Evaluating Cost-Effectiveness in Later-line Chronic Myeloid Leukemia (CML): Ponatinib in the Third-Line Treatment of CML in Canada

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Disclosures

• Dr. Lipton has received consultancy income and research funding from ARIAD Pharmaceuticals, Novartis, BMS, and Pfizer.

• Mr. Iannazzo has received consultancy income and research funding from ARIAD Pharmaceuticals.

• Dr. Chiroli and Ms. McGarry are employees of ARIAD and hold stocks and options in ARIAD.
CML Disease Overview

• Rare cancer: 595 Canadians diagnosed in 2012\(^1\)

• Malignant blood stem cells → excessive proliferation of myeloid white blood cells:\(^2\)
  – *BCR-ABL* oncogene → overstimulated tyrosine kinase activity

• Historical median survival in pre-tyrosine kinase inhibitor (TKI) era: 3–5 years\(^2\)

• Historically, 3 phases:\(^2\)
  – Chronic phase (CP): indolent
  – Accelerated phase (AP): intermediate, lasts <1.5 years
  – Blast phase (BP): aggressive, fatal within 3–6 months

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\(^1\)Statistics Canada. 2016. *CANSIM Table 103-0550*

CML Treatment Options

• 3 generations of TKIs:¹
  - 1G
    - Imatinib
  - 2G
    - Dasatinib
    - Nilotinib
    - Bosutinib
  - 3G
    - Ponatinib
      Inhibits all BCR-ABL variants, including T315I → resistance to other TKIs (not reimbursed publicly in Canada)

• Allogeneic hematopoietic stem cell transplantation (allo-SCT)²

• Best supportive care (BSC):²
  - Hydroxyurea
  - Interferon-α

²Laneuville P et al. Curr Oncol 2006;13(6):201-21
Proportion of patients achieving CCyR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Probability*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAF, BOS, DAS, OR NIL:</td>
<td>22–26%</td>
</tr>
<tr>
<td>BOS: [Khoury, 2012]</td>
<td></td>
</tr>
<tr>
<td>DAS: [Garg, 2009]</td>
<td></td>
</tr>
<tr>
<td>DAS: [Quintas-Cardama, 2007]</td>
<td></td>
</tr>
<tr>
<td>DAS or NIL: [Garcia-Gutierrez, 2012]</td>
<td></td>
</tr>
<tr>
<td>DAS or NIL: [Ibrahim, 2010]</td>
<td></td>
</tr>
<tr>
<td>DAS or NIL: [Russo Rossi, 2011]</td>
<td></td>
</tr>
<tr>
<td>NIL: [Garg, 2009]</td>
<td></td>
</tr>
<tr>
<td>NIL: [Giles, 2010]</td>
<td></td>
</tr>
<tr>
<td>NIL: [Nicolini, 2012]</td>
<td></td>
</tr>
<tr>
<td>PONATINIB: [Cortes, 2012]</td>
<td></td>
</tr>
<tr>
<td>PONATINIB: [Cortes, 2012]</td>
<td>60%</td>
</tr>
<tr>
<td>PONATINIB: [Cortes, 2012]</td>
<td>60%</td>
</tr>
<tr>
<td>PONATINIB: PACE</td>
<td></td>
</tr>
<tr>
<td>PONATINIB: PACE non-T315I</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Node size in graph represents patient numbers; line signifies derived 95% confidence interval.

*Probability of achieving a CCyR calculated by pooling studies according to treatment used, with studies allowing a choice of dasatinib or nilotinib pooled separately from dasatinib-only and nilotinib-only studies.
Decision Problem

What is the cost-effectiveness of ponatinib in third-line (3L) treatment of patients in CP-CML?
Challenges to Economic Evaluation of 3L CML Therapy

• Appropriate comparators undefined
  – May differ by province/payer
  – Most alternatives not evaluated in 3L setting

• Limited evidence supporting 3L use of TKIs
  – Small pool of potential trial subjects in later-line therapy
    • Due to success of 1L and 2L therapy
    • Survival of a newly diagnosed CP-CML patient is virtually identical to age-matched controls
  – Ethical issues preclude head-to-head trials when no effective prior comparator exists (eg, for T315I mutation)
  – Long-term outcomes have yet to accrue

2Sasaki K et al. Blood 2014;124(21):1801
Challenges to Economic Evaluation of 3L CML Therapy (cont.)

• Limited Canada-specific data
  – Healthcare resource utilization estimated by panel of Canadian CML experts
  – Drug and healthcare costs from standard Ontario sources
  – Health utilities estimated from Canadian general population

• Uncertainty re ponatinib dosing (has cost implications)
  – Product Monograph recommends 45-mg starting dose for most patients, and consideration of dose reduction with response
  – Clinical trial (PACE; Phase II ponatinib trial) and real-world evidence (ex-Canada) suggests many patients receive doses <45 mg; dose decreased over time
  – Efficacy data from PACE are based on observed average dose in trial of <30 mg/day
  – Current studies examining lower doses and step-down dosing schedules (OPTIC, OPTIC-2L)

1ICLUSIG™ (ponatinib) Product Monograph. March 31, 2015
Cost-effectiveness Model

• Markov model with 3-month cycles and lifetime horizon
• Considers range of potential treatment modalities
  – TKIs: ponatinib, dasatinib, nilotinib; bosutinib not included because not listed in public payer formulary at time of analysis
  – BSC: hydroxyurea, interferon-α
  – Allo-SCT
• Perspective: Canadian public healthcare system
  – Direct medical costs for treatment, managing CML and adverse events (AEs)
  – Discounting: 5% per annum (costs and health outcomes)
• Patients
  – In CP-CML at model entry
  – Aged 60 years (median age in PACE\(^1\))
• Outcomes
  – Cost per quality-adjusted life-year (QALY) gained
  – Cost per life-year gained (LYG)

Markov Model Structure

Model entry

Comparators

Direct allo-SCT

Allo-SCT in CP-CML

Relapse-free

Relapsed

Transition to Death possible from every state (not shown)

Outcomes of TKI treatment are driven by best response achieved at 12 months

CP-CML

CCyR

PCyR

CHR

NR

BP-CML

Allo-SCT in progressed disease

Relapse-free

Relapsed

Ponatinib

Dasatinib

Nilotinib

Hydroxyurea

Interferon-α
Clinical Outcome Data Sources

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ponatinib</td>
<td>PACE Phase II study(^1)</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Retrospective analysis(^2) Cohort study(^3)</td>
</tr>
<tr>
<td></td>
<td>NICE technology appraisal(^4)</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Retrospective analysis(^2) Phase II study(^5)</td>
</tr>
<tr>
<td></td>
<td>ENACT expanded-access study(^6)</td>
</tr>
<tr>
<td></td>
<td>NICE technology appraisal(^4)</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>Systematic review(^7)</td>
</tr>
<tr>
<td>Interferon-(\alpha)</td>
<td>Systematic review(^7)</td>
</tr>
<tr>
<td>Allo-SCT</td>
<td>Retrospective analyses(^8,9)</td>
</tr>
</tbody>
</table>

\(^2\) Garg RJ et al. *Blood* 2009;114(20):4361-8
\(^4\) Loveman E et al. *Health Technol Assess* 2012;16(23):iii-xiii, 1-137
\(^5\) Giles FJ et al. *Leukemia* 2010;24(7):1299-301
\(^6\) Nicolini FE et al. *Cancer* 2012;118(1):118-26
\(^7\) Dalziel K et al. *Health Technol Assess* 2004;8(28):iii, 1-120
\(^8\) Jabbour E et al. *Blood* 2011;117(13):3641-7
Best Response

- Best response at 12 months is used to stratify patients on each therapy at the beginning of the simulation:

<table>
<thead>
<tr>
<th>Therapy</th>
<th>CCyR</th>
<th>PCyR</th>
<th>CHR</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ponatinib</td>
<td>56%</td>
<td>11%</td>
<td>30%</td>
<td>3%</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>25%</td>
<td>8%</td>
<td>36%</td>
<td>31%</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>24%</td>
<td>8%</td>
<td>38%</td>
<td>30%</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>0%</td>
<td>0%</td>
<td>41%</td>
<td>59%</td>
</tr>
<tr>
<td>Interferon-α</td>
<td>0%</td>
<td>0%</td>
<td>47%</td>
<td>53%</td>
</tr>
<tr>
<td>Allo-SCT</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
</tbody>
</table>
Durability of Response

• Duration of response
  – Estimated for each TKI
  – Extrapolated through parametric survival analysis

• Progression-free survival (PFS)
  – Estimated for each level of response
  – Not treatment-specific
  – Derived from a 2L study of dasatinib\(^1\)
  – Extrapolated through parametric survival analysis

\(^1\)Loveman E et al. *Health Technol Assess* 2012;16(23):iii-xiii, 1-137
Health State Valuations

- Health-state utility valuations for CML recently derived (via time-trade off) in international study in general public\(^1\)

Utilities from Canadian respondents:

<table>
<thead>
<tr>
<th>CP-CML Response</th>
<th>CP-CML NR</th>
<th>AP-CML</th>
<th>BP-CML</th>
<th>AE (1 cycle only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.78</td>
<td>0.61</td>
<td>0.46</td>
<td>0.25</td>
<td>0.35</td>
</tr>
</tbody>
</table>

- Many rare diseases lack health-related quality of life (HRQoL) data; eg, no estimate for allo-SCT utility in patients with CML → model uses value for allo-SCT in patients with lymphoma (0.55)\(^2\)

\(^1\)Szabo SM et al. Value Health 2010;13(1):103-11
Drug Dosing

• Ponatinib:
  – PACE data used for dosing\(^1\)
  – All patients started trial on 45 mg/day
  – Most patients reduced dose
  – Quantified proportion of days on therapy at each ponatinib dose
  – If no CHR at 3 months, assume discontinued per Product Monograph\(^2\)
  – Sensitivity analysis for dose reduction

• Comparator drugs:
  – Relative dose intensity (RDI) calculated as proportion of standard dose received (per references on Slide 11)

<table>
<thead>
<tr>
<th>Ponatinib dose (mg/day)</th>
<th>Proportion of days on treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>11.3%</td>
</tr>
<tr>
<td>15</td>
<td>16.6%</td>
</tr>
<tr>
<td>30</td>
<td>27.8%</td>
</tr>
<tr>
<td>45</td>
<td>44.3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Dose</th>
<th>RDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasatinib</td>
<td>100 mg/day</td>
<td>100.0%</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>800 mg/day</td>
<td>99.7%</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>2000 mg/day</td>
<td>100.0%</td>
</tr>
<tr>
<td>Interferon-(\alpha)</td>
<td>9M IU/day</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

\(^2\)ICLUSIG\textsuperscript{TM} (ponatinib) Product Monograph. March 31, 2015
Costs

• Canadian costs for:
  – Pharmacologic therapy\(^1\)
  – Monitoring and follow-up care\(^2\)–\(^5\)
  – AEs\(^6\)
  – End-of-life care\(^6\)

• No Canadian cost available for allo-SCT
  – Estimated from UK NHS costs\(^7\)
  – £ converted to $CAD; inflated to $2014

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ponatinib(^*)</td>
<td>$7,566</td>
</tr>
<tr>
<td>Dasatinib(^1)</td>
<td>$4,653</td>
</tr>
<tr>
<td>Nilotinib(^1)</td>
<td>$4,822</td>
</tr>
<tr>
<td>Hydroxyurea(^1)</td>
<td>$124</td>
</tr>
<tr>
<td>Interferon-(\alpha)(^1)</td>
<td>$6,659</td>
</tr>
</tbody>
</table>

*Assumed ponatinib cost for analysis
\(^2\)Ontario Ministry of Health and Long-Term Care. *OHIP Schedule of Benefits and Fees*. 2014
\(^3\)Ontario Ministry of Health and Long-Term Care. *Ontario Case Costing Initiative (OCCI)*. 2011
\(^4\)BC MSP. *Laboratory medicine*. August 2013
\(^6\)ARIAD Pharmaceuticals, ICON Health Economics. *Survey of hematologists*.
Results

- Ponatinib increased overall and HRQoL-adjusted survival vs comparators, at increased cost
- Incremental cost-effectiveness ratio (ICER) range:
  - $33,506–$57,399/LYG
  - $39,859–$68,454/QALY gained

<table>
<thead>
<tr>
<th>Ponatinib vs</th>
<th>Δ Costs*</th>
<th>Δ LY*</th>
<th>Δ QALY*</th>
<th>ICER, Δ Costs/LYG</th>
<th>ICER, Δ Costs/QALY gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasatinib</td>
<td>$213,519</td>
<td>3.72</td>
<td>3.22</td>
<td>$57,372</td>
<td>$66,351</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>$211,114</td>
<td>3.68</td>
<td>3.21</td>
<td>$57,399</td>
<td>$65,708</td>
</tr>
<tr>
<td>Allo-SCT</td>
<td>$185,047</td>
<td>3.25</td>
<td>2.86</td>
<td>$56,950</td>
<td>$64,659</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>$248,656</td>
<td>4.34</td>
<td>3.63</td>
<td>$57,322</td>
<td>$68,454</td>
</tr>
<tr>
<td>Interferon-α</td>
<td>$143,310</td>
<td>4.28</td>
<td>3.60</td>
<td>$33,506</td>
<td>$39,859</td>
</tr>
</tbody>
</table>

*Ponatinib - comparator
Sensitivity Analyses

• Most influential parameters were:
  – Monthly cost of ponatinib at base-case dosing
  – Resource use for response testing
  – Age at treatment initiation

• Assuming dose reduction 45 mg → 15 mg at achievement of MCyR per Product Monograph¹:
  – ICERs vs TKIs decrease by ~50%
  – ICER vs allo-SCT decreases by >50%

<table>
<thead>
<tr>
<th>Ponatinib vs</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
<th>Allo-SCT</th>
<th>Hydroxyurea</th>
<th>Interferon-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-case ICER</td>
<td>66,351</td>
<td>65,708</td>
<td>64,659</td>
<td>68,454</td>
<td>39,859</td>
</tr>
<tr>
<td>(CAD$/QALY gained)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose-reduced ICER</td>
<td>36,394</td>
<td>35,704</td>
<td>30,974</td>
<td>41,915</td>
<td>13,047</td>
</tr>
<tr>
<td>(CAD$/QALY gained)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% decrease</td>
<td>45%</td>
<td>46%</td>
<td>52%</td>
<td>39%</td>
<td>67%</td>
</tr>
</tbody>
</table>

¹ICLUSIG™ (ponatinib) Product Monograph. March 31, 2015
Conclusions

• Ponatinib has been demonstrated to provide durable efficacy for patients with CP-CML who have exhausted other treatment options

• Ponatinib appears to be cost-effective in the context of care for 3L CP-CML patients
  – Sensitivity analyses show robustness of model results

• Ethical and feasibility limitations impact the evidence base available to populate cost-effectiveness analyses for rare cancers like CML:
  – Models may need to incorporate data from uncontrolled studies and retrospective analyses
  – Health plans should recognize inherent evidence limitations