YONDELIS® (TRABECTEDIN) FOR THE TREATMENT OF SOFT TISSUE SARCOMA

RESPONSE TO EVIDENCE REVIEW GROUP QUERIES (16th March 2009)

30th MARCH 2009

Trabectedin for the treatment of advanced metastatic soft tissue sarcoma

Literature search	
Ref	Clarification point
A1	Please provide a search strategy for the clinical effectiveness searches in MEDLINE, EMBASE, and COCHRANE

Please see the supplied search strategies. These were omitted from section 10.3.4 in error.

Search for clinical evidence

MEDLINE and EMBASE search:

The name of the database searched: MEDLINE and EMBASE
The name of the host/system used: EMBASE.com
The date when the search was run: 20/1/2009
The years covered by the search: all - no restrictions

#	Term	Hits
1	Yondelis/exp	354
2	Yondelis:ti,ab,de	70
3	trabectedin/exp	336
4	trabectedin:ti,ab,de	356
5	ecteinascidin 743'/exp	336
6	ecteinascidin 743':ti,ab,de	264
7	et 743'/exp	336
8	et 743':ti,ab,de	187
9	et743/exp	336
10	et743:ti,ab,de	187
11	OR:1-10	578
12	soft tissue sarcoma'/exp	6,178
13	soft tissue sarcoma':ti,ab,de	7,575
14	sts/exp	6,134
15	sts:ti,ab,de	5,071
16	soft part sarcoma'/exp	6,178
17	soft part sarcoma':ti,ab,de	564
18	OR:12-17	13,514
19	11 AND 18	136
20	11 AND 18 AND [humans]/lim	132

Cochrane library search:

The name of the database searched: Cochrane library;
The date when the search was run: 27/1/2009;
The years covered by the search: 1800-2009

#	Term	Hits
1	(Yondelis) or (trabectedin) or (ecteinascidin)	5
2	(soft tissue sarcoma) or (sts) or (soft part sarcoma)	392
3	#1 AND #2	2

A2	i) Please explain the choice to search MEDLINE and EMBASE together via EMBASe.com rather than to search each separately. ii) Please clarify whether EMBASE.com can ensure consistency when mapping MeSH terms to EMTREE terms? iii) Please clarify whether searching EMBASE and MEDLINE separately give the same results minus MEDLINE duplicates as searching EMBASE.com?
	i) EMBASE.com was selected as the platform to search EMBASE and MEDLINE as it is possible to search both databases with a single search string. This saves time when running searches, an important business consideration when the decision was made to subscribe to a searchable database service. Regarding the additional questions of consistency, these were forwarded to EMBASE who supplied the following answers – *ii) When searching EMBASE.com with a MESH term, this term will be mapped to the EMTREE term (all MESH terms have already been added to EMTREE) so the results are comparable but the tree structures do differ so if you explode your search, there may be some differences in your search results.* *iii). When we add MEDLINE to EMBASE.com, we map the MEDLINE indexing to EMBASE indexing and so it is difficult to compare the searches directly. Due to the difference in indexing, you often do not get exactly the same number of results. You should however be able to compare the relevancy of your results.* Bearing the responses from EMBASE in mind and subsequent searches (see A3 below) it is felt that using EMBASE.com does not prejudice against finding all relevant articles as part of a defined search strategy.
A3	Searching conducted by the ERG on EMBASE alone provided 521 results searching for trabectedin as an index term and a free text term, whereas in he submission it states 360 results when searching both MEDLINE and EMBASE for this term (on EMBASE.com). Please provide details of the limits used to yield only 360 results.
	This difference between the results from the search performed by the ERG and the submission is due to differences in the way in which EMBASE.com searches for indexed terms. The preferred terms used for EMTREE may change over time. Previously used preferred terms are kept in EMTREE as synonyms. The search carried out in the submission did not automatically include synonyms in the search, but used a search of 'Trabectedin' both as an exploded search and a text search of the title, abstract and index terms. As noticed in the search strategy (attached), this pair of searches identified 336 and 356 hits respectively. The search string in the submission also includes other search terms for trabectedin; these terms include all synonyms used previously in EMTREE for this drug (i.e. ecteinascidin 743; et 743; et743; yondelis). These terms were included as separate search terms in the search string. They were searched using the same methodology described in the previous paragraph (i.e. exploded search and a text search of the title, abstract and index terms). When all these synonyms are combined, as in search term 11 in the strategy, this search string has a similar number of hits to the search carried out by the ERG, i.e. 540 in EMBASE alone (see table below).

Search string	**Database**	**Hits**
('yondelis'/exp OR yondelis:ti,ab,de) OR ('trabectedin'/exp OR trabectedin:ti,ab,de) OR ('ecteinascidin 743'/exp OR 'ecteinascidin 743':ti,ab,de) OR ('et 743'/exp OR 'et 743':ti,ab,de) OR ('et743'/exp OR 'et743':ti,ab,de)	EMBASE and MEDLINE	594
('yondelis'/exp OR yondelis:ti,ab,de) OR ('trabectedin'/exp OR trabectedin:ti,ab,de) OR ('ecteinascidin 743'/exp OR 'ecteinascidin 743':ti,ab,de) OR ('et 743'/exp OR 'et 743':ti,ab,de) OR ('et743'/exp OR 'et743':ti,ab,de)	EMBASE	540

Note: search carried out on 23/3/2009, therefore number of hits differs slightly from the original search carried out on 20/1/2009

A4	Some index terms are used where no index term exists on EMBASE, for example 'Yondelis' and 'soft part sarcoma'. Please explain the choice of these terms
	Although these terms are not currently used as index terms in EMTREE, they were used as index terms in the past, and are currently included in EMTREE as synonyms. For instance, the currently used index term of 'soft tissue sarcoma' has as synonyms: sarcoma, soft tissue and soft part sarcoma. The currently used index term of 'trabectedin' has as synonyms: ecteinascidin 743; et 743; et743; yondelis. Searching using these synonym terms allows the identification of records that used old index terms.
A5	Please explain why searching on MEDLINE was omitted. MEDLINE in process is a core database to search for the clinical effectiveness evidence
	MEDLINE was searched via the EMBASE.com portal. However, as the facility of searching MEDLINE *in process* is not yet available using this portal, a search of MEDLINE *in* process was carried out via PubMed. The searches for both the clinical and economic data used a shortened search string which was more inclusive than the search string develop when searching EMBASE.com. PubMed was searched utilising the citation status subset "inprocess[sb]" to restrict the search to MEDLINE *in process*. The results of these searches were erroneously omitted from the original submission, but recently rerun searches are included in these comments. ***The search string for clinical data***: The name of the database searched: MEDLINE (restricted to MEDLINE *in process)* The name of the host/system used: PubMed The date when the search was run: 23/3/2009 The years covered by the search: use of "inprocess[sb]" to restrict search to MEDLINE *in process* records

#	**Term**	**Hits**
1	"trabectedin "[Substance Name]	180
2	"trabectedin"[All Fields]	214
3	"NSC 684766"[All Fields]	1
4	"Yondelis"[All Fields]	61
5	"ecteinascidin 743"[All Fields]	114
6	"ET-743"[All Fields]	148
7	OR/1-6	256
8	#7 AND in process[sb]	5

The following inclusion/exclusion criteria were used:

Inclusion/exclusion criteria
Publication should be in English
Publication should contain clinical efficacy or safety data
Publication should be soft tissue sarcoma
Publication should deal with trabectedin
Publication should present original data not previously published

Of the 5 hits, all were rejected;

Paper was not in English: n = 1
Paper did not contain clinical efficacy or safety data: n =2
Paper did not present original research findings: n = 2

The search string for economic data:
The name of the database searched: MEDLINE (restricted to MEDLINE *in process)*
The name of the host/system used: PubMed
The date when the search was run: 23/3/2009
The years covered by the search: use of "inprocess[sb]" to restrict search to MEDLINE *in process* records

#	**Term**	**Hits**
1	"soft"[All Fields] AND "tissue"[All Fields] AND "sarcoma"[All Fields]	9076
2	"soft tissue sarcoma"[All Fields]	3290
3	soft[All Fields] AND part[All Fields] AND ("sarcoma"[MeSH Terms] OR "sarcoma"[All Fields])	920
4	OR:1-3	9461
5	#4 AND in process[sb]	211

The following inclusion/exclusion criteria were applied:

Inclusion/exclusion criteria
Publication should be in English
Publication should be an economic evaluation in the form of cost-utility analysis
Publication should be about chemotherapy
Publication should be on STS patients

Of these 211 hits, 211 were rejected
Paper was not in English: n = 16
Paper was not an economic evaluation in the form of cost-utility: n = 195

Confidentiality status	
B1	Please note that some study details provided in the submission (referenced from the clinical study reports) are only available in the Academic-in-Confidence paper, not the published abstracts or EMEA documents (notably TTP rates at 3 months and 6 months) Please confirm the status (AIC,CIC or not confidential) of these data. (It is noted that Figure 2 is marked as 'In confidence'
	Study details can be considered not confidential; however details of the planned publication are respectfully requested to be kept AIC until it is published.
Economic Evaluation	
C1	The model currently assumes a body surface area of 1.7m2. Please use the BSA observed in study STS-201. If this information is not available, please use referenced sources. In addition please explore the impact of BSA in one-way sensitivity analysis.
	The model has been updated to reflect the mean Body Surface Area (BSA) observed in the STS-201 clinical trial. This has changed the estimate from 1.7m2 to 1.84m2. The mean dose is therefore 2.24mg, assuming a mean dose intensity of 1.22mg/m^2. Table 1 below reports the results of the model with the mean BSA observed in the clinical trial. Other changes to the model (C4, C5, C6, C7) detailed in this document are incorporated in this analysis.

Table 1: Model outcomes with observed BSA

Outcome	Trabectedin	No trabectedin available	Incremental
Costs	£21,931	£1,567	£20,364
Life years gained	1.61	0.76	0.85
QALYS gained	0.86	0.36	0.50
Incremental cost per life year gained			***£24,073***
Incremental cost per QALY			***£41,022***

The results of one-way sensitivity analysis around the mean BSA result in the following cost per QALYs.

Table 2: One-way sensitivity analysis around BSA

	Inc. costs	Inc. QALYs	ICER
BSA 2.5th CI	£20,364	0.50	***£41,022***
BSA 97.5th CI	£22,396	0.50	***£45,115***

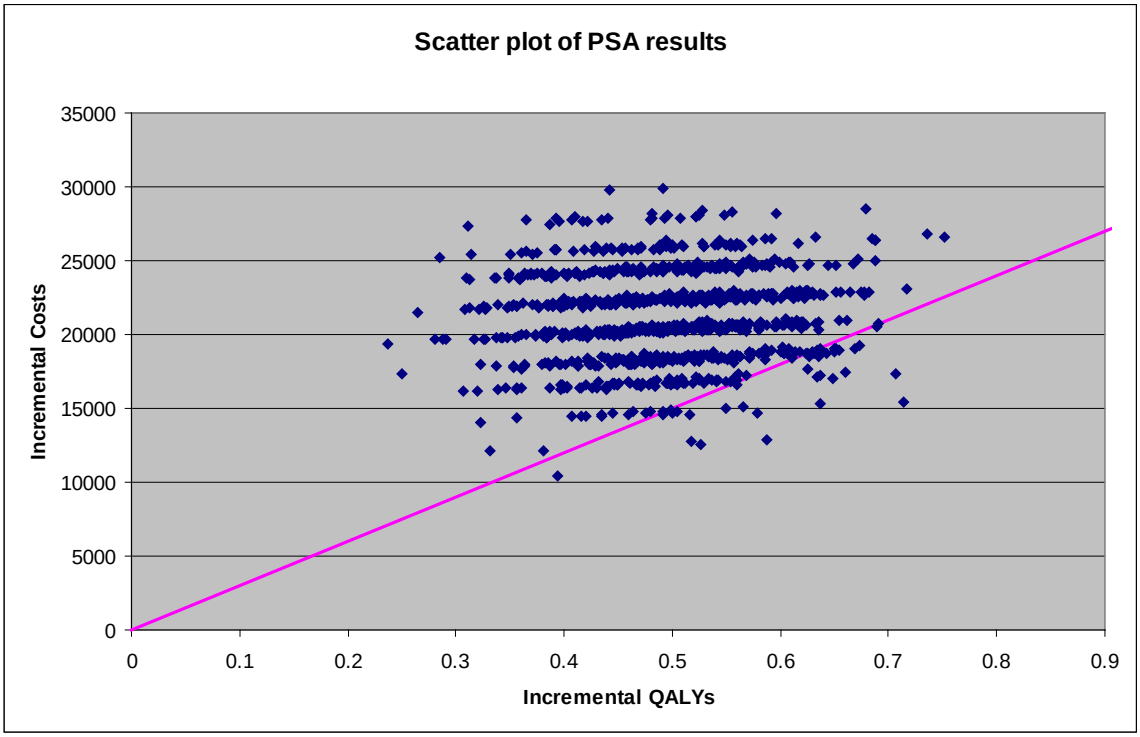
The cost per QALY does not change when BSA is set to the lower confidence interval because the same number of vials is used with a larger amount of wastage.

C2

Transition probabilities in the model are based on survival curves. It is assumed that the survival curves were estimated independently please confirm whether this is the case. Please provide the rationale for not maintaining the correlation between these outcomes and, if it is not possible to undertake this analysis, give an indication of the likely effect of the incremental cost-effectiveness ratio.

It has not been possible to incorporate the correlation between these variables in the model. A sensitivity analysis to test the impact of correlating these parameters was run by linking the Weibull parameters to the same random numbers in the PSA. ("Survival Analysis!G18:G19"). In this analysis the following assumptions are incorporated into the analysis: C4, C5, C6, and C7.

The scatter plot below shows the results of the probabilistic sensitivity analysis when TTP and OS are correlated.



The results of the probabilistic sensitivity analysis are not notably different from the base case model results detailed here on page . Therefore, we conclude that correlating the survival curves does not have a large effect on the model outcomes.

C3

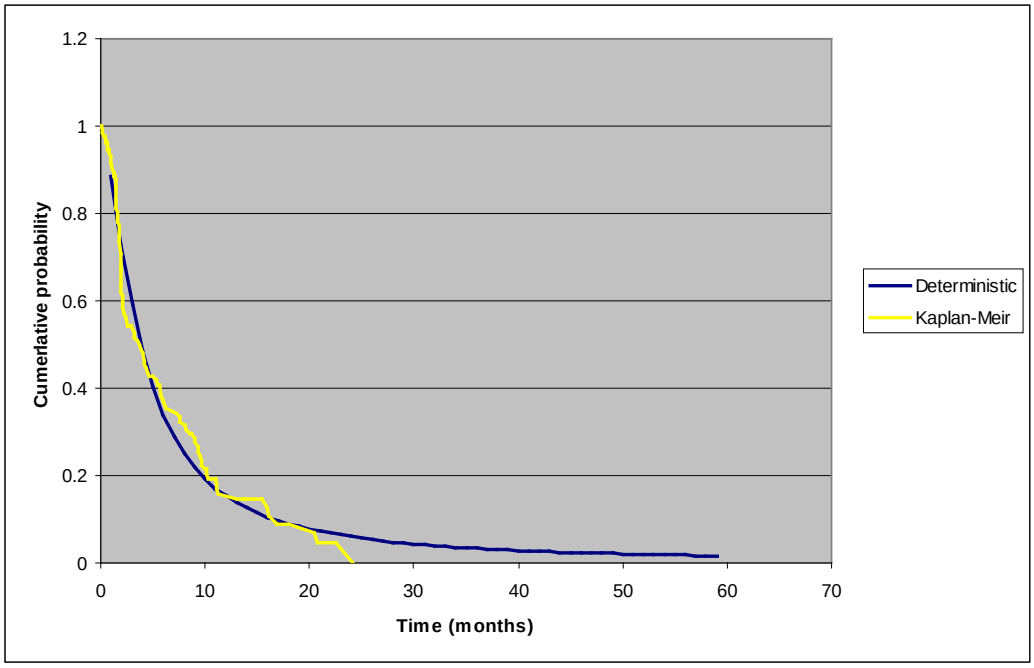
It is noted that the extrapolation of the survival curves has been carried out using Weibull functions. Please confirm whether any other statistical forms (for example, gompertz or log-logistic) were tested. It is noted that visually the Weibull appears a reasonable fit.
Please provide details of the patient level data if possible

The log-logistic and gompertz statistical forms have been estimated for the trabectedin survival curves. The alternative statistical forms were estimated in Stata 9.2.

Log-logistic

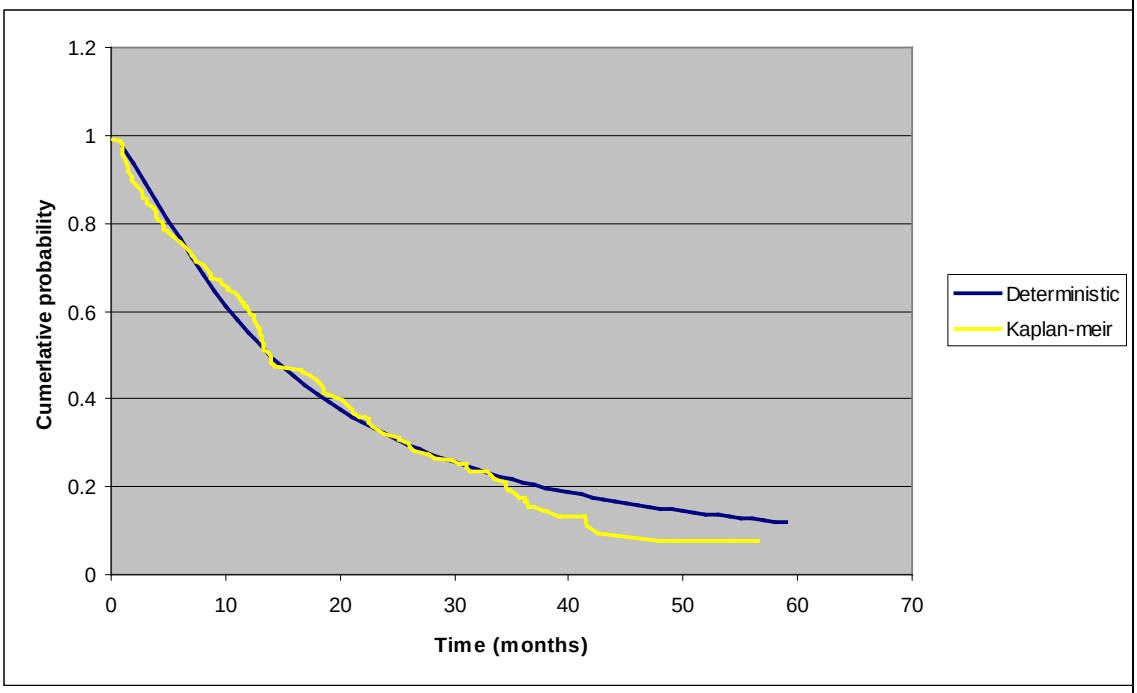
Trabectedin – TTP

	Parameter
Lambda	1.35
Gamma	0.66



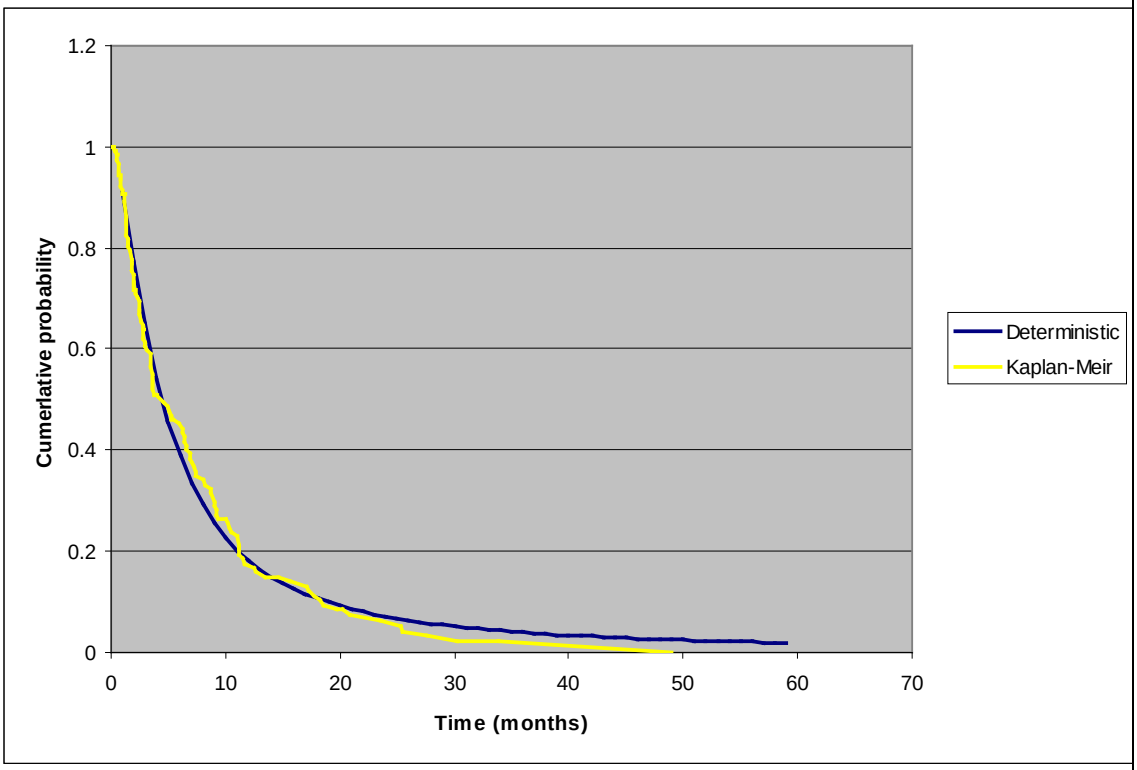
Trabectedin – OS

	Parameter
Lambda	2.6316
Gamma	0.7196



Best supportive care – OS-TTP

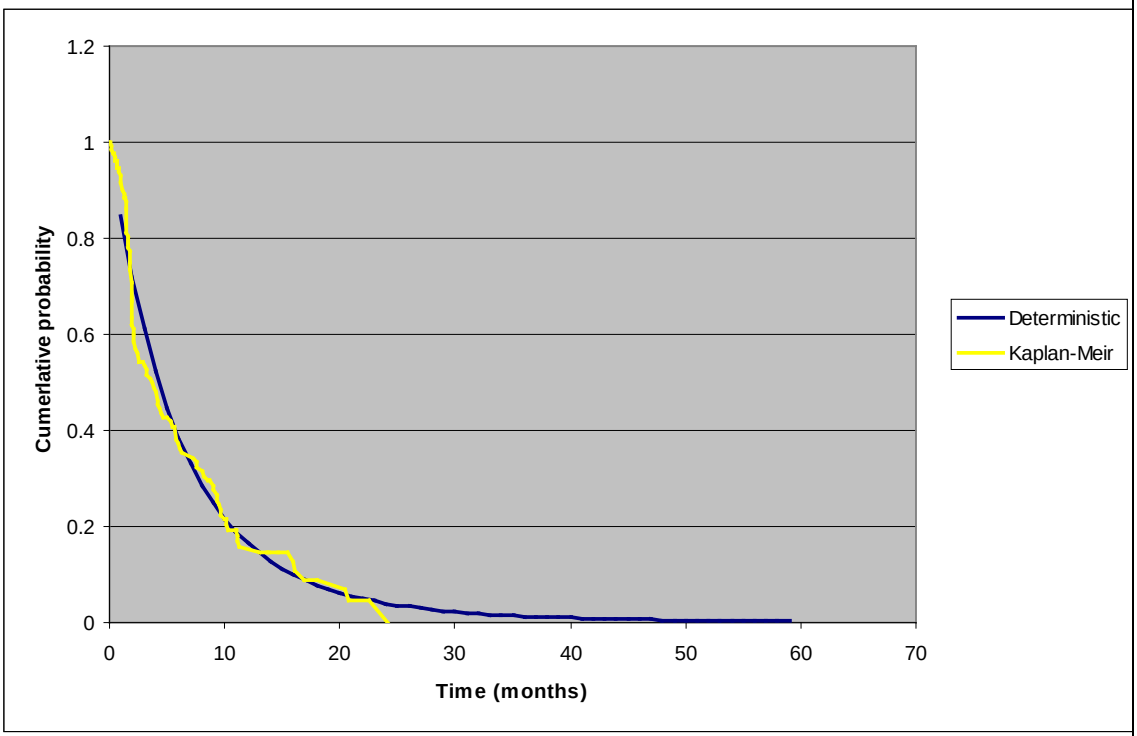
	Parameter
Lambda	1.5003
Gamma	0.6539



Gompertz

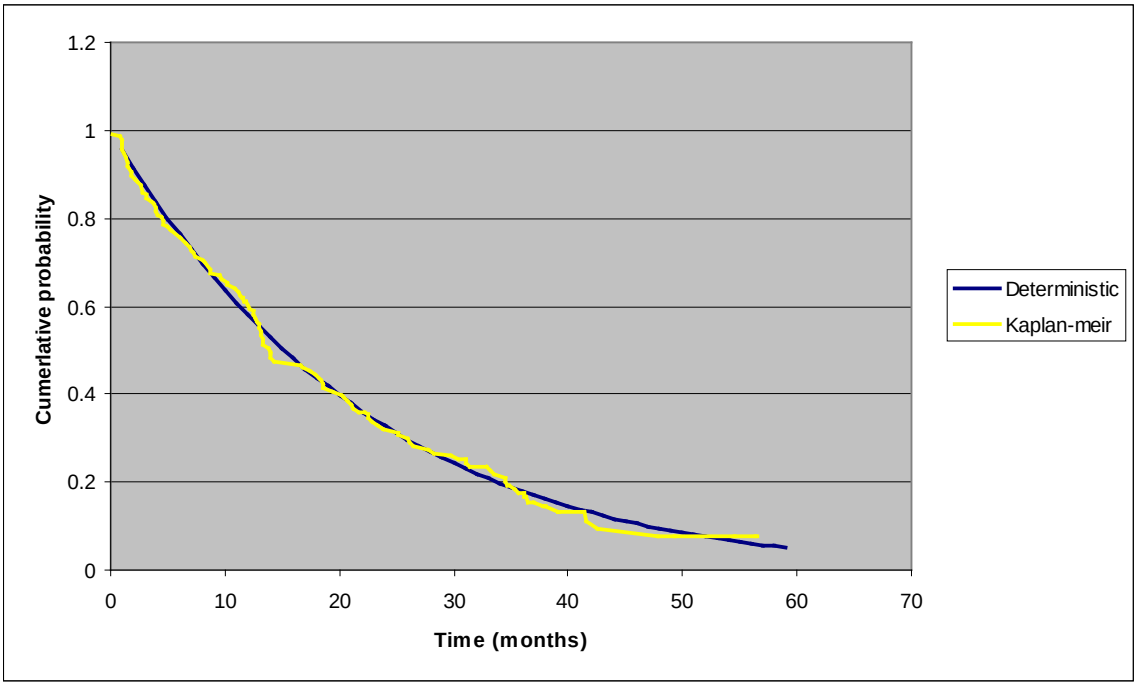
Trabectedin – TTP

	Parameter
Lambda	-1.7759
Gamma	-0.0203



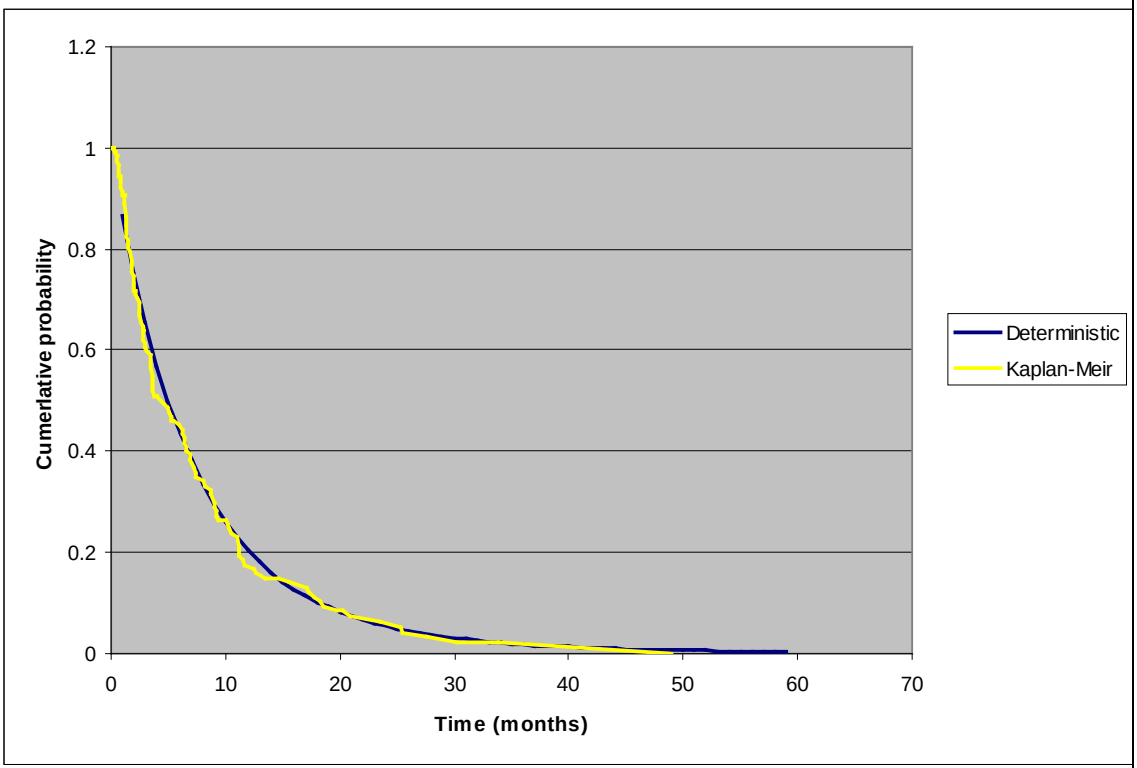
Trabectedin – OS

	Parameter
Lambda	-3.1197
Gamma	0.0044



BSC – OS-TPP

	Parameter
Lambda	-1.9282
Gamma	-0.0155



Log-logistic and Gompertz survival estimates for time to progression on trabectedin, and overall survival on trabectedin, were input into the model to assess the impact on the results. The survival functions for Best Supportive Care are estimated using the Weibull function as described in C4. The results for each analysis are detailed in Table 3 and Table 4.

Table 3: Trabectedin vs. Best Supportive Care with log-logistic survival functions

Outcome	Trabectedin	No trabectedin available	Incremental
Costs	£23,710	£1,567	£22,143
Life years gained	1.68	0.76	0.92
QALYS gained	0.90	0.36	0.544
Incremental cost per life year gained			***£23,994***
Incremental cost per QALY			***£40,731***

Table 4: Trabectedin vs. Best Supportive Care with Gompertz survival functions

Outcome	Trabectedin	No trabectedin available	Incremental
Costs	£23,586	£1,567	£22,019
Life years gained	1.60	0.76	0.85
QALYS gained	0.86	0.36	0.500
Incremental cost per life year gained			***£26,057***
Incremental cost per QALY			***£43,997***

The results show that the incremental utilities for the log-logistic and gompertz functions were 0.048 and 0.004 respectively. The difference in results between the three methods is small. All statistical forms fit the Kaplan-Meir curves well. The Weibull was chosen as the most appropriate in terms of computational simplicity and transparency in review.

Patient level data has been provided.

C4

A key concern is the potential non-comparability between patients in the treatment and BSC arms. It is noted that the populations may not be comparable, since the treatment arm includes only patients with liposarcomas and leiomyosarcoma, while the BSC arm includes other sarcoma types (and treatment was shown to be more effective in the L-sarcoma population) Further to that, page 63 of the submission indicates that patients were less severely affected in terms of the WHO performance status in the treatment arm than in the BSC arm

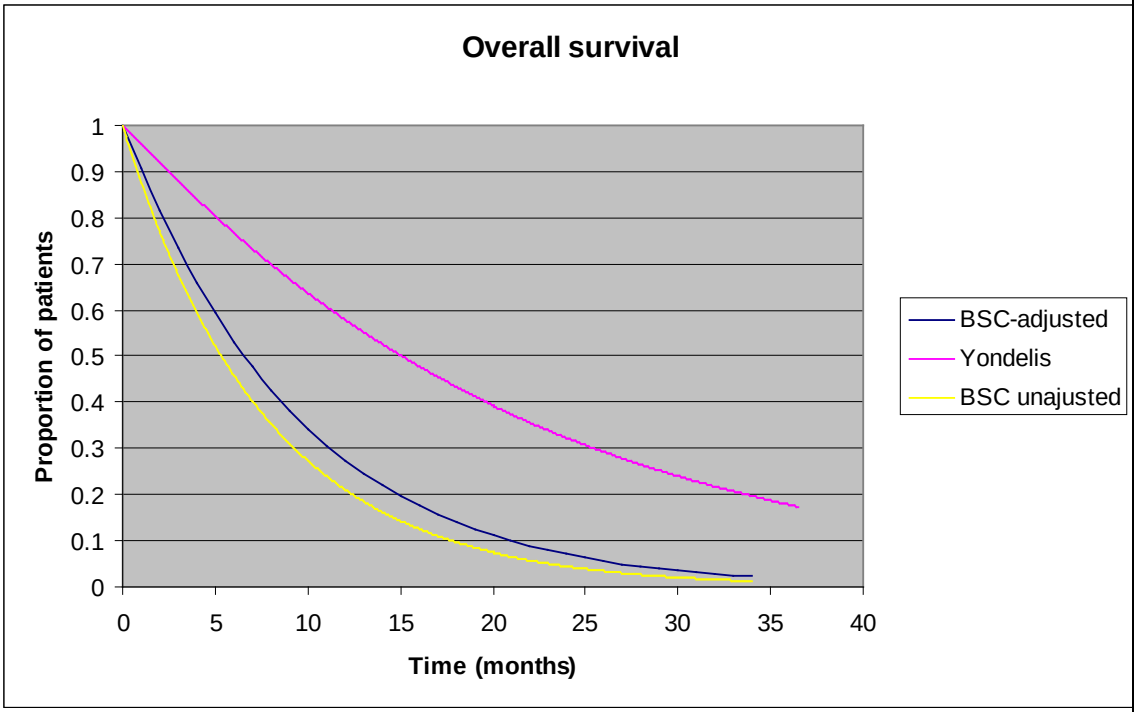
The non-comparability between patients in the treatment and BSC arms has been accounted for using covariates in the BSC Weibull regression. Dummy variables for WHO status1, WHO status 2, and L-sarcoma were included as independent variables in the Weibull regression. The overall survival following progression is estimated assuming that all patients have L-sarcomas and 50% of patients are WHO status 1.

The results of the Weibull regression are detailed in Table 3.

Table 5: Results of the Weibull regression for Best Supportive Care with covariates

	Coefficient	Standard error	P-value
Cons	-2.357506	0.2478364	0
WHO1	0.508553	0.1990129	0.011
WHO2	1.464187	0.4895098	0.003
L-sarcomas	-0.2122605	0.1862266	0.254
Log-gamma	0.0347325	0.0659091	0.598

The impact on overall survival in the model is illustrated below.

	 Details of the updated base case results can be found on page 16.
C5	It is unclear why only hospitalisations due to nausea and vomiting were included. In the submission, it is stated that almost 47% of patients develop grade 3/4 neutropenia and other severe adverse events. Please consider the cost and utility impact of all events graded 3/4 regardless of whether they were associated with hospitalisation.
	The model considers all hospital stays due to drug related adverse events recorded in the relevant arm of the STS-201 trial. However, detailed diagnosis for each hospital stay was not available therefore the model assumes the cost of nausea and vomiting related hospitalisation in the selection of a relevant NHS HRG code. Nausea and vomiting was selected as it was the most common drug related adverse event. Grade 3/4 neutropenia adverse events were not included in the cost estimates because although these events were common, they did not lead to hospitalisation. Neutropenia was reversible and did not follow a cumulative trend. It was rarely associated with fever or infection (febrile neutropenia occurred in 2% of patients and in < 1% of cycles). Equally enzyme elevations did not follow a cumulative trend and ceased without relevant clinical consequences of liver abnormality in the vast majority of patients. However, we have incorporated a utility decrement associated with neutropenia. In the model 47% of patients experience a week's utility decrement in the first cycle of the model. This has been included independently of the decrement associated with nausea and vomiting. These changes have been incorporated into the base case model and sensitivity analysis. The results of the current base case model can be found on page 16.
C6	In the submission it states that the outcomes are half-cycle corrected, but this does not appear to be correct. Please review and clarify.
	A half cycle correction has been incorporated into the model by halving the costs, life years gained, and utilities aggregated in cycle 0 and 59 of the model. Treatment costs, adverse event costs, and adverse event utility decrements are not half cycle corrected.
C7	It appears that it has been assumed that all treatment costs occur at baseline (which overestimates the treatment cost). Please apply the treatment cost based on the schedule observed in the trial.

The treatment costs have been adjusted in the model to calculate cost per cycle. The schedule of treatments within the trial were used to estimate a per cycle cost of treatment. The changes to the treatment cost were incorporated into the base case model detailed on page 16. Details of the estimated cost per cycle can be found in Table 4.

Table 6: Cost per cycle

			Source
A	Mean 1mg vials	1.84	STS-201
B	Mean 0.25mg vials	2.43	STS-201
D	Cost of 1mg vial	£1,366	Pharmamar
E	Cost of 0.25mg vial	£363	Pharmamar
F	Total cost per dose	£3,395	D*A+E*B
H	Cost per chemotherapy administration	£319.61	NHS reference cost
I	Cost of dexamethasone per administration	£4.96	BNF
J	Total cost per cycle	£3,419.57	F+I+J

The treatment cost associated with each cycle of the model was estimated by multiplying the proportion of patients in the STS-201 trial who were receiving treatment at each month of the trial by the estimated cost per cycle. The treatment cost for each cycle of the model is detailed in Table 3.

Table 7: Treatment cost inputs

Cycle no.	Proportion of patients	Total cost
0	0.9412	£3,501.27
1	0.8235	£3,063.61
2	0.5588	£2,078.88
3	0.4926	£1,832.70
4	0.4118	£1,531.81
5	0.3529	£1,312.98
6	0.3015	£1,121.50
7	0.2500	£930.03
8	0.2059	£765.90
9	0.1691	£629.13
10	0.1544	£574.43
11	0.1250	£465.01
12	0.1029	£382.95
13	0.0956	£355.60
14	0.0882	£328.24
15	0.0662	£246.18
16	0.0441	£164.12
17	0.0441	£164.12
18	0.0441	£164.12
19	0.0441	£164.12
20	0.0441	£136.77
21	0.0368	£109.41
22	0.0294	£109.41
23	0.0294	£82.06
24	0.0221	£54.71
25	0.0147	£54.71
26	0.0147	£54.71
27	0.0147	£54.71
28	0.0147	£54.71
29	0.0147	£54.71
30	0.0147	£54.71
31	0.0147	£54.71
32	0.0147	£54.71

33	0.0147	£27.35
34	0.0074	£27.35
35	0.0074	£27.35
36	0.0074	£0.00
37	0	

C8

For patients in the progression-free state treated with trabectedin, the model assumes that no costs are involved. The omission of follow-up costs may have been driven by the fact that these apply to both the treatment and best supportive care arms; however, it is suspected that where there are differences in he mortality rates, this approach may underestimate the costs associated with treatment.
Please provide details of the patient cost data

Follow-up costs have been included in the base case model. The per-cycle cost is estimated to be 50% of the progressed cycle cost. Details of the follow-up costs used in the base case model are details in Table 4.

Table 8: Follow-up costs

	Cost per cycle	Source
Progression free	£85.96	Assumption
Progressed disease	£171.91	Judson et al. (2007)

No patient cost data was collected as part of the STS-201 trial.

C9

Please clarify the mean dosage considered in the model per BSA. Currently the model assumes a mean dosage of 1.22mg/m2, based on trial data. However, it is likely that this value was calculated not taking into account the potential wastage (that is, open vials that were not used completely).
Please provide the mean number of vials (of both sizes) used by patient within the STS-201 study.

The cost per cycle of treatment was previously estimated using the mean dose per BSA. The model has changed to estimate cost per cycle based on the mean number of each vial size used in the model. Data on the actual number of vials used for the q3wk 24-h regimen were not available. Data on the dose received by patient at each cycle of treatment was obtained. Estimates of the number of vials used for each cycle of treatment were made. The mean number of each vial size was obtained from this estimate. Details of the number of vials used in the clinical trial are reported in Table 9.

Table 9: Mean number of vials estimated from individual dose data

	Mean	Source
1mg vial	1.84	STS-201
0.25mg vial	2.43	STS-201

C10

Some inconsistencies between the report and the model have been noted. The submission states that the mean number of cycles, while the model reports the median.

There was a typing error in the model. The model was estimated based on the mean number of cycles from the STS-201 clinical study report.

Please note that the current base case model does not use the number of cycles to estimate treatment cost.

C11

In the submission it is assumed that utilities for lung cancer are a good proxy for the utilities in STS patients. The model assumes that the utilities remain constant over time. It is felt that this is unlikely, as in lung cancer, the quality of life generally decreased with time for the individuals in the progressive state.
Please provide validation of the assumptions used, and explore the impact of varying utilities on the incremental cost-effectiveness ratio in sensitivity analyses.

The utility estimates for non small cell lung cancer on second-line treatment were extracted from a study of UK societal based utility estimates for stages of disease and toxicities. The utilities reported in this study estimate the utility decrement associated with disease progression. The study does not explore changes in utility over time.

<table>
<tr><td></td><td>The utilities have been applied appropriately in the model. Altering utilities over time would require arbitrary assumptions, which would further increase the uncertainty in the model.</td></tr>
<tr><td>C12</td><td>Please provide clarification on how the cost for the progression state was estimated</td></tr>
<tr><td></td><td>A cost of illness study by Judson et al, 2007 (55) reports the cost of management of metastatic soft tissue sarcoma. The total cost of managing MSTS from a sample of 47 patients is reported. As part of this analysis the non-chemotherapy related cost of care is reported. Non-chemotherapy related costs include diagnostic tests, inpatient stay, hospice stay and palliative drugs. Costs associated with hospice stay and palliative drugs were assumed to be incurred in terminal care rather than the ongoing care of patients. Consequently, they were excluded from the estimation of cost of progressed disease. The costs associated of diagnostic tests and inpatient stay was inflated to 2008 prices. An average cost per patient was estimated based on a sample size of 47.

Table 10 Ongoing costs associated with progressed disease
<table>
<tr><td>Cost category</td><td>Total cost</td><td>Average cost per patient</td></tr>
<tr><td>Diagnostic tests</td><td>£17,273.06</td><td>£367.51</td></tr>
<tr><td>Inpatient stay (administration, adverse events, terminal care)</td><td>£79,686.53</td><td>£1695.46</td></tr>
<tr><td>Total</td><td></td><td>£2,062.97</td></tr>
</table>

The Judson et al, 2007 (55) study reported that the mean survival from diagnosis of metastatic disease until death was 1 year. Accounting for this data, the total average cost per one month cycle was £171.91. This cost is applied in each cycle of the economic model to all patients who have exhausted anthracycline, ifosfamide and trabectedin.</td></tr>
<tr><td>C13</td><td>The references appear to be incorrect. Please review and correct referencing for ease of understanding.</td></tr>
<tr><td></td><td>An error in the referencing of Keizer et al. (1997) and Buesa et al. (1991) was identified and amended.</td></tr>
</table>

1 Updated Results

1.1 Base case results

The following results are taken from the deterministic element of the economic model. In this analysis trabectedin is compared with BSC, assumed equal to patients failing treatment in the EORTC database.

Table 11 Results of the base case analysis

	Trabectedin	Best Supportive Care	Difference
Total costs	£23,613	£1,567	£22,047
Total life years	1.61	0.76	0.846
Total QALYs	0.86	0.36	0.496
Cost per life year			***£26,062***
Cost per QALY			***£44,410***

Sensitivity Analysis

Sensitivity analysis - Comparator

The secondary analysis to include 33% patients receiving chemotherapy, which utilised time to progression data from the EORTC trials are detailed below.

Table 12 Results of the analysis comparing trabectedin against 33% active comparator / 67% BSC in L-sarcoma patients

	Trabectedin	Best Supportive Care	Difference
Total costs	£23,613	£1,927	£21,686
Total life years	1.61	0.86	0.75
Total QALYs	0.86	0.42	0.43
Cost per life year			***£28,898***
Cost per QALY			***£50,059***

Additional analysis was conducted to compare trabectedin with chemotherapy only. The results are detailed below:

Table 13 Results of the analysis comparing trabectedin against 100% active comparator in L-sarcoma patients

	Trabectedin	Comparator	Difference
Total costs	£23,613	£2,659	£20,955
Total life years	1.61	1.05	0.56
Total QALYs	0.86	0.55	0.30
Cost per life year			***£37,649***
Cost per QALY			***£68,733***

Sensitivity Analysis – Trabectedin patient population

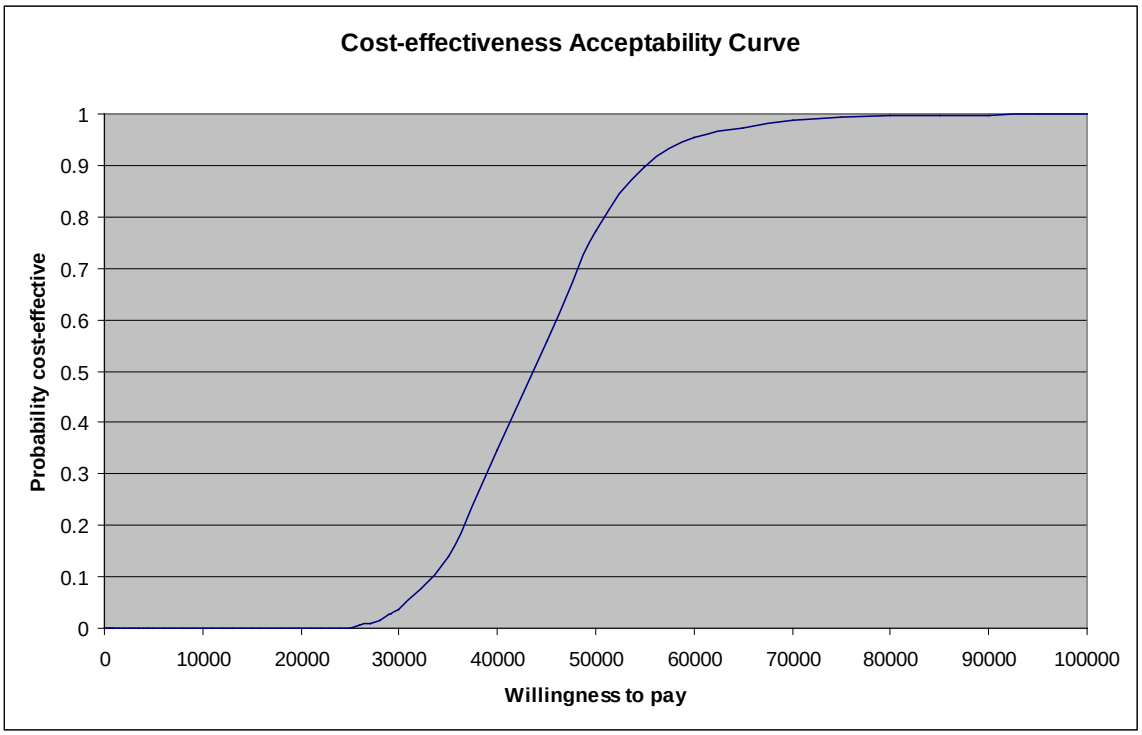
Additional analysis was conducted using pooled data from three Phase II non-comparative studies to describe the effectiveness of trabectedin. These studies included L-sarcoma and non-L-sarcoma patients.

Table 14 Results of the pooled trabectedin analysis: L-sarcoma and non-L-sarcoma patients

	Trabectedin	Best Supportive Care	Difference
Total costs	£23,216	£1,567	£21,649
Total life years	1.33	0.76	0.57
Total QALYs	0.69	0.36	0.33
Cost per life year			***£38,062***
Cost per QALY			***£64,665***

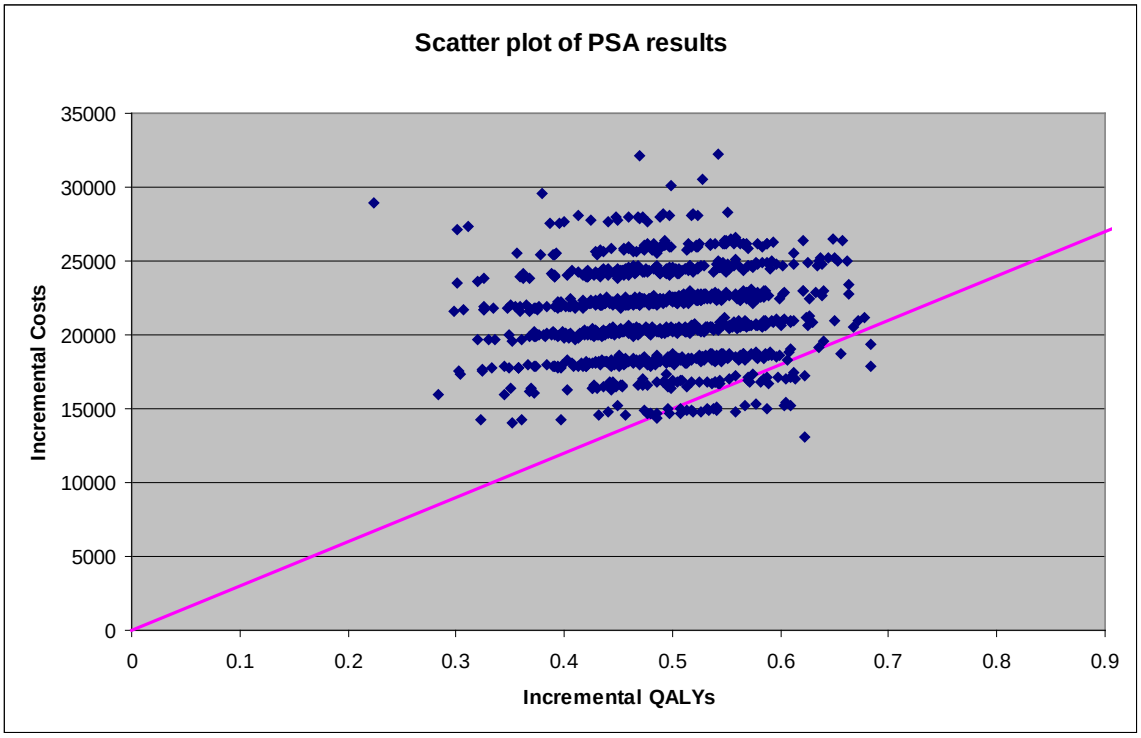
Probabilistic Sensitivity Analysis

Figure 1 Cost-effectiveness acceptability curve: base case comparison



Although trabectedin has a low probability of being cost-effective at the £30,000 threshold there is relatively low uncertainty in the results of the PSA. There is very little variation in the results of the sensitivity analysis as illustrated in the scatter-plot in Figure 15. The pink line represents the £30,000 cost-effectiveness threshold.

Figure 2 Scatter plot of PSA results



The scatter plot illustrates that all ICERs generated in the PSA fall within the North-East quadrant of the cost-effectiveness plane. The results of the net benefit analysis are detailed in Table 45.

Table 15 Net benefit analysis

	Willingness to pay = £20,000		***Willingness to pay = £30,000***		***Willingness to pay = £40,000***	
	Expected net benefit	***Probability CE***	***Expected net benefit***	***Probability CE***	***Expected net benefit***	***Probability CE***
Trabectedin	-£5,779.79	0.000	£2,734	0.037	£11,248	0.348
Best Supportive Care	£5,655.60	1.000	£9,272	0.963	£12,888	0.652

Discount rate sensitivity analysis

Table 16 Results of the discount rate sensitivity analysis

	Inc. costs	Inc. QALYs	ICER
Discount rate is zero	£22,265	0.518	£42,944
Discount rate is 6%	£21,903	0.482	£45,425
Discount rate is 6% for costs and 1.5% for outcomes	£21,903	0.509	£43,057

Univariate sensitivity analysis

The results of the univariate sensitivity analysis are detailed below.

Table 17 Results of the univariate sensitivity analysis

	Inc. costs	Inc. QALYs	ICER
Trabectedin's indicated dose for the treatment of metatstatic STS	£22,047	0.496	£44,410
Number of vials set to 2.5th CI	£21,817	0.496	£43,948
Number of vials set to 97.5th CI	£22,276	0.496	£44,873
Trabectedin administration assumed to occur on an outpatient basis (HRG SB12Z)	£21,209	0.496	£42,723
Chemotherapy administration cost to lower quartile	£21,332	0.496	£42,971
Chemotherapy administration cost to upper quartile	£23,347	0.496	£47,031
AE hospitalisation cost decreased to lower quartile	£22,035	0.496	£44,388
AE hospitalisation cost increased to upper quartile	£22,059	0.496	£44,435
Utility data set to 2.5th CI	£22,047	0.442	£49,913

Utility data set to 97.5th CI	£22,047	0.541	£40,754
Trabectedin time to progression at 2.5th CI (loglambda)	£22,212	0.468	£47,495
Trabectedin time to progression at 97.5th CI (loglambda)	£21,814	0.537	£40,627
Trabectedin overall survival at 2.5th CI (loglambda)	£20,828	0.217	£96,083
Trabectedin overall survival at 97.5th CI (loglambda)	£23,518	0.834	£28,194
BSC survival after progression at 2.5th CI (loglambda)	£22,624	0.629	£35,977
BSC survival after progression at 97.5th CI (loglambda)	£21,173	0.296	£71,562