

Guidelines for the Evaluation of Immunotherapy Activity in Solid Tumors

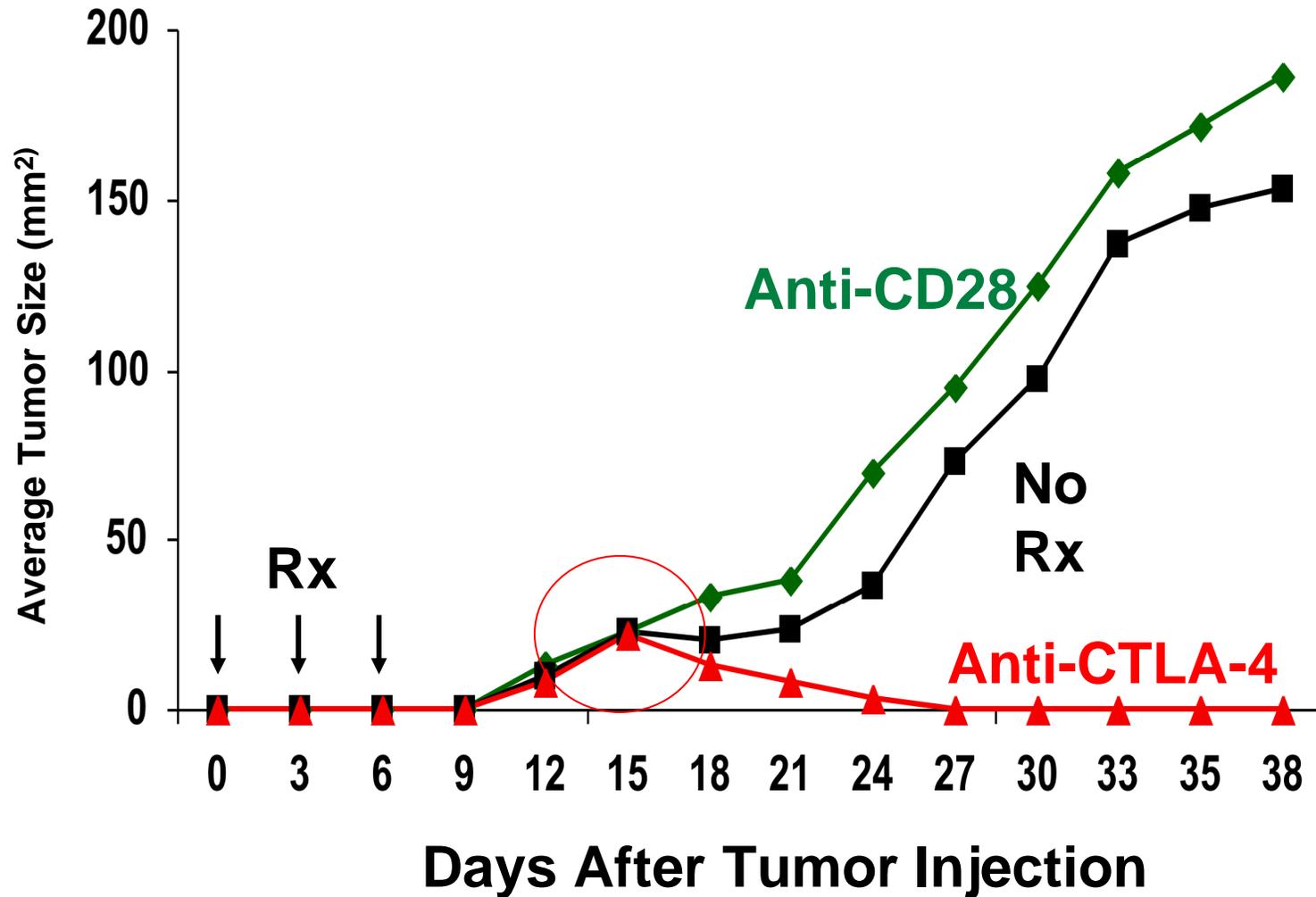
Jedd Wolchok, MD, PhD



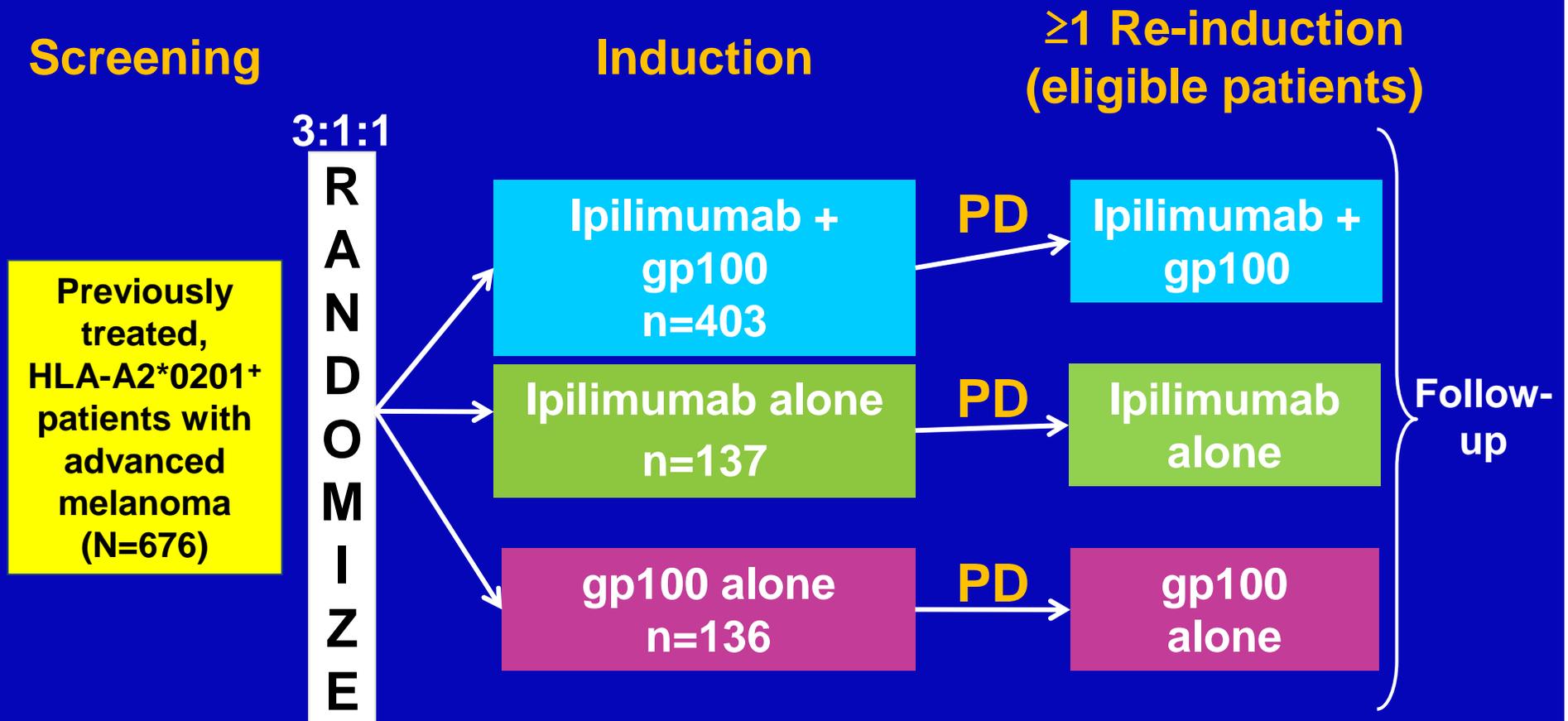
Memorial Sloan-Kettering
Cancer Center

**LUDWIG
CANCER
RESEARCH**

Anti-CTLA-4 Induces Regression of Transplantable Colon Carcinoma



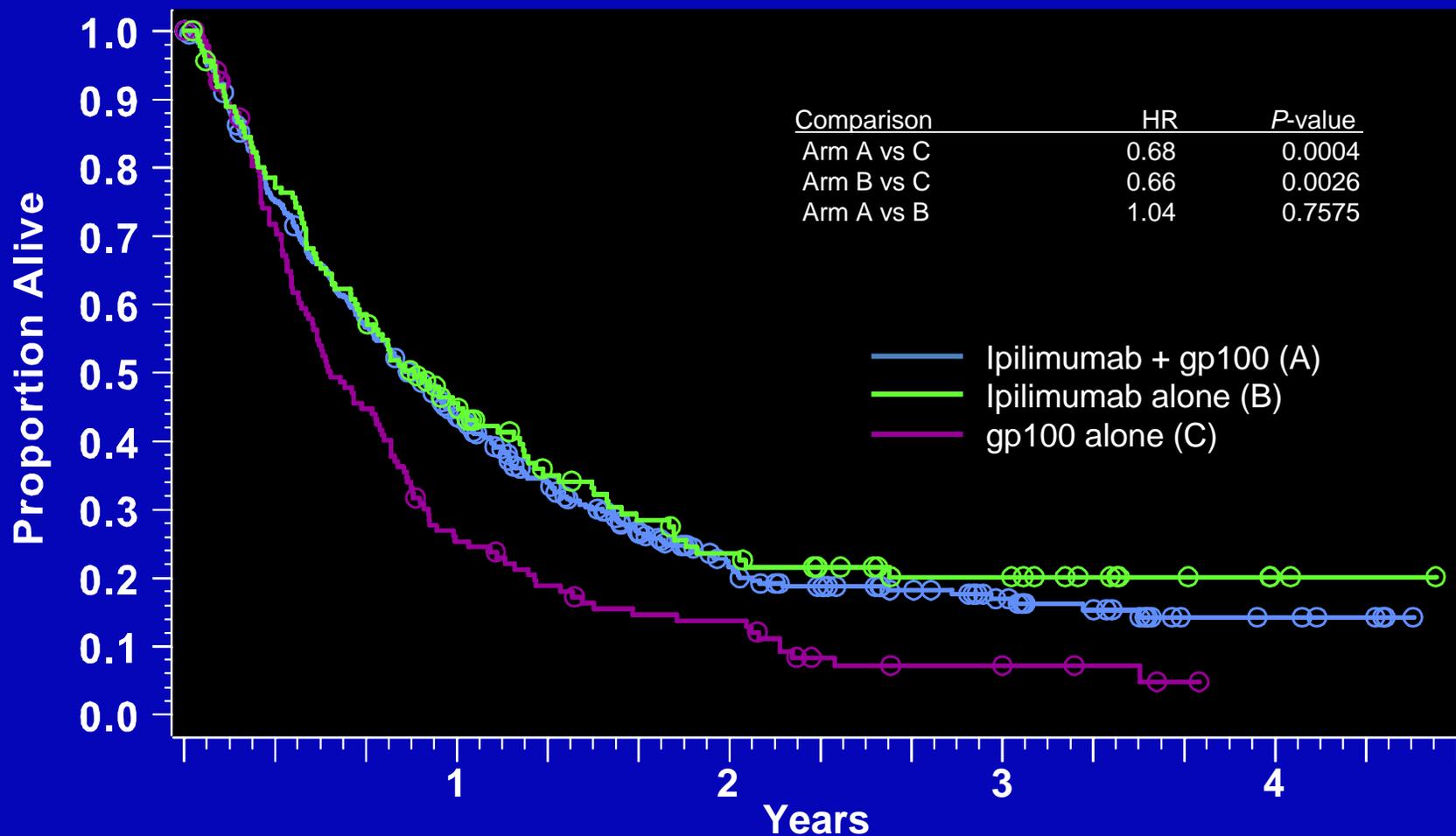
MDX010-20 Study Schema



Induction: Ipilimumab at 3 mg/kg, with or without gp100, every 3 weeks for 4 treatments

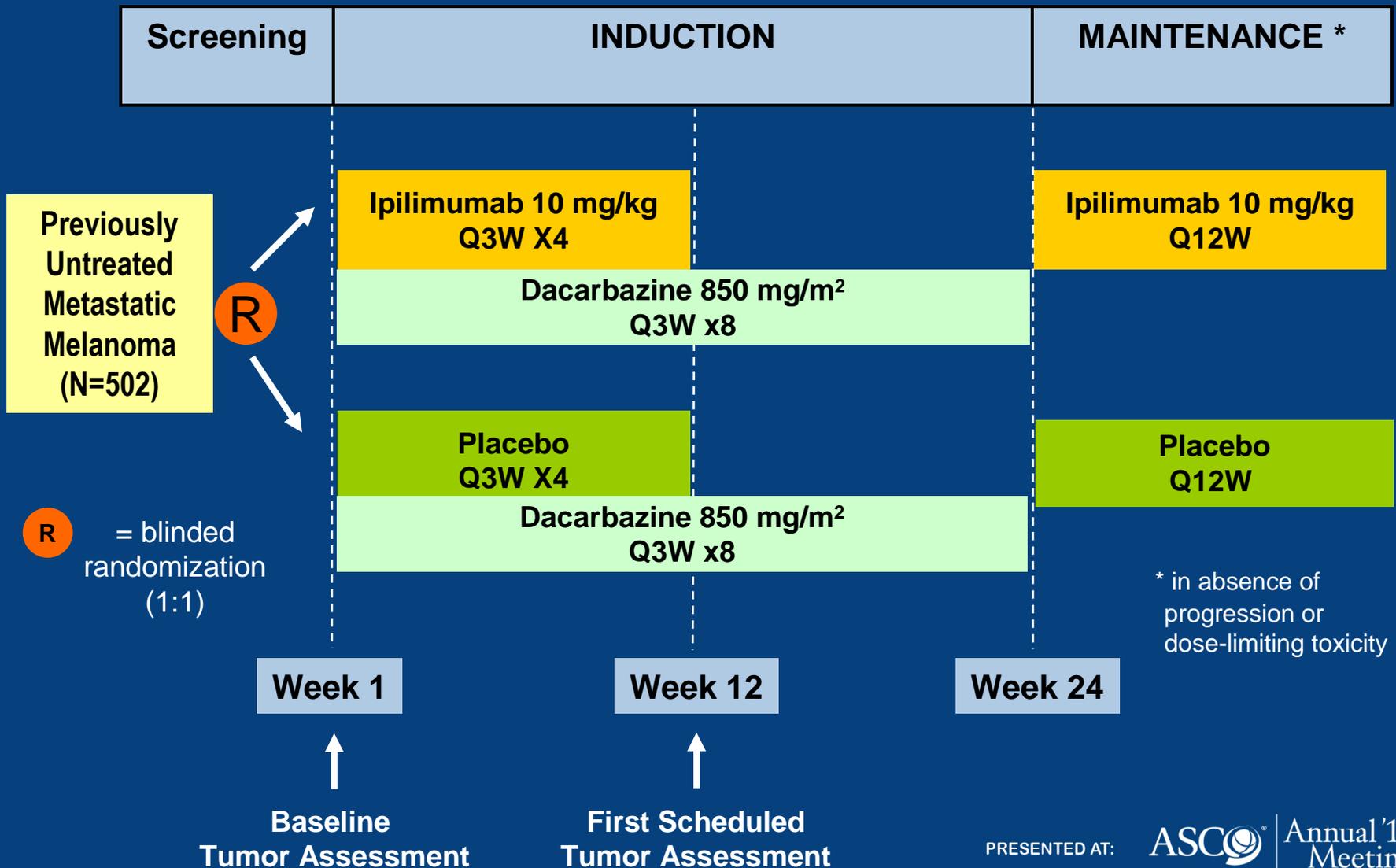
Reinduction: Patients with SD for 3 months' duration from week 12, or a confirmed CR or PR, could receive additional therapy with their assigned treatment regimen upon PD

Kaplan-Meier Analysis of Survival

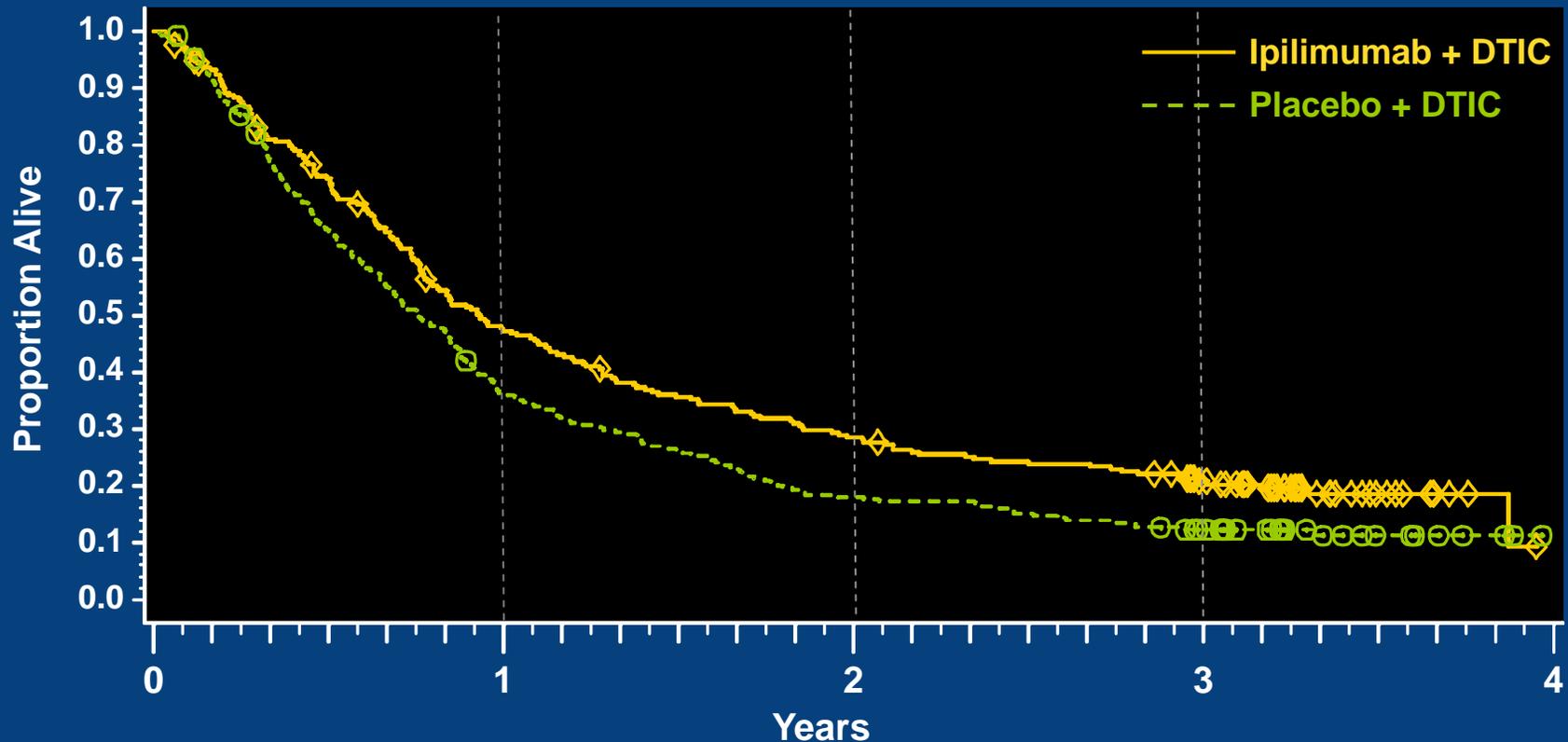


Survival Rate	Ipilimumab + gp100	Ipilimumab alone	gp100 alone
1-year	44%	46%	25%
2-year	22%	24%	14%

Study 024: Design



Study 024: Overall Survival

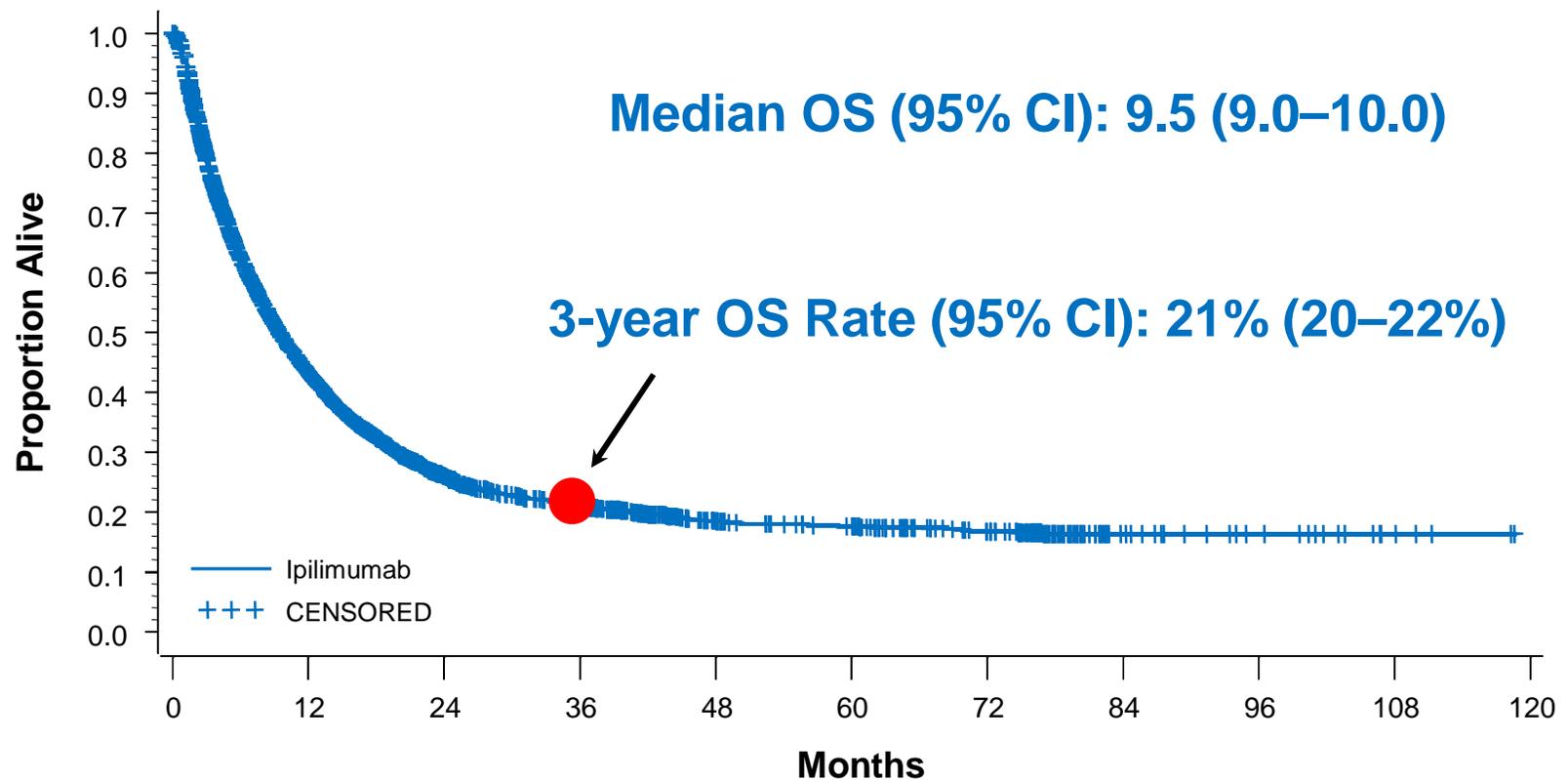


Estimated Survival Rate	1 Year	2 Year	3 Year*
Ipilimumab + DTIC n=250	47.3	28.5	20.8
Placebo + DTIC n=252	36.3	17.9	12.2

*3-year survival was a post-hoc analysis



Pooled OS Analysis Including EAP Data: 4846 Patients



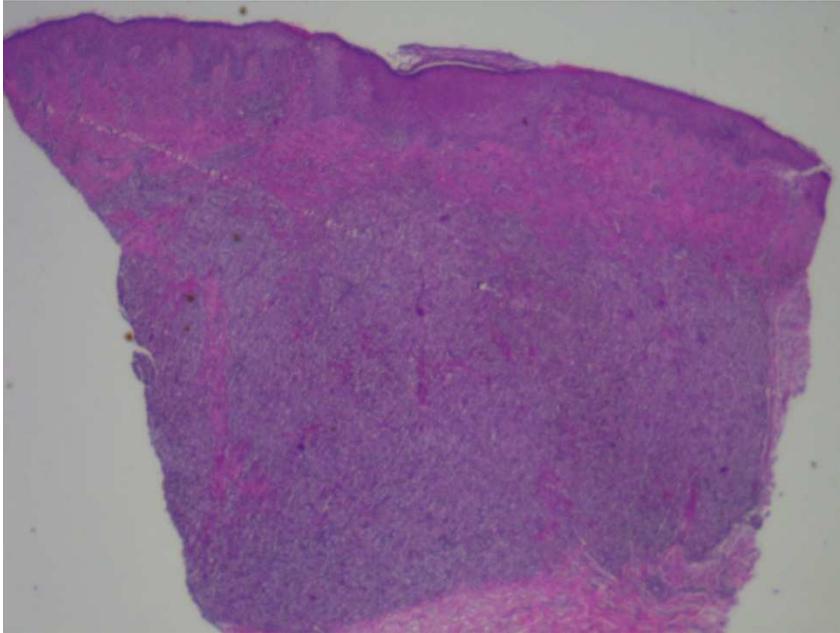
Patients at Risk

Ipilimumab	4846	1786	612	392	200	170	120	26	15	5	0
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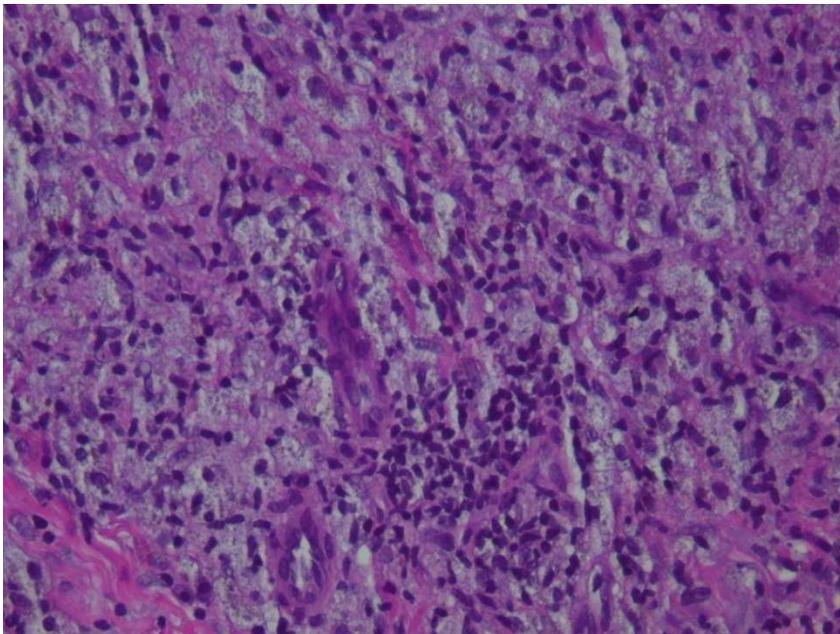
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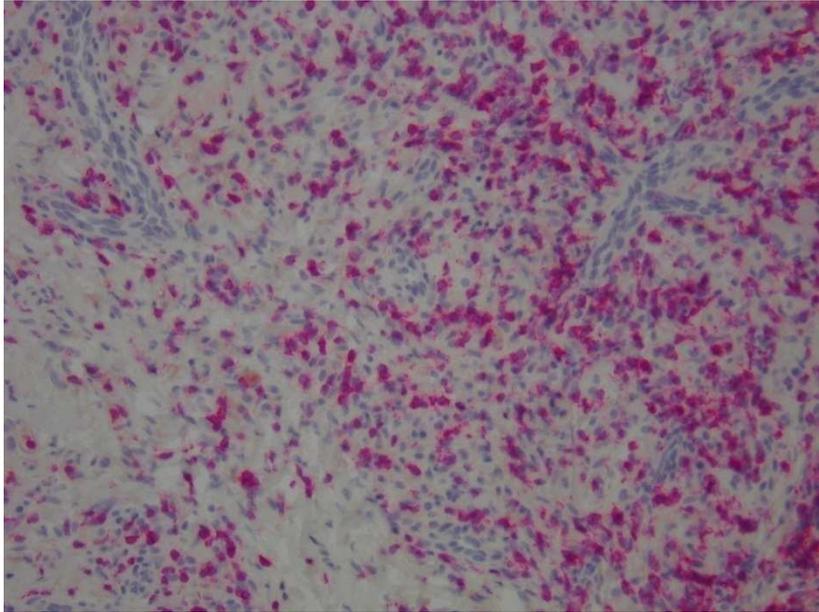




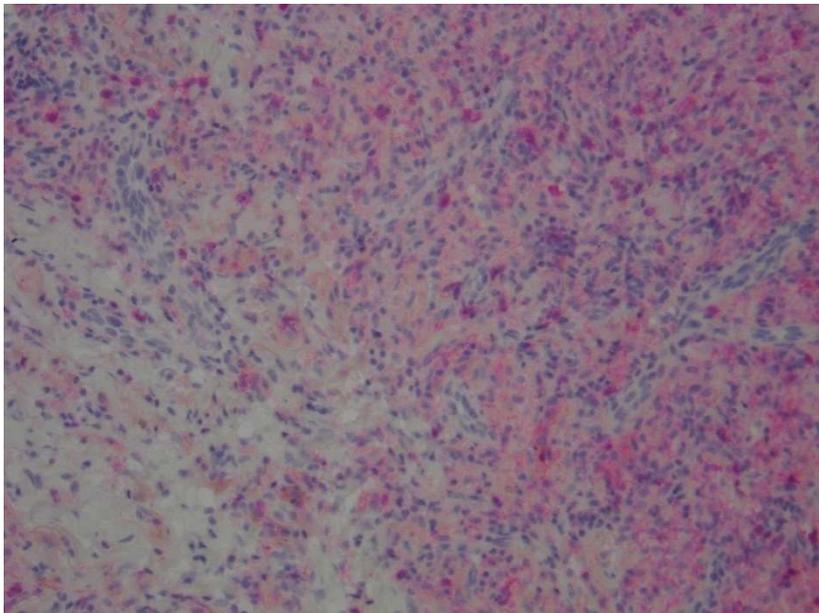
Tumorous nodule
with melanin pigment
(macrophages and
lymphocytes;
no melanocytes)



Macrophages and
lymphocytes are present,
but no tumor cells

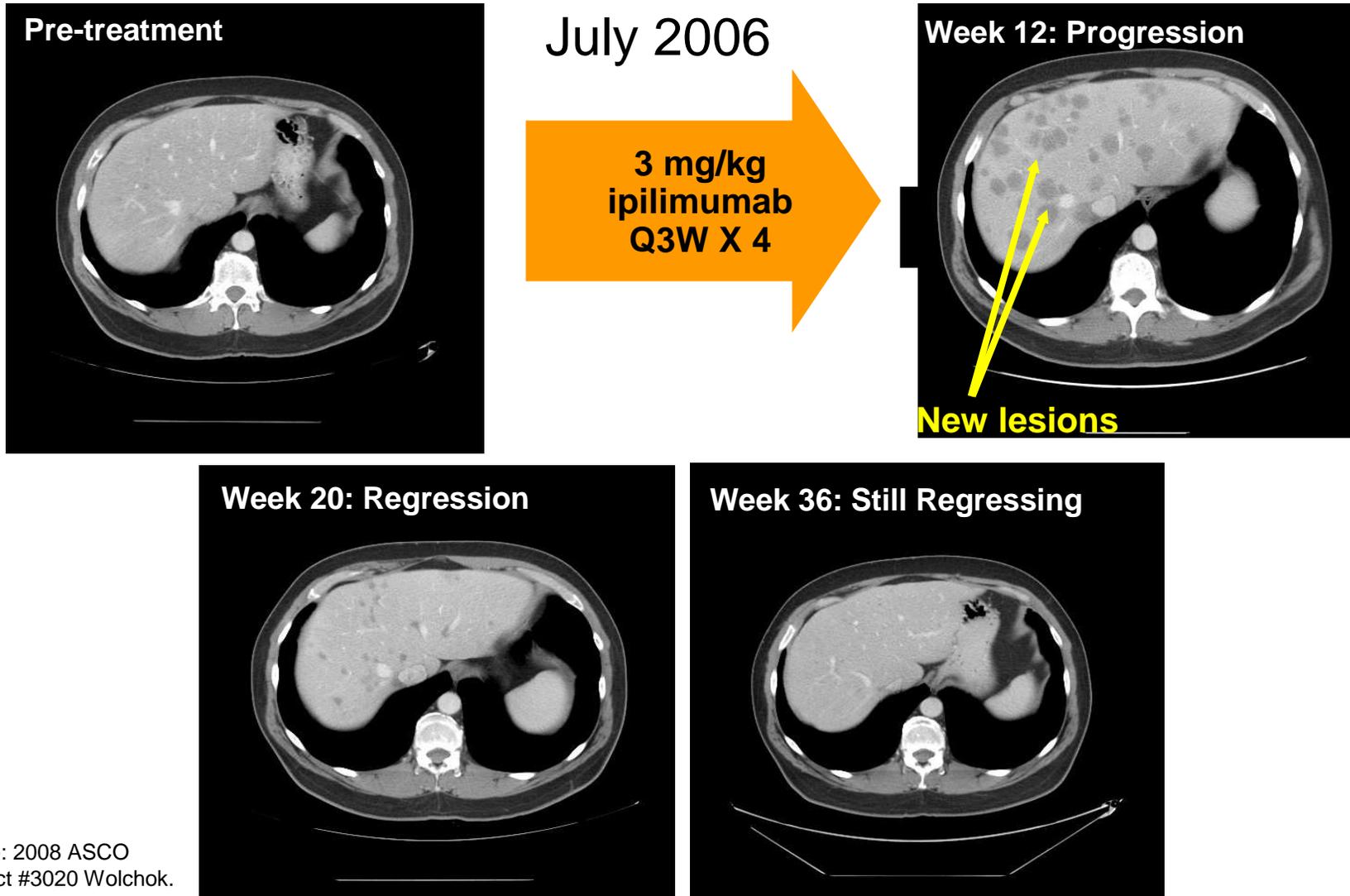


CD8-positive T-cells



CD4-positive T-cells
(macrophages are also
weakly pos for CD4)

Ipilimumab Pattern of Response: Responses After the Appearance and Subsequent Disappearance of New Lesions

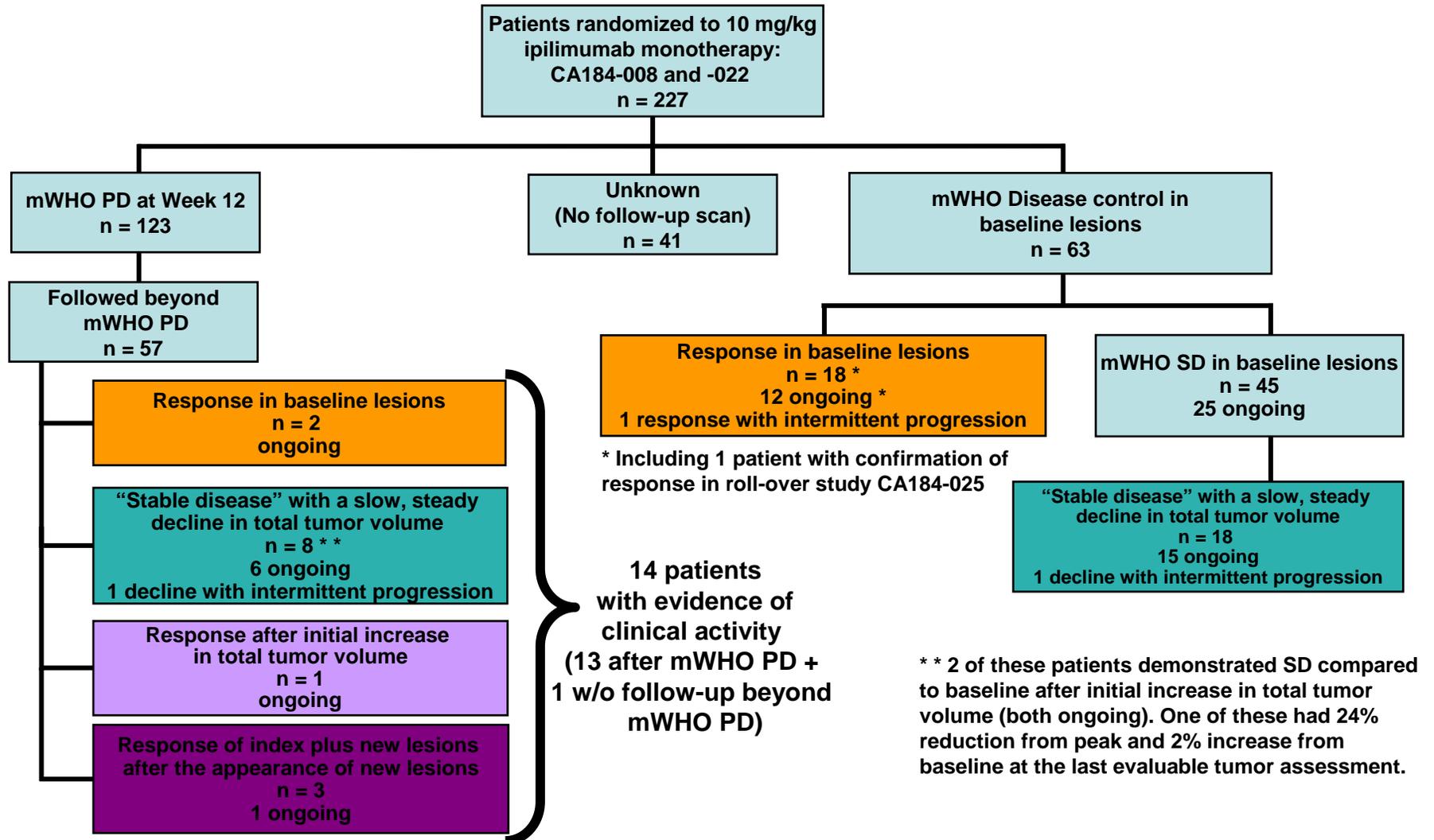


Source: 2008 ASCO
Abstract #3020 Wolchok.

Four Patterns of Response to Ipilimumab Therapy were Observed

- 2 conventional:
 - Response in baseline lesions
 - ‘Stable disease’ with slow, steady decline in total tumor volume
- 2 novel:
 - Response after initial increase in total tumor volume
 - Response in index plus new lesions at or after the appearance of new lesions

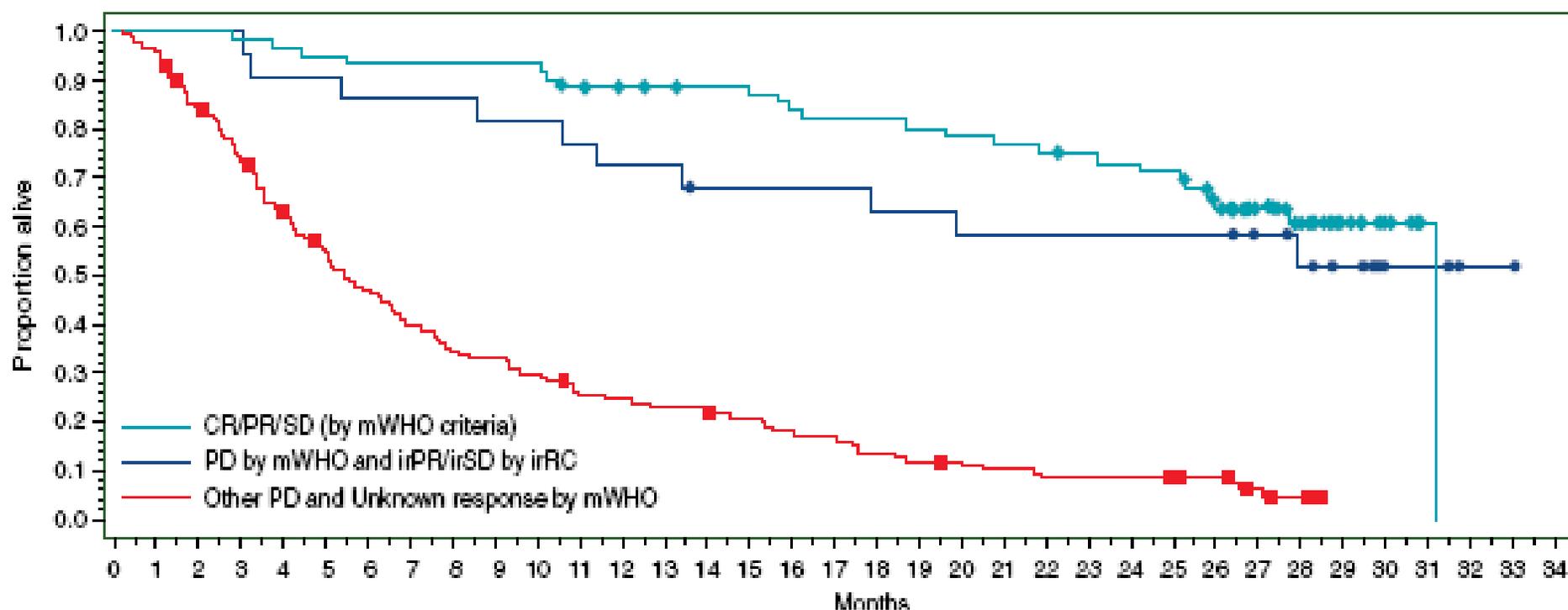
Proportion of Response to Ipilimumab



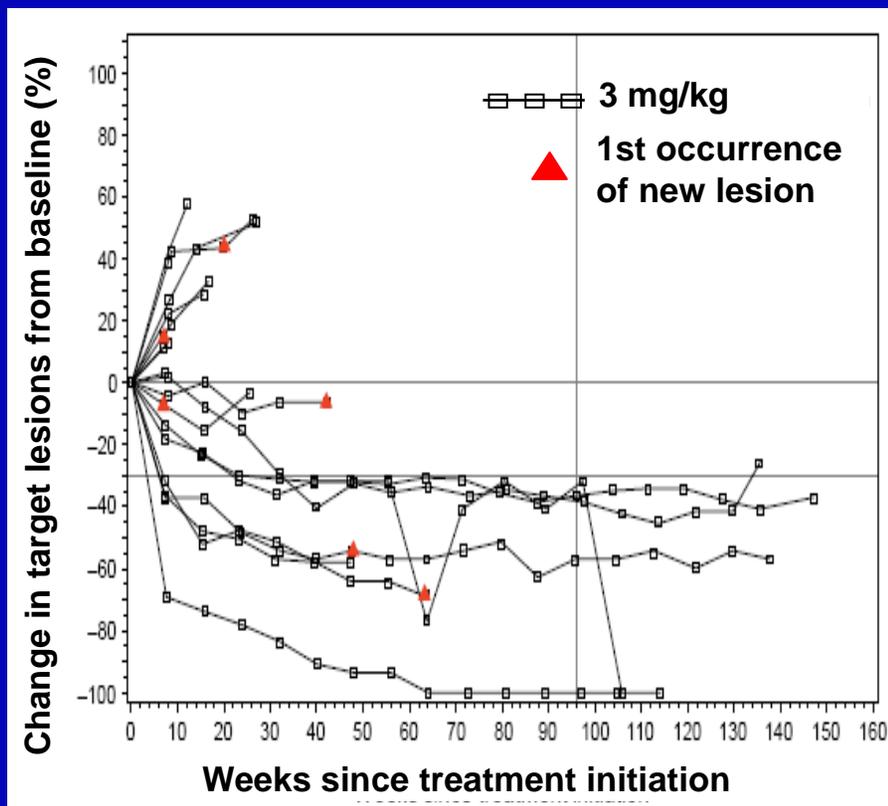
Ongoing = response or SD ongoing at the last evaluable tumor assessment (prior to alternate non-ipilimumab therapy) unless patient died.
 Slow steady decline is defined as a $\geq 25\%$ reduction from baseline in total tumor volume at the last evaluable tumor assessment, unless otherwise noted.

irRC Identifies Survivors in Patients with Progressive Disease by mWHO

Pooled data from phase II studies CA184-008 and CA184-022:
ipilimumab monotherapy 10 mg/kg (N=227)



Changes in Tumor Burden in Patients with Melanoma Receiving Nivolumab 3 mg/kg

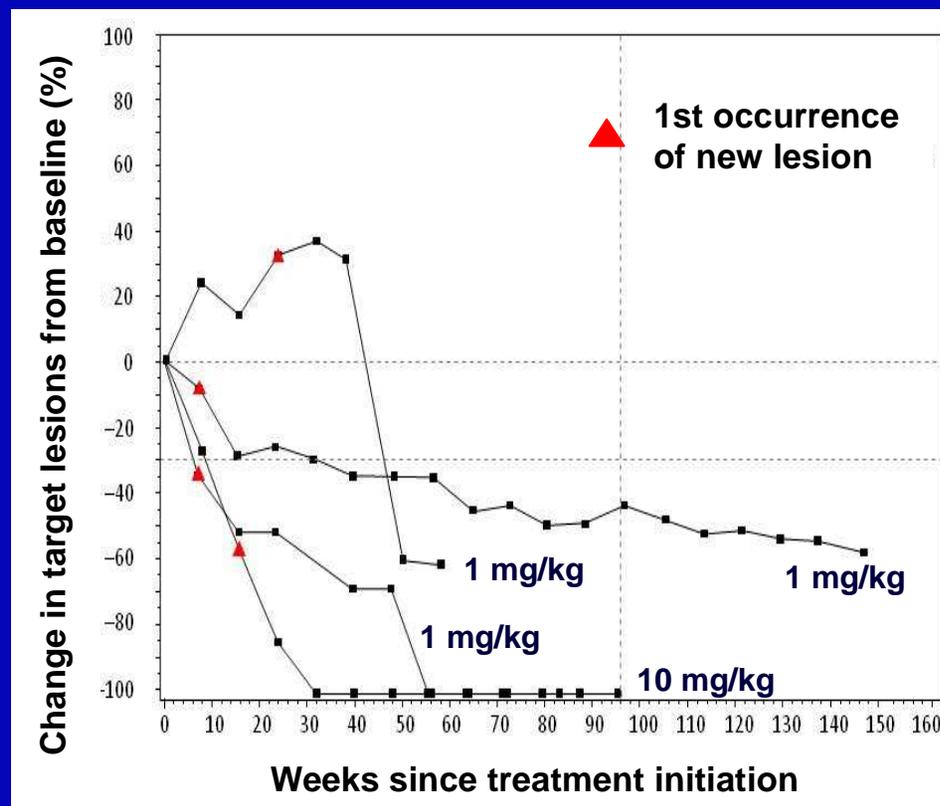


All Mel patients treated with 3 mg/kg nivolumab

Vertical line at 96 weeks = maximum duration of continuous nivolumab therapy

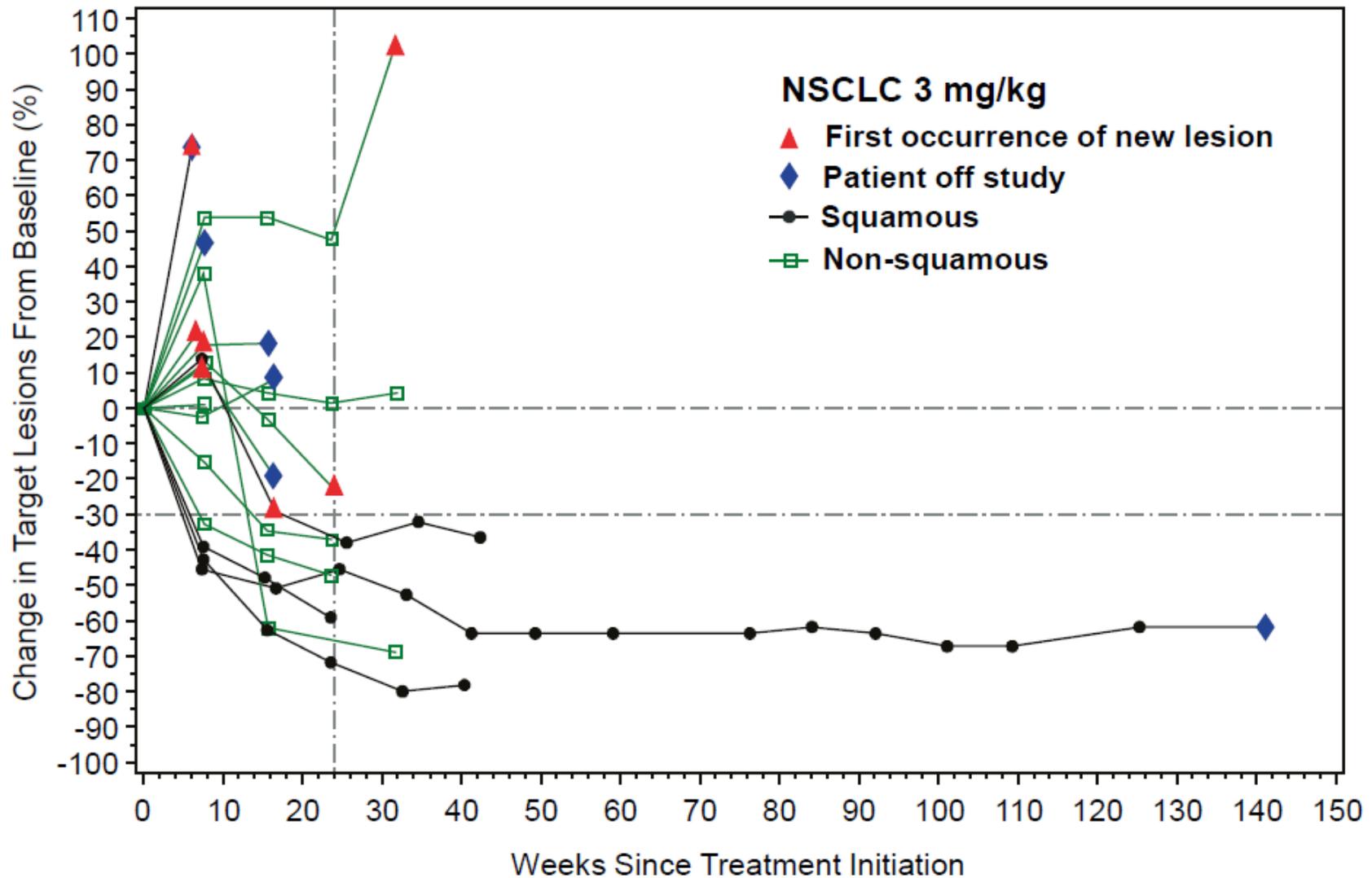
Horizontal line at -30% = threshold for defining objective response (partial tumor regression) in absence of new lesions or non-target disease according to RECIST

Unconventional response = response patterns that did not meet RECIST criteria (e.g., persistent reduction in target lesions in the presence of new lesions, or regression following initial progression)

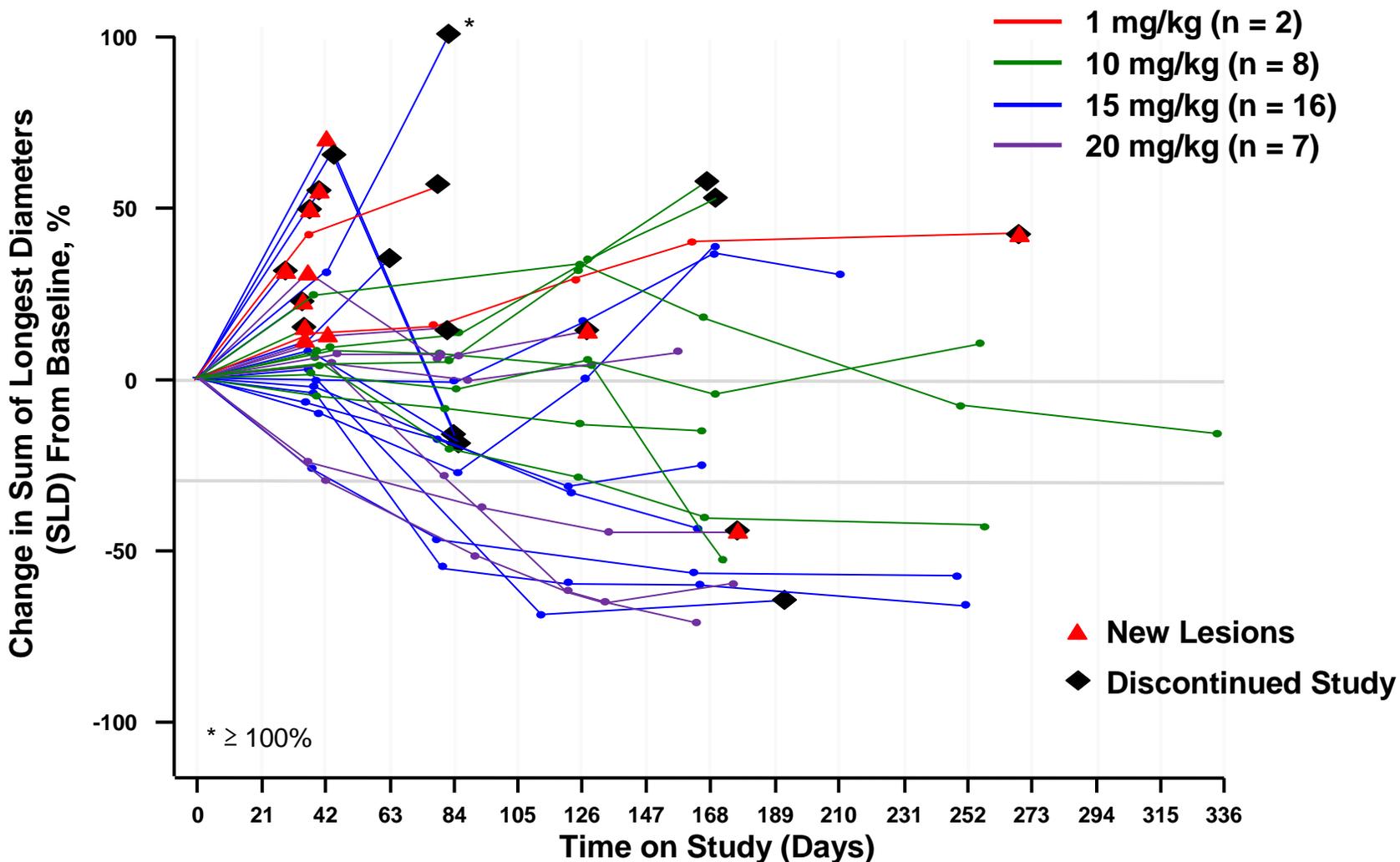


4 Mel patients treated with unconventional responses from nivolumab

Changes in Target Lesions Over Time in NSCLC Patients

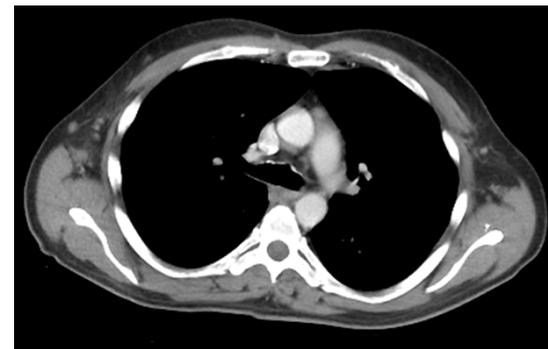
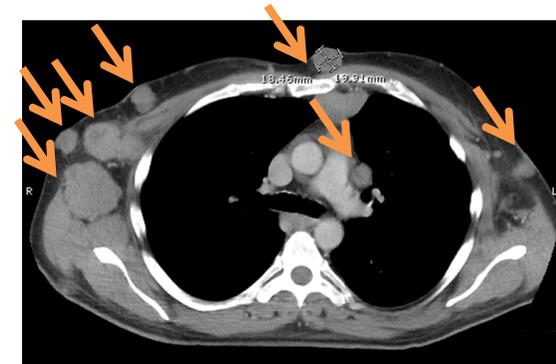
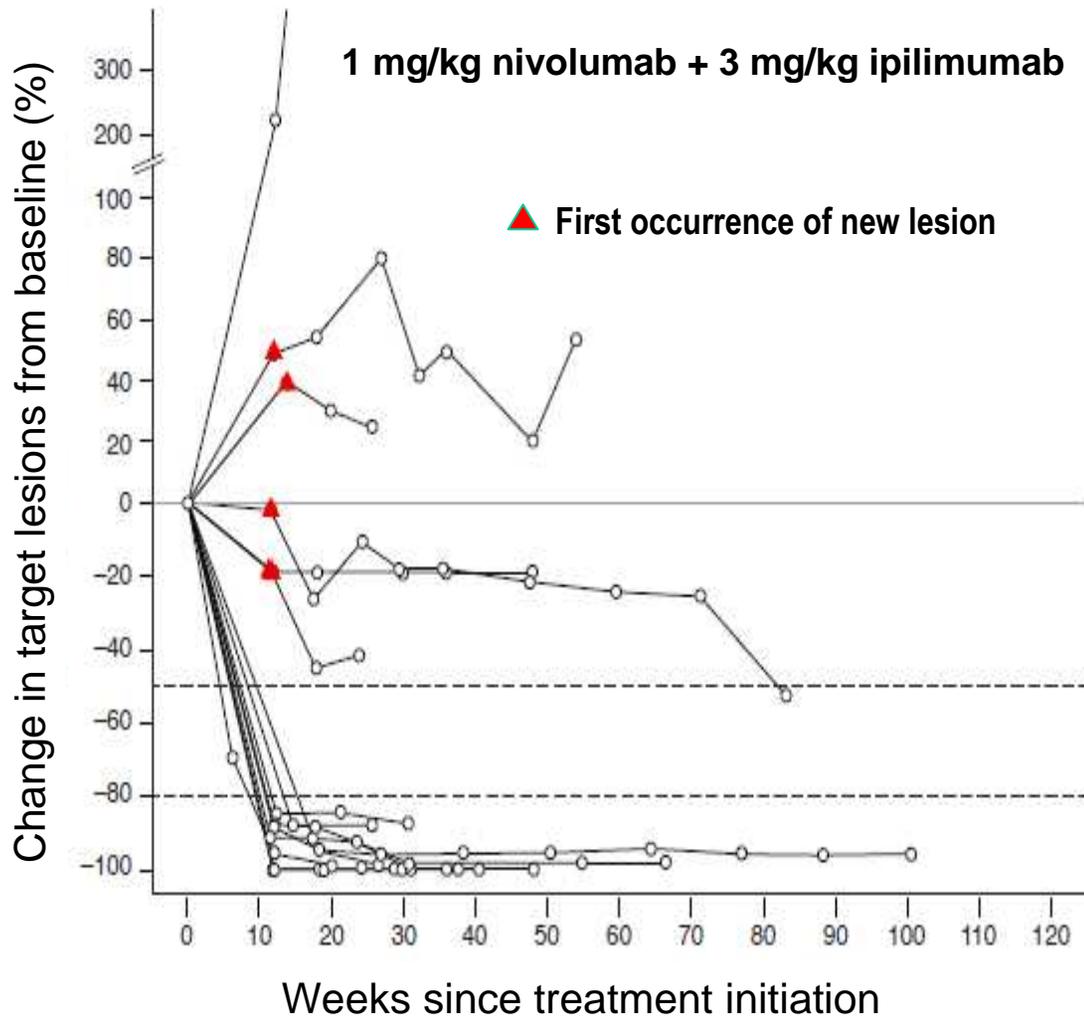


MPDL3280A Phase Ia: Tumor Burden Over Time (Melanoma)



Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012 with at least 1 post-baseline evaluable tumor assessment; data cutoff Feb 1, 2013.

Rapid and Durable Changes in Target Lesions



- A 52-year-old patient presented with extensive nodal and visceral disease
- Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting
- Within 4 wk, LDH normalized and symptoms resolved
- At 12 wk, there was marked reduction in all areas of disease as shown

Summary

- Responses to immunotherapy can have unconventional responses.
- Overall survival is 'gold standard' endpoint.
- Proposed immune related response criteria incorporate the unique biology of immunotherapy.