Clinical experience with kinase inhibitors for the treatment of cancer

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6th RSC / SCI Symposium on kinase inhibitor design
Overview

• Kinase inhibitors approved by FDA (1998-2013)
  • Targets
  • Inhibitor types

• Kinase inhibitors in the real world
  • Do more selective compounds make better drugs?
  • Dose selection
  • Combinations
  • Exploiting oncogene addiction for patient selection

• Resistance and ‘mutant kinases’
  • Bcr-Abl
  • EGFR
  • EML4-ALK

• Future directions
The Kinase Revolution

- More than 50% of current oncology clinical trials

- Kinases are still the most ‘drugable oncogenes’

- Kinase inhibitors have been at the forefront of personalised medicine and diagnostic development

- Launch of Imatinib was truly revolutionary
FDA Approved kinase inhibitors for cancer
- Approvals have doubled since 2010
## Kinase inhibitor families

- **Approved drugs and research in narrow focus**

<table>
<thead>
<tr>
<th></th>
<th>Kinase Family</th>
<th>Drugs</th>
<th>Tumors/Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bcr-Abl</td>
<td>Imatinib, Dasatinib, Nilotinib, Bosutinib, Ponatinib</td>
<td>CML (GIST)</td>
</tr>
<tr>
<td>2</td>
<td>EGFR</td>
<td>Gefitinib, Erlotinib, Afatinib, Panitumumab</td>
<td>NSCLC (CRC)</td>
</tr>
<tr>
<td>3</td>
<td>ErbB2</td>
<td>Trastuzumab, Lapatinib</td>
<td>Breast Cancer</td>
</tr>
<tr>
<td>4</td>
<td>VEGFR</td>
<td>Bevacizumab, Pegaptinib, Sorafenib, Sunitinib, Axitinib, Regorafenib, Pazopanib</td>
<td>RCC, CRC, NSCLC, HCC</td>
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<tr>
<td>5</td>
<td>VEGFR / Ret</td>
<td>Vandetinib, Cabozantib</td>
<td>Thyroid cancer</td>
</tr>
<tr>
<td>6</td>
<td>Ros1 / ALK</td>
<td>Crizotinib</td>
<td>NSCLC</td>
</tr>
<tr>
<td>7</td>
<td>Braf / MEK</td>
<td>Vemurafenib, Trametinib, Debrafenib</td>
<td>Melanoma</td>
</tr>
<tr>
<td>8</td>
<td>JAK</td>
<td>Ruxolitinib</td>
<td>Myelofibrosis</td>
</tr>
<tr>
<td>9</td>
<td>BTK</td>
<td>Ibrutinib</td>
<td>MCL, CLL</td>
</tr>
</tbody>
</table>

*Nature Chemical Biology, 2010, 6, 166169*
Most of kinome has yet to be drugged
- Tyrosine kinase inhibitors dominate approved drugs

- Literature review highlighted the total clinical pipeline in 2010.
- Of 23 FDA-approved small molecule inhibitors, 16 are in just 3 classes (VEGFR, EGFR, Abl)
- This analysis suggests that Flt3, c-kit, Aurora, CDK, FGFR, Src are over-invested

*ALK, BTK

Nature Chemical Biology, 2010, 6, 166169
ATP-competitive inhibitors
- 18 of 20 Tyrosine Kinase Inhibitors are type I / II

- Type I (DFG - in)
  - Gefitinib, Erlotinib, Vandetinib
  - Lapatinib, Ruxolitinib, Sunitinib
  - Dasatinib, Axitinib,

- Type II (DFG – out)
  - Sorafenib, Imatinib, Nilotinib
Other Mechanisms of Action
- Novel Modes of Inhibition

- ‘Allosteric inhibitors’
  - Trametinib

- Covalent binders
  - Afatinib, Ibrutinib
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  • Do more selective compounds make better drugs?
  • Safety and tolerability
  • Exploiting oncogene addiction for patient selection

• Resistance and ‘mutant kinases’
  • Bcr-Abl
  • EGFR
  • EML4-ALK

• Future directions
Dose and Schedule
- Monotherapy still dominates

- With exception of Lapatinib, kinase inhibitors typically dosed as continuous monotherapy
- Three quarters of compounds given once daily (qd)
- Median daily dose is 275 mg/day although this is lower for recently approved compounds

Lapatanib – 1250mg qd dose delivered as 5 x 250mg tablets
When lack of selectivity pays off...
- Crizotinib and Vandetinib

- Crizotinib, originally selected as a c-Met inhibitor, first dosed to patients in 2006
- ALK activity established pre-clinically in 2005 (20 fold more potent) ...also ROS1
- First reports on EML4-ALK fusion published July 2007
- First ALK-fusion patient dosed with Crizotinib in December 2007
- FDA approval in EML4-ALK NSCLC cancer granted in 2011

- Vandetanib originally developed as VEGFR inhibitor with some EGFR activity
- Completed a Phase III study in NSCLC in combination with docetaxel (2009)
- Ret activity demonstrated after start of Phase I by collaborator (2002)
- Clinical studies in thyroid cancer started in 2004
- FDA approval in medullary thyorid cancer granted in 2011

Drug Design, Development and Therapy 2011:5
But, ultimately, selectivity is important
- Crizotinib v PF-06463922

Issues with Crizotinib
- Weak activity against other mutant forms of ALK
- Limited brain penetration
- Response rate ‘only’ 57%
- Limited duration of response (~7 months)
- >60% patients suffer visual impairment
- ~0.4% incidence of fatal liver failure
Tolerability of kinase inhibitors

- Better than cytotoxics but not clean...

• In a study of 34 patients on Sorafenib and Sunitinib:
  • 10 patients (34%) had stabilization of disease, 8 patients (28%) had a partial response, and 11 patients (38%) had progression of disease
  • Grade 3 or 4 adverse event occurred in 19 patients (56%)
  • 8 patients (24%) required drug discontinuation and 11 patients (32%) required dose reductions, but were able to resume the targeted dose

• Toxicity due to both lack of selectivity and role of kinases in normal physiology

• 11 of 26 FDA-approved kinase inhibitors carry black box warnings:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sponsor</th>
<th>Target</th>
<th>Black box warning(s)</th>
<th>FDA AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>Genentech</td>
<td>HER2</td>
<td>Pulmonary toxicity, cardiomyopathy and a confusion warning</td>
<td>25/09/1998</td>
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<tr>
<td>Bevacizumab</td>
<td>Genentech</td>
<td>VEGF</td>
<td>GI perforation, haemorrhage and wound healing complications</td>
<td>26/02/2004</td>
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<tr>
<td>Sunitinib</td>
<td>Pfizer</td>
<td>VEGFR, PDGFR</td>
<td>Hepatotoxicity</td>
<td>26/01/2006</td>
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<tr>
<td>Panitumumab</td>
<td>Amgen</td>
<td>EGFR</td>
<td>Dermatologic reactions and infusion reactions</td>
<td>10/10/2006</td>
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<td>Lapatinib</td>
<td>GlaxoSmithKline</td>
<td>ErbB2</td>
<td>Hepatotoxicity</td>
<td>13/03/2007</td>
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<tr>
<td>Nilotinib</td>
<td>Novartis</td>
<td>Bcr-Abl</td>
<td>QT interval prolongation and electrolyte anomalies</td>
<td>29/10/2007</td>
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<tr>
<td>Pazopanib</td>
<td>GlaxoSmithKline</td>
<td>VEGFR, PDGFR, c-KIT</td>
<td>Hepatotoxicity</td>
<td>19/10/2009</td>
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<tr>
<td>Vandetanib</td>
<td>AstraZeneca</td>
<td>VEGFR, EGFR, RET, BRK</td>
<td>QT interval prolongation</td>
<td>21/04/2011</td>
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<tr>
<td>Regorafenib</td>
<td>Bayer</td>
<td>RET, VEGFR, PDGFR</td>
<td>Hepatotoxicity</td>
<td>27/09/2012</td>
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<tr>
<td>Cabozantinib</td>
<td>Exelixis</td>
<td>RET, c-Met, VEGFR</td>
<td>GI haemorrhage, perforation and fistula</td>
<td>29/11/2012</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>ARIAD</td>
<td>Bcr-Abl, PDGFR, FGFR, ...</td>
<td>Liver failure, blood clots and hepatotoxicity</td>
<td>14/12/2012</td>
</tr>
</tbody>
</table>
Activating Mutations - 1
- EGFR and lung adenocarcinoma

- Gefitinib trial in unselected patients shows marginal PFS benefit
- Being female, of Asian origin and a non-smoker increased benefit
- iPass trial (below) showed dramatic differences in wt and mutant patients

- Gefitinib used with diagnostic test in 18-35% patients who have EGFR mutations
- Most common genetic events are exon 19 deletion and L858R mutation (exon 21)
Activating Mutations - 2
- JAK2 and Myelofibrosis

• 60% patients with myelofibrosis (IMF) have V617F mutation in JAK2
• Ruxolitinib trials recruited roughly equal numbers of V617F JAK2 +/- patients
• Level of reduction of splenomegaly considerably better than with placebo
• Impact on overall survival less clear

- Level of reduction of splenomegaly (above) has no significant link with JAK2 mutation status (‘low molecular risk’ v ‘high molecular risk’)

• Ruxolitinib used without diagnostic test in all patients with IMF
Kinase Translocation and Fusion Proteins
- Highly oncogenic but often rare genetic events

- The first protein kinase translocation was the Philadelphia chromosome t(9;22) in CML

- Other fusion proteins have been found with cytosolic tyrosine kinases
  - TEL - JAK2
  - TEL – SYK
  - ITK - SYK

- Other fusion proteins have been found with receptor tyrosine kinases
  - FIP1L1 - PDGFRA
  - EML4 - ALK
  - TACC3 – FGFR3
  - TACC1 – FGFR1
  - RET – PTC
Amplification and Overexpression - ErbB2 and Breast Cancer

- Approximately 20% of invasive breast cancers overexpress Her2, and are associated with poor prognosis.
- Overexpression of the Her2 protein is primarily due to amplification of the HER2 oncogene on chromosome 17.
- However, increased HER2 copies may also result from chromosome 17 polysomy.
Patient selection strategies
- Diagnostic Development

- 18 (of 19) FDA-approved companion diagnostics for oncology are for kinase targets, of which 10 are for Her2
- Imatinib uses Philadelphia chromosome status (Ph+)
- Numbers of diagnostics set to increase rapidly

<table>
<thead>
<tr>
<th>FDA</th>
<th>Device Trade Name</th>
<th>Product</th>
<th>Target</th>
<th>Device Manufacturer</th>
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<tbody>
<tr>
<td>1</td>
<td>therascreen KRAS RGQ PCR Kit</td>
<td>Cetuximab</td>
<td>Kras (EGFR-wt)</td>
<td>Qiagen Manchester, Ltd.</td>
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<tr>
<td>2</td>
<td>DAKO EGFR PharmDx Kit</td>
<td>Cetuximab, Panitumumab</td>
<td>EGFR</td>
<td>Dako North America, Inc.</td>
</tr>
<tr>
<td>3</td>
<td>DAKO C-KIT PharmDx</td>
<td>Afatinib</td>
<td>EGFR</td>
<td>Qiagen Manchester, Ltd.</td>
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<td>4</td>
<td>INFORM HER-2/NEU</td>
<td>Trastuzumab</td>
<td>Her2</td>
<td>Ventana Medical Systems, Inc.</td>
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<td>5</td>
<td>PATHVYSION HER-2 DNA Probe Kit</td>
<td>Trastuzumab</td>
<td>Her2</td>
<td>Abbott Molecular Inc.</td>
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<td>6</td>
<td>PATHWAY ANTI-HER-2/NEU (4B5) Rabbit Monoclonal Primary Antibody</td>
<td>Trastuzumab</td>
<td>Her2</td>
<td>Ventana Medical Systems, Inc.</td>
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<tr>
<td>7</td>
<td>INSITE HER-2/NEU KIT</td>
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<td>Her2</td>
<td>Biogenex Laboratories, Inc.</td>
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<tr>
<td>8</td>
<td>SPOT-LIGHT HER2 CISH Kit</td>
<td>Trastuzumab</td>
<td>Her2</td>
<td>Life Technologies, Inc.</td>
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<tr>
<td>9</td>
<td>Bond Oracle Her2 IHC System</td>
<td>Trastuzumab</td>
<td>Her2</td>
<td>Leica Biosystems</td>
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<td>10</td>
<td>HER2 CISH PharmDx Kit</td>
<td>Trastuzumab</td>
<td>Her2</td>
<td>Dako Denmark A/S</td>
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<tr>
<td>11</td>
<td>INFORM HER2 DUAL ISH DNA Probe Cocktail</td>
<td>Trastuzumab</td>
<td>Her2</td>
<td>Ventana Medical Systems, Inc.</td>
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<tr>
<td>12</td>
<td>HERCEPTEST</td>
<td>Trastuzumab, Pertuzumab</td>
<td>Her2</td>
<td>Dako Denmark A/S</td>
</tr>
<tr>
<td>13</td>
<td>HER2 FISH PharmDx Kit</td>
<td>Trastuzumab, Pertuzumab</td>
<td>Her2</td>
<td>Dako Denmark A/S</td>
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<tr>
<td>14</td>
<td>THxID™ BRAF Kit</td>
<td>Trametinib, Debrafenib</td>
<td>Braf</td>
<td>bioMérieux Inc.</td>
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<td>15</td>
<td>cobas EGFR Mutation Test</td>
<td>Erlotinib</td>
<td>EGFR</td>
<td>Roche Molecular Systems, Inc.</td>
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<tr>
<td>16</td>
<td>VYSIS ALK Break Apart FISH Probe Kit</td>
<td>Crizotinib</td>
<td>EML4-ALK</td>
<td>Abbott Molecular Inc.</td>
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<tr>
<td>17</td>
<td>COBAS 4800 BRAF V600 Mutation Test</td>
<td>Vemurafenib</td>
<td>Braf</td>
<td>Roche Molecular Systems, Inc.</td>
</tr>
</tbody>
</table>
Rational combinations have huge promise
- Braf-MEK combination

- Comparison of Trametinib + Debrafenib v Debrafenib
- Median PFS for the combination was 9.4 months, as compared with 5.8 months for Debrafenib (HR = 0.39)
- 0.25 to 0.62; P<0.001).
- The rate of CR/PR was 76%, (54% for monotherapy)

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  • EGFR
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• Future directions
Mutant kinases
- Bcr-Abl: Imatinib’s real world performance

- Imatinib has revolutionised treatment of CML
- Patients typically stay on drug > 3 years
- However, the benefit of Imatinib is greatest in early stages of disease (lower clonal burden)
- Resistance to Imatinib through both Bcr-Abl mutations and overexpression
Mutant kinases
- Bcr-Abl : Imatinib resistance mutations

- Initially 33 mutations were found, now over 90, although many are very rare
Mutant kinases
- Bcr-Abl: clonal evolution

- Baseline mutational status established for patients who are resistant to Imatinib
- Over half patients harbour mutations
- Thus there is high clonal heterogeneity before Imatinib treatment
Mutant kinases

- **Bcr-Abl**: enter Dasatinib

  - In contrast to Imatinib, Dasatinib is a type I (DFG-in) RTK inhibitor
    - Much more potent against Abl
    - Effective against all mutant forms except T315I (gatekeeper)
    - Also active against Src family
    - Broader RTK activity

  - Pattern of resistant mutants different from Imatinib (Sawyers, 2004)
Mutant kinases
- EGFR : post Gefitinib or Erlotinib

• Median time on Erlotinib or Gefitinib is around 10 months
• Afatinib (irreversible) claims to increase this by 2 months but toxicity is greater
• In contrast to Imatinib, T790M is the dominant resistant clone
• Activation of other RTKS (cMet, her2) also important resistance mechanisms
• Transformation to Small Cell Lung Cancer (or squamous histology) is reported, but incompletely understood

• Only about 4% of patients have detectable T790M at first biopsy
Mutant kinases
- **T790M EGFR**

- T790M +ve has better prognosis (19 month PFS) v T790M –ve (12 month PFS)

- In 2010 William Pao reported 5 patients with germ-line T790M (ages 50-72)

- 3 of the 5 patients also had the L858 (exon 19 mutation)

- The T790M mutation merely restores ATP affinity to the level of the WT kinase.

<table>
<thead>
<tr>
<th>Kinase</th>
<th>$K_m[ATP]$, μM</th>
<th>$k_{cat}$, s⁻¹</th>
<th>$k_{cat}/K_m[ATP]$, μM⁻¹·s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>5.2 ± 0.2</td>
<td>0.026</td>
<td>5.00E-3</td>
</tr>
<tr>
<td>T790M</td>
<td>5.9 ± 0.1</td>
<td>0.137</td>
<td>2.32E-2</td>
</tr>
<tr>
<td>L858R</td>
<td>148 ± 4</td>
<td>1.484</td>
<td>1.00E-2</td>
</tr>
<tr>
<td>L858R/T790M</td>
<td>8.4 ± 0.3</td>
<td>0.456</td>
<td>5.43E-2</td>
</tr>
</tbody>
</table>

*PNAS, 2007, 2070-75*

*Clin Cancer Res 2011;17:1616-1622*
Mutant kinases

- Irreversible inhibitors bind T790M EGFR

Irreversible inhibitors overcome the increased Km for ATP shown by T790M
- The Cysteine at residue 797 traps onto the Michael acceptor in the inhibitor
- The inhibitor avoids steric interaction with the bulkier methionine at residue 790
Mutant kinases
EML4-ALK – post Crizotinib

• Median duration of treatment on Crizotinib is ~8 months
• Patient numbers are small but resistance mutations account for lower % of resistance
• No dominant clones
• Many clones seem to be less indolent than the original EML4 fusion

• Vey different situation to both Imatinib and Gefitinib resistance
• But likely to be very drug dependent

• Resistance to second generation compound (LDK378, PF-06463922) will differ
Future Directions
- Predictions for the 2020 talk...

• Rational combinations of kinase inhibitors – Braf / MEK will not be unique
• More effective combinations with non-chemotherapy backbone treatments
• More sophisticated scheduling to maximise pathway inhibition

• Other protein kinases will have approved inhibitors, e.g.
  - CDK4/6, CDK9, PLK1, Aurora A/B,
  - Wee1, Chk1/2, ATR,
  - IRAK4, AKT
• Lipid kinase inhibitors will be approved (e.g. PI3Kα, PI3Kδ...)
• Increasing use of non-ATP competitive inhibition strategies

• Patients will stay on therapy longer due to improved efficacy in resistant clones
• Patient selection will use Next Generation Sequencing (NGS) and will be provide longitudinal data
• Disease monitoring will routinely use blood borne markers (e.g. cfDNA)