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

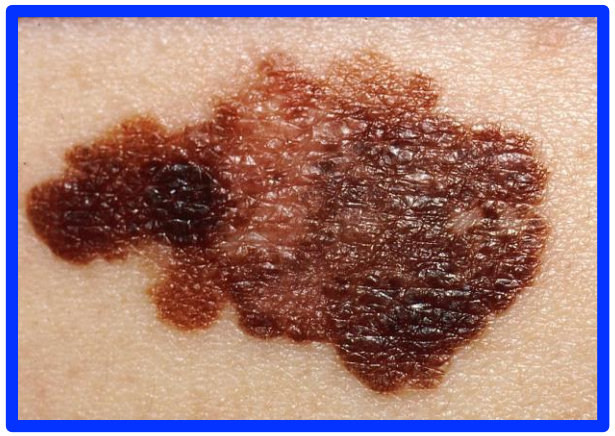
sitc Society for Immunotherapy of Cancer

Disclosures

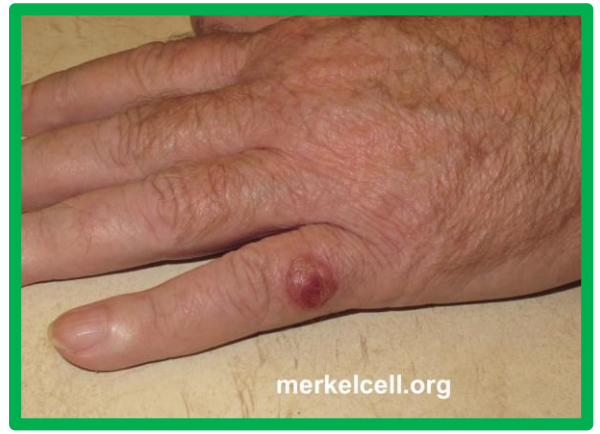
- No disclosures
- I will be discussing non-FDA approved indications during my presentation.

Differentiating skin cancers

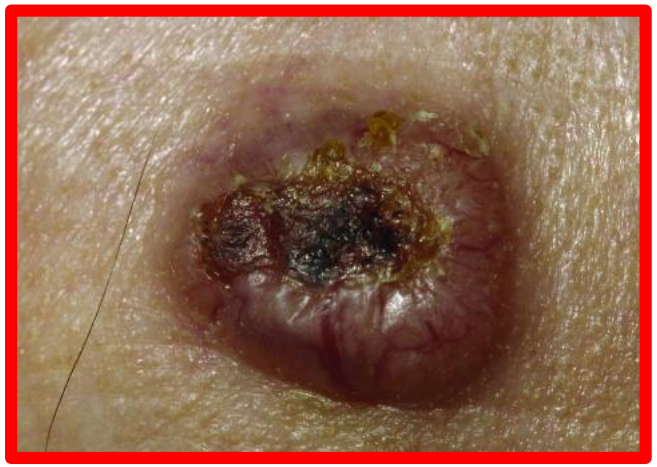
- **Basal Cell Carcinoma/Squamous cell**
  - Common cancers
  - UV exposure dominant risk factor
- **Merkel Cell**
  - 3 per 1,000,000 people
- **Melanoma**
  - 5% of skin cancers
  - 2017: ~90,000 new cases, 10,000 deaths
  - Local: 90% 5/y survival
  - Metastatic: 20% 5y survival
    - **Chemotherapy/targeted therapy**
    - **Clinical trial**



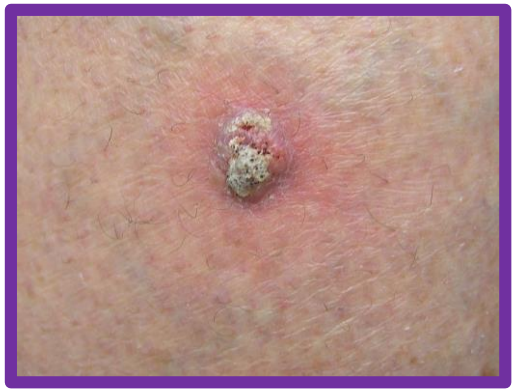
Melanoma



Merkel cell carcinoma



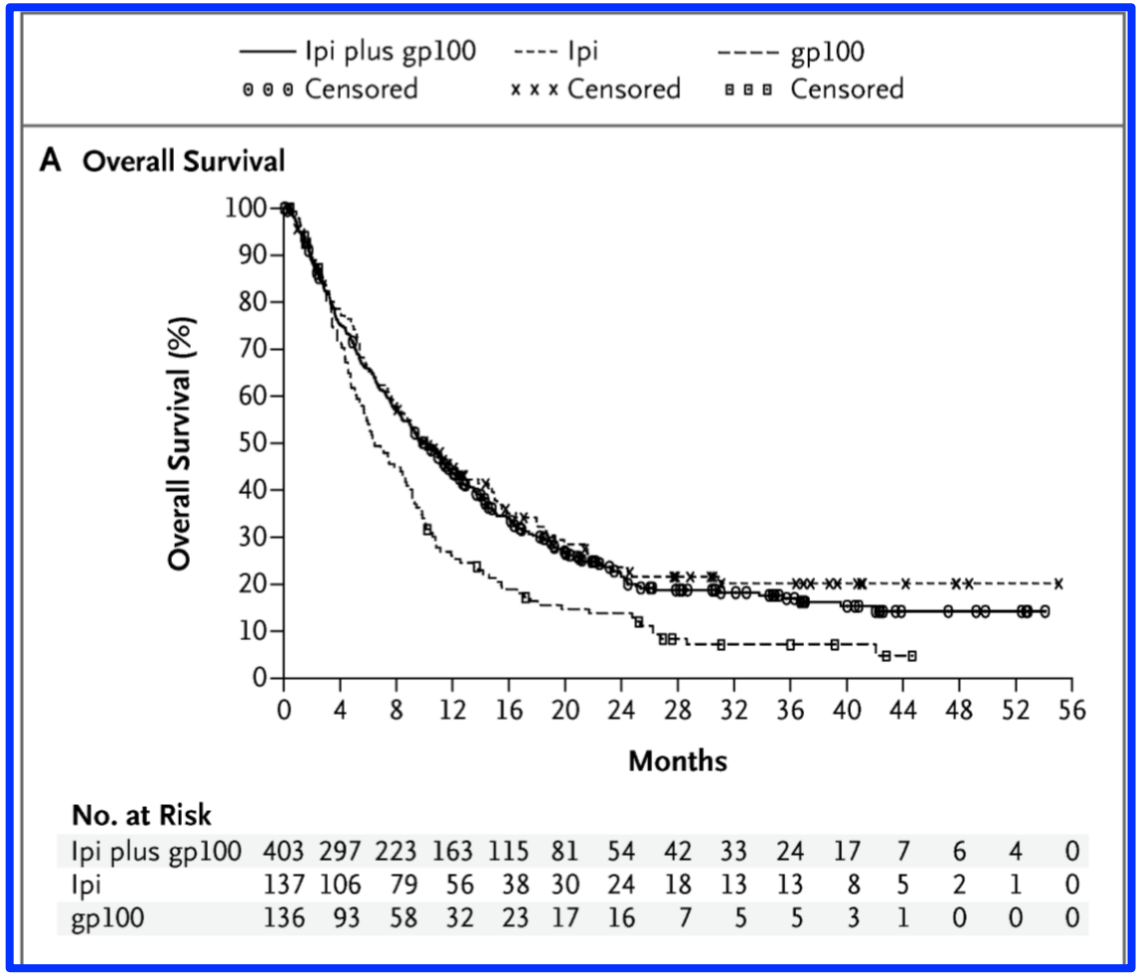
Basal cell carcinoma



Squamous cell carcinoma

MerkelCell.org/clinicalphotos
Sullivan, *JITC*, 2019

CTLA-4 blockade demonstrates efficacy for metastatic melanoma in 2010



Median survival:
10 months (Ipilumumab) vs 6 months (gp100)

First randomized trial to show survival benefit in patients with advanced melanoma

Melanoma has been a foundational disease state for immunotherapies

Hodi, NEJM 2010

FDA-approved immunotherapies in melanoma

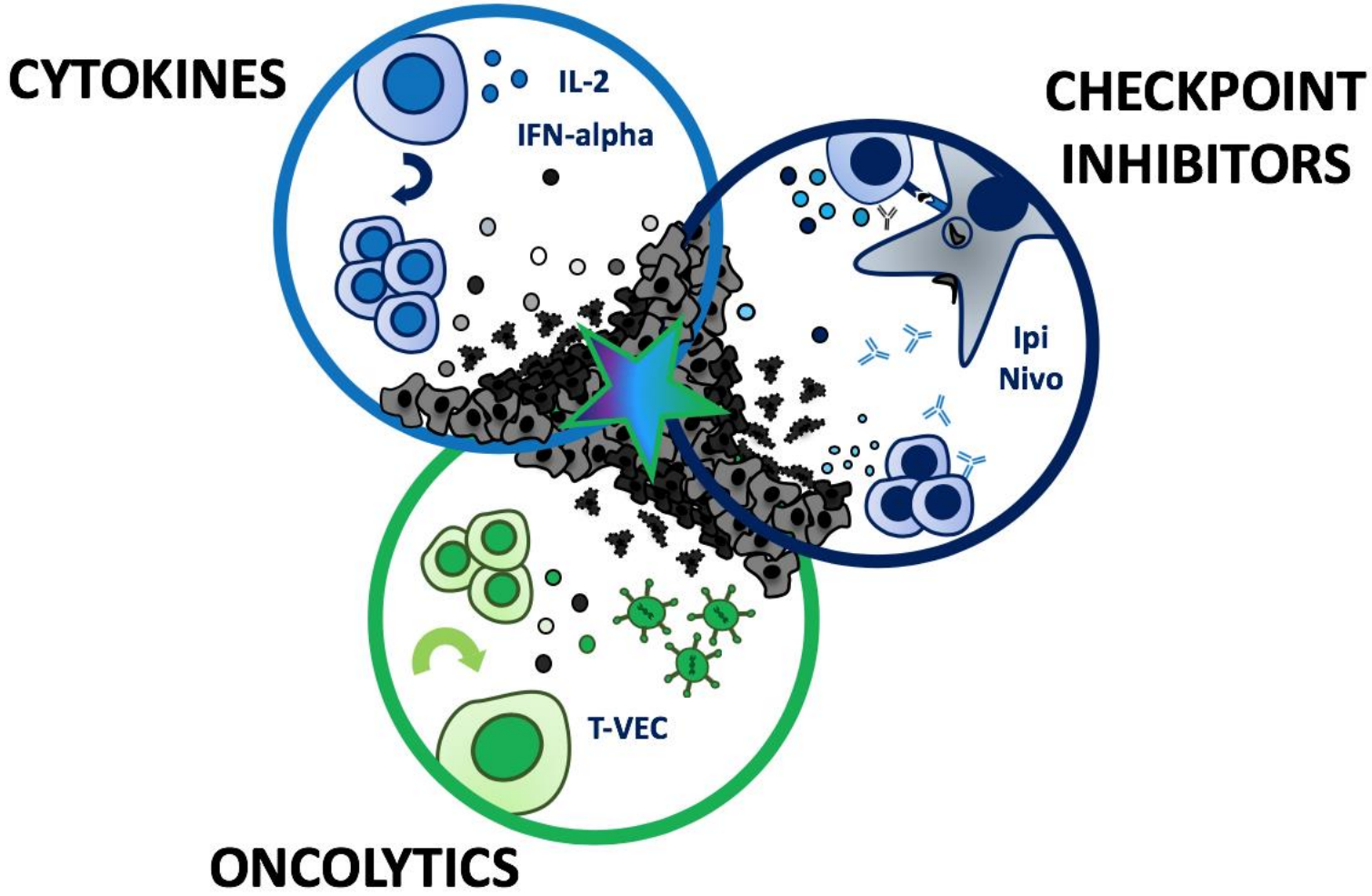


Figure adapted from
Knochelmann et al, *Frontiers in Immunology* 2018

FDA-approved **cytokines** in melanoma

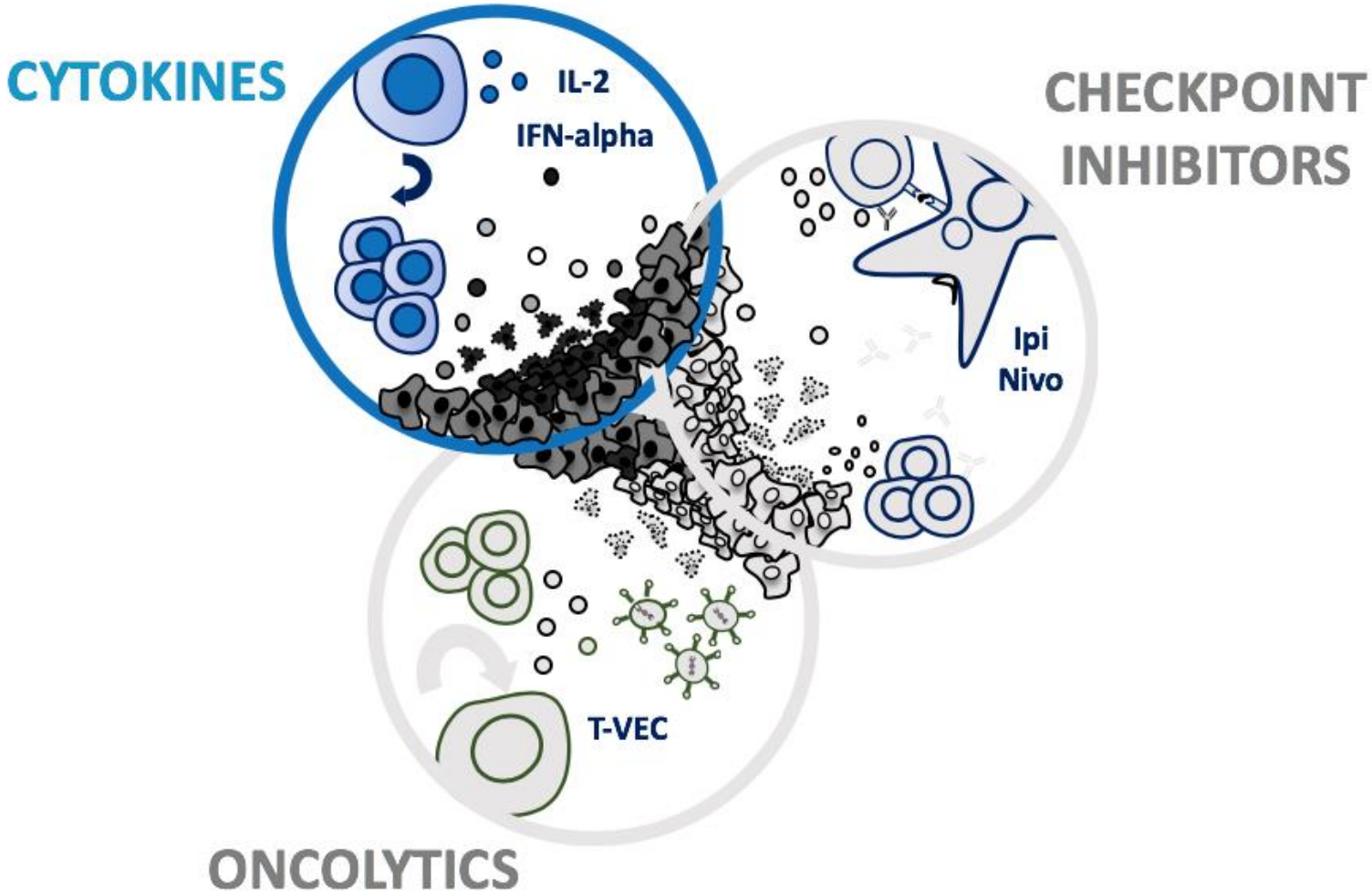


Figure adapted from
Knochelmann et al, *Frontiers in Immunology* 2018

Approved cytokines in melanoma

Drug	Indication	Dose
High-dose interferon alpha-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
Pegylated Interferon alpha-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
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

FDA-approved **checkpoint inhibitors** in melanoma

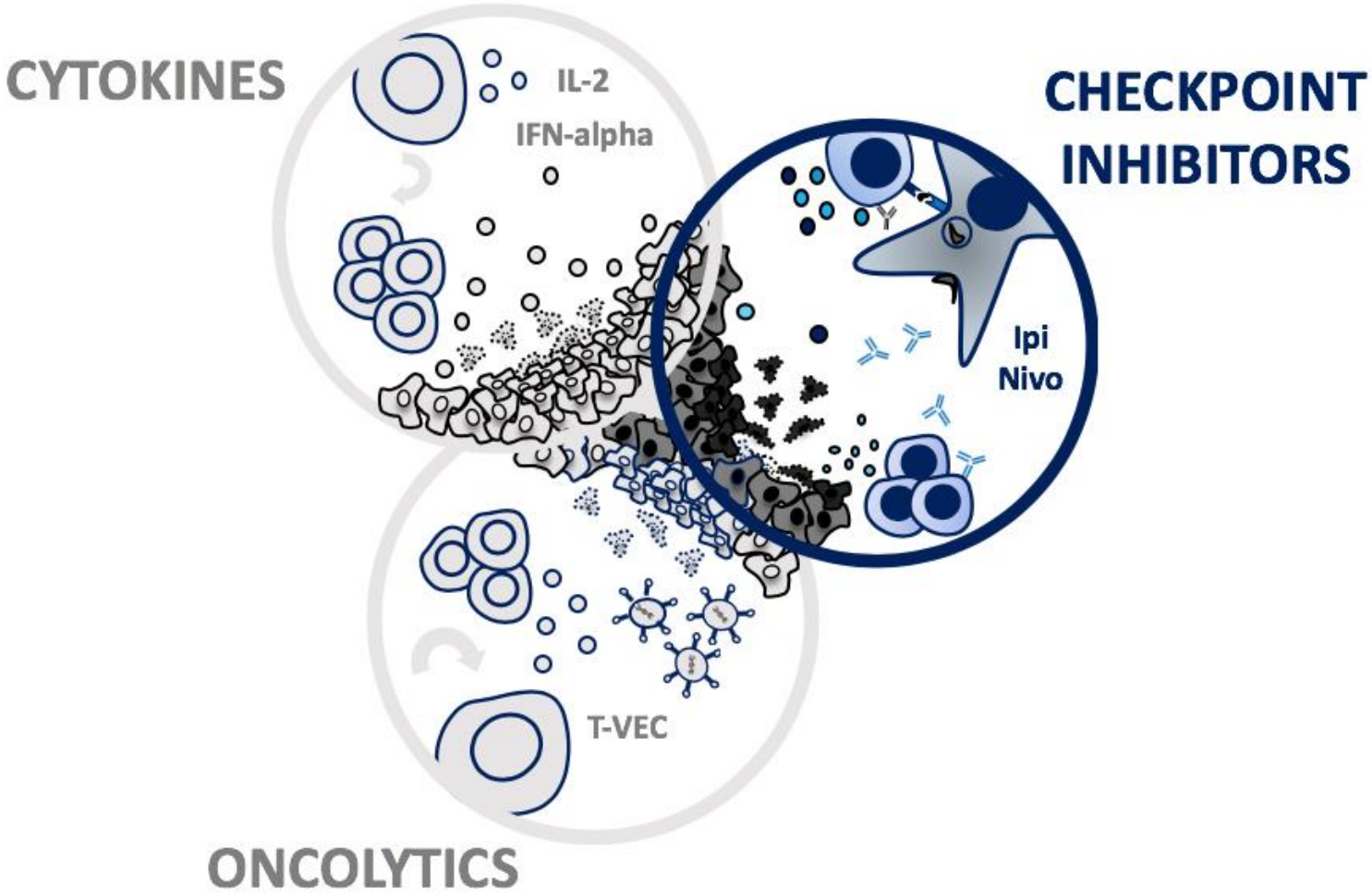


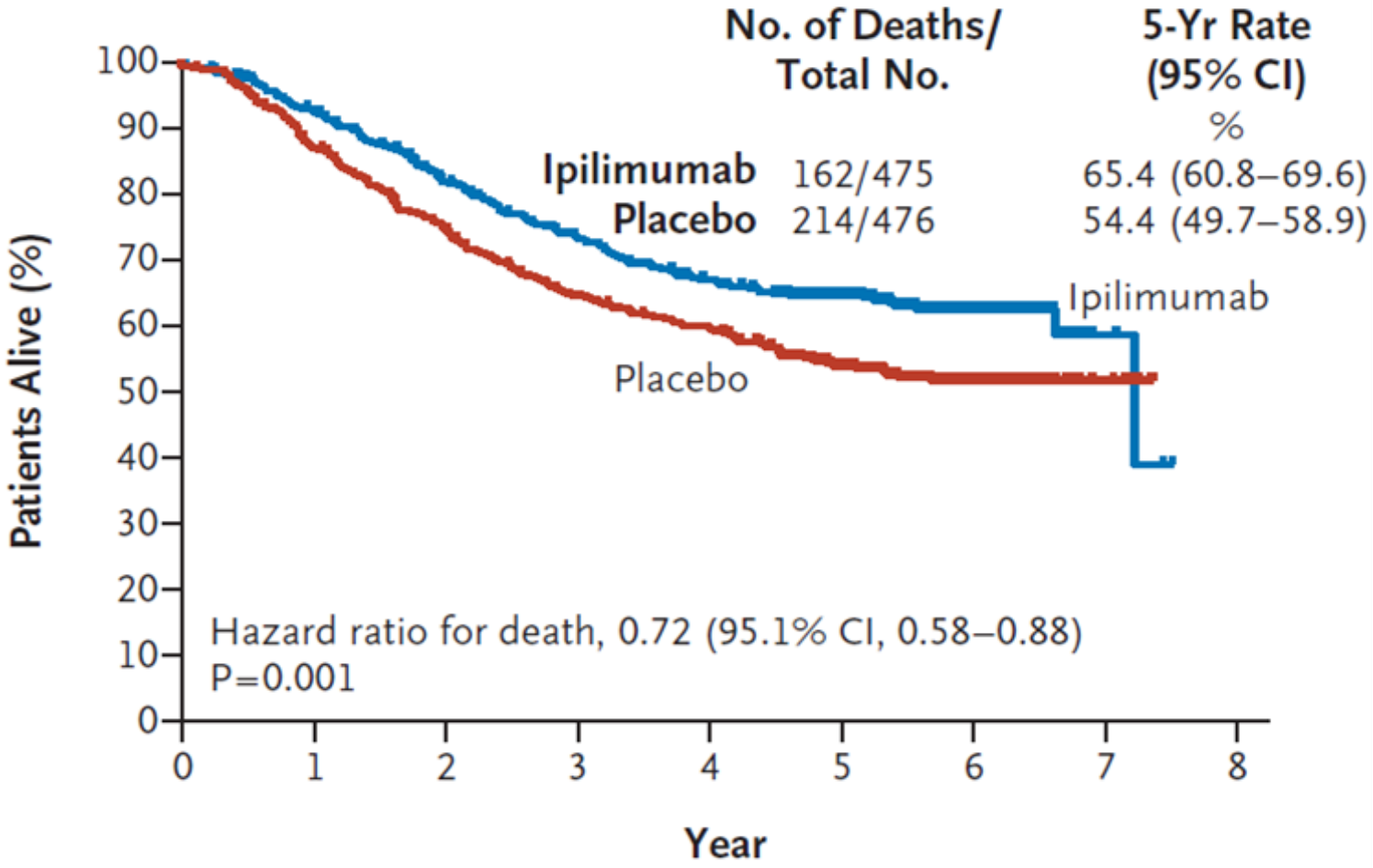
Figure adapted from
Knochelmann et al, *Frontiers in Immunology* 2018

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



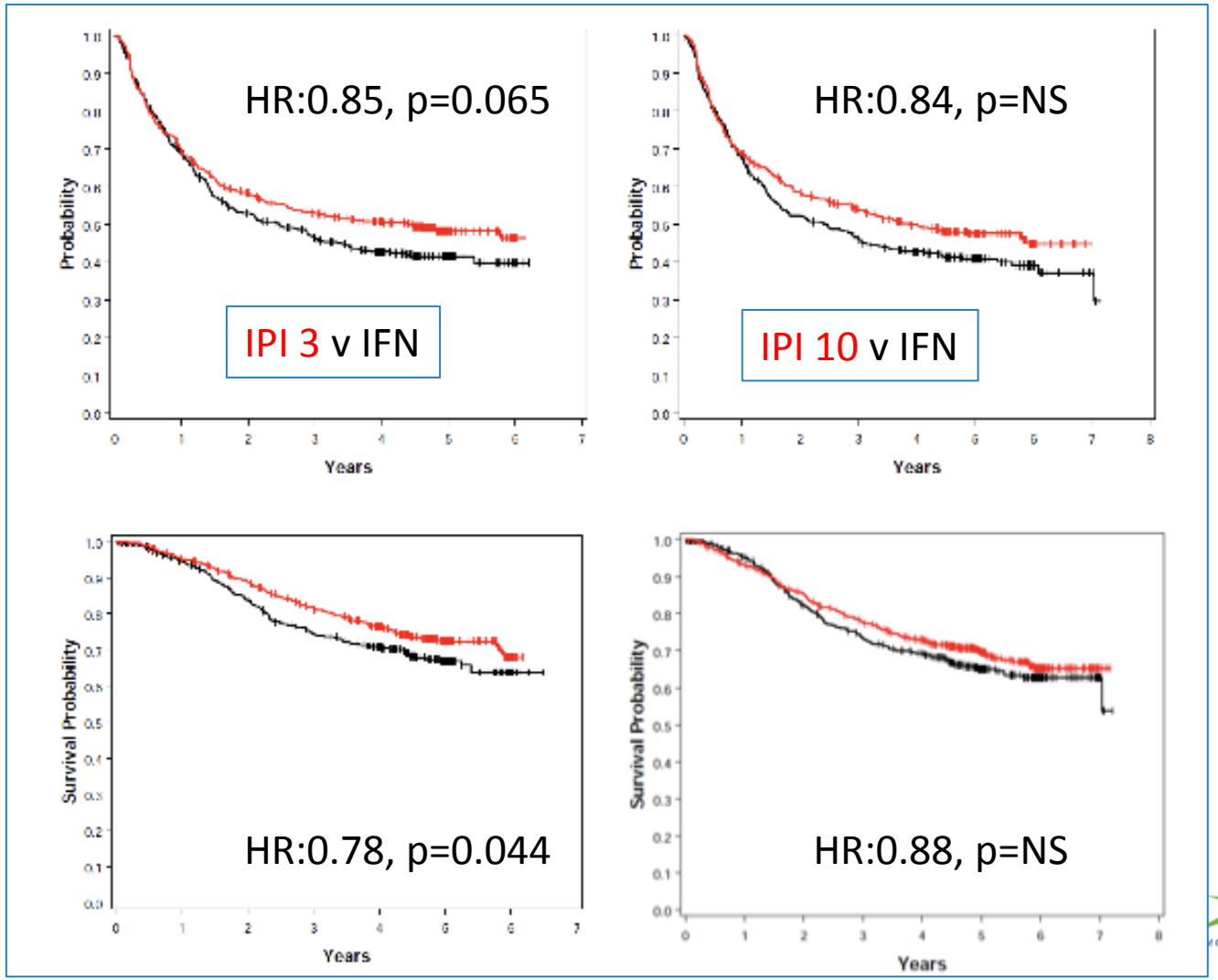
Eggermont, NEJM 2016.

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

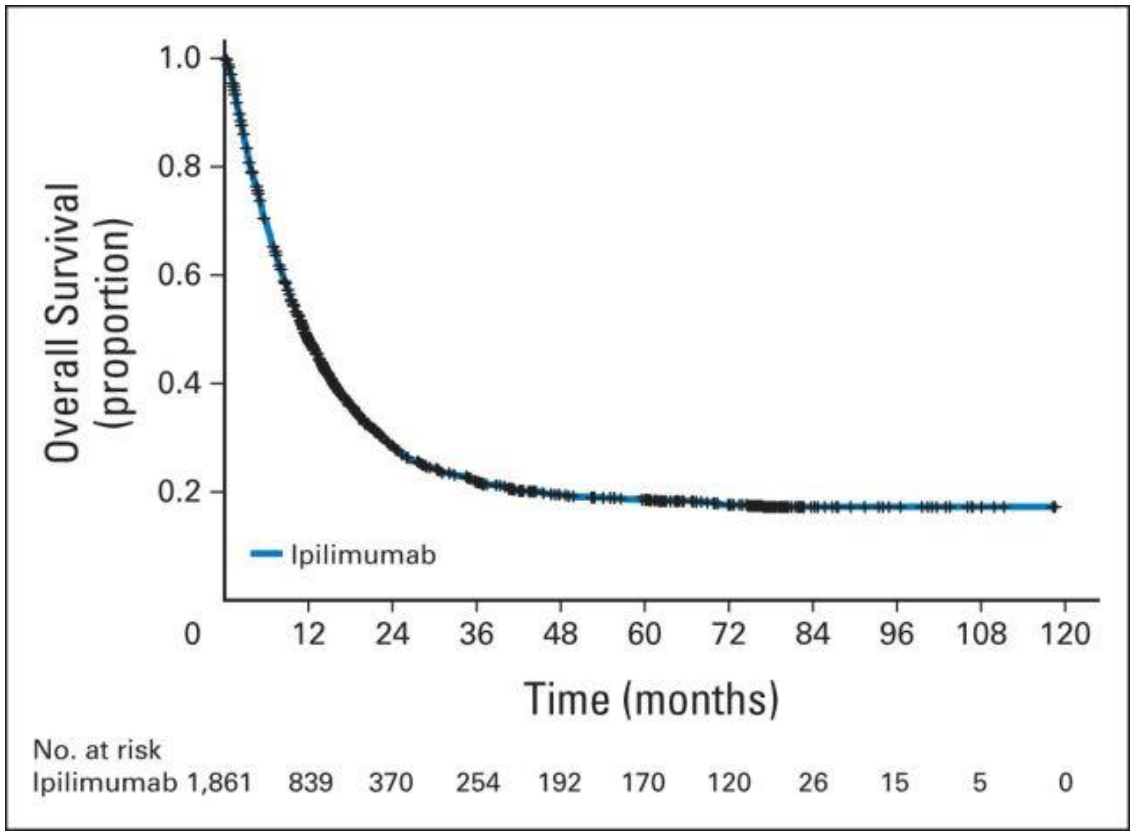
OS



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)



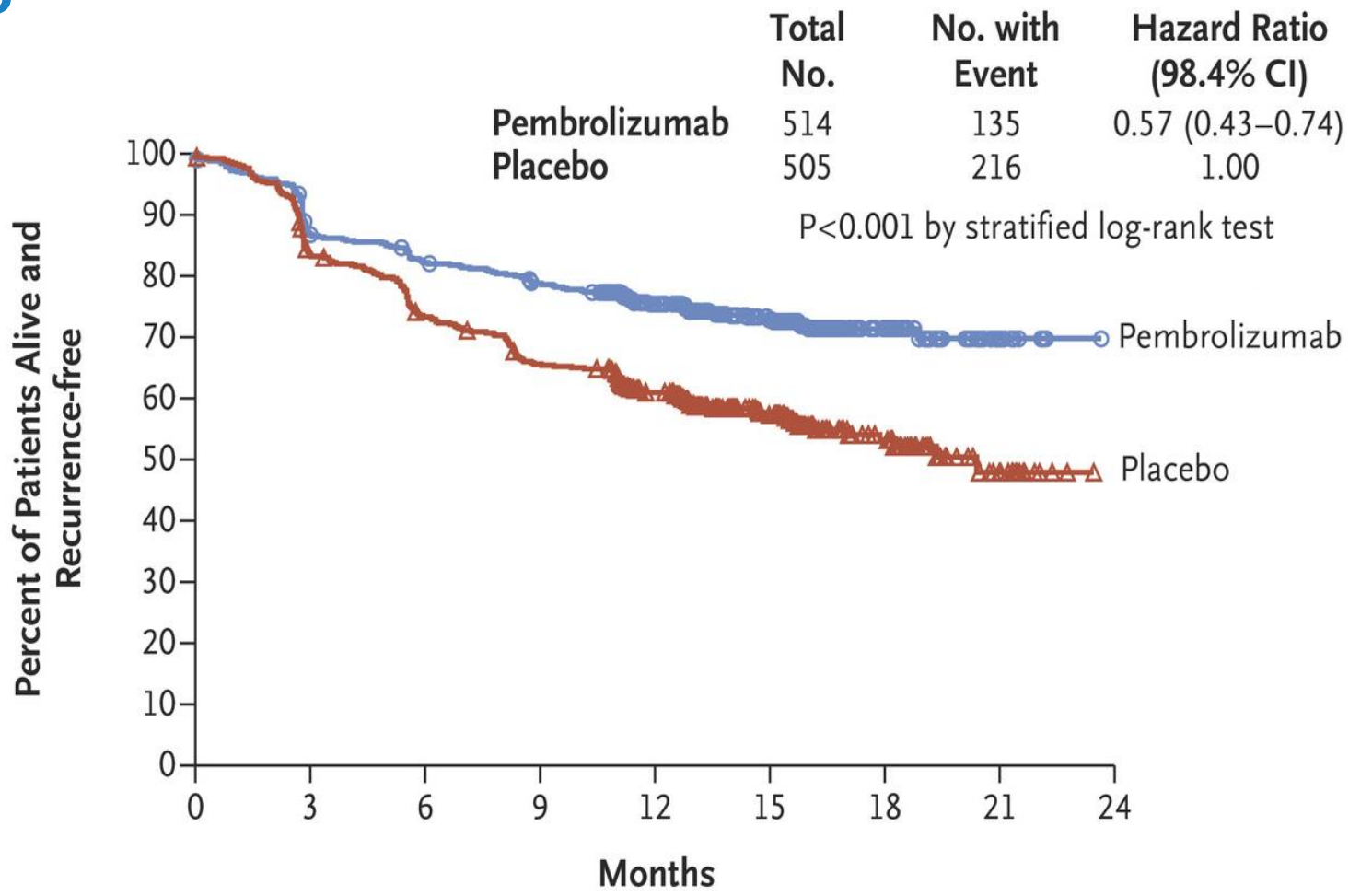
Schadendorf, JCO 2015.

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

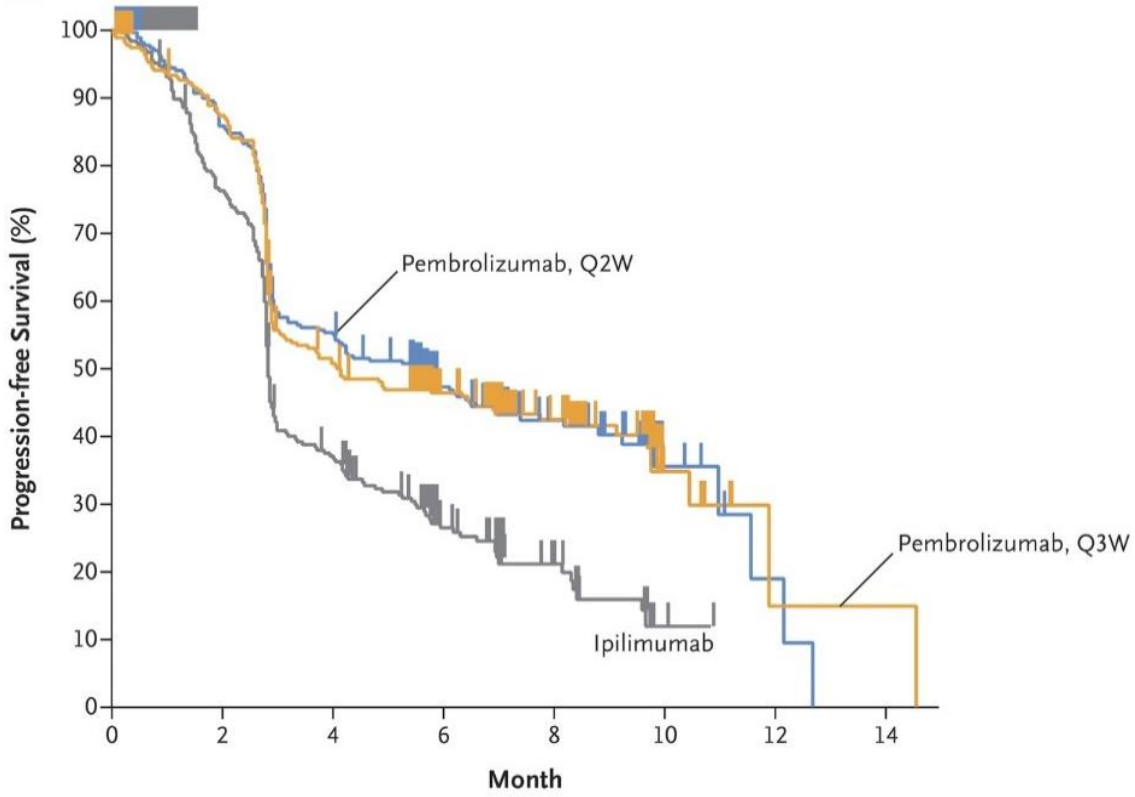
- EORTC 1325/KEYNOTE-054 phase III trial
  - NCT02362594
  - Adjuvant pembrolizumab vs placebo
  - Pembrolizumab 200mg Q3W for up to 1 year (~18 total doses)

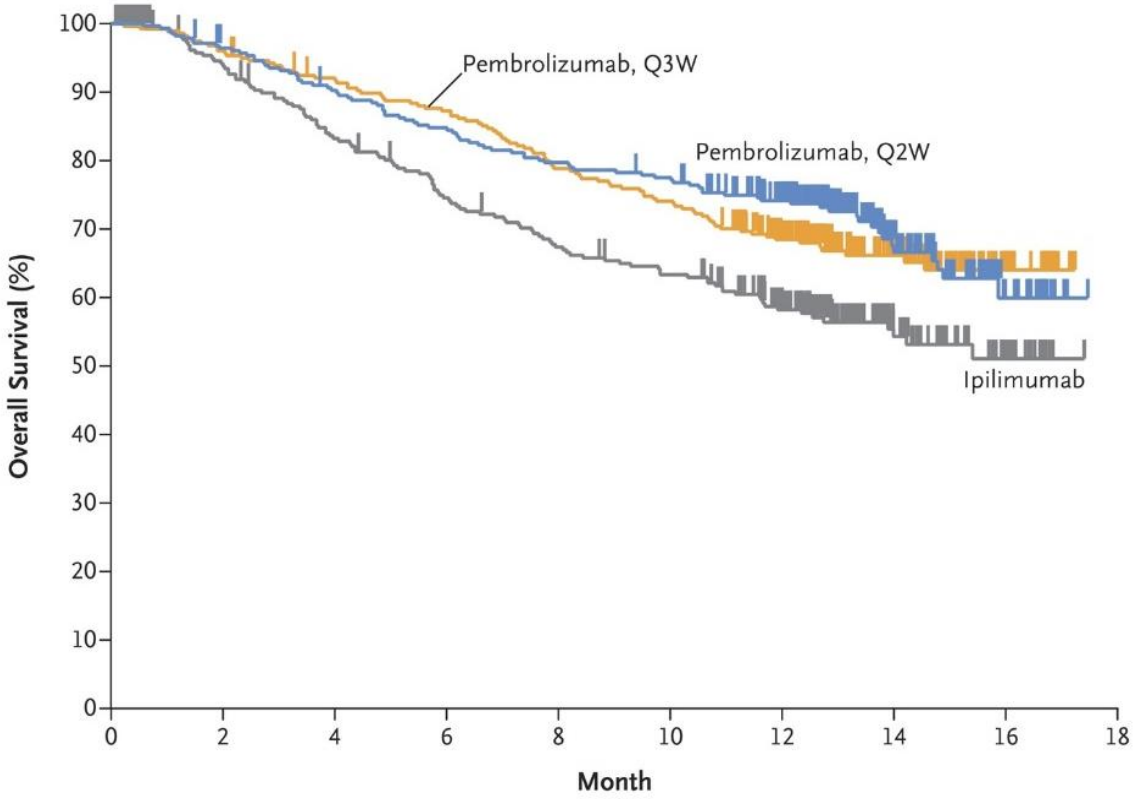


Eggermont, NEJM 2018.

Pembrolizumab in Stage III/IV Melanoma

Phase III KEYNOTE-006 Trial





Robert, NEJM 2015.

Approved checkpoint inhibitors in melanoma

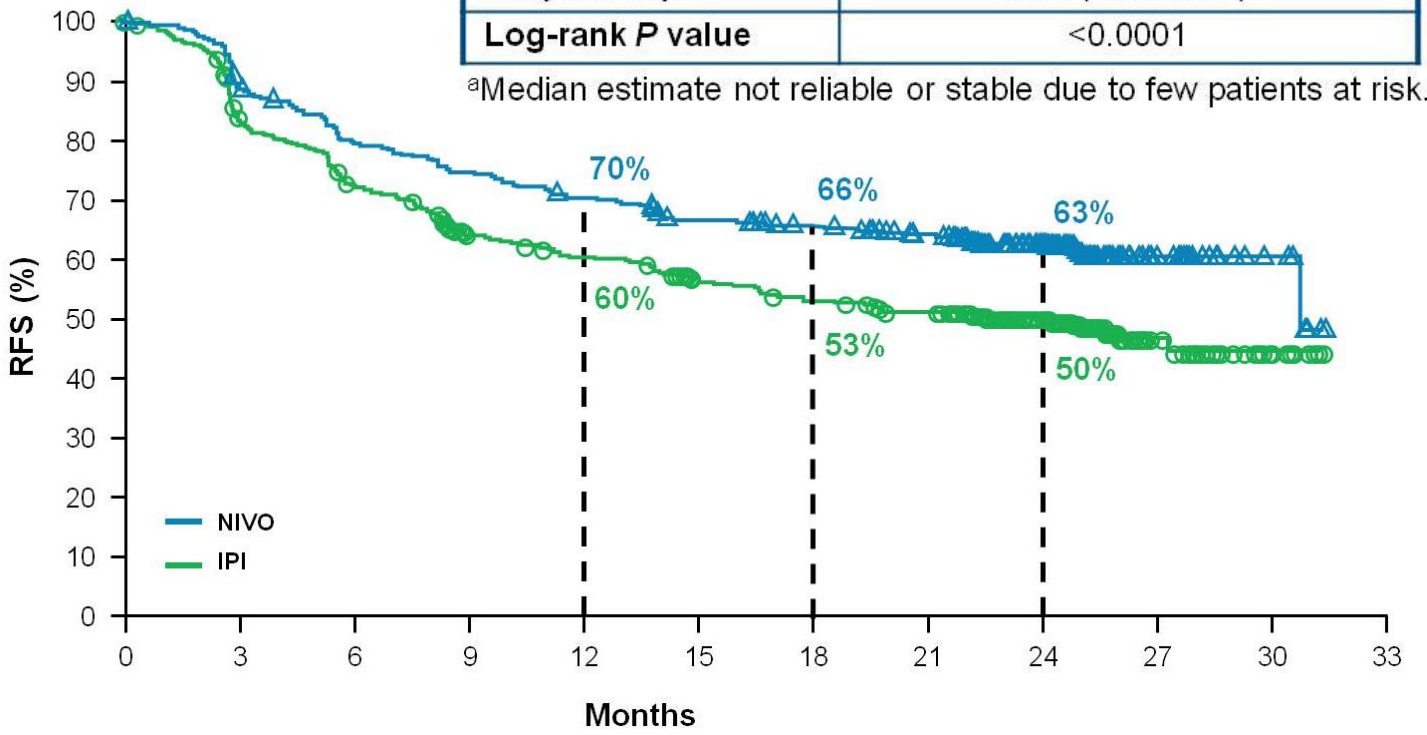
Drug	Approved	Indication	Dose
Nivolumab	2014	Unresectable/metastatic melanoma with progression after other therapy	240 mg Q2W or 480 mg Q4W*
	2017	Adjuvant treatment of melanoma after complete resection	240 mg Q2W or 480 mg Q4W
*Original approval was 3 mg/kg Q2W, updated to flat dosing regimen			

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.



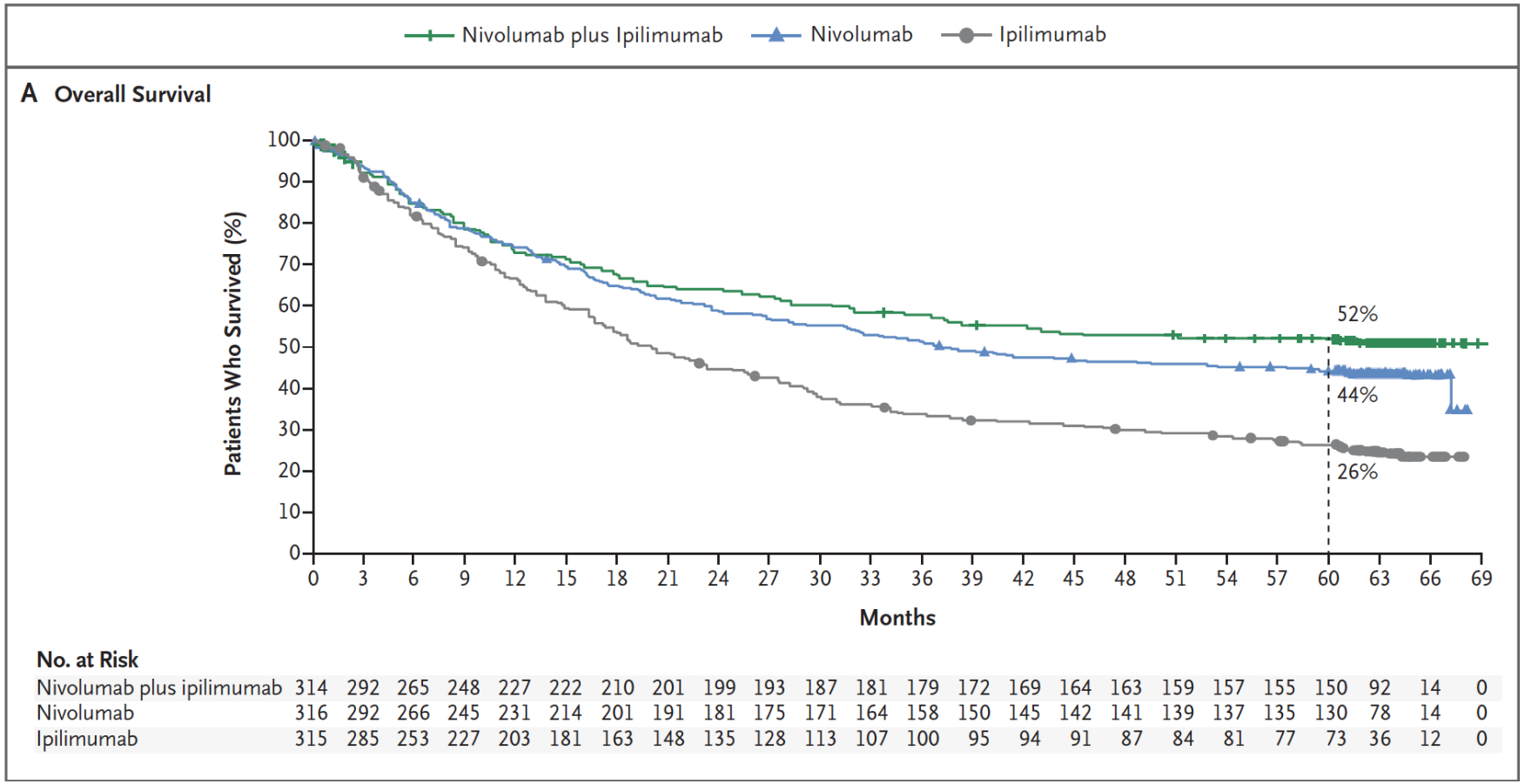
Miller, ASCO 2018.

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



No. at Risk

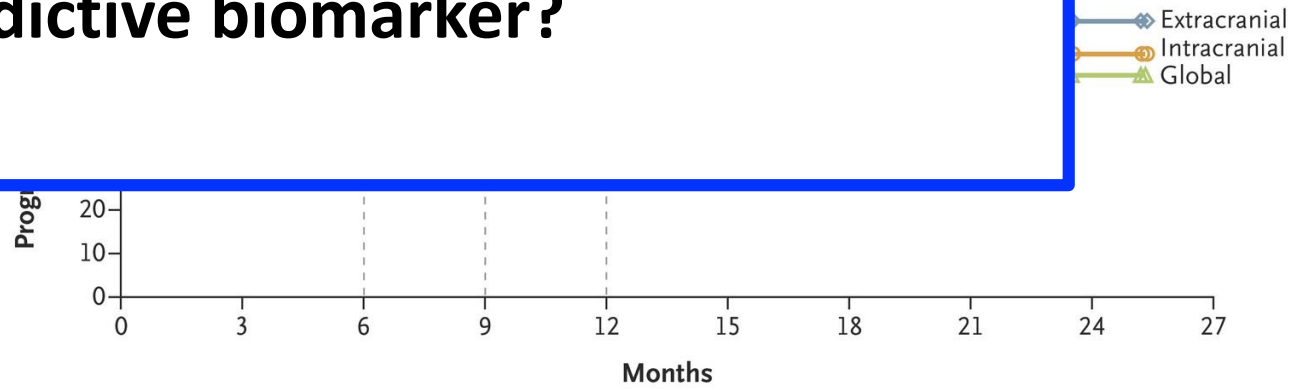
Nivolumab plus ipilimumab	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
Nivolumab	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

Larkin, NEJM 2019

Combination Ipilimumab + Nivolumab for Patients with Asymptomatic Brain Metastases

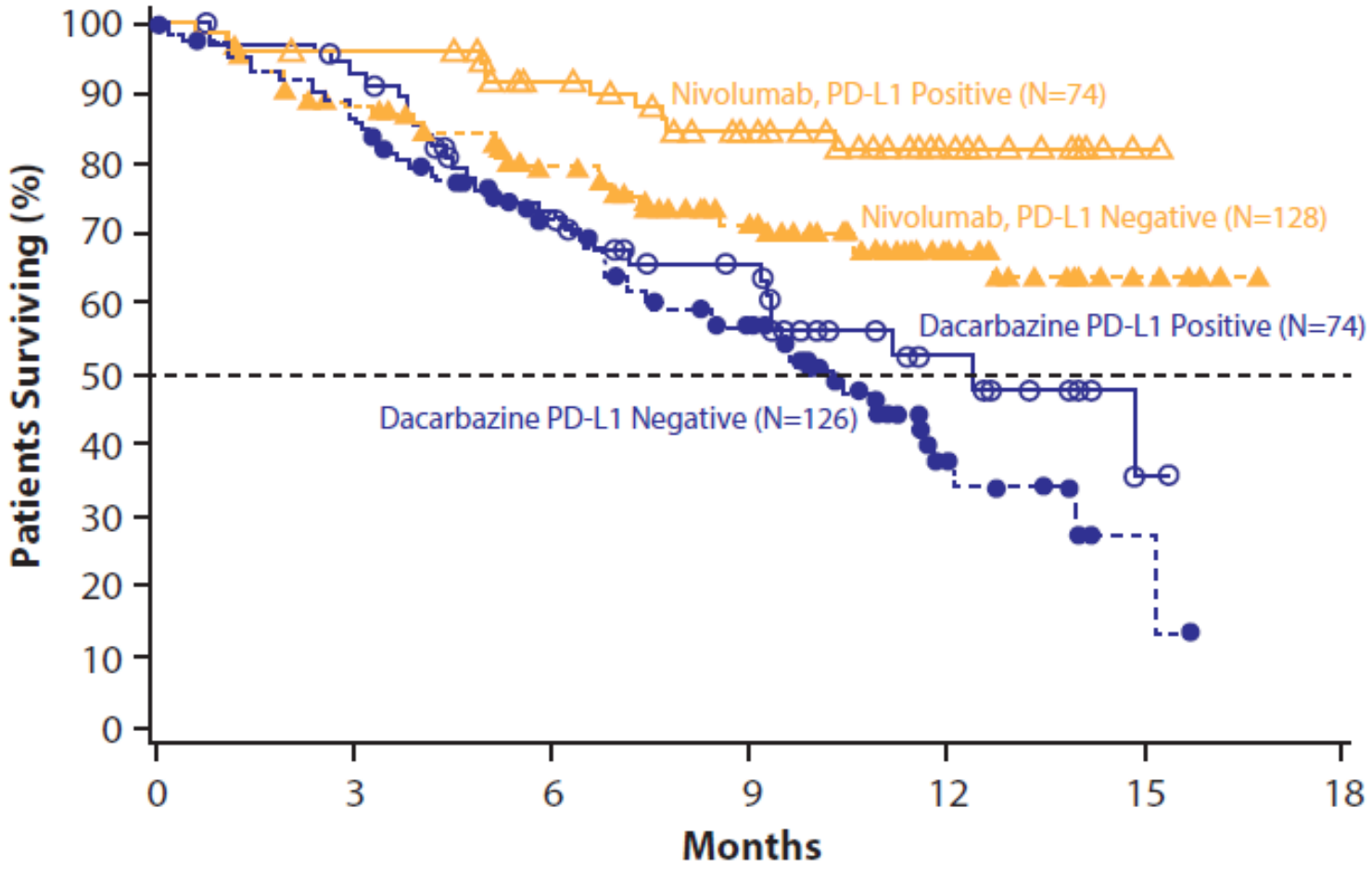
Variable	Intracranial (N=94)	Extracranial (N=94)	Global (N=94)
Best overall response (%)*			
Complete r			
Partial resp			
Stable disea			
Progressive			
Could not b			
Objective response‡			
No. of patients	52	47	48
Percent of patients (95% CI)	55 (45–66)	50 (40–60)	51 (40–62)
Clinical benefit§			
No. of patients	54	53	53
Percent of patients (95% CI)	57 (47–68)	56 (46–67)	56 (46–67)

Is PD-L1 a predictive biomarker?



Tawbi, NEJM 2018.

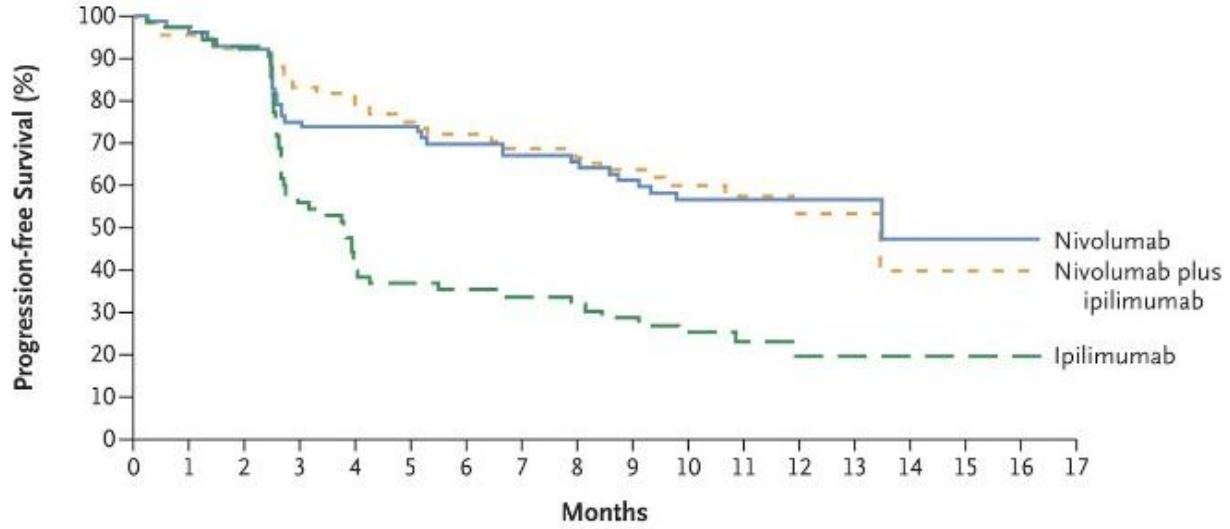
Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy



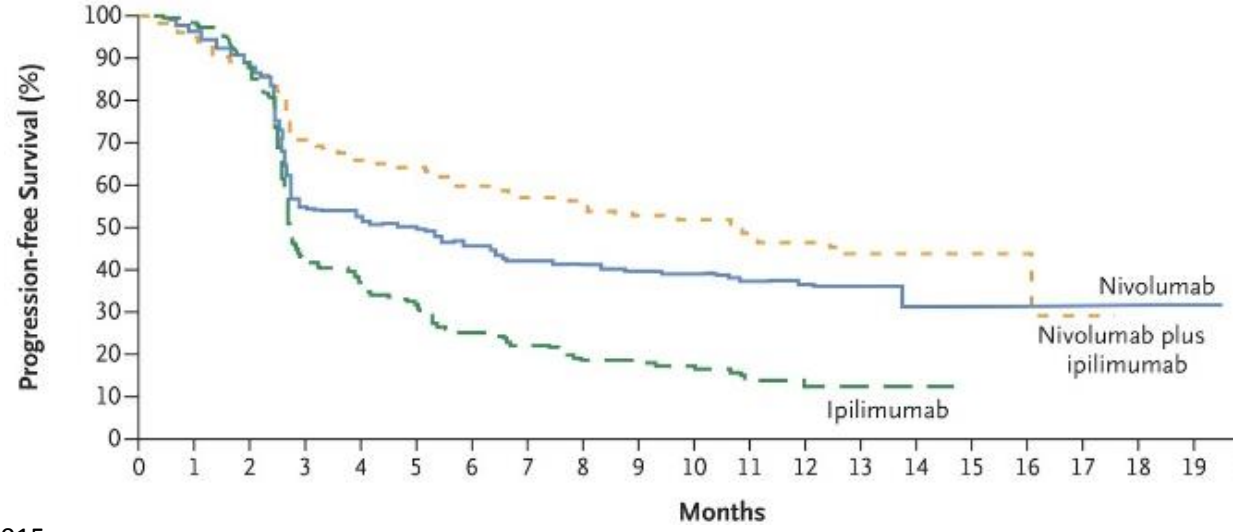
	Patients Who Died *n/N*	Median Survival *mo (95% CI)*
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

Robert, NEJM 2015.

Importance of Tumor PD-L1 Status



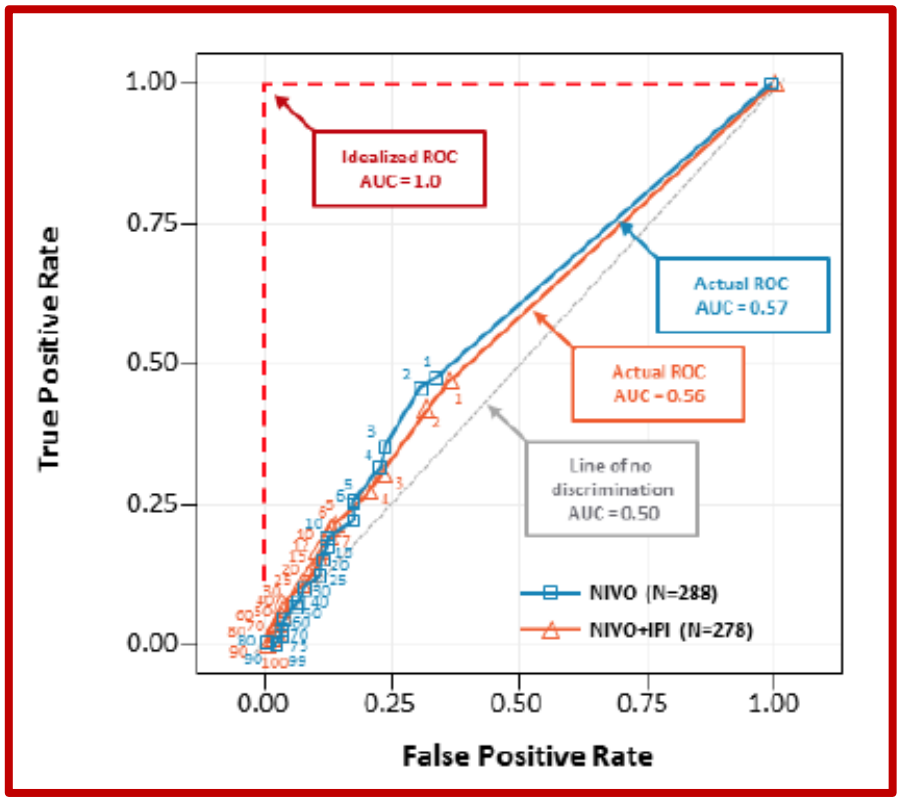
Tumor PD-L1 Positive Patients



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.

FDA-approved **oncolytic viruses** in melanoma

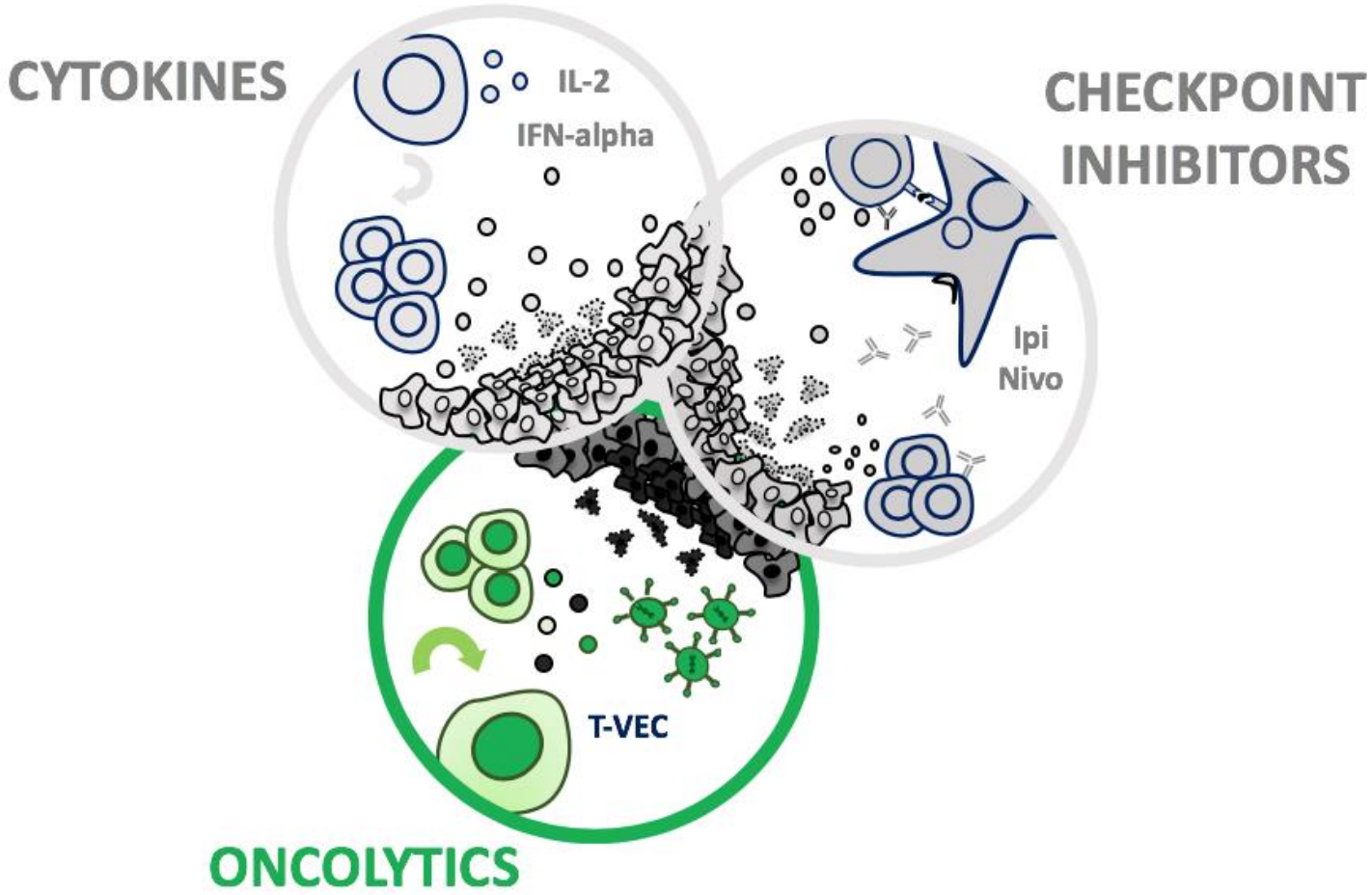
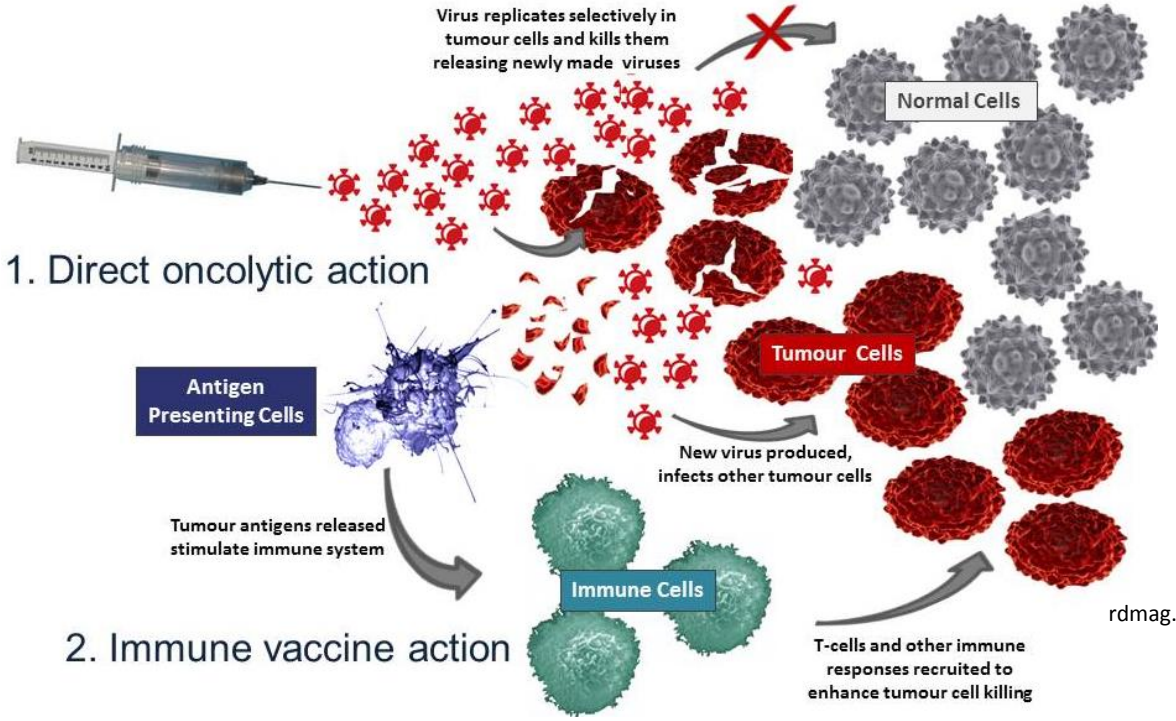


Figure adapted from
Knochelmann et al, *Frontiers in Immunology* 2018

Approved oncolytic virus in melanoma

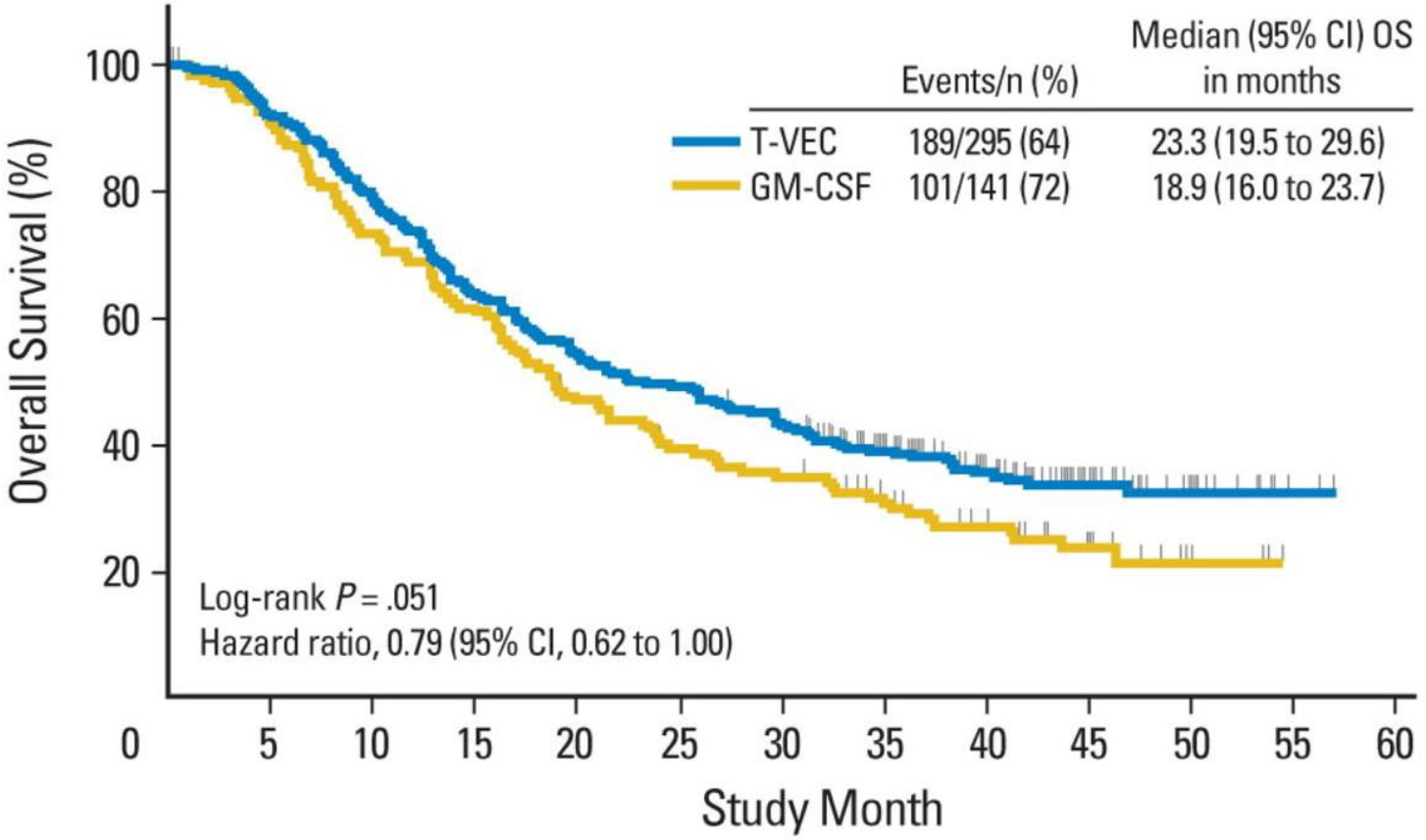


rdmag.com

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



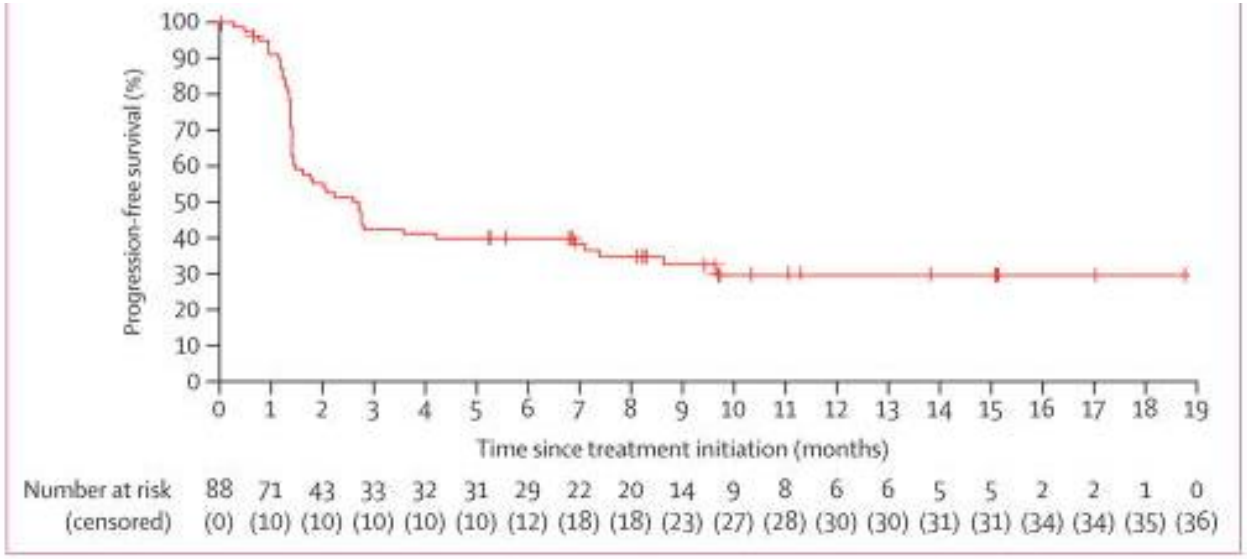
Andtbacka, Kaufman, JCO 2015.

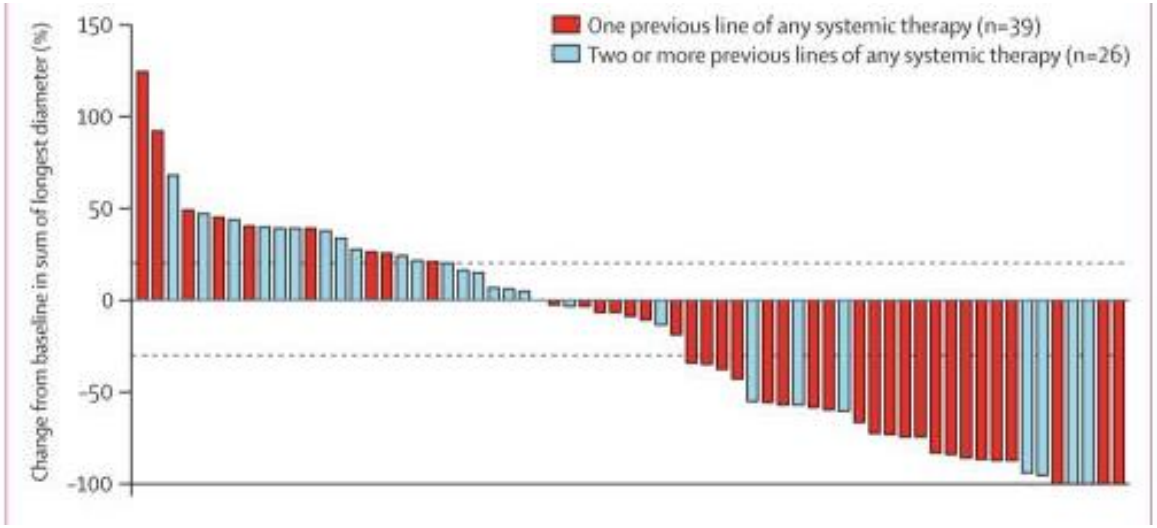
Approved checkpoint inhibitors in other skin cancers

Drug	Approved	Indication	Dose
Avelumab (PD-L1)	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 (PD-1)	2018	Metastatic cutaneous **squamous cell carcinoma**, not candidate for curative therapies	350 mg Q3W

Avelumab in 2nd-line metastatic Merkel Cell carcinoma (2017)

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

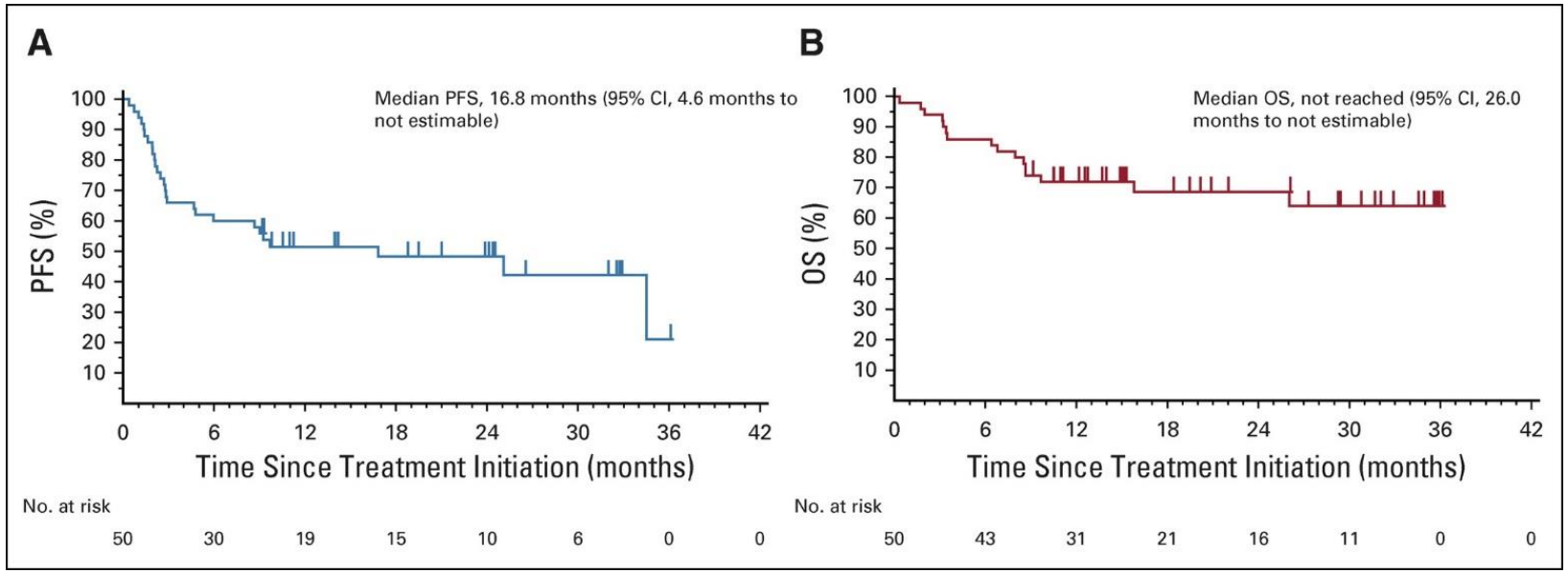




Kaufman, Lancet Oncol 2016.

Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma (2018)

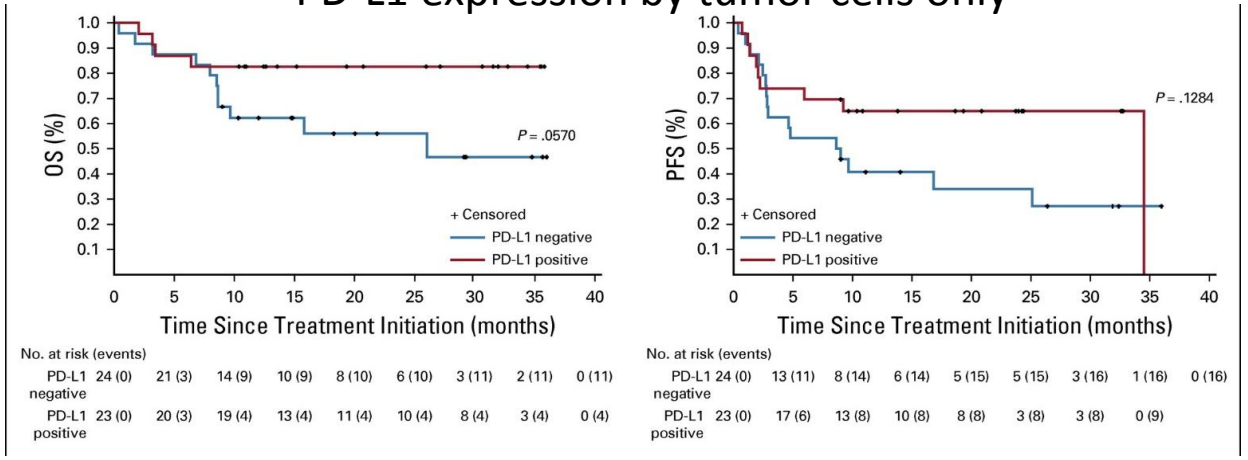
- KEYNOTE-017
- Pembrolizumab 2 mg/kg Q3W up to 2 years
- mPFS: 16.8 months (compared to 90 days for chemo)
- 24-month OS: 68.7%



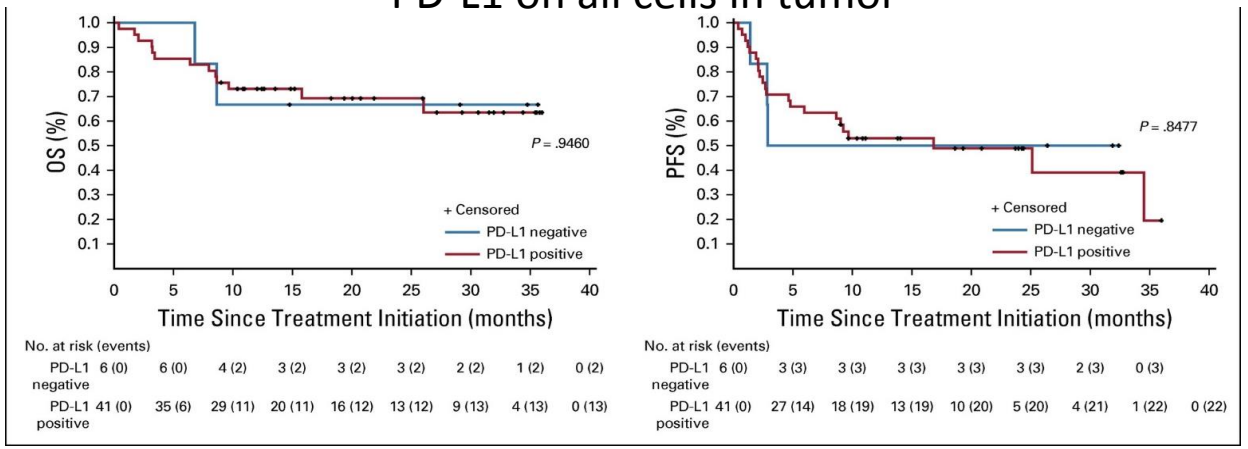
Nghiem, J Clin Oncol 2019.

Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

PD-L1 expression by tumor cells only



PD-L1 on all cells in tumor

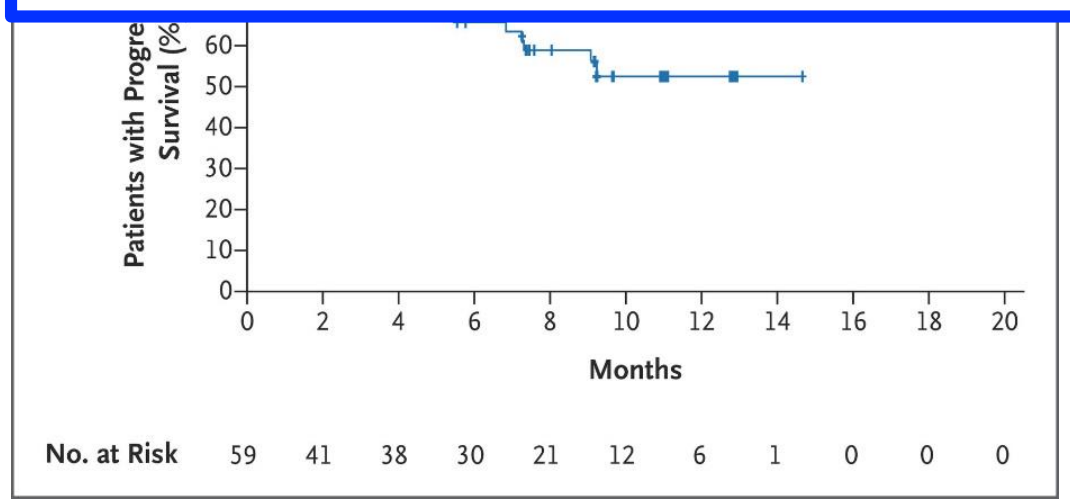


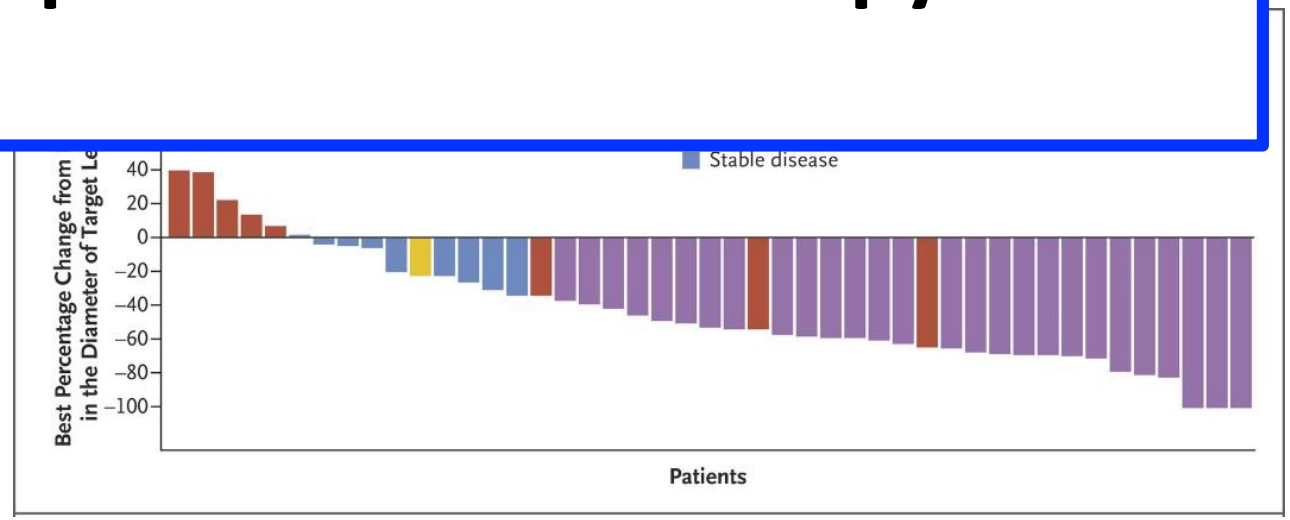
Nghiem, J Clin Oncol 2019.

Cemiplimab in advanced/metastatic cutaneous **squamous-cell carcinoma**

- Cemiplimab 3mg/kg Q2W

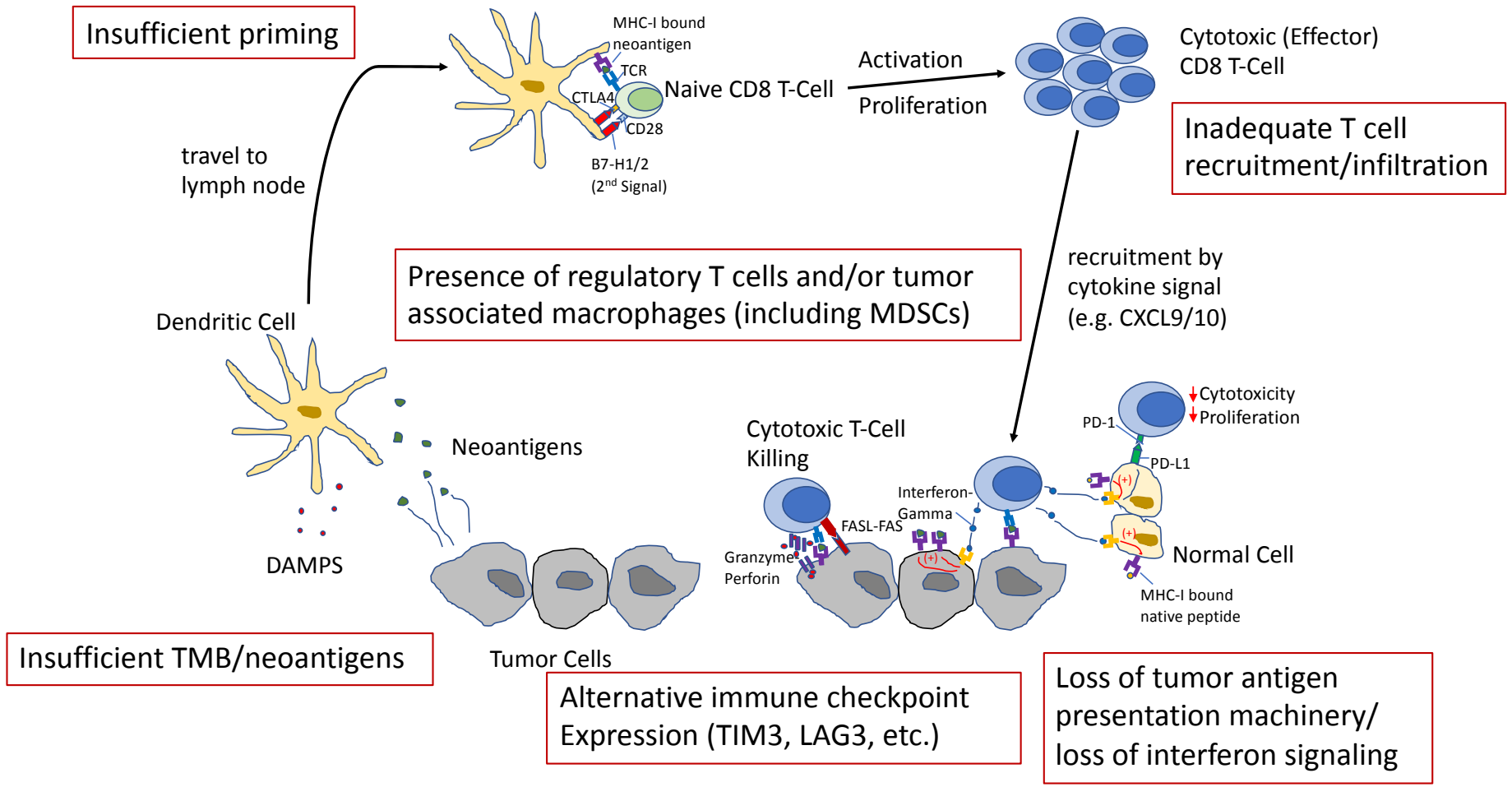
How does immune checkpoint inhibitor therapy fail?





Migden, NEJM 2018.

Developmental Immunotherapeutic Strategies for Melanoma

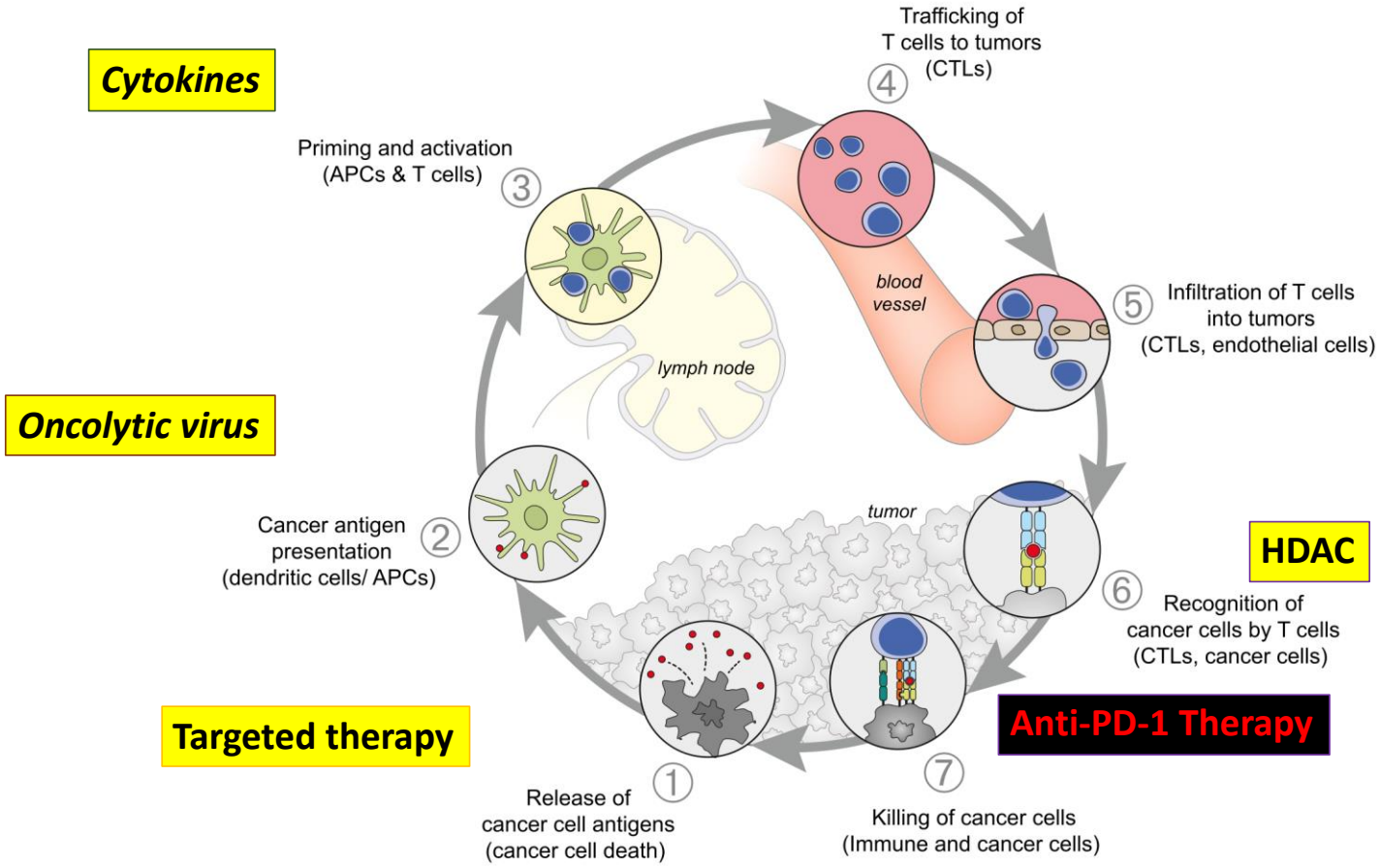


Modified from Liu, Jenkins, Sullivan. Amer J Clin Derm 2018.

Developmental Immunotherapeutic Strategies for Melanoma

How do we overcome resistance?

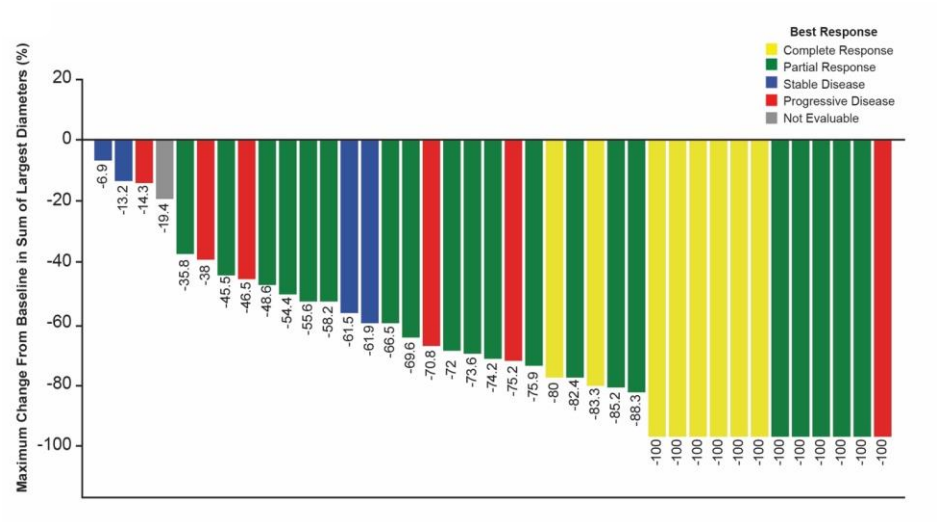
Combination therapy

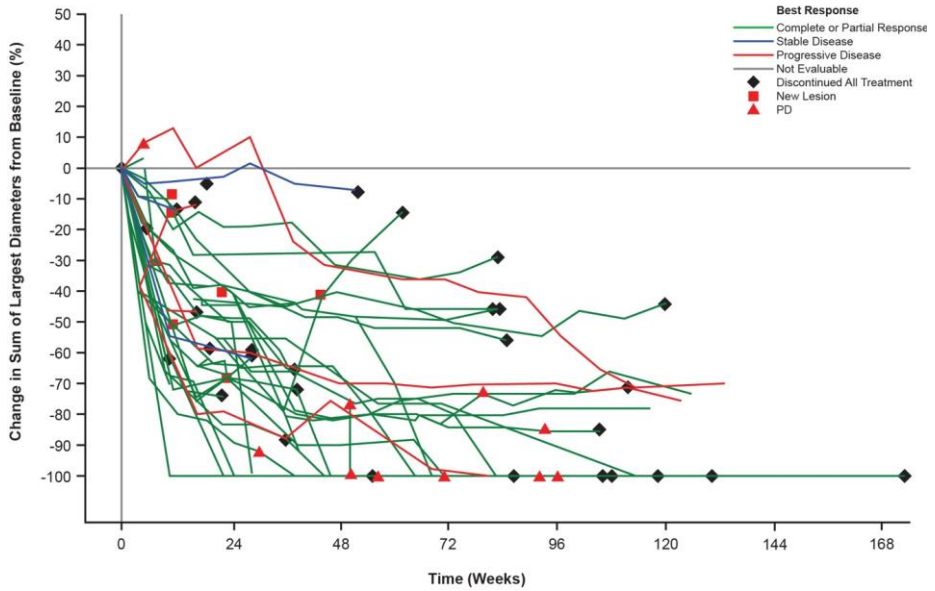


Modified from Chen and Melman. Immunity 2015.

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)

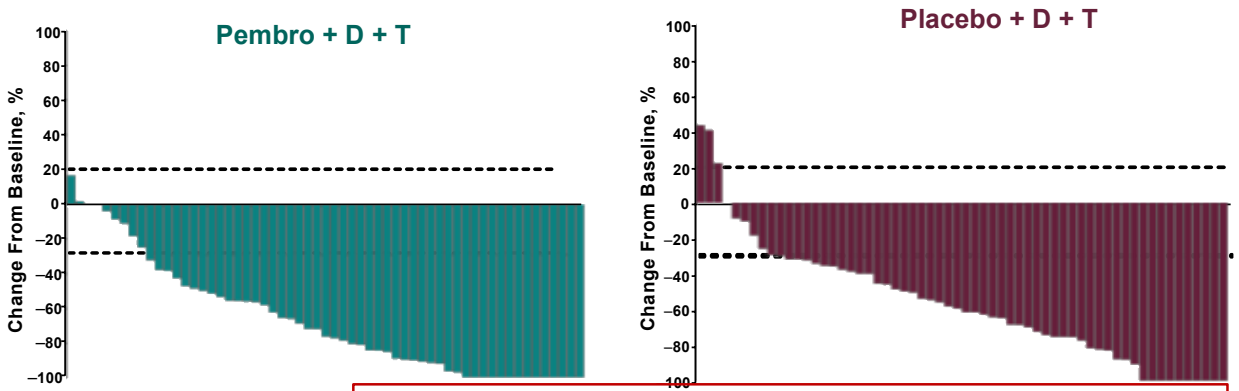
R (1:1)
N = 120

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

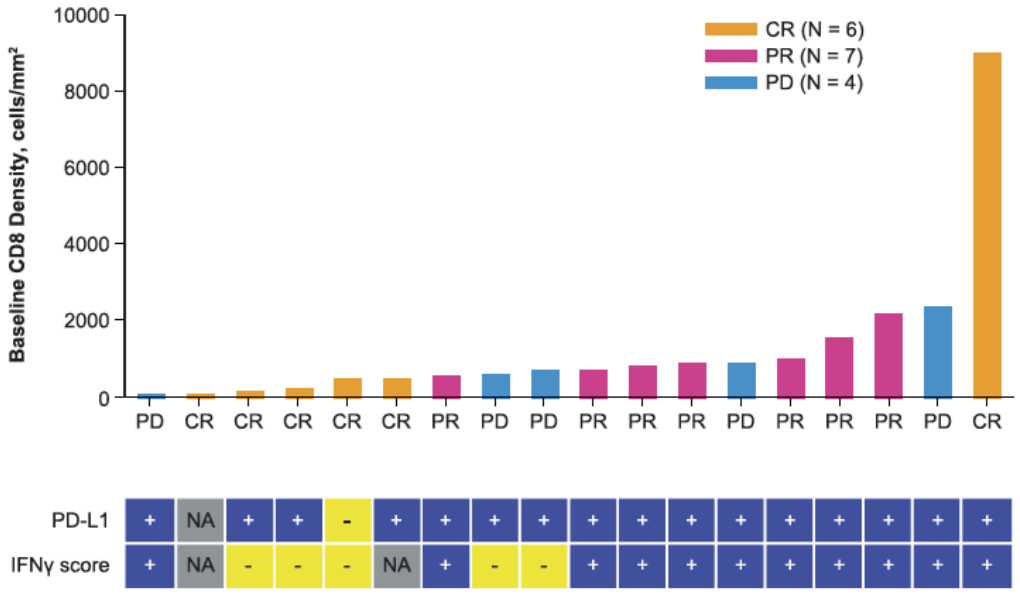
[a]Owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.



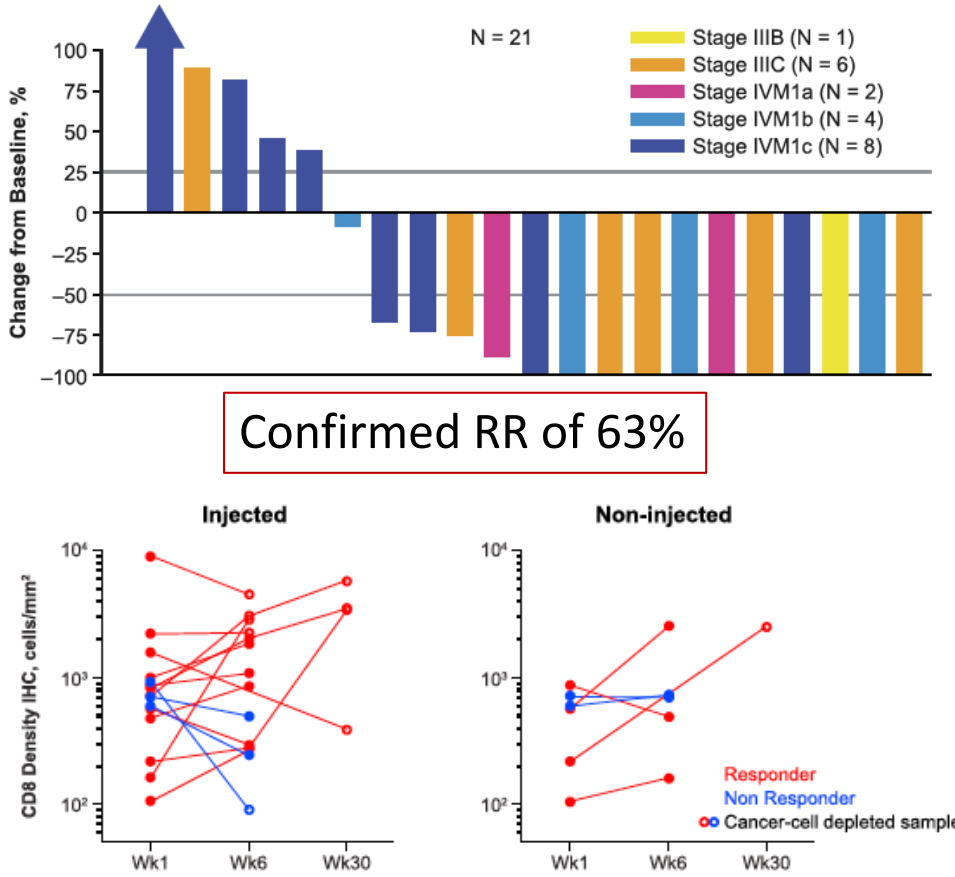
	Pembro + D + T	Placebo + D + T
ORR	63%	72%
CR	18%	13%
≥ 60% red	63%	51%

Ascieto et al, *Nature Med* 2019.

In development: Combined IO with Oncolytic Virus



Phase I: Pembrolizumab + TVEC

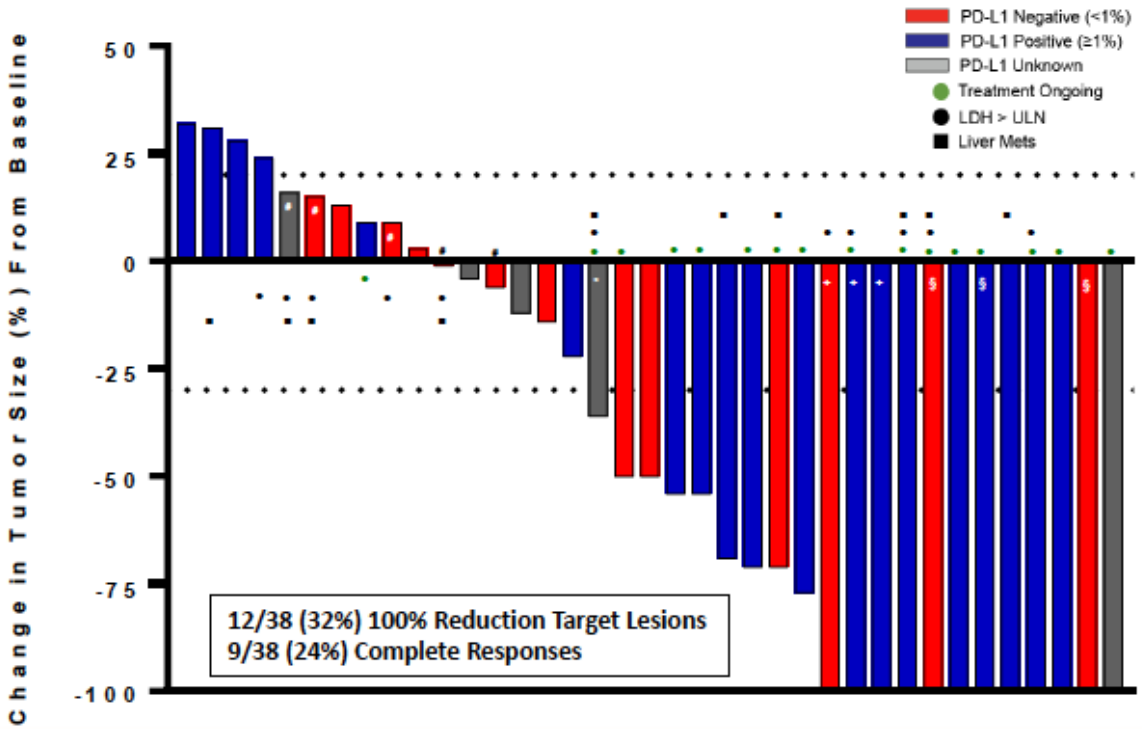


Confirmed RR of 63%

Ribas et al Cell 2017

In development: Combined Nivo with CD122 agonist (NKTR-214)

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



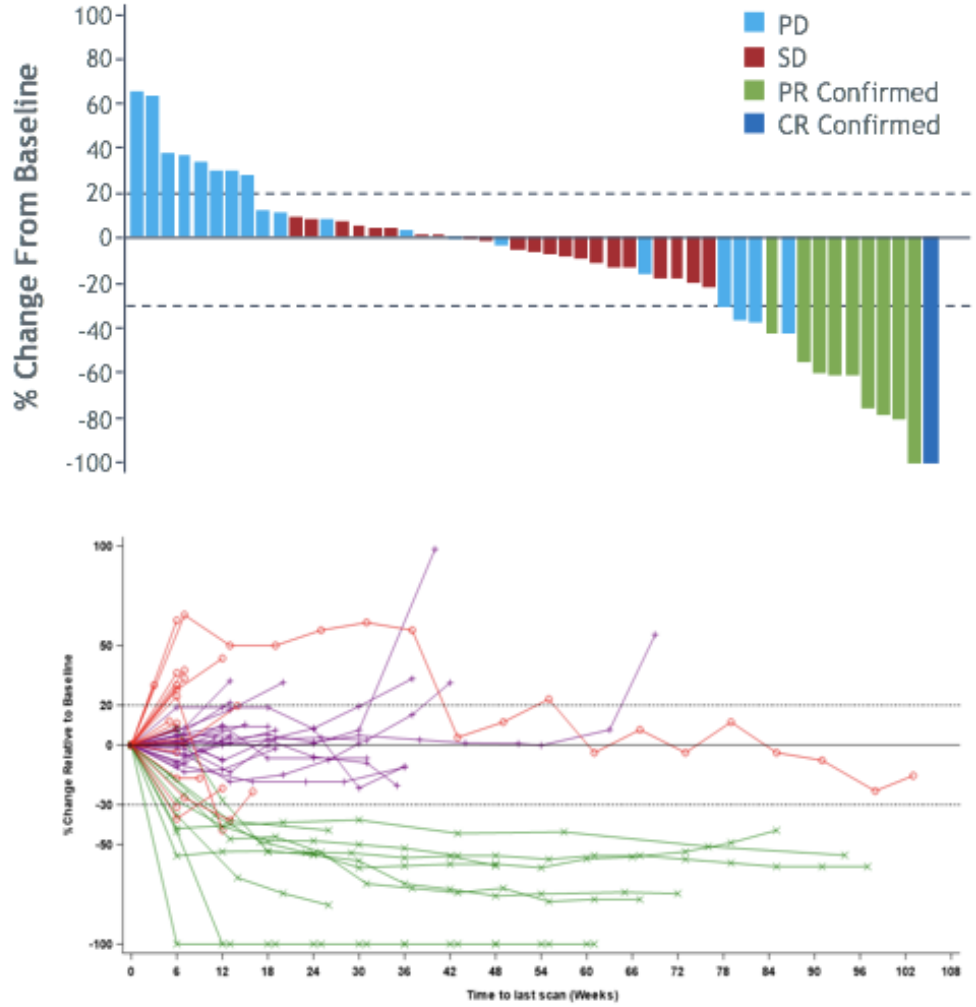
1L Melanoma (n=38 Efficacy Evaluable)	Overall Response Rate
Confirmed ORR (CR+PR)	20 (53%)
CR	9 (24%)
DCR (CR+PR+SD)	29 (76%)
PD-L1 negative (n=14)	6 (43%)
PD-L1 positive (n=19)	13 (68%)
PD-L1 unknown (n=5)	1 (20%)
LDH > ULN (n=11)	5 (45%)
Liver metastases (n=10)	5 (50%)

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

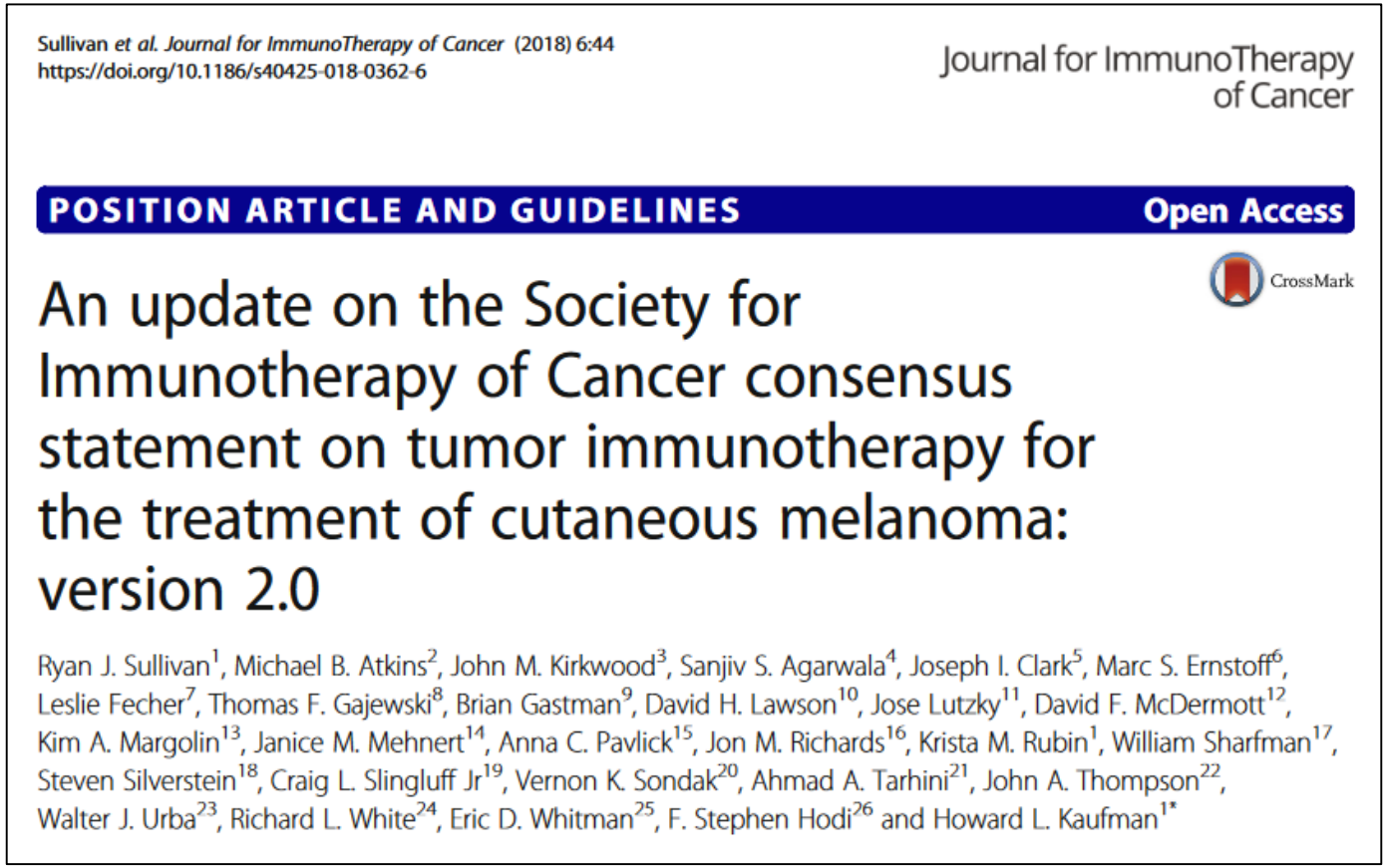


Sullivan et al, AACR 2019.

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*]

Case Studies: Immune-related toxicities

JAMA Oncology | Original Investigation

Five-Year Survival and Correlates Among Patients With Advanced Melanoma, Renal Cell Carcinoma, or Non–Small Cell Lung Cancer Treated With Nivolumab

No pain, no gain?

Suzanne L. Topalian, MD; F. Stephen Hodi, MD; Julie R. Brahmer, MD; Scott N. Gettinger, MD; David C. Smith, MD; David F. McDermott, MD; John D. Powderly, MD; Jeffrey A. Sosman, MD; Michael B. Atkins, MD; Philip D. Leming, MD; David R. Spigel, MD; Scott J. Antonia, MD, PhD; Alexander Drilon, MD; Jedd D. Wolchok, MD, PhD; Richard D. Carvajal, MD; M. Brent McHenry, PhD; Fareeda Hosein, MD; Christopher T. Harbison, PhD; Joseph F. Grosso, PhD; Mario Sznol, MD

Results: Overall survival was significantly **longer among patients with treatment-related AEs of any grade** (median, 19.8 months; 95%CI, 13.8-26.9 months**) or grade 3 or more** (median, 20.3 months; 95%CI, 12.5-44.9 months) **compared with those without treatment-related AEs** (median, 5.8 months; 95%CI, 4.6-7.8 months) (P < .001 for both comparisons based on hazard ratios).

Topalian et al, *JAMA Oncol*, 2019

Case Study

Hantel et al, *JITC*, 2018

35-yo woman with history of locally advanced **malignant melanoma of the left upper extremity** 10 months prior underwent complete surgical resection with sentinel lymph node biopsy showing melanoma with Breslow depth of 2.2mm. Resection was followed by complete level three axillary lymph node dissection, which was negative for metastasis.

She received 4 cycles of **adjuvant ipilumumab**, complicated by panhypopituaritism. After adjuvant treatment, she presented with cough, and was found to have **metastatic disease** in the lungs and axial skeleton. She then received **dual immunotherapy with ipilumumab and nivolumab.**

In clinic, she presents with progressive fatigue, pre-syncope, upper respiratory symptoms, pallor, low-grade fevers.

Physical Exam:

Vitals: 121, 82/45
Gen: pale, jaundiced
CV: regular rhythm, Tachycardia
Pulm: CTA
Abdomen: benign, palpable splenomegaly

Labs: Hgb (2.9), teardrops, anisopoikilcytosis
Plt (79), Bilirubin (2.0mg/dL), LDH (1029 U/L), CRP (202mg/L), haptoglobin <20mg/dL
Ferritin (5474 ng/mL), fasting TAG (336 mg/dL)
Retic index (0.6)
ID workup negative

Case Study

Moving forward, which of the following would you order?

A) Serum IL-6

B) Bone marrow biopsy

C) Liver biopsy

D) G6PDH level

Case Study

Moving forward, which of the following additional tests would you order?

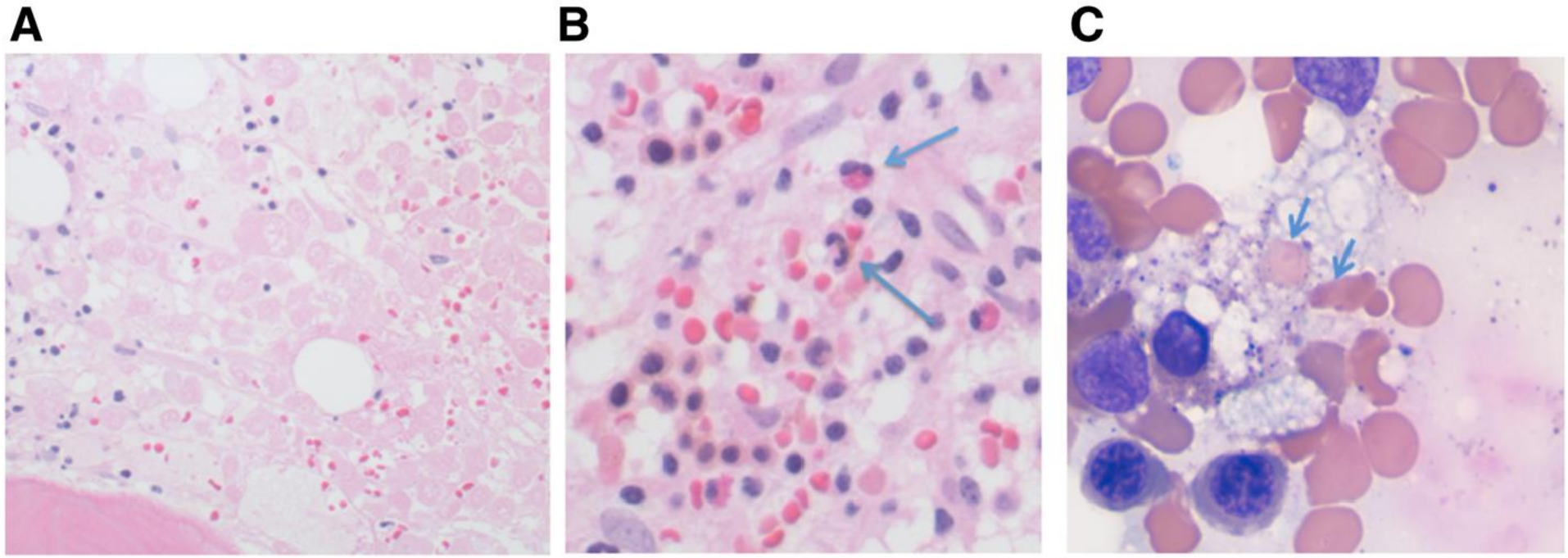
A) Serum IL-6 (CRP is elevated, so this is unlikely to provide additional useful information)

B) **Bone marrow biopsy** (given low hemoglobin and platelet counts, nl/low reticulocyte index, teardrops)

C) Liver biopsy

D) G6PDH level (low reticulocyte index)

Bone marrow



Melanoma necrosis

Histiocytes with phagocytosed RBCs

Hantel et al, *JITC*, 2018

Case Study

Which of the following would be consistent with the suspected diagnosis?

A) High NK cell activity

B) Elevated soluble CD25

C) Hyperfibrinogenemia

D) Low ferritin

Case Study

Which of the following would be consistent with the suspected diagnosis?

A) High NK cell activity

B) Elevated soluble CD25

C) Hyperfibrinogenemia

D) Low ferritin

The patient was evaluated for soluble CD25: levels were significantly elevated (2840 U/mL)

Hantel et al, *JITC*, 2018

HLH following checkpoint inhibitors

Given the patient's presentation and clinical symptoms, **hemophagocytic lymphohistiocytosis (HLH**) was suspected

Diagnostic criteria: 5 of 8

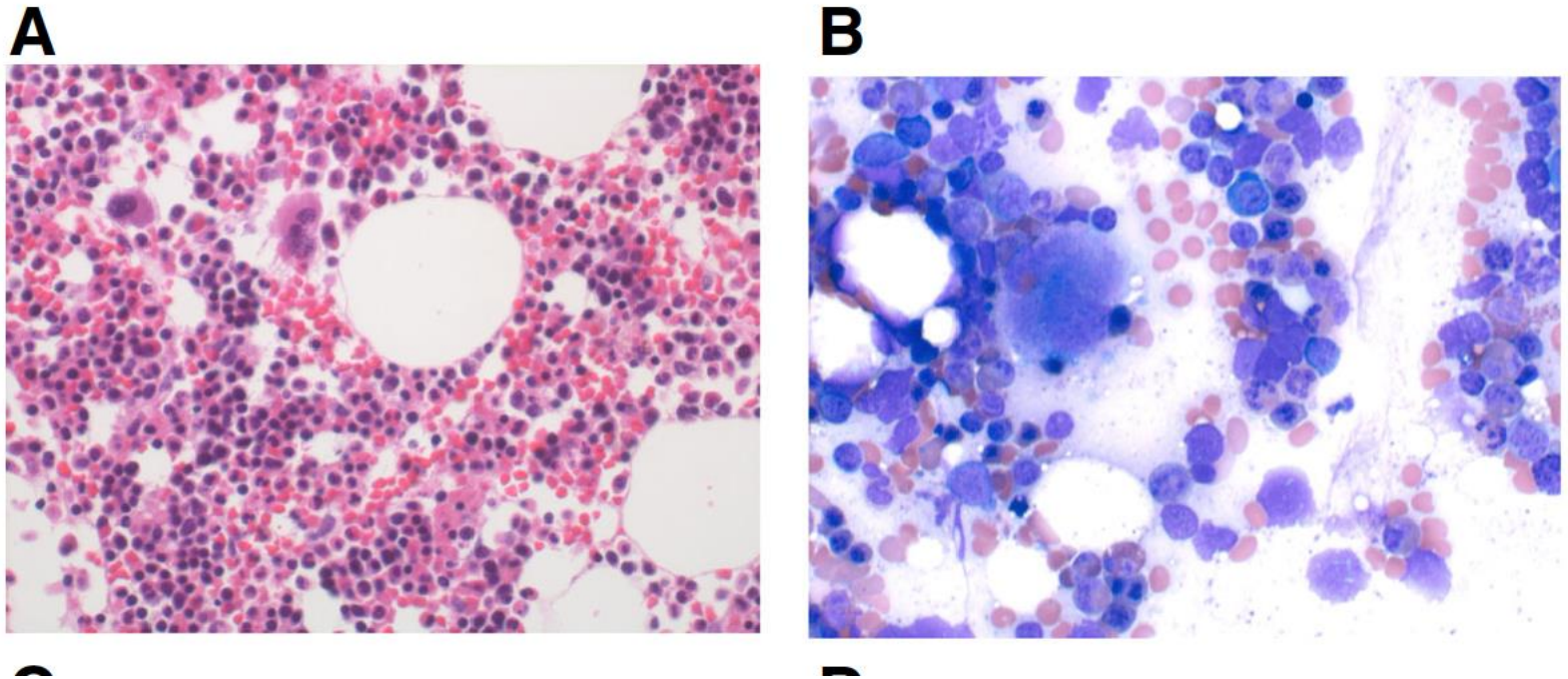
1. Fever
2. Splenomegaly
3. 2+ cytopenias
4. Hypertriglyceridemia +/- Hypofibrinogenemia
5. Hemophagocytosis
6. Elevated ferritin
7. Elevated soluble CD25
8. Low to absent NK cell activity

Management:

- Patient was given 1.5mg/kg methylprednisone every 8 hours
- Steroids decreased to 1.0 mg/kg oral prednisone
- Hemoglobin began to recover. On discharge, hemoglobin returned to 9.0 mg/dL without further transfusions

Hantel et al, *JITC*, 2018

Case Study Follow up



No evidence of melanoma involvement

Patient remains off treatment, in complete remission, 12 months later.

Hantel et al, *JITC*, 2018

HLH post ICI

Noseda *et al. Journal for ImmunoTherapy of Cancer* (2019) 7:117
https://doi.org/10.1186/s40425-019-0598-9

Journal for ImmunoTherapy of Cancer

SHORT REPORT Open Access

Haemophagocytic lymphohistiocytosis in patients treated with immune checkpoint inhibitors: analysis of WHO global database of individual case safety reports

Roberta Noseda[1*], Raffaela Bertoli[1], Laura Müller[1] and Alessandro Ceschi[1,2]

38 total cases have been reported suspecting ICIs as inciting drugs, most commonly in melanoma

HLH developed a median of 6.7 weeks after initiation of ICI therapy

Questions