

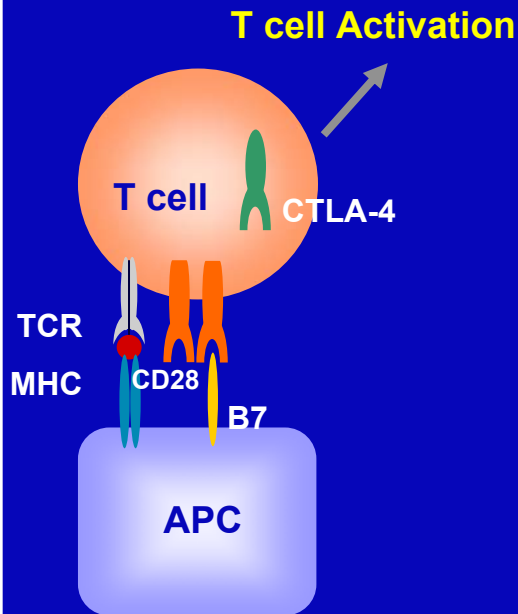
# Overall Survival and New Patterns of Response in Patients with Advanced Melanoma Treated with Ipilimumab

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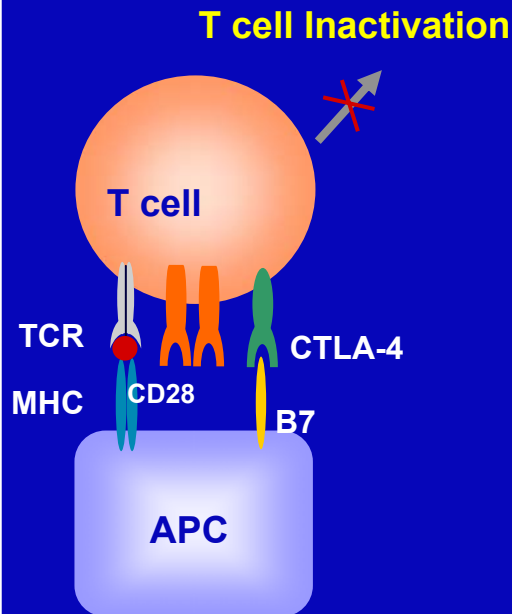
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# Ipilimumab is a Member of a Novel Class of Immunotherapeutic Antibodies

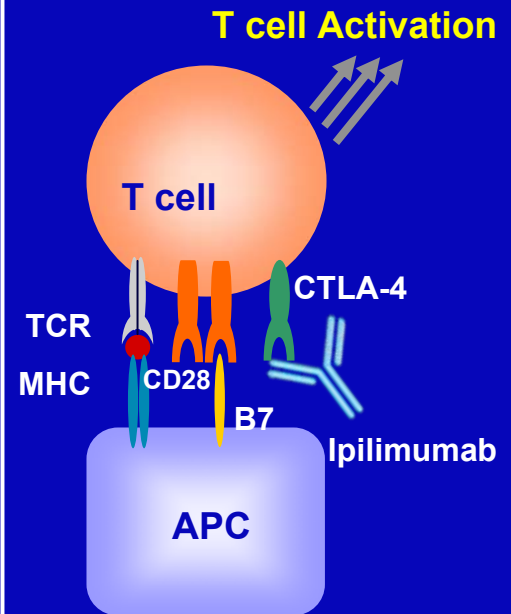
1. Co-stimulation via CD28 ligation transduces T cell activating signals



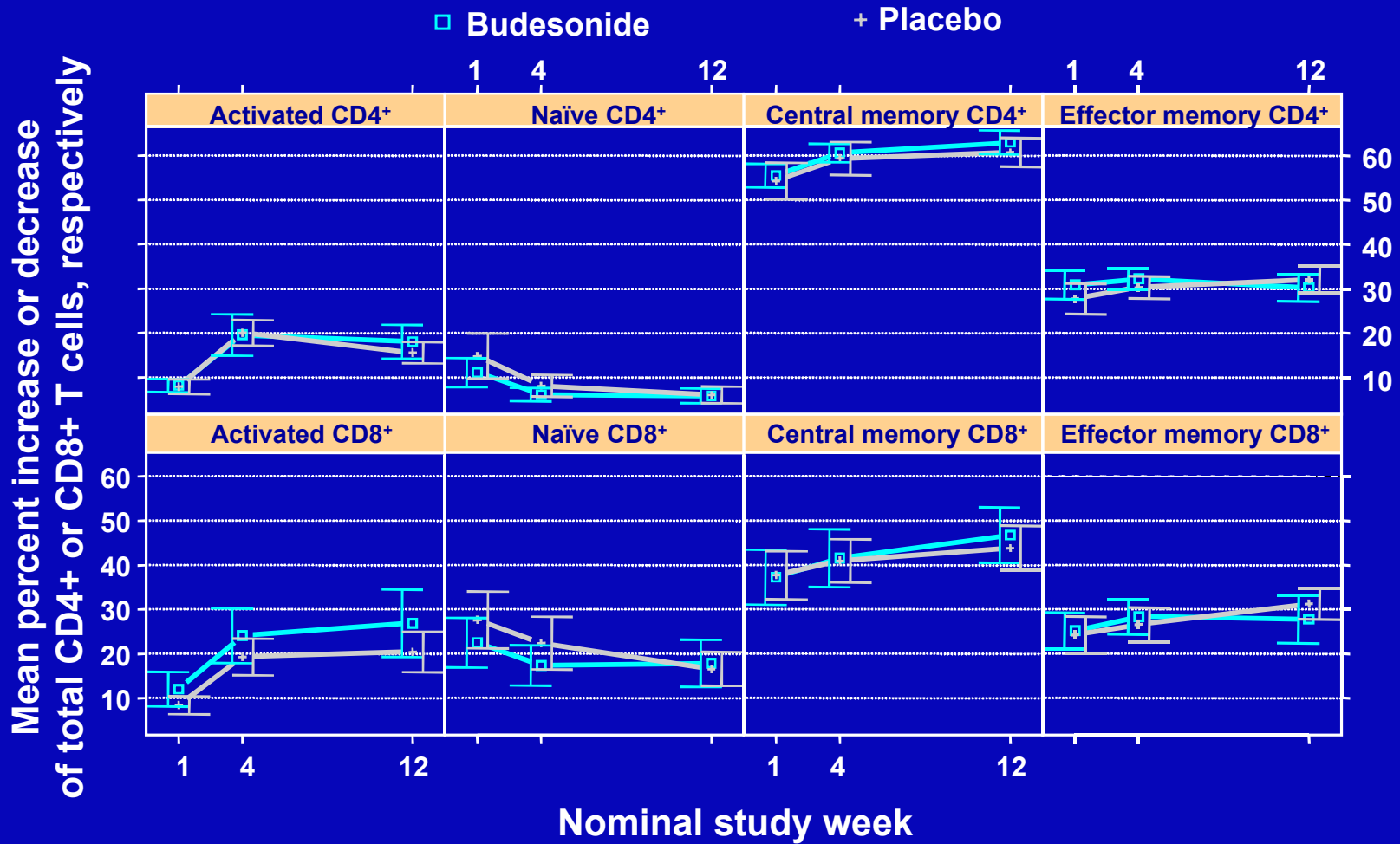
2. CTLA-4 ligation on activated T cells down-regulates T cell responses



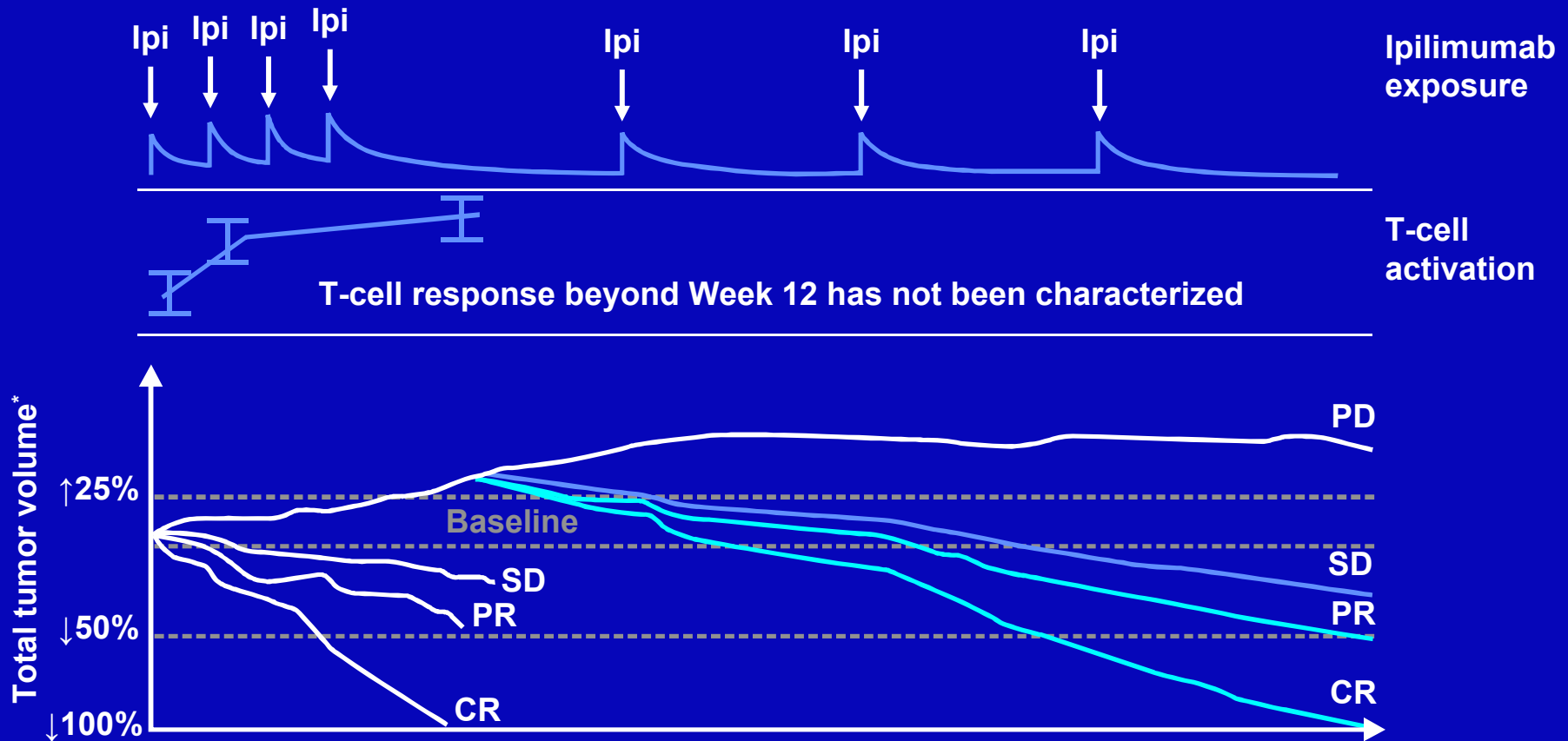
3. Blocking CTLA-4 ligation enhances T cell responses



# Immune Activation in Response to Ipilimumab Occurs by Week 4



# Time Course of Measurable Clinical Effect with Ipilimumab



Immune-cell activation and proliferation begins early

Measurable clinical effect occurs at variable time points

\*Tumor volume can include immune-cell infiltrates and tumor cells

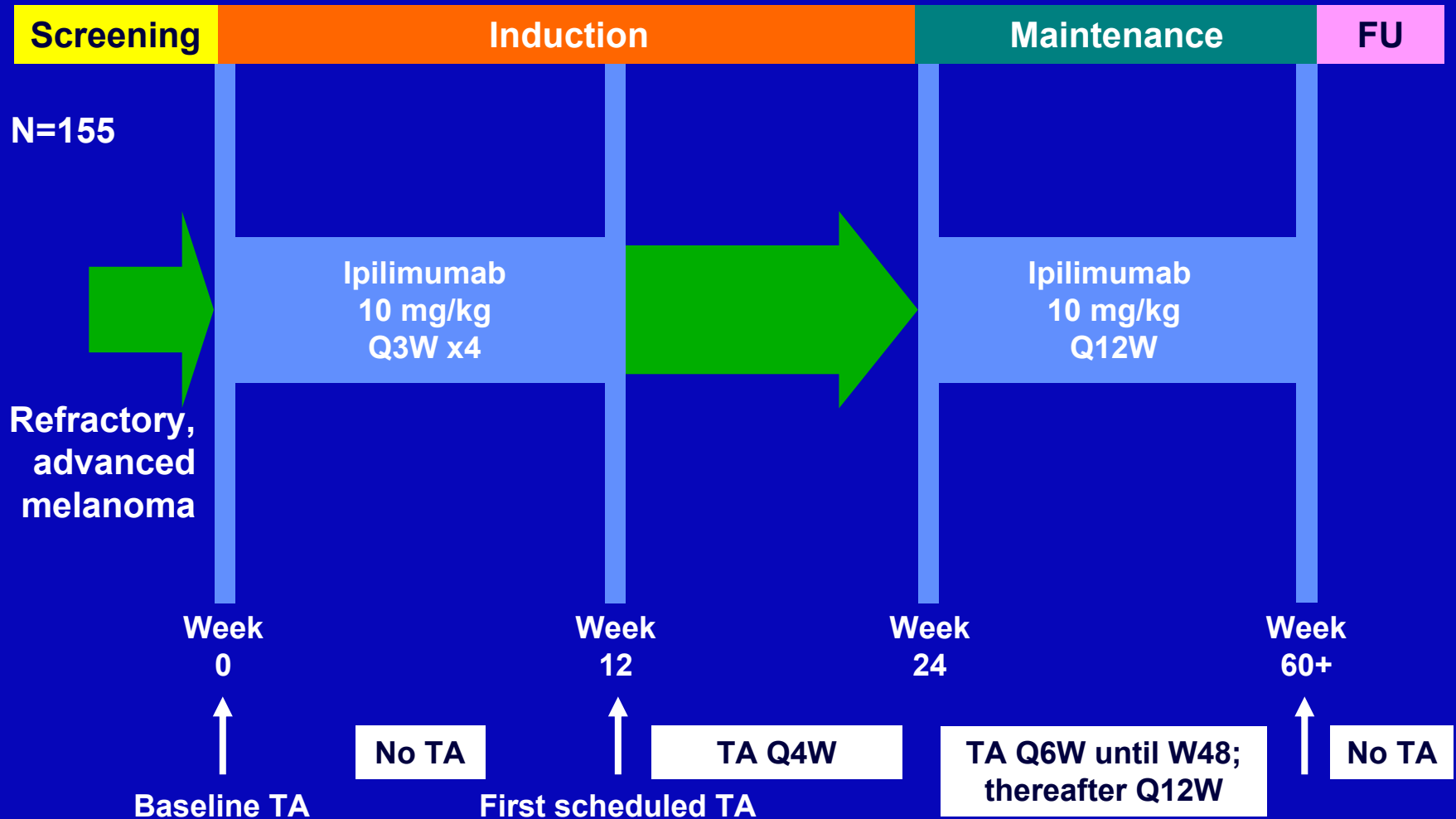
Adapted from Hodi FS, et al. *J Clin Oncol*. 2008;26(19S):3008

# Updated Response Criteria May be Valuable to Evaluate Immunotherapeutic Activity

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- **WHO and RECIST criteria limitations**
  - Evaluate activity of cytotoxic chemotherapeutic agents soon after the start of treatment
  - Consider the appearance of new lesions as ‘progression’ and drug failure

# CA184-008 Study Design



FU = follow-up; TA = tumor assessment

# Study Objectives

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- **Primary endpoint: best overall response rate per modified WHO (mWHO)**
- **Secondary endpoints included: OS and 1-year survival rate**
- **Conventional mWHO response criteria were used**
- **Also used: immune-related response criteria (irRC), modified from mWHO**
- **All patients were evaluated using both mWHO criteria and irRC**

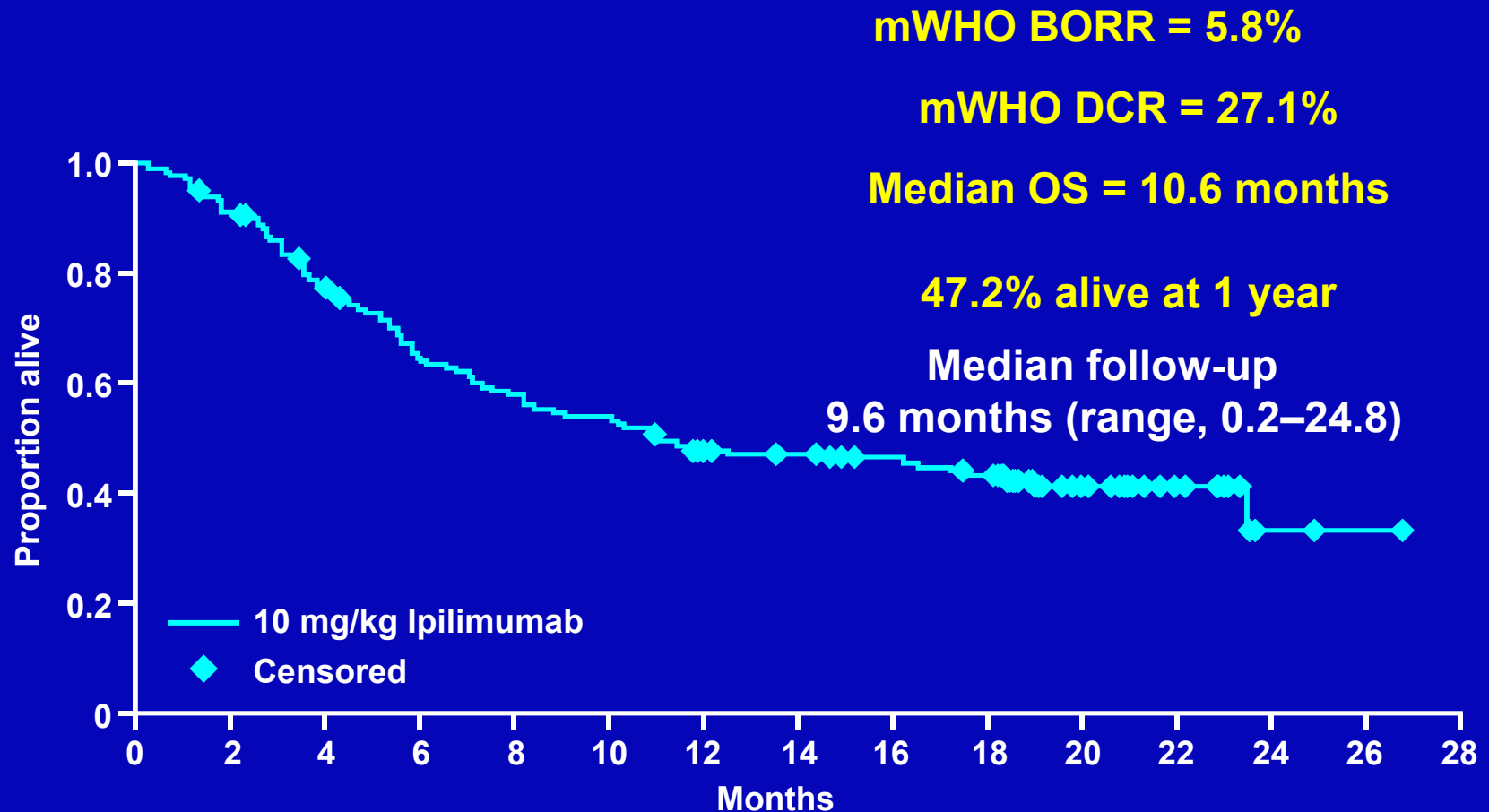
# Evolution of mWHO to irRC

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	CR	PR	SD	PD
mWHO	All lesions gone	SPD of <b>index lesions</b> decreases $\geq 50\%$ from baseline  <b>new lesions <u>not</u> allowed</b>	SPD of <b>index lesions</b> neither CR, PR or PD;  <b>new lesions <u>not</u> allowed</b>	SPD of <b>index lesions</b> increases $\geq 25\%$ from nadir &/OR  <b>Unequivocal progression of non-index lesions and/or new lesions</b>
irRC	All lesions gone	SPD of <b>index + any new lesions</b> decreases $\geq 50\%$ from baseline  <b>new lesions allowed</b>	SPD of <b>index + any new lesions</b> neither irCR, irPR nor irPD  <b>new lesions allowed</b>	SPD of <b>index + any new lesions</b> increases $\geq 25\%$ from nadir  <b>PD per irRC is based on SPD only</b>

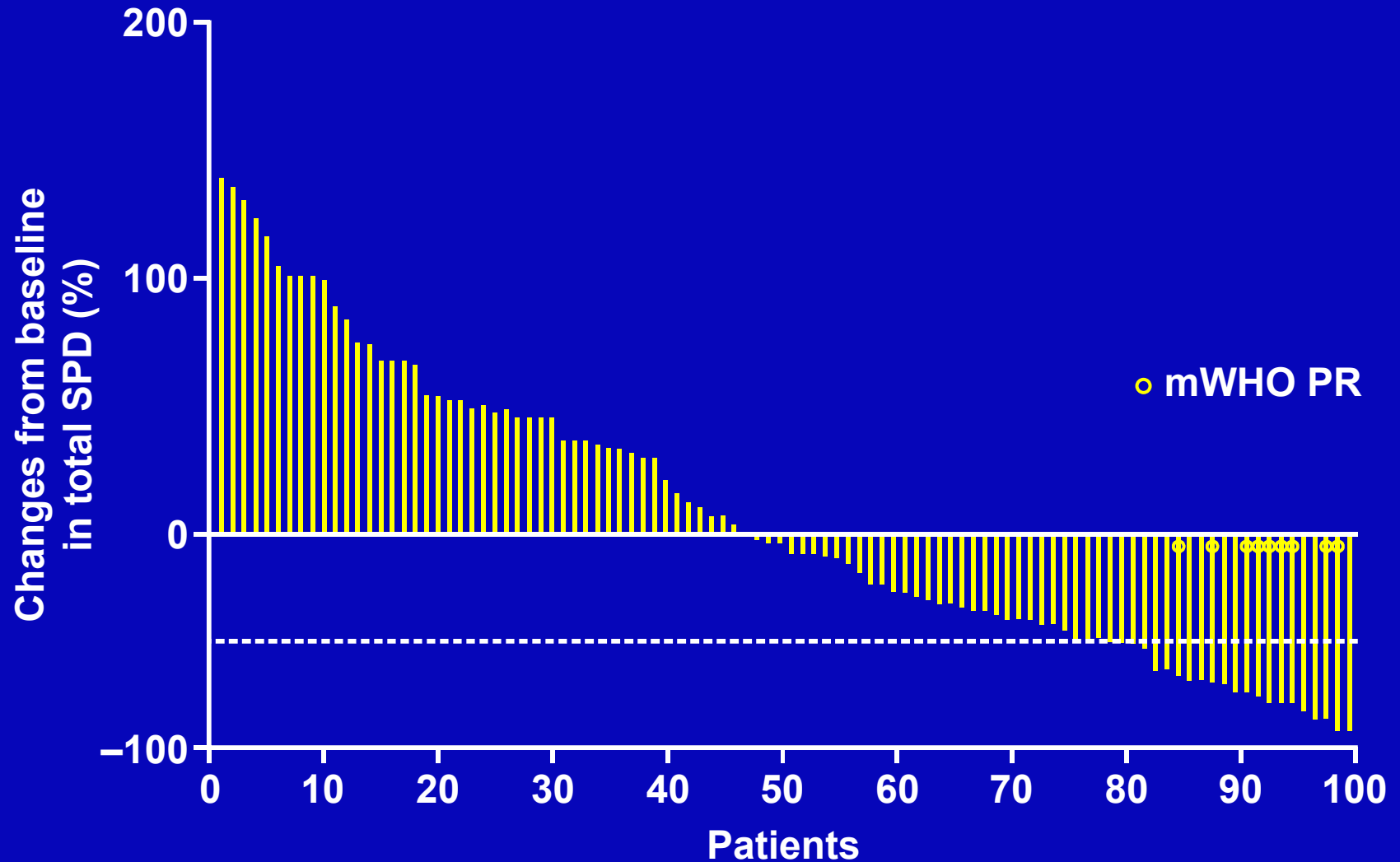
mWHO= modified World Health Organization; irRC = immune-related response criteria;  
SPD = sum of the perpendicular diameters

# Objective Response and Prolonged Survival are Observed with Ipilimumab



Number of deaths/number of patients: 87/155  
(Data as of cut-off date: June 2008)

# Reduction from Baseline in Total Tumor Volume (index + new lesions)



SPD = sum of the perpendicular diameters

# Consistent DCR and Survival Benefit of Ipilimumab 10 mg/kg Across Studies

	Study 008 <sup>1</sup>	Study 022 <sup>2</sup>	Study 007 <sup>3</sup>
<b>BORR by IRC, %</b>	<b>6</b>	<b>11</b>	<b>16</b>
<b>DCR by IRC, %</b>	<b>27</b>	<b>29</b>	<b>35</b>
<b>Median OS, mo</b>	<b>10.6</b>	<b>11.0</b>	<b>17.2</b>
<b>Alive at 1 year, %</b>	<b>47</b>	<b>48</b>	<b>62</b>

IRC, independent review committee.

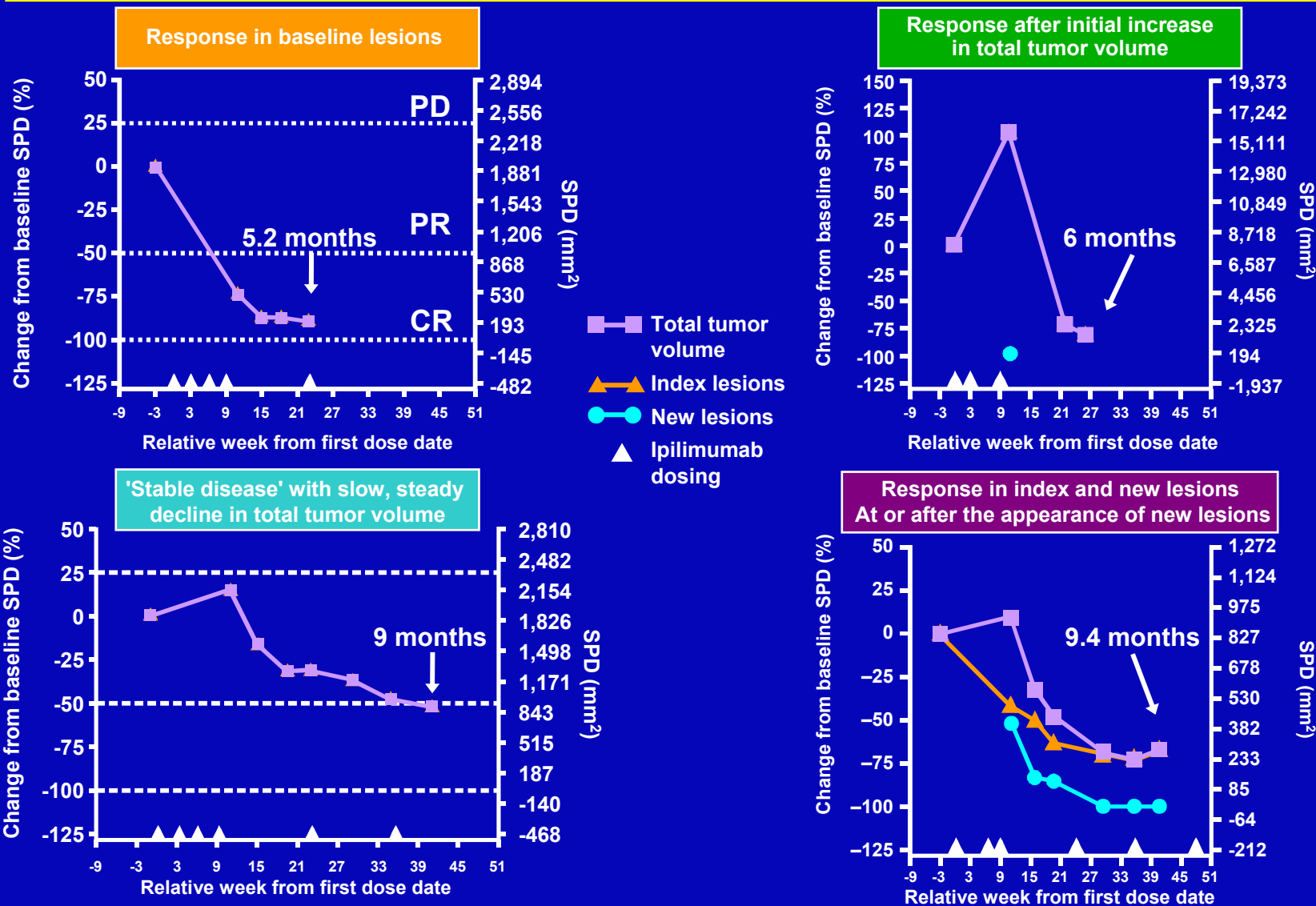
1. O'Day S et al. ASCO 2008. Abstract 9021. Updated from poster presentation. 2. Hamid O et al. ASCO 2008. Abstract 9025. Updated from poster presentation. 3. Weber JS et al. ASCO 2008. Abstract 9010. Updated from oral presentation.

# Four Patterns of Response to Ipilimumab Therapy were Observed

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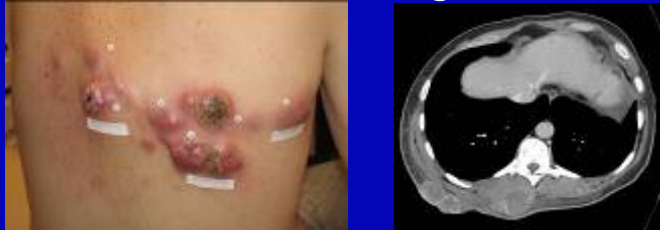
- **2 Conventional Responses:**
  - Response in baseline lesions
  - ‘Stable disease’ with slow, steady decline in total tumor volume
- **2 Novel Responses:**
  - Response after initial increase in total tumor volume
  - Response in index plus new lesions at or after the appearance of new lesions

# Examples of Response Patterns



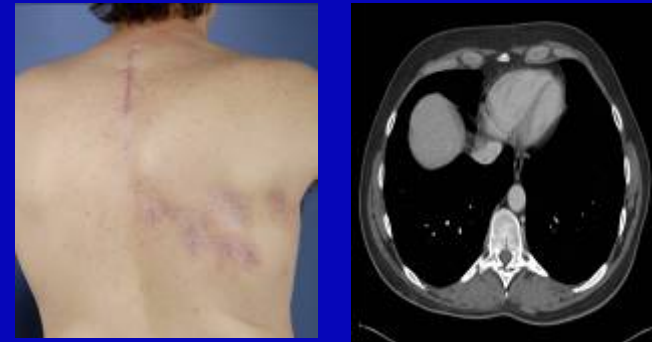
# Long-Term Survival in a Melanoma Patient with Skin and Lung Disease

Screening



Week 72

Durable & ongoing response without signs of irAEs

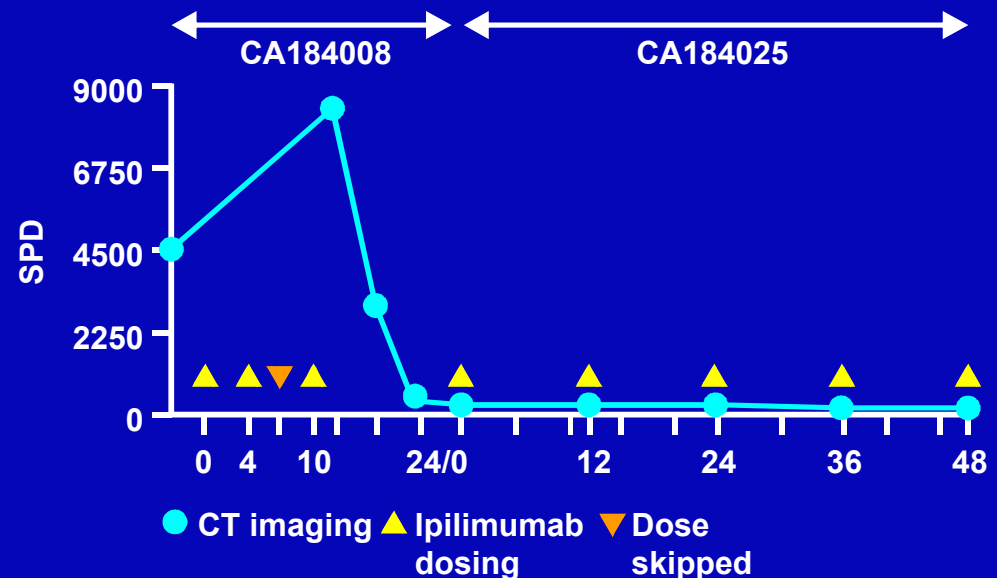


Week 12

Initial increase in total tumour burden (mWHO PD)



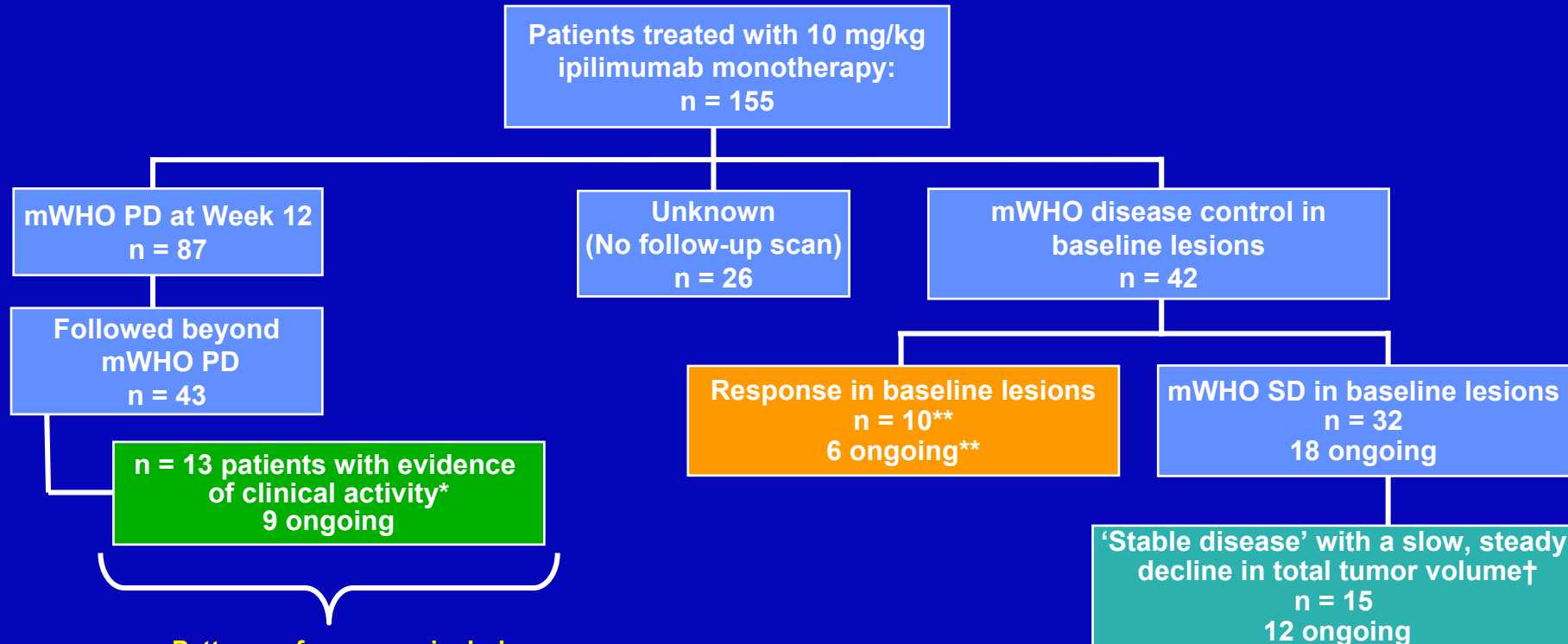
Week 16  
Responding



Courtesy of Kaan Harmankaya

SPD = Sum of the Product of the perpendicular Diameters (a measure of tumor volume)

# Four Patterns of Response to Ipilimumab



**Patterns of response include:**  
 Response in baseline lesions

'Stable disease' with a slow, steady decline in total tumor volume†

Response after initial increase in total tumor volume

Response in index + new lesions after the appearance of new lesions

Ongoing = response or SD ongoing at the last evaluable tumor assessment (prior to alternate non-ipilimumab therapy) unless patient died.

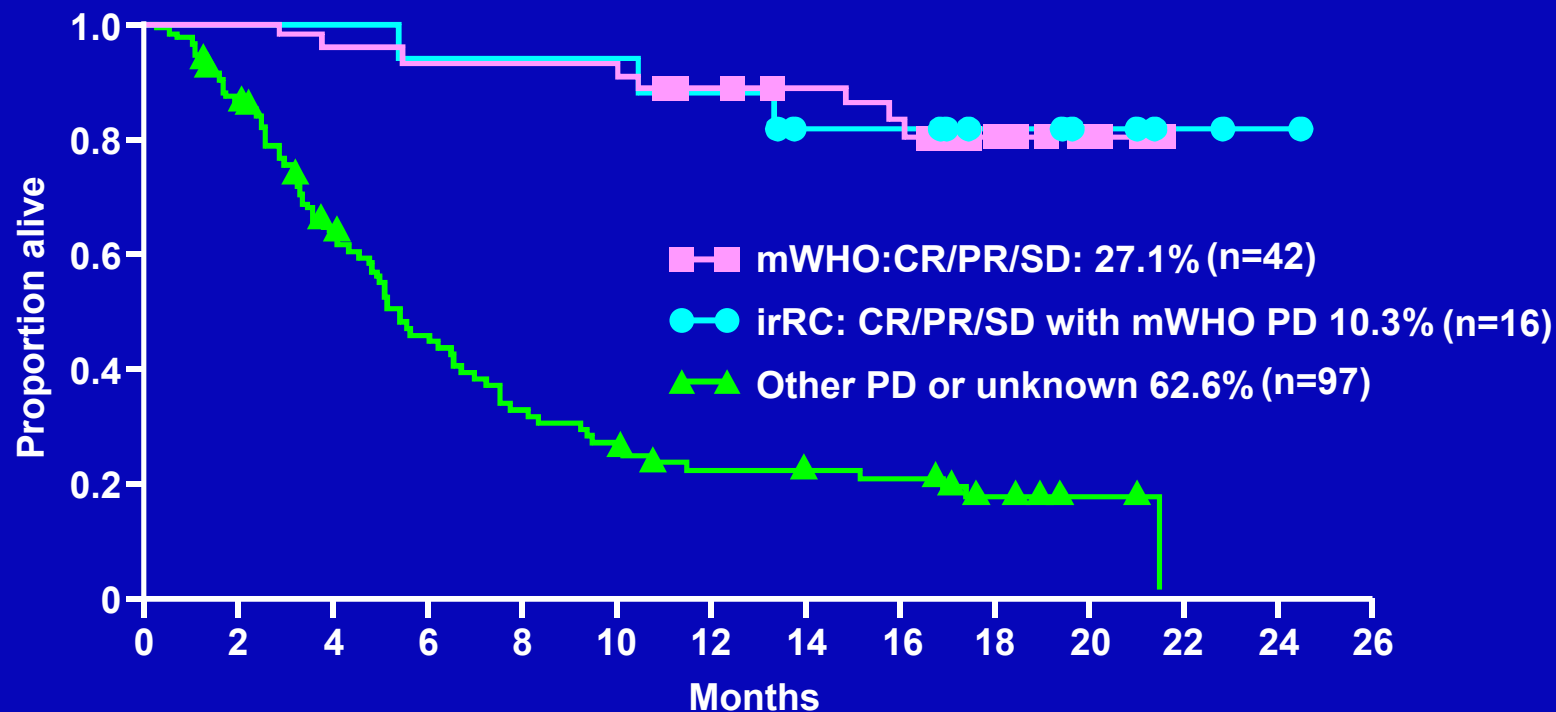
Slow steady decline is defined as a  $\geq 25\%$  reduction from baseline in total tumor volume at the last evaluable tumor assessment, unless otherwise noted.

\*12 with and 1 without follow-up beyond mWHO PD

†1 decline with intermittent progression

\*\*Including 1 patient with confirmation of response in roll-over study CA184-025

# OS of mWHO Response/SD Compared with mWHO Progressors Classified as Response/SD by the irRC in Study CA184-008



Group	# of deaths/# of patients	Median (95% CI)
BOR=CR/PR/SD	8/42	—
BOR=PD and irBOR=irPR/irSD	3/16	—
Other PD or Unknown	76/97	5.2 (4.3–6.6)

# Conclusions

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- **Despite Modest ORR (5-15%), DCR of 30% and late durable responses after PD (10%) are encouraging leading to impressive 1 year OS rates of 50%. Longer follow up suggests plateau of OS curve between 30-40%.**
- **WHO and RECIST are not optimal surrogates of drug failure in patients with advanced melanoma on ipilimumab. Immune Response Criteria (irRC) more comprehensively captures overall clinical benefit.**
- **Long-term survival follow-up is ongoing**
  - **A planned OS analysis to be performed in December 2008 (up to 30 month follow up)**
- **Prospective use of the irRC in ipilimumab studies is ongoing**
  - **The exploration of the irRC in studies with other immunotherapies is warranted**

# Acknowledgments

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- Editorial and writing assistance provided by Gardiner-Caldwell US, funded by Bristol-Myers Squibb