NICE National Institute for Health and Care Excellence

Public observer slides – fully redacted

Asciminib for treating chronic myeloid leukaemia after 2 or more tyrosine kinase inhibitors [ID3813]

Lead team presentation

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Company: Novartis

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Chronic myeloid leukaemia

- CML is a rare form of cancer, characterised by proliferation of myeloid cells in bone marrow and subsequent release into peripheral blood. Defined by presence of Philadelphia chromosome (Ph). The molecular consequence is activation of multiple signal-transduction cascades driving growth and differentiation of haematopoietic cells
- Symptoms include weight loss/loss of appetite, splenomegaly (increased spleen size), skin rash, anaemia, sweating, drowsiness, abdominal fullness, sleep disturbances, muscle soreness/cramping and memory loss/difficulty remembering
- 720 new cases each year in England
- CML is classified into 3 phases; chronic phase (CP), accelerated phase (AP), or blast phase (BP)
  - at diagnosis, 90–95% present in CP. If CP not treated successfully, it can progress to AP and may be followed by BP, where survival is poor
  - typical disease course from CP to AP & BP without treatment is 3.5–5 years
  - Asciminib expected to be used in the chronic phase of CML
- Estimated 5-year survival for CML in England for men is 70% and women is 75%
- TKIs have improved survival in CML, with people in CP having a 2-year survival of 98%
- While allo-SCT is potentially curative, it is not a therapeutic option for a majority of people due to patient/disease characteristics

allo-SCT: allogenic stem cell transplant; CML: chronic myeloid leukaemia; TKI: tyrosine kinase inhibitor

Asciminib (Scemblix, Novartis)

Anticipated marketing authorisation	[redacted] MHRA has granted positive scientific opinion on use of asciminib as 3rd-line treatment option for adults with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) **without T315I mutation** under the UK Early Access to Medicines Scheme (EAMS)
Mechanism of action	BCR-ABL1 inhibitor
Administration	Oral tablet. Taken twice daily without food. Food consumption should be avoided for ≥2 hours before and 1 hour after administration
Price	40mg, 60-tablet pack list price: [redacted] Annual cost at list price: [redacted] A confidential patient access scheme for asciminib has been agreed

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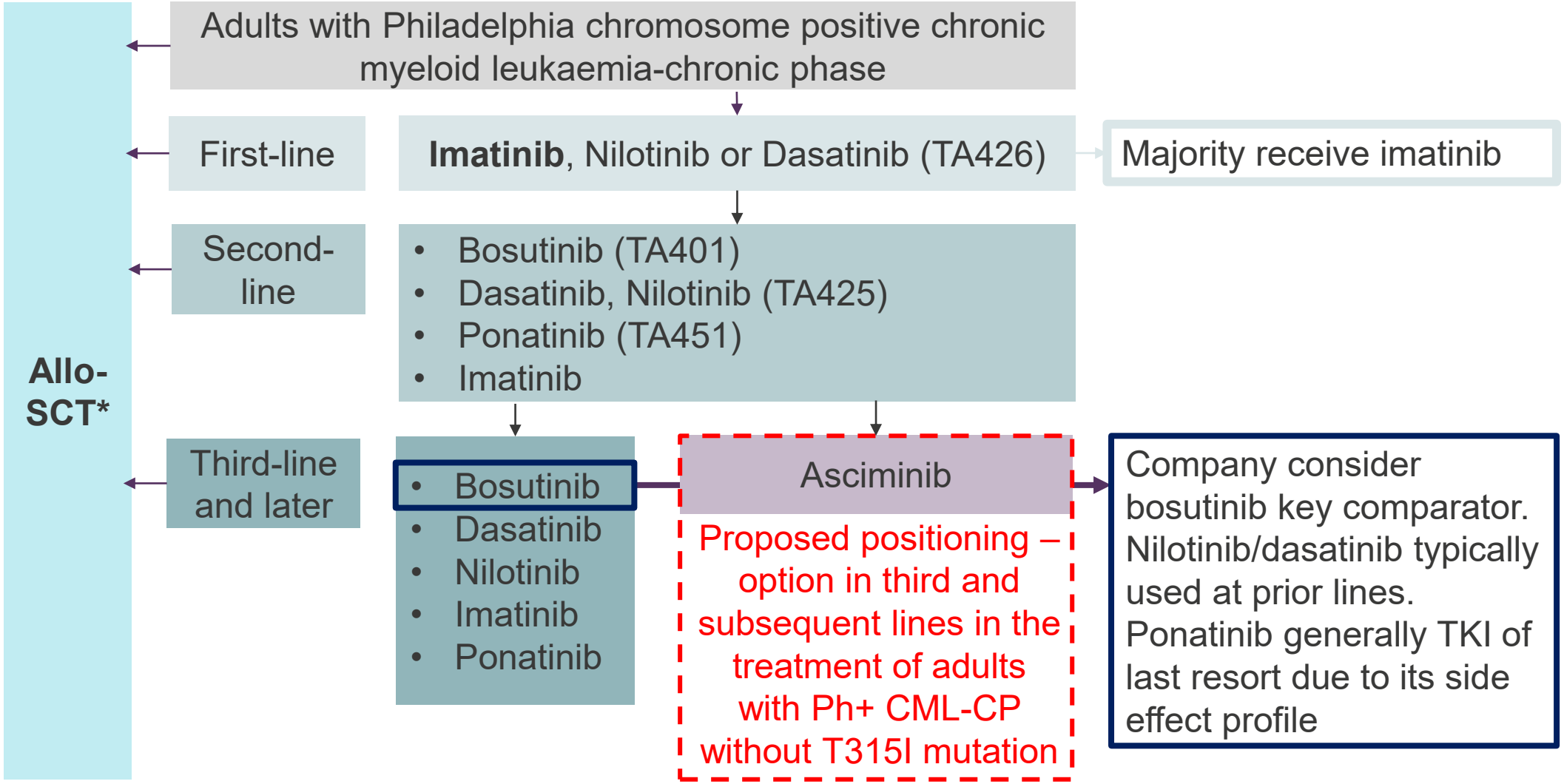
BCR: breakpoint cluster region protein

Treatment pathway & proposed position



* allo-SCT likely treatment of last resort for subset of fitter and younger patients, therefore exclusion of allo-SCT as a comparator is likely to be appropriate

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Allo-SCT: allogeneic stem cell transplantation; Ph+ CML-CP: Philadelphia chromosome positive chronic myeloid leukaemia-chronic phase; TKI: tyrosine kinase inhibitor

Patient expert perspectives

Submissions from The Chronic Myeloid Leukaemia Support Group and Leukaemia Care and Patient with Lived Expertise

- CML has a significant impact on quality of life of patients, their families and carers
- Symptoms and side-effects of treatment impact every day life
- Substantial psychological impact and impact on work or education
- CML treatment revolutionised by TKIs
- Once an appropriate and functioning TKI is identified, a patient can live a normal, productive and fulfilling life
- A minority for whom all existing TKIs prove to be either ineffective or not tolerated
- Treatment is focused on achieving 3 things:
  1. Survival and avoiding disease progression
  2. Avoiding stem cell transplant
  3. As few side effects as possible

"Living with CML can be debilitating, which leads to reduced quality of life for many patients"

"Asciminib provides the potential for a TKI which has a novel mode of action"

"CML diagnosis can have a ripple effect on family members and friends of the patient"

"[It's] 5 years since I began my treatment with Asciminib… My condition is stable… and there no signs of any relapse or deterioration. For the last 5 years, my wife and young children have had the benefit of a pretty normal life with their father…[I'm at work…having avoided] the draconian alternative of transplant surgery with all of the accompanying risk factors and inevitable cessation of work and major disruption to family life."

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CML: chronic myeloid leukaemia; TKI: tyrosine kinase inhibitor

Clinical expert perspectives

Submissions from British Society of Haematology, Royal College of Pathologists, Royal College of Physicians

- 5 TKIs currently available to treat CML
- All current TKIs are inhibitors of ATP binding site of BCR-ABL → risk of resistance from the same mutations or compound mutations
- Approximately 75-80% of people respond satisfactorily to imatinib/nilotinib/dasatinib and achieve complete cytogenetic responses. The remaining 25% either cannot tolerate them due to side effects and toxicity, or are refractory to TKIs and fail to achieve adequate responses
- Asciminib is allosteric inhibitor of BCR-ABL so binds to a different part of the BCR-ABL molecule → resistance profile is different
- Asciminib has a favourable safety profile, which may improve QoL compared to existing approved TKIs

"Asciminib works in a slightly different way and appears to have a favourable safety profile compared to existing 2nd and 3rd generation TKIs"

ATP: adenosine triphosphate; BCR: breakpoint cluster region protein; CML: chronic myeloid leukaemia; QoL: quality of life; TKI: tyrosine kinase inhibitor

Key issues

Key issues		Status	Impact
1	No evidence in T315I mutation	**Resolved: T315i mutation not included**	
2	Concerns with ASCEMBL trial	**Resolved: bias in TTD likely to be small**	
3	Lack of evidence on survival outcomes	**Resolved with uncertainty: no evidence asciminib inferior to bosutinib**	
4 & 6	TTD to inform the economic analysis and model structure	**For discussion**	
5	Limitations of MAIC analysis	**For discussion**	
7	Removal of retreatment	**Resolved with uncertainty: remove retreatment with primary TKI treatment**	
8	Extrapolation of TTD	**Resolved: use of log-logistic**	
9	Duration of post-discontinuation survival	**For discussion**	
10	SCT survival	**Resolved with uncertainty: Use of Niederwieser 2021**	
11	Age-adjusted utilities	**Resolved: multiplicative approach**	
12	Comparator dosing	**Resolved: use company TE approach**	

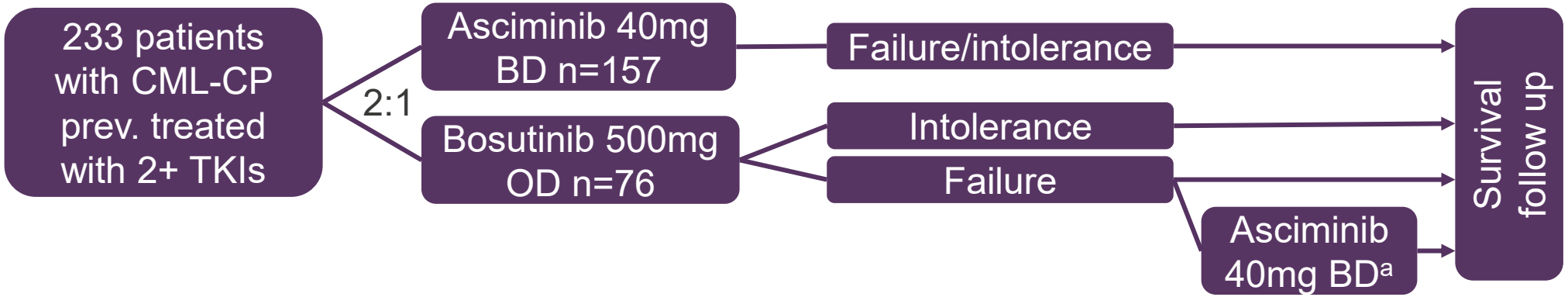
NICE  **Model driver**  **Unknown impact**  **Small impact**

MAIC: matched adjusted indirect comparison; TTD: time to treatment discontinuation

Key clinical trial - ASCEMBL

- ASCEMBL is currently ongoing (a 96-week analysis is expected in Quarter 2 2022)

	ASCEMBL (n=233) open-label (not-blinded), randomised trial
Population	Adult patients with Ph+ CML-CP previously treated with ≥ 2 TKIs
Intervention	Asciminib (40 mg twice a day) (n=157)
Comparator	Bosutinib (500 mg once a day) (n=76)
Primary outcome	MMR rate at 24 weeks (data cut-off: 25th May 2020)
Key secondary outcome	MMR rate at 96 weeks while on study treatment without meeting any treatment failure criteria (only 24 & 48 weeks presented)
Other secondary outcomes	Additional MMR outcomes, cytogenic response, time to treatment failure (TTF), progression free survival (PFS), OS, and safety



[a] efficacy data collected after patients switching to asciminib following bosutinib failure were analysed separately as exploratory endpoints and not included for primary and secondary study endpoints

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BD: twice daily CML-CP: chronic myeloid leukaemia chronic phase; MMR: major molecular response; OD: once daily; OS: overall survival; TKI: tyrosine kinase inhibitor

ASCEMBL clinical evidence

Outcome	Asciminib 40 mg BD (N=157)	Bosutinib 500 mg OD (N=76)
CCyR, n (%)	24 wks: 42 (40.78) 48 wks: [redacted]	24 wks: 15 (24.19) 48 wks: [redacted]
PFS, % (95% CI)	48 wks: [redacted]	48 wks: [redacted]
OS, % (95% CI)	48 wks: [redacted]	48 wks: [redacted]
MMR, n (%)	24 wks: 43 (27.39); 48 wks: [redacted]; 60 wks: [redacted]	24 wks: 11 (14.47); 48 wks: [redacted]; 60 wks: [redacted]
TTD, % event free (95% CI)	48 wks: [redacted]	48 wks: [redacted]

Used in cumulative survival model

Used in surrogate survival model

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CCyR: complete cytogenic response; CI: confidence interval; MMR: major molecular response; OS: overall survival; PFS: progression free survival; wks: weeks

Matching-Adjusted Indirect Treatment Comparison

- Unanchored MAIC conducted to compare TTD for asciminib vs ponatinib, nilotinib and dasatinib. TTD main focus as it is used to estimate OS in cost-effectiveness analysis

MAIC included studies

Comparator	Outcome	Study
Ponatinib	TTD/response	[redacted]
Nilotinib	TTD	[redacted]
Dasatinib	TTD	[redacted]

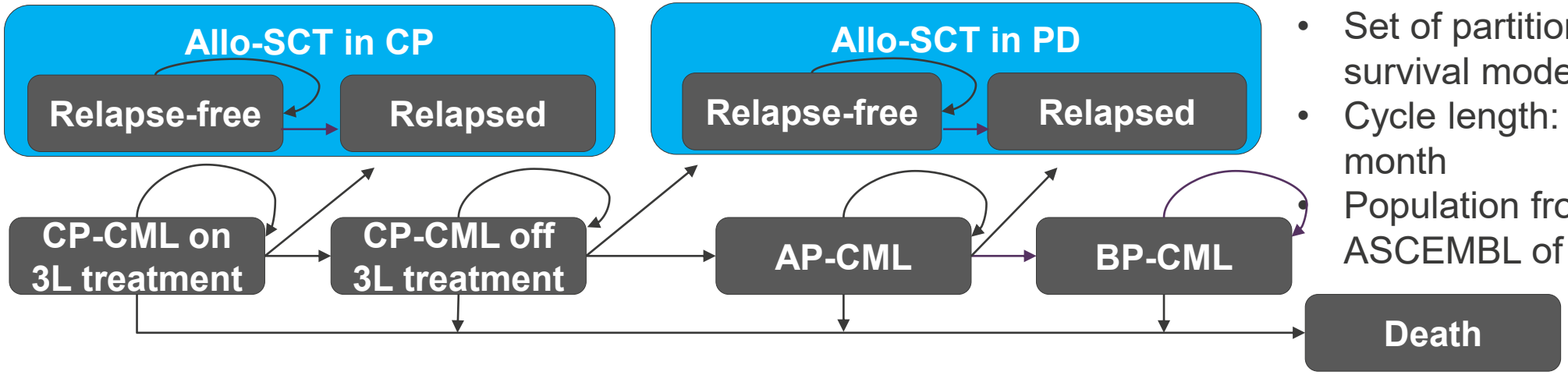
MAIC results

Comparator	Median TTD (months)	Asciminib unadjusted median TTD (months)	Asciminib adjusted median TTD (months)
Ponatinib	32.1	[redacted]	[redacted]
Nilotinib	11	[redacted]	[redacted]
Dasatinib	14	[redacted]	[redacted]

- Company also submitted anchored MAIC comparing ASCEMBL to HMRN data as requested by ERG
- Limitations of the MAIC are discussed in key issue 5 on slides 17 – 19

HMRN: Haematological Malignancy Research Network; MAIC: matching-adjusted indirect treatment comparison; OS: overall survival; TTD: time to treatment discontinuation

Company's model structure – cumulative survival approach



- Set of partitioned survival models
- Cycle length: 1 month
- Population from ASCEMBL of 3L+

- People who do not have allo-SCT, captures progression of CML through 3 main phases: CP (on/off treatment), AP and BP
- State occupancy determined by a series of partitions derived from TTD curve
- Proportion of patients in CP is based on TTD curves
- Assume fixed 7-year survival after discontinuation of third-line treatment (OS = cumulative TTD + 7-year post-progression survival). In 7 years, 10 months in AP and 6 months in BP
- People who have allo-SCT → at discontinuation of therapy or progression to AP or BP
- In response to clarification, the company presented an alternative model structure, surrogate survival approach, based on model used in TA451 (ponatinib)

3L: third-line treatment; Allo-SCT: allogeneic stem cell transplantation; AP: accelerated phase; BP: blast crisis phase; CP: chronic phase; CML: chronic myeloid leukaemia; PD: progressed disease; TTD: time to treatment discontinuation; TKI: tyrosine kinase inhibitor.

Unresolved issues after technical engagement

Model driver
Unknown impact
Small impact

Issue	Impact	Question for committee
4 and 6. TTD as a measure of effectiveness and model structure		• Is the cumulative survival approach or surrogate survival approach preferred? Or should both approaches be considered in decision making?
5. Limitations of the MAIC analyses		• Is the MAIC analysis provided by the company appropriate for decision making?
9. Post-discontinuation survival		• Is 7 years or 10.1 years an appropriate post-discontinuation survival estimate?
Other considerations		• Are there any equality considerations? • Is asciminib innovative?

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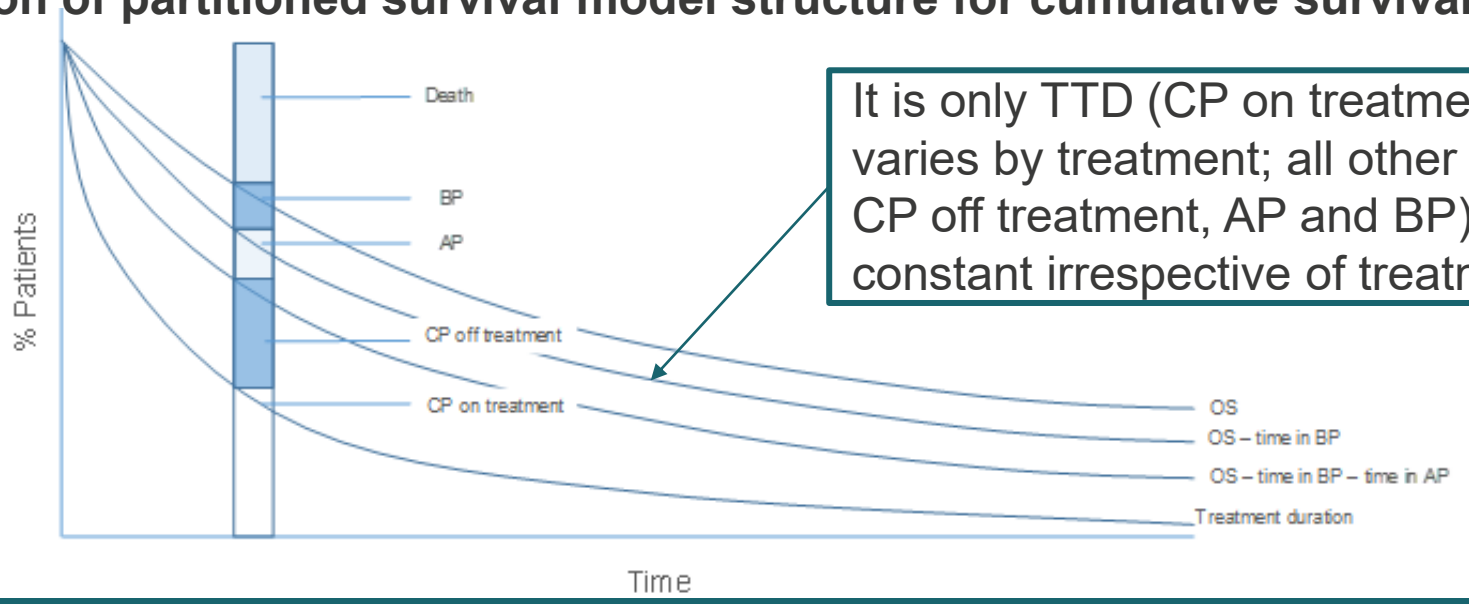
MAIC: matched adjusted indirect comparison; TTD: time to treatment discontinuation

Issues 4 and 6: Use of TTD and model structure [1]

Background

- Original submission based on "cumulative survival approach" – PSM-based model using TTD curves with 7 years post-discontinuation survival. OS and PFS trial evidence immature and insufficient to inform long-term disease progression and survival outcomes. Therefore company's indirect comparisons with other TKIs and economic model rely heavily on TTD
- Following ERG request at clarification, company presented a second model, the "surrogate survival approach" – PSM-based model where the duration of PFS is modelled as a function of cytogenetic and haematological response

Illustration of partitioned survival model structure for cumulative survival approach



It is only TTD (CP on treatment) which varies by treatment; all other stages (e.g. CP off treatment, AP and BP) remain constant irrespective of treatment selected

AP: accelerated phase; BP: blast phase; CP: chronic phase; OS: overall survival; PFS progression free survival; PSM: partitioned survival model; TTD: time to treatment discontinuation; TKI: tyrosine kinase inhibitor

Issues 4 and 6: Use of TTD and model structure [2]

Stakeholder technical engagement response

- TTD accounts for stopping treatment for lack of efficacy and poor tolerability – remaining on treatment implies responding and tolerating treatment
- Although not ideal and both models have advantages and disadvantages, cumulative survival model seems acceptable → TTD a good surrogate for survival

Cumulative survival approach (company)	Surrogate survival approach (ERG)
Plausible relationship between duration of response and duration of treatment	Response-based approach substantively more grounding in literature
Lack of evidence for TTD as a measure of effectiveness and linking TTD with PFS and OS	Clearer value as a clinical outcome
Concerns about validity of comparing TTD across studies	Immature evidence from 2nd line population, may be optimistic estimate in 3rd line
Previous NICE appraisals - TA401 and TA426 used cumulative survival approach. Issues with surrogate relationship between MCyR and OS	Most recent previous appraisal - TA451 (ponatinib) used a surrogate survival approach

- Both approaches introduce structural uncertainty. Results from both models broadly consistent with regard to bosutinib

MCyR: major cytogenic response; OS: overall survival; PFS progression free survival; PSM: partitioned survival model; TTD: time to treatment discontinuation

Issues 4 and 6: Use of TTD and model structure [3]

ERG comments

- Differences in TTD between TKIs could be confounded by a number of factors, including availability of other subsequent treatments
- TTD may not be a suitable surrogate for response or survival outcomes → inappropriate choice of outcome for indirect comparison.
- Outcomes that are more robust and relevant should be of interest, including response outcomes (MMR, CCyR) and survival outcomes (OS, PFS)
- ERG acknowledges that this remains a finely balanced decision, but the two principal advantages of surrogate survival approach remain: i) That response is an objective and widely accepted measure of clinical benefit in CML, and ii) That evidence supports the surrogate value of response in a CML population

Is the cumulative survival approach or surrogate survival approach preferred? Or should both approaches be considered in decision making?

CCyR: complete cytogenic response; CML: chronic myeloid leukaemia; MMR: major molecular response; OS: overall survival; PFS progression free survival; TTD: time to treatment discontinuation; TKI: tyrosine kinase inhibitor

Issue 5: Limitations of the MAIC [1]

Background

- Company performed MAIC analysis to compare asciminib to other interventions not included in ASCEMBL (e.g. dasatinib, nilotinib, ponatinib)

ERG comments

ERG concern with MAIC	Company TE response
Excluded comparator studies	Bosutinib studies single arm. Excluded due to small size, inappropriate comparator/population, or lack of baseline data
No comparison with HMRN	Comparison with HMRN – For TTD, asciminib offered [redacted] compared to bosutinib in majority of unadjusted and adjusted comparisons. Results provide further evidence of the effectiveness of asciminib
Limited set of variables adjusted for	Not possible to adjust for all variables identified as potentially prognostic. Prioritised to include the most influential variables
Limited or incomplete reporting of outcomes	OS and PFS immature in ASCEMBL. Considered insufficient to support comparison with published studies
Reporting of relative estimates of effectiveness	Reporting of the results of the MAIC was limited to Kaplan-Meier curves for TTD before and after weighting

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CCyR: complete cytogenic response; HMRN: Haematological Malignancy Research Network; MAIC: matched adjusted indirect comparison; MMR: major molecular response; TTD: time to treatment discontinuation

Issue 5: Limitations of the MAIC [2]

Company comments

Time to treatment discontinuation for unadjusted and population-matched asciminib (ASCEMBL) vs dasatinib (HMRN) and common comparator arm (bosutinib)

MAIC: matched adjusted indirect comparison; TTD time to treatment discontinuation

Issue 5: Limitations of the MAIC [3]

ERG comments post technical engagement

- Trials included in MAIC likely to be only trials for which a robust MAIC could be performed → only 1 trial per comparator, so robustness of the MAICs to different trials and their varying characteristics cannot be assessed
- Company MAIC analyses demonstrates TTD with asciminib appears superior to nilotinib and dasatinib, but slightly inferior to ponatinib
- Concerns using TTD in MAIC analyses due to:
  - potential for subjective grounds for discontinuation
  - reasons for discontinuation may not be consistent across trials
  - the substantial difference between results in ASCEMBL and HMRN
  - the consequent large differences between anchored and unanchored MAIC analyses
  - inconsistency with results for MMR → in response to TE, company provided MAIC for MMR. When asciminib and dasatinib were indirectly compared, there was [redacted] between odds of experiencing MMR by 6 months
- Remains no conclusive evidence to demonstrate any difference in effectiveness between asciminib and dasatinib, nilotinib or ponatinib
- ERG's concerns regarding robustness and completeness of indirect comparisons remain

Is the MAIC analysis provided by the company appropriate for decision making?

MAIC: matched adjusted indirect comparison; MMR; major molecular response; TE: technical engagement; TTD time to treatment discontinuation

Issue 9: Duration of post-discontinuation survival [1]

Background

- OS in the cumulative survival model is based on TTD plus an additional 7 years
- 7 years survival post-discontinuation based on ERG estimates of mean OS from TA401

ERG comments

- Acknowledge precedent for 7 years but substantive concerns regarding the data
- OS was in people who did not receive SCT or TKI following imatinib discontinuation
- Subsequent treatments included tipifarnib; hydroxyurea; lonafarnib; decitabine; cytarabine; homoharringtonine and interferon-α, which no longer represent practice in the UK and are not included in the current NICE treatment pathway
- Estimates overly pessimistic given changes to pathway and improvements in care
- HMRN reports [redacted] of fourth-line patients alive at 5 years. Median therefore still yet to be reached at 60 months and assuming 50% median survival of 5 years implies that mean OS is likely to be greater than 7 years
- Similar evidence from PACE, 73% 5-year OS, suggesting median OS over 5 years
- Likely post-discontinuation survival >7 years

OS: overall survival; PFS: progression free survival; SCT: stem cell transplant; TKI: tyrosine kinase inhibitor; TTD: time to treatment discontinuation

Issue 9: Duration of post-discontinuation survival [2]

Company comments

- Digitised KM curve from HMRN (n=48)
- Considered all estimates overly optimistic as higher than clinical opinion (range of mean OS [redacted])

Stakeholder technical engagement response

- Subject to substantial uncertainty
- 7 years seems very modest figure. Whilst median OS of 14-19 years, as suggested by the ERG on the extrapolated ponatinib data from PACE seems very optimistic
- 7 years reasonable for people resistant to TKIs. Survival in people intolerant to TKIs will be higher, as they will encounter a TKI that they are able to take on a daily basis

HMRN: Haematological Malignancy Research Network; KM: Kaplan–Meier; OS: overall survival

Issue 9: Duration of post-discontinuation survival [3]

ERG comments post technical engagement

- Clinical opinion on this issue is somewhat divided
- 2 sources of evidence (HMRN and PACE) seem to support a longer period of post-discontinuation survival
- ERG favours 10.1 years post-discontinuation survival - lies in overlap of predicted OS from both sources and is most conservative extrapolation based on OS evidence from PACE

Undiscounted predicted LYs from the model for each comparison with 7 or 10.1 years post-discontinuation survival

Asciminib comparison	Including SCT				Excluding SCT			
	Asciminib LYs		Comparator LYs		Asciminib LYs		Comparator LYs	
	7 yrs	10.1 yrs	7 yrs	10.1 yrs	7 yrs	10.1 yrs	7 yrs	10.1 yrs
vs bosutinib	14.52	16.43	11.88	13.99	12.54	14.92	9.4	12.17
vs ponatinib	11.83	13.97	12.91	15	9.36	12.13	10.7	13.32
vs nilotinib	12.54	14.364	11.01	13.17	10.24	12.91	8.32	11.2
vs dasatinib	12.39	14.51	11.29	13.44	10.06	12.75	8.67	11.51

Is 7 years or 10.1 years an appropriate post-discontinuation survival estimate? This only applies to the cumulative survival model (company preferred)

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HMRN: Haematological Malignancy Research Network; OS: overall survival; SCT: stem cell transplant TKI: tyrosine kinase inhibitor; yrs: years

Other considerations

Equality considerations

Comments from patient and clinical expert submissions

- The approval of this technology would allow more tolerable and effective treatment options to be made available for older / unfit patients and those from ethnic minorities who are currently unable to benefit from the potential existing alternative treatment which is allogeneic haemopoietic stem cell transplantation.

Innovation

Comments from company, patient and clinical expert submissions

- Asciminib, with a novel mode of action, presents the possibility of a new and effective TKI therapy for patients for whom existing TKIs are either ineffective, or not sufficiently effective, or to which they are intolerant

End of life

- End of life criteria are not met

Is asciminib considered innovative? Are there any potential equalities issues?

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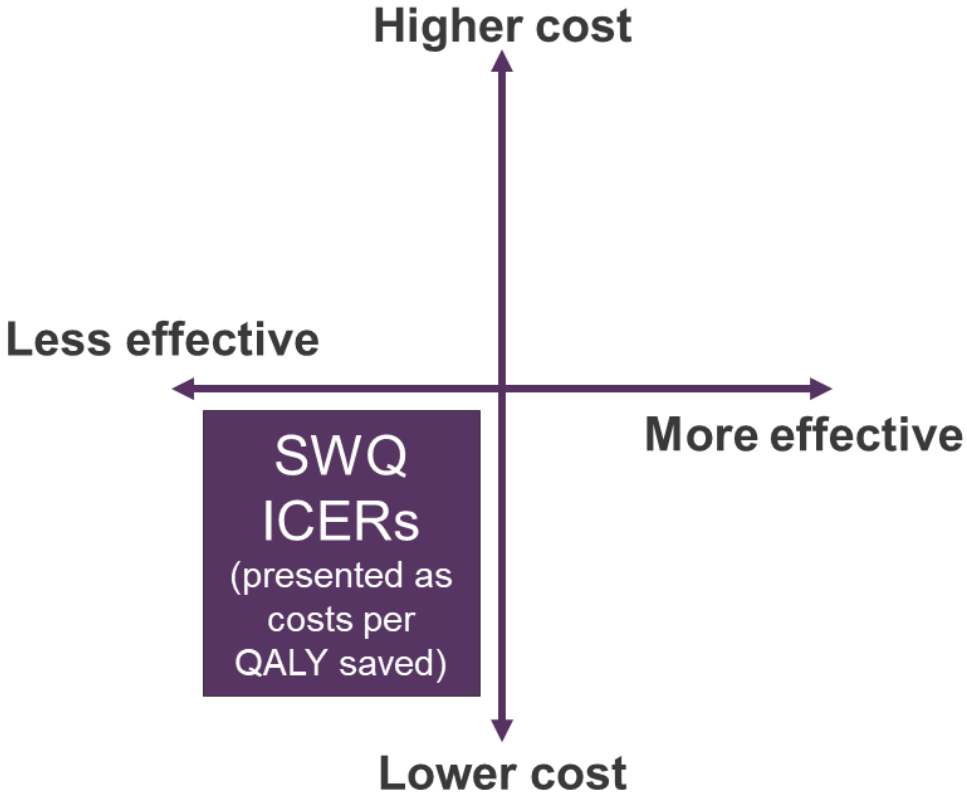
TKI: tyrosine kinase inhibitor

Decision-making with south west quadrant ICERs

- South-west quadrant ICERs are presented as costs saved per QALY lost.
- The higher the ICER, the more cost is saved per QALY lost, so high ICERs are better here and the commonly assumed decision rule of accepting ICERs below a given threshold is reversed
- Positive recommendations are made when the costs saved are sufficient to cover the QALY loss. Usually, SWQ ICERs have led to positive recommendations when ICERs are substantially above £30,000 per QALY lost.



ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life years; SWQ: south-west quadrant

Company updated base case (deterministic)

- **After technical engagement**
- **See part 2 slides for decision making ICERs with comparator commercial discounts**
- Probabilistic ICERs are similar to deterministic
- Base-case includes:
  - asciminib PAS price
  - removal of retreatment (key issue 7 - resolved)
  - log-logistic model to extrapolate TTD (key issue 8 – resolved)
  - Niederwieser 2021 for stem-cell transplant survival (key issue 10 – resolved)
  - multiplicative adjustment model for age adjusted utilities (key issue 11 - resolved)
  - 53.3% of people reduce ponatinib dose to 15 mg at 12 months (key issue 12 - resolved)
  - **cumulative survival model (key issue 4 and 6)**
  - **7 years post-discontinuation survival (key issue 9)**

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Asciminib vs bosutinib	£7,549	1.33	**£5,659**
Asciminib vs ponatinib	-£61,154	-0.55	**£111,470***
Asciminib vs nilotinib	-£2,803	0.91	**Dominant**
Asciminib vs dasatinib	-£9,970	0.61	**Dominant**

*ICER falls in the south-west quadrant of the cost-effectiveness plane (i.e. less costly and less effective). An increase in the ICER means asciminib becomes, relatively speaking, more cost-effective.

ERG base case (deterministic)

- Following Technical Engagement, the updated ERG base-case retains majority of the same assumptions as the company base-case with the exception of:
  - **Surrogate survival model (key issue 4 and 6) and therefore no post-discontinuation survival assumption (key issue 9)**

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG base case			
Asciminib vs bosutinib	-£3,840	1.07	**Dominant**
Asciminib vs ponatinib	-£43,767	-0.18	**£240,186***
Asciminib vs nilotinib	£61,873	2.29	**£27,016**
Asciminib vs dasatinib	£66,669	2.18	**£30,538**

*ICER falls in the south-west quadrant of the cost-effectiveness plane (i.e. less costly and less effective). An increase in the ICER means asciminib becomes, relatively speaking, more cost-effective.

ERG scenario analysis

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Scenario 1: ERG base case assuming equivalence between asciminib and ponatinib; and equivalence between bosutinib, nilotinib and dasatinib			
Asciminib v ponatinib	-£23,397	-0.07	**£348,379***
Asciminib vs nilotinib	£55,235	2.32	**£23,816**
Asciminib vs dasatinib	£63,222	2.24	**£28,163**
Scenario 2: company revised base case + post-discontinuation survival of 10.1 years			
Asciminib vs bosutinib	£4,644	1.16	**£3,998**
Asciminib vs ponatinib	-£48,618	-0.48	**£101,733***
Asciminib vs nilotinib	-£15,992	0.81	**Dominant**
Asciminib vs dasatinib	-£14,920	0.54	**Dominant**

- Scenario 2 has been included as post-discontinuation survival assumption does not impact the surrogate survival model (ERG-preferred approach) but does impact the cumulative survival model (company-presented approach)

*ICER falls in the south-west quadrant of the cost-effectiveness plane (i.e. less costly and less effective). An increase in the ICER means asciminib becomes, relatively speaking, more cost-effective.

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ICER: incremental cost-effectiveness ratio

Part 2

- ICERs include a confidential commercial arrangement for comparators bosutinib, ponatinib, nilotinib and dasatinib – provided to committee in part 2 (private) part of the committee meeting