Melanoma and other skin cancers

2021

UW CME Board Review Lecture

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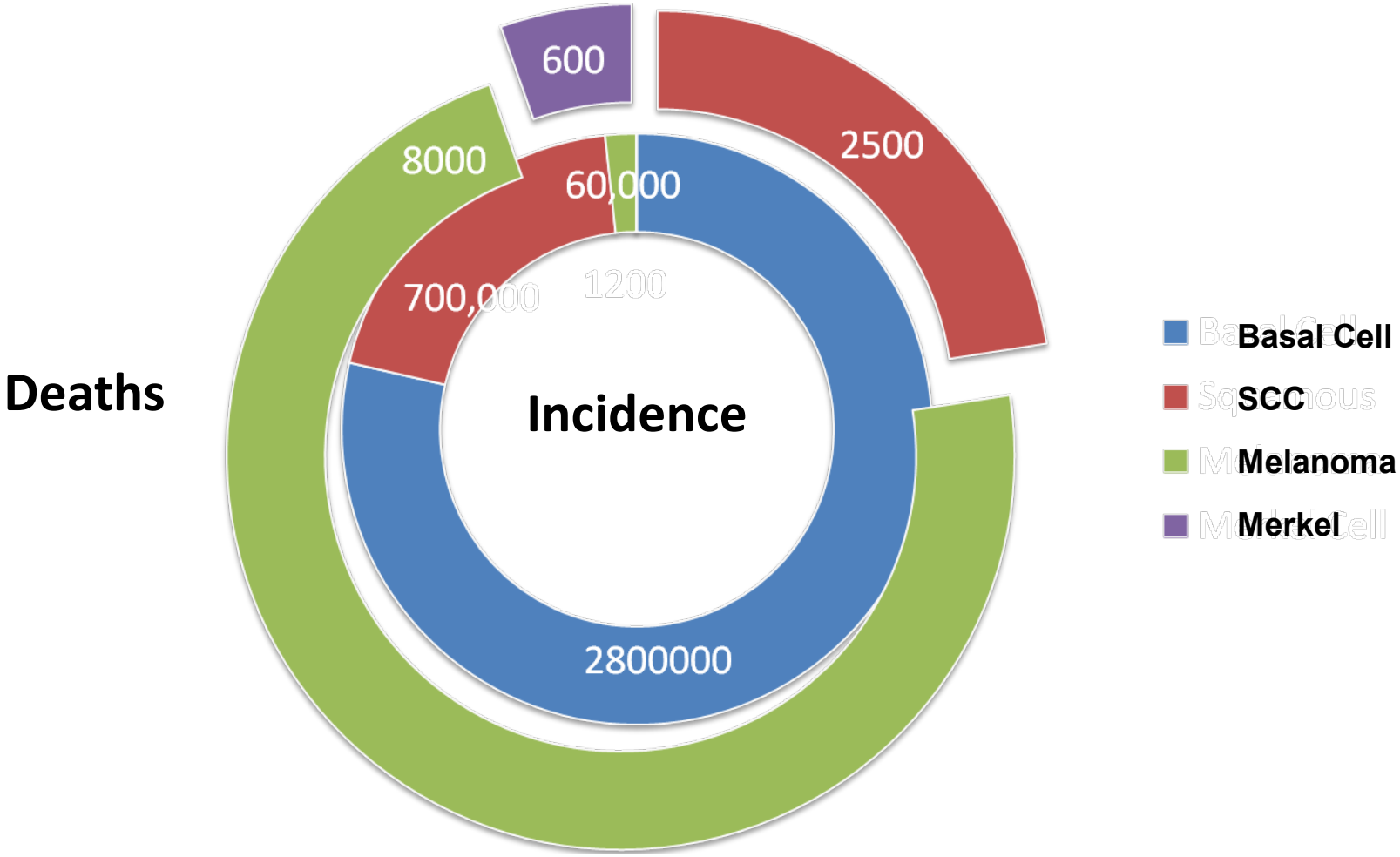
Disclosures

- **Research support (to UW)**: *BMS, EMD-Serono, Immune Design, Merck, Novartis, Oncosec, Nantkwest, Exicure, Nektar, Amphivena, Checkmate, Xencor.*

- **Advisory Board**: *Genentech, BMS, EMD-Serono, Sanofi-Genzyme*

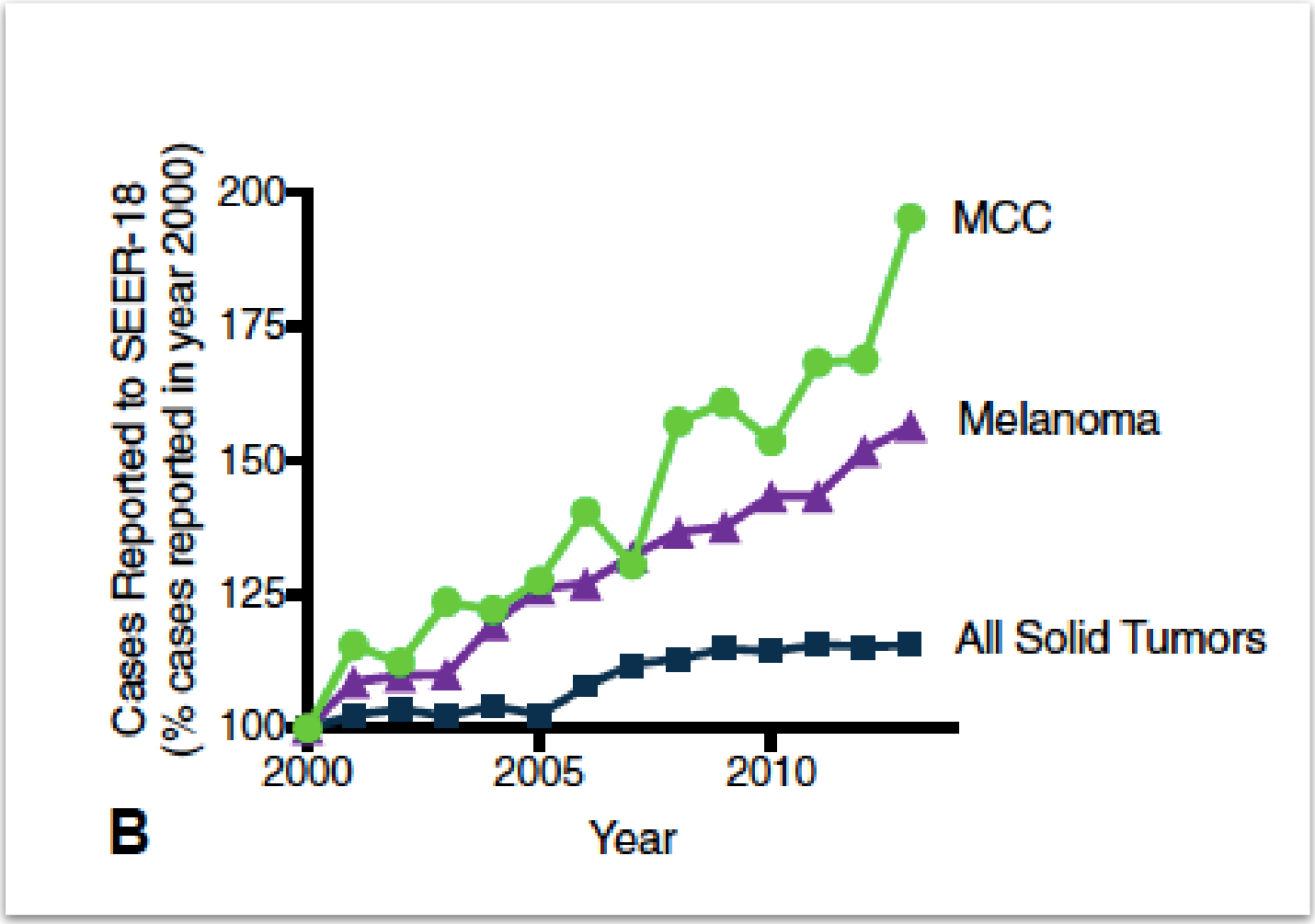
- **Stock:** *Moderna*

Skin, the largest organ, is also the most vulnerable to cancer development



NOTE: The numbers listed in this figure do not reflect the most up-to-date statistics.

The incidence of skin cancers is increasing steadily.

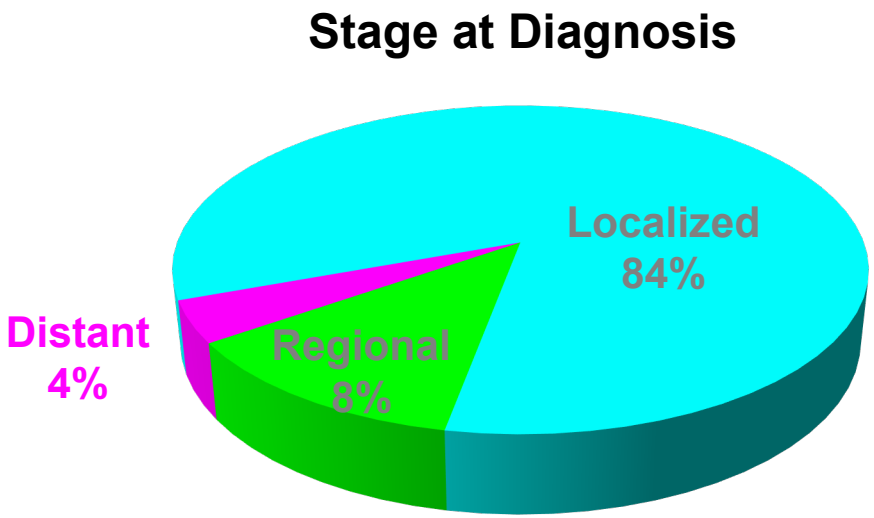


Paulson K et al. *JAAD* 2017

I. Melanoma

Incidence, Mortality and Stage Distribution of Melanoma

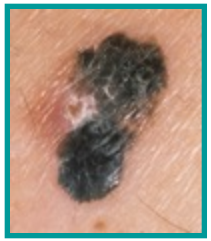
- 91,270 new cases of cutaneous melanoma in U.S. in **2018**
  - ~9,320 deaths
- 100,350 new cases of cutaneous melanoma in U.S. in **2020**
  - ~6,850 deaths



American Cancer Society. Cancer.org 2020
Siegel R. *CA Cancer J Clin*. 2018 and 2020.

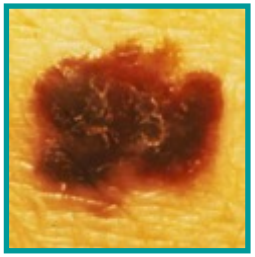
The ABCDEs of Melanoma Diagnosis

Asymmetry



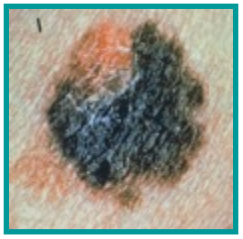
One half of the lesion is shaped differently than the other

Border



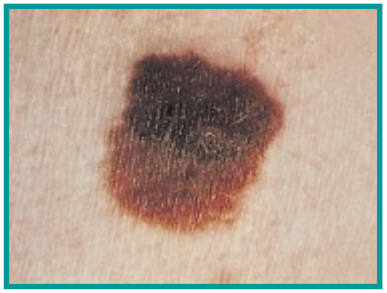
The border of the lesion is irregular, blurred, or ragged

Color



Inconsistent pigmentation, with varying shades of brown and black

Diameter



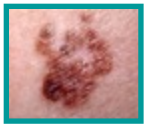
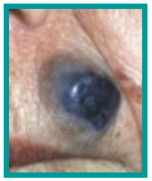
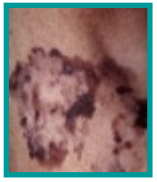
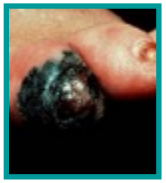
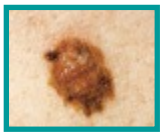
>6 mm, or a progressive change in size

Evolution

History of change in the lesion

Photos courtesy of the American Cancer Society.

Morphologic Types of Melanoma

	Type	*Frequency*	*Features*
	**Superficial spreading**	**60%-70%**	**Flat during early phase; notching, scalloping, areas of regression**
	**Nodular**	**15%-30%**	**Darker and thicker than superficial spreading, rapid onset; commonly blue-black or blue-red (5% amelanotic)**
	**Lentigo maligna**	**~5%**	**Enlarge slowly; usually large, flat, tan or brown**
	**Acral lentiginous**	**Uncommon Asians (46%), Blacks (70%)**	**On soles, palms, beneath nail beds; usually large, tan or brown; irregular border; subungual melanoma more common in older, dark-skinned people**
	**Desmoplastic**	**1.7%**	**Rare, locally aggressive, occur primarily on head and neck in elderly**

Data from Lotze MT, et al. *Cutaneous Melanoma.* In: DeVita VT Jr,. et al, eds. *Cancer: Principles & Practice of Oncology.* 6th ed. Philadelphia, PA: Lippincott-Raven; 2001.

Wide Local Excision (WLE)

PRINCIPLES OF SURGICAL MARGINS FOR WIDE EXCISION OF PRIMARY MELANOMA

Tumor Thickness	Recommended Clinical Margins[2]
In situ[1]	0.5–1.0 cm
≤1.0 mm	1.0 cm (category 1)
>1.0–2 mm	1–2 cm (category 1)
>2.0–4 mm	2.0 cm (category 1)
>4 mm	2.0 cm (category 1)

Margins may be modified to accommodate individual anatomic or functional considerations.

NCCN Guidelines version 3.2018

Sentinel Lymph Node Biopsy (SLNB)

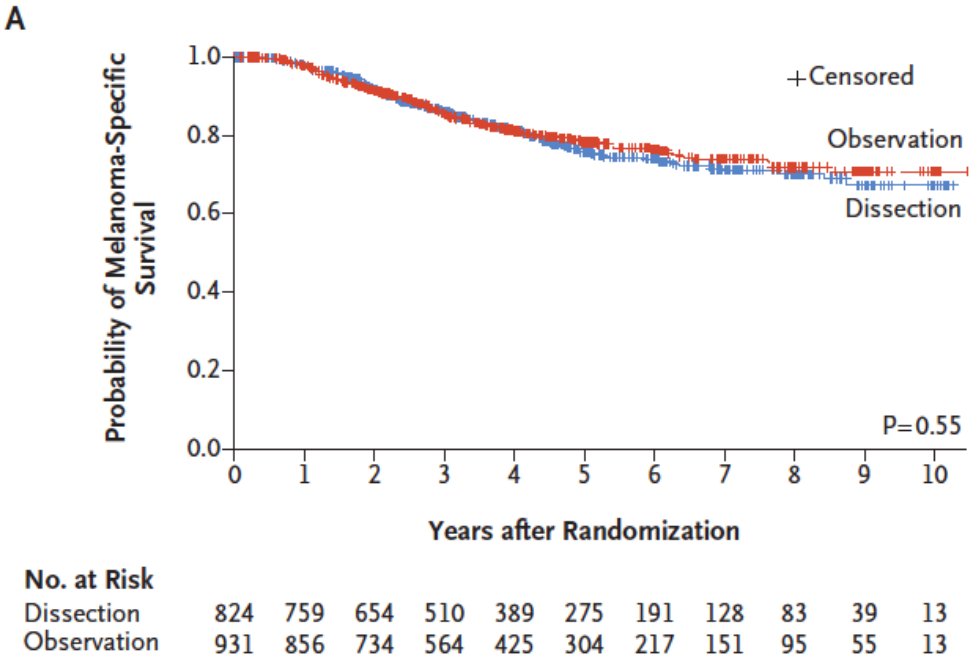
In patients with clinical stage I/II melanoma, SLN status is the strongest predictor of, but does not impact, survival.

Breslow Thickness (mm)	Mitotic rate		Ulceration		Adverse factors*	
	$<1/mm^2$	$\geq 1/mm^2$	No	Yes	No	Yes
≤ 0.8	No	Consider	No	Consider	No	Consider
0.8-1.0	Consider	Consider	Consider	Consider	Consider	Consider
>1.0	Offer	Offer	Offer	Offer	Offer	Offer

* Adverse features include positive margins, Lympho-vascular invasion (LVI), or a combination of these factors

NCCN Guidelines version 3.2018

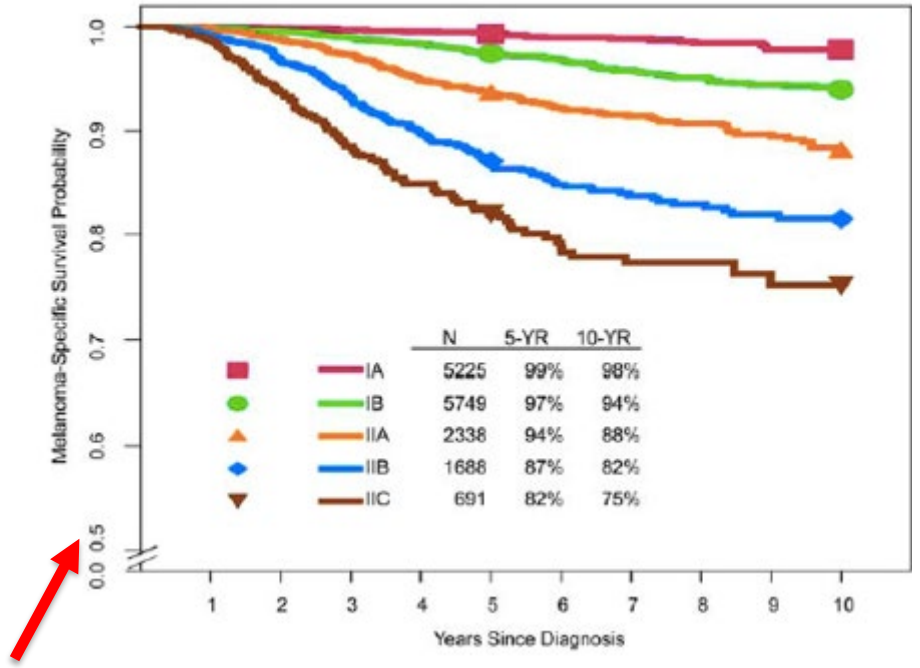
Completion Lymph Node Dissection (CLND)

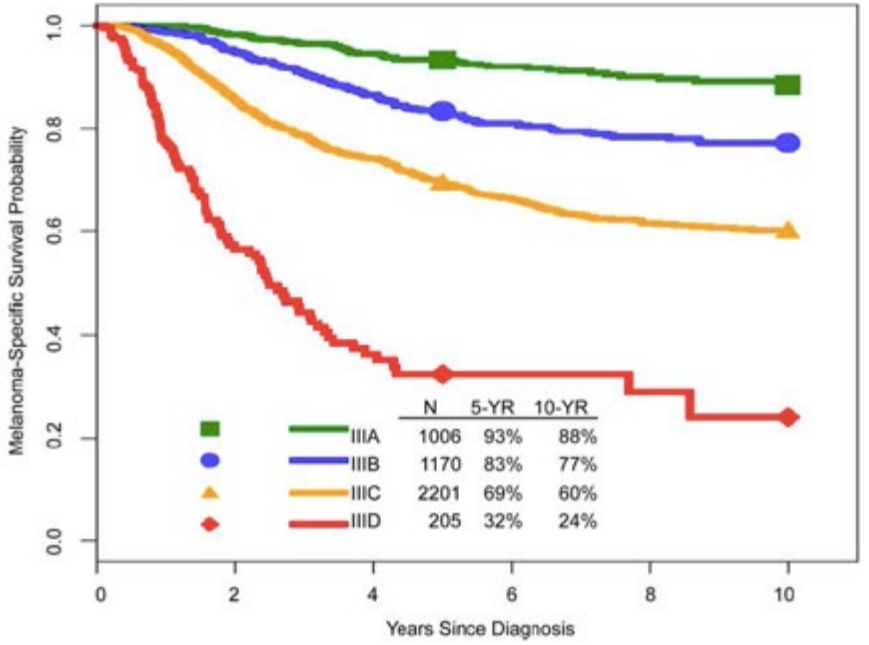


CONCLUSIONS

Immediate completion lymph-node dissection increased the rate of regional disease control and provided prognostic information but did not increase melanoma-specific survival among patients with melanoma and sentinel-node metastases. (Funded by the National Cancer Institute and others; MSLT-II ClinicalTrials.gov number, NCT00297895.)

Despite aggressive surgery, metastatic disease is frequent and life-threatening.





NOTE: These figures include data reflected in the **AJCC 8th edition staging** system

[Gershenwald J et al. *CA Cancer J Clin* 2017]

Metastatic Melanoma (Stage IV)

Until 2011, few effective systemic therapy options existed.

US-FDA approved therapies for metastatic melanoma prior to 2011.

Dacarbazine (1975)

High-dose IL-2 (1998)

} No proven OS benefit

Treatment of Metastatic Melanoma: An Overview
Bhatia S et al. ONCOLOGY. 2009; 23:6; 488-500

Since 2011, multiple new drugs have been FDA-approved.

IMMUNOTHERAPY

Ipilimumab (2011)

Pembrolizumab (2014)

Nivolumab (2014)

Ipilumumab + Nivolumab (2015)

TVEC (2015)

CHEMOTHERAPY

Vemurafenib (2011)

Dabrafenib (2013)

Trametinib (2013)

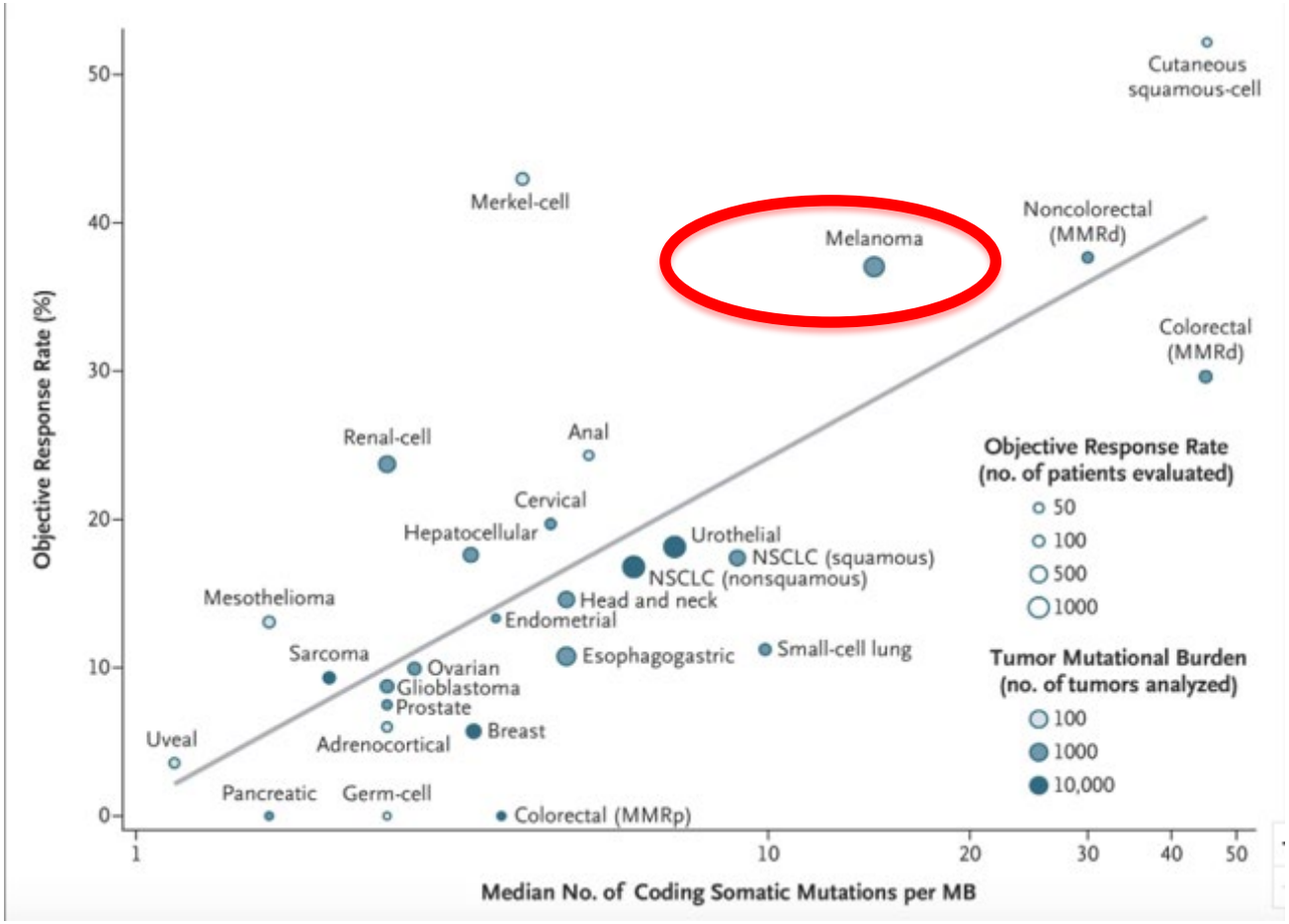
Dabrafenib + Trametinib (2014)

Vemurafenib + Cobimetinib (2015)

Encorafenib + Binimetinib (2018)

Vemurafenib + Cobimetinib + Atezolizumab (07/2020)

Immunogenicity of melanoma: High mutational burden (Neoantigens)



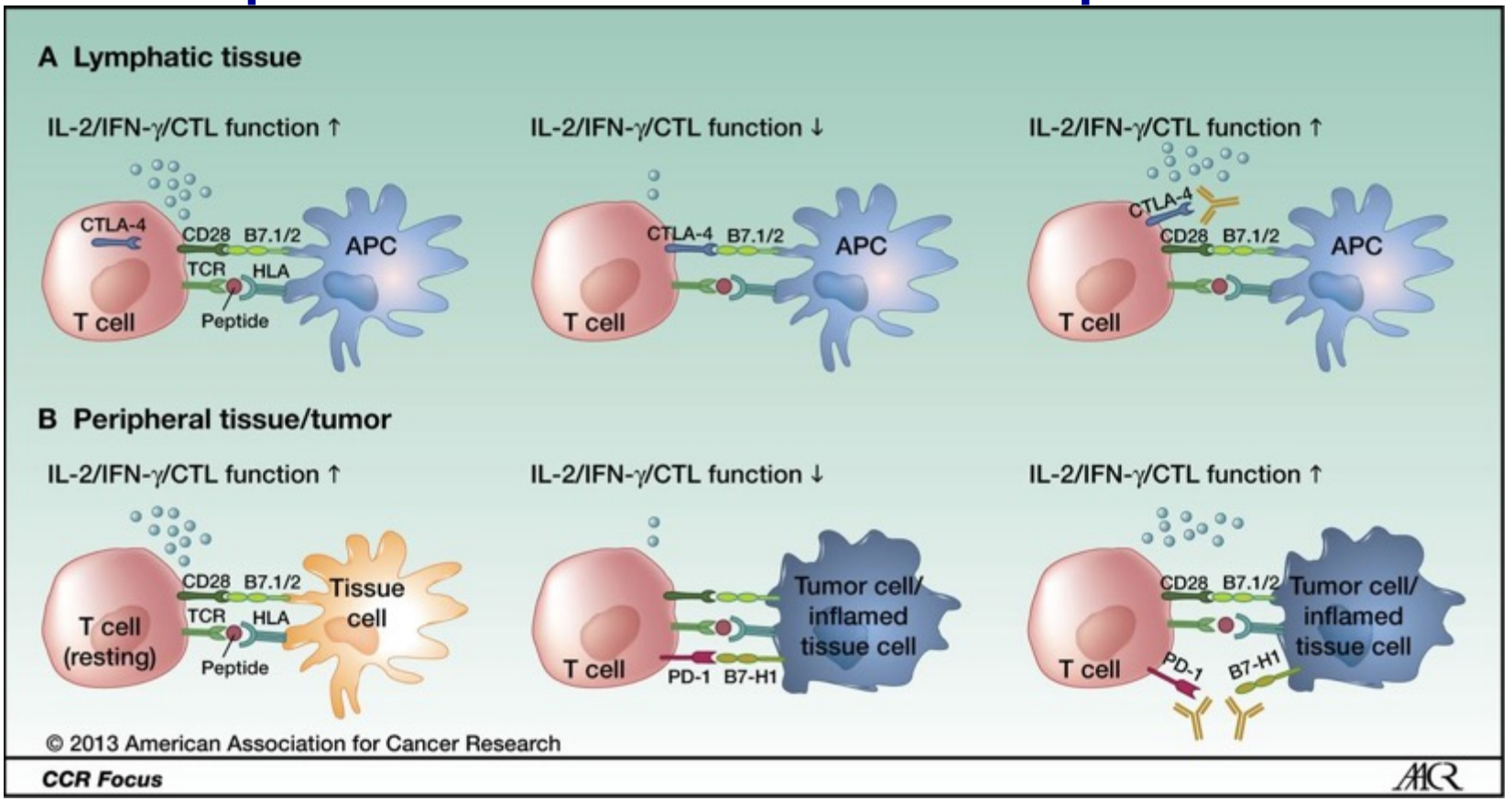
[Yarchoan M *NEJM* 2017]

IMMUNOTHERAPY

Anti-PD-1 agents (as monotherapy or in combination with ipilimumab) are regarded as the current standard-of-care for immunotherapy of metastatic melanoma.

- Pembrolizumab
- Nivolumab

CTLA-4 and PD-1 modulate different aspects of the T-cell response

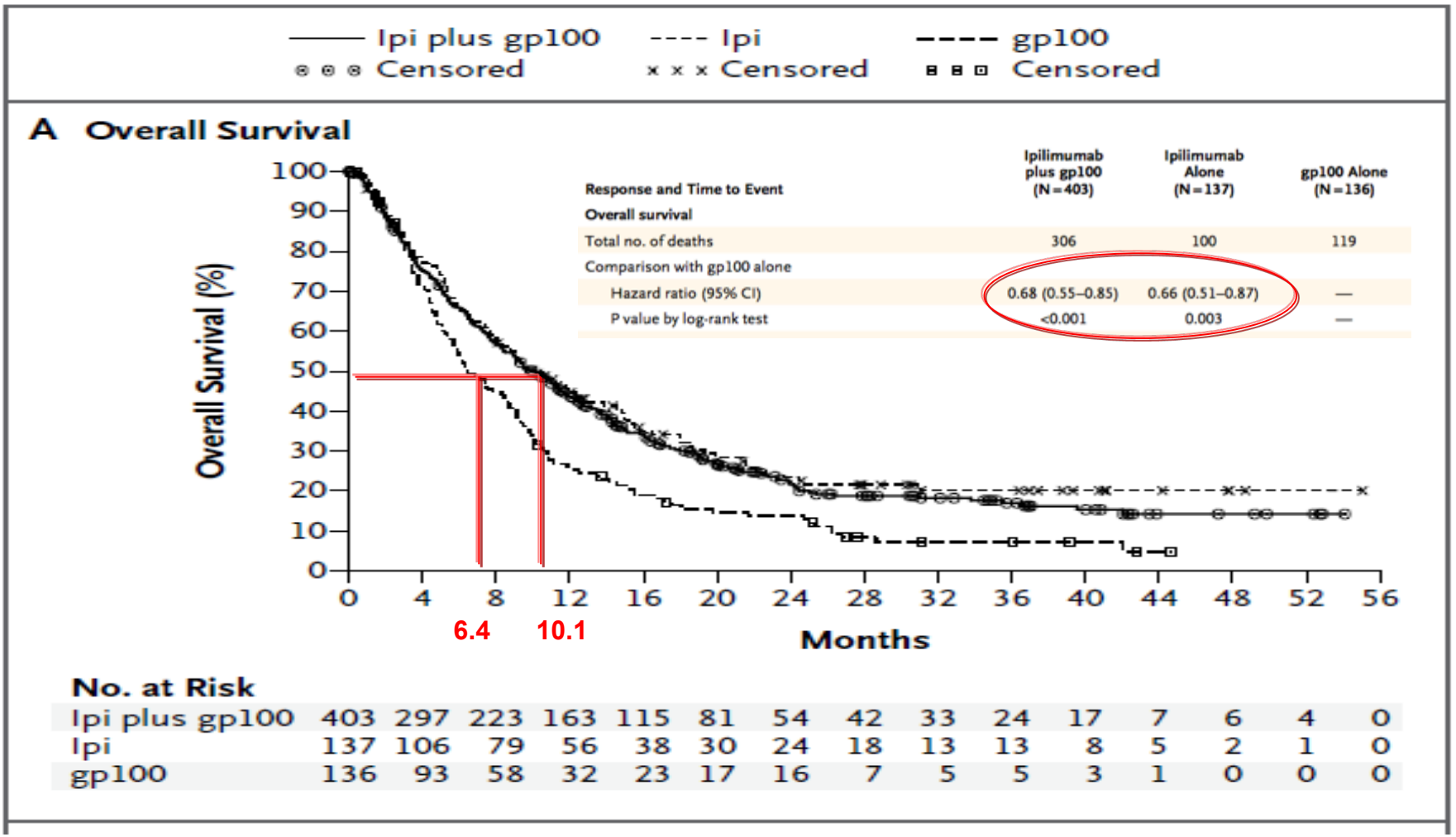


A, CTLA-4 is upregulated after antigen-specific activation of a naïve or memory T cell in lymphatic tissue, leading to decreased effector function (early activation phase).

B, PD-1 is mainly expressed on antigen-experienced memory T cells in peripheral tissues cells. Tumor cells use this regulatory mechanism to evade a tumor-directed T-cell response by upregulating the PD-1 ligands.

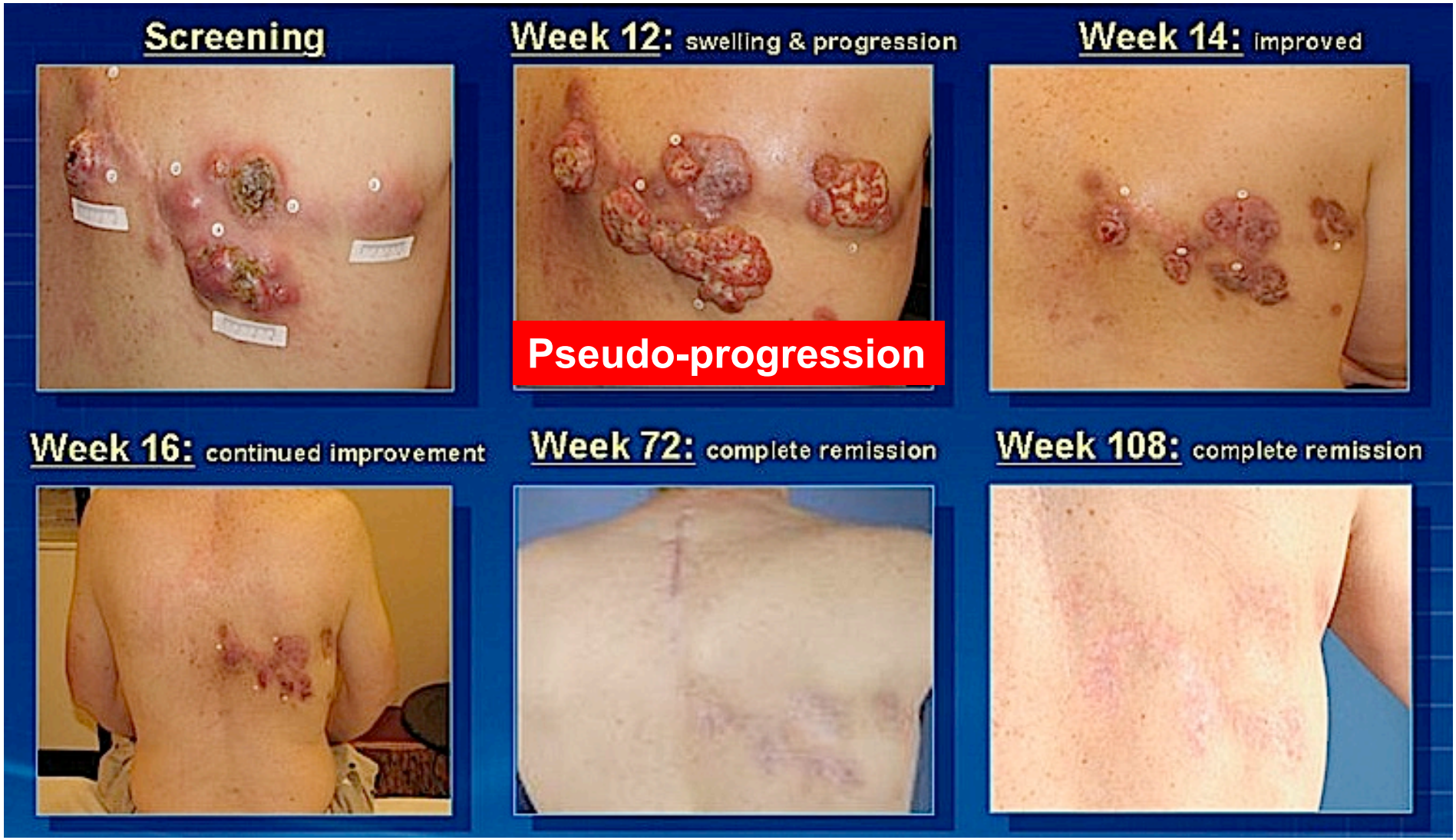
[Patrick A. Ott et al. Clin Cancer Res 2013;19:5300-5309]

Improved Overall Survival was seen in both the Ipilimumab arms (3 mg/kg q3 wks x4)



Hodi FS et al. NEJM. 2010

Ipilimumab: Impressive clinical responses



Pembrolizumab versus Ipilimumab: Improved efficacy with Lower toxicity

	Response rate (%)	Grade 3 or higher IRAE (%)
Ipilimumab	12	20
Pembrolizumab	33	10

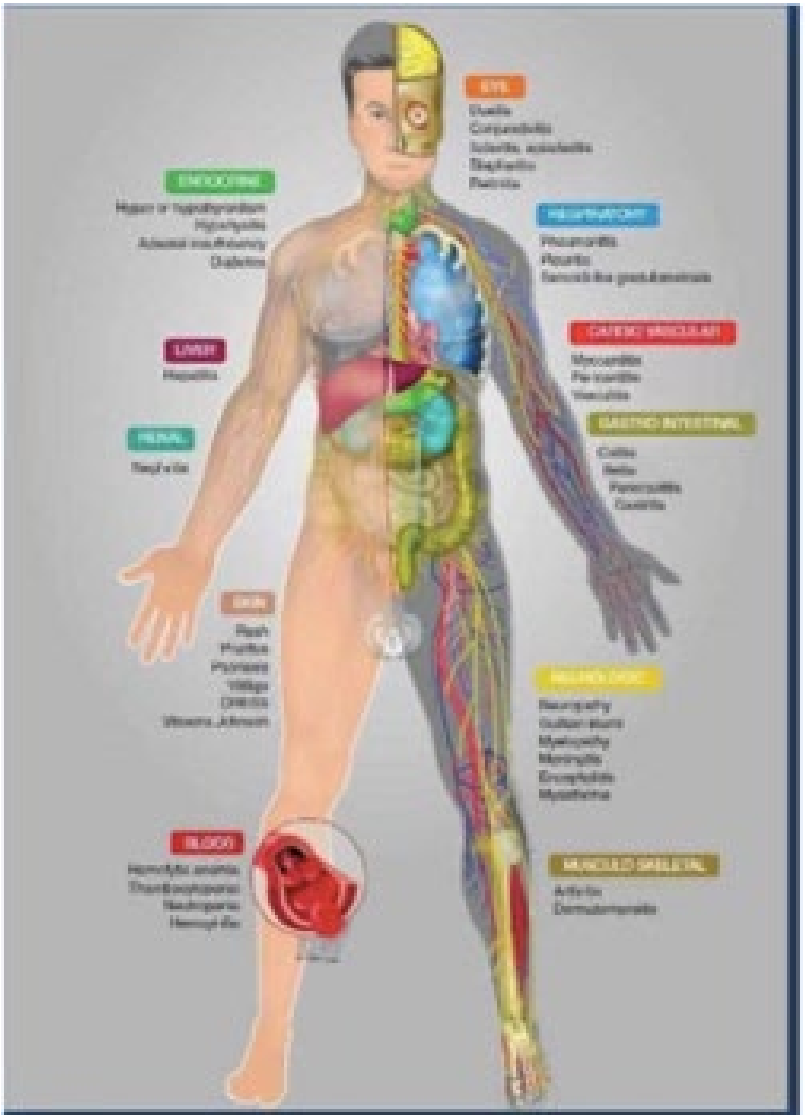
[Robert C et al. NEJM]

Nivolumab versus Ipilimumab

	Response rate (%)	Grade 3 or higher IRAE (%)
Ipilimumab	19	27
Nivolumab	44	16

[*Larkin J et al* NEJM *2015*]

Immune-related Adverse events (IRAEs)



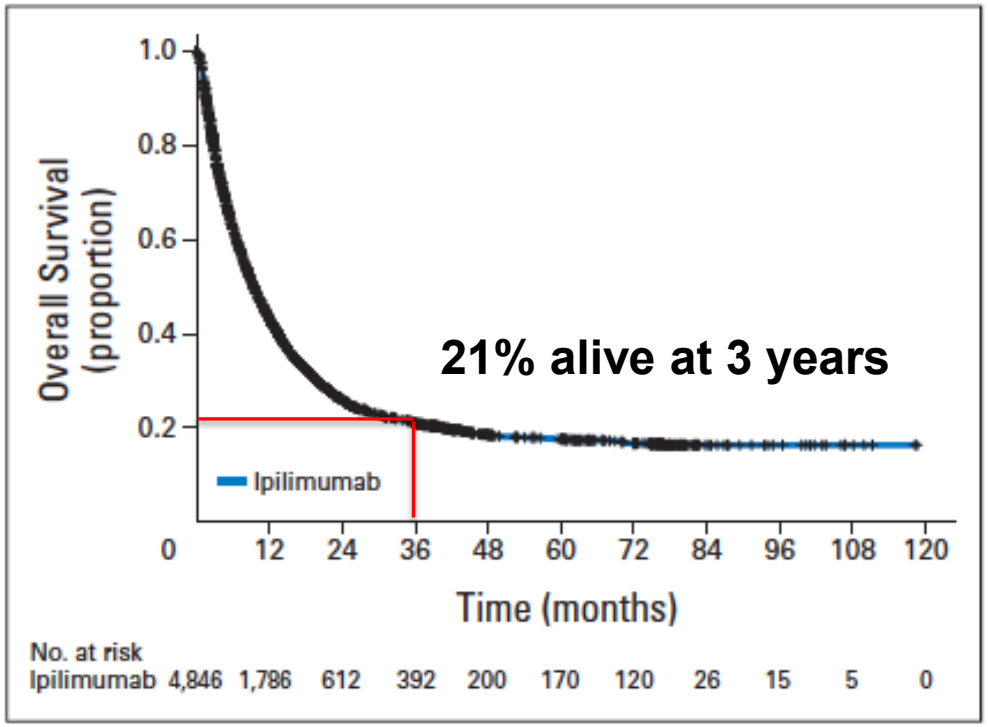
- Risk of Death (~1%)
- Permanent side-effects affecting QoL (hypophysitis, type I DM, neuropathy)
- Require careful counseling, close monitoring, and aggressive management.
- **NCCN guidelines** exist.

Efficacy of nivolumab is comparable in BRAF-mut and BRAF-WT melanoma

Variable	*BRAF* WT (n = 217)	*BRAF* Mut (n = 74)
Best overall response, No. (%)		
Complete	9 (4.1)	2 (2.7)
Partial	66 (30.4)	20 (27.0)
Stable disease	53 (24.4)	13 (17.6)
Progressive disease	74 (34.1)	33 (44.6)
Unknown	15 (6.9)	6 (8.1)
Objective response rate, % (95% CI)[a]	34.6 (28.3-41.3)	29.7 (19.7-41.5)
Mut over WT, OR (95% CI)	0.8 (0.5-1.4)	
Time to objective response, mo		
Median (range)	2.2 (1.6-14.8)	2.2 (1.7-7.9)
Mean (SD)	3.3 (2.2)	3.0 (1.7)
Duration of objective response, median (95% CI) [range], mo[b]	14.8 (11.1-24.0) [1.4-30.5]	11.1 (7.3-22.9) [2.8-27.6]

[*Larkin J et al* JAMA Oncol *2015*]

Potential for long-term survival with immunotherapy



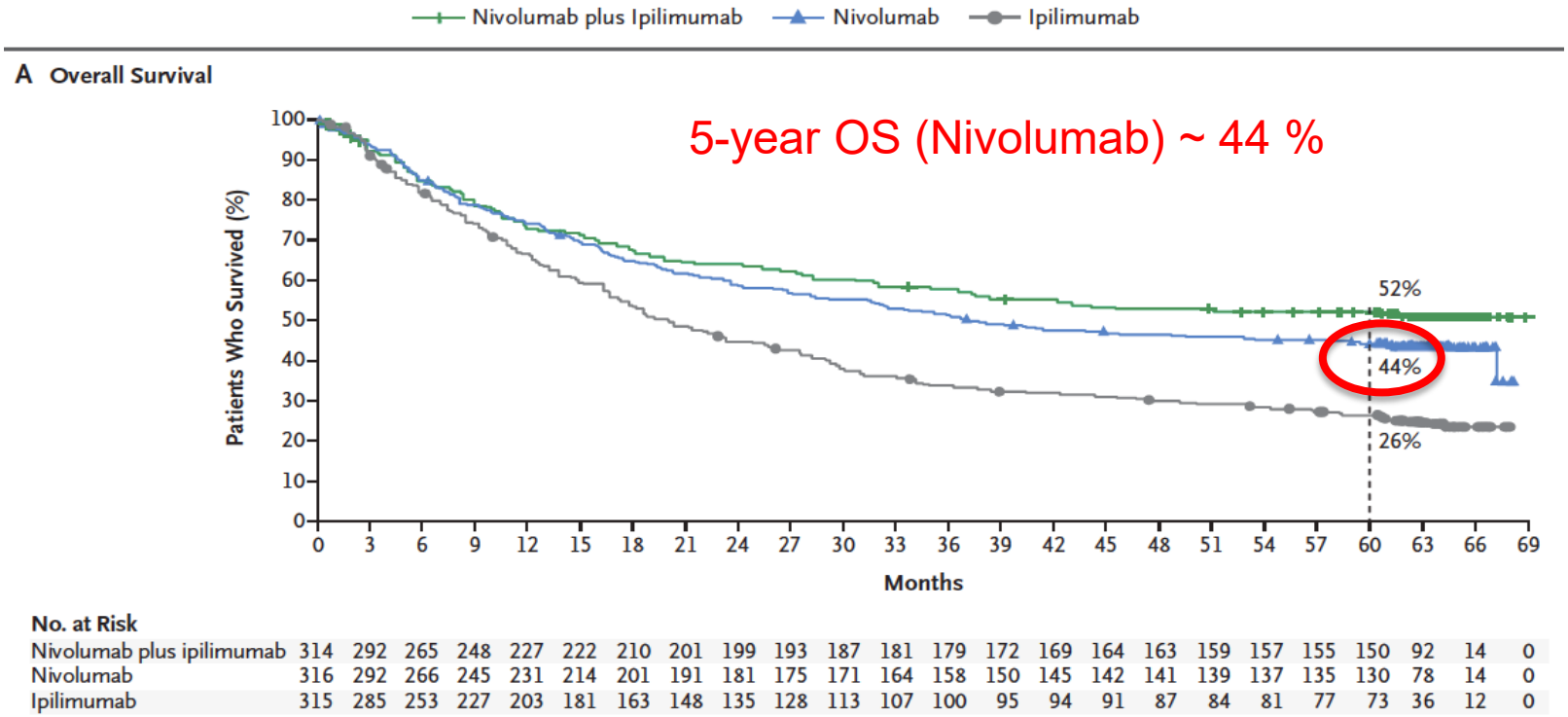
- Retrospective analysis of 4,846 patients treated with Ipilimumab on several clinical trials.

[Schadendorf D et al. 2015 *JCO*]

Long-term survival with PD-1-blockade

Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.-J. Grob, P. Rutkowski, C.D. Lao,



DOI: 10.1056/NEJMoa1910836

Ipilimumab *plus* Nivolumab combination

Combination was approved by the US FDA in **September 2015**

Approved dose is Ipilimumab 3 mg/kg plus Nivolumab 1 mg/kg administered IV every 3 weeks x 4 doses [**Induction**] followed by Nivolumab 3 mg/kg administered IV every 2 weeks [**Maintenance**].

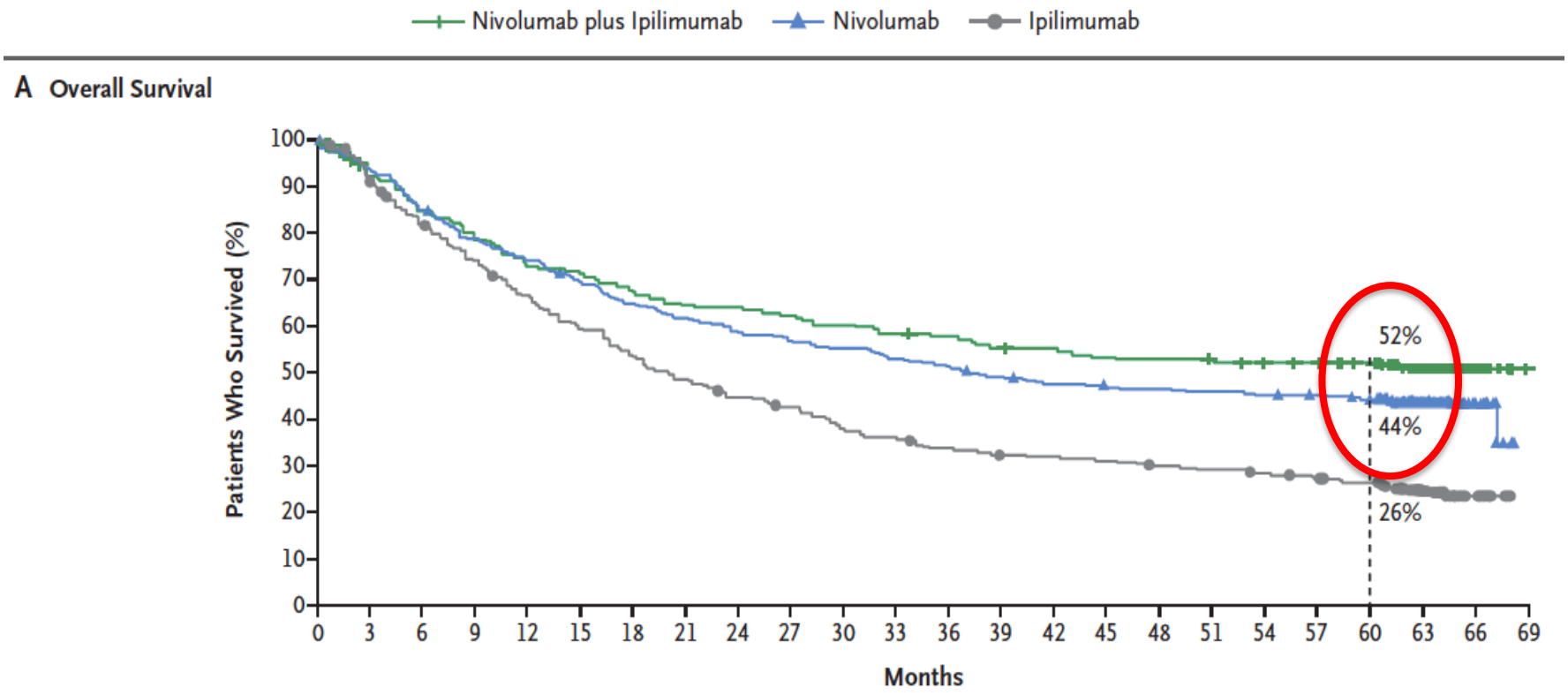
Systemic immunotherapy: Outcomes in melanoma

	Response rate (%)	Grade 3 or higher IRAE (%)
Ipilimumab	19	27
Nivolumab	44	16
Ipi plus Nivo	58	**55**

[*Larkin J et al* NEJM *2015*]

Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.-J. Grob, P. Rutkowski, C.D. Lao,

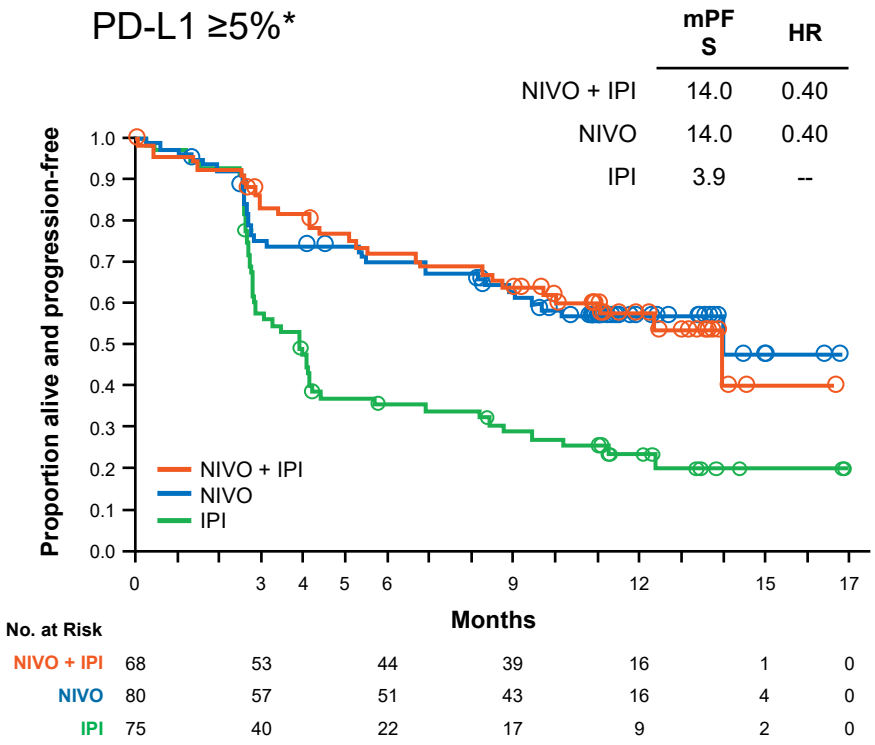


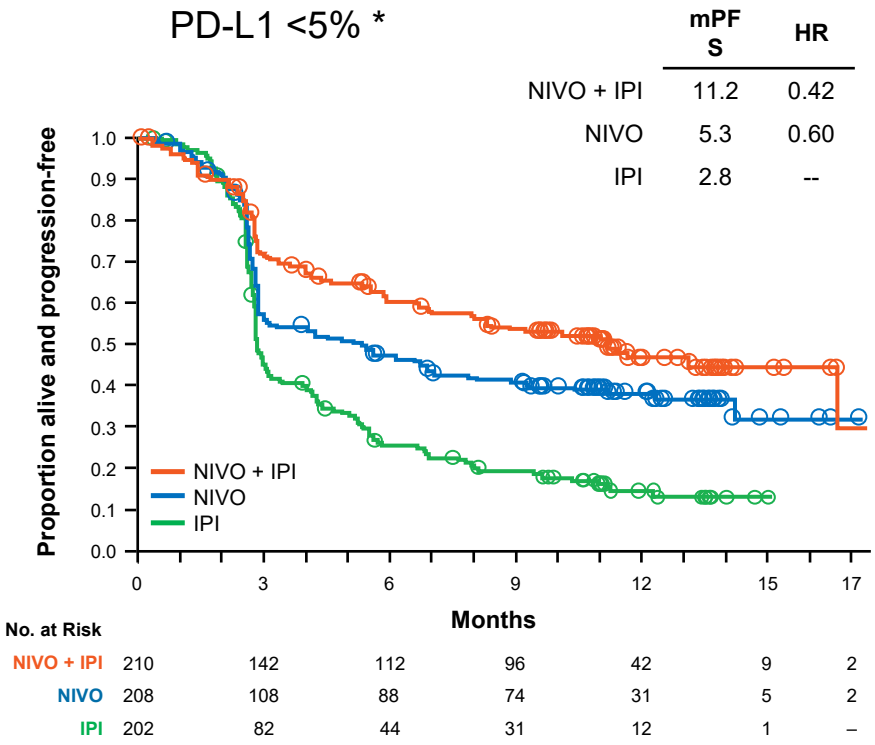
No. at Risk

Nivolumab plus ipilimumab	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
Nivolumab	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

DOI: 10.1056/NEJMoa1910836

Ipi plus Nivo: PFS by PD-L1 Expression Level





*Per validated PD-L1 immunohistochemical assay with expression defined as ≥5% of tumor cells showing PD-L1 staining in a section of at least 100 evaluable tumor cells.

My conclusions on Immunotherapy

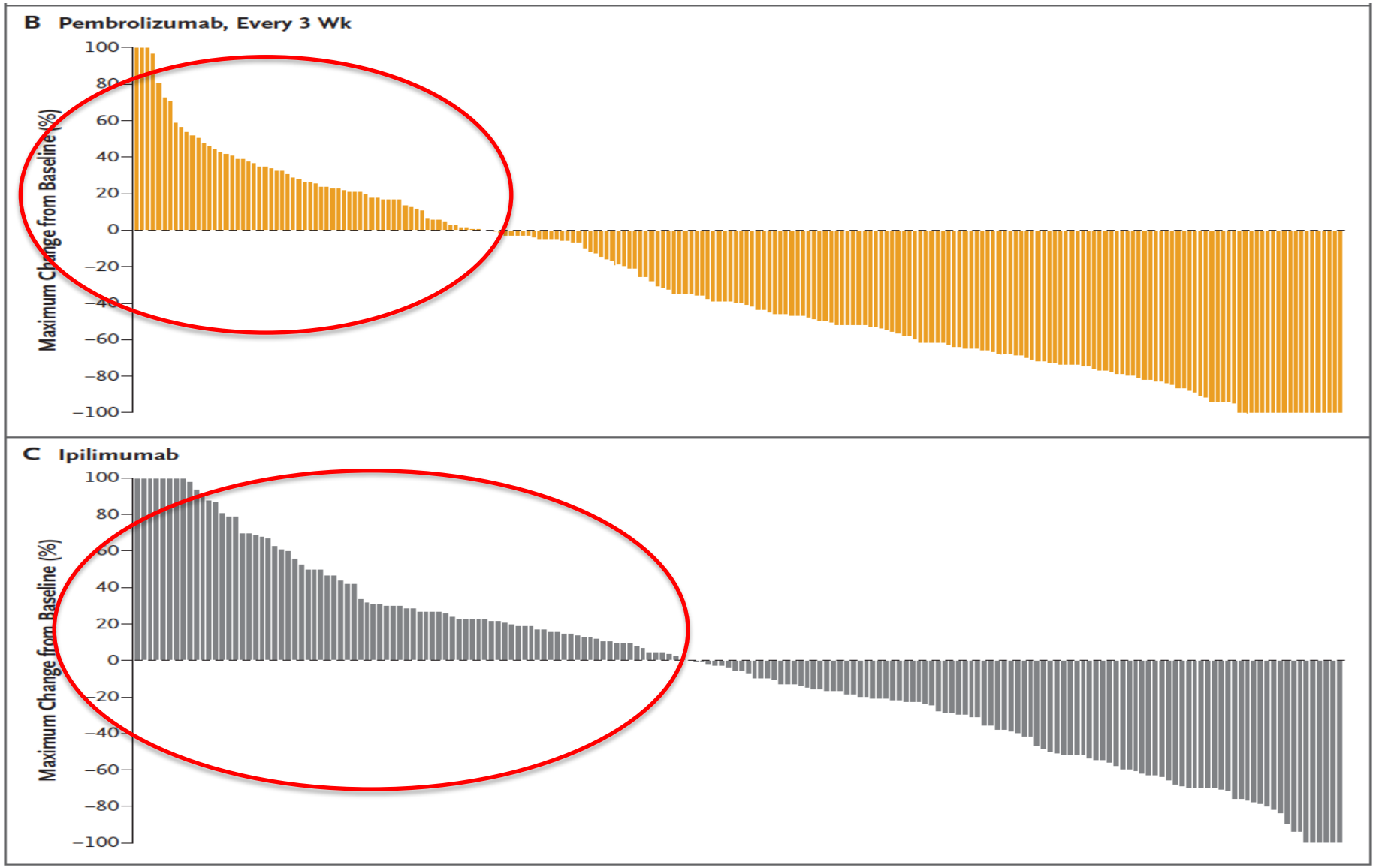
1. Immunotherapy leads to **durable responses and long-term survival** in a subset of melanoma patients, regardless of BRAF status.

2. **PD-1 monotherapy is superior to Ipilimumab** (better efficacy; lesser toxicity)

3. **Ipi-Nivo leads to more immune activation (higher ORR and toxicity), with sustained OS benefit (statistically NS, but likely clinically meaningful)** over nivolumab; utility of PDL-1 for selecting patients warrants further confirmation.

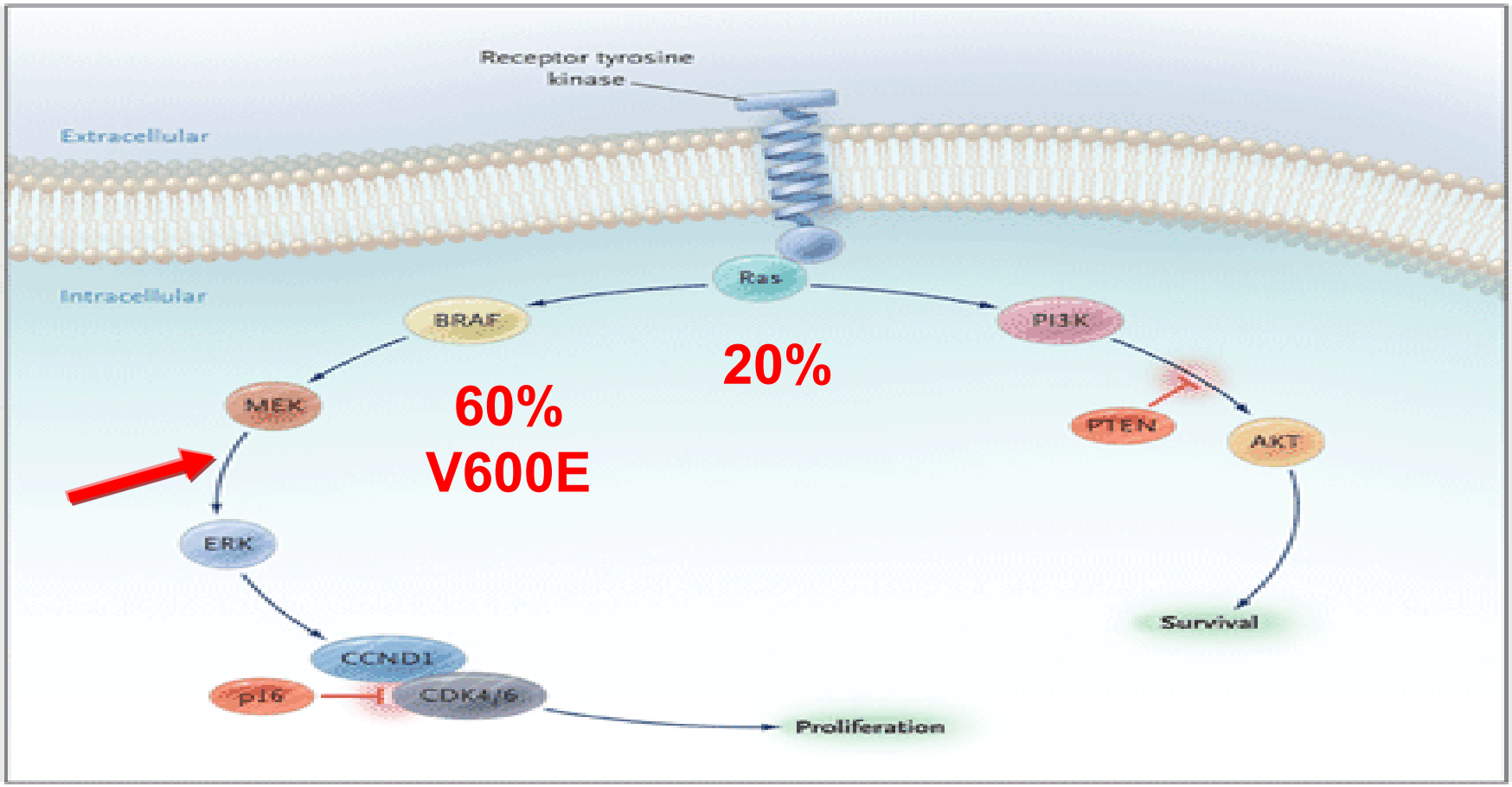
4. Clinical decisions must be individualized based on patient's desire for aggressive therapy and risk tolerance.

Immunotherapy does not work all the time



[Robert C et al. NEJM]

Mutations in BRAF and NRAS are frequent in cutaneous melanomas



[Curtin JA et al. NEJM 2005]

Multiple targeted agents are efficacious in BRAF-mutated melanoma

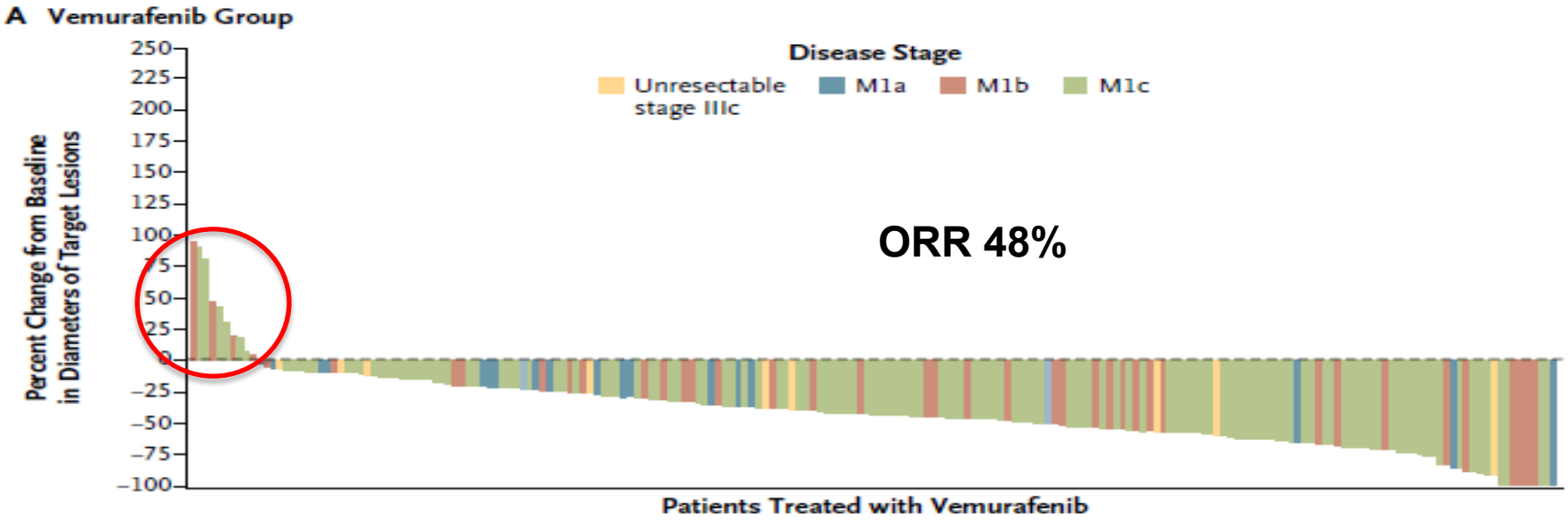
BRAFi

- Vemurafenib
- Dabrafenib
- Encorafenib

MEKi

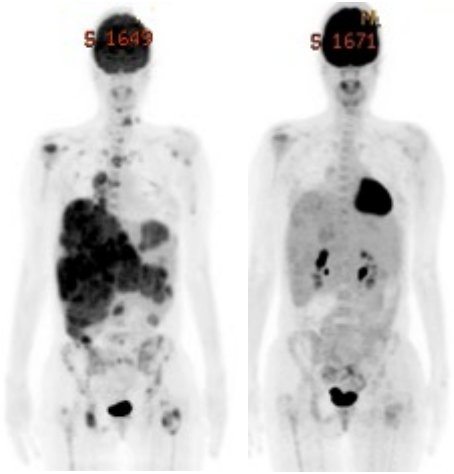
- Trametinib
- Cobimetinib
- Binimetinib

BRAFi (+/-MEKi) are associated with tumor regressions in **vast majority** of patients with BRAF-mutant melanoma

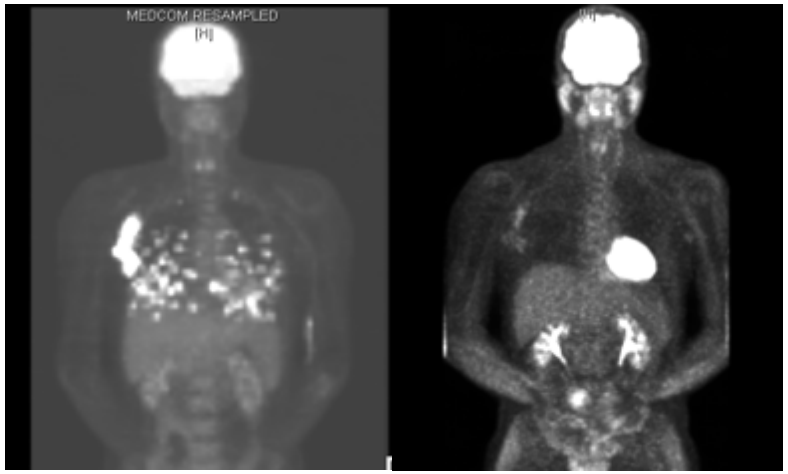


[Chapman P et al. NEJM. 2011]

Onset of tumor regression is **fairly rapid** with BRAFi (median TTR ~6 weeks)



Baseline Day 15



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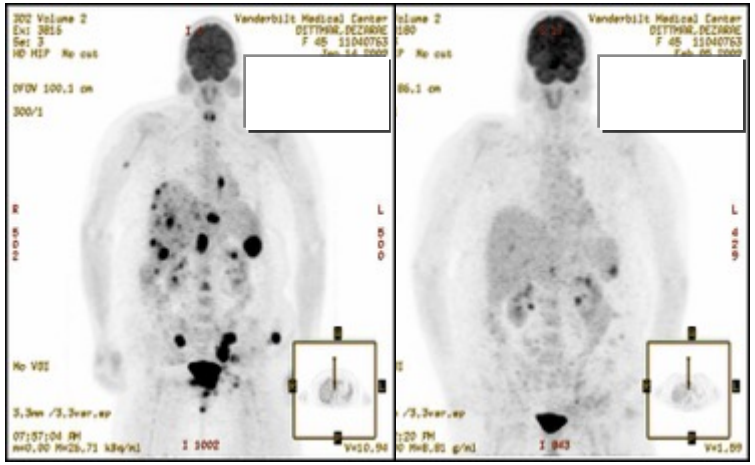
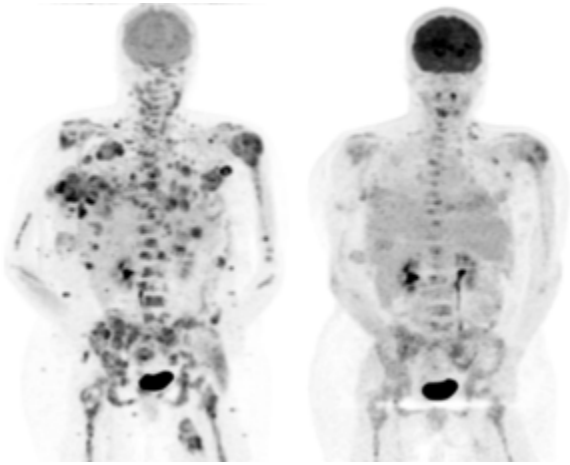
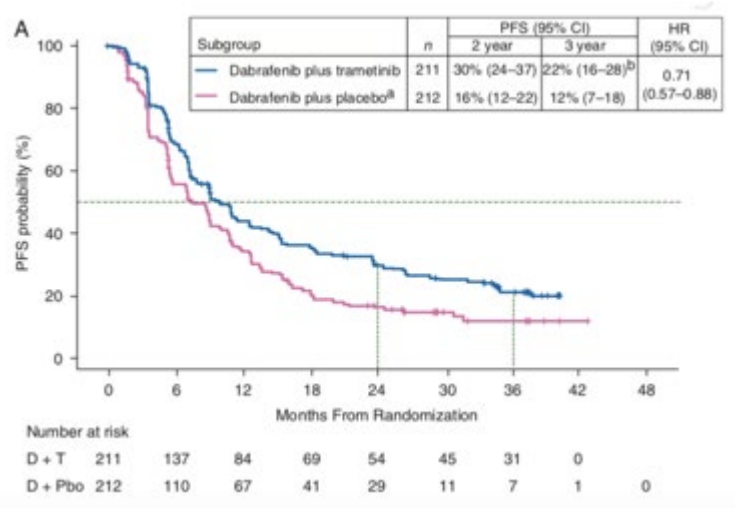
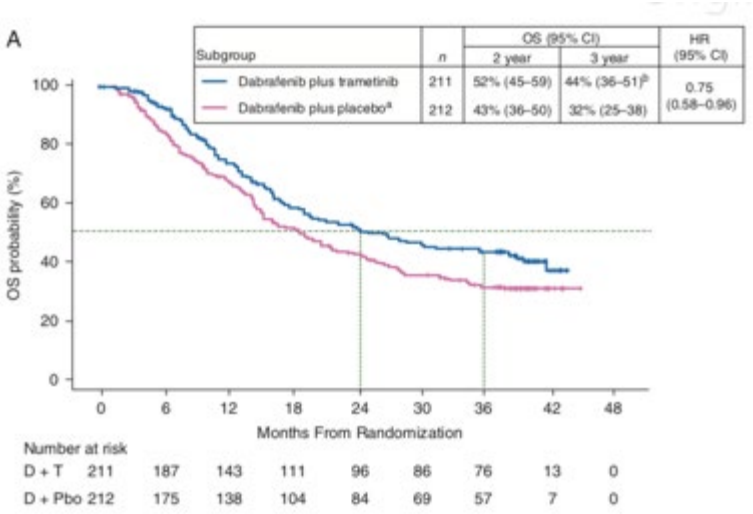




BRAFi + MEKi more efficacious (and not more toxic) than BRAFi alone



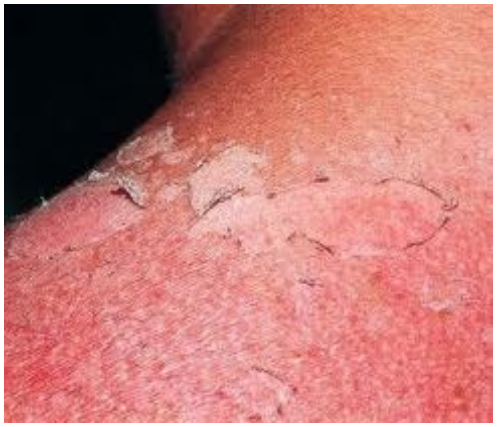


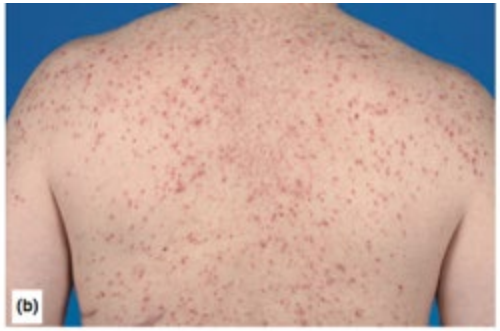
TOXICITY

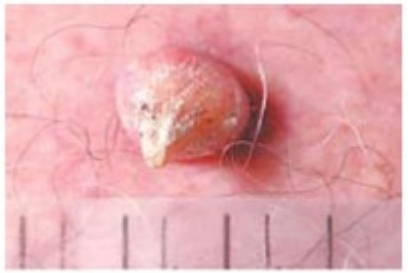
- Rate of Grade 3 or higher AEs similar in D+T (48%) vs D (50%) arms
- Pyrexia/chills, GI toxicities, edema higher in D+T arm
- SCC/KA, hyperkeratosis, Skin papillomas higher in D arm

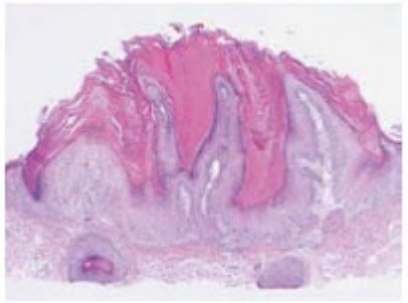
[Long G et al. Ann Oncol. 2017]

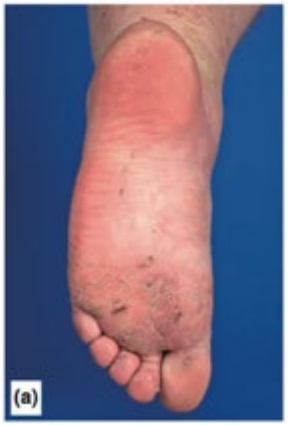
Also, toxicity can be substantial and continues for the duration of the treatment with effects on QoL

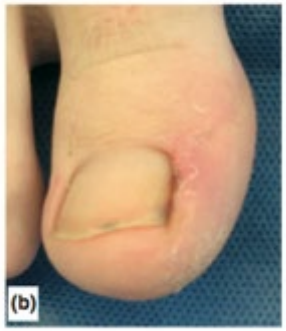




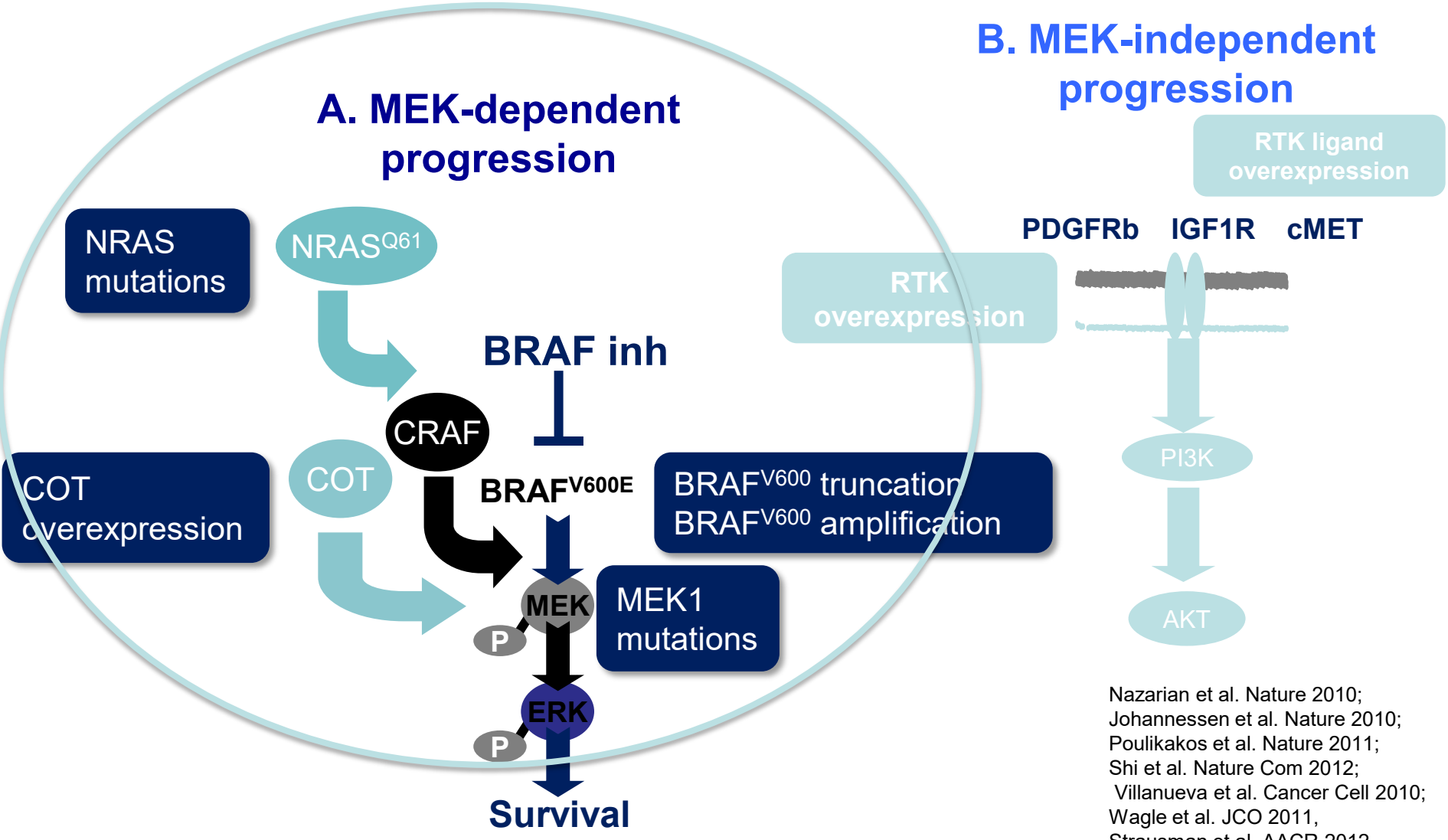








Unfortunately, resistance develops after initial benefit in the majority of patients



Nazarian et al. Nature 2010;
Johannessen et al. Nature 2010;
Poulikakos et al. Nature 2011;
Shi et al. Nature Com 2012;
Villanueva et al. Cancer Cell 2010;
Wagle et al. JCO 2011,
Strausman et al. AACR 2012

How to choose amongst therapeutic options?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Cutaneous Melanoma

FIRST-LINE THERAPY[2]

Metastatic or unresectable disease →

- **Preferred regimens**
  - **Anti PD-1 monotherapy[3,4]**
    - ◊ **Pembrolizumab (category 1)**
    - ◊ **Nivolumab (category 1)**
  - **Combination targeted therapy if *BRAF* V600-activating mutation;[6] preferred if clinically needed for early response[7,8,9,10]**
    - ◊ **Dabrafenib/trametinib (category 1)**
    - ◊ **Vemurafenib/cobimetinib (category 1)**
    - ◊ **Encorafenib/binimetinib (category 1**
- **Useful in certain circumstances**
  - **Nivolumab/ipilimumab (category 1)[3,4,5]**

How to choose amongst therapeutic options?

1. **Establish goals of care**
   - Durable disease-control
   - Rapid symptom palliation
   - Quality-of-life

2. **Match desired goals to the safety/efficacy characteristics of the therapy**
   - Rate of tumor regression (ORR) or clinical benefit
   - Kinetics of response (rapid vs delayed)
   - Duration of response
   - AEs
   - ?Cost

Table Treatment Characteristics and Endpoints to Consider in Tailoring Treatment for a Patient With Metastatic Melanoma

Desired Goal(s) of Care	Relevant Clinical Trial Endpoint to Consider	Treatment [Study]					
		High-dose IL-2[74,77,78]	Ipilimumab [18,27,36]	Pembrolizumab, Nivolumab [19,21,23,24,30,79]	Ipilimumab Plus Nivolumab [25,26]	BRAFi [4,53,54,56-59]	BRAFi Plus MEKi [56-58]
Cure (tumor eradication)	CR rate (%)	6	2	3–7	5 (Near CR: 31%)	4–9	9–13
	Median CR duration	NR (> 3.5 yr)	NA	NA	NA	NA	NA
Prolonged survival (improved disease control)	Median OS	11 mo	10–12 mo	17 mo	39 mo	14–17 mo	NR
	2-year OS (%)	25	30	43–48	75	NA	NA
	5-year OS (%)	NA	18	NA	NA	NA	NA
	Median PFS	1.6 mo	< 3 mo	4–7 mo	NA	5–9 mo	9–11 mo
	1-year PFS (%)	5	20–25	30–40	40	30–35	35–45
Symptom palliation (rapid tumor regression)	ORR (%)	10–15	10	28–40	53	45–51	64–76
	Median time to response	NA	Slow (14–16 wk)	9 wk	< 12 wk	Rapid (< 8 wk)	Rapid (< 8 wk)
Improved quality of life (less toxicity)	Grade 3+ drug-related AE rate (%)	80	15	11-22	53	37-63	35-65
	Drug discontinuation rate (%)	NA	NA	7	21	5-12	9-13

AE = adverse events; BRAFi = BRAF-inhibitors; CR = complete response; IL-2 = interleukin-2; MEKi = MEK-inhibitor; NA = not available; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

Bhatia S *et al,* 2015 Oncology (Williston Park)

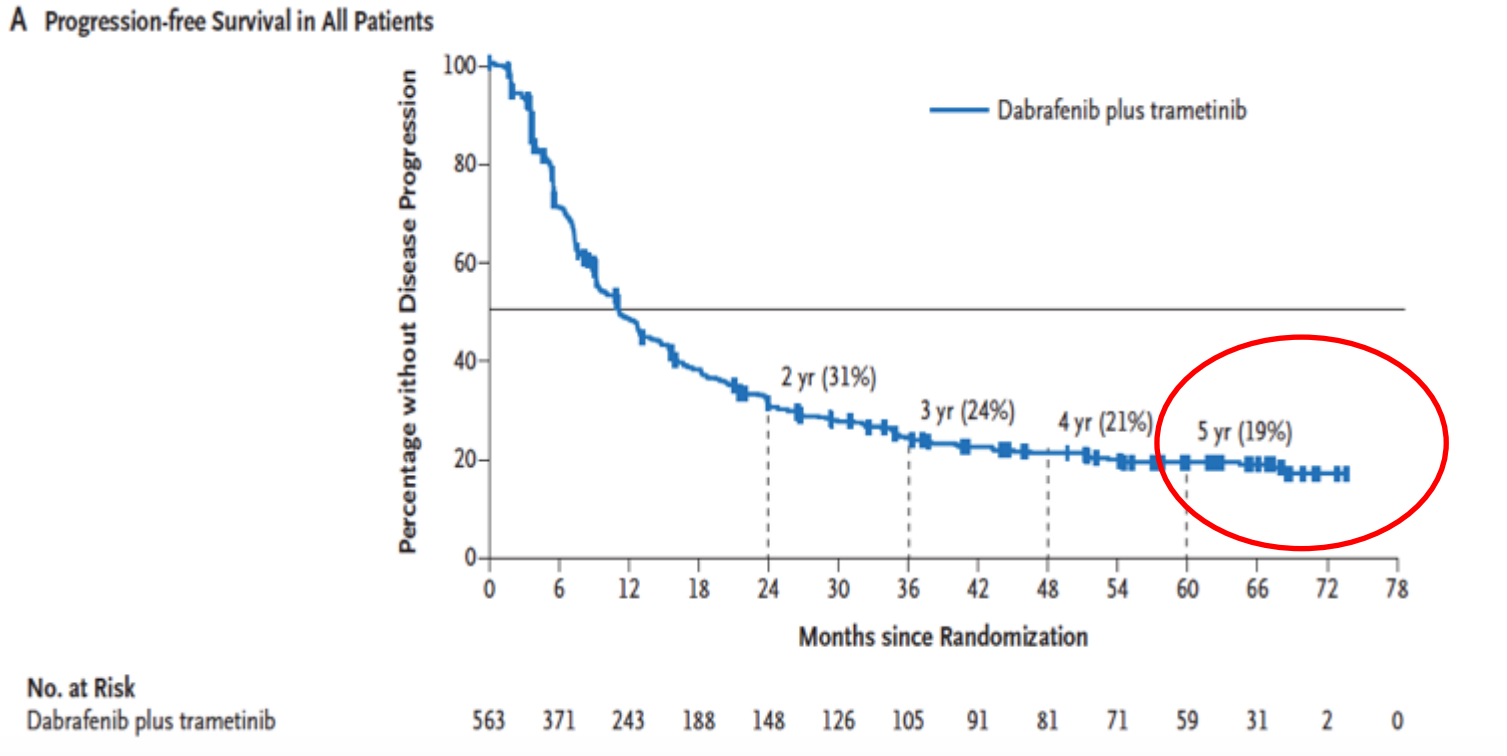
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma

C. Robert, J.J. Grob, D. Stroyakovskiy, B. Karaszewska, A. Hauschild, E. Levchenko, V. Chiarion Sileni, J. Schachter, C. Garbe, I. Bondarenko, H. Gogas, M. Mandalá, J.B.A.G. Haanen, C. Lebbé, A. Mackiewicz, P. Rutkowski, P.D. Nathan, A. Ribas, M.A. Davies, K.T. Flaherty, P. Burgess, M. Tan, E. Gasal, M. Voi, D. Schadendorf, and G.V. Long

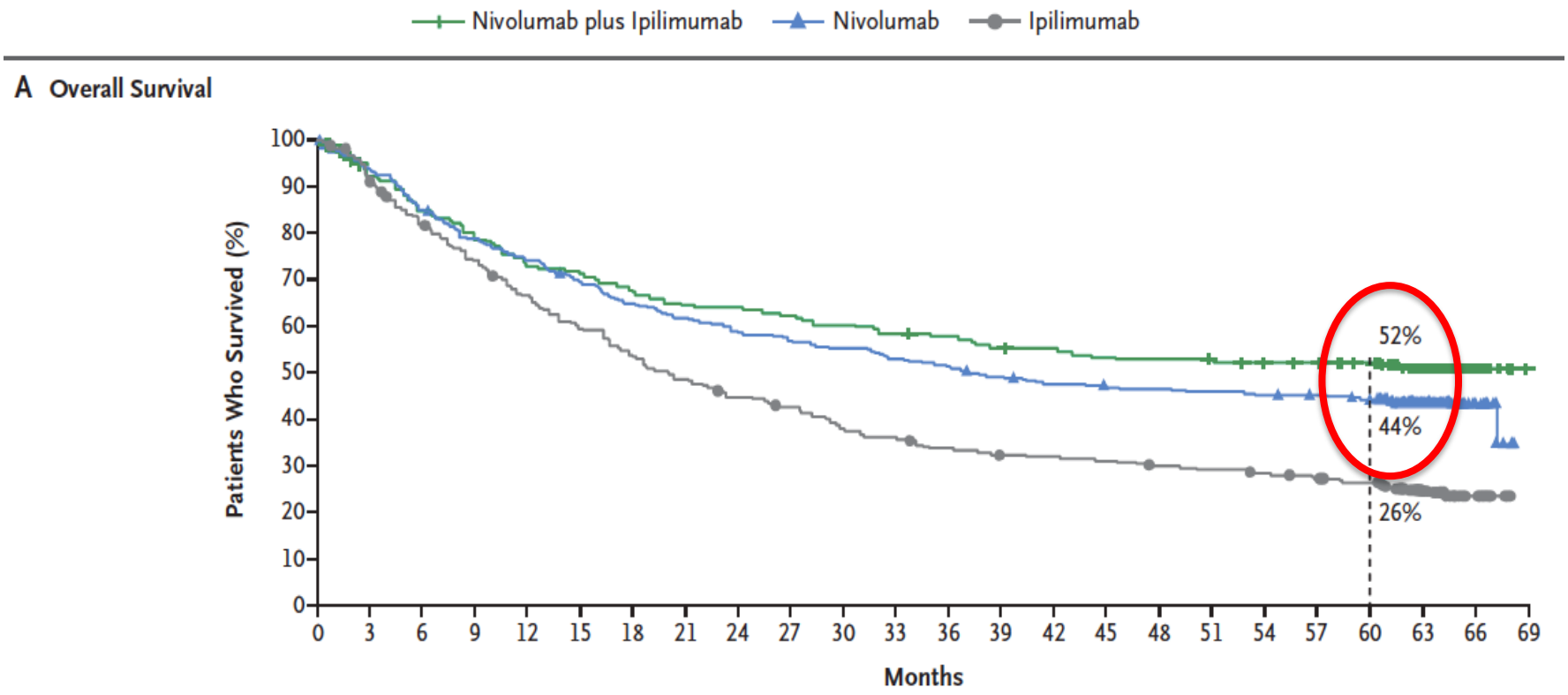
Durable PFS with BRAF-MEKi in some pts



88% (52/59) of patients, who were ongoing on trial and progression-free at 5-years, were **still receiving treatment (Dab or Tram or both).**

Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.-J. Grob, P. Rutkowski, C.D. Lao,

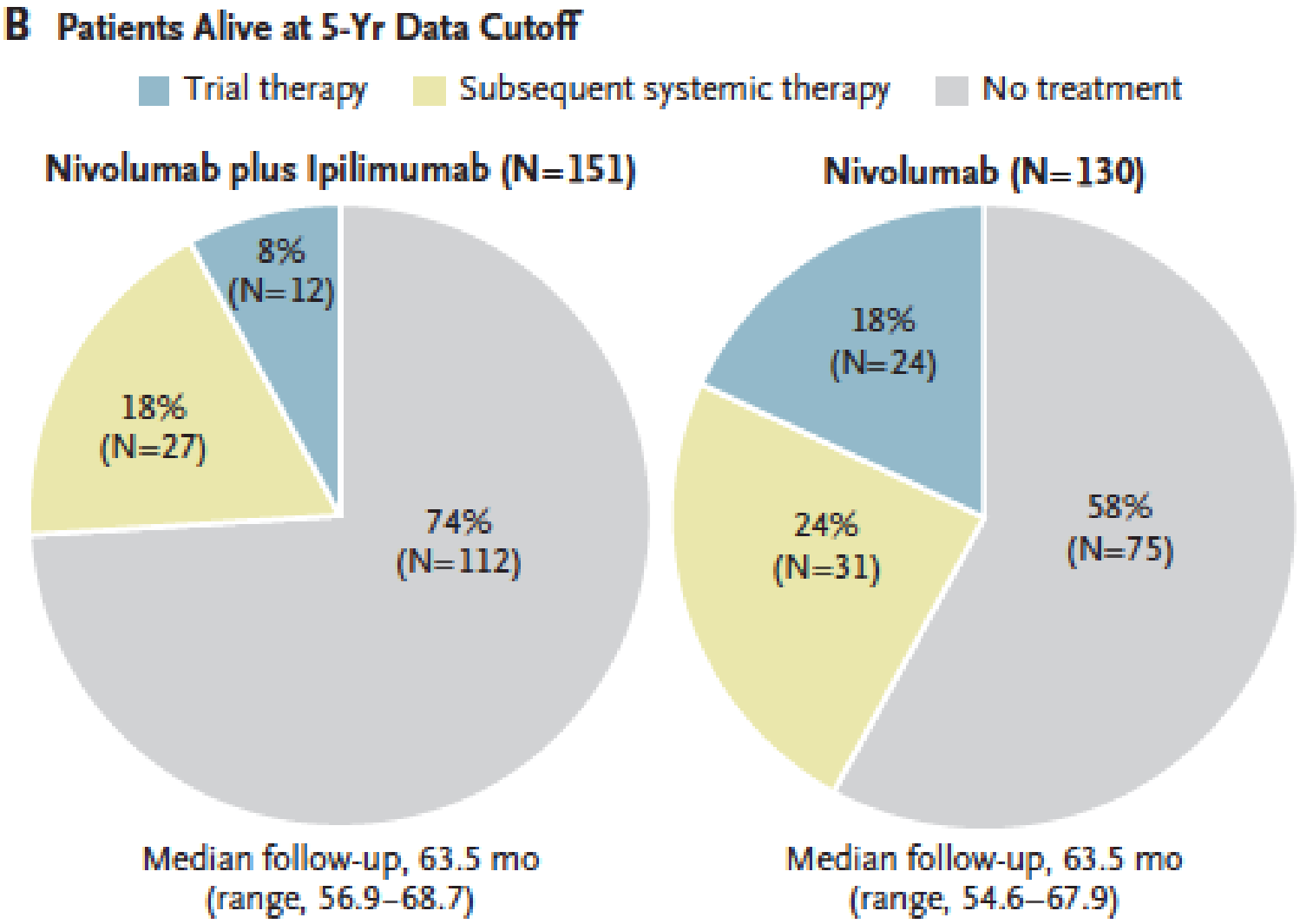


No. at Risk

Nivolumab plus ipilimumab	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
Nivolumab	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

DOI: 10.1056/NEJMoa1910836

Treatment-free status after Immunotherapy



DOI: 10.1056/NEJMoa1910836

Immunotherapy vs BRAF-MEKi: LTFU

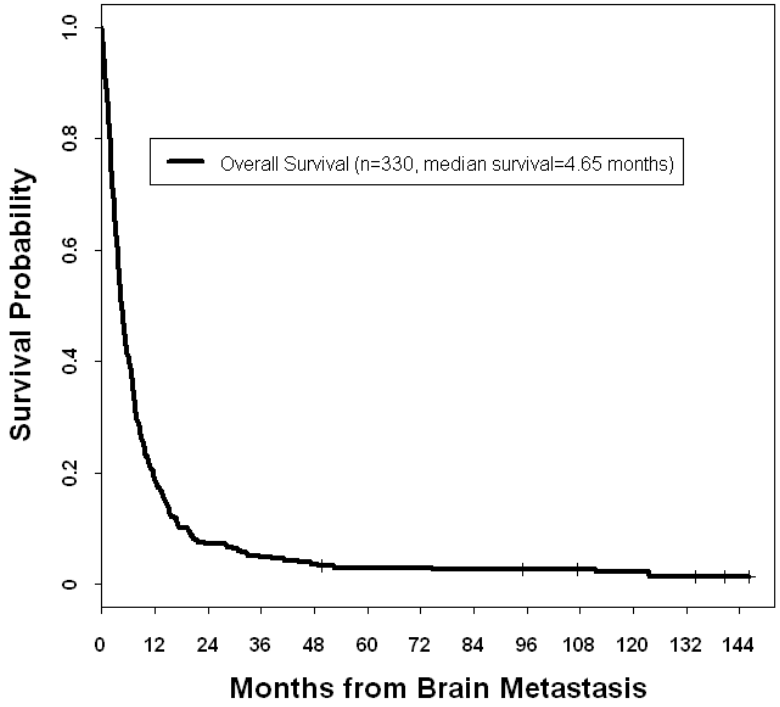
	BRAF-MEKi (Combi-D and -V)	Ipi-Nivo (Checkmate 067)
ORR	**68%**	58%
CR	19%	21%
4-yr PFS	21%	37%
4-yr OS	37%	**62%**
Ongoing Study Treatment	**88%**	**11%**

How to choose amongst therapeutic options?

SB approach	BRAF wild type	BRAF mutated
Low Volume, Asymptomatic disease	**Immunotherapy** (anti PD-1 alone or in combination)	**Immunotherapy (preferred)** **BRAFi +/- MEKi (acceptable)**
Bulky disease, Symptomatic	**Immunotherapy** (anti PD-1 alone or in combination) **Chemotherapy**	**BRAFi +/- MEKi followed by Immunotherapy**

Melanoma Brain Metastases (MBMs)

- Among the highest risk of brain metastases among common solid tumors
  - 10-20% at diagnosis of stage IV
  - Up to 50% over course of disease
  - Up to 70% in autopsy studies
- Common site of treatment failure for systemic therapies
- Historically median OS ~ 4 months



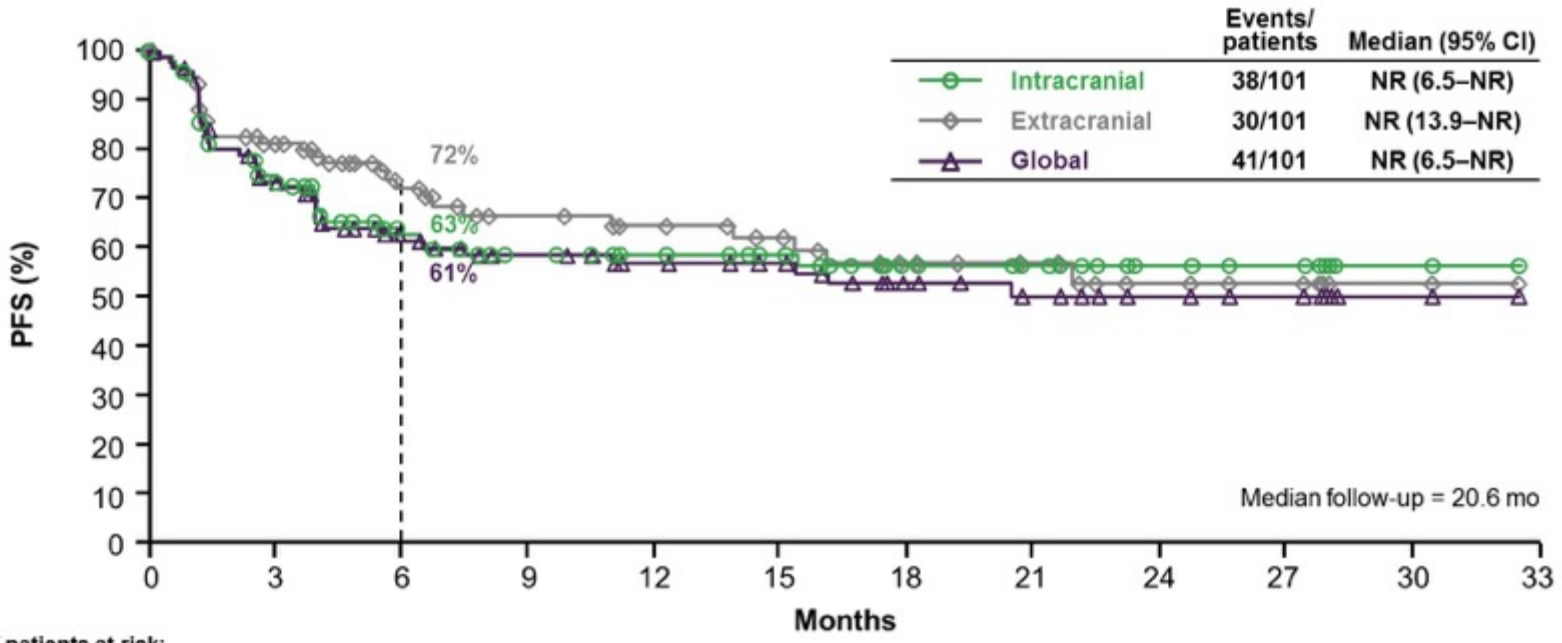
Davies, *Cancer,* 2011
Cohen et al, *PCMR,* 2016

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

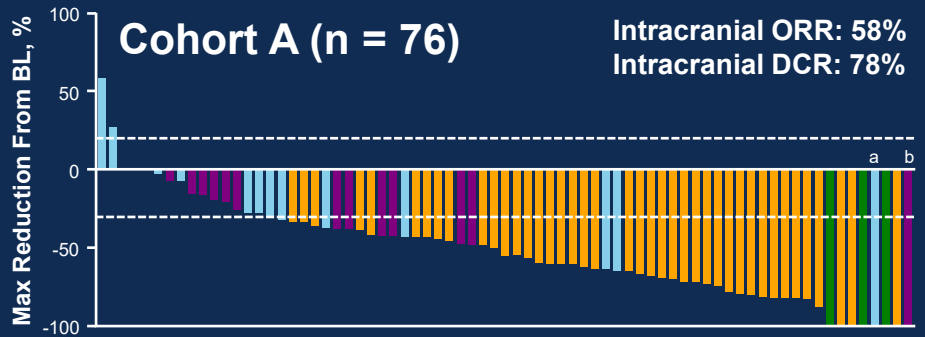
CheckMate 204

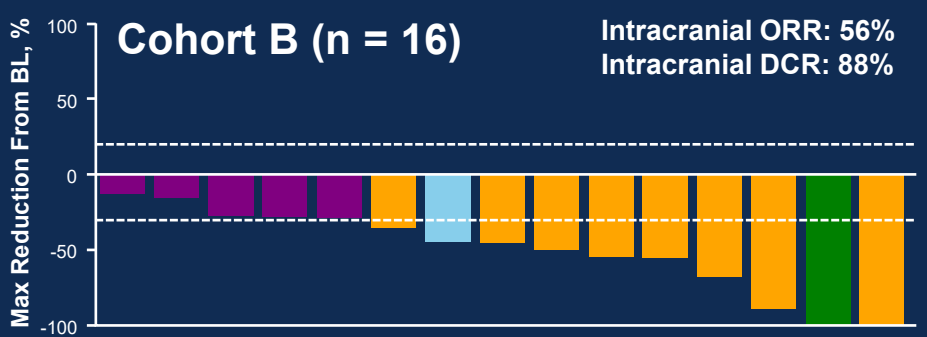
Progression-Free Survival – Asymptomatic Patients

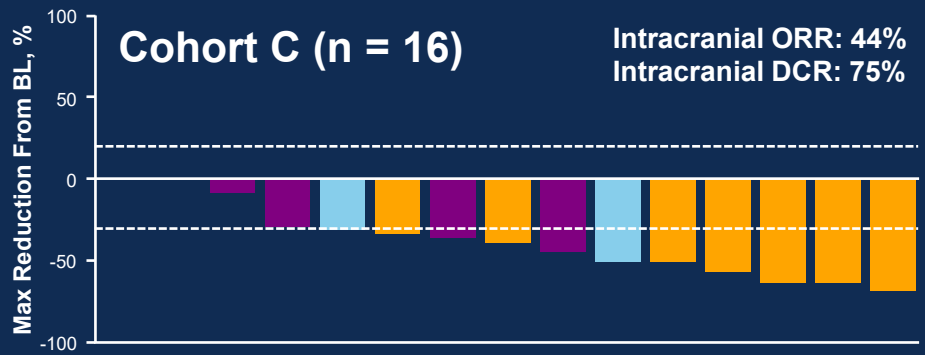


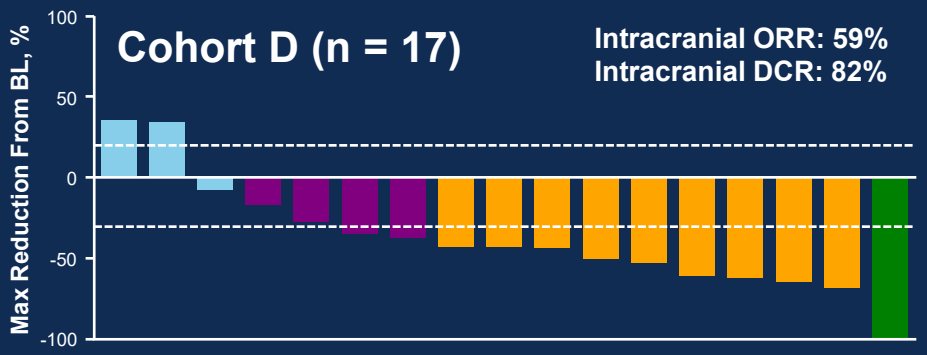
BRAF-MEKi in MBMs

Intracranial Response









Best Confirmed IR[c]: CR PR SD PD

CR, complete response; SD, stable disease.
[a] Patient had a CR in the target lesion, but best confirmed response was determined to be PD due to development of an unequivocal new lesion; [b] Patient had an unconfirmed CR, but best confirmed response was SD; [c] Investigator assessed; these results were supported by independent review.

MBMs: Conclusions

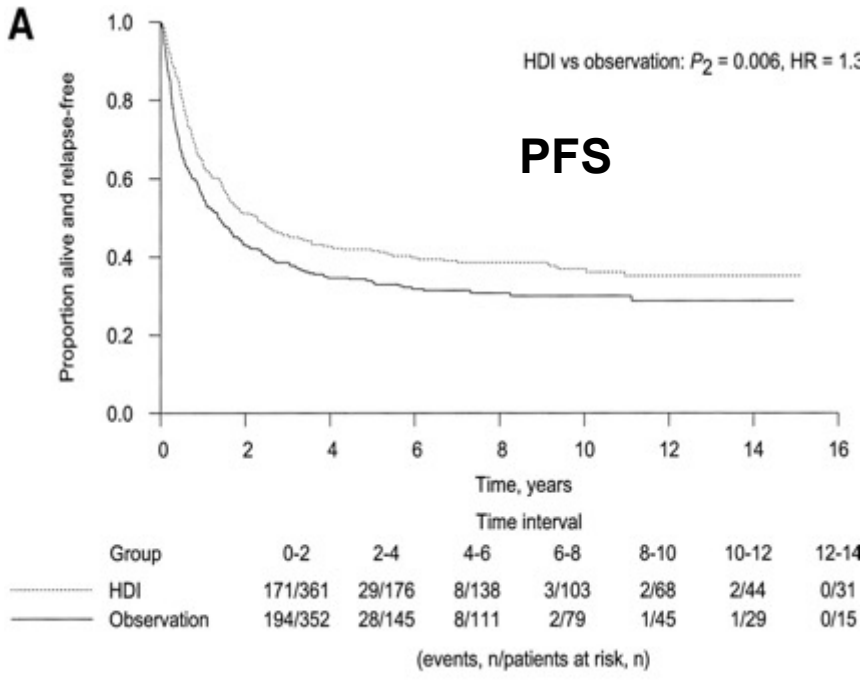
- MBMs need **systemic** therapy for long-term control.

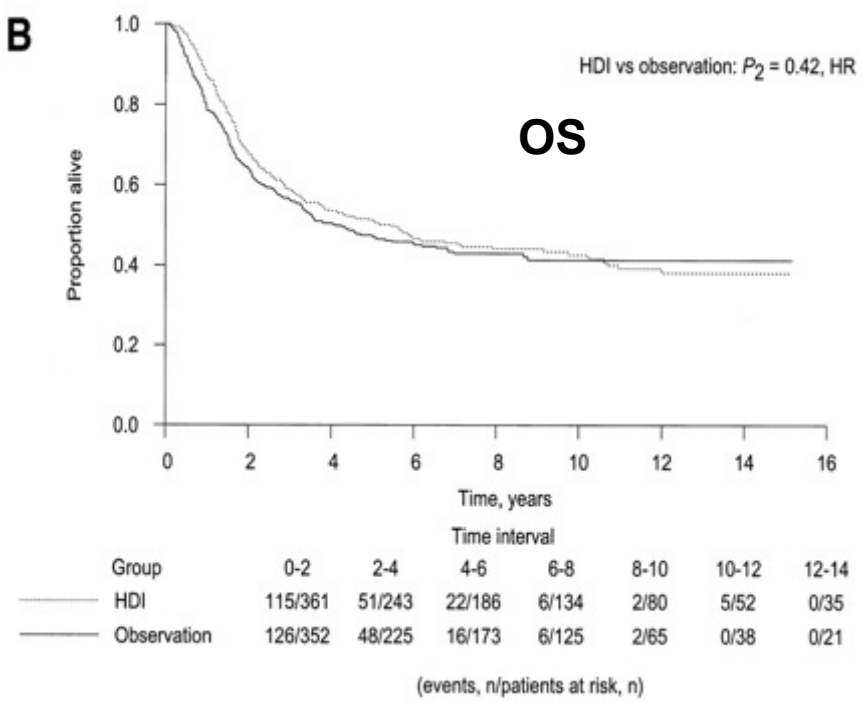
- The durable intracranial responses observed in patients with asymptomatic brain metastases supports the use of NIVO+IPI as first-line therapy.

- Symptomatic patients remain difficult to treat, but can benefit from the high rate of initial intra-cranial responses with BRAF-MEKi in the BRAF-mutant melanoma, although duration of responses shorter than in extracranial sites.

Adjuvant therapy in high-risk melanoma

Adjuvant interferon-alfa was the (poor) standard-of-care for decades





Dubious efficacy

<u>Considerable toxicity</u>

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy

A.M.M. Eggermont, V. Chiarion-Sileni, J.-J. Grob, R. Dummer, J.D. Wolchok, H. Schmidt, O. Hamid, C. Robert, P.A. Ascierto, J.M. Richards, C. Lebbé, V. Ferraresi, M. Smylie, J.S. Weber, M. Maio, L. Bastholt, L. Mortier, L. Thomas, S. Tahir, A. Hauschild, J.C. Hassel, F.S. Hodi, C. Taitt, V. de Pril, G. de Schaetzen, S. Suciu, and A. Testori

- **Toxicity**: Grade 3 or higher IRAEs rate > 40%

- **Approximate cost of 3-year course at current prices:** $1.5 million

However, toxicity and cost remain concerns to utilization

- **Toxicity**: Grade 3 or higher IRAEs rate > 40%
- **Approximate cost of 3-year course at current prices:** $1.5 million

The NEW ENGLAND JOURNAL of MEDICINE

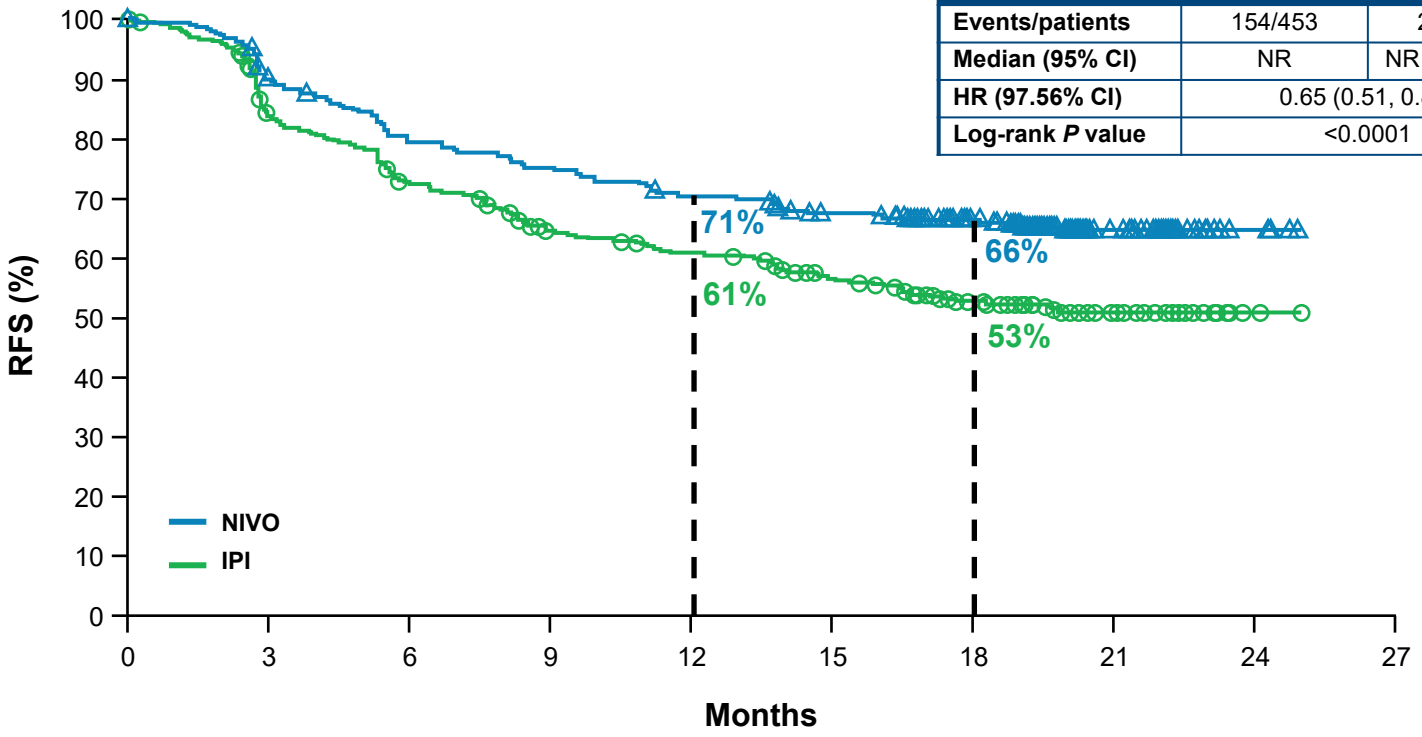
ORIGINAL ARTICLE

Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma

J. Weber, M. Mandala, M. Del Vecchio, H.J. Gogas, A.M. Arance, C.L. Cowey, S. Dalle, M. Schenker, V. Chiarion-Sileni, I. Marquez-Rodas, J.-J. Grob, M.O. Butler, M.R. Middleton, M. Maio, V. Atkinson, P. Queirolo, R. Gonzalez, R.R. Kudchadkar, M. Smylie, N. Meyer, L. Mortier, M.B. Atkins, G.V. Long, S. Bhatia, C. Lebbé, P. Rutkowski, K. Yokota, N. Yamazaki, T.M. Kim, V. de Pril, J. Sabater, A. Qureshi, J. Larkin, and P.A. Ascierto, for the CheckMate 238 Collaborators*

Primary Endpoint: RFS

	NIVO	IPI
Events/patients	154/453	206/453
Median (95% CI)	NR	NR (16.6, NR)
HR (97.56% CI)	0.65 (0.51, 0.83)	
Log-rank *P* value	<0.0001	

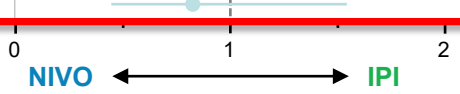


Number of patients at risk

NIVO	453	399	353	332	311	291	249	71	5	0
IPI	453	364	314	269	252	225	184	56	2	0

RFS: Prespecified Subgroups

Subgroup		No. of events/no. of patients		Unstratified HR (95% CI)	Unstratified HR (95% CI)
		NIVO 3 mg/kg	IPI 10 mg/kg		
Overall	Overall	154/453	206/453	0.66 (0.53, 0.81)	
Age	<65 years	106/333	147/339	0.65 (0.51, 0.84)	
	≥65 years	48/120	59/114	0.66 (0.45, 0.97)	
Sex	Male	99/258	133/269	0.68 (0.53, 0.88)	
	Female	55/195	73/184	0.63 (0.44, 0.89)	
Stage (CRF)	Stage IIIb	41/163	54/148	0.67 (0.44, 1.00)	
	Stage IIIc	79/204	109/218	0.65 (0.49, 0.87)	
	Stage IV M1a-M1b	25/62	35/66	0.63 (0.38, 1.05)	
	Stage IV M1c	8/20	8/21	1.00 (0.37, 2.66)	
	Not reported	1/2	0/0		
Stage III: Ulceration	Absent	58/201	94/216	0.59 (0.42, 0.82)	
	Present	60/153	64/135	0.73 (0.51, 1.04)	
	Not reported	2/15	5/15	0.39 (0.07, 2.00)	
Stage III: Lymph node involvement	Microscopic	41/125	55/134	0.71 (0.47, 1.07)	
	Macroscopic	72/219	101/214	0.62 (0.46, 0.84)	
	Not reported	7/25	7/18	0.60 (0.21, 1.72)	
PD-L1 status	<5%/indeterminate	123/300	149/299	0.71 (0.56, 0.90)	
	≥5%	31/152	57/154	0.50 (0.32, 0.78)	
***BRAF* mutation status**	Mutant	63/187	84/194	0.72 (0.52, 1.00)	
	Wild-type	67/197	105/214	0.58 (0.43, 0.79)	
	Not reported	24/69	17/45	0.83 (0.45, 1.54)	

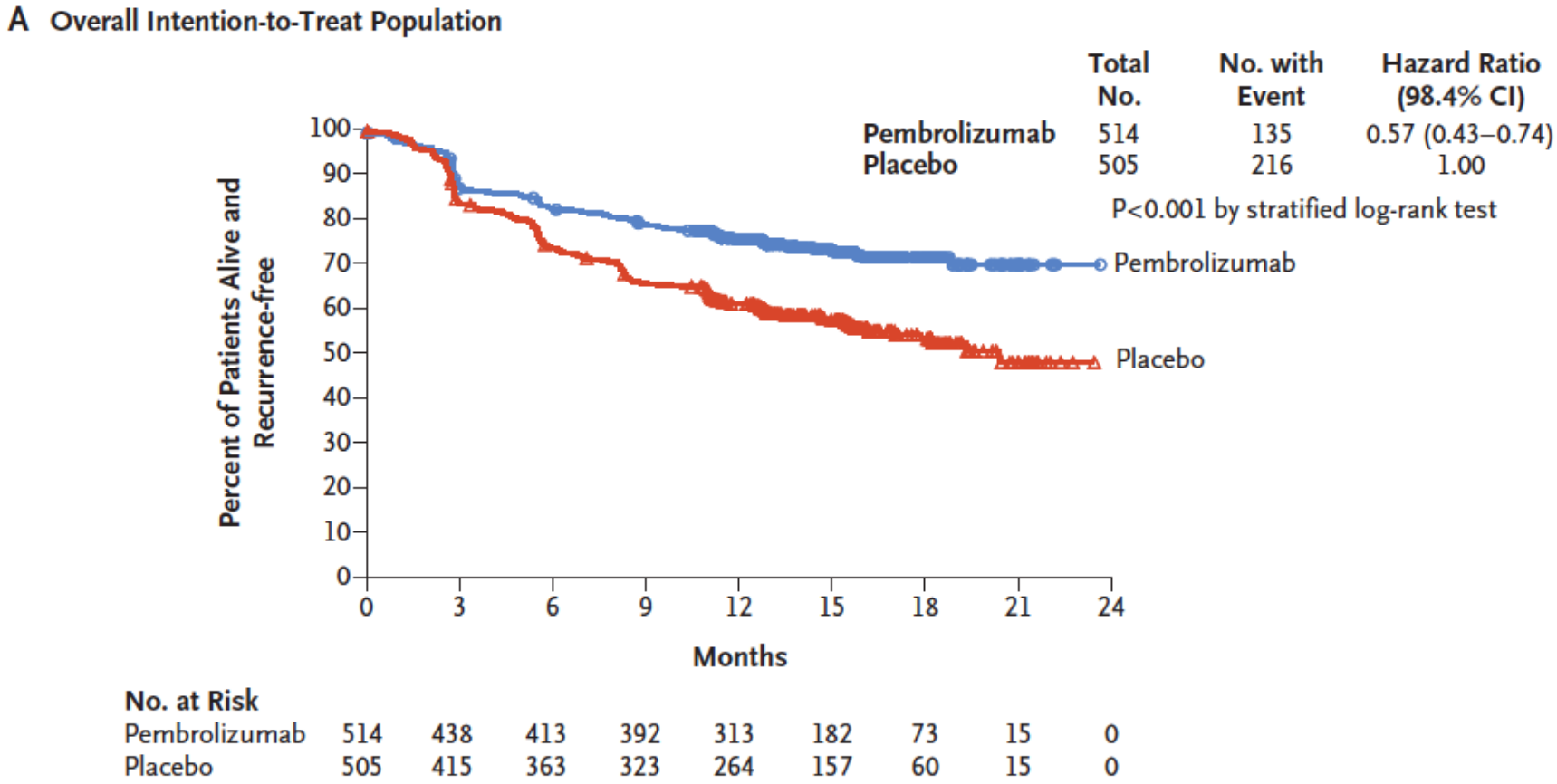


Safety Summary

AE, n (%)	NIVO (n = 452)		IPI (n = 453)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AE	438 (97)	115 (25)	446 (98)	250 (55)
Treatment-related AE	385 (85)	65 (14)	434 (96)	208 (46)
Any AE leading to discontinuation	44 (10)	21 (5)	193 (43)	140 (31)
Treatment-related AE leading to discontinuation	35 (8)	16 (4)	189 (42)	136 (30)

- There were no treatment-related deaths in the NIVO group
- There were 2 (0.4%) treatment-related deaths in the IPI group (marrow aplasia and colitis), both >100 days after the last dose

Adjuvant Pembro in Melanoma



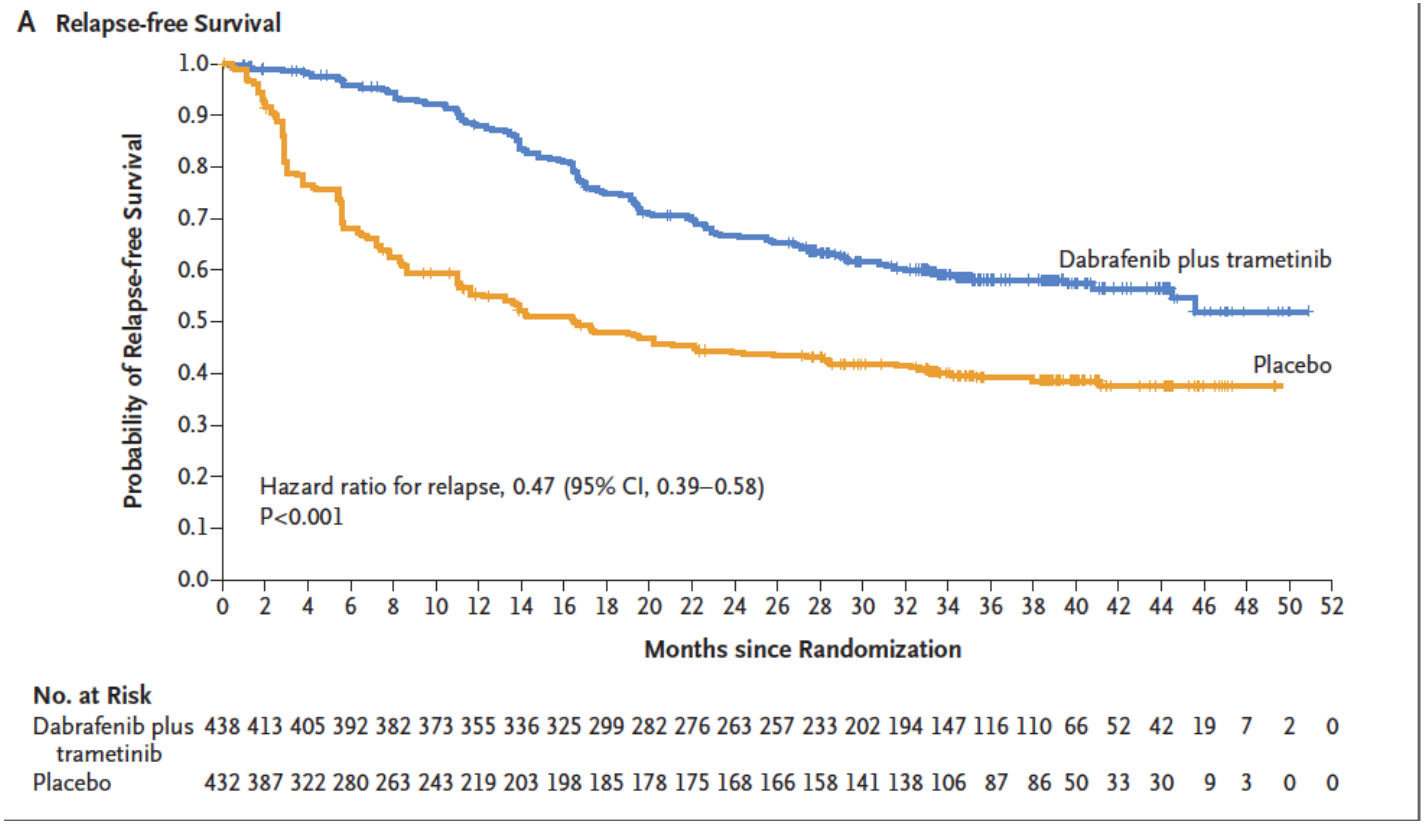
{Eggermont AM et al *NEJM* 2018}

The NEW ENGLAND JOURNAL of MEDICINE

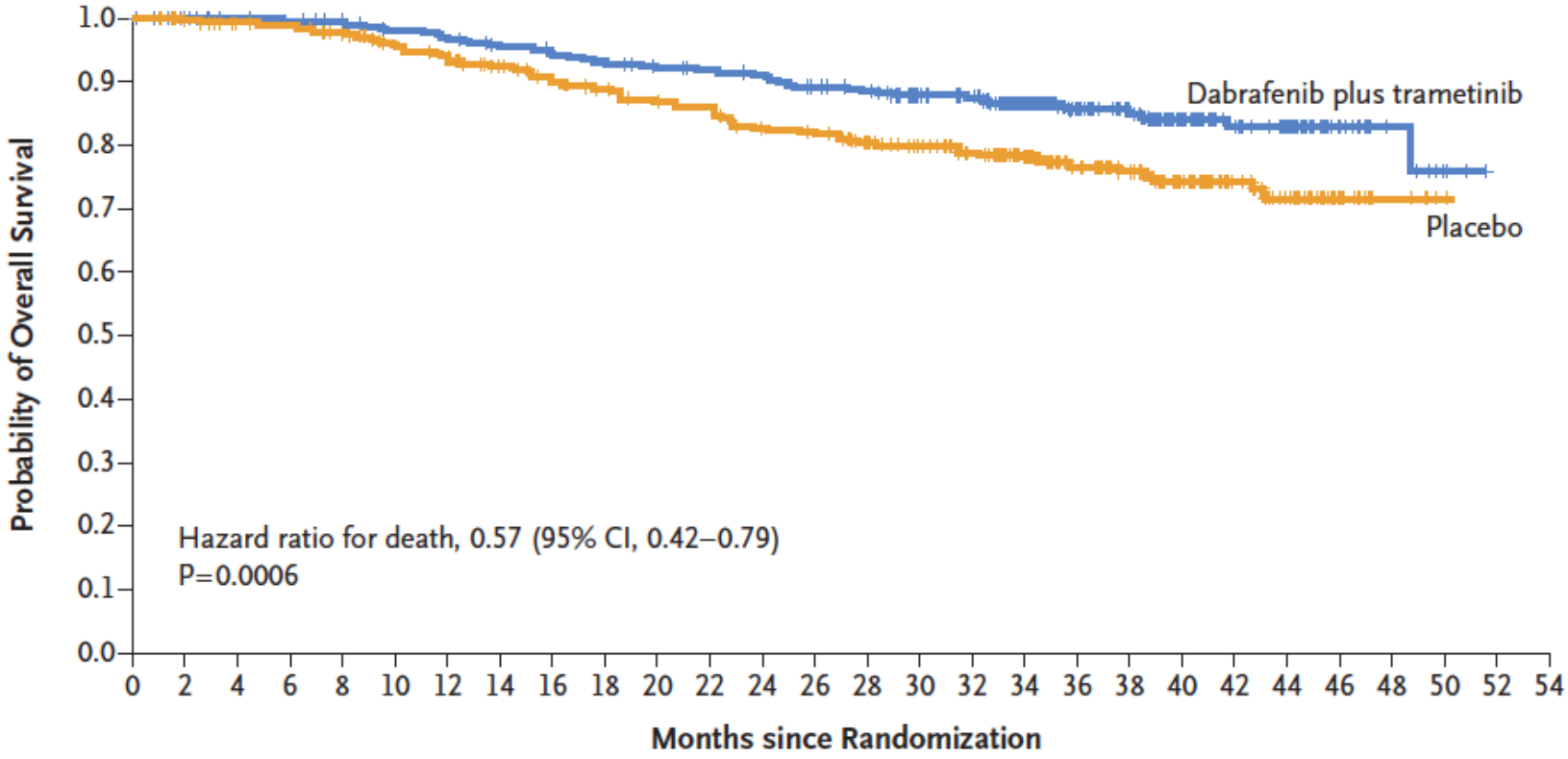
ORIGINAL ARTICLE

Adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma

G.V. Long, A. Hauschild, M. Santinami, V. Atkinson, M. Mandalà, V. Chiarion-Sileni, J. Larkin, M. Nyakas, C. Dutriaux, A. Haydon, C. Robert, L. Mortier, J. Schachter, D. Schadendorf, T. Lesimple, R. Plummer, R. Ji, P. Zhang, B. Mookerjee, J. Legos, R. Kefford, R. Dummer, and J.M. Kirkwood



B **Overall Survival**



No. at Risk

Dabrafenib plus trametinib	438	426	416	414	408	401	395	387	381	376	370	366	362	352	328	301	291	233	180	164	105	82	67	28	12	5	0	0
Placebo	432	425	415	410	401	386	378	362	346	337	328	323	308	303	284	269	252	202	164	152	94	64	51	17	7	1	0	0

What should we do in clinic?

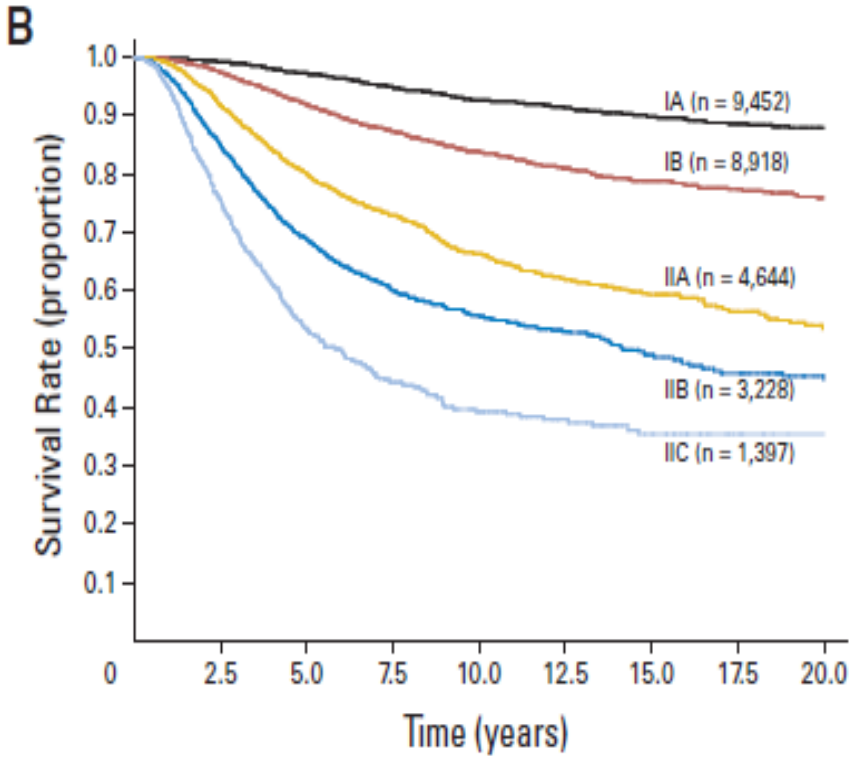
For BRAF-WT patients, PD-1 monotherapy is most appropriate at this time.

Better efficacy, lower toxicity than HD-Ipi

For BRAF-mutant patients, should we use anti-PD-1 or Dab-tram?

	2-year RFS (%)	Toxicity > Gr 3 AEs (%)
All melanoma		
Placebo	43	
Ipilimumab	51	42
Nivolumab	66	9
BRAF-mutant melanoma		
Placebo	44	
Dab-Tram	67	41

High-risk stage II patients are finally getting attention



Safety and Efficacy of Pembrolizumab Compared to Placebo in Resected High-risk Stage II Melanoma (MK-3475-716/KEYNOTE-716)

ClinicalTrials.gov Identifier: NCT03553836

N=954

Open at SCCA

Balch , J Clin Oncol 2009; 27(36):6199-6206

Thank you!!

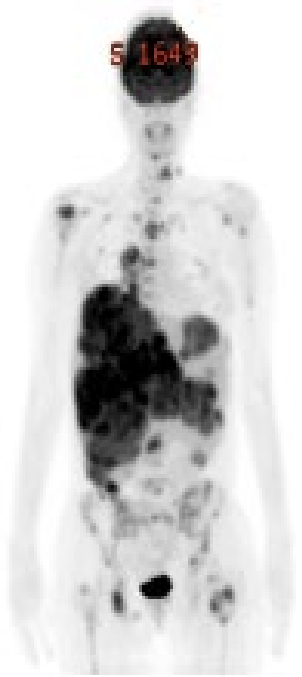
Case

A 75-year old man presents with progressive anorexia, weight loss, night sweats, fatigue and right-sided abdominal pain for the last few weeks.

Imaging studies show **widely disseminated metastase** in multiple organs, including **greater than 50% liver involvement**. Brain MRI showed **5 brain metastases (largest was 1.5 cm in R-frontal lobe)**; he denied neurologic symptoms and neuro exam was WNL.

Biopsy of a liver tumor reveals **metastatic melanoma** with **BRAF V600E mutation present**.

Laboratory analyses reveal Hemoglobin 10, **AST 75, AL. 85, ALK-P 375 and Bilirubin 1.5**. His ECOG **performance score is 2**.



Baseline

What will you recommend next?

A. Whole brain radiation therapy.

B. PD-1 blockade (Pembrolizumab or Nivolumab)

C. Ipilimumab plus Nivolumab

D. BRAFi + MEKi

E. Hospice

Melanoma Subtypes

Ocular (uveal) melanoma

Frequent somatic mutations of *GNAQ* in uveal melanoma and blue naevi

Catherine D. Van Raamsdonk[1], Vladimir Bezrookove[2], Gary Green[2], Jürgen Bauer[3,4], Lona Gaugler[2], Joan M. O'Brien[3], Elizabeth M. Simpson[5], Gregory S. Barsh[6] & Boris C. Bastian[2]

Local therapy options: Proton RT; Plaque Brachytherapy; Enucleation)

High-risk of **liver metastases**; can have **prolonged dormancy**

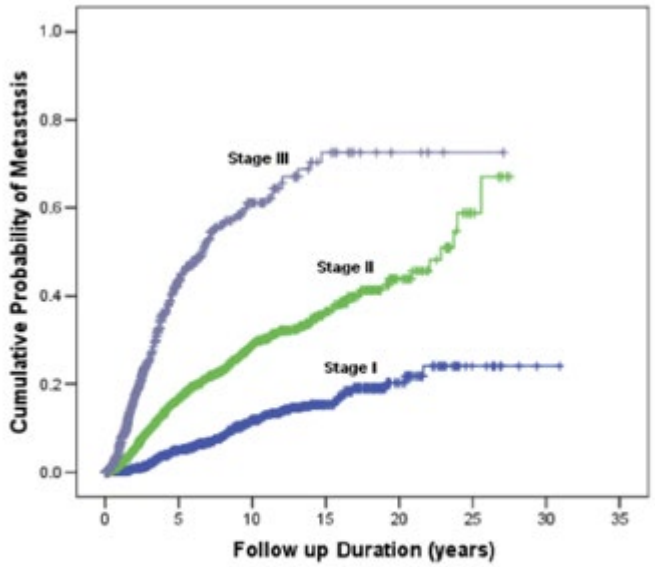


Figure 2. Kaplan–Meier estimate of metastasis from posterior uveal melanoma in 7731 patients, based on the American Joint Cancer Committee (AJCC) tumor staging.

Frequent Mutation of *BAP1* in Metastasizing Uveal Melanomas

J. William Harbour,[1,3*] Michael D. Onken,[1] Elisha D. O. Roberson,[2] Shenghui Duan,[2] Li Cao,[2] Lori A. Worley,[1] M. Laurin Council,[2] Katie A. Matatall,[1] Cynthia Helms,[2] Anne M. Bowcock[2,3*]

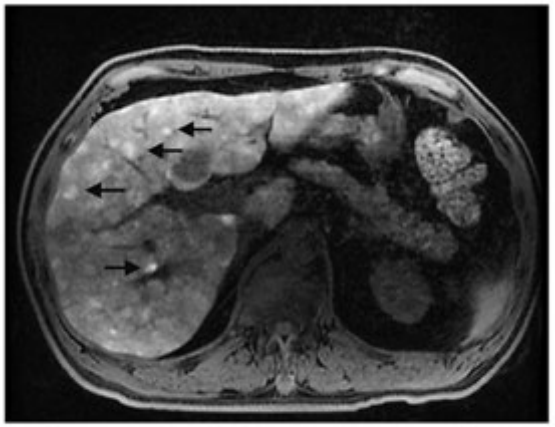
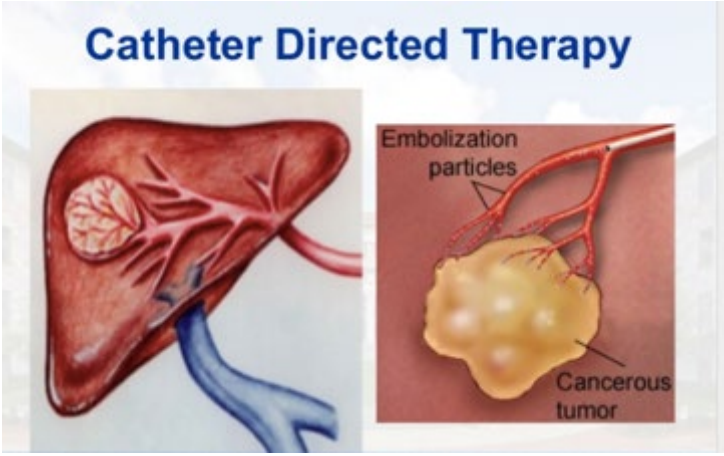


Fig. 3. Numerous T1-weighted fat suppressed hyperintense lesions on MRI compatible with melanoma metastases (arrows).



Imatinib for Melanomas Harboring Mutationally Activated or Amplified *KIT* Arising on Mucosal, Acral, and Chronically Sun-Damaged Skin

F. Stephen Hodi, Christopher L. Corless, Anita Giobbie-Hurder, Jonathan A. Fletcher, Meijun Zhu, Adrian Marino-Enriquez, Philip Friedlander, Rene Gonzalez, Jeffrey S. Weber, Thomas F. Gajewski, Steven J. O'Day, Kevin B. Kim, Donald Lawrence, Keith T. Flaherty, Jason J. Luke, Frances A. Collichio, Marc S. Ernstoff, Michael C. Heinrich, Carol Beadling, Katherine A. Zukotynski, Jeffrey T. Yap, Annick D. Van den Abbeele, George D. Demetri, and David E. Fisher

Hodi FS. JCO 2013

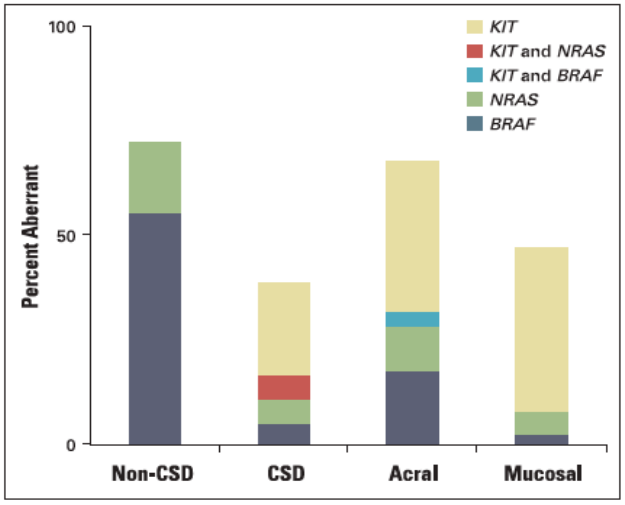
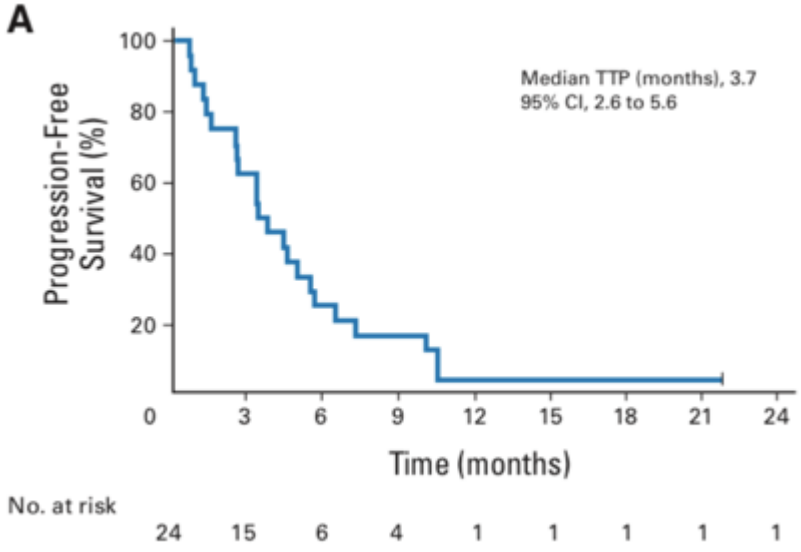


Fig 2. Frequency distribution of genetic alterations in BRAF, *NRAS*, and *KIT* among four groups of melanoma. Non-CSD, melanomas on skin without chronic sun-induced damage; CSD, melanomas on skin with chronic sun-induced as evidenced by the presence of marked solar elastosis; acral, melanomas on the soles, palms, or sub-ungual sites; mucosal, melanomas on mucosal membranes. One CSD melanoma had a *KIT* and an *NRAS* mutation, and one acral melanoma had a *KIT* and a *BRAF* mutation.

Curtin JA. JCO 2006

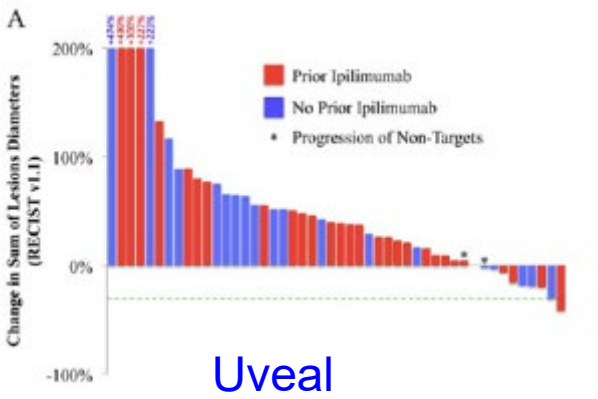
BORR was 54% (7/13) in KIT-mutant (0% in KIT-amplified)



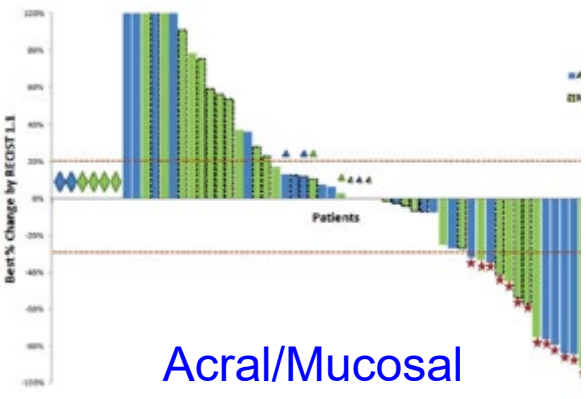
Editorial

Disparate Clinical Activity of PD-1 Blockade in Melanoma Subtypes: Know thy Enemy!

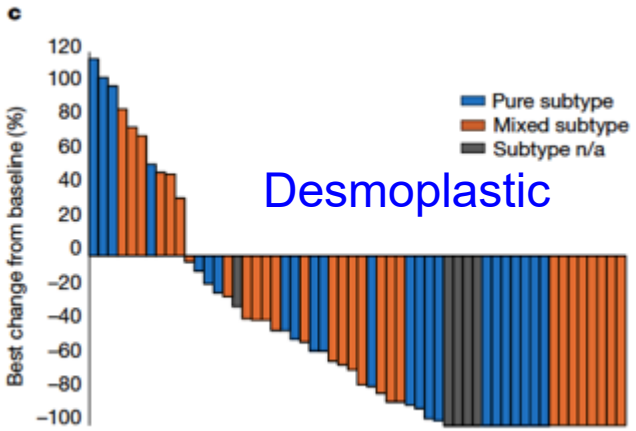
Shailender Bhatia, MD[1,2] and Kim Margolin, MD[3]



Uveal



Acral/Mucosal



Desmoplastic

LETTER

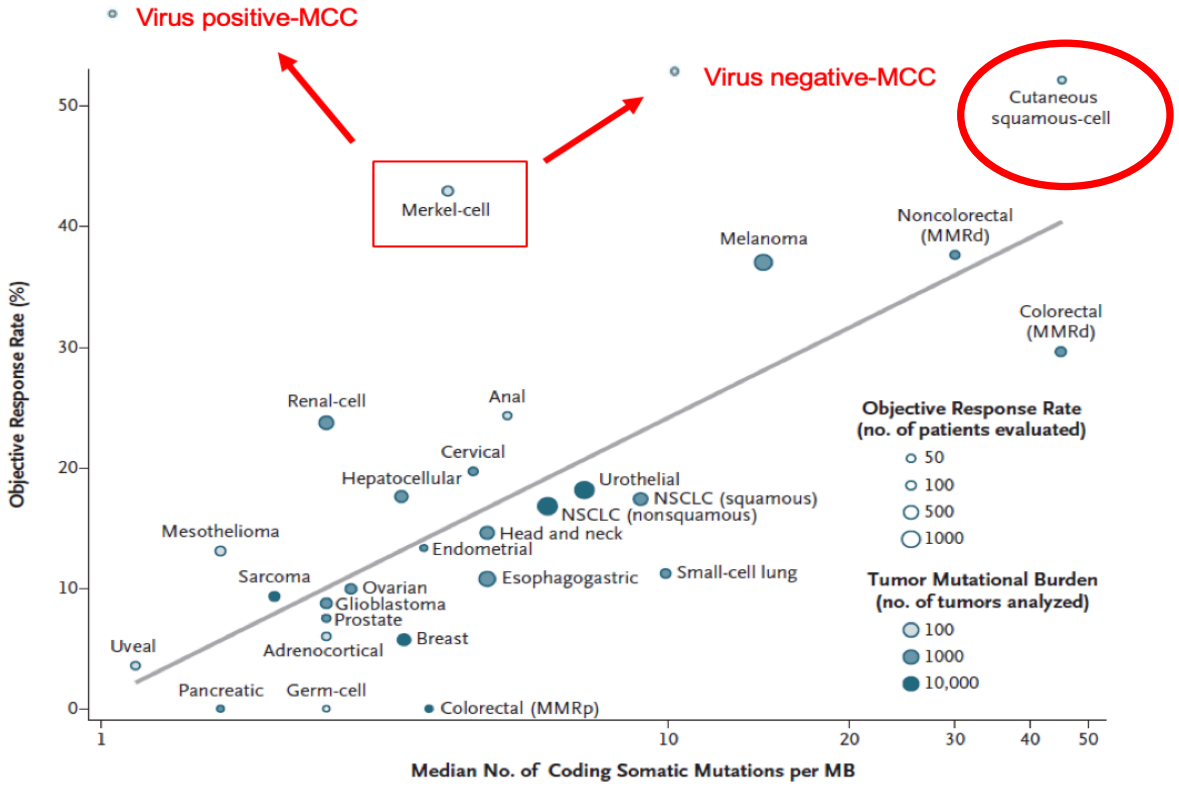
doi:10.1038/nature25187

High response rate to PD-1 blockade in desmoplastic melanomas

Zeynep Eroglu[1,2*], Jesse M. Zaretsky[1*], Siwen Hu-Lieskovan[1*], Dae Won Kim[2,3], Alain Algazi[4], Douglas B. Johnson[5], Elizabeth Liniker[6], Ben Kong[7], Rodrigo Munhoz[8,9], Suthee Rapisuwon[10], Pier Federico Gherardini[11], Bartosz Chmielowski[1], Xiaoyan Wang[1], I. Peter Shintaku[1], Cody Wei[1], Jeffrey A. Sosman[5†], Richard W. Joseph[12], Michael A. Postow[8,9], Matteo S. Carlino[6,7,13], Wen-Jen Hwu[3], Richard A. Scolyer[6,13,14], Jane Messina[2], Alistair J. Cochran[1], Georgina V. Long[6,13,15] & Antoni Ribas[1]

II. Non Melanoma Skin Cancers

NMSCs have a strong rationale for immunotherapy



BCC also has a very high TMB (median ~45/MB)

Yarchoan, et al, NEJM 2017
Harms, et al, CA Res, 2015
Walter A, et al, CCR 2010
Paulson, et al, unpublished

Merkel cell Carcinoma (MCC)

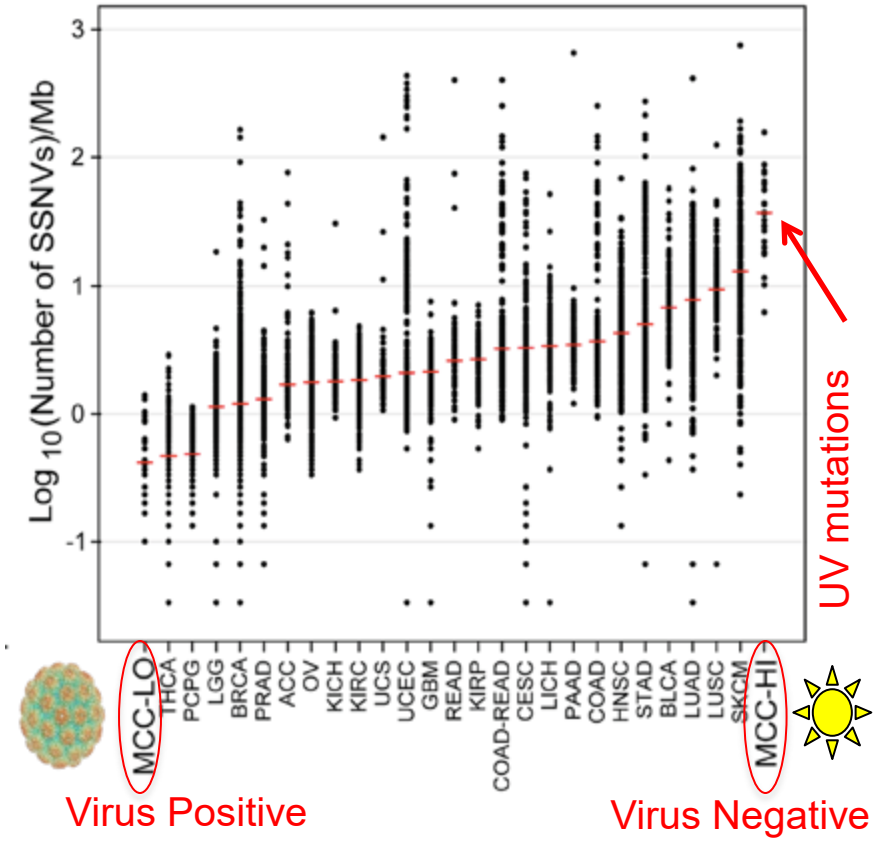
- Merkel cell polyoma virus (MCPyV) in 80% of MCC tumors

{Feng H et al *Science* 2008}

- UV-induced high mutational load (Neoantigens)

- Immune exhaustion of TILs [reversible with Immune Checkpoint Inhibitors (ICIs)]

[Afanasiev O et al. *Clin Cancer Res*. 2013]



{Goh et al. Oncotarget 2015}

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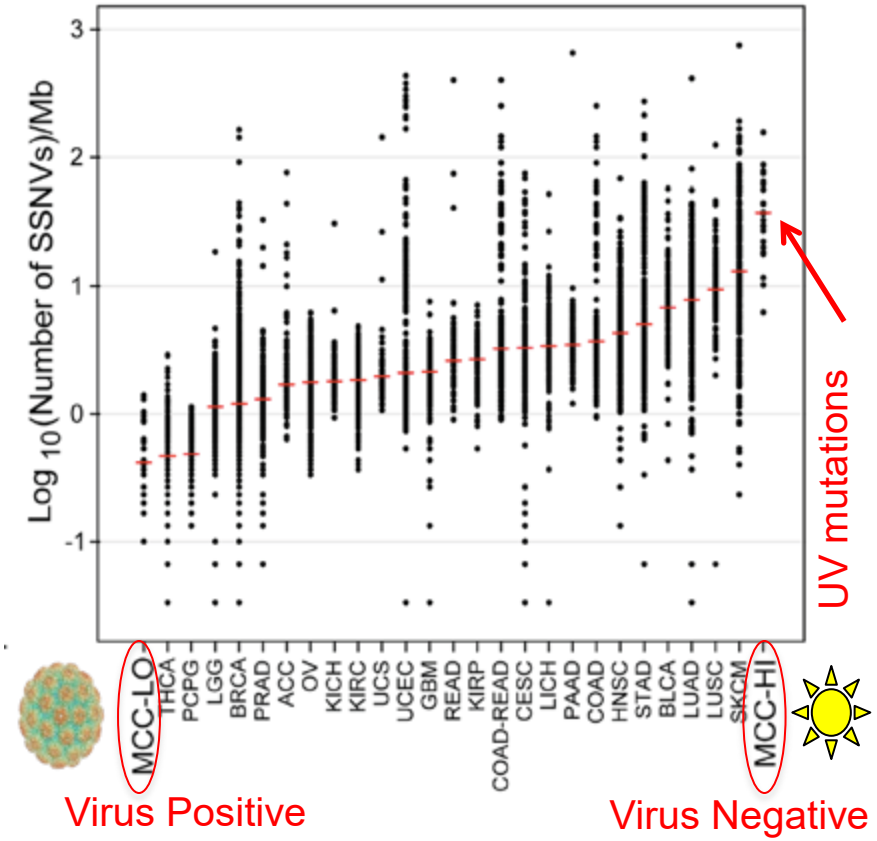
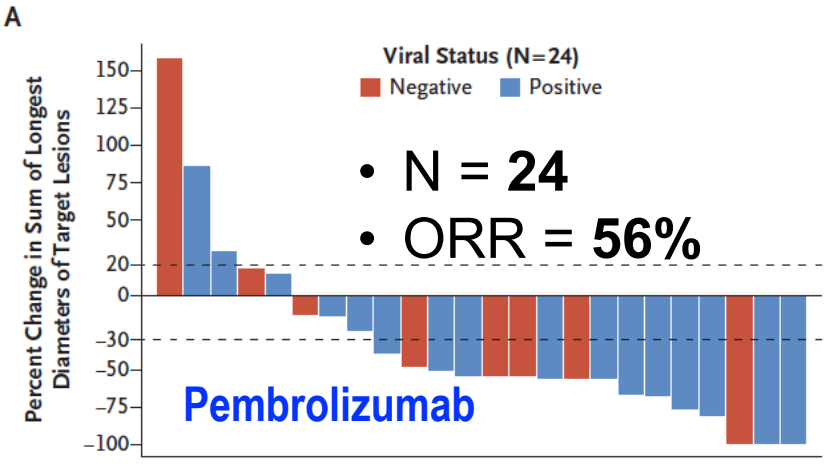
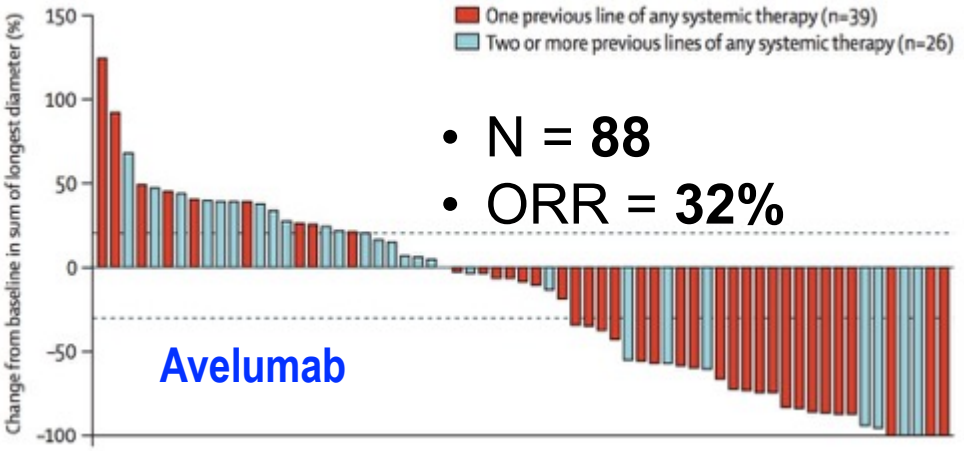


{Goh et al. Oncotarget 2015}

High response rates with ICIs in MCC



{Nghiem P, Bhatia S et al. 2016 *NEJM*}



{Kaufman H et al. *The Lancet Oncology* 2016}

- **Avelumab (anti-PD-L1) and pembrolizumab (anti-PD-1) are both FDA-approved ICIs for advanced MCC.**
- **Responses are rapid-onset and generally durable.**
- **Responses occur regardless of viral status/TMB or PD-L1 expression.**

Cutaneous Squamous cell carcinoma (cSCC)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

M.R. Migden, D. Rischin, C.D. Schmults, A. Guminski, A. Hauschild, K.D. Lewis, C.H. Chung, L. Hernandez-Aya, A.M. Lim, A.L.S. Chang, G. Rabinowits, A.A. Thai, L.A. Dunn, B.G.M. Hughes, N.I. Khushalani, B. Modi, D. Schadendorf, B. Gao, F. Seebach, S. Li, J. Li, M. Mathias, J. Booth, K. Mohan, E. Stankevich, H.M. Babiker, I. Brana, M. Gil-Martin, J. Homsi, M.L. Johnson, V. Moreno, J. Niu, T.K. Owonikoko, K.P. Papadopoulos, G.D. Yancopoulos, I. Lowy, and M.G. Fury

- Cemiplimab was FDA-approved in 09/2018 for advanced CSCC
- 350 mg IV q3 weeks

N Engl J Med 2018;379:341-51.
DOI: 10.1056/NEJMoa1805131

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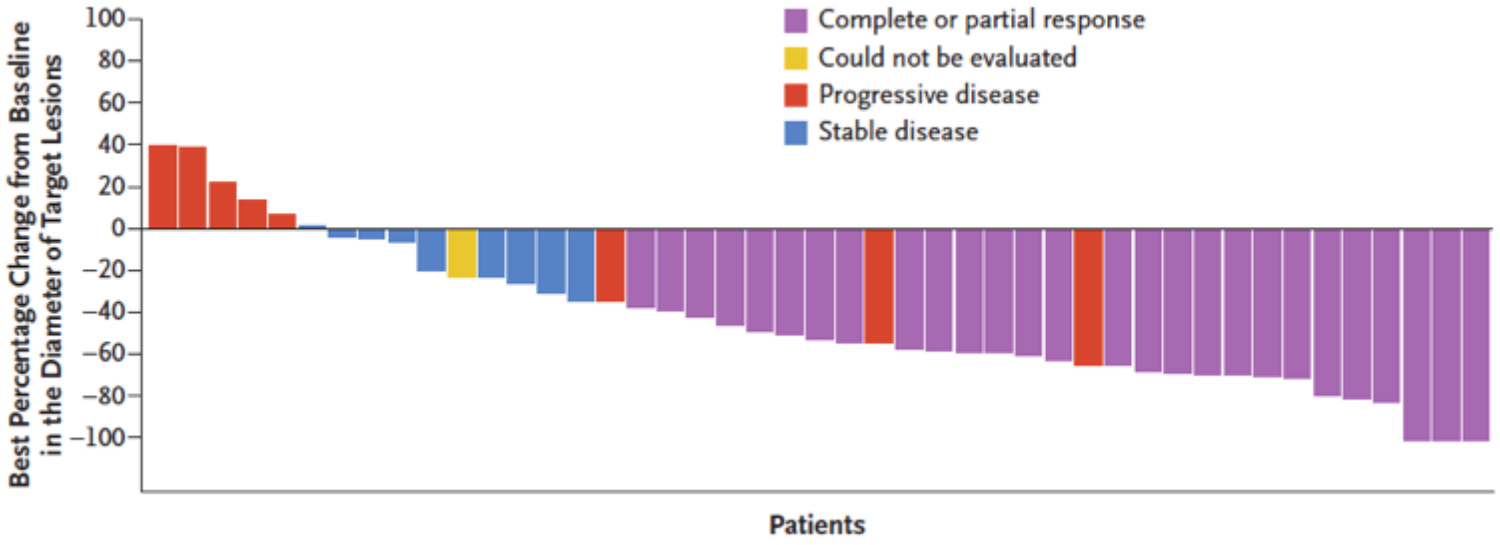
A **Best Tumor Response for 45 Patients in the Phase 2 Study**



Pembrolizumab Monotherapy for Recurrent or Metastatic Cutaneous Squamous Cell Carcinoma: A Single-Arm Phase II Trial (KEYNOTE-629)

Jean-Jacques Grob, MD, PhD[1]; Rene Gonzalez, MD[2]; Nicole Basset-Seguin, MD, PhD[3]; Olga Vornicova, MD[4]; Jacob Schachter, MD[5]; Abhishek Joshi, MBBS, MD[6]; Nicolas Meyer, MD, PhD[7]; Florent Grange, MD, PhD[8]; Josep M. Piulats, MD, PhD[9]; Jessica R. Bauman, MD[10]; Pingye Zhang, PhD[11]; Burak Gumuscu, MD, PhD[11]; Ramona F. Swaby, MD[11]; and Brett G. M. Hughes, BSc, MBBS[12,13]

- Pembrolizumab was FDA-approved in **June, 2020** for advanced CSCC

Phase II Study of Pembrolizumab As First-Line, Single-Drug Therapy for Patients With Unresectable Cutaneous Squamous Cell Carcinomas

Eve Maubec, MD, PhD[1,2]; Marouane Boubaya, MSc[1]; Peter Petrow, MD[3,4]; Marie Beylot-Barry, MD, PhD[5]; Nicole Basset-Seguin, MD, PhD[6]; Lydia Deschamps, MD[7]; Jean-Jacques Grob, MD, PhD[8]; Brigitte Dréno, MD, PhD[9]; Isabelle Scheer-Senyarich, PhD[1]; Coralie Bloch-Queyrat, MD, PhD[1]; Marie-Thérèse Leccia, MD, PhD[10]; Andreea Stefan, MD[11]; Philippe Saiag, MD, PhD[12]; Florent Grange, MD, PhD[13]; Nicolas Meyer, MD, PhD[14]; Julie de Quatrebarbes, MD[15]; Monica Dinulescu, MD[16]; Delphine Legoupil, MD[17]; Laurent Machet, MD, PhD[18]; Olivier Dereure, MD, PhD[19]; Ouidad Zehou, MD[20]; Henri Montaudié, MD[21]; Ewa Wierzbicka-Hainaut, MD[22]; Yannick Le Corre, MD[23]; Sandrine Mansard, MD[24]; Sarah Guégan, MD[25]; Jean-Philippe Arnault, MD[26]; Sophie Dalac, MD[27]; François Aubin, MD, PhD[28]; Céline Alloux, PharmD[29]; Isabelle Lopez, MD[3]; Soufian Cherbal, MSc[1]; Annick Tibi, PharmD[29];and Vincent Lévy, MD, PhD[1,2]; on behalf of Groupe de Cancérologie Cutanée[30]

- 200 mg IV q 3 weeks

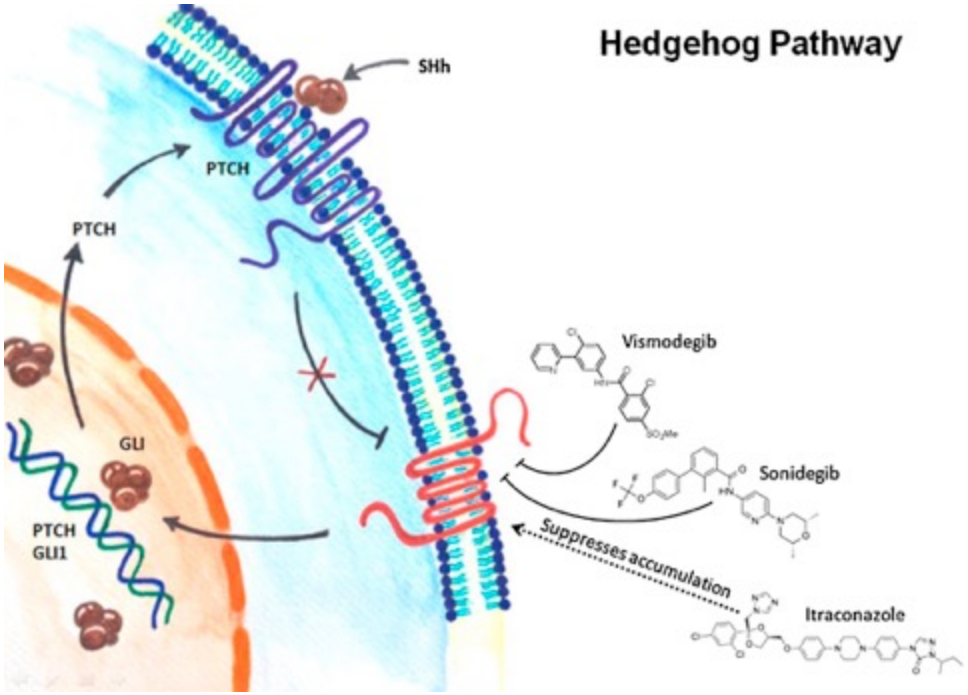
J Clin Oncol 38.

Basal cell carcinoma (BCC)

Hedgehog inhibition in BCC: Vismodegib, sonidegib

The hedgehog pathway is active during embryonic development but thought generally to be dormant after birth

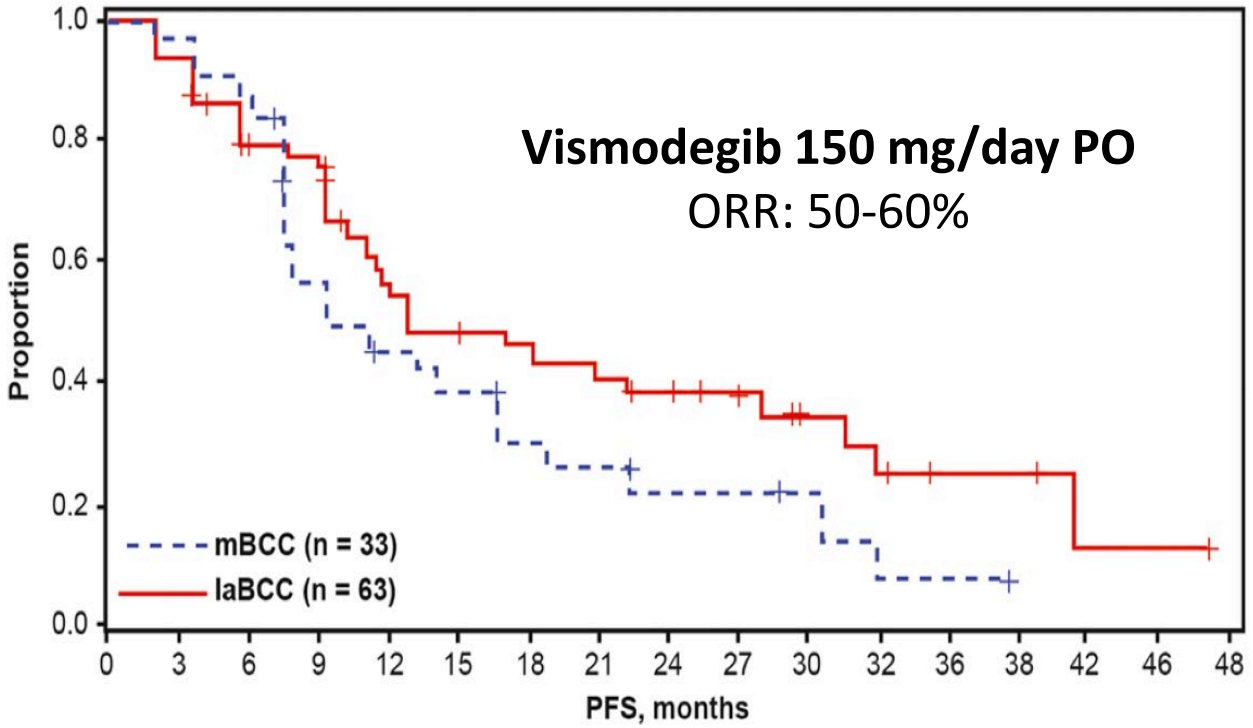
<u>Basal cell nevus syndrome</u>: Germline mutation in PTCH gene



Pros	Cons
Oral	Not well tolerated
High efficacy	Primary/secondary resistance
Can get histologic clearance	

Critical Reviews in Oncology / Hematology 2016 98, 235-241

Hedge-hog inhibition works in BCC, although resistance eventually develops



- Grade 3 (or higher) TRAE incidence: 55%
- AEs impact QoL

Sekulic et al. BMC Cancer (2017) 17:332

Case reports of successful use of PD-1 blockade

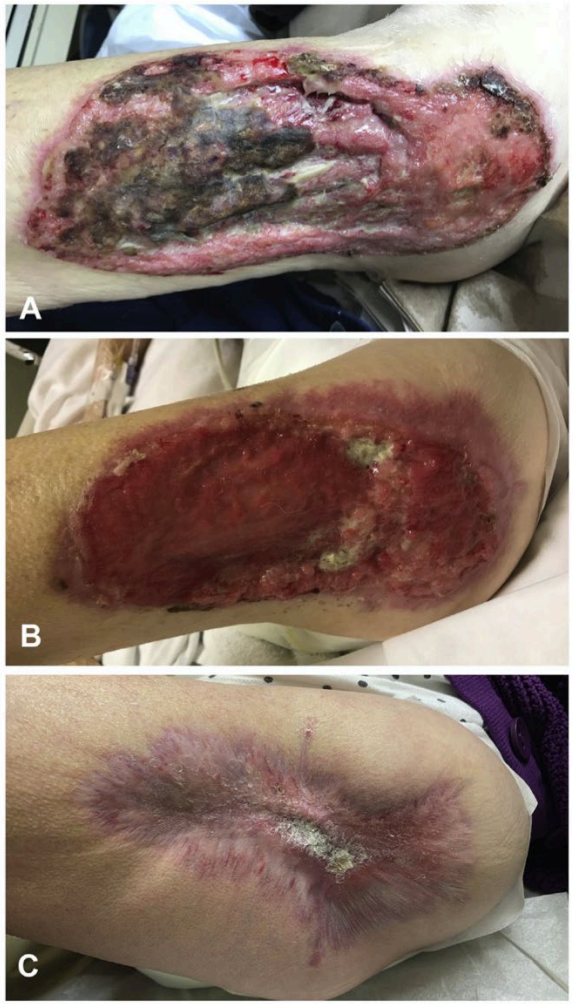


Fig 1. Unresectable basal cell carcinoma of the left thigh of a 70-year-old female patient both before and after frontline treatment with nivolumab. **A**, Tumor at initial presentation. **B**, Before fifth cycle of nivolumab. **C**, Seven months after completion of nivolumab therapy.

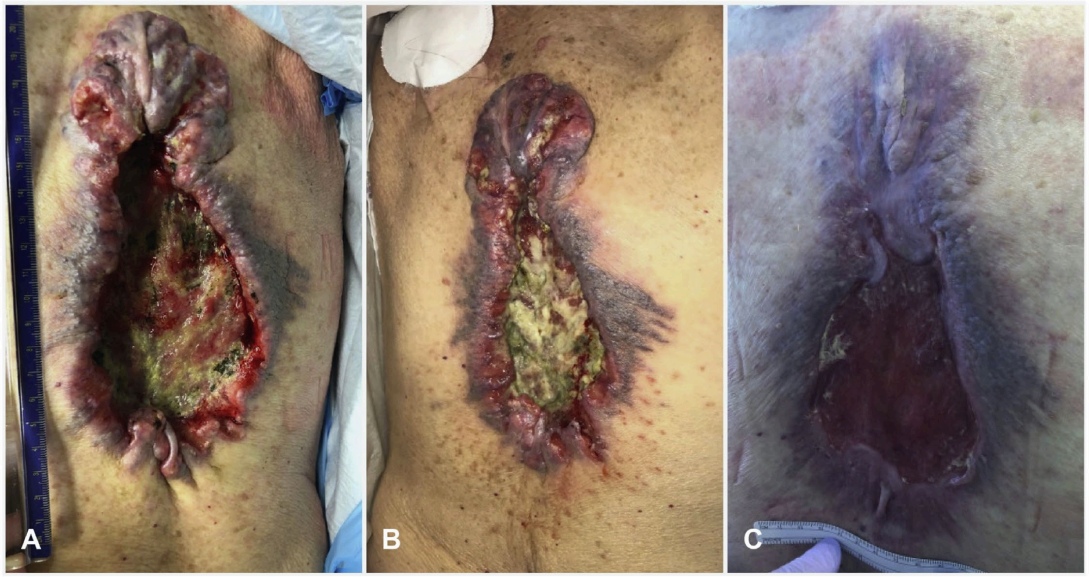


Fig 2. Locally advanced, unresectable basal cell carcinoma on the back of a 77-year-old female patient before and after first-line treatment with pembrolizumab. **A**, Tumor at initial presentation. **B**, Before fifth cycle of pembrolizumab. **C**, Before seventh cycle of pembrolizumab.

Ligtenburg et al. *JAAD Case Reports* 2020

Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multi-centre, single-arm, phase 2 trial

Lancet Oncol 2021; 22: 848–57

	Patients (n=84)
Objective response	26 (31%; 21–42)*
Best overall response	
Complete response	5 (6%)
Partial response	21 (25%)
Stable disease	41 (49%)
Progressive disease	9 (11%)
Not evaluable†	8 (10%)
Disease control	67 (80%; 70–88)
Durable disease control	50 (60%; 48–70)
Median time to response, months‡	4·3 (4·2–7·2)
Observed duration of response‡	
Range, months	2–21
≥6 months	19 (79%)
≥12 months	11 (46%)
Kaplan-Meier estimation of duration response‡	
Median	Not reached
Remained in response at 6 months	91% (68–98)
Remained in response at 12 months	85% (61–95)

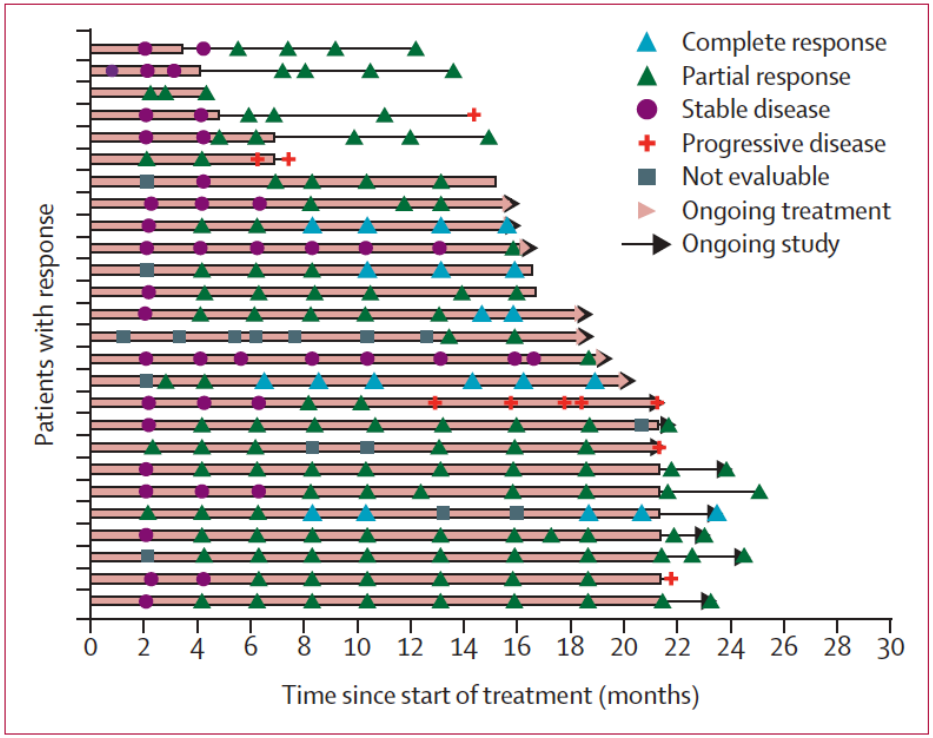


Figure 1: Tumour response to cemiplimab per independent central review

Cemiplimab was FDA-approved for laBCC and mBCC in 02/2021