The Good, The Bad, and Ugly

David S. Hong MD
Assistant Professor
Clinical Medical Director of the Clinical Center for Targeted Therapy
The Good, The Bad and The Ugly
Cancer now causes 23% of all US deaths & is leading cause of death in those aged <85 yrs

Every 57 seconds another American dies of cancer: 63 over the past hour
Life-time probability of developing cancer:
A problem coming soon to a family near you?

Males: 45%
Females: 38%
Once a Molecular Black Box
Today an Open Box

Growth Factors

Hormones

Changes in Gene Expression

Cytoplasm

Nucleus

Image by Joanne Kelly © 2011.
New Directions in Oncology

• Angiogenesis
• Apoptosis
• Signal Transduction
• Immunotherapy
• Other Targets
• Personal Therapy
PERSONALIZED CANCER MEDICINE

PATIENTS WITH SAME DIAGNOSIS ARE NOT ALL THE SAME

Predicted good response to drug or combination of drugs

Predicted poor or no response to drug or combination of drugs

Increased likelihood of toxicity of drug or combination of drugs

CHANGE DRUGS

CHANGE DRUGS
The Regulatory Traffic Jam
Factors Behind the Regulatory Traffic Jam

**US Gov’t Agencies:**
- FDA
- NCI
- OHRP
- CLIA
- HIPAA
- IRS
- MEDICARE
- OFFICE INSPECTOR GENERAL
- PATENT OFFICE
- JAHCO
- TORT LAWS
→ Massive Regulatory Traffic Jam →

- Costs ⬆️⬆️
- Delays ⬆️⬆️
- Frustrations ⬆️⬆️
- Efficiency ↓️↓️
- New ideas tested ↓️↓️
- Investigator initiated trials ↓️↓️
- US competitiveness ↓️↓️
- Rate of Progress ↓️↓️
- Lives lost

The ⬆️⬆️ costs mean you can’t do trials without lots of funding → those with the money then drive the agenda!
Dimasi JA, Grabowski HG. JCO 2007
Grant System Leads Cancer Researchers to Play It Safe. NY Times, June 6th 2009

“These grants are not silly, but they are only likely to produce incremental progress,” said Dr. Robert C. Young, chancellor at Fox Chase Cancer Center in Philadelphia and chairman of the Board of Scientific Advisors
Enrollment problems delay more than 70% of clinical trials from one to six months, according to a 2007 survey by CenterWatch, a Boston-based company that publishes information on clinical trials. In cancer care, less than 5% of patients enter clinical trials, even though more than 700 cancer therapies -- many that are highly promising -- clog the research pipeline.
Target Cancer

New Drugs Stir Debate on Rules of Clinical Trials.  Amy Harmon, September 18th, 2010
Mission

To translate laboratory discoveries and clinical observations into hypothesis-driven clinical trials leading to targeted, tailored and personalized cancer treatments
Dept of Investigational Cancer Therapeutics

Timeline

- July 04: Phase I Program initiated
- Sept 04: Phase I Clinic started
  (Clinical Center for Targeted Therapy)
- March 05: Phase I Inpatient Service started
- July 07: Dept of Investigational Cancer Therapeutics established
Investigational Cancer Therapeutics
Distinguishing Features

- Treatment is not disease-based but target-based. Diverse cancers treated.

- Treatment is based on early phase clinical trial. Correlative/translational aspects are critical.

- Treatment is not conventional. Virtually all patients are on trial.
  - Specialized business center
  - Regulatory infrastructure
What kinds of trials do we do?

- Studies with new first-in-human molecules
- Trials of new combinations of experimental or approved drugs
- Protocols using new routes of delivery of drugs
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

12/14 patients with Castleman’s on study have responded
Pt X (55/M) (medullary thyroid cancer)
Treatment = RET kinase inhibitor XL184

Pre-Treatment

Post-Treatment week #3
Pt M (28/F) (Ewing’s sarcoma): Rx = IGFR Inhibitor

Dec. 8, ’06
Jan. 25, ’07
Mar. 1, ’07
Histology-Independent
Target-Based Trials

BRAF inhibitor: BRAF mutation+ (thyroid, melanoma, colon etc)

MEK inhibitor: Raf+ or Ras+ mutations

PI3K or mTOR inhibitor: PI3K+ mutations/PTEN loss

PI3K plus MEK inhibitor: PI3K+ mutation or PTEN loss & Ras+ or Raf+
Personalized Targeted Cancer Therapy

Profile-Related Evidence Determining Individualized Cancer Therapy

PREDICT
Of the 36 patients with \textit{PIK3CA} mutations, 24 (67\%) were enrolled in clinical trials that included a PI3K/AKT/mTOR inhibitor.

These patients had a median of 3 prior therapies (1-12).

Types of cancer of the 24 treated patients:

- Bowel (N=7)
- Ovarian (N=6)
- Endometrial (N = 5)
- Breast (N=3)
- Cervix: squamous (N=3)
Waterfall plot of patients with *PIK3CA* mutations treated with therapies targeting the PI3K/AKT/mTOR pathway.

Patients

- Colorectal
- Breast
- Ovarian
- Endometrial
- Small intestine
- Cervical
Waterfall Plot. Response of BRAF+ Patients to BRAF or MEK Inhibitors (n=57)

PR/CR = 17/2 (29.8%/3.5%)
OR = 33.3%
Overall Survival in BRAF+ Patients. RAF/MEK vs. Other Phase I Therapies

BRAF+ pts enrolled on RAF/MEK inhibitors
## Ongoing Phase I protocols

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Pathway Target</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLN8237 (2009-0474)</td>
<td>Aurora Kinase Inhibition</td>
<td>enrolling</td>
</tr>
<tr>
<td>MLN8237+Paclitaxel (2009-0493)</td>
<td>Aurora Kinase Inhibition</td>
<td>enrolling</td>
</tr>
<tr>
<td>ABT-348 (2009-0936)</td>
<td>Aurora Kinase Inhibition</td>
<td>enrolling</td>
</tr>
<tr>
<td>ABT-348+Gemcitabine+Carboplatin (2009-0936)</td>
<td>Aurora Kinase Inhibition</td>
<td>pending</td>
</tr>
<tr>
<td>ABT-348 +Docetaxol (2009-0936)</td>
<td>Aurora Kinase Inhibition</td>
<td>pending</td>
</tr>
<tr>
<td>Avastin+Sorafenib (2006-0638)</td>
<td>c-kit+VEGFR</td>
<td>enrolling</td>
</tr>
<tr>
<td>Dastanib+Avastin+Paclitaxel (2009-0521)</td>
<td>c-kit,SRC+VEGF</td>
<td>enrolling</td>
</tr>
<tr>
<td>Valproic Acid+Sorafenib (2007-0170)</td>
<td>HDAC+c-kit</td>
<td>enrolling</td>
</tr>
<tr>
<td>Valproic Acid+Sutent (2007-0170)</td>
<td>HDAC+c-kit</td>
<td>enrolling</td>
</tr>
</tbody>
</table>
# Ongoing Phase I protocols

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Pathway Target</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK2118436/GSK1120212 (2009-0949)</td>
<td>BRAF/MEK</td>
<td>enrolling</td>
</tr>
<tr>
<td>GSK1120212+Docetaxol,Erlotinib, Premetrexed, Abraxane</td>
<td>MEK+Chemo</td>
<td>pending</td>
</tr>
<tr>
<td>AZD8330 (2006-1097)</td>
<td>MEK</td>
<td>enrolling</td>
</tr>
<tr>
<td>Doxil+Velcade+Gemcitabine (2003-1002)</td>
<td>Proteosome inhibition+Chemo</td>
<td>pending</td>
</tr>
<tr>
<td>GSK1120212/GSK2141795 (2010-0122)</td>
<td>MEK+AKT</td>
<td>pending</td>
</tr>
<tr>
<td>GSK2126458 (2009-0048)</td>
<td>PIK3CA</td>
<td>enrolling</td>
</tr>
<tr>
<td>PX866 (2007-0935)</td>
<td>PIK3CA</td>
<td>enrolling</td>
</tr>
<tr>
<td>Valproic Acid+Avastin (2005-0676)</td>
<td>HDAC+VEGF</td>
<td>enrolling</td>
</tr>
<tr>
<td>CUDC-101 (2010-0483)</td>
<td>HDAC, EGFR, HER2</td>
<td>enrolling</td>
</tr>
</tbody>
</table>
# Ongoing Phase I protocols

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Pathway Target</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI-009 nab-rapamycin (2006-1107)</td>
<td>mTOR</td>
<td>enrolling</td>
</tr>
<tr>
<td>Avastin+Temsirolimus+Carbo (arm1)</td>
<td>VEGF+mTOR+Chemo</td>
<td>enrolling</td>
</tr>
<tr>
<td>Avastin+Temsirolimus+Paclitaxel (arm2) (2010-0486)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R7112 (2007-0683)</td>
<td>MDM2</td>
<td>enrolling</td>
</tr>
<tr>
<td>Sirolimus+Cetuximab (2009-0226)</td>
<td>mTOR+EGFR</td>
<td>enrolling</td>
</tr>
<tr>
<td>Sirolimus+Docetaxol (2009-0558)</td>
<td>mTOR+Chemo</td>
<td>enrolling</td>
</tr>
<tr>
<td>Sirolimus+Vorinostat (2009-0729)</td>
<td>mTOR+HDAC</td>
<td>enrolling</td>
</tr>
<tr>
<td>Temsirolimus/Topotecan/Bortezomib (2008-0425)</td>
<td>mTOR+Proteosome inh+Chemo</td>
<td>enrolling</td>
</tr>
<tr>
<td>CVS-426</td>
<td>IGFR+Ang2</td>
<td>pending (April 2011)</td>
</tr>
<tr>
<td>BIIB-021+Imatinib</td>
<td>HSP90+c-kit</td>
<td>pending (April 2011)</td>
</tr>
</tbody>
</table>
• “Not only so, but we also rejoice in our sufferings, because we know that suffering produces perseverance; \(^4\) perseverance, character; and character, hope. \(^5\) And hope does not disappoint us” Romans 5:3-5