How did the introduction of low-cost generics change clinical decision making in first-line therapy?

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To be short,

NO CHANGE AT ALL, OR MARGINAL CHANGES
My perception,

In Italy, many (most) CML docs prescribe 2nd Gen TKIs in High Risk and “Young” patients.
Addressing the basic question from a different viewpoint:

**Is there any condition where NOT using 2nd gen front-line can be considered unethical or a “mistake”?**
5-years OS is similar in different trials

ENESTnd: Nilotinib vs Imatinib

DASISION: Dasatinib vs Imatinib

It is CLEAR that only Nilotinib 800 is associated with a tiny, but significant advantage in PFS and OS

<table>
<thead>
<tr>
<th></th>
<th>5-years deaths</th>
<th>5-years leuk death</th>
<th>PFS* 5Y %</th>
<th>OS 5Y %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENESTnd Nilo 600¹</td>
<td>6,4%</td>
<td>2,1%</td>
<td>92,2</td>
<td>93,7</td>
</tr>
<tr>
<td>ENESTnd Nilo 800</td>
<td>3,6%</td>
<td>1,4%</td>
<td>95,8</td>
<td>96,2</td>
</tr>
<tr>
<td>ENESTnd Ima 400</td>
<td>7,8%</td>
<td>5,7%</td>
<td>91</td>
<td>91,7</td>
</tr>
<tr>
<td>Dasision Dasa²</td>
<td>10,0%</td>
<td>3,5%</td>
<td>85</td>
<td>91</td>
</tr>
<tr>
<td>Dasision Imatinib</td>
<td>10,0%</td>
<td>6,5%</td>
<td>86</td>
<td>90</td>
</tr>
</tbody>
</table>

PFS IN DASISION is EFS³

Survival according to relative risk (Cox model analysis)

'Straining' population

\[ n = 361 \]

All 3 progressions to AP/BC on study reported since the 4-year analysis occurred in patients with high Sokal risk scores at baseline; all 3 patients also had BCR-ABL IS > 10% at 3 months.

- All progressions in patients with low/intermediate Sokal risk scores occurred during the first 2 years on study.

Data cutoff: September 30, 2013

Progression to AP/BC or death due to advanced CML on core treatment or during follow-up after discontinuation of core treatment.

Progression to AP/BC on Study According to Sokal Risk Score

New events reported since the 4-year analysis

- Nilotinib 300 mg BID
- Nilotinib 400 mg BID
- Imatinib 400 mg QD
### ELN 2013 – Response to Front-line Treatment (Imatinib, Nilotinib, and Dasatinib)

<table>
<thead>
<tr>
<th>Time</th>
<th>Optimal Conditions</th>
<th>Warning Conditions</th>
<th>Failure Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>NA</td>
<td>-High risk, -CCA/Ph+ (Major route)</td>
<td>NA</td>
</tr>
<tr>
<td>3 months</td>
<td>Ph+ ≤ 35% and/or BCR-ABL ≤ 10%</td>
<td>Ph+ 36-95% and/or BCR-ABL &gt; 10%</td>
<td>No CHR and/or Ph+ &gt; 95%</td>
</tr>
<tr>
<td>6 months</td>
<td>Ph+ 0% and/or BCR-ABL ≤ 1%</td>
<td>Ph+ 1-35% and/or BCR-ABL 1-10%</td>
<td>Ph+ &gt; 35% and/or BCR-ABL &gt; 10%</td>
</tr>
<tr>
<td>12 months</td>
<td>BCR-ABL ≤ 0.1%</td>
<td>BCR-ABL &gt; 0.1-1%</td>
<td>Ph+ &gt; 0% and/or BCR-ABL &gt; 1%</td>
</tr>
<tr>
<td>Then</td>
<td>BCR-ABL ≤ 0.1%</td>
<td>BCR-ABL 0.1-1%</td>
<td>BCR-ABL &gt; 1%</td>
</tr>
</tbody>
</table>

2018, the weight of the choice of 1\textsuperscript{st} line Treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Drugs</th>
<th>Physician</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk, comorbidities</td>
<td>Efficacy and time to response</td>
<td>Personal Experience</td>
</tr>
<tr>
<td>Personal Expectations</td>
<td>Side Effects</td>
<td>Experience</td>
</tr>
<tr>
<td>Education, compliance</td>
<td>Long term safety</td>
<td></td>
</tr>
<tr>
<td>Advocacies</td>
<td>Costs</td>
<td></td>
</tr>
</tbody>
</table>

ENDPOINTS
CML, Same Endpoints for Everybody?

34 yrs old, female, intermediate risk (Sokal), no comorbidities

74 yrs old, male, low risk (Sokal), mild COPD, hypertension, dislipidemia.

COPD, chronic obstructive pulmonary disease
~40% of patients treated for at least 3 years with imatinib and with CMR4.5 for at least 2 years maintain CMR4.5 after imatinib discontinuation.

ENESTnd: cumulative incidence of MR4.5 by 6 years

KM-estimated median times to first MR4.5 were:
- Nilotinib 300 mg BID: 45.5 months (hazard ratio [HR] vs imatinib, 2.0387 [95% CI, 1.5807-2.6295]; nominal \( P < .0001 \))
- Nilotinib 400 mg BID: 49.8 months (HR vs imatinib, 1.7770 [95% CI,1.3780-2.2915]; nominal \( P < .0001 \))
- Imatinib 400 mg QD: 61.1 months

\(^{a}\)P values are nominal.

ENEST1st Final Analysis

Cumulative Incidence of MMR, MR^4, and MR^4.5

By 12 mo
- MMR: 68.9%
- MR^4: 37.1%
- MR^4.5: 20.7%

By 18 mo
- MMR: 77.2%
- MR^4: 48.7%
- MR^4.5: 31.7%

By 24 mo
- MMR: 80.4%
- MR^4: 55.2%
- MR^4.5: 38.6%

Cumulative Incidence of Response, %

Time Since Study Entry, mo
Cumulative Incidence of MR$^{4.5}$ in Patients Without MR$^{4.5}$ at Baseline (ITT analysis)

- In a subgroup analysis when only responses up to crossover were counted, 47% versus 24% of patients in the nilotinib and imatinib arms, respectively, achieved MR$^{4.5}$ ($P = .0003$)

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