FRIENDS of CANCER RESEARCH

Center for Health Policy at BROOKINGS

FRIENDS / BROOKINGS ANNUAL MEETING

Supported by:

Susan G. Komen

FRIENDS of CANCER RESEARCH

Center for Health Policy at BROOKINGS

Friends / Brookings Annual Meeting

Panel One: Modernizing Measurement of Tumor Response to Therapy

FRIENDS of CANCER RESEARCH

Center for Health Policy at BROOKINGS

FRIENDS / BROOKINGS ANNUAL MEETING

NANCY ROACH
FIGHT COLORECTAL CANCER

FRIENDS / BROOKINGS ANNUAL MEETING

Panel One: Modernizing Measurement of Tumor Response to Therapy

Lalitha K. Shankar, MD, PhD Chief, Diagnostic Imaging Branch,

Cancer imaging Program, Division of Cancer Treatment and Diagnosis,

National Cancer Institute

NIH NATIONAL CANCER INSTITUTE

November 17, 2015

RECIST 1.0

RECIST 1.0

- Established in 1995 to review the objective response criteria in use at the time and to explore the utility of the use of unidimensional measurements in response assessment
- Working group was led by academic members of the EORTC, NCIC (Canada) and NCI (USA), with a database being created and maintained under the governance of the EORTC
- Membership expanded over the years to include subject matter experts (Radiology and Nuclear Medicine) and representatives from Pharma
- Implemented in 2000 for Phase II trials, and adapted for Phase III studies.

RECIST 1.1

- Implemented in 2009 to further improve the ease of tracking tumor measurements in oncology clinical trials, based on community feedback.
- The updates were made after testing the new guidelines in the EORTC database of more than 40.000 cases on clinical trials.
- The required number of lesions to be tracked decreased from 10 to 5, with no more than 2 from 1 organ system.
- More accurate lymph node measurements.
- Introduction of FDG PET for defining disease progression.
- Refining of acquisition parameters for CT and MR.

LIMITATIONS OF RECIST

Challenges in Using RECIST for Response Assessment

- Morphologic assessment.
- Changes is tumor size can be slow or static and not reflective of tumor status.
- Limited utility in certain malignancies such as mesothelioma and neuroendocrine tumors

Modernizing Measurement of Tumor Response to Therapy

Where do we go next?

Working Groups in the RECIST committee evaluating/updating RECIST for Response Assessment

- Assessment of RECIST 1.1 in trials involving Cytostatic therapies
- Assessment of incorporation of FDG-PET response assessment.
  - Reliability of quantitative metrics assessing change in FDG uptake.
  - Assessment of how FDG-PET performs compared to morphologic imaging in evaluating response assessment.
- Assessment of RECIST 1.1 in trials involving Immunotherapies

Collaborations

- Assessment of volumetrics in lieu of unidimensional measurement
  - With Prof. Larry Schwartz
- Assessment of brain metastases with RANO

Shankarl@mail.nih.gov

240-276-5936

www.cancer.gov **www.cancer.gov/espanol**

The need for patient-based objective criteria for response and progression

Geoffrey R. Oxnard, MD
Assistant Professor of Medicine
Dana-Farber Cancer Institute
Brigham & Women's Hospital
Harvard Medical School

Response vs progression

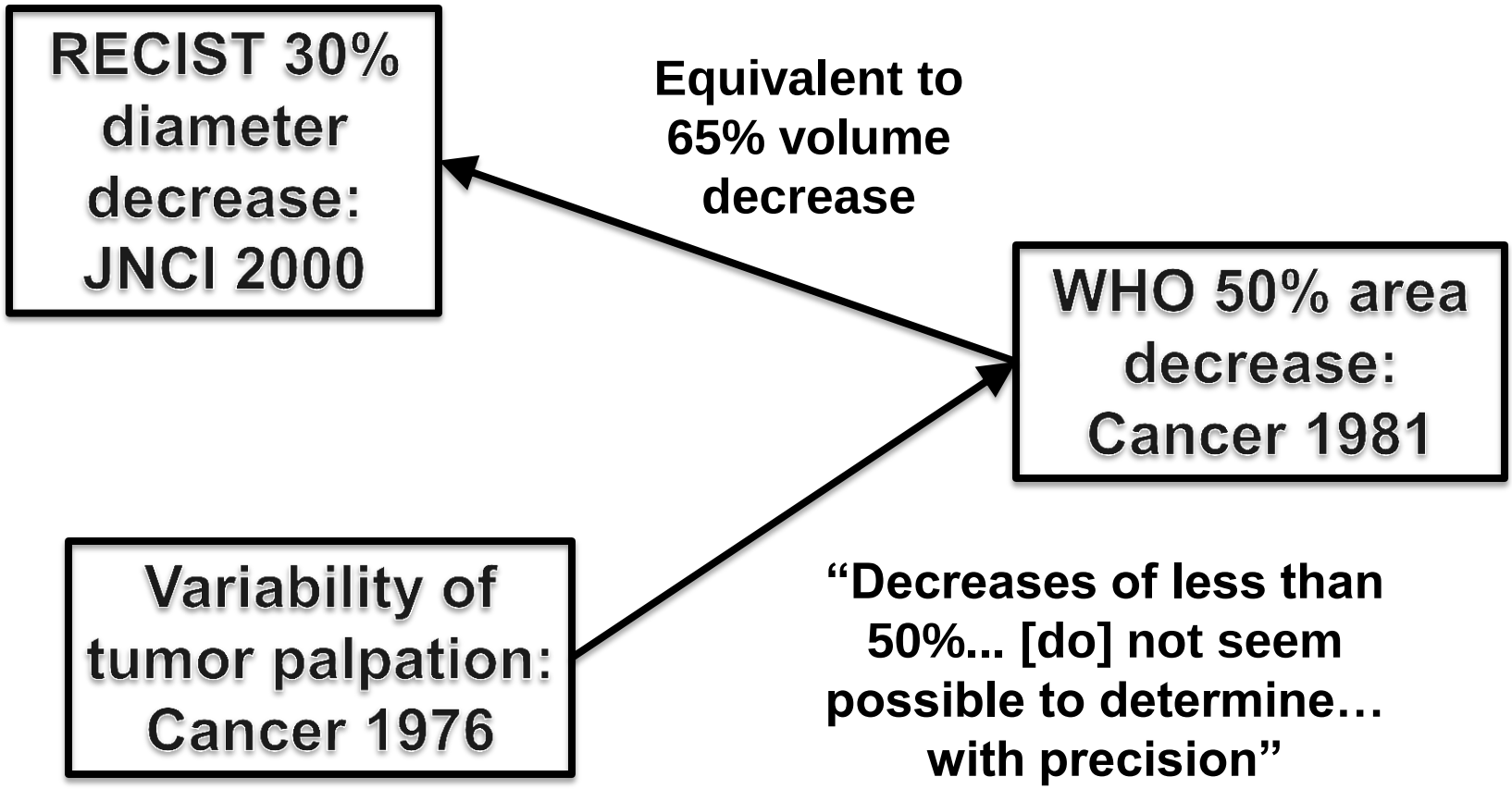
	Response	Progression
Timing of assessment:	Assessed early in treatment course	Assessed at intervals until change of therapy
Role in clinical practice:	Not normally used to determine whether to change therapy	Commonly used to determine when to change therapy
Role in clinical research:	Primarily used to calculate overall response rate	Primarily used to calculate time to progression endpoints

Figure 1. Response and progression as distinct events in solid tumor oncology care and research. Because response and progression play two very different roles, the two may be better conceptualized as distinct events rather than as the two ends of a single spectrum, and each can be studied and critiqued separately.

Oxnard et al, JNCI, 2012

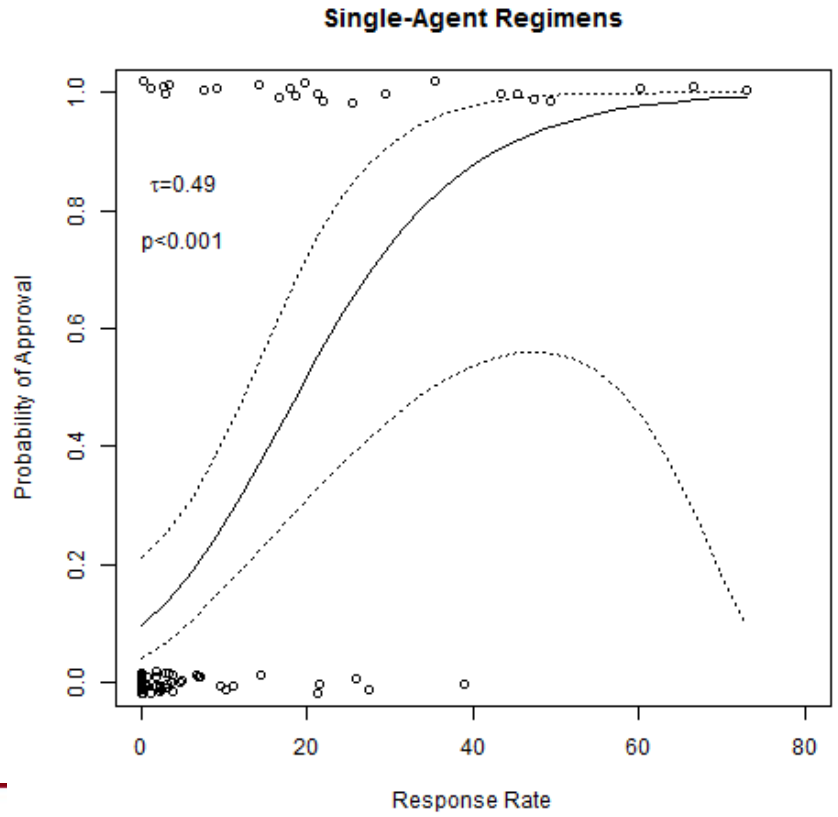
Response assessment

RECIST guidelines have historical precedent:



Response assessment

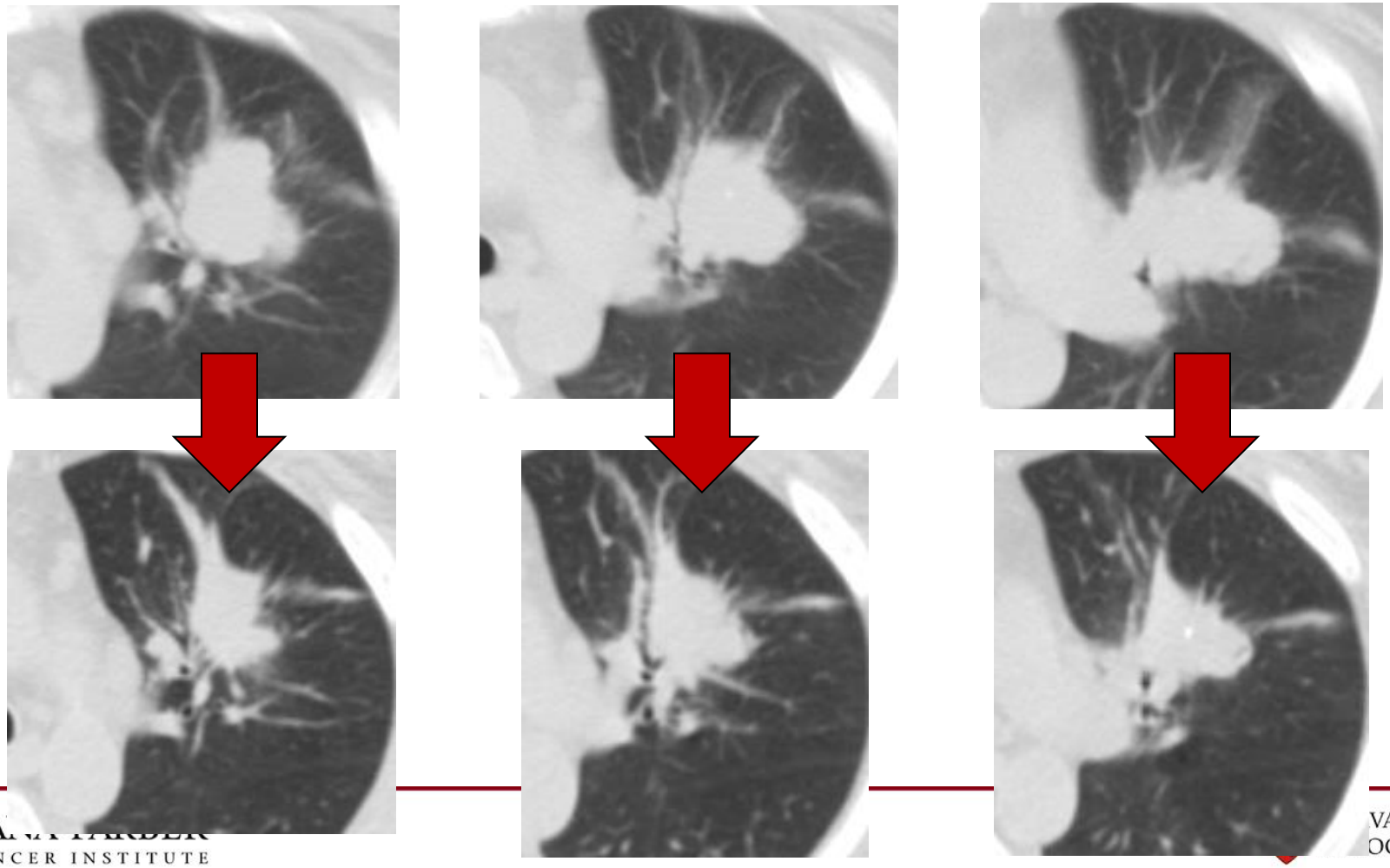
- Single-agents demonstrating a high response (>30%) have a high likelihood of regulatory approval



Oxnard et al, under review

Response assessment

What counts as a response?



Response assessment

What counts as a response?

Calculated measurement changes:

- **1D: Diameter decrease = 9%**
- **2D: Cross-product decrease = 25%**
- **3D: Volumetric decrease = 47%**

Response assessment

What counts as a response?

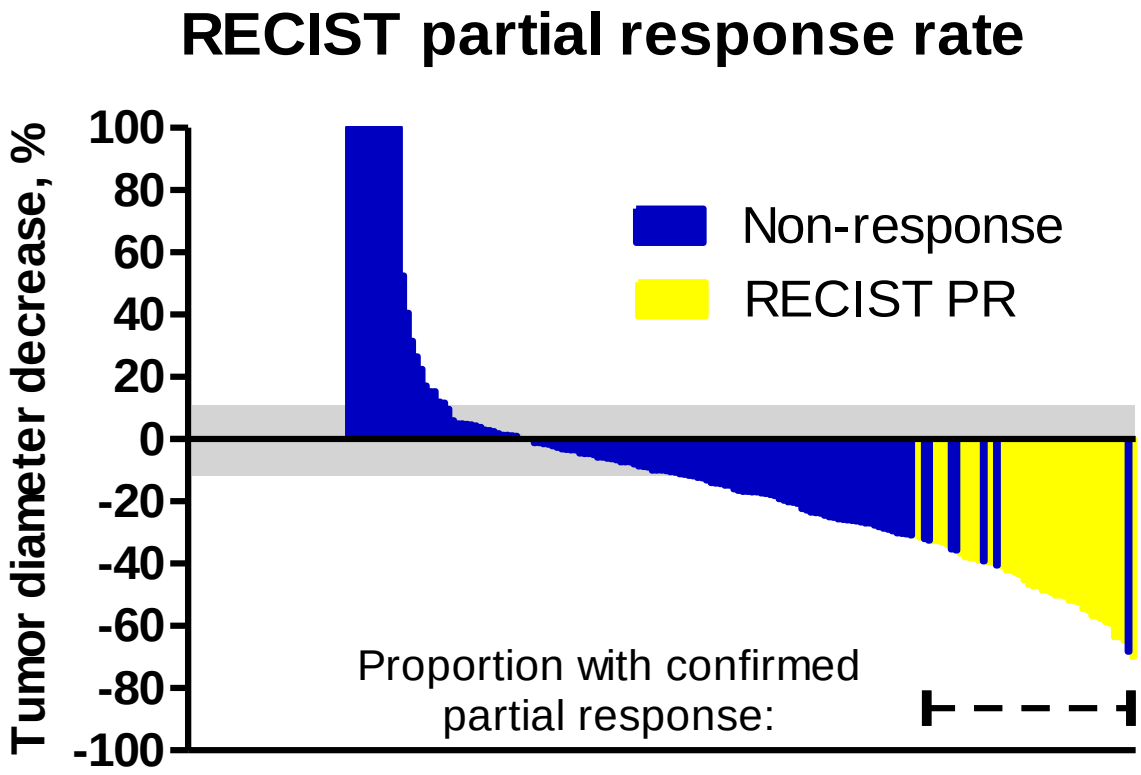
Calculated measurement changes:

- **1D: Diameter decrease = 9%**
- **2D: Cross-product decrease = 25%**
- **3D: Volumetric decrease = 47%**

Response assessment

What counts as a response?

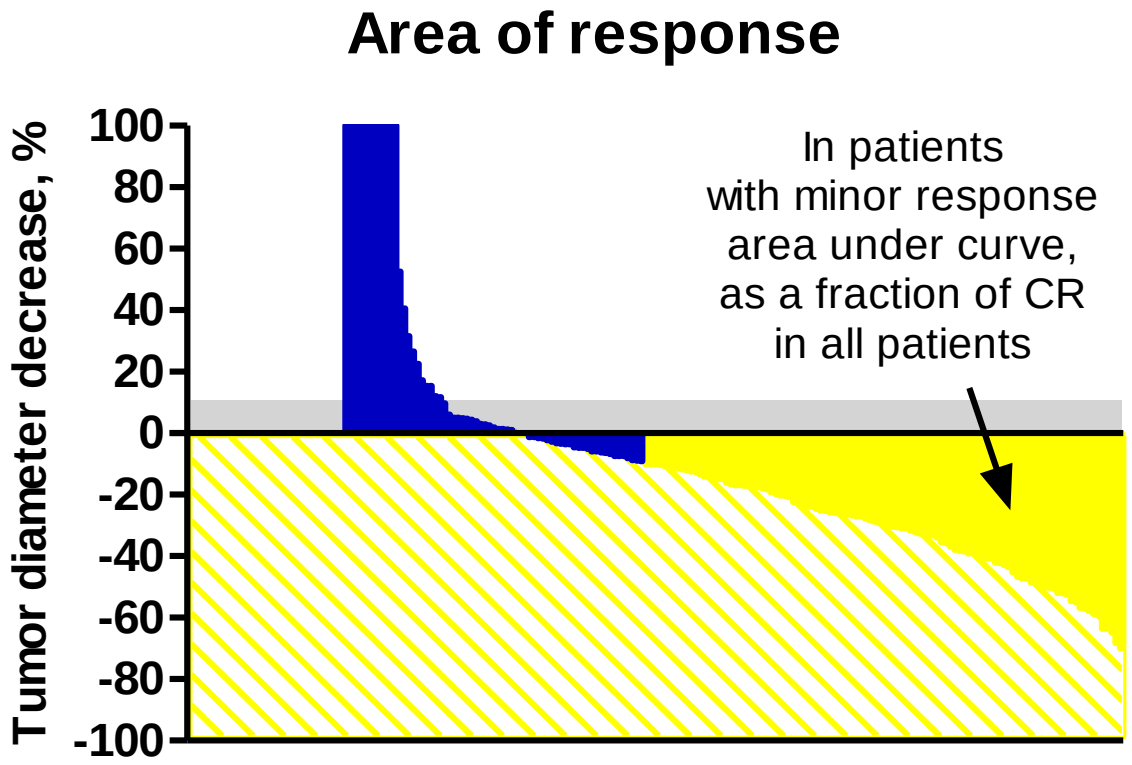
- **RECIST does not consider depth of response**



Response assessment

What counts as a response?

- **RECIST does not consider depth of response**



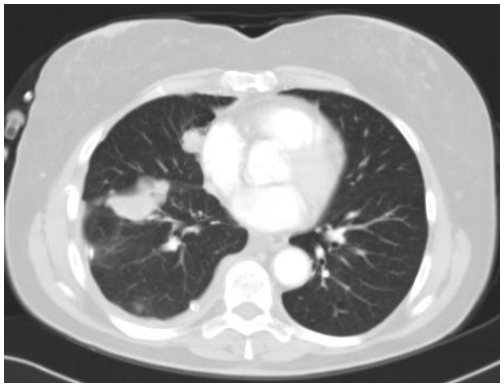
Response assessment

- Improved metrics for studying response could reduce variability

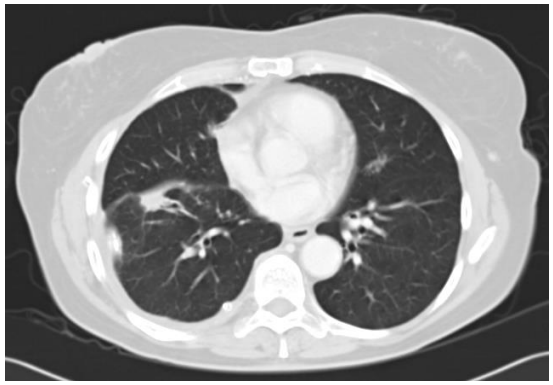
Ramalingam et al, JCO, 2010		**Belani et al, ESMO, 2009**	
NCI-supported consortia		Industry sponsored	
94 patients		253 patients	
Carbo/taxol:	12.5% RR 4.1m PFS	Carbo/taxol:	29.3% RR 5.5m PFS
& vorinostat:	34.0% RR 6.0m PFS	& vorinostat:	22.4% RR 4.3m PFS
A POSITIVE TRIAL		**A NEGATIVE TRIAL**	

Progression assessment

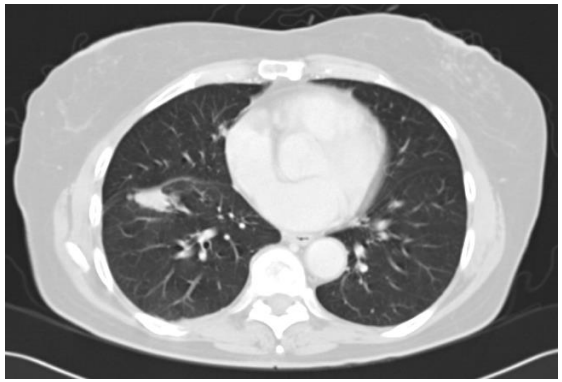
- When is progression clinically meaningful?



Baseline: Start TKI



3m: Response

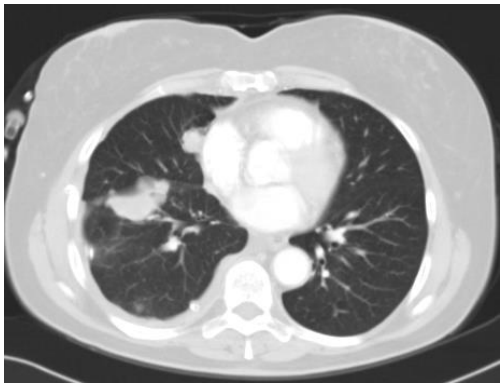


14m: RECIST PD

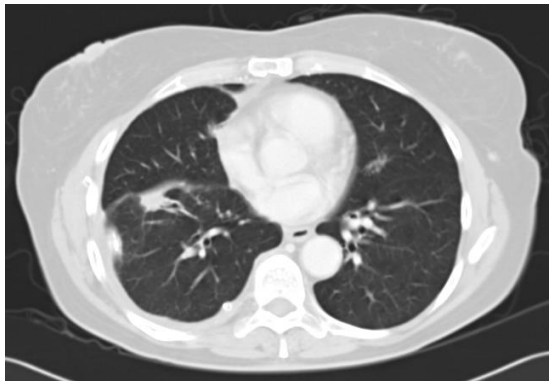
Oxnard et al, ASCO, 2012

Progression assessment

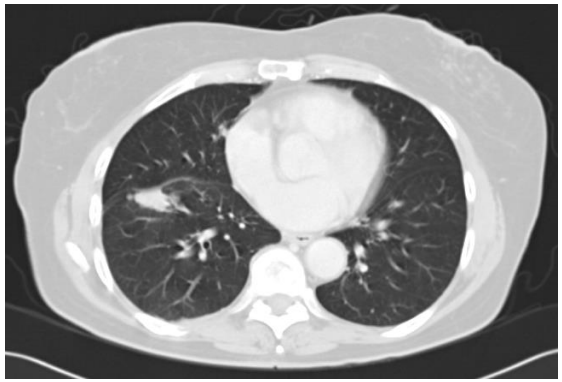
- When is progression clinically meaningful?



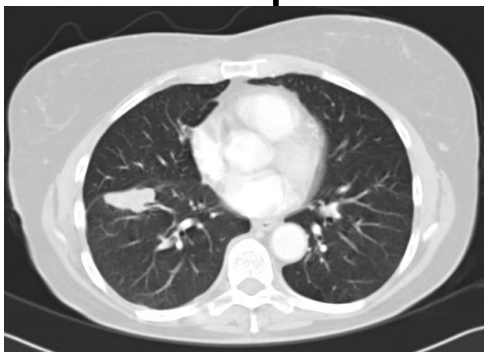
Baseline: Start TKI



3m: Response



14m: RECIST PD

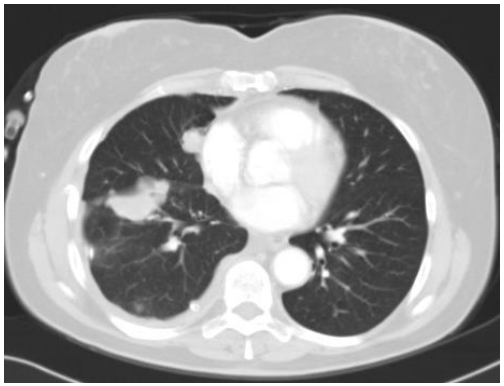


18m

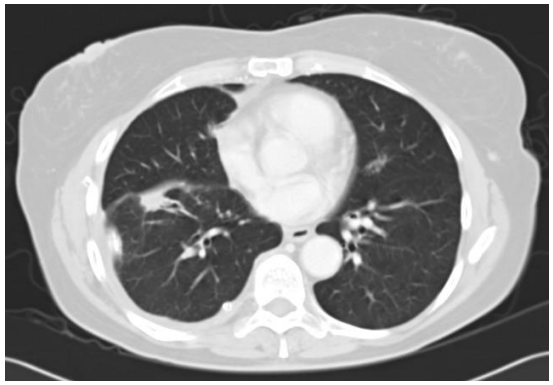
Oxnard et al, ASCO, 2012

Progression assessment

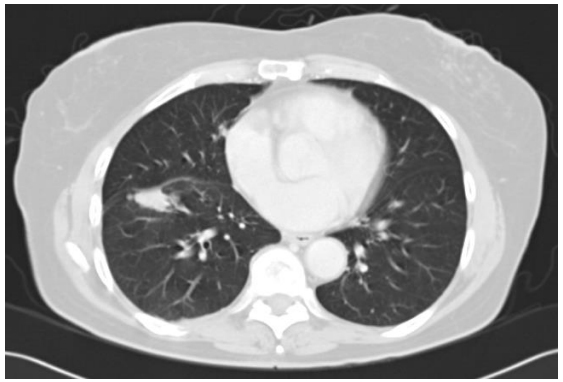
- When is progression clinically meaningful?



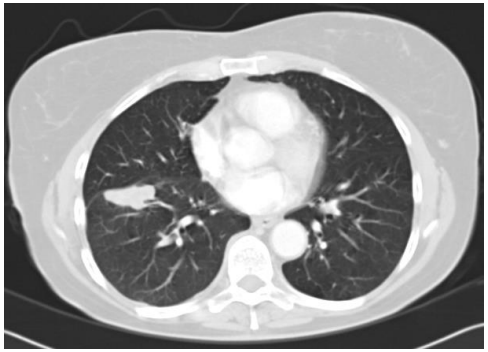
Baseline: Start TKI



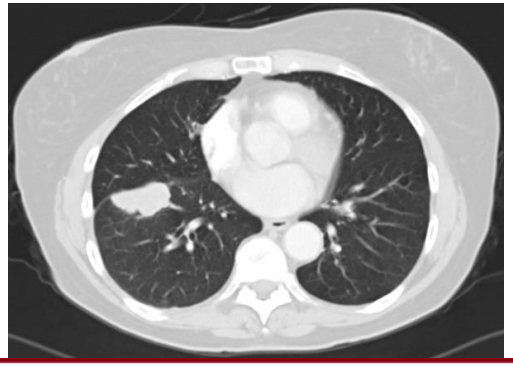
3m: Response



14m: RECIST PD



18m

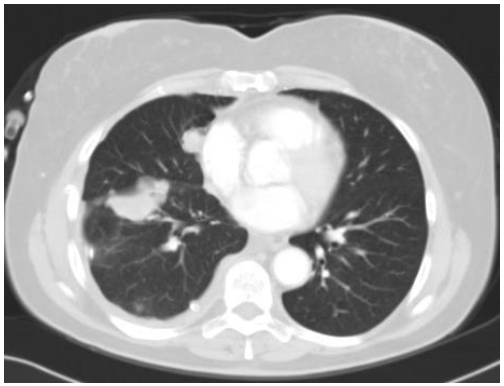


24m

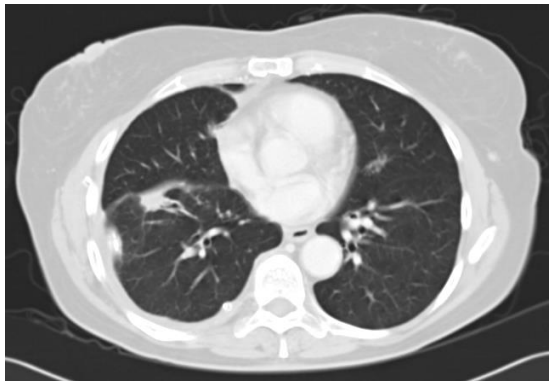
Oxnard et al, ASCO, 2012

Progression assessment

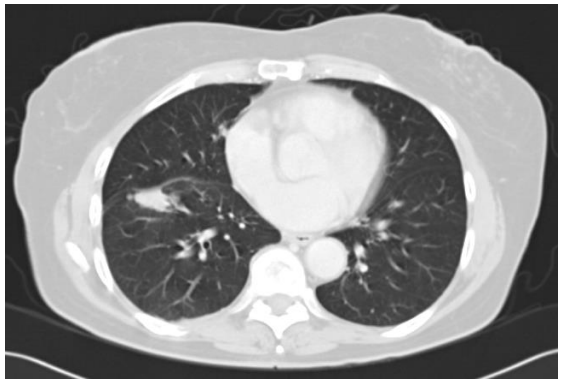
- When is progression clinically meaningful?



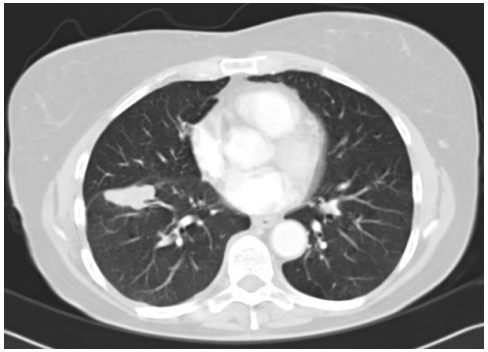
Baseline: Start TKI



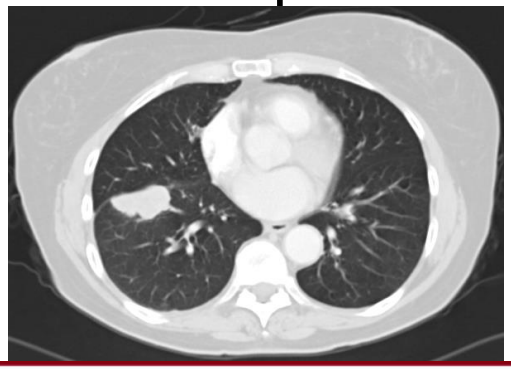
3m: Response



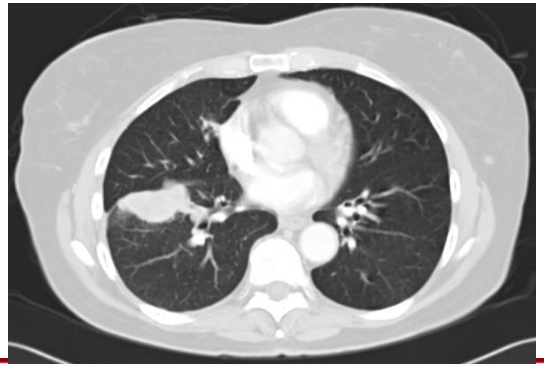
14m: RECIST PD



18m

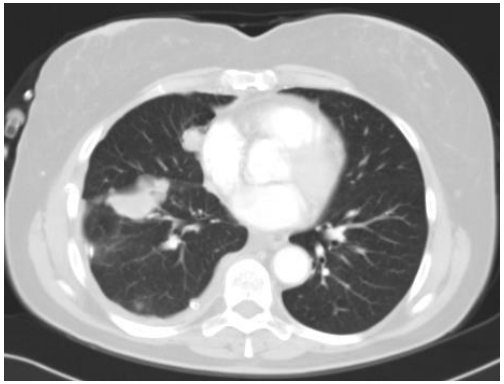


24m

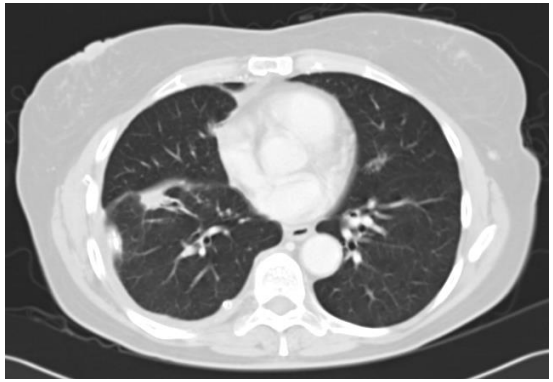


30m

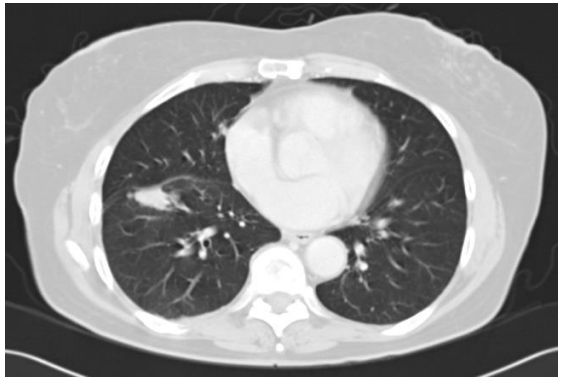
Oxnard et al, ASCO, 2012



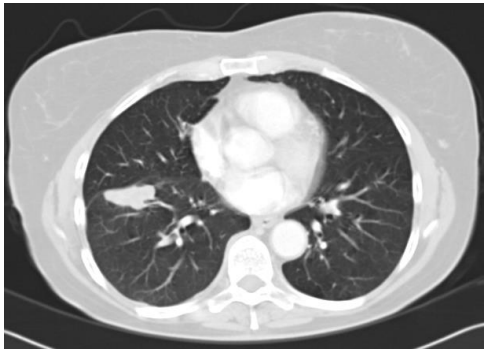
Baseline: Start TKI



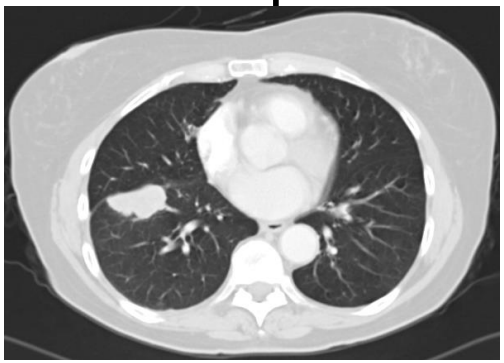
3m: Response



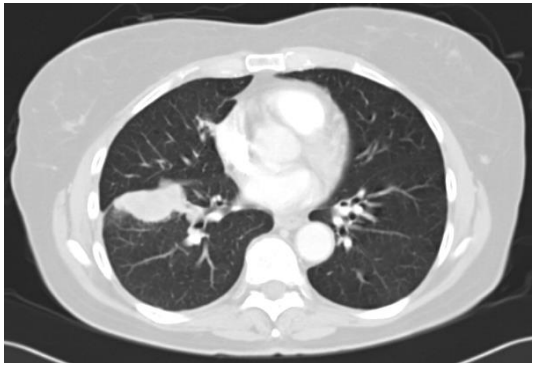
14m: RECIST PD



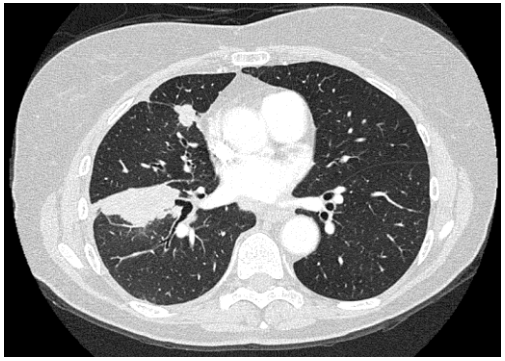
18m



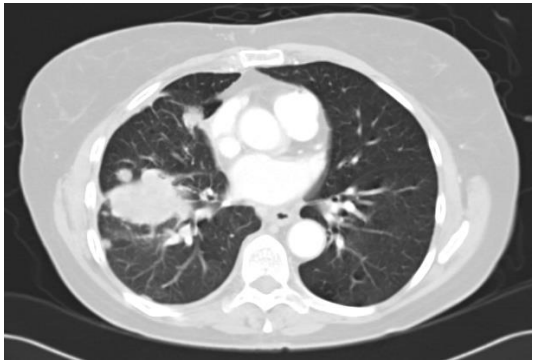
24m



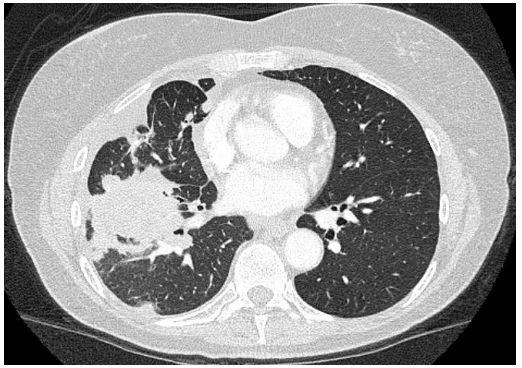
30m



35m



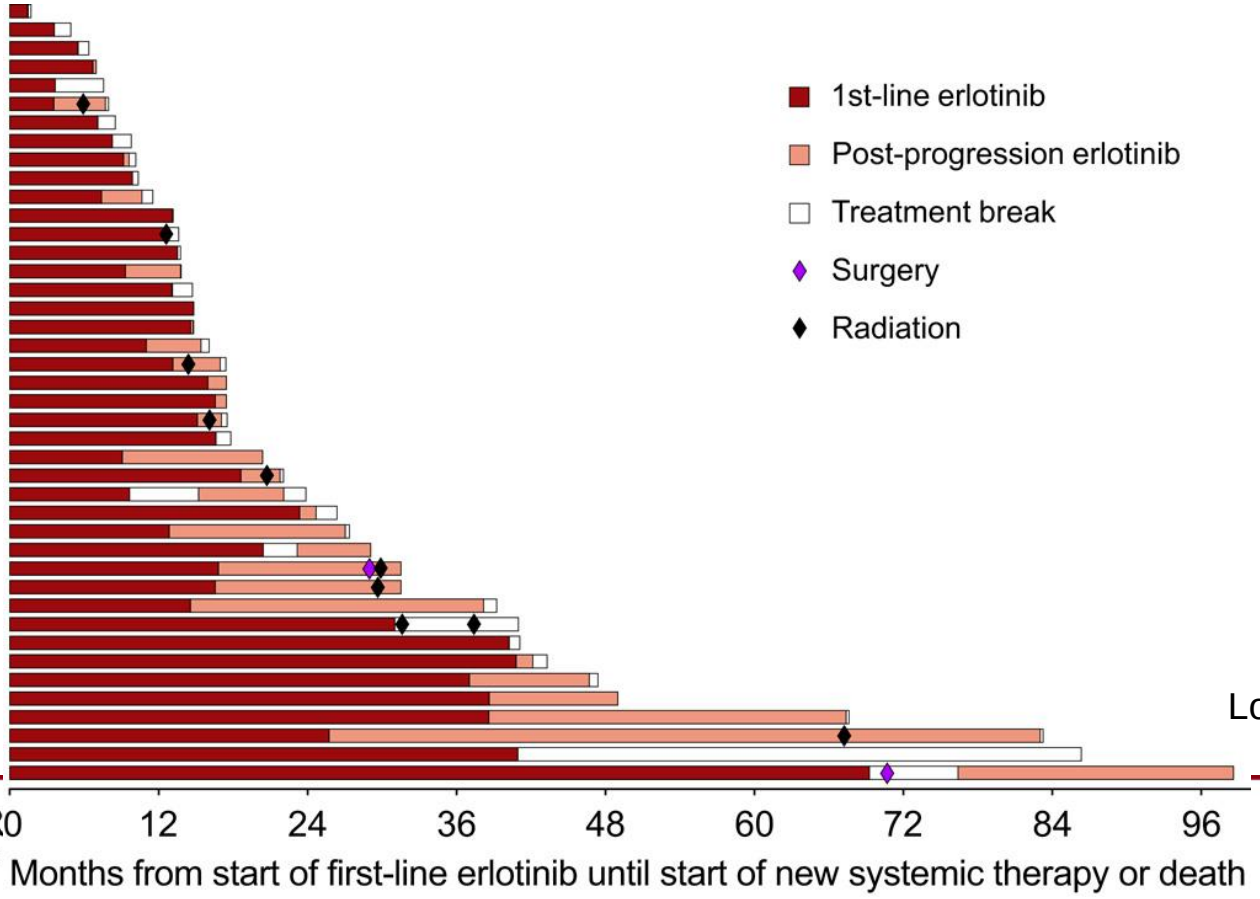
37m: Stop TKI



39m: First dyspnea

Progression assessment

- Patients often stay on therapy after RECIST PD
  - >50% of pts with EGFR-mutant NSCLC on TKI can delay treatment change more than 3m after PD

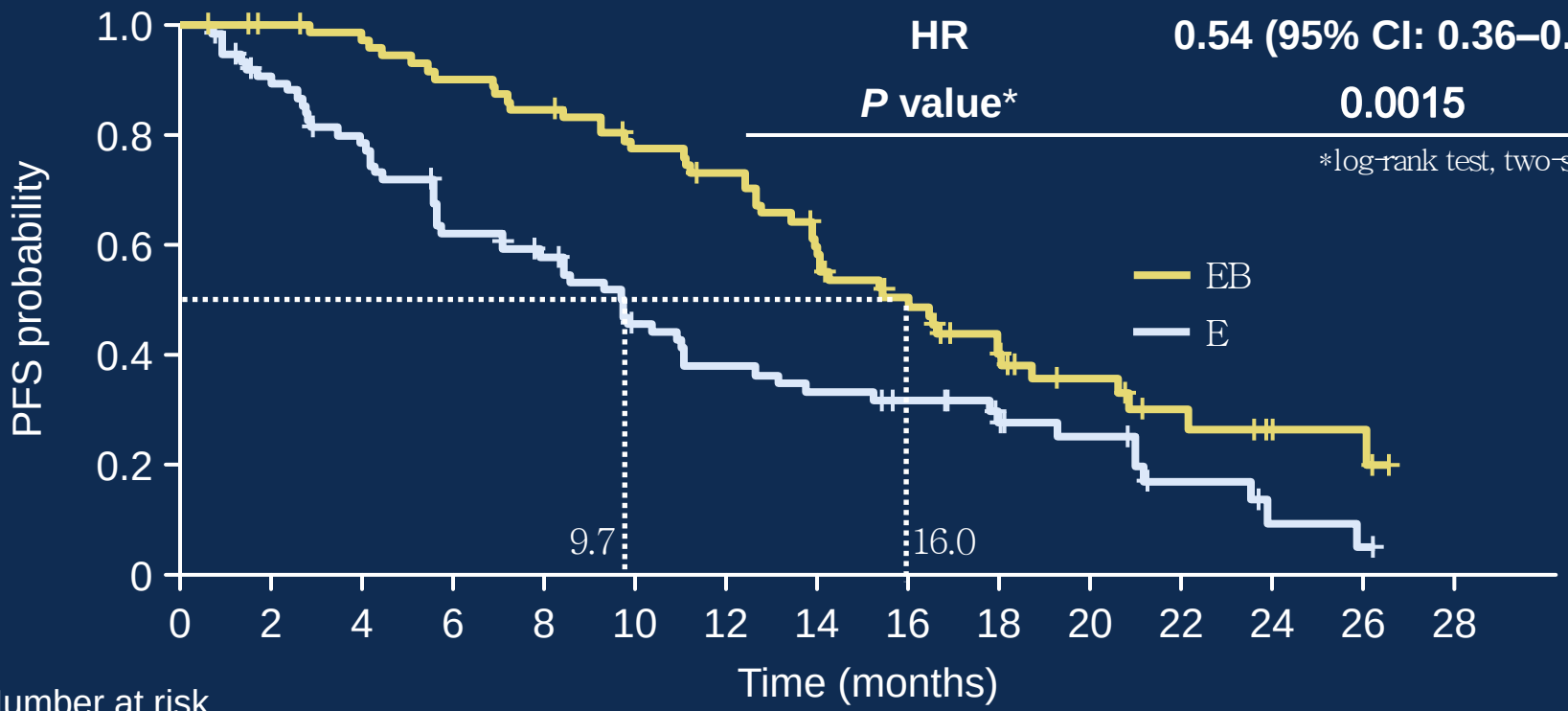


Lo et al, Cancer, 2015

Erlotinib & bevacizumab: Prolonged PFS

	EB	E
Median (months)	16.0	9.7
HR	0.54 (95% CI: 0.36–0.79)	
P value*	0.0015	

*log-rank test, two-sided



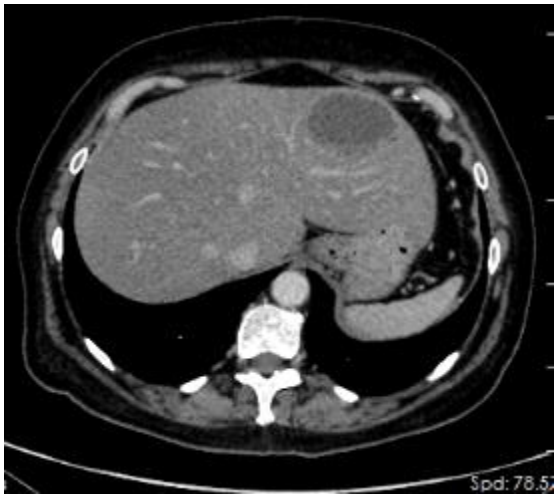
Number at risk

EB	75	72	69	64	60	53	49	38	30	20	13	8	4	4	0
E	77	66	57	44	39	29	24	21	18	12	10	5	2	1	0

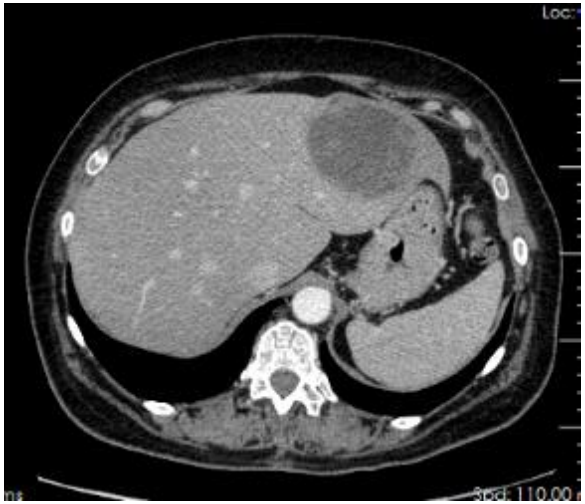
Progression assessment

- **Patients receiving immune checkpoint inhibitors can exhibit objective progression following by dramatic clinical benefit**
  - **Pt with melanoma receiving pembrolizumab**

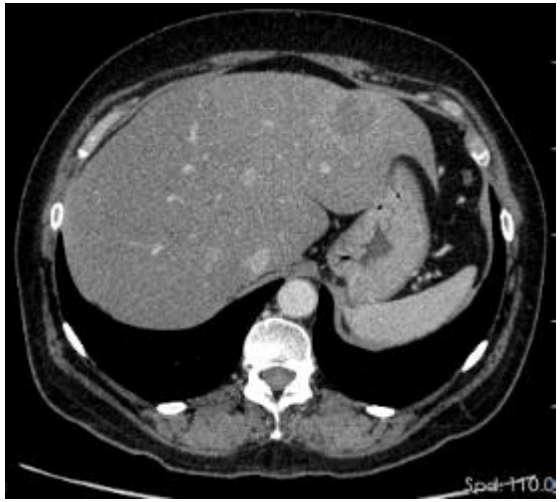
Baseline



Cycle 2



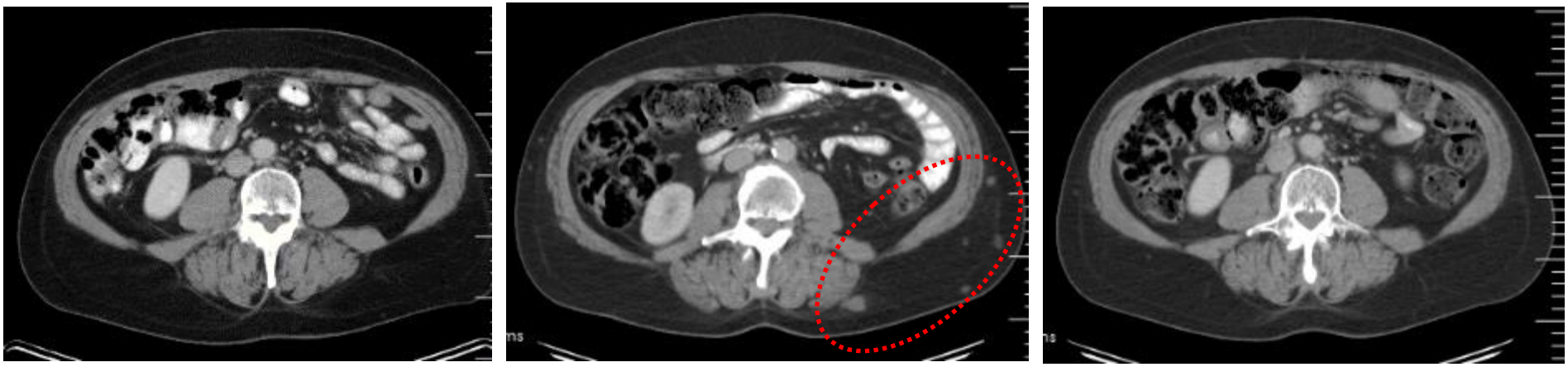
Cycle 6



Progression assessment

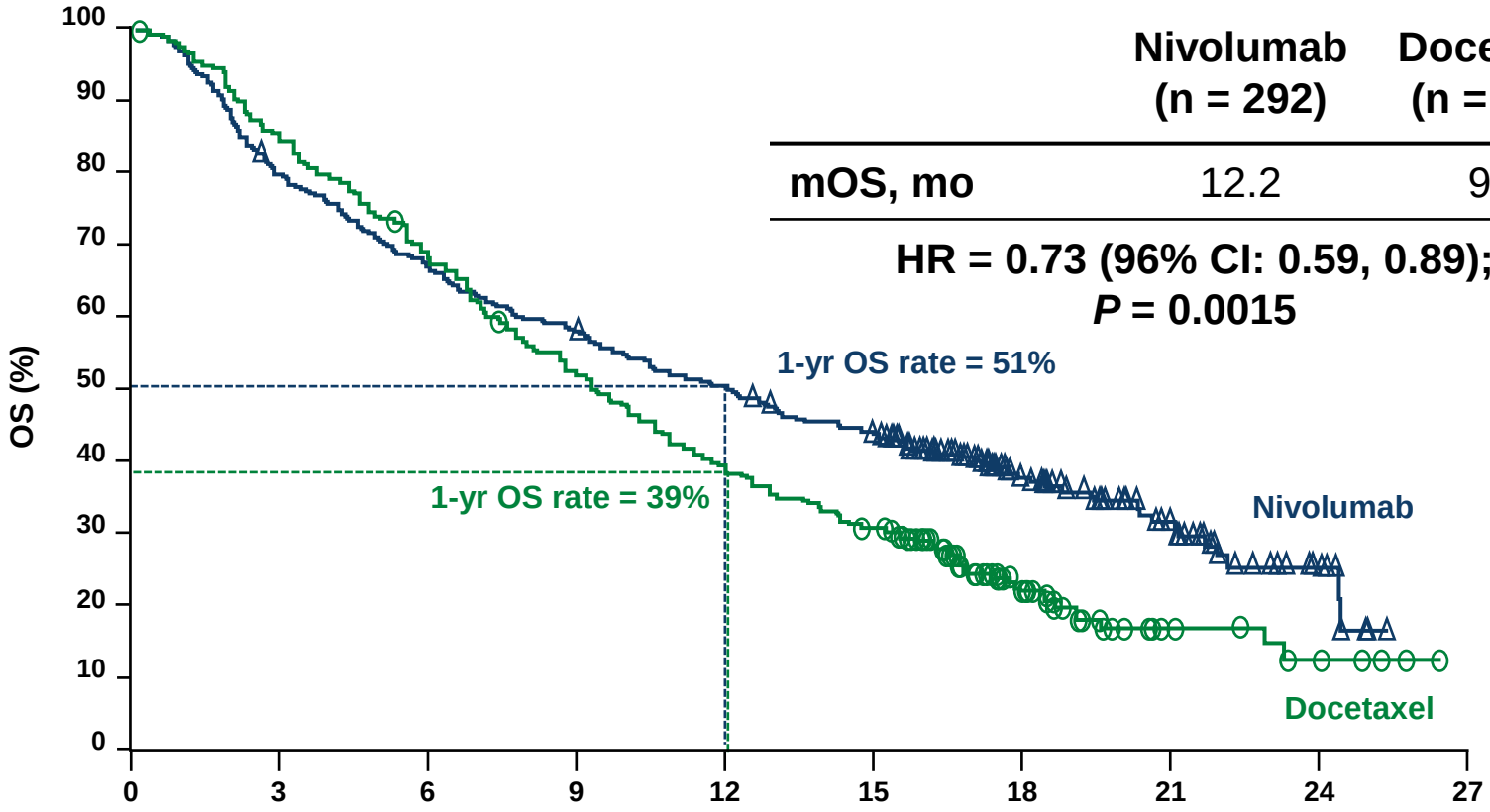
- **Patients receiving immune checkpoint inhibitors can exhibit objective progression following by dramatic clinical benefit**
  - **Pt with melanoma receiving pembrolizumab**

Baseline Cycle 2 Cycle 4



Nivolumab in nonsquamous NSCLC

Overall Survival



	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4

HR = 0.73 (96% CI: 0.59, 0.89);
***P* = 0.0015**

Number of Patients at Risk

Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Symbols represent censored observations.

Paz-Arez et al, ASCO, 2015

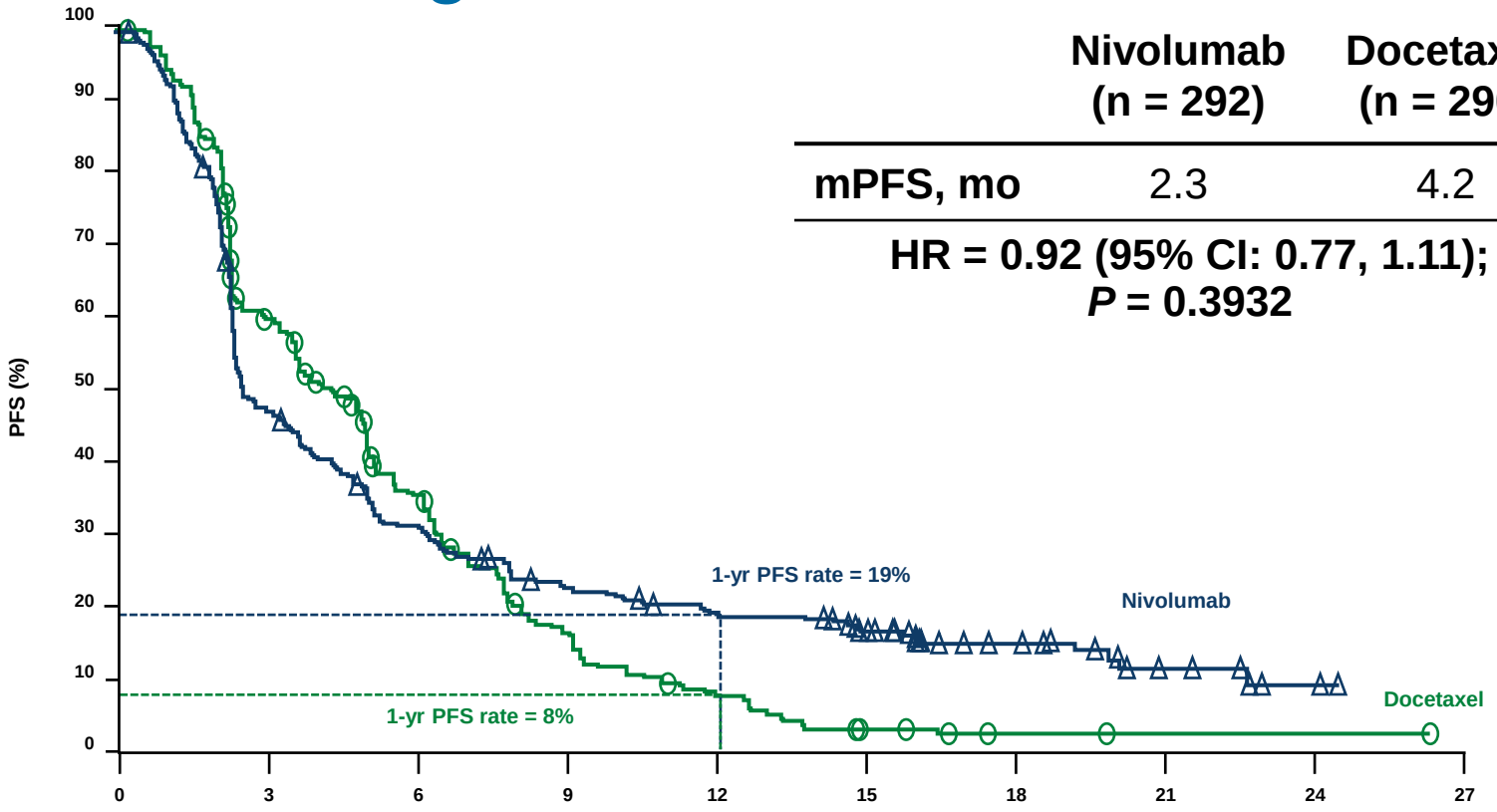
PRESENTED AT: ASCO Annual '15 Meeting

Nivolumab in nonsquamous NSCLC

Progression Free Survival

	Nivolumab (n = 292)	Docetaxel (n = 290)
mPFS, mo	2.3	4.2

HR = 0.92 (95% CI: 0.77, 1.11); *P* = 0.3932



Number of Patients at Risk										
Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

Symbols represent censored observations.

Paz-Arez et al, ASCO, 2015

PRESENTED AT: ASCO Annual '15 Meeting

Conclusions

- **While an endpoint with historical precedent (RECIST) is essential for single-arm studies, there is more flexibility for randomized studies**
- **Development of new clinically-relevant criteria for response and progression could result in more informative randomized trials for:**
  - **Genotype-directed targeted therapies**
  - **Immune checkpoint inhibitors**
- **An extensive database of existing trials will be needed for such an effort**

FRIENDS of CANCER RESEARCH

Center for Health Policy at BROOKINGS

FRIENDS / BROOKINGS ANNUAL MEETING

LARRY SCHWARTZ, MD

COLUMBIA UNIVERSITY MEDICAL CENTER

VOL - PACT:
Improving Volumetric CT Metrics for Precision Analysis of Clinical Trial Results

Geoffrey R. Oxnard, MD, Dana-Farber Cancer Institute,

Lawrence H. Schwartz, MD, Binsheng Zhao, DSC,
Columbia University Medical Center,

Mithat Gonen, PhD, Chaya Moskowitz PhD, Patrick Hilden,
Memorial-Sloan Ketting Cancer Center,

Michael Maitland, MD PhD, University of Chicago

COLUMBIA UNIVERSITY MEDICAL CENTER
Discover. Educate. Care. Lead.

DANA-FARBER CANCER INSTITUTE

THE UNIVERSITY OF CHICAGO

MEMORIAL SLOAN-KETTERING CANCER CENTER

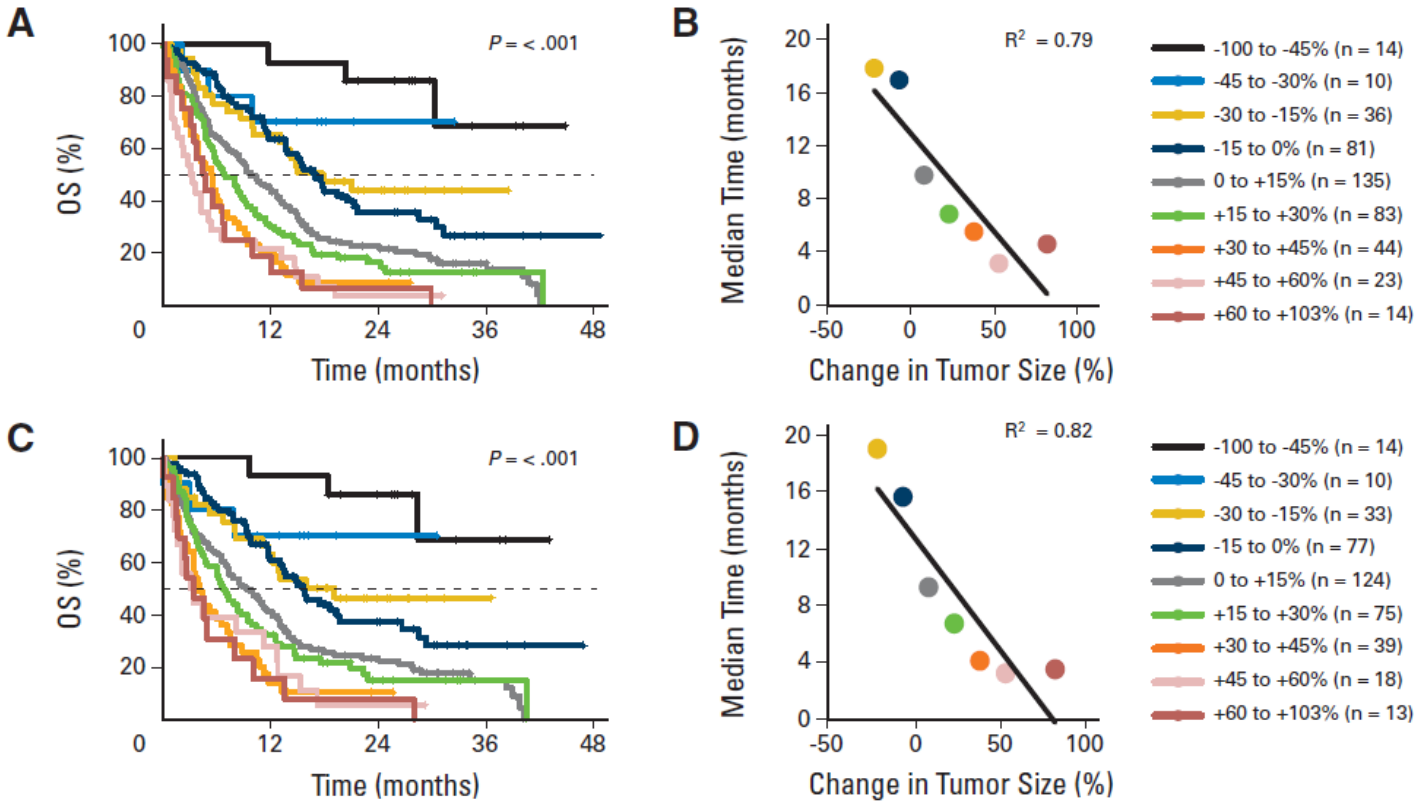
Problem statement

- Oncology drug development is inefficient
  - 62.5% of phase III trials are negative
- Therapeutic progress has inherently made drug development more difficult
  - More active drugs leads to greater use of randomized phase II trials
  - However, trials continue to study traditional endpoints (ORR, PFS)
- Development of new, modern trial endpoints is needed

Gan et al, JNCI, 2012

Response Magnitude

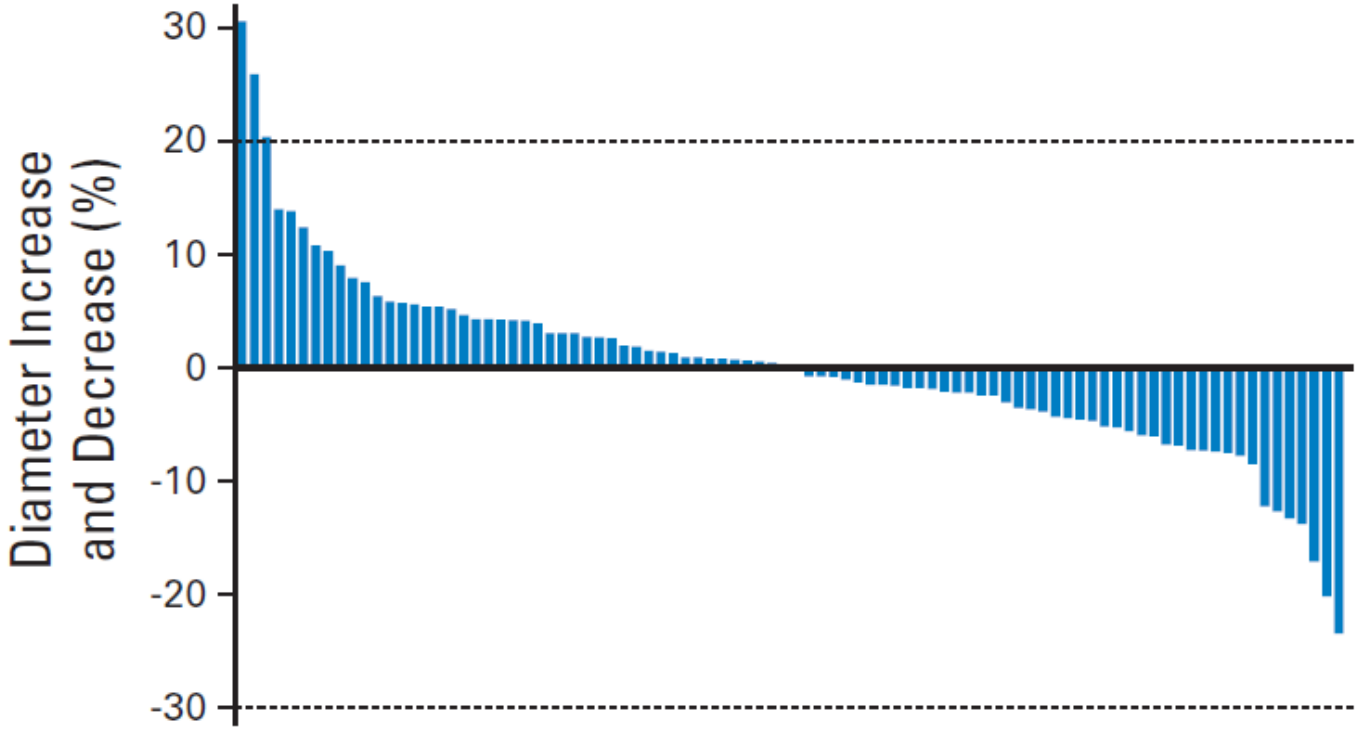
- It has recently been shown that a greater magnitude of response is associated with a better prognosis for an individual patient



Jain et al, JCO, 2012

Response Magnitude

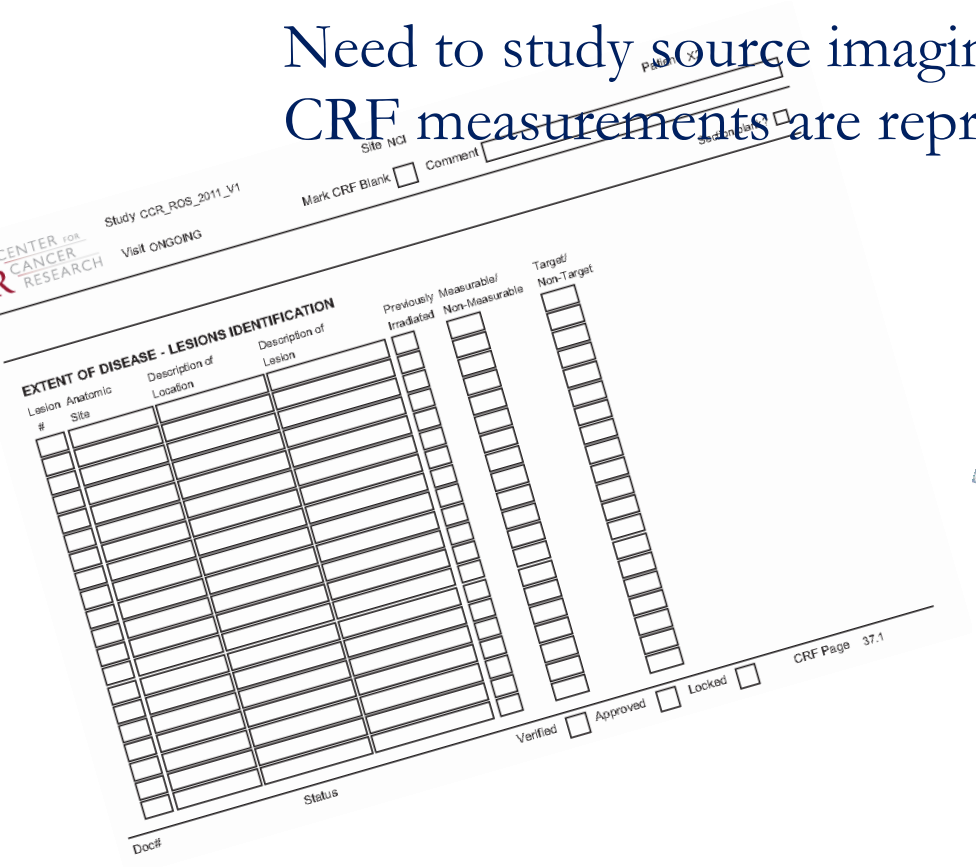
- Prior repeat CT study has shown that small changes (>10% diameter, >20% volume) can be reliable

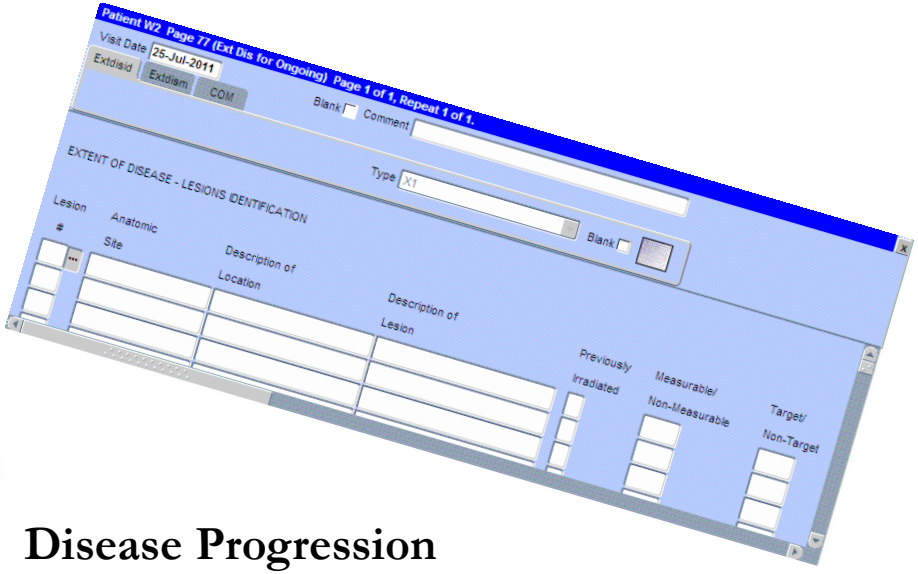


Oxnard et al, JCO, 2011

Getting the best measurements

Need to study source imaging data rather than trusting that CRF measurements are representative of truth





Disease Progression

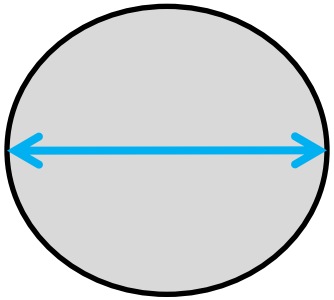
- Sum of target lesions
- Non target progression
- "New Lesion" progression

Li et al, ***submitted***

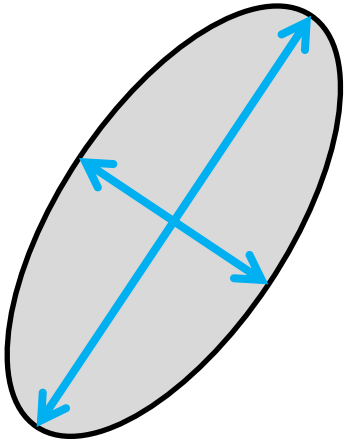
Getting the best measurements

Furthermore, advanced imaging of the whole tumor volume can may characterize the biology of tumor growth and response

Diameter (RECIST) 1D



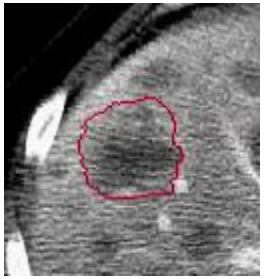
Cross-product (WHO) 2D

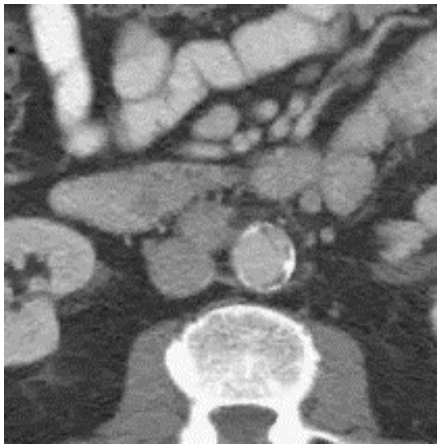


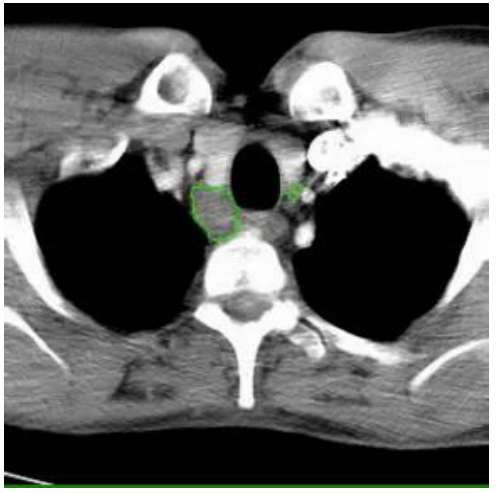
Volume 3D

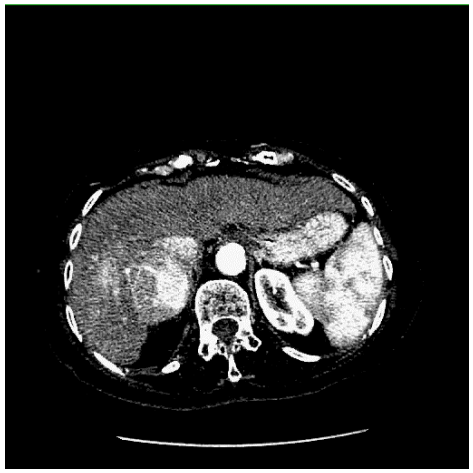
Getting the best measurements

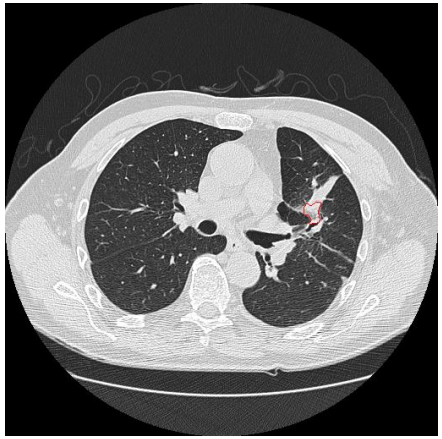
Furthermore, advanced imaging of the whole tumor volume can may characterize the biology of tumor growth and response











Hypothesis

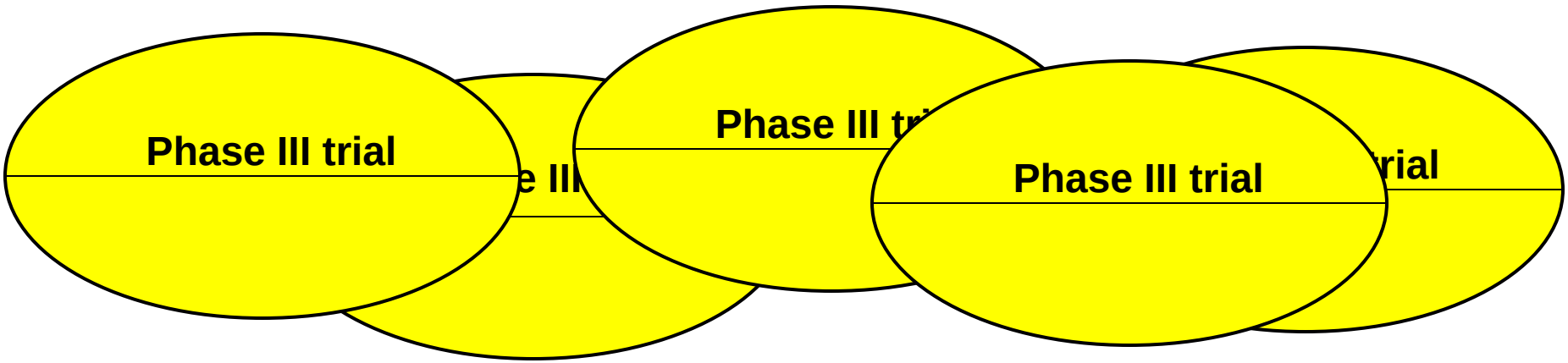
- Quantitative analysis of tumor response as a continuous variable will improve the ability of randomized phase II trials to accurately predict phase III results
- Detailed assessment of the entire tumor burden using volumetric CT will improve efficiency and accuracy of phase II trial analysis

Aims

- Assess feasibility of collection and analysis of images from completed phase III trials to:
  - (A) simulate of phase II trial results, and
  - (B) develop quantitative metrics for improved prediction of phase III trial results
- Assess which quantitative metrics most accurately and reliably predict phase III results across different trials
- Quantify the added value of volumetric tumor measurement as compared to conventional measurement only

Step 1: Collect data

1) Collection of existing trial data
   - Focus on large completed landmark trials (>300 patients)
   - Measurable carcinomas: NSCLC, RCC, CRC
   - Collect DICOM imaging from imaging core labs holding scans for pharma
   - IRB has approved receipt of these de-identified images at Columbia



Step 1: Collect data

Trial Sponsor	Disease	Drug	Trial ID	N	Data Sharing Agreement	Data Transfer	Data Analysis
Sanofi	CRC	FOLFIRI +/- aflibercept	VELOUR	1226	√	√	√
GSK/ Novartis	RCC	Pazopanib vs. placebo	VEG105192	435	√	√	Ongoing
GSK/ Novartis	RCC	Pazopanib vs. sunitinib	COMPARZ	1110	√	√	
Amgen	CRC	FOLFOX +/- panitumumab	PRIME	1183	√	Ongoing	
Amgen	CRC	BSC +/- panitumumab	20020408	463	√	Ongoing	
Pfizer	RCC	Sunitinib vs. IFN	SUTENT	750	√		
Pfizer	RCC	Axitinib vs. sorafenib	NCT00678392	723	√		
TBD	Mel	Immuno therapy	TBD		Ongoing		
TBD	Mel	Immuno therapy	TBD		Ongoing		

Step 2: Generate measurements

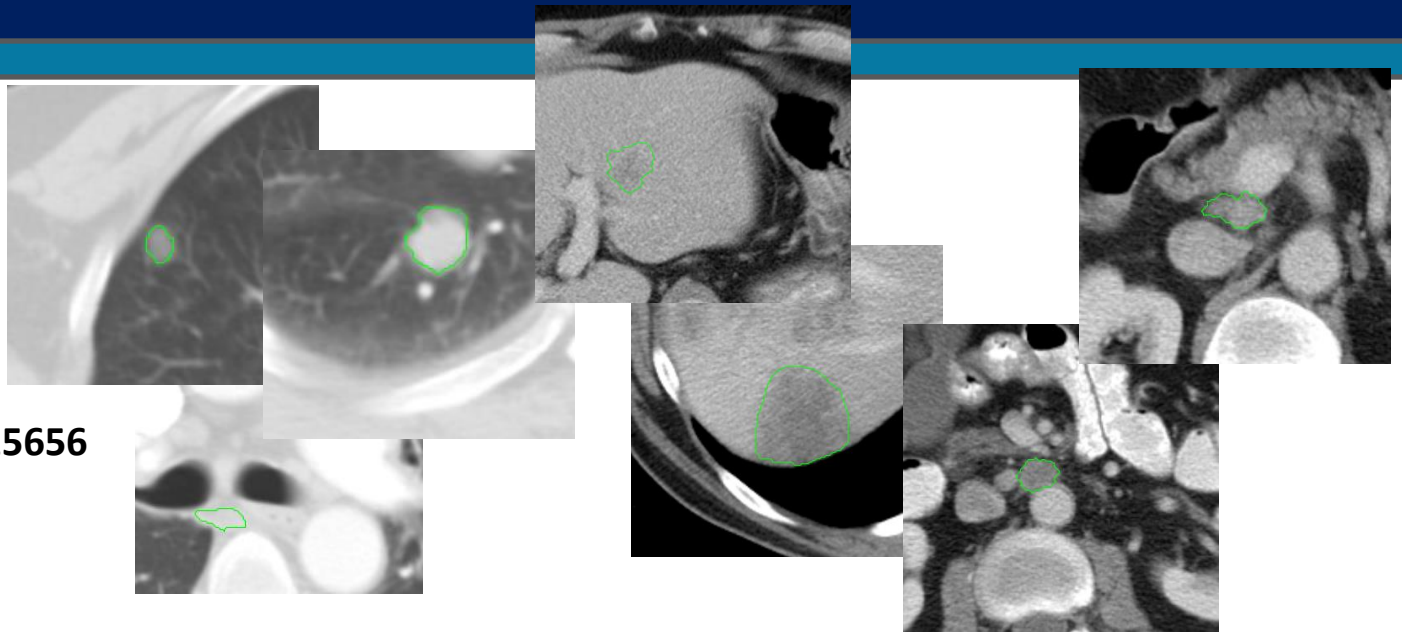
2) Generate semi-automated tumor measurements
   - DICOM images will be studied at a lab experienced with volumetry
   - Computer generated tumor contours will be corrected as needed by an experienced technician
   - Measurements in 1D, 2D, 3D will be calculated for all lesions >= 1cm (up to 10 lesions) at each time point

VELOUR trial (Sanofi)

Aflibercept Versus Placebo in Combination With Irinotecan and 5-FU in the Treatment of Patients With Metastatic Colorectal Cancer After Failure of an Oxaliplatin Based Regimen (VELOUR)

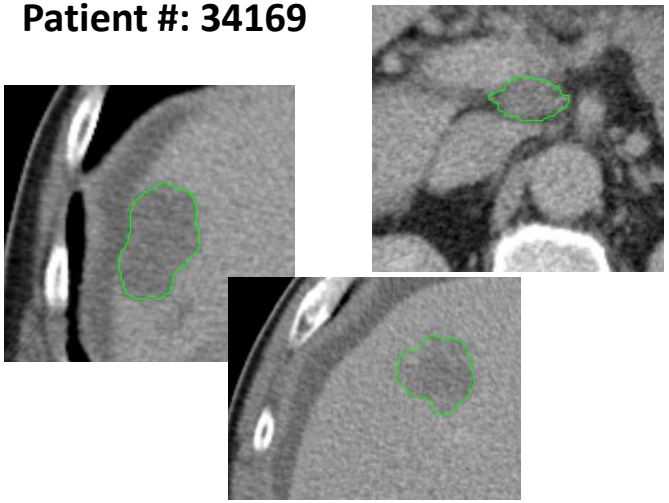
Patients:	930
Time points per patient:	Median 4 (2-18)
Total imaging studies (CT C/A/P):	4561
Total images:	3 million, 1.37 Tb
Total lesions analyzed:	14,060
Total lesions segmented:	3,081
Patients with progression by >20%	53%
Patients with progression by new lesion	11%

Target lesion selection on baseline study

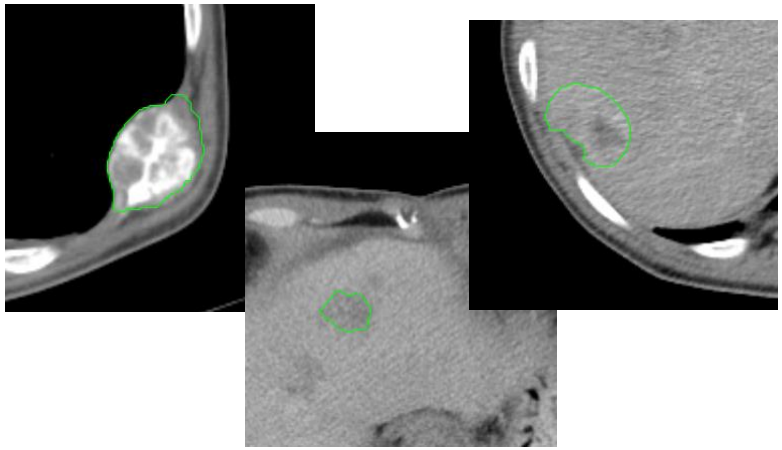


Patient #: 15656

Patient #: 34169

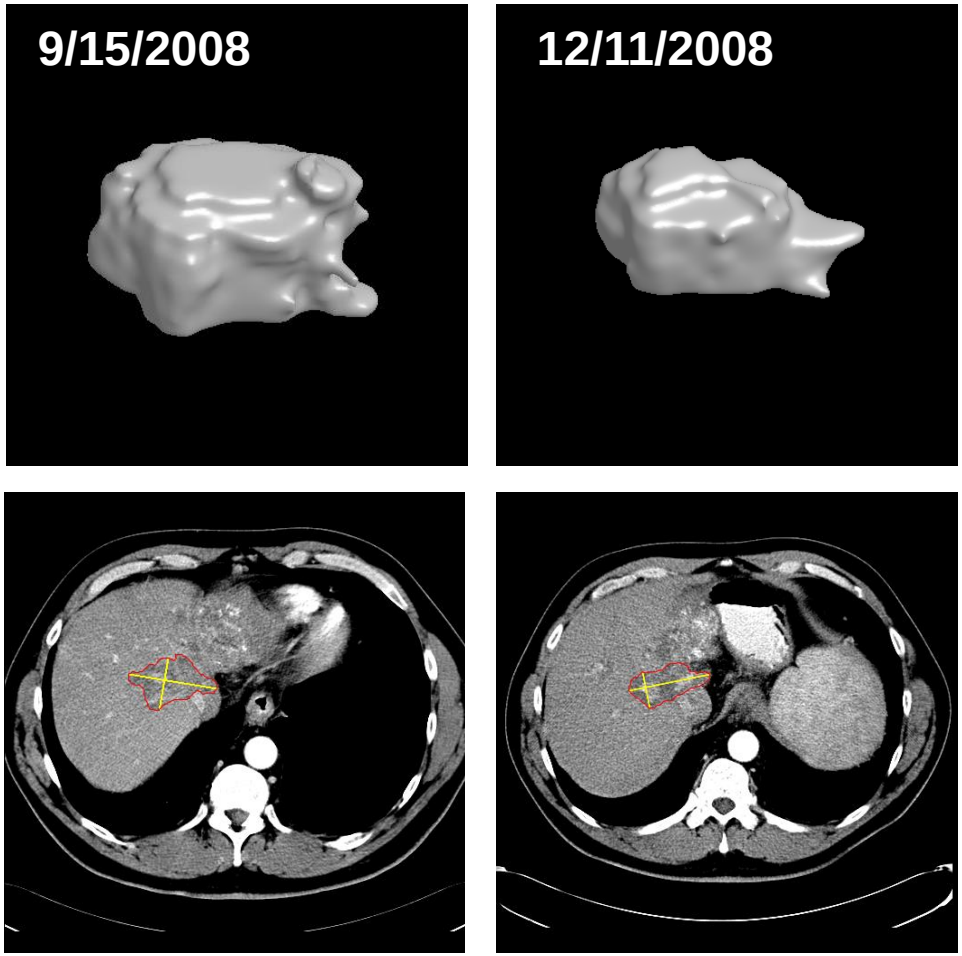


Patient #: 19175



3D Visualization and Measurement

Liver



Subject ID	Date	Uni (mm)	Volume (cm^3)
14753	9/15/2008	67.9	64.4
14753	12/11/2008	67.4	33.0
Change Rate		**-0.7%**	**-48.7%**

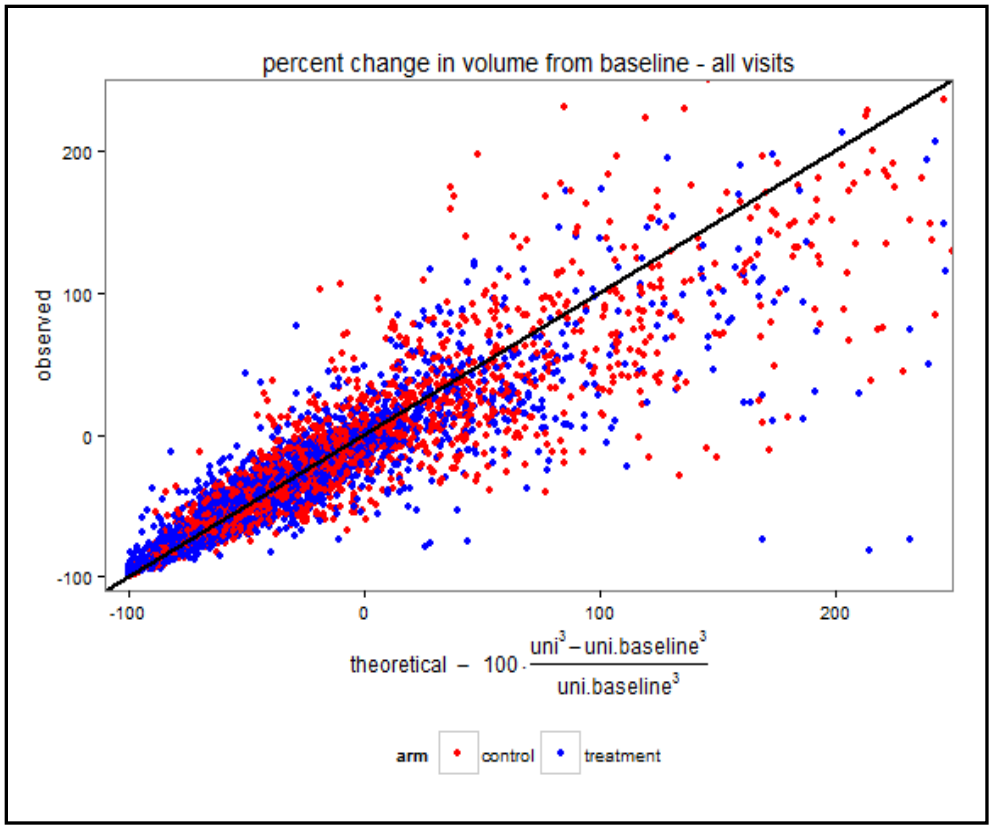
Measurement table for VELOUR study

N154

	A	B	C	E	F	G	H	K	L	M	N	O	P
1	Patient ID	Date	Target Lesion #	Lesion Site	Non-target	Non-measureable	Uni (mm)	Volume (mm^3)					
143	15656	2009-01-06	1	lung	3 lung, 3 liver		16.2	1116.1					
144	15656	2009-01-06	2	lung			25.4	4008.2					
145	15656	2009-01-06	3	medistinum LN			37.7	8654.2					
146	15656	2009-01-06	4	liver			63.5	53490.0					
147	15656	2009-01-06	5	liver			41.4	9529.3					
148	15656	2009-01-06	6	retroperitoneal LN			33.8	4375.3					
149	15656	2009-01-06	7	retroperitoneal LN			25.4	2291.5					
151	15656	2009-02-17	1	lung	3 lung, 3 liver		13.3	901.0					
152	15656	2009-02-17	2	lung			21.4	2387.9					
153	15656	2009-02-17	3	medistinum LN			32.9	3552.2					
154	15656	2009-02-17	4	liver			64.9	33511.9					
155	15656	2009-02-17	5	liver			35.0	6114.3					
156	15656	2009-02-17	6	retroperitoneal LN			28.0	3396.4					
157	15656	2009-02-17	7	retroperitoneal LN			34.0	3911.8					
159							-5.7	-35.6	% change in sum				
177													
178	36953	2008-02-26	1	lung			16.6	710.6					
179	36953	2008-02-26	2	lung			17.6	1148.5					
180	36953	2008-02-26	3	liver			46.4	8024.9					
181	36953	2008-02-26	4	liver			59.1	31306.8					
183	36953	2008-04-14	1	lung			16.6	633.3					
184	36953	2008-04-14	2	lung			20.0	794.4					
185	36953	2008-04-14	3	liver			37.0	6174.7					
186	36953	2008-04-14	4	liver			48.0	16746.1					
188							-13.0	-40.9	% change in sum				
189													
190	45629	2008-04-10	1	liver	1 lung lesion(too small)		92.1	70032.8					
191	45629	2008-04-10	2	liver			23.9	2173.9					
193	45629	2008-05-26	1	liver	lung lesion disappear		84.8	53727.2					
194	45629	2008-05-26	2	liver			41.9	8261.9					
196							9.2	-14.2	% change in sum				
197													
198	29478	2008-05-07	1	lung			31.0	5236.6					
199	29478	2008-06-30	1	lung			18.7	1208.1					
200							-39.8	-76.9	% change in sum				
201													

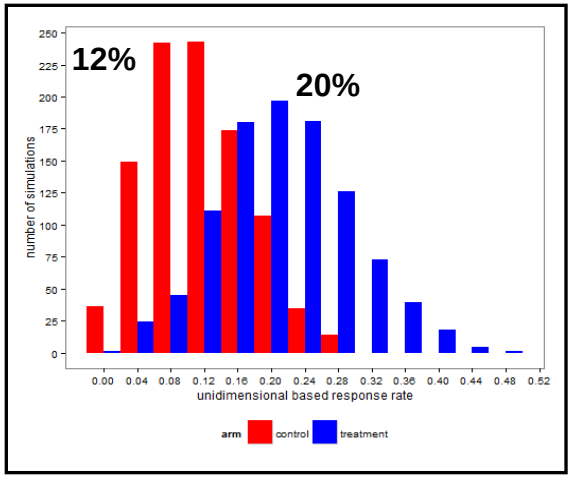
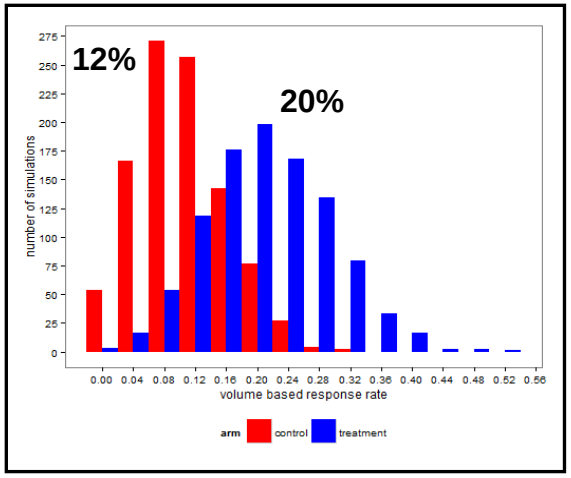
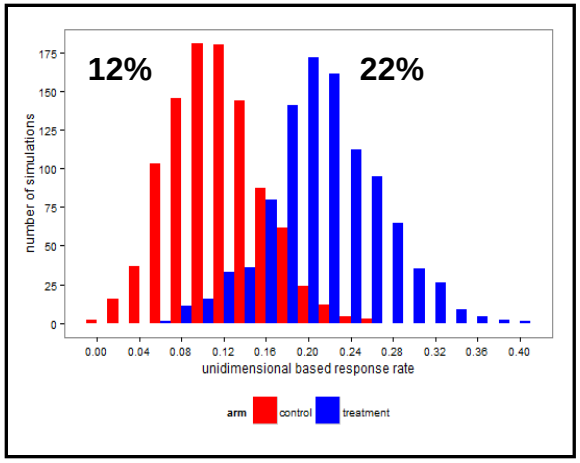
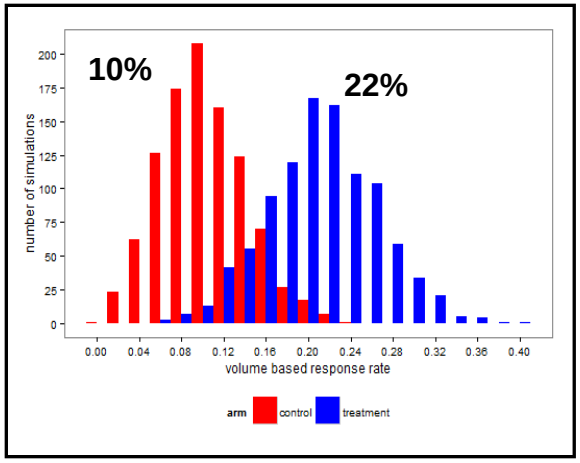
Step 2: Generate measurements

Volumetric measurements commonly differ from the expected volumetric change based on the observed diameter change



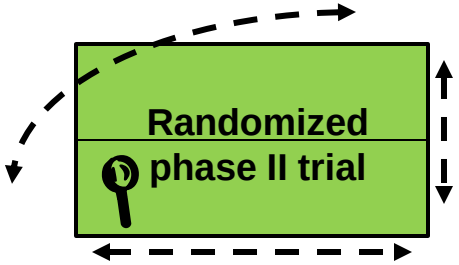
Step 3: Phase II trial simulations

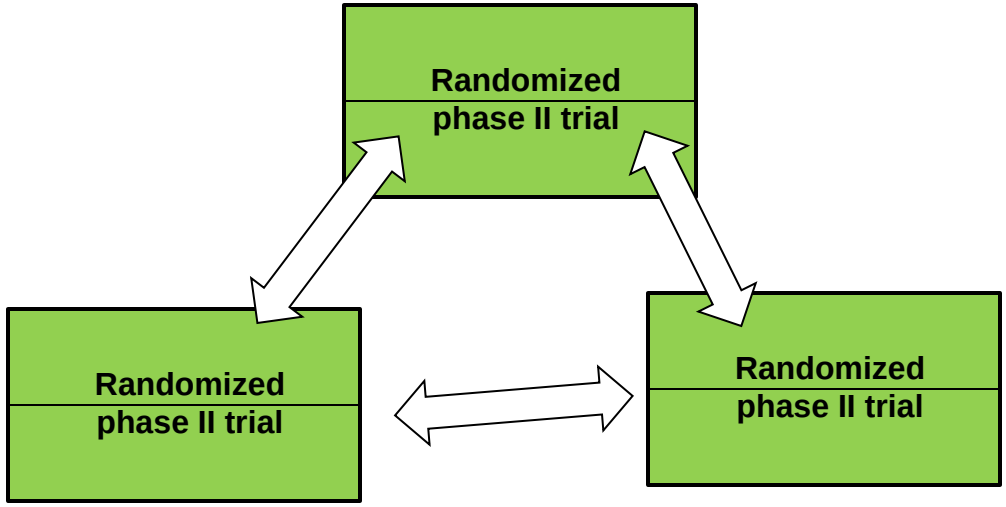
Distribution of ORR:

	Uni	Vol
25 pts per arm		
50 pts per arm		

Step 4: Analysis of simulated phase II trials

4) Comprehensively study each simulated randomized phase II trial with multiple metrics
   - Entire spectrum of measurement data will be studied, not just "best response"
   - Compare multiple simulations of the same trial to assess the reliability of each metric





Step 5: Predictive ability

5) Compare simulated trial results with the results from the parent phase III trials

Fisher exact test, $p<0.05$

25 per arm

	vol			
uni	control	treatment	no difference	total
control	0	0	0	0
treatment	0	51	25	76
no difference	0	35	889	924
total	0	86	914	1000

50 per arm

	vol			
uni	control	treatment	no difference	total
control	0	0	0	0
treatment	0	118	50	168
no difference	0	79	753	832
total	0	197	803	1000

Next steps

1) Study more response metrics
2) Quantify the added value from 1D, 2D, 3D measurement
3) Analyze more trials

Metric	Sensitivity	False positive rate
RECIST RR		
Disease control rate		
Minor response rate		
Tumor shrinkage rate		
Best response magnitude		
Initial response magnitude		

Immunotherapy

- There is a unique need for improved response and progression metrics given the atypical response kinetics seen with immune checkpoint inhibitors

Immunotherapy

The challenge:

- In diseases where PFS is a standard regulatory endpoint (breast cancer, colorectal cancer), PFS may not accurately capture the benefit of immune checkpoint inhibitors

The opportunity:

- Several agents (ipilimumab, nivolumab, pembrolizumab) are now approved from several sponsors (BMS, Merck).
- We can learn from this experience to facilitate future drug development

Immune Related Response Criteria(irRC)
Why?

- Mechanism of action of immunotherapy MAY result in lesion(s) in patient(s) which have a transient **increase** in size of existing lesions usually on the first or second follow up which do not persist – they ultimately decrease
- Small lesions (below the resolution of CT) may appear as "**new lesions**" usually on the first or second follow up which do not persist – they ultimately decrease

What are the differences between RECIST and irRC

	RECIST 1.1	irRC
SD	Neither 30% decrease compared to baseline nor 20% increase compared to nadir	Neither 50% decrease compared to baseline nor 25% increase compared to nadir
CR	Disappearance of all target and non-target lesions Nodes must regress to < 10mm short axis	Disappearance of all target and non-target lesions Nodes must regress to < 10mm short axis
PR	≥ 30% decrease in tumor burden compared with baseline	≥ 50% decrease in tumor burden compared with baseline Confirmation required

What are the differences between RECIST and irRC

	RECIST 1.1	irRC
PD	≥ 20% increase tumor burden compared with nadir AND/OR Appearance of new lesions	≥ 25% increase tumor burden compared with nadir Confirmation required at 2 consecutive time points New lesions are added to the sum of target lesions (up to 5) rather than representing automatic PD

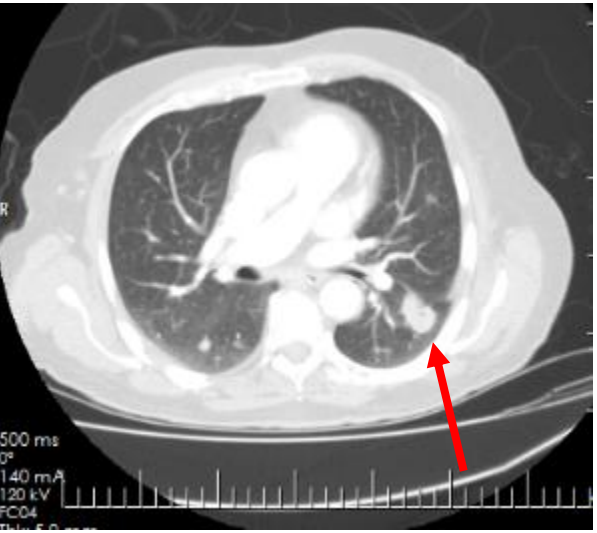
Value Statement

The potential power of new imaging metrics:

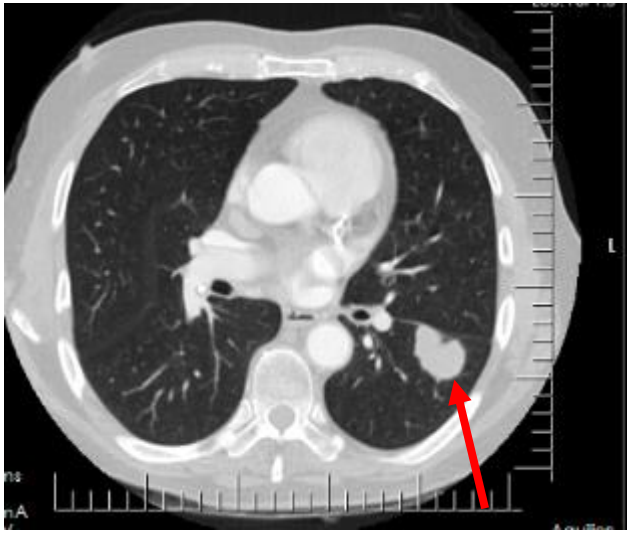
- Greater clarity for go/no-go decisions regarding phase III drug development
- More efficient trials, earlier results
- Flexibility to perform innovative subset analyses and dose finding
- Improved biomarker development and prognostication

Lung Lesion

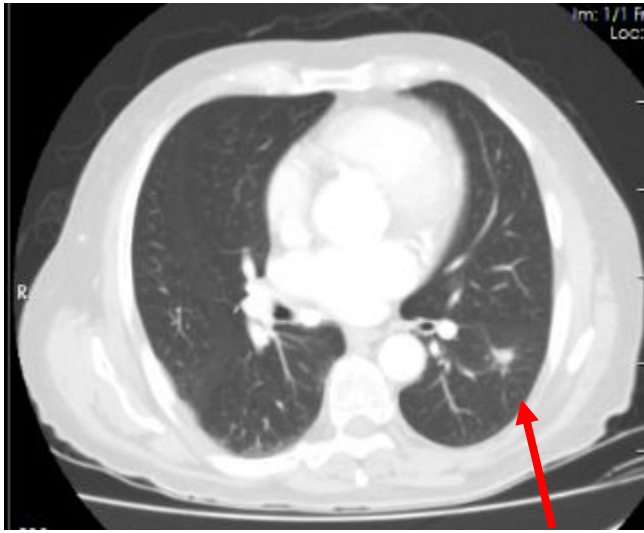
Baseline



Cycle 2

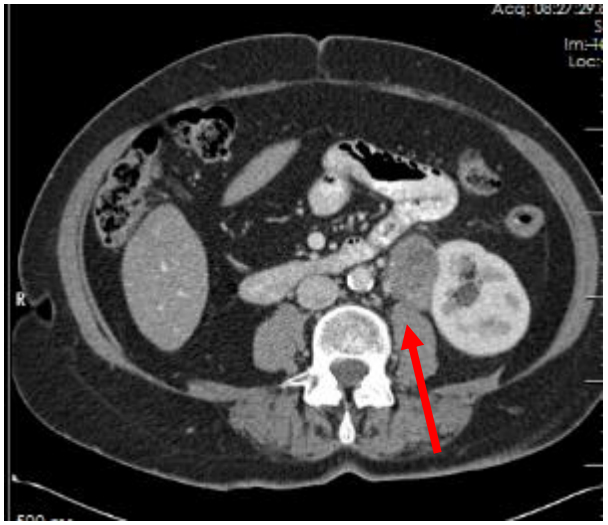


Cycle 4

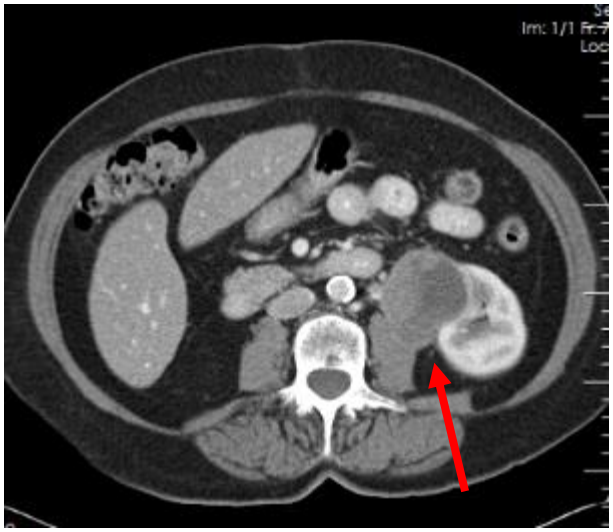


Peri-renal Mass

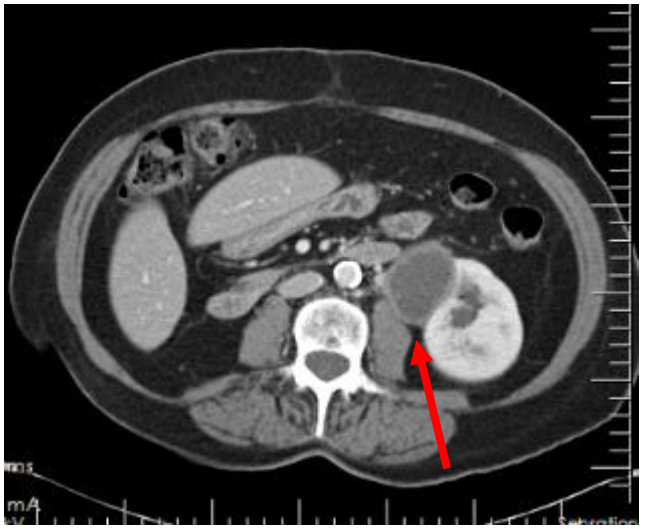
Baseline



Cycle 2

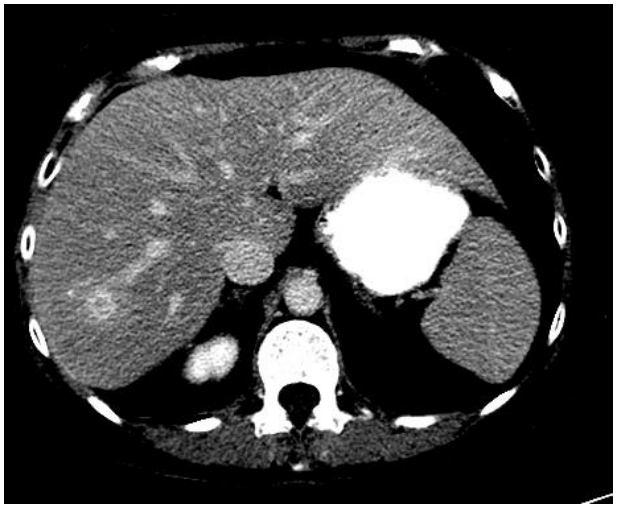


Cycle 6

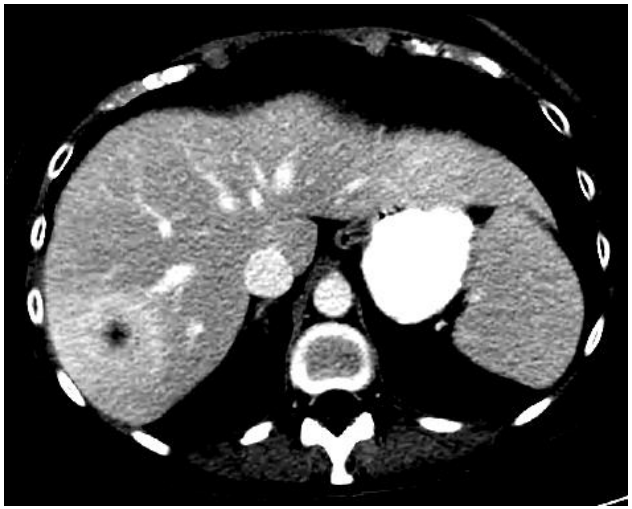


Hepatic Metastasis

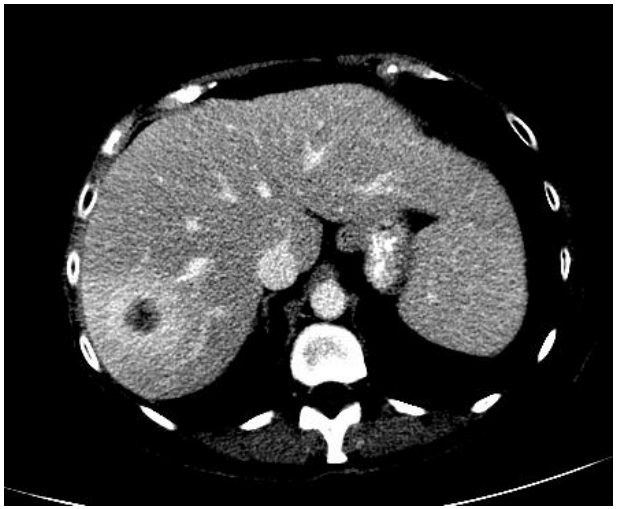
Baseline



Cycle 2



Cycle 4



Moving Forward . . .

- Problem Statement:
  - Oncology drug development is inefficient
    - 62.5% of phase III trials are negative
- Immunotherapy
    - Flare
    - New Lesions
    - Tumor shrinkage and growth

FRIENDS of CANCER RESEARCH

Center for Health Policy at BROOKINGS

FRIENDS / BROOKINGS ANNUAL MEETING

WENDY HAYES, MD

BRISTOL-MYERS SQUIBB

FRIENDS of CANCER RESEARCH

Center for Health Policy at BROOKINGS

FRIENDS / BROOKINGS ANNUAL MEETING

MARC THEORET, MD

FOOD AND DRUG ADMINISTRATION

Regulatory Perspective of ORR as an Endpoint in Oncology Drug Development

Marc R. Theoret, M.D.
Lead Medical Officer, Melanoma/Sarcoma Team
Division of Oncology Products 2
Office of Hematology and Oncology Products (OHOP)

November 17, 2015

Views expressed in this presentation are those of the presenter and not necessarily those of the U.S. FDA

Efficacy Endpoints: Categories

Direct Measures of Clinical Benefit

- **Endpoints Directly Measure How a Patient "Feels, Functions or Survives"**
  - **Overall survival (OS); measures of symptoms or function**

Surrogate Measures Predict (?) Clinical Benefit

- **Endpoints Not Direct Measures of Clinical Benefit**
- **Commonly Radiographic Measurements of Tumor Burden Changes (Specified Thresholds)**
  - **Time-dependent–e.g., progression-free survival (PFS)**
  - **Time-independent–e.g., objective response rate (ORR)**

FDA Guidance For Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Objective Response Rate: Multiple Variables

Considered in Response Determination

- **Location of Tumor**
- **Initial Tumor Burden – Qualitative**
- **Relative Change in Tumor Burden**
  - **Complete responses / Partial Responses**

Not Considered

- **Overall Tumor Burden - Quantitative**
- **Tumor Reduction Below Threshold (e.g., <30%)**
- **Duration of Responses**

ORR: Strengths and Limitations

Strengths:

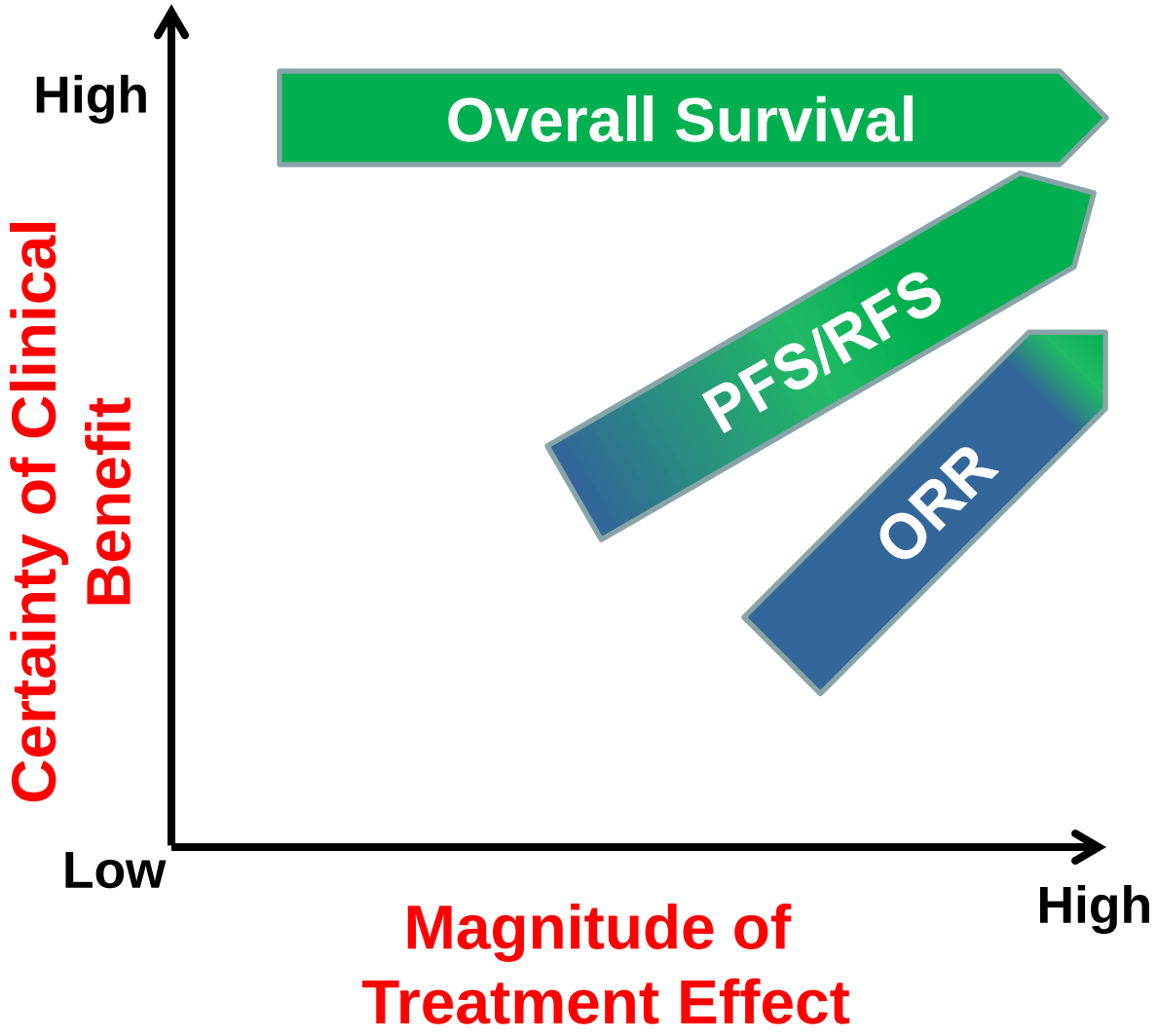
- **Direct Measure of Drug Effect**
  - **Decreases in tumor burden unlikely due to anything other than the therapy being studied**
  - **Allows for use of single-arm trials**
- **Early Event = Minimize Trial Duration, Fewer Patients**
- **Objective and Verifiable with Archived Scans**
- **Coupled with Response Durations Facilitates Benefit – Risk (B-R) Assessment**

ORR: Strengths and Limitations

Limitations:

- **In Enriched Populations, Historic Control Unclear**
- **Single-arm Trial – Challenging Safety Evaluation**
- **Few Regular Approvals Based on ORR**

Efficacy Endpoints: Magnitude of Treatment Effect



Approval Pathway:

- Accelerated
- Regular

FDA Expedited Programs for Serious Conditions - Drugs & Biologics

- **Accelerated Approval**
- **Priority Review Designation**
- **Breakthrough Therapy Designation**
- **Fast Track Designation**

All consider the available therapies to treat the serious condition for the disease context to determine whether there is an unmet medical need, or if the new therapy appears to provide an improvement or advantage over available therapies.

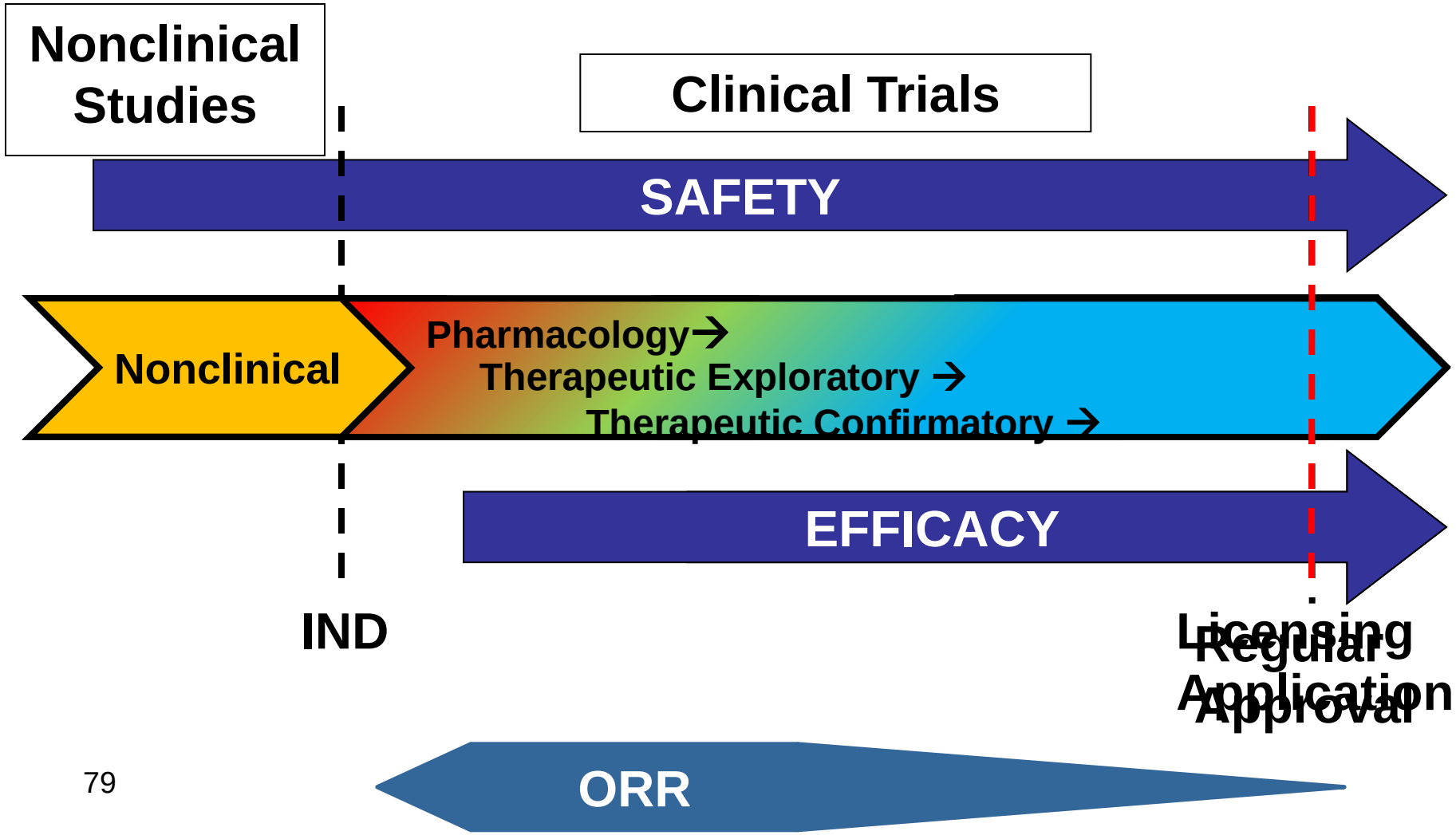
FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics

Expedited Programs - ORR

- **Breakthrough Therapy Designation Requests**
  - **CDER Analysis from 9/2012 to 12/2014***
  - **Hematology/Oncology – 86 (42%) of the 203 requests**
    - **27 (31%) Grant; 18 (21%) Withdrawn; 41 (48%) Denied**
    - **18 (67%) of 27 Granted Based on ORR**
- **NME Approvals (Oncology) in OHOP 2014-2015**
  - **Of the 20 NME Approvals, 11 were Accelerated Approvals**
  - **ORR → Primary Endpoint in 8 of the 11 Accelerated Approvals**

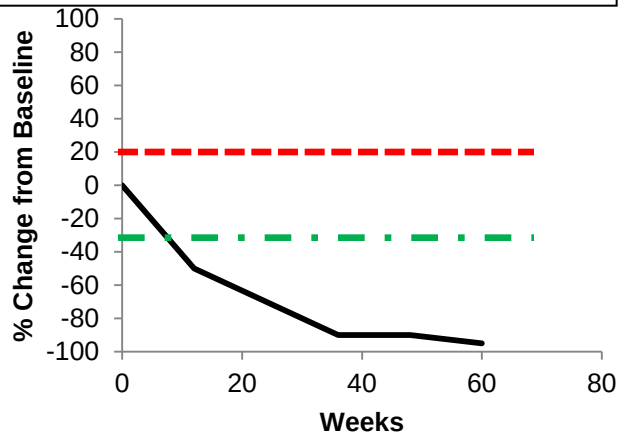
*Breakthrough Therapy Designation: Exploring the Qualifying Criteria; 4/24/15

Evolving Drug Development Paradigm

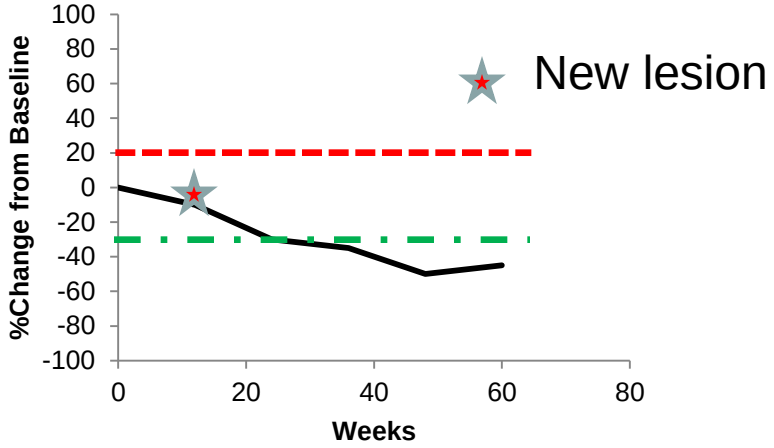


Immunotherapy: Patterns of Response

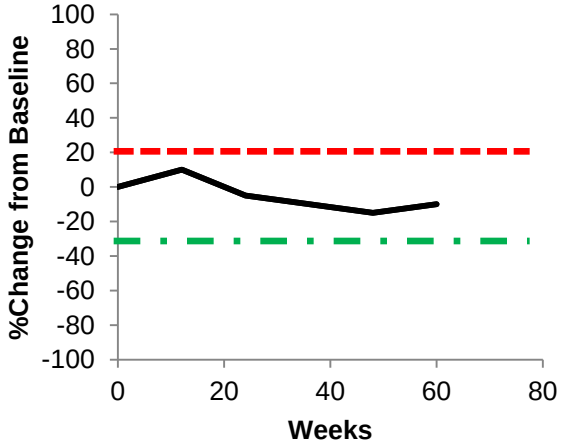
Continued Reduction in Lesions



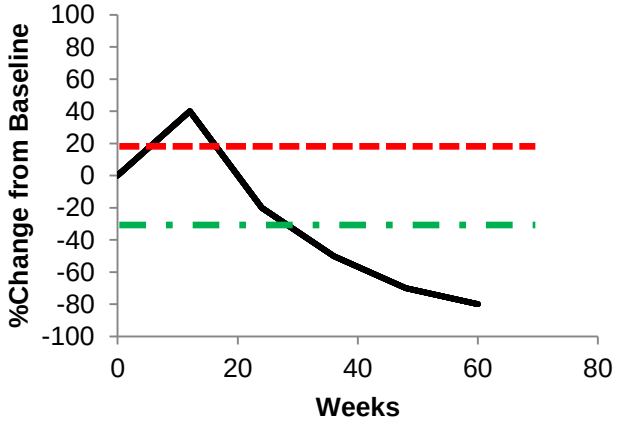
Reduction in Lesions with New Lesions



Stable Lesions



Initial Increase then Decrease in Lesions



Adapted from Wolchok, 2009, Clin Cancer Res

Immunotherapy: Progression of Disease and Patient Management on Trials

Example of Minimum Criteria for Continuing:

- **Absence of Symptoms And Signs Indicating Disease Progression**
- **No Decline in Performance Status**
- **Absence of Rapid Progression of Disease or of Progressive Tumor at Critical Anatomical Sites (e.g., Cord Compression) Requiring Urgent Alternative Medical Intervention**

Summary

- **ORR is an Important Endpoint for Oncology Drug Development**
  - **Directly measures effect of drug on disease**
  - **Standardized ORR criteria facilitate use of historical controls (i.e., single-arm trials)**
  - **Common endpoint to support FDA Expedited Program(s) for serious conditions**
  - **Magnitude and duration of response – key components of B-R**
- **Some Immunotherapy Response Patterns not Captured by Conventional Response Criteria**

Acknowledgements

- **Paul Kluetz, M.D.**
- **Patricia Keegan, M.D.**
- **Richard Pazdur, M.D.**

FRIENDS of CANCER RESEARCH

Center for Health Policy at BROOKINGS

FRIENDS / BROOKINGS ANNUAL MEETING

Supported by:

Susan G. Komen