Immunotherapy for the Treatment of Skin Cancers

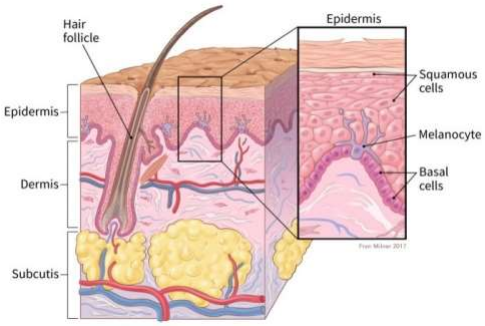
Mark R. Albertini, M.D.
Professor of Medicine
University of Wisconsin-Madison

Disclosures

- Contracted Research: Bristol-Myers Squibb, Merck Sharpe & Dohme, Aperion Biologics,Array BioPharma
- I will be discussing non-FDA approved indications during my presentation.

Background

- Skin cancer is the most common type of cancer
- Three most common types of skin cancers:
  - Basal cell carcinoma
  - Squamous cell carcinoma
  - Melanoma
- Melanoma was one of the foundational disease states for testing immunotherapies



Approved cytokines in melanoma

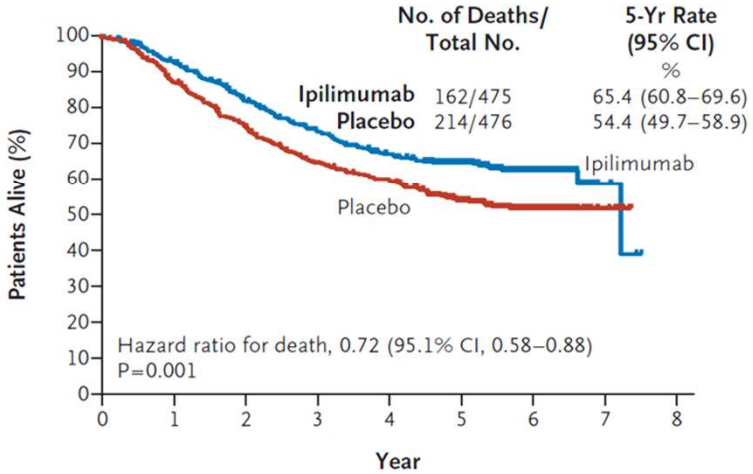
Drug	Indication	Dose
High-dose interferon alfa-2b	Adjuvant – high risk for systemic recurrence	Induction: 20m IU/m^2 IV 5x/wk for 4 wks Maintenance: 10m IU/m^2 s.c. 3x/wk for 48 wks
Interleukin-2 (Aldesleukin)	Stage IV	600k IU/kg/dose Q8hr, up to 14 doses; 9 days of rest; can repeat up to 28 doses per course
Pegylated Interferon alfa-2b (Sylatron)	Adjuvant – microscopic or gross nodal involvement	6 mcg/kg/wk s.c. for 8 doses, then 3 mcg/kg/wk s.c. for up to 5 years

Approved checkpoint inhibitors in melanoma

Drug	Approved	Indication	Dose
Ipilimumab	2011	Unresectable/Metastatic melanoma: newly diagnosed or after progression	3 mg/kg Q3W for 4 doses
	2015	Adjuvant therapy in stage III melanoma after complete resection	10 mg/kg Q3W for 4 doses, then 10 mg/kg Q12W for 3 years
	2017	Unresectable/Metastatic melanoma: newly diagnosed or after progression, all patients ≥ 12 yr	3 mg/kg Q3W for 4 doses

Adjuvant Ipilimumab in High-Risk Stage III Melanoma

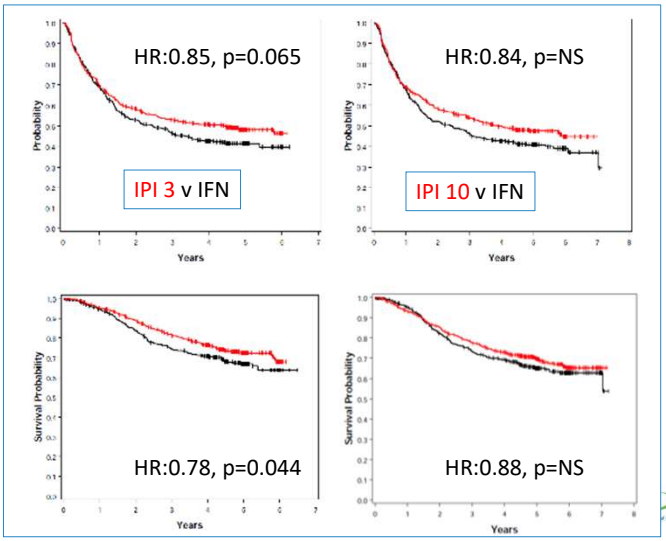
- EORTC 18071 phase III trial
  - NCT00636168
  - Adjuvant ipilimumab vs placebo
  - Ipilimumab 10mg/kg Q3W for four doses, then every 12 weeks for up to 3 years



Eggermont, NEJM 2016.

Adjuvant Ipilimumab in High-Risk Stage III Melanoma

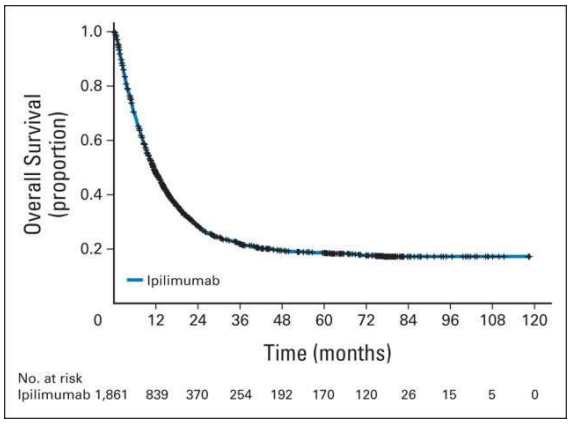
- ECOG 1609
  - NCT01274338
  - Adjuvant interferon (IFN) vs ipilimumab 3 mg/kg (IPI 3) vs ipilimumab 10 mg/kg (IPI 10)
  - Ipilimumab Q3W for four doses, then every 12 weeks for up to 3 years
  - IPI 3 "better than IFN", IPI 10 trend but not statistically significant
  - IPI3 better tolerated than IPI 10



Tarhini, ASCO Annual Meeting 2019.

Ipilimumab in Stage III/IV Melanoma

- Pooled OS data from 10 phase II/III trials
  - Previously treated (n = 1,257) or treatment-naïve (n = 604)
  - Ipilimumab 3 mg/kg (n = 965) or 10 mg/kg (n = 706)



Schadendorf, JCO 2015.

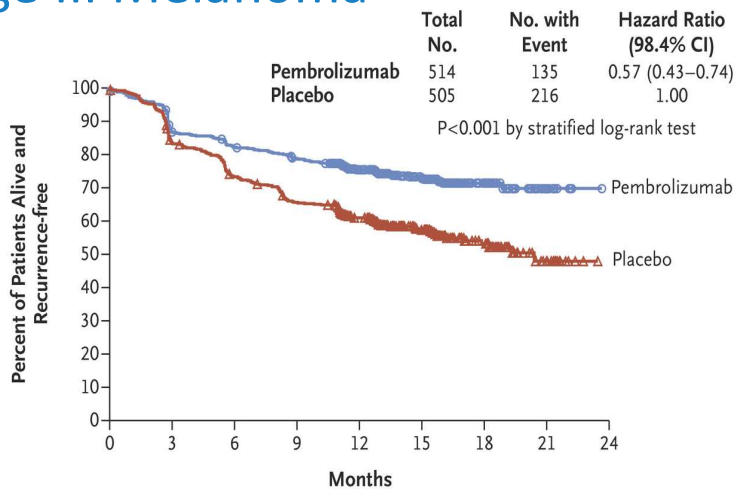
Approved checkpoint inhibitors in melanoma

Drug	Approved	Indication	Dose
Pembrolizumab	2014	Advanced/unresectable melanoma with progression after other therapy	200 mg Q3W*
	2015	1st line unresectable/metastatic melanoma; currently one of the NCCN First Line Preferred Systemic therapies for Metastatic Melanoma (category 1)	200 mg Q3W*
	2019	Adjuvant therapy of melanoma following complete resection	200 mg Q3W

*Original approvals were 2 mg/kg Q3W – updated to flat dosing regimen; current approval also includes 400 mg every 6 weeks

Adjuvant Pembrolizumab in High-Risk Stage III Melanoma

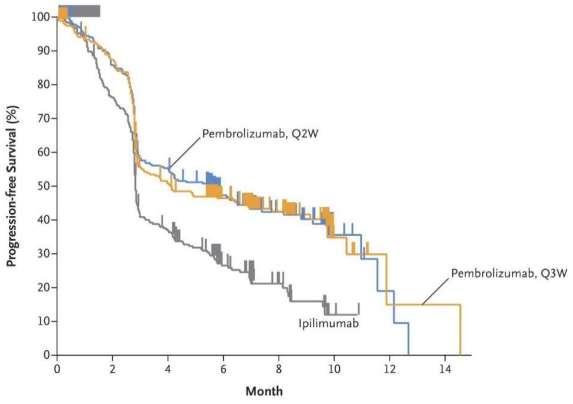
- EORTC 1325/KEYNOTE-054 phase III trial
  - NCT02362594
  - Adjuvant pembrolizumab vs placebo
  - Pembrolizumab 200mg Q3W for up to 1 year (~18 total doses)

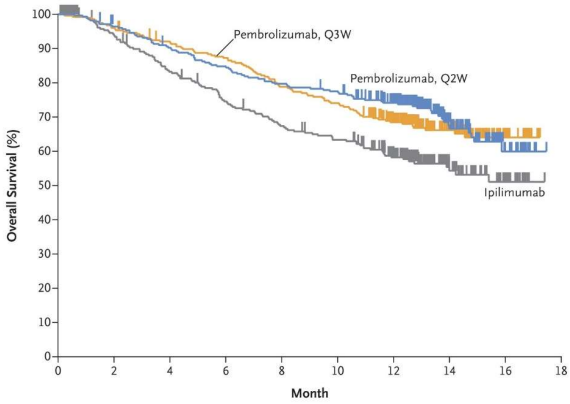


Eggermont, NEJM 2018.

Pembrolizumab in Stage III/IV Melanoma

Phase III KEYNOTE-006 Trial





Robert, NEJM 2015.

Approved checkpoint inhibitors in melanoma

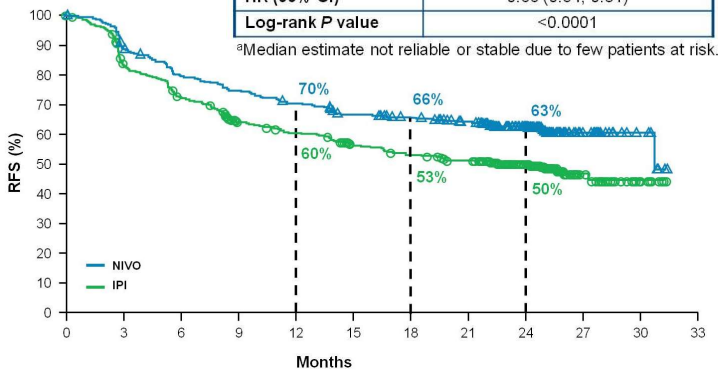
Drug	Approved	Indication	Dose
Nivolumab	2014	Unresectable/metastatic melanoma with progression after other therapy (original indication); currently one of the NCCN First Line Preferred Systemic therapies for Metastatic Melanoma (category 1)	240 mg Q2W or 480 mg Q4W*
	2017	Adjuvant treatment of melanoma after complete resection	240 mg Q2W or 480 mg Q4W
*Original approval was 3 mg/kg Q2W, updated to flat dosing regimen			

Adjuvant Nivolumab vs Ipilimumab in High-Risk Stage III Melanoma

- CheckMate 238 phase III trial
  - NCT02388906
  - Ipilimumab 10mg/kg Q3W for four doses, then every 3 months for up to 1 year
  - Nivolumab 3mg/kg Q2W for four doses, then every 3 months for up to 1 year

	NIVO	IPI
Events/patients	171/453	221/453
Median (95% CI)	30.8 (30.8, NR)[a]	24.1 (16.6, NR)
HR (95% CI)	0.66 (0.54, 0.81)	
Log-rank *P* value	<0.0001	

[a]Median estimate not reliable or stable due to few patients at risk.



Miller, ASCO 2018.

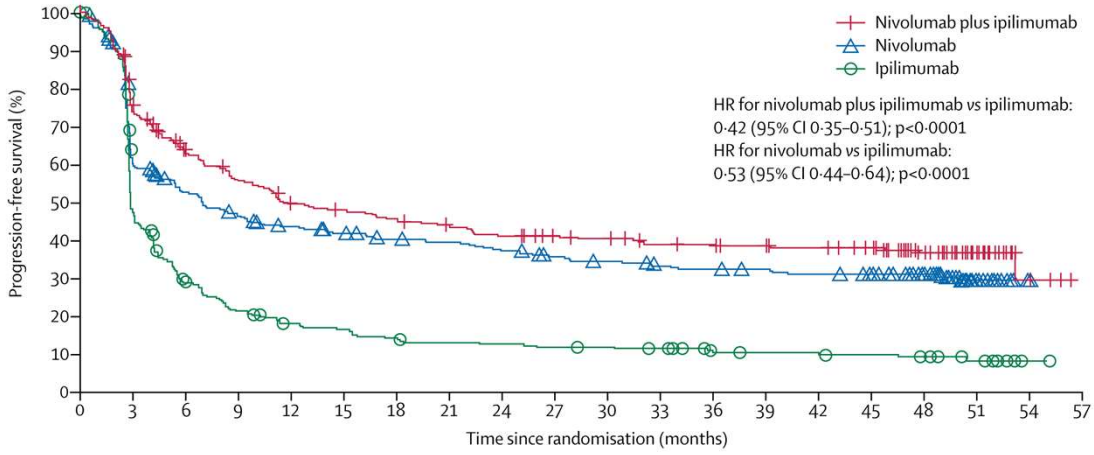
Approved checkpoint inhibitors in melanoma

Drug	Approved	Indication	Dose
Nivolumab + Ipilimumab	2015	BRAF V600 WT unresectable/metastatic melanoma	1 mg/kg nivolumab + 3 mg/kg ipilimumab Q3W for 4 doses, then nivolumab 240 mg Q2W or 480 mg Q4W
	2016	BRAF V600 WT or mutant unresectable/metastatic melanoma	1 mg/kg nivolumab + 3 mg/kg ipilimumab Q3W for 4 doses, then nivolumab 240 mg Q2W or 480 mg Q4W

currently one of the NCCN First Line Preferred Systemic therapies for Metastatic Melanoma (category 1)

Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma

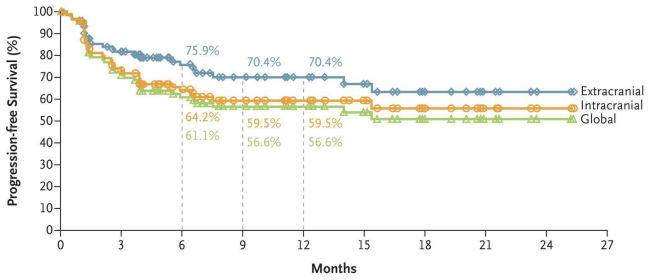
Phase III CheckMate 067 Trial



Hodi, Lancet Oncol 2018.

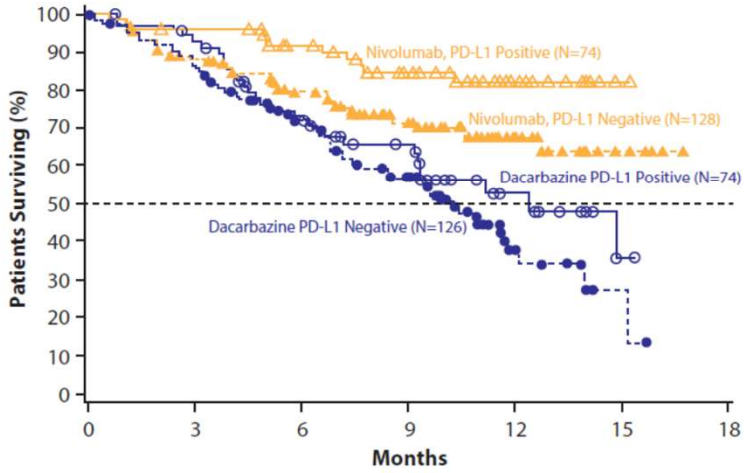
Combination Ipilimumab + Nivolumab for Patients with Asymptomatic Brain Metastases

Variable	Intracranial (N=94)	Extracranial (N=94)	Global (N=94)
Best overall response — no. (%)*			
Complete response	24 (26)	7 (7)	8 (9)
Partial response	28 (30)	40 (43)	40 (43)
Stable disease for ≥6 mo	2 (2)	6 (6)	5 (5)
Progressive disease	31 (33)	28 (30)	33 (35)
Could not be evaluated†	9 (10)	13 (14)	8 (9)
Objective response‡			
No. of patients	52	47	48
Percent of patients (95% CI)	55 (45–66)	50 (40–60)	51 (40–62)
Clinical benefit§			
No. of patients	54	53	53
Percent of patients (95% CI)	57 (47–68)	56 (46–67)	56 (46–67)



Tawbi, NEJM 2018.

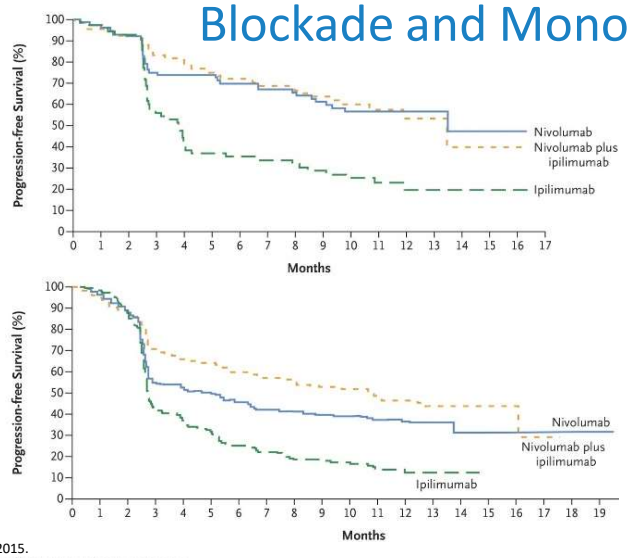
Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy



	Patients Who Died *n/N*	Median Survival *mo (95% CI)*
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

Robert, NEJM 2015.

Importance of Tumor PD-L1 Status between Combination Checkpoint Blockade and Monotherapy

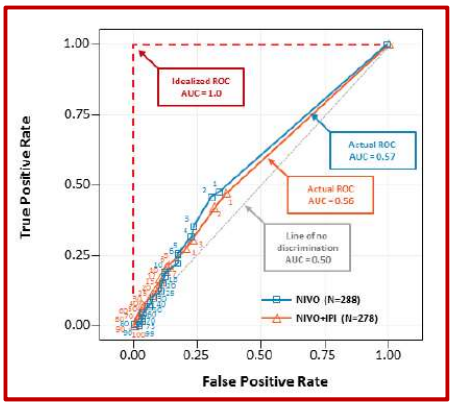


Tumor PD-L1 Positive Patients

Tumor PD-L1 Negative Patients

Larkin, NEJM 2015.

The use of PD-L1 status to predict overall survival is poor with single-agent PD-1 or combined ipi/nivo…



PDL-1 (%)	≥ 1	< 1	≥ 5	< 5	➢ 10	< 10
Ipilimumab	19%	18%	21%	17%	20%	18%
Nivolumab	54%	35%	58%	42%	58%	44%
Ipi/Nivo	65%	54%	72%	56%	85%	55%

…but, PD-L1 status predicts higher response rate with anti-PD1 therapy at every PD-L1 expression cut-off

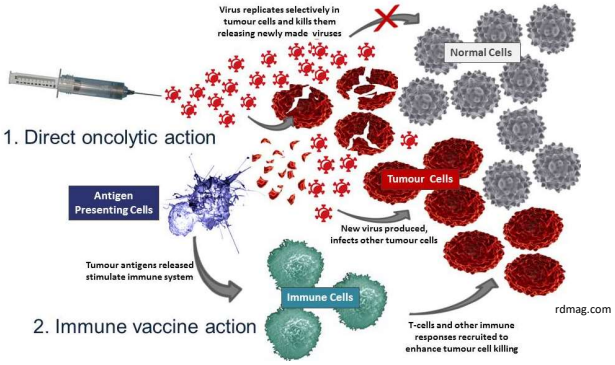
Wolchok, NEJM 2017.

In development: Neoadjuvant immunotherapy in advanced melanoma

Trial	Regimen	N	pCR (%)	med RFS (mo)	med FU (mo)
Amaria Lancet Oncol 2018	*Dab/Tram*	21	58	19.7	18.6
Long Lancet Oncol 2019	*Dab/Tram*	35	49	23.0	27.0
Blank Nat Med 2018	Ipi+nivo	10	33	NR	32
Amaria Nat Med 2018	Nivo Ipi+nivo	12 11	25 45	NR NR	20
Huang Nat Med 2019	Pembro	30	19	NR	18
Rozeman Lancet Oncol 2019	Ipi+nivo	86	57	NR	8.3

Menzies ASCO Annual Meeting 2019.

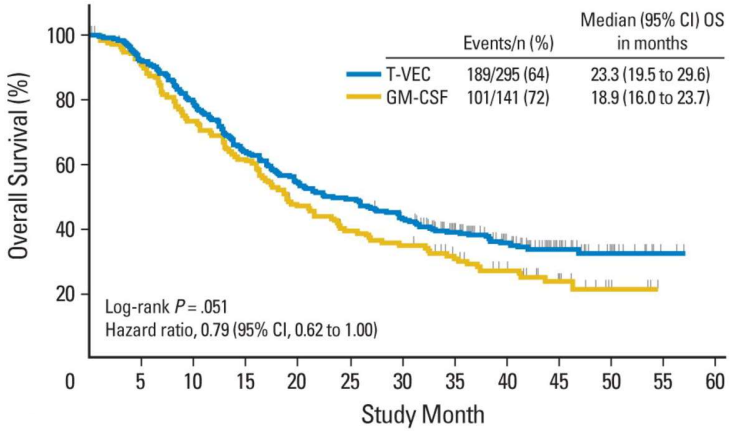
Approved oncolytic virus in melanoma



Drug	Approved	Indication	Dose
Talimogene laherparepvec (T-Vec)	2015	Local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in recurrent melanoma after surgery	Intralesional injection: ≤4 mL at 10^6 PFU/mL starting; 10^8 PFU/mL subsequent

Talimogene laherparepvec (T-VEC) in Stage III/IV Melanoma

- Phase III OPTiM Trial
  - Oncolytic, genetically-engineered herpes virus
  - Intralesional T-VEC 106 pfu/mL, 108 pfu/mL 3 weeks after initial dose, then Q2W
  - Subcutaneous GM-CSF



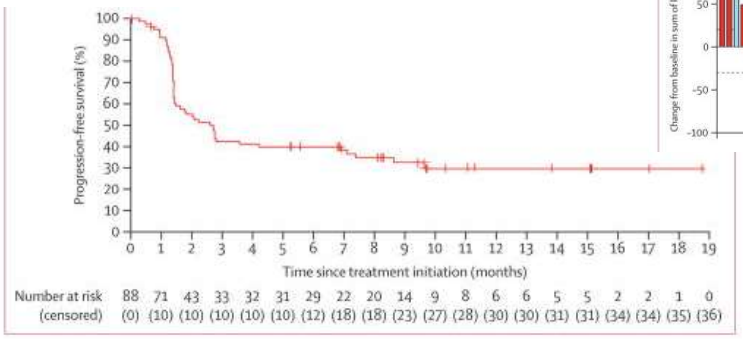
Andtbacka, Kaufman, JCO 2015.

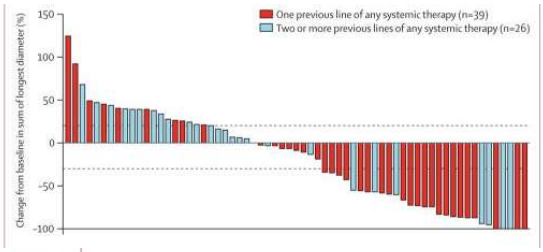
Approved checkpoint inhibitors in other skin cancers

Drug	Approved	Indication	Dose
Avelumab	2017	Patients >12 yr with metastatic **Merkel cell carcinoma**	800 mg Q2W + premedication (first 4 cycles)
Pembrolizumab	2018	Adult/pediatric with recurrent advanced/metastatic **Merkel cell carcinoma**	Adults: 200 mg Q3W Pediatric: 2 mg/kg (up to 200 mg) Q3W
Cemiplimab-rwlc	2018	Metastatic **cutaneous squamous cell carcinoma**, not candidate for curative therapies	350 mg Q3W

Avelumab in 2nd-line metastatic Merkel Cell carcinoma

- 1st FDA-approved treatment for this status
- Avelumab 10 mg/kg Q2W
- ORR: 32%, CR: 9%; PR: 23%

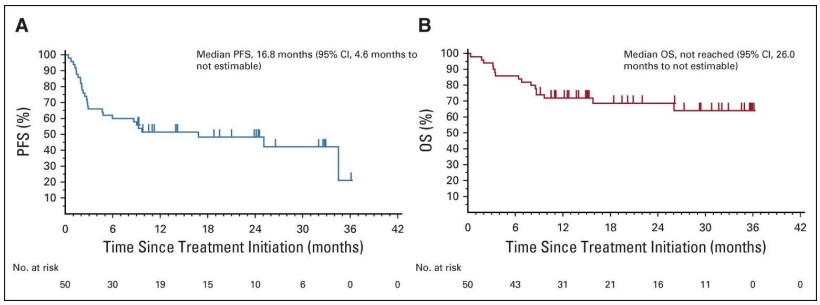




Kaufman, Lancet Oncol 2016.

Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

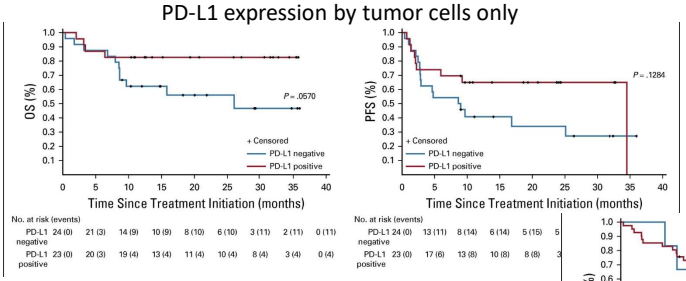
- KEYNOTE-017
- Pembrolizumab 2 mg/kg Q3W up to 2 years
- mPFS: 16.8 months (compared to 90 days for chemo)
- 24-month OS: 68.7%



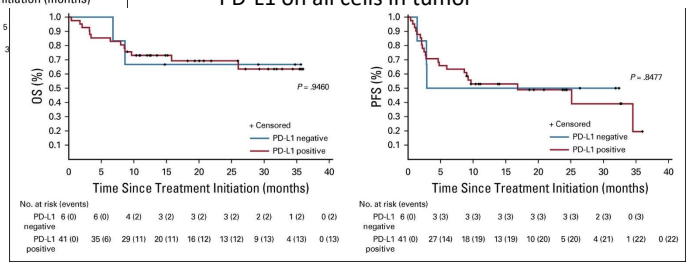
Nghiem, J Clin Oncol 2019.

Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

PD-L1 expression by tumor cells only



PD-L1 on all cells in tumor



Nghiem, J Clin Oncol 2019.

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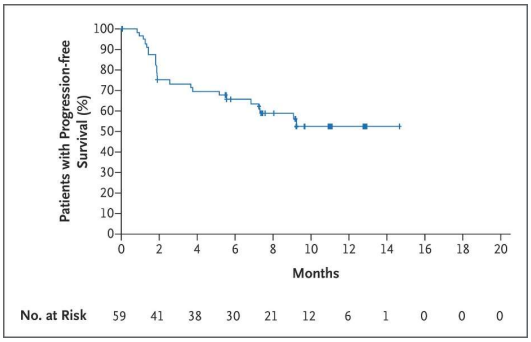
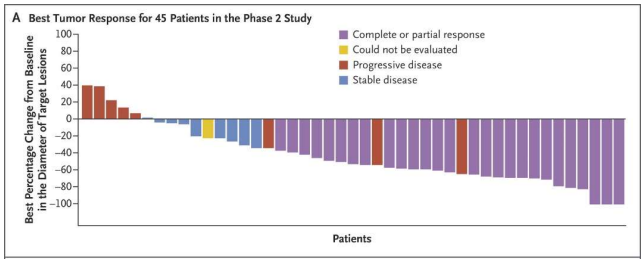
Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

- Cemiplimab 3mg/kg Q2W
- 47% response rate in metastatic patients
- 60% of locally advanced had objective response

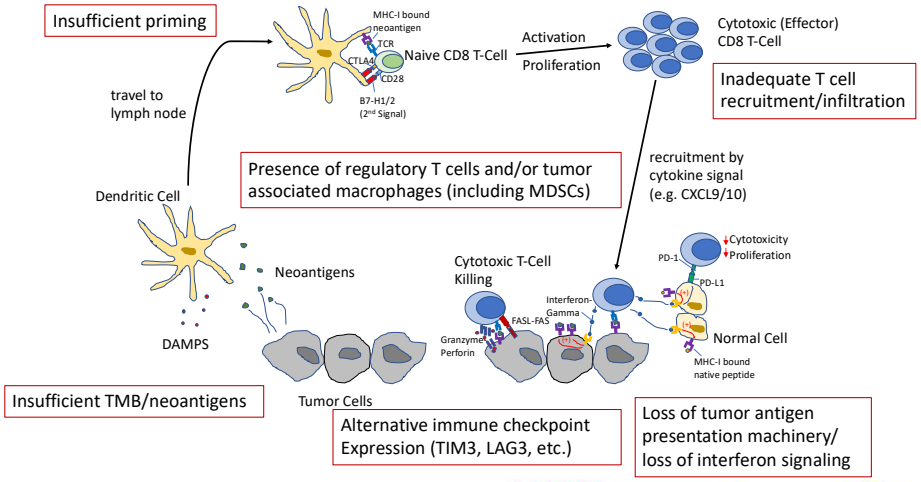




Migden, NEJM 2018.

Developmental Immunotherapeutic Strategies for Melanoma

How does immune checkpoint inhibitor therapy fail?

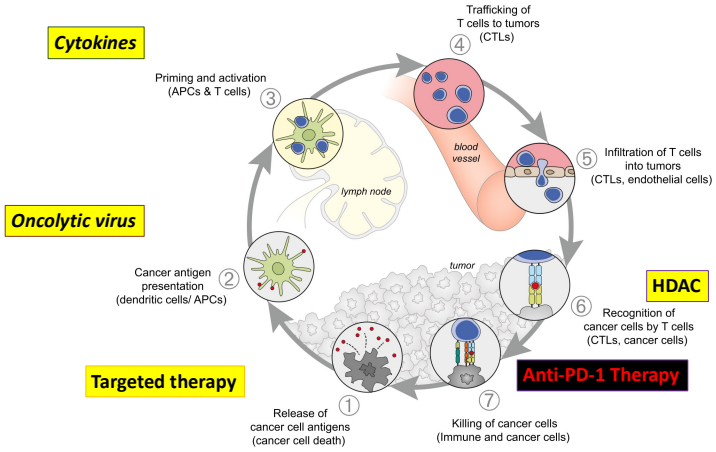


Modified from Liu, Jenkins, Sullivan. Amer J Clin Derm 2018.

Developmental Immunotherapeutic Strategies for Melanoma

How do we overcome resistance?

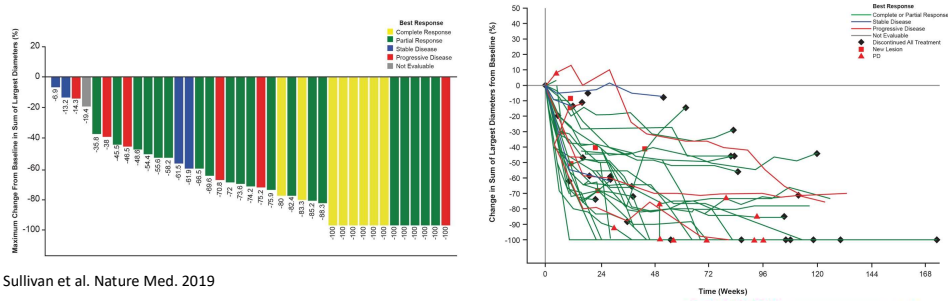
Combination therapy



Modified from Chen and Melman. Immunity 2015.

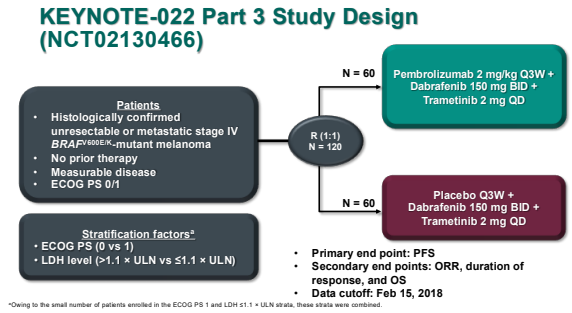
Recently approved: Combined IO with BRAF targeted therapy

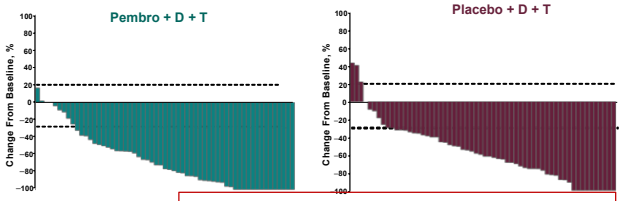
- Cobimetinib + vemurafenib + atezolizumab
- ORR: 71.8%
- Median duration of response: 17.4 mo



Sullivan et al. Nature Med. 2019

In development: Combined IO with BRAF targeted therapy



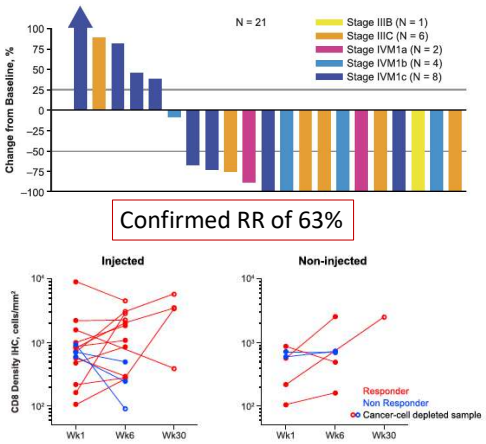


ORR	63%	72%
CR	18%	13%
≥ 60% red	63%	51%

Ascieto et al, *Nature Med* 2019.

In development: Combined IO with Oncolytic Virus

Phase I: Pembrolizumab + TVEC



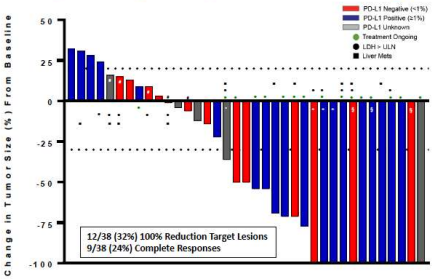
Confirmed RR of 63%

Ribas et al Cell 2017

In development: Combined IO with IL-2 (NKTR-214)

Efficacy (response rate) data from non-randomized cohorts of urothelial bladder cancer, renal cell carcinoma, and melanoma looks promising

Stage IV IO-Naïve 1L Melanoma Cohort at RP2D Best Overall Response by Independent Radiology



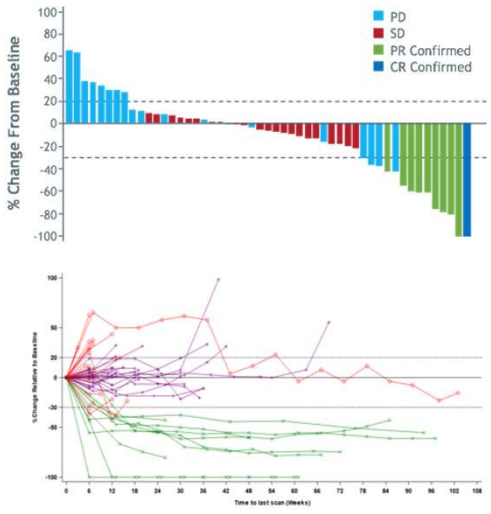
1L Melanoma (n=38 Efficacy Evaluable)	Overall Response Rate
Confirmed ORR (CR+PR)	20 (53%)
CR	9 (24%)
DCR (CR+PR+SD)	29 (76%)
PD-L1 negative (n=14)	6 (43%)
PD-L1 positive (n=19)	13 (68%)
PD-L1 unknown (n=5)	1 (20%)
LDH > ULN (n=11)	5 (45%)
Liver metastases (n=10)	5 (50%)

High level of concordance in ORR between independent central radiology (53%) and investigator-assessed 19/38 (50%).

Diab et al, ASCO 2018.
Diab et al, SITC 2018.

In development: Combined IO with HDAC inhibitor

- Entinostat + pembrolizumab
- 19% ORR (1 CR, 9 PR)
- Median duration of response: 13 mo
- 9 additional patients with SD for >6 mo



Sullivan et al, AACR 2019.

Pilot Study: Radiotherapy (RT) + Intratumoral Immunocytokine (IT-IC) + Ipilimumab + Nivolumab for Advanced Melanoma

A UWCCC Clinical Trial

Goals:

A. **First in human Phase-I testing of IT-IC with an IC that can bind to tumor and mediate ADCC**
B. **First in human IT-IC of such an IC immunologically timed after local RT**
C. **First in human testing of this in combination with anti-CTLA4 and/or anti-PD1**
D. **Toxicity/Tolerance/Anti-tumor effects**
E. **Serial biopsies of the same lesions, to look for the changes seen in murine tumors**

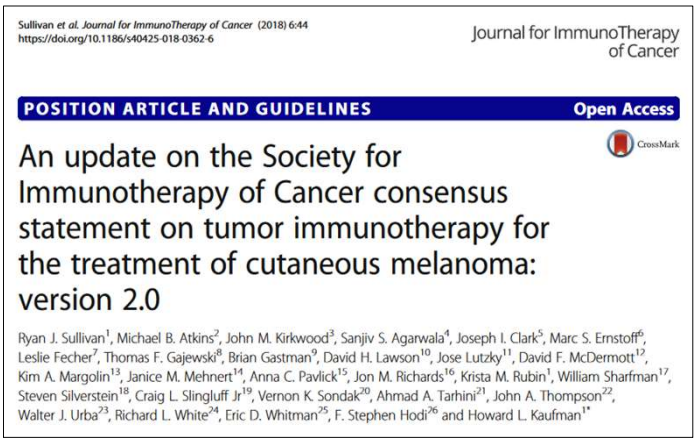
Protocol chair: Mark R Albertini, M.D.
Radiation Oncology Co-Chair: Zachary Morris, M.D., Ph.D.
Laboratory Co-Chair: Jacqueline A. Hank, Ph.D.
Pathology Co-Chair: Erik Ranheim, M.D., Ph.D.
NCI Grant (R35 CA197078-01) PI: Paul M. Sondel, M.D., Ph.D.

The initial patient intratumoral immunocytokine injection was given 2-17-2020.

Conclusions

- Melanoma was one of the foundational disease states for testing immunotherapies
- Avelumab and pembrolizumab are now approved for Merkel cell carcinoma, and cemiplimab is approved for cutaneous squamous cell carcinoma
- Combination immunotherapies may lead to higher response rates and more durable responses

Additional Resources



Sullivan et al. Journal for ImmunoTherapy of Cancer (2018) 6:44
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Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES — Open Access

An update on the Society for Immunotherapy of Cancer consensus statement on tumor immunotherapy for the treatment of cutaneous melanoma: version 2.0

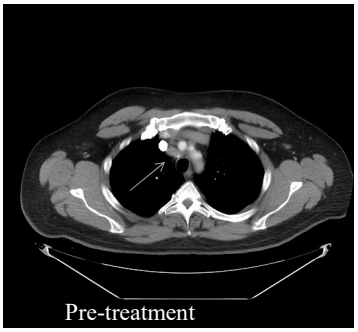
Ryan J. Sullivan[1], Michael B. Atkins[2], John M. Kirkwood[3], Sanjiv S. Agarwala[4], Joseph I. Clark[5], Marc S. Ernstoff[6], Leslie Fecher[7], Thomas F. Gajewski[8], Brian Gastman[9], David H. Lawson[10], Jose Lutzky[11], David F. McDermott[12], Kim A. Margolin[13], Janice M. Mehnert[14], Anna C. Pavlick[15], Jon M. Richards[16], Krista M. Rubin[1], William Sharfman[17], Steven Silverstein[18], Craig L. Slingluff Jr[19], Vernon K. Sondak[20], Ahmad A. Tarhini[21], John A. Thompson[22], Walter J. Urba[23], Richard L. White[24], Eric D. Whitman[25], F. Stephen Hodi[26] and Howard L. Kaufman[1*]

Case Studies

Case #1: Metastatic Melanoma BRAF mutant

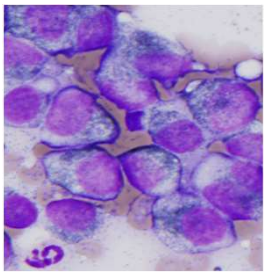
49 y/o male melanoma patient

- Presented with biopsy confirmed mediastinal LN involvement; melanoma had $BRAF^{V600E}$ mutation



Courtesy of Dr. Meghan Lubner

Cytology following fine needle aspiration of mediastinal lymph node



Courtesy of Dr. Erik Ranheim

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What treatment is not an acceptable first line treatment?

- Anti-PD1 monotherapy (pembrolizumab or nivolumab)
- Nivolumab + Ipilimumab
- Ipilimumab
- BRAF inhibitor + MEK inhibitor (dabrafenib + trametinib, vemurafenib + cobimetinib, or encorafenib + binimetinib)

What treatment is not an acceptable first line treatment for metastatic BRAF mutant melanoma?

- Ipilimumab (less effective than either anti-PD1 alone or anti-PD1 in combination with ipilimumab)

What treatments are acceptable first line treatments for metastatic BRAF mutant melanoma?

NCCN First Line Preferred Systemic therapy for Metastatic Melanoma (category 1)

- Anti-PD1 monotherapy (pembrolizumab or nivolumab)
- Nivolumab + Ipilimumab
- BRAF inhibitor + MEK inhibitor if BRAF V600 activating mutation present (dabrafenib + trametinib, vemurafenib + cobimetinib, or encorafenib + binimetinib)

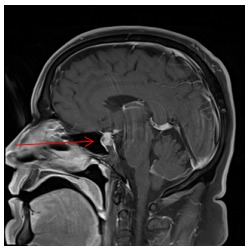
What is the best sequencing of treatment for patients with advanced BRAF V600 mutant melanoma?

- EA6134: A Randomized Phase III Trial of Dabrafenib + Trametinib followed by Ipilimumab + Nivolumab at Progression vs Ipilimumab + Nivolumab followed by Dabrafenib + Trametinib at Progression in Patients with Advanced BRAFV600 Mutant Melanoma

Case #1: Metastatic Melanoma BRAF mutant

- Initial Therapy:
  - Ipilimumab and nivolumab
  - Tolerated therapy with minimal side effects for the first 2 cycles

Presented with significant headaches as well as nausea with vomiting 12 days after cycle #3 of ipilimumab and nivolumab



2 weeks after cycle #3 of Ipi/Nivo

- Comprehensive laboratory studies including cortisol, TSH, T3, T4, testosterone

Courtesy of Dr. Meghan Lubner

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What immediate treatment decision will maximize the likelihood for durable antitumor benefit?

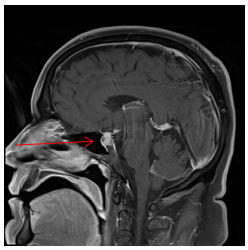
- Transition to anti-PD1 monotherapy (pembrolizumab or nivolumab)
- Continue nivolumab + Ipilimumab
- Transition to BRAF inhibitor + MEK inhibitor (dabrafenib + trametinib, vemurafenib + cobimetinib, or encorafenib + binimetinib)
- Treat with high dose steroids

The following immediate treatment decisions will not take care of a serious immune-related side effect and could result in serious toxicity or death.

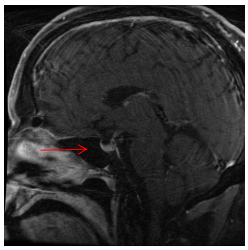
- Transition to anti-PD1 monotherapy (pembrolizumab or nivolumab)
- Continue nivolumab + Ipilimumab
- Transition to BRAF inhibitor + MEK inhibitor (dabrafenib + trametinib, vemurafenib + cobimetinib, or encorafenib + binimetinib)

Management of Case #1

- Methylprednisolone 1 mg/kg IV twice daily followed by transition to oral prednisone with a prolonged taper
- GI Prophylaxis: omeprazole
- PJP Prophylaxis: bactrim
- Fungal prophylaxis: clotrimazole
- levothyroxine

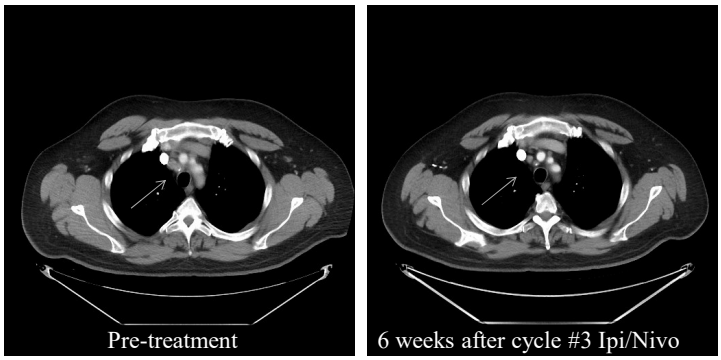


2 weeks after cycle #3 of Ipi/Nivo



6 weeks after cycle #3 of Ipi/Nivo

Courtesy of Dr. Meghan Lubner



Courtesy of Dr. Meghan Lubner

Clinical Status 2.5 years after cycle #3 Ipi/Nivo

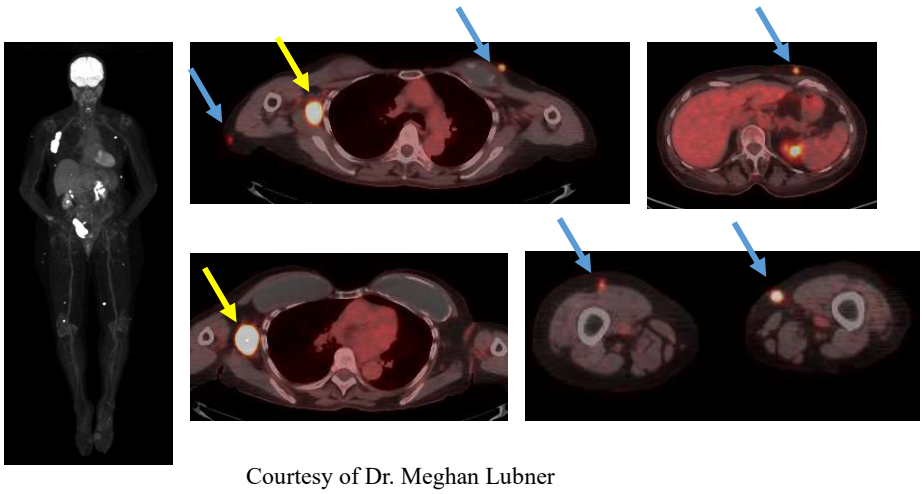
- CT scans stable and without evidence for progression
- Remains on hydrocortisone 10 mg in the AM and 5 mg in the PM as well as replacement levothyroxine

Case #2: Metastatic Melanoma BRAF mutant

76 y/o female patient

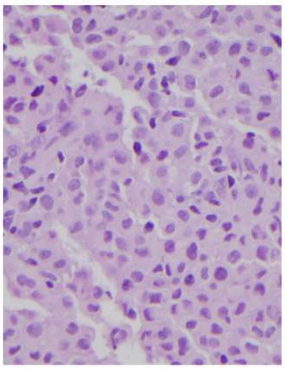
- H/o stage IIC ovarian cancer
- Diagnosis of metastatic melanoma of unknown primary after presenting with enlarged bilateral axillary lymph nodes
- Ultrasound-guided core needle biopsies of right and left axillary lymph nodes revealed metastatic melanoma
- BRAF mutation in codon 600 of the BRAF gene was detected (V600E mutation)

Pre-treatment

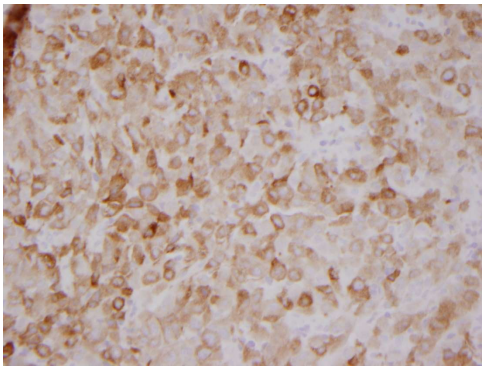


Courtesy of Dr. Meghan Lubner

Ultrasound guided core needle biopsy of right axillary lymph node



Hematoxylin and Eosin stain



Immunostains for Melanoma Cocktail (HMB 45 and Melan A)

Courtesy of Dr. Erik Ranheim

What immunotherapy option(s) would you consider?

- Anti-PD1 alone OR anti-PD1 in combination with Ipilimumab
- Ipilimumab alone
- Interferon alpha 2b
- Interleukin 2

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Appropriate first line immunotherapy options to consider

NCCN preferred first line immunotherapy options (category 1)

- Anti-PD1 monotherapy (pembrolizumab or nivolumab)
- Nivolumab + Ipilimumab

Immunotherapy options that are not acceptable first line treatments for this patient

- Ipilimumab (less effective than either anti-PD1 alone or anti-PD1 in combination with ipilimumab)
- Interferon alpha 2b (not an appropriate treatment for metastatic melanoma due to minimal activity and high toxicity)
- High-dose IL-2 (not appropriate as a first line treatment due to lower activity, high toxicity, and typically not given to patients over 60 y/o due to high toxicity)

PD-L1 Immunohistochemistry

PD-L1 immunohistochemistry was performed and was positive in less than 1 % of the tumor cells.

Which of the following statements about treatment considerations for this patient is false?

- Both anti-PD1 monotherapy and anti-PD1 + ipilimumab combination therapy may provide durable disease control
- Combination therapy is associated with higher clinical response rates, progression-free survival, and overall survival at the expense of more frequent and more severe immune-related adverse events
- Melanomas with low PD-L1 expression can respond to either anti-PD1 monotherapy or anti-PD1 + ipilimumab therapy
- PD-L1 is a validated biomarker for selection of anti-PD1 monotherapy or anti-PD1 + ipilimumab therapy

The following statements are correct

- Both anti-PD1 monotherapy and anti-PD1 + ipilimumab combination therapy may provide durable disease control
- Combination therapy is associated with higher clinical response rates, progression-free survival, and overall survival at the expense of more frequent and more severe immune-related adverse events
- Melanomas with low PD-L1 expression can respond to either anti-PD1 monotherapy or anti-PD1 + ipilimumab therapy

The following statements is not correct

- PD-L1 is a validated biomarker for selection of anti-PD1 monotherapy or anti-PD1 + ipilimumab therapy

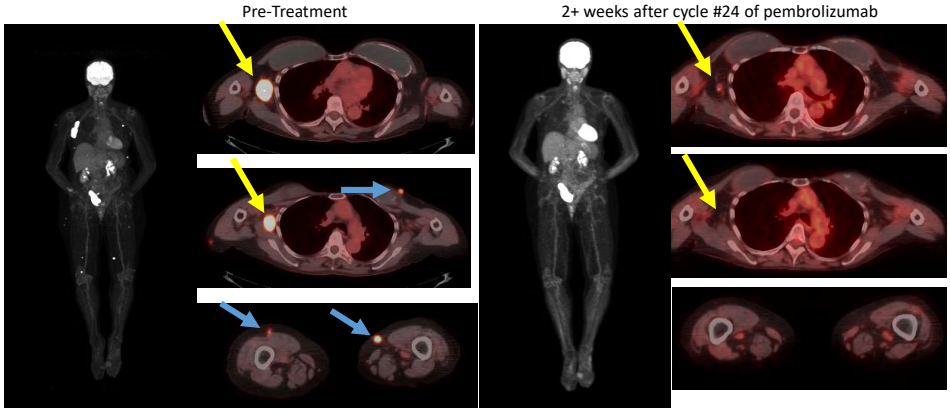
- Explanation: The use of PD-L1 as a biomarker for selection of anti-PD1 monotherapy or anti-PD1 + ipilimumab therapy is a topic of ongoing investigtion

Case 2 Management

- Treatment with pembrolizumab with repeat disease assessments every 3 months
- No significant treatment-associated toxicity
- Significant anti-tumor response
- Treatment stopped after cycle 26 (approx. 18 months of treatment) due to separate medical and social considerations

Pre-Treatment

2+ weeks after cycle #24 of pembrolizumab



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Clinical status after stopping pembrolizumb

- Remains without evidence for disease progression when last evaluated over 2 years after stopping pembrolizumab