Old Generics or New Drugs

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BCR/ABL Inhibitors

Glivec, Tasigna, Sprycell, Bosulif

1999-2009

Imatinib (Gleevec, STI-571)
Nilotinib (Tasigna, AMN107)
Dasatinib (Sprycel, BMS-354825)
Bosutinib (SK-606)
CML-related survival by age groups in the TKIs cohort

Probability

0.00  0.25  0.50  0.75  1.00

Months

Age 18–29
Age 30–59
Age ≥60

P = 0.079

95%
93%
89%
Never ever give up!
PONATINIB
A PAN-BCR-ABL INHIBITOR

- Rationally designed inhibitor of BCR-ABL
- Active against T315I mutant
  - Unique approach to accommodating gatekeeper residue
- Potent activity against an array of BCR-ABL variants
- Also targets other therapeutically relevant kinases
  - Inhibits FLT3, FGFR, VEGFR and PDGFR, and c-KIT
- Once-daily oral activity in murine models

FLT3 = FMS-like tyrosine kinase receptor-3; FGFR = fibroblast growth factor receptor; VEGFR = vascular endothelial growth factor receptor
Adjusted OS of CP-CML Patients

<table>
<thead>
<tr>
<th>Survival (%): Overall survival (months), median (IQR)</th>
<th>Ponatinib (N = 64)</th>
<th>SCT (N = 26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR (45.9 - NR)</td>
<td>103.3 (6.6 - 103.3)</td>
<td>0.013*</td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.37 (0.16, 0.84)</td>
<td>Ref.</td>
<td>0.017*</td>
</tr>
</tbody>
</table>

* p-value <0.05. Ref. = reference group; NR = not reached.

Frank Nicolini et al, ASH 2013
CLINICAL PRESENTATION

Chronic phase CML

Treatment Considerations:
- Patient comorbidities and drug toxicities
- Monitor response
- Evaluate patient compliance and drug interactions
- Early toxicity monitoring

Low-risk score
(See Risk Calculation Table CML-A)

Intermediate- or high-risk score
(See Risk Calculation Table CML-A)

PRIMARY TREATMENT

First generation TKI (Imatinib or generic imatinib 400 mg QD) (category 1) or
Second generation TKI (Bosutinib 400 mg QD [category 1] or Dasatinib 100 mg QD [category 1] or Nilotinib 300 mg BID [category 1]) or Clinical trial

See Evidence Blocks on CML-2A

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5-year OS is similar in different trials

ENESTnd: Nilotinib vs Imatinib

DASISION: Dasatinib vs Imatinib

Survival according to relative risk (Cox model analysis)

“Training” population

n = 361

ENESTnd: Nilotinib vs imatinib frontline
KM estimated rates of OS on study among patients with (A) low, (B) intermediate, or (C) high Sokal risk

Impact of age on efficacy and toxicity of nilotinib in patients with chronic myeloid leukemia in chronic phase (CML-CP): ENEST1st sub-analysis

More than 1 thousand patients, Europe, 2010

Francis J. Giles, Delphine Rea, Michele Baccarani, Nicholas C.P. Cross, Juan Luis Steegmann, Laimonas Griskevicius, Philipp le Coutre, Daniel Coriu, Ljubomir Petrov, Gert J. Ossenkoppele, Francois-Xavier Mahon, Martin C. Müller, Andrzej Hellmann, Kimmo Porkka, Tim H. Brümmendorf, Gunther Gastl, Angela Pellegrino, Luca Dezzani, Gianantonio Rosti, Andreas Hochhaus
ENEST1st: Cumulative incidence of MMR, MR^4, and MR^4.5

By 12 mo  By 18 mo  By 24 mo

Cumulative Incidence of Response, %a

Time Since Study Entry, mo

- MMR
- MR^4
- MR^4.5

*Molecular analysis population (n = 1052).*
QOL in CML Patients (n. 456) Receiving Imatinib > 24 months with Compared with the General Population.

Efficace et al, for GIMEMA Blood, 2011
Patients’ follow up status

**Phase of treatments**

<table>
<thead>
<tr>
<th>Phase of treatments</th>
<th>Induction (n=344)</th>
<th>Maintenance (median 24.6 mo.)</th>
<th>Discontinuation (median 37 mo.)</th>
</tr>
</thead>
</table>

**Induction therapy**
- Nilotinib 2x300 mg
- Nilotinib 2x300 mg + PEG-IFNα2b

**Maintenance therapy**
- cont. Nilotinib
- PEG-IFNα2b

**Cure?**
- >36 mo. therapy
  - >24 mo. assessment
  - confirmed MMR
  - ≥12 mo. MR4

**Discontinuation (n=116)**
- Nilo intolerance -> Imatinib
- Nilo resistance -> Transplantation/Dasatinib recommended
- Suboptimal response: -> Nilotinib 400 mg BID
ABL001

Potent allosteric inhibitor with good pharmacologic properties

<table>
<thead>
<tr>
<th>Assay</th>
<th>ABL001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical IC(_{50}), ABL(^{WT})</td>
<td>1.2 nM</td>
</tr>
<tr>
<td>Cellular IC(_{50}) BCR-ABL(^{WT})</td>
<td>1 nM</td>
</tr>
<tr>
<td>Cellular IC(_{50}) BCR-ABL(^{T315I})</td>
<td>25 nM</td>
</tr>
<tr>
<td>Cellular IC(_{50}) WT BaF/3</td>
<td>&gt;10 (\mu)M</td>
</tr>
<tr>
<td>hERG</td>
<td>&gt;30 (\mu)M</td>
</tr>
<tr>
<td>Qpatch Clamp</td>
<td>26 (\mu)M</td>
</tr>
<tr>
<td>PAMPA class, F %</td>
<td>36</td>
</tr>
<tr>
<td>CYP3A4,2D6,2C9</td>
<td>&gt;20 (\mu)M</td>
</tr>
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</table>
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*Imatinib, dasatinib, nilotinib, bosutinib, ponatinib*
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Cumulative incidence of MR$^{4.5}$

- Nilotinib 300 mg BID (n = 282)
- Nilotinib 400 mg BID (n = 281)
- Imatinib 400 mg QD (n = 283)

By 5 years:
- 54%; $P < .0001$

By 4 years:
- 40%; $P < .0001$
- 37%; $P = .0002$

$\Delta$ 21% to 23%

$\Delta$ 14% to 17%

31%

MR$^{4.5}$, molecular response ≥4.5-logs (BCR-ABL$^5 \leq 0.0032\%$).


Data cutoff: September 30, 2013.