# Melanoma and Other Skin Cancers

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UW Comprehensive Oncology Review Course

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Fred Hutch Cancer Center

# Disclosures

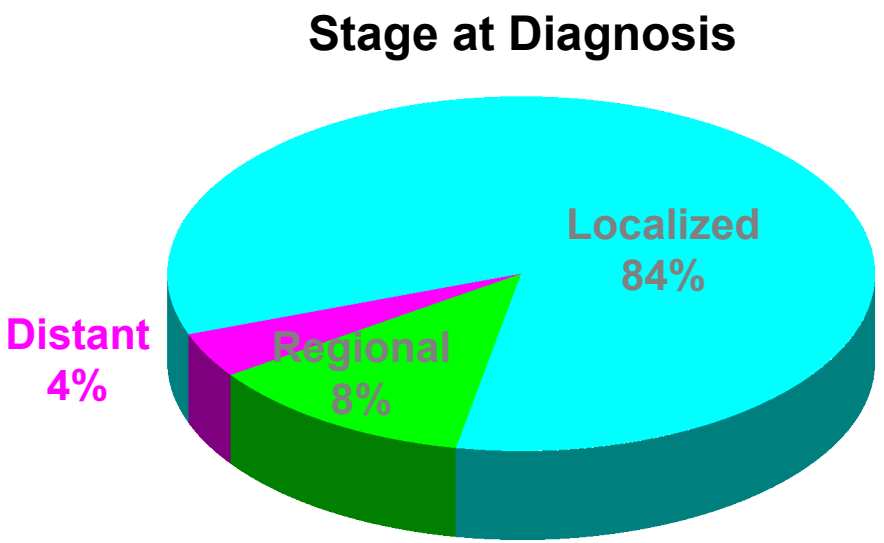
- **Research support (to UW)**: *BMS, EMD-Serono, Merck, Novartis, Exicure, Nektar, Xencor, Agenus, Trisalus, Checkmate/Regeneron.*

- **Advisory Board/Consultant**: *BMS, Incyte*

# I. Melanoma

# Incidence, Mortality and Stage Distribution of Melanoma

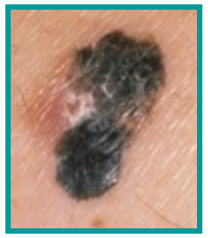
- 91,270 new cases of cutaneous melanoma in U.S. in **2018**
  - ~9,320 deaths
- 99,780 new cases of cutaneous melanoma in U.S. in **2022**
  - ~7,650 deaths




American Cancer Society. Cancer.org 2020
Siegel R. *CA Cancer J Clin*. 2018 and 2022.

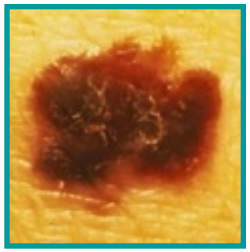
# The ABCDEs of Melanoma Diagnosis

**Asymmetry**



One half of the lesion is shaped differently than the other

**Border**

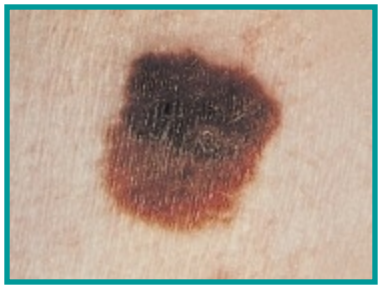


The border of the lesion is irregular, blurred, or ragged

**Color**

Inconsistent pigmentation, with varying shades of brown and black

**Diameter**



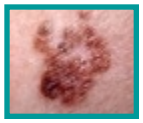
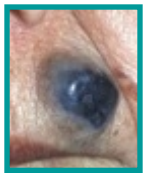
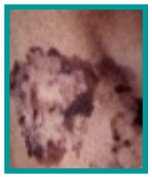
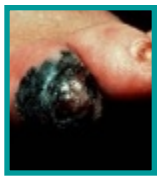
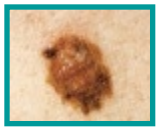
>6 mm, or a progressive change in size

**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<br>Asians (46%),<br>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)

sive **NCCN Guidelines Version 1.2023**
**Melanoma: Cutaneous**

**PRINCIPLES OF SURGICAL MARGINS FOR WIDE EXCISION OF PRIMARY MELANOMA**

| Tumor Thickness | Recommended Peripheral Surgical Margins[b,1-10] |
|---|---|
| In situ[a] | 0.5–1 cm |
| ≤1.0 mm | 1 cm (category 1) |
| >1.0–2.0 mm | 1–2 cm (category 1) |
| >2.0–4.0 mm | 2 cm (category 1) |
| >4.0 mm | 2 cm (category 1) |

NCCN Guidelines version 1.2023

# 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.**

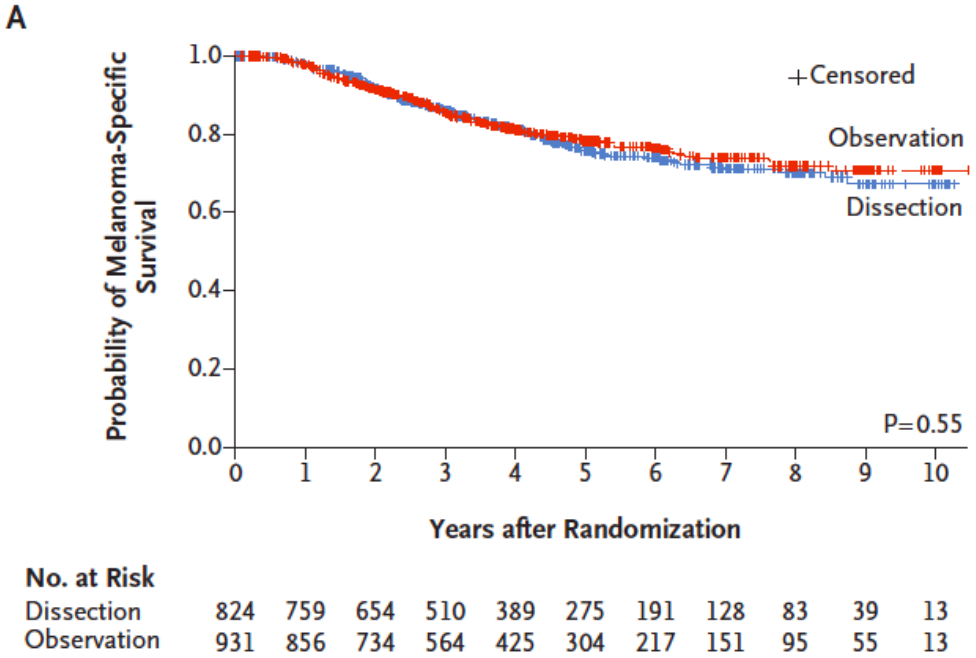
| Breslow Thickness (mm) | Mitotic rate | | Ulceration | | Adverse factors* | |
|---|---|---|---|---|---|---|
| | $<1/mm^2$ | $\geq 1/mm^2$ | No | Yes | No | Yes |
| $\leq 0.8$ | No | Consider | No | Consider | No | Consider |
| 0.8-1.0 | Consider | Consider | Consider | Consider | Consider | Consider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

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

**Approximate probability of positive SLN**: <5% (No), 5-10% (Consider) and >10% (Offer)

Adapted from NCCN Guidelines

# Completion Lymph Node Dissection (CLND)

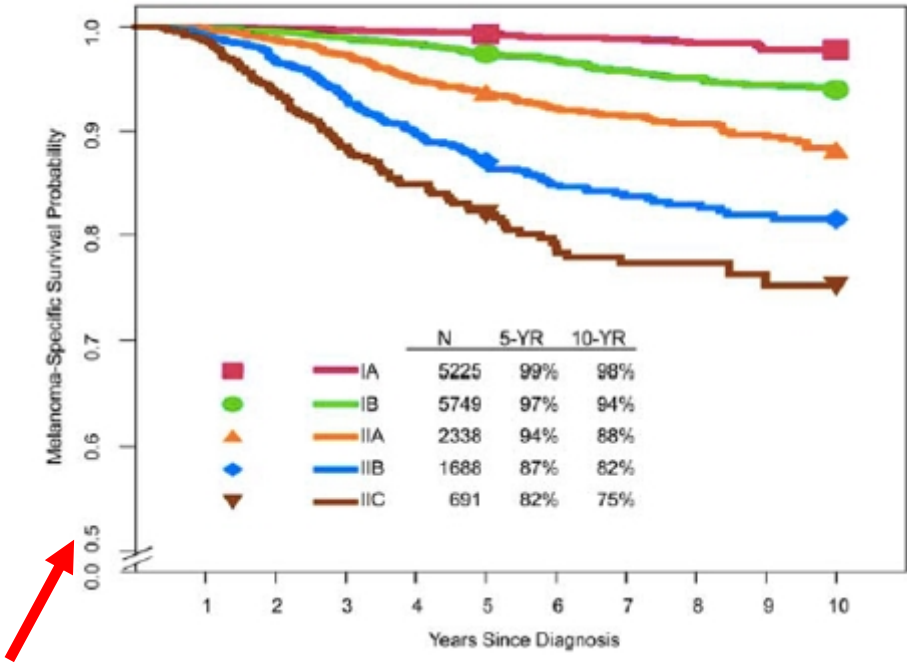


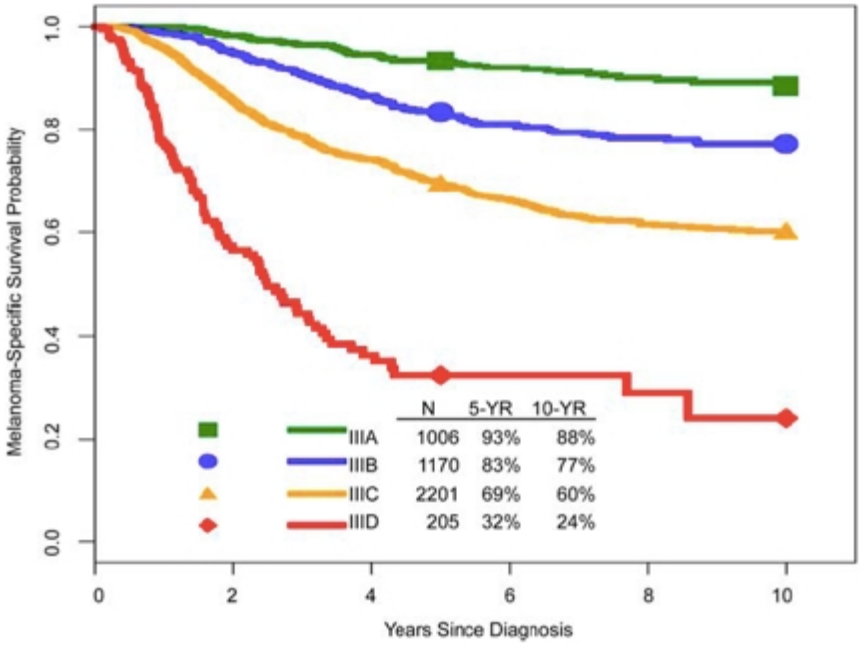


**CONCLUSIONS**

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) | No proven OS benefit |
| High-dose IL-2 | (1998) | |

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)

Relatimab + Nivolumab (2022)

Lifileucel or TILs (2024)

## TARGETED CHEMOTHERAPY

Vemurafenib (2011)

Dabrafenib (2013)

Trametinib (2013)

Dabrafenib + Trametinib (2014)

Vemurafenib + Cobimetinib (2015)

Encorafenib + Binimetinib (2018)

Vemurafenib + Cobimetinib + Atezolizumab (2020)

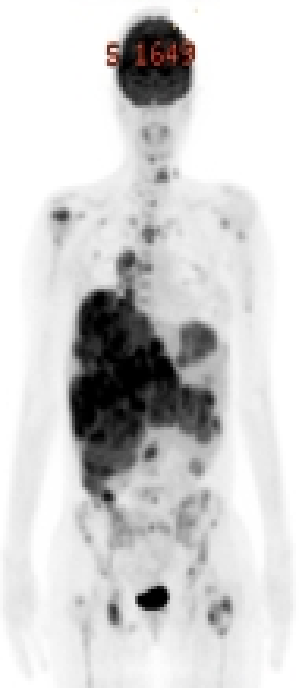
# Case # 1

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 metastases** 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, ALT 85, ALK-P 375 and Bilirubin 1.5**. His ECOG **performance score is 2**.



# Case # 1 (contd.)

**What will you recommend next?**

A. Whole brain radiation therapy.

A. PD-1 blockade (Pembrolizumab or Nivolumab)

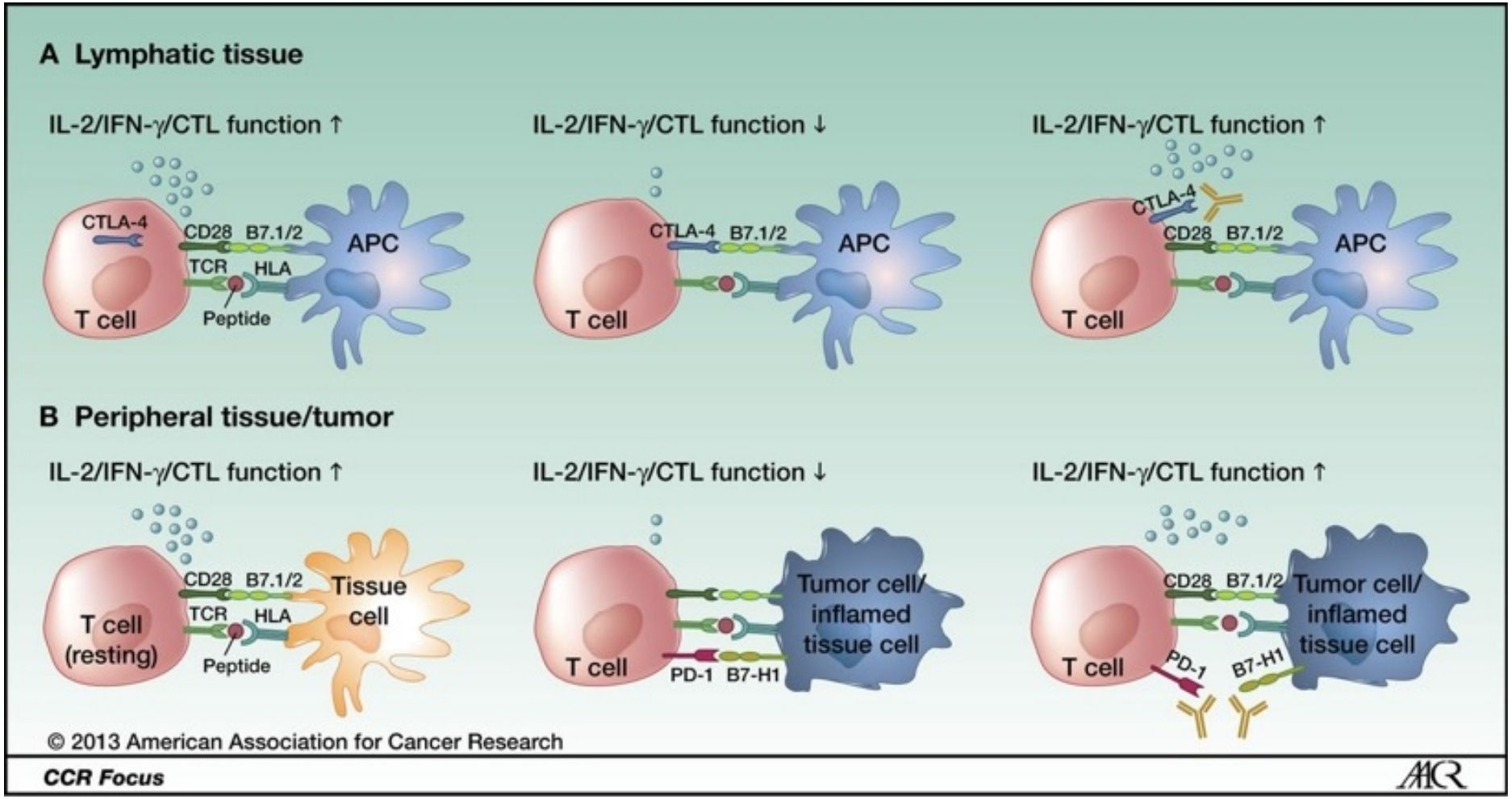
A. Ipilimumab plus Nivolumab

A. Relatlimab-Nivolumab

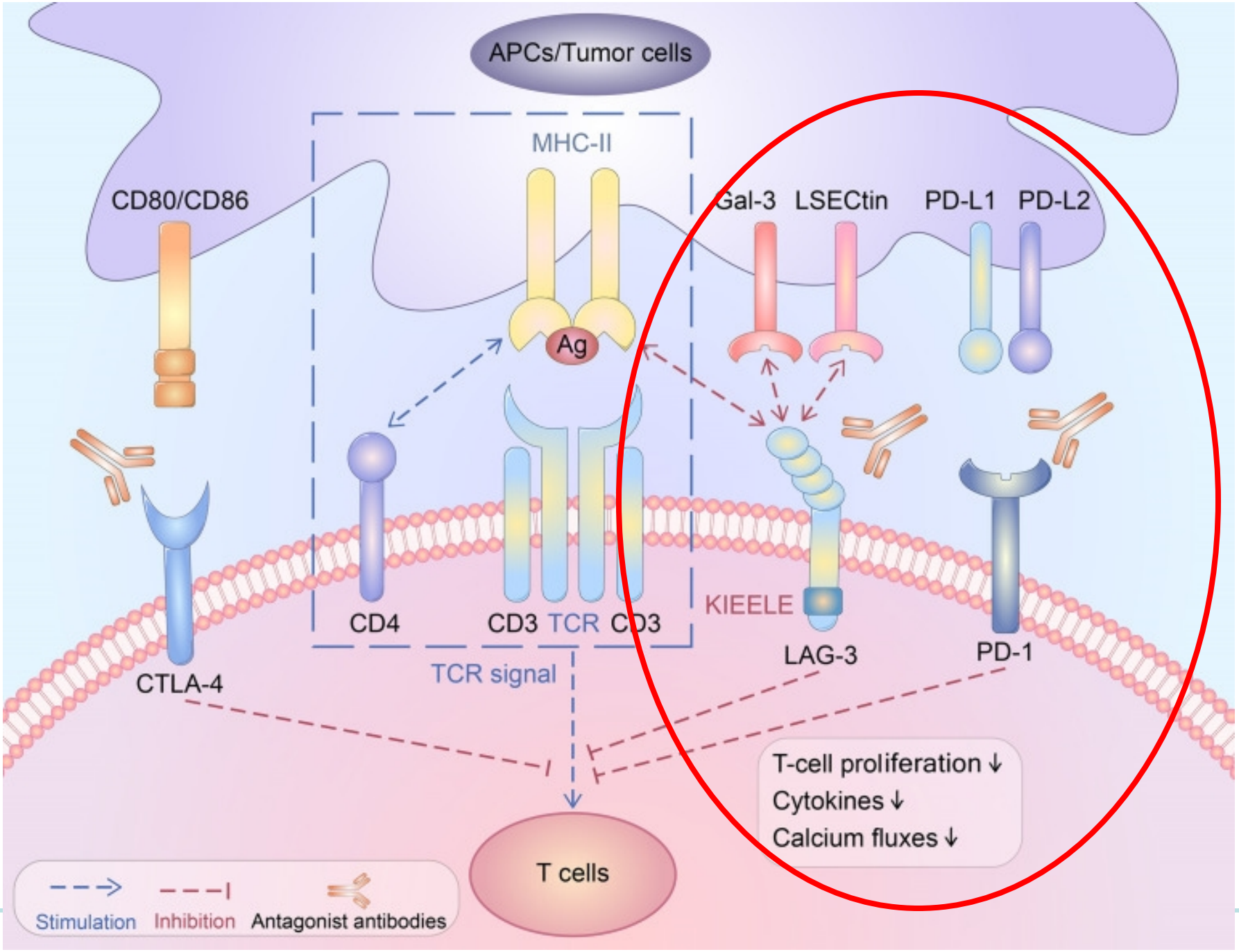
A. BRAFi + MEKi

# IMMUNOTHERAPY

# Different ICIs have unique mechanisms of modulating T-cell function




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


APCs/Tumor cells
MHC-II
CD80/CD86
Gal-3
LSECtin
PD-L1
PD-L2
Ag
CD4
CD3
TCR
CD3
KIEELE
LAG-3
PD-1
CTLA-4
TCR signal
T-cell proliferation ↓
Cytokines ↓
Calcium fluxes ↓
T cells
Stimulation
Inhibition
Antagonist antibodies

# Immunotherapy

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

- Pembrolizumab
- Nivolumab

# Anti-PD-1 versus Ipilimumab: Improved efficacy with Lower toxicity

| | Response rate (%) | Grade 3 or higher IRAE (%) |
|---|---|---|
| **Ipilimumab** | 12 | 20 |
| **Pembro-lizumab** | 33 | 10 |

[Robert C et al. NEJM]

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

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

# Question # 1

Monotherapy

vs

Combination Immunotherapy?

# Ipilimumab *plus* Nivolumab combination

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

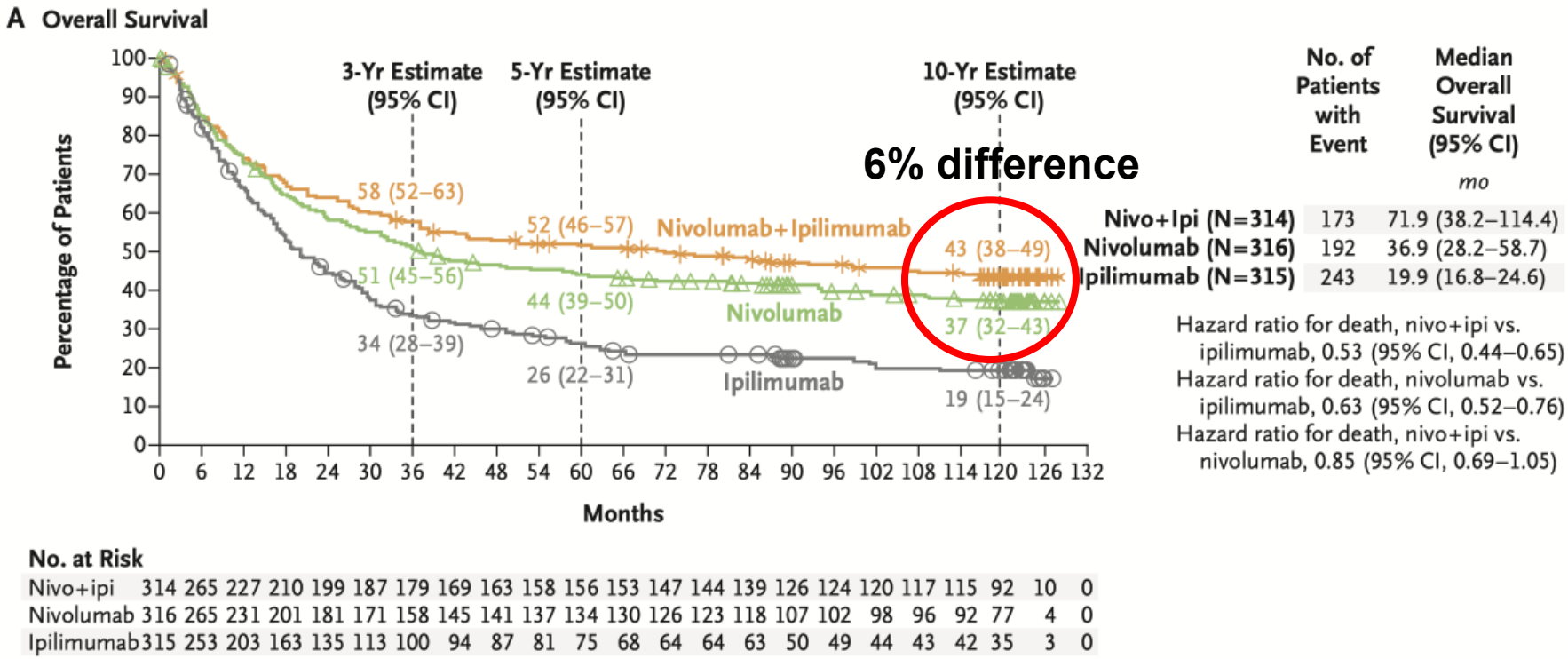
Approved dose is Ipilimumab 3 mg/kg plus Nivolumab 1 mg/kg administered IV every 3 weeks x 4 doses [**Induction**] followed by Nivolumab 3 mg/kg administered IV every 2 weeks [**Maintenance**].

# Mono- vs Combination Immunotherapy (Checkmate-067)

| | Response rate (%) | Grade 3 or higher IRAE (%) |
|---|---|---|
| **Nivolumab** | 44 | 16 |
| **Ipi 3 + Nivo 1** | 58 | **55** |

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

# Checkmate-067 LTFU (10 yrs) suggests best outcomes with Ipi-Nivo




{Larkin J et al. *NEJM* 2024}

**Median OS**

**Ipi-Nivo = 72 mos**

**(Historical OS = 8 mos)**

# Question # 2

Which combination regimen to choose?

# Ipi-Nivo flip dosing regimens (Checkmate-511)

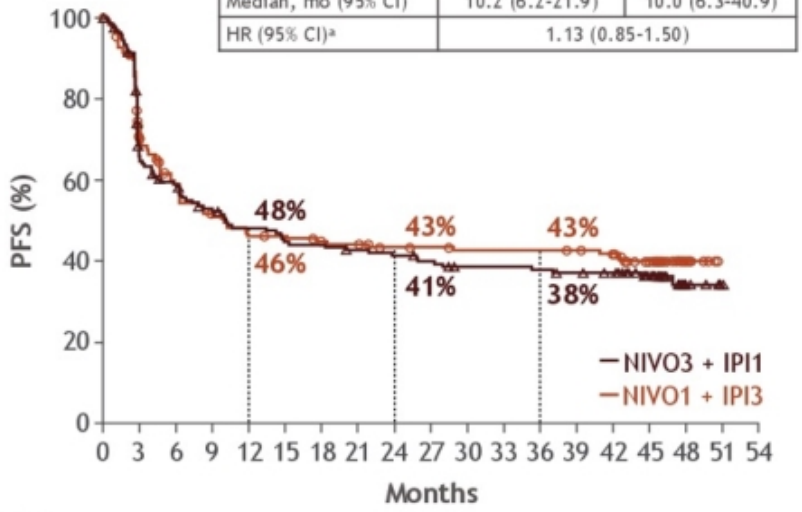
| | Response rate (%) | Grade 3 or higher IRAE (%) |
|---|---|---|
| **Ipi 3 + Nivo 1** | 52 | **48** |
| **Ipi 1 + Nivo 3** | 47 | **34** |

[*Lebbe C et al ASCO 2021* ]

# Survival outcomes

## PFS

| | NIVO3 + IPI1 (n = 180) | NIVO1 + IPI3 (n = 178) |
|---|---|---|
| Events, n | 100 | 93 |
| Median, mo (95% CI) | 10.2 (6.2-21.9) | 10.0 (6.3-40.9) |
| HR (95% CI)[a] | 1.13 (0.85-1.50) | |

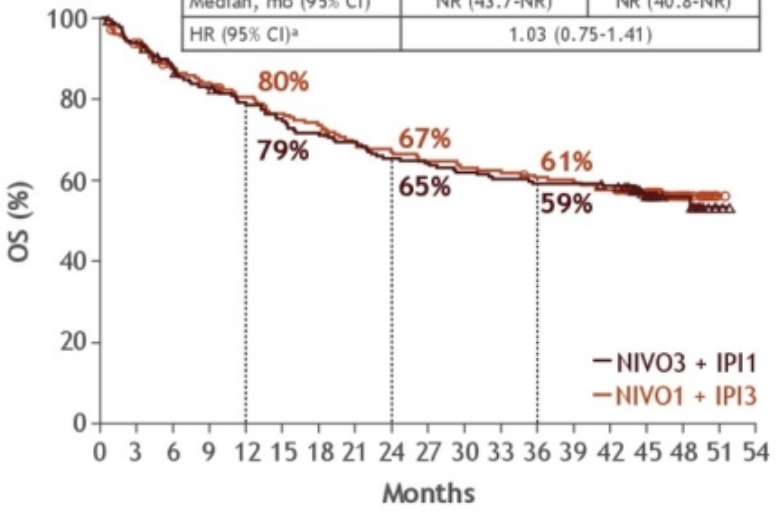



No. at risk

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO3 + IPI1 | 180 | 105 | 90 | 79 | 71 | 66 | 65 | 62 | 60 | 57 | 53 | 53 | 52 | 50 | 48 | 34 | 7 | 1 | 0 |
| NIVO1 + IPI3 | 178 | 111 | 88 | 75 | 68 | 67 | 64 | 62 | 58 | 57 | 55 | 55 | 55 | 53 | 48 | 36 | 10 | 0 | 0 |

## OS

| | NIVO3 + IPI1 (n = 180) | NIVO1 + IPI3 (n = 178) |
|---|---|---|
| Events, n | 78 | 75 |
| Median, mo (95% CI) | NR (43.7-NR) | NR (40.8-NR) |
| HR (95% CI)[a] | 1.03 (0.75-1.41) | |




No. at risk

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO3 + IPI1 | 180 | 168 | 156 | 145 | 138 | 131 | 125 | 121 | 114 | 112 | 108 | 105 | 103 | 103 | 101 | 82 | 29 | 3 | 0 |
| NIVO1 + IPI3 | 178 | 165 | 152 | 145 | 138 | 131 | 127 | 118 | 114 | 110 | 107 | 106 | 102 | 101 | 97 | 80 | 29 | 1 | 0 |

- Across patient subgroups, OS outcomes were generally similar with both regimens

[a]NIVO3 + IPI1 vs NIVO1 + IPI3. The study was not designed or powered to formally compare NIVO3 + IPI1 with NIVO1 + IPI3 for the secondary efficacy endpoints. All statistical analyses are descriptive only.



[*Lebbe C et al ASCO 2021* ]

# Mono- vs Combination ICI in 1st-line melanoma (RELATIVITY-047)

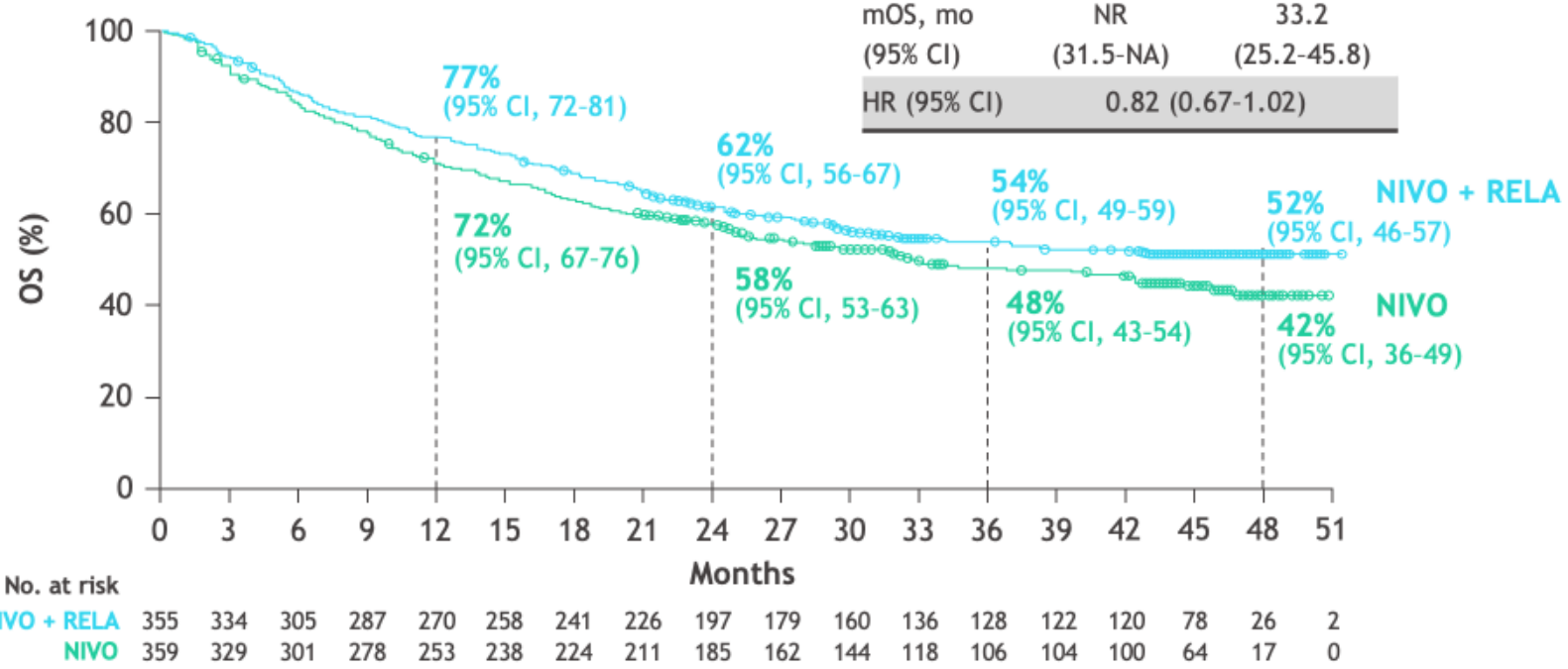
| | Response rate (%) | Grade 3 or higher IRAE (%) |
|---|---|---|
| **Nivolumab** | 33 | 11 |
| **Rela-Nivo** | 43 | **21** |

[*Tawbi HA et al* NEJM *2022* ]

# OS

## *Updated secondary endpoint*

| | NIVO + RELA (n = 355) | NIVO (n = 359) |
|---|---|---|
| mOS, mo | NR | 33.2 |
| (95% CI) | (31.5-NA) | (25.2-45.8) |
| HR (95% CI) | 0.82 (0.67-1.02) | |




RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months.
Descriptive analysis. Statistical model for HR: stratified Cox proportional hazard model. Stratified by LAG-3, *BRAF* mutation status, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

[*Tawbi HA et al* ASCO Annual Mtg *2023* ]

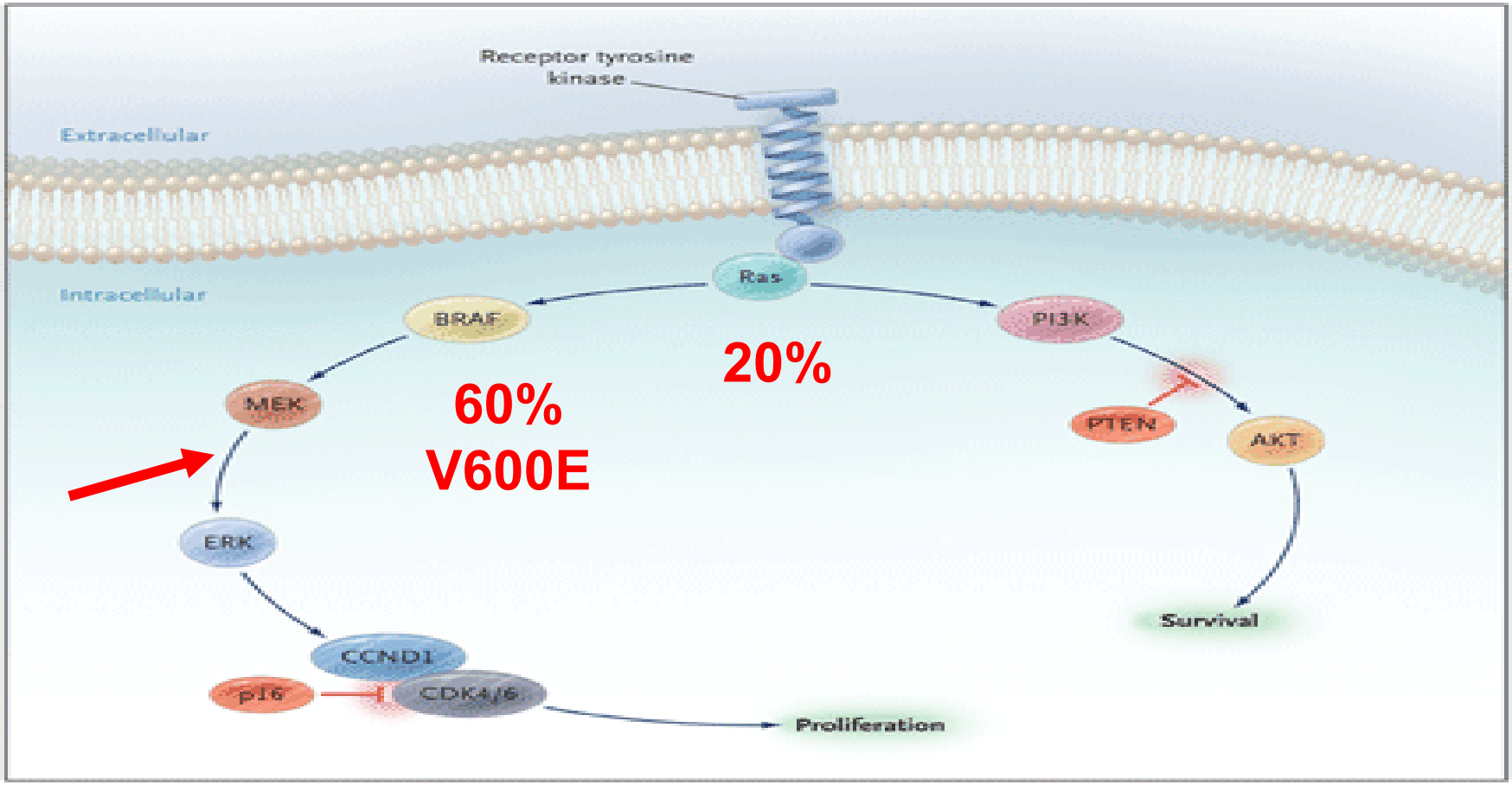
# My conclusions on Immunotherapy

- Ipi-Nivo and Rela-Nivo lead to **more immune activation** as compared to PD-1 monotherapy (higher ORR and toxicity)
- There is **sustained absolute OS benefit of ~6%** (statistically NS, likely clinically meaningful) at 10 years with Ipi-Nivo; OS data with Rela-Nivo is still maturing.
- Toxicity rates are also higher with combination immunotherapy
  **(Ipi3+N1) > {(Ipi1+N3) vs (Lag-3+N)} > (PD-1 mono)**
- Clinical decisions must be individualized based on patient's desire for aggressive therapy and risk tolerance.

**? COST (Financial toxicity to patients and society)**

# **Targeted Chemotherapy**
(BRAFi/MEKi)

# 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

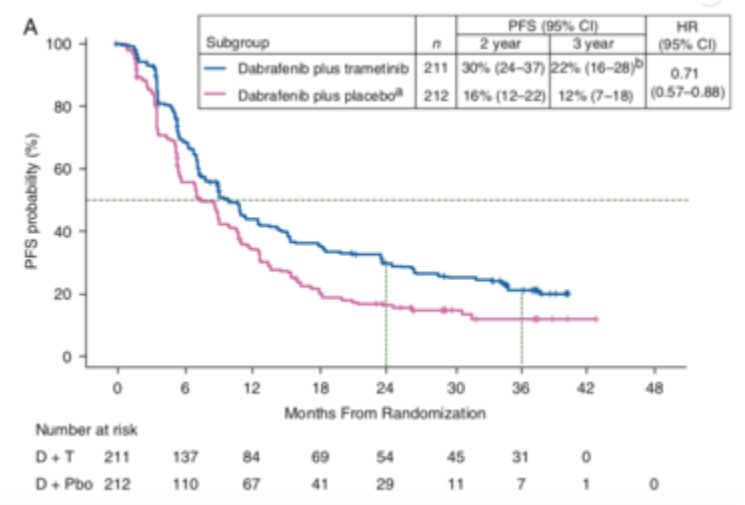
## BRAFi

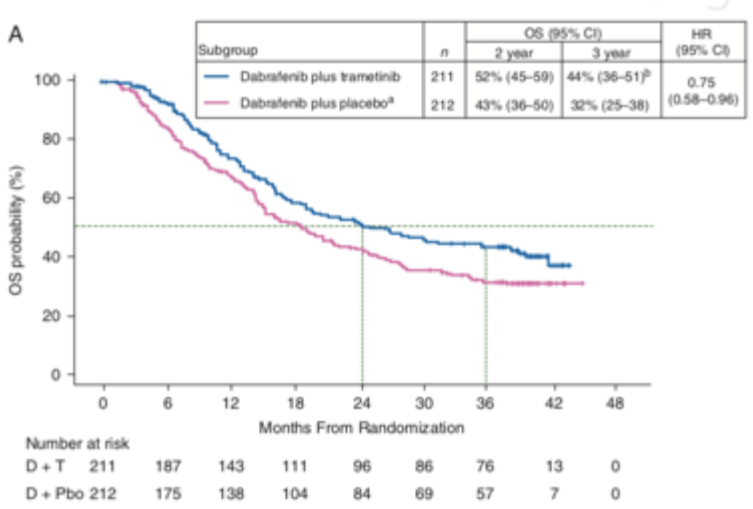
- Vemurafenib
- Dabrafenib
- Encorafenib

## MEKi

- Cobimetinib
- Trametinib
- Binimetinib

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



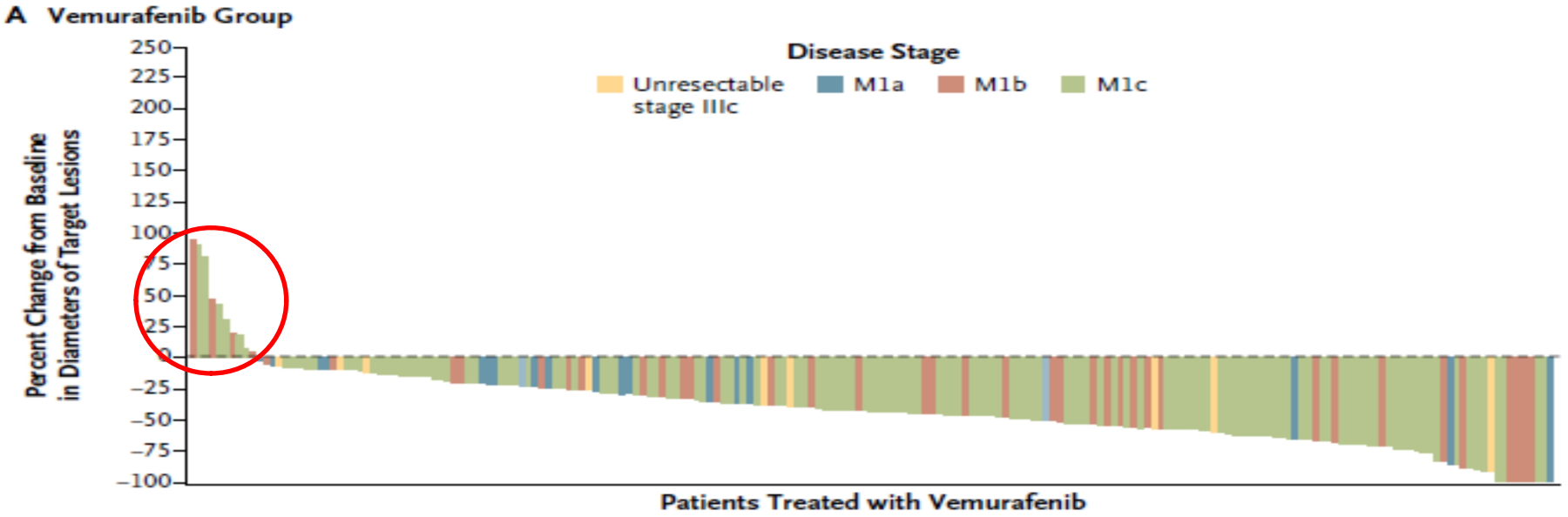




## TOXICITY

- 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

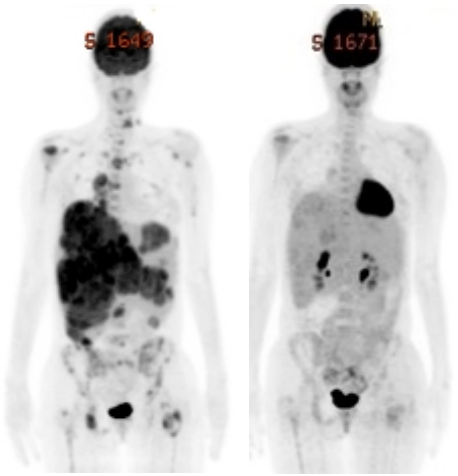
[Long G et al. Ann Oncol. 2017]

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

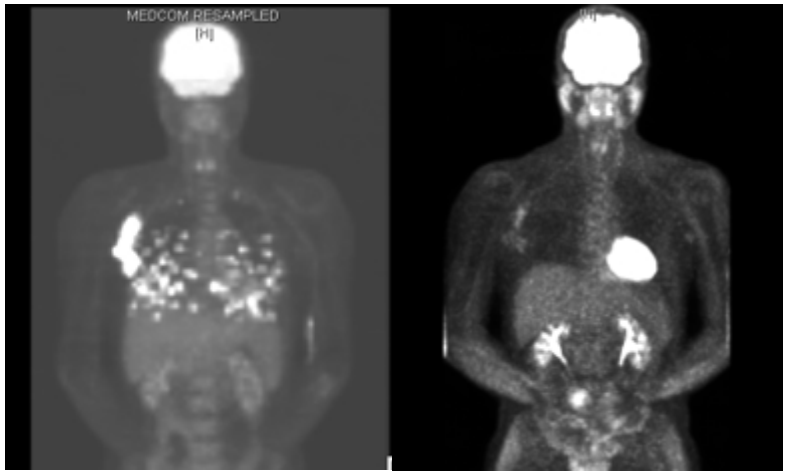



[Chapman P et al. NEJM. 2011]

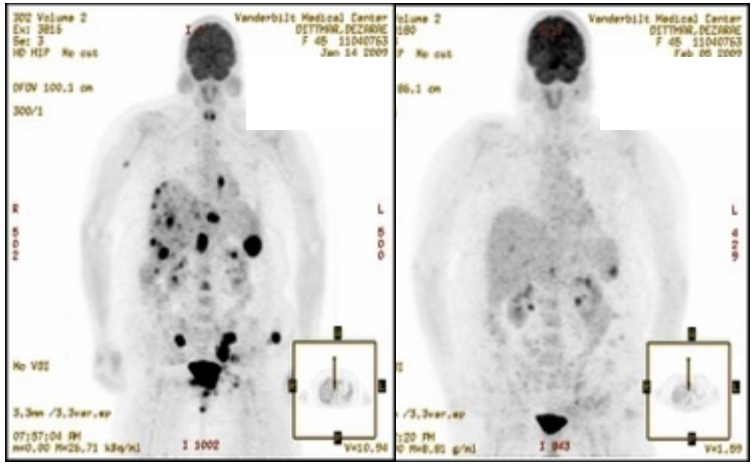
# Onset of tumor regression is **fairly rapid** with BRAFi (median TTR ~6 weeks)

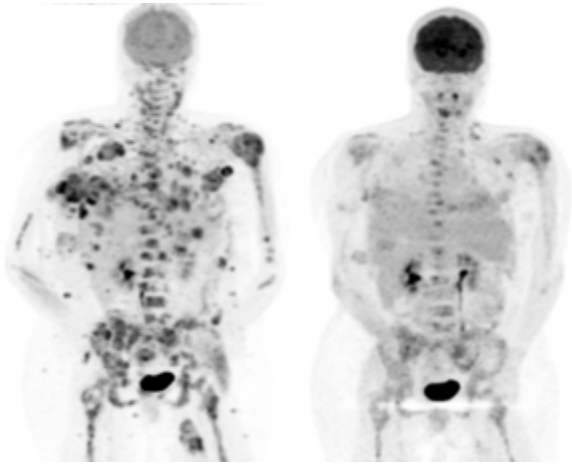


Baseline Day 15

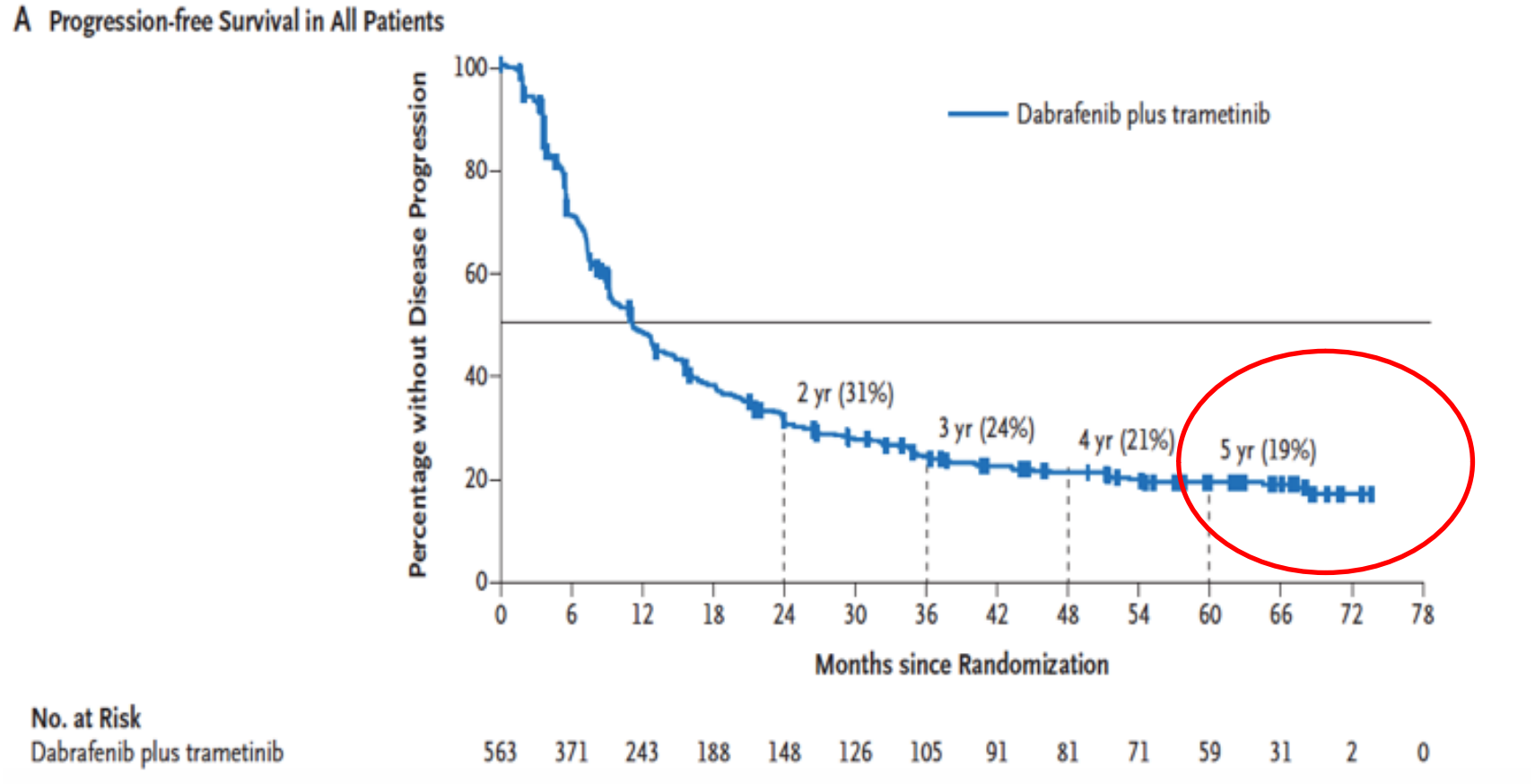



Baseline Day 15

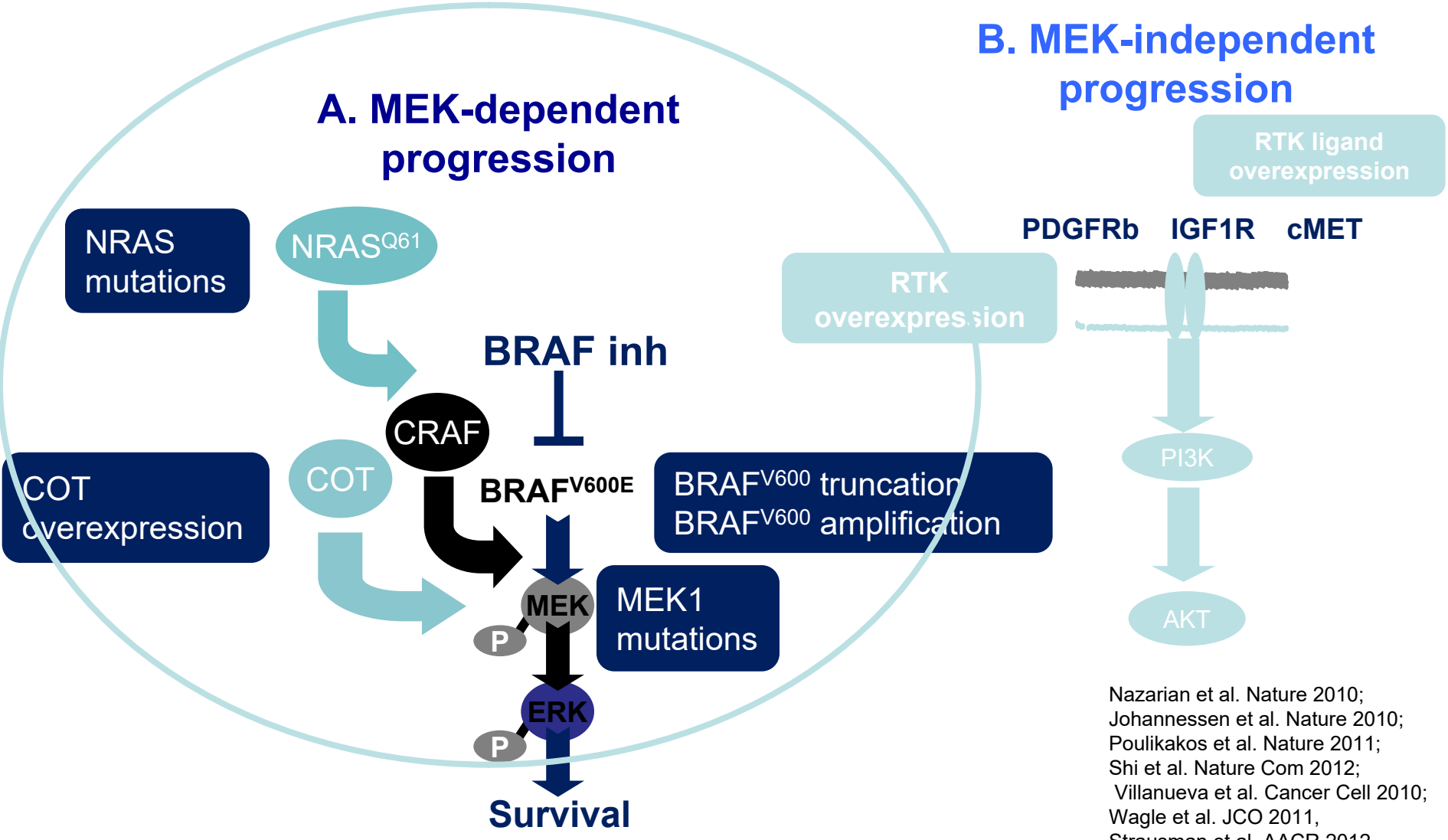




# Unfortunately, resistance develops after initial benefit in the majority of patients



# MAPK-pathway reactivation is the dominant mechanism of resistance in most 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

# Question # 3

**Immunotherapy** versus

**Targeted Chemotherapy**?

(for frontline treatment of BRAF-V600 mutant melanoma)

# Combination Dabrafenib and Trametinib Versus Combination Nivolumab and Ipilimumab for Patients With Advanced *BRAF*-Mutant Melanoma: The DREAMseq Trial—ECOG-ACRIN EA6134

JCO 2022

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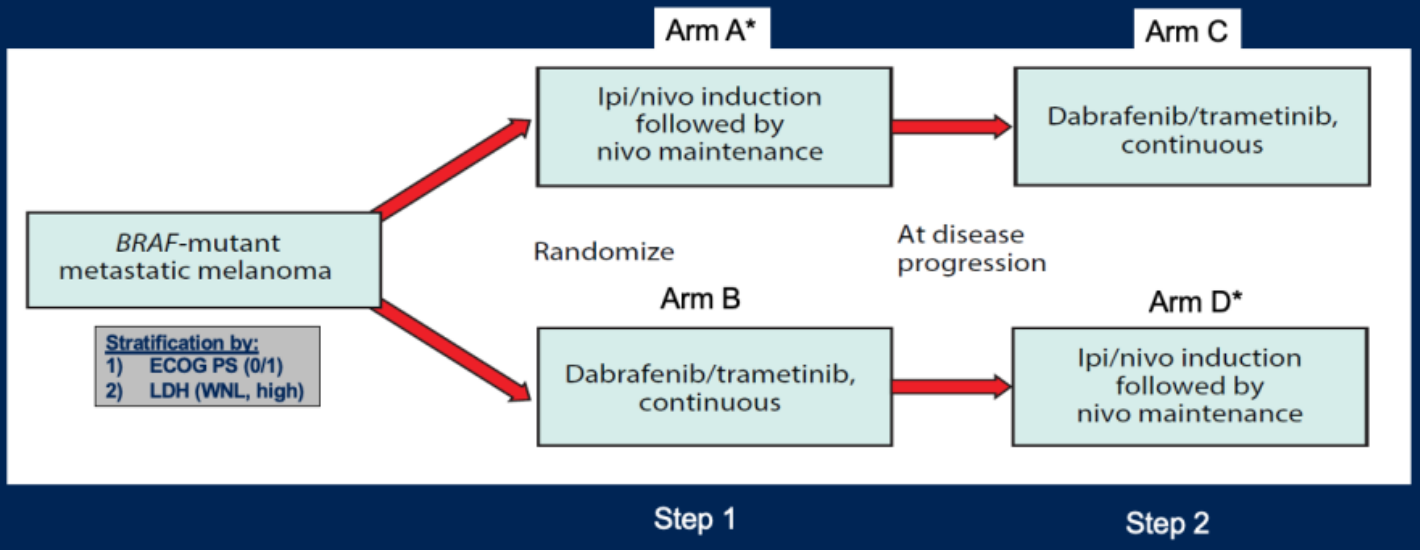
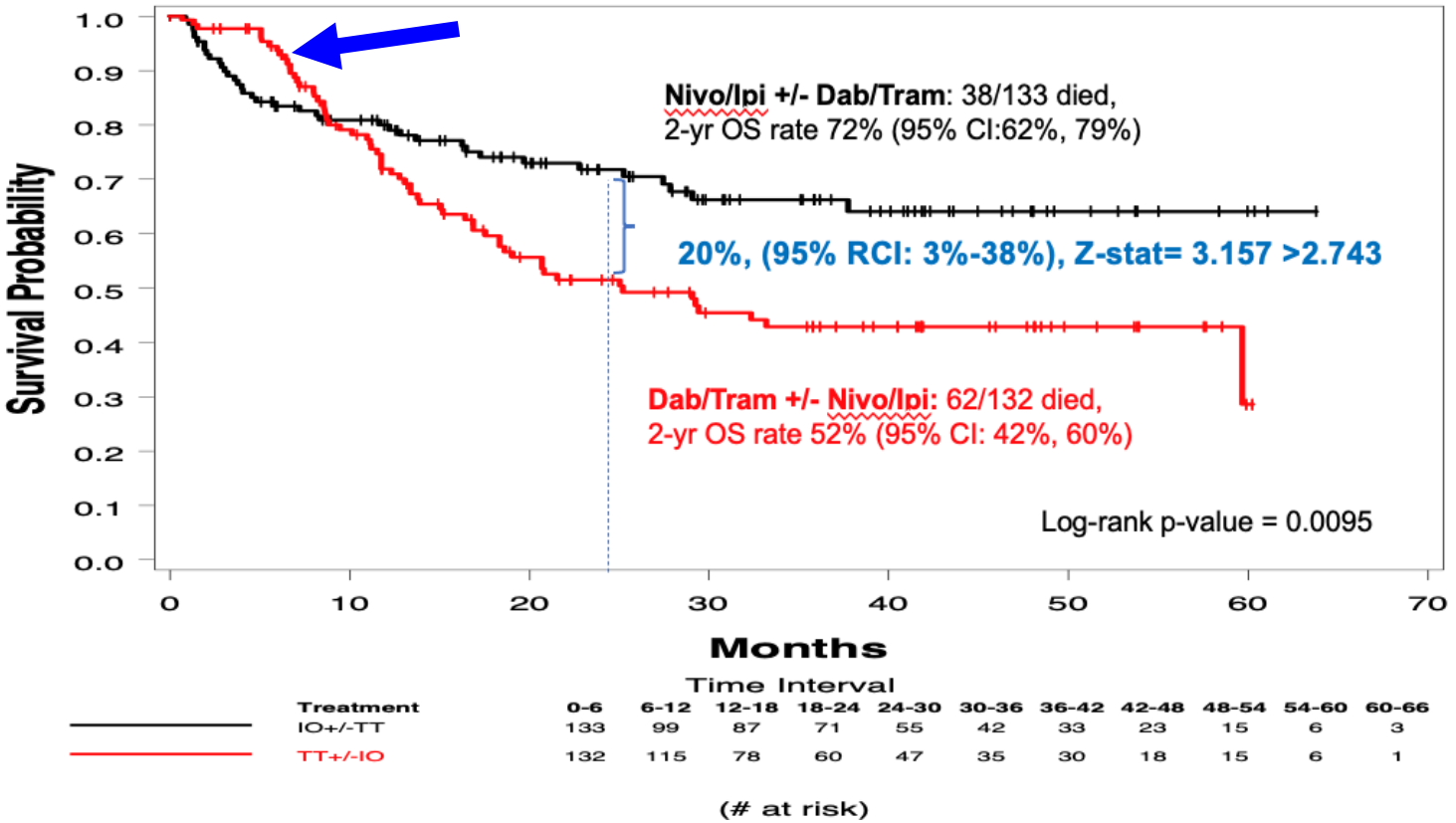
## DREAMseq Trial Treatment Schema



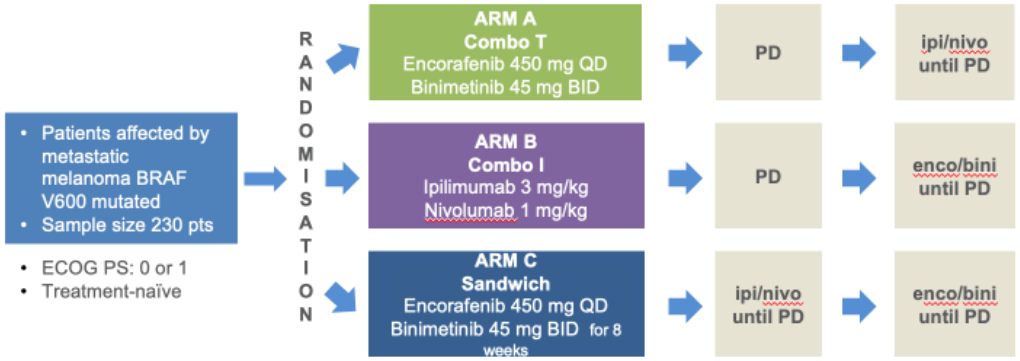

*Nivo/Ipi Induction = 12 wks; nivo maintenance = 72 wks

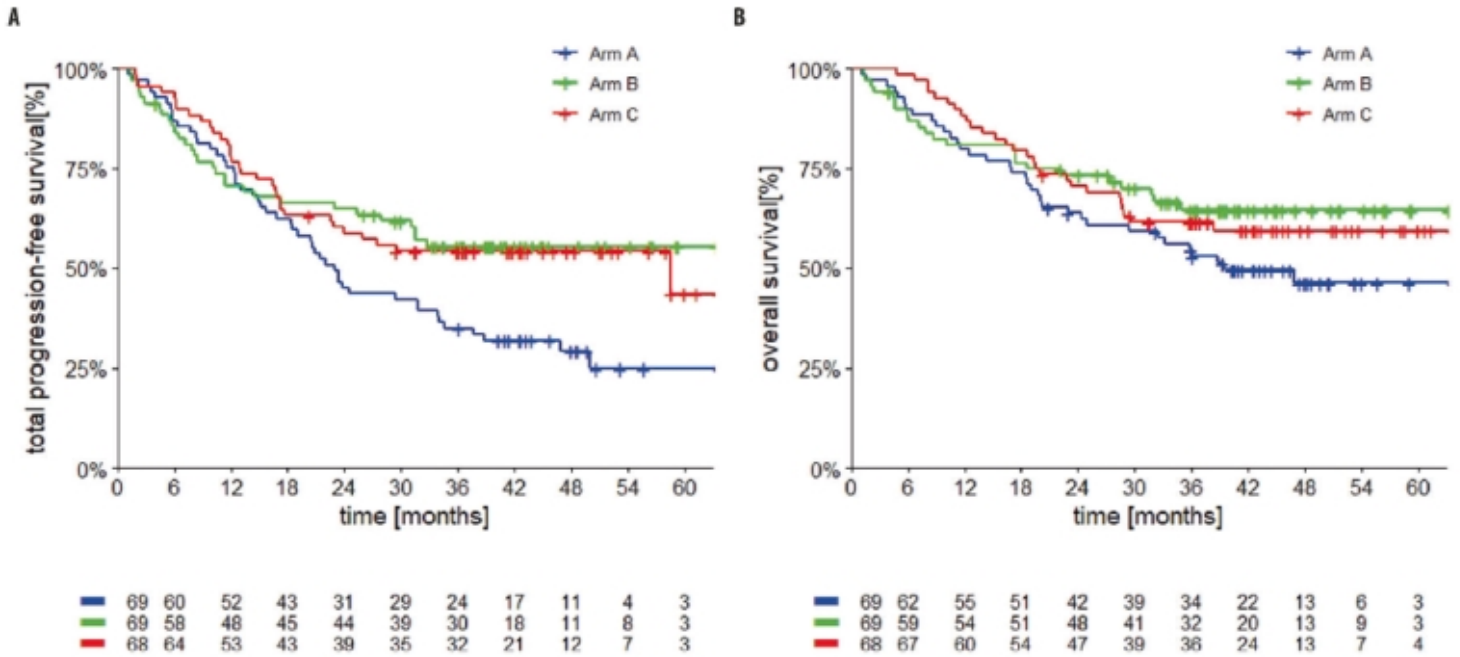
# Overall Survival (OS): Step 1 +/- Step 2




Nivo/ipi followed by BRAF/MEKi (if necessary) should be the preferred treatment sequence for the **MAJORITY** of pts with BRAF mutant melanoma.

# Sequential immunotherapy and targeted therapy (SECOMBIT)




[Ascierto P et al. Nat Comm. 2024]

# 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)**<br>**BRAFi + MEKi (acceptable)** |
| Bulky/Symptomatic Disease (Reliable, quick response needed) | **Immunotherapy** (anti PD-1 alone or in combination)<br>**Chemotherapy** | **BRAFi + MEKi followed by Immunotherapy** |

# Adjuvant therapy in high-risk melanoma

# Case # 2

42-year-old man presented with **3.4 mm thick, ulcerated primary melanoma (pT3b)** located on the right arm. Wide local excision revealed no residual melanoma and sentinel lymph node biopsy showed **1 of 1 axillary lymph node** involved with metastatic melanoma (size of deposit 5 mm) **(pN1a)**.

Staging FDG-PET scan and brain MRI did not show any metastatic disease. Stage is **IIIC (**AJCC 8th ed**).**

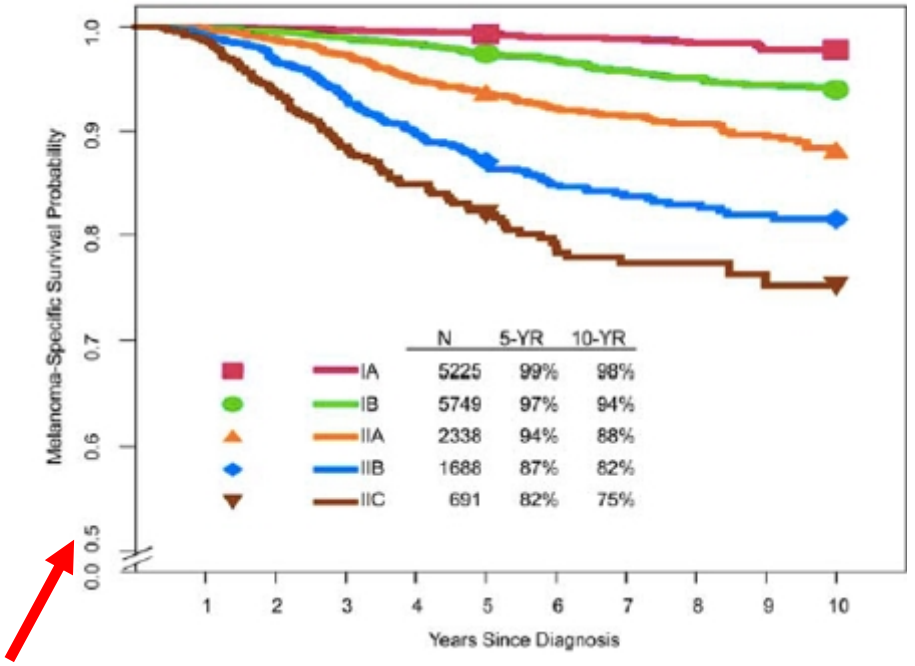
BRAF testing of the primary tumor was negative for the presence of BRAF V600E mutation.

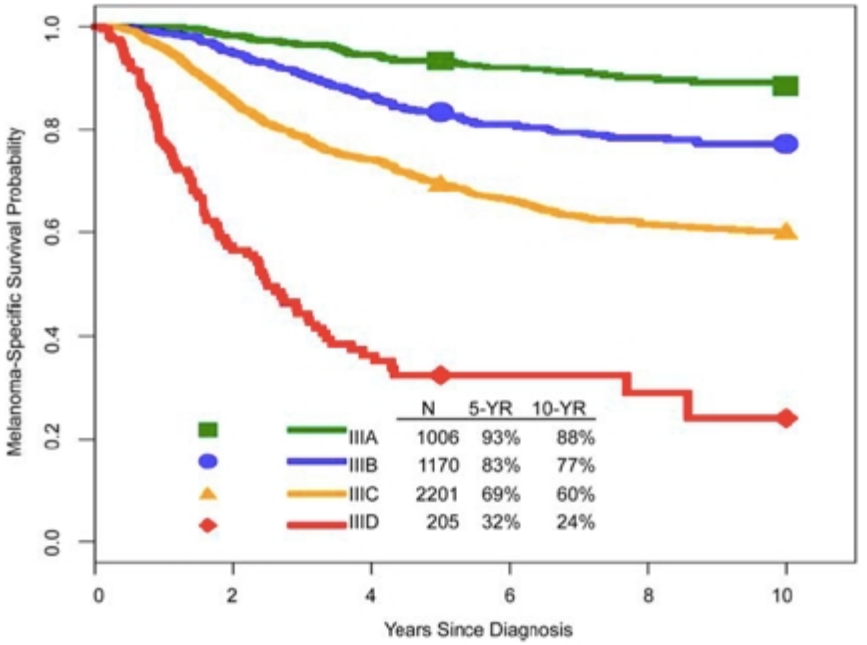
**What is the most appropriate next step in treatment?**

# Case # 2 (contd.)

a) Completion axillary lymph node dissection
b) Adjuvant radiation therapy to the right axillary basin
c) Adjuvant systemic therapy with nivolumab or pembrolizumab
d) Adjuvant systemic therapy with ipilimumab plus nivolumab
e) Adjuvant systemic therapy with relatlimab plus nivolumab
f) None of the above

# 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]

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ORIGINAL ARTICLE

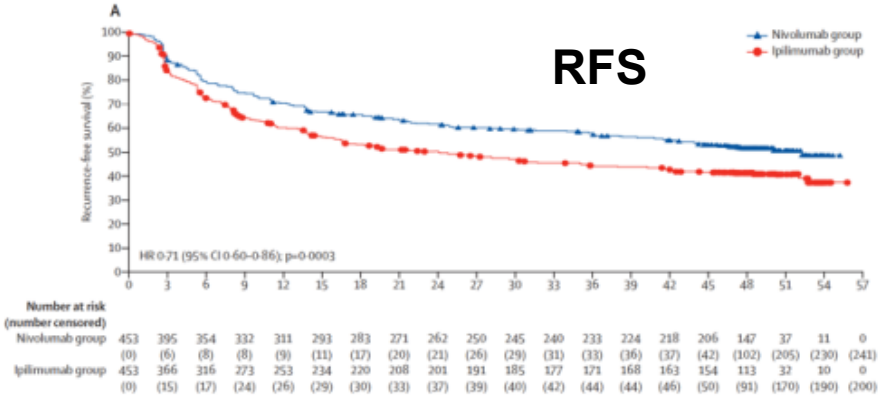
# Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma

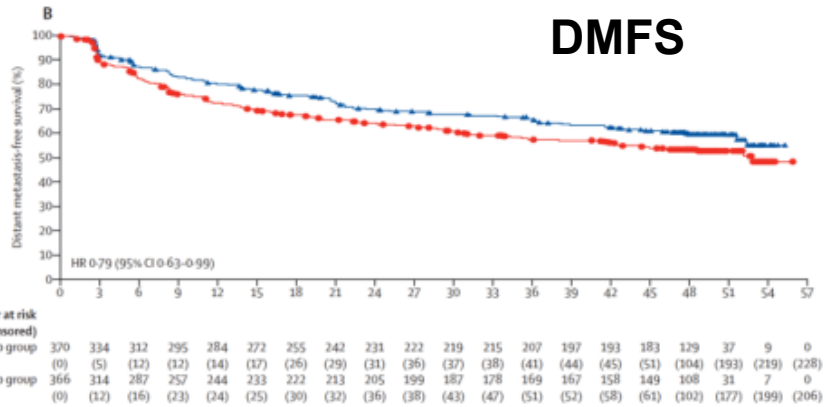
J. Weber, M. Mandala, M. Del Vecchio, H.J. Gogas, A.M. Arance, C.L. Cowey, S. Dalle, M. Schenker, V. Chiarion-Sileni, I. Marquez-Rodas, J.-J. Grob, M.O. Butler, M.R. Middleton, M. Maio, V. Atkinson, P. Queirolo, R. Gonzalez, R.R. Kudchadkar, M. Smylie, N. Meyer, L. Mortier, M.B. Atkins, G.V. Long, S. 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*

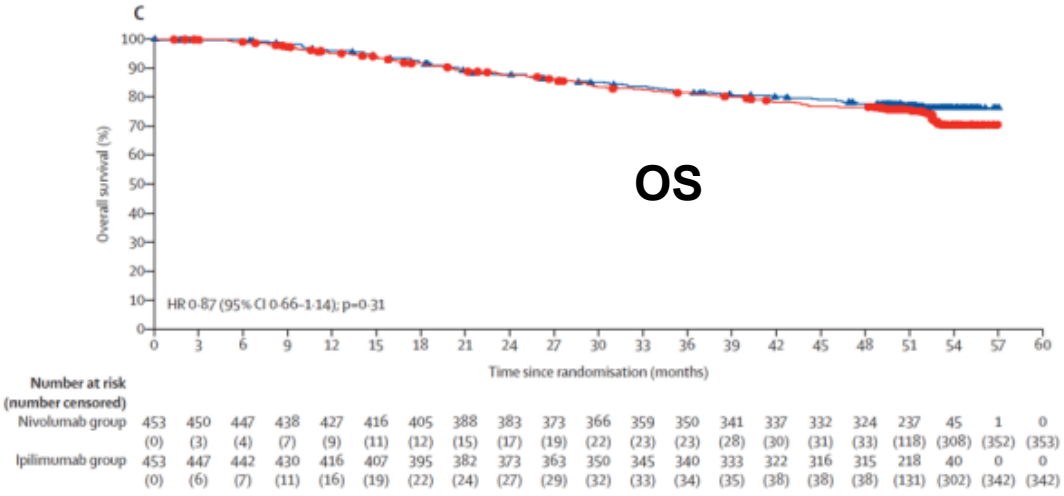
{Weber J et al *NEJM* 2020}

# Adjuvant nivolumab versus ipilimumab in resected stage IIIB–C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial

*Paolo A Ascierto, Michele Del Vecchio, Mario Mandalá, Helen Gogas, Ana M Arance, Stephane Dalle, C Lance Cowey, Michael Schenker, Jean-Jacques Grob, Vanna Chiarion-Sileni, Iván Márquez-Rodas, Marcus O Butler, Michele Maio, Mark R Middleton, Luis de la Cruz-Merino, Petr Arenberger, Victoria Atkinson, Andrew Hill, Leslie A Fecher, Michael Millward, Nikhil I Khushalani, Paola Queirolo, Maurice Lobo, Veerle de Pril, John Loffredo, James Larkin*, Jeffrey Weber**

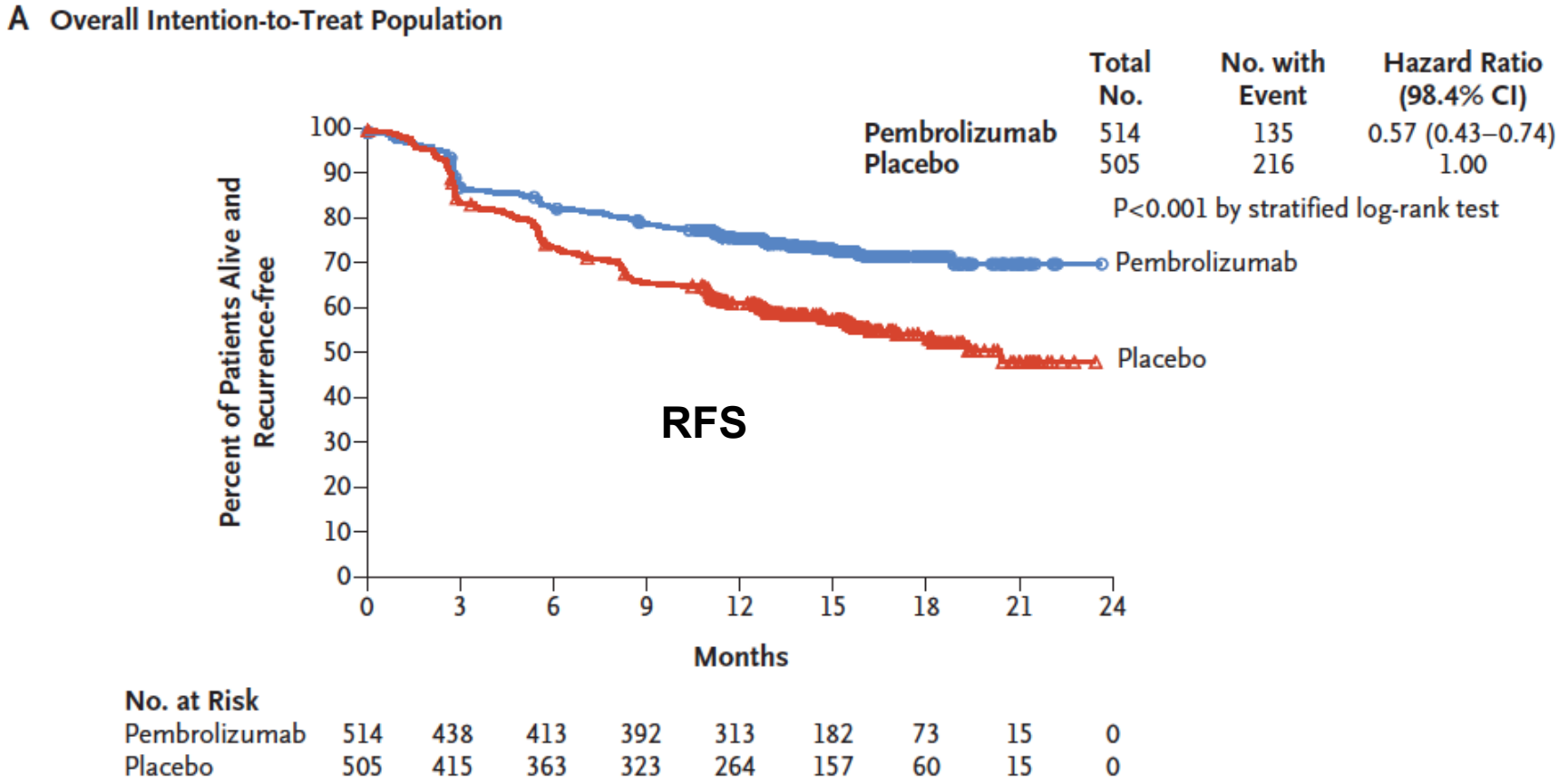



{Ascierto PA et al *Lancet Oncol* 2020}

# Adjuvant Pembro in Melanoma




{Eggermont AM et al *NEJM* 2018}

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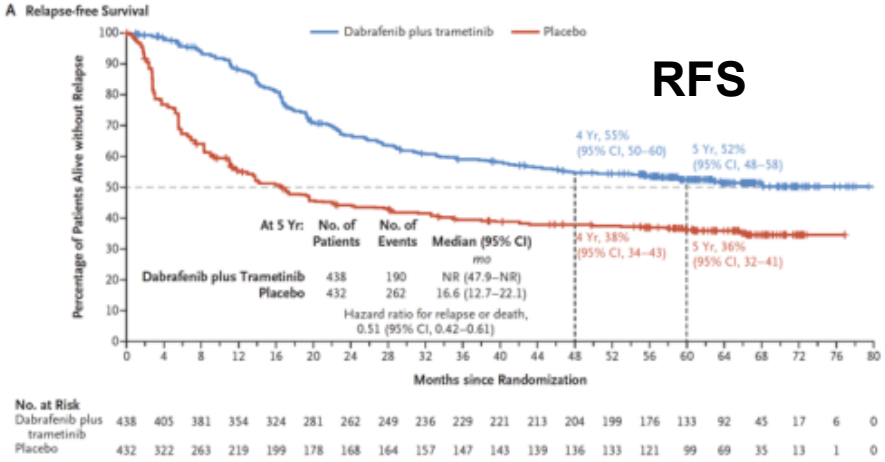
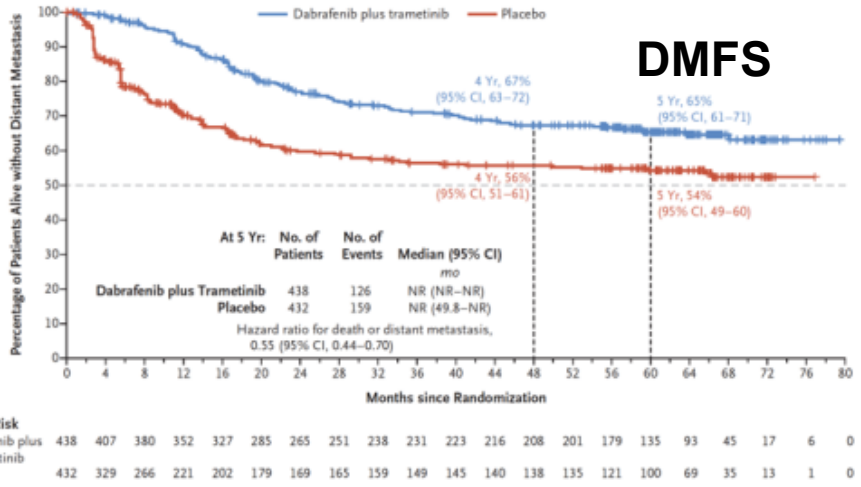
ORIGINAL ARTICLE

# Five-Year Analysis of Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma

R. Dummer, A. Hauschild, M. Santinami, V. Atkinson, M. Mandalà, J.M. Kirkwood, V. Chiarion Sileni, J. Larkin, M. Nyakas, C. Dutriaux, A. Haydon, C. Robert, L. Mortier, J. Schachter, T. Lesimple, R. Plummer, K. Dasgupta, E. Gasal, M. Tan, G.V. Long, and D. Schadendorf



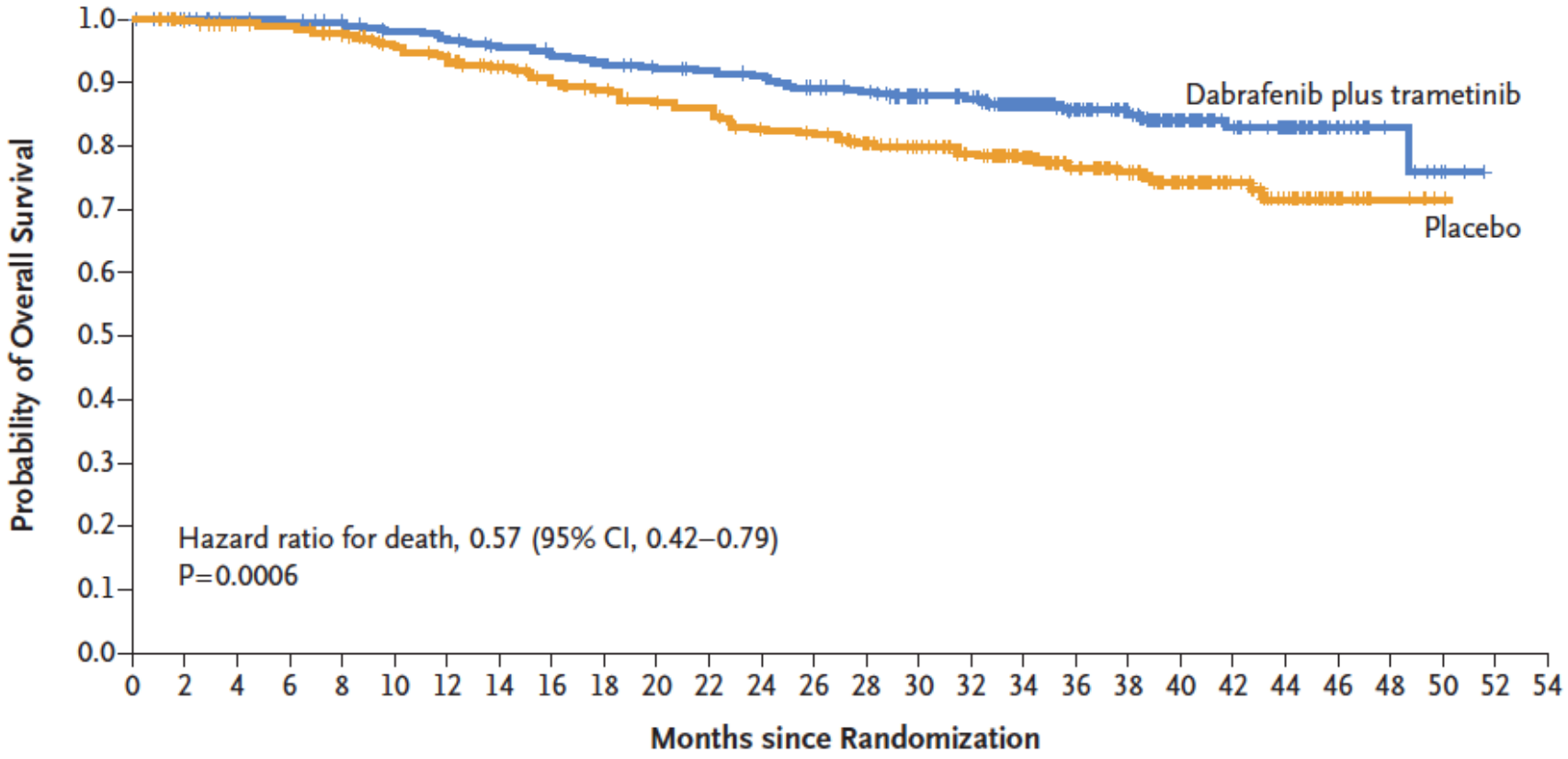

RFS




DMFS

{Dummer R *et a*l, *NEJM* 2020}

**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.**

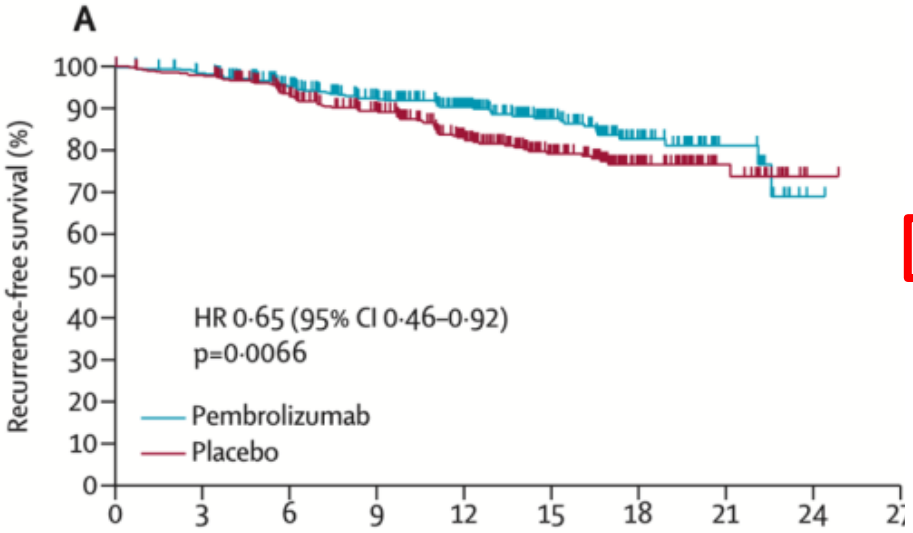
Better efficacy, lower toxicity than HD-Ipi

# 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 finally have an adjuvant therapy option

## Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial




| | Pembrolizumab group (n=487) | Placebo group (n=489) |
|---|---|---|
| Patients with an event | 72 (15%) | 115 (24%) |
| Local, regional, or locoregional* | 38 (8%) | 50 (10%) |
| Distant recurrence | 31 (6%) | 60 (12%) |
| Death | 3 (1%) | 5 (1%) |

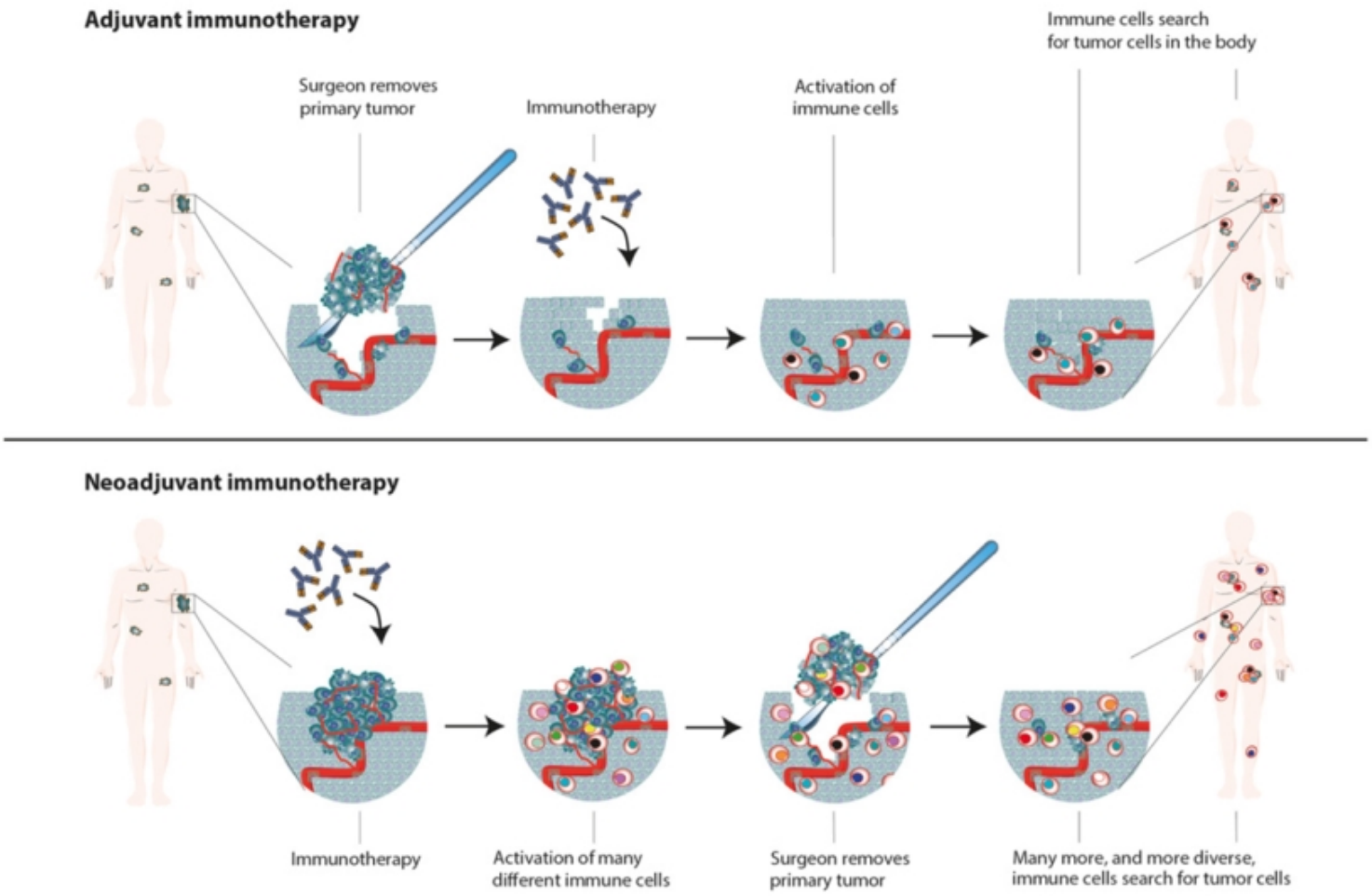
*Includes recurrence in the immediate vicinity of the primary tumour (local), regional lymph node basin involvement (regional), or both recurrence in the immediate vicinity of the primary tumour and regional lymph node basin involvement without spread beyond regional lymph nodes (locoregional).

*Table 2:* **Patterns of disease recurrence at the second interim analysis (data cutoff June 21, 2021)**

{Luke J et al *Lancet* 2022}

# Neo-Adjuvant Therapy in Resectable Stage III Melanoma

# Rationale for Neo-adjuvant therapy




www.esmo.org *2018*

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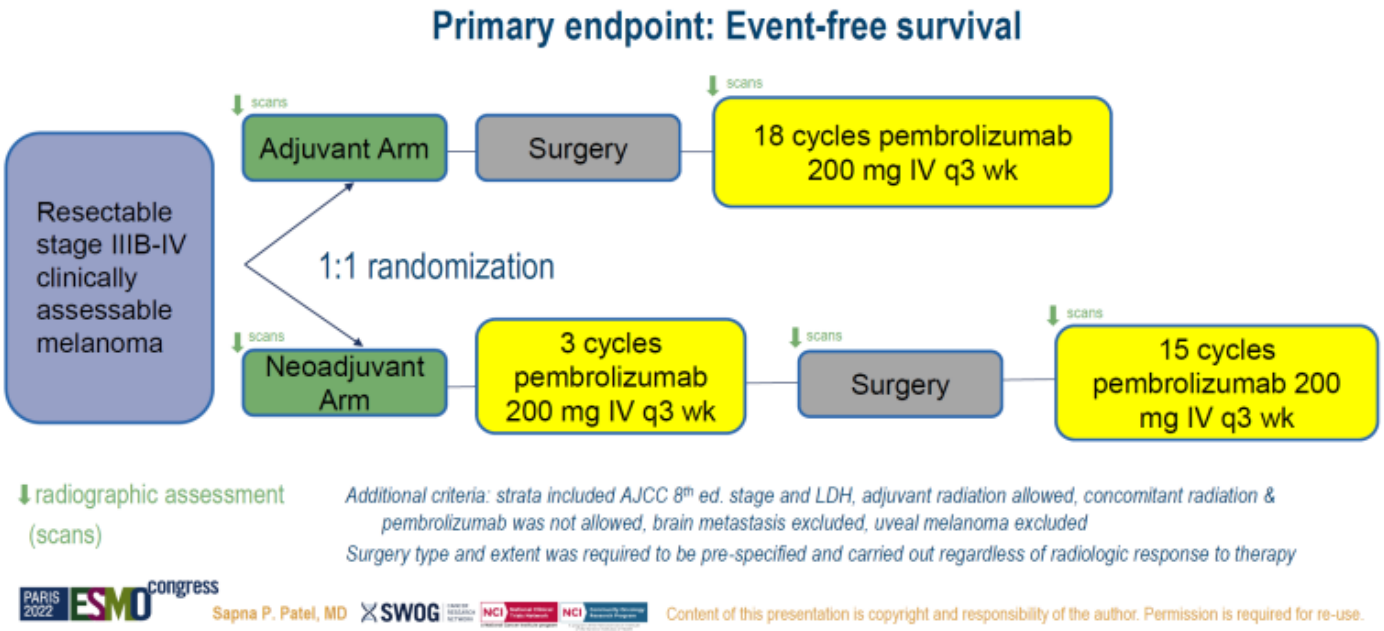
ORIGINAL ARTICLE

# Neoadjuvant–Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

## S1801 Study Schema

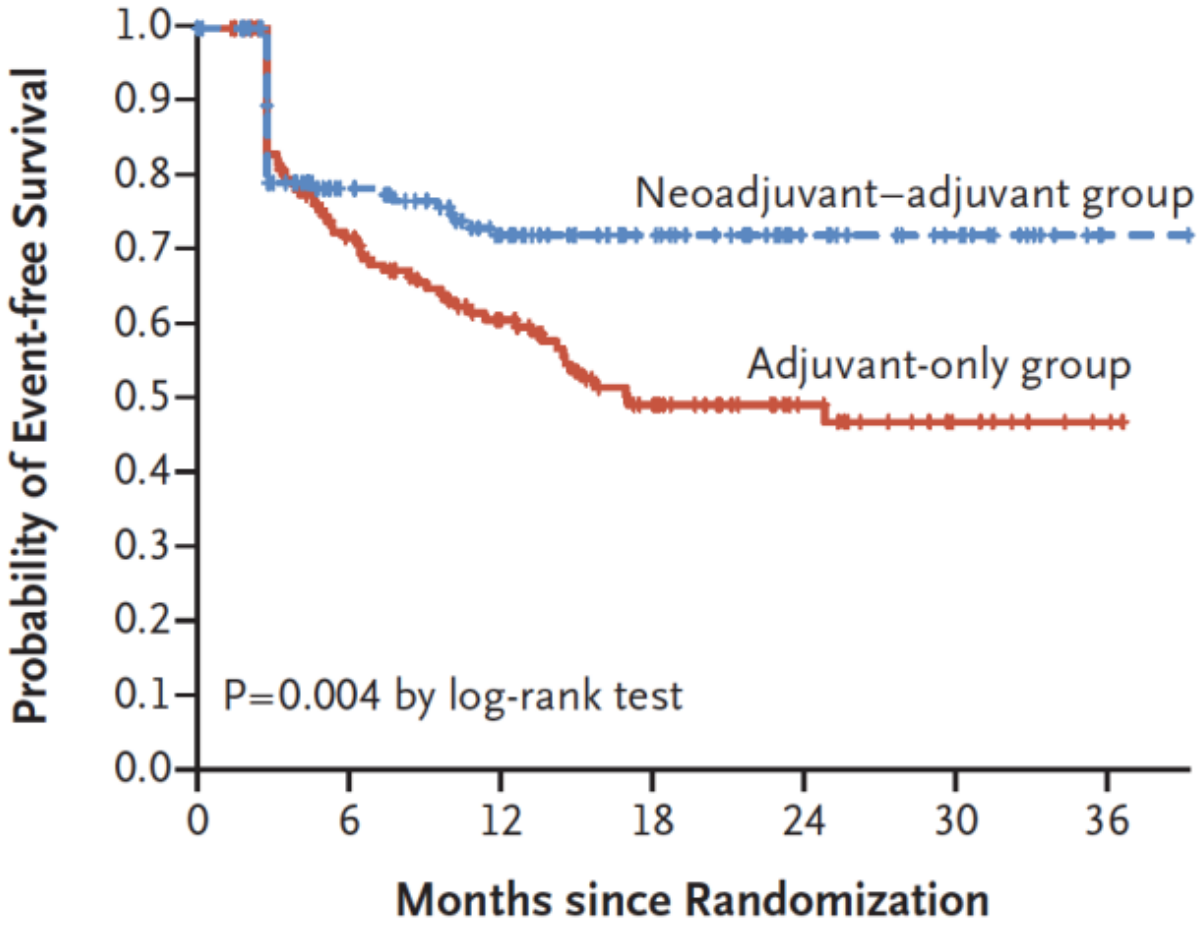






{Patel S et al *NEJM* 2023}

# SWOG 1801 – Primary Endpoint (EFS)




**No. at Risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Neoadjuvant–adjuvant group | 154 | 96 | 69 | 46 | 25 | 17 | 1 |
| Adjuvant-only group | 159 | 98 | 67 | 40 | 22 | 10 | 2 |

{Patel S et al *NEJM* 2023}

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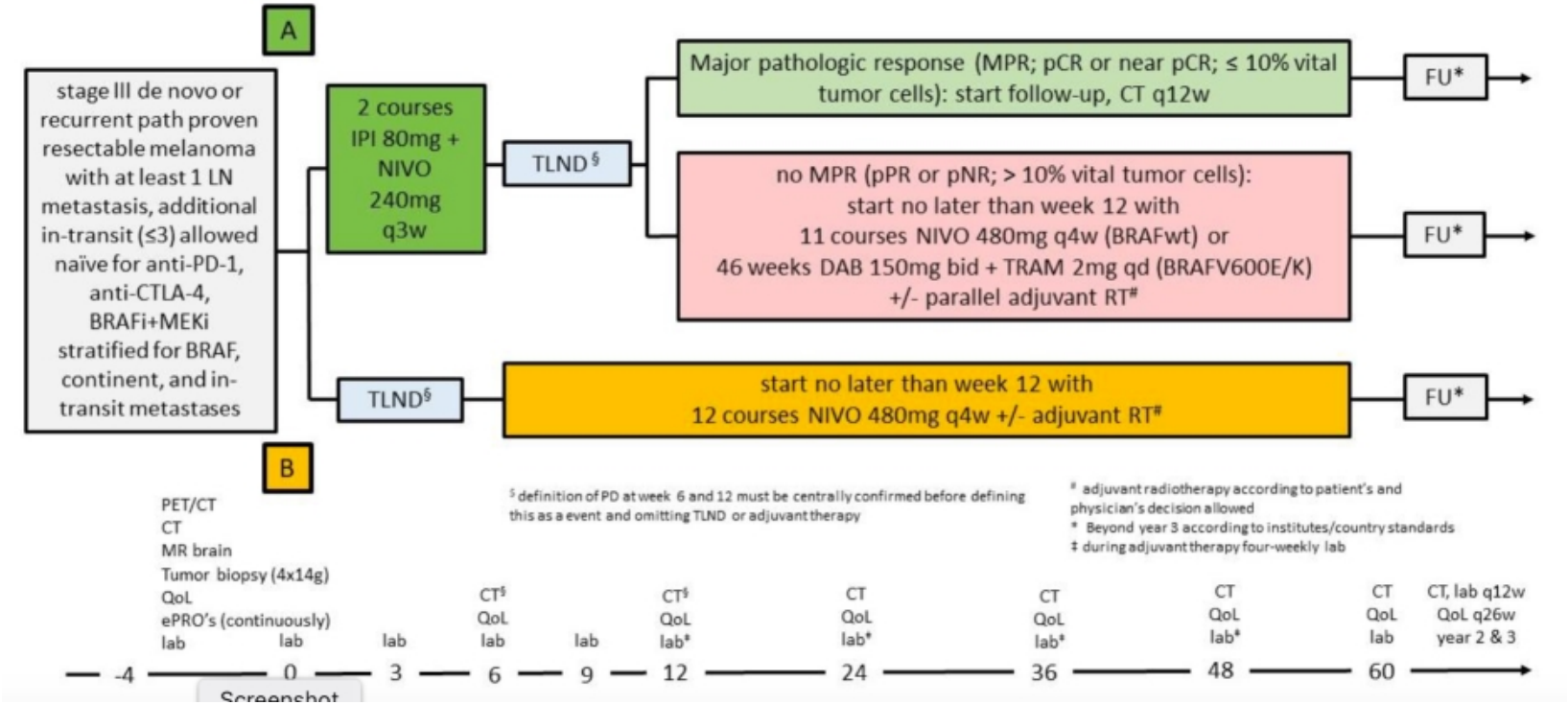
ORIGINAL ARTICLE

# Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma




{Blank C et al *NEJM* 2024}

# NADINA trial – Primary Endpoint (EFS)

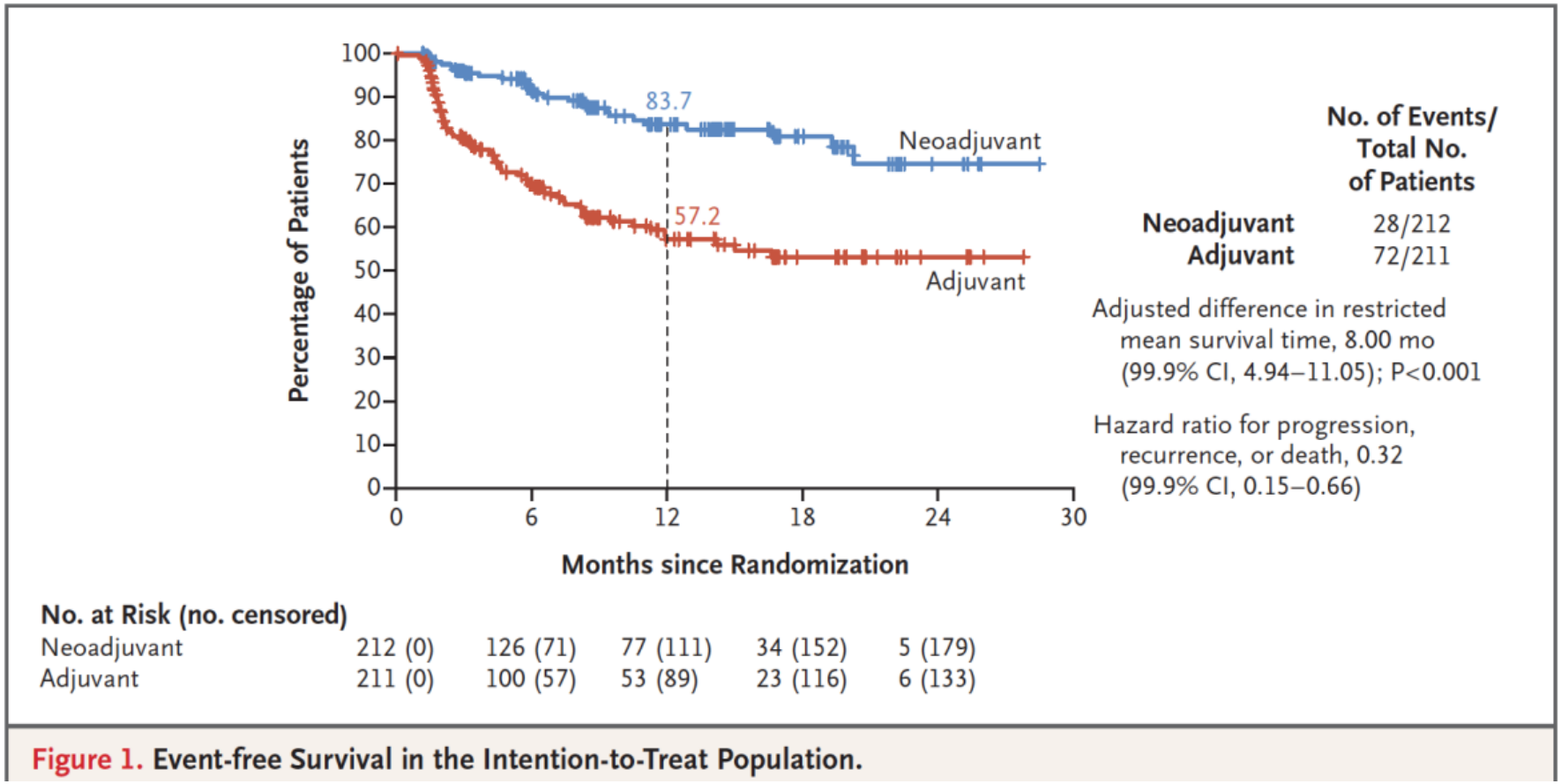



**Figure 1. Event-free Survival in the Intention-to-Treat Population.**

{Blank C et al *NEJM* 2024}

# (Neo-)Adjuvant Systemic Therapy: Take-home messages

- Earlier incorporation of systemic therapy improves many efficacy endpoints, although impact on OS is still unclear in the modern era.
- Neo-adjuvant systemic therapy may potentially be better than adjuvant, although OS benefit remains to be proven.
- Not all patients need systemic therapy – consider absolute (vs relative) risk reduction and NNT (Number need to treat).
- Toxicity considerations, including long term QoL, are even more relevant in non-metastatic settings.

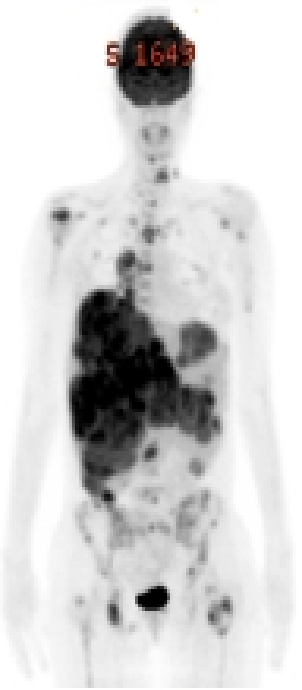
# Case # 1

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 metastases** 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, ALT 85, ALK-P 375 and Bilirubin 1.5**. His ECOG **performance score is 2**.



# Case # 1 (contd.)

## What will you recommend next?

A. Whole brain radiation therapy.

A. PD-1 blockade (Pembrolizumab or Nivolumab)

A. Ipilimumab plus Nivolumab

A. Relatlimab-Nivolumab

**A. BRAFi + MEKi**

# Case # 2

42-year-old man presented with **3.4 mm thick, ulcerated primary melanoma (pT3b)** located on the right arm. Wide local excision revealed no residual melanoma and sentinel lymph node biopsy showed **1 of 1 axillary lymph node** involved with metastatic melanoma (size of deposit 5 mm) **(pN1a)**.

Staging FDG-PET scan and brain MRI did not show any metastatic disease. Stage is **IIIC (**AJCC 8th ed**).**

BRAF testing of the primary tumor was negative for the presence of BRAF V600E mutation.

**What is the most appropriate next step in treatment?**

# Case # 2 (contd.)

a) Completion axillary lymph node dissection
b) Adjuvant radiation therapy to the right axillary basin
**c) Adjuvant systemic therapy with nivolumab or pembrolizumab**
d) Adjuvant systemic therapy with ipilimumab plus nivolumab
e) Adjuvant systemic therapy with relatlimab plus nivolumab
f) None of the above

# Thank you!!

Suggested topics for additional reading:

- IRAEs
- Melanoma Brain Metastases
- BRAFi + MEKi + anti-PD-1
- Melanoma Subtypes (Uveal, acral, mucosal, desmoplastic)
- Non Melanoma Skin Cancers (MCC, cSCC, BCC)

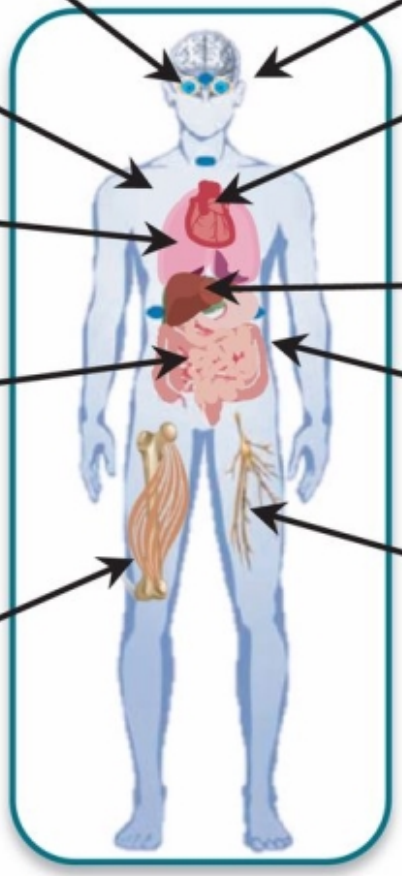
# Immune-related Adverse events (IRAEs)

# Immune-related Adverse events (IRAEs)

**Skin**
- Dermatitis, erythroderma
- Erythema multiforme
- Stevens–Johnson syndrome
- Toxic epidermal necrolysis
- Psoriasis
- Vitiligo
- Alopecia

**Eyes**
- Conjunctivitis
- Uveitis, iritis, retinitis
- Scleritis, episcleritis
- Blepharitis

**Endocrine system**
- Hypo- or hyperthyroidism
- Hypophysitis, hypopituitarism
- Adrenal insufficiency
- Type 1 diabetes



**Cardiovascular system**
- Myocarditis
- Pericarditis
- Vasculitis

**Lungs**
- Pneumonitis
- Pleuritis
- Interstitial lung disease

**Liver**
- Hepatitis

**Gastrointestinal tract**
- Colitis
- Ileitis
- Pancreatitis
- Gastritis
- Perforation

**Kidneys**
- Nephritis
- Lupus-like glomerulonephritis

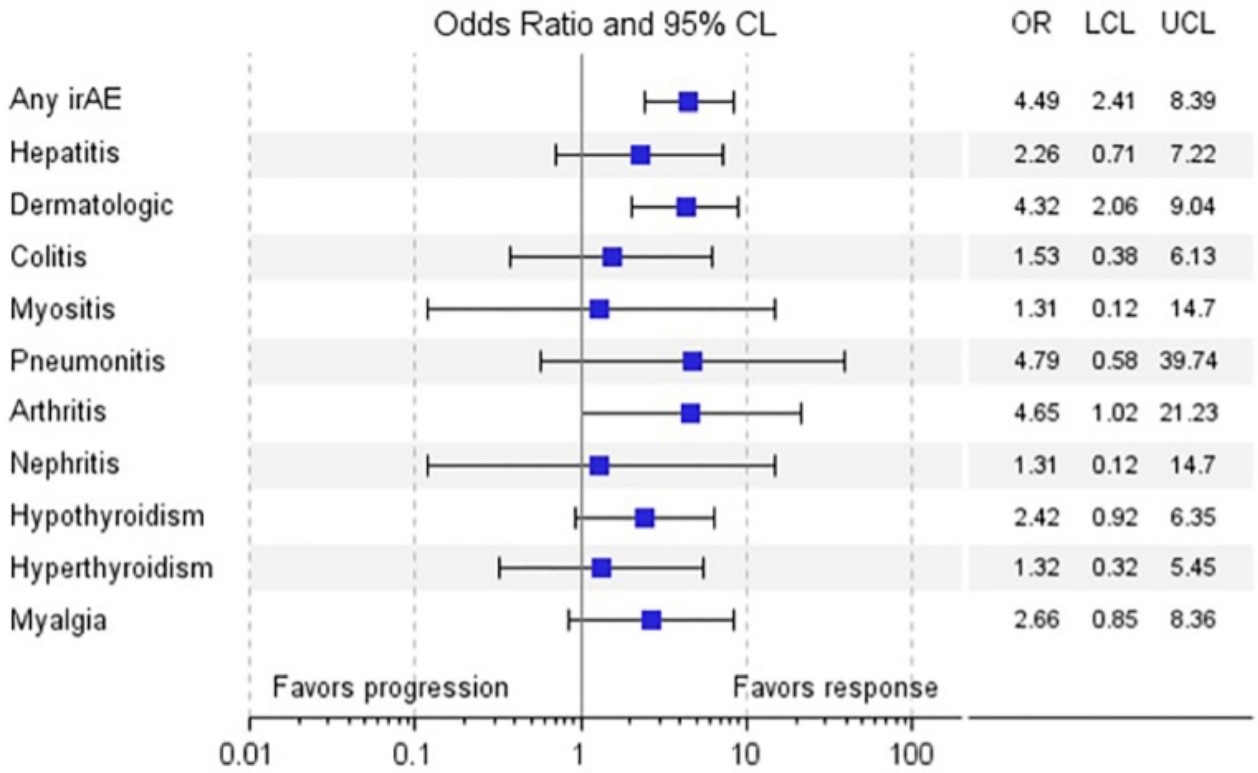
**Musculoskeletal system**
- Arthralgias, arthritis
- Myalgias, myositis
- Enthesitis

**Neurologic system**
- Neuropathy
- Myelopathy
- Guillain–Barré syndrome
- Myasthenia gravis–like syndrome
- Encephalitis, meningitis

# Immune-related Adverse events (IRAEs)

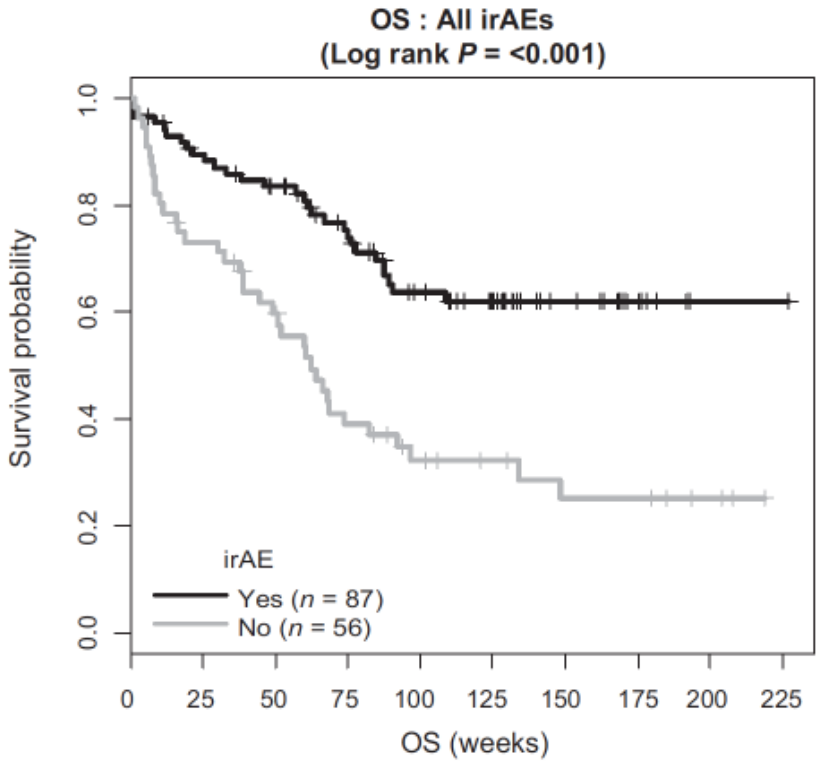
- Risk of Death (~0.5%) – MMM (Myocarditis, Myositis, Myasthenia), neurologic diseases, pneumonitis *et cetera*
- Permanent side-effects affecting QoL (hypophysitis, type I DM, neuropathy)
- Require careful counseling, close monitoring, and aggressive management.
- **NCCN guidelines** exist.

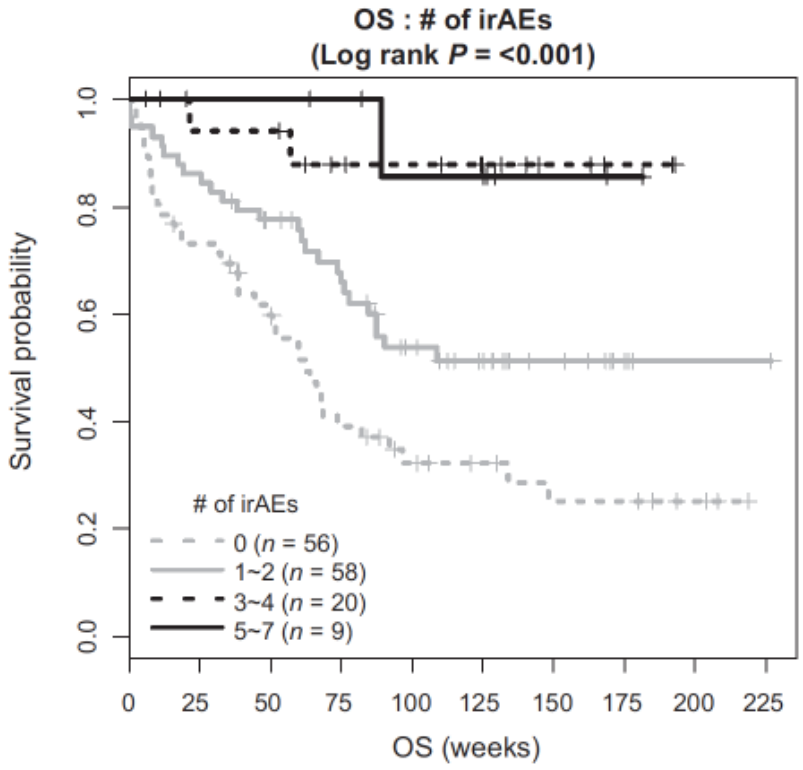
# IRAEs associated with higher ORR in Melanoma




{Bastacky ML et al, *Front Onc* 2021}

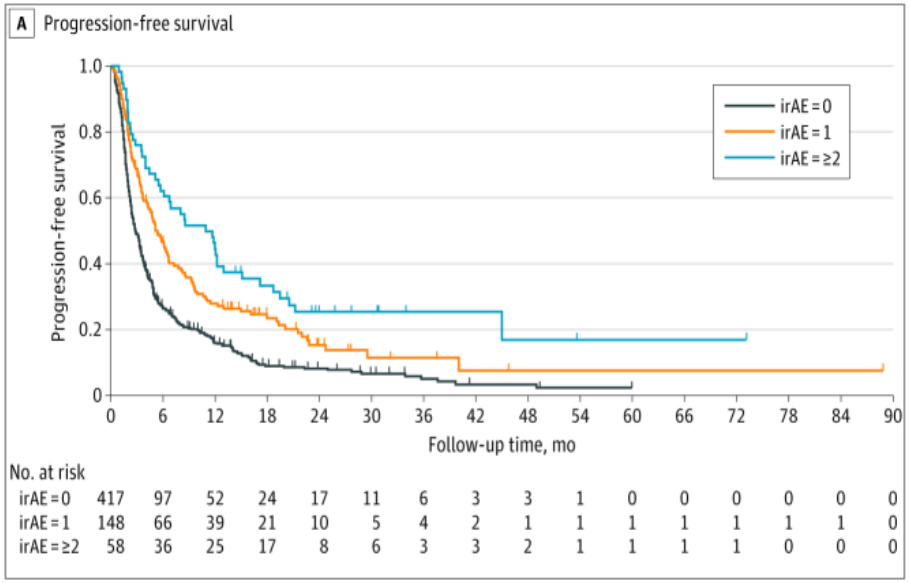
# IRAEs associated with better OS in Melanoma



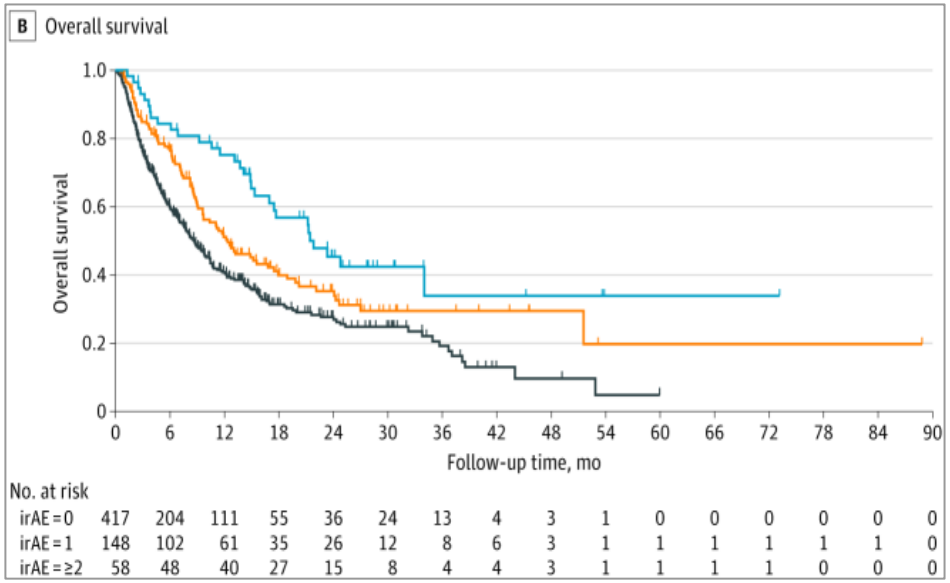




{Freeman-Keller et al, *Clin Cancer Res* 2016}

# Multisystem-IRAEs: Incremental Benefit




1 irAE: HR 0.67, **p=0.001**
≥2 irAEs: HR 0.38, **p<0.0001**




1 irAE: HR 0.86, P = 0.253
≥2 irAEs: HR 0.56, **P=0.005**

{Shankar, Naidoo et al, *JAMA Oncol* 2020}

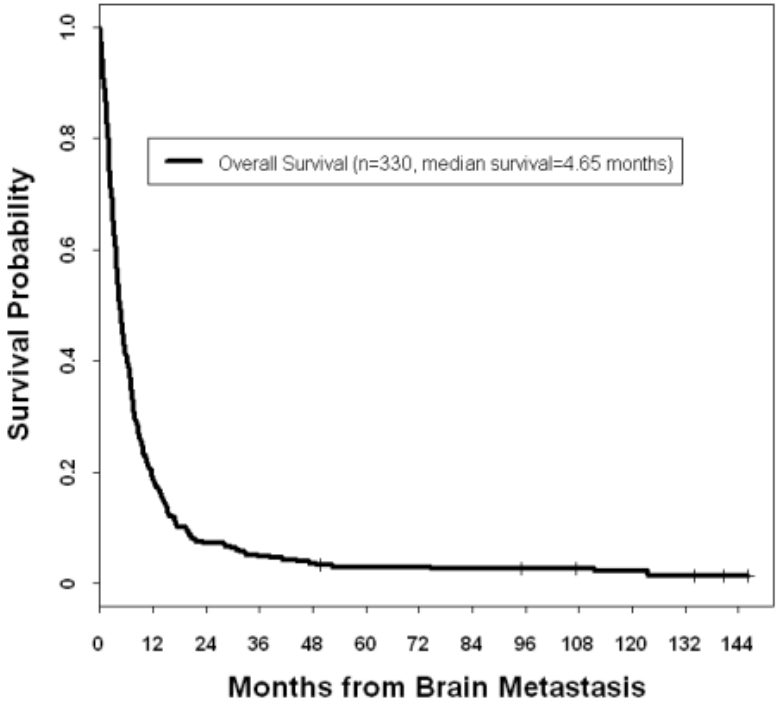
# Take-home messages for IRAEs

- Do not let the fear of IRAEs compromise the utilization of ICI.
- Patient education and monitoring is essential throughout ICI treatment.
- Accurate diagnosis of IRAE (vs other causes) is important.
- Prompt, decisive and aggressive interventions are essential with serious IRAEs.
- Early use of selective agents may reduce steroid exposure.
- Don’t hesitate to seek help with tricky cases!

# Melanoma Brain Metastases

# 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

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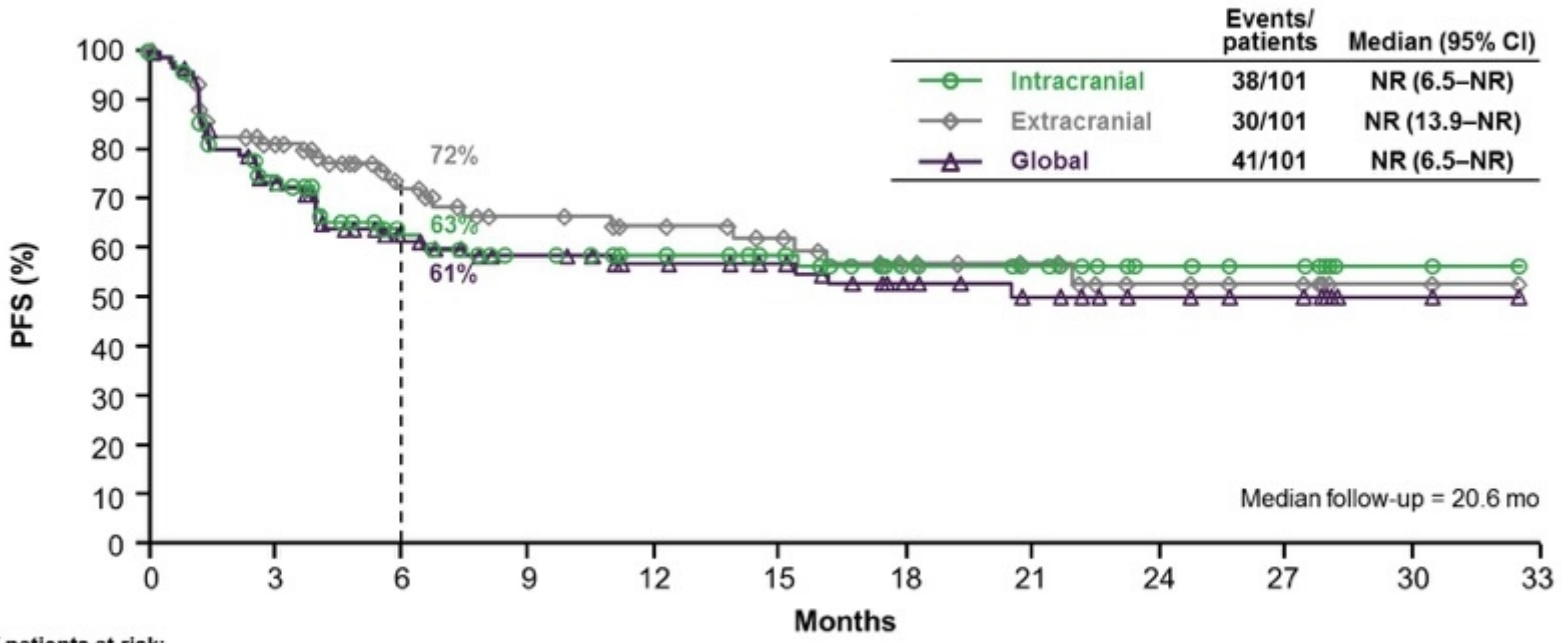
ORIGINAL ARTICLE

# Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

CheckMate 204

## Progression-Free Survival – Asymptomatic Patients

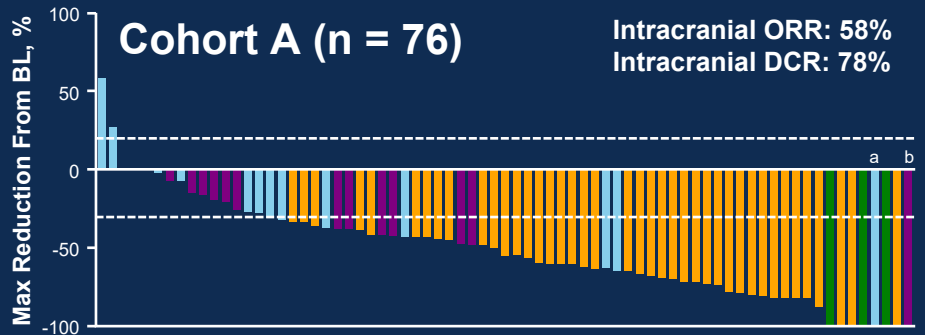


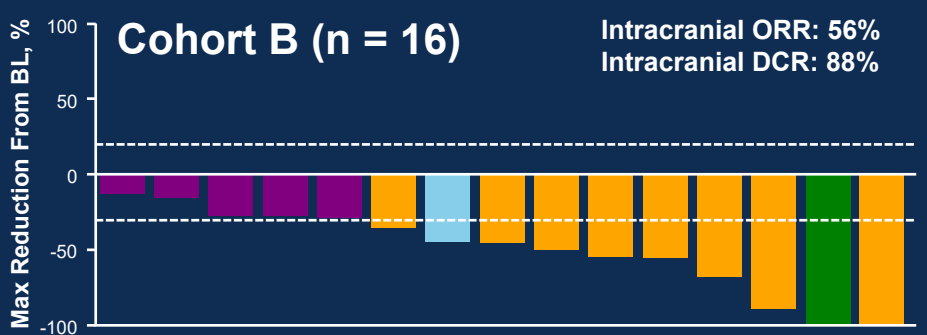

Number of patients at risk:

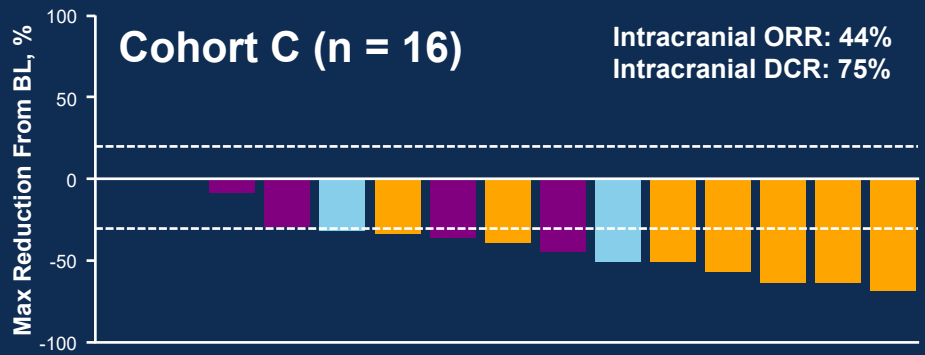
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Intracranial: | 101 | 65 | 46 | 38 | 34 | 30 | 21 | 18 | 10 | 8 | 2 | 0 |
| Extracranial: | 101 | 62 | 42 | 33 | 29 | 25 | 19 | 16 | 9 | 7 | 2 | 0 |
| Global: | 101 | 64 | 45 | 38 | 33 | 30 | 21 | 17 | 10 | 8 | 2 | 0 |

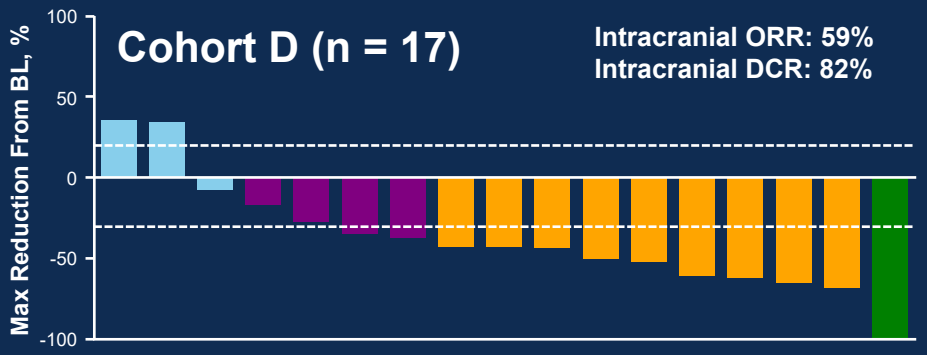
# BRAF-MEKi in MBMs

## 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.
- Asymptomatic brain metastases

  **- Ipi-Nivo** has best long-term outcomes.

- Symptomatic brain mets:
  - **Initial BRAFi+MEKi** in the BRAF-mutant melanoma has high ORR, although duration of responses is short.
  - Consider **proactive transition to Ipi-Nivo**.
  - **BRAFi+MEKi+PD-1** is an acceptable option too for symptomatic brain mets with possibly longer duration of responses, especially if proactive transition to Ipi-Nivo is not feasible or successful.

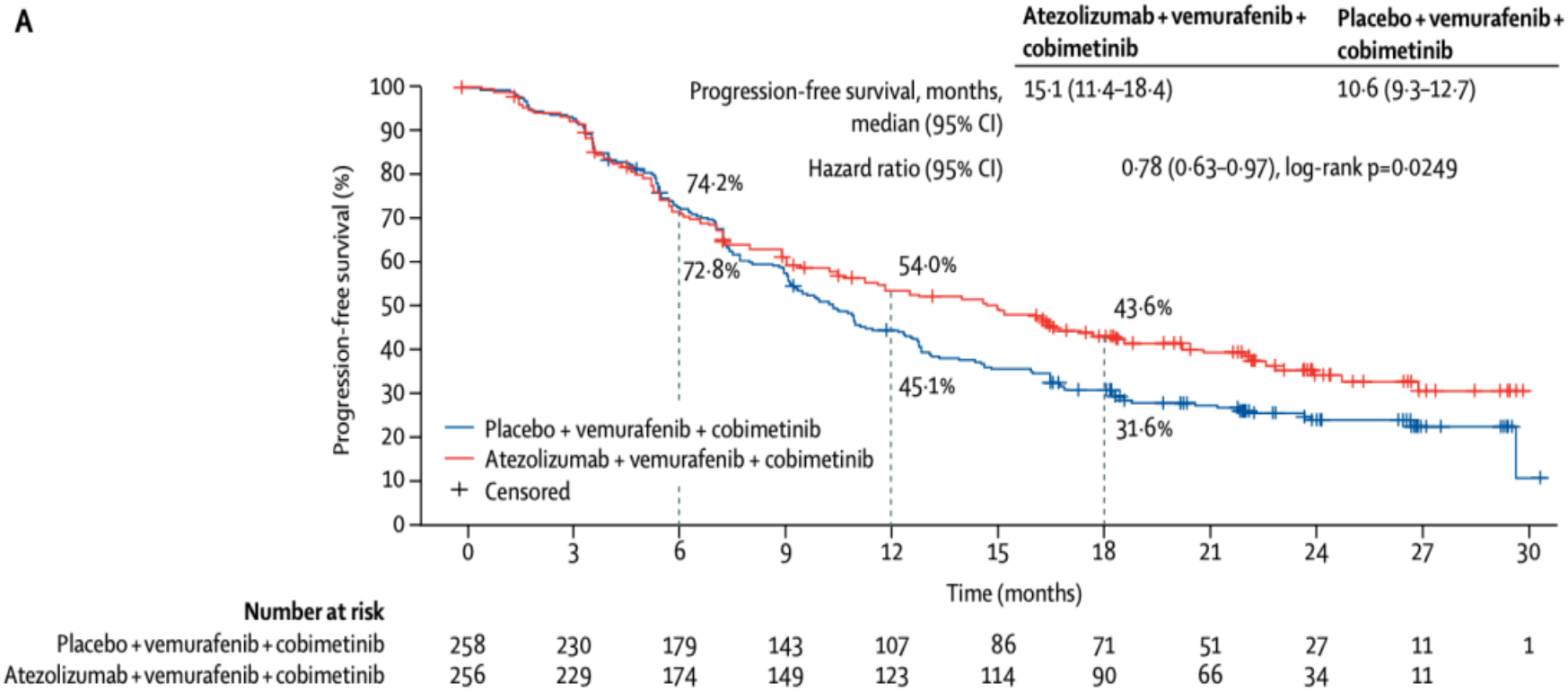
# BRAFi + MEKi + anti-PD-1

# Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced *BRAF*$^{V600}$ mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial

*Ralf Gutzmer, Daniil Stroyakovskiy, Helen Gogas, Caroline Robert, Karl Lewis, Svetlana Protsenko, Rodrigo P Pereira, Thomas Eigentler, Piotr Rutkowski, Lev Demidov, Georgy Moiseevich Manikhas, Yibing Yan, Kuan-Chieh Huang, Anne Uyei, Virginia McNally, Grant A McArthur*, Paolo A Ascierto**

*Lancet* 2020; 395: 1835–44

# Results – Investigator-assessed PFS




Gutzmer R *et al*, Lancet 2020.

# Results – ORR and Duration of response

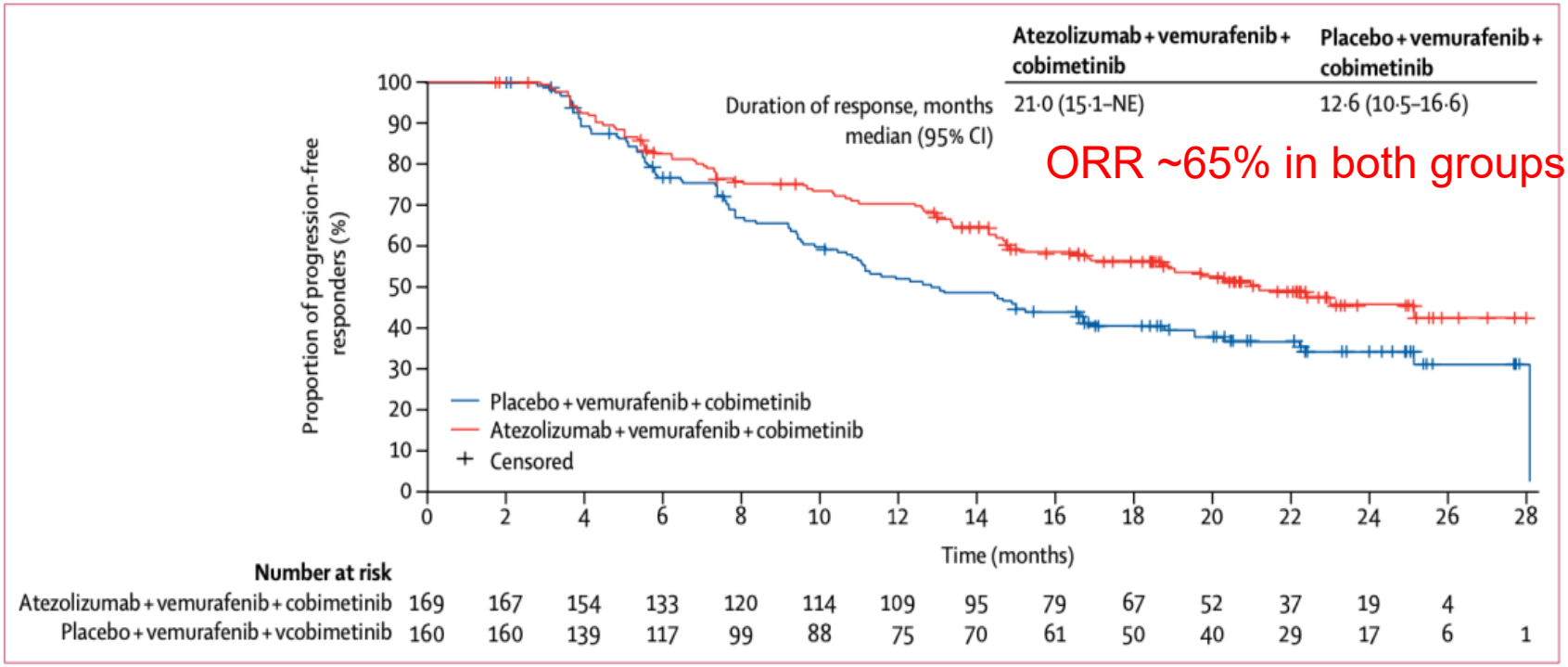
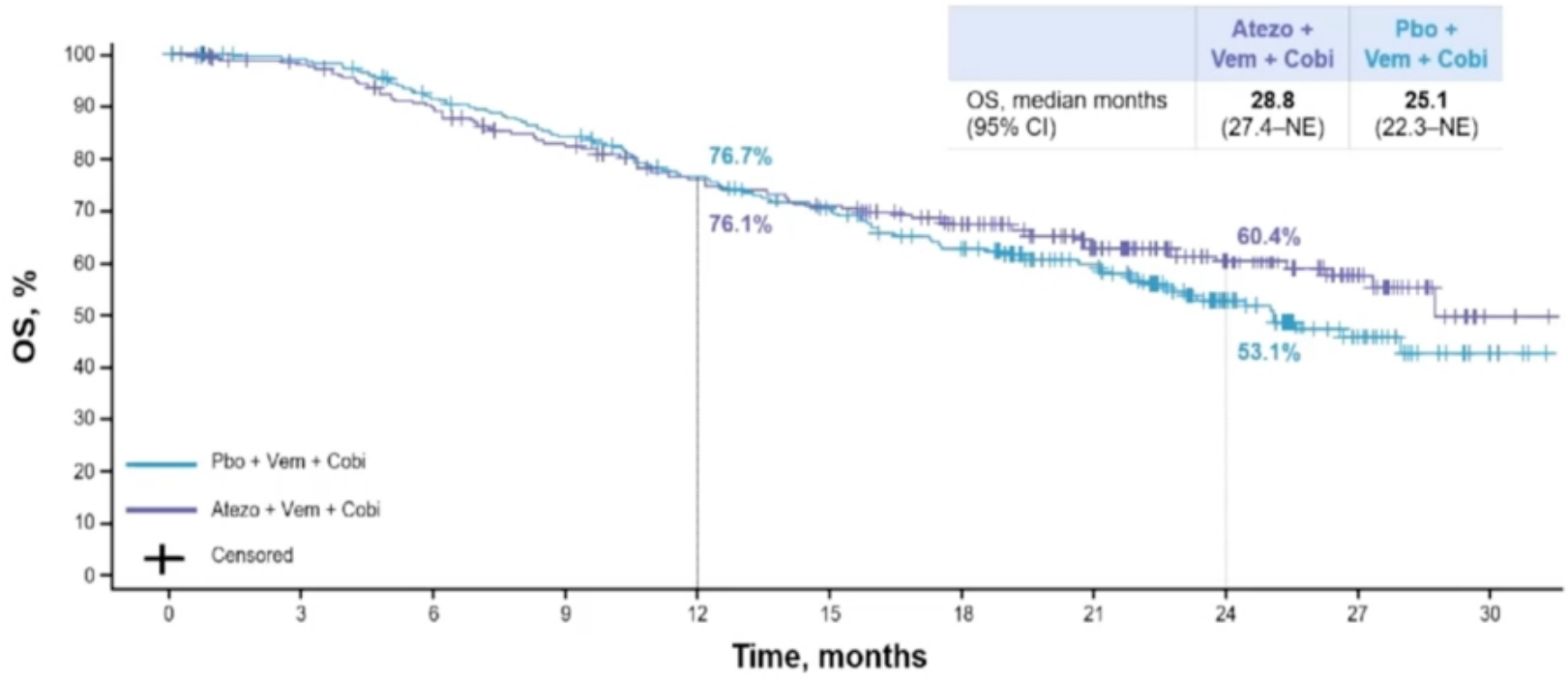



**Figure 3: Kaplan-Meier estimate of duration of response in the intention-to-treat population**
NE=not estimable.

Gutzmer R *et al*, Lancet 2020.

# Results – Overall survival




McArthur, AACR 2020.

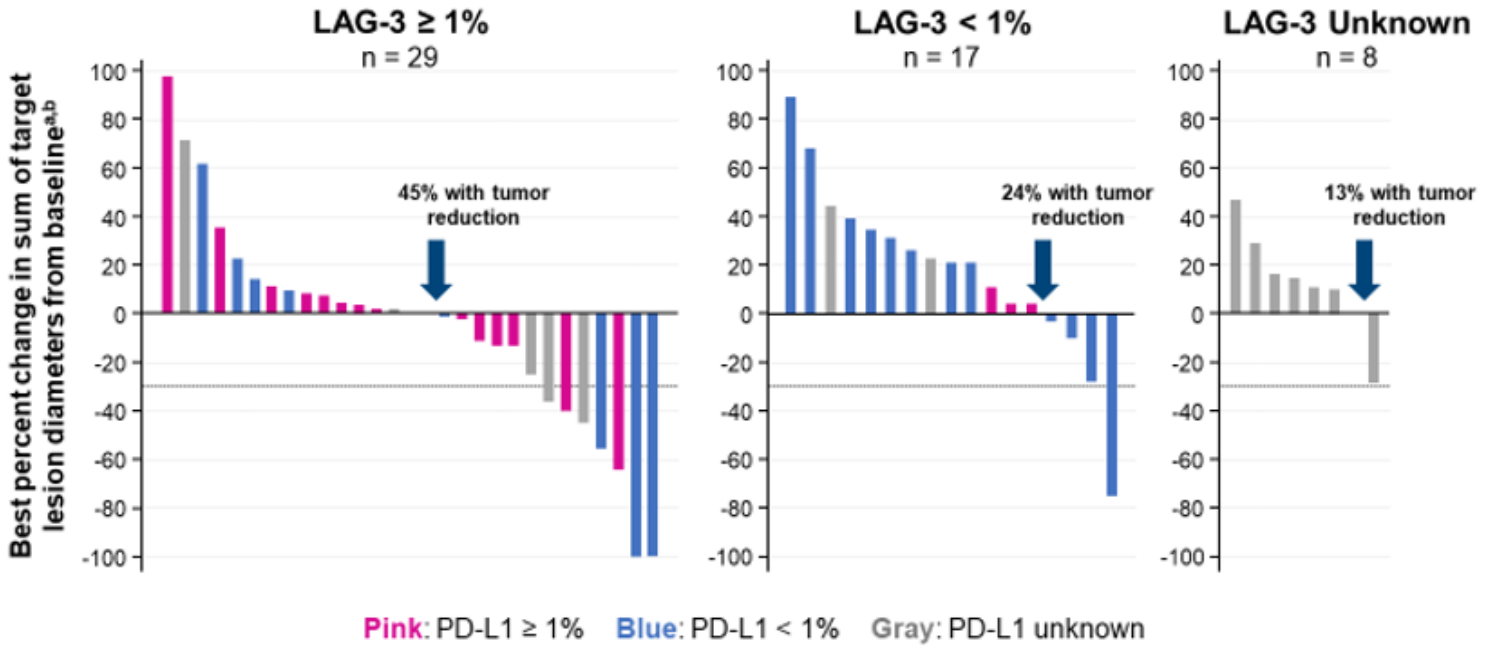
# My Conclusions on BRAFi+MEKi+IO

- PFS improvement appears to be clinically meaningful, although OS data will be more definitive towards superiority of the triple combo.
- Toxicity appears manageable (although rate of steroid use was higher than anticipated in both arms reflecting challenges of identifying the culprit medications).
- Lack of PD-1 monotherapy comparator limits widespread clinical application of this triple combination, since many clinicians would favor using immunotherapy (such as Ipi-Nivo) in frontline therapy of metastatic melanoma.

**In my practice, I use this data to support the addition of PD-1/PD-L1 blockade in patients who are going to get BRAF-MEKi anyways.**

# Refractory Melanoma

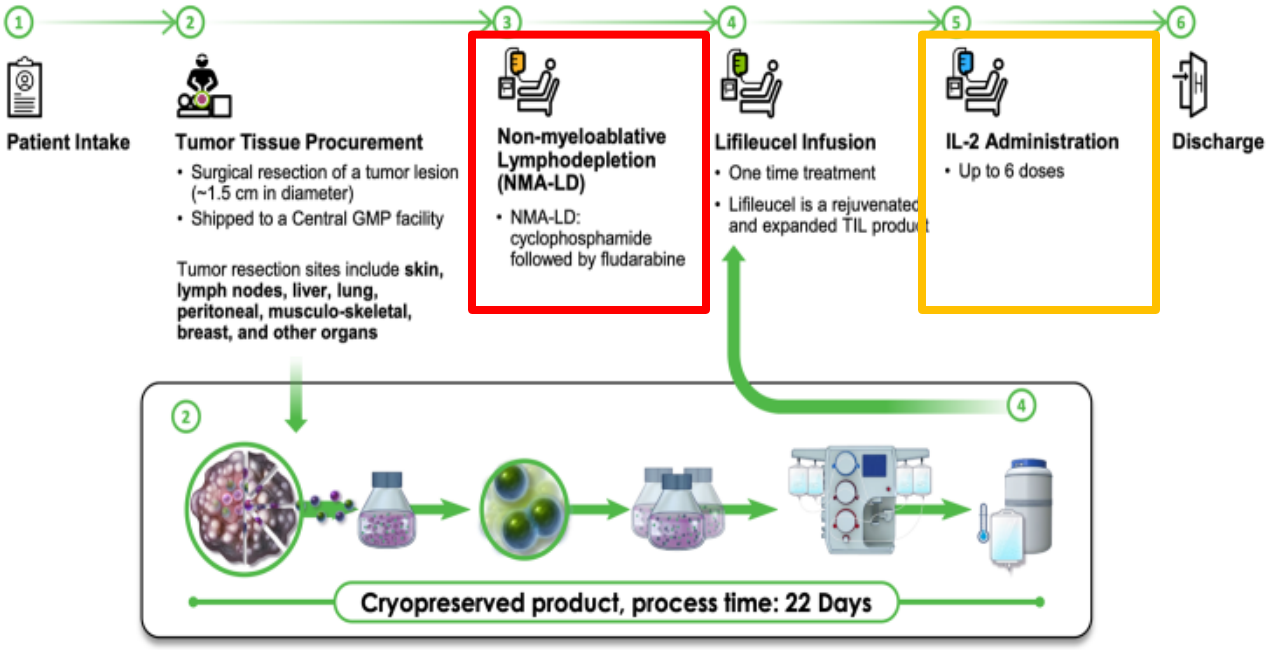
# Lag-3 + PD-1 blockade can rescue a subset of patients with anti-PD-1




nivo + rela post PD-1 progression

[Ascierto P et al 2017]

# Lifileucel: TILs for melanoma



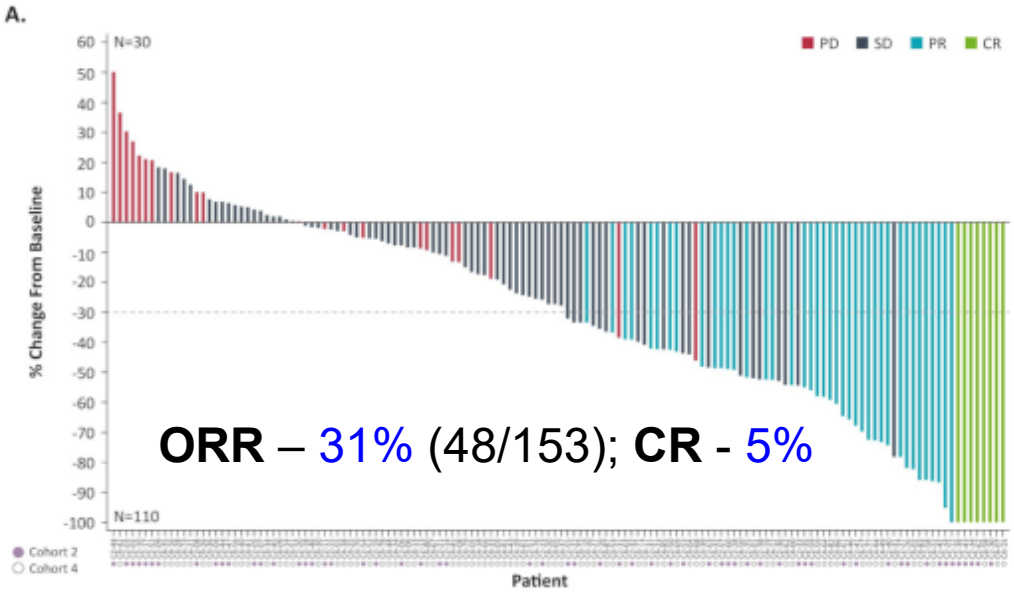

Cyclophosphamide 60 mg/kg for 2 days
Fludarabine 25 mg/m2 daily for 5 days

IL-2 (aldesleukin) at 600,000 IU/kg
every 8 to 12 hours for up to 6 doses

(Chesney J et al. AACR, 2021; Lifileucel pa

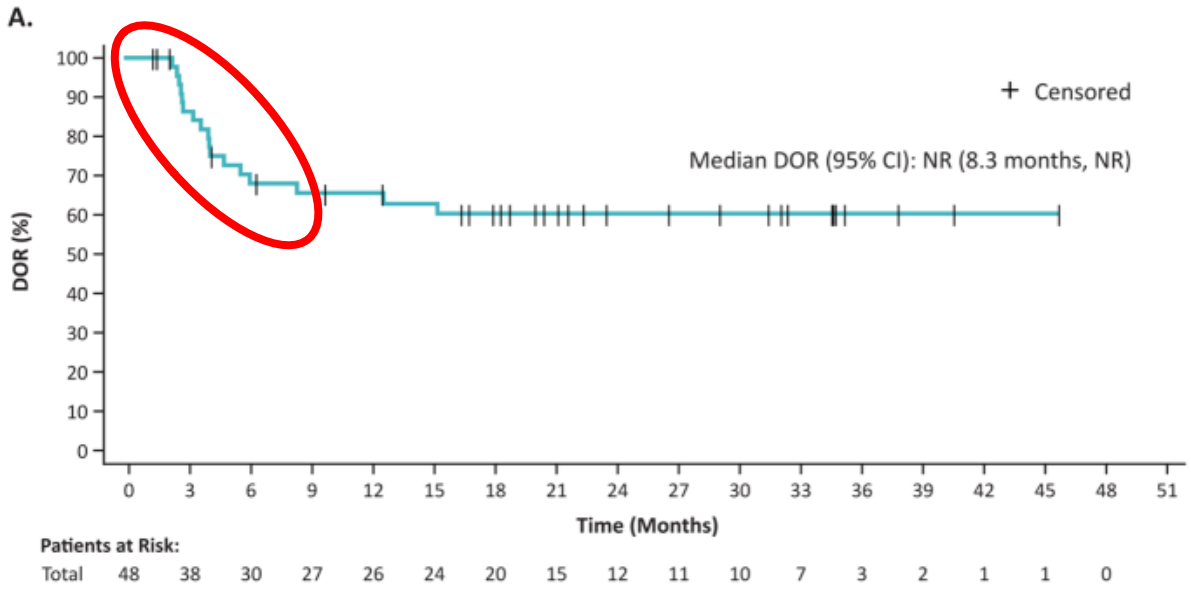
# Lifileucel: Responses in refractory melanoma patients

**Median age**: 56 [20-79]; **ECOG** 0/1
**Median prior therapies**: 3 [1-9]; Prior anti-PD-1 (100%)




{Chesney J, *JITC*, 2022}

# Lifileucel: Responses can be durable!

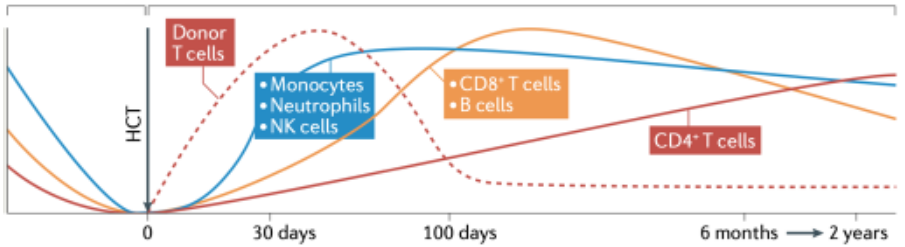



{Chesney J, *JITC*, 2022}

# Lymphodepletion: A double-edged sword!

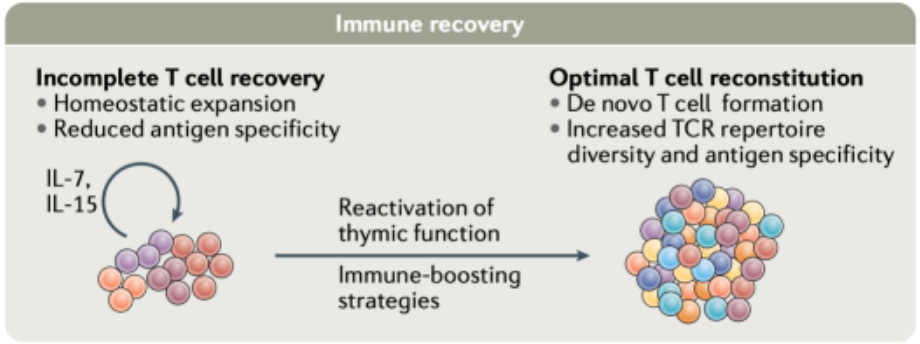
**Delayed kinetics of immune reconstitution!**

Cyclophosphamide 60 mg/kg for 2 days
Fludarabine 25 mg/m2 daily for 5 days




**Potential mechanisms of efficacy:**

- Elimination of suppressor T cells.
- Decreased competition by endogenous lymphocytes for homeostatic regulatory cytokines like IL-7 or IL-15.

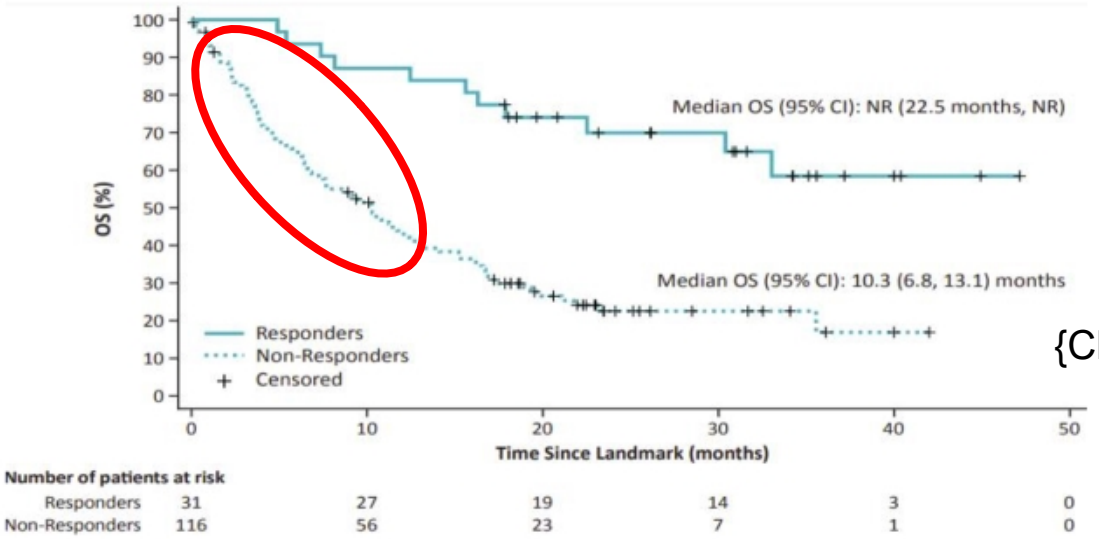



{Dudley ME et al. *JCO* 2005}

{Velardi E et al. 2021 *Nat Rev Immunol*}

# Lifileucel: Poor OS in non-responders (?Immunosuppression related to Lymphodepletion)

**Supplementary Figure 4. Overall Survival, by Response Status at 1.5 Months After Lifileucel Infusion**




Number of patients at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| Responders | 31 | 27 | 19 | 14 | 3 | 0 |
| Non-Responders | 116 | 56 | 23 | 7 | 1 | 0 |

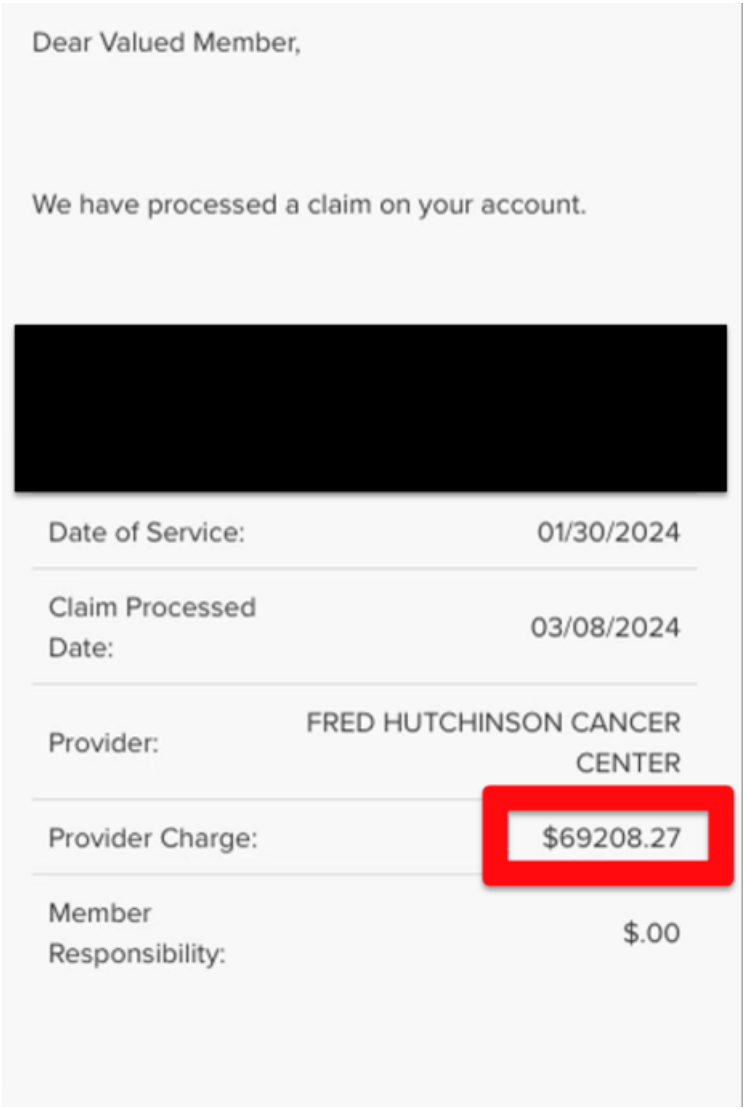
{Chesney J, *JITC*, 2022}

**CAUTION: Use of TILs in earlier settings may compromise responses to subsequent IO!**

# Financial Toxicity

# Total cost for 2 years of treatment

- **Nivo alone** = $374,103.08
- **Nivo3/Ipi1** = $425,323.66
- **Nivo1/Ipi3** = $504,552.58
- **Relatlimab/Nivo** = $726,336



Dear Valued Member,

We have processed a claim on your account.

[redacted]

| | |
|---|---|
| Date of Service: | 01/30/2024 |
| Claim Processed Date: | 03/08/2024 |
| Provider: | FRED HUTCHINSON CANCER CENTER |
| Provider Charge: | $69208.27 |
| Member Responsibility: | $.00 |

# First Line Immunotherapy for Metastatic Melanoma: Can Cost Effectiveness Guide the Choice?

Hiba Khan, MD, MPH[1,2,3], Christopher Maerzluft[3], Evan Hall, MD, MPhil[1,2], Scott Ramsey, MD, PhD[2,3], Veena Shankaran, MD, MS[1,2,3], Carolyn Rutter, PhD[3], Shailender Bhatia, MD*[1,2]

1) University of Washington, Hematology/Oncology 2) Fred Hutchinson Cancer Center (FHCC), Clinical Research Division, 3) FHCC, Hutchinson Institute for Cancer Outcomes Research.

*Presenting Author; **Correspondence**: hkhan@fredhutch.org ; sbhatia@uw.edu

UW Medicine

Fred Hutch Cancer Center

| Regimen | | PFS | | OS | |
|---|---|---|---|---|---|
| | Regimen costs for 2 yrs of therapy (USD)# | PF-LYG per 100 pts | Incremental Cost/PF-LYG (USD) | LYG per 100 pts | Incremental Cost/LYG (USD) |
| NIVO | $374,103 | *Reference group* | | | |
| ★ NIVO3-IPI1 | $425,324 | 40.8 | $141,087 | 42.1 | $136,569 |
| NIVO1-IPI3 | $504,553 | 83.3 | $173,903 | 59.1 | $245,085 |
| RELA-NIVO | $726,336 | 86.1 | $279,051 | 74.9 | $320,815 |


Hiba Khan

***NIVO3-IPI1 should be the preferred IO combination for patients and clinicians desiring a lower toxicity and cost-effective alternative to NIVO1-IPI3***

# 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**

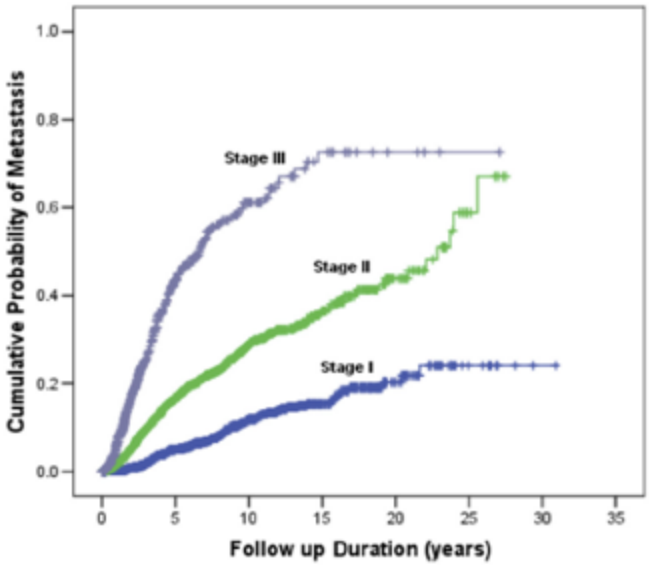



**Figure 2.** Kaplan–Meier estimate of metastasis from posterior uveal melanoma in 7731 patients, based on the American Joint Cancer Committee (AJCC) tumor staging.

## 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*]

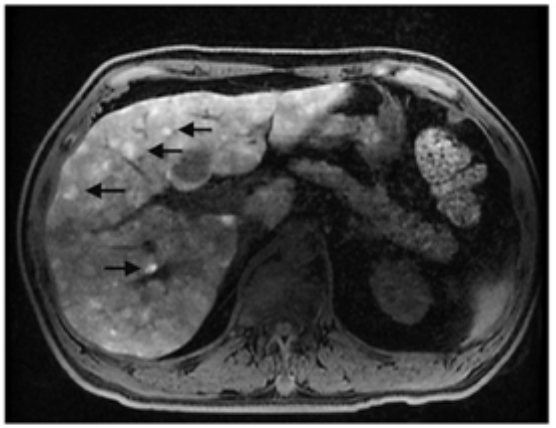
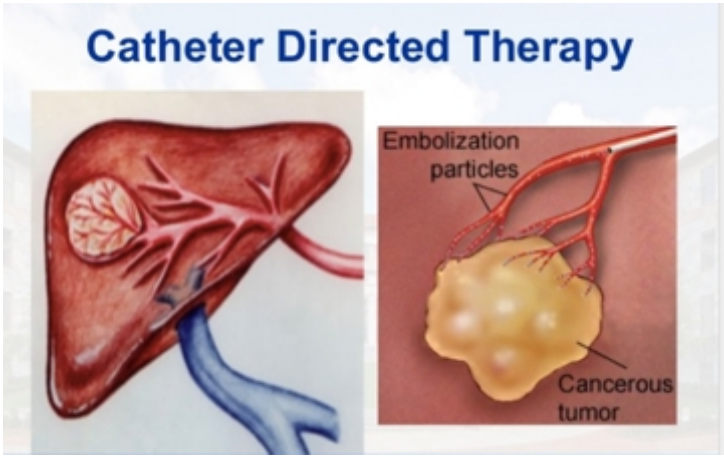
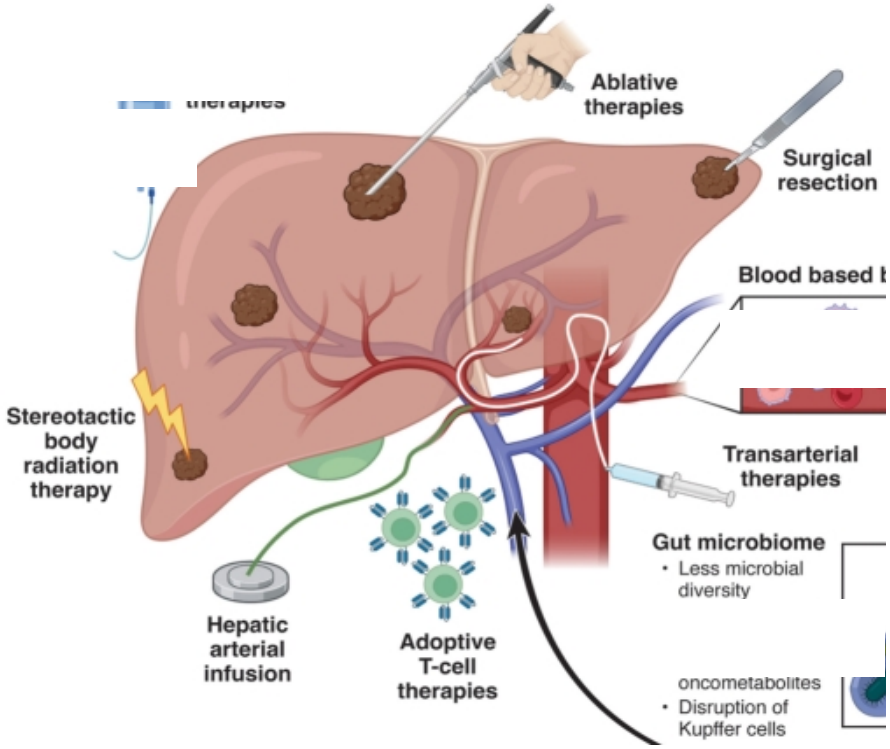


**Fig. 3.** Numerous T1-weighted fat suppressed hyperintense lesions on MRI compatible with melanoma metastases (arrows).

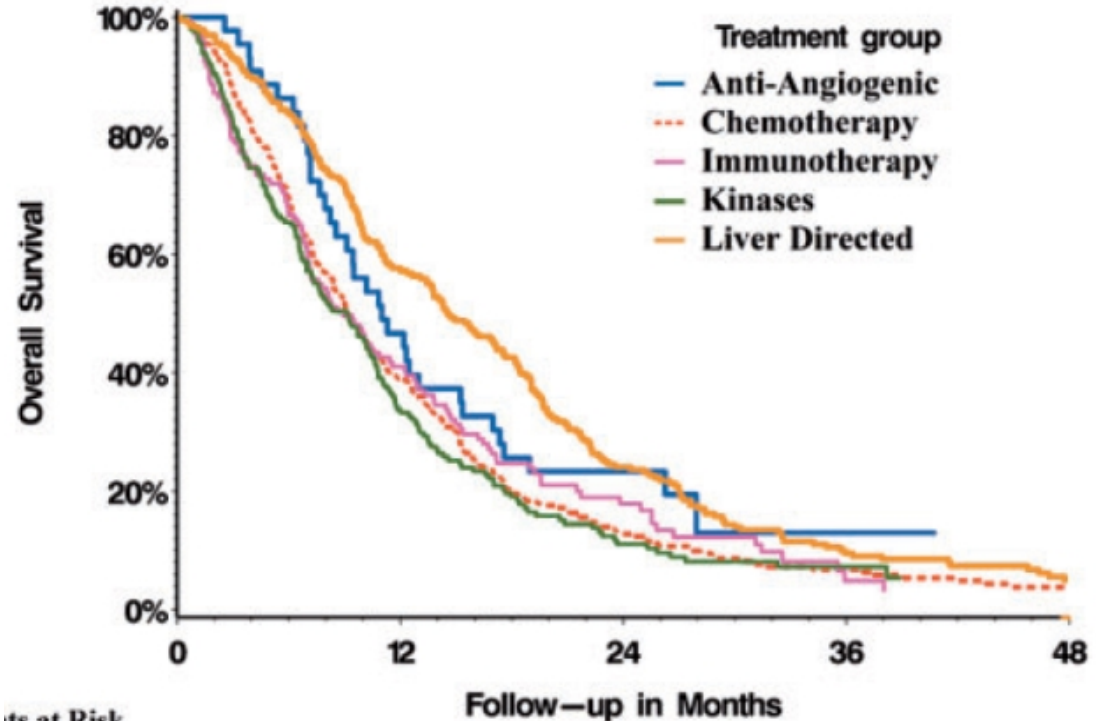


# Liver-Directed Therapies (LDT)




- Surgery
- Radiation
- Ablation [Cryo-, Thermo - etc.]
- Trans-arterial embolization (Chemotherapy, Y90)
- IHP and PHP (Melphalan)
- Histotripsy

# LDT is associated with best survival impact!



# 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

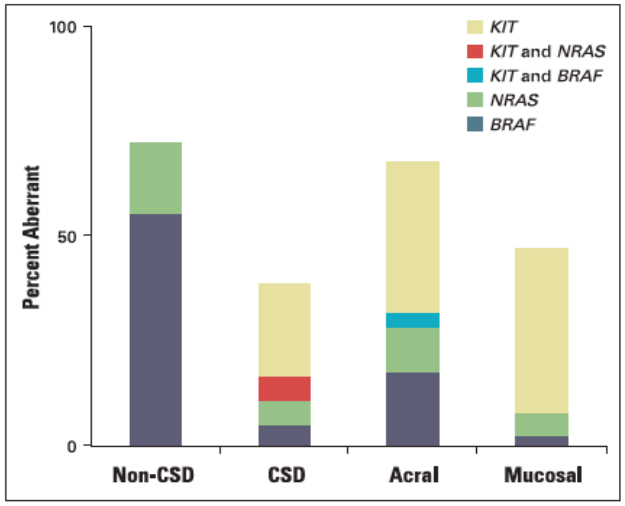
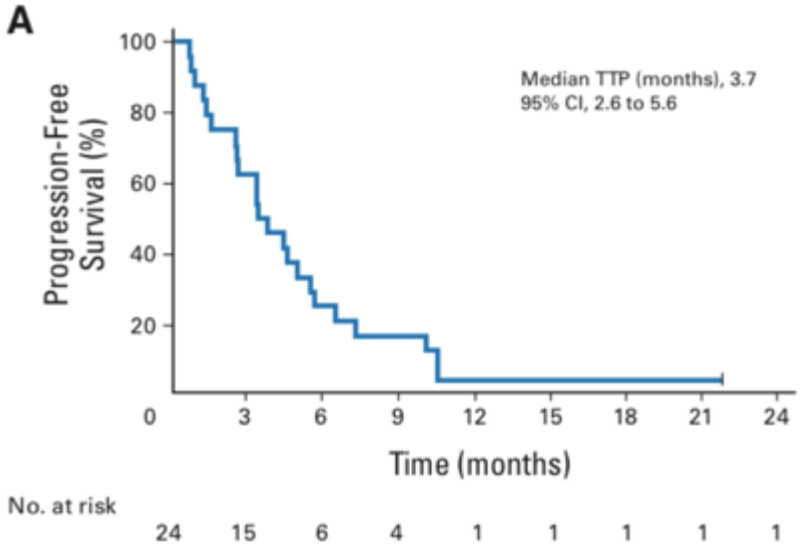



**Fig 2.** Frequency distribution of genetic alterations in BRAF, *NRAS*, and *KIT* among four groups of melanoma. Non-CSD, melanomas on skin without chronic sun-induced damage; CSD, melanomas on skin with chronic sun-induced as evidenced by the presence of marked solar elastosis; acral, melanomas on 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

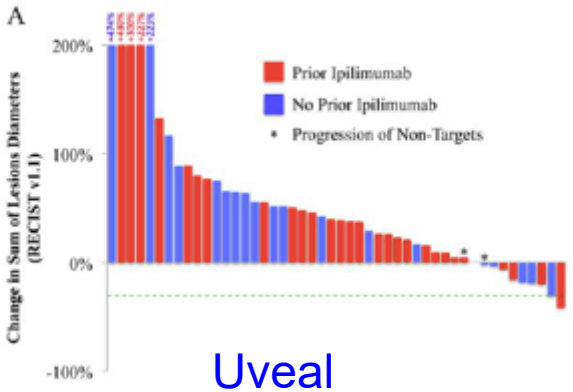
BORR was 54% (7/13) in KIT-mutant (0% in KIT-amplified)



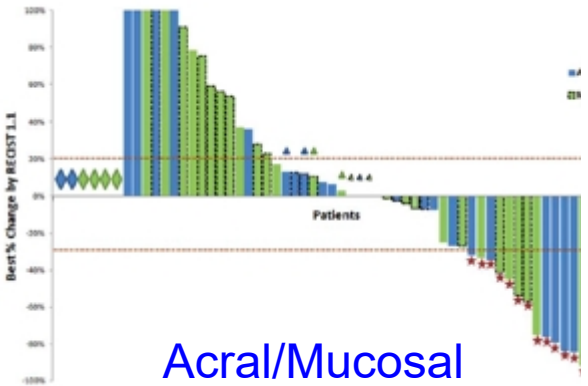
Editorial

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

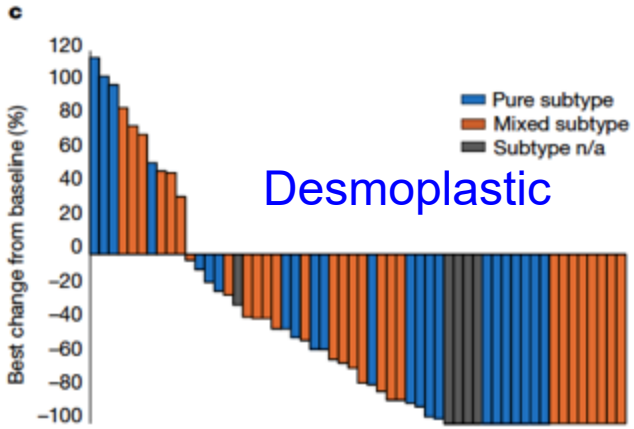
Shailender Bhatia, MD[1,2] and Kim Margolin, MD[3]




Uveal




Acral/Mucosal




Desmoplastic

LETTER

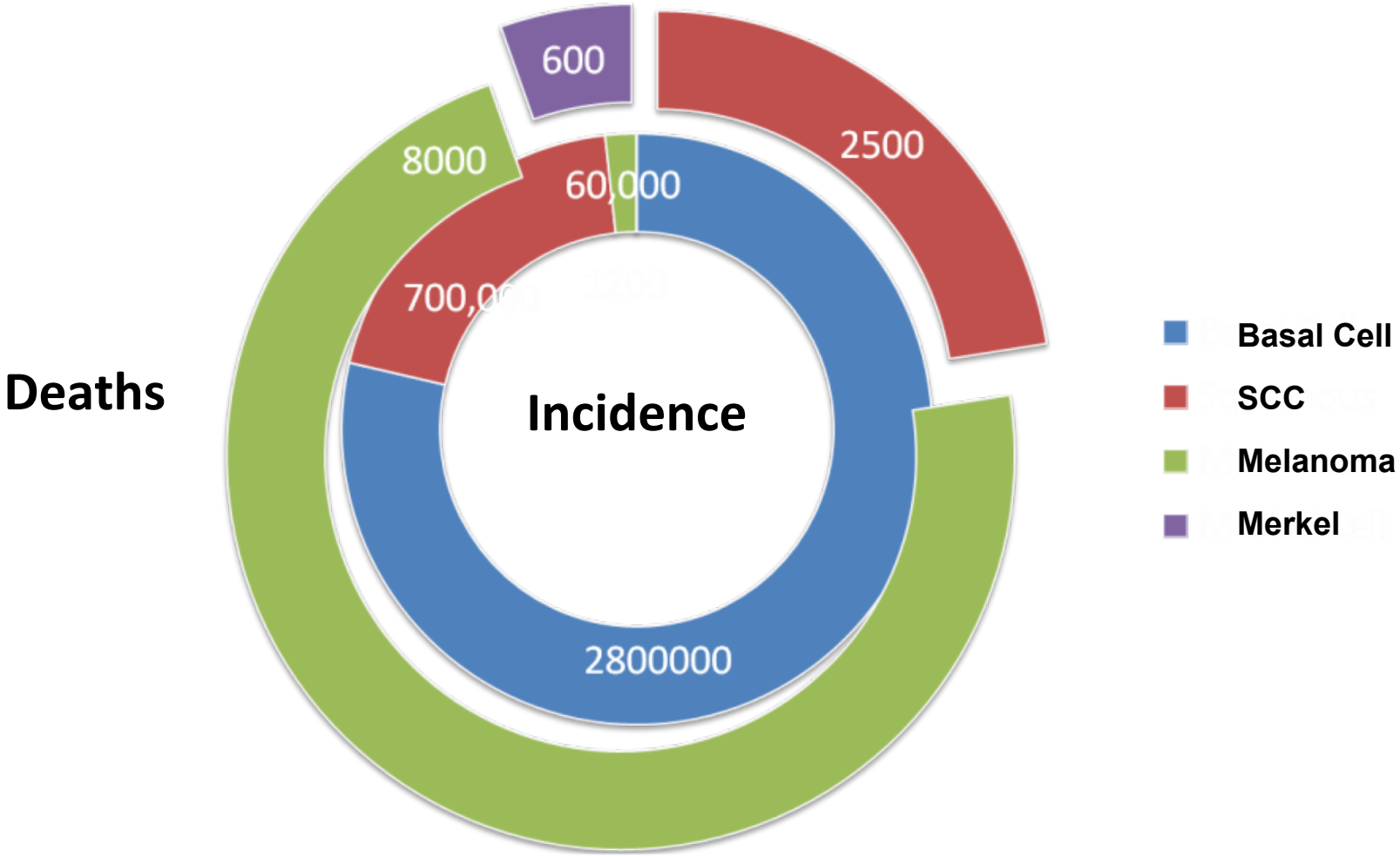
doi:10.1038/nature25187

## 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]

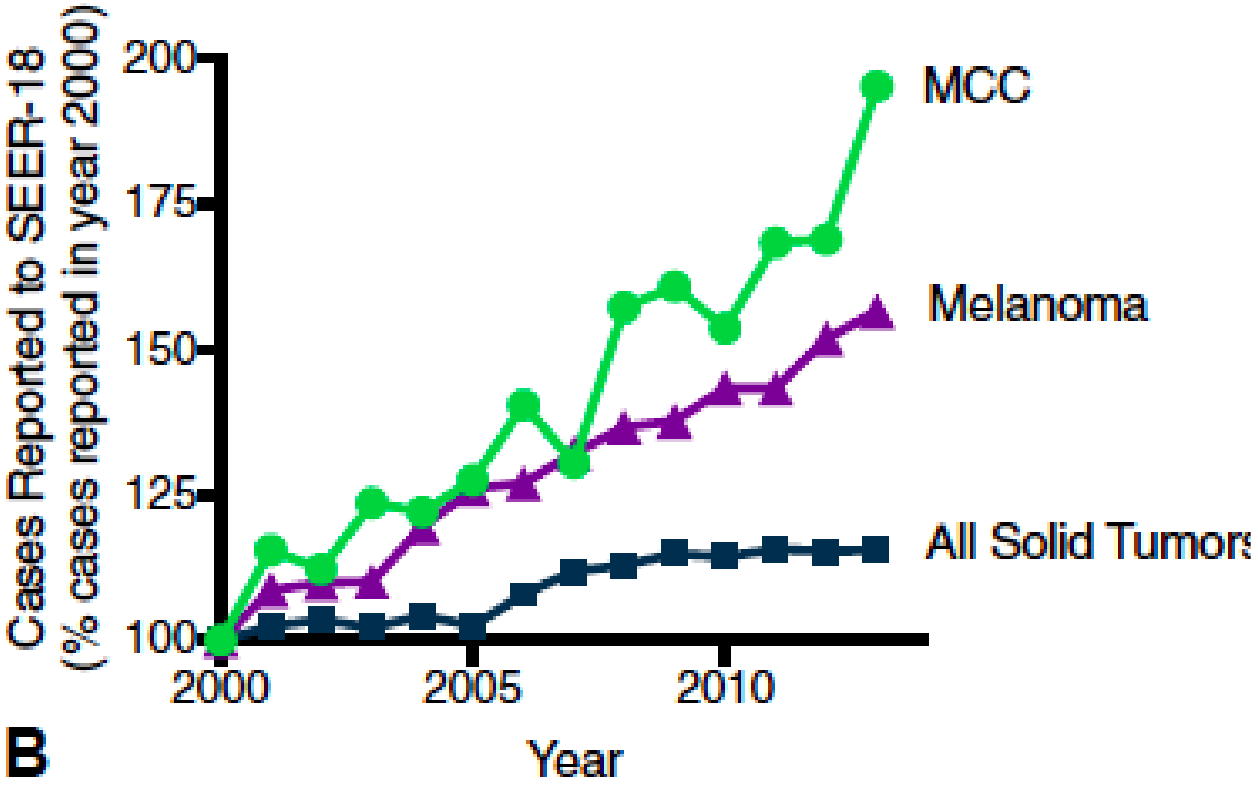
# Non Melanoma Skin Cancers

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



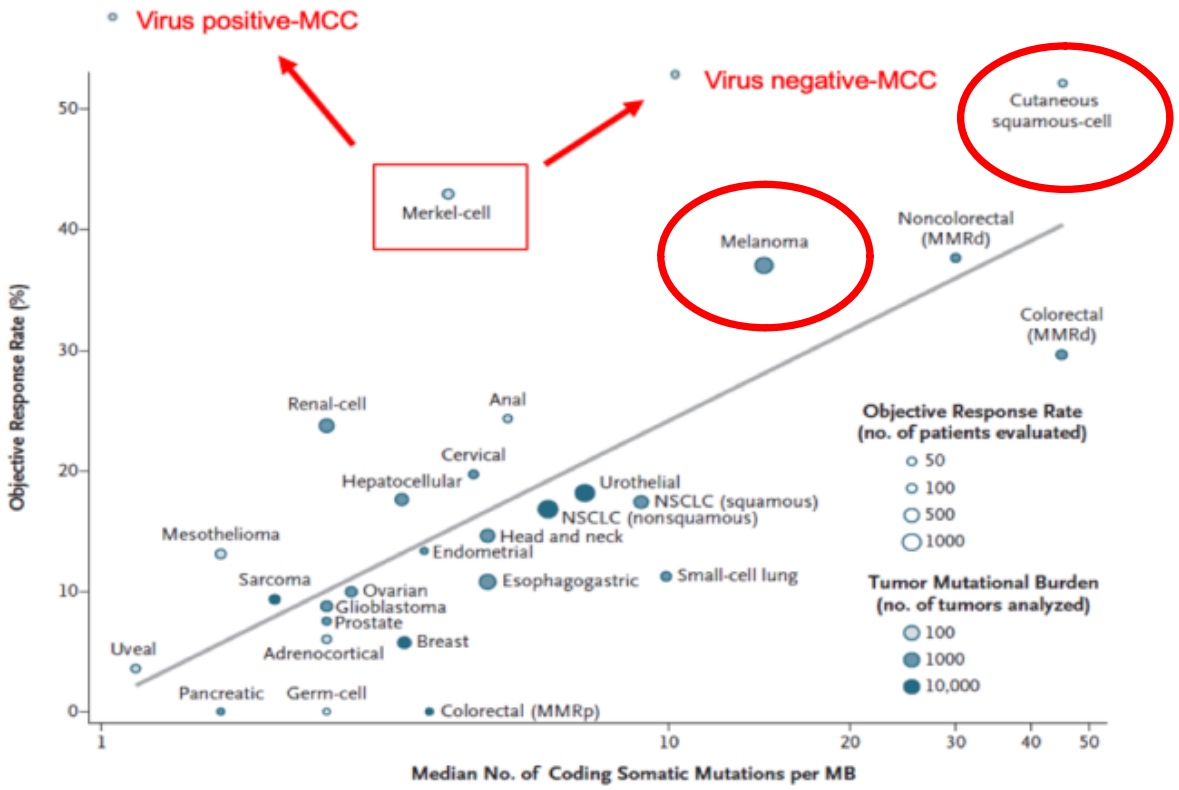

***NOTE***: The numbers listed in this figure do not reflect the most up-to-date statistics.

# The incidence of skin cancers is increasing steadily.




Paulson K et al. *JAAD* 2017

# Skin cancers 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)

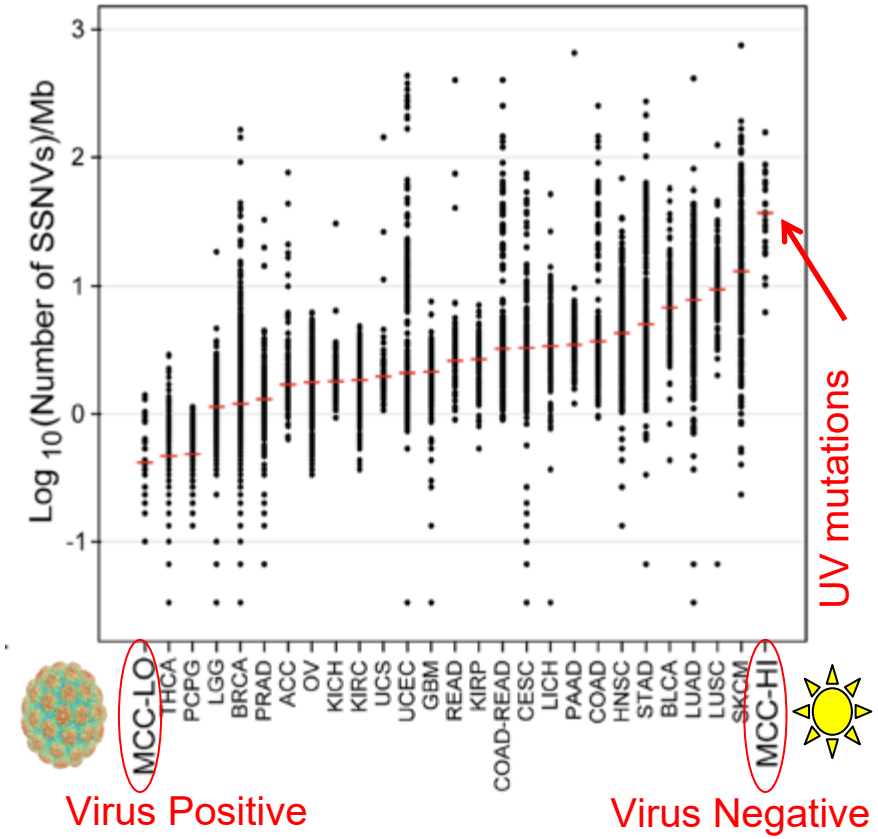
- Merkel cell polyoma virus (MCPyV) in 80% of MCC tumors

{Feng H et al *Science* 2008}

- UV-induced high mutational load (Neoantigens)

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

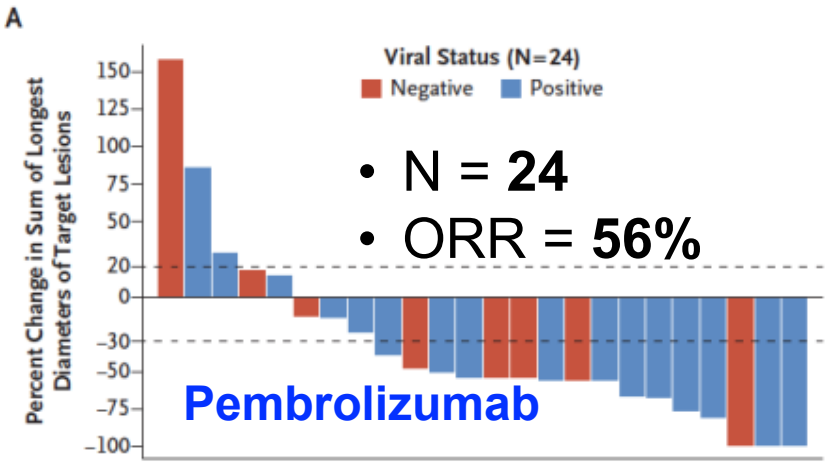
[Afanasiev O et al. *Clin Cancer Res*. 2013]



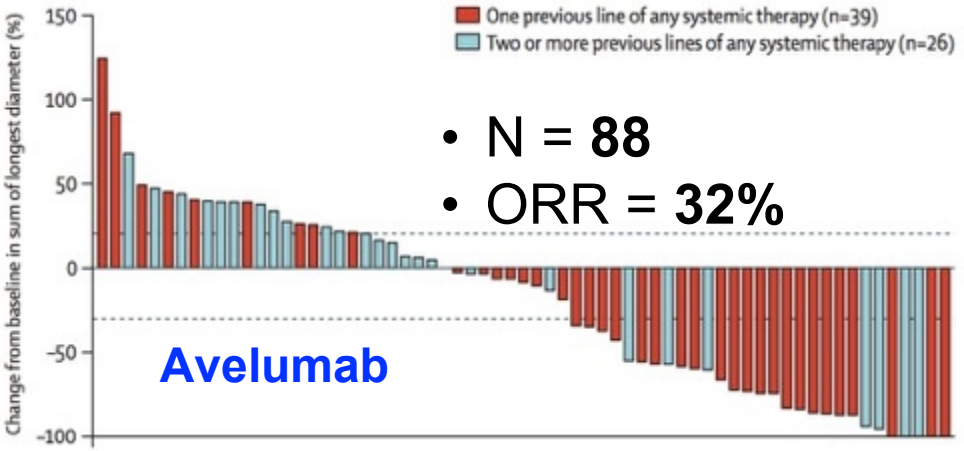



{Goh et al. Oncotarget 2015}

# 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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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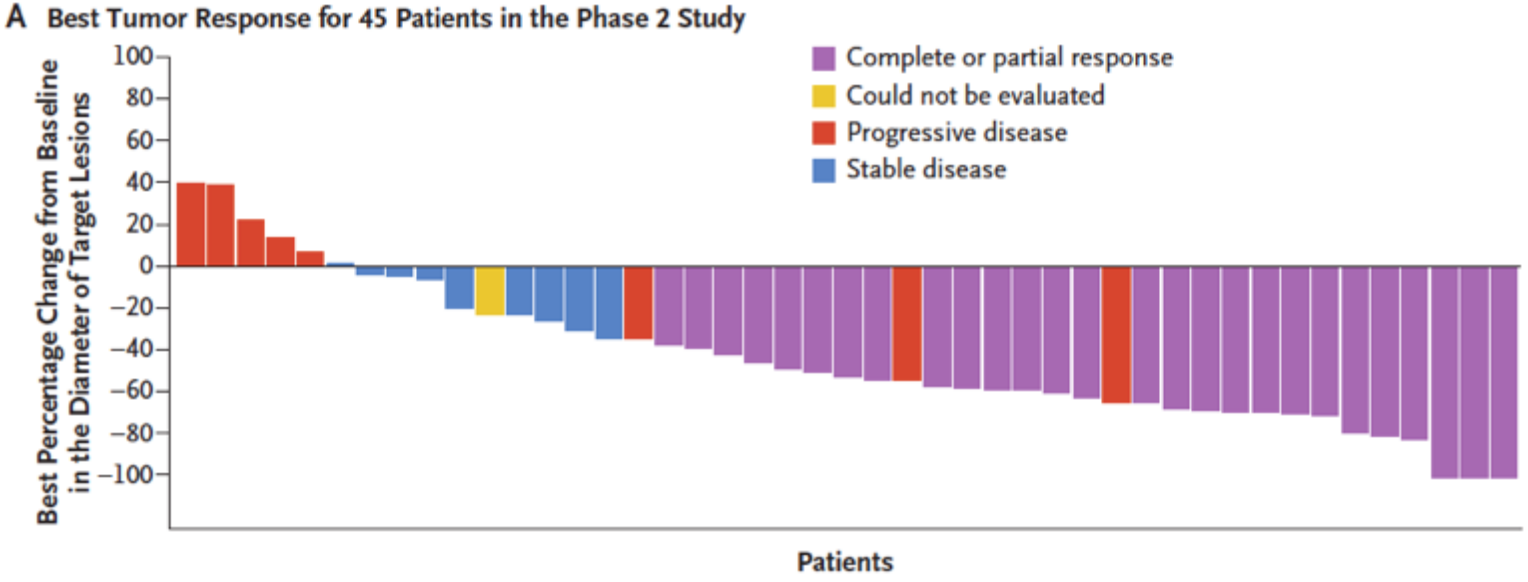

# Pembrolizumab Monotherapy for Recurrent or Metastatic Cutaneous Squamous Cell Carcinoma: A Single-Arm Phase II Trial (KEYNOTE-629)

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

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- Pembrolizumab was FDA-approved in **June, 2020** for advanced CSCC
- 200 mg IV q 3 weeks

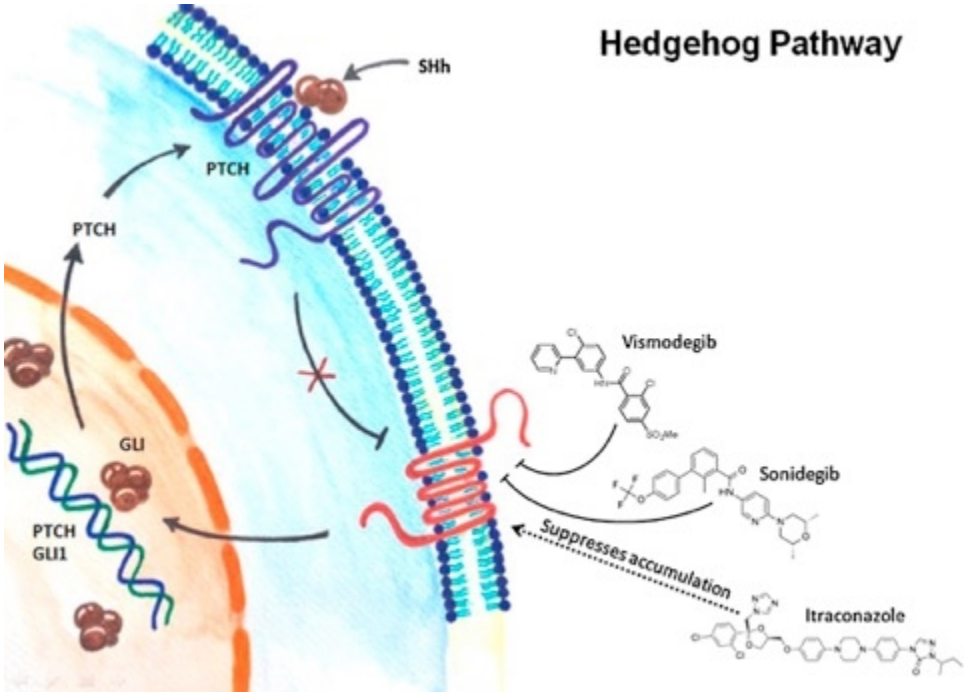
J Clin Oncol 38. 

# 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**

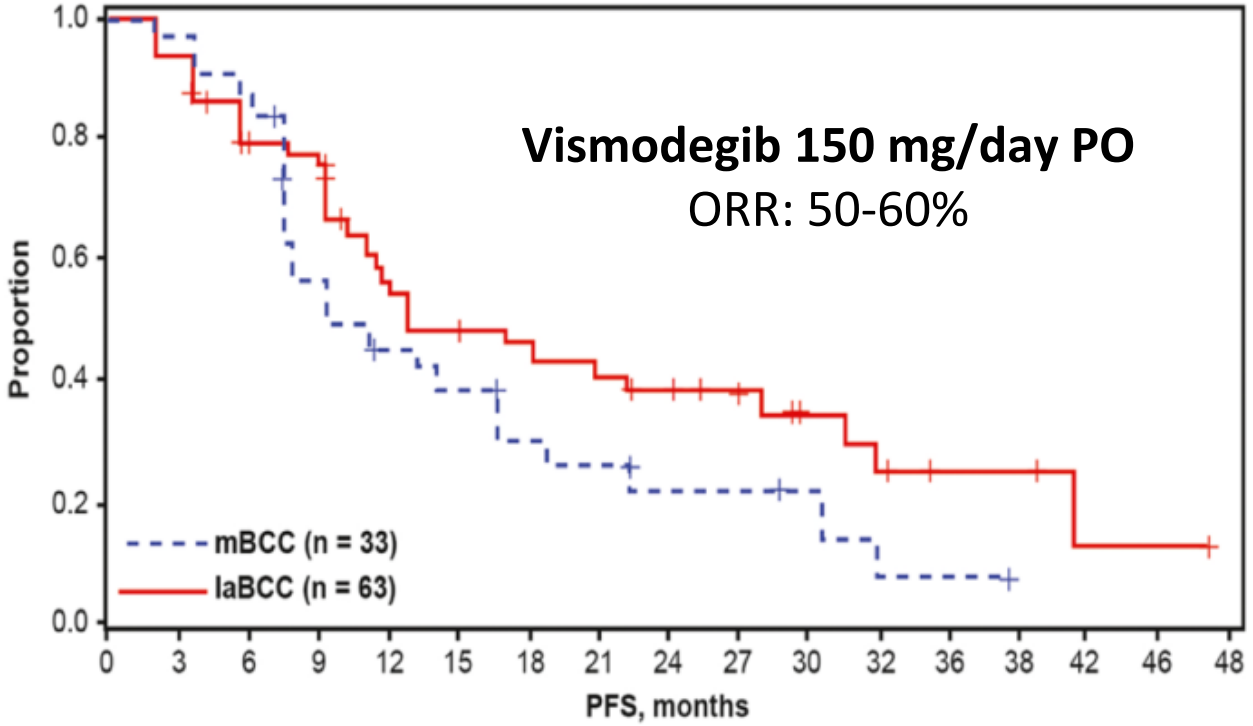
**<u>Basal cell nevus syndrome</u>: Germline mutation in PTCH gene**




| 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

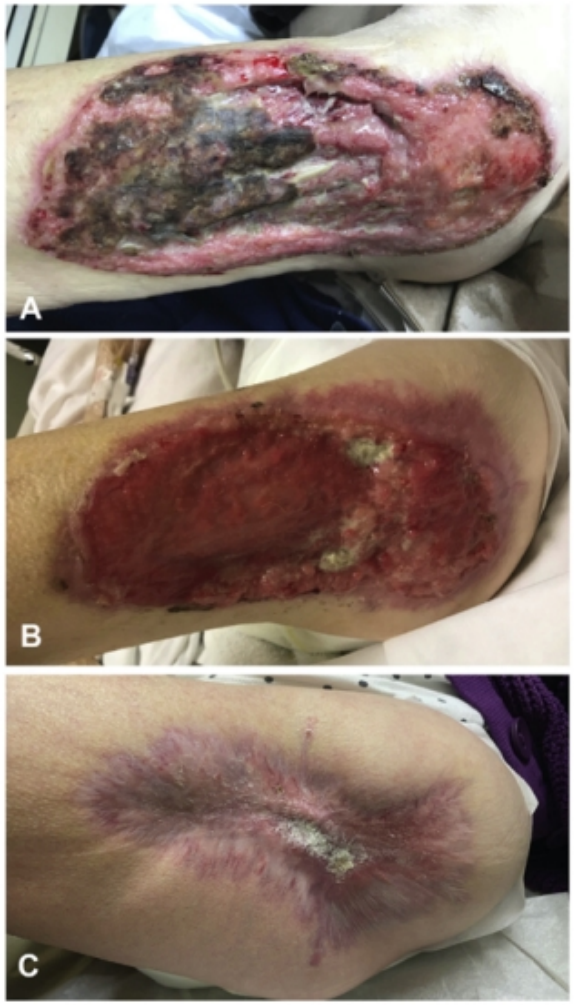



**Fig 1.** Unresectable basal cell carcinoma of the left thigh of a 70-year-old female patient both before and after frontline treatment with nivolumab. **A**, Tumor at initial presentation. **B**, Before fifth cycle of nivolumab. **C**, Seven months after completion of nivolumab therapy.

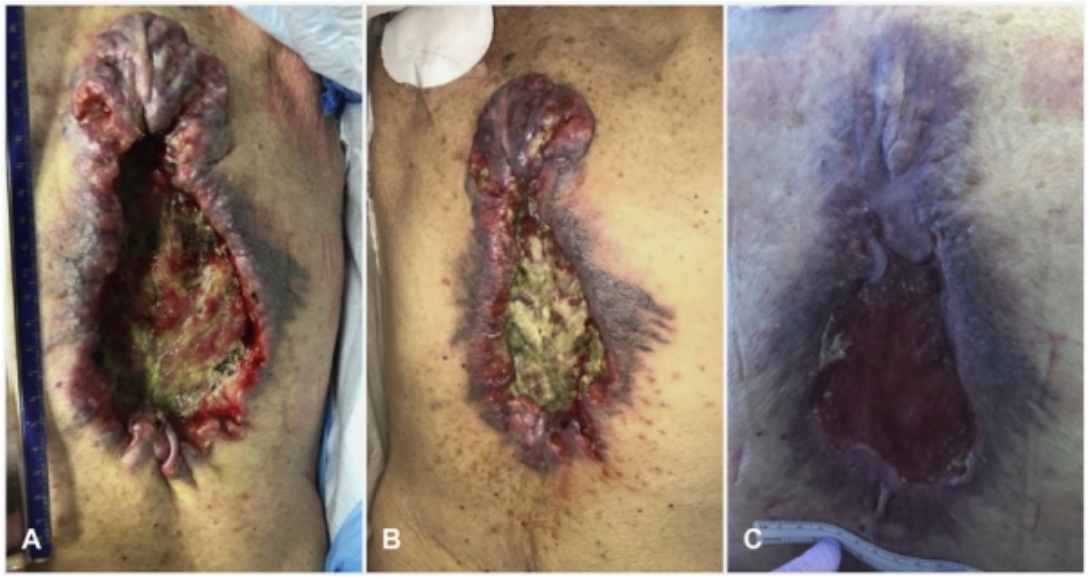



**Fig 2.** Locally advanced, unresectable basal cell carcinoma on the back of a 77-year-old female patient before and after first-line treatment with pembrolizumab. **A**, Tumor at initial presentation. **B**, Before fifth cycle of pembrolizumab. **C**, Before seventh cycle of pembrolizumab.

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) |

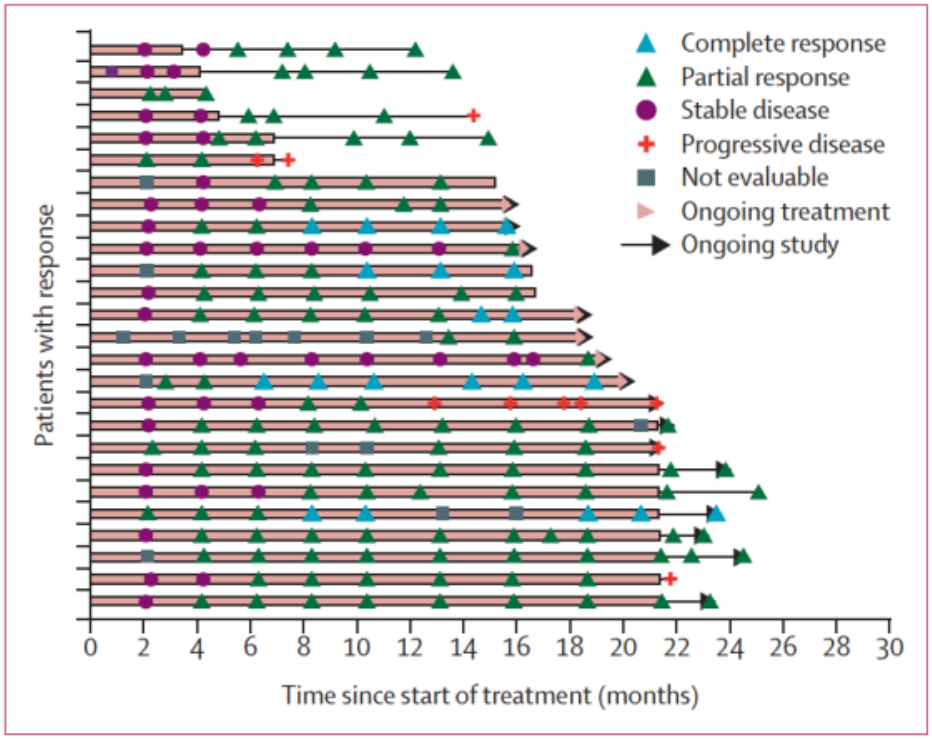



*Figure 1:* Tumour response to cemiplimab per independent central review

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