Malignant Melanoma 2023

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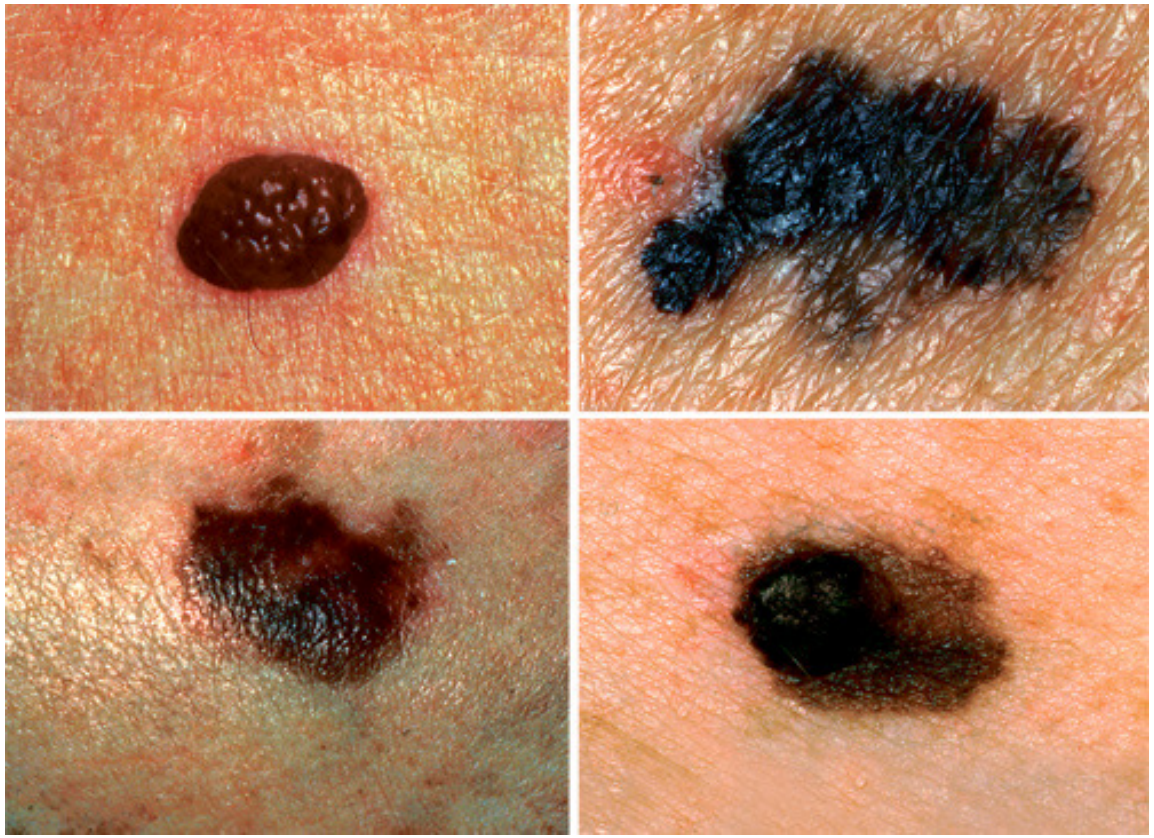
University of Colorado
Anschutz Medical Campus

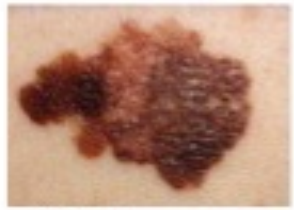
No Conflicts of interest

"Melanoma is the tumor that gives cancer a bad name."

George Canellos, M.D., Dana-Farber Cancer Center
American Society of Clinical Oncology
1990



Different Types of Melanomas Have Different Mutations



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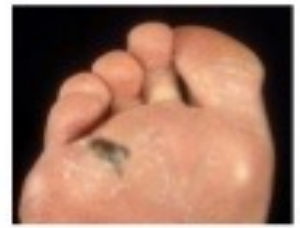
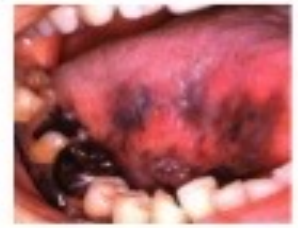
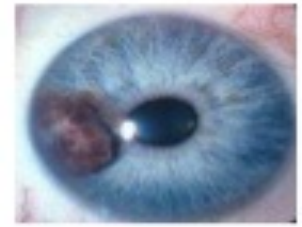




Acral Melanoma
Mucosal Melanoma



Uveal

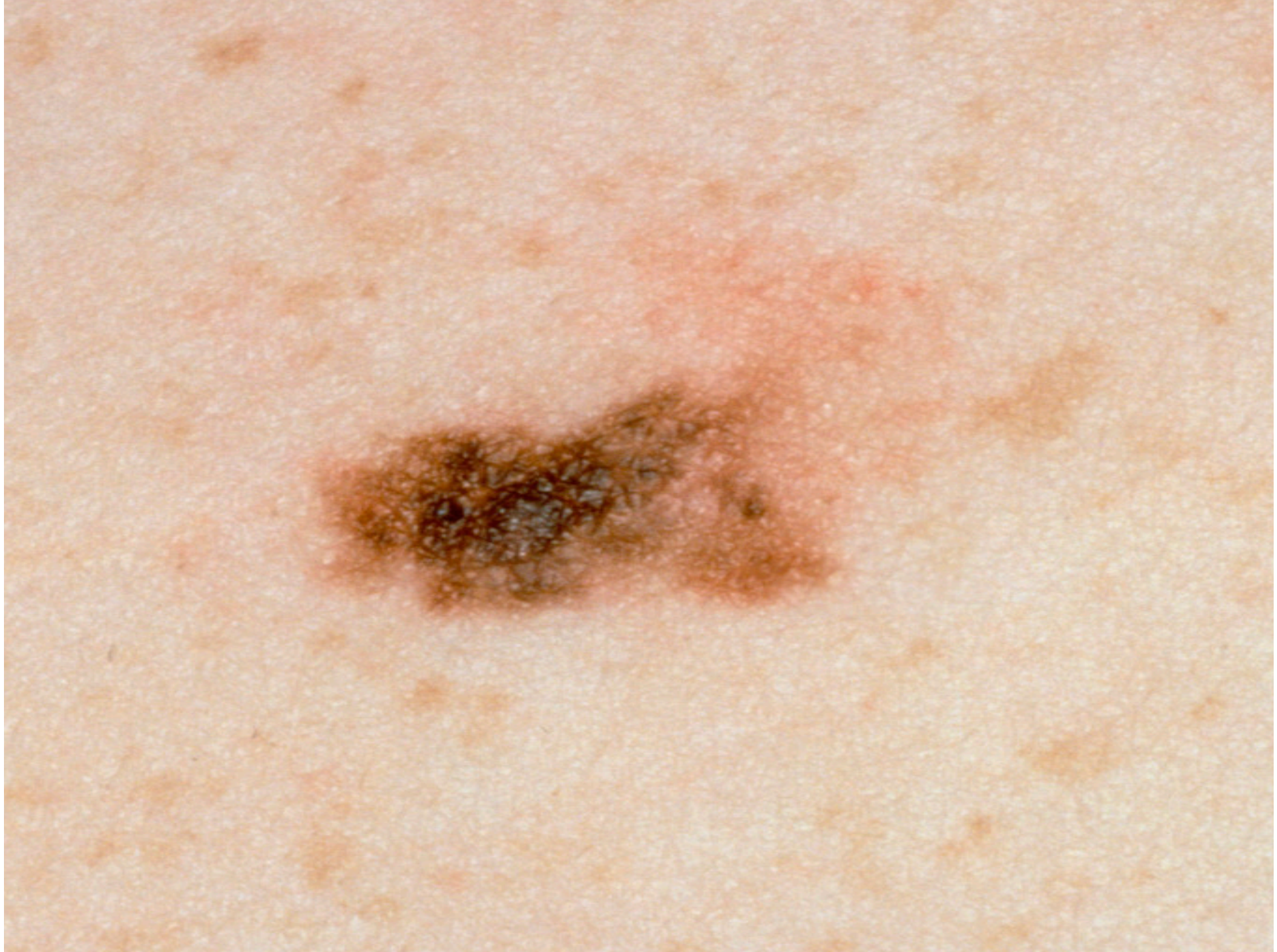
45% BRAF Mutations
20% NRAS Mutations

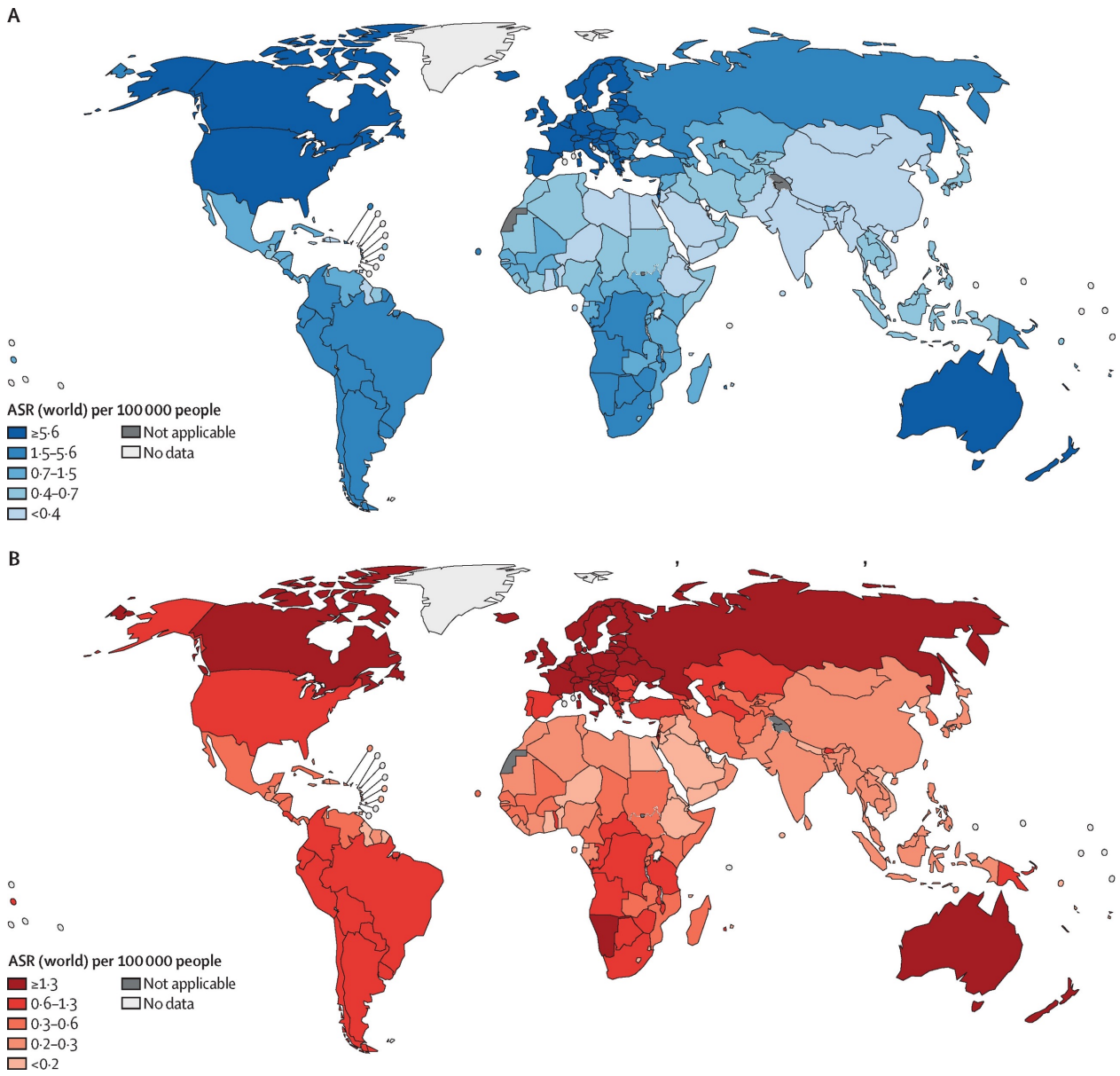
Acral: 20% BRAF 10% NRAS
Mucosal: 3% BRAF 5% NRAS

Virtually No BRAF/NRAS

20-30% mutations in c-KIT

~80% mutations in GNAQ/GNA11




A
ASR (world) per 100 000 people
≥5·6
1·5–5·6
0·7–1·5
0·4–0·7
<0·4
Not applicable
No data
B
ASR (world) per 100 000 people
≥1·3
0·6–1·3
0·3–0·6
0·2–0·3
<0·2
Not applicable
No data

Treatment of Primary Cutaneous Melanoma

Surgery: Wide local excision Surgical margins are radial and should be measured from the edge of the biopsy site or residual intact component.

The width of the margin is determined by the histologically assessed tumour thickness.

Wide local excision is performed down to, but not including, the underlying muscular fascia, the extent of which might be modified to accommodate anatomical or functional considerations.

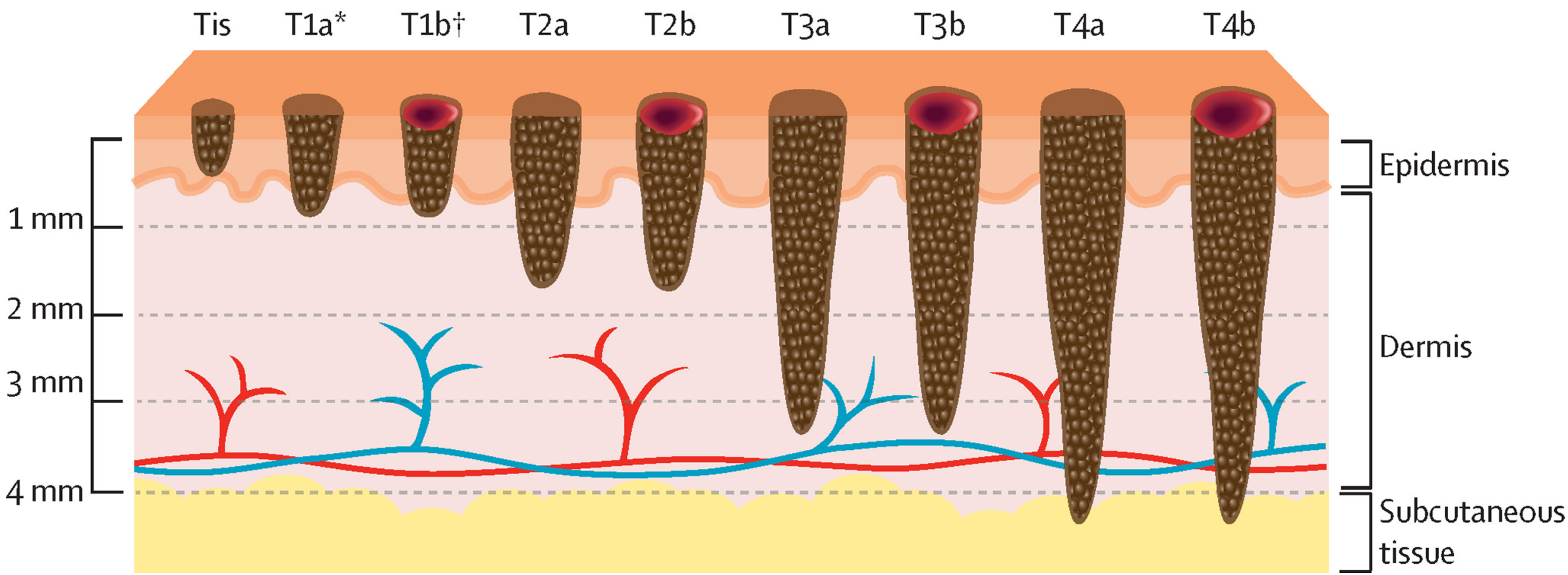
Tumor thickness of 0.7 mm or less (T1) WLE only. 1 to 2cm margins

Thickness > 0.7mm or greater than 2 mm (T3–T4), a 1 to 2 cm radial surgical with sentinel lymph node

Thickness > 4mm – consider evaluation for systemic disease before surgery

Role of MOHS surgery remains unclear

Depth of Invasion of Primary Guides Treatment and Prognosis



The Immunotherapies for Melanoma

Do not directly kill cancer cells, but get rid of the immune suppression and allow the normal immune system to do the work

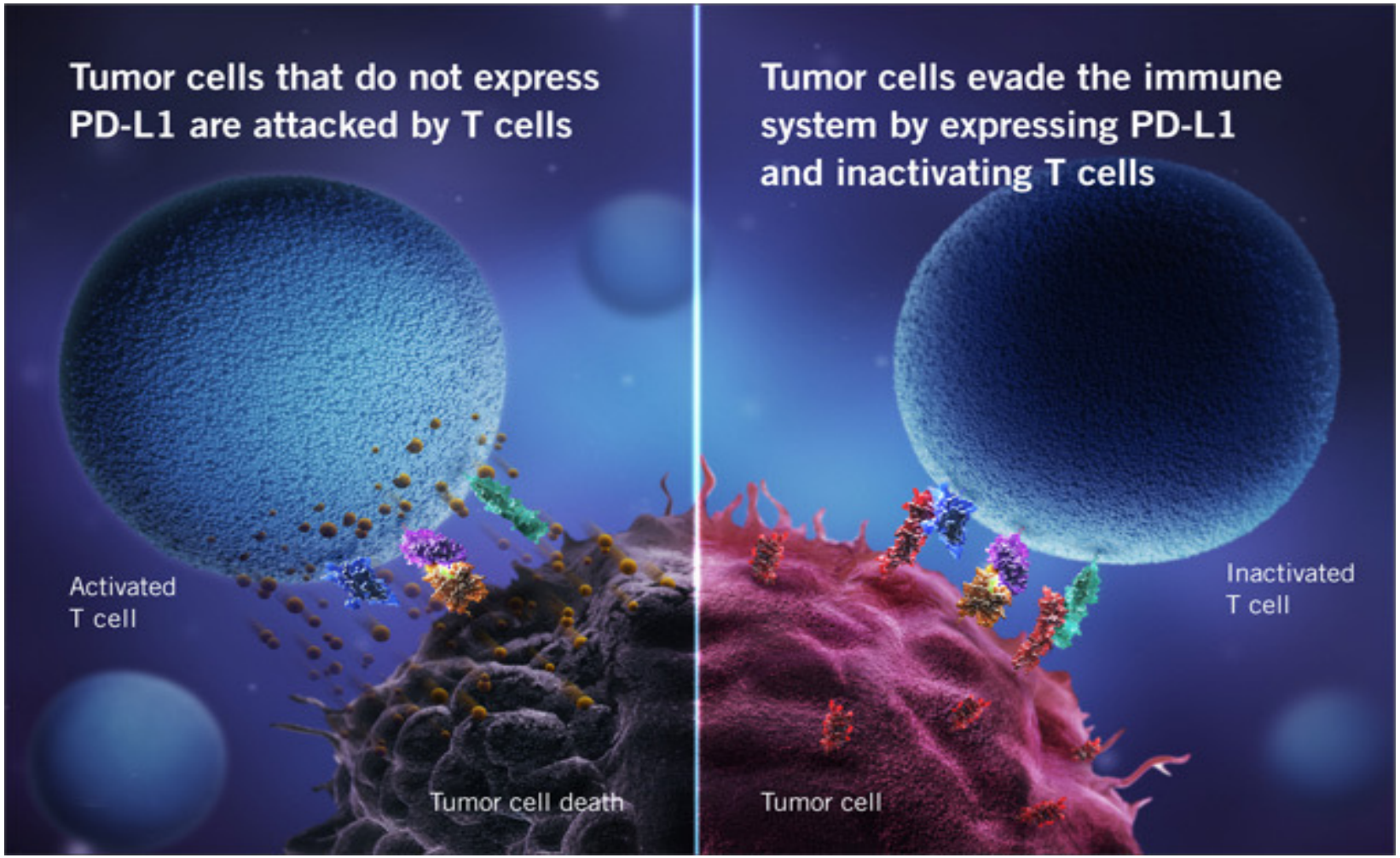
Act on immune suppressor mechanisms CTLA-4 and PD-1, LAG 3

High response rates, but side effects, but many questions remain

Anti PD-1
- Pembroluzimab
- Nivolumab

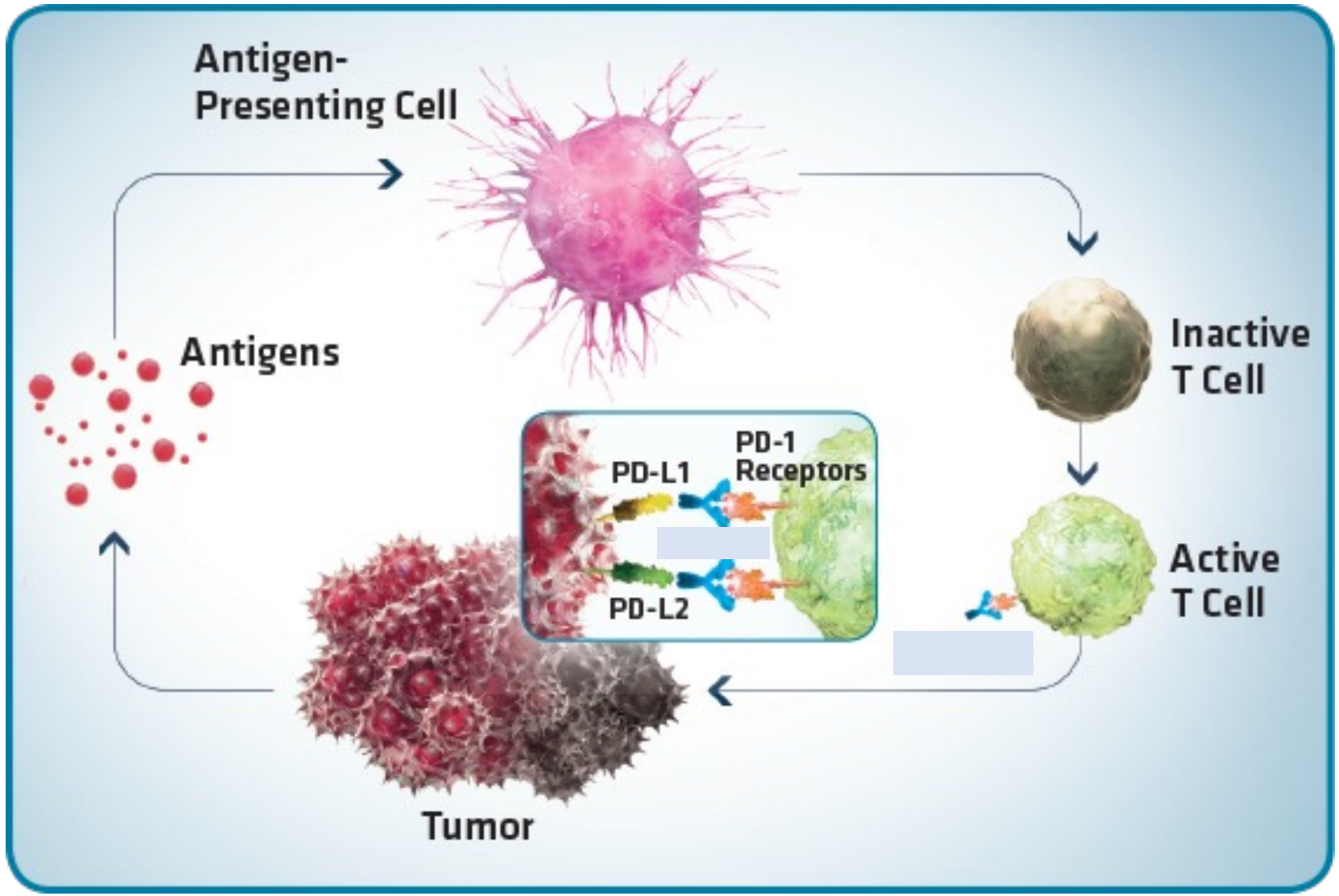
Other
- Ipilumimab

Activating the Patients own Immune System
Anti-PDL-1



Normal Immune Response Restored with Anti-PD-1 antibodies

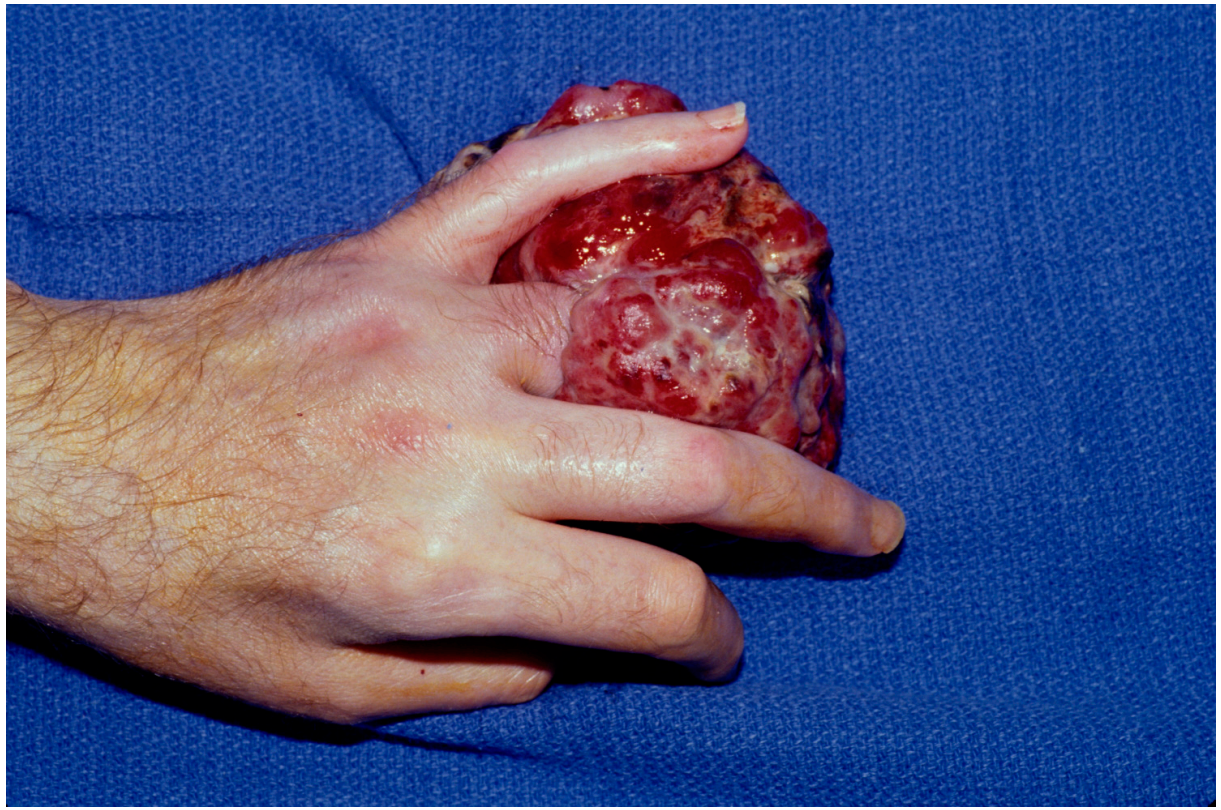
T-cell reactivation and decreased tumor growth* through PD-1 immune checkpoint inhibition. While having an effect on the tumor, this could also affect normal cells



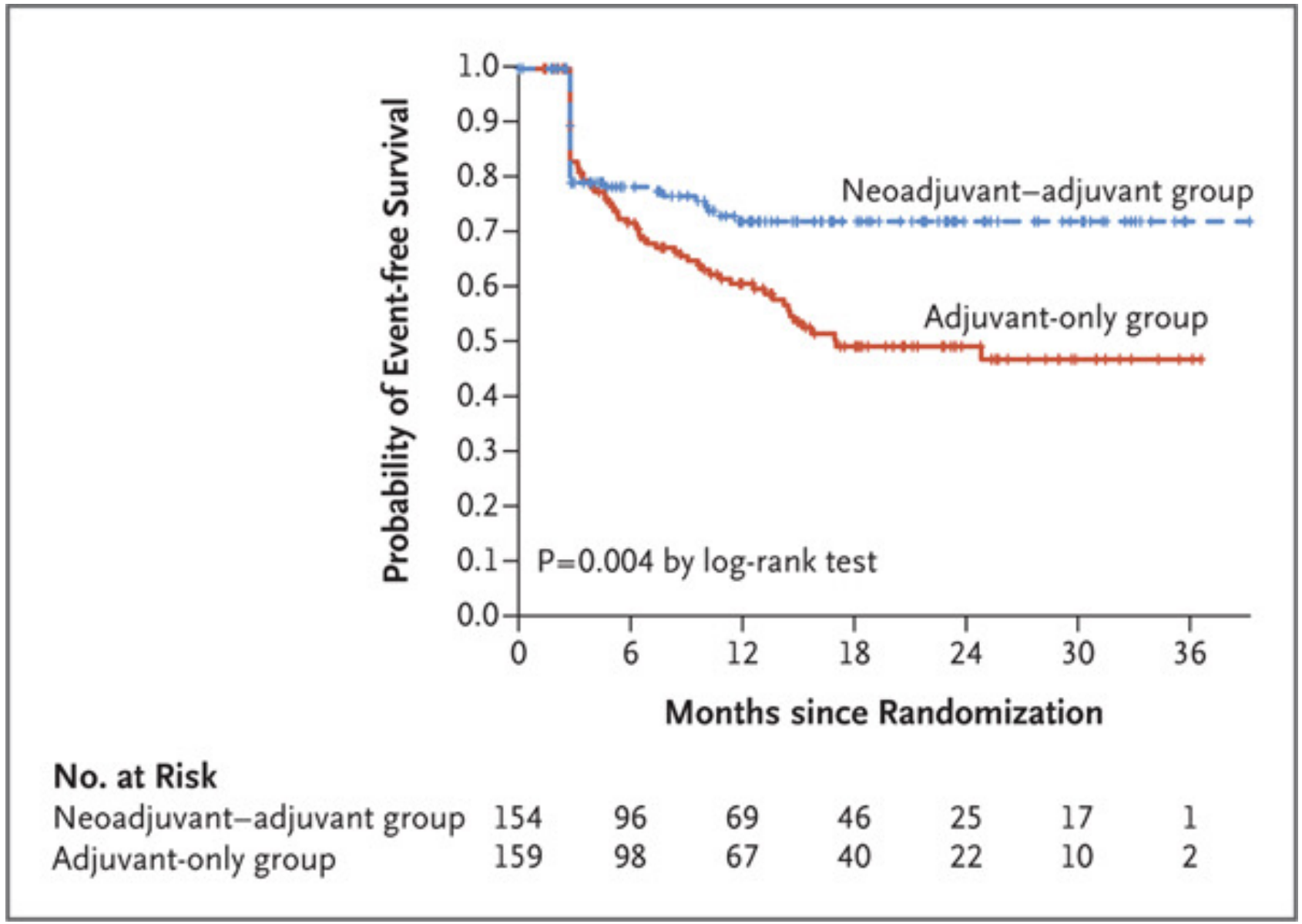
Adjuvant or Neoadjuvant Therapy of Melanoma

Based on success in treating metastatic disease

Currently used for those with high risk – greater than 50% recurrence



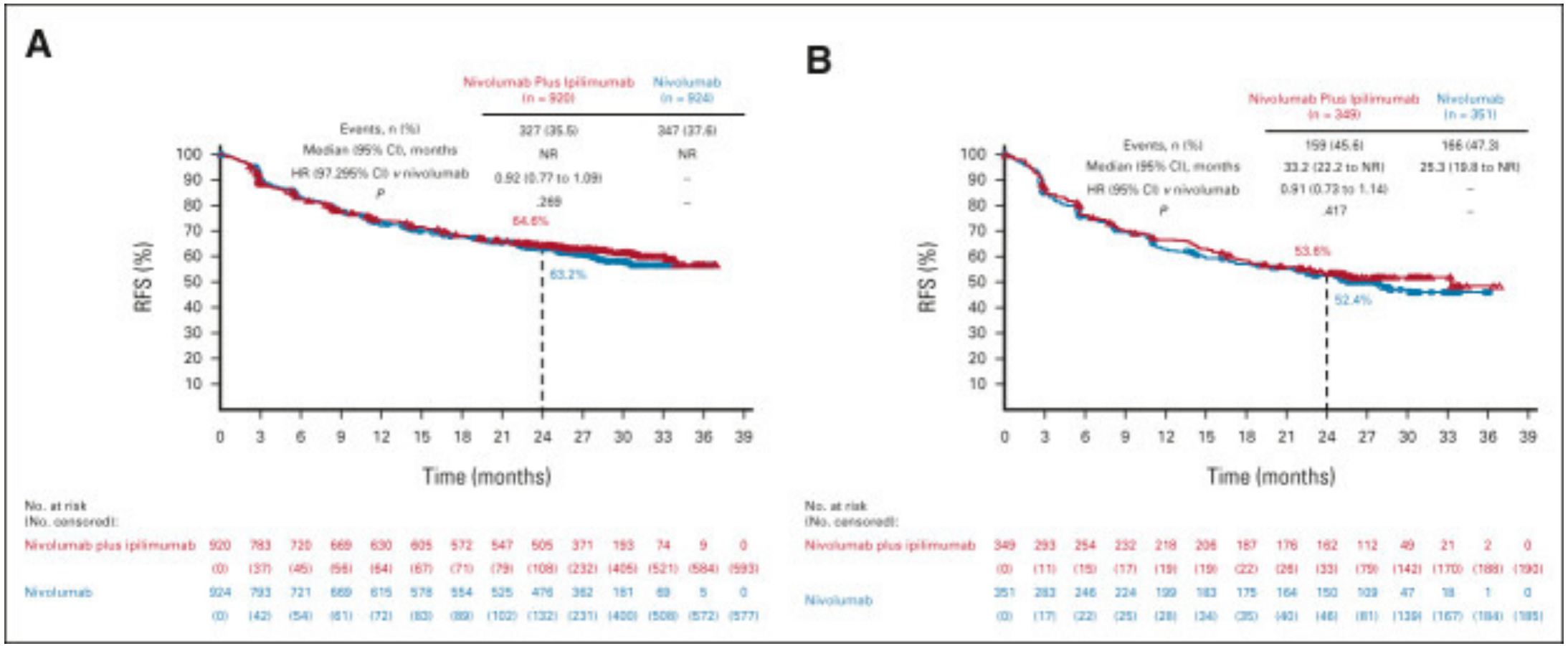
Neoadjuvant or adjuvant Pembroluzimab Therapy in Melanoma



Patel et al 2023

Adjuvant Therapy for High risk Patients after Surgery.
Is combination therapy Better

Nivo alone vs Nivo plus Ipilumimab
No benefit of Combination



Should all patients with melanoma receive adjuvant immunotherapy

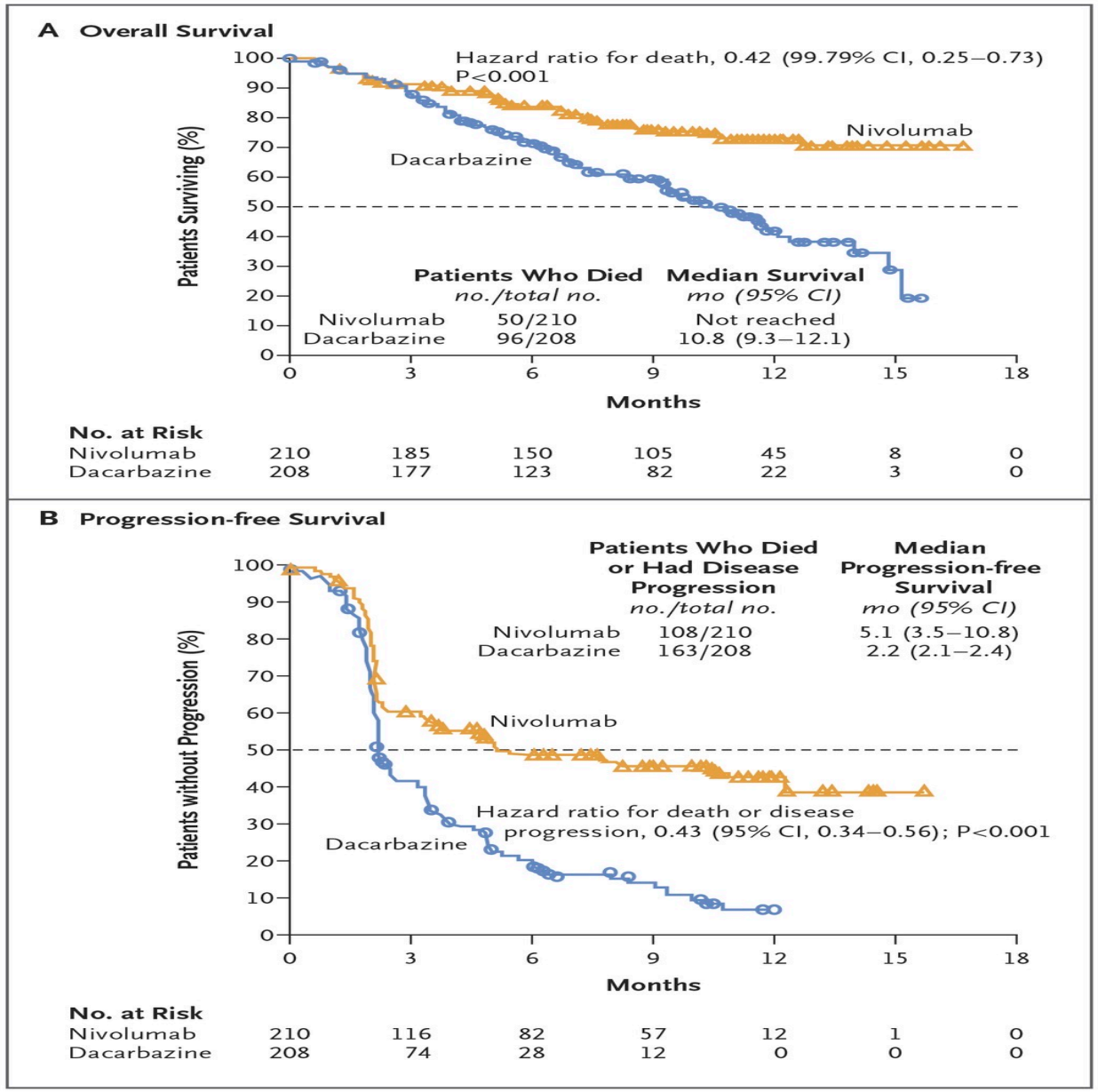
Malignant Melanoma - treatment of metastatic disease

In general we prefer to start with combination immunotherapy
- Nivolumab plus Ipilumimab
- Rela/nivo Lag3 inhibitor plus nivo

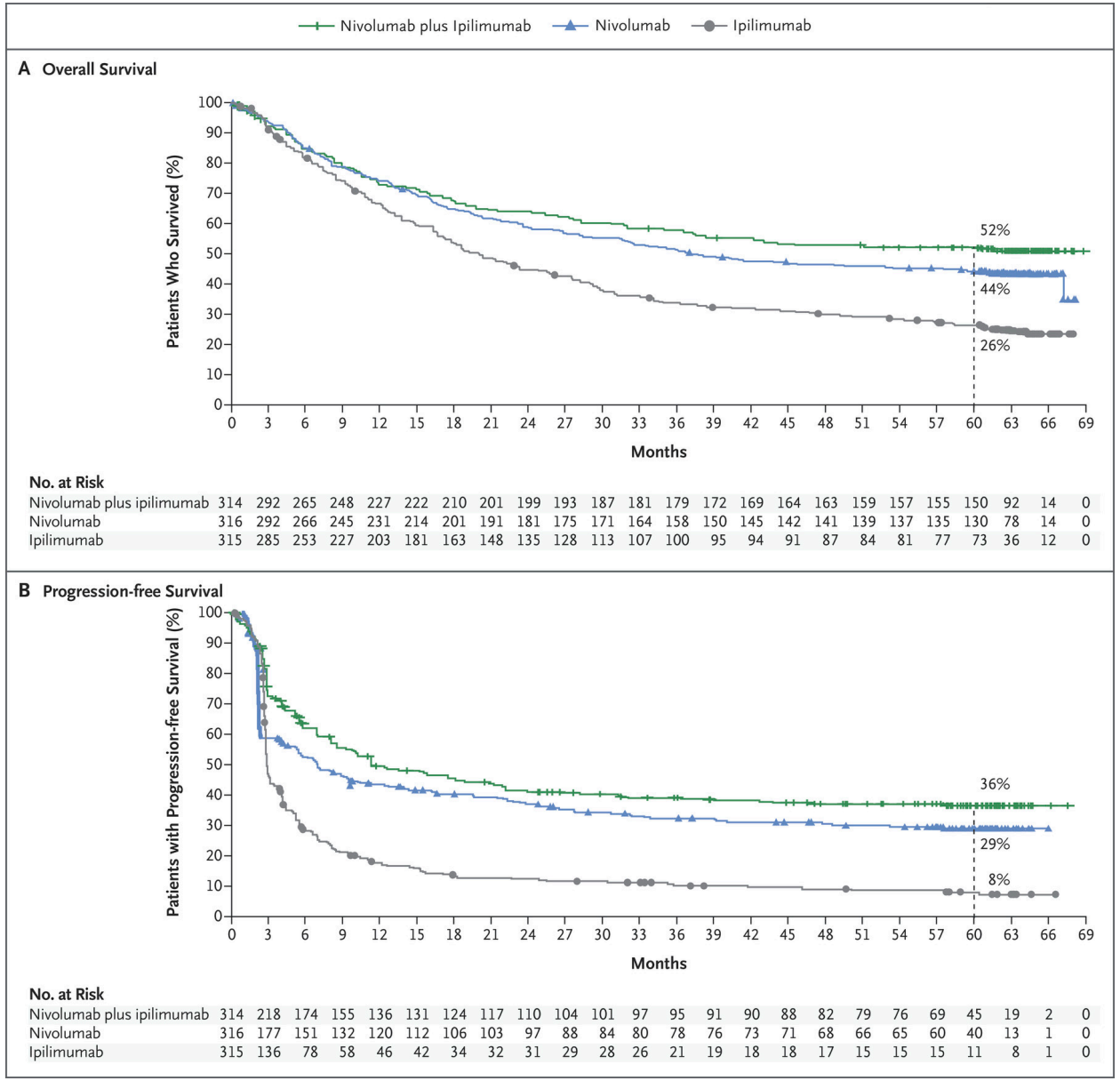
Need a rapid response
- BRAF and MEK inhibitors

Failed or relapsed after immunotherapy
- BRAF and MEK inhibitors

Early Studies with ImmunoRx in Melanoma



Combination Immunotherapy is Better



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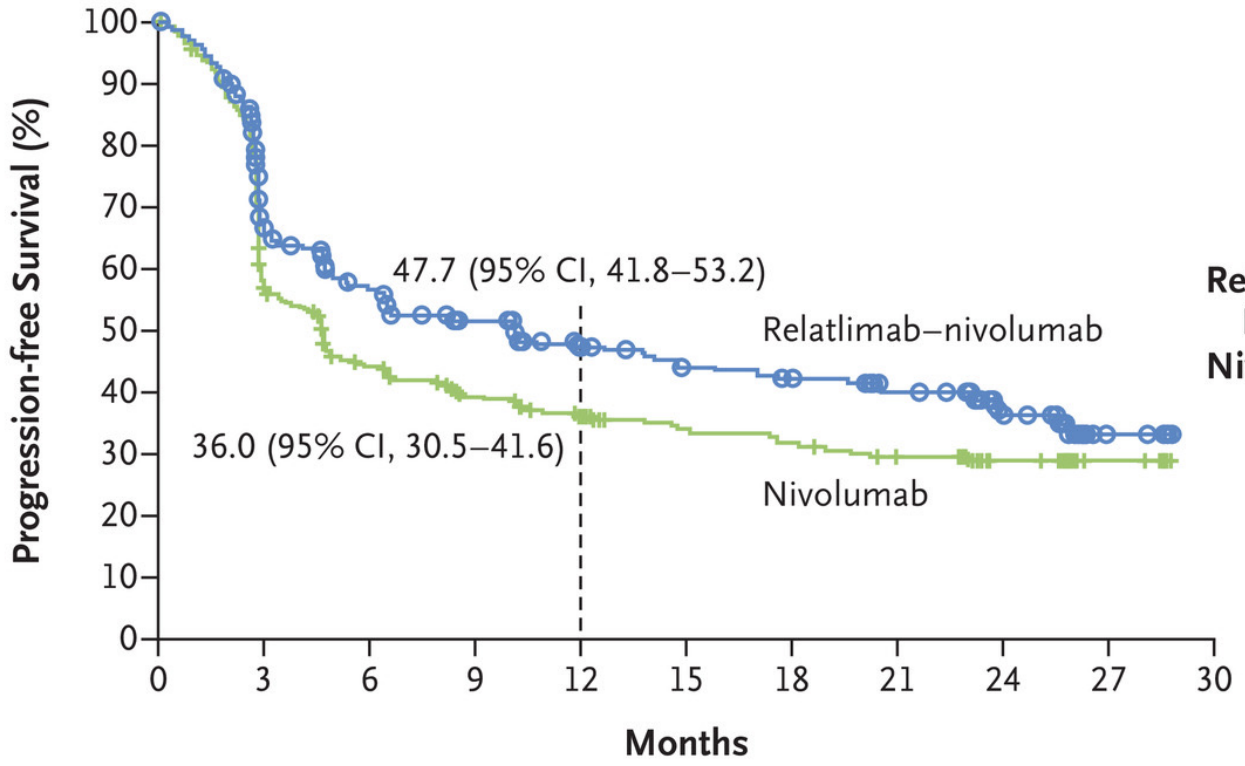
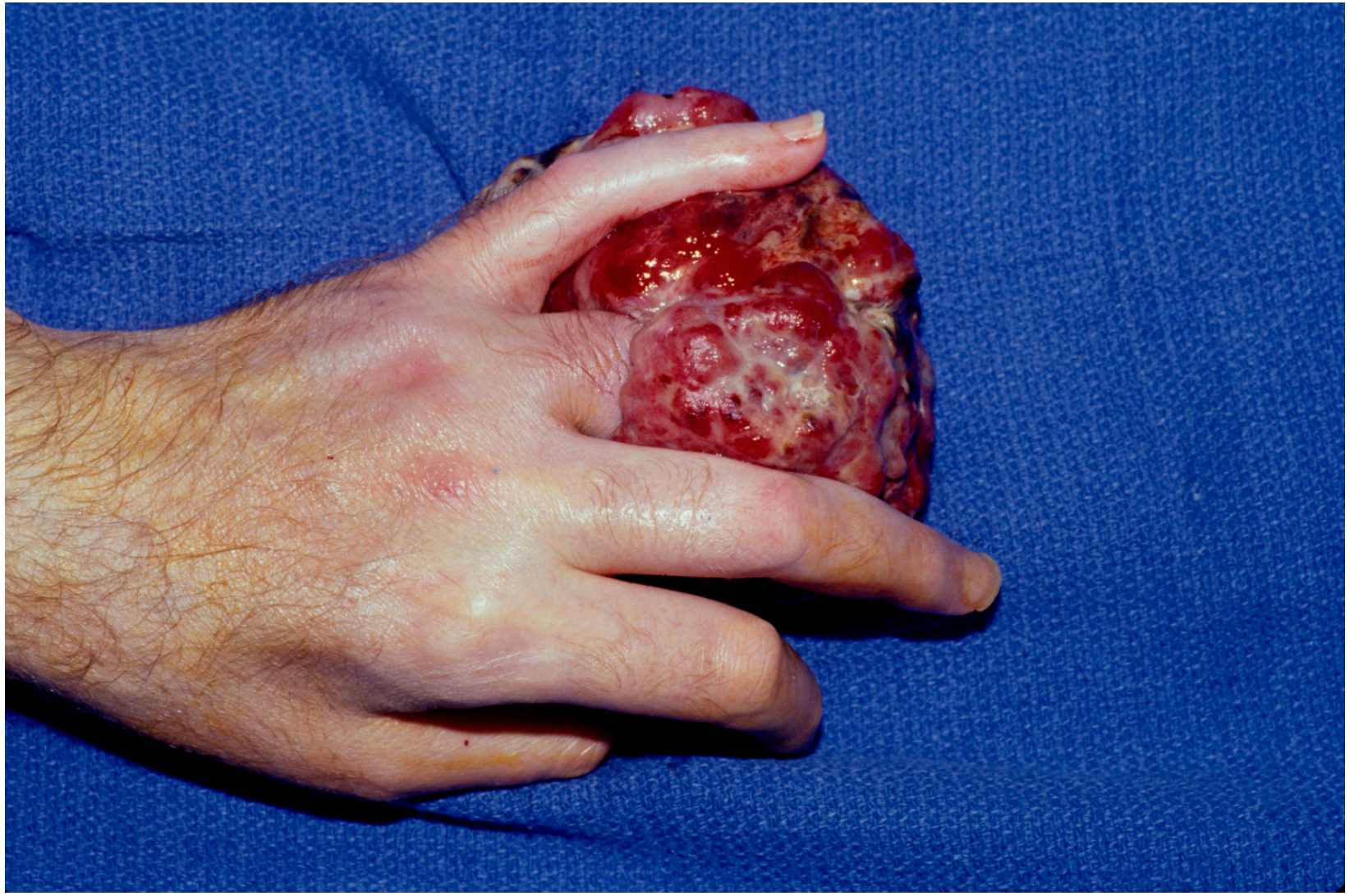


	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Relatlimab–Nivolumab	355	10.12 (6.37–15.74)
Nivolumab	359	4.63 (3.38–5.62)

Hazard ratio for progression or death, 0.75 (95% CI, 0.62–0.92)
P=0.006

No. at Risk											
Relatlimab–nivolumab	355	201	163	132	99	81	75	67	30	6	0
Nivolumab	359	174	124	94	72	61	57	49	27	6	0



Braf Inhibitors and Treatment of Metastatic Melanoma

Three are commercially available

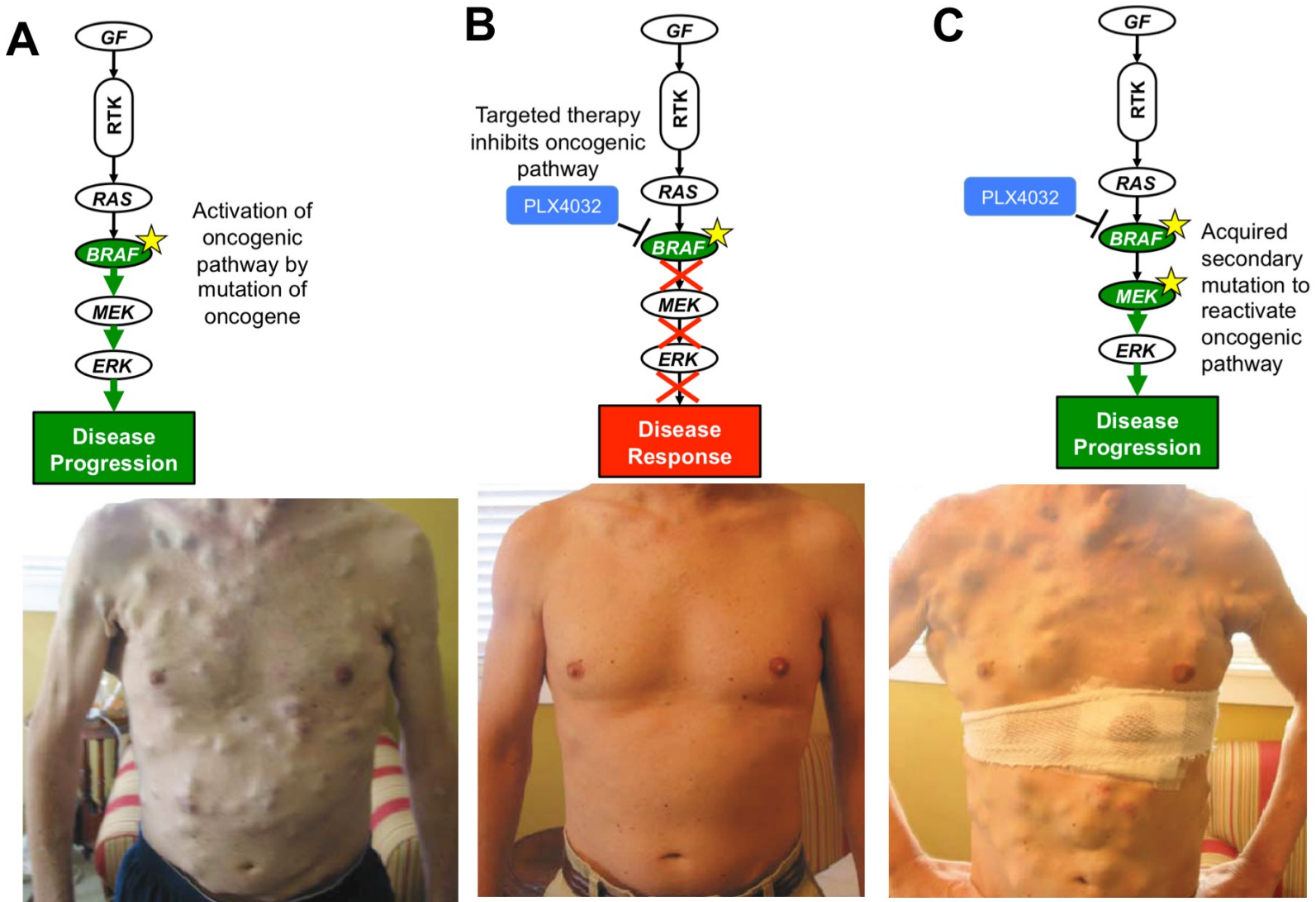
Beneficial only in those with mutation

Oral drugs given daily

High response rate. Short duration.

Lots of side effects: Fatigue, skin rash, SCC

Targeting mutated genes with Targeted Therapy

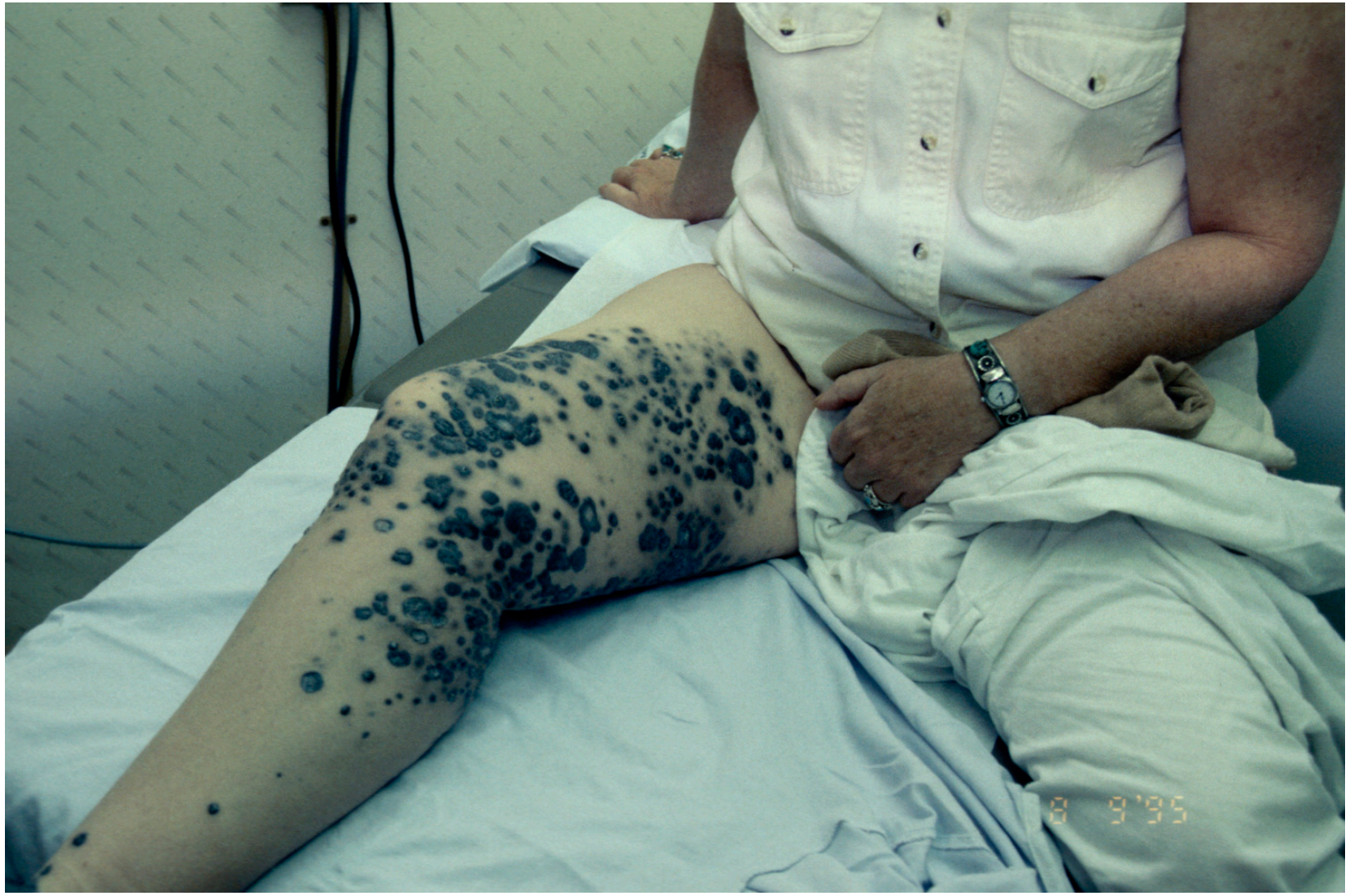


Pre-treatment
(38 yo melanoma patient with BRAF mut)

Post-treatment
15 weeks on PLX4032 (BRAFi)

Relapse (acquired resistance)
23 weeks on PLX4032 (BRAFi)

(Patient Image From: *Wagle et al JCO 2011*)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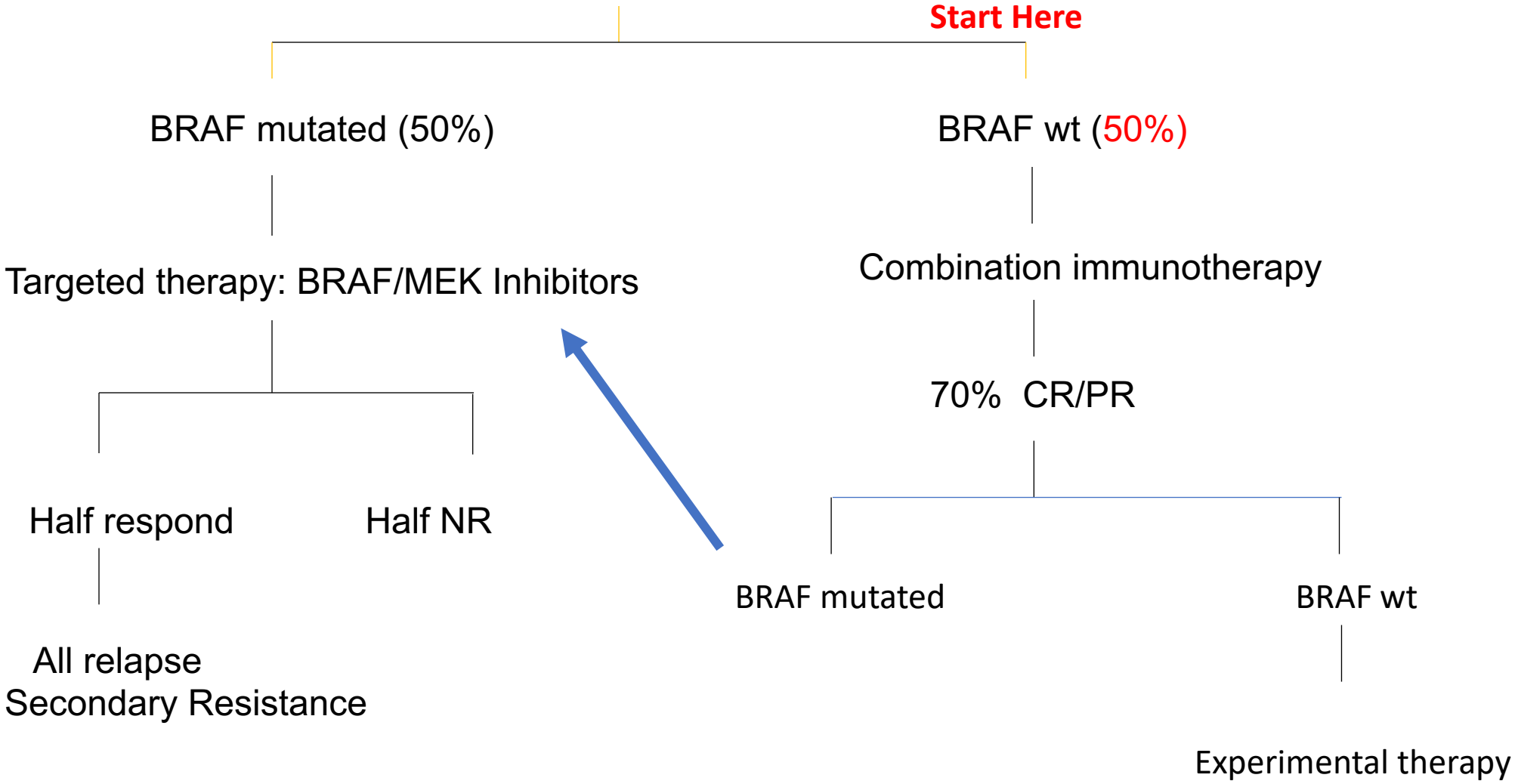
Current Treatment of Metastatic Melanoma



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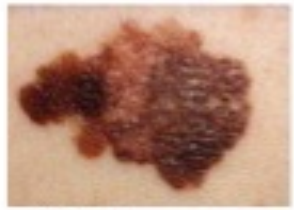

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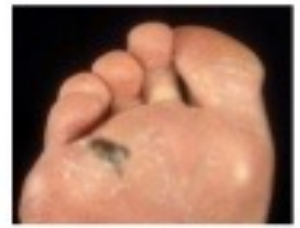

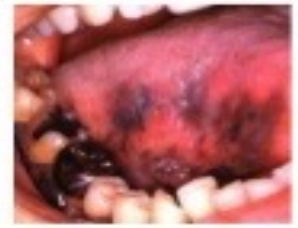

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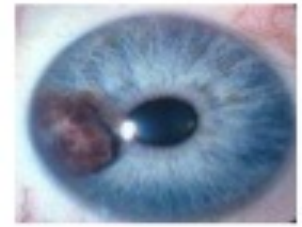

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Mucosal Melanomas

University of Colorado

Type	*Number*	*Percent*
Anal/Rectal	*14*	*16*
Mouth	*4*	*4*
Nasopharynx	*27*	*30*
Subungual	*12*	*13*
Vulvovaginal	*32*	*36*
Total	*89*	*100*

What is on the Horizon for Metastatic Melanoma

mRNA vaccines

Pro apoptosis like venetoclax – MCL 1 inhibitors

Cell cycle blockers like palbociclib - CDK 4-6 mimics

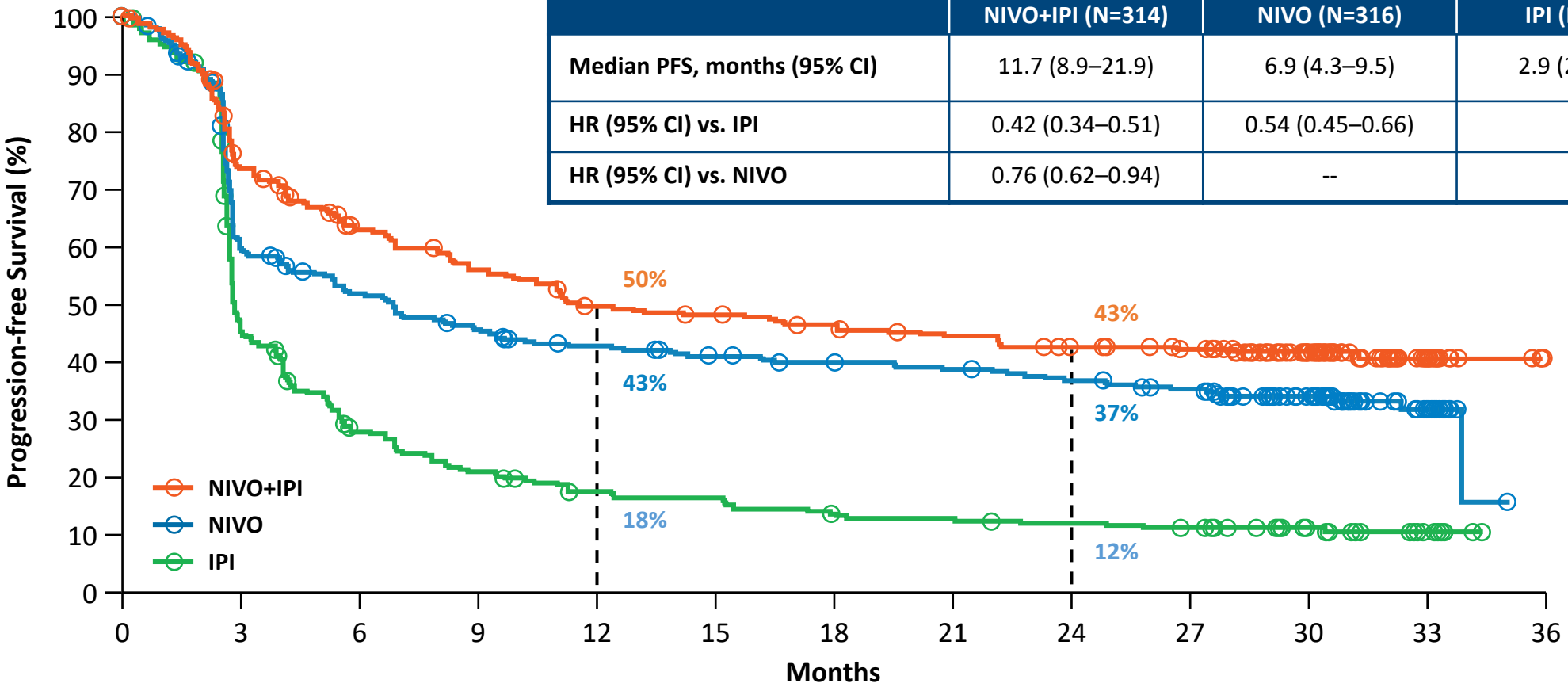
Combinations

Triple therapy BRAFi, MEKi & CDK4i (encorafenib, binimetinib & palbociclib)

- Stage 1- Dose escalation and identification of recommended phase 2 dose
- Stage 2- recommended phase 2 dose
  - Cohort A- Patients with primary or acquired resistance to BRAF and MEK inhibitors (30 patients).
  - Cohort B- Patients naïve to BRAF and MEK inhibitors (30 patients).
  - ***At least 6 patients in cohort A and B require disease suitable for early on treatment biopsy.***

Targeting Immune Checkpoints- Resistance?

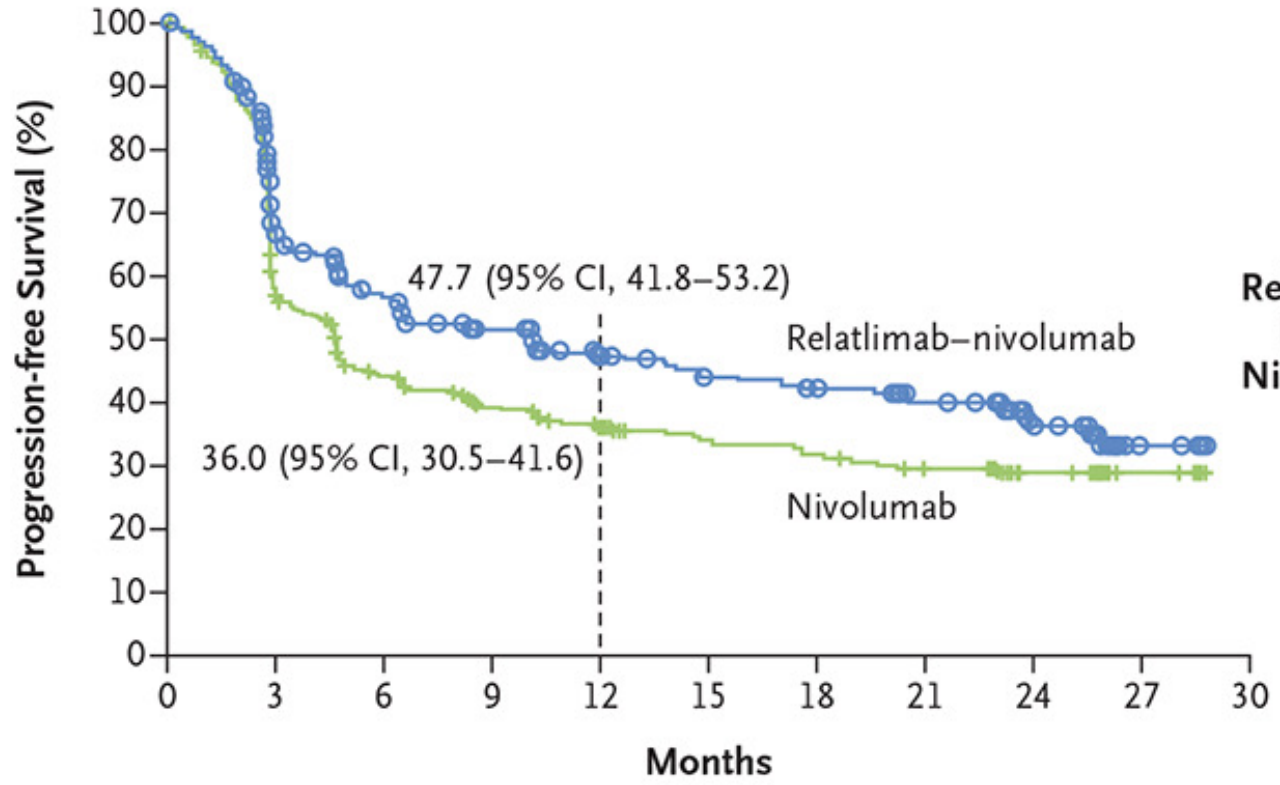
	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.7 (8.9–21.9)	6.9 (4.3–9.5)	2.9 (2.8–3.2)
HR (95% CI) vs. IPI	0.42 (0.34–0.51)	0.54 (0.45–0.66)	--
HR (95% CI) vs. NIVO	0.76 (0.62–0.94)	--	--



Number of patients at risk:

NIVO+ IPI	314	218	176	156	137	132	125	118	110	104	71	16	0
NIVO	316	178	151	132	120	112	107	103	97	88	62	16	0
IPI	315	136	77	58	46	43	35	33	30	27	16	5	0

Database lock: Sept 13, 2016



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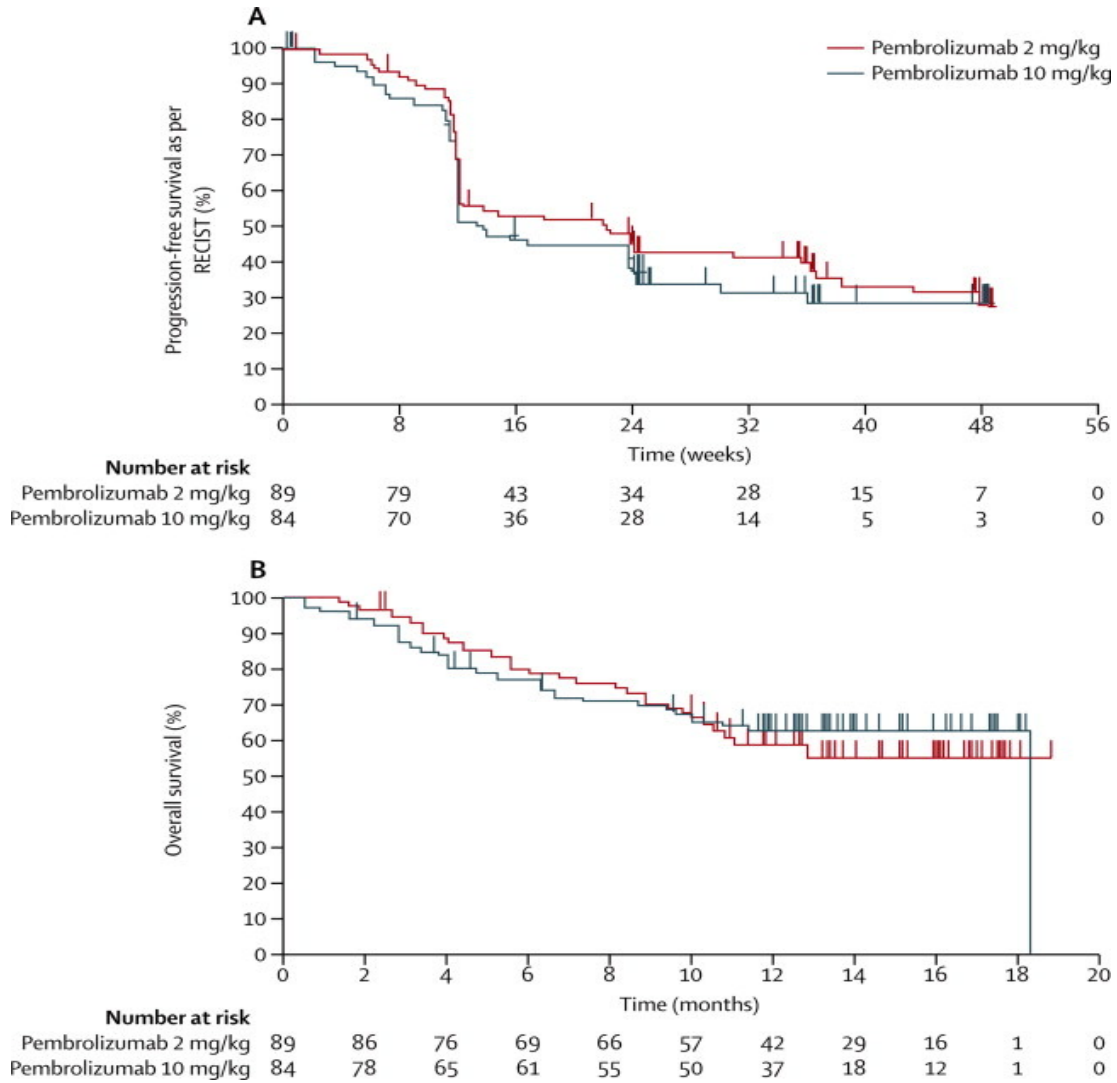
Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial

Caroline Robert et al Lancet July 15,2014



Melanoma

What changed in 20 years: New techniques, completion of the human genome project and hard work by dedicated scientific investigators in laboratories and clinics throughout the world

1. A better understanding of molecular (gene) changes that occur in melanoma and the development of “targeted” therapy. (BRAF and MEK inhibitors)

2. Understanding of how melanoma escapes immune control and development of therapies to overcome the immune blockade (anti CTLA4 and PD1)

The Mucosal Melanomas

Studies at the University of Colorado

Molecular profiling seeking molecular targets (Kasey Couts, Jackie Turner, Jennifer Hintzsche)

Identifying the role of mutated SF3B1 (Kelsey Nassar, AC Tan)

Characterization of the microbiome in mucosal melanomas (Theresa Medina, Carol Amato

Enhancing the immune response in mucosal melanoma (Richard Tobin, Kasey Couts, Martin McCarter, Eduardo Davilla)

Searching for microbial causes (William Robinson, Jennifer Hintzsche)

The Mucosal Melanomas

Much less common than cutaneous melanomas

Not related to sun exposure. No clear causative factors.

Not inherited, occupation related.

Different mutational profiles than skin melanomas

Poor prognosis overall – late diagnosis, differences in mutational profile

BRAF, MEK and CDK4 inhibition in BRAF-mutant melanoma