Personalized Cancer Medicine: Successes and Challenges

WIN Symposium

June 23, 2014

John Mendelsohn, M.D.
Director, Institute for Personalized Cancer Therapy
and Past President, The University of Texas
MD Anderson Cancer Center
“Personalized/Precision Cancer Therapy” takes advantage of all information available about the patient and his or her cancer, and in the world’s literature on biomedical research, to prescribe treatments that are most likely to be successful in achieving cure or substantial prolongation of life.
1. Create the infrastructure and platforms for genetic analysis of large numbers of clinical cancer specimens.
2. Support clinical trials bringing therapies to patients that target the genetic aberrations in their cancers.
3. Provide decision support to create personalized cancer treatment plans.
4. Demonstrate the value of this approach so that it will become standard of practice and reimbursed.
5. Educate the next generation of clinical investigators.
Multiple Pathways Involved in the Pathogenesis and Progression of Lung Tumors: The BATTLE “Umbrella” Clinical Trial

Hong W.K.
Heymach J. MDACC, Houston, 2006

E. Kim, Cancer Discovery 2012
Department of Investigational Cancer Therapeutics

**Matched therapy**  
N=175

<table>
<thead>
<tr>
<th>Response</th>
<th>N</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>CR</td>
<td>4</td>
<td>2</td>
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<tr>
<td>PR</td>
<td>43</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
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** Therapy without matching**  
N=116

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<th>Response</th>
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<td>0</td>
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<tr>
<td>PR</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>5</td>
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</table>

\( p < .0001 \)

**Patients**  
SD>6mo  
N=40  
23%

\( \geq 20\% \) increase = PD (RECIST)

TTF and Survival by Therapy. Patients with 1 Molecular Aberration

TTF

<table>
<thead>
<tr>
<th>Matched</th>
<th>N</th>
<th>Failed</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>175</td>
<td>149</td>
<td>5.2</td>
</tr>
<tr>
<td>No</td>
<td>116</td>
<td>111</td>
<td>2.2</td>
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p < .0001

Survival

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<tr>
<th>Matched</th>
<th>N</th>
<th>Died</th>
<th>Median</th>
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<tr>
<td>Yes</td>
<td>175</td>
<td>94</td>
<td>13.4</td>
</tr>
<tr>
<td>No</td>
<td>116</td>
<td>67</td>
<td>9.0</td>
</tr>
</tbody>
</table>

p = .017

Tsimberidou et al, Clin Cancer Res. 2012; 18:6373-83
TTF. Comparison with Previous Systemic Therapy

Matched therapy
N=175, 1 aberration

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Failed</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched</td>
<td>149</td>
<td>5.2</td>
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<tr>
<td>Previous systemic</td>
<td>173</td>
<td>3.1</td>
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Paired analysis
$p < .0001$

Non-matched therapy
N=116, 1 aberration

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Failed</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Matched</td>
<td>111</td>
<td>2.2</td>
</tr>
<tr>
<td>Previous systemic</td>
<td>113</td>
<td>2.8</td>
</tr>
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</table>

Paired analysis
$p = .56$

Tsimberidou et al, Clin Cancer Res. 2012; 18:6373-83
Personalized Cancer Therapy – Recent Successes


4. Gefitinib against the EGF receptor as first line therapy for advanced NSCLC. Mok, NEJM 2009


<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Resistance Mechanisms</th>
<th>Laboratory</th>
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<tbody>
<tr>
<td>Vemurafenib</td>
<td>BRAF (V600E) (colon)</td>
<td>Activated EGFR</td>
<td>Bernards (Prahallad A) et al. Nature. 2012;483(7387):100-103</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>BRAF (V600E) (melanoma)</td>
<td>• Mutation in MEK • Increased copy number BRAF • Aberrant BRAF • PTEN loss reduces apoptosis • Increased IGF-RI</td>
<td>Many</td>
</tr>
<tr>
<td>Many Experimental Drugs</td>
<td>PIK3CA</td>
<td>• Receptor tyrosine kinases</td>
<td>Engelman (Ebi H) et al. J clin Invest. 2011;121:4311-21</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>ALK rearrangements</td>
<td>• Activated EGFR</td>
<td>Yamaguchi N et al. Lung Cancer 2014;83:37–43</td>
</tr>
</tbody>
</table>
CLIA Compliant Genomic Assays
Laboratory of Molecular Diagnostics

2009  Sanger, Pyrosequencing – single mutation hot spots

2011  Sequenom – 72 hot spots, 11 genes

2011  Illumina – exons of 200 Genes (not CLIA): T200

2012  Ion Torrent – 739 hot spots, 46 genes: CMS46

2014  Ion Proton – exons of 400 genes: CMS 400

2014  Oncomine/Match (Life Technologies) – actionable hot spot genes (66), copy number variants (43), suppressors (25), gene fusions (16)
All potentially eligible patients consented & physician notified

Archival block requested
Biopsy only if clinically indicated or part of trial

T200 (non-CLIA)

Oncologists has access to research data

CMS50 (CLIA)

CLIA validation of clinically relevant findings

Standard of care treatment
Or
Active umbrella trials
Or
Phase I, II, III trials

Data Capture and Database development
• Mutation frequency
• Track trial enrollment
• Clinical trial alert
• Response and survival
• Call-back program

F. Meric-Bernstam and G. Mills
1200 patients eligible to enter trials
Hot Spot Mutation CMS46 (Ion Torrent)
Potentially Actionable 35%
Patients with Potentially Actionable Alterations by Tumor Type

- Melanoma/Skin: 74.41%
- Colorectal: 70.10%
- Lung: 47.50%
- Breast: 34.50%
- Gastric: 22.20%
- Ovarian: 22.00%
- Head & Neck: 19.20%
- Brain: 18.50%
- Esophageal: 17.40%
- Sarcoma: 8.90%
- Prostate: 7.10%
Copy number could increase the number of patients eligible for genomics-based trials
Aberrations In Ovarian Cancer In Clearinghouse Comparison To TCGA

Important to know MDACC numbers for patients likely to enter on trials for trial design
1. Subset not high grade serous
2. Selection of cases?
3. Mets and recurrence different?

<table>
<thead>
<tr>
<th></th>
<th>% Patients with 'Actionable' Mutation</th>
</tr>
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<tbody>
<tr>
<td>Clear Cell</td>
<td>50%</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>33%</td>
</tr>
<tr>
<td>Germ Cell</td>
<td>0%</td>
</tr>
<tr>
<td>High Grade Serous</td>
<td>17%</td>
</tr>
<tr>
<td>Low Grade Serous</td>
<td>100%</td>
</tr>
<tr>
<td>Mucinous</td>
<td>50%</td>
</tr>
</tbody>
</table>

G. Mills
Recruiting Basket Trials to MDACC T200 data

BRCA1/2 mutation/deletion (49/525)
- Kidney
- Brain
- Colorectal
- Sarcoma
- H & N
- Neuro endocrin
- Thyroid
- Germ cell
- Uterine
- Lung
- Liver
- Skin

ALK mutant 30/525
- Kidney
- Brain
- Cervix
- Endometria
- Lung
- Thyroid
- Liver
- Breast
- Skin
- Colorectal
- Other

TSC1/2 17/528
- Brain
- Prostate
- Thyroid
- Throat
- Gastric
- Colorectal
- Breast
- Skin

mTOR 13/525
- Kidney
- Skin
- Bladder
- Brain
- Breast

AKT AMP 47/525
- Skin
- Breast
- Ovarian
- Kidney
- Liver
- Gastric
- Sarcoma
- Neuroendocrine
- Other
Industry Sponsored Basket Trials, 2014

Dovitinib
- VEGF $^{M/T}$
- FGFR $^{M/T}$
- cKIT $^{M/T}$
- CSFR1 $^{M/T}$
- PDGFR $^{M/T}$

Neratinib
- HER2 $^M$
- EGFR $^{M/A}$

BKM120
- PIK3CA $^{M/A}$
- PTEN $^{M/L}$
- PIK3R1 $^M$

Legend:

| M | Mutation |
| T | Translocation |
| A | Amplification |
| L | Loss |

F. Meric-Bernstam
<table>
<thead>
<tr>
<th>MUTATIONS SCREENED</th>
<th>Genotype Selected Trials for CMS50 Platform, 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL1</td>
<td>CSF1R</td>
</tr>
<tr>
<td>AKT1</td>
<td>CTNNB1</td>
</tr>
<tr>
<td>ALK</td>
<td>EGFR</td>
</tr>
<tr>
<td>APC</td>
<td>ERBB2</td>
</tr>
<tr>
<td>ATM</td>
<td>ERBB4</td>
</tr>
<tr>
<td>BRAF</td>
<td>EZH2</td>
</tr>
<tr>
<td>CDH1</td>
<td>FBXW7</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>FGFR1</td>
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</table>
Patients with Potentially Actionable Genomic Aberrations in PIK3CA, PTEN, AKT1 and RAF

<table>
<thead>
<tr>
<th>Enrollment in Clinical Trials</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Genotype Selected Trials</td>
<td>10%</td>
</tr>
<tr>
<td>Genotype Relevant Trials</td>
<td>5%</td>
</tr>
<tr>
<td>Genotype Relevant off Protocol</td>
<td>9%</td>
</tr>
<tr>
<td>Genotype Relevant Trial prior to Multiplex Testing</td>
<td>3%</td>
</tr>
<tr>
<td>Genotype Relevant off Protocol prior to Multiplex Testing</td>
<td>10%</td>
</tr>
<tr>
<td>Other Trials</td>
<td>12%</td>
</tr>
<tr>
<td>Not enrolled in trials</td>
<td>51%</td>
</tr>
</tbody>
</table>
  - Alternative RX
  - No trial or slot available
  - Declining performance
  - Logistics/travel
1. CLIA-compliant sequencing of over 3,000 patients’ cancers for hot spots on 50 “actionable genes” and dissemination of results (Pathology and IPCT)

2. Data on incidence of genomic aberrations in each tumor type

3. Recruitment of patients to targeted clinical trials

4. Genetic screening of tumors has been introduced into our clinical care culture

5. Identified need for decision support

6. Identified need for more clinical trials

7. Identified need for “champions” in each disease site to design trials

8. Data sharing agreement in place internally, needed externally

9. Need for trials with combinations of targeted drugs and immunotherapies
**PIK3CA Alterations**

**Overview**

PIK3CA is the proto-oncogene that encodes the p110alpha catalytic subunit of the phosphatidylinositol 3-kinase (PI3K), an essential signaling molecule in the pathways driven by receptor tyrosine kinases, such as epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2). PIK3CA mutations are commonly found in various malignancies, including breast cancer. Missense mutations in PIK3CA have been associated with the development and progression of tumors, particularly in breast cancer. PIK3CA mutations can lead to constitutive activation of the PI3K-AKT signaling pathway, which is involved in multiple cellular processes, including cell proliferation, survival, and angiogenesis.

**Altering Mutations**

- Single nucleotide variations and copy number gains of PIK3CA are common events in multiple cancer types. These alterations have been shown to be important tumor driving events as well as mechanisms of therapy resistance.

**How was this information retrieved?**

Large-scale studies and computational approaches have identified PIK3CA alterations in various cancer types and have elucidated their functional significance. These studies have used next-generation sequencing technologies to identify mutations in PIK3CA and have correlated these findings with clinical outcomes. The integration of these data with other genomic and proteomic analyses has provided insights into the mechanisms by which PIK3CA alterations contribute to tumor growth and progression.

**Therapeutic Implications**

**Level 1A Evidence**

- There is Level 1A evidence for PIK3CA alterations that predict therapeutic response.

**Level 1B Evidence**

- There is Level 1B evidence for PIK3CA alterations that predict therapeutic response.

**Level 3 Evidence**

- PIK3CA/PI3K inhibitors, such as BKM120 and AZD5363, have shown promising results in clinical trials, particularly in breast cancer. These inhibitors target the PI3K-AKT signaling pathway, leading to the suppression of tumor growth and viability. Clinical trials have shown improved outcomes in PIK3CA-mutant tumors, indicating the potential for targeted therapy in these cases.
Unusual Responder Program (T200)

• Support for biopsies of unusual responders to targeted therapies and molecular profiling:
  1) Responders (compare with non-responders)
  2) Patients who had tumor progression after a partial or complete clinical response
  3) Patients with mixed response (partial response in one accessible tumor, with progression of another accessible lesion)
  4) Patients with unexpected rapid progression
  5) Survivors free of disease, who have a late relapse
1. More trials, including combinations of therapies
   – Identify optional therapies and combinations based on biomarkers, using computational and systems biology
   – Plan and fund trials with drugs from multiple pharmaceutical companies
   – Plan efficient studies of toxicity and optimal sequencing of therapies with new combinations
2. **Information management and sharing**
   - Massive amounts of clinical and research data to analyze and store
   - Lack of standardization and interoperability of biomedical electronic data today
   - Data often balkanized in silos
   - Gathering the results of clinical trials and information from preclinical studies into a vast “knowledge network” will create a research computational platform that can advance science and precision medicine.