Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia

Single Technology Appraisal

2nd Committee meeting: 16 March 2017

Committee C

FOR PUBLIC

NICE National Institute for Health and Care Excellence

Key issues

- Absence of direct comparative evidence. Evidence consisted of one phase II trial – PACE study
- Appropriateness of matching adjusted indirect comparison (MAIC) undertaken by the company
- Choice of curve of best fit for progression free survival (extrapolation)
- Uncertainty around the ICER value (ranges presented based on choices of curves of best fit and other scenarios)
- Company's new evidence – updated PAS

Ponatinib

- 3rd generation TKI which inhibits the kinase activity of native BCR-ABL gene, and all mutant variants, including 'gatekeeper' T315I
- Administered orally and available in 15mg, 30mg, and 45mg dose tablets
- The company 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.
- New evidence at ACD stage – update to the PAS discount

Ponatinib – marketing authorisation

Adults with CP, AP, or BP-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.

Adults with Ph+ ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation

ACD preliminary recommendations

1.1 Ponatinib is recommended as an option for treating chronic myeloid leukaemia (CML) in adults with:

- chronic phase CML

  -only when the T315I gene mutation is present

- accelerated phase or blast phase CML

  -when the disease is resistant to dasatinib or nilotinib or

  -when they cannot have dasatinib or nilotinib and for whom imatinib is not clinically appropriate or

  -when the T315I gene mutation is present and

  - the company provides ponatinib with the discount agreed in the patient access scheme.

ACD preliminary recommendations

1.2 Ponatinib is recommended, within its marketing authorisation, as an option for treating Philadelphia chromosome positive acute lymphoblastic leukaemia in adults when:

-the disease is resistant to dasatinib or

-they cannot have dasatinib and for whom imatinib is not clinically appropriate or

-the T315I gene mutation is present and

-the company provides the drug with the discount agreed in the patient access scheme.

Summary of evidence

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 (lowered in October 2013)	Major cytogenetic response (MCyR) in patients with CP-CML Major haematologic response (MaHR) in patients with AP-CML, BP-CML and Ph+ ALL

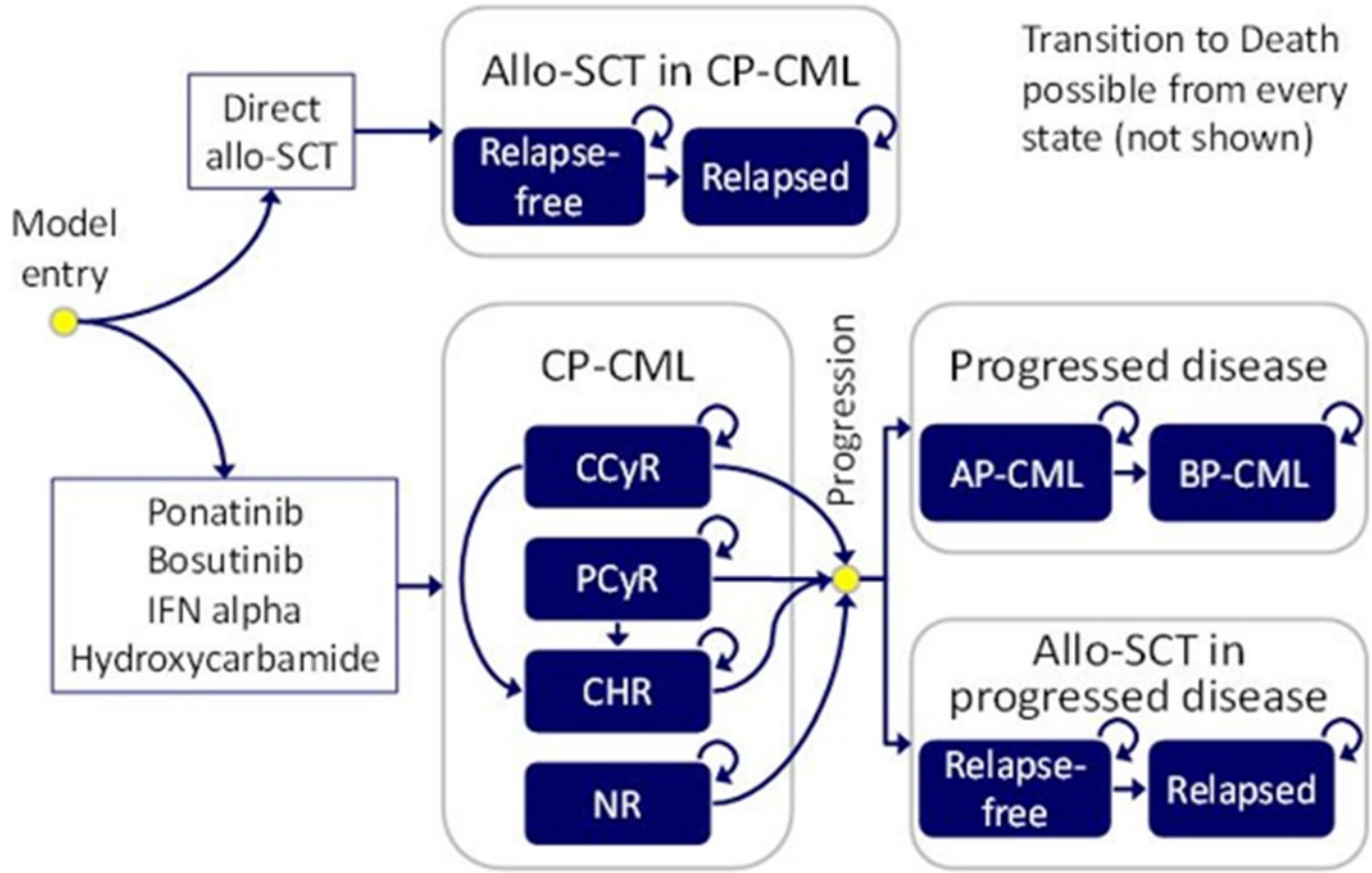
Summary of results: clinical effectiveness

Outcome	All lines 12 months
Major cytogenetic response	CP 56% (50-62%) AP 39% BP 23% ALL 47%
Major haematological response	AP 55% (44-66%) BP(6 month) 31% (20-44%) ALL 41% (24-59%)
Progression free survival	CP 80% AP 55% BP 19% ALL 7%
Overall survival	CP 94% AP 84% BP 29% ALL 40%

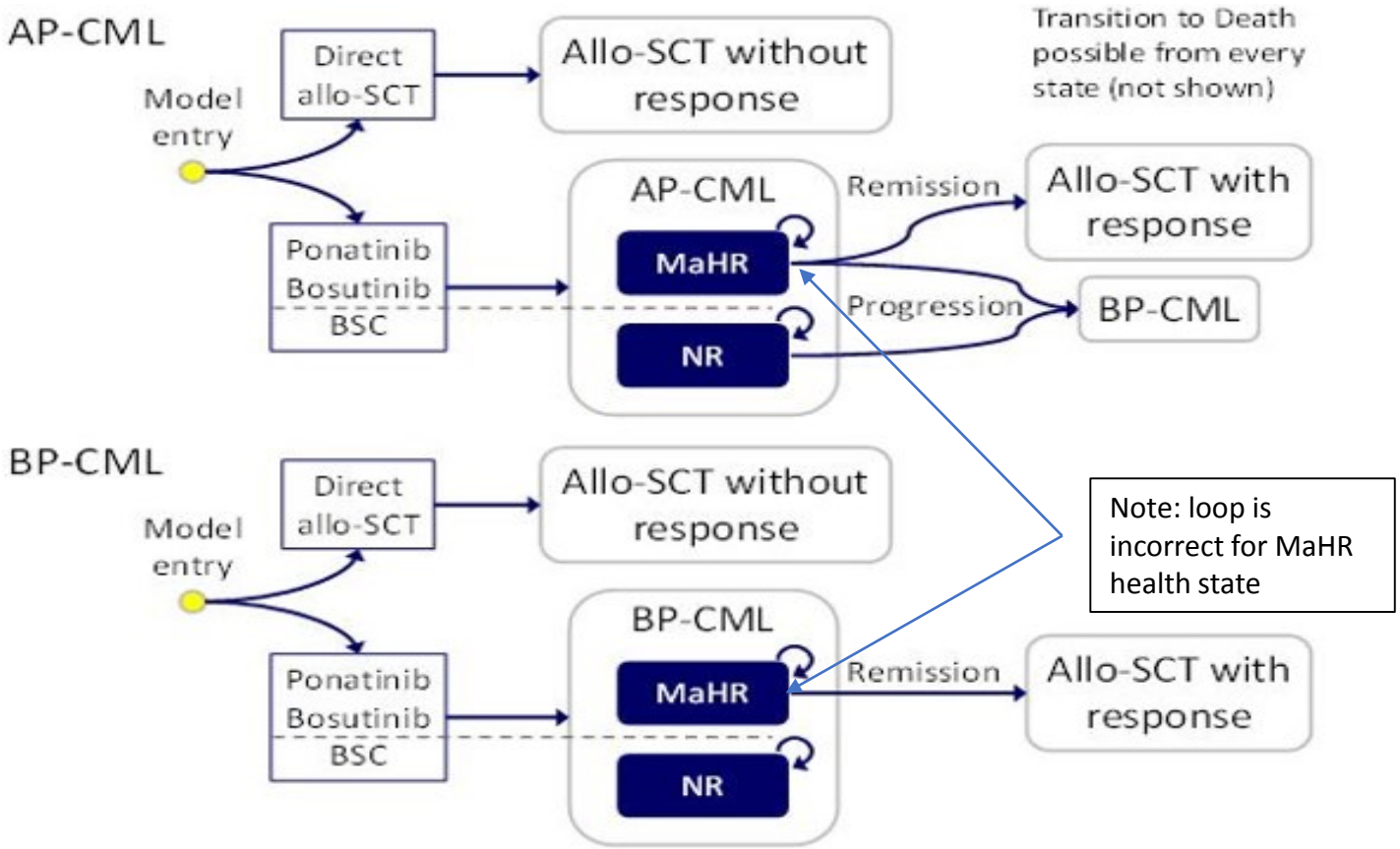
ACD key issues: clinical effectiveness

- The PACE trial was well conducted but non-comparative
- The committee considered the matching adjusted indirect comparison (MAIC) appropriate but noted concerns:
  - Individual patient data from the PACE trial was matched with aggregate data from Khoury et al (2012).
  - Only involved CP-CML patients
  - involved several assumptions to allow for matching patient characteristics across a range of covariates and to account for unobserved heterogeneity
  - Requires considerable overlap between the 2 populations is needed to prevent all the weighting being given to a few patients
- Patient numbers in the Ph+ ALL subgroup in the PACE study was small (n=32) and lacked statistical power. Patients received nilotinib which was un-representative of the NHS

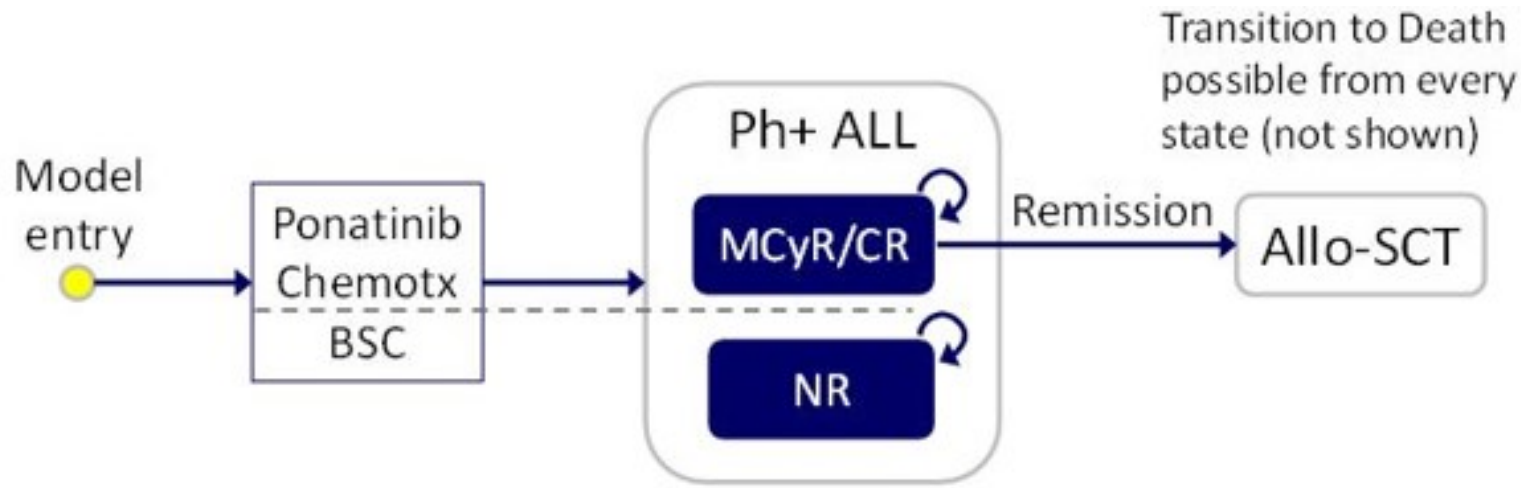
Company's model, CP-CML



Model: AP and BP-CML



Model structure Ph+ ALL



ACD committee considerations

- Model structure adopted for the economic evaluation is generally appropriate. However the committee noted concerns:
  - probabilistic sensitivity analyses done by the company were 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
  - the company chose its parametric distributions based on the Akaike information criterion (AIC) and Bayesian information criterion (BIC), but did not take into account clinical expert advice on the plausibility of the curves that were selected for its base case

ACD committee conclusion (1)

- The ICER values fell within a range, and there was uncertainty where within that range the ‘true value’ lay
- The ICERs for ponatinib vs bosutinib in CP-CML population were outside the range normally considered to be cost effective (£20,000 to £30,000 per QALY)
- It was judged that AP and BP-CML and Ph+ALL met the end of life criteria but not CP-CML
- The Committee concluded that based on existing ICER values, or when applying end of life criteria, ponatanib was a cost effective treatment for AP and BP-CML and Ph+ ALL

ACD committee conclusion (2)

- However in CP-CML, since the end of life criteria did not apply, and the ICER range contained values over £30k, the Committee concluded that it could not recommend ponatinib in these patients
  - Unless they had the T315I gene mutation

Consultation comments

- Comments received from:
  - Clinical and patient experts
  - Patient and professional organisations:
    - CML support group
    - Leukaemia CARE
    - Royal College of Pathologists
    - Royal College of Physicians
  - Public
  - Company: Incyte
  - Commentators:
    - Pfizer
    - Department of Health

Comments on the ACD: web response

- Dasatinib is not currently commissioned in England for Ph+ALL, and on the NICE website it is stated that dasatinib for Ph+ ALL was removed from the appraisals programme in December 2008, and is not currently available through the CDF
  - Therefore the NICE recommendation is misleading as it implies that dasatinib should be accessed before ponatinib (unless T315I mutation), when this is not possible

Comments on the ACD: clinical expert (1)

- The recommendation for CP-CML means that the patients disease will be allowed to unnecessarily progress before ponatinib is given
- Bosutinib (a 2nd generation TKI) is an inappropriate comparator for ponatinib
  - Ponatinib has greater potency and covers a broader spectrum of disease
  - There is questionable benefit of giving patients bosutinib if they are resistant to dasatinib or nilotinib

Comments on the ACD: clinical expert (2)

- The current recommendations for CP-CML, are illogical
  - The patient numbers excluded are small (est. 50-60 a year)
  - Some will have to be offered allo-SCT as the only other alternative which is costly and risky
  - Their disease will be allowed to progress to a point where their disease can no longer be controlled before receiving ponatinib
- Bosutinib is not an appropriate comparator to ponatinib in the indicated patients
  - Bosutinib is a 2nd generation TKI and is less potent
  - In patients who have demonstrated resistance to dasatinib or nilotinib, it makes little sense to offer them bosutinib
  - Intolerance is less clear cut, but for patients who are intolerant to 2, 2nd generation TKI, ponatinib is a suitable treatment

Comments on the ACD: patient experts and groups

- The recommendation in CP-CML leaves those without the T315I mutation, who have exhausted other treatments, without a treatment option, except to wait for their disease to progress onto AP or BP
- The recommendation for CP-CML is not consistent with 2015 “Achieving World Class Cancer Outcomes: A Strategy for England 2015-2020” where early definitive diagnosis closely followed by rapid movement to the treatment clinical opinion decides is the most effective remains the best guarantor for overall survival

Comments on the ACD: patient experts and groups

- The committee did not fully explore the place and performance of ponatinib. Joint societies submission reported that ponatinib outperforms all other TKIs in all lines of treatment other than first using the achievement of CCyR as a baseline
- The present recommendation disadvantages people in England (and potentially Wales) compared to Scotland
- Draw committee's attention to osimertininb where an ICER range of £41-£89k was accepted (CDF recommendation)

Comments on ACD: Professional societies

- The recommendation limiting ponatinib to CP-CML patients only with T315I is disappointing
  - numbers with CML currently excluded (and otherwise eligible) is low.
  - we risk their condition deteriorating, reducing their chance of survival and making it more difficult and costly to treat
  - T315I mutation is rare, and does not predict response to ponatinib. Most patients with the T315I were treated with ponatinib second line, which has been omitted from the decision making procress
- Bosutinib is not an appropriate comparator
  - It should be considered the same as the other 2nd gen TKI
  - No benefit in giving it to those suitable for ponatinib, as they will have received other 2nd gen TKIs
- Resistance and intolerance should be considered as different indications and the recommendations tailored accordingly

Comments on ACD: commentator – comparator company

- The results from the MAIC should be viewed with extreme caution when finalising rec's
  - PACE study patients heavily pre-treated with multiple TKIs
  - Only used patients with CP-CML where data was sufficient

Comments on ACD: company (1)

- PAS simple discount increased to provide access to the full indicated population
- This and new evidence to support company rationale and change committee preliminary ACD decision.

Comments on ACD: company (2)

- The company argue that the exponential is the most appropriate fit for PFS, the choice of the log normal is inappropriate and leads to implausible results where PFS in non responders is better than in those with complete haematological response. Data from the PACE study included in submission but not replicated here, confirm that that PFS in non-responders is worse than PFS among patients who achieved CHR on ponatinib

Comments on ACD: company (3)

- The ACD should mention the potential for lower ponatinib dosing with maintained response as per the new SmPC dosing guidance
  - Currently, Section 4.2 of the ACD refers to dose reduction to manage side effects, and Incyte believes that for completeness this section should also mention the new dosing guidance among patient with chronic phase CML who have achieved a MCyR

Comments on ACD: company (4)

- BSC should be considered the appropriate comparator in other patient populations in addition to the T315I positive group
  - There are 7 other BCR/ABL mutations (besides T315I +ve) which confer high to moderate resistance to bosutinib. In these patients ponatinib is the only effective treatment and BSC would be the most appropriate comparator – sect 4.23 and 4.30

Comments on ACD: company (5)

- Ponatinib is provided in tablet form not vial, wastage is not an issue.
  - Any missed doses will be taken later, suggest change wastage to adherence – 4.21
- Table 1, ICER range for ponatinib v bosutinib should be changed to £22,995 - £42,637
- Section 4.8, reference to an earlier push to prescribe ponatinib following failure of imatinib should be removed as it does not align with the SmPC

Comments on the ACD: company (6)

- In section 4.19, criticism that the company had not fully explored the effect of alternative distributions on the ICER is inaccurate
  - Ignores analyses carried out by company using Guyot methodology in response to the ERG clarification letter. These analyses improved the cost effectiveness results for ponatinib

Other comments on ACD: Factual changes

- 4.4 and 4.7 : clarifications on reduction in tumour load at 3 months, and on RQ-PCR
- 4.8: T315I –ve patients who fail imatinib would be offered at least one 2nd generation TKI, before ponatinib
- 4.11: Ignores evidence of the increased potency of ponatinib over bosutinib (to be presented at future British Society of Haematology meeting)
- 4.29: Suggested life expectancy of 4 years with no treatment in the appraised patients is not realistic

ERG additional analyses in CP-CML (calculated by ERG using PAS price for ponatinib)

Ref No	Exploratory Analyses	Pon vs Bos	Pon vs BSC	Pon vs allo-SCT
0	N/A (company's base case)	14,922	12,887	806
1a	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	10,387 – 37,401	9582 – 19,512	Dominant – 8416
1b	As 1a, but using the same distribution for DoR for ponatinib and bosutinib (range)	11,792 – 33,336	N/A	N/A
1c	As 1a, but solely using the company's exponential distribution for PFS in NR (range)	10,387 – 23,426	9582 – 18,463	Dominant – 8416
1d	Combining 1b and 1c	11,972 – 21,238	12,771 – 19,582	Dominant – 3624
2a	Recalculation of the survivor functions (excluding PFS exponentials)	13,010	11,320	Dominant
2b	As 2a, but use of the ERG's estimated exponential distribution for PFS in NR	13,603	12,384	Dominant
2c	As 2a, but use of the ERG's estimated exponential distributions for PFS for all response groups	14,566	12,906	Dominant
3	Assuming drug wastage	26,273	21,095	12,081
4	Including a 3 month stopping rule for bosutinib	21,313	15,200	4042

ERG's additional analyses in CP-CML (calculated using updated PAS for ponatinib)

Ref No	Exploratory Analyses	Pon vs Bos	Pon vs BSC	Pon vs allo-SCT
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) As 11a, but assuming the same distribution for Duration of response for ponatinib and bosutinib (range) **As 11a, but assuming an exponential distributions for PFS (range)**	16,959 – 45,896 19,680 – 37,381 18,987 – 31,377	 N/A 17,297 – 23,945	N/A 20,634 – Dominated

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ERG's exploratory deterministic analyses in AP-CML
(calculated by ERG using updated PAS price for ponatinib, comparator list prices)

		Cost per QALY gained (£) – Ponatinib vs	
Ref No	Exploratory Analyses	BSC	Allo-SCT
0	N/A (company's base case)	14,590	12,996
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	7350 – 15,703	Dominant – 94,062
2	Recalculation of the survivor functions	10,215	11,985
3	Assuming drug wastage	15,061	13,832
4	No half-cycle correction of intervention costs	16,251	15,880
5	Including treatment-related deaths	14,584	12,377
6	Assuming life table data are probabilities not rates	14,594	13,003
7	2,3, 4, and 6 using the curves believed most credible by the company	12,590	15,787
8 ERG base case ICER	As 7, but choosing alternative distributions in addition to those selected by the company (range)	7123 – 17,625	Dominant – 61,896

ERG's exploratory deterministic analyses in BP-CML
(calculated by ERG using updated PAS price for ponatinib, comparator list prices)

		Cost per QALY gained (£)	
Ref No	**Exploratory Analyses**	**Ponatinib vs bosutinib**	**Allo-SCT vs Ponatinib**
0	N/A (company's base case)	17,130	Dominated
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	10,873 – 18,330	8604 - Dominated
2	Recalculation of the survivor functions	15,401	159,990
3	Assuming drug wastage	17,476	Dominated
4	Incorporating a three-month stopping rule for bosutinib	21,440	N/A
5	No half-cycle correction of intervention costs	17,263	Dominated
6	Including treatment-related deaths	16,174	Dominated
7	Assuming life table data are probabilities not rates	17,131	Dominated
8	2,3, 4,5, and 7 using the curves believed most credible by the company	20,107	110,415
9 ERG base-case ICER	1,2,3, 4,5, and 7 (range)	16,209 – 21,404	5053 - Dominated

ERG's additional analyses (updated ponatinib PAS price): Ph+ ALL

For whom allo-SCT is suitable		Cost per QALY (£)	
Ref No	Exploratory Analyses	P vs induction chemotherapy	P vs BSC
	Company deterministic base case	29,812	26,319
1	Recalculation of the OS post allo-SCT curve	54,615	52.949
2	Choosing alternative distributions in addition to those selected by company, using the company's fits (range)	22,840 – 51,337	19,694 – 31,577
3	Assuming drug wastage	31,062	26,610
4	No half-cycle correction of intervention costs	41,293	28,992
5	Including treatment related deaths	26,739	25,524
6	Removal of immortality for a small subset of patients	30,523	26,653
7a	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the ponatinib value	Dominant	12,661
7b	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the BSC value	Dominant	18,690
8	1, 3,4 and 6 using the curves believed most credible by the company	84,570	61,273
9	1, 3,4, 6 and 7a using the curves believed most credible by the company	4138	29,995
10 ERG	As 9, but choosing alternative distributions in addition to those selected by the company (range)	Dominant - 4138	7156 – 29,995

ERG's additional analyses (updated ponatinib PAS price): Ph+ ALL

For whom allo-SCT is unsuitable		Cost per QALY (£)
Ref No	Exploratory Analyses	Ponatinib vs BSC
0	Company Base Case	31,210
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	24,790 – 33,105
2	Assuming drug wastage	33,826
3	No half-cycle correction of intervention costs	44,031
4	Including treatment related deaths	27,489
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	47,884
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 to Dominant

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- Appropriateness of matching adjusted indirect comparison (MAIC) undertaken by the company
- Choice of curve of best fit for progression free survival (extrapolation)
- Uncertainty around the ICER value (ranges presented based on choices of curves of best fit and other scenarios)
- Company's new evidence – updated PAS