PUBLIC OBSERVER SLIDES

# CML: Lead team presentation Ponatinib for treating chronic myeloid leukaemia [ID671] - STA

1st Appraisal Committee meeting

**Background and Clinical Effectiveness**

Committee C

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ERG: SCHaRR

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18 January 2017

# CML: Disease Background

- Chronic myeloid leukaemia (CML) is a rare form of cancer affecting the blood, characterised by an excessive proliferation of myeloid cells at all stage of maturation
- Approximately 95% of people with CML have acquired chromosomal abnormality known as Philadelphia chromosome positive disease (Ph+)
- Office for National Statistics figures for 2014 show 631 people in England were newly diagnosed with CML
- Approximately one third to one half of patients are asymptomatic at diagnosis and identified through routine screening. Over 90% of patients with CML are diagnosed in the early chronic phase
- More than 70% of men and nearly 75% of women diagnosed with CML survive for 5 years or more following diagnosis. Prognosis is negatively affected by older age, and how far the disease has progressed at diagnosis

# CML: Phases of CML

- CML is typically characterised as having three distinct phases.
  - An initial chronic phase (CP-CML) which lasts for several years
  - An intermediate accelerated phase (AP-CML), which lasts for less than 1.5 years
  - An aggressive blast phase (BP-CML) that is usually fatal within 3 to 6 months
- People with CP-CML can transition to either AP-CML or BP-CML
- The phases are defined mainly by the percentage of blast cells in the blood and bone marrow

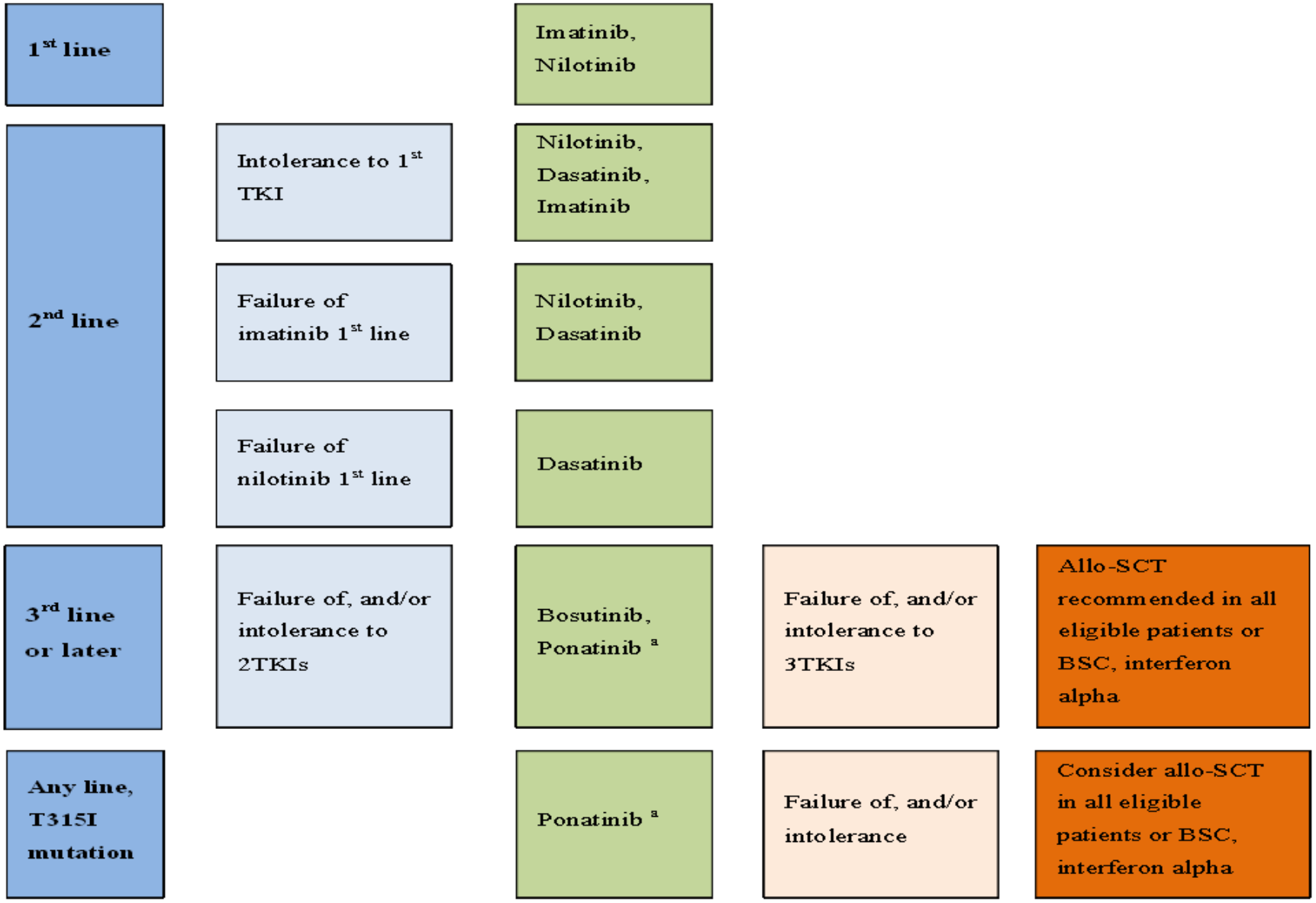
# CML: Preview - Key issues: clinical effectiveness

- What is the committee's view on the evidence base considering it is non comparative and thus has a high potential for bias?
- What is the committee's view on the company's MAIC?
  - The ERG commented that using this methodology the company had to adjust PACE study to fit with bosutinib study, due to absence of individual patient data for bosutinib
- In some of the by line treatment subgroups, the study was insufficiently powered. What is the committee's view on the power of the subgroups?
- The optimal dosing of ponatinib is uncertain. The initial dose (45mg) was lowered during study; therefore it is unclear whether the lower dosing regimen would have been as clinically effective over study period. What is the committee's view on the impact of this uncertainty on the estimate of treatment effect?
- What is the committee's view regarding the use of ponatinib for T315I CML?
- The duration of ponatinib treatment uncertain
  - where complete response is achieved, allo-SCT would be considered if eligible, therefore ponatinib treatment would cease;
  - Would patients ineligible for allo-SCT continue treatment indefinitely?

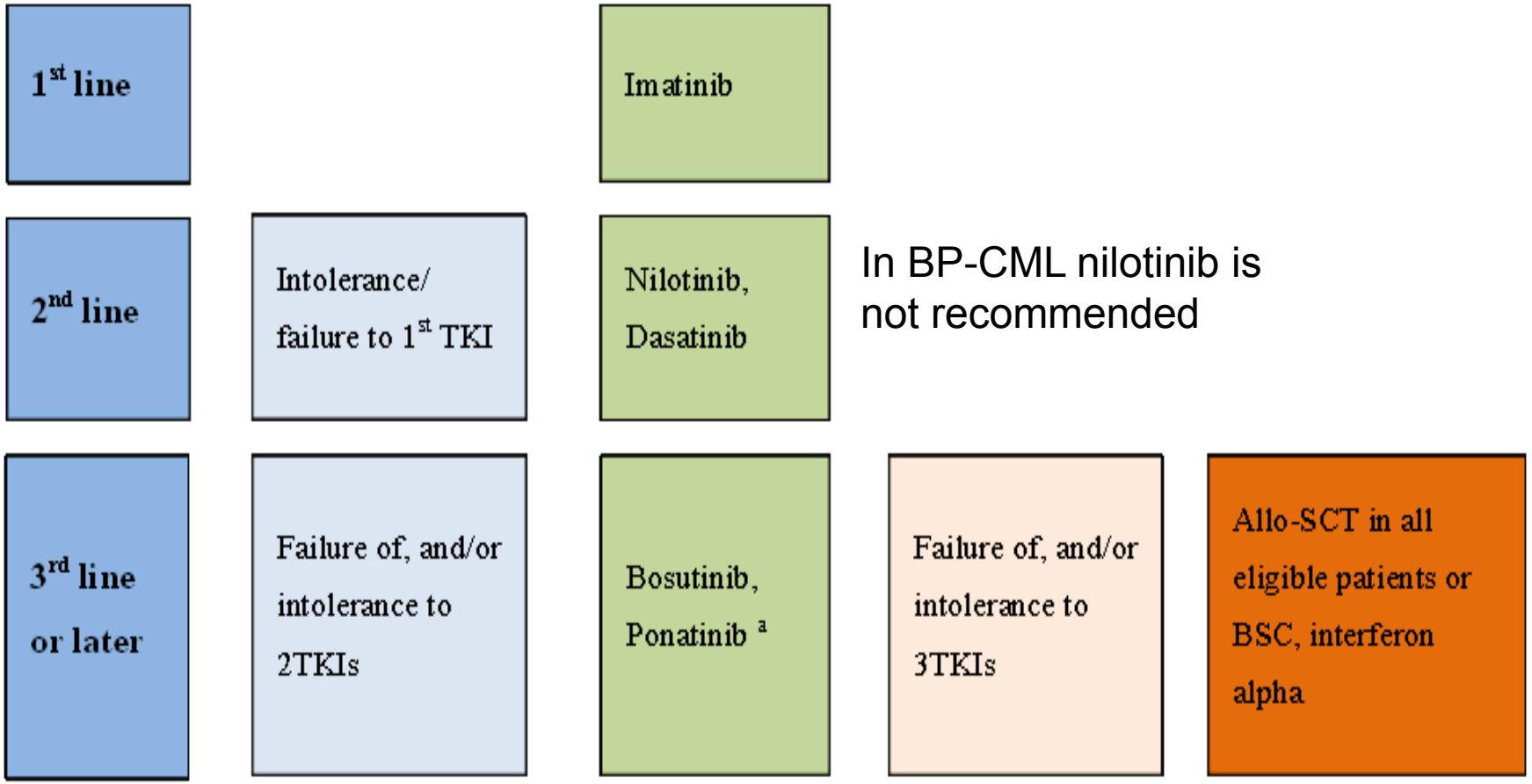
# CML: Technology

| | |
|---|---|
| Details of the technology | Ponatinib (Iclusig, Incyte Corporation) |
| Marketing authorisation | Adults *"with chronic phase (CP), accelerated phase (AP), or blast phase (BP) chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation"*<br>European marketing authorisation was granted in July 2013 |
| Mechanism of action | Inhibits the kinase activity of native BCR-ABL gene, and all mutant variants, including 'gatekeeper' T315I |
| Administration | Oral – 15mg, 30mg (Q1, 2017) and 45mg daily dose tablets |
| Acquisition cost (excl. VAT) | 30 tablets: 15mg £2525; 30mg £5050; 45mg £5050.<br>The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of ponatinib with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. |

# CML: Care pathway, patients with chronic phase (CP-)CML



# CML: Care pathway patients with accelerated (AP) and blast phase (BP) CML



# CML: Decision problem

| | NICE final scope | Any changes made by company |
|---|---|---|
| Population | As per marketing authorisation (see notes)[1] | N/A |
| Intervention | Ponatinib | N/A |
| Comparator(s) | • Bosutinib<br>• Allo-SCT; with or without chemotherapy<br>• Interferon alfa<br>• BSC (including but not limited to hydroxycarbamide) | Interferon alfa not included. |
| Outcomes | • Overall survival (OS)<br>• Progression-free survival/ event-free survival<br>• Response rates<br>• Time to response<br>• Duration of response (DoR)<br>• Adverse effects of treatment<br>• Health-related quality of life | Trial data for response rates used. Duration of response not used. |

# CML: Expert Comments

- TKIs are expensive but effective first line treatments for CML, so much so that the majority of patients now die of other causes.
- Generic imatinib becomes available in December 2016, and it is likely that physicians will be encouraged to start all newly diagnosed patients on this.
- The best indicator of outcome in terms of survival is depth of response at various points in the first year, measured by a molecular test known as RQ-PCR
- Optimal response is defined as RQ-PCR results of <10%, <1% and <0.1% at 3, 6 and 12 months respectively after initiating treatment[1]
- For imatinib as a 1st line treatment around 25% of patients fail to achieve these milestones. A further 25% will have changed treatment at 5 years, despite good responses, due to toxicity. For dasatinib and nilotinib the corresponding figures are around 10% and 20% respectively.
- Patients who fail imatinib because of disease resistance are frequently resistant to subsequent drugs. These account for 10 to 15% of CML patients and include those who would benefit from ponatinib

The Royal College of Pathologists

[1]Based on European LeukemiaNet recommendations for the management of chronic myeloid leukemia (Baccarani et al, 2013)

# CML: Expert Comments

- Approx 20-25% of patients do not respond satisfactorily to first line treatments (Imatinib/ Nilotinib) due to side effects and toxicity, or they are refractory. One cause of non-response is the acquisition of BCR-ABL mutations.
- Ponatinib provides a more effective treatment (measured by complete cytogenetic response) after failure of 1st line nilotinib than an alternative 2nd generation TKI (nilotinib, dasatinib or bosutinib), reducing the need for subsequent allo-SCT. It is more effective third line treatment following 2nd line treatment with one of the 2nd generation TKIs, than treatment with an alternative 2nd generation TKI. It has superior potency than other TKIs in patients with BCR-ABL mutations, and remains the only oral agent for the treatment of T315I
- Non TKI treatments options for CML (allo-SCT, interferon) have a low response rate of 10-15% and have significant side effects
- Arterial thrombotic events is the most important side effect and is reported in 20% of patients compared to roughly 10% for nilotinib.

NCRI/RCP/RCR/ACP

# CML: Patient/carer perspective 1
# Living with CML

- Profound psychological and emotional impact of a cancer diagnosis
- *"When I was diagnosed, it was like I had been hit by a truck"*
- Often followed a routine blood test
- Scary, feel numb and helpless
- Made worse by being rare
- Symptoms include:
  - fatigue, pain, frequent infections, bruises, fever, joint pain and breathlessness
- Untreated CML will progress and is fatal
- Reassurance needed about uncertainty of future treatments
- An unmet need for some patients

# CML: Patient/carer perspective 2
# Current treatments

- Repeated failure is a common experience
- Best supportive care
  - not viewed as a treatment
- Interferon alpha
  - has punishing side effects
- Stem-cell transplant seen as a treatment of last resort
  - for fitter patients
- Common side effects related to TKIs
  - hypertension, abdominal pain, fatigue, dry skin, constipation, rash, headache, fever, joint pain and nausea.
- Severe side effects
  - Tumour lysis syndrome (TLS), liver toxicity and gastrointestinal perforation

# CML: Ponatinib pivotal study

| Study | Location (sites) | Design | Population | Intervention and comparator | Primary outcome measures |
|---|---|---|---|---|---|
| PACE | 66 centres in 12 countries (including 5 sites in the UK, n=30) | Phase II, single arm open-label, non-comparative study (n=449) | 449 Patients (aged ≥ 18 years) with CP-CML (n=270), AP-CML (n=85), BP-CML (n=62) or Ph+ ALL (n=32) who were resistant or intolerant to either dasatinib or nilotinib, or who had the T315I mutation after any TKI therapy | Ponatinib 45mg tablet taken orally once daily (in October 2013, dose lowered to 15mg/day in CP-CML with a major cytogenetic response or better, and to 30mg/day in CP-CML who had not, and patients with AP-CML) | Major cytogenetic response (MCyR) in patients with CP-CML<br><br>Major haematologic response (MaHR) in patients with AP-CML, BP-CML and Ph+ ALL |

# CML: PACE study

- Patients were assigned to 1 of 6 cohorts dependent upon
  - Disease phase (chronic, accelerated or blast)
  - Resistance or intolerance to dasatinib or nilotinib
  - Presence of the T315I mutation
- 5 of the 449 patients were excluded from the effectiveness analysis (but not safety) as they had a history of T315I, unconfirmed at baseline, and had not received nilotinib or dasatinib
- Patients were pre-treated with prior TKIs (imatinib, dasatinib, nilotinib or bosutinib) and conventional therapy
- Ponatinib as a 3rd line treatment (after 2 TKIs)
  - CP-CML, 97/270 (36%)[1]; AP-CML, 33/85 (39%); BP-CML, 22/62 (35%)
- Ponatinib as a 4th line treatment (after 3 TKIs)
  - CP-CML, 142/270 (53%)[1]; AP-CML, 44/85 (52%); BP-CML, 34/62 (55%)
- Patients received a starting dose of 45mg/day, which was reduced or delayed following AEs. This was lowered in October 2013 at the request of the FDA to 15mg/day in CP-CML who had achieved a major cytogenetic response or better, to 30mg/day in CP-CML who had not achieved a major cytogenetic response, and patients with advanced phase (AP-)CML

# CML: PACE study

- Major cytogenetic response (MCyR), the primary endpoint for CP-CML was measured at any time within the first 12 months after initiation of treatment, and defined as complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR)
- Major haematologic response (MaHR), the primary endpoint for AP-CML and BP-CML, was measured within the first six months after initiation of treatment, and defined as complete haematologic response (CHR) or no evidence of leukaemia (confirmed by blood analyses after ≥28 days)
- Secondary endpoints for all diagnoses included: a major molecular response, the time to the response, the duration of the response, PFS, OS, and safety.

# CML: Results CP-CML at 12 mo. and 4 yrs

| Outcome | All lines (n=267) | 3rd line (n=98)[1] | 4th line (n=141) |
|---|---|---|---|
| **At 12 months** | | | |
| Major cytogenic response (MCyR) | 56% (95% CI: 50–62) | 67%, 95% CI:=57-76 | 45%, 95% CI:37-54 |
| Complete cytogenic response | 46% | 56%, 95% CI:46-66 | 39%, 95% CI:31-48 |
| Duration of response | 1 day to 19.4 months | N/R | N/R |
| PFS | 80% | N/R | N/R |
| OS | 94% | N/R | N/R |
| **At 4 years** | | | |
| MCyR | N/R | 71% | 49% |
| Complete cytogenic response | N/R | 65% | 45% |
| PFS | 56% | 68% | 52% |
| OS | 77% | 79% | 80% |

Source: Table 9, page 45, ERG report, Company's clarification response A13. Results reported at 9 November 2012

[1] One patients was misclassified at the time analysis, therefore at 4 years n=97

# CML: Results AP-CML at 12 mo. and 4 years

| Outcome | All lines (n=83) | 3rd line (n=33) | 4th line (n=44) |
|---|---|---|---|
| **At 12 months** | | | |
| Major haematological response (MaHR) by 6 mo. | 55% (95% CI: 44–66) | 61% | 50% |
| Major cytogenic response | 39% | 42% | 30% |
| Duration of response | MaHR:1 to 21 months or more (median: 12 months) | N/R | N/R |
| PFS | 12 month: 55% (median: 18 mo.) | N/R | N/R |
| OS | 12 month: 84% | N/R | N/R |
| **At 4 years** | | | |
| MaHR by 6 mo. | [redacted] | [redacted] | [redacted] |
| MCyR | [redacted] | [redacted] | [redacted] |
| Duration of response | [redacted] | N/R | N/R |
| PFS | [redacted] | N/R | N/R |
| OS | [redacted] | N/R | N/R |

Source: table 11, page 48, ERG report

# CML: Result BP-CML at 12 mo. and 4 years

| | At 12 months for BP-CML patients only | At 4 years for BP-CML and Ph+ ALL combined | | |
|---|---|---|---|---|
| Outcome | All lines (n=62) | All lines (n=94) | 3rd line (n=38) | 4th line (n=48) |
| MaHR by 6 months | 31% (95% CI: 20–44) | [redacted] | [redacted] | [redacted] |
| MCyR | 23% | [redacted] | [redacted] | [redacted] |
| CCyR | 18% | N/R | [redacted] | [redacted] |
| Median time to response | MaHR: 4.1 weeks (range: 1.7–16.1)<br>MCyR: 1.9 months (range: 0.9–5.5) | N/R | N/R | N/R |
| Duration of response | MaHR:1 to 20 months or more (median: 5 months) | N/R | N/R | N/R |
| Maintained response | MaHR at 12 months: 42%<br>MCyR at 12 months: 66% | N/R | N/R | N/R |
| PFS | 12 month: 19% (median: 4 months) | [redacted] | N/R | N/R |
| OS | 12 month OS:29%,median:7 months | [redacted] | N/R | N/R |



Adapted from Table 13, page 55, ERG CML report

# CML: Results by T315I mutation status

| | 12 months | | 4 years | |
|---|---|---|---|---|
| Outcome | Overall | T315I mutation | Overall | T315I mutation |
| CP-MCyR | 56% | 70% | 59% | 72% |
| CP-CCyR | 46% | 66% | 54% | 70% |
| CP-PFS | 80% | 83% | 56% | 56% |
| CP-OS | 94% | 92% | 77% | 72% |
| AP-MaHR* | 55% | 50% | [redacted] | [redacted] |
| AP-MCyR | 39% | 56% | [redacted] | [redacted] |
| AP-CCyR | 24% | 33% | [redacted] | [redacted] |
| AP-PFS | 55% | N/R | 22% | [redacted] |
| AP-OS | 58% | N/R | 51% | [redacted] |
| BP-MaHR | 31% | 29% | [redacted] | [redacted] |
| BP-MCyR | 23% | 29% | [redacted] | [redacted] |
| BP-CCyR | 18% | 21% | [redacted] | [redacted] |
| BP-PFS | 19% | N/R | [redacted] | [redacted] |
| BP-OS | 29% | N/R | [redacted] | [redacted] |

Source: tables 10, 12 and 14 in the ERG CML report

# CML: Company adverse reactions

- During PACE study, ponatinib was found to be associated with arterial occlusive events (AOEs) which resulted in FDA dose reduction recommendation changes to protocol
- CHMP concluded that benefit-risk balance of ponatinib remains favourable taking into account the product information amendments and subject to the risk minimisation measures and additional pharmacovigilance activities agreed

At 12 months

- The most common non-haematologic adverse event was a rash, which occurred in patients with CP (40%), AP (29%) and BP (24%)
- The most common haematologic adverse event was thrombocytopenia which occurred in patients with CP (41%), AP (42%) and BP (27%).

Similar figures were reported for the 4 year follow up point

- Adverse events, haematologic, non-haematologic, and arterial occlusive were most common in CP patients and least common in BP patients

# CML: Matching-adjusted indirect comparison (MAIC)

- Based on Signorovitch et al (2012)
- In the absence of head-to-head randomised trials, indirect comparisons of treatments across separate trials can be performed
  - These analyses may be biased by cross-trial differences in patient populations, sensitivity to modelling assumptions, and differences in the definitions of outcome measures.
- Aim of MAIC is to lessen confounding, adjusting individual level data from a trial with individual patient level data (e.g. PACE) to match patients on the basis of inclusion/exclusion criteria specified in the ponatinib trial and reweight to match exactly the baseline characteristics reported for the comparator study (Khoury et al.) reported at study level
- It can address several limitations that arise in analyses based only on aggregate data

# CML: Indirect treatment comparison

- No direct comparative evidence between ponatinib and the comparator TKIs was identified
- The company therefore conducted a matching adjusted indirect comparison (MAIC) between ponatinib and bosutinib ONLY in CP-CML patients to facilitate an indirect comparison and inform their economic model.
  - No MAIC was done for AP or BP-CML groups due to lack of comprehensive third line setting data.
- MAIC involves using individual patient data to match patient characteristics across separate trails involving different interventions
- MAIC was performed using the baseline characteristics in CP group of patients only.

| Best response | Bosutinib (Khoury et al., Phase I/II study) n=118 | Ponatinib PACE Cortes et al. (Phase II) n=97[a] | Ponatinib MAIC n=69[b] |
|---|---|---|---|
| CCyR, n/N (%) | 26/108 (24.07%) | 63/97 (64.95%) | 61.34% |
| PCyR, n/N (%) | 9/108 (8.33%) | 6/97 (6.19%) | 8.46% |
| CHR, n/N (%) | 44/116 (37.93%) | 17/97 (17.53%) | 18.19% |
| No response, n/N (%) | (29.66%)[c] | 11/97 (11.34%) | 12.01% |

CCyR, complete cytogenetic response; CHR, complete haematologic response; PCyR, partial cytogenetic response



Source: table 32 in ERG report and CS Table 4-4 and response to clarification question A12.

# CML: ERG comments

- The ERG is confident that the company identified all relevant studies in its submission
- The ERG considered PACE to be a large well designed non comparative study, and the study population included in the trial to be reflective of the CML population in England
- In the absence of 'within-study' estimates based on randomised comparison (due to ethical considerations), it was necessary to use an alternative approach to make indirect comparison. The MAIC has several limitations:
  - It matches PACE population (said to be reflective of UK practice) onto Khoury et al which is not representative of UK practice
  - Median age of PACE population is 59, but 50 for MAIC
  - The lack of an internal control group increases the potential for bias in the trial results and in the MAIC.
- While the safety and efficacy outcomes for all lines combined met the company's reported power calculation, the majority of those individual lines of therapy were not adequately powered.

# CML: Key issues: clinical effectiveness

- What is the committee's view on the evidence base considering it is non comparative and thus has a high potential for bias?
- What is the committee's view on the company's MAIC?
  - The ERG commented that using this methodology the company had to adjust PACE study to fit with bosutinib study, due to absence of individual patient data for bosutinib
- In some of the by line treatment subgroups, the study was insufficiently powered. What is the committee's view on the power of the subgroups?
- The optimal dosing of ponatinib is uncertain. The initial dose (45mg) was lowered during study; therefore it is unclear whether the lower dosing regimen would have been as clinically effective over study period. What is the committee's view on the impact of this uncertainty on the estimate of treatment effect?
- What is the committee's view regarding the use of ponatinib for T315I CML?
- The duration of ponatinib treatment uncertain
  - where complete response is achieved, allo-SCT would be considered if eligible, therefore ponatinib treatment would cease;
  - Would patients ineligible for allo-SCT continue treatment indefinitely?

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# CML: Lead team presentation Ponatinib for treating chronic myeloid leukaemia [ID671] - STA

1st Appraisal Committee meeting

**Cost effectiveness**

Committee C

Lead team: Prithwiraj Das, Kamal Balakrishnan, David Chandler

ERG: SCHaRR

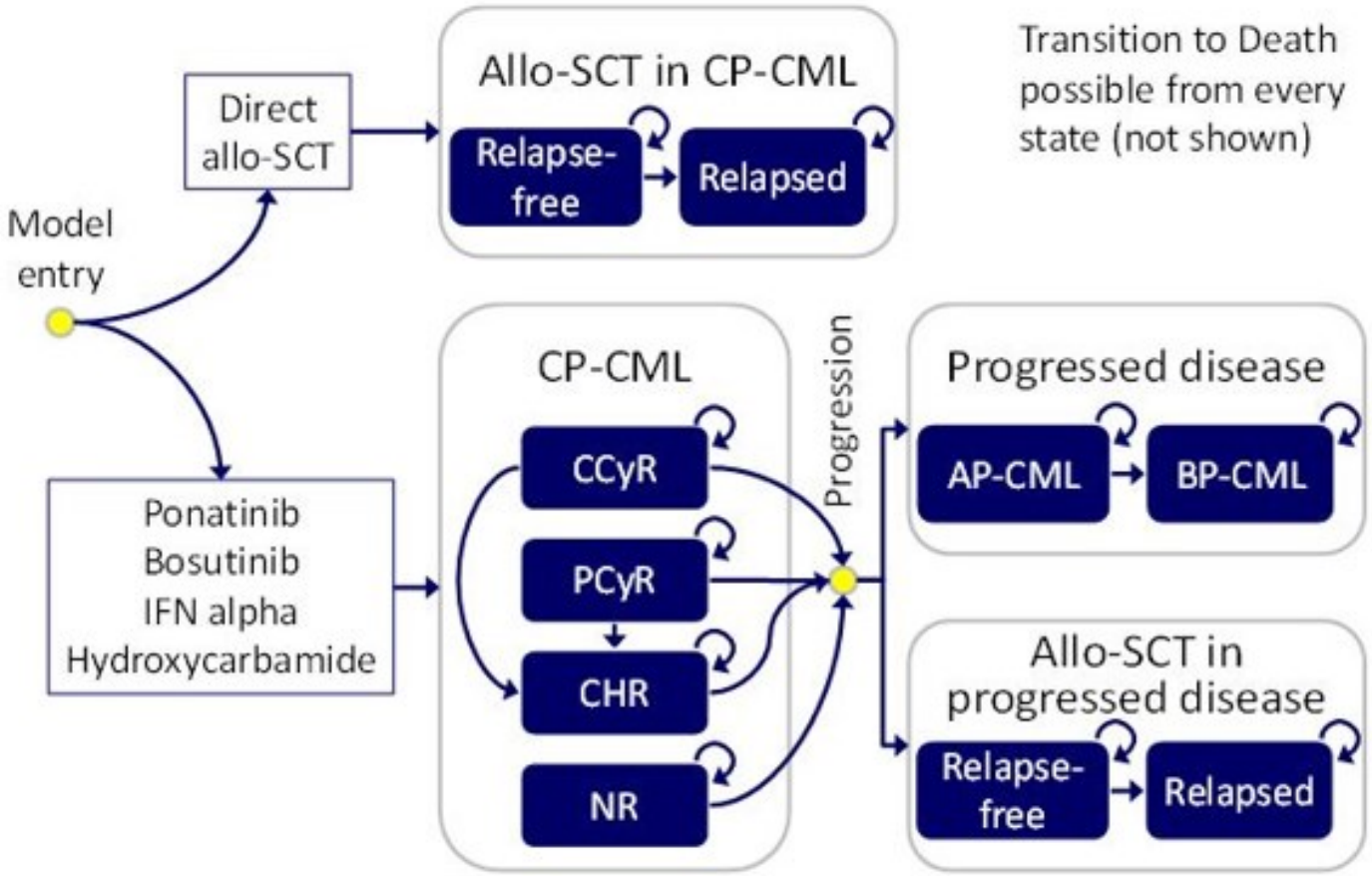
NICE technical team: Neil Hewitt – technical analyst
Richard Diaz – technical adviser

18 January 2017

# CML: Preview Key issues: cost effectiveness

- What is the committee's view on the treatment effectiveness estimates used in the company's model from the matched adjusted indirect comparison and naive unadjusted indirect comparisons, considering the ethical issues around the trial design of the PACE study?
- Did the company fully explore the impact on the ICER of the selection of alternative curves? Is it possible to determine which curves are considered the most plausible?
- Treatment-related death was not incorporated into the company's model. What is the committee's view on this?
- What is the committee's view on the company's PSA which the ERG considered was not robust due to the inappropriate characterisation of uncertainty in the curves, lack of correlation and the arbitrary selection of the size of the standard error used for many parameters?
- What is the committee's view on innovation and end-of-life?

# CML: Model structure chronic phase (CP-CML)




Source: Pg 117-122 of the company's submission and page 89 ERG CML report;
CHR - complete haematological response; CCyR – complete cytogenetic response;
PCyR – partial cytogenetic response; NR - No response

# CP-CML: Company model details

- On entering the model patients could receive 1 of 5 interventions:
  - Ponatinib
  - Bosutinib
  - Interferon alfa
  - Hydroxycarbamide (proxy for BSC)
  - Allo-SCT

  Non-Allo
- The modelling approach for all non-allo interventions was identical but differed between non-allo and allo-SCT
- Death could occur at any point
- A lifetime horizon was used (up to 100 years)
- The model employed 3 month Markov cycles with a half cycle correction

# CP-CML: Company model details allo-SCT

- After entering the model, the next event, if moving out of the relapse free state was relapse or death
- Once a patient had relapsed the only next possible state outside of this was death

# CP-CML: Company model details non-allo-SCT treatments (1)

- Treatment occurred in the first cycle only after which the patients moved into 1 of 4 mutually exclusive and exhaustive states, ranked in descending order of benefit: CCyR; PCyR; CHR; and NR. The model included an option to discontinue ponatinib if non responsive.
- The next possible state besides their existing state for NR and complete haematological response patients was death, disease progression or treatment discontinuation
- Discontinuation of treatment was assumed not to happen for those on interferon alfa or BSC
- Patients in the CCyR or PCyR state could become unresponsive to treatment and regress to complete haematological response

CCyR = Complete cytogenetic response; PCyR = Partial cytogenetic response; CHR = Complete haematologic response
NR = No response; BSC = best supportive care; Allo-SCT = Allogeneic stem cell transplant

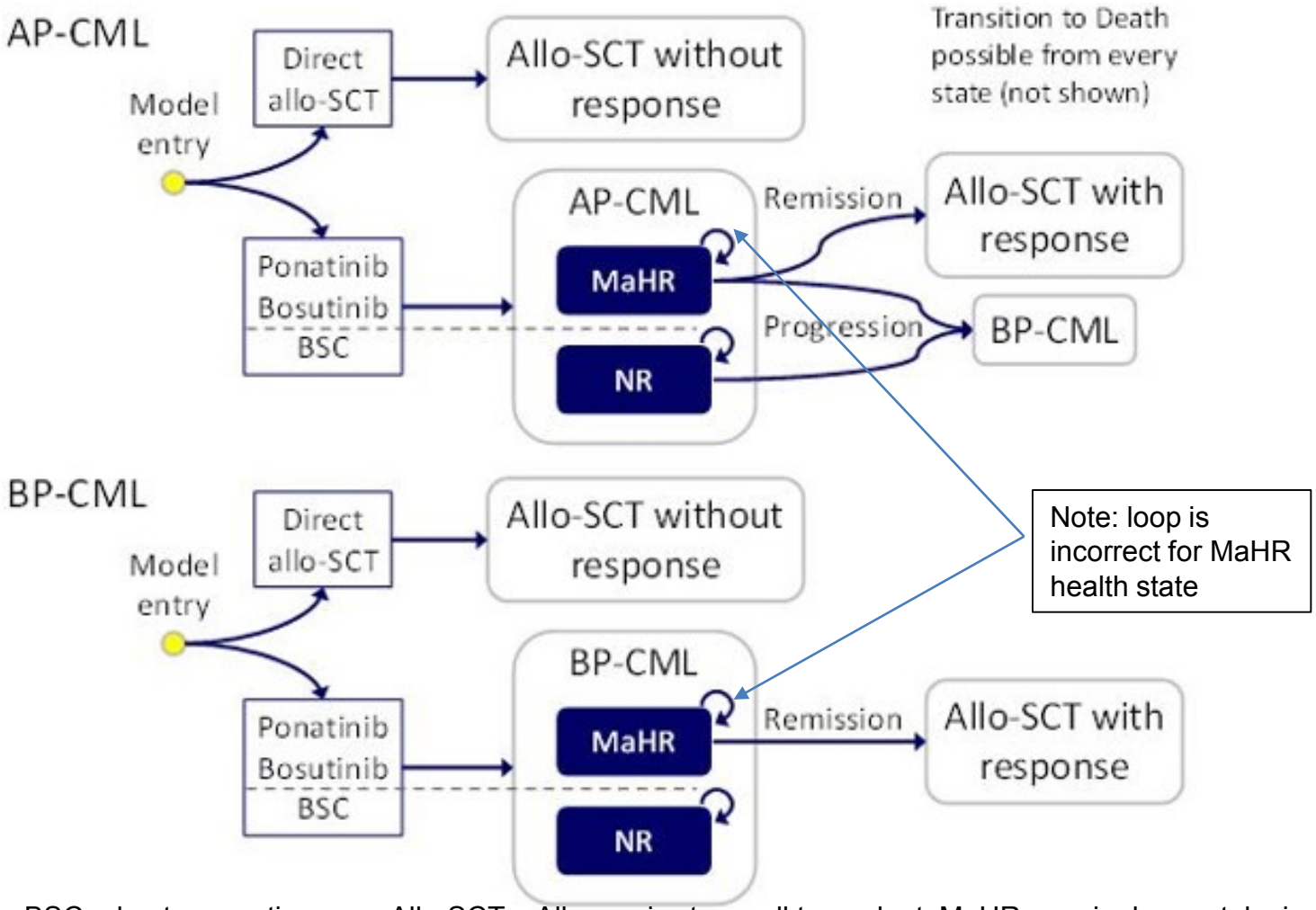
# CP-CML: Company model details non-allo-SCT treatments (2)

- Following discontinuation of treatment in PCyR, CHR or NR, patients would regress to NR, with possibility of an immediate CHR due to subsequent BSC use. Patients in CCyR were assumed to stay in CCyR
- Following progression patient received allo-SCT if appropriate or entered AP. For AP next event (beside same) is either death or progression to BP. Once a patient entered the BP health state the only possible event was death
- For patients receiving allo-SCT, the next event was either death or relapse. Once a patient relapsed the only event possible was death

CCyR = Complete cytogenetic response; PCyR = Partial cytogenetic response; CHR = Complete haematologic response
NR = No response; BSC = best supportive care; Allo-SCT = Allogeneic stem cell transplant

# Accelerated phase (AP) and blast phase (BP)-CML Company model

Source: Figure 3 of ERG CML report




NR = No response; BSC = best supportive care; Allo-SCT = Allogeneic stem cell transplant; MaHR – major haematologic response

# AP- and BP-CML company model details

- Patients are assumed to have a major haematologic response (MaHR) or have no response to treatment
- Patients who have an MaHR would have allo-SCT. All patients are assumed suitable for allo-SCT
- For patients starting with accelerated phase (AP)-CML, the next event after allo-SCT is death. In non-responsive patients, the next event is death or progression to blast phast (BP)-CML, from which the next event is death
- For patients starting with blast phase (BP)-CML, after allo-SCT, the next event is death, for those who are non-responsive the next event is death
- Those who go to allo-SCT on entry can only move to the death state

# CML: Clinical data used in company model

| Variable | Value | Reference |
|---|---|---|
| Age (years) | 54.5 CP; 54.6 AP; 50.4 BP | MAIC for CP<br>PACE for AP and BP |
| % male | 44.9 CP; 41.8 AP; 60 BP | |
| Response rates (%) for ponatinib in CP patients | CCyR 61.34; PCyR 8.46; CHR 18.19; NR 12.01 | MAIC |
| Response rates (%) for bosutinib in CP patients | CCyR 24.07; PCyR 8.33; CHR 37.93; NR 29.66 | Khoury et al |
| Response rates (%) for interferon alfa in CP patients | CCyR 0; PCyR 0; CHR 47; NR 53 | Dalziel et al |
| Response rates (%) for BSC in CP patients | CCyR 0; PCyR 0; CHR 41; NR 59 | Dalziel et al |
| Response rates (%) for ponatinib in AP patients | MaHR 55.7; Non-MaHR 44.3 | PACE |
| Response rates (%) for bosutinib in AP patients | MaHR 29.2; Non-MaHR 70.8 | Gambacorti-Passerini et al |
| Response rates (%) for BSC in AP patients | MaHR 0; Non-MaHR 100 | Company assumption |
| Response rates (%) for ponatinib in BP patients | MaHR 31.7; Non-MaHR 68.3 | PACE |
| Response rates (%) for bosutinib in BP patients | MaHR 4.3; Non-MaHR 95.7 | Gambacorti-Passerini et al |
| Response rates (%) for BSC in BP patients | MaHR 0; Non-MaHR 100 | Company assumption |

Source: table 36, 37 and 38 ERG CML report; AP – accelerated phase; BP – blast phase; CP – chronic phase CCyR = Complete cytogenetic response; PCyR = Partial cytogenetic response; CHR = Complete haematologic response NR = No response; BSC = best supportive care; MaHR – major haematologic response

# CML: Company extrapolation of outcomes

- In cases when the company did not have access to patient-level time-to-event data, the company digitised published Kaplan-Meier survivor functions and used the Solver add-in in Excel to generate parametric survivor functions by minimising the sum of squared errors (SSE) between the predicted survival curve and that of the digitised points.
- The company based their choice of parametric model on the AIC and BIC when patient level data were available.
- ERG commented that the method to reconstruct the patient-level data proposed by Guyot et al. could have been used
- ERG considered that extrapolating survivor functions using sample data alone was inappropriate, particularly in cases where there were few events in studies with relatively short duration of follow-up, and should be informed by external clinical data / opinion where possible
- ERG expressed concern that the approach does not give sufficient weight to expert clinical knowledge and the expected shape of the hazard function over time in the target population of patients
- ERG cautioned that using AIC and BIC alone to determine choice of parametric model did not establish whether it is a good model or would result in a clinical plausible estimate of event rates beyond the duration of the study.

# CML: Company assumed adverse event rates (non-vascular)

| Adverse event | CP-CML | | AP-CML | | BP-CML | |
|---|---|---|---|---|---|---|
| | Ponatinib | Bosutinib | Ponatinib | Bosutinib | Ponatinib | Bosutinib |
| Abdominal pain | 14.40% | 0.00% | - | - | - | - |
| Anaemia | 4.20% | 6.78% | 12.90% | 21.00% | 32.91% | 20.31% |
| Diarrhoea | 0.00% | 8.47% | - | - | - | - |
| Hyperglycaemia | 0.00% | 0.00% | - | - | - | - |
| Hypophosphatemia | 0.00% | 0.00% | - | - | - | - |
| Leukocytopaenia | 5.20% | 0.00% | 5.90% | - | 6.33% | 18.75% |
| Lipase increased | 10.30% | 0.00% | 12.90% | 11.30% | - | - |
| Neutropenia | 19.60% | 15.25% | 29.40% | 17.70% | - | - |
| Pancreatitis | 8.20% | 0.00% | 5.90% | - | - | - |

Data Adapted from Tables 40, 41 and 42, pages 97 and 98 ERG CML report

# CML: Company assumed adverse event rates (vascular)

| Adverse event | CP-CML | | AP-CML | | BP-CML | |
|---|---|---|---|---|---|---|
| | Ponatinib | Bosutinib | Ponatinib | Bosutinib | Ponatinib | Bosutinib |
| ALT elevation | 9.30% | 5.93% | - | - | 7.59% | - |
| GGT increased | 6.20% | 0.00% | - | - | - | - |
| Thrombocytopenia | 35.10% | 26.27% | 35.30% | 25.80% | 44.30% | 35.94% |
| Cardiovascular events | 1.34% | - | 0.58% | - | 1.98% | - |
| Cerebrovascular events | 0.63% | - | 0.29% | - | - | - |
| Peripheral vascular event | 0.86% | - | 0.44% | - | 0.67% | - |
| Venous thromboembolism event | 0.22% | - | 0.15% | - | - | - |

Data adapted from Tables 40, 41 and 42, pages 97 and 98 ERG CML report
ALT - alanine aminotransferase; GGT - gamma-glutamyltransferase

# CML: Company health-related quality of life

- Evidence searches by the company identified 3 studies which provided HRQoL data on the disease.
- These involved time-to-trade-off and/or standard gamble methods, involved the general population and included UK respondents
- The company reported the sources used for utility values in patients with allo-SCT but not how they were selected. One of these had been used in a previous evaluation of CML.
- The utility decrements were applied to HRQoL from the UK general population

See CS pages 140-143, CML ERG pages 130-132.

# CML: HRQoL reported by Szabo et al (2010) and utility decrements assumed in company model

| Health State | Estimated HRQoL (95% CI) | Utility decrement |
|---|---|---|
| CP-CML responding to treatment | 0.91 (0.89 – 0.94) | 0 |
| CP-CML not responding to treatment | 0.73 (0.69 – 0.78) | 0.116 |
| AP-CML responding to treatment | 0.78 (0.74 – 0.82) | 0.006 |
| AP-CML not responding to treatment | 0.53 (0.48 – 0.58) | 0.316 |
| BP-CML responding to treatment | 0.56 (0.52 – 0.60) | 0.286 |
| BP-CML not responding to treatment | 0.29 (0.24 – 0.33) | 0.556 |
| Treatment withdrawal due to SAEs | 0.52 (0.46 – 0.58) | 0.326 |

Adapted from Table 48, page 131 ERG CML report
AP – accelerated phase; BP – blast phase; CP – chronic phase

# CML: Utility decrements used following allo-SCT in the company model

| Period after allo-SCT | Utility decrement | Source. |
|---|---|---|
| Up to 3 months post-allo-SCT | 0.296 | Van Agthoven *et al*. |
| Between 3 and 6 months post-allo-SCT | 0.216 | Assumption: midpoint between value up to 3 months and beyond 6 months |
| 6 months and longer post-allo-SCT | 0.136 | Loveman *et al*. |
| Post-relapse | 0.260 | Kantarjian *et al*. and Olaverria *et al*. |

Adapted from Table 49, page 132 ERG CML report

# CML: Costs used in company model – Adverse events

| **Adverse event** (assumed to only occur once within first 3 month cycle) | **Unit cost (£)** | **Source** |
|---|---|---|
| Abdominal pain | 752.10 | Ref costs 2014/15 |
| Anaemia | 1,827.13 | NHS ETF 2015/16 |
| Diarrhoea | 801.95 | Ref costs 2014/15 |
| Hyperglycaemia | 1,271.46 | Ref costs 2014/15 |
| Hypophosphatemia | 721.00 | See notes 1 |
| Leukocytopaenia | 633.26 | See notes 2 |
| Lipase increased | 721.00 | See notes 1 |
| Neutropenia | 633.26 | Ref costs 2014/15 |
| Pancreatitis | 1,121.98 | Ref costs 2014/15 |
| ALT (alanine aminotransferase) elevation | 1,121.98 | Ref costs 2014/15 |
| GGT (gamma-glutamyltransferase) “ | 1,121.98 | Ref costs 2014/15 |
| Thrombocytopenia | 421.74 | Ref costs 2014/15 |
| **Serious adverse event** | | |
| Cardiovascular events | 2,357.00 | NHS ETF 2015/16 |
| Cerebrovascular events | 2,962.00 | NHS ETF 2015/16 |
| Peripheral vascular event | 2,872.00 | NHS ETF 2015/16 |
| Venous thromboembolism event | 552.00 | NHS ETF 2015/16 |

Adapted from tables 40, 41 and 42, pages 97 and 98 ERG CML report

Contains CIC

# CML: Costs used in company model – Treatment cycles

| Intervention | Acquisition cost per 3 month cycle (£) (ponatinib list price) |
|---|---|
| Ponatinib in CP-CML (CCyR) | [redacted] |
| Ponatinib in CP-CML (PCyR) | [redacted] |
| Ponatinib in CP-CML (CHR) | [redacted] |
| Ponatinib in CP-CML (NR) | [redacted] |
| Dasatinib | 7624 |
| Imatinib | 5590 |
| Nilotinib | 7910 |
| Interferon alfa | 6833 |
| Bosutinib | 10,714 |
| BSC | 38 |

Source: table 54, page 138, ERG CML report

CP – chronic phase; CCyR – complete cytogenetic response; PCyR – partial cytogenetic response; CHR – complete haematologic response; NR – no response

# CML: Other costs used in company model

| Costs per 3 month cycle | Value (£) |
|---|---|
| CP- CML with CCyR | 208 |
| CP-CML without CCyR | 495 |
| AP- CML | 2648 |
| BP-CML | 20,319 |
| Average end-of-life care cost | 5,765.76 |
| Allo-SCT | 60,092 |
| Per-cycle follow-up cost after allo- STC, year 1 | 12,214 |
| Per-cycle follow-up cost after allo- STC, year 2 | 3518 |
| Per-cycle follow-up cost after allo- STC, year 3+ | 420 |

Sources: tables 56, 57 and section 5.2.8.3, ERG CML report
AP – accelerated phase; BP – blast phase; CP – chronic phase; CCyR – complete cytogenetic response

# CML: Company base case chronic phase (CP)-CML

## (calculated by ERG using ponatinib PAS price and list prices for comparators)

| Treatment | LYG | Discounted costs (£) | Discounted QALYs | Deterministic ICER (£/QALY gained) | |
|---|---|---|---|---|---|
| | | | | Ponatinib versus comparator | Full Incremental analysis |
| BSC | 4.64 | 136,666 | 2.24 | 15,200 | |
| Bosutinib | 8.38 | 150,811 | 4.00 | 18,213 | 8,072 |
| Interferon alfa | 4.72 | 188,917 | 2.30 | 6395 | Dominated |
| Allo-SCT | 8.77 | 209,258 | 3.93 | 4042 | Dominated |
| Ponatinib | [redacted] | [redacted] | [redacted] | - | 18,213 |

| **Probabilistic analyses results** |
|---|
| Results of the PSA are consistent with the ICER analysis results estimated from the base-case analysis, with few extreme values |

Sources: tables 58 and 59, ERG CML report

The probability of ponatinib having an ICER below the following values were estimated to be: £20,000 (51%); £30,000 (81%); and £50,000 (91%)

# CML: Company base case accelerated phase (AP)-CML
## (calculated by ERG using ponatinib PAS price and list prices for comparators)

| Treatment | LYG | Discounted costs (£) | Discounted QALYs | Deterministic ICER (£/(cost per QALY gained) | |
|---|---|---|---|---|---|
| | | | | Ponatinib versus comparator | Full Incremental analysis |
| BSC | 1.91 | 95,263 | 0.58 | 14,750 | - |
| Allo SCT | 3.20 | 166,635 | 1.86 | 13,279 | Extendedly dominated |
| Ponatinib | [redacted] | [redacted] | [redacted] | - | 14,750 |
| Bosutinib | 6.77 | 162,419 | 2.62 | Dominant | Dominant |

| **Probabilistic analyses results** |
|---|
| Results of the PSA are consistent with the ICER analysis results estimated from the base-case analysis, with few extreme values |

Sources: table 60 and 61 ERG CML report

The probability of ponatinib having an ICER below the following values were estimated to be: £20,000 (71%); £30,000 (90%); and £50,000 (99%)

# CML: Company base case blast phase (BP)-CML
## (calculated by ERG using ponatinib PAS price and list prices for comparators)

| Treatment | LYG | Discounted costs (£) | Discounted QALYs | Deterministic ICER ((cost (£) per QALY gained) | |
|---|---|---|---|---|---|
| | | | | Ponatinib versus comparator | Full Incremental analysis |
| Bosutinib | 0.85 | 71,473 | 0.37 | 17,601 | - |
| Ponatinib | [redacted] | [redacted] | [redacted] | - | 17,601 |
| BSC | 1.16 | 101,961 | 0.28 | Dominant | Dominant |
| Allo-SCT | 1.34 | 103,748 | 0.85 | Dominant | Dominant |

| **Probabilistic analyses results** |
|---|
| Results of the PSA are consistent with the ICER analysis results estimated from the base-case analysis, with few extreme values |

Sources: tables 62 and 63 CML ERG report

The probability of ponatinib having an ICER below the following values were estimated to be: £20,000 (67%); £30,000 (94%); and £50,000 (100%)

# CML: ERG comments

- Model structure adopted for the economic evaluation is generally appropriate though similar to other CML topics, there has been a reliance on surrogate endpoints.
- There is inherent uncertainty introduced by the use of a MAIC, and the matching of the PACE study participants to the Khoury et al. (bosutinib) trial participants may have an impact on the relevance of the MAIC population to UK practice.
- The biggest concern of the ERG is that the parametric distributions fitted where individual patient data were not available is inappropriate, and that for all distributions there was insufficient exploration of the impact on the ICER of the selection of alternative curves that were considered plausible
- The model also ignored any possibility of treatment-related death, which was favourable to ponatinib compared with BSC
- The ERG believes that the PSA undertaken by the company was not robust because of the inappropriate characterisation of uncertainty in the curves, lack of correlation and the arbitrary selection of the size of the standard error used for many parameters.

# CML: ERG exploratory analyses

- In chronic phase (CP)-CML, the ERG varied the choice of parametric curves for OS, PFS, duration of response and relapse-free survival. These changes affected the ICER, as did assuming drug wastage, and reducing costs post-progression in both CP-CML and post allo-SCT for CP-CML patients.
- In accelerated phase (AP)-CML, the ERG varied the choice of parametric curves among other changes. The largest change in the ICER was caused by the selection of curves.
- In blast phase (BP)-CML, the ERG varied the choice of parametric curves among other changes. The largest changes in the ICER were caused by the selection of curves and the introduction of a 3-month stopping rule for bosutinib

# CP-CML: ERG's exploratory deterministic analyses in CP-CML (calculated by ERG using PAS price for ponatinib, comparator list prices) (1)

| Ref No | Exploratory Analyses | Pon vs Bos | Pon vs BSC | Pon vs allo-SCT |
|---|---|---|---|---|
| 0 | N/A (company's base case) | 18,213 | 15,200 | 4042 |
| 1a | Choosing alternative distributions in addition to those selected by the company, using the company's fits (range) | 13,747 – 43,344 | 12,063 – 22,295 | Dominant – 12,091 |
| 1b | As 1a, but using the same distribution for DoR for ponatinib and bosutinib (range) | 15,319 – 38,710 | N/A | N/A |
| 1c | As 1a, but solely using the company's exponential distribution for PFS in NR (range) | 13,747 – 27,616 | 12,063 – 21,150 | Dominant – 12,091 |
| 1d | Combining 1b and 1c | 15,319 – 25,181 | 12,063 – 21,150 | Dominant – 12,091 |
| 2a | Recalculation of the survivor functions (excluding PFS exponentials) | 16,297 | 13,661 | Dominant |
| 2b | As 2a, but use of the ERG's estimated exponential distribution for PFS in NR | 17,073 | 14,860 | Dominant |
| 2c | As 2a, but use of the ERG's estimated exponential distributions for PFS for all response groups | 18,092 | 15,424 | Dominant |
| 3 | Assuming drug wastage | 30,754 | 24,245 | 16,487 |



Source: table 66 ERG CML report

# CP-CML: ERG's exploratory deterministic analyses in CP-CML (calculated by ERG using PAS price for ponatinib, comparator list prices) (2)

| Ref No | Exploratory Analyses | Pon vs Bos | Pon vs BSC | Pon vs allo-SCT |
|---|---|---|---|---|
| 4 | Including a 3 month stopping rule for bosutinib | 21,313 | 15,200 | 4042 |
| 5 | No half-cycle correction of intervention costs | 17,785 | 15,709 | 5472 |
| 6 | Including treatment-related deaths | 18,099 | 16,810 | 6143 |
| 7a | Costs post-progression in CP-CML or post allo-SCT for CP-CML patients equal to those for BSC. | 21,717 | 18,688 | 21,712 |
| 7b | Reducing costs post-progression in CP-CML or post allo-SCT for CP-CML patients to that estimated for generic imatinib. | 21,584 | 18,555 | 21.039 |
| 8 | Assuming life table data are probabilities not rates | 18,226 | 15,211 | 4043 |
| 9a | Assuming ratios of HRQoL between CP-CML and other CML states are maintained | 18,017 | 15,035 | 4096 |
| 9b | Assuming decrements of HRQoL between CP-CML and other CML states are maintained | 17,920 | 14,954 | 4125 |
| 10 | 2a, 4,5, 7a, 8 and 9a, using the curves believed most credible by the company | 23,059 | 18,308 | 27,649 |
| 11. ERG base case ICERs | (11a)- 1a, 2a, 4,5, 7a, 8 and 9a (range)<br><br>As 11a, assuming same distribution for duration of response for ponatinib and bosutinib (range) | 19,986 – 52,121<br><br>22,995 – 42,637 | 18,246 – 27,667<br><br>N/A | 18,279 – Dominated<br><br>N/A |

Source: table 66 ERG CML report erratum

# AP-CML: ERG's exploratory deterministic analyses in AP-CML (calculated by ERG using PAS prices for ponatinib and list price for comparators)

| | | Cost per QALY gained (£) – Ponatinib vs | |
|---|---|---|---|
| Ref No | Exploratory Analyses | BSC | Allo-SCT |
| 0 | N/A (company's base case) | 14,750 | 13,279 |
| 1 | Choosing alternative distributions in addition to those selected by the company, using the company's fits (range) | 7479 – 15,861 | Dominating – 95,313 |
| 2 | Recalculation of the survivor functions | 10,358 | 12,217 |
| 3 | Assuming drug wastage | 15,267 | 14,199 |
| 4 | No half-cycle correction of intervention costs | 16,580 | 16,465 |
| 5 | Including treatment-related deaths | 14,747 | 12,671 |
| 6 | Assuming life table data are probabilities not rates | 14,754 | 13,285 |
| 7 | 2,3, 4, and 6 using the curves believed most credible by the company | 12,975 | 16,412 |
| 8 ERG base case ICER | As 7, but choosing alternative distributions in addition to those selected by the company (range) | 7475 – 18,005 | Dominating – 63,701 |

Source: table 67 ERG CML report

# BP-CML: ERG's exploratory deterministic analyses in BP-CML (calculated by ERG using PAS prices for ponatinib and list price for comparators)

| | | ICER (£) | |
|---|---|---|---|
| | | **Cost per QALY gained (£)** | |
| **Ref No** | **Exploratory Analyses** | **Ponatinib vs bosutinib** | **Allo-SCT vs Ponatinib** |
| 0 | N/A (company's base case) | 17,601 | Dominated |
| 1 | Choosing alternative distributions in addition to those selected by the company, using the company's fits (range) | 11,184 – 18,808 | 8,251 - Dominated |
| 2 | Recalculation of the survivor functions | 15,812 | 157,193 |
| 3 | Assuming drug wastage | 18,022 | Dominated |
| 4 | Incorporating a three-month stopping rule for bosutinib | 21,910 | Dominated |
| 5 | No half-cycle correction of intervention costs | 18,396 | Dominated |
| 6 | Including treatment-related deaths | 16,665 | Dominated |
| 7 | Assuming life table data are probabilities not rates | 17,601 | Dominated |
| 8 | 2,3, 4,5, and 7 using the curves believed most credible by the company | 21,254 | 102,612 |
| 9 ERG base case ICER | As 8, but choosing alternative distributions in addition to those selected by the company (range) | 17,066 – 22,545 | 4,004 - Dominated |

Source: table 68 ERG CML report erratum

# CML: Innovation

- Ponatinib is a significant advance in treatment of CML for patients whose disease is resistant or intolerant to imatinib or 2$^{nd}$ generation tyrosine kinase inhibitors with or without the T315I mutation.
- Few treatment options are available

# CML: End of life

Chronic phase (CP)-CML

- Company's model estimates that patients' life expectancy is more than 4 years regardless of treatment

Accelerated phase (AP)-CML

- Company's model estimates that, on average, those patients receiving bosutinib would live in excess of 6 years; those that receive allo-SCT would live in excess of 3 years, whilst those who receive BSC would live slightly under 2 years
- The model predicts a large extension in health for ponatinib compared with BSC, in excess of 6 years, potentially satisfying criteria for population for whom allo-SCT or bosutinib are not comparators

Blast phase (BP)-CML

- the company's model estimates that those patients receiving bosutinib, allo-SCT or BSC would not live greater than two years, although this value increases greatly if it is assumed that OS following allo-SCT is characterised by a Gompertz distribution
- model predicts ponatinib provides >3 months extension of life compared with the comparators and could satisfy the end of life criteria for patients with BP-CML, unless it is assumed that the OS following allo-SCT is lengthier than the company assumed in its base case.

# CML: Potential equality issues

- None identified at scoping stage nor in submissions.
- However the company note a number of potential equality benefits from the use of ponatinib namely:
  - It provides an additional treatment option for patients with CML and Ph+ ALL who currently have limited treatment options
  - While allo-SCT is suitable for these patients, there is unequal access to it among ethnic groups due to differences in donor rates
  - Ponatinib is the only tyrosine kinase inhibitor active against the T315I mutation

# CML: Key issues: cost effectiveness

- What is the committee's view on the treatment effectiveness estimates used in the company's model from the matched adjusted indirect comparison and naive unadjusted indirect comparisons, considering the ethical issues around the trial design of the PACE study?
- Did the company fully explore the impact on the ICER of the selection of alternative curves? Is it possible to determine which curves are considered the most plausible?
- Treatment-related death was not incorporated into the company's model. What is the committee's view on this?
- What is the committee's view on the company's PSA which the ERG considered was not robust due to the inappropriate characterisation of uncertainty in the curves, lack of correlation and the arbitrary selection of the size of the standard error used for many parameters?
- What is the committee's view on innovation and end-of-life?

PUBLIC OBSERVER SLIDES

# ALL: Lead team presentation Ponatinib for treating Ph+ acute lymphoblastic leukaemia [ID671] - STA

1st Appraisal Committee meeting

**Background and Clinical Effectiveness**

Committee C

Lead team: Kamal Balakrishnan, Prithwiraj Das, David Chandler

ERG: SCHaRR

NICE technical team: Neil Hewitt – technical analyst
Richard Diaz – technical adviser

18 January 2017

# ALL: Preview Key issues: clinical effectiveness

- There is limited, non comparative evidence base (due to ethical reasons – EMA agreed with the non-comparative design of study)
  - High risk of bias (selection, performance and detection bias) in absence of a comparator
  - Magnitude of treatment effect uncertain in absence of control group
- Small Ph+ ALL subgroup (n=32) lacks statistical power
- Optimal dosing uncertain. Initial dose (45mg) was lowered during study; therefore it is unclear whether the lower dosing regimen would have been as clinically effective over study period
- Duration of treatment uncertain
  - where complete response is achieved, allo-SCT would be considered if eligible
  - Would patients ineligible for allo-SCT continue treatment indefinitely
- Ph+ ALL population in trial similar to population in England, but clinical practice used in PACE trial was not representative of treatment in NHS (people received nilotinib which is not used in routine clinical practice)
- What is the committee's view on the available evidence?

# ALL: Disease Background

- Acute lymphoblastic leukaemia (ALL) is a rare form of cancer, characterised by the overproduction and accumulation of immature white blood cells
- ALL accounts for around 20% of all leukaemias in adults and is the most common form of childhood leukaemia
- Approximately 25% of adults with ALL have acquired chromosomal abnormality known as Philadelphia chromosome positive disease (Ph+)
- Cancer research UK figures show that in 2014, 654 people in the UK were newly diagnosed with ALL. The company estimate that 33 people received ponatinib according to its licence indication
- Prognosis once diagnosed is poor but improving. Prognosis is usually poorer with Ph+

# ALL: Treatment phases of Ph+ ALL

- Treatment is usually carried out in 3 stages.
  - Induction: Initial treatments which aim to kill the leukaemia cells in the bone marrow
  - Consolidation: Aims to further reduce tumour burden including any leukaemia cells that have penetrated into the central nervous system
  - Maintenance: Involves regular doses of chemotherapy to prevent the leukaemia returning
- During these treatment phases patients are treated with chemotherapy doses including tyrosine kinase inhibitor (TKI) therapy.
- Ponatinib is currently only available through the CDF to patients with the T315I mutation.

# ALL: Treatment pathway

- Induction phase: Imatinib plus chemotherapy
- Following failure or intolerance to imatinib: Dasatinib plus chemotherapy
- Following failure or intolerance to imatinib and dasatinib: Ponatinib
- On any line of therapy, or treatment, where complete response is achieved, allo-SCT should be considered in all eligible patients
- Patients with the T315I mutation should be routed straight to ponatinib
- Patients who relapse or have refractory disease should receive combination chemotherapy plus an alternative TKI to one previously received.
- In older patients with co-morbidities consider adding corticosteroids to patients receiving imatinib or dasatinib and chemotherapy

# ALL: Patient/carer perspective
# Living with ALL

- A younger population are the most common group
- Hugh emotional and physical toll
- Patients and family feel anguish and disbelief
- Usually diagnosed after symptoms have started
  - often as an emergency presentation (64%)
  - symptoms often non-specific
- The chance of relapse is high
- Disease reoccurrence is considered the most frequent cause of treatment failure
- Patients feel there is an unmet need for new therapies
- Although remission can be achieved
  - Stem cell transplant is the only curative treatment

# ALL: PACE study

- Patients were pre-treated with prior TKIs (imatinib, dasatinib, nilotinib or bosutinib) and conventional therapy
- 14/32 (44%) patients received ponatinib as a 3rd line treatment (after 2 TKIs)
- Ph+ ALL patients were able to maintain 45mg per day for 96% of the entire treatment duration. Average daily dose over the course of the study was 42.3mg (figures at April 2012)

# ALL: Results – Ph+ ALL only

| Outcome | Nov 2012, 12 month (n=32) | Feb 2015 (n=32) |
|---|---|---|
| Major Haematologic response (MaHR) by 6 mo. | 41% (95% CI:24-59) | N/R |
| Major cytogenetic response (MCyR) | 47% | N/R |
| Complete cytogenetic response | 38% | N/R |
| Median time to response | MaHR: 2.9 weeks (range: 1.6–24); MCyR: 1 month (range: 0.9-3.7) | N/R |
| Duration of response | MaHR: 2 to 14 months or more (median: 3 months) | N/R |
| Maintained response | MaHR at 12 months: 8%<br>MCyR at 12 months: 32% | N/R |
| PFS | 12 month: 7% (median 3 months) | N/R |
| OS | 12 month: 40% (median: 8 months) | 36 month: 16% |

Adapted from Table 6, page 32, ERG report

# ALL: Results by T315I mutation status at 12 months

| Outcome | Overall (n=32) | Resistant/ Intolerant (n=10) | T315I mutation (n=22) |
|---|---|---|---|
| Major Haematologic response by 6 months | 41% | 50% | 36% |
| Major cytogenetic response | 47% | 60% | 41% |
| Complete cytogenetic response | 38% | 50% | 32% |
| PFS | 12 month: 7% | N/R | N/R |
| OS | 12 month: 40% | N/R | N/R |

Adapted from Table 7, page 33, ERG report
Results reported 9 November 2012

# ALL: Ph+ ALL Adverse reactions

At 12 months

- The most common non-haematologic adverse event were dry skin (22%), rash (19%), abdominal pain (19%) and constipation (19%)
- The most common haematologic adverse event were anaemia (16%), neutropaenia (12%) and thrombocytopenia (9%)

Similar figures were reported for the 4 year follow up point

- At the 4 year cut off, Ph+ ALL [redacted] patients had a treatment-emergent grade 5 arterial occlusive adverse event
  - Following a review of updated clinical trial data on ponatinib revealing an accumulation of treatment-emergent vascular occlusive events, the EMA issued a set of recommendations regarding the use of ponatinib in November 2013. The EMA recommends that the cardiovascular status of patients be assessed and that cardiovascular risk factors be actively managed prior to, and monitored during, treatment

# ALL: ERG comments

- The ERG is confident that the company identified all relevant studies in its submission
- The ERG considered PACE to be a large well designed non comparative study. It considered that the study population included in the trial was reflective of the Ph+ ALL population in England in terms of age and gender. However the treatment pathway was not since patients received nilotinib which is not used in the NHS
- The ERG noted expert concerns on the primary outcome measure (major haematologic response). The ERG's clinical advisor suggested this to be a weak measure in this patient population who are resistant to tyrosine kinase inhibitors and most likely taking ponatinib as a bridge to allogeneic stem cell transplant.
  - A more appropriate endpoint would have been minimal residual disease levels in the bone marrow (not assessed in PACE study)

# ALL: Key issues: clinical effectiveness

- There is limited, non comparative evidence base (due to ethical reasons – EMA agreed with the non-comparative design of study)
  - High risk of bias (selection, performance and detection bias) in absence of a comparator
  - Magnitude of treatment effect uncertain in absence of control group
- Small Ph+ ALL subgroup (n=32) lacks statistical power
- Optimal dosing uncertain. Initial dose (45mg) was lowered during study; therefore it is unclear whether the lower dosing regimen would have been as clinically effective over study period
- Duration of treatment uncertain
  - where complete response is achieved, allo-SCT would be considered if eligible
  - Would patients ineligible for allo-SCT continue treatment indefinitely
- Ph+ ALL population in trial similar to population in England, but clinical practice used in PACE trial was not representative of treatment in NHS (people received nilotinib which is not used in routine clinical practice)
- What is the committee's view on the available evidence?

PUBLIC OBSERVER SLIDES

# ALL: Lead team presentation Ponatinib for treating Ph+ acute lymphoblastic leukaemia [ID671] - STA

1st Appraisal Committee meeting

**Cost effectiveness**

Committee C

Lead team: Kamal Balakrishnan, Prithwiraj Das, David Chandler

ERG: SCHaRR

NICE technical team: Neil Hewitt – technical analyst
Richard Diaz – technical adviser

18 January 2017

# ALL: Preview- Key issues: Cost effectiveness

- What is the committee's view on the treatment effectiveness estimates used in the company's model from naive unadjusted indirect comparisons, considering the ethical issues around the trial design of the PACE study?
- Major cytogenic response more difficult to achieve than complete remission – unadjusted comparison would be unfavourable to ponatinib. What is the committee's view of the impact of the company's choice of outcome measure?
- The ERG considered the PSA results were not robust. What is the committee's view on those results?
- Setting the same OS for no response independent of treatment reduces the ICER. What is the committee's view on this?
- What is the committee's view on innovation and end-of-life?

# ALL: Company model structure Ph+ ALL

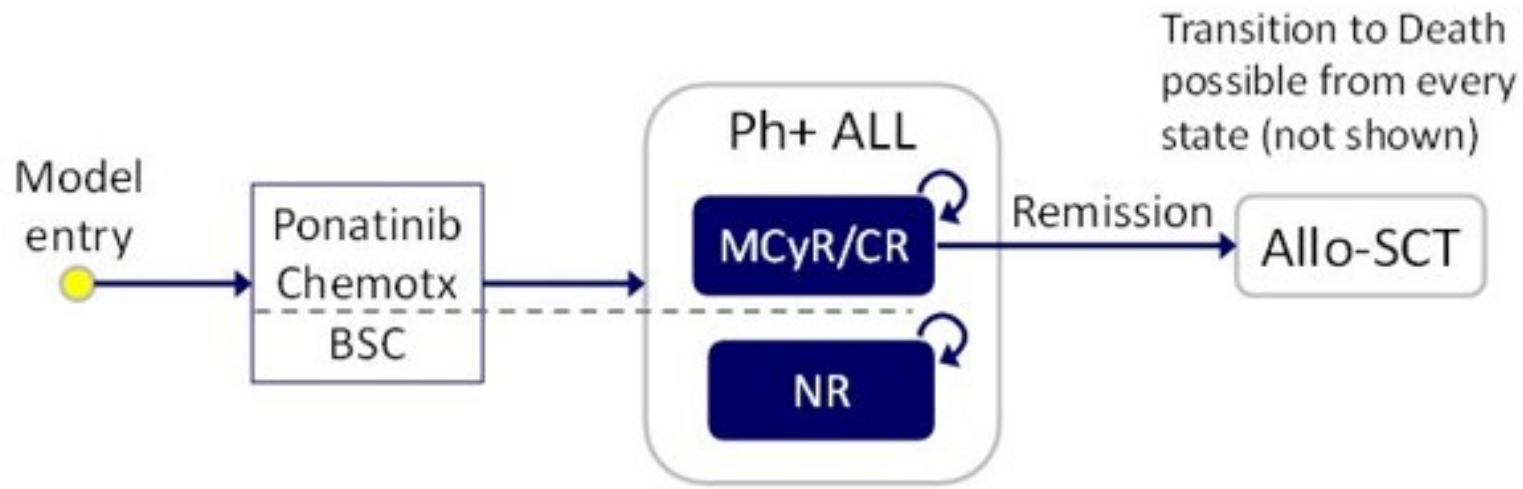



Figure 5-26 of the CS, p215: NR - No response; CR= complete remission; BSC = best supportive care; Allo-SCT= Allogeneic stem cell transplant; MCyR – Major Cytogenetic response; Chemotx - chemotherapy

# ALL: Company model details

- On entering the model patients could receive 1 of 3 interventions:
  - Ponatinib
  - Induction chemotherapy
  - Hydroxycarbamide (proxy for BSC)
- If a patient who received ponatinib or induction chemotherapy had a major cytogenic response or a complete remission (respectively), they were assumed to receive allo-SCT, if eligible
- Patients receiving BSC were assumed to have no response and remain in that state
- Transition to death possible from any state
- A lifetime horizon was used (up to 100 years)
- The model employed 3 month Markov cycles with a half cycle correction

# ALL: Company clinical data used in model

| Variable | Value | Reference |
|---|---|---|
| Age (years) | 53 | PACE, CP-CML population |
| % male | 62.5 | |
| Response rates (%) for ponatinib | MCyR 46.88 NR 53.12 | PACE |
| Response rates (%) for induction chemotherapy | CR 37.04; NR 62.96 | Tavernier et al |
| Response rates (%) for BSC | MCyR/CR 0; NR 100 | Company assumption |
| Rates of: Abdominal pain | 6.30% | Ref costs 2014/15 |
| Anaemia | 12.50% | NHS ETF 2014/15 |
| Lipase increased | 6.30% | Assumed to require one day in hospital |
| Neutropenia | 12.50% | Ref costs 2014/15 |
| Thrombocytopaenia | 6.30% | Ref costs 2014/15 |
| Peripheral vascular event | 5.43% | Ref costs 2014/15 |
| Venous thromboembolism event | 3.65% | Ref costs 2014/15 |

Sources: tables 17, 18 and 19, ERG Ph+ ALL report; MCyR - major cytogenetic response, NR – no response

# ALL: Company - treatment costs

| Treatment | | Cost (£) | Source |
|---|---|---|---|
| Ponatinib per cycle (drug costs)[1] | Proportion of time receiving each dose [redacted] | [redacted] (List Price) | PACE study; ARIAD Pharmaceuticals |
| Induction chemotherapy per 6 week cycle[2] | | 17.999.73 | BNF |
| BSC per cycle[2] | | 4,063.87 | Pagano *et al*. 2000 |
| Monitoring and hospital costs per cycle for patients who responded to ponatinib | | 208.00 | |
| Monitoring and hospital costs per cycle for patients who did not responded to ponatinib | | 24,070.00 | |

Source: table 23, ERG Ph+ ALL report

# ALL: Company's base case results (ponatinib PAS price, comparator list price)

| **Deterministic analyses results** | | | | | |
|---|---|---|---|---|---|
| Treatment | Life years gained | Costs (£) | QALYs | ICER (cost per QALY gained) (£) | |
| | | | | Ponatinib versus comparator | Full Incremental analysis |
| **For whom allo-SCT is suitable** | | | | | |
| BSC | 0.32 | 40,875 | 0.09 | 26,624 | - |
| Induction chemotherapy | 2.96 | 84,854 | 1.84 | 31,123 | 25,258 |
| Ponatinib | [redacted] | [redacted] | [redacted] | - | 31,123 |
| **For whom allo-SCT is unsuitable** | | | | | |
| BSC | 0.32 | 40,875 | 0.09 | | |
| Ponatinib | [redacted] | [redacted] | [redacted] | 33,954 | |

| **Probabilistic analyses results** |
|---|
| Results of the PSA are consistent with the ICER analysis results estimated from the base-case analysis, with few extreme values |

Source: tables 24 and 25 of ERG Ph+ ALL report

# ALL: ERG comments

- ERG considers that the uncertainty in the decision has been considerably underestimated by the company.
- The naïve indirect comparison which resulted in differential OS for those with no response (NR) on BSC treatment and those who experience NR on ponatinib treatment.
- Additionally, there was a naïve indirect comparison between ponatinib and induction chemotherapy relating to the proportion of patients that receive major cytogenetic response (MCyR)/complete remission (CR), although the ERG notes that MCyR which was reported in the ponatinib study is harder to achieve than CR, which was reported in the induction chemotherapy study.
- The results of PSA were not considered robust

# ALL: ERG's deterministic exploratory analyses (ponatinib PAS price, comparator list price) (1)

| **For whom allo-SCT is suitable** | | Cost per QALY (£) | |
|---|---|---|---|
| Ref No | Exploratory Analyses | Ponatinib vs induction chemo | Ponatinib vs BSC |
| | Company deterministic base case | 31,123 | 26,624 |
| 1 | Recalculation of the OS post allo-SCT curve | 57,140 | 53,603 |
| 2 | Choosing alternative distributions in addition to those selected by company, using the company's fits (range) | 23,838 – 52,559 | 14,203 – 45,218 |
| 3 | Assuming drug wastage | 32,499 | 26,944 |
| 4 | No half-cycle correction of intervention costs | 43,766 | 29,568 |
| 5 | Including treatment related deaths | 28,635 | 25,864 |
| 6 | Removal of immortality for a small subset of patients | 31,989 | 26,999 |

Source: Table 1, ERG Ph+ ALL report

# ALL: ERG's deterministic exploratory analyses (ponatinib PAS price, comparator list price) (2)

| **For whom allo-SCT is suitable** | | Cost per QALY (£) | |
|---|---|---|---|
| Ref No | Exploratory Analyses | Ponatinib vs induction chemo | Ponatinib vs BSC |
| 7a | Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the ponatinib value | Dominant | 12,983 |
| 7b | Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the BSC value | Dominant | 18,959 |
| 8 | 1, 3,4 and 6 using the curves believed most credible by the company | 90,325 | 62,801 |
| 9 | 1, 3,4, 6 and 7a using the curves believed most credible by the company | 11,727 | 31,696 |
| 10 ERG base case | As 9, but choosing alternative distributions in addition to those selected by the company (range) | Dominant – 11,727 | 7,892 – 31,696 |

Source: Table 1, ERG Ph+ ALL report; NR – no response

# ALL: ERG's revised base case analyses (ponatinib PAS price, comparator list price)

| **For whom allo-SCT is unsuitable** | | Cost per QALY (£) |
|---|---|---|
| Ref No | Exploratory Analyses | Ponatinib vs BSC |
| | Company Base Case | 33,954 |
| 1 | Choosing alternative distributions in addition to those selected by the company, using the company's fits (range) | 25,902 – 36,037 |
| 2 | Assuming drug wastage | 36,835 |
| 3 | No half-cycle correction of intervention costs | 48,073 |
| 4 | Including treatment related deaths | 30,432 |
| 5a | Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the ponatinib value | Dominant |
| 5b | Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the BSC value | Dominant |
| 8 | 2 and 3 using the curves believed most credible by the company | 52,317 |
| 9 | 1, 3,4, 6 and 7a using the curves believed most credible by the company | Dominant |
| 10 ERG | As 9, but choosing alternative distributions in addition to those selected by the company (range) | Dominant - Dominant |

Source: Table 2, ERG Ph+ ALL report; NR – no response

# ALL: Innovation

- Ponatinib is a significant advance in treatment of Ph+ALL for patients whose disease is resistant or intolerant to imatinib or 2$^{nd}$ generation tyrosine kinase inhibitors with or without the T315I mutation.
- Few treatment options are available

# ALL: End of life

- For whom allo-SCT is suitable
  - Company's model estimates that
    - patients receiving induction chemotherapy live more than 6 years
    - patients who receive BSC live less than half a year
  - The model predicts that ponatinib provides an extension of life in excess of 7 years compared with BSC, and is likely to satisfy the end of life criteria where BSC is the only comparator for patients suitable for allo-SCT
- For whom allo-SCT is unsuitable
  - patients receiving BSC live less than half a year
  - Model predicts that ponatinib provides an extension of life of almost 1 year compared with BSC and is likely to satisfy the end of life criteria for patients unsuitable for allo-SCT

# ALL: Potential equality issues

- None identified at scoping stage nor in submissions.
- However the company note a number of potential equality benefits from the use of ponatinib namely:
  - It provides an additional treatment option for patients with CML and Ph+ ALL who currently have limited treatment options
  - While allo-SCT is suitable for these patients, there is unequal access to it among ethnic groups due to differences in donor rates
  - Ponatinib is the only tyrosine kinase inhibitor active against the T315I mutation

# ALL: Key issues: Cost effectiveness

- What is the committee's view on the treatment effectiveness estimates used in the company's model from naive unadjusted indirect comparisons, considering the ethical issues around the trial design of the PACE study?
- Major cytogenic response more difficult to achieve than complete remission – unadjusted comparison would be unfavourable to ponatinib. What is the committee's view of the impact of the company's choice of outcome measure?
- The ERG considered the PSA results were not robust. What is the committee's view on those results?
- Setting the same OS for no response independent of treatment reduces the ICER. What is the committee's view on this?
- What is the committee's view on innovation and end-of-life?