First line treatment of CML with Imatinib: 
the IRIS trial and the GIMEMA trials 
Michele Baccarani
IRIS Protocol: Study Design

**RANDOMIZE**

- **Imatinib**
  - n = 553

- **IFN-a + Ara-C**
  - n = 553

Crossover for:
- Lack of response
- Loss of response
- Intolerance of treatment
- Reluctance to continue IFN

O'BRIEN et al, NEJM, 2003
IRIS 7 Year Update: Main Points

• What happened to all the patients?
  – Discontinuation
  – Survival
• Late progression events
• Durability of complete cytogenetic response (CCR)
  – Is CCR a ‘safe haven’?
• PCR data
• Adverse Events
• Conclusions
What Happened To The Patients After 7 Years?

All randomized to imatinib (n= 553; 100%)

- Discontinued study imatinib* (n = 221; 40%)
  - Safety (n = 43; 8%)
  - Efficacy (n = 82; 15%)
  - Other (n = 96; 17%)

- Still receiving study imatinib (n = 332; 60%)
  - In CCR (n = 317; 57%)
  - No CCR (n = 15; 3%)

- Alive (n = 17; 40%)
- Dead** (n = 26; 60%)
- Alive (n = 52; 63%)
- Dead (n = 30; 37%)
- Alive (n = 81; 84%)
- Dead (n = 15; 16%)

**Including primary discontinuation reason ‘Death’ (n=13)

*Patients may have continued imatinib off study.


IRIS 7 year update
Overall Survival (ITT Principle): Imatinib Arm

Estimated overall survival at 7 years is 86% (94% considering only CML-related deaths)

### Annual Event Rates: Imatinib Arm

- KM estimated EFS at 7 years = 81%
- KM estimated rate without AP/BC at 7 years = 93%

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Loss of CHR, Loss of MCR, AP/BC, Death during treatment</th>
<th>AP/BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.3</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>7.5</td>
<td>2.8</td>
</tr>
<tr>
<td>3</td>
<td>4.8</td>
<td>1.6</td>
</tr>
<tr>
<td>4</td>
<td>1.7</td>
<td>0.9</td>
</tr>
<tr>
<td>5</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>2.0*</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Total events (n=5) including loss of MCR (n=3) and deaths (n=2, one of which was coded as progression to AP/BC in a patient in CMR 6 months prior to death).


IRIS 7 year update
Durability of Cytogenetic Response

- 456 of 553 (82%) of first-line imatinib patients achieved CCR
- 317 (57%) patients randomized to imatinib remained on protocol and were in complete cytogenetic response (CCR)

![Diagram](image)

Rates of Progression in Patients After CCR

- Progression to AP/BC occurred in 15 (3%) of the 456 patients who had achieved a CCR
- Of 456 patients who achieved CCR, 10 (2%) died from CML

<table>
<thead>
<tr>
<th>Year After Achievement of CCR</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number Progressing After CCR</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Time to CCR
- ≤12 months (n = 373)
- >12- ≤24 months (n = 50)
- >24 months (n = 33)

Not shown: 1 event in seventh year after CCR - cause of death uncertain but suspected to be related to CML

Molecular Response Rates

- Major molecular response (MMR) and the depth of molecular response increase over time

See abstract 334 for complete data

IRIS SAEs in Years 6 and 7

- No unique, previously unreported AEs attributed to imatinib observed over the past 24 months
- In years 6 and 7, 13 SAEs with suspected relationship to imatinib were reported:
  - Congestive Heart Failure (n=3): all of the patients had pre-existing cardiac disease prior to study entry
  - Second malignancy (n=3)*
  - Myositis (n=1); elevated CK (n=1); multiple sclerosis (n=1)
  - Pancreatitis (n=1); vomiting (n=1)
  - Renal failure (n=1)
  - Dermatitis (n=1)

*With >400,000 patient years of estimated imatinib exposure, the analysis of clinical safety data from clinical trials and spontaneous reports did not provide evidence for an increased incidence of malignancies for patients treated with imatinib compared to that of the general population

IRIS 7-Year Update: Conclusions

- Overall Survival 86%
- Event Free Survival 81%; 7% progressed to AP/BC on imatinib
- 40% patients discontinued *study* imatinib
- CCR achieved by 456 of 553 (82%) of patients
  - 17% of those achieving CCR subsequently lost CCR
  - 3% of those achieving CCR progressed to AP/BC
  - Of 456 patients who achieved CCR, 10 (2%) died from CML
  - Time taken to achieve CCR did not correlate with rates of progression to AP/BC
- MMR rates and the depth of molecular responses in patients increase over time
- No new safety issues observed
- Imatinib 400 mg daily confirmed as the standard of care for the initial therapy of chronic-phase CML

LONG-TERM OUTCOME OF 559 PH+ CML PATIENTS TREATED WITH IMATINIB IN EARLY CHRONIC PHASE

GIMEMA CML WP
559 Early Chronic Phase patients accrued between Jan 2004 and Apr 2007 in 3 multicentric studies:

- **CML/021, phase II** 82 pts
  imatinib 800 mg in intermediate Sokal risk

- **CML/022, phase III, randomized** 112 pts
  imatinib 400 vs 800 mg in high Sokal risk

- **CML/023, observational** 365 pts
  imatinib 400 mg, all risks
<table>
<thead>
<tr>
<th>Age, years; median (range)</th>
<th>52 (18-84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 years or older; n (%)</td>
<td>115 (21)</td>
</tr>
<tr>
<td>Splenomegaly, cm; median (range)</td>
<td>1 (0-24)</td>
</tr>
<tr>
<td>Platelet count, 10^9/L; median (range)</td>
<td>352 (74-4553)</td>
</tr>
<tr>
<td>Peripheral blasts, %; median (range)</td>
<td>1.0 (0-10.0)</td>
</tr>
<tr>
<td>Eosinophils, %; median (range)</td>
<td>3.0 (0-15.0)</td>
</tr>
<tr>
<td>Basophils, %; median (range)</td>
<td>2.0 (0-19.0)</td>
</tr>
<tr>
<td>Relative Risk; n (%)</td>
<td></td>
</tr>
<tr>
<td>• Low</td>
<td>219 (39)</td>
</tr>
<tr>
<td>• Intermediate</td>
<td>216 (39)</td>
</tr>
<tr>
<td>• High</td>
<td>124 (22)</td>
</tr>
<tr>
<td>Variant Translocations; n (%)</td>
<td>30 (5)</td>
</tr>
<tr>
<td>CCA Ph+; n (%)</td>
<td>21 (4)</td>
</tr>
<tr>
<td>Der(9) deletions; n (%)</td>
<td>60 (11)</td>
</tr>
<tr>
<td>400 mg; n (%)</td>
<td>423 (76)</td>
</tr>
<tr>
<td>800 mg; n (%)</td>
<td>136 (24)</td>
</tr>
<tr>
<td>Follow-up, months; median (range)</td>
<td>42 (1-64)</td>
</tr>
</tbody>
</table>

Sokal Hasford

N = 559
## RESPONSE TO TREATMENT (ITT)

<table>
<thead>
<tr>
<th>Cytogenetic Response</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete, n (%)</td>
<td>381 (68)</td>
<td>441 (79)</td>
<td>439 (79)</td>
</tr>
<tr>
<td>Partial, n (%)</td>
<td>67 (12)</td>
<td>35 (6)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Minor, n (%)</td>
<td>14 (3)</td>
<td>6 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Minimal, n (%)</td>
<td>15 (3)</td>
<td>6 (1)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Absent, n (%)</td>
<td>16 (3)</td>
<td>28 (5)</td>
<td>42 (8)</td>
</tr>
<tr>
<td>Not evaluable, n (%)</td>
<td>66 (12)</td>
<td>43 (8)</td>
<td>59 (11)</td>
</tr>
<tr>
<td>Failures (cumulative), n (%)</td>
<td>21 (3.8)</td>
<td>41 (7.3)</td>
<td>63 (11.3)</td>
</tr>
</tbody>
</table>
GIMEMA CML WP
EARLY CHRONIC PHASE - RESPONSE TO IMATINIB AND AGE

CYTOGENETIC RESPONSE

CCyR  PCyR  < MCyR

105 PATIENTS MORE THAN 65 YEARS OLD
(MEDIAN 71, INTERVAL 65-84) vs
382 PATIENTS LESS THAN 65 YEARS OLD
(MEDIAN 56, INTERVAL 18-64)

ROSTI G et al, Haematologica 2007; 92: 101-105
**Overall responses and long-term outcome**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCgR at 12 months; %</td>
<td>79</td>
</tr>
<tr>
<td>MMoIR at 12 months; %</td>
<td>54</td>
</tr>
<tr>
<td>MMoIR % of CCg responders</td>
<td>68</td>
</tr>
<tr>
<td>Overall Survival; %</td>
<td>93</td>
</tr>
<tr>
<td>Progression-Free Survival; %</td>
<td>92</td>
</tr>
<tr>
<td>Failure Free-Survival; %</td>
<td>82</td>
</tr>
<tr>
<td>Event-Free Survival; %</td>
<td>74</td>
</tr>
</tbody>
</table>

Failures (ELN criteria): no CHR at 6 mos, no CgR at 6 mos, no PCgR at 12 mos, no CCgR at 18 mos, loss CHR or CCgR, progression to accelerated/blastic phase and death.  
Events: failures, off-treatment for toxicity, refusal and lost to follow-up.
CCgR durability

491 patients (88%): CCgR as best CgR

26 patients (5%): CCgR not confirmed

465 patients (83%): confirmed CCgR (2 or more times)

24 patients (4%): lost CCgR

CCgR duration (months)
median (range): 13 (3 - 42)

441 patients (79%): stable CCgR

CCgR duration (months)
median (range): 35 (4 - 55)

384 patients \( \geq \) 24 months
211 patients \( \geq \) 36 months
<table>
<thead>
<tr>
<th>Patients on Study / Discontinuations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL</strong></td>
</tr>
<tr>
<td>Follow-up, months; median (range)</td>
</tr>
<tr>
<td><strong>On imatinib study treatment, n (%)</strong></td>
</tr>
<tr>
<td><strong>Discontinuation, n (%)</strong></td>
</tr>
<tr>
<td>- Side effects/SAEs</td>
</tr>
<tr>
<td>- Deaths (unrelated to CML)</td>
</tr>
<tr>
<td><strong>- Lack of efficacy / progression</strong></td>
</tr>
<tr>
<td>- Other reason (refusal, lost to follow-up)</td>
</tr>
</tbody>
</table>
SUMMARY OF THE RESULTS OF IMATINIB TREATMENT (STANDARD DOSE 400 MG, FRONT-LINE) IN Ph POS CHRONIC MYELOID LEUKEMIA

COMPLETE HEMATOLOGIC RESPONSE ≥ 95%
COMPLETE CYTOGENETIC RESPONSE 75-90%
MAJOR MOLECULAR RESPONSE 50-70%
“COMPLETE” MOLECULAR RESPONSE 10-40%
6-YEARS EVENT-FREE SURVIVAL AND ON IMATINIB 60-70%
6-YEARS PROGRESSION-FREE SURVIVAL 85-90%
6-YEARS OVERALL SURVIVAL 90-95%

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