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

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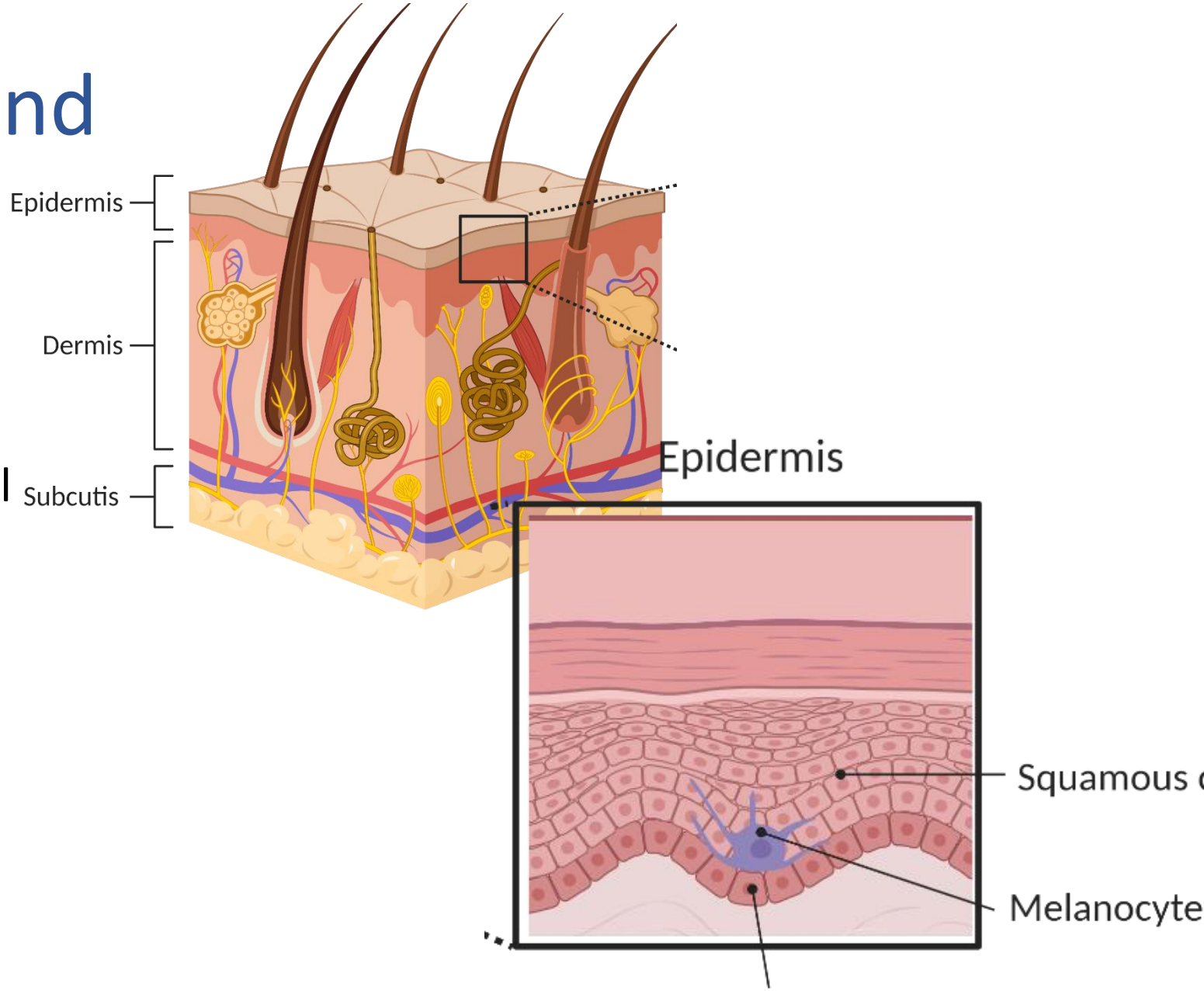
Disclosures

- Consulting Fees: Iovance DMC, ImaginAb SAB, Checkmate Pharma DSMB, Xilio, Werewolf
- I will be discussing non-FDA approved indications during my presentation.

Background

- Skin cancer—most common
  - Basal—least aggressive
  - Squamous cell carcinoma—not very aggressive except in special circumstances
  - Melanoma—most aggressive
- Melanoma—the first cancer in which immunotherapy was tested, responses provided proof of concept



Outline of topics to cover

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

Immunotherapy treatments approved for metastatic melanoma

Treatment	Indication	Dose
Ipilimumab	Unresectable/metastatic melanoma	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 cobi/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 safely accessible melanoma meastases	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 vax*	403	Pretreated advanced melanoma	5.7%	10.0	2.76
	Ipilimumab	137		10.9%	10.1	2.86
	gp100 vax	136		1.5%	6.4	2.76
KEYNOTE-006	Pembrolizumab	368	Advanced melanoma, 0-1 prior treatment	33.7%, 32.9%	32.7	8.4
	Ipilimumab	181		11.9%	15.9	3.4
CheckMate 037	Nivolumab	272	Melanoma after 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.

Front-line advanced melanoma trials

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* V600mu advanced/metastatic melanoma	66.3%	15.1	2-year: 60%	79%
	Cobimetinib + vemurafenib	258		65.0%	10.6	2-year: 53%	73%

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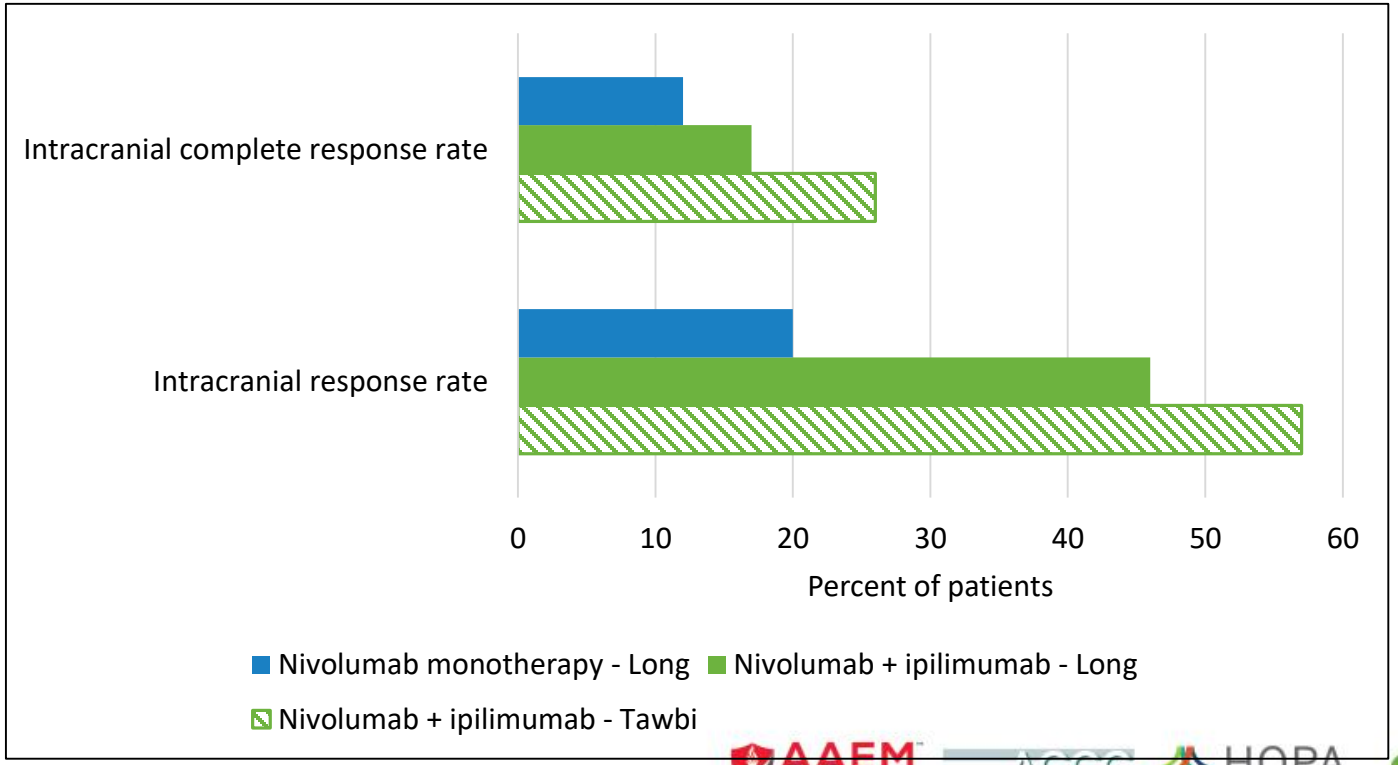
Choosing the optimal regimen

- Is the patient a candidate for combination ipilimumab/nivolumab? This is particularly important for:
  - Brain metastases if not on steroid or having symptoms
  - Mucosal melanoma, poorly-responsive to single-agent therapy
  - High disease burden
  - Prior adjuvant therapy with PD-1 antibody

Patients with brain metastases (ASx)

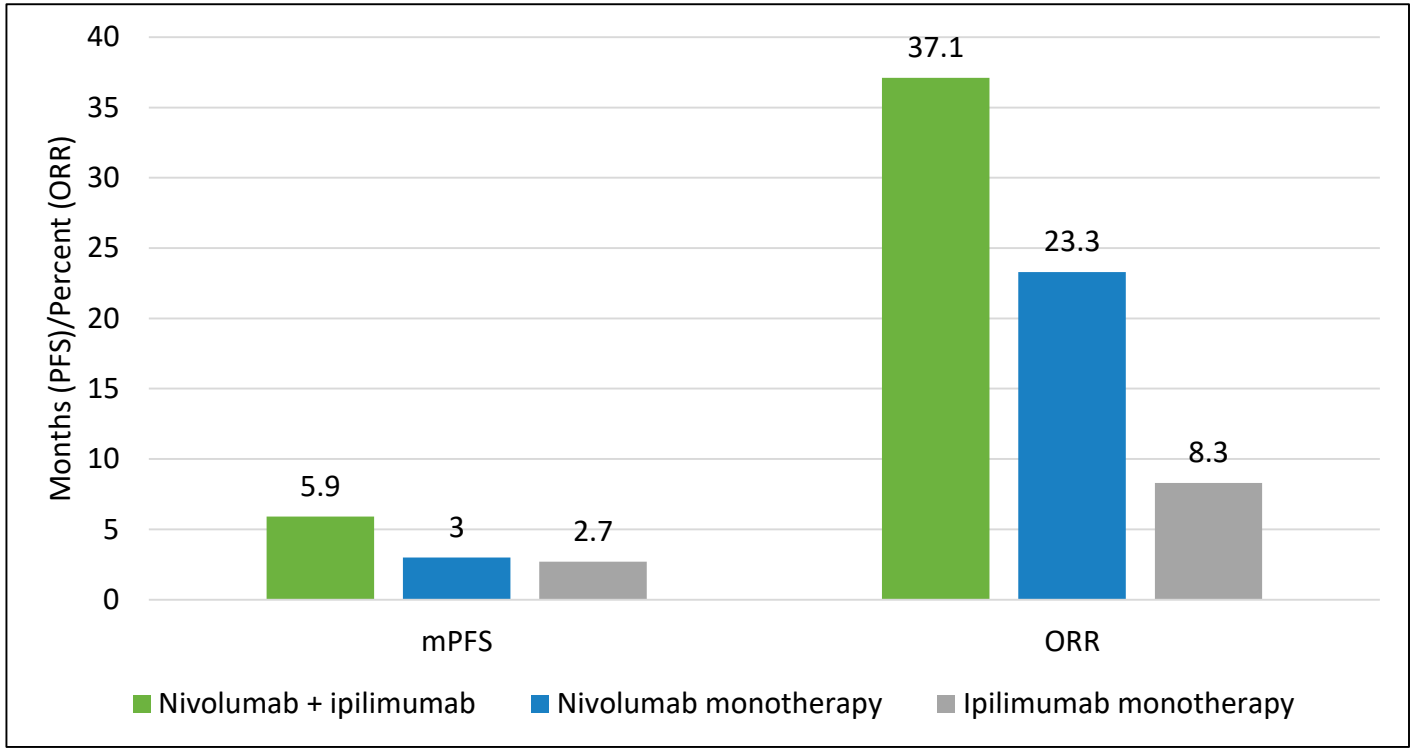
- Complete response rate and overall response rate of intracranial disease to ipilimumab and nivolumab
  - Brain metastases
  - Mucosal melanoma
  - High disease burden



Long, Lancet Oncol 2018; Tawbi, N Engl J Med 2018.

Patients with advanced mucosal melanoma

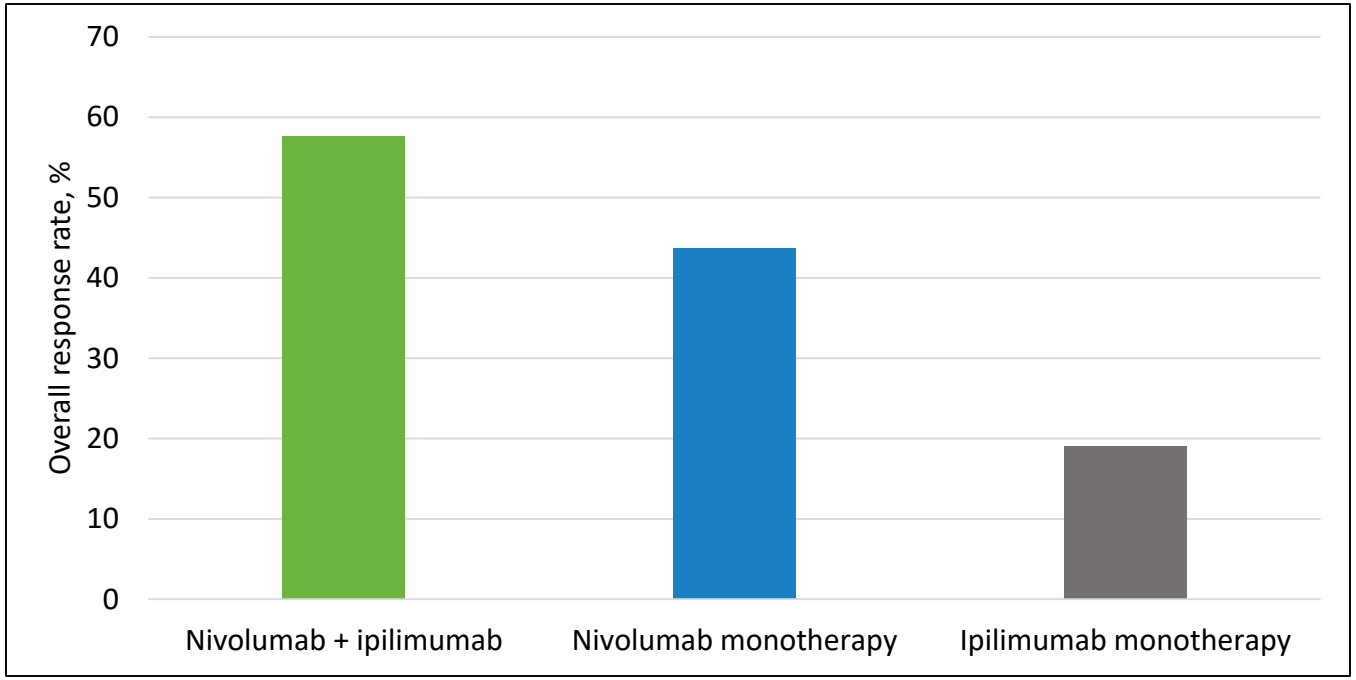
- Consider combination ipilimumab/nivolumab up-front for patients with:
  - Brain metastases
  - Mucosal melanoma
  - High disease burden



D'Angelo, J Clin Oncol 2016.

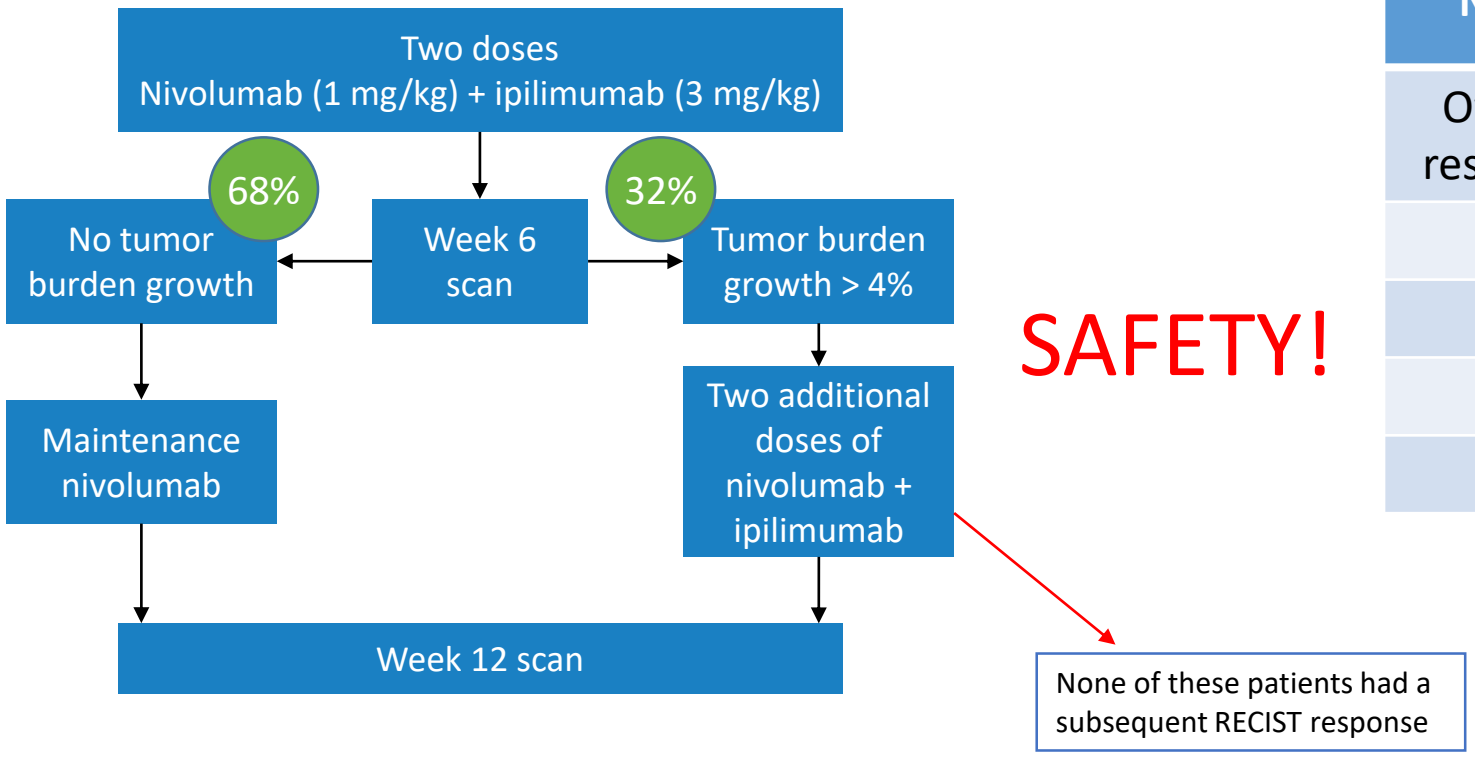
Patients with unfavorable characteristics or high disease burden

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



Larkin, N Engl J Med 2015.

What is optimal duration of combination immune checkpoint blockade?



SAFETY!

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

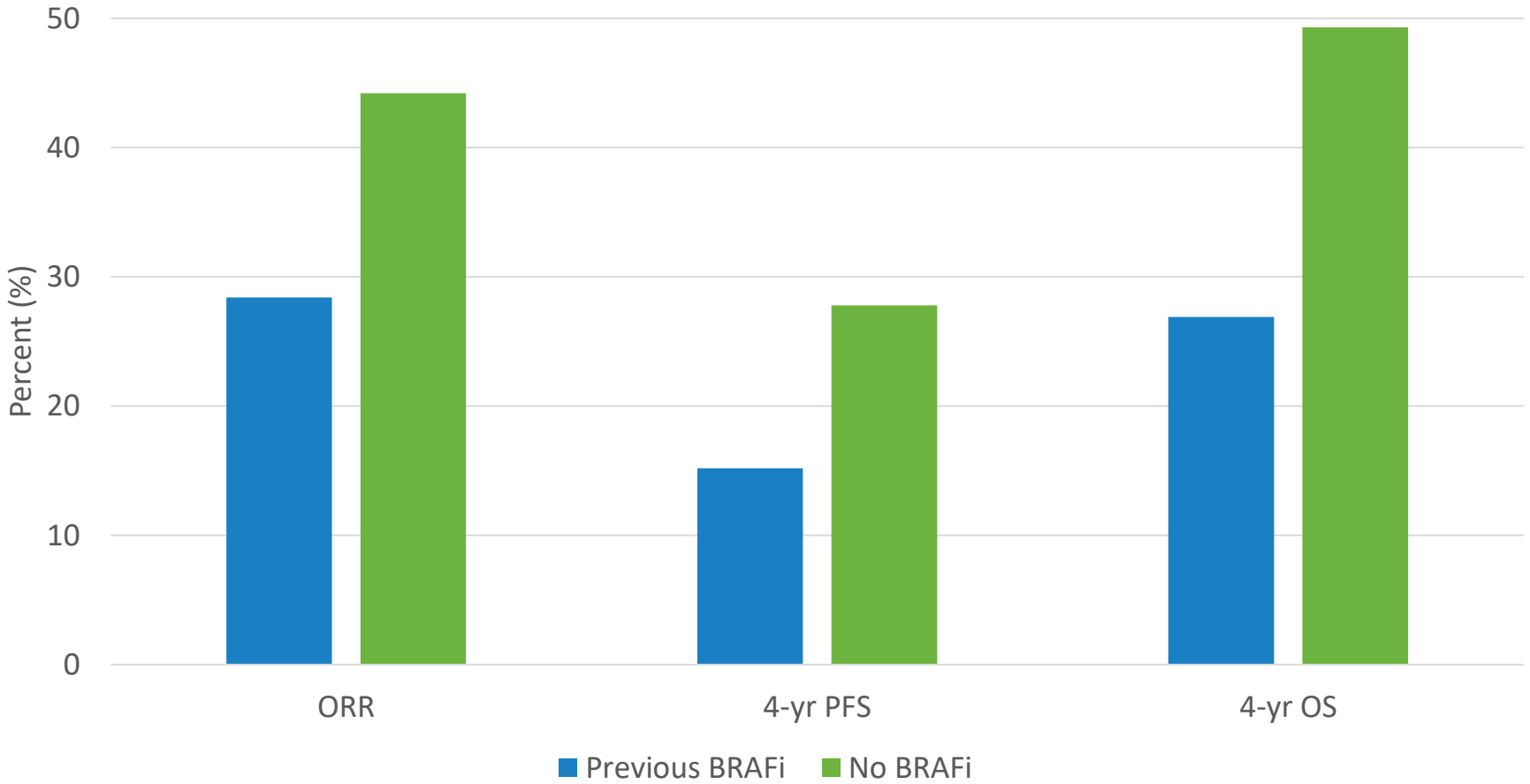
Postow, ASCO 2020.

Does sequence of targeted therapy and immunotherapy impact response?

Historically, targeted→IO did worse than IO→targeted, many possible explanations.

Sequencing targeted and IO combinations is ongoing.

Pooled analyses showed BRAFmu melanoma is equally responsive to IO as BRAF w.t.



Puzanov, JAMA Oncol 2020.

How to treat pts progressing on PD-1 blockade

Stage III/IV melanoma patients (n=355)

Anti-PD-1 monotherapy

Adjuvant or metastatic setting

Recurrence or progression

- Ipilimumab (n=162)
- Ipilimumab + anti-PD-1 (n=193)

Retrospective study

Overall response rates:

IPI + PD-1: 32%

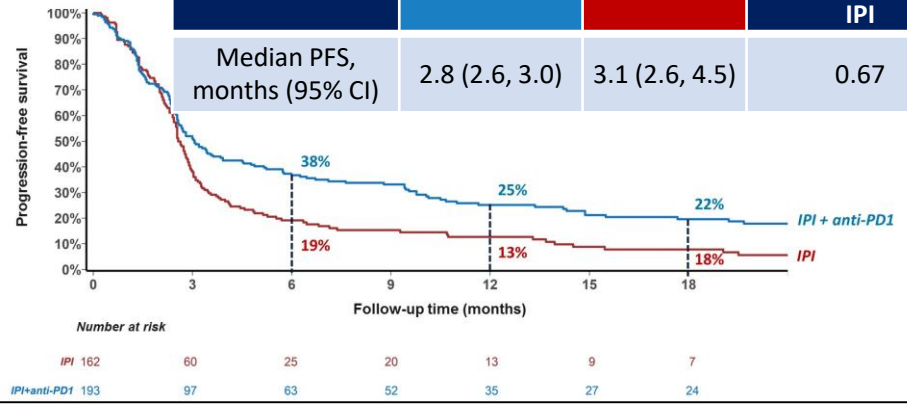
IPI: 13%

Grade 3+ adverse events:

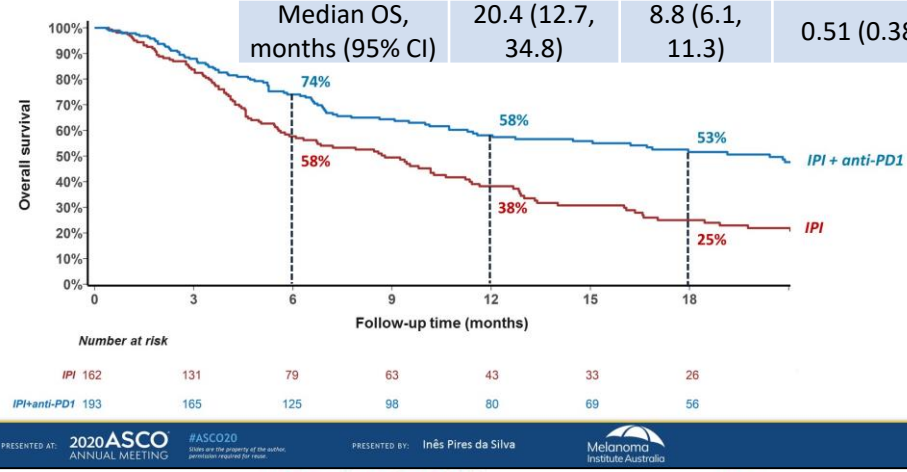
IPI + PD-1: 31%

IPI: 33%

	IPI + anti-PD-1	IPI	HR (95% CI) IPI + anti-PD-1 over IPI	*p-value*
Median PFS, months (95% CI)	2.8 (2.6, 3.0)	3.1 (2.6, 4.5)	0.67	0.0005



	IPI + anti-PD-1	IPI	HR (95% CI) IPI + anti-PD-1 over IPI	*p-value*
Median OS, months (95% CI)	20.4 (12.7, 34.8)	8.8 (6.1, 11.3)	0.51 (0.38, 0.67)	<0.0001



Pires da Silva, ASCO 2020.

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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

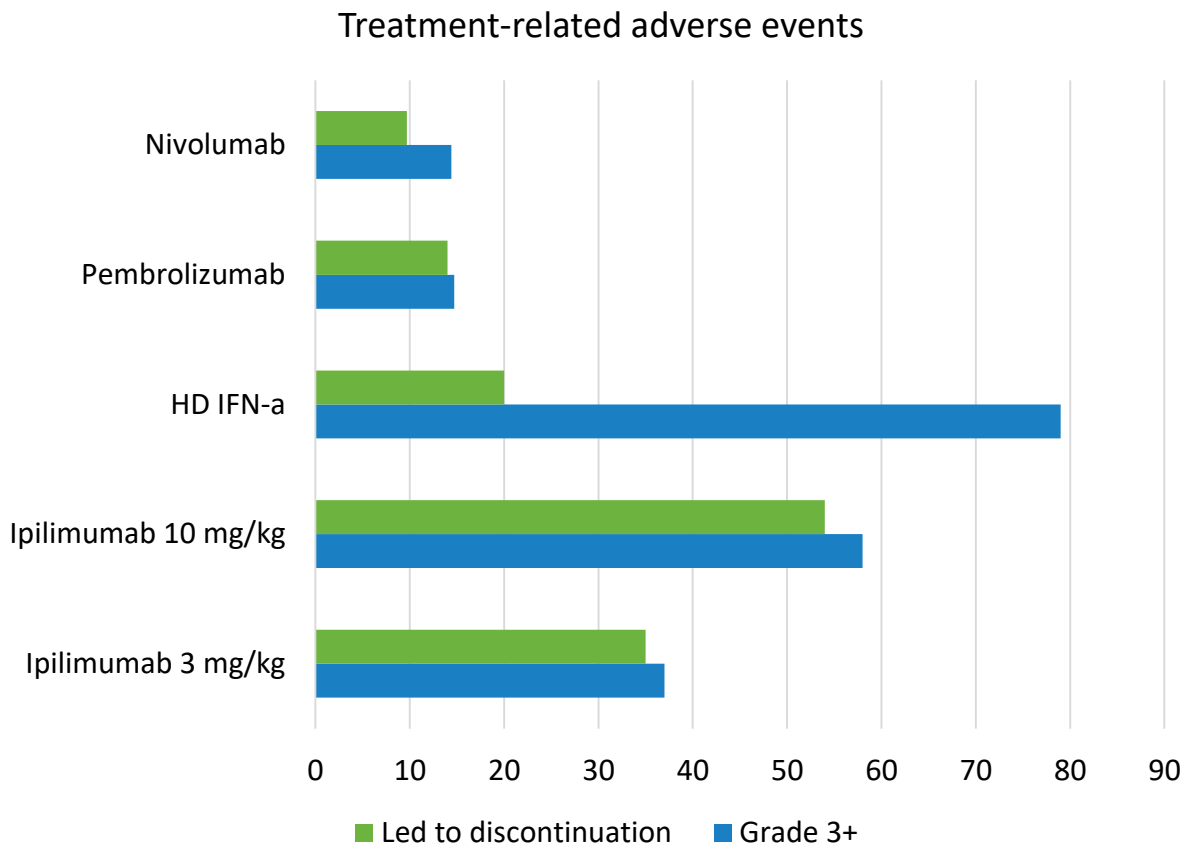
[+]Not an immunotherapy; for reference
**not commonly used in this setting; historical reference*

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 regimen considerations

- Goals of adjuvant therapy are to prolong the relapse-free interval and reduce the relapse rate.
- Long-term toxicities must be considered
- Survival benefits hinge on whether early intervention is superior to intervention only AT relapse and only IN relapsers
- Selection criteria are mostly lacking
  - Purely based on volume of disease
  - Do not take into account the biology of the tumor/therapy/host relationship



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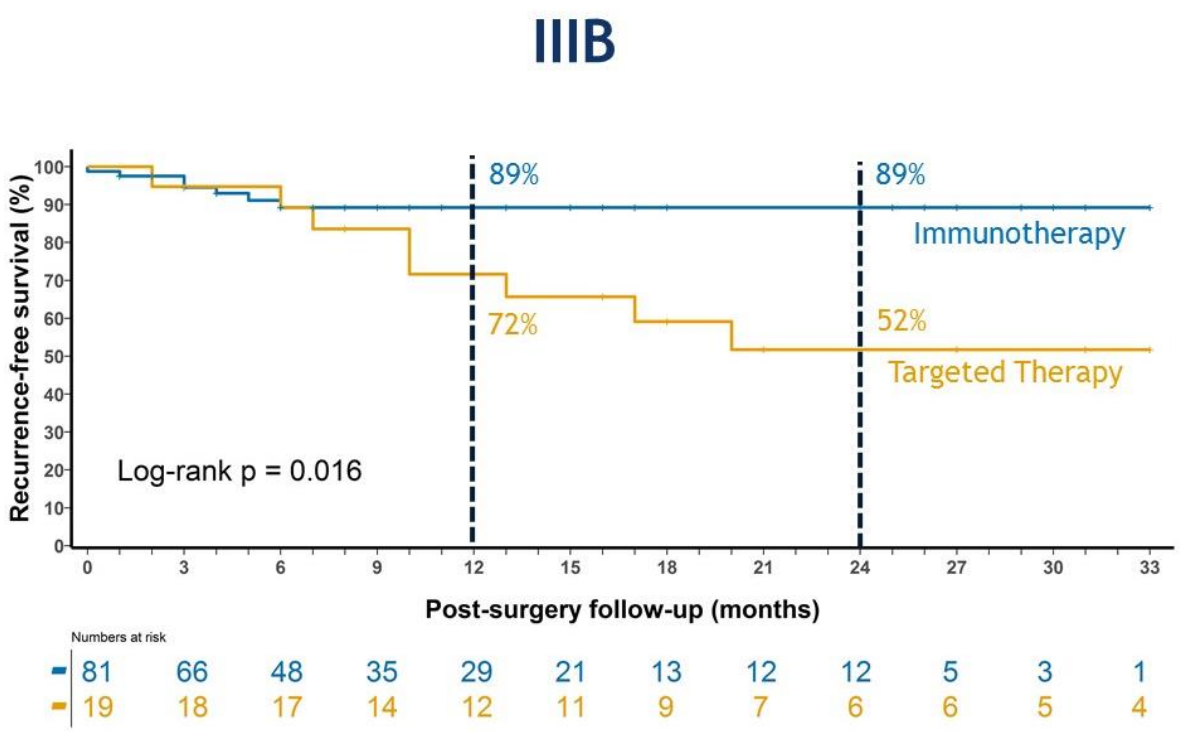
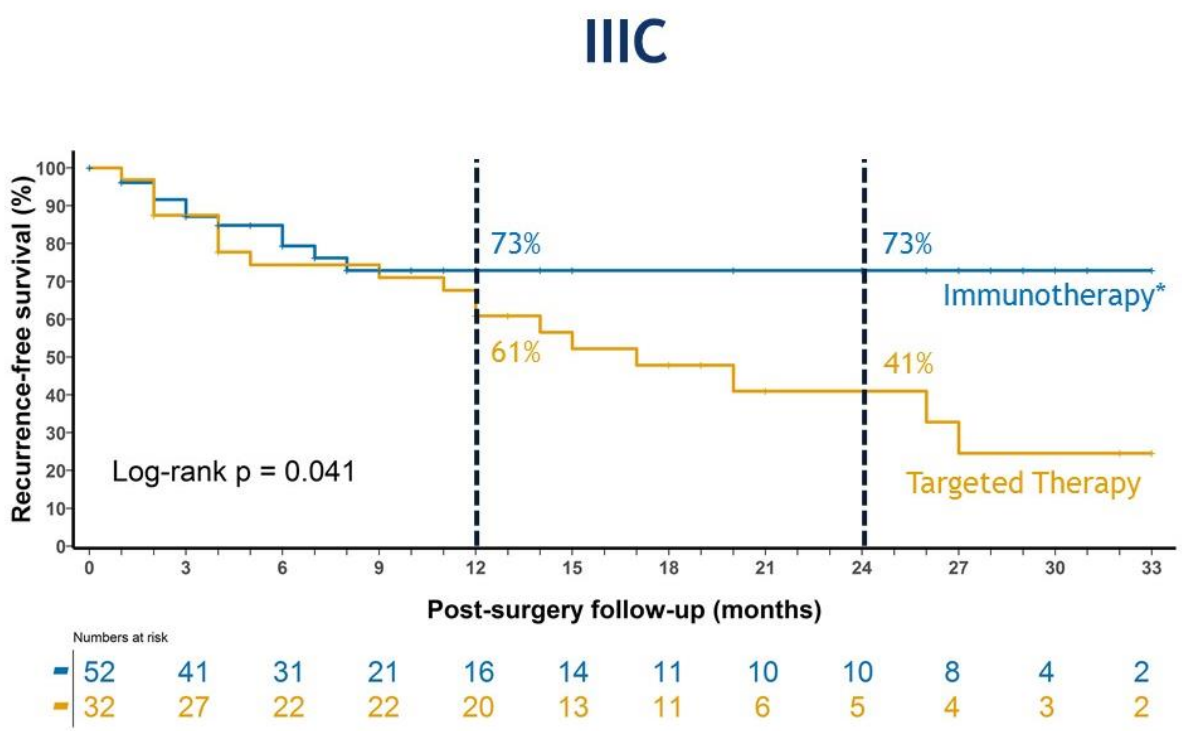
In development: Neoadjuvant immunotherapy in advanced melanoma

Trial	Regimen	N	pCR (%)	Median RFS (months)	Median follow-up (months)
Amaria Lancet Oncol 2018 (reference non-IO trial)	*Dabrafenib + trametinib*	*21*	*58*	*19.7*	*18.6*
Long Lancet Oncol 2019 (reference non-IO trial)	*Dabrafenib + trametinib*	*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

Menzies ASCO Annual Meeting 2019.

In development: Neoadjuvant immunotherapy in advanced melanoma





Menzies ASCO Annual Meeting 2019.

Outline of topics—cont'd

- Melanoma
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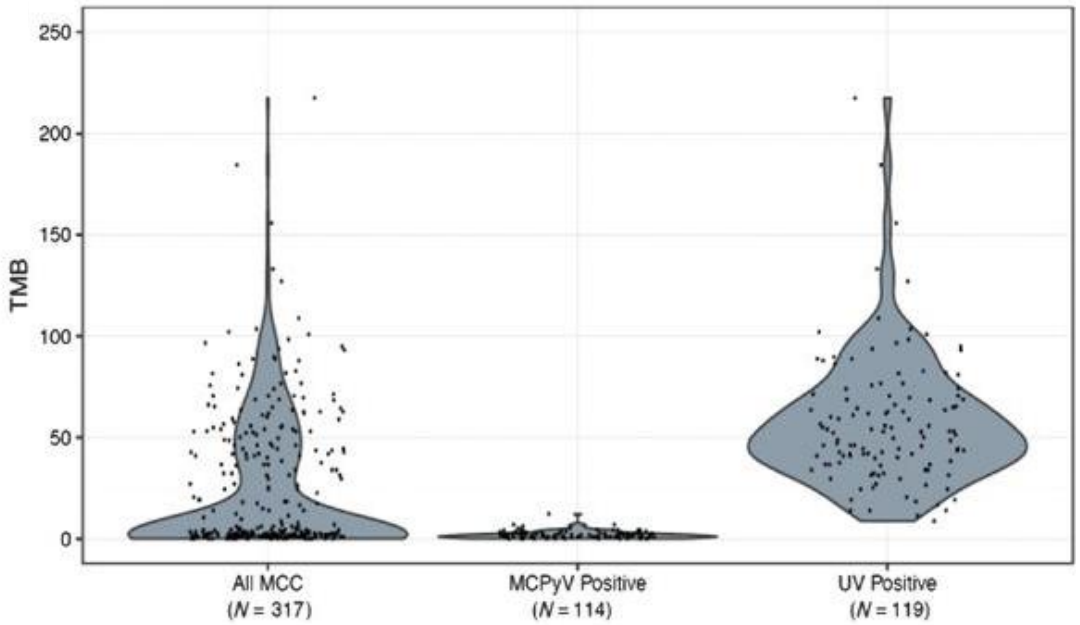
- Merkel cell carcinoma
- Squamous cell and basal cell carcinoma
- Future areas of research

Merkel cell carcinoma

- Associated with Merkel cell polyomavirus infection in ~75%
- Higher incidence in elderly and pts w/ weakened immune system (e.g.heme malignancy, immunosuppression)
- Distinct genomic profiles for UV and virus
  - Virus is a strong immunogen, fewer mutations
  - UV causes high mutation rate in MCPyV- MCC
- Chemo highly active but not curative—no longer used first-line



Knepper, Clin Cancer Res 2019.

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Approved checkpoint inhibitors in Merkel cell carcinoma

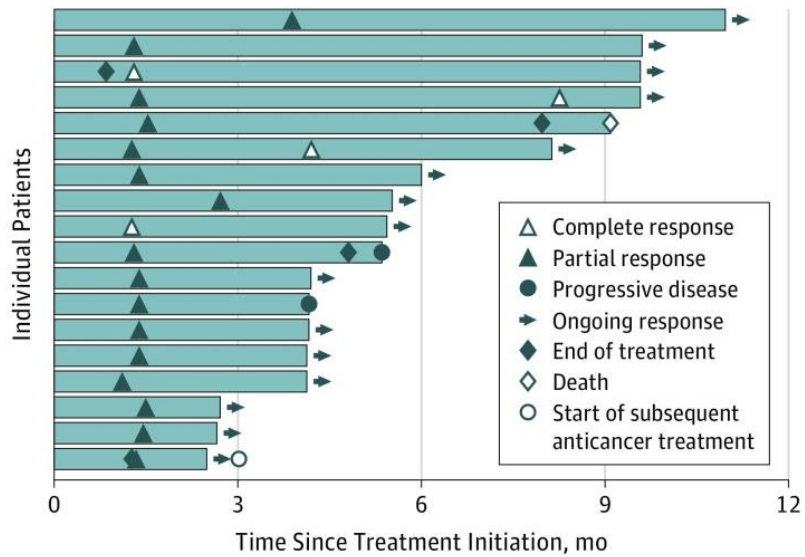
Drug	Indication	Dose
Avelumab*	Adults w/metastatic **Merkel cell carcinoma**	800 mg Q2W + premedication (first 4 cycles)
Pembrolizumab	Adult/pediatric with recurrent advanced/metastatic **Merkel cell carcinoma**	Adults: 200 mg Q3W or 400 mg Q6W Pediatric: 2 mg/kg (up to 200 mg) Q3W

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

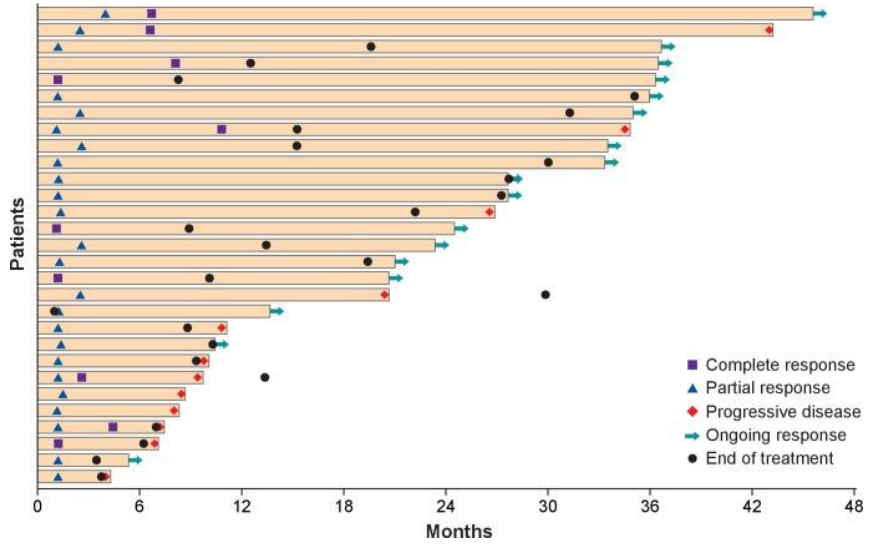
Avelumab in Merkel cell carcinoma

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

First line



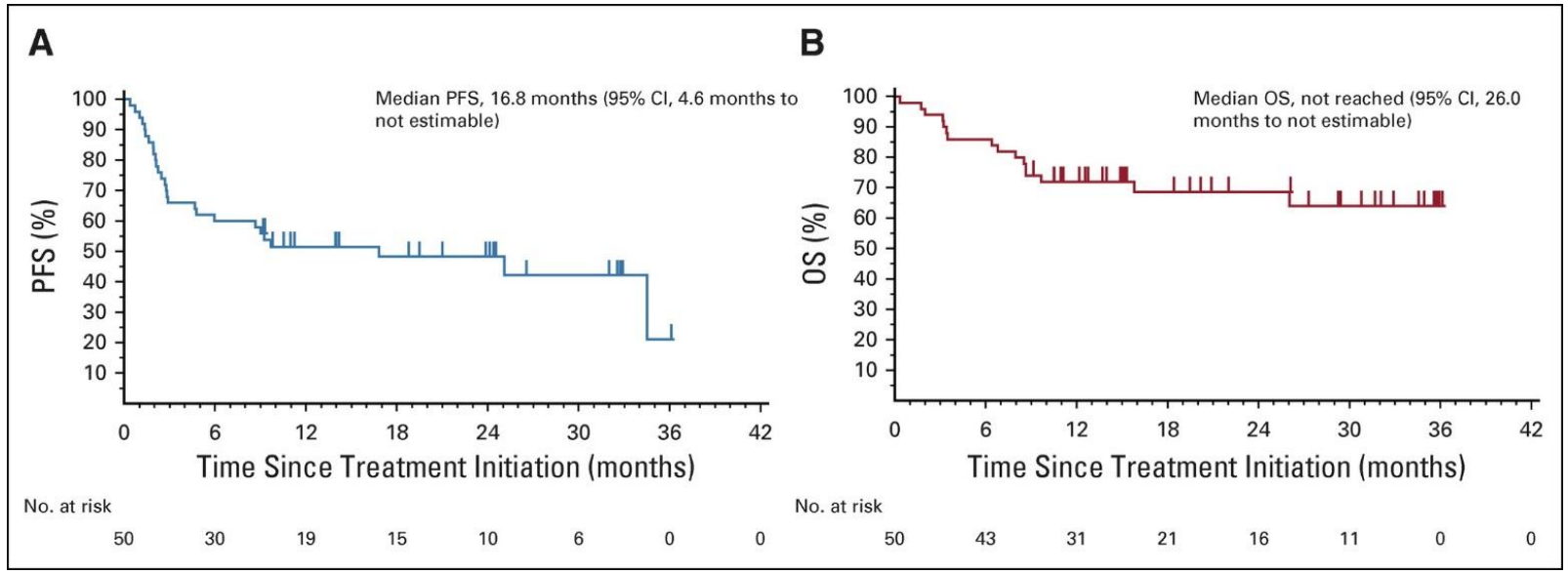
Second+ line



D'Angelo, JAMA Oncol 2018.
D'Angelo, J Immunother Cancer 2020.

1st-line Pembrolizumab in advanced MCC

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).

Nghiem, J Clin Oncol 2019.

Outline of topics—cont'd

- Melanoma
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- Squamous and basal cell carcinoma
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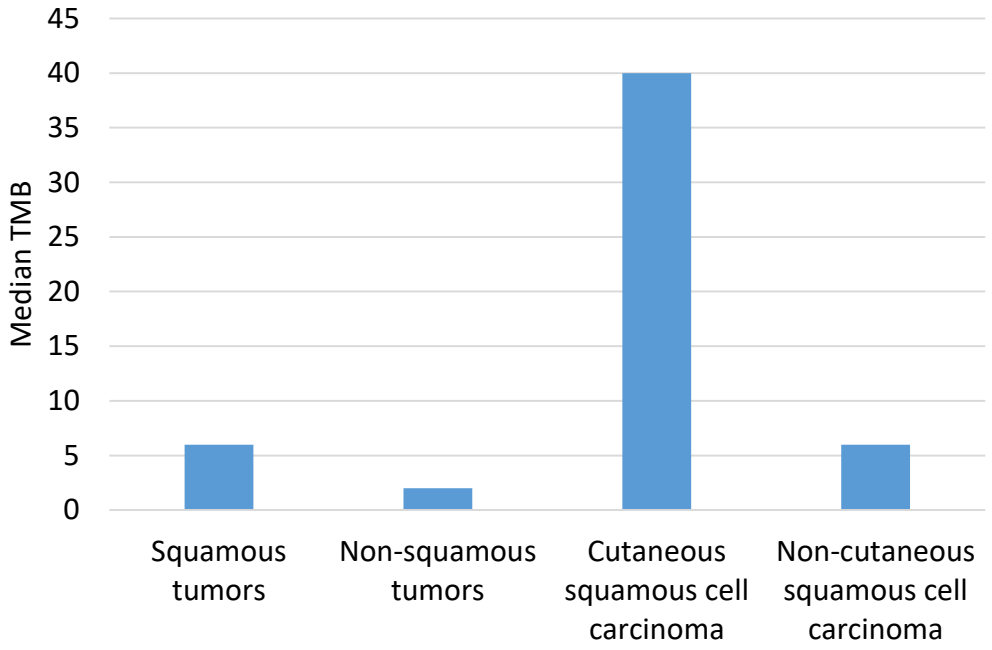
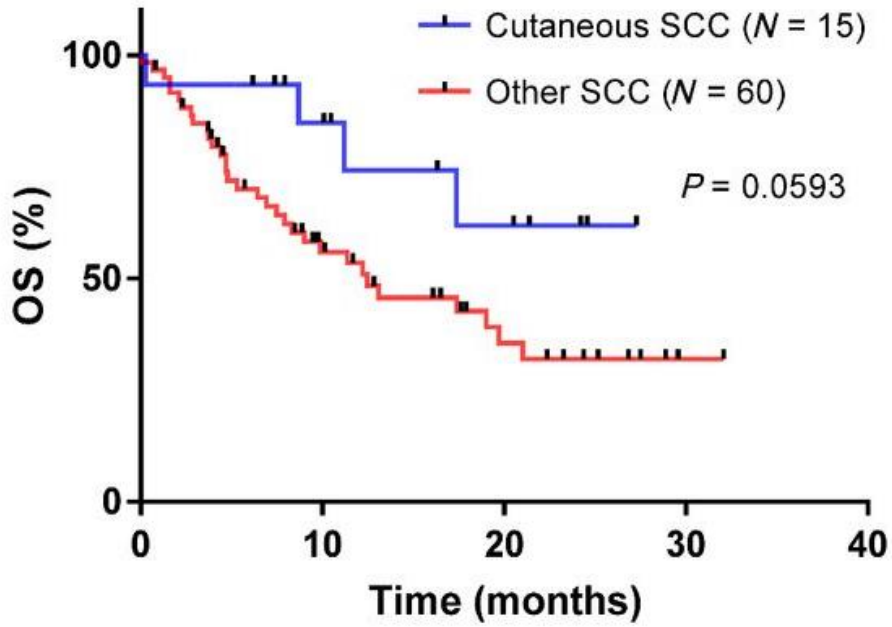
Cutaneous squamous cell carcinoma

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





Goodman, Cancer Immunol Res 2019.

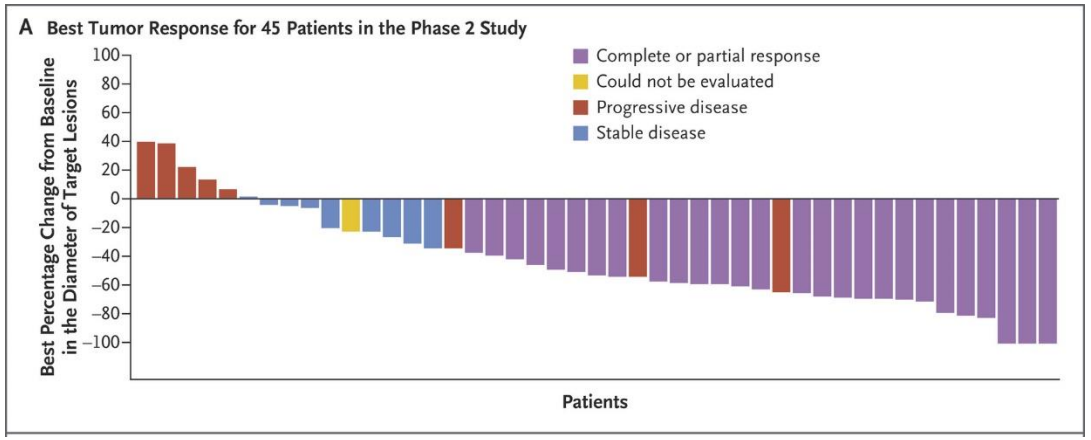
Approved checkpoint inhibitors for cutaneous squamous cell carcinoma

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

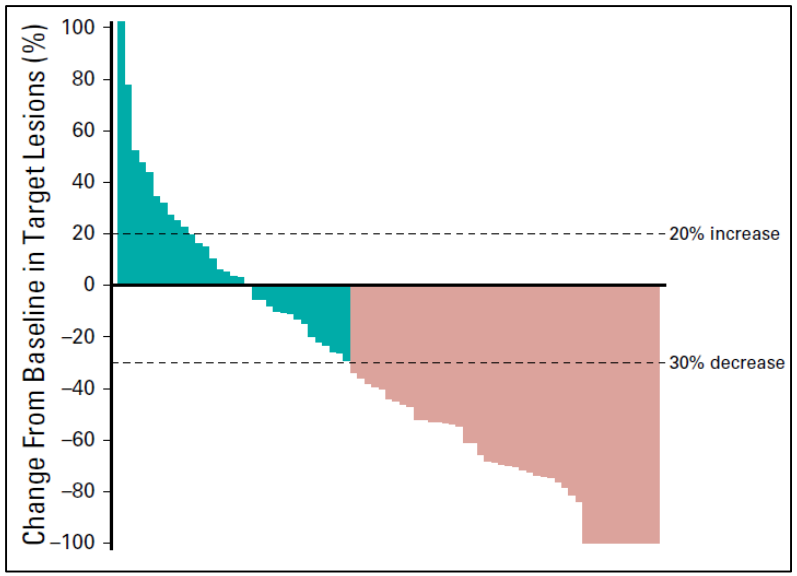
Trials for R/M cutaneous SCC

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



Grob, J Clin Oncol 2020.
Migden, N Engl J Med 2018.

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

Metastatic disease
ORR: 21%
PR: 6/28

US FDA Announcement

Outline of topics—final

- Melanoma
  - Front-line treatment
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- Merkel cell carcinoma
- Squamous cell carcinoma
- Future areas of research

In development: Combination 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

R (1:1) N = 120

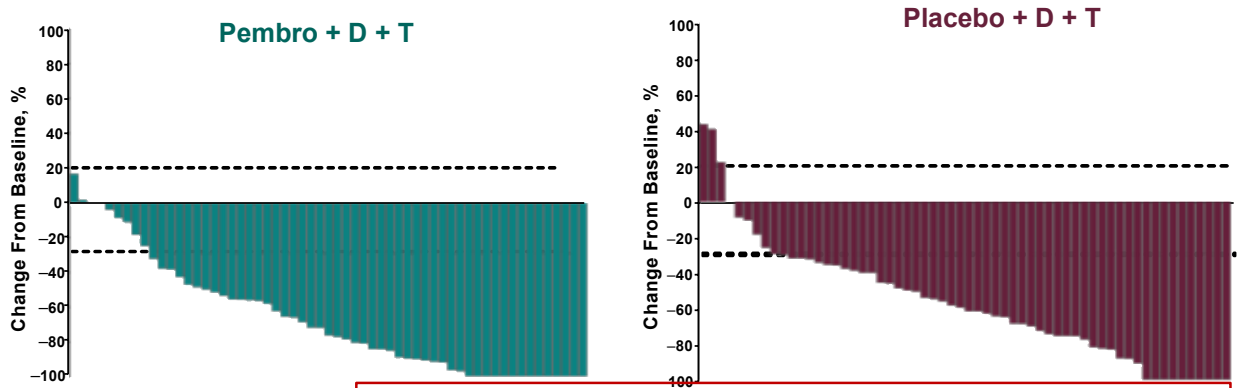
N = 60 → Pembrolizumab 2 mg/kg Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD

N = 60 → Placebo Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD

Stratification factors[a]
- ECOG PS (0 vs 1)
- LDH level (>1.1 × ULN vs ≤1.1 × ULN)

- 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.

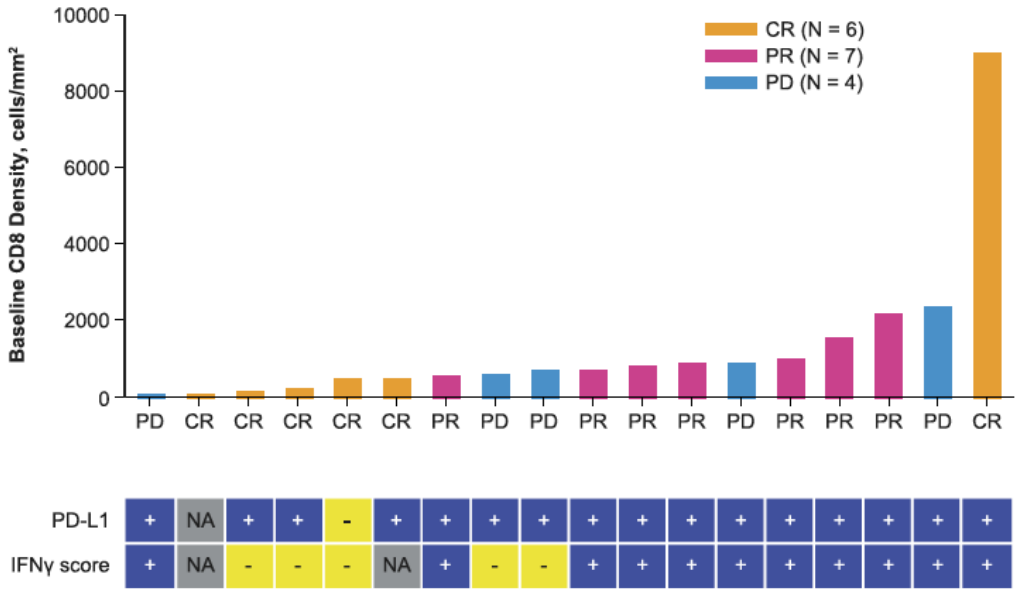


	Pembro + D + T	Placebo + D + T
ORR	63%	72%
CR	18%	13%
≥ 60% red	63%	51%

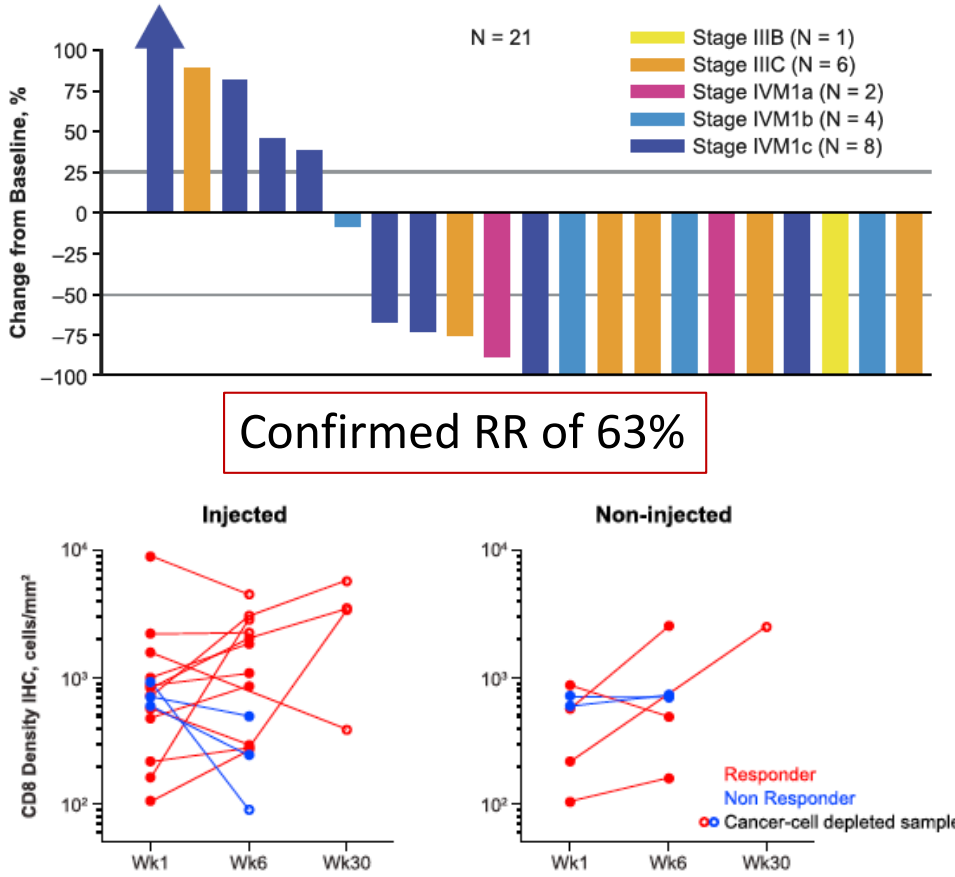
Multiple other triplet regimens are being tested.

Ascierto et al, *Nature Med* 2019.

In development: Combination IO with oncolytic virus



Phase I: Pembrolizumab + TVEC



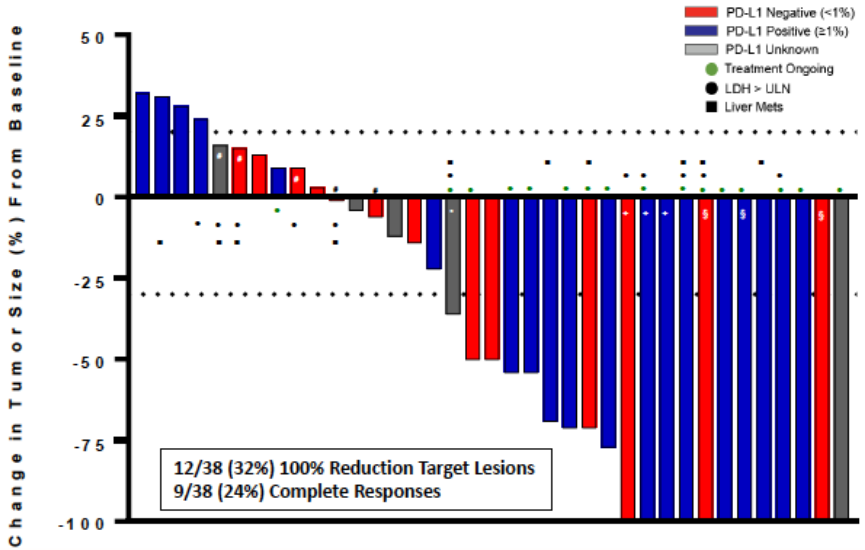
Confirmed RR of 63%

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



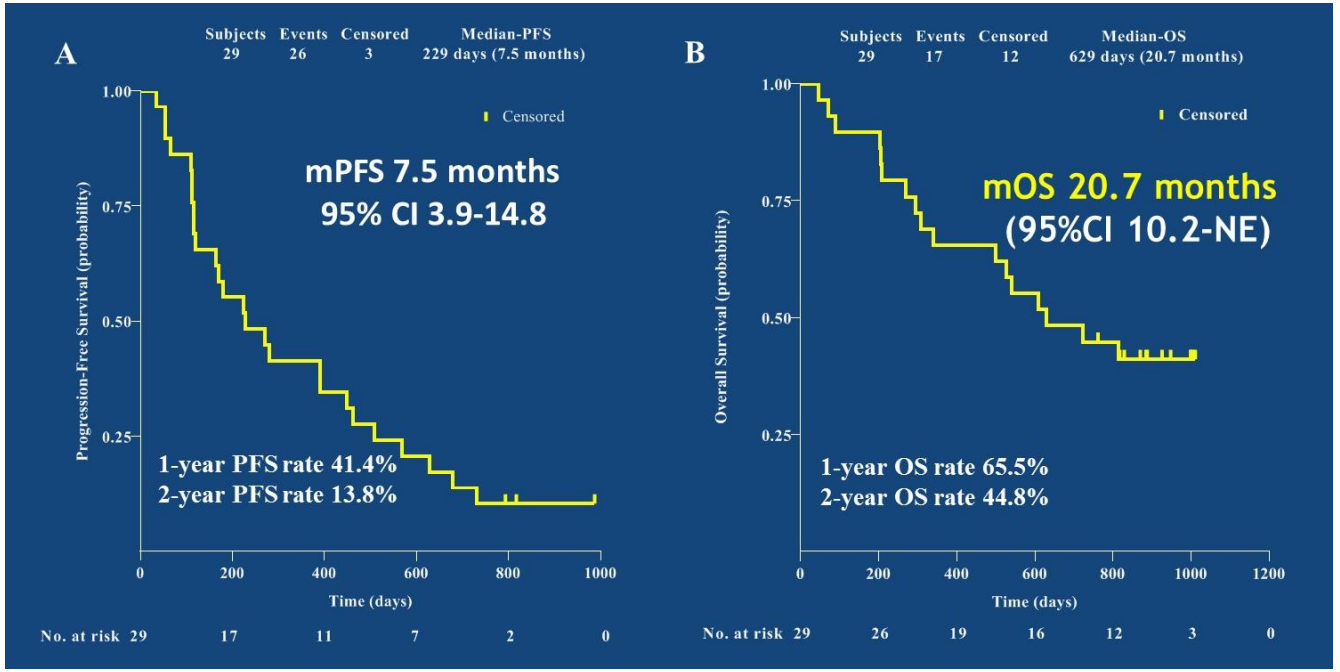
1L Melanoma (n=38 Efficacy Evaluable)	Overall Response Rate
Confirmed ORR (CR+PR)	20 (53%)
CR	9 (24%)
DCR (CR+PR+SD)	29 (76%)
PD-L1 negative (n=14)	6 (43%)
PD-L1 positive (n=19)	13 (68%)
PD-L1 unknown (n=5)	1 (20%)
LDH > ULN (n=11)	5 (45%)
Liver metastases (n=10)	5 (50%)

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

Diab et al, ASCO 2018.
Diab et al, SITC 2018.

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

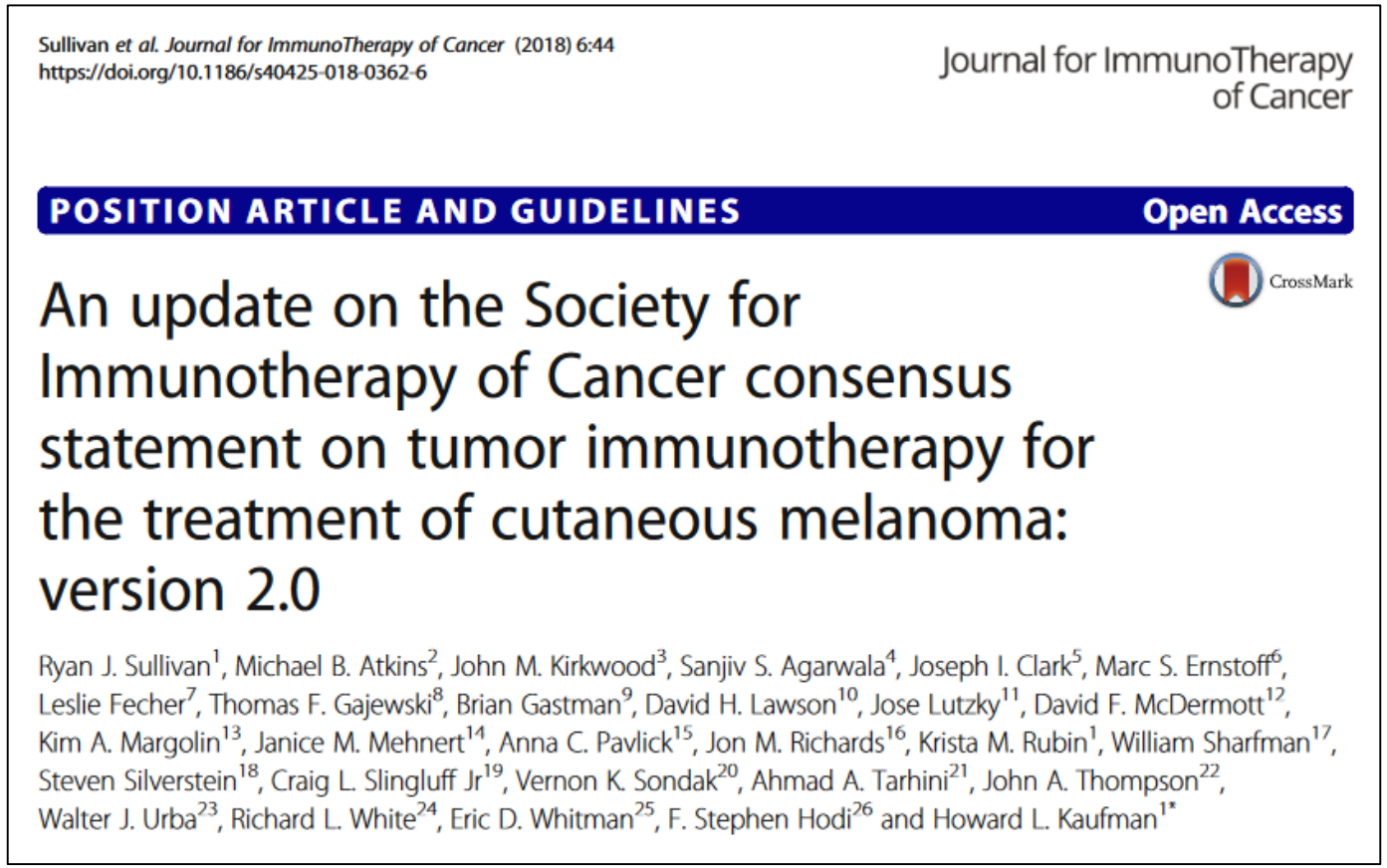


Guo, ASCO 2020.

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
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POSITION ARTICLE AND GUIDELINES Open Access

An update on the Society for Immunotherapy of Cancer consensus statement on tumor immunotherapy for the treatment of cutaneous melanoma: version 2.0

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Case Studies

Case Study 1—JD

1. JD is a 55 yo Caucasian man with melanoma of probable cutaneous origin metastatic to liver/lungs/pleura, large, very symptomatic L pleural effusion. He developed bilateral pulmonary emboli during diagnostic W/U treated with anticoagulation. In 2000, the patient noted a pigmented lesion on R lateral thigh which he removed by mechanical force in 2017 and then auto-thermoablated later with a hot poker. Serum LDH is 1.7 x upper limit of institutional normal, alk phos is 1.3x upper limit, and other tests are WNL

What should be done next?

A. Empiric use of Dabrafenib and Trametinib pending molecular sequencing Not approved/recommended
B. High-dose interleukin-2 Never with third-space fluid collections
C. Ipilimumab and nivolumab Appropriate but must first relieve Sx, improve PR
D. Frequent thoracenteses until the fluid is gone Not approved/recommended
E. Thoracentesis followed by placement of a PleurX catheter Correct answer—optimal overall approach

Case Study 1—JD

3. The results of DNA sequencing show the tumor has a BRAFv600^{E} mutation. The patient has experienced relief of dyspnea with the PleurX catheter and has no bleeding from his anticoagulation. He is treated with Dabrafenib and Trametinib for 8 weeks and experiences major resolution of dyspnea and significant reduction of the pleural effusion on chest Xray, allowing safe removal of the catheter. He experiences 2 bouts of fever and chills, which leave him tired and lead him to reduce the dose of Dabrafenib x 50% while maintaining full dose of Trametinib

What should be done next?

A. Switch therapy to encorafenib and binimetinib No indication to switch MAPKi with this level of toxicity
B. Switch therapy to ipilimumab and nivolumab No reason to switch from MAPKi (responding) to immunotherapy
C. Resume the dabrafenib and escalate quickly to full dose as tolerated, with Trametinib Correct answer
D. Resume dabrafenib at full dose with trametinib and add pembrolizumab This combination neither indicated nor approved
E. Discontinue all therapy and refer patient to hospice No rationale for this

Case Study 1—JD

4. The patient experiences a partial response lasting 8 months and is then found, on MRI of brain, to have 2 asymptomatic cerebral metastases less than 2 cm and without significant perilesional edema. Extracranial staging scans reveal small new liver metastases, and the pleural disease remains controlled, with a small residual effusion on L.

What should be the next step?

A. Stereotactic radiotherapy and continue targeted agents No, pt is progressing in both brain and extracranially
B. Pembrolizumab This agent alone is insufficient to control metastatic disease in brain
C. Ipilimumab and stereotactic radiotherapy CTLA4 blockade has low activity in both brain and extracranially
D. Ipilimumab and nivolumab at full doses Correct—ORR in both intra- and extracranial sites ~55% if Asx, steroid-free
E. Stereotactic radiotherapy followed by high-dose interleukin-2 Contraindicated by effusion, poor therapeutic Index, questionable activity post brain mets

Case Study 2—BR

1. BR is a 28 yo Latino man with R lower conjunctival fornix melanoma arising at site of longstanding pigmented macules, resected in 8/2019, pT3A with + margins and 5-10 mitoses/mm2. Re-resected with no residual melanoma; SNB not done. Staging PET-CT showed 3 mm SUV 3.6 R intraparotid node. No palpable mass on f/u in 3/2021, and just a 1-2 mm pearly nodule at site of resection that causes feeling of sand in eye. New PET-CT shows growth to 1 cm and SUV to 24 at same site, still not palpable and pt ASx.

Which of the following should be done next?

A. Resect the new conjunctival nodule Invasive, risk of false negative, and likely unnecessary
B. Radiate the new conjunctival nodule Not appropriate without supporting tissue Dx
C. Needle biopsy the node under CT guidance Correct answer
D. Blood assay for circulating tumor DNA Not validated as diagnostic of relapse
E. Talimogene laherparepvec (TVEC) injection of node under CT guidance First need tissue Dx, molecular analysis

Case Study 2—BR

2. The patient undergoes a needle biopsy of the node which shows melanoma. There is insufficient tissue for sequencing. The conjunctival lesion is evaluated by ophthalmic oncology, where it is felt to represent scar tissue.

What should be done next?

A. Send the archival tissue from original conjunctival primary for sequencing — Correct answer
B. Therapeutic lymph node dissection and send tissue for sequencing — This is also a reasonable approach but precludes neo-adjuvant systemic Rx
C. Empiric trial of Encorafenib and Binimetinib — Not approved/ recommended
D. Radiate the the cervical lymph node chain — Less favorable therapeutic index than surgery
E. Ipilimumab and nivolumab standard regimen — May not need such aggressive systemic Rx

Case Study 2—BR

3. The archival material is sequenced and has no actionable mutations. Pt is seen by surgical oncology and has a radiographic marker placed at the site of the node followed by Rx with neo-adjuvant ipilimumab 1 mg/kg x 2 and nivolumab 3 mg/kg x 2. PET-CT is repeated 10 weeks after start of immunotherapy and shows a 5 mm residual node on CT at the site of the marker, with SUV 1.8 on FDG.

What should be done next?

A. Radiation to the site of prior lymphadenopathy Not indicated in melanoma
B. Therapeutic lymph node dissection followed by 1 year of adjuvant nivolumab Neoadjuvant data suggest this is unnecessary
C. Excisional biopsy of the marked node Correct answer
D. Complete 2 years of immunotherapy with single-agent nivolumab This regimen for advanced melanoma and probably excessive
E. TVEC injections at the site of the residual adenopathy on CT scan

Not indicated

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