

Immunotherapy for the Treatment of Skin Cancers

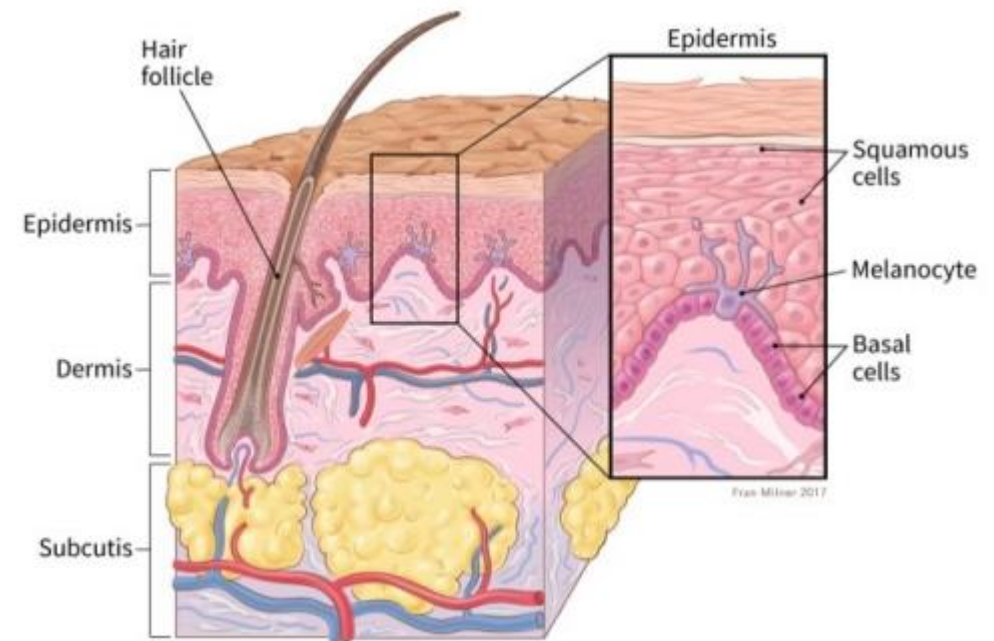
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Disclosures

- I have served on advisory boards for Array, BMS, Trieza and Novartis.
- I receive clinical trial support from BMS, Checkmate, Novartis, and Genentech.
- I will be discussing non-FDA approved indications during my presentation.

Background

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



Approved cytokines in melanoma

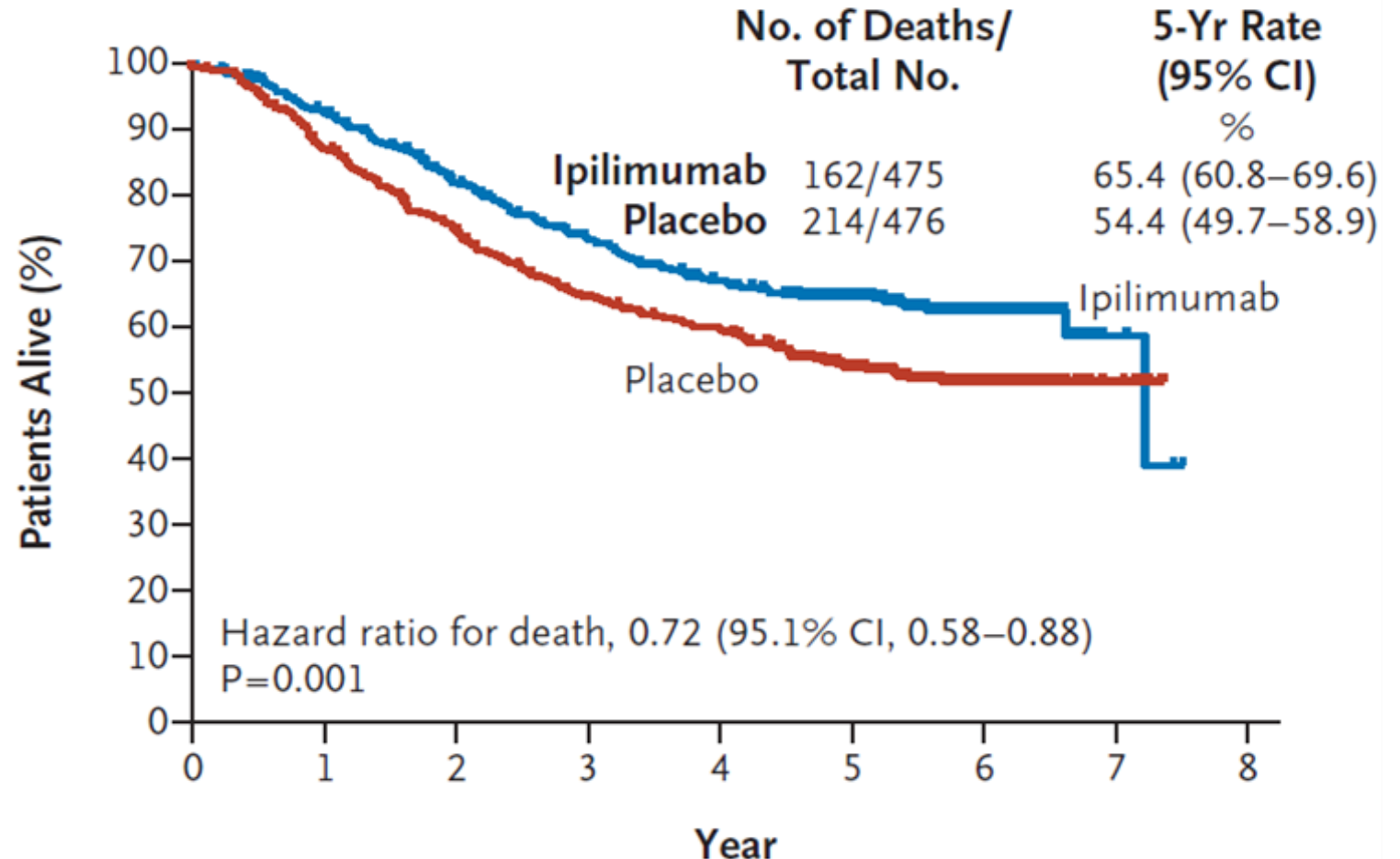
Drug	Indication	Dose
High-dose interferon alfa-2b	Adjuvant – high risk for systemic recurrence	Induction: 20m IU/m ² IV 5x/wk for 4 wks Maintenance: 10m IU/m ² s.c. 3x/wk for 48 wks
Interleukin-2 (Aldesleukin)	Stage IV	600k IU/kg/dose Q8hr, up to 14 doses; 9 days of rest; can repeat up to 28 doses per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

Approved checkpoint inhibitors in melanoma

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

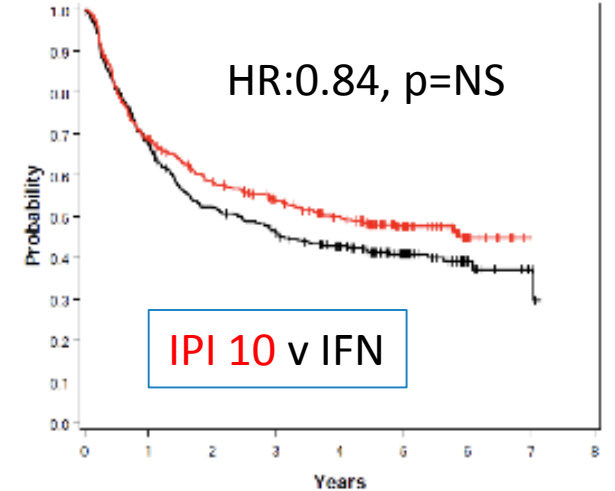
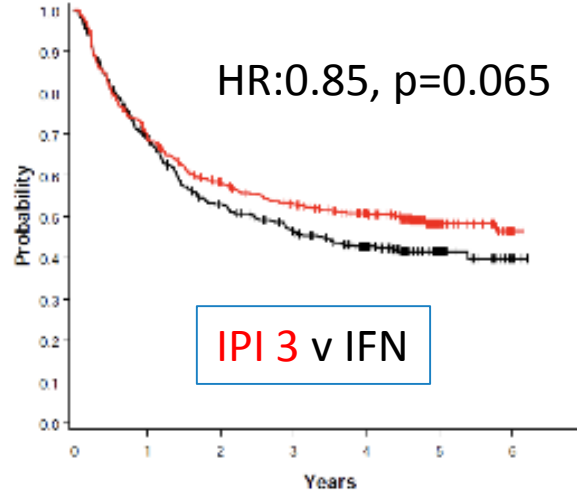


Adjuvant Ipilimumab in High-Risk Stage III Melanoma

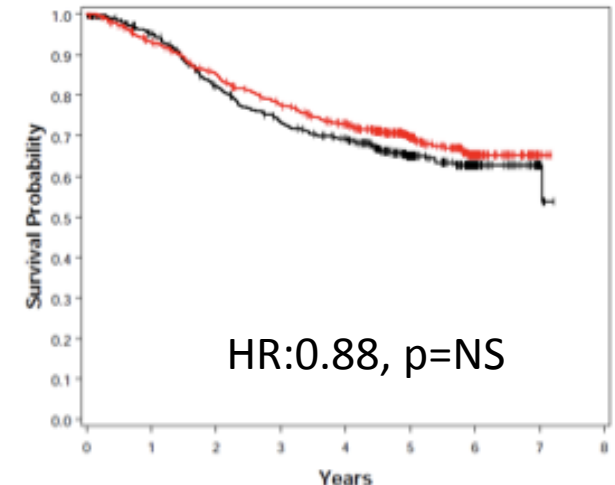
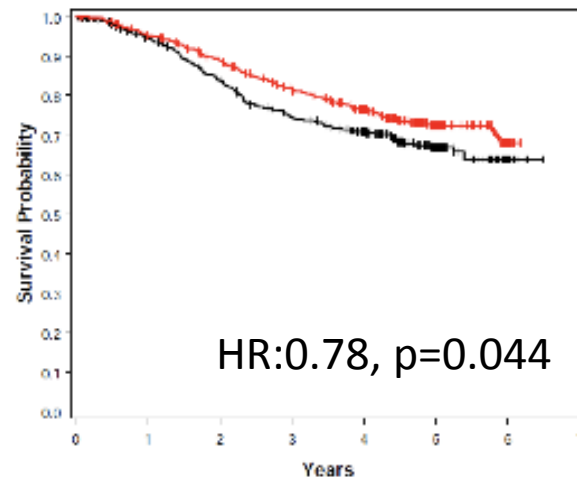
- ECOG 1609

- 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

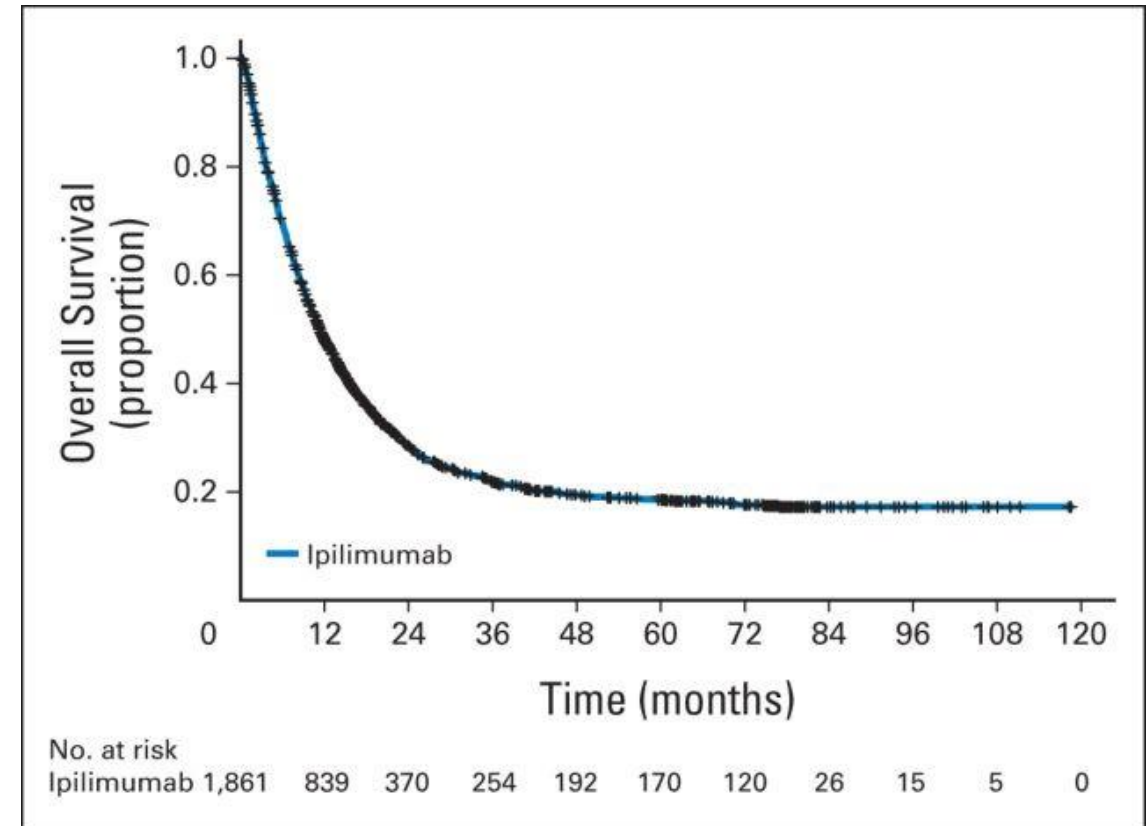


OS



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)

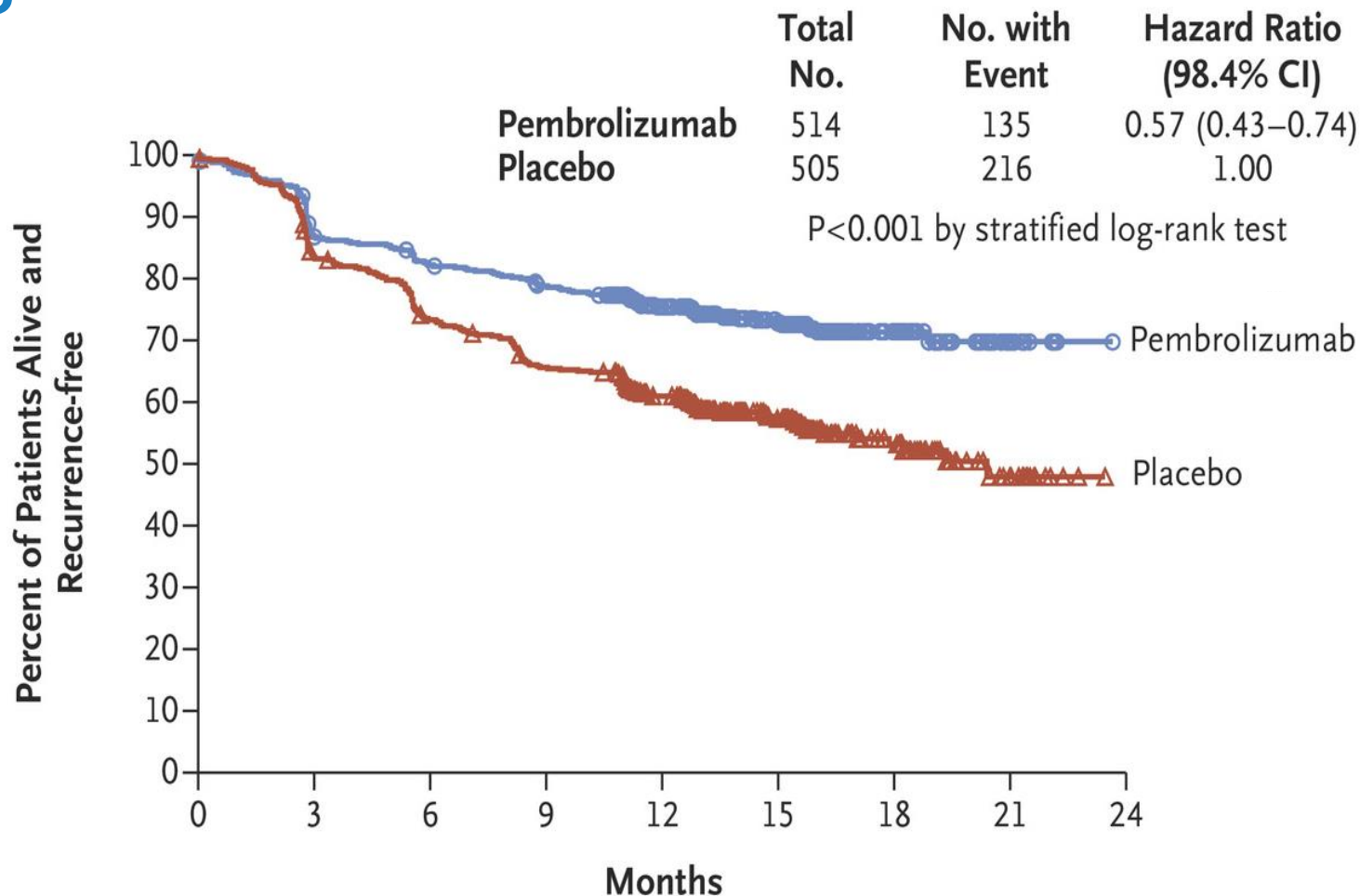


Approved checkpoint inhibitors in melanoma

Drug	Approved	Indication	Dose
Pembrolizumab	2014	Advanced/unresectable melanoma with progression after other therapy	200 mg Q3W*
	2015	1 st 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			

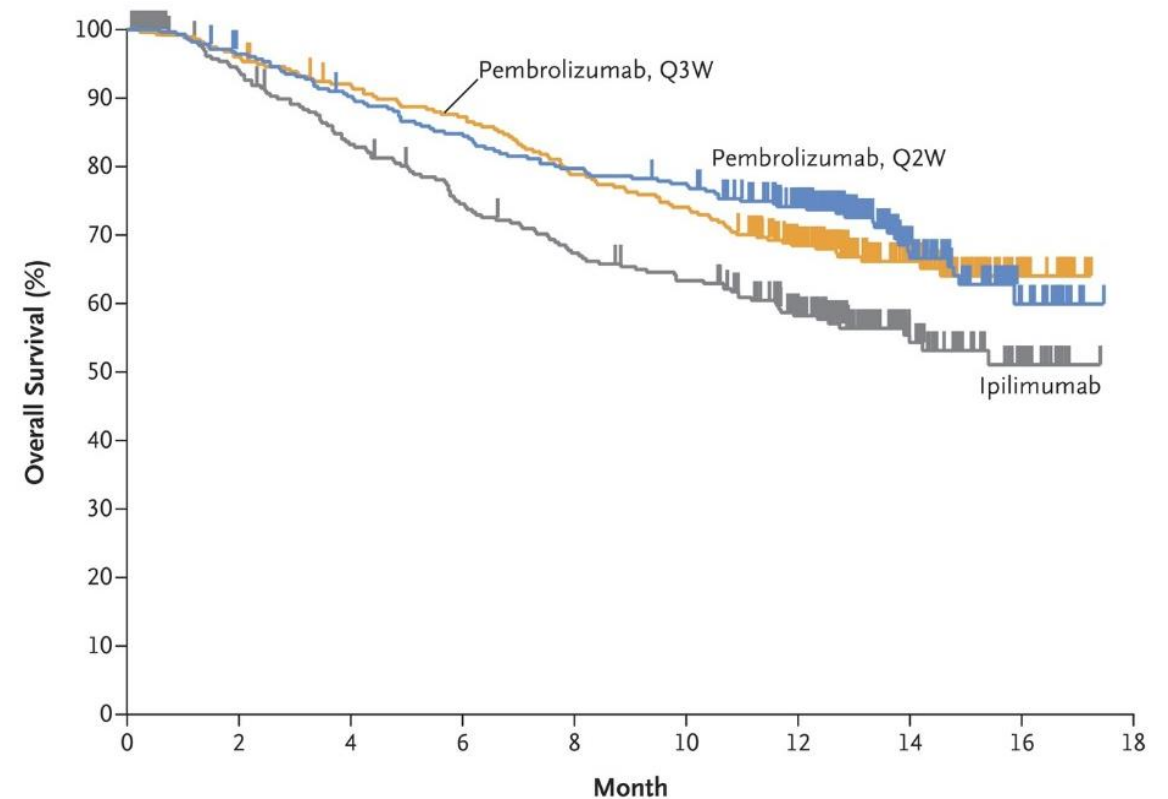
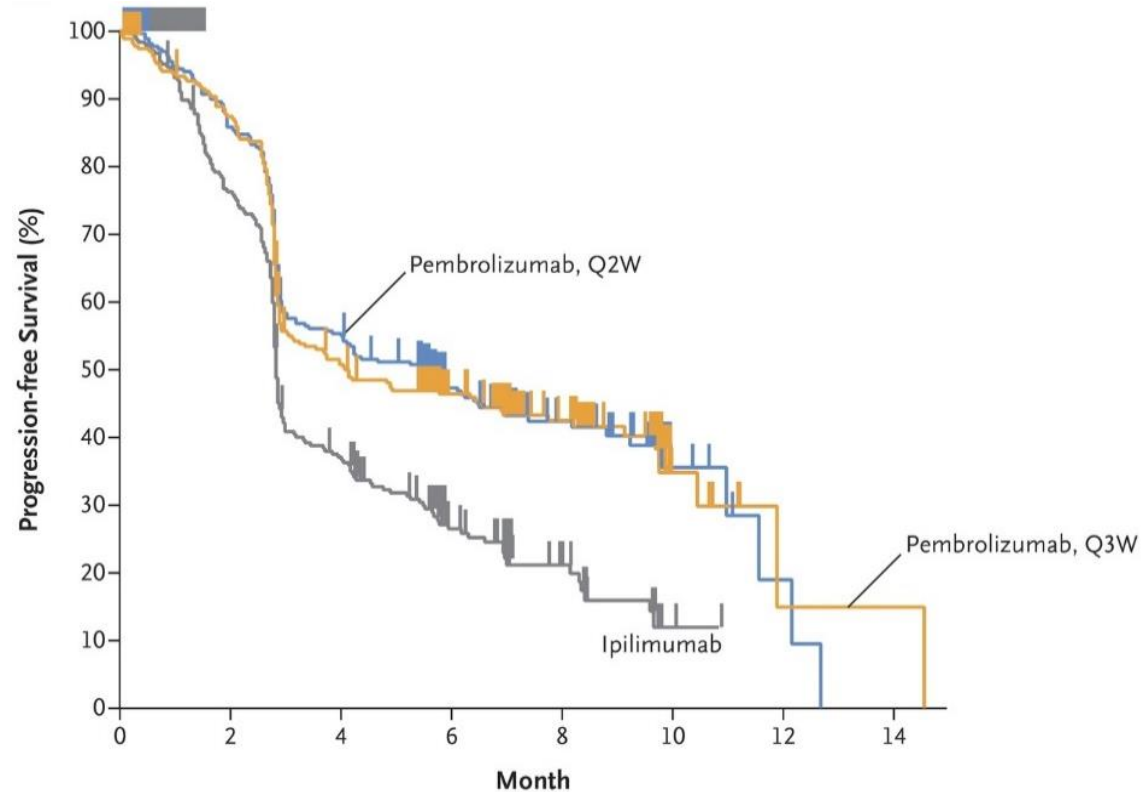
Adjuvant Pembrolizumab in High-Risk Stage III Melanoma

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



Pembrolizumab in Stage III/IV Melanoma

Phase III KEYNOTE-006 Trial



Approved checkpoint inhibitors in melanoma

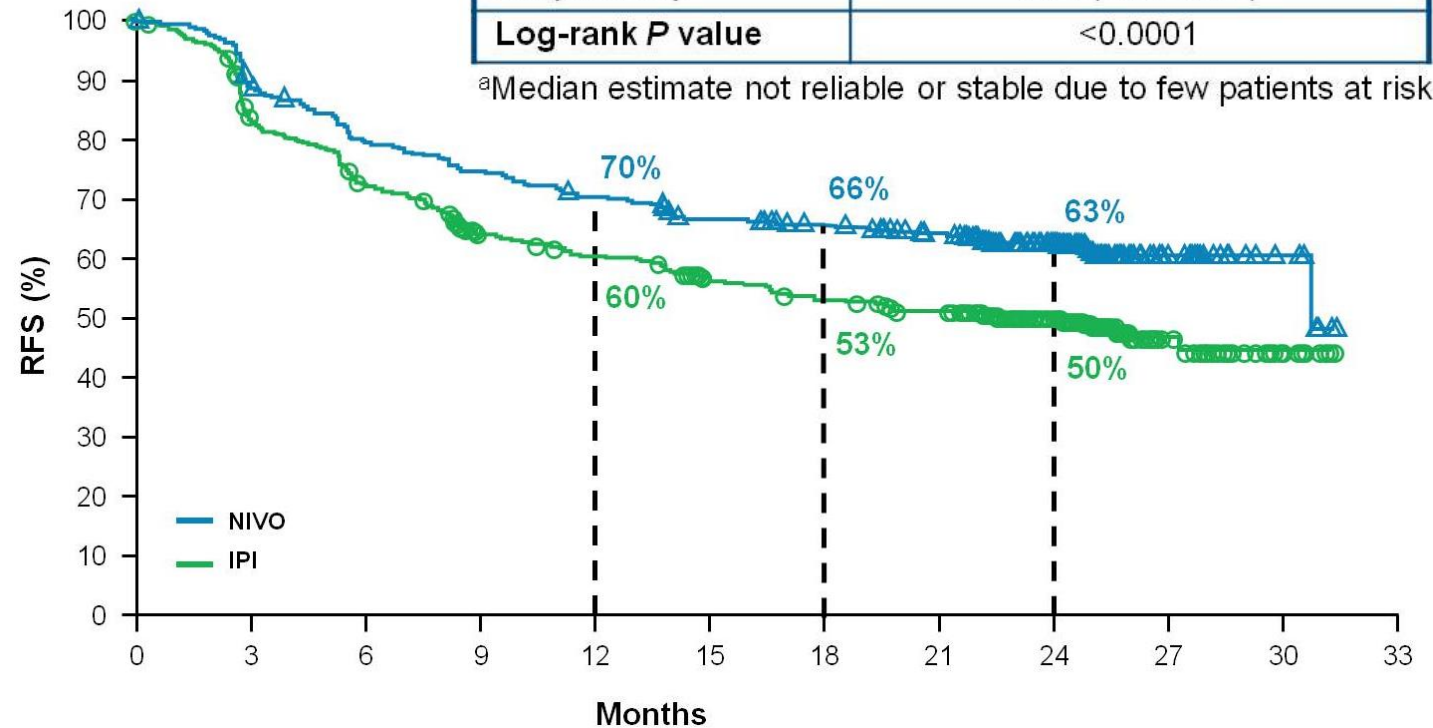
Drug	Approved	Indication	Dose
Nivolumab	2014	Unresectable/metastatic melanoma with progression after other therapy	240 mg Q2W or 480 mg Q4W*
	2017	Adjuvant treatment of melanoma after complete resection	240 mg Q2W or 480 mg Q4W
*Original approval was 3 mg/kg Q2W, updated to flat dosing regimen			

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	

^aMedian estimate not reliable or stable due to few patients at risk.

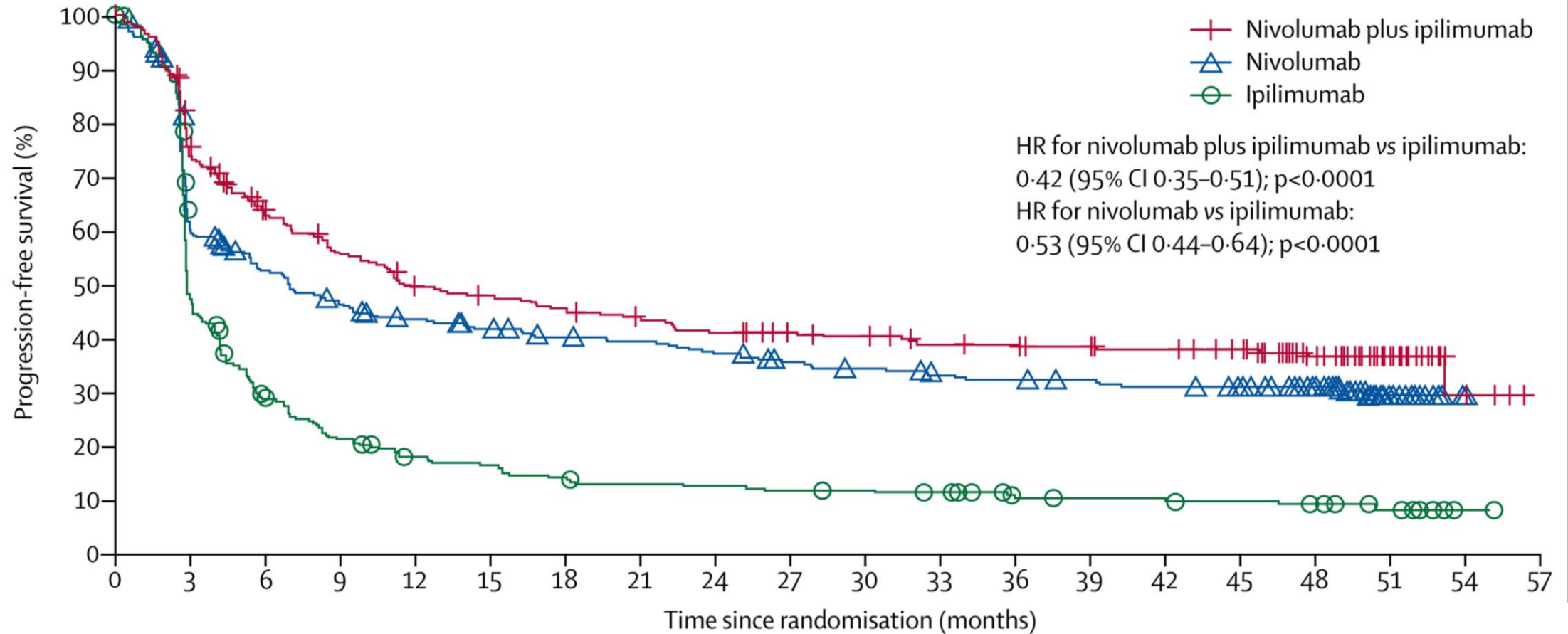


Approved checkpoint inhibitors in melanoma

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

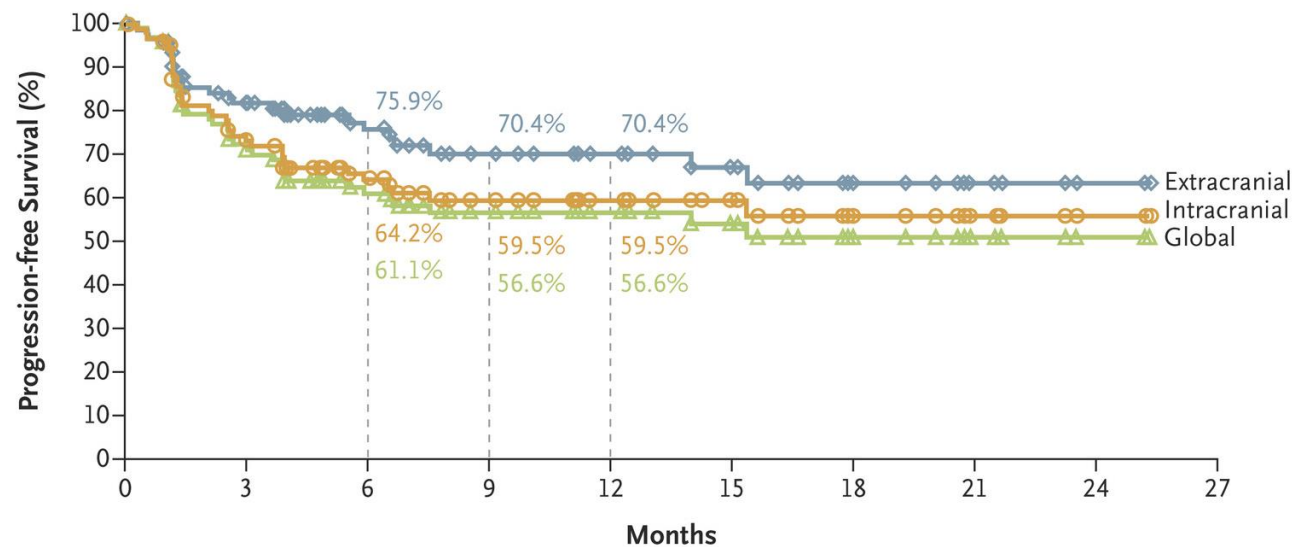
Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma

Phase III CheckMate 067 Trial

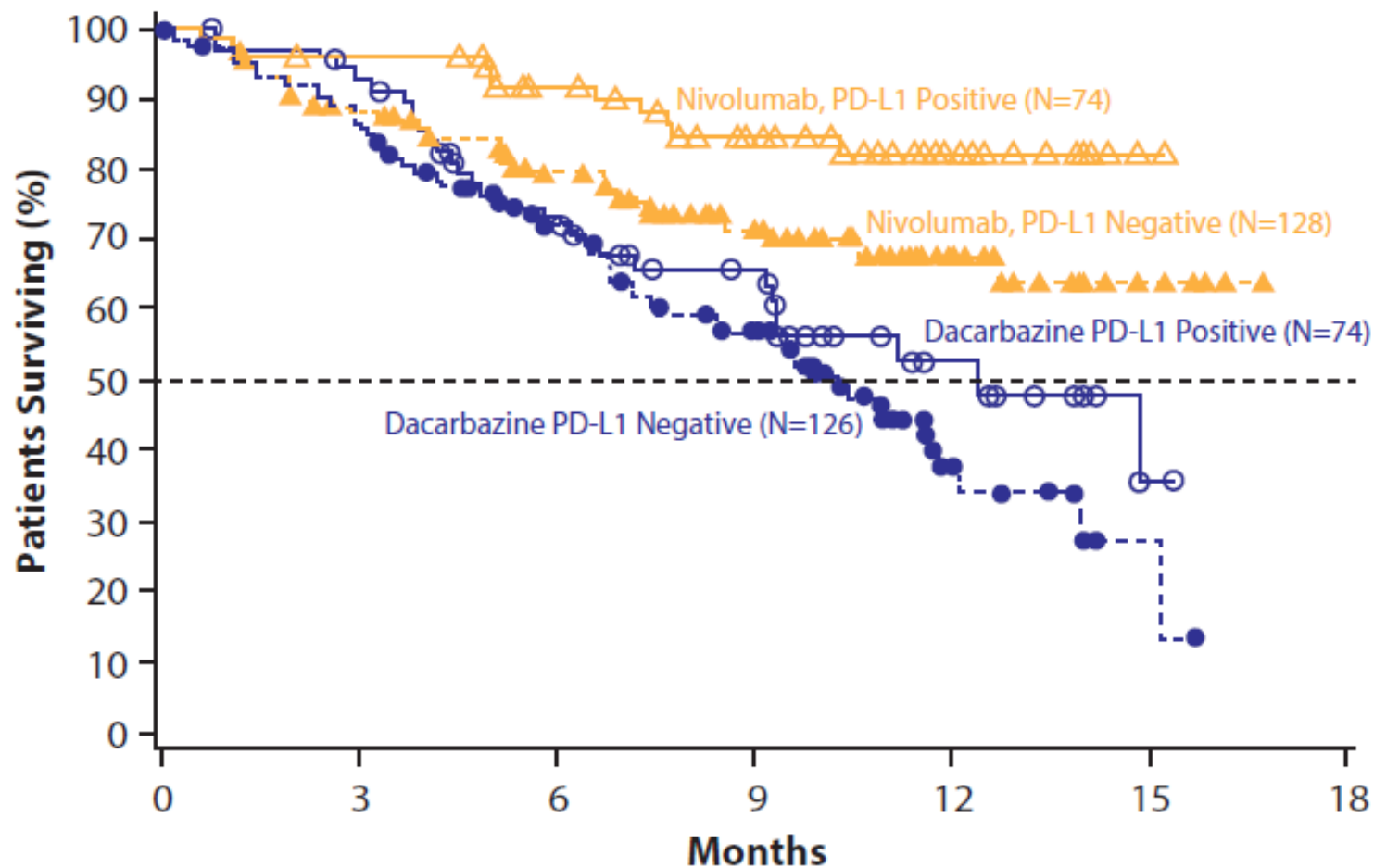


Combination Ipilimumab + Nivolumab for Patients with Asymptomatic Brain Metastases

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)

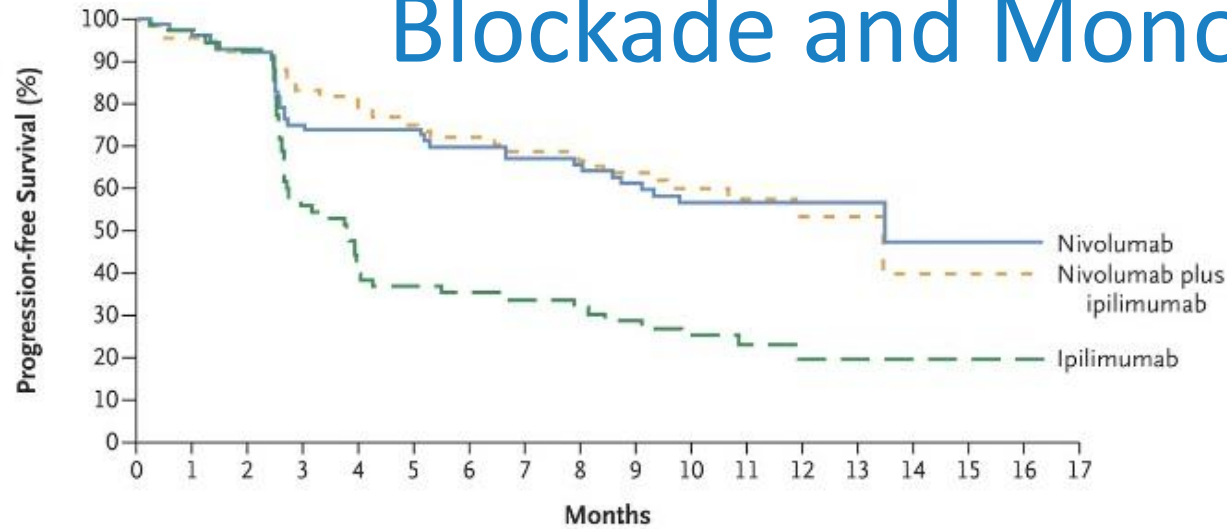


Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy

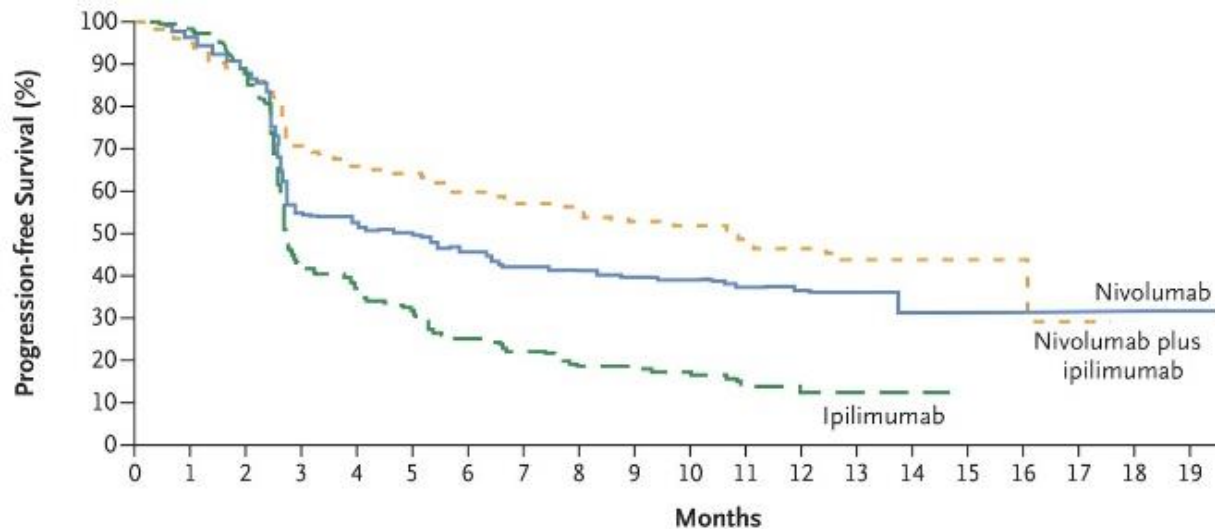


	Patients Who Died n/N	Median Survival mo (95% CI)
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

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

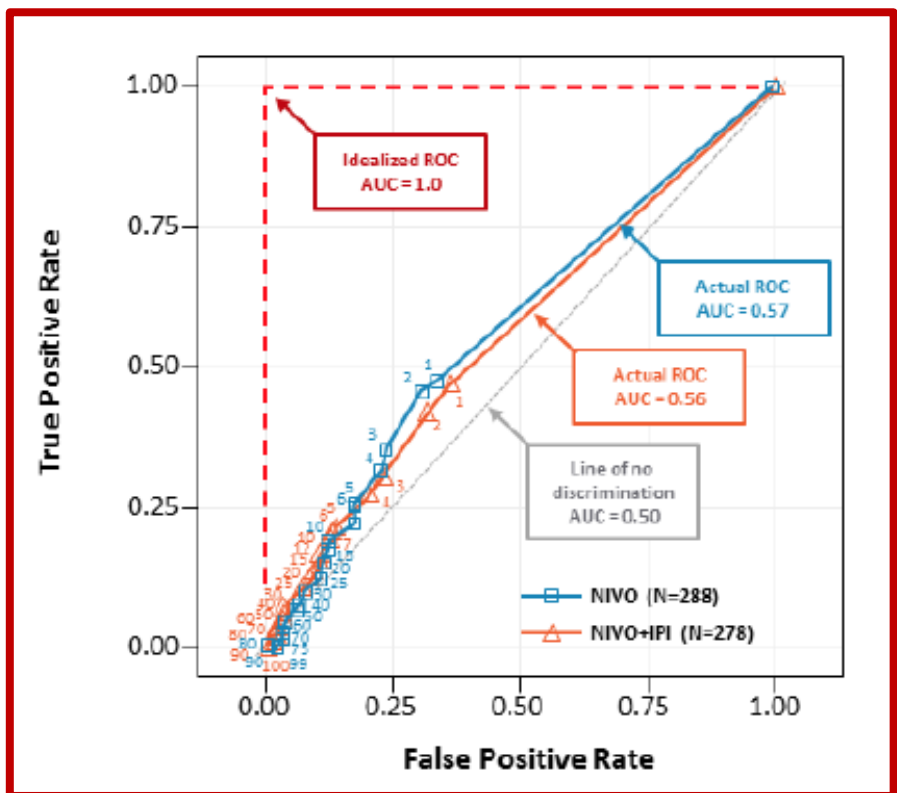


Tumor PD-L1 Positive Patients



Tumor PD-L1 Negative Patients

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



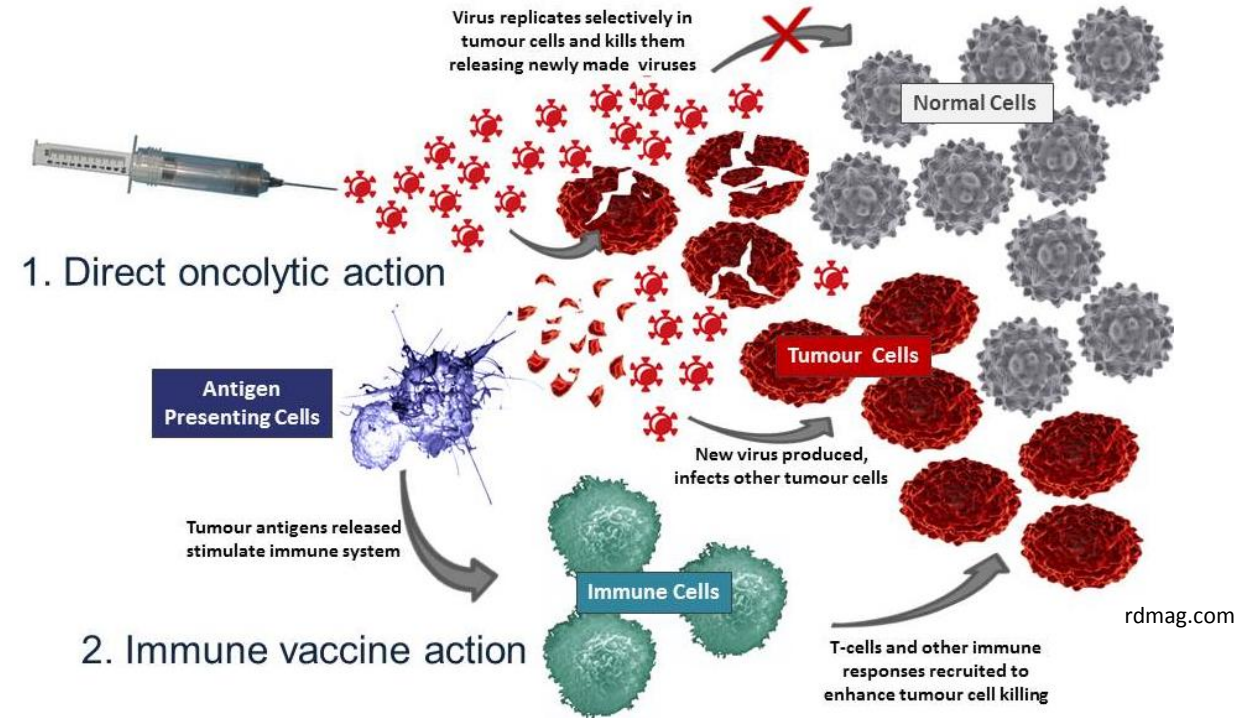
PDL-1 (%)	≥ 1	< 1	≥ 5	< 5	≥ 10	< 10
Ipilimumab	19%	18%	21%	17%	20%	18%
Nivolumab	54%	35%	58%	42%	58%	44%
<u>Ipi/Nivo</u>	65%	54%	72%	56%	85%	55%

...but, PD-L1 status predicts higher response rate with combo at every PD-L1 expression cut-off

In development: Neoadjuvant immunotherapy in advanced melanoma

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

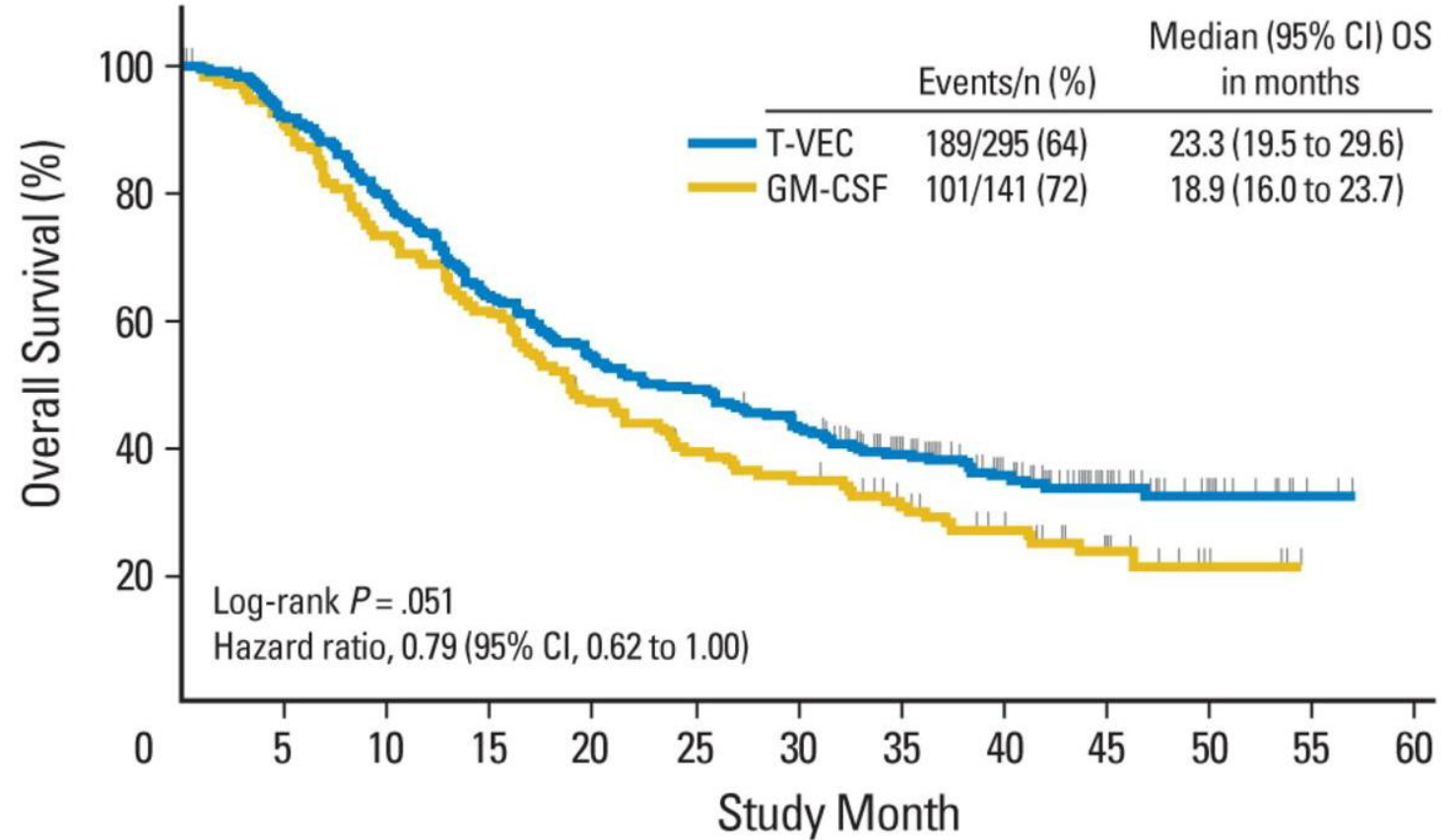
Approved oncolytic virus in melanoma



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

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

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

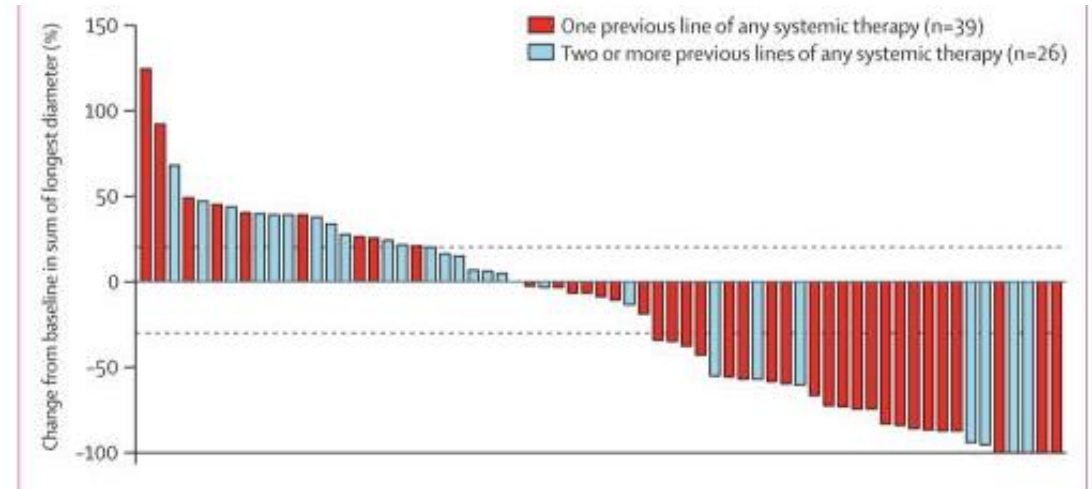
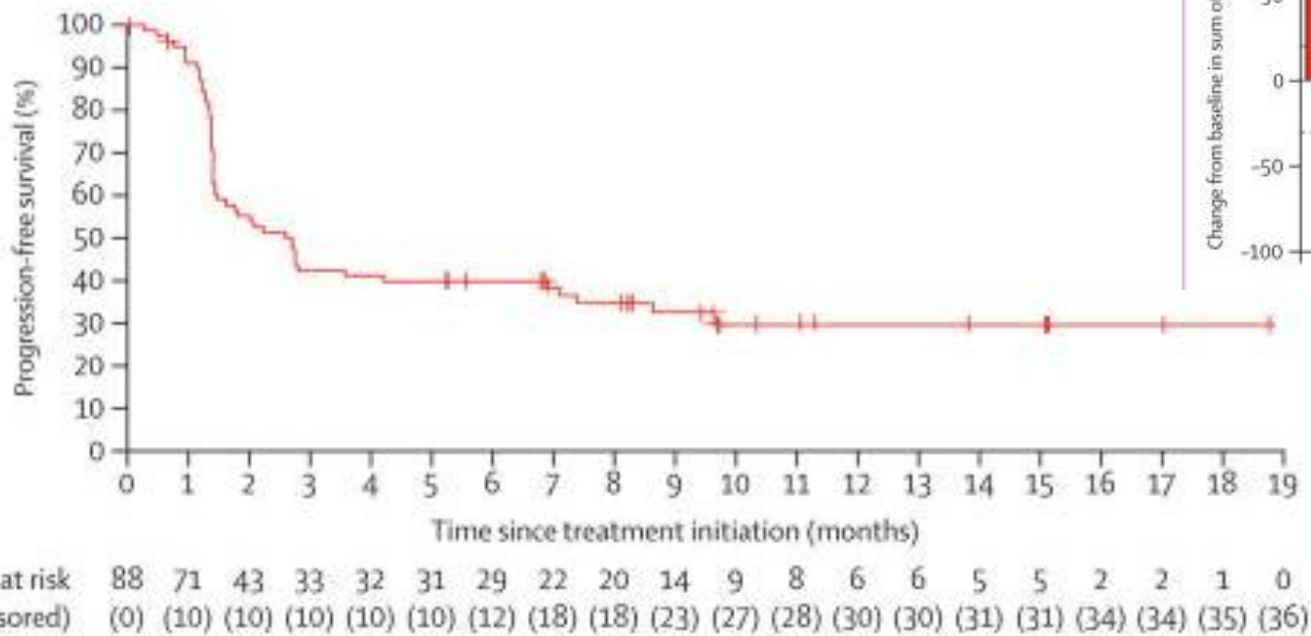


Approved checkpoint inhibitors in other skin cancers

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

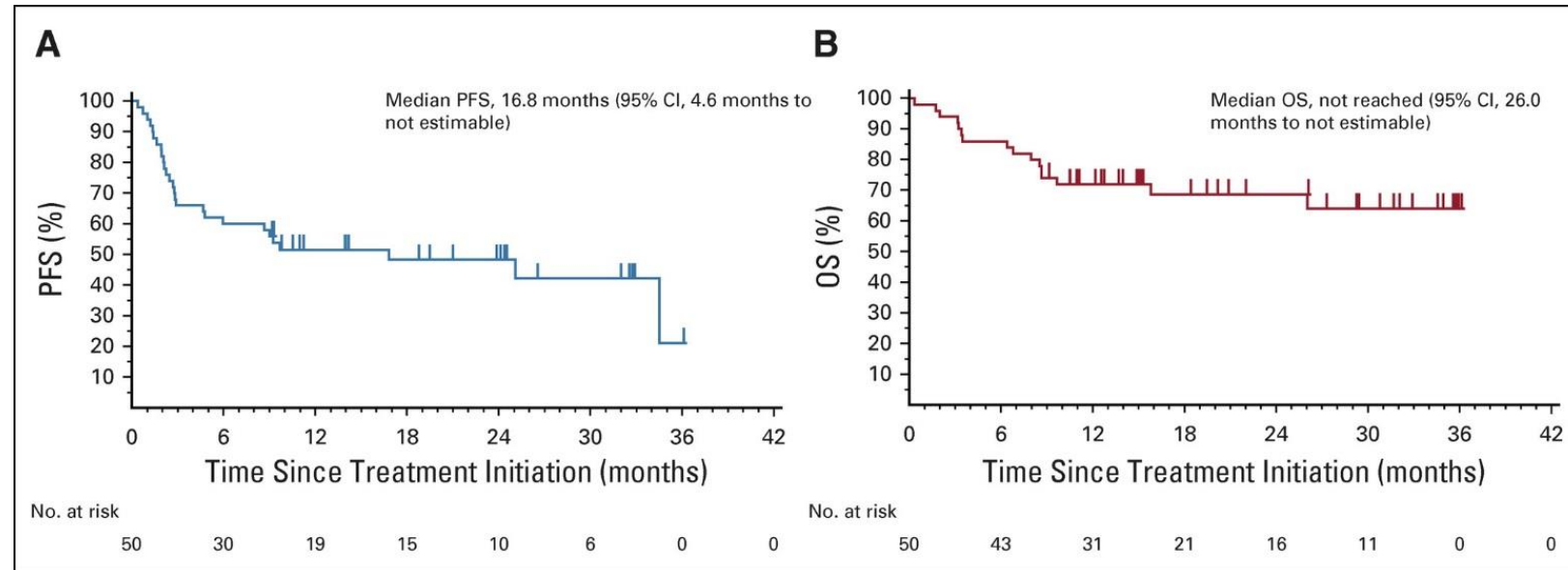
Avelumab in 2nd-line metastatic Merkel Cell carcinoma

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



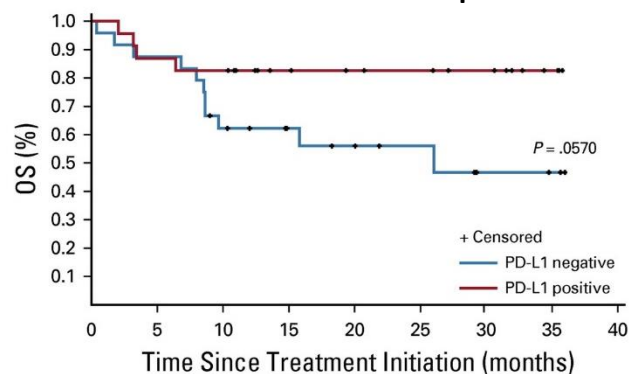
Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

- 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%

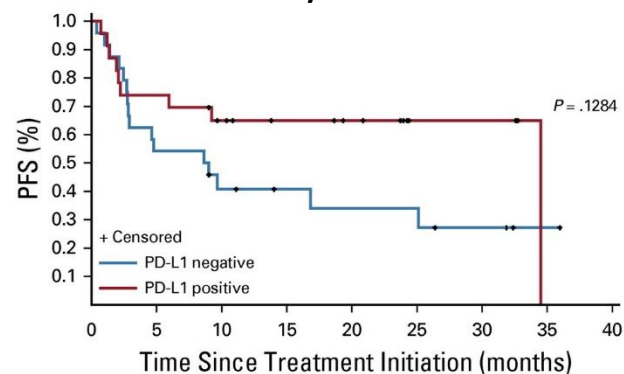


Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

PD-L1 expression by tumor cells only

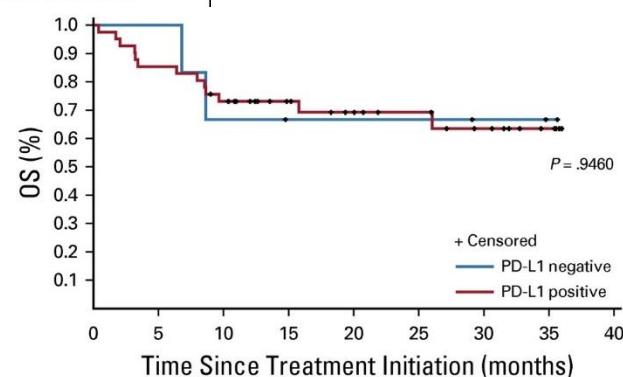


No. at risk (events)									
PD-L1 negative	24 (0)	21 (3)	14 (9)	10 (9)	8 (10)	6 (10)	3 (11)	2 (11)	0 (11)
PD-L1 positive	23 (0)	20 (3)	19 (4)	13 (4)	11 (4)	10 (4)	8 (4)	3 (4)	0 (4)

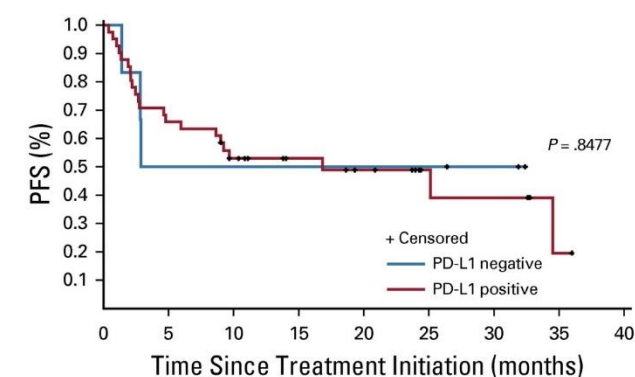


No. at risk (events)									
PD-L1 negative	24 (0)	13 (11)	8 (14)	6 (14)	5 (15)	5			
PD-L1 positive	23 (0)	17 (6)	13 (8)	10 (8)	8 (8)	3			

PD-L1 on all cells in tumor



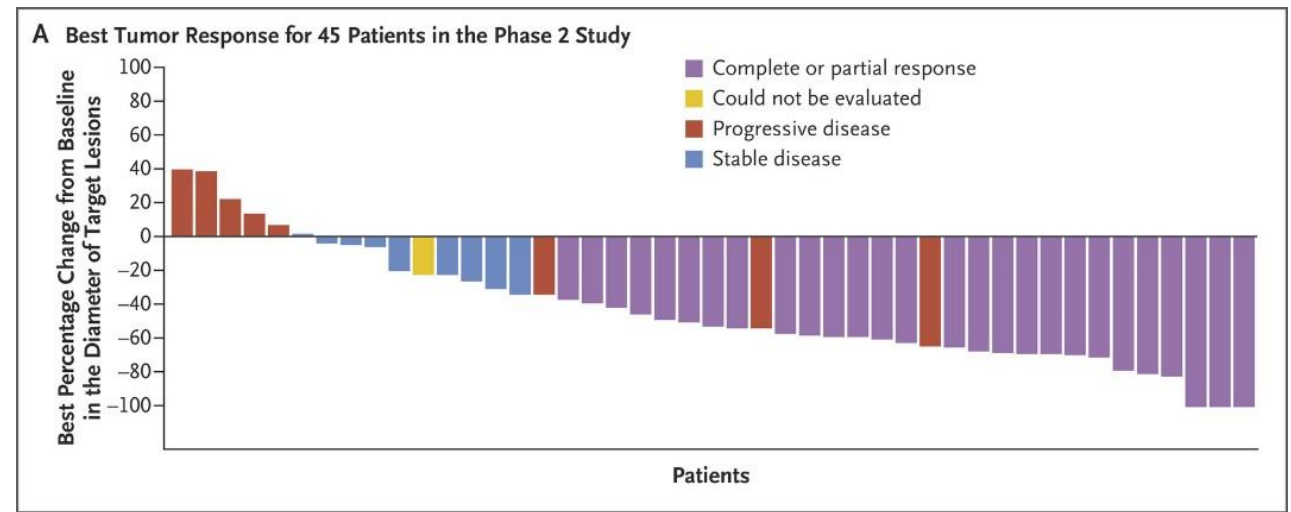
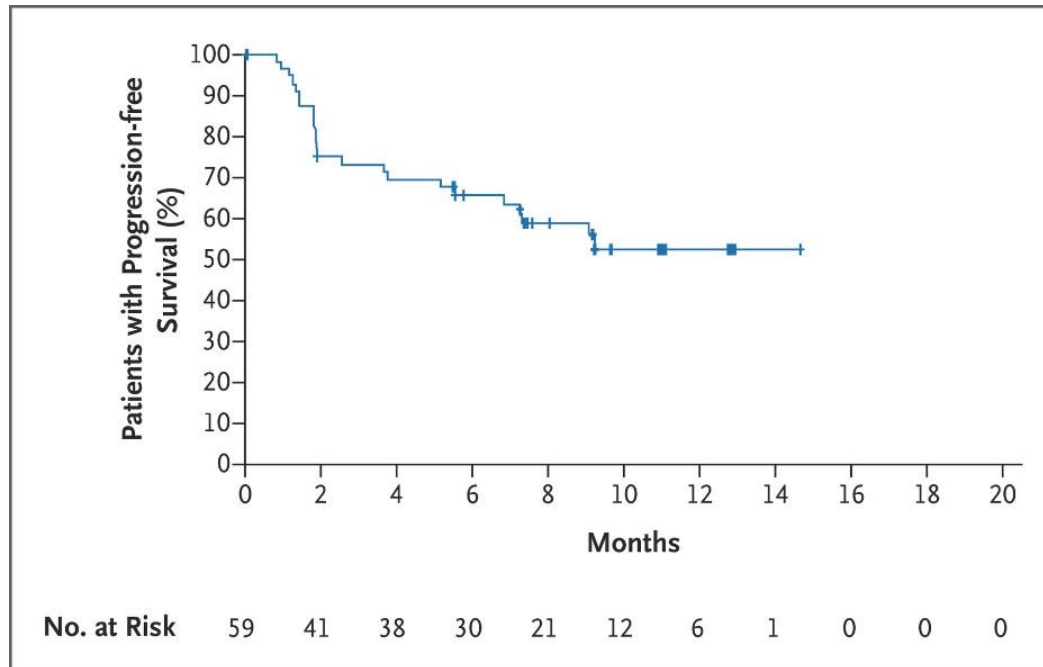
No. at risk (events)									
PD-L1 negative	6 (0)	6 (0)	4 (2)	3 (2)	3 (2)	2 (2)	1 (2)	0 (2)	
PD-L1 positive	41 (0)	35 (6)	29 (11)	20 (11)	16 (12)	13 (12)	9 (13)	4 (13)	0 (13)



No. at risk (events)									
PD-L1 negative	6 (0)	3 (3)	3 (3)	3 (3)	3 (3)	3 (3)	2 (3)	0 (3)	
PD-L1 positive	41 (0)	27 (14)	18 (19)	13 (19)	10 (20)	5 (20)	4 (21)	1 (22)	0 (22)

Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

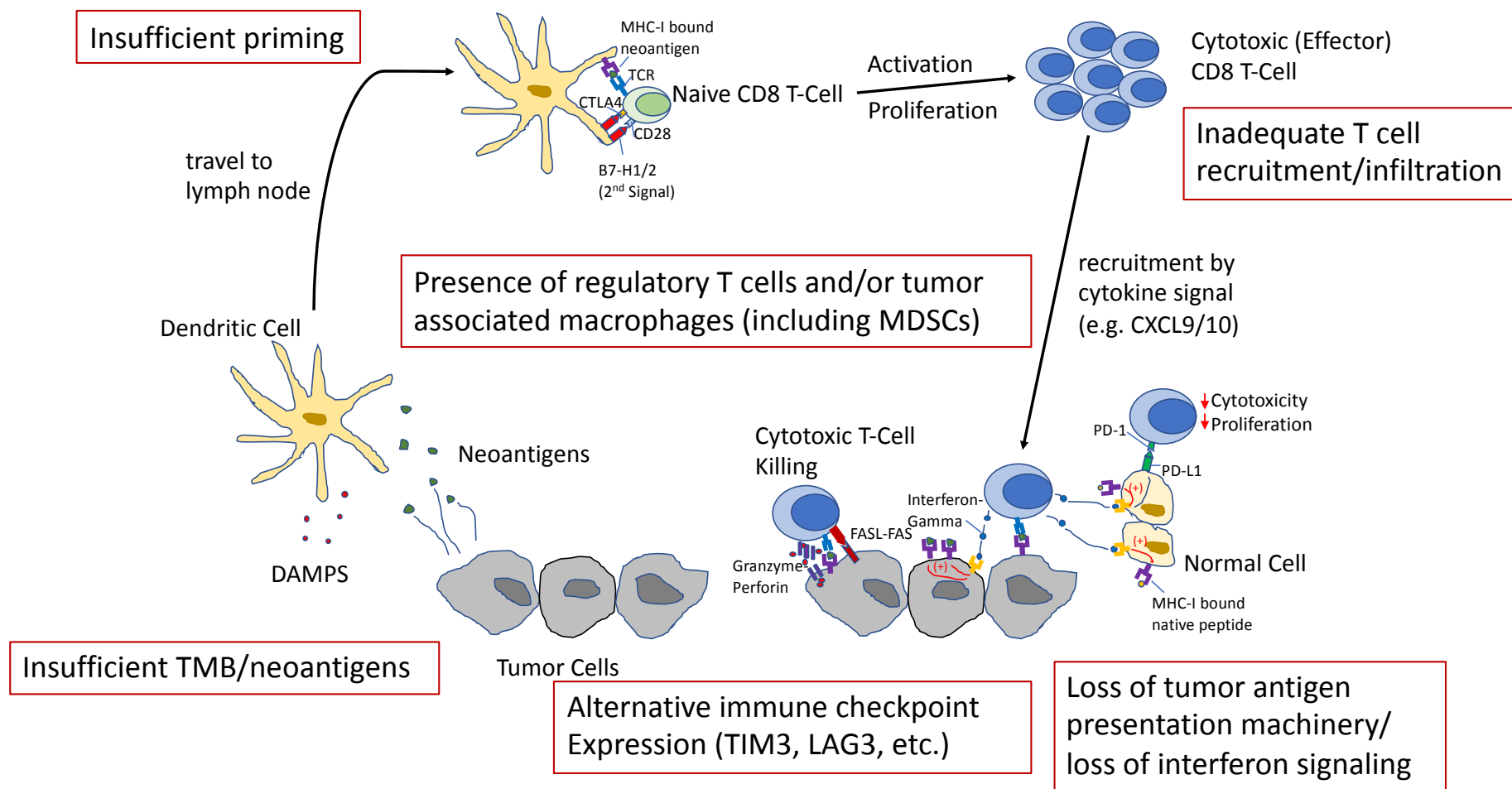
- Cemiplimab 3mg/kg Q2W
- 47% response rate in metastatic patients
- 60% of locally advanced had objective response



Migden, NEJM 2018.

Developmental Immunotherapeutic Strategies for Melanoma

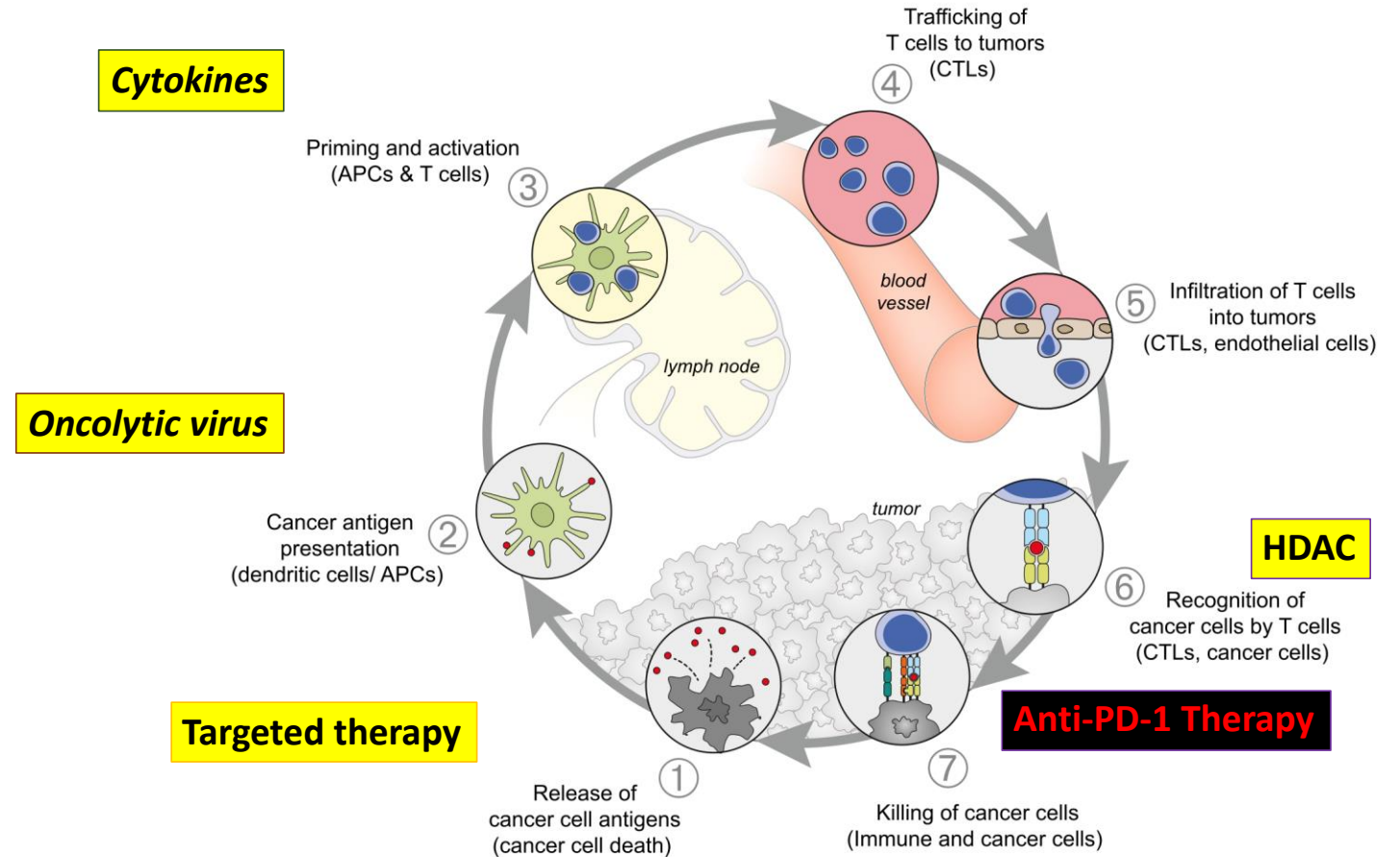
How does immune checkpoint inhibitor therapy fail?



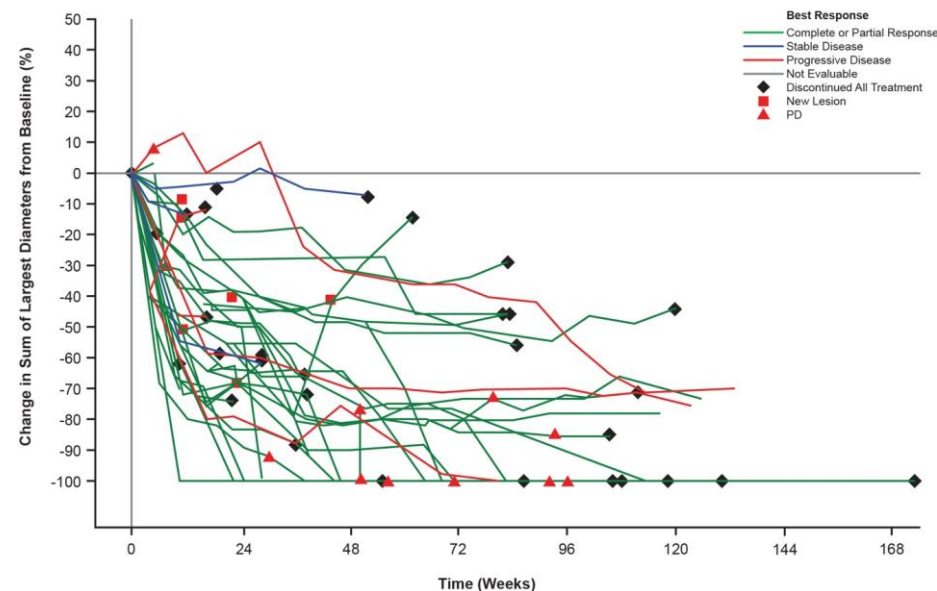
Developmental Immunotherapeutic Strategies for Melanoma

How do we overcome resistance?

Combination therapy



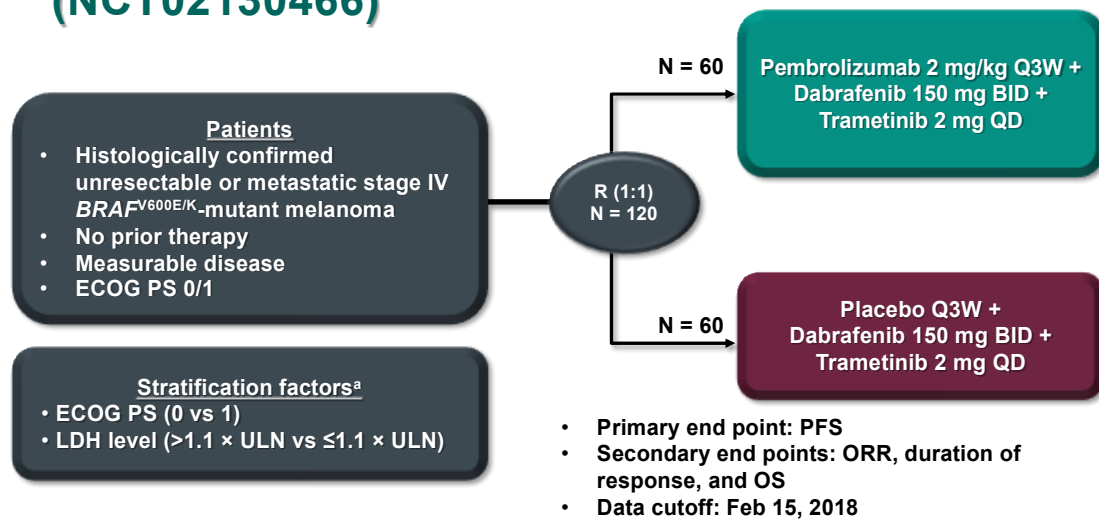
- Cobimetinib + vemurafenib + atezolizumab
- ORR: 71.8%
- Median duration of response: 17.4 mo



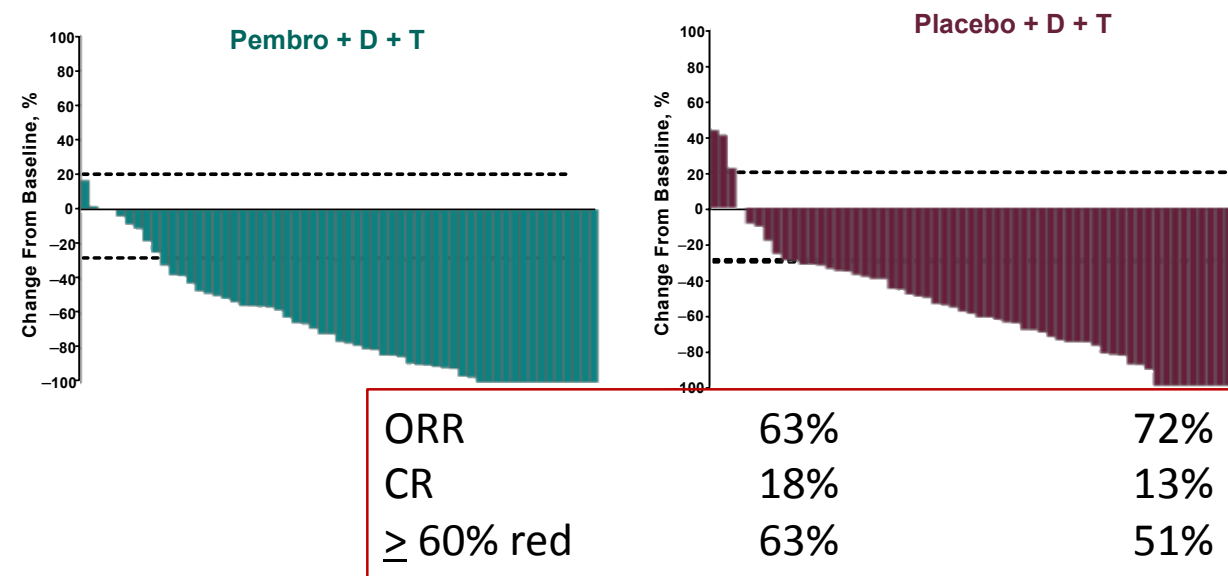
Sullivan et al. Nature Med. 2019

In development: Combined IO with BRAF targeted therapy

KEYNOTE-022 Part 3 Study Design (NCT02130466)



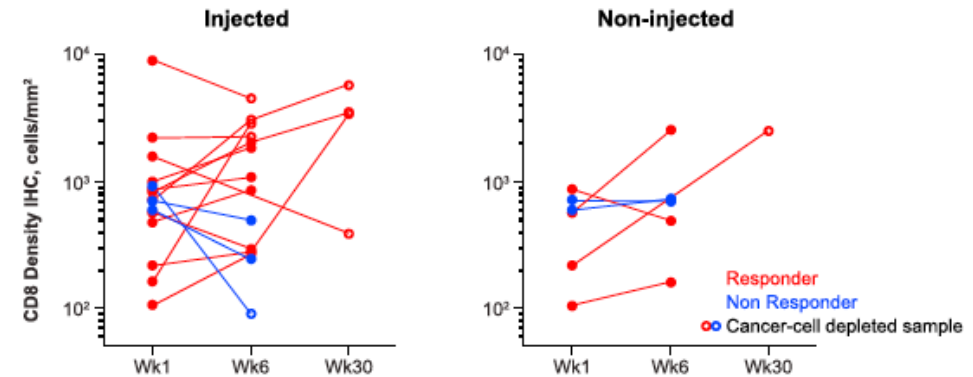
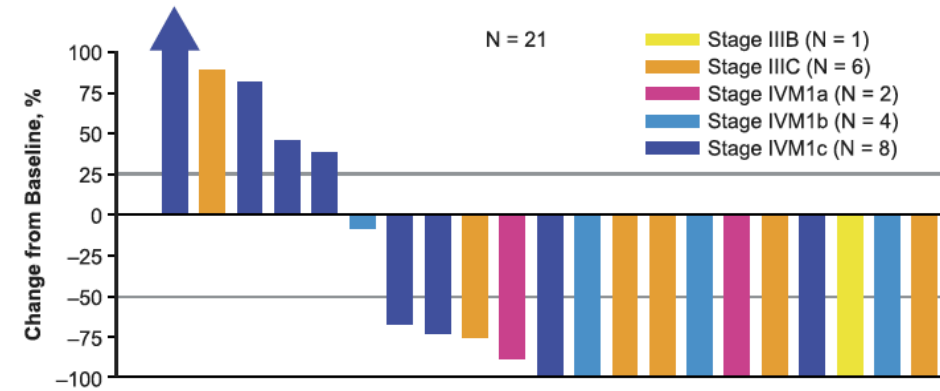
^aOwing to the small number of patients enrolled in the ECOG PS 1 and LDH $\leq 1.1 \times ULN$ strata, these strata were combined.



In development: Combined IO with Oncolytic Virus



Phase I: Pembrolizumab + TVEC

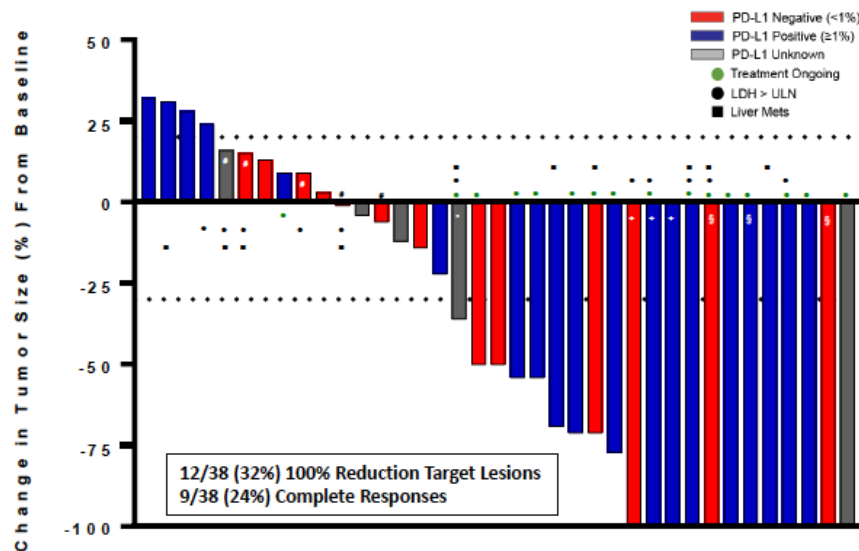


Ribas et al Cell 2017

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

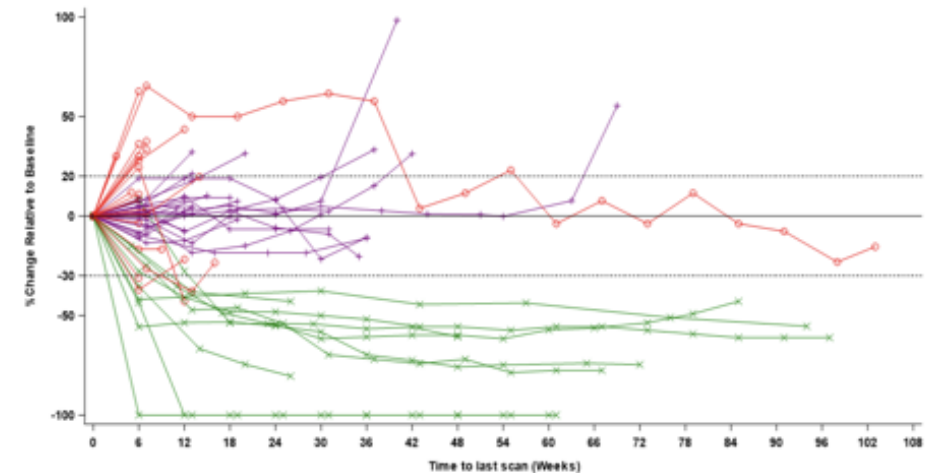
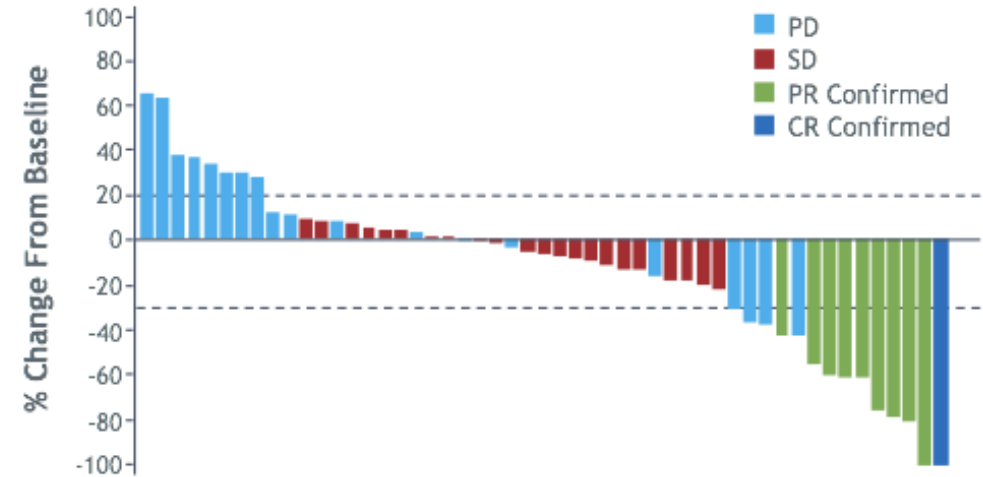


1L Melanoma (n=38 Efficacy Evaluable)	Overall Response Rate
Confirmed ORR (CR+PR)	20 (53%)
CR	9 (24%)
DCR (CR+PR+SD)	29 (76%)
PD-L1 negative (n=14)	6 (43%)
PD-L1 positive (n=19)	13 (68%)
PD-L1 unknown (n=5)	1 (20%)
LDH > ULN (n=11)	5 (45%)
Liver metastases (n=10)	5 (50%)

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

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



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 #1: stage IV

JS, male patient in 60s

- Patient with a history of melanoma 10 years prior, back lesion, <1mm, non-ulcerated, at the time no SLN or adjuvant therapy
- Found to have new pulmonary lesion concerning for primary lung cancer, thoracic surgeon feels this is unresectable
- Biopsy performed and reveals malignant melanoma, BRAF wt

Case #1: stage IV BRAF wt

- Systemic therapy
 - Nivolumab
 - Pembrolizumab
 - Ipilimumab
 - Nivolumab plus ipilimumab
 - High-dose IL-2
 - Targeted Rx based on next-generation sequencing
 - Clinical trial

Case #1: stage IV BRAF wt

- Systemic therapy
 - **Nivolumab**
 - **Pembrolizumab**
 - Ipilimumab
 - Nivolumab plus ipilimumab
 - High-dose IL-2
 - Targeted Rx based on next-generation sequencing
 - Clinical trial

Case #2: stage IV

JS, male patient in 60s – SAME PATIENT

- Patient with a history of melanoma 10 years prior, back lesion, <1mm, non-ulcerated, at the time no SLN or adjuvant therapy
- Found to have new pulmonary lesion concerning for primary lung cancer
- Biopsy performed and reveals malignant melanoma, BRAF MUTATED

Case #2: stage IV BRAF mutant

- Systemic therapy
 - Nivolumab
 - Pembrolizumab
 - Ipilimumab
 - Nivolumab plus ipilimumab
 - High-dose IL-2
 - BRAF/MEK targeted therapy

Case #2: stage IV BRAF mutant

- Systemic therapy
 - **Nivolumab**
 - **Pembrolizumab**
 - Ipilimumab
 - Nivolumab plus ipilimumab
 - High-dose IL-2
 - BRAF/MEK targeted therapy

Case #3: stage IV

JS, male patient in 60s – SAME PATIENT

- Patient with a history of melanoma 10 years prior, back lesion, <1mm, non-ulcerated, at the time no SLN or adjuvant therapy
- Found to have new pulmonary lesion concerning for primary lung cancer
- Biopsy performed and reveals malignant melanoma, BRAF MUTATED
- Patient having hip pain and found to have right acetabular bony lesion

Case #3: stage IV BRAF mutant

- Systemic therapy
 - Nivolumab
 - Pembrolizumab
 - Ipilimumab
 - Nivolumab plus ipilimumab
 - High-dose IL-2
 - BRAF/MEK targeted therapy

Radiation to hip lesion

Case #3: stage IV BRAF mutant

- Systemic therapy
 - Nivolumab
 - Pembrolizumab
 - Ipilimumab
 - **Nivolumab plus ipilimumab**
 - High-dose IL-2
 - BRAF/MEK targeted therapy

Radiation to hip lesion

Case #3: What if the patient is found to have a brain metastasis?

- Systemic therapy
 - Nivolumab
 - Pembrolizumab
 - Ipilimumab
 - Nivolumab plus ipilimumab
 - High-dose IL-2
 - BRAF/MEK targeted therapy

Radiation to brain lesion?

Case #3: What if the patient is found to have a brain metastasis?

- Systemic therapy
 - Nivolumab
 - Pembrolizumab
 - Ipilimumab
 - **Nivolumab plus ipilimumab**
 - High-dose IL-2
 - BRAF/MEK targeted therapy

Radiation to brain lesion?