Cancer Research Diagnostics, Therapeutics and Clinical Trials

Razelle Kurzrock, MD
Murray Professor of Cancer Research
Senior Deputy Director for Clinical Science
Director, Center for Personalized Cancer Therapy and Clinical Trials Office
Vice Chief, Division of Hematology/Oncology

UNIVERSITY of CALIFORNIA
SAN DIEGO
MEDICAL CENTER
MOORES CANCER CENTER
Why are cancers difficult to treat?

-Agents work only in those with a sensitizing aberration

Braiteh….MCT  2007

Lung Cancer

Sharma, Nat Rev Cancer 2010
Molecular matching can result in high response rates

<table>
<thead>
<tr>
<th>Drug</th>
<th>Biomarker</th>
<th>Disease</th>
<th>Response Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>BCR-ABL fusion</td>
<td>CML</td>
<td>~80%</td>
</tr>
<tr>
<td>Imatinib</td>
<td>KIT mutation</td>
<td>GIST</td>
<td>~50%</td>
</tr>
<tr>
<td>Olaparib</td>
<td>BRCA1, 2 mutations</td>
<td>Diverse cancers</td>
<td>~40%</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>BRAF mutation</td>
<td>Melanoma</td>
<td>~50%</td>
</tr>
<tr>
<td>vismodegib</td>
<td>PTCH1 mutation</td>
<td>Basal cell cancer</td>
<td>~30 to 43%</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>EML4-ALK fusion</td>
<td>NSCLC</td>
<td>~50 to 60%</td>
</tr>
<tr>
<td>PI3K/AKT/mTOR inhibitor-based Rx</td>
<td>PIK3CA mutation</td>
<td>Diverse cancers</td>
<td>~35%</td>
</tr>
</tbody>
</table>
PIK3CA mutations were found in 10% of 1,000 patients with advanced cancers

- Endometrial cancers (29%)
- Breast cancers (24%)
- Colon cancers (17%)
- Ovarian cancers (14%)
- Lung cancer (13%)
- Head and neck squamous cell cancers (13%)
- Pancreatic cancers (13%)

Molecular aberrations do not segregate well by organ of origin
Genomic Technology: Rapid Progress

Current (2013)

- ~10 days
- ~$5000
- 30-50X

Genome sequencing costs and progress over time, showing a significant decrease in cost and increase in number of genomes sequenced.
What if every patient with metastatic disease is different?

<table>
<thead>
<tr>
<th>Pt number</th>
<th>Molecular Results (Foundation Medicine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PIK3CA amplification, SOX2 amplification, TP53 G302fs<em>42, FLT3 L260</em></td>
</tr>
<tr>
<td>2</td>
<td>AKT1 (E17K)</td>
</tr>
<tr>
<td>4</td>
<td>EGFR amplification, CCND1 amplification, CDKN2A/B loss, FGFR1 amplification, MYC amplification, TP53 P151A</td>
</tr>
<tr>
<td>42</td>
<td>ERBB2 amplification, PIK3CA H1047L, AURKA amplification, TP53 R342P, CREBBP P858S, ZNF217 amplification</td>
</tr>
<tr>
<td>25</td>
<td>ERBB2 amplification, MYC amplification, CDK6 amplification, TP53 R213*</td>
</tr>
<tr>
<td>7</td>
<td>ESR1 Y537S</td>
</tr>
<tr>
<td>13</td>
<td>GATA3 <em>445fs</em>2+</td>
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<tr>
<td>16</td>
<td>RET C634R, GATA3 P436fs*11+</td>
</tr>
<tr>
<td>18</td>
<td>AKT3 amplification, MYC amplification, MYCL1 amplification, TP53 R248Q</td>
</tr>
<tr>
<td>54</td>
<td>NF1 R1276Q</td>
</tr>
</tbody>
</table>
Pt #49; Gastric Cancer
FGFR2 amplification, CDKN2A loss, MYC amplification, APC I1307K, ARID1A P2139fs*62, TP53 F113C (p14ARF is alternate reading frame (ARF) of CDKN2A)

San Diego Supercomputer Center, UCSD

Analyzed by by Dr. Igor F. Tsigelny,
Tip of the Iceberg

Genomics

Transcriptome

Proteomics

Epigenetic changes
Transforming Outcomes in Solid Tumors? Is It About Time?
Lessons from the Chronic Myelogenous Leukemia (CML) Story
A Fatal Disease Transformed

- Median survival in 1980s was about 4 years
- Median survival in 2012 is 20+ years
Treatment of Medulloblastoma with Hedgehog Pathway Inhibitor GDC-0449

Figure 1. Tumor Response on Positron-Emission Tomographic (PET) Scanning.
Whole-body projections from $^{18}$F-fluorodeoxyglucose (FDG)–PET scans are shown. Panel A shows the pretreatment scan; Panel B, the repeat scan after 2 months of therapy with the hedgehog pathway inhibitor GDC-0449; and Panel C, the repeat scan after 3 months of therapy.
Metastases = Blast Crisis in Leukemia
Key factors leading to the revolution in outcome of chronic myelogenous disease

- Key factors:
  - Known driver target (Bcr-Abl)
  - Targeted agent (imatinib)
  - Treat newly-diagnosed patients

Response rates:
- Newly diagnosed: >90%
- Accelerated phase: ~20%
- Blast crisis: <10%
Evolution of Clinical Trial Design

Smaller Trials, Bigger Chance for Success

OLD MODEL: Large numbers of patients, not selected by molecular characteristics; lower chance of demonstrating effectiveness, since many participants do not have the molecular defects being targeted.

NEW MODEL: Small patient populations, all with the relevant mutations or genetic defects; greater chance of desired results, since all participants have the potential to respond.
Problems with stage 1 novel paradigms if majority of patients with metastatic cancer are unique

- Each patient needs specially tailored treatment regimen
- If there are 300 drugs in oncology, number of two drug combinations is ~45,000, number of three drug combinations ~4,455,100
- It will take over 1,000 years to figure this out
Redesigning clinical trials
Stage 2

- Use multiplex markers to diagnose/classify cancers
- Validate a strategy, not just a drug(s) or a marker(s)
- Understand convergence pathways
- Use rule of thumb for safe combinations
- Proof of principle trials in metastatic disease—then treat early
Barriers to personalized trials

Medication acquisition/repurposing drugs

Increased regulatory burden for molecular trials

Need for new clinical trial paradigms
  → N of One strategies
  → Trials earlier in the disease
  → Customized combinations
THANK YOU
and
Questions??