Targeted cancer therapy – towards molecular chemotherapy

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In Iraq.....

Conventional chemotherapy is a dirty bomb from the terrorists

Molecular targeted therapy is a smart bomb from the coalition force

.......... if you know where Bin Ladin & Al Qaeda are.
Traditional chemotherapy

- Attempts to address the limitless replicative potential of tumours

- Targets elements of the cell cycle machinery to inhibit growth and proliferation
  - highly effective against cells with a short doubling time
  - non-selective and cytotoxic → normal cells undergoing constant renewal are also affected
Targeted cancer therapy

- Hormone therapy for hormone receptor positive breast cancers
- Targeting high risk patients for adjuvant chemotherapy
  - Colon cancer: stage III (node+)
  - Breast cancer: axillary node+, large 1\textsuperscript{y} size, poor prognosis gene signature
Targeted cancer therapy

• Improved therapeutic index
• Surgery
  – Soft tissue sarcoma, breast conservation surgery
• Radiotherapy
  – Brachytherapy
  – 3D-conformal radiotherapy
  – Radiosurgery of Gamma- or X-knife
  – Intensity Modulated Radiotherapy
  – Imaged Guided Radiotherapy
  – Tomotherapy, Cyberknife
Intracavitary brachytherapy for cervical cancer
Catheter Based Brachytherapy

Traditional Free-Hand Multi-catheter Technique

Kuske template
Targeted conventional chemotherapy

- Capecitabine – oral 5-fluorouracil
- Liposomal doxorubicin
5FU & Capecitabine

IV 5-Fluorouracil

5-fluorouracil in tumor cells

5-fluoro-2-deoxyuridine Monophosphate (FdUMP) + 5-fluorouridine triphosphate (FUTP)

blocks thymidine synthetase

Cell DNA/RNA injury

*Levels of thymidine phosphorylase higher in tumor than normal tissue
5FU & Capecitabine

IV 5-Fluorouracil

- 5-fluorouracil in tumor cells
- 5-fluoro-2-deoxyuridine Monophosphate (FdUMP)
  + 5-fluorouridine triphosphate (FUTP)
  - blocks thymidylate synthetase
  - Cell DNA/RNA injury

Oral Capecitabine

- 5’-DFCR → 5’-DFUR in liver
  - thymidine phosphorylase*
  - 5-FU
    - FdUMP + FUTP
    - blocks thymidylate synthetase
    - Cell DNA/RNA injury

*Tumor cell

*Levels of thymidine phosphorylase higher in tumor than normal tissue
Molecular targeted therapy (MTT)

- Precision therapy targeting cancer cells
- Therapy targeting a critical biological process or a molecular pathway related to cancer growth or survival
- Target measurable and correlating with clinical outcome
- Milder toxicity, sparing normal cells to achieve higher therapeutic index
MTT approved by FDA

• 1st MTT approved in 1997 – rituximab

• 150 claims of use of oncology drugs from 1997 – 2006 approved

• 37 (25%) approvals for MTT

• 50% of FDA approvals for oncology in 2006 were for MTT
Key physiological changes in cancer

- Unlimited cell growth
- Insensitivity to antigrowth signals
- Reduced sensitivity to apoptosis
- Functional immortality
- Development and maintenance of vasculature (angiogenesis)
- Invasion and metastasis

Identifying the optimal target

- Identify agents that exploit tumour-specific molecules
  - limited effects on normal cells $\rightarrow$ increased specificity

- Identify the optimal target, or multiple targets, that
  - are redundant in normal cells
  - are overexpressed/uniquely expressed by tumour cell
  - drive tumour growth and proliferation
Adapted from:
Hanahan and Weinberg (2000) Cell, 100, 57
Blocking Signal Transduction

- Researchers believe that blocking specific proliferation-dependent signals in cancer cells may lead to arrest of tumor growth
- Blocking proliferative signals inhibits downstream signaling that regulates:
  - Proliferation
  - Migration
  - Angiogenesis
Reception, Transduction and Response

Extracellular Fluid → Cytoplasm → Reception → Transduction → Response

Signal-Transduction Pathway

Activation of Cellular Responses

cAMP

Earl W. Sutherland (Nobel Prize – 1971)
Design for Inhibiting Tumor Cell Growth

- Ligand binding site
- Ligand
- Inhibition of ligand binding to a receptor
- Receptor
- Transmembrane region of the receptor
- Cell membrane
- ATP binding site
- ATP
- Tyrosine kinase domain
- Nucleus
- DNA
- Growth factors
- Proliferation
- Migration
- Angiogenesis
- Tumor cell
Cancer cells are more sensitive to signal-transduction inhibitors than normal cells.

Targeting strategies

- Monoclonal antibodies (MAb)
  - bind to and inhibit growth factors or their cell surface receptors to block intracellular growth signals
  - bind to tumour cell-specific proteins, allowing tumour cells to be attacked by the immune system

- Tyrosine kinase inhibitors (TKIs)
  - block signalling pathways
  - single-targeting agents (Tarceva®, gefitinib)
    - highly specific
  - multitargeting agents (ZD6474, PTK787)
    - less specific
Types of Targeted Cancer Therapies

- **Monoclonal Antibodies**
  - Antibodies are proteins created by the immune system to recognize specific antigens.
  - MAbs are mass-produced in laboratory from a single clone (monoclonal) and are typically designed to recognize only one specific site on an antigen.
  - MAbs can be made to react with specific receptors on a cancer cell to enhance patient's immune system.
Strategies Using Monoclonal Antibodies

Diagram showing interactions between tumor cells, normal cells, growth factors, anti-ligand MAb, anti-receptor MAb, receptor, ligand binding site, transmembrane region of the receptor, tyrosine kinase domain, DNA, and nucleus.
Properties of Monoclonal Antibodies

- MAbs are large, cannot enter cells; function extracellularly
- Administered intravenously
- Examples:
  - Avastin™ (bevacizumab), directed against ligand VEGF
  - Erbitux™ (cetuximab), directed against extracellular region of EGFR
  - Herceptin® (trastuzumab), directed against extracellular region of human epidermal growth factor receptor 2 (HER2)
Types of Targeted Cancer Therapies

- **Small Molecule Tyrosine Kinase Inhibitor (TKI)**
  - Designed to inhibit kinase activity, e.g. phosphorylation, of certain proteins
  - Can bind to ATP-binding site in the intercellular region of growth factor receptor
  - Receptor was inactivated
  - can be designed to inhibit specific signal pathways
Binding of a Small-Molecule TKI to ATP-Binding Site
Properties of Small-Molecule TKIs

- Small and simple enough to be absorbed across the gut—orally administered
- Function intracellularly
- Can be designed to inhibit more than one growth factor receptor
- Examples:
  - Glivec® (imatinib mesylate)
  - Iressa® (gefitinib)
  - Tarceva™ (erlotinib)
  - Nexavar® (sorafenib tosylate)
Where do we go from here?

- Antireceptor antibodies ± toxins
- Tyrosine kinase inhibitors
- Farnesyl transferase inhibitors
- Apoptosis agonists
- Hormone agonists and antagonists
- Intracellular signalling molecules
- Nucleus
- Antimetabolites
- Microtubule inhibitors
- Tumour cell
- Growth factor receptors
- Immune system activation (e.g., vaccines)
- Metalloproteinase inhibitors
- Matrix degradation (collagenases, gelatinases & stromelysins)
- Angiogenesis inhibitors (Anti-VEGF)
- Antisense
Epidermal Growth Factor Receptor (EGFR)
Epidermal growth factor receptor

- EFGR, HER1 or c-Erb-1
- Transmembrane glycoprotein
- Constitutively expressed in normal epithelial tissues (skin, hair follicles)
Binding of EGFR to Transforming Growth Factor α results in receptor dimerization. Tyrosine kinase autophosphorylation initiates intracellular signaling, resulting in a variety of effects that may increase tumor growth.
Targeting EGFR-mediated signalling

- The EGF pathway is critical in regulating tumour cell growth and invasion
- Excessive EGFR signalling in tumours; overexpression, EGFR activating mutations
- Multiple registered and currently studied drugs block the EGFR signalling pathway
EGFR expression in solid tumours

EGFR is expressed in a variety of solid tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer</td>
<td>72-82%</td>
</tr>
<tr>
<td>Head &amp; neck cancer</td>
<td>95-100%</td>
</tr>
<tr>
<td>Lung cancer (NSCLC)</td>
<td>40-80%</td>
</tr>
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<td>Breast cancer</td>
<td>14-91%</td>
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<td>35-70%</td>
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<td>Renal cell cancer</td>
<td>50-90%</td>
</tr>
</tbody>
</table>

**Tumour EGFR expression as a prognostic factor**

EGFR expression correlates with poor prognosis

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Prognosis</th>
<th>Survival</th>
<th>Risk of metastasis</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>Poor</td>
<td>-</td>
<td>Increased</td>
<td>Hemming (1992)</td>
</tr>
<tr>
<td>Lung (NSCLC)</td>
<td>Poor; Poor</td>
<td>Decreased OS; Decreased DFS; Decreased OS</td>
<td>-; Increased</td>
<td>Ohsaki (2000); Pavelic (1993)</td>
</tr>
<tr>
<td>Head and neck (SCCHN)</td>
<td>Poor</td>
<td>Decreased DFS; Decreased OS</td>
<td>-</td>
<td>Grandis (1998); Maurizi (1996)</td>
</tr>
</tbody>
</table>

EGFR expression is also linked to reduced response and/or increased resistance to chemotherapy

DFS = Disease-free survival; OS = overall survival
Targeting EGFR-mediated signalling

- EGFR
- PI3-K
- Ras
- Raf
- SOS
- Grb-2
- MEK-1
- PTEN
- Akt
- STAT
- MAPK
- DNA
- PP
- Myc
- Cyclin D1
- Jun Fos
- Myc
- Cyclin D1

Proliferation / maturation
Survival / apoptosis
Angiogenesis
Metastasis
Mechanism of action of cetuximab

Cetuximab

Membrane

Nucleus

Cell proliferation
Apoptosis
Angiogenesis
Metastasis

EGF/IGF

EGF/IGF

X

X

X

X
Effects of cetuximab

- **Anti-tumour effects**
  - EGFR signalling pathway blockade
  - Down-regulation of pro-angiogenic factors
  - Induction of antibody-dependent cell-mediated cytotoxicity

- **Anti-angiogenic effects**
  - Pro-angiogenic growth factors (TGFα, VEGF, IL-8) generated by tumour cells are down-regulated
  - Leads to inhibition of endothelial cell proliferation and will therefore suppress tumour-induced angiogenesis
  - Effect is potentiated by combined treatment with cytotoxic drugs or ionising radiation
Erbitux™

- **Erbitux™** (cetuximab)/ Bristol-Myers Squibb/ ImClone

  - Approved February 2004
  - MAb directed against the extracellular region of EGFR
  - Indicated to be used in combination with Camptosar® for patients with EGF-expressing metastatic CRC who failed on Camptosar®, also as single agent for metastatic CRC who are intolerant to Camptosar®
  - Administered as initial dose of 400 mg IV as 120-minute infusion, 250 mg/m² IV over 60 minutes
Binding of a Small-Molecule TKI to ATP-Binding Site
Advanced or metastatic Non small cell lung cancer
Lung cancer

- Oral TKI benefits advanced inoperable or metastatic cancer failing 1st, 2nd, 3rd line chemotherapy
  - RR ~10 –20%
  - Survival benefit of ≤ 2 months
- Better response in Asians, adenocarcinoma, female patients

  *Fukuoka JCO 2003; Kris JAMA 2003; Shepherd NEJM 2005; Thatcher Lancet 2005*

- Not conferring survival benefits when combined with chemotherapy in 1st line therapy

  *Giaccone JCO 2004; Herbst JCO 2004; Herbst JCO 2004; Gatzameier JCO 2007*
Iressa®

- Iressa® (gefitinib)/AstraZeneca
  - Approved May 2003
  - Small-molecule TKI—targets EGFR
  - Indicated for the treatment of advanced NSCLC in patients whose disease has progressed after at least 2 other chemotherapies have failed
  - Administered orally
  - Administered at daily doses of 250 mg
Tarceva™

- Tarceva™ (erlotinib)/OSI/Genentech
  - Approved November 2004
  - Small-molecule TKI—targets EGFR
  - Indicated as single agent for treatment of locally advanced or metastatic NSCLC in patients whose cancer has progressed despite other treatments
  - Administered orally
  - Administered in daily doses of 150 mg taken at least 1 hour before or 2 hours after the ingestion of food
Metastatic CRC
Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer.

• A multicenter, randomized, controlled clinical trial was conducted in 329 patients randomized to receive either ERBITUX plus irinotecan (218 patients) or ERBITUX monotherapy (111 patients).

• In both arms of the study, ERBITUX was administered as a 400-mg/m^2 initial dose, followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicity.

EGFR-inhibitor induced skin reactions

THERAPY SUGGESTIONS

Topical anti-acne creams (drying effect)  Pulse dye laser  Emollients  Hydrocolloid dressing or Propylene glycol +/- acetylsalicyl  Anti-septic soaks  Silver nitrate (pyogenic granuloma)

+/- tetracyclines  +/- antihistamines

pictures S Segaert & E Van Cutsem - Leuven
HNC
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Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck.

*Bonner et al. NEJM 2006; 354:567-578*
### Table 4. Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Radiotherapy Alone (N = 212)</th>
<th>Radiotherapy plus Cetuximab (N = 208)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grades 3–5</td>
<td>All Grades</td>
</tr>
<tr>
<td>Mucositis</td>
<td>94</td>
<td>93</td>
<td>56</td>
</tr>
<tr>
<td>Acneiform rash</td>
<td>10</td>
<td>87</td>
<td>17</td>
</tr>
<tr>
<td>Radiation dermatitis</td>
<td>90</td>
<td>86</td>
<td>23</td>
</tr>
<tr>
<td>Weight loss</td>
<td>72</td>
<td>84</td>
<td>11</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>71</td>
<td>72</td>
<td>5</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>63</td>
<td>65</td>
<td>26</td>
</tr>
<tr>
<td>Asthenia</td>
<td>49</td>
<td>56</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>37</td>
<td>49</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>30</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>Taste perversion</td>
<td>28</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Pain</td>
<td>28</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td>Anorexia</td>
<td>23</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Fever</td>
<td>11</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>19</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Dehydration</td>
<td>19</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>22</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Coughing</td>
<td>19</td>
<td>20</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Voice alteration</td>
<td>22</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>19</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td><strong>Infusion reaction</strong></td>
<td>2</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>14</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>9</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Increased sputum</td>
<td>15</td>
<td>13</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Infection</td>
<td>9</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9</td>
<td>11</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Chills</td>
<td>5</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td><strong>Anaemia</strong></td>
<td>13</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

* Adverse events that occurred in at least 10 percent of patients in either treatment group are shown, regardless of cause.

†P values were determined with the use of Fisher’s exact test.

Bonner et al. *NEJM* 2006; 354:567-578
HER-2
The EGFR/HER Family

Mendelsohn and Baselga, Oncogene, 2000;19:6550.
Olayioye et al., EMBO J. 2000;19:3159.
Harari and Yarden, Oncogene, 2000;19:8102.
\textbf{HER-2/neu in Breast Cancer}

- **HER-2 oncogene amplification**
- **HER-2 oncoprotein overexpression**
- **Shortened survival**

- Median survival from first diagnosis:
  - \textit{HER-2} overexpression: 3yrs
  - \textit{HER-2} normal: 6-7yrs

\textit{Slamon et al, 1987; Slamon San Antonio, 1998}
HER2- Positive Status

- Fluorescence in-situ hybridization (FISH)
- quantifies the level of HER2 gene amplification
Herceptin®

- Herceptin® (trastuzumab) /Genentech
  - Approved September 1998
  - MAAb directed against extracellular region of HER2
  - Indicated as monotherapy for patients with HER2-positive metastatic breast cancer and in combination with paclitaxel for first-line treatment of HER2-positive metastatic breast cancer
  - Administered as initial dose of 4 mg/kg, IV as 90-minute infusion, then weekly maintenance dose of 2 mg/kg IV over 30 minutes
Trastuzumab actions on Her-2 receptors of breast cancer cells

- Recruits natural killer cells and activates release of substances perforating cancer cell membrane

- Prevents formation of p95 – active truncated form of Her-2 receptor cleaved by protease – from Her-2 receptor

- Blocks Her-2 activated intracellular signaling leading to cell proliferation

- Blocks Her-2 induced release of factors promoting angiogenesis
Treatment algorithm for MBC

Hormone-receptor +
- HER2-
  - Tamoxifen
  - Fulvestrant
  - Aromatase inhibitor
  - Ovarian suppression
  - (chemotherapy)
- HER2+
  - Herceptin ± chemotherapy

Hormone-receptor -
- HER2+
  - Anthracyclines
  - Taxanes
  - Xeloda
  - Vinorelbine
  - Liposomal doxorubicin
  - Gemcitabine
  - Combinations
- HER2-
  - Other factors:
    - Prior adjuvant therapy
    - Disease-free interval
    - Burden and distribution of disease

Novel targeted agents: Avastin; lapatinib
Novel cytotoxic agents: Abraxane; epothilones
Herceptin in Early Breast Cancer - Rationale

- HER-2 overexpressed in 20-30% of breast cancer, associated with poorer prognosis
- Herceptin demonstrated survival benefit in metastatic breast cancer. Greater benefit with earlier treatment
- Non-cross-resistant with chemo
- Low toxicity
### Adjuvant Herceptin trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HERA (ex-USA)</strong> (n=5090)</td>
<td>Any CT ± RT → Observation H q3w x 12 months, H q3w x 24 months</td>
</tr>
<tr>
<td><strong>NSABP-B31 (USA)</strong> (n=2030)</td>
<td>AC x 4 → P q3w x 4 or qw x 12, AC x 4 → P q3w x 4 or qw x 12 + H qw x 52</td>
</tr>
<tr>
<td><strong>NCCTG N9831 (USA)</strong> (n=3505)</td>
<td>AC x 4 → P qw x 12, AC x 4 → P qw x 12 + H qw x 52</td>
</tr>
<tr>
<td><strong>BCIRG 006 (global)</strong> (n=3222)</td>
<td>AC x 4 → D q3w x 4, AC x 4 → D q3w x 4 + H qw x 12 → H q3w x 13, D + Carbo q3w x 6 + H qw x 18 → H q3w x 11</td>
</tr>
<tr>
<td><strong>FinHer (Finland)</strong> (n=232a)</td>
<td>D q3w x 3 or V qw x 8 → CEF q3w x 3, D q3w x 3 or V qw x 8 + H qw x 9 → CEF q3w x 3</td>
</tr>
</tbody>
</table>

*a HER2+ subgroup
H, Herceptin; A, doxorubicin; P, paclitaxel; Carbo, carboplatin; E, epirubicin; V, vinorelbine; D, docetaxel
Adjuvant Herceptin in early breast cancer: DFS

- HERA H 1 year: 1 year
- B31 / N9831 AC→PH: 2 years
- BCIRG 006 AC→DH: 2 years
- BCIRG 006 DCarboH: 2 years
- FinHer\(^a\) VH / DH→CEF: 3 years

\(^a\)Recurrence-free survival

Median follow-up, years:
- HERA H 1 year: 1 year
- B31 / N9831 AC→PH: 2 years
- BCIRG 006 AC→DH: 2 years
- BCIRG 006 DCarboH: 2 years
- FinHer\(^a\) VH / DH→CEF: 3 years

Overall survival (ITT) Median FU 2 yrs

1 year trastuzumab

Patients (%)

100
90
80
70
60
50
40
30
20
10
0

Observation

Events

OS

HR

95% CI

p value

3-year

59
92.4
0.66
0.47, 0.91
0.0115

90
89.7

Months from randomisation

No. at risk

HERA trial
<table>
<thead>
<tr>
<th>Event</th>
<th>Observation n=1708</th>
<th>1 yr trastuzumab n=1678</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Severe CHF (NYHA III and IV)</td>
<td>0 (0.0)</td>
<td>10 (0.6)</td>
</tr>
<tr>
<td>Symptomatic CHF (II, III and IV)</td>
<td>3 (0.2)</td>
<td>36 (2.1)</td>
</tr>
<tr>
<td>Confirmed significant LVEF drop</td>
<td>9 (0.5)</td>
<td>51 (3.0)</td>
</tr>
<tr>
<td>Trastuzumab discontinued due to cardiac problems</td>
<td></td>
<td>72 (4.3)</td>
</tr>
</tbody>
</table>

HERA trial
Conclusions

- Trastuzumab following adjuvant CT significantly improves overall survival (HR 0.66) in women with HER2 +ve breast cancer
- The DFS gain after 1 year median FU is maintained after 2 years median FU
- The risk of cardiac toxicity remains low
- Long-term follow-up will provide
  - Continuing safety data
  - Information on trastuzumab treatment duration (1 vs 2 years)
  - Information on delayed switching to trastuzumab

HERA trial
Adjuvant Herceptin + chemotherapy

- Reduce BC-related events by ~50%
- Reduce early mortality by 1/3
- Cardiotoxicity reducable with drug sorting
- $ a lesser concern for short-term Herceptin
- HER-2 negative women (~70-80%) need other MTT
Rituximab in Lymphoma
Non-Hodgkin Lymphoma

- Chemo-sensitive cancer
- B cell >>> T cell
- 10th commonest cancer (HK, 2003)
- CHOP – gold standard >30 years
- CD20 receptors in B cell lymphoma & normal B cells
- Monoclonal antibody (Rituximab) targeting CD20 receptor tumoricidal
NK – natural killer cell

Tumor Cell

Receptor

Antibody

NK

NK
The body's immune system may sense the foreign substance (RITUXAN) on the B cells and send an army of natural defenses to kill these marked B cells.

RITUXAN may work by turning on a "switch" that causes the B cells to die.

The third way may involve restoring normal cell functions that allow cells to die when they are supposed to.
# Role of rituximab in lymphoma

<table>
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<tr>
<th>Scenario</th>
<th>Benefit</th>
<th>Evidence</th>
</tr>
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<tbody>
<tr>
<td>1st line Rx for elderly DLBCL</td>
<td>Incr PFS/FFS &amp; OS</td>
<td>GELA, NEJM 02 &amp; JCO 05</td>
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<tr>
<td></td>
<td></td>
<td>US Intergp, JCO06</td>
</tr>
<tr>
<td>1st line Rx for young DLBCL</td>
<td>Incr EFS &amp; OS</td>
<td>MiNT, Lancet Oncol 06</td>
</tr>
<tr>
<td>1st line Rx for low grade lymphoma</td>
<td>Incr TTP/TTF/PFS &amp; OS</td>
<td>Blood 05 (R-CVP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood 05 (R-CHOP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JNCI 07 (R+) (meta-A)</td>
</tr>
<tr>
<td>Salvage Rx for low grade lymphoma</td>
<td>Incr PFS/R duration &amp; OS</td>
<td>Blood 06 (RCHOP+mR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood 06 (RFCM+mR)</td>
</tr>
</tbody>
</table>
Fig 1. (A) Event-free survival, (B) progression-free survival, and (C) overall survival with a median follow-up of 5 years in patients treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), and rituximab plus CHOP (R-CHOP).

Radioimmunotherapy
for lymphoma

- Relapsed or refractory low-grade, follicular, or transformed B cell NHL, including Rituximab-refractory follicular NHL
- Tags *Yttrium or *Iodine to mouse mab
- $^90\text{Y}$ – 5mm penetration (100-200 cells) beta radiation, 2.7 days
- $^{131}\text{I}$ – 0.8mm, gamma + beta, 8 days
- HAMA 1-10%
Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma

<table>
<thead>
<tr>
<th></th>
<th>Zevalin</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>80%</td>
<td>56%</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>34%</td>
<td>20%</td>
</tr>
<tr>
<td>Median duration of response</td>
<td>13.9 months</td>
<td>11.8 months</td>
</tr>
<tr>
<td>Median TTP</td>
<td>10.6 months</td>
<td>10.1 months</td>
</tr>
</tbody>
</table>

Angiogenesis
Angiogenesis is involved throughout tumour formation, growth and metastasis.

Premalignant stage (Avascular tumour) → Malignant stage (Angiogenic switch) → Tumour growth (Vascularised tumour) → Vascular invasion (Tumour cell intravasation) → Dormant micrometastasis (Seeding in distant organs) → Overt metastasis (Secondary angiogenesis)

Stages at which angiogenesis plays a role in tumour progression

VEGF is a central mediator of angiogenesis
(Vascular endothelial growth factor)

Haemangioblast → Endothelial progenitors → VEGF → SMC progenitor → SMC
Artery → Vein → Vasculogenesis → Angiogenesis → Mature vasculature

SMC = smooth muscle cell
Adapted from Carmeliet P. Nat Med 2003;9:653–60
VEGF and other signals promote the angiogenic switch in tumours

Small tumour (1–2mm)
- avascular
- dormant

Larger tumour
- vascular
- metastatic potential

Angiogenic switch
Results in overexpression of pro-angiogenic signals, such as VEGF

VEGF actions

- Binds to membrane receptor tyrosine kinase, stimulating signal transduction cascades, in blood vessel or tumor cells
Functions of VEGF in tumour growth

- VEGF stimulates tumour angiogenesis
  - Angiogenesis is essential for tumour growth
- Tumour blood vessels created by VEGF are abnormal
  - Leaky and twisted
  - Improperly matured
- VEGF acts as a survival factor for immature tumour blood vessels
Normal and tumour vasculature

**Normal blood vessels**
- Maturation factors present
- Less dependent on cell survival factors
- Less permeable
- Reduced integrin expression
- Supporting cells present

**Tumour blood vessels**
- Leaky
- Fewer supporting cells
- Preferential expression of $\alpha_\beta_2$, $\alpha_\beta_5$, and $\alpha_\beta_1$ integrins
- Growth and survival factors (e.g., VEGF) present
How and Why Do Anti-Angiogenic Drugs Facilitate Activity of Chemotherapeutic Agents

- Temporary normalization of abnormal tumor vasculature, \textit{with increase in blood flow} and drop in high intratumor interstitial fluid pressure

- Chemotherapy itself may target tumor vasculature and circulating CPEs – inhibiting VEGF amplifies this effect

- Inhibiting VEGF may chemosensitize VEGF-R+ tumor cells
Agents targeting the VEGF pathway

- Antibodies inhibiting VEGF receptors (e.g., Avastin)
- Soluble VEGF receptors (VEGF-TRAP)
- Antibodies inhibiting VEGF (e.g., Avastin)
- Cation channel
- Migration, permeability, DNA synthesis, survival
- Ribozymes (Angiozyme)
- Angiogenesis
- Lymphangiogenesis
- Small-molecules inhibiting VEGF receptors (TKIs) (e.g., SU11248)
Bevacizumab

- IgG1 monoclonal antibody
- Binds with great affinity to VEGF
- Directly inhibits the activity of VEGF
- Prevents interaction of VEGF with VEGFR1 (FLT-1) and VEGFR2 (KDR) on the surface of endothelial cells to inhibit angiogenesis
Summary: Avastin mechanism of action

- Avastin may act against tumours in three ways
  - regression of existing microvasculature
  - normalisation of mature vasculature
  - inhibition of production of new vasculature
Abnormal vasculature normalised following VEGF inhibition\textsuperscript{1*}

\textsuperscript{*}Anti-VEGF agent: AG013736 (VEGF tyrosine kinase inhibitor); terminal half-life of 2–5 hours\textsuperscript{2}

\textsuperscript{1}Inai, et al. Am J Pathol 2004; \textsuperscript{2}Rugo, et al. JCO 2005
Direct effects of anti-VEGF therapy on tumour cells

- VEGF receptors are not restricted to endothelial cells
  - several preclinical studies have shown functional VEGF receptors to be present on colorectal, lung and renal cancer cells

- Tumour cell VEGF receptor-1 plays a role in tumour cell migration and invasion

- These data support growing evidence that VEGF has a direct effect on tumour cells and that anti-VEGF therapy may contribute to a direct antitumour effect in addition to anti-angiogenic effects

¹Fan, et al. Oncogene 2005
³Fox, et al. J Pathol 2004
VEGF: a candidate for anticancer therapy

- Tumours rely on their existing vasculature for survival
  - VEGF is a powerful survival factor for the immature vessels that comprise tumour microvasculature\(^1\)

- The abnormal structure and function of tumour vasculature inhibits the action of conventional therapies\(^2\)
  - Inhibition of VEGF normalises existing vasculature\(^3\)

- Tumours require new vasculature for growth and metastasis\(^4\)
  - VEGF is a potent stimulator of new vessel growth

- VEGF has a limited role in healthy adults,\(^5\) so anti-VEGF therapy should have minimal physiological effects

Anti-angiogenesis therapy in metastatic CRC
Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.

<table>
<thead>
<tr>
<th>End Point</th>
<th>IFL plus Placebo</th>
<th>IFL plus Bevacizumab</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (mo)</td>
<td>15.6</td>
<td>20.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hazard ratio for death</td>
<td></td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>One-year survival rate (%)</td>
<td>63.4</td>
<td>74.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression-free survival (mo)</td>
<td>6.2</td>
<td>10.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hazard ratio for progression</td>
<td></td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Overall response rate (%)</td>
<td>34.8</td>
<td>44.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Complete response</td>
<td>2.2</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>32.6</td>
<td>41.0</td>
<td></td>
</tr>
<tr>
<td>Median duration of response (mo)</td>
<td>7.1</td>
<td>10.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Hazard ratio for relapse</td>
<td></td>
<td>0.62</td>
<td></td>
</tr>
</tbody>
</table>

* IFL denotes irinotecan, fluorouracil, and leucovorin.

Hurwitz et al
Avastin plus chemotherapy in clinical practice: BRiTE – study overview

- Previously untreated metastatic, locally advanced and unresectable CRC (n=1,953)
- Avastin plus chemotherapy
- PD

- Chemotherapy regimen and Avastin dose/schedule at investigator discretion
- Patients are followed for up to 3 years and clinical data updated every 3 months
- Objectives
  - safety: incidence of adverse events possibly related to Avastin
  - efficacy: time to progression, response rate and overall survival

Kozloff, et al. ASCO GI 2007
## BRIITE: efficacy by first-line chemotherapy regimens used on study

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=1,953)</th>
<th>FOLFOX (n=1,092)</th>
<th>FOLFIRI (n=280)</th>
<th>IFL (n=189)</th>
<th>5-FU bolus/LV (n=132)</th>
<th>XELOX (n=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median progression-free survival (months)</td>
<td>10.1</td>
<td>10.0</td>
<td>10.9</td>
<td>9.0</td>
<td>9.2</td>
<td>11.2</td>
</tr>
<tr>
<td>1-year survival (%)</td>
<td>74.7</td>
<td>75.6</td>
<td>79.4</td>
<td>67.7</td>
<td>64.8</td>
<td>81.2</td>
</tr>
<tr>
<td>Median overall survival (months)</td>
<td>27.1</td>
<td>27.3</td>
<td>NE</td>
<td>20.5</td>
<td>19.9</td>
<td>27.5</td>
</tr>
<tr>
<td>Exposure to three active agents (%)</td>
<td>35.7</td>
<td>43.0</td>
<td>35.0</td>
<td>30.7</td>
<td>7.6</td>
<td>37.2</td>
</tr>
</tbody>
</table>

- Avastin combined with standard first-line chemotherapy regimens has produced the highest ever overall survival benefit in patients with metastatic CRC

Kozloff, et al. ASCO GI 2007
Chemotherapy in metastatic CRC
Benefit and evolution

Median overall survival (months)

- Supportive Care: 8 months
- 5-FU bolus: 12.6 months
- 5-FU infusion: 14.1 months
- Irinotecan/5-FU bolus: 14.8 months
- Irinotecan/5-FU infusion: 17.4 months
- Oxaliplatin + 5-FU infusion: 19.5 months
- Irinotecan/5-FU bolus/bevacizumab: 20.3 months
- Irinotecan/5-FU inf. followed by oxaliplatin/inf. 5-FU: 21.5 months
- Irinotecan/5-FU bolus/bevacizumab followed by oxaliplatin: 25.1 months
Are MTT fool-proof?

- few randomized studies with mature results
- Exact cell-kill mechanism speculative
- Works best with chemotherapy
- Indications of value can be specific for any cancer e.g. lung
  - Oral TKI beneficial as 2\textsuperscript{nd} or 3\textsuperscript{rd} line therapy
  - No additional benefit when combined with first line chemotherapy
Are MTT non-toxic?

- Not as innocuous as initially thought
- Collateral damage even for smart bomb

- Monoclonal antibody
- EGFR Mab/TKI
- Anti-angiogenesis
- CD-20 Mab/RIT
- Trastuzumab
Resistance to MTT

• Dependence on single target?

• Cross-talk between different pathways

• Over-expression of targeted receptor?

• Multi-targeting agent Vs combination of selective targeting agents
Prohibitive cost and access

• R & D costs

• Clinical studies to target patients likely benefiting using surrogate biomarker

• Translational research
### Figure 1. Responses in a clinical trial of a molecularly targeted agent.

A) Response is determined by target expression. In this set of clinical trials, the response rate is 80% in patients whose tumor expresses the appropriate target. As the target frequency varies from 10% to 90%, the overall clinical response ranges from 8% to 72%.

B) Response depends on expression and activation. In this example, the target is expressed in all patients, but is activated in 10% to 90% of patients. The response rate to the agent is again 80%, but only in patients with target expression and activation, thus, the overall clinical response ranges from 8% to 72%.

<table>
<thead>
<tr>
<th>A</th>
<th>Target frequency</th>
<th>Target response rate</th>
<th>Observed response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 patients</td>
<td>90%</td>
<td>80%</td>
<td>72%</td>
</tr>
<tr>
<td>100 patients</td>
<td>50%</td>
<td>80%</td>
<td>40%</td>
</tr>
<tr>
<td>100 patients</td>
<td>25%</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>100 patients</td>
<td>10%</td>
<td>80%</td>
<td>8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B</th>
<th>Target expression</th>
<th>Target activation</th>
<th>Target response rate</th>
<th>Observed response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 patients</td>
<td>100%</td>
<td>90%</td>
<td>80%</td>
<td>72%</td>
</tr>
<tr>
<td>100 patients</td>
<td>100%</td>
<td>50%</td>
<td>80%</td>
<td>40%</td>
</tr>
<tr>
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<td>100%</td>
<td>25%</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>100 patients</td>
<td>100%</td>
<td>10%</td>
<td>80%</td>
<td>8%</td>
</tr>
</tbody>
</table>
Conclusions

• MTT – a breakthrough therapy

• Integral and essential component in treatment algorithm in many common cancers with no comparable alternative

• sometimes the only available effective treatment in some uncommon cancers – unresponsive cancer becoming responsive to therapy

• Many unresolved issues but MTT is here to stay
Current strategic roles of MTT
<table>
<thead>
<tr>
<th>Drug</th>
<th>Structure class</th>
<th>Molecular Target</th>
<th>Clinical benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab (MacThera)</td>
<td>Monoclonal antibody</td>
<td>CD20 receptor on cell surface</td>
<td>Improves overall survival (OS) &amp; progression free survival (PFS) as 1&lt;sup&gt;st&lt;/sup&gt; line treatment for CD-20+ diffuse large B-cell or follicular / low grade non-Hodgkin’s lymphoma; effective for relapsed or low grade follicular non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>Monoclonal antibody</td>
<td>Her-2 receptor of the EGFR family on cell surface</td>
<td>Improves OS &amp; PFS in high risk Her-2+ breast cancer when combined with adjuvant chemotherapy; as single agent in 2&lt;sup&gt;nd&lt;/sup&gt; line therapy or combined with paclitaxel as 1&lt;sup&gt;st&lt;/sup&gt; line therapy for HER-2+ metastatic breast cancer</td>
</tr>
<tr>
<td>Imatinib (Glivec)</td>
<td>Small Tyrosine Kinase Inhibitor (TKI) molecules</td>
<td>brc-Abl protein, C-kit receptor, platelet derived growth factor</td>
<td>Effective 1&lt;sup&gt;st&lt;/sup&gt; and 2&lt;sup&gt;nd&lt;/sup&gt; line therapy for Ph+ CML; 1&lt;sup&gt;st&lt;/sup&gt; line therapy for inoperable / metastatic GIST</td>
</tr>
<tr>
<td>Drug</td>
<td>Structure class</td>
<td>Molecular Target</td>
<td>Clinical benefit</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------</td>
<td>----------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Gefitinib (Iressa)</td>
<td>Small TKI</td>
<td>Intracellular portion of HER-1 of EGFR</td>
<td>Effective 3&lt;sup&gt;rd&lt;/sup&gt; line therapy for advanced NSCLC failing 1&lt;sup&gt;st&lt;/sup&gt; &amp; 2&lt;sup&gt;nd&lt;/sup&gt; lines chemotherapy</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>Small TKI</td>
<td>Intracellular portion of HER-1 of EGFR</td>
<td>Effective 2&lt;sup&gt;nd&lt;/sup&gt;/3&lt;sup&gt;rd&lt;/sup&gt; line therapy for advanced NSCLC failing 1&lt;sup&gt;st&lt;/sup&gt; line chemotherapy; OS &amp; PFS benefits combined with gemcitabine as 1&lt;sup&gt;st&lt;/sup&gt; line therapy for advanced pancreatic cancer</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Monoclonal</td>
<td>VEGF</td>
<td>OS &amp; PFS benefits as 1&lt;sup&gt;st&lt;/sup&gt; line therapy when combined with chemotherapy for metastatic colorectal carcinoma (CRC)</td>
</tr>
<tr>
<td>Cetuximab (Erbitux)</td>
<td>Monoclonal</td>
<td>Extracellular portion of EGFR</td>
<td>Effective 2&lt;sup&gt;nd&lt;/sup&gt; line therapy in metastatic CRC either alone or combined with irinotecan chemotherapy after failing irinotecan chemotherapy; Improves OS &amp; loco-regional control in advanced head &amp; neck cancer (HNC) when combined with 1&lt;sup&gt;st&lt;/sup&gt; definitive RT; effective therapy as single agent for advanced HNC failing cisplatinum chemotherapy</td>
</tr>
<tr>
<td>Drug</td>
<td>Structure class</td>
<td>Molecular Target</td>
<td>Clinical benefit</td>
</tr>
<tr>
<td>------</td>
<td>----------------</td>
<td>------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Bortezomib (Velcade)</td>
<td>Small molecules</td>
<td>Proteasome enzyme complex</td>
<td>Effective 2nd or 3rd line therapy for multiple myeloma and 2nd line therapy for relapsing mantle-cell lymphoma</td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>Small multi-targeted TKI molecules</td>
<td>Raf kinase and VEGF-receptor kinases</td>
<td>PFS benefits as 2nd line therapy for advanced renal cell carcinoma (RCC) failing 1st line therapy</td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
<td>Small multi-targeted TKI molecules</td>
<td>Multiple kinases involved in tumor growth and angiogenesis</td>
<td>PFS benefits for advanced RCC as 1st or 2nd line therapy; improved PFS as 2nd line therapy for GIST failing Glivec</td>
</tr>
<tr>
<td>Ibritumomab tiuxetan (Zevalin), Tositumomab (Bexxar)</td>
<td>Radioactive conjugates of monoclonal antibody</td>
<td>CD20 receptor on cell surface</td>
<td>As salvage therapy for relapsed or refractory CD-20+ low grade or follicular or transformed lymphoma failing chemotherapy or Rituximab</td>
</tr>
</tbody>
</table>
Thank you for attending
Glivec in GIST
GIST Overview (1)

- Most common GI sarcoma
- Highest incidence in 40-60 year age group
- Historically misclassified and diagnosis still challenging in some cases
- All GIST have the potential to become malignant
- 95% are positive for KIT (CD117)
c-KIT and GIST

- c-KIT proto-oncogene codes for KIT
- KIT– member of receptor tyrosine kinase family
- Wild type (normal) KIT binds SCF / MCF → dimerisation → activation of intracellular domain → intracellular signaling cascade
- Mutated KIT → gain of function with constitutive KIT signaling → proliferation
- Imatinib → binds to intracellular KIT ATP binding site
Imatinib (GIST)

Effect of Normal (Panel A) and Abnormal (Panel B) c-kit Function on Platelet-Derived Growth Factor and Gastrointestinal Stromal Tumors.

Summary (I)

- GISTs are an uncommon malignancy. Consider referral to centre using a multidisciplinary approach
- Surgery is the principal treatment modality for resectable nonmetastatic GIST
- Any recurrence should be considered as metastatic disease
- Imatinib 400 mg/day ± surgery is the recommended first-line treatment for recurrent or metastatic GIST
- Dose escalation (to 800 mg/day) may be considered in patients who progress or develop secondary resistance
Summary (II)

- Adjuvant/neoadjuvant imatinib is not advised as standard therapy for resectable nonmetastatic GIST
- Neoadjuvant imatinib should be considered for “functionally unresectable” GIST
- Report treatment imatinib according to RECIST guidelines but incorporate CT changes in tumour enhancement
Recurrent or Metastatic GIST

Recurrent = Metastatic

- Localized Resectable
  - Imatinib mesylate 400 mg/d
- Multifocal, Multiorgan

Disease Progression

- Disease Resectable
  - Surgical Resection
    - Y: Clinical Oncology consultation
    - Clinical trial
    - Continue imatinib and dose-escalate to 800 mg in patient progressing on 400 mg of imatinib
  - N: Resectable?

Clonal Progression

- Clonal Progression
Figure 1. Kaplan-Meier Estimates of Overall Survival and Time to Treatment Failure for All Patients. Each arrowhead represents the point at which a patient's data were censored.

Response to Imatinib for advanced GIST

<table>
<thead>
<tr>
<th>Best response</th>
<th>400mg (73)</th>
<th>600mg (74)</th>
<th>Either dose (147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>36 (49%)</td>
<td>43 (58%)</td>
<td>89 (54%)</td>
</tr>
<tr>
<td>SD</td>
<td>23 (32%)</td>
<td>18 (24%)</td>
<td>41 (28%)</td>
</tr>
<tr>
<td>PD</td>
<td>12 (16%)</td>
<td>8 (11%)</td>
<td>20 (14%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>2 (3%)</td>
<td>5 (7%)</td>
<td>7 (5%)</td>
</tr>
</tbody>
</table>

Figure 2. Sequential PET Scans Obtained in the Same Patient at Base Line (before Treatment, Panel A), 1 Month after Imatinib Treatment Began (Panel B), and after 16 Months of Continuous Treatment (Panel C). The images at each point include a two-dimensional PET scan of the body (top), an axial PET scan of a slice through the site of the pelvic tumor (middle), and a correlating CT scan at the corresponding level. The standardized uptake values for the tumor at the three time points were 4.5 (Panel A), 1.24 (Panel B), and 0.75 (Panel C). The uptake in the cardiac blood pool, the myocardium, the liver, the bowel, the bilateral renal collecting system, and the bladder is within physiologic limits in this patient. Images were obtained with the use of similar doses of [(18)F]fluoro-2-deoxy-D-glucose, acquisition times, and protocols at the three time points. The patient also had similar blood glucose concentrations at each of these three time points.

Pre- 1month 16 month Glivec

Glivec in CML
### CML: a Progressive and Fatal Disease

<table>
<thead>
<tr>
<th>Chronic phase</th>
<th>Advanced phases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Accelerated phase</td>
</tr>
<tr>
<td>Median duration 5–6 years</td>
<td>Median duration 6–9 months</td>
</tr>
</tbody>
</table>

![Diagram showing the progression from Chronic phase to Accelerated phase to Blast crisis with median duration and survival times.]
CML: Linked to a Single Molecular Abnormality

The Philadelphia (Ph) Chromosome: $t(9;22)$ Translocation

Fusion Protein with Tyrosine Kinase Activity
Glivec®

- **Glivec® (imatinib myselate)/Novartis**
  - Approved May 2001 (CML) and 2002 (GIST)
  - Small-molecule TKI - targets KIT, PDGFR, and BCR-ABL
  - Indicated for the treatment of CML and GIST
  - Administered orally
  - Administered at daily doses of 400 mg or 600 mg in adults, may be increased to 800 mg/day
  - Doses of 130 mg/m² BID in children after stem cell transplant
CML: Its Cause and Management

- The Ph chromosome generates the Bcr-Abl tyrosine kinase—the molecular cause of CML
  - Constitutive activation leads to malignant transformation

- Eliminating the Ph chromosome—a primary goal of therapy
  - Complete cytogenetic response (0% Ph+ cells)
  - Major cytogenetic response (≤35% Ph+ cells)
  - Patients who achieved a complete/major cytogenetic response with SCT or IFN-α had prolonged survival vs patients without such a response
  - Patients with Ph+ CML treated with Gleevec had estimated overall survival rates of 91% in late chronic phase, 46% (at 400mg/day) and 66% (at 600mg/day) in accelerated phase, and 18% in blast crisis 2 years after initiating treatment
Figure 1. Schematic representation of the mechanism of action of STI571. The bcr-abl tyrosine kinase is a constitutively active kinase which functions by binding ATP and transferring phosphate from ATP to tyrosine residues on various substrates. This causes the excess proliferation of myeloid cells characteristic of CML. STI571 functions by blocking the binding of ATP to the bcr-abl tyrosine kinase, inhibiting its activity. In the absence of tyrosine kinase activity, substrates required for bcr-abl function cannot be phosphorylated and subsequent cellular events are abrogated.
Gleevec® Targets the Cause of CML

- Gleevec—a specific inhibitor of a small family of tyrosine kinases, including Bcr-Abl, Kit, and PDGF receptor
IRIS: The Largest Phase III CML Study to Date

1106 patients enrolled from June 2000 to January 2001

Gleevec® (n=553)
- IF:
  - Loss of MCR or CHR
  - Increasing WBC count
  - Intolerance of treatment
  - Failure to achieve MCR at 12 (vs 24) mos*
  - Failure to achieve CHR at 12 (vs 24) mos*
  - Request to discontinue IFN-α*

IFN-α + ara-C (n=553)

S = screening.
R = randomization.

*Independent Data Monitoring Board recommended protocol amendment.
Longer Time to Progression With Gleevec®*

Patients Free of Any Disease Progression*

- Estimated rate at 12 months:
  - Gleevec: 97%†
  - IFN-α + ara-C: 80%

Patients Free of Progression to Advanced Disease*

- Estimated rate at 12 months:
  - Gleevec: 98%†
  - IFN-α + ara-C: 93%

*IRIS study; n=553 in each arm.
†P<0.0001.
Gleevec® Has Advanced the Treatment of Ph+ CML

- Therapy specifically designed to target the molecular cause of CML (Bcr-Abl)
- High rates of cytogenetic and hematologic response in all phases of disease
- Significant delay in time to disease progression for patients in chronic phase
- Mild to moderate side-effect profile
- Convenient, once-daily, oral dosing*
- Evolving first-line therapy for CML

*800 mg should be administered as 400 mg twice a day.

For important safety information, please see slide 3 or full Prescribing Information.
NCCN* CML Guidelines for Monitoring Response to Gleevec®

3-month evaluation

- Gleevec initiated
  - Hematologic response
    - Continue Gleevec
      - Monitor cytogenetics every 3 to 6 months
  - No hematologic response
    - Increase dose of Gleevec or switch to IFN-α ± ara-C, or perform SCT if feasible

12-month evaluation

- Complete cytogenetic response
  - Continue Gleevec
- Partial cytogenetic response or no cytogenetic response
  - Increase dose of Gleevec or continue same dose or switch to IFN-α ± ara-C, or perform SCT if feasible, or join clinical trial

*National Comprehensive Cancer Network
www.nccn.org/physician_gls/index.html
RCC
Renal cell carcinoma

• Uncommon cancer of kidney
• Typically clear cell histology
• Very vascular with pulsatile metastases and early hematogenous metastases to lung, bone and brain

• Von Hippel Lindau tumor suppressor gene mutation → loss of VHL protein → VEGF / PDGF over-expression
Sunitinib Mechanism of Action in RCC

Loss of VHL Protein Function

\[ \uparrow \text{VEGF} \quad \uparrow \text{PDGF} \]

Vascular Endothelial Cell

- Vascular permeability
- Cell survival, proliferation, migration

Pericyte/Fibroblast/Vascular Smooth Muscle

- Vascular formation, maturation

RCC pathogenesis and progression
Sunitinib Mechanism of Action in RCC

Loss of VHL Protein Function

↑ VEGF

VEGFR

VEGF

Vascular Endothelial Cell

→ Sunitinib

↓ Vascular permeability

↓ Cell survival, proliferation, migration

Pericyte/Fibroblast/Vascular Smooth Muscle

↑ PDGF

PDGFR

PDGF

Vascular formation, maturation

Inhibition of RCC pathogenesis and progression
Multi-targeting Tyrosine Kinase Inhibitors

**Figure 1.** Sorafenib and sunitinib have targets in both the tumor cell and the tumor vasculature, thus inhibiting both tumor growth and angiogenesis. Abbreviations: FLT-3, fms-like tyrosine kinase 3; KIT, stem cell factor receptor; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.
Randomization Scheme

N=750

Stratification Factors
- LDH $\leq 1.5$ vs $>1.5\times$ULN
- ECOG PS 0 vs 1
- Presence vs Absence of Nephrectomy

Randomization

Sunitinib
(N=375)

IFN-$\alpha$
(N=375)
Progression-Free Survival
(Independent Central Review)

Hazard Ratio = 0.415
(95% CI: 0.320–0.539)
P < 0.000001

No. at Risk Sunitinib: 235 90 32 2
No. at Risk IFN-α: 152 42 18 0

Sunitinib
Median: 11 months
(95% CI: 10–12)

IFN-α
Median: 5 months
(95% CI: 4–6)
Overall Survival

Hazard Ratio = 0.65
(95% CI: 0.449–0.942)
\( P = 0.0219^* \)

- Sunitinib (n=375)
  - Median not reached
- IFN-\(\alpha\) (N=375)
  - Median not reached

No. at Risk Sunitinib: 341 190 84 15 1
No. at Risk IFN-\(\alpha\): 296 162 66 10 0

*The observed \( p \)-value did not meet the pre-specified level of significance for this interim analysis*
## Outcome Summary

<table>
<thead>
<tr>
<th></th>
<th>Sunitinib</th>
<th>IFN-α</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Median Progression-free Survival</em>, mos (95% CI)</em>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent Review Investigator</td>
<td>11 (10-12)</td>
<td>5 (4-6)</td>
</tr>
<tr>
<td></td>
<td>11 (8-14)</td>
<td>4 (4-5)</td>
</tr>
<tr>
<td><em><em>Objective response</em>, % (95% CI)</em>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent Review Investigator</td>
<td>31 (26-36)</td>
<td>6 (4-9)</td>
</tr>
<tr>
<td></td>
<td>37 (32-42)</td>
<td>9 (6-12)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Acceptable</td>
<td>—</td>
</tr>
<tr>
<td><strong>Patient-reported Outcomes</strong></td>
<td>Superior</td>
<td>—</td>
</tr>
</tbody>
</table>

*Sunitinib vs IFN-α: P <0.000001*
Cytotoxic chemotherapy

- Chemotherapy drugs act primarily on DNA synthesis
- Chemotherapy selectively kills cancer cells
  - Cells kinetics
  - proliferation characteristics
  - cell biology
- Cells of rapidly proliferating normal tissue affected – therapeutic index