Evidence Review Group's Report

Trabectedin for the treatment of advanced metastatic soft tissue sarcoma

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None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Abbreviations

AE	Adverse events
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BSC	Best supportive care
CEAC	Cost effectiveness acceptability curve
CI	Confidence interval
ECOG	Eastern Cooperative Oncology Group
EORTC STBSG	European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group
ERG	Evidence review group
GIST	Gastrointestinal stromal tumour
HR	Hazard ratio
HRQoL	Health related quality of life
i.v.	intra venous
L-sarcoma	Leiomyosarcoma or liposarcoma
MS	Manufacturer's submission
OS	Overall survival
PD	Progressed disease
PFS	Progression-free survival
PS	Performance status
QALY	Quality adjusted life year
q3wk 24-h	every 3 weeks as 24-hour i.v. infusion
qwk 3-h	every week as 3-hour i.v. infusion
RCT	Randomised controlled trial
SPC	Summary of Product Characteristics
STS	Soft tissue sarcoma
TTP	Time to progression

1 SUMMARY

1.1 Scope of the submission

The manufacturer's submission (MS) broadly reflects the scope of the appraisal issued by NICE, in terms of population and outcomes. The intervention is considered at the dose within the marketing authorisation. The comparator in the scope was best supportive care (BSC), Patients simulated in the model are those failing darcarbazine, etoposide or ifosfamide treatment.

1.2 Summary of submitted clinical effectiveness evidence

Although the MS does not seem to have missed any studies meeting the inclusion criteria from the scope, limited data were available. The main evidence in the manufacturer's submission (MS) is derived from one phase II randomised trial, in which the licensed dose of trabectedin was compared with a different dose of trabectedin. The population in this trial was limited to L-sarcomas. Supplementary data were presented from three uncontrolled phase II trials of the licensed dose of trabectedin.

1.3 Summary of submitted cost effectiveness evidence

The cost per QALY gained of trabectedin compared to BSC was estimated to be £56,985 for the base case using effectiveness from the STS-201 trial for trabectedin and a pool analysis of the EORTC dataset for BSC. This analysis was constrained to patients with L-sarcomas only.

The Evidence Review Group (ERG) were concerned that patients in the trabectedin arm began in a different health state than those in the BSC arm and that those on trabectedin were assumed to have a higher starting utility. An exploratory analysis by the manufacturers in amending this assumption raised the cost per QALY gained for trabectedin compared with BSC to be £61,064.

In addition to the base case, the manufacturer presented three additional scenarios. The first scenario used the pooled effectiveness of trabectedin from

three uncontrolled phase II studies which was not limited to patients with L-sarcomas; this produced a cost per QALY gained of £50,017. In the second and third scenarios, the manufacturer assumed that a proportion of patients in BSC would receive further chemotherapies (either 33% or 100% patients). The cost per QALY gained for these two scenarios was estimated to be £62,044 and £80,279 respectively. None of these three scenarios amended the model to take into consideration the different starting utilities between the trabectedin and BSC arms.

Results were sensitive to the change in health state utilities for the base case in one-way sensitivity analysis. When the joint uncertainty between parameters was considered, the cost-effectiveness acceptability curve showed that trabectedin has a very low probability of being cost-effective at a threshold of £30,000 per QALY gained compared with BSC for any scenario.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

It is unlikely that any additional trials meeting the inclusion criteria would have been identified if the search had been broadened.

The identified phase II randomised controlled trial (RCT), which represents the main clinical efficacy evidence, was thoroughly described in the MS, and was of reasonable methodological quality, and measured appropriate and clinically relevant outcomes.

1.4.2 Weaknesses

There is no randomised controlled evidence on the efficacy of trabectedin compared with BSC.

The RCT of trabectedin (STS-201), which compared two different dosing regimes included only liposarcomas or leiomyosarcomas (L-sarcomas); the appropriateness of these data to other types of soft tissue sarcomas (STS) is uncertain.

1.4.3 Areas of uncertainty

The primary uncertainty relates to the potential non-comparability between studies used to represent the effectiveness for trabectedin and the data for BSC. While survival curves for BSC were adjusted for baseline characteristics observed in studies used for trabectedin, the effectiveness of trabectedin compared to BSC in a similar population remains unclear, particularly as BSC data were from the 1980's and 1990's.

Additionally, the base case analysis focuses only on patients with L-sarcomas and it is unclear how these results relate to other forms of STS, although a scenario using pooled effectiveness of trabectedin taken from three non-controlled phase II studies may be more applicable.

Furthermore, results may be bias in favour of trabectedin given the structure of the model as patients receiving BSC and trabectedin enter the model in a different state than those receiving trabectedin. Finally, there is uncertainty about the appropriateness of the use of health state utilities from another condition (lung cancer).

1.5 Key issues

The ERG has concerns regarding the structure of the model and its ability to capture the cost-effectiveness of trabectedin for adults with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide.

The primary concerns were

- The potential non-comparability between patients included in studies to derive the effectiveness for trabectedin and BSC despite the adjustment of the Weibull curves for age, gender, histopathology and WHO performance score
- The STS-201 trial focuses to patients with L-sarcomas and may not be generalisable to patients with other forms of STS
- The structure of the model which assumed that patients receiving trabectedin start in a different health state than those receiving BSC

which favours trabectedin since these patients have a greater initial utility. The manufacturer provided exploratory analyses to adjust for this error.

- The appropriateness of using utility values for patients with lung cancer for patients with STS.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The description of the underlying health problem in section 4.1 of the manufacturer submission (MS) is adequate and generally relevant. The MS gives the estimated incidence and prevalence of soft tissue sarcomas (STS) as 0.4 and 2 cases respectively per 10,000 population in the European Union. NICE guidance on sarcoma[1] reports the annual incidence (1996-2000) of soft tissue sarcomas coded as ICD-10 C49, thought to represent 53% of STS, as 21.13 per million, which gives an estimated annual incidence of STS of 0.399 per 10,000 in England and Wales. This translated as approximately 2000 soft tissue sarcomas each year in England and Wales.[1]

The MS reports that STS constitute a heterogeneous group of malignancies and identifies the most frequent types as leiomyosarcoma and liposarcoma, which account for approximately 40-50% of all STS. The scope covers patients with advanced disease. The MS states that approximately 50% of patients present with or develop advanced or metastatic disease. The population included in the scope are those failing anthracycline and ifosfamide or for whom these agents are unsuitable. Section 4.1 of the MS gives objective response rates for these agents in first-line therapy as in the 15-20% range, suggesting a non-response rate of 80-85%. Section 4.4 of the MS states that response rates of 10–25% are obtained with anthracycline or ifosfamide in monotherapy, with higher response rates when these agents are given in combination (percentage response rate not given), suggesting a non-response rate of 75% or perhaps lower.

2.2 Critique of manufacturer's overview of current service provision

The manufacturer's overview of current service provision is accurate although further detail, and references, would have been beneficial. Section 4.1 of the MS states that current treatment options for STS include surgery, chemotherapy and radiotherapy which is usually palliative. For patients with advanced metastatic STS who have failed anthracycline and ifosfamide, either in combination as first-line therapy or in sequence as first and second-line therapy, no effective therapies are generally accepted. Section 4.1 of the MS states that dacarbazine is considered active by some oncologists, usually combined with other antitumour agents. Section 4.4 reports that trabectedin may be considered as second or third-line therapy following anthracycline and ifosfamide. Section 4.5 states that for patients not prescribed trabectedin, therapy may include off-label chemotherapy, non-chemotherapy drugs, palliative care and radiotherapy. Trabectedin is the only form of chemotherapy approved for use in patients with advanced metastatic STS who have failed anthracycline and ifosfamide.

3 Critique of manufacturer's definition of decision problem

Table 1 shows the decision problem from the scope, and as addressed in the MS.

Table 1: The decision problem

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults with advanced metastatic soft tissue sarcoma after failure of anthracyclines and ifosfamide, or whom these agents are unsuitable	Adults with advanced metastatic soft tissue sarcoma after failure of anthracyclines and ifosfamide The basecase population in the model is patients with L-sarcomas who failed both anthracyclines and ifosfamide. A scenario using the pooled effectiveness of trabectedin from three previous phase II studies was presented for all STS.
Intervention	Trabectedin (dose as per UK market authorisation)	Trabectedin (dose as per UK market authorisation)
Comparator(s)	Best supportive care (BSC)	Clinical effectiveness study (of trabectedin at the licensed dose) has a comparator of trabectedin at dose not licensed in UK. The comparator used in the model is appropriate
Outcomes	Overall survival Progression-free survival Response rates (including stabilisation) Adverse effects of treatment Health-related quality of life	Overall survival Progression-free survival Response rates (includes stabilisation) Adverse effects of treatment Health-related quality of life
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments	Cost effectiveness was reported as a cost per QALY ratio. The time horizon and perspective

	Final scope issued by NICE	Decision problem addressed in the submission
	should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from a NHS and Personal Social Services Perspective.	of costs are appropriate.

3.1 Population

The manufacturer's statement of the decision problem appropriately defines the population.

Section 4.1 of the MS gives reason for excluding gastrointestinal stromal tumour (GIST) as alternative therapy is available (imatinib), and trabectedin has no activity in GIST. This was considered an appropriate approach by our clinical advisors.

3.2 Intervention

Section 1.5 of the MS states that trabectedin has obtained marketing authorisation for all EU. The licensed dose is 1.5 mg/m^2 every 3 weeks as 24-hour i.v. infusion (q3wk 24-h).

3.3 Comparators

MS, section 2, states that there are no clinical trials that capture comparisons of trabectedin versus other agents nor versus best supportive care. Best investigators choice was not considered an option in the submitted RCT.

3.4 Outcomes

MS states section 2 states that quality of life data are not available for patients with STS.

3.5 Time frame

The time horizon of the model was 5 years, modelled as 60 monthly cycles. At this time point the majority of simulated patients were dead. The time horizon appeared appropriate.

3.6 Other relevant factors

Other considerations from the final scope issued by NICE were as follows.

The scope states: If evidence allows different histological types of STS with improved response to trabectedin or other non-standard chemotherapy regimens will be considered as subgroups. Data were too limited to attempt subgroup analysis.

The scope states: Details of the components of best supportive care should be clearly described. BSC was clearly defined.

The scope states: Guidance will be issued in accordance with the marketing authorisation. Section 7.2 of the MS describes trabectedin's indicated dose for the treatment of patients with advanced STS as 1.5 mg/m^2 administered over 24 hours every three weeks. This dose is one of the interventions in the RCT included in the clinical effectiveness section, section 6 of the MS.

The scope states: trabectedin may be continued if disease stabilisation is achieved in the absence of disease progression. In section 6 of the MS, outcome of stable disease is included in the data on best overall response.

The scope states: Special consideration should be given as to whether the appraisal of trabectedin in GIST and rhabdomyosarcomas should be carried out given that these conditions follow different treatment protocols. Section 4.1 of the MS gives reason for excluding gastrointestinal stromal tumour (GIST) as alternative therapy is available (imatinib), and trabectedin has no activity in GIST. Patients with GIST were excluded from the RCT included in the clinical effectiveness section, section 6 of the MS.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

The ERG could not replicate exactly the search results undertaken by the manufacturer, which is discussed further in Appendix 1. However the ERG does not believe that any relevant clinical effectiveness studies have been missed.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The inclusion/exclusion criteria in section 6.2 of the MS appear to be appropriate. The MS has chosen not to exclude trials that do not have BSC as a comparator. If they had done this, no RCTs would have been included.

4.1.3 Table of identified studies. What studies were included in the submission and what were excluded.

Included studies of trabectedin are shown in table 2.

Table 2: Included studies of trabectedin

Study	Design	Participants	Intervention(s)	Outcomes
ET743-STS-201	Phase II RCT	Advanced L-sarcomas refractory to previous treatment with anthracyclines and ifosfamide (n = 270 randomised, of which n=136 on licensed dose)	Two doses of trabectedin: 1.5 mg/m^2 administered as a 24-hour IV infusion every 21 days (q3wk 24-h regimen, licensed dose); or 0.58 mg/m^2 administered as a 3-hour IV infusion on days 1, 8 and 15 of a 28-day cycle (qwk 3-h regimen)	Primary endpoint time to progression (TTP); secondary endpoints progression-free survival (PFS), overall survival (OS), overall objective response rate. Also assessed adverse events
Garcia-Carbonero et al (2004)	Single arm multicentre (3 institutions in the USA), phase II study	Histologically confirmed recurrent or metastatic STS, Disease progression despite prior chemotherapy with ≤2 prior regimens (n = 36)	1.5 mg/m^2 administered as a 24-hour IV infusion every 21 days (q3wk 24-h)	Primary endpoint: response rate (RR). Secondary endpoints: response duration, TTP, OS, safety and pharmacokinetics

Yovine et al (2004)	Single arm multicentre (4 institutions in France) phase II study	Advanced or metastatic, histologically proven STS. Two cohorts 1) prior therapy with one or two single agents or one combination 2) prior therapy with ≥ 3 single agents or ≥ 2 combinations (n = 54)	1.5 mg/m^2 administered as a 24-hour IV infusion every 21 days (q3wk 24-h)	Primary endpoint RR Secondary endpoints: response duration, TTP, OS, safety
Le Cesne et al (2005)	Single arm, multicentre (8 European centres) phase II study	Histologically proven metastatic or unresectable loco- regional recurrent STS (non-GIST) with prior chemotherapy (n = 104)	1.5 mg/m^2 administered as a 24-hour IV infusion every 21 days (q3wk 24-h)	Primary endpoint: RR Secondary endpoints: response duration, TTP, OS

One RCT was included which compared the licensed dose of trabectedin (1.5mg/m^2 24-hour i.v. infusion once every 3 weeks, q3wk 24-h) with another dose of trabectedin (0.58mg/m^2 3-hour i.v. infusion every week for 3 weeks of a 4-week cycle, qwk 3-h). This was available as 5 published abstracts, one of which was excluded as it presented only preliminary data of a later analysis

reported in one of the included abstracts. The MS also used data from the manufacturer's clinical study reports. One full paper describing the study, currently in press, was provided as Academic In Confidence, but no data additional to that in the MS has been used in this report. The RCT does not have a BSC arm, meaning the comparator for this RCT does not fit the final scope. However, the MS section 6.4 postulates that it is highly unlikely that the survival data of the comparator dose of trabectedin regimen is inferior to that expected with a placebo or inactive agents. This seems to be a reasonable assumption. However placebo, along with lack of efficacy, would not convey adverse events.

In section 6.8 of the MS supplementary data were presented from three uncontrolled phase II trials of trabectedin (Table 2). These all studied trabectedin at the licensed dose. These studies included patients with L-sarcomas and also those with other types of STS, synovial sarcoma[2,3,4] malignant Schwannoma,[2,3] malignant fibrous histiocytoma or fibrosarcoma,[3,4] neurosarcoma angiosarcoma.[3] Participants in all three of these studies had performance status (PS) 0 or 1. Prior chemotherapy is reported as all patients had been previously treated with anthracyclines, and 80% had also received prior ifosfamide therapy,[2] or 98% prior anthracycline 91% prior anthracycline and ifosfamide,[4] or 94% prior chemotherapy for advanced STS.[3]

Due to the lack of relevant comparator group in the included trabectedin trials, the MS section 6.4 reports data from other studies that may equate to BSC.

The MS acknowledged that there are limitations of historical comparisons, in this case data were from the 1980s and 1990s.

For OS, the data for the proposed comparators were taken from four phase II studies of adult advanced pre-treated STS patients in an EORTC STBSG database. The data presented in the MS was taken from an unpublished analysis of these studies, which had been submitted to EMEA and was made available to ERG.[5] Patients failing ifosfamide as second-line therapy, with no further chemotherapy, with survival calculated from failure of ifosfamide,

provided a suitable comparator in terms of prior therapy. In the ifosfamide studies 64% of patients were taking chemotherapy after failure of ifosfamide[5] rather than just BSC. The ifosfamide studies included patients with L-sarcomas and other types of STS[6,7] but the EORTC reference[5] also provides data restricted to L-sarcomas and PS 0 or 1, which would be equivalent to eligibility to the phase II RCT of trabectedin.

OS data were also provided for patients on dacarbazine or etoposide, with OS calculated from start of this therapy. OS data calculated from progression on dacarbazine or etoposide were not presented. The ERG is informed by clinical advisors that it is unlikely that etoposide would be used for this indication due to lack of proven activity. Dacarbazine may be used in UK practice as second or third line therapy, and so might be considered a suitable comparator, although it is not BSC and therefore doesn't match the final scope. The population in the phase II EORTC STBSG study of high dose dacarbazine (20 min i.v. infusion at an initial dosage of 1200 mg/m^2, every 3 weeks)[8] differed from that of the included RCT in that approximately 30% of the population had L-sarcomas, whereas the RCT had L-sarcoma as the eligibility criterion. The rest of the population of the phase II study of dacarbazine comprised synovial cell sarcoma, malignanfti brous histiocytoma, fibrosarcoma, neurofibrosarcoma, miscellaneous. The phase II study of dacarbazine had 14% patients with ECOG performance status 2, with the rest 0-1, whereas the RCT had all patients with ECOG PS 0-1.

For PFS, the data for the comparator were taken from a paper[9] that reported on phase II studies from the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC STBSG). The included studies varied in treatment and prior treatment of the populations, and the MS has selected the pre-treated population studies as being more relevant, which is appropriate. However, it is apparent from the paper[9] that for some patients pre-treatment was adjuvant rather than for advanced disease. Table 3 of the MS describes treatment regimens as: active agents ifosfamide or dacarbazine after failure of an anthracycline-containing regimen; Inactive agents mitozolomide, nimustine, fotemustine,

miltefosine, liposomal muramyl tripeptide phosphatidylethanolamide, temozolamide, etoposide, tomudex and gemcitabine – with the possible exception of gemcitabine these agents would not be used in UK practice. From this it appears that active agents are the closer approximation for a relevant comparator, although it is unclear whether those patients on dacarbazine have been exposed to ifosfamide (unlike the population specified in the final scope), and for those on ifosfamide the PFS rates would be calculated from start of ifosfamide therapy rather than following failure.

4.1.4 Details of any relevant studies that were not included in the submission?

The ERG is confident that there are no published or ongoing randomised trials comparing trabectedin with BSC. The ERG does not know whether additional studies could have been found to provide data on effectiveness of BSC following failure of anthracycline and ifosfamide therapy, or whether the data provided in the MS from studies of ifosfamide, dacarbazine or etoposide included all relevant studies of these chemotherapies.

4.1.5 Description and critique of manufacturers approach to validity assessment

The validity assessments performed by the manufacturer for the included RCT and phase II studies were appropriate. There was no validity assessment for data proposed as equivalence for BSC comparators. The MS section 6.3.6 found the RCT to be of adequate methodological quality with some limitations. The MS has stated that allocation was not concealed, however allocation concealment generally refers to randomisation of participants, that is avoiding selection of patients to a particular arm of the trial, rather than blinding of participants or investigators. The randomisation technique described by the MS suggests that both randomisation technique and allocation concealment were adequate. The trial had both blinded and unblinded outcome assessors, the MS reports both sets of results. The MS acknowledges that the cross-over design of the study will affect the OS results. The study population was limited to L-sarcomas and the MS suggests this represents approximately 40-50% of all STS in the UK.

4.1.6 Description and critique of manufacturers outcome selection

The ERG judged this to be an appropriate approach.

4.1.7 Describe and critique the statistical approach used

No meta-analysis was presented as there was only one RCT. This was the appropriate approach.

4.1.8 Summary statement

The MS provided a thorough account of the only available randomised controlled trial, a phase II study, on trabectedin in the relevant population, and also provided details of three uncontrolled phase II studies of trabectedin. The ERG believes that no relevant studies of trabectedin have been missed. However studies addressing the decision problem directly are not available. The MS attempts to present data approximating BSC, but acknowledges there are limitations to this approach. Within the phase II RCT, the population, while relevant, consisted only of L-sarcomas, representing approximately 40-50% of all STS. MS section 6.3 states that the phase II studies suggested a slightly higher efficacy for trabectedin in L-sarcomas relative to other histological types.

4.2 Summary of submitted evidence

4.2.1 Summary of results

This section presents the main clinical effectiveness evidence, as reported in the MS, considering the outcomes included in the final scope. Data presented from the included RCT is the blinded (rather than unblinded) outcome assessors' data, and intention to treat data.

Overall survival

The RCT included in the MS section 6.4, found no significant difference (p=0.1985) between trabectedin regimens, with median survival 13.9 months (95% CI: 12.5-18.6) for the q3wk 24-h regimen and 11.8 months (95% CI: 9.9-14.9) for the qwk 3-h regimen.

One-year OS rates did not differ significantly (p=0.0770), at 60.3% (95% CI: 52.0-68.5) for the q3wk 24-h regimen and 50.0% (95% CI: 41.5-58.4) for the qwk 3-h regimen.

From the phase II uncontrolled trials overall survival was reported as median 12.8 months[4] or 9.2 months[3], or overall survival rate at 1 year 72%.[2]

For the data from EORTC STBSG as proposed comparator, which were historical controls including patients on further chemotherapy or BSC, the MS reports median OS of 5.9 months (n=105) for patients failing second-line ifosfamide.[5] [redacted] Although likely to be less relevant comparators, reported median OS for patients from start of dacarbazine was 6.6 months (n=50), or 6.3 months (n=26) for patients treated with etoposide.

Progression-free survival

The RCT included in the MS section 6.4, reported significantly (p=0.04), superior PFS for the licensed dose of trabectedin (median 3.3 months) over the comparator trabectedin dose (median 2.3 months). (Table 55 of MS) The PFS rates for the licensed dose of trabectedin q3wk 24-h were 51.5% (95% CI: 43.0 - 60.1%) at three months and 35.5% (95% CI: 27.1 - 43.9%) at six months. For the comparator dose of trabectedin the PFS rates were 44.7% (95% CI: 36.0 - 53.3) at three months and 27.5% (95% CI: 19.4 - 35.5) at six months.

From the phase II uncontrolled trials progression-free survival was reported as median 1.9 months,[4] or estimated progression-free survival at 6 months 24.4%[2] or 29%.[3]

The data presented from EORTC STBSG (pooled studies) give PFS rates as 39% at 3 months, and 14% at 6 months for patients treated with ifosfamide or dacarbazine after failure of anthracycline. Although likely to be a less relevant

comparator, PFS rates reported for patients from pooled studies on “inactive” regimens were 21% at 3 months, and 8% at 6 months.

The MS section 6.4 also states that the primary endpoint of the included RCT was time to progression, and that was significantly superior (HR 0.734, p=0.03) for the licensed dose of trabectedin (median 3.7 (95% CI: 2.1 - 5.4) months) over the comparator trabectedin dose (median 2.3 (95% CI: 2.0 - 3.5) months).

Response rates (including disease stabilisation)

The MS section 6.4 gives response rates from the included study. With no complete responses, as assessed by blinded outcome assessors, the response rates were based on partial responses of seven patients (5.1%) in the licensed dose of trabectedin group and two patients (1.5%) in the comparator trabectedin dose (non-significant between groups p=0.1724). Stable disease was the best response for 66 patients (48.5%) in the licensed dose of trabectedin group and 52 patients (38.8%) in the comparator trabectedin dose group. The PD rate was 38.2% in the licensed dose q3wk 24-h group and 51.5% in the comparator dose of trabectedin qwk 3-h group.

Adverse effects of treatment

The MS section 6.7 presents safety data for the licensed dose of trabectedin from the included RCT and three phase II studies. For the RCT, deaths attributed to trabectedin occurred in 3.1% in the licensed dose, and 2.3% in the comparator group. Across the four included studies, rates of grade 3/4 haematological events varied: neutropenia 34-61%; febrile neutropenia 0.8-7%; thrombocytopenia 12-19%; anaemia 8-22%.

Across the four included studies, rates of grade 3/4 non-haematological events varied: aspartate aminotransferase (AST) elevation 26-48%; alanine aminotransferase (ALT) elevation 20-57%; Nausea 4-7%; Vomiting 2-9%; Asthenia/fatigue 0-15%.

Health-related quality of life

No health-related quality of life (HRQoL) data was presented in section 6 of the MS.

4.2.2 Critique of submitted evidence syntheses

No meta-analysis was possible as only one RCT was included in the MS.

4.2.3 Summary

Limited data were available to address the decision problem. The manufacturer's search strategy was adequately reported. Processes and validation of study screening and data extraction appear to have been appropriate. The RCT gives data on the licensed dose of trabectedin in patients with L-sarcomas and with ECOG PS 0-1, and showed improvement over a comparator dose of trabectedin. Uncontrolled phase II studies suggested L-sarcomas may have responded better to trabectedin than other types of sarcoma. Data approximating BSC were presented, the MS acknowledged there are limitations with providing historical controls.

5 ECONOMIC EVALUATION

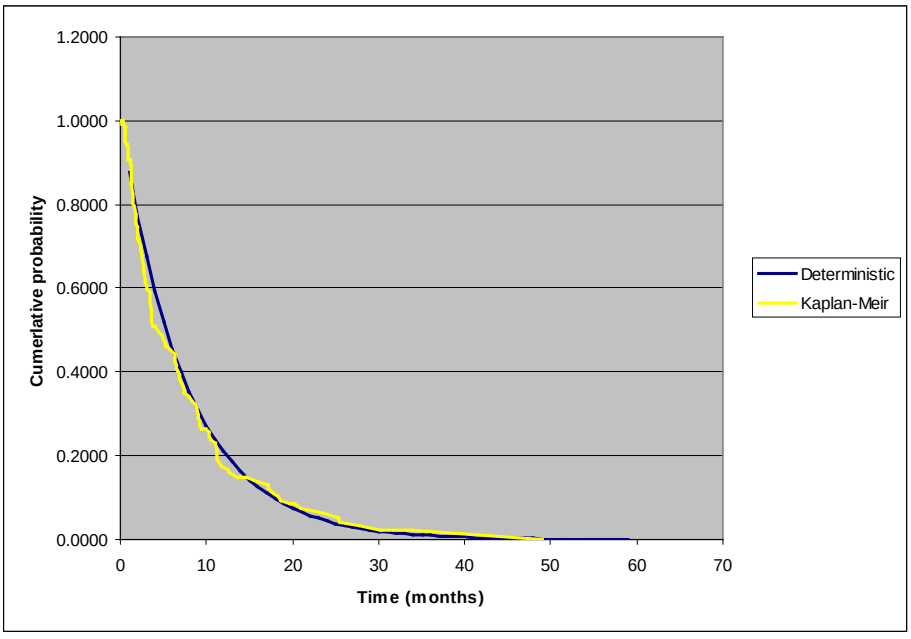
5.1 Overview of manufacturer's economic evaluation

5.1.1 Natural history

The natural history for patients who receive BSC after failure with anthracyclines and ifosfamide has been estimated from pooled data of four previously published trials obtained from the EORTC STBSG. It is believed that the effectiveness was taken from the point where the patient failed chemotherapy (ifosfamide, dacarbazine or etoposide), although the survival data could not be verified by the ERG. The natural history may therefore not be appropriate for patients who are contraindicated for anthracyclines and / or ifosfamide.

All patients receiving BSC start the model in a progressed disease state (PD) and therefore only OS has been evaluated from the EORTC dataset for the natural history arm. A Weibull model was fitted to these data with the fit shown in Figure 1, which is a reproduction of Figure 11, p68 of the MS.

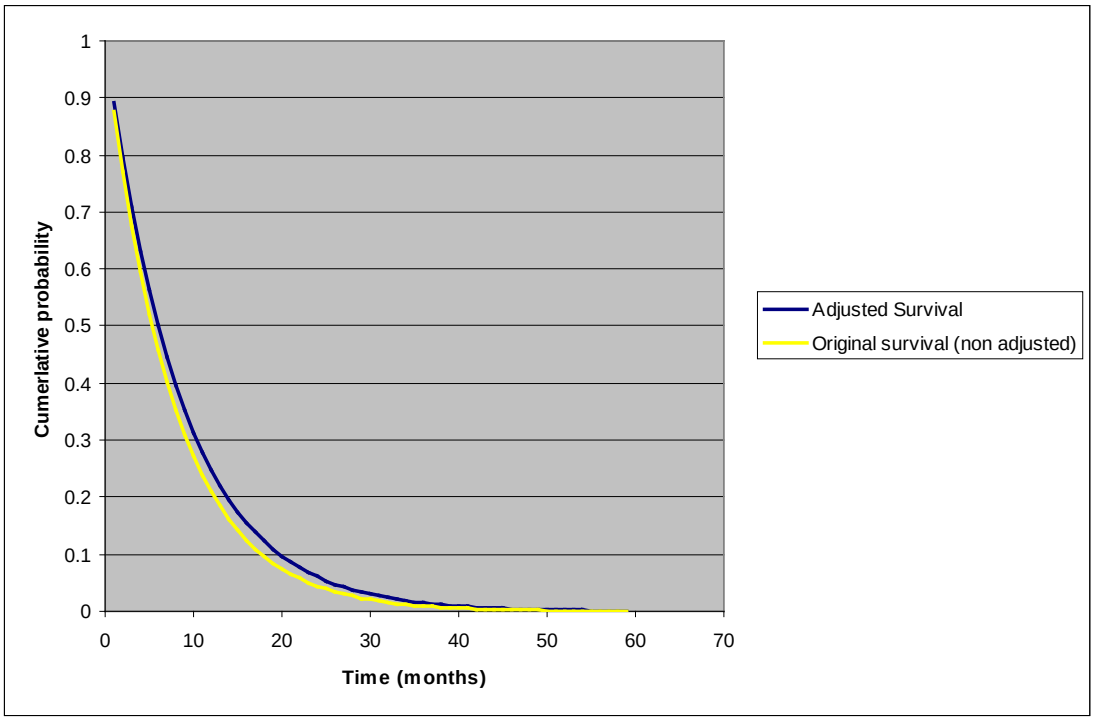
Figure 1: Fit of the Weibull curve for the OS for BSC



Patient characteristics were different between the treatment and BSC arm. Following correspondence with the ERG the manufacturer adjusted the survival curve for OS for BSC by using dummy variables for the WHO

performance score, histopathology (L-sarcomas), age and gender. The comparison for the Weibull curve for OS before and after adjustment is shown below in Figure 2. It is seen that his adjustment increased the expected survival of patients on BSC.

Figure 2: Fit of the Weibull curve for OS for BSC before and after adjustment



5.1.2 Treatment effectiveness within the submission

The primary RCT (STS-201 trial) used to model the effectiveness of trabectedin was conducted in patients with L-sarcomas only after prior treatment with a regimen containing at least an anthracycline and ifosfamide (combined or sequential). Effectiveness from the 24-hrq3wk arm from the STS-201 trial was selected to represent the effectiveness of trabectedin for the base case, as this is the licensed dose. As a sensitivity analysis, the pooled effectiveness from three initial phase II non comparative studies conducted among 183 soft tissue sarcoma patients (100 with L-sarcomas; 83 with non-L-sarcomas) was also modelled.

Weibull curves were fitted to the Kaplan-Meier curve for the TTP and OS assuming that these were independent. At the request of the ERG, Log-

logistic and Gompertz distributions were also explored. The manufacturer reported that the use of these distributions had only a little impact on the results.

The analyses used the TTP curve, rather than the progression free survival (PFS) curve. It was believed that the PFS curve would have been more appropriate as this includes all mortality, rather than just death due to STS, and because TTP and OS were fitted independently. The use of TTP with OS allows for a patient to die, but not be recorded as progressing. This was changed by the manufacturer allowing results to be generated using either TPP or PFS. The use of PFS instead of TTP had little impact on results.

Finally, as commented in 5.1.1, a revised model submitted by the manufacturer adjusted the survival curve for BSC to take into account differences in patient characteristics between the BSC and trabectedin arm. Following a request by the ERG, Weibull curves for trabectedin were also calculated using age, gender and severity as covariates. These Weibull curves for TTP for trabectedin are provided in Figure 3 and Figure 4.

Figure 3: Fit of the Weibull curve for TTP for trabectedin

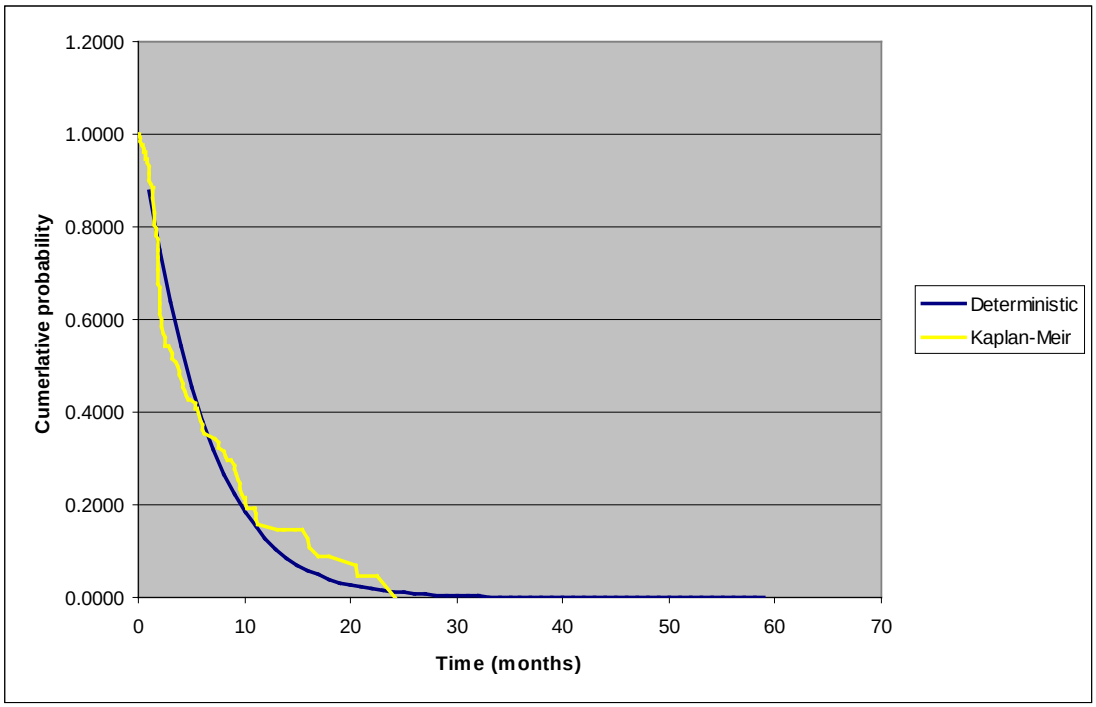
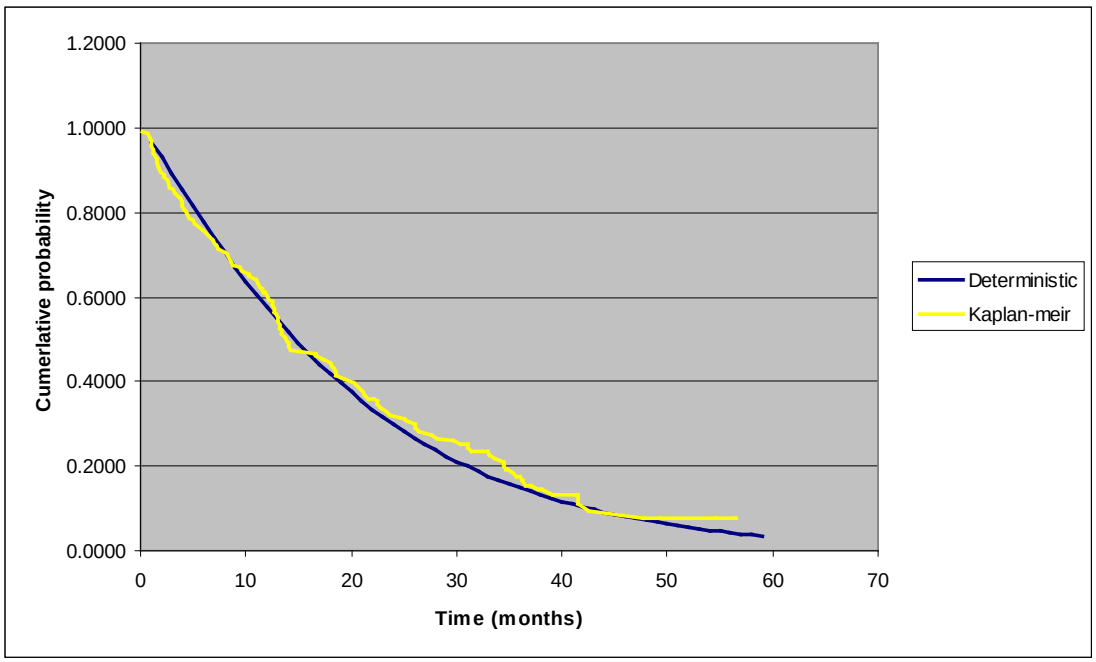


Figure 4: Fit of the Weibull curve for OS for trabectedin



5.1.3 Health related quality of life

No studies were identified by the manufacturer regarding the quality of life of STS patients. The manufacturer used health states utilities for lung cancer as a proxy for utilities in STS, following discussion with their clinical experts on the comparable prognosis and disease stage. These values were calculated

from a mixed-model with random effect[10] and have been used in a previous appraisal for lung cancer.[11] The average utility during PFS and PD was assumed to be 0.653 and 0.4734 respectively. The manufacturer assumed that health state utilities in PFS or PD were similar for patients independent of treatment.

The manufacturer estimated the utility associated with hospitalisations due to adverse event associated with trabectedin treatment was equal to that associated with nausea and vomiting (0.61), as this was reported to be a frequent adverse event, with the further assumption that this condition would last a full month. This would equate to a QALY decrement of 0.004 for every patient that was hospitalised. Adverse events were assumed to occur only in the first cycle of trabectedin treatment.

In response to comments made by the ERG, the manufacturer included the disutility associated with developing grade 3 or 4 neutropenia, which occurred in 47% of patients in the STS-201 trial. The utility associated with neutropenia (0.56) was assumed to last one week. This would equate to a QALY decrement of 0.002 for every patient with neutropenia.

No disutility due to adverse events was modelled for BSC patients.

5.1.4 Resources and costs

Three main categories of costs were considered:

- Costs associated with trabectedin treatment
- Costs associated with disease management
- Costs associated with adverse events.

5.1.4.1 Costs associated with trabectedin treatment

The original model submitted by the manufacturer calculated the average cost per patient based on the mean dose intensity per cycle and a hypothetical body surface area (BSA) of 1.7 m^2 with all treatment costs applied in the first cycle of the model. The ERG had concerns that the BSA was not consistent

with that reported in the trial, in that all the costs were applied within the first time period and that the methodology used would underestimate costs as trabectedin is packaged in discrete vials of 1mg or 0.25mg, which would be discarded once open.

In response to these concerns, the manufacturer changed the methodology used to estimate the acquisition cost of the drug. The cost per cycle of treatment was calculated using the mean numbers of vials of 1 mg and 0.25 mg used per cycle in the STS-201 trial.

In addition, the manufacturer used the proportion of patients receiving trabectedin at each cycle of the model based on the proportion observed in the STS-201 trial. Note that this proportion is lower compared with the proportion in PFS, which is assumed to account for those patients who may, for varying reasons, not receive treatment within a cycle. However, discrepancies were observed for the proportion when comparing the raw data to that used within the model. The manufacturer was contacted regarding this issue and corrected the model. This correction, together with other amendments that had little impact, increased the cost per QALY ratio from £44,410 to £56,985 per QALY gained.

The manufacturer had used the proportion observed in the STS-201 trial for the pooled trabectedin analysis, which was not considered appropriate. The manufacturer was contacted about this issue and provided the distribution observed for the pooled analysis. This decreased the cost per QALY ratio from £64,665 to £50,017 per QALY gained.

In addition to the costs of trabectedin, the manufacturer included the cost associated with chemotherapy administration assuming that the drug would be administered during an inpatient stay. The cost was assumed to be NHS reference code SB12Z, with the 2006/2007 cost inflated to 2007/2008 prices[12] with a resulting cost of £319.61. In sensitivity analysis, trabectedin was assumed to be administered on an outpatient basis.

The cost associated with the injection of 20 mg of dexamethasone prior to chemotherapy was also included as recommended in the Summary of Product

Characteristics (SPC). The cost of dexamethasone was taken from the BNF[13] and was estimated to be £4.96 per injection.

5.1.4.2 Costs associated with disease management cost

The cost for individuals in PD was derived from a cost of illness study by Judson et al.,[14] which was conducted retrospectively among 47 patients in four centres throughout the UK. The manufacturer included the costs of diagnostic tests and inpatient stay that were not considered related to chemotherapy. This equated to a cost of £171.91 per month.

Following dialogue with the manufacturer, a cost was subsequently included for patients in PFS and was assumed, in the absence of data, to be half the cost for patients in PD (i.e. £85.96 per month). The cost associated with hospice stay and palliative care[14] was also included and was applied when patients entered the death state.

5.1.4.3 Costs associated with adverse events

Only the costs associated with adverse events which resulted in hospitalisation were included in the MS. Originally, the cost of hospitalisation was assumed to be equal to the cost associated with nausea and vomiting given that these were considered the most common drug adverse events leading to hospitalisation.

After comment by the ERG, the detailed diagnosis for each hospital stay was obtained and the average cost was calculated based on their respective unit cost.[12]

Costs associated with other adverse events such as neutropenia were excluded as the manufacturer argued that they did not lead to hospitalisation, were reversible, did not follow a cumulative trend and were rarely associated with fever and infection.

No adverse event costs were modelled for patients in the BSC arm.

Furthermore, no monitoring costs were included in the MS.

5.1.5 Discounting

Future costs and benefits were discounted at 3.5% annually as specified in the NICE reference case.[15]

5.1.6 Sensitivity analyses

Uncertainty was explored in one-way sensitivity and probabilistic sensitivity analyses (PSA).

The following parameters were tested in the one-way sensitivity analysis:

- the discount rate
- the number of vials set at the lower or upper value of the 95% CI limit
- the cost of the administration of chemotherapy set at the lower or upper value of the 95th CI limit
- health state utilities set at the lower or upper value of the 95th CI limit
- administration of chemotherapy on an outpatient basis

The shapes, scales and covariate coefficients of the Weibull curves, disease management costs, adverse event rates, the number of vials per cycle and health state utilities were varied in the PSA.

Three additional scenarios were also presented:

- using pooled effectiveness for trabectedin from three uncontrolled phase II trials
- assuming that 33% of patients in BSC receive further chemotherapy
- assuming that 100% of patients in BSC receive further chemotherapy

5.1.7 Model validation

The manufacturer states that third party validation was conducted by an experienced programmer in terms of:

- accuracy of input data: checking by comparing the model inputs against data sources referenced,
- top down test: change in model inputs to identify failure in model logic or material computation errors,
- computation checks of sensitivities: checking of the translation of drug prices into state costs; derivation of transition rates from clinical inputs; derivation of state distributions from transition rates,
- report: the model input and output was checked by reviewing the report against the model.

5.2 Critique of approach used

5.2.1 Cost-effectiveness searches

The ERG could not replicate exactly the search results undertaken by the manufacturer, which is discussed further in Appendix 2. However the ERG does not believe it likely that relevant cost-effectiveness studies involving trabectedin have been not identified.

5.2.2 Cost-effectiveness model

5.2.2.1 Model structure

The model developed by the manufacturer is a simple state-transition model with individuals moving between three discrete health states:

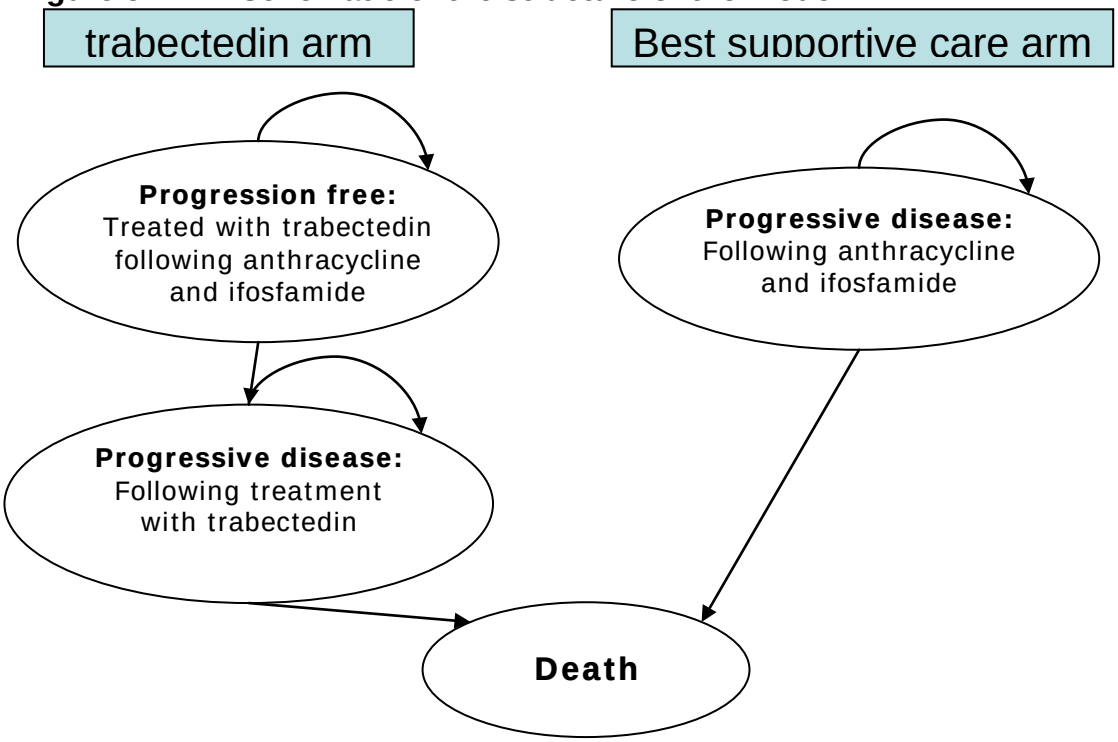
- PFS
- PD
- and death.

The comparator selected for analysis is BSC. Administration of other chemotherapies in addition to BSC was explored in a sensitivity analysis.

Individuals in BSC enter the model in PD while patients treated with trabectedin enter the model in PFS. For patients in PFS, individuals were assumed to remain in this state until they experience disease progression and/or death. Individuals in PD remain in the current health state until death. A time horizon of 5 years with a monthly cycle length was employed.

The model schematic is shown in Figure 5, which was Figure 8 (p 65) in the MS.

Figure 5: A schematic of the structure of the model



The ERG had concerns that individuals treated with trabectedin entered the model in PFS whilst those on BSC entered the model in a PD. As the utility of being in PD is assumed to be 0.18 lower than that of being in PFS the different starting states will bias the model in favour of trabectedin.

Therefore, the ERG requested that the manufacturer provide additional analyses to estimate the likely cost per QALY where the patients assumed to enter the model at the same state regardless of treatment arm. In response, the MS presented a scenario where the utility for patients in BSC was adjusted assuming the utility for PFS (0.653) the first cycle of the model followed by a linear decline over the next four cycles to reach the utility for PD (0.473). The cost per QALY ratio rose from £56,985 to £61,064 per QALY gained.

5.2.2.2 Modelled population

The ERG had several concerns about the appropriateness of the modelled population.

Firstly, the population modelled for the base case using the STS-201 trial were adults with L-sarcomas after prior treatment with a regimen containing at least an anthracycline and ifosfamide (combined or sequential). It is unclear how the answers produced would relate to patients with all forms of STS, rather than just those with L-sarcomas.

Secondly, despite attempts to adjust the BSC survival curve there will still be uncertainty in the comparability between the BSC and trabectedin arm as it is believed that patients in the STS-201 trial were highly selected and that the subgroup of patients included in the trial already had a high survival. In this trial, 2/3 of patients had received additional agents prior to anthracyclines and ifosfamide treatment with the median number of lines of chemotherapy for patients included in the trial being 1 (range: 0 – 6). Furthermore it is uncertain whether the use of historic data for BSC affected the estimated cost effectiveness.

Thirdly, the manufacturer presented a scenario where a proportion of patients in BSC was treated with other chemotherapies. After discussion with our clinical experts the ERG considered that the scenario was not relevant for the decision problem given the small proportion of patient treated with these chemotherapies after failure with anthracyclines and ifosfamide. In addition, numbers of errors were found for this scenario increasing the uncertainty in results. It is noted that the estimated cost-effectiveness ratio in these scenarios were less favourable to trabectedin.

5.2.2.3 Effectiveness data and extrapolation

The method used to estimate the effectiveness of trabectedin and the natural history was considered appropriate after the adjustment of Weibull curves by for demographic and patient characteristics. Furthermore, the data required little extrapolation as the vast majority of patients had died by the end of the data collection period. The ERG comment, however, that as the natural

history and intervention data have not been taken from an RCT, the comparability of these data is uncertain.

5.2.2.4 Costs

5.2.2.4.1 Drug costs

The ERG found the general method used to estimate the cost of trabectedin appropriate. However, there are limitations in this approach. Firstly, the cost of trabectedin is underestimated given that few individuals were still being treated at the end of the trial follow-up period who were assumed to not incur future cost in the model. Secondly, the proportion of patients receiving each cycle of treatment was assumed to be fixed and did not change in the PSA.

Concerns were also expressed on the method used to estimate the cost associated with other chemotherapies presented in sensitivity analysis. It is unclear how the cost of other chemotherapies was calculated. Firstly, a different method was used to estimate the cost of other chemotherapies using the proportion of patients in TTP instead of the actual proportion of patients who would receive these chemotherapies which would overestimate the cost. Secondly, the cost was calculated assuming a hypothetical BSA of 1.7 m2. For comparison, the average BSA in the STS-201 trial was 1.84. Importantly, it appears that the calculated cost per cycle was adjusted to the proportion of patients who would receive these chemotherapies but this was already done in the result section. Finally, it appears that the calculated cost per cycle presented by the manufacturer corresponded in fact to a cost per patient assuming 6 cycles of treatment. As stated previously the ERG does not consider the scenarios where other chemotherapies are used as appropriate.

5.2.2.4.2 Disease management costs

The model has an NHS perspective which is appropriate. The method was also considered appropriate given the absence of other data. One concern was that no management costs were included in PFS for the chemotherapy scenario.

5.2.2.4.3 Adverse event costs

The ERG believes that the approach used to model the cost of adverse events was appropriate. However, there appeared to be discrepancies in the denominator when calculating the adverse event rate. Discrepancies were also observed between the mean values for the deterministic and probabilistic analyses. Alternative values for adverse event rates were explored by the ERG and were seen to have a minimal impact on the cost per QALY ratio.

In addition, based on the SPC, additional monitoring of haematological parameters bilirubin, alkaline phosphatase, aminotransferases and CPK should occur weekly during the first two cycles of therapy, and at least once between treatments in subsequent cycles. This was not included in the manufacturer model which could thus underestimate the cost per QALY ratio.

Furthermore, adverse event rates from the STS-201 trial were used for the pooled trabectedin analysis which may not be appropriate given the differences in patient characteristics.

Finally, no cost due to adverse event was included for patients who would receive further chemotherapies in addition to BSC.

5.2.2.5 Health state utilities

As described in section 5.1.3, health state utilities taken from patients with lung cancer were used as a proxy for the utility for patients with STS. The source used to estimate utility has already been used in a previous NICE appraisal.[11] It is unclear how comparable the utility values are between patients with STS and those patients with lung cancer.

For patients hospitalised due to adverse events, the manufacturer assumed that the QALY decrement associated with hospitalisations was similar to the QALY decrement associated with nausea and vomiting. This may not be appropriate given that vomiting was only one of the seven causes for hospitalisation. The QALY decrement of 0.004 per patient hospitalised appears, at face value, to be low. However, an exploratory analysis was conducted by the ERG by varying the disutility associated with nausea and

vomiting between 0.05 to 0.6 and showed to have little impact on the cost per QALY ratio (£57,270 using extreme value of 0.6).

The utility for individuals receiving trabectedin or BSC was also different at baseline, which biases the results in favour of trabectedin. Applying a higher utility for patients in BSC than previously assumed for the first 4 cycle of the model would increase the cost per QALY ratio from £56,985 to £61,064.

Finally, as for costs, no disutility due to adverse events was modelled for patients who would receive further chemotherapies in addition to BSC.

5.2.2.6 Discounting

Discount rates of 3.5% per annum were used for both costs and benefits. This is in accordance with the NICE methods.[15]

5.2.2.7 Half-cycle transitions

Initially, a half cycle correction was incorporated into the model by halving the costs, life years gained, and utilities in the first and last time cycles. This methodology was considered accurate only when undiscounted values are used. The manufacturer was requested to use the usual methodology of averaging the numbers of patients in $time_t$ and $time_{t+1}$ to estimate the average number of patients in each health state throughout the cycle. This was corrected by the manufacturer. However, the last cycle of the model was not taken into account in the MS. This was revised by the ERG assuming that all patients had died after 5 years. This had a minimal effect on the cost per QALY ratio.

5.2.2.8 Model validation

Despite the manufacturer validation, a number of errors were found in the final model submitted to the ERG.

Errors included:

- Cells not correctly linked for the result of the PSA for the pooled trabectedin analysis (sheets ’results’: Cells(c64:d65))

- Discrepancies in the denominator for the calculation of adverse event rate (sheets 'Inputs': Cells(c33), Cell(c43))
- Discrepancies in parameters of the beta distribution for the adverse event rate due to neutropenia (sheets 'Inputs': Cells(c117:c118))
- Cell not correctly linked for the calculation of management costs for the PSA (sheets 'Inputs': Cells(b39))
- Half cycle correction did not include the last monthly cycle
- Cell not correctly linked for the calculation of QALY in the first cycle for PFS for the pooled analysis in the trabectedin arm for the PSA (sheets 'trabectedin trace': Cells(x202))
- New methodology for half-cycle correction not correctly linked for BSC
- Cell not correctly linked for discount rate in BSC for the calculation of life years gained for the PSA
- In the chemotherapy scenario, the cost for death was not linked to half cycle results (sheets 'chemo trace': Cells(h271:329))
- The data for the CEAC and scatterplot for the pooled analysis were not correctly linked.

Furthermore, transcribing errors were also found between the results of the model and results reported by the manufacturer in his final responses to the ERG clarification points. A discrepancy was found for results of the one way sensitivity analysis, and deterministic results for the pooled analysis. The CEAC and scatterplot reported for the pooled analysis were also subject to transcription error.

5.2.2.9 Assessment of uncertainty

The following parameters were varied stochastically in the PSA:

- health state utility values
- management costs
- the number of vials required
- the rate of adverse events
- the shapes, scales and covariate coefficients of the Weibull curves for TTP and OS.

Medical management costs were varied between ± 25% and were modelled using a gamma distribution which is an appropriate statistical form. Utilities and rates of adverse events were modelled using beta distributions which are appropriate distributions. The parameters of the Weibull distributions were assumed multivariate normal which is appropriate methodology.

The model assumed no correlation between TTP and OS, nor correlation between the utility estimates for health states nor the number of 1mg and 0.25mg vials used. Furthermore, the proportion of patients treated did not vary according to the proportion of patients in PFS. It is unclear how incorporating these correlations would change the mean cost per QALY, although it is likely that the range in the results generated from the PSA would increase.

The 95% CI for some utilities have not been correctly calculated as the lower 95% CI for two distributions have been combined. This methodology is incorrect and will over-estimate the width of the CI for that state.

In addition, only vials of 1 mg were varied in one sensitivity analysis. The disutility associated with neutropenia was also not included. Finally, the cost of administration in outpatient basis was assumed to be £170 in the model while stated to be £181.29 in the report.

5.3 Results included in manufacturer's submission

The ERG twice contacted the manufacturer to provide clarification about the methodology used. For simplification, only the results submitted in the manufacturer's final response to the ERG are presented here. Note that results are presented using the TTP curve and with the BSC arm adjusted to take into account differences in patient casemix.

In the revised base case analysis (page 8 in the manufacturer response to the ERG of the 24 April 2009) the manufacturer estimated that trabectedin would provide 0.81 QALYs with an associated cost of £29,110. The corresponding

values for BSC were 0.34 and £1,965 which equates to a cost per QALY gained of trabectedin versus BSC of £56,985.

In sensitivity analysis, a scenario was presented for all STS types assuming the efficacy of trabectedin to be that observed from three previous Phase II non comparative studies. The results from the model differed from those reported in the revised submission. Given that the results in the MS were subject to transcription error we use those in the model. The cost per QALY for this scenario was £50,017.

Two further scenarios were explored: 33% of patients on BSC receiving chemotherapy and 100% of patients on BSC receiving chemotherapy. The corresponding cost per QALY ratios were £62,044, £80,279 respectively (page 9 in the manufacturer response to the ERG of the 24 April 2009). It is noted that the ERG do not consider these scenarios appropriate.

Table 3 and 4 summarises the results produced by the univariate sensitivity analyses. The results reported were subject to transcription error and so reported in the model are used. Results for the base case are presented in bold. Results were sensitive only to the change in utility values.

Table 3: Results of the discount rate sensitivity analysis

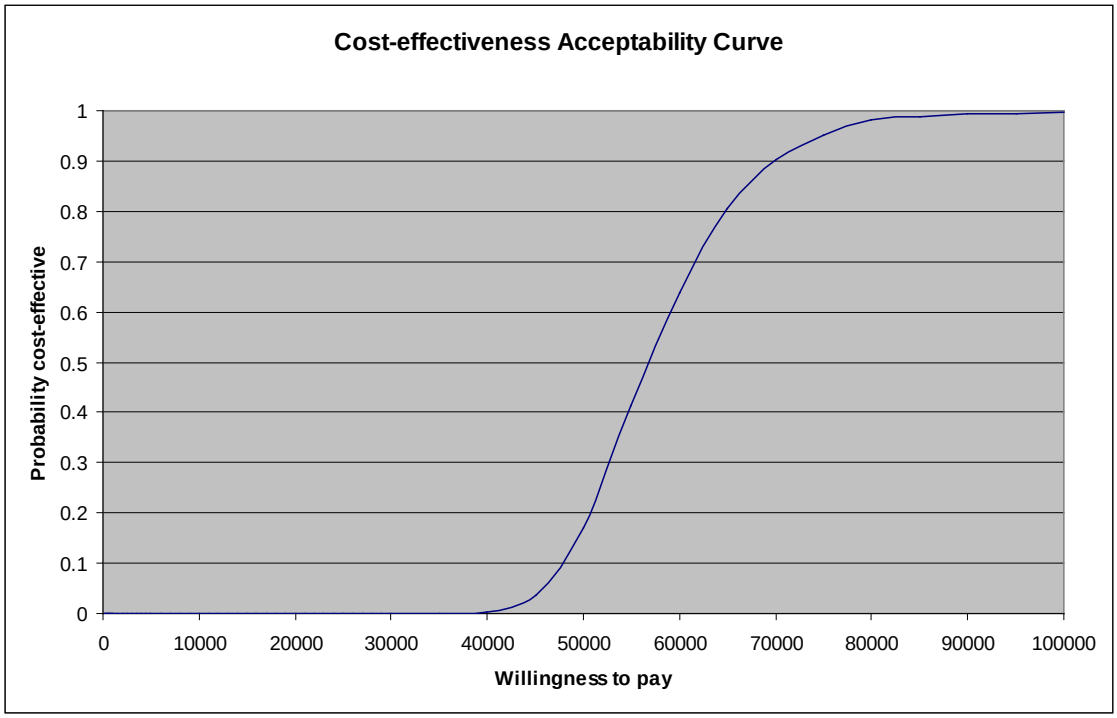
	Inc. costs	Inc. QALYs	ICER
Discount rate is 3.5% for both costs and benefits (Base case)	**£27,145**	**0.476**	**£56,985**
Discount rate is zero	£27,290	0.494	£55,199
Discount rate is 6%	£27,049	0.465	£58,216
Discount rate is 6% for costs and 1.5% for outcomes	£27,049	0.486	£55,609

Table 4: Results of the univariate sensitivity analysis

	Inc. costs	Inc. QALYs	ICER
(Base Case)	**£27,145**	**0.476**	**£56,985**
Number of vials set to lower 95% CI value	£26,859	0.476	£56,385
Number of vials set to upper 95% CI value	£27,430	0.476	£57,584
trabectedin administration assumed to occur on an outpatient basis (HRG SB12Z)	£26,102	0.476	£54,796
Chemotherapy administration cost to lower quartile	£26,255	0.476	£55,118
Chemotherapy administration cost to upper quartile	£28,764	0.476	£60,385
Utility data at lower 95% CI value	£27,145	0.422	£64,265
Utility data at upper 95% CI value	£27,145	0.521	£52,144

PSA was conducted to explore the uncertainty in the cost per QALY ratio. The cost-effectiveness acceptability curve (CEAC)[16] for the base case is provided in Figure 6 and a scatterplot provided in Figure 7 which correspond to Figure 1 and Figure 2 (page 10-11 in the manufacturer response to the ERG of the 24 April 2009). Summary data on the cost-effectiveness of trabectedin at different willingness to pay values per QALY are provided in Table 5 which corresponds to Table 11 (page 11 in the manufacturer response to the ERG of the 24 April 2009).

Figure 6: Cost-effectiveness acceptability curve: base case comparison



The CEAC showed that trabectedin has a very low probability of being cost-effective at a threshold of £30,000 per QALY gained.

Figure 7: Scatter plot of PSA results

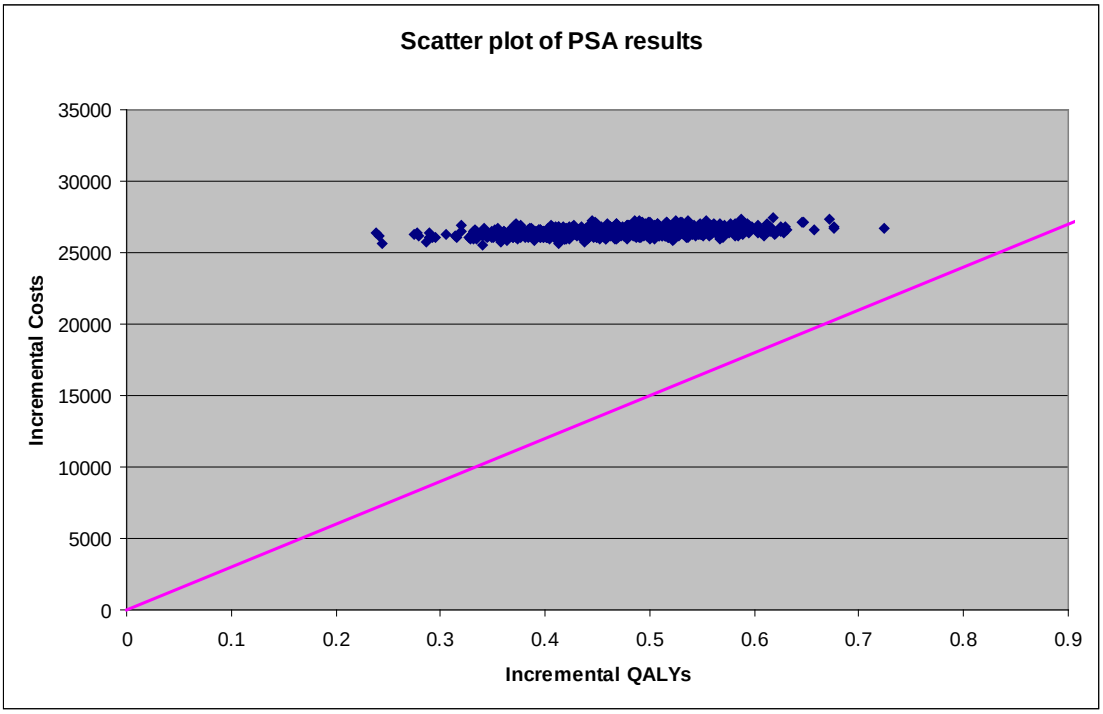


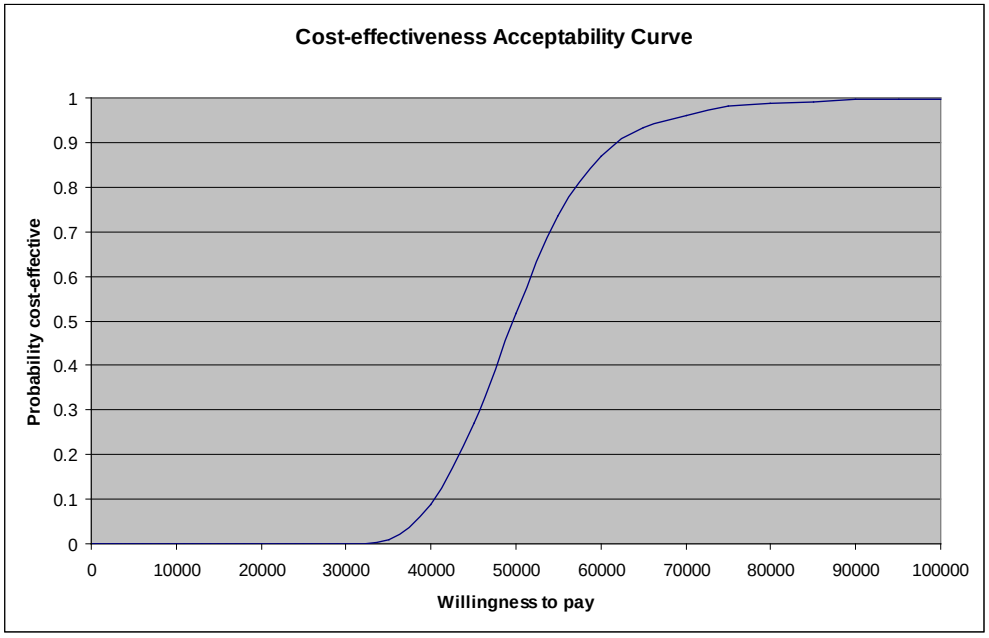
Table 5: Net benefit analysis

	Willingness to pay = £20,000		***Willingness to pay = £30,000***		***Willingness to pay = £40,000***	
	ENB	***P (CE)***	***ENB***	***P (CE)***	***ENB***	***P (CE)***
Trabectedin	-£3,768.79	0.000	£2,964	0.000	£9,696	0.098
BSC	£5,738.70	1.000	£9,192	1.000	£12,645	0.902

ENB = Expected Net Benefit P(CE) denotes the probability of cost effectiveness

Following a request by the ERG, PSA results for the pool analysis of trabectedin were presented by the manufacturer. CEAC is provided in Figure 8 and the scatterplot in Figure 9. These have been adjusted by the ERG as cells were not correctly linked within the supplied model. Summary data on the cost-effectiveness of trabectedin at different willingness to pay values per QALY are provided in Table 6.

Figure 8: Cost-effectiveness acceptability curve: using the non-comparative phase II studies (corrected by the ERG)



The CEAC showed that trabectedin has a low probability of being cost-effective at a threshold of £30,000 per QALY gained.

Figure 9: Scatter plot of PSA results using the non-comparative phase II studies (corrected by the ERG)

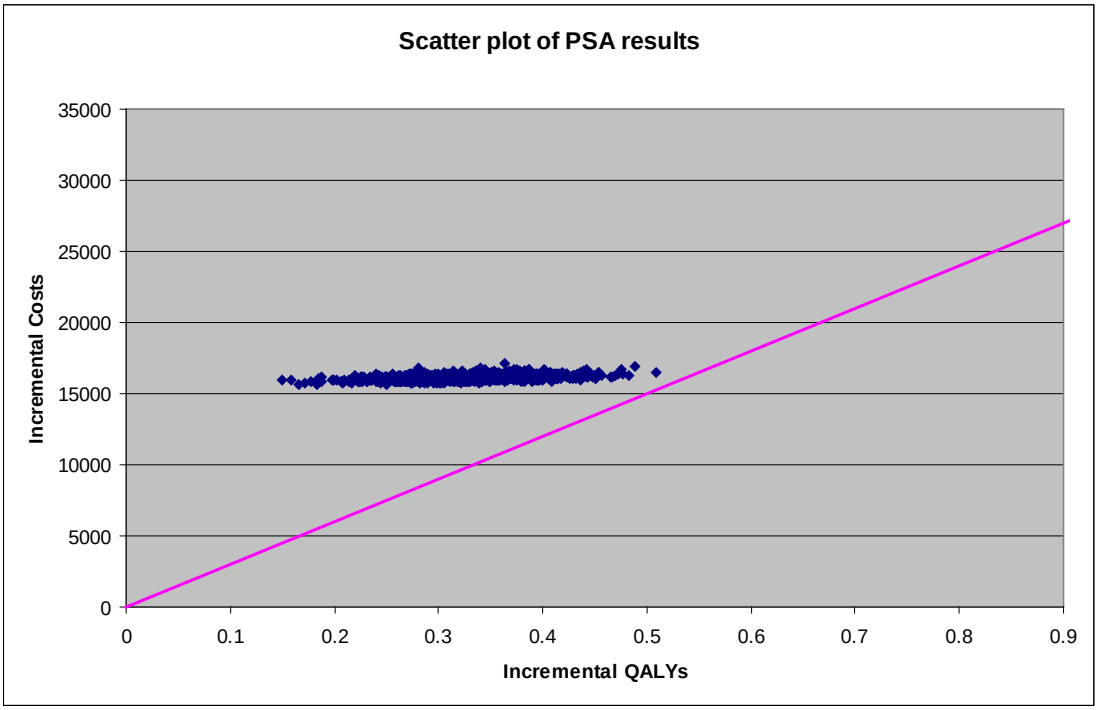


Table 6: Net benefit analysis

	Willingness to pay = £20,000		***Willingness to pay = £30,000***		***Willingness to pay = £40,000***	
	ENB	***P (CE)***	***ENB***	***P (CE)***	***ENB***	***P (CE)***
Trabectedin	-£3,768.79	0.000	£2,964	0.000	£9,696	0.098
BSC	£5,738.70	1.000	£9,192	1.000	£12,645	0.902

ENB = Expected Net Benefit P(CE) denotes the probability of cost effectiveness

5.4 Comment on validity of results presented with reference to methodology used

The errors reported in section 5.2.2.8 were corrected by the ERG and were shown to have a limited impact on either the cost per QALY ratio for the deterministic or probabilistic analyses (Table 7). Note that these results are underestimated because patients start in a different health state for trabectedin and BSC. An exploratory analysis conducted by the manufacturer assuming a higher utility for BSC the first 4 cycles of the model shown that the cost per QALY ratio would increase from £56,985 to £61,064. Results for the scenarios including further chemotherapies in addition to BSC are not presented as these were considered inappropriate.

Table 7: corrected cost per QALY ratio

	MS	ERG
BASE CASE	£56,985	£56,949
Pool analysis	£50,017	£49,992
PSA - Base case	£56,755	£57,375
PSA - Pool analysis	£48,033	£51,228

See accompanying text on discussion that the basecase is an underestimate of the cost per QALY gained ratio.

The ERG had concerns regarding the structure of the model and its ability to capture the cost-effectiveness of trabectedin for adults with advanced STS after failure of anthracyclines and ifosfamide.

Firstly, the ERG had concerns about the potential non-comparability between patients included in studies to derive the effectiveness for trabectedin and BSC, although it is noted that the manufacturer (following a request by the ERG) has explicitly included WHO severity score, histopathology, age and gender as explanatory variables for survival. Comparisons with historical data were necessary, as no RCT has been undertaken using BSC as a comparator; as such all effectiveness estimations will be subject to uncertainty. It is believed that patients in the STS-201 trial were highly selected and that the subgroup of patients included in the trial already had a high survival. In this trial, 2/3 of patients had received additional agents prior to anthracyclines and ifosfamide treatment with the median number of lines of

chemotherapy for patients included in the trial being 1 (range: 0 – 6).The impact of historical data for BSC is unclear.

Secondly, the analysis using the STS-201 trial focuses only on patients with L-sarcomas. It is unclear how the estimated cost per QALY ratio would relate to patients with other forms of STS.

Thirdly, health states utilities were taken from patients with lung cancer in the absence of data in STS patients, which may not be appropriate. The cost per QALY ratio was shown to be sensitive to changes in assumed health state utilities.

Finally, while a PSA was conducted to account for the joint uncertainty between parameters, it is believed that the uncertainty would be underestimated given:

- the lack of correlation between Weibull curves for TTP and OS,
- the proportion of patient receiving trabectedin remained fixed. Only the cost per cycle was varied
- No correlation was included between the number of vials of 1mg and 0.25 mg
- the lack of correlation between health state utilities

5.5 Summary of uncertainties and issues

The primary concerns were

- The potential non-comparability between patients included in studies to derive the effectiveness for trabectedin and BSC

- The focus purely in terms of patients with L-sarcomas only for the base case analysis using the STS-201 trial, meaning that assumptions must be made when considering other patients with soft tissue sarcoma

- The different starting health states for patients in BSC and trabectedin, which would introduce a bias favourable to trabectedin. An exploratory

analysis undertaken by the manufacturer has shown an increase in cost per QALY to £61,064 when this is taken into consideration

- The appropriateness of using utility values for patients with lung cancer for patients with STS
- The lack of correlation included within the model.

6 Additional work undertaken by the ERG

The iterations of dialogue between the ERG and the manufacturers resulted in a number of changes between the model initially submitted and the final model with the cost per QALY of the manufacturers' basecase increasing from £44,410 to £56,985. The larger concerns were corrected by the manufacturer and only a small number of analyses were undertaken by the ERG.

Given the uncertainty of the applicability of utility for lung cancer for patients with STS, the ERG explored the use of different combination of utility values for PFS and PD to estimate the likely effect on the cost per QALY ratio. Note that the disutility associated with adverse events was not changed. These analysis show that the cost per QALY ratio is sensitive to changes in the utility values.

Table 8: Change in utilities

Utility for PFS	**Utility for PD**	**Cost per QALY ratio**
Base case		
0.653	0.4734	***£56,985***
Sensitivity analysis		
0.8	0.7	***£43,760***
0.8	0.6	***£46,148***
0.8	0.5	***£48,811***
0.8	0.4	***£51,801***
0.7	0.6	***£50,297***
0.7	0.5	***£53,477***
0.7	0.4	***£57,087***
0.6	0.5	***£59,129***
0.6	0.4	***£63,574***
0.5	0.4	***£71,725***

7 Discussion

7.1 Summary of clinical effectiveness issues

The manufacturer's submission (MS) contains one RCT only and does not appear to have missed any relevant RCTs. The MS thoroughly describes the included RCT. The outcomes reported were relevant and appropriate.

The RCT only includes L-sarcomas, although non-comparative phase II studies include other forms of STS. However, the RCT compares two doses of trabectedin, and has no BSC comparator. From OS data presented to approximate BSC, the most suitable comparator was from patients having failed ifosfamide. Although populations were broadly similar to that of the RCT in terms of condition, they were from historical cohorts, included some patients with worse ECOG PS scores, and non-L-sarcomas, which would tend to bias against the BSC comparator. However, assuming that patients on the comparator dose of trabectedin in the RCT did not do worse than similar patients on BSC, there is evidence for the effectiveness of trabectedin at least in terms of PFS, for the selected group of L-sarcoma patients with ECOG PS of 0-1. There was a rate of deaths due to toxicity of 3.1% for the licensed dose of trabectedin in the RCT. Most common severe adverse events were neutropenia, although with low rate of febrile neutropenia, thrombocytopenia, and AST and ALT elevation although these were reported to be non-cumulative and reversible.

7.2 Summary of cost effectiveness issues

The manufacturer adjusted survival data for patients on BSC using WHO severity, age, gender and type of STS and reported a cost per QALY gained of £56,985 for the base case. It is unclear the effect that the historical nature of BSC data, which was taken from a different source than the trabectedin data would have.

The base case focuses on patient with L-sarcomas and it is unclear how results can be generalisable to other STS.

Patients in trabectedin and BSC enter the model in a different state which biases results in favour of trabectedin. An exploratory analysis undertaken by the manufacturer estimated that the cost per QALY would increase to over £60,000.

Uncertainties also exist about health state utility values. The appropriateness of using utility values for patients with lung cancer for patients with STS remain unclear, and the cost per QALY ratio was shown to be sensitive to this variable.

7.3 Implications for research

Ideally an RCT comparing trabectedin with BSC in comparable populations is needed to provide a measure of the efficacy of trabectedin. Were such a trial to be undertaken the utility of patients should also be recorded.

8 Appendices

Appendix 1: Search critique for clinical effectiveness searches

1) Re-run of the Medline and Embase Search Strategies

As, the ERG do not have access to Embase.com, the searches were carried out in Medline and Embase separately.

The search was re-run in MEDLINE (via OVID, 1950-March 2009) on 3rd April 2009 (see below). Not all index terms used in the Embase.com search could be translated to Medline as these index terms did not exist. This generated 64 references.

1	Yondelis/exp	0 results as not indexed on MEDLINE
2	Yondelis:ti,ab,de	56
3	trabectedin/exp	0 results as not indexed on MEDLINE
4	trabectedin:ti,ab,de	81
5	ecteinascidin 743'/exp	0 results as not indexed on MEDLINE
6	ecteinascidin 743':ti,ab,de	110
7	et 743'/exp	0 results as not indexed on MEDLINE
8	et 743':ti,ab,de	140
9	et743/exp	0 results as not indexed on MEDLINE
10	et743:ti,ab,de	20
11	OR:1-10	226
12	soft tissue sarcoma/exp	96326 Substituted for exp sarcoma/ as doesn't exist in Medline
13	soft tissue sarcoma:ti,ab,de	3143
14	sts/exp	0 results as not indexed on MEDLINE
15	sts:ti,ab,de	4230
16	soft part sarcoma/exp	0 results as not indexed on MEDLINE
17	soft part sarcoma:ti,ab,de	420
18	OR:12-17	100505
19	11 AND 18	67
20	11 AND 18 AND [humans]/lim	64

The search was re-run in Embase (via OVID, 1980-March 2009) on 3rd April 2009 (see below). Not all index terms used in the Embase.com search could

be translated to Embase via Ovid as these index terms did not exist. This generated 125 references.

1 exp Yondelis/ (512)
2 Yondelis.ti,ab,de. (56)
3 exp trabectedin/ (512)
4 trabectedin.ti,ab,de. (529)
5 ecteinascidin 743'.ti,ab,de. (112)
6 et 743'.ti,ab,de. (143)
7 et743.ti,ab,de. (20)
8 or/1-7 (541)
9 exp Soft Tissue Sarcoma/ (5725)
10 soft tissue sarcoma.ti,ab,de. (6433)
11 sts.ti,ab,de. (3526)
12 soft part sarcoma.ti,ab,de. (320)
13 11 or 10 or 9 or 12 (9617)
14 8 and 13 (128)
15 limit 14 to human (125)

In total, 140 unique clinical effectiveness results were retrieved by searching Medline and Embase separately (39 of the 140 were found in both Embase and Medline). The remaining 101 references were unique to Medline or Embase. This is comparable to the number cited by the sponsor submission (132). The slight difference in the numbers may be due to further references being added in the time period since the original searches or due to differences in the way Embase.com indexes articles.

The searches were replicated in the Cochrane Library and the same number of results was retrieved as stated by the sponsor submission.

Searching Medline in process (via Pubmed) also produced comparable numbers as stated by sponsor submission (this was not exactly the same as some time has passed between sponsor submission and re-running of searches). However, the ERG is satisfied these searches were carried out appropriately.

2) Search critique

Search strategy: The search strategy is adequate.

Sources: An adequate number of sources have been searched as directed by the guidance for sponsor submissions by Nice (i.e. Medline, Embase, Medline In-Process, The Cochrane Library). Other sources might have been included such as CINAHL, Science and Social Science Citation Index, BIOSIS. An extensive number of trial registries were searched. For cancer topics, key references are often found in the conference proceedings of the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO); these were not searched.

Limits: Papers were limited by using the 'human' limit

Overall, the searches are of adequate quality and adequate numbers of sources have been used according to guidance from NICE. In the 'Response to Evidence Review Group Queries' document, the manufacturers state the following from Embase.com:

"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.

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"

It would be preferable if Medline and Embase were searched separately to provide clarity and transparency of the search results. Embase.com is not a widely-used search platform.

The manufacturers also made significant effort to search trial registries for the clinical effectiveness evidence.

Appendix 2: The validity of the cost-effectiveness searches

1) Re-run of the Medline Search Strategy
The search was re-run in MEDLINE (via OVID, 1950-March 2009) on 3rd April 2009 (see below). Not all index terms used in the Embase.com search could be translated to Medline as these index terms did not exist. This generated 302 references.

1 Yondelis.ti,ab,de. (56)
2 trabectedin.ti,ab,de. (81)
3 ecteinascidin 743'.ti,ab,de. (110)
4 et 743'.ti,ab,de. (140)
5 et743.ti,ab,de. (20)
6 or/1-5 (226)
7 exp Sarcoma/ (96326)
8 soft tissue sarcoma.ti,ab,de. (3143)
9 sts.ti,ab,de. (4230)
10 soft part sarcoma.ti,ab,de. (420)
11 or/7-10 (100505)
12 6 or 11 (100664)
13 exp Economics, Pharmaceutical/ (2001)
14 pharmacoeconomics.ti,ab,de. (609)
15 13 or 14 (2289)
16 12 and 15 (1)
17 health economics.ti,ab,de. (1148)
18 economic aspect.ti,ab,de. (98)
19 economic evaluation.ti,ab,de. (2930)
20 cost utility analysis.ti,ab,de. (637)
21 (economic$ and (evaluat* or analy*)).ti,ab,de. (44196)
22 (resource$ and utili$).ti,ab,de. (11191)
23 (cost$ and (effect$ or utili$ or benefit$)).ti,ab,de. (126127)
24 (cost$ and (minim$ or stud$ or effic$)).ti,ab,de. (125242)
25 (economic$ and model$).ti,ab,de. (18110)
26 or/17-25 (222741)
27 26 and 12 (320)
28 27 or 16 (320)
29 limit 28 to english language (302)

The search was re-run in Embase (via OVID, 1980-March 2009) on 3rd April 2009 (see below). Not all index terms used in the Embase.com could be translated to Embase via Ovid as these index terms did not exist. This generated 205 references.

1 exp Yondelis/ (512)
2 Yondelis.ti,ab,de. (56)
3 exp trabectedin/ (512)
4 trabectedin.ti,ab,de. (529)
5 ecteinascidin 743'.ti,ab,de. (112)
6 et 743'.ti,ab,de. (143)

7 et743.ti,ab,de. (20)
8 exp Soft Tissue Sarcoma/ (5725)
9 soft tissue sarcoma.ti,ab,de. (6433)
10 sts.ti,ab,de. (3526)
11 soft part sarcoma.ti,ab,de. (320)
12 6 or 4 or 1 or 3 or 7 or 2 or 5 (541)
13 8 or 11 or 10 or 9 (9617)
14 13 or 12 (10030)
15 exp Pharmacoeconomics/ (56261)
16 pharmacoeconomics.ti,ab,de. (1861)
17 16 or 15 (56818)
18 17 and 14 (46)
19 exp Health Economics/ (231963)
20 health economics.ti,ab,de. (10930)
21 exp Economic Aspect/ (386344)
22 economic aspect.ti,ab,de. (71297)
23 exp Economic Evaluation/ (103163)
24 economic evaluation.ti,ab,de. (6314)
25 exp "Cost Utility Analysis"/ (2505)
26 cost utility analysis.ti,ab,de. (2709)
27 (economic$ and (evaluat* or analy*)).ti,ab,de. (40964)
28 (resource$ and utili$).ti,ab,de. (9385)
29 (cost$ and (effect$ or utili$ or benefit$)).ti,ab,de. (114200)
30 (cost$ and (minim$ or stud$ or effic$)).ti,ab,de. (111809)
31 (economic$ and model$).ti,ab,de. (13616)
32 or/19-31 (462472)
33 32 and 14 (213)
34 33 or 18 (213)
35 limit 34 to english language (205)

In total, 437 unique cost effectiveness results were retrieved by searching Medline and Embase separately (70 references were found in both Medline and Embase). This is somewhat different to the number cited by the sponsor submission (312). The difference in the numbers may be due to further references being added in the time period since the original searches, due to differences in the way Embase.com indexes articles or due to difficulty in translating the search strategy to Medline when Embase.com index terms have been used that are not present in Medline.

The searches were replicated in the NHS EED and the same number of results was retrieved as stated by the sponsor submission.

Searching Medline in process (via Pubmed) also produced comparable numbers as stated by sponsor submission (this was not exactly the same as some time has passed between sponsor submission and re-running of searches). However, the ERG is satisfied these searches were carried out appropriately.

2) Search critique
Search strategy: The search strategy is adequate. A number of terms have been used to describe costs and economics. However, the ERG is unsure whether this is a validated economics search filter.

Sources: An adequate number of sources have been searched as directed by the guidance for sponsor submissions by Nice (i.e. Medline, Embase, Medline In-Process, NHS EED, HEED).
Limits: The searches are limited to English language

Overall, the searches are of adequate quality and adequate numbers of sources have been used according to guidance from NICE. It is difficult to comment on the discrepancies in numbers between the cost effectiveness search conducted in Medline and Embase separately via OVID and that conducted in Embase.com. In the 'Response to Evidence Review Group Queries' document, the manufacturers state the following from Embase.com:

"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.

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"
It would be preferable if Medline and Embase were searched separately to provide clarity and transparency of the search results. Embase.com is not a widely-used search platform.

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