

Immunotherapy for the Treatment of Skin Cancers

David Portnoy, MD, FACP

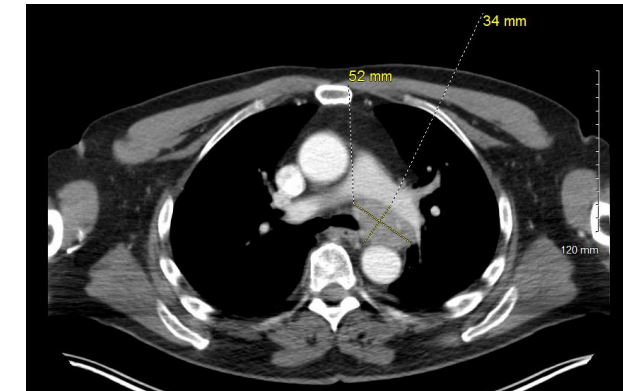
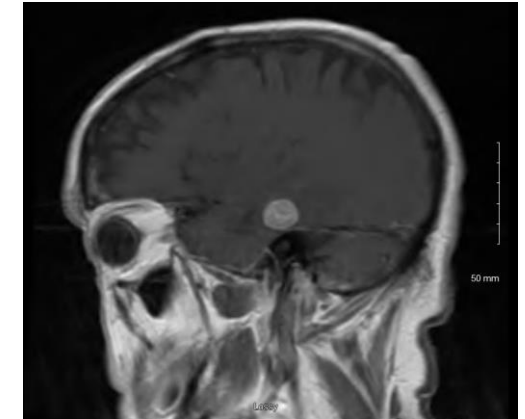
West Cancer Center and Research Institute

Disclosures

- No conflicts of interest
- I will be discussing non-FDA approved indications during my presentation.

Case #1

- 70-year-old male with a history of prostate cancer, status post radical prostatectomy in 2006, and a history of melanoma resected from his abdominal wall in 2008 presents with intermittent left hand numbness
- MRI reveals intracranial lesions
- PSA undetectable
- PET-CT shows metastatic disease to the right temporal lobe, mediastinal lymph nodes, lungs, right chest wall musculature, and left acetabulum
- Lymph node biopsy reveals metastatic melanoma
- Molecular profiling reveals BRAF wild type, NRAS mutated, PD-L1 90%, TMB 12 mutations/Mb

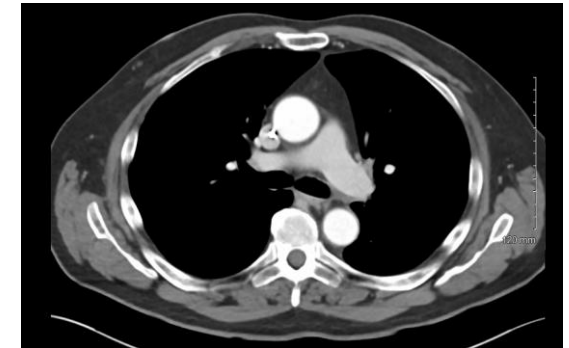
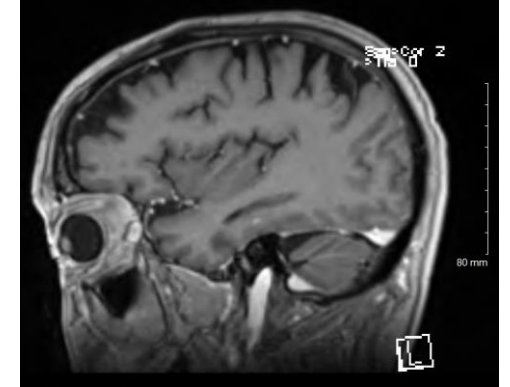


Case #1

- What is the most appropriate initial treatment option?
 - A. Pembrolizumab alone
 - B. Ipilimumab
 - C. Nivolumab and ipilimumab
 - D. Temozolomide
 - E. Dabrafenib and trametinib

Case #1

- Started on nivolumab and ipilimumab
- Scans show drastic improvement
- Never receives SRS
- Treatment complicated by development of pruritus and hypophysitis. Started on steroids but able to resume therapy.



Case #2

- A 64-year-old male with no PMH presents with a skin lesion on his right upper extremity that had been increasing in size for “several months”.
- Biopsy reveals squamous cell carcinoma
- CT shows right axillary lymphadenopathy but no evidence of distant metastatic disease
- Noted to be confused at initial visit. Labs revealed a calcium of 16 and blood cultures grew *Pseudomonas*



Case #2

- After treatment of his hypercalcemia and sepsis, what would be the most appropriate systemic therapy option?
 - A. Cemiplimab
 - B. Ipilimumab and nivolumab
 - C. Vismodegib
 - D. Cetuximab

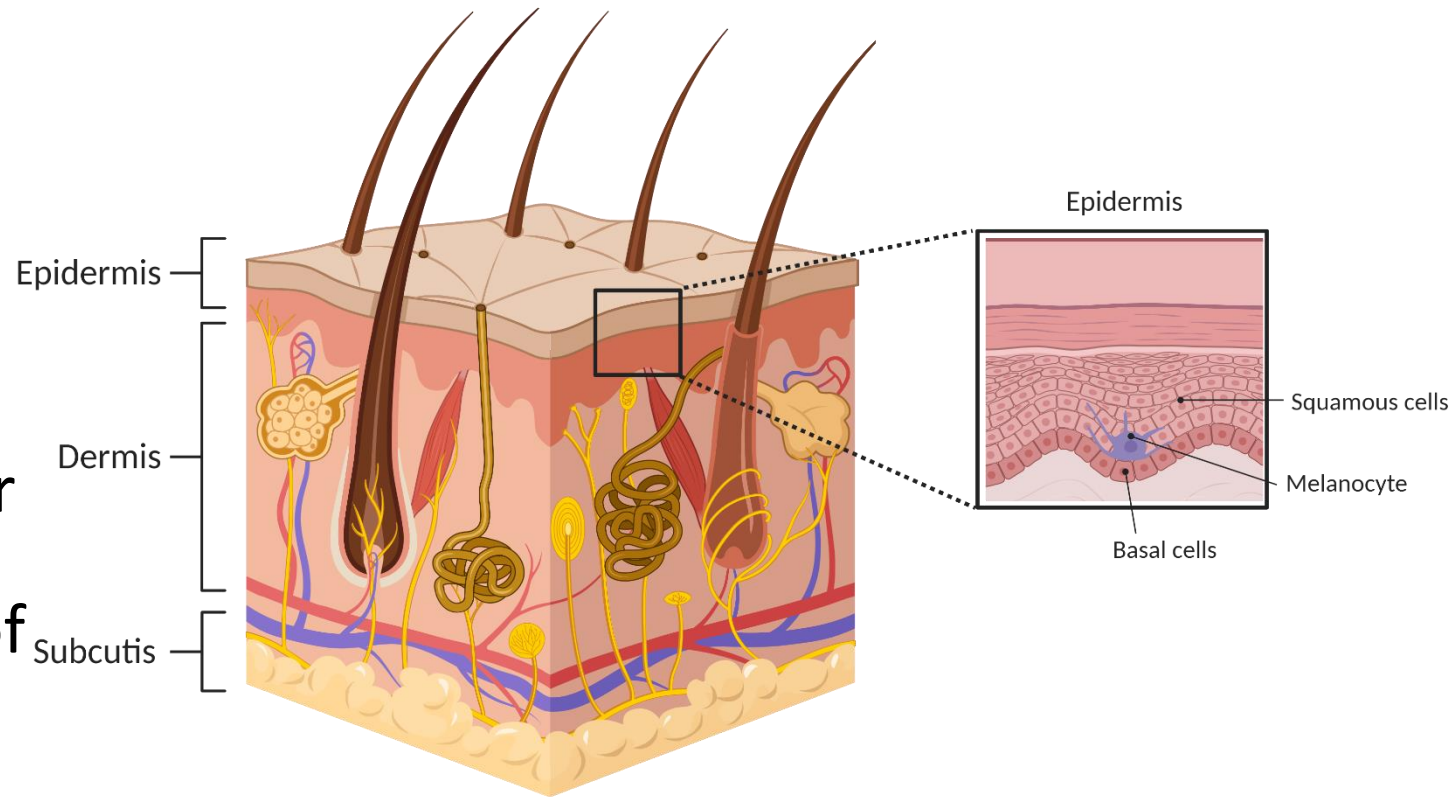
Case #2

- Started on cemiplimab with rapid improvement in appearance of the primary lesion and improvement in lymphadenopathy
- Hypercalcemia resolves
- Regains weight and performance status improves



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 tumor types for which immunotherapy was tested and provided proof of concept



Outline

- Melanoma
 - Front-line treatment
 - Second-line or later
 - Adjuvant and neoadjuvant settings
- Merkel cell carcinoma
- Squamous cell and basal cell carcinoma
- Future areas of research

Immunotherapy treatment options for metastatic melanoma

Treatment	Indication	Dose
Ipilimumab	Unresectable/Metastatic melanoma: newly diagnosed or after progression, all patients ≥ 12 yr	3 mg/kg Q3W for 4 doses
Pembrolizumab	Unresectable/metastatic melanoma	200 mg Q3W or 400 mg Q6W
Nivolumab	Unresectable/metastatic melanoma	240 mg Q2W or 480 mg Q4W
Nivolumab + ipilimumab	Unresectable/metastatic melanoma	1 mg/kg nivo followed by 3 mg/kg ipi Q3W, Maintenance: nivolumab 240 mg Q2W or 480 mg Q4W
Atezolizumab + cobimetinib + vemurafenib	BRAF V600 mutation-positive unresectable/metastatic melanoma	28-day cycle of cob/vem, then atezolizumab 840 mg every 2 weeks with cobimetinib 60 mg orally once daily (21 days on/7 days off) and vemurafenib 720 mg orally twice daily
Talimogene laherparepvec (T-Vec)	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

Trials leading to initial approvals

Trial	Treatment arms	n	Patient selection criteria	ORR	Median OS (months)	Median PFS (months)
NCT00094653	Ipilimumab + gp100	403	Pretreated advanced melanoma	5.7%	10.0	2.76
	Ipilimumab	137		10.9%	10.1	2.86
	Gp100	136		1.5%	6.4	2.76
KEYNOTE-006	Pembrolizumab	368	Advanced melanoma, ≤1 prior treatment	33.7%, 32.9%	32.7	8.4
	Ipilimumab	181		11.9%	15.9	3.4
CheckMate 037	Nivolumab	272	Melanoma with progression on ipilimumab	27%	16	3.1
	Chemotherapy	133		10%	14	3.7
OPTiM	T-VEC	295	Unresectable stage IIIB-IV melanoma	26.4%	23.3	TTF: 8.2
	GM-CSF	141		5.7%	18.9	TTF: 2.9

Robert, N Engl J Med 2015; Robert, Lancet 2019; Hodi, N Engl J Med 2010; Larkin, J Clin Oncol 2018.

Trials in front-line melanoma

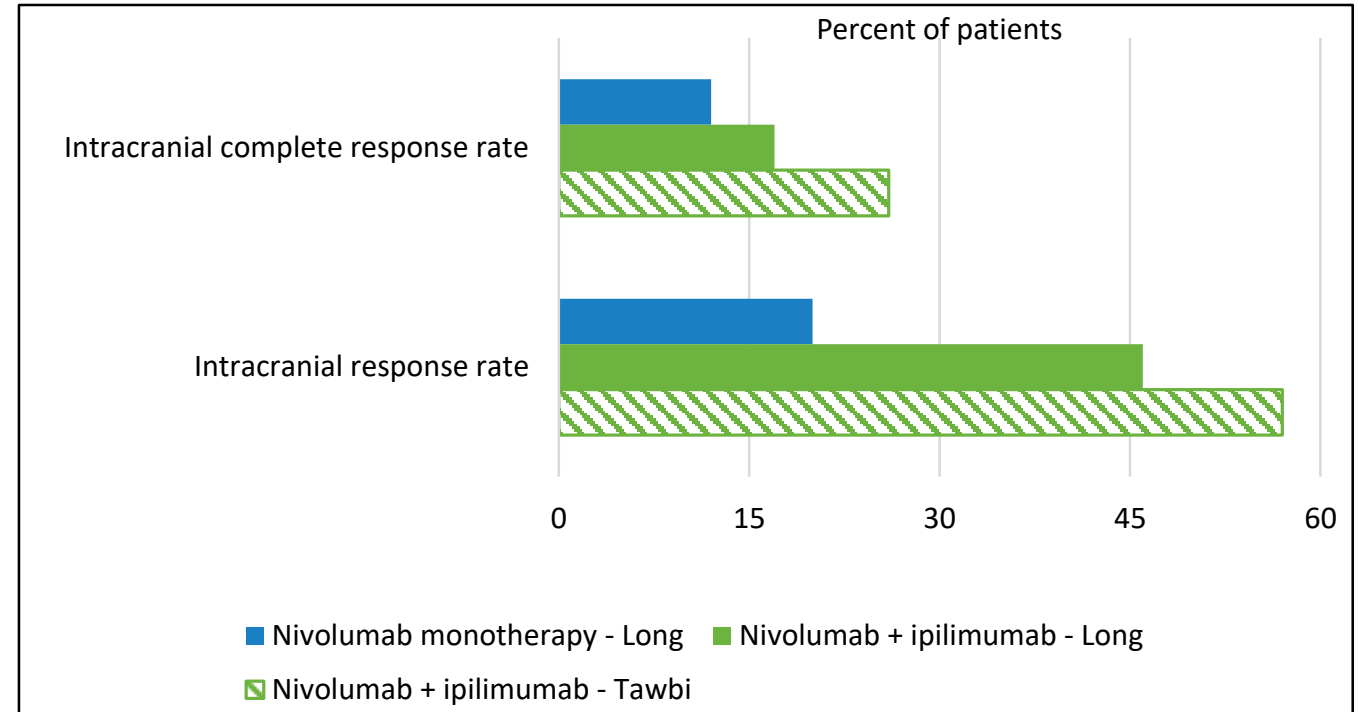
Trial	Treatment arm(s)	N	Patient selection criteria	ORR	Median PFS (months)	Landmark OS rate	Grade 3+ adverse events (%)
KEYNOTE-001	Pembrolizumab	655	Front-line	52%	16.9	5-year: 41%	17%
			ITT	41%	8.3	5-year: 34%	
CheckMate 067	Nivolumab + ipilimumab	314	Untreated stage III or IV melanoma	58%	11.5	5-year: 52%	59%
	Nivolumab	316		45%	6.9	5-year: 44%	23%
	Ipilimumab	315		19%	2.9	5-year: 26%	28%
CheckMate 066	Nivolumab	210	Untreated BRAF WT advanced melanoma	42.9%	5.1	3-year: 51.2%	15%
	Dacarbazine	208		14.4%	2.2	3-year: 21.6%	17.6%
IMspire150	Atezolizumab + cobimetinib + vemurafenib	256	BRAF V600 mutation-positive advanced/metastatic melanoma	66.3%	15.1	2-year: 60%	79%
	Cobimetinib + vemurafenib	258		65.0%	10.6	2-year: 53%	73%

Choosing appropriate regimens

- Consider combination ipilimumab/nivolumab up-front for patients with:
 - Brain metastases
 - Mucosal melanoma
 - High disease burden

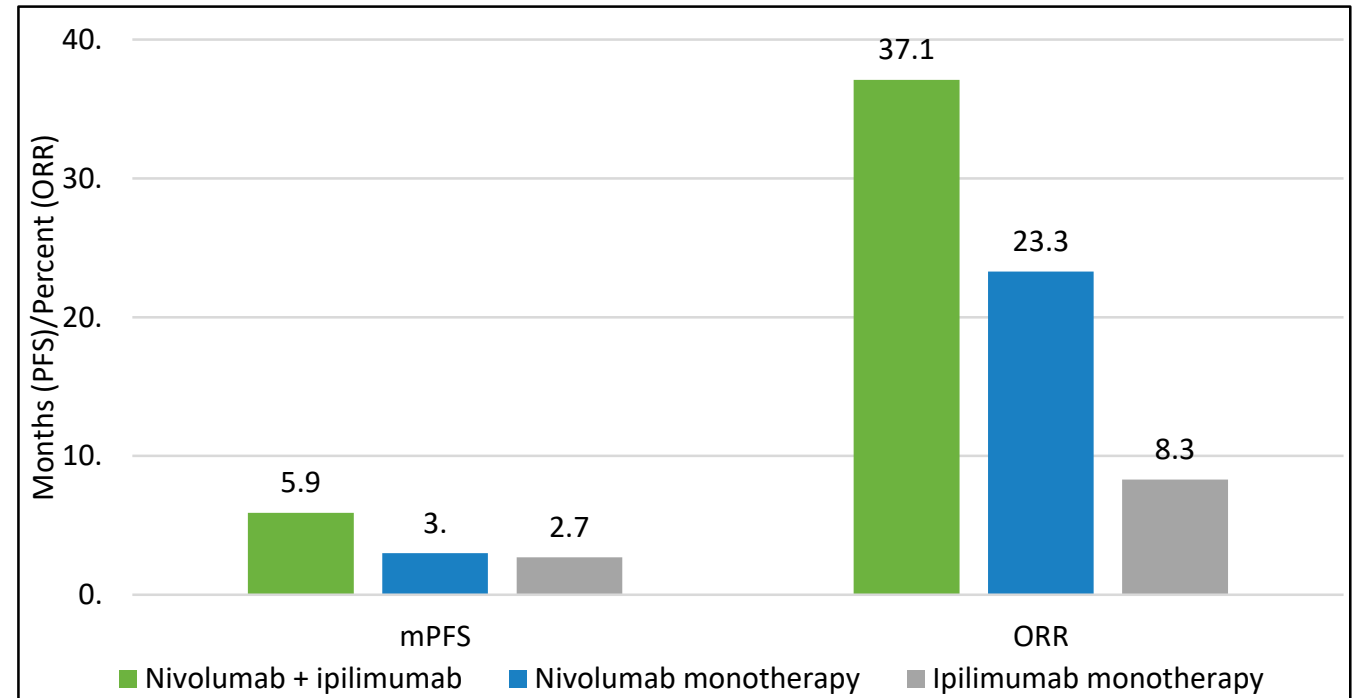
Choosing appropriate regimens

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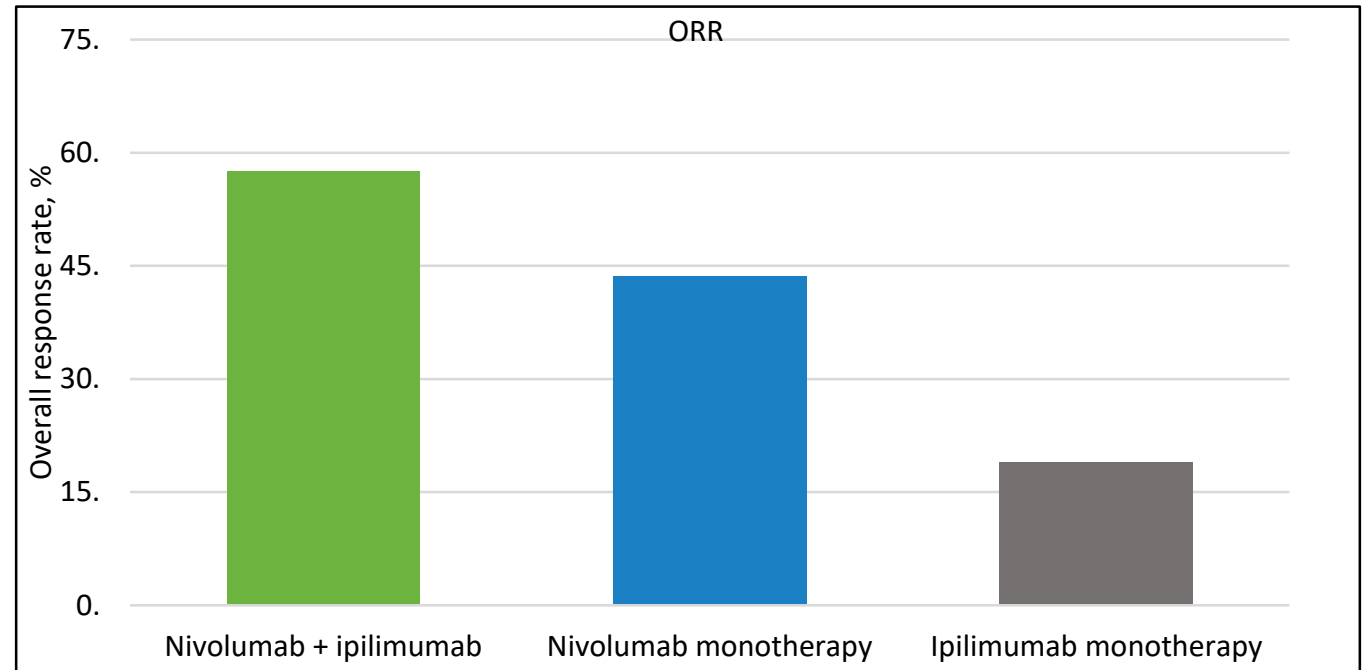
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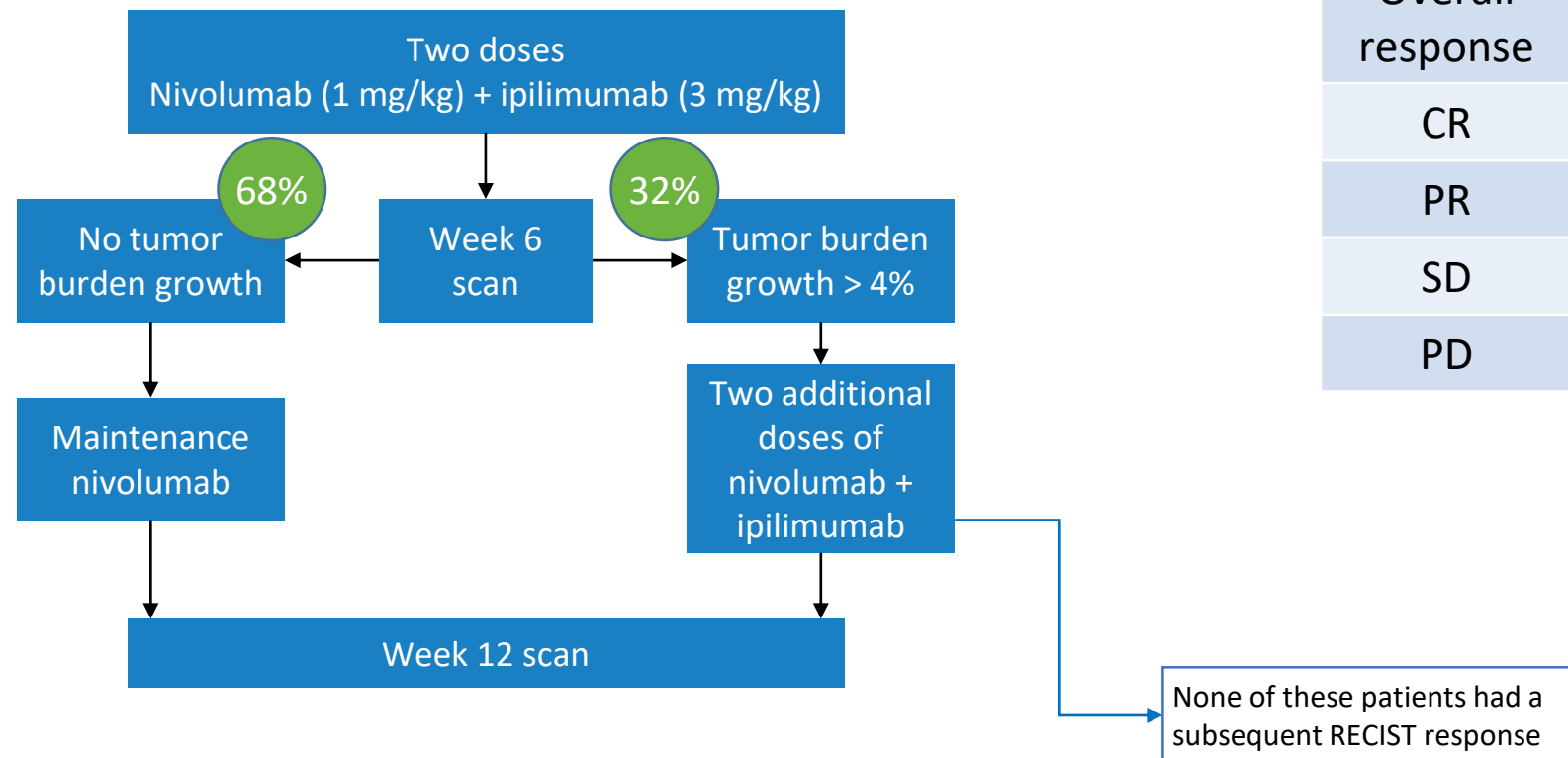


Choosing appropriate regimens

- Consider combination ipilimumab/nivolumab up-front for patients with:
 - Brain metastases
 - Mucosal melanoma
 - High disease burden



Question: How many combination doses to give



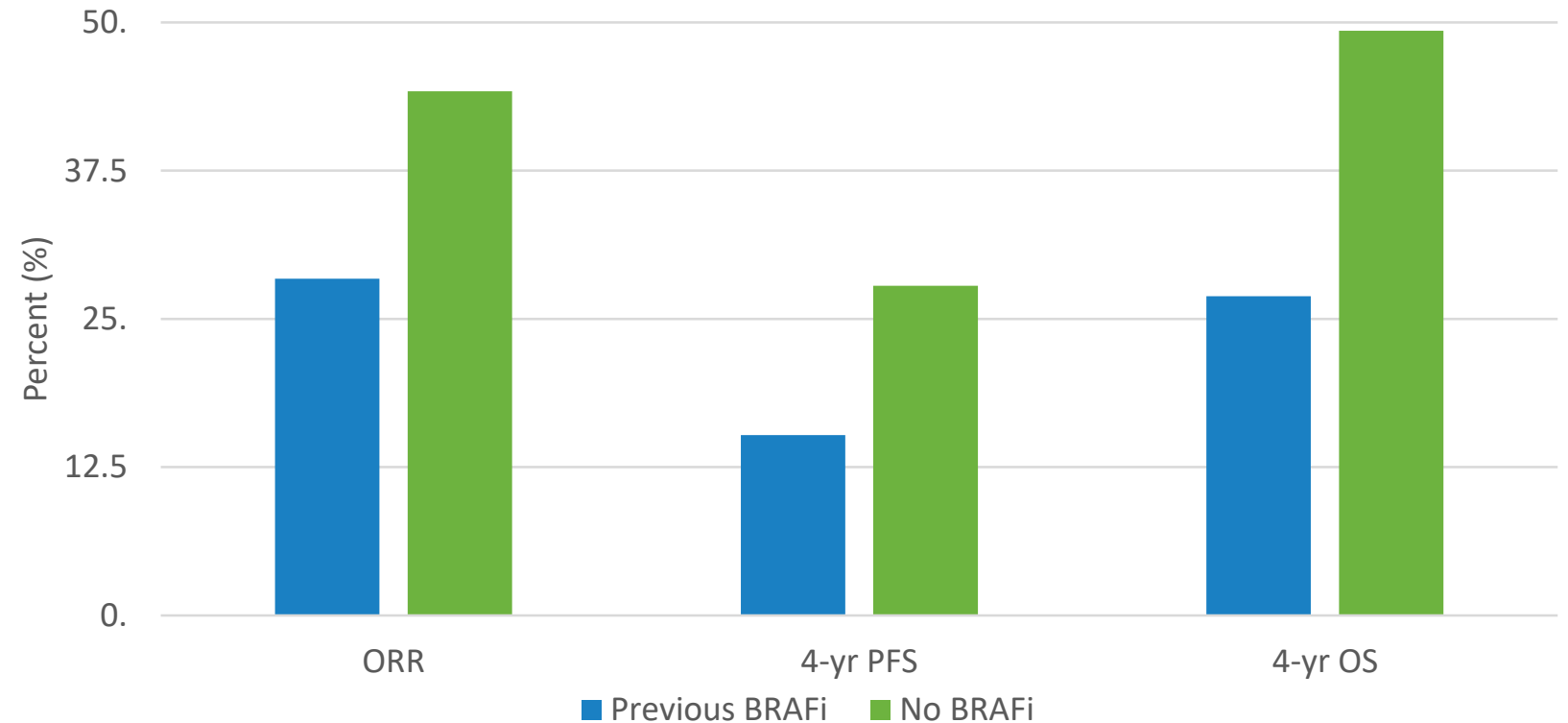
N=60	Week 6	Week 12	Best overall response rate
Overall response	35%	48%	57%
CR	0	5%	18%
PR	35%	43%	38%
SD	43%	18%	22%
PD	22%	30%	22%

Adverse events

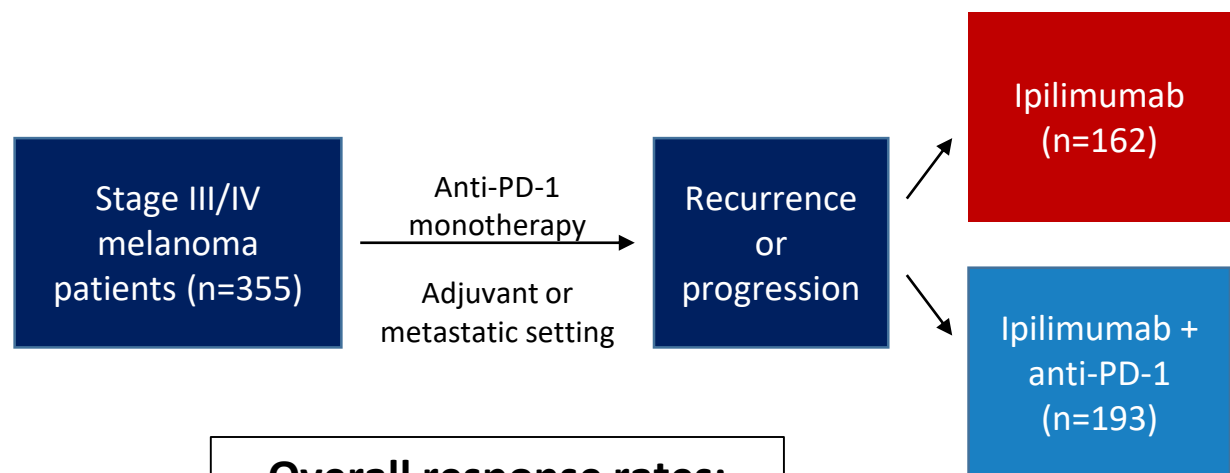
- 100% of patients had any-grade irAEs, regardless of how many doses received
- 57% had grade 3-4 irAEs

Question: Does the sequence of targeted therapy and immunotherapy impact response?

Retrospective data suggests that patients who received BRAF inhibitors prior to treatment with pembrolizumab tended to have poorer outcomes on pembrolizumab therapy than those patients without prior BRAF inhibitor exposure.



Question: what to do after PD-1 progression



Overall response rates:

IPI + PD-1: 32%

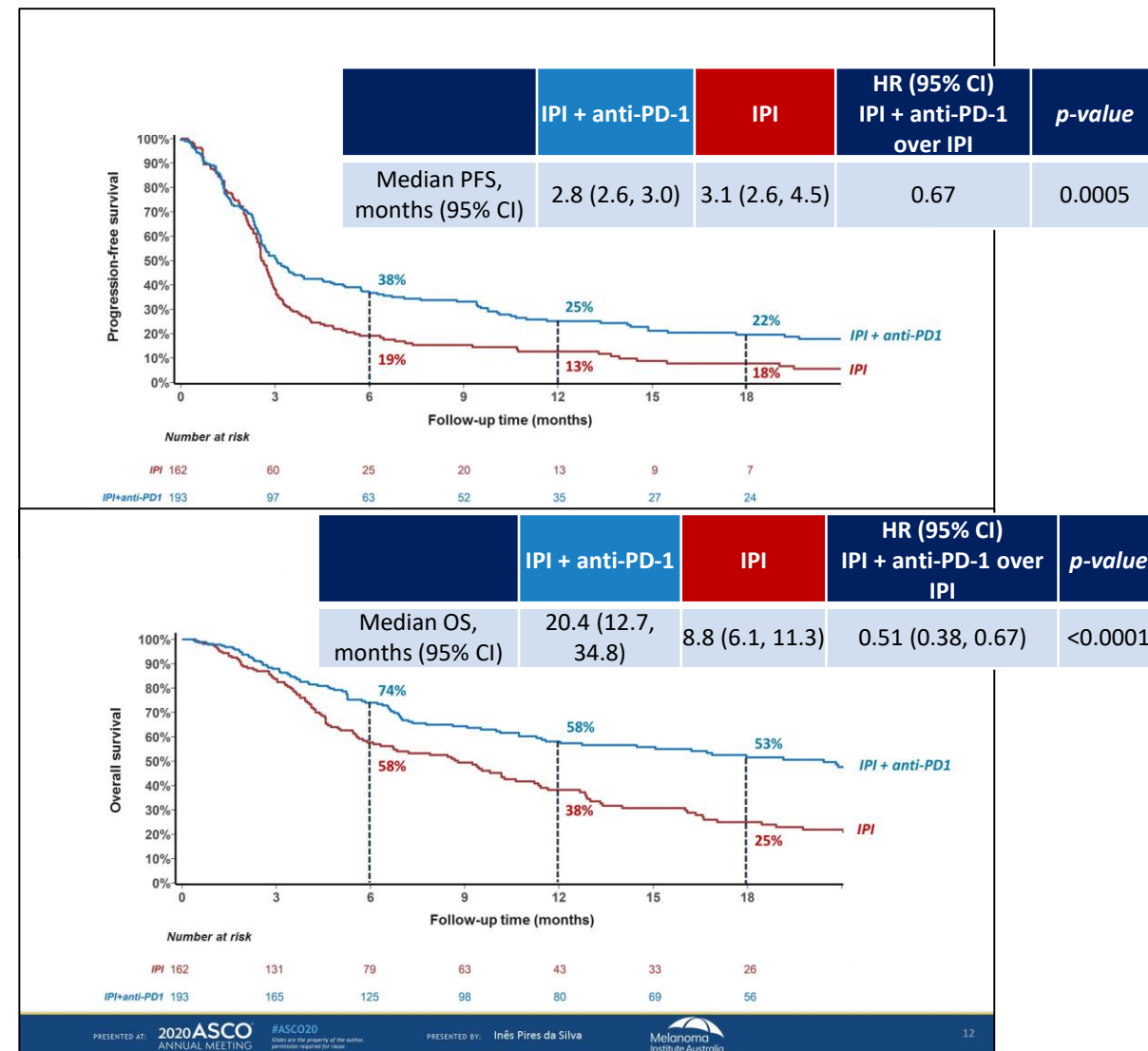
IPI: 13%

Grade 3+ adverse events:

IPI + PD-1: 31%

IPI: 33%

Retrospective study



Adjuvant treatment options for melanoma

Drug	Indication	Dose
Dabrafenib + trametinib ⁺	Adjuvant BRAF+ melanoma with lymph node involvement following complete resection	Dabrafenib 150 mg twice daily + trametinib 2 mg daily
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
Ipilimumab*	Adjuvant therapy in stage III melanoma after complete resection	10 mg/kg Q3W for 4 doses, then 10 mg/kg Q12W for 3 years
Pembrolizumab	Adjuvant therapy of melanoma following complete resection – 1 year	200 mg Q3W or 400 mg Q6W
Nivolumab	Adjuvant treatment of melanoma after complete resection – 1 year	240 mg Q2W or 480 mg Q4W

⁺*Not an immunotherapy; for reference*

^{*}*not commonly used in this setting; historical reference*

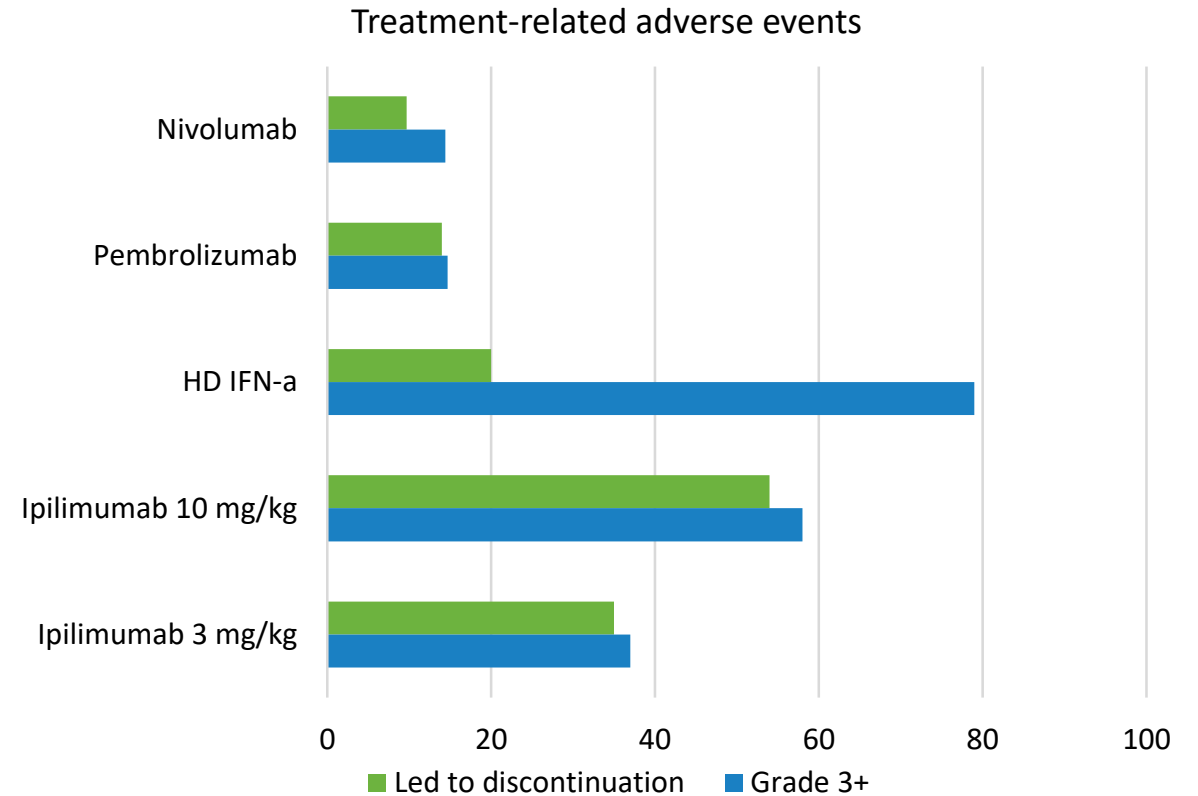
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Trials of adjuvant immunotherapy

Trial	Arms	Patient population	N	Key outcomes
EORTC 18071	Ipilimumab	Completely resected stage III melanoma	475	RFS HR: 0.76 OS HR: 0.72
	Placebo		476	
EORTC 1325-MG/KEYNOTE-054	Pembrolizumab	High risk resected stage III melanoma	514	RFS HR: 0.56
	Placebo		505	
CheckMate 238	Nivolumab	Resected stage IIIb or IV melanoma	453	RFS HR: 0.66
	Ipilimumab		453	
E1609	Ipilimumab 3 mg/kg	Resected stage IIIb-M1b melanoma	523	RFS HR: 0.85 OS HR: 0.78
	Ipilimumab 10 mg/kg		511	RFS HR: 0.84 OS HR: 0.88
	High-dose interferon alfa		636	

Adjuvant treatment considerations

- Goals of adjuvant treatment are different than goals of primary treatment
- Toxicity and quality of life are important considerations

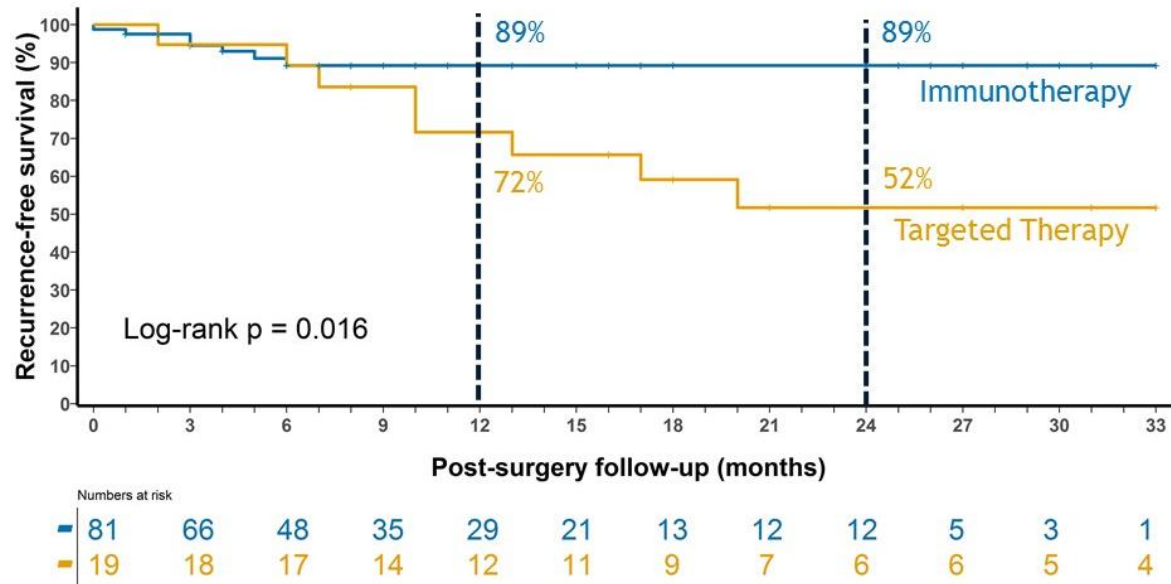


In development: Neoadjuvant immunotherapy in advanced melanoma

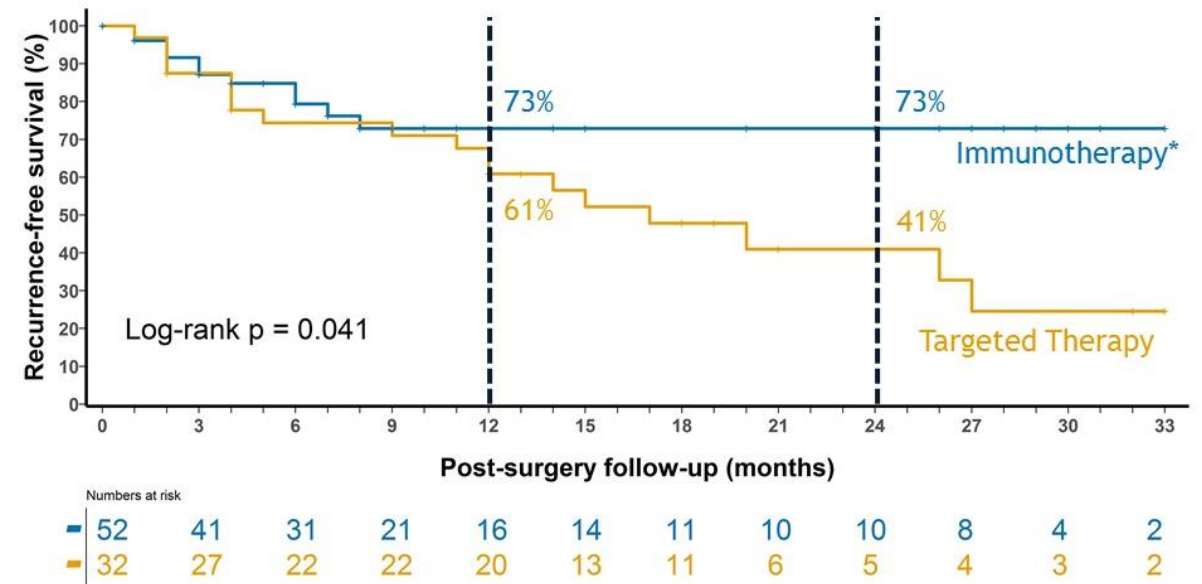
Trial	Regimen	N	pCR (%)	Median RFS (months)	Median follow-up (months)
<i>Amaria Lancet Oncol 2018 (reference non-IO trial)</i>	<i>Dabrafenib + trametinib</i>	21	58	19.7	18.6
<i>Long Lancet Oncol 2019 (reference non-IO trial)</i>	<i>Dabrafenib + trametinib</i>	35	49	23.0	27.0
Blank Nat Med 2018	Ipilimumab + nivolumab	10	33	NR	32
Amaria Nat Med 2018	Nivolumab	12	25	NR	20
	Ipilimumab + nivolumab	11	45	NR	
Huang Nat Med 2019	Pembrolizumab	30	19	NR	18
Rozeman Lancet Oncol 2019	Ipilimumab + nivolumab	86	57	NR	8.3

In development: Neoadjuvant immunotherapy in advanced melanoma

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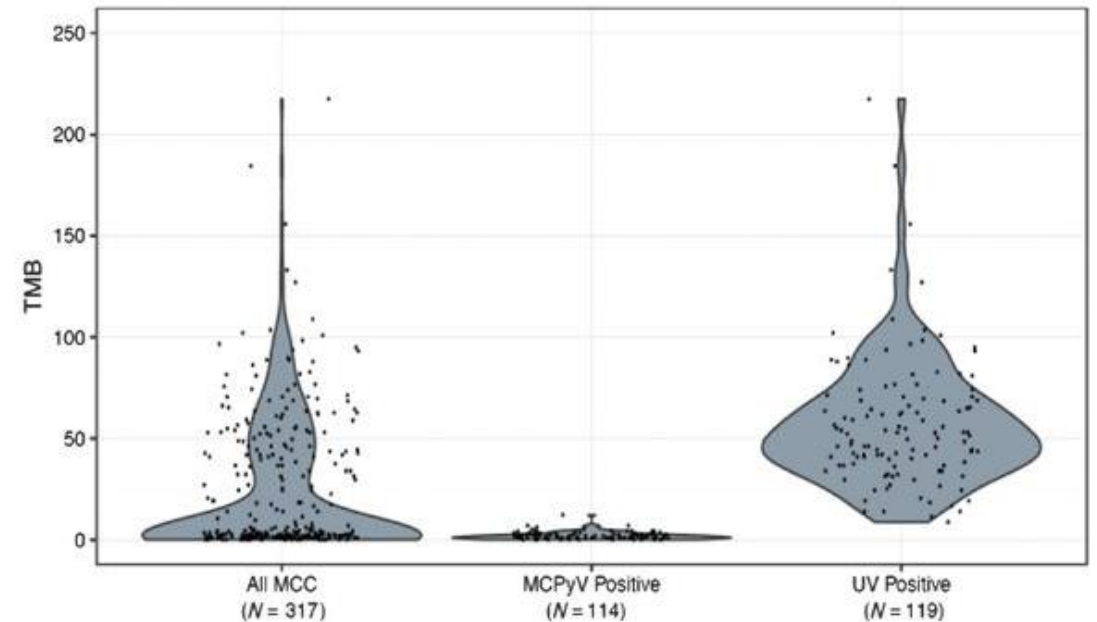


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- Melanoma
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 - Adjuvant and neoadjuvant settings
- **Merkel cell carcinoma**
- Squamous cell and basal cell carcinoma
- Future areas of research

Merkel cell carcinoma

- Associated with Merkel cell polyomavirus infection
- Higher incidence with weakened immune system (HIV, immunosuppressives) and increased age
- Distinct genomic profiles for UV- and virus-driven carcinomas
- Median PFS with chemo: ~90 days



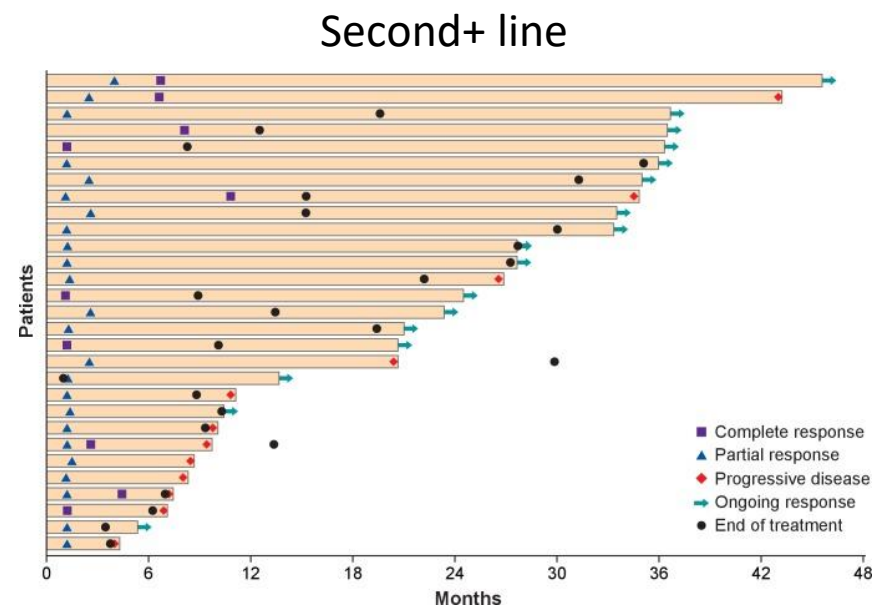
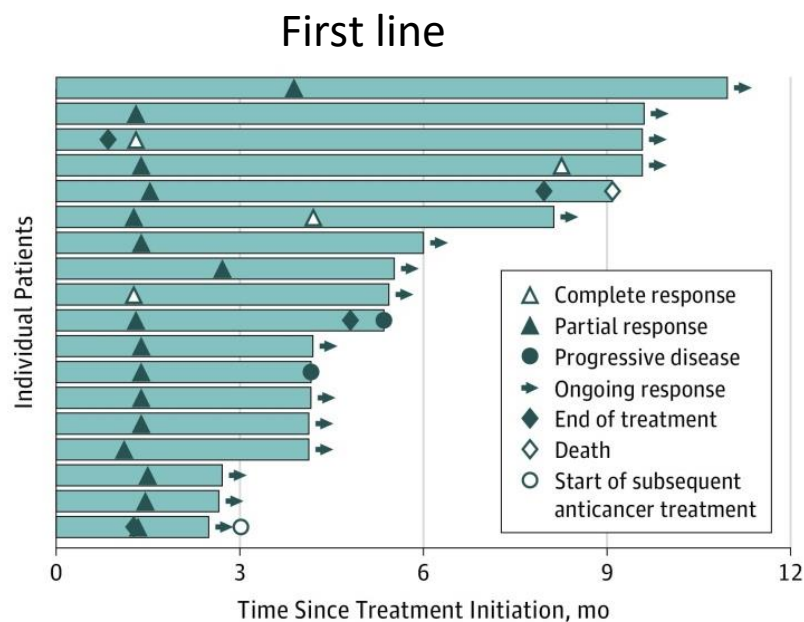
Approved checkpoint inhibitors in Merkel cell carcinoma

Drug	Indication	Dose
Avelumab*	Patients >12 yr with metastatic Merkel cell carcinoma	800 mg Q2W + premedication (first 4 cycles)
Pembrolizumab	Adult/pediatric with recurrent advanced/metastatic Merkel cell carcinoma	Adults: 200 mg Q3W or 400 mg Q6W Pediatric: 2 mg/kg (up to 200 mg) Q3W

**Requires premedication with an antihistamine and acetaminophen prior to first four infusions*

Avelumab in Merkel cell carcinoma

Setting	N	ORR	Median PFS	Median OS
First line	39	62.1%	9.1 months	
Second+ line	88	33.0%		12.6 months



D'Angelo, JAMA Oncol 2018.

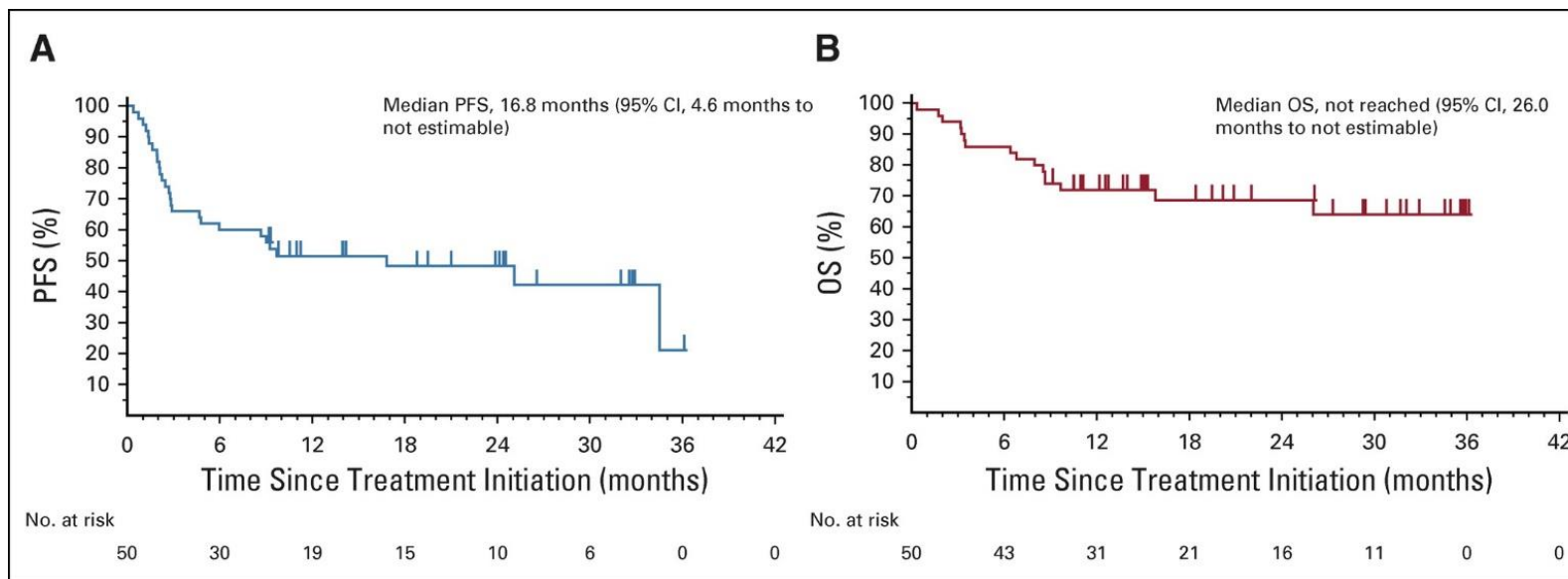
D'Angelo, J Immunother Cancer 2020.

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Pembrolizumab in 1st-line advanced Merkel cell carcinoma

Study	N	ORR	Median OS	Median PFS
KEYNOTE-017	50	56%	NR	16.8 months



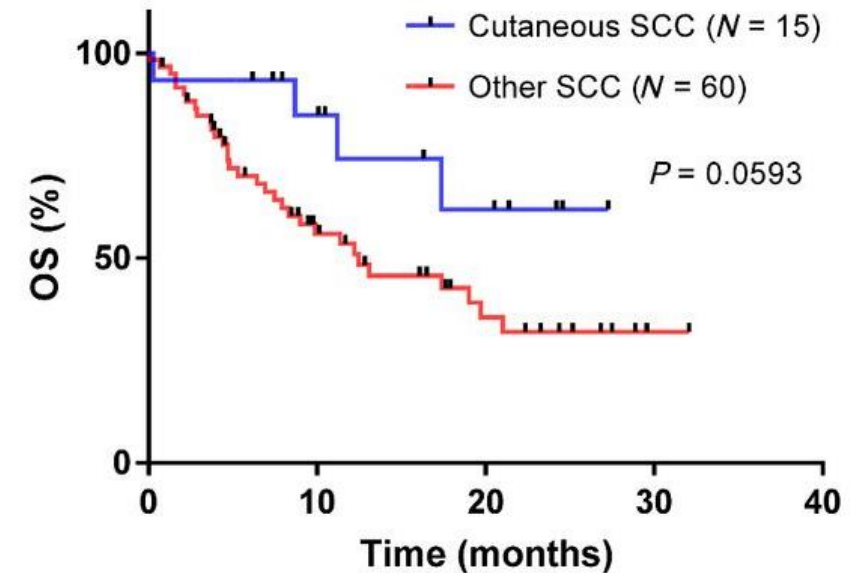
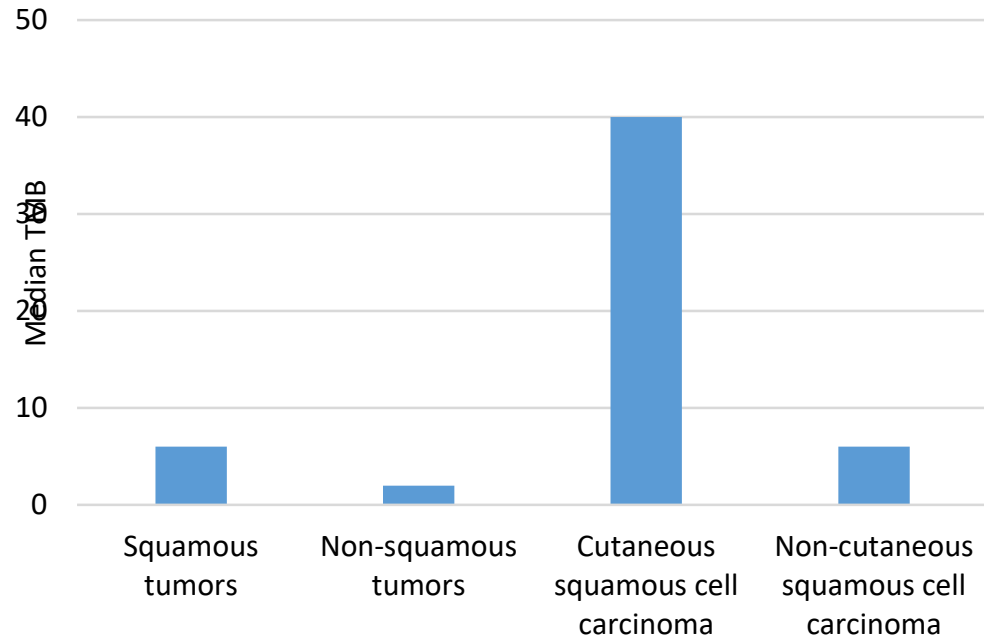
Also an ongoing trial of adjuvant pembrolizumab for Merkel cell carcinoma (NCT03712605).

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Cutaneous squamous cell carcinoma

- Second-most common skin cancer
- Associated with high TMB and immunotherapy responsiveness



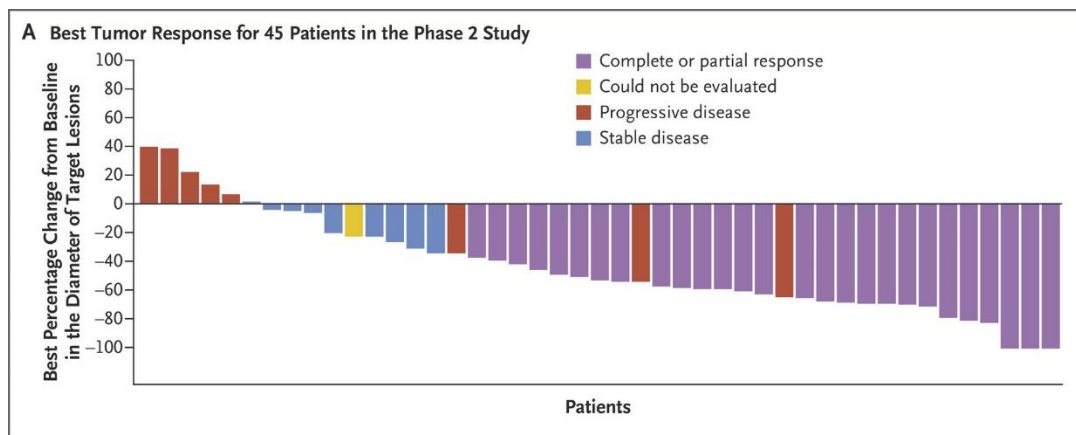
Approved checkpoint inhibitors for cutaneous squamous cell carcinoma

Drug	Indication	Dose
Cemiplimab-rwlc	Metastatic cutaneous squamous cell carcinoma, not candidate for curative therapies	350 mg Q3W
Pembrolizumab	Metastatic cutaneous squamous cell carcinoma	200 mg Q3W or 400 mg Q6W

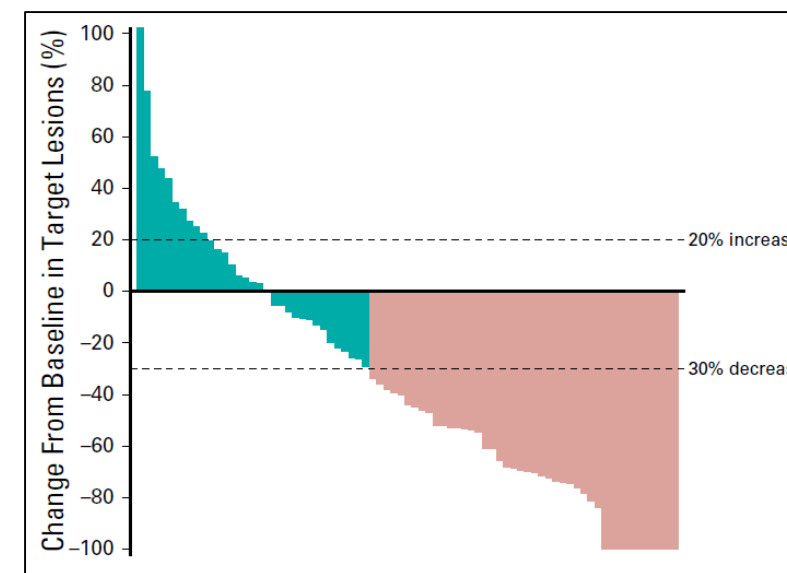
Trials for R/M cutaneous SCC

Trial	Treatment	N	ORR	Median OS	Median PFS
KEYNOTE-629	Pembrolizumab	105	34.3%	NR	6.9 months
NCT02760498	Cemiplimab	59	47%	NR	NR

Cemiplimab



Pembrolizumab



Approved checkpoint inhibitor for basal cell carcinoma

Drug	Indication	Dose
Cemiplimab	Locally advanced BCC previously treated with hedgehog pathway inhibitor or for whom HHI is not appropriate	350 mg Q3W
	Metastatic BCC previously treated with hedgehog pathway inhibitor or for whom HHI is not appropriate*	

**Accelerated approval*

Locally advanced disease

ORR: 29%
 CR: 5/84
 PR: 19/84

Metastatic disease

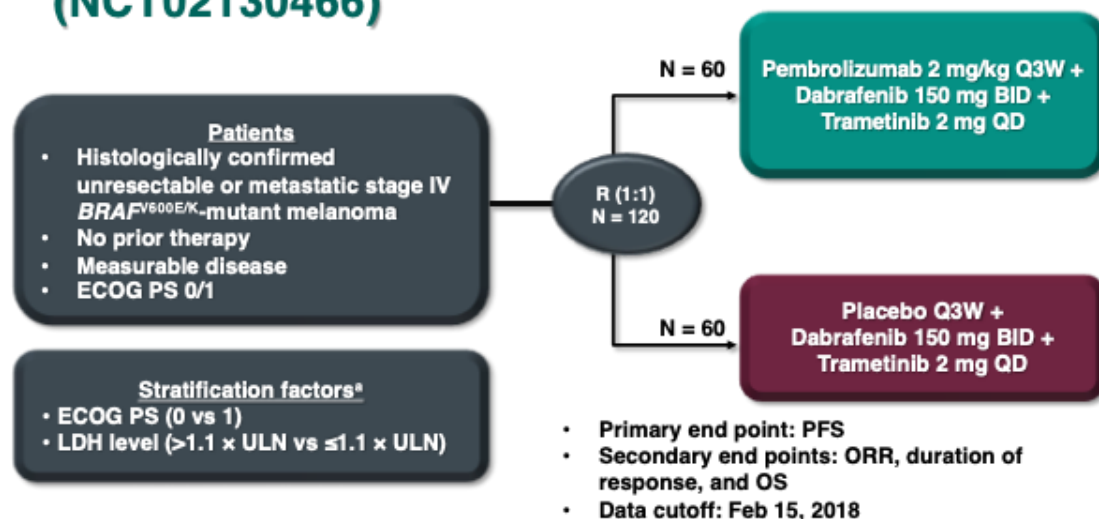
ORR: 21%
 PR: 6/28

Outline

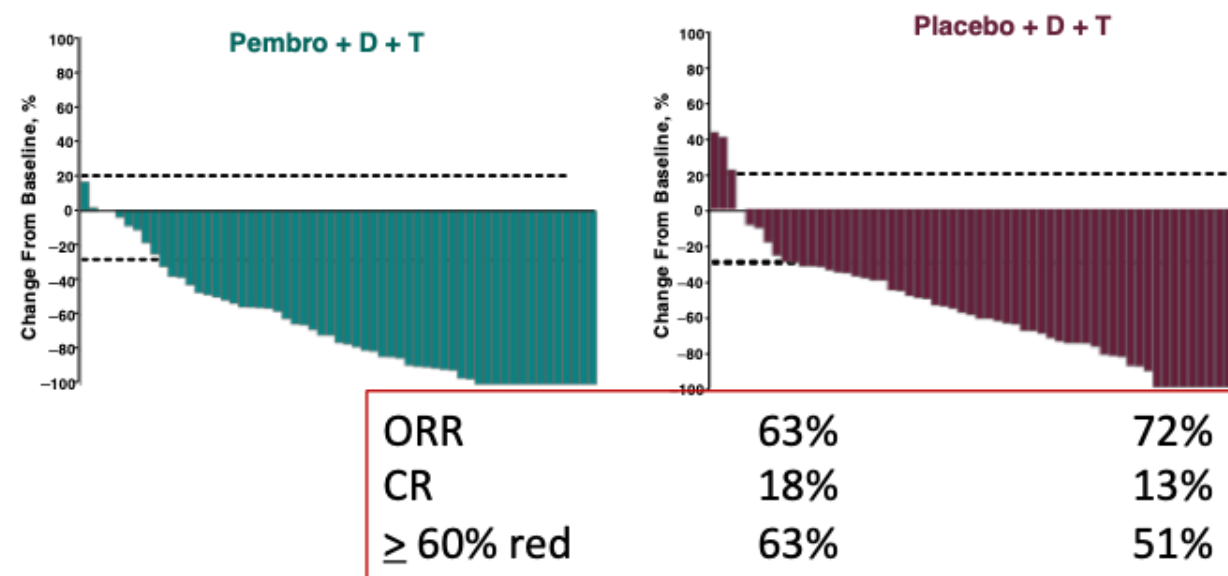
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In development: Combination IO with BRAF targeted therapy

KEYNOTE-022 Part 3 Study Design (NCT02130466)

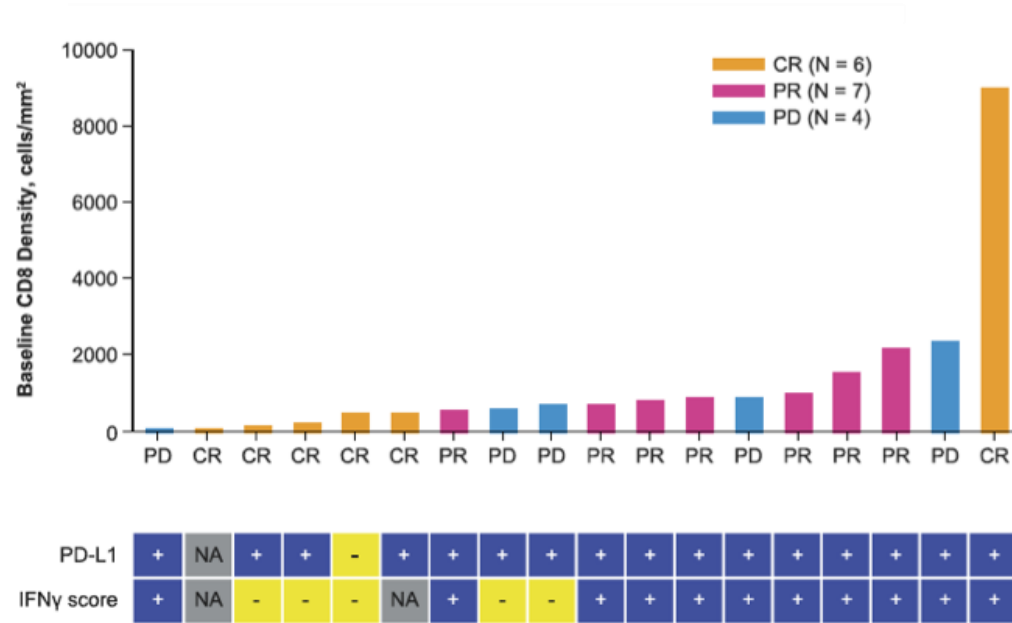


*Owing to the small number of patients enrolled in the ECOG PS 1 and LDH $\leq 1.1 \times \text{ULN}$ strata, these strata were combined.

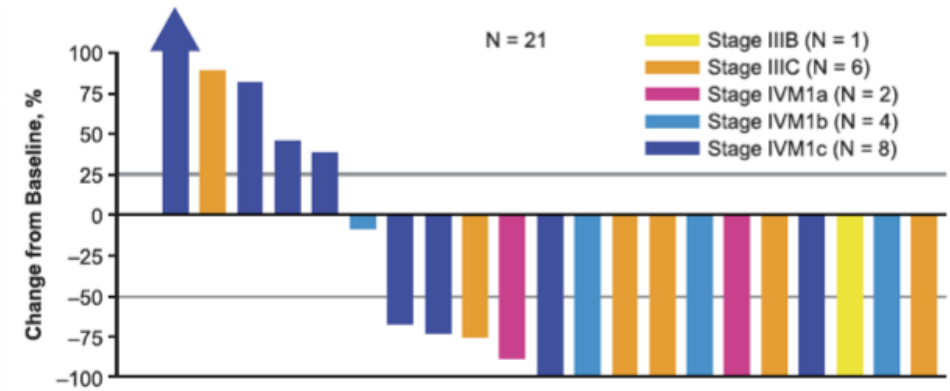


Multiple other triplet regimens are being tested.

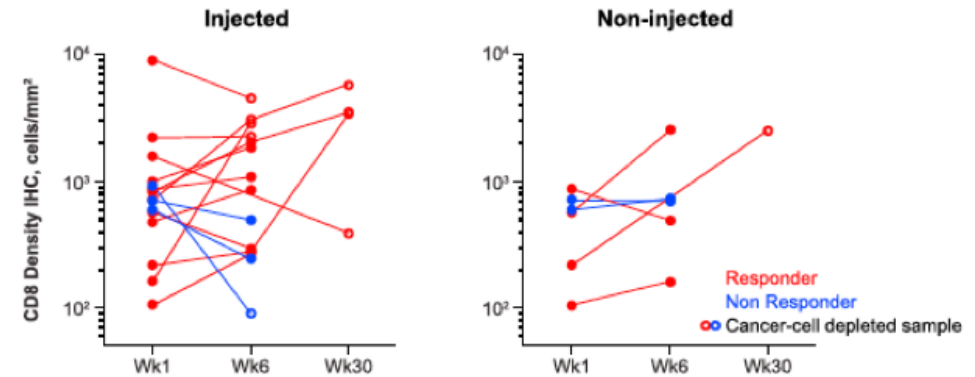
In development: Combination IO with oncolytic virus



Phase I: Pembrolizumab + TVEC



Confirmed RR of 63%

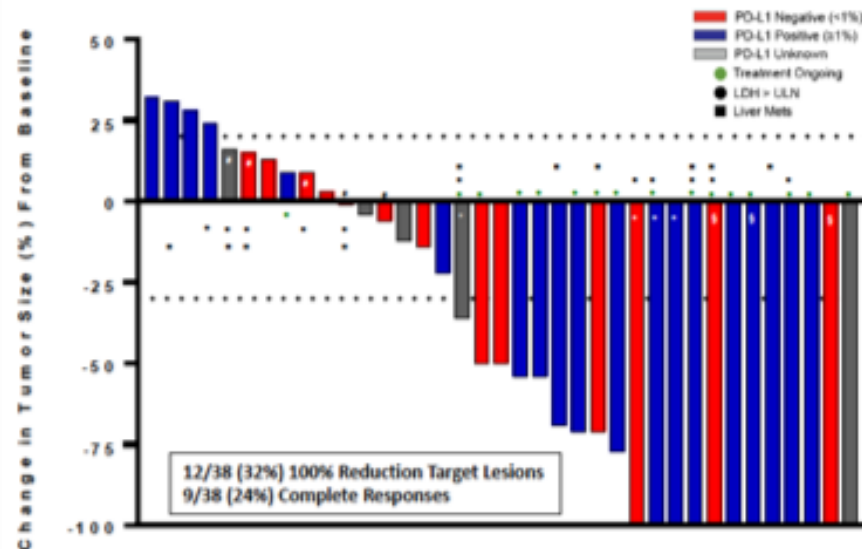


Ribas et al Cell 2017

In development: Combination IO with pegylated 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

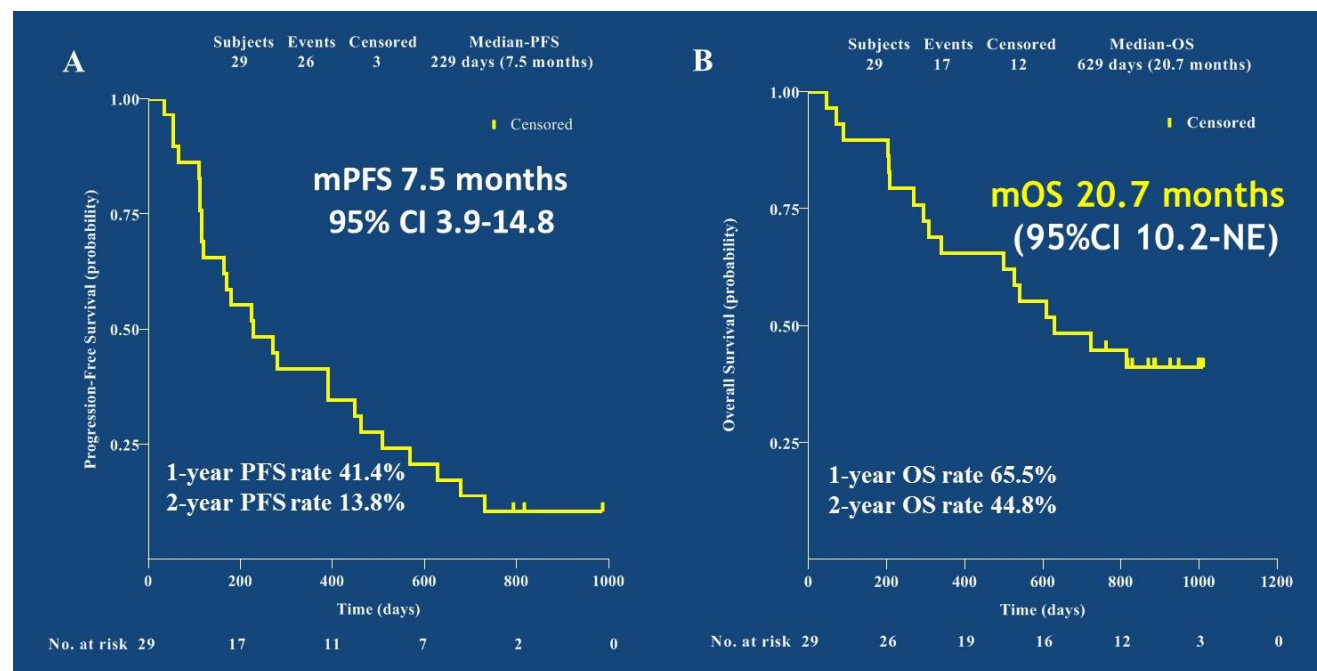


1L Melanoma (n=38 Efficacy Evaluable)	Overall Response Rate
Confirmed ORR (CR+PR)	20 (53%)
CR	9 (24%)
DCR (CR+PR+SD)	29 (76%)
PD-L1 negative (n=14)	6 (43%)
PD-L1 positive (n=19)	13 (68%)
PD-L1 unknown (n=5)	1 (20%)
LDH > ULN (n=11)	5 (45%)
Liver metastases (n=10)	5 (50%)

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

In development: Combination IO and TKI in mucosal melanoma

Treatment	N	ORR	Median PFS	Median OS
Toripalimab + axitinib	33	48.5%	7.5 months	20.7 months



Conclusions

- Melanoma was one of the foundational disease states for testing immunotherapies
- Avelumab and pembrolizumab are now approved for Merkel cell carcinoma, and cemiplimab and pembrolizumab are 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. Sullivan¹, Michael B. Atkins², John M. Kirkwood³, Sanjiv S. Agarwala⁴, Joseph I. Clark⁵, Marc S. Ernstoff⁶, Leslie Fecher⁷, Thomas F. Gajewski⁸, Brian Gastman⁹, David H. Lawson¹⁰, Jose Lutzky¹¹, David F. McDermott¹², Kim A. Margolin¹³, Janice M. Mehnert¹⁴, Anna C. Pavlick¹⁵, Jon M. Richards¹⁶, Krista M. Rubin¹, William Sharfman¹⁷, Steven Silverstein¹⁸, Craig L. Slingluff Jr¹⁹, Vernon K. Sondak²⁰, Ahmad A. Tarhini²¹, John A. Thompson²², Walter J. Urba²³, Richard L. White²⁴, Eric D. Whitman²⁵, F. Stephen Hodi²⁶ and Howard L. Kaufman^{1*}