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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

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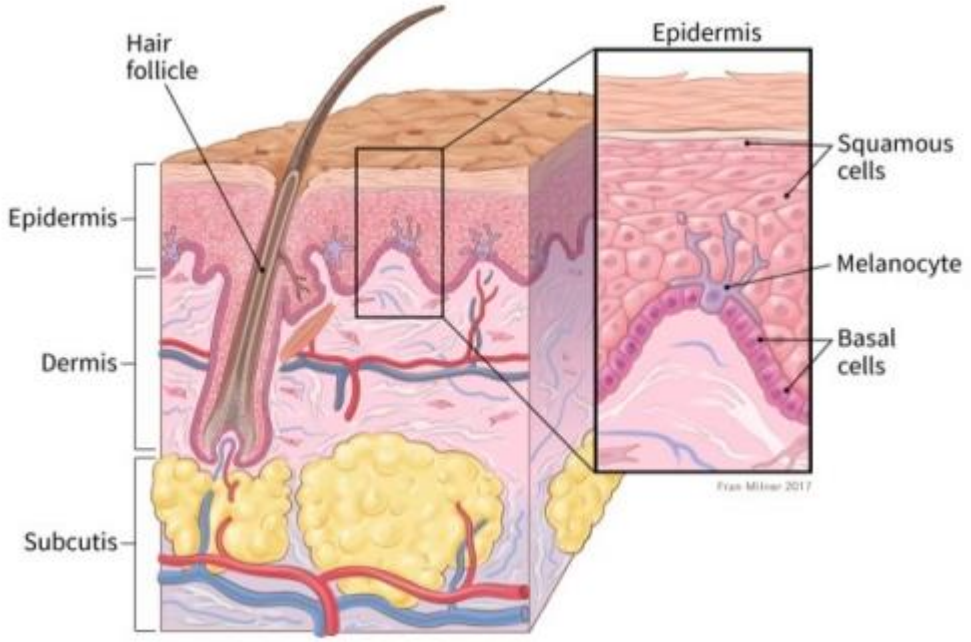
Disclosures

- No disclosures
- 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 has been a proving ground for immunotherapy



Cancer.org

Approved cytokines in melanoma

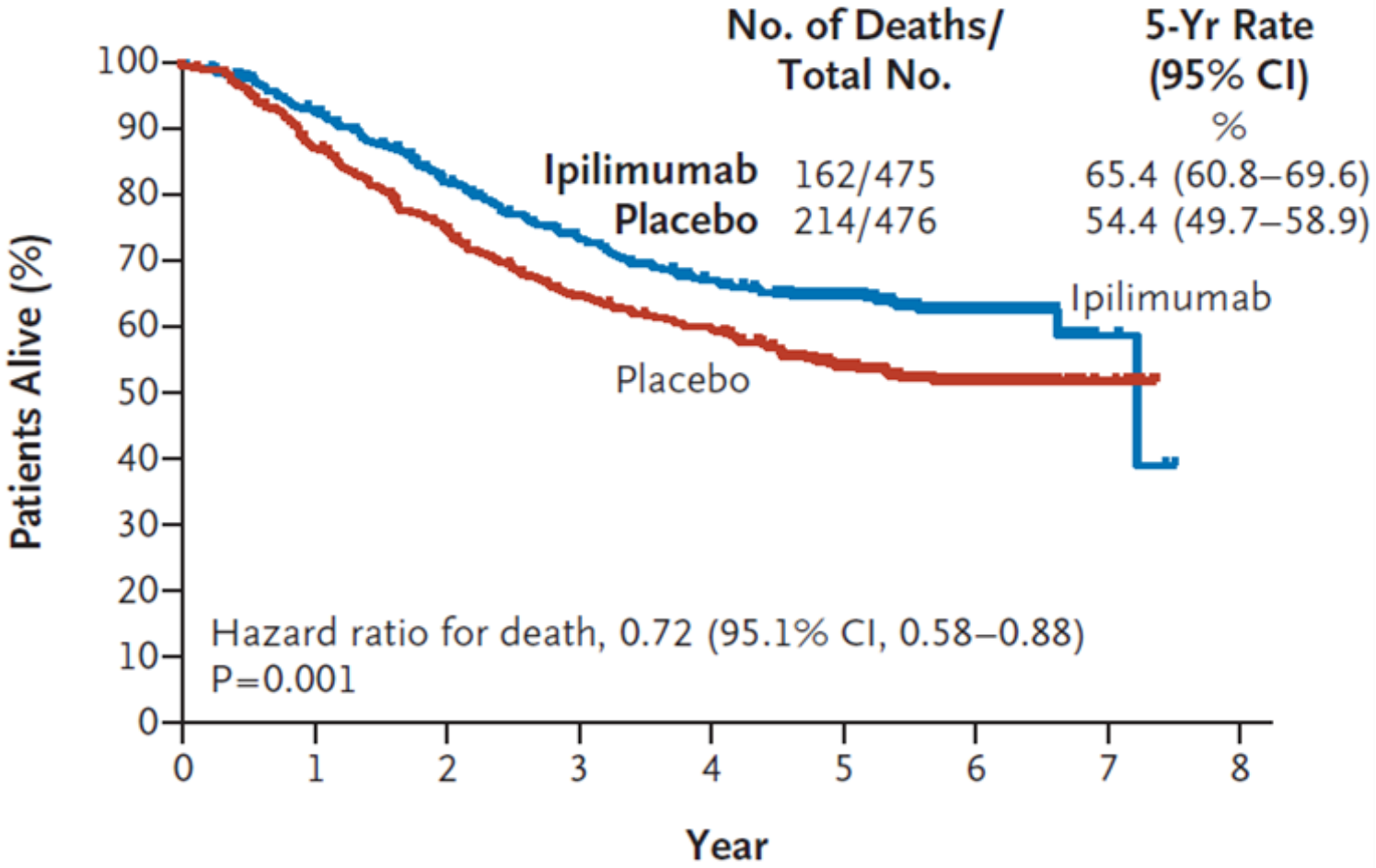
Drug	Indication	Dose
High-dose interferon alfa-2b	Adjuvant – high risk for systemic recurrence	Induction: IV at MTD for 5d/week for 4 weeks Maintenance: SQ 3x/wk for remainder of year
Interleukin-2	Stage IV	IV 3x/day for 5 days, 9 days of rest, 5 days of treatment – significant toxicity
Pegylated Interferon alfa-2b	Adjuvant – microscopic or gross nodal involvement	Induction: SQ high dose for 8 doses Maintenance: SQ low dose for up to 5 yr

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 3 months for up to 3 years



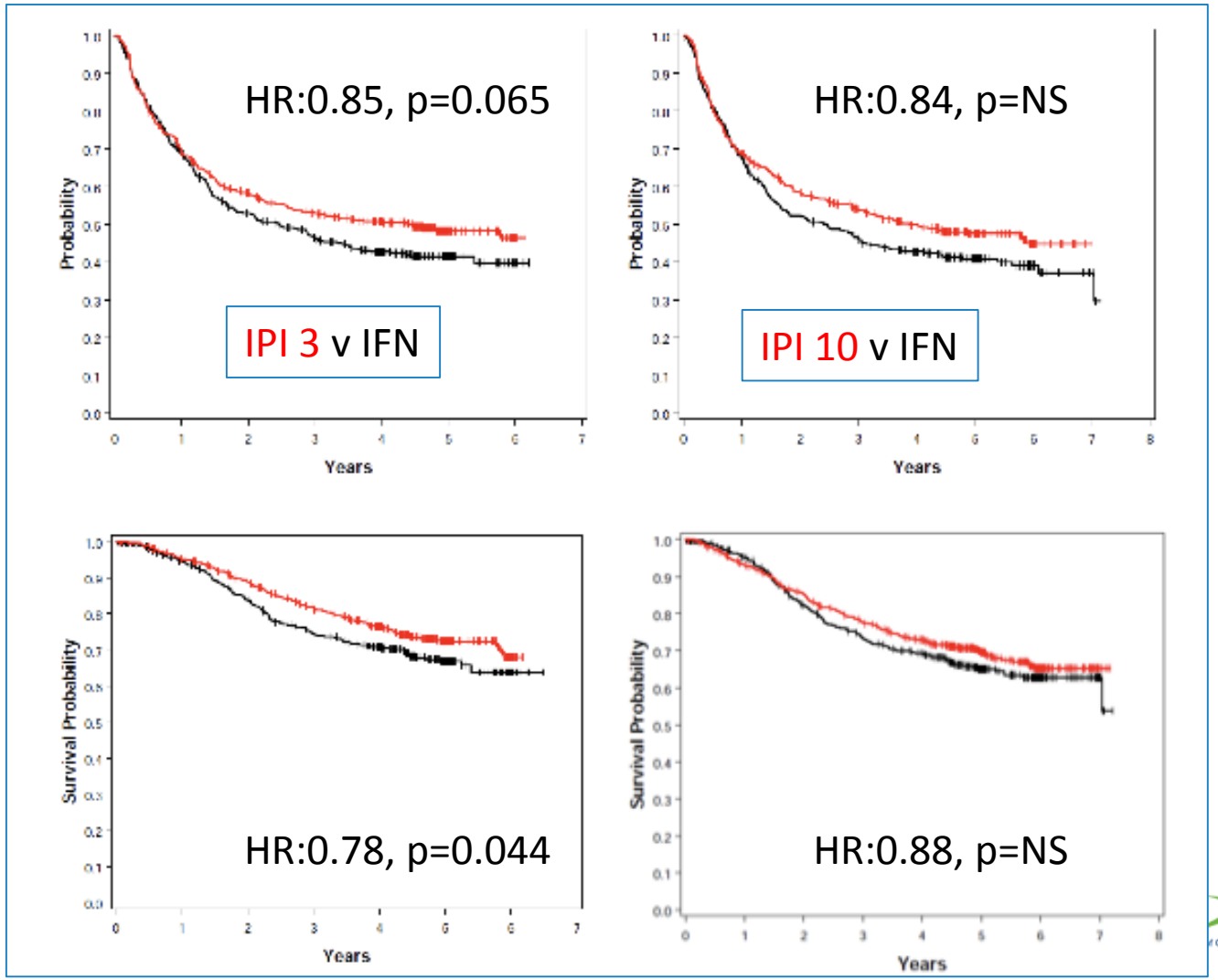
Eggermont, NEJM 2016.

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 3 months for up to 3 years
  - IPI 3 “better than IFN”, IPI 10 “not better than IFN”
  - IPI 3 better tolerated than IPI 10

RFS

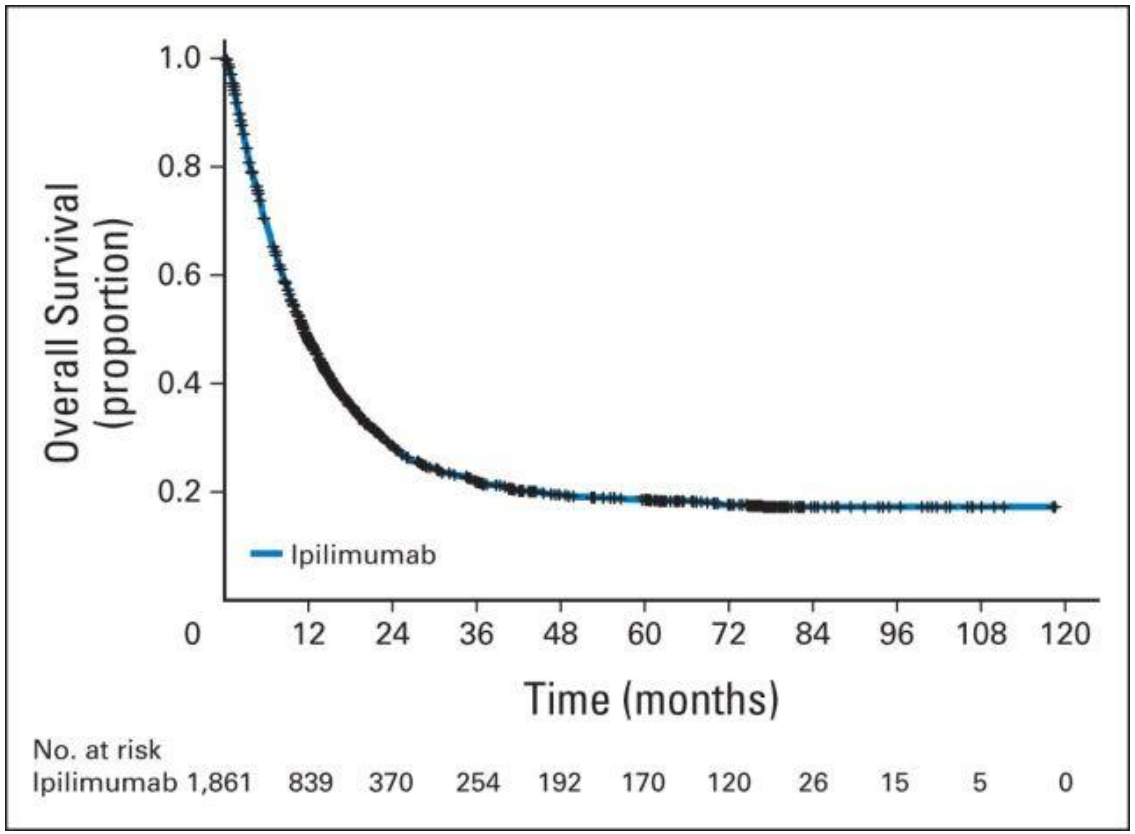
OS



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)



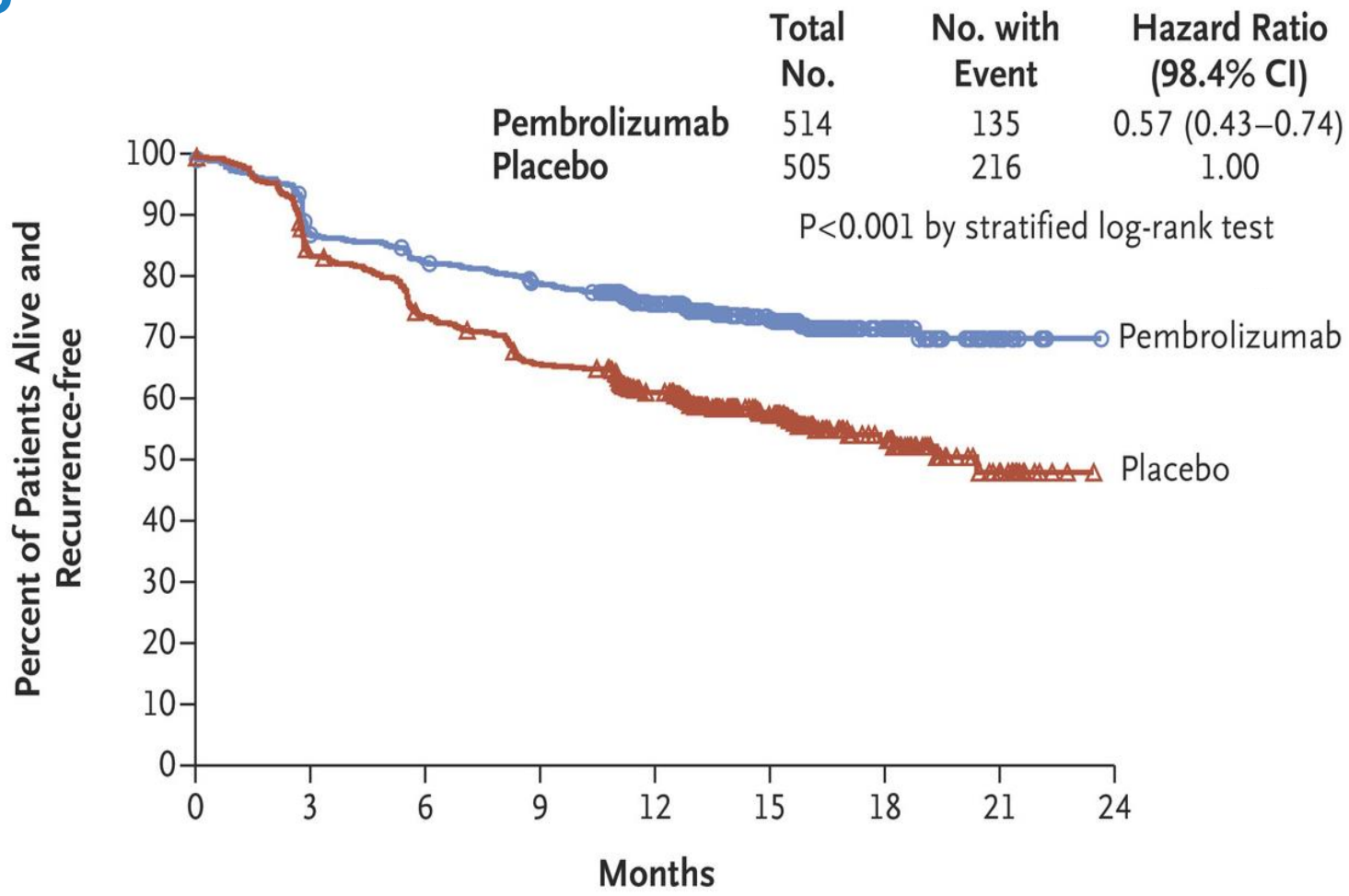
Schadendorf, JCO 2015.

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

Adjuvant Pembrolizumab in High-Risk Stage III Melanoma

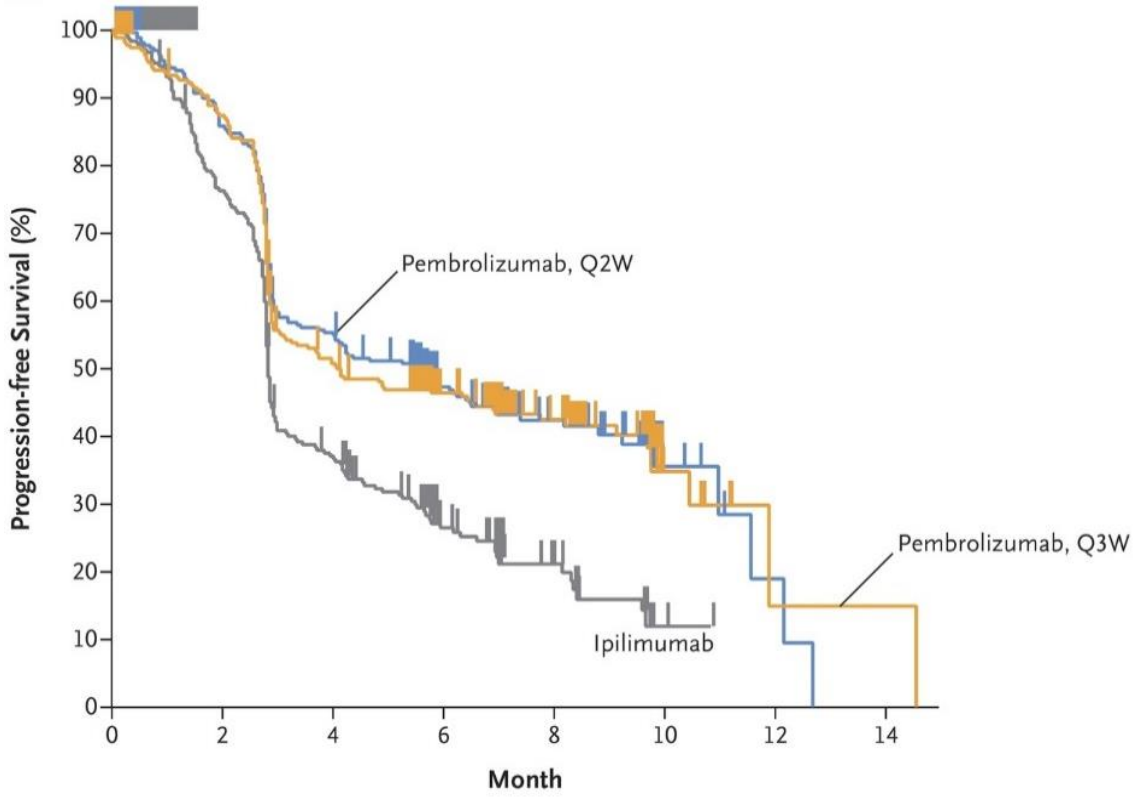
- EORTC 1325/KEYNOTE-054 phase III trial
  - NCT02362594
  - Adjuvant pembrolizumab vs placebo
  - Pembrolizumab 200mg Q3W for up to 1 year (~18 total doses)

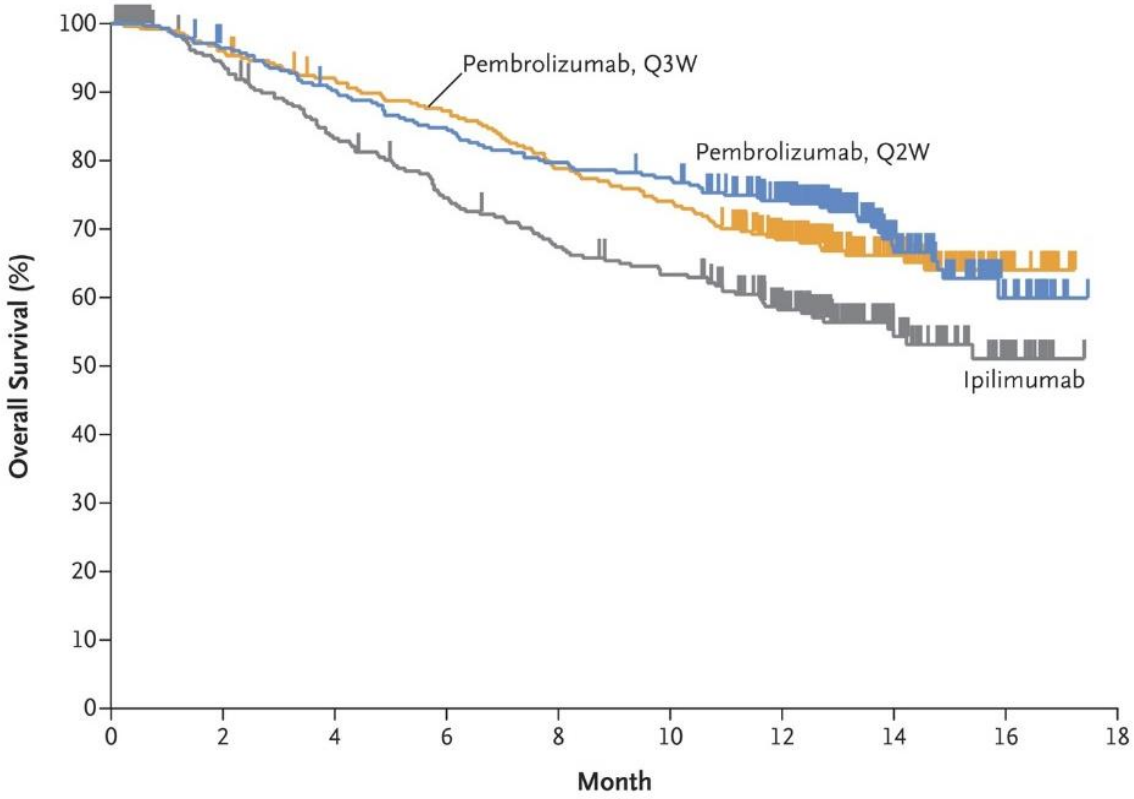


Eggermont, NEJM 2018.

Pembrolizumab in Stage III/IV Melanoma

Phase III KEYNOTE-006 Trial





Robert, NEJM 2015.

Approved checkpoint inhibitors in melanoma

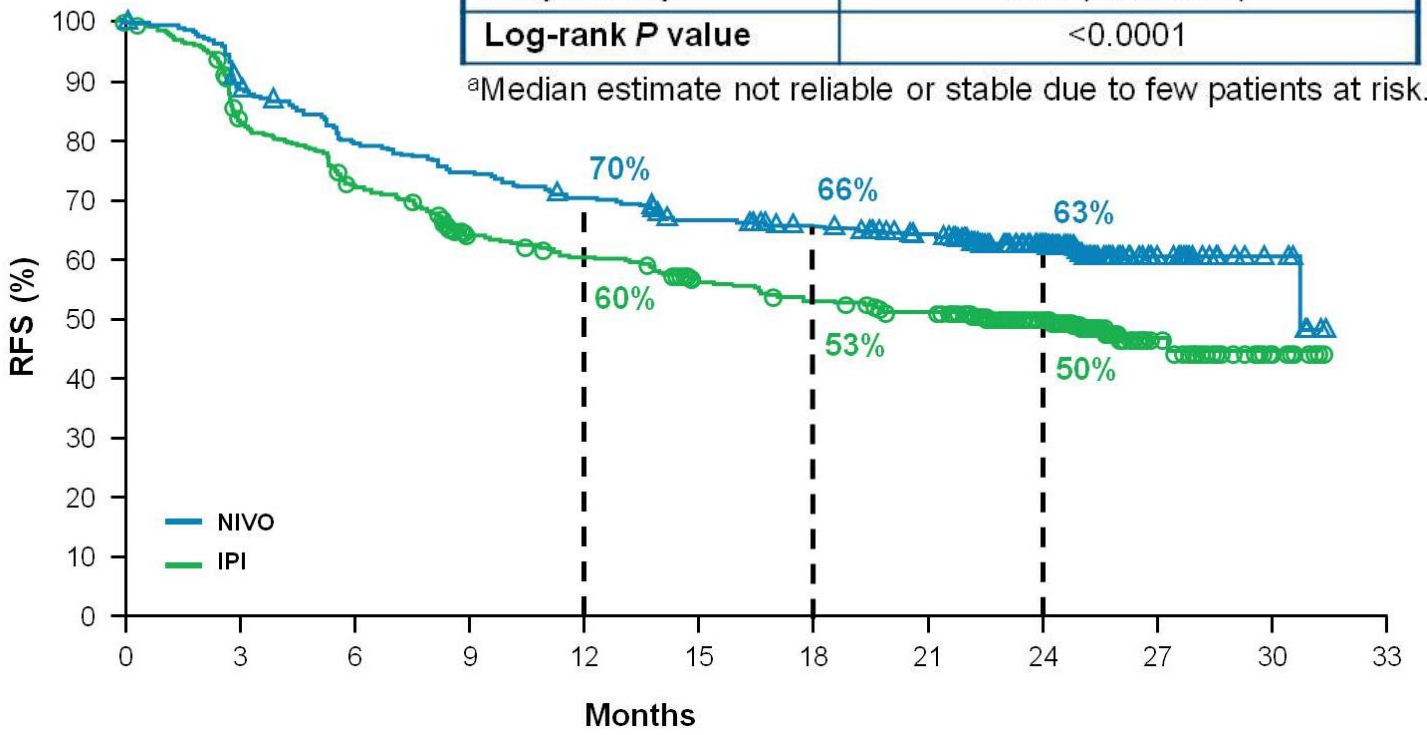
Drug	Approved	Indication	Dose
Nivolumab	2014	Unresectable/metastatic melanoma with progression after other therapy	240 mg Q2W or 480 mg Q4W
	2017	Adjuvant treatment of melanoma after complete resection	240 mg Q2W or 480 mg Q4W

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.



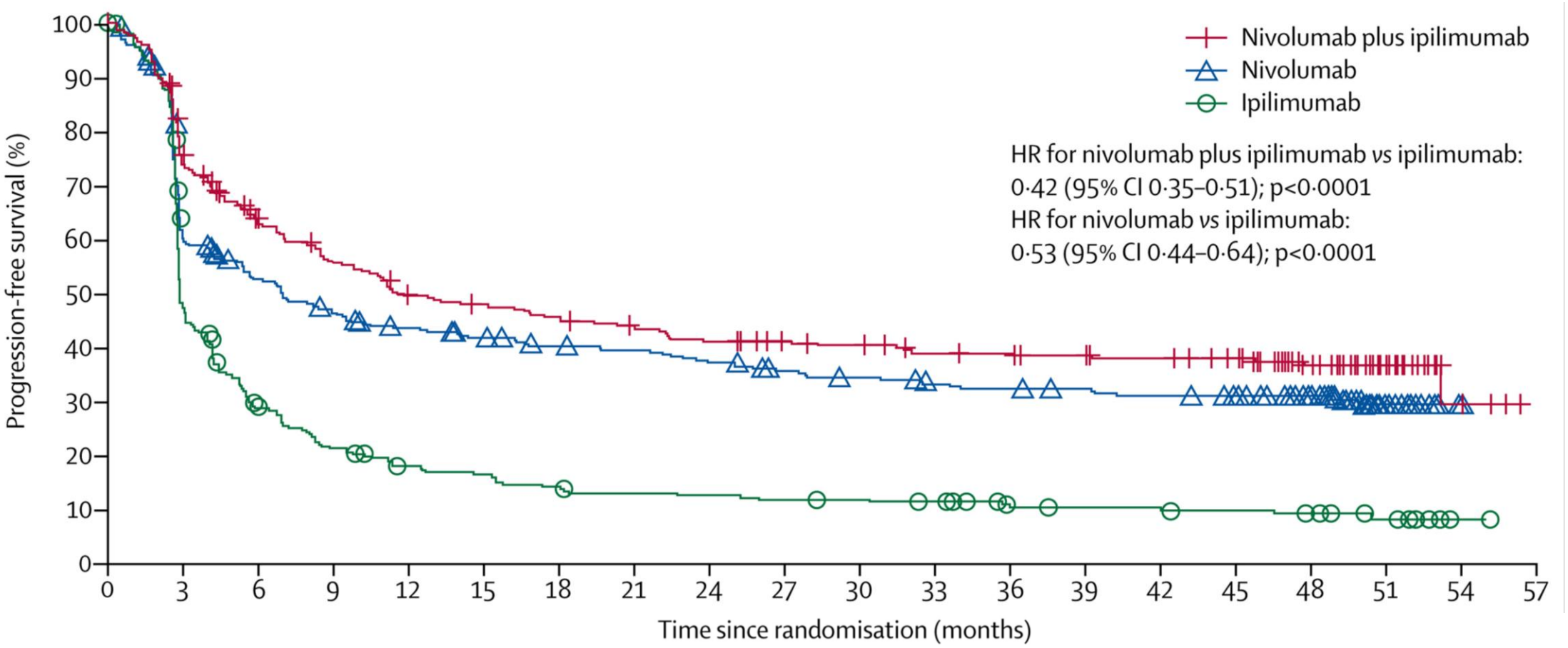
Miller, ASCO 2018.

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

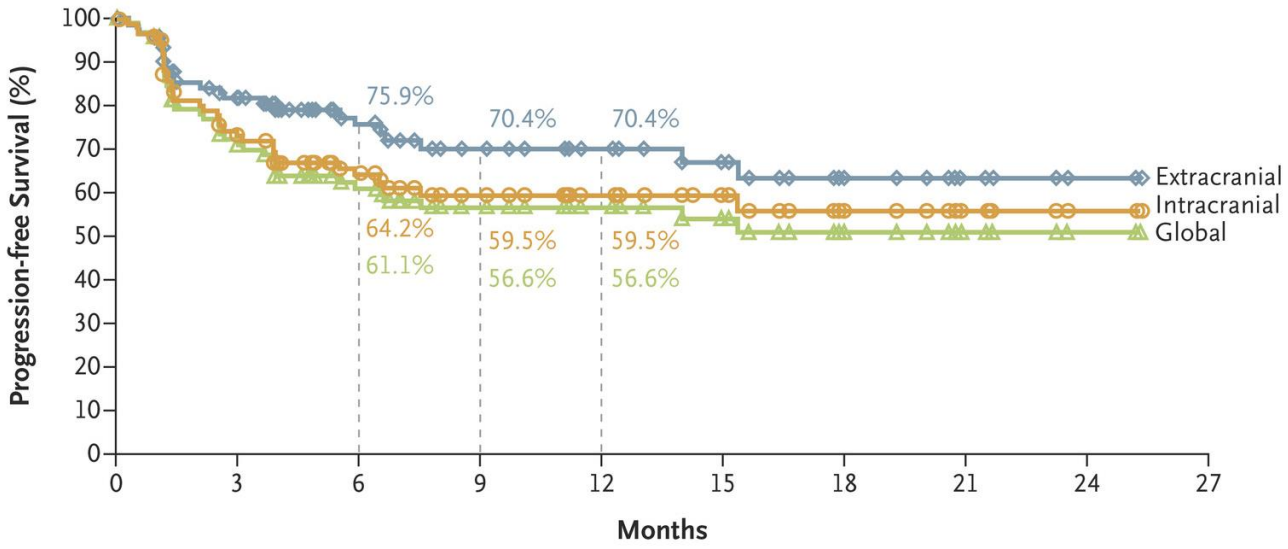
Phase III CheckMate 067 Trial



Hodi, Lancet Oncol 2018.

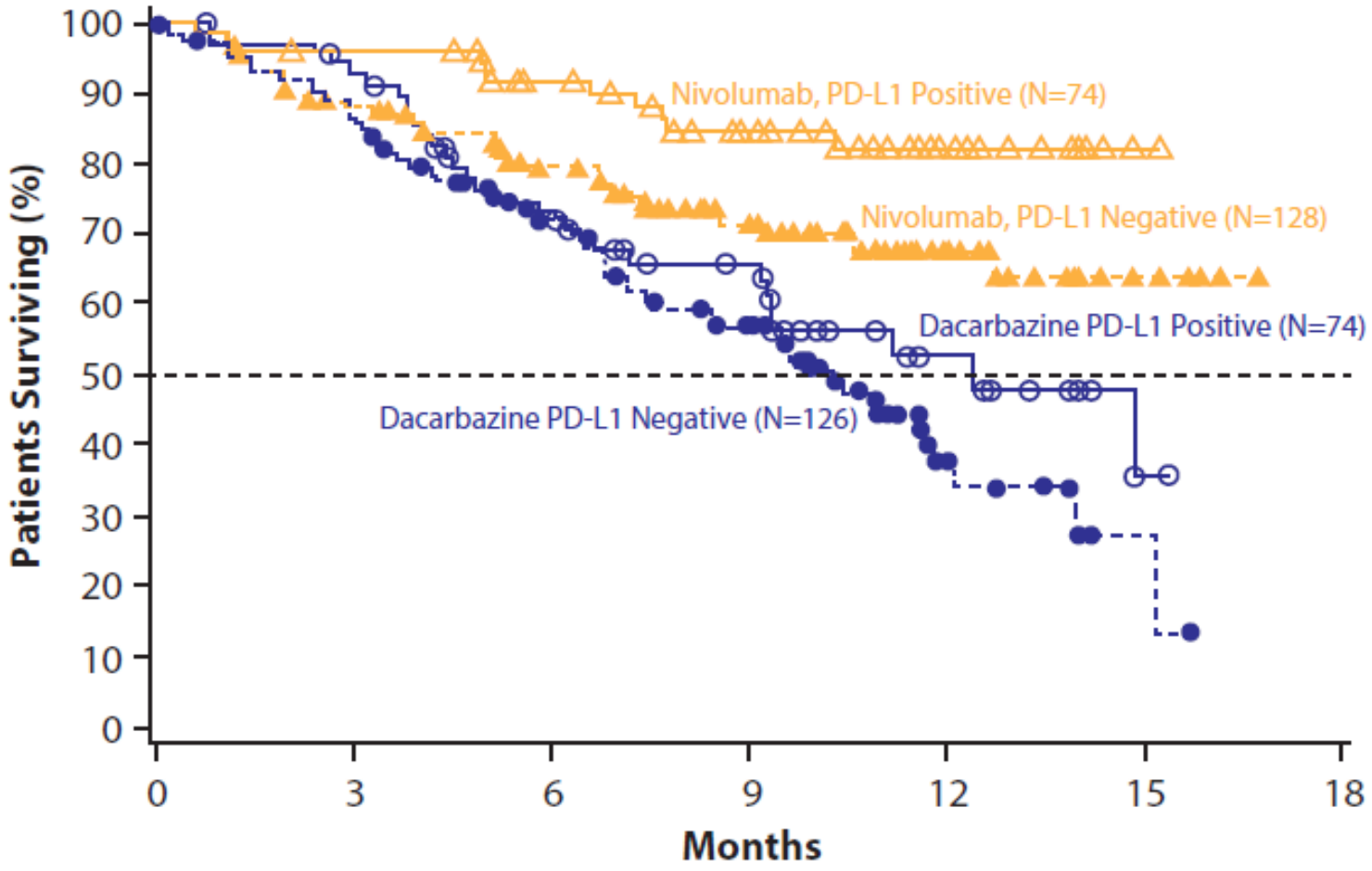
Combination Ipilimumab + Nivolumab for Patients with Asymptomatic Brain Metastases

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.

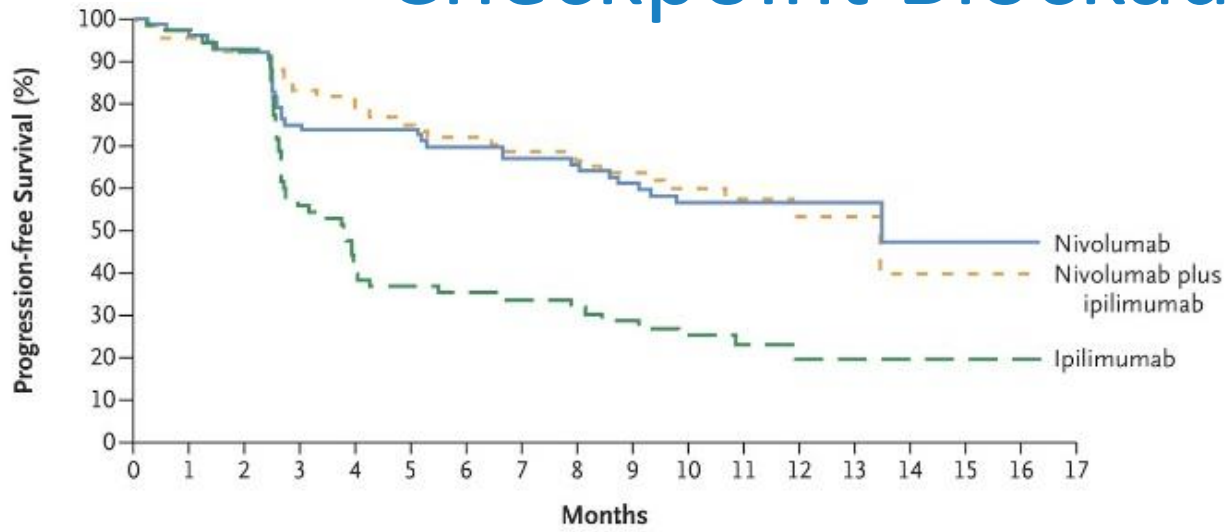
Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy



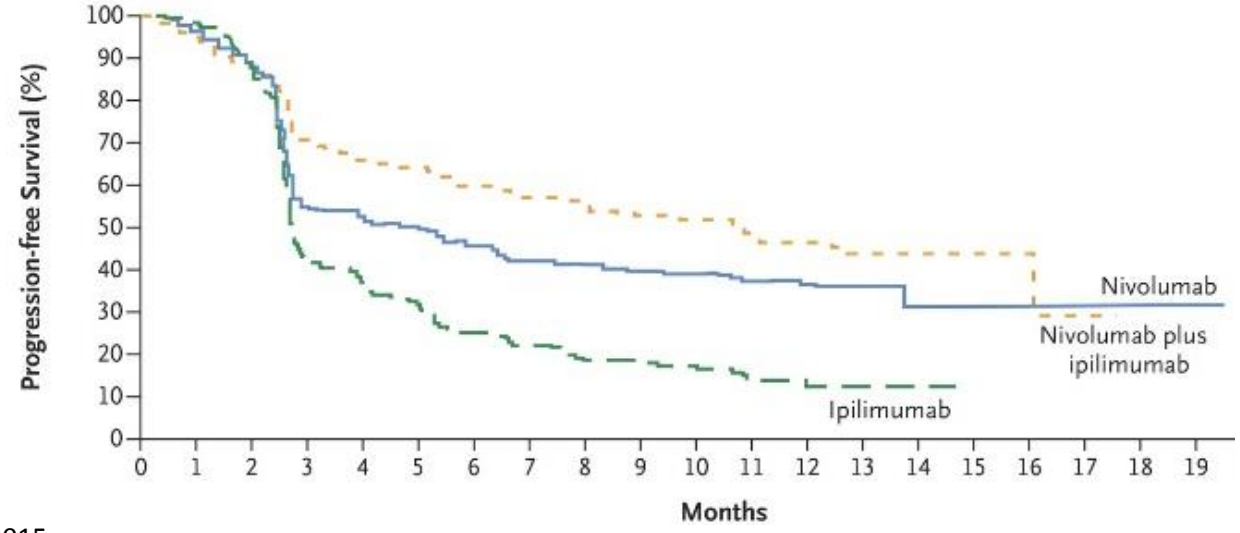
	Patients Who Died *n/N*	Median Survival *mo (95% CI)*
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

Robert, NEJM 2015.

Tumor PD-L1 Status in Combination Checkpoint Blockade and Monotherapy



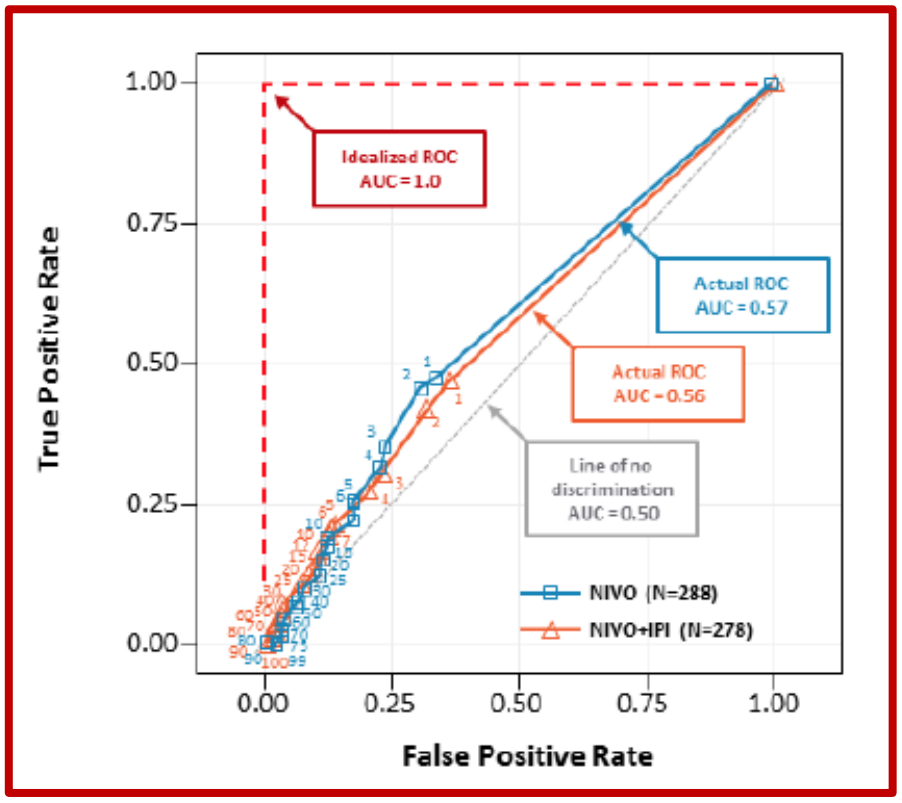
Tumor PD-L1 Positive Patients



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

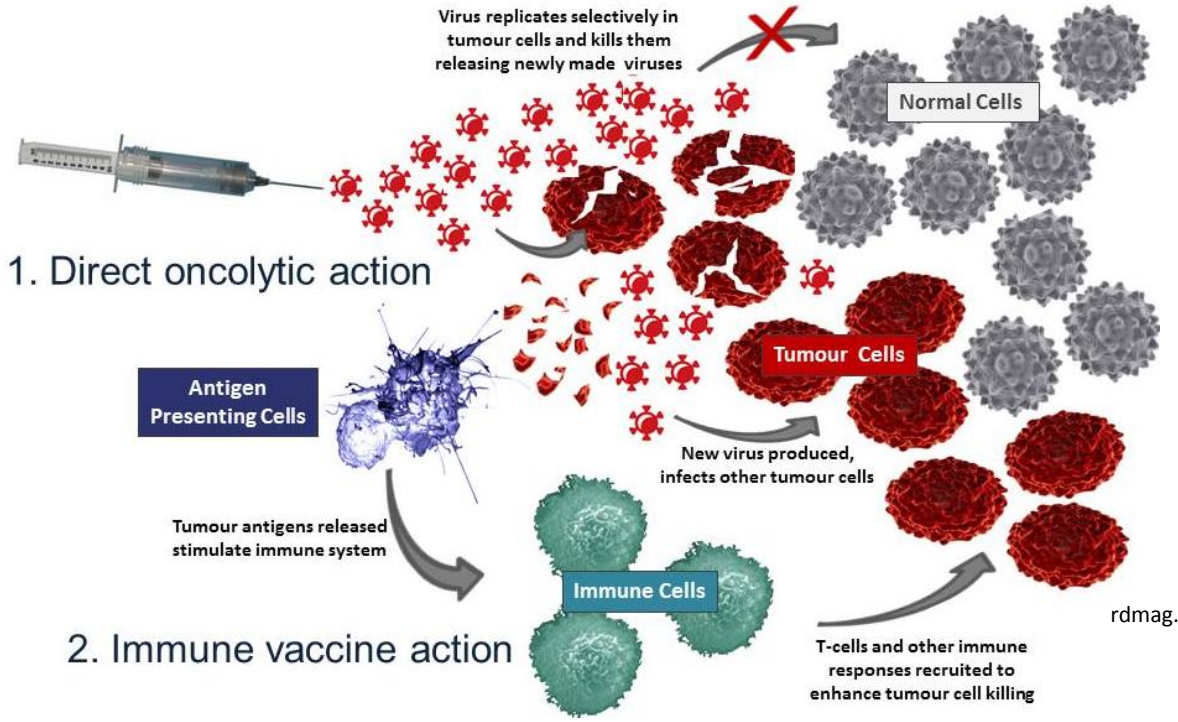
Wolchok, NEJM 2017.

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

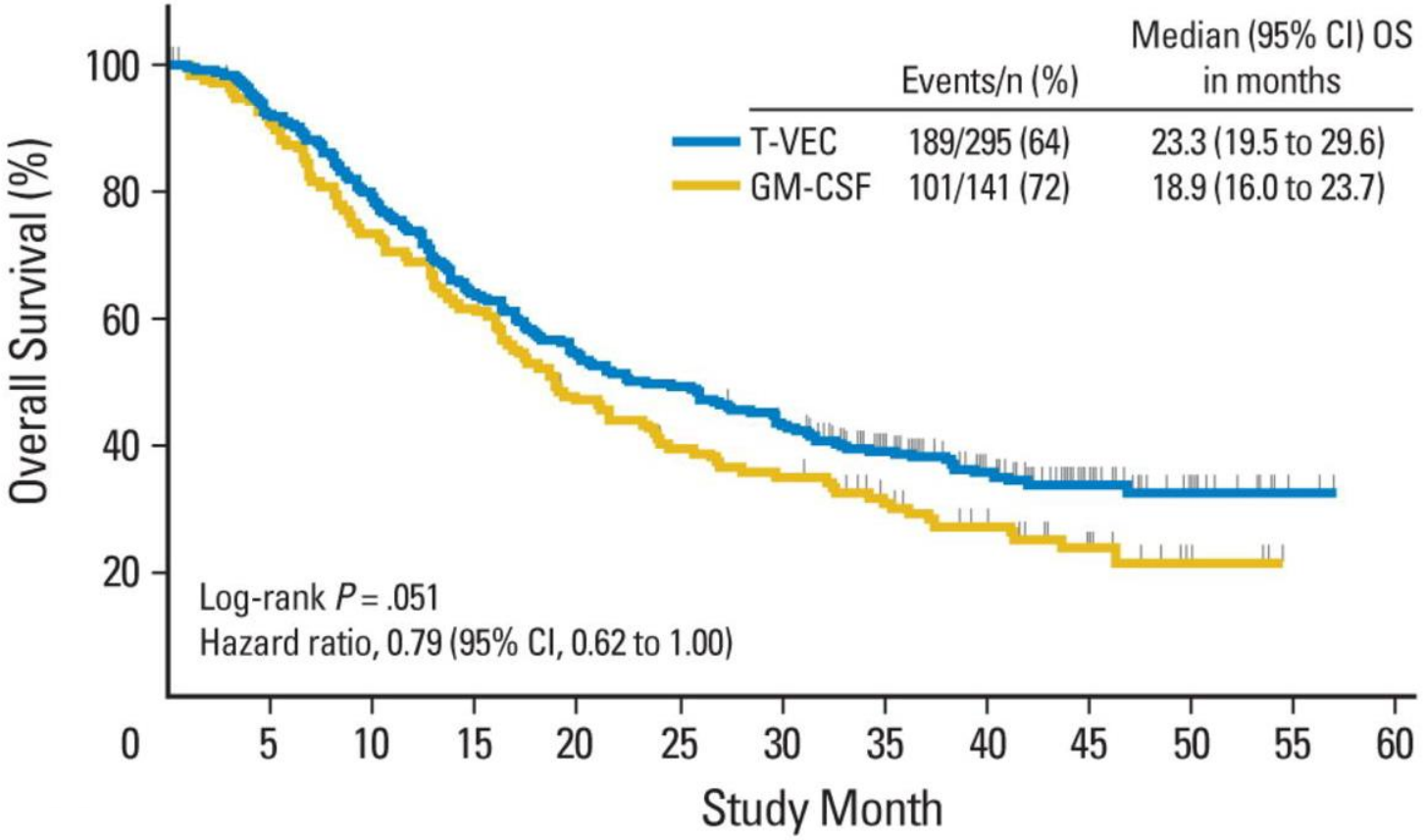


rdmag.com

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



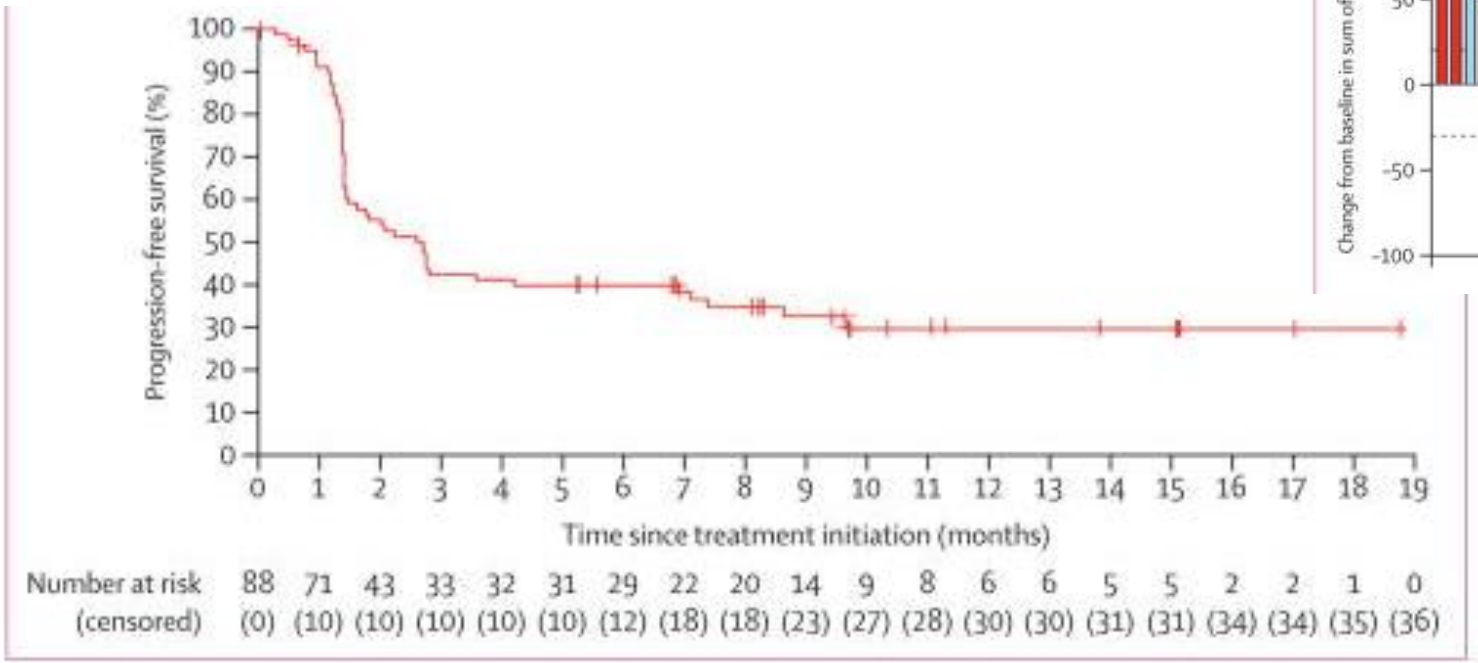
Andtbacka, Kaufman, JCO 2015.

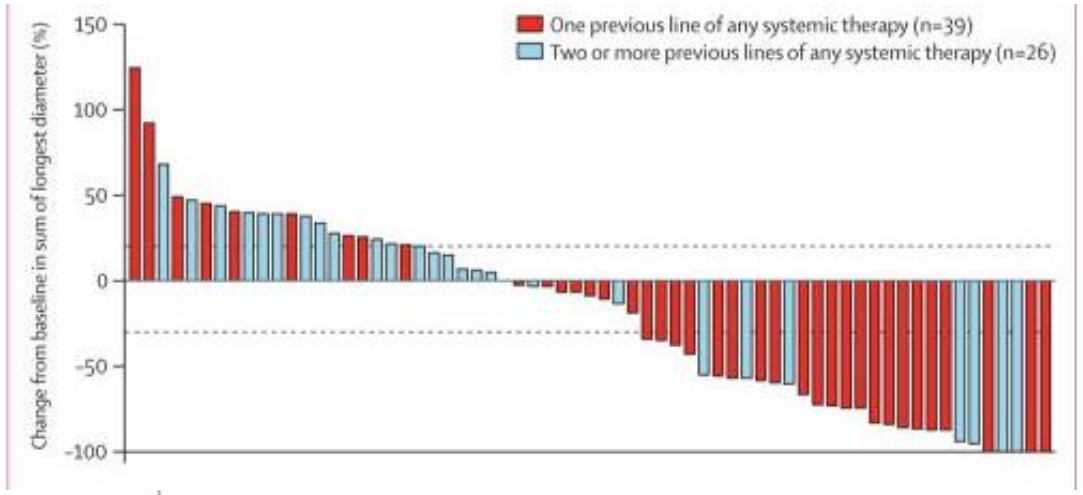
Approved checkpoint inhibitors in other skin cancers

Drug	Approved	Indication	Dose
Avelumab	2017	Patients >12 yr with metastatic **Merkel cell carcinoma**	800 mg Q2W + premedication
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%

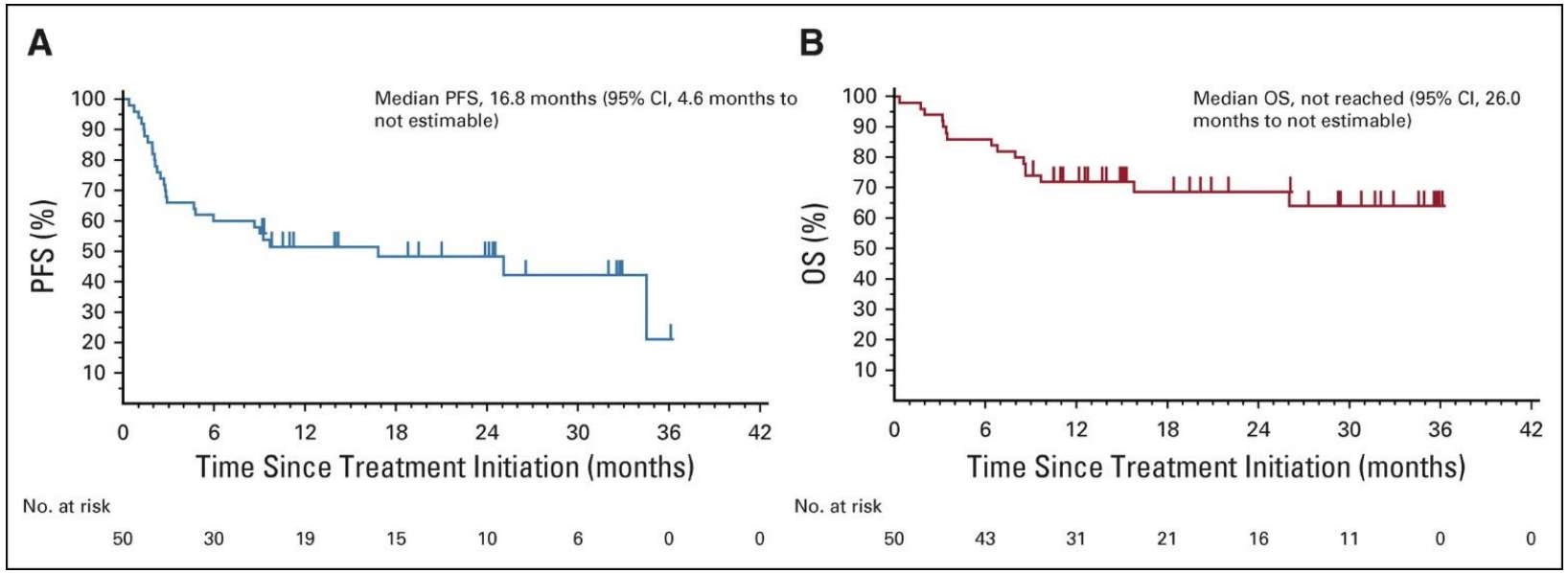




Kaufman, Lancet Oncol 2016.

Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

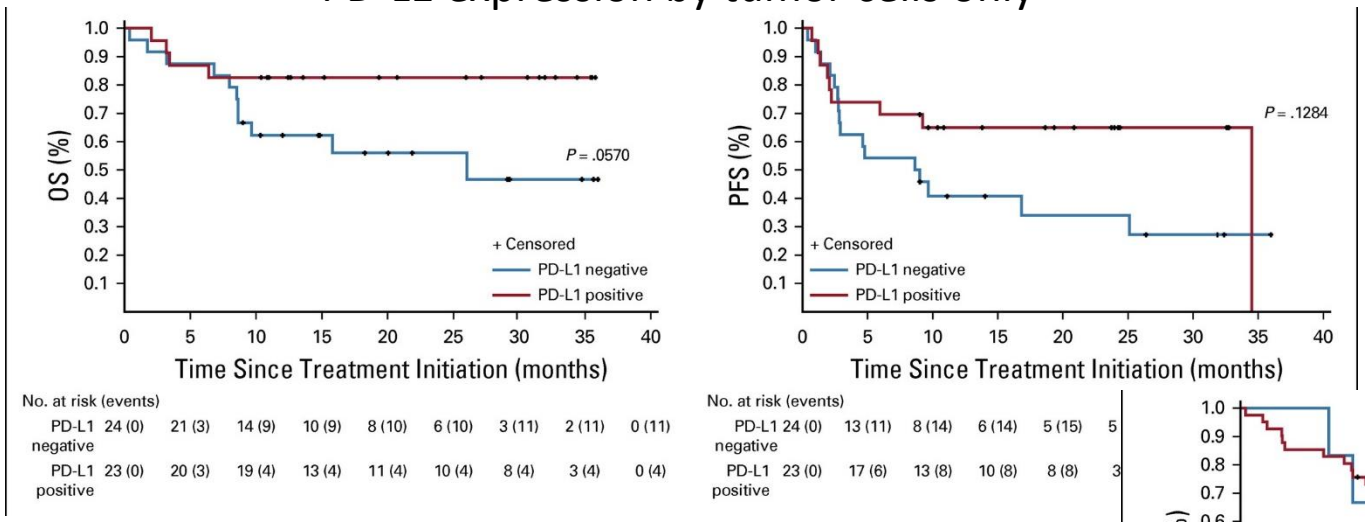
- KEYNOTE-017
- Pembrolizumab 2 mg/kg Q3W up to 2 years
- mPFS: 16.8 months (compared to 90 days for chemo)
- 24-month OS: 68.7%



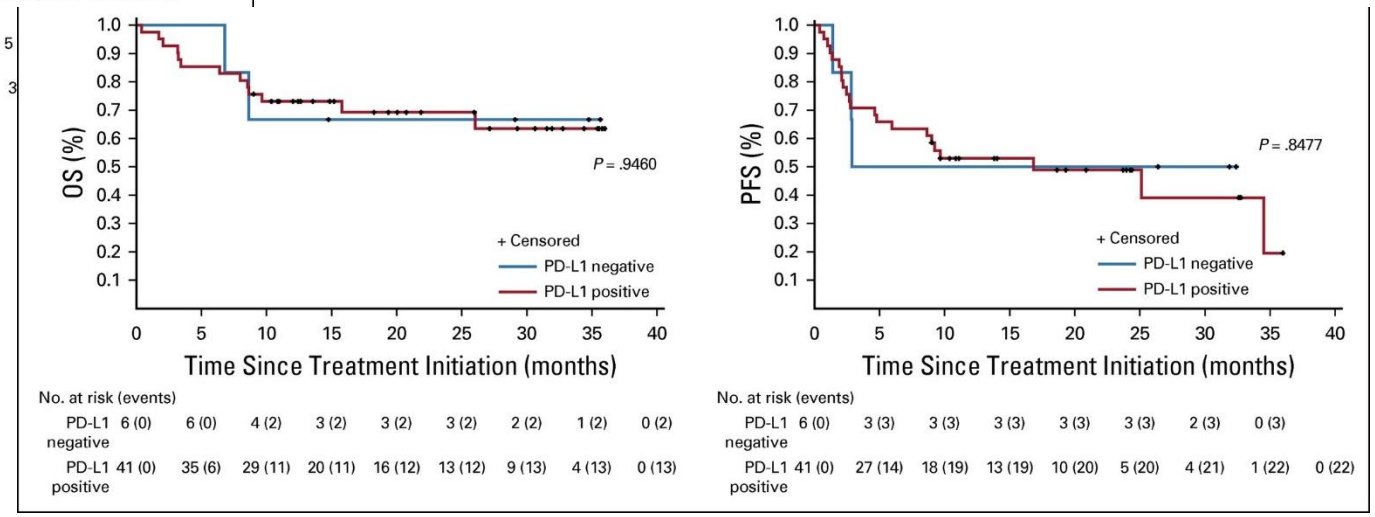
Nghiem, J Clin Oncol 2019.

Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

PD-L1 expression by tumor cells only



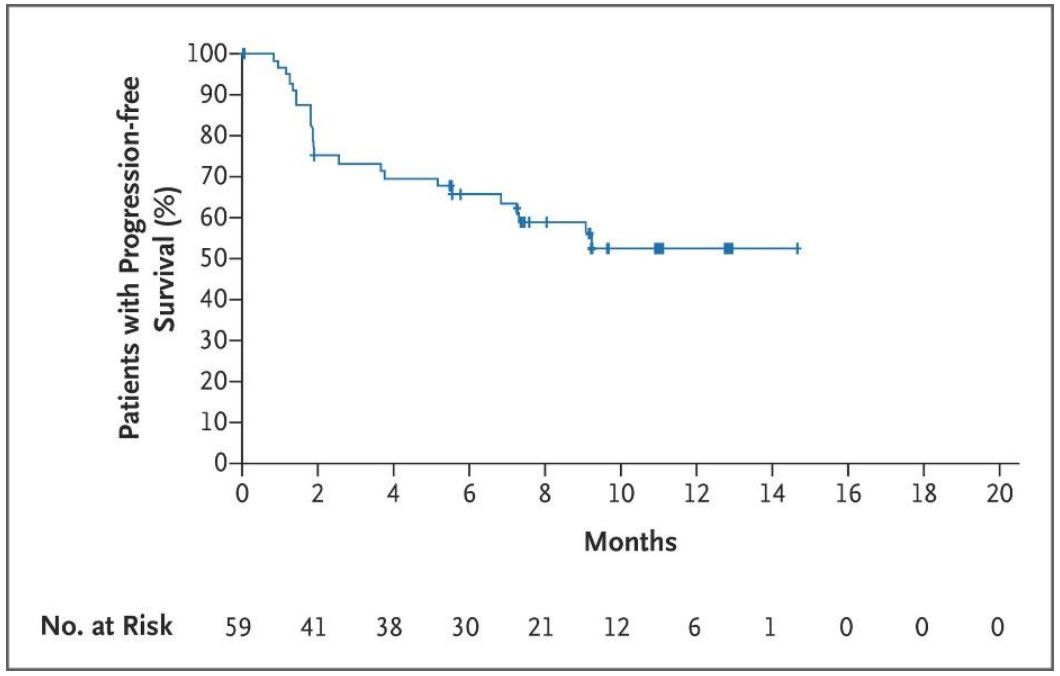
PD-L1 on all cells in tumor

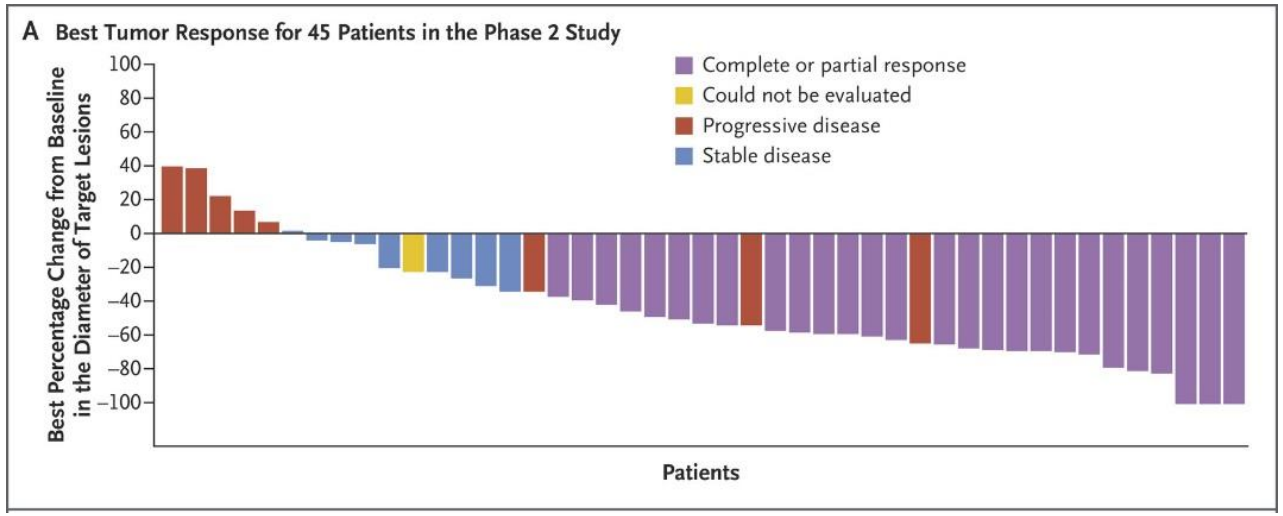


Nghiem, J Clin Oncol 2019.

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

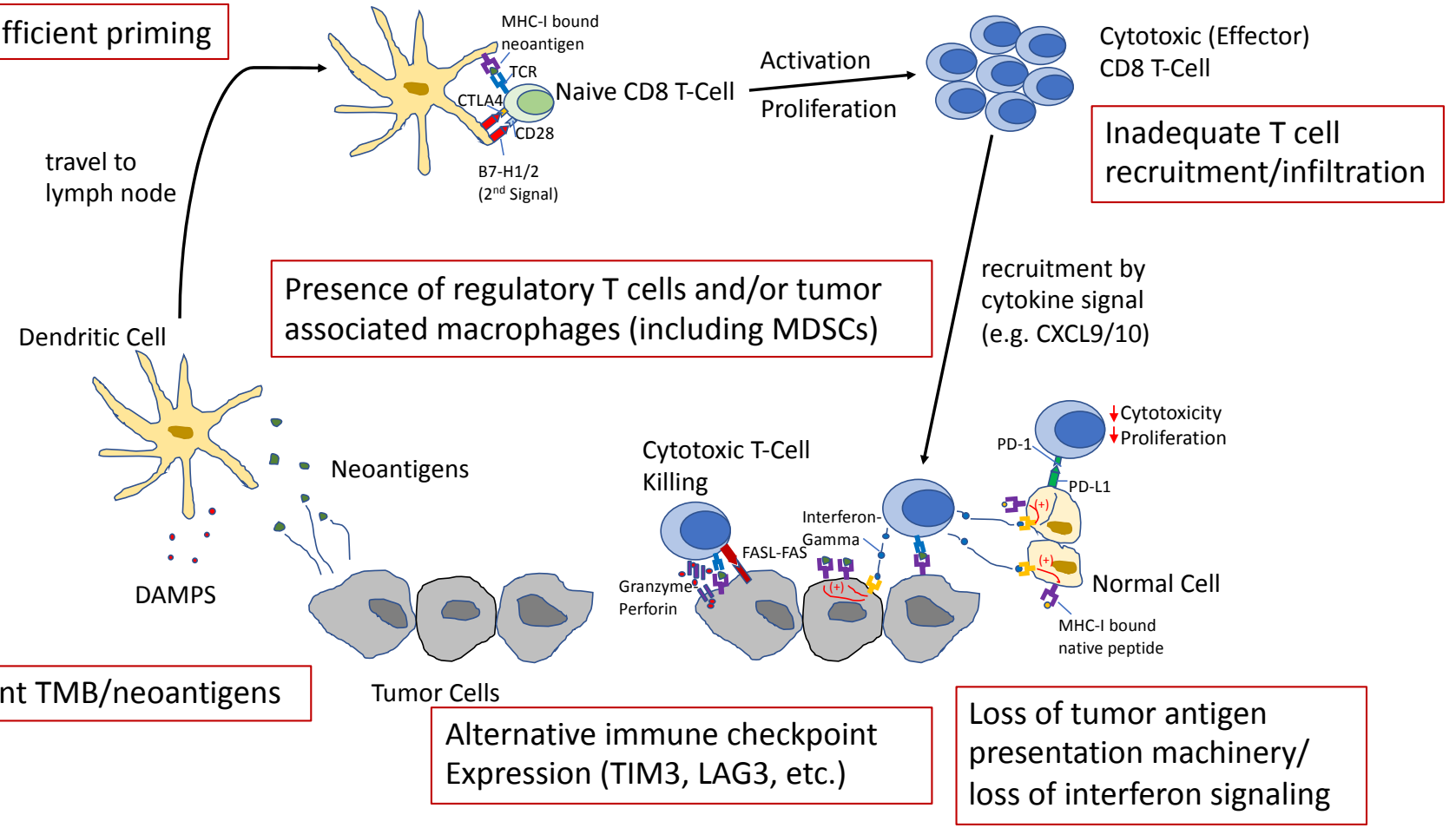




Migden, NEJM 2018.

Developmental Immunotherapeutic Strategies for Melanoma

How does immune checkpoint inhibitor therapy fail?

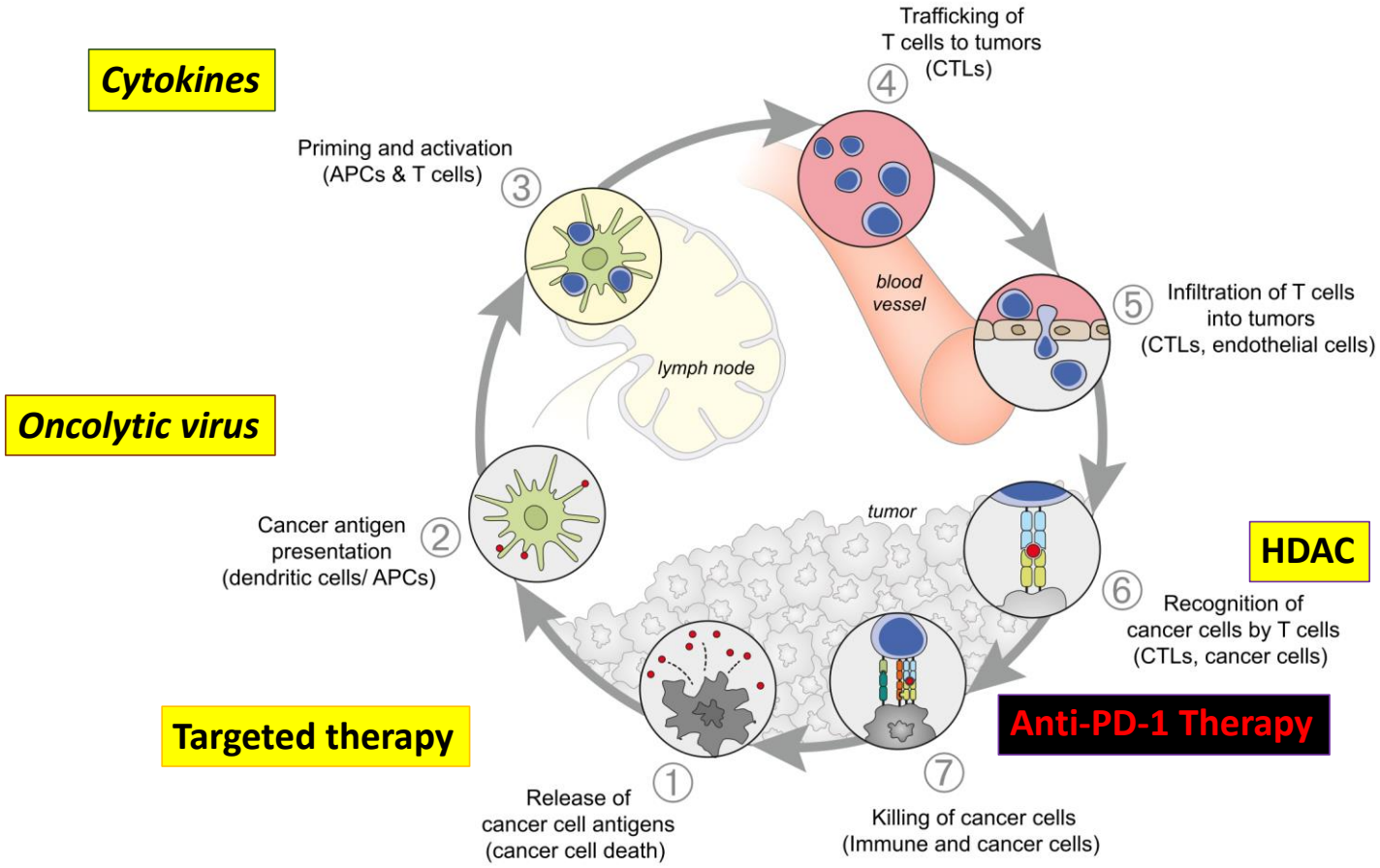


Modified from Liu, Jenkins, Sullivan. Amer J Clin Derm 2018.

Developmental Immunotherapeutic Strategies for Melanoma

How do we overcome resistance?

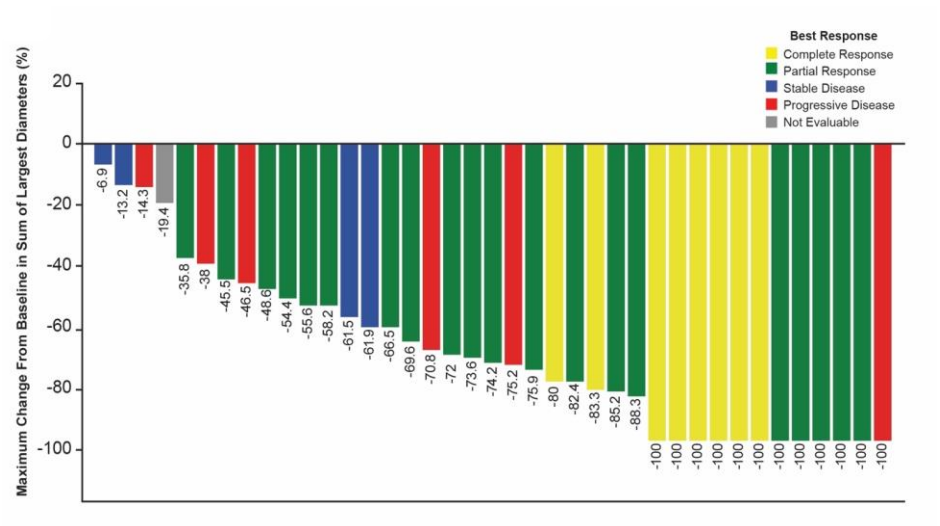
Combination therapy



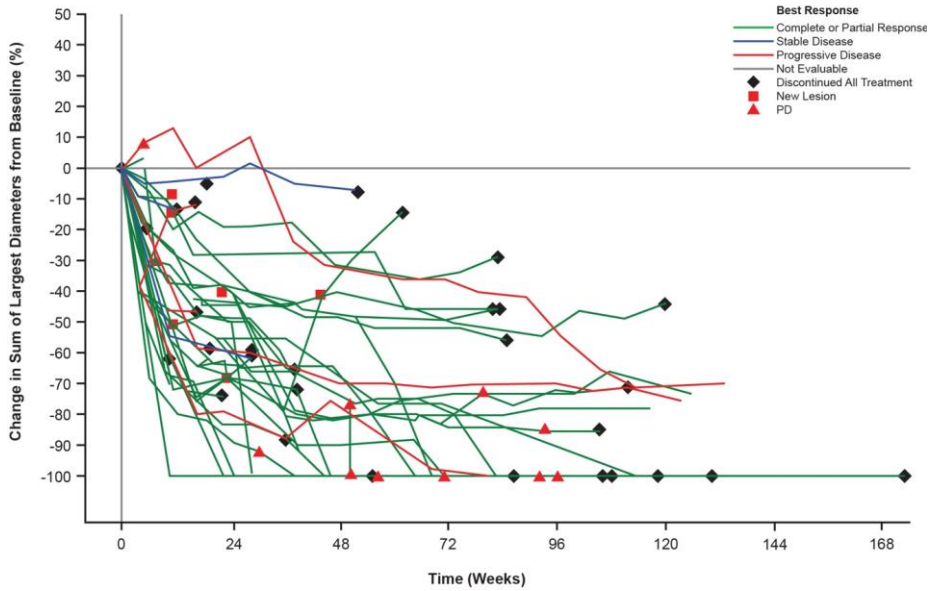
Modified from Chen and Melman. Immunity 2015.

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)

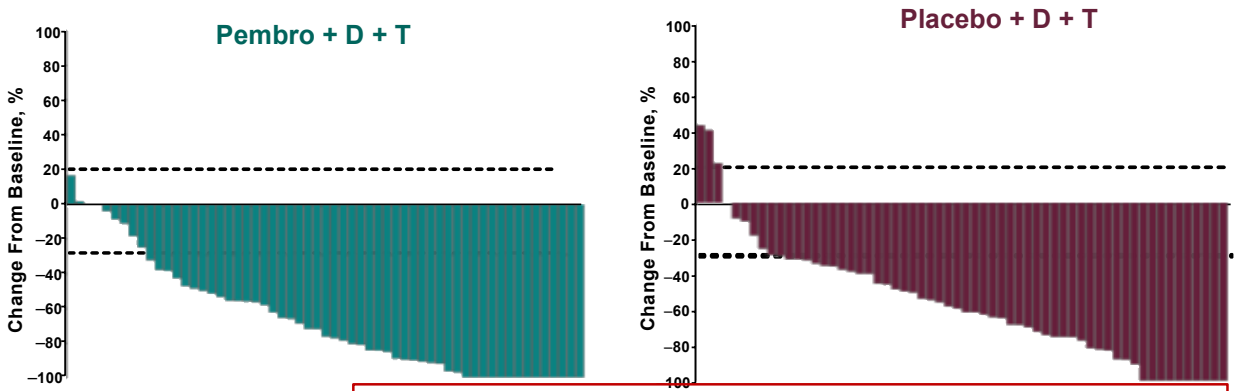
R (1:1)
N = 120

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

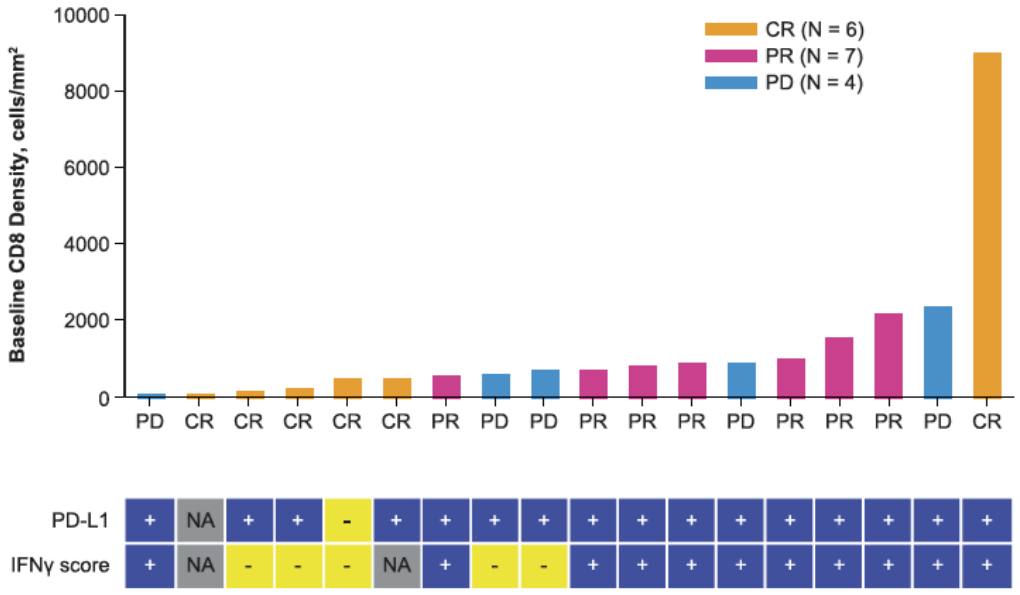
[a]Owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.



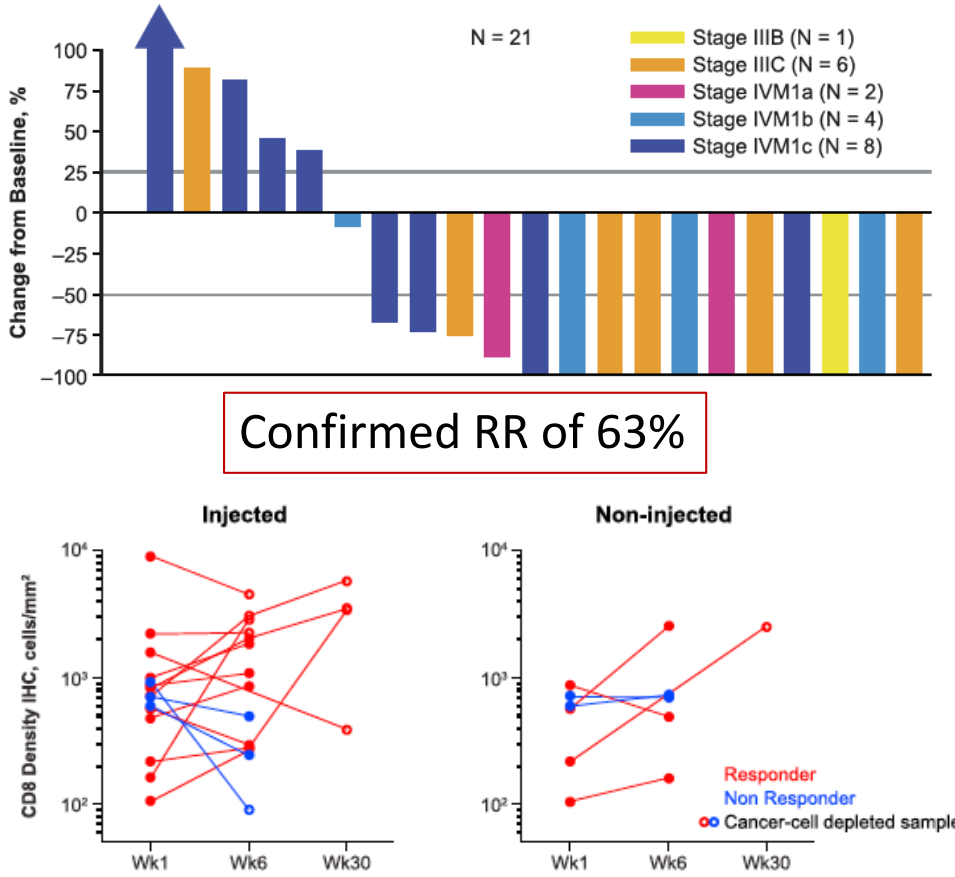
	Pembro + D + T	Placebo + D + T
ORR	63%	72%
CR	18%	13%
≥ 60% red	63%	51%

Ascieto et al, *Nature Med* 2019.

In development: Combined IO with Oncolytic Virus



Phase I: Pembrolizumab + TVEC



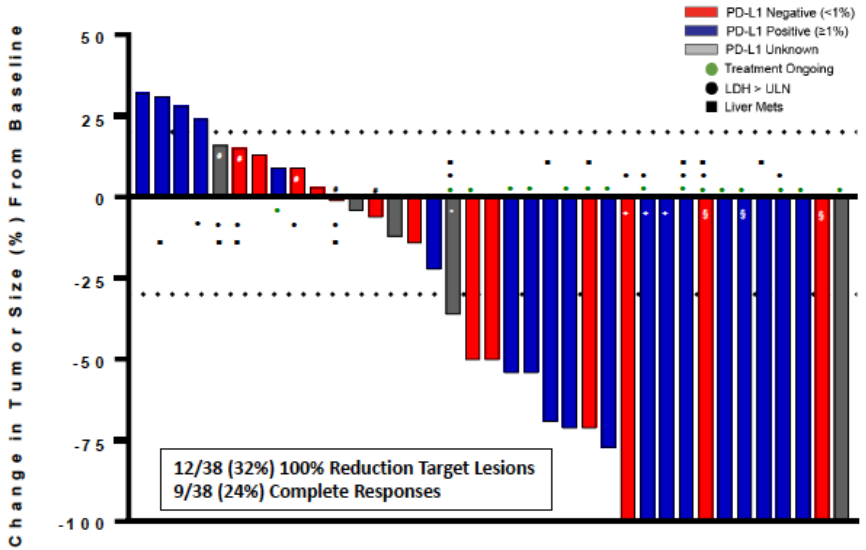
Confirmed RR of 63%

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



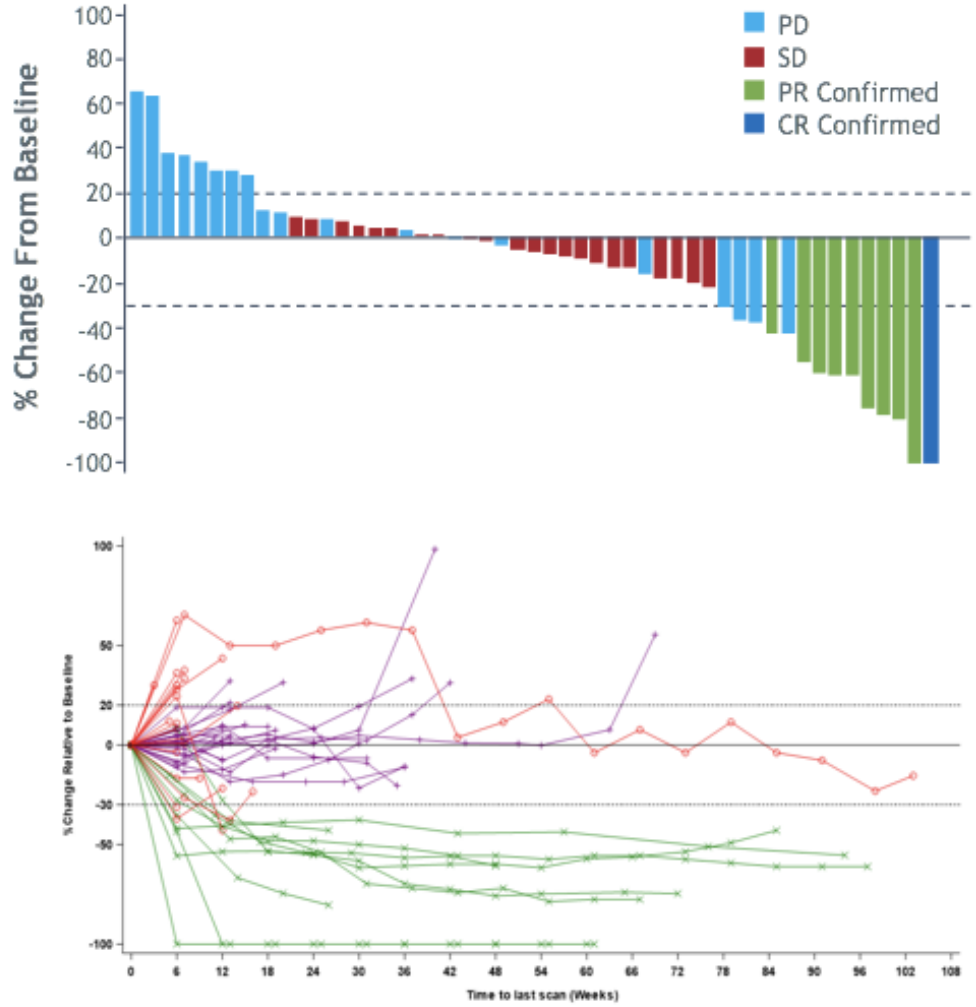
1L Melanoma (n=38 Efficacy Evaluable)	Overall Response Rate
Confirmed ORR (CR+PR)	20 (53%)
CR	9 (24%)
DCR (CR+PR+SD)	29 (76%)
PD-L1 negative (n=14)	6 (43%)
PD-L1 positive (n=19)	13 (68%)
PD-L1 unknown (n=5)	1 (20%)
LDH > ULN (n=11)	5 (45%)
Liver metastases (n=10)	5 (50%)

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.

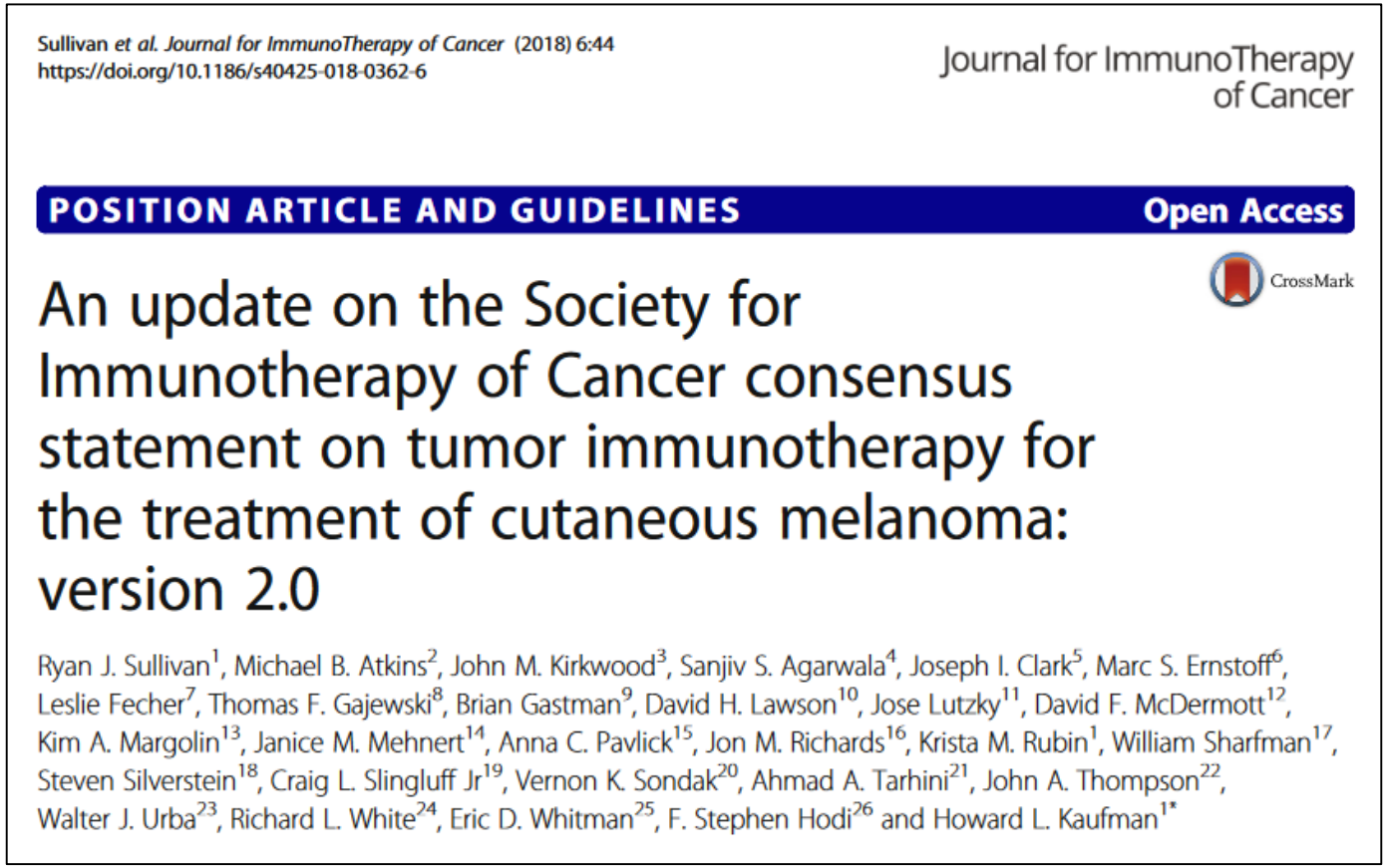
In development: Combined IO with HDAC inhibitor

- 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.

Additional Resources



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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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Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

Case Studies

Case Study 1: Adjuvant

- A 53 year old male presents with a growing pruritic pigmented lesion on his back. No palpable lymph nodes are apparent on physical exam.
- Shave biopsy reveals a superficial spreading melanoma with a Breslow depth of 2.5mm which is ulcerated.
- Wide local excision shows no evidence of melanoma, and sentinel lymph node biopsy is reported with 1 out of 2 lymph nodes containing a micrometastatic deposit of melanoma measuring 1.5mm.
- BRAF IHC staining for the V600E mutation is negative.
- PET CT and MRI brain show no evidence of distant metastatic disease.

Case Study 1: Q1

Q1. Which immunotherapy agents are approved for the adjuvant therapy of resected melanoma?

A. Interferon Alpha

B. Ipilimumab

C. Nivolumab

D. Pembrolizumab

E. All of the above

Case Study 1: A1

Q1. Which immunotherapy agents are approved for the adjuvant therapy of resected melanoma?

A. Interferon Alpha – approved in 1995

B. Ipilimumab – approved at 10mg/kg dose in 2015 although newer data support 3mg/kg

C. Nivolumab – approved in 2017

D. Pembrolizumab – approved in 2018

E. All of the above

Case Study 1: Q1

Q1. Which immunotherapy agents are approved for the adjuvant therapy of resected melanoma?

A. Interferon Alpha

B. Ipilimumab

C. Nivolumab

D. Pembrolizumab

E. All of the above

Case Study 2: Metastatic

- After being presented with adjuvant options, this patient opted for surveillance with routine imaging.
- Eighteen months later, surveillance imaging shows a 3cm lesion in the right lobe of the liver.
- Pathologic review of a CT guided biopsy sample reveals metastatic melanoma.
- MRI of the brain shows a T1 hyperenhancing lesion in the right parietal lobe.
- He is completely asymptomatic.

Case Study 2: Q1

Q1. Which immunotherapy agents are approved for the systemic treatment of metastatic/unresectable melanoma?

A. Interferon Alpha

B. Ipilimumab

C. Talimogene Laherparepvec

D. B and C

E. A, B, and C

Case Study 2: Q1

Q1. Which immunotherapy agents are approved for the systemic treatment of metastatic/unresectable melanoma?

A. Interferon Alpha – approved for adjuvant only

B. Ipilimumab – approved in 2011

C. Talimogene Laherparepvec – approved in 2016

D. B and C

E. A, B, and C

- Approved therapeutic immunotherapy options for metastatic melanoma in the first line setting include ipilimumab/nivolumab, single agent nivolumab or pembrolizumab, and in appropriate settings, talimogene laherparepvec or single agent ipilimumab

Case Study 2: Q2

Q2. Is PD-L1 status necessary to obtain prior to starting immunotherapy for melanoma?

A. Yes

B. No

C. Not sure

Case Study 2: Q2

Q2. Is PD-L1 status necessary to obtain prior to starting immunotherapy for melanoma?

A. Yes

B. **No**

C. Not sure

- None of the FDA approvals for immunotherapy, whether for the adjuvant or metastatic setting, require PD-L1 status