Personalized Medicine in Oncology
Dawn of the Genomics and Immunotherapy Era

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Director, Clinical Trials Office
Team Leader, Experimental Therapeutics
Chief, Division of Hematology/Oncology
The Pillars of Targeted Therapeutics
Precision Medicine

Genomics  Immunotherapy

The future is here.
Question: Is it precision medicine or personalized medicine?

Answer: Both

“Precisionalized Medicine”
<table>
<thead>
<tr>
<th>Drug</th>
<th>Tumor</th>
<th>Survival Gain</th>
<th>CR (single agent)</th>
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<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>Lung</td>
<td>2 months</td>
<td>≈ 0%</td>
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<tr>
<td>sorafenib</td>
<td>renal</td>
<td>2 months</td>
<td>≈ 0%</td>
</tr>
<tr>
<td>temozolamide</td>
<td>glioblastoma</td>
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<td>≈ 0%</td>
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<tr>
<td>docetaxel</td>
<td>prostate</td>
<td>2.4 months</td>
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<tr>
<td>cetuximab</td>
<td>colon</td>
<td>1.5 months</td>
<td>≈ 1-2%</td>
</tr>
</tbody>
</table>
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
• Targeted therapy in of itself is not effective

• Insulin is a great drug but not if given to patients with pneumonia

• Penumonia would be viewed as a difficult disease to treat if insulin and heart medications were given to the patients.

• It is about matching patients with the right therapy
Meta Analysis of 32,149 Patients in Phase II Clinical Trials

- Non-personalized targeted arms led to poorer outcomes than cytotoxics arms

(All P<0.0001, except P=0.048 for OS meta-analysis).

<table>
<thead>
<tr>
<th>ARMS type</th>
<th>POOLED Analysis</th>
<th>Meta-analysis</th>
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<tr>
<td></td>
<td>RR (%)</td>
<td>PFS (Mos)</td>
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<td>Non-personalized targeted</td>
<td>4</td>
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<tr>
<td>Cytotoxic</td>
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<tr>
<td>Personalized targeted</td>
<td>30</td>
<td>6.9</td>
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Schwaederle……Kurzrock, JCO, 2015
Precision Medicine

Lessons Learned

• Each patient has a unique and complex molecular portfolio
• Use combinations of matched drugs for metastatic or complex tumors
• Harness the immune system
• 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
Accelerated New Drug Development

Approval After Phase I: 
Ceritinib Runs the Three-Minute Mile
THE GENOMICS & IMMUNOTHERAPY ERA

First generation studies

First generation technology
Master Protocol

Profile-Related Evidence Determining Individualized Cancer Therapy

PREDICT

- Histology-Independent targeted approach
- Multiple molecular aberrations assessed
- Patients matched with targeted agents
The Reclassification of Cancer

*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
Matching patients with targeted drugs increases response rates

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

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

Janku….Kurzrock, MCT, 2011; Tsimberidou..... Kurzrock, CCR, 2012;
Janku…..Kurzrock, JCO, 2012; Janku…..Kurzrock, Cell Reports, 2014
The Light Microscope
Invented in 1590
Still used to diagnose cancer
Next Gen Sequencing
Actionable Cancer Gene Sequencing [CLIA]
The Molecular Microscope

<table>
<thead>
<tr>
<th>ABL1</th>
<th>BRCA2</th>
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Genomic Technology: Breathtaking Progress

**QUICKER, SMALLER, CHEAPER**

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<tbody>
<tr>
<td>Time taken (start to finish)</td>
<td>13 years</td>
<td>4 years</td>
<td>4.5 months</td>
<td>~1 days</td>
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<tr>
<td>Number of scientists listed as authors</td>
<td>&gt; 2,800</td>
<td>31</td>
<td>27</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>~$1000</td>
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<tr>
<td>Coverage</td>
<td>8-10 ×</td>
<td>7.5 ×</td>
<td>7.4 ×</td>
<td>30-50X</td>
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<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>
</tr>
</tbody>
</table>

**Costs**

- **Venter**
- **Watson**

**Genomes**

- African, Asian, Cancer pair
- 169 in Genbank
- Individual Genome Sequencing

**Time**

- 2007
- 2008
- 2009
- 2010
- 2011
- 2012

**Cost per Human Genome**

- $100M
- $10M
- $1M
- $100k
- $10k
- $10k
- $1,000
- $100k
- $10M
- $10B
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
Harnessing the Immune System

The immune system is the epitome of machinery that is precise and personalized.

T-cell killing cancer cell
How Does Immunotherapy Work?

Tumor cells bind to T-cells to deactivate them

Immunotherapy drugs can block tumor cells from deactivating T-cells

T-cell  Tumor  T-cell  Drug   Tumor
Combinatorial immune blockade is likely the rule, not the exception


ASCO 2014 update

- 2 year survival rate: 79%
  - Comparison: dacarbazine monotherapy 2-year survival rate: 18%
  - Prior therapies (1-3+) in 38%

Predicting super-responders to immunotherapy

Biomarker
- PDL-1 negative: 0-17%
- PDL-1 positive: 36-100%

Unique characteristics
- Delayed responses with initial progression
- Subset of patients with advanced disease that have long-term complete remission (?cure)

Patel and Kurzrock, MCT 2015
Bridging Genomics and Immunotherapy

Immune system responds to mutanome

High mutational burden and specific alterations
  • PDL1 amplification
  • MSI-H
  • DNA repair gene alterations

Combination therapies (genomically and immunotherapeutically targeted)
Center for Personalized Cancer Therapy at Moores Cancer Center

Developmental Therapeutics
Phase I Trials/Immunotherapy

Discovery to Bedside Enabling Program
Rare Tumor Clinic
Molecular Tumor Board
Hereditary Cancer Predisposition Genetic Counselling
Molecular Pathway Clinic
Adolescent and Young Adult Clinic

San Diego Biotech, Pharma, Genomics

UCSD Super Computer Center

Financial Aid Laboratory Processing

UCSD, Salk, Scripps, Sanford-Burnham
Molecular Tumor Board

- Initiated December 12, 2012
- Three weeks per month
- Multidisciplinary discussion of patients
- Molecular profiling (N ~ 3500 patients)
- Targeted, tailored treatment recommendations

Schwaederle…..Kurzrock, Oncologist, 2014; Parker…..Kurzrock, JOP, 2015
Potential Actionability

- N = 439 patients
- NGS = 236 genes
- 20% actionable by on-label approved drug
- 70% actionable by on- or off-label approved drug
- 90% actionable by approved or experimental drug

Schwaederle M...Kurzrock R. On the Road to Precision Cancer Medicine: Genomic Actionability in 439 Patients. MCT, 2015
What about the host?

Host and Toxicity/Response/Immunity/Microenvironments
Cutting-Edge Technology
Liquid Biopsy Program

Doing genomics on DNA from a small tube of blood or from urine

No tissue biopsy

~1000 patients
Molecular Heterogeneity

Interpatient heterogeneity

Intratumour heterogeneity

Intertumour heterogeneity
Tracking EGFR T790M Mutations in Lung Cancer

Early Detection of Progression

IRB-approved HRPP 130794; H. Husain and R. Kurzrock (manuscript in prep)

Urine T790M Copies/100K GE

T790M detected

Progression on CAT scan

4/11/2014
5/21/2014
6/30/2014
8/9/2014
9/18/2014
10/28/16
High Levels of Circulating Tumor DNA are Associated with Poor Survival

![Graph showing survival rates for different ctDNA levels](image)
Circulating Tumor DNA Applications

- Serial levels for response
- Early detection of resistance alterations
- Assess shed DNA from multiple metastatic sites
- Assess difficult-to-biopsy patients
- More information on potentially actionable alterations
Case 1: Serial ctDNA (liquid biopsies)
MET mutation disappears on MET inhibitor

Somatic Alteration Burden  2.1%  1.0%

EGFR K806fs
TP53 H179Y
PTEN L139*

TP53 R273C
MET Y501C

Hepatocellular Cancer
Case 1: Serial ctDNA (liquid biopsies)
MET mutation disappears on MET inhibitor

EGFR K806fs
TP53 H179Y
PTEN L139*
TP53 R273C
MET Y501C
Genomics and Immunotherapy

Using genomics to find the best immunotherapy match
Metastatic Basal Cell Carcinoma
Ultra-rare tumor

55 year old man, having failed multiple treatments

Treatment history
- Vismodegib (5/2014-10/2014), PD
- SBRT to right frontal lobe (11/2014)
- Paclitaxel/Cisplatin (11/2014-3/2015), PD
- Buparlisib/Sonidegib (4/28/2015-7/1/2015), PD
- Vismodegib + weekly taxol (7/2015-9/2015), intolerant
- Vandetanib (9/2015-9/2015), intolerant
Molecular profiling (liver biopsy tissue)

*Next Generation sequencing, 315 genes:*

- **PDL1** amplification,
- **PDL2** amplification,
- **JAK2** amplification,
- **PTCH1** Q1366*, W197*,
- **FLT1** E487K,
- **PDGFRA** E459K
- **PIK3R2** Q412*,
- **CDKN2A** p16INK4a P81L,
- **TP53** P278S,
- **CDKN1A** R140Q,
- **CTNNA1** R383H,
- **LRP1B** splice site 9121-1G>A, W2334*,
- **MLL2** splice site 4132-1G>A,
- **NOTCH1** W287*,
- **SLIT2** K325*,
- **SMARCA4** Q1166*,
- **TERT** promoter -139_-138CC>TT
Response to Genomically Matched Immunotherapy

Pre-Nivolumab (anti-PD1)  
Post: 2 months
Summary

• Tumors and patients have unique AND complex molecular alterations
• Find the perfect match for each patient---customize
• Marry genomics and immunotherapy in combinations
The genomic/immunotherapy era will revolutionize not just cancer medicine
BEYOND CANCER
Changing the lives of patients

Bladder Cancer

Dwarfism

FGFR3 Mutation

Twin Boys
Normal Achondroplasia
THANK YOU
for your time and interest

Questions??

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teoam2011@gmail.com
35 minutes and 10 minutes for questions