Immunooncology-new possibilities in the fight against cancer:

Clinical experience in melanoma

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Possible conflicts of interest:

- Advisor for Astra Zeneca
- Advisor and speaker honoraria for/from Amgen, BMS, MSD, Novartis and Roche

Question 1

Modern immunooncology-drugs block inhibitory receptors on immune cells.

Yes

No

Question 2

Modern immunotherapy is so great because it does not have any serious side-effects

Yes

No

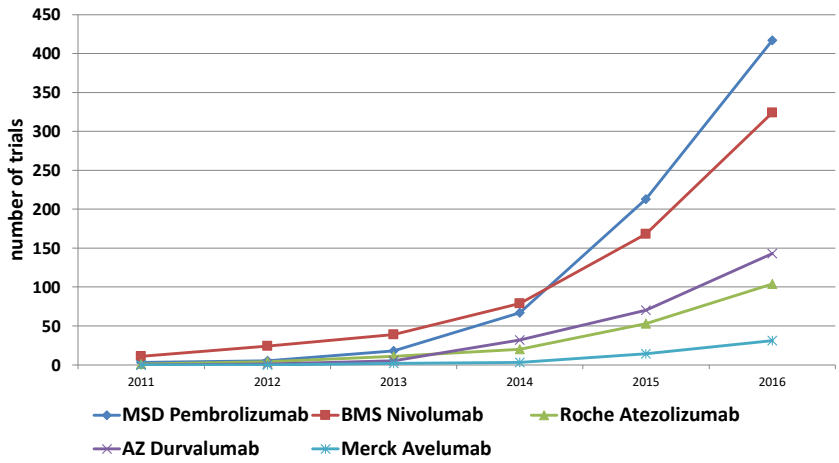
Question 3

In the future immuno-oncology will be based on combinations of two or more drugs with PD-1 or PD-L1 inhibitors as the most frequent backbone drugs.

Yes

No

Immuno-Oncology trials of leading pharmaceutical companies



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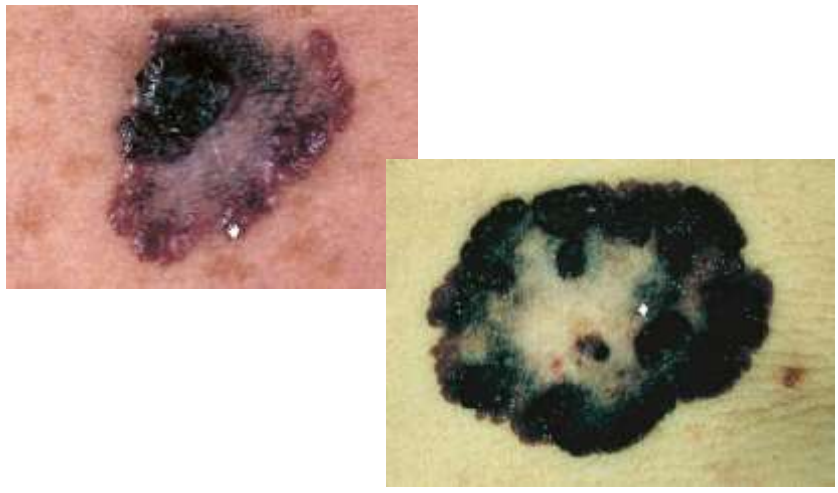
Source: clinical trials.gov, courtesy of Dr. Kernbauer-Hölzl

Why has Melanoma become the model tumor for IO-therapies?

Melanoma shows a high rate of spontaneous regression of primary lesions



Patients with unknown primary melanoma have a better prognosis

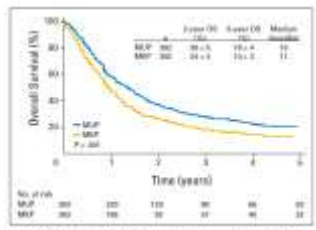
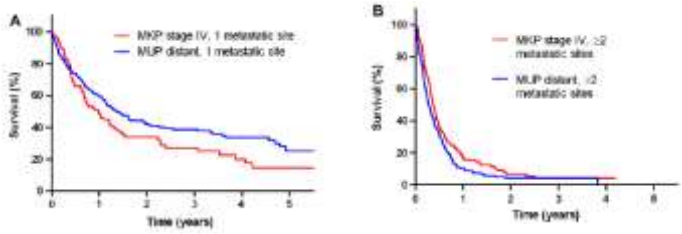


Table 4. Initial Treatment of Matched MUP and MKP Patients

Treatment	MKP Patients No.	MKP Patients %	MUP Patients No.	MUP Patients %
Surgery	80	23	103	34
Immunotherapy*	75	19	43	11
Biochemotherapy/chemotherapy	74	19	60	17
Radiation therapy	35	9	38	10
Other	45	11	42	11
No therapy/supportive care	73	19	70	18

Abbreviations: MUP, melanoma of unknown primary; MKP, melanoma of known primary.
*Eleven MKP and 13 MUP patients received whole-cell melanoma vaccines; most of the remaining patients received nonspecific immunomodulators.



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Lee CC et al, JCO 27 (2009) 3489-3495; A.C. de Waal et al. Eur J Cancer 49 (2013) 676–683

Immunotherapy of Melanoma

	Vaccines	Adoptive T-Cell Therapy	High-dose Il2
Response Rate	3-30%	49-72%	16%
Overall Survival (months)	No overall survival benefit	NA (8-44% Complete Response)	12 months (11% durable response >5 a)
Applicability	Peptide based good, DCs require specialized lab, HLA restriction	Low due to specialized technique and high cost	Low due to severe side effects
Current Status	experimental	experimental	Approved (US, Denmark)

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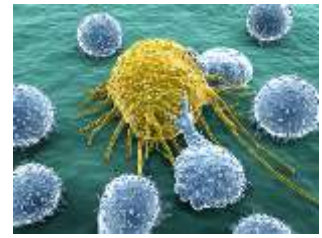
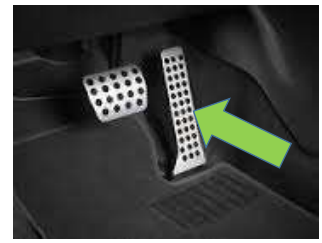
Immunotherapy of Melanoma

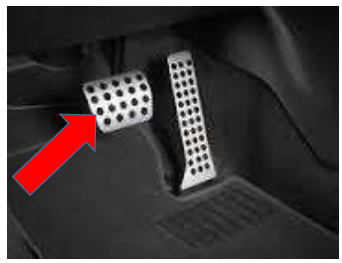
Tumor-Vaccines

T-Cell Transfer

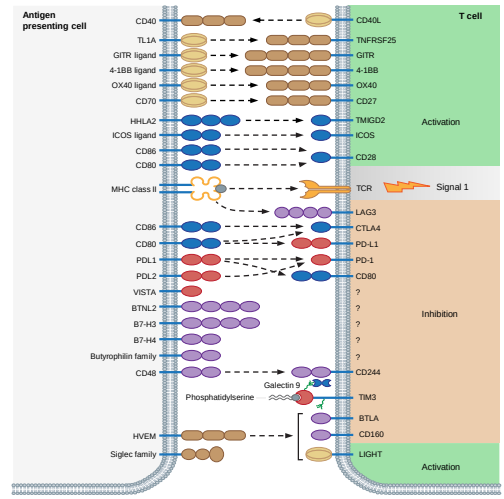




Breaks in the immune-response: “Checkpoints”



- Inhibitory checkpoints are important for limiting an inflammatory repsonse
- Prevent tissue damage

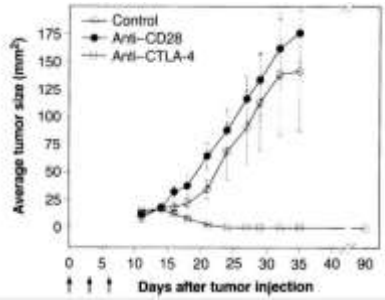


Mahoney KM, et al. *Nat Rev Drug Discov*. 2015;14(8):561-584.

Blocking inhibitory check-points can start an immune response

Enhancement of Antitumor Immunity by CTLA-4 Blockade

Dana R. Leach, Matthew F. Krummel, James P. Allison*

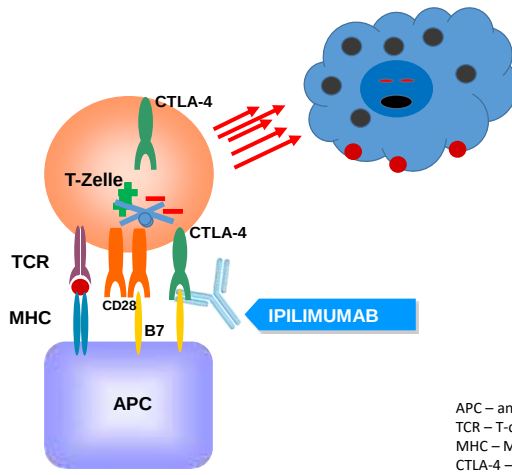


James P. Allison

Furthermore, this rejection resulted in immunity to a secondary exposure to tumor cells. These results suggest that blockade of the inhibitory effects of CTLA-4 can allow for, and potentiate, effective immune responses against tumor cells.

Leach DR et al. *Science*. 1996 Mar 22;271(5256):1734-6.

CTLA-4 counteracts early T-cell activation



APC – antigen presenting cell
TCR – T-cell receptor
MHC – Major histocompatibility antigen
CTLA-4 – Cytotoxic T-Lymphocyte Antigen 4
B7 – Ligand for CD28
CD28 – costimulatory receptor

The NEW ENGLAND JOURNAL of MEDICINE

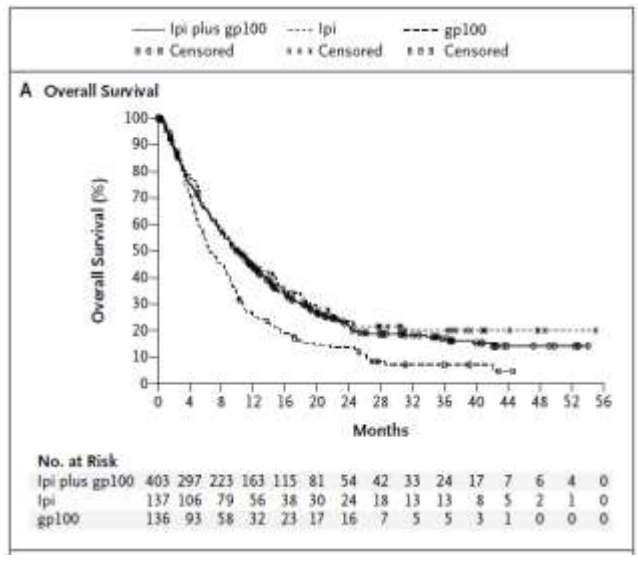
ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

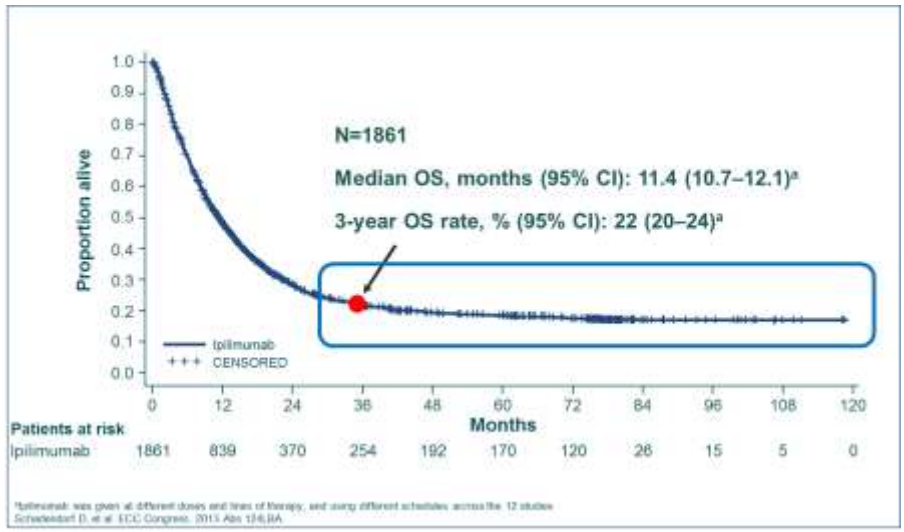
 Hodi FS et al, N Engl J Med, 2010,711-23

Ipilimumab – 3mg/kg



 Hodi FS et al, N Engl J Med, 2010,711-23

Long term survival is seen in up to 20% of patients on CTLA-4 inhibition



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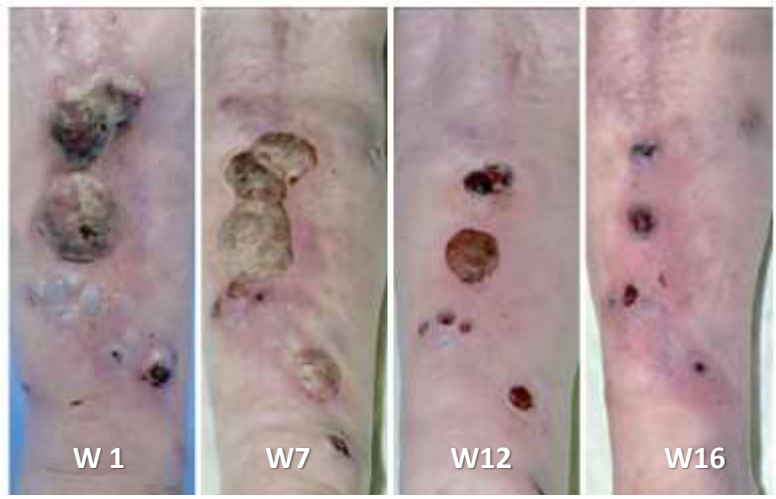
Schadendorf et al., J Clin Oncol. 2015 Jun 10;33(17):1889-94

CTLA-4 inhibition with Ipilimumab Response during Therapy



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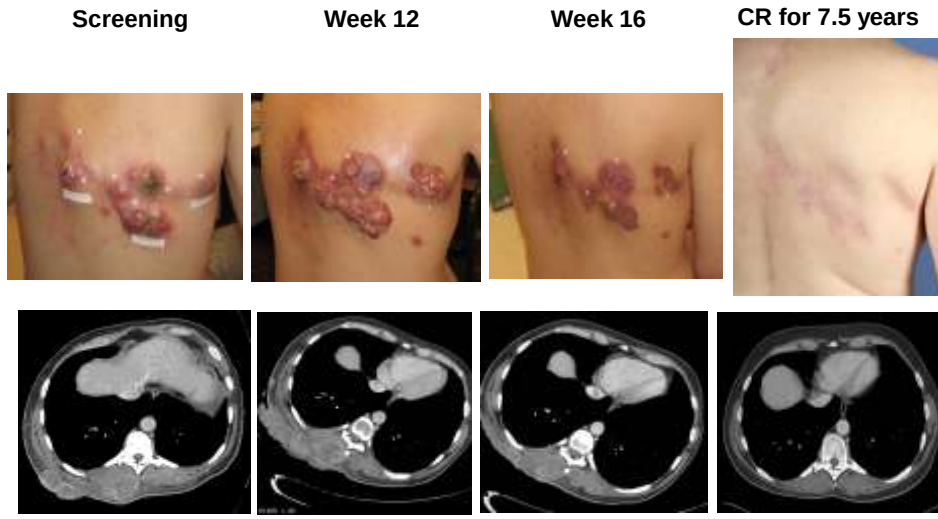
Initial PD with delayed response and CR

Corresponding CT-Scans



Harmankaya K et al, Med Oncol 2010

Check point inibitor induced T-Cell Activation

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Efficacy: Anti-tumor response through T-cells infiltrating metastases

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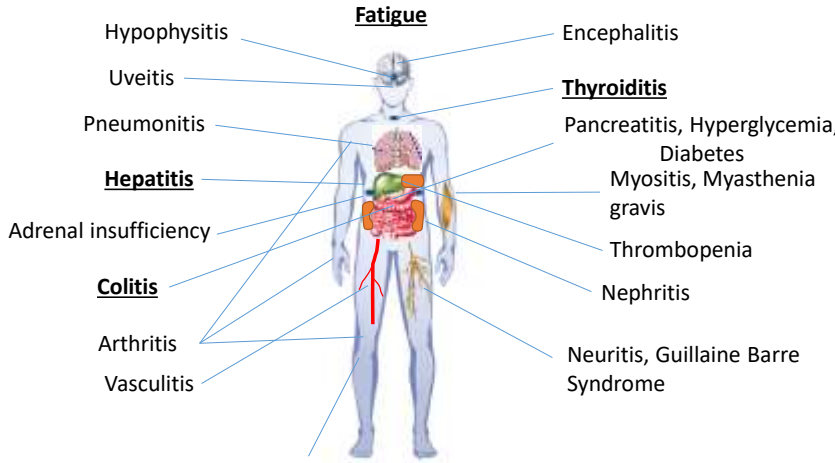
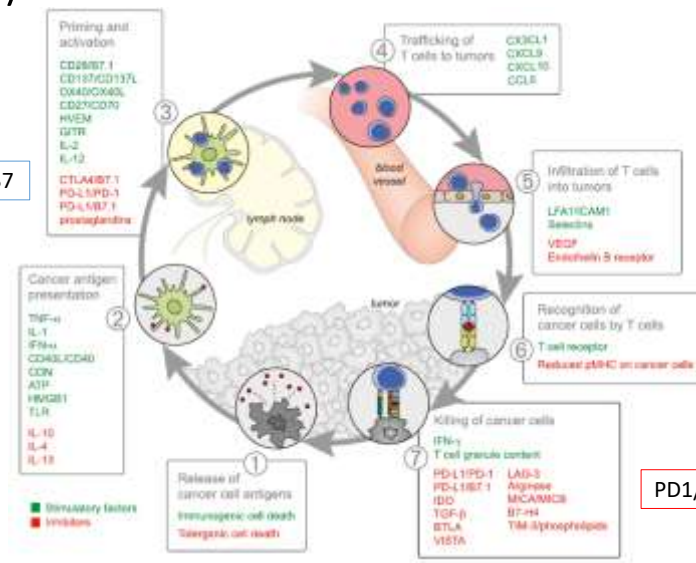
Safety: Immune related Adverse Events (IrAE) through T-cell activation

Side effects observed under treatment with checkpoint inhibitors



Stimulatory and inhibitory factors in the cancer immunity cycle

CTLA4/B7

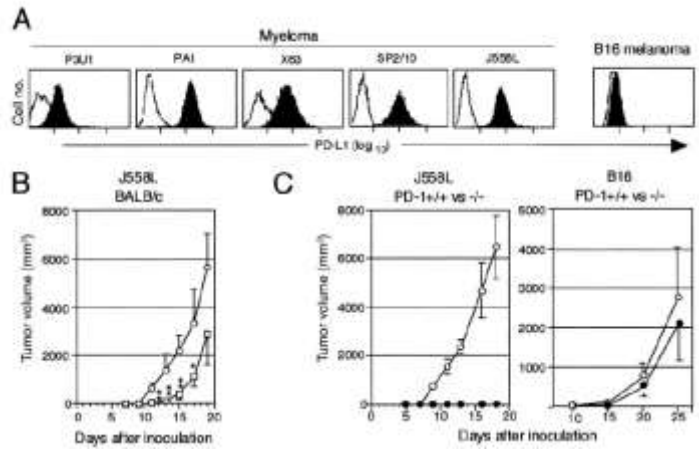


PD1/PD-L1

Chen & Mellman, Immunity 2013

Blocking PD-1/PDL-1 (Programmed-death (Ligand) 1): the next break released

Tasuku Honjo



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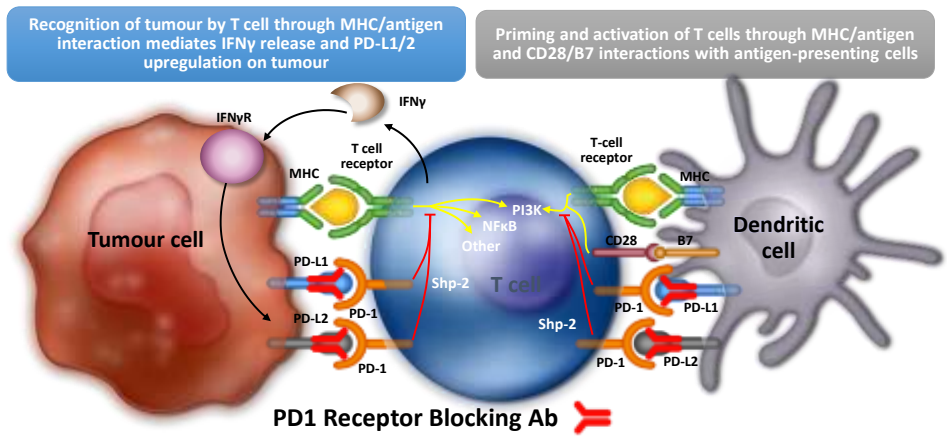
Iway et al.,PNAS 2002

PD1 – Blockade: Mode of action



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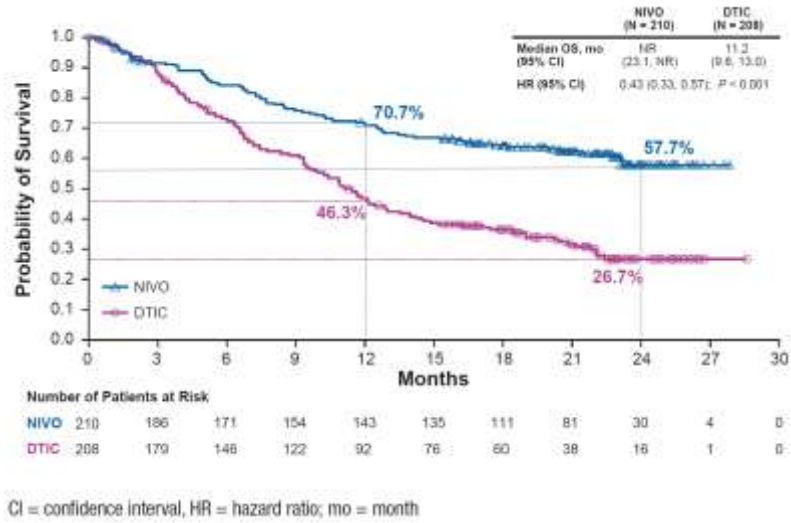
Pardoll DM. *Nat Rev Cancer*. 2012 Mar 22;12(4):252-64.

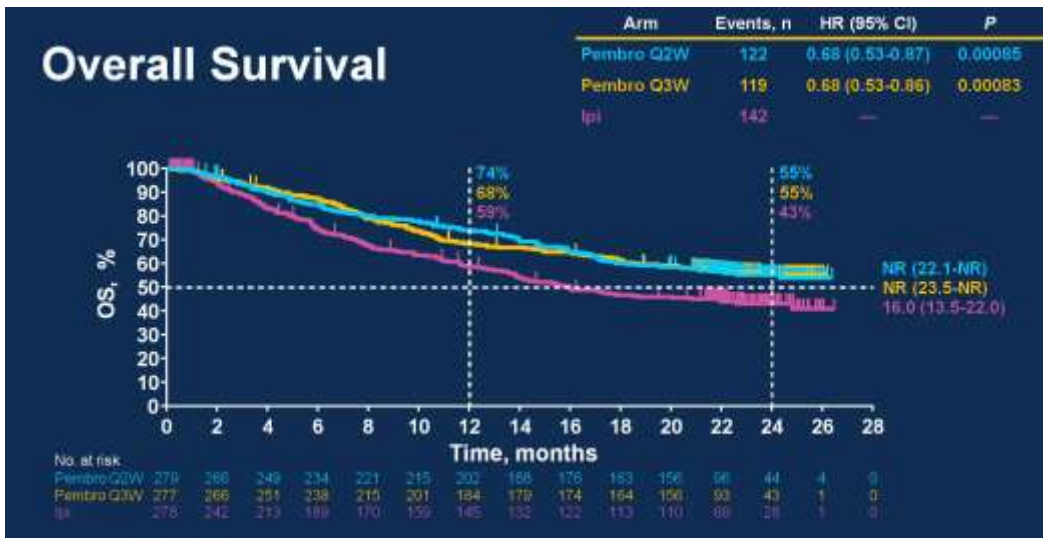
PD-1 Blockade is superior to chemotherapy: Nivolumab vs. DTIC



CI = confidence interval, HR = hazard ratio; mo = month

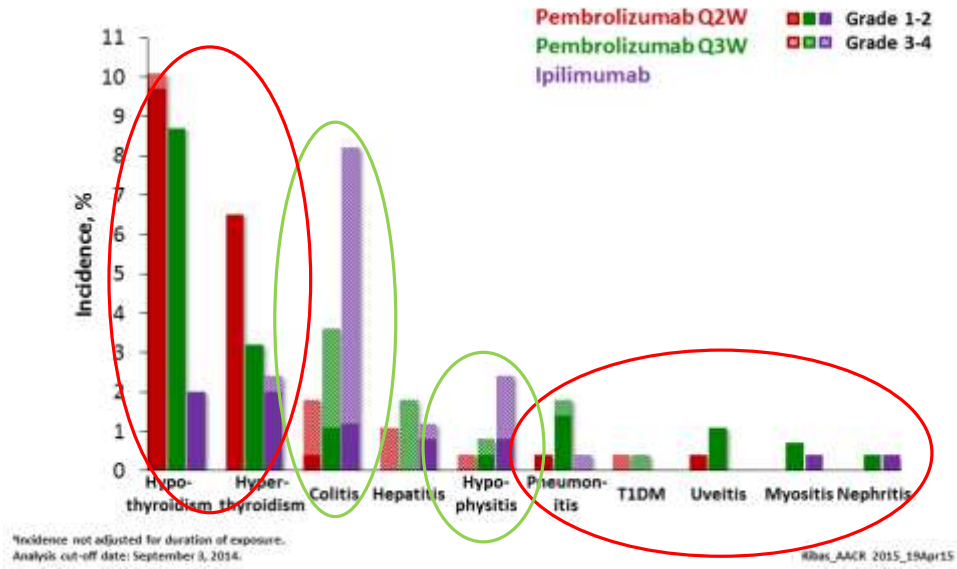
G Long et al., N Engl J Med. 2015 Jan 22;372(4):320-30; Atkinson et al, SMR 2015

Blocking PD-1 is superior to blocking CTLA-4: Pembrolizumab vs. Ipilimumab

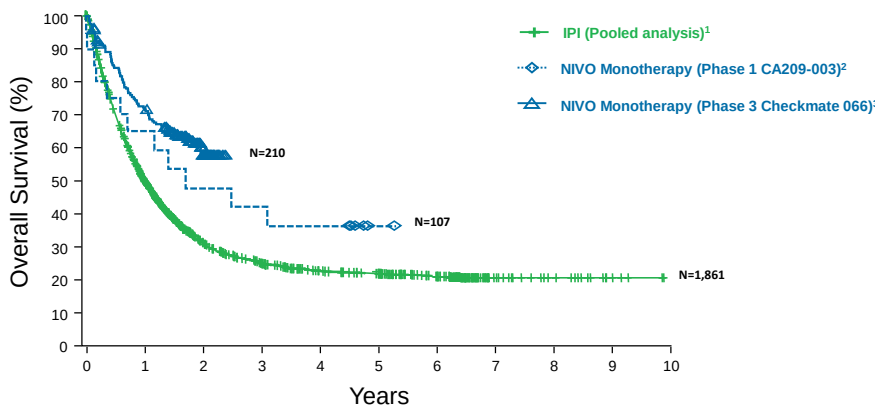


Presented By Jacob Schachter at 2016 ASCO Annual Meeting

Lower rate of important immune-related adverse events with PD-1 inhibition



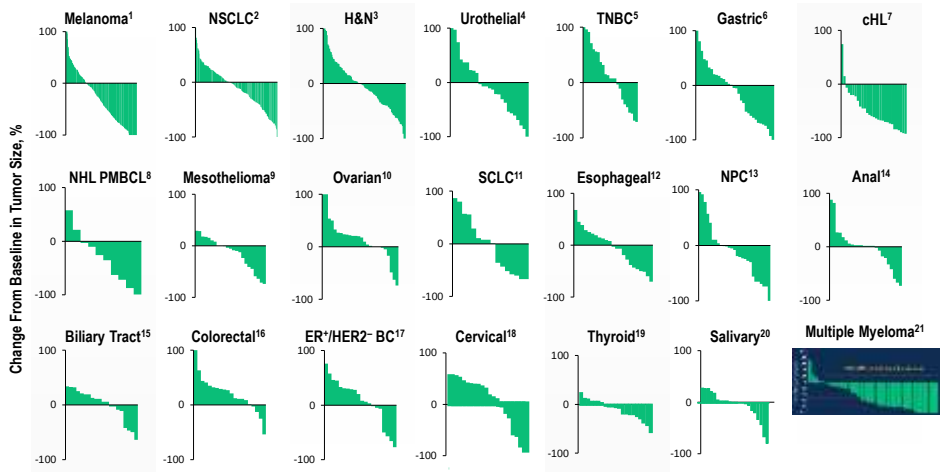
PD-1 Blockade vs. CTLA-4 Blockade: do we see the plateau move up?



1. Schadendorf et al. *J Clin Oncol* 2015;33:1889-1894; 2. Current analysis; 3. Poster presentation by Dr. Victoria Atkinson at SMR 2015 International Congress.

Hodi et al., presented at AACR 2016

Activity of Pembrolizumab across tumor types



1. Daud A et al. ASCO 2015; 2. Garon EB et al. ESMO 2014; 3. Seiwert T et al. ASCO 2015; 4. Plimack E et al. ASCO 2015; 5. Nanda R et al. SABCS 2014; 6. Bang YJ et al. ASCO 2015 ; 7. Moskowitz C et al. ASH 2014; 8. Zinzani PL et al. ASH 2015; 9. Alley EA et al. AACR 2015; 10. Varga A et al. ASCO 2015; 11. Ott PA et al. 2015 ASCO; 12. Doi T et al. ASCO 2015; 13. Hsu C et al. ECC 2015; 14. Ott PA et al. ECC 2015; 15. Bang Y-J et al. ECC 2015; 16. O'Neil B et al. ECC 2015; 17. Rugo HS et al. SABCS 2015; 18. Frenel JS et al. ASCO 2016; 19. Mehnert JM et al. ASCO 2016; 20. Cohen R et al. ASCO 2016., 21 Mateos et al, ASCO 2016 (M-Protein)

Talimogene Laherparepvec (TVEC)

Talimogene laherparepvec is an oncolytic herpes simplex virus type 1 (HSV-1) strain engineered to selectively replicate in tumor cells and to express human GM-CSF

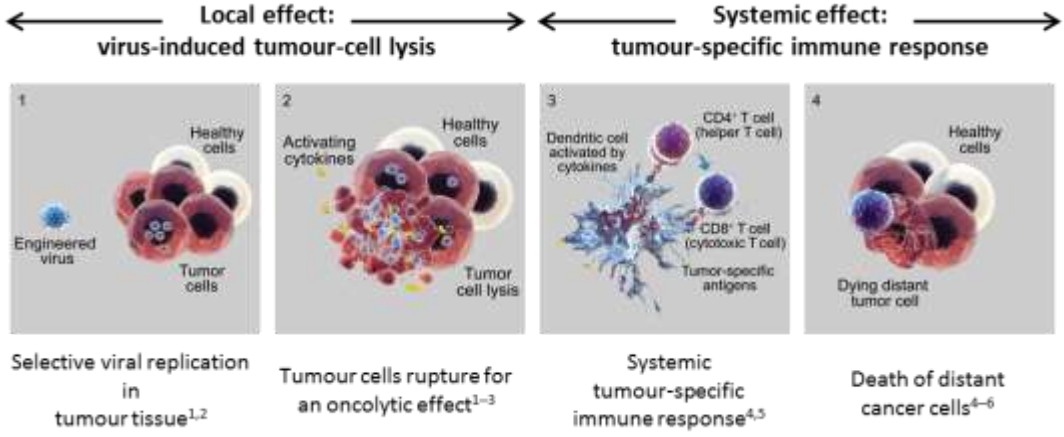
- ICP34.5 deletion (neurovirulence factor)
- ICP47 deletion
- Insertion of GM-CSF
- Created in JS1 virus strain

Talimogene laherparepvec (JS1/ICP34.5-/ICP47-/hGM-CSF)

HSV: Herpes simplex virus; ICP: Infected cell protein; CMV: Cytomegalovirus promoter

Liu BL, et al. *Gene Therapy*. 2003;10:292-303.

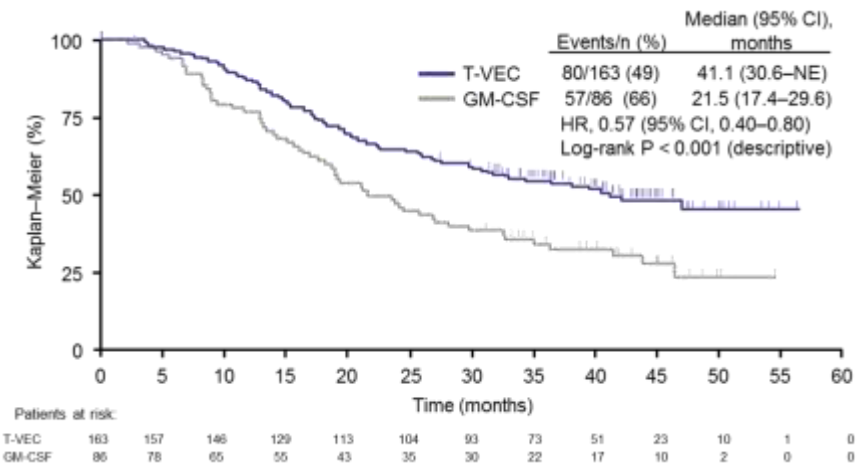
T-VEC – a HSV1 based oncolytic Immunotherapy



1. Hawkins LK, et al. Lancet Oncol 2002;3:17–26; 2. Fukuhara H and Todo T. Curr Cancer Drug Targets 2007;7:149–155; 3. Pol JG, et al. Virus Adapt Treat 2012;4:1–21; 4. Melcher A, et al. Mol Ther 2011;19:1008–16; 5. Dranoff G. Oncogene 2003;22:3188–92; 6. Liu BL, et al. Gene Ther 2003;10:292–303.

Andtbacka RHI, et al. J Clin Oncol 2015;33:2780–8.

Exploratory subgroup analysis – OS in the Stage IIIB/C, IV M1a subpopulation*



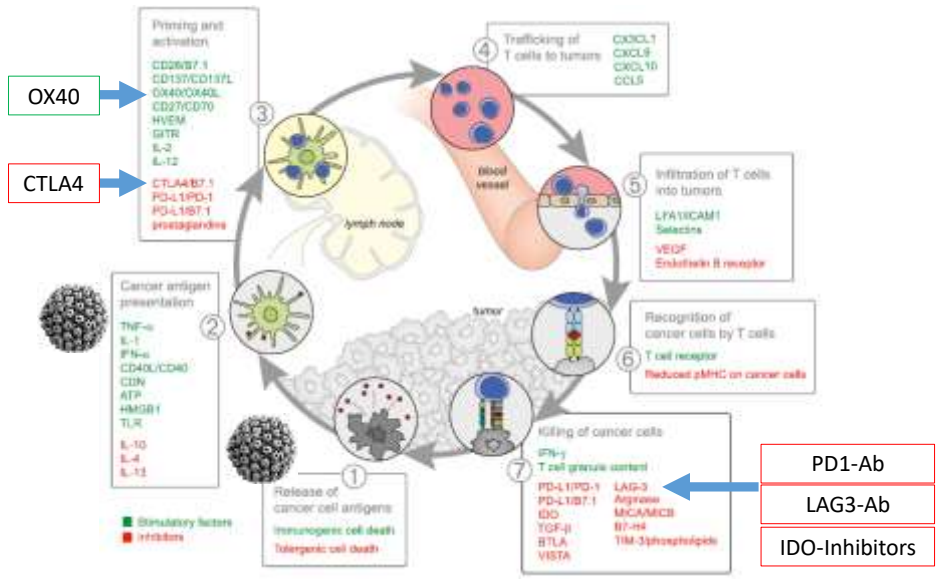
*Due to the exploratory nature of the analysis and based on the current evidence, it has not been established that T-VEC is associated with an effect on OS.

Andtbacka RHI, et al. J Clin Oncol 2015;33:2780–8.

Where to from here?

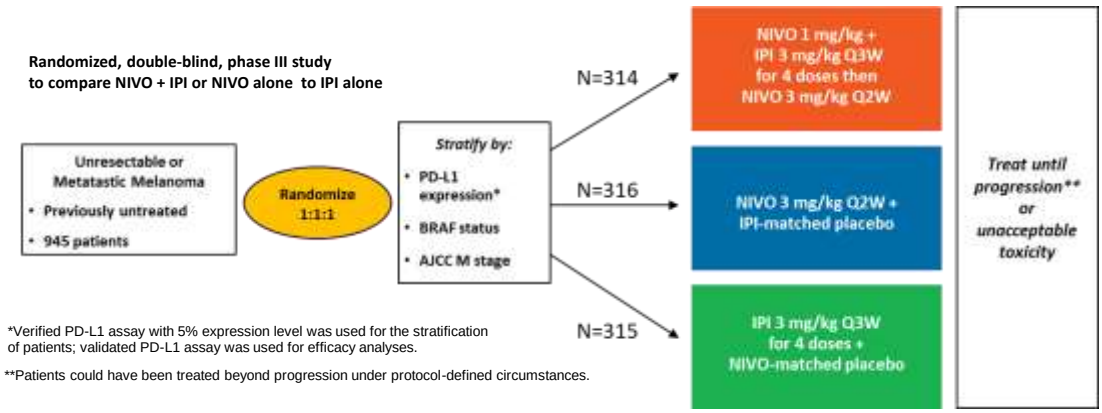
- Adjuvant use
- Neo-adjuvant use
- New targets
- Combining therapies

Combining therapies - the new standard



Chen & Mellman, Immunity 2013

Combined CTLA-4 & PD-1 Blockade Checkmate-067



Nivo = Nivolumab = PD-1 blockierender Antikörper
Ipi = Ipilimumab = CTLA-4 blockierender Antikörper

Larkin et al., N Engl J Med 2015; Wolcok J, presented at ASCO 2015

Checkmate 067:Response Rates

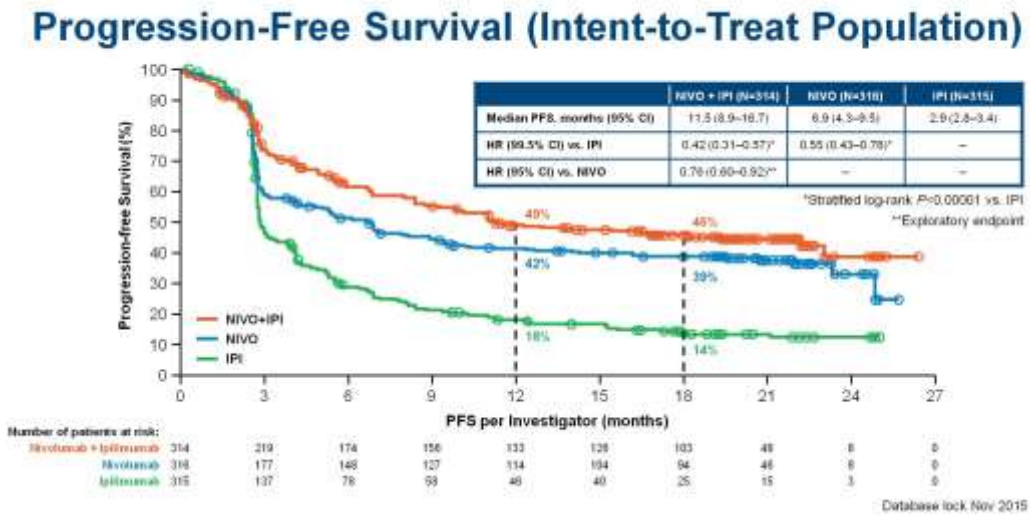
	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
ORR, % (95% CI)*	**57.6** (52.0–63.2)	**43.7** (38.1–49.3)	**19.0** (14.9–23.8)
Two-sided *P* value vs IPI	<0.001	<0.001	--
Best overall response — %			
Complete response	12.1	9.8	2.2
Partial response	45.5	33.9	16.8
Stable disease	13.1	10.4	21.9
Progressive disease	22.6	38.0	48.9
Unknown	6.7	7.9	10.2
Median duration of response, months (95% CI)	**NR** (20.5–NR)	**22.3** (20.7–NR)	**14.4** (8.3–NR)
Ongoing response among responders, %	**72.5**	**72.4**	**51.7**

*By RECIST v1.1. NR = not reached.

Database lock Nov 2015

Larkin et al., N Engl J Med 2015; Wolcok J, presented at ASCO 2016

Checkmate 067: Progression-free survival



Larkin et al., N Engl J Med 2015; Wolcok J, presented at ASCO 2016

Checkmate 067: Side effects

- 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	

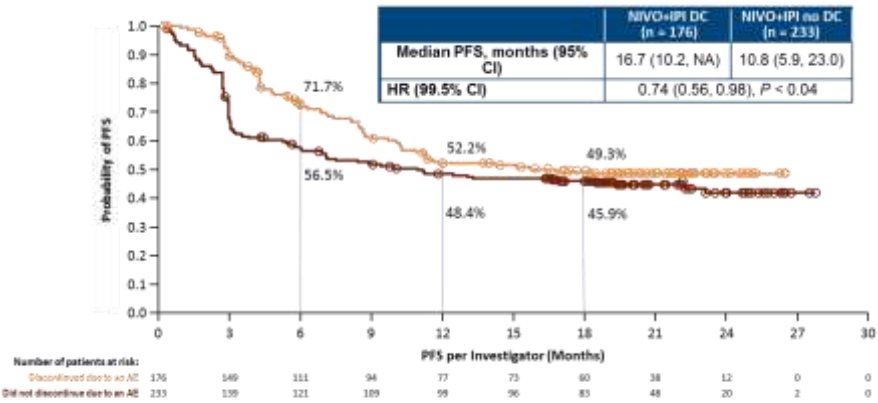
- 68.8% of patients who discontinued NIVO+IPI due to treatment-related AEs achieved a response

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

Database lock Nov 2015

Larkin et al., N Engl J Med 2015; Wolcok J, presented at ASCO 2016

Pooled analysis of patients who discontinued (DC) therapy due to AEs on Nivolumab + Ipilimumab PFS per Investigator



- **Minimum follow-up of 18 months, median length of follow-up = 21.3 months**

DC = patients who discontinued due to an AE; NA = not available; no DC = patients who did not discontinue due to an AE

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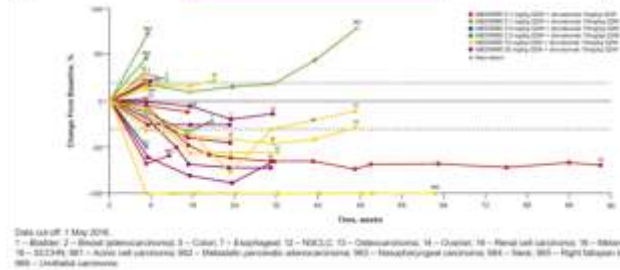
Schadendorf et al. Presented at EADO 2016, Vienna

Blocking PD1 and PDL-1

Combination of MEDI0680, an Anti-PD–1 Antibody, With Durvalumab, an Anti–PD-L1 Antibody: A Phase 1, Open-label Study in Advanced Malignancies



n (%)	Total N=30
Any AE	30 (100)
Any grade ≥3 AE	16 (53)
Any deaths	0
Serious AE	10 (33)
AE leading to discontinuation	6 (20)
AE related to either drug	23 (77)
Grade ≥3 AE related to other drug	6 (20)
Death related to either drug	0
Serious AE related to either drug	3 (10)
AE leading to D/C related to either drug	2 (7)

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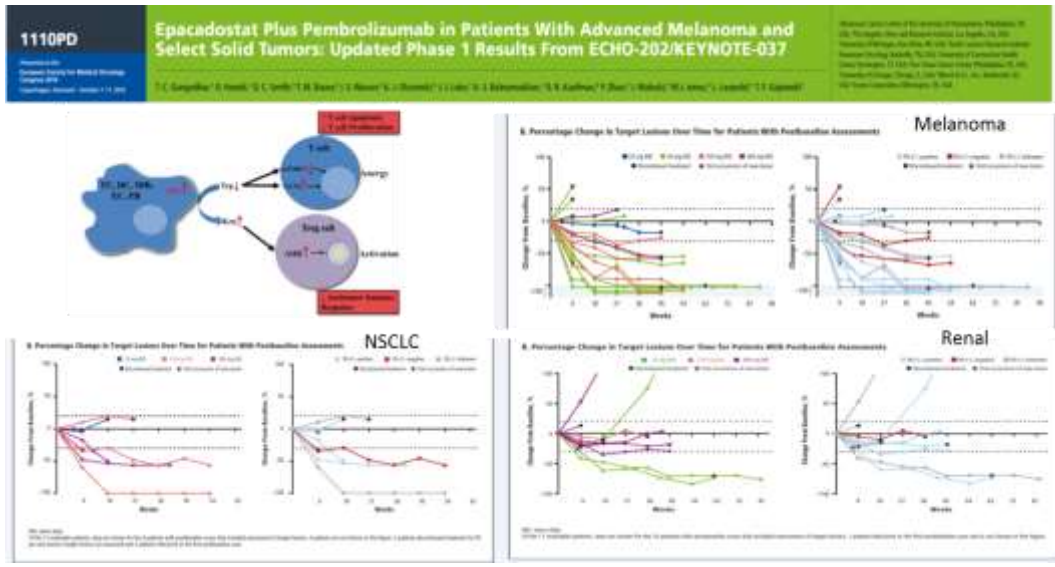
Poster presented at ESMO 2016

Indoleamine 2-3 Dioxygenase (IDO)



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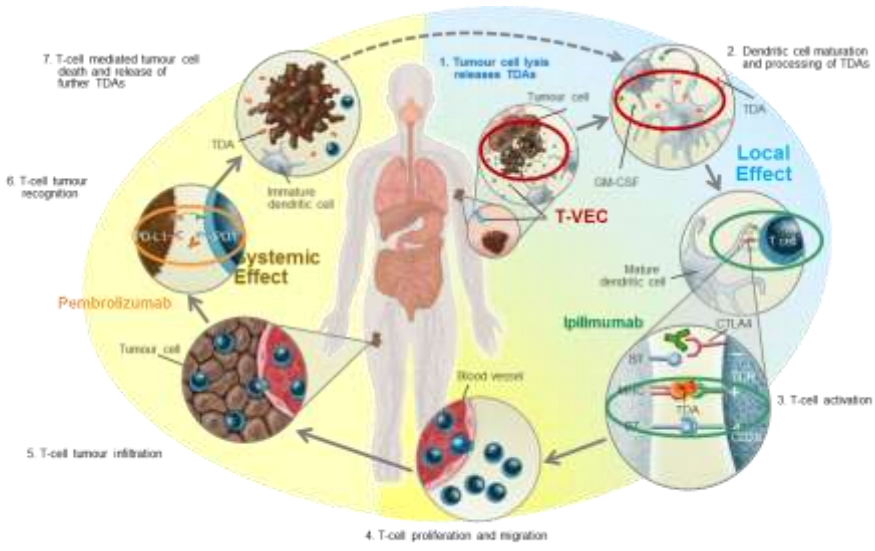
Poster presented at ESMO 2016

TVEC & Check-point Inhibitors



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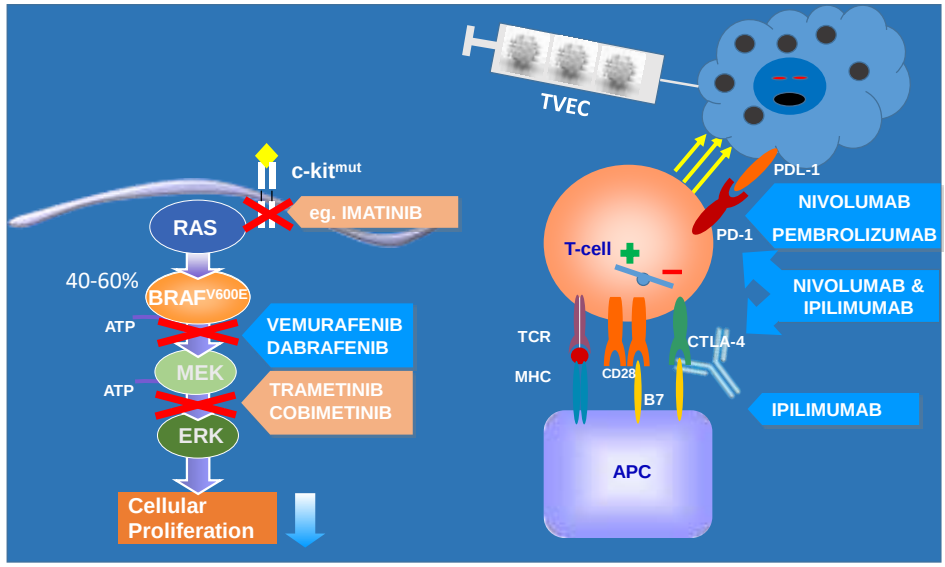
Melanoma Therapies 2017



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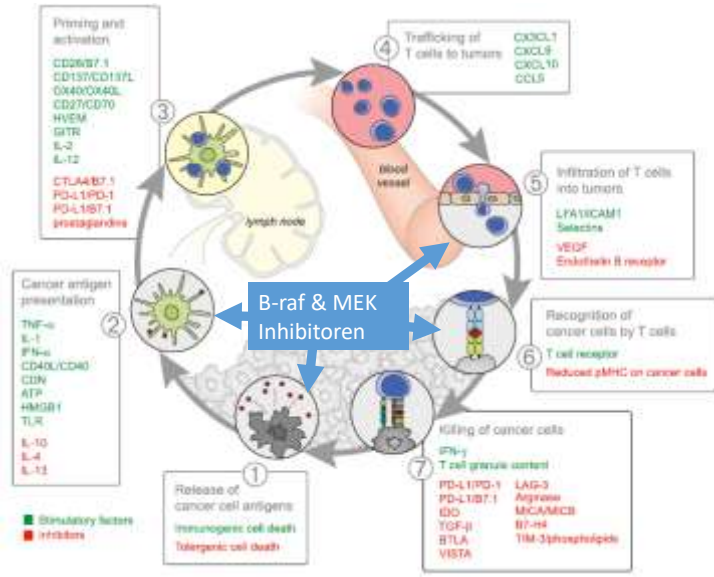
Targeted therapies have an impact on immunity



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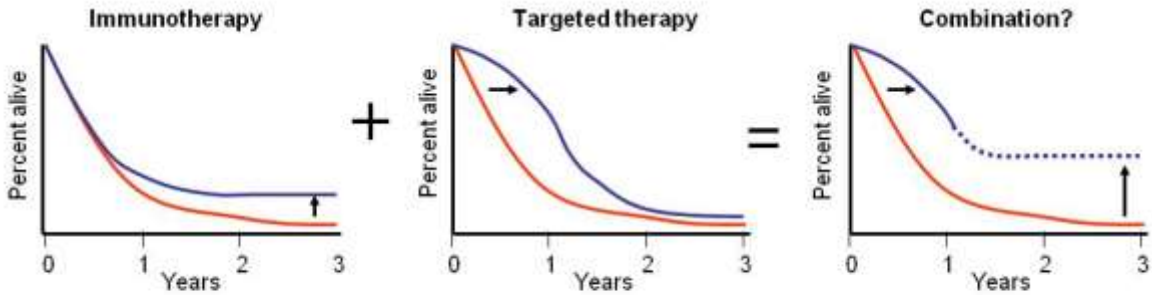
Chen & Mellman, Immunity 2013

Potential improvement through combinations of immunotherapy and targeted therapy

Current treatment options for *BRAF*^{V600} mutated melanoma include:

- BRAF alone or BRAF/MEK inhibitors → rapid clinically significant responses usually with limited durability
- Immunotherapy → less frequent objective responses but clinically significant durability



Hypothesis: Combining anti-PD-L1 with BRAF and MEK inhibitors may result in higher frequency of long-lasting responses in patients with advanced *BRAF*^{V600} mutated melanoma

Modified from Ribas et al. Clinical Cancer Research 2012

PRESENTED AT: ASCO Annual '15 Meeting

Presented By Antoni Ribas at 2015 ASCO Annual Meeting

PD-1/PD-L1 + B-RAF/MEK inhibition

Phase 1 study combining anti-PD-L1 (MEDI4736) with BRAF (dabrafenib) and/or MEK (trametinib) inhibitors in advanced melanoma

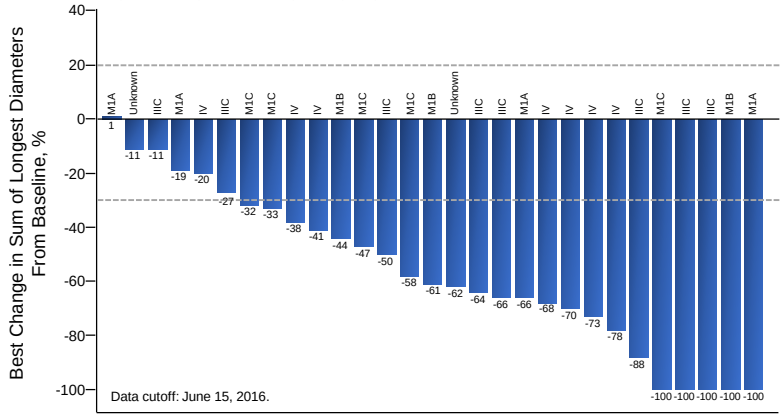
Safety and Clinical Activity of Atezolizumab + Cobimetinib + Vemurafenib in *BRAF* V600 Mutant Metastatic Melanoma

Ryan Sullivan,[1] Omid Hamid,[2] Rene Gonzalez,[3] Jeffrey Infante,[4] Manish Patel,[5] F. Stephen Hodi,[1] Karl Lewis,[3] Jeffrey Wallin,[6] Bethany Pitcher,[6] Edward Cha,[6] Nicole Richie,[6] Marcus Ballinger,[6] Patrick Hwu[7]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]The Angeles Clinic and Research Institute, Los Angeles, CA; [3]University of Colorado Cancer Center, Aurora, CO; [4]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [5]Florida Cancer Specialists & Research Institute/Sarah Cannon Research Institute, Sarasota, FL; [6]Genentech, Inc., South San Francisco, CA; [7]MD Anderson Cancer Center, Houston, TX

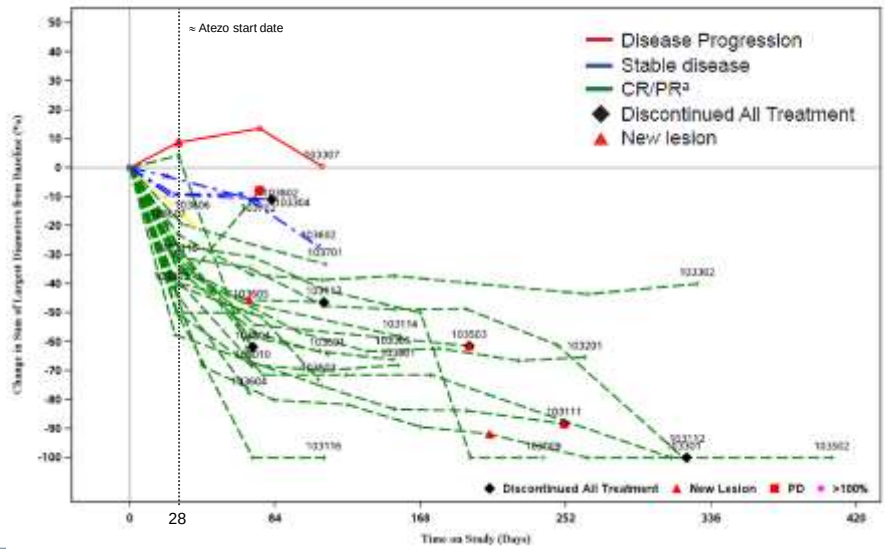
Pembrolizumab in Combination With Dabrafenib and Trametinib for *BRAF*-Mutant Advanced Melanoma: Phase 1/2 KEYNOTE-022 Study

Atezolizumab + Vemurafenib + Cobimetinib: Reduction in Tumor Burden

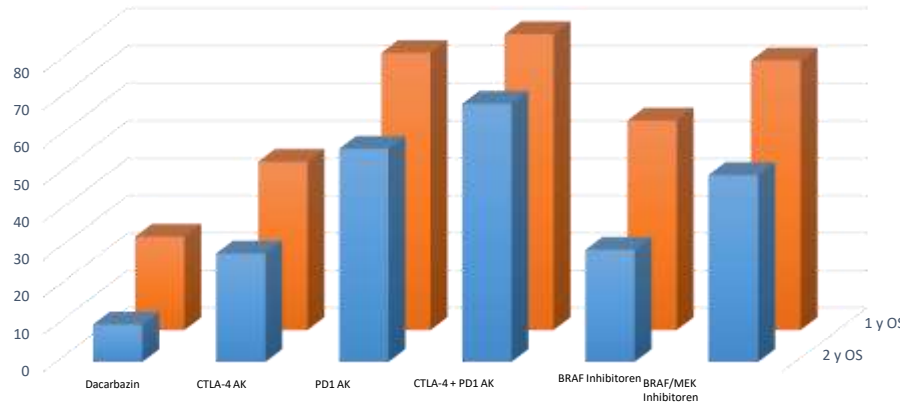


- 5 patients had a 100% reduction in tumor burden
  - 3 of these patients were considered PRs due to the lack of confirmatory scans or remaining target lesions
- Due to limited follow-up time at data cutoff, the median DOR and median PFS was not estimable

Atezolizumab + Vemurafenib + Cobimetinib: Reduction in Tumor Burden



“Landmark-OS” of current melanoma therapies



Important: The patient populations are not equivalent and data from different trials cannot be compared directly

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Question 1

Modern immunooncology-drugs block inhibitory receptors on immune cells.

Yes

No

Question 2

Modern immunotherapy is so great because it does not have any serious side-effects

Yes

No

Question 3

In the future immuno-oncology will be based on combinations of two or more drugs with PD-1 or PD-L1 inhibitors as the most frequent backbone drugs.

Yes

No

Take home messages

- Immuno-oncology drugs will become the principal therapy for the majority of malignant tumors with drugs targeting the PD-1/PD-L1 axis as the main group.
- Knowledge of the mode of action as well as the management of immune mediated adverse events is a prerequisite for the safe use of these drugs.
- Novel targets, use as adjuvant or neo-adjuvant therapy and most importantly combinations of IO- with IO- or other anti-tumor agents are the major strategies currently in clinical development.

Thank you for your attention!

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