Imatinib Therapy for Chronic Myeloid Leukaemia (CML)
Introduction

Objectives

- Review properties of imatinib as therapy for CML,
- Describe key efficacy and safety results from clinical trials
- Discuss strategies to achieve optimal dosing

Topics covered

- Imatinib indication in CML
- Mechanism of action
- Rationale for use
Introduction (cont’d)

Additional topics covered

• Update of key clinical trials
  – Phase 1 results
  – Phase 2 studies post–interferon-alpha (IFN-α) (48- and 60-month results)
  – Phase 3 International Randomised Study of Interferon and STI571 (IRIS) in newly diagnosed CML (60-month results)
• Dose-optimisation techniques
• Safety and side-effect profile in CML
• Pharmacokinetic profile
Imatinib: Indication in CML

- Imatinib (Glivec®, Gleevec®) is indicated for treatment of
  - Patients with newly diagnosed Philadelphia chromosome–positive (Ph+) CML for whom bone marrow transplantation (BMT) is not considered as the first line of treatment
  - Patients with Ph+ CML in chronic phase (CP) after failure of IFN-α therapy or in accelerated phase (AP) or blast crisis (BC)

Imatinib: Doses in CML

- Recommended starting doses for adult patients with CML
  - CP: 400 mg/d
  - AP or BC: 600 mg/d
- Recommended starting doses for children with CML
  - CP or AP: 340 mg/m$^2$ body surface area
Imatinib: Dose Escalation

• Dose escalation is permitted in the following circumstances
  – Disease progression
  – Failure to achieve a satisfactory HR after at least 3 months of treatment
  – Failure to achieve a CyR after 12 months of treatment
  – Loss of HR and/or CyR

CyR, cytogenetic response; HR, haematological response.
Imatinib: Molecular Structure

- Member of the 2-phenylaminopyrimidine class of small molecules\textsuperscript{1,2}
- High affinity and selectivity for ABL\textsuperscript{2}

\[ \text{C}_{29}\text{H}_{31}\text{N}_{7}\text{O} \cdot \text{CH}_{4}\text{SO}_{3} \]

Molecular weight
589.7 daltons

Imatinib: Binding Characteristics

- Binds to ABL, precluding adenosine triphosphate (ATP) binding\textsuperscript{1,2}
- Binding to inactive conformation of ABL activation loop critical to the high selectivity\textsuperscript{2,3}
- Interacts with P loop to prevent normal accommodation of ATP phosphate groups\textsuperscript{1,2}

Imatinib, a specific inhibitor of a small family of tyrosine kinases, including BCR-ABL, blocks the ATP-binding domain and prevents substrate phosphorylation, thereby interrupting BCR-ABL signal transduction pathways that lead to leukaemic transformation.\textsuperscript{1,2}

**Imatinib Selectively Inhibits Tyrosine Kinases in Addition to BCR-ABL**

<table>
<thead>
<tr>
<th>Inhibited Kinases</th>
<th>Kinases Not Inhibited</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCR-ABL</td>
<td>EGFR-R-ICD</td>
</tr>
<tr>
<td>v-Abl</td>
<td>Her-2/neu</td>
</tr>
<tr>
<td>c-Abl</td>
<td>Insulin receptor</td>
</tr>
<tr>
<td>Tel-Abl</td>
<td>IGF-I-R</td>
</tr>
<tr>
<td>PDGFRα</td>
<td>c-Lyn</td>
</tr>
<tr>
<td>PDGFRβ</td>
<td>Fit-3</td>
</tr>
<tr>
<td>Tel-PDGFR</td>
<td>Kdr</td>
</tr>
<tr>
<td>KIT</td>
<td>Jak-2</td>
</tr>
<tr>
<td>Arg</td>
<td></td>
</tr>
<tr>
<td>c-Fms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TPK</td>
</tr>
<tr>
<td></td>
<td>c-Src</td>
</tr>
<tr>
<td></td>
<td>v-Src</td>
</tr>
<tr>
<td></td>
<td>c-Fgr</td>
</tr>
<tr>
<td></td>
<td>Fit-1</td>
</tr>
<tr>
<td></td>
<td>Tek</td>
</tr>
<tr>
<td></td>
<td>c-Met</td>
</tr>
<tr>
<td></td>
<td>PPK</td>
</tr>
</tbody>
</table>

Imatinib Pharmacokinetics

- Rapidly and completely absorbed from gastrointestinal tract
  - $C_{\text{max}}$: 2-4 hours; $t_{1/2}$: 18 (adults), 14.8 (children)$^1$
  - Absolute bioavailability: 98%$^{1,2}$
  - Fully bioavailable in fed and fasting states$^1$
- Mean plasma levels increase in dose-proportional manner$^1$
- $\sim$95% of circulating imatinib bound to plasma proteins$^{3,4}$
- Metabolised in the liver via cytochrome P450 (CYP) enzyme system$^1$
  - Primary isoenzyme involved: CYP3A4
- 81% of imatinib and its metabolites eliminated within 7 days of ingestion$^1$

$C_{\text{max}}$, peak plasma concentration; $t_{1/2}$, terminal half-life.

Imatinib Pharmacokinetics: Special Populations

Hepatic insufficiency¹

- Minimum dose of 400 mg/d recommended for patients with hepatic dysfunction
- Peripheral blood counts/liver enzymes should be monitored

Renal insufficiency

- Imatinib not significantly excreted via the kidney¹
- No ongoing studies in patients with decreased renal function¹
- One case study indicated no changes in pharmacokinetics in patients with renal disease on haemodialysis²

# Imatinib Efficacy, Tolerability Demonstrated in All CML Phases

<table>
<thead>
<tr>
<th>Chronic Phase</th>
<th>Accelerated Phase</th>
<th>Myeloid Blastic Phase</th>
</tr>
</thead>
</table>
| **Study 0001** (phase 1; N = 83)  
Dose-escalation trial for patients with Ph+ CML in CP resistant to or intolerant of IFN-α | **Study 109** (phase 2; N = 235)  
Patients with Ph+ CML in AP | **Study 102** (phase 2; N = 260)  
Patients with Ph+ CML in myeloid BC |
| **Study 110** (phase 2; N = 532)  
Patients with Ph+ CML in late CP resistant to or intolerant of IFN-α | | |
| **Study 106** (phase 3; N = 1106)  
IRIS  
Patients with newly diagnosed Ph+ CML in early CP | | |

Imatinib in CP-CML: Phase 1 Study Results – Safety

• Generally well tolerated
  – Most nonhaematological adverse events (AEs) of grade 1 or 2 severity
  – Grade 3 thrombocytopenia and neutropenia in 16% and 14%, respectively, of patients at doses >200 mg
  – AEs not dose limiting
  – No maximum tolerated dose identified up to 1,000 mg/d

Imatinib in CP-CML: Phase 1 Study Results – Efficacy

- At doses ≥300 mg/d
  - CHR maintained in 98% of patients (median follow-up: 265 days)
    - CHR typically occurred in first 4 weeks
  - MCyR observed in 31% of patients
    - 13% CCyR
- Significant antileukaemic activity in late CP patients after IFN-α failure

CHR, complete haematological response (normal white blood cell [WBC] and platelet counts maintained for ≥4 weeks); MCyR, major cytogenetic response (≤35% of cells in metaphase positive for Ph chromosome); CCyR, complete cytogenetic response (0% of cells in metaphase positive for Ph chromosome)

Imatinib in CP-CML: Dosing Rationale for Phase 2

- Imatinib generally well tolerated and efficacious in phase 1\(^1\)
- Results prompted initiation of 3 international phase 2 trials\(^2-4\)
- Dosing rationale for phase 2 program\(^1-4\)
  - No maximum tolerated dose established (phase 1) up to 1,000 mg/d\(^1\)
  - Most AEs grade 1/2
  - Trend towards increased grade 3/4 AEs at doses >600 mg/d\(^1\)
  - 400 mg/d chosen for phase 2 in CP\(^2\)
  - 400/600 mg/d chosen for phase 2 in AP/BC\(^3,4\)
  - Dose escalation allowed with insufficient or lost response\(^2-4\)

Imatinib in CML: Phase 2 Study Designs

Study 110\textsuperscript{1}: CP-CML after IFN-\(\alpha\) failure or intolerability
- 532 enrolled
- 454 confirmed CP-CML

Imatinib 400 mg/d
Dose escalation to 800 mg/d permitted

Study 109\textsuperscript{2}: AP-CML
- 235 enrolled
- 181 confirmed AP-CML

Imatinib 400 mg/d
Study 109: \(n = 77\)
Study 102: \(n = 37\)

Study 102\textsuperscript{3}: Newly diagnosed BC (imatinib-naive; prior IFN-\(\alpha\) therapy allowed)
- 260 enrolled
- 229 confirmed myeloid BC

Imatinib 600 mg/d
Study 109: \(n = 158\)
Study 102: \(n = 223\)

Dose escalation to 800 mg/d permitted

## Haematological Responses in Phase 2 Studies (4-Year Follow-up)

<table>
<thead>
<tr>
<th>HR</th>
<th>Study 110(^1) CP, IFN-α Failure</th>
<th>Study 109(^2) AP</th>
<th>Study 102(^2) Myeloid BC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>400 mg N = 532</td>
<td>400 mg N = 77</td>
<td>400 mg N = 37</td>
</tr>
<tr>
<td></td>
<td>600 mg N = 158</td>
<td>600 mg N = 223</td>
<td></td>
</tr>
<tr>
<td>MHR</td>
<td>NA</td>
<td>66%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>96%</td>
<td>76%</td>
<td>34%</td>
</tr>
<tr>
<td>CHR</td>
<td>31%</td>
<td>45%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MHR, major haematological response.

Cytogenetic Responses in Phase 2 Studies (4- and 5-Year Follow-up)

<table>
<thead>
<tr>
<th>CyR</th>
<th>Study 110&lt;sup&gt;1&lt;/sup&gt; CP, IFN-α Failure</th>
<th>Study 109&lt;sup&gt;2&lt;/sup&gt; AP</th>
<th>Study 102&lt;sup&gt;2&lt;/sup&gt; Myeloid BC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>400 mg N = 532</td>
<td>400 mg N = 77</td>
<td>400 mg N = 37</td>
</tr>
<tr>
<td>MCyR</td>
<td>67%</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>CCyR</td>
<td>57%</td>
<td>11%</td>
<td>–</td>
</tr>
<tr>
<td>PCyR</td>
<td>10%</td>
<td>–</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>600 mg N = 158</td>
<td>600 mg N = 223</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25%</td>
<td>8%</td>
</tr>
</tbody>
</table>

PCyR, partial cytogenetic response.

### Phase 2 Study 110 in IFN-α–Pretreated Patients: 60-Month Results*

<table>
<thead>
<tr>
<th>Status</th>
<th>n = 454 (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still on treatment</td>
<td>227 (50.0)</td>
</tr>
<tr>
<td>Discontinued treatment due to</td>
<td>227 (50.0)</td>
</tr>
<tr>
<td>Unsatisfactory therapeutic effect</td>
<td>117 (25.8)</td>
</tr>
<tr>
<td>Deaths from any cause</td>
<td>18 (4.0)</td>
</tr>
<tr>
<td>AEs/toxicities</td>
<td>33 (7.3)</td>
</tr>
<tr>
<td>BMT</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Withdrew consent/lost/administrative problems</td>
<td>49 (10.8)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Patients with MCyR (includes CCyR)</td>
<td>304 (67.0)</td>
</tr>
<tr>
<td>Patients achieving CCyR</td>
<td>259 (57.0)</td>
</tr>
<tr>
<td>Patients achieving PCyR</td>
<td>45 (9.9)</td>
</tr>
<tr>
<td>% patients free of progression to AP/BC at 60 months</td>
<td>69.0 [64.4-73.6]</td>
</tr>
<tr>
<td>Overall survival at 60 months</td>
<td>79.1 [75.3-82.9]</td>
</tr>
</tbody>
</table>

*Patients with confirmed diagnosis.

Cl, confidence interval.

Phase 2 Study 110 in IFN-\(\alpha\)–Pretreated Patients: Long-Term (60-Month) Survival*

Overall Survival by Cytogenetic Response at 12 Months

- CCy (n = 167)
- PCyR (n = 76)
- Minor (n = 27)
- Minimal (n = 43)
- No CyR (n = 95)

\(\text{III} = \text{Censored observations}\)

*Patients with confirmed diagnosis.

Phase 3 IRIS Study (106)
Study Design and Patient Status at 60 Months

To Roll In Randomize

**Imatinib**
- n = 553

**IFN-α + Ara-C**
- n = 553

Crossover
- 382 (69%)
- 16 (3%)

**Reasons for crossover:**
- Loss of complete hematologic response (CHR)
- Loss of major cytogenetic response (MCyR)
- Increasing white blood cell (WBC) count
- Intolerance of treatment
- Failure to achieve a MCyR at 12 months
- Failure to achieve a CHR at 12 months
- Patient request to discontinue first-line treatment (for patients not meeting any of the above criteria)

Ara-C, cytarabine.

### Patient Status at 60 Months

<table>
<thead>
<tr>
<th>Patients</th>
<th>Imatinib</th>
<th>IFN-α + Ara-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised</td>
<td>553</td>
<td>553</td>
</tr>
<tr>
<td>Continuing on first line</td>
<td>382 (69%)</td>
<td>16 (3%)</td>
</tr>
<tr>
<td>Discontinued first line</td>
<td>157 (28%)</td>
<td>178 (32%)</td>
</tr>
<tr>
<td>Crossed over</td>
<td>14 (2.5%)</td>
<td>359 (65%)</td>
</tr>
<tr>
<td>Discontinued second line</td>
<td>14 (2.5%)</td>
<td>108 (19.5%)</td>
</tr>
</tbody>
</table>

Kaplan-Meier Estimates of the Cumulative Best Response to Initial Imatinib Therapy

Kaplan Meier Estimates of Time to Response to Initial Imatinib Therapy

% Responding

Months Since Randomisation to Imatinib

Kaplan-Meier Estimates of the Rates of Event-Free Survival and Survival Without Progression to AP or BC for Patients Receiving Imatinib

Progression events:
- 6.3% AP/BC
- 5.1% loss of MCR
- 2.5% loss of CHR
- 1.6% CML-unrelated deaths

Estimated rate at 60 months (with 95% CI)
- Survival without AP/BC: 93% (90-96)
- EFS: 83% (80-87)

EFS, event-free survival.
# Annual Event Rates on First-Line Imatinib

<table>
<thead>
<tr>
<th>Year</th>
<th>All Events*</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>1.5%</td>
<td>0.9%</td>
</tr>
<tr>
<td>5</td>
<td>0.9%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

*All deaths or loss of response, including progression to AP/BC.

Rates of Survival Without Progression to AP or BC on the Basis of CyR After 12 Months of Imatinib Therapy

Response at 12 months

- CCyR: n = 350
- PCyR: n = 86
- No MCyR: n = 73

Estimated rate at 60 months

- CCyR: 97%
- PCyR: 93%
- No MCyR: 81%

\[ P < 0.001 \] \quad \{ P = 0.020 \}

Rates of Survival Without Progression to AP or BC on the Basis of CyR After 18 Months of Imatinib Therapy

Response at 18 months
- CCyR, n = 358
- PCyR, n = 66
- No MCyR, n = 56

Estimated rate at 60 months
- CCyR: 99%
- PCyR: 90%
- No MCyR: 83%

\[
\text{P} < 0.001 \quad \text{P} = 0.001
\]

Rates of Survival Without Progression to AP or BC on the Basis of CyR After 24 Months of Imatinib Therapy

Response at 24 months

- CCyr: n = 362
- PCyR: n = 55
- No MCyR: n = 39

Estimated rate at 60 months

- CCyr: 99%
- PCyR: 93%
- No MCyR: 82%

\[ P < 0.001 \]
\[ P = 0.004 \]

Survival Without AP/BC at 60 Months by Level of Cytogenetic Response

<table>
<thead>
<tr>
<th>Level of Cytogenetic Response</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCyR</td>
<td>97</td>
<td>93</td>
<td>81</td>
</tr>
<tr>
<td>% with CCyR after landmark</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCyR</td>
<td>99</td>
<td>90</td>
<td>83</td>
</tr>
<tr>
<td>No MCyR</td>
<td>99</td>
<td>93</td>
<td>82</td>
</tr>
<tr>
<td>% without AP/BC at 60 Months</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Survival Without AP/BC by Sokal Group in Patients With CCyR on First-Line Imatinib

Estimated rate at 60 months

- Low risk: n = 179, 99% (P < 0.16)
- Intermediate risk: n = 91, 95% (P = 0.09)
- High risk: n = 49, 95% (P = 0.200 overall)

PD, progressive disease.

### Annual Event Rates in Patients After Achievement of CCyR on First-Line Imatinib

<table>
<thead>
<tr>
<th>Year After Achieving CCyR</th>
<th>All Events*</th>
<th>AP/BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.5%</td>
<td>2.1%</td>
</tr>
<tr>
<td>2</td>
<td>2.3%</td>
<td>0.8%</td>
</tr>
<tr>
<td>3</td>
<td>1.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>4</td>
<td>0.4%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*All deaths or loss of response, including progression to AP/BC.

Rates of Survival Without Progression to AP or BC on the Basis of Molecular Response After 12 Months of Imatinib Therapy

Estimated rate at 60 months

- CCyR with ≥3-log red. n = 136 100% \( P < 0.001 \)
- CCyR with <3-log red. n = 94 95% \( P = 0.007 \)
- No CCyR n = 138 88%

Rates of Survival
Without Progression to AP or BC on the Basis of Molecular Response After 18 Months of Imatinib Therapy

Response at 18 months
- CCyR with $\geq$3-log red. n = 139
- CCyR with <3-log red. n = 54
- No CCyR n = 88

Estimated rate at 60 months
- 100% (P < 0.001)
- 98% (P = 0.11)
- 87% (P = 0.06)

Survival Without AP/BC at 60 Months by Molecular Response at 12 and 18 Months

- CCyR With ≥3-Log Reduction: 100% at 12 months, 95% at 18 months
- CCyR With <3-Log Reduction: 98% at 12 months, 98% at 18 months
- No CCyR: 88% at 12 months, 87% at 18 months

Overall Survival Among Patients Treated With Imatinib Based on an ITT Analysis

Estimated rate at 60 months (with 95% CI)
- CML-related deaths: 4.6% (2-7)
- All deaths: 10.6% (8-14)

ITT, intent to treat.
Imatinib Increases Probability of MMR

- MR used to evaluate IRIS patients with CyR
- At 12 months, level of BCR-ABL transcripts decreased by ≥3 log in
  - 57% of CCyR patients treated with imatinib
  - 24% of CCyR patients treated with IFN-α + Ara-C
  - $P = 0.003$ for imatinib vs IFN-α + Ara-C
- ≥3-log reduction in BCR-ABL transcripts represents a MMR
- Likelihood of achieving MMR significantly greater with imatinib vs IFN-α + Ara-C
- MMR associated with prolonged survival

**BCR-ABL Log Reduction in CCyR Patients at 1 and 4 Years**

- At 1 year, 66 (53%) of the CCyR patients had a ≥3-log reduction.
- At 4 years, 99 (80%) of these CCyR patients had ≥3-log reduction.
- Patients with ≥4-log reduction increased from 22% to 41% at 4 years.

<table>
<thead>
<tr>
<th>Log Reduction at 1 Year</th>
<th>Patients (%)</th>
<th>Patients (%)</th>
<th>Log Reduction at 4 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≥3 Log</td>
<td>3 to &lt;4 Log</td>
</tr>
<tr>
<td>&lt;3 log</td>
<td>58 (47)</td>
<td>15</td>
<td>26</td>
</tr>
<tr>
<td>3 to &lt;4 log</td>
<td>39 (31)</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>≥4 log</td>
<td>27 (22)</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>124 (100)</td>
<td>25 (20)</td>
<td>48 (39)</td>
</tr>
</tbody>
</table>

BCR-ABL Log Reduction Category at 4 Years by Sokal Risk Group

Phase 3 Study 106: IRIS
Durable Reduction in *BCR-ABL* mRNA

Imatinib Safety in CML
Imatinib Safety Profile in CML: Most AEs Mild to Moderate, Manageable

- Imatinib generally well tolerated in all studies\(^1,2\)
- AEs are generally manageable, may be transient, and tend to be most troublesome in the first 3 months of treatment\(^2\)
- In phase 2 studies, most side effects are mild to moderate in severity\(^2,3\)
- Fewer than 2% discontinuations owing to drug-related AEs
- Discontinuation required in\(^1\)
  - 2% newly diagnosed
  - 4% late CP\(^*\)
  - 4% AP\(^*\)
  - 5% BC\(^*\)
- Greater incidence and severity in advanced disease\(^1\)

*After failure of IFN-α.

Grade 3/4 Adverse Events to First-Line Imatinib at 60 Months

<table>
<thead>
<tr>
<th>Haematologic/liver</th>
<th>Overall Cumulative Incidence (n = 553)</th>
<th>Onset After 2 Years (n = 456)</th>
<th>Onset After 4 Years (n = 409)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropaenia</td>
<td>17</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9</td>
<td>1.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Anaemia</td>
<td>4</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>5</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Other drug-related AEs</td>
<td>17</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

# IRIS Study in CML:
## Grade 3/4 Haematological AEs

<table>
<thead>
<tr>
<th></th>
<th>Imatinib (n = 553) (%)</th>
<th>IFN + Ara-C (n = 553) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>12.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Anaemia</td>
<td>3.1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*P* < 0.001 difference in grade 3 plus grade 4 abnormalities between 2 treatment groups.

IRIS Study in CML: Few Grade 3/4 Nonhaematological AEs

## Nonhaematological Drug-Related AEs in Patients Treated With Imatinib or IFN-α + Ara-C

<table>
<thead>
<tr>
<th>AE</th>
<th>All Grades</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Imatinib</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>54%</td>
</tr>
<tr>
<td>Superficial oedema</td>
<td>53%</td>
</tr>
<tr>
<td>Other fluid-retention events</td>
<td>5%</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>38%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>14%</td>
</tr>
<tr>
<td>Rash and related terms</td>
<td>25%</td>
</tr>
<tr>
<td>Joint pain</td>
<td>14%</td>
</tr>
</tbody>
</table>

Data on file. Basel, Switzerland: Novartis Pharma AG.
Imatinib Therapy in CML: Summary and Conclusions

- Imatinib has broad indications in CML, covering all disease phases
  - Targets molecular cause of CML
- 60-Month update of phase 2 study in pretreated CP
  - Response durable (MCyR, 67%; CCyR, 57%)
  - Translates to prolonged survival (OS, 79%)
  - PFS without AP/BC, 69%
- 48-Month update of phase 2 results in pretreated AP/BC patients
  - Durable response with important survival benefits
    - OS, 45% in AP, 14% in BC
Imatinib Therapy in CML: Summary and Conclusions (cont’d)

- 60-Month update of phase 3 (IRIS) first-line therapy (400 mg/d) in CP
  - Demonstrated benefits and durability of first-line therapy (CCyR, 87%)
  - Annual risk of progression decreases with time
  - Increases likelihood of MR with prolonged survival
  - 89% overall survival at 5 years with imatinib exceeds that of all other CML therapies, with <5% of deaths related to CML

- Analyses of Molecular Response
  - Superior reductions in \( BCR-ABL \) levels vs IFN-\( \alpha \) + Ara-C
  - \( BCR-ABL \) reductions linked to freedom from CML progression
  - MRs improve with time

- Dose intensification (600 or 800 mg/d) results in increased response at all phases