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

Society for Immunotherapy of Cancer

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Disclosures

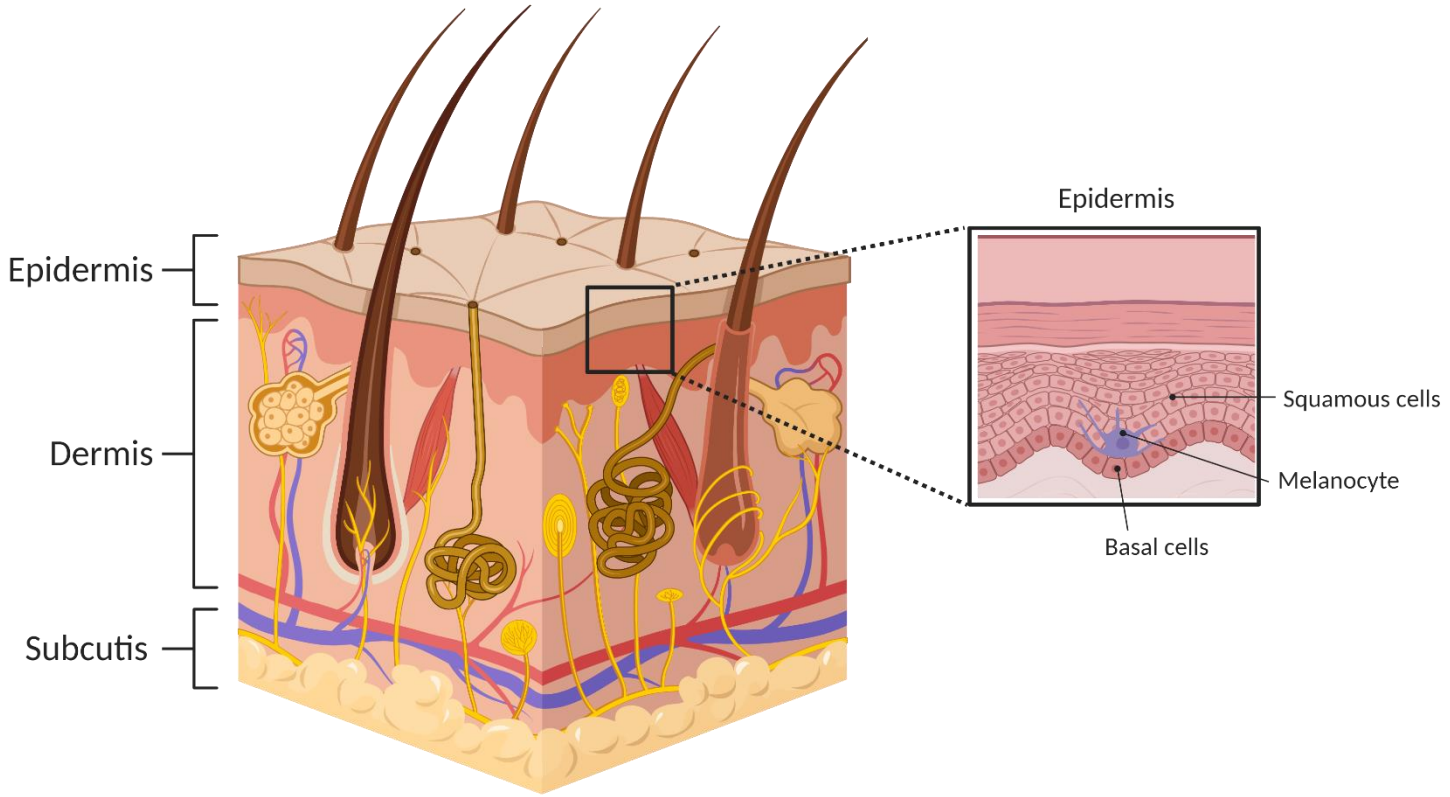
- Consulting Fees: Bristol-Myers Squibb, Regeneron, Genentech, Novartis, Merck, Sapience Therapeutics, and Exicure
- Contracted Research: Exelixis (institutional support)
- I will be discussing non-FDA approved indications during my presentation.

Outline

- Melanoma
  - First-line / Second-line treatment
  - Adjuvant and neoadjuvant settings
- Promising areas of clinical research
- Non-Melanoma Skin Cancers
  - Merkel cell carcinoma
  - Squamous cell carcinoma
  - Basal cell carcinoma

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



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

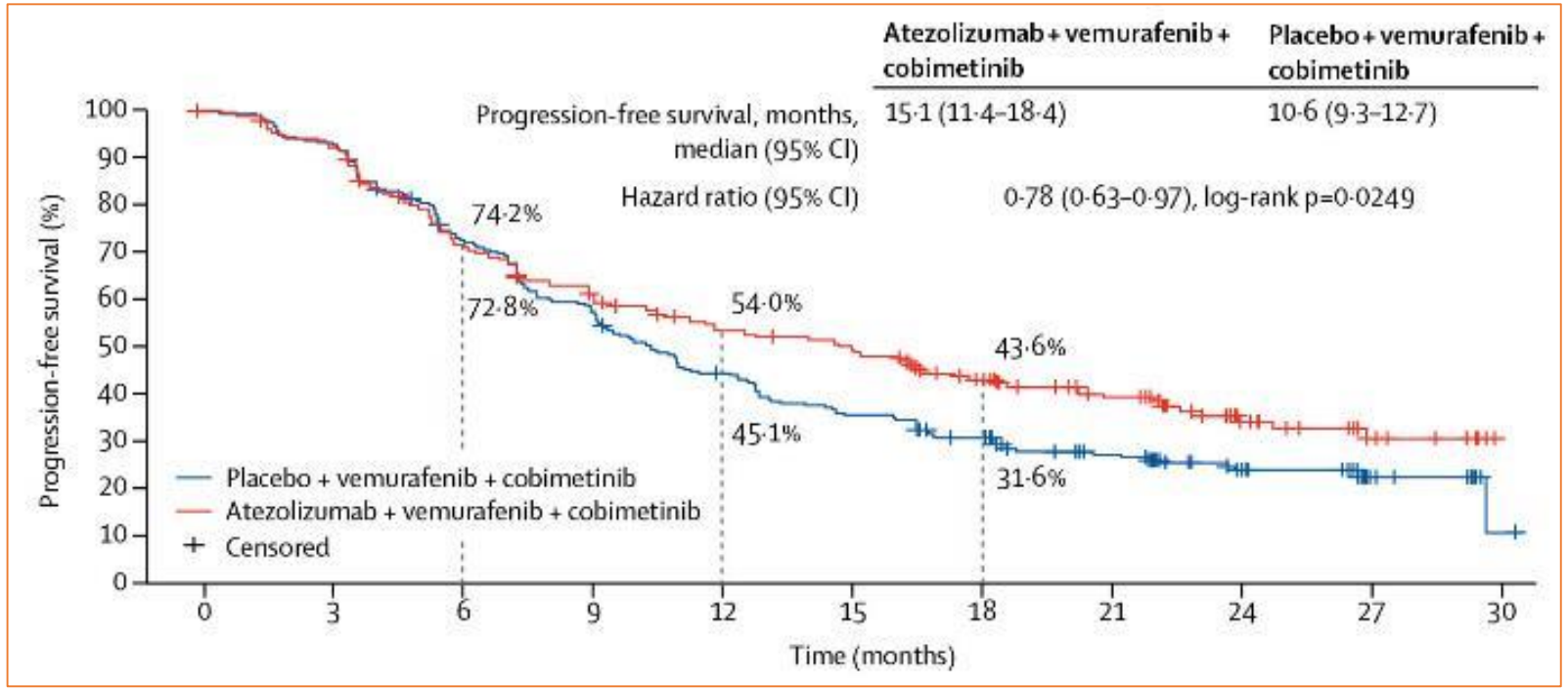
Trials in front-line melanoma

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%

IMspire150: Phase III Study of Atezolizumab vs Placebo + Vemurafenib/Cobimetinib

- 21 day lead in Vem/Cobi alone, then Vem dose reduced (720mg bid) with Atezo (placebo arm continued on full dose Vem)
- ORR 66% A/V/C vs 63% P/V/C
- Grade 3 TRAEs 79% A/V/C vs 73% P/V/C

(Increased CPK, AST/ALT, and amylase, and rash more freq in A/V/C)



Gutzmer R, et al. Lancet Oncol 2020

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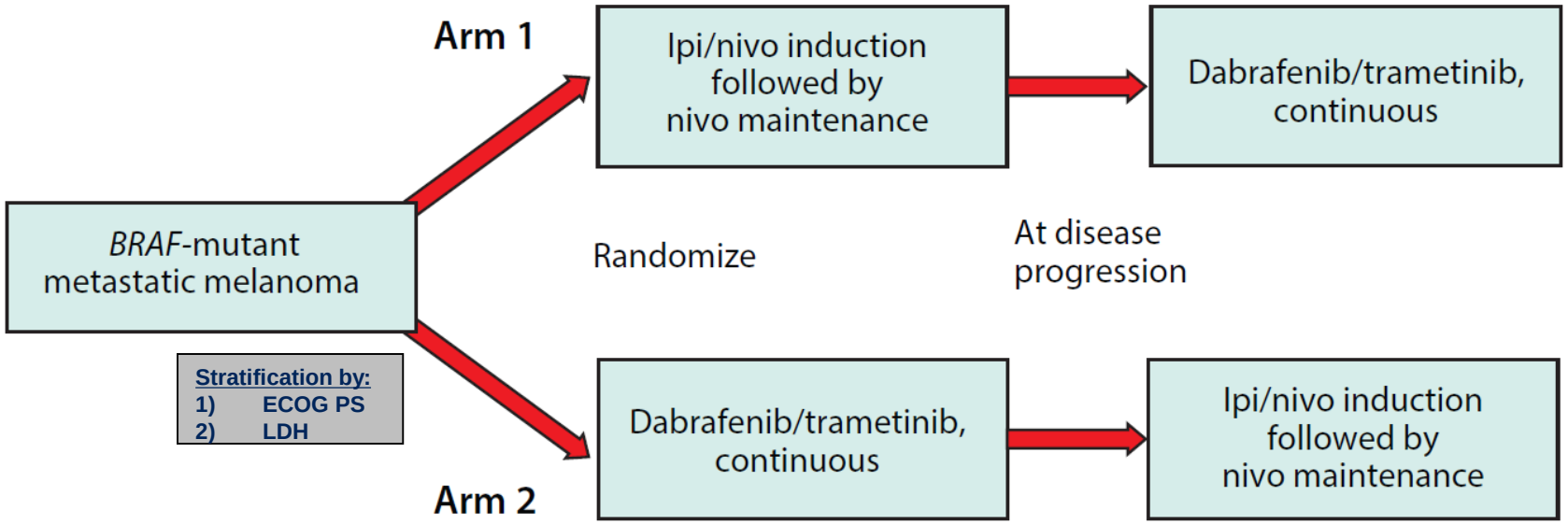
DREAM-Seq (EA6134) Trial

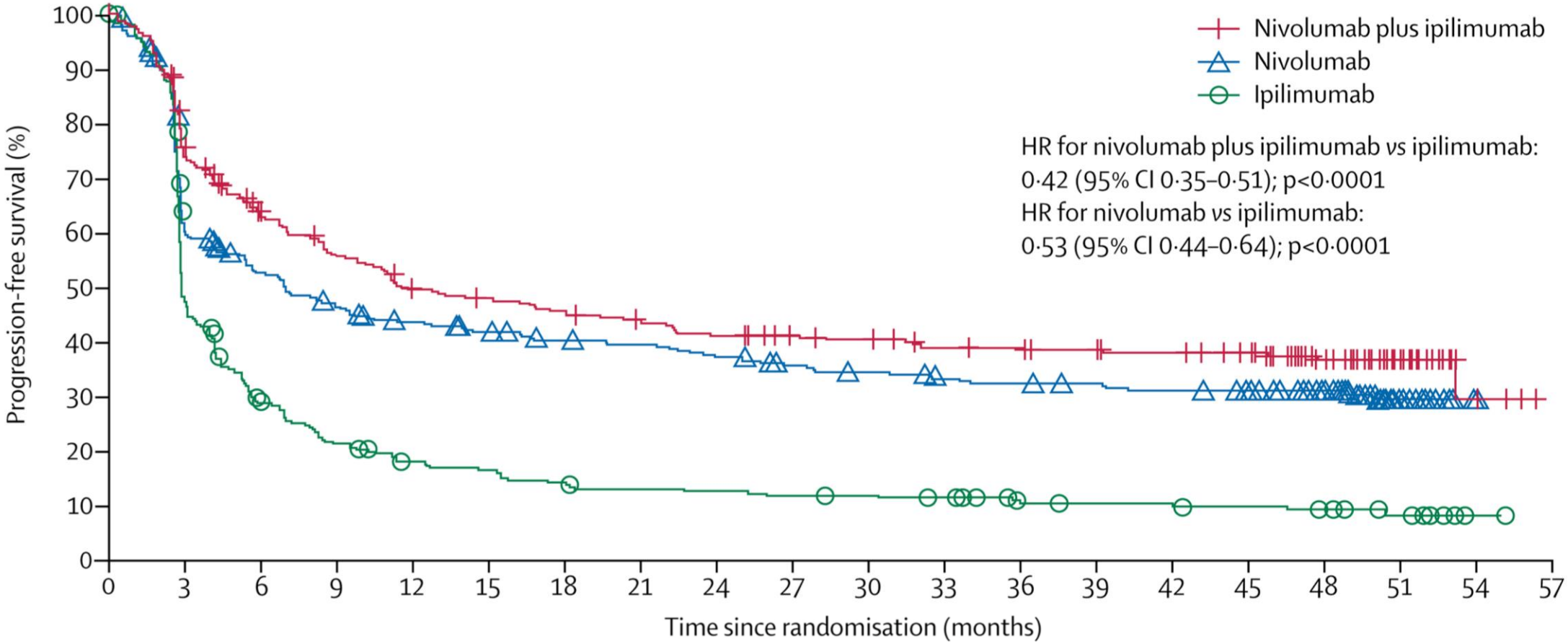


- Total Accrual Goal = 300 subjects
- Primary Endpoint = 2 year overall survival rate (70% vs 50%)
- Baseline tumors (pretreatment) and blood available for biomarker studies

Study Chair:
Michael B. Atkins, MD

Combination Ipilimumab + Nivolumab in Stage III/IV Melanoma

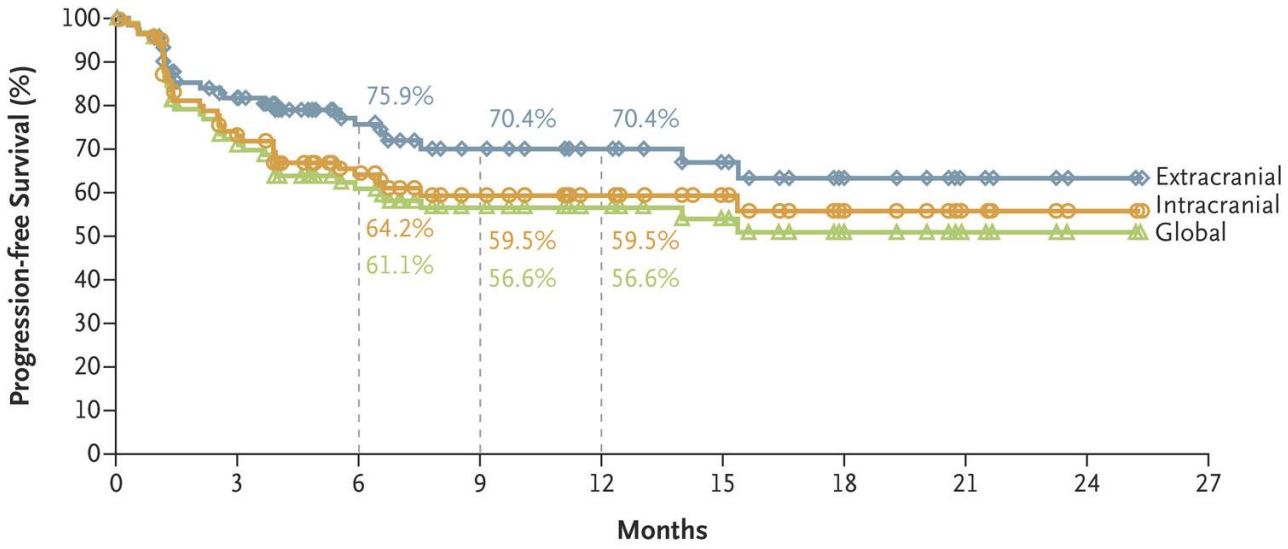
Phase III CheckMate 067 Trial



Hodi, Lancet Oncol 2018.

Combination Ipilimumab + Nivolumab for Patients with Asymptomatic Brain Metastases

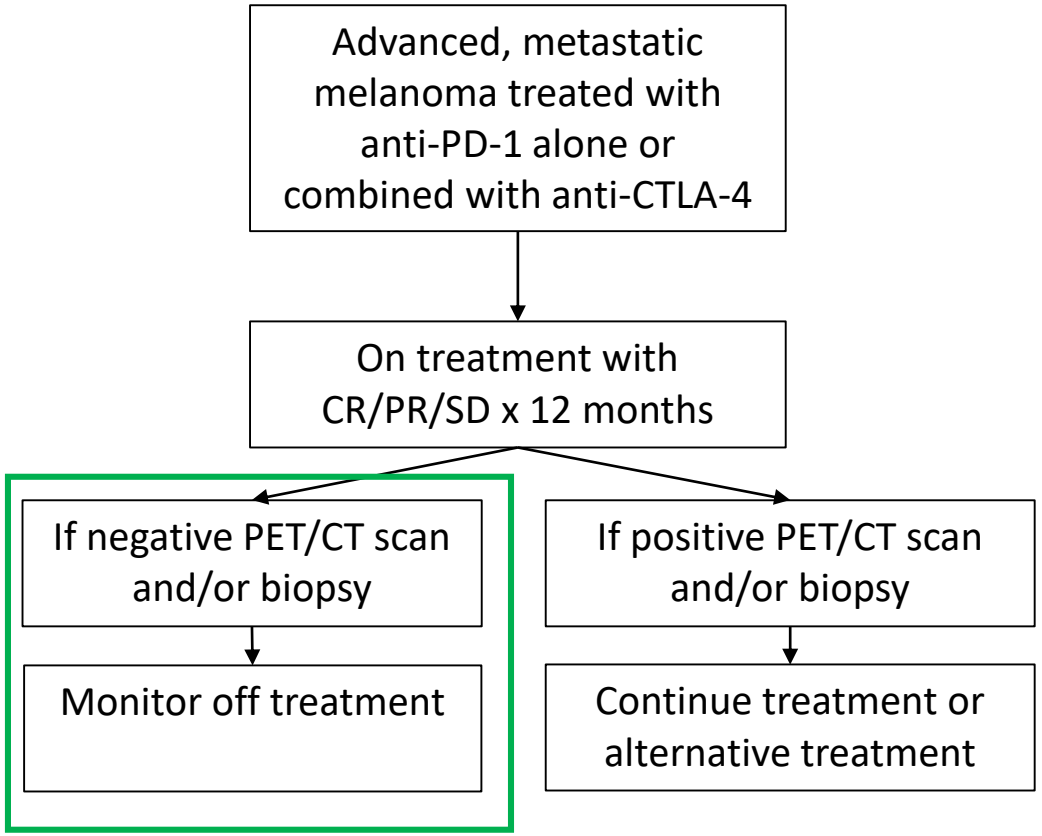
Variable	Intracranial (N=94)	Extracranial (N=94)	Global (N=94)
Best overall response — no. (%)*			
Complete response	24 (26)	7 (7)	8 (9)
Partial response	28 (30)	40 (43)	40 (43)
Stable disease for ≥6 mo	2 (2)	6 (6)	5 (5)
Progressive disease	31 (33)	28 (30)	33 (35)
Could not be evaluated†	9 (10)	13 (14)	8 (9)
Objective response‡			
No. of patients	52	47	48
Percent of patients (95% CI)	55 (45–66)	50 (40–60)	51 (40–62)
Clinical benefit§			
No. of patients	54	53	53
Percent of patients (95% CI)	57 (47–68)	56 (46–67)	56 (46–67)

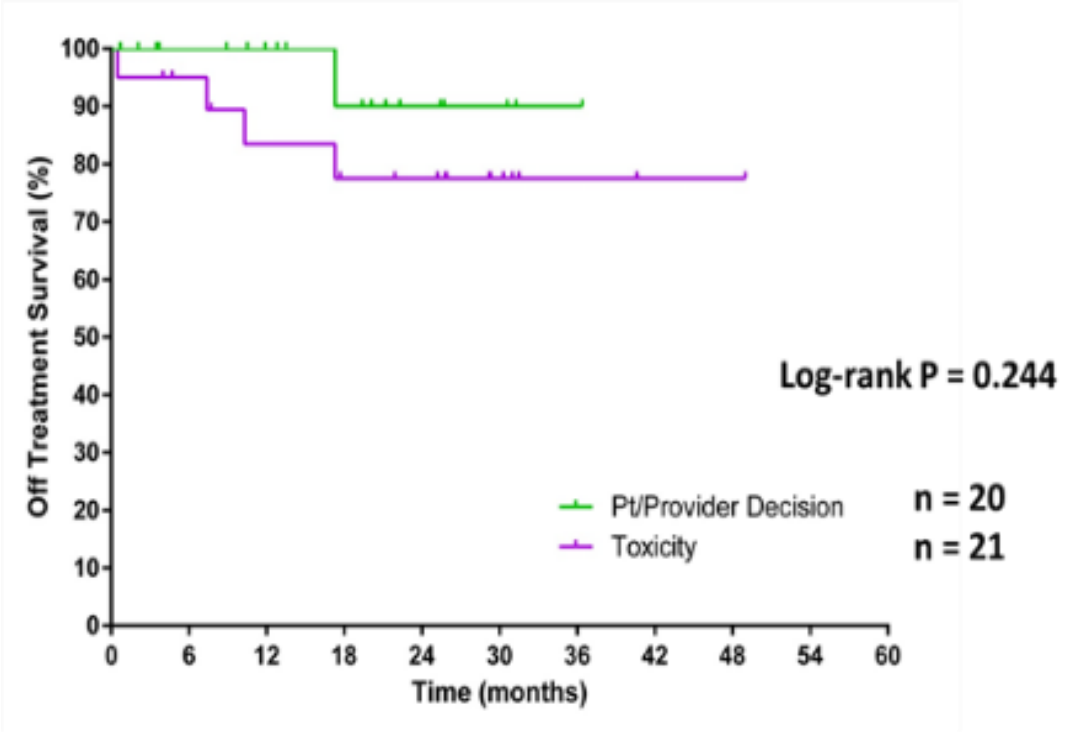


Tawbi, NEJM 2018.

- When can you safely discontinue anti-PD-1 therapy in a responding patient?
- Is there a reliable biomarker for safe discontinuation of therapy?

Off Treatment Survival after CR, negative PET/CT, or negative tumor biopsy

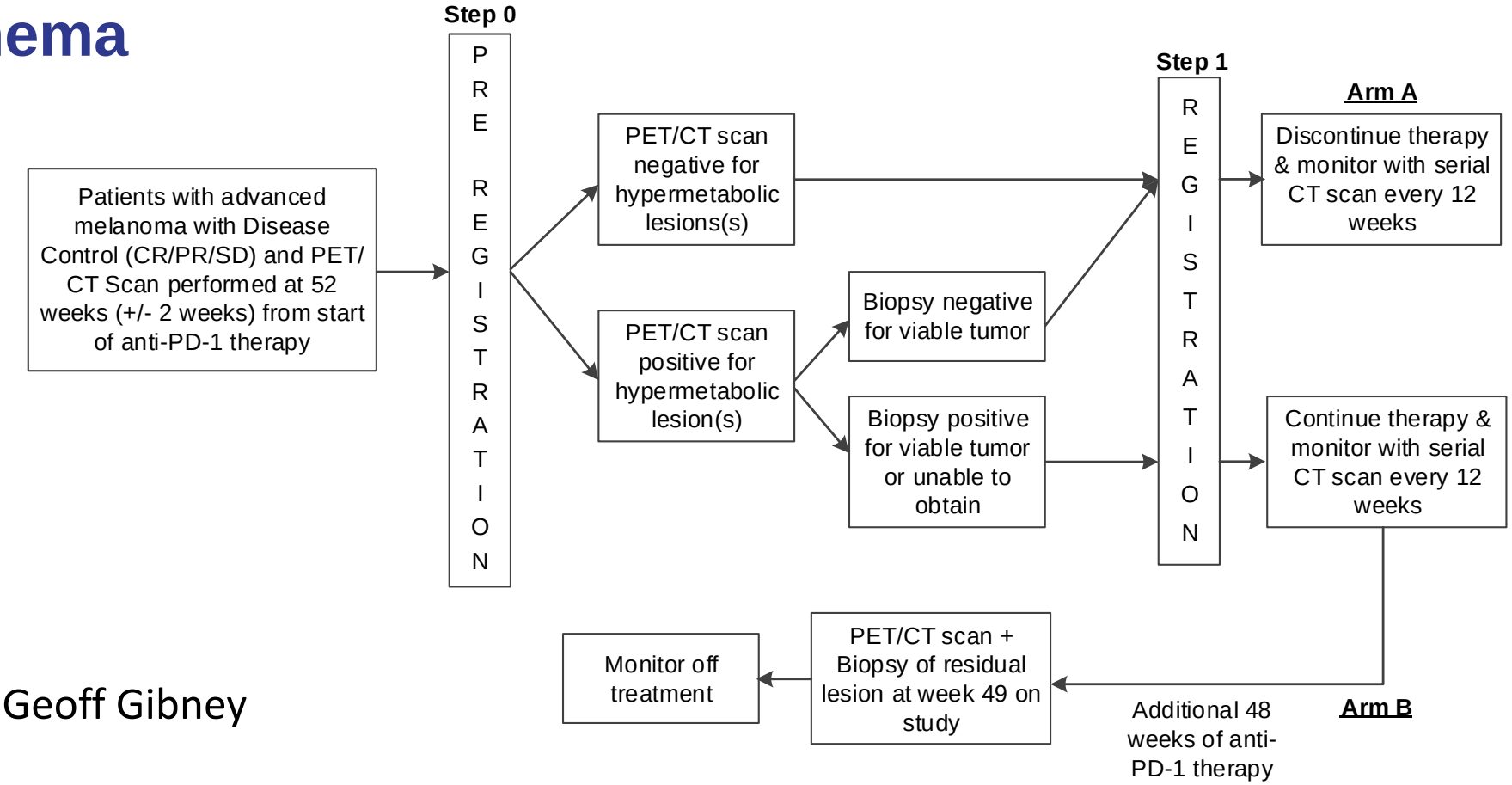




Presented by Christiansen S, et al, ASCO 2018, abstract 9554

A Phase II Study of Biomarker Driven Early Discontinuation of Anti-PD-1 Therapy in Patients with Advanced Melanoma (PET-Stop)

Study Schema



Study Chair: Geoff Gibney

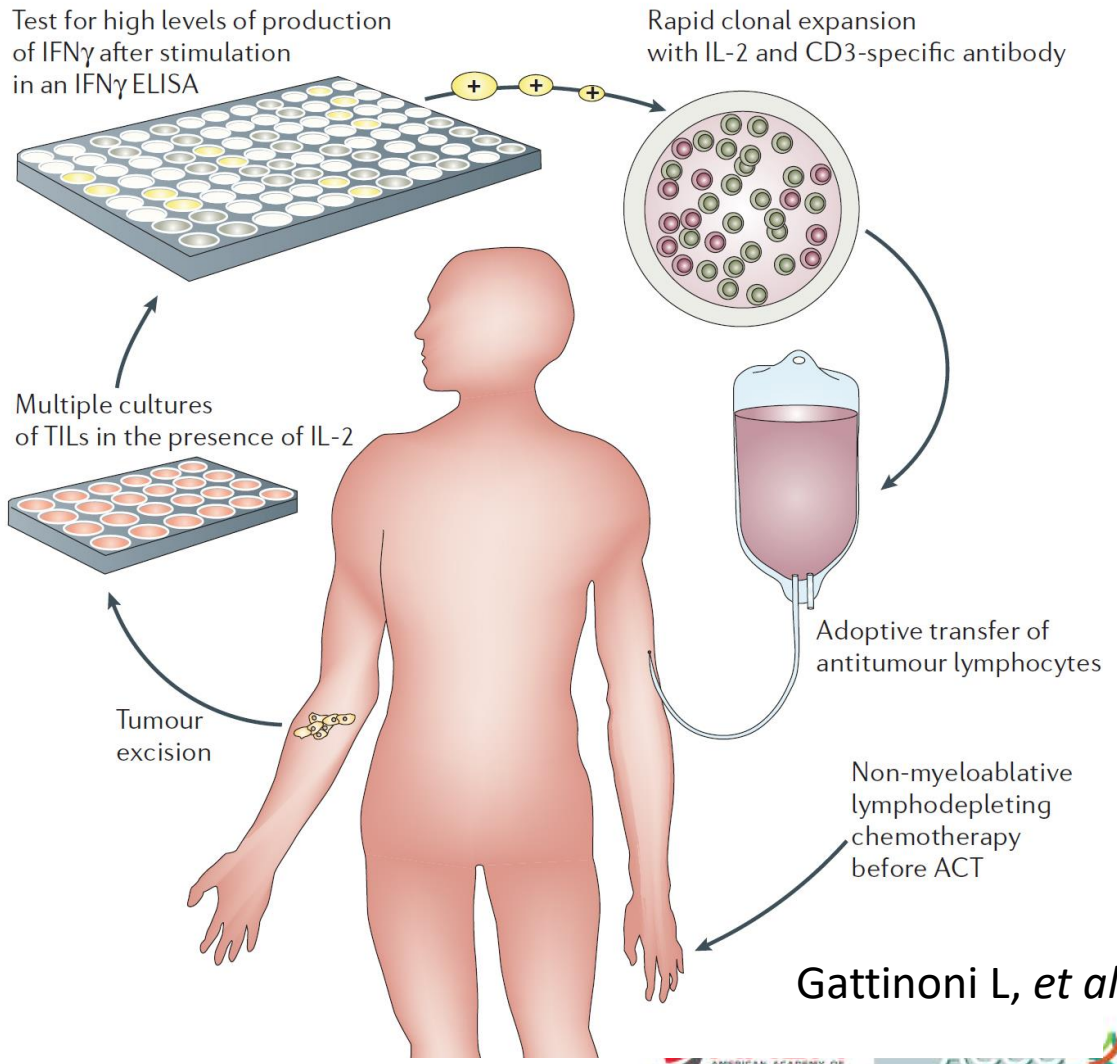
https://www.clinicaltrials.gov/ct2/show/NCT04462406

Updates on Clinical trials for Advanced Melanoma

- MASTERKEY-265/KEYNOTE-034: Phase III study of TVEC plus pembro reportedly stopped for futility after an interim analysis by the Data Monitoring Committee.
- Checkmate-047 (CA224-047): Phase II/III study of relatlimab plus nivo vs nivo alone met its primary endpoint of progression-free survival.
- Iovance C-144-01: Phase II study of autologous TIL therapy (lifileucil) demonstrated meaningful efficacy in PD-1 refractory disease.

Adoptive Cell Therapy (TIL) Overcomes Immune Suppressive TME

- TIL are expanded ex-vivo
- TIL selected for melanoma recognition
- Lymphodepletion reduces suppressive immune cell population



Gattinoni L, *et al.*, Nat Rev, 2006

C-144-01 Cohort 2 Efficacy: Best Overall Response

81% (50/62) of patients had a reduction in tumor burden

ORR = 36% (3% CR)

Three subjects had no post TIL disease assessment due to early death, and one due to start of new anti-cancer therapy

Iovance C-144-01 Cohort 2 Safety:

Treatment Emergent Adverse Events (≥ 30%)

PREFERRED TERM	Cohort 2 (N=66)		
	Any Grade, n (%)	Grade 3/4, n (%)	Grade 5, n (%)
Number of patients reporting at least one Treatment-Emergent AE	66 (100)	64 (97.0)	2 (3.0)*
Thrombocytopenia	59 (89.4)	54 (81.8)	0
Chills	53 (80.3)	4 (6.1)	0
Anemia	45 (68.2)	37 (56.1)	0
Pyrexia	39 (59.1)	11 (16.7)	0
Neutropenia	37 (56.1)	26 (39.4)	0
Febrile neutropenia	36 (54.5)	36 (54.5)	0
Hypophosphatemia	30 (45.5)	23 (34.8)	0
Leukopenia	28 (42.4)	23 (34.8)	0
Fatigue	26 (39.4)	1 (1.5)	0
Hypotension	24 (36.4)	7 (10.6)	0
Lymphopenia	23 (34.8)	21 (31.8)	0
Tachycardia	23 (34.8)	1 (1.5)	0

* One death was due to intra-abdominal hemorrhage considered possibly related to TIL and one was due to acute respiratory failure assessed as not related to TIL per investigator assessment.
Patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term.
Treatment-Emergent Adverse Events refer to all AEs starting on or after the first dose date of TIL up to 30 days.

PRESENTED BY: Amod Sarnaik, MD
H. Lee Moffitt Cancer Center, Tampa, FL, USA

Presented By Amod Sarnaik at TBD

Adjuvant treatment options for melanoma

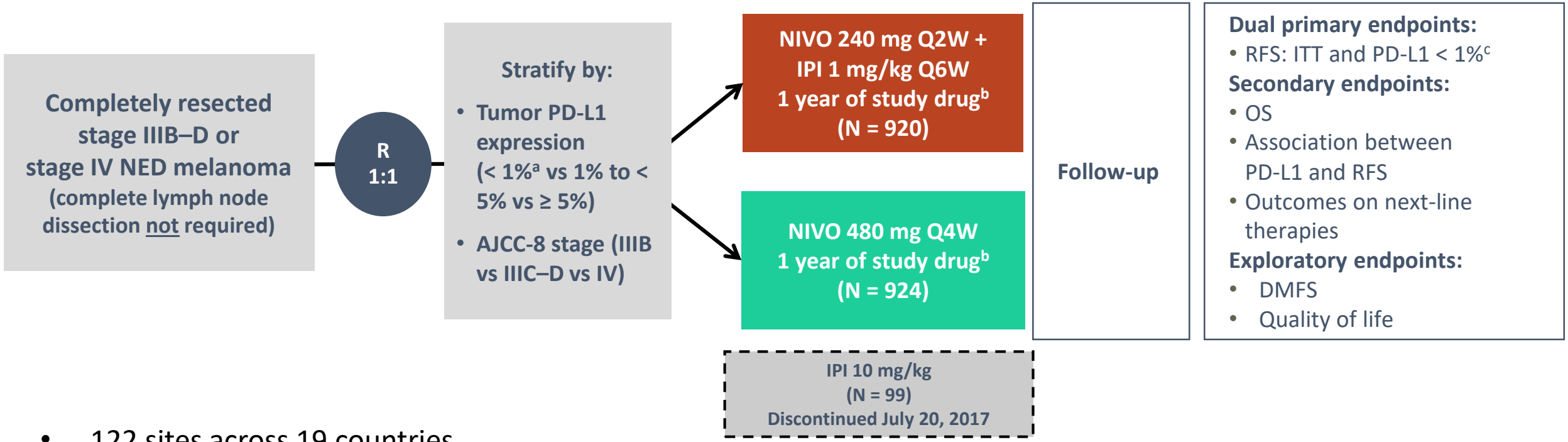
Drug	Indication	Dose
Dabrafenib + trametinib[+]	Adjuvant BRAF+ melanoma with lymph node involvement following complete resection	Dabrafenib 150 mg twice daily + trametinib 2 mg daily
High-dose interferon alfa-2b*	Adjuvant – high risk for systemic recurrence	Induction: 20m IU/m^2 IV 5x/wk for 4 wks Maintenance: 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	

CheckMate 915 study design



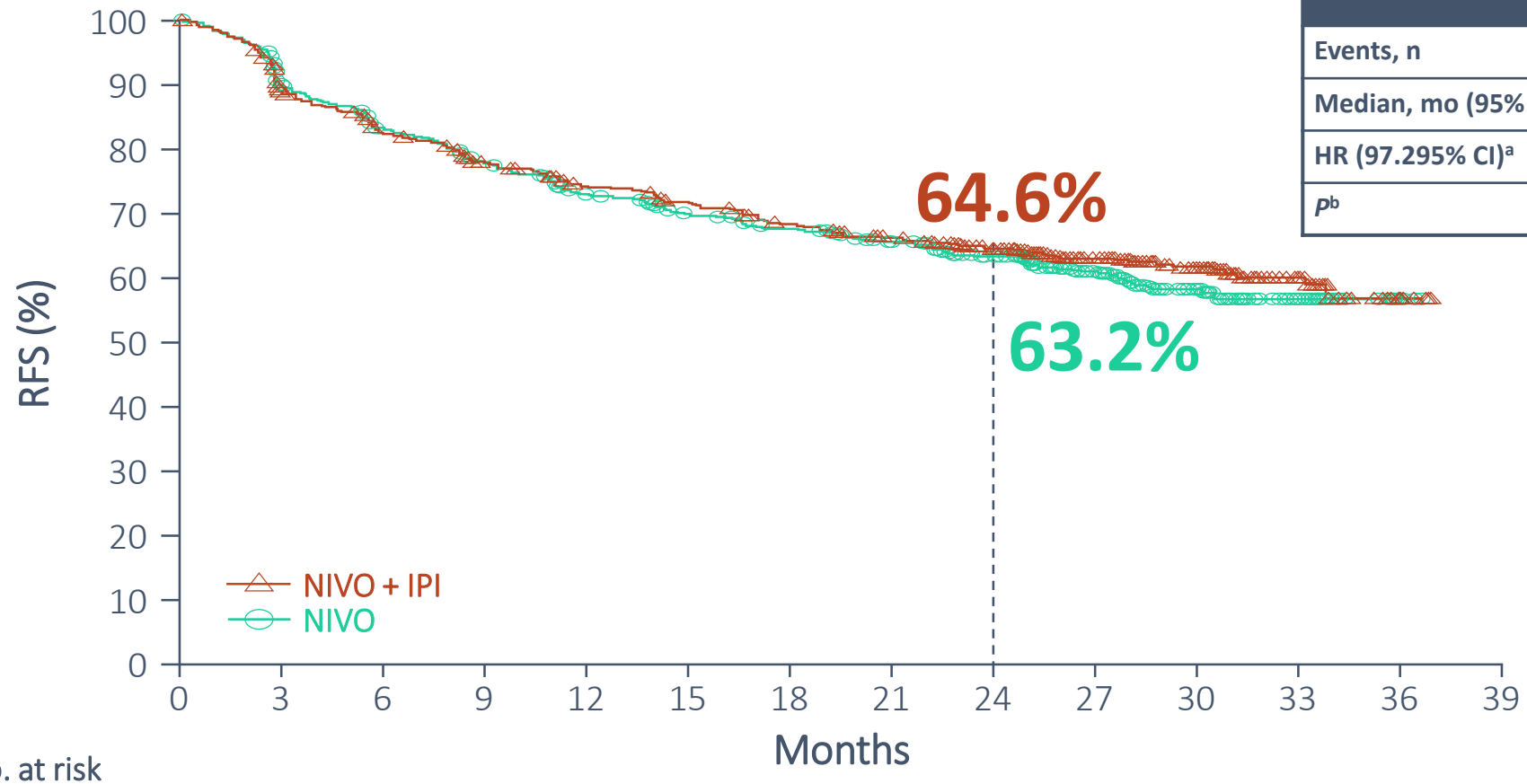
- 122 sites across 19 countries
- Database lock Sept 8, 2020
- Minimum follow-up of approximately 24 months (median 28 months)

Presented by Long G, et al, AACR, 2021

[a]Or indeterminate; [b]Until recurrence, unacceptable toxicity, or 1 year of treatment; [c]In November 2019, the data monitoring committee indicated that the dual primary endpoint of RFS in patients with tumor PD-L1 < 1% was not met; the study remained blinded until the ITT endpoint was evaluable. AJCC, American Joint Committee on Cancer; DMFS, distant metastasis-free survival; NED, no evidence of disease; PD-L1, programmed death-ligand 1.

Dual primary endpoint: RFS in ITT population

	NIVO + IPI (n = 920)	NIVO (n = 924)
Events, n	327	347
Median, mo (95% CI)	NR	NR
HR (97.295% CI)[a]	0.92 (0.77–1.09)	
P[b]	0.269	



No. at risk

NIVO + IPI	920	783	720	669	630	605	572	547	505	371	193	74	9	0
NIVO	924	793	721	669	615	578	554	525	476	362	181	69	5	0

[a]Stratified log-rank test. NR, not yet reached.

Adjuvant treatment options

	Pros	Cons
Dabrafenib plus Trametinib	• Reduces relapse by 53% • AEs are self-limited • Improves OS by 43%*	• Higher discontinuation rate due to AEs • Some AEs may be frustrating
Nivolumab or Pembrolizumab	• Reduces relapse by 43% • Only 10-15% of patients have serious treatment related AEs	• No OS advantage so far • Some AEs can be permanent such as hypothyroidism and diabetes

AEs = adverse events
OS = overall survival
*Not statistically significant as predefined

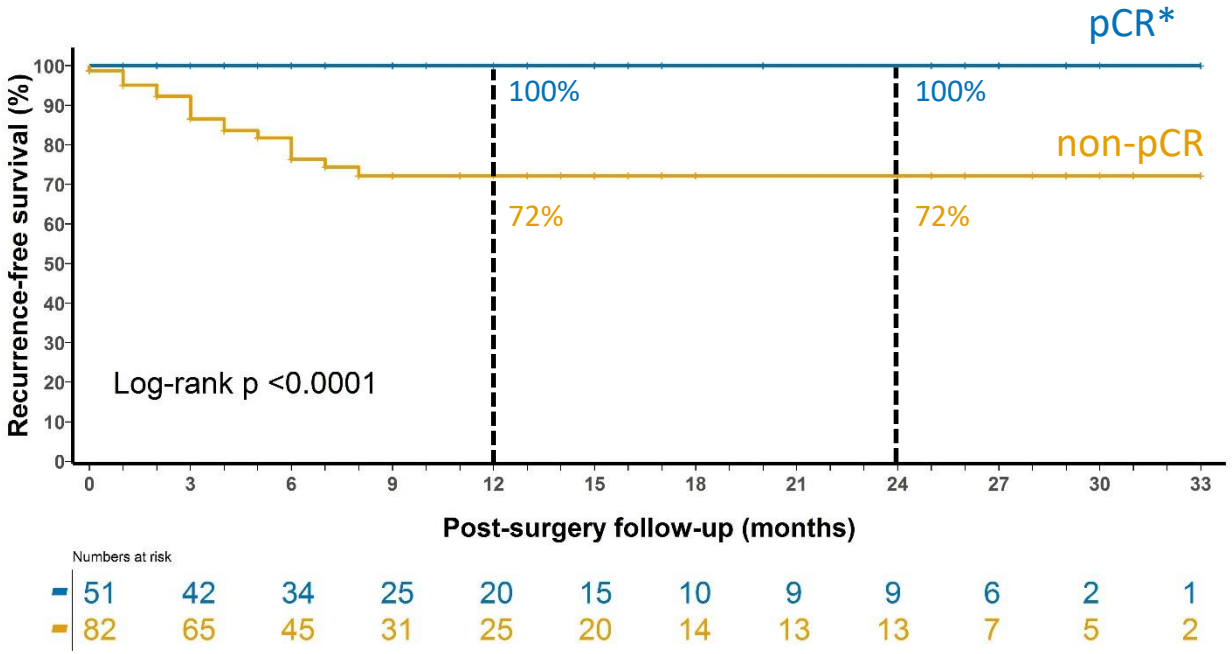
In development: Neoadjuvant immunotherapy in advanced melanoma

Trial	Regimen	N	pCR (%)	med RFS (mo)	med FU (mo)
Amaria Lancet Oncol 2018	*Dab/Tram*	21	58	19.7	18.6
Long Lancet Oncol 2019	*Dab/Tram*	35	49	23.0	27.0
Blank Nat Med 2018	Ipi+nivo	10	33	NR	32
Amaria Nat Med 2018	Nivo Ipi+nivo	12 11	25 45	NR NR	20
Huang Nat Med 2019	Pembro	30	19	NR	18
Rozeman Lancet Oncol 2019	Ipi+nivo	86	57	NR	8.3

Menzies ASCO Annual Meeting 2019.

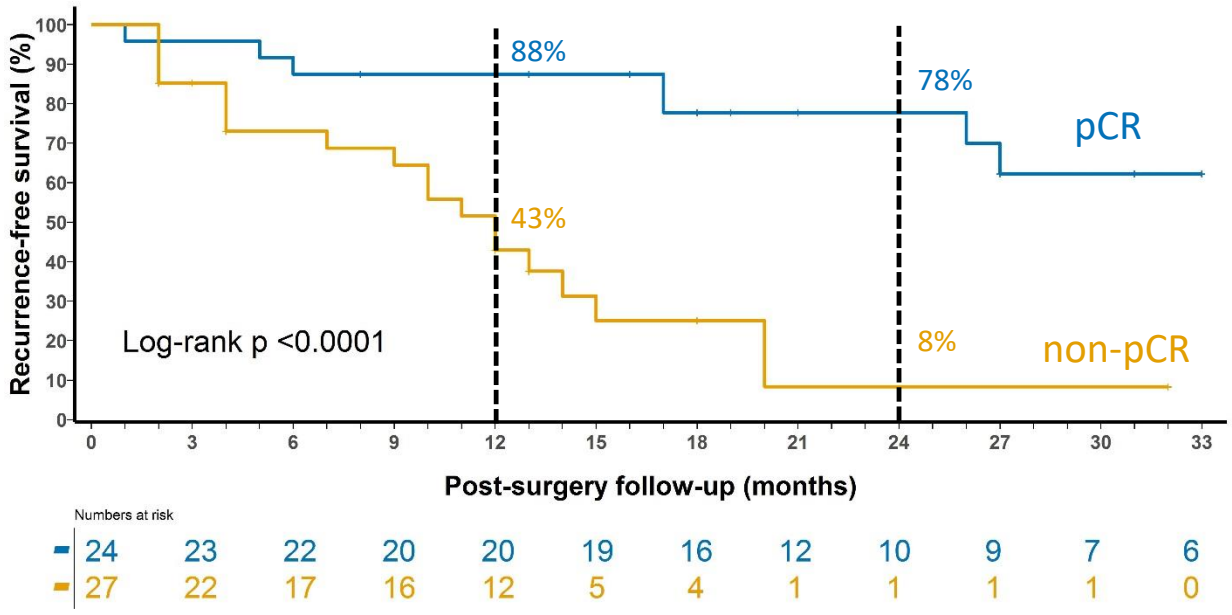
RFS by pathological response and drug

Immunotherapy



Med f/u 10 mo

Targeted Therapy

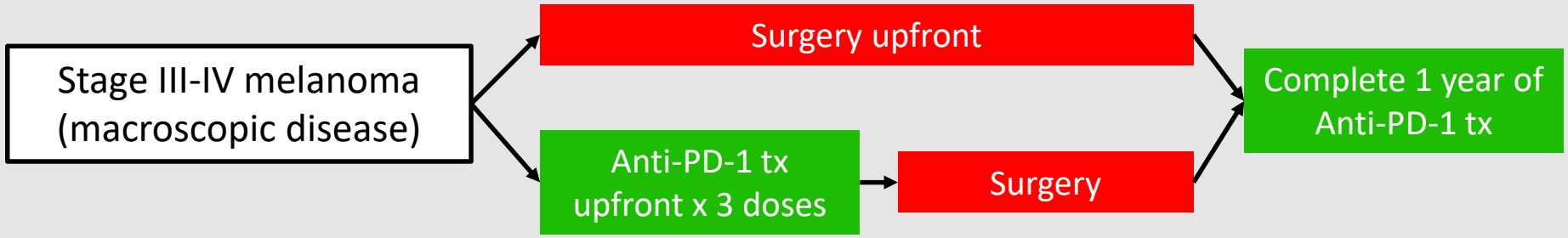


Med f/u 22 mo

Menzies ASCO Annual Meeting 2019.

Approach to management of stage III melanoma patient with macroscopic disease (or limited stage IV disease)

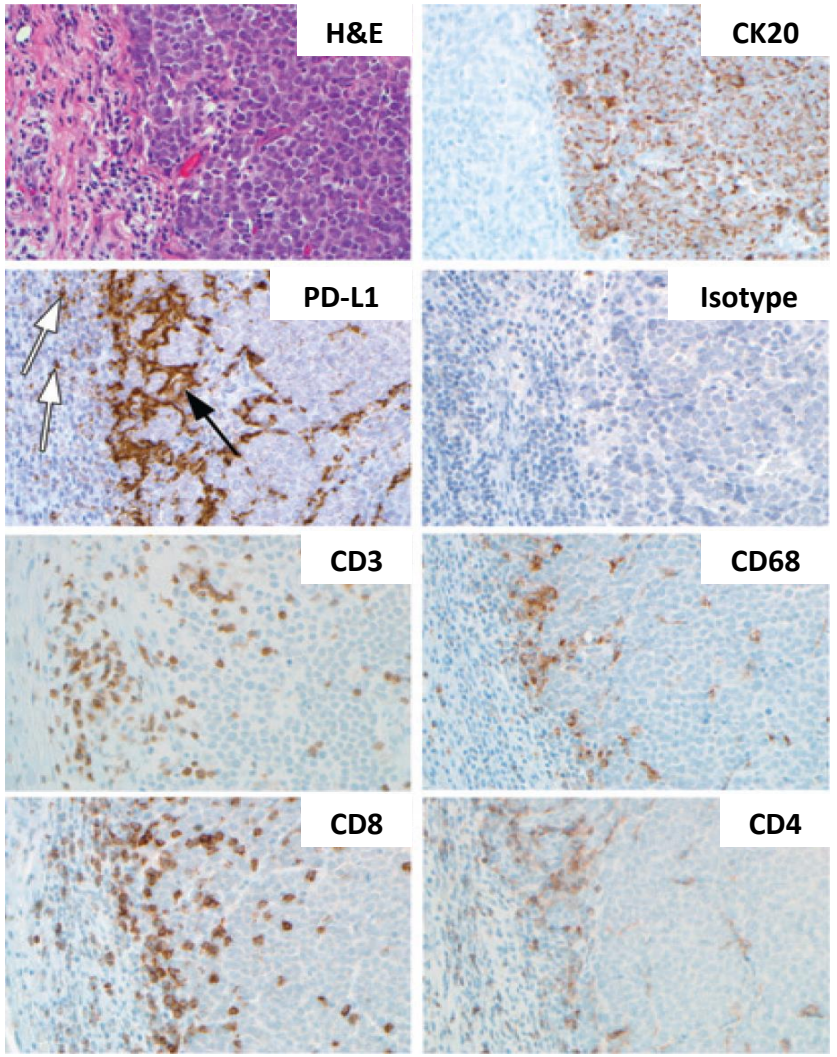
SWOG 1801 Study – Currently Enrolling at Georgetown and other centers



Primary endpoint: Event Free Survival

Immunotherapy in Non-Melanoma Skin Cancers

- 49% of patients with PD-L1+ tumors (≥5% cutoff)
- 100% of PD-L1+ tumors had concurrent TIL (compared to 47% of PD-L1- tumors)
- High TMB and MCPyV subtypes both immunogenic



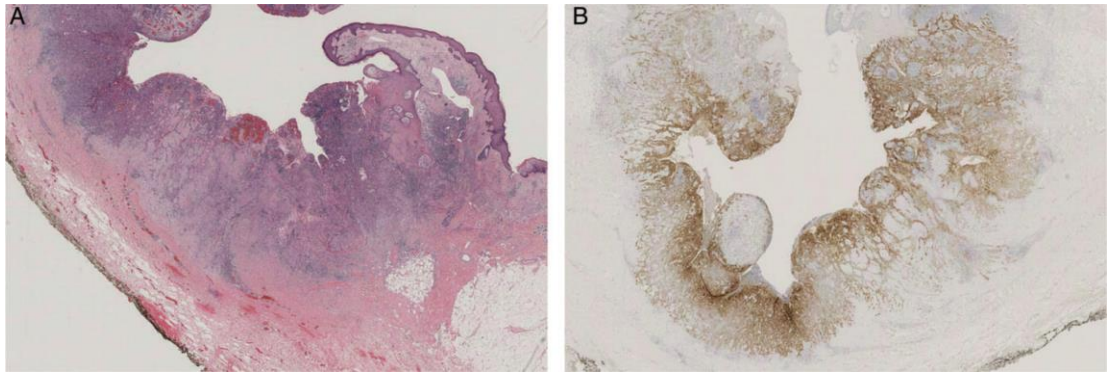
Lipson EJ et al. *Cancer Immunol Res*. 2013.

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

Immunotherapy in Non-Melanoma Skin Cancers

cutSCC

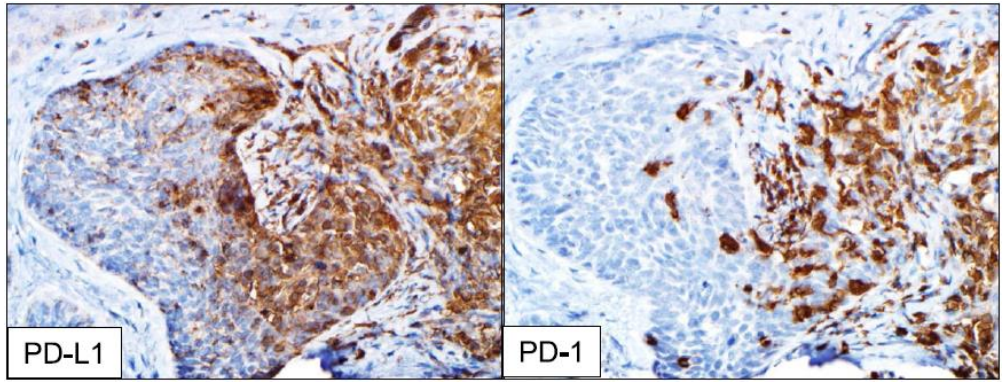
- Low risk: 20% (4/20) PD-L1+
- High risk: 70% (14/20) PD-L1+
- Mets: 100% (5/5) PD-L1+
- Lymphocytes at tumor border



Slater NA, et al, J Cut Pathol, 2016

BCC

- 22% (9/40) PD-L1+
- 100% (40/40) TIL+ or lymphocytes in the extratumoral stroma.



Lipson EJ, et al, JITC, 2017

Approved checkpoint inhibitors in Non-Melanoma Skin Cancers

	Drug	Indication	Dose
MCC	Avelumab*	Patients >12 yr with metastatic **Merkel cell carcinoma**	800 mg Q2W
MCC	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
cutSCC	Cemiplimab	Metastatic cutaneous squamous cell carcinoma, not candidate for curative therapies	350 mg Q3W
cutSCC	Pembrolizumab	Metastatic cutaneous squamous cell carcinoma	200 mg Q3W or 400 mg Q6W
BCC	Cemiplimab	Locally advanced BCC previously treated with hedgehog pathway inhibitor or for whom HHI is not appropriate*	350 mg Q3W

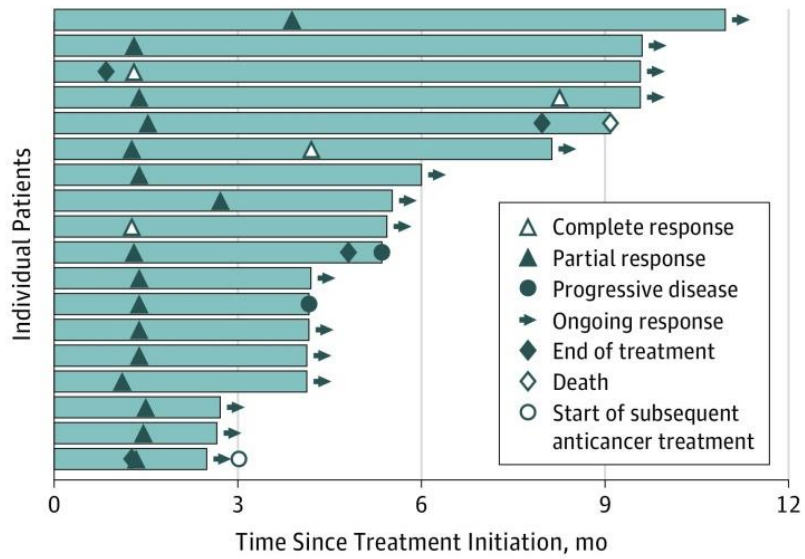
**Requires premedication with an antihistamine and acetaminophen prior to first four infusions*

***Accelerated approval for metastatic BCC*

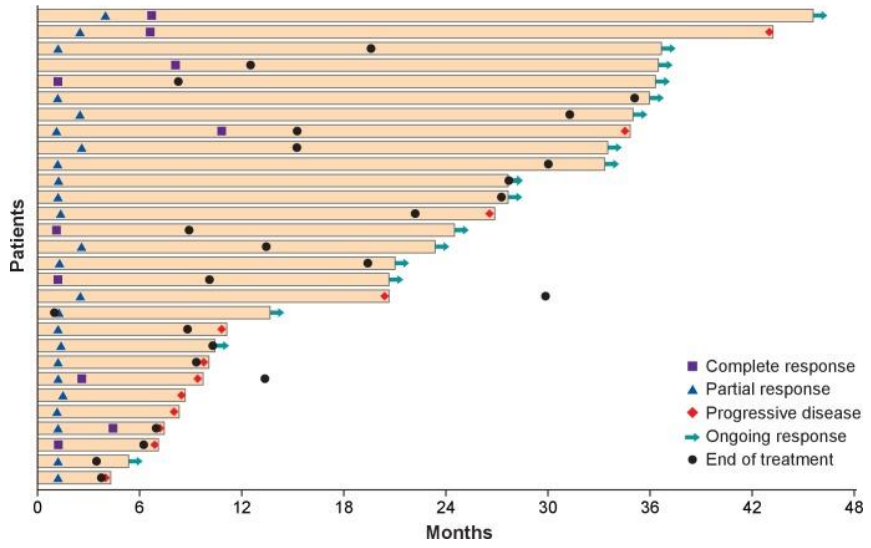
Avelumab in Merkel cell carcinoma

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



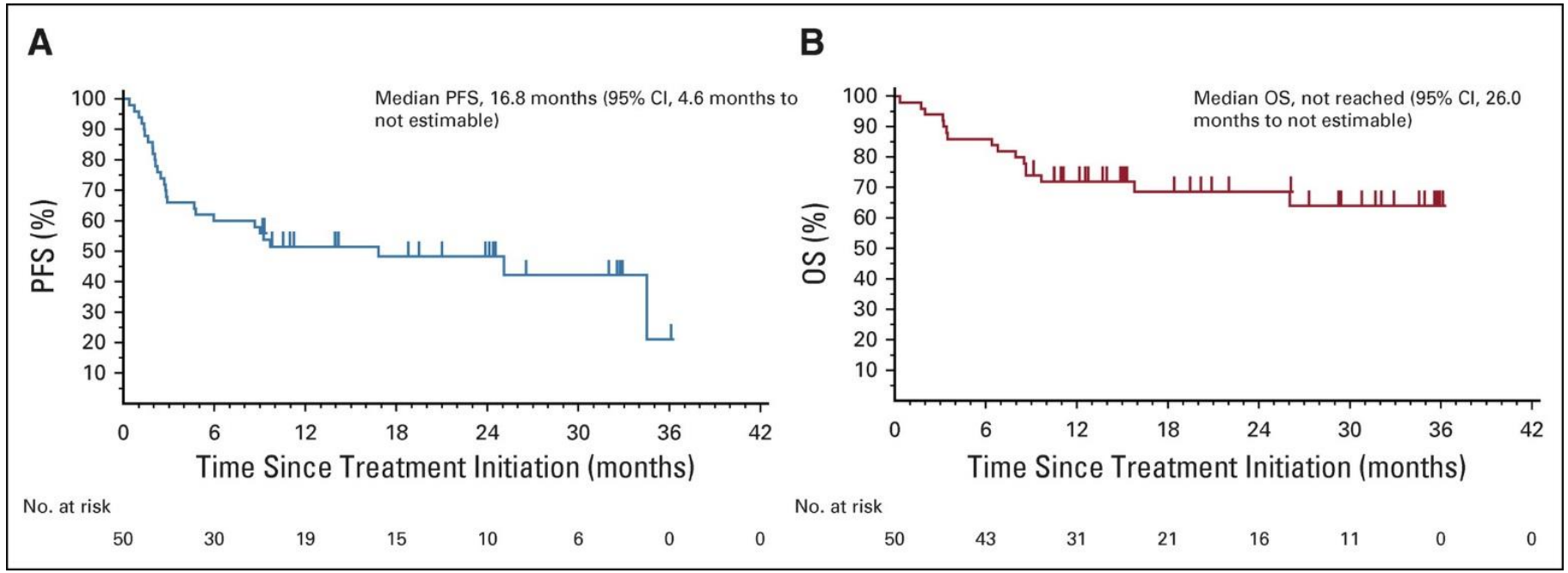
Second+ line



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

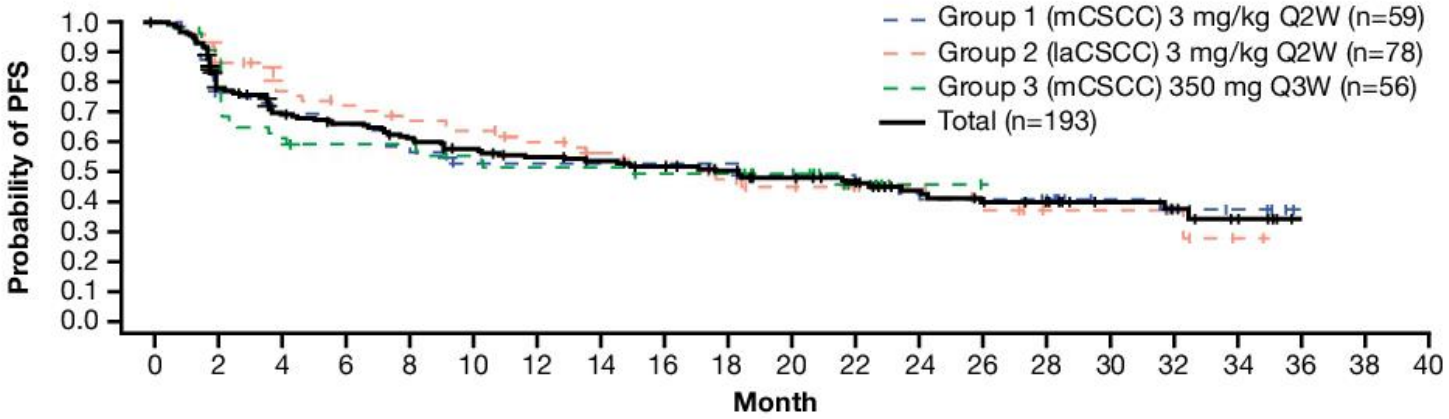


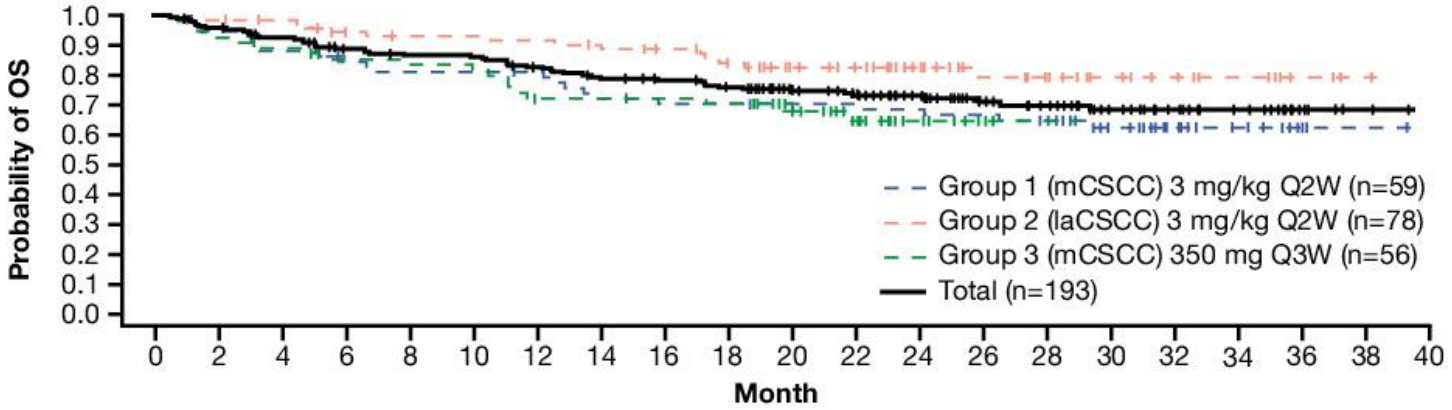
Also an ongoing trial of adjuvant pembrolizumab for Merkel cell carcinoma (NCT03712605).

Nghiem, J Clin Oncol 2019.

Long-term Follow up on the phase 2 study of Cemiplimab advanced cutSCC

	Overall (n=193)
ORR	46%
CR	16%
PR	30%
SD	24%
Median DOR	NR
Ongoing response 12months	88%
Ongoing response 24months	69%



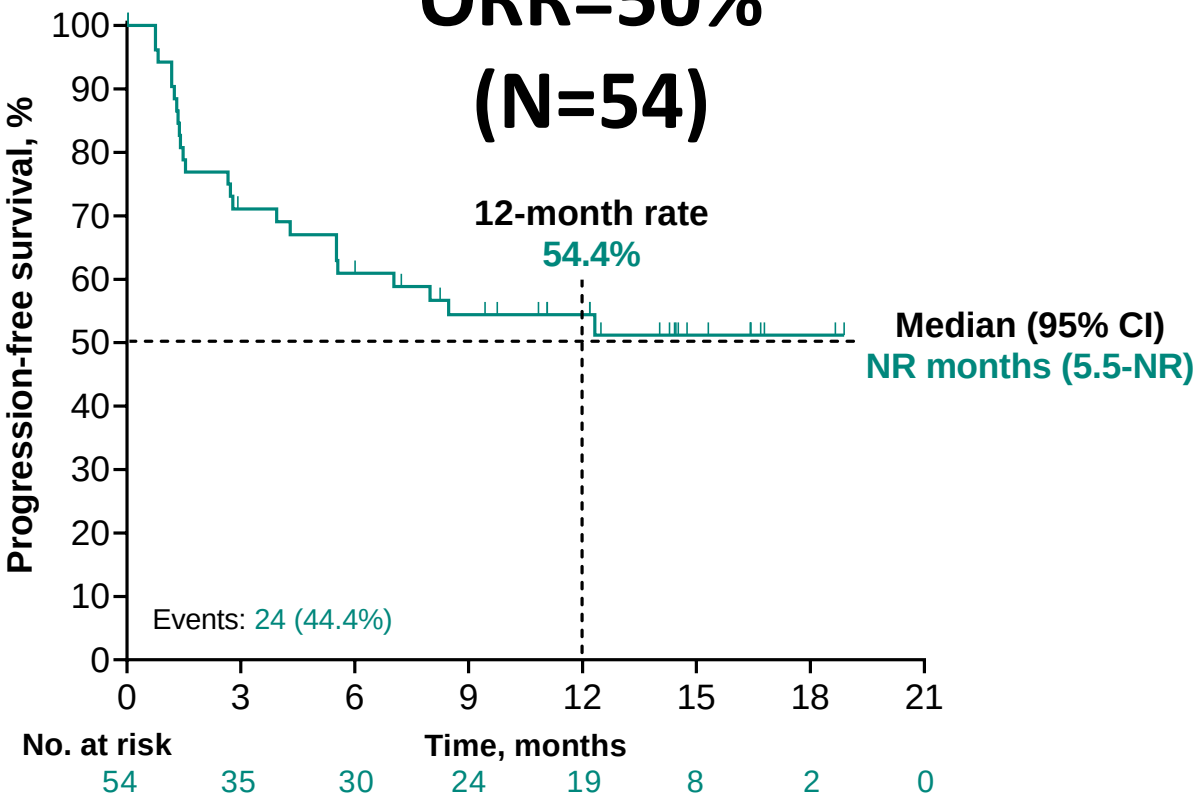


**Firstline systemic therapy in 66% of patients*

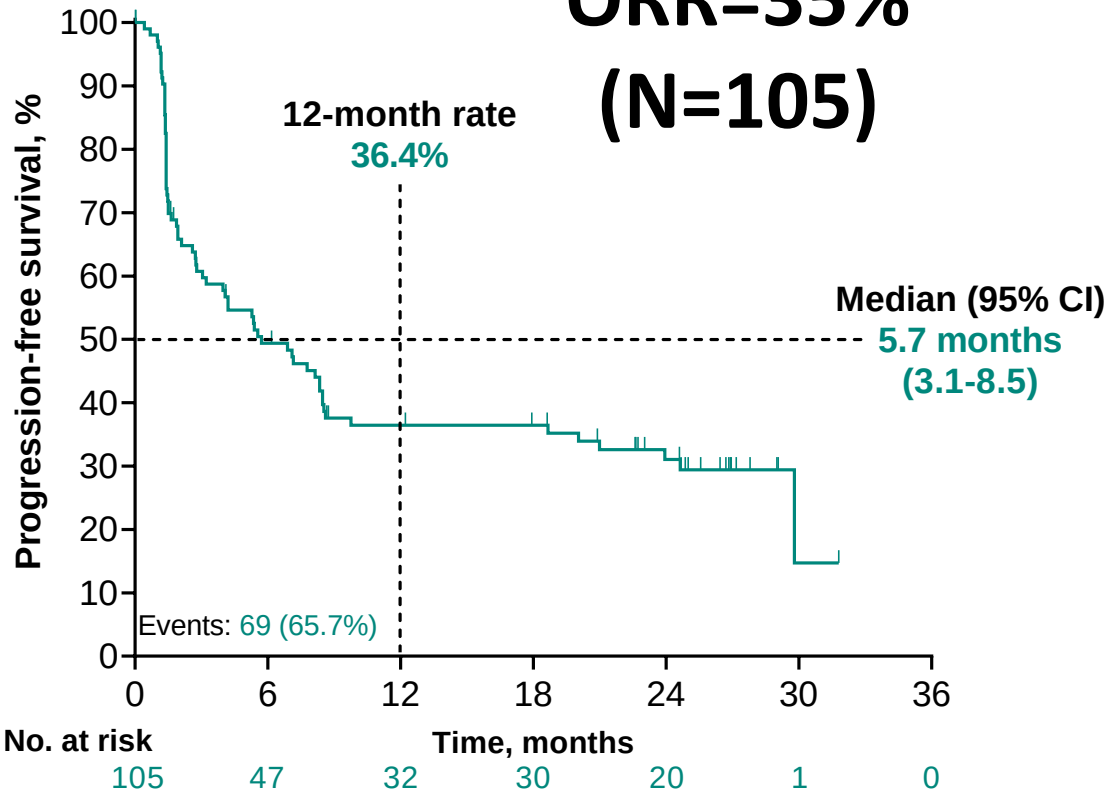
Rischin D, et al, ASCO, 2020

Keynote 629: Phase II Pembrolizumab in locoregional/metastatic cutSCC

LA Cohort ORR=50% (N=54)



R/M Cohort ORR=35% (N=105)



Data cutoff: July 29, 2020

Presented by Hugh BGM, et al, AACR, 2021

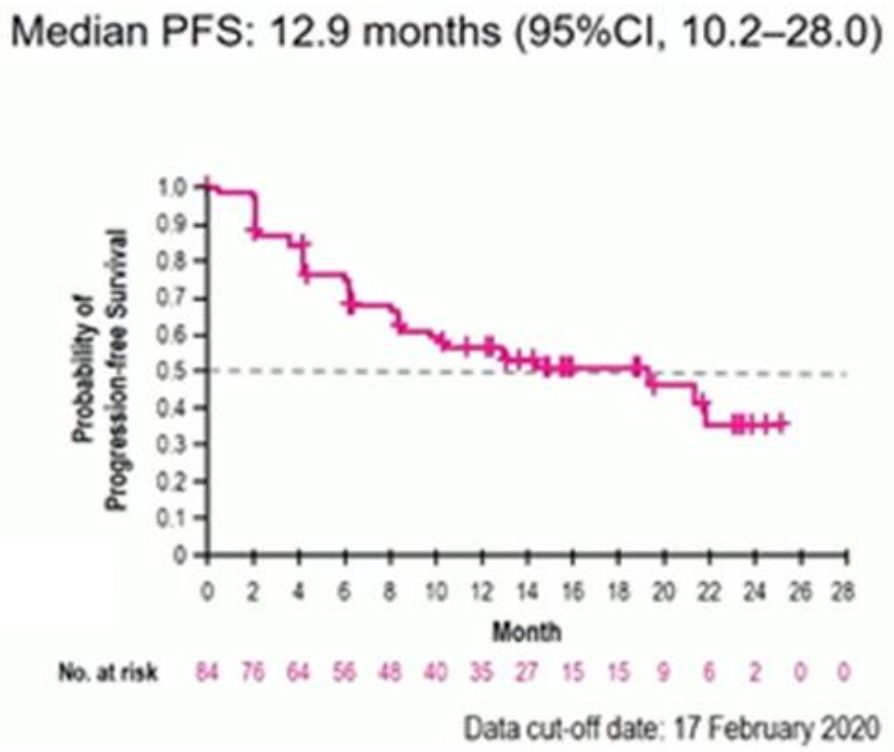
Phase 2 Study Cemiplimab in locally advanced/metastatic BCC

- Refractory or Intolerant to HHI

	laBCC (n=84)	metBCC (n=28)
ORR	31%*	21%
CR	6%	0
PR	25%	21%
SD	49%	--

*ORR 29% in FDA label information

laBCC



Algarra SM, ESMO 2020

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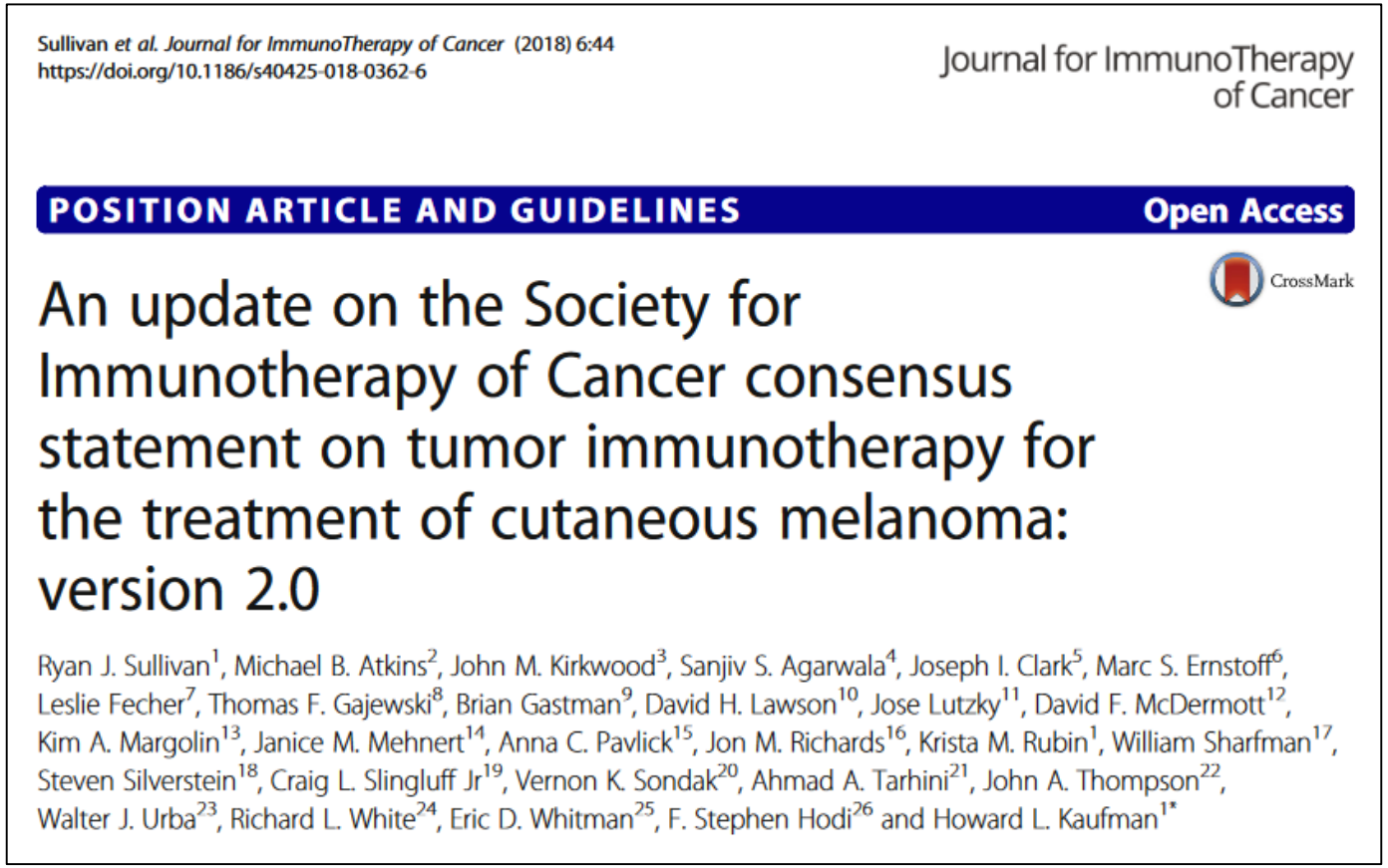
Conclusions

- Melanoma was one of the foundational disease states for testing immunotherapies
- Avelumab and pembrolizumab are approved for Merkel cell carcinoma, and cemiplimab and pembrolizumab are approved for cutaneous squamous cell carcinoma
- **New approval for cemiplimab in BCC**
- Emerging neoadjuvant and cellular therapies hold promise to further improve patient outcomes.

Additional Resources



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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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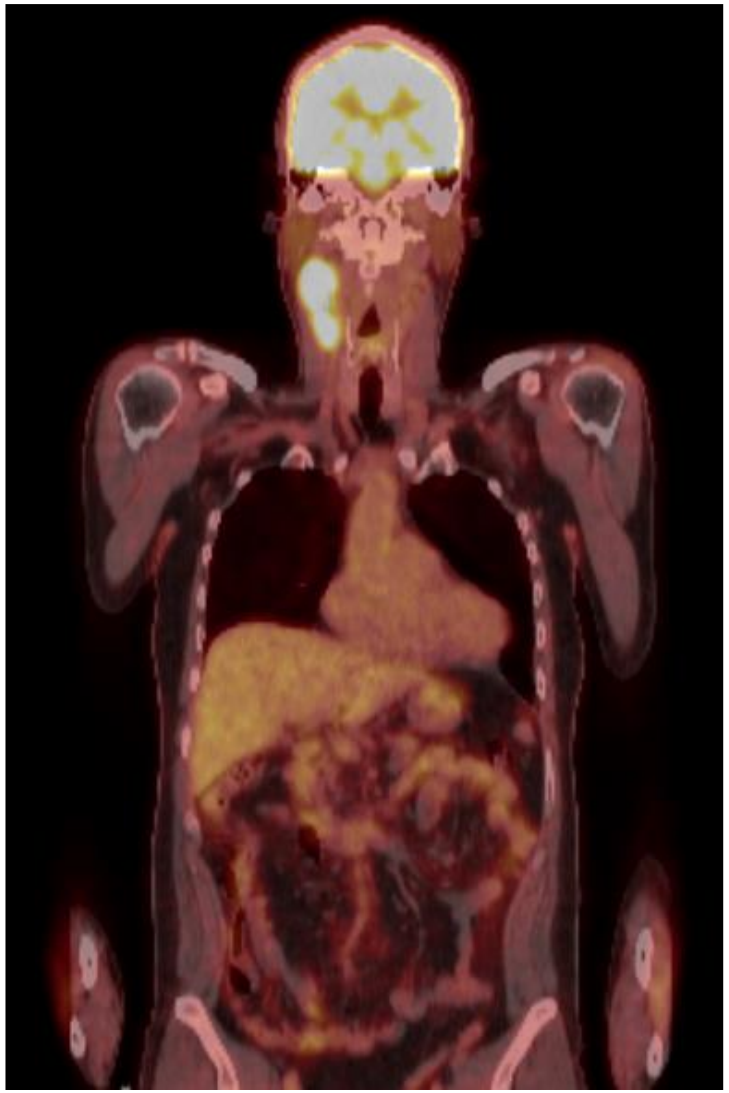
Case Studies

Case Study 1

- 45 y/o M with no prior history of melanoma presents with palpable adenopathy in the right neck
- Biopsy demonstrates metastatic melanoma, BRAF V600E mutant
- No other sites of disease on staging scans and no primary identified by dermatology.
- Stage IIIB vs IIIC (5yr MSS 83-69%)



What would you do next?

1) Start with Surgery versus Systemic therapy (Neoadjuvant)?
   a. Therapeutic LN dissection
   b. Neoadjuvant Systemic Therapy
2) If surgery upfront, which adjuvant therapy?
   a. Nivolumab or Pembrolizumab
   b. Nivolumab/Ipilimumab
   c. Dabrafenib/Trametinib
3) If systemic therapy upfront, which strategy?
   a. Nivolumab or Pembrolizumab
   b. Nivolumab/Ipilimumab
   c. BRAFi/MEKi

Case 1 continued

- Patient underwent therapeutic LN dissection. Overall stage IIIB.
- Received 1 year of adjuvant nivolumab without complications.
- 6 months after completion of adjuvant nivolumab, colonoscopy performed for GIB and showed a metastatic deposit of melanoma in the colon. Scans otherwise unrevealing.

What are the next steps?

a. Metastectomy +/- further systemic therapy
b. Nivolumab/Ipilimumab
c. BRAFi/MEKi
d. Clinical trial