NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [ID1484]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [ID1484]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Response to the Appraisal Consultation Document from Astellas:**
   a. Company ACD response
   b. Additional Evidence
   c. Additional Evidence

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Leukaemia Care
   b. Royal College of Pathologists

   There were no responses to the consultation from the invited experts or through the website consultation.

4. **Evidence Review Group critique of company additional evidence post-ACD**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	Leukaemia Care	We are concerned about the unfair delay in access for patient in need of this treatment as a result of this ACD. This is now the only FLT3+ inhibitor for relapsed/refractory AML being considered for use on the NHS in England, following the pause of the quizartinib appraisal in late 2019. There is considerable unmet need in this group and clinicians are in agreement that FLT3+ inhibitors can meet this need in clinical practice.	Comment noted. The committee understood that current treatment for relapsed or refractory AML is limited and people with relapsed or refractory AML would welcome a new treatment that improves survival and quality of life. See FAD section 3.1
2	Consultee	Leukaemia Care	The committee has decided that the cure point for the purposed of modelling is to be 3 years. However, the company argued that this should be 2 years in the committee meeting and the clinical expert agreed that this was more reasonable. The clinical expert has since confirmed that this was his opinion. We have consulted with two leading AML clinicians, who concurred with the clinical expert's viewpoint that 2 years was the most reasonable assumption in this patient population. The standard for clinical trials is 5 years, but the majority of relapses will occur much earlier. Whilst the 3 year cure point was the standard used in the midostaurin appraisal (TA523), this was in reference to an untreated population of patients and so may not be applicable to the indication considered here. Clinical experts indicated that relapses will occur earlier in this relapsed/refractory population, likely within the first 12 months. We urge the committee to take on board the recommendations of the clinical experts and allow modelling with a cure point of 2 years.	Comment noted. The committee concluded that a cure point between 2 years and 3 years is plausible, and it is more likely to be closer to 2 years. See FAD section 3.5
3	Consultee	Leukaemia Care	We are aware that the company have further data cuts available, which should provide further information on the outcomes of these patients. As one of the main points of discussion is uncertainty of post-transplant survival and utility values of these patients, we urge the company to submit this data and for the committee to consider this at the next committee meeting. We would also ask that Leukaemia Care have the opportunity to nominate a patient expert to attend this meeting to discuss this key clinical effectiveness issue.	Comment noted. The company provided data for the updated data-cut (September 2019). The committee took the latest information on the evidence into account when made its final recommendation. No action required.
4	Consultee	Leukaemia Care	The input we have received from leading AML clinicians is that quality of life gains from outpatient, oral treatment have not been fully represented in the disutility value.	Comment noted. The committee agreed that these were important

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				benefits of gilteritinib but concluded that it had not been presented with evidence of any demonstrable and distinct substantial additional benefits that could not be captured in the measurement of QALYs. See FAD section 3.16
5	Consultee	Leukaemia Care	The committee has indicated that this drug could not be considered for the CDF because "there is not plausible potential to satisfy the criteria for routine use because the committee's preferred ICER was over £90,000 per QALY gained." We are concerned about the precedent set by this statement. Addendum PMG9 of the appraisal process and methods guide states the ICERs "presented have the plausible potential for satisfying the criteria for routine use, taking into account the end-of-life criteria when appropriate". However, the addendum to the guide does not set a precise value for the threshold for 'plausible potential'. Should NICE wish to introduce such a threshold, there is ample opportunity in the upcoming methods review, and we would encourage you to do so from a transparency perspective. However, it is unreasonable for an individual committee to arbitrarily differ from other NICE committees and introduce such a threshold. We could find no evidence where a particular value for the threshold has been used in the past. We would like an explanation as to why an ICER threshold of £90,000 has been considered appropriate in this instance.	Comment noted. The £90,000 figure is a description of the committee's preferred ICER from the first committee meeting as the true ICER was confidential and couldn't be reported. This is not a threshold value. No action required.
6	Consultee	Royal College of Pathologists	The reference costs for FLAG-IDA administration are not an accurate reflection of NHS costs- £1,418.51 (table 30 ACD committee papers). This appears to simply cover the costs of drug administration. This is always an in-patient regimen that requires admission for induction therapy usually for 4-6 weeks, a toxic regimen with inevitable infections and possibility of ITU admission. NHS income for such admission is around £30,000.00 (the associated anti-fungal therapy is usually £2,000.00). Simplistically the concept that the administration costs for the other regimens (AZA and LDAC) really questions the credibility of this analysis. If the reference costs have been taken from the ADMIRAL study costing would not take account of 'standard of care' costs within such a trial. I have raised this previously with the committee but am unable to see this accounted for within the document- apologies if this is my oversight.	Comment noted. The committee understood that the figures for in-patient therapy might be higher than what was included in the company's model. Although, the costs were applied in an unusual way which would overestimate costs in the model. It was not presented with evidence to be able to accept the updated figures. See FAD section 3.11
7	Consultee	Royal College of Pathologists	2-year survival/cure point seems sensible- few events occur after 12 months and overwhelmingly patients alive and in remission 12 months post-transplant are mostly cured.	Comment noted. The committee concluded that a cure point between 2 years and 3 years is plausible, and it is more likely to be

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				closer to 2 years. See FAD section 3.5
8	Consultee (company)	Astellas Pharma	**1. Additional data from the ADMIRAL trial, in particular supporting post-HSCT OS** Section 1 and 3.5 of the ACD notes that the Appraisal Committee considered the ADMIRAL trial was the most appropriate source for modelling the post-HSCT OS. In Section 3.14 the ACD also comments that the modelling of overall survival data after stem cell transplant was uncertain, and that the Appraisal Committee noted that additional data on overall survival after stem cell transplant could potentially resolve this uncertainty. In the Company Submission, Astellas communicated that the post-HSCT ADMIRAL data from the September 2018 data cut were immature (with both low numbers and short-term follow-up) and as such, Astellas considered the use of other comparable post-HSCT datasets to support the understanding of the expected long-term outcomes. Astellas had been told by its Global colleagues that there were to be no further data cuts and analyses from ADMIRAL. This has changed and Astellas has been able to obtain an updated data cut (data cut off September 2019) to support this submission and discussions with NICE. These data were not available at time of the initial Company Submission or during previous communications through the process to date. The updated dataset builds on the understanding of the clinical effectiveness of gilteritinib in FLT3 positive relapsed or refractory AML patients. The data continues to support the effectiveness of gilteritinib; in particular, gilteritinib post-HSCT and the longer term response rates. The new data cut means that many patients who were censored in the data presented in the initial Company Submission are now contributing to the results. This is particularly important for the 63 patients who were transplanted on the gilteritinib arm, where previously there was extensive censoring in the first year, but now with further follow up there is little censoring before day 650 (22 months). The updated analysis is presented below; critical to the model are the updated OS data, post-HSCT OS data and the mean treatment duration (which is now [redacted] cycles). The clinical data overview is presented and the updated cost-effectiveness summary is provided below that. To confirm, all data presented below is from the ADMIRAL September 2019 data cut which has also been used to underpin the cost effectiveness analysis. The ICERs presented represent figures with the updated Patient Access Scheme (PAS) which Astellas	Comment noted. The committee took the latest evidence into account when made its final recommendation. The committee considered that the updated data from the ADMIRAL study did not suggest a benefit for gilteritinib over chemotherapy for overall survival after stem cell transplant. See FAD section 3.7 It also considered that in ADMIRAL people could only restart gilteritinib in certain conditions, such as being in complete remission after stem cell transplant. It also noted that including a maintenance therapy hazard ratio leads to a survival projection that is more favourable than the observed gilteritinib data from the trial. Although the committee understood there might be a clinical benefit to gilteritinib maintenance treatment after stem cell transplant, it did not see robust evidence supporting this benefit. Therefore, the committee also concluded that any guidance for gilteritinib would be limited,

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			is putting forward. A cumulative base case ICER is presented with this applied. With end of life criteria met, in order to meet the ICER threshold Astellas has increased the Patient Access Scheme (PAS) discount from [redacted] **Overall Survival** Overall survival was a co-primary outcome in ADMIRAL, the median OS was longer in patients receiving gilteritinib (9.3 months; 95% CI: 7.7 to 10.5) compared to patients treated with salvage chemotherapy (5.6 months; 95% CI 4.7 to 7.3) (hazard ratio [HR]: 0.679 [95% CI: 0.527 to 0.875; p<0.001), see Figure 1. The 2 year survival rate was higher in patients receiving gilteritinib versus salvage chemotherapy (20.3% versus 14.2%), One-year and 6-month OS was also higher with gilteritinib (36.6%, 65.5%) versus salvage chemotherapy (19.2%, 48.9%), respectively, see Table 1. **Figure 1 Kaplan-Meier Plot of Overall Survival by Treatment Arm**	and treatment with gilteritinib should not restart as maintenance therapy after stem cell transplant. See FAD sections 3.6 – 3.8

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

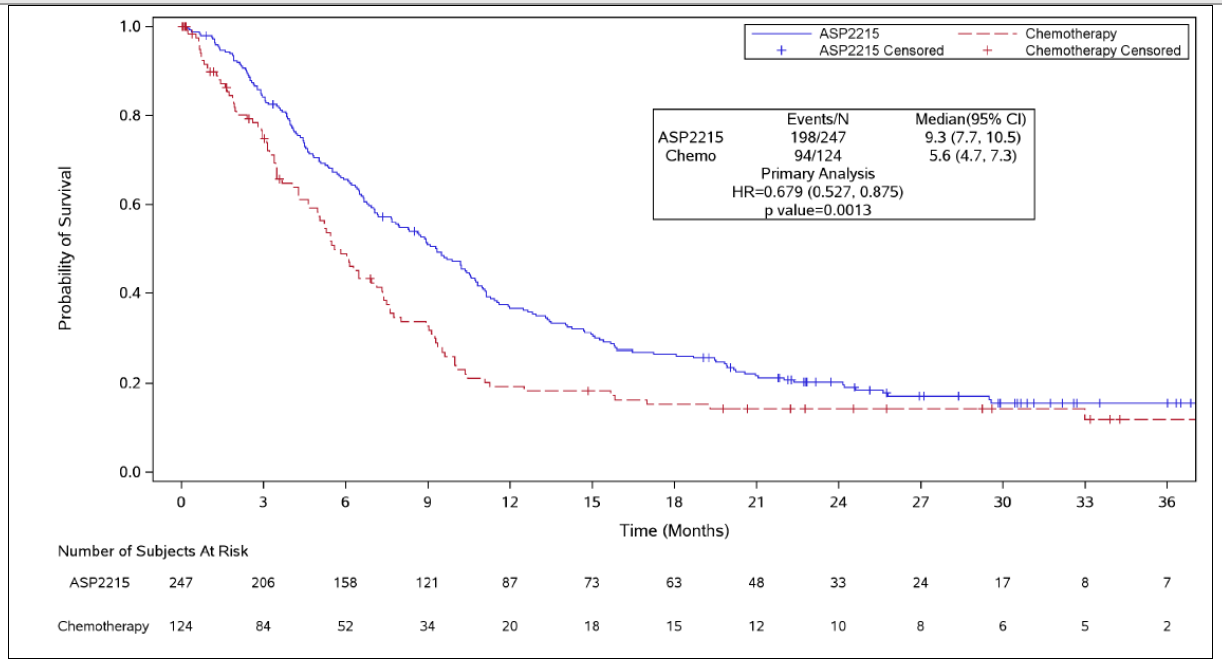
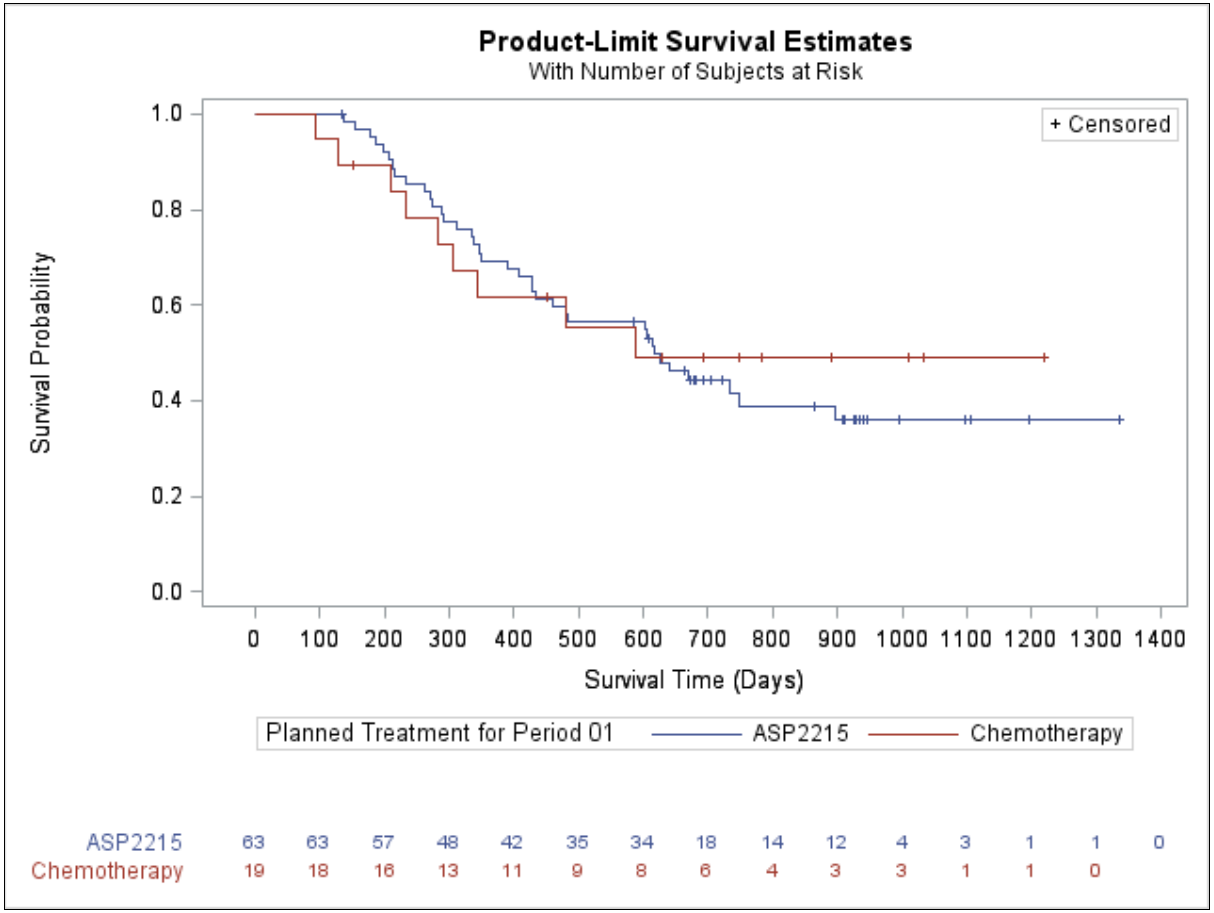
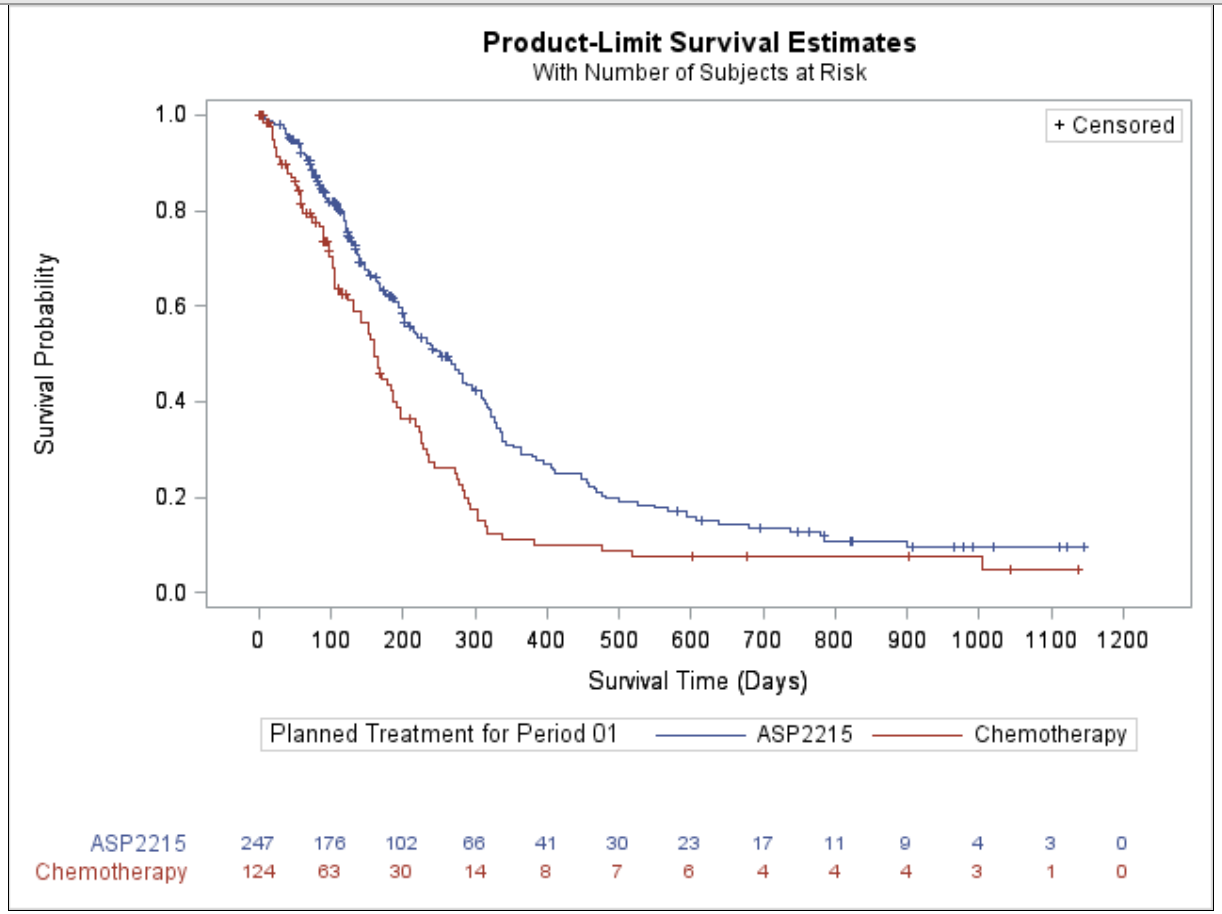


Table 1 Clinical Effectiveness: Overall Survival, ADMIRAL

Outcomes	Gilteritinib (N=247)	Salvage chemotherapy (N=124)
Overall Survival, median months (95% CI)	9.3 (7.7, 10.5)	5.6 (4.7, 7.3)
Overall Survival Rate % (95%CI)		
6 months	65.5 (59.2, 71.1)	48.9 (39.3, 57.8)
12 months	36.6 (30.6, 42.7)	19.2 (12.4, 27.2)
24 months	20.3 (15.4, 25.7)	14.2 (8.3, 21.6)

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Post-HSCT Survival The median OS was longer in post-HSCT patients receiving gilteritinib (610 days) compared to HSCT patients treated with salvage chemotherapy (482 days) (hazard ratio [HR]: 1.108 [95% CI: 0.534 to 2.292; p<0.7836). See Figure 2. **Figure 2 Kaplan-Meier Plot of Overall Survival Post-HSCT (ITT population)**  *Note: ASP2215 is gilteritinib. Day 0 is randomisation*	

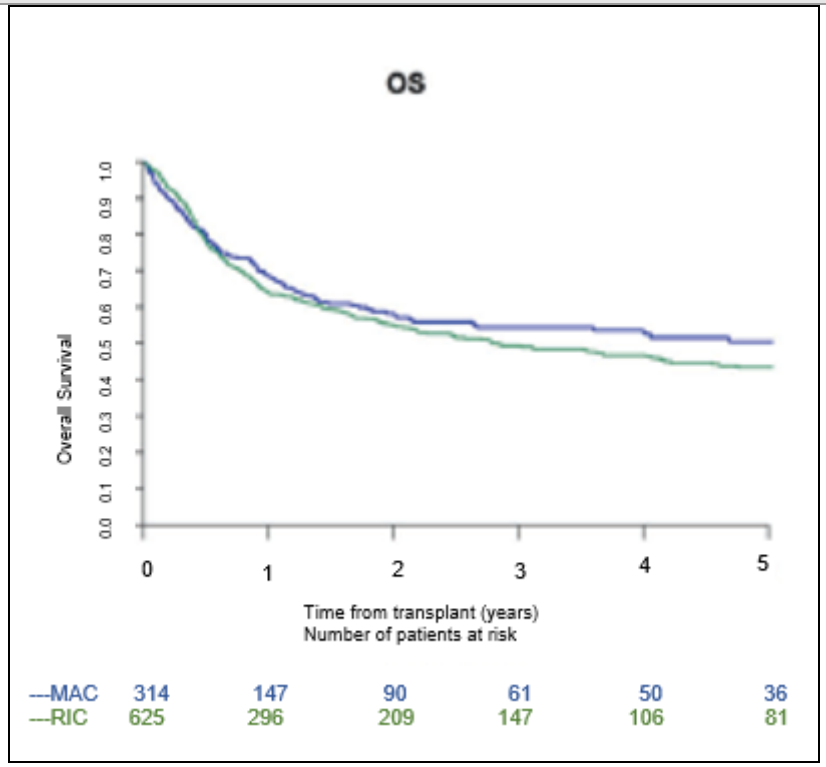
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Overall OS Data Censored for HSCT The median OS censored for HSCT was longer patients receiving gilteritinib (156 days) compared to HSCT patients treated with salvage chemotherapy (103 days) (hazard ratio [HR]: 0.600 [95% CI: 0.460 to 0.782; p<0.001). This data shows that when removing the treatment benefits patients receive with the HSCT, the OS benefit remains clear with gilteritinib. See Figure 3 below. **Figure 3 Kaplan-Meier Plot of Overall Survival, Censored for HSCT (ITT population)**	

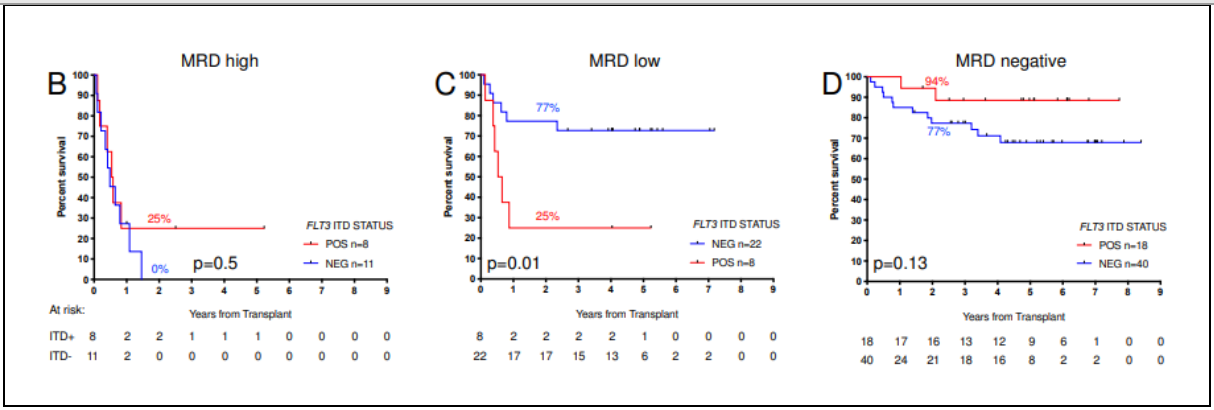
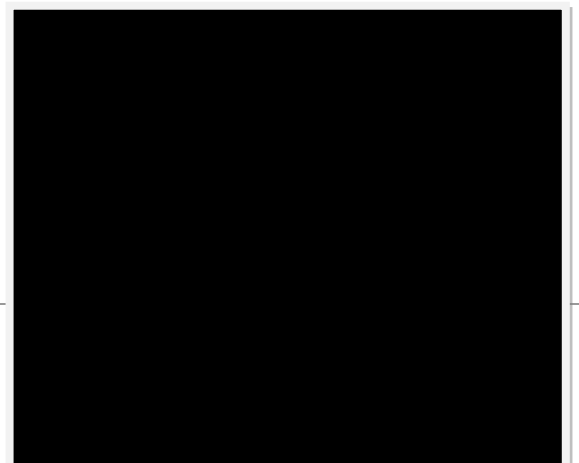
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 *Note: ASP2215 is gilteritinib* In conclusion, this updated ADMIRAL analysis confirms the benefit of gilteritinib for FLT3 positive relapsed or refractory AML patients. The updated data shows that with an extra year of follow up, the HR for OS remains consistent. In addition, this follow up has reduced the extent of censoring post HSCT which leads to increased confidence in this data and the associated curves which support the CE case.	

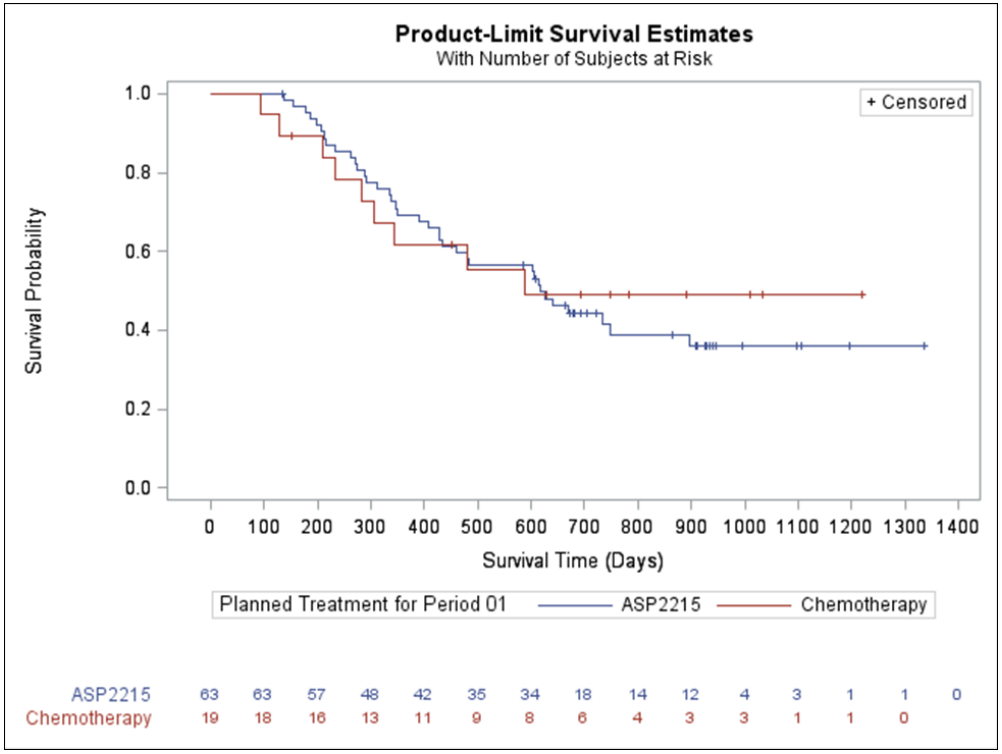
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Cost Effectiveness Summary and Interpretation The OS and EFS data from the ADMIRAL September 2019 data cut were used in a cost-effectiveness analysis for both patients with and without HSCT, in addition to the updated mean treatment duration with gilteritinib ([redacted] cycles i.e. [redacted] treatment days). The approach taken was to add the new data to the preferred base case analysis put forward by the ERG, as well as to apply some subsequent assumptions discussed below (and BSC). The resultant ICER is presented in **Error! Reference source not found.**. It is of interest that the updated ADMIRAL analysis shows that, in the first 1-2 years post-HSCT, the ADMIRAL curve aligns to Evers et al in terms of OS. Previously, Astellas used Evers to inform post-HSCT OS because the data from ADMIRAL had high uncertainty due to low patient numbers and short follow-up. The updated ADMIRAL analysis has less censoring and therefore higher patient numbers as well as longer follow up, and now show that survival is similar in ADMIRAL. Astellas believes that with longer follow up, the ADMIRAL post-HSCT data will show a similar (or potentially more favorable) survival curve to Evers – supporting the rationale for using Evers in the initial Company Submission, which is still a plausible approach. The use of Evers to inform the long-term outcomes has been explored as a scenario. The resultant ICERs are presented in **Error! Reference source not found.**.	
9	Consultee (company)	Astellas Pharma	**2. Additional evidence to inform the choice of cure point** Section 3.4 of the ACD states that the Appraisal Committee concluded it had not been presented with evidence for a 2-year cure point. Astellas agrees that the commentary around the cure point submitted to date has had limitations. The Company acknowledges that it has changed the cure assumption from a conservative 3 year position to an earlier time point, however, we consider this to be more realistic and a better reflection of the evidence and clinical expert input that has emerged through the process. Astellas wishes to submit new evidence, which supports a clinically plausible cure point of between 18 and 24 months. For modelling the base case Astellas has used the 2 year time point. During this appraisal, Astellas has continued to validate the key inputs that drive the CE model. In clinical practice AML patients can be under lifelong surveillance due to high risk of relapse. A “cure” can be defined as the point when the risk of relapse is very low. The clinical expert accepted this	Comment noted. The committee noted that using a 2-year cure point appears to overestimate the long-term overall survival for the gilteritinib arm in the observed period of the trial. The committee had concerns about applying a 2-year cure point, because the population in the evidence used to support the 2 year cure point was different to the ADMIRAL trial, and because of the lack of good visual fit of the extrapolated 2-year cure to the Kaplan–Meier data. However, taking it account

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			definition of cure during AC meeting in December. The NICE TA for midostaurin (TA523, June 2018), for use in newly diagnosed AML patients, concluded to use a 3 year cure point. This seems to have been based on “best fit” to model this part of the disease pathway. This was the cure point assumed by Astellas in its initial submission. Since then, further insight has been published and gathered on relapsed or refractory AML patients, which help our understanding of the outcome of such patients post HSCT. The only way for patients with relapsed AML to achieve cure currently, is to receive stem cell transplantation. For that reason, we focus on data on patients who have received transplantation following relapse. Data from Gilleece, Dillon, ADMIRAL, Evers, Ustun and Poiree are presented in Figure 4 below. Across these sources, the post-HSCT curves generally flatten at the 18 – 24 month point, supporting this as a suitable cure point for this post-HSCT population. These publications were identified via a targeted literature review which was updated based on feedback from NICE and external clinical input. Gilleece, Dillon and ADMIRAL are discussed in more detail below as they are the mains sources of data which have emerged since the original submission in June 2019. **Figure 4 Comparison Chart of Post-HSCT OS to Support Cure Point of 18-24 Months** 	clinical expert advice, it concluded that a cure point between 2 years and 3 years is plausible, and it is more likely to be closer to 2 years. See FAD section 3.5

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			One source of insight is the Gilleece et al 2020 publication, which analysed data from the European Society for Blood and Marrow Transplantation (EBMT) database which included 1,879 patients from 230 European transplant centers, including the UK. This data relates to AML patients who have received allogenic stem cell transplantation after relapse from their first remission and includes all cytogenetic and molecular profiles, as well as risk groups, including FLT3 positive patients. Figure 5 shows the OS curve flattening at 2 years especially for the MAC (myelo-ablative conditioning) group. It is likely (given that FLT3 is an adverse risk category with a high risk of relapse, and MAC is known to have lower relapse outcome post-transplant) that most FLT3 patients will receive a MAC conditioning regimen. **Figure 5 OS Post-Transplant, RIC vs MAC, allogeneic Haemopoietic Cell Transplant in Patients Aged 50 or Older**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 *Abbreviations: OS: overall survival; RIC reduced intensity conditioning; MAC myeloablative conditioning* Another source is Dillon et al 2020, with a median follow up of 4.9 years. This informs our understanding of FLT3 positive patients post HSCT in the UK. Figure 6 shows OS in FLT3 positive and negative patients and the curve flattens before year 2; no deaths occur after that time point for FLT3 positive patients. Furthermore, data from this study, not included in the publication, but shared with Astellas shows all FLT3 positive patients in the study who relapsed had done so by year 1. See Figure 7. The curves seen in Figure 6 demonstrate that OS in FLT3 positive patients (red line) plateaus before 2 years and Figure 7 shows that when these three curves are combined the same result is seen. **Figure 6 Effect of FLT3 ITD on Outcome According to Pre-transplant MRD status**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 *Note: Percentages indicate estimated 2 year overall survival. (B-D) Overall survival from transplant for patients with high (B), low (C) and negative (D) pre-transplant MRD. MRD: Measurable residual disease* **Figure 7 OS in FLT3 Positive Patients who Received HSCT in AML17 trial** 	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Finally, data from ADMIRAL[Error! Bookmark not defined.] shows that of those patients who underwent a transplant (n=63) the OS curve flattens at 22 months from randomisation. See Figure 8 below. **Figure 8 OS Post-HSCT ADMIRAL, September 2019**  	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Note: ASP2215 is gilteritinib During the Appraisal Committee meeting the clinical expert expressed the view that in clinical practice, patients who receive a transplant in the relapse setting, and who were in remission 2 years post-transplant, would unlikely relapse after that time point. In addition, Astellas has sought input from AML clinical experts through the process and since the Appraisal Committee meeting and receipt of the ACD. These experts have supported the view that that it is meaningful to describe the point beyond which patients are unlikely to relapse as between 18 – 24, as most events (relapses and deaths) have occurred by then. Some have cited this period as short as 9 – 12 months. This links to the definition of cure point provided above. In conclusion, Astellas believes published data, along with the clinical expert insights provided both to Astellas and to the Appraisal Committee, supports an 18 – 24 month cure point for FLT3 positive relapsed/refractory AML patients post HSCT. Cost-effectiveness analysis was conducted using a 2 year cure point, with post-progression costs applied for 2 years only, in line with ERG feedback in the Appraisal Committee slides (see slide 29 footnote). The resultant ICER is presented in **Error! Reference source not found.**.	
10	Consultee (company)	Astellas Pharma	3. **Quality of life and costs associated with administration** Section 3.9 notes the concern that the potential quality of life benefits of oral gilteritinib had not been adequately addressed in the Company's submission. Astellas agrees that the potential quality of life benefits of oral gilteritinib, with less time in hospital, compared with the inpatient chemotherapy with frequent debilitating complications, was not adequately captured in ADMIRAL. Astellas also agrees that the disutility arising from the associated use of high intensity chemotherapy has not been adequately taken in to account in the base case – in part due to the limited PRO questionnaire completion by the patients in the salvage chemotherapy arm of ADMIRAL. From a clinical point of view, the importance of this was raised during Technical Engagement and is further supported by a patient survey presented at the American Society of Haematology (ASH) annual meeting December 2019 by the Acute Leukemia Advocacy Network (ALAN). Astellas acknowledges that the previous base case cost-effectiveness analysis assigns the same disutility value to patients experiencing each adverse event, irrespective of treatment received. Hence	Comment noted. The committee was concerned that the potential quality-of-life benefits of oral gilteritinib had not been adequately addressed in the model. It concluded that additional disutilities should be included in the model. See FAD section 3.11 It also noted that it is likely that the company's new approach overestimates the true costs of hospitalisation for the high-intensity chemotherapy regimens. It concluded that the increased costs for high-intensity chemotherapy

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			the additional disutility of receiving more intensive chemotherapy regimens is not accounted for in the original analysis. Astellas has considered this by amending the disutilities experienced by salvage chemotherapy patients whilst on treatment. Astellas has previously assigned a disutility of -0.044 to patients receiving high-intensity chemotherapy (FLAG-IDA, MEC), a value reported by Wehler et al 2018 . This value represents a conservative approach and is representative of patients receiving therapy and experiencing minimal adverse events (only the most impactful event was included). This study also reports disutility values for patients receiving high-intensity chemotherapy regimen, hypomethylating agents and low-intensity chemotherapy regimens (LoDAC) and includes disutility for all events experienced. The values for high-intensity chemotherapy, hypomethylating agents and low-intensity chemotherapy are reported as -0.190, -0.225 and -0.166 respectively. A revised cost-effectiveness analysis with these utility values applied to the relevant regimens in the weighted comparator has been submitted. Based on feedback received during the Appraisal Committee meeting, these disutility values are only applied for the first 3 cycles, to reflect the time-on-treatment for patients receiving chemotherapy regimens in the economic model i.e. patients receive 2.24 cycles of azacitidine. The previous approach of applying a full month of hospitalisation costs to patients receiving the high-intensity chemotherapy regimens has been retained. The resultant ICER is presented in Table 2.	should be excluded from the model. See FAD section 3.11
11	Consultee (company)	Astellas Pharma	**4. Drug wastage** Section 3.7 of the ACD notes that the Appraisal Committee felt it was reasonable to assume 14 days' supply of gilteritinib may be wasted. No evidence was presented to support this assumption. Astellas agrees that a random event such as death could be one of the causes of drug wastage, and it could be appropriate that 14 days wastage could be applied for these patients, but Astellas believes that the majority of patients would discontinue in a more managed way i.e. following consultation with a clinical expert whereby no further treatment is prescribed. This was also as discussed at the Appraisal Committee meeting, where the clinical expert commented that the majority of discontinuation is likely to occur through clinical management, i.e. at the presentation of symptoms of progression. This reduces the potential for drug wastage, as further medication is not dispensed to such patients who are identified as unlikely to benefit from continuing treatment.	Comment noted. The committee heard from clinical experts that treatment is closely monitored and treatment with gilteritinib would usually stop after completing a course of therapy. It concluded that wastage of 7 days' supply of gilteritinib should be accounted for in the model. See FAD section 3.9

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			A similar logic was followed in TA451 (ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia) where it was stated by clinical experts that people whose disease responded to treatment would have prescriptions for several months but would be monitored during that period to ensure a response was being maintained. Astellas believes that a more accurate way to reflect the causes of discontinuation is to incorporate the cost of 7 days' wastage. The resultant ICER is presented in Table 2.	
12	Consultee (company)	Astellas Pharma	5. **Revised Base Case** Astellas requests that the analyses described above are accepted as the new base case and applied cumulatively. With end of life criteria met, in order to meet the ICER threshold Astellas has increased the Patient Access Scheme (PAS) discount from [redacted] This leads to a cumulative base case ICER, with the updated PAS applied of £49,968. See Table 2 below.	Comment noted. Applying the committee's preferred assumptions (see section 3.13) and including all commercial arrangements in the model resulted in an ICER which was below £50,000 per QALY gained for gilteritinib compared with salvage chemotherapy (the ICER is confidential and cannot be reported here). With the discount agreed in the commercial arrangement, the most plausible ICER was within the range that NICE normally considers an acceptable use of NHS resources for a life-extending treatment at the end of life. Therefore, the committee recommended gilteritinib as an option for treating relapsed or refractory FLT3 mutation-positive AML in adults, although gilteritinib should not be given as maintenance therapy after a haematopoietic stem cell transplant. See FAD

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				section 3.14

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [ID1484]

Additional Evidence

February 2020

File name	Version	Contains confidential information	Date
ID1484 Gilteritinib AML Post-ACD Additional Evidence ACIC	Redacted	Yes	17th February 2020

1. Additional data from the ADMIRAL trial, in particular supporting post-HSCT OS

Section 1 and 3.5 of the ACD notes that the Appraisal Committee considered the ADMIRAL trial was the most appropriate source for modelling the post-HSCT OS. In Section 3.14 the ACD also comments that the modelling of overall survival data after stem cell transplant was uncertain, and that the Appraisal Committee noted that additional data on overall survival after stem cell transplant could potentially resolve this uncertainty.

In the Company Submission, Astellas communicated that the post-HSCT ADMIRAL data from the September 2018 data cut were immature (with both low numbers and short-term follow-up) and as such, Astellas considered the use of other comparable post-HSCT datasets to support the understanding of the expected long-term outcomes. Astellas had been told by its Global colleagues that there were to be no further data cuts and analyses from ADMIRAL. This has changed and Astellas has been able to obtain an updated data cut (data cut off September 2019) to support this submission and discussions with NICE[1]. These data were not available at time of the initial Company Submission or during previous communications through the process to date.

The updated dataset builds on the understanding of the clinical effectiveness of gilteritinib in FLT3 positive relapsed or refractory AML patients. The data continues to support the effectiveness of gilteritinib; in particular, gilteritinib post-HSCT and the longer term response rates. The new data cut means that many patients who were censored in the data presented in the initial Company Submission are now contributing to the results. This is particularly important for the 63 patients who were transplanted on the gilteritinib arm, where previously there was extensive censoring in the first year, but now with further follow up there is little censoring before day 650 (22 months).

The updated analysis is presented below; critical to the model are the updated OS data, post-HSCT OS data and the mean treatment duration (which is now [redacted] cycles). The clinical data overview is presented and the updated cost-effectiveness summary is provided below that. To confirm, all data presented below is from the ADMIRAL September 2019 data cut which has also been used to underpin the cost effectiveness analysis.

The ICERs presented represent figures with the updated Patient Access Scheme (PAS) which Astellas is putting forward. A cumulative base case ICER is presented with this

applied. With end of life criteria met, in order to meet the ICER threshold Astellas has increased the Patient Access Scheme (PAS) discount from [redacted].

Overall Survival

Overall survival was a co-primary outcome in ADMIRAL, the median OS was longer in patients receiving gilteritinib (9.3 months; 95% CI: 7.7 to 10.5) compared to patients treated with salvage chemotherapy (5.6 months; 95% CI 4.7 to 7.3) (hazard ratio [HR]: 0.679 [95% CI: 0.527 to 0.875; p<0.001), see Figure 1.

The 2 year survival rate was higher in patients receiving gilteritinib versus salvage chemotherapy (20.3% versus 14.2%), One-year and 6-month OS was also higher with gilteritinib (36.6%, 65.5%) versus salvage chemotherapy (19.2%, 48.9%), respectively, see Table 1.

Figure 1 Kaplan-Meier Plot of Overall Survival by Treatment Arm

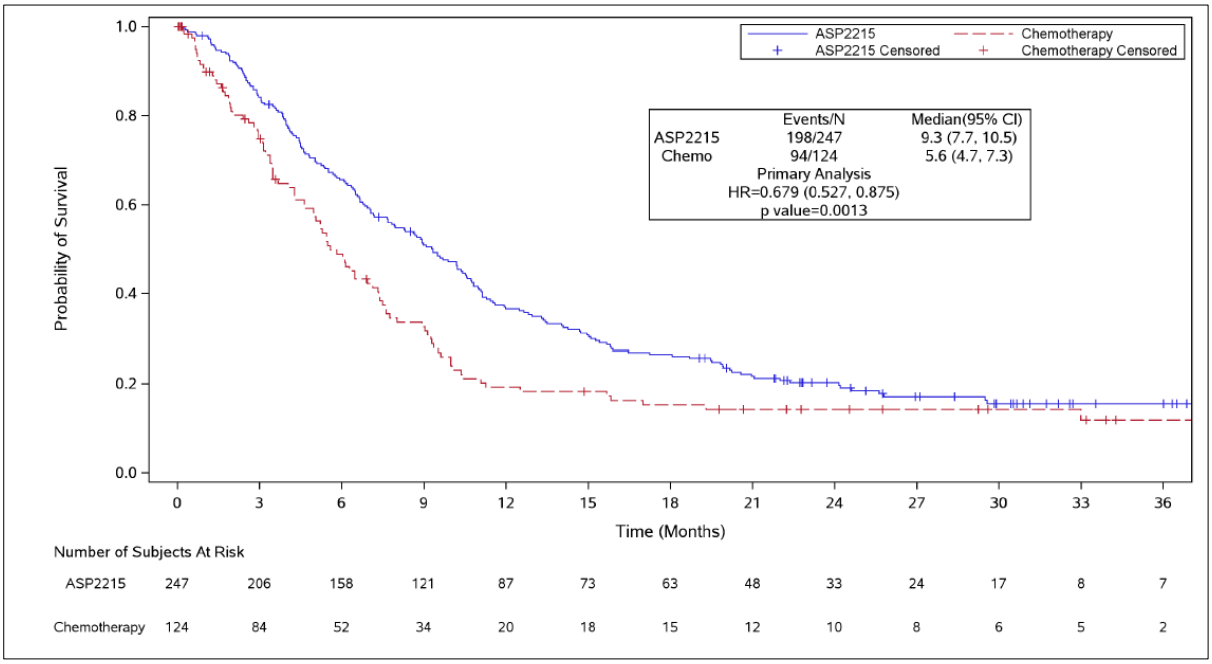


Table 1 Clinical Effectiveness: Overall Survival, ADMIRAL

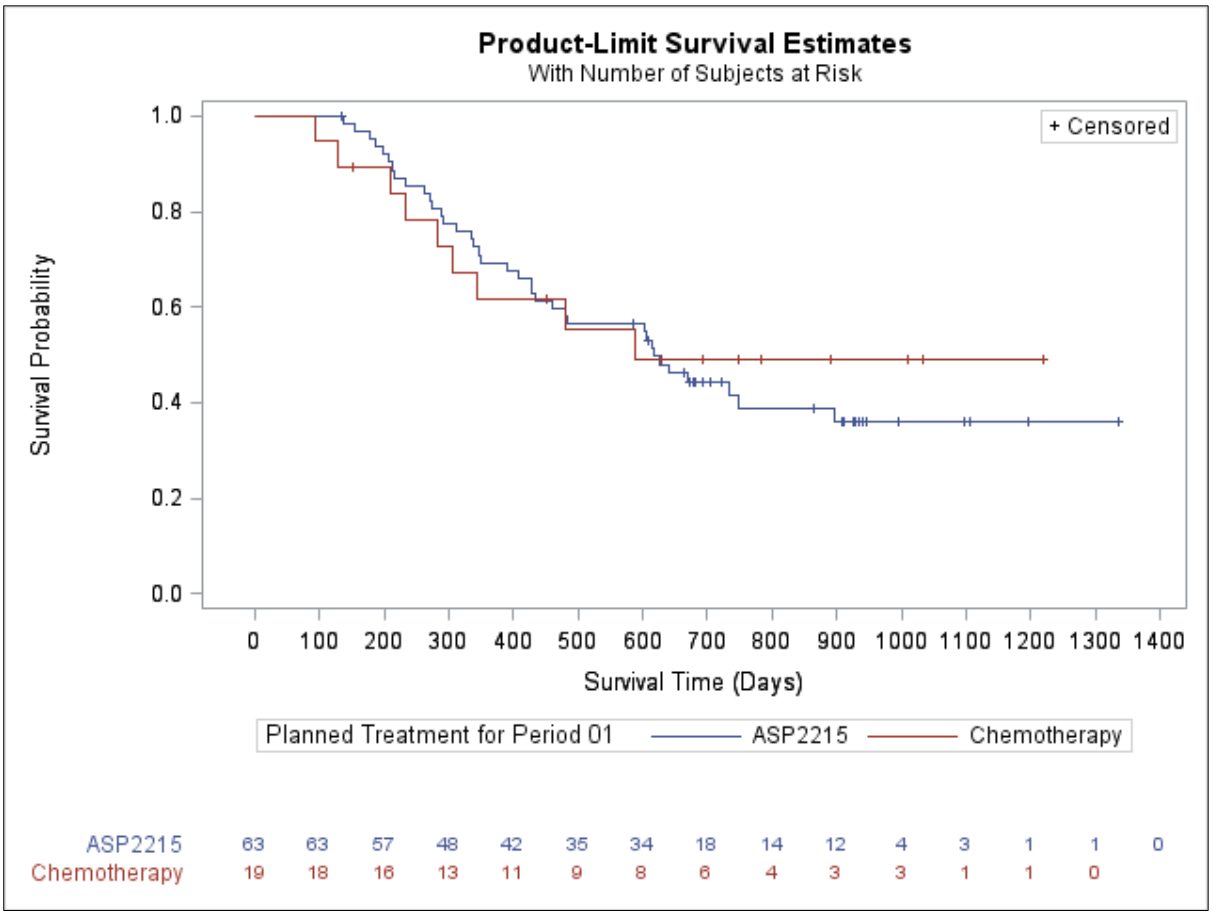
Outcomes	Gilteritinib (N=247)	Salvage chemotherapy (N=124)
Overall Survival, median months (95% CI)	9.3 (7.7, 10.5)	5.6 (4.7, 7.3)
Overall Survival Rate % (95%CI)		

6 months	65.5 (59.2, 71.1)	48.9 (39.3, 57.8)
12 months	36.6 (30.6, 42.7)	19.2 (12.4, 27.2)
24 months	20.3 (15.4, 25.7)	14.2 (8.3, 21.6)

Post-HSCT Survival

The median OS was longer in post-HSCT patients receiving gilteritinib (610 days) compared to HSCT patients treated with salvage chemotherapy (482 days) (hazard ratio [HR]: 1.108 [95% CI: 0.534 to 2.292; p<0.7836). See Figure 2.

Figure 2 Kaplan-Meier Plot of Overall Survival Post-HSCT (ITT population)

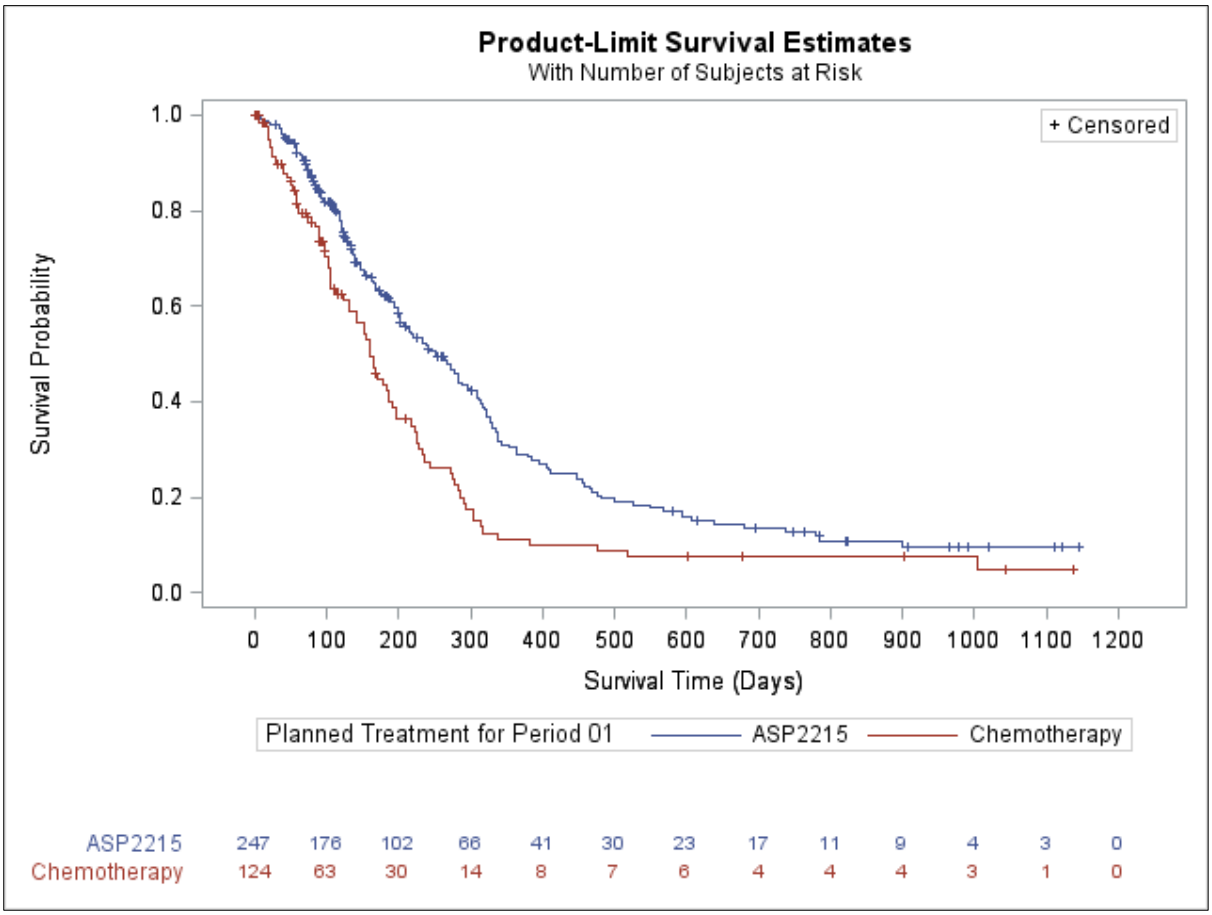


Note: ASP2215 is gilteritinib. Day 0 is randomisation

Overall OS Data Censored for HSCT

The median OS censored for HSCT was longer patients receiving gilteritinib (156 days) compared to HSCT patients treated with salvage chemotherapy (103 days) (hazard ratio [HR]: 0.600 [95% CI: 0.460 to 0.782; p<0.001). This data shows that when removing the treatment benefits patients receive with the HSCT, the OS benefit remains clear with gilteritinib. See Figure 3 below.

Figure 3 Kaplan-Meier Plot of Overall Survival, Censored for HSCT (ITT population)



Note: ASP2215 is gilteritinib

In conclusion, this updated ADMIRAL analysis confirms the benefit of gilteritinib for FLT3 positive relapsed or refractory AML patients. The updated data shows that with an extra year of follow up, the HR for OS remains consistent. In addition, this follow up has reduced the extent of censoring post HSCT which leads to increased confidence in this data and the associated curves which support the CE case.

Cost Effectiveness Summary and Interpretation

The OS and EFS data from the ADMIRAL September 2019 data cut were used in a cost-effectiveness analysis for both patients with and without HSCT, in addition to the updated mean treatment duration with gilteritinib ([redacted] cycles i.e. [redacted] treatment days). The approach taken was to add the new data to the preferred base case analysis put forward by the ERG, as well as to apply some subsequent assumptions discussed below (and BSC).

The resultant ICER is presented in Table 2.

It is of interest that the updated ADMIRAL analysis shows that, in the first 1-2 years post-HSCT, the ADMIRAL curve aligns to Evers et al[2] in terms of OS. Previously, Astellas used Evers to inform post-HSCT OS because the data from ADMIRAL had high uncertainty due to low patient numbers and short follow-up. The updated ADMIRAL analysis has less censoring and therefore higher patient numbers as well as longer follow up, and now show that survival is similar in ADMIRAL.

Astellas believes that with longer follow up, the ADMIRAL post-HSCT data will show a similar (or potentially more favorable) survival curve to Evers – supporting the rationale for using Evers in the initial Company Submission, which is still a plausible approach. The use of Evers to inform the long-term outcomes has been explored as a scenario. The resultant ICERs are presented in Table 3.

2. Additional evidence to inform the choice of cure point

Section 3.4 of the ACD states that the Appraisal Committee concluded it had not been presented with evidence for a 2-year cure point.

Astellas agrees that the commentary around the cure point submitted to date has had limitations. The Company acknowledges that it has changed the cure assumption from a conservative 3 year position to an earlier time point, however, we consider this to be more realistic and a better reflection of the evidence and clinical expert input that has emerged through the process. Astellas wishes to submit new evidence, which supports a clinically plausible cure point of between 18 and 24 months. For modelling the base case Astellas has used the 2 year time point.

During this appraisal, Astellas has continued to validate the key inputs that drive the CE model. In clinical practice AML patients can be under lifelong surveillance due to high risk of relapse. A “cure” can be defined as the point when the risk of relapse is very low. The clinical expert accepted this definition of cure during AC meeting in December.

The NICE TA for midostaurin (TA523, June 2018)[3], for use in newly diagnosed AML patients, concluded to use a 3 year cure point. This seems to have been based on “best fit” to model this part of the disease pathway. This was the cure point assumed by Astellas in its initial submission. Since then, further insight has been published and gathered on

relapsed or refractory AML patients, which help our understanding of the outcome of such patients post HSCT.

The only way for patients with relapsed AML to achieve cure currently, is to receive stem cell transplantation. For that reason, we focus on data on patients who have received transplantation following relapse.

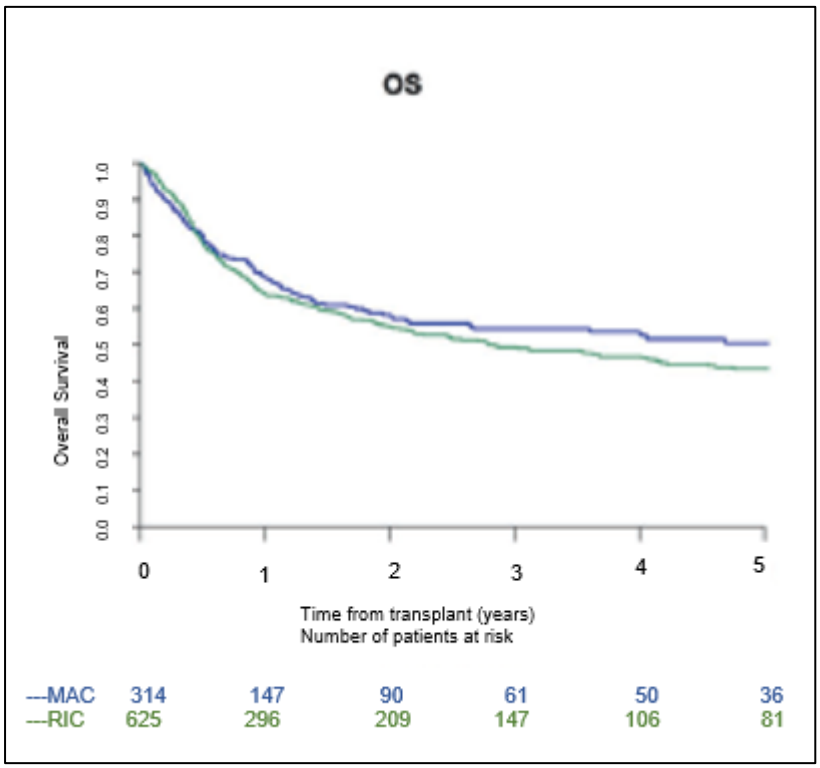
Data from Gilleece[6], Dillon[7], ADMIRAL[8], Evers[2], Ustun[4] and Poiree[5] are presented in Figure 4 below. Across these sources, the post-HSCT curves generally flatten at the 18 – 24 month point, supporting this as a suitable cure point for this post-HSCT population. These publications were identified via a targeted literature review which was updated based on feedback from NICE and external clinical input. Gilleece, Dillon and ADMIRAL are discussed in more detail below as they are the mains sources of data which have emerged since the original submission in June 2019.

Figure 4 Comparison Chart of Post-HSCT OS to Support Cure Point of 18-24 Months

One source of insight is the Gilleece et al 2020 publication[6], which analysed data from the European Society for Blood and Marrow Transplantation (EBMT) database which included 1,879 patients from 230 European transplant centers, including the UK. This data relates to AML patients who have received allogenic stem cell transplantation after relapse from their

first remission and includes all cytogenetic and molecular profiles, as well as risk groups, including FLT3 positive patients. Figure 5 shows the OS curve flattening at 2 years especially for the MAC (myelo-ablative conditioning) group. It is likely (given that FLT3 is an adverse risk category with a high risk of relapse, and MAC is known to have lower relapse outcome post-transplant) that most FLT3 patients will receive a MAC conditioning regimen.

Figure 5 OS Post-Transplant, RIC vs MAC, allogeneic Haemopoietic Cell Transplant in Patients Aged 50 or Older

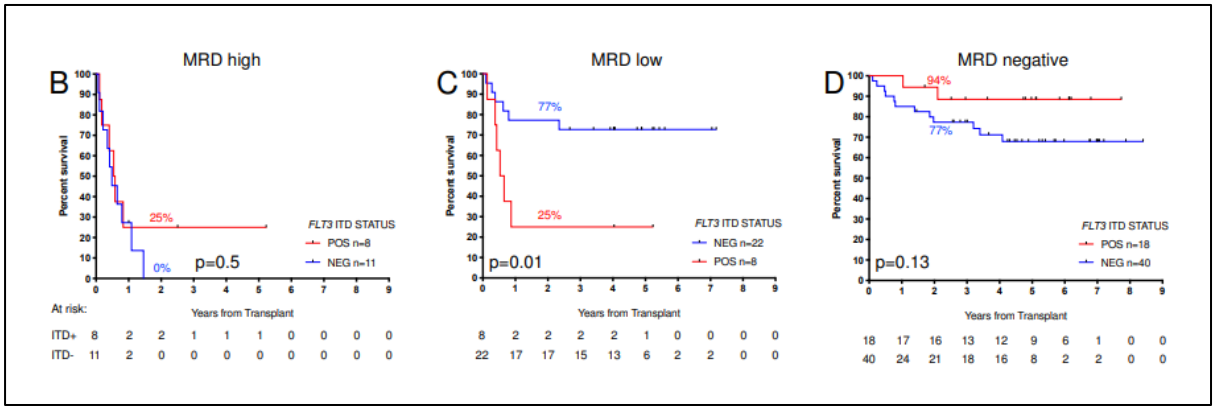


Abbreviations: OS: overall survival; RIC reduced intensity conditioning; MAC myeloablative conditioning

Another source is Dillon et al 2020[7], with a median follow up of 4.9 years. This informs our understanding of FLT3 positive patients post HSCT in the UK. Figure 6 shows OS in FLT3 positive and negative patients and the curve flattens before year 2; no deaths occur after that time point for FLT3 positive patients. Furthermore, data from this study, not included in the publication[8], but shared with Astellas shows all FLT3 positive patients in the study who relapsed had done so by year 1. See Figure 7.

The curves seen in Figure 6 demonstrate that OS in FLT3 positive patients (red line) plateaus before 2 years and Figure 7 shows that when these three curves are combined the same result is seen.

Figure 6 Effect of FLT3 ITD on Outcome According to Pre-transplant MRD status



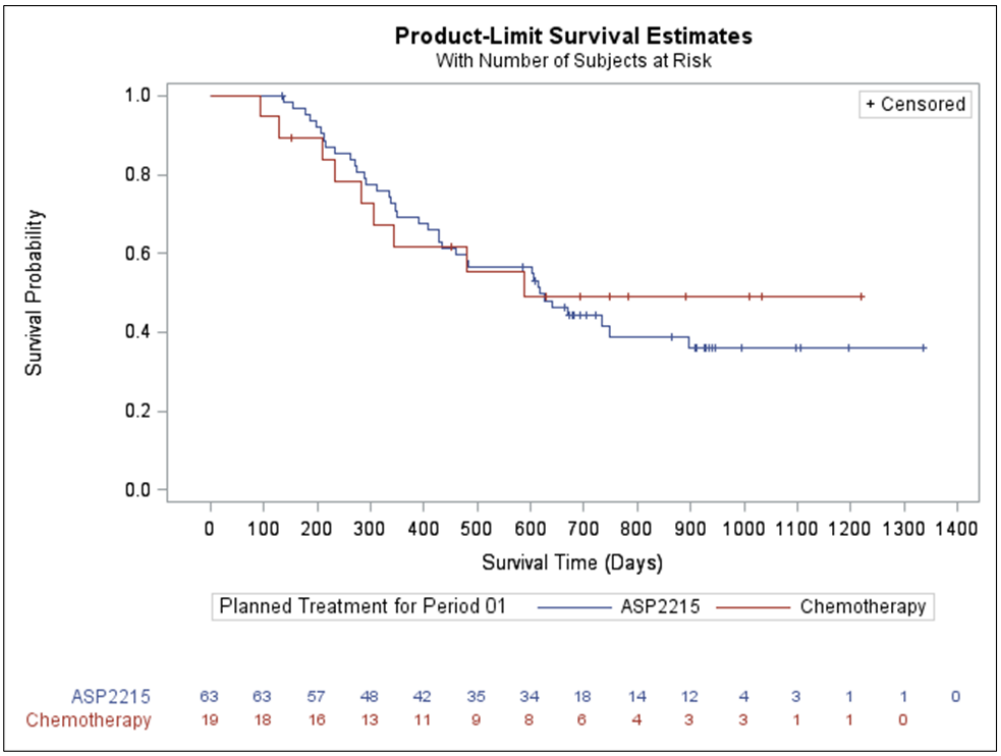
Note: Percentages indicate estimated 2 year overall survival. (B-D) Overall survival from transplant for patients with high (B), low (C) and negative (D) pre-transplant MRD. MRD: Measurable residual disease

Figure 7 OS in FLT3 Positive Patients who Received HSCT in AML17 trial

Finally, data from ADMIRAL[1] shows that of those patients who underwent a transplant (n=63) the OS curve flattens at 22 months from randomisation. See

Figure ***8*** below.

Figure 8 OS Post-HSCT ADMIRAL, September 2019



Note: ASP2215 is gilteritinib

During the Appraisal Committee meeting the clinical expert expressed the view that in clinical practice, patients who receive a transplant in the relapse setting, and who were in remission 2 years post-transplant, would unlikely relapse after that time point.

In addition, Astellas has sought input from AML clinical experts through the process and since the Appraisal Committee meeting and receipt of the ACD. These experts have supported the view that that it is meaningful to describe the point beyond which patients are unlikely to relapse as between 18 – 24, as most events (relapses and deaths) have occurred by then. Some have cited this period as short as 9 – 12 months. This links to the definition of cure point provided above.

In conclusion, Astellas believes published data, along with the clinical expert insights provided both to Astellas and to the Appraisal Committee, supports an 18 – 24 month cure point for FLT3 positive relapsed/refractory AML patients post HSCT. Cost-effectiveness analysis was conducted using a 2 year cure point, with post-progression costs applied for 2 years only, in line with ERG feedback in the Appraisal Committee slides (see slide 29 footnote).

The resultant ICER is presented in Table 2.

3. Quality of life and costs associated with administration

Section 3.9 notes the concern that the potential quality of life benefits of oral gilteritinib had not been adequately addressed in the Company's submission.

Astellas agrees that the potential quality of life benefits of oral gilteritinib, with less time in hospital, compared with the inpatient chemotherapy with frequent debilitating complications, was not adequately captured in ADMIRAL. Astellas also agrees that the disutility arising from the associated use of high intensity chemotherapy has not been adequately taken in to account in the base case – in part due to the limited PRO questionnaire completion by the patients in the salvage chemotherapy arm of ADMIRAL.

From a clinical point of view, the importance of this was raised during Technical Engagement and is further supported by a patient survey presented at the American Society of Haematology (ASH) annual meeting December 2019 by the Acute Leukemia Advocacy Network (ALAN).

Astellas acknowledges that the previous base case cost-effectiveness analysis assigns the same disutility value to patients experiencing each adverse event, irrespective of treatment received. Hence the additional disutility of receiving more intensive chemotherapy regimens is not accounted for in the original analysis.

Astellas has considered this by amending the disutilities experienced by salvage chemotherapy patients whilst on treatment.

Astellas has previously assigned a disutility of -0.044 to patients receiving high-intensity chemotherapy (FLAG-IDA, MEC), a value reported by Wehler et al 2018[9]. This value represents a conservative approach and is representative of patients receiving therapy and experiencing minimal adverse events (only the most impactful event was included). This study also reports disutility values for patients receiving high-intensity chemotherapy regimen, hypomethylating agents and low-intensity chemotherapy regimens (LoDAC) and includes disutility for all events experienced. The values for high-intensity chemotherapy, hypomethylating agents and low-intensity chemotherapy are reported as -0.190, -0.225 and -0.166 respectively.

A revised cost-effectiveness analysis with these utility values applied to the relevant regimens in the weighted comparator has been submitted. Based on feedback received during the Appraisal Committee meeting, these disutility values are only applied for the first 3 cycles, to reflect the time-on-treatment for patients receiving chemotherapy regimens in the economic model i.e. patients receive 2.24 cycles of azacitidine.

The previous approach of applying a full month of hospitalisation costs to patients receiving the high-intensity chemotherapy regimens has been retained.

The resultant ICER is presented in Table 2.

4. Drug wastage

Section 3.7 of the ACD notes that the Appraisal Committee felt it was reasonable to assume 14 days' supply of gilteritinib may be wasted. No evidence was presented to support this assumption.

Astellas agrees that a random event such as death could be one of the causes of drug wastage, and it could be appropriate that 14 days wastage could be applied for these patients, but Astellas believes that the majority of patients would discontinue in a more managed way i.e. following consultation with a clinical expert whereby no further treatment is prescribed.

This was also as discussed at the Appraisal Committee meeting, where the clinical expert commented that the majority of discontinuation is likely to occur through clinical management, i.e. at the presentation of symptoms of progression. This reduces the potential for drug wastage, as further medication is not dispensed to such patients who are identified as unlikely to benefit from continuing treatment.

A similar logic was followed in TA451[10] (ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia) where it was stated by clinical experts that people whose disease responded to treatment would have prescriptions for several months but would be monitored during that period to ensure a response was being maintained.

Astellas believes that a more accurate way to reflect the causes of discontinuation is to incorporate the cost of 7 days' wastage.

The resultant ICER is presented in Table 2.

5. Revised Base Case

Astellas requests that the analyses described above are accepted as the new base case and applied cumulatively. With end of life criteria met, in order to meet the ICER threshold Astellas has increased the Patient Access Scheme (PAS) discount from [redacted].

This leads to a cumulative base case ICER, with the updated PAS applied of £49,968.

See Table 2 below.

Table 2 Submission CE Revisions and Impact on the Cost-Effectiveness Ratio

Analysis	Description	ICER (vs. weighted comparator)	Cumulative ICER	ICER (vs. weighted comparator) with revised PAS discount	Cumulative ICER with revised PAS discount
Technical team's preferred scenario	As per slide 27 in Committee slides	£98,498			
Technical team's preferred scenario (without incorporation of Issue 8 or updated dispensing fee)	As per slide 27 in Committee slides	£102,085			
Technical team's preferred scenario (without incorporation of Issue 8) with updated dispensing fee	As row above, with monthly dispensing fee applied to gilteritinib	£103,066			
Incorporation of ADMIRAL trial data from September 2019 data cut	As row above, with ADMIRAL data	£78,192		£68,665	
The analyses below are conducted on the row above, as one-way analyses and cumulative analyses:					
QoL Impact: Incorporation of revised disutility, costs for chemotherapy regimens	Revised disutility, costs for chemotherapy regimens added	£72,345	£72,345	£63,050	£63,050
Cure point: Application of 2-year cure point	Patients cured at 2 years (including removal of post-progression treatment costs post-cure point)	£64,588	£59,958	£56,636	£52,167
BSC: Inclusion of best supportive care (BSC) in weighted comparator	10% BSC included in weighted comparator	£76,228	£58,518	£67,254	£51,225
Wastage: Gilteritinib wastage costs 7 days	Cost of 7 days of wastage assigned to gilteritinib	£76,215	£57,086	£66,930	**£49,968**

Table 3 Scenario Analysis Based on Evers to Inform Post-HSCT

Analysis	Description	ICER (vs. weighted comparator)	
Technical team's preferred scenario	As per slide 27 in Committee slides	£98,498	
Technical team's preferred scenario (without incorporation of Issue 8 or updated dispensing fee)	As per slide 27 in Committee slides	£102,085	
Technical team's preferred scenario (without incorporation of Issue 8) with updated dispensing fee	As row above, with monthly dispensing fee applied to gilteritinib	£103,066	
		Cumulative ICER	**Cumulative ICER (with revised PAS discount)**
Incorporation of Evers data	As row above, with Evers and updated treatment duration: [redacted] cycles	£72,637	£63,784
QoL Impact: Incorporation of revised disutility, costs for chemotherapy regimens	Revised disutility, costs for chemotherapy regimens added	£67,327	£58,673
Cure point: Application of 2-year cure point	Patients cured at 2 years (including removal of post-progression treatment costs post-cure point)	£56,772	£49,394
BSC: Inclusion of best supportive care (BSC) in weighted comparator	10% BSC included in weighted comparator	£55,156	£48,279
Wastage: Gilteritinib wastage costs 7 days	Cost of 7 days of wastage assigned to gilteritinib	£53,830	£47,116

REFERENCES

[1] Astellas Data on File, ADMIRAL Sept 2019 Data Cut

[2] Evers G, Beelen DW, Braess J, et al. Outcome of Patients with Acute Myeloid Leukemia (AML) Undergoing Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) Beyond First Complete Remission (CR1). Blood. 2018;132(Suppl 1):4649-4649. doi:10.1182/blood-2018-99-116964

[3] National Institute for Health and Care Excellence (NICE). Midostaurin for untreated acute myeloid leukaemia. Technology appraisal guidance [TA523]. NICE. https://www.nice.org.uk/guidance/ta523/history . Published June 13, 2018

[4] Ustun, C. et al. Outcomes of UCB transplantation are comparable in FLT3+ AML: results of CIBMTR, EUROCORD and EBMT collaborative analysis. Leukemia 31, 1408–1414 (2017)

[5] Poiré, Xavier et al. Allogeneic stem cell transplantation benefits for patients≥ 60 years with acute myeloid leukemia and FLT3 internal tandem duplication: a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. haematologica 103, 256–265 (2018)

[6] Gilleece M et al. Allogeneic heamapoietic transplantation for acute myeloid leukaemia in second complete remission: a registry report by the Acute Leukaemia working Party of the EBMT. Leukemia. 2020 Jan;34(1):87-99

[7] Dillon R et al. Molecular MRD status and outcome after transplantation in NPM1 mutated AML: results from the UK NCRI AML17 study. Blood. 2020 Jan 13. pii: blood.2019002959 [Epub ahead of print]

[8] Astellas Data on File, AML 17

[9] Wehler E, Storm M, Kowall S, Campbell C, Boscoe A. A Health State Utility Model Estimating the Impact of Ivosidenib on Quality of Life in Patients with Relapsed/Refractory Acute Myeloid Leukemia. Presented at the 23rd Congress of the European Hematology Association, 14-17 June 2018, Stockholm, Sweden

[10] National Institute for Health and Care Excellence (NICE). Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia. Technology appraisal guidance [TA451]. NICE https://www.nice.org.uk/guidance/ta451. Published June 2017

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [ID1484]

ACD Response and Additional Evidence Clarification questions

February 2020

File name	Version	Contains confidential information	Date
ID1484 Gilteritinib AML ACD Clarification Questions ACIC	ACIC	No	25th February 2020

1. Please provide the Kaplan-Meier OS data for the ITT population in list form (2019 data cut).

The Kaplan-Meier (KM) Overall Survival (OS) data for the ITT population based on the 2019 ADMIRAL data cut is provided in the accompanying Excel file (ID1484 Gilteritinib AML_ACD Clarifications_KM Data), in the following sheets:

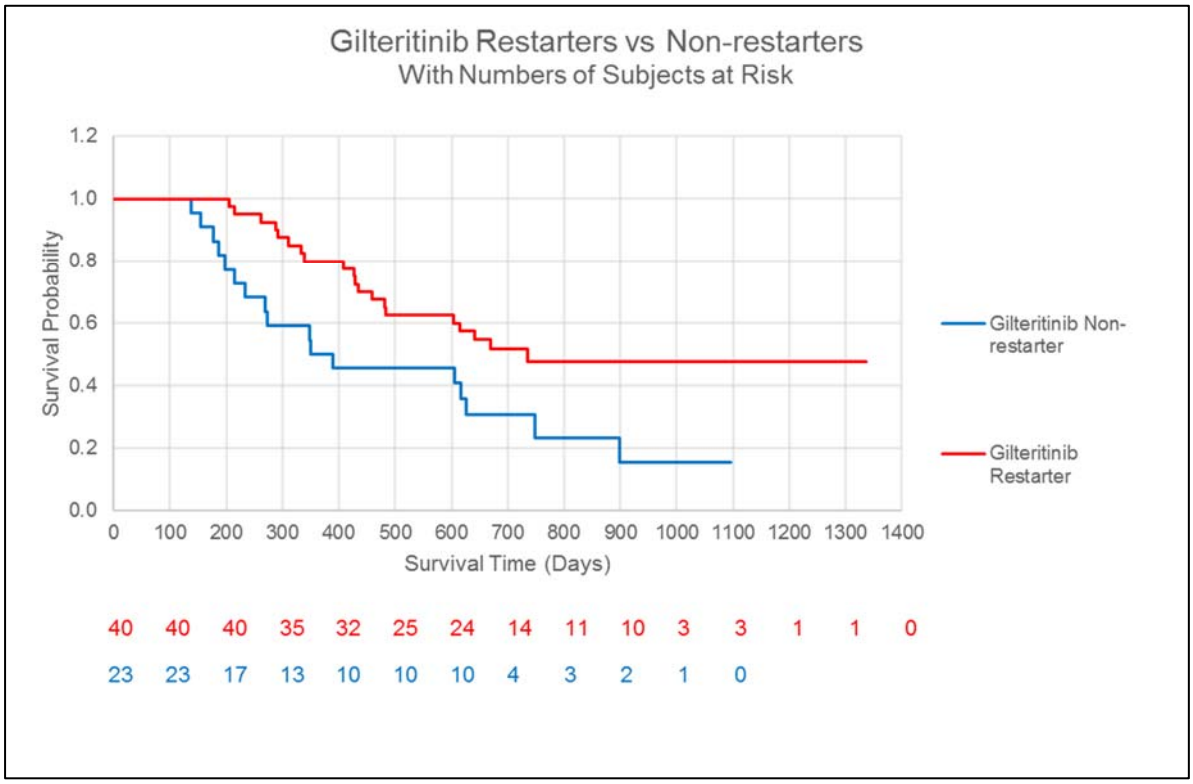
- D1 – Gilteritinib; KM data table
- D1 – Chemo; KM data table
- D1 – Graph; plotted KM curves

2. In response to clarification question 2, you report the HR for gilteritinib restarters versus non-restarters. Please provide the KM curves for these groups and the confidence interval around this HR.

The KM curves for the Post-HSCT OS for gilteritinib restarters and non-restarters based on the 2019 ADMIRAL data cut is shown in Figure 1.

The response to clarification question 2 reported the HR for overall survival between gilteritinib restarters and non-restarters as 0.57. Following clarification with Biostatistics colleagues, Astellas wishes to update this HR for overall survival in restarters vs non-restarters to 0.46 (95% CI: 0.24 to 0.88).

Figure 1. Kaplan Meier Plot of Post-HSCT Overall Survival for Gilteritinib Restarters vs Non-restarters (ITT population)



3. In response to clarification question 5, you state the number of patients who were still receiving gilteritinib at the last exposure date. Please clarify how many of these are patients who underwent HSCT and subsequently received gilteritinib maintenance therapy.

The numbers of remaining on study at the point of the September 2019 data cut, split by whether they underwent HSCT or not, are given below in Table 1. All 13 subjects who were HSCT recipients were gilteritinib restarters after transplantation, that is, went back on study treatment gilteritinib post-transplantation.

Table 1. Number of Subjects on Study Treatment gilteritinib at September 2019 Cut-off Date (=17 September 2019) by HSCT Recipient Status in ITT population

	HSCT Recipient Status	Subjects[a] continuing on gilteritinib at September 2019 Cutoff Date
Gilteritinib	HSCT Recipients	13
	HSCT non-Recipients[b]	6
	Overall	19

(a) Subjects alive who have not discontinued from study treatment gilteritinib at the September 2019 cut-off date and have a non-missing last exposure date.
(b) There is one additional subject who has not discontinued from study treatment gilteritinib and has a last exposure date of 9 October 2019 after the September 2019 cut-off date.

4. In response to clarification question 3b, you stated that the With HSCT data relate to time from randomisation to death. The ERG believes that this may not be accurate as the modelled curve appears to only fit the KM function when the time lag for HSCT is also included (i.e. zero deaths for 3-4 months, followed by the parametric function). Please double-check this.

Astellas confirms the data presented is events from time of randomisation to death. The first death happened on Day 137 (after randomisation) in the gilteritinib treatment arm and on Day 95 in the salvage chemotherapy treatment arm.

Clarification questions

1) Please provide the version of the model used as the starting point that will allow the ERG to replicate all of the ICERs in the ACD response using the model change log. Please ensure that every step is fully described for each ICER in the table.

   A model with the Company original base case, with corrections - ICER of £54,844/QALY – has been provided, along with a model change log which outlines the steps taken to produce the ACD response model.

2) Please justify why the HR for OS for gilteritinib maintenance therapy is included in the updated model.

   According to the licence, gilteritinib may be re-initiated in patients following haematopoietic stem cell transplantation (HSCT). In the ADMIRAL trial 40 patients did re-initiate gilteritinib after transplant, referred to here as "maintenance therapy".

   Astellas continues to apply a HR of 0.69 to reflect an on-treatment benefit associated with gilteritinib maintenance therapy after HSCT. Post-HSCT survival estimates, either from Evers et al. or from the observed ADMIRAL data, are used as a baseline survival rate reflecting the outcomes of all transplanted patients (i.e. including those previously treated with SC or those not restarting gilteritinib). While some of the benefit received by patients restarting gilteritinib may already be captured in the ADMIRAL data, it is still plausible (and supported by post hoc analyses of ADMIRAL) that these patients will outperform those not receiving maintenance therapy. In a post-hoc analysis of the more mature September 2019 ADMIRAL data, the HR for overall survival in restarters vs non-restarters was 0.57.

   This approach is balanced by including costs of maintenance therapy. As in the previous submission, the duration and cost of treatment includes patients receiving maintenance therapy in the gilteritinib arm. We draw the reviewer's attention to the previously submitted sensitivity analysis that suggested removing both the costs and benefits of maintenance therapy had a marginal impact on the ICER. It is also likely that removing the post-HSCT costs of gilteritinib based on the new data cut would lower the ICER, since it is intuitive that the majority of additional treatment described in the updated (Sept 2019) analysis would have been received as maintenance therapy.

3) Please clarify which data have been used to inform With HSCT OS:
   a. Are these pooled data across both arms? Or just the gilteritinib group?

Yes, the data has been pooled across both arms.

b. Do these data relate to time from randomisation to death, or time from HSCT to death?

These data relate to time from randomisation to death.

c. It appears that the Gompertz model is selected for this subgroup. Please justify this selection.

Parametric survival models were selected using the same methods outlined in section B.3.3.5 of the original Company Submission. The goodness-of-fit criteria (AIC, BIC) which have been estimated for each parametric model are presented in Table 1 below. Using an aggregate view across the two measures, Gompertz was the best-fitting model.

Table 1: Summary of Goodness of Fit Statistics for all treatments – OS with HSCT

Treatment	Efficacy inputs	Parametric Function	AIC	BIC
All treatments	OS with HSCT	Exponential	395.697	398.104
		Weibull	396.964	401.778
		Log-logistic	393.609	398.422
		Log-normal	394.718	399.531
		Gompertz	**393.496**	**398.309**
		Generalised gamma	396.383	403.603

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival

4) The updated survival analysis is not described in the additional evidence document:
   a. Please explain how the models were fitted.

Model fit was evaluated using the same methods as outlined in section B.3.3.1 of the original Company Submission, namely AIC/BIC tests, visual inspection, log-cumulative hazard plots examination, proportional hazards assumption testing and clinical input.

   b. Please comment on the selection of distributions for EFS and OS for the no HSCT subgroups.

Parametric survival models were selected using the same methods outlined in B.3.3.3 (for EFS) and B.3.3.2 (for OS) of the original Company Submission. The goodness-of-fit criteria (AIC, BIC) which have been estimated for each parametric model in the treatment arms are presented in the tables below.

Log-logistic was the best-fitting EFS model for the gilteritinib arm under both AIC and BIC criteria, and for consistency, this was also selected for the salvage chemotherapy arm, using the methods outlined in section B.3.3.3 of the original Company Submission.

Log-logistic was the best-fitting OS model for the gilteritinib and salvage chemotherapy arms under both AIC and BIC criteria.

Table 2: Summary of Goodness of Fit Statistics for gilteritinib - EFS without HSCT

Treatment	Efficacy inputs	Parametric Function	AIC	BIC
Gilteritinib	EFS without HSCT	Exponential	488.662	491.236
		Weibull	489.815	494.964
		Log-logistic	**472.575**	**477.724**
		Log-normal	475.707	480.857
		Gompertz	479.258	484.407
		Generalized gamma	477.445	485.169

Table 3: Summary of Goodness of Fit Statistics for salvage chemotherapy - EFS without HSCT

Treatment	Efficacy inputs	Parametric Function	AIC	BIC
Salvage Chemotherapy	EFS without HSCT	Exponential	63.366	65.477
		Weibull	65.331	69.553
		Log-logistic	**62.459**	**66.681**
		Log-normal	61.140	65.362
		Gompertz	64.110	68.332
		Generalized gamma	60.870	67.203

Table 4: Summary of Goodness-of-fit Statistics for gilteritinib - OS without HSCT

Treatment	Efficacy inputs	Parametric Function	AIC	BIC
Gilteritinib	OS without HSCT	Exponential	1,086.839	1,090.054
		Weibull	1,087.564	1,093.993
		Log-logistic	**1,066.129**	**1,072.558**
		Log-normal	1,070.102	1,076.532
		Gompertz	1,086.501	1,092.931
		Generalised gamma	1,071.796	1,081.441

Table 5: Summary of Goodness-of-fit Statistics for salvage chemotherapy- OS without HSCT

Treatment	Efficacy inputs	Parametric Function	AIC	BIC
Salvage Chemotherapy	OS without HSCT	Exponential	508.996	511.650
		Weibull	510.983	516.291
		Log-logistic	**498.367**	**503.675**
		Log-normal	501.810	507.118
		Gompertz	506.266	511.574
		Generalised gamma	503.243	511.205

5) Please explain how the additional 2019 datacut was obtained. Were the same data collection mechanisms used as those in the main trial?

Yes. The updated data cutoff 17SEP2019 follows the same data collection mechanisms used as for the primary analysis at 17SEP2018, using the same protocol.

Data request

1) Based on the 2019 datacut, please provide a summary of survival status in a 2x2 table reporting number of patients alive/dead by treatment group arm (as per ERG report Table 35).

Please see Table 6 below. The event rate in the chemotherapy arm is likely to be an underestimate due to patients being lost to follow-up after short exposure to chemotherapy.

Table 6 Total Number of Events and Number of Censored Events for OS in ITT Population

	Events (%)	Censored (%)
Gilteritinib	198 (80.16%)	49 (19.84%)
Chemotherapy	94 (75.81%)	30 (24.19%)

2) Please provide the summary data underlying the Kaplan-Meier plot for the With HSCT OS (in list format sufficient to generate the KM plot).

Please see below.

Table 7 Survival Estimates and Number of Events and Censored Events for OS by Timepoint and Treatment Arm in HSCT Recipients in ITT Population

Stratum 2: Planned Treatment for Period 01 = ASP2215 HSCT Recipient = Y

Product-Limit Survival Estimates

survtime_os		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.00		1.0000	0	0	0	63
135.00	*	.	.	.	0	62
137.00		0.9839	0.0161	0.0160	1	61
155.00		0.9677	0.0323	0.0224	2	60
177.00		0.9516	0.0484	0.0273	3	59
187.00		0.9355	0.0645	0.0312	4	58
197.00		0.9194	0.0806	0.0346	5	57
206.00		0.9032	0.0968	0.0375	6	56
214.00		0.8871	0.1129	0.0402	7	55
215.00		0.8710	0.1290	0.0426	8	54
233.00		0.8548	0.1452	0.0447	9	53
262.00		0.8387	0.1613	0.0467	10	52
270.00		0.8226	0.1774	0.0485	11	51
273.00		0.8065	0.1935	0.0502	12	50
289.00		0.7903	0.2097	0.0517	13	49
292.00		0.7742	0.2258	0.0531	14	48
311.00		0.7581	0.2419	0.0544	15	47
334.00		0.7419	0.2581	0.0556	16	46
339.00		0.7258	0.2742	0.0567	17	45
348.00		0.7097	0.2903	0.0576	18	44
351.00		0.6935	0.3065	0.0585	19	43
390.00		0.6774	0.3226	0.0594	20	42
409.00		0.6613	0.3387	0.0601	21	41
427.00		0.6452	0.3548	0.0608	22	40
429.00		0.6290	0.3710	0.0613	23	39
434.00		0.6129	0.3871	0.0619	24	38
459.00		0.5968	0.4032	0.0623	25	37
481.00		0.5806	0.4194	0.0627	26	36
484.00		0.5645	0.4355	0.0630	27	35
586.00	*	.	.	.	27	34
604.00		0.5479	0.4521	0.0633	28	33
606.00		0.5313	0.4687	0.0635	29	32
610.00	*	.	.	.	29	31
614.00		0.5142	0.4858	0.0637	30	30

616.00		0.4970	0.5030	0.0639	31	29
626.00		0.4799	0.5201	0.0639	32	28
641.00		0.4628	0.5372	0.0639	33	27
663.00	*	.	.	.	33	26
665.00	*	.	.	.	33	25
670.00		0.4442	0.5558	0.0640	34	24
674.00	*	.	.	.	34	23
678.00	*	.	.	.	34	22
681.00	*	.	.	.	34	21
692.00	*	.	.	.	34	20
694.00	*	.	.	.	34	19
694.00	*	.	.	.	34	18
705.00	*	.	.	.	34	17
722.00	*	.	.	.	34	16
735.00		0.4165	0.5835	0.0657	35	15
749.00		0.3887	0.6113	0.0669	36	14
864.00	*	.	.	.	36	13
898.00		0.3588	0.6412	0.0681	37	12
908.00	*	.	.	.	37	11
910.00	*	.	.	.	37	10
926.00	*	.	.	.	37	9
929.00	*	.	.	.	37	8
933.00	*	.	.	.	37	7
940.00	*	.	.	.	37	6
947.00	*	.	.	.	37	5
995.00	*	.	.	.	37	4
1096.00	*	.	.	.	37	3
1106.00	*	.	.	.	37	2
1196.00	*	.	.	.	37	1
1336.00	*	0.3588	.	.	37	0

Stratum 4: Planned Treatment for Period 01 = Chemotherapy HSCT Recipient = Y

Product-Limit Survival Estimates						
survtime_os		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.00		1.0000	0	0	0	19
95.00		0.9474	0.0526	0.0512	1	18
130.00		0.8947	0.1053	0.0704	2	17
152.00	*	.	.	.	2	16
211.00		0.8388	0.1612	0.0854	3	15
232.00		0.7829	0.2171	0.0963	4	14
283.00		0.7270	0.2730	0.1044	5	13
305.00		0.6711	0.3289	0.1103	6	12
343.00		0.6151	0.3849	0.1144	7	11
452.00	*	.	.	.	7	10
482.00		0.5536	0.4464	0.1184	8	9
588.00		0.4921	0.5079	0.1201	9	8
629.00	*	.	.	.	9	7
693.00	*	.	.	.	9	6
747.00	*	.	.	.	9	5
784.00	*	.	.	.	9	4
890.00	*	.	.	.	9	3
1010.00	*	.	.	.	9	2
1032.00	*	.	.	.	9	1
1221.00	*	0.4921	.	.	9	0

3) Please provide the number of patients still receiving gilteritinib at 2019 datacut

There are 19 patients still receiving gilteritinib.

Table 8 Gilteritinib Patients Remaining in ADMIRAL

	Subjects[a, b] continuing on gilteritinib at September 2019 Cutoff Date
Gilteritinib	19

(a) Subjects alive who have not discontinued from study treatment gilteritinib at the September 2019 cut-off date and have a non-missing last exposure date.

(b) There is one additional subject who has not discontinued from study treatment gilteritinib and has a last exposure date of 9 October 2019 after the September 2019 cut-off date.

NICE National Institute for Health and Care Excellence

Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [ID1484]

Consultation on the appraisal consultation document – deadline for comments **5pm on 5 February 2020**, email: **NICE DOCS**

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Leukaemia Care
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	n/a
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [ID1484]

Consultation on the appraisal consultation document – deadline for comments **5pm on 5 February 2020**, email: **NICE DOCS**

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned about the unfair delay in access for patient in need of this treatment as a result of this ACD. This is now the only FLT3+ inhibitor for relapsed/refractory AML being considered for use on the NHS in England, following the pause of the quizartinib appraisal in late 2019. There is considerable unmet need in this group and clinicians are in agreement that FLT3+ inhibitors can meet this need in clinical practice.
2	The committee has decided that the cure point for the purposed of modelling is to be 3 years. However, the company argued that this should be 2 years in the committee meeting and the clinical expert agreed that this was more reasonable. The clinical expert has since confirmed that this was his opinion. We have consulted with two leading AML clinicians, who concurred with the clinical expert's viewpoint that 2 years was the most reasonable assumption in this patient population. The standard for clinical trials is 5 years, but the majority of relapses will occur much earlier. Whilst the 3 year cure point was the standard used in the midostaurin appraisal (TA523), this was in reference to an untreated population of patients and so may not be applicable to the indication considered here. Clinical experts indicated that relapses will occur earlier in this relapsed/refractory population, likely within the first 12 months. We urge the committee to take on board the recommendations of the clinical experts and allow modelling with a cure point of 2 years.
3	We are aware that the company have further data cuts available, which should provide further information on the outcomes of these patients. As one of the main points of discussion is uncertainty of post-transplant survival and utility values of these patients, we urge the company to submit this data and for the committee to consider this at the next committee meeting. We would also ask that Leukaemia Care have the opportunity to nominate a patient expert to attend this meeting to discuss this key clinical effectiveness issue.
4	The input we have received from leading AML clinicians is that quality of life gains from outpatient, oral treatment have not been fully represented in the disutility value.
5	The committee has indicated that this drug could not be considered for the CDF because "there is not plausible potential to satisfy the criteria for routine use because the committee's preferred ICER was over £90,000 per QALY gained." We are concerned about the precedent set by this statement. Addendum PMG9 of the appraisal process and methods guide states the ICERs "presented have the plausible potential for satisfying the criteria for routine use, taking into account the end-of-life criteria when appropriate". However, the addendum to the guide does not set a precise value for the threshold for 'plausible potential'. Should NICE wish to introduce such a threshold, there is ample opportunity in the upcoming methods review, and we would encourage you to do so from a transparency perspective. However, it is unreasonable for an individual committee to arbitrarily differ from other NICE committees and introduce such a threshold. We could find no evidence where a particular value for the threshold has been used in the past. We would like an explanation as to why an ICER threshold of £90,000 has been considered appropriate in this instance.
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted,

Please return to: **NICE DOCS**

Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [ID1484]

Consultation on the appraisal consultation document – deadline for comments **5pm on 5 February 2020**, email: **NICE DOCS**

please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [ID1484]

Consultation on the appraisal consultation document – deadline for comments **5pm on 5 February 2020**, email: **NICE DOCS**

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Royal College of Pathologists**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Gilteritinib for treating relapsed or refractory acute myeloid leukaemia [ID1484]

Consultation on the appraisal consultation document – deadline for comments **5pm on 5 February 2020**, email: **NICE DOCS**

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The reference costs for FLAG-IDA administration are not an accurate reflection of NHS costs- £1,418.51 (table 30 ACD committee papers). This appears to simply cover the costs of drug administration. This is always an in-patient regimen that requires admission for induction therapy usually for 4-6 weeks, a toxic regimen with inevitable infections and possibility of ITU admission. NHS income for such admission is around £30,000.00 (the associated anti-fungal therapy is usually £2,000.00). Simplistically the concept that the administration costs for the other regimens (AZA and LDAC) really questions the credibility of this analysis. If the reference costs have been taken from the ADMIRAL study costing would not take account of 'standard of care' costs within such a trial. I have raised this previously with the committee but am unable to see this accounted for within the document- apologies if this is my oversight.
2	2-year survival/cure point seems sensible- few events occur after 12 months and overwhelmingly patients alive and in remission 12 months post-transplant are mostly cured.
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or

Please return to: **NICE DOCS**

not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Gilteritinib for treating relapsed or refractory acute myeloid leukaemia: A Single Technology Appraisal

Addendum: ERG comments on company's additional evidence following the ACD

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK Aline Navega Biz, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
Date completed	3rd March 2020

1. Introduction

In January 2020, the National Institute for Health and Care Excellence (NICE) published its Appraisal Consultation Document (ACD) on the use of gilteritinib for treating relapsed or refractory (R/R) acute myeloid leukaemia (AML).[1] The ACD includes the following recommendation: *"Gilteritinib is not recommended, within its marketing authorisation, for treating relapsed or refractory FLT3-mutation-positive acute myeloid leukaemia in adults"* (NICE ACD,[1] page 3).

The NICE ACD[1] states that the Appraisal Committee concluded that the most plausible incremental cost-effectiveness ratio (ICER) for gilteritinib was above the range that NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life. A key driver of the ICER for gilteritinib relates to the evidence source used to inform outcomes for patients who undergo haematopoietic stem cell transplantation (HSCT) following either gilteritinib or chemotherapy: the company's base case used external evidence to inform post-HSCT overall survival (OS; Evers *et al*[2]), whilst the ERG's preferred base case analysis used OS data from the ADMIRAL trial.[3] The ACD states that the Appraisal Committee considered that the ADMIRAL trial is the most appropriate source because it included the population relevant to this appraisal.[1] The ERG's preferred analysis using the OS data from the ADMIRAL trial for patients undergoing HSCT resulted in an ICER for gilteritinib versus salvage chemotherapy of £102,085 per QALY gained (see ERG report,[4] Table 39, page 113). As discussed within both the ERG report and the company's submission (CS), the OS data for patients undergoing HSCT in ADMIRAL were uncertain due to the limited number of events and short follow-up. During the appraisal, the company indicated that the September 2018 data-cut of ADMIRAL was final;[5] hence, no further analyses of longer-term follow-up data were expected.

Following the negative ACD recommendation for gilteritinib, the company's position has changed and a further data-cut of the ADMIRAL trial has been obtained (data cut-off September 2019). In response to the ACD, the company submitted additional economic analyses that include the September 2019 data-cut from ADMIRAL, together with other model amendments. The company's ACD response includes the following documents and analyses:

(a) A document detailing the company's response to the ACD[6]

(b) A document which describes the additional evidence obtained from the 2019 data-cut of ADMIRAL, further amendments to the model, and new cost-effectiveness estimates based on an updated version of the company's model[7]

(c) Five spreadsheets which contain updated parameter estimates for survival models fitted to clinical time-to-event data used in the company's updated economic model, based on the ADMIRAL 2019 data-cut (event-free survival [EFS] and OS for patients who did not undergo HSCT in the gilteritinib and salvage chemotherapy arms, and OS for the pooled population of patients who received HSCT)

(d) An updated economic model which includes data from the 2019 data-cut of ADMIRAL, as well as other amendments to the company's base case (see Sections 2.2 and 2.3)
(e) A model change log that details how to implement elements of the company's new analyses.

In addition, the company provided two sets of responses to clarification questions from the ERG relating to the additional evidence from ADMIRAL and the updated economic model.[8]

The company's updated model includes an updated Patient Access Scheme (PAS) discount of [redacted] (previous PAS discount = [redacted]).

2. Summary and ERG critique of company's updated evidence

2.1 Updated time-to-event data based on the 2019 data-cut of ADMIRAL

The updated Kaplan-Meier plot for OS for the intention-to-treat population (ITT) using the 2019 data-cut is shown in Figure 1. The company's additional evidence document[7] reports that median OS was 9.3 months (95% confidence interval [CI] 7.7 to 10.5 months) for gilteritinib and 5.6 months (95% CI 4.7 to 7.3 months) for salvage chemotherapy. The hazard ratio (HR) for OS was 0.679 (95% CI 0.53 to 0.88; $p<0.001$). The median OS estimates for the 2019 data-cut are very similar to those obtained using the 2018 data-cut; however, the ERG notes that the HR obtained from the updated 2019 data-cut is less favourable (HR from previous 2018 data-cut = 0.637; 95% CI 0.490 to 0.830; $p=0.0004$). During the interval between the 2018 and 2019 data-cuts, there were an additional 27 events in the gilteritinib arm and an additional four events in the salvage chemotherapy arm (see ERG report,[4] Figure 2, page 33 and Figure 1 below).

As discussed in the ERG report[4] (Section 5.2.2, pages 47-50), the data for the ITT population shown in Figure 1 are not used directly in the company's economic model; rather, data for each treatment group are sub-divided into patients who subsequently received HSCT and patients who did not receive HSCT (hereafter referred to as "With HSCT" and "No HSCT" patients, respectively). OS for With HSCT patients is a key driver of the ICER for gilteritinib. Updated OS data for With HSCT patients by treatment group (from the time of randomisation) are shown in Figure 2. The equivalent data pooled across the treatment arms, which are used to inform OS for With HSCT patients in the company's updated model, are shown in Figure 3 (a side-by-side comparison of the same pooled data in each data-cut is shown in Figure 7 in Appendix 1). The updated 2019 Kaplan-Meier OS plots for the With HSCT group indicate more censoring towards the tails of the survivor functions and a more favourable probability of survival at later timepoints compared with the previous 2018 data-cut.

Figure 1: Kaplan-Meier plot of OS by treatment arm in ITT population, ADMIRAL 2019 data cut-off (reproduced from company's additional evidence document, Figure 1)

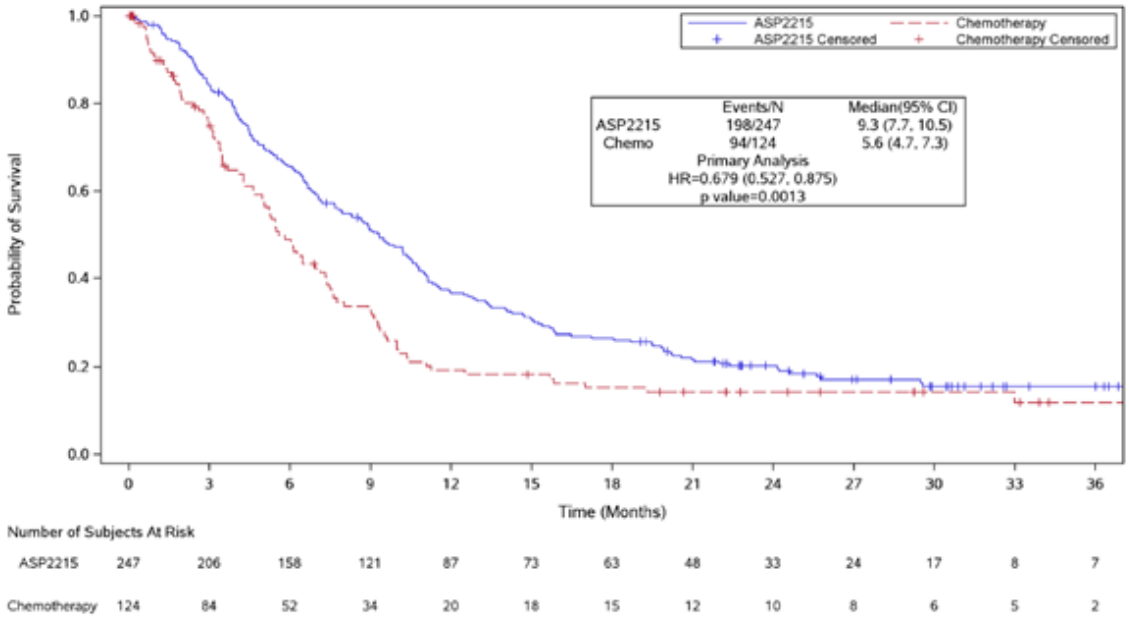


Figure 2: Kaplan-Meier plot of OS from randomisation, With HSCT patients, ADMIRAL 2019 data cut-off (reproduced from company's additional evidence document, Figure 2)

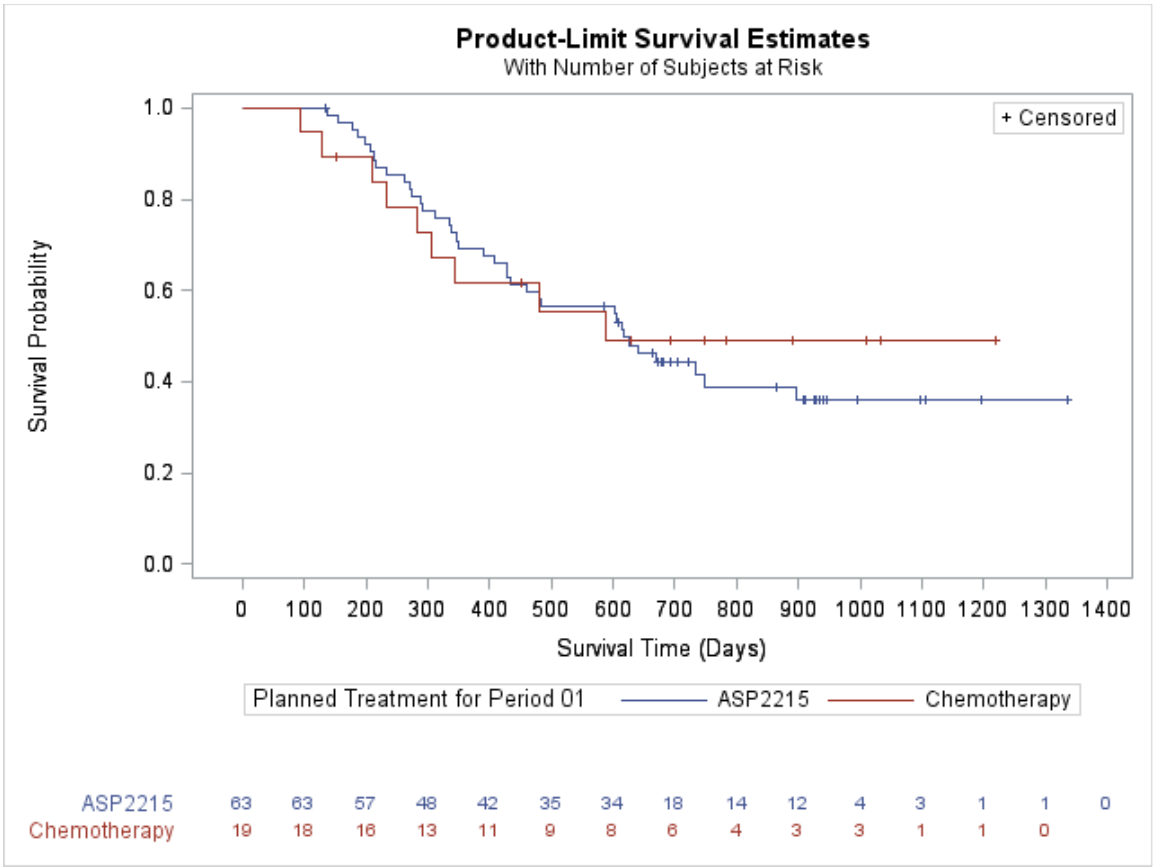
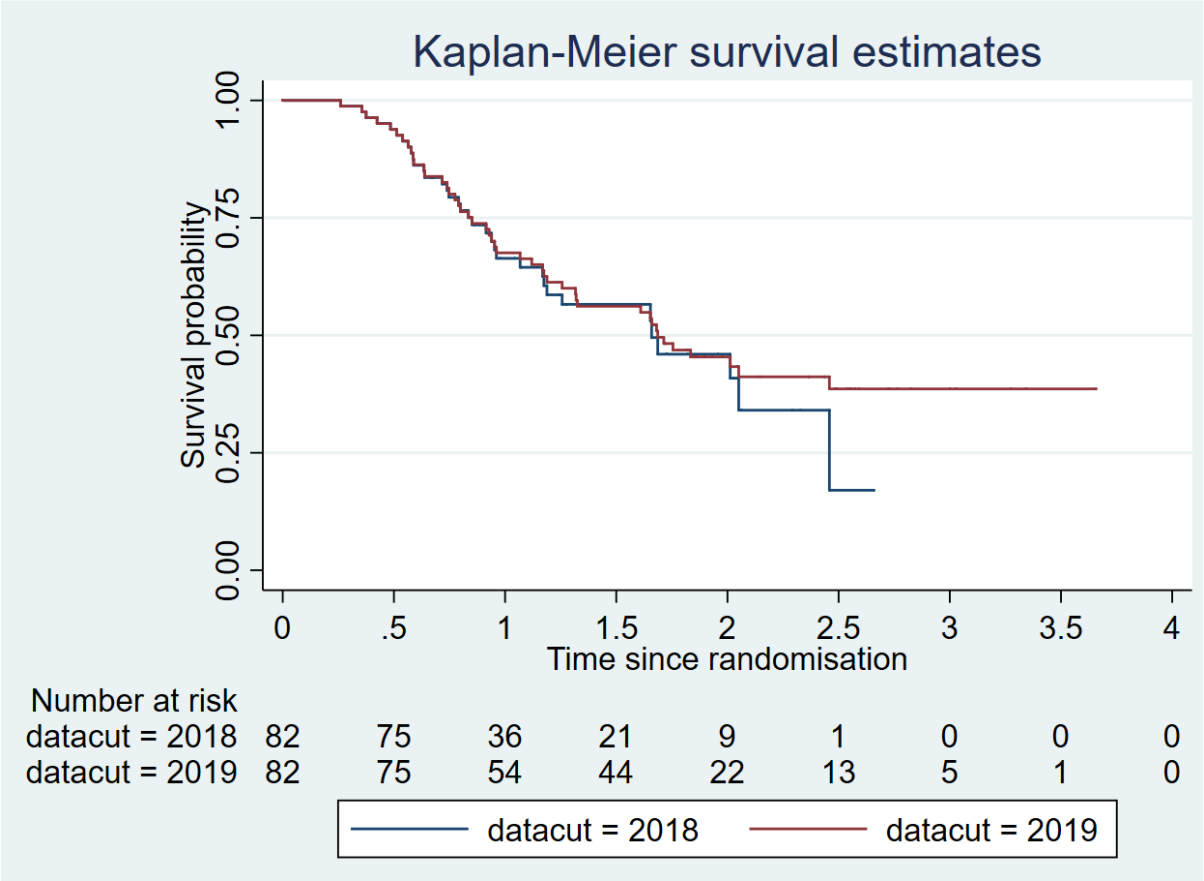


Figure 3: Kaplan-Meier plot of OS from randomisation, With HSCT patients, pooled across treatment groups, ADMIRAL 2018 and 2019 data-cuts (generated by the ERG)



2.2 Summary of new economic analyses presented by company

According to the company's additional evidence document,[7] the company's updated cost-effectiveness analyses are based on the NICE technical team's preferred model,[1] which in turn, are largely based on the ERG's preferred base case model.[4] The company's updated model includes the following amendments:

1. Updated data from the ADMIRAL 2019 data-cut[7]
    a) Updated EFS and OS models for No HSCT patients by treatment group and an updated OS function for With HSCT patients (both treatment groups pooled)
    b) Updated treatment failure probabilities (not described in the company's documentation, but included in the company's updated model)
    c) Updated mean number of cycles of gilteritinib ([redacted] cycles – increased from [redacted] cycles in the previous 2018 data-cut)
2. Re-introduction of the gilteritinib maintenance therapy HR for OS, based on a naïve indirect comparison using data from Evers *et al*[2] and ADMIRAL[3] (HR previously set equal to 1.0 in the ERG's preferred base case analysis)

3. Assumed cure point set equal to 2 years (previously 3 years in the company's original base case and the ERG's preferred base case)
4. Inclusion of additional costs associated with chemotherapy for FLAG-IDA and MEC (first month assumed hospitalised). Additional disutilities are also applied during first 3 cycles for all chemotherapy regimens.
5. Inclusion of best supportive care (BSC) as part of the blended comparator (10% weighting – previously considered as a separate comparator)
6. Wastage assumed to be 7 days (previously excluded from the company's original base case, 14 days included in the ERG's preferred base case)
7. PAS discount increased to [redacted] of the list price (previously [redacted]).

The company's updated base case results are presented in Table 2 of the company's additional evidence document.[7] The company's additional evidence document also presents results of sensitivity analyses using Evers *et al* as the source of OS for With HSCT patients. The company's preferred deterministic ICER for gilteritinib, which incorporates all of the above changes, is estimated to be £49,968 per QALY gained. However, the ERG identified programming errors in the company's new analyses and considers that the results presented in the company's additional evidence document should be disregarded.

The ERG re-implemented the company's intended analyses within the NICE technical team's preferred version of the model. The impact of each individual model amendment is shown in Table 1. Based on the ERG's corrected version of the company's analyses, the company's base case ICER is £46,961 per QALY gained. As shown in the table, the two key drivers of the lower ICER are the re-introduction of the HR for gilteritinib maintenance therapy and the inclusion of an assumption of a 2-year cure point.

Table 1: Impact of individual model amendments, based on NICE technical team's preferred model, including ADMIRAL 2019 data-cut and updated PAS for gilteritinib, includes ERG's corrections

Model amendment	Inc. LYGs*	Inc. QALYs	Inc. Cost	ICER
Updated NICE Technical Team preferred model (2019 ADMIRAL data-cut)	1.22	[redacted]	[redacted]	**£90,803**
Maintenance HR=0.69	1.66	[redacted]	[redacted]	**£67,685**
2-year cure point	1.58	[redacted]	[redacted]	**£70,473**
Wastage=0.25 packs	1.22	[redacted]	[redacted]	**£88,458**
BSC included in comparator	1.41	[redacted]	[redacted]	**£82,752**
Include additional disutilities for chemotherapy	1.22	[redacted]	[redacted]	**£85,535**
Include additional costs for chemotherapy	1.22	[redacted]	[redacted]	**£85,460**
All amendments combined (company's revised base case, with ERG corrections)	2.25	[redacted]	[redacted]	**£46,961**

** Undiscounted*

2.3 ERG's comments on company's updated economic analyses

This section provides a commentary on the model amendments which together form the company's updated base case.

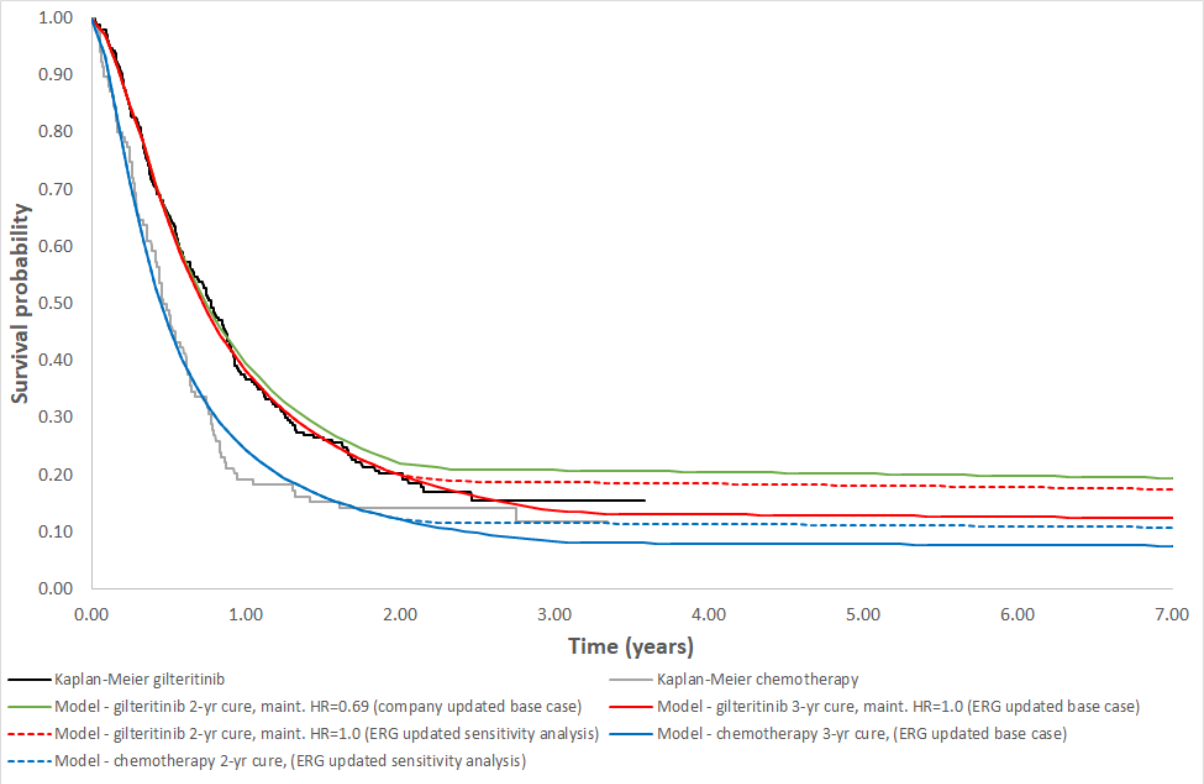
1. Updated data from ADMIRAL 2019 data-cut

The company's updated model includes new parameter estimates for EFS and OS based on the 2019 data-cut of ADMIRAL.[7] Overall, the ERG believes that the inclusion of additional data from ADMIRAL is appropriate. However, the ERG makes the following observations with respect to the company's new analyses:

- The company's additional evidence document[7] does not include any information regarding the updated survival analyses that were undertaken using the updated 2019 ADMIRAL dataset. In response to a request for clarification from the ERG,[8] the company stated that the approach used to fit the parametric survival models, and to select the preferred survival models, were the same as those presented in the original CS.[9]
- The company's additional evidence document[7] does not describe which data have been used to model OS for With HSCT patients. In response to a request for clarification from the ERG,[8] the company stated that the With HSCT OS data were pooled across treatment groups; this is in line with the approach used in the ERG's original exploratory analyses. The company's clarification response also states that the time origin used in the With HSCT OS dataset is the time of randomisation; however, the ERG does not believe that this is accurate, as the updated economic model trace includes a time lag to account for the mean time from randomisation to transplant (during which With HSCT patients cannot die) and the company's selected Gompertz model does not provide a reasonable visual fit to the Kaplan-Meier OS function unless this time lag is included. The ERG would have preferred that the With HSCT survival models were fitted to data on OS from the point of randomisation.
- Whilst the company's updated model includes additional information resulting from the longer follow-up in the 2019 data-cut, additional information influencing the tail of the With HSCT OS distribution is ignored as the company has brought forward the assumed 3-year cure point to 2 years.
- As with their original survival analyses,[9] the company has fitted only standard parametric models to the available time-to-event data. The company has not attempted to model cure using the updated ADMIRAL 2019 dataset (e.g. estimating cure fractions using mixture-cure models).
- The company's projection of OS for the overall modelled population (which includes the 2-year cure point and an HR for gilteritinib maintenance therapy, discussed below) does not provide a good representation of the observed OS data from the ADMIRAL 2019 data-cut. Figure 4 presents a comparison of observed OS in each group compared with the company's

updated base case assumptions (2-year cure point, maintenance HR=0.69) and the ERG's preferred assumptions (3-year cure point, maintenance HR=1.0). As shown in the figure, the company's model overestimates OS in the gilteritinib group after around 1 year. Conversely, the ERG's preferred OS assumptions result in an OS projection which closely represents the available data for the gilteritinib group. The ERG notes that the model does not provide a close representation of the OS data after around 9 months, irrespective of whether a 2-year or 3-year cure point is assumed.

Figure 4: Observed versus predicted OS, ITT population – comparison of company's updated model and ERG's preferred OS assumptions versus Kaplan-Meier plots (generated by the ERG)



2. Re-introduction of maintenance therapy HR for OS

The company's updated model re-introduces the company's previous assumption of a relative treatment effect on OS for gilteritinib maintenance therapy versus no maintenance therapy (HR=0.69). This HR was based on a naïve indirect comparison of OS data for patients who received gilteritinib maintenance therapy in the ADMIRAL 2018 data-cut[3] ("gilteritinib restarters", n=40) versus OS data for patients who received chemotherapy in Evers *et al*.[2] This treatment effect was excluded from the ERG's exploratory analyses because: (a) the ERG did not consider the company's estimated HR to be reliable, and; (b) the 2018 ADMIRAL dataset did not suggest conclusive evidence of a difference in post-HSCT OS between the gilteritinib and salvage chemotherapy groups. The ERG's preferred base case analysis

pooled the OS data across both treatment groups and set the HR for gilteritinib maintenance therapy equal to 1.0.

In their response to a request for clarification from the ERG regarding the justification for re-introducing this HR in the revised model, the company stated: *"While some of the benefit received by patients restarting gilteritinib may already be captured in the ADMIRAL data, it is still plausible (and supported by post hoc analyses of ADMIRAL) that these patients will outperform those not receiving maintenance therapy. In a post-hoc analysis of the more mature September 2019 ADMIRAL data, the HR for overall survival in restarters vs non-restarters was 0.57"* (Company's clarification response,[8] question 2). The company later stated that this HR for gilteritinib restarters vs non-restarters is 0.46 (95% CI 0.24 to 0.88). The company's clarification response further comments that this approach is *"balanced"* by including the costs of maintenance therapy and that removing both the costs and effects of maintenance therapy would lower the ICER for gilteritinib.

The ERG has several concerns regarding the company's re-introduction of the maintenance therapy HR:

- The ERG's concerns regarding the lack of robustness of the company's indirect comparison have not changed (see ERG report,[4] Section 5.4, pages 100-101).
- The company has not updated the indirect comparison using the ADMIRAL 2019 data-cut.
- Similar to the earlier data-cut, the ADMIRAL 2019 dataset does not conclusively suggest a benefit for gilteritinib versus chemotherapy for OS in With HSCT patients (see Figure 2).
- The company has estimated an HR of 0.46 based on gilteritinib restarters versus non-restarters. The observed OS data for gilteritinib restarters and non-restarters are presented in Figure 5, together with the equivalent OS data for With HSCT patients in the salvage chemotherapy group. The data indicate that gilteritinib restarters had better OS compared with gilteritinib non-restarters. However, OS for the salvage chemotherapy group was also markedly better than that for gilteritinib non-restarters. The Clinical Study Report for ADMIRAL[3] states that patients could only restart gilteritinib if the following conditions were met: [redacted] It is therefore possible that the differences between the survival functions shown in Figure 5 are the result of confounding caused by a selection bias.
- The ERG believes that it is appropriate to include the costs of gilteritinib maintenance therapy in the economic model, irrespective of whether that maintenance therapy provides an additional benefit compared with no maintenance therapy, as these resources were consumed in the ADMIRAL trial.

- The inclusion of the maintenance therapy HR leads to a survival projection which is more favourable than the observed cumulative survival estimates in both arms of the trial (see grey dashed line in Figure 6). The ERG believes that this issue contributes to the poor OS model fit for the overall population shown in Figure 4.
- The ERG notes that at the September 2019 data-cut, 19 patients were still receiving gilteritinib, of whom, 13 had restarted treatment after HSCT;[8] this represents 20.63% of all gilteritinib-treated patients who proceeded to HSCT. The company's updated model does not include any additional costs associated with ongoing treatment for these patients. As such, the company's ICER is likely to be underestimated, although the magnitude of this is unclear.
- Overall, the ERG does not believe that the maintenance therapy HR should be included in the analysis.

Figure 5: Kaplan-Meier plot for OS, With HSCT patients, gilteritinib restarters versus non-restarters versus chemotherapy (generated by the ERG)

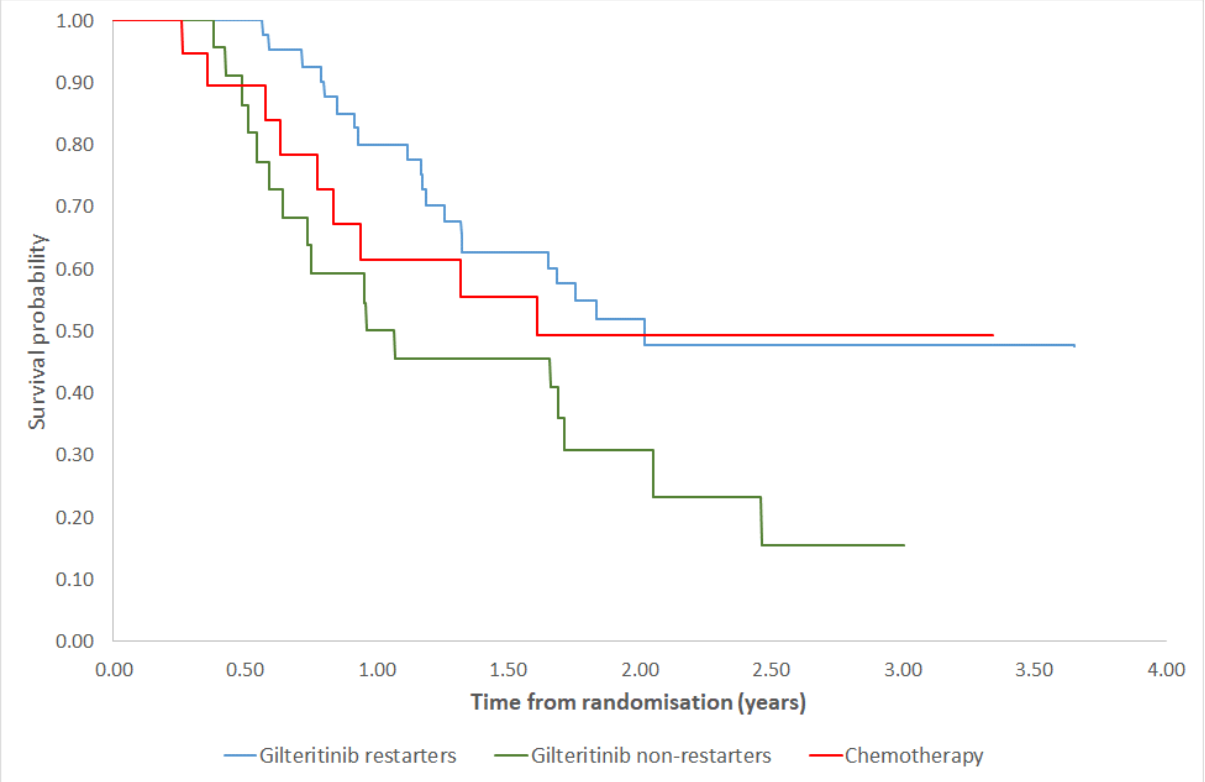
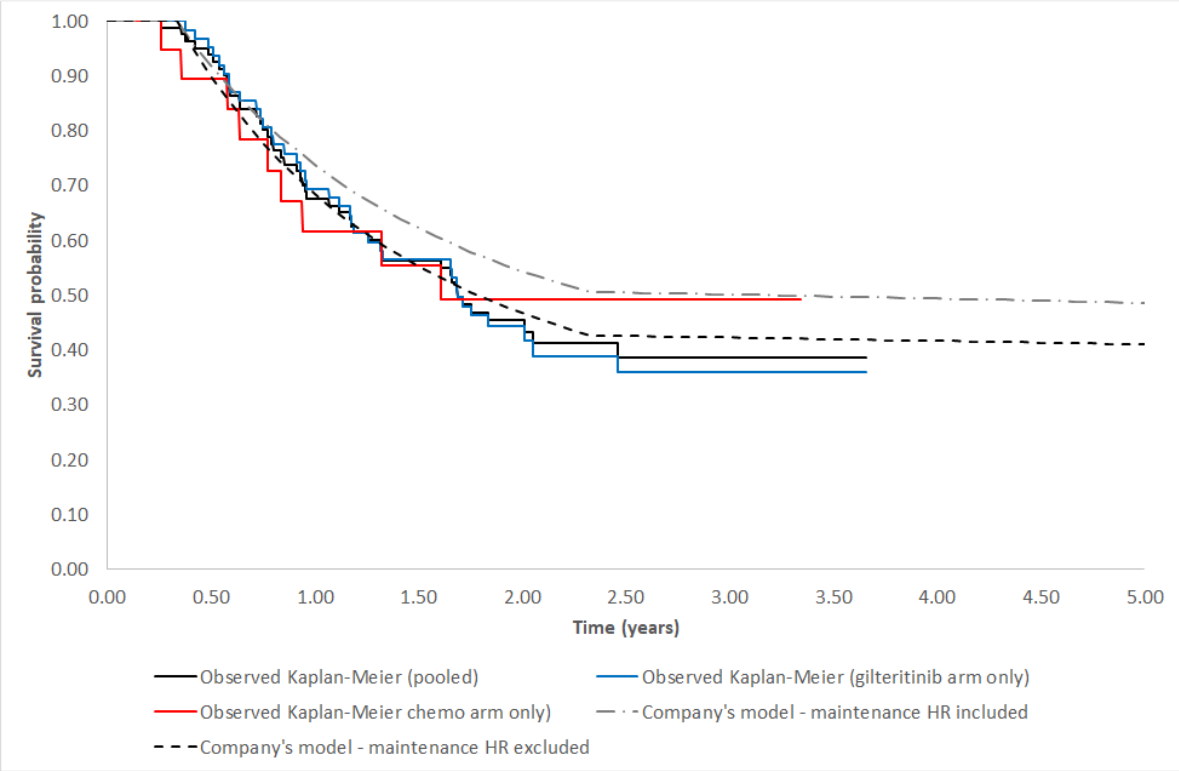


Figure 6: Observed versus predicted OS, With HSCT patients (pooled), modelled OS including/excluding maintenance therapy HR versus Kaplan-Meier plots (generated by the ERG)



3. Assumed cure point changed from 3 years to 2 years

The company's updated model assumes a cure point of 2 years, rather than the assumption of 3 years which was previously applied in the company's original base case.[9] With respect to this issue, the ERG notes the following:

- As part of their additional evidence document, the company refers to two new studies, Dillon *et al*[10] and Gileece *et al*,[11] as evidence to support the notion of an earlier cure point. However, neither of these studies specifically reports on long-term OS outcomes for patients with R/R FLT3+ AML. As noted in the ERG report,[4] cure fractions, if present, are likely to be specific to the population under consideration.
- The updated 2019 data-cut of ADMIRAL[7] shows that more censoring occurs towards the tails of the curves (see Figure 7 in Appendix 1). However, the updated dataset also indicates that 3 death events occurred after 2 years. All of these events were in the gilteritinib group.
- As shown in Figure 4, applying a cure point at 2-years appears to over-estimate long-term OS for the gilteritinib group within the observed period of the trial.
- Given the uncertainty around the assumed cure point, ERG has presented scenarios at 2 years and 3 years as exploratory analyses (see Section 3).

4. Additional costs associated with chemotherapy and disutilities applied to chemotherapy group

The company's updated model includes increased costs for high-intensity chemotherapy to reflect an assumption that patients receiving FLAG-IDA or MEC would require inpatient treatment for the entire first 1-month cycle. The ERG agrees that it is reasonable to expect that hospitalisation costs for patients receiving high-intensity chemotherapy will be higher in the first month. However, within the company's original model, hospitalisation costs were estimated as being conditional on time spent alive and event-free; hence, the costs associated with the observed number of hospitalisations in the trial were spread across the whole EFS interval, including both time on and off treatment. This approach should reflect the total number of hospitalisation days observed in the trial. As the company's updated model includes a higher hospitalisation cost for the first monthly cycle, but retains the original hospitalisation cost for all subsequent cycles, it is likely that the company's new approach overestimates the true costs of hospitalisation for the high-intensity chemotherapy regimens (company's original model=23.39 hospitalisation days; company's updated model=45.90 hospitalisation days). The ERG does not believe that this model amendment is appropriate.

The company's updated model also includes additional utility decrements for all patients receiving salvage chemotherapy. Disutilities of -0.190, -0.225 and -0.166 are applied to high-intensity chemotherapy (FLAG-IDA and MEC), hypomethylating agents (azacitadine) and low-intensity chemotherapy (LoDAC), respectively, for the event-free states (for With HSCT patients and No HSCT patients). These estimates are based on a study reported by Wehler *et al*.[12] The ERG has several concerns regarding the utility decrements included in the company's updated model:

- It is unclear how the Wehler *et al* study[12] was identified and whether other more appropriate sources exist.
- The company's model already included a disutility associated with adverse events (AEs). The inclusion of further disutilities for salvage chemotherapy may represent double counting.
- The company's updated model includes a programming error whereby the utility values for patients receiving BSC (which is assumed to represent 10% of the comparator group in the company's updated base case) are erroneously excluded from the weighted utility values for the comparator group. As a result, utility values for the event-free and post-event states in the comparator group are incorrectly down-weighted by 10% in the company's updated model.
- The company's additional evidence document[7] states that these disutilities are applied for 3 months to reflect time-on-treatment, noting that patients in the salvage chemotherapy group received 2.24 cycles of azacitadine. However, in ADMIRAL, patients received fewer cycles of the other chemotherapy regimens (FLAG-IDA=1.02 cycles; MEC=1.13 cycles; LDAC=1.68 cycles). Whilst toxicity may persist beyond treatment discontinuation, this is not justified in the company's additional evidence document. In addition, the disutilities are not applied in the

post-event states; hence, the company's intended assumption about the relationship between treatment exposure and patient utility is unclear.

- Overall, the ERG has doubts regarding the robustness of the company's disutility estimates. However, these are included in the additional analyses presented by the ERG (see Section 3).

5. Inclusion of BSC as part of blended comparator

The ERG agrees that BSC is a relevant comparator for gilteritinib. As detailed in the ERG report,[4] the evidence available to compare gilteritinib versus BSC is very limited, and the company's economic model relies on a naïve indirect comparison between ADMIRAL[3] and Sarkozy *et al*.[13] The company's updated model includes BSC as part of the weighted comparator (see Table 2). In their ACD response,[6] the company suggests that 20% of patients currently receive BSC, and half of these patients could receive gilteritinib and would achieve the same outcomes as the gilteritinib arm in ADMIRAL.

Table 2: Composition of weighted comparator in company's updated model

Regimen	Weight applied in company's original model	Weight applied in company's updated model
Azacitidine	[redacted]	[redacted]
LoDAC	[redacted]	[redacted]
MEC	[redacted]	[redacted]
FLAG-IDA	[redacted]	[redacted]
BSC	0.00%	10.00%

The ERG believes that BSC should be excluded from the weighted comparator for several reasons:

- BSC was not included as part of the salvage chemotherapy comparator in ADMIRAL[3]
- The company's updated model includes an assumption that patients receiving BSC would not proceed to transplant; therefore, the probability of undergoing HSCT in the weighted comparator group is reduced by 10%. However, the probability of undergoing HSCT in the gilteritinib group is assumed to remain unchanged. This therefore assumes that patients who opt for BSC would have the same propensity to proceed to HSCT if they had instead received gilteritinib. The ERG believes that this is an optimistic assumption which is not supported by evidence.
- Given the weaknesses in the company's indirect comparison using ADMIRAL and Sarkozy *et al*,[13] the ERG believes that BSC should be considered as a separate comparison.

6. Wastage assumed to be 7 days

The company's model assumes a lower amount of gilteritinib wastage than that included in the ERG's preferred analysis (7 days versus 14 days). The company's additional evidence document[7] justifies this on the basis that *"that the majority of patients would discontinue in a more managed way i.e. following consultation with a clinical expert whereby no further treatment is prescribed"* (Company's additional

evidence document,[7] page 12). However, the ACD[1] notes that the Appraisal Committee believed that 14 days wastage was appropriate. The ERG notes that the appropriateness of this assumption will depend on how gilteritinib prescribing is managed in usual practice.

7. New PAS discount included

The company's model includes an updated PAS. The ERG has no comments relating to this.

3. ERG's additional analyses

The ERG implemented four additional analyses using the ERG-corrected version of the company's updated model. The starting point for all of these analyses is the NICE technical team's preferred analysis using the 2018 ADMIRAL data-cut.[1] The features of the ERG's additional analyses are summarised in Table 3. The results of the ERG's analyses are presented in Table 4.

Table 3: Features of ERG's additional analyses

Model feature	Analysis 1: NICE technical team preferred model	Analysis 2: Company's new base case (corrected)	Analysis 3: ERG preferred analysis	Analysis 4: ERG sensitivity analysis
Higher gilteritinib dispensing fee	Yes	Yes	Yes	Yes
Maintenance HR	1.00	0.69	1.00	1.00
ADMIRAL data-cut	2018	2019	2019	2019
Assumed cure point	3 years	2 years	3 years	2 years
BSC included in comparator (10% weight)	No	Yes	No	No
Gilteritinib wastage	14 days	7 days	14 days	14 days
Additional disutilities for chemotherapy*	No	Yes	Yes	Yes
Additional hospitalisation costs for chemotherapy	No	Yes	No	No
Updated PAS	Yes	Yes	Yes	Yes

** Additional disutility applied to all alive states for first 3 cycles*

Table 4: Results of ERG's additional analyses, gilteritinib versus weighted comparator, deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Analysis 1: NICE technical team preferred model (2018 ADMIRAL data-cut)†							
Gilteritinib	2.68	[redacted]	[redacted]	0.98	[redacted]	[redacted]	**£90,468**
Weighted comparator	1.69	[redacted]	[redacted]	-	-	-	-
Analysis 2: Company's new base case (corrected)							
Gilteritinib	4.84	[redacted]	[redacted]	2.25	[redacted]	[redacted]	**£46,961**
Weighted comparator	2.59	[redacted]	[redacted]	-	-	-	-
Analysis 3: ERG preferred analysis							
Gilteritinib	3.44	[redacted]	[redacted]	1.22	[redacted]	[redacted]	**£85,535**
Weighted comparator	2.22	[redacted]	[redacted]	-	-	-	-
Analysis 4: ERG sensitivity analysis							
Gilteritinib	4.42	[redacted]	[redacted]	1.58	[redacted]	[redacted]	**£67,210**
Weighted comparator	2.84	[redacted]	[redacted]	-	-	-	-

ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year
** Undiscounted*
† The NICE technical team preferred model is the same as the ERG's preferred base case model, with the addition of a higher dispensing fee for gilteritinib

As shown Table 4, the inclusion of the updated PAS within the NICE technical team's preferred model (Analysis 1) results in an ICER for gilteritinib versus salvage chemotherapy of £90,468 per QALY gained. The company's updated base case ICER, including corrections of errors identified by the ERG (Analysis 2), is estimated to be £46,961 per QALY gained. The key drivers of this lower ICER are: (a) the re-introduction of the maintenance therapy HR and; (b) the assumption of a 2-year cure point. The survival model fitted to the updated 2019 With HSCT OS data from ADMIRAL does not have a material impact on the ICER, as the company's 2-year cure assumption overrides the predictions of this model for patients surviving up to that timepoint. The ERG's preferred model (Analysis 3) suggests that the ICER for gilteritinib versus salvage chemotherapy is £85,535 per QALY gained. This ICER is considerably higher than the company's corrected base case estimate because: (a) the maintenance therapy HR has been set equal to 1.0, and; (b) the assumed cure point has been set equal to 3 years. The use of a 2-year cure point (Analysis 4) reduces the ICER to £67,210 per QALY gained.

4. References

1. National institute for Health and Care Excellence. Gilteritinib for treating relapsed or refractory acute myeloid leukaemia - Appraisal Consultation Document. NICE: London; 2020.
2. Evers G, Beelen DW, Braess J, Sauerland C, Kolb HJ, Reichle A*, et al.* Outcome of patients with acute myeloid leukemia (AML) undergoing allogeneic hematopoietic stem cell transplantation (HSCT) beyond first complete remission (CR1). *Blood* 2018;132:4649.
3. Astellas Pharma Ltd. A Phase 3 open-label, multicenter, randomized study of gilteritinib versus salvage chemotherapy in patients with relapsed or refractory acute myeloid leukemia (AML) with FLT3 Mutation.. ADMIRAL Clinical Study Report. Astellas: Surrey, UK; 2019.
4. Tappenden P, Simpson E, Stevens J, Navega Biz A, Wong R, Pillai S. Gilteritinib for treating relapsed or refractory acute myeloid leukaemia: A Single Technology Appraisal. University of Sheffield: Sheffield; 2019.
5. Astellas Pharma Ltd. Gilteritinib (XOSPATA) for treating relapsed or refractory acute myeloid leukaemia ID1484. Company's response to clarification questions from the ERG. Astellas: Surrey, UK; 2019.
6. Astellas pharma Ltd. Gilteritinib for treating relapsed or refractory acute myeloid leukaemia - company's ACD response. Astellas: Surrey; 2020.
7. Astellas Pharma Ltd. Gilteritinib for treating relapsed or refractory acute myeloid leukaemia - Additional evidence document (post-ACD). Astellas: Surrey; 2020.
8. Astellas Pharma Ltd. Gilteritinib for treating relapsed or refractory acute myeloid leukaemia - company's response to clarification questions from the ERG on the additional evidence document (post-ACD). Astellas: Surrey; 2020.
9. Novartis Pharmaceuticals Ltd. Midostaurin for newly diagnosed acute myeloid leukaemia [ID894]. Company's evidence submission to the National Institute for Health and Care Excellence. Astellas: Surrey, UK; 2017.
10. Dillon R, Hills R, Freeman S, Potter N, Jovanovic J, Ivey A*, et al.* Molecular MRD status and outcome after transplantation in NPM1 mutated AML: results from the UK NCRI AML17 study. *Blood* 2020 (epub ahead of print).
11. Gilleece MH, Labopin M, Savani BN, Yakoub-Agha I, Socie G, Gedde-Dahl T*, et al.* Allogeneic heamapoietic transplantation for acute myeloid leukaemia in second complete remission: a registry report by the Acute Leukaemia working Party of the EBMT. *Leukemia* 2020;34:87-99.
12. Wehler E, Storm M, Kowall S, Campbell C, Boscoe A, . A health state utility model estimating the impact of ivosidenib on quality of life in patients with relapsed/refractory acute myeloid leukemia. . *Presented at the 23rd Congress of the European Hematology Association, 14-17 June 2018*.
13. Sarkozy C, Gardin C, Gachard N, Merabet F, Turlure P, Malfuson JV. Outcome of older patients with acute myeloid leukemia in first relapse. *American Journal of Hematology* 2013;88:758-64.

Appendix 1: Comparison of ADMIRAL 2018 and 2019 data-cuts

Figure 7: Kaplan-Meier plot of OS from randomisation, With HSCT patients, pooled across treatment groups, side-by-side comparison of ADMIRAL 2018 and 2019 data-cuts (generated by the ERG)