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# Immunotherapy for the Treatment of Melanoma

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Association of Community Cancer Centers

Society for Immunotherapy of Cancer

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# Disclosures

- Consultant for Novartis and Genentech
- Advisory Board for Incyte and Newlink Genetics
- Speakers Bureau for Merck and Genentech
- I will be discussing non-FDA approved indications during my presentation.



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# 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)

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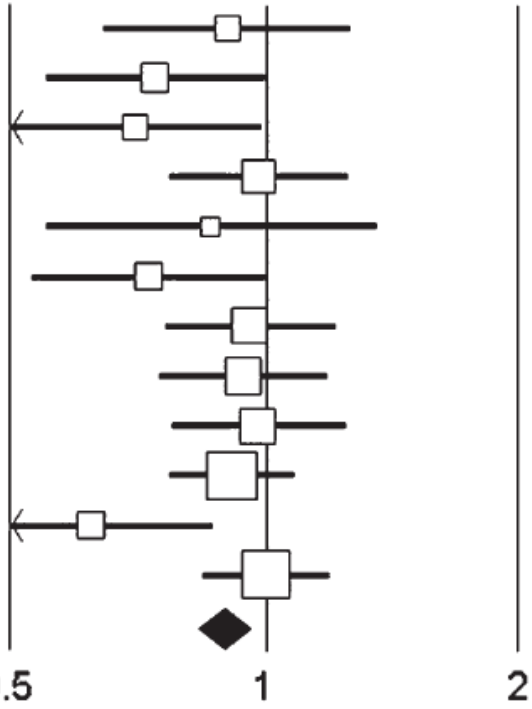
# Adjuvant Treatment of High-Risk Melanoma

| | 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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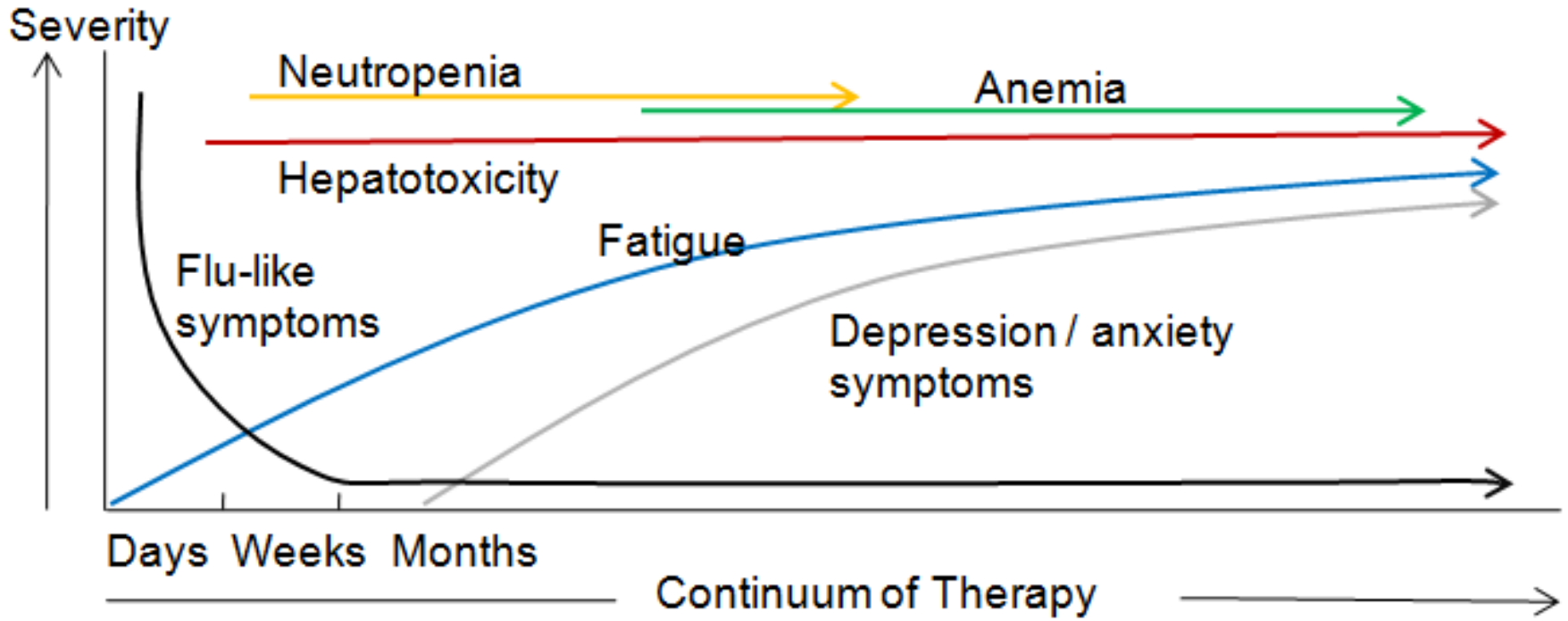
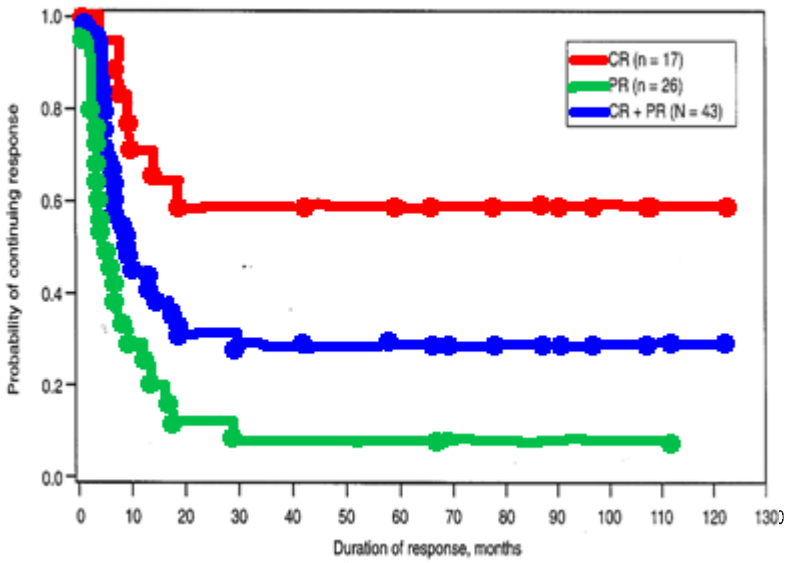
# Toxicity of Adjuvant Interferon-α




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

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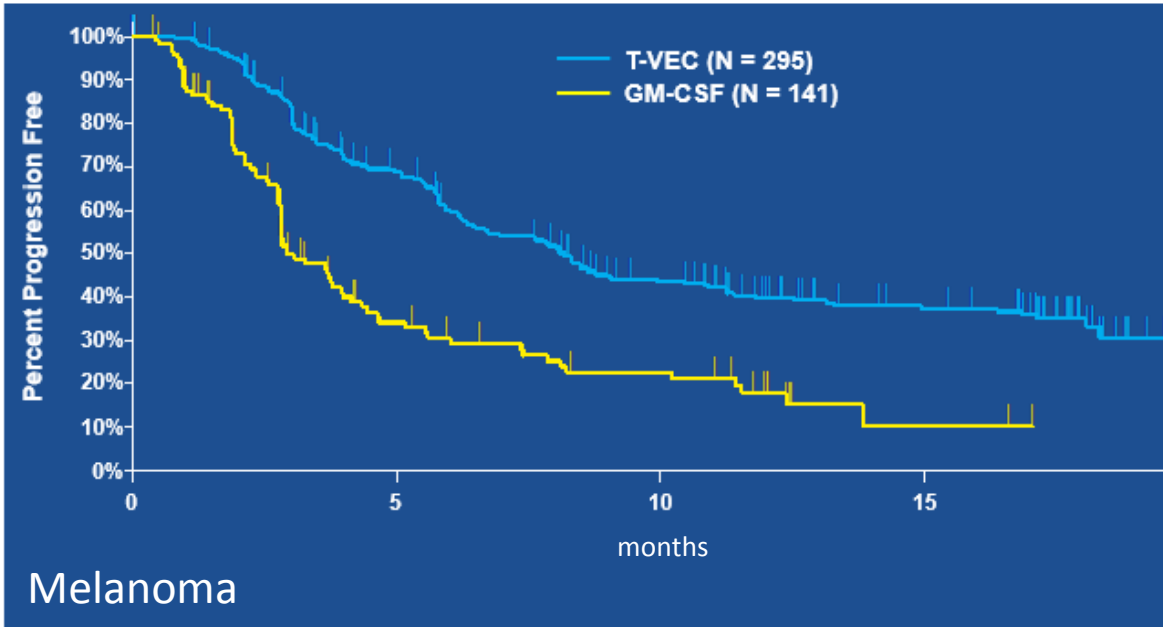
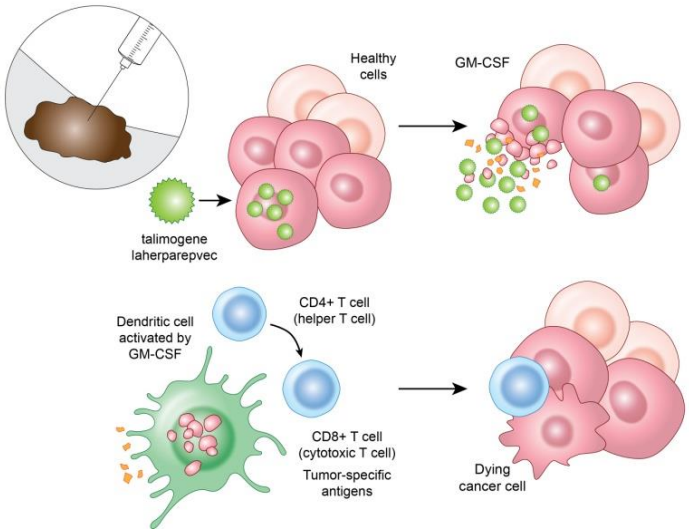
# Phase III Trial of T-VEC vs GM-CSF PFS per Investigator




Melanoma




Andtbacks et al. ASCO 2013; LBA9008



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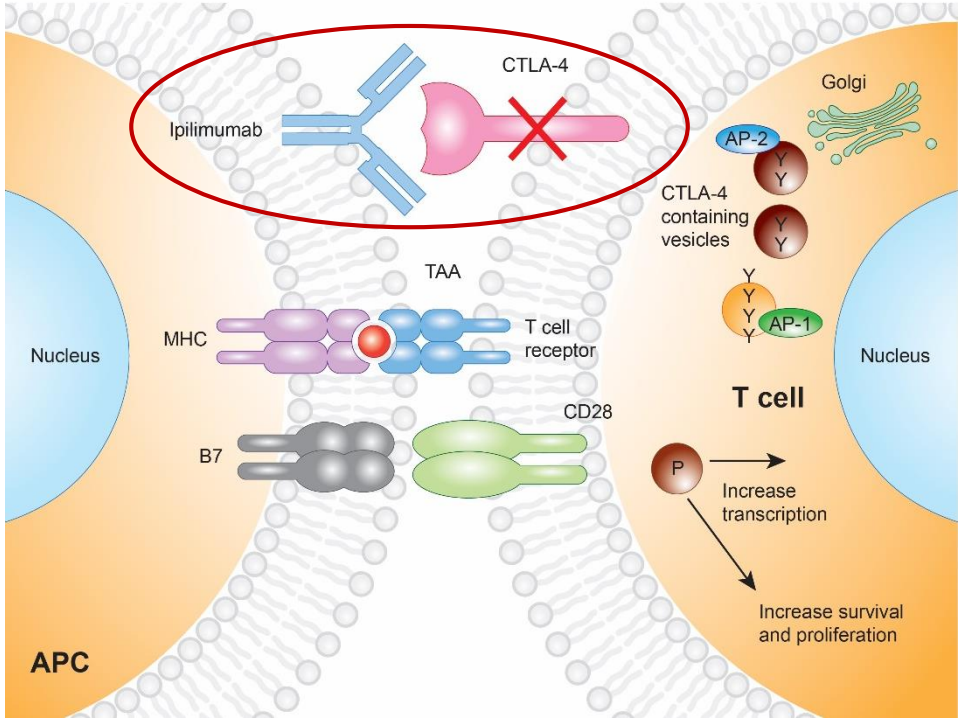
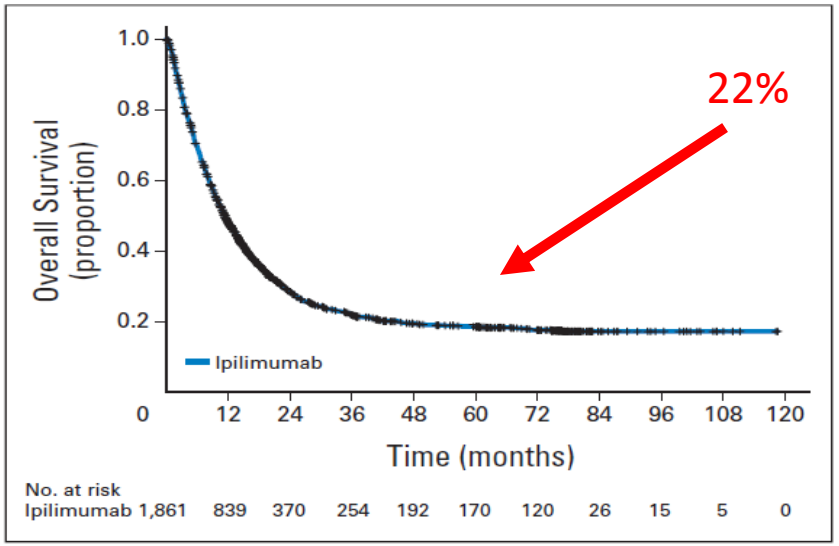
# Ipilimumab & Immune Check-Point Blockade




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



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# Case #1: stage IIIC

40 yo female patient

- Presented with metastatic melanoma to the left axilla with unknown primary; underwent therapeutic lymph node dissection and pathology showed 8/20 LNs involved with melanoma (stage IIIC); BRAF WT
  - Randomized to pembrolizumab on SWOG-1404 adjuvant trial
  - 4 cycles: no significant irAEs
- Relapsed in the left anterior chest wall



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# Case #1: stage IIIC on adjuvant pembrolizumab with recurrent disease

## Systemic therapy

- High-dose IL-2
- Nivolumab plus ipilimumab
- Targeted Rx based on next-generation sequencing
- Ipilimumab 3 mg/kg x 4
- Nivolumab?

## Intralesional therapy

- Talimogene laherparepvec

## Resect, then Adjuvant therapy

- Ipilimumab 10 mg/kg x 4 then maintenance
- IFN-α (PEG- or unmodified)

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# Best Therapies ⟶ Clinical Trials

- Tumor-infiltrating lymphocytes (TILs)
- Novel intralesional therapies
- New/improved immune checkpoint agents w/immunomodulators
  - combination with LAG-3 antibodies
  - other suppressive mechanisms (indoleamine dioxygenase inhibitors)
  - agonistic costimulatory antibodies (CD137, OX40)
  - hypofractionated or stereotactic radiotherapy

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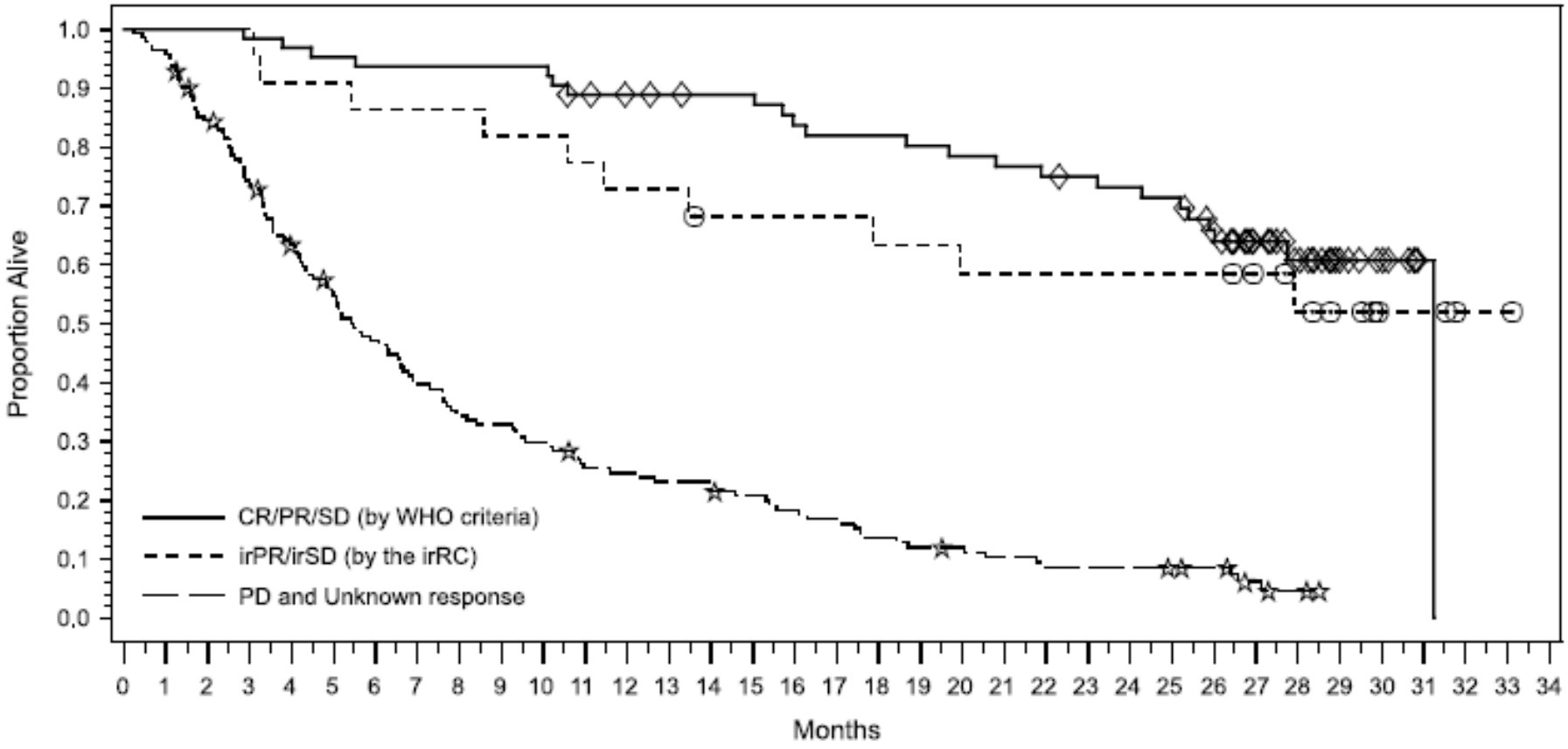
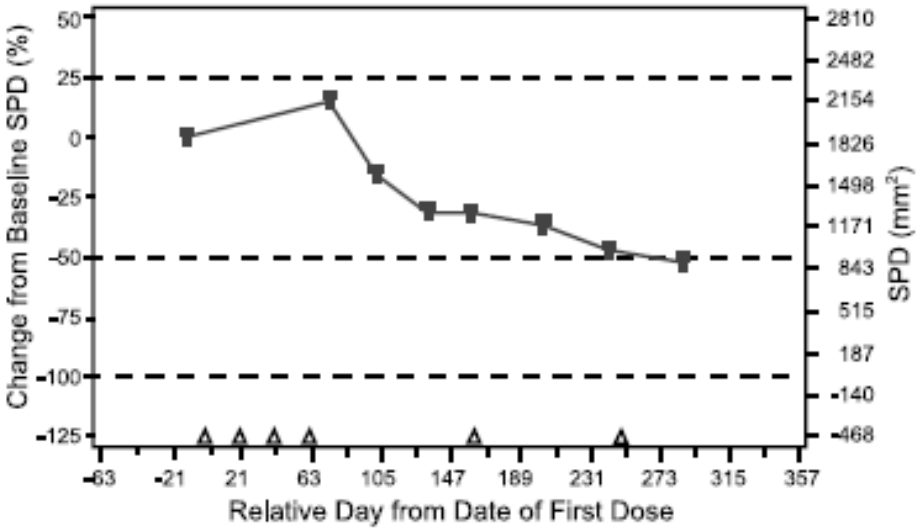
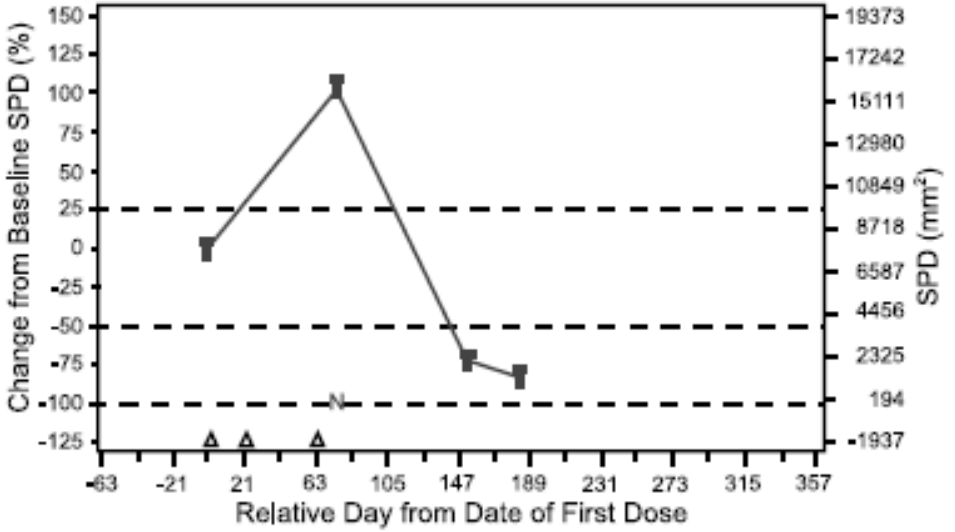
# Immune Related Response Criteria




Wolchok et al. Clin Can Res 2009

# Immune Related Response Criteria

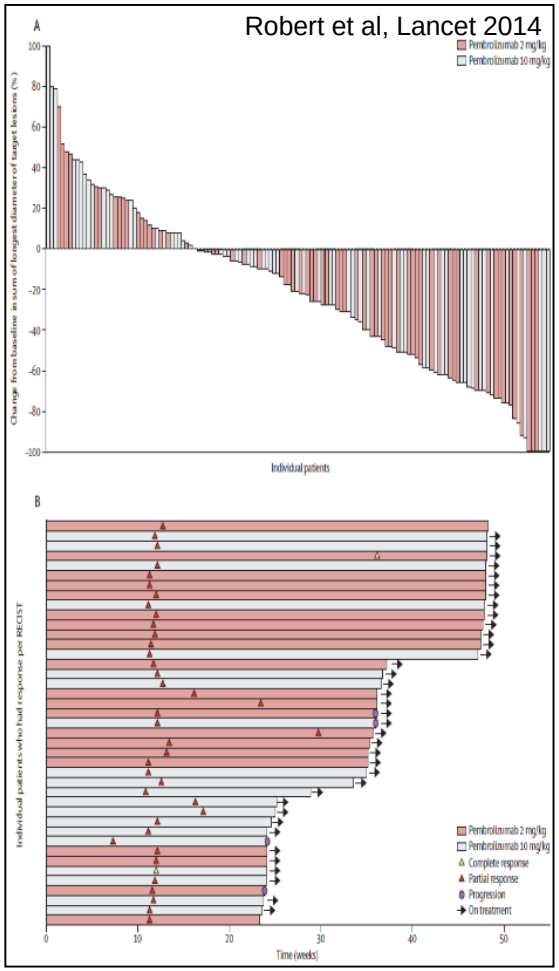


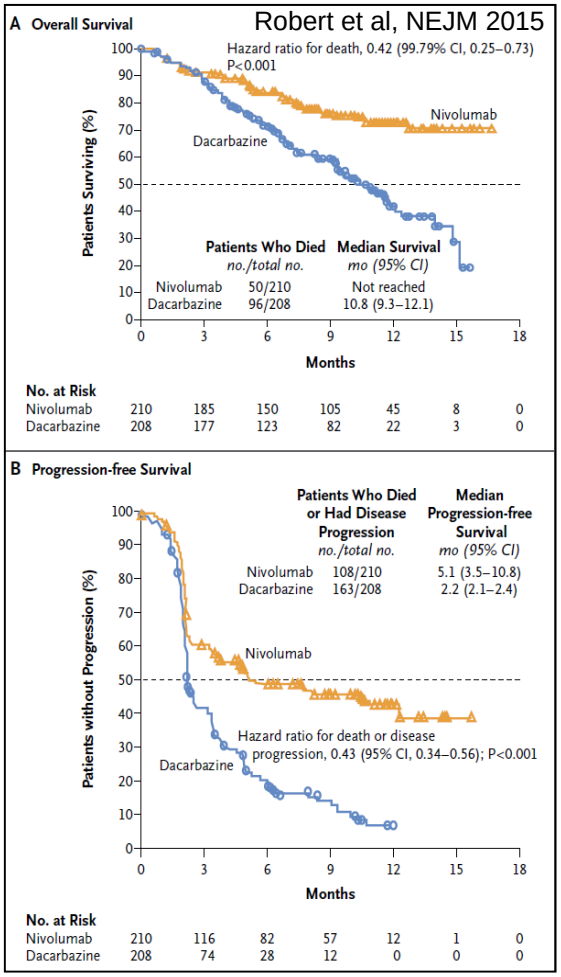

Wolchok et al. Clin Can Res 2009

# Anti-PD1 in Melanoma

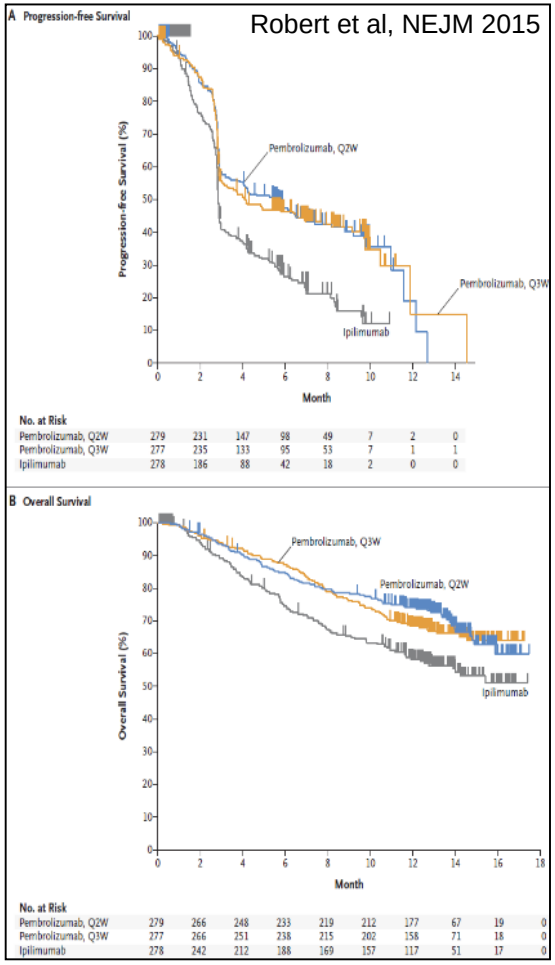
## Anti-PD1 (pembrolizumab) *after* ipilimumab




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




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



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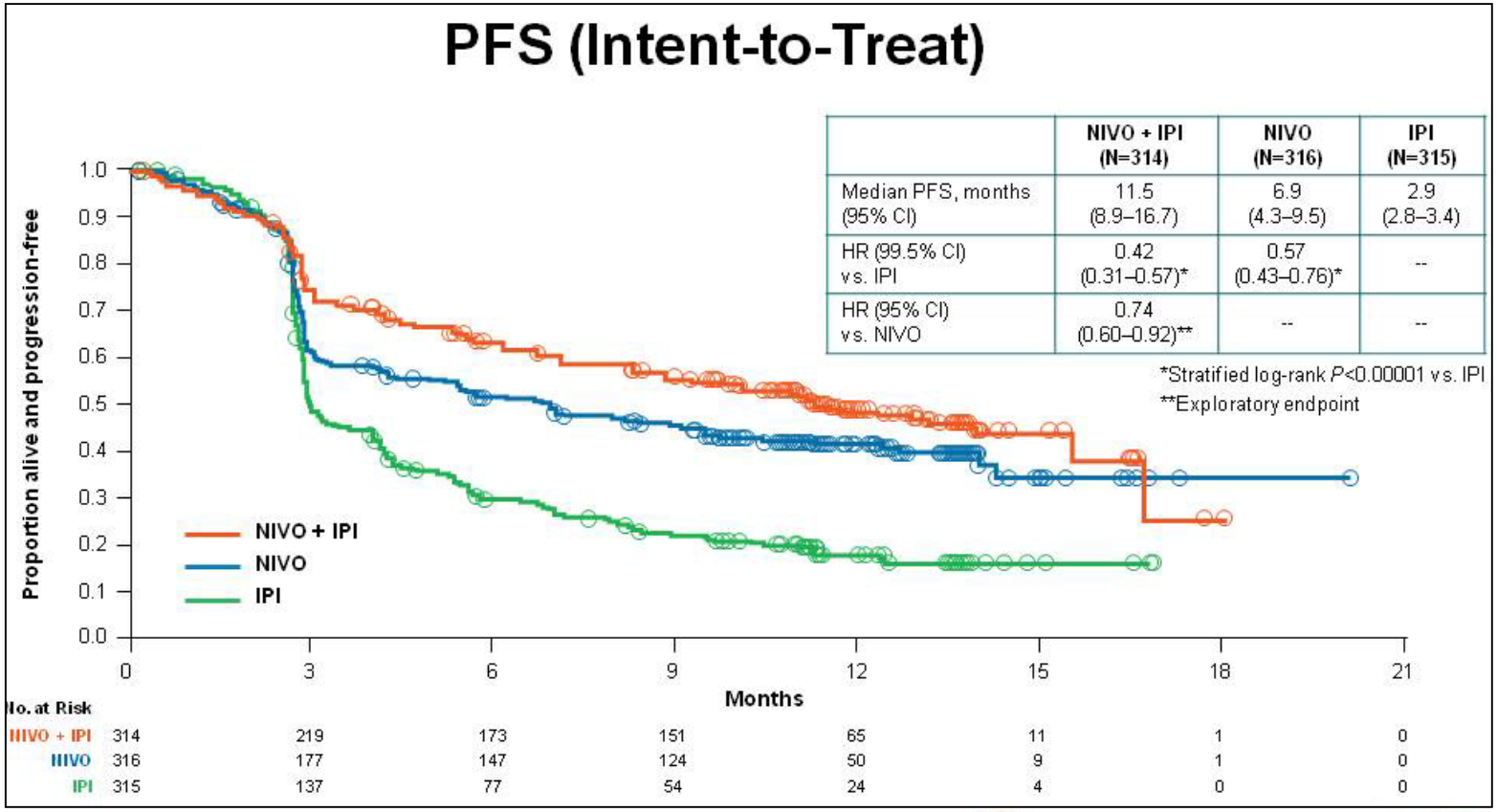
Ipilimumab: CTLA-4

Nivolumab: PD-1

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




| | 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)* | 0.57 (0.43–0.76)* | -- |
| HR (95% CI) vs. NIVO | 0.74 (0.60–0.92)** | -- | -- |

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

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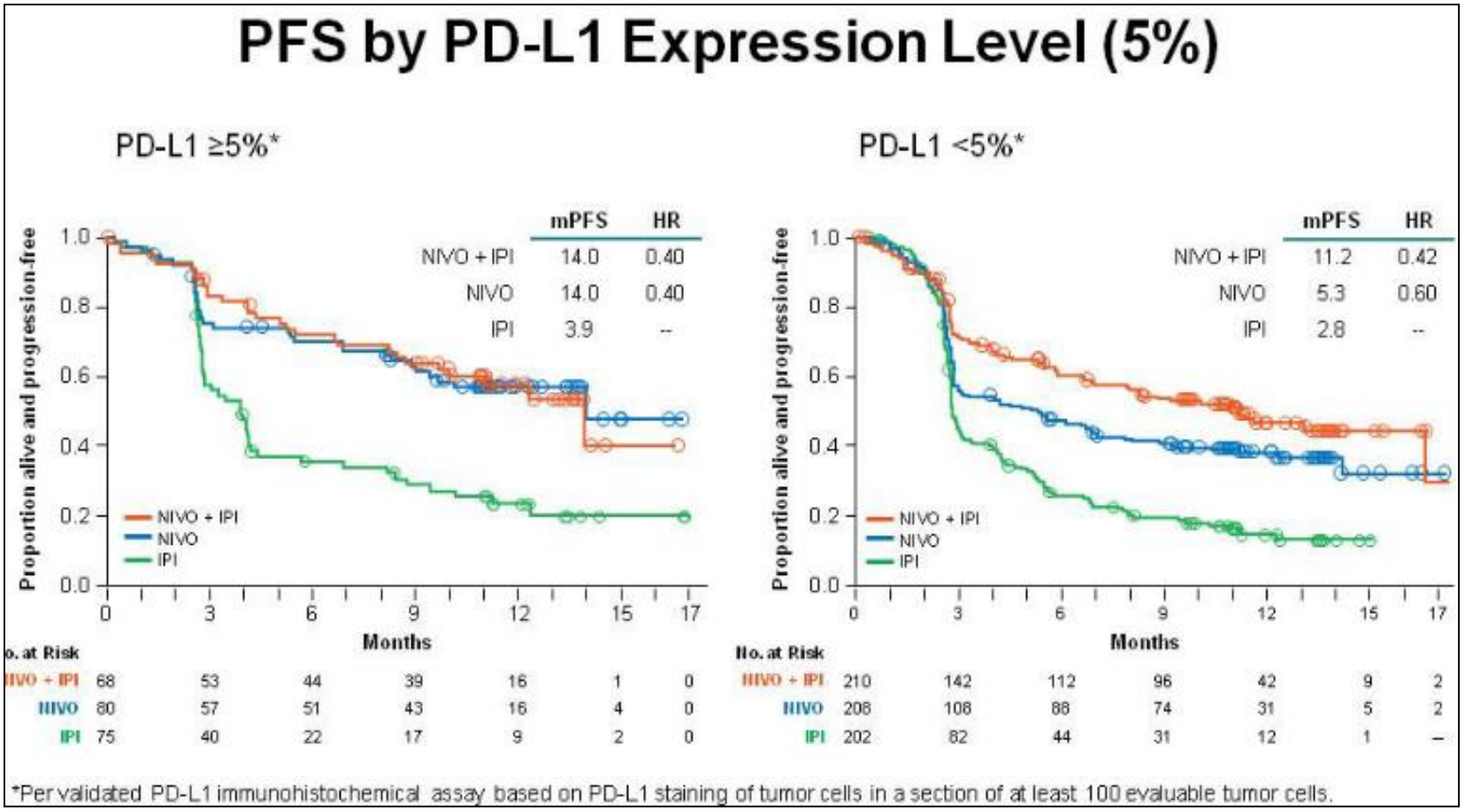
Ipilimumab: CTLA-4

Nivolumab: PD-1

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

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Ipilimumab: CTLA-4

Nivolumab: PD-1

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

## Safety Summary

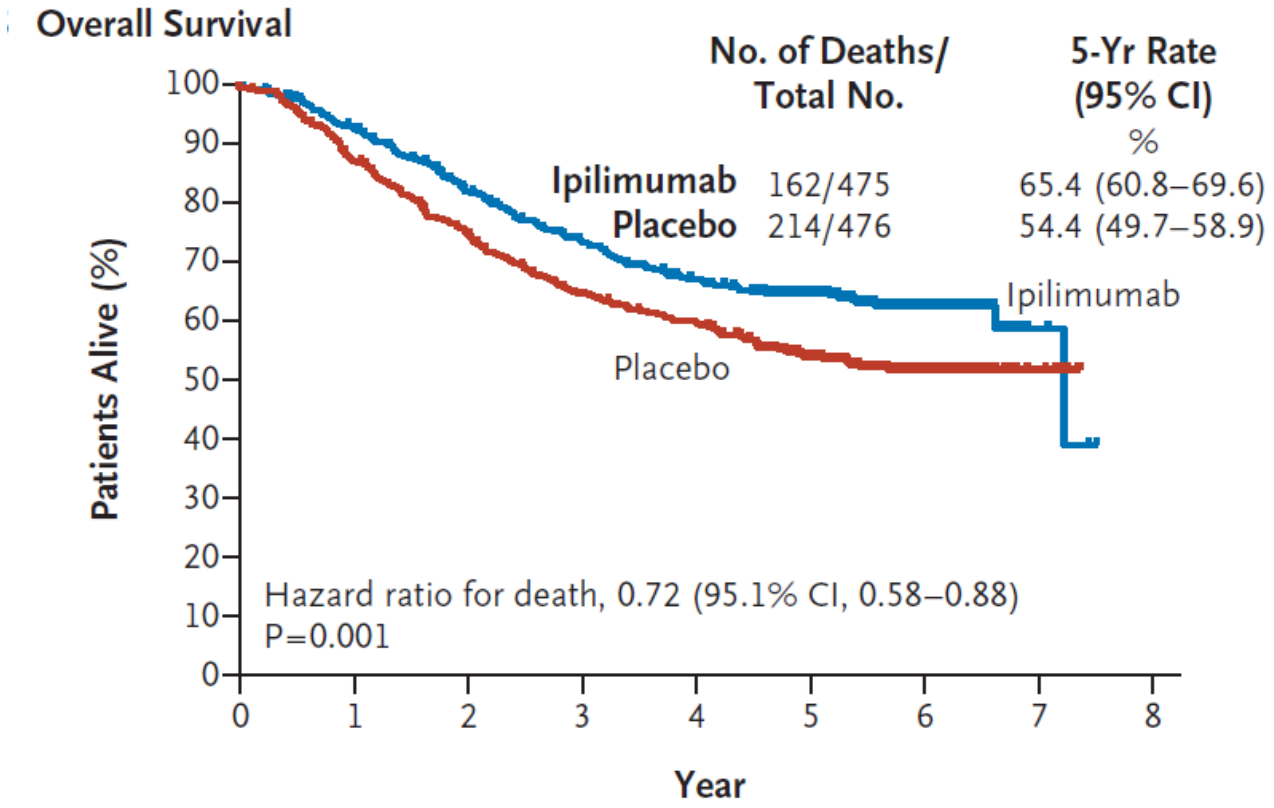
| Patients Reporting Event, % | NIVO + IPI (N=313) | | NIVO (N=313) | | IPI (N=311) | |
|---|---|---|---|---|---|---|
| | Any Grade | Grade 3–4 | Any Grade | Grade 3–4 | Any Grade | Grade 3–4 |
| Treatment-related adverse event (AE) | 95.5 | 55.0 | 82.1 | 16.3 | 86.2 | 27.3 |
| Treatment-related AE leading 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)

# Adjuvant Ipilimumab in High-Risk Melanoma




Eggermont *et al*. NEJM 2016

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# Case #1 follow up

How I treated patient:

- Tumor resected, sent for molecular testing
- Margins close but clear
- Ipilimumab at “adjuvant” dose of 10mg/kg with maintenance

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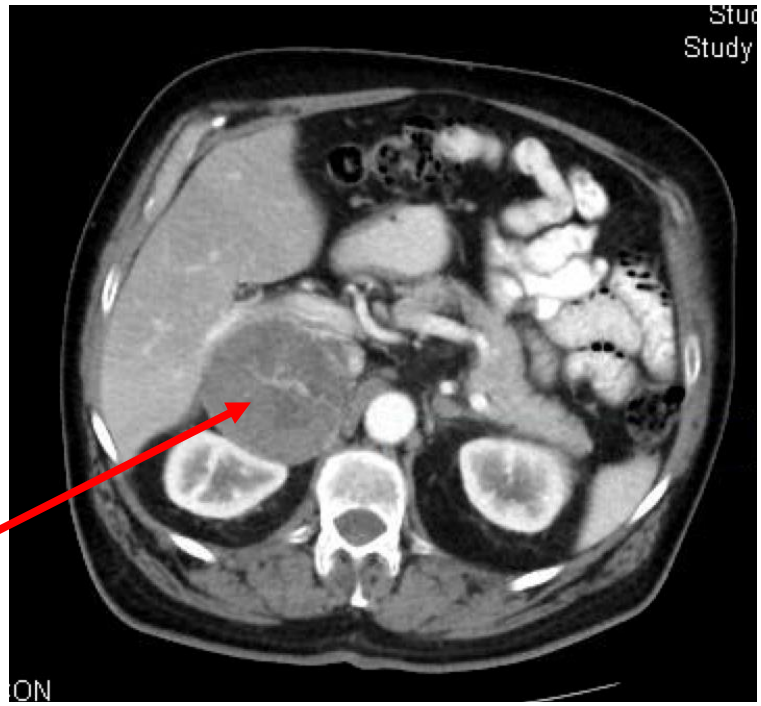
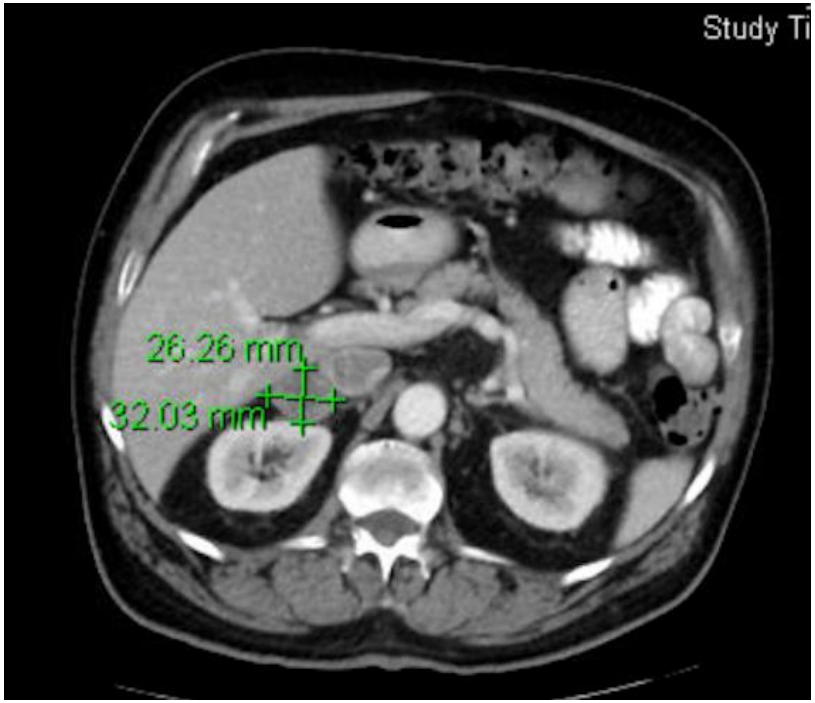
## Case #2: metastatic melanoma BRAF mutant

60 yo male

- Presented with symptomatic pulmonary metastases 8/2015 and a large R adrenal mass. Biopsy confirmed metastatic melanoma, $BRAF^{V600E}$ mutant.
- Initial Therapy:
  - dabrafenib and trametinib
  - Near CR x 18 months
  - Tolerated therapy with minimal side effects—mainly peripheral edema
- Progression in R adrenal metastasis but controlled in lung; new 5mm asymptomatic brain metastasis
- Checkmate 209204
  - nivolumab plus ipilimumab for metastatic melanoma to brain

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



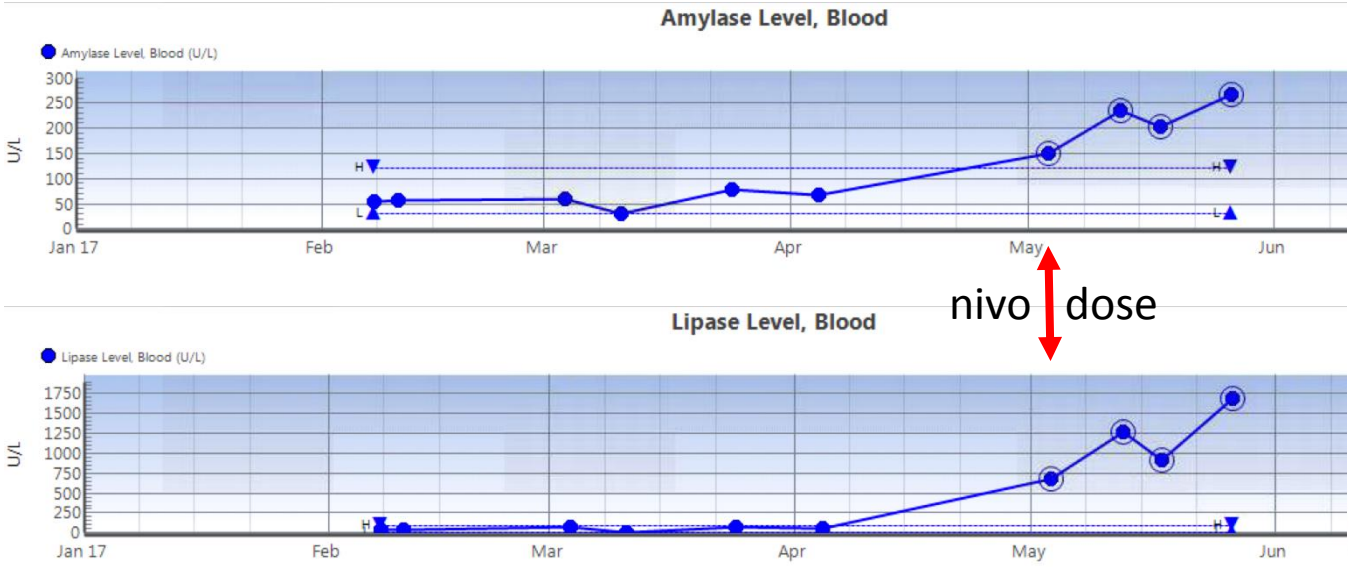



# Toxicity management issues

Patient developed grade 3 diarrhea with Nivo/Ipi combination
Immunotherapy held and patient treated with corticosteroids

Patient recovered fully and continued treatment with nivolumab in the maintenance phase

Pt developed chemical pancreatitis, initially without Sx, now with mild abdominal pain—enzymes rising despite skipping last dose nivolumab→steroid? [US not diagnostic, CT is negative, pt continues to work, eat, perform ADLs normally



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# 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?



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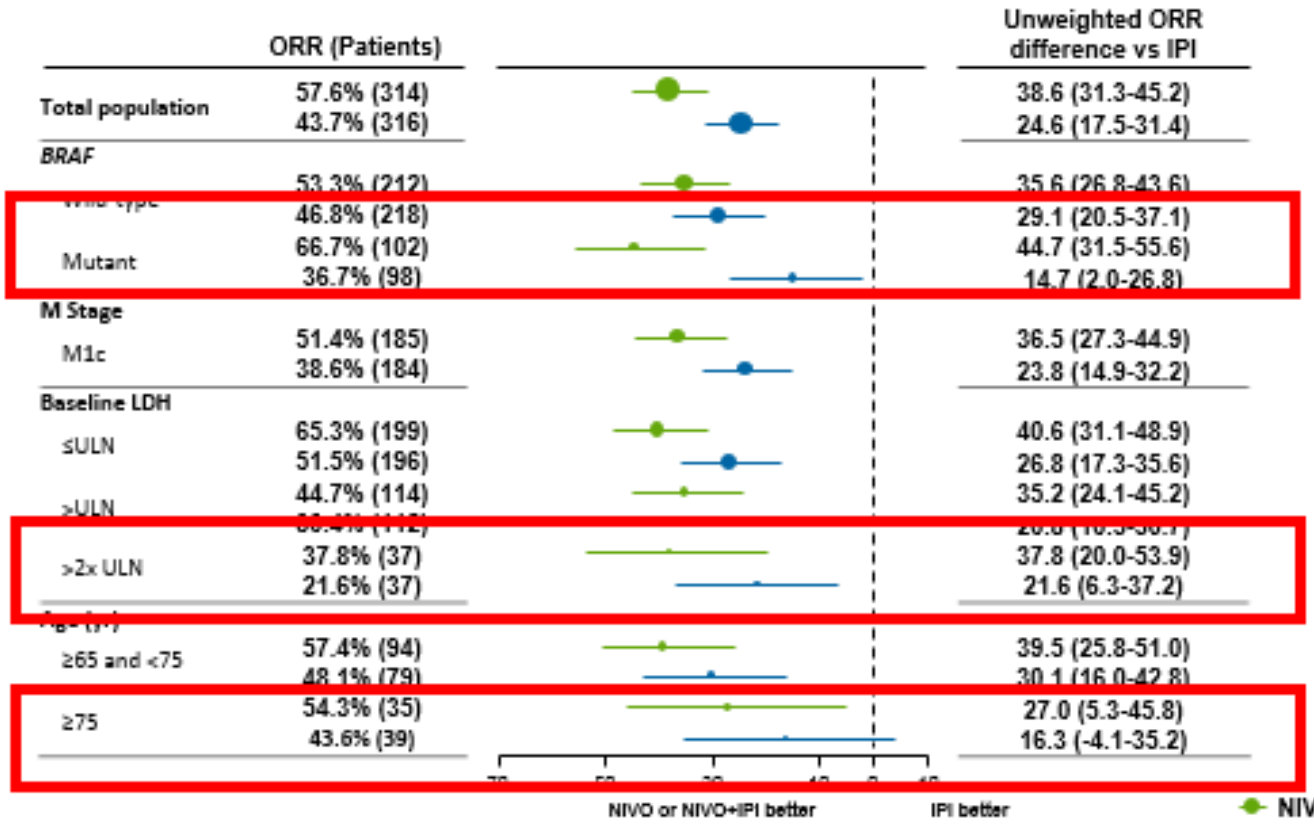
# Ipi-Nivo vs Nivo Overall Response Rate in Patient Subgroups



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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



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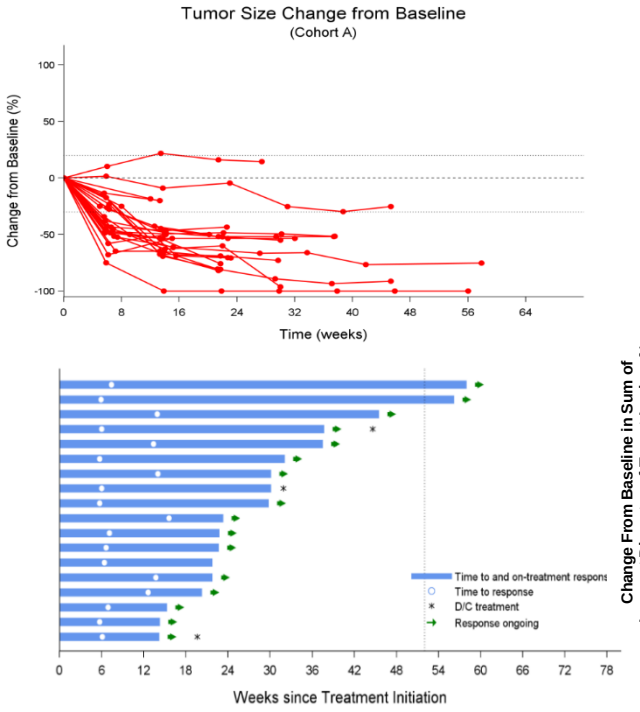
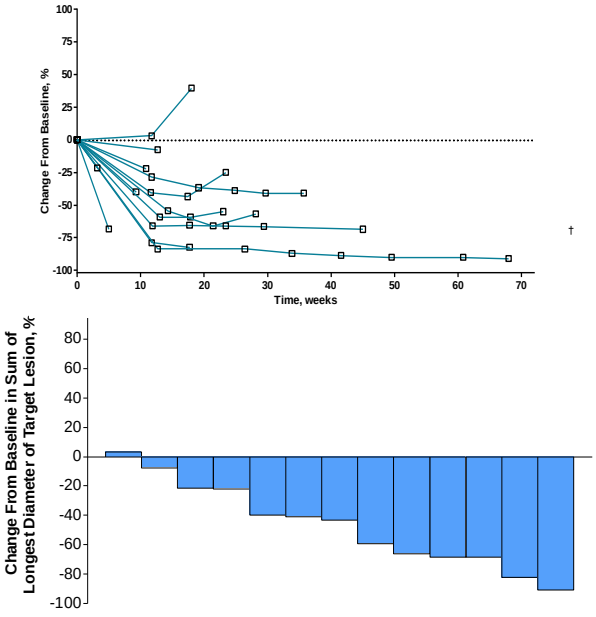
# Target-Immuno Triplets: BRAF + MEK + PD1/L1

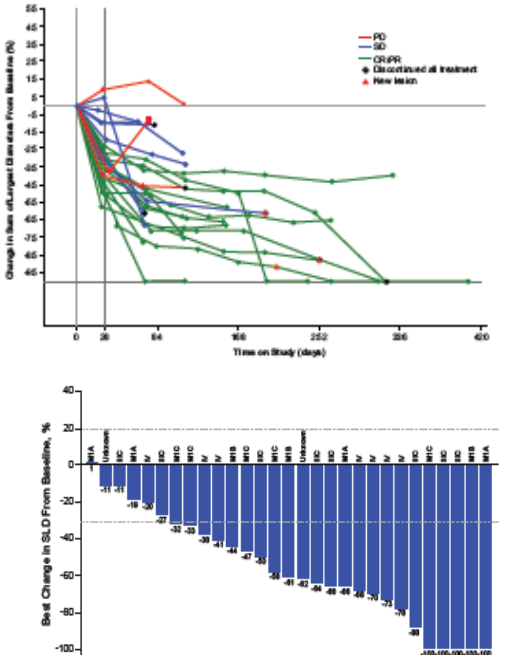
## Dabrafenib+Trametinib+ Durvalumab




## Dabrafenib+Trametinib+ Pembrolizumab




## Vemurafenib+Cobimetinib+ Atezolizumab



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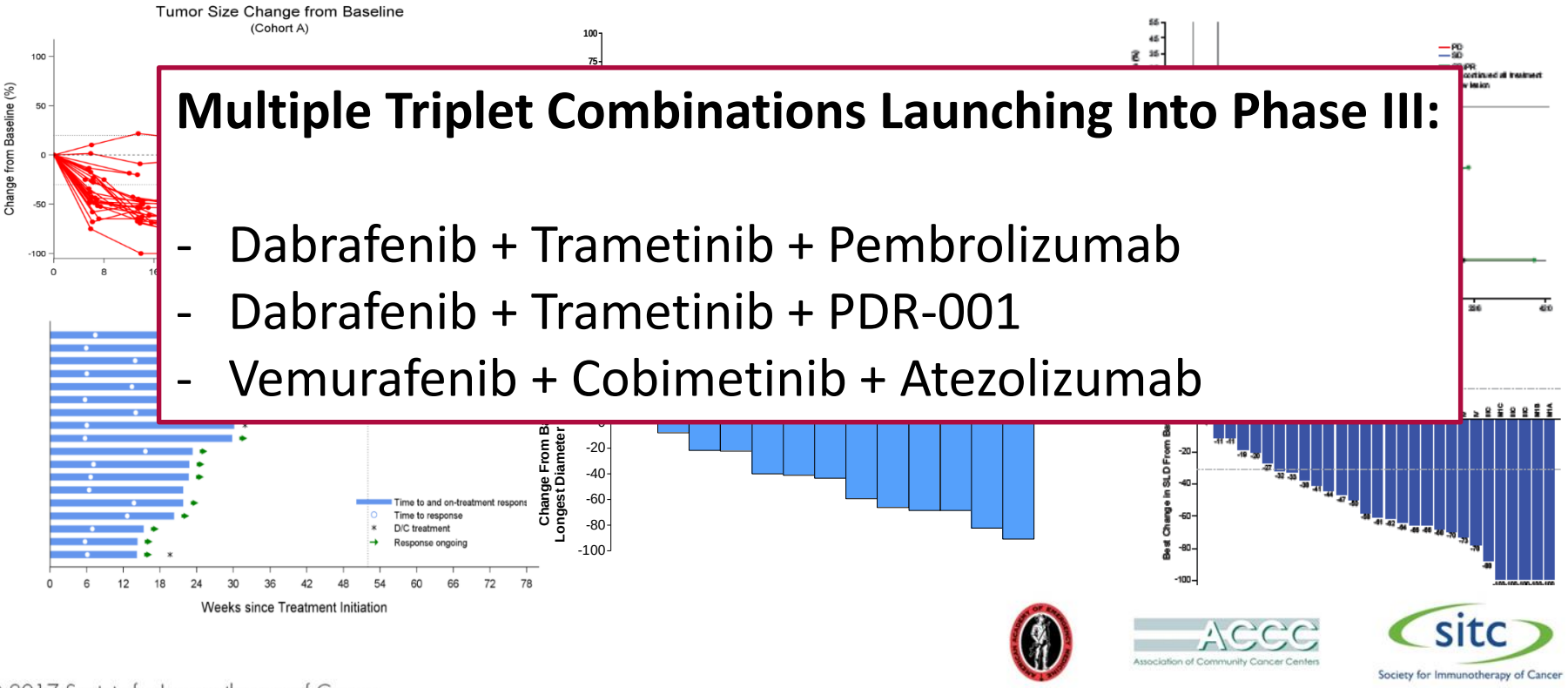
# Target-Immuno Triplets: BRAF + MEK + PD1/L1

Dabrafenib+Trametinib+ Durvalumab

Dabrafenib+Trametinib+ Pembrolizumab

Vemurafenib+Cobimetinib+ Atezolizumab




**Multiple Triplet Combinations Launching Into Phase III:**

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

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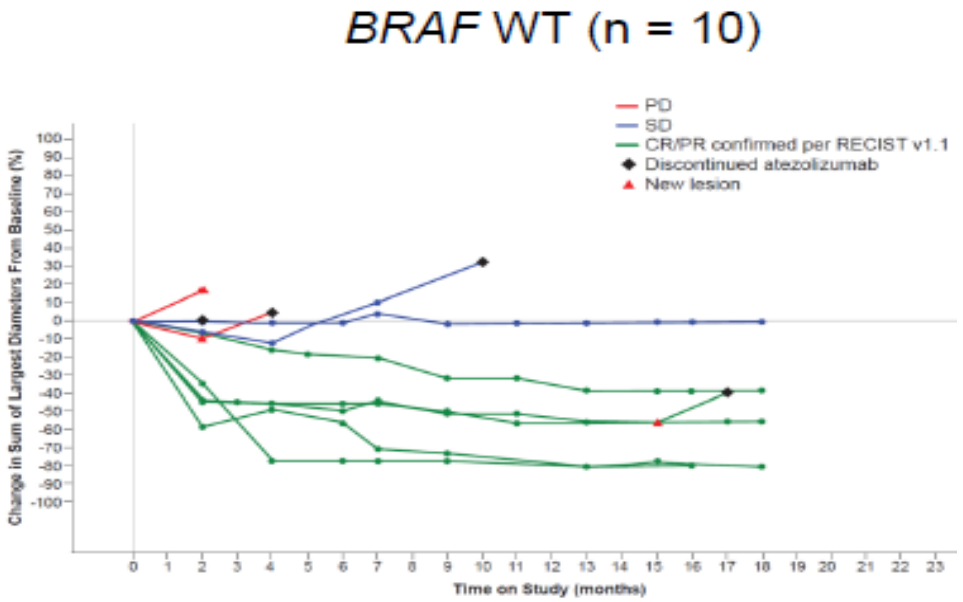
# MEK inhibitor + PDL-1 for BRAFwt Melanoma Phase I Cobimetinib + Atezolizumab




| | 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%) |

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

**PROTOCOL NUMBER: CO39722**

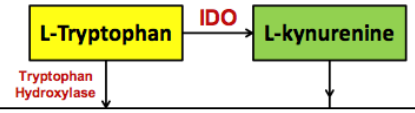
Atezolizumab: PD-L1

Pembrolizumab : PD-1

# IDO inhibitor epacadostat + pembrolizumab

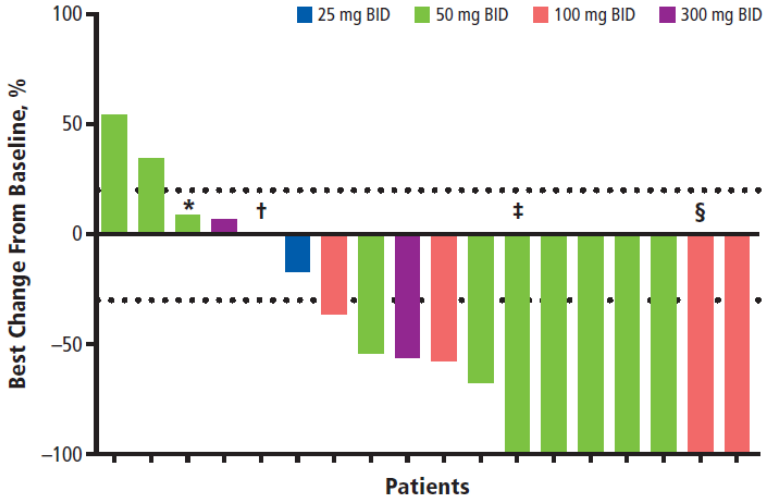
**Indoleamine Dioxygenase-1 (IDO1)**

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




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

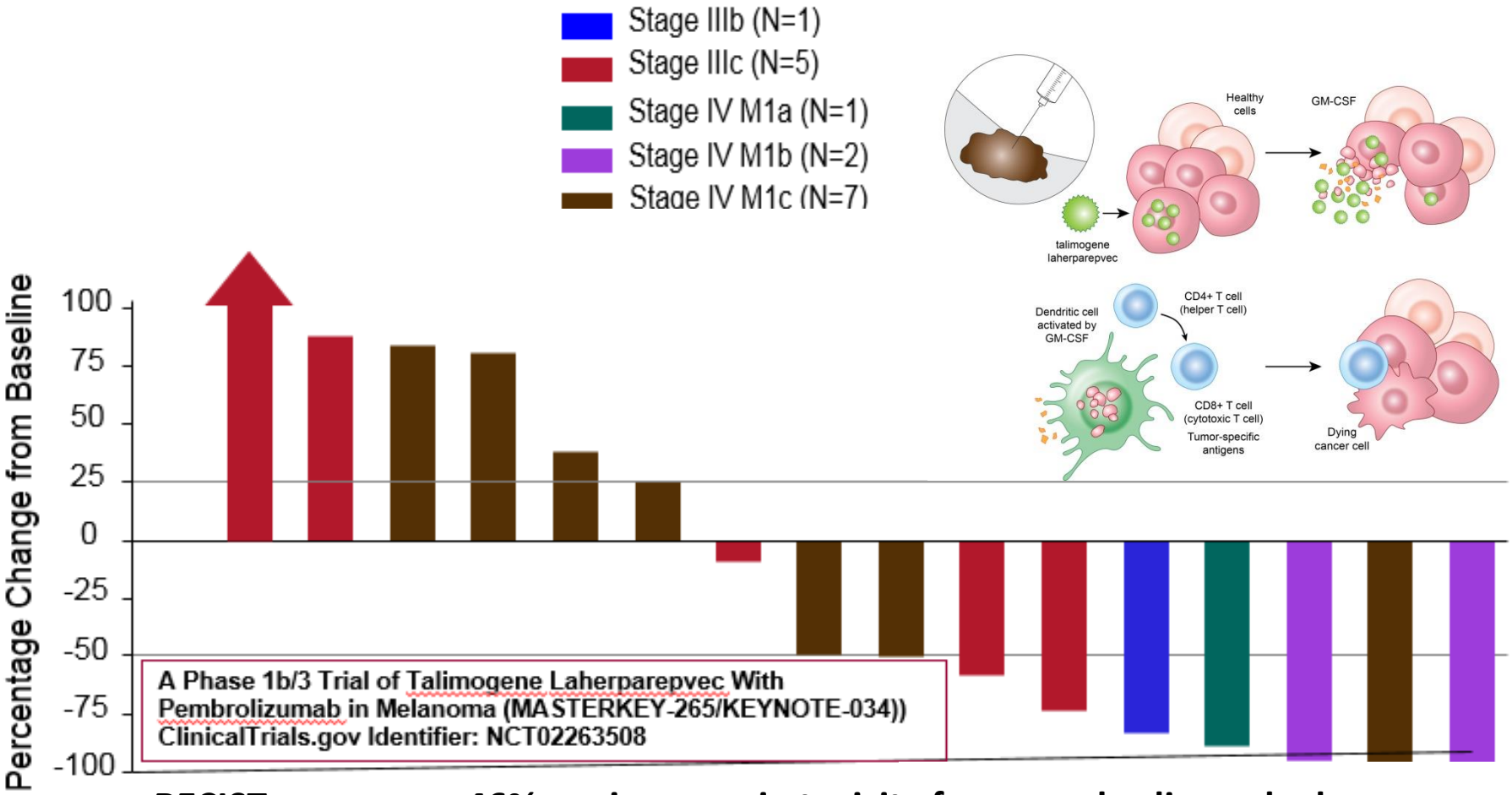
**A Phase 3 Study of Pembrolizumab + Epacadostat or Placebo in Subjects With Unresectable or Metastatic Melanoma (Keynote-252 / ECHO-301)**
**ClinicalTrials.gov Identifier: NCT02752074**




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

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

# 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

- 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!