NICE National Institute for Health and Care Excellence

Slides for public [Redacted]

Tisagenlecleucel for treating relapsed or refractory DLBCL after 2 or more systemic therapies [ID1166]

Chair's presentation

2nd appraisal committee meeting

Committee C, 23rd October 2018

Lead team: Matt Stevenson, Alex Cale & Judith Wardle

ERG: York

NICE technical team: Abi Senthinathan and Alex Filby

Company: Novartis

Key issues

- Is it appropriate to use updated (May 2018) data from JULIET for tisagen arm?
  - Most appropriate extrapolation for tisagen?
  - What should the cure point be?
- Which data source(s) should be used to model survival in comparator arm?
  - Most appropriate extrapolation for the comparator arm?
- Are end of life criteria met?
- Most plausible ICER?
- CDF considerations?

[redacted]

Tisagenlecleucel (Novartis)

Mechanism of action	A chimeric antigen receptor (CAR) T cell therapy that uses autologous T cells engineered to express a novel surface receptor directed against the tumour antigen CD19
Administration and dosage	• Patients T cells are extracted via leukapheresis • Patient can receive bridging chemotherapy between leukapheresis and infusion at the discretion of the treating physician • Patient receives preparative low dose lymphodepleting regimen before infusion • Genetically altered T cells are administered as a one time, single dose intravenous infusion • Tocilizumab and emergency equipment must be available prior to infusion of tisagenlecleucel and during the recovery period
Marketing authorisation	Marketing authorisation: 'Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.'
List price	£282,000, commercial arrangement (simple discount patient access scheme - commercial in confidence)

[redacted] Source: Table 2 in company submission

Key results for tisagen: JULIET & Schuster (2017)

- JULIET single-arm open label RCT (all previously treated with rituximab)
- Schuster (2017) case series in USA
- Trial population: Patients who could not have autologous stem cell transplant or whose disease had not responded to it. ECOG 0 to 1.

	JULIET (n=111 Dec 2017 data cut)	Schuster 2017 (n=14)
Overall survival	Median 11.7 months (6.6 to not estimable)	22.2 months (NR)
Median progression-free survival (months)	Censored†: [redacted] months ([redacted]) Not censored: [redacted] months ([redacted])	3.2 months (0.9 to not reached)
Event-free survival*	Median [redacted] months ([redacted])	N/A

*defined as the time from infusion to the earliest of: death due to any cause, disease progression/relapse, new anticancer therapy (including subsequent SCT, censored at time of SCT). [redacted]censoring for starting a new anti-cancer therapy & [redacted] censoring for subsequent SCT.
†investigator assessed, events were censored at the time of SCT after tisagenlecleucel infusion.

[redacted]

Key committee considerations in ACD (1)

Issue	Committee consideration
Treatment pathway	• Not appropriate to position tisagenlecleucel for people who cannot have stem cell transplant because this group cannot easily be defined. • Need to consider population in full anticipated marketing authorisation.
Clinical effectiveness	• Evidence for tisagenlecleucel is from single-arm study so benefit compared with salvage chemotherapy is uncertain • Reasonable to use unadjusted pooled data from JULIET & Schuster (2017) • CORAL extension most appropriate data for salvage chemotherapy • Unadjusted naïve indirect comparison acceptable but ↑ uncertainty around benefit with tisagenlecleucel
Survival: tisagen	• company's hybrid survival model and a cure point between 2 and 5 years was the most clinically plausible
Survival: salvage chemo	• Appropriate to use CORAL extension & assume 12.5% have SCT • Model OS and PFS using single parametric model (Gompertz curve)
Other	• ERG changes to resource use and costs are appropriate • Utility values and costs should be in line with assumed cure point

Key committee considerations in ACD (2)

Issue	Committee consideration
Most plausible ICER ACM 1	• Company scenario (hybrid model, cure point after 2 years & no SCT) around £54,000 per QALY gained • Most plausible ICER ↑ if take into account SCT, later cure point & probabilistic analyses
Committee preferred assumptions	• **Hybrid survival model (general population mortality between 2 to 5 years)** • **Utility values and costs consistent with assumed cure point** • **CORAL data for comparator assuming 12.5% had subsequent SCT**
End of life	• short expectancy criterion not met when using predicted mean OS from CORAL • OS model predictions > 3 months
CDF	• company did not make a case for CDF • ICERs too high, tisagen does not have plausible potential to be cost effective • long-term data on disease progression after treatment with tisagen would help to address the uncertainties around the survival benefit
Conclusion	• most plausible ICER above range normally considered to be a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

ACD Preliminary Recommendation

Tisagenlecleucel is not recommended, within its marketing authorisation, for treating relapsed or refractory diffuse large B-cell lymphoma in adults after 2 or more systemic therapies.

[redacted]

ACD comments (1)

- 5 responses: Bloodwise, Royal College of Pathologists and British Society of Haematology (RCP-BSH), Lymphoma Action, NHSE, company (revised base case). No web comments.

Issue	Comments
Rare disease & cure	**Lymphoma Action**: does not take sufficient account of the rarity of the indication. Clinical trials are small because population fit enough for treatment is small. ACD denies patients' access to the only treatment that may offer a potential cure.
End of life	**Bloodwise:** need to assess EOL consistently compared with axicabtagene **RCP-BSH**: do not agree that EOL is not met → majority have exhausted all valid treatment options and have a limited life expectancy of few to several months. 35 to 40% chance of long term survival is significant advance in this group. **Company**: • tisagenlecleucel meets the EOL criteria given that life-expectancy for majority of patients (>80%) after two or more lines of therapy is less than 24 months. • Decision inconsistent with other appraisals • Unpredictability around mean

[redacted]

ACD comments (2)

Issue	Comments
Comparator	**NHSE**: not appropriate to include 4th and 5th line treatment as tisagen will replace 3rd line treatment → inclusion of HMRN data is not relevant and large proportion of comparator population in company's revised base case is not correct.
Long-term effects	**NHSE**: PFS and OS data still immature. Reasonable to assume excess mortality risk only disappears after 5 years
CDF	**Bloodwise:** CDF would allow direct evidence to be collected **Lymphoma Action:** would enable more robust data to be gathered whilst offering a lifeline to those patients who are most likely to benefit **NHSE:** ideal candidate for CDF with potentially great impact on outcomes but data is immature → will allow trial data to mature & collection of real word data to help address uncertainties **Company**: acknowledge uncertainty due to short follow-up → tisagen good candidate

[redacted]

Committee preferences and company's new analysis

Committee preference:	Did company include?	Revised base case
Hybrid survival model for tisagenlecleucel (general population mortality after 2 to 5 years)	✓ **(partially)**	• Use updated JULIET data but only include general population mortality after 2/3 years (4/5 years not reported) • PFS extrapolation: 3 knot spline
Utility values and costs consistent with assumed cure point (between 2 to 5 years)	✓	• Include 'long-term survivor' costs & utilities consistent with cure point
CORAL data for comparator: • weighted approach for 'SCT' & 'no SCT' • single Gompertz curve • 12.5% had subsequent SCT	✓	• Yes but include combined CORAL (3rd line) & HMRN (4th and later line) • CORAL 'no SCT'→ 2 knot spline • Scenarios with CORAL data only
• Cover full MA population	✓	• CORAL includes 'SCT' and 'no SCT'

[redacted]

Recap of company's ACM 1 evidence: tisagen OS data from JULIET (Dec 2017 data cut)

- Company used meta-analysis for tisagen (N=125, JULIET n=111, Schuster n=14)
- Median OS follow-up [redacted] months (JULIET)

ERG: 'plateau' is based on small numbers of patients at risk. Committee noted in ACD 'from month 20 there were very few patients at risk so the tails of survival curves highly uncertain'

[redacted]

Company's new evidence: tisagen
Updated OS data from JULIET (May 2018)

[redacted]

Company:
- May 2018 data consistent with Dec 2017 (emerging plateau for OS & PFS)
- New data include [redacted] more patients (from Japan & had tisagen since Dec 2017)
- Median OS follow up [redacted] months (max OS follow up [redacted] months)

ERG: Only small difference in median OS follow up ([redacted]). After 24 months number of patients at risk still very low therefore data too immature to reliably estimate long-term survival

Company's new evidence: tisagen
Updated PFS data from JULIET (May 2018)

Company's new evidence: tisagen

PFS extrapolation (May 2018)

[redacted]

Company's new evidence: tisagen
OS extrapolation May 2018 (SMR=1.0)

2 year cure point

3 year cure point

Tisagenlecleucel (observed) — 1-knot spline — Gompertz

Committee preference: 1 knot spline, cure point after 2 to 5 years (ACD: 2 year cure point is optimistic & 5 years is pessimistic. 4 and 5 year cure not reported by company

Company's new evidence: tisagen
ERG comments

[redacted]

ERG:

- Using May 2018 data ↓ ICER for ERG base case (approx. £14,000), this is driven by OS extrapolation as incremental QALYs ↑
- median and maximum follow-up of updated JULIET data still too short to exclude possibility of late relapse
- Gompertz to model OS may overestimate survival, especially later cure points
- SMR=1.00 excludes possibility of excess mortality after cure

[redacted]

Company's new evidence: comparator
HMRN data source for OS & PFS

ACD: committee aware of 2 other possible comparator data sources: a subpopulation of ORCHARRD and the HMRN → not included in the company or ERG analyses.

- **Company**: CORAL extension (n=203) is 3rd line population & only reflects 50% of full population *(after 2 or more systemic treatments)*
  - likely to reflect fitter population who have better outcomes, this is confirmed by one of authors of CORAL extension.
  - Mean OS of 43 months not reflective of clinical outcomes in patients having salvage chemotherapy after 2 or more lines of systemic therapy
- HMRN database covers an ongoing, UK population-based cohort, ('real-world' evidence) used for 4th and later line
  - 'median follow-up was [redacted] years (range: [redacted])

Line of therapy	Median OS, years (95% CI)	% alive (95% CI)			Median PFS, years (95% CI)
		6 months	1 year	2 years	
4th line (N=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5th line (N=[redacted])	[redacted]	Not reported	Not reported	Not reported	Not reported

Company's new evidence: comparator HMRN baseline characteristics

Company

- 3,329 patients were newly diagnosed with DLBCL between 2004–2015
- Baseline data only available for [redacted] new cases
- Patient characteristics at each subsequent line of therapy not available from HMRN analysis

ERG:

- Company do not present baseline characteristics for the [redacted] patients included for 4th and 5th line treatment, therefore cannot assess if eligible for tisagen.
  - Baseline data of the [redacted] patients provided not relevant → includes all cases of DLBCL (can't assess if comparable to JULIET & size/direction of bias)
  - Unable to verify if extrapolations were appropriate using company data
- Using HMRN data has large impact on ICER
- ERG do not include HMRN data from company in revised analyses

[redacted]

Company's new evidence: comparator OS extrapolation for HMRN

4th line treatment

5th line treatment

Company's revised base case:

- Lognormal curve for 4th line HMRN
- Weibull curve for 5th line HMRN
- Weighted curve using CORAL & HMRN (slide 21)

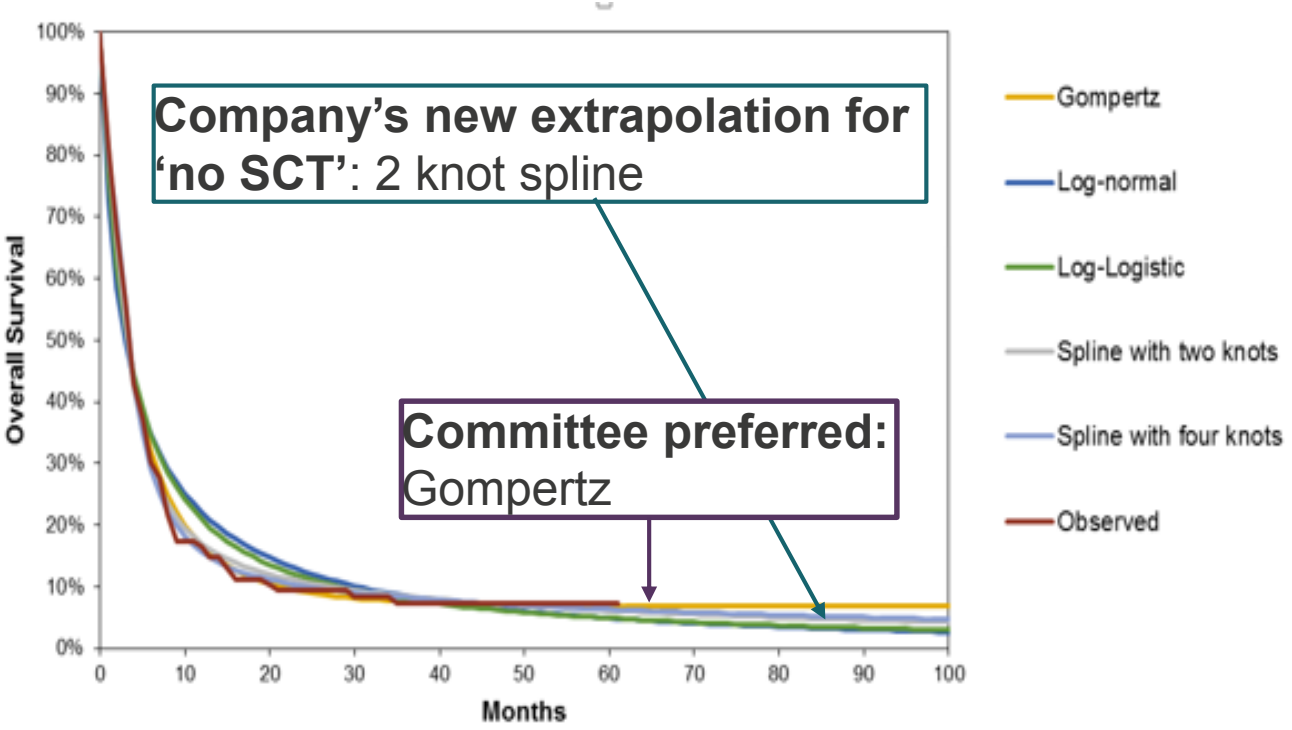
Company's new evidence: comparator CORAL data

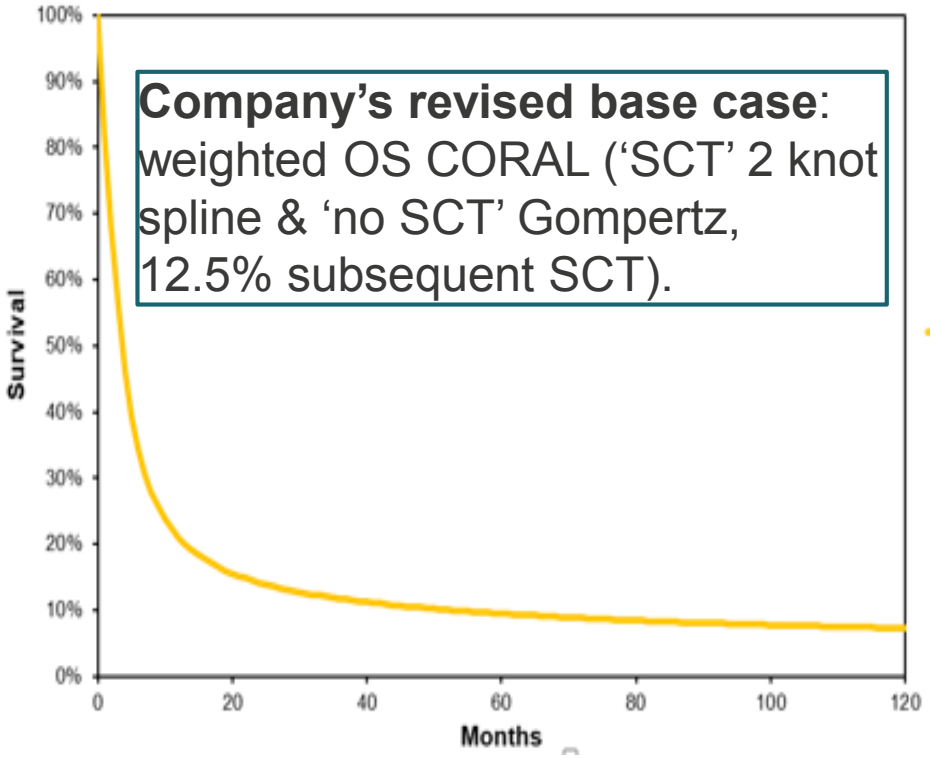
Committee preference in ACD: weighted OS combining SCT and no SCT data from CORAL extension (assuming 12.5% have subsequent SCT) and single Gompertz curve to extrapolate survival

- **Company**: Gompertz likely to overestimate survival in 'no SCT' group
  - Gompertz produces plateau in survival → not expected for 'no SCT' group given that treatment would be given with palliative intent
  - possibility of a potential 'cure'/long-term survival for the salvage chemotherapy already accounted for in 'SCT' group (Gompertz is more plausible for this group)
  - 2 knot spline for 'no SCT' group gives good statistical fit and long-term survival that is more clinically plausible

- **ERG:** Gompertz still provides best fit for 'no SCT' curve
  - Not able to re-estimate extrapolations based on company's re-digitised curves (not submitted by company)
  - Company's re-digitised curves provide more precise prediction of survival plateau **ERG analyses**: Gompertz for both 'SCT' & 'no SCT', use company re-digitised data

Company's new evidence: comparator CORAL OS extrapolation for 'no SCT'

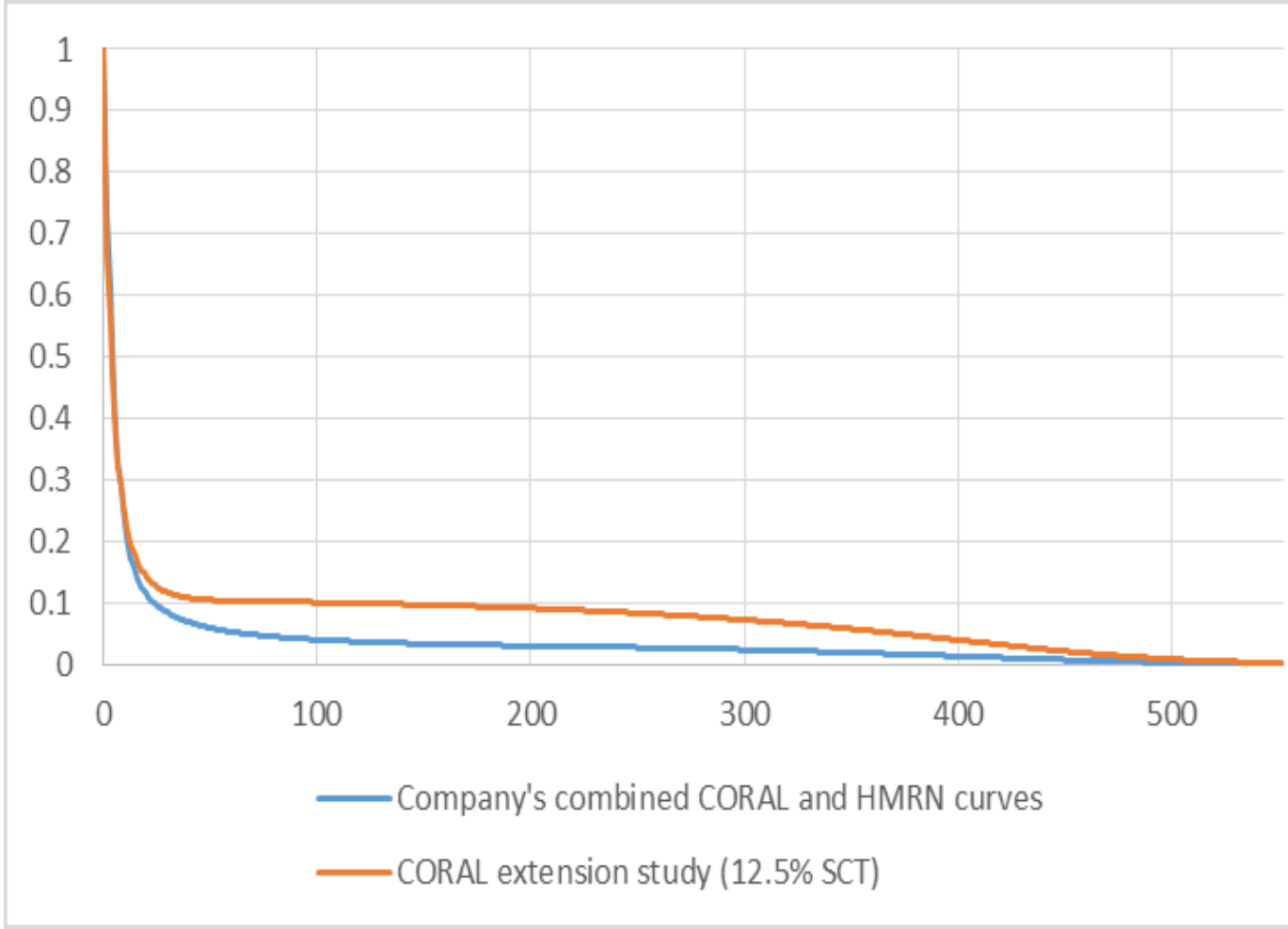




Company scenarios: CORAL data only for comparator arm & committee preferred extrapolation: Gompertz for both 'SCT' and 'no SCT'

[redacted]

Company's new evidence: comparator ERG comments



ERG:

- Company's revised base case using combined CORAL & HMRN data may provide optimistic ICERs because:
  - HMRN may introduce bias of unknown size and direction
  - Only include 2/3 year cure point
  - Exclude excess mortality
  - Extrapolation for 'No SCT' in CORAL not robustly supported by goodness of fit data

[redacted]

End of life considerations

ACD: committee concluded tisagenlecleucel does not meet short life expectancy criterion when using CORAL as comparator data source

Company:

- Majority of patients die within 24 months (see table below). This was acknowledged in axicabtagene in virtually the same patient population.
- Mean misleading due to poor data source (CORAL alone) and skewed by small % of cured patients

Scenario	Median OS	Predicted Mean OS	% 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 (2 knot spline for 'no SCT')	4.00	33.10	34	21	14	12	10	10
3: Company's revised base case (combined CORAL & HMRN)	5.00	20.40	38	19	10	7	6	5

[redacted]

End of life considerations

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3: Company's revised base case (combined CORAL & HMRN)	5.00	20.40	38	19	10	7	6	5

Mean OS driven by model predictions that small proportion will have long-term survival with current treatments (there is uncertainty in long-term survival in CORAL).

ERG: ERG exploration show undiscounted life year range from 0.85 (exponential) to 3.41 (Gompertz) for salvage chemo using alternative OS distributions

Summary of company & ERG revised analyses

	Company revised base case A	ERG preferred analyses
Tisagen survival modelling	• Hybrid 1-knot spline using May 2018 data from JULIET • 3-knot spline for PFS	Hybrid 1-knot spline using May 2018 data from JULIET for OS and PFS
Salvage chemo survival modelling	• CORAL & HMRN • 2-knot spline to extrapolate 'no SCT' in CORAL • re-digitised CORAL curves	• CORAL only • Gompertz to extrapolate both groups • re-digitised CORAL curves
Cure point	2 years (3 years also reported)	2 to 5 years
Excess mortality after cure for tisagen	No, SMR=1	Yes, SMR=1.00 or 1.09
Note: both company and ERG include committee preferred costs and HRQoL		

[redacted]

Company revised base case (PAS)
CORAL & HMRN for comparator arm

	Scenario	Δ Costs	Δ QALYs	ICER with alternative cure points
Company's revised base case A (updated JULIET)				
1	• **Tisagen 'hybrid' model (1 knot spline)** ***committee preferred in ACD*** • CORAL (use 2 knot spline for 'no SCT') & HMRN for comparator	[redacted]	[redacted]	2 year cure: £46,325 3 year cure: £53,021
ERG exploratory analyses (company base case A)				
2	• 4 year cure & no excess mortality (SMR=1.00) • 4 year cure & excess mortality (SMR=1.09) • 5 year cure & no excess mortality (SMR=1.00)	[redacted]	[redacted]	4 year: £58,282 4 year: £59,231 5 year: £62,658
Company's revised base case B				
3	Base case A + tisagen 'hybrid' model (Gompertz)	[redacted]	[redacted]	2 year cure: £46,901 3 year cure: £51,773
ERG exploratory analyses (company base case B)				
4	• 4 year cure & no excess mortality (SMR=1.00) • 4 year cure & excess mortality (SMR=1.09) • 5 year cure & no excess mortality (SMR=1.00)	[redacted]	[redacted]	4 year: £53,414 4 year: £54,287 5 year: £53,834

[redacted]

Company revised scenario analyses (PAS)
CORAL alone for comparator arm

	Scenario	Δ Costs	Δ QALYs	ICER with alternative cure points
1	Company scenario 1A • **CORAL data only + committee preferred Gompertz to extrapolate both groups *(committee preferred in ACD)***	[redacted]	[redacted]	2 year cure: £56,356 3 year cure: £65,822
2	Company scenario 1B Scenario 1A + tisagen 'hybrid' model (Gompertz)	[redacted]	[redacted]	2 year cure: £57,210 3 year cure: £63,858
3	Company scenario 2A • CORAL data only + company's preferred 2 knot spline to extrapolate 'no SCT' group	[redacted]	[redacted]	2 year cure: £51,644 3 year cure: £59,386
ERG exploratory analyses (company scenario 2A)				
4	• 4 year cure & no excess mortality (SMR=1.00) • 4 year cure & excess mortality (SMR=1.09) • 5 year cure & no excess mortality (SMR=1.00)	[redacted]	[redacted]	4 year: £65,342 4 year: £66,666 5 year: £70,411
5	Company scenario 2B Scenario 2A + tisagen 'hybrid' model (Gompertz)	[redacted]	[redacted]	2 year cure: £52,362 3 year cure: £57,789
ERG exploratory analyses (company scenario 2B)				
6	• 4 year cure & no excess mortality (SMR=1.00) • 4 year cure & excess mortality (SMR=1.09) • 5 year cure & no excess mortality (SMR=1.00)	[redacted]	[redacted]	4 year: £59,175 4 year: £60,280 5 year: £59,067

ERG exploratory analyses

- ERG preferred analyses include:
  - Committee-preferred costs and HRQoL from ACD
  - May 2018 JULIET data
  - CORAL re-digitised extension data alone to extrapolate OS (Gompertz curve for 'SCT' and 'no SCT')

	Scenario	Δ Costs	Δ QALYs	ICER
ERG preferred analyses (re-digitised OS curves from CORAL)				
1	Mixture cure lognormal and cure at 5 years	[redacted]	[redacted]	£61,007
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	1-knot spline and SMR=1.09 after 5 years	[redacted]	[redacted]	£77,895

[redacted]

CDF considerations

Starting point: drug not recommended for routine use due to **clinical uncertainty**

1. Is the model structurally robust for decision making? (omitting the clinical uncertainty)

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data? & 5. Is CDF data collection via SACT relevant and feasible?

Consider recommending entry into CDF (invite company to submit CDF proposal)

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required , and number of patients in NHS in England needed to collect data.

[redacted]

- Company's ACD response: '*acknowledge the uncertainty due to the relatively short-term follow-up data, tisagen, represents a good candidate for CDF'*
- No CDF proposal submitted by company
- JULET ongoing, no other ongoing trials identified
- Areas of uncertainty in ACD
  - OS data (immature)
  - Use of allogenic stem cell transplant

Key issues

- Is it appropriate to use updated (May 2018) data from JULIET for tisagen arm?
  - Most appropriate extrapolation for tisagen?
  - What should the cure point be?
- Which data source(s) should be used to model survival in comparator arm?
  - Most appropriate extrapolation for the comparator arm?
- Are end of life criteria met?
- Most plausible ICER?
- CDF considerations?

[redacted]