Genomic Complexity of Metastatic Disease
The Conundrum of Combinations

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No conflicts of interest
Advanced, Integrated Omics
Lessons Learned

→ Use combinations of matched drugs for metastatic or complex tumors

→ Treat newly diagnosed patients

→ Omics is a disruptive technology; retrofitting the reality unveiled into traditional paradigms is suboptimal

→ Transformative changes will require new models for clinical research and practice
Why are cancers difficult to treat?

Divide and Conquer

Agents work only in those with a sensitizing aberration

Braiteh….Kurzrock, MCT  2007

Munoz J, Swanton C, Kurzrock R, Molecular Profiling and the Reclassification of Cancer; Am Soc Clin Oncol Educ Book. 2013:

Sharma, Nat Rev Cancer 2010
Traditional drugs/trials give incremental benefits

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tumor</th>
<th>Survival Gain</th>
<th>CR (single agent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>gemcitabine</td>
<td>pancreas</td>
<td>1.5 months</td>
<td>≈ 0%</td>
</tr>
<tr>
<td>bevacizumab</td>
<td>colon</td>
<td>2.2 months</td>
<td>≈ 0%</td>
</tr>
<tr>
<td>erlotinib</td>
<td>pancreas</td>
<td>11 days</td>
<td>≈ 0%</td>
</tr>
<tr>
<td>bevacizumab</td>
<td>NSCLC</td>
<td>2 months</td>
<td>≈ 0%</td>
</tr>
<tr>
<td>sorafenib</td>
<td>renal</td>
<td>2 months</td>
<td>≈ 0%</td>
</tr>
<tr>
<td>temozolamide</td>
<td>glioblastoma</td>
<td>2.5 months</td>
<td>≈ 0%</td>
</tr>
<tr>
<td>docetaxel</td>
<td>prostate</td>
<td>2.4 months</td>
<td>≈ 0%</td>
</tr>
<tr>
<td>cetuximab</td>
<td>colon</td>
<td>1.5 months</td>
<td>≈ 1-2%</td>
</tr>
</tbody>
</table>
Master Protocol

Profile-Related Evidence Determining Individualized Cancer Therapy

PREDICT

- Histology-Independent targeted approach
- Multiple molecular aberrations assessed
- Patients matched with targeted agents
*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.
Best RECIST Response.
Patients with 1 mutation

Matched therapy
N=175
Complete/Partial Response = 27%

Therapy without matching
N=116
Complete/Partial Response = 5%
p<.0001

Failure free survival (FFS2) improves with Phase I matched therapy but not unmatched compared to prior conventional therapy FFS1.
# Genomic Technology: Breathtaking Progress

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Time taken (start to finish)</td>
<td>13 years</td>
<td>4 years</td>
<td>4.5 months</td>
<td>~10 days</td>
</tr>
<tr>
<td>Number of scientists listed as authors</td>
<td>&gt; 2,800</td>
<td>31</td>
<td>27</td>
<td></td>
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<tr>
<td>Cost of sequencing (start to finish)</td>
<td>$2.7 billion</td>
<td>$100 million</td>
<td>&lt; $1.5 million</td>
<td>~$5000</td>
</tr>
<tr>
<td>Coverage</td>
<td>8-10 ×</td>
<td>7.5 ×</td>
<td>7.4 ×</td>
<td>30-50X</td>
</tr>
<tr>
<td>Number of institutes involved</td>
<td>16</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Number of countries involved</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td></td>
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</tbody>
</table>

**QUICKER, SMALLER, CHEAPER**

![Graph showing the decrease in cost per human genome over time](image-url)

- **Venter**
- **Watson**
- **African, Asian, Cancer pair**
- **169 in Genbank**
- **Individual Genome Sequencing**
Malignant Snowflakes
Metastatic Cancer

Wheler J……Kurzrock R. Oncotarget, 2014
<table>
<thead>
<tr>
<th>Pt number</th>
<th>Molecular Results (Foundation Medicine)</th>
</tr>
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<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>
</tr>
<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>
Tip of the Iceberg

Genomics
Transcriptome
Proteomics
Epigenetic changes
Hereditary Predispositions

Host and Toxicity/Response/Immunity/Microenvironments
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
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.
Response Rate of Chronic Myelogenous Leukemia Rises Rapidly in Newly Diagnosed Disease
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
Strategies

- Combinations for Advanced Disease
- Treat Newly Diagnosed Disease
Evolution of Clinical Trial Design
Redesigning Cancer Trials: Stage 1

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

• Drug-centric to patient-centric
• Testing a “strategy” not a drug
• The issue of combinations

The strategy is customized drug regimens based on molecular matching
Drug-Centric Trial (Traditional)

**Strategy**: Find common feature between patients (e.g. type of cancer or type of molecular aberration) and place all on same drugs.
Instead of using a consistent drug between patients even in the presence of different molecular profiles (old way), use a consistent strategy (molecular matching) but allow different drugs
Patient-Centric Trial (New)

Patient 1
Aberrant A, B, C

Drug A

Drug B

Drug C

Patient 2
Aberrant C, E, F

Drug C

Drug F

Drug E

Strategy: Molecular matching for each patient with customized therapy combination
Patient-Centric Therapy
We already customize treatment

Patient 1
Diabetes, CHF, RA

- metformin
- digitalis
- tofacitinib

Patient 2
Diabetes, Infection, Depression,

- metformin
- fluoxetine
- clarithromycin
- metformin
- flouxetine
Are combinations of drugs safe?

Patient R with breast cancer

• Alprazolam
• Arformoterol tartrate
• ASA
• CoQ10
• Folate / Vit B6 / Vit B12
• Levothyroxine
• Beclomethasone dipropionate
• Tiotropium bromide
• Bupropion
• Benzonatate
• Saliva substitutes topical
• Dextromethorphan and guaifenesin
• Ipratropium nasal
• Levalbuterol
• Spironolactone
• Fondaparinux
• ado-trastuzumab emtansine (TDM1)
Key Features of Next Generation Trials

- Use multiplex markers to diagnose/classify cancers
- Validate a strategy, not just a drug(s) or a marker(s)
- Patient centric
- Understand convergence pathways
- Use rule of thumb for safe combinations

Proof of principle trials in metastatic disease—then treat early
Cutting-Edge Trials
WINThER
Signature Trial of Worldwide Innovative Network for Personalized Cancer Therapy
6 centers, 5 countries
JC Soria (PI), R Kurzrock (co-PI)

Arm A
WINThER ARM A: Genomics

Arm B
WINThER ARM B: Transcriptomics
SPRING
Combinations to Improve Survival in Lung Cancer
Leadership Team: Kurzrock, Rodon, Lazar

Genomics  Transcriptomics
## Poor Prognosis

<table>
<thead>
<tr>
<th>Cases Diagnosed 2003-2006</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2014 National Cancer Database</strong></td>
<td>2-yr Mortality</td>
<td>2-yr Mortality</td>
</tr>
<tr>
<td><strong>Pancreas</strong>*</td>
<td>86.5%</td>
<td>93.3%</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>83.0%</td>
<td>93.3%</td>
</tr>
<tr>
<td><strong>Intrahepatic bile duct</strong></td>
<td>79.1%</td>
<td>92.8%</td>
</tr>
<tr>
<td><strong>Esophagus</strong></td>
<td>70.6%</td>
<td>90.3%</td>
</tr>
<tr>
<td><strong>Bile duct (other)</strong></td>
<td>70.5%</td>
<td>92.2%</td>
</tr>
<tr>
<td><strong>Lung, Bronchus - NSCLC</strong></td>
<td>65.3%</td>
<td>88.7%</td>
</tr>
<tr>
<td><strong>Stomach</strong></td>
<td>63.9%</td>
<td>90.0%</td>
</tr>
</tbody>
</table>

*UCSD-specific data; others are all NCDB cases
The Activation Traffic Jam

CLIA
IDE
PRMC/IRB
Drug Acquisition
Nothing will ever be attempted if all possible objections must first be overcome

Samuel Johnson
I-PREDICT
(Investigation of Profile-Related Evidence Determining Individualized Cancer Therapy)

FEASIBILITY STUDY IN NEWLY-DIAGNOSED MALIGNANCIES

J Sicklick and R Kurzrock

High risk: 30% chance of mortality in two years

Group 1 (N=75)
Newly Diagnosed
Borderline resectable disease
Unresectable disease
Medically unfit for surgical resection

Group 2 (N=75)
Newly Diagnosed
Metastatic disease

Group 3 (N=75)
≥ 1 Prior Treatment
Metastatic or Unresectable Disease

Foundation One NGS Genomics
THANK YOU
and
Questions??

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