Friends / Brookings Annual Meeting

Panel One: Modernizing Measurement of Tumor Response to Therapy
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
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 in tumor size can be slow or static and not reflective of tumor status.
- Limited utility in certain malignancies such as mesothelioma and neuroendocrine tumors.
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
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240-276-5936
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

<table>
<thead>
<tr>
<th></th>
<th>Response</th>
<th>Progression</th>
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<tbody>
<tr>
<td>Timing of assessment:</td>
<td>Assessed early in treatment course</td>
<td>Assessed at intervals until change of therapy</td>
</tr>
<tr>
<td>Role in clinical</td>
<td>Not normally used to determine whether to change therapy</td>
<td>Commonly used to determine when to change therapy</td>
</tr>
<tr>
<td>practice:</td>
<td></td>
<td></td>
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<tr>
<td>Role in clinical</td>
<td>Primarily used to calculate overall response rate</td>
<td>Primarily used to calculate time to progression endpoints</td>
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<tr>
<td>research:</td>
<td></td>
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**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:

- **RECIST 30% diameter decrease:** JNCI 2000
- **Equivalent to 65% volume decrease**
- **WHO 50% area decrease:** Cancer 1981

Variability of tumor palpation: Cancer 1976

“Decreases of less than 50%... [do] not seem possible to determine... with precision”
Response assessment

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

RECIST partial response rate

Proportion with confirmed partial response:

Non-response

RECIST PR
Response assessment

What counts as a response?

- RECIST does not consider depth of response

Area of response

In patients with minor response area under curve, as a fraction of CR in all patients
Response assessment

- Improved metrics for studying response could reduce variability

<table>
<thead>
<tr>
<th>Ramalingam et al, JCO, 2010</th>
<th>Belani et al, ESMO, 2009</th>
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<tbody>
<tr>
<td>NCI-supported consortia</td>
<td>Industry sponsored</td>
</tr>
<tr>
<td>94 patients</td>
<td>253 patients</td>
</tr>
<tr>
<td>Carbo/taxol: 12.5% RR</td>
<td>Carbo/taxol: 29.3% RR</td>
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<tr>
<td>4.1m PFS</td>
<td>5.5m PFS</td>
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<tr>
<td>&amp; vorinostat: 34.0% RR</td>
<td>&amp; vorinostat: 22.4% RR</td>
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<tr>
<td>6.0m PFS</td>
<td>4.3m PFS</td>
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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

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

**Median (months)**

<table>
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<tr>
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<tr>
<td>HR</td>
<td>0.54</td>
<td>0.54</td>
</tr>
<tr>
<td>CI</td>
<td>0.36–0.79</td>
<td>95% CI: 0.36–0.79</td>
</tr>
<tr>
<td>P value*</td>
<td>0.0015</td>
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</table>

*log-rank test, two-sided

Presented by: Terufumi Kato
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
--- | --- | ---

![Baseline Image](image1)
![Cycle 2 Image](image2)
![Cycle 6 Image](image3)
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
---|---|---

![Baseline Image](image1.png)  |  ![Cycle 2 Image](image2.png)  |  ![Cycle 4 Image](image3.png)
Nivolumab in nonsquamous NSCLC Overall Survival

<table>
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<th>Nivolumab (n = 292)</th>
<th>Docetaxel (n = 290)</th>
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<tr>
<td>mOS, mo</td>
<td>12.2</td>
<td>9.4</td>
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<tr>
<td>HR</td>
<td>0.73 (96% CI: 0.59, 0.89);</td>
<td>(P = 0.0015)</td>
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<tr>
<td>1-yr OS rate</td>
<td>51%</td>
<td>39%</td>
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Symbols represent censored observations.

Paz-Arez et al, ASCO, 2015
Nivolumab in nonsquamous NSCLC

Progression Free Survival

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<td>(n = 292)</td>
<td>(n = 290)</td>
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<tr>
<td>mPFS, mo</td>
<td>2.3</td>
<td>4.2</td>
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<tr>
<td>HR</td>
<td>0.92 (95% CI: 0.77, 1.11);</td>
<td>P = 0.3932</td>
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Number of Patients at Risk

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<th>Docetaxel</th>
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<td>292</td>
<td>290</td>
</tr>
<tr>
<td>1-yr PFS rate</td>
<td>19%</td>
<td>8%</td>
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Paz-Arez et al, ASCO, 2015
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
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 Kettering Cancer Center,
Michael Maitland, MD PhD, University of Chicago
• 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
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
• Prior repeat CT study has shown that small changes (>10% diameter, >20% volume) can be reliable
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
Furthermore, advanced imaging of the whole tumor volume can characterize the biology of tumor growth and response.

Diameter (RECIST) 1D

Cross-product (WHO) 2D

Volume 3D
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

<table>
<thead>
<tr>
<th>Trial Sponsor</th>
<th>Disease</th>
<th>Drug</th>
<th>Trial ID</th>
<th>N</th>
<th>Data Sharing Agreement</th>
<th>Data Transfer</th>
<th>Data Analysis</th>
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<td>Sanofi</td>
<td>CRC</td>
<td>FOLFIRI +/- aflibercept</td>
<td>VELOUR</td>
<td>1226</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>GSK/Novartis</td>
<td>RCC</td>
<td>Pazopanib vs. placebo</td>
<td>VEG105192</td>
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<td>✓</td>
<td>✓</td>
<td>Ongoing</td>
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<tr>
<td>GSK/Novartis</td>
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<td>Pazopanib vs. sunitinib</td>
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<tr>
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<td>CRC</td>
<td>BSC +/- panitumumab</td>
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<td>463</td>
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<td>TBD</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
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

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<th>Subject ID</th>
<th>Date</th>
<th>Uni (mm)</th>
<th>Volume (cm^3)</th>
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<td>14753</td>
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Change Rate

- 0.7%
- 48.7%
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<th>Patient ID</th>
<th>Date</th>
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<th>Lesion Site</th>
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<th>Volume (mm³)</th>
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<td>2009-01-06</td>
<td>1</td>
<td>lung</td>
<td>3 lung, 3 liver</td>
<td>16.2</td>
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<th>Lesion Site</th>
<th>Non-target</th>
<th>Non-measurable</th>
<th>Uni (mm)</th>
<th>Volume (mm³)</th>
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<td>2008-06-10</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Date</th>
<th>Target Lesion #</th>
<th>Lesion Site</th>
<th>Non-target</th>
<th>Non-measurable</th>
<th>Uni (mm)</th>
<th>Volume (mm³)</th>
</tr>
</thead>
</table>
| 201        |            |                 |                     | 39.8 | 78.9 | 76.9 | % change in sum


Step 2: Generate measurements

Volumetric measurements commonly differ from the expected volumetric change based on the observed diameter change.
Distribution of ORR:

Step 3: Phase II trial simulations

Distribution of ORR:

25 pts per arm

50 pts per arm

Uni

Vol
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

<table>
<thead>
<tr>
<th>uni</th>
<th>control</th>
<th>treatment</th>
<th>no difference</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>treatment</td>
<td>0</td>
<td>51</td>
<td>25</td>
<td>76</td>
</tr>
<tr>
<td>no difference</td>
<td>0</td>
<td>35</td>
<td>889</td>
<td>924</td>
</tr>
<tr>
<td>total</td>
<td>0</td>
<td>86</td>
<td>914</td>
<td>1000</td>
</tr>
</tbody>
</table>

50 per arm

<table>
<thead>
<tr>
<th>uni</th>
<th>control</th>
<th>treatment</th>
<th>no difference</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>treatment</td>
<td>0</td>
<td>118</td>
<td>50</td>
<td>168</td>
</tr>
<tr>
<td>no difference</td>
<td>0</td>
<td>79</td>
<td>753</td>
<td>832</td>
</tr>
<tr>
<td>total</td>
<td>0</td>
<td>197</td>
<td>803</td>
<td>1000</td>
</tr>
</tbody>
</table>
Next steps

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

<table>
<thead>
<tr>
<th>Metric</th>
<th>Sensitivity</th>
<th>False positive rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease control rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor response rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor shrinkage rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best response magnitude</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial response magnitude</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
There is a unique need for improved response and progression metrics given the atypical response kinetics seen with immune checkpoint inhibitors.
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
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

<table>
<thead>
<tr>
<th></th>
<th>RECIST 1.1</th>
<th>irRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD</td>
<td>Neither 30% decrease compared to baseline nor 20% increase compared to nadir</td>
<td>Neither 50% decrease compared to baseline nor 25% increase compared to nadir</td>
</tr>
<tr>
<td>CR</td>
<td>Disappearance of all target and non-target lesions</td>
<td>Disappearance of all target and non-target lesions</td>
</tr>
<tr>
<td></td>
<td>Nodes must regress to &lt; 10mm short axis</td>
<td>Nodes must regress to &lt; 10mm short axis</td>
</tr>
<tr>
<td>PR</td>
<td>$\geq 30%$ decrease in tumor burden compared with baseline</td>
<td>$\geq 50%$ decrease in tumor burden compared with baseline</td>
</tr>
<tr>
<td></td>
<td>Confirmation required</td>
<td>Confirmation required</td>
</tr>
</tbody>
</table>
What are the differences between RECIST and irRC

<table>
<thead>
<tr>
<th></th>
<th>RECIST 1.1</th>
<th>irRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>≥ 20% increase tumor burden compared with nadir AND/OR Appearance of new lesions</td>
<td>≥ 25% increase tumor burden compared with nadir Confirmation required at 2 consecutive time points</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New lesions are added to the sum of target lesions (up to 5) rather than representing automatic PD</td>
</tr>
</tbody>
</table>
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
• Problem Statement:
  • Oncology drug development is inefficient
    • 62.5% of phase III trials are negative
• Immunotherapy
  • Flare
  • New Lesions
  • Tumor shrinkage and growth
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)
Objectives 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

Certainty of Clinical Benefit

- High
- Low

Magnitude of Treatment Effect

- Low
- High

Overall Survival

PFS/RFS

ORR

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.
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

Nonclinical Studies

Clinical Trials

SAFETY

Pharmacology → Therapeutic Exploratory → Therapeutic Confirmatory →

EFFICACY

IND

Licensing Application

ORR
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.
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- Richard Pazdur, M.D.