Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Skin Cancers

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

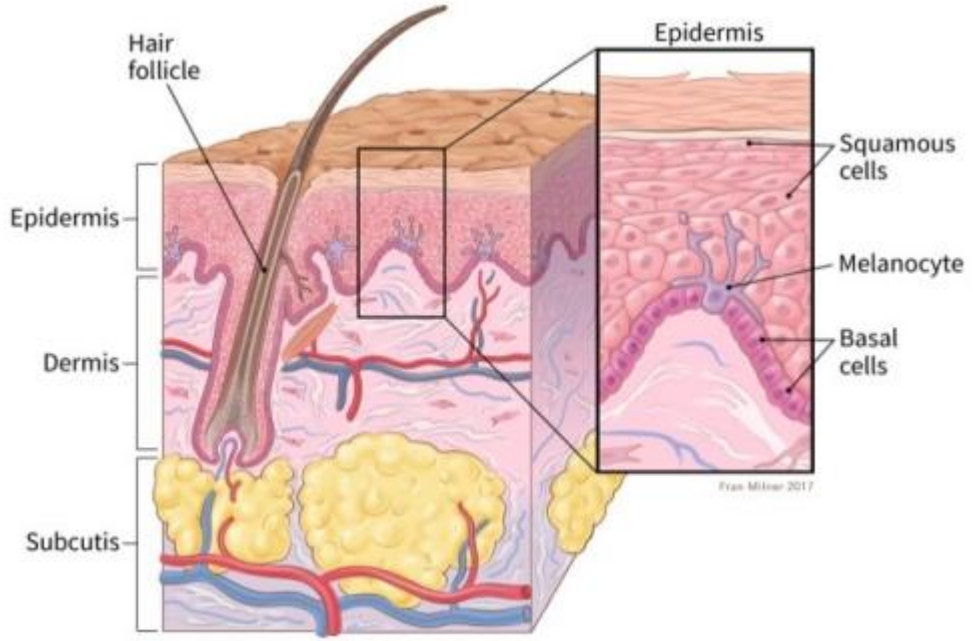
Disclosures

- Consulting Fees:
  - Novartis

- 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



Cancer.org

Approved cytokines in melanoma

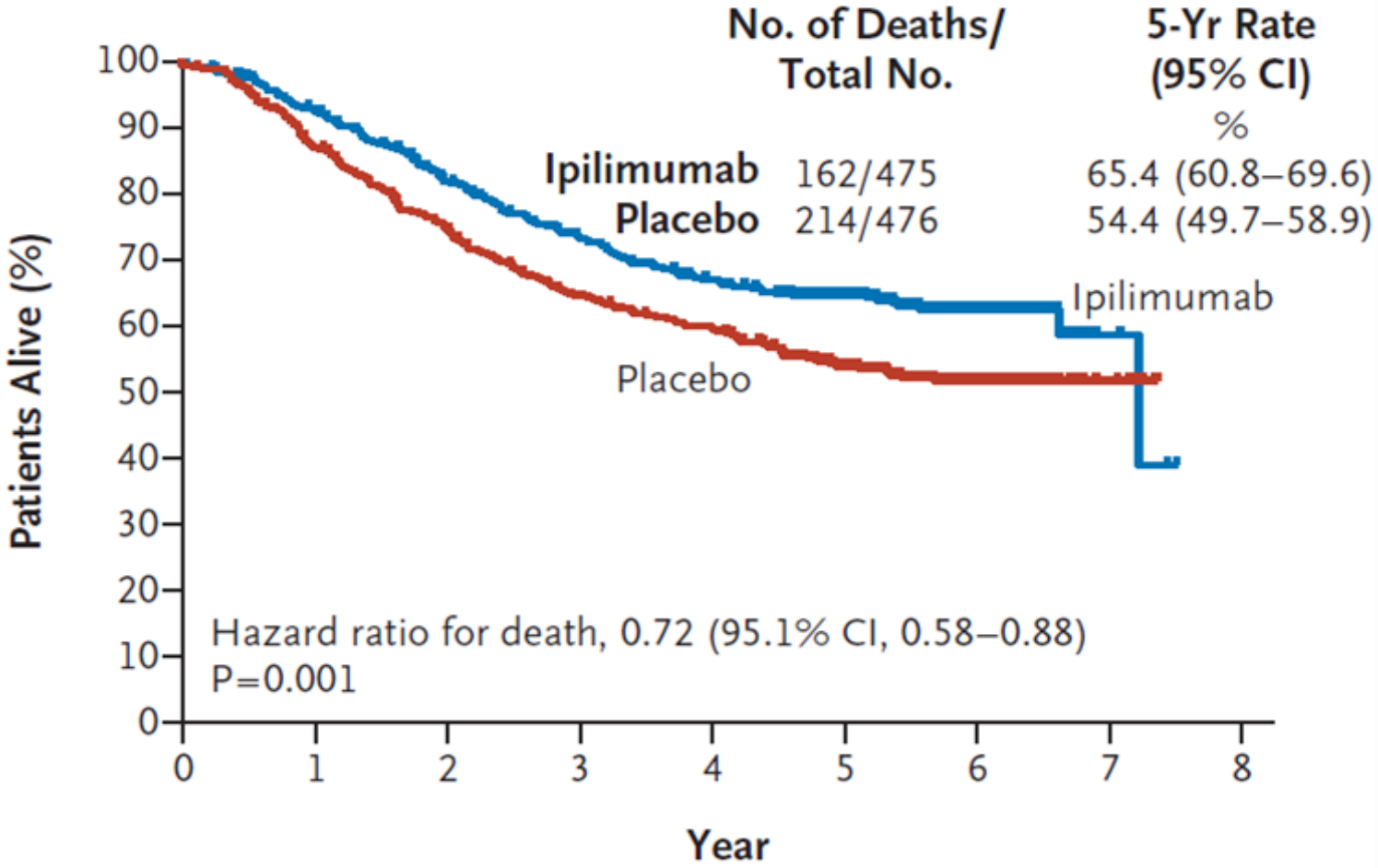
Drug	Indication	Dose
High-dose interferon alfa-2b	Adjuvant – high risk for systemic recurrence	Induction: 20m IU/m^2 IV 5x/wk for 4 wks Maintenance: 10m IU/m^2 s.c. 3x/wk for 48 wks
Interleukin-2 (Aldesleukin)	Stage IV	600k IU/kg/dose Q8hr, up to 14 doses; 9 days of rest; can repeat up to 28 doses per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



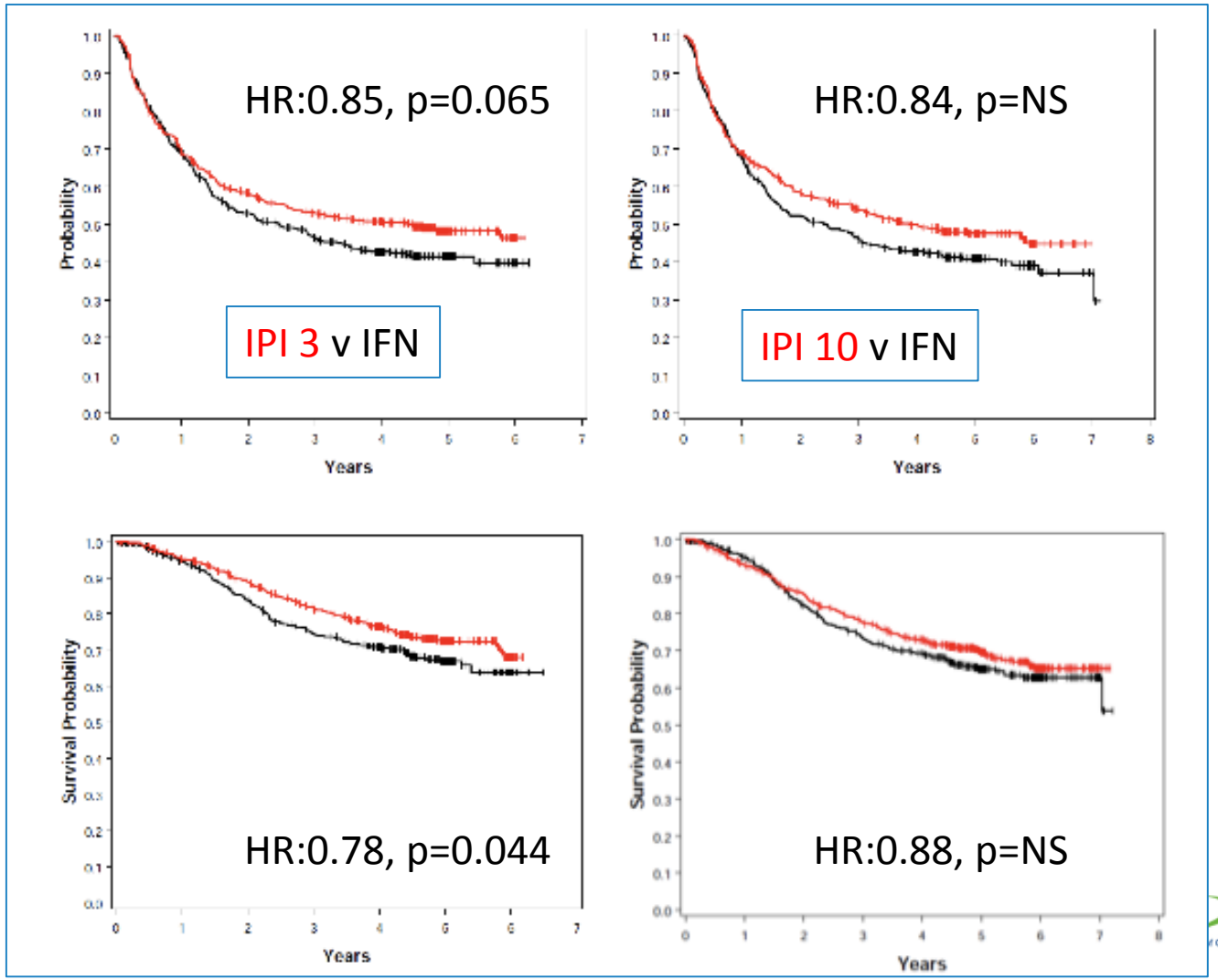
Eggermont, NEJM 2016.

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 “not better than IFN”
  - IPI3 better tolerated than IPI 10

RFS

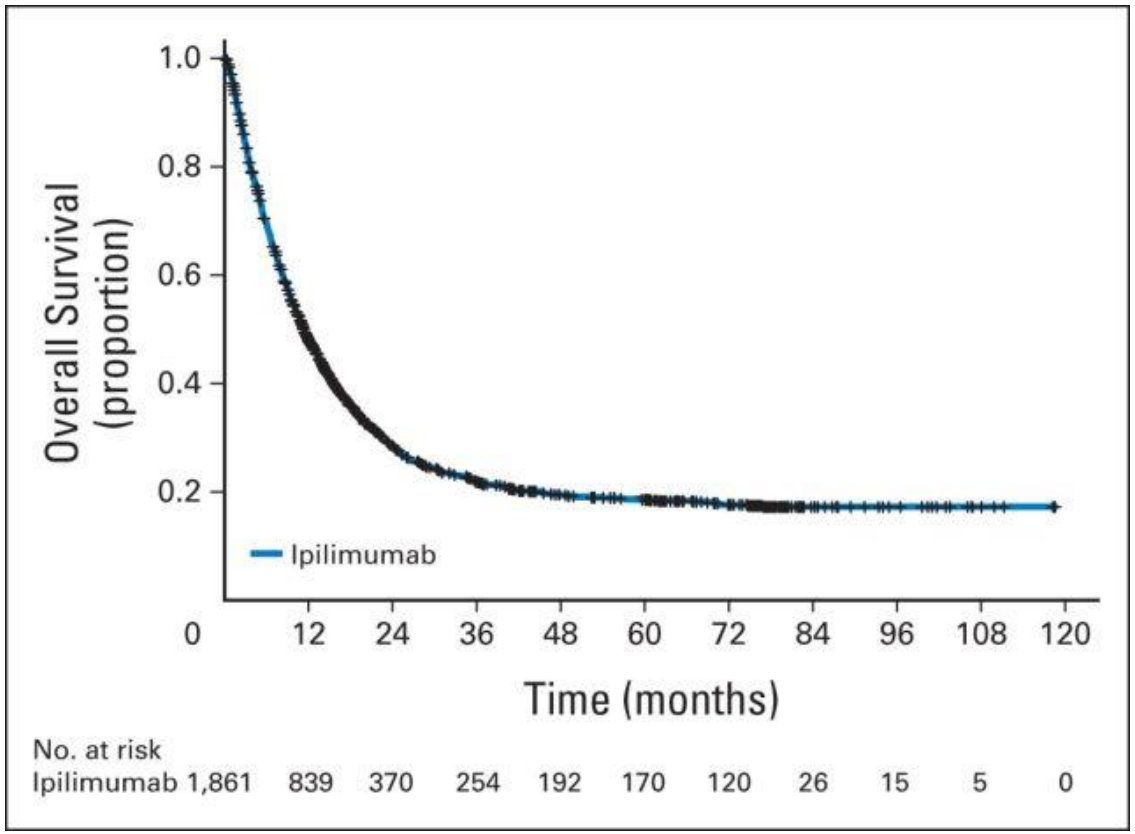
OS



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)



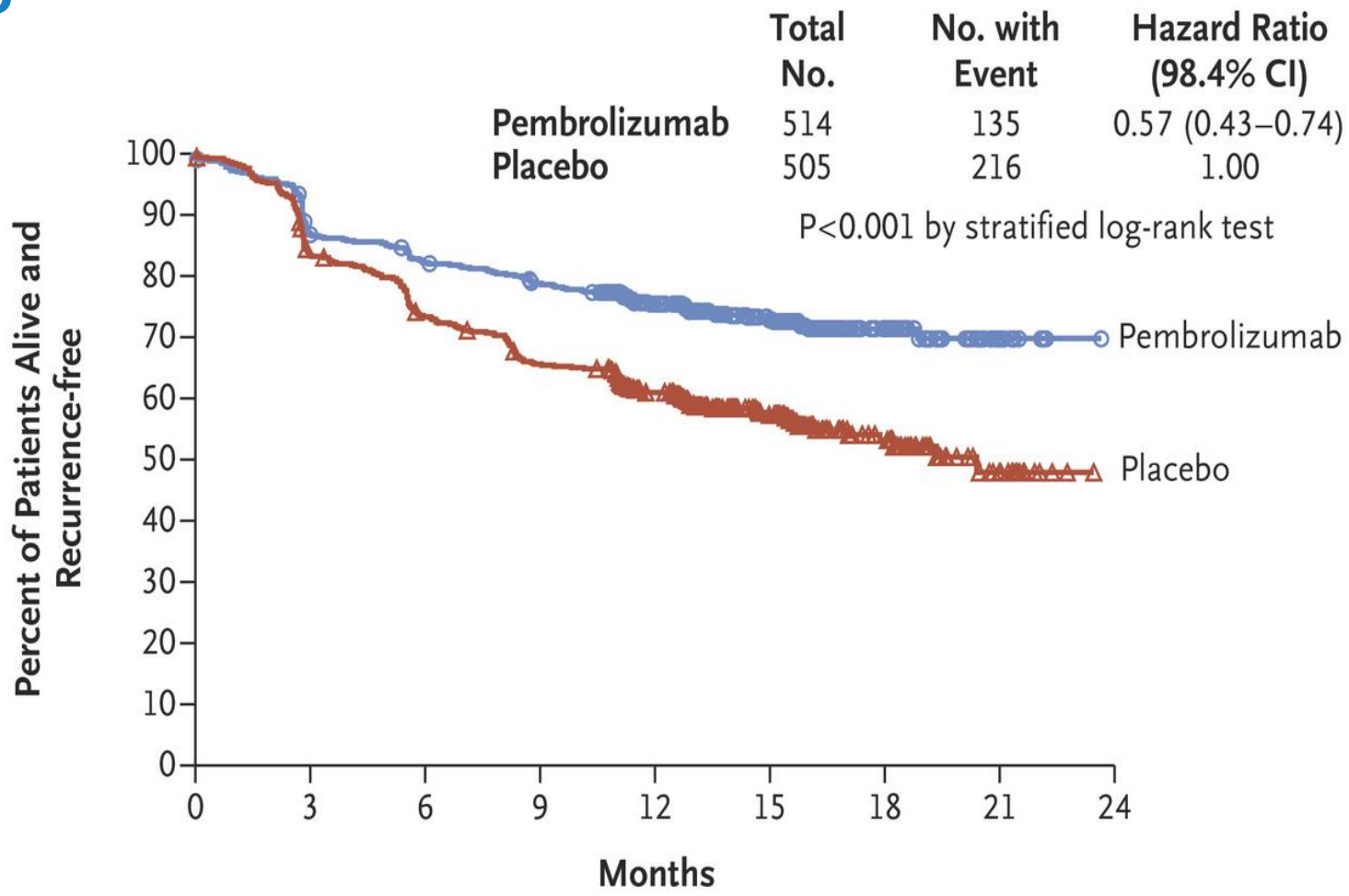
Schadendorf, JCO 2015.

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	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			

Adjuvant Pembrolizumab in High-Risk Stage III Melanoma

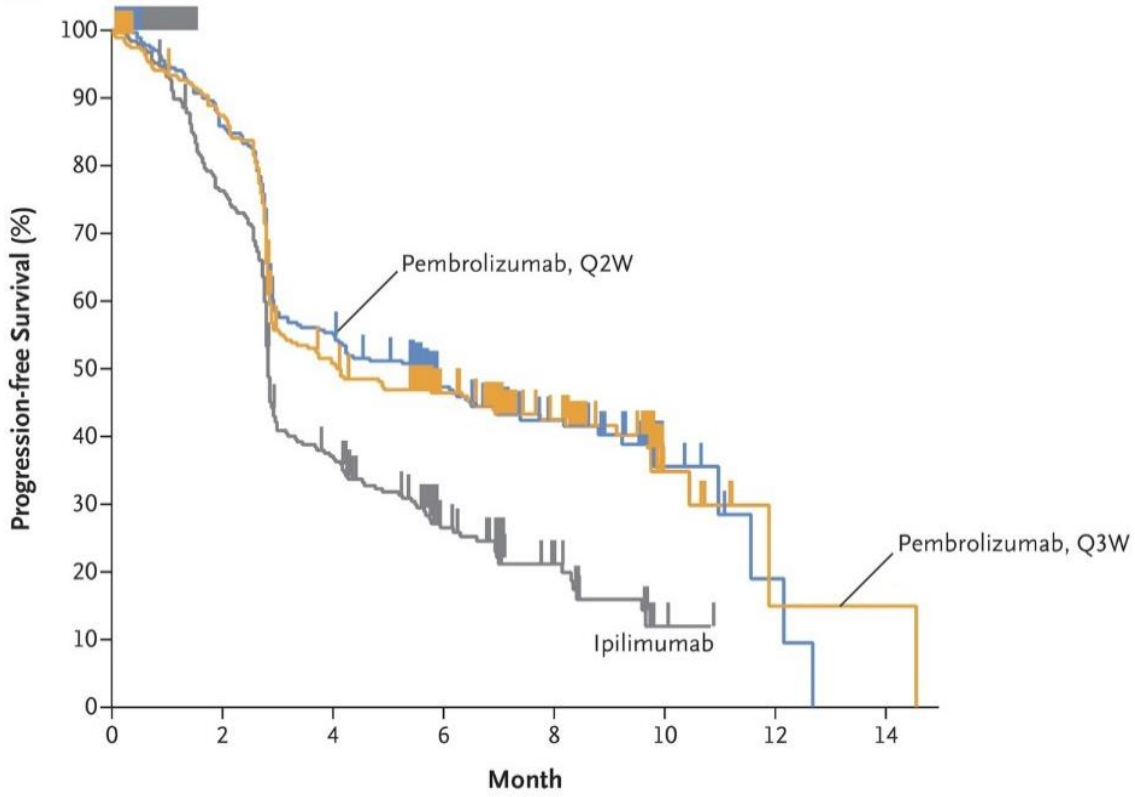
- EORTC 1325/KEYNOTE-054 phase III trial
  - NCT02362594
  - Adjuvant pembrolizumab vs placebo
  - Pembrolizumab 200mg Q3W for up to 1 year (~18 total doses)

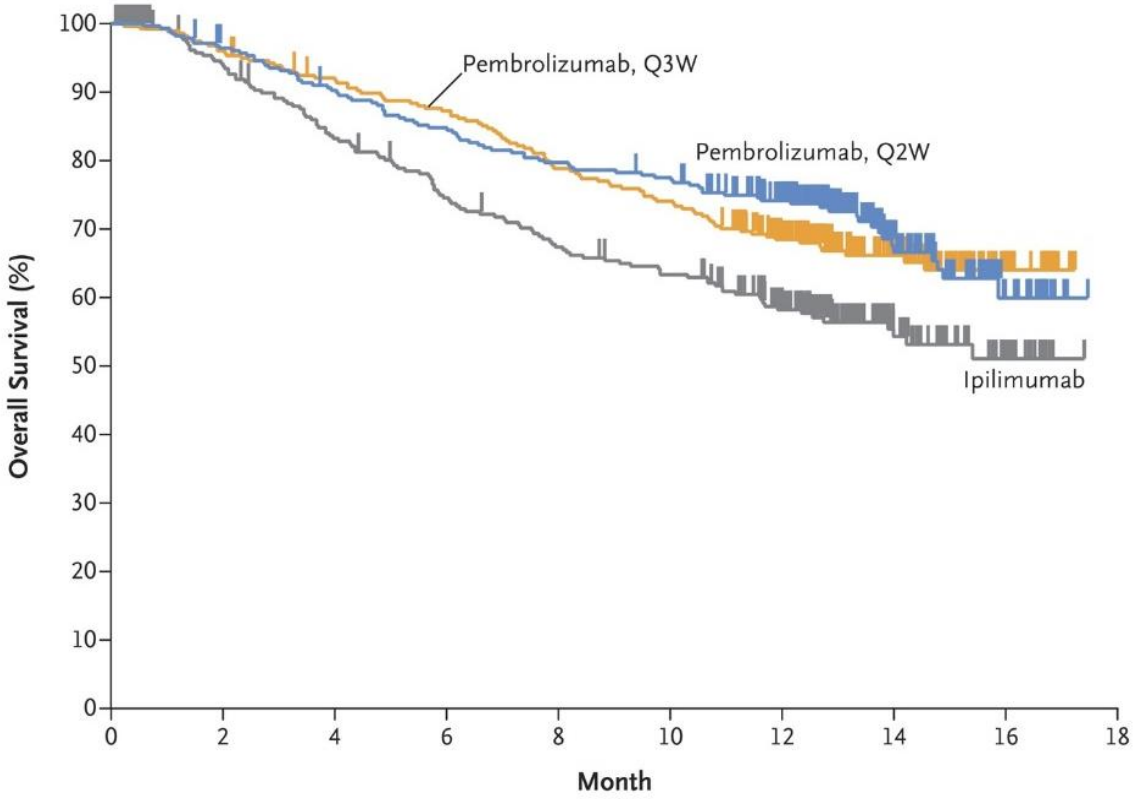


Eggermont, NEJM 2018.

Pembrolizumab in Stage III/IV Melanoma

Phase III KEYNOTE-006 Trial





Robert, NEJM 2015.

Approved checkpoint inhibitors in melanoma

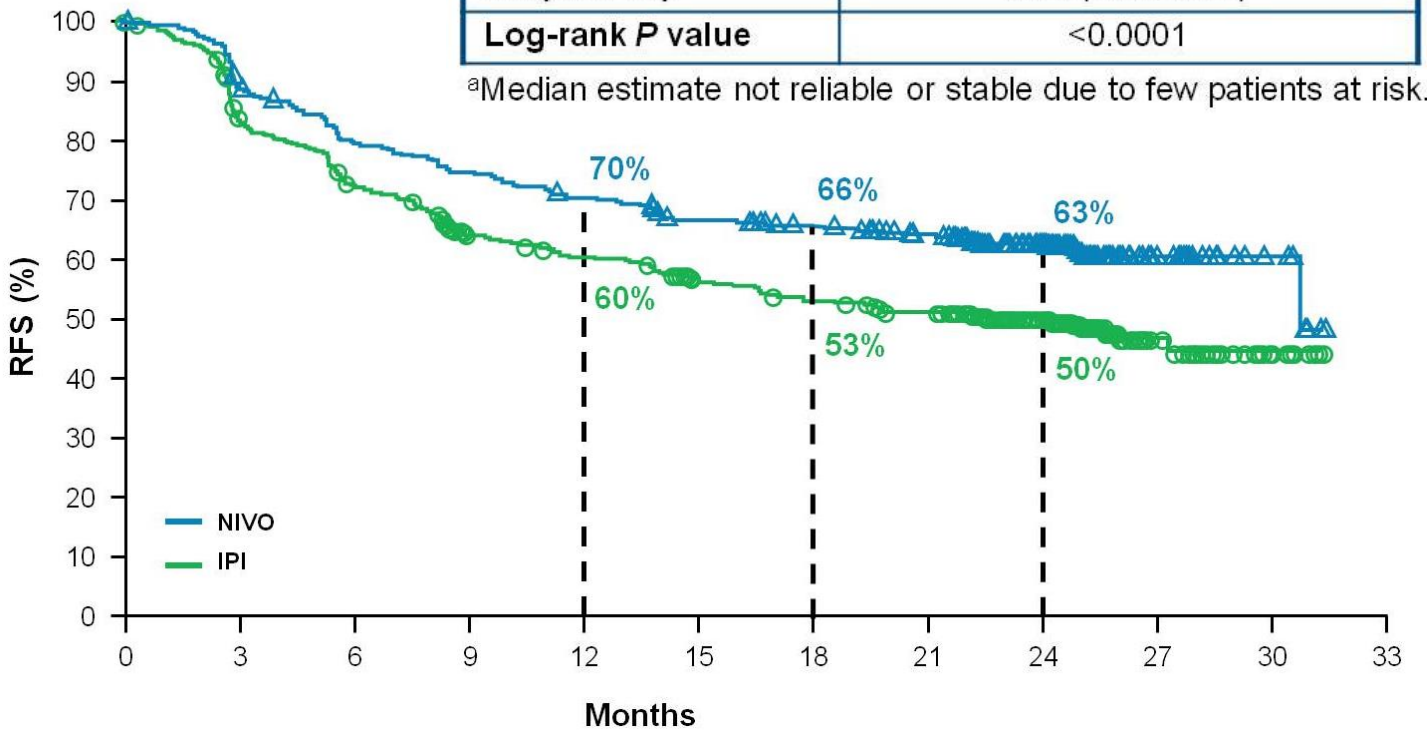
Drug	Approved	Indication	Dose
Nivolumab	2014	Unresectable/metastatic melanoma with progression after other therapy	240 mg Q2W or 480 mg Q4W*
	2017	Adjuvant treatment of melanoma after complete resection	240 mg Q2W or 480 mg Q4W
*Original approval was 3 mg/kg Q2W, updated to flat dosing regimen			

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.



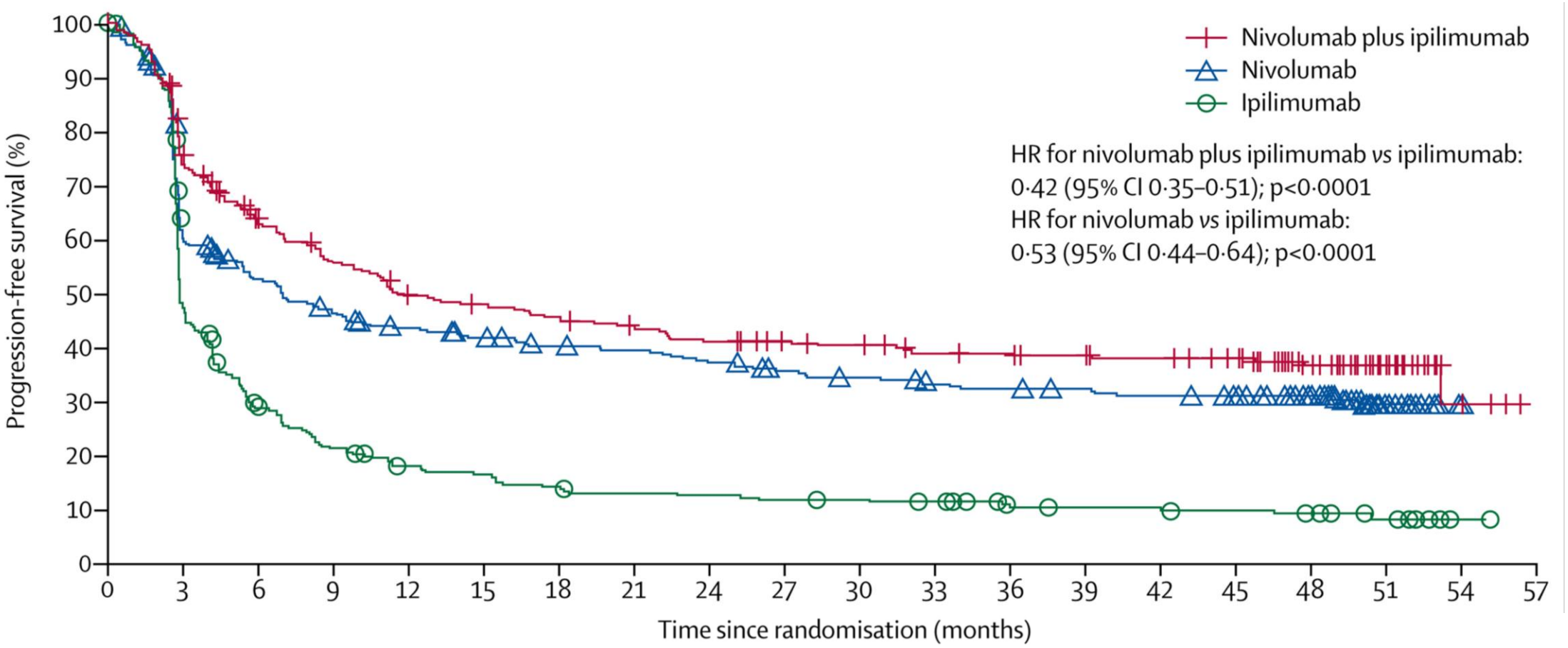
Miller, ASCO 2018.

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

Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma

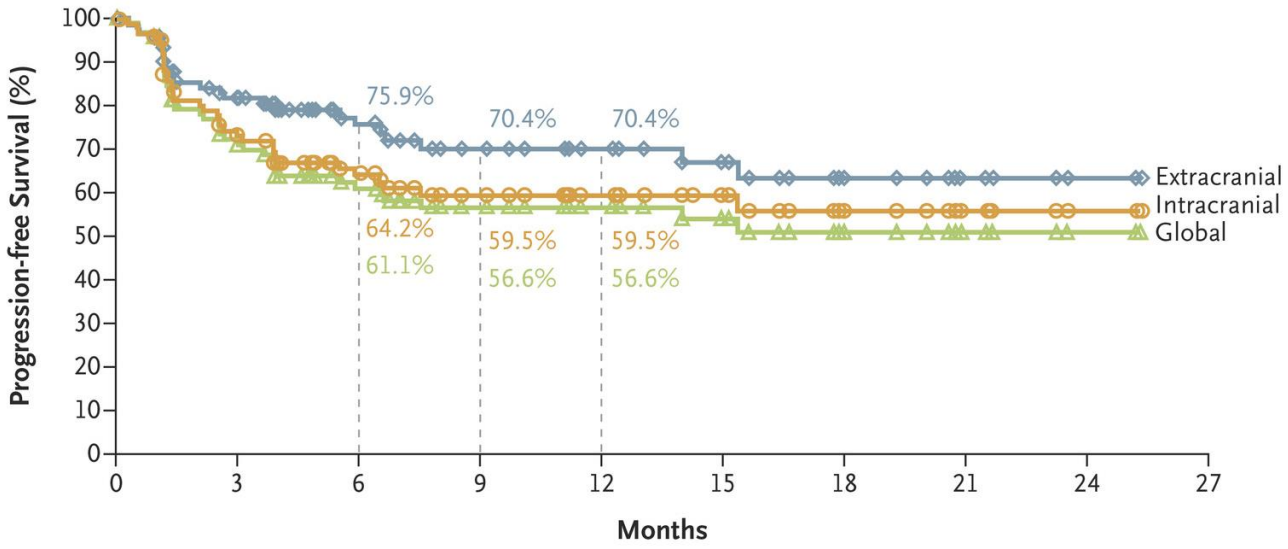
Phase III CheckMate 067 Trial



Hodi, Lancet Oncol 2018.

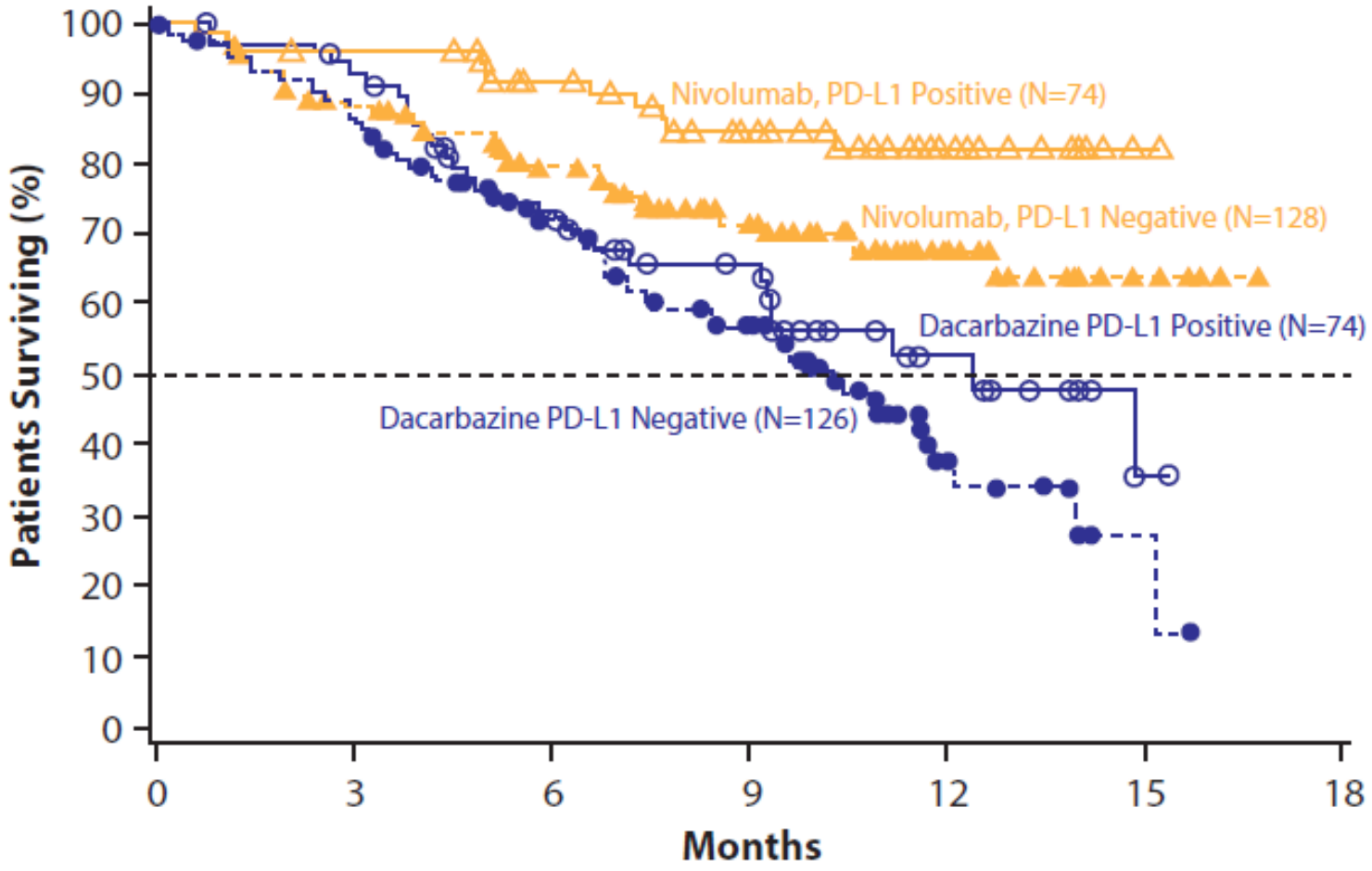
Combination Ipilimumab + Nivolumab for Patients with Asymptomatic Brain Metastases

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.

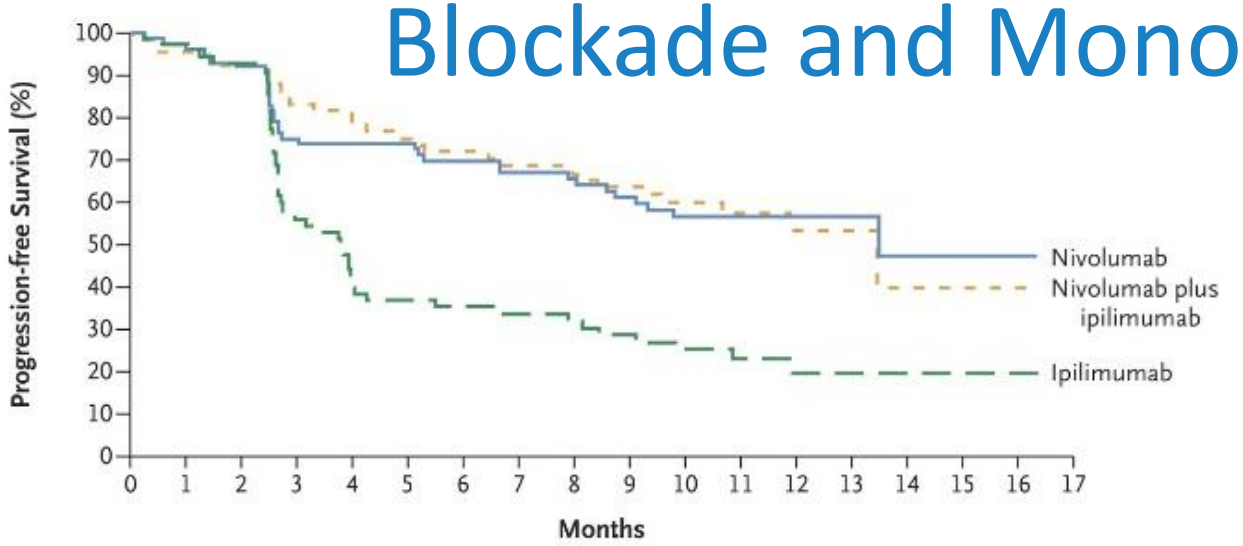
Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy



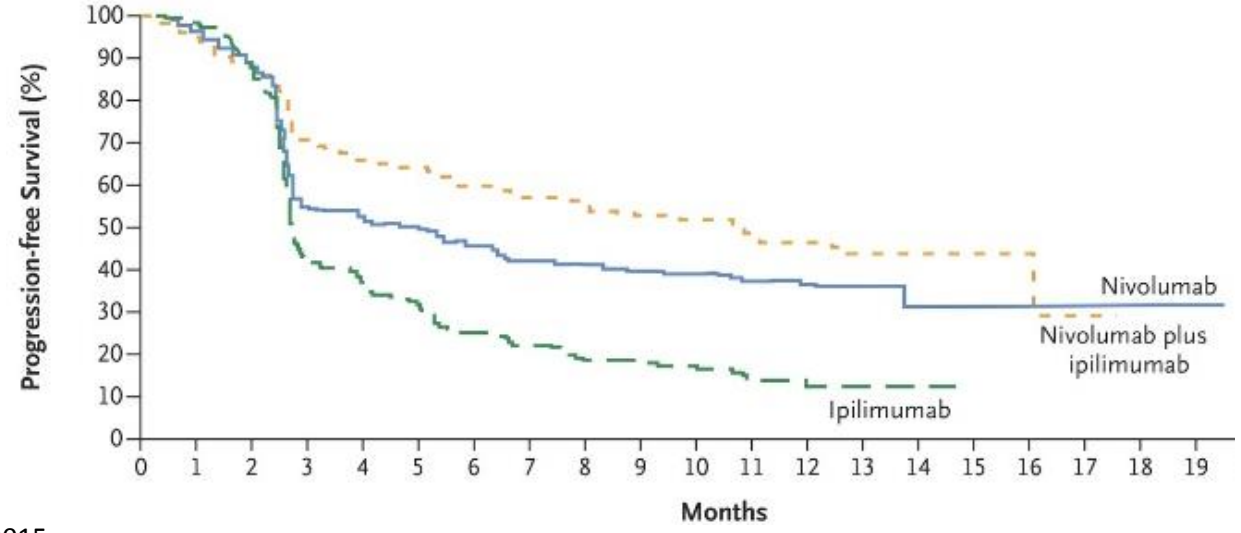
	Patients Who Died *n/N*	Median Survival *mo (95% CI)*
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

Robert, NEJM 2015.

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



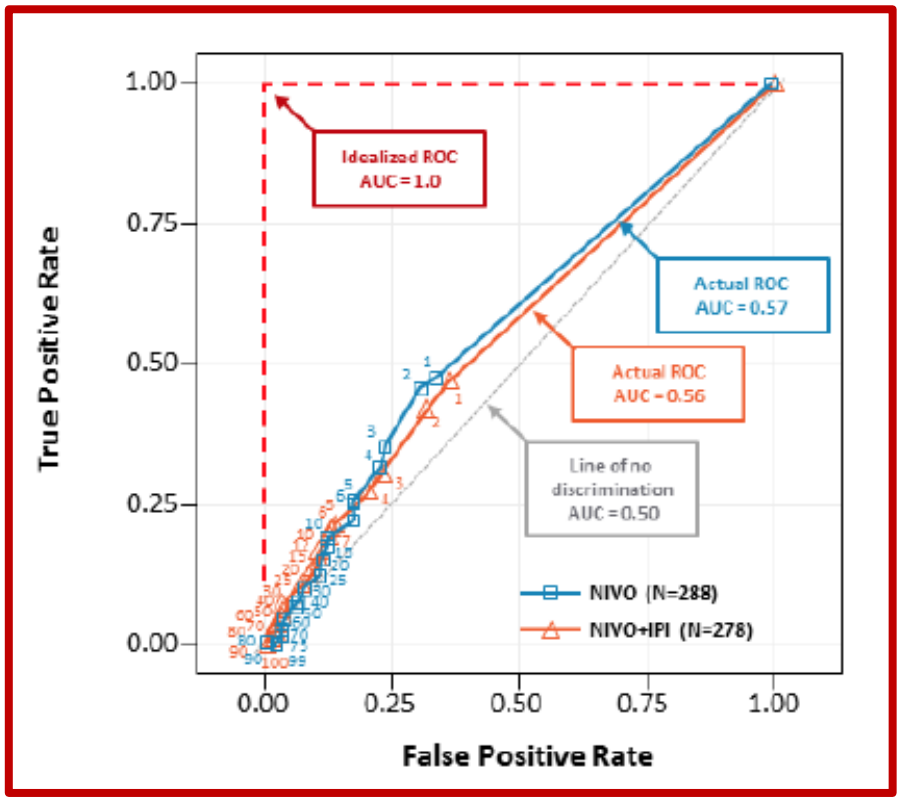
Tumor PD-L1 Positive Patients



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 combo at every PD-L1 expression cut-off

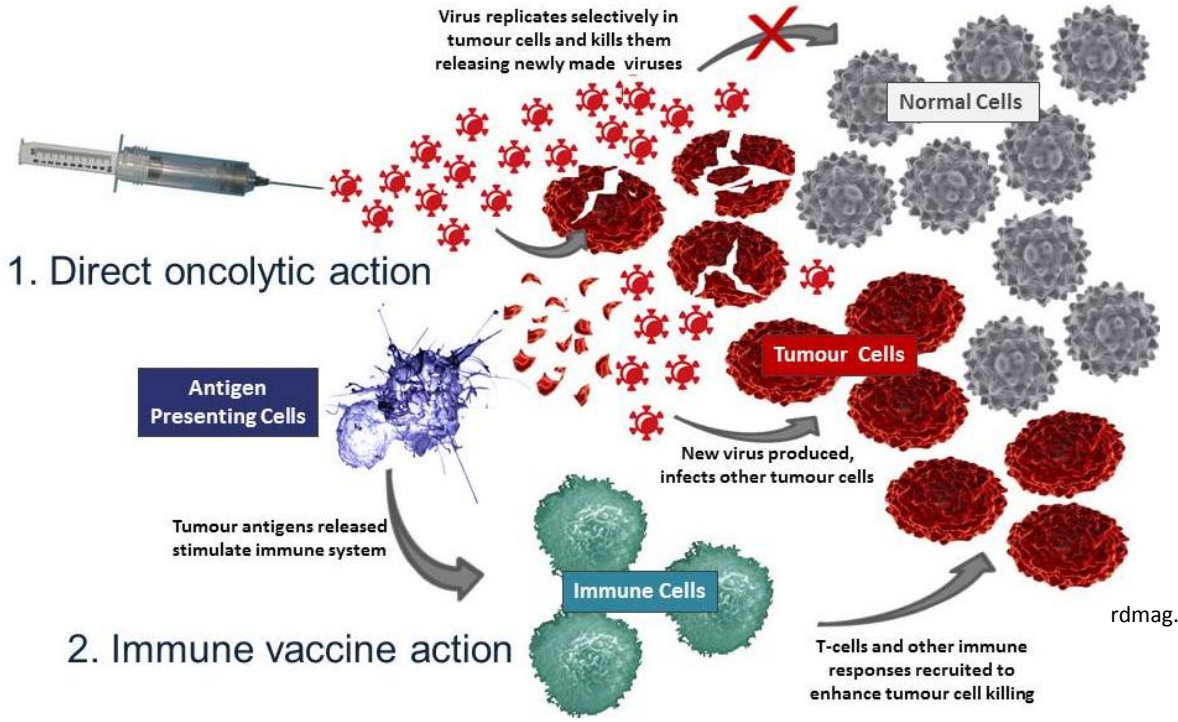
Wolchok, NEJM 2017.

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

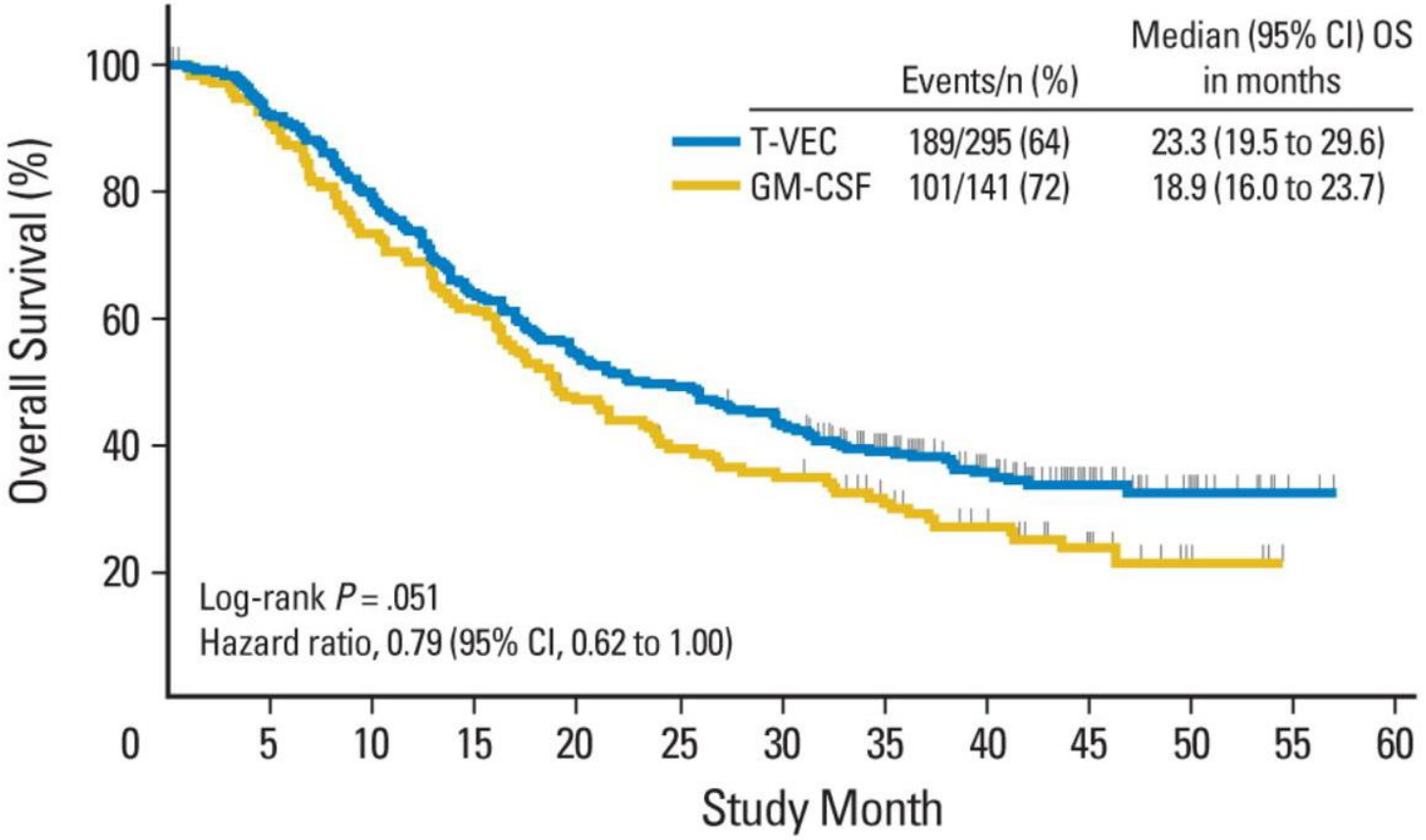


rdmag.com

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



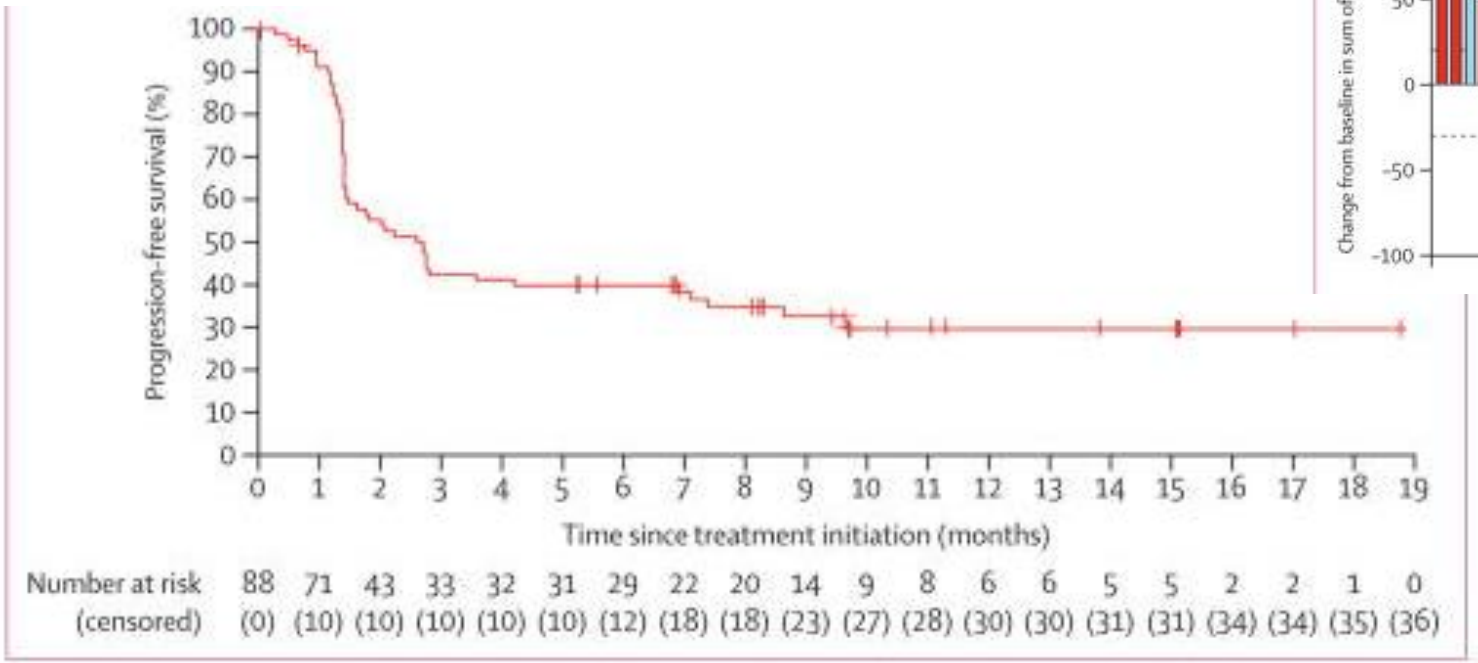
Andtbacka, Kaufman, JCO 2015.

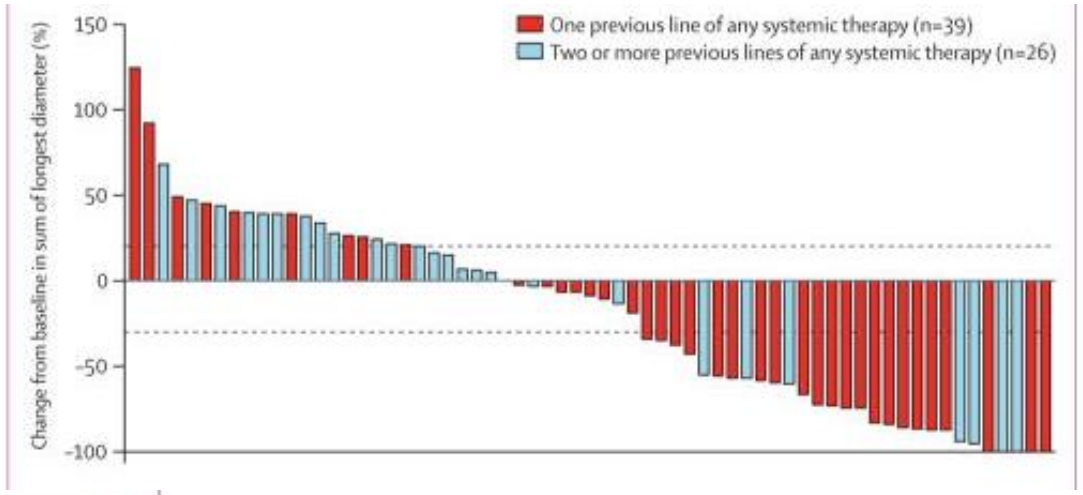
Approved checkpoint inhibitors in other skin cancers

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%

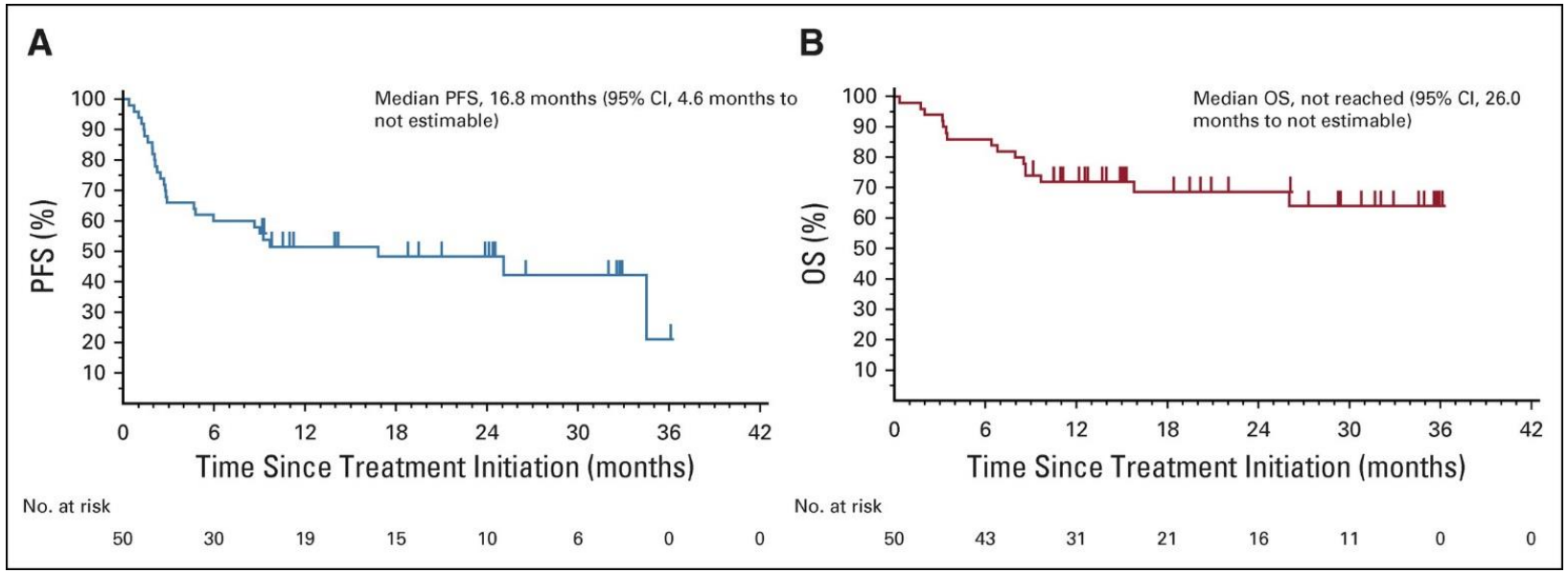




Kaufman, Lancet Oncol 2016.

Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

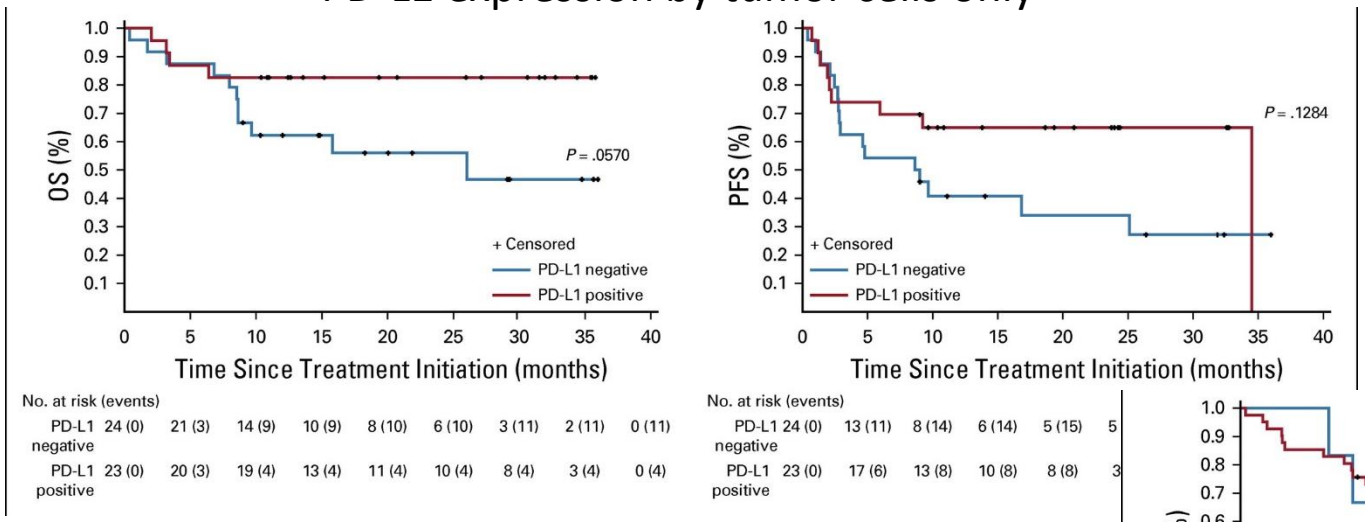
- KEYNOTE-017
- Pembrolizumab 2 mg/kg Q3W up to 2 years
- mPFS: 16.8 months (compared to 90 days for chemo)
- 24-month OS: 68.7%



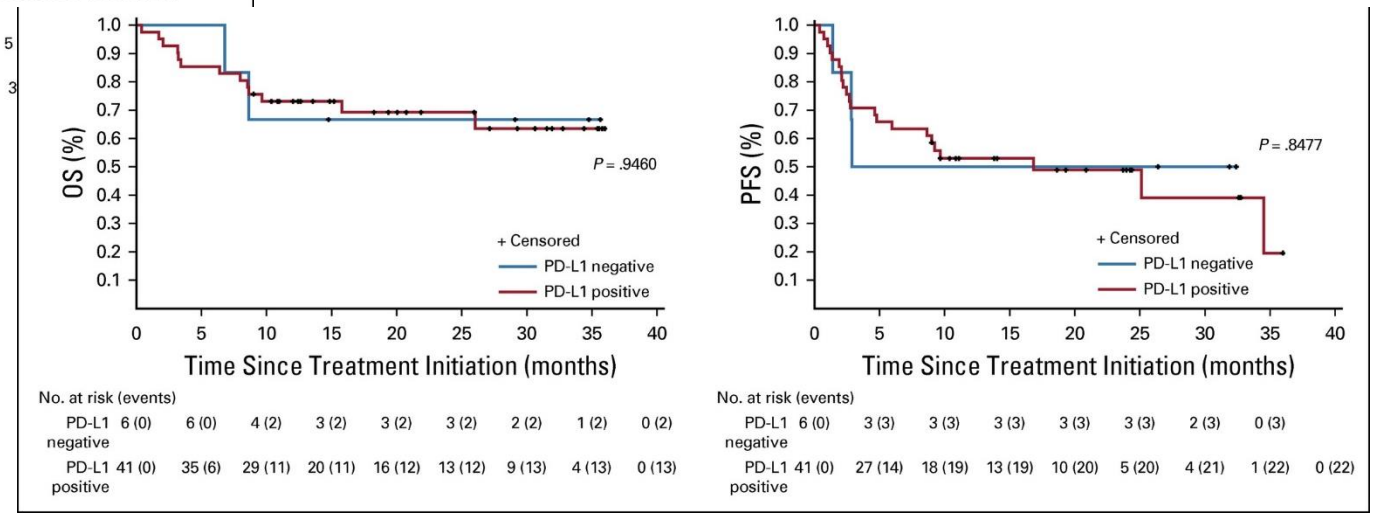
Nghiem, J Clin Oncol 2019.

Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

PD-L1 expression by tumor cells only



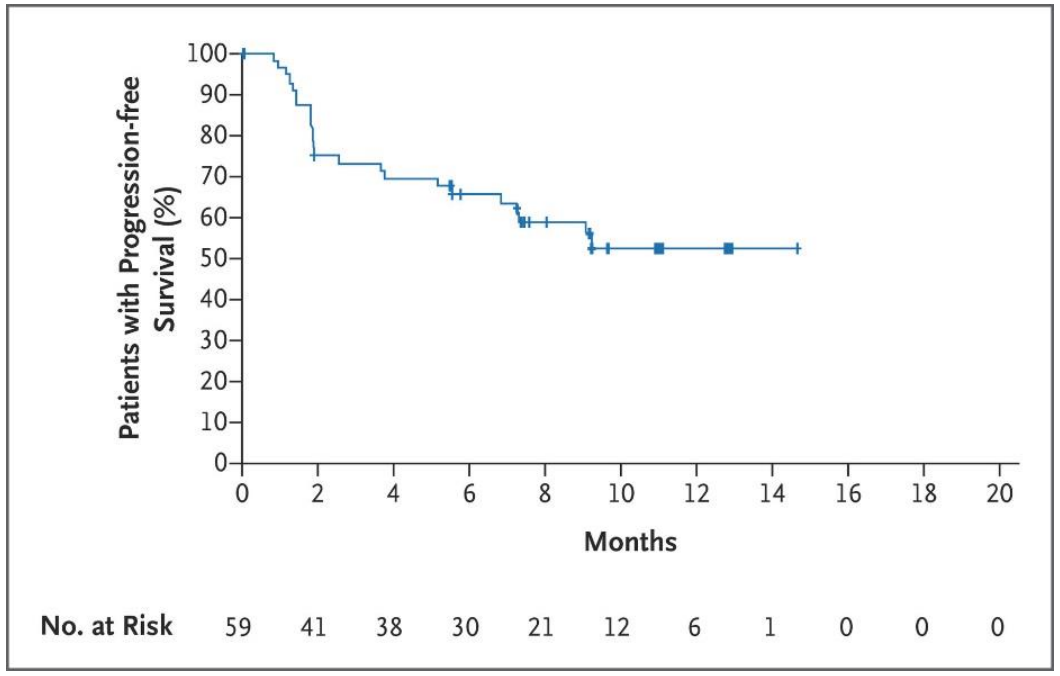
PD-L1 on all cells in tumor

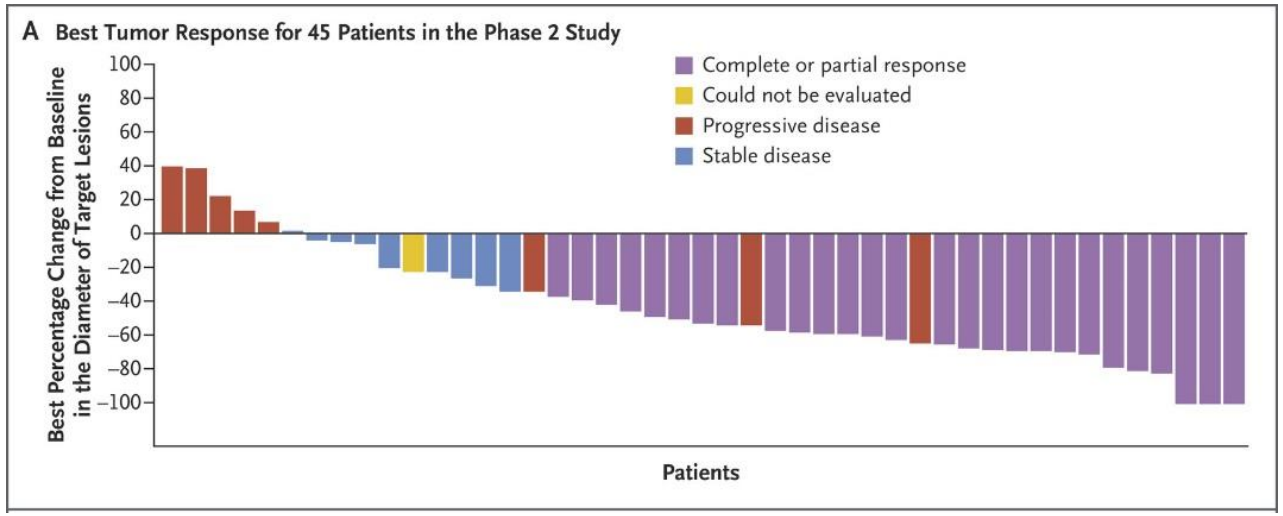


Nghiem, J Clin Oncol 2019.

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

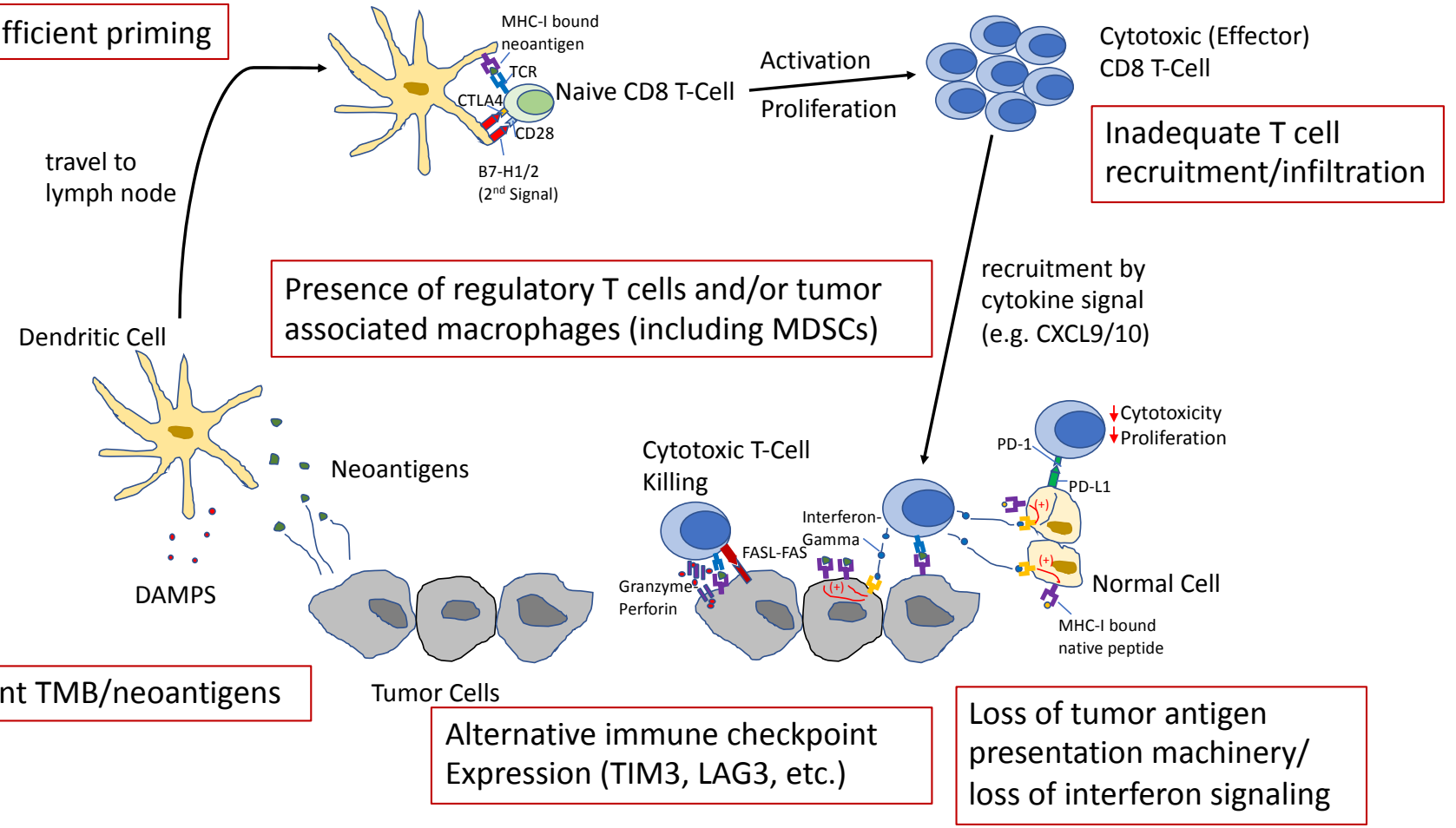




Migden, NEJM 2018.

Developmental Immunotherapeutic Strategies for Melanoma

How does immune checkpoint inhibitor therapy fail?

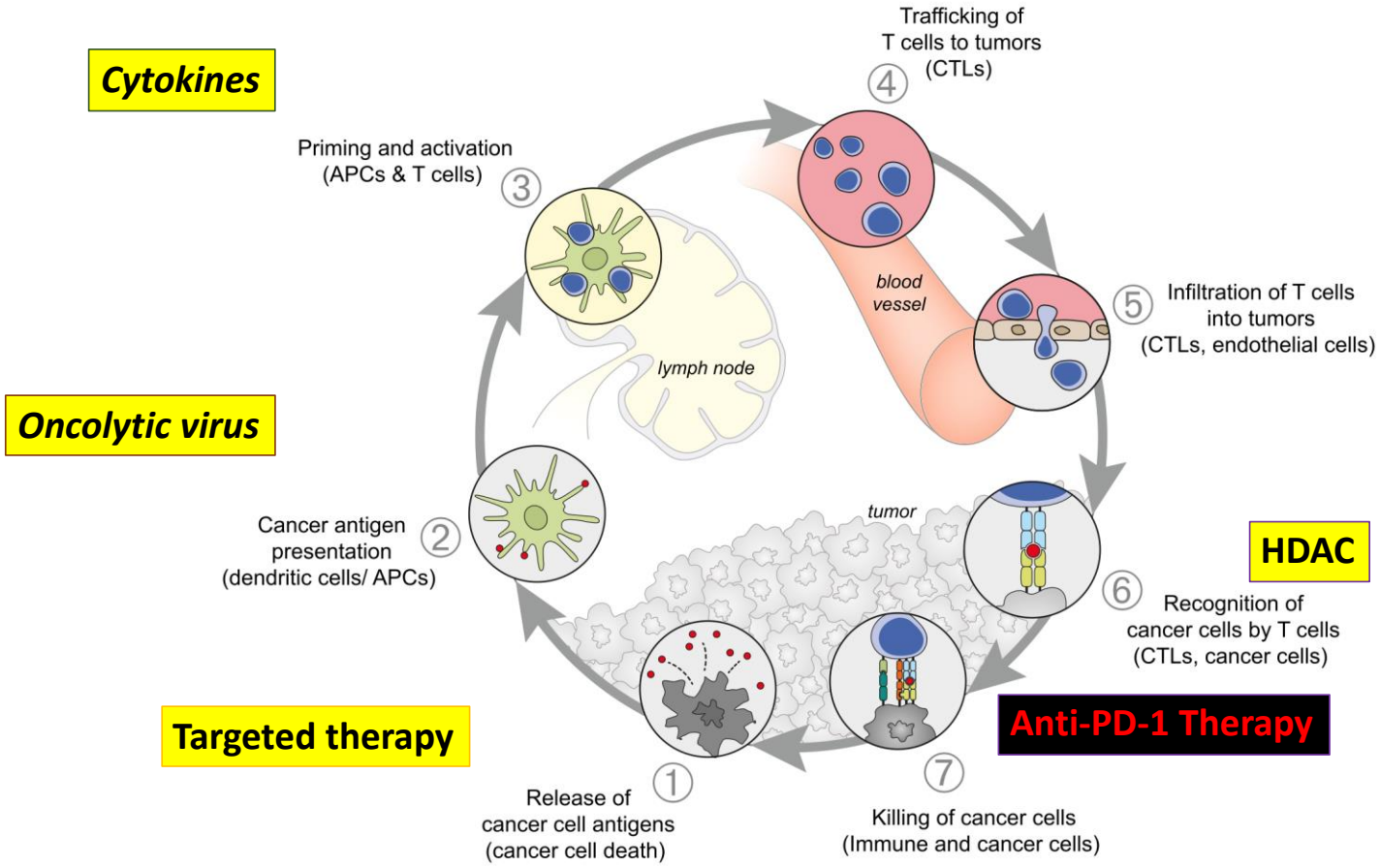


Modified from Liu, Jenkins, Sullivan. Amer J Clin Derm 2018.

Developmental Immunotherapeutic Strategies for Melanoma

How do we overcome resistance?

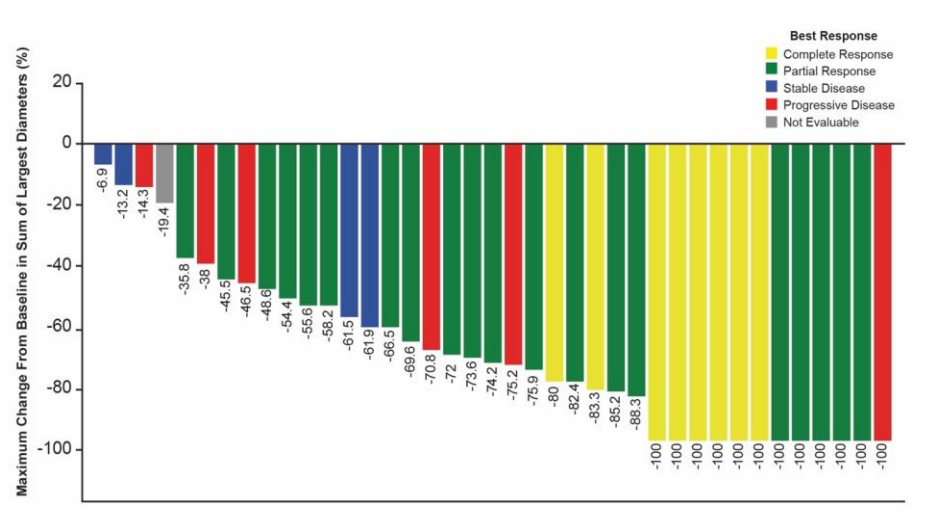
Combination therapy



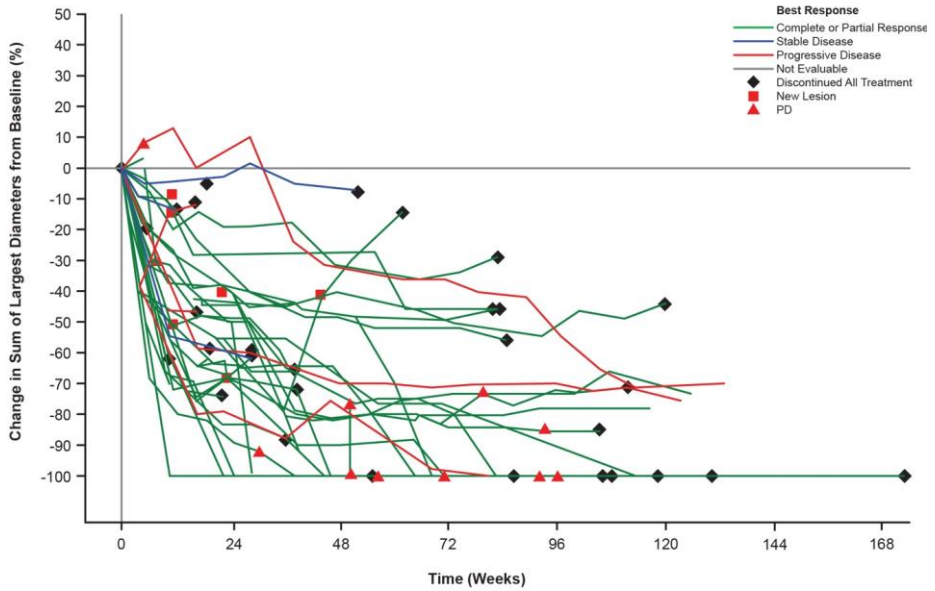
Modified from Chen and Melman. Immunity 2015.

In development: 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

KEYNOTE-022 Part 3 Study Design (NCT02130466)

Patients
- Histologically confirmed unresectable or metastatic stage IV *BRAF*$^{V600E/K}$-mutant melanoma
- No prior therapy
- Measurable disease
- ECOG PS 0/1

Stratification factors[a]
- ECOG PS (0 vs 1)
- LDH level (>1.1 × ULN vs ≤1.1 × ULN)

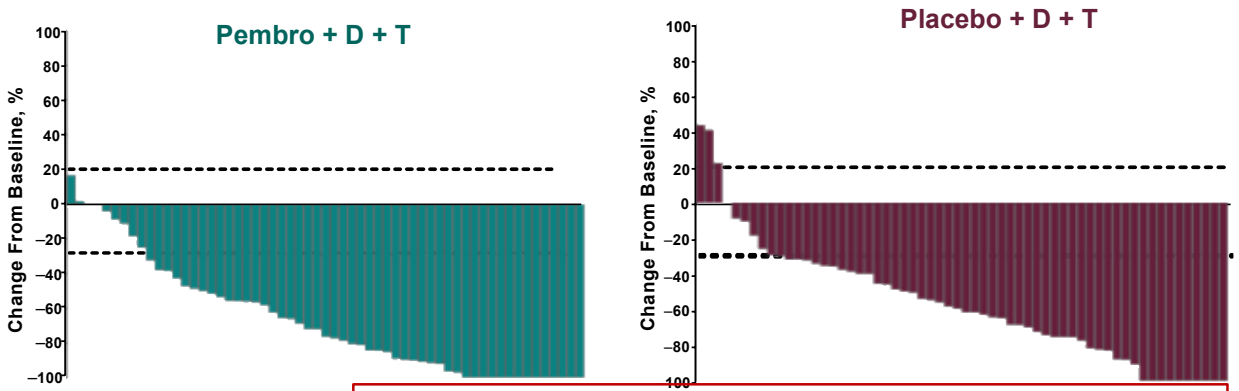
R (1:1)
N = 120

N = 60 → Pembrolizumab 2 mg/kg Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD

N = 60 → Placebo Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD

- Primary end point: PFS
- Secondary end points: ORR, duration of response, and OS
- Data cutoff: Feb 15, 2018

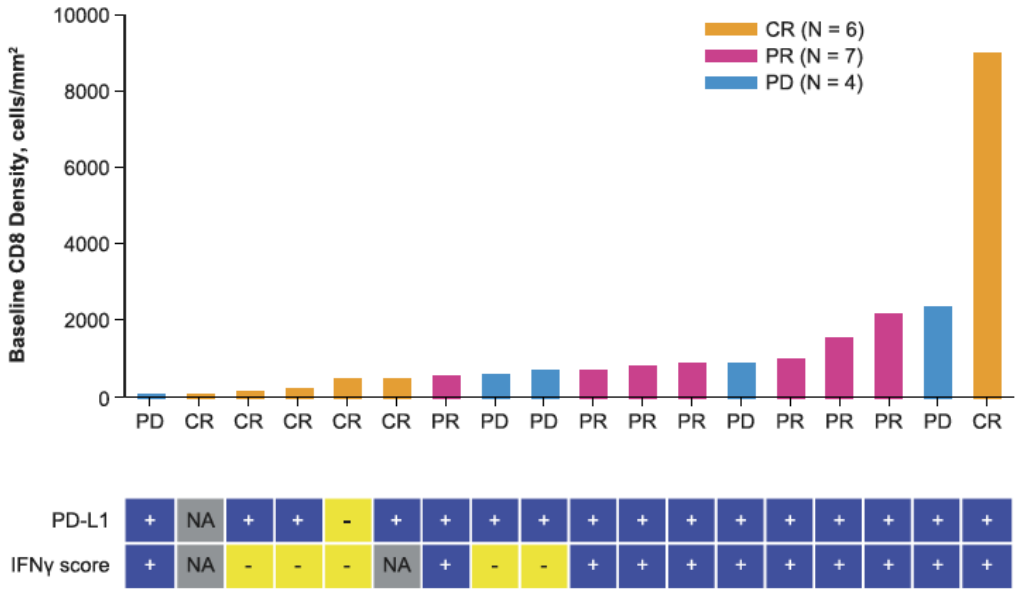
[a]Owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.



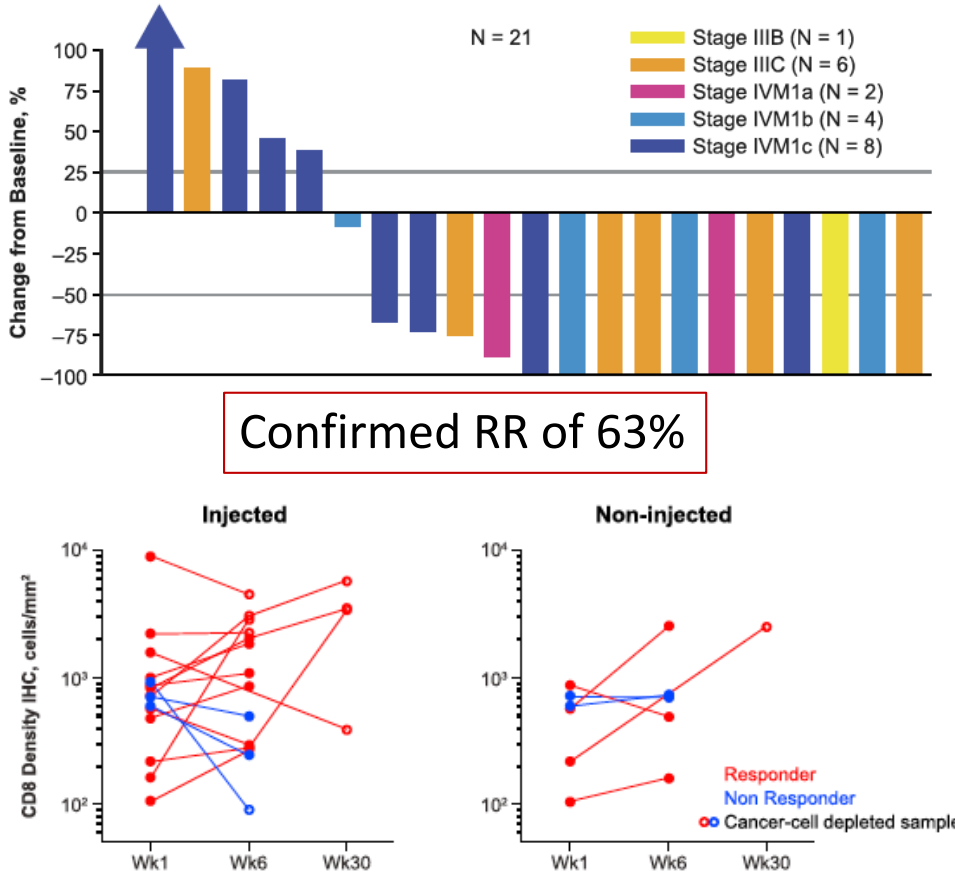
	Pembro + D + T	Placebo + D + T
ORR	63%	72%
CR	18%	13%
≥ 60% red	63%	51%

Ascieto et al, *Nature Med* 2019.

In development: Combined IO with Oncolytic Virus



Phase I: Pembrolizumab + TVEC



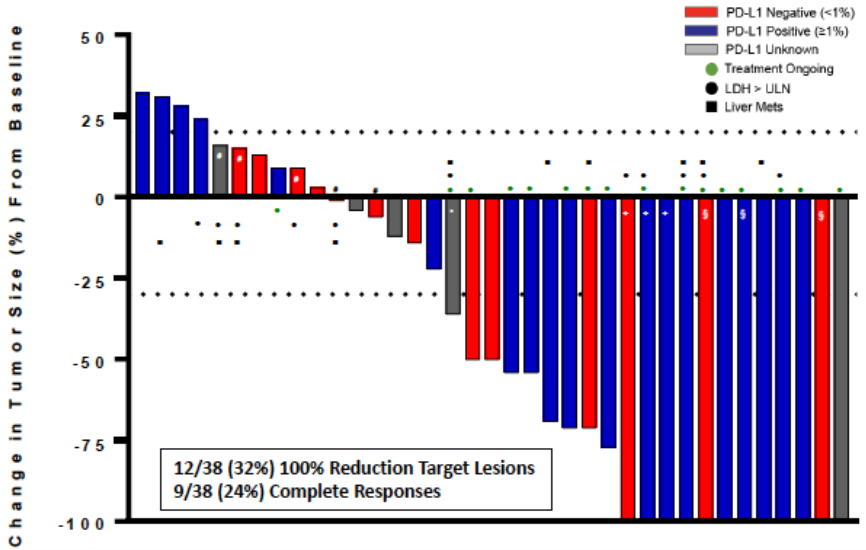
Confirmed RR of 63%

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



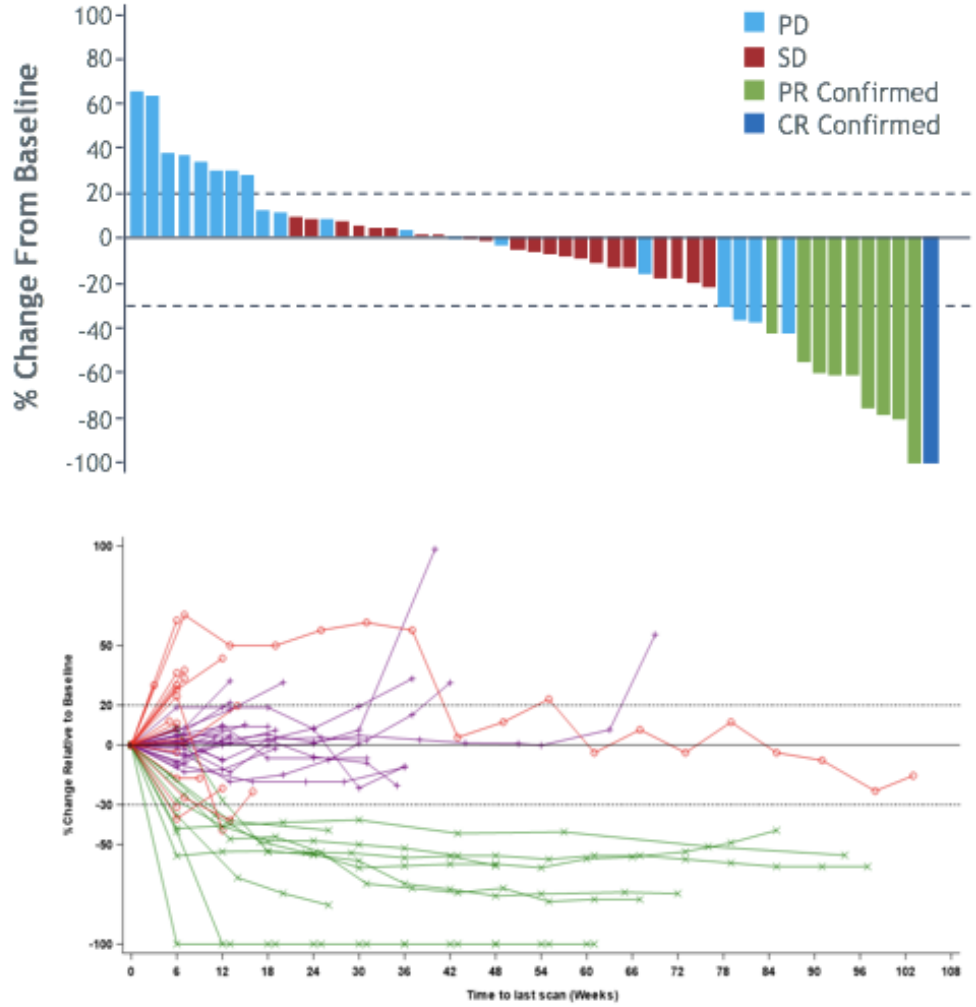
1L Melanoma (n=38 Efficacy Evaluable)	Overall Response Rate
Confirmed ORR (CR+PR)	20 (53%)
CR	9 (24%)
DCR (CR+PR+SD)	29 (76%)
PD-L1 negative (n=14)	6 (43%)
PD-L1 positive (n=19)	13 (68%)
PD-L1 unknown (n=5)	1 (20%)
LDH > ULN (n=11)	5 (45%)
Liver metastases (n=10)	5 (50%)

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

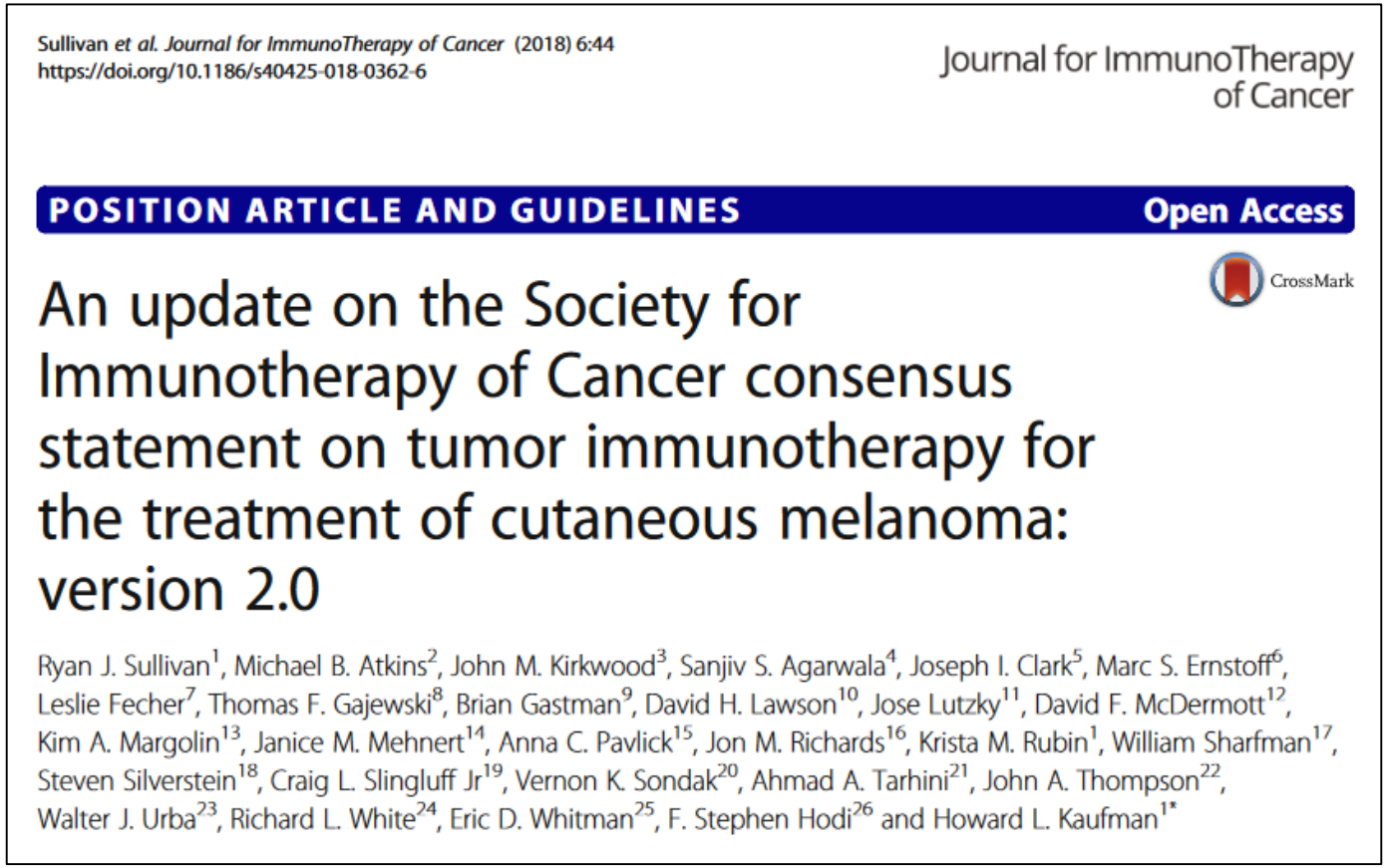


Sullivan et al, AACR 2019.

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
https://doi.org/10.1186/s40425-018-0362-6

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*]

Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

Case Studies

Case Study 1

CASE 1: Treatment decisions

50-year-old male, melanoma of right neck

- ≥ 6.5 mm, ulceration (T4b), mitoses ~ 12/mm^2, no LVI.
- MRI brain: No evidence of metastatic disease
- PET/CT: Right neck lymph node and right axillary tail node/mass FDG avid, cN2b disease (palpable)
- Final workup Stage: IIIC (pT4b, cN2b, cM0)

Question #1

50-year-old male with newly diagnosed stage III melanoma, BRAF unknown.

What is the next best plan of treatment?

A. Complete lymphadenectomy
B. BRAF targeted therapy
C. Observation
D. Immunotherapy
E. Talimogene laherparepvec

Answer #1

50-year-old male with newly diagnosed stage III melanoma, BRAF unknown.

What is the next best plan of treatment?

A. Complete lymphadenectomy: *This patient had macroscopic lymphadenopathy. Standard care includes CLND.*
B. BRAF targeted therapy: *BRAF status is unknown; targeted therapy not indicated*
C. Observation
D. Immunotherapy: *With BRAF status unknown, PD-1 inhibitor is SOC*
E. Talimogene laherparepvec

Recurrence in 2016

- Patient was treated in 2014 and received interferon – discontinued post 3 doses
- PET/CT 2016: widespread metastatic disease
  - Neck
  - Chest
  - Abdomen
  - Pelvis
  - Upper and lower extremities

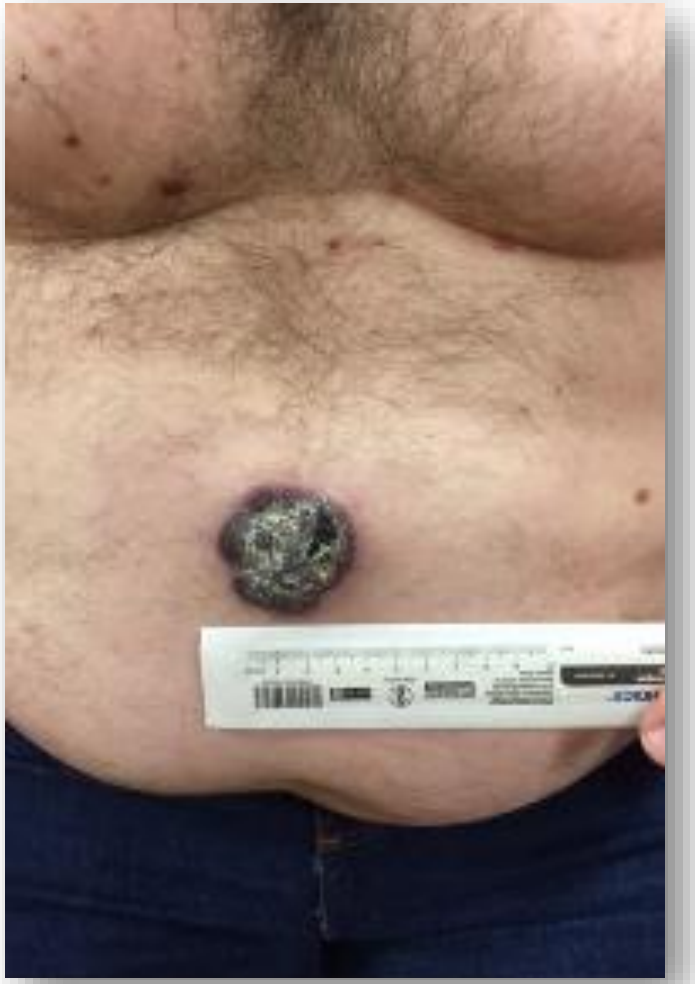


Image © AJ Olszanski

Question #2

What are the current best options for this patient?

50-year-old male with recurrent/metastatic melanoma: BRAF V600E+

A. High-dose IL-2
B. Darcarbazine
C. PD-1 and CTLA4 combination
D. Ipilimumab
E. BRAF/MEK – targeted therapy

Answer #2

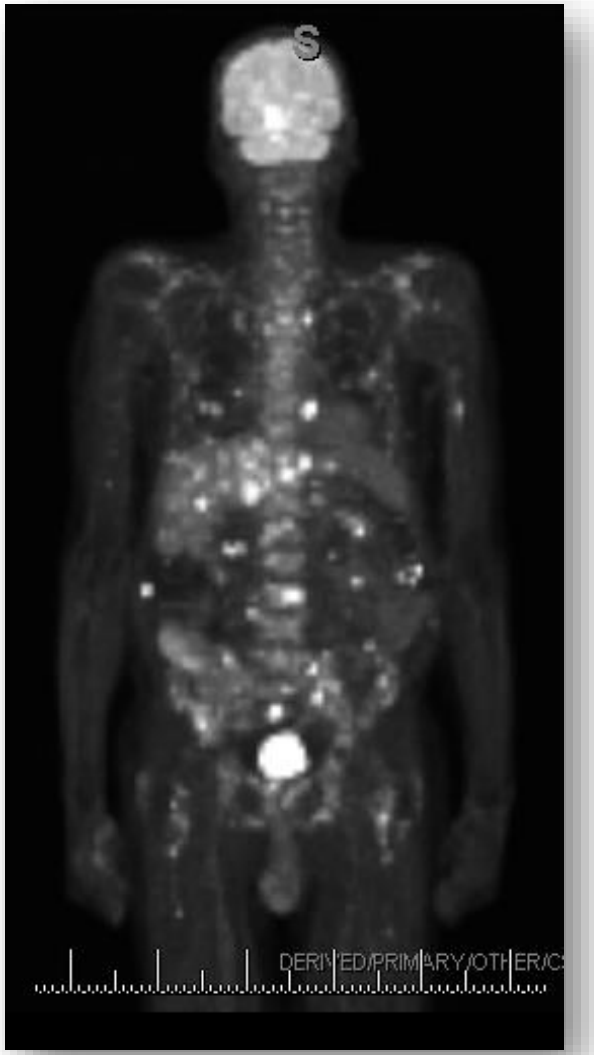
What are the current best options for this patient?

50-year-old male with recurrent/metastatic melanoma: BRAF V600E+

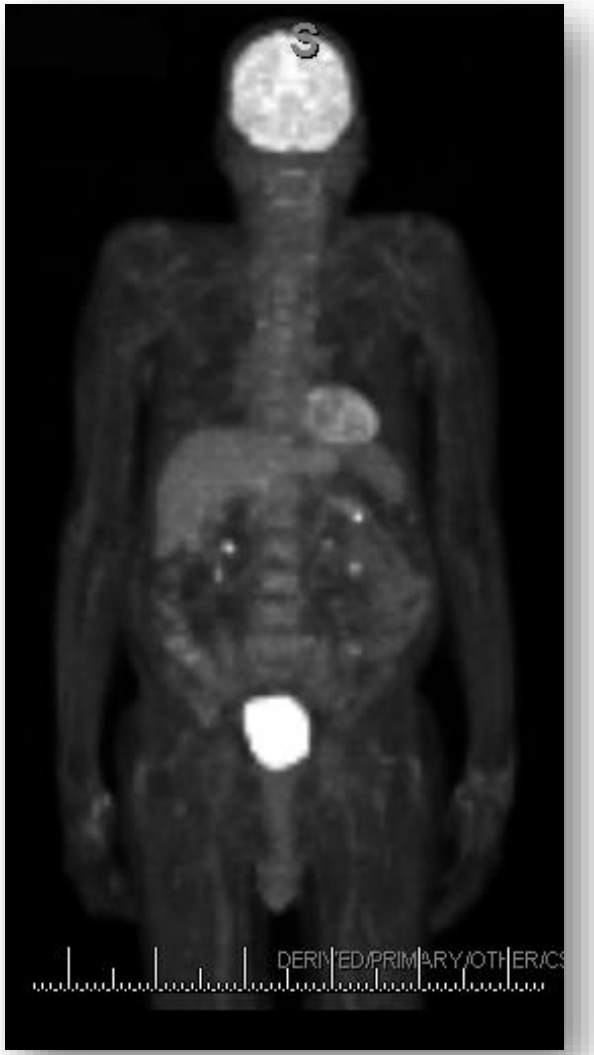
A. High-dose IL-2
B. Darcarbazine
C. PD-1 and CTLA4 combination: *This is a preferred regimen*
D. Ipilimumab
E. BRAF/MEK – targeted therapy: *This is a reasonable option*

Checkpoint Efficacy

Before treatment



After treatment



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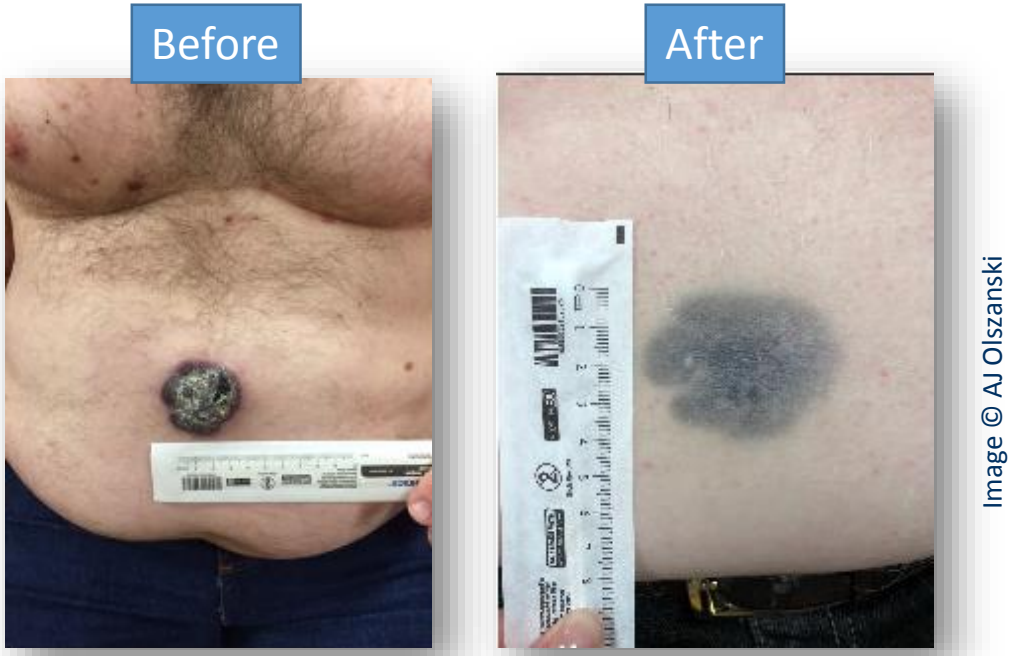
Treatment Decisions

- Underwent surgical resection of subcutaneous nodules
- Wide local excision of the abdominal lesion failed to show any viable tumor
  - (+) heavily pigmented cells
- Apparent complete pathologic response to therapy



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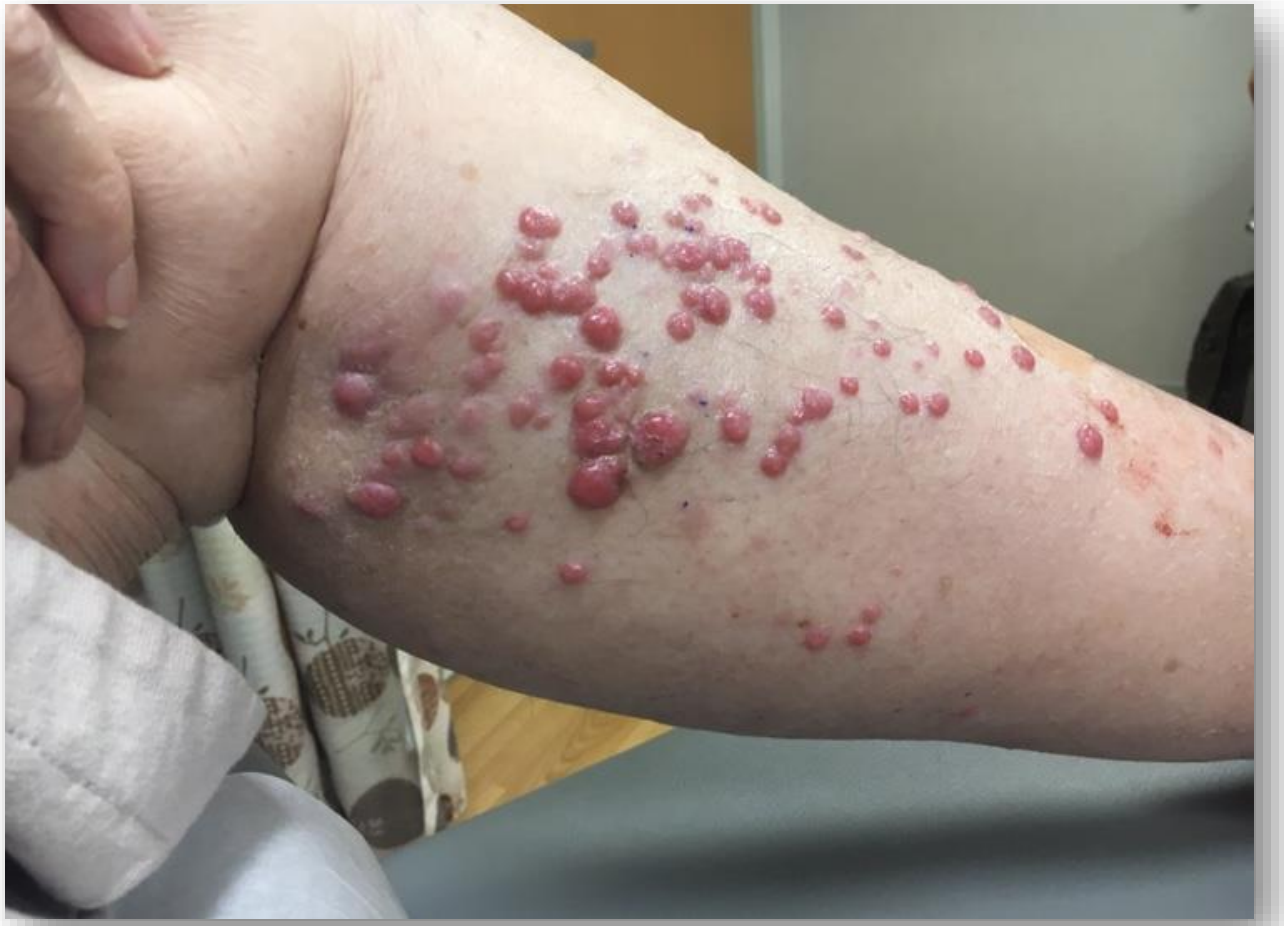
Case Study 2

Case 2: In-transit metastasis

- 76 year-old-female
  - develops “rash” fall 2016
  - unresolved with antibiotics
  - worsens
- 1/2018: biopsy → melanoma
- PET scan
  - no clear primary
    - Left inguinal adenopathy
- History of ulcerative colitis (active)
- BRAF negative



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Question #1

Note: Significant comorbidity of ulcerative colitis
- required immunosuppression
- intermittent diarrhea/abdominal pain

What is most appropriate recommendation?

A. Topical imiquimod
B. PD-1 therapy
C. CTLA-4 therapy
D. Oncolytic vaccine
E. Palliative care

Answer #1

Note: Significant comorbidity of ulcerative colitis
- required immunosuppression
- intermittent diarrhea/abdominal pain

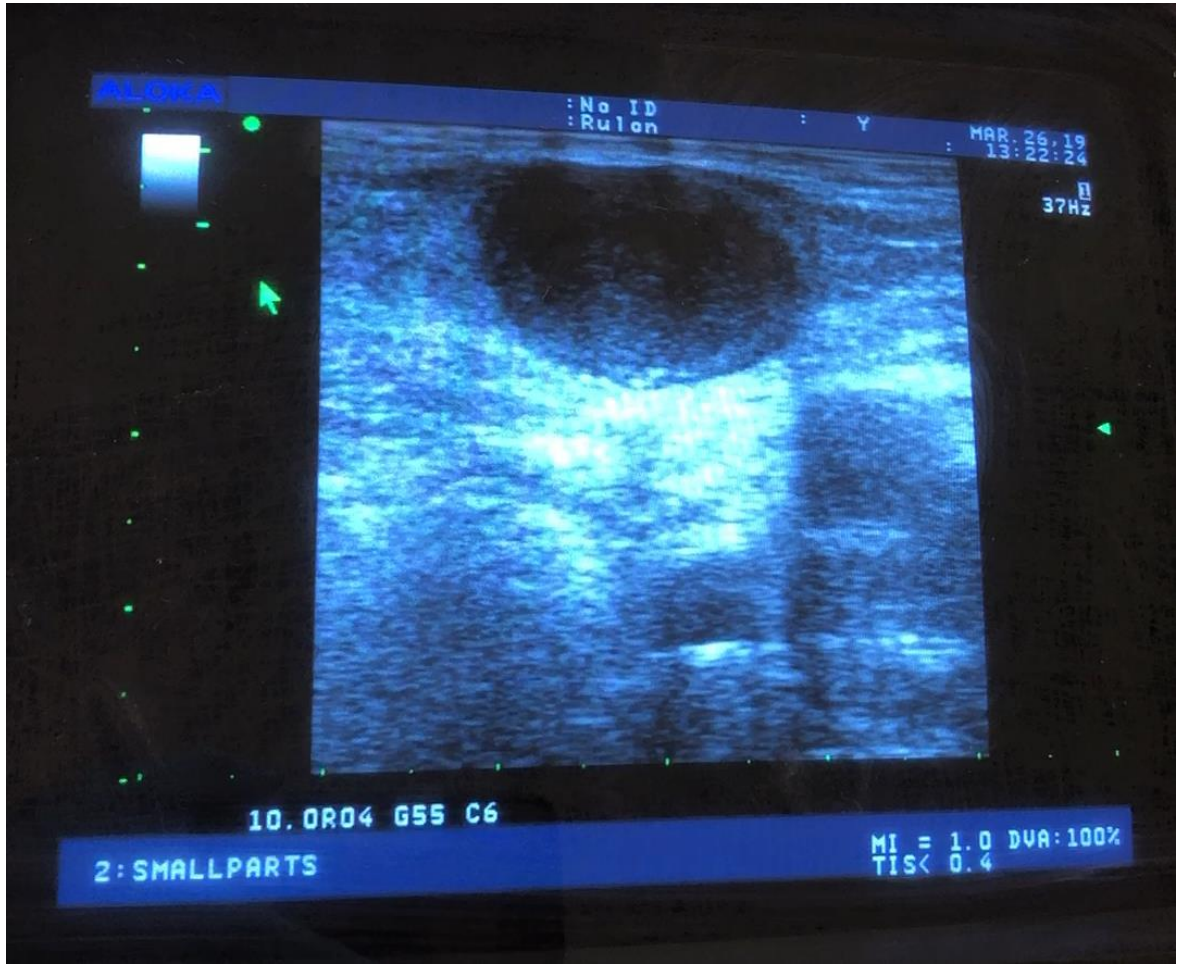
What is most appropriate recommendation?

A. Topical imiquimod
B. PD-1 therapy
C. CTLA-4 therapy — *Relative contraindication*
D. Oncolytic vaccine: *Preferred in this patient who has injectable disease and is on immunosuppression for colitis*
E. Palliative care

Injections

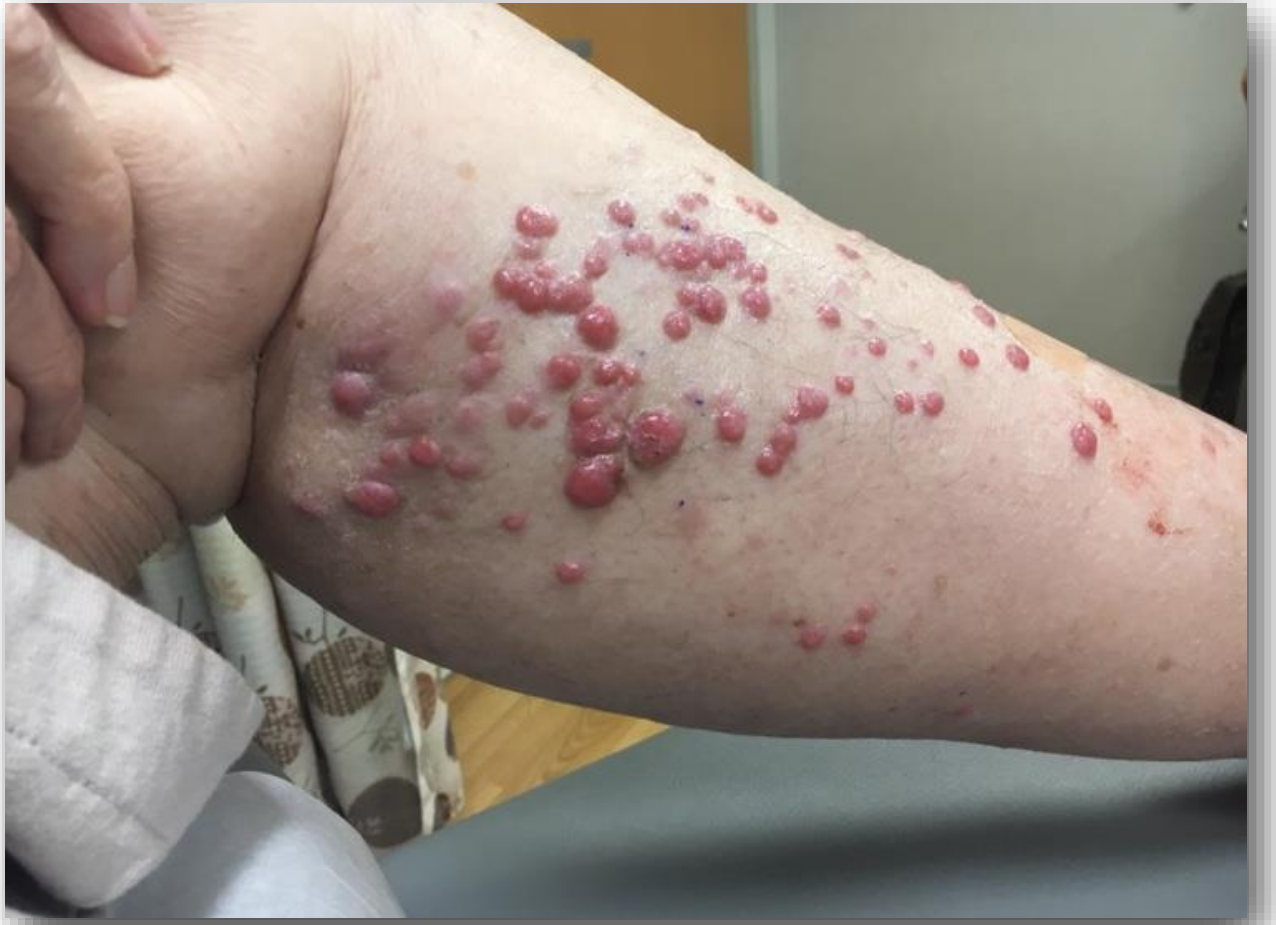
- In-office
- Local anesthetic
- Minimally-invasive
- US guidance with appropriate training
  - Intra-nodal injections
  - Intra-tumor injections
- Raises logistical issues

Video demonstration



Post TVEC

- Initiated TVEC 3/8/2017
- Completed 1/2/2018
  - no remaining injectable disease
- 15 injection sessions
- Groin node (not injected) smaller
- Now 78 years old and ambulating again



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Case Study 3

Patient workup

30 year-old-female, initially Stage IIIC melanoma RUE

- WLE and SLNB: 2.5 mm nodular melanoma with 15 mitoses/mm^2
- Ulcerated
- No LVI.
- 2 of 6 sentinel nodes positive
- pT3b, pN2a

Workup

- MRI brain - normal
- PET/CT – worrisome lesion in right iliac bone
- Biopsy
- NGS sent

→ metastatic melanoma

Pathologic Stage IV disease

- Final TNM stage pT3b, pN2a, pM1c

Question #1

30 year-old-female, stage IV melanoma, BRAF WT

What is the best first line treatment?

A. BRAF/MEK therapy
B. Chemotherapy
C. IL-2 with XRT
D. PD-1 + CTLA-4 combination
E. Resection of metastatic site

Answer #1

30 year-old-female, stage IV melanoma, BRAF WT

What is the best first line treatment?

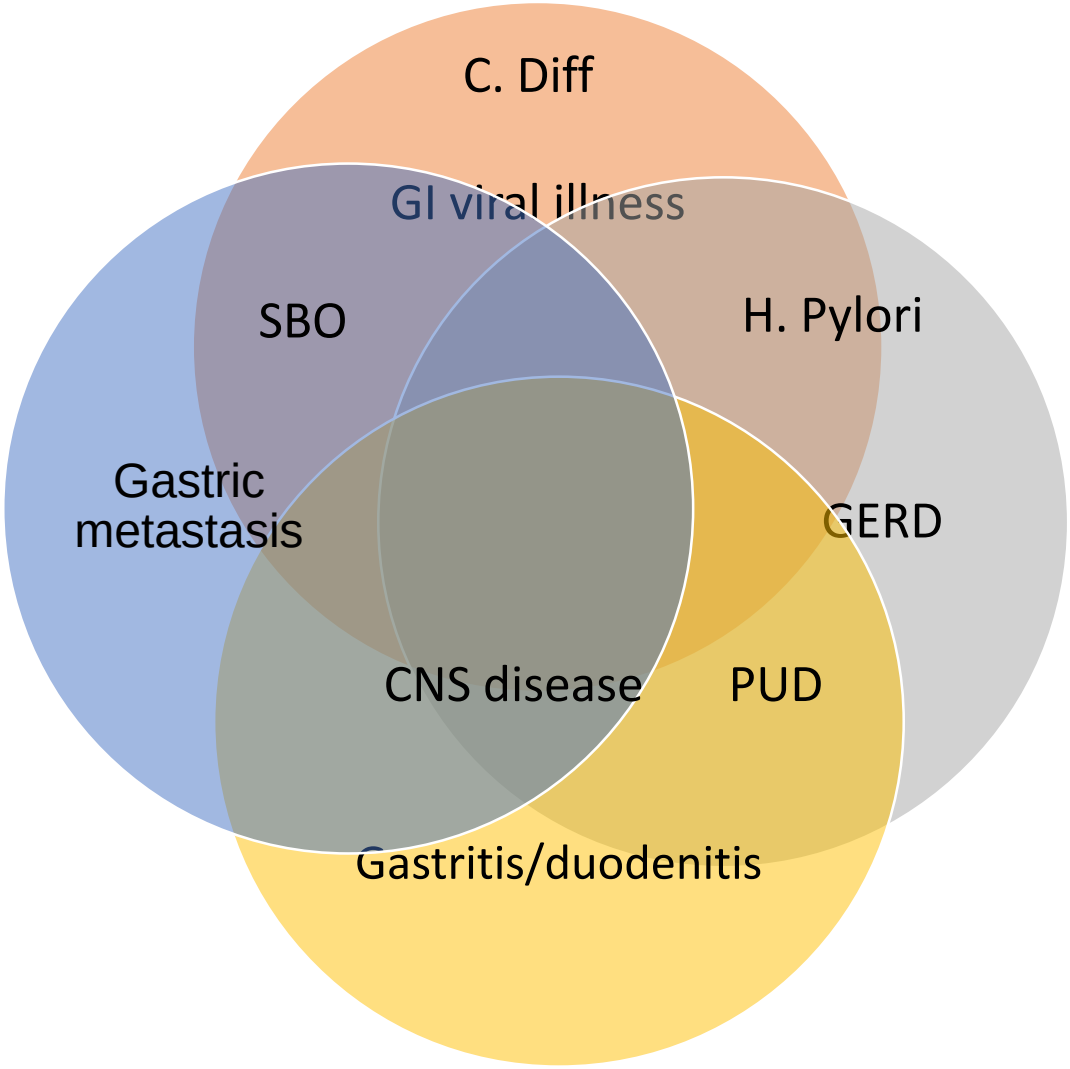
A. BRAF/MEK therapy
B. Chemotherapy
C. IL-2 with XRT
D. PD-1 + CTLA-4 combination: *This is standard of care*
E. Resection of metastatic site

Toxicity Management

Status post 3 doses of dual agent immunotherapy -- developed side effects including

- Nausea, vomiting
- GERD symptoms
- Weight loss
- Early satiety
- Anorexia

Differential diagnosis? Treatment and work-up?



Ondasetron, prochlorpherazine, omeprazole:

No improvement

Consult with GI team:

- Recommend EGD

Results of EGD

Stomach:	• Severe active gastritis • consistent with immune checkpoint inhibitor therapy effect
Duodenum:	• Erosive duodenitis • consistent with immune checkpoint inhibitor therapy effect

Question #2

What treatment(s) for immune-mediated gastritis would be appropriate?

A. Proton-pump inhibitor
B. H. Pylori prophylaxis
C. Oral steroids 0.5 mg/kg
D. High dose IV steroids 1-2 mg/kg
E. Dose reduction of immunotherapy

Answer #2

What treatment(s) for immune-mediated gastritis would be appropriate?

A. Proton-pump inhibitor: *This should be added but is not a primary treatment*
B. H. Pylori prophylaxis
C. Oral steroids 0.5 mg/kg
D. High dose IV steroids 1-2 mg/kg: *This is most appropriate*
E. Dose reduction of immunotherapy

Treatment course

Completed 4 doses of ipi/nivo combo, initiated single agent nivolumab

Developed severe arthralgias and myalgias after 1 dose

Second hospital admission for IV steroids

- symptoms again resolved with a 1 month taper of steroids

Treatment course

Re-initiated single agent nivolumab

- received 2 additional doses

New Symptoms

- significant fatigue
- new headaches
- mild nausea
- general malaise

Question #3

What is the most likely diagnosis?

A. Recurrent gastritis/duodenitis
B. Hypophysitis
C. CNS metastasis
D. Viral illness
E. Hyperthyroidism

Answer #3

What is the most likely diagnosis?

A. Recurrent gastritis/duodenitis: *Possible given history, but symptoms are different*
B. Hypophysitis: *Based on the myriad of symptoms, this is the most likely diagnosis*
C. CNS metastasis: *CNS disease should be ruled out*
D. Viral illness: *Possible but other more serious etiologies should have first consideration*
E. Hyperthyroidism: *Not likely based on symptoms*

Question #4

Which diagnostic test should be ordered?

A. Prolactin
B. Cortisol and ACTH
C. TSH
D. FSH/LH levels
E. Human gonadotropin

Answer #4

Which diagnostic test should be ordered?

A. Prolactin

B. Cortisol and ACTH:

C. TSH

D. FSH/LH levels

E. Human gonadotropin

Diagnostic test results

- Random cortisol (12:10 PM) = 0.5 (3-16)
- 9 AM cortisol < 0.4 (5-23)
- ACTH < 5 (6-50)

Immune-mediated side effects

Immune-related AEs

- Occurs across a wide range of organ systems
- HCPs must remain vigilant and have heightened sensitivity

Hypophysitis

- Required 3rd hospital admission for IV steroids
- Now requires lifelong steroid repletion for hypophysitis/adrenal insufficiency