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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [ID1166]

Final Appraisal Determination Document

The following documents are made available to the Committee:

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:**
   - Novartis UK
   - Bloodwise
   - Lymphoma Action
   - NHS England

3. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Sridhar Chaganti – Clinical Expert nominated by Royal College of Pathologists-British Society of Haematology
   - Prof Peter Clark – CDF Clinical Lead

   Comments on the Appraisal Consultation Document received through the NICE website:
   None

4. **Company appendix of new evidence** – submitted by Novartis Pharmaceuticals Ltd
   - Scenarios and ICERs with PAS and CDF rebate

5. **Evidence Review Group critique of company ACD comments** - prepared by York Centre for Reviews and Dissemination

6. **Evidence Review Group appendix to critique of company ACD comments** - prepared by York Centre for Reviews and Dissemination

7. **Evidence Review Group review of company appendix of new evidence following the committee meeting** - prepared by York Centre for Reviews and Dissemination

Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies

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	Bloodwise	We recognise the challenges in defining *'people who are ineligible for stem cell transplants'* and therefore Kymriah's proposed placement in the treatment pathway. Given the current lack of treatment options available to people with relapsed or refractory DLBCL, we hope everyone with relapsed disease could potentially benefit from Kymriah in future, as per the likely marketing authorisation.	Thank you for your comment. The committee considered the full marketing authorisation for tisagenlecleucel when making its recommendations.
2	Consultee	Bloodwise	Although JULIET data does demonstrate a high frequency of adverse events, we understand from patients with DLBCL that have undergone treatment for Yescarta that they were willing to tolerate potentially significant adverse events, given that their only alternative was salvage chemotherapy or death. We believe this same principle would apply to people undergoing treatment for Kymriah.	Thank you for your comment. The submissions from patients and patient groups were considered during the development of this appraisal. The consideration of adverse events is included in section 3.10 of the FAD.
3	Consultee	Bloodwise	It is not possible for us to comment on whether Kymriah should meet the 'end of life' criteria, given that the comparative overall survival data provided by the company is confidential. However, the committee's acknowledgement that *'in the axicabtagene ciloleucel appraisal, the committee had not been presented with any reliable comparator data that was representative of the population, therefore, it made a judgement that it was plausible that the criterion for short life expectancy could apply'* appears inconsistent, given the decision in the case of Yescarta was made speculatively. Bloodwise takes no view on whether one treatment is preferable to another, however, we feel it is important that both are assessed consistently on the basis of available evidence.	The committee considered the end of life criteria at the second meeting and after considering median and mean survival data from CORAL, the uncertainty in long-term outcomes and the end-of-life decision in an ongoing appraisal in the same population, it concluded that end of life criteria had been met (see section 3.18 of the FAD).
4	Consultee	Bloodwise	We do not agree that the provisional recommendations are a sound and suitable basis for the NHS. Bloodwise recognises the committee's concern that of a lack of comparative data to establish the extent of effectiveness, and with it,	Thank you for your comments. The appraisal committee considered the new evidence at the second appraisal committee meeting and recommended tisagenlecleucel for use within the Cancer Drugs Fund. See section 1.1 of the 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
			cost-effectiveness. However, we also note that the treatment is extremely promising and is considered to be 'clinically very promising' by clinical experts. We therefore recommend that Kymriah for DLBCL be introduced to the Cancer Drugs Fund, in order to develop direct comparative evidence of the effectiveness of the treatment versus salvage chemotherapy.	
5	Consultee	Lymphoma Action	We are concerned that this recommendation denies patients' access to the only type of treatment that may offer a potential cure. There is urgent unmet need for patients who have failed several courses of treatment and whose options are now mainly palliative or a clinical trial. This technology appears to be the only option that offers a potential cure to patients who have failed other therapies.	Thank you for your comments. The appraisal committee considered the new evidence at the second appraisal committee meeting and recommended tisagenlecleucel for use within the Cancer Drugs Fund. See section 1.1 of the FAD.
6	Consultee	Lymphoma Action	This recommendation does not seem to take sufficient account of the rarity of the indication. Clinical trials in this indication are small because the patient population fit enough for this type of treatment is small.	Thank you for your comment. NICE considers that it should evaluate drugs to treat rare condition in the same way as any other treatment (please see NICE social value judgements for more details).
7	Consultee	Lymphoma Action	We are concerned that this recommendation is not taking into account the specific needs of patients who are refractory to chemotherapy. These patients are unable to have an autologous stem cell transplant. This treatment offers a lifeline to those patients, who otherwise have exhausted comparator therapies, and whose only other option may be a clinical trial or palliative care.	Thank you for your comment. The committee considered the unmet need in this population (see section 3.1 of the FAD). The appraisal committee considered the new evidence at the second appraisal committee meeting and recommended tisagenlecleucel for use within the Cancer Drugs Fund. See section 1.1 of the FAD.
8	Consultee	Lymphoma Action	This recommendation seems to be assessing a potentially durable and even curative response with the new technology against a short-lived response with comparators. There is no true comparator as the comparators do not meet the needs of the patients. The lack of a suitable comparator should not therefore restrict access to this treatment.	Thank you for your comment. The committee considered the evidence for the comparator arm at the second appraisal committee meeting (see sections 3.8, 3.14 and 3.15 of the FAD for more details). The appraisal committee considered the new evidence at the second appraisal committee meeting and recommended tisagenlecleucel for use within the Cancer Drugs Fund. See section 1.1 of the FAD.
9	Consultee	Lymphoma Action	With regards to long-term data, this can only come if the treatment is used. The durability of the treatment looks better than any alternatives. This treatment and similar treatments are being used in other parts of the world and for other indications. Could treatment centres in the US give	Thank you for your comments. The appraisal committee considered the new evidence at the second appraisal committee meeting and recommended tisagenlecleucel for use within the

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			further advice?	Cancer Drugs Fund. See section 1.1 of the FAD. Data will be collected in line with the managed access agreement. See section 3.21 of the FAD.
10	Consultee	Lymphoma Action	The patients who might benefit from this technology need treatment urgently. We heard from patients who are being told about this type of treatment and how it would be their best option after failing other treatments, only to learn that they cannot access it via a clinical trial as there is great demand for places and NICE propose not to recommend it. This puts tremendous strain on patients and carers.	Thank you for your comments. The appraisal committee considered the new evidence at the second appraisal committee meeting and recommended tisagenlecleucel for use within the Cancer Drugs Fund. See section 1.1 of the FAD.
11	Consultee	Lymphoma Action	Limiting treatment to specialist centres and to patients most likely to benefit from it (e.g. low ECOG score, refractory to chemotherapy) would enable more information about the treatment to be gathered whilst offering a lifeline to those patients who are most likely to benefit.	Thank you for your comments. The appraisal committee considered the new evidence at the second appraisal committee meeting and recommended tisagenlecleucel for use within the Cancer Drugs Fund. See section 1.1 of the FAD.
12	Consultee	Lymphoma Action	The main barrier to this recommendation appears to be cost. We hope an agreement can be reached with the pharmaceutical company to allow this treatment to be accessed on the NHS even if only on a limited basis while more robust data are collected.	Thank you for your comments. The appraisal committee considered the new evidence at the second appraisal committee meeting and recommended tisagenlecleucel for use within the Cancer Drugs Fund. See section 1.1 of the FAD.
13	Consultee	Novartis	Thank you for the opportunity to respond to the Appraisal Consultation Document (ACD) as part of the appraisal of tisagenlecleucel for treating relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) after two or more systemic therapies [ID1166]. In response to the ACD, Novartis would like to bring the following points to the Committee's attention: **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** **End of life criteria – see Section 1.1** • The decision not to grant "end of life status" is not consistent with the available evidence or the views of clinicians • Novartis believe that tisagenlecleucel meets the end-of-life criteria given that life-expectancy for the majority of patients (>80%) with r/r DLBCL after two or more lines of therapy is less than 24 months • In Novartis' revised base case, mean overall survival (OS) predicted by the model was less than 24 months for salvage chemotherapy	Thank you for your comments. The appraisal committee considered the new evidence at the second appraisal committee meeting and recommended tisagenlecleucel for use within the Cancer Drugs Fund. See section 1.1 of the FAD. The committee considered the end of life criteria at the second meeting and after considering median and mean survival data from CORAL, the uncertainty in long-term outcomes and the end-of-life decision in an ongoing appraisal in the same population, it concluded that end of life criteria had been met (see section 3.18 of the FAD) The committee considered the updated data cut

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			Has all of the relevant evidence been taken into account? **More mature tisagenlecleucel data – see Section 2.1** • JULIET data from the more mature May 2018 data cut (highlighted to NICE prior to the Appraisal Committee meeting) have now been included in Novartis' revised cost-effectiveness analysis **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** **The CORAL extension study is not the most appropriate comparator data for salvage chemotherapy – see Section 3.1 and Section 3.2** • The CORAL extension study only represents around 50% of the population eligible for tisagenlecleucel and only includes patients in the third-line setting who are likely to have improved outcomes compared to patients in later-line settings. The CORAL extension study alone is therefore not an appropriate source of comparator efficacy for the full patient population of interest • The extrapolation of data from the CORAL study for patients in the 'no SCT' arm does not adequately reflect the expected survival of patients in clinical practice who do not receive stem cell transplantation (SCT) **Survival data from the Haematological Malignancy Research Network (HMRN) can be used to address one of the major the limitations of the CORAL extension study – see Section 3.3** • As highlighted in the ACD, the Committee recognised the limitations of all the potential data sources for the comparator arm and suggested that the Haematological Malignancy Research Network (HMRN) database may help in their decision making. Therefore, an analysis incorporating HMRN data has been presented as additional evidence to this response and has been included in Novartis' revised base case. This revised base case is likely to better represent the full eligible population to receive tisagenlecleucel in the NHS **A 'cure' point at 2 years is most clinically plausible for tisagenlecleucel – see Section 3.4** • The evidence presented to the Committee supports the assumption that patients who are alive after 24 months would	for tisagenlecleucel (see section 3.4 of the FAD) HMRN data (see section 3.8 of FAD), alternative cure points (see section 3.13 of the FAD) and IVIG (see section 3.16 of the FAD) at the second appraisal committee meeting and recommended tisagenlecleucel to be used as part of the Cancer Drugs Fund.

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			have mortality similar to the general population. Novartis therefore believe that the cost-effectiveness results using the 2-year timepoint for assuming a 'cure' are the most plausible, however exploratory results for a 3-year timepoint are also presented in the revised cost-effectiveness analysis **Intravenous immunoglobulin therapy duration – see Section 3.5** • As presented as part of the technical engagement response, Novartis believe that the duration of intravenous immunoglobulin (IVIG) therapy for B-cell aplasia has been overestimated in the analyses currently preferred by the Committee • Based on UK clinical expert feedback, the estimate of 11.4 months used in the original company evidence submission was already considered conservative. However, given the limited impact of the duration of IVIG therapy on cost-effectiveness results, the Committee's preferred assumption of 36 months has been used in the Novartis' revised base case **Revised cost-effectiveness analysis** When taking into account all of the above, Novartis have presented a revised base case in Section 4 which includes the following: • The latest data from the JULIET trial for tisagenlecleucel • An alternative extrapolation of survival in the 'no SCT' arm of the CORAL extension study • An alternative approach to modelling survival salvage chemotherapy, which includes data from both the CORAL extension study and the HMRN database, in order to address one of the major limitations of the CORAL study and provide estimates of survival that are reflective of the full patient population of interest (i.e. r/r DLBCL after two or more lines of systemic therapy) Based on Novartis' revised base case tisagenlecleucel is associated with an ICER of £46,325 per QALY gained versus [R-]GDP with the PAS applied for tisagenlecleucel. The evidence used to inform Novartis' revised base case and the full results of this analysis and additional scenario analyses are presented in a separate appendix. Based on the results of Novartis' revised base case and scenario analyses, it is plausible that tisagenlecleucel would represent a cost-	

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			effective use of NHS resources for a condition for which life expectancy is less than two years for the majority of patients. However, Novartis acknowledge the uncertainty due to the relatively short-term follow-up data and, therefore, represents a good candidate for the cancer drugs fund (CDF) inclusion. Novartis, therefore, asks the Committee to reconsider the draft guidance provided in the ACD having appraised the additional evidence presented as part of this response.	
14	Consultee	NHS England	Tisagenlecleucel is an innovative new treatment which represents a step-change in the treatment of relapsed or refractory diffuse large B-cell lymphoma; a patient population with unmet need for whom this new treatment option that may improve the chance of survival. NHS England would welcome a positive recommendation from NICE, which would give patients access to this ground-breaking new technology and the associated benefits. However, NHS England is supportive of NICE's decision based on the uncertainty around how much benefit tisagenlecleucel offers compared with the current treatment and cost-effectiveness estimates being above the range normally considered to be a cost-effective use of NHS resources	Thank you for your comment. The appraisal committee considered the new evidence at the second appraisal committee meeting and recommended tisagenlecleucel for use within the Cancer Drugs Fund. See section 1.1 of the FAD.
15	Consultee	NHS England	A number of issues are highlighted in the Appraisal Consultation Document (ACD) for Novartis to address and NHS England hopes that these will be addressed to enable NICE to consider these points further.	Thank you for your comment, the new evidence submitted by the company after consultation are summarised in the FAD.
16	Consultee	NHS England	NHS England and Novartis are continuing to work together to ensure a number of sites across England are ready to deliver a safe and high quality service for patients by the end of autumn 2018. Working jointly with Novartis and the Joint Accreditation Committee ISCT-Europe & EBMT (JACIE), NHS England aims to introduce new services in a phased manner, ramping up provision to deliver a safe and effective service covering the anticipated patient population by the end of March 2020.	Thank you, your comments have been noted.
17	Consultee	NHS England	Whilst tisagenlecleucel has the potential to offer patients great clinical benefits, the uncertainty around the size of the benefits and the immaturity of the survival data make tisgenlecleucel an ideal candidate for the Cancer Drugs Funds (CDF). Allowing more time for clinical trial data to mature during a CDF managed access period and using real world data as an additional source of data could help to address the uncertainties highlighted by NICE.	Thank you for your comments. The appraisal committee considered the new evidence at the second appraisal committee meeting and recommended tisagenlecleucel for use within the Cancer Drugs Fund. See section 1.1 of the FAD.
18	Consultee	Royal College of Pathologists	The NICE recommendation not to fund Tisa-Cel is based on an ICER that works out to more than £54,000 per QALY. This is highly speculative and	Thank you for your comments. The appraisal committee considered the new evidence at the

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		and British Society of Haematology	is based on a number of assumptions which may or may not be true. The expected survival in the comparator arm varies depending on the chosen comparator. Similarly expected long-term survival in the Tisa-cel arm is speculative based on assumptions that a hybrid model incorporating predicted 2 yr and 5 yr survival rates.	second appraisal committee meeting and recommended tisagenlecleucel for use within the Cancer Drugs Fund. See section 1.1 of the FAD.
19	Consultee	Royal College of Pathologists and British Society of Haematology	We do not agree with the view of the NICE committee that Tisa-cel does not meet criteria to be considered life extending treatment at the end of life. A majority of patients meeting criteria for this treatment as per its marketing authorisation would have exhausted all valid treatment options and have a limited life expectancy of few to several months. So, for most patients in this situation, their illness would be considered “as end of life.” A 35 – 40% chance of long term survival (as offered by Tisa-cel) would be seen as a significant advance in this patient population.	Thank you for your comments. The appraisal committee considered the new evidence at the second appraisal committee meeting and recommended tisagenlecleucel for use within the Cancer Drugs Fund. See section 1.1 of the FAD. The committee considered the end of life criteria at the second meeting and after considering median and mean survival data from CORAL, the uncertainty in long-term outcomes and the end-of-life decision in an ongoing appraisal in the same population, it concluded that end of life criteria had been met (see section 3.18 of the FAD)

10th October 2018

National Institute for Health and Care Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT

Re: Novartis response to the Appraisal Consultation Document for ID1166 – tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies

Dear Stephanie,

Thank you for the opportunity to respond to the Appraisal Consultation Document (ACD) as part of the appraisal of tisagenlecleucel for treating relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) after two or more systemic therapies [ID1166]. In response to the ACD, Novartis would like to bring the following points to the Committee's attention:

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

End of life criteria – see Section 1.1

- The decision not to grant "end of life status" is not consistent with the available evidence or the views of clinicians
- Novartis believe that tisagenlecleucel meets the end-of-life criteria given that life-expectancy for the majority of patients (>80%) with r/r DLBCL after two or more lines of therapy is less than 24 months
- In Novartis' revised base case, mean overall survival (OS) predicted by the model was less than 24 months for salvage chemotherapy

Has all of the relevant evidence been taken into account?

More mature tisagenlecleucel data – see Section 2.1

- JULIET data from the more mature May 2018 data cut (highlighted to NICE prior to the Appraisal Committee meeting) have now been included in Novartis' revised cost-effectiveness analysis

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The CORAL extension study is not the most appropriate comparator data for salvage chemotherapy – see Section 3.1 and Section 3.2

- The CORAL extension study only represents around 50% of the population eligible for tisagenlecleucel and only includes patients in the third-line setting who are likely to have improved outcomes compared to patients in later-line settings. The CORAL extension study alone is therefore not an appropriate source of comparator efficacy for the full patient population of interest
- The extrapolation of data from the CORAL study for patients in the 'no SCT' arm does not adequately reflect the expected survival of patients in clinical practice who do not receive stem cell transplantation (SCT)

Survival data from the Haematological Malignancy Research Network (HMRN) can be used to address one of the major the limitations of the CORAL extension study – see Section 3.3

- As highlighted in the ACD, the Committee recognised the limitations of all the potential data sources for the comparator arm and suggested that the Haematological Malignancy Research Network (HMRN) database may help in their decision making. Therefore, an analysis

incorporating HMRN data has been presented as additional evidence to this response and has been included in Novartis' revised base case. This revised base case is likely to better represent the full eligible population to receive tisagenlecleucel in the NHS

A 'cure' point at 2 years is most clinically plausible for tisagenlecleucel – see Section 3.4

- The evidence presented to the Committee supports the assumption that patients who are alive after 24 months would have mortality similar to the general population. Novartis therefore believe that the cost-effectiveness results using the 2-year timepoint for assuming a 'cure' are the most plausible, however exploratory results for a 3-year timepoint are also presented in the revised cost-effectiveness analysis

Intravenous immunoglobulin therapy duration – see Section 3.5

- As presented as part of the technical engagement response, Novartis believe that the duration of intravenous immunoglobulin (IVIG) therapy for B-cell aplasia has been overestimated in the analyses currently preferred by the Committee
- Based on UK clinical expert feedback, the estimate of 11.4 months used in the original company evidence submission was already considered conservative. However, given the limited impact of the duration of IVIG therapy on cost-effectiveness results, the Committee's preferred assumption of 36 months has been used in the Novartis' revised base case

Revised cost-effectiveness analysis

When taking into account all of the above, Novartis have presented a revised base case in Section 4 which includes the following:

- The latest data from the JULIET trial for tisagenlecleucel
- An alternative extrapolation of survival in the 'no SCT' arm of the CORAL extension study
- An alternative approach to modelling survival salvage chemotherapy, which includes data from both the CORAL extension study and the HMRN database, in order to address one of the major limitations of the CORAL study and provide estimates of survival that are reflective of the full patient population of interest (i.e. r/r DLBCL after two or more lines of systemic therapy)

Based on Novartis' revised base case tisagenlecleucel is associated with an ICER of £46,325 per QALY gained versus [R-]GDP with the PAS applied for tisagenlecleucel. The evidence used to inform Novartis' revised base case and the full results of this analysis and additional scenario analyses are presented in a separate appendix.

Based on the results of Novartis' revised base case and scenario analyses, it is plausible that tisagenlecleucel would represent a cost-effective use of NHS resources for a condition for which life expectancy is less than two years for the majority of patients. However, Novartis acknowledge the uncertainty due to the relatively short-term follow-up data and, therefore, represents a good candidate for the cancer drugs fund (CDF) inclusion.

Novartis, therefore, asks the Committee to reconsider the draft guidance provided in the ACD having appraised the additional evidence presented as part of this response.

Yours Sincerely,

[redacted]

Health Economics and Outcomes Research Manager,
Novartis Pharmaceuticals UK Ltd

Detailed Response to Matters Arising from the Appraisal Consultation Document

1 Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

1.1 End of life criteria: Novartis believe that tisagenlecleucel meets the end-of-life criteria given that life-expectancy for the majority of patients (>80%) with r/r DLBCL after two or more lines of therapy is less than 24 months

Novartis is disappointed with the Appraisal Committee's decision not to grant "end of life" status in relation to the above appraisal and as detailed in the ACD. This decision is perverse in the light of the available evidence and inconsistent with clinical opinion and decisions made in previous appraisals with similar levels of evidence.

It is generally recognised that the vast majority of patients (>80%) with r/r DLBCL after two or more lines of therapy patients die within 24 months. For example, the results from ERG's revised model predict that approximately 14% of patients would be alive after 24 months. Furthermore, at the 2nd appraisal committee meeting of axicabtagene ciloleucel, which covers virtually the same population as that for tisagenlecleucel, it was acknowledged that 80% of patients were dead within 24 months.[1]

It is unclear why, in the case of the tisagenlecleucel appraisal, the decision has been based on a predicted mean OS rather than median OS, as has been the case in numerous previous appraisals. In this instance the predicted mean OS is likely to be misleading for the following two main reasons. Firstly, the mean OS was extrapolated from a source of data that does not fully or robustly represent the entire tisagenlecleucel DLBCL eligible patient population. It was acknowledged by clinicians attending the tisagenlecleucel Appraisal Committee meeting that the ERG's preferred source of comparator evidence was limited in its ability to represent the full tisagenlecleucel eligible population. Therefore, using predicted mean OS from a source of data (the CORAL extension study) that is recognised to be limited introduces additional uncertainty regarding extrapolated OS. Secondly, the shape of the extrapolated OS curve is skewed by the small proportion of patients who receive, and are cured by, SCT causing the OS curve to plateau. In other words, the vast majority of patients (>80%) have a very short life expectancy represented by a short median OS. However, the small proportion of patients who are cured following SCT dramatically skews the distribution of OS values thus resulting in a much longer predicted mean OS than median OS.

Results from Novartis' revised cost-effectiveness model for predicted OS are presented in Table 1 and for each of these analyses (described briefly below and in full in Section 2 of the Appendices) the proportion of patients alive at 24 months is less than 15%:

1. ERG's revised model which uses the CORAL extension study (Gompertz for extrapolating the 'no SCT' arm and the 'SCT' arm)
2. Novartis' revised model in which CORAL has been redigitised and alternative survival models explored (Gompertz for extrapolating the 'SCT' arm and the spline model with two knots for extrapolating the 'no SCT' arm) – see Section 3.2
3. Novartis' revised base case in which data from the HMRN have been used in combination with the CORAL extension study in order to address one of the major limitations of the CORAL study – see Section 3.3

In Novartis' revised base case (scenario 3 in the table below), the proportion of patients predicted to be alive at two years was 10% and the predicted mean OS is less than 24 months (20.4 months).

Table 1: Mean and median OS for salvage chemotherapy

Scenario	Median OS (months)	Predicted Mean OS (months)	% predicted alive at month					
			6	12	24	36	48	60
1: CORAL as per ERG's analysis	4.00	43.03	38	22	14	12	11	11
2: CORAL (spline with two knots for 'no SCT')	4.00	33.10	34	21	14	12	10	10
3: CORAL (for third line) and HMRN (for fourth- and later-lines) combined = revised base case	5.00	20.40	38	19	10	7	6	5

Abbreviations: ERG: Evidence Review Group; HMRN: Haematological Malignancy Research Network; OS: overall survival; SCT: stem cell transplantation.

In cases like this, where there is uncertainty around the predicted mean OS and there is general agreement that life expectancy is likely to be less than two years for the majority of patients it would be more reasonable to base the decision on median OS. There are 13 recent examples where Appraisal Committees have based the "end of life" decision on median rather than mean OS, including four made by the current Committee (Committee C*)*.[2-5]

It is widely acknowledged that the population in question i.e., adult DLBCL patients who are relapsed/refractory to at least 2 previous lines of therapy, have poor life expectancy that can be counted in months rather than years. Clinicians, both at the tisagenlecleucel and axicabtagene ciloleucel Appraisal Committee meetings, stated that these patients would not be expected to live beyond 2 years. Furthermore, the ERG who assessed tisagenlecleucel confirmed that in their view the "end of life" criteria were satisfied. The results from Novartis' revised base case, which is believed to be more reflective of the full patient population of interest (i.e. third- and later-lines) than the CORAL extension study alone, predicts that mean OS for salvage chemotherapy would be less than 24 months, thus adding further support to the belief that tisagenlecleucel meets the end-of-life criteria for this indication, regardless of whether median or mean OS is considered.

For the reasons given above, the decision not to grant "end of life" is:

- perverse in the light of the evidence and
- inconsistent with other appraisals

Consequently, we respectfully request that NICE and the Appraisal Committee to reconsider the negative "end of life" decision.

2 Has all of the relevant evidence been taken into account?

2.1 More mature tisagenlecleucel data: the latest data from the JULIET trial have been included in Novartis' revised cost-effectiveness analysis

As part of the response to the technical engagement consultation, Novartis provided a summary of the latest data available from the JULIET trial. The latest data cut from JULIET (21st May 2018) provides more mature data to the 8th December 2017 data cut-off that was presented in the initial company submission. The results from this more mature data set are consistent with those from the data cut-off presented previously, which showed emerging plateaus in the analysis of OS and progression-free (PFS). This supports the sustainability of response of tisagenlecleucel, which has also been demonstrated in the Schuster 2017 (NCT02030834) case-series study.[6] These data highlight the robustness of the data presented initially and continue to support the clinical benefits of tisagenlecleucel in adult patients with r/r DLBCL after two lines of systemic therapy.

As the May 2018 data cut was only available in August it was not possible to provide updated cost-effectiveness analyses in time for the first Appraisal Committee meeting. However, cost-effectiveness results which incorporate the latest JULIET data are presented in this document. It should be noted that the new data cut includes [redacted] more patients who received tisagenlecleucel since the previous data cut and the median and maximum follow-up for OS was [redacted] months and [redacted] months, respectively.[7] The following inputs have been updated in the revised cost-effectiveness model based on the May 2018 data cut: baseline characteristics, decision tree inputs for the proportion of patients receiving an infusion with tisagenlecleucel, OS, PFS, incidence of adverse events, subsequent SCT, and resource use associated with tisagenlecleucel (e.g. average length of stay in hospital and proportion of patients using lymphodepleting regimens).

The incorporation of the latest survival data from the JULIET trial into the cost-effectiveness model is detailed in Section 1 of the Appendices accompanying this document. Also provided in the appendices is a list of parameters that have been changed in the model and their corresponding sheet locations.

With the availability of more recent data from the JULIET trial, the cost-effectiveness results from the revised model should be considered by the Committee to ensure that the latest, relevant evidence for tisagenlecleucel in this indication is taken into account during decision making.

3 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

3.1 The CORAL extension study is not an appropriate source of comparator efficacy for the full patient population of interest

Based on the options of comparator efficacy presented to the Committee at the time of first appraisal committee meeting (CORAL, PIX301 and Eyre 2016), the Committee concluded that the CORAL extension studies were the most appropriate source of comparator efficacy but noted that there were "*limitations of all the potential data sources for the comparator arm* (ACD; Section 3.8)."

The main limitations of the CORAL extension study used in the ERG's base case is that the patient population included in this analysis only represents around 50% of the full patient population for the decision problem (i.e. r/r DLBCL after two or more lines of systemic therapy) and is likely to represent a patient population that is fitter, and therefore have better outcomes, compared to the full population of interest. This view, which is summarised in the statement below, has been confirmed with one of the authors of the CORAL study, who is a clinician in the UK:[8]

"The Van den Neste CORAL extension is not representative of the entire tisagenlecleucel eligible population but rather a subpopulation representing 50% or less of the eligible population.

The CORAL extension survival results are an overestimate of the OS expected in the tisagenlecleucel eligible population because many in the CORAL extension were in CR/PR at baseline. As quoted in the paper "a proportion of the 203 patients were in response (CR, n=26; PR, n=30) at CORAL withdrawal". Since OS survival analyses in this extension were based on all 203 patients and 28% of those were in CR or PR at baseline, this CORAL extension will overestimate the survival expected in a true relapsed/refractory population.

In addition, the CORAL extension only included 3rd line patients (i.e. 2 previous lines of therapy) whereas patients eligible for tisagenlecleucel may have had 2 or more previous lines of therapy. The prognosis for patients deteriorates with each successive line of therapy and so the CORAL extension is likely to overestimate survival as it does not include patients with more than 2 previous lines of therapy. By contrast over half the patients in the JULIET study were on their 3rd, 4th or beyond line of treatment."

Novartis therefore strongly believes that a mean OS of 43.03 months (see Table 1) is not reflective of clinical outcomes in r/r DLBCL patients after two or more lines of systemic therapy currently receiving salvage chemotherapy. As with any modelling, if the results are not reflective of clinical reality then the resulting ICERs are associated with a high degree of uncertainty.

For the reasons provided above, the CORAL extension study is not considered to be generalisable to the full patient population of interest, with the results from the study representing an overly optimistic estimate of survival for all patients with r/r DLBLC after two lines of therapy. To address the final limitation of the CORAL extension study described above, Novartis have explored the use of data from the HMRN for later lines of therapy in combination with data from the CORAL extension study in order to provide estimates of survival that are more reflective of patients treated in the third- and later-line settings (see Section 3.3).

3.2 The ERG's Gompertz extrapolation of OS for patients who do not receive SCT in the CORAL extension is likely to overestimate survival in this population of patients

The extrapolation of CORAL extension OS data using the Gompertz distribution for patients who do not receive SCT, as per the ERG's revised model (which was accepted by the Committee), is not consistent with the expectations of long-term survival that may be achieved by these patients in UK clinical practice. The Gompertz distribution produces a plateau in the survival profile which would not be expected for patients in the 'no SCT' arm, given that treatment for these patients would be given with palliative intent, and the possibility of a potential 'cure'/long-term survival for the salvage chemotherapy cohort in the model is already accounted for in the 'SCT' arm (for which the Gompertz distribution is more plausible).

Novartis has therefore updated the ERG's cost-effectiveness analysis to include the latest cut-off data from JULIET trial, with and without alternative extrapolation for the 'no SCT' arm of the CORAL extension study (see Table 2; further detail regarding these analyses can be found in Section 2 of the Appendices). As shown in Table 2, the incorporation of the latest JULIET data and maintaining all of the ERG's previous assumptions has resulted in a reduction in the ERG's base case ICER using the CORAL extension (results have been presented assuming a 2- or 3-year 'cure' point for tisagenlecleucel). Furthermore, using an alternative approach and more clinically plausible curve to extrapolate OS for the 'no SCT' arm of the CORAL extension study – i.e. the spline with two knots, which is associated with a better statistical fit to the observed data and more accurately reflects the expected survival profile of patients treated with palliative intent – has resulted in a further reduction in the ICER.

For these and all subsequent analyses presented in this document, the ERG/Committee's preferred assumptions have been left unchanged in Novartis' revised model; these include[i]:

- 'Hybrid' model was used for tisagenlecleucel OS in which the spline model with one knot extrapolation was used up to a specified 'cure' point followed by general population mortality (standardised mortality rate = 1)
- The rate of subsequent SCT for salvage chemotherapy (and weighting for the CORAL arms) was 12.5%
- 'Long-term survivor' costs and utilities were applied for all treatment arms at the same point at which the 'cure' point was assumed for the tisagenlecleucel 'hybrid' model

[i] Two discrepancies in the choice of inputs between the original company evidence submission and the ERG's revised model have been resolved by updates from the latest data cut-off date of the JULIET trial:
1. As the number of patients in the Efficacy Analysis Set (EAS) is equal to the number of patients in the Full Analysis Set (FAS) (N=[redacted]), the proportion of patients who received subsequent stem cell transplantation in the JULIET trial is the same, regardless of whether the EAS or FAS is used as the denominator
2. As the number of patients with Grade 3 or 4 cytokine release syndrome (CRS) is equal to the number of patients reporting duration of intensive care unit (ICU) stay (n=[redacted]), the proportion of patients assumed to have CRS in the model is the same, regardless of whether the original approach (Grade 3 or 4 CRS) or the ERG's approach (ICU due to CRS) is used for the numerator

- The duration of IVIG therapy for tisagenlecleucel patients with B-cell aplasia was assumed to be 36 months
- Discounting was included for subsequent SCT costs
- The choice of salvage chemotherapy selected for patients who discontinue prior to tisagenlecleucel infusion was assumed to be the same as the regimen used for the comparator arm
- The model included the ERG's approach for incorporating age-adjusted utilities
- The hospitalisation rate for tisagenlecleucel infusion was assumed to be 100%

Table 2: ICERs for tisagenlecleucel (with PAS) versus [R-]GDP – using updated JULIET data for tisagenlecleucel and the CORAL extension study for salvage chemotherapy

Scenario description	ICER	
	2-year 'cure' point	3-year 'cure' point
Reference: CORAL as per ERG's analysis • Original JULIET data for tisagenlecleucel (spline with one knot up to 24 months or 36 months) • CORAL as per the ERG's revised model ('No SCT' = Gompertz and 'SCT' = Gompertz)	£59,204	£72,115
1: CORAL as per ERG's analysis • Updated JULIET data for tisagenlecleucel (spline with one knot up to 24 months or 36 months) • CORAL as per the ERG's revised model ('No SCT' = Gompertz and 'SCT' = Gompertz)	£56,356	£65,822
2: CORAL (spline with two knots for 'no SCT') • Updated JULIET data (spline with one knot up to 24 months or 36 months) • Redigitised CORAL ('No SCT' = spline with two knots and 'SCT' = Gompertz)	£51,644	£59,386

Abbreviations: ERG: Evidence Review Group; ICER, incremental cost-effectiveness ratio; PAS: Patient Access Scheme; SCT: stem cell transplantation.

However, neither of these analyses address the general limitations of CORAL extension study as a source of comparator efficacy and given that these limitations are expected to result in patients having improved survival outcomes compared to the full population of interest, the most plausible ICER is expected to be lower than those presented. In order to address one of the major limitations of the CORAL extension study (third-line only), Novartis have explored the use of additional evidence from the HMRN in the cost-effectiveness analysis, as described in the section below.

3.3 Survival data from the Haematological Malignancy Research Network (HMRN) database can be used to address one of the major limitations of the CORAL extension study

Novartis acknowledges that each of the sources of comparator efficacy data that have been presented to the Committee thus far are associated with limitations: the CORAL extension study represents an overly optimistic estimate of survival (for the reasons described above), whereas the Eyre 2016 study and the comparator arm of the PIX301 subgroup analysis, in which no patients received subsequent SCT (i.e. treated with palliative intent only), are likely to represent the least fit patients who may be eligible for tisagenlecleucel.[9-11] In response to the Committee's suggestions in the ACD, Novartis have therefore explored the use of data from the HMRN database as an additional source of comparator efficacy data.[ii]

[ii] The ORCHARRD study which was also mentioned in the ACD was not explored. The published evidence from the overall population of the ORCHARRD study was identified as part of the systematic literature review of clinical trials but was excluded from the review as it only included patients treated in the second-line setting.

The HMRN database covers an ongoing, UK population-based cohort which was established in 2004 to provide robust, generalisable data to inform clinical practice and research on haematological malignancies.[12] Patients included in the HMRN database are from a region comprising a total population of 3.8 million which covers the area formerly served by the Yorkshire and the Humber and Yorkshire Coast Cancer Networks. According to the HMRN database, a total of 3,329 patients were newly diagnosed with DLBCL between 2004–2015.[13] Median follow-up was [redacted] years (range: [redacted]) and medical records were abstracted for [redacted]% of patients.[13]

The HMRN therefore provides a large source of real-world, long-term data for patients diagnosed with DLBCL in the UK. Following a request to the HMRN, an analysis of survival (OS and PFS) for 4th line therapy and beyond was undertaken.[13] The results from this analysis, which provides survival data for DLBCL patients treated in the UK in the fourth- and later-line settings, have been used to address one the major limitations of the CORAL extension study, namely, that patients were exclusively treated in the third-line setting and would therefore be expected to have better outcomes compared to the full patient population of interest (i.e. third- and later-line settings). Specifically, OS and PFS for salvage chemotherapy have been modelled using a combination of survival data from CORAL (for third-line) and the HMRN (for fourth- and later-lines), with the contribution of each source/line of therapy to the final survival curve(s) being weighted based on the proportion of patients in the JULIET trial receiving the corresponding number of lines of prior systemic therapy.

The estimates of OS and PFS derived from this approach, which incorporate both the Committee's preferred source of comparator efficacy (CORAL extension study) and relevant data from the HMRN database are considered to represent a more appropriate source of comparator efficacy data for the full patient population of interest (i.e. r/r DLBCL after two or more lines of systemic therapy, and not just third-line only), and so have been used by Novartis as part of a revised base case analysis). In the revised base-case analysis (see Table 3 in Section 4), tisagenlecleucel was associated with an ICER of £46,325 per QALY gained versus [R-]GDP with the PAS applied for tisagenlecleucel.

Further details of the HMRN analysis and the combined CORAL and HMRN analysis are presented in Section 2 of the appendices.

3.4 The evidence presented to the Committee supports the assumption that patients who are alive after 24 months would have mortality similar to the general population

The Committee has expressed a clear preference for the approach of modelling tisagenlecleucel OS that was explored as a scenario analysis in the original company evidence submission (termed the 'hybrid' model in the ACD). In Section 3.12 of the ACD, it was noted that:

"The committee preferred the hybrid model, noting that it was easier to validate clinically and allowed clinical experts to specify a time point at which patients were assumed to be cured."

In our submission the "hybrid" model scenario analysis uses a cure point of 24 months and assumed that patients who were alive after 24 months would have mortality similar to the general population. Whilst we acknowledge that there may be uncertainty regarding the timing of the cure point, the weight of available evidence indicates that the 24-month timepoint is appropriate:

- Published data from Maurer *et al.* (2014) show that DLBCL patients who were alive and relapse-free at 24 months would be expected to have mortality that is not significantly different to the general population. This finding was observed in two different cohorts (DLBCL patients in the USA and France).[14]
- The pooled data from the JULIET and Schuster 2017 (NCT02030834) studies were consistent with the findings from Maurer *et al.* (2014): The shape of the PFS and OS curves were similar at 24 months and plateaus were emerging in both survival curves by 24 months (see Section 1 of the Appendices for the latest data from the JULIET trial).[6, 7, 15]

- UK clinician feedback included as part of original evidence submission was that patients who are alive and free from disease at 24 months are considered to be effectively 'cured' and would no longer be routinely followed up.[16] This was supported by clinical expert opinion provided to the Committee:

  "*The clinical experts explained that patients with diffuse large B-cell lymphoma whose disease had not relapsed after 2 years were often considered to be cured and did not usually need further clinical follow-up*." [Section 3.12; ACD]

In summary the weight of evidence suggests that a 2-year cure point is appropriate. This is also supported by the predicted OS for salvage chemotherapy from the various analyses explored in the cost-effectiveness model (see Table 1), in which the proportion of patients alive after 24 months remained relatively stable. Therefore, the revised base case is based on a 2-year cure point. However, as requested by the Committee and in order to explore uncertainty, a scenario analysis is also presented using a 3-year time point.

Analyses have not been conducted using later timepoints as the assumption that patients would only be considered 'cured' after 4 or 5 years is considered to be less plausible (based on the available evidence and clinical opinion expressed at the Committee meeting on 22nd August). Furthermore, it would be inconsistent with the NICE clinical guideline (NG52) which states:

Section 1.10.1
"For people in complete remission after first-line treatment with curative intent for diffuse large B-cell lymphoma:

- *Offer regular clinical assessment consider stopping regular clinical assessment aimed at detecting relapse 3 years after completing treatment for people in ongoing complete remission"*

Section 1.11.3
"*At 3 years after a person with non-Hodgkin's lymphoma completes a course of treatment, consider switching surveillance of late effects of treatment to nurse-led or GP-led services*"

And also the British Committee for Standards in Haematology (BCSH) 2016 Guideline about follow-up and survivorship for patients with DLBCL which states:[17]

"Patients who achieve a CR following treatment should be followed up on a 3–4 monthly basis for up to 2 years…. The risk of relapse beyond 2 years is <10% (Larouche et al, 2010; Vose et al, 2010). It is therefore reasonable to discharge patients back to their primary care physician at that stage with advice and support."

Tisagenlecleucel is a potentially curative therapy which has demonstrated durable responses and sustained PFS and OS, it would be reasonable to assume that patients who are still alive following treatment with tisagenlecleucel would also be assumed to be 'cured' after 2–3 years. The latest data from the JULIET trial which supports the sustained efficacy of tisagenlecleucel are presented in Section 1 of the Appendices.

3.5 The duration of IVIG therapy for B-cell aplasia has been overestimated

As stated in Novartis' response to the technical engagement document, the proportion of patients who may be expected to have B-cell aplasia that persists beyond 1-year post-infusion with tisagenlecleucel will be small. Similarly, feedback from clinicians in the UK was that the duration of IVIG treatment in DLBCL patients who would be eligible for treatment with tisagenlecleucel would typically be six months.

The assumption used in the ERG's base case for the duration of IVIG therapy (36 months) is therefore likely to represent an overestimate of how long, on average, patients would receive IVIG

therapy for B-cell aplasia in clinical practice. Based on UK clinical expert feedback, the estimate of 11.4 months used in the original company evidence submission was already considered conservative. Even though this is not a key driver of the cost-effectiveness results, Novartis would like to point out that the ICERs would decrease if the assumption of 11.4 months (as per clinicians' feedback) was used. However, the revised base case analysis presented in this document uses the Committee preferred assumption of 3 years.

4 Revised cost-effectiveness analysis

As part of the response to the ACD, Novartis have presented a revised base case for the cost-effectiveness analysis which incorporates the following changes to the assumptions preferred by the Committee and included in the ERG's revised model[iii]:

- Model inputs based on the JULIET trial were updated with data from the latest data cut-off date (21st May 2018) [iv]
    - As per the ERG/Committee's preferred approach, the 'hybrid' model was selected for tisagenlecleucel OS, with the spline model with one knot extrapolation used up to 24 months followed by general population mortality (standardised mortality rate = 1)
    - The spline model with three knots was selected for extrapolation of tisagenlecleucel PFS
- The CORAL extension (third line) and HMRN (fourth- and later-lines) combined analysis was used as the source of OS and PFS data for salvage chemotherapy
    - The Gompertz distribution was used for extrapolation of the 'SCT' arm (as per the ERG's preferred base case) and the spline model with two knots was used for the extrapolation of the 'no SCT' arm (Gompertz used in the ERG's preferred base case)
    - The contribution of the CORAL extension and HMRN curves to the final estimates of OS and PFS for salvage chemotherapy were weighted by the proportion of patients in the JULIET trial who received the corresponding number of prior lines of therapy

As noted in Sections 2.1 and 3.3 of this response, these changes have been proposed in order to a) ensure that the latest, relevant evidence are available to the Committee, and b), to provide a more plausible interpretation of the evidence available from the CORAL extension study, with additional evidence from the HMRN database used to address one of the major limitations in the CORAL study (as described by one of the study authors).

A summary of results from Novartis' revised base case are presented in Table 3. Based on the results of the revised base case, tisagenlecleucel may be considered a cost-effective use of NHS resources, being associated with an ICER of £46,325 per QALY gained versus [R-]GDP with the PAS applied for tisagenlecleucel. A full description of the revised base case is presented in Section 3 of the Appendices, as are full cost-effectiveness results from the base case and exploratory scenario analyses.

The results from the analysis in which patients are assumed to be 'cured' after 24 months are considered by Novartis to be the most appropriate (as described in Section 3.4) – results are also presented using a 3-year timepoint to explore the uncertainty in the timepoint used and to reflect the latest recommended duration of follow-up for DLBCL patients in clinical guidelines.[17, 18] Given the exploration of later timepoints, an alternative survival model for tisagenlecleucel which provides a better fit to the plateau in the observed data beyond 24 months has been explored (Gompertz), full details of which are presented in Section 1 of the Appendices. Even using the 3-year timepoint, these ICERs are still within the region of £50,000 per QALY gained, thus supporting the plausibility of tisagenlecleucel as a cost-effective treatment option.

[iii] The list of ERG/Committee-preferred assumptions that have remain unchanged in Novartis' revised model are presented in Section 3.2

[iv] The survival models used in Novartis' revised base case for the extrapolation tisagenlecleucel OS and PFS using the latest data from the JULIET trial are consistent with those in original company evidence submission (see Section 1 of the Appendices)

Novartis would also wish to emphasise that alternative assumptions for the cost-effectiveness analysis, such as assuming a lower proportion of patients receive SCT (e.g. 10% which was described in the ACD as the lower bound expected for SCT; see Section 3.13 of the ACD) or a shorter duration of IVIG therapy, which have not been explored here but may also be considered to be plausible, would result in a reduction in the ICERs presented below for tisagenlecleucel versus salvage chemotherapy.

Table 3: ICERs for tisagenlecleucel (with PAS) versus [R-]GDP – using Novartis' revised base case

Scenario description		ICER			
	'Cure' point:	2-year		3-year	
	JULIET extrapolation:	Spline with one knot	Gompertz	Spline with one knot	Gompertz
3: CORAL (for third line) and HMRN (for fourth- and later-lines) combined = revised base case • Updated JULIET data for tisagenlecleucel (spline with one knot or Gompertz up to 24 or 36 months months) • Redigitised CORAL ('No SCT' = spline with two knots and 'SCT' = Gompertz) for third-line and HMRN for fourth- and later-lines		£46,325	£46,901	£53,021	£51,773

Abbreviations: ERG: Evidence Review Group; ICER, incremental cost-effectiveness ratio; PAS: Patient Access Scheme; SCT: stem cell transplantation.

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Tisagenlecleucel-T for treating relapsed or refractory diffuse large B-cell lymphoma [ID1166]

Consultation on the appraisal consultation document – deadline for comments 5pm on 10 October 2018 email: TACommC@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):	Bloodwise
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.
1	We welcome the committee's acknowledgement that *'tisagenlecleucel is clinically effective'* and recognise that there are uncertainties about the degree of effectiveness. However, we support the clinical advisors' view that Kymriah is a potential cure for small numbers of patients, particularly as salvage chemotherapy is the only option for people with relapsed disease.

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NICE National Institute for Health and Care Excellence

Tisagenlecleucel-T for treating relapsed or refractory diffuse large B-cell lymphoma [ID1166]

Consultation on the appraisal consultation document – deadline for comments 5pm on 10 October 2018 email: TACommC@nice.org.uk/NICE DOCS

2	We recognise the challenges in defining *'people who are ineligible for stem cell transplants'* and therefore Kymriah's proposed placement in the treatment pathway. Given the current lack of treatment options available to people with relapsed or refractory DLBCL, we hope everyone with relapsed disease could potentially benefit from Kymriah in future, as per the likely marketing authorisation.
3	Although JULIET data does demonstrate a high frequency of adverse events, we understand from patients with DLBCL that have undergone treatment for Yescarta that they were willing to tolerate potentially significant adverse events, given that their only alternative was salvage chemotherapy or death. We believe this same principle would apply to people undergoing treatment for Kymriah.
4	It is not possible for us to comment on whether Kymriah should meet the 'end of life' criteria, given that the comparative overall survival data provided by the company is confidential. However, the committee's acknowledgement that *'in the axicabtagene ciloleucel appraisal, the committee had not been presented with any reliable comparator data that was representative of the population, therefore, it made a judgement that it was plausible that the criterion for short life expectancy could apply'* appears inconsistent, given the decision in the case of Yescarta was made speculatively. Bloodwise takes no view on whether one treatment is preferable to another, however, we feel it is important that both are assessed consistently on the basis of available evidence.
5	We do not agree that the provisional recommendations are a sound and suitable basis for the NHS. Bloodwise recognises the committee's concern that of a lack of comparative data to establish the extent of effectiveness, and with it, cost-effectiveness. However, we also note that the treatment is extremely promising and is considered to be 'clinically very promising' by clinical experts. We therefore recommend that Kymriah for DLBCL be introduced to the Cancer Drugs Fund, in order to develop direct comparative evidence of the effectiveness of the treatment versus salvage chemotherapy.

Insert extra rows as needed

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 18 September 2018 **email:** tacommc@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):	Lymphoma Action
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.

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Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 18 September 2018 **email:** tacommc@nice.org.uk / 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 that this recommendation denies patients' access to the only type of treatment that may offer a potential cure. There is urgent unmet need for patients who have failed several courses of treatment and whose options are now mainly palliative or a clinical trial. This technology appears to be the only option that offers a potential cure to patients who have failed other therapies.
2	This recommendation does not seem to take sufficient account of the rarity of the indication. Clinical trials in this indication are small because the patient population fit enough for this type of treatment is small.
3	We are concerned that this recommendation is not taking into account the specific needs of patients who are refractory to chemotherapy. These patients are unable to have an autologous stem cell transplant. This treatment offers a lifeline to those patients, who otherwise have exhausted comparator therapies, and whose only other option may be a clinical trial or palliative care.
4	This recommendation seems to be assessing a potentially durable and even curative response with the new technology against a short-lived response with comparators. There is no true comparator as the comparators do not meet the needs of the patients. The lack of a suitable comparator should not therefore restrict access to this treatment.
5	With regards to long-term data, this can only come if the treatment is used. The durability of the treatment looks better than any alternatives. This treatment and similar treatments are being used in other parts of the world and for other indications. Could treatment centres in the US give further advice?
6	The patients who might benefit from this technology need treatment urgently. We heard from patients who are being told about this type of treatment and how it would be their best option after failing other treatments, only to learn that they cannot access it via a clinical trial as there is great demand for places and NICE propose not to recommend it. This puts tremendous strain on patients and carers.
7	Limiting treatment to specialist centres and to patients most likely to benefit from it (e.g. low ECOG score, refractory to chemotherapy) would enable more information about the treatment to be gathered whilst offering a lifeline to those patients who are most likely to benefit.
8	The main barrier to this recommendation appears to be cost. We hope an agreement can be reached with the pharmaceutical company to allow this treatment to be accessed on the NHS even if only on a limited basis while more robust data are collected.

Insert extra rows as needed

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Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [ID1166]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 10 October 2018 **email:** tacommc@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):	NHS England
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.

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Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [ID1166]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 10 October 2018 **email:** tacommc@nice.org.uk / NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Tisagenlecleucel is an innovative new treatment which represents a step-change in the treatment of relapsed or refractory diffuse large B-cell lymphoma; a patient population with unmet need for whom this new treatment option that may improve the chance of survival. NHS England would welcome a positive recommendation from NICE, which would give patients access to this ground-breaking new technology and the associated benefits. However, NHS England is supportive of NICE's decision based on the uncertainty around how much benefit tisagenlecleucel offers compared with the current treatment and cost-effectiveness estimates being above the range normally considered to be a cost-effective use of NHS resources
2	A number of issues are highlighted in the Appraisal Consultation Document (ACD) for Novartis to address and NHS England hopes that these will be addressed to enable NICE to consider these points further.
3	NHS England and Novartis are continuing to work together to ensure a number of sites across England are ready to deliver a safe and high quality service for patients by the end of autumn 2018. Working jointly with Novartis and the Joint Accreditation Committee ISCT-Europe & EBMT (JACIE), NHS England aims to introduce new services in a phased manner, ramping up provision to deliver a safe and effective service covering the anticipated patient population by the end of March 2020.
4	Whilst tisagenlecleucel has the potential to offer patients great clinical benefits, the uncertainty around the size of the benefits and the immaturity of the survival data make tisgenlecleucel an ideal candidate for the Cancer Drugs Funds (CDF). Allowing more time for clinical trial data to mature during a CDF managed access period and using real world data as an additional source of data could help to address the uncertainties highlighted by NICE.

Insert extra rows as needed

NICE National Institute for Health and Care Excellence

Tisagenlecleucel-T for treating relapsed or refractory diffuse large B-cell lymphoma [ID1166]

Consultation on the appraisal consultation document – deadline for comments 5pm on 10 October 2018 email: TACommC@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):	Royal College of Pathologists and British Society of Haematology.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to disclose.
Name of commentator person completing form:	Dr Sridhar Chaganti

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.
Example 1	We are concerned that this recommendation may imply that ……..
1	The NICE recommendation not to fund Tisa-Cel is based on an ICER that works out to more than £54,000 per QALY. This is highly speculative and is based on a number of assumptions which may or may not be true. The expected survival in the comparator arm varies depending on the chosen

Tisagenlecleucel-T for treating relapsed or refractory diffuse large B-cell lymphoma [ID1166]

Consultation on the appraisal consultation document – deadline for comments 5pm on 10 October 2018 email: TACommC@nice.org.uk/NICE DOCS

	comparator. Similarly expected long-term survival in the Tisa-cel arm is speculative based on assumptions that a hybrid model incorporating predicted 2 yr and 5 yr survival rates.
2	We do not agree with the view of the NICE committee that Tisa-cel does not meet criteria to be considered life extending treatment at the end of life. A majority of patients meeting criteria for this treatment as per its marketing authorisation would have exhausted all valid treatment options and have a limited life expectancy of few to several months. So, for most patients in this situation, their illness would be considered “as end of life.” A 35 – 40% chance of long term survival (as offered by Tisa-cel) would be seen as a significant advance in this patient population.
3	
4	
5	
6	

Insert extra rows as needed

NHS England submission for the second meeting of the NICE appraisal of tisagenlecleucel for the treatment of patients with relapsed/refractory diffuse large B cell lymphoma (DLBCL)

1. NHS England observes that Novartis has included patients in its comparator population for tisagenlecleucel who have received 4th and 5th lines of chemotherapy, the reason being that such patients are within the marketing authorisation. This is wholly inappropriate as the comparison in a NICE appraisal must be with the treatment that the new technology will potentially replace. Treatment with tisagenlecleucel will replace 3rd line chemotherapy and must be compared with 3rd line salvage chemotherapy. Tisagenlecleucel will not replace 4th or 5th line chemotherapy in DLBCL as it will be used after patients have failed 2 lines of chemotherapy. The inclusion by Novartis of patients beyond 3rd line chemotherapy makes the comparator outcomes worse and thus of course improves the Novartis estimate of the cost effectiveness of tisagenlecleucel.
2. NHS England thus agrees with the ERG conclusion that the comparator population should include patients who have failed only 2 lines of chemotherapy. The inclusion of the HMRN data by Novartis is thus irrelevant. NHS England is very concerned that [redacted] of the comparator population submitted in the Novartis base case represents patients who are not the correct population with which to compare the clinical and cost effectiveness of tisagenlecleucel.
3. NHS England notes the updated tisagenlecleucel data cut submitted by Novartis and notes that this provides an additional [redacted] weeks to the median duration of follow up from [redacted] to [redacted] months.
4. NHS England still regards the PFS and OS data as being very immature. In the cost effectiveness analysis, there are virtually no patients at risk after 18 and 20 months for progression free survival and overall survival, respectively. NHS England notes that there have been survival events at 18 and 21 months. NHS England therefore is pleased to see the scenario analyses of both 2 year and 3 year cure points and notes the increased ICER for the 3 year cure point assumption.
5. NHS England observes that the marginally greater duration of follow-up in the Novartis submission makes a significant difference to the ICERs - in terms of the ERG's ICER using the ERG assumptions for the 1st meeting: the ICER reduces from £93.8K to 79.8K, this substantial reduction being driven by the extrapolation of survival which results in a considerably greater mean OS. NHS England notes that a tiny change in median duration of follow up can make a large difference to the ICER – a clear demonstration of the uncertainty associated with the benefits of tisagenlecleucel with such great immaturity of data.
6. NHS England supports the ERG position concerning the excess mortality associated with the 2 lines of previous chemotherapy (including high dose

chemotherapy in many instances) that patients will have had prior to CAR T treatment. NHS England agrees that the most reasonable position is to assume that the excess mortality risk only disappears after 5 years.

7. NHS England regards tisagenlecleucel as being a very promising treatment with a potentially great impact on outcomes. It is a very costly technology with great immaturity of data. NHS England therefore regards tisagenlecleucel as being an excellent candidate for inclusion in the CDF so that NICE can re-appraise tisagenlecleucel in DLBCL at a time when the survival outcomes are securely known.

Prof Peter Clark
NHS England Chemotherapy Clinical Reference Group chair and clinical lead for the Cancer Drugs Fund

October 2018

Appendices

Re: Novartis response to the Appraisal Consultation Document for ID1166 – tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies

1 Appendix: The latest data from the JULIET trial have been included in Novartis' revised cost-effectiveness analysis

At the time of the latest data cut-off date of the JULIET trial (21st May 2018 data cut-off), an additional [redacted] patients (all patients from Japan) had received an infusion with tisagenlecleucel (N=[redacted]; [redacted]).[1] All [redacted] infused patients had been followed for at least 3 months or discontinued earlier and therefore the Efficacy Analysis Set (EAS) was the same as the Full Analysis Set (FAS).[1] The results of the latest data cut-off date of the JULIET trial continue to support the clinical benefits of tisagenlecleucel in adult patients with r/r DLBCL and demonstrate that sustained treatment responses and durable survival can be achieved by patients who receive tisagenlecleucel.

Given the availability of more recent data from the JULIET trial, which could be used to inform the cost-effectiveness analyses, the draft recommendation in the Appraisal Consultation Document (ACD) does not take into account all of the available clinical evidence for tisagenlecleucel. A summary of progression-free survival (PFS) and overall survival (OS) from the latest data cut-off date of the JULIET trial (21st May 2018 data cut-off) and the results from revised cost-effectiveness analyses incorporating these data (see Section 0 of these Appendices for full results) have therefore been presented below to allow the Committee to make a decision based on the latest clinical data for tisagenlecleucel in this indication.

1.1 Survival data used in the cost-effectiveness analysis

Overall survival

At the 21st May 2018 cut-off date, [redacted] patients ([redacted]%) had died after tisagenlecleucel infusion and median OS was [redacted] months (95% CI: [redacted], [redacted]).[1] Median follow-up for OS was [redacted] months and maximum follow-up was [redacted] months.[1] The estimated probability of survival was [redacted]% (95% CI: [redacted], [redacted]), [redacted]% (95% CI: [redacted], [redacted]) and [redacted]% (95% CI: [redacted], [redacted]) at Months 6, 12 and 24, respectively.[1] The probability of survival [redacted]. The Kaplan-Meier plot of OS is presented in Figure 1.

Figure 1: Kaplan-Meier plot of overall survival (Full Analysis Set) from JULIET at the 21st May 2018 data cut-off

Full Analysis Set comprises all patients who received tisagenlecleucel infusion. Time was relative to first tisagenlecleucel infusion date, 1 month = 30.4375 days.
Abbreviations: CI: confidence intervals; NE: not estimable.
Source: JULIET Data on File (21st May 2018)[1]

Progression-free survival

According to the study protocol for the analysis of PFS, patients who proceeded to stem cell transplantation (SCT) after tisagenlecleucel infusion were censored at the time of SCT. At the time of the latest data cut-off (21st May 2018), a total of [redacted] patients had received subsequent SCT (all [redacted] patients received an allogeneic SCT and [redacted] patient received an autologous SCT and an allogeneic SCT).[1] [redacted].

Median PFS was [redacted] months (95% CI: [redacted], [redacted]) at the time of the latest data cut-off (21st May 2018), with a median follow-up of [redacted] months (maximum follow-up: [redacted] months).[1] The estimated progression-free probability was [redacted]% (95% CI: [redacted], [redacted]), [redacted]% (95% CI: [redacted], [redacted]), [redacted]% (95% CI: [redacted], [redacted]), and [redacted]% (95% CI: [redacted], [redacted]) at Months 3, 6, 9 and 12, respectively.[1] The estimated progression-free probability [redacted]. The Kaplan-Meier plot of PFS is presented in Figure 2.

Figure 2: Kaplan-Meier plot of progression-free survival from JULIET with censoring for SCT by IRC assessment (Full Analysis Set) at the 21st May 2018 data cut-off

Full Analysis Set comprises all patients who received tisagenlecleucel infusion. Time is relative to first tisagenlecleucel infusion date, 1 month = 30.4375 days.
Abbreviations: IRC: independent review committee; PFS: progression-free survival; SCT: stem cell transplantation.
Source: JULIET Data on File (21st May 2018)[1]

Pooled data from JULIET (21st May 2018) and Schuster 2017 (NCT02030834)

As in the original company evidence submission, the individual patient-level data (IPD) for OS and PFS from the JULIET trial were pooled (without adjustment) with pseudo-IPD generated from the Kaplan-Meier curves published from the Schuster 2017 (NCT02030834) study. Reconstructed survival curves using the pooled data are presented in Figure 3 and Figure 4.

The pooled survival data were then used as part of the revised cost-effectiveness analyses, as described in the section below.

Figure 3: Progression-free survival from the pooled analysis of JULIET and Schuster 2017 (NCT02030834)

Figure 4: Overall survival from the pooled analysis of JULIET and Schuster 2017 (NCT02030834)

1.2 Tisagenlecleucel survival inputs

The pooled survival data (JULIET and Schuster 2017 [NCT02030834]), using the latest data from the JULIET trial, have been incorporated in to Novartis' revised cost-effectiveness model. The extrapolation of these survival data using standard parametric distributions and flexible models was explored as per the approach described in the original company evidence submission.

Overall survival

Table 1 summarises the AIC and BIC values for each survival model, and the extrapolations of OS using each model up to 10 years are presented in Figure 5.

Table 1: Summary of goodness-of-fit data for tisagenlecleucel overall survival

Distribution	AIC	BIC
Exponential	552.72	555.58
Weibull	551.33	557.05
Gompertz	538.94	544.66
Log-Normal	537.58	543.30
Log-Logistic	542.48	548.20
Generalised gamma	531.73	540.31
Spline with single knot	529.02	537.60
Spline with two knots	531.08	542.52
Spline with three knots	533.02	547.32
Spline with four knots	535.02	552.17

A smaller AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 5: Extrapolation of overall survival using parametric and spline models – tisagenlecleucel

As per the original company evidence submission, the spline model with a single knot provides the best statistical fit. On visual inspection of the curves, none of the models, with the possible exception of the Gompertz model, adequately captured the expected plateau in OS with tisagenlecleucel.

As per the Committee's preference, a 'hybrid' model was used whereby the observed data were extrapolated up to a certain timepoint after which general population mortality was applied to those tisagenlecleucel patients who were still alive in the model (standardised mortality rate of 1). For the revised base case, the observed data were extrapolated up to 24 months for the reasons provided as

part of Novartis' response to the ACD. Cost-effectiveness results are also provided using a timepoint of 36 months to reflect the latest point at which UK treatment guidelines suggest DLBCL patients should be regularly followed-up for (see Novartis' response to the ACD).[2, 3]

In order to include longer-term extrapolations of the pooled tisagenlecleucel data, the Gompertz was also explored for the extrapolation of tisagenlecleucel OS in the revised cost-effectiveness analyses, as this provided a better visual fit to the tail of the observed data, particularly when using the later timepoints for the assumed 'cure', and also generated a survival curve which lies closer to the earlier part of the emerging plateau in the observed data (see Figure 6 for 24-month timepoint and Figure 7 for 36-month timepoint). Cost-effectiveness results have therefore been presented using the spline with one knot and the Gompertz distribution for extrapolating tisagenlecleucel OS, with an assumed 'cure' at 24 months (base case) and 36 months (scenario) (see Section 0 of these Appendices for full results).

Figure 6: Extrapolation of overall survival using the 'hybrid' model of Gompertz or spline with one knot up to 24 months followed by general population mortality (SMR=1) – tisagenlecleucel

To ensure that OS extrapolations did not provide implausible estimates of mortality, the mortality rates used in the model were bound by the age- and gender-specific natural mortality of the general population as a minimum – not shown in the above curve.
Abbreviations: SMR: standardised mortality rate.

Figure 7: Extrapolation of overall survival using the 'hybrid' model of Gompertz or spline with one knot up to 36 months followed by general population mortality (SMR=1) – tisagenlecleucel

To ensure that OS extrapolations did not provide implausible estimates of mortality, the mortality rates used in the model were bound by the age- and gender-specific natural mortality of the general population as a minimum – not shown in the above curve.
Abbreviations: SMR: standardised mortality rate.

Progression-free survival

Table 2 summarises the AIC and BIC values for each survival model, and the extrapolations of PFS using each model up to 5 years are presented in Figure 8.

Table 2: Summary of goodness-of-fit data for tisagenlecleucel progression-free survival

Distribution	AIC	BIC
Exponential	533.42	536.28
Weibull	496.23	501.95
Gompertz	433.13	438.85
Log-Normal	467.51	473.23
Log-Logistic	472.92	478.64
Generalised gamma	422.80	431.38
Spline with single knot	405.28	413.85
Spline with two knots	404.70	416.14
Spline with three knots	396.55	410.85
Spline with four knots	399.17	416.33

A smaller AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 8: Extrapolation of progression-free survival using parametric and spline models – tisagenlecleucel

As per the original company evidence submission, the spline model with three knots provides the best statistical fit and also provides a reasonable fit to the observed data on visual inspection of the extrapolated survival curves. and the extrapolation using the spline model with three knots is consistent of the assumption used for modelling OS – i.e. if patients alive at 24 months are expected to have mortality similar to the general population, it would be reasonable to expect that these patients would not have progressed.

The spline model with three knots was therefore used in the revised base case (see Section 0 of these Appendices).

1.3 Additional inputs from the JULIET trial used in the cost-effectiveness analysis

Model inputs based on the JULIET trial were also updated with the latest data cut-off date. These changes are listed in Table 3 and have been made in the revised cost-effectiveness model using green, bold text (as used for all new or altered inputs in Novartis' revised model).

Of note, two discrepancies in the choice of inputs between the original company evidence submission and the Evidence Review Group (ERG)'s revised model have been resolved by updates from the latest data cut-off date:

1. As the number of patients in the EAS is equal to the number of patients in the FAS (N=),[1] the proportion of patients who received subsequent stem cell transplantation in the JULIET trial is the same, regardless of whether the EAS or FAS is used as the denominator
2. As the number of patients with Grade 3 or 4 cytokine release syndrome (CRS) is equal to the number of patients reporting duration of intensive care unit (ICU) stay (n=), the proportion of patients assumed to have CRS in the model is the same, regardless of whether the original approach (Grade 3 or 4 CRS) or the ERG's approach (ICU due to CRS) is used for the numerator

Table 3: Changes to the cost-effectiveness model based on the latest data from the JULIET trial (21st May 2018)

Sheet location	Model parameter	Description of change
Parameter Estimates (OS)	JULIET, pooled JULIET and UPENN, and JULIET (matched to Eyre 2016) OS efficacy parameters for standard survival analysis parametric functions and splines	Updated to incorporate May 2018 data cut
Parameter Estimates (PFS)	JULIET and pooled JULIET and UPENN PFS efficacy parameters for standard survival analysis parametric functions and splines	Updated to incorporate May 2018 data cut
Parameter Estimates (cure)	JULIET and pooled JULIET and UPENN OS and PFS efficacy parameters for mixture cure model	Updated to incorporate May 2018 data cut
Adverse Events	pp_CRS_3_4 (proportion of patients with grade 3 or 4 CRS)	Updated based on May 2018 data cut
Probabilities (Tx1)	Observed data and OS/PFS spline parameters for JULIET, JULIET and UPENN pooled, and JULIET (matched to Eyre 2016)	Updated to incorporate May 2018 data cut
Drug cost input (UK)	Weights for lymphodepleting regimen	Updated based on May 2018 data cut
AE Cost inputs (UK)	CRS cost input (percentage of patients with tocilizumab, total number of tocilizumab dose, mean ICU duration and % with ICU) and IVIG cost input (% of patients with IVIG treatment)	Updated based on May 2018 data cut
Medical cost input (UK)	Number and length of stay for tisagenlecleucel for: total hospitalisations, all-cause ICU and CRS-related ICU	Updated based on May 2018 data cut
Population inputs	Tisagenlecleucel decision tree inputs and population demographics	Updated based on May 2018 data cut
Subsequent SCT inputs	Subsequent auto and allo SCT rate for tisagenlecleucel, proportion of patients with prior autologous SCT	Updated based on May 2018 data cut
AE rates – CSR	Adverse event rates for tisagenlecleucel	Updated based on May 2018 data cut
Tisagen_OS_Pooled_Cure, Tisagen_PFS_Pooled_Cure, Tisagen_OS_MAIC, Tisagen_OS_JULIET, Tisagen_PFS_JULIET, Tisagen_OS_Pooled, Tisagen_PFS_Pooled	Bootstrapping inputs for all survival analysis parametric functions	Updated based on May 2018 data cut

2 Appendix: The CORAL extension study is not the most appropriate comparator data for salvage chemotherapy

Novartis recognise that each of the sources of comparator efficacy data that have been presented to the Committee thus far (CORAL, PIX301 and Eyre 2016) are associated with limitations. In particular, the CORAL extension study, which the Committee described as being the most appropriate source of comparator data in the ACD, is believed to represent an overly optimistic estimate of survival (as described in Novartis' response to the ACD), due in part by the inclusion of patients receiving treatment in the third-line setting only. Furthermore, Novartis believe that the extrapolation of CORAL OS data used in the ERG's cost-effectiveness analysis for patients who do not receive SCT (i.e. using the Gompertz distribution) is not consistent with the expectations of long-term survival that may be achieved by these patients in UK clinical practice, given that treatment for these patients would be given with palliative intent.

As such, Novartis do not believe that the use of the CORAL extension study, as per the ERG's cost-effectiveness analysis (which was accepted by the Committee in the ACD), is the most reasonable interpretation of the current evidence as only around 50% of the tisagenlecleucel eligible population are represented and these represent patients who are expected to be fitter than those in the full patient population of interest (as confirmed by one of the study authors).[4] In an attempt to address one of the major limitations of the CORAL study (i.e. that it exclusively includes third-line patients only), Novartis have incorporated additional evidence from the Haematological Malignancy Research Network (HMRN) into the revised cost-effectiveness model.

Specifically, Novartis have explored the following as part of the revised model:

- Using spline models to extrapolate OS data from the CORAL extension study (see Section 2.1)
- Using survival data from the HMRN for patients treated in the fourth- and later-line settings in combination with CORAL survival data (third-line only) to model OS for salvage chemotherapy, with weightings between the different sources/lines of therapy based on the proportion of patients in the JULIET trial receiving the corresponding number of lines of prior systemic therapy (see Section 0)

Full descriptions of each of these additional analyses are presented below.

2.1 CORAL extension study

In addition to the standard parametric distributions used by the ERG, spline models were also explored for the extrapolation of OS data from the CORAL extension study. The survival data reported from the CORAL extension studies in Van den Neste *et al.* (2016) were presented as Kaplan-Meier plots for those who did or did not receive subsequent SCT.[5] In the absence of IPD, pseudo-IPD were generated from each Kaplan-Meier plot using the algorithm described by Guyot *et al.* (2012).[6]

Overall survival

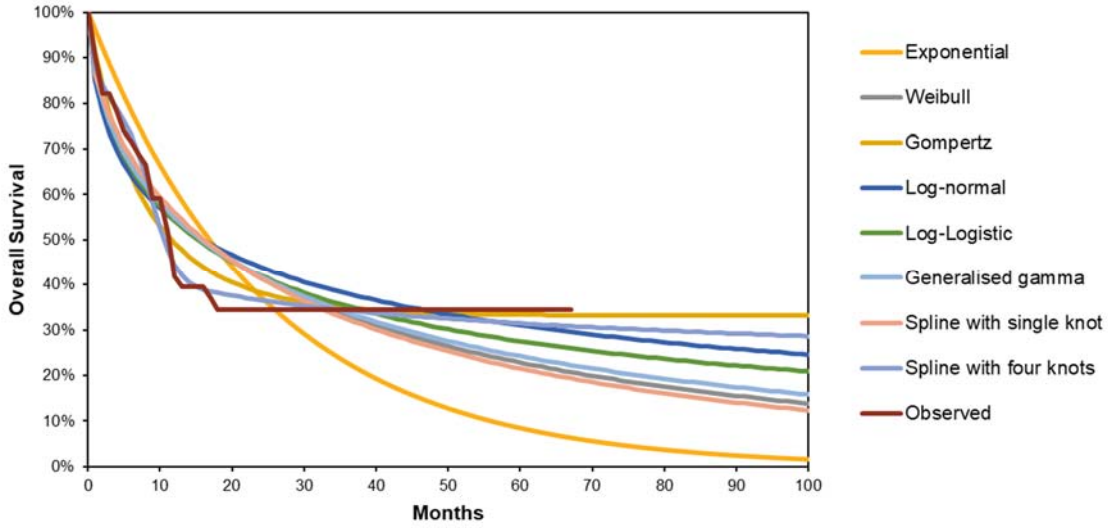
Table 4 summarises the AIC and BIC values for each survival model at each line of therapy, and the extrapolations of OS using each model up to 10 years are presented in Figure 9 (SCT) and Figure 10 (no SCT).

Table 4: Summary of goodness-of-fit data for salvage chemotherapy overall survival

Distribution	SCT		No SCT	
	AIC	BIC	AIC	BIC
Exponential	261.86	264.02	701.35	704.21
Weibull	245.37	249.69	658.84	664.56
Gompertz	246.98	251.30	655.37	661.09
Log-Normal	244.98	249.30	649.05	654.77
Log-Logistic	245.56	249.88	641.49	647.21
Generalised gamma	247.23	253.71	654.40	662.98
Spline with single knot	247.19	253.67	655.98	664.56
Spline with two knots	N/A	N/A	640.26	651.70
Spline with three knots	N/A	N/A	639.46	653.76
Spline with four knots	238.99	251.95	636.27	653.43

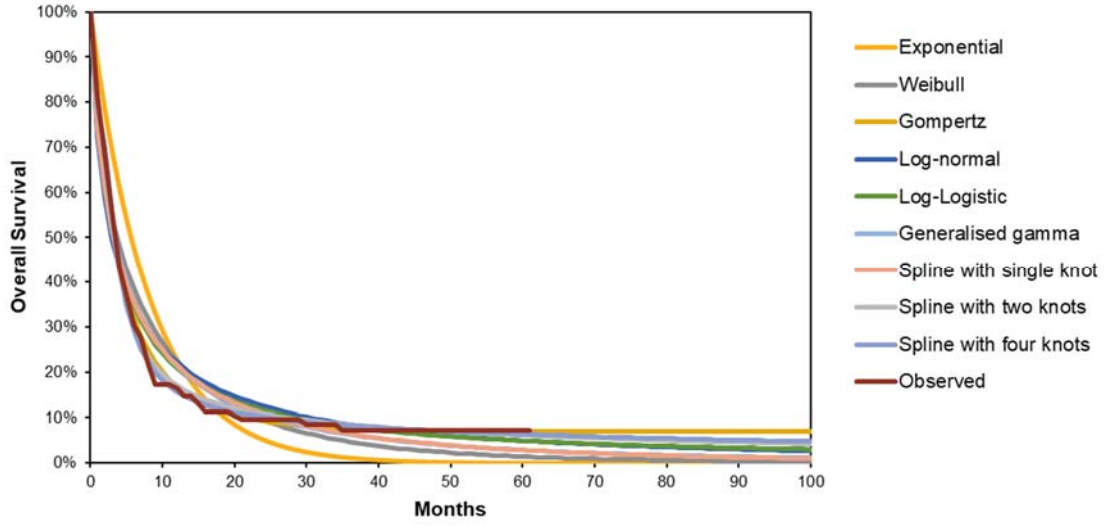
A smaller AIC or BIC value represents a better goodness of fit. Spline models with two and three knots did not converge for SCT.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; N/A: not applicable; SCT: stem cell transplantation.

Figure 9: Extrapolation of overall survival using parametric and spline models – salvage chemotherapy (SCT)



Abbreviations: SCT: stem cell transplantation.

Figure 10: Extrapolation of overall survival using parametric and spline models – salvage chemotherapy (no SCT)



Abbreviations: SCT: stem cell transplantation.

Despite providing a good statistical fit in terms of AIC, spline models for 'SCT' survival tended to produce unrealistic curves based on visual inspection, and BIC values were no better than those for standard parametric approaches. Therefore, the Gompertz model was considered to be the most appropriate for the revised base case, as per the ERG's own analyses.

For the 'no SCT' arm, the Gompertz distribution, which was used in the ERG's cost-effectiveness analysis, is considered to provide an overly optimistic estimate of long-term survival in the 'no SCT' arm. The survival profile for these patients would not be expected to include a plateau that extends well beyond 60 months given that treatment would be given with palliative intent only. Instead, the possibility of a potential 'cure'/long-term survival for the salvage chemotherapy cohort in the model is accounted for in the 'SCT' arm. Novartis therefore consider it more appropriate to use the Gompertz distribution for the 'SCT' arm (treated with curative intent) and an alternative curve, which is not associated with such a plateau in survival, for the 'no SCT' arm (treated with palliative intent). Of the alternative curves explored by Novartis, the spline model with two knots provided a better statistical fit compared to the standard parametric approaches and on visual inspection, produced a curve with long-term survival that was considered to be more clinically plausible compared to the Gompertz, given the lower expectation of a 'cure' for these patients. As such, the spline with two knots for extrapolating OS in the 'no SCT' arm was considered to be the most appropriate for Novartis' revised base case.

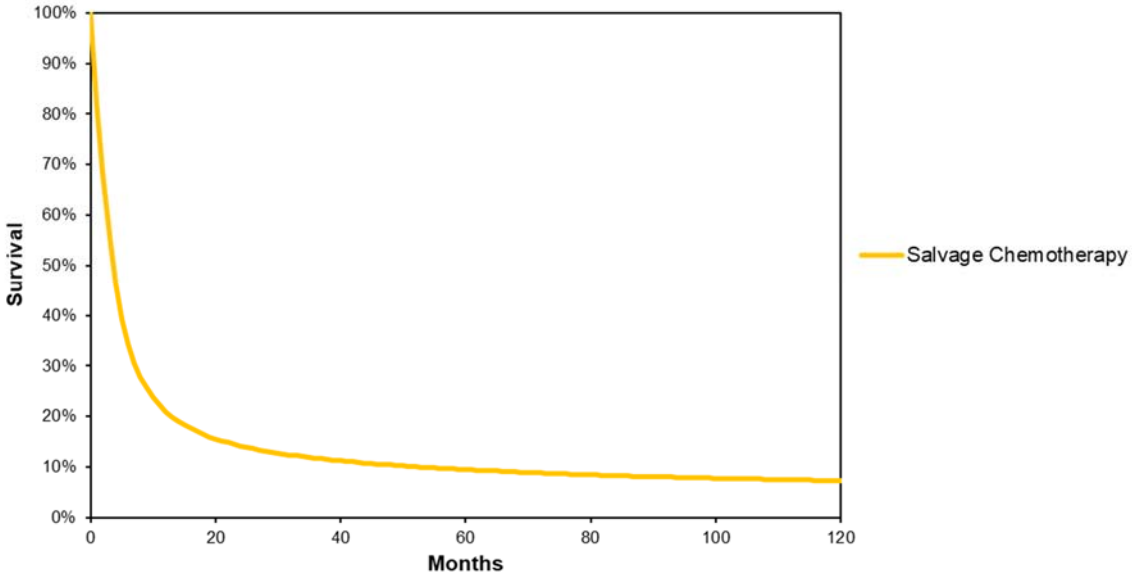
As per the Committee's preferred assumption, 12.5% of patients treated with salvage chemotherapy were assumed to receive subsequent SCT, with this percentage used as the weighting between the 'SCT' and 'no SCT' arms to derive the final weighted OS curve for salvage chemotherapy (see Figure 11). The approach to determining PFS for salvage chemotherapy was unchanged from the ERG's model i.e. this was based on the application of a hazard ratio between OS and PFS.

Cost-effectiveness results using the CORAL extension study (alone) for salvage chemotherapy efficacy, as well as the latest data from the JULIET trial for tisagenlecleucel, have been presented in Section 0 for the following analyses:

- Using Gompertz distribution for both the 'SCT' and 'no SCT' arms, as per the ERG's model (accepted by the Committee in the ACD)
- Using the Gompertz distribution for the 'SCT' arm (as per ERG's preferred base case) and the spline model with two knots for the 'no SCT' arm (considered to be more clinically plausible)

However, neither of these analyses address the general limitations of CORAL study as a source of comparator efficacy and so additional evidence which incorporates data from the HMRN has been presented in the sections below to inform Novartis' revised base case.

Figure 11: Extrapolation of overall survival based on the CORAL extension study – salvage chemotherapy (weighted – 'SCT' using Gompertz and 'no SCT' using spline with two knots; 12.5% subsequent SCT)



Abbreviations: SCT: stem cell transplantation.

Table 5: Changes to the cost-effectiveness model based on the addition of all standard parametric functions and splines for the CORAL efficacy source for salvage chemotherapy

Sheet location	Model parameter	Description of change
Consolidated Probabilities	CORAL OS and PFS traces and option of curve selection for OS SCT and no SCT	Sheet updated for additional flexibility for salvage chemotherapy efficacy source
CORAL OS no SCT	OS efficacy parameters for standard survival analysis parametric functions and splines for CORAL no SCT subpopulation	New sheet added for additional flexibility for salvage chemotherapy efficacy source
CORAL OS SCT	OS efficacy parameters for standard survival analysis parametric functions and splines for CORAL SCT subpopulation	New sheet added for additional flexibility for salvage chemotherapy efficacy source

The options in the model for using either the ERG's original survival inputs or Novartis' revised survival inputs from CORAL (redigitised) are labelled as 'CORAL SCT weighted (ERG)' and 'CORAL SCT weighted (company)', respectively, in the Specification sheet

2.2 Haematological Malignancy Research Network (HMRN)

As described in Novartis' response to the ACD, survival data collected from the HMRN database for patients treated in the fourth- and later-line settings were explored in Novartis' revised cost-effectiveness analysis in order to address one of the major limitations of the CORAL extension study (i.e. included patients treated in the third-line setting only).

The data from the HMRN are considered to highly relevant to the decision problem in that it provides 'real-world' evidence of survival outcomes for r/r DLBCL patients treated in the UK and the HMRN was suggested by the Committee in the ACD as a potential souce of comparator efficacy data (see Section 3.8 of the ACD). Based on the HMRN database, a total of 3,329 patients were newly

diagnosed with DLBCL between 2004–2015.[7] Median follow-up for DLBCL patients in the HMRN (all lines) was [redacted] years (range: [redacted]) and medical records were abstracted for [redacted]% of patients.[7] The baseline characteristics of patients included in the HMRN analysis (all lines) and survival outcomes reported from HMRN (fourth- and later-lines) are presented below.

Baseline characteristics

As prognostic data are only routinely collected for the first diagnosis, baseline prognostic data were only available from the HMRN for *de novo* cases of DLBCL (n=[redacted] all lines; see Table 6).[7] Patient characteristics at each subsequent line of therapy were not available from the HMRN analysis and so limited comparisons between the HMRN patient population and the JULIET and Schuster 2017 (NCT02030834) populations can be made.

Stage of disease and IPI score at the time of initial diagnosis are however reported from the JULIET trial (as well as time of study entry). Compared to newly-diagnosed, *de novo* DLBCL patients from the HMRN database, a higher proportion of patients in the JULIET trial had later stage of disease ([redacted]) and higher IPI scores ([redacted] i.e. low-intermediate risk or higher) at initial diagnosis.[1, 7] This may not be unexpected given that the HMRN also includes newly-diagnosed patients who may go on to respond to first-line therapy, but this comparison at least demonstrates that patients included in the JULIET trial had a prognosis at diagnosis which was no more favourable than those diagnosed in UK clinical practice.

Table 6: Baseline characteristics at the time of diagnosis for *de novo* cases of DLBCL in the HMRN (2004–2015)

Characteristic	HMRN (n=[redacted])
ECOG, n (%)	
0	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
Not known	[redacted]
B-Symptom – Yes, n (%)	[redacted]
Disease stage, n (%)	
Stage I	[redacted]
Stage II	[redacted]
Stage III	[redacted]
Stage IV	[redacted]
Not fully staged	[redacted]
Marrow involvement – Yes, n (%) (of those with a bone marrow assessment)	[redacted]
CNS involvement – Yes, n (%) (of those tested)	[redacted]
IPI, n (%)	
Low	[redacted]
Low-intermediate	[redacted]

Characteristic	HMRN (n=[redacted])
High-intermediate	[redacted]
High	[redacted]
Not known	[redacted]
IPI components	
Age >60 – Yes, n (%)	[redacted]
Stage III or IV, n (%)	
No	[redacted]
Yes	[redacted]
Not fully staged	[redacted]
Extra nodal sites ≥2	
No	[redacted]
Yes	[redacted]
Not fully staged	[redacted]
Elevated LDH	
No	[redacted]
Yes	[redacted]
Not done	[redacted]
ECOG ≥2	
No	[redacted]
Yes	[redacted]
Not known	[redacted]
β2-microglobulin (mg/L), mean (SD)	[redacted]
Haemoglobin (g/dL), mean (SD)	[redacted]
White blood cell count (10^9/L), mean (SD)	[redacted]

Abbreviations: CNS: central nervous system; DLBCL: diffuse large B-cell lymphoma; ECOG: Easter Cooperative Oncology Group; HMRN: Haematological Malignancy Research Network; IPI: International Prognostic Index; LDH: lactate dehydrogenase; SD: standard deviation.
Source: HMRN: Clinical Management, Outcome and Resource Utilisation of Diffuse Large B-cell Lymphoma (01.05.2018)[7]

Survival data

A summary of the OS and PFS for patients treated in the fourth- and later-line settings are presented in Table 7 with Kaplan-Meier plots provided below.

Table 7: Summary of OS and PFS from the HMRN by line of therapy

Line of therapy	Median OS, years (95% CI)	% alive (95% CI)			Median PFS, years (95% CI)
		6 months	1 year	2 years	
Fourth line (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fifth line (N=[redacted])	[redacted]	Not reported	Not reported	Not reported	Not reported

Abbreviations: CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; HMRN: Haematological Malignancy Research Network; OS: overall survival; PFS: progression-free survival.
Source: HMRN: Clinical Management, Outcome and Resource Utilisation of Diffuse Large B-cell Lymphoma (01.05.2018)[7]

Figure 12: Overall survival from the HMRN

A. Fourth line

B. Fifth line

Abbreviations: DLBCL: diffuse large B-cell lymphoma; HMRN: Haematological Malignancy Research Network.
Source: HMRN: Clinical Management, Outcome and Resource Utilisation of Diffuse Large B-cell Lymphoma (01.05.2018)[7]

Figure 13: Progression-free survival from the HMRN

A. Fourth line

PFS was only reported up to fourth line in the HMRN analysis.
Abbreviations: DLBCL: diffuse large B-cell lymphoma; HMRN: Haematological Malignancy Research Network.
Source: HMRN: Clinical Management, Outcome and Resource Utilisation of Diffuse Large B-cell Lymphoma (01.05.2018)[7]

2.3 Survival inputs for Novartis' revised base case of the cost-effectiveness analysis: CORAL (for third line) and HMRN (for fourth- and later-lines) combined

As part of Novartis' revised base case analysis, the following approach was taken for the modelling of OS and PFS for salvage chemotherapy:

- Survival data from the CORAL extension study (based on a weighted curve between 'SCT' and 'no SCT' for OS and the application of a hazard ratio to OS for PFS) were used for the proportion of patients who were assumed to receive salvage chemotherapy in the third-line setting
- Survival data by line of therapy from the HMRN were used for the proportion of patients who were assumed to receive salvage chemotherapy in the fourth- and later-line settings

In order to produce a single survival curve for salvage chemotherapy (one for OS and one for PFS), the contribution of each source of comparator efficacy/line of therapy was determined by the proportion of patients in the JULIET trial who received the corresponding number of prior lines of therapy (see Table 8).[1]

These estimates of OS and PFS, which incorporate both the Committee's preferred source of comparator efficacy (CORAL extension study) and relevant data from the HMRN to address the one of the major limitations of the CORAL study, are considered to represent a more appropriate source of comparator efficacy data for the full patient population of interest (i.e. r/r DLBCL after two or more lines of systemic therapy, and not just third-line only), and so have been used by Novartis as part of a revised base case analysis (see Section 0).

Table 8: Weightings for salvage chemotherapy survival curves by line of therapy based on the number of prior lines of systemic therapy received in the JULIET trial

Overall survival			Progression-free survival		
Line of therapy	**% patients in the JULIET trial[a]**	**Source of survival data**	**Line of therapy**	**% patients in the JULIET trial[a]**	**Source of survival data**
Third line	[redacted]	CORAL extension study (weighted curve for 'SCT' and no 'SCT')	**Third line**	[redacted]	Hazard ratio applied to OS from CORAL extension study
Fourth line	[redacted]	HMRN fourth line	**Fourth and later line[b]**	[redacted]	HMRN fourth line
Fifth and later line	[redacted]	HMRN fifth line	**-**	-	-

[a] The proportion of patients from the JULIET trial was calculated by excluding the [redacted].
[b] PFS was only reported up to fourth line in the HMRN analysis.
Abbreviations: DLBCL: diffuse large B-cell lymphoma; HMRN: Haematological Malignancy Research Network.
Source: JULIET Data on File (21st May 2018)[1]

In the absence of IPD from the HMRN at the time of submission, pseudo-IPD were generated using the algorithm described by Guyot *et al.* (2012) and the Kaplan-Meier plots presented in the report (see Figure 12 and Figure 13 for the original Kaplan-Meier plots).[6] Survival curves for each line of therapy were then generated using standard parametric approaches and spline models to extrapolate the pseudo-IPD, as described below.

Overall survival

Table 9 summarises the AIC and BIC values for each survival model at each line of therapy (fourth and fifth), and the extrapolations of OS using each model up to 10 years are presented in Figure 14 (line 4) and Figure 15 (line 5).

Table 9: Summary of goodness-of-fit data for salvage chemotherapy overall survival from the HMRN

Distribution	Line 4		Line 5	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	3177.67	966.01	287.46	57.76
Weibull	2959.18	900.39	282.70	57.29
Gompertz	2861.08	889.05	273.32	57.85
Log-Normal	2864.43	865.05	273.77	58.70
Log-Logistic	2847.77	851.10	273.17	57.65
Generalised gamma	2834.41	885.12	274.47	59.29
Spline with single knot	2808.08	877.63	276.95	59.29
Spline with two knots	2809.83	846.66	278.66	61.00
Spline with three knots	2809.55	848.25	276.66	59.55
Spline with four knots	2811.16	850.11	277.56	60.17

A smaller AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; HMRN: Haematological Malignancy Research Network.

Figure 14: Extrapolation of overall survival using parametric and spline models – HMRN (Line 4)

Abbreviations: HMRN: Haematological Malignancy Research Network.

Figure 15: Extrapolation of overall survival using parametric and spline models – HMRN (Line 5)

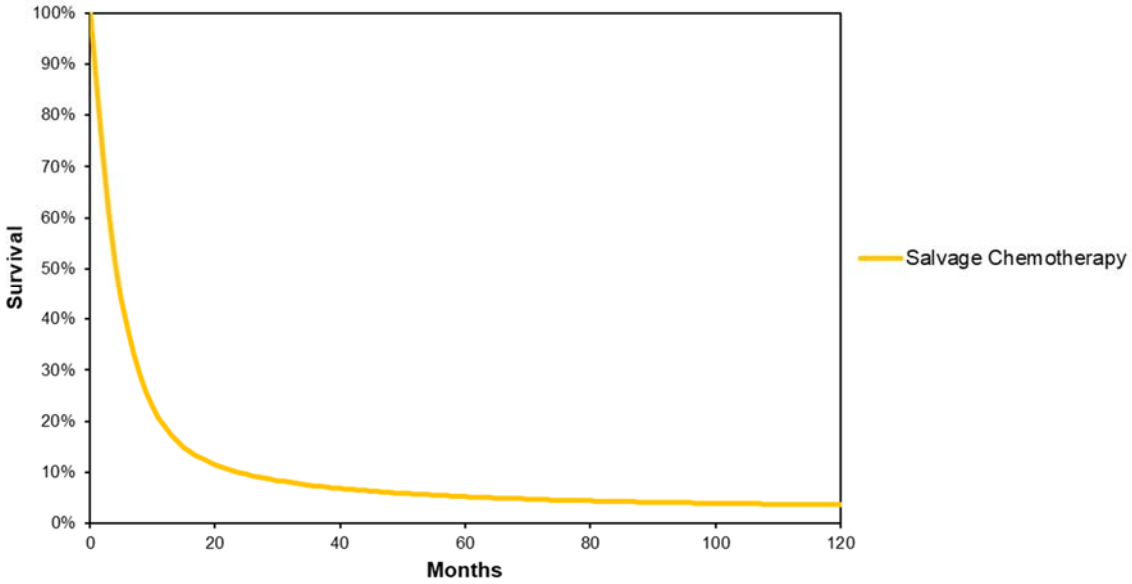
Abbreviations: HMRN: Haematological Malignancy Research Network.

In terms of statistical fit, the Gompertz (line 4) and Weibull (line 5) provided the best fit to the observed data. On visual inspection of the curves, the long-term survival predicted by the lognormal (line 4; similar AIC and BIC to the Gompertz) was considered to be more realistic compared to the

Gompertz, given the low expectation of a 'cure' for patients in the later lines of therapy[i] – based on similar arguments presented for the extrapolation of OS for the 'no SCT' arm of the CORAL extension study. The following survival models were therefore selected for the salvage chemotherapy OS curve: lognormal (line 4) and Weibull (line 5).

The final weighted curve using both the CORAL (third line) and HMRN (fourth- and later-lines) survival data, which is used in the revised base case for salvage chemotherapy OS, is presented in **Error! Not a valid bookmark self-reference.**

Figure 16: Extrapolation of overall survival using CORAL (third line) and HMRN (fourth- and later-lines) survival data – salvage chemotherapy



Abbreviations: HMRN: Haematological Malignancy Research Network.

Given the long-term data available from the HMRN database and CORAL extension study, which included patients who received SCT, and the reasonable fit to the observed data provided by the standard parametric approaches and spline models, long-term survival with salvage chemotherapy was believed to be adequately captured by the survival curve presented in Figure 16. The 'hybrid' model for extrapolating OS with tisagenlecleucel was not therefore considered for salvage chemotherapy in the revised cost-effectiveness analysis.

A comparison of predicted OS for salvage chemotherapy from each of the analyses considered in Novartis' response to the ACD is presented in Table 10.

- Using the CORAL and HMRN combined analysis, which was included in the revised base case, the proportion of patients predicted to be alive at two years was 10%
- Across all analyses, the proportion of patients alive after 24 months remained relatively stable, thus supporting the assumption that patients who are still alive at 24 months would be expected to be 'cured'

[i] Only [redacted] in the HMRN received a subsequent SCT in the fourth- or later-line settings.

Table 10: Mean and median OS for salvage chemotherapy

Scenario	Median OS (months)	Mean OS (months)	% predicted alive at month					
			6	12	24	36	48	60
1: CORAL as per ERG's analysis	4.00	43.03	38	22	14	12	11	11
2: CORAL (spline with two knots for 'no SCT')	4.00	33.10	34	21	14	12	10	10
3: CORAL (for third line) and HMRN (for fourth- and later-lines) combined = revised base case	5.00	20.40	38	19	10	7	6	5

Abbreviations: ERG: Evidence Review Group; HMRN: Haematological Malignancy Research Network; OS: overall survival; SCT: stem cell transplantation.

Progression-free survival

Table 11 summarises the AIC and BIC values for each survival model for the fourth line of therapy (PFS on patients in later lines of therapy were not available), and the extrapolations of PFS up to 10 years is presented in Figure 17.

Table 11: Summary of goodness-of-fit data for salvage chemotherapy progression-free survival

Distribution	Line 4	
	AIC	BIC
Exponential	830.66	227.14
Weibull	779.66	195.29
Gompertz	745.97	198.29
Log-Normal	742.67	193.61
Log-Logistic	741.16	196.29
Generalised gamma	747.75	198.19
Spline with single knot	744.08	198.78
Spline with two knots	746.59	198.95
Spline with three knots	750.28	200.34
Spline with four knots	754.90	203.48

A smaller AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; HMRN: Haematological Malignancy Research Network.

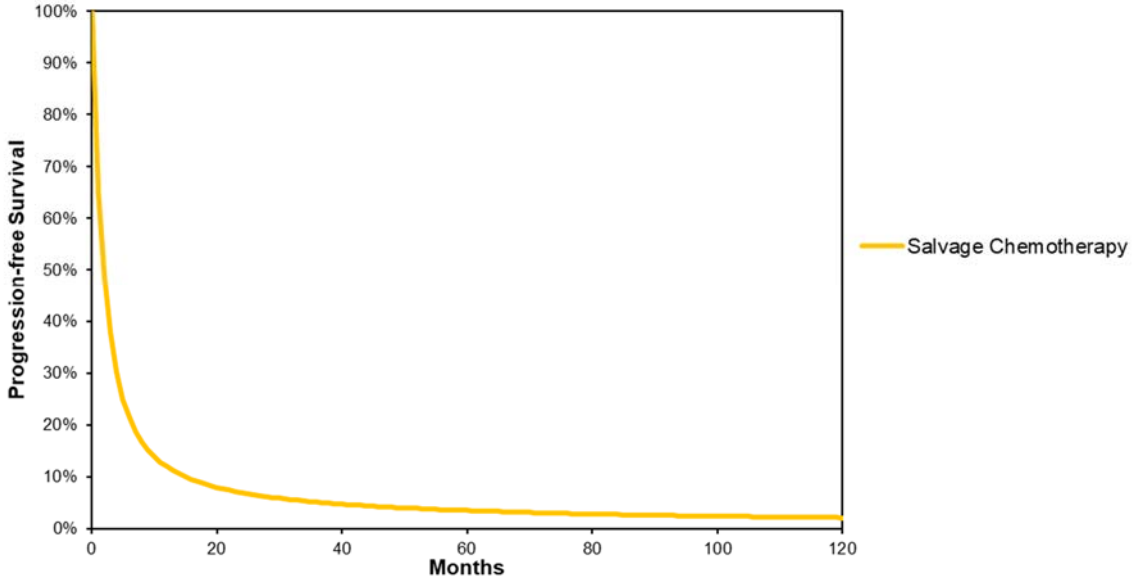
Figure 17: Extrapolation of progression-free survival using parametric and spline models – HMRN (Line 4)

Abbreviations: HMRN: Haematological Malignancy Research Network.

In terms of statistical fit, the loglogistic curve provided the best fit to the observed data and a reasonable fit on visual inspection. The loglogistic curve was therefore used to model PFS in the fourth- and later-line settings for salvage chemotherapy in the revised base case analysis.

The final weighted curve using both the CORAL (third line) and HMRN (fourth- and later-lines) survival data, which is used in the revised base case for salvage chemotherapy PFS, is presented in Figure 18.

Figure 18: Extrapolation of progression-free survival using CORAL (third line) and HMRN (fourth- and later-lines) survival data – salvage chemotherapy



Abbreviations: HMRN: Haematological Malignancy Research Network.

Table 12: Changes to the cost-effectiveness model based on the addition of HMRN (fourth- and later-lines) as an efficacy source for salvage chemotherapy

Sheet location	Model parameter	Description of change
Consolidated Probabilities	Weighted HMRN OS and PFS traces	Added as extra efficacy source for salvage chemotherapy
CORAL plus HMRN	HMRN OS and PFS survival analysis parameters and traces for separate lines of therapy	Added as extra efficacy source for salvage chemotherapy
CORAL_HMRN_OS and HMRN_PFS	Bootstrapping inputs for all survival analysis parametric functions	Added as extra efficacy source for salvage chemotherapy

This option in the model for the input source for salvage chemotherapy is labelled as 'CORAL with HMRN later lines' in the Specification sheet

3 Appendix: Revised base case and scenario analyses

In response to the ACD, Novartis have proposed a revised base case for the cost-effectiveness analysis incorporating more recent data from the JULIET trial, as well as additional evidence from the HMRN database for patients treated with salvage chemotherapy. The base case inputs and assumptions are summarised below.

- The 'hybrid' model was selected for tisagenlecleucel OS, with the spline model with one knot extrapolation up to 24 months followed by general population mortality (standardised mortality rate = 1)
- The spline model with three knots was selected for extrapolation of tisagenlecleucel PFS
- The CORAL (third line) and HMRN (fourth- and later-lines) combined analysis was used as the source of OS and PFS data for salvage chemotherapy
    - For CORAL, the Gompertz distribution was used for extrapolation of the 'SCT' arm and the spline model with two knots was used for the extrapolation of the 'no SCT' arm
    - The contribution of the CORAL and HMRN curves to the final estimates of OS and PFS for salvage chemotherapy were weighted by the proportion of patients in the JULIET trial who received the corresponding number of prior lines of therapy
- Model inputs based on the JULIET trial were updated with data from the latest data cut-off date (21st May 2018)
- All other inputs and assumptions were based on the ERG's revised model as follows:
    - The rate of subsequent SCT for salvage chemotherapy (and weighting for the CORAL arms) was 12.5%, as per the Committee's preferred assumption
    - 'Long-term survivor' costs and utilities were applied for all treatment arms at the same point at which the 'cure' point was assumed for the tisagenlecleucel 'hybrid' model
    - The duration of intravenous immunoglobulin (IVIG) therapy for tisagenlecleucel patients with B-cell aplasia was assumed to be 36 months, as per the Committee's preferred assumption
    - The model included discounting for subsequent SCT
    - The choice of salvage chemotherapy selected for patients who discontinue prior to tisagenlecleucel infusion was assumed to be the same as the regimen used for the comparator arm
    - The model included the ERG's approach for incorporating age-adjusted utilities
    - The hospitalisation rate for tisagenlecleucel infusion was assumed to be 100%

Deterministic cost-effectiveness results versus [R-]GDP are presented in (list price) Table 13 and Table 14 (with confidential PAS discount of [redacted]%), respectively, for the revised base case. Cost-effectiveness results are also presented assuming a 3-year time point for the assumed 'cure' point in the tisagenlecleucel 'hybrid' model (as well as the 2-year time point), and using the Gompertz distribution to model tisagenlecleucel OS up to the assumed 'cure' point (as well as the spline model with one knot).

- Results have also been presented from analyses using the alternative CORAL analyses for salvage chemotherapy efficacy, the results of which are presented from Use of CORAL extension study data, as per the ERG's revised model (i.e. Gompertz for both 'SCT' and 'no SCT' arms using the ERG's digitisation of CORAL)
    - All other inputs and assumptions were based on the ERG/Committee's preferred assumptions, using the latest data from the JULIET trial

Table 17 to Table 24. These scenarios included:

- Use of CORAL extension study data, as per the ERG's revised model
- Use of CORAL extension study data, using the spline model with two knots for the 'no SCT' arm

In the scenario using the CORAL extension study data with the spline model with two knots for the 'no SCT' arm (which represents a more plausible fit for patients are receiving treatment with palliative intent), the ICER for tisagenlecleucel versus [R-]GDP with the PAS applied for tisagenlecleucel was £51,644. Given the limitations of the CORAL extension study, each of which are expected to result in

patients having improved survival outcomes compared to the full population of interest, these analyses are expected to overestimate the ICER for tisagenlecleucel versus salvage chemotherapy.

Based on the results of Novartis' revised base case, which uses the HMRN data to address one of the major limitations of the CORAL extension study, tisagenlecleucel may be considered a cost-effective use of NHS resources, being associated with an ICER of £46,325 per QALY gained versus [R-]GDP with the PAS applied for tisagenlecleucel.

Revised base case

- CORAL (third line) and HMRN (fourth- and later-lines) combined analysis
    - For CORAL, the Gompertz distribution was used for extrapolation of the 'SCT' arm and the spline model with two knots was used for the extrapolation of the 'no SCT' arm
    - The contribution of the CORAL and HMRN curves to the final estimates of OS and PFS for salvage chemotherapy were weighted by the proportion of patients in the JULIET trial who received the corresponding number of prior lines of therapy
    - All other inputs and assumptions were based on the ERG/Committee's preferred assumptions, using the latest data from the JULIET trial

Table 13: Revised base case A (list price) – tisagenlecleucel 'hybrid' model using spline with one knot and CORAL (third line) and HMRN (fourth- and later-lines) combined analysis for salvage chemotherapy

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
2-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HMRN: Haematological Malignancy Research Network; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 14: Revised base case A (with PAS) – tisagenlecleucel 'hybrid' model using spline with one knot and CORAL (third line) and HMRN (fourth- and later-lines) combined analysis

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
2-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,325
3-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,021

Abbreviations: HMRN: Haematological Malignancy Research Network; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS: Patient Access Scheme; QALYs, quality-adjusted life years.

Table 15: Revised base case B (list price) – tisagenlecleucel 'hybrid' model using Gompertz and CORAL (third line) and HMRN (fourth- and later-lines) combined analysis for salvage chemotherapy

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
2-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HMRN: Haematological Malignancy Research Network; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 16: Revised base case B (with PAS) – tisagenlecleucel 'hybrid' model using Gompertz and CORAL (third line) and HMRN (fourth- and later-lines) combined analysis for salvage chemotherapy

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
2-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,901
3-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,773

Abbreviations: HMRN: Haematological Malignancy Research Network; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS: Patient Access Scheme; QALYs, quality-adjusted life years.

Scenario 1

- Use of CORAL extension study data, as per the ERG's revised model (i.e. Gompertz for both 'SCT' and 'no SCT' arms using the ERG's digitisation of CORAL)
    - All other inputs and assumptions were based on the ERG/Committee's preferred assumptions, using the latest data from the JULIET trial

Table 17: Scenario 1A (list price) – tisagenlecleucel 'hybrid' model using spline with one knot and CORAL for salvage chemotherapy as per the ERG's analysis

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
2-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ERG: Evidence Review Group; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 18: Scenario 1A (with PAS) – tisagenlecleucel 'hybrid' model using spline with one knot and CORAL for salvage chemotherapy as per the ERG's analysis

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
2-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,356
3-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£65,822

Abbreviations: ERG: Evidence Review Group; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS: Patient Access Scheme; QALYs, quality-adjusted life years.

Table 19: Scenario 1B (list price) – tisagenlecleucel 'hybrid' model using Gompertz and CORAL for salvage chemotherapy as per the ERG's analysis

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
2-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ERG: Evidence Review Group; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 20: Scenario 1B (with PAS) – tisagenlecleucel 'hybrid' model using Gompertz and CORAL for salvage chemotherapy as per the ERG's analysis

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
2-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,210
3-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£63,858

Abbreviations: ERG: Evidence Review Group; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS: Patient Access Scheme; QALYs, quality-adjusted life years.

Scenario 2

- Use of CORAL extension study data, using the spline model with two knots for the 'no SCT' arm
    - Based on redigitised CORAL, the Gompertz distribution was used for extrapolation of the 'SCT' arm (as per the ERG's analysis) and the spline model with two knots was used for the extrapolation of the 'no SCT' arm
    - All other inputs and assumptions were based on the ERG/Committee's preferred assumptions, using the latest data from the JULIET trial

Table 21: Scenario 2A (list price) – tisagenlecleucel 'hybrid' model using spline with one knot and CORAL (spline with two knots for no SCT) for salvage chemotherapy

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
2-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SCT: stem cell transplant.

Table 22: Scenario 2A (with PAS) – tisagenlecleucel 'hybrid' model using spline with one knot and CORAL (spline with two knots for no SCT) for salvage chemotherapy

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
2-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,644
3-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£59,386

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS: Patient Access Scheme; QALYs, quality-adjusted life years; SCT: stem cell transplant.

Table 23: Scenario 2B (list price) – tisagenlecleucel 'hybrid' model using Gompertz and CORAL (spline with two knots for no SCT) for salvage chemotherapy

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
2-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SCT: stem cell transplant.

Table 24: Scenario 2B (with PAS) – tisagenlecleucel 'hybrid' model using Gompertz and CORAL (spline with two knots for no SCT) for salvage chemotherapy

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£/QALY)
2-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,362
3-year timepoint							
Tisagenlecleucel	[redacted]	[redacted]	[redacted]				
[R-]GDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,789

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS: Patient Access Scheme; QALYs, quality-adjusted life years; SCT: stem cell transplant.

4 References

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3. National Institute for Health and Care Excellence. NG52: Non-Hodgkin's lymphoma: diagnosis and management. Available at: https://www.nice.org.uk/guidance/NG52/chapter/Recommendations#management-of-diffuse-large-bcell-lymphoma. [Last accessed: 14 November 2017].
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5. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone marrow transplantation 2016;51:51-57.
6. Guyot P, Ades A, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC medical research methodology 2012;12:9.
7. Haematological Malignancy Research Network. Clinical Management, Outcome and Resource Utilisation of Diffuse Large B-cell Lymphoma. Report. 01.05.2018.

Dear Frances,

Thank you very much for agreeing to talk on the phone to us at such short notice. As requested, please find below the scenarios and ICERs with the current PAS ([redacted]) and scenarios and ICERs with current PAS ([redacted]) + additional CDF rebate ([redacted]) with the Committee's preferred assumptions:

#	Scenario	Δ Costs	Δ QALYs	ICER at current PAS ([redacted])
2	1-knot spline and SMR=1.09 after 2 years	[redacted]	[redacted]	£56,509
3	1-knot spline and SMR=1.09 after 3 years	[redacted]	[redacted]	£65,836
4	1-knot spline and SMR=1.09 after 4 years	[redacted]	[redacted]	£73,286

#	Scenario	Δ Costs	Δ QALYs	ICER with current PAS ([redacted]) + CDF rebate ([redacted])
2	1-knot spline and SMR=1.09 after 2 years	[redacted]	[redacted]	£42,991
3	1-knot spline and SMR=1.09 after 3 years	[redacted]	[redacted]	£49,963
4	1-knot spline and SMR=1.09 after 4 years	[redacted]	[redacted]	£55,403

The CE model that was used to generate the above will be sent separately as it is too big to fit on an email.

As discussed the updated ICERs are based on the current PAS ([redacted]) and an additional rebate of [redacted] managed via the CDF. This equates to an overall discount of [redacted] (equivalent to an acquisition cost of [redacted]). This scheme was deemed transactable by NHSE. We are awaiting confirmation from the HMRC regarding VAT status and do not currently anticipate that it will apply. However, if this is not the case then as per Novartis standard procedures VAT will be rebated.

Please let us know if you require anything further.

Kind regards,

[redacted]
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UNITED KINGDOM

Single Technology Appraisal (STA)

Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [ID1166]

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 17/10/18

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 Overview

The company's response to the Appraisal Consultation Document (ACD) included:

1 New data cut for the efficacy data for tisagenlecleucel;
2 Efficacy data for 4th and 5th line salvage chemotherapy from the Haematological Malignancy Research Network (HMRN) to be used (together with CORAL) to define the efficacy of the comparator;
3 Cost-effectiveness results from an updated model including a revised company base-case;
4 Discussion on the applicability of the End of Life criteria.

The Evidence Review Group (ERG) was requested by NICE to provide commentary and validity checks on the additional analyses submitted by the company in response to the ACD and to identify any areas of remaining uncertainty.

Due to the limited time available, the additional work undertaken by the ERG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission. However, the ERG checked the implementation of the proposed changes and successfully replicated the main results presented by the company. The ERG also undertook a series of exploratory analyses to address any areas of remaining uncertainty.

2 ERG commentary on the revised company analysis

The company proposed several revisions to the cost-effectiveness of tisagenlecleucel, some reflecting the Committee's stated preferences (in the ACD) and others claiming to address key uncertainties raised in the ACD.

The changes that related to the Committee's stated preferences in terms of costs and health-related quality of life (HRQoL) were:

- The assumed rate of subsequent stem cell transplant (SCT) for salvage chemotherapy (which also provides the weights for combining the overall survival [OS]curves for the CORAL extension study) is 12.5%
- 'Long-term survivor' costs and utilities applied for all treatment arms from the point of 'cure' assumed for tisagenlecleucel
- Duration of intravenous immunoglobulin (IVIG) therapy for tisagenlecleucel patients with B-cell aplasia - 36 months
- Follow-up costs of subsequent SCT are now discounted at a 3.5% annual rate
- Salvage chemotherapy selected for patients who discontinue prior to tisagenlecleucel infusion was assumed to be the same as the regimen used for the comparator arm
- ERG's approach for incorporating age-adjusted utilities
- Setting of tisagenlecleucel infusion - 100% as inpatient

These were not challenged by the ERG as they directly reflected the Committee's preferences. These were implemented across all scenarios evaluated by the company and ERG. Note that all of these were already implemented in the ERG report.

The company implemented further changes to the modelling claimed to address key uncertainties raised in the ACD. These are discussed in turn over the next sections and cover:

Section 2.1 –New data cut from the JULIET trial (May 2018 cut off)
Section 2.2 – Revised cost-effectiveness analyses
Section 2.3 – Comparator clinical data: Efficacy data for 4th and 5th line salvage chemotherapy from the Haematological Malignancy Research Network (HMRN)
Section 2.4 – Further considerations for the application of the End of Life criteria for tisagenlecleucel

2.1 New data cut for the JULIET trial

The company considered a new data cut from the JULIET trial, which has only become available after the first appraisal meeting. These relate to a May 2018 data cut-off. In the original submission the data cut-off point was December 2017. An additional [redacted] patients who received tisagenlecleucel were included in the May 2018 dataset. The company did not submit any evidence on these patient characteristics or an updated baseline patient characteristics table for the new JULIET data cut.

Table 1 compares follow up data and results for these two data cut-off points. There is only a [redacted] in median follow up for OS [redacted] At the May 2018 cut-off the median OS is [redacted] of patients had died, which is [redacted] than the December 2017 cut-off results (median OS 11.7 months, 48% had died).

Table 1 Comparison of JULIET trial results for different data cut-off points

Result	December 2017 data cut-off	May 2018 data cut-off
Number of patients who received a Tisagenlecleucel infusion	111	[redacted]
Proportion who died	[redacted]	[redacted]
Median follow up for OS (months)	[redacted]	[redacted]
Median OS (months)	11.7 (95% CI 6.6 to NE)	[redacted]
Median follow up for PFS (months)	[redacted]	[redacted]
Median PFS (months)	[redacted]	[redacted]

NE Not estimable

For the *pooled* dataset only Kaplan Meier plots for OS and progression free survival (PFS) were presented (the pooled dataset was comprised of the JULIET trial plus the Schuster case series; [redacted] received Tisagenlecleucel). The OS plot is presented below; it is evident that some patients die between the [redacted] Moreover, the number of patients still alive who have reached these time points (the number 'at risk') is [redacted] Beyond 24 months the number of patients 'at risk' is [redacted]. This emphasises that fact that the clinical data for tisagenlecleucel remains immature.

Figure 1 Overall survival from the pooled analysis of JULIET and Schuster 2017 [redacted]

ERG commentary

Although the updated May 2018 follow up results are broadly consistent with those for December 2017 they are nevertheless still too immature to yield reliable estimates of longer-term survival rates. This is because deaths have occurred between the 12 and 24 month time points and the number of patients 'at risk' is still low for several key time points within and beyond the 12-24 month period.

2.2 Revisions to cost-effectiveness analysis

The company modified the cost-effectiveness analysis to reflect the following:

Section 2.2.1 – Use of the new data cut for the JULIET trial (May 12018);

Section 2.2.2 – Revised fitting to new JULIET data cut (May 2018), and revisiting of extrapolation assumptions (assumed cure at two alternative timepoints of two and three years, both shifting survival rates to general population values i.e. no excess mortality was assumed after the cut-off point);

Section 2.2.3 – The extrapolation of survival data from the CORAL extension study (redigitised by the company) was modified by fitting alternative models;

Section 2.2.4 – Modelling survival salvage chemotherapy: weighted average of the OS data from the CORAL extension study and the HMRN database, according to the proportion of patients at 3rd, 4th and 5th line of treatment in the JULIET trial.

The ERG will examine the effect of each modification in turn. All cost-effectiveness results in the following sections are deterministic, and assume the company's proposed patient access scheme (PAS) discount over tisagenlecleucel list price ([redacted]).

2.2.1 Use of the new data cut for the JULIET trial, implications for cost-effectiveness

Following the use of the new data cut for JULIET (May 2018), a number of model inputs related to the effectiveness of tisagenlecleucel were updated by the company (Table 3, Company's detailed response to the ACD - Appendix). These include not only PFS and OS, but also other parameters, namely: rates of cytokine release syndrome (CRS) and associated resource use and cost; administration costs of tisagenlecleucel including lymphodepleting regimens; tisagenlecleucel decision tree inputs and population demographics; and subsequent auto and allo SCT rate for tisagenlecleucel. The ERG notes that, upon a brief inspection of the model, changes to these other model inputs appeared to be small and are unlikely to impact considerably on the cost-effectiveness results.

ERG commentary

Table 2 presents the implications to incremental cost-effectiveness ratios (ICERs) of applying the updated JULIET data (May 18 data cut) to the analysis. To make explicit the incremental effect of the changes implemented by the company, we examine here a model with the Committee's preferred assumptions in terms of costs and HRQoL (see beginning of Section 2) and with the new data cut form JULIET. Regarding the modelling of OS for tisagenlecleucel (that JULIET informs alongside Schuster 2017 [NCT02030834]) the ACD stated a preference for the 'hybrid' statistical model: applying a fitted parametric distribution up to a certain timepoint, after which patients who are predicted to be alive are assumed cured and, from that point onwards, face the general population mortality with or without excess mortality (parameterised using a standardised mortality ratio [SMR]). The parametric distribution fitted to the tisagenlecleucel OS data (pooled JULIET and Schuster 2017 [NCT02030834]) prior to the cure point that supported the Committee's decision making was a one knot spline model. This model had been implemented on one of the revised ERG base-case analyses (ERG report) with patients assumed cure at 5 years, and without any excess mortality afterwards (SMR=1). The results of this model are reproduced from the ERG report (December 2017 data cut) in Table 2, alongside revised results suing the most recent JULIET data cut (May 2018).

Table 2 ICER comparison for the ERG report revised base-case

OS modelling approach	Tisagenlecleucel data	Incremental costs, £	Incremental QALYs	ICER (£ per QALY)	Tisagenlecleucel extrapolation	
					Mean OS (months)	Mean PFS (months)
Single knot spline + SMR=1.00 after 5 years	JULIET (December 2017)	[redacted]	[redacted]	£93,862	103.87	99.03
	JULIET (May 2018)	[redacted]	[redacted]	£79,839	114.09	109.82

*Assumes the ERG's approach to extrapolate CORAL extension study data and that health state costs and HRQoL become the same as for PFS after the point of cure, as well as the Committee's preferred assumptions on costs and HRQoL

Table 2 shows that once the model is updated with the JULIET latest data cut (May 2018) the ICER reduces from £93,862 to £79,839 per additional QALY. This reduction in the ICER is largely driven by the extrapolation of the OS for tisagenlecleucel based on the most recent JULIET data cut. The results show that the inclusion of the updated JULIET trial, increases the average incremental QALYs of tisagenlecleucel vs salvage chemotherapy across all scenarios when compared to the previous JULIET data cut, while having a marginal impact on costs. The increase in HRQoL benefit is driven by the extrapolation of the pooled OS data for tisagenlecleucel, which predicts considerably greater mean OS for patients receiving tisagenlecleucel when the updated JULIET trial is considered.

Figure 2 illustrate the impact of the data cut on the extrapolation of tisagenlecleucel.

Figure 2 Comparison of extrapolation of tisagenlecleucel OS for the two JULIET data cuts

2.2.2 Revised fitting to new JULIET data cut, and assumptions over the cure timepoint

In the ACD, the Committee declared a preference for the 'hybrid' OS extrapolation model for the tisagenlecleucel group. The company accepts this but revisits the selection of the single knot spline model to extrapolate OS up to the point of cure and argues for replacing this model by a Gompertz distribution. The company argues that, despite the better statistical fit for the single knot spline model, the Gompertz distribution may also be relevant given that it *"provided a better visual fit to the tail of the observed data, particularly when using the later timepoints for the assumed 'cure'"*. Thus, the company presents their revised base-case for both the single knot spline model and Gompertz distribution.

The company also presents cost-effectiveness results for two cure time points, two and three years, using the latest data cut from JULIET (pooled with Schuster 2017). The company further states that cure at 2 years is supported by published data from Maurer et al. (2014) and the survival plateau suggested by the pooled OS data from the JULIET and Schuster 2017 studies. A three years cure time point is considered alongside the two years assumption to explore uncertainty around the timing for cure. The ICERs for tisagenlecleucel compared to salvage chemotherapy are £56,356 and £65,822 per additional QALY for cure at 2 and 3 years, respectively, assuming the single knot spline model followed by general population without excess mortality after the point of cure (SMR=1.00; Table 18 in the company's response to the ACD – Appendix). When a Gompertz distribution is used to model the OS of tisagenlecleucel before the point of cure, the ICERs become £57,210 and £63,858 per

additional QALY for cure at 2 and 3 years, respectively (Table 20 in the company's response to the ACD – Appendix).

ERG commentary

The committee considered the cure time point of the 'hybrid' model a key uncertainty. The ERG notes that the company does not present additional evidence which reduces the uncertainty on the timing of cure, with the median and maximum follow-up of the updated JULIET trial remaining too short ([redacted] and [redacted], respectively) to exclude the possibility of late relapses. Furthermore, the ERG would like to reiterate that cure from diffuse large B-cell lymphoma (DLBCL) may not equate with a return to the life expectancy of the general population and that excess mortality may remain after cure from the primary cancer. The Howlader et al. (2017) study, which followed up patients for up to 11 years and had a large sample size (n= 18,047), suggests that it is only from five years post-diagnosis onward that no statistically significant excess mortality can be identified for DLBCL patients. The ACD considered a 2-year cure point to be optimistic (and 5 years pessimistic), and too short to switch to general population mortality given the short follow-up of the tisagenlecleucel effectiveness data and the evidence on excess mortality form Howlader et al. (2017). Thus, the ERG considers that the company's revised cure timepoints (i) do not fully account for the uncertainty on the timing of cure and remain likely to be optimistic; and ii) ignore the possibility of excess mortality after the point of cure by setting the SMR to 1.00.

The ERG challenges the company's selection of OS distributions for the 'hybrid' model with the latest data cut from JULIET (May 2018). The implications of the choice between the two curves for the extrapolated survival of tisagenlecleucel is illustrated on

Figure 3 and Figure 4, respectively for the company's two and three years cure 'hybrid' models. At 2 years, both the Gompertz and one-knot spline model predict around 40% cured; at 3 years the Gompertz maintains a prediction close to 40% but the one-knot spline model prediction reduces to 35%. The disparity between the two statistical models further increases as the point of 'cure' occurs at a more distant point in time.

Figure 3 Extrapolation of overall survival using the 'hybrid' model of Gompertz or spline with one knot up to 24 months followed by general population mortality (SMR=1) – tisagenlecleucel

Company's response to ACD - Appendix, p6

Figure 4 Extrapolation of overall survival using the 'hybrid' model of Gompertz or spline with one knot up to 36 months followed by general population mortality (SMR=1) – tisagenlecleucel

Company's response to ACD - Appendix, p7

As stated above, the follow-up from JULIET (May 2018 data cut) is still short with a very small number of patients determining the later part of the curve. There is hence significant uncertainty in the later part of the curve, and the possibility of late relapses needs to be retained. For these reasons, the

ERG has concerns that the use of the Gompertz to model OS survival may overestimate the proportion of patients alive when treated with tisagenlecleucel, particularly as when later cure timepoints are applied.

The results in Table 3 illustrate the implications of the choice of survival modelling approaches, cure timepoints, and excess mortality after cure to cost-effectiveness results. The table reports cost-effectiveness results using the CORAL extension study data to model the effectiveness of salvage chemotherapy (as per ERG report and the committee's preferred specification in the ACD) alongside intermediate time points for cure. The ICERs for tisagenlecleucel vs salvage chemotherapy range from £56,356 to £79,839 per additional QALY depending on the assumed timing of cure and whether cured patients have any excess mortality compared to the general population. The timing of cure appears to have a greater impact on estimates of cost-effectiveness than the assumed excess mortality on the post-cure period.

Table 3 Deterministic ICERs with PAS for tisagenlecleucel, JULIET May 2018

Analysis*	**Incremental costs, £**	**Incremental QALYs**	**ICER (£ per QALY)**
Mixture cure lognormal and cure at 5 years	[redacted]	[redacted]	£62.147
Single knot spline + SMR=1.00 after 2 years**	[redacted]	[redacted]	£56,356
Single knot spline + SMR=1.09 after 2 years	[redacted]	[redacted]	£57,551
Single knot spline + SMR=1.00 after 3 years**	[redacted]	[redacted]	£65,822
Single knot spline + SMR=1.09 after 3 years	[redacted]	[redacted]	£67,230
Single knot spline + SMR=1.09 after 4 years	[redacted]	[redacted]	£75,009
Single knot spline + SMR=1.00 after 5 years	[redacted]	[redacted]	£79,839

*Assumes the ERG's approach to extrapolate CORAL extension study data and that health state costs and HRQoL become the same as for PFS after the point of cure; **Company's Scenario 1A

The ERG notes that the analyses where tisagenlecleucel OS is modelled with a single knot spline until cure at 2 years followed by general population mortality (with or without excess mortality) has an ICER substantially lower than that for the analysis with a mixture-cure survival approach for tisagenlecleucel and cure in terms of costs and HRQoL at 5 years. The mixture cure model had been highlighted in the ERG report as a clinically plausible approach, but likely to be optimistic towards the cost-effectiveness of tisagenlecleucel.

2.2.3 Extrapolation of CORAL extension study survival data

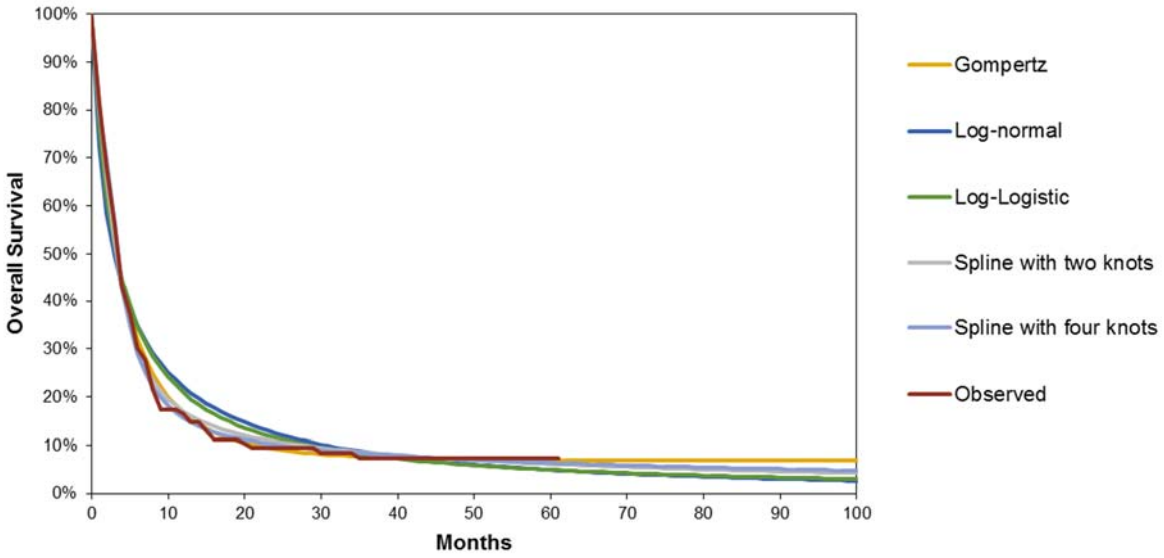
The committee considered the CORAL extension study an appropriate data source of effectiveness for the comparator arm (ACD, section 3.8). OS data from the CORAL extension study was modelled separately for individuals with and without subsequent SCT. The committee agreed with the use of the Gompertz distribution to model the OS of both the 'no SCT' and 'SCT' curves

The company redigitised the CORAL extension OS Kaplan Meier curves, so as to model additional parametric distributions. The company agreed with the use of the Gompertz distribution to model the 'SCT' curve, but argues that the extrapolation of the 'no SCT' OS curve from the CORAL extension study with the Gompertz distribution generates overly optimistic survival estimates, despite the better visual fit of this parametric model. The company argues for replacing the Gompertz by a two-knots spline model to describe the 'no SCT' OS curve. Using the two-knots spline leads to lower mean OS predictions for salvage chemotherapy than the Gompertz (33.10 vs 41.2 months, respectively). This change is not conservative and will generate more favourable cost-effectiveness results for tisagenlecleucel. The company presents goodness-of-fit statistics based on the Akaike information criteria (AIC) and Bayesian information criteria (BIC) for a number of alternative models (Table 4, Company's response to the ACD – Appendix).The numbers presented indicate that the two-knot model fits the data better than the Gompertz (AIC 640.26 vs 655.37 respectively).

ERG commentary

The ERG notes that the company's document shows significant inconsistency in the ranking of statistical fit for the 'no SCT' curve according to AIC and according to BIC (Table 4, Company's response to the ACD – Appendix), and also with the original statistical fits in the ERG report (using the ERGs digitalisation of the CORAL curves). The ERG then checked the goodness of fit visually (Figure 5), and found considerable discrepancy with the goodness of fit statistics presented. For example, the Log-Logistic curve, which has the 4th and 1st best statistical fit according to AIC and BIC, appears to fit less well than the Gompertz to all parts of the Kaplan Meier curve. However, the Gompertz ranked less well (7th and 6th best fitting model according to AIC and BIC, respectively). It is also unclear to the ERG why the two knot spline model was preferred to the four knot spline model, when the latter has better statistical (on both AIC and BIC) and visual fit. Therefore, the ERG believes the statistical evaluation of the goodness of fit conducted by the company is not robust, and hence the conclusion drawn by the company that the two-knots spline model fits best may be incorrect.

Figure 5 Extrapolation of overall survival using selected parametric and spline models – salvage chemotherapy (no SCT)



Company's response to ACD – Electronic model

The ERG's notes that using visual fit, the Gompertz still seems to provide the best fit. This is also consistent with the statistical fit in the ERG report, Appendix 9.2, using the originally digitised curve. While our preference would be to re-estimate the extrapolation models on the company's pseudo individual patient data (generated from the digitised Kaplan Meier curves), these data were not submitted by the company. Therefore, the ERG considers that the Gompertz distribution is the most appropriate extrapolation model for the 'no SCT' OS curve.

However, the ERG also notes that the company's digitisation of the 'SCT' curve from the CORAL extension study appears to provide a more precise prediction of the survival plateau for the SCT patients (starting approximately at 35%, whereas the ERG approach would place it approximately at 38%). The ERG hence revises their base-case to use the fittings based on the data re-digitised by the company, but retains its choice of the Gompertz (for both 'no SCT' and 'SCT' curves) to extrapolate the comparator's OS.

2.2.4 ERG revised base-case analysis

The ERG updated their revised base case analysis which includes:

1 Committee stated preferences in terms of costs and HRQoL;
2 The May 2018 data cut for the JULIET trial;
3 OS extrapolation for tisagenlecleucel with:
   a. Mixture cure (lognormal);
   b. Single knot spline model until point of cure (2, 3 and 4 years)followed by general population mortality with SMR=1.09;
   c. Single knot spline model until point of cure (5 years)followed by general population mortality with SMR=1.00;
4 OS extrapolation for salvage chemotherapy CORAL extension study (redigitised by the company) with Gompertz distributions fitted to the 'no SCT' and 'SCT' survival data, weighted by 12.5% SCT rate.

Table 4 shows the results of the ERG revised base-case with the changes described above.

Table 4 ERG revised base case with alternative survival assumptions for tisagenlecleucel and JULIET data (May 2018)

Analysis*	Incremental Costs	Incremental QALYs	ICER (per QALY)
1. Mixture cure lognormal and cure at 5 years	[redacted]	[redacted]	£61,007
2. Single knot spline + SMR=1.09 after 2 years	[redacted]	[redacted]	£56,509
3. Single knot spline + SMR=1.09 after 3 years	[redacted]	[redacted]	£65,836
4. Single knot spline + SMR=1.09 after 4 years	[redacted]	[redacted]	£73,286
5. Single knot spline + SMR=1.00 after 5 years	[redacted]	[redacted]	£77,895

*Assumes health state costs and HRQoL become the same as for PFS after the point of cure

Under the revised assumptions on the effectiveness of tisagenlecleucel (as updated by the JULIET May 2018 data cut) and of salvage chemotherapy (redigitised OS curves from CORAL extension study), the ICERs for tisagenlecleucel vs salvage chemotherapy range between £56,509 and £77,895 per additional QALY. The timing of cure remains an important driver of cost-effectiveness, but also a key area of uncertainty.

2.3 Company's alternative approach to model the effectiveness of salvage chemotherapy

While the committee considered the CORAL extension study an appropriate data source of effectiveness for the comparator arm (ACD, section 3.8), it also recognised the limitations of this data source to inform the effectiveness of the comparator arm.

The CORAL extension study only included patients at the third line of treatment, while the tisagenlecleucel license allows for treatment at further lines. Furthermore, the JULIET trial included patients (approximately [redacted]) who had previously received treatment at third line or later (see Table 6 of the original company's submission) i.e. for whom tisagenlecleucel would be the fourth or later line of treatment.

The company sought to address this limitation by combining the effectiveness data from the CORAL extension study with that of the HMRN for those patients with DLBCL who received a 4th and 5th line of treatment. The HMNR collects data on haematological malignancies and is set within the former adjacent UK Cancer Networks of Yorkshire and the Humber and the Yorkshire Coast. All haematological malignancy diagnoses within the region (whether originating from the NHS or private sources and irrespective of assumed prognosis and treatment intent) are made at a single specialist haematopathology laboratory from which all HMRN patients are ascertained. Following diagnosis, patients are individually tracked, and full details of all treatments, responses and outcomes are collected to clinical trial standards.

The HMRN database had been identified on the ACD has a potential source of effectiveness data for the comparator. Table 5 summarises the effectiveness data for the subset of DLBCL patients in the HMRN database who were at 4th and later line of treatment.

Table 5 Summary of OS and PFS from the HMRN by line of therapy

Line of therapy	Median OS, years (95% CI)	% alive (95% CI)			Median PFS, years (95% CI)
		6 months	1 year	2 years	
Fourth line (N=48)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fifth line (N=10)	[redacted]	Not reported	Not reported	Not reported	Not reported

The company presents in their response to the ACD their approach to fitting OS survival models separately to the observed OS for patients at 4th and 5th line of treatment in the HMRN database. The parametric survival models considered more appropriate by the company were then implemented in the electronic model and combined with the CORAL extension study OS data to yield one weighted

curve to extrapolate OS for the salvage chemotherapy group. The weights applied to each OS curve were the proportion of patients in the JULIET trial (May 2018 data-cut) at the corresponding line of treatment (3rd line - [redacted] 4th line – [redacted]; 5th line – [redacted]). A similar approach was followed to extrapolate the PFS for 4th and 5th line of salvage chemotherapy using HMRN data, but an additional assumption of equivalent PFS for 4th and 5th line of treatment was applied as HMRN did not include PFS data for patients at 5th line of treatment.

The company's revised base-case included:

- Updated tisagenlecleucel data (May 2018);
- Combined effectiveness data from the CORAL extension study and HMRN database for salvage chemotherapy;
- Company's preferred assumptions in terms of cure and fitting of OS data for tisagenlecleucel.

The ICERs for this analysis are presented in Table 6. Full cost-effectiveness results are presented on the company's response to the ACD (Table 13 and 14 - Appendix).

Table 6 ICERs for tisagenlecleucel vs salvage chemotherapy – using Novartis' revised base case

Scenario description		ICER			
	'Cure' point:	**2-year**		**3-year**	
	JULIET extrapolation:	**Spline with one knot**	**Gompertz**	**Spline with one knot**	**Gompertz**
CORAL (for third line) and HMRN (for fourth- and later-lines) combined • Updated JULIET data for tisagenlecleucel • Redigitised CORAL ('No SCT' = spline with two knots and 'SCT' = Gompertz) for third-line and HMRN for fourth- and later-lines		£46,325	£46,901	£53,021	£51,773

From the Company's detailed response to the ACD (Table 3, p11)

ERG commentary

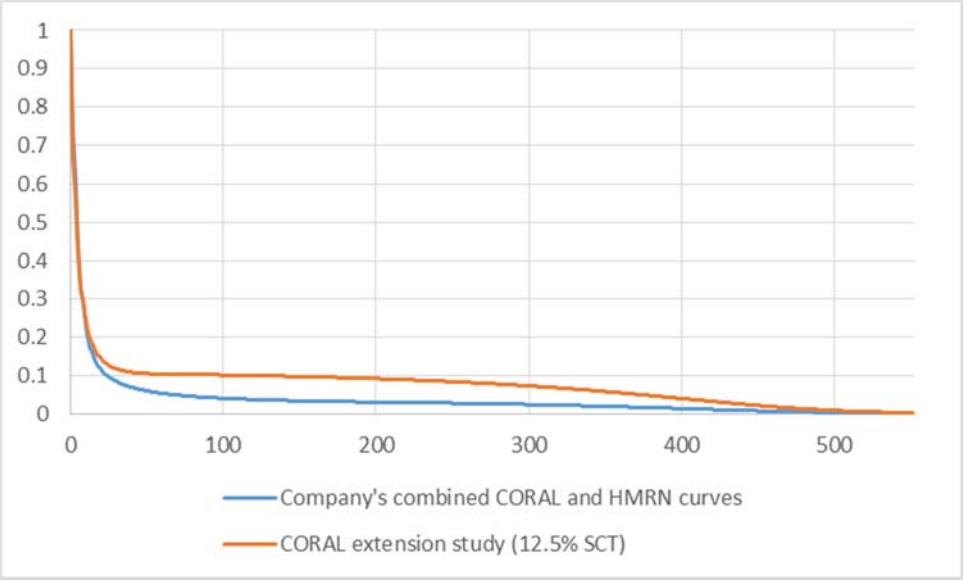
The ERG recognises the company's attempt to incorporate a potentially relevant source of effectiveness data for salvage chemotherapy. However, it is impossible to assess whether the subset of patients in the HMRN database whose survival data were included in the company's revised base-

case analysis would have been eligible for treatment with tisagenlecleucel. The baseline prognostic data for the HMRN patients - presented by the company in Table 6 of their ACD comments appendix - are of extremely limited relevance to this assessment. This is because data is reported for all *de novo* cases of DLBCL (i.e. at 1st line), which relates to 3,000 patients, and not to the 58 patients of interest. Without any data on these patients' characteristics, specially their age and performance status, it is impossible to determine i) if they are comparable to the JULIET trial population, and ii) the size and the direction of potential biases associated with their inclusion in the analysis.

Furthermore, the ERG is also unable to verify whether the survival extrapolation approach for these data was appropriate, as it is not possible to distinguish between the curves on the basis of the graphs illustrating the visual fit of the alternative extrapolation distributions. The ERG is also unable to explore the impact of alternative survival models to extrapolate survival on 4th and 5th line of chemotherapy on cost-effectiveness estimates, as the electronic model only includes the company's preferred survival distribution for each line of treatment.

Figure 6 shows the alternative salvage chemotherapy OS extrapolation when applying the company's preferred approach (CORAL extension study for 3rd line treatment [with two knots spline for 'no SCT' curve and 12.5% SCT rate] and HMRN for 4th and 5th line treatments) and the approach taken in the ERG's revised base-case (CORAL extension study, redigitised by the company with Gompertz distributions fitted to the 'no SCT' and 'SCT' survival data and weighted by 12.5% SCT rate).

Figure 6 Comparison of OS extrapolation for the Company's and ERG's preferred approaches



The company's revised base-case ICERs for tisagenlecleucel compared to salvage chemotherapy range between £46,325 and £53,021 per additional QALY, depending on the assumed cure time point

and OS fitting for tisagenlecleucel. The ERG notes that these ICERs may be overly optimistic towards the cost-effectiveness of tisagenlecleucel and are affected by the following limitations:

- Use of a source of effectiveness data for salvage chemotherapy (HMNR) that may introduce bias of unknown size and direction in the cost-effectiveness estimates;
- Only include early cure assumptions that are not supported by any additional data, and do not account for the possibility of late relapses;
- Do not consider the possibility that cured patients retain excess mortality compared to the general population;
- Survival fitting for patients at third line of salvage chemotherapy (without subsequent SCT) with single knot spline is not robustly supported by the goodness of fit data submitted by the company.

2.4 End of Life

The ACD concluded that tisagenlecleucel does not meet the criteria to be considered a life-extending treatment at the end of life. The committee based this decision on the fact that the mean overall survival estimated for salvage chemotherapy from the model using the committee's preferred data source was considerably greater than 24 months. The ACD, however, recognised the limitations of all the potential data sources for the comparator arm.

The ACD acknowledged the potential inconsistency with a recent appraisal in the same population where end-of-life criteria had been considered to be met (see NICE's technology appraisal guidance on axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma), but notes that the survival modelling approach and data sources for salvage chemotherapy were very different.

The company response document reiterates that the decision not to grant "*end of life status*" is inconsistent with the appraisal for axicabtagene ciloleucel (henceforth referred to as axi-cel) in the same indication. The company recognised that only a small proportion that have longer term survival which leads to an important difference between the mean and median survival estimates. However, the company argues life-expectancy for the majority of patients (>80%) with relapsed/refractory DLBCL after two or more lines of therapy is less than 24 months. The median OS predicted in the company's revised base case model is approximately 4 months.

The ERG notes that the company has not presented new evidence to support the claim to meet the end of life criteria. However, the ERG supports the company's claim for end of life. The critical feature that makes the median OS so different to the mean OS also applies here. This relates to the fact that a

large proportion of patients have a short life expectancy (in modelling the CORAL extension study data, 86% are expected to die within 24 months), and the remaining patients have an extremely high life expectancy (reflecting the potential for cure from SCT). For this reason, the estimate of mean OS (the basis for the end of life criterion at stake here) is very sensitive to extrapolation assumptions that affect the life expectancy of the remainder cured. The company argues that the mean OS estimate is skewed towards these 14% -- on the contrary, the mean OS estimate must reflect the favourable life expectancy of the 14% -- however, the particular circumstances of the appraisal (the possibility of cure, with large difference in life expectancy between cured and not cured) mean that the OS estimate is heavily dependent on, and very sensitive to, the extrapolation assumptions. In other words, mean OS estimates are driven by the model predictions that a small proportion of patients will experience long term survival with current treatment options. The ERG considers that the uncertainty surrounding these longer term survival estimates should hence be taken into consideration. It should be considered that, using CORAL data, there is significant uncertainty over whether the mean OS for the salvage chemotherapy arm is below or above 24 months.

As a consequence of basing lifetime extrapolations on censored survival data, inevitably the clinical appropriateness and robustness of the subsequent predictions need to be carefully considered. There are three key sources of uncertainty surrounding the extrapolations for the salvage chemotherapy arm: i) the data source, ii) the fitting of distributions, and iii) the % of patients that would receive an SCT.

To illustrate the implications of uncertainty in the extrapolation, the ERG looked more closely at the implications of uncertainty surrounding the choice of distribution to model OS for salvage chemotherapy (item ii) of the three sources of uncertainty mentioned above).Whilst we do not aim to challenge here the choice of distribution in the ACD, we will estimate the undiscounted life years using a range of alternative distributions to illustrate the implications of uncertainty. These are summarised in

Table 7. In the ACD, the Gompertz distribution was considered as the best fitting model for the OS extrapolation of salvage chemotherapy.

Table 7: Undiscounted life-years for salvage chemotherapy using alternative distributions

OS distribution for salvage chemotherapy*	**Undiscounted Life Years (mean)**
Gompertz (base case)	3.41
Exponential	0.85
Generalised Gamma	1.31
Log logistic	1.92
Lognormal	1.95
Weibull	1.14

Table 7 clearly shows that the undiscounted life year estimates for salvage chemotherapy appear extremely sensitive to the choice of survival function, with estimates ranging from 0.85 to 3.41 years. The ERG notes that the Gompertz chosen in the ACD predicts significantly longer mean survival compared to the other distributions. The ERG also notes that 5 of the 6 distributions result in estimates of mean life years less than 24 months.

In summary, the disparity between median and mean OS estimates for salvage chemotherapy highlight a specific feature of the population where a high proportion is expected to have very small life expectancy and the remaining a very high life expectancy (consistent with cure after SCT). This means that the estimates of OS benefits are particularly sensitive to the extrapolation assumptions, which create additional uncertainty over the OS estimate. The ERG analyses showed that while the majority of patients survive less than 24 months, whether mean OS is below or above 24 months is highly uncertain. This should be considered when discussing whether end of life is appropriate.

3 Conclusions

The ERG provided commentary and validity checks on the additional analyses submitted by the company in response to the ACD. These pertained to the following topics and the ERG's conclusions on each were:

1) New data cut from the JULIET trial (May 2018 cut off).

The updated May 2018 data cut results for the JULIET study are broadly consistent with those for December 2017. The new data cut includes [redacted] new patients and extends the median follow-up by approximately less than [redacted], however, the results are nevertheless still too immature to yield reliable estimates of longer-term survival rates. The use of the latest data cut (May 2018) in the cost-effectiveness model reflecting the ACD's stated preferences leads to a reduction in the ICER (from £93,862 to £79,839 per additional QALY), driven by small differences in the extrapolation of the OS for tisagenlecleucel.

2) Revised fitting to the new JULIET data cut, and assumptions over the cure point.

The company proposed the use of a different parametric function (Gompertz) to the one preferred in the original appraisal. The ERG determined that the fit of this function to the observed data is similar to that of the distribution preferred in the ACD (a one-knot spline function). However, the Gompertz generates much higher predictions of the proportion of patients alive in the extrapolation period, showing a plateau [redacted]. The ERG considers that, given the significant uncertainty in the later part of the observed OS curve (due to the very small number of patients being followed-up at that stage), the possibility of late relapses happening needs to be retained. For these reasons, the ERG has concerns that the use of the Gompertz may overestimate the proportion of patients alive when treated with tisagenlecleucel.

Critically, the company also proposed 2 new scenarios on the cure time point of the 'hybrid' model and the SMR used, identified as key uncertainties in the ACD. The two scenarios consider a 2 year and a 3 year cure point and no excess mortality after those timepoints (SMR=1). The ERG re-iterates the finding from the Howlader et al. (2017) study that suggests that it is only from five years post-diagnosis onward that no statistically significant excess mortality can be identified for DLBCL patients. Given this evidence, the company's new analyses can be seen as optimistic. The ERG presents additional analyses for cure at 3 and 4 years and SMR of 1.09, to support the committee's decision making if required.

3) Extrapolation of CORAL extension study survival data.

The committee considered the CORAL extension study, modelled separately for individuals with and without SCT, an appropriate data source of effectiveness for the comparator arm (ACD, section 3.8). The committee agreed with the use of the Gompertz distribution to model both. In response to the ACD the company challenges the choice of the Gompertz, only for the non-SCT group and argues for a two-knots spline model leading to lower mean OS predictions for salvage chemotherapy than the Gompertz. In validating the fit statistics the ERG found that, visually, the Gompertz still provides better fit to the two-spline model. Hence the ERG considers that the Gompertz distribution is the most appropriate extrapolation model for the 'no SCT' OS curve.

4) Company's alternative approach to model the effectiveness of salvage chemotherapy.

While the committee considered the CORAL extension study an appropriate data source of effectiveness for the comparator arm (ACD, section 3.8), it also recognised the limitations of this data source to inform the effectiveness of the comparator arm. The company sought to address this limitation by combining the effectiveness data from the CORAL extension study with that of the HMRN for those patients with DLBCL who received a 4th and 5th line of treatment. The ERG recognises the company's attempt to incorporate a potentially relevant source of effectiveness data for salvage chemotherapy. However, no information was provided on the features of the dataset and on the patients included in analyses. It is hence impossible to assess whether the subset of patients analysed from the HMRN database would have been eligible for treatment with tisagenlecleucel.

The ERG presents a revised base-case analysis (using the new JULIET data cut, re-digitised CORAL curves and presents new scenarios for the alternative cure cut time points). The ERG considers that the response of the company to the ACD did not provide any new evidence that could resolve the critical uncertainties identified at the original appraisal and discussed by the committee (as per ACD). Uncertainty over the clinical effectiveness and OS implications of the treatment (arising from the uncontrolled nature of the clinical study and the uncertainty in the extrapolations) still remain the main weaknesses and areas of uncertainty identified by the ERG.

As highlighted in the ACD, there are many similarities between this appraisal and the ongoing appraisal on axi-cel. The ACD considered the populations and the interventions covered similar.

Critically, the outcomes observed in the clinical studies are also comparable: the ZUMA study for axi-cel showed approximately 50% of patients alive at 18 months and no further deaths in the study until the end of follow-up at 27 months (Neelapu et al, 2017). The pooled tisagenlecleucel data suggests a comparable proportion of patients alive at 24 months of around 40%. Hence, considerations on the value for money of axi-cel should have implications for committee decisions on tisagenlecleucel, particularly if their prices differ.

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Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma

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

Produced by	Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE)
Date	19/10/18

Background

This appendix reports the results of additional analyses requested by the NICE technical team prior to the second appraisal committee meeting for tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma.

Additional analyses requested by the NICE technical team

The NICE technical team requested that the company's revised base case (Company's response to ACD) were replicated assuming an additional cure timepoint (4 years) after which overall survival (OS) estimates are derived from general population mortality data. Table 1 summarises the cost-effectiveness results of this analysis (Table 1, Analysis 1-6), with and without excess mortality (standardised mortality rate [SMR] equal to 1.09 and 1.00, respectively) applied to general population survival rates after the point of cure. The table also presents scenario analyses (Table 1, Analysis 7-12) for the same set of assumptions on cure and using the company's preferred approach to model the CORAL extension study data. Results presented in this document are deterministic and include the company's proposed patient access scheme discount ([redacted]) to tisagenlecleucel list price.

The ERG reiterates that the use of Haematological Malignancy Research Network (HMNR) data in the company's base case may introduce bias of unknown size and direction in the cost-effectiveness estimates, and its use in the model could not be appropriately validated by the ERG.

Table 1 Cost-effectiveness results for tisagenlecleucel compared to salvage chemotherapy – additional analyses

Analysis*	Tisagenlecleucel OS approach**	Salvage chemotherapy OS approach	Incremental Costs	Incremental QALYs	ICER (per QALY)
1	Single knot spline + cure at 4 years, SMR=1.00	Combined OS: • CORAL extension study*** - SCT curve – Gompertz - No SCT – two knots spline • HMRN	[redacted]	[redacted]	£58,282
2	Single knot spline + cure at 4 years, SMR=1.09		[redacted]	[redacted]	£59,231
3	Single knot spline + cure at 5 years, SMR=1.00		[redacted]	[redacted]	£62,658
4	Gompertz + cure at 4 years, SMR=1.00		[redacted]	[redacted]	£53,414
5	Gompertz +cure at 4 years, SMR=1.09		[redacted]	[redacted]	£54,287
6	Gompertz + cure at 5 years, SMR=1.00		[redacted]	[redacted]	£53,834
7	Single knot spline + cure at 4 years, SMR=1.00	CORAL extension study • SCT curve – Gompertz • No SCT – two knots spline	[redacted]	[redacted]	£65,342
8	Single knot spline + cure at 4 years, SMR=1.09		[redacted]	[redacted]	£66,666
9	Single knot spline + cure at 5 years, SMR=1.00		[redacted]	[redacted]	£70,411
10	Gompertz + cure at 4 years, SMR=1.00		[redacted]	[redacted]	£59,175
11	Gompertz +cure at 4 years, SMR=1.09		[redacted]	[redacted]	£60,280
12	Gompertz + cure at 5 years, SMR=1.00		[redacted]	[redacted]	£59,067

HMRN, Haematological Malignancy Research Network; OS, overall survival; SCT, stem cell transplant, SMR, standardised mortality rate.

*Assumes health state costs and utilities become the same as for PFS after the point of cure, **OS based on i) extrapolation of pooled JULIET (May 2018) and Schuster 2017 data with a parametric model up to point of cure, and ii) after on the general population mortality affected by a SMR, ***SCT and no SCT curves weighted assuming a 12.5% rate of SCT.

Single Technology Appraisal (STA)

Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [ID1166]

ERG validity check of the company's analyses submitted after the second appraisal committee meeting

Produced by Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE)

Date 31/10/18

Note on the text

All commercial-in-confidence (CIC) data and academic-in-confidence (AIC) data are redacted

The Evidence Review Group (ERG) was requested by NICE to provide validity checks on the additional analyses submitted by the company after the second appraisal committee meeting. The company's additional analyses include:

1. The assumptions preferred by the Committee at the first appraisal meeting (see Appraisal Consultation Document [ACD]);
2. New data cut from the JULIET trial (May 2018 cut off);
3. 'Hybrid' one-knot spline model followed by general population mortality after the point of cure to extrapolate overall survival (OS) of tisagenlecleucel;
4. Excess mortality applied to survival estimates (parameterised using a standardised mortality ratio [SMR] = 1.09) beyond 2 to 4 year cure points;
5. Salvage chemotherapy OS modelled using only CORAL extension study data (company re-digitised curves) weighted by rate of subsequent stem cell transplant (SCT);
6. Extrapolation of salvage chemotherapy curves with the Gompertz distribution for both 'SCT and 'no SCT' groups in the CORAL extension study;
7. Health state costs and health-related quality of life (HRQoL) become the same as for progression free survival after the point of cure for tisagenlecleucel and salvage chemotherapy;
8. The company's proposed patient access scheme (PAS) discount over tisagenlecleucel's list price ([redacted] and an additional Cancer Drugs Fund (CDF) rebate [redacted]) resulting in an overall discount of [redacted].

The ERG checked the implementation of these changes and successfully replicated the results presented by the company. The deterministic cost-effectiveness results of the company scenario analysis are presented without the CDF additional rebate on Table 1 (scenarios 2 to 4) and including it on Table 2 (scenarios 2 to 4).

Table 1 Additional cost-effectiveness results with PAS discount

#	Scenario – tisagenlecleucel OS extrapolation	Δ Costs	Δ QALYs	ICER with current PAS ([redacted])
2	1-knot spline and SMR=1.09 after 2 years	[redacted]	[redacted]	£56,509
3	1-knot spline and SMR=1.09 after 3 years	[redacted]	[redacted]	£65,836
4	1-knot spline and SMR=1.09 after 4 years	[redacted]	[redacted]	£73,286
5	Mixture-cure (lognormal) and cure* after 4 years	[redacted]	[redacted]	£61,572

Table 2 Additional cost-effectiveness results with PAS discount and CDF rebate

#	Scenario – tisagenlecleucel OS extrapolation	Δ Costs	Δ QALYs	ICER with current PAS ([redacted]) + CDF rebate ([redacted])
2	1-knot spline and SMR=1.09 after 2 years	[redacted]	[redacted]	£42,991
3	1-knot spline and SMR=1.09 after 3 years	[redacted]	[redacted]	£49,963
4	1-knot spline and SMR=1.09 after 4 years	[redacted]	[redacted]	£55,403
5	Mixture-cure (lognormal) and cure* after 4 years	[redacted]	[redacted]	£46,621

*assumes costs and HRQoL are the same as PFS for both treatment groups beyond cure point

The ERG conducted one additional scenario analysis whereby the tisagenlecleucel OS extrapolation was performed using a mixture-cure model (with lognormal distribution) and health state costs and HRQoL are assumed the same as for PFS beyond 4 years for both tisagenlecleucel and salvage chemotherapy (scenario 5, Table 1 and 2).

When the additional CDF rebate is applied, the incremental cost-effectiveness ratios (ICERs) for all scenario analyses lie below the £50,000 per QALY cost-effectiveness threshold, except for the scenario which assumes cure at 4 years and applies the 'hybrid' extrapolation model for tisagenlecleucel OS. However, the scenario applying the mixture-cure model with equivalent assumptions on time of cure (4 years) yields a more favourable ICER of £46,621 per QALY. The ERG reiterates that mixture-cure model remains a clinically plausible approach alongside the 'hybrid' model.