ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Melanoma

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ACCC Association of Community Cancer Centers

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Disclosures

- Advisory boards: BMS, Novartis, Array
- Speaker: BMS, Novartis, Roche
- I will be discussing non-FDA approved indications during my presentation.

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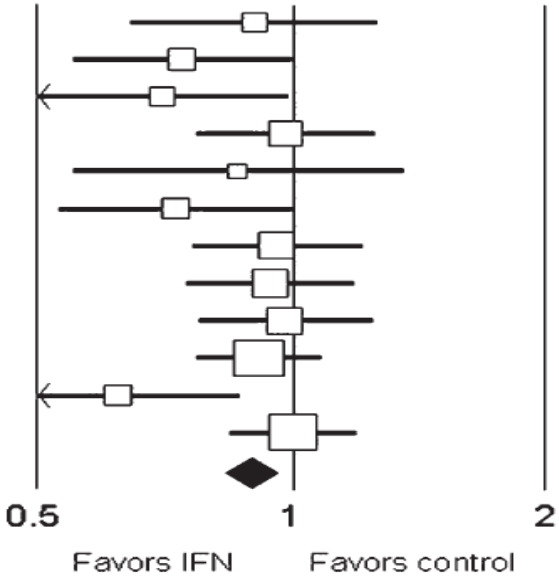
Current FDA Approved Immunotherapy For Melanoma

- *High-dose IL-2*: advanced melanoma
- *Interferon alpha-2b*: HD, pegylated: adjuvant high risk resected
- *Ipilimumab*: advanced melanoma and adjuvant treatment of high risk resected
- *Pembrolizumab*: advanced melanoma
- *Nivolumab*: advanced melanoma, adjuvant therapy
- *Ipilimumab + nivolumab*: advanced melanoma
- *Talimogene Laherparepvec*: unresectable cutaneous, subcutaneous and nodal

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		

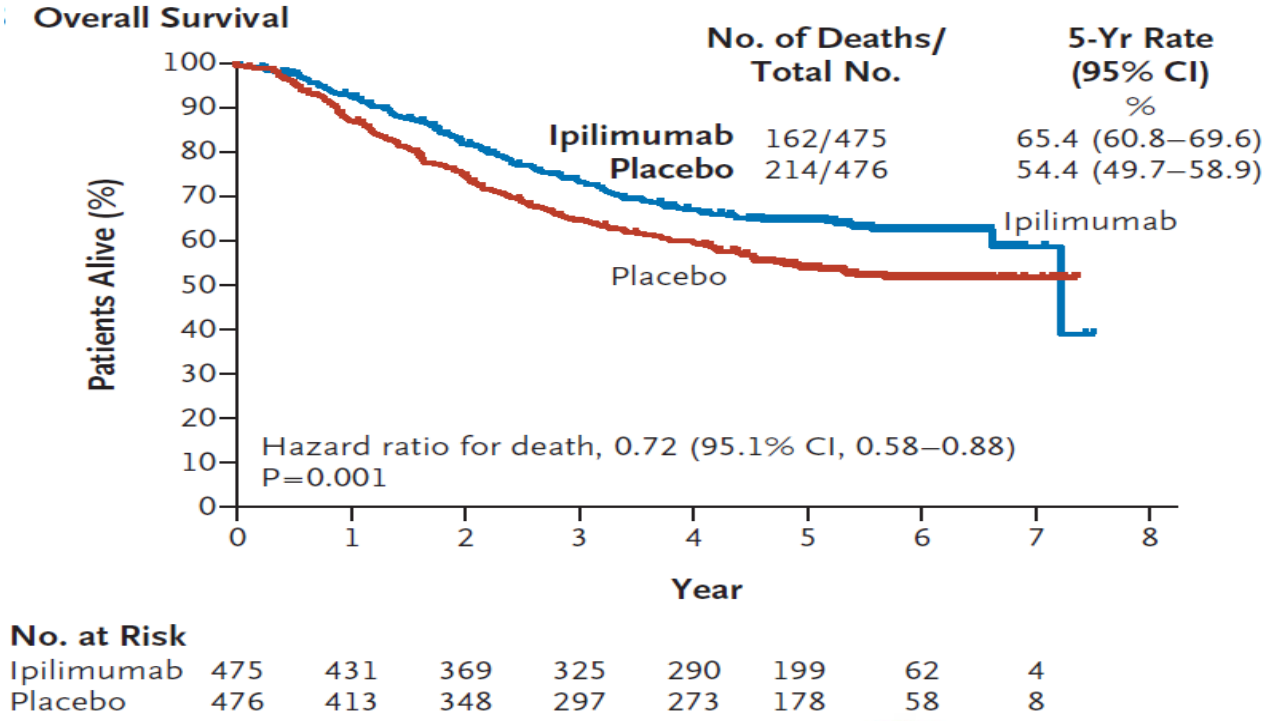


Adjuvant high-dose interferon alpha has been estimated to improve OS in high risk melanoma by an absolute 3-5%.

Not all trials showed a survival benefit. Most showed RFS benefit.

Mocellin et al. JNCI. 2010

Adjuvant Ipilimumab in High-Risk Melanoma



Eggermont *et al*. NEJM 2016

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Adjuvant nivolumab vs ipilimumab in High-Risk Melanoma
3 mg/kg IV q 2 weeks x 1 year

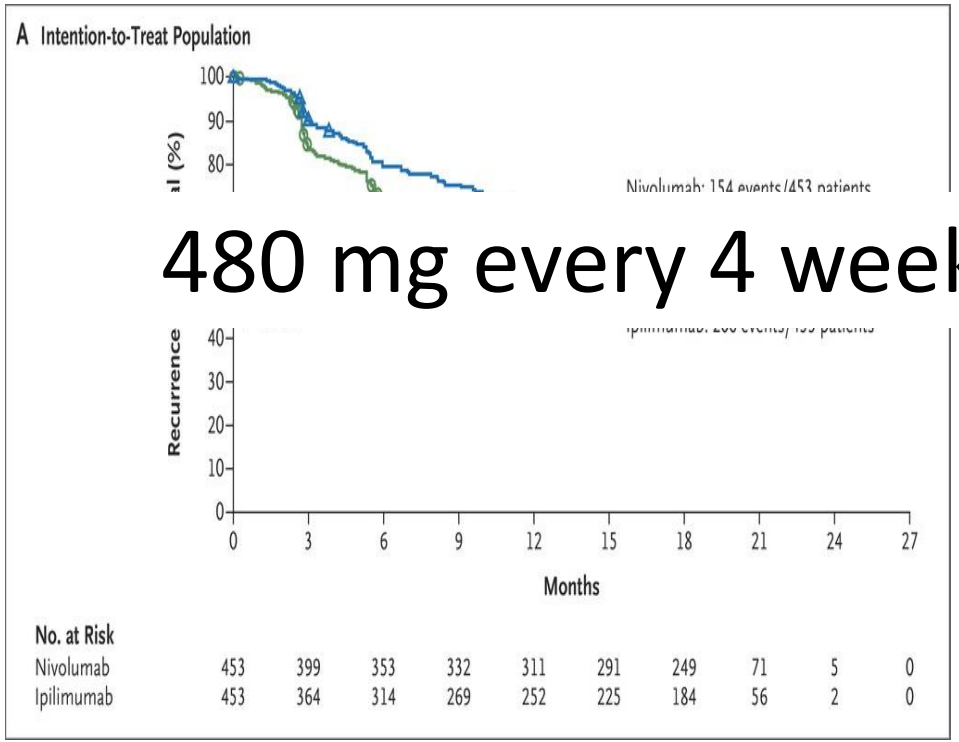

Table 2. Adverse Events*

Event	Nivolumab (N=452)		Ipilimumab (N=453)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)			
Any adverse event	438 (96.9)	115 (25.4)	446 (98.5)	250 (55.2)
				208 (45.9)
				43 (9.5)
				5 (1.1)
Rash	90 (19.9)	5 (1.1)	133 (29.4)	14 (3.1)
Nausea	68 (15.0)	1 (0.2)	91 (20.1)	0
Arthralgia	57 (12.6)	1 (0.2)	49 (10.8)	2 (0.4)
Asthenia	57 (12.6)	1 (0.2)	53 (11.7)	4 (0.9)
Hypothyroidism	49 (10.8)	1 (0.2)	31 (6.8)	2 (0.4)
Headache	44 (9.7)	1 (0.2)	79 (17.4)	7 (1.5)
Abdominal pain	29 (6.4)	0	46 (10.2)	1 (0.2)
Increase in ALT level	28 (6.2)	5 (1.1)	66 (14.6)	26 (5.7)
Increase in AST level	25 (5.5)	2 (0.4)	60 (13.2)	19 (4.2)
Maculopapular rash	24 (5.3)	0	50 (11.0)	9 (2.0)
Hypophysitis	7 (1.5)	2 (0.4)	48 (10.6)	11 (2.4)
Pyrexia	7 (1.5)	0	54 (11.9)	2 (0.4)
Any adverse event leading to discontinuation	44 (9.7)	21 (4.6)	193 (42.6)	140 (30.9)
Treatment-related adverse event leading to discontinuation	35 (7.7)	16	189 (41.7)	136

480 mg every 4 weeks FDA approved

Weber *et al*. NEJM 2017

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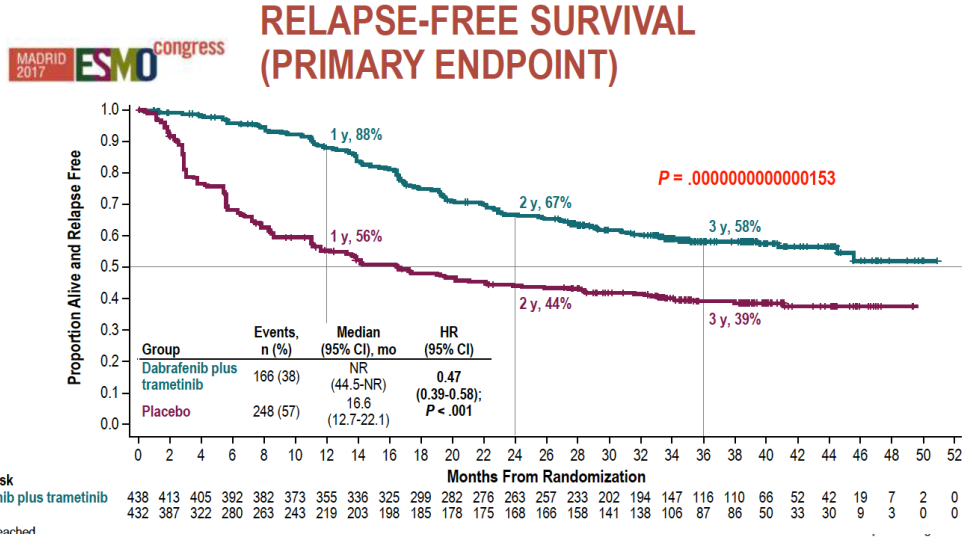
Other adjuvant trials with pending data

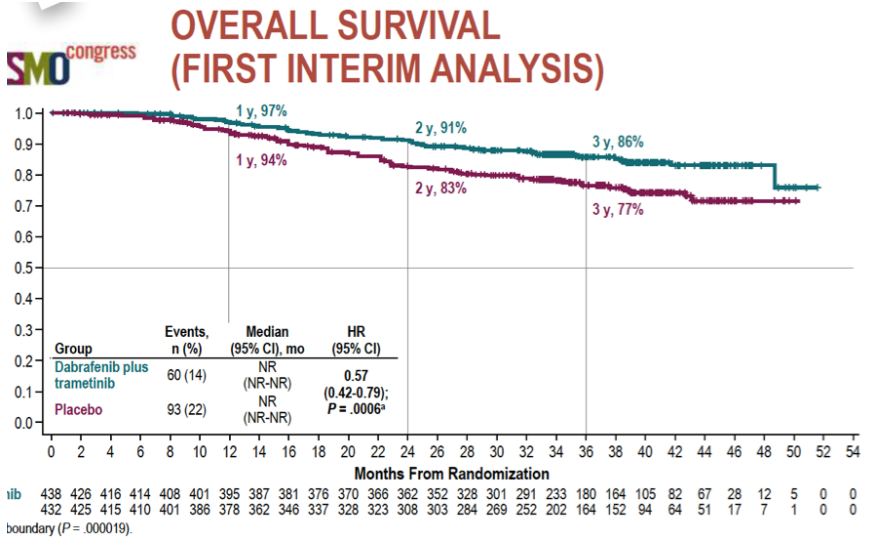
- S1404
  - IFN/ipilimumab vs. pembrolizumab
  - Accrued; results pending
  - Inclusion criteria: IIIA (N2a), IIIB, IIIC, IV

- EORTC-1325/KEYNOTE-054
  - pembrolizumab vs. placebo
  - RFS (primary endpoint) HR=0.57 favoring pembrolizumab
  - Inclusion criteria: IIIA (> 1mm nodal met), IIIB, IIIC

- CheckMate 915
  - nivolumab vs ipilimumab + nivolumab (attenuated)
  - Ongoing
  - Inclusion criteria: IIIB,IIIC,IIID, IV (AJCC 8th edition)

Adjuvant therapy of high risk BRAF V600 mutant melanoma





Long, GV et al. NEJM, 2017

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A 36 year-old man with a changing congenital mole

- Bx 10/2012: superficial spreading melanoma 2.5 mm, non-ulcerated, mitotic rate >4/mm2: T3a, N0
- Treated with WLE, negative R axillary LN bx.
- In January 2017: metastatic melanoma in two right inguinal palpable lymph nodes treated with complete nodal dissection: 11/16 LN +, extranodal disease present.
- Tumor showed a BRAF V600E mutation.

Question 1

How would you treat this patient TODAY?

a. adjuvant high dose interferon for one year
b. dabrafenib plus trametinib for one year
c. adjuvant ipilimumab at 10 mg/kg for 2 years
d. adjuvant nivolumab 3 mg/kg every 2 weeks for one year
e. none of the above

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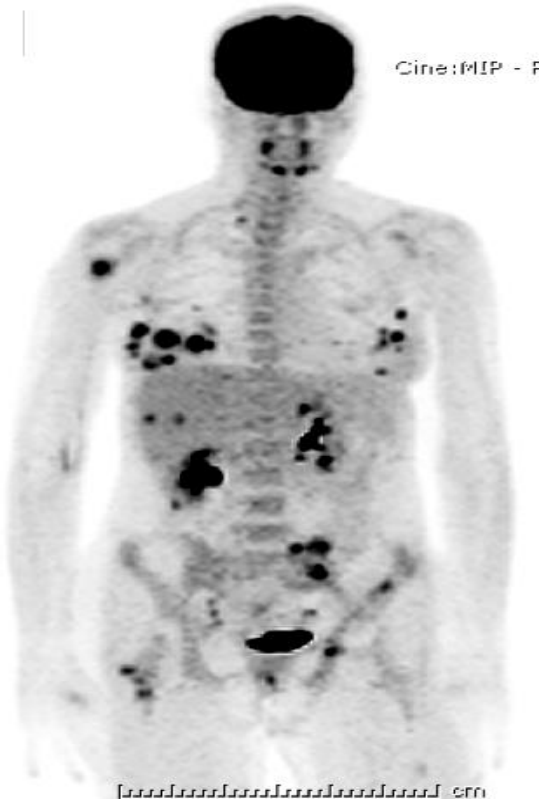
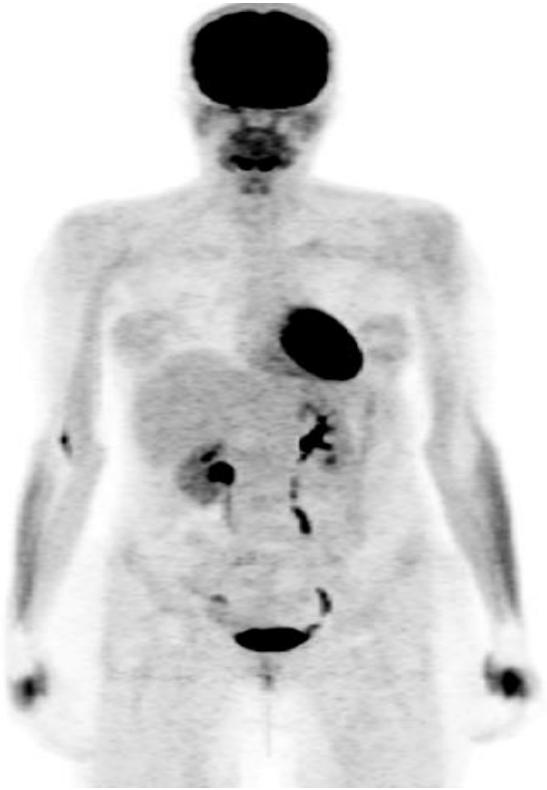
32 year old pregnant singer treated with CTLA-4 blocking Ab



January 2006



January 2018

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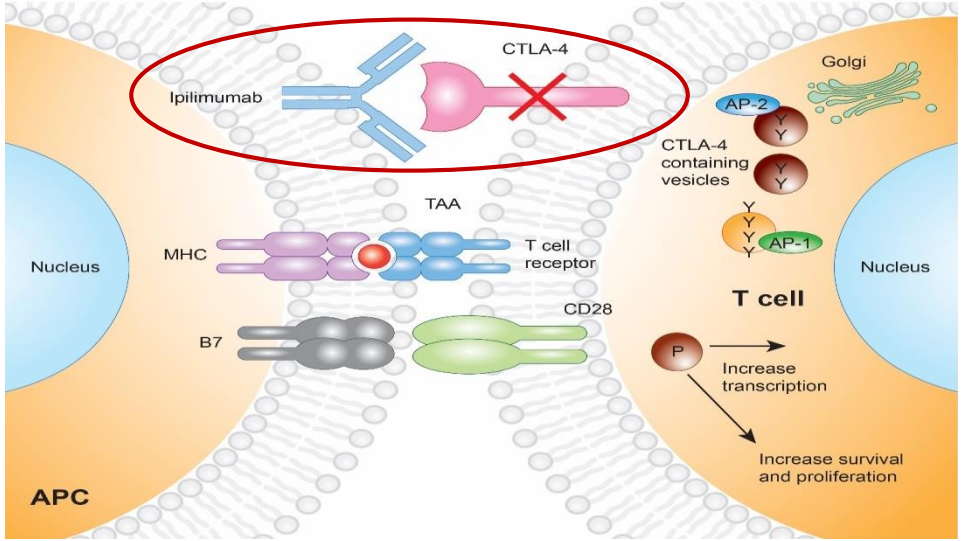
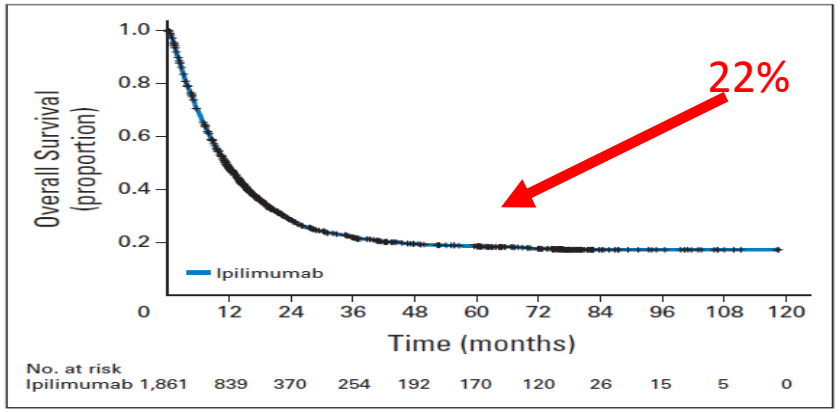
Ipilimumab & Immune Check-Point Blockade





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

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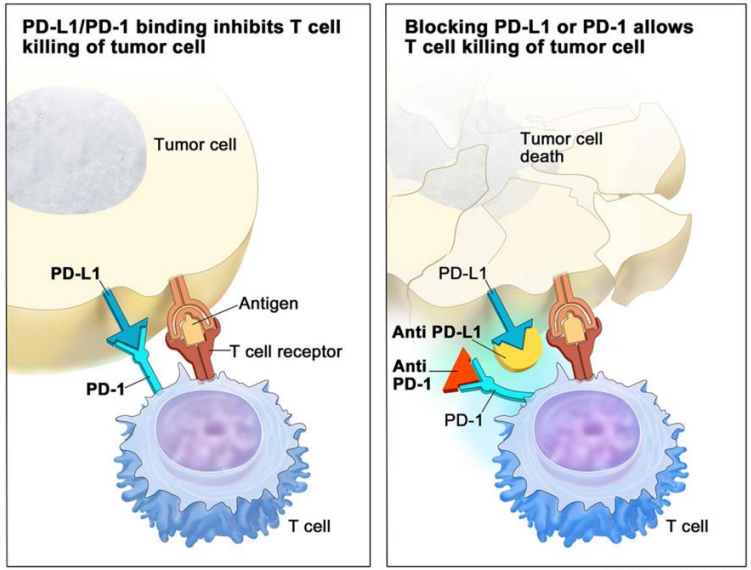
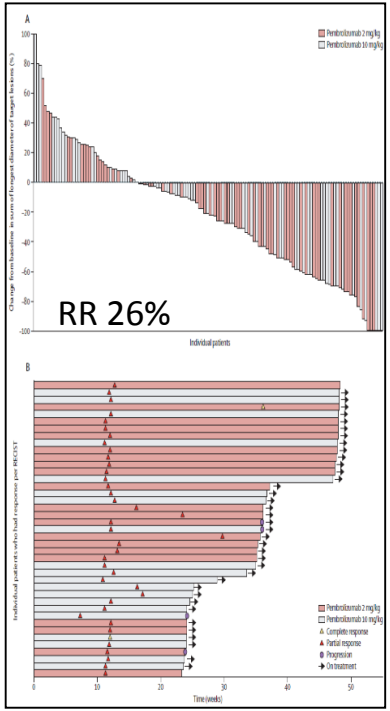
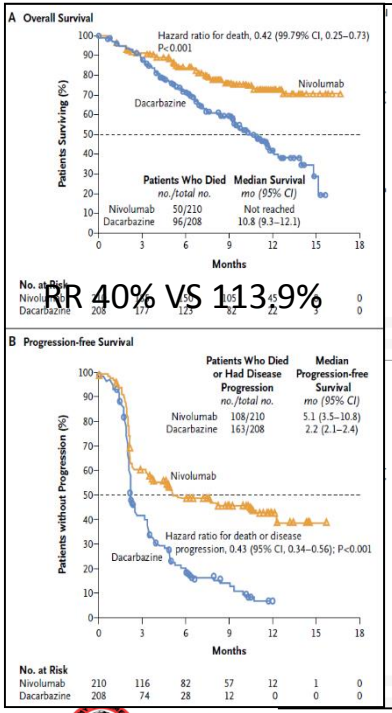
Anti-PD1 in Melanoma

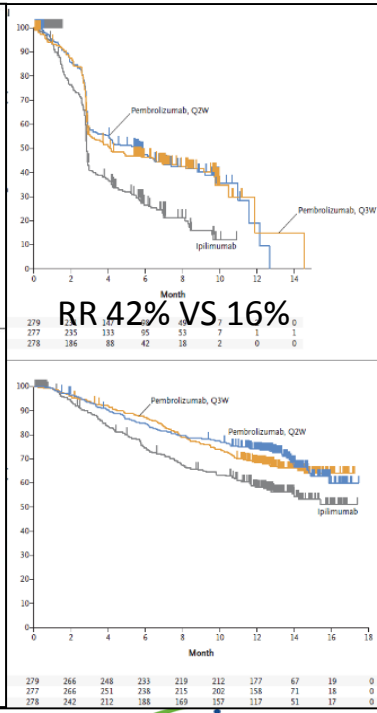
Robert et al, Lancet 2014	Robert et al, NEJM 2015	Robert et al, NEJM 2015
Anti-PD1 (pembrolizumab) *after* ipilimumab	Front-line anti-PD1 (nivolumab) vs. DTIC	Front-line anti-PD1 (pembrolizumab) vs. ipilimumab







RR 40% VS 13.9%



RR 42% VS 16%

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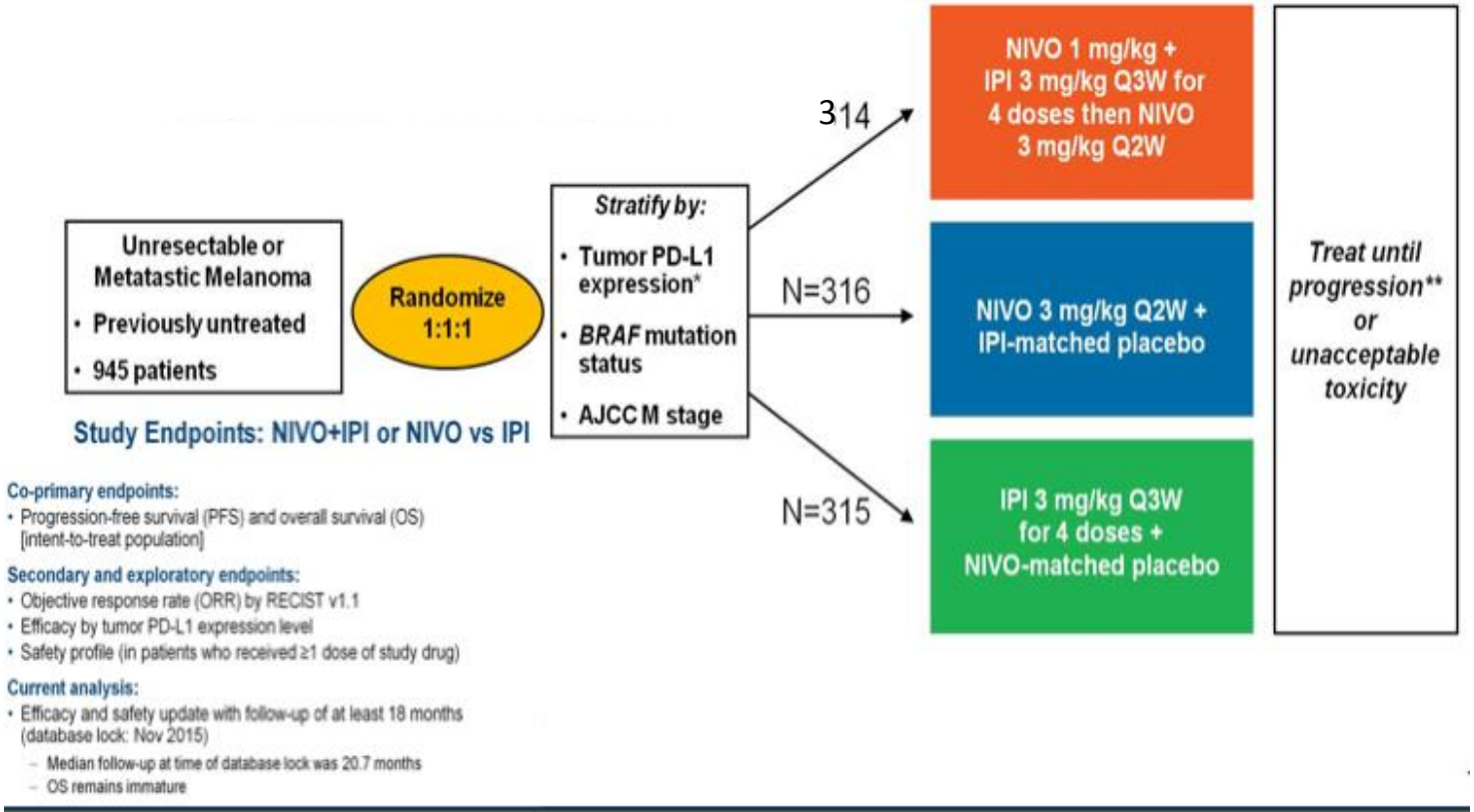
CheckMate 067



Study Endpoints: NIVO+IPI or NIVO vs IPI

Co-primary endpoints:
- Progression-free survival (PFS) and overall survival (OS) [intent-to-treat population]

Secondary and exploratory endpoints:
- Objective response rate (ORR) by RECIST v1.1
- Efficacy by tumor PD-L1 expression level
- Safety profile (in patients who received ≥1 dose of study drug)

Current analysis:
- Efficacy and safety update with follow-up of at least 18 months (database lock: Nov 2015)
  - Median follow-up at time of database lock was 20.7 months
  - OS remains immature

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Response To Treatment.

Table 1. Response to Treatment.*

Variable	Nivolumab plus Ipilimumab (N=314)	Nivolumab (N=316)	Ipilimumab (N=315)
Best overall response — no. (%)†			
Complete response	61 (19)	52 (16)	16 (5)
Partial response	122 (39)	88 (28)	43 (14)
Stable disease	38 (12)	31 (10)	69 (22)
Progressive disease	74 (24)	121 (38)	159 (50)
Unable to determine	19 (6)	24 (8)	28 (9)
Objective response‡			
No. of patients with response	183	140	59
% of patients (95% CI)	58 (53–64)	44 (39–50)	19 (15–24)
Estimated odds ratio (95% CI)§	6.46 (4.45–9.38)	3.57 (2.48–5.15)	—
P value	<0.001	<0.001	—
Median duration of response (95% CI) — mo	NR	NR (36.3–NR)	19.3 (8.3–NR)

* NR denotes not reached.
† The best overall response was assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors, version 1.1.
‡ Data included patients with a complete response and those with a partial response. The calculation of the 95% confidence interval was based on the Clopper–Pearson method.
§ The comparison is with the ipilimumab group.

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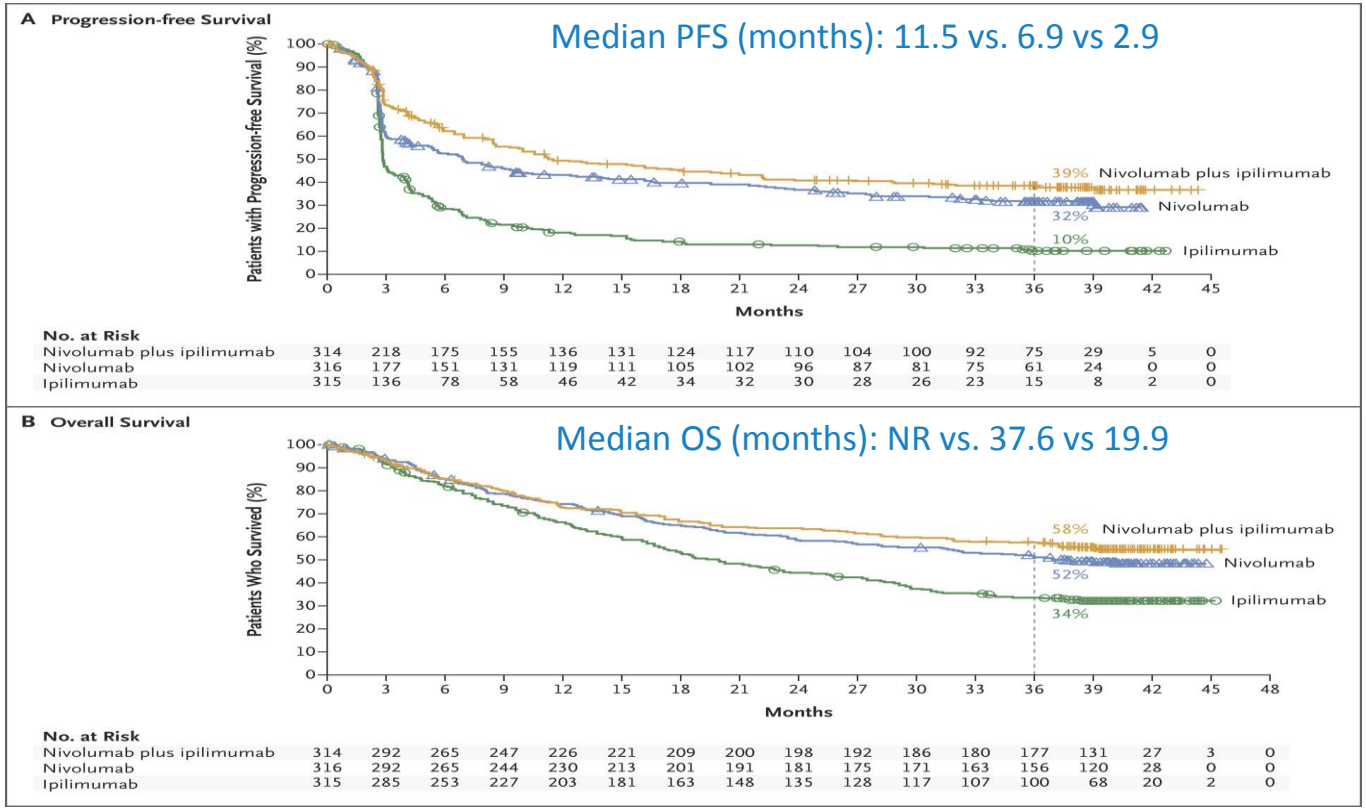
Wolchok JD Et Al. N Engl J Med 2017;377:1345-1356

Kaplan–Meier Estimates of Survival (f/u 36 mos)



Wolchok JD et al. N Engl J Med 2017;377:1345-1356

Treatment-related Adverse Events.

Table 2. Treatment-Related Adverse Events.*

Event	Nivolumab plus Ipilimumab (N = 313)		Nivolumab (N = 313)		Ipilimumab (N = 311)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)					
Any treatment-related adverse event	300 (96)	184 (59)	270 (86)	67 (21)	268 (86)	86 (28)
Rash	93 (30)	10 (3)	72 (23)	1 (<1)	68 (22)	5 (2)
Pruritus	112 (35)	6 (2)	67 (21)	1 (<1)	113 (36)	1 (<1)
Vitiligo	28 (9)	0	29 (9)	1 (<1)	16 (5)	0
Maculopapular rash	38 (12)	6 (2)	15 (5)	2 (1)	38 (12)	1 (<1)
Fatigue	119 (38)	13 (4)	114 (36)	3 (1)	89 (29)	3 (1)
Asthenia	30 (10)	1 (<1)	25 (8)	1 (<1)	17 (5)	2 (1)
Pyrexia	60 (19)	2 (1)	21 (7)	0	21 (7)	1 (<1)
Diarrhea	142 (45)	29 (9)	67 (21)	9 (3)	105 (34)	18 (6)
Nausea	88 (28)	7 (2)	41 (13)	0	51 (16)	2 (1)
Vomiting	48 (15)	7 (2)	22 (7)	1 (<1)	24 (8)	1 (<1)
Abdominal pain	26 (8)	1 (<1)	18 (6)	0	28 (9)	2 (1)
Colitis	40 (13)	26 (8)	7 (2)	3 (1)	35 (11)	24 (8)
Headache	35 (11)	2 (1)	24 (8)	0	23 (8)	1 (<1)
Arthralgia	43 (14)	2 (1)	31 (10)	1 (<1)	22 (7)	0
Increased lipase level	44 (14)	34 (11)	27 (9)	14 (4)	18 (6)	12 (4)
Increased amylase level	26 (8)	9 (3)	20 (6)	6 (2)	15 (5)	4 (1)
Increased aspartate aminotransferase level	51 (16)	19 (6)	14 (4)	3 (1)	12 (4)	2 (1)
Increased alanine aminotransferase level	60 (19)	27 (9)	13 (4)	4 (1)	12 (4)	5 (2)
Decreased weight	19 (6)	0	10 (3)	0	4 (1)	1 (<1)
Hypothyroidism	53 (17)	1 (<1)	33 (11)	0	14 (5)	0
Hyperthyroidism	35 (11)	3 (1)	14 (4)	0	3 (1)	0
Hypophysitis	23 (7)	5 (2)	2 (1)	1 (<1)	12 (4)	5 (2)
Decreased appetite	60 (19)	4 (1)	36 (12)	0	41 (13)	1 (<1)
Cough	25 (8)	0	19 (6)	2 (1)	15 (5)	0
Dyspnea	36 (12)	3 (1)	19 (6)	1 (<1)	12 (4)	0
Pneumonitis	22 (7)	3 (1)	5 (2)	1 (<1)	5 (2)	1 (<1)
Treatment-related adverse event leading to discontinuation	123 (39)	95 (30)	37 (12)	24 (8)	49 (16)	43 (14)

* Shown are treatment-related adverse events of any grade that occurred in more than 5% of the patients in any treatment group who had one or more treatment-related adverse events of grade 3 or 4. The relatedness of the adverse event to treatment was determined by the investigators. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Two deaths that were considered by the investigators to be related to a study drug occurred in the nivolumab group (neutropenia) and in the ipilimumab group (colonic perforation) within 100 days after the last dose of study drug; two additional deaths in the nivolumab-plus-ipilimumab group (one due to cardiac insufficiency and autoimmune myocarditis, and one due to liver necrosis) that were considered by the investigator to be related to a study drug were reported more than 100 days after the last dose of study drug.

Wolchok JD et al. N Engl J Med 2017;377:1345-1356

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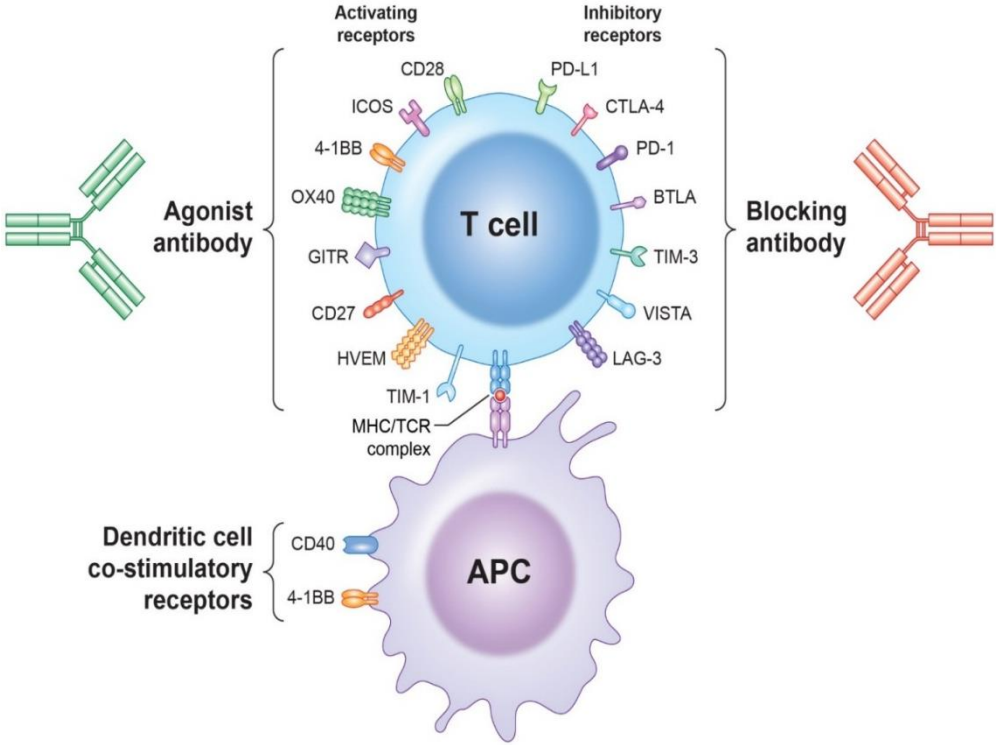
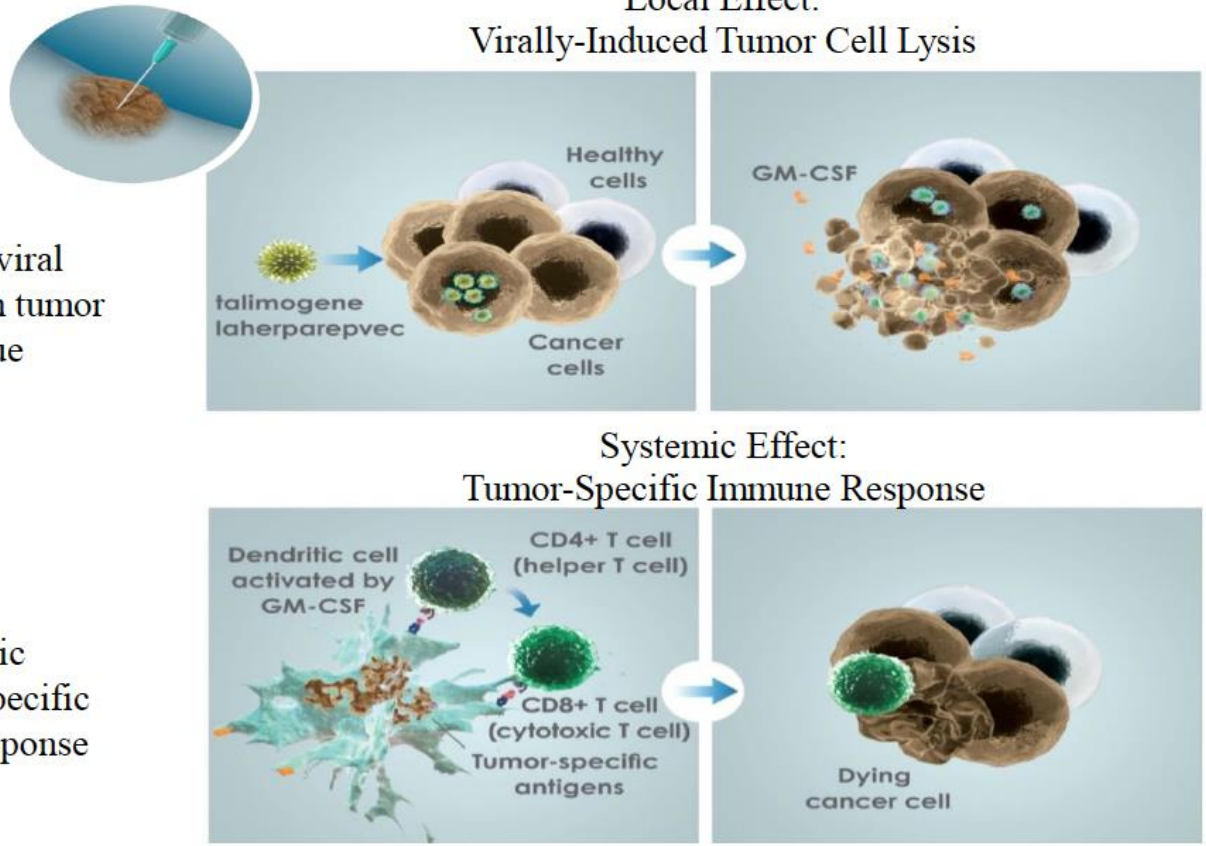
T cell checkpoint modulation

- ***Single Agents***
  - **Agonists**
    - **Anti-ICOS**
    - **Anti-GITR**
    - **Anti-OX40**
    - **Anti-41BB (CD 137)**
    - **Anti-CD27**
  - **Antagonists**
    - **Anti-LAG3**
    - **Anti-TIM3**
    - **Anti-VISTA**
- ***Combinations***
  - **IDO + ipi/pembro/durva**
  - **TVEC+ ipi/pembro**
  - **pembro/ipi + IFN**
  - **pembro + JAK/STAT inhibitors**
  - **nivo + CD 137/TRAIL-R2 Ab/LAG-3**
  - **ipi + nivo + HDAC inhibitors**

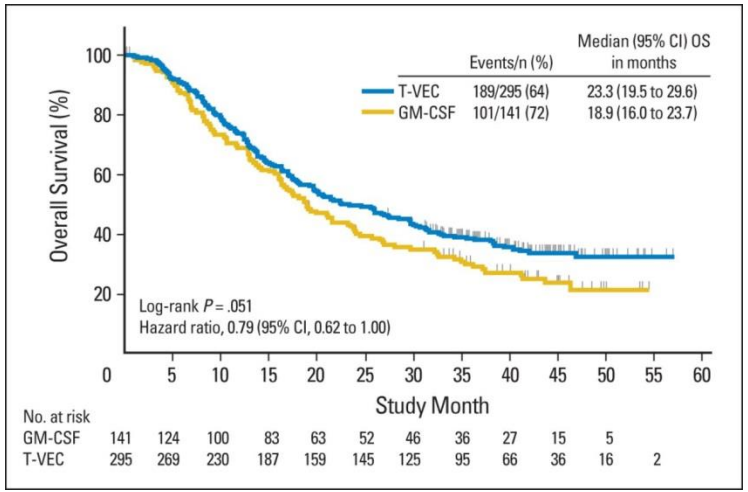


T-VEC: An HSV-1-Derived Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects



Kaufman et al. ASCO (2014), abstr LBA9008

Talimogene laherparepvec(TVEC) pivotal trial



Response	T-VEC (n = 295)	GM-CSF (n = 141)	P
DRR			< .001
Patients with durable response, No.	48	3	
DRR, %*	16.3	2.1	
95% CI	12.1 to 20.5	0 to 4.5	
Unadjusted odds ratio	8.9		
95% CI	2.7 to 29.2		

Approved in 2015 for treatment of unresectable *cutaneous, subcutaneous and nodal* melanoma

Antbacka RH et al. J Clin Oncol. 2015 Sep 1;33(25):2780-8.

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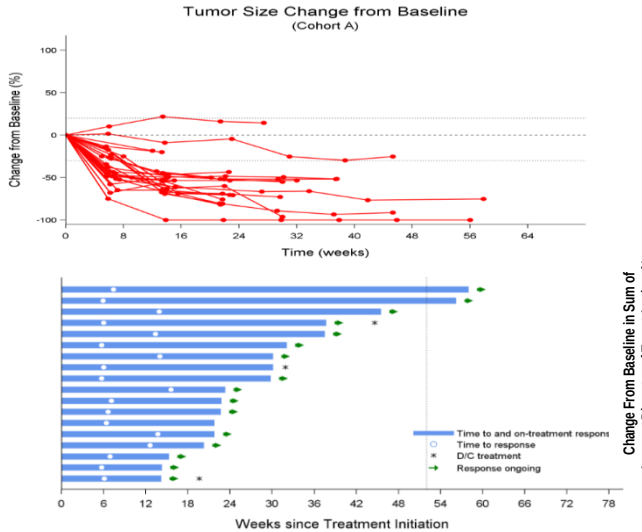
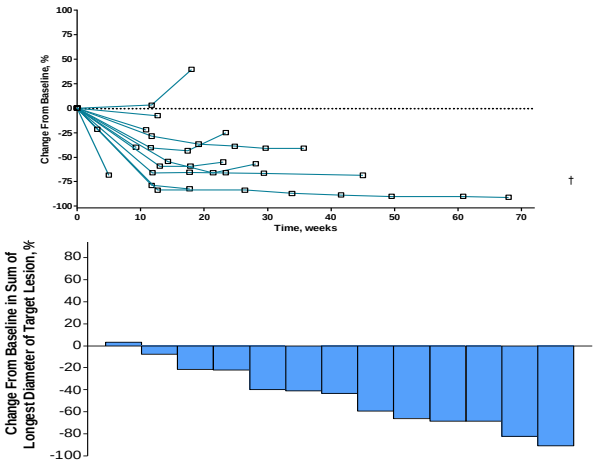
Target-Immuno Triplets: BRAF + MEK + PD1/L1

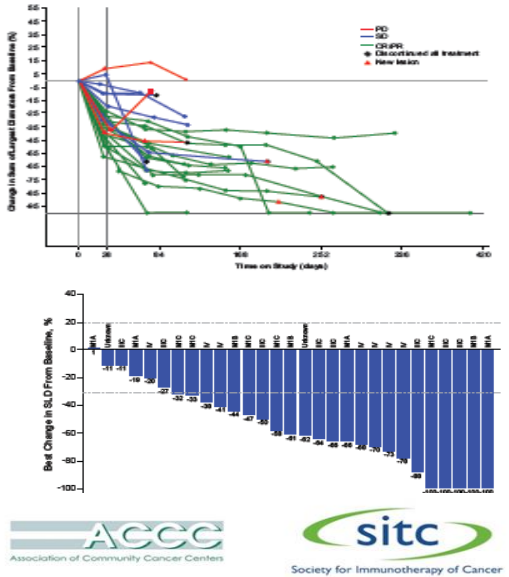
Dabrafenib+Trametinib+ Durvalumab



Dabrafenib+Trametinib+ Pembrolizumab



Vemurafenib+Cobimetinib+ Atezolizumab



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

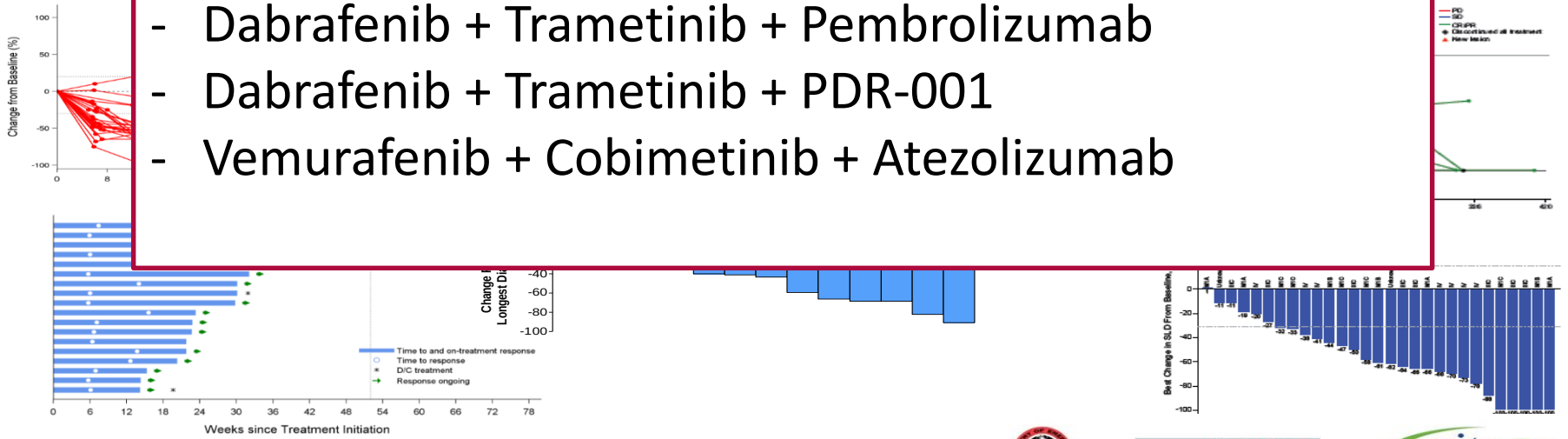
Dabrafenib+Trametinib+ Durvalumab

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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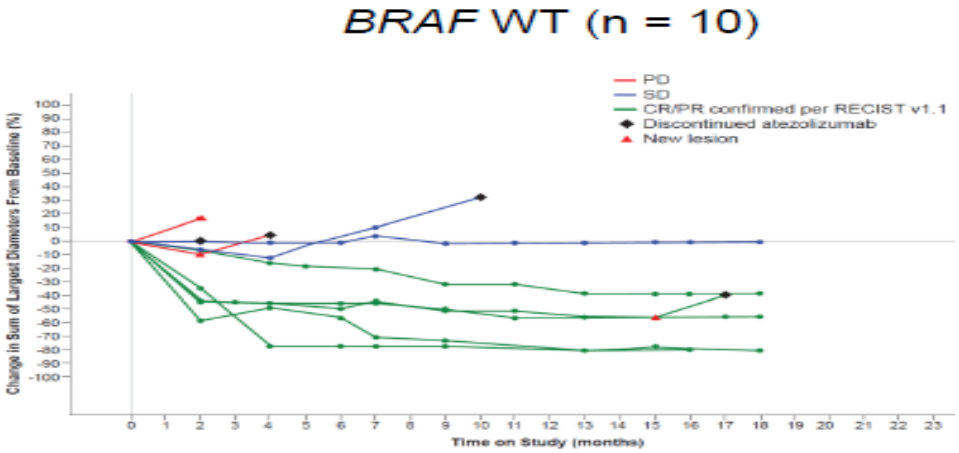
Cobimetinib (MEK inhibitor) + Atezolizumab (PDL-1 Ab)for BRAF WT Melanoma Phase I



	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

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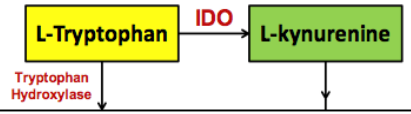
IDO inhibitor epacadostat + pembrolizumab

Indoleamine Dioxygenase-1 (IDO1)

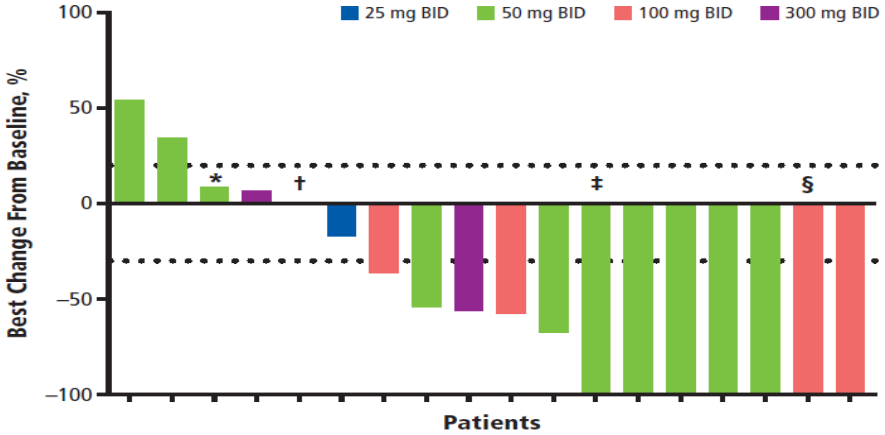
- IDO1 is a heme-containing monomeric oxidoreductase that metabolizes tryptophan to kynurenine



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

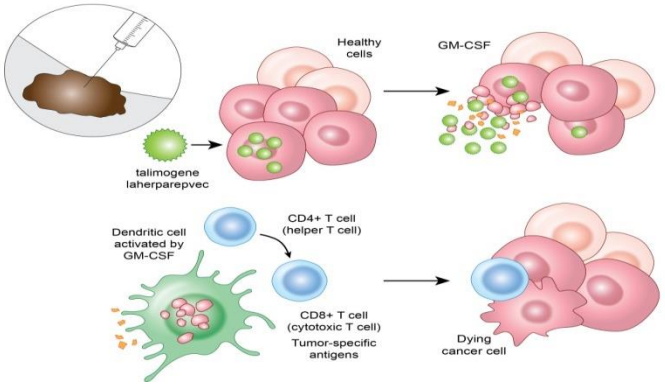
Phase 1/2 Study of **Epacadostat** (INCB024360) + **Pembrolizumab** in Patients With Melanoma



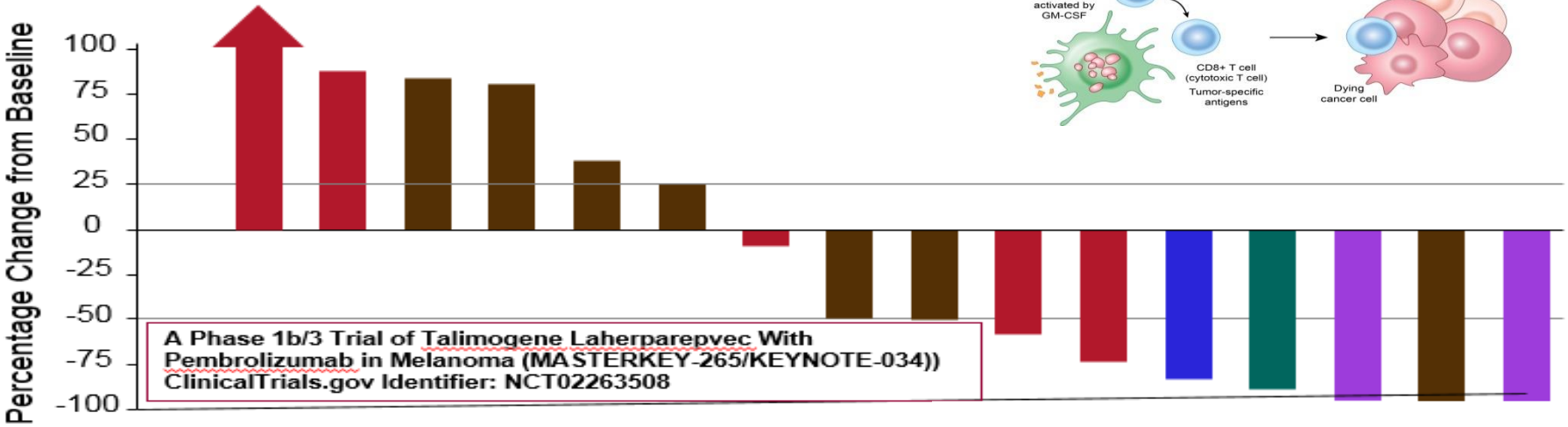
Beatty et al. ASCO (2012) Abstract 2500^
Gangadhar *et al*. ESMO 2016

T-VEC + Pembrolizumab in Stage IIIB-IV Melanoma

- Stage IIIb (N=1)
- Stage IIIc (N=5)
- Stage IV M1a (N=1)
- Stage IV M1b (N=2)
- Stage IV M1c (N=7)



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



Long et al. SMR 2015

ADVANCES IN Cancer IMMUNOTHERAPY™

The Immunotherapy Plot Thickens

- RT and the immune system
- Innate Immune Sensing
  - TLRs, STING, oncolytic viruses
- Tumor infiltrating lymphocytes:
  - TIL
  - Modified TIL
  - Other TCRs
- Metabolism
  - Adenosine (A2A receptor block)
  - Arginine depletion
  - Glutamine depletion
  - Hypoxia inducible factor-1 (HIF-1) inhibition
  - Oxidative phosphorylation (OXPHOS): metformin
- Gut microbiome

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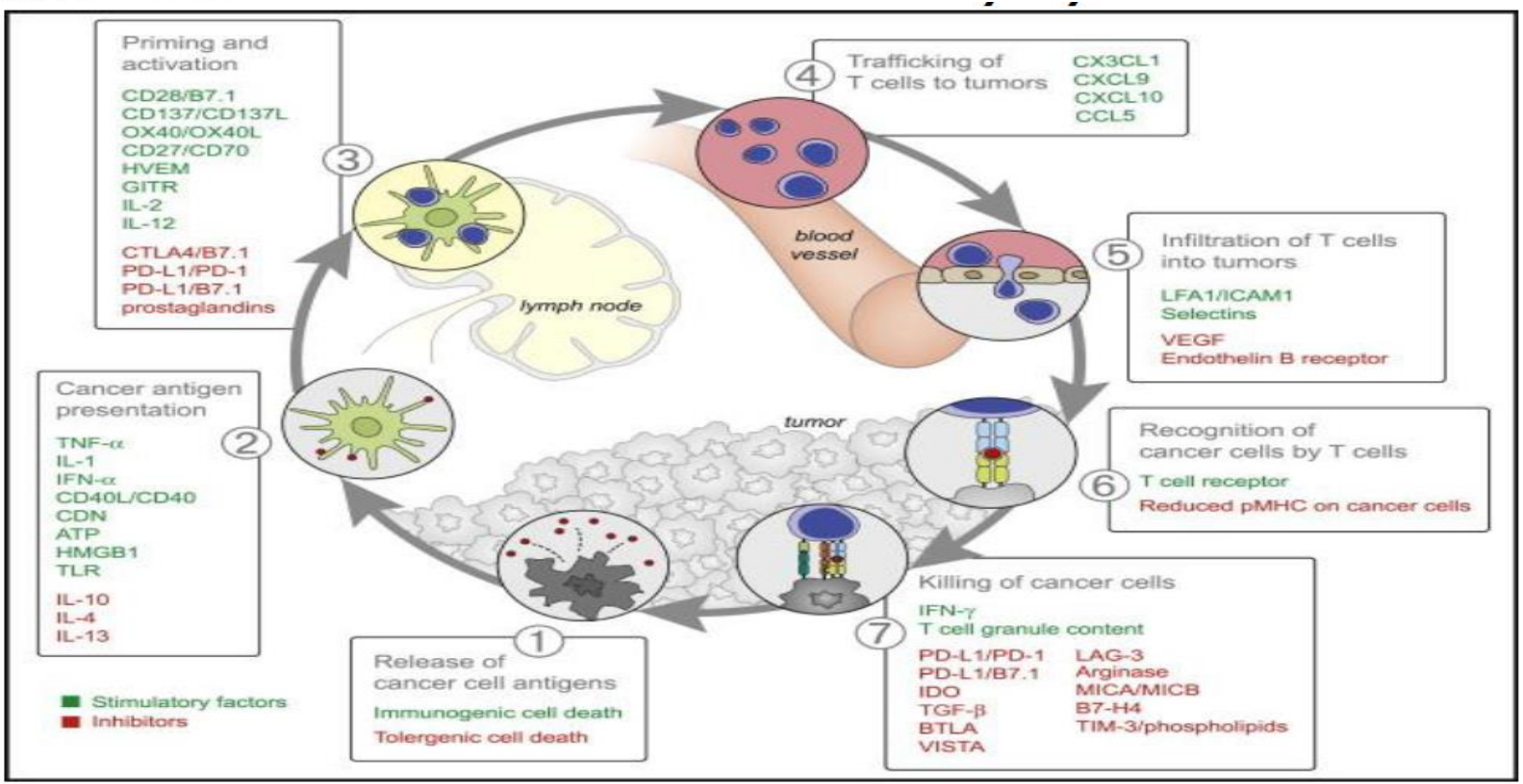
The Immune System and Cancer



Sosman, J. Presented at SITC Annual Meeting 2017.

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Conclusions

- Immunotherapy is the standard of care in melanoma
- Likely first and second line in most patients
- irAEs can be managed effectively
- Understanding mechanisms of action important
- Immunotherapy combinations are likely the future for melanoma and possibly most malignancies.