NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Liposomal cytarabine and daunorubicin for untreated acute myeloid leukaemia [ID1225]

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
    a. Jazz Pharmaceuticals (company)
    b. Leukaemia Care

    There were 'no comment' responses from Novartis and Department of Health & Social Care, and no comments from the clinical or patient experts

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Additional evidence** submitted by Jazz Pharmaceuticals

5. **Company Response to Clarification Questions on additional evidence** submitted by Jazz Pharmaceuticals

6. **Evidence Review Group critique of company additional evidence** prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

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

Liposomal cytarabine and daunorubicin for untreated acute myeloid leukaemia

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	Company	Jazz Pharmaceuticals	We are pleased that the ERG and committee has concluded that CPX-351 (liposomal cytarabine and daunorubicin) improves overall survival and qualifies as a life extending treatment at the end of life. The committee recognised the unmet need that exists for people with high risk (secondary) AML and the benefit of a new treatment that could improve survival, quality of life and the opportunity of getting a stem cell transplant. It is disappointing that the committee did not recommend CPX-351 due to concerns of data maturity, particularly after haematopoietic stem cell transplantation (HSCT). This view is in contrast to national UK AML experts, who confirm that in the context of HSCT for high-risk disease, the majority of all death events (both transplant-related and due to AML relapse) occur within 1 year of transplant. The 301 study prospectively collected post-HSCT survival data and with a median of 20.5 months follow up from randomisation, the post-HSCT curves are consistent with the expert clinical feedback with very little censoring within 1 year. Therefore, within the context of HSCT for high-risk AML, these results are mature and robust. The company will submit additional evidence to further demonstrate the clinical plausibility of these results.	Thank you for your comment. The committee considered the company's additional evidence and revised patient access scheme discount and was able to recommend liposomal cytarabine and daunorubicin for use within its marketing authorisation. See FAD section 1.
2	Company	Jazz Pharmaceuticals	We note that the committee was not able to recommend CPX-351 at the time of the review, identifying remaining concerns about the cost effectiveness estimates. We believe that the ACD recommendations do not take into account the true clinical	Thank you for your comment. The committee considered the company's additional evidence and revised patient access scheme discount and was able to

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
			benefit to patients and the value to the NHS by concluding that an alternative modelling approach would yield a poorer estimate of cost-effectiveness. The company has made recommended changes to the economic model to include the committee's preferred methodology and in addition has included a revised confidential PAS. Together, this yields ICERs below the threshold for an end of life treatment option and confirms that CPX-351 is a cost-effective treatment for routine use in the NHS.	recommend liposomal cytarabine and daunorubicin for use within its marketing authorisation. See FAD section 1.
3	Consultee	Leukaemia Care	There has been limited progression in AML treatments over the last few decades and it is, therefore, disappointing that Liposomal cytarabine and daunorubicin, a life-extending, innovative and well-tolerated treatment, has not be recommended for the treatment of high-risk AML. High-risk AML patients currently have limited options and poor survival, with a clear end of life setting.	Comment noted. The committee agreed that people with therapy-related acute myeloid leukaemia and acute myeloid leukaemia with myelodysplasia-related changes would welcome a new treatment. See FAD section 3.1.
4	Consultee	Leukaemia Care	The committee acknowledged that liposomal cytarabine and daunorubicin extended the life of patients by more than 3 months from a median of 5 months. This is a significant amount of time for the patient and their family, which they will not be given by preventing access to the treatment.	Comment noted. The committee agreed that liposomal cytarabine and daunorubicin improved overall survival compared with standard cytarabine and daunorubicin (see FAD section 3.4). Based on the company's additional evidence and revised patient access scheme discount, the committee was able to recommend liposomal cytarabine and daunorubicin for use within its marketing authorisation. See FAD section 1.
5	Consultee	Leukaemia Care	Stem cell transplant is the only curative option for patients and in our survey, 89% of AML patients reported that they would positively welcome a treatment that enabled/bridged to stem cell transplant. We note that while the additional benefit after transplant may be unclear from the data, in the trial, liposomal cytarabine and daunorubicin treatment allowed more patients to	Comment noted. The committee considered that more people in the liposomal cytarabine and daunorubicin group had a stem cell transplant. It also noted that the analysis of survival benefit after stem cell transplant was based on a

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
			receive a SCT than the standard treatment. This could be significantly important for improving survival of high-risk AML.	small, non-randomised population and that there was some uncertainty about how much survival was improved after stem cell transplant. See FAD section 3.4.
6	Consultee	Leukaemia Care	If more mature data is required, we recommended that access to liposomal cytarabine and daunorubicin be considered through the Cancer Drugs Fund (CDF). This would allow extended period of data collection to provide more long-term evidence of the benefit of the treatment in high-risk AML patients and also, will offer these patients a life-extending and innovative treatment option.	Thank you for your comment. The committee considered the updated survival data provided by the company. See FAD section 3.4. The committee concluded that liposomal cytarabine and daunorubicin could be recommended for routine use, within its marketing authorisation. See FAD section 1.
7	Consultee	NCRI-ACP-RCP	Getting more data will be essential including longer term follow up on the Company 302 trial as well as the results of the NCRI AML 18 and 19 trials which are recruiting well in the UK and Denmark.	Thank you for your comment. The committee considered the updated survival data provided by the company. See FAD section 3.4. The guidance will be considered for review 3 years after publication. Any evidence from the NCRI trials may be taken into account at this point.
8	Public	University Hospitals Bristol NHS Trust	'The committee concluded that liposomal cytarabine and daunorubicin improved overall survival in the whole population compared to standard cytarabine and daunorubicin, but that the additional benefit after stem cell transplant, particularly in the long term lacked clinical plausibility.' The improvement of post transplant survival in CPX arm shown in the post hoc analysis is clinically plausible and is a very encouraging finding in this poor risk patients . Whilst clinically plausible and very interesting, the scientific rationale of this finding is not entirely understood i.e is it deeper remission achieved by CPX or better organ function at the time of transplant, conferring this benefit, as this data was not collected	Thank you for your comment. The committee considered the updated survival data provided by the company. See FAD section 3.4. The committee considered that more people in the liposomal cytarabine and daunorubicin group had a stem cell transplant. It also noted that the analysis of survival benefit after stem cell transplant was based on a small, non-randomised population and that there was some uncertainty about how much survival was improved after stem cell transplant. See FAD section

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
			in the 301 study. This understanding and information might become apparent from current trials. Patients in the DA3+7 arm may not achieve the same plateau if disease relapse risk or TRM is higher. For a poor risk disease with high mortality early in the treatment, 2 year survival data favouring one treatment over another, is compelling enough for clinical decisions to be made in favour of the treatment offering superior survival.	3.4. However, based on the company's additional evidence and revised patient access scheme discount the committee was able to recommend liposomal cytarabine and daunorubicin for use within its marketing authorisation. See FAD section 1.
9	Public		This is a very useful and well tolerated drug which has a palce in the intensive treatment of a group of patients with poor prognosis and AML	Thank you for your comment. The committee concluded that liposomal cytarabine and daunorubicin could be recommended for use within its marketing authorisation. See FAD section 1.
10	Public		The proposed treatment is the only one that clearly shows a survival benefit in a difficult cohort of patients (secondary AML) and currently there is a lack of options for this group of patients who are often refractory to treatment with standard DA I disagree with the outcome on younger patients as this can be slightly better by using CPX as they do not express the MDR gene as much as the older patients and often in patients above the age of 60 there are undiagnosed comorbidities which become obvious after treatment started. Especially the improvement in cardiotoxicity with liposomal cytarabine and daunorubicin may further improve outcomes in older patients and later on less hospital resources will be therefore needed to support the side effects encountered from standard DA especially the cardiotoxic effects	Thank you for your comment. The committee agreed that patients would welcome a new treatment for high-risk acute myeloid leukaemia. Based on the company's additional evidence and revised patient access scheme discount, the committee was able to recommend liposomal cytarabine and daunorubicin for use within its marketing authorisation. See FAD section 1.
11	Public		Based on personal experience. Delivered to a patient with AML-MRC with comparable disease characteristics to those within Study 301. Importantly the patient was <60. Alternative treatment options considered were DA or	Thank you for your comment. The committee concluded that liposomal cytarabine and daunorubicin could be recommended for use within its marketing authorisation. See FAD section 1. The

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
			FLAG-IDA - I think it is fair to use DA as the comparator in the first instance. CPX proved very easy to administer; could potentially be administered on an out-patient basis. It was well tolerated - grade 1 nausea and grade 2 infection only. It resulted in a slower count recovery than with DA, the time frame was consistent with that reported and comparable to that expected with FLAG-IDA. The patient obtained a CRi with no reduction in PS. I ask if high risk MDS might be included in the eligibility criteria?	recommendation is for the whole population in the marketing authorisation, that is, for newly diagnosed, therapy-related acute myeloid leukaemia or acute myeloid leukaemia with myelodysplasia-related changes. See FAD section 1.

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 13/09/2018 **email:** TACommF@nice.org.uk/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):	Jazz Pharmaceuticals
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. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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2	We note that the committee was not able to recommend CPX-351 at the time of the review, identifying remaining concerns about the cost effectiveness estimates. We believe that the ACD recommendations do not take into account the true clinical benefit to patients and the value to the NHS by concluding that an alternative modelling approach would yield a poorer estimate of cost-effectiveness. The company has made recommended changes to the economic model to include the committee's preferred methodology and in addition has included a revised confidential PAS. Together, this yields ICERs below the threshold for an end of life treatment option and confirms that CPX-351 is a cost-effective treatment for routine use in the NHS.

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

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resubmit your comments form without attachments, it must send it by the deadline.

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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. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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Liposomal cytarabine and daunorubicin for untreated acute myeloid leukaemia [ID1225]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 13/09/2018 **email:** TACommF@nice.org.uk/NICE DOCS

1	There has been limited progression in AML treatments over the last few decades and it is, therefore, disappointing that Liposomal cytarabine and daunorubicin, a life-extending, innovative and well-tolerated treatment, has not be recommended for the treatment of high-risk AML. High-risk AML patients currently have limited options and poor survival, with a clear end of life setting.
2	The committee acknowledged that liposomal cytarabine and daunorubicin extended the life of patients by more than 3 months from a median of 5 months. This is a significant amount of time for the patient and their family, which they will not be given by preventing access to the treatment.
3	Stem cell transplant is the only curative option for patients and in our survey, 89% of AML patients reported that they would positively welcome a treatment that enabled/bridged to stem cell transplant. We note that while the additional benefit after transplant may be unclear from the data, in the trial, liposomal cytarabine and daunorubicin treatment allowed more patients to receive a SCT than the standard treatment. This could be significantly important for improving survival of high-risk AML.
4	If more mature data is required, we recommended that access to liposomal cytarabine and daunorubicin be considered through the Cancer Drugs Fund (CDF). This would allow extended period of data collection to provide more long-term evidence of the benefit of the treatment in high-risk AML patients and also, will offer these patients a life-extending and innovative treatment option.

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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Please return to: **TACommF@nice.org.uk** / NICE DOCS

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	
Organisation	University Hospitals Bristol NHS Trust
Location	England
Conflict	N/A
Notes	N/A
Comments on the ACD:	
'The committee concluded that liposomal cytarabine and daunorubicin improved overall survival in the whole population compared to standard cytarabine and daunorubicin, but that the additional benefit after stem cell transplant, particularly in the long term lacked clinical plausibility.' The improvement of post transplant survival in CPX arm shown in the post hoc analysis is clinically plausible and is a very encouraging finding in this poor risk patients . Whilst clinically plausible and very interesting, the scientific rationale of this finding is not entirely understood i.e is it deeper remission achieved by CPX or better organ function at the time of transplant, conferring this benefit, as this data was not collected in the 301 study. This understanding and information might become apparent from current trials. Patients in the DA3+7 arm may not achieve the same plateau if disease relapse risk or TRM is higher. For a poor risk disease with high mortality early in the treatment, 2 year survival data favouring one treatment over another, is compelling enough for clinical decisions to be made in favour of the treatment offering superior survival.	

Name	[redacted]
Role	NHS Professional
Other role	
Organisation	
Location	N. Ireland
Conflict	N/A
Notes	N/A
Comments on the ACD:	
This is a very useful and well tolerated drug which has a palce in the intensive treatment of a group of patients with poor prognosis and AML	

Name	[redacted]
Role	NHS Professional
Other role	
Organisation	
Location	England
Conflict	N/A
Notes	N/A
Comments on the ACD:	

The proposed treatment is the only one that clearly shows a survival benefit in a difficult cohort of patients (secondary AML) and currently there is a lack of options for this group of patients who are often refractory to treatment with standard DA

I disagree with the outcome on younger patients as this can be slightly better by using CPX as they do not express the MDR gene as much as the older patients and often in patients above the age of 60 there are undiagnosed comorbidities which become obvious after treatment started. Especially the improvement in cardiotoxicity with liposomal cytarabine and daunorubicin may further improve outcomes in older patients and later on less hospital resources will be therefore needed to support the side effects encountered from standard DA especially the cardiotoxic effects

Name	[redacted]
Role	NHS Professional
Other role	
Organisation	
Location	Scotland
Conflict	N/A
Notes	N/A
Comments on the ACD:	
Based on personal experience. Delivered to a patient with AML-MRC with comparable disease characteristics to those within Study 301. Importantly the patient was <60. Alternative treatment options considered were DA or FLAG-IDA - I think it is fair to use DA as the comparator in the first instance. CPX proved very easy to administer; could potentially be administered on an out-patient basis. It was well tolerated - grade 1 nausea and grade 2 infection only. It resulted in a slower count recovery than with DA, the time frame was consistent with that reported and comparable to that expected with FLAG-IDA. The patient obtained a CRi with no reduction in PS. I ask if high risk MDS might be included in the eligibility criteria?	

Name	[redacted]
Role	Committee manager
Other role	
Organisation	NCRI-ACP-RCP
Location	England
Conflict	
Notes	
Comments on the ACD:	
We have liaised with our experts and would like to make the following comment. Getting more data will be essential including longer term follow up on the Company 302 trial as well as the results of the NCRI AML 18 and 19 trials which are recruiting well in the UK and Denmark.	

CPX-351 for untreated high-risk (secondary) acute myeloid leukaemia (ID1225):

Additional evidence post-ACD

24 September 2018

List of Tables

List of Figures

1.1 List of abbreviations

ACD: appraisal consultation document

AIC: Akaike information criterion

AML: acute myeloid leukaemia

AML-MRC: acute myeloid leukaemia with myelodysplasia related changes

BIC: Bayesian information criterion

CI: confidence interval

DSUR: drug safety update report

EFS: event-free survival

EMA: European Medicines Agency

ERG: Evidence Review Group

HR: hazard ratio

HSCT: haematopoietic stem cell transplantation

ICER: incremental cost-effectiveness ratio

ITT: intent to treat

KM: Kaplan-Meier

LTFU: lost to follow up

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

OS: overall survival

PAS: Patient Access Scheme

QALY: Quality-adjusted life year

t-AML: therapy-related AML

SMR: standardised mortality ratio

1 Executive Summary

Patients with high-risk (secondary) acute myeloid leukaemia (AML) represent a small group of patients for whom life expectancy is exceptionally poor. CPX-351 is the first proven advance in intensive chemotherapy for this subset of AML patients in more than forty years. It combines two existing antineoplastic agents, daunorubicin and cytarabine, in an advanced liposomal nanotechnology, designed to deliver high concentrations of both drugs into leukaemia cells, in a fixed synergistic molar ratio.

On 27 August 2018, the EMA approved CPX-351 for the treatment of adults with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC) based upon the results of the pivotal phase III trial, CLTR0310-301. This trial met its primary endpoint; CPX-351 demonstrated an improvement in overall survival (OS) compared to the 3+7 treatment regimen, achieving a median OS of 9.56 months vs 5.95 months (hazard ratio [HR]=0.69 [95% confidence interval (CI): 0.52, 0.90]; p=0.005). In addition, a higher proportion of patients in the CPX-351 group proceeded to HSCT (34% vs 25%). These gains in efficacy were achieved with no clinically meaningful changes in safety from the well-established profile of daunorubicin and cytarabine.

Jazz Pharmaceuticals believes that CPX-351 offers significant clinical benefit to a high risk patient group and can be delivered to the UK Health Service in a cost-effective way. The company thanks the committee for their review and consideration of the evidence submitted to date. The appraisal consultation document (ACD) recognised the high unmet need that exists for people with t-AML and AML-MRC and the benefit of a new treatment that could improve survival, quality of life and the chance of getting a haematopoietic stem cell transplantation (HSCT). The ACD recognised that CPX-351 met NICE's criteria for being considered a life-extending treatment for people with high risk (secondary) AML. Despite the positive assessment described above, the committee was not able to recommend CPX-351 at the time of the review, identifying remaining concerns about the clinical certainty and cost effectiveness estimates for CPX-351.

Jazz Pharmaceuticals has therefore compiled this document to provide further evidence to address the concerns of the committee. Additional clinical analyses from a more mature data set (approximately 4 year OS analysis) are provided, in order to address the committee's concerns regarding clinical plausibility of long term post-HSCT survival. These analyses confirm that the substantial OS benefits of CPX-351 versus 7+3 seen in the original Kaplan-Meier (KM) OS results are robust and that the additional benefit post HSCT is maintained over an extended period of time. In addition, to address the committee's concerns and request relating to the economic model, the company has made recommended changes, including developing a cure model for the whole population and applying the survival plateau, supported by the extended data set. Based upon these changes and an updated Patient Access Scheme (PAS), the company concludes that the most plausible incremental cost-effectiveness ratio (ICER) for CPX-351 is below £50,000 per quality-adjusted life year (QALY) gained and on this basis believes that CPX-351 presents a cost-effective treatment option for routine use in the NHS.

1. Additional evidence supporting plausibility of clinical benefit of liposomal cytarabine and daunorubicin (CPX-351)

1.1 Maturity of data

In sections 3.4 and 3.6 of the ACD document, NICE outlines several points relating to study 301 leading to the conclusion that the additional benefit after HSCT, particularly in the long term, lacked clinical plausibility. Specifically highlighted was the limited follow-up (and therefore lack of maturity of the data) and the censoring of a substantial number of patients in the analysis.

The pivotal phase III trial, CLTR0310-301, a multicentre, open-label, randomised controlled trial of 309 patients aged 60−75 years, diagnosed with high-risk (secondary) AML, met its primary endpoint; CPX-351 demonstrated a significant improvement in OS compared to the 3+7 treatment regimen, achieving a median OS of 9.56 months vs 5.95 months (hazard ratio [HR]=0.69 [95% confidence interval (CI): 0.52, 0.90]; p=0.005). CPX-351 also demonstrated a significantly higher rate of complete remission compared with 3+7 (37.3% vs 25.6%; p=0.036), and a higher proportion of patients receiving CPX-351 proceeded to HSCT (34% vs 25%). These data, which formed the basis of the recent EMA approval, were taken from a data cut in December 2015, by which time the median follow up of patients was 20.5 months in CPX-351 group vs 21.2 months in 3+7 group.

In order to address specific comments from the committee regarding maturity of data and longer term follow up of patients in the pivotal trial, Jazz Pharmaceuticals has performed an additional, unplanned OS analysis of the pivotal trial using drug safety update report (DSUR) data from 3 August 2018.

1.1.1 Patient Status and Follow-up

By 3 August 2018, 266 (86%) patients were documented to have died: 123 (80.4%) in the CPX-351 arm and 143 (91.7%) in the 3+7 arm. There were 43 patients not known to have died with 3 patients considered lost to follow up (LTFU). Thus there were 40 patients considered to be alive and subject to follow up activities, with 27 patients in the CPX-351 arm and 13 patients in the 3+7 arm (Table 1). 35/40 (87.5%) patients were successfully contacted on or after January 2018 (24 patients in the CPX-351 arm and 11 patients in 3+7) (Table 2). At the time of this analysis, 27/27 (100%) surviving patients on the CPX-351 arm and 9/13 (69%) surviving patients from the 3+7 arm come from the group of transplanted patients.

This analysis provides an additional ~2.6 years of follow up data from the original December 2015 data cut and is the equivalent of a ~4 year OS analysis.

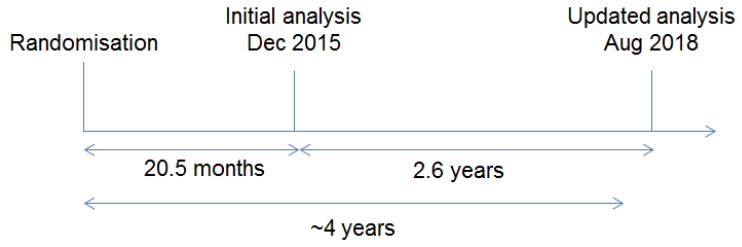


Table 1. Patient status as of 3 August 2018

	CPX-351 (n=153)	**3+7 (n=156)**
Dead	123 (80.4%)	143 (91.7%)
Alive	27 (17.6%)	13 (8.3%)
LTFU	3 (2.0%)	0

Table 2. Contact and transplant status of patients (3 Aug 2018, n=43)

Patient	**CPX-351 (n=30)**			**3+7 (n=13)**		
		HSCT	No HSCT		HSCT	No HSCT
LTFU	3			0		
		1	2		0	0
Alive and Contacted	27	27	0	13	9	4
Before 2017	1			1		
		1	0		0	1
During 2017	2			1		
		2	0		1	0
During 2018	24			11		
		24	0		8	3

1.2 Updated overall survival – ITT

Figures 1 and 2 show the KM plots for the primary endpoint of OS (ITT population) using the original 31 December 2015 cut-off (original evidence submission) and the 3 August 2018 DSUR data (approximately 4 year OS analysis), respectively.

The two sets of curves are very consistent, with the updated results continuing to demonstrate a substantial OS improvement for CPX-351 versus 3+7, with only one censored patient in the first 27 months post-randomisation. The OS curves remain clearly separated with no evidence of convergence over an extended period of time. This additional analysis confirms that CPX-351 improves survival vs standard intensive chemotherapy in the ITT population.

Figure 1. Original Kaplan-Meier OS Analysis, ITT population (31 December 2015; original evidence submission Figure 4 page 49)

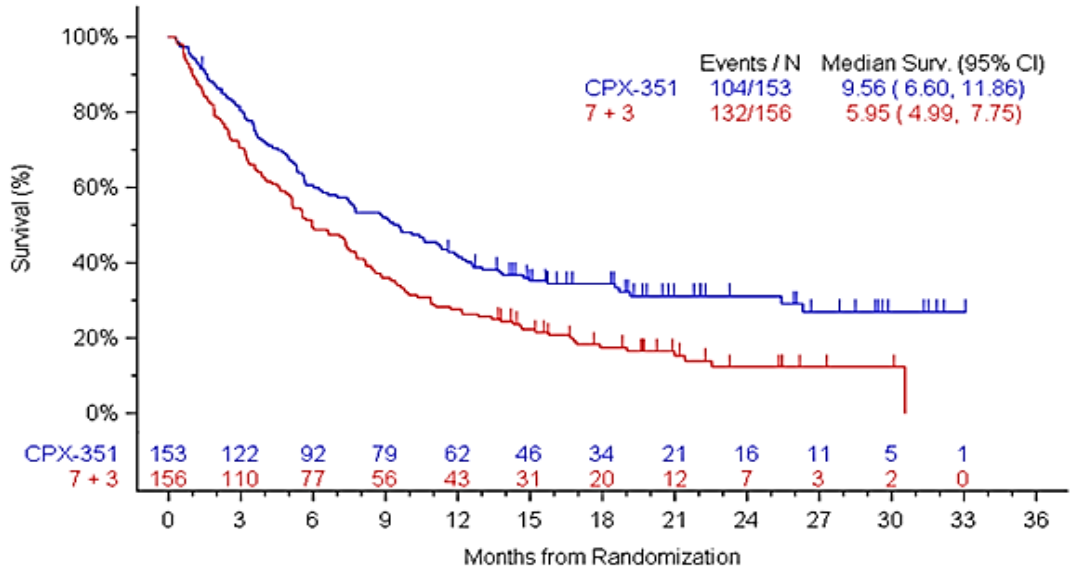
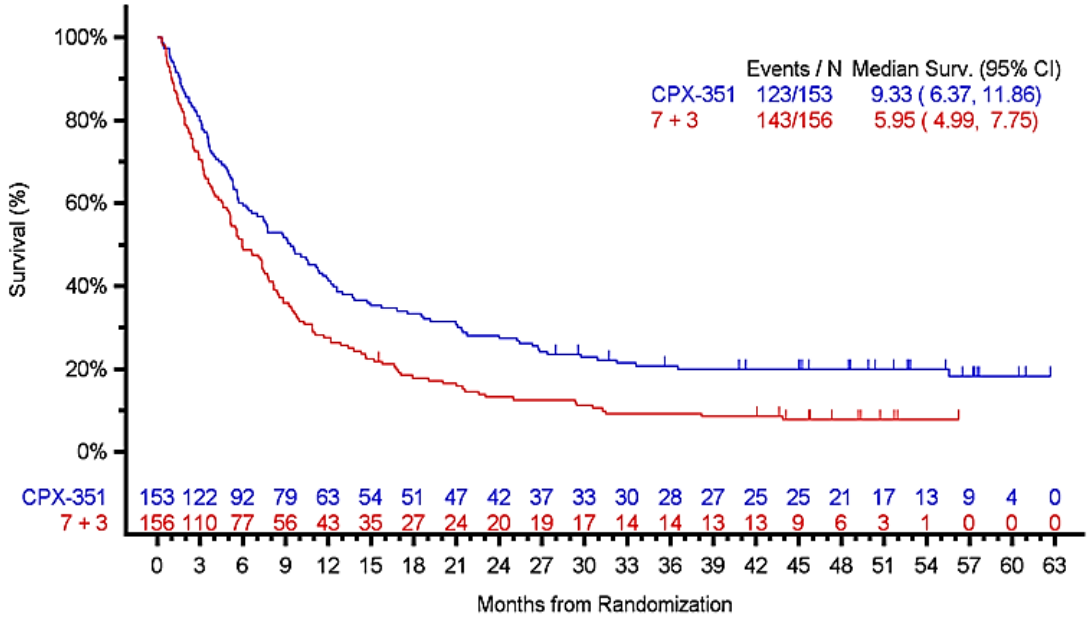


Figure 2. Updated Kaplan-Meier OS Analysis, ITT population (3 Aug 2018)



1.3 Updated Overall Survival – Post HSCT

Figures 3 and 4 show the KM OS plots landmarked at point of HSCT (all transplanted patients) using the original 31 December 2015 cut-off (original evidence submission) and the DSUR data from 3 August 2018 (approximately 4 year OS analysis), respectively.

Consistent with the 31 Dec 2015 analysis, the updated KM OS curves continue to demonstrate a substantial post HSCT OS benefit for CPX-351 versus 3+7. It is notable that in the 3 August 2018 update, the median has still not been reached on the CPX-351 arm, indicating an unprecedented >50% of patients achieving a plateau post-HSCT. A plateau at approximately 20% survival following HSCT can now be observed in the 3+7 arm. The attainment of plateaus for both study arms occurs at similar time-points which is consistent with the expert clinical opinion stated in Section 3.4 of the ACD and published literature [Wingard 2011; Shimoni 2016].

Importantly, in the updated analysis, the majority of censoring events are now shifted well beyond the KM curve plateau points for both arms. The divergence of the CPX-351 and 3+7 KM curves occurs in data that is not impacted by censoring. Jazz Pharmaceuticals recently convened an advisory board (5 September 2018) with 8 UK AML national experts, who confirmed that, in the context of high risk (secondary) AML, the majority of transplant-related mortality and relapse deaths are expected within the first year of transplantation.

Therefore, these updated results can be considered mature and specifically address the committee's concerns regarding the plateau points and censoring of the CPX-351 arm and provides a clinically plausible and reliable dataset for generating long-term OS extrapolations.

Figure 3. Original Kaplan-Meier OS Analysis landmarked at time of HSCT, ITT population (31 December 2015; original evidence submission Figure 7 page 54)

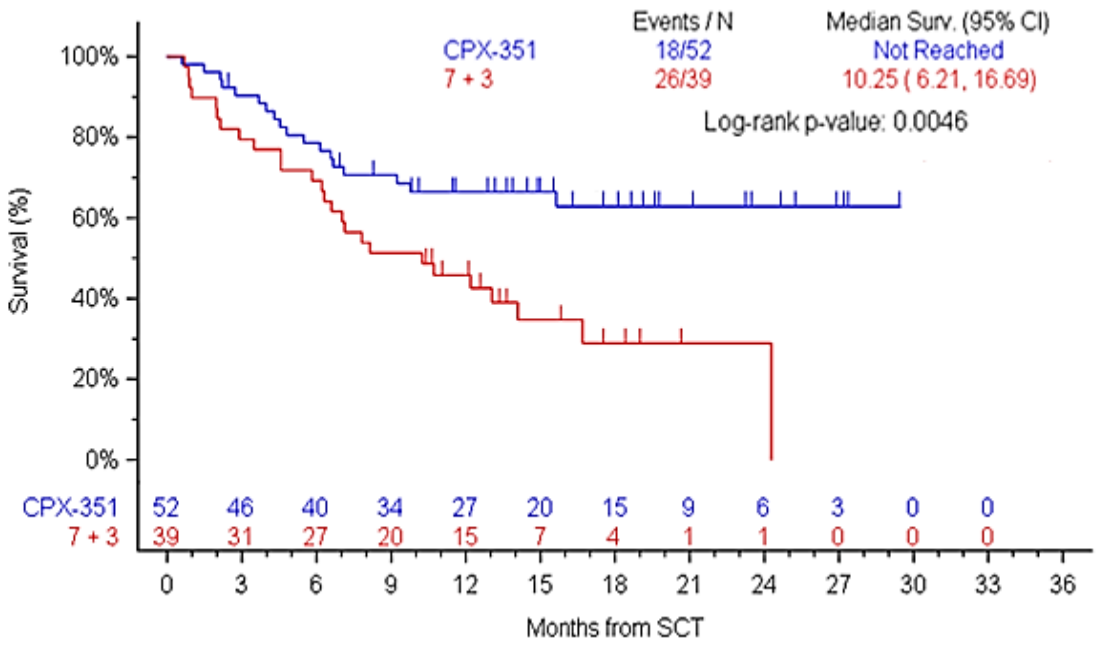
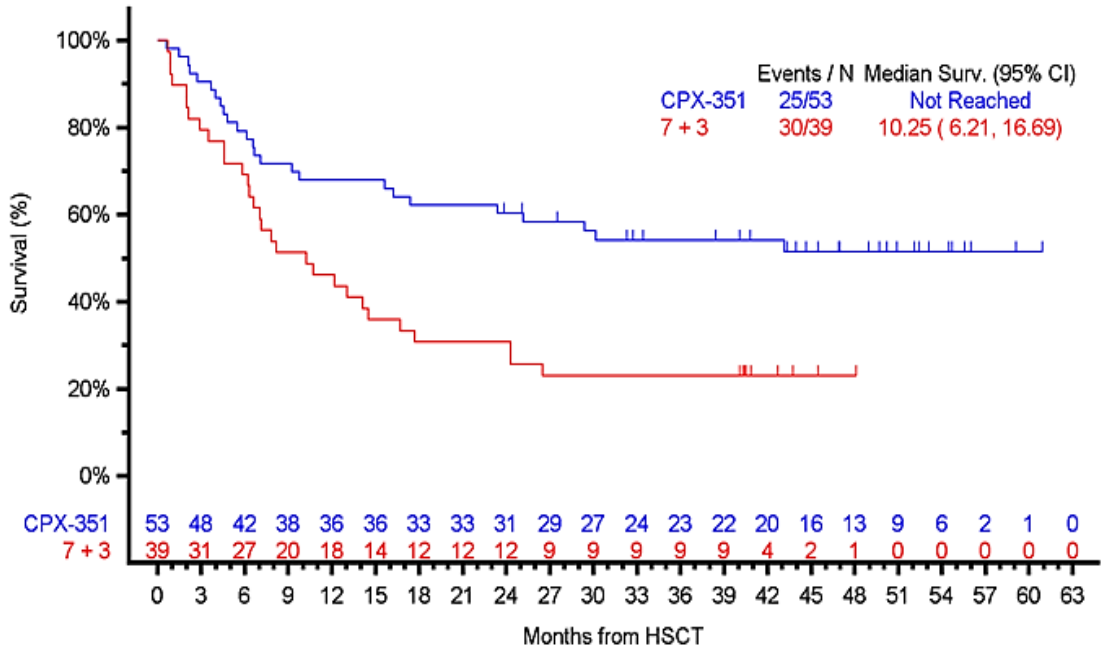


Figure 4. Updated Kaplan-Meier OS analysis landmarked at time of HSCT, ITT population (3 Aug 2018)



1.4 Concluding Points on Clinical Effectiveness

Jazz Pharmaceuticals has undertaken an unplanned OS analysis of the pivotal Phase III trial based on DSUR data. This mature data set confirms that the OS benefit seen in the study is real and persists in both the ITT and post-HSCT populations out to 4 years follow up. These data are sufficient to confidently measure the long term OS in both the ITT and post-HSCT populations. These updated results also specifically address the concerns regarding censoring on the CPX-351 arm and attainment of plateaus post-HSCT for both study arms (ACD sections 3.4 and 3.6). These results therefore provide an important and clinically plausible dataset to improve the reliability of the long-term OS extrapolations.

2 Additional evidence supporting the cost-effectiveness of CPX-351

2.1 Economic model update

In consideration of the committee's concerns regarding the reliability of the long-term survival extrapolations and the updated clinical evidence, several model updates have been conducted.

- In order to capture the fraction of the population with long-term survival in the 3+7 arm, the model was updated to incorporate a cure model post-HSCT for both the CPX-351 and the 3+7 arms. A scenario has been added manually setting the fraction of patients who survive long-term after receiving HSCT treatment to 20% in the 3+7 arm.
- In order to capture the committee and clinical expert opinion, a conservative scenario with 20% of patients below age 60 has been incorporated.
- In order to offer a simpler method for comparison of modelling post-transplant outcomes to the literature, a new output graph for all patients with HSCT has been added to the "OS and EFS by treatment pathway" sheet in the model.
- The cost and quality of life assumptions incorporated in the base case have been updated to those described in the ACD.

The ERG modifications that were taken into account and considered in the model as described in ACD section 3.11 are:

- basing post-transplant outcomes only on overall survival
- adjusting post-transplant mortality rates to 2.35
- using some alternative utility values
- using a different method to calculate vial use
- reducing the number of hospital days in consolidation

It was not feasible to develop a model that included the longer follow-up clinical data directly, due to the lack of individual patient data. However, the updated KM survival curves have been used as reference points for comparison to the updated model outcomes to ensure that the modelling results were consistent with and not more optimistic than observed data. In addition, a cure statistical analysis has been performed on the ITT population from the original data cut as a second reference point for comparison to the modelled outcomes; the aim was to evaluate the consequences of the long-term extrapolation from the model versus the committee's proposed method.

2.2 Economic model survival projections versus trial data

The cure analysis for the post-HSCT population was conducted using the original trial data. A Gompertz survival curve fitted to the UK general population with a conservative SMR of 2.35 was applied for the cured population. For the CPX-351 arm, very similar results were obtained regardless of the fitting form chosen for the non-cured population. The Weibull form was chosen on the strength of a marginally better BIC, but the lognormal has very similar fit statistics. None of the analyses for the 3+7 treatment arm converged, due to the use of the original data cut, which did not show a plateau for this arm post-HSCT. In order to reflect the

updated KM data, however, a 20% cure-fraction was manually applied in the model for the 3+7 treatment arm.

Table 3. Statistical assumptions for cure proportion and fits

	Cure proportion	AIC	BIC
Weibull	70.9%	154.8782	159.4816
Lognormal	69.5%	154.4909	159.8688
Gamma	69.2%	156.4852	163.1394

2.3 Survival curves comparison

To further highlight similarities of estimates and confirming the model methodology, four survival projection approaches are compared below.

- In (a), overall survival is projected using the ERG weighted analysis approach for post-HSCT survival.
- In (b), overall survival is projected using the Gompertz form for post-HSCT survival (as in the original submission).
- In (c), overall survival is projected using a new cure form for post-HSCT survival for CPX-351.
- Finally, in (d) overall survival is projected using a new cure form for post-HSCT for CPX-351 and 3+7, forcing the cure fraction in the 3+7 arm to be 20% aligned with the updated KM curves.

Using the cure-model forms for post-HSCT survival (scenarios c and d), the modelled survival for the overall population in the CPX-351 arm slightly undershoots the original KM data and is in very good agreement with the updated KM data. The updated model predictions are very similar to those using a Gompertz survival extrapolation post-HSCT and marginally higher than those using the ERG weighted analysis. There is modest separation between different model fits over the longer time horizon of the updated KM, with the cure-model showing the best agreement with the KM data, and the ERG weighted approach (scenario a) the most deviation. At the long time end of the curves, the model projections using the cure-model underestimate the updated KM data by 3 percentage points (16% projected vs 19% observed), while the ERG weighted approach underestimates by 8 percentage points (11% projects vs 19% observed). (see Figure 5 and Figure 6)

Figure 5. OS ITT for CPX-351- comparison between estimates and original KM curve

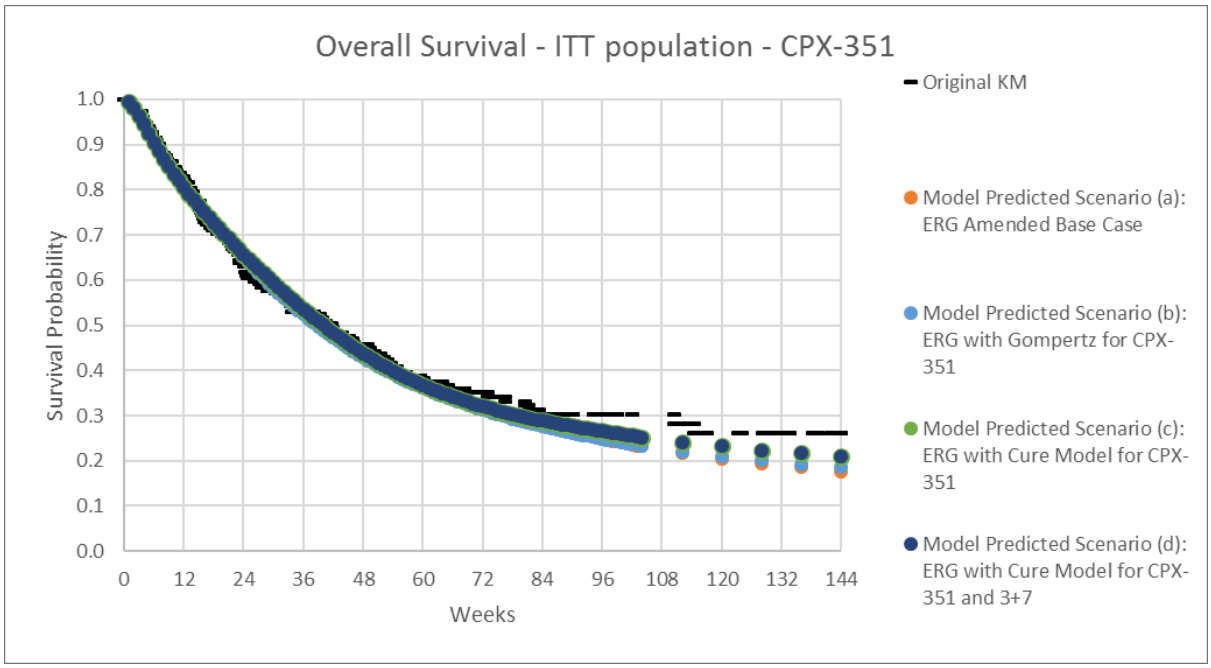
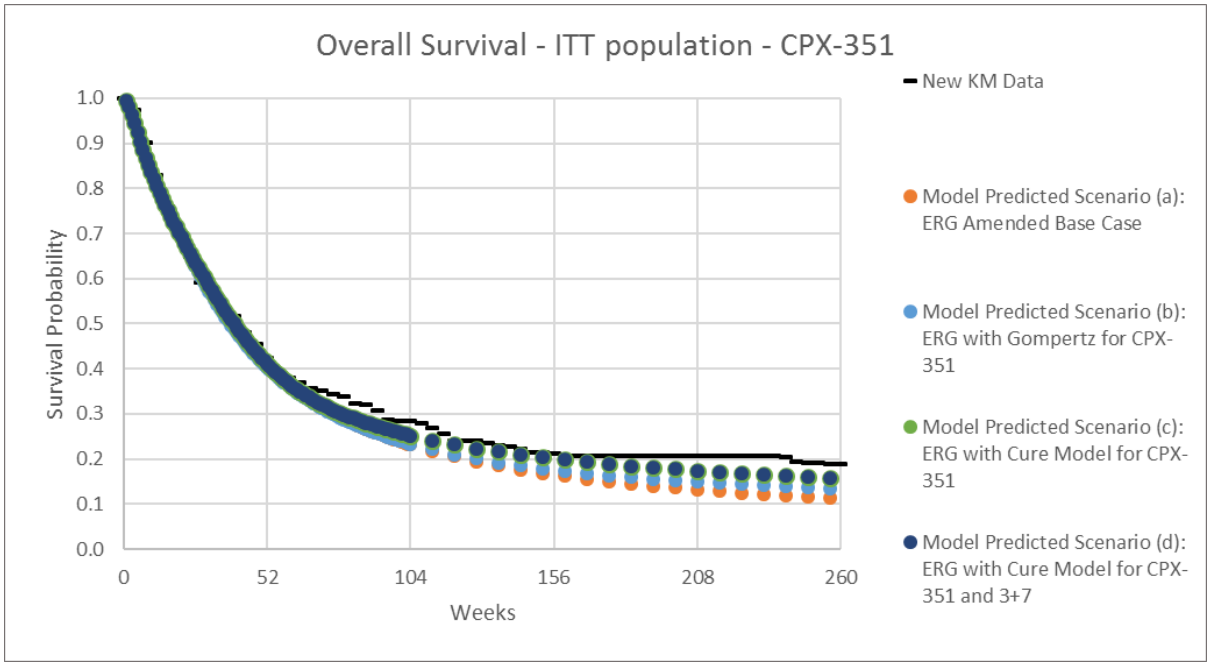


Figure 6. OS ITT for CPX-351- comparison between estimates and new KM curve



Similarly, in the 3+7 arm, the model projections agree well with both the original and the updated KM curve. The model projections using the cure-model forcing a 20% cure fraction (scenario d) underestimate the updated KM data by 3 percentage points (6% vs 9%) at long times, while those in which the cure-fraction is permitted to be zero underestimate the observed KM by 6 percentage points (3% projected vs 9% observed) (for reference, see Figure 7 and Figure 8)

Figure 7. OS ITT for 3+7- comparison between estimates and original KM curve

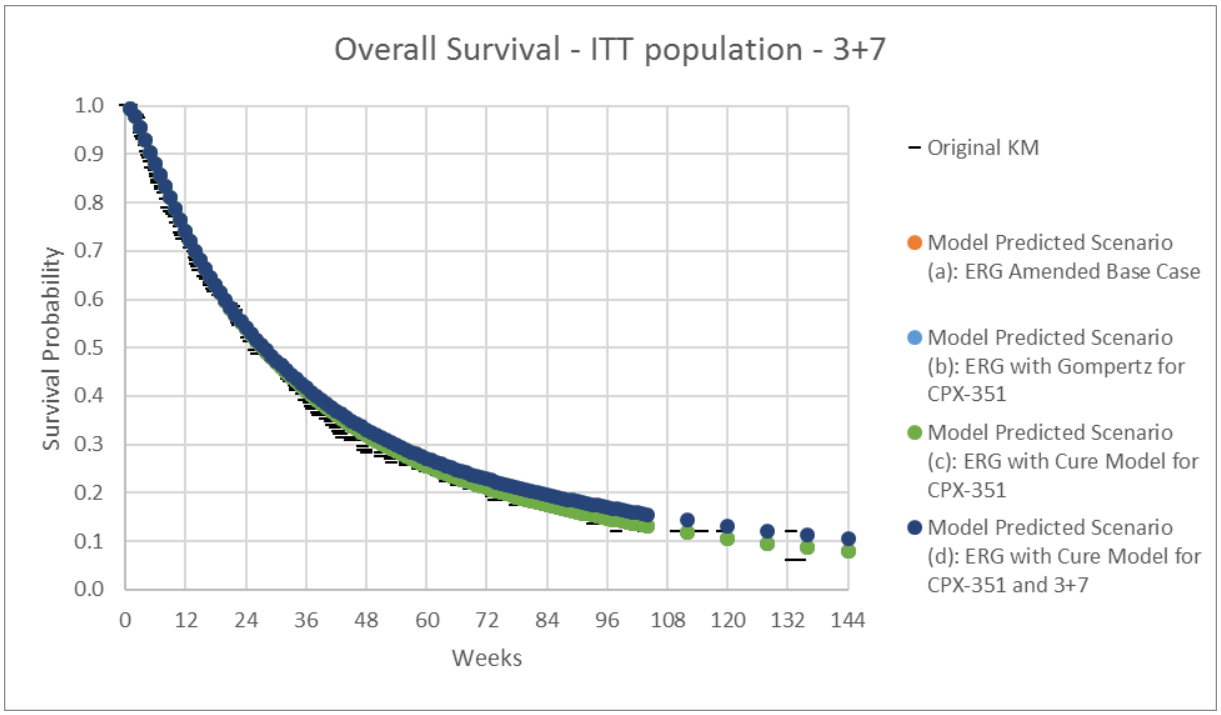
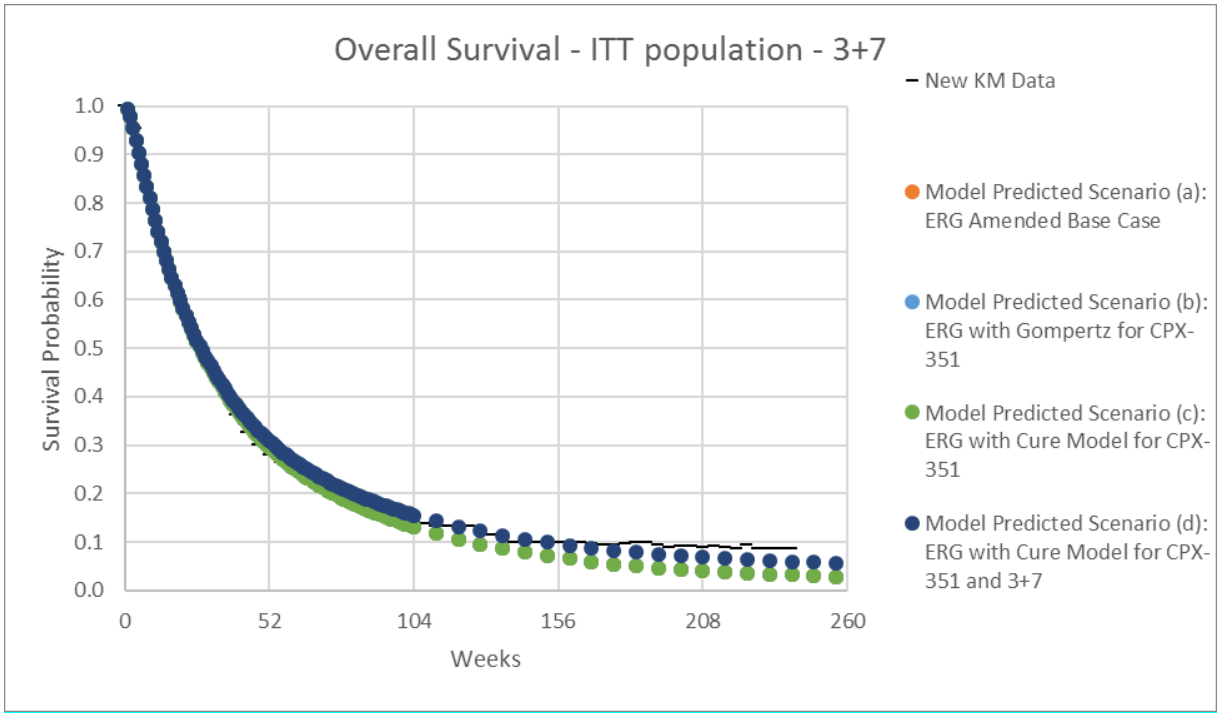


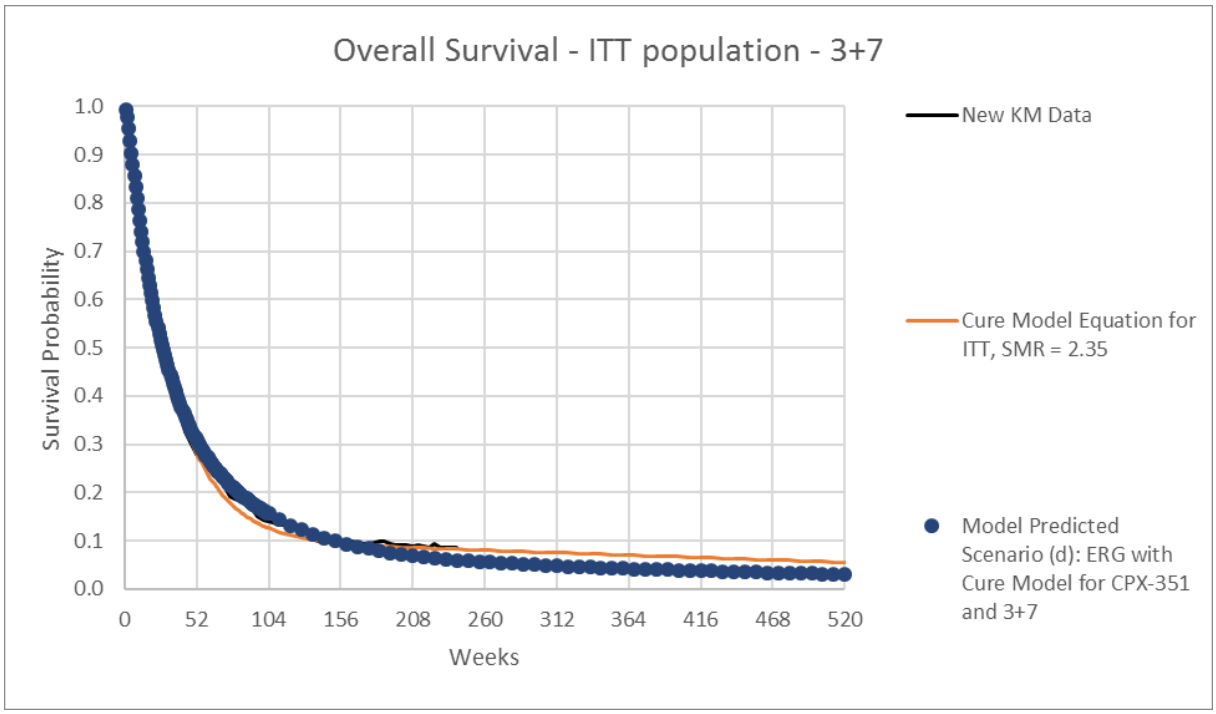
Figure 8. OS ITT for 3+7 - comparison between estimates and updated KM curve



Taken together, these comparisons support scenario d (cure models post-HSCT for both arms, with a 20% cure fraction forced for the 3+7 arm) as the best representation of the trial data with small and equal deviations from the updated data in both arms at long times.

To further evaluate if a cure model fit to the ITT population would provide a different projection of long-term survival, a cure analysis was conducted on the full ITT population using the original data. As shown below, the cure analysis for the ITT population yields results that are in very good agreement with the KM estimates (including the new KM data) over the horizon of the available data for the 3+7 arm (Figure 9). Over very long time horizons, the cure methodology and the model projections remain close to one another, suggesting that differences in OS outcomes between the current modelling approach and one based on a cure model of the ITT population would be modest.

Figure 9. OS ITT population - Comparison for cure



2.4 Economic model results

As expected, the economic model results are sensitive to the approach to long-term survival projections. The new updated base case which the company would like to present considering ACD and committee recommendations was selected to be scenario (d), in which cure models are used for post-HSCT survival, with a 20% cure fraction forced for 3+7 for a population which includes 20% of patients under the age of 60 years. This scenario has the best fit to the trial data and is consistent with the clinical literature on survival post-transplant and produces an ICER of [redacted]

The ICER for the base case and the scenarios are detailed below. Considering a population that excludes patients below age 60 increases the ICER to [redacted]. All other sensitivity analyses result in lower ICERs, as the settings recommended by the committee for the base case are generally conservative in each case (

Table 4).

Table 4 Model results

Scenario	ICER	Population
Base case (scenario d) (cure model applied to CPX-351 and 3+7)	[redacted]	20% of patients below age 60
Base case with trial population only	[redacted]	All patients older than 60
Assuming no cure fraction post-transplant for 3+7	[redacted]	20% of patients below age 60
Assuming Gompertz survival function for both CPX-351 and 3+7	[redacted]	All patients > 60
Assuming Gompertz survival function for both CPX-351 and 3+7 with transplant from unrelated donors	[redacted]	All patients > 60
Post-transplant remission utility value, age-adjusted utility values for general population, and treatment-related utility simultaneously (company)	[redacted]	All patients > 60
Post-transplant remission utility value (company)	[redacted]	All patients > 60
Age-adjusted utility values for general population (company)	[redacted]	All patients > 60
Treatment-related utility (company)	[redacted]	All patients > 60
Using a different method to calculate vial use (company)	[redacted]	All patients > 60
Reducing the number of hospital days in consolidation (company)	[redacted]	All patients > 60

In addition, the company presents the ICER results with the confidential PAS in

Table 5, which showcase that all of them are below £50,000 per QALY gained.

Table 5 Model results (with PAS)

Scenario	ICER	Population
Base case (scenario d) (cure model applied to CPX-351 and 3+7)	£42,681	20% of patients below age 60
Base case with target population	£48,991	All patients older than 60
Assuming no cure fraction post-transplant for 3+7	£33,755	20% of patients below age 60
Assuming Gompertz survival function	£45,103	All patients > 60
Post-transplant remission utility value, age-adjusted utility values for general population, and treatment-related utility simultaneously (company)	£40,395	All patients > 60
Post-transplant remission utility value (company)	£42,704	All patients > 60
Age-adjusted utility values for general population (company)	£46,664	All patients > 60
Treatment-related utility (company)	£48,580	All patients > 60
Using a different method to calculate vial use (company)	£46,084	All patients > 60
Reducing the number of hospital days in consolidation (company)	£47,260	All patients > 60

2.5 Concluding point on cost-effectiveness

In order to further remove doubts about the model robustness, uncertainty and long-term extrapolation, the company updated its cost-effectiveness model to accommodate implementation of a cure model post-HSCT with a plateau post-transplantation in both treatment arms. The comparisons between the updated OS KM curve from the DSUR data and model projections confirm that there is very strong agreement between the model projections and the observed data in phase 3 study to nearly five years post-randomisation. Contrary to the committee concerns, these modifications did not produce an ICER which is higher compared to the ERG alternative base case.

This new evidence and implementation of a cure-model post-HSCT, produces an ICER of [redacted]. When applying the confidential PAS, the ICER decreases to £42,681. In addition, all conducted sensitivity analyses met the cost-effectiveness criteria for an end of life treatment.

References:

Shimoni A et al. Long-term survival and late events after allogeneic stem cell transplantation from HLA-matched siblings for acute myeloid leukemia with myeloablative compared to reduced-intensity conditioning: a report on behalf of the acute leukemia working party of European group for blood and marrow transplantation. J Hematol Oncol 2016 Nov 8;9(1):118.

Sengsayadeth et al. Conditioning intensity in secondary AML with prior myelodysplastic syndrome/myeloproliferative disorders: an EBMT ALWP study. Blood Advances 2018; 2(16): 2127-2135.

Wingard JR et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. J Clin Oncol. 2011 Jun 1;29(16):2230-9

Liposomal cytarabine and daunorubicin for untreated acute myeloid leukaemia [ID1225]

Company response to clarification questions

3. Please explain why the company does not have the individual patient data for the study, as stated in section 2.1 of the company's response.

The company would like to clarify its response with regards to the availability of individual patient data for the study. As part of the clinical trial design for study 301, individual patient data on dead/alive status were prospectively and routinely collected to determine overall survival of patients randomised to CPX-351 or control. In Dec 2015, with 236 deaths recorded, there were sufficient data to perform the primary endpoint analysis and this formed the company's original regulatory filing submission. The study has continued to prospectively and routinely collect individual patient data on dead/alive status as part of the ongoing safety update reporting process, with a plan to generate 5 years of follow up data by 2020. In response to the request of NICE for more mature data, the company undertook an unplanned analysis of patient dead/alive status, contacting sites directly and using data collected up until August 2018 in order to generate new KM curves with longer term follow up. Therefore individual patient data regarding dead/alive status are available and have been added to the original data set to generate the new KM curves.

Regarding the statement in section 2.1 of the company's response, the company would like to clarify that only a limited dataset of updated individual patient data, i.e. specifically dead/alive status and not event-free status, was available to be used for the economic model.

4. Please explain why the company has only provided cure models for post-HSCT OS, not for the full population.

In response to the committee's preference for cure models of OS in the ITT population, the company began implementing cure models based on the original data set, while analyses for updated KM curves were also being conducted. The model extrapolations were then compared with the updated survival analyses for the ITT population to explore the overlap and fit. These extrapolations found that a cure model of OS in the ITT population from the original data set would overestimate survival and give an overly favourable and unrealistic ICER for CPX-351 (Figure 9a).

The company then explored a cure model for post-HSCT OS, where the clinical evidence best supports a cure assumption. In doing so, we found that scenario "d", a cure model post-HSCT in both arms based on the original data, with an imposed 20% cure fraction for the 3+7 arm,

reproduced the new aggregated data very well. In particular, for both arms the economic model predicted OS for the ITT population, which agreed well with the new KM data over the entire follow-up period. In addition, the model predictions underestimated the new KM data equally in each arm (by 3%) at the end of available follow-up. Given the length of follow-up in the updated data, all patients alive at that time will be subject only to general population mortality with an appropriate SMR (i.e. only cured patients will remain), regardless of the modelling method chosen. Thus the economic model predictions using a post-HSCT cure model were judged to provide a good basis for estimating cost-effectiveness. The deviation in long-term OS projections from the observed data were small in both arms and equal in magnitude.

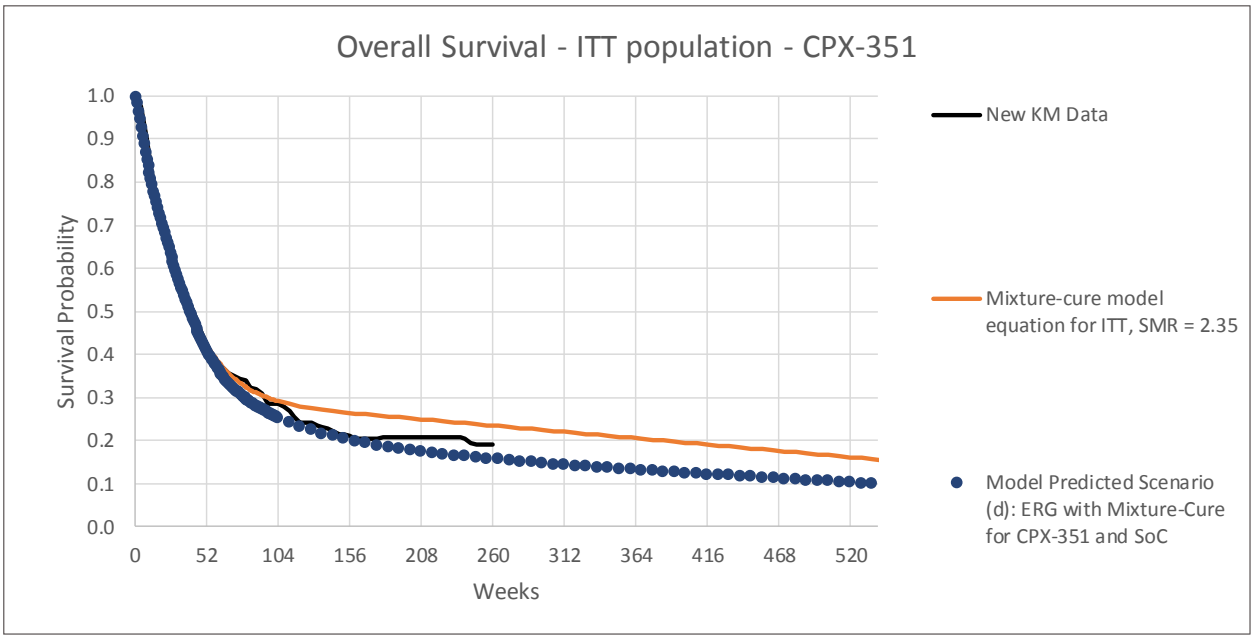
As noted in question 3, the updated data did not reduce the censoring of relapse events and, in addition, developing a new model could introduce new errors. Given these challenges and the observation that the alternate method would yield a very similar extrapolation of OS beyond the trial period and thus of cost-effectiveness, the company believed that the cure model for post-HSCT OS was appropriate for decision making and also clinically relevant.

5. **Regarding figure 9 of the company's ACD response, please explain why only the 3+7 group is presented. Please also confirm whether the curve labelled as 'scenario d' in figure 9 is the same as the curve labelled 'scenario d' in figure 8 i.e. post-HSCT only.**

The curves labelled scenario "d" in figures 8 and 9 are the same. The intent of figure 9 was to show how the use of a cure model for the post-HSCT OS compares to the cure model for the ITT population. Please note that with the availability of the KM data up to approximately 260 weeks, it is mainly the period from 260 to 520 weeks that is of interest in this comparison. Unfortunately, the cure model for the CPX-351 population using the original data did not yield a plausible extrapolation of long-term survival based on a comparison to the KM graphs using the updated analyses. Consequently, only the 3+7 arm was presented in figure 9.

As shown below, the cure analysis with the original data for the ITT population in the CPX-351 arm yields results that overestimate survival (compared to the new KM data) over the horizon of the available data (Figurea). Given the overestimated survival compared to the new KM data, this did not represent an appropriate comparison point to the model predictions.

Figure 9a. OS ITT population - Comparison for cure model



6. Regarding figure 8: as this is a graph for the 3+7 group, please clarify what the green line represents, which is labelled CPX-351.

We have attempted to maintain consistent labelling across all graphs. In each graph, the dotted curves are the model outputs (using separate cohorts based on treatment path). The orange represents scenario “a”, the light blue dotted curve scenario “b”, the green dotted curve scenario “c”, and the dark blue dotted curve scenario “d”. KM data from the trial are indicated with the solid black lines, while the equation for a cure model of the ITT population is shown in a solid orange line. In all of the first three scenarios, the 3+7 OS curve is the same and thus these scenario descriptions included only the fit approach used for the CPX-351 arm. The green line in figure 8 represents the model projection for the 3+7 arm in scenario “c” – in which a cure model is used for CPX-351 and the original Gompertz model for 3+7. Because the fitting of the 3+7 arm does not change between scenarios “a”, “b”, and “c” only one line for all three is visible on the graph for 3+7.

Single Technology Appraisal (STA)

Liposomal cytarabine and daunorubicin for untreated acute myeloid leukaemia [ID1225]

ERG commentary on the response submitted by the company to the ACD

Produced by **CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD**

Date **26/09/2018**

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

1 ERG commentary on the amended company analysis

Please note that given the time contraints and capacity of the ERG project team, the commentary on the company's response to the ACD for this appraisal is limited to a set of brief notes.

1.1 The company executable model

- It was not possible for the ERG to fully replicate ERG analyses in the new company model. The ERG preferred ICER in the orginal model was [redacted]. The ERG-preferred ICER in the new model as [redacted] (£12 higher). This small difference is due to a difference in the total costs associated with CPX 351 and 3+7.

1.2 Company submitted clinical data with new data cut

- The updated evidence is more robust and reduces the uncertainty about the longer-term OS results. The data are significantly more mature and the median follow-up longer.
- No hazard ratios were reported by the company on the updated ITT analysis of overall survival. The original HR was 0.69 [95% CI 0.52, 0.90, p-value = 0.005]
- Visual inspection of the updated KM OS analysis (Figure 3) indicates that most events occurred broadly within the first 12 months post-HSCT, which appears clinically plausible.
- The company did not provide further explanation on the clinical plausibility of the observed survival benefit post-HSCT for CPX compared with 3+7.
- Due to the lack of IPD, there still uncertainty about the longer-term outcomes according to HSCT/response status, although any analyses would be based on small numbers of patients.
- Overall survival after HSCT: the ERG notes that the plateau in the updated KM curve is lower for CPX than in the original KM curve, appearing to be around 50-55% from visual inspection. There seems to be a plateau for 3+7 at around 20-25%.

1.3 The cure modelling approach for post-HSCT overall survival

- These were not based on the updated data cut, which compromises their robustness.
- The method used was not clearly reported by the company and it was not clear on how general population mortality was taken into account.
- The ERG noted that the cure fractions for CPX-351 that were applied in the model were different to those in the response document.
- Additionally, the cure fraction for CPX-351 was different depending on whether the SMR for background mortality was applied. The cure fraction was much higher if the SMR was applied, which was the committee's and the ERG's preferred assumption regarding mortality.

However, the unadjusted curves provide higher survival estimates over time, and are considered less plausible.

- These cure fractions appear high – higher than the plateau that appears in the KM graph.

Table 1 Cure fractions for CPX-351

Distribution	Modelled (without SMR)	Modelled (with SMR)	Reported in ACD document
Weibull	[redacted]	[redacted]	70.9%
Lognormal	[redacted]	[redacted]	69.5%
Gamma	[redacted]	[redacted]	69.2%

- It was not possible to determine the cure fraction for 3+7 as there were few patients in the tail in the original KM curve.
- The company forced a 20% cure rate, with the survival of the uncured proportion based on the original survival analysis. This is not a robust method, but it appears to fit the trial data better and provides more plausible long-term survival predictions than the company's original survival method (the standard parametric Gompertz model)
- The 20% cure rate appears to be based on visual inspection, and no other cure fractions were explored. The ERG considers that 25% could be considered an upper limit.
- The ERG noted that the survival of uncured CPX-351 patients, most were dead by 2 years, whether unadjusted or adjusted methods were used.

1.4 Comparison of cure models

- For CPX, all curves fit relatively well to the trial data. The ERG's concern relates more to the long-term extrapolation and predictions offered by these survival curves.
- The ERG tested the different cure models for CPX and they provided similar ICERs to each other. It was not possible without a model re-structure to explore alternative mixture cure models (MCM) survival models for 3+7.

Table 2 Model fit statistics

	AIC	BIC
Weibull - MCM	154.8782	159.4816
Lognormal- MCM	154.4909	159.8688
Gamma- MCM	156.4852	163.1394
Gompertz- SP	[redacted]	[redacted]
Weibull- SP	[redacted]	[redacted]
Loglogistic- SP	[redacted]	[redacted]
Lognormal- SP	[redacted]	[redacted]
Exponential- SP	[redacted]	[redacted]
Gen gamma- SP	[redacted]	[redacted]

MCM: mixture cure model. SP: simple parametric

- For CPX, the MCM curves provide higher survival estimates and produce more LYs than all simple parametric curves in the original company model.
- The opposite effect appears for 3+7.
- There remains considerable uncertainty in the long-term survival that has not been addressed by the MCM, given that these were not based on the updated data cut.

Figure 1 Long-term survival (CPX-351, post-HSCT OS)

Figure 2 Long-term survival (3+7, post-HSCT OS

1.5 Company modelling scenarios

Results of the company's analyses are provided in the CPAS document that accompanies this report.

Modelling assumptions

- The company used the committee-preferred assumptions in their new analyses, which included:
    - All ERG corrections,
    - Cure model using the SMR adjustment (Weibull for CPX and Gompertz for SoC),
    - Basing post-transplant outcomes only on overall survival ,
    - Adjusting post-transplant mortality rates to 2.35 ,
    - Utility values adjusted for aging, using utility of 0.75 for functionally cured patients, and treatment-related utility not applied,
    - The ERG's method to calculate vial use based on distribution of BSA,
    - Reducing the number of hospital days in consolidation,
    - If aged under 60, applied a OR of 1.35 of remission
    - The company's original value for stem cell transplant costs.
- The committee considered that SCT are likely to be from related donors nowadays. However, the ERG does not consider that this should relate to a rejection of the ERG's alternative costing approach. The ERG's changes to stem cell costs consisted of additional follow up costs (which should apply regardless of the source of the donor stem cells), and exclusion of the cost of maintaining the stem cell registry (of which costs are often borne by charities, not included in any previous NICE appraisals for HSCTs, and may not be realised in practice as they were estimated through a bottom-up approach). However, this assumption is not a driver of the model (makes little difference to ICER, where the ERG single change scenario reduced ICER by ~£1,000)

Age scenarios

- The company included 20% of patients under the age of 60 in their new base-case scenario. This was associated with an adjustment to the number of patients who achieved remission (odds ratio of 1.35), which increased the absolute number of patients who receive transplant, and therefore increases survival overall. This effect is proportionally more so for the CPX-351 arm.
    - In the ACD, the clinical experts explained that about a quarter of patients who would be eligible for treatment in England would be under 60 years of age.

- There is no biological reason to expect the benefit of treatment to be any different than the benefit seen in people aged 65 to 70 years in the trial.
- The committee concluded that the clinical-effectiveness evidence from Study 301 was relevant to clinical practice in England.
- ERG did not include this assumption in their base-case and noted the limitations associated with the adjustment in their original report. Specifically, that the impact of age on response in the trial was not significant (confidence interval of 0.83,2.19), and that the trial did not capture treatment effectiveness of patients under the age of 60 and so can not be robustly used to predict response in patients in this age group.

Other potential scenarios

- The ERG noted that the ACD did not include the comment on the representative body surface area made by Peter Clark (NHSE) who stated that the trial-based BSA is representative. The BSA area in the trial is higher than that used by the company and the ERG (company: 1.79, ERG: 1.83, Trial: 2.0). This has an impact on vial use for CPX-351, and the ERG estimated that it would increase the ICER for CPX-351 vs 3+7. A scenario run by the ERG (MCM for CPX-351 and 3+7, all patients over 60, no PAS applied, committee-preferred assumptions) increased the ICER from [redacted] to [redacted].
- If the cure fraction for 3+7 is increased from 20% to 25%, the ICER is increased. A scenario run by the ERG (MCM for CPX-351 and 3+7, all patients over 60, no PAS applied, committee-preferred assumptions) increased the ICER from [redacted] to [redacted].