The Road to Amiens
Winning the War Against Cancer with Personalized Treatment

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Director, Center for Personalized Cancer Therapy and Clinical Trials Office
Chief, Division of Hematology/Oncology
Where is Amiens and what does it have to do with cancer?
Battle of Amiens (1918)

Start of the Hundred Day Offensive that led to the end of World War I

Prior to Amiens, advances were incremental—just a few feet at a time

Proved the effectiveness of shifting from stagnant trench warfare to mobile, multifaceted, targeting

Allied forces advanced 7 miles in one day, one of the greatest advances in the war
Kurzrock Experience:
Largest Early Clinical Trials Department World Wide:  MDACC
PUBLIC ENEMY No. 1
Annual Age-Adjusted Cancer Death Rate 1975-2008

If we keep up the momentum, we will have licked the cancer problem in 1200 years

What can patients expect from approved drugs?

<table>
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<tr>
<th>Drug</th>
<th>Tumor</th>
<th>Survival Gain</th>
<th>CR (single agent)</th>
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<td>pancreas</td>
<td>1.5 months</td>
<td>≈ 0%</td>
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<td>bevacizumab</td>
<td>colon</td>
<td>2.2 months</td>
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<td>11 days</td>
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<td>sorafenib</td>
<td>renal</td>
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<td>temozolamide</td>
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<td>2.5 months</td>
<td>≈ 0%</td>
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<td>docetaxel</td>
<td>prostate</td>
<td>2.4 months</td>
<td>≈ 0%</td>
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<tr>
<td>cetuximab</td>
<td>colon</td>
<td>1.5 months</td>
<td>≈ 1-2%</td>
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Extending survival
for moments that matter
High Drug Development Failure Rates

Accelerated New Drug Development
MDACC Phase I Department

Phase I to III (with no Phase II) = 3 drugs

Phase I to approval (5-year span) = 5 drugs

- Regorafenib → colorectal cancer
- Cabozantinib → medullary thyroid cancer
- Dabrafenib → melanoma
- Trametanib → melanoma
- Siltuximab → Castleman’s disease
Why are common cancers difficult to treat?

-Targeted agents work only in those with a sensitizing mutation

Braiteh....Kurzrock, MCT 2007

Lung Cancer

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<td>MEKI</td>
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Winning the War Against Cancer

We must shift from stagnant trench warfare to mobile, multifaceted, targeting

Western Front of the First World War

Location: East of Amiens, France
Result: Decisive Allied Victory
Mobile Multifaceted Targeting (Genomics and Immunotherapy)

• Advanced molecular profiling for every patient, repeated frequently

• Match patients with the right drug(s) — personalized therapy

• Cancer can be complex; use more than one targeted drug

• Treat earlier in the course of the disease — the leukemia (CML) model

• Harness the immune system
Therapeutic Efficacy

Can Molecular Testing Make A Difference?
While it is often claimed that we need new drugs to treat cancer, a more fundamental problem may be the way we classify cancer.

It is well understood that, for instance, insulin is a great drug, but not if we use it to treat pneumonia.

Similarly, pneumonia would be a difficult illness to treat, if we used insulin rather than penicillin to treat it.

In the same way, we may have excellent drugs, but they work poorly because we treat patients with the wrong cancers with them.
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
We have the drugs

Cell membrane

p85

PIK3CA

PIP2

PIP3

PTEN

PI3K

mTOR

AKT

RECEPTOR TYROSIINE KINASE

RAS

RAF

MEK
### Best RECIST Response

**Patients with 1 mutation**

**Matched therapy**  
N=175  
Complete/Partial Response = 27%  
p<.0001

**Therapy without matching**  
N=116  
Complete/Partial Response = 5%

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<th>Change in tumor size, %</th>
<th>Matched therapy</th>
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<td>-100</td>
<td>CR: 4 (2%)</td>
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<td>-90</td>
<td>PR: 43 (25%)</td>
<td>PR: 6 (5%)</td>
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<td>-80</td>
<td>SD&gt;6m: 40 (23%)</td>
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**Complete/Partial Response = 27%**

Janku….Kurzrock, MCT, 2011; Tsimberidou….. Kurzrock, CCR, 2012; Janku…..Kurzrock, JCO, 2012;
With targeted therapy, patients can achieve remarkable responses without side effects
Pt H (42/F) (Castleman’s disease): Rx = anti-IL-6 Ab [CNTO328]

Castleman’s Disease is driven by IL-6

Pt H (Baseline)  
Pt H s/p 2 doses  
Pt H s/p 6 doses
Transforming Cancer Treatment

The future is here.
The Light Microscope
Invented in 1590
Still used to diagnose cancer
Next Gen Sequencing
Actionable Cancer Gene Sequencing [CLIA]
The Molecular Microscope

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Genomic Technology: Breathtaking Progress

Current (2013)
- ~10 days
- ~$5000
- 30-50X

Genomic Technology: Genomes and Costs Over Time

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

Costs per Human Genome
- $100M
- $10M
- $1M
- $100k
- $10k

Genomes
- 1M
- 100k
- 10k
- 1,000
- 100
What if every patient with metastatic disease is different?
Breast Cancer → Malignant Snowflakes
No two are alike?

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<th>Pt number</th>
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Strategies for Transforming Outcomes

- Customized Combinations for Advanced Disease
- Treat Newly Diagnosed Disease
n=19 drugs

I \rightarrow II

n=51 trials

I \rightarrow III

N=3 trials

11/25/2014 SKM
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 to 25 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.
Conventional Wisdom

The outcome of CML was transformed by targeted therapy with median survival increasing from about 4 years to 20-25 years.

Solid tumors are more complex than CML.

Therefore the outcomes in CML are an aberration and we are not likely to see such a transformation in outcomes in solid tumors.

Elucidating the combinations needed to treat solid tumors is a herculean task because of their complexity.
Time changes everything

This thing all things devours:
Birds, beasts, trees, flowers;
Gnaws iron, bites steel;
Grinds hard stones to meal;
Slays king, ruins town,
And beats high mountain down

J.R.R. Tolkien
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
Center for Personalized Cancer Therapy at Moores Cancer Center

Developmental Therapeutics
Phase I Trials/
Genomics/Immunotherapy

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

San Diego Biotech, Pharma, Genomics

UCSD Super Computer Center

Financial Aid
Laboratory Processing

UCSD, Salk, Scripps, Sanford-Burnham
Center for Personalized Cancer Therapy at Moores Cancer Center

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UCSD Super Computer Center
Molecular Tumor Board

- Initiated December 12, 2012
- Three weeks per month
- Multidisciplinary discussion of patients
- Molecular profiling (N ~ 1000 patients)
- Targeted, tailored treatment recommendations
Center for Personalized Cancer Therapy at Moores Cancer Center

Developmental Therapeutics
Phase I Trials/
Genomics/Immunotherapy

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

San Diego Biotech, Pharma, Genomics
UCSD Super Computer Center

Financial Aid
Laboratory Processing

UCSD, Salk, Scripps, Sanford-Burnham
Immunotherapy Program

Nivolumab plus Ipilimumab in Advanced Melanoma

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• ASCO 2014 update
  • 2 year OS rate- 79%
    • Comparison: dacarbazine monotherapy 2 year OS rate- 18%
    • Prior therapies (1-3+) in 38%

• Bladder Cancer
• Lung cancer
• Lymphomas

Center for Personalized Cancer Therapy at Moores Cancer Center

Developmental Therapeutics
Phase I Trials/
Genomics/Immunotherapy

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

Financial Aid
Laboratory Processing

San Diego Biotech, Pharma, Genomics
UCSD Super Computer Center

UCSD, Salk, Scripps, Sanford-Burnham
Cutting-Edge Technology
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)
Tip of the Iceberg

Genomics

Transcriptome

Proteomics

Epigenetic changes
3D *In Silico* Modeling for Predicting Response
UCSD Supercomputer Center

**Wild-type EGFR**

Exon 20 aberration
D770_P772del-<sub>ins</sub>KG

**Exon 20**

D770>GY
T790M

**Exon 19**

ΔE764-A750

**Exon 19**

D770_P772del-<sub>ins</sub>KG

ΔE764-A750
75 year old man
Non small cell lung cancer
exon 20 (D770>GY) → known EGFR kinase inhibitor resistant
Achieved PR on Cetuximab-based treatment (42+ months)
Liquid Biopsy Program: Genomics on Blood Samples

Schwarzenbach Nat Rev Cancer 2011
Cutting-Edge Trials
WIN Ther
Signature Trial of Worldwide Innovative Network for Personalized Cancer Therapy
6 centers, 5 countries
JC Soria (PI), R Kurzrock (co-PI)

WINTher Arm A: Genomics
WINTher Arm B: Transcriptomics
Barriers to Personalized Medicine:
The Regulatory/Resource Traffic Jam
Barriers to personalized trials

The activation energy for trials with no patient selection is far lower than that for trials with biomarker/genomics selection.

Yet, patients may have a lower chance of benefit/higher risk of harm in trials with no selection.
August 2014: ~120 patients enrolled in Europe and Canada
## Poor Prognosis

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

*UCSD-specific data; others are all NCDB cases*
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
Hereditary Predispositions

Host and Toxicity/Response/Immunity/Microenvironments
The genomic era will revolutionize not just cancer medicine.
BEYOND CANCER
Changing the lives of patients

Bladder Cancer

Dwarfism

FGFR3 Mutation

Twin Boys
Normal Achondroplasia
The Center for Personalized Cancer Therapy
UC San Diego Moores Cancer Center

• Advanced molecular testing for all cancer patients (hereditary and acquired aberrations)
  → tumor biopsy
  → liquid biopsy

• Real-time results of complex analysis of actionable DNA abnormalities

• Information access/processing (UCSD Supercomputer Center)

• Broad repertoire of potent, targeted drugs (approved or experimental) available

• World-class Phase I clinical trials unit

• Rare Tumor Clinic

• Immunotherapy Clinic (target mutanome etc)

Personalized Medicine—not just cancer
(UC San Diego as health care destination)
“Campus Benefits from Generosity of Irwin and Joan Jacobs with Latest Gift to Fund Cancer Care”
THANK YOU for your time and interest

Questions??

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