Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Skin Cancers

Ding Wang, MD, PhD., May 1st, 2021

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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

Society for Immunotherapy of Cancer

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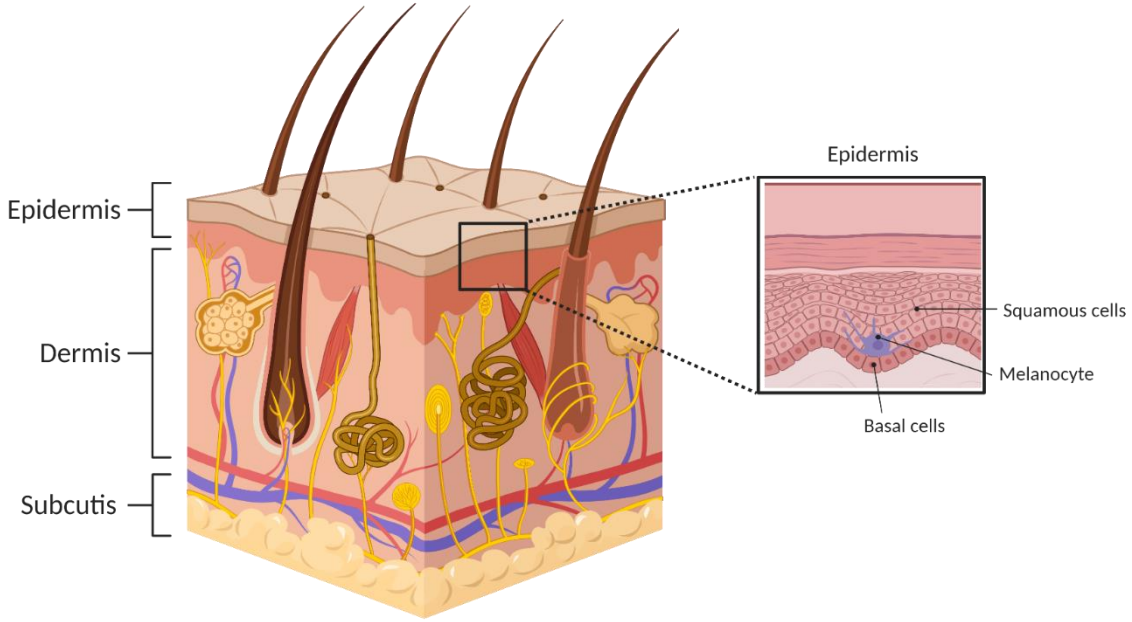
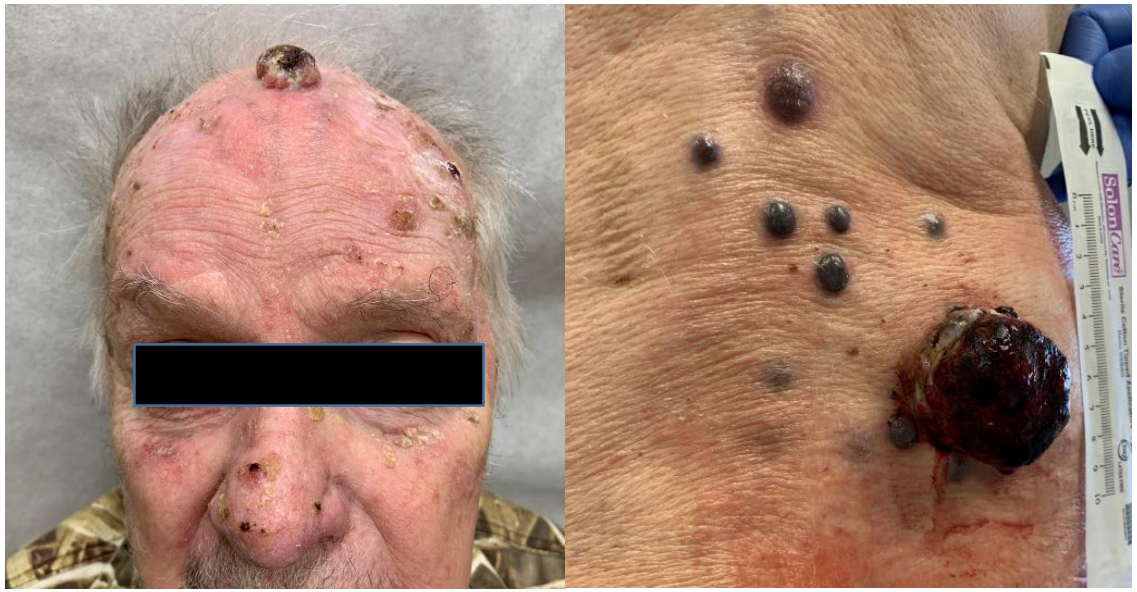
Disclosures

- Clinical Trial Research Sponsors with funding support to clinical trial operation
  - SWOG, NRG Oncology
  - Abbvie, ABM Therapeutics, Amgen, Astellas, Astrazeneca/MedImmune, Bayer, Bolt Biotherapeutics, Eisai, Elicio, Exelisis, EMD Serono, Hookipa, InCyte, Innovent Biologics, Istari, Jacobio, Jounce Therapeutics, LaNova-TigerMed, Merck, Mersana, Moderna, Nektar, Pfizer, Regeneron, Shasqi, Synermore, Takeda, Tarveda
- Advisory/Consultant Role: Castle BioSciences, Qurgen
- 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





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Outline

- Melanoma
  - Historical management
  - Front-line treatment for metastatic melanoma (MM)
  - Second-line or later therapeutic options from MM
  - Adjuvant and neoadjuvant settings for surgical resectable melanoma
- Merkel cell carcinoma
- Squamous cell and basal cell carcinoma
- Future areas of research

Historical Survival Data from Metastatic Melanoma

Meta-analysis of 42 phase II trials in a total of 2100 patients with metastatic melanoma:

Survival Benchmark	Result (95% CI)
Progression-Free Survival	
Median (95% CI)	1.7 (1.6-1.8) months
6-month rate (95% CI)	14.5% (13%-16%)
Overall Survival	
Median (95% CI)	6.2 (5.9-6.5) months
1-year rate (95% CI)	25.5% (23.6%-27.4%)

Significant prognostic factors included PS for both PFS and OS and visceral disease status for OS.

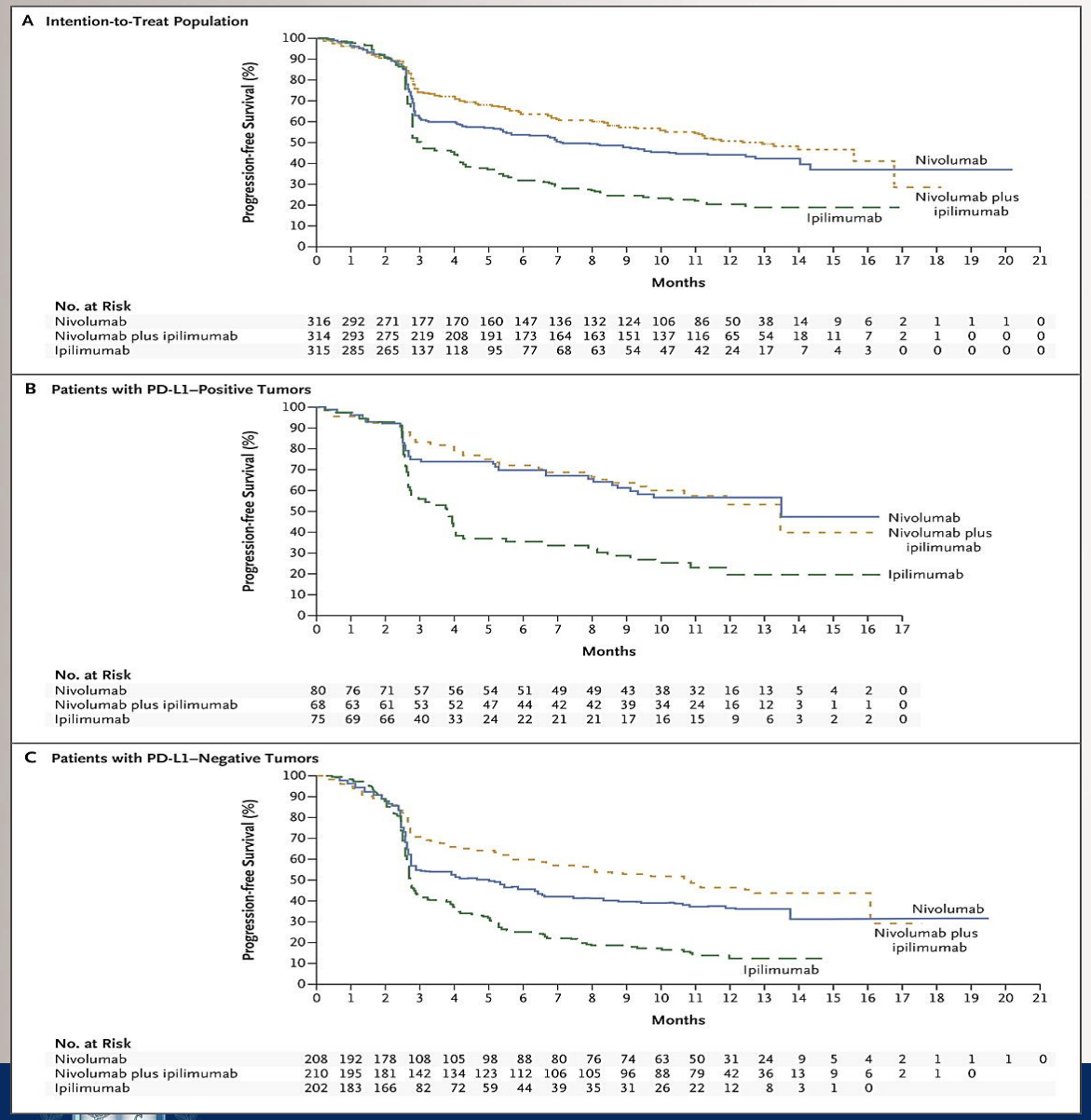
Korn et al. *J Clin Oncol 26:527-34, 2008*

Ipilimumab Improves Overall Survival Compared to Control

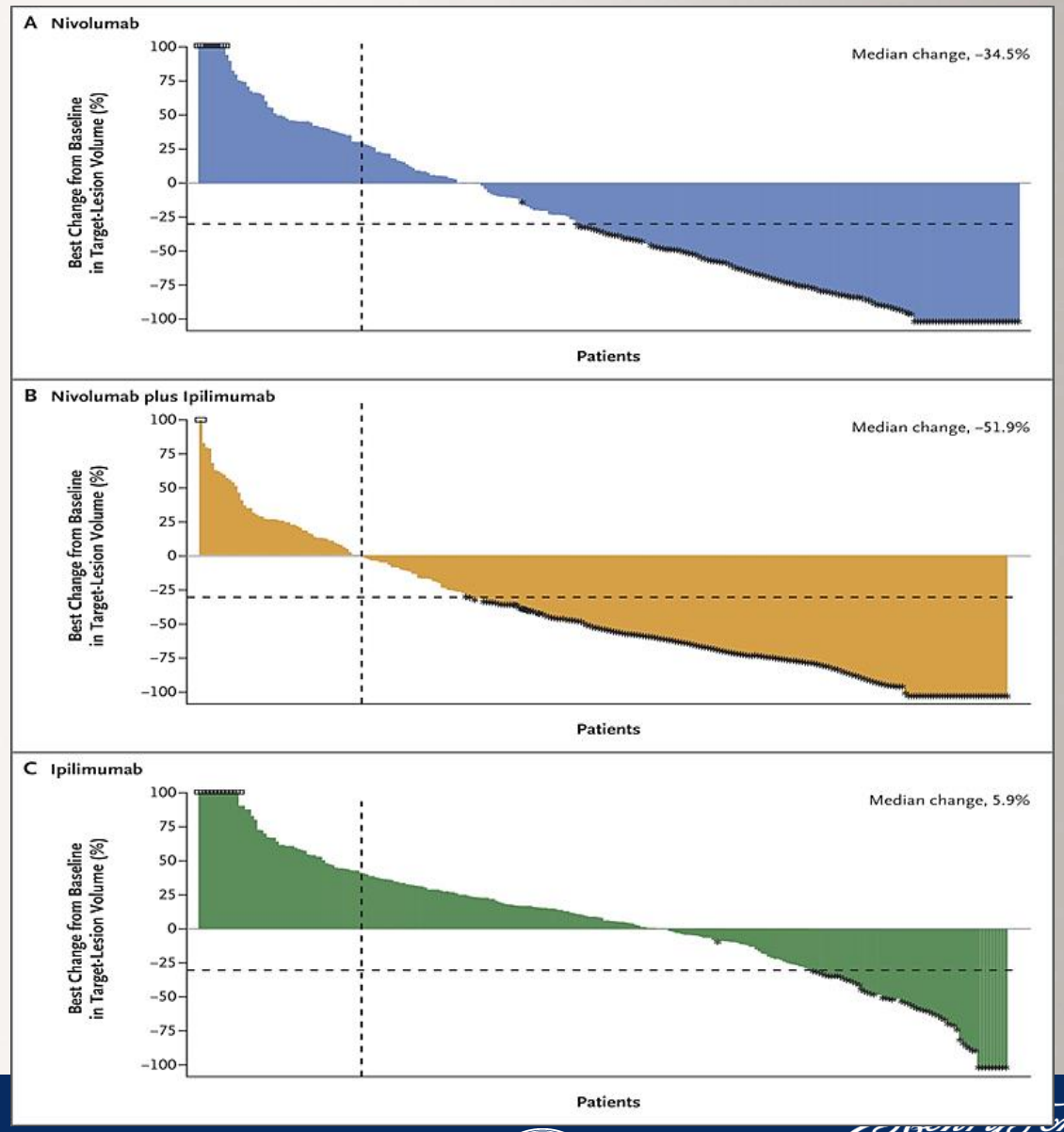
	Ipilimumab/ gp100 (Arm A) (n = 403)	Ipilimumab/ Placebo (Arm B) (n = 137)	gp100/ Placebo (Arm C) (n = 136)	Arm A vs. Arm C	Arm B vs. Arm C	Arm A vs. Arm B
Best Overall Response Rate	6%	11%	1.5%	*P* = .0433	*P* = .0012	*P* = .0402
Disease Control Rate	20%	28.5%	11%	*P* = .0179	*P* = .0002	*P* = .0429
Median Overall Survival	10.0 months	10.1 months	6.4 months	HR 0.68 (95% CI, 0.55-0.85) *P* = .0004	HR 0.66 (95% CI, 0.51-0.87) *P* = .0026	HR 1.04 (95% CI, 0.83-1.30) *P* = .7575
Survival Rate						
1 year	44%	46%	25%	NR	NR	NR
2 years	22%	24%	14%	NR	NR	NR

Hodi FS et al. N Engl J Med 2010;363:711-723

Progression-free Survival



Tumor Burden Change in Target Lesions



Larkin J et al. N Engl J Med 2015;373:23-34.

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

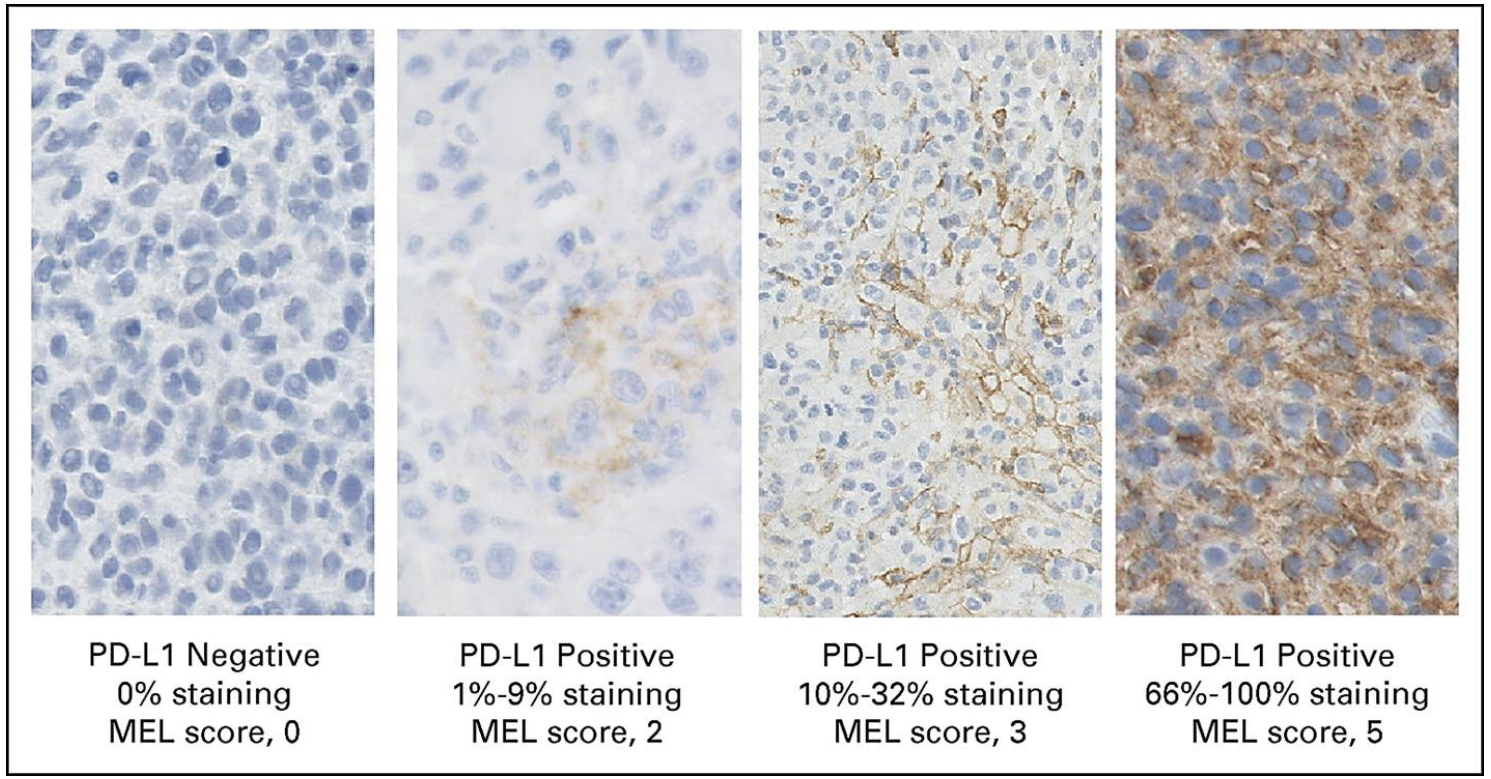
Robert, N Engl J Med 2015; Robert, Lancet 2019; Hodi, N Engl J Med 2010; Larkin, J Clin Oncol 2018.

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:
  - Tumor biology:
    - PD-L1 expression
    - TMB
  - Brain metastases
  - Mucosal melanoma
  - High disease burden



JCO ***2016,*** *34, 4102-4109.*

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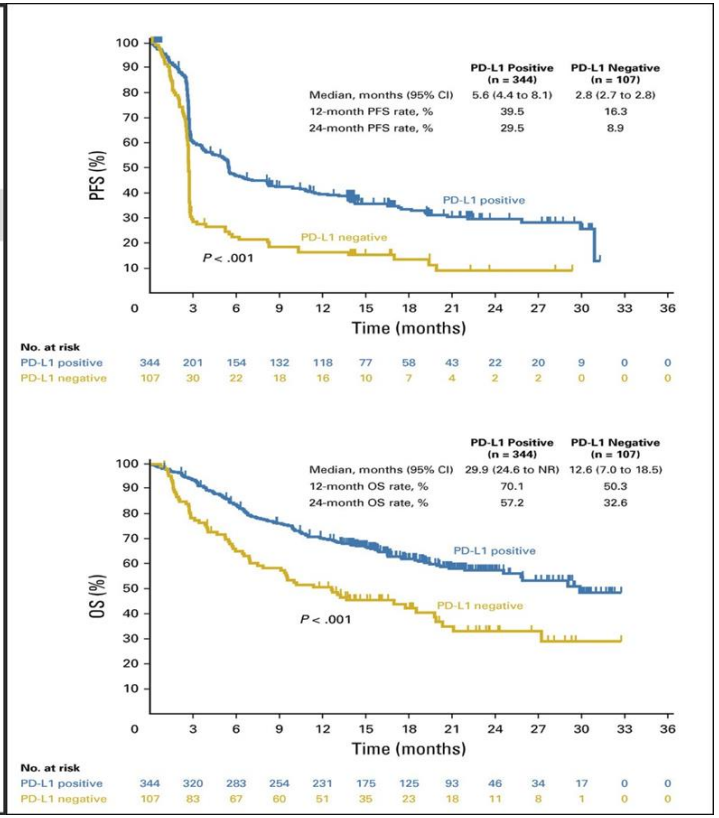
Table 1. Melanoma (MEL) Scoring System for PD-L1 Expression

Definition	MEL Score
No membrane staining	0
Membrane staining in tumor and tumor-associated immune cells, range	
> 0% - < 1%	1
≥ 1% - < 10%	2
≥ 10% - < 33%	3
≥ 33% - < 66%	4
≥ 66%	5

NOTE. PD-L1 expression was assessed by immunohistochemistry using the 22C3 antibody. MEL score ≥ 2 is considered PD-L1 positive.
Abbreviation: PD-L1, programmed death-ligand 1.



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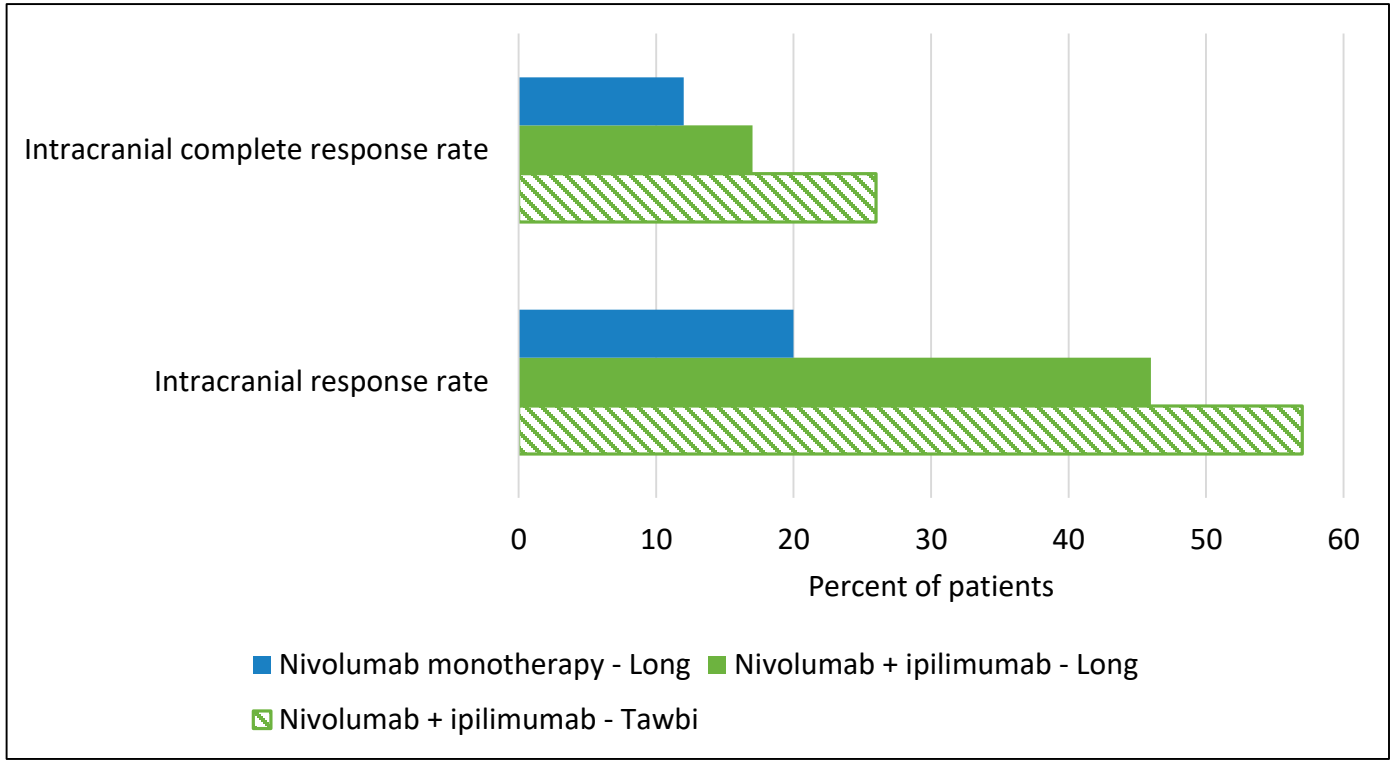

Long, Lancet Oncol 2018; Tawbi, N Engl J Med 2018.

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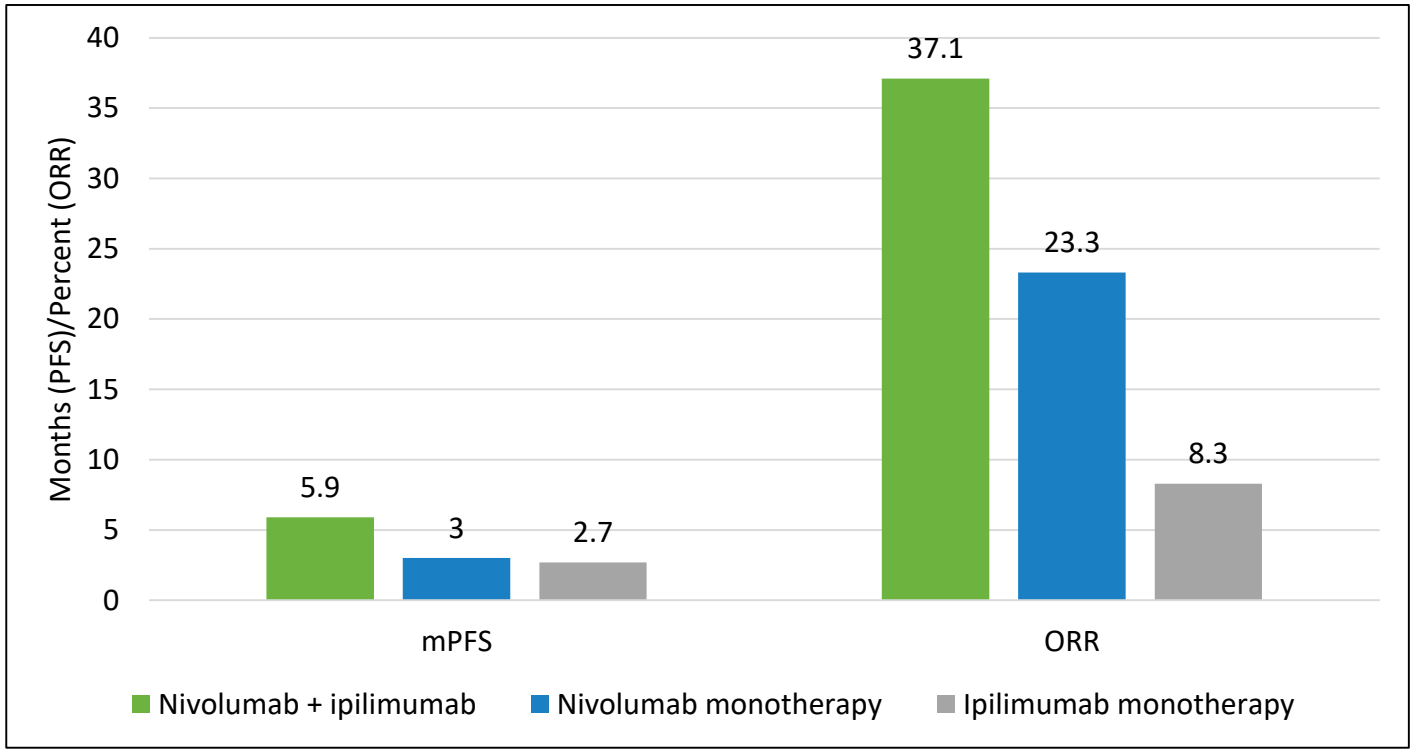

D'Angelo, J Clin Oncol 2016.

Choosing appropriate regimens

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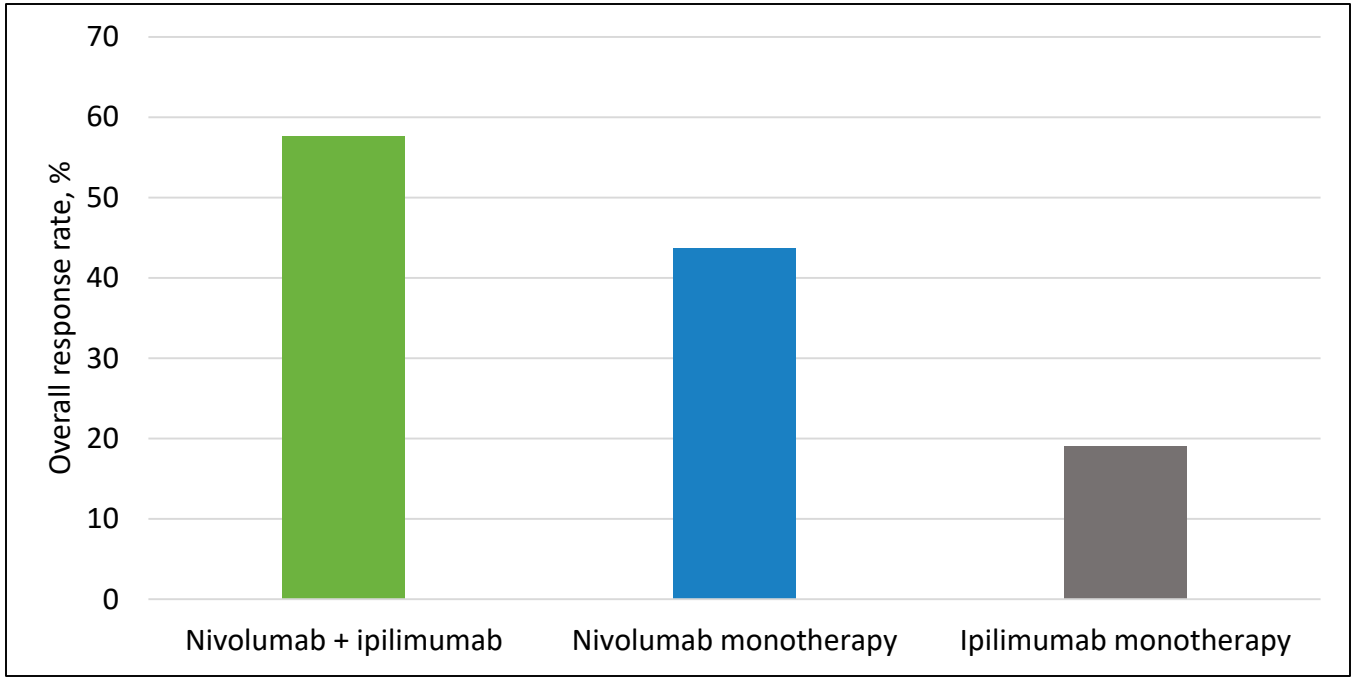
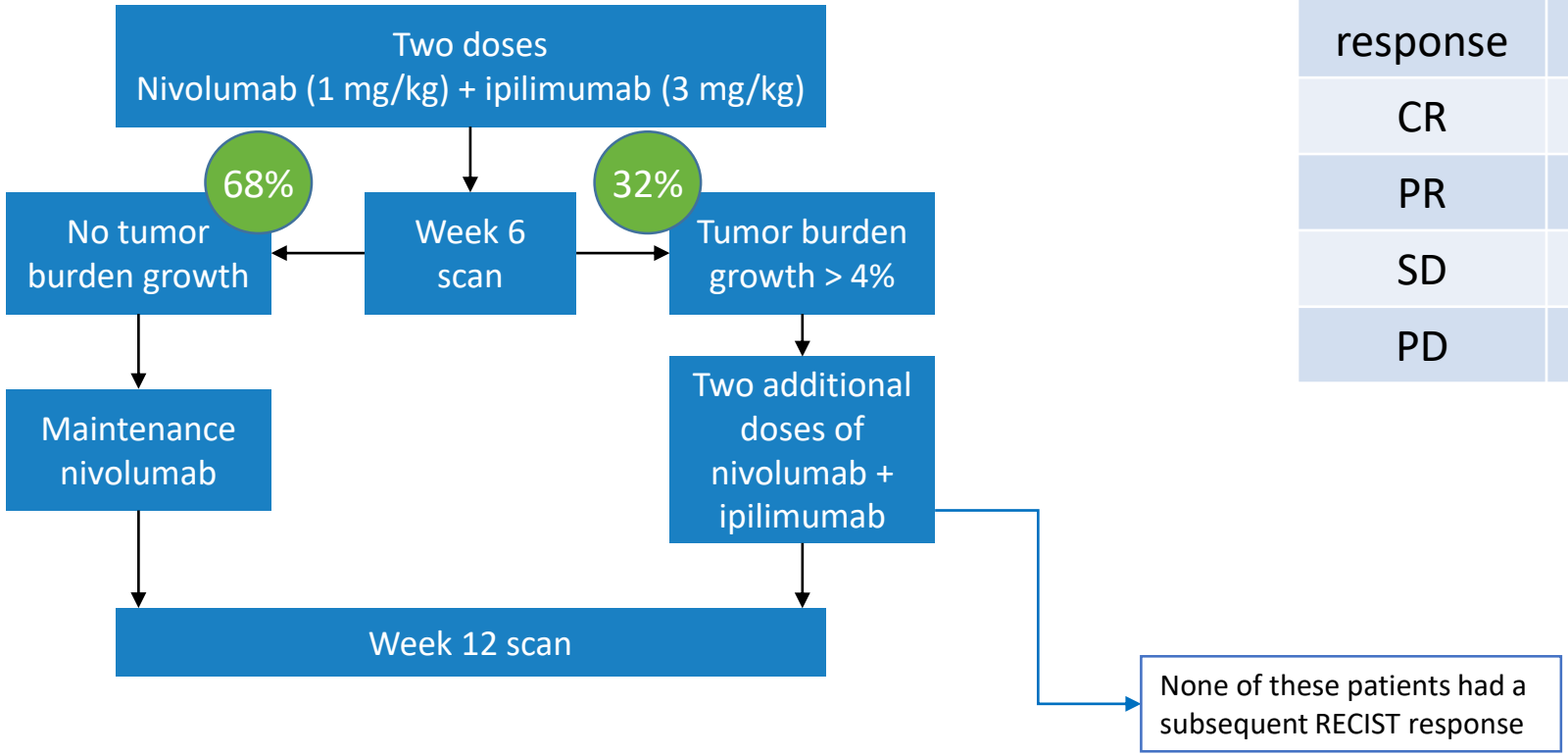


Larkin, N Engl J Med 2015.

Question: How many combination doses to give



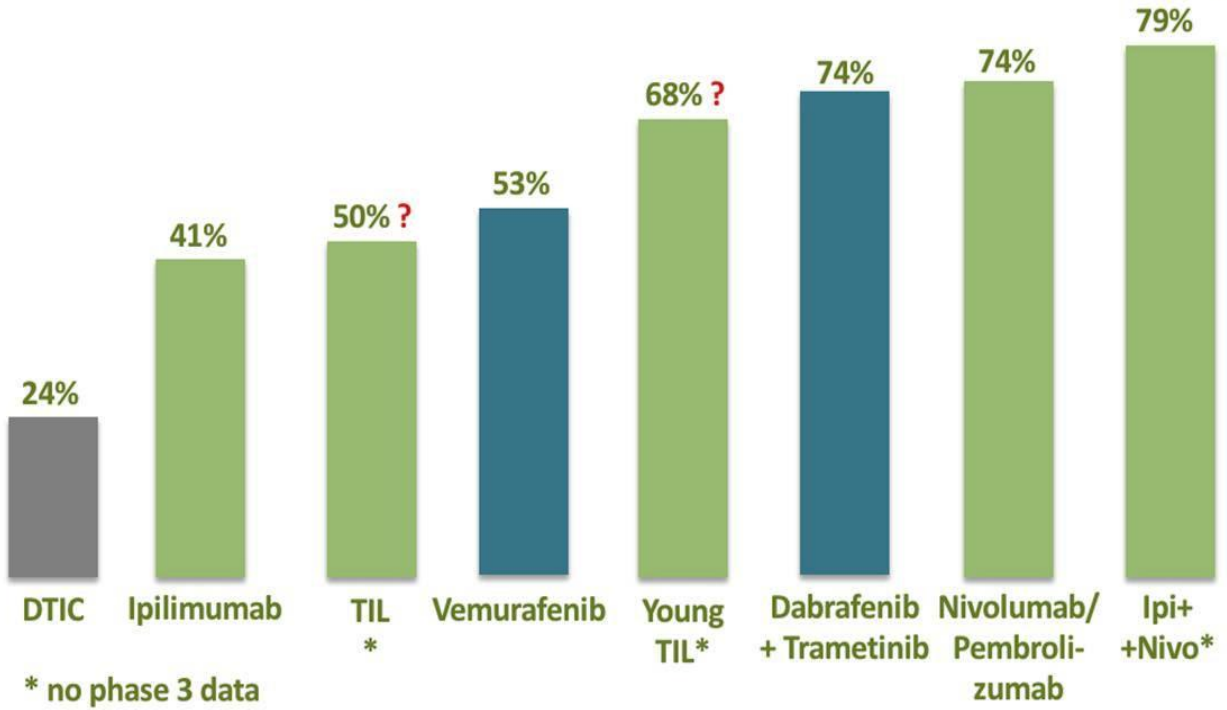
N=60	Week 6	Week 12	Best overall response rate
Overall response	35%	48%	57%
CR	0	5%	18%
PR	35%	43%	38%
SD	43%	18%	22%
PD	22%	30%	22%

Adverse events

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

Postow, ASCO 2020.

Improved 1 year OS of stage IV melanoma patients thanks to targeted and and immunotherapy

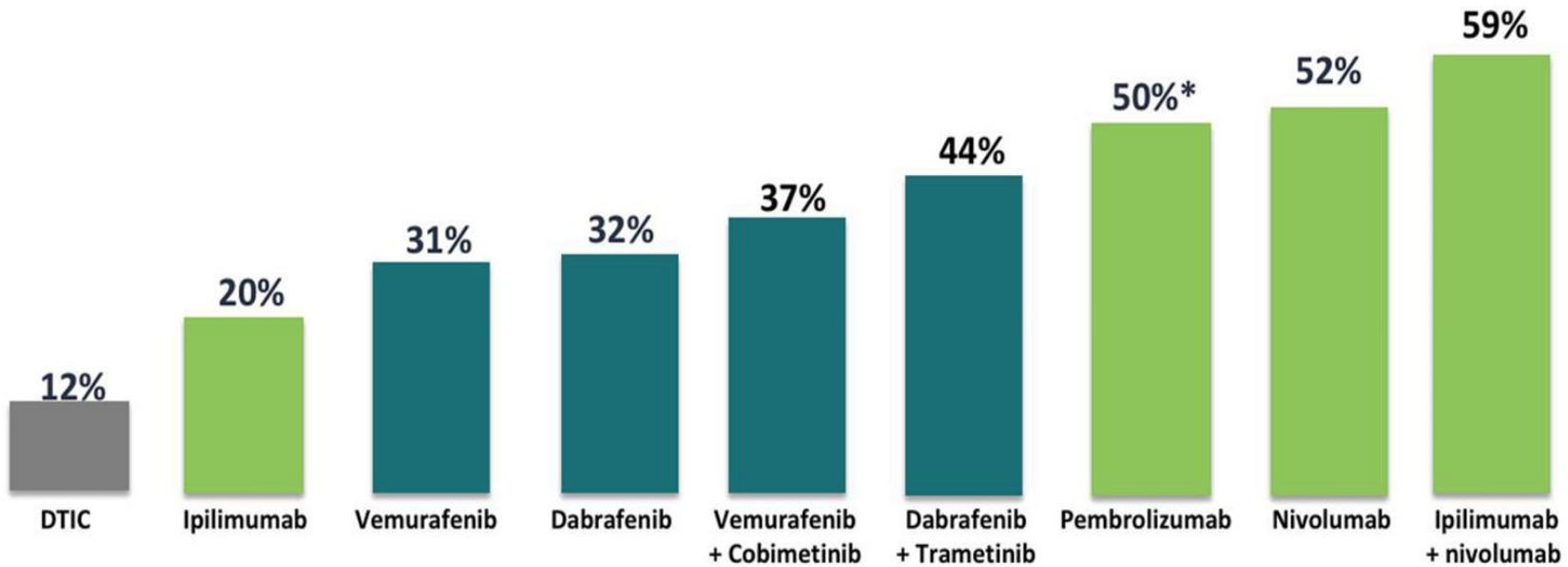


McArthur et al. Lancet Oncol 2014; Hodi et al. NEJM 2010; based on Rosenberg and Dudley Curr Opin Immunol 2009; McArthur et al. Lancet Oncol 2014; based on Dudley et al. JCO 2013; Long et al. Lancet 2015; based on Robert et al. NEJM 2015; prediction based on Larkin et al. NEJM 2015 and Sznol et al. ASCO 2014, Postow et al. AACR 2016

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY:

Targeted therapy and immunotherapy have improved 3 year OS of stage IV melanoma patients



*OS rate at 33 months

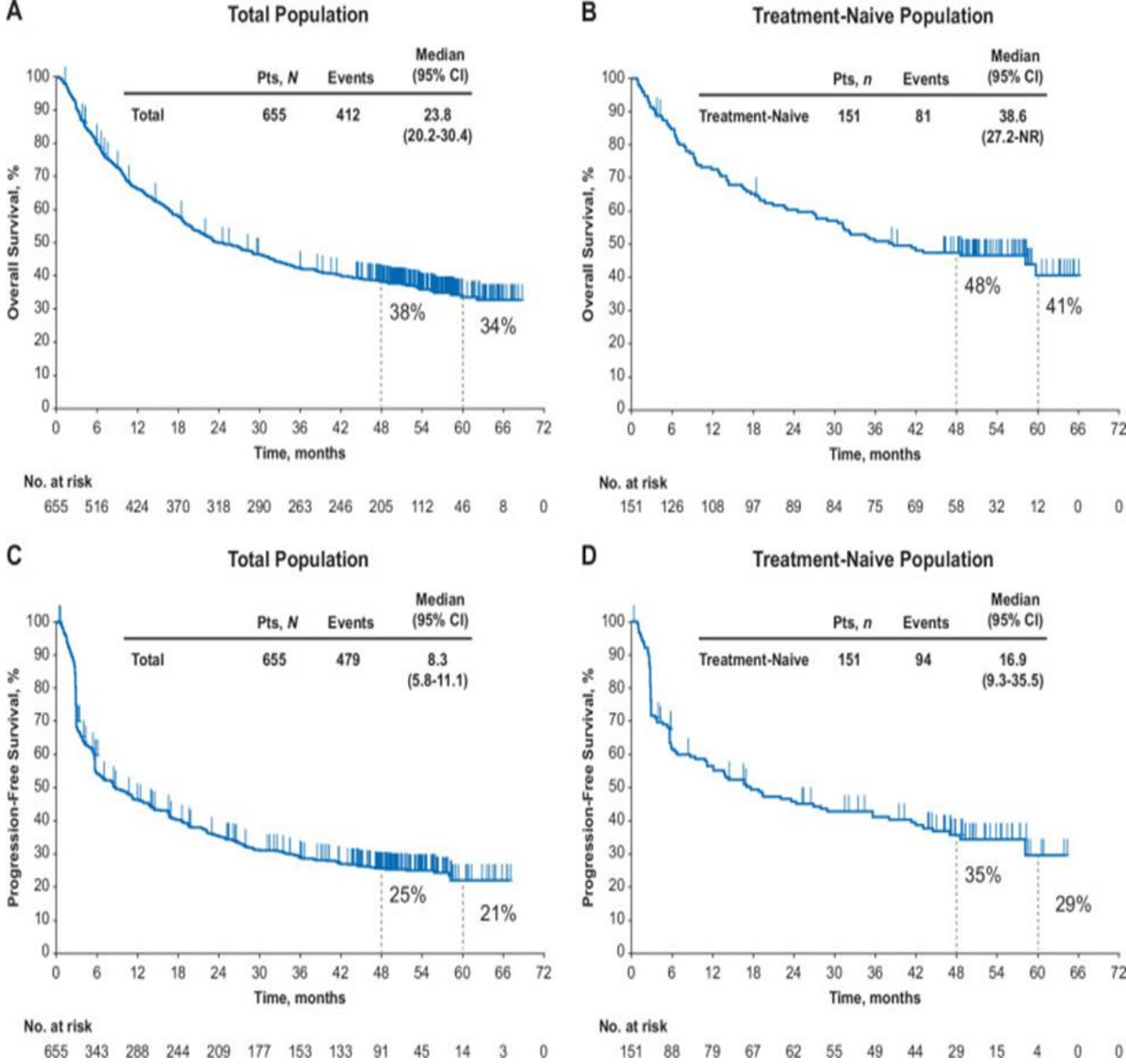
Hodi et al., NEJM 2010; Robert et al., NEJM 2011; COMBI-d ASCO 2016; COMBI-v ESMO 2016; Co-BRIM - SMR 2016, Keynote 006 - ASCO 2017; Wolchok et al NEJM 2017

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY:

Five-year survival for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001

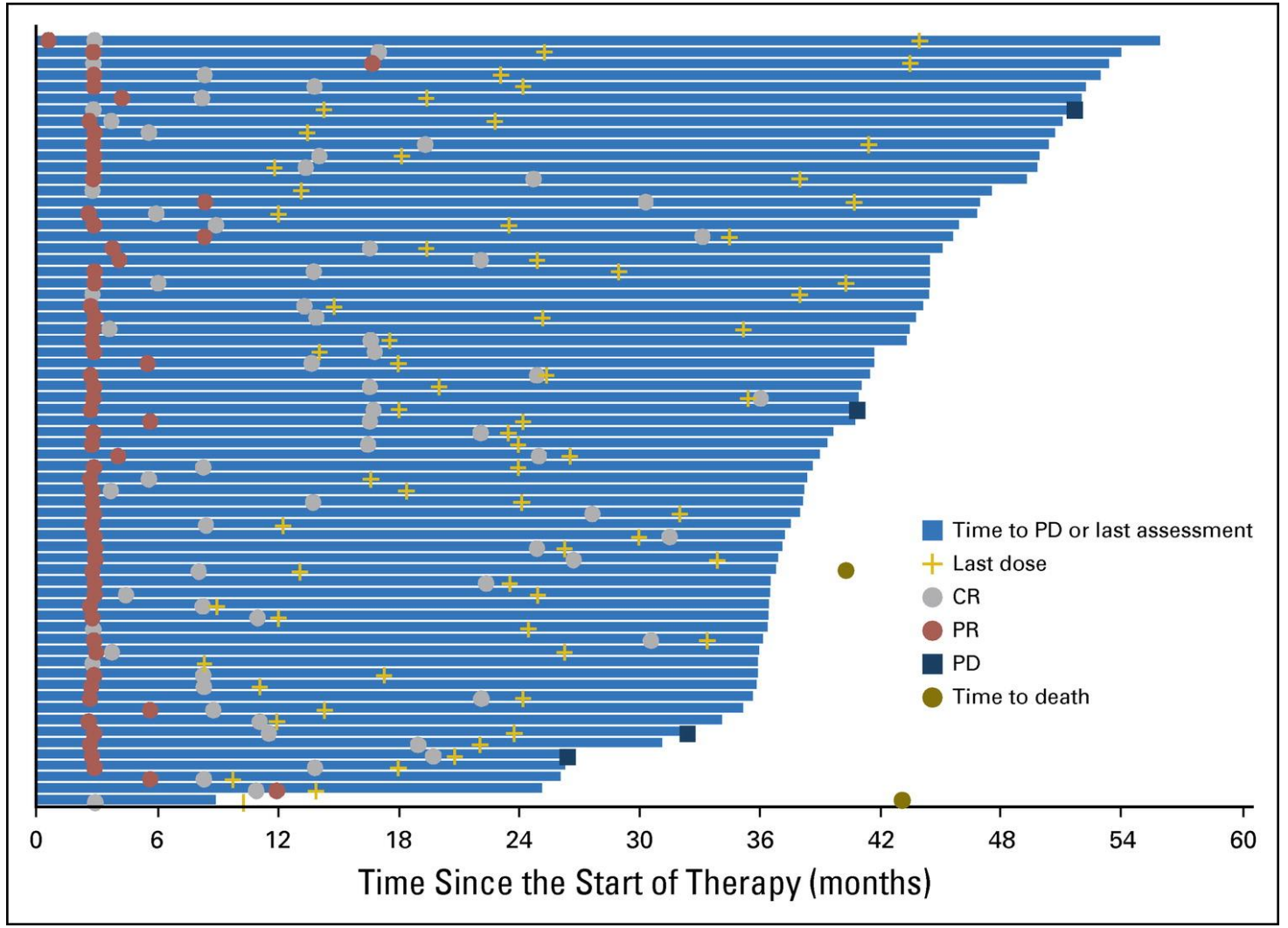
- KEYNOTE-001 enrolled 655 patients with melanoma
- Median follow-up was 55 months
- 5-year OS rate was 34% in all patients vs 41% in Tx-naive patients
- Median OS 23.8 months (95% CI, 20.2–30.4) in all vs **38.6 months** (95% CI, 27.2–not reached) in Tx-naïve patients
- 5-year PFS rates were 21% in all patients vs 29% in treatment-naive patients;
- Median PFS was 8.3 months (95% CI, 5.8–11.1) in all vs **16.9** months (95% CI, 9.3–35.5) Tx-naïve
- Median response duration was not reached;
- ORR was 73% in all vs 82% of treatment-naive patients with ongoing responses at the data cut-off with the longest response ongoing at 66 months.
- Four patients out of complete response (CR)] had disease progression during observation subsequently received second-course pembrolizumab
- Treatment-related AEs (TRAEs) occurred in 86% of patients and resulted in study discontinuation in 7.8%; 17% experienced grade 3/4 TRAE



 Annals of Oncology 2019 30582-588DOI: (10.1093/annonc/mdz011)

5-Year Follow-up of Clinical Responded Patients with MM in Keynote-001

- KN-001 (n=655): 105 patients (16%) achieved CR
- Follow-up 43 months, 91 of 105 patients (86.7%) pembrolizumab had been discontinued, 67 of 105 patients (63.8%) entered observation without additional therapy
- DFS rate at 24 months from time of CR achieved_90.9% (105 pts), 89.9% of 67 pts having discontinued Pembro after CR
- 4 of 67 pts (6%) had PD



Published in: Caroline Robert; Antoni Ribas; Omid Hamid; Adil Daud; Jedd D. Wolchok; Anthony M. Joshua; Wen-Jen Hwu; Jeffrey S. Weber; Tara C. Gangadhar; Richard W. Joseph; Roxana Dronca; Amita Patnaik; Hassane Zarour; Richard Kefford; Peter Hersey; Jin Zhang; James Anderson; Scott J. Diede; Scot Ebbinghaus; F. Stephen Hodi; *Journal of Clinical Oncology* 2018 361668-1674.

Site-specific response patterns, pseudoprogression, and acquired resistance in patients with melanoma treated with ipilimumab combined with anti–PD-1 therapy

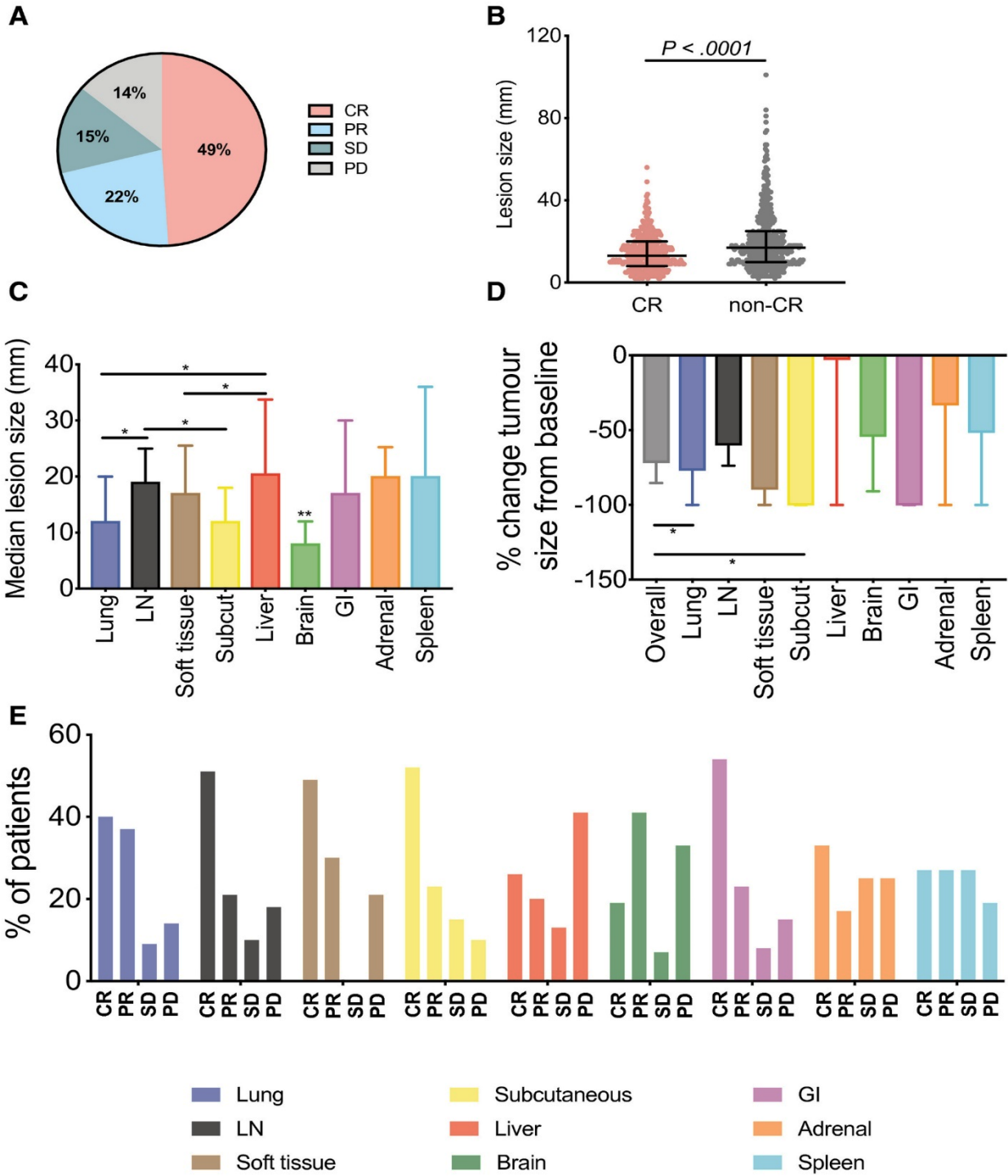
(A) The best lesional response is illustrated according to RECIST

(B) Metastases that had a CR were significantly smaller than non-CR metastases (median, 13 vs 17 mm; *P* < .0001).

(C) The median lesion size per site of disease is illustrated. GI indicates gastrointestinal; LN, lymph node.

(D) The best percentage tumor size change from baseline is illustrated per site of disease.

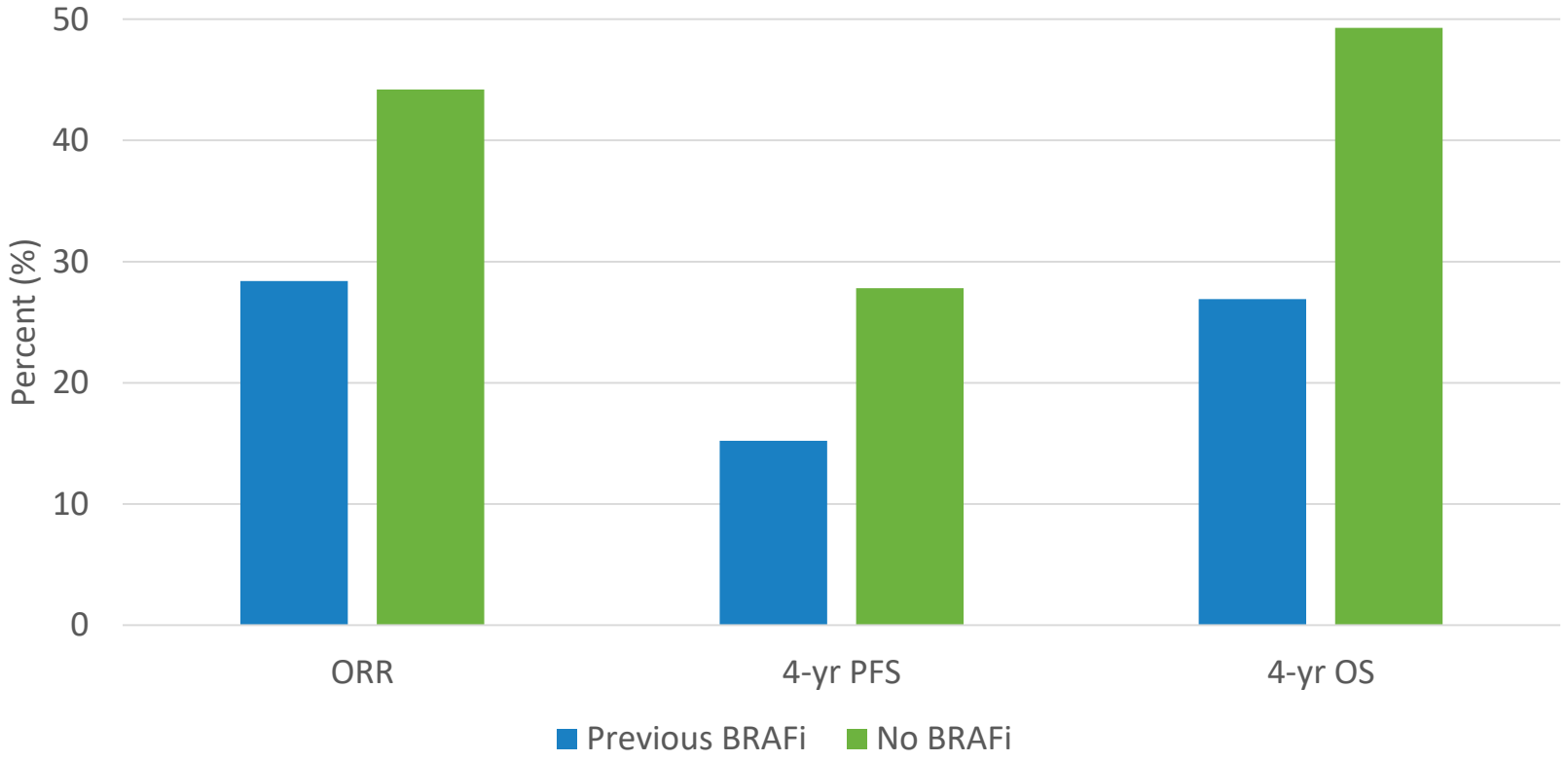
(E) The best response per site of disease is illustrated.



Cancer, Volume: 126, Issue: 1, Pages: 86-97, 2019

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 unanswered: what if combine the ICI with targeted therapy?
  - Keynote-022 data (Slide#41)
  - SWOG S2000: Randomized Phase 2 trial between Encorafenib+Binimetinib+Nivolumab vs Ipilimumab+Nivolumab in BRAF-V600E mutant melanoma with brain metastases



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%

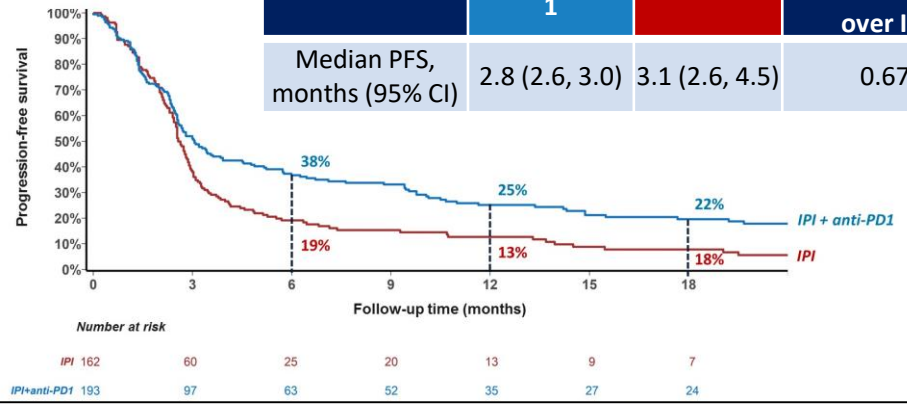
Grade 3+ adverse events:

IPI + PD-1: 31%

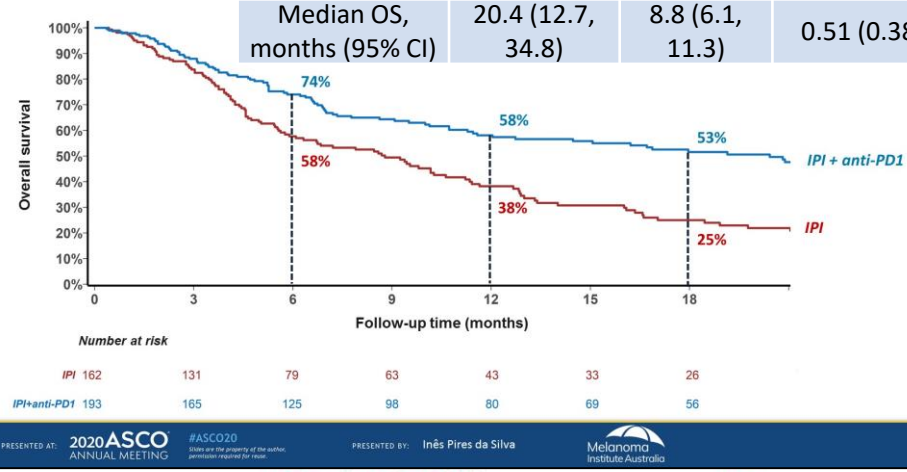
IPI: 33%

Encourage clinical trial enrollment

	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

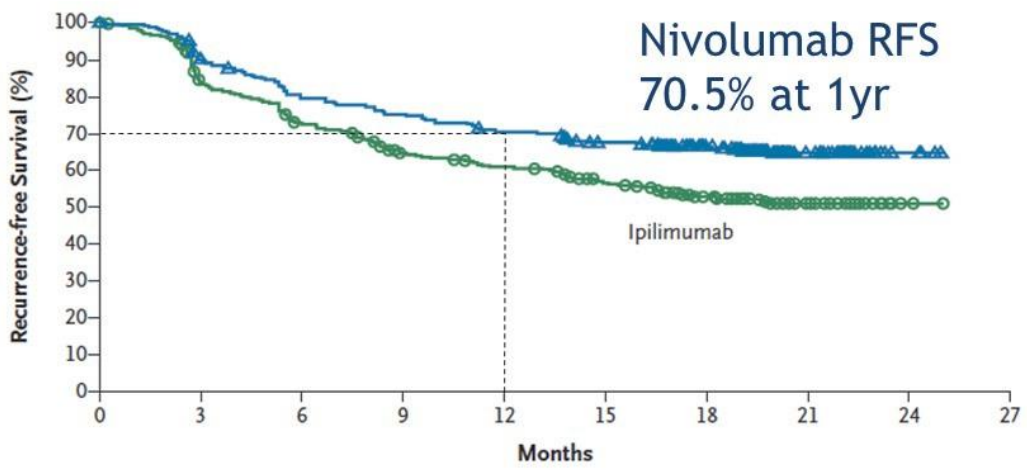
[+]Not an immunotherapy; for reference
**not commonly used in this setting; historical reference*

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	

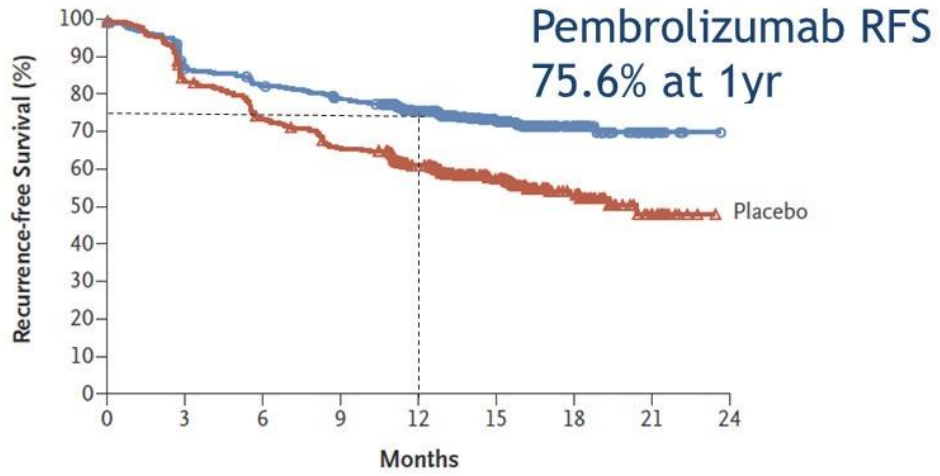
Background; adjuvant anti-PD1 (adj-PD1)

- A new standard of care in high-risk resected melanoma
- 40-45% risk reduction in recurrence or death at 1yr



Weber et al, NEJM 2017

Resected IIIB, IIIC, IV



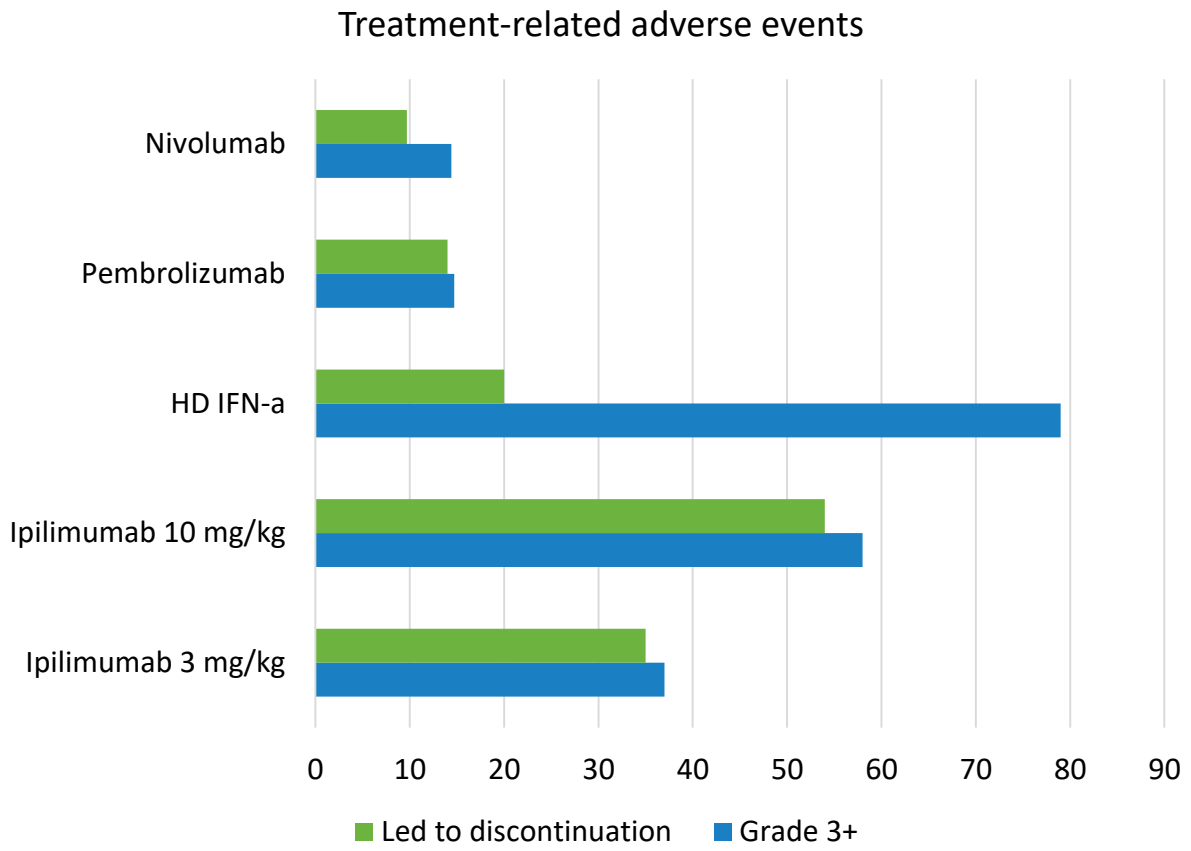
Eggermont et al, NEJM 2018

Resected IIIA, IIIB, IIIC

Presented By Carina Owen at 2019 ASCO Annual Meeting

Adjuvant treatment considerations

- Goals of adjuvant treatment are different than goals of primary treatment
- Toxicity and quality of life are important considerations
- Clinical decision made through justifications



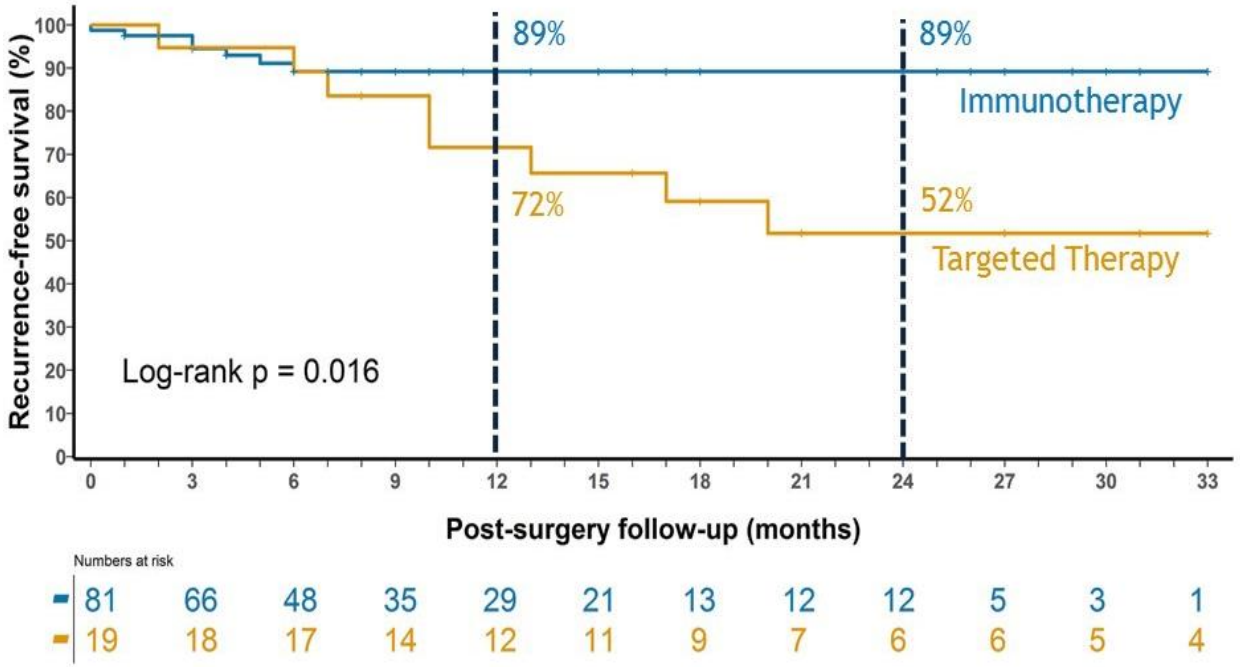
In development: Neoadjuvant immunotherapy in advanced melanoma

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.

Relapse-Free Survival of Neoadjuvant immunotherapy in advanced melanoma by stage and by Drug Class

IIIB



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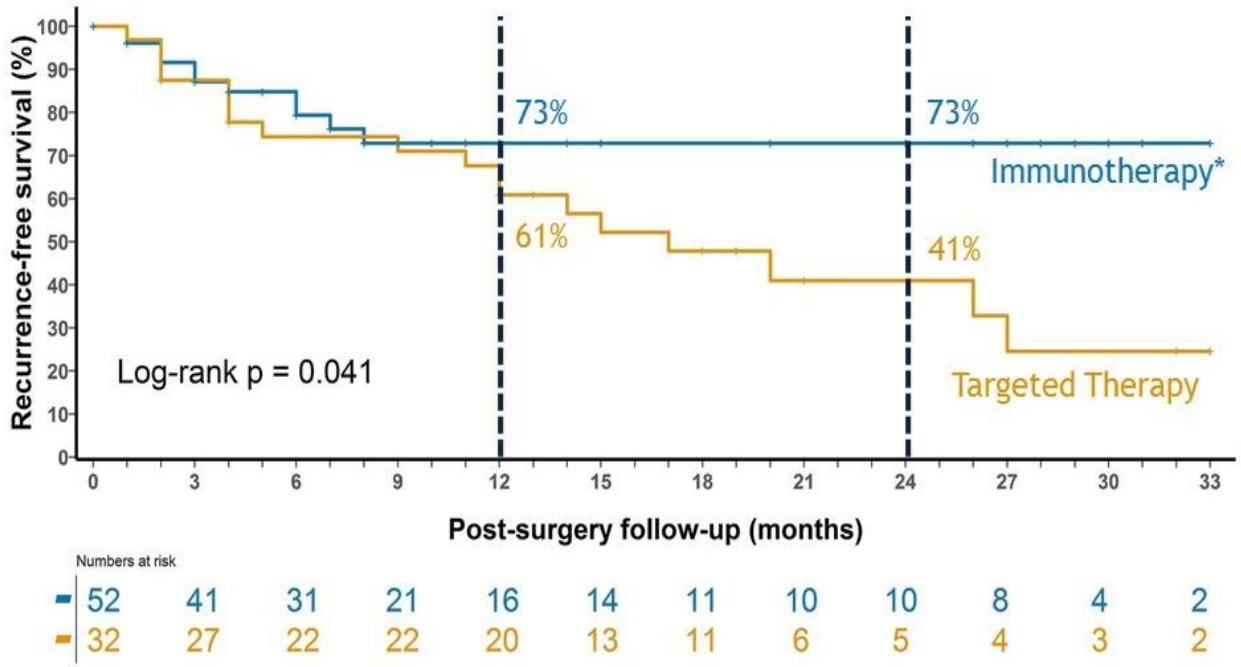

Menzies ASCO Annual Meeting 2019.

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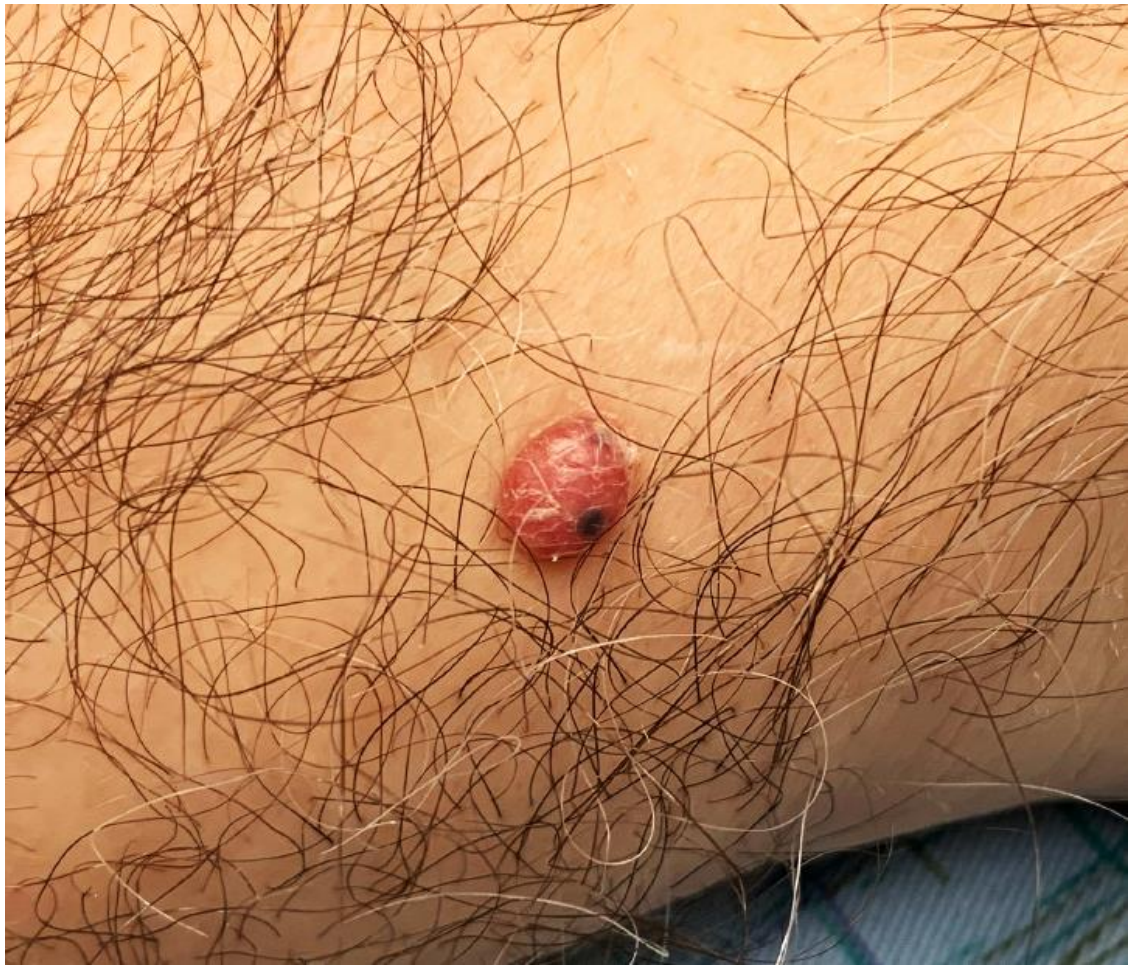
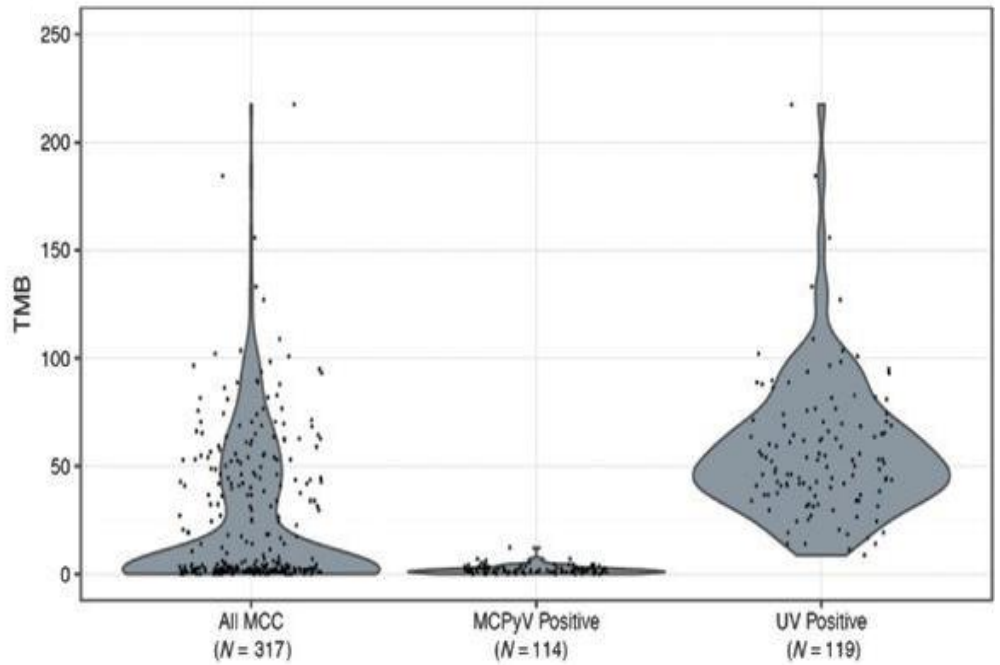
Outline

- 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



Merkel cell carcinoma



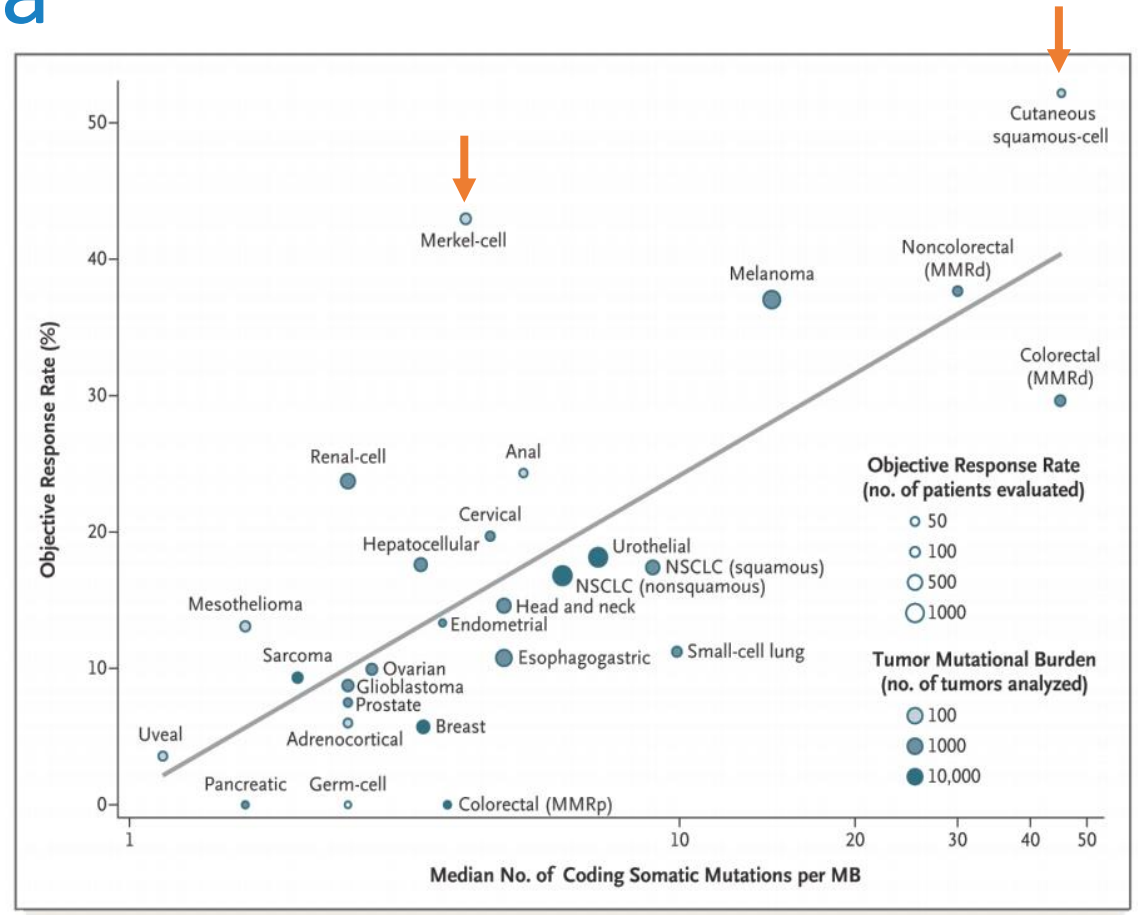


Figure 1. Correlation between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti-PD–L1 Therapy in 27 Tumor Types.

- Associated with Merkel cell polyomavirus infection (MCPyV)
- 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.

Yarchoan M., et al. NEJM 2017

Approved checkpoint inhibitors in Merkel cell carcinoma

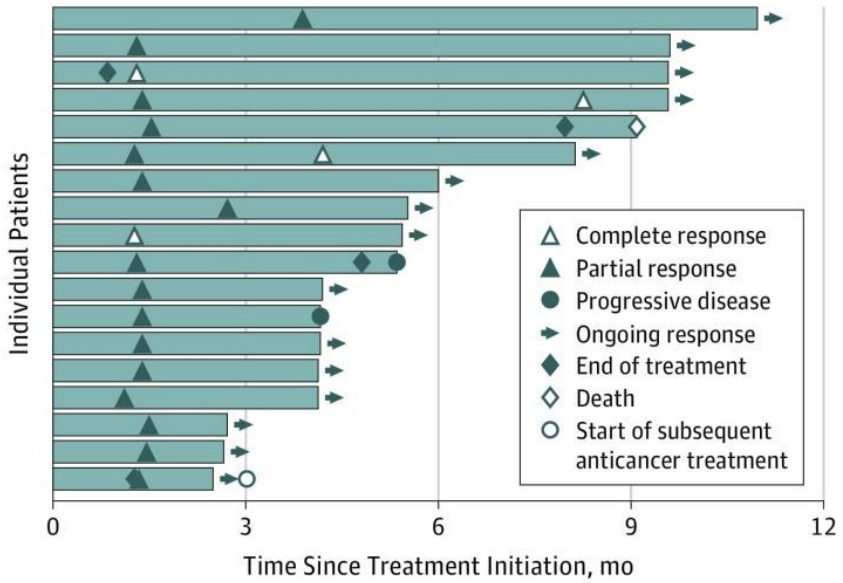
Drug	Indication	Dose
Avelumab*	Patients >12 yr with metastatic **Merkel cell carcinoma**	800 mg Q2W + premedication (first 4 cycles)
Pembrolizumab	Adult/pediatric with recurrent advanced/metastatic **Merkel cell carcinoma**	Adults: 200 mg Q3W or 400 mg Q6W Pediatric: 2 mg/kg (up to 200 mg) Q3W

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

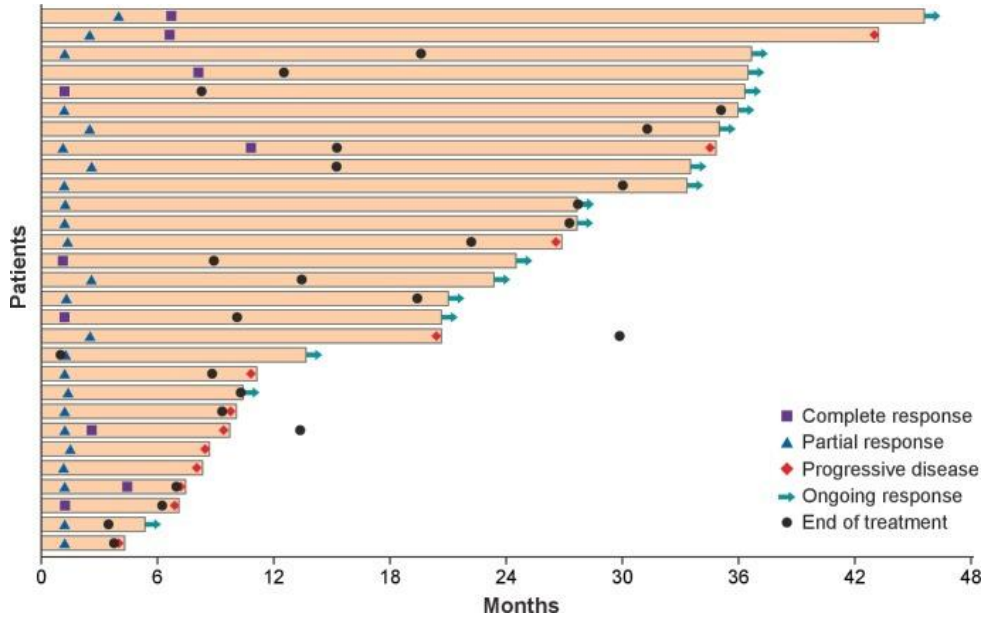
Avelumab in Merkel cell carcinoma

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



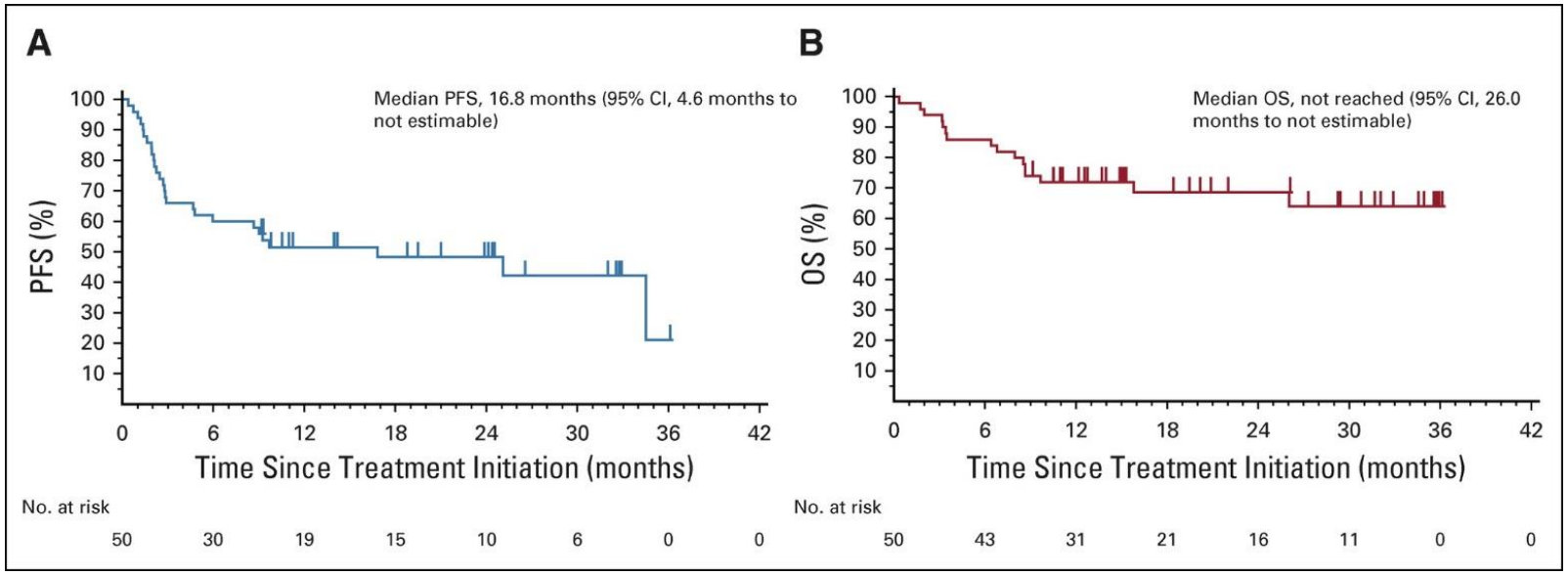
Second+ line



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

- Melanoma
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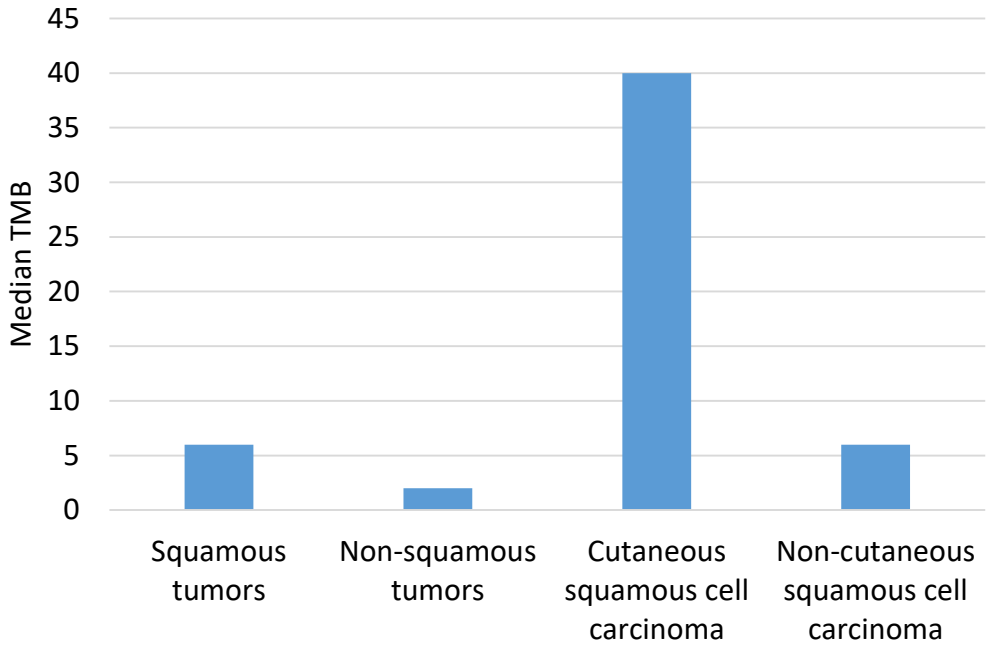
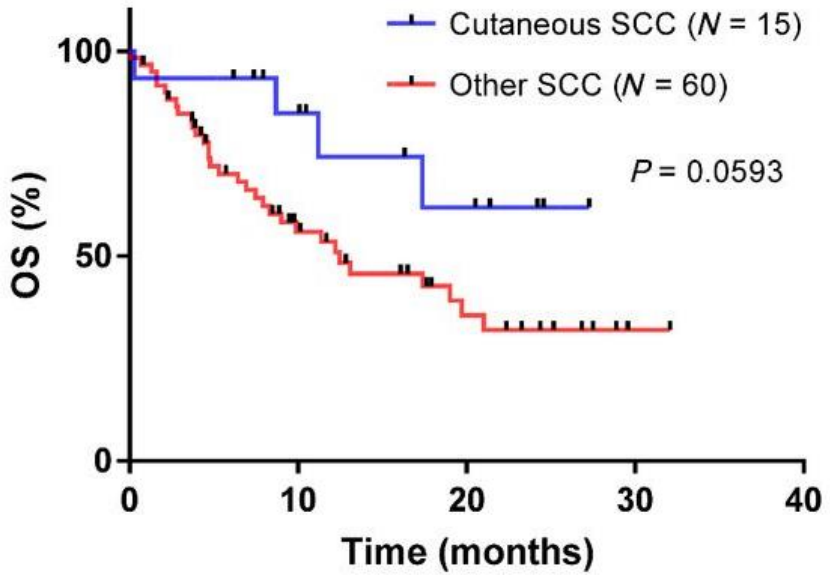
Cutaneous squamous cell carcinoma

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





Goodman, Cancer Immunol Res 2019.

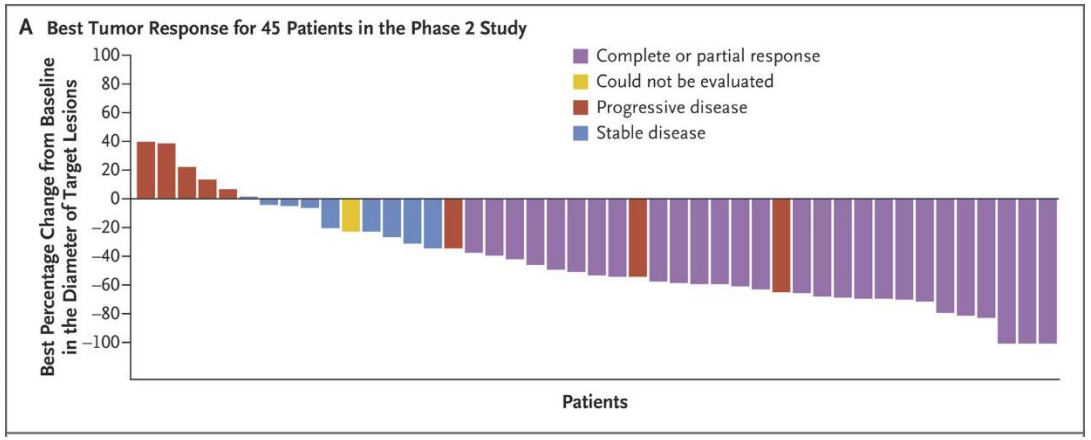
Approved checkpoint inhibitors for cutaneous squamous cell carcinoma

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

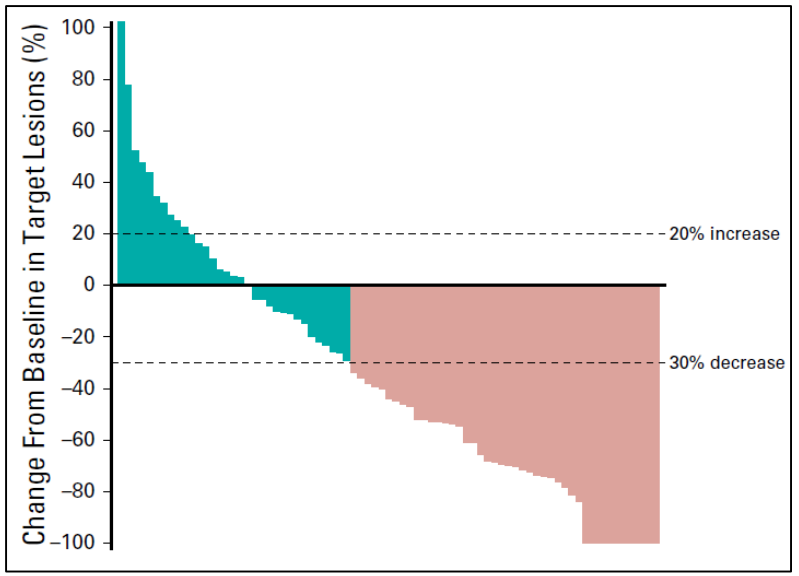
Trials for R/M cutaneous SCC

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

Outline

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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

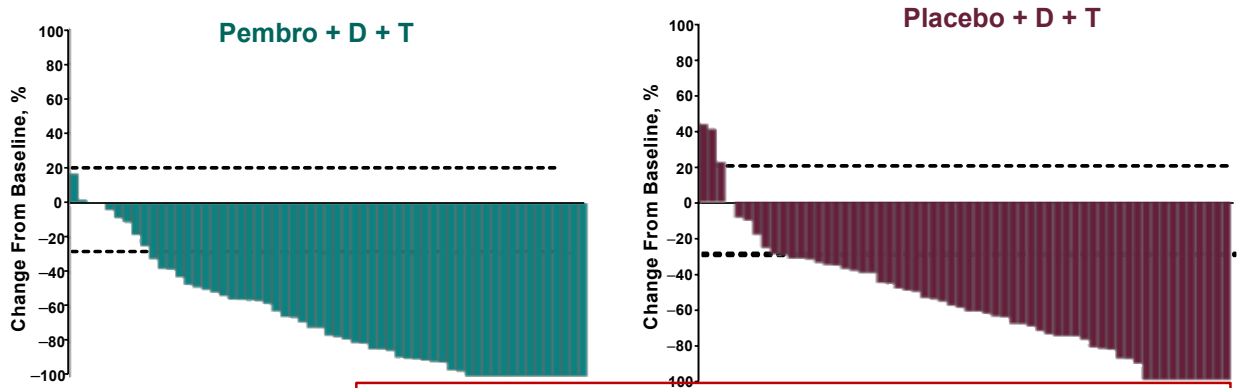
N = 60 → Pembrolizumab 2 mg/kg Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD

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.

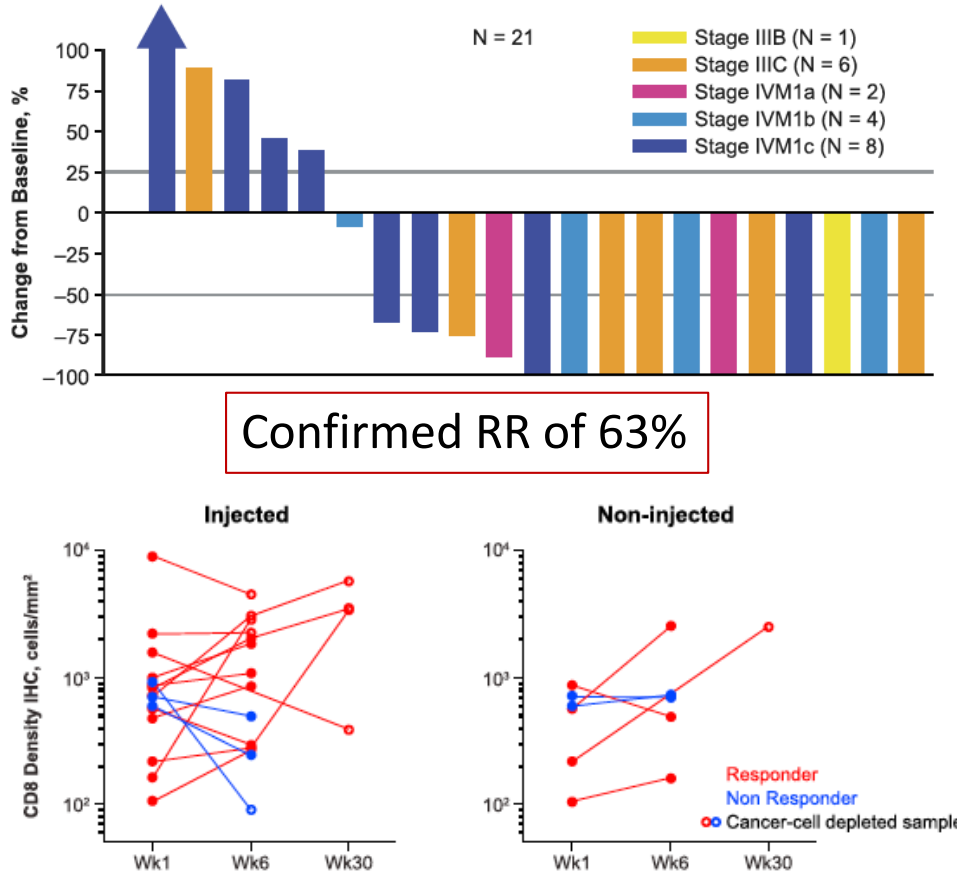


	Pembro + D + T	Placebo + D + T
ORR	63%	72%
CR	18%	13%
≥ 60% red	63%	51%

Multiple other triplet regimens are being tested.

Ascierto et al, *Nature Med* 2019.

In development: Combination IO with oncolytic virus



Confirmed RR of 63%

Phase I: Pembrolizumab + TVEC

Phase II: SWOG S1607 (completed accrual)

Ribas et al Cell 2017

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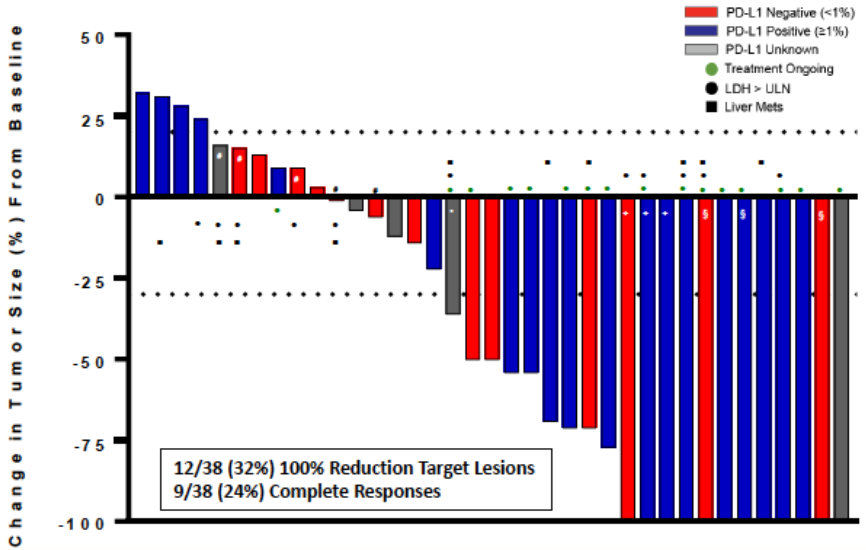
In development: Combination IO with pegylated IL-2 (NKTR-214)

Efficacy (response rate) data from non-randomized cohorts of urothelial bladder cancer, renal cell carcinoma, and melanoma looks promising

NKTR-262 (IT)+NKTR-214 (iv)+Nivolumab (iv)(REVEAL) completed melanoma expansions

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%)

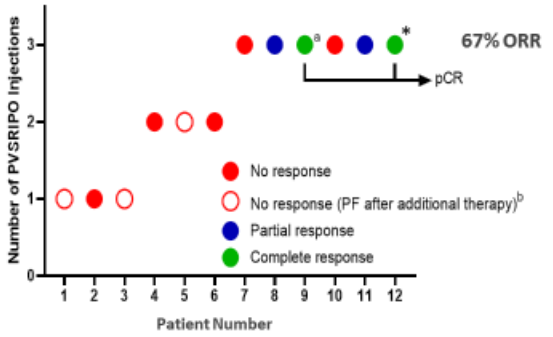
High level of concordance in ORR between independent central radiology (53%) and investigator-assessed 19/38 (50%).

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

PVSRIPO Phase 1 & 2 Clinical Trial Treatment for PD-1 Experienced MM

Phase 1 Results: Efficacy

Results Summary by Number of PVSRIPO Injections



[a]Biopsy on 1 injected lesion and 1 non-injected lesion at Day 63 had melanophages only (dead tumor); [b]At time of data cut off; Patients 1, 3 (for 9 months), and 5 were PF after receiving additional anti-PD-1 therapy; patients 1 and 3 in combination with ipilimumab (patient 1's 1st exposure), following PVSRIPO therapy (see Table 1). * Possible pseudoprogression on checkpoint monotherapy prior to injection

PVSRIPO Anti-Tumor Response Relative to ICI Administration and Post-Study Disease Status

Time since anti-PD-1 relative to PVSRIPO	ORR per irRC % (n/N)	Proportion treated with ICI post-PVSRIPO % (n/N)	Progression-free post PVSRIPO alone or PVSRIPO followed by ICI % (n/N)	Median duration of follow-up (months)[a]
≤30 days	60% (3/5)	80% (4/5)	60% (3/5)	10
>30 days	14% (1/7)	86% (6/7)	43% (3/7)	16
Overall	33% (4/12)	83% (10/12)	50% (6/12)	12

[a]As of data cut off.

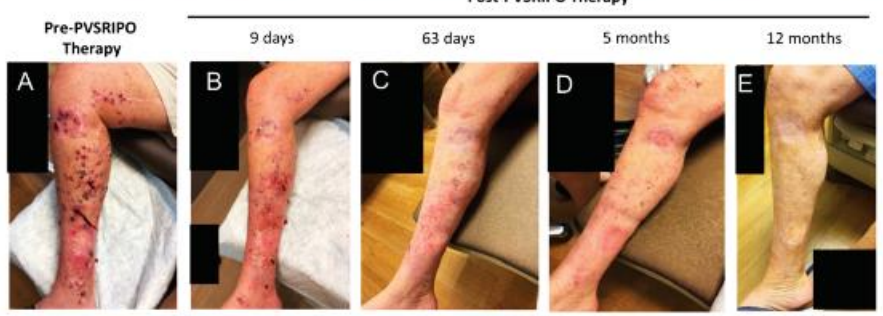
ICI, immune checkpoint inhibitor; irRC, immune-related response criteria; ORR, overall response rate; pCR, pathological complete response; PD-1, programmed death-receptor 1; PF, progression free.

Adapted from Beasley et al presented at the Virtual 2020 Society for Immunotherapy of Cancer (SITC) Annual Meeting, November 9-14, 2020

IQVIA BIOTECH 10

Case Study #1: Treatment Response

- Lesions in Patient 9 Prior to PVSRIPO Administration/Baseline (**A**) and Post-PVSRIPO Therapy (**B-E**)



- Patient 9 presented with Stage IIIB in-transit melanoma (**2A**)
- PVSRIPO therapy was initiated 15 days following last anti-PD-1 treatment.
  - Lesion regression apparent 9-days post-PVSRIPO therapy (**2B**)
- Day 63 biopsy (**2C**) demonstrated a pCR (defined as the absence of viable tumor) in injected and non-injected lesions
- At least 12 months post-PVSRIPO therapy, patient had scattered, flat, pigmented, stable lesions remaining, consistent with pCR (**2D-E**)

pCR, pathologic complete response; PD-1, programmed death-receptor 1

Adapted from Beasley et al presented at the Virtual 2020 Society for Immunotherapy of Cancer (SITC) Annual Meeting, November 9-14, 2020

IQVIA BIOTECH 11

- PVSRIPO: is genetically modified serotype 1 live-attenuated (Sabin) Poliovirus (PV1S) with neuro-incompetent human rhinovirus 2 (HRV2) IRES element
- Establish and build anti-cancer immunity based on anti-polio-specific memory T-cells recruitment in to TME

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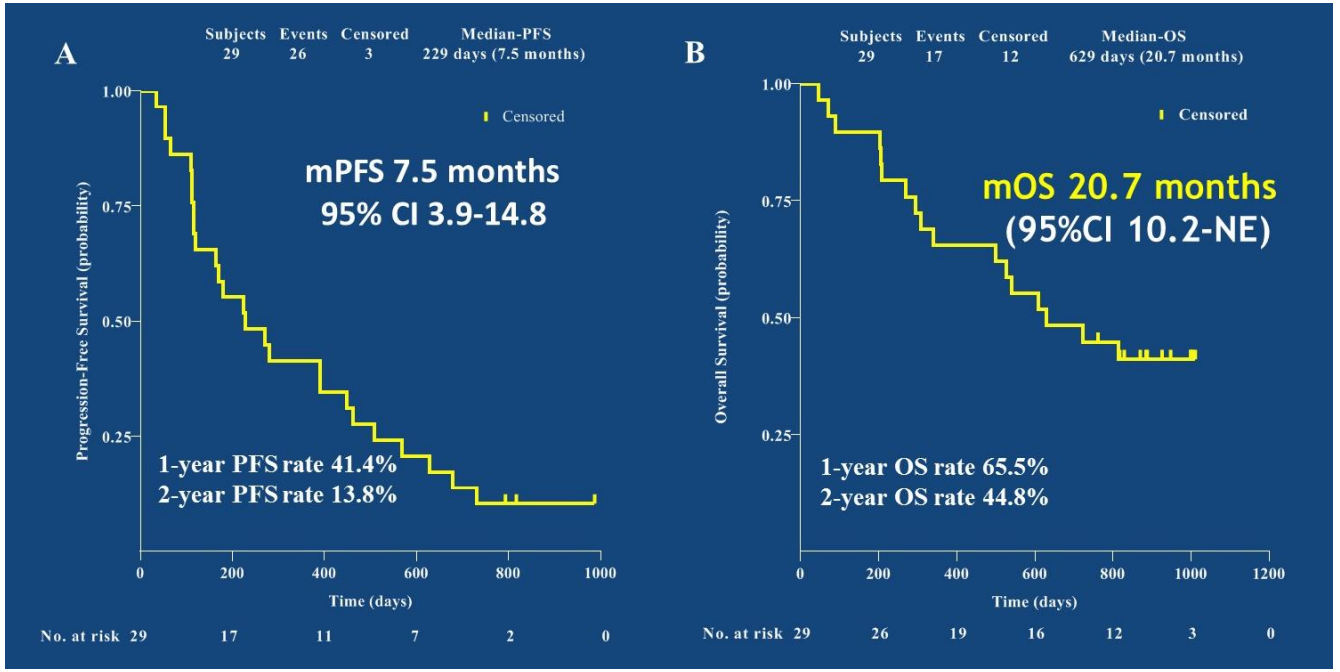
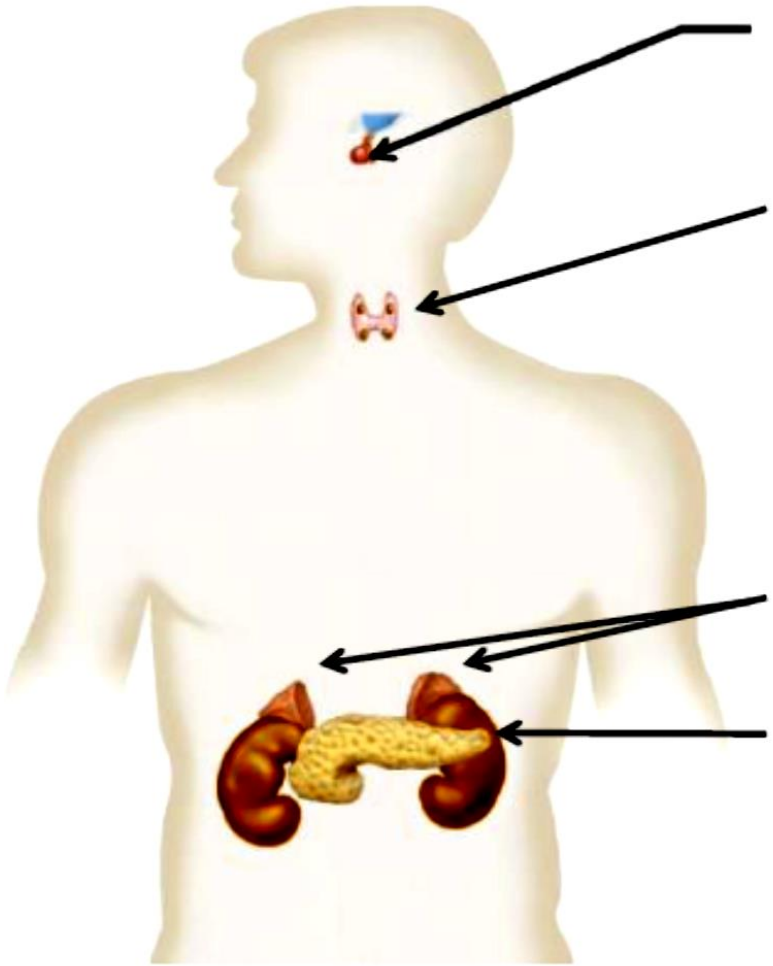
In development: Combination IO and TKI in mucosal melanoma

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



Guo, ASCO 2020.

ICI Safety and Therapy-related Adverse Effects



Pituitary gland
- Hypophysitis
- Corticotropin (ACTH) decrease
- Secondary adrenal insufficiency[a]

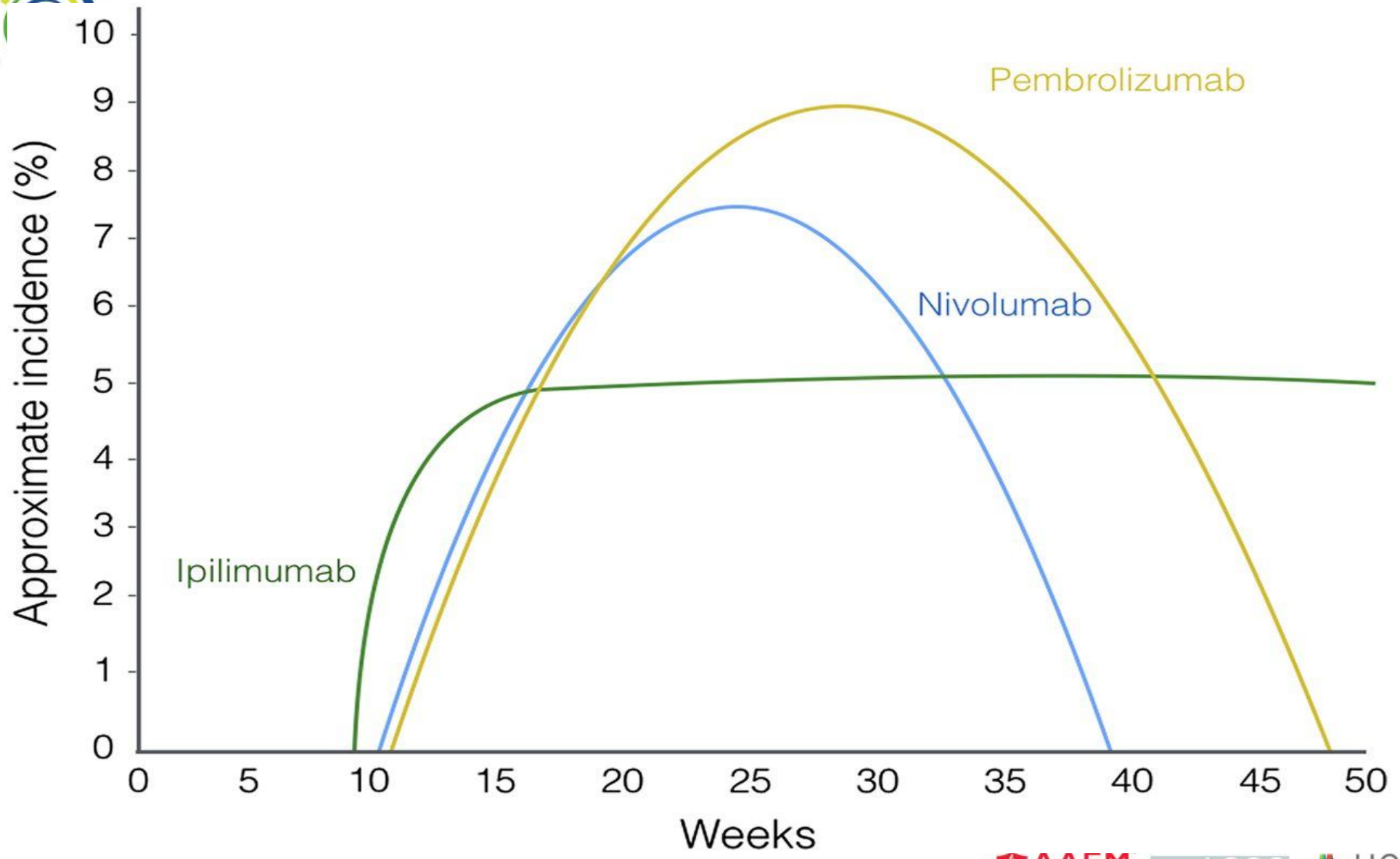
Thyroid gland
- Hyperthyroidism
- Hypothyroidism
- TSH increase or decrease
- Thyroiditis
- Free thyroxine increase or decrease
- Autoimmune thyroiditis

Adrenal glands
- Primary adrenal insufficiency[b]

Pancreas
- Diabetes mellitus

González-Rodríguez E., & Rodríguez-Abreu D. The Oncologist 2016;21:804-816

Timing pattern of endocrine adverse events

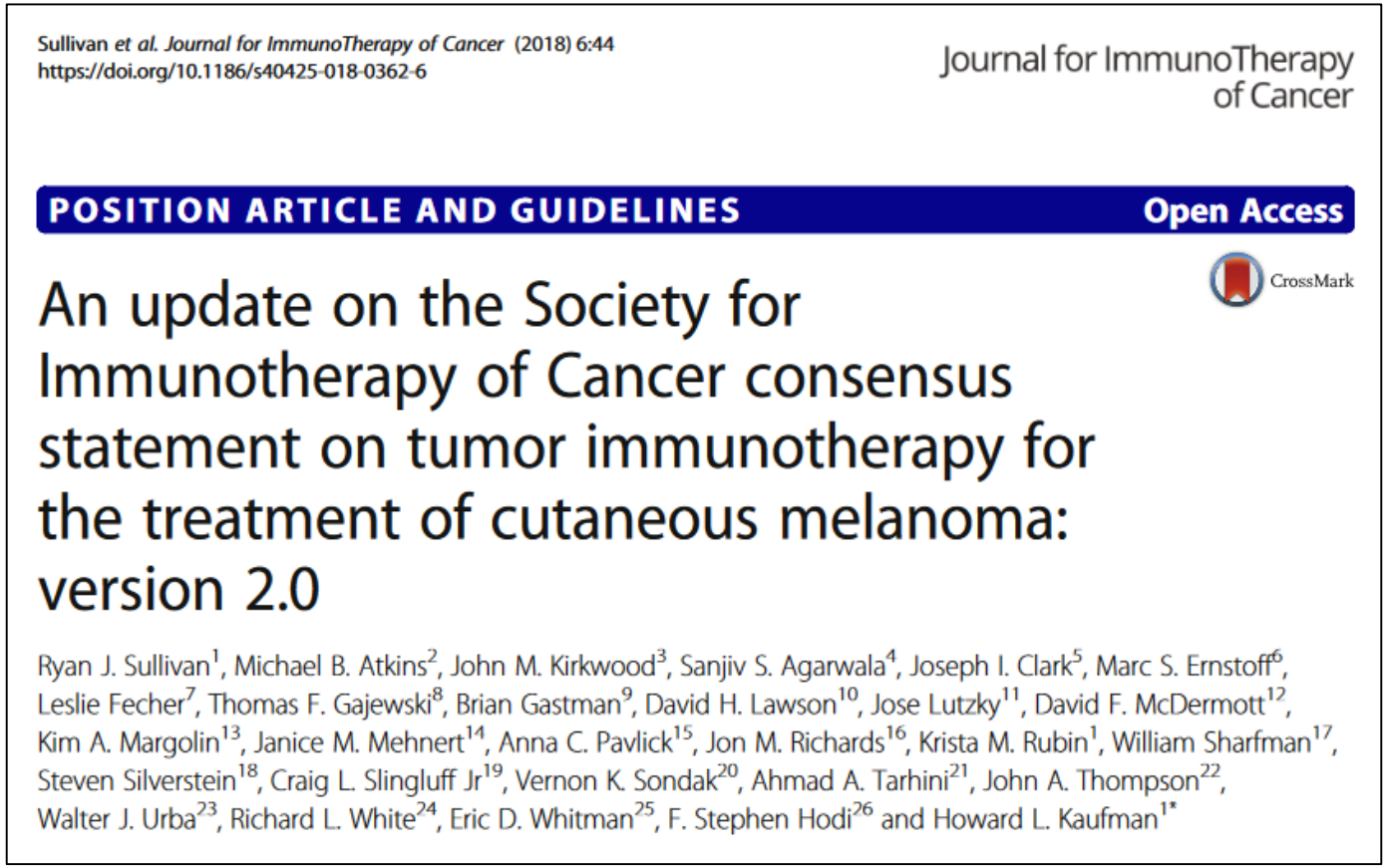


González-Rodríguez E., & Rodríguez-Abreu D. The Oncologist 2016;21:804-816

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
- Immune checkpoint inhibitors (ICI) have completely changed therapeutic landscape and outcomes of metastatic melanoma and many other cancers while its therapy-related adverse events can be serious, even fatal

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

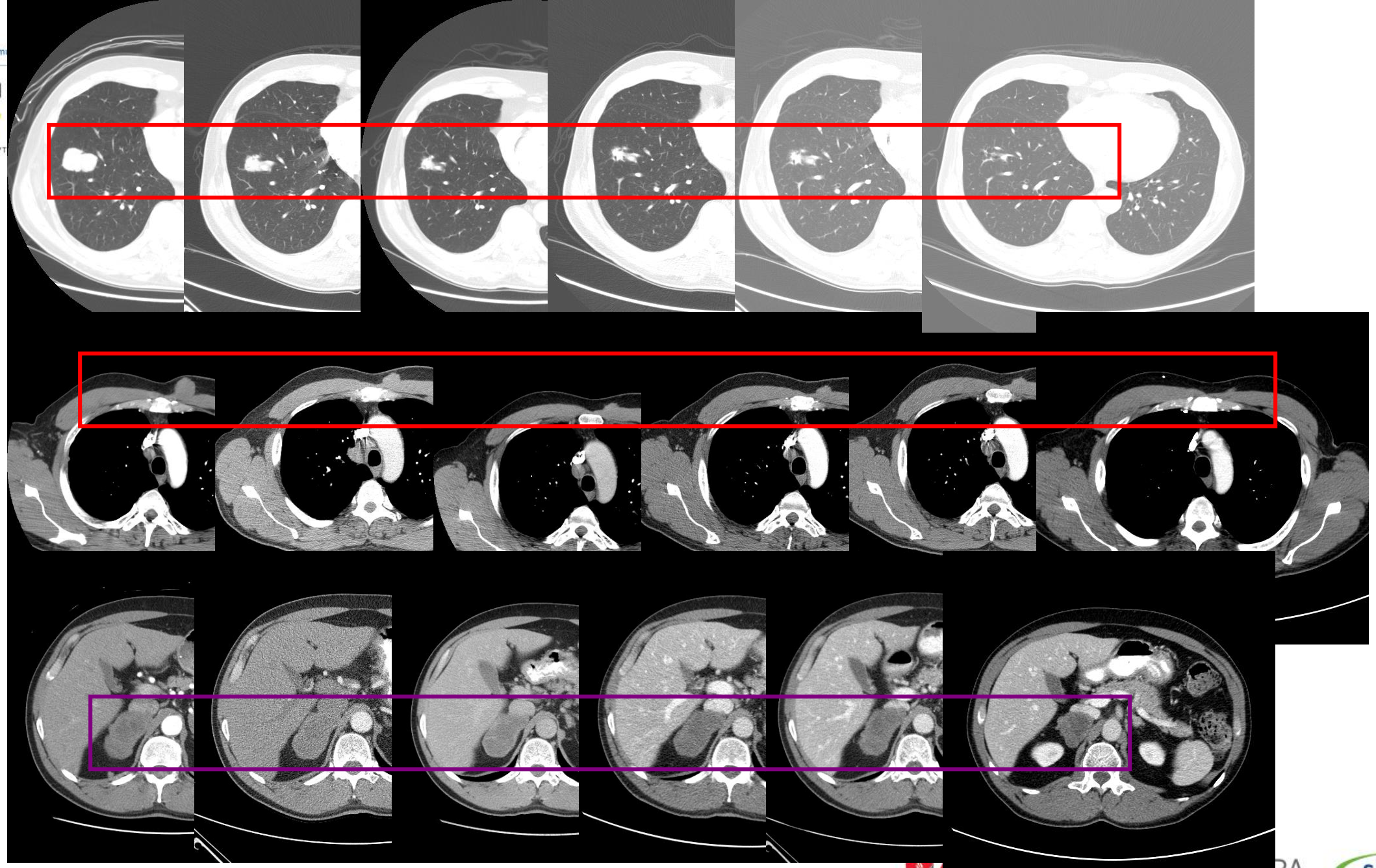
An update on the Society for Immunotherapy of Cancer consensus statement on tumor immunotherapy for the treatment of cutaneous melanoma: version 2.0

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

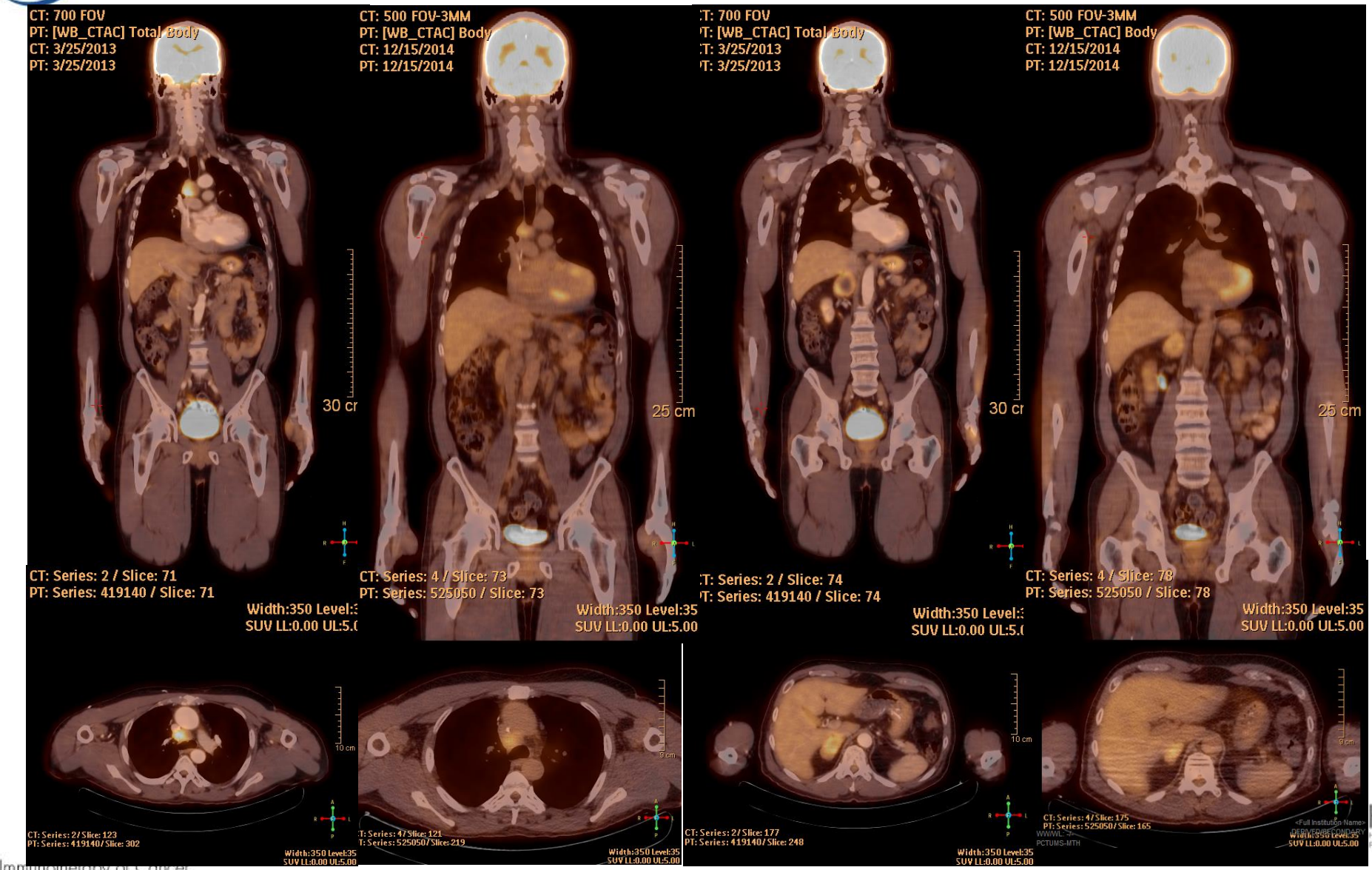
Case-1

- 52 yo male with initial diagnosis of melanoma in his left upper back (2001)
- First recurrent as left axillary mass and lung nodules
- S/P multiple-line chemotherapies, clinical trials including sorafenib, pazopanib and other small molecules
- Week#1 (8-9-2010) Missed week 4 injection due to SBO and IPD admission
- Resumed week 7 and 10 treatment (completed on 10-12-2010) with good tolerance
- No AE reported otherwise
- Most recent follow up 9-23-2013



Baseline Week 12 Week 23 Week 36 Week 48 > Week 152

Persistent PET-CT Activity at 4 Years Post-Ipilimumab Follow-Up

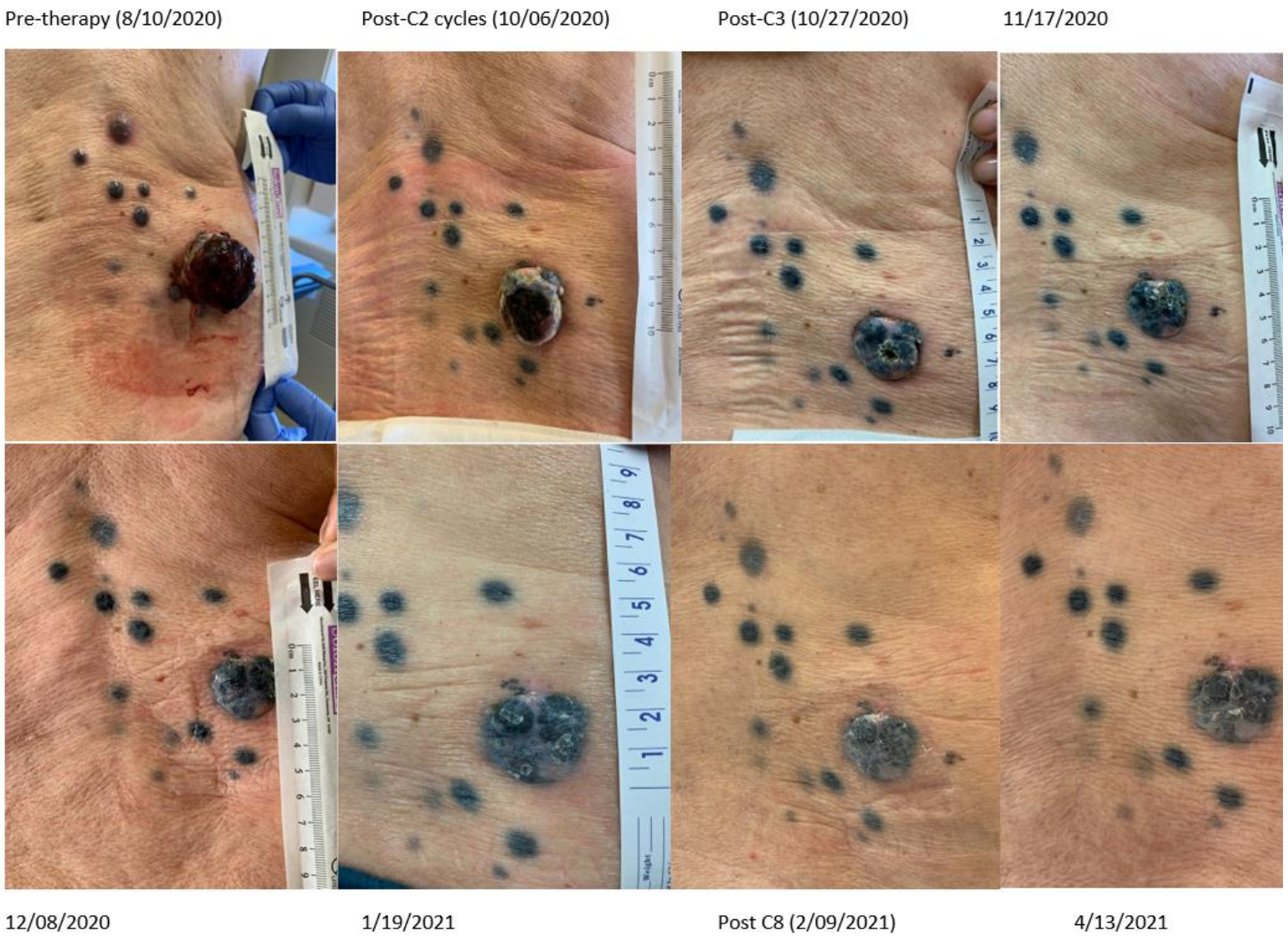


Case-2

- 85 yo white male presented with a progressively enlarged left lower back skin bleeding mass over the past year
- Physical examination multiple satellite melanoma in-transits observed
- Pathology reported malignant melanoma
- Patient lived alone, operated over 300 acres farm
- Patient has been enrolled and received clinical trial treatment (REGN3767)
- Patient has demonstrated clinical tumor regressiojn

Case-2

- Patient reported having nausea/diarrhea after Cycle 8 treatment
- Presented to ED after a syncope
- Remains feeling weak, ambulates requiring a walker for assistance



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ENDOCRINOLOGY								
Cortisol	*10.9 **	*9.8 **	*11.9 **	*12.1 **	*10.1 **	*1.2 **	*0.5 **	*0.6 **

Acknowledgements

- Some figures created using Biorender.com