2019, the weight of the choice of 1\textsuperscript{st} line Treatment

**Patient**
- Risk, comorbidities
- Personal Expectations
- Education, compliance
- Advocacies

**Drugs**
- Efficacy and time to response
- Side Effects
- Long term safety
- Costs

**Physician**
- Personal Experience
- Experience
2019, the weight of the choice of 1st line Treatment

Patient
- Risk, comorbidities
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- Education, compliance
- Advocacies

Drugs
- Efficacy and time to response
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- Long term safety
- Costs

Physician
- Personal Experience
- Experience

ENDPOINTS

Age and QOL
## TKIs for CML Therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Imatinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
<th>Bosutinib</th>
<th>Ponatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Abl</td>
<td>Src &amp; Abl</td>
<td>Abl</td>
<td>Src &amp; Abl</td>
<td>Src &amp; Abl</td>
</tr>
<tr>
<td>Standard dose</td>
<td>400 mg QD</td>
<td>100 mg QD</td>
<td>400 mg BID</td>
<td>500 mg QD</td>
<td>45 mg QD</td>
</tr>
<tr>
<td>IC50, Bcr-Abl1</td>
<td>260-679</td>
<td>0.8-1.8</td>
<td>10-25</td>
<td>42</td>
<td>0.5</td>
</tr>
<tr>
<td>IC50, c-Kit</td>
<td>99</td>
<td>18</td>
<td>209</td>
<td>10000</td>
<td>12</td>
</tr>
<tr>
<td>IC50, PDGFR</td>
<td>72</td>
<td>2.9</td>
<td>75</td>
<td>3.0</td>
<td>1.1</td>
</tr>
<tr>
<td>IC50, Src</td>
<td>&gt;1000</td>
<td>0.1</td>
<td>&gt;1000</td>
<td>3.0</td>
<td>5.4</td>
</tr>
<tr>
<td>IC50, VEGFR2</td>
<td>10000</td>
<td>NA</td>
<td>3720</td>
<td>NA</td>
<td>1.5</td>
</tr>
<tr>
<td>IC50, BTK</td>
<td>&gt;5000</td>
<td>1.1</td>
<td>NA</td>
<td>2.5</td>
<td>849</td>
</tr>
</tbody>
</table>

34 yrs old, female,
EUTOS Population-based Patients
Sex distribution by age groups

![Graph showing the sex distribution of patients by age groups. The graph displays data for both males (blue line) and females (red line). The percentage of male patients peaks around the 40-49 age group, while female patients have their peak slightly younger.](image-url)
74 yrs old, male, Hypertension, dislipidemia.
## CML – Disease Risk

<table>
<thead>
<tr>
<th>Score</th>
<th>SOKAL OVERALL SURVIVAL CONVENTIONAL CHT</th>
<th>EURO OVERALL SURVIVAL α – INTERFERON</th>
<th>EUTOS CCyR at 18 Months IMATINIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>0.0166 x (Age-43.4)</td>
<td>0.666 x Age (&gt; 50)</td>
<td>-</td>
</tr>
<tr>
<td>Spleen (cm)</td>
<td>0.0345 x (Spleen-7.51)</td>
<td>0.042 x Spleen</td>
<td>4 x Spleen</td>
</tr>
<tr>
<td>Platelets (10³/μL)</td>
<td>0.188 x [(PLT/700)²-0.563]</td>
<td>1.0956 x PLT (&gt; 1500)</td>
<td>-</td>
</tr>
<tr>
<td>Myeloblast (%)</td>
<td>0.0887 x (MB-2.1)</td>
<td>0.0584 x MB</td>
<td>-</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>-</td>
<td>0.20399 x Bas (&gt; 3)</td>
<td>7 x Bas</td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>-</td>
<td>0.0413 x Eos</td>
<td>-</td>
</tr>
</tbody>
</table>

### Relative risk

<table>
<thead>
<tr>
<th>Relative risk</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>≤ 0.80</td>
<td>0.81 – 1.20</td>
<td>&gt; 1.21</td>
</tr>
<tr>
<td>SOKAL OVERALL SURVIVAL</td>
<td>≤ 780</td>
<td>781-1480</td>
<td>&gt; 1481</td>
</tr>
<tr>
<td>EUTOS CCyR at 18 Months IMATINIB</td>
<td>≤ 87</td>
<td>-</td>
<td>&gt; 87</td>
</tr>
</tbody>
</table>

HASFORD et al. JNCI 1998; 90: 850-858  
Survival according to relative risk (Cox model analysis)

Sokal High-Risk Patients Had Significantly Worse Responses on Imatinib

ONLY IMATINIB AT THAT TIME!

<table>
<thead>
<tr>
<th>Sokal risk score</th>
<th>n</th>
<th>PFS at 60 months(^1)</th>
<th>EFS at 54 months(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>201</td>
<td>97%</td>
<td>90%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>111</td>
<td>92%</td>
<td>83%</td>
</tr>
<tr>
<td>High</td>
<td>71</td>
<td>83%</td>
<td>71%</td>
</tr>
</tbody>
</table>

\(^1\) P<0.001
\(^2\) P<0.001

Data from the IRIS trial
2. Baccarani M. Relative Risk (Sokal & Hasford)
   Available at: http://www.leukemia-net.org/content/leukemias/cml/research/research/
The CHOICE, BASED on WHAT?

EARLY MOLECULAR MILESTONES

IMATINIB OR 2nd GENERATION TKIs?

HOW MUCH TREATMENT D/C IS ATTRACTIVE?

COPD, chronic obstructive pulmonary disease
34 yrs old, female,
Cumulative Incidence of MR$^{4.5}$

By 1 Year
- Nilotinib 300 mg BID (n = 282):
  - 11%; $P < .0001$
- Nilotinib 400 mg BID (n = 281):
  - 7%; $P < .0001$
- Imatinib 400 mg QD (n = 283):
  - $\Delta 6\%$ to $10\%$

By 4 Years
- Nilotinib 300 mg BID (n = 282):
  - 54%; $P < .0001$
- Nilotinib 400 mg BID (n = 281):
  - 40%; $P < .0001$
- Imatinib 400 mg QD (n = 283):
  - 37%; $P = .0002$
  - $\Delta 14\%$ to $17\%$

By 5 Years
- Nilotinib 300 mg BID (n = 282):
  - 54%; $P < .0001$
- Nilotinib 400 mg BID (n = 281):
  - 52%; $P < .0001$
  - $\Delta 21\%$ to $23\%$
- Imatinib 400 mg QD (n = 283):
  - 31%

$\Delta$, difference.

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

Data cutoff: September 30, 2013

Hughes et al., EHA 2014 annual congress. Abstract S677
QOL in CML Patients (n. 456) Receiving Imatinib > 24 months with Compared with the General Population.
Higher frequency of splenomegaly and greater spleen size
Lower CCyR and MMR rates (TKIs)
Higher probability of transformation to AP/BP (TKIs)
74 yrs old, male, **LOW** risk (Sokal), COPD, Hypertension, dislipidemia.
QOL in CML Patients (n. 456) Receiving Imatinib > 24 months with Compared with the General Population.
74 yrs old, male, **HIGH** risk (Sokal), COPD, Hypertension, dislipidemia.