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

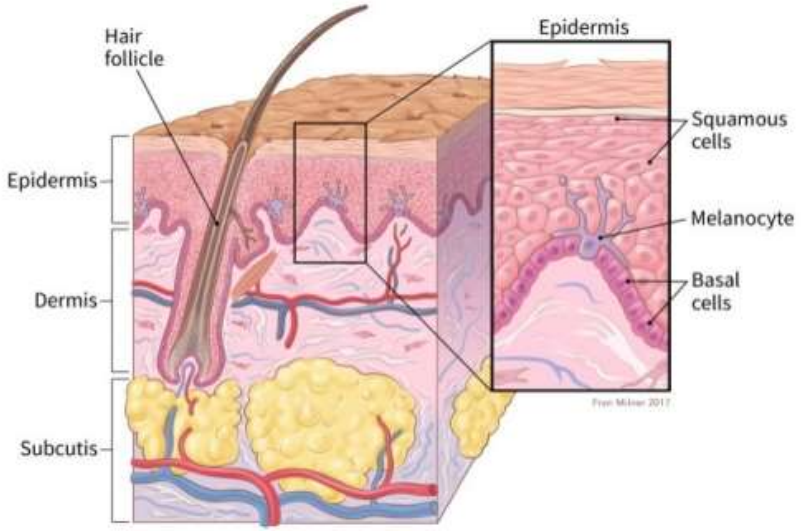
sitc Society for Immunotherapy of Cancer

Disclosures

- Consulting Fees: Novartis, BMS, EMD Serrono
- I will be discussing non-FDA/non-Health Canada 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 (for *historical* interest only)

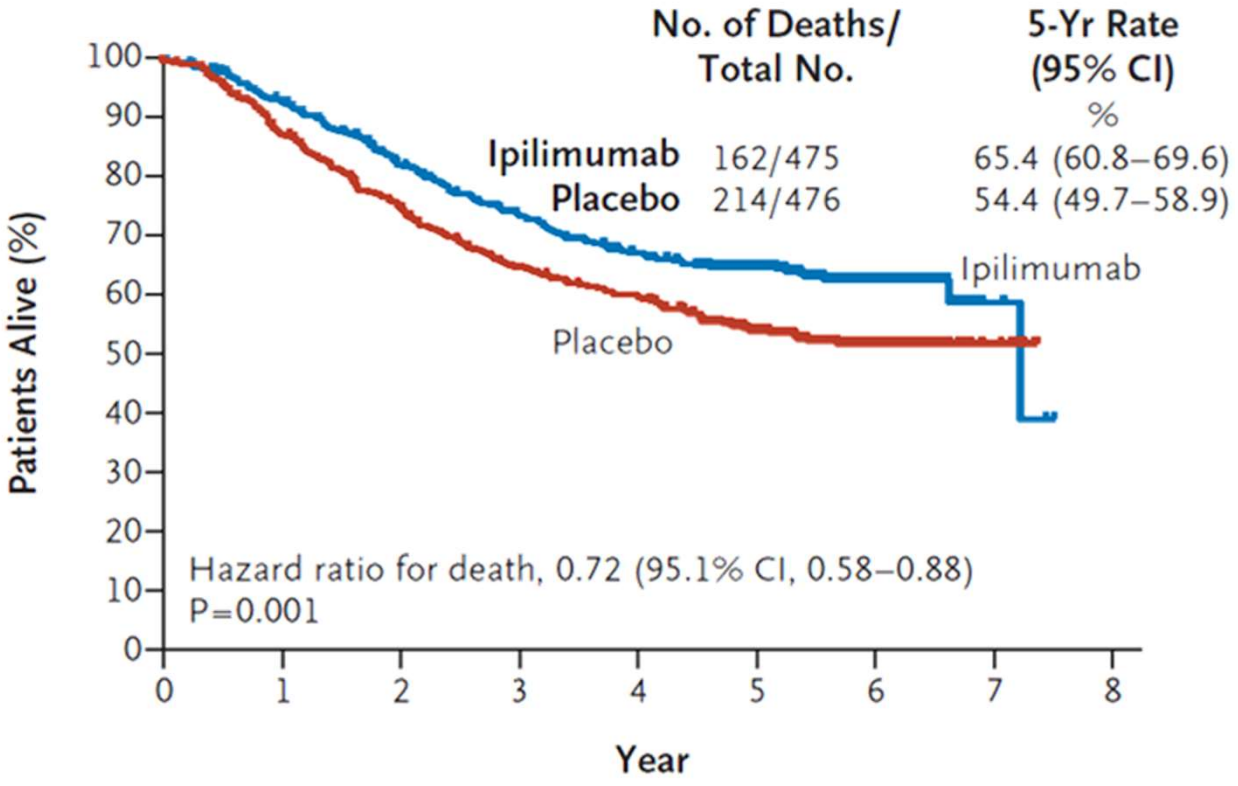
Drug	Indication	Dose
High-dose interferon alfa-2b	Adjuvant – high risk for systemic recurrence	Induction: 20m IU/m^2 IV 5x/wk for 4 wks Maintenance: 10m IU/m^2 s.c. 3x/wk for 48 wks
Interleukin-2 (Aldesleukin)	Stage IV	600k IU/kg/dose Q8hr, up to 14 doses; 9 days of rest; can repeat up to 28 doses per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



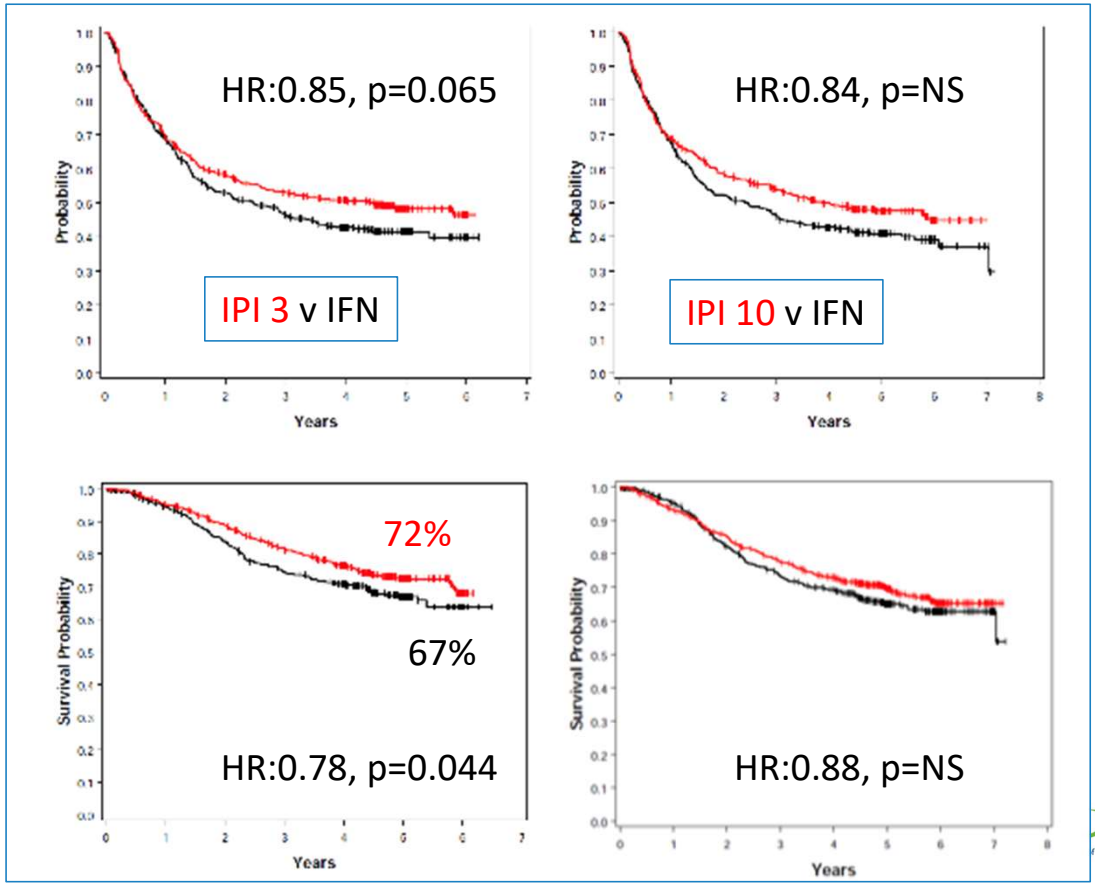
Eggermont, NEJM 2016.

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

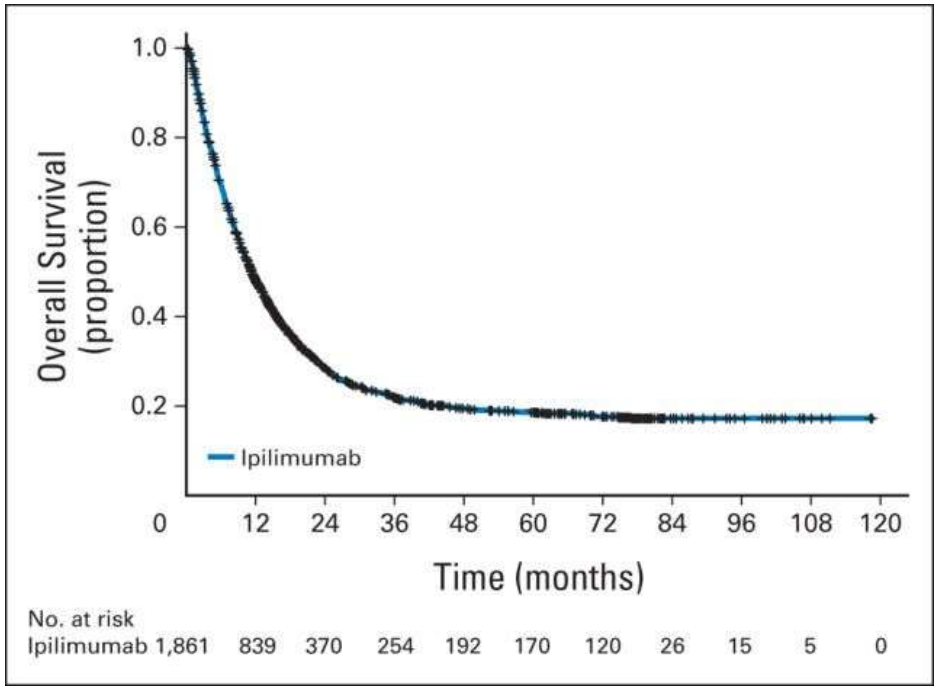
OS



J Clin Oncol 38:567-575 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.

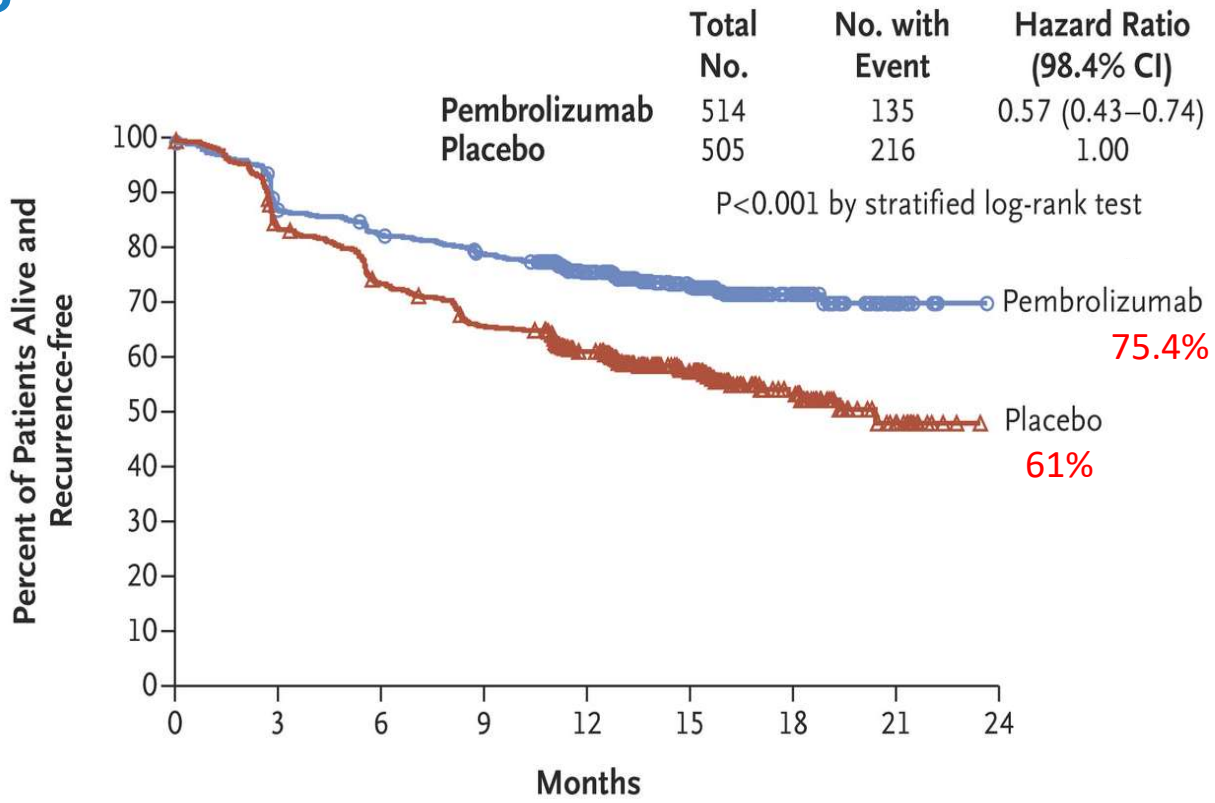
Approved checkpoint inhibitors in melanoma

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
  - Stage IIIA/B/C
  - Adjuvant pembrolizumab vs placebo
  - Pembrolizumab 200mg Q3W for up to 1 year (~18 total doses)

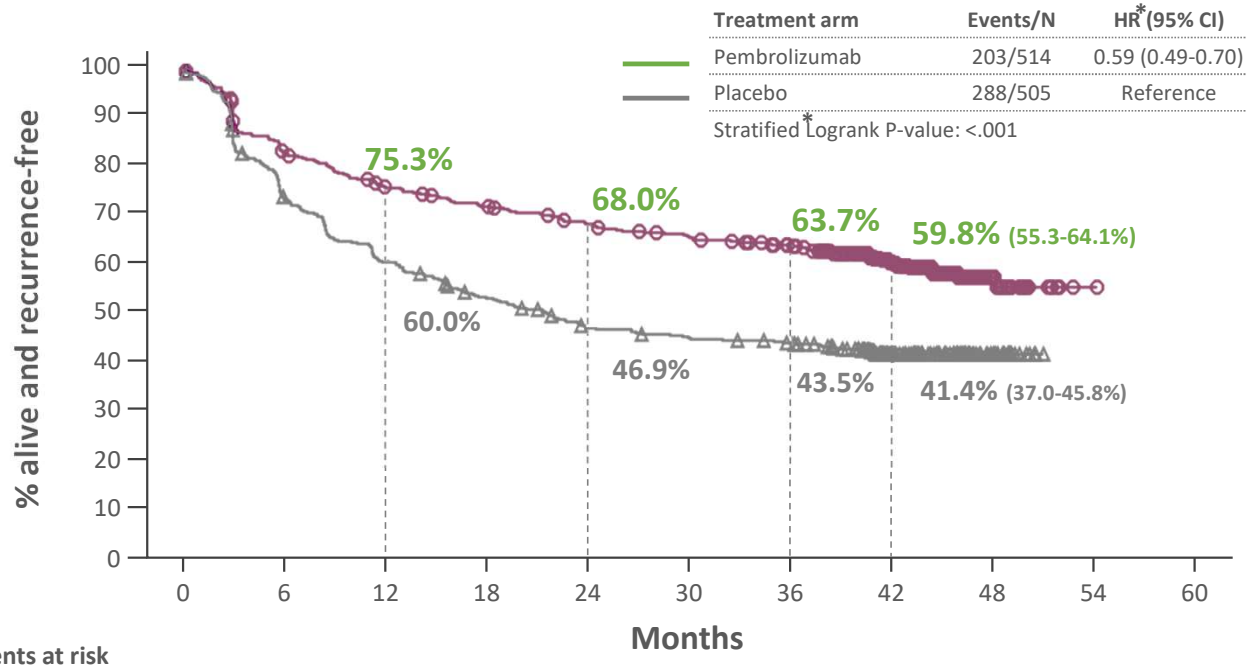
*Allowed cross-over



Eggermont, NEJM 2018.

Updated RFS analysis (ESMO 2020)

Median duration of follow-up: 3.5 years; 491 RFS events



Patients at risk

Pembrolizumab	514	412	375	353	333	316	300	163	30	1	0
Placebo	505	359	297	258	225	213	205	115	26	0	0

HR .59

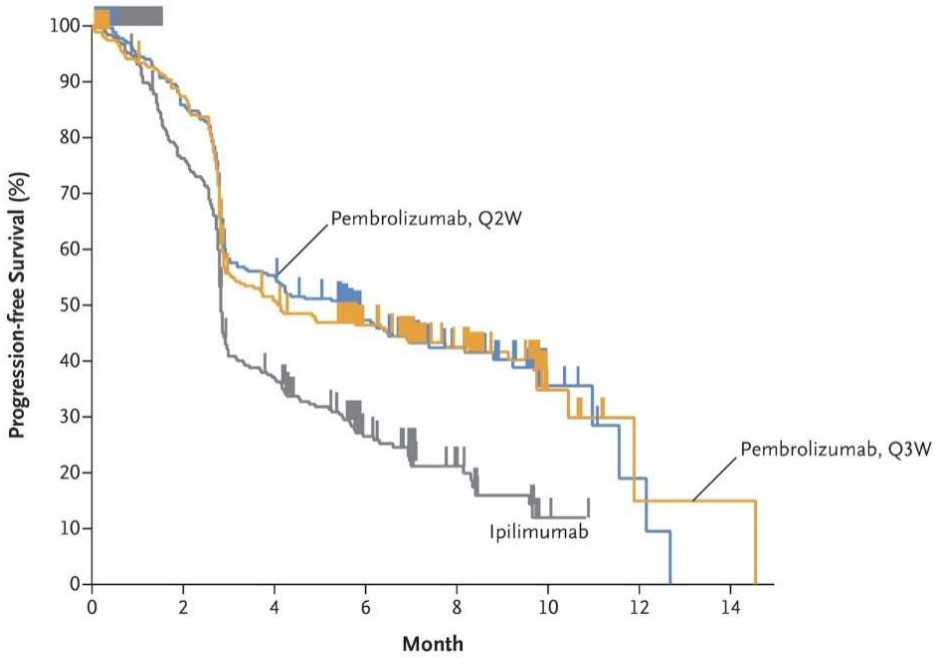
*Stratified by stage given at randomization

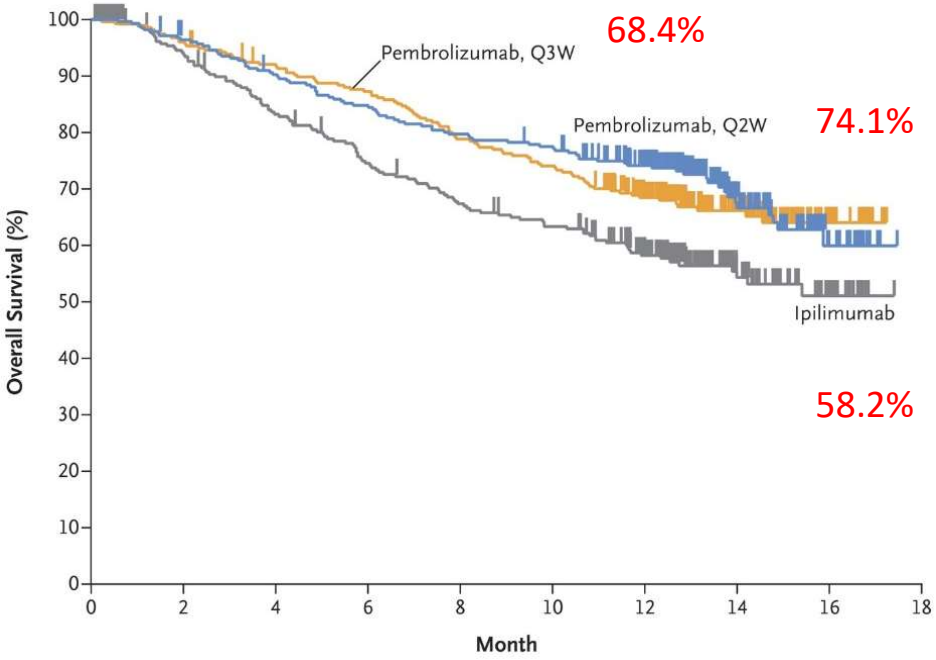
Alexander M.M. Eggermont

Eggermont AM, et al. *JAMA Oncology* 2020;6:519-27

Pembrolizumab in Stage III/IV Melanoma

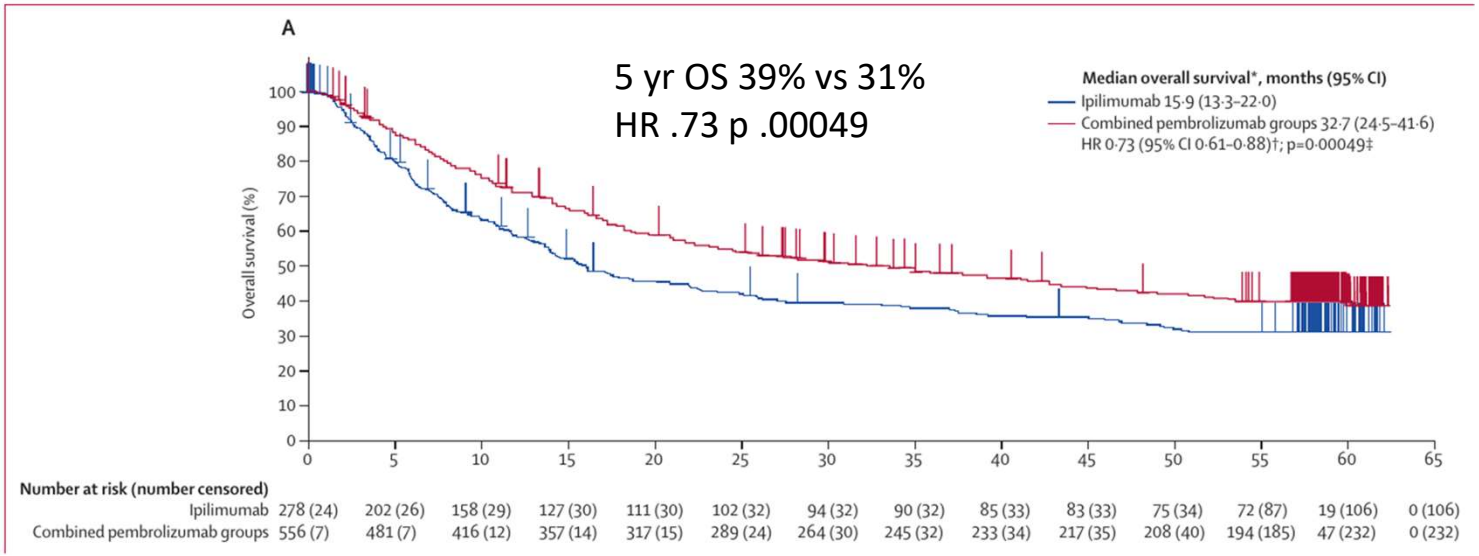
Phase III KEYNOTE-006 Trial





Robert, NEJM 2015.

Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study



Lancet Oncol 2019; 20: 1239–51

Approved checkpoint inhibitors in melanoma

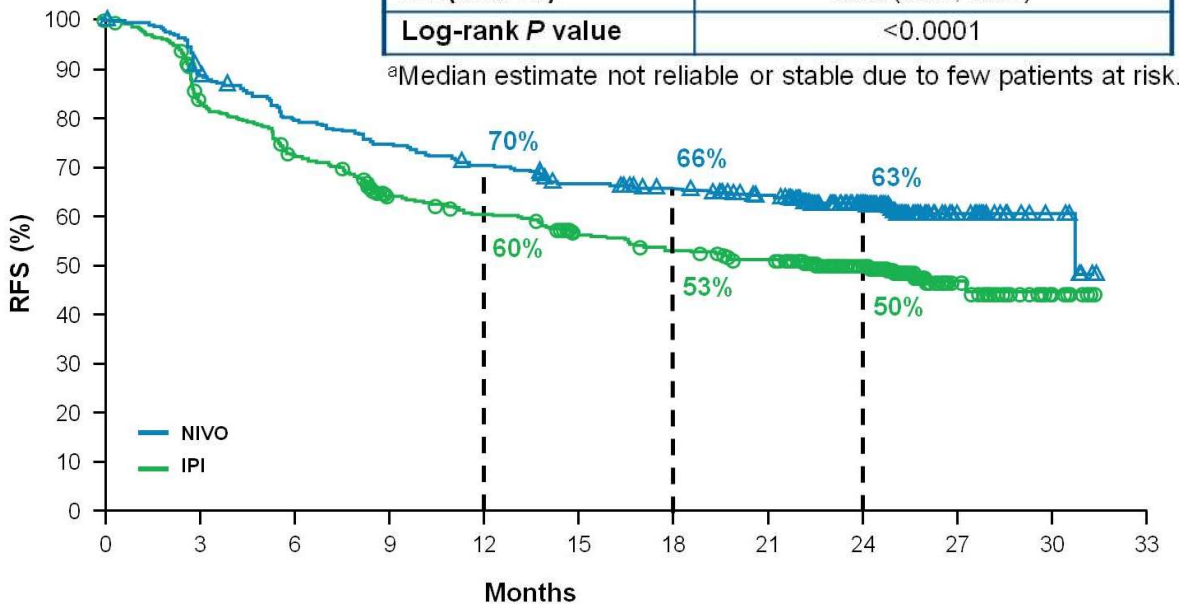
Drug	Approved	Indication	Dose
Nivolumab	2014	Unresectable/metastatic melanoma with progression after other therapy	240 mg Q2W or 480 mg Q4W*
	2017	Adjuvant treatment of melanoma after complete resection	240 mg Q2W or 480 mg Q4W
*Original approval was 3 mg/kg Q2W, updated to flat dosing regimen			

Adjuvant Nivolumab vs Ipilimumab in High-Risk Stage III Melanoma

- CheckMate 238 phase III trial
  - NCT02388906
  - Stage IIIB/C - Stage IV
  - Ipilimumab 10mg/kg Q3W for four doses, then every 3 months for up to 1 year
  - Nivolumab 3mg/kg Q2W 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	

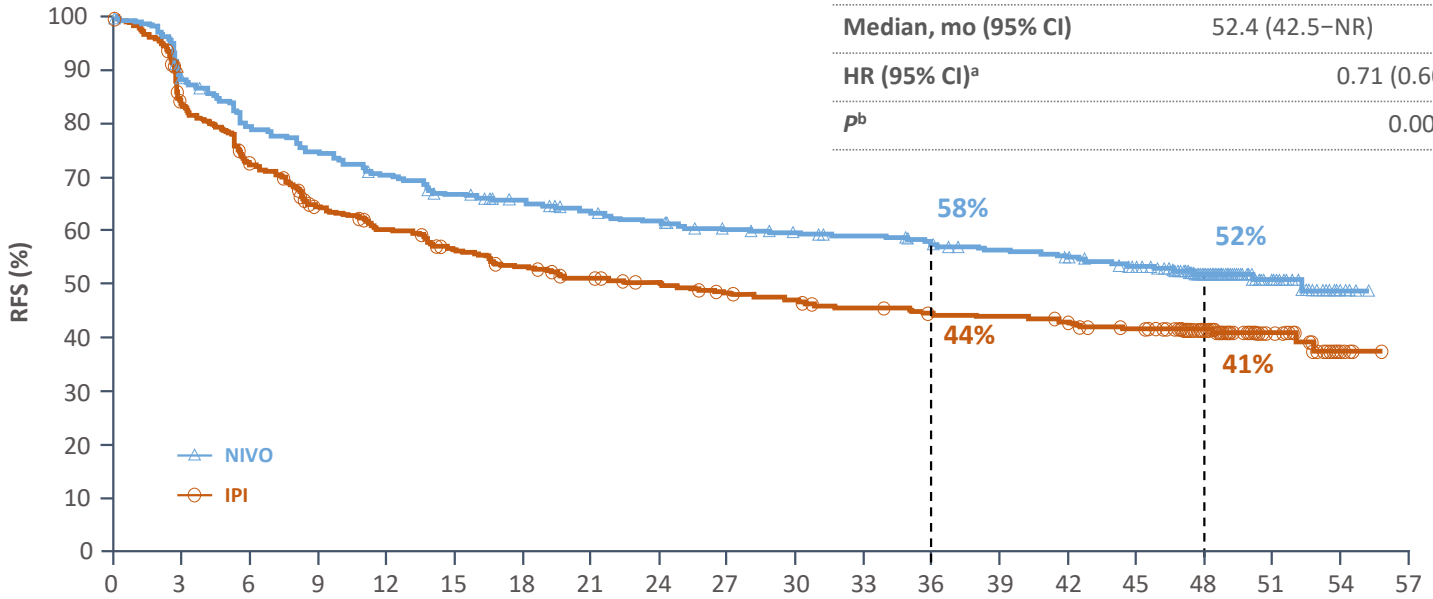
[a]Median estimate not reliable or stable due to few patients at risk.



Miller, ASCO 2018.

Primary endpoint: 48-month RFS in all patients

	NIVO (n = 453)	IPI (n = 453)
Events, n	212	253
Median, mo (95% CI)	52.4 (42.5–NR)	24.1 (16.6–35.1)
HR (95% CI)[a]	0.71 (0.60–0.86)	
P[b]	0.0003	

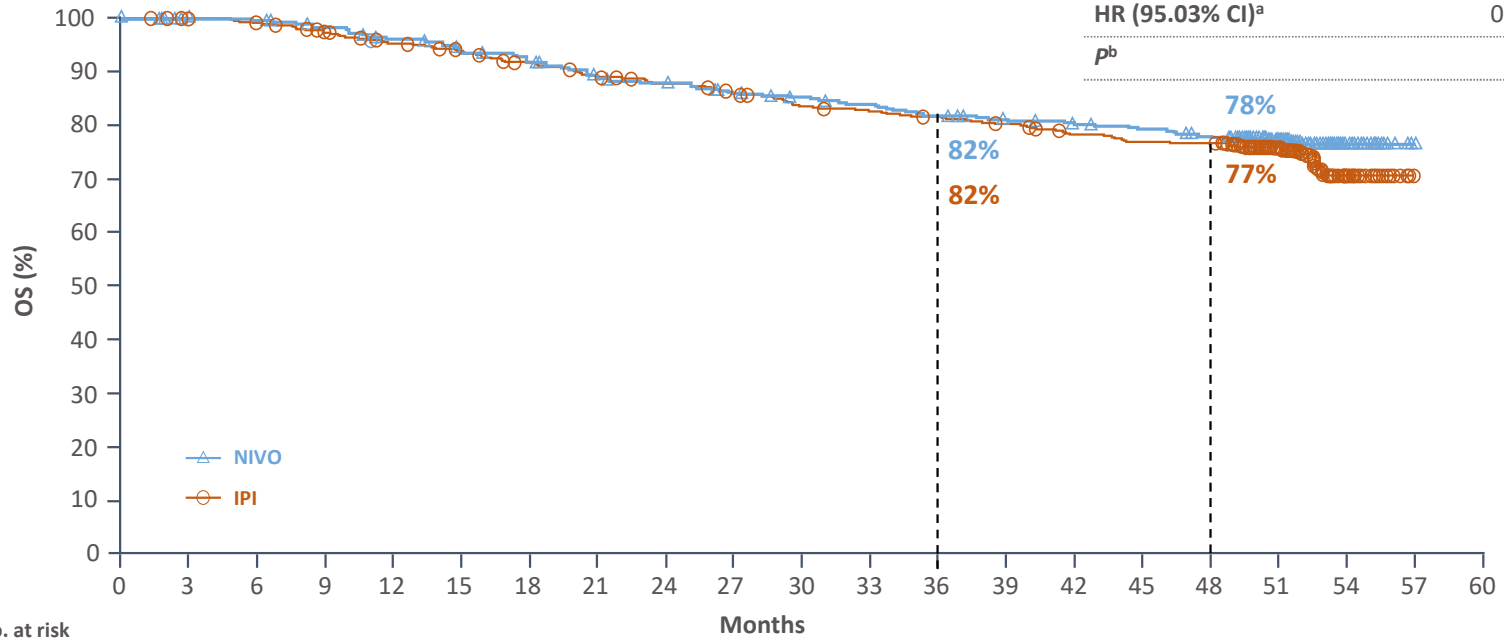


No. at risk																			
NIVO 3 mg/kg	453	395	354	332	311	293	283	271	262	250	245	240	233	224	218	206	147	37	11	0
IPI 10 mg/kg	453	366	316	273	253	234	220	208	201	191	185	177	171	168	163	154	113	32	10	0

[a]Stratified; [b]Log-rank test. NR, not yet reached.

Secondary endpoint: 48-month OS in all patients

	NIVO (n = 453)	IPI (n = 453)
Events, n	100	111
Median, mo (95% CI)	NR	NR
HR (95.03% CI)[a]	0.87 (0.66–1.14)	
P[b]	0.315	



No. at risk																				
NIVO 3 mg/kg	453	450	447	438	427	416	405	388	383	373	366	359	350	341	337	332	324	237	45	1	0
IPI 10 mg/kg	453	447	442	430	416	407	395	382	373	363	350	345	340	333	322	316	315	218	40	0	0

211 of 302 anticipated events (approximately 73% power)

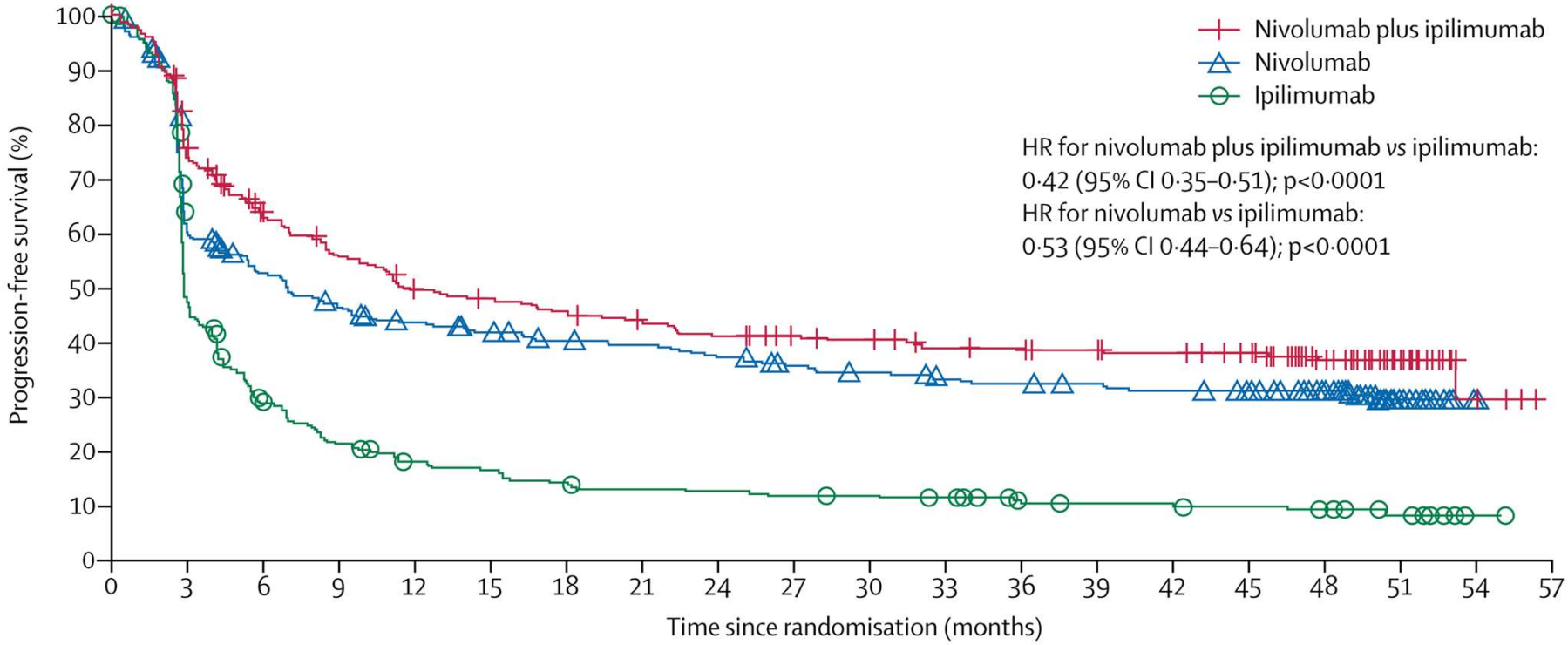
[a]Stratified; [b]Log-rank test.

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

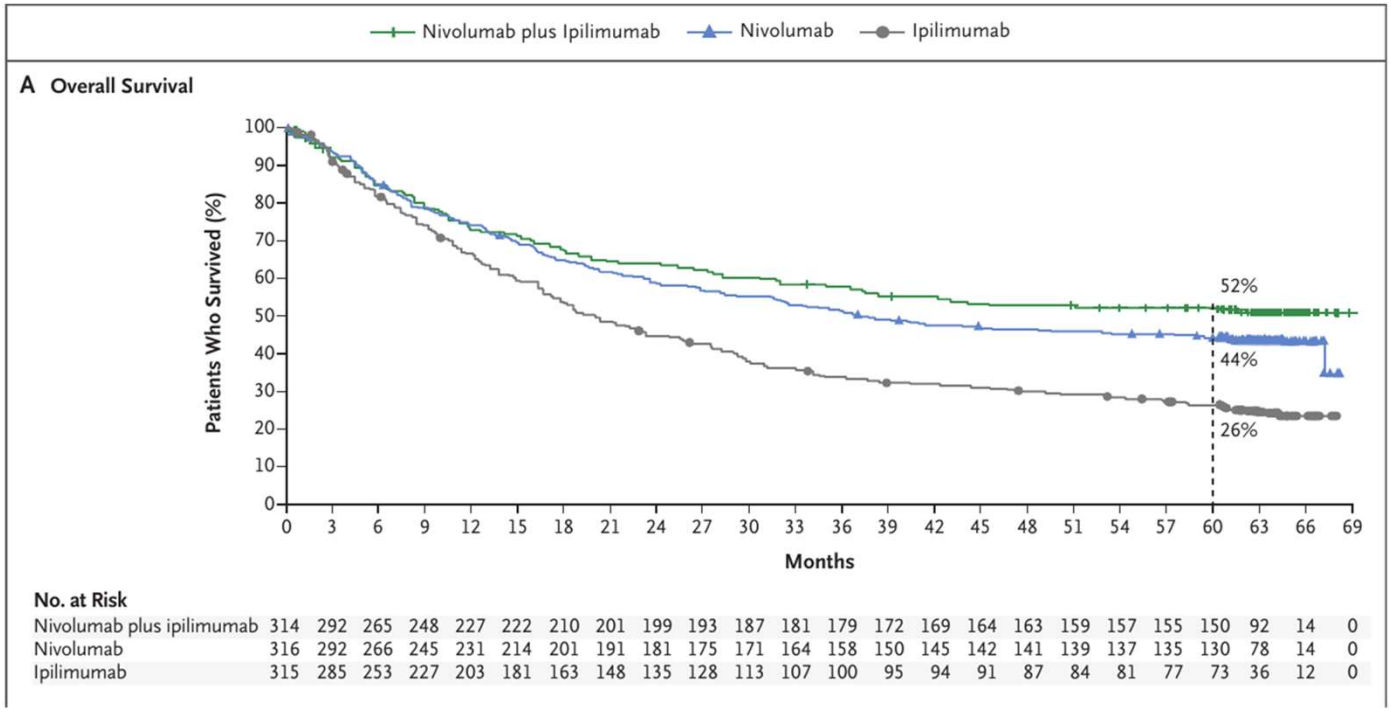
Phase III CheckMate 067 Trial



Hodi, Lancet Oncol 2018.

5 yr Survival Update:

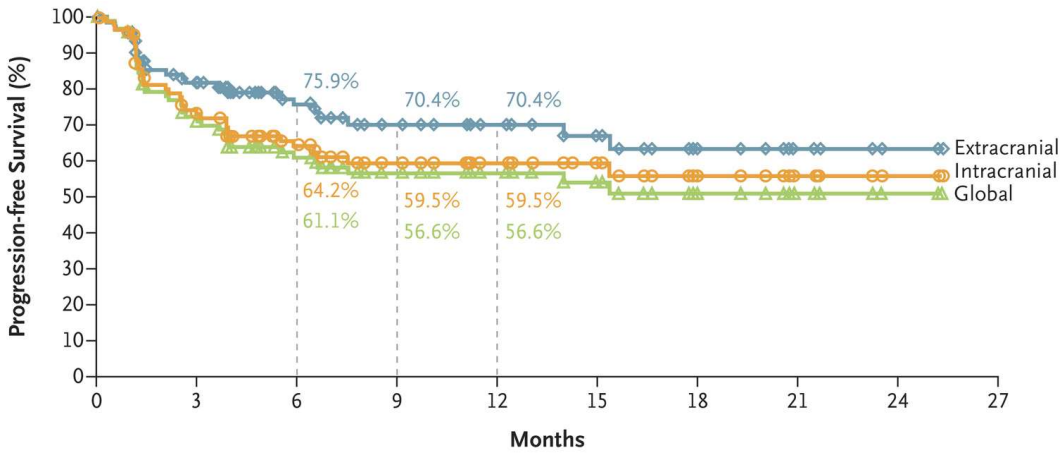
Phase III CheckMate 067 Trial



Hodi, Lancet Oncol 2018.

Combination Ipilimumab + Nivolumab for Patients with Asymptomatic Brain Metastases

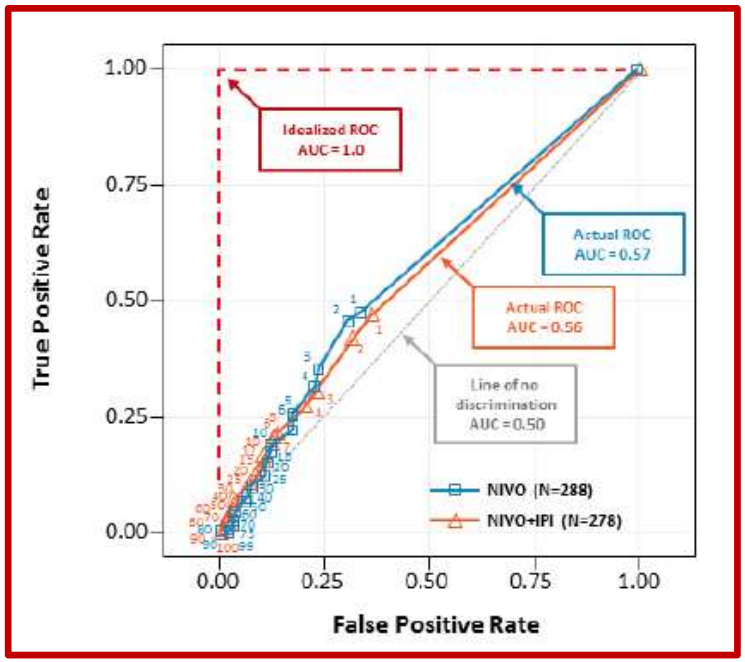
Variable	Intracranial (N=94)	Extracranial (N=94)	Global (N=94)
Best overall response — no. (%)*			
Complete response	24 (26)	7 (7)	8 (9)
Partial response	28 (30)	40 (43)	40 (43)
Stable disease for ≥6 mo	2 (2)	6 (6)	5 (5)
Progressive disease	31 (33)	28 (30)	33 (35)
Could not be evaluated†	9 (10)	13 (14)	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)



- 52% 1 brain met
- 24% 2 lesions
- 22% ≥ 3 lesions
  91% no SRS

Tawbi, NEJM 2018.

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

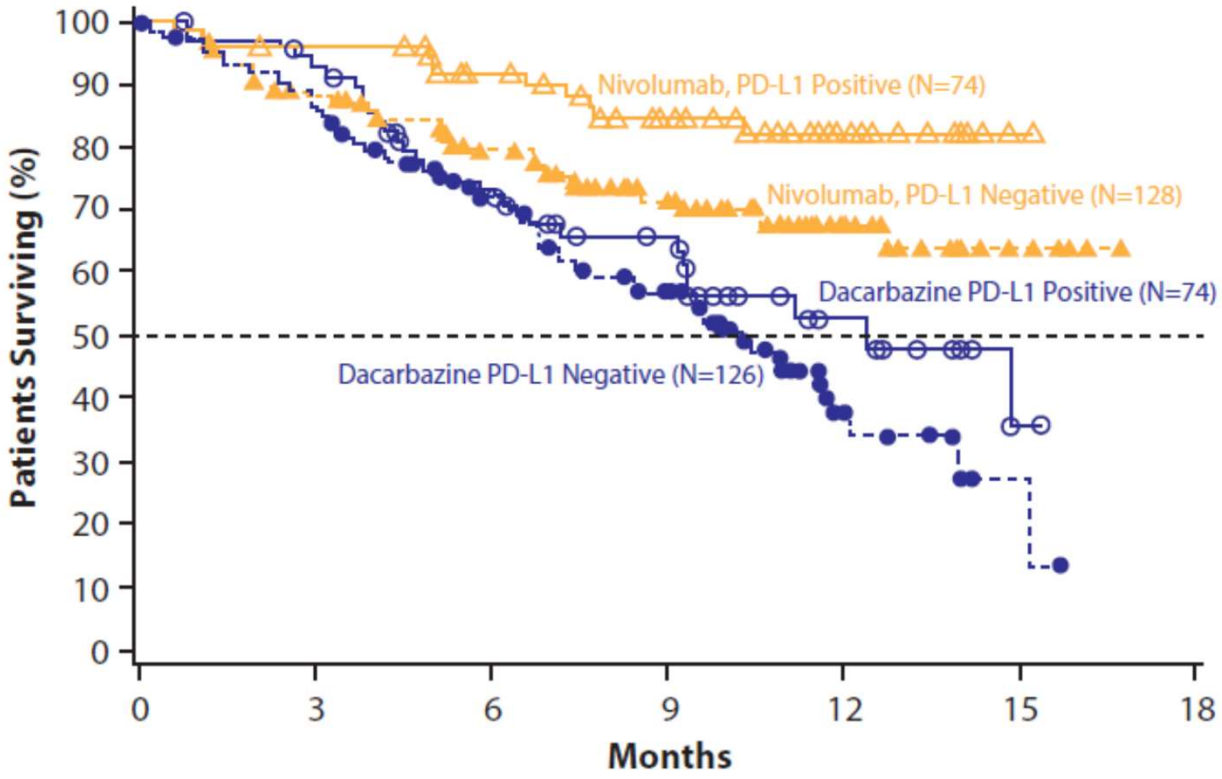


PDL-1 (%)	≥ 1	< 1	≥ 5	< 5	➢ 10	< 10
Ipilimumab	19%	18%	21%	17%	20%	18%
Nivolumab	54%	35%	58%	42%	58%	44%
Ipi/Nivo	65%	54%	72%	56%	85%	55%

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

Wolchok, NEJM 2017.

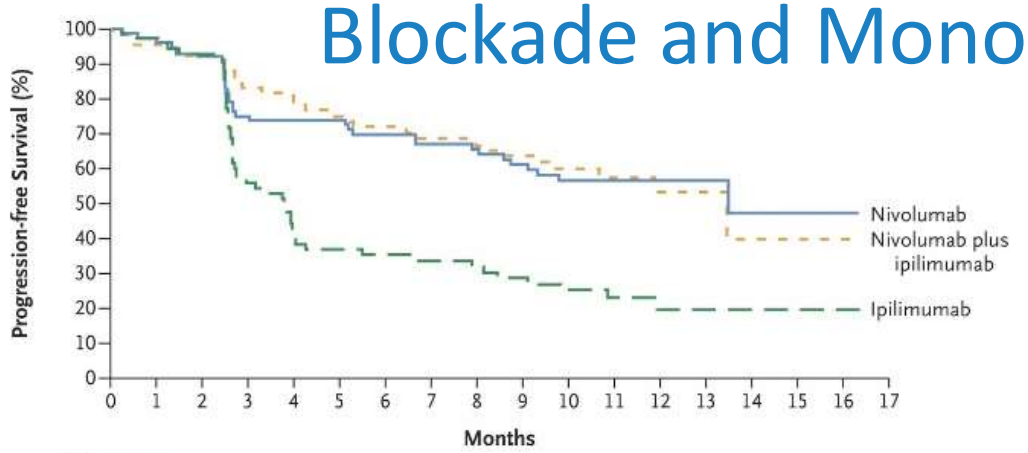
Importance of Tumor PD-L1 Status with Anti-PD-1 Monotherapy



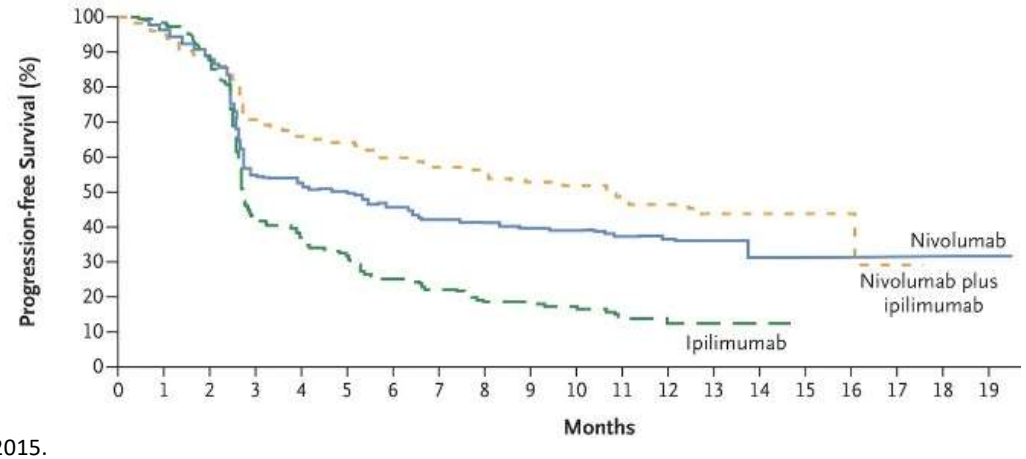
	Patients Who Died *n/N*	Median Survival *mo (95% CI)*
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

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.

Approved combination therapy in melanoma

Drug	Approved	Indication	Dose
Atezolizumab + cobimetinib + vemurafenib	2020	BRAF V600 mutation-positive unresectable or metastatic melanoma	28-day cycle of vem/cobi, then atezo 840 mg Q2W + cobi 60 mg Q1D (21 D on, 7 D off) + vem 720 mg twice daily

IMspire150 – BRAFV600-positive melanoma

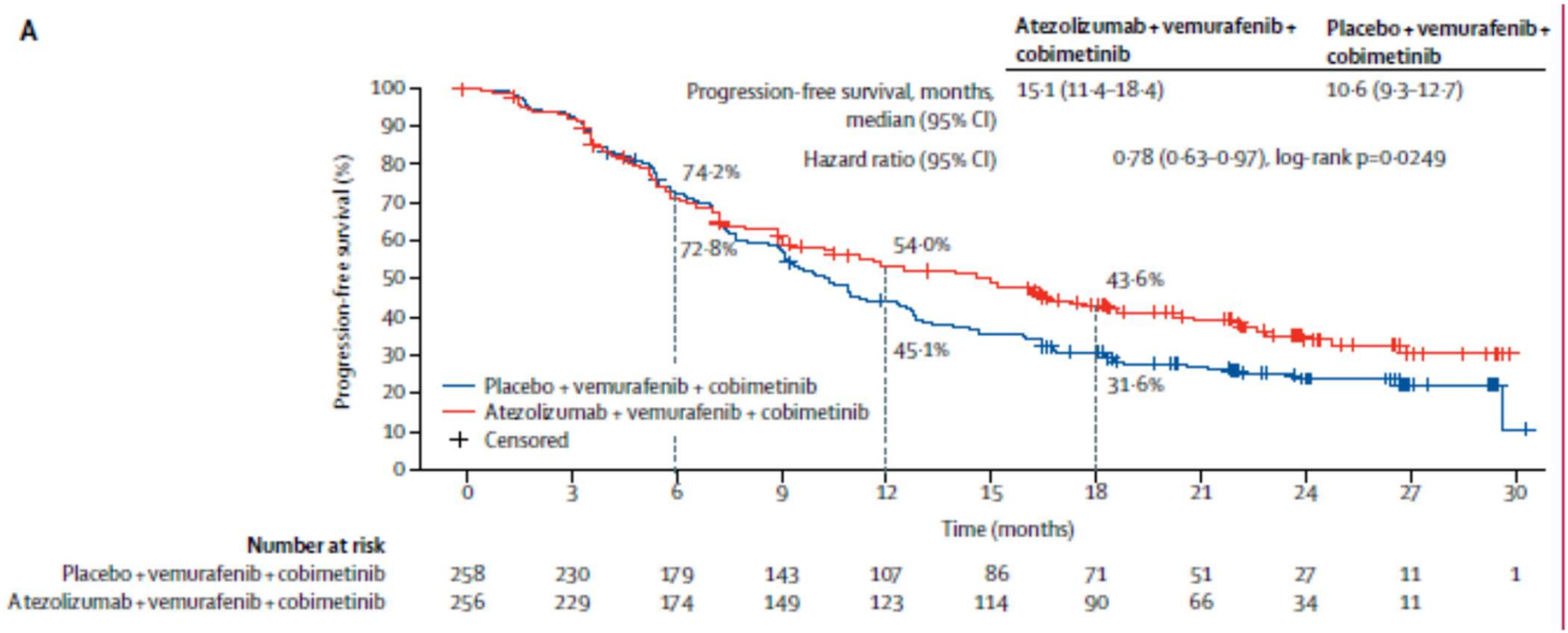
Atezolizumab + cobimetinib + vemurafenib vs Placebo + cobimetinib + vemurafenib

Median PFS: 15.1 vs 10.6 months

AEs leading to discontinuation: 13% vs 16%

Gutzmer, Lancet 2020

Atezolimumab plus Vemurafenib + Cobimetinib: PFS



Lancet 2020; 395: 1835–44

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)

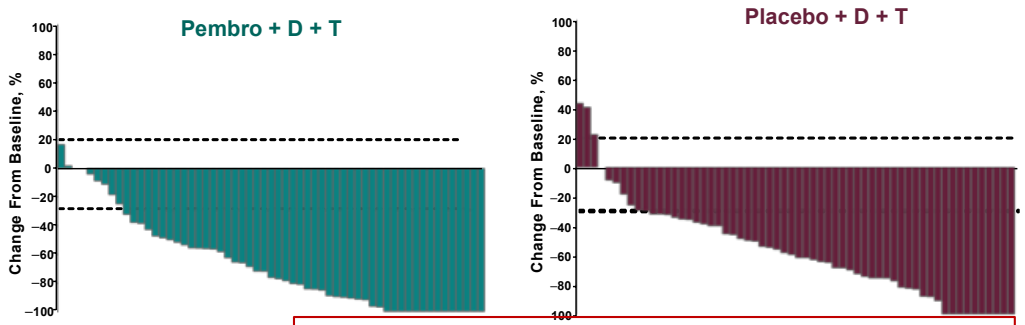
R (1:1) N = 120

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.

Combined IO with BRAF targeted therapy

- Dabrafenib plus Trametinib failed to meet primary endpoint – Investigator assessed PFS: 4.2 months

- IMspire 150 – med PFS 4.5 months

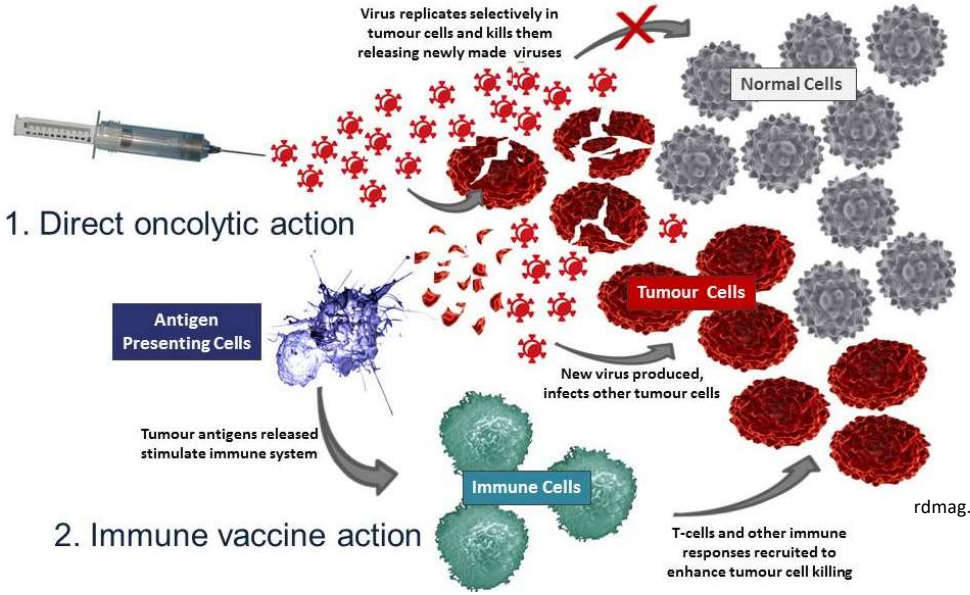
Ascieto et al, *Nature Med* 2019.

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.

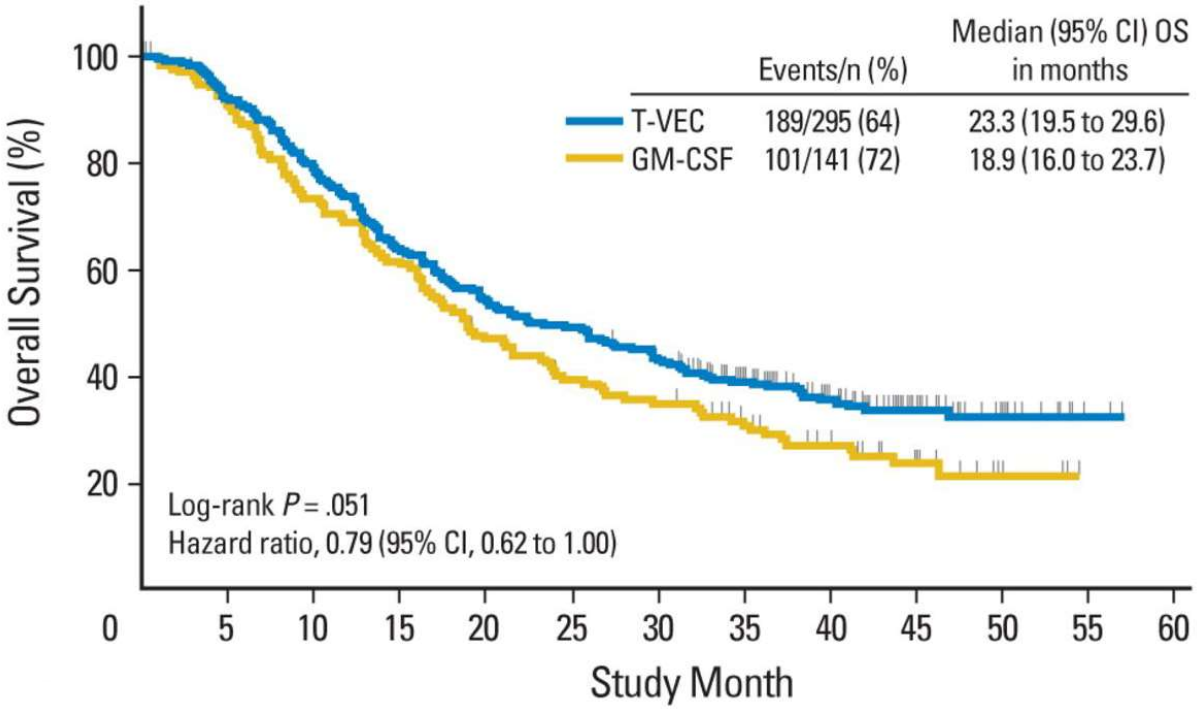
Approved oncolytic virus in melanoma



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



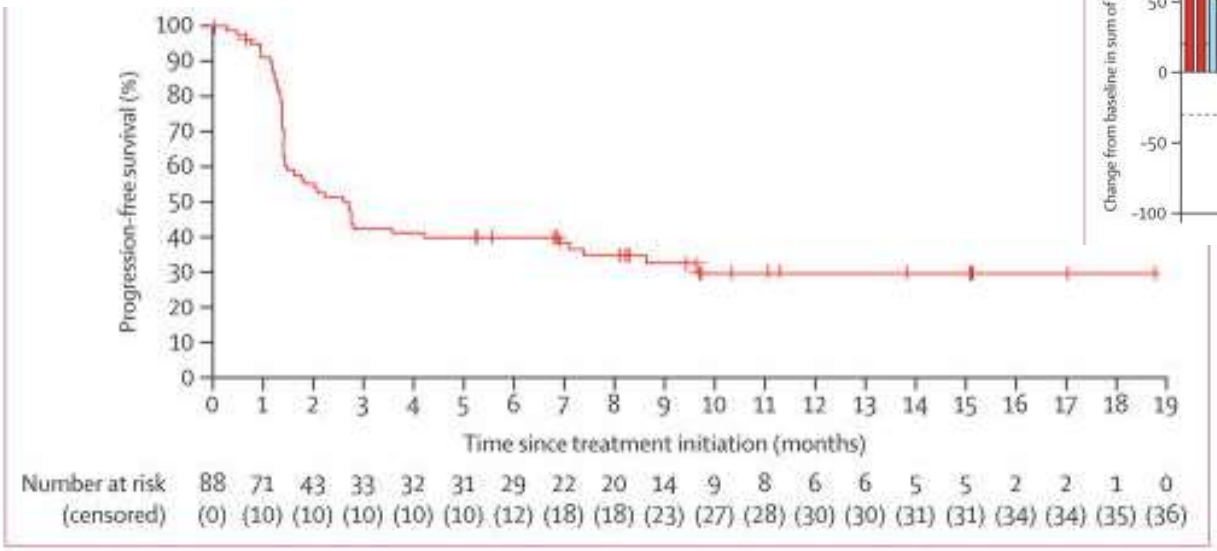
Andtbacka, Kaufman, JCO 2015.

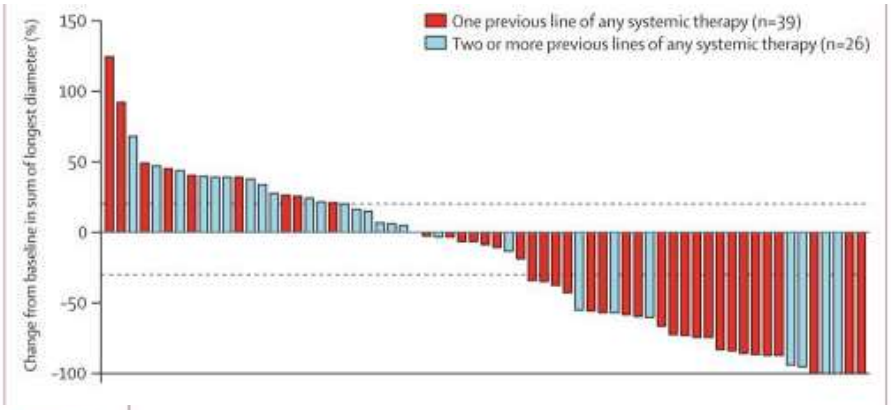
Approved checkpoint inhibitors in other skin cancers

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
Pembrolizumab	2020	Metastatic cutaneous squamous cell carcinoma	200 mg Q3W or 400 mg Q6W

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%

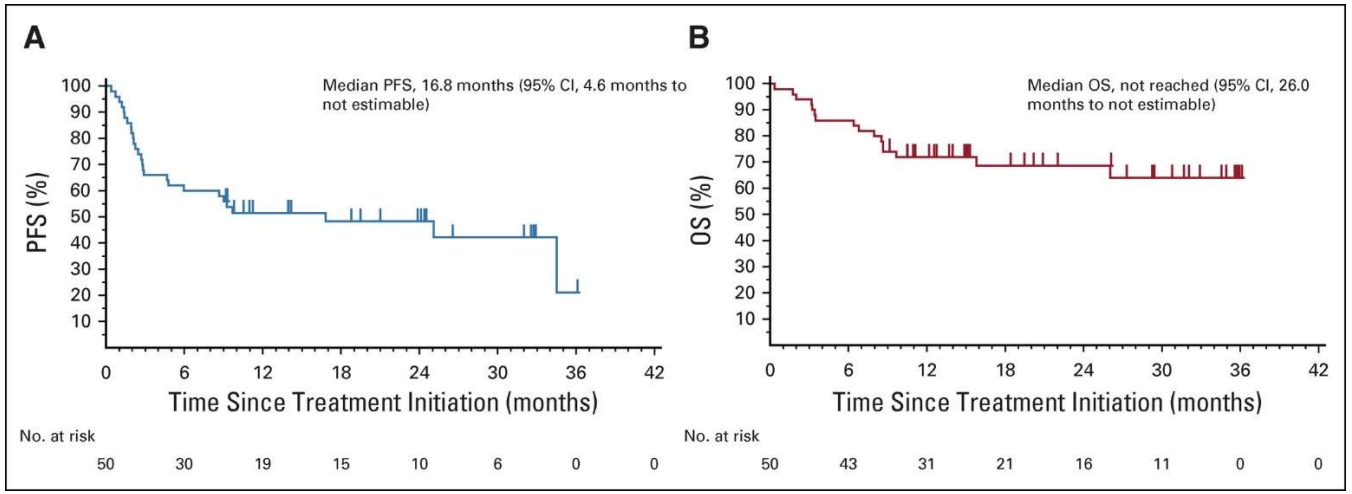




Kaufman, Lancet Oncol 2016.

Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

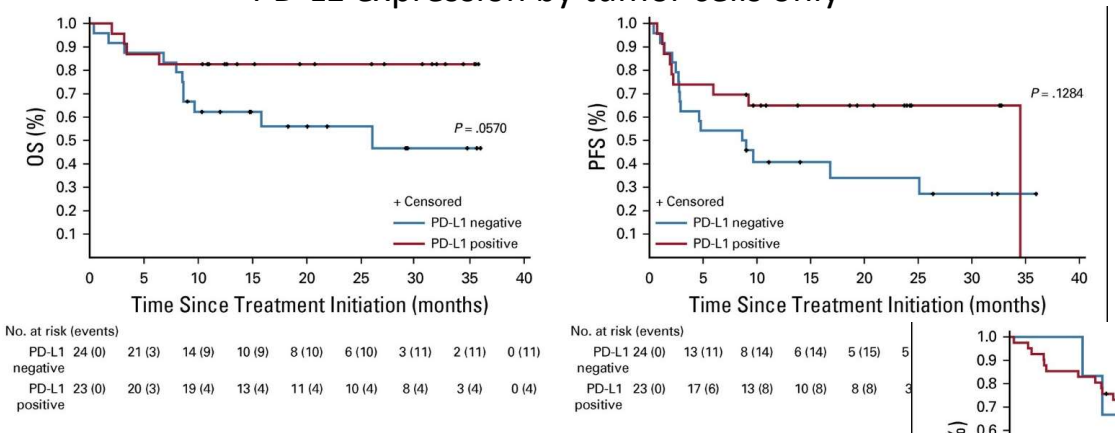
- KEYNOTE-017
- Pembrolizumab 2 mg/kg Q3W up to 2 years
- mPFS: 16.8 months (compared to 90 days for chemo)
- 24-month OS: 68.7%



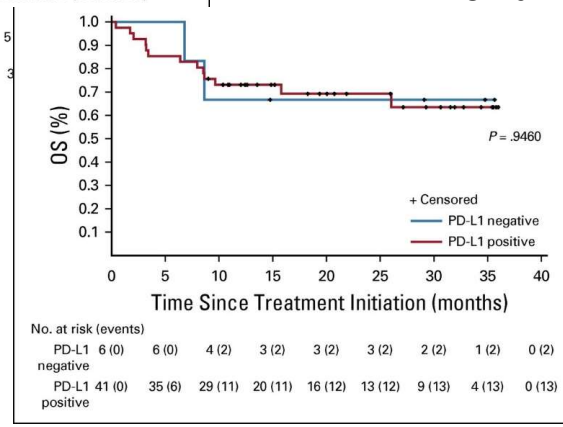
Nghiem, J Clin Oncol 2019.

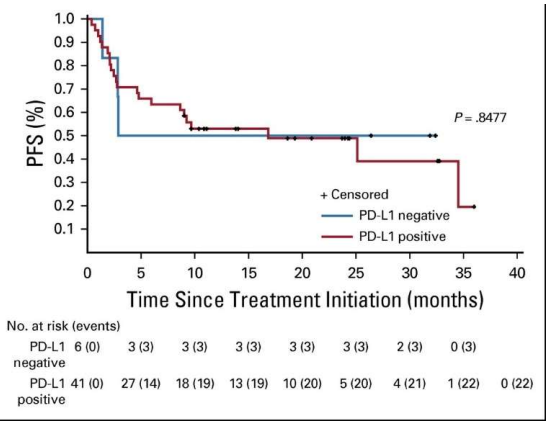
Pembrolizumab in 1st-line advanced Merkel Cell Carcinoma

PD-L1 expression by tumor cells only



PD-L1 on all cells in tumor

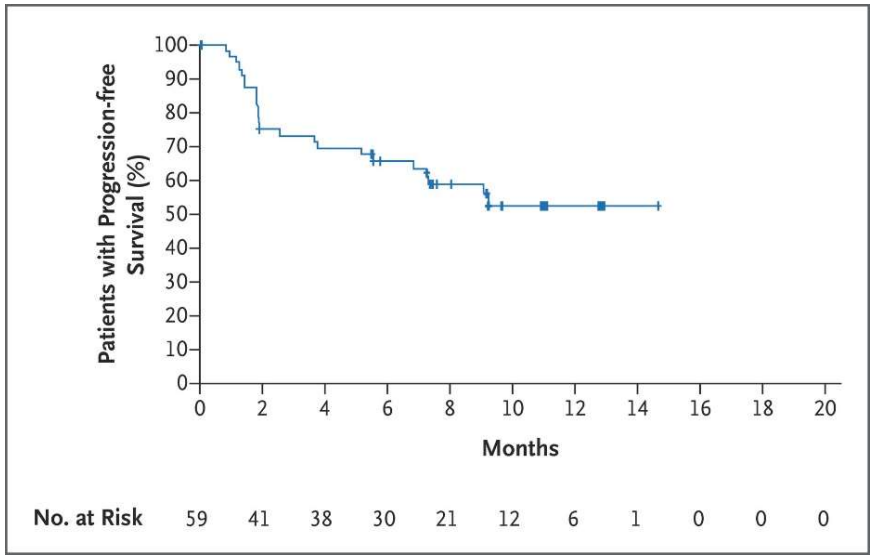


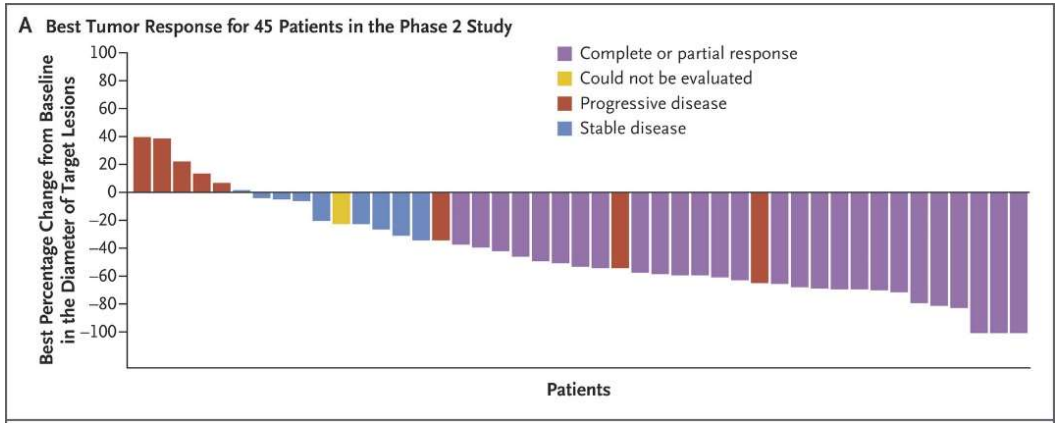


Nghiem, J Clin Oncol 2019.

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

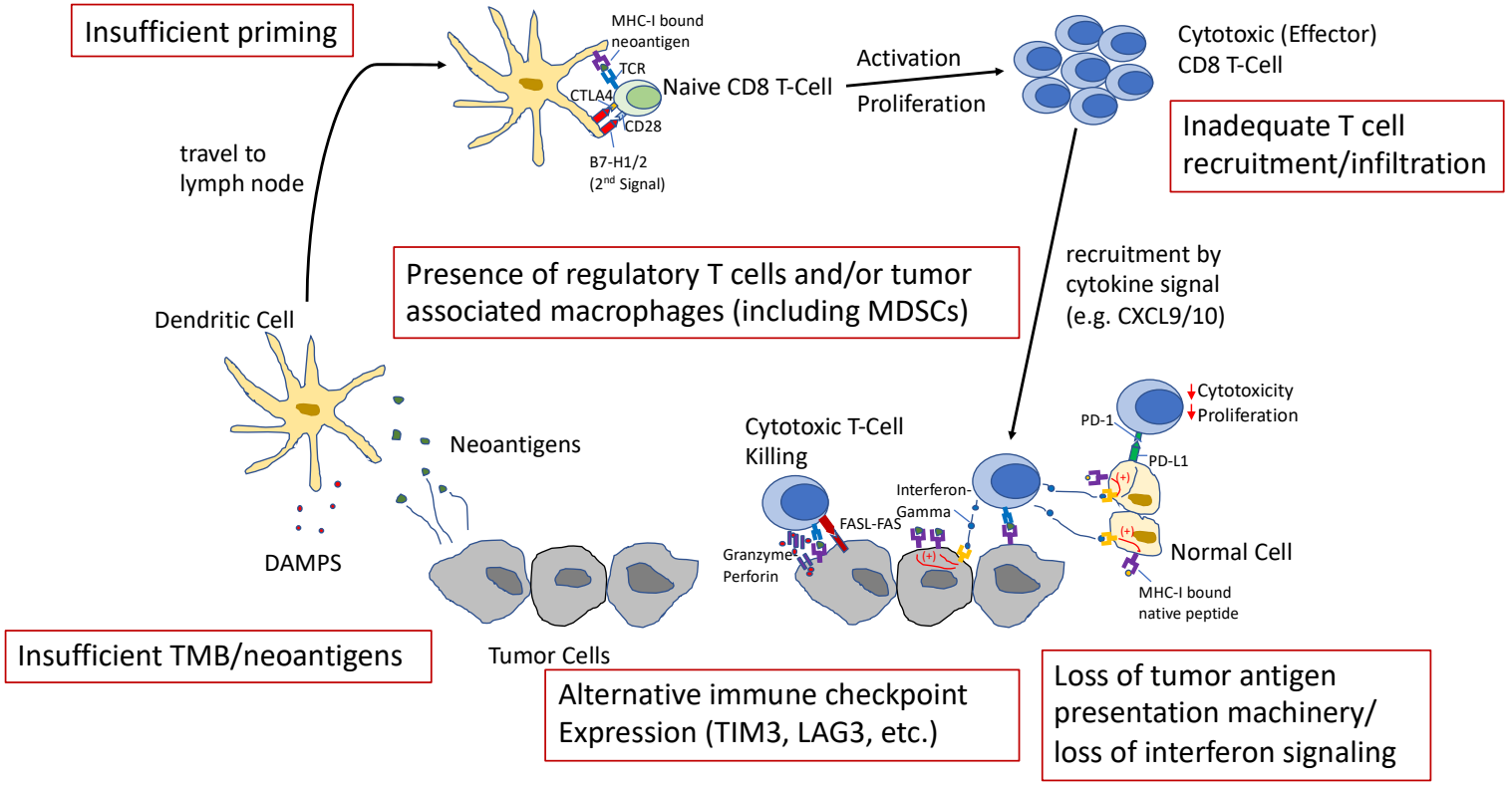




Migden, NEJM 2018.

Developmental Immunotherapeutic Strategies for Melanoma

How does immune checkpoint inhibitor therapy fail?

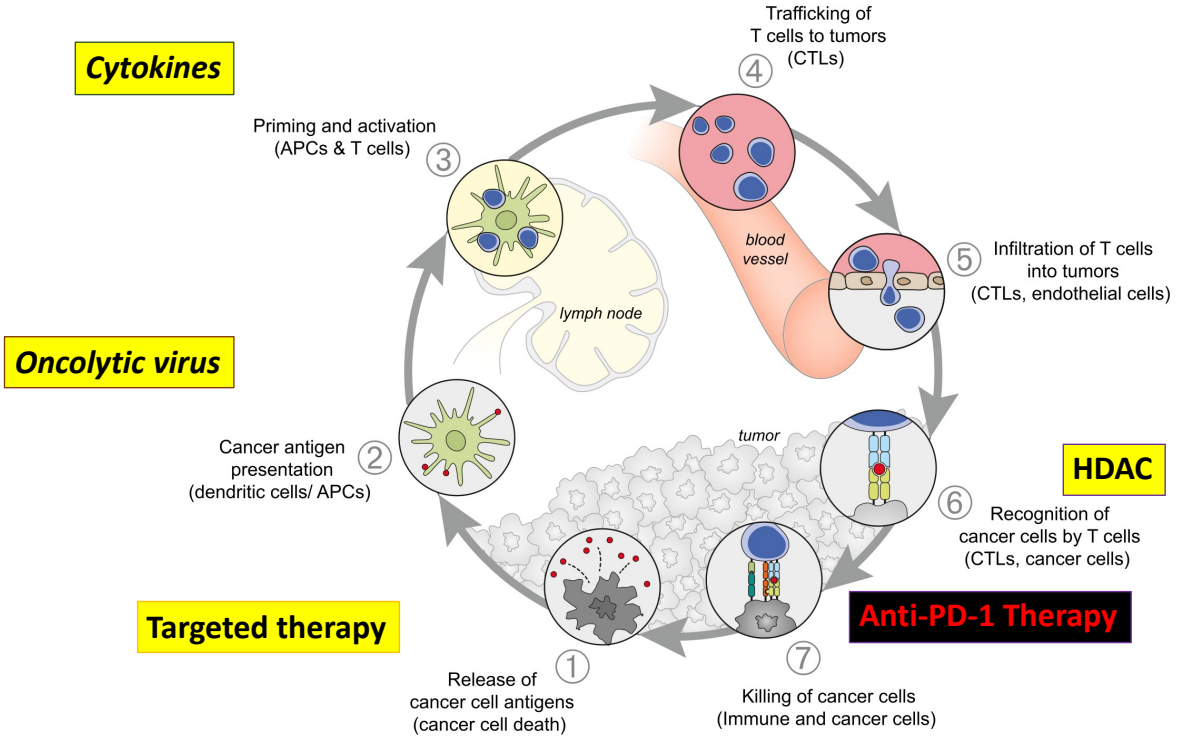


Modified from Liu, Jenkins, Sullivan. Amer J Clin Derm 2018.

Developmental Immunotherapeutic Strategies for Melanoma

How do we overcome resistance?

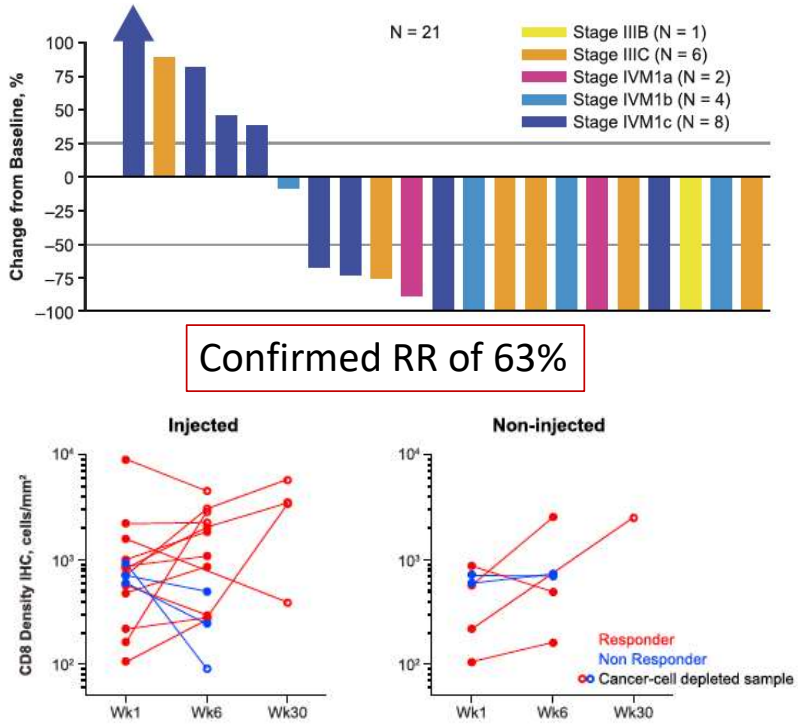
Combination therapy



Modified from Chen and Melman. Immunity 2015.

In development: Combined IO with Oncolytic Virus

Phase I: Pembrolizumab + TVEC



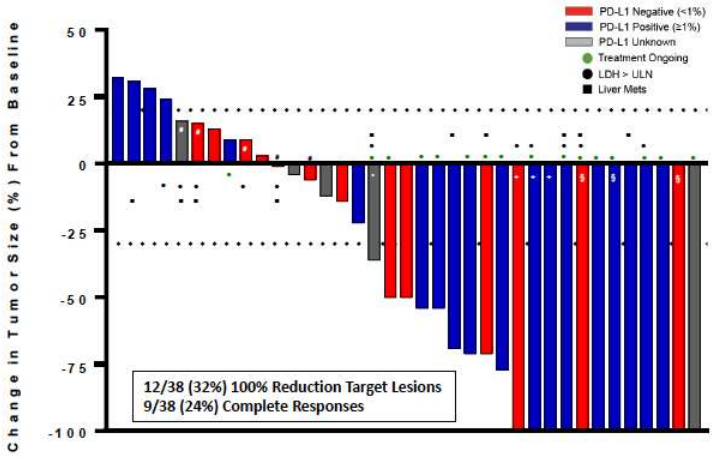
Confirmed RR of 63%

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



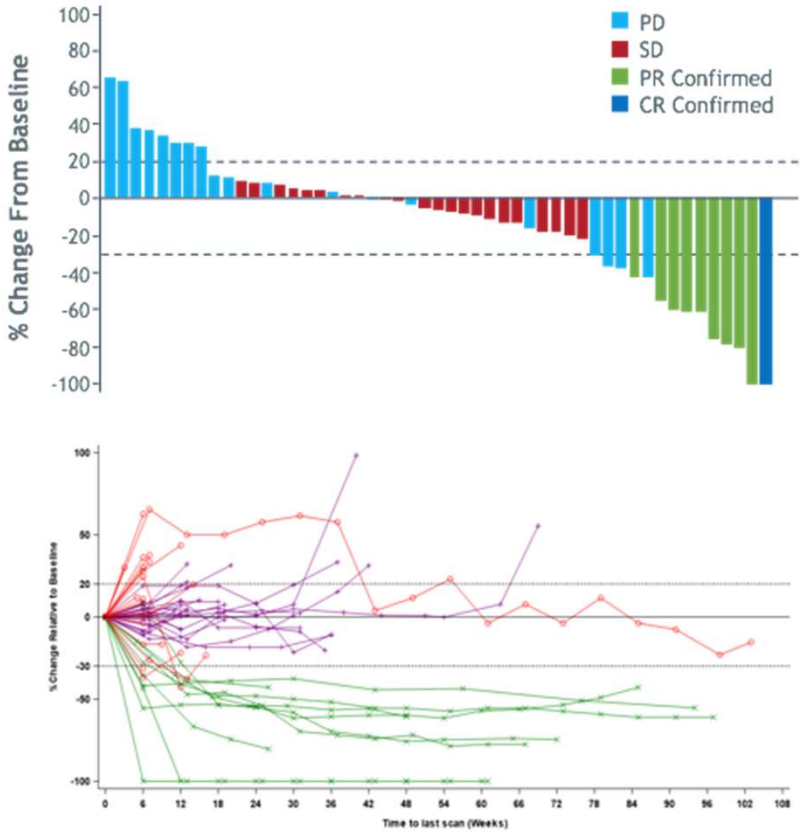
1L Melanoma (n=38 Efficacy Evaluable)	Overall Response Rate
Confirmed ORR (CR+PR)	20 (53%)
CR	9 (24%)
DCR (CR+PR+SD)	29 (76%)
PD-L1 negative (n=14)	6 (43%)
PD-L1 positive (n=19)	13 (68%)
PD-L1 unknown (n=5)	1 (20%)
LDH > ULN (n=11)	5 (45%)
Liver metastases (n=10)	5 (50%)

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.

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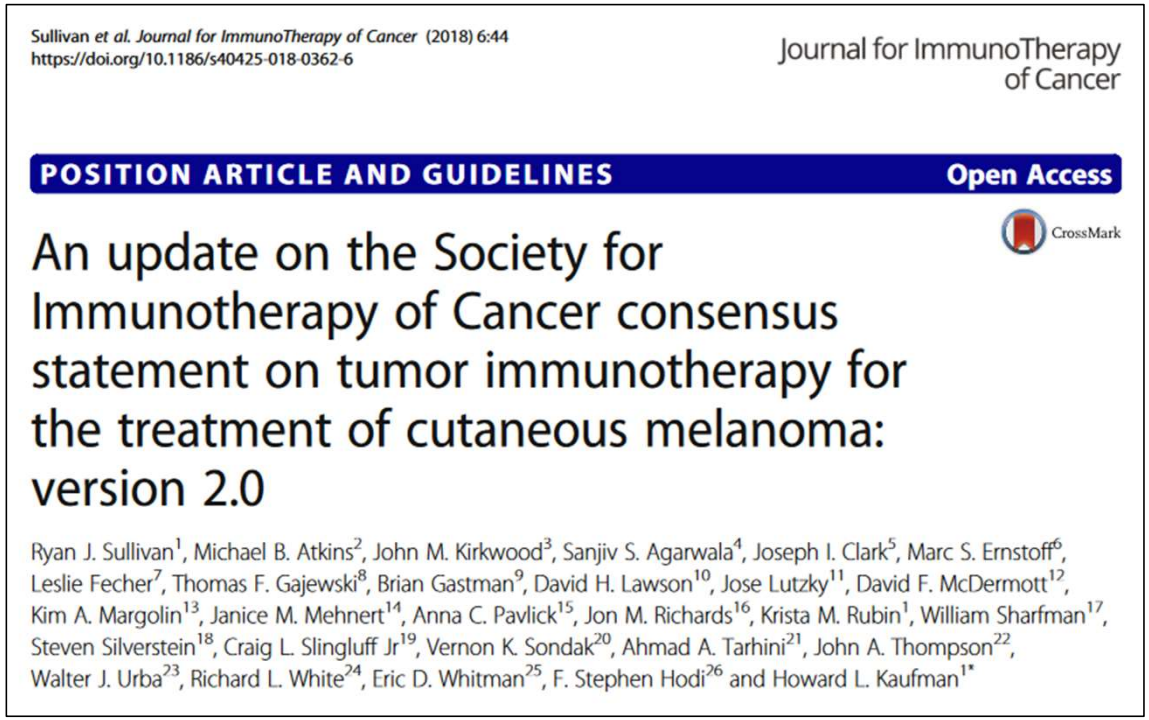
Conclusions

- 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*]

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Case Studies

Case Study 1

- Mr Smith, a 37 M, is referred back to you in May 2019 by a surgeon from his local hospital
- He has been a patient since 2017, when he presented with a stage IIb melanoma; 4.2 mm, non ulcerated, Breslow level IV lesion of the right upper arm. BRAF mutation positive. There were 14 mitoses/mm2 and 0/4 positive SLN. He was undergoing annual staging CT CAP, last one 3 months ago
- He presented to his local ER with abdominal pain, CT abdo/pelvis demonstrating small bowel obstruction d/t intussusception
- He underwent a small bowel resection , with pathology showing a 2.7 cm polyploid melanoma, margins clear
- Presently he is well, other than anxiety, which he manages with occasional marijuana
- What are your next steps?

INSERT POLL NEXT SLIDE

Case Study 1: POLL

1. Restage with CT chest, abdo, pelvis
2. MRI Brain
3. PET Scan
4. 1+2
5. 3+4

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Case Study 1: POLL Results

Case Study 1: POLL

1. Restage with CT chest, abdo, pelvis
   - Scan in emerg was 4 weeks ago, and didn't include chest
2. MRI Brain
   - High risk for brain metastases
3. PET Scan
   - Consider for further assessment of small bowel and other lesions outside of CAP
4. 1+2
5. 3+4

Case Study 1 – POLL 2

What adjuvant treatment would you offer him?

1. Adjuvant Dabrafenib plus Trametinib
2. Adjuvant PD1 Inhibitor
3. Adjuvant Nivolumab plus Ipilimumab
4. Clinical Trial
5. Close clinical and radiographic observation

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POLL RESULTS

Case Study 1 - Rationale

1. Adjuvant Dabrafenib plus Trametinib
   - COMBI-AD did not include resected Stage IV
2. Adjuvant Nivolumab
   - CheckMate 238 – 52% vs 41% RFS at 48 months
3. Adjuvant Nivolumab plus Ipilimumab
   - IMMUNED trial: RPII Nivo/Ipi vs Nivo vs placebo in resected stage IV melanoma
   - 2 yr RFS 70% vs 42% vs 14%
4. Clinical Trial
   - Await results of CheckMate 915 (low dose ipi + nivo)
5. Close clinical and radiographic observation
   - Only if pt declined adjuvant nivolumab

Case Study 1 - Outcome

- Patient opted for adjuvant nivolumab
- Well tolerated, other than rash
- Remains clinically and radiographically free of disease thusfar

Case Study 2

- 59M, stage IIIC malignant melanoma resected October 2012:
- 4.3mm ulcerated lesion of right arm , with mitotic rate 3/mm2 and a 2mm satellite nodule. 1/3 positive sentinel nodes (largest focus 1 cm), completion right axillary dissection negative
- Completed 1 yr high dose IFN December 2013
- October 2014, metastatic nodes to right neck and axilla. Undergoes right axillary dissection, and right level 3,4,5 neck dissection:
- 4/26 right axillary nodes +, largest 2 cm with no ECE. 3/31 right neck nodes +, largest 2 cm, no ECE
- Adjuvant radiation to right neck and axilla.
- On active surveillance, restaging CT neck + CAP June 2019: significant intra-abdominal LN. Biopsy confirms melanoma. MRI brain clear. LDH 336 (ULN=220)
- Patient having mild abdo pain, 10lb weight loss, ECOG 0. BRAF mutation positive.
- No other significant PMHx

Case Study 2 POLL

- What first line therapy would you offer?

1. Dabrafenib plus Trametinib
2. Ipilimumab plus Nivolumab
3. Single Agent PD-1 inhibitor
4. Vemurafenib plus Cobimetinib plus Atezolizumab

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Case Study 2: POLL results

Case Study 2 POLL

- What first line therapy would you offer?

1. Dabrafenib plus Trametinib
2. Ipilimumab plus Nivolumab
3. Single Agent PD-1 inhibitor
4. Vemurafenib plus Cobimetinib plus Atezolizumab