CANCER THERAPIES
FACTS, FIGURES AND THE FUTURE
The Facts

• 1 in 3 people will be diagnosed by cancer in their lifetime.
• 10 million Americans are living with cancer today.
• Each day, more than 1,500 Americans lose their lives to cancer.
• This year alone:
  – 1.4 million Americans will be diagnosed with cancer.
  – 560,000 will lose their lives to this disease.
  – Cancer will cost our economy more than $400 Billion dollars.
The Trends

• The 5-year relative survival rate for all cancers diagnosed between 1996 and 2003 is 66%, up from 50% in 1975-1977.

• The improvement in survival reflects progress in diagnosing certain cancers at an earlier stage and improvements in treatment.

Survival rates are on the rise, thanks to clinical cancer research trials.
Cancer Incidence by State

Illinois 6th highest in the nation
Cancer Drug Development

1940 to 1970
Cancer Drug Development

- Ft. Detrick, Maryland 1940
- Biological Division of the Army
- Animal studies with dogs receiving Nitrogen Mustard
- Cause of death- topical, inhaled, and intravenous
- First patient treated
Cancer Drug Development

• Early years – mechanisms not known primitive understanding of cell biology
• Melphalan or phenylalanine mustard was thought to be a potential building block in the formation of melanin and was first tried in melanomas.
• Amethopterin
• Actinomycin-D
• 5-flurouracil
Cancer Drug Development

1970 to 2000
Cancer Drug Development

- Ames assay
- National Cancer Institution cell culture panel
- Tumor models
- Small animals
- Large animals
- Man
Cancer Drug Development

- Two types of Phase-I studies
- Dose escalation per group
- Dose escalation in an individual
- Looking for “Maximum Dose”
- Starting dose one level below the max dose or “maximum tolerated dose” also called the “MTD”
Cancer Drug Development

• Phase-II studies used the MTD as a single agent in various cell types i.e. breast cancer, colon cancer, lung cancer, etc.

• Usual study was 0 of 15 responses and the study was closed, 1 of 15 and the study would be held open until 34 patients were entered.
Cancer Drug Development

• A drug could be given in a different schedule, e.g. day one every three weeks, weekly, Monday/Wednesday/Friday
• Route could be changed (i.e. IV, PO subcutaneous)
• Given as bolus or timed infusions
Cancer Drug Development

• Phase-III studies test a new drug(s) against “best” therapy.
• Chop vs. R-Chop
Cancer Drug Development

2000 to Present
Cancer Drug Development

• Dr. Drucker changed the way we think about cancer.
• CML is a disease with one major pathway that is abnormal.
• CML has a 9-22 translocation
• This causes some of the DNA on 9 to be fused with DNA on 22 to produce a fusion molecule called BCR/ABL.
• BCR/ABL is stuck in the on position. It is folded in a way that allows a tyrosine kinase to fit and so doing fuels the protein. Drucker looked at this site and developed an inhibitor to fit in this site and by robbing it of energy shut off this signal.
Cancer Drug Development

• We now know that cancers have key pathways that are regulated up or down and this gives the cancer its special characteristics.

• We are now looking for the inhibitors of these pathways.
Surrogate Signatures - A Link with Pathway Activation
Vandetanib Selectively Targets VEGFR, EGFR, and RET Tyrosine Kinase Activity

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC_{50} (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR-2 (KDR)</td>
<td>0.04</td>
</tr>
<tr>
<td>VEGFR-3 (Flt-4)</td>
<td>0.11</td>
</tr>
<tr>
<td>RET</td>
<td>0.13</td>
</tr>
<tr>
<td>EGFR</td>
<td>0.50</td>
</tr>
<tr>
<td>VEGFR-1 (Flt-1), PDGFR-β, Tie-2, FGFR1</td>
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</tr>
<tr>
<td>MEK, CDK2</td>
<td>≥10</td>
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<tr>
<td>c-kit, erbB2, FAK, PDK1</td>
<td>≥20</td>
</tr>
<tr>
<td>AKT</td>
<td>≥100</td>
</tr>
<tr>
<td>IGF-1R</td>
<td>≥200</td>
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Agents Targeting the VEGF Pathway

- Anti-VEGF antibodies (bevacizumab)
- Soluble VEGFRs (VEGF-Trap)
- Anti-VEGFR antibodies (IMC-1121b)

**VEGF**

**Endothelial cell**

**VEGFR-1**

**VEGFR-2**