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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

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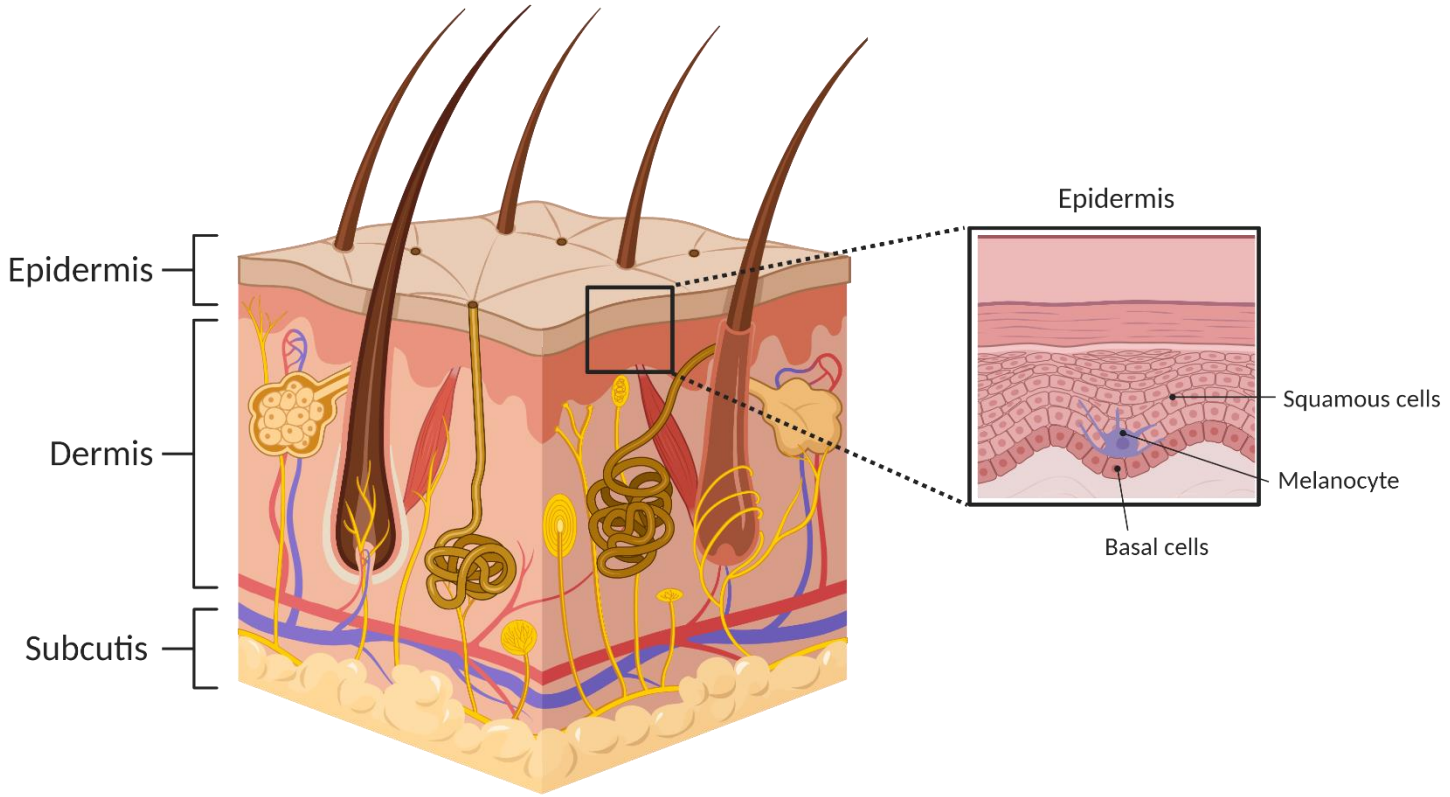
Disclosures

- Consulting Fees: Merck, Clinigen, Nektar
- Contracted Research: Galectin Therapeutics, Clinigen, BMS (Institution), AZ (Institution)
- I am neither employed nor have equity interests in any company or entity whose products/drugs will be discussed today.
- 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 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 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 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

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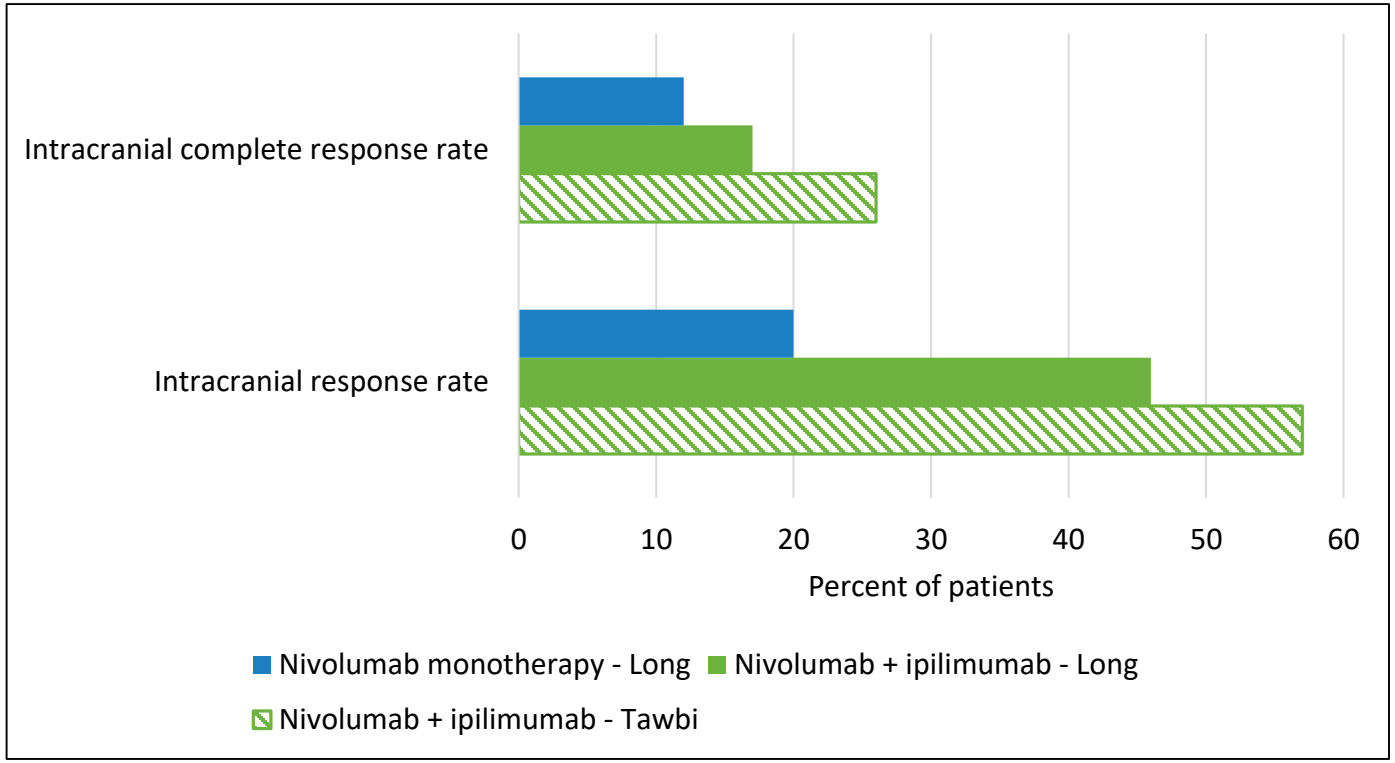

Long, Lancet Oncol 2018; Tawbi, N Engl J Med 2018.

Choosing appropriate regimens

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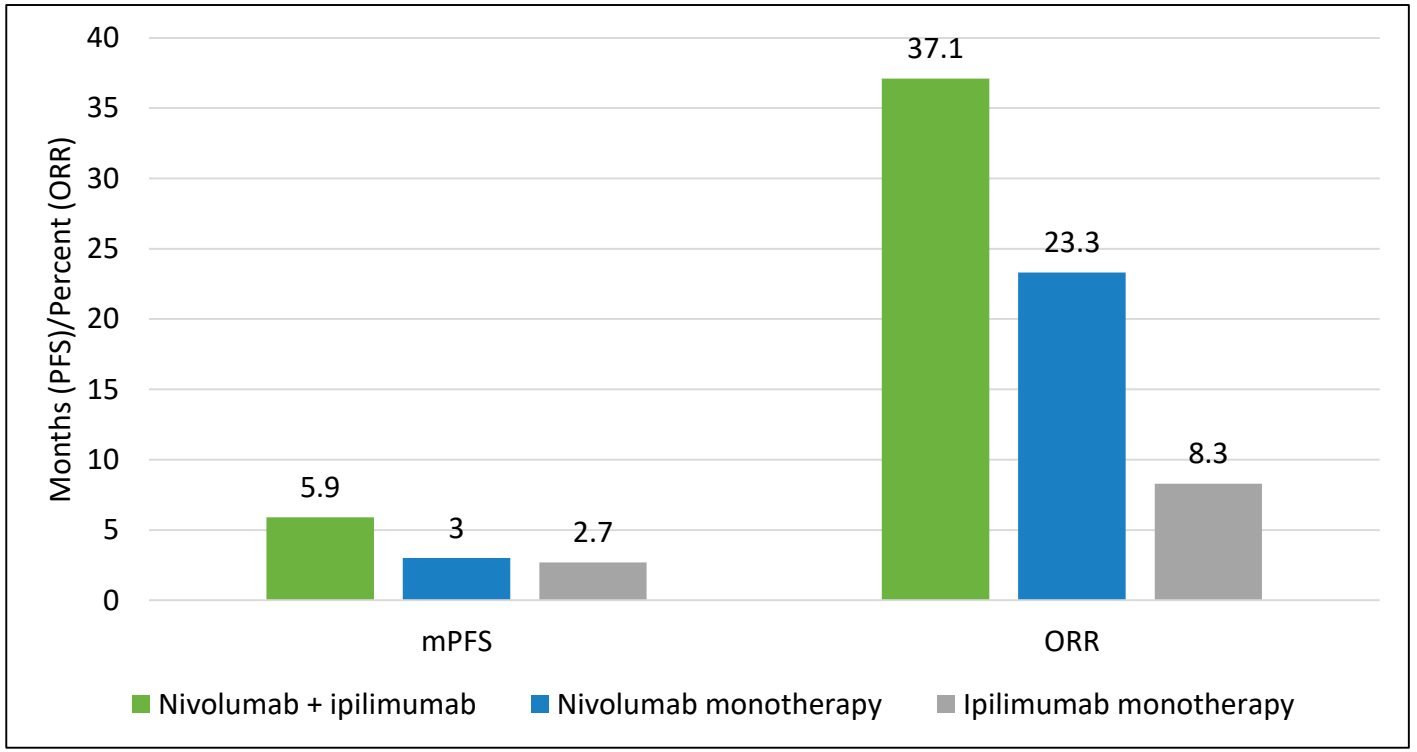

D'Angelo, J Clin Oncol 2016.

Choosing appropriate regimens

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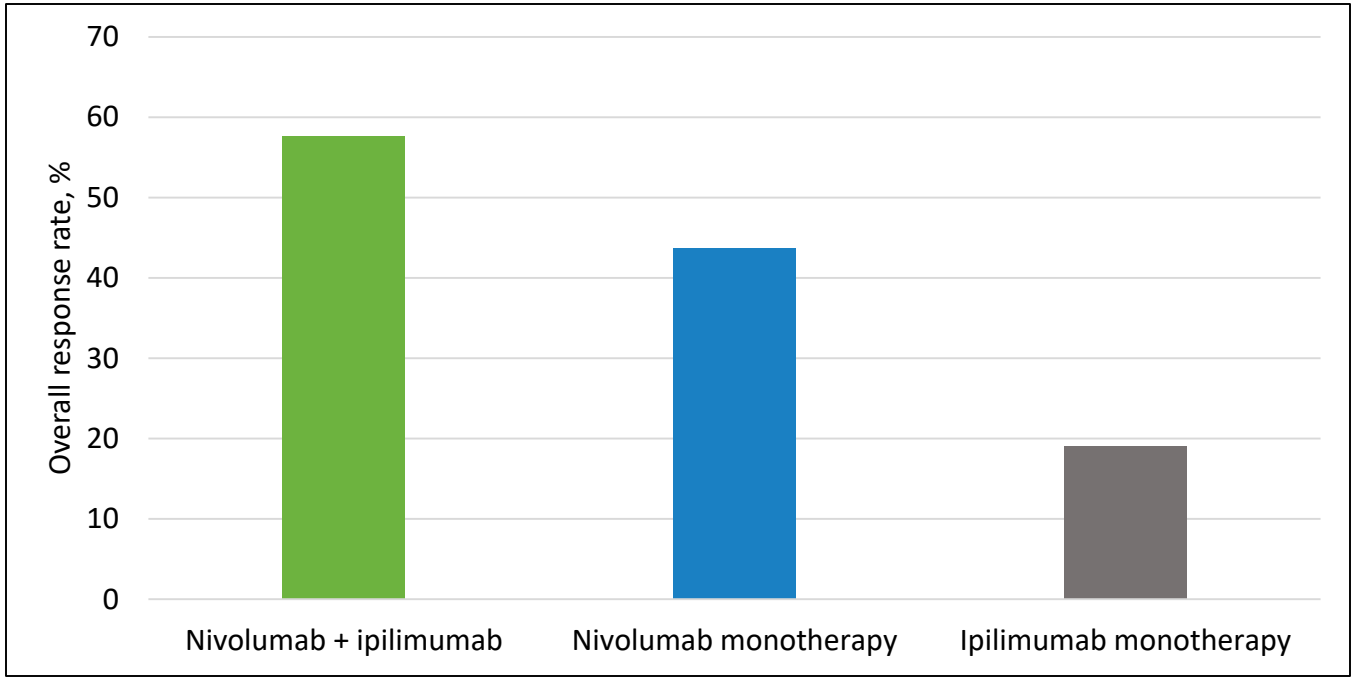
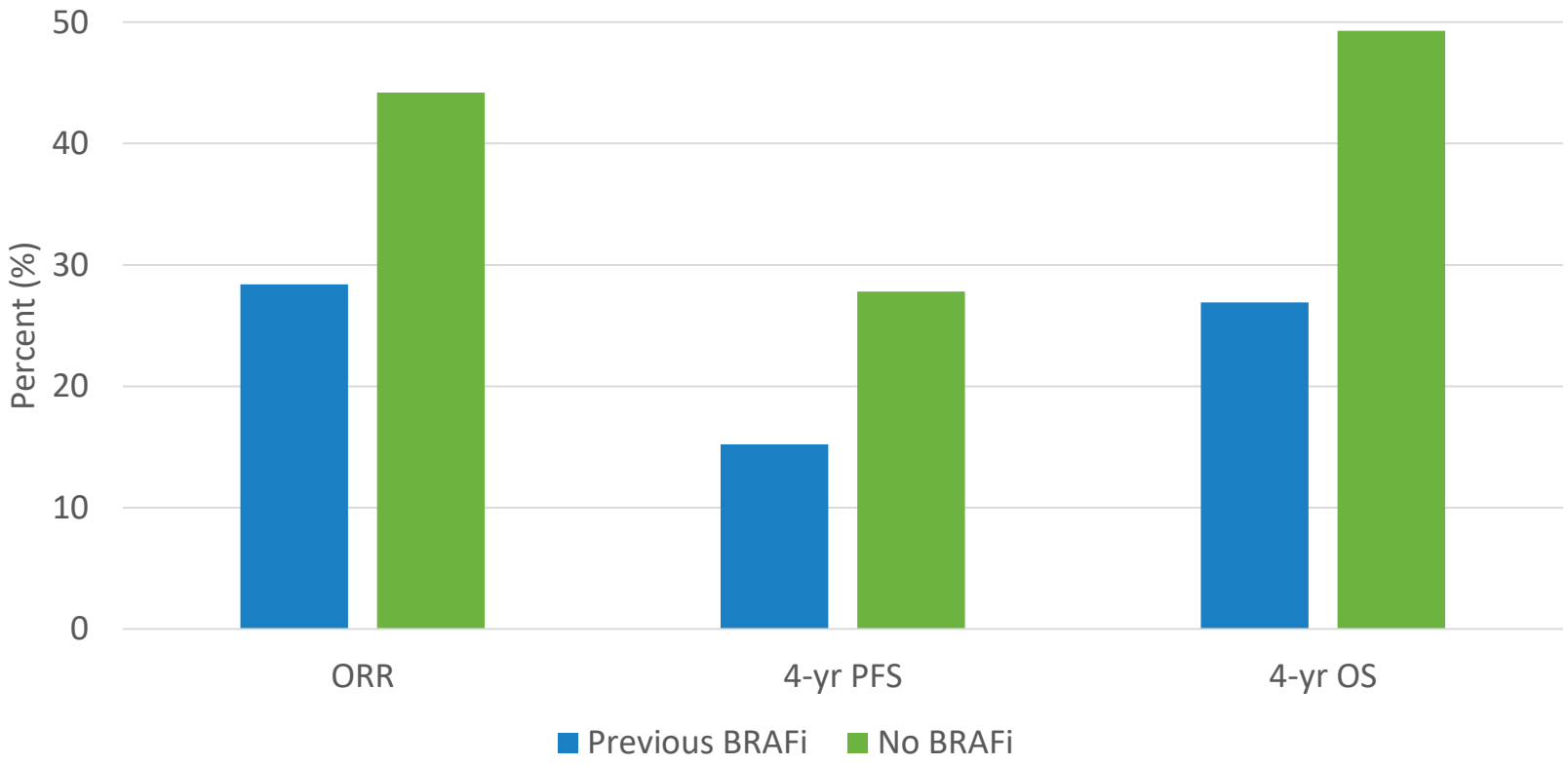


Larkin, N Engl J Med 2015.

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.



Puzanov, JAMA Oncol 2020.

Question: what to do after PD-1 progression

Stage III/IV melanoma patients (n=355)

Anti-PD-1 monotherapy

Adjuvant or metastatic setting

Recurrence or progression

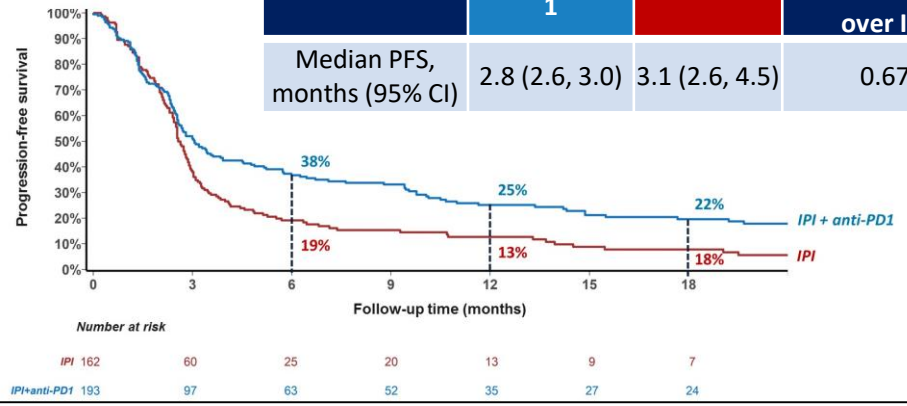
Ipilimumab (n=162)

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

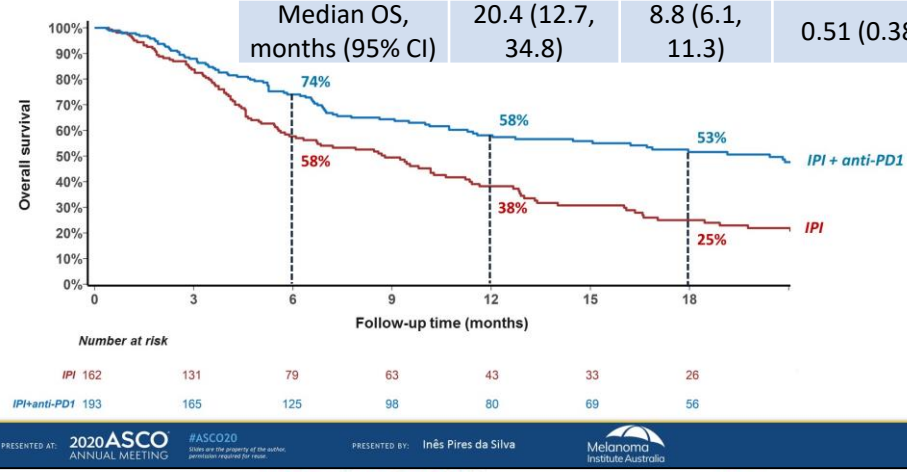
Retrospective study

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

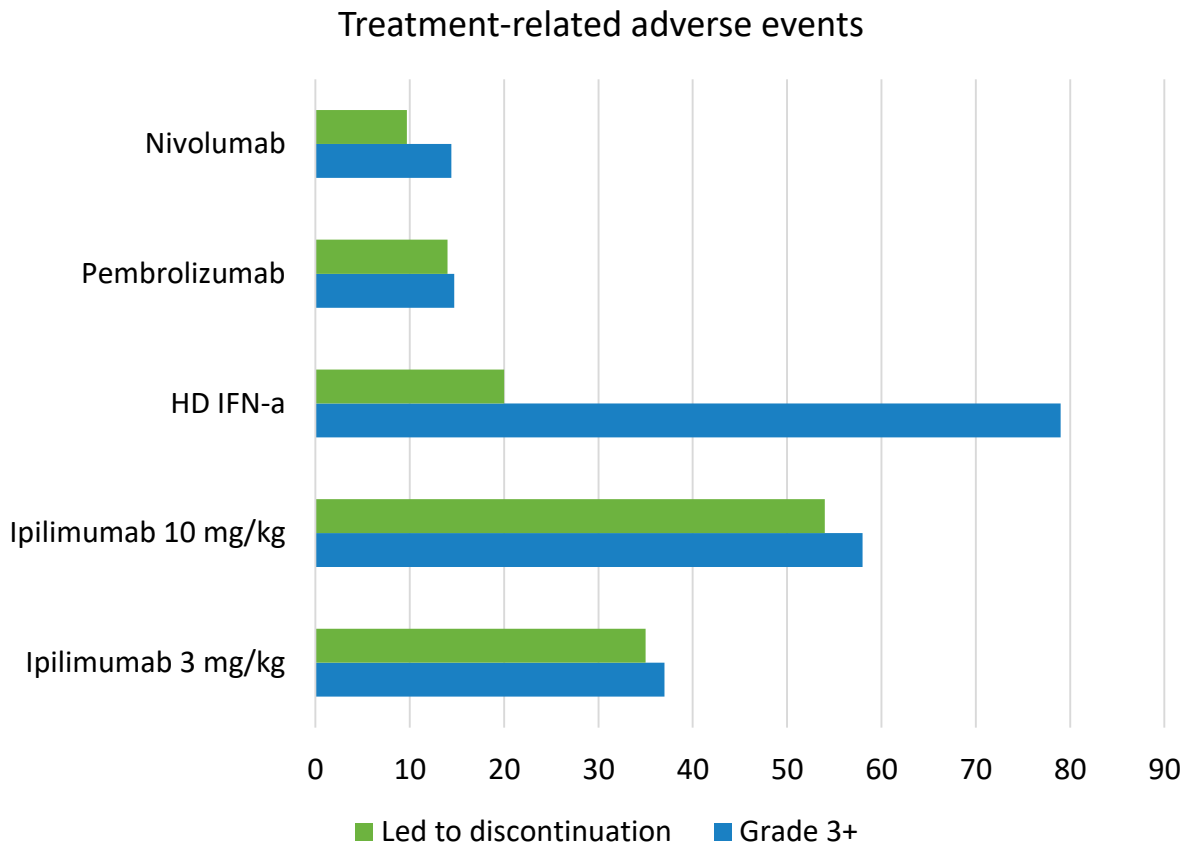
[+]Not an immunotherapy; for reference
**not commonly used in this setting; historical reference*

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 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)
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.

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- Merkel cell carcinoma
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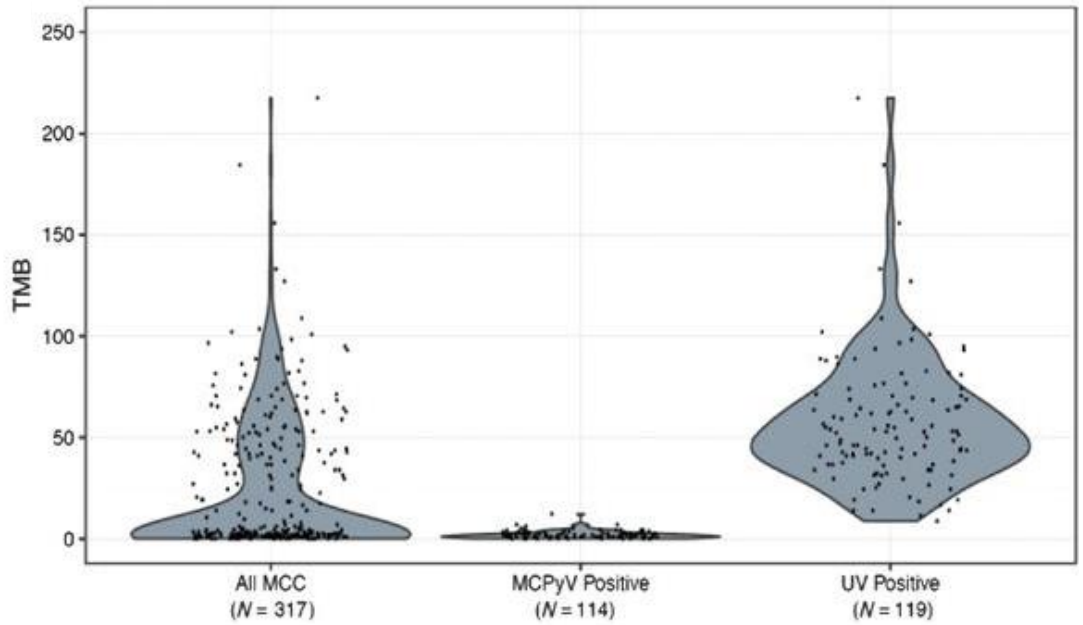
Merkel cell carcinoma

- 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



Knepper, Clin Cancer Res 2019.

Approved checkpoint inhibitors in Merkel cell carcinoma

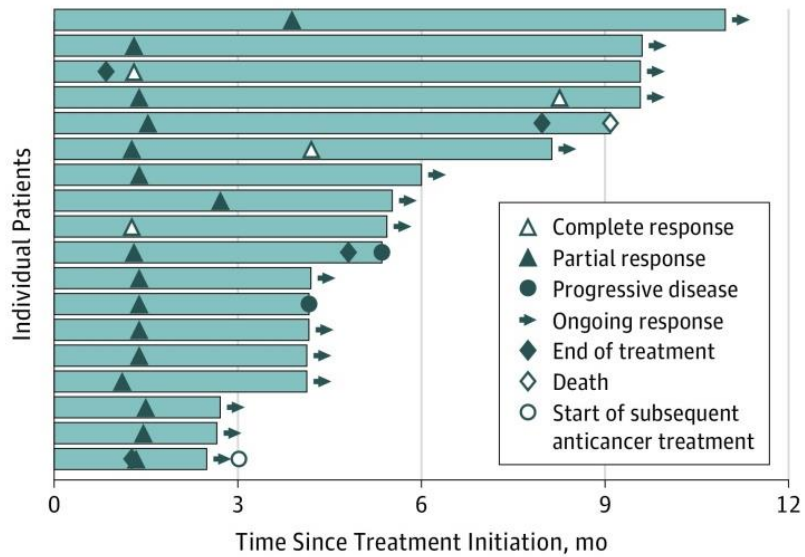
Drug	Indication	Dose
Avelumab*	Patients >12 yr with metastatic **Merkel cell carcinoma**	800 mg Q2W + premedication (first 4 cycles)
Pembrolizumab	Adult/pediatric with recurrent advanced/metastatic **Merkel cell carcinoma**	Adults: 200 mg Q3W or 400 mg Q6W Pediatric: 2 mg/kg (up to 200 mg) Q3W

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

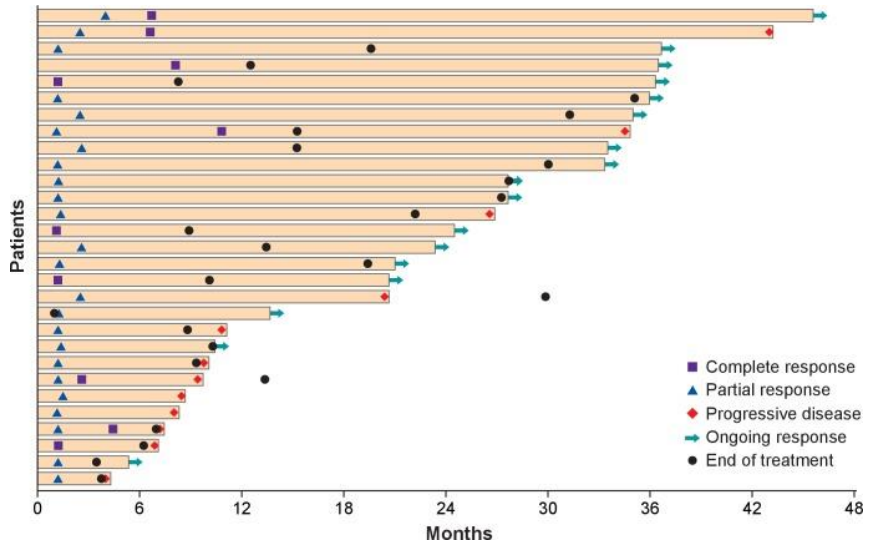
Avelumab in Merkel cell carcinoma

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

First line



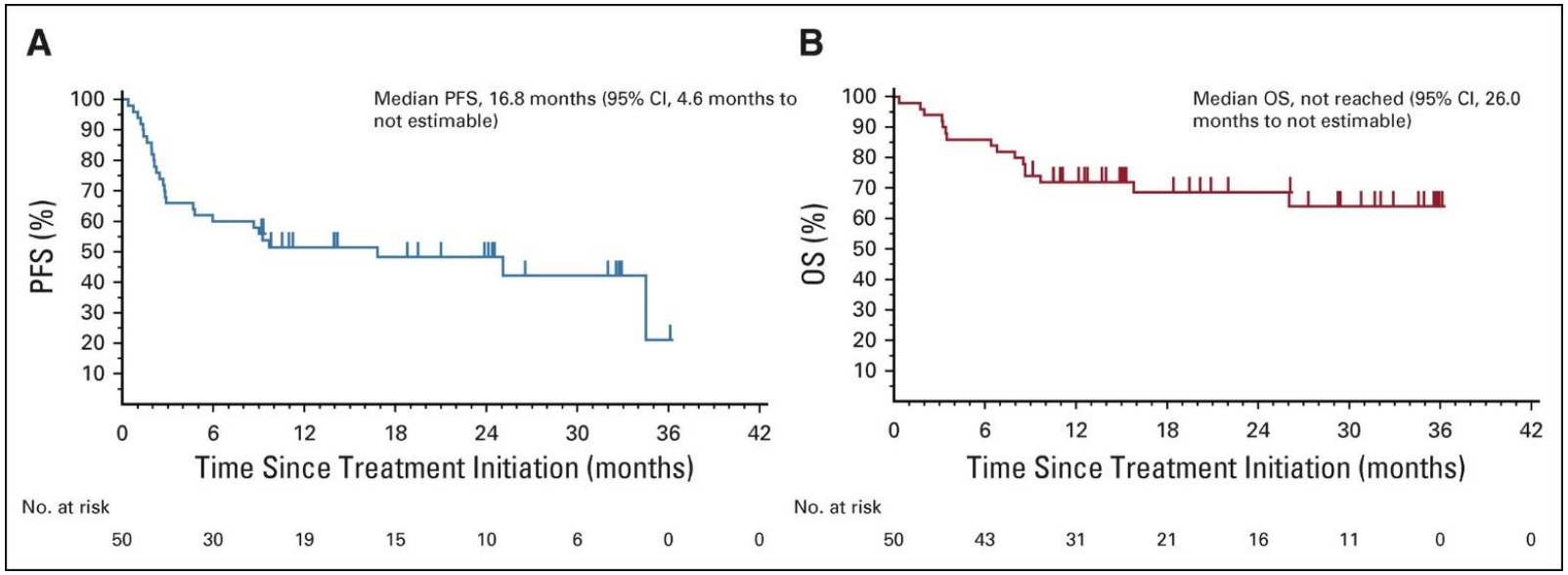
Second+ line



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

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).

Nghiem, J Clin Oncol 2019.

Outline

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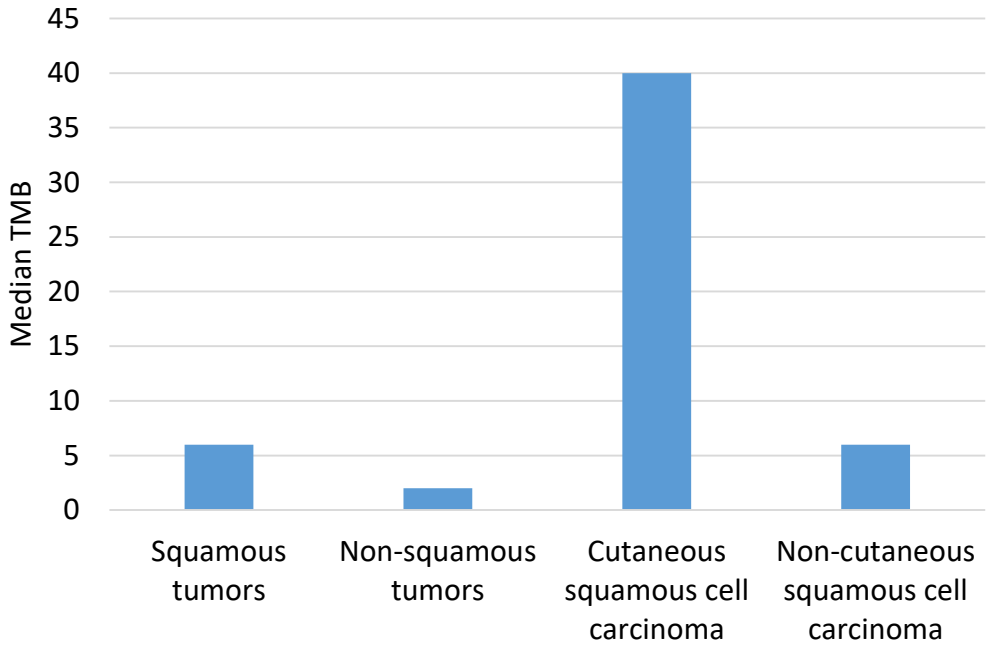
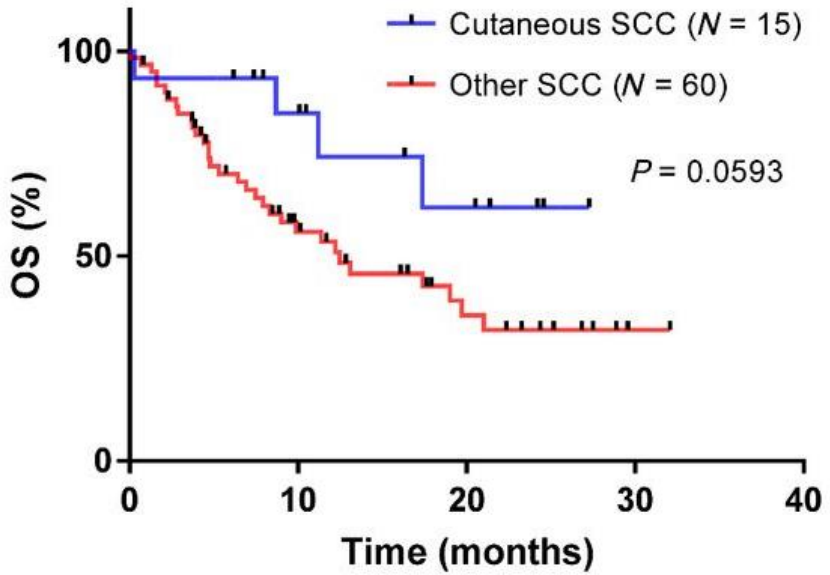
Cutaneous squamous cell carcinoma

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





Goodman, Cancer Immunol Res 2019.

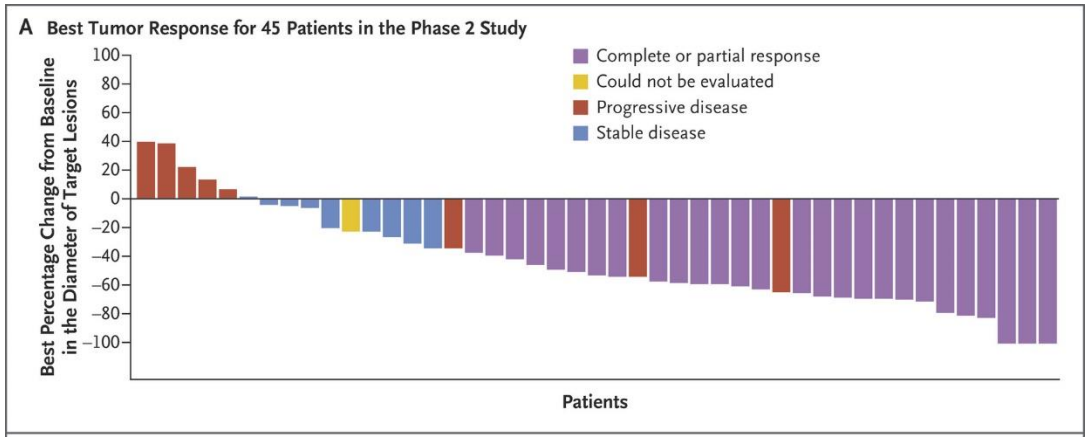
Approved checkpoint inhibitors for cutaneous squamous cell carcinoma

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

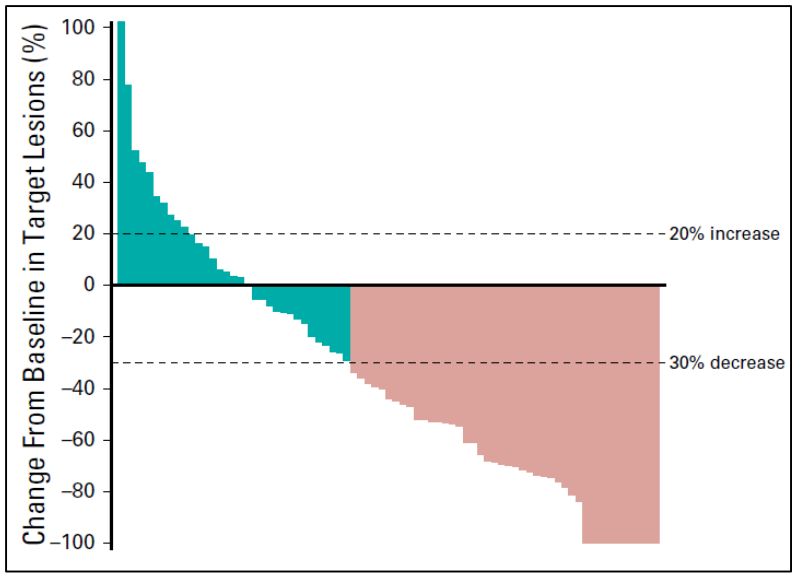
Trials for R/M cutaneous SCC

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

Metastatic disease
ORR: 21%
PR: 6/28

US FDA Announcement

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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

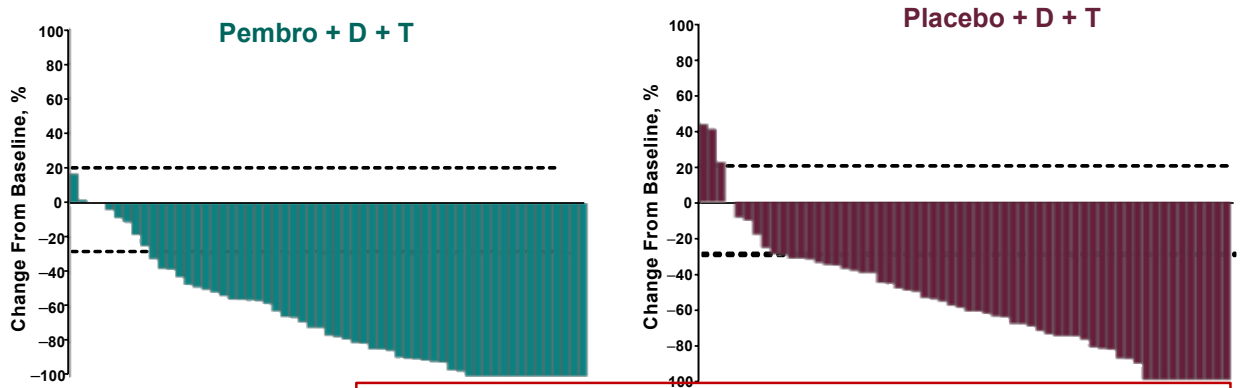
N = 60 → Pembrolizumab 2 mg/kg Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD

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.



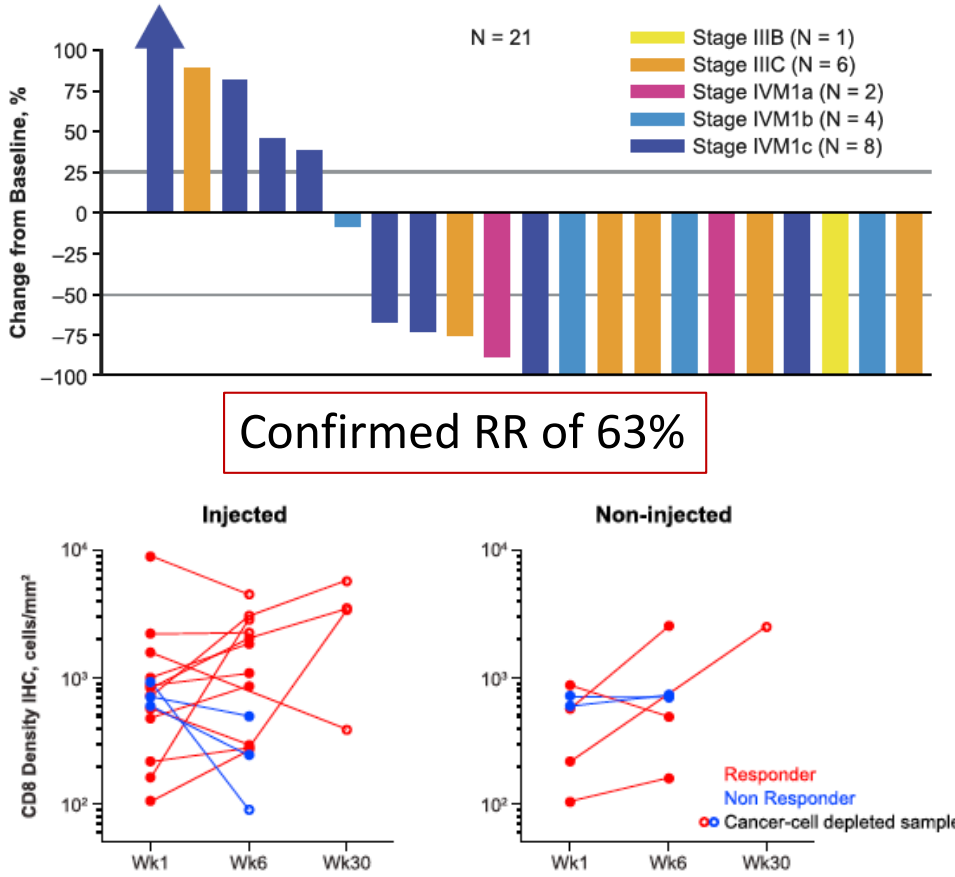
	Pembro + D + T	Placebo + D + T
ORR	63%	72%
CR	18%	13%
≥ 60% red	63%	51%

Multiple other triplet regimens are being tested.

Ascierto et al, *Nature Med* 2019.

In development: Combination IO with oncolytic virus

Phase I: Pembrolizumab + TVEC



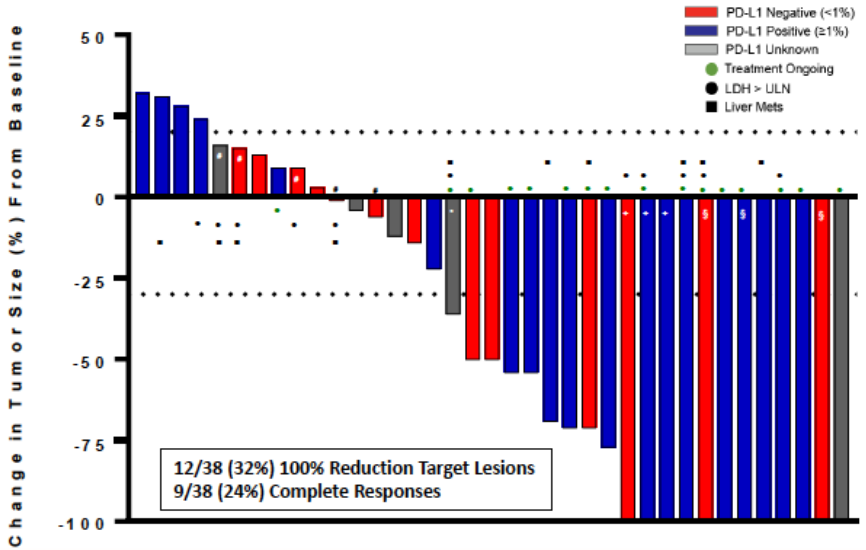
Confirmed RR of 63%

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.

Other Selected Melanoma Research Areas:

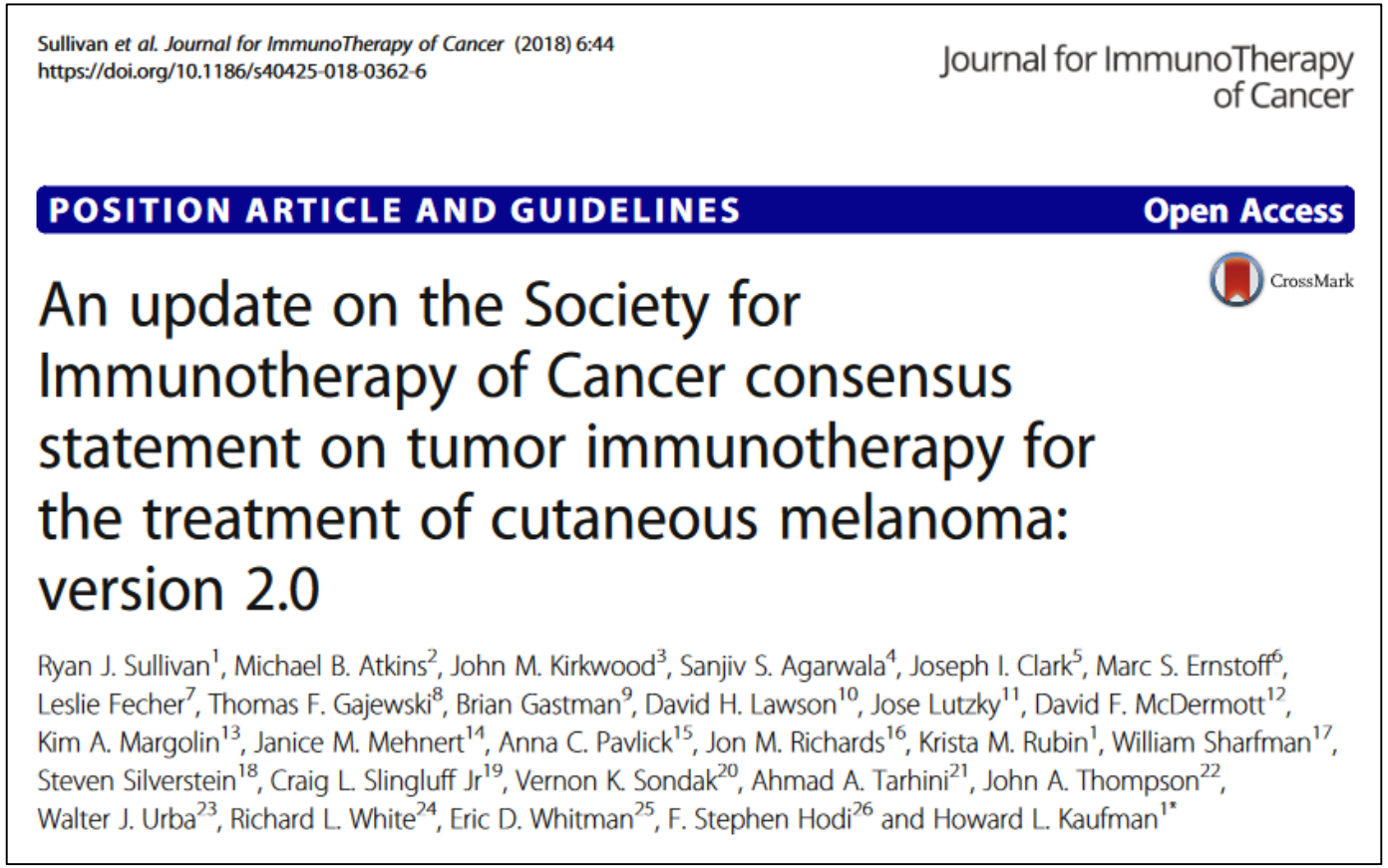
- Tebentafusp (bispecific antibody targeting gp100 and CD3) in uveal melanomas
- Tumor infiltrating lymphocytes (TIL) after progression on T-cell checkpoint therapies
- Agents that modulate the tumor microenvironment + checkpoints
  - GR-MD-02 (belapectin) + pembrolizumab
  - STING agonists
  - Beta-catenin inhibition
  - (many others)

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
https://doi.org/10.1186/s40425-018-0362-6

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

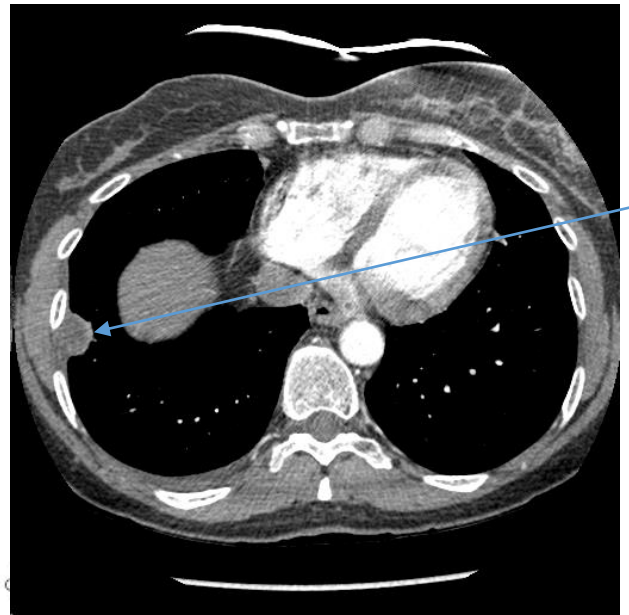
An update on the Society for Immunotherapy of Cancer consensus statement on tumor immunotherapy for the treatment of cutaneous melanoma: version 2.0

Ryan J. Sullivan[1], Michael B. Atkins[2], John M. Kirkwood[3], Sanjiv S. Agarwala[4], Joseph I. Clark[5], Marc S. Ernstoff[6], Leslie Fecher[7], Thomas F. Gajewski[8], Brian Gastman[9], David H. Lawson[10], Jose Lutzky[11], David F. McDermott[12], Kim A. Margolin[13], Janice M. Mehnert[14], Anna C. Pavlick[15], Jon M. Richards[16], Krista M. Rubin[1], William Sharfman[17], Steven Silverstein[18], Craig L. Slingluff Jr[19], Vernon K. Sondak[20], Ahmad A. Tarhini[21], John A. Thompson[22], Walter J. Urba[23], Richard L. White[24], Eric D. Whitman[25], F. Stephen Hodi[26] and Howard L. Kaufman[1*]

Case Studies

Case 1

- 50 year old woman who presented with a changing pigmented lesion of the left temple in 2013. Biopsy showed a 0.91 mm melanoma without ulceration and < 1 mitosis/mm^2. SLN was negative. The initial pathological stage was pT1apN0M0 (Stage 1A).
- She developed RUQ pain in May 2017. She reported to the ER and CT showed:



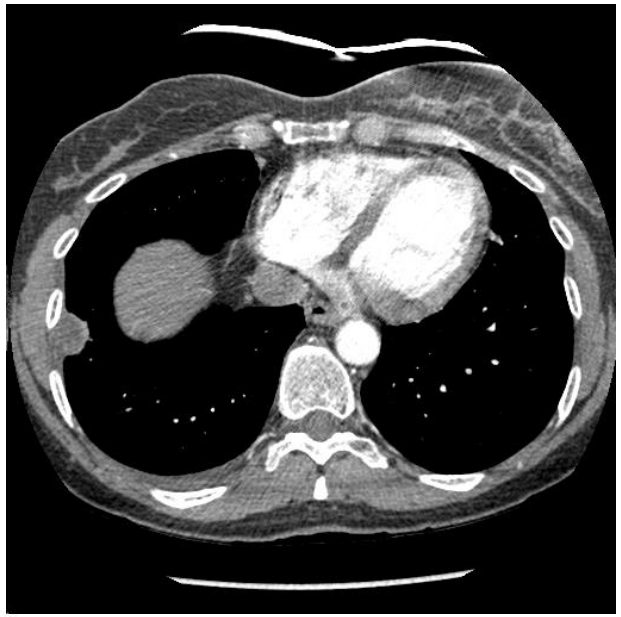
There were multiple pulmonary, lymph node and soft tissue nodules. Biopsy confirmed melanoma and a BRAF V600E mutation was present. There was no PD-L1 expression detected.

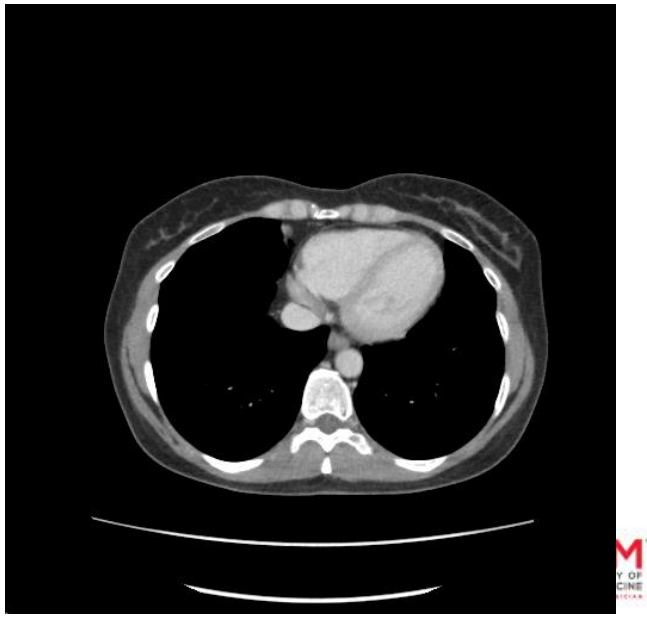
What is the best treatment option?

A. Ipilimumab + nivolumab
B. BRAF-targeted therapy (e.g.: vemurafenib or dabrafenib)
C. TVEC
D. BRAF + MEK targeted therapy (e.g.: dabrafenib + trametinib)
E. Clinical trial

Case 1 continued:

- The patient volunteered for the E6134 study (DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing), A Phase III Study) and was randomized to ipilimumab + nivolumab.
- Restaging imaging showed:



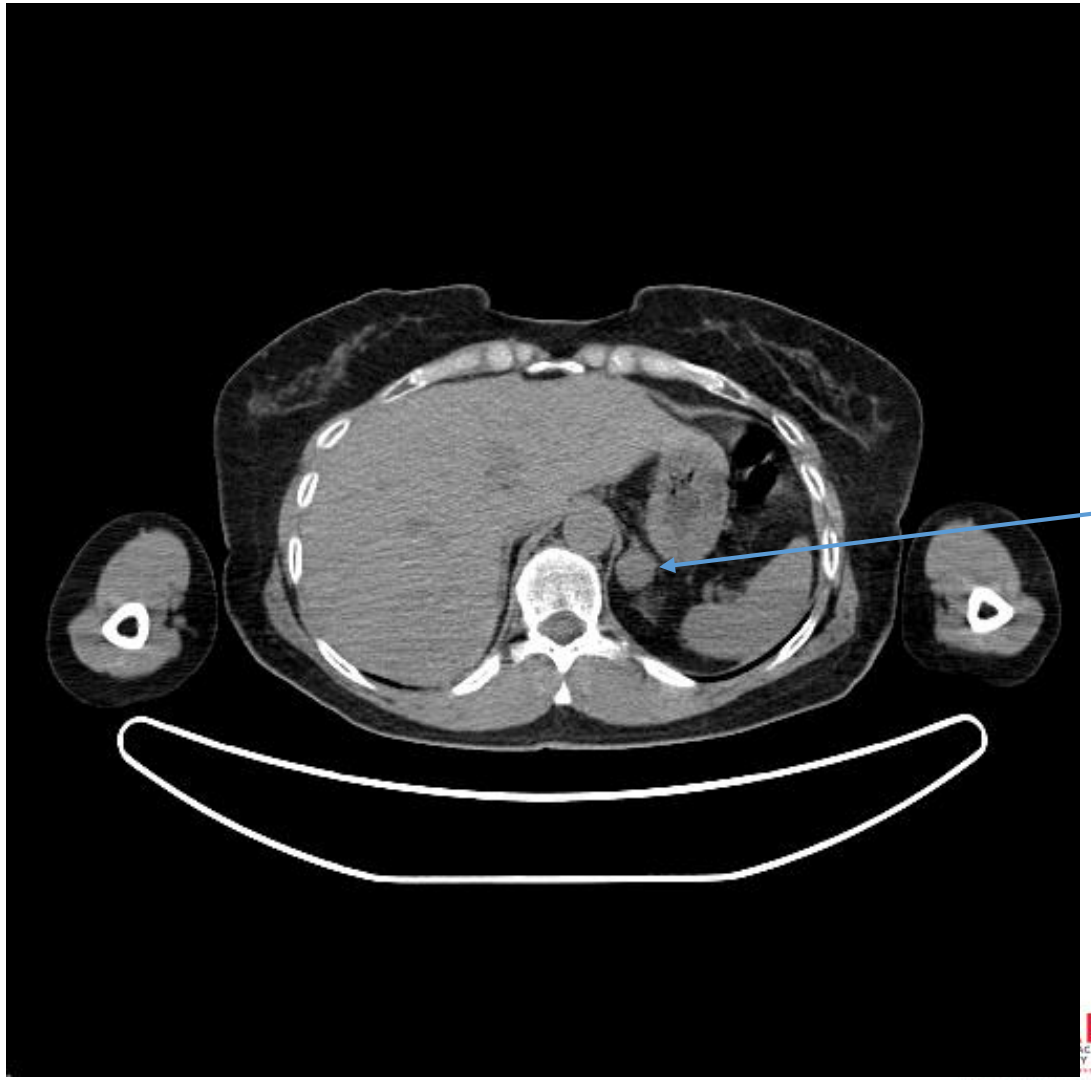


Complete response of all target lesions, lasting ~ 36 months after diagnosis. . .

Case 1 continued:

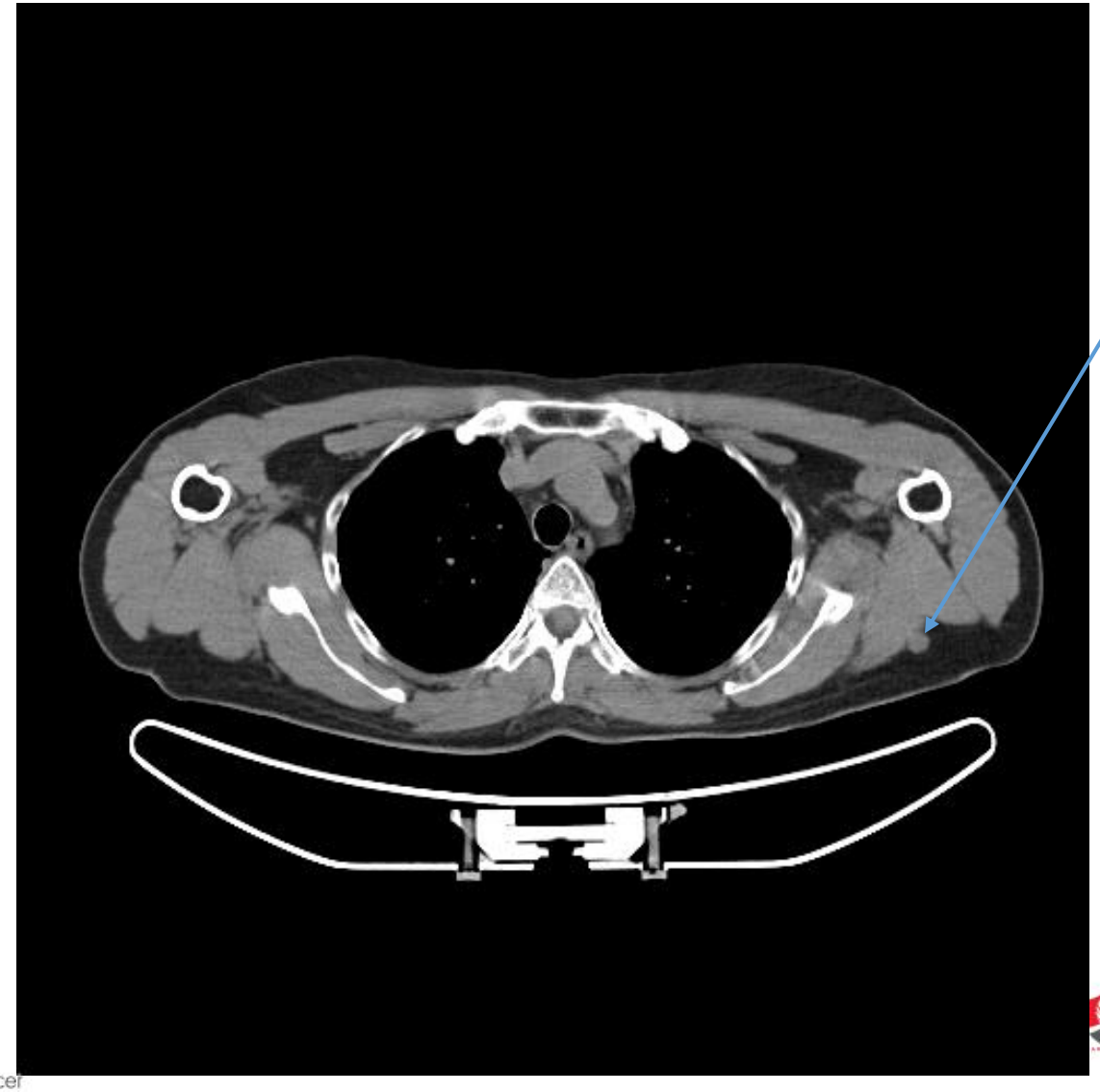
- Ipilimumab + Nivolumab was administered x 3 cycles only
- Immune-mediated adverse events included:
  - Grade 3 diarrhea
  - Grade 3 transaminitis (ALT max ~300)
  - Grade 3 hypothyroidism (TSH ~80)
- High dose oral steroids with a slow taper and levothyroxine (ongoing) have addressed the irAEs.

Case I continued:



36 months after ipilimumab and nivolumab, a new solitary left adrenal metastasis appears. Treatment options include SBRT or initiation of BRAF-targeted therapy.

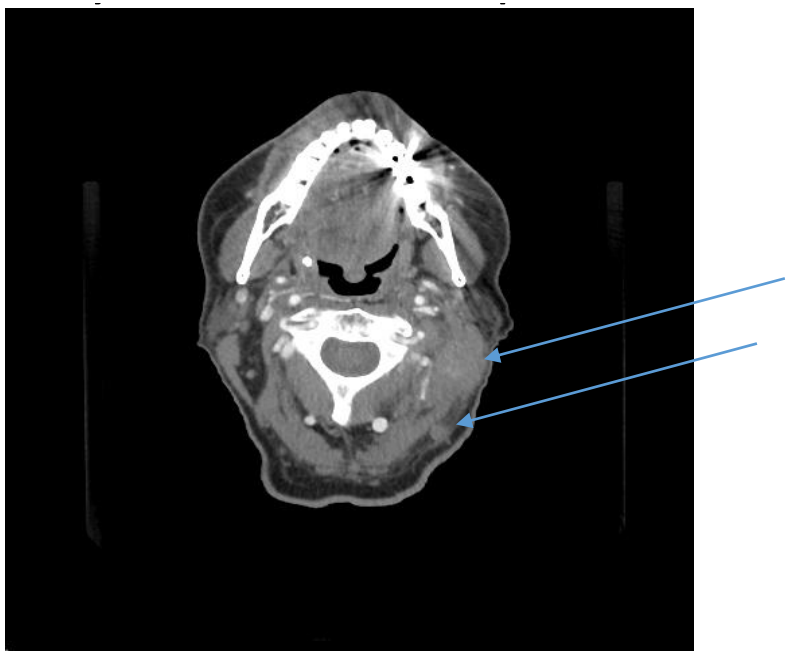
Case I continued:



2 months after SBRT, the adrenal nodule is regressing, but a new SQ nodule appears.

Case 2

- 72 year old man who presented with a changing lesion on the scalp vertex. Biopsy reveals a BRAF wild type melanoma with a Breslow depth of 1.7mm, ulceration and 14 mitoses per mm^2. Initial therapy is WLE and SLN procedure; 1 out of 6 LNs contain melanoma. Initial stage is pT2bpN1aM0 stage IIIB.
- After surgery:
  - Adjuvant nivolumab x 1 year. Developed grade IV lichenoid mucositis requiring steroids and mycophenolate mofetil.
  - Melanoma-free for ~10 months and then develops new scalp and neck nodules:

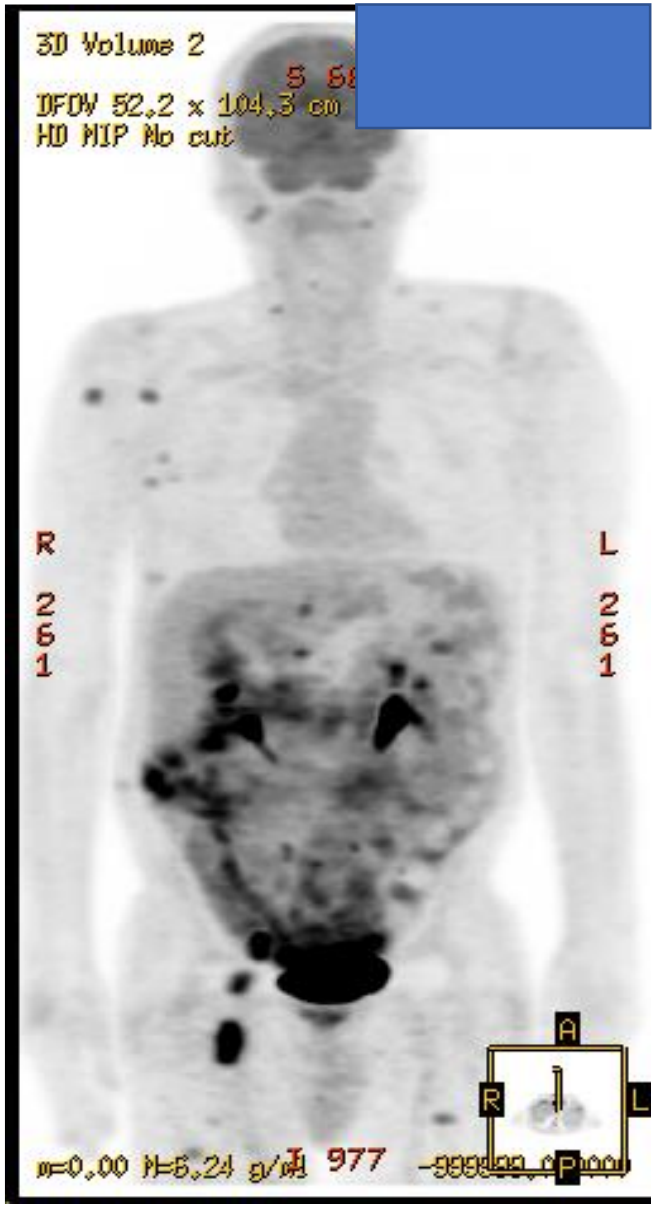


What treatment option would you recommend?

A. Another trial of T-cell checkpoint therapy (e.g.: Ipi/Nivo)
B. Talimogene laherparepvec (TVEC)
C. Clinical trial
D. High dose IL-2

Case 2 continued:

- He opts for TVEC, which was well tolerated.
- Best response to TVEC was PD in < 3 months with ~30 new SQ, intramuscular and LN sites.



Case 2 continued:

- Treatment options considered were:
  - Resumption of T-cell checkpoint antibody therapy
  - Clinical trial
  - High-dose IL-2
- The patient opts for high-dose IL-2
- He experiences anticipated toxicities including hypotension, acute kidney injury, metabolic acidosis, thrombocytopenia and hypoglycemia (hypothesized due to T cell metabolism from IL-2)
- Residual lichen planus from prior checkpoint immunotherapy gradually resolved during IL-2.

Case 2: Complete Response after IL-2
(occurring after checkpoint and TVEC progression)