Panel One:

Alternative Trial Designs Based on Tumor Genetics/Pathway Characteristics
Alternative Trial Designs Based on Tumor Genetics and/or Pathway Characteristics Instead of Histology

George D. Demetri, MD
Senior Vice President for Experimental Therapeutics
Dana-Farber Cancer Institute
Ludwig Center at Dana-Farber/Harvard Cancer Center
Harvard Medical School
Boston, Massachusetts
gdemetri@partners.org
We now have better understanding of pathways in cancer

Adapted from Dawelbait G et al. Bioinformatics 2007;23:i115-i124
Mapping relevant interactions and pathways in cancer cells

Adapted from Dawelbait G et al. Bioinformatics 2007;23:i115-i124

Hanahan and Weinberg, Cell 2011
TUMOR TYPE 1

BREAST CANCER

TUMOR TYPE 3

PANCREAS C"

...SARCOMAS...
Cancers are often managed based on where the first tumor starts.
What is the “standard process” for anticancer drug development?
How can we accelerate this process to bring the right new drugs to the right patients as efficiently as possible?
A MOLECULAR TARGET THAT DRIVES CANCER
Identifying challenges to the success of this process
Challenge # 1: Measuring the value of tumor cell origin (histology) while aggregating cancers by molecular target
Challenge # 2:

Working with regulatory authorities to agree on transparent metrics for success of new trial designs across cancer types
Challenge # 3:

Biology and complexity of cancer
USERNAME / SmilesforMiles01
“Mowing the lawn is very therapeutic.”
Different perspectives in addressing this today:

Patient and Advocate Perspective:
Josh Sommer (Chordoma Foundation)

NCI perspective: Dr. James Doroshow

A Modest Proposal with Industry Support:
Dr. Perry Nisen (GlaxoSmithKline)

FDA perspective: Dr. Robert Becker

Regulatory Overview: Dr. Janet Woodcock (FDA)
Conference on Clinical Cancer Research

Alternative Trial Designs Based on Tumor Genetics/Pathway Characteristics

Josh Sommer, Patient Advocate
The Chordoma Foundation

November 10, 2011 • Washington, DC
Alternative Trial Designs Based on Tumor Genetics/Pathway Characteristics Instead of Histology

James H. Doroshow, M.D.
Deputy Director for Clinical and Translational Research
National Cancer Institute
1985-2005: *Dogma*: Two-stage Fleming or Simon Designs; occasional randomized phase II’s

- Purpose: Estimate an objective response rate of patients with a specified tumor type to a particular drug
- At least two trials with ‘adequate’ numbers of patients in each major tumor type (N=14-25)
- All patients entered must have measurable disease
- All patients must have maximum performance status and minimum prior therapy
- If no objective responses seen in 25 patients, drop Rx
- Large phase II studies to define levels of activity are generally not indicated

R. Wittes et al., *Cancer Treat. Rep.* 70: 1105, ‘86
Published Phase II Cancer Treatment Trials: 1965-2005

Exclusive Use of Histology-Based Ph II Designs
Most Drugs Fail in Late Stages of Development—Particularly in Oncology

Rates of success for compounds entering first in man that progress to subsequent phase

- 70% of oncology drugs that enter Phase 2 fail to enter Phase 3
- 59% of oncology drugs that enter Phase 3 fail
- Late stage failure leads to enormous risk

Kola & Landis; Nature Reviews Drug Discovery 2004
Why Continue to Focus On A “Given Tumor Type”?

“Primary objective of phase II trials is to screen for preliminary evidence of efficacy in a given tumor type.” [Defined histologically; J. Clin. Oncol. 26: 1346, 2008]

- Limited by modest availability of qualified molecular classifiers in therapeutics
- Limited by the complexity of performing evaluations of appropriate molecular markers in Phase II
- Limited by the lack of funding for these critical studies
Target Inhibition as the Endpoint of a Phase II Trial: Proof of Concept Study of Oral Topotecan in Advanced Solid Neoplasms Expressing HIF-1α

NCI-05-C-0186: Giovanni Melillo, MD PI

• Eligibility: HIF-1α +ve solid tumors of any histology (>10% of tumor cells by IHC)
• Treatment: Oral chronic topotecan (1.2 mg/m2 PO daily x 5 days x 2 wks q28 days)
• Primary endpoint: Inhibition of HIF-1α expression in tumor
• Schema:

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>PET</th>
<th>DCE-MRI</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>D1</td>
<td>D8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PET DCE-MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D29</td>
<td>D36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Biopsy PET DCE-MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CT</td>
</tr>
</tbody>
</table>

Cycle 1  Cycle 2

PD endpoints:
• IHC (MVD, Glut-1)
• mRNA expression (HIF-1 target genes, VEGF, PGK-1, CAIX)
• serum/plasma markers (VEGF, osteopontin)
• CEP (circulating endothelial precursor cells)
Pilot Study of Oral Topotecan in Advanced Solid Neoplasms Expressing HIF-1α

✓ Accrual: 16 patients
  • 12 evaluable: 1 melanoma, 1 bladder, 1 breast, 2 ovarian ca., 1 SCLC, 1 bladder, 1 H/N, 4 CRC [PRs in SCLC, Ovarian cancer]
  • 4 not evaluable: 1 ASPS, 1 adrenal, 1 colon, 1 pancreas
✓ Toxicities: myelosuppression, diarrhea (first 2 pts., at 1.6 mg/m²), well tolerated at 1.2 mg/m²

HIF-1α staining in patient #4 (breast cancer)

Baseline Biopsy
After 2 Cycles of Topotecan

mRNA Expression of HIF-1α Downstream Targets After Topotecan

Design Studies Based on Molecular Characteristics

*Because:*

- Current trial designs are not based on predictive, disease-specific preclinical models or (often) on predictive tumor biology
- Potentially more efficient: decrease regulatory and administrative burden—1 protocol; still requires appropriate sample sizes for each investigational group studied
- May speed up the evaluation of target effects of agent(s) across tumor types with potential to improve biomarker development/qualification
- May provide opportunity “borrow” efficacy and toxicity experience across all patients enrolled in the study
Conference on Clinical Cancer Research

Alternative Trial Designs Based on Tumor Genetics/Pathway Characteristics

Perry Nisen
Oncology R & D, GlaxoSmithKline

November 10, 2011 • Washington, DC
Alternative Trial Designs Based on Tumor Genetics/Pathway Characteristics

Bob Becker
CDRH, U.S. FDA

November 10, 2011 • Washington, DC
Conference on Clinical Cancer Research

Alternative Trial Designs Based on Tumor Genetics/Pathway Characteristics

Janet Woodcock
CDER, U.S. FDA

November 10, 2011 • Washington, DC