NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Trabectedin for the treatment of advanced metastatic soft tissue sarcoma

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to:

- **provide further clarification of the identification and selection of evidence for the submission**
- **confirm the confidentiality status of trial data**
- **provide further explanation of a number of assumptions relating to model structure, utility estimates, adverse event proxies, curve extrapolation and cost calculation**
- **provide access to patient-level data**
- **provide specified re-analyses of the economic evaluation, including (but not limited to): the adjustment of survival curves for significant variables; the use of data for progression-free survival in place of data for time to progression; and the modelled entry of all patients into the same initial health state.**

Licensed indication

Trabectedin (Yondelis, PharmaMar) has a UK marketing authorisation for the treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents.

Trabectedin has been authorised under 'exceptional circumstances' because soft tissue sarcoma is rare and there is limited information about trabectedin as a treatment. However, the European Medicines Agency (EMEA) will be reviewing any new information on trabectedin on an annual basis.

Key issues for consideration

Clinical effectiveness

- Does the Committee consider the populations in the studies used to derive the effectiveness estimates for trabectedin and best supportive care to be sufficiently comparable with regard to:
  - the overall use of historical controls
  - the number of pre-treatments used in participants receiving best supportive care and in those receiving trabectedin
  - those participants with contraindications for anthracycline or ifosfamide therapy?
- What is the Committee's view on which historical control studies should be considered to represent best supportive care?
- What is the Committee's view on the fact that participants in the trabectedin randomised controlled trial (RCT) had a performance score of 0 or 1 only? Should the studies of best supportive care also only include participants with these scores, and what assumptions must be made when considering other patients with performances scores of 3 or 4?
- What is the Committee's view of the use of data based primarily on patients with L-sarcomas, and the assumptions that must be made when considering patients with other types of soft tissue sarcoma?

Cost effectiveness

- Does the Committee consider the health-state utility estimates for lung cancer to be appropriate proxies for soft tissue sarcoma?
- Does the Committee consider that the use of different starting health states for participants receiving best supportive care and those receiving trabectedin biases the cost-effectiveness analyses in favour of trabectedin?
- What is the Committee's view of the extent to which there remains uncertainty in the model, despite efforts to account for uncertainty in the probabilistic sensitivity analysis (PSA)?

- What is the Committee's view of the cost inputs used in the model, including:
  - those associated with the management of adverse events
  - the total drug costs for trabectedin and other chemotherapies, and
  - the costs of administering trabectedin (as inpatient or as outpatient therapy)?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Table 1 Decision problem in the manufacturer's submission

Population	Adults with advanced metastatic soft tissue sarcoma after failure of anthracyclines and ifosfamide
Intervention	Trabectedin (dosage as per UK marketing authorisation)
Comparators	Best supportive care
Outcomes	Overall survival Progression-free survival Response rates (includes stabilisation) Adverse effects of treatment Health-related quality of life
Economic evaluation	Cost–utility analysis: results presented as incremental cost per quality-adjusted life year. Time horizon: 5 years Perspective: NHS perspective

1.2 Evidence Review Group comments

1.2.1 Population

The ERG considered that the manufacturer's statement of the decision problem appropriately defined the population. It should be noted that the manufacturer stated that only patients with L-sarcomas (liposarcomas or leiomyosarcomas) were included in their base-case population because only

participants with L-sarcomas were included in the trabectedin RCT (L-sarcomas account for 40–50% of soft tissue sarcoma).

1.2.2 Intervention

The ERG did not comment on the specification of the intervention. The ERG noted that the licensed dosage in the UK is 1.5 mg/m² every 3 weeks given as a 24-hour intravenous infusion.

1.2.3 Comparators

The ERG considered best supportive care to be an appropriate comparator. The ERG noted that its clinical advisors did not agree with some of the chemotherapies that the manufacturer suggested would be used as best supportive care (namely etoposide and dacarbazine).

1.2.4 Outcomes

The ERG did not comment on the specified outcome measures. The ERG noted that no quality of life data were available for patients with soft tissue sarcoma. The ERG noted that the scope stated that trabectedin may be continued if disease stabilisation is achieved in the absence of disease progression. The manufacturer stated that the outcome stable disease was included in the data on best overall response.

1.2.5 Economic evaluation

The ERG considered that the time horizon of the model was appropriate.

1.2.6 Other factors in scope

The ERG noted that the scope stated that if evidence allowed different histological types of soft tissue sarcoma would be considered separately. The ERG accepted that data were too limited to allow subgroups analyses, although the MS presents a pre-planned subgroup analysis.

The ERG also noted that the scope stated that special consideration should be given as to whether gastrointestinal stromal tumours and rhabdomyosarcomas should be included in the appraisal. The ERG

considered that the reasons given for excluding gastrointestinal stromal tumour were appropriate (see page 11 of the MS). Because rhabdomyosarcomas are rare tumours most commonly seen in children and the summary of product characteristics (SPC) states that trabectedin should not be given to children, it seemed appropriate not to consider rhabdomyosarcomas in this appraisal.

1.3 Natural history of the disease

Current treatment options for soft tissue sarcoma include surgery, chemotherapy and radiotherapy. Approximately 50% of patients present with or develop advanced or metastatic soft tissue sarcoma. For these patients chemotherapy is the only available treatment and its goal is palliative. Despite chemotherapy, the prognosis of these patients is very poor, with an estimated median survival of 8–13 months from the start of first-line anthracycline therapy. For patients with advanced metastatic soft tissue sarcoma in whom anthracyclines and ifosfamide have failed, either in combination as first-line therapy or in sequence as first- and second-line therapy, median survival is about 6 months. Trabectedin is the only form of chemotherapy with UK marketing authorisation for patients with advanced metastatic soft tissue sarcoma in whom anthracycline and ifosfamide have failed.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The key clinical evidence in the MS comes from one randomised trial (STS-201) evaluating the efficacy of trabectedin in participants with advanced soft tissue sarcoma. Additional supporting clinical evidence from three uncontrolled phase II trials of trabectedin is provided (183 participants with soft tissue sarcoma, 100 with L-sarcomas and 83 with other types of sarcoma). In the absence of relevant comparator data in the included trials, the manufacturer reports historical control data for best supportive care and further chemotherapy derived from studies in the European Organisation for

Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC STBSG) database (see section 7.2.3 of the MS).

The pivotal phase II trial presented in the MS (STS-201) compared use of the licensed dosage of trabectedin (1.5 mg/m^2 every 3 weeks as a 24-hour intravenous infusion) in 136 participants with another dosage of trabectedin (0.58 mg/m^2 every week as a 3-hour intravenous infusion) in 134 participants. All participants had L-sarcomas and a performance score of 0 or 1.

The primary endpoint of the RCT was time-to-progression (TTP); secondary endpoints included progression-free survival (PFS), overall survival (OS) and best overall response (BSR). Treatment with trabectedin continued as long as therapeutic benefit was derived, until disease progression, or for at least two courses of therapy beyond confirmed response. Cross-over was allowed for participants in either arm who experienced disease progression. The manufacturer acknowledges that the cross-over design of the study affects the OS results.

2.1.1 Results

The MS reports the blinded intention-to-treat median TTP (defined as time between randomisation and the first documentation of disease progression or death as a result of progressive disease) as statistically significantly longer (hazard ratio [HR] 0.734, p = 0.03) for the licensed dosage of trabectedin (median 3.7 months, 95% confidence interval [CI] 2.1 to 5.4) than with the comparator trabectedin dosage (median 2.3 months, 95% CI 2.0 to 3.5). For more details, see table 2 and figure 3 on page 37 of the MS.

The MS presents historical control data to approximate best supportive care, but acknowledges there are limitations to this approach. For OS estimates, data for ifosfamide, dacarbazine and etoposide were taken from an unpublished analysis of four phase II studies in the EORTC STBSG database of adults with advanced pre-treated soft tissue sarcoma. For estimates of PFS, data for the comparators were taken from a paper that reported on phase II studies from the EORTC STBSG database. The studies varied in

treatment and prior treatment of the populations; the manufacturer selected the pre-treated populations that were considered to be most relevant (see page 38 of the MS).

Tables 2 and 3 show the OS and PFS for participants in the trabectedin RCT (STS-201) compared with the historical control data for best supportive care.

Table 2 Overall survival for participants in the trabectedin trial (STS-201) and historical control data from studies in the EORTC STBSG database

	STS-201		Historical controls		
	Trabectedin (3-hour infusion weekly)	Trabectedin (24-hour infusion every 3 weeks)	Ifosfamide	Dacarbazine	Etoposide
Number	134	136	86	50	26
Events	119 (88.8%)	116 (85.3%)	82 (95.3%)	17 (34.0%)	19 (73.1%)
Censored	15 (11.2%)	20 (14.7%)	4 (4.7%)	33 (66.0%)	7 (26.9%)
Median OS (months) (95% CI)	11.8 (9.9-14.9)	13.9 (12.5-18.6)	6.6 (from start of therapy) (5.0-9.0) 5.9 (from failure; n=105)	6.6 (4.3-8.4)	6.3 (4.4-8.9)

(Adapted from table 4 in the MS, page 39, and ERG report, page 23.)

Table 3 Progression-free survival for participants in the trabectedin trial (STS-201) and historical control data from studies in the EORTC STBSG database

	Historical controls		STS-201 (all randomised – independent review)	
	Inactive regimen in pre-treated patients	Active regimen in pre-treated patients	24-hour infusion every 3 weeks	3-hour infusion weekly
Number	234	146	136	134
PFS at 3 months	21±3%*	39± 4%*	51.5% (43.0–60.1%)**	44.7% (36.0–53.3)**
PFS at 6 months	8± 2%*	14±3%*	35.5% (27.1–43.9%)**	27.5 % (19.4–35.5)**

*Mean ± standard error (EORTC STBSG data).

**95% confidence interval.

Active agents (EORTC STBSG): ifosfamide and dacarbazine after failure of an anthracycline-containing regimen.

Inactive agents (EORTC STBSG): mitozolomide, nimustine, fotemustine, miltefosine, liposomal muramyl tripeptide phosphatidylethanolamide, temozolamide, etoposide, tomudex and gemcitabine in pre-treated patients.

(Reported as table 3 in MS, page 38)

The manufacturer reports that the objective response rate per investigator's assessment was 2.2% (95% CI 0.5 to 6.4) in the group receiving weekly 3-hour infusions and 11.0% (95% CI 6.3 to 17.5) in the group receiving 24-hour infusions every 3 weeks (Fisher's p value = 0.0058); the objective response rates per independent review were 1.5% (95% CI 0.2 to 5.3) and 5.1% (95% CI 2.1 to 10.3), respectively (Fischer's p value=0.1724). Further details of overall best response and objective response rate are given in table 6 on page 43 of the MS.

The MS reports a pre-planned subgroup analysis indicating that regardless of the study arm, efficacy outcomes appeared to be more favourable in liposarcomas than in leiomyosarcomas. The manufacturer commented that histological subtype is a well-known prognostic factor in soft tissue sarcoma.

2.1.2 Adverse events

The manufacturer reported that the main treatment-related severe (grade 3/4) adverse events observed in all studies were transient, reversible and non-

cumulative neutropenia and transaminase elevations without clinical consequences. Grade 3/4 nausea and vomiting were also observed in some participants. The manufacturer states that unlike with other commonly used cytotoxic agents, no cardiotoxicity or neurotoxicity was observed with trabectedin (see pages 44 and 45 of the MS).

No health-related quality of life data were presented in the clinical effectiveness section of the MS as none were obtained from the trials.

2.2 Evidence Review Group comments

The ERG did not consider that any relevant clinical effectiveness studies of trabectedin had been excluded. The ERG did not know whether additional studies could have been found to provide data on the effectiveness of best supportive care 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.

The ERG noted that the trabectedin RCT (STS-201) included only participants with L-sarcomas. It drew attention to the statement in section 6.3 of the MS (beginning on page 24 of the MS) that the phase II studies suggested a slightly higher efficacy for trabectedin in L-sarcomas than in sarcomas of other histological type. The ERG further noted that the patient populations in the EORTC STBSG studies might not be comparable, particularly with regard to prior treatment. For more details, see page 20 of the ERG report.

The ERG was informed by clinical advisors that it is unlikely that etoposide would be used for this indication because of a lack of proven activity. It noted that dacarbazine may be used in UK practice as second- or third-line therapy, and so might be considered a suitable comparator, but is not considered best supportive care. The ERG stated that it is not clear whether patients receiving dacarbazine had been given ifosfamide, and therefore these patients may not match the populations as defined in the final scope.

The ERG considered that the validity assessments performed by the manufacturer for the trabectedin RCT (STS-201) and the phase II studies

were appropriate. It noted that there was no validity assessment for data proposed as equivalent to best supportive care.

2.3 Statements from professional/patient groups and nominated experts

Patient groups noted that few patients in the UK currently receive trabectedin, and professional groups stated that access varies greatly by region.

Clinical specialists noted that the management of soft tissue sarcoma is complex, with a degree of treatment selection according to histological subtype. They suggested that the heterogeneous nature of soft tissue sarcoma means that some subgroups will benefit more than others from treatment with trabectedin.

Patient groups reported that trabectedin addresses an unmet need for patients with a poor prognosis in whom first-line treatments have failed or in whom these treatments are contraindicated. They stated that lack of data for certain subgroups should not limit access to trabectedin for patients in those subgroups.

Professional groups stated that most patients will be treated within specialist sarcoma units and that trabectedin should be administered by consultant oncologists within specialist clinics. Clinical specialists and patient groups noted that good liver function is a prerequisite for prescribing trabectedin.

Patient and professional groups agreed that trabectedin is well tolerated and is associated with milder adverse events than first-line therapies. Patient and professional groups also agreed that the finding in clinical trials that trabectedin prolongs PFS is important, noting the need to prolong and sustain life at a certain level of quality.

3 Cost effectiveness

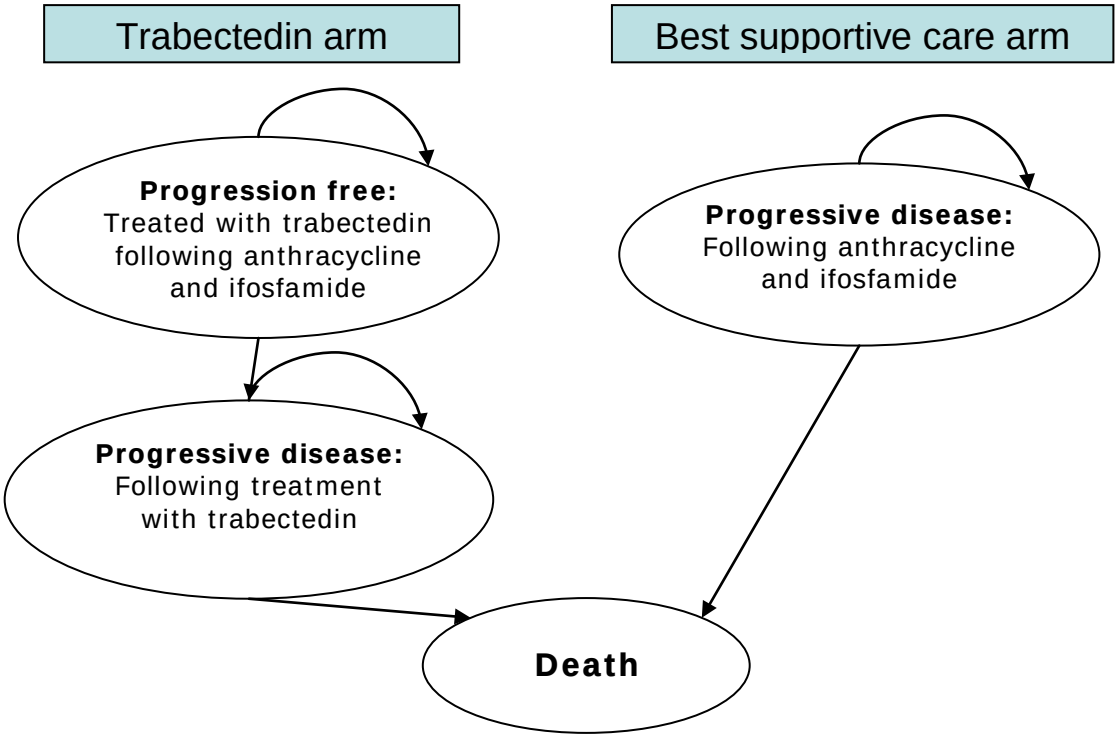
3.1 Cost effectiveness in the manufacturer's submission

The manufacturer explained that a systematic search was undertaken, but no existing studies of the cost-effectiveness of trabectedin were identified. The manufacturer submitted a de novo economic model.

3.1.1 Model structure

The MS presents a two-arm state-transition model developed in Excel. The first arm is designed to capture the costs and outcomes associated with treatment with trabectedin; the second arm is designed to capture the costs and outcomes associated with treatment with best supportive care. Administration of other chemotherapies in addition to best supportive care was explored in a sensitivity analysis. The model includes four mutually exclusive health states (see figure 1).

Figure 1 A schematic representation of the model structure



(Reported as figure 8 in the MS, page 63)

Patients in the best supportive care arm enter the model in the progressive disease state (and therefore only OS has been evaluated from the EORTC STSBG dataset), whereas patients treated with trabectedin enter the model in the progression-free state. Patients in the progression-free state were assumed to remain in this state until they experienced disease progression and/or died. Patients with progressive disease remain in the current health state until death. A time horizon of 5 years with a monthly cycle length was employed.

3.1.2 Model inputs: effectiveness

The trabectedin RCT (STS-201) used to model the effectiveness of trabectedin included only participants with L-sarcomas after they had been treated with a regimen containing at least an anthracycline and ifosfamide (combined or sequential). Effectiveness data from participants receiving a 24-hour infusion of trabectedin every 3 weeks were selected to represent the base case. As a sensitivity analysis, the pooled effectiveness from the three initial phase II uncontrolled studies of trabectedin was also modelled.

Transition probabilities for the trabectedin arm were estimated from Weibull parameters derived from the patient-level data for TTP from the trabectedin RCT (STS-201). Weibull curves were fitted to Kaplan–Meier curves for TTP and OS. The Weibull estimates were considered by the manufacturer to be sufficiently comparable to the Kaplan–Meier curves. Following a request by the ERG arising because of differences in patient characteristics between the treatment and best supportive care arms, Weibull curves for trabectedin were also calculated using age, gender and severity as covariates (see page 4, response to ERG queries in April 2009). Log-logistic and Gompertz distributions were also explored; the manufacturer reported that the use of these distributions had little impact on the results. The use of PFS data instead of TTP was reported to have little impact on the results. For more details, see pages 64–70 of the MS and pages 7–11 of the response to ERG queries in March 2009.

The natural history for patients who receive best supportive care after failure of anthracyclines and ifosfamide was estimated from pooled data of four previously published trials obtained from the EORTC STBSG database. The EORTC STBSG data were used in the same manner as the STS-201 data to estimate the transition probabilities (in this case only from progression to death). In response to requests for clarification, the manufacturer submitted a revised model in which the survival curves were adjusted for the differences in patient characteristics between the trabectedin and best supportive care arms. For more details, see pages 64–70 of the MS, page 11 of the response to

ERG queries in March 2009, and page 4 of the response to ERG queries in April 2009.

3.1.3 Model inputs: utilities

The manufacturer did not identify any studies of quality of life in patients with soft tissue sarcoma. The manufacturer used health-states utilities for lung cancer as a proxy for utilities in soft tissue sarcoma, after discussion with their clinical experts on the comparable prognosis and disease stage. These values were calculated from a mixed model with random effect and have been used in a previous NICE technology appraisal ('Pemetrexed for the treatment of non-small-cell lung cancer', NICE technology appraisal guidance 124). The manufacturer assumed that health-state utilities in PFS and progressive disease (PD) were similar for all patients irrespective of treatment. The utility during PFS and PD was assumed to be 0.653 and 0.473, respectively.
The manufacturer estimated that the utility associated with hospitalisations because of adverse events associated with trabectedin treatment was equal to that associated with nausea and vomiting (0.61), because this was reported to be a frequent adverse event, and was assumed to last a full month (which would equate to a QALY decrement of 0.004 for every patient that was hospitalised). In response to comments made by the ERG, the manufacturer further included the disutility associated with developing grade 3 or 4 neutropenia (0.56), which was assumed to last 1 week and therefore equate to a QALY decrement of 0.002 for every patient with neutropenia. Adverse events were assumed to occur only during the first cycle of trabectedin treatment. No disutility associated with adverse events was modelled for patients receiving best supportive care. For more details, see pages 73–76 of the MS and pages 12 and 16 of the response to ERG queries in March 2009.

3.1.4 Model inputs: costs

Following concerns raised by the ERG about the calculation of the average cost per patient, the manufacturer revised the methodology used to estimate the acquisition cost of the drug. Patient-level data from the trabectedin RCT

(STS 201) were used to calculate the average number of 1-mg and 0.25-mg vials used per patient and the proportion of patients receiving trabectedin in each cycle. This equated to a cost per patient of £23,719 excluding administration costs, and £25,986 when administration costs and a pre-treatment injection of dexamethasone were included. For further details, see pages 13 and 14 of the response to ERG queries in March 2009.

Management costs for patients in PD were extracted from a cost of illness study (for further details see page 82 of the MS). Following comments made by the ERG, management costs for patients in PFS were also included and were assumed, in the absence of data, to be half the cost for PD. Additional costs were included when a patient died. For further details, see page 15 of the response to ERG queries in March 2009.

Following concerns raised by the ERG, the methodology for calculating the costs associated with hospitalisations was revised to more closely match the average costs associated with the appropriate diagnoses. Costs associated with neutropenia were excluded because the manufacturer stated that neutropenia did not lead to hospitalisation, was reversible and was rarely associated with fever and infection. The cost of treating adverse events was not applied to the best supportive care arm. No monitoring costs were included in the MS.

Discount rates of 3.5% per annum were used for both costs and benefits.

3.1.5 Results

Only the revised results submitted in the manufacturer's final response to ERG queries in April 2009 are presented here (table 4). For the manufacturer's initial results see pages 90–99 of MS. Note that the results are presented using the TTP curve with the best supportive care arm adjusted to take into account difference in patient characteristics.

Table 4 Base-case results

Intervention	Costs	QALYs	ICER
Best supportive care	£1,965	0.34	–
Trabectedin	£29,110	0.81	**£56,985**

Four additional scenarios were presented by the manufacturer and revised incremental cost-effectiveness ratios (ICERs) were presented by the manufacturer in their response to ERG queries in April 2009:

- Using pooled effectiveness for trabectedin from three uncontrolled phase II trials. This decreased the ICER to £50,017.
- Assuming that 33% of patients receiving best supportive care receive further chemotherapy. This increased the ICER to £62,044.
- Assuming that 100% of patients receiving best supportive care receive further chemotherapy. This increased the ICER to £80,279.
- Assuming the utility for PFS is modelled as 0.653 the first cycle, followed by a linear decline over the next four cycles to reach the utility for PD (0.473). This increased the ICER to £61,064.

Uncertainty was explored in one-way sensitivity and PSA. The ICER appeared most sensitive to changes in utility estimates. For detailed results of the sensitivity analyses, see section 7.2.11 of the MS for the manufacturer's initial results and pages 42–47 of the ERG report for the manufacturer's revised results.

3.2 Evidence Review Group comments

The ERG expressed concern that patients treated with trabectedin entered the model in the PFS health state and those treated with best supportive care entered in the PD health state. It noted that the utility of being in the PD health state was assumed to be lower than that of being in the PFS health state, and thus considered the model to bias results in favour of trabectedin. In response

to a clarification request on this point by the ERG, the manufacturer presented a scenario in which higher utilities were allocated to the PD health state in the best supportive care arm of the model. The ERG considered this adjustment appropriate, noting, however, that this adjustment was not included in the final base case.

The ERG considered the method used to estimate the effectiveness of trabectedin and the natural history as appropriate after the adjustment of Weibull curves according to demographic and patient characteristics. However, the ERG expressed concerns about the potential lack of comparability between patients included in the studies used to derive the effectiveness for trabectedin and best supportive care. It noted that the estimates of effectiveness for the comparisons with historical data are subject to uncertainty because the natural history and intervention data were not taken from an RCT. The ERG also noted that the natural history data may not be appropriate for patients who have contraindications for or are intolerant of ifosfamide and/or anthracyclines.

The ERG noted that the trabectedin RCT (STS-201) included only participants with L-sarcomas. It is unclear how the estimated cost per QALY ratio would relate to patients with other types of soft tissue sarcoma. The ERG noted that there is uncertainty about the comparability of the best supportive care and trabectedin arms, because it believed that participants in the STS-201 trial were highly selected and already had a high rate of survival at the time of inclusion.

The ERG commented that it is unclear how comparable the utility values are for patients with soft tissue sarcoma and those with lung cancer. It noted that the cost per QALY ratio was shown to be sensitive to changes in assumed health state utilities. The results of additional work undertaken by the ERG exploring the effect of utility values is presented in table 8, page 50 of the ERG report.

The ERG noted (page 41 of the ERG report) that the results of the PSA may not reflect the full uncertainty in the model because there was a lack of correlation between Weibull curves for TTP and OS, the proportion of patients receiving trabectedin remained fixed, no correlation was included between the numbers of vials of different sizes, and there was a lack of correlation between health-state utilities.

The ERG found that the general revised method used to estimate the cost of trabectedin was appropriate. It noted, however, that the cost of trabectedin may be underestimated because few participants were still being treated at the end of the follow-up period who were assumed not to incur future cost in the model. Also the proportion of patients receiving each cycle of treatment was assumed to be fixed and did not change in the PSA. The ERG considered that the approach used to model the cost of adverse events was appropriate. For more detail on costs, see pages 37 and 38 of the ERG report.

The ERG identified a number of errors in the model submitted by the manufacturer, as described on page 39 of the ERG report. These errors were corrected by the ERG and shown to have limited impact on the results. Table 5 presents the results of these corrections. It should be noted that 'pooled analysis' refers to the analysis that includes pooled data from the three phase III non-comparative studies of trabectedin and 'utility-adjusted analysis' refers to the analysis that included adjusted utility estimates for PD in the best supportive care arm of the model. The ERG did not present corrected results for the utility-adjusted scenario. For more details, see page 47 of the ERG report.

Table 5 Results from the manufacturer's model corrected by the ERG

	Manufacturer	ERG
Base case	£56,985	£56,949
Pooled analysis	£50,017	£49,992
Utility-adjusted analysis	£61 064	-
PSA – base case	£56,755	£57,375
PSA-– pooled analysis	£48,033	£51,228

Adapted from table 7, page 47 ERG report

3.3 Further considerations following premeeting briefing teleconference

In order to allow the Appraisal Committee to consider the applicability of the 'end-of-life' criteria, the following section summarises the pertinent parameters:

- The UK marketing authorisation for trabectedin is for the treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. The patient population for advanced soft tissue sarcoma is approximately 1000 people in England and Wales per year. It is unclear in how many patients treatment with anthracyclines and ifosfamide will have failed, but it can be assumed that the patient population eligible to receive trabectedin will be fewer than 1000.
- Using the historical data from the EORTC STBSG database as the proposed best supportive care comparator, the median overall survival for people with advanced soft tissue sarcoma after failure of second-line ifosfamide was 5.9 months. [redacted]
- The median overall survival in the trabectedin RCT (STS-201) for participants receiving the licensed dosage (1.5 mg/m^2 every 3 weeks as a 24-hour intravenous infusion) was 13.9 months. This represents an increase in survival of 8 months [redacted] with trabectedin treatment.

- There are currently no generally accepted alternative treatment options for people with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents.

4 Authors

Whitney Miller and Joanna Richardson, with input from the Lead Team (Dr Ray Armstrong, Ms Nathalie Verin and Mrs Eleanor Grey).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The evidence review group (ERG) report for this appraisal was prepared by the School of Health and Related Research (ScHARR), The University of Sheffield.

- Simpson EL, Rafia R, Stevenson MD, et al., Trabectedin for the treatment or advanced metastatic soft tissue sarcoma, May 2009

B Submissions or statements from the following organisations:

I Manufacturer/sponsor

- PharmaMar

II Professional/specialist, patient/carer and other groups:

- Royal College of Pathologists
- Rarer Cancers Forum
- Sarcoma UK
- The British Sarcoma Group
- Royal College of Physicians on behalf of NCRI/RCP/RCR/ACP/JCCO