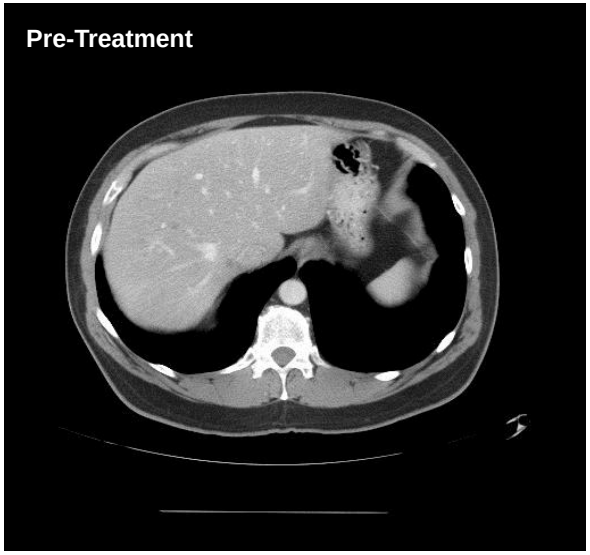
Monday, 29 September 2014, 14:30 - 14:45
Patient cases “Immunotherapy in clinical practice”

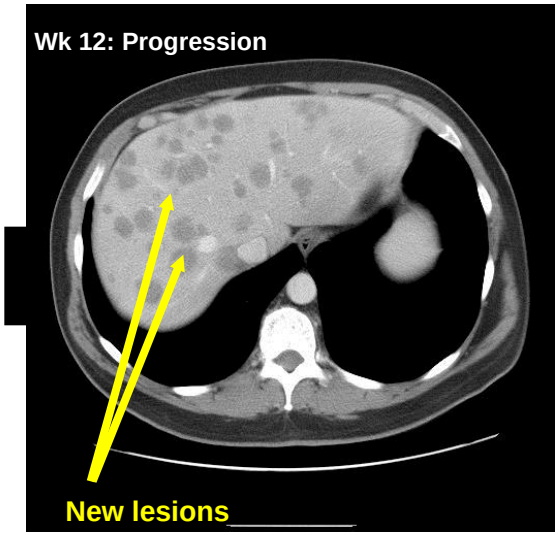
Challenges in the assessment of response to cancer immunotherapy

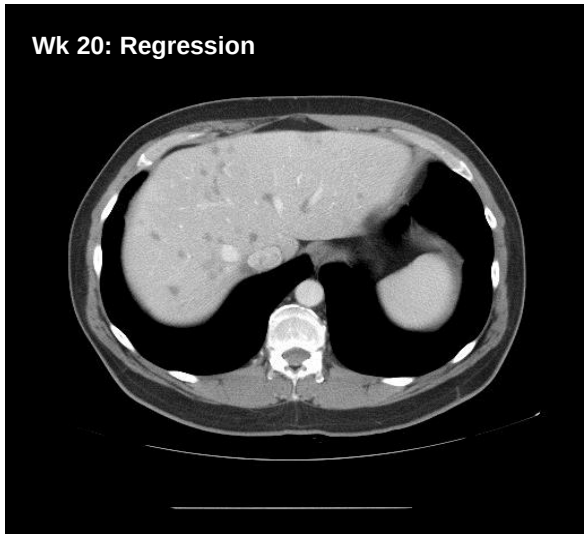
Antoni Ribas, M.D., Ph.D.
Professor of Medicine
Professor of Surgery
Professor of Molecular and Medical Pharmacology
Director, Tumor Immunology Program,
Jonsson Comprehensive Cancer Center (JCCC)
University of California Los Angeles (UCLA)
Chair, Melanoma Committee at SWOG

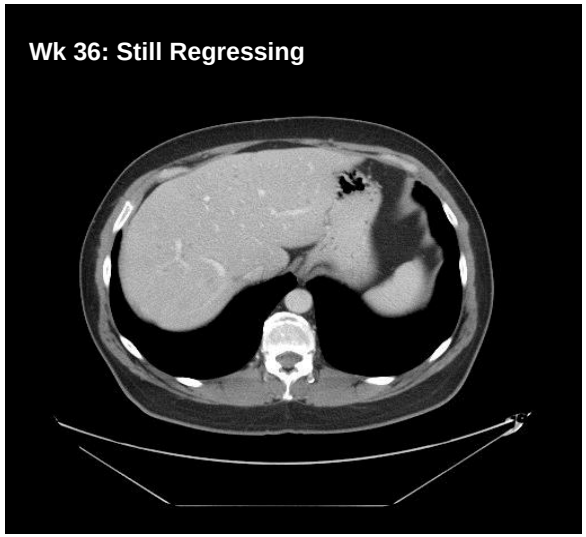
The Wolchok Case: Ipilimumab Responses After the Appearance and Subsequent Disappearance of New Lesions



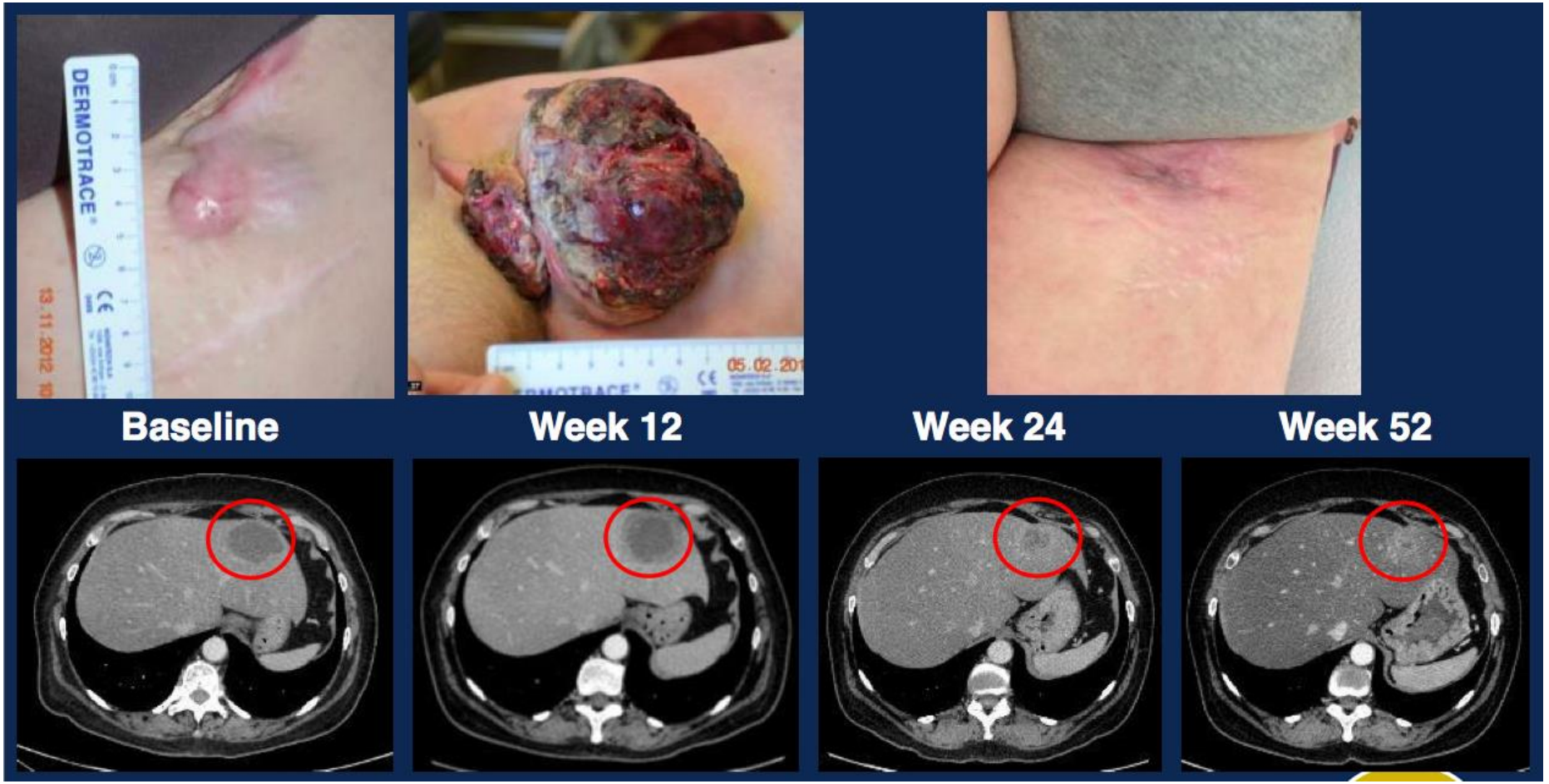
3 mg/kg
Ipilimumab
q3wks X 4







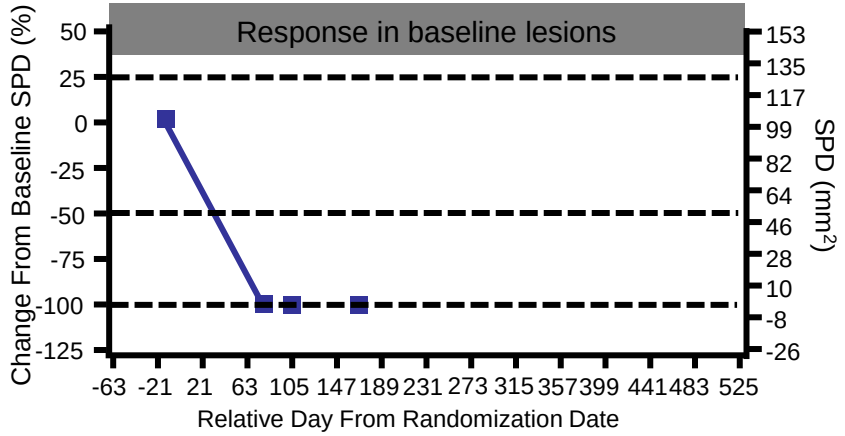
The Robert Case: Early pseudoprogression with pembrolizumab – response after initial progression

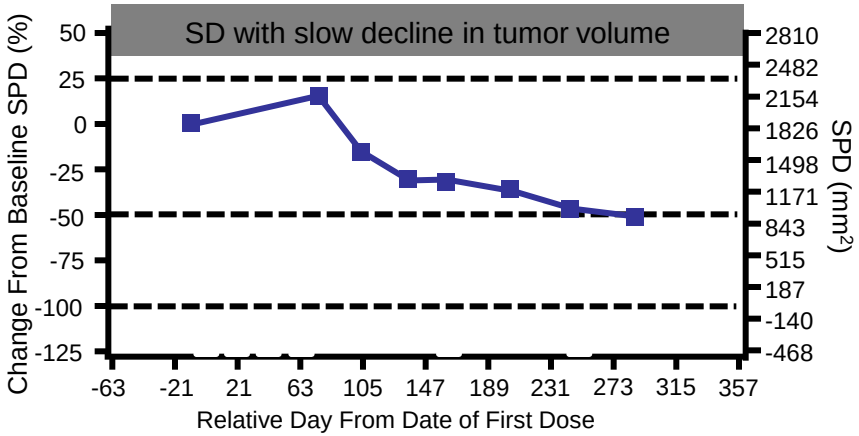


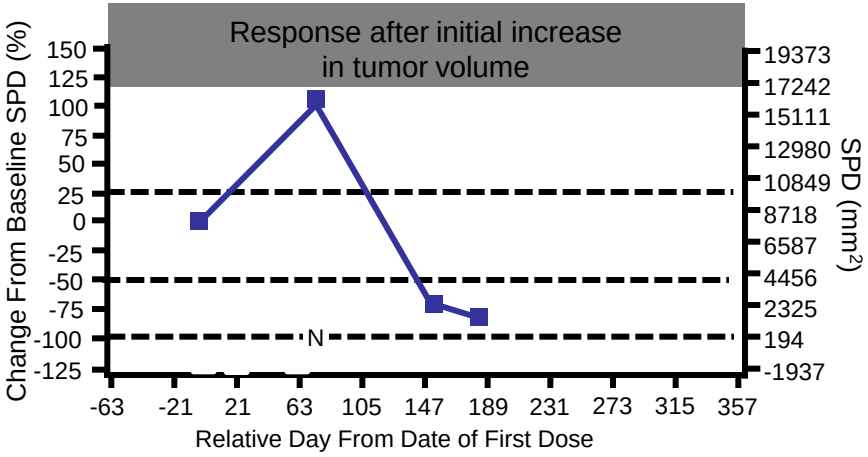
Case courtesy of Caroline Robert, Gustave Roussy, Villejuif

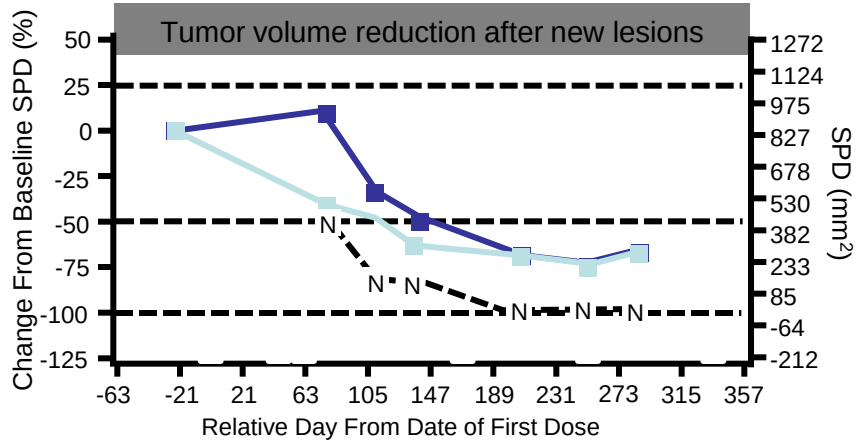
Ipilimumab Heterogeneous Response Patterns

- 4 distinct response patterns associated with favorable OS



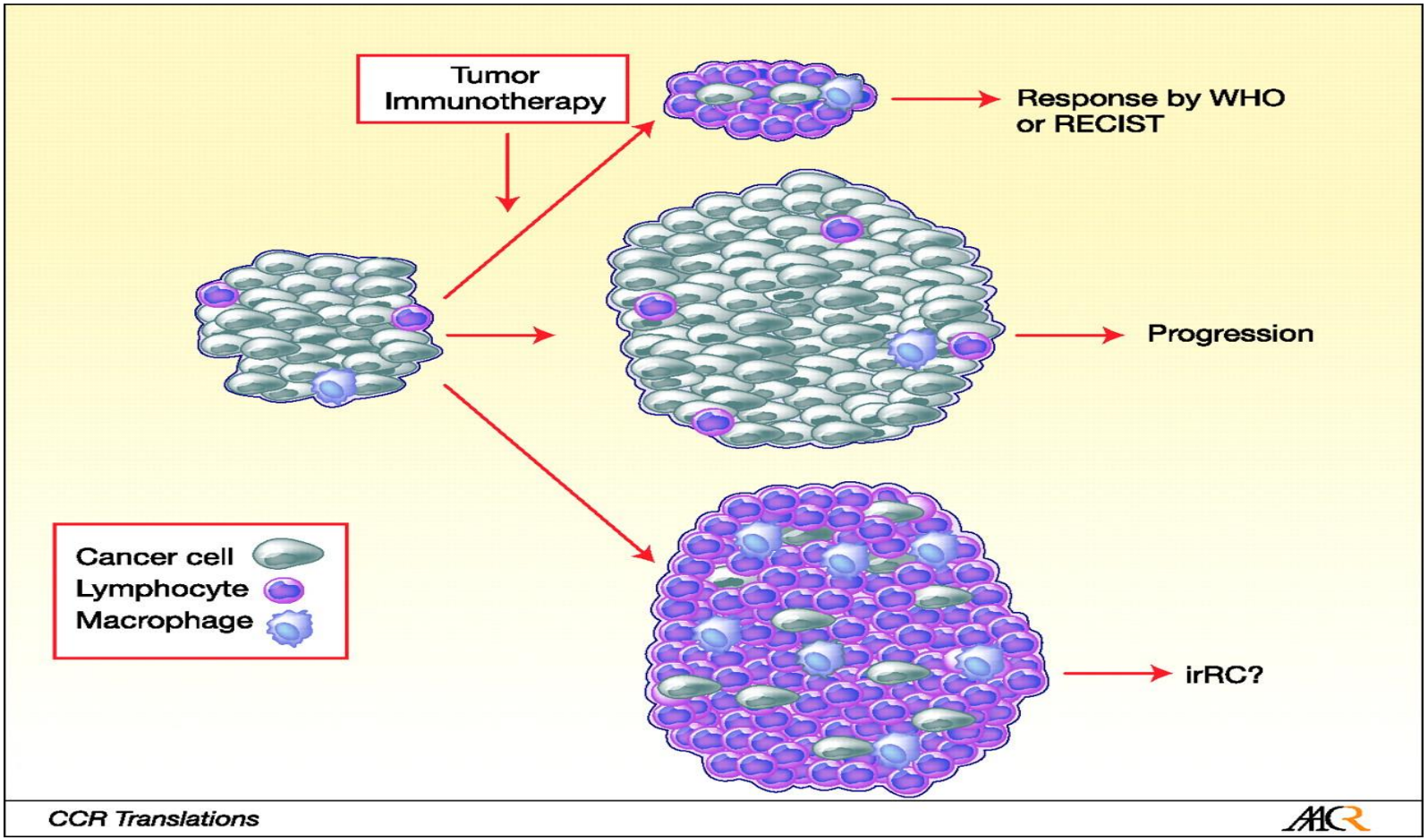






Wolchok JD, et al. Clin Cancer Res. 2009;15:7412-7420.
Schadendorf D, et al. *Ann Oncol*. 2009;20 Suppl 6:vi41-50;

Immune-Related Response Criteria: Rationale



CR=complete response; irRC=immune-related response criteria; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; WHO=World Health Organization.

Defining Response: RECIST v1.1 vs irRC

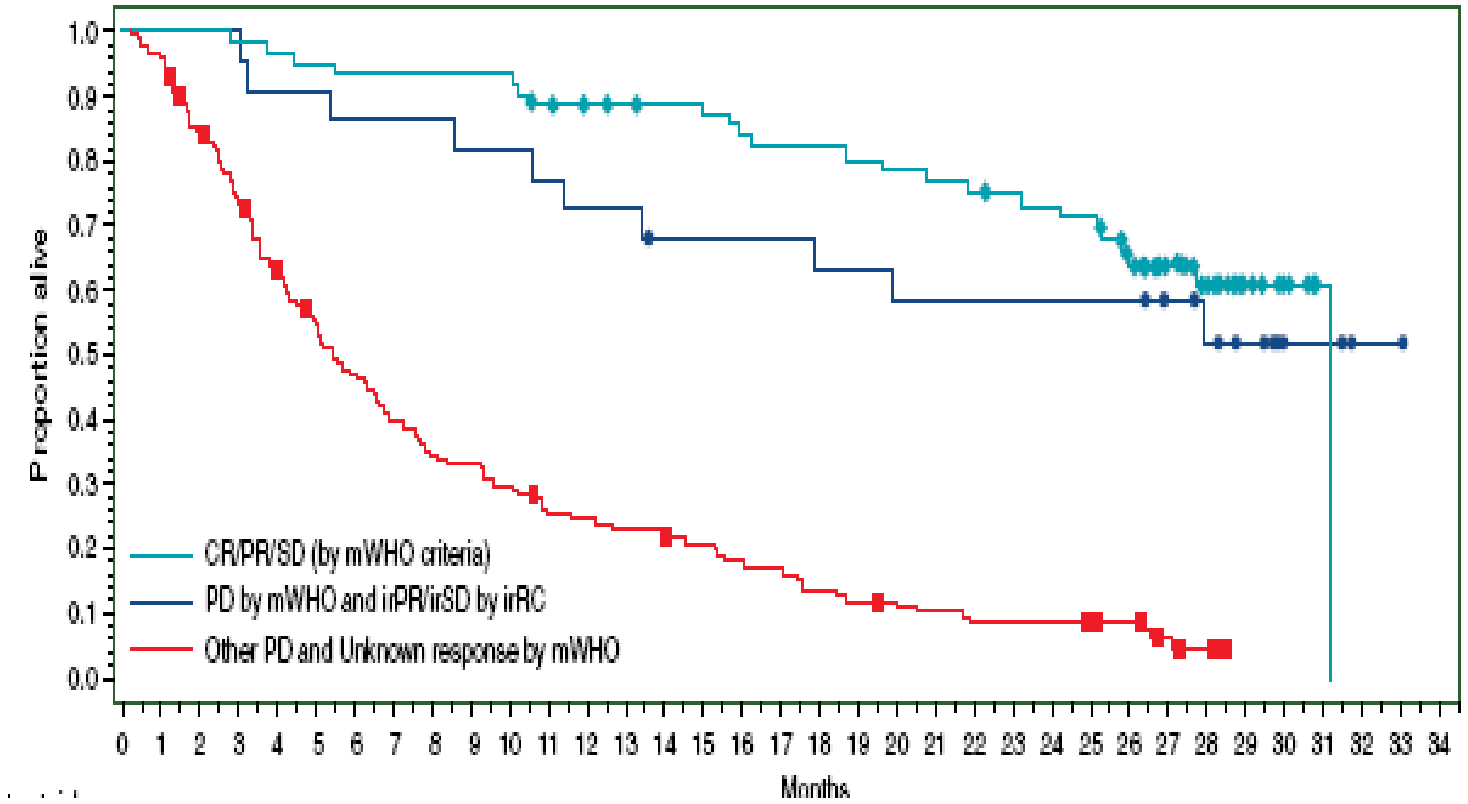
Category	RECIST v1.1[1]	irRC[2] (immune-related response criteria)
Measurement of tumor burden	• Unidimensional	• Bidimensional
Complete response (CR)	• Disappearance of all target and non-target lesions • Nodes must regress to <10 mm short axis • No new lesions • Confirmation required	
Partial response (PR)	• ≥30% decrease in tumor burden compared with baseline • Confirmation required	• ≥50% decrease in tumor burden compared with baseline[a] • Confirmation required
Progressive disease (PD)	• ≥20% + 5 mm absolute increase in tumor burden compared with nadir • Appearance of new lesions or progression of non target	• ≥25% increase in tumor burden compared with baseline, nadir, or "reset" baseline[a] • New lesions added to tumor burden • Confirmation required
Stable disease (SD)	• Neither PR nor PD	

Hodi et al, ASCO 2014, abstract 3006

Problems with irRC

- Low incidence of “pseudoprogresion” followed by response: <5%?
- Retrospective selection of patients who do well plotted against patients who don’t do well is likely to give impressive KM plots
- Plotting responses based on multiplying bidimensional measurements vs unidimensional measurements will result in different spider plots and waterfalls

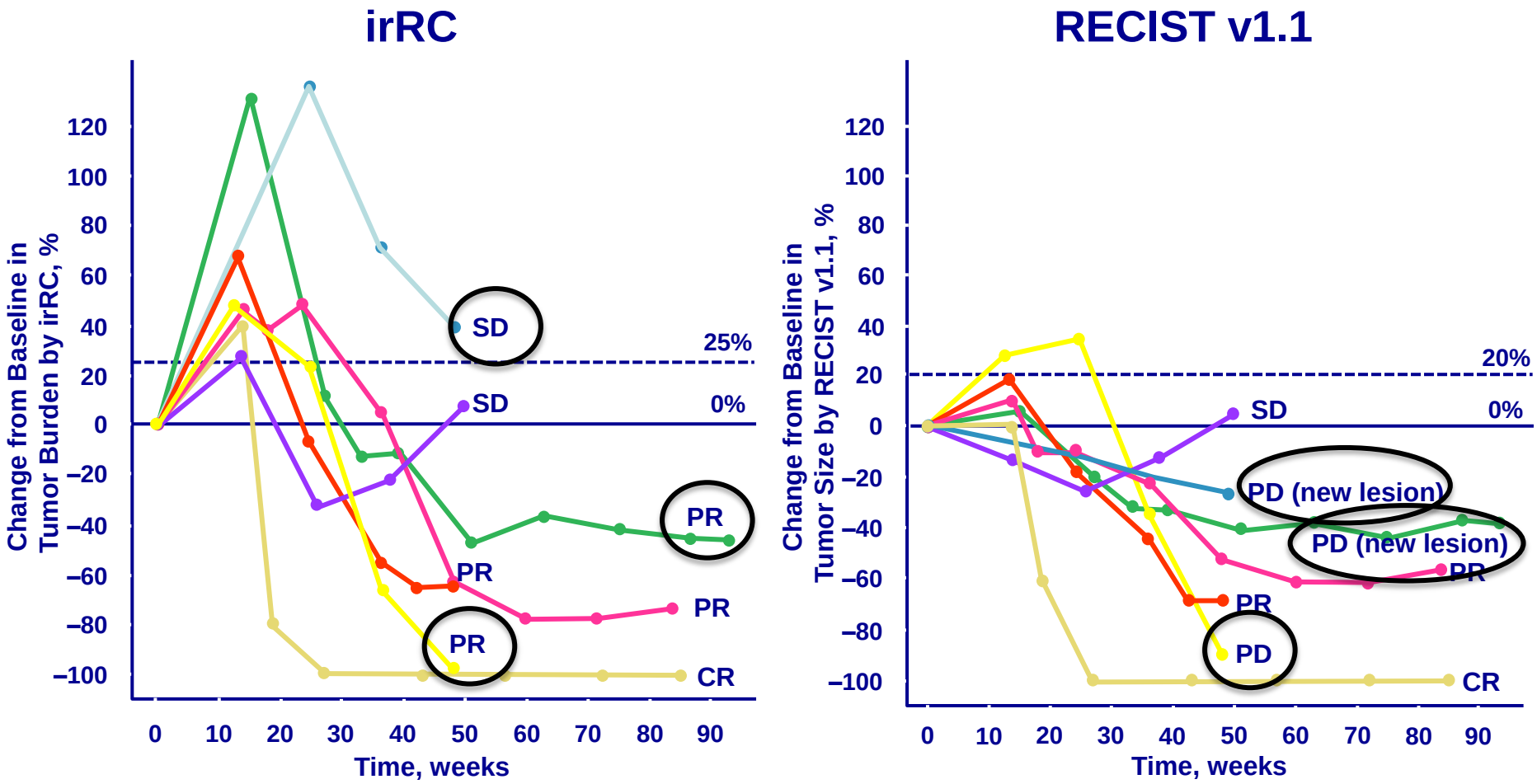
irRC Identifies Survivors in Patients With Progressive Disease by mWHO



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

mWHO = modified World Health Oncology criteria.
Wolchok et al, 2009.

Early pseudoprogression observed with pembrolizumab

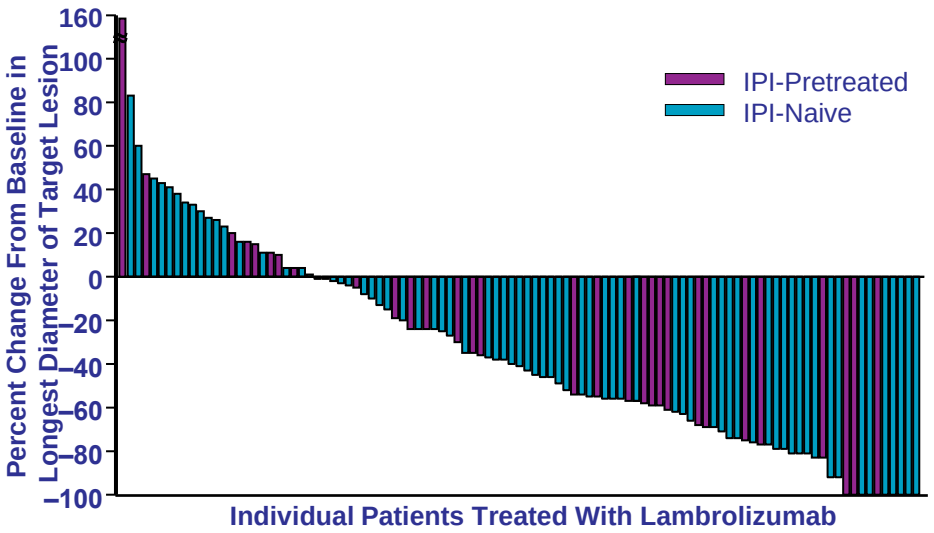


7 of 192 patients (3.6%) showed ≥25% increase of tumor burden at week 12 that was not confirmed as irRC PD at the next assessment

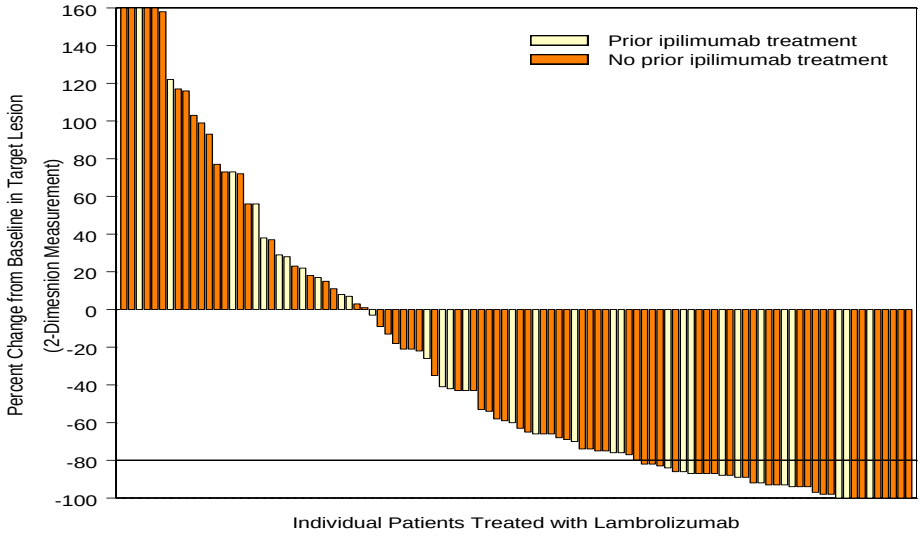
Hodi et al, ASCO 2014, abstract 3006

Differences of a waterfall by RECIST or WHO: Data with pembrolizumab

RECIST



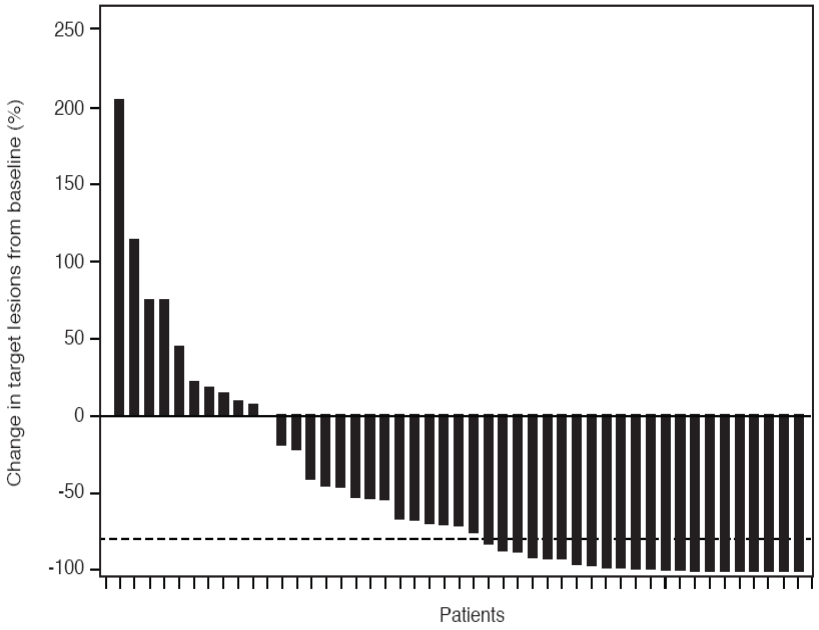
WHO



Modified from Ribas *et al*. ASCO 2013

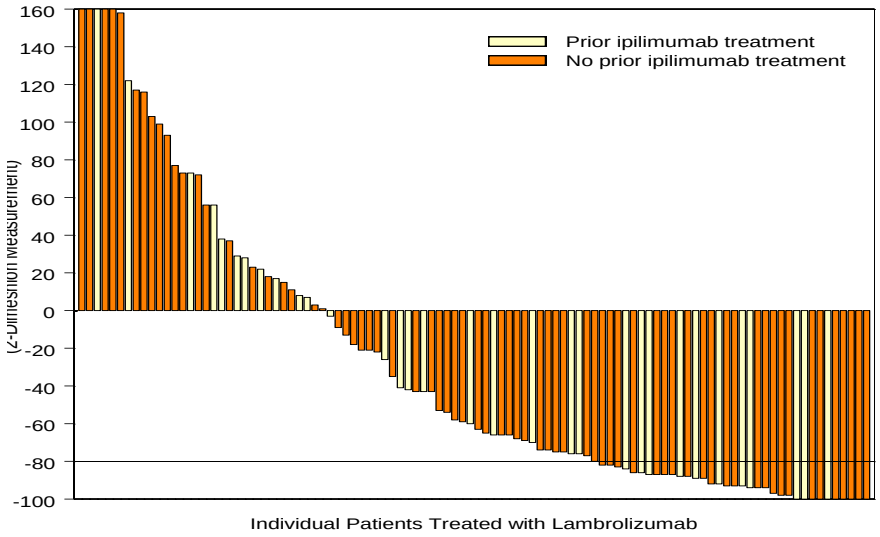
WHO waterfalls with combination nivolumab + ipilimumab or single agent pembrolizumab

Nivolumab + Ipilimumab



Change from baseline using WHO measurements

MK-3475



The “depth of the response” is in part an artifact of how the data is presented when using WHO (bidimensional measurements) in a waterfall plot

Modified from Wolchok *et al*. and Ribas *et al*. ASCO 2013

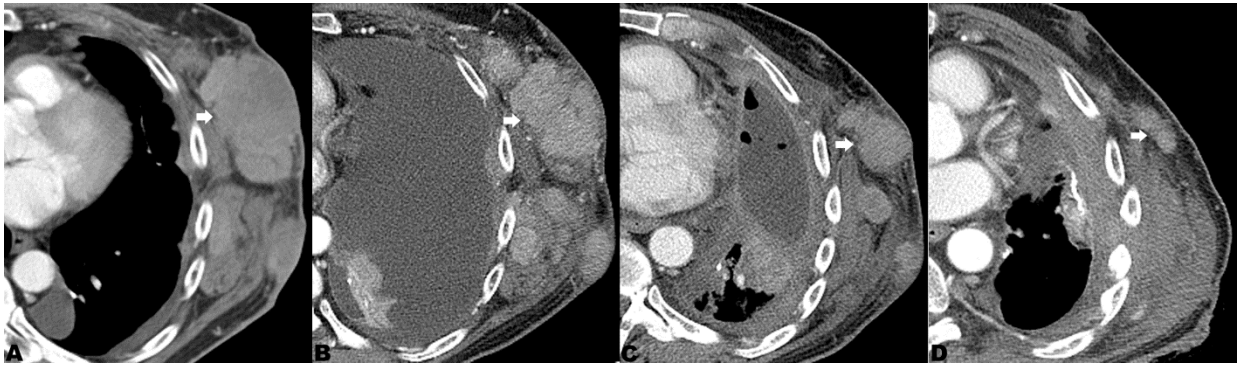
Central review RECIST 1.1 vs Investigator-assessed irRC

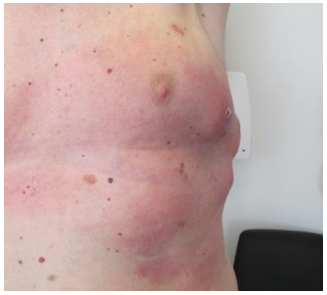
Pembrolizumab phase 1 expansion

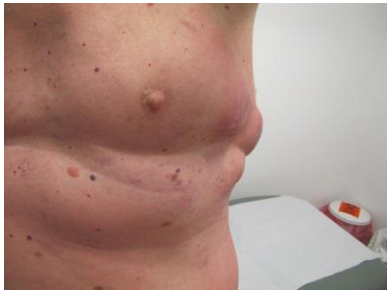
	N	CR, %	ORR, % (95% CI)		N	CR, %	ORR, % (95% CI)
RECIST v1.1[a]				**irRC[b]**			
IPI-N	**168**	**8**	**40 (32-48)**	**IPI-N**	**190**	**8**	**43 (36-51)**
IPI-T	**197**	**2**	**28 (22-35)**	**IPI-T**	**221**	**3**	**31 (25-37)**
Total	**365**	**5**	**34 (29-39)**	**Total**	**411**	**5**	**37 (32-41)**

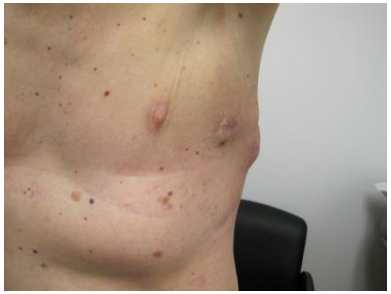
3% difference!

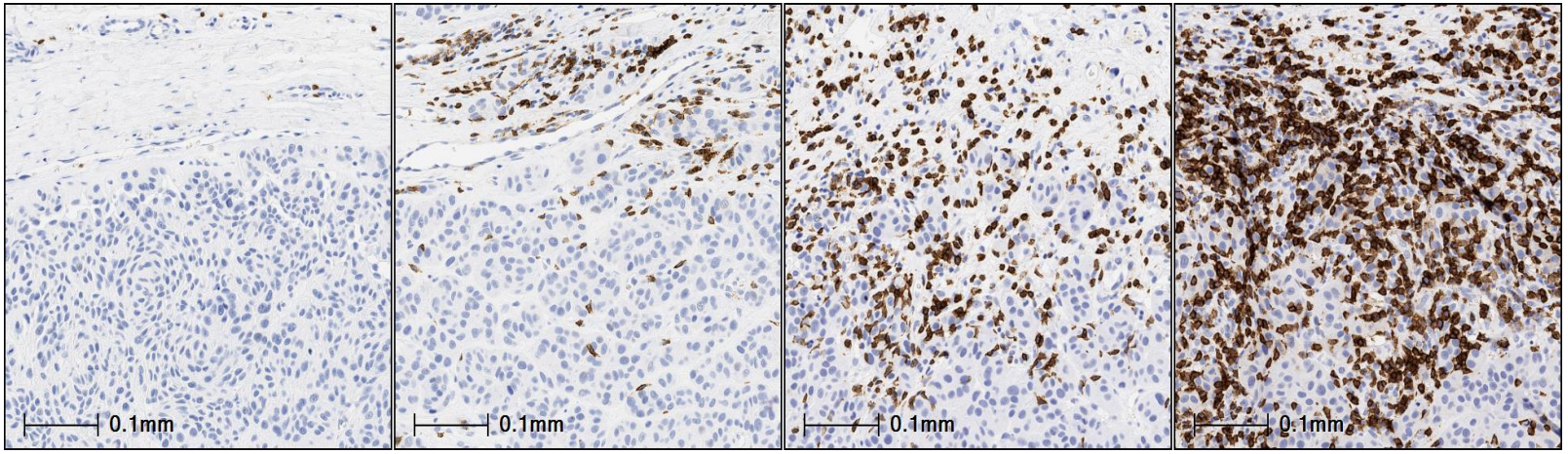
Response to PD-1 blockade after transient progression











Baseline Day +27 Day +92 Day +130

Conclusions

- Responses to cancer immunotherapy cannot be evaluated exactly the same as when using chemotherapy or targeted therapy:
  - Early increase in size or new lesions may not always mean that there is disease progression
  - Response to therapy may require additional time to become evident
- It would be desirable to generate a new version of irRC:
  - Based on unidimensional measurements
  - Based on best response on therapy
  - With incorporation of radiologist's input on response criteria
- Understanding the mechanism of "pseudoprogression" would help in better interpreting responses to immunotherapy:
  - When in doubt, biopsy to assess if there is a T cell response