NICE National Institute for Health and Care Excellence

PART 1

Slides for public observers

Gilteritinib for treating relapsed or refractory acute myeloid leukaemia

Lead team presentation

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Company: Astellas
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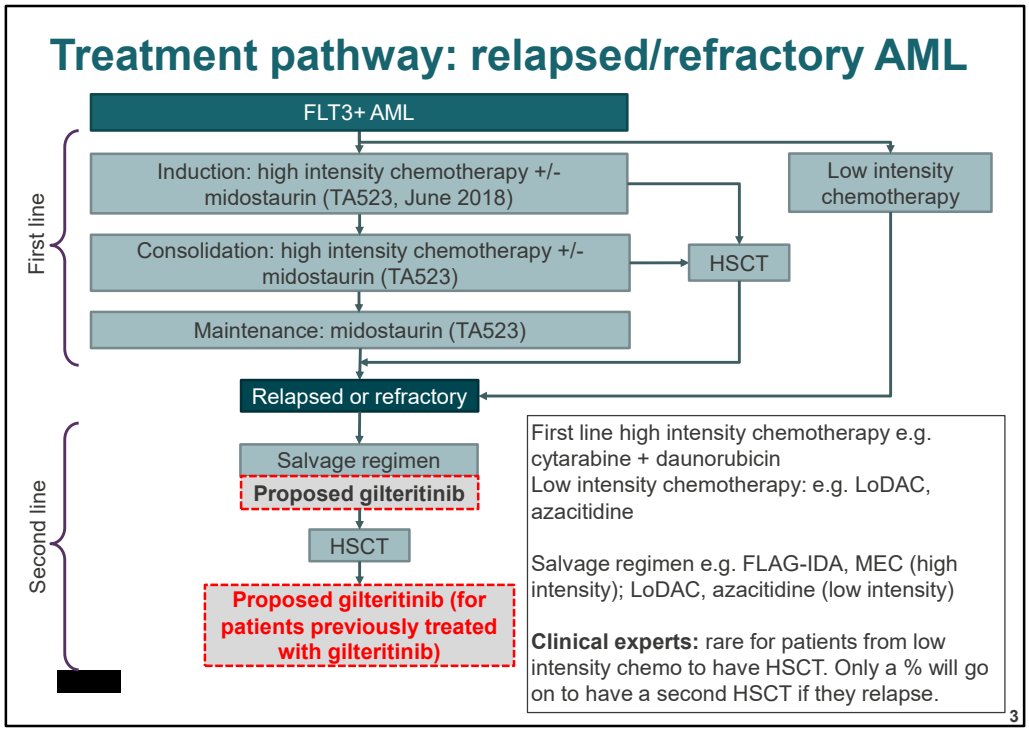
Gilteritinib

Marketing authorisation	Gilteritinib as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation
Mechanism of action	Tyrosine kinase-3 (FLT3) and AXL inhibitor
Administration	Oral tablet
Price	List price: £14,188 per 28-day pack. The average cost of a course of treatment of gilteritinib is anticipated to be [redacted] per patient (at list price) A patient access scheme has been agreed.

[redacted]



Notes

- Based on recommendations of European LeukemiaNet
- IDAC, intermediate-dose cytarabine; Allo, allogenic; Auto, autologous; HSCT, haematopoietic stem cell transplant; MEC, mitoxantrone, etopside and intermediate-dose cytarabine; FLAG-Ida, fludarabine, cytarabine and granulocyte-colony stimulating factor with idarubicin.

Background

Comparators	Salvage chemotherapy, BSC
Clinical trial	ADMIRAL (n=371). Open-label, randomised trial comparing gilteritinib and salvage chemotherapy
Key results	Statistically significant improvement in OS Gilteritinib: 9.3 months, salvage chemo: 5.6 months HR: 0.64 (95%CI 0.49, 0.83)
Comparison with BSC	Naive indirect comparison
Key result	HR 2.86 applied to gilteritinib OS. But very uncertain due to several issues with methods.
Model	Decision tree followed by a partitioned survival-based model. 3 health states: pre-progression, post-progression, death for patients who have HSCT and do not have HSCT
Company revised ICER	£43,346/QALY gained
Technical team preferred ICER	£98,324/QALY gained
ICER ranges across plausible scenarios	£50,897/QALY gained to £102,085/QALY gained

[redacted]

Patient and carer perspectives

- AML is a rapidly progressing disease. Patients with a FLT3 mutation know that they're more likely to relapse and to relapse quicker.

> "If I had more energy, I'd be chasing joy. As things are, I'm spending time managing my pennies and my anxiety."

- Leukaemia Care's survey: patients with relapsed or refractory AML want new treatments that deliver longer survival and good QoL.
- AML patients want a treatment plan that is based around their life goals and treatment preferences. A key need is to understand remaining life expectancy v the time to benefit.

> "There's more to life than survival."

- Current option is salvage chemotherapy with the backbone of best supportive care.
- Gilteritinib is self-managed and allows people to remain at home with a weekly visit to the hospital v the disruption and loss of autonomy of in-hospital treatment.
- Being at home is valuable to patients, their friends and families

Clinical evidence

	ADMIRAL (n=371) Open-label, randomised trial
Population	Adults with relapsed/refractory FLT3 mutation positive AML
Intervention	Gilteritinib 120mg/day
Comparator	Salvage chemo – investigator's choice (LoDAC, azacitidine, MEC, FLAG-Ida)
Primary outcomes	OS, CR/CRh
Secondary outcomes	EFS, LFS, duration of remission

Abbreviations: CR complete remission, OS overall survival, LFS leukaemia-free survival, CR/CRh complete remission and complete remission with partial haematological recovery, EFS event-free survival

ADMIRAL	Median		HR vs salvage chemo	p value
	Gilteritinib monotherapy	Salvage chemotherapy		
Overall survival	9.3 months	5.6 months	0.64 (95%CI 0.49, 0.83)	p<0.001
CR/CRh	34.0%	15.3%	-	p<0.001

CR/CRh: Complete remission or complete remission with partial haematological recovery

[redacted]

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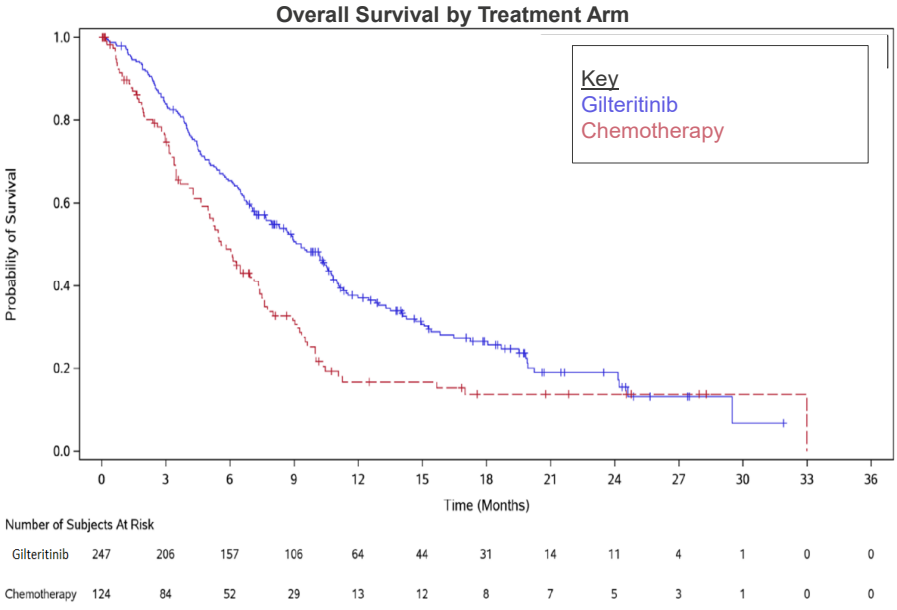
Key clinical trial results - ADMIRAL



Number of Subjects At Risk

Gilteritinib	247	206	157	106	64	44	31	14	11	4	1	0	0
Chemotherapy	124	84	52	29	13	12	8	7	5	3	1	0	0

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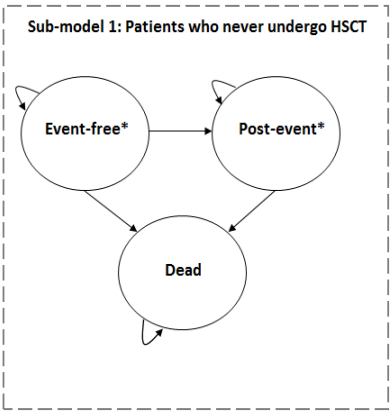
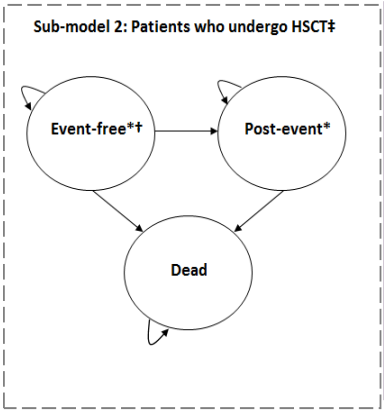
Company's model structure





- 1 month cycle length
- Lifetime time horizon (40 years)
- weighted comparator
- Decision tree followed by partitioned survival model
- Gilteritinib used as maintenance following HSCT in a proportion of patients

** Surviving patients are assumed to be "cured" (SMR=2) after 3 years in original model (2 years in updated company model)*

† HSCT is assumed to occur at fixed timepoint (gilteritinib - [redacted]; salvage chemotherapy - [redacted]). All patients in the HSCT sub-models remain alive and event-free until this timepoint

‡ Proportion of patients entering the HSCT sub-model dependent on treatment group

[redacted]

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Key issues	Status
1 – Comparators – BSC as a relevant comparator	Resolved
- Should BSC be included in the weighted comparator?	For discussion
2 – Is it plausible that prior midostaurin use would affect gilteritinib effectiveness in clinical practice?	For discussion
3 – Cure assumptions	Resolved
4 – Is it more appropriate to use external data or ADMIRAL trial data to estimate the relative effectiveness of gilteritinib after HSCT?	For discussion
5 – If external data is most appropriate, is it plausible that there is an additional benefit of gilteritinib after HSCT?	For discussion
6 – Utilities	Resolved
7 – Costs **a – How much drug wastage should be included in the model for gilteritinib? 0.5 or 0.25 packs?**	For discussion
b – Is it acceptable to apply drug costs as a one-off cost in the first cycle of the model?	For discussion
c – Resource use after cure point	Resolved
d – Progression costs after 3 years	Resolved
e – FLT3 testing	Resolved
8 – Is it appropriate to include a disutility of -0.044 to high intensity chemotherapy?	For discussion

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Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
1	*(Partially resolved)* The company did not include best supportive care in its original base case model, but did include it in a scenario analysis.	Around 20% of people with relapsed or refractory FLT3+ AML in NHS clinical practice would receive BSC.	BSC is a relevant comparator.	Company ✓ ERG x
3	The company assumed all patients who were alive at 3 years were 'cured' whether or not they had progressed or had HSCT. The ERG noted this assumption was not based in ADMIRAL.	Considered it reasonable that patients could be considered 'cured' after 3 years.	It is appropriate to model a 3 year cure point.	Company x (2 yrs) ERG ✓
6	After the 3 year cure point, the company based health state utility values on age-adjusted general population values estimated using Janssen et al. The ERG preferred to use values from Ara and Brazier because the data was collected more recently and is more granular.	Ara and Brazier may be more plausible.	Values from Ara and Brazier should be used although this has a limited impact on the ICER.	Company ✓ ERG ✓

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Company included a 2 year cure point in its updated base case but also included a scenario analysis with a 3 year cure point.

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
7c	The company assumed there would be no follow-up costs for all patients surviving after the 3-year cure point, whether or not they had HSCT. The ERG did an analysis where people alive after 3 years had 1 outpatient visit a year if they had HSCT, and 1 outpatient visit every 6 months if they did not have HSCT.	After 3 years, people who had HSCT may have a visit every 2-4 months. People who don't have HSCT may have a visit every 6 months.	The ERG's scenario analyses are reasonable.	Company ✓ ERG ✓

[redacted]

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
7d	The company applied the cost of relapse and progression to patients considered 'cured' after 3 years.	Patients would not incur costs of relapse or progression after the cure point.	It is not reasonable to include relapse and progression costs to patients considered 'cured'.	Company ✓ ERG ✓
7e	The company's model assumed 2 FLT3 tests are needed to identify 1 person with FLT3 positive disease. The ERG considered 3.3 tests would be needed.	FLT3 testing is current practice. It is reasonable to assume that 3.3 FLT3 tests are needed to identify 1 patient.	It is reasonable to assume 3.3 tests are needed. There is a small impact on the ICER.	Company ✓ ERG ✓

[redacted]

Outstanding issues after technical engagement

- **Issue 1:** Comparators
  - Slide 14, unknown impact on ICER
- **Issue 2:** Prior midostaurin use
  - Slide 15, unknown impact on ICER
- **Issue 4:** Gilteritinib effectiveness after stem cell transplant
  - Slide 17, large impact on ICER, 2 options
- **Issue 5:** Gilteritinib maintenance therapy
  - Slide 21, large impact on ICER, 2 options
- **Issue 7a:** Drug wastage
  - Slide 23, small impact on ICER, 2 options
- **Issue 7b:** Application of drug costs
  - Slide 23, unknown impact on ICER
- **Issue 8:** Quality of life and costs associated with administration
  - Slide 24, small impact on ICER, 2 options
- **Other:** End of life considerations
  - Slide 25

Model driver

Unknown impact

Small impact

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Issue 1: Comparators

Background
- In original model, company included best supportive care (BSC) as a scenario analysis by applying a HR of 2.86 to gilteritinib OS, informed by a naive indirect comparison
- Including BSC in the blended comparator reduces the ICER

ERG comments
- Several concerns about the method used for indirect comparison including:
  - Assumption that LoDAC is equivalent to salvage chemotherapy
  - Source of HR used unclear
  - Proportional hazards assumed, which may not be appropriate.

Company revised model
- Included BSC in the weighted comparator at 20%, 25%, and 30%
- ERG considers this inappropriate because characteristics of people who would receive BSC would be different to those who receive chemotherapy, e.g. they would be less likely to receive a HSCT (but HSCT rate is the same within the weighted comparator)
- ERG's clinical advisor suggested that the HSCT rate for gilteritinib in this less fit population may be approximately 10%

Is the company's method of including BSC in the model appropriate?

[redacted]

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Issue 2: Prior midostaurin use [1]

Background

- In ADMIRAL, 13% of the gilteritinib group and 11.3% of the salvage chemotherapy groups had prior FLT-3 inhibitors
- Subgroup results (OS) for patients with no prior FLT-3 inhibitor (n=[redacted]): gilteritinib was [redacted] (HR=[redacted], 95% CI [redacted]; p=[redacted]).
- For the 46 patients with prior use of a FLT3 inhibitor, the [redacted](HR [redacted], 95% CI [redacted]; p=[redacted]).

Stakeholder comments

- Gilteritinib would be given after midostaurin because gilteritinib is a more potent FLT3 inhibitor and at relapse, AML cells with the ITD mutation are very dependent upon that pathway for survival
- No evidence to suggest prior exposure to a FLT3 inhibitor would affect gilteritinib effectiveness
- The proportion of people having midostaurin in practice is higher than in the trial

[redacted]

Issue 2: Prior midostaurin use [2]

Company's new evidence post-engagement:
ADMIRAL Kaplan-Meier curve for patients who had prior midostaurin or sorafenib vs. all patients

Is it plausible that prior midostaurin use would affect gilteritinib effectiveness in clinical practice?

[redacted]

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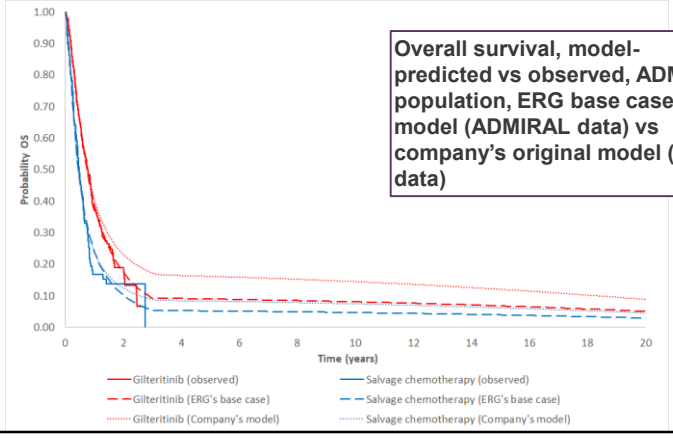
Issue 4: Gilteritinib effectiveness after HSCT [1]

Background

- In the company's model, post-HSCT OS is based on a Gompertz curve fitted to data from Evers et al. (N=128 in CR2, post-HSCT)
- The company did not use ADMIRAL data because there was a small sample size and limited follow up (median follow up post-HSCT [redacted] months)



Overall survival, model-predicted vs observed, ADMIRAL population, ERG base case model (ADMIRAL data) vs company's original model (Evers data)

[redacted]

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Issue 4: Gilteritinib effectiveness after HSCT [2]

Comparison of OS predictions between the company's Gompertz model, the ERG's standard log normal model and the ERG's mixture-cure models (With HSCT group), including 2-year cure point assumed in company's revised model

[redacted]

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Issue 4: Gilteritinib effectiveness after HSCT [3]

Summary of censoring and death times in ADMIRAL With HSCT group, gilteritinib arm

[redacted]

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Issue 4: Gilteritinib effectiveness after HSCT [4]

ERG comments
- Considers ADMIRAL is the most relevant data source
- Patients in Evers et al. did not all have FLT3 positive disease
- External information should supplement evidence from ADMIRAL
- Company's original base case model assumptions required all patients who were censored to be cured at 3 years
- Proportion surviving to 2 years in trial is known to be less than estimate of 60% predicted by company's model, despite censoring

Stakeholder comments
- The trial data appear robust
- ADMIRAL is the best available data
- Both have limitations

Company comments
- There are [redacted] patients with follow-up data beyond year 1, [redacted] patients after year 2
- Also considered a study by Ustun et al (N=91 in unrelated donor group), which is in a population with FLT3 mutation positive AML (although 80% in CR1) and provided a scenario analysis using this data to inform post-HSCT survival.

Is it more appropriate to use external data or ADMIRAL trial data to estimate the relative effectiveness of gilteritinib after HSCT?

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Issue 5: Gilteritinib maintenance therapy [1]

Background

- The Kaplan-Meier from ADMIRAL from HSCT to death does not show a favourable effect of gilteritinib post-HSCT but company notes that there are small patient numbers and high levels of censoring
- The company stated that the post-HSCT OS data are immature and so derived a HR from an indirect comparison using data from Evers et al.
- The company applied the hazard ratio (HR) to the post-HSCT OS Gompertz model to reflect additional survival benefit associated with gilteritinib maintenance therapy after HSCT

ERG comments

- It is unclear if the data from ADMIRAL show conclusive evidence of a difference in treatment effect in post-HSCT OS.
- The available evidence suggests the proportional hazard assumption is violated so applying a HR is inappropriate
- There was no adjustment for differences in patient characteristics between studies
- It is inconsistent to use a subset of ADMIRAL post-HSCT OS data to estimate the hazard ratio given that the company point out the data are immature
- Did an analysis using a HR of 1 (pooling both treatment arms post-HSCT)

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Issue 5: Gilteritinib maintenance therapy [2]

Stakeholder comments
- Gilteritinib would be used as maintenance therapy after HSCT in clinical practice
- It is plausible there is an additional effect of maintenance therapy on overall survival
- However there is no clear randomized data to support using FLT3 inhibitors in this setting - there is an ongoing study (MORPHO) of gilteritinib treatment after HSCT (expected completion date April 2025)

Company comments
- The summary of product characteristics for gilteritinib permits maintenance treatment, likely to be in a small population
- In the ERG scenario with a HR of 1, company considers costs should also be removed

ERG comments post-engagement
- If maintenance use in practice is lower than ADMIRAL this will affect ICER if maintenance therapy is associated with additional OS gain
- Company claimed inappropriate to use ADMIRAL data for OS outcomes for patients who had HSCT, but use this data to estimate additional OS effect with gilteritinib maintenance therapy

[NB. If ADMIRAL trial data are used after HSCT, this point is not relevant.]

Is it plausible that there is an additional benefit of gilteritinib after HSCT? 22

Issue 7: Costs

Background	Company response
a) Drug wastage: Company did not originally include. ERG analysis included 14 days' supply of wastage for all patients who died before 3-year cure point **Stakeholders:** Wastage would occur in practice but likely could be minimal.	Revised base case includes wastage of 7 days' supply of gilteritinib because this amount included in NICE's appraisal of sorafenib for advanced hepatocellular carcinoma (TA474)
b) Application of drug costs: Company included the costs of gilteritinib and chemotherapy as one-off costs in the first cycle **ERG:** highlighted that • discounting not applied properly • treatment duration not linked to progression • gilteritinib treatment duration (and cost) underestimated as some people still having gilteritinib at data cut off ERG estimates this approach likely decreases ICER (amount unknown)	• Considers using the original method has negligible effect on model results • Gilteritinib costs included are a small overestimate
c) Resource use after cure point	Resolved
d) Progression costs after 3 years	Resolved
e) FLT3 testing	Resolved

How much drug wastage should be included in the model for gilteritinib?
- **0.5 packs or 0.25 packs?**

Is it acceptable to apply drug costs as a one-off cost in the first cycle of the model?

Issue 8: Quality of life and costs of administration

Background

- During technical engagement, a clinical expert highlighted there is a benefit of gilteritinib over salvage chemotherapy because it is an oral treatment and does not need to be administered in hospital
- The difference in costs is reflected in the administration costs in the model, but no quality of life difference is reflected

Company comments

- Difficulty in collecting patient reported outcomes from salvage chemotherapy group in ADMIRAL
- Identified disutility associated with high intensity chemotherapy from literature: Wehler et al. (2018)
- Applied disutility of -0.044 to high intensity chemotherapy
- Model assumes patients on high intensity chemotherapy were in hospital for 28 days in cycle 1, and from cycle 2 onwards, hospitalisation estimate from ADMIRAL applied

ERG comments

- Disutility is applied in every model cycle for whole time horizon. Unclear if this is clinically appropriate
- Updated hospital costs appear reasonable

Is it appropriate to include a disutility of -0.044 to high intensity chemotherapy in every model cycle?

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End of life considerations

Criterion	Data source	Overall survival	
		Median	Mean
Short life expectancy, normally < 24 months	ADMIRAL salvage chemotherapy group	5.6 months	-
	Company's revised base case – weighted comparator	-	2.54 years*
	ERG's base case – salvage chemo	-	1.69 years
	ERG's base case – BSC	-	0.33 years
Extension to life, normally of a mean value of ≥ 3 months		**Increase with gilteritinib**	
		Median	Mean
	ADMIRAL	3.7 months	-
	Company's revised base case	-	2.54 years*
	ERG's base case vs chemo	-	0.98 years
	ERG's base case vs BSC	-	2.34 years

**obtained by NICE technical team using company model, total undiscounted life years*

[redacted]

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Additional issues and areas of uncertainty

Uncertainty	Why issue is important	Impact on ICER
High dropout rate in salvage chemotherapy group of trial	Most patients in the salvage chemotherapy group finished study treatment by cycle 2 of treatment. This led to high censoring for duration of remission and leukaemia-free survival (LFS) endpoints; [redacted]% of patients were censored early. The comparative effectiveness estimates are therefore uncertain.	Unknown

Innovation

- Company considers gilteritinib to be innovative
- Are all relevant benefits associated with the drug adequately captured in the model?

Equality considerations

- None identified
- Are there any equality issues?

Cancer Drugs Fund

- Company has not expressed an interest in gilteritinib being considered for funding through the Cancer Drugs Fund
- No further data cuts are expected from ADMIRAL

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Cost effectiveness results

Include PAS for gilteritinib but not confidential discount for azacitidine – see part 2 slides

Technical team's preferred scenario	Inc costs (£)	Inc QALYs	ICER (£/QALY)	Cumulative ICER
Company original base case (with corrections)	[redacted]	[redacted]	**£54,844**	-
Issue 4: Gilteritinib effectiveness after HSCT				
Use ADMIRAL data to inform effectiveness	[redacted]	[redacted]	£95,642	-
Issue 6: Utilities				
a. Use Ara and Brazier utilities	[redacted]	[redacted]	£54,532	£95,177*
b. remove AE double counting of progression	[redacted]	[redacted]	£54,760	£94,969*
Issue 7: Costs				
a. Include 0.5 packs' gilteritinib wastage b. Resource use after cure point updated, no follow up costs after 3 years and 3.3 FLT3 tests	[redacted]	[redacted]	£58,355 £54,999	£101,713* £102,085
Issue 8: Quality of life				
Include disutility for high-intensity chemotherapy and revised hospital costs	[redacted]	[redacted]	£51,613*	£97,524
Technical team's preferred assumptions (all above and updated dispensing fee) (does not include BSC because results too uncertain)	[redacted]	[redacted]	-	**£98,498**

*calculated by NICE technical team

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Scenario analyses

Scenario	Inc costs (£)	Inc QALYs	ICER (£/QALY)
Technical team's preferred assumptions (including 0.5 packs' gilteritinib wastage)	[redacted]	[redacted]	**£98,498**
Issue 7: Costs			
Include 0.25 packs' gilteritinib wastage	[redacted]	[redacted]	£95,152*

**calculated by NICE technical team*

[redacted]

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Company's updated base case

- **After technical engagement**
- Includes:
  - Updated dispensing fee
  - BSC in the weighted comparator at 25% (Issue 1)
  - 2 year cure point (Issue 3)
  - Using external data for post-HSCT OS (Issue 4)
  - Utilities updated as in technical team's preferred assumptions (Issue 6)
  - Costs updated as in technical team's preferred assumptions, 0.25 packs' gilteritinib wastage (Issue 7)
  - Disutility and costs for inpatient treatment with high-intensity chemotherapy (Issue 8)

	Inc costs (£)	Inc QALYs	ICER (£/QALY)
Company's updated base case	[redacted]	[redacted]	**£43,346**

Scenarios on updated base case	1-year cure point	2-year cure point	3-year cure point
BSC = 20%	£30,547	£43,455	£51,796
BSC = 25%	£30,630	£43,346	£51,589
BSC = 30%	£30,708	£43,242	£51,390

ERG notes that post-progression costs are applied for 3 years, although the cure point was changed to 2 years, and also notes an error in implementation of outpatient visit costs

[redacted]

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Key issues	Status
1 – Comparators – BSC as a relevant comparator	Resolved
- Should BSC be included in the weighted comparator?	For discussion
2 – Is it plausible that prior midostaurin use would affect gilteritinib effectiveness in clinical practice?	For discussion
3 – Cure assumptions	Resolved
4 – Is it more appropriate to use external data or ADMIRAL trial data to estimate the relative effectiveness of gilteritinib after HSCT?	For discussion
5 – If external data is most appropriate, is it plausible that there is an additional benefit of gilteritinib after HSCT?	For discussion
6 – Utilities	Resolved
7 – Costs **a – How much drug wastage should be included in the model for gilteritinib? 0.5 or 0.25 packs?**	For discussion
b – Is it acceptable to apply drug costs as a one-off cost in the first cycle of the model?	For discussion
c – Resource use after cure point	Resolved
d – Progression costs after 3 years	Resolved
e – FLT3 testing	Resolved
8 – Is it appropriate to include a disutility of -0.044 to high intensity chemotherapy?	For discussion

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