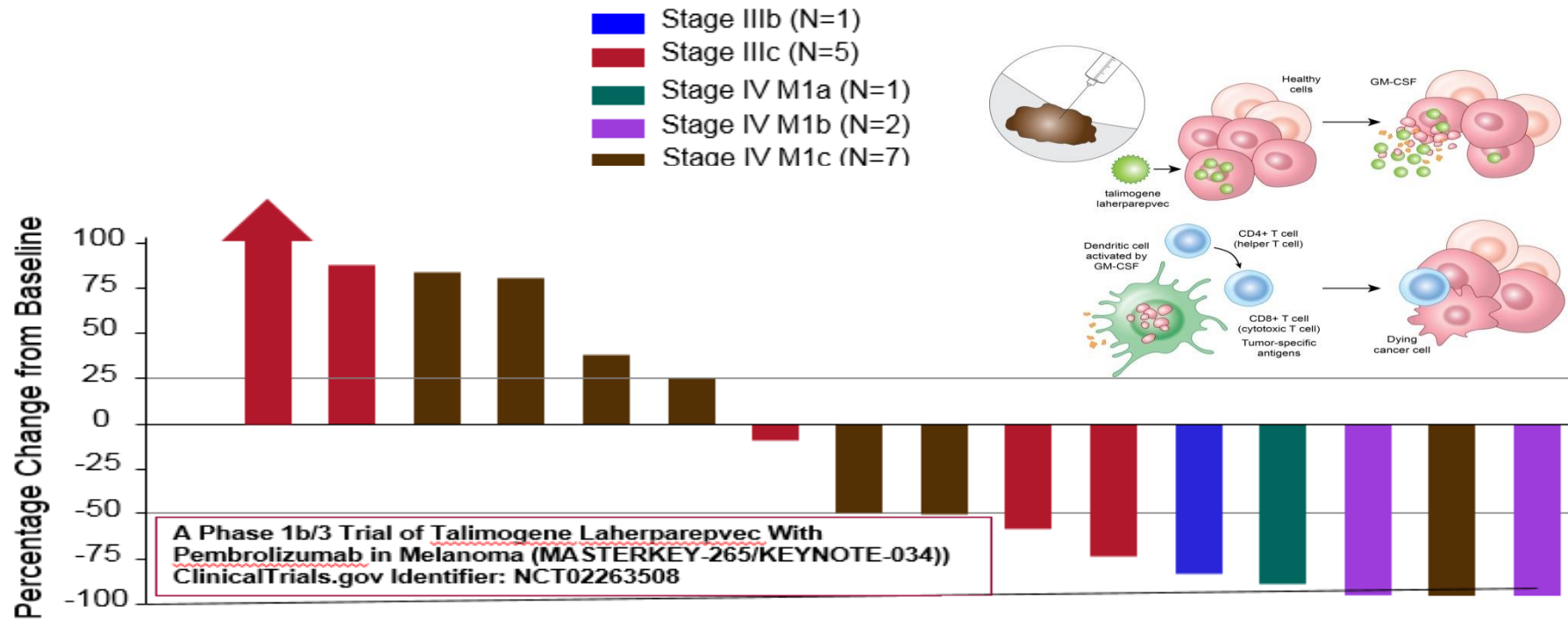
RECIST response = 58%, no increase in toxicity from pembrolizumab alone

Beatty et al. ASCO (2012) Abstract 2500[^]
Gangadhar et al. ESMO 2016

Phase 1/2 Study of Epacadostat (INCB024360) + Pembrolizumab in Patients With Melanoma



T-Vec + Pembrolizumab in Stage IIIB-IV Melanoma



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

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!