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

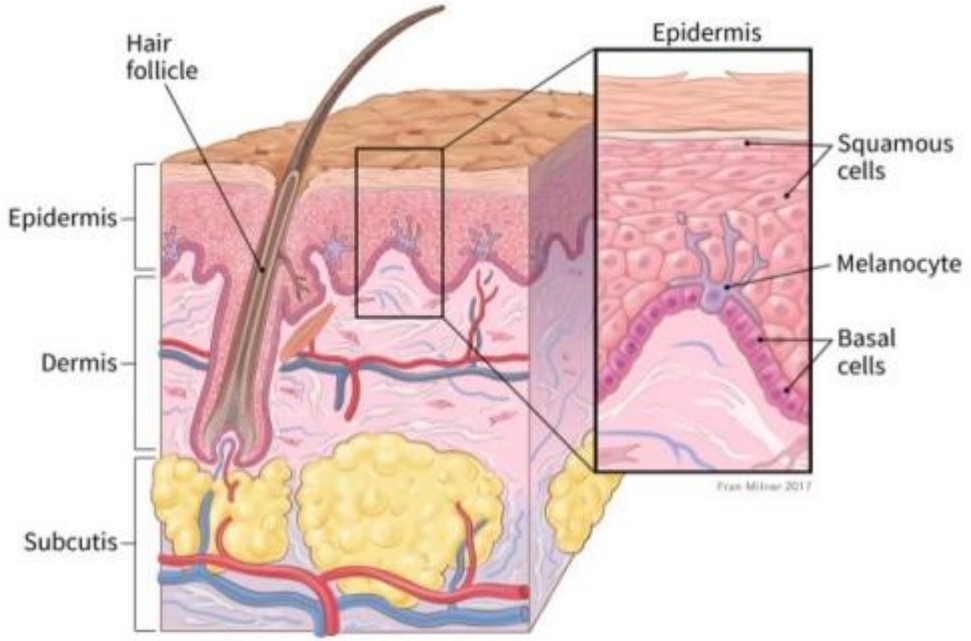
Society for Immunotherapy of Cancer

Disclosures

- Speaker and Advisory Board participant for Regeneron and Sanofi.
- 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

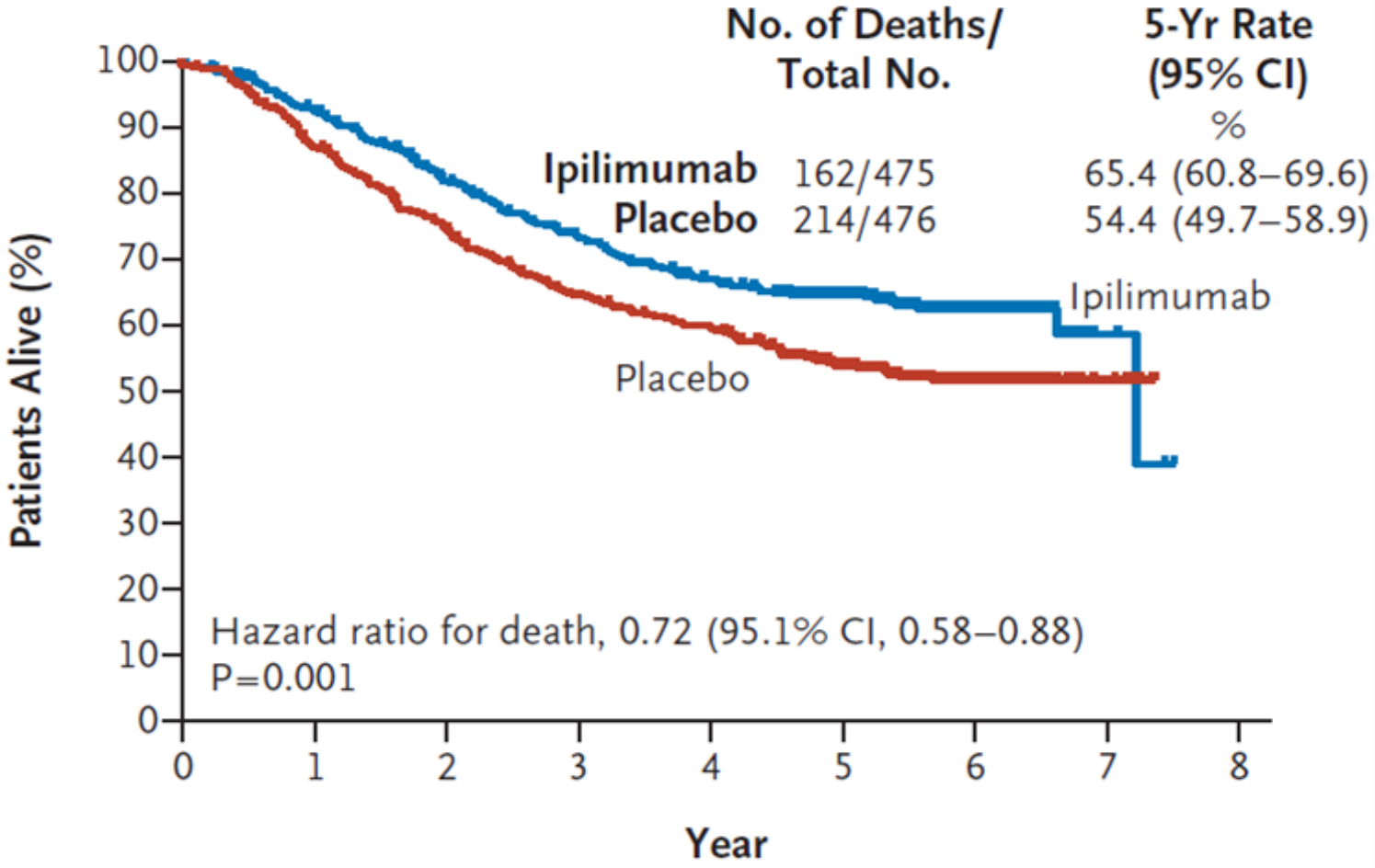
Drug	Indication	Dose
High-dose interferon alfa-2b	Adjuvant – high risk for systemic recurrence	Induction: 20m IU/m^2 IV 5x/wk for 4 wks Maintenance: 10m IU/m^2 s.c. 3x/wk for 48 wks
Interleukin-2 (Aldesleukin)	Stage IV	600k IU/kg/dose Q8hr, up to 14 doses; 9 days of rest; can repeat up to 28 doses per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



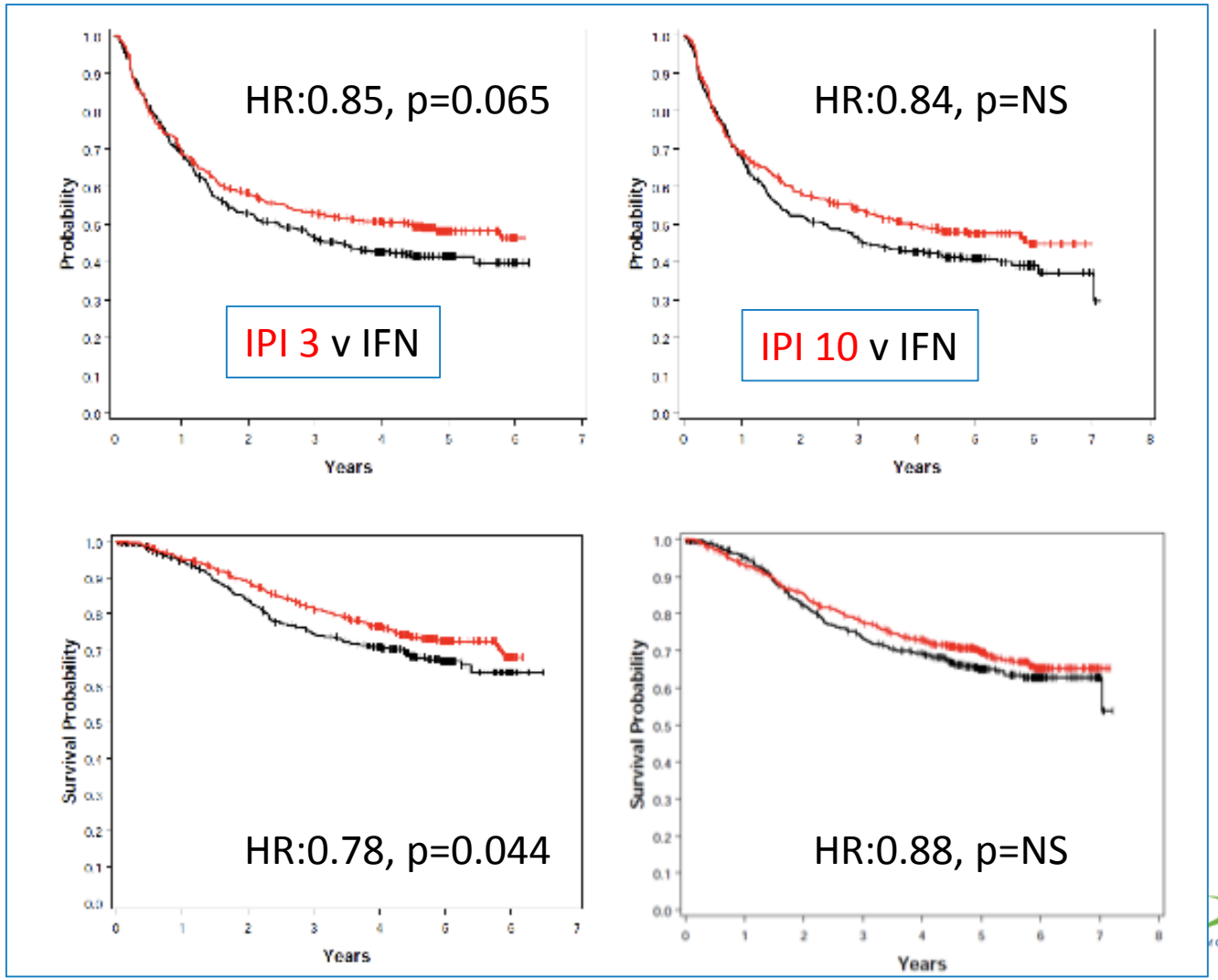
Eggermont, NEJM 2016.

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

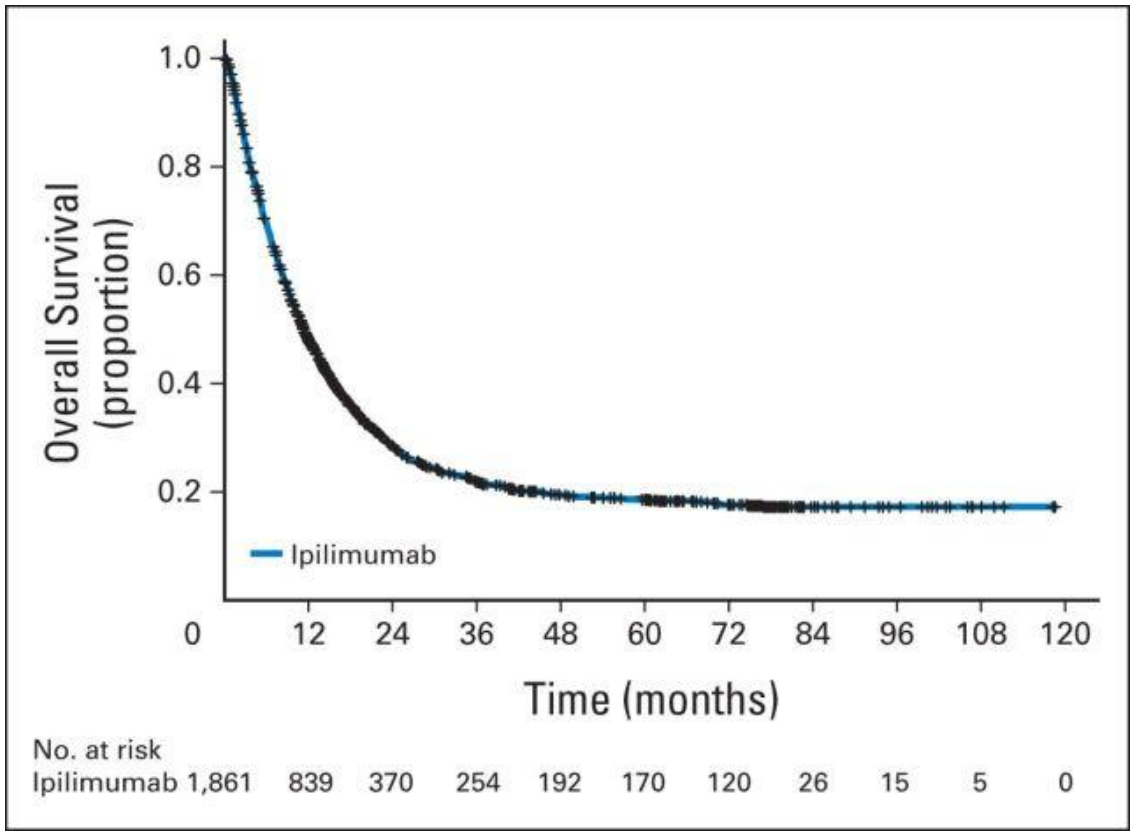
OS



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)



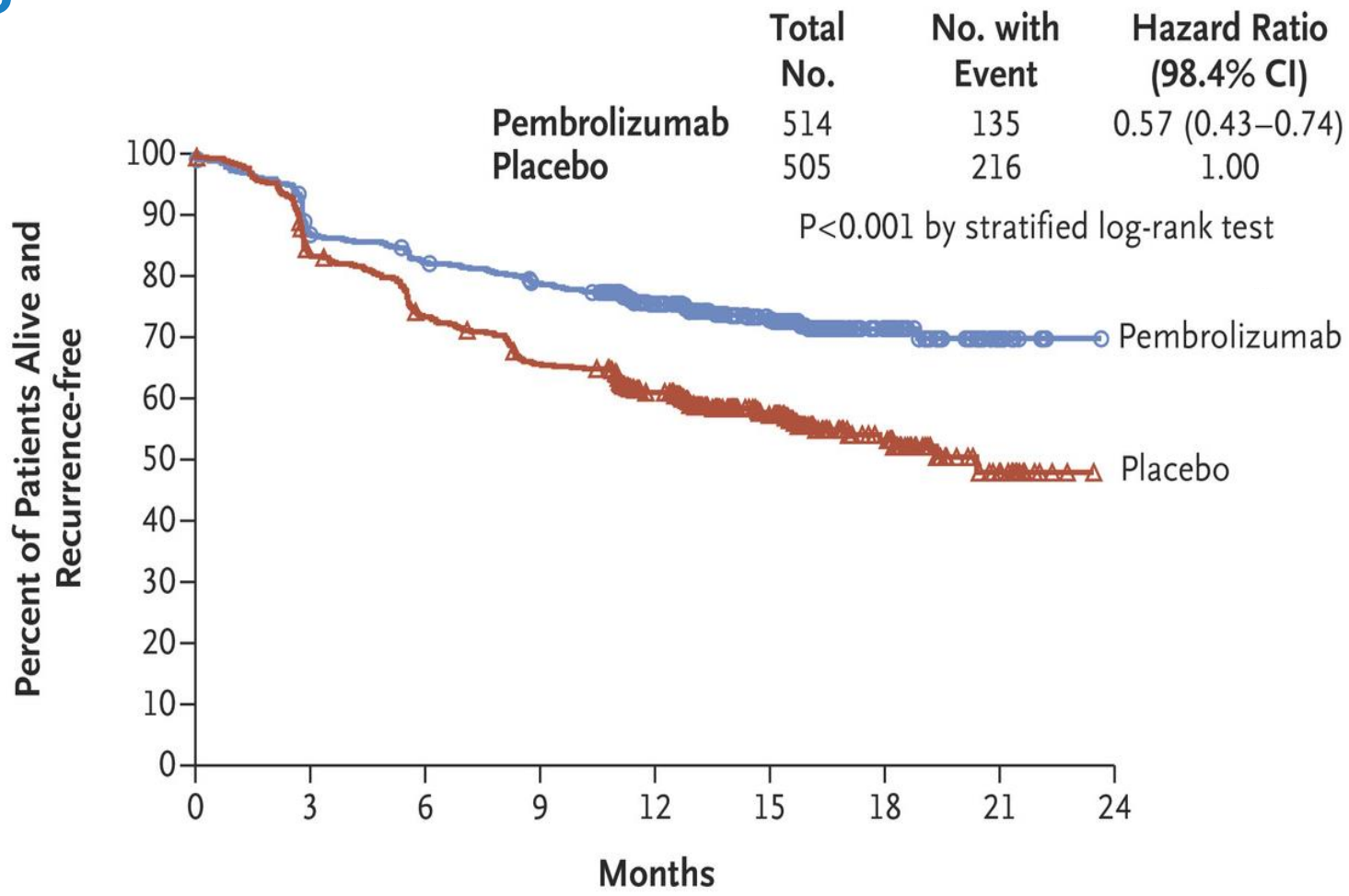
Schadendorf, JCO 2015.

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

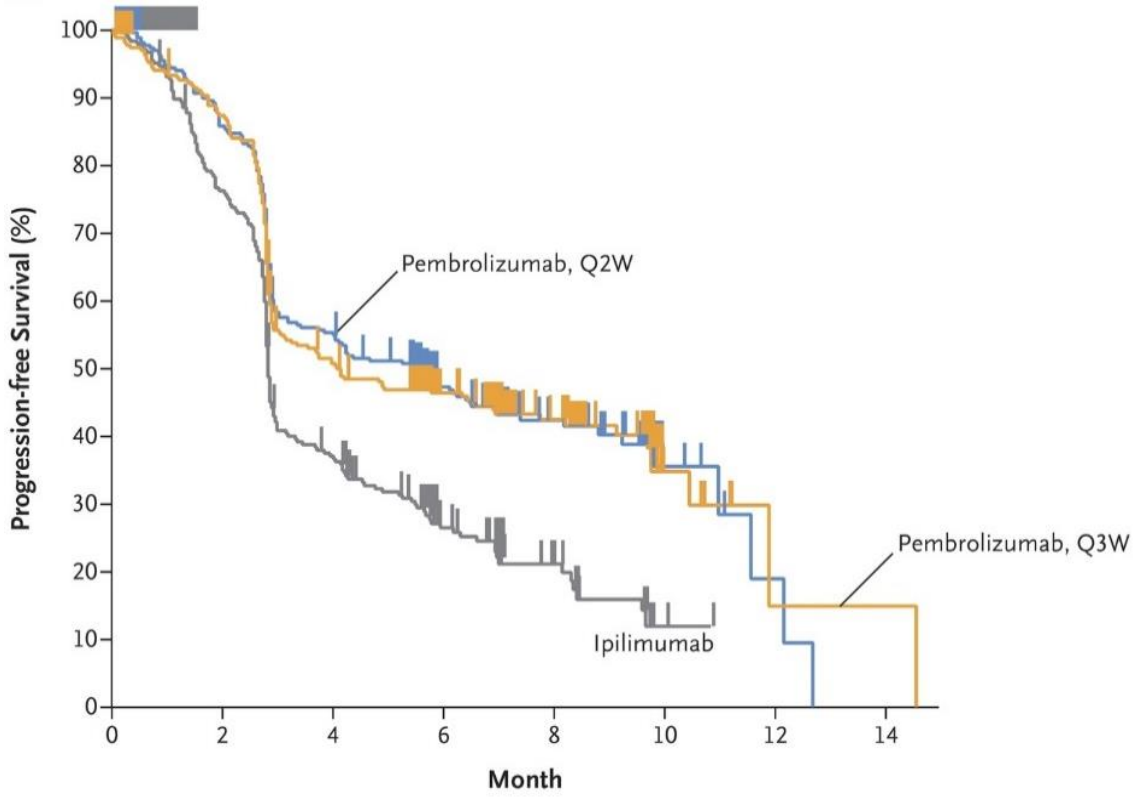
- EORTC 1325/KEYNOTE-054 phase III trial
  - NCT02362594
  - Adjuvant pembrolizumab vs placebo
  - Pembrolizumab 200mg Q3W for up to 1 year (~18 total doses)

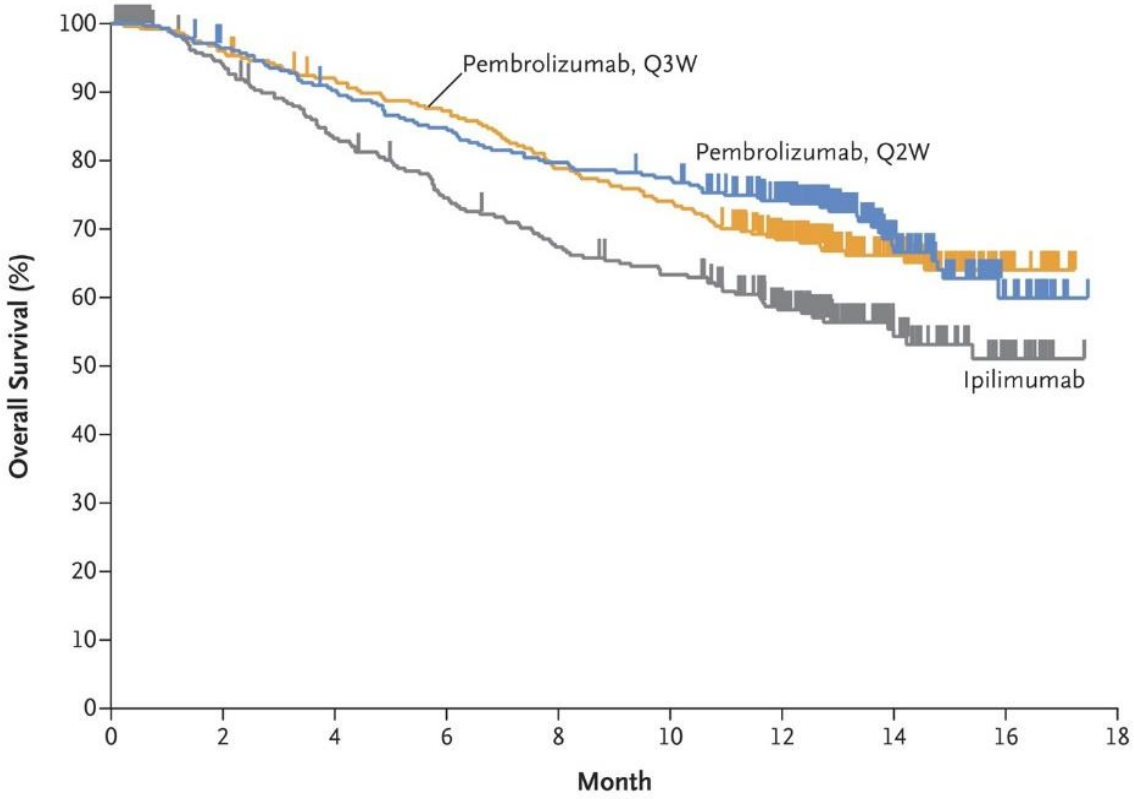


Eggermont, NEJM 2018.

Pembrolizumab in Stage III/IV Melanoma

Phase III KEYNOTE-006 Trial





Robert, NEJM 2015.

Approved checkpoint inhibitors in melanoma

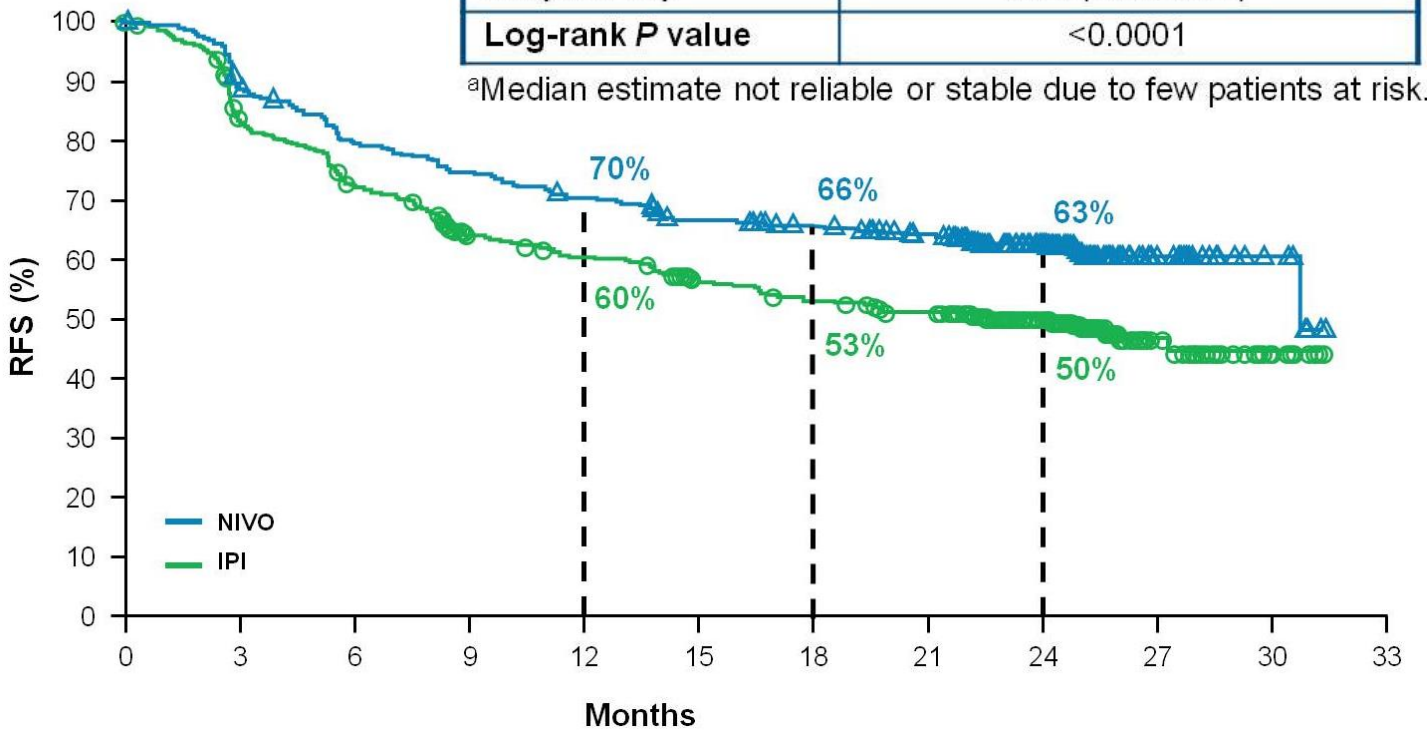
Drug	Approved	Indication	Dose
Nivolumab	2014	Unresectable/metastatic melanoma with progression after other therapy	240 mg Q2W or 480 mg Q4W*
	2017	Adjuvant treatment of melanoma after complete resection	240 mg Q2W or 480 mg Q4W
*Original approval was 3 mg/kg Q2W, updated to flat dosing regimen			

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.



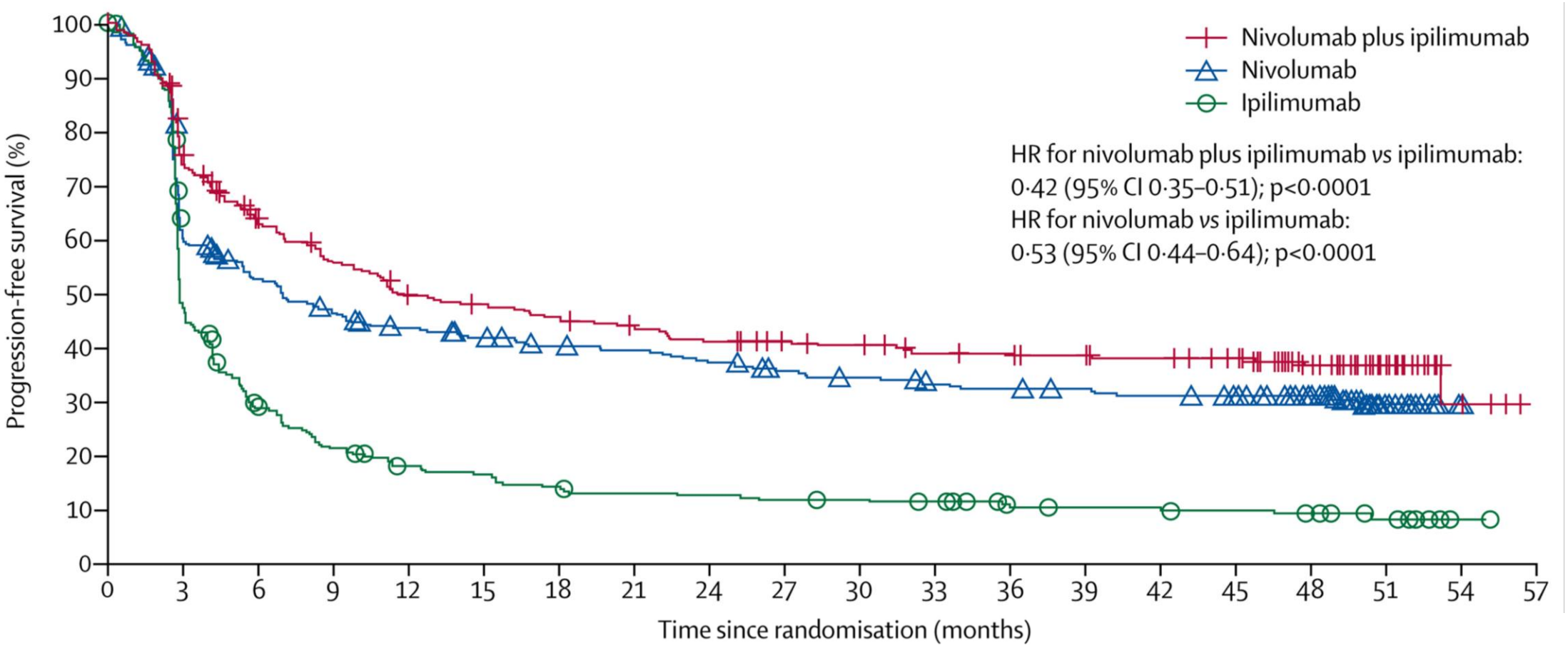
Miller, ASCO 2018.

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

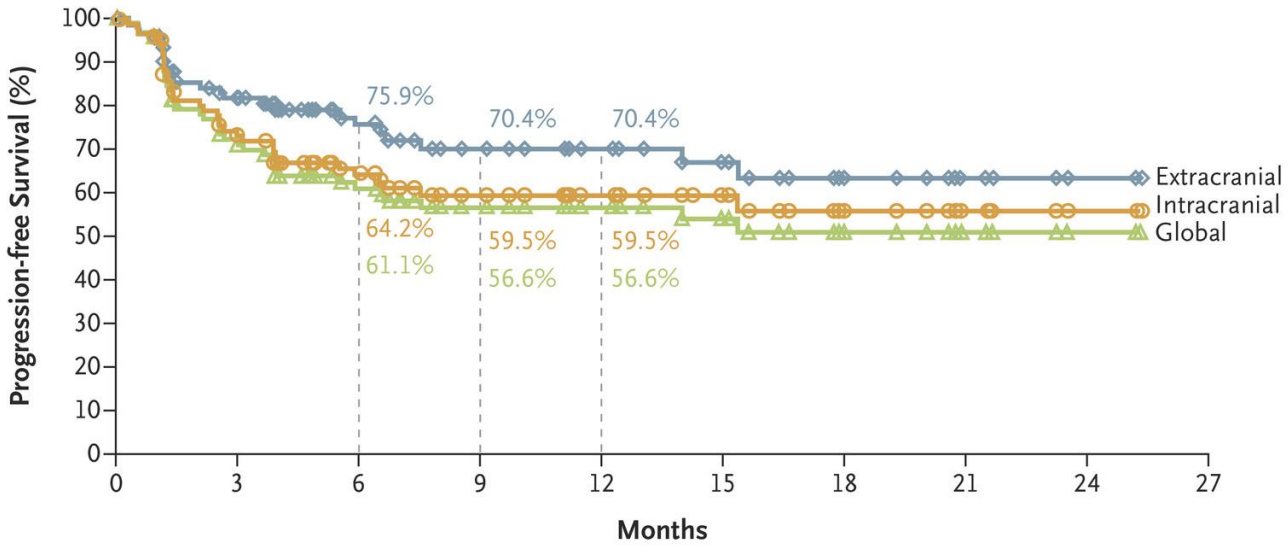
Phase III CheckMate 067 Trial



Hodi, Lancet Oncol 2018.

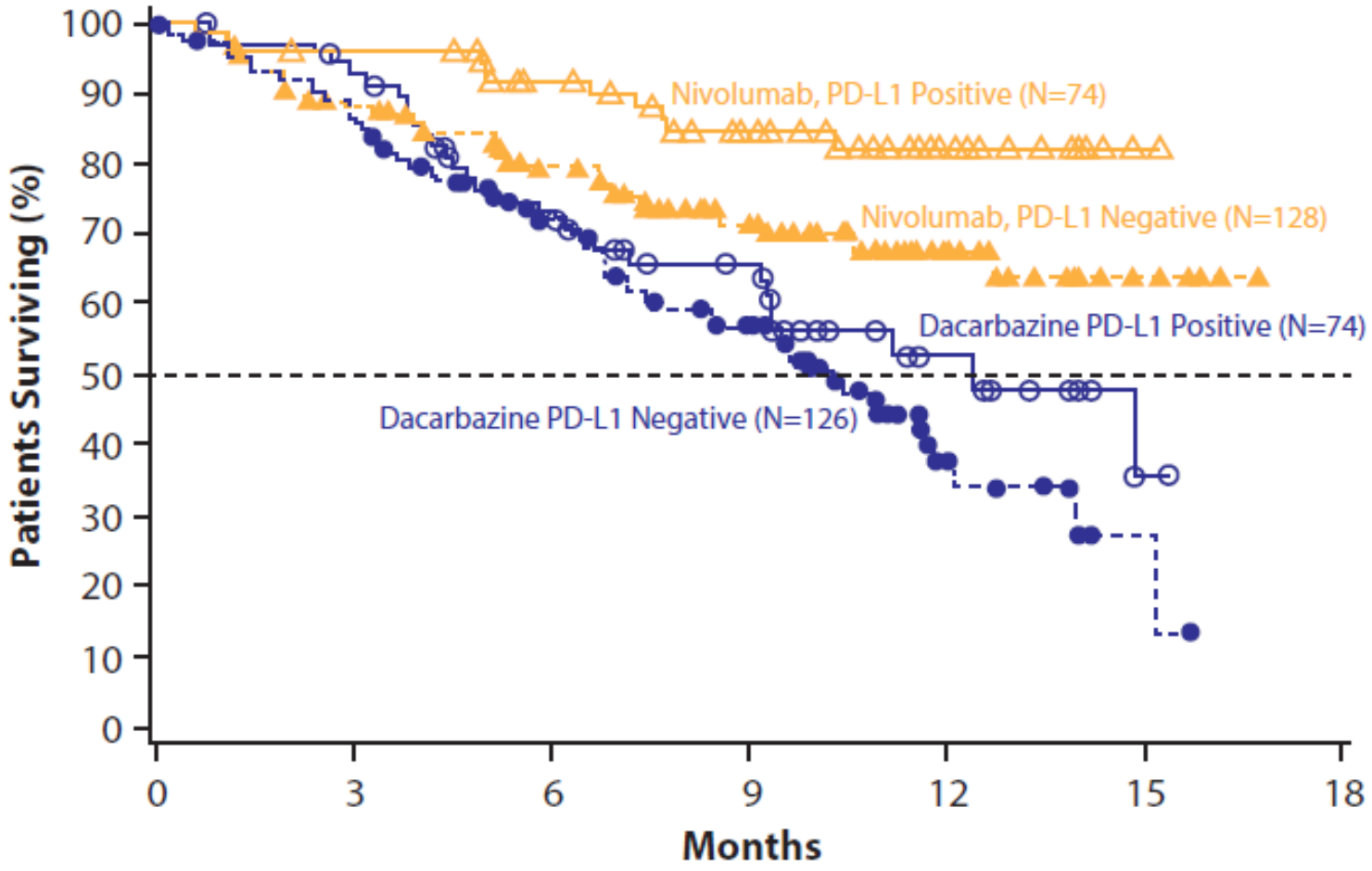
Combination Ipilimumab + Nivolumab for Patients with Asymptomatic Brain Metastases

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.

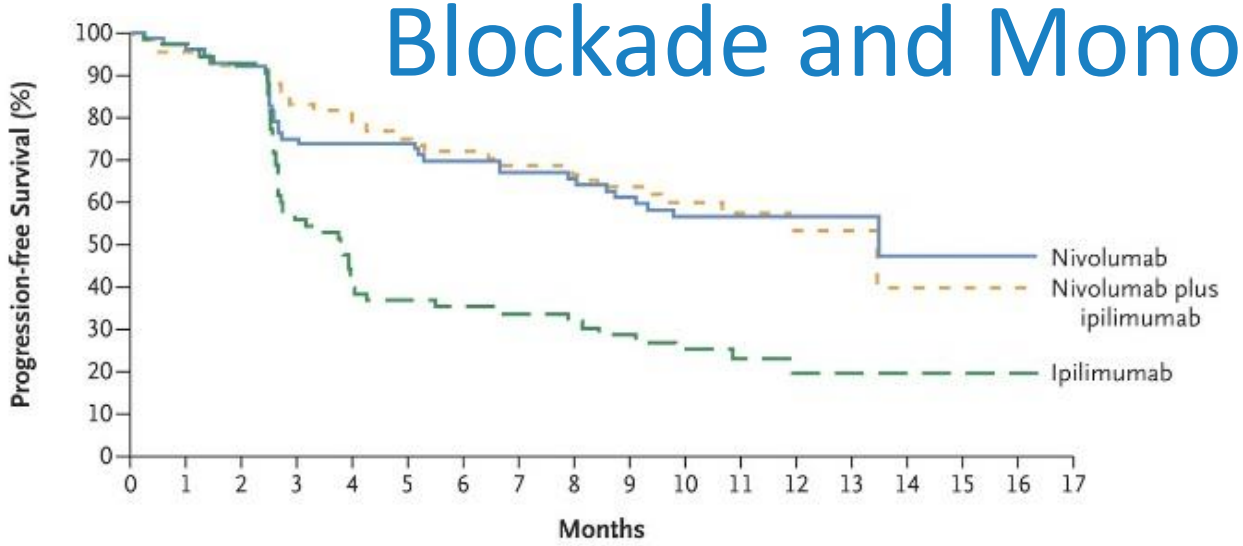
Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy



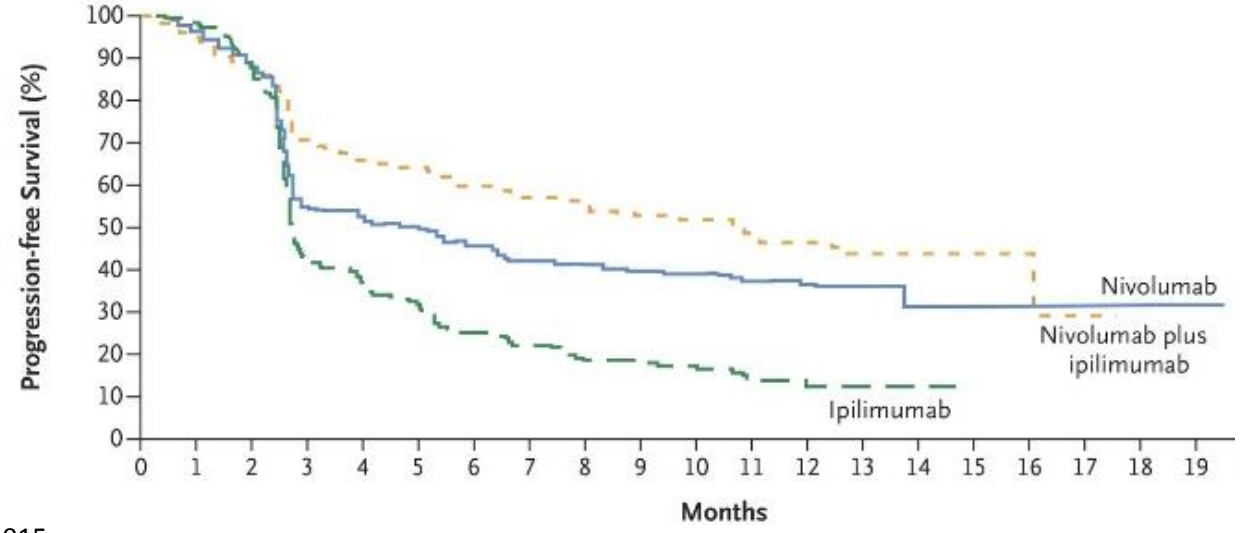
	Patients Who Died *n/N*	Median Survival *mo (95% CI)*
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

Robert, NEJM 2015.

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



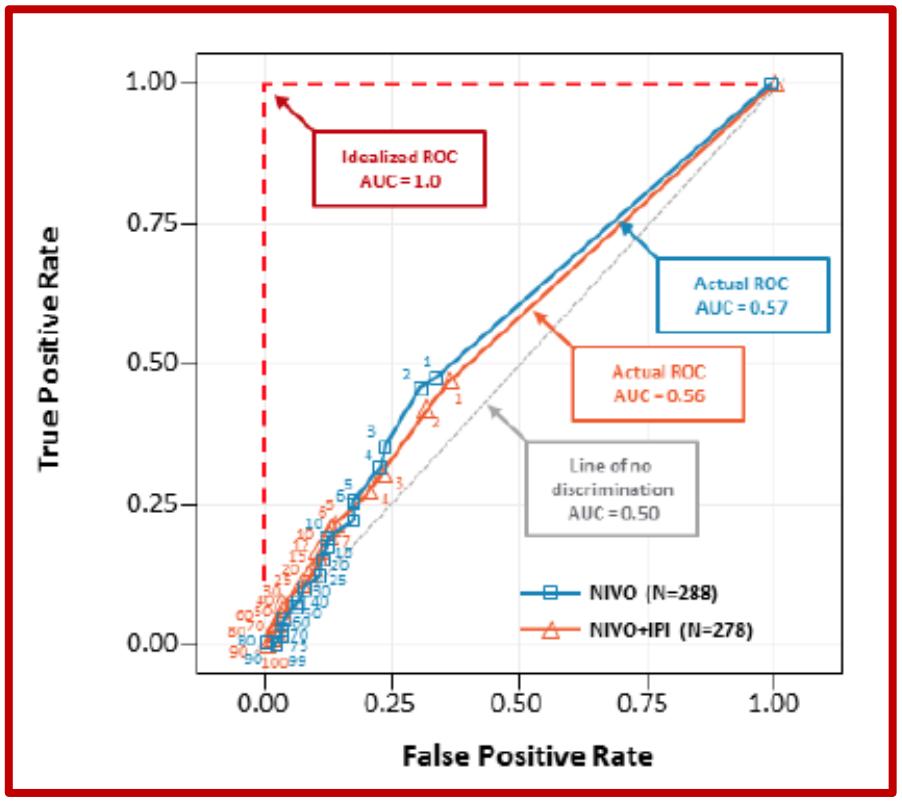
Tumor PD-L1 Positive Patients



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

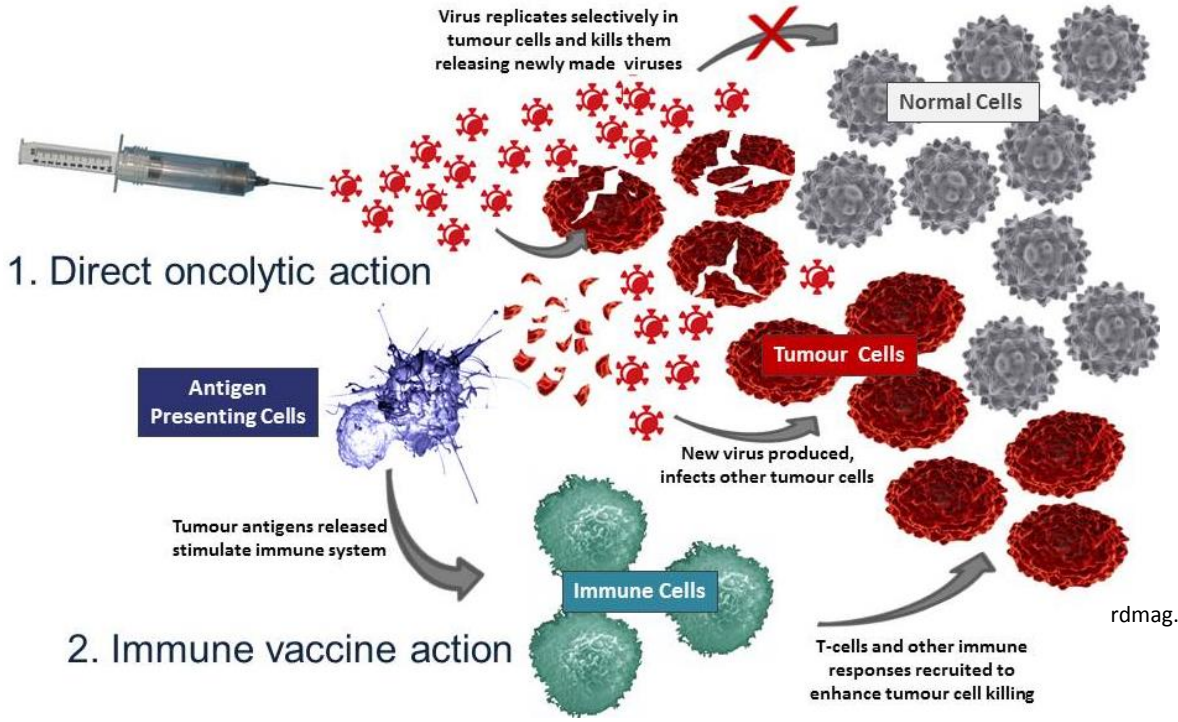
Wolchok, NEJM 2017.

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

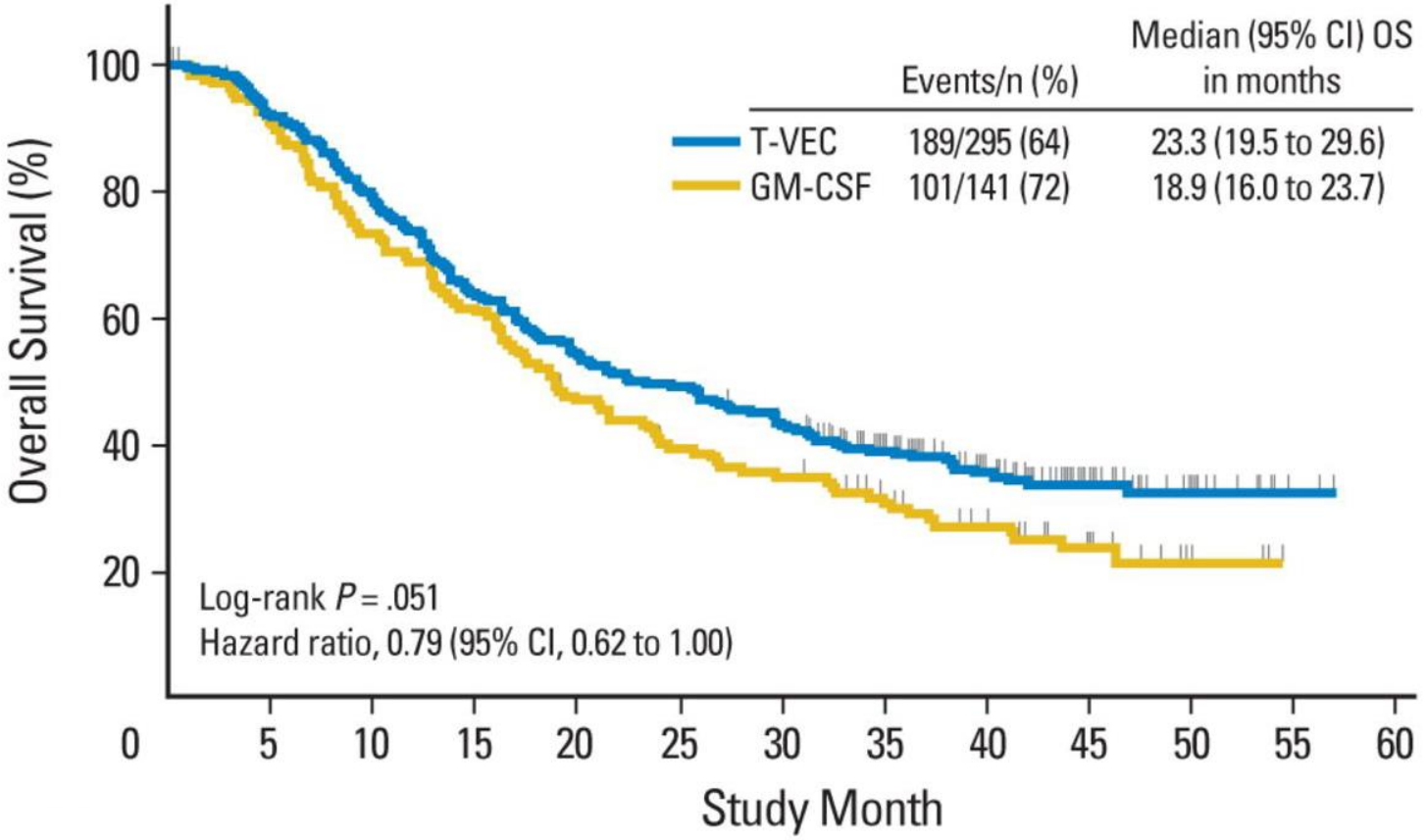


rdmag.com

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



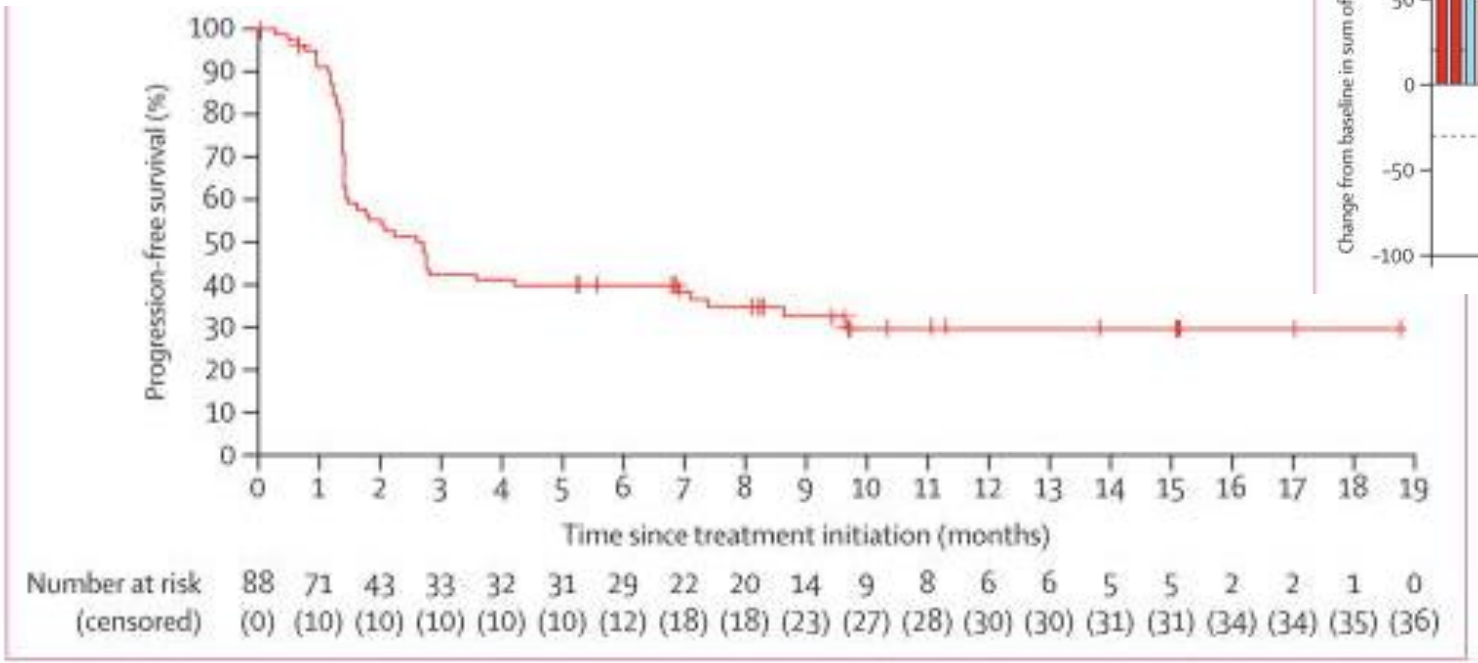
Andtbacka, Kaufman, JCO 2015.

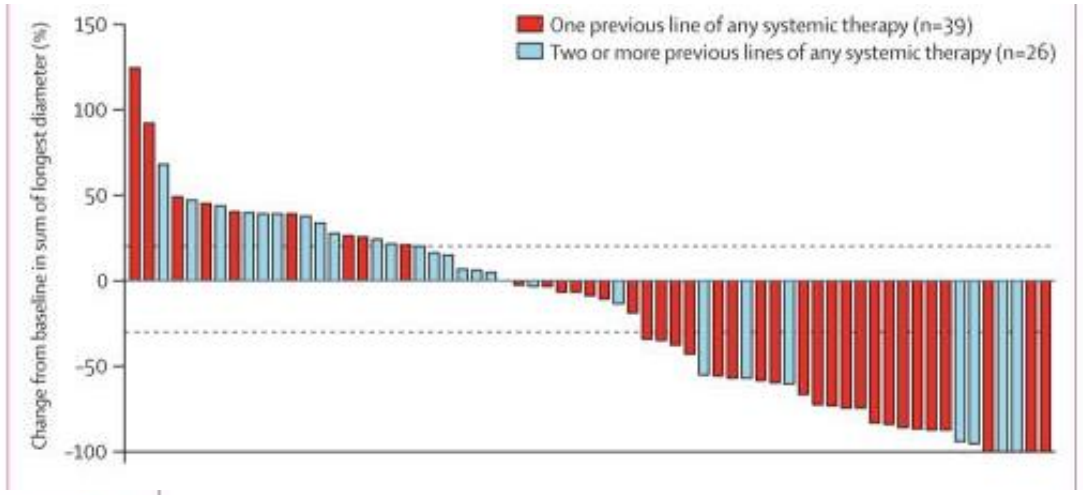
Approved checkpoint inhibitors in other skin cancers

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%

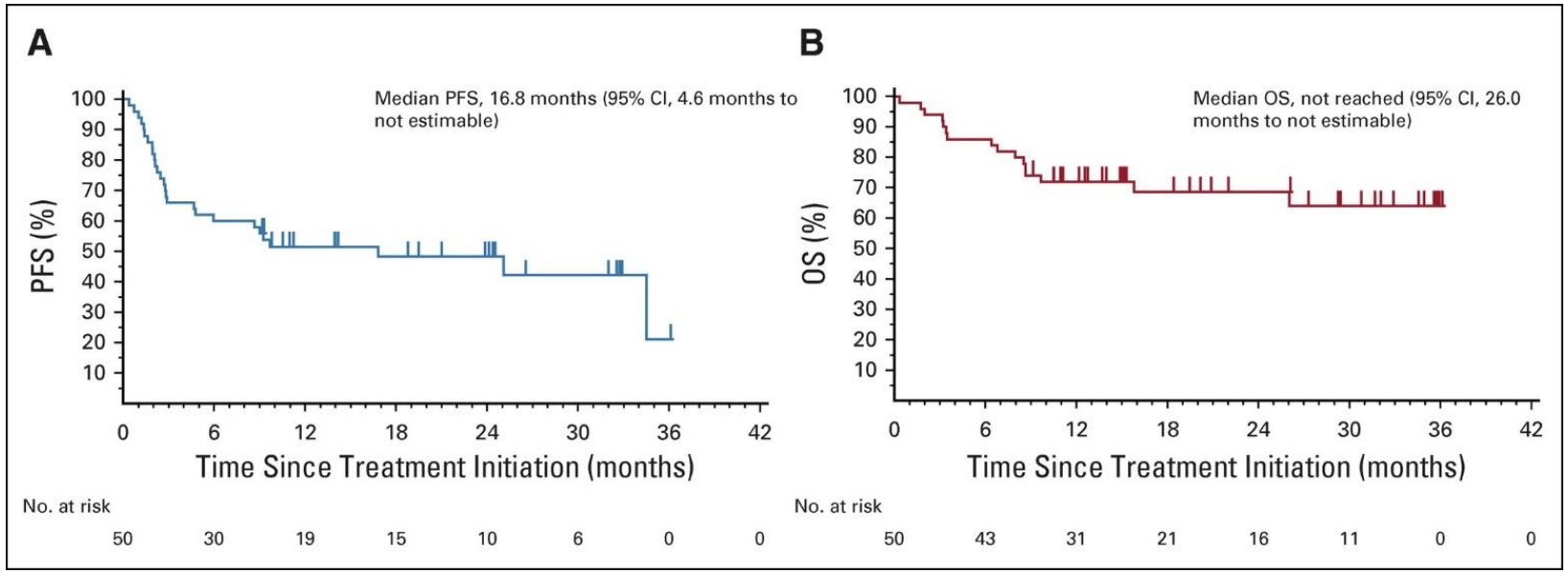




Kaufman, Lancet Oncol 2016.

Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

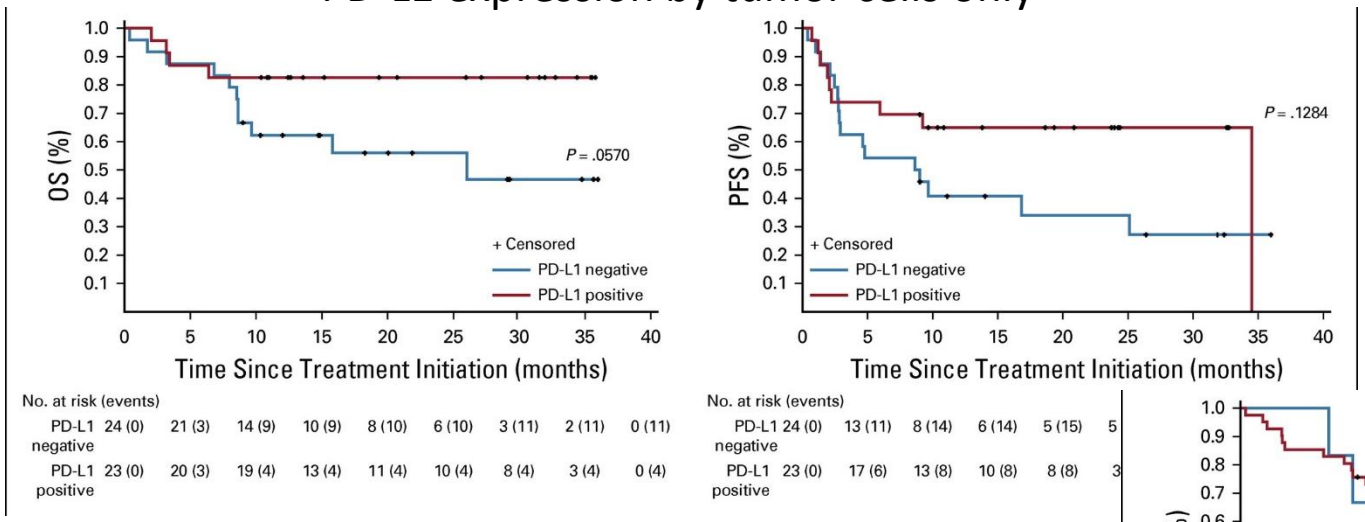
- KEYNOTE-017
- Pembrolizumab 2 mg/kg Q3W up to 2 years
- mPFS: 16.8 months (compared to 90 days for chemo)
- 24-month OS: 68.7%



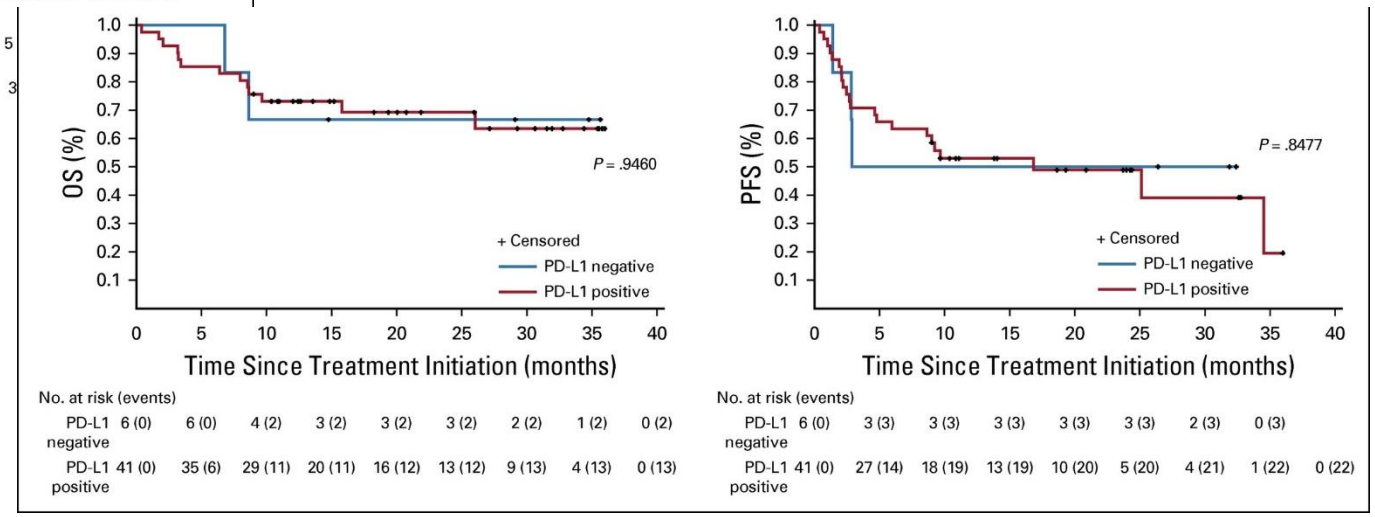
Nghiem, J Clin Oncol 2019.

Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

PD-L1 expression by tumor cells only



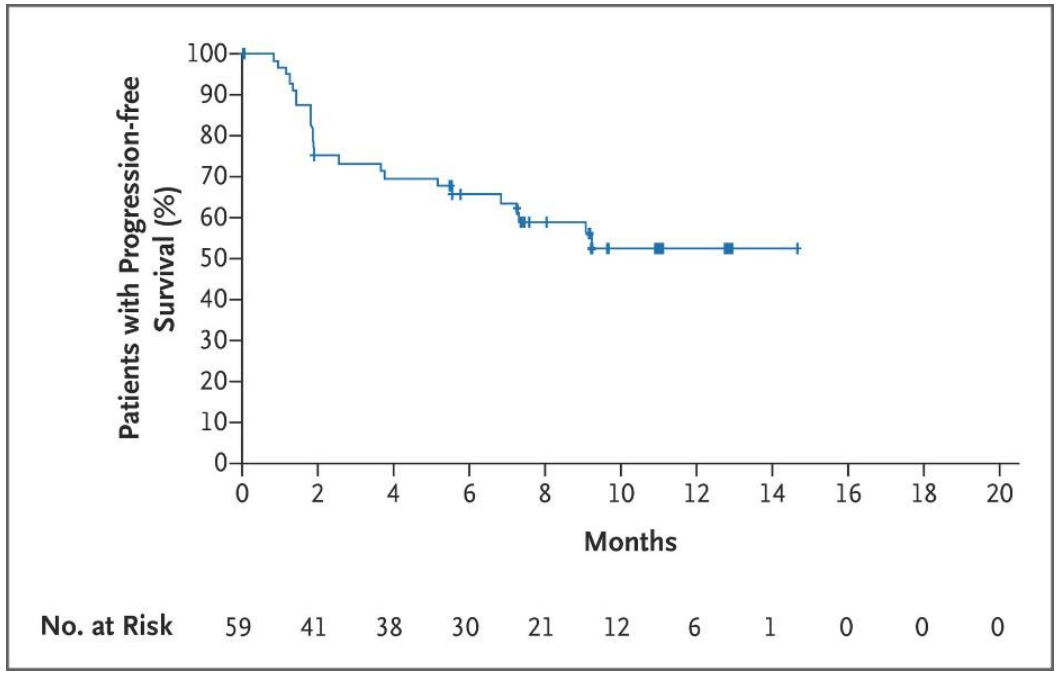
PD-L1 on all cells in tumor

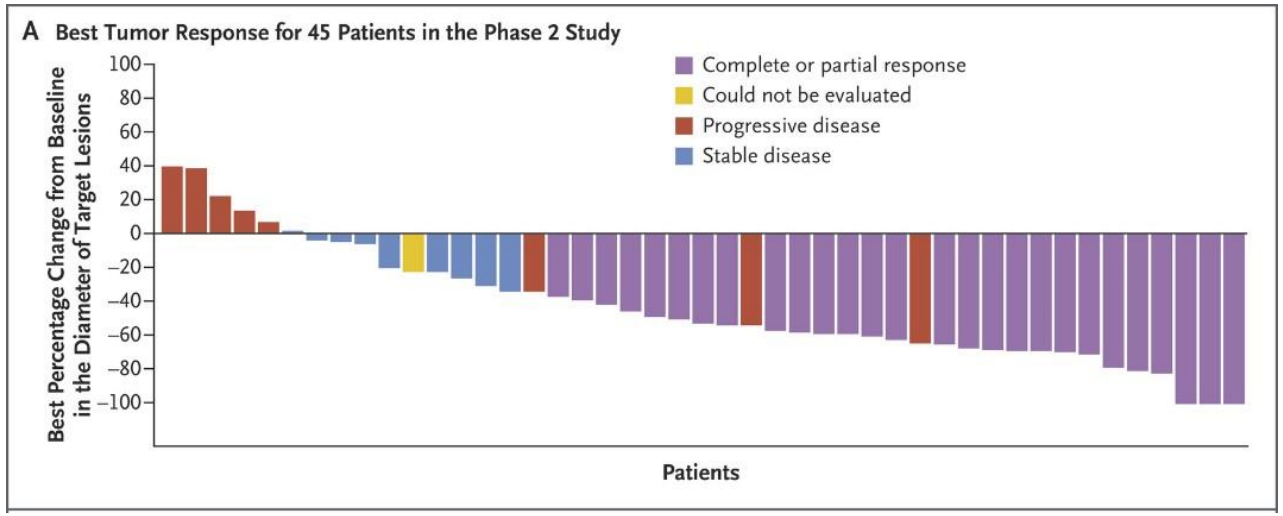


Nghiem, J Clin Oncol 2019.

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

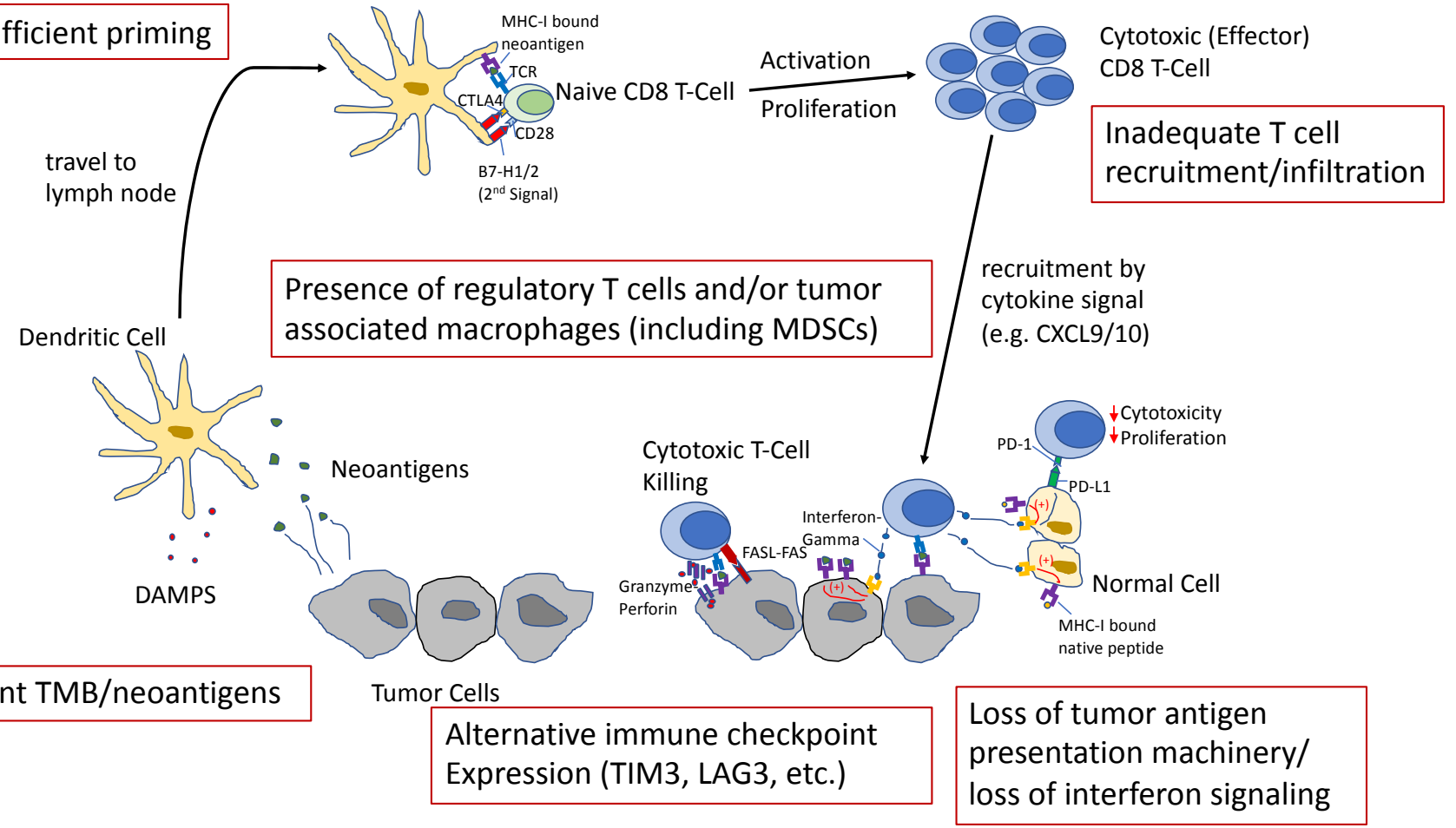




Migden, NEJM 2018.

Developmental Immunotherapeutic Strategies for Melanoma

How does immune checkpoint inhibitor therapy fail?

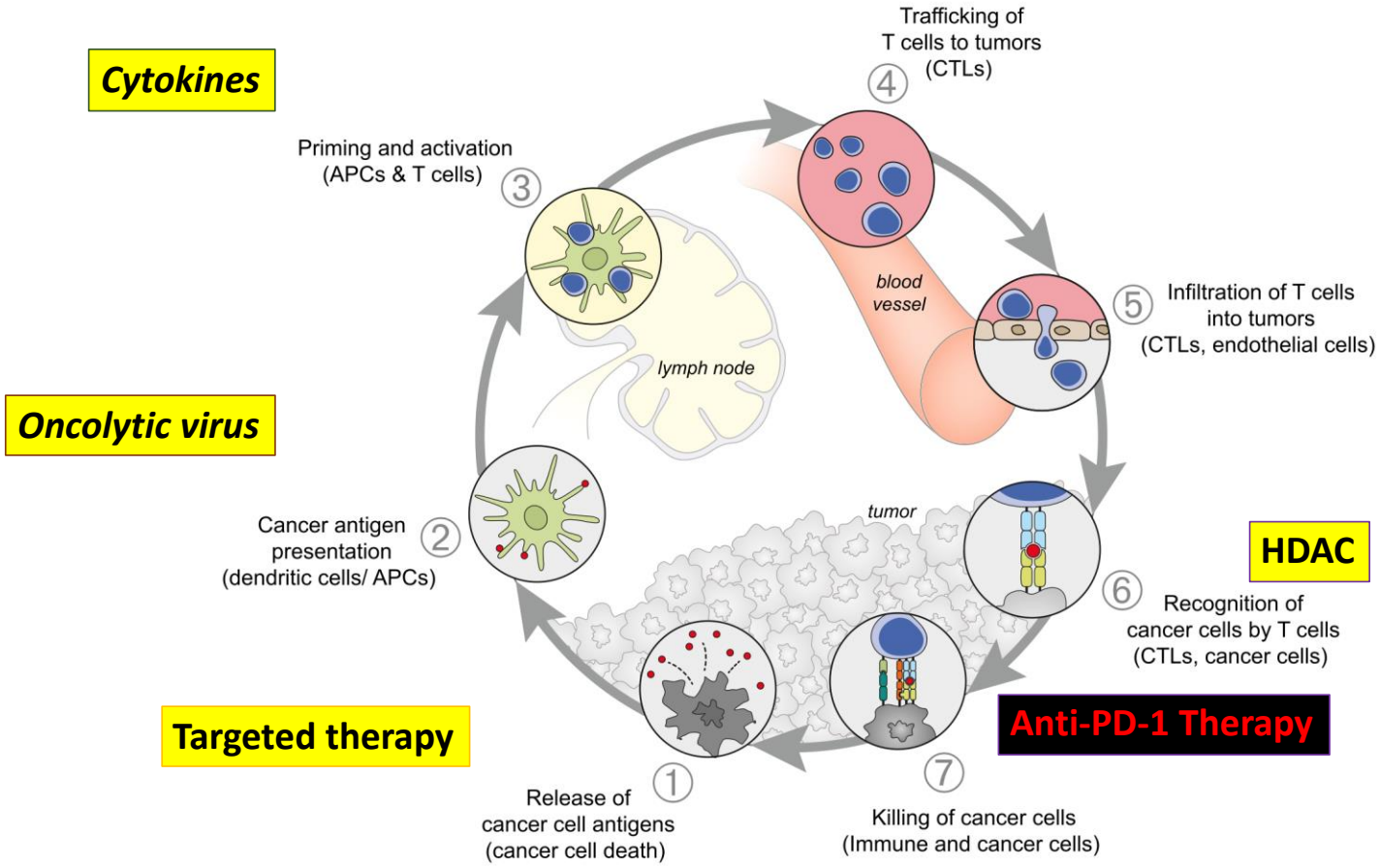


Modified from Liu, Jenkins, Sullivan. Amer J Clin Derm 2018.

Developmental Immunotherapeutic Strategies for Melanoma

How do we overcome resistance?

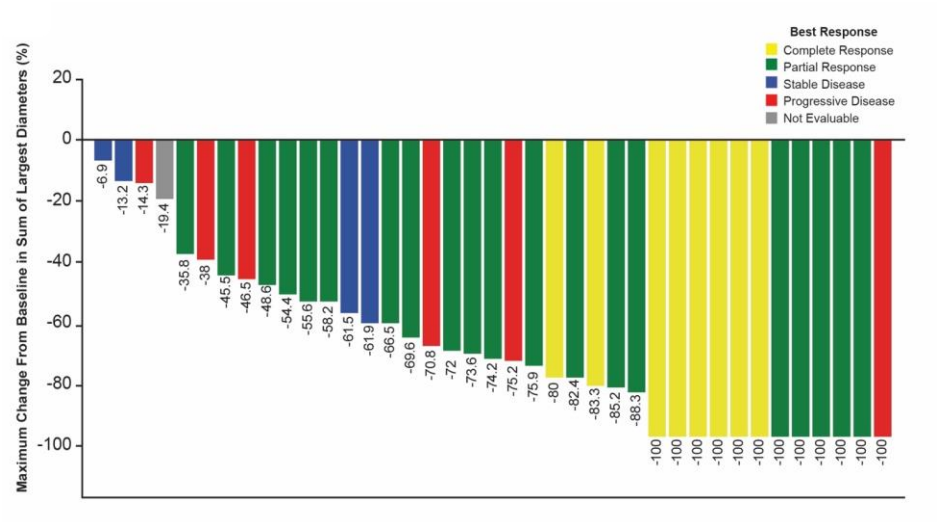
Combination therapy

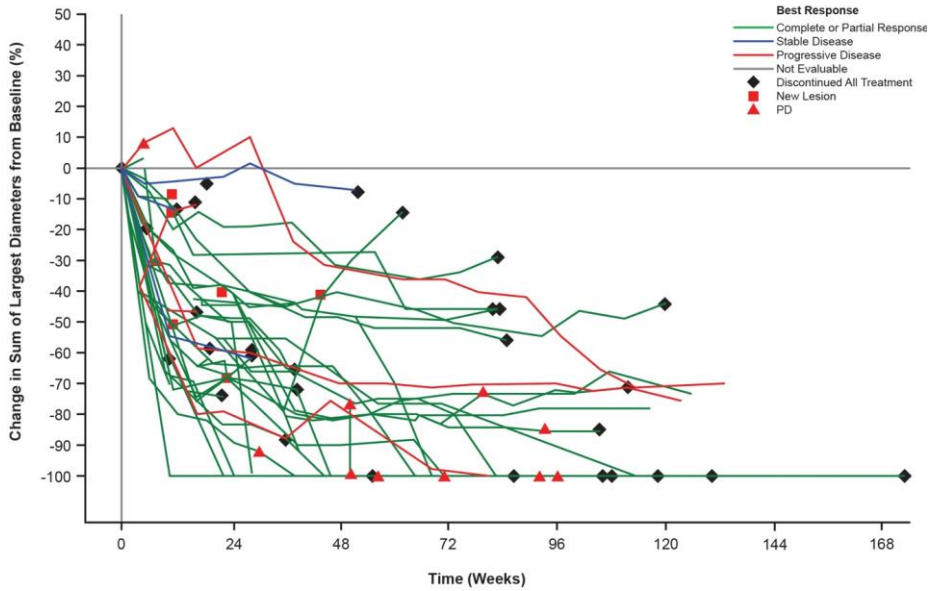


Modified from Chen and Melman. Immunity 2015.

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)

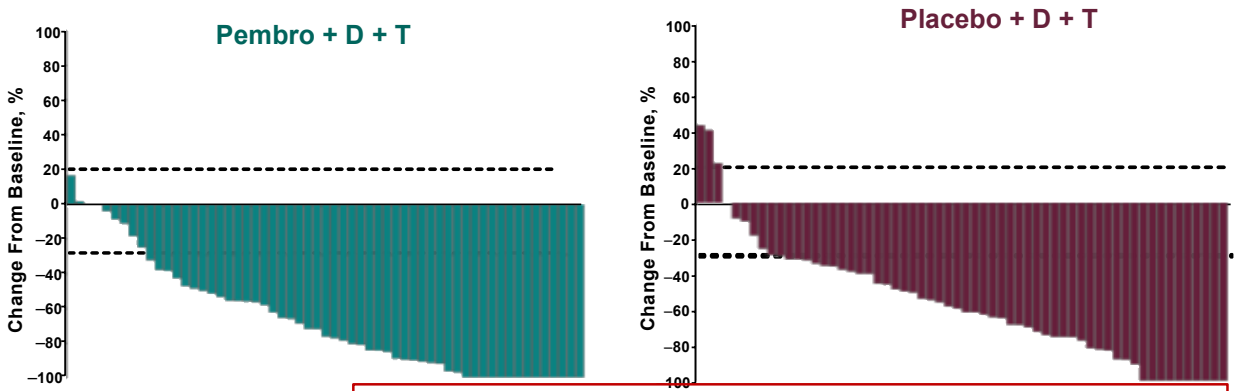
R (1:1)
N = 120

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

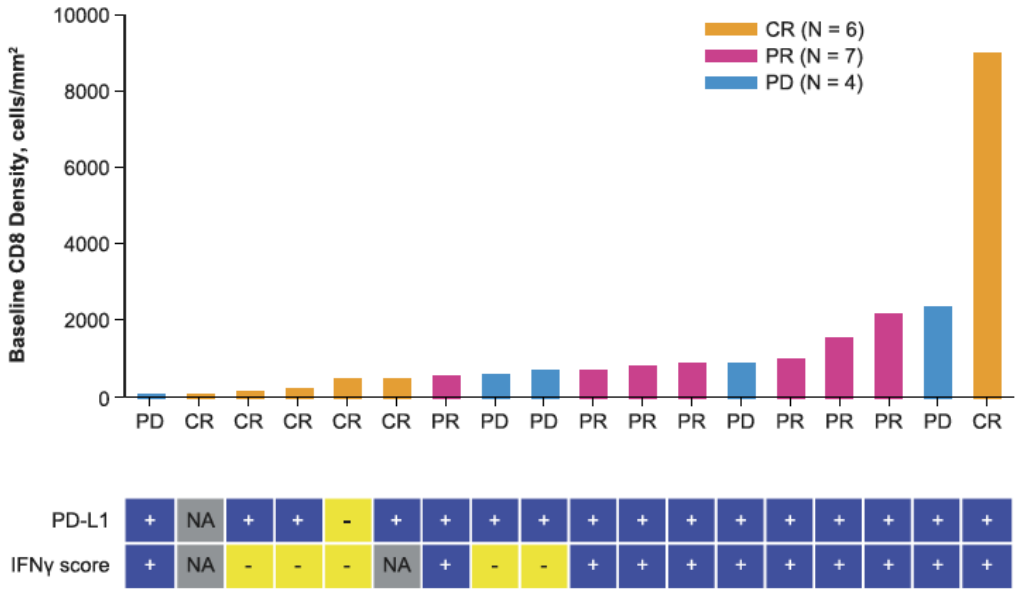
[a]Owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.



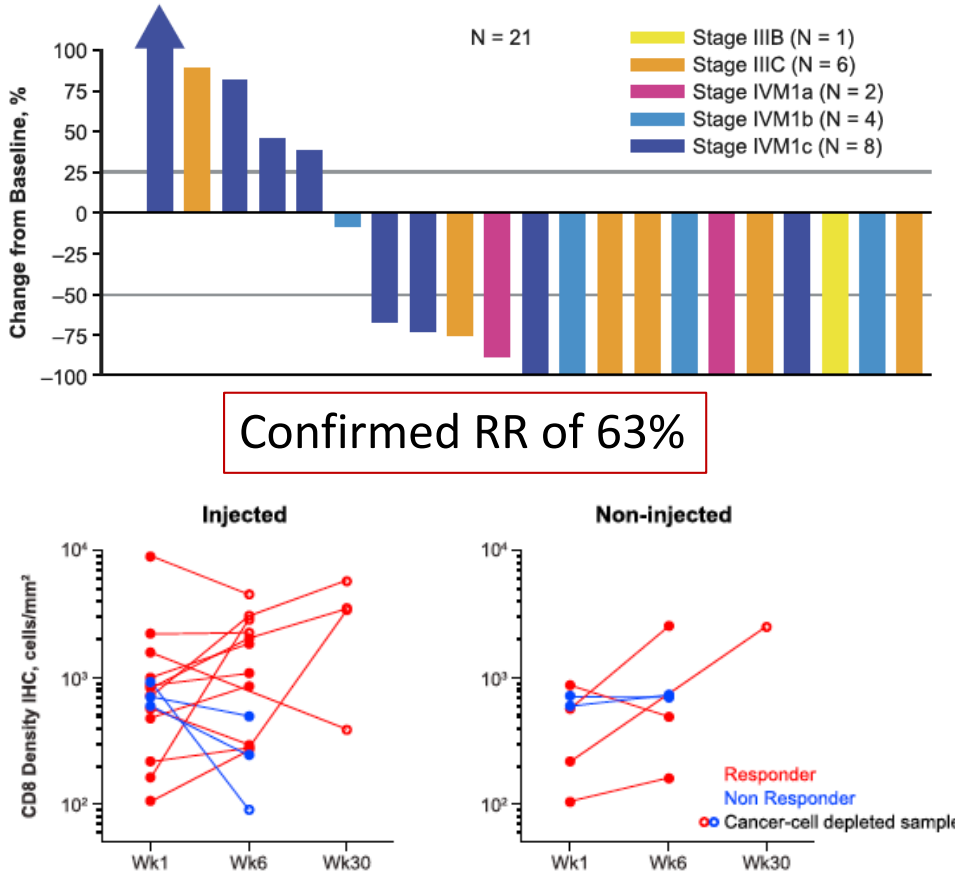
	Pembro + D + T	Placebo + D + T
ORR	63%	72%
CR	18%	13%
≥ 60% red	63%	51%

Ascieto et al, *Nature Med* 2019.

In development: Combined IO with Oncolytic Virus



Phase I: Pembrolizumab + TVEC



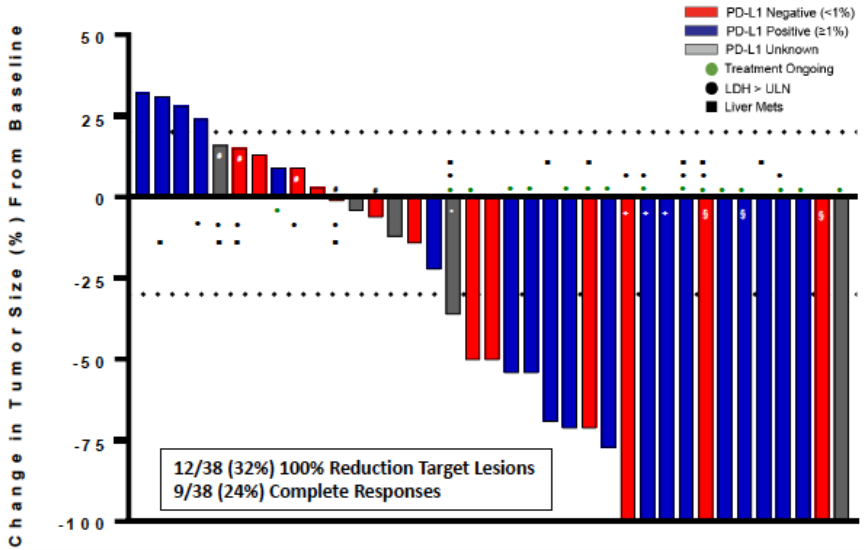
Confirmed RR of 63%

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



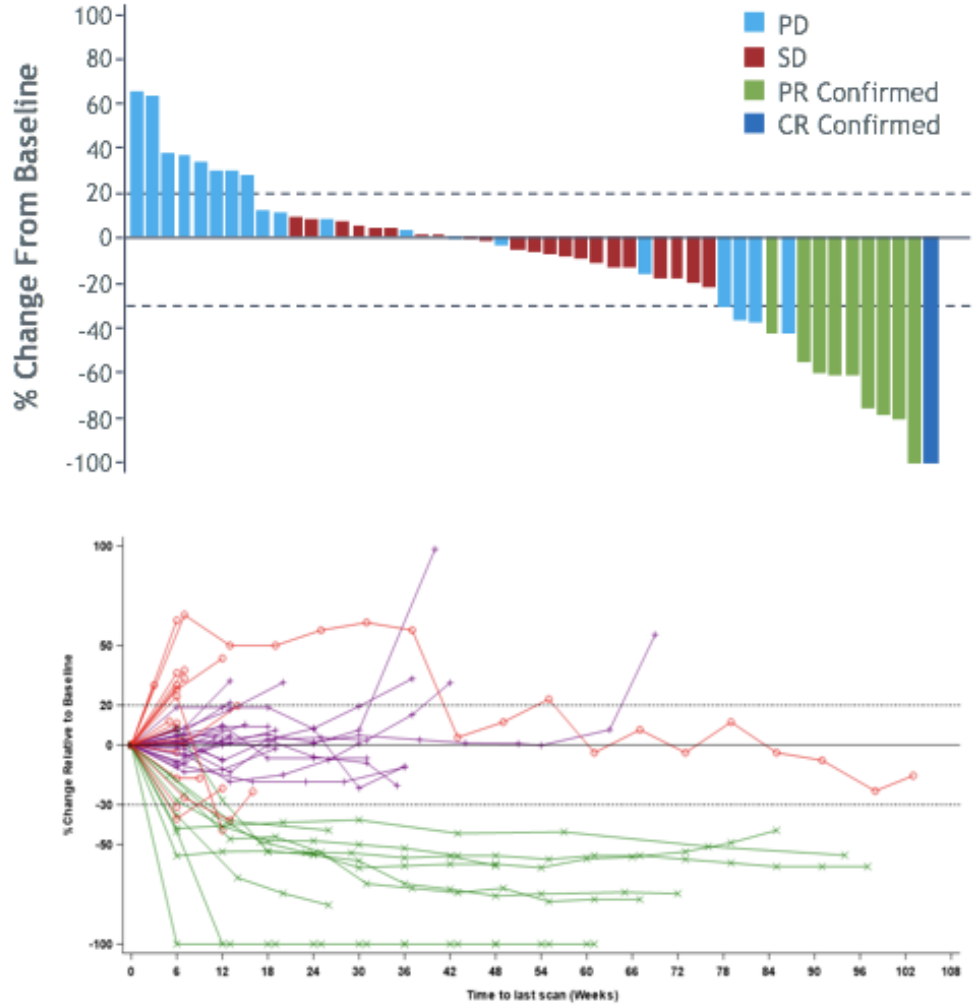
1L Melanoma (n=38 Efficacy Evaluable)	Overall Response Rate
Confirmed ORR (CR+PR)	20 (53%)
CR	9 (24%)
DCR (CR+PR+SD)	29 (76%)
PD-L1 negative (n=14)	6 (43%)
PD-L1 positive (n=19)	13 (68%)
PD-L1 unknown (n=5)	1 (20%)
LDH > ULN (n=11)	5 (45%)
Liver metastases (n=10)	5 (50%)

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

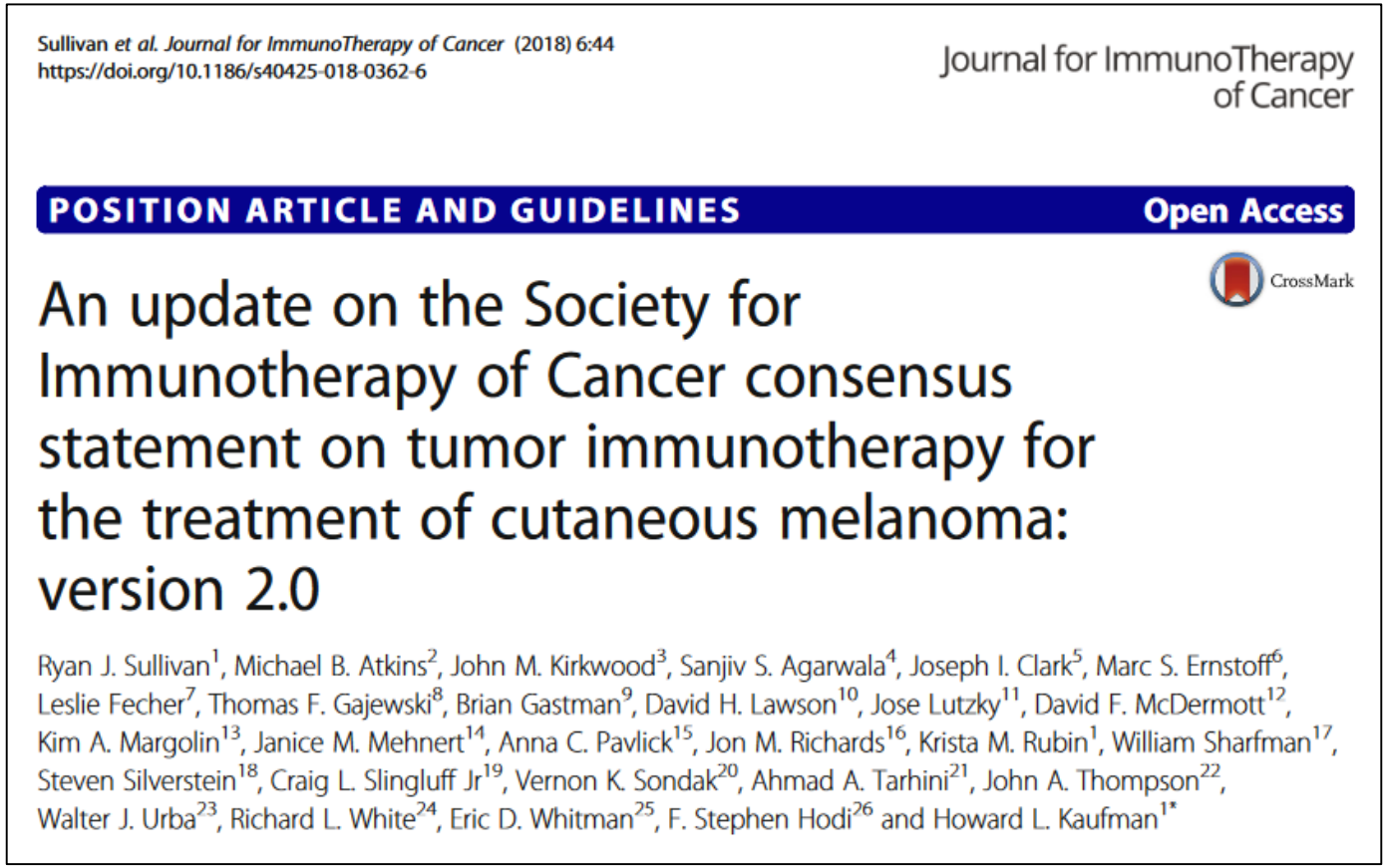


Sullivan et al, AACR 2019.

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

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Case Studies

Case Study 1

- **CHIEF COMPLAINT:** Melanoma of the back
- **ONCOLOGY HISTORY:** 50 y/o man with melanoma. Briefly
- 2/18-RIGHT upper back biopsy=Melanoma
- WLE and NO SLN. pT3acN0M0
- 5/19-Noted swelling RIGHT neck
- 5/29/19-US neck with RIGHT supraclav LN
- 6/21/19-FNA=melanoma
- CXR “abnormal”, CT chest "normal"
- 7/10/19-Feeling well. Palpable node in the RIGHT neck, not tender. NO headaches. NO cough. NO GI issues. ECOG=0

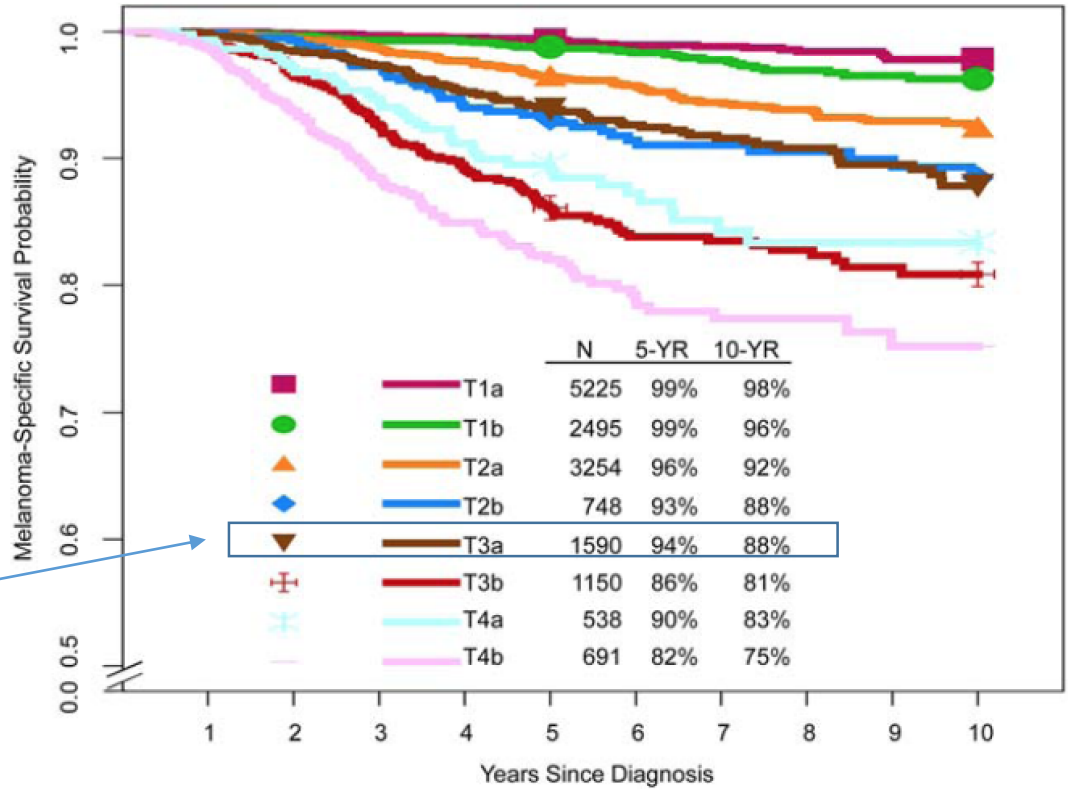


FIGURE 1. Kaplan-Meier Melanoma-Specific Survival Curves According to T Subcategory for Patients With Stage I and II Melanoma From the Eighth Edition International Melanoma Database. Patients with N0 melanoma have been filtered, so that patients with T2 to T4 melanoma were included only if they had negative sentinel lymph nodes, whereas those with T1N0 melanoma were included regardless of whether they underwent sentinel lymph node biopsy.

Case Study 1

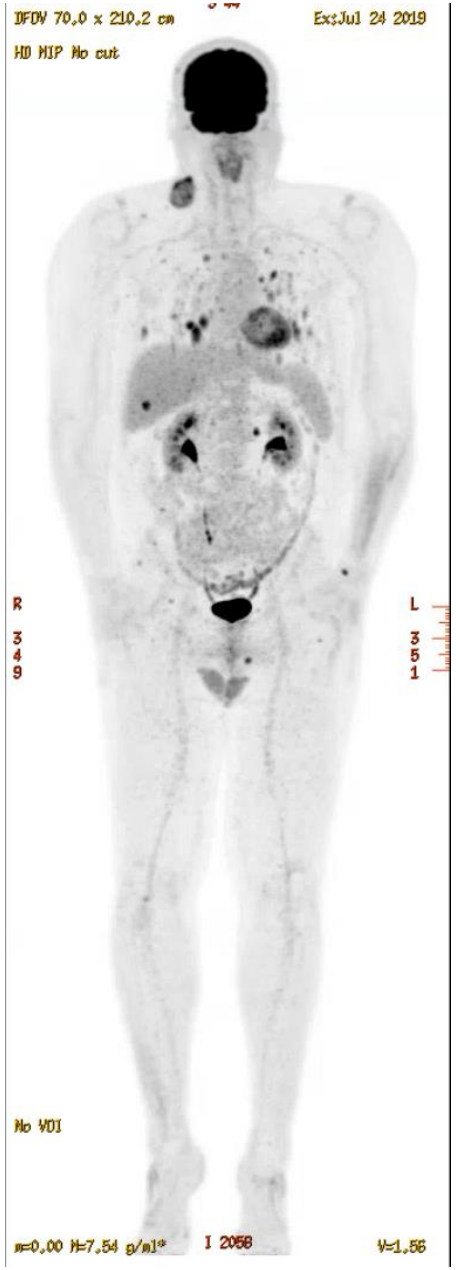
- What would you do first?
  A. Restage with PET/CT and MR brain
  B. Obtain NGS in anticipation of offering adjuvant therapy
  C. Adjuvant ipilimumab for 4 doses following by up to three years of every three-month infusion
  D. Adjuvant Pembrolizumab
  E. Resect the local recurrence as this was likely his sentinel lymph node and he now requires a completion lymph node dissection

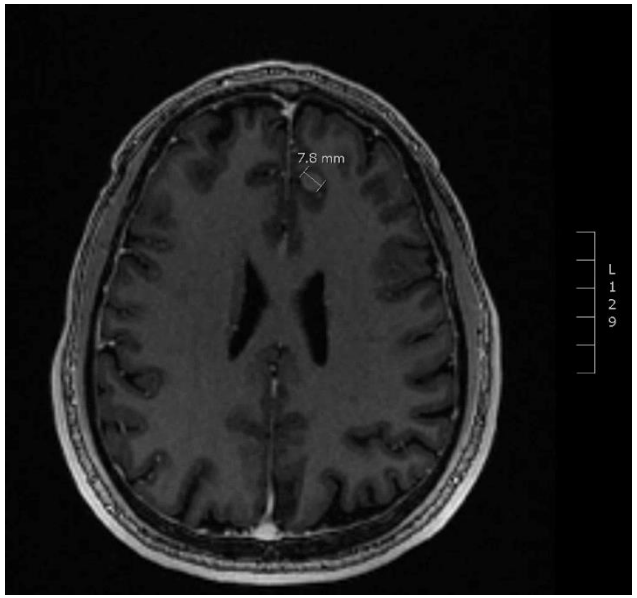
Case Study 1

- What would you do first?
  - **A. Restage with PET/CT and MR brain-**While there are imaging from the outside, these are limited and given the clinical recurrence, this patient needs restaging. PET/CT is most appropriate although CT NCAP would be acceptable too**.**
  - B. Obtain NGS in anticipation of offering adjuvant therapy-BRAF determination is advised in any advanced patient considering adjuvant or systemic options. Next generation sequencing is not required in all patients and particularly in patients considering adjuvant therapy
  - C. Adjuvant ipilimumab for 4 doses following by up to three years of every three-month infusion-This is no longer a preferred option in adjuvant therapy
  - D. Adjuvant Pembrolizumab-Reasonable to discuss but restaging takes priority as this patient has gross disease and minimally would require surgical resection to get to no evidence of disease.
  - E. Resect the local recurrence as this was likely his sentinel lymph node and he now requires a completion lymph node dissection-As above, needs restaging. If the restaging scans confirm localized (one lymph node bed involvement), surgical resection followed by adjuvant therapy would be an option.

Case Study 1

*Hypermetabolic **right neck** mass consistent with known malignancy. Innumerable bilateral hypermetabolic **lung nodules** consistent with pulmonary metastatic disease. Several hypermetabolic **mesenteric and omental soft tissue** nodules, suspicious for metastatic disease. Right **scalp focus** and several hypermetabolic subcutaneous and intramuscular foci, suspicious for metastatic disease. Right **T3 and left femoral neck focus,** suspicious for osseous metastatic disease. Consider bone scan for further characterization.*





Multiple enhancement masses (12) and associated T2/FLAIR signal hyperintensity are consistent for brain metastasis in this patient with known metastatic melanoma.

Case Study 1

PD-L1 EXPRESSION

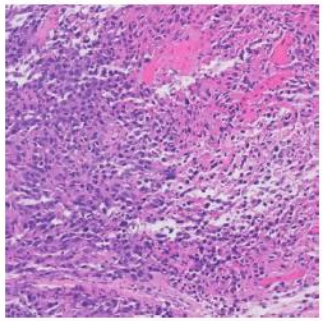
Tumor cell staining (membranous)

<1%

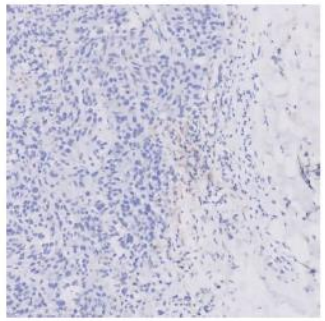
Tumor-associated immune cell staining

1%

200x



H&E



PD-L1

GENOMIC VARIANTS

Somatic - Potentially Actionable — Variant Allele Fraction

- NRAS — p.Q61R Missense variant (exon 3) - GOF — 66.2%
- TERT — c.-146C>T Variant - Promoter mutation — 53.5%
- MDM2 — Copy number gain

Somatic - Biologically Relevant

- DDX3X — p.L270fs Frameshift - LOF — 62.8%
- IRS2 — Copy number gain

Germline - Pathogenic / Likely Pathogenic

The patient has not consented to receive sequencing results on inherited variants.

Pertinent Negatives

No pathogenic single nucleotide variants, indels, or copy number changes found in:

BRAF KIT

IMMUNOTHERAPY MARKERS

Tumor Mutational Burden

7.7 m/MB — 92nd percentile

- What is the next best option?
  - A. Whole brain radiation with temozolamide
  - B. Stereotactic radiotherapy followed by PD1 pathway inhibitor
  - C. Ipilimumab and Nivolumab combination
  - D. Trametanib 2mg daily
  - E. Pembrolizumab or Nivolumab monotherapy

Case Study 1

- What is the next best option?

A. Whole brain radiation with temozolamide-Patient is asymptomatic in the brain with no critical area involvement. Whole brain radiation has not demonstrated survival benefit in patients. The addition to temozolomide to radiation therapy was also shown not to impact survival of patients.

B. Stereotactic radiotherapy followed by PD1 pathway inhibitor-Reasonable option however I would not favor this approach given the multiple lesions, the high burden of nonCNS disease and the low PDL1 staining.

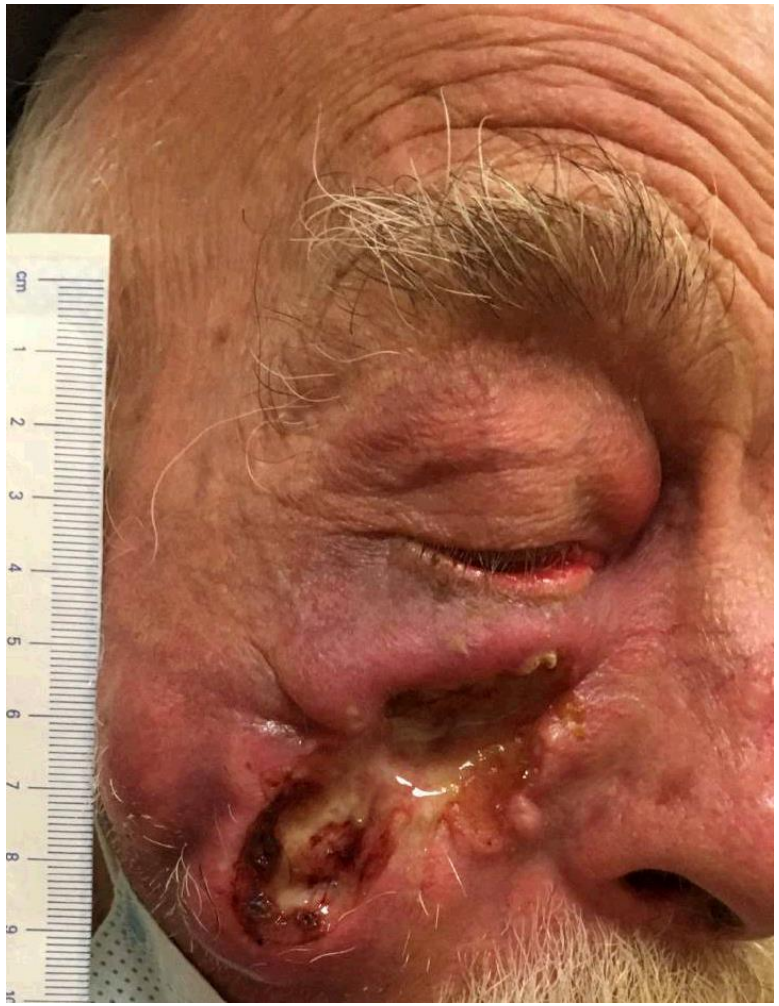
C. Ipilimumab and Nivolumab combination-Best choice given the largest lesion of about 8mm, relatively healthy with no concerns for increased irAEs and the need for systemic disease control.

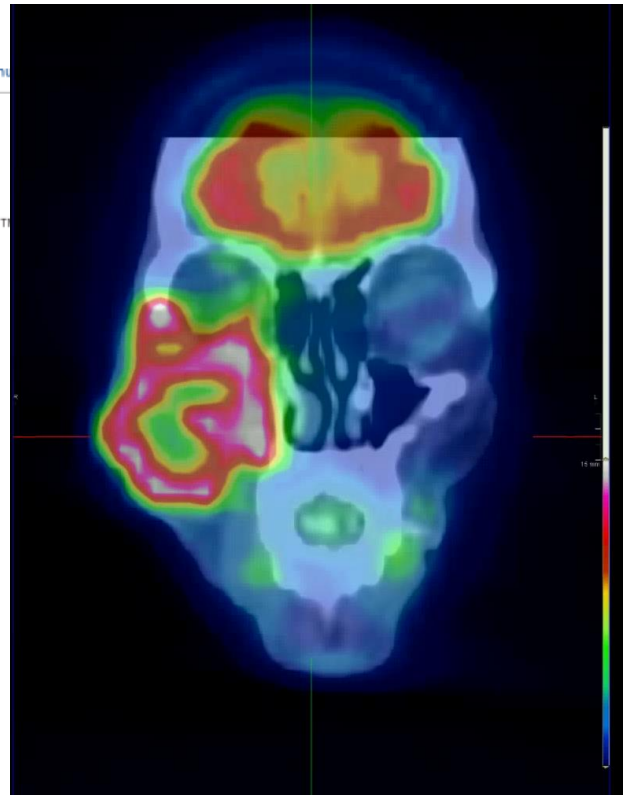
D. Trametanib 2mg daily-While suggested on the NGS panel, this would be a poor choice given the low benefit rate of MEK inhibition in this group (NRAS mutated) and the other options available.

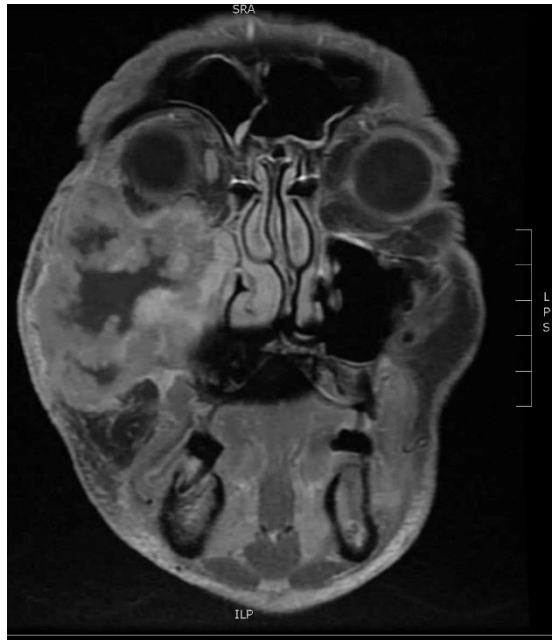
E. **Pembrolizumab or Nivolumab monotherapy**-While no comparative trials are available, the apparent higher CNS response rates of combination therapy makes option C preferred.

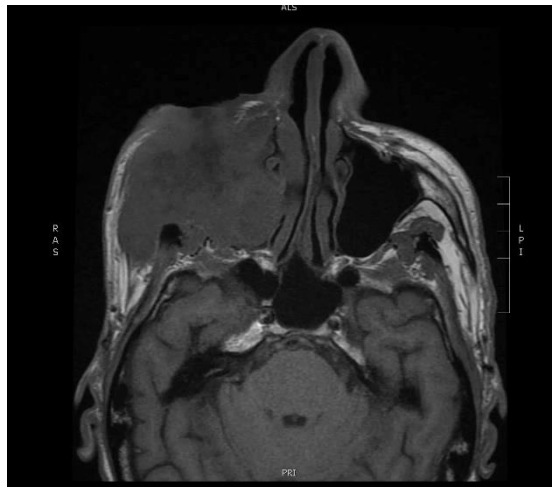
Case Study 2

- **ONCOLOGY HISTORY:** 70 y/o man with advanced cuSCC. Briefly,
- 2015-Multiple surgical resections of skin lesion with dermatology
- 2016-Lost funding
- 2017-Progressive enlargement and discomfort.
- 12/12/17-Biopsy=cuSCC
- **CANCER RISK FACTORS:** Smokes, sun exposure.
- 1/12/18-PET/CT with RIGHT orbital extension.









Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

- 24 genomic findings
- 17 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 43 clinical trials

TUMOR TYPE: SKIN SQUAMOUS CELL CARCINOMA (SCC)

Genomic Alterations Identified†

EGFR amplification
FGFR3 K650M – subclonal‡
HRAS A146V
MET amplification
CDK6 amplification – equivocal‡
HGF amplification – equivocal‡
RICTOR amplification
STAT3 Y640F – subclonal‡
CDKN2A p14ARF P72L, p16INK4a R58* and p14ARF P72L
CRKL amplification
DICER1 R640*
FOXP1 K393*
FUBP1 G606fs*44
GRIN2A E1461K
KMT2C (MLL3) G2357*
LYN amplification – equivocal‡
NOTCH1 E2071*
RUNX1T1 R458C
TERT promoter -146C>T
TP53 E62*, P27fs*17

Additional Findings†

Microsatellite status MS-Stable
Tumor Mutation Burden TMB-High; 80 Muts/Mb

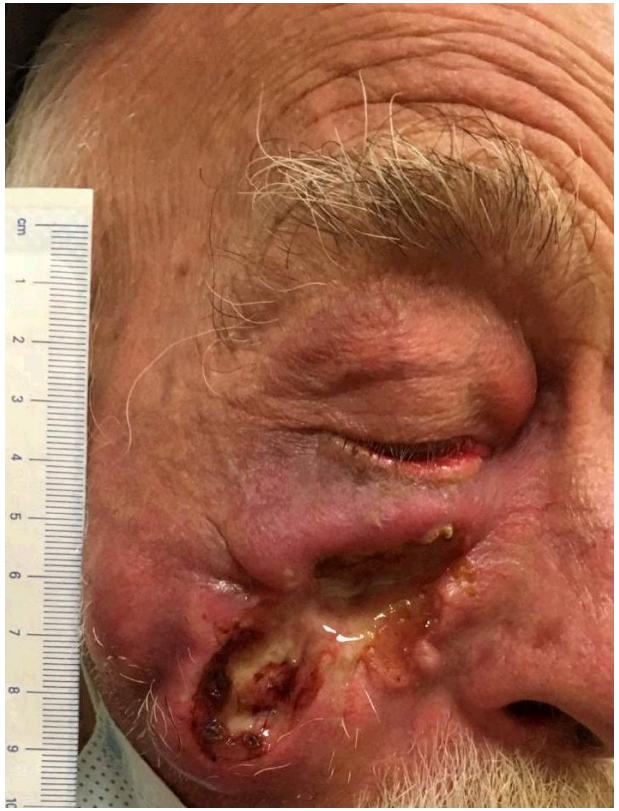
† For a complete list of the genes assayed and performance specifications, please refer to the Appendix
‡ See Appendix for details

- What is the next best option?
  - A. Radiation with weekly cisplatin
  - B. Surgical resection followed by adjuvant radiation
  - C. Cetuximab
  - D. Trametanib 2mg daily
  - E. Cemiplimab

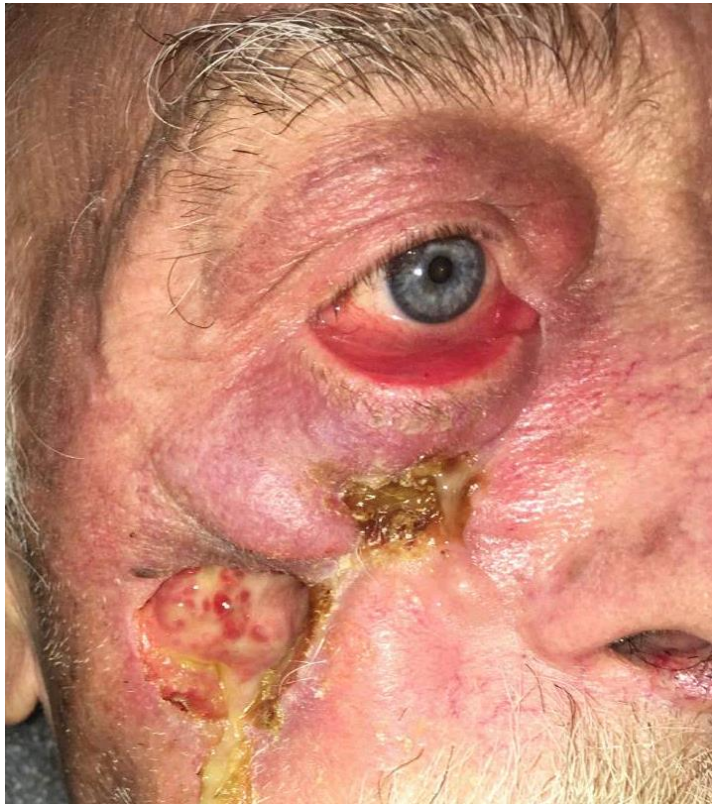
Case Study 2

- What is the next best option?
  - A. Radiation with weekly cisplatin-Unlikely to cure, will result in RIGHT sided vision loss.
  - B. Surgical resection followed by adjuvant radiation-Morbid surgery. Need for multidisciplinary discussion.
  - C. Cetuximab-Modest single agent response rate with moderate toxicity makes this a poor choice.
  - D. Trametanib 2mg daily-Although has a HRAS mutation, there is no known activity with MEK inhibition in cuSCC
  - **E. Cemiplimab**-Best first choice for an advanced or metastatic cuSCC in a patient where surgery or radiation therapy are unlikely to cure the patient or have unacceptable morbidity.

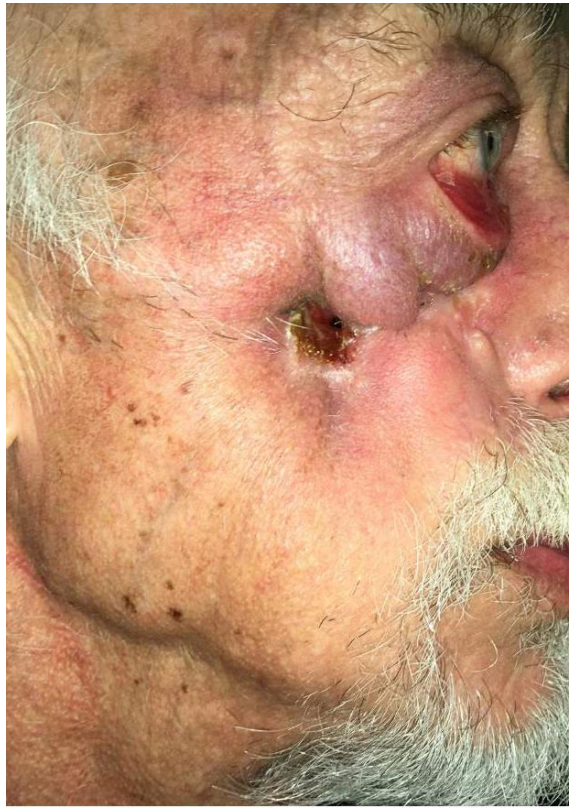
Case Study 2



1/26/18
Pain
Drainage



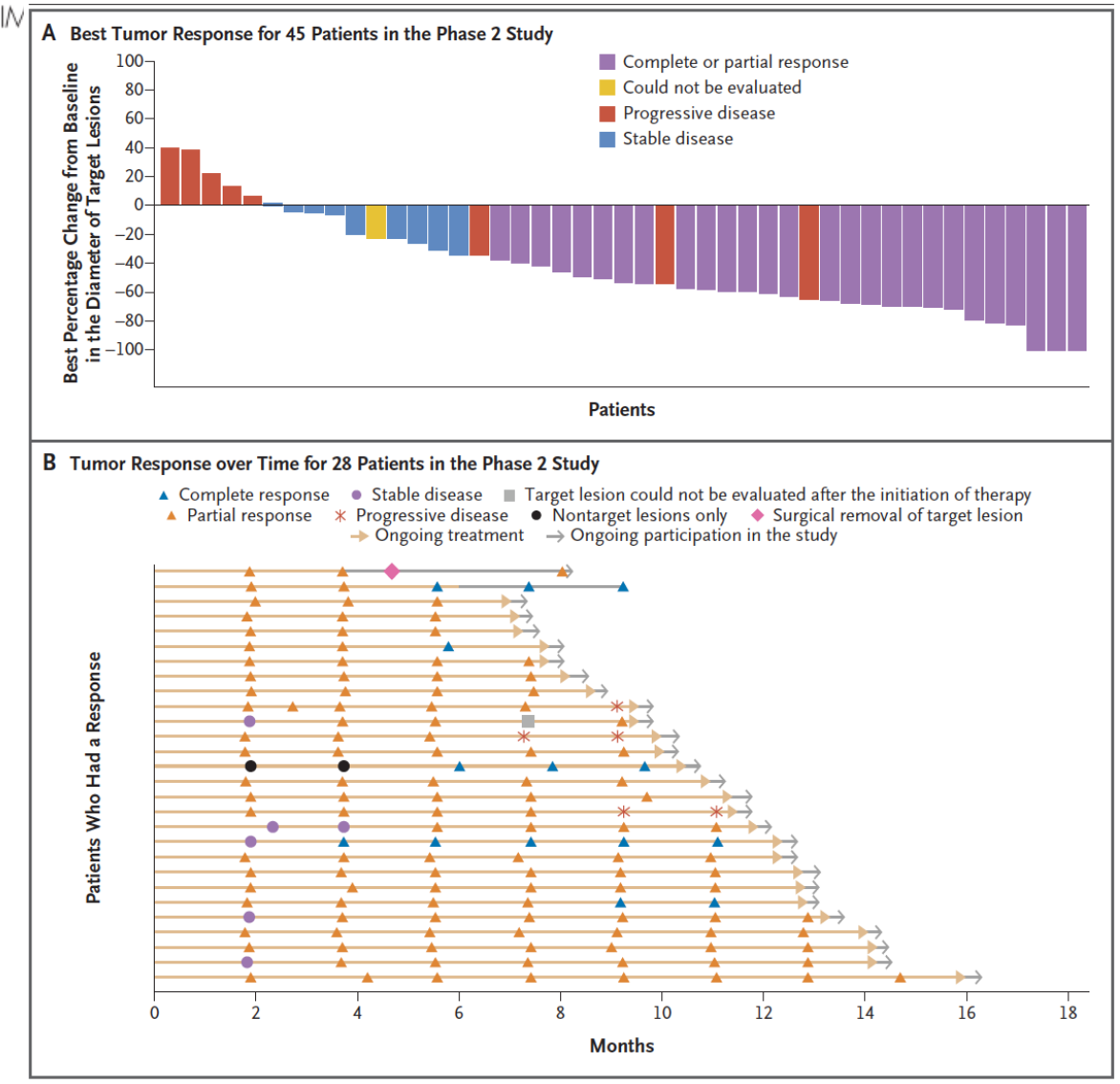
3/7/18
PD-1 therapy



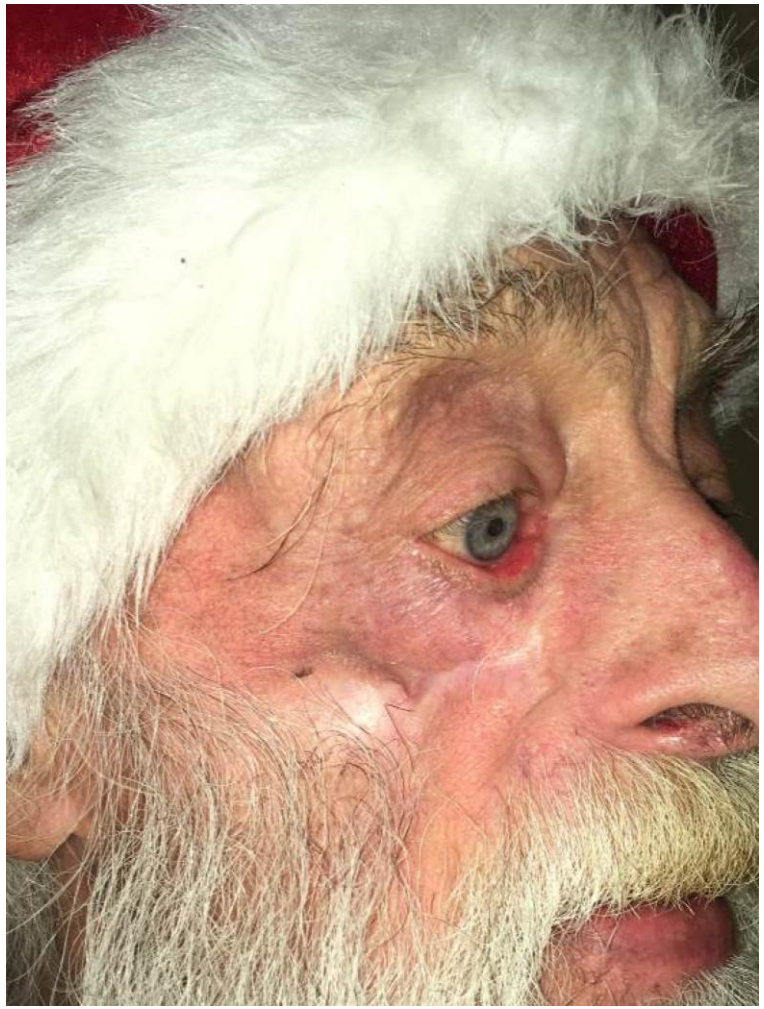
3/23/18
2 weeks
Pain resolved

4/6/18
4 weeks
Drainage stopped

Case Study 2



Migden Fury NEJM 2018



Four months off therapy