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

RESPONSE TO EVIDENCE REVIEW GROUP QUERIES (15th April 2009)

24th APRIL 2009

Clinical effectiveness	
Ref	Clarification point
A1	Please indicate if the phase II dacarbazine study is the Buesa 1991 reference.
	Yes. Buesa 1991 refers to the EORTC study from which the dacarbazine analysis has been conducted.
A2	Please clarify whether the presented overall survival (OS) data were calculated from studies referenced 29-31, or were these data calculated from additional studies? The OS data presented does not appear to be available from references 29-31.
	The presented OS data were calculated as part of a pooled analysis of studies referenced 29-31. This pooled analysis is not published however was presented to EMEA as part of the Trabectedin MAA and is attached along with this response document.
A3	Please indicate if the median OS of 5.9 months was calculated from the end of the ifosfamide therapy (i.e. patients were no longer receiving chemotherapy)
	OS was calculated using the Kaplan-Meier method from the first documentation of disease progression on study treatment (ifosfamide) until death, for patients with performance status (PS=0, 1).
A4	Please provide and explanation as to why only 44 out of 50 patients in the dacarbazine column of Table 19 have gender and WHO severity scores.
	The gender and severity scores in Table 19 were extracted from Buesa 1991. This paper reports demographic data for 44 patients recruited into the study who were considered "evaluable". A further 6 patients were recruited but not included in the publication as they were considered "not evaluable". We included data for all 50 recruited patients in the model.
Cost effectiveness	
B1	Please provide the rationale behind the following assumption: All patients who receive trabectedin treatment enter the model in the progression-free state, whereas those receiving best supportive care (BSC) enter the model in the progressed disease state. As the utility of being in the progressed disease state is lower than being in progression-free disease, this mismatch in the entry states of the patient appears to bias the model in favour of trabectedin. Further to this, please indicate the likely affect this bias has on the cost per QALY ratio.
	The four studies included in the BSC arm of the model studied patients who had previously been treated with chemotherapy. Analysis of patients post-progression in these studies is assumed equivalent to the patients studied in the trabectedin trials. Patients in BSC do not receive active treatment in the model; therefore they cannot progress through the model along the same pathway as the trabectedin patients. We have provided two additional analyses where 33% or 100% of patients in the comparator arm receive further chemotherapy. In these analyses either 33% or 100% of patients start the model in the progression free health state. The data for these analyses is taken from the EORTC studies. The results of this analysis can be found in the results section towards the end of this document. It should be noted that the efficacy of other chemotherapy is taken from studies of second line treatment. Consequently, this may over-estimate the survival of the patients in this arm. We have conducted further sensitivity analysis on this issue to investigate the impact of allocating higher utilities to the progressed health state in the BSC arm of the model. The adjusted utilities allocated to the first 5 cycles of the model are detailed in Table 1.

Table 1: Health state utilities for BSC

Cycle number	BSC Health state utilities (Base case model)	BSC Health state utilities (Sensitivity analysis)
0	0.473	0.653
1	0.473	0.608
2	0.473	0.563
3	0.473	0.518
4	0.473	0.473

The results of the model with these adjustments to the BSC health states are detailed inTable 2.

Table 2: Results of utility adjustment in BSC

	Trabectedin	Best Supportive Care	Difference
Total costs	£29,110	£1,965	£27,145
Total life years	1.529	0.71	0.820
Total QALYs	0.81	0.37	0.445
Cost per life year			***£33,121***
Cost per QALY			***£61,064***

B2 Please repeat the analyses using the progression-free survival curve instead of the time-to-progression survival curve.

Progression free survival (PFS) is available from the company studies. However PFS was not calculated separately for the EORTC trials. We attempted to estimate PFS for the EORTC trials using time to progression and overall survival data using an ad hoc algorithm. However we identified patients in the EORTC datasets who were censored for TTP up to 12 months before confirmed mortality. We have no further data to impute PFS events in the censored period and we considered the resulting PFS estimates to be unreliable. Consequently, we have maintained the Time to Progression (TTP) estimates in the base case analysis as this endpoint is comparable between data sources.

Sensitivity analysis has been conducted to test the impact of including the PFS estimates for the trabectedin studies in the model. However, the survival curve for the BSC arm was estimated using TTP data. The results of this analysis are reported in Table **3**. A drop down list has been added to the Results sheet in the model to switch between TTP and PFS for trabectedin.

Table 3: Result of the sensitivity analysis for progression free survival

	Trabectedin	Best Supportive Care	Difference
Total costs	£29,110	£1,965	£27,145
Total life years	1.529	0.71	0.820
Total QALYs	0.81	0.34	0.476
Cost per life year			***£33,121***
Cost per QALY			***£56,985***

B3 Please account for all significant variables (including gender) in the adjustment of the survival curves in the revised model, in addition to those already addressed (i.e., WHO performance score and histopathology (L sarcoma)). Additionally, please explore the effects on the cost per QALY ratio of adjusting the trabectedin survival curve, as opposed to the BSC survival curve.

All survival analyses have been conducted with all available variables. The covariates included in each survival calculation are presented in Table 4.

Table 4: Covariates included in the model

Survival analysis	Covariates included	Adjustment applied
TTP trabectedin STS-201	Female	0.68
	Age	53
	Performance status = 1	0.48
OS trabectedin STS-201	Female	0.68
	Age	53
	Performance status = 1	0.48
OS-TTP Best supportive care	Female	0.68
	Age	53
	Performance status = 1	0.48
	Performance status = 2	0
	L-sarcoma	1
TTP trabectedin pooled	Female	0.54
	Age	50
	Performance status = 1	0.56
	L-sarcoma	0.55
OS trabectedin pooled	Female	0.54
	Age	50
	Performance status = 1	0.56
	L-sarcoma	0.55
OS-TTP Best supportive care	Female	0.54
	Age	50
	Performance status = 1	0.56
	Performance status = 2	0
	L-sarcoma	0.55

<table>
<tr><td></td><td></td></tr>
<tr><td>B4</td><td>Please explain the rationale behind the decision to use a monthly time cycle, as opposed to one of 3 weeks. Further to this, please provide justification for mismatch between the costs per cycle (which relate to a 3-week cycle) and the utilities (which refer to one month).</td></tr>
<tr><td></td><td>The monthly cycle was selected because the time to event data was estimated in monthly units. The mismatch between trabectedin treatment costs and the model cycle length has been corrected in the model. The outcomes of the updated model can be found in the Results section towards the end of this document.</td></tr>
<tr><td>B5</td><td>Please resolve the following discrepancy: the model now contains a worksheet (‘Costs’) that estimates the proportion of patients receiving set number of cycles. The proportion reported appears to be consistent with the raw data provided to the ERG. In this data, 130 out of 136 patients (95.6%) received at least one treatment cycle, however the model reports this value to be 94.1%.</td></tr>
<tr><td></td><td>The discrepancy has been resolved. The outcomes of the updated model can be found in the Results section towards the end of this document.</td></tr>
<tr><td>B6</td><td>Please explain why the methodology for calculating the cost of treatment differs between the deterministic and probabilistic analyses. The deterministic analyses use a mean number of vials used. Despite these values having an associated standard error, sampling from these is not undertaken. Please explore the impact on the ICER of sampling the number of vials used.</td></tr>
<tr><td></td><td>The model has been updated so that the cost of treatment in the probabilistic sensitivity analysis is calculated using the standard error of the number of vials used in each cycle of treatment.</td></tr>
<tr><td>B7</td><td>Please present a re-analysis in which management costs, such as palliative care and hospice care for patients in the progressive state, are included.</td></tr>
<tr><td></td><td>The cost of palliative drugs and hospice care are reported in Judson et al. (2007) and are detailed in Table 5.

Table 5: End of life care costs
<table>
<tr><td></td><td>Total cost</td><td>Total cost (2008 prices)</td><td>Per patient cost</td></tr>
<tr><td>Hospice care</td><td>£20,488</td><td>£21,172</td><td>£450</td></tr>
<tr><td>Palliative drugs</td><td>£2,608</td><td>£2,695</td><td>£57</td></tr>
</table>
The cost per patient was incurred by all patients in the model as they transition from progressed disease to death.</td></tr>
</table>

B8	The submission states that the cost for hospitalisation due to nausea and vomiting (from PA29Z) was selected to represent the costs for adverse events; however, this cost relates to abdominal pain, rather than vomiting as reported. Please also confirm that the average length of stay for hospitalised patients was similar to that of the average patient hospitalised for whichever proxy measure is deemed most appropriate.
	It was not possible to access the length of stay of hospitalisation due to adverse event. However, the individual reasons for hospitalisation due to adverse event related to the study drug were obtained to avoid the use of proxy costs. A list of the hospitalisations and the costs assigned to them are detailed in Table 6. Costs were accessed from the 2006-07 NHS reference costs of non-elective stay in hospital. All hospitalisation have an appropriate cost allocated from the reference costs, except extravasation. In this case the cost of other hospitalisation associated with a neoplasm was used.

Table 6: Cost of hospitalisation due to adverse event

Adverse event	Cost	HRG code	HRG description
Small intestinal obstruction	£3,606	FA07B	Major Small Intestine Procedures without CC
Non-cardiogenic pulmonary oedema	£1,423	DZ20Z	Pulmonary Oedema
Vomiting	£621	PA28B	Feeding Difficulties and Vomiting without CC
Deep vein thrombosis	£932	EB11Z	Deep Vein Thrombosis
Pneumonia	£880	DZ11C	Lobar, Atypical or Viral Pneumonia without CC
Extravasation	£1,515	WA17Y	Other admissions related to neoplasms without CC
Pyrexia	£726	PA20Z	Pyrexia of Unknown Origin

B9	Please confirm that the 47% of patients (Table 9) who experienced neutropenia were calculated from 136 patients. This would be consistent with the assumed beta distribution, but is not clearly marked in the submission.
	The 47% of patients who experienced neutropenia were calculated from the 130 patients who received treatment. The beta distribution has been corrected to reflect this.
B10	Please use the method of calculating the number of patients in a health state as the average between time $_{t}$ and time $_{t+1}$ to perform the half-cycle correction.
	The method of averaging between time t and time t+1 has been incorporated into the model.
B11	In the revised model, the BSC survival curve has been adjusted for WHO severity and histology relative to the proportions in the base case analysis. This survival curve is then used for the pooled analysis, despite this being a different mix of severity and histology. As a result, the BSC curve is not compatible with the mix of patients in the pooled analysis. Please adjust the trabectedin and BSC curves to be more consistent with one another. If this is not possible, please comment on the likely effect this incompatibility has on the cost per QALY ratio.
	A separate BSC curve is estimated using different adjustments for severity, age, gender and histology for the pooled analysis. The outcomes of the pooled analysis can be found in the Results section of this document.
B12	For the pooled analysis, the same proportion of patients treated at each cycle was assumed to be as observed in STS-201. Please use the proportion of patients receiving treatment in the pooled analysis. If this is not possible, please discuss the likely effect this assumption has on the ICER.
	The treatment costs for the pooled analysis have been estimated from the number of cycles of treatment observed in the Phase II studies. The treatment cycle cost (3 weekly) for the pooled analysis is described in Table 7.

Table 7: Per cycle cost of trabectedin in the pooled Phase II studies

Treatment cycle number	Proportion of patients	Cost
0	1.0000	£3,720.10
1	0.8162	£3,036.26
2	0.5147	£1,914.76
3	0.4706	£1,750.64
4	0.3382	£1,258.27
5	0.2794	£1,039.44
6	0.1691	£629.13
7	0.1397	£519.72
8	0.0809	£300.89
9	0.0809	£300.89
10	0.0735	£273.54
11	0.0588	£218.83
12	0.0588	£218.83
13	0.0515	£191.48
14	0.0294	£109.41
15	0.0221	£82.06
16	0.0147	£54.71
17	0.0147	£54.71
18	0.0074	£27.35
19	0.0074	£27.35
20	0.0074	£27.35

B13	Please include probabilistic analyses for the pooled analysis. This will require the variance-covariance matrix of PFS and OS curve.
	Probabilistic sensitivity analysis for the pooled analysis is reported below in the Results section.

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 8 Results of the base case analysis

	Trabectedin	**Best Supportive Care**	**Difference**
Total costs	£29,110	£1,965	£27,145
Total life years	1.529	0.71	0.820
Total QALYs	0.81	0.34	0.476
Cost per life year			***£33,121***
Cost per QALY			***£56,985***

2 Sensitivity Analysis

2.1 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 9 Results of the analysis comparing trabectedin against 33% active comparator / 67% BSC in L-sarcoma patients

	Trabectedin	Best Supportive Care	Difference
Total costs	£29,110	£3,815	£25,295
Total life years	1.53	0.82	0.71
Total QALYs	0.81	0.40	0.41
Cost per life year			***£35,730***
Cost per QALY			***£62,044***

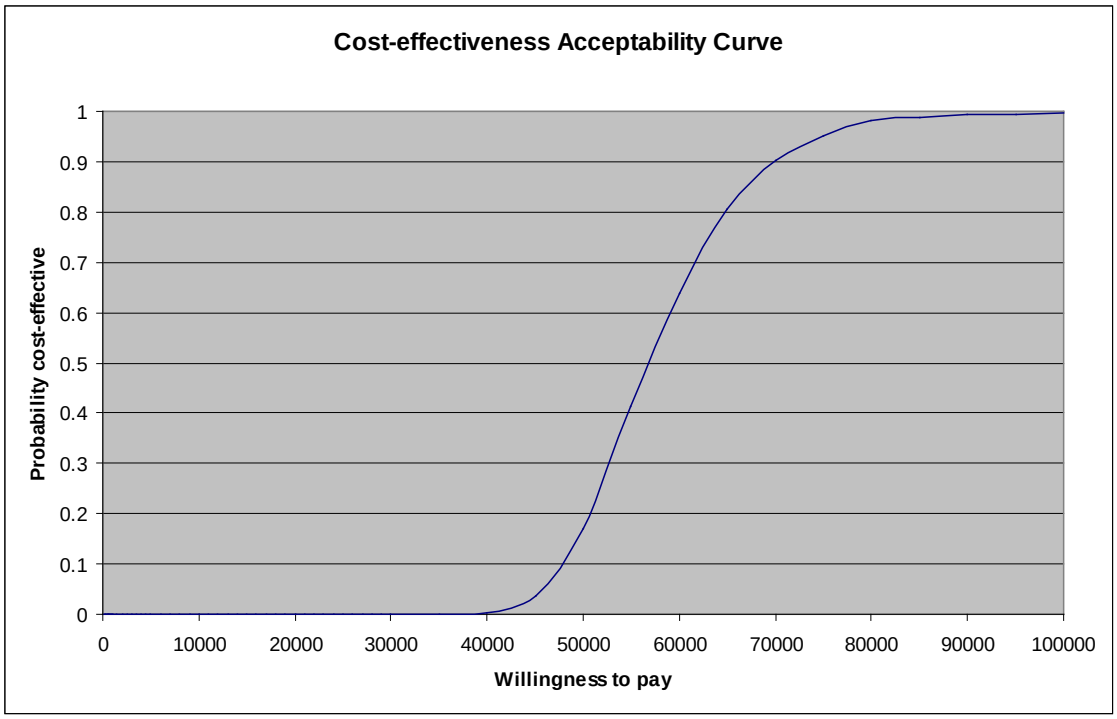
Additional analysis was conducted to compare trabectedin with chemotherapy only. The results are detailed below:

Table 10 Results of the analysis comparing trabectedin against 100% active comparator in L-sarcoma patients

	Trabectedin	Comparator	Difference
Total costs	£29,110	£7,571	£21,539
Total life years	1.53	1.05	0.48
Total QALYs	0.81	0.54	0.27
Cost per life year			***£44,751***
Cost per QALY			***£80,279***

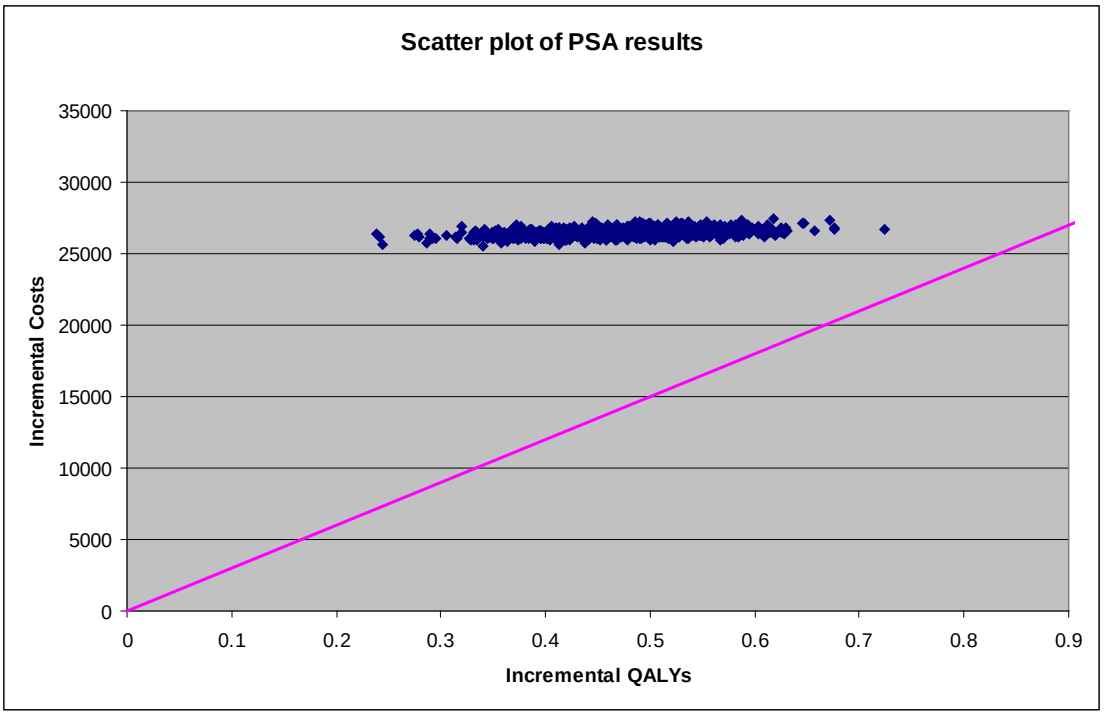
2.2 Probabilistic Sensitivity Analysis

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 2. The pink line represents the £30,000 cost-effectiveness threshold. The scatter plot illustrates that all ICERs generated in the PSA fall within the North-East quadrant of the cost-effectiveness plane.

Figure 2 Scatter plot of PSA results



The results of the net benefit analysis are detailed in Table 11.

Table 11 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	-£3,768.79	0.000	£2,964	0	£9,696	0.098
Best Supportive Care	£5,738.70	1.000	£9,192	1	£12,645	0.902

2.3 Discount rate sensitivity analysis

Table 12 Results of the discount rate sensitivity analysis

	Inc. costs	Inc. QALYs	ICER
Discount rate is zero	£27,290	0.494	£55,199
Discount rate is 6%	£27,049	0.465	£58,216
Discount rate is 6% for costs and 1.5% for outcomes	£27,049	0.486	£55,609

2.4 Univariate sensitivity analysis

The results of the univariate sensitivity analysis are detailed below.

Table 13 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
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

3 Sensitivity Analysis – Trabectedin patient population

3.1 Base case results

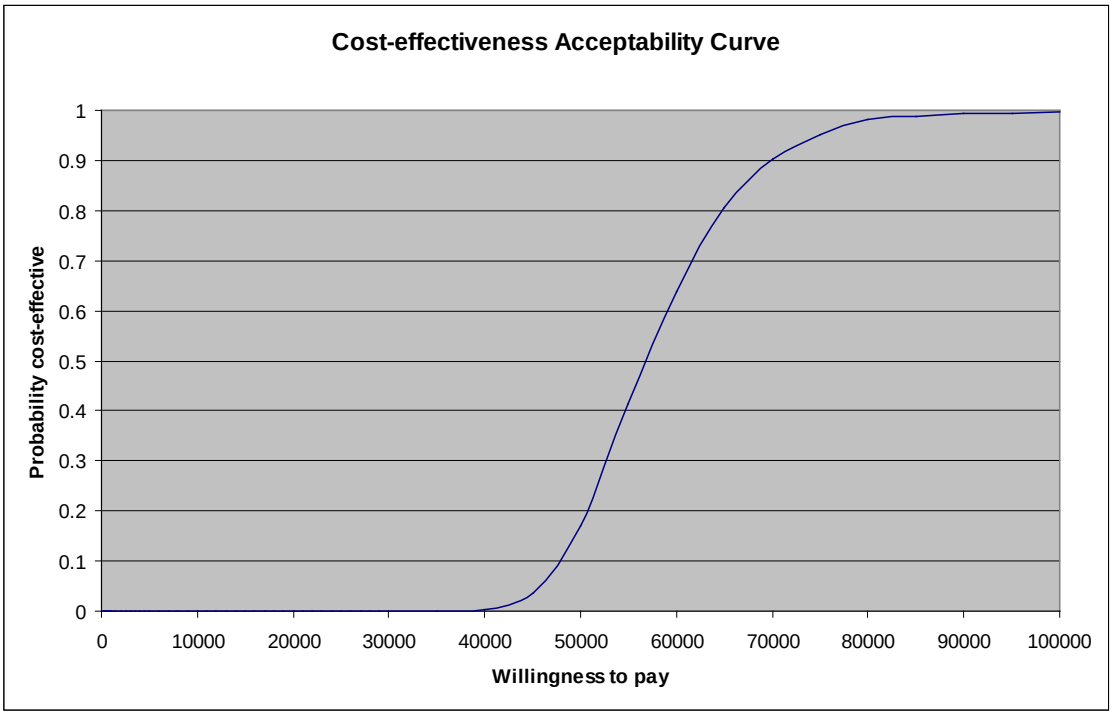
Additional analysis was conducted using pooled data from three Phase II non-comparative studies to describe the effectiveness of trabectedin. These studies included L-sarcoma and non-L-sarcoma patients.

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

	Trabectedin	Best Supportive Care	Difference
Total costs	£29,110	£1,965	£27,145
Total life years	1.529	0.71	0.820
Total QALYs	0.81	0.34	0.476
Cost per life year			***£33,121***
Cost per QALY			***£56,985***

3.2 Probabilistic sensitivity analysis

Figure 3: Cost-effectiveness acceptability curve for pooled analysis



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 4. The pink line

represents the £30,000 cost-effectiveness threshold. The scatter plot illustrates that all ICERs generated in the PSA fall within the North-East quadrant of the cost-effectiveness plane.

Figure 4: Scatter plot of PSA results for pooled analysis

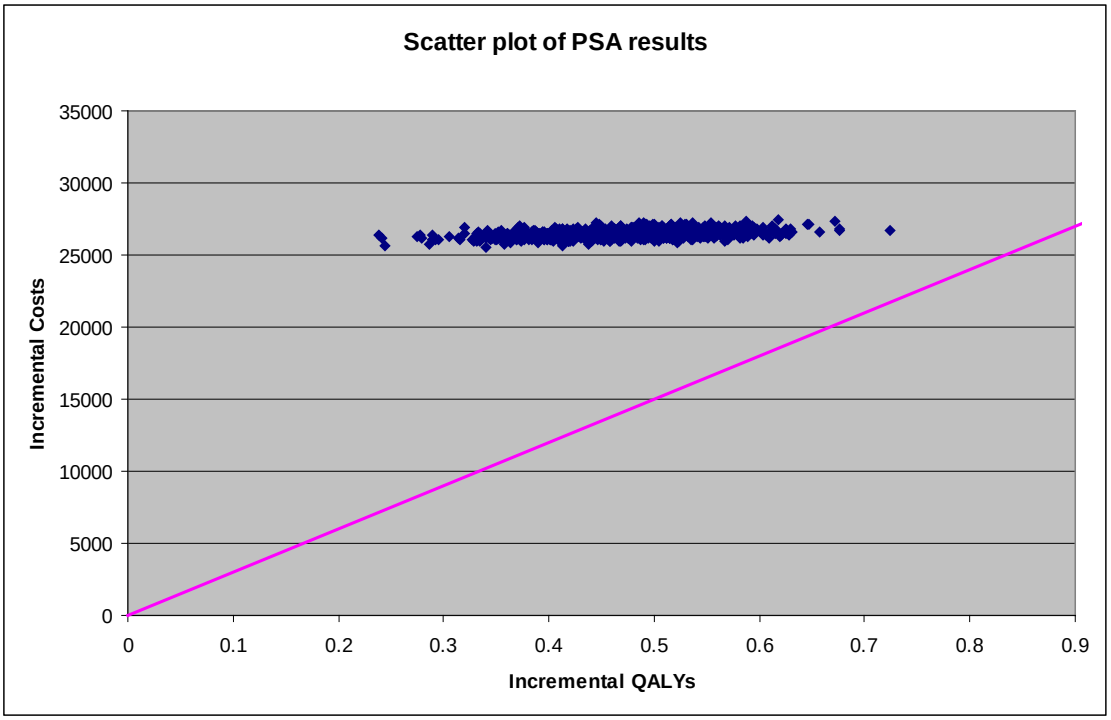


Table 15: Net benefit analysis

	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	-£3,847.93	0.000	£2,859	0	£9,567	0.088
Best Supportive Care	£5,749.20	1.000	£9,189	1	£12,628	0.912