The melanoma revolution: immune and targeted therapies

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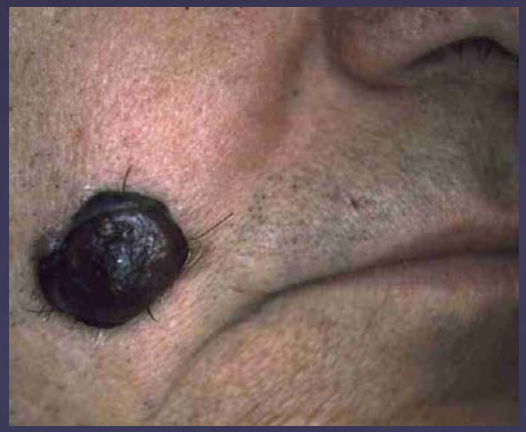
Melanoma Incidence Predictions



870 new cases of invasive melanoma in the US predicted for 2015

5,480 cases predicted for Florida*

* Second-most cases of any state in the US after California, (8,560 cases); New York third (4,270 cases)

The Melanoma Revolution
FDA Approved Agents

Before 2011

acarbazine (1970s)
- Response rate <10%
- Time to progression 2 months
- Median survival 10 months
- One-year survival ~25%

terferon-alfa (1995)

terleukin-2 (1998)

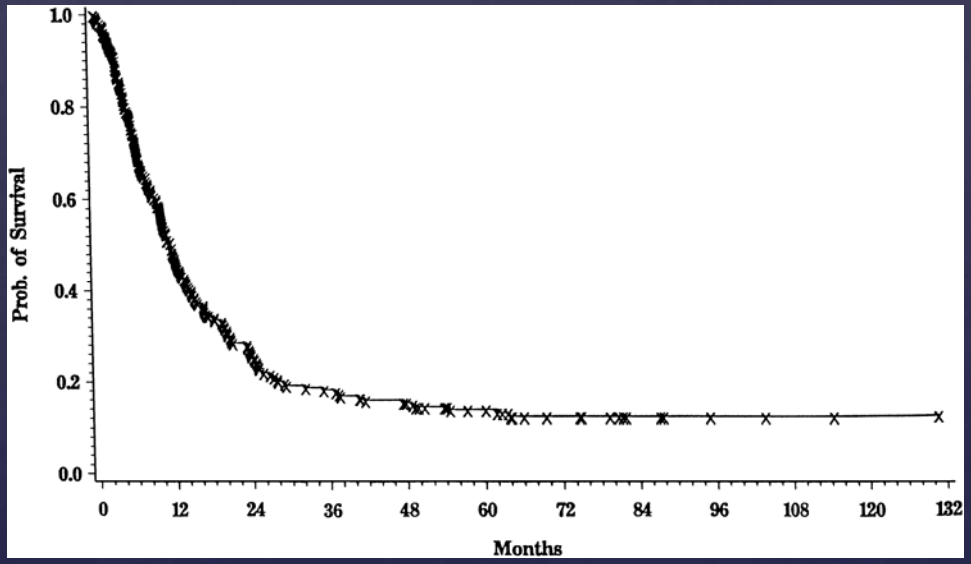
Since 2011

- Ipilimumab
- Vemurafenib
- Pegylated interferon-alfa
- Dabrafenib
- Tilmanocept
- Trametinib
- Pembrolizumab
- Nivolumab
- Talimogene laherparepvec

Why use immunologic approaches to treat melanoma?

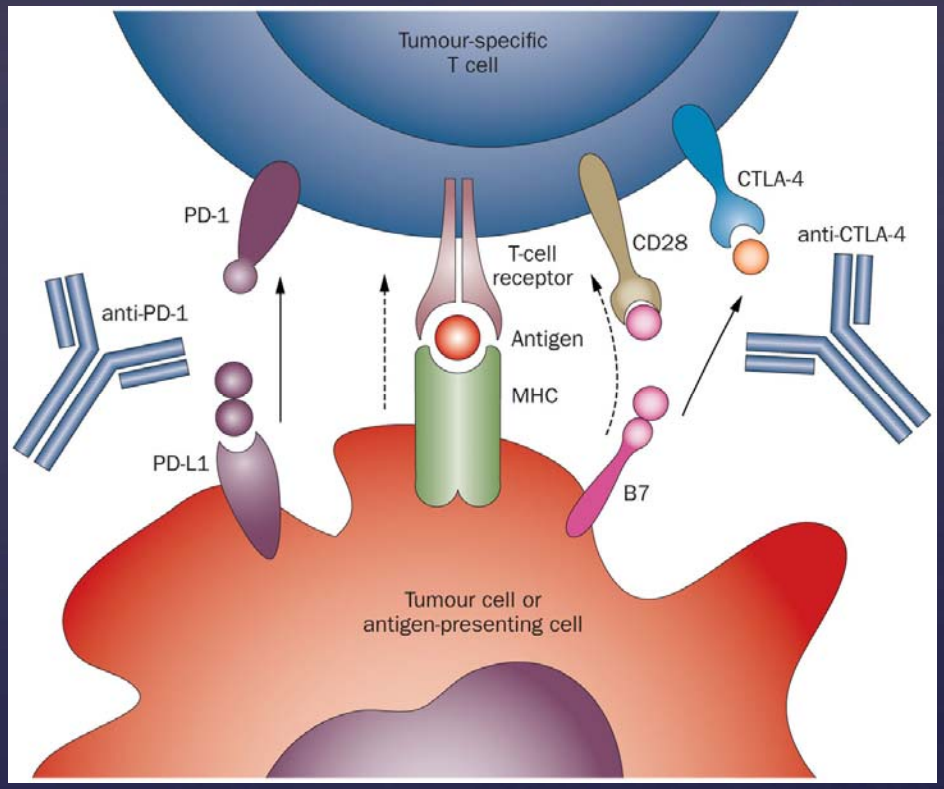
The immune system has long been of interest to those treating Melanoma patients.

One of the first effective therapies was the non-specific Immune stimulant IL-2



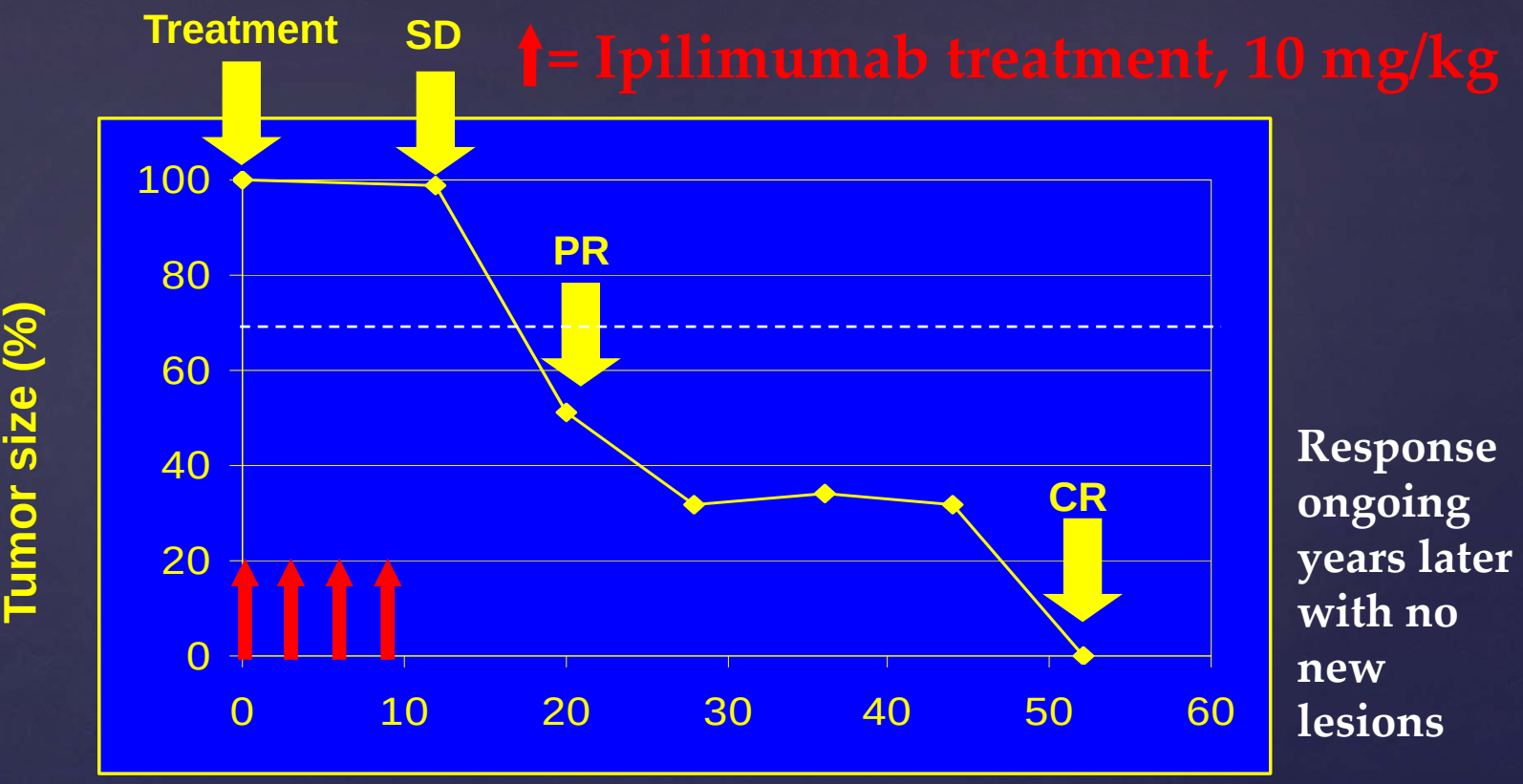
Toxicity very severe
CR ~5%

Ipilimumab and nivolumab release the brakes on immune cells



y be better to release the inhibition of the immune system rather than stimulate

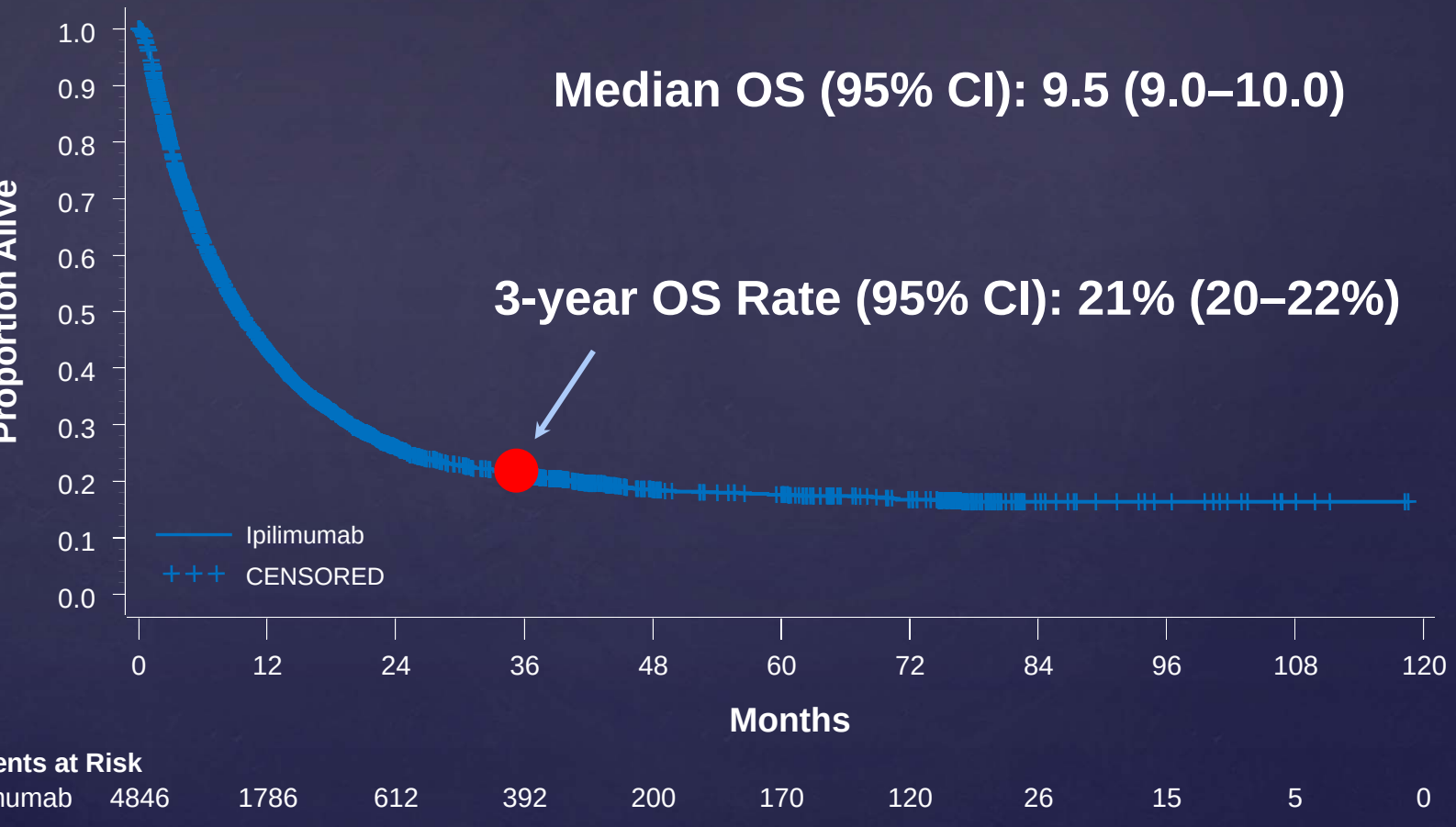
eting T cells with Ipilimumab (Anti-CTLA4 body) Leads to Durable Response



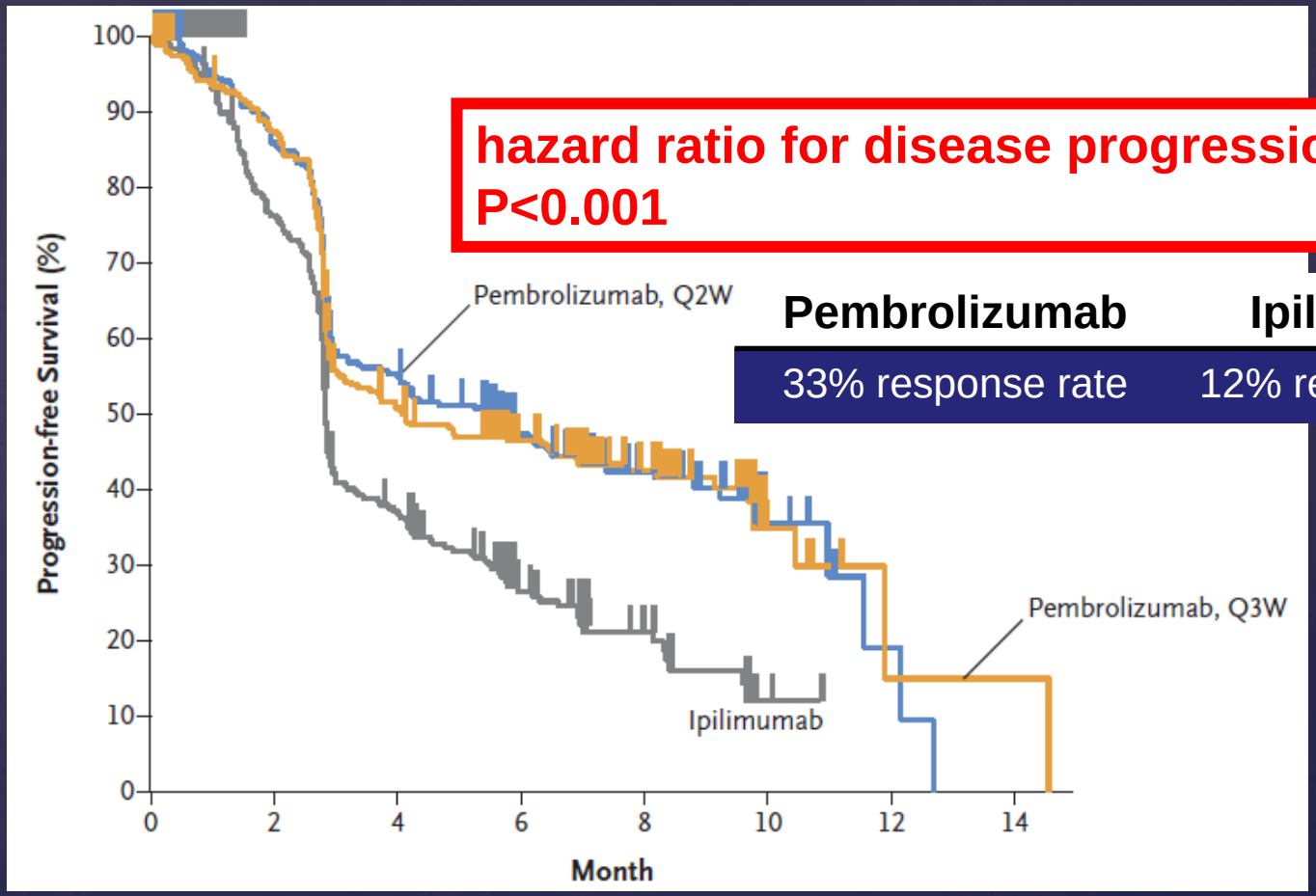
Response ongoing years later with no new lesions

Weber J, Oncologist 2008;13(supp4):16

Ipilimumab (Anti-CTLA4) Improves Overall Survival in Stage IV Melanoma



rolizumab (Anti-PD1 Antibody) Leads To More Responses and ngs Progression-free Survival vs Ipilimumab

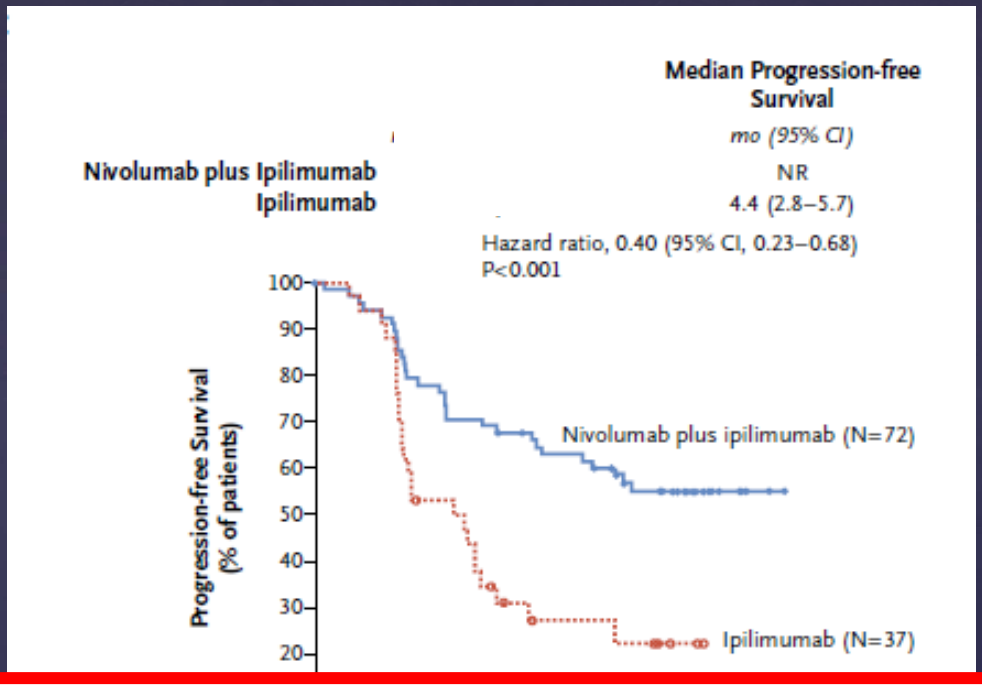


hazard ratio for disease progression 0.58
P<0.001

Pembrolizumab	Ipilimumab
33% response rate	12% response rate

Robert et al, NEJM 2015;372:2521

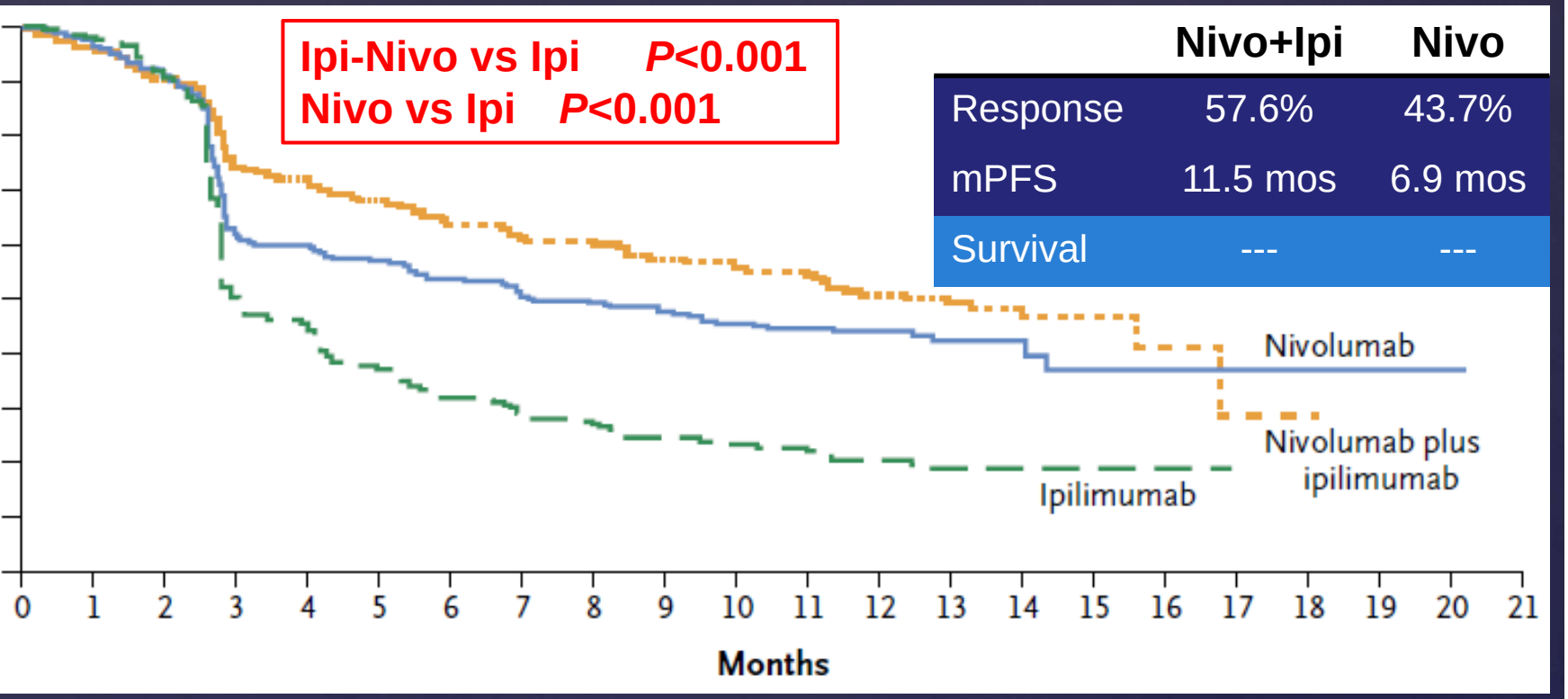
mbining nivolumab and ipilimumab is better n ipilimumab alone



But is it better than nivolumab alone????

Postow et al, N Engl J Med 2015;372:2006

mbining nivolumab and ipilimumab may be tter than nivolumab alone



	Nivo+Ipi	Nivo
Response	57.6%	43.7%
mPFS	11.5 mos	6.9 mos
Survival	---	---

Larkin et al, N Engl J Med 2015;373:23

mbining nivolumab and ipilimumab is more ic than ipilimumab alone

Table 3. Treatment-Related Adverse Events.*

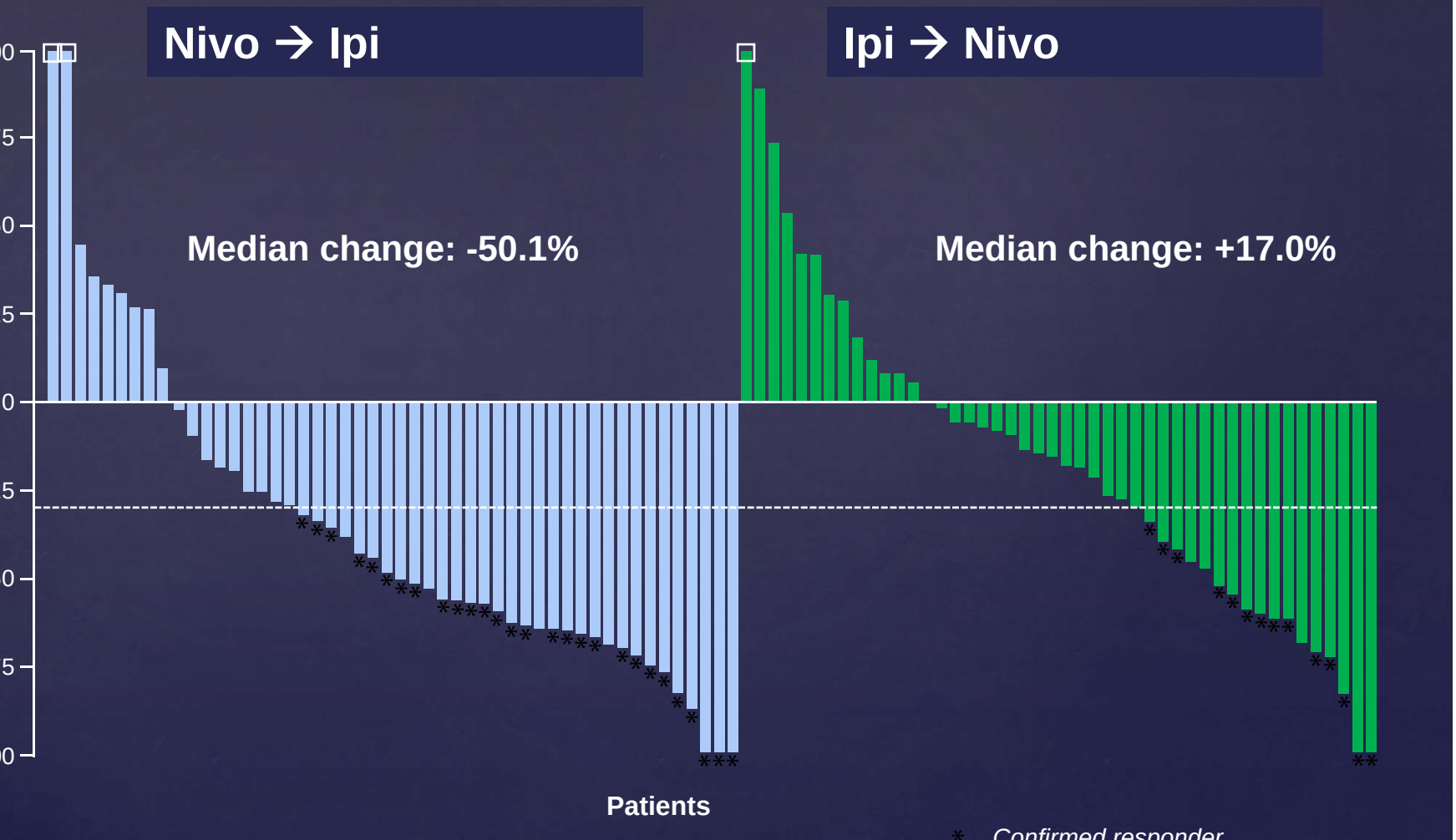
Event	Nivolumab plus Ipilimumab (N=94)		Ipilimumab (N=46)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any treatment-related adverse event	86 (91)	51 (54)	43 (93)	11 (24)
Most common treatment-related adverse events†				
Diarrhea‡	42 (45)	10 (11)	17 (37)	5 (11)
Rash	39 (41)	5 (5)	12 (26)	0
Fatigue	37 (39)	5 (5)	20 (43)	0
Increased lipase	12 (13)	8 (9)	2 (4)	1 (2)
Hypophysitis	11 (12)	2 (2)	3 (7)	2 (4)
Pneumonitis§	10 (11)	2 (2)	2 (4)	1 (2)
Arthralgia	10 (11)	0	4 (9)	0
Chills	10 (11)	0	3 (7)	0
Vitiligo	10 (11)	0	4 (9)	0
Abdominal pain	10 (11)	0	4 (9)	1 (2)
Constipation	10 (11)	1 (1)	4 (9)	0
Myalgia	9 (10)	0	6 (13)	0
Dyspnea	9 (10)	3 (3)	5 (11)	0
Asthenia	8 (9)	0	5 (11)	0
Pruritic rash	5 (5)	0	5 (11)	0
Treatment-related adverse event leading to discontinuation of treatment	44 (47)	36 (38)	8 (17)	6 (13)

e as many Grade 3 or 4 AEs (54% vs 24%)

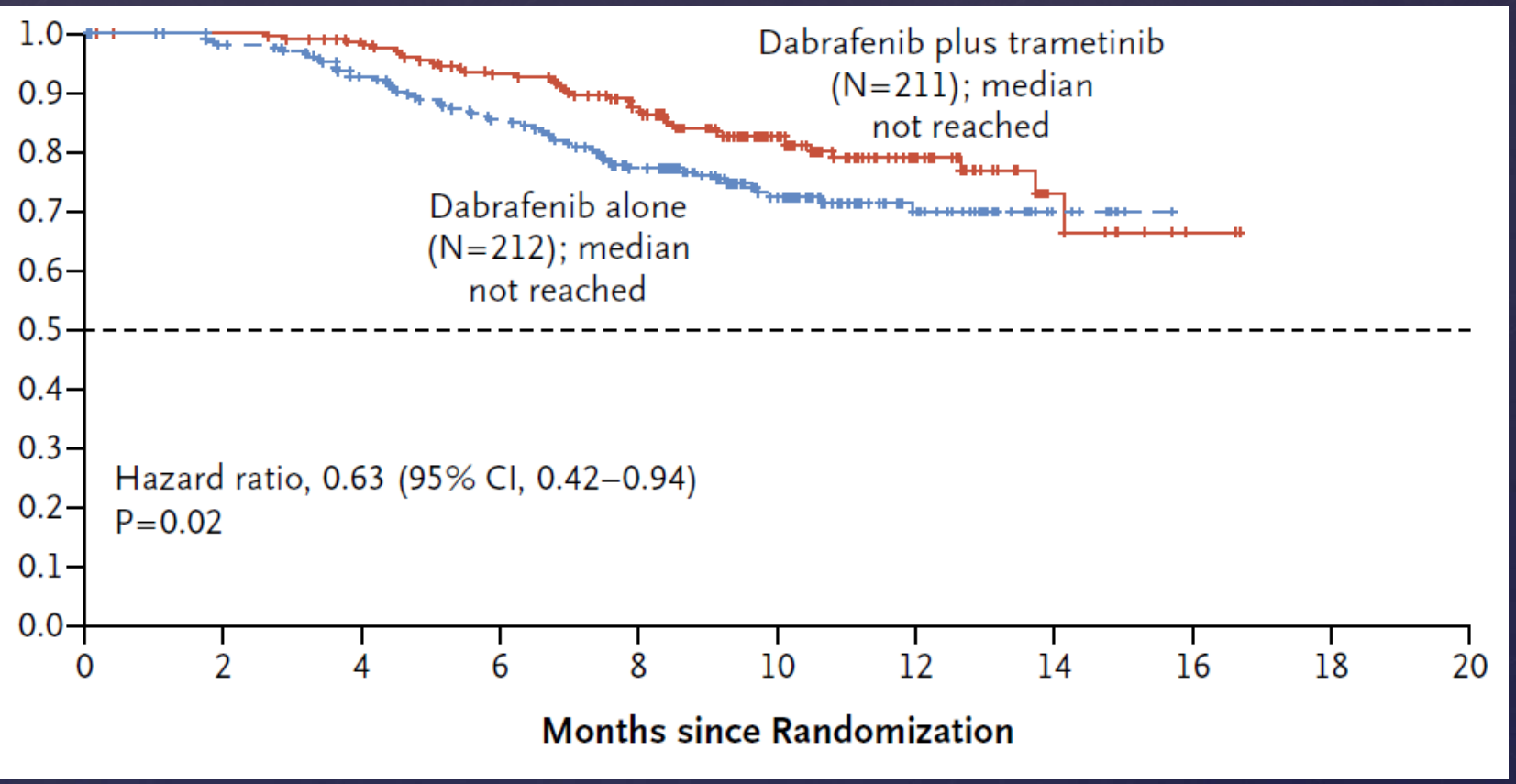
e times as many Grade 3 or 4 AEs leading to treatment discontinuation vs 13%)

Postow et al, N Engl J Med 2015;372:2006

Can sequential treatment provide similar benefits with less toxicity?



brafenib + Trametinib Improves Survival Compared to Dabrafenib Alone in BRAF Mutant Melanoma



Long et al, NEJM 2014;371:1877

Latest OS estimation is >25 months

How to treat and when?

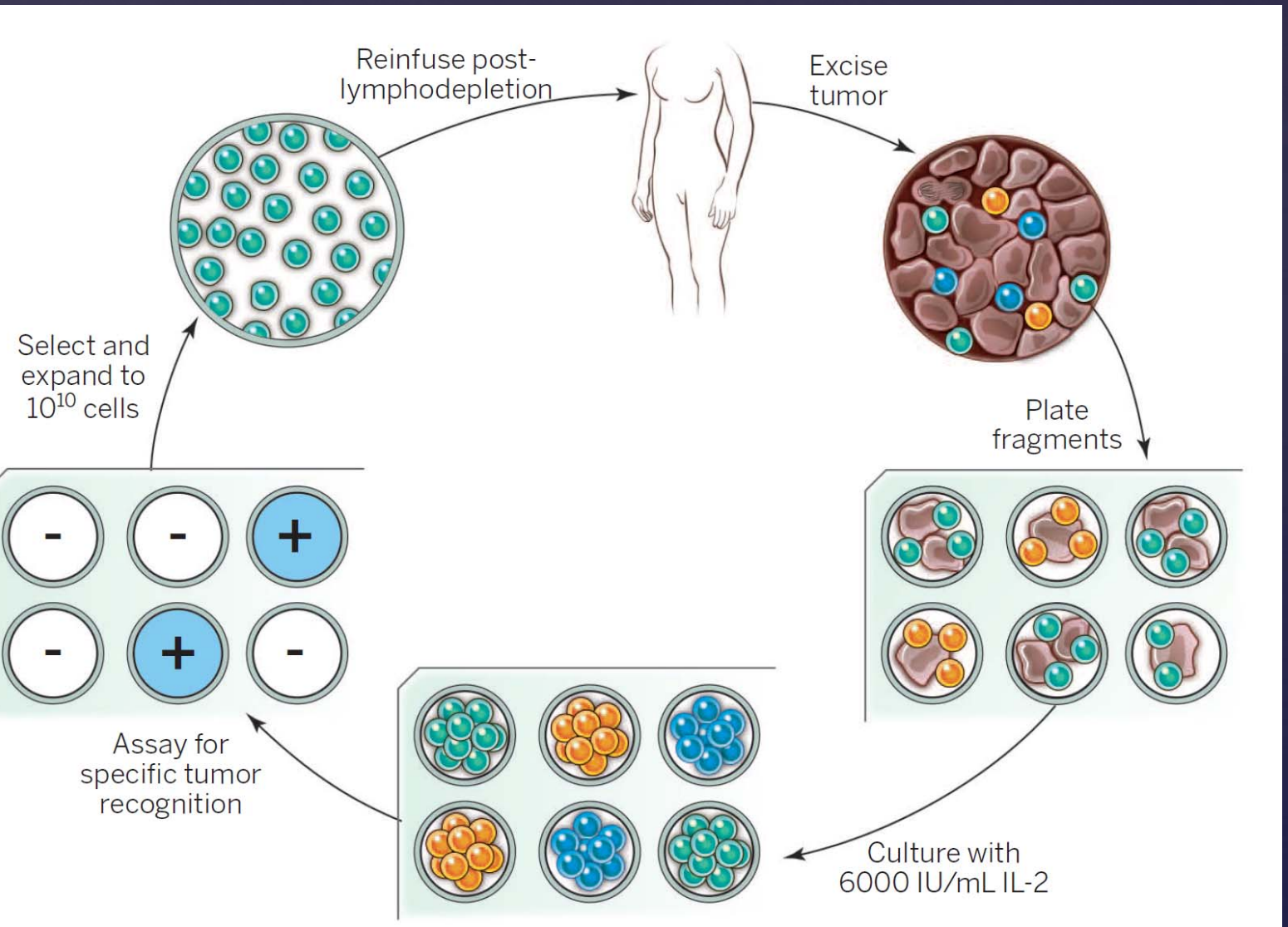
Speed of disease progression

- Need to be determined through sequential scans
- Plasma LDH levels
- Rapidly progressing brain mets

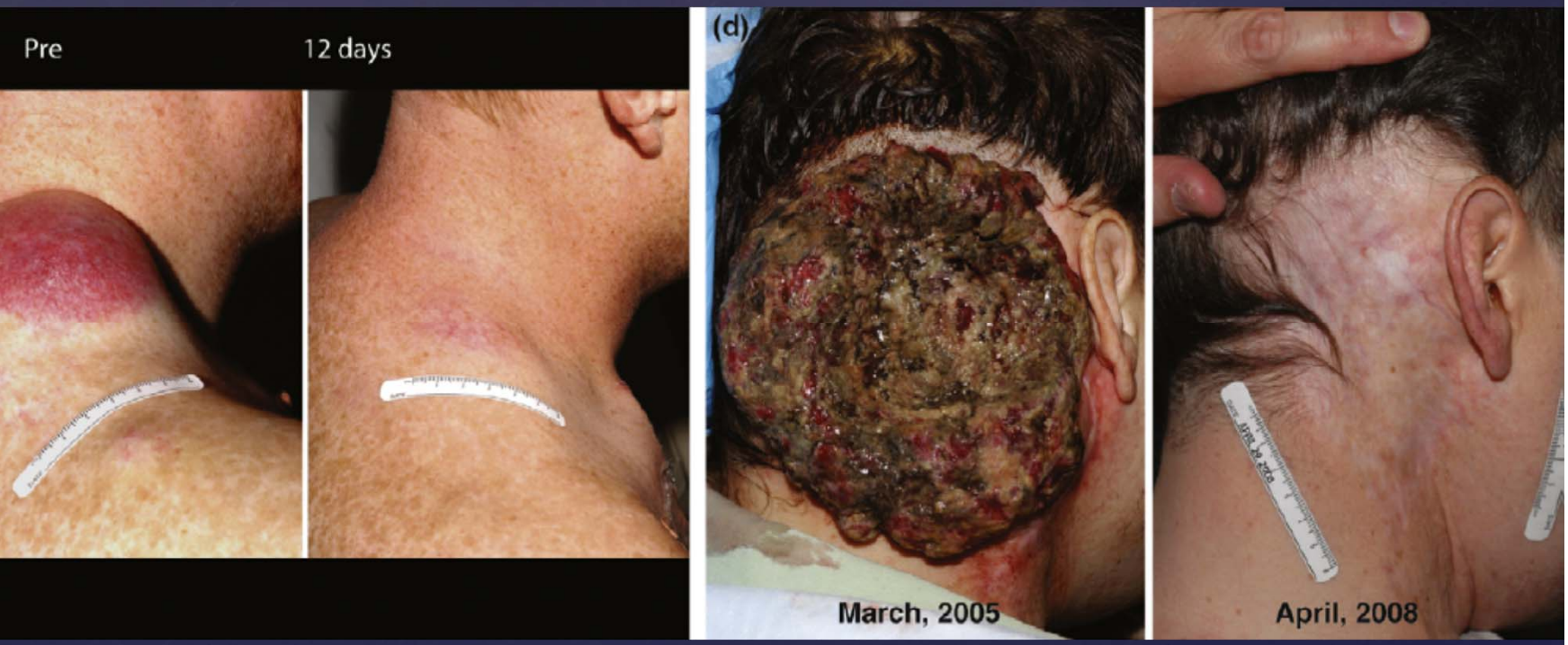
BRAF mutant melanoma patients may be better to get immunotherapy first

Still very much a work in progress

Adoptive Cell Therapy Schema



Example of Clinical Response to Adoptive Cell Therapy in Advanced Melanoma at the NCI

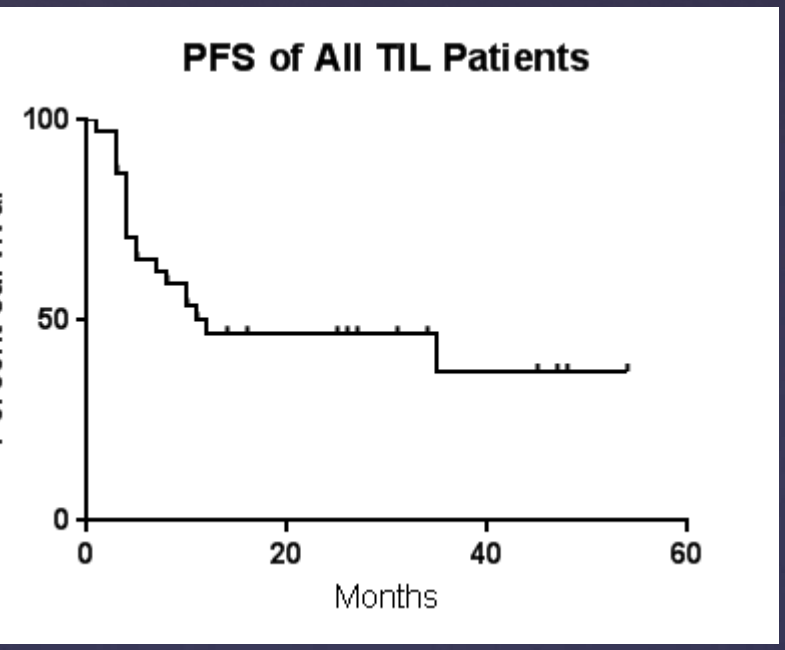


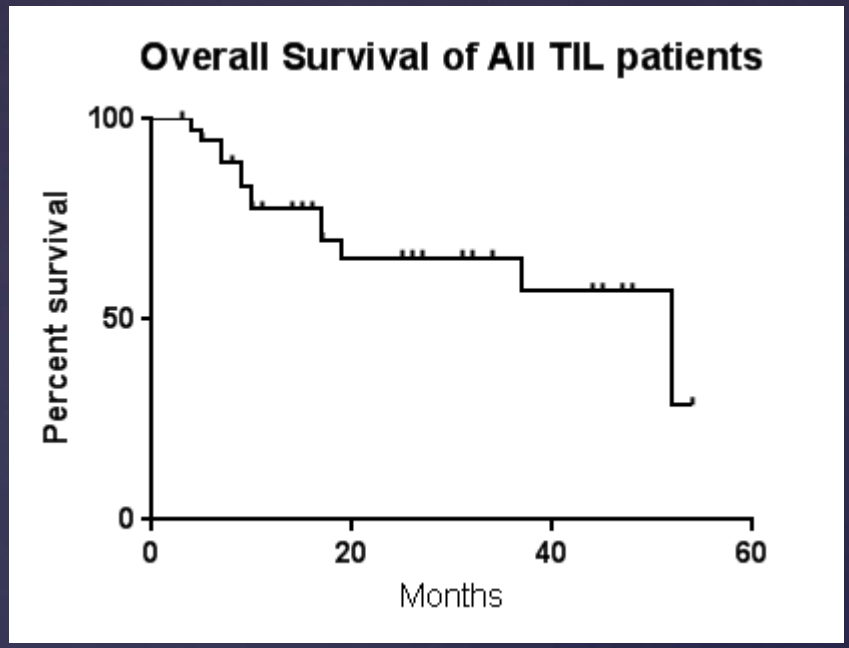
Rapid Expansion

Rapid expansion starts after 30 million TIL are generated in plates; the process involves a fixed two week time period. 30-60 bags are required.

*TIL preparation cost = $52k
½ of cost due to IL-2

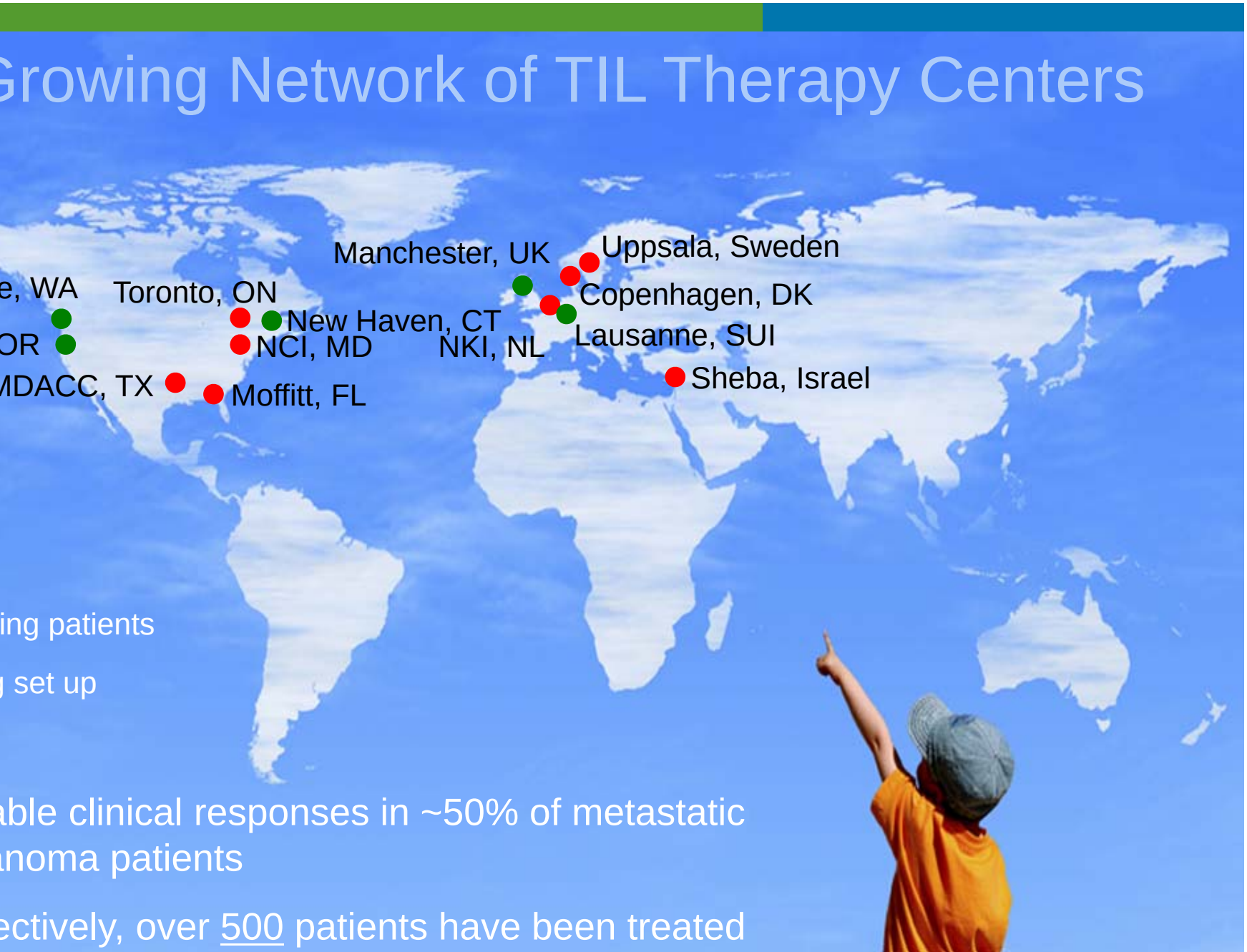
rvival Results After TIL at Moffitt





4 of 47 successful TIL expansions (94%)
0 treated with TIL of 47 resected patients (85%)
Median PFS 12 months; projected median OS is 52 months
3 of 36 (36%) patients have durable ongoing responses ranging
om 16-55 months. Median follow up is 17 months.

Growing Network of TIL Therapy Centers



ing patients

g set up

able clinical responses in ~50% of metastatic
anoma patients

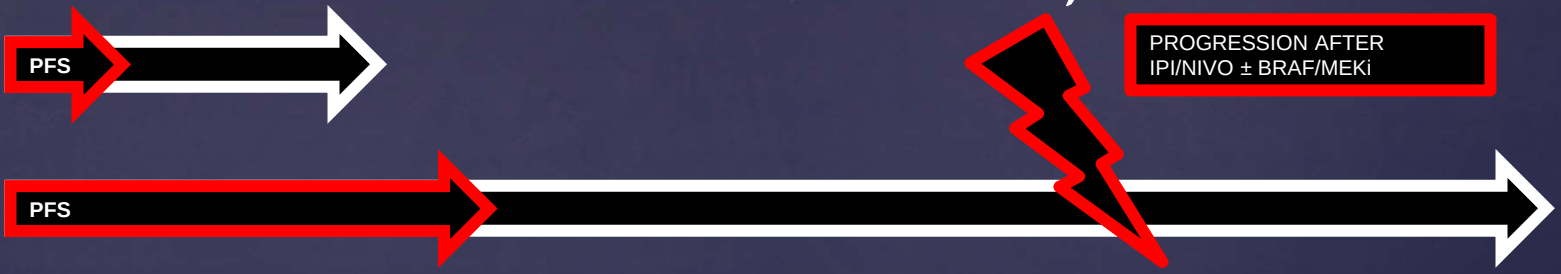
ectively, over 500 patients have been treated

The Melanoma Revolution

Results of Phase III Trials in Metastatic Disease

Phase III Trial Results

DTIC: **PFS 1.6 months, OS 10 months**



BRAFi+MEKi: **PFS 11 months, OS**

Pembro: **PFS 5 months, OS >18 months**

Ipi+Nivo: **PFS 11.5 months, OS ?**

Bedikian et al, J Clin Oncol 2006;24:4738; Long et al, Lancet 2015;386:444; Robert et al; N Engl J Med 2015;372:30; Larkin et al, N Engl J Med 2015;373:23.

Moffitt contributions to the melanoma revolution

Immune therapy

Major contributor to all of the key trials on ipilimumab and nivolumab

First to demonstrate that patients tolerate nivolumab even following severe toxicity to ipilimumab

Conducted the first randomized trial comparing ipi>nivo and nivo>ipi which may ultimately become standard of care

Targeted therapy

Provided the preclinical rationale for BRAF-MEK inhibition

Accrued the most patients to the pivotal BRAF-MEK inhibitor trial

Initiating the first three agent targeted therapy trial for BRAF mutant

Ongoing Research in the Melanoma and Skin Cancers Research Center of Excellence

anoma signaling/genetics

an Smalley, PhD: **Developing personalized therapy egies for melanoma**

umar Chellappan, PhD: **YAP-1 signaling in noma**

Koomen, PhD: **Phosphoproteomic analysis of noma**

gyu Yang, PhD: **Mechanisms of melanoma cell sion/metastasis.**

ung Kim, PhD: **Novel signaling pathways in noma (R-Ras and Ral-A)**

Rix, PhD: **Using chemical proteomics to determine therapeutic targets in melanoma**

am Mahajan, PhD: **Wee1 as a novel therapeutic et in melanoma**

Lau, PhD: **The role of fucosylation in melanoma lopment and progression**

e Morse, PhD: **Targeted radiopharmaceuticals for l melanoma**

r Kanetsky, MPH, PhD: **Melanoma metabolomics**

r Forsyth, MD: **Melanoma brain metastases and omeningeal melanoma metastases**

Chen, PhD: **Genetic analysis of melanoma**

n Wan, PhD: **Protein homeostasis in melanoma**

an Karreth (starting May 2016): **ceRNAs and noma development/progression**

Melanoma immunology and tumor microenvironment

Shari Pilon-Thomas, PhD: **Mechanisms of melanoma related T-cell suppression**

James Mulé, PhD: **Chemokine signatures/ectopic lymph nodes in melanoma**

Daniel Abate-Daga: **CAR T-cells and melanoma**

Amod Sarnaik, MD: **Optimizing TIL therapy for melanoma**

Joseph Markowitz, MD: **STAT1 nitrosylation and immune therapy escape**

Robert Gillies, PhD: **Hypoxia in the tumor microenvironment**

Regional therapy

Jonathan Zager, MD: **Regional intraarterial and intralesional therapy of skin and hepatic metastases**

Non-melanoma skin cancer

Dana Rollison, PhD, MPH: **Role of HPV in non-melanoma skin cancer development**

Ken Tsai, MD, PhD (starting Aug 2016): **miRNAs for the prevention of SCC**

Sungjune Kim, MD, PhD: **Radiation combined with immunotherapy in Merkel cell carcinoma**