All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

AWMSG ADVICE SUPERSEDED BY NICE GUIDANCE (TA185)

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Final Appraisal Report

Trabectedin (Yondelis®▼) for advanced soft tissue sarcoma

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Advice No: 1408 – August 2008

Recommendation of AWMSG

Trabectedin (Yondelis®▼) is not recommended for use within NHS Wales for the treatment of patients with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents.

Key factor/s influencing the recommendation:
The case for clinical and cost effectiveness has not been proven.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday, 13th August 2008

The recommendation of AWMSG is:

Trabectedin (Yondelis®▼) is not recommended for use within NHS Wales for the treatment of patients with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents.

Key factor/s influencing the recommendation:
The case for clinical and cost effectiveness has not been proven.

Additional notes:

- There are several uncertainties and limitations in the economic model provided within the submission.
- AWMSG considered that while there was evidence that trabectedin (Yondelis®▼) might slow disease progression, the evidence of how this translates into clinical benefit for patients was lacking.
- AWMSG considered that trabectedin (Yondelis®▼) satisfies the AWMSG criteria for ultra orphan drug status.

2.0 PRODUCT DETAILS

2.1 Licensed indication:

Trabectedin (Yondelis®▼) is indicated for the treatment of patients with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents[1].

Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients[1].

2.2 Dosing:

The recommended dose of trabectedin is 1.5mg/m^2 body surface area, administered as an intravenous (IV) infusion over 24 hours with a three-week interval between cycles. Administration through a central venous line is strongly recommended. In clinical trials, there were no pre-defined limits to the number of cycles administered. Treatment continued whilst clinical benefit was noted[1].

The Summary of Product Characteristics (SPC) stipulates haematological, renal function and hepatic function parameter values that must be met before each administration cycle. Information on the management of toxicity through dose reductions or discontinuation of treatment is outlined in the SPC[1].

All patients must receive 20mg of dexamethasone intravenously 30 minutes prior to trabectedin as anti-emetic prophylaxis and also because it appears to have hepatoprotective effects[1].

2.3 Market authorisation date:

EMEA granted marketing authorisation 17th September 2007, under exceptional circumstances (due to the rarity of the disease it has not been possible to obtain complete information on the product). The company has committed to explore further the population that might benefit most from the treatment as a specific obligation of the marketing authorisation[2].

2.4 UK Launch date:

Trabectedin was launched in the UK 11th October 2007[3].

3.0 DECISION CONTEXT

Soft tissue sarcomas (STS) are rare tumours, accounting for around 1% of all adult cancers[4]. They may arise anywhere in the body, but the majority occur in the nonepithelial tissue such as muscle, fat or fibrous supporting structures of the limbs, the limb girdle, or within the abdomen. There are many different types of STS and most (but not all) have names based on the type of normal cell from which the cancer might have started; for example those arising in the smooth muscle are termed leiomyosarcomas and those in fat cells are termed liposarcomas[5]. STS have traditionally been managed by wide excision surgery and radiotherapy, which is often curative. Around 50% of patients, however, ultimately develop local recurrence or metastases[3,4].

Chemotherapy is generally reserved for advanced disease and is palliative for most patients with unresectable or metastatic disease. In these cases, there are only few active chemotherapeutic options available and the expected median survival after diagnosis of metastatic disease is about one year[3,4]. Established first-line treatment options include doxorubicin and ifosfamide as monotherapy or in combination

regimens[3,4]. Recent products licensed for specific STS types include imatinib (Glivec®▼), which is indicated for the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST) and dermatofibrosarcoma protuberans, and sunitinib (Sutent®▼), which is indicated for the treatment of GIST after failure of imatinib due to resistance or intolerance[6,7]. Trabectedin has a different structure and mode of action to these agents. It is a tetrahydro-isoquinoline and is a synthetic version of an extract from the marine tunicate *Ecteinascidia* [2]. When it binds to DNA, it triggers a cascade of events affecting several transcription factors, DNA binding proteins, and DNA repair pathways, which results in perturbation of the cell cycle[1].

Trabectedin is licensed for the treatment of patients with advanced STS after failure of anthracyclines and ifosfamide, or who are unsuited to receive such agents[1]. In most cases, these patients would have no other treatment options beyond best supportive care (BSC). The company suggests that around nine patients per year would be eligible for treatment with trabectedin[3] (although a revised incidence estimate for STS, issued since the company submission was made, indicates this may be an underestimate[8]). This revised incidence estimate suggests that trabectedin meets the AWMSG criteria for ultra-orphan drug status[9].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The main efficacy data is from a multicentre, open-label phase II trial involving 270 patients with advanced leiomyosarcoma or liposarcoma (L-sarcomas), virtually all of whom had received prior treatment with both anthracycline and ifosfamide. Patients were randomised to one of two trabectedin regimens, the recommended regimen (trabectedin 1.5mg/m^2 infused over 24 hours once every three weeks) or the regime of 0.58mg/m^2 infused over three hours once each week for three out of four weeks. Following interim analysis, the initial primary efficacy endpoint was changed from a composite of response levels to time to progression (TTP). Results demonstrated that median TTP was statistically significantly longer with the recommended regimen, as was median progression free survival. Median overall survival at 12 months was not significantly different. Three smaller, single-arm, phase II studies assessed the recommended regimen in patients with L-sarcomas and other, mainly non-GIST, STS. Objective response rates, which are based on specific changes in tumour/lesion size, were low in the four studies. From the response data available, trabectedin appears to exert its effect mainly by inducing or maintaining stable disease, rather than inducing partial or complete responses. Around 40% of trial patients experienced grade 3 or 4 adverse events, the most common being haematological and hepatobiliary. There are no direct comparative data against any other treatment in the patient population for which trabectedin is licensed. Most data for trabectedin have been derived in patients with L-sarcomas and there is a need for further data in other types of STS.

4.2 Review of the evidence on cost-effectiveness

A Markov model-based cost effectiveness analysis of trabectedin against end-stage treatment (EST) is provided. This estimates a cost per life year gained of £21,257 compared with EST as described in the model. There are a number of uncertainties that limit the interpretation of the economic evidence presented.

The EST arm of the model is populated with combined efficacy data from two studies of ifosfamide and the extent to which they reflect EST as defined for the analysis is uncertain. Further, the costs of EST are based on a weighted average of etoposide and

dacarbazine costs and, although ongoing costs of EST are considered, no ongoing costs of treatment with trabectedin appear to be included. Incremental costs per additional QALY are considered only in scenario analyses, which generate estimates in the range of £29,954 to £31,808. The scenarios that are considered however are geared to favour trabectedin and, as there are reported to be no published data to inform the utility weights, this is a source of potential bias and uncertainty. Based on the data presented, it is most unlikely that the most plausible cost per QALY gained falls below £20,000, and unclear whether it is below £30,000.

5.0 LIMITATIONS OF DECISION CONTEXT

- There are no direct comparative data against any other treatment in the patient population for which trabectedin is licensed.
- Most data for trabectedin have been derived in patients with leiomyosarcoma or liposarcoma and there is very limited data in other types of STS Due to the rarity of STS, and especially the patient population in which trabectedin is currently licensed, there is a paucity of robust data on potential comparators and there are no reliable data to inform estimates of quality of life, which further limits the economic evidence presented in the company submission.

6.0 CLINICAL EVIDENCE

6.1 Clinical efficacy:

The company submission provides details of a pivotal phase II study conducted in patients with locally advanced or metastatic leiomyosarcoma or liposarcoma (L-sarcomas)[3]. This study assessed two dosing regimens with trabectedin and has been published in abstract only[10]. Three smaller, single-arm, phase II studies assessed the recommended 24-hour continuous infusion every three weeks (24-h q3wk) regimen in patients with L-sarcomas and other, mainly non-GIST, STS[11-13]. There are no direct comparative data against BSC (or any other type of care) as none of the trials employed any other internal control arm[2] (see Table 1A, Appendix 1).

6.1.1 Pivotal phase II study (ET-743-STS-201)[10]

This was a multicentre, randomised, open-label trial of 270 patients, of which 213 had a confirmed L-sarcoma diagnosis. All had good performance status (0 or 1) and adequate organ function, and had experienced disease progression despite prior treatment with chemotherapy. Virtually all (99.3%) had received prior treatment with both anthracycline and ifosfamide, and nearly two-thirds (62%) had previously received additional chemotherapy regimens[2,3,10].

Patients were randomised to one of two trabectedin dose regimens; the recommended regimen (1.5mg/m^2 infused over 24 hours once every three weeks [24-h q3wk]), or 0.58mg/m^2 infused over three hours once every week for three out of four weeks (3-h qwk).

The initial primary efficacy endpoint was clinical benefit, which was defined as a composite of confirmed complete response, partial response or stable disease lasting for at least 24 weeks[2]. Preliminary data suggested that the 24-h q3wk regimen might be more efficacious than the 3-h qwk regimen. This led to extension of the study to allow a formal comparison between the two trabectedin regimens. The primary endpoint was therefore changed to time to progression (TTP). Secondary endpoints

included best overall response (based on RECIST criteria), progression-free survival (PFS) and overall survival (OS)[2].

Table 1A of Appendix 1 lists the key efficacy data. Final analysis of the primary endpoint (TTP) occurred at a median follow-up of 14.7 months and 10.8 months in the 24-h q3wk and the 3-h qwk regimens, respectively[3]. Median TTP was statistically significantly longer with the 24-h q3wk regimen (3.7 months versus 2.3 months, hazard ratio [HR] 0.734, p=0.0320), as was median PFS (3.3 months versus 2.3 months, HR 0.755, p=0.0418)[10]. Median survival at this time (n=175 events) was not statistically significantly different (13.8 months versus 11.8 months, HR 0.823, p=0.1984)[10], although patients experiencing progression were allowed to cross over to the alternate treatment regimen, which may have influenced the OS data[2].

The best overall response observed in most patients at interim analysis was stable disease (41.7% versus 34.3% in the 24-h q3wk and 3-h qwk regimens, respectively), followed by progressive disease (31.8% versus 39.6%). Partial response was observed in 3.0% and 0.7%, respectively, and there were no complete responses in either group. Around 25% of patients were not evaluable for best overall response rates[2].

Updated survival analyses were conducted by the company (cut off date May 2007) when a total of 206 deaths had been reported in all randomised patients. At this point median follow up was 30.0 months (95% Confidence Interval [CI] 25.0 to 36.6 months) in the 24-h q3wk regimen and 27.9 months (95% CI: 23.6 to 37.3 months) in the 3-h qwk regimen groups[2]. These further analyses indicated very similar results to those above (median OS 13.9 months versus 11.8 months, HR 0.838, p=0.2052) in the all randomised population (n=270)[14]. When the data were censored for the 32.1% of patients who crossed over from the 3-h qwk to the 24-h q3wk group and the 4.4% of patients who crossed over the other way, the reductions in the relative risk of death were more profound[2]. These did not reach statistical significance in the randomised population, but did when the analyses were restricted to 'all treated patients' (n=260, HR 0.724, p=0.0368) and 'all randomised patients with a confirmed L-sarcoma diagnosis' (n=213, HR 0.685, p=0.0264)[14]. The final OS data are not yet available as the required number of events specified in the protocol (234 deaths) has not yet been reached[3]. The latest reported interim OS data still indicate no statistically significant difference in the one-year OS rates in the randomised population, either uncensored or censored for patient cross over. Overall, 12-month survival rates were 48.5-51.4% in the 3-h qwk groups and 60.2-66.7% in the 24-h q3wk groups[2,14]. Nevertheless, in the 'patients treated' and the 'all patients randomised with a confirmed L-sarcoma diagnosis' populations, the difference in one-year OS rates are statistically significantly in favour of the 24-h q3wk regimen.

6.1.2 Supporting phase II studies

Around 55% of the patients in the three supporting studies had L-sarcomas, and prior treatment histories were similar to those of the pivotal study[11-13]. Table 1A of Appendix 1 provides a summary of the studies. The European Public Assessment Report provides pooled analyses of data from L-sarcoma and non-L-sarcoma STS patients in these studies[2] (Table1).

Table 1. Pooled results from three supporting phase II studies of trabectedin 24-h q3wk[2]

	L-sarcoma n=100	**Non-L-sarcoma STS*** n=83
Median TTP	3.4 months (95% CI 1.7 to 3.9)	1.9 months (95% CI 1.6 to 3.0)
Median PFS	2.7 months (95% CI 1.7 to 3.7)	1.8 months (95% CI 1.5 to 2.9)
Median OS	11.2 months (95% CI 9.1 to 17.2)	8.7 months (95% CI 5.7 to 13.9)
Objective response rate	12.0% (95% CI 6.4 to 20.0)	2.4% (95% CI 0.3 to 8.4)
*excludes 4 GIST and 2 Ewings sarcoma patients		

As in the pivotal study, no patients with L-sarcomas in the three supporting studies experienced complete response; similar number of L-sarcoma patients experienced stable disease (42%) and progressive disease (43%), and 12.0% experienced a partial response[2]. Pooled two-year OS data are available from these studies, which indicate that 34.7% of patients with L-sarcoma were alive at two years, compared with 22.8% of patients with non-L-sarcoma STS[2].

Points to note:

- Both trabectedin regimens induced tumour shrinkage in the pivotal phase II study. There was a statistically significant difference in favour of the 24 h q3wk regimen versus the 3-h qwk regimen (50.5% versus 32.4% of patients, p=0.0008)[14].
- Objective response rates, which are based on specific changes in tumour/lesion size, were low in the four studies. From the response data available, trabectedin appears to exert its effect mainly by inducing or maintaining stable disease, rather than inducing partial or complete responses.
- Most data relate to patients with L-sarcomas. The limited data available in other STS types indicate numerically lower TTP, PFS, OS and objective response rates compared with L-sarcoma patients, although patient numbers are relatively low, and confidence intervals are wide and overlap.
- The company submission considers that BSC was not a realistic comparator for the pivotal study due to the poor prognosis of patients, which precludes a non-active treatment arm. Furthermore, it considers that the use of investigator's choice among drugs that are sometimes used, but which are not specifically licensed for use, in this clinical setting would have resulted in a heterogeneous control arm[3].
- Updated trabectedin survival data from study ET-743-STS-201 is expected later this year. No other study is expected to report results in the next six to 12 months[3].
- No information on any concomitant medicines, other than antiemetic prophylaxis, is provided.

6.2 Safety:
In patients who received the recommended trabectedin regimen (24-h q3wk) in the various clinical studies (n=596), including patients with cancers other than STS, not discussed above, approximately 91% experienced adverse events of any grade. The most common were nausea, fatigue, vomiting, anorexia, neutropenia, and increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT)[1]. The SPC suggests that 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[1].
Around 40% experienced grade 3 or 4 adverse events, the most common being haematological and hepatobiliary. Grade 3 or 4 adverse events are discussed below.

Grade 3 and 4 neutropenia occurred in 26% and 24% of patients, and the analysis per cycle showed these occurred in approximately 19% and 8% of cycles, respectively. Febrile neutropenia occurred in 2% of patients and in < 1% of cycles. Grade 3 and 4 thrombocytopenia occurred in 11% and 2% of patients, and in approximately 3% and < 1% of cycles, respectively. Bleeding events associated to thrombocytopenia occurred in < 1% of patients. Grade 3 and 4 anaemia occurred in 10% and 3% of patients, and in approximately 3% and 1% of cycles, respectively. Notably, 46% of patients were anaemic to some degree at baseline[1].

Transient grade 3 increases of AST and ALT were observed in 38% and 44% of patients, and grade 4 increases in 3% and 7% of patients, respectively. The median time to reach the peak values was five days for both AST and ALT, and most of the values had decreased to grade 1 or resolved by day 14 to 15. Grade 3 elevations of AST and ALT occurred in 12% and 20% of cycles, and grade 4 elevations occurred in 1% and 2% of cycles, respectively. ALT and AST increases did not follow a cumulative pattern but showed a tendency towards less severe elevations over time[1].

Other grade 3 or 4 adverse events included nausea and vomiting (6% and 6.5% of patients, respectively), fatigue/asthenia (9% and 1% of patients), and increases in creatine phosphokinase (4% of patients)[1].

Drug related serious adverse events (SAEs) occurred in 7% of patients receiving trabectedin 24-h q3wk[2]. Those that occurred in more than one patient were nausea (2%), vomiting (2%), neutropenia (1%), and pyrexia (1%). Grade 3-4 drug-related SAEs occurred in 6% of patients. Treatment discontinuation due to adverse events occurred in 8% of patients. One dose reduction was required by 7% of patients, 22% had two dose reductions, and 4% had three or more dose reductions. Most dose reductions were the result of nonhaematologic toxicity. However, haematological toxicity was responsible for most dose delays, which were required in 56% of patients[2]. Fatal adverse events occurred in 1.9% of patients and were often the result of a combination of events including pancytopenia, febrile neutropenia, some of them with sepsis, hepatic involvement, renal failure and rhabdomyolysis[1].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator treatment:

There are no other treatment options licensed specifically for STS patients after failure of anthracyclines and ifosfamide, or for those who are unsuited to receive these agents. Patients would receive BSC alone or some may also receive further off-label chemotherapy[3].

Imatinib (Glivec®▼) and sunitinib (Sutent®▼) are licensed for specific STS types (see Section 3.0), but are not considered relevant comparators for trabectedin [6,7].

7.2 Clinical effectiveness issues:

- The population of STS patients after failure of anthracyclines and ifosfamide is considered to be heterogenous and clinical efficacy data for trabectedin are mainly based on L-sarcoma patients. There is currently a lack of data in other STS-types due to the rarity of the disease. The marketing authorisation was granted under exceptional circumstances and the manufacturer has committed to explore further the population that might benefit most from the treatment as a specific obligation[2].
- Treatment options for patients with advanced and metastatic STS are limited and there are no other agents licensed specifically for use following failure of first/second line anthracycline and ifostamide chemotherapy. Some patients however do go on to receive other off-label or continuing chemotherapy and there are no direct comparative data for trabectedin against this type of care.
- The company submission refers to published data from a European Organisation for Research and Treatment of Cancer (EORTC) database, which reports PFS rates in 146 patients with STS treated with ifosfamide or dacarbazine after failure of an anthracycline containing regimen. These were 39% at three months and 14% at six months[15]. These PFS rates are noted to be lower than those reported for trabectedin in the pivotal ET-743-STS-201 study (51.5% at three months and 35.5% at six months using the recommended 24-h q3wk regimen – see Table 1A, Appendix 1). It should be noted that the EORTC data refer to patients with a wide range of STS types, including GIST that was not classed separately to leiomyosarcoma at the time the various studies that contributed to the database were conducted[15].
- The company submission also refers to four studies[16-19], which it suggests demonstrate lower OS with the treatments ifosfamide, dacarbazine or etoposide following failure on standard chemotherapy compared with trabectedin[3]. There are however a number of issues that limit the interpretation of the data as presented in the company submission (see Panel 1A, Appendix 1).
- Despite having advanced and metastatic STS, patients in the trabectedin clinical studies generally had good performance status (0 or 1), had normal hepatic and renal function, adequate neutrophil counts and the vast majority were aged less than 65 years[2,11-13]. The SPC stipulates haematological, renal function and hepatic function are parameter values that must be met before each administration cycle[1].

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issues for AWMSG to consider are whether the additional benefits offered by trabectedin (Yondelis®▼) over the relevant comparator justify the additional costs and if so, whether the total budgetary impact of supporting the use of trabectedin (Yondelis®▼) is acceptable.

8.2 Review of published evidence on cost-effectiveness

Standard searches conducted by WMP have not identified any published evidence on the cost effectiveness of trabectedin.

8.3 Review of the company's submission on cost-effectiveness

8.3.1 Description and critique of the company's submission

The company submission describes a cost effectiveness analysis of trabectedin, at the recommended dose of 1.5mg/m^2 administered as an IV infusion over 24 hours with a three-week interval between cycles, compared with what has been called end-stage treatment (EST)[3]. The company submission considers that EST comprises a number of treatments, which may include off-label chemotherapy, non-chemotherapy drugs, palliative care and possibly radiotherapy. The EST arm of the model is populated with efficacy data derived from two studies of ifosfamide[16,17]. The trabectedin arm of the model used data from study ET-743-STS-201, which was conducted in patients with L-sarcomas only.

A Markov model has been developed. Patients with metastatic STS enter the model after failing on treatment with anthracycline and ifosfamide. Patients who receive trabectedin may experience stabilised disease, progressive disease or death. Those who experience stabilised disease may then subsequently remain free of disease progression, experience disease progression, or die. At any point of disease progression, patients are assumed to discontinue trabectedin and receive EST. Patients who receive EST initially or subsequent to trabectedin may only experience progressive disease with ongoing EST or death.

There are several limitations to the model. The efficacy of EST is based on combined data from two ifosfamide studies, and the extent to which these adequately represent EST is uncertain. The costs of EST are based on a weighted average cost of etoposide and dacarbazine, which are then reduced to 33% as this is the assumed proportion of patients who would seek further treatment following failure of standard chemotherapy. Ongoing costs of EST are assumed from a cost of illness study, but no ongoing costs of treatment with trabectedin, beyond the drug and administration costs, appear to be included. Due to a reported lack of quality of life data in this patient group, the base case model outputs are expressed as incremental cost per life year gained, with QALYs considered in sensitivity analyses. However, the utility values assumed in the sensitivity analyses are geared to favour trabectedin and, as there are reported to be no published data to inform the utility weights, this remains a potential source of bias in the model. This is further complicated by counterintuitive incremental cost per QALY outputs.

The model has been provided to WMP and it is reported that Welsh expert clinicians were involved in determining model inputs.

8.3.2 Population

Modelled patients are stated to be adults with advanced STS who have previously received both anthracyclline and ifosfamide, either separately or in combination[3]. The trabectedin data used in the model is obtained from study ET-743-STS-201, which was conducted exclusively in patients with L-sarcomas. The limited trabectedin data available in other STS types indicate numerically lower TTP, PFS, OS and objective response rates compared with L-sarcoma patients, although patient numbers are relatively low, and confidence intervals are wide and overlap (see section 6). There would therefore appear to be some uncertainty in the extent to which the model relates to patients with STS types other than L-sarcomas.

Although study ET-743-STS-201 was not conducted in any UK-based centres, there is no reason to suggest the results of that study would not be applicable to L-sarcoma patients in Wales[3].

8.3.3 Perspective and time horizon

The perspective of the analysis is that of NHS Wales. The company submission states that a lifetime time horizon has been adopted, but the actual time horizon used is 60 months, on the basis that the vast majority of patients will have died by this point.

Each cycle of the model is one month, despite the fact that treatment cycles were three weeks long in study ET-743-STS-201, as it is reported that clinical data has been presented in monthly units. Half-cycle correction has been applied to the outcomes data and the costs of ongoing treatment but not to the costs of chemotherapy, which are assigned in the first cycle[3] (see section 8.3.6).

8.3.4 Comparator

The company submission states that the model compares trabectedin against EST, which is considered to comprise a number of treatments such as off-label chemotherapy, non-chemotherapy drugs, palliative care and possibly radiotherapy. The EST arm of the model is populated with efficacy data from two studies of ifosfamide[16,17]. These studies considered the use of ifosfamide as first or second line treatment in patients with advanced STS (including types other than L-sarcomas). Combined data relating to the use of ifosfamide as second-line treatment has reportedly been used to estimate transition probabilities for use in the EST arm of the model[3]. However, there are some inconsistencies in the data presented and the extent to which these data would reflect EST treatment is uncertain. The company submission states that these data were used to populate the EST arm as these were the most relevant available in the EORTC dataset. Studies of other agents were excluded if those agents were not approved (presumably meaning not specifically licensed) for use in metastatic STS. Studies of dacarbazine and etoposide were excluded on this basis, and also because they were considered to have poor follow up. It should be noted, however, that despite not being formally licensed for use in metastatic STS, the company submission reports results of interviews with Welsh and Scottish expert clinicians in which these agents are claimed to be used in this patient population[3]. The exclusion of studies of these agents solely on the basis of licensed indications would therefore not be appropriate.

It is assumed that only 33% of patients would seek further chemotherapy following failure of standard chemotherapy, reportedly on the basis of discussions with clinical experts[3]. The costs of EST therapy are therefore reduced to 33% (see section 8.3.6.1) of those that are assumed, which implicitly assumes that the EST arm efficacy data from the two ifosfamide studies (see section 8.3.5.1) relates to the 33% of patients who have received some form of chemotherapy and the 67% of patients who have not.

8.3.5 Clinical inputs

8.3.5.1 Efficacy data

Transition probabilities for the trabectedin arm of the model are derived from study ET-743-STS-201. Data are reported to have been analysed to note the number of months that it took for approximately 20% of the study population to remain progression-free (i.e. number of months for 80% of the study population to have experienced disease progression), which was around 9 months. This is reported to have been done to exclude those outlier patients who took an unusually long time to progress relative to the rest of the patient population and who would have potentially distorted the estimated transition probabilities had they been included. The monthly transitions beyond 9 months are assumed to be the same as calculated using the probabilities derived at 9 months. These modelled data have been compared with the actual data and are reported to demonstrate a good fit. As this estimate of the transition probabilities includes those who transition to death as well as those who transition to progressive disease, the proportion attributed to death has been estimated by analysing the proportion of patients for whom the TTP was equal to the OS and has been applied equally to all patients treated with trabectedin in any given cycle.

The probability of patients transitioning from progressive disease to death following trabectedin treatment is derived by taking the last month at which around 20% of patients remained free from progression to death in study ET-743-STS-201. This was taken as 26 months (at which point 21.54% of patients were reportedly alive), and this time point was used to estimate the per-cycle probability. This transition probability is applied to all cycles in the trabectedin arm of the model, rather than using the actual time-dependent probabilities observed in the study.

The only transition applicable to patients treated with EST in the model is the transition from progressive disease to death. Combined data derived from two trials of patients receiving ifosfamide as second-line treatment have been used to estimate this transition probability[16,17]. The same approach as above is used, in which the last month that around 20% of patients remain progression-free and the associated progression rate at that point are used to calculate the per-cycle probability (11 months, 73.83%). This was used to extrapolate progression over the long term. These modelled data have been compared with the actual data and are reported to demonstrate a good fit. However, there are some inconsistencies with the combined data that is presented and the extent to which they reflect EST as defined is uncertain.

8.3.5.2 Adverse events

Adverse events are not explicitly considered as clinical inputs. Dose reductions (which will have resulted from adverse events) and the adverse events of nausea and vomiting only are considered from a cost perspective (see 8.3.6.2).

8.3.5.3 Utility weights

The company submission states that literature reviews did not identify quality of life data appropriate to use in the population that is being modelled[3]. Therefore, utility weights are not incorporated in the base case model, which limits the model outputs to estimates of incremental costs per life year gained. Three QALY assumptions have been explored in scenario analyses, each of which assumes that treatment with trabectedin is associated with a utility weight of 0.8 and that treatment with EST is associated with a lower utility weight (0.7, 0.65, or 0.6)[3]. In the absence of published or elicited utility weight estimates, there is considerable uncertainty with this approach, which implicitly assumes that treatment with trabectedin is associated with improved quality of life compared with EST. The median age of patients in the pivotal ET-743-

STS-201 study of trabectedin was 53 years[2]. For reference, the mean EQ-5D-derived UK population norm for individuals aged 45 to 54 years is 0.85 and for individuals aged 55 to 64 years is 0.80[20].

8.3.6 Healthcare resource utilisation and cost

8.3.6.1 Drug and administration costs

The recommended dose of trabectedin is 1.5mg/m^2. The company submission states that the actual mean dose administered to patients over the course of study ET-743-STS-201 was 1.22mg/m^2, which is referenced to data on file and not verifiable. The economic model assumes that patients had an average body surface area of 1.7m^2, which means the per-patient dose of trabectedin used in the model is 2.07mg. This would be presented as two 1mg vials plus one 0.25mg vial, at a cost (British National Formulary) of £3,095 per cycle[21]. The company submission states that the average number of drug cycles per patient in STS-201 was 4.90 (data on file, corresponds with median number of cycles of five reported in an abstract[10]). Including the cost of dexamethasone 20mg IV that is also required, the "average" cost of trabectedin across all cycles in the model is assumed to be around £15,200. This is applied equally to all patients and is assumed to be accrued in the first cycle of chemotherapy (i.e. averaged across all patients irrespective of number of cycles a given patient would actually receive).

EST efficacy data assumed in the model is based on ifosfamide data, but the costs of EST assumed in the model are actually based on the costs of etoposide and dacarbazine, given over six cycles and weighted by the estimated distribution of treatment types (67% etoposide, 33% dacarbazine). These agents and the distribution of use are stated in the company submission to be based on discussions with Welsh and Scottish clinical experts. However, as also acknowledged in the company submission, the type of chemotherapy administered at this point in the care pathway will vary from patient and patient[3].

It is assumed that all patients survive the duration of treatment used in the model from a cost point of view (4.9 cycles for trabectedin, 6 cycles for EST)[3]. It is assumed that all patients are treated on an inpatient basis, which the company submission asserts is a conservative approach as trabectedin can be administered using ambulatory pumps. The costs of administration are based on the costs of simple parenteral chemotherapy (at first visit) using 2006-7 NHS reference costs. It is further assumed that only 33% of patients seek further chemotherapy, therefore the drug and administration costs (which are already weighted to account for the different administration regimens by the assumed distribution of use of etoposide and decarbazine) are reduced accordingly. The EST drug costs are applied at the beginning of the first cycle in the EST arm of the model. For those patients in the trabectedin arm of the model who subsequently switch to EST because of disease progression, the costs are applied once patients move off trabectedin[3].

There are therefore a range of assumptions employed in the estimation of drug and administration costs.

8.3.6.2 Adverse event costs

The model does not assume any costs for adverse effects associated with EST. For the trabectedin arm, only those adverse effects associated with hospitalisation are included in the model, the most common drug-related adverse events being vomiting and nausea. The company submission states that there were seven hospitalisations for drug-related adverse events, which is a rate of 0.05 in the relevant trabectedin arm.

The costs of abdominal pain as listed in the 2006-7 NHS reference costs has been assumed for this adverse event[3].

8.3.6.3 Other resource use and costs

Ongoing non-chemotherapy costs associated with EST are incorporated in the model based on data collected retrospectively for a cost of illness study in 47 UK patients with metastatic STS[22]. These include diagnostic tests, and inpatient stay costs of administration, adverse events and terminal care, which are estimated to total around £2,000 per patient. Data on file collected as part of this cost of illness study is reported to show that there was an average of 119 days between a patient's final progression and death. This is used to average the ongoing non-chemotherapy costs associated with EST across each cycle (£510.79). This is applied in each cycle of EST treatment. No other ongoing costs associated with trabectedin are included (e.g. the monitoring of certain parameters mentioned previously and outlined in the SPC [1]).

The costs of resource use associated with the final stages of life, such as hospice and other palliative care, are also derived from the cost of illness study, and are applied in the model at the point of death[3].

8.3.7 Discounting

Costs and outcomes are discounted at 3.5%[3], which is the preferred discount rate.

8.3.8 Results

8.3.8.1 Base case analysis

In the base case analysis, the incremental cost per life year gained is estimated as £21,257 compared with EST as described in the model.

8.3.9 Sensitivity analysis

8.3.9.1 One way sensitivity analyses

A range of one-way sensitivity analyses have been conducted that basically explore the impact of varying the cost components of the model. Results are as would be expected. Of the analyses conducted, the model is most sensitive to the dose assumed for trabectedin. When the recommended dose of trabectedin (1.5mg/m^2) is used in the model, the cost of trabectedin assumed in the model increases such that the incremental cost per life year gained increases to £24,630. However, as this analysis does not link dose to outcomes in the model (either beneficial or adverse), this analysis is of limited use.

8.3.9.2 Additional scenario analyses

Three scenario analyses have been conducted to explore possible outputs as incremental costs per QALY. Each of these assumes that treatment with trabectedin is associated with a utility weight of 0.8 and that treatment with EST is associated with a lower utility weight[3]:

At an EST utility weight of 0.7, the incremental cost per QALY is estimated as £29,954.

At an EST utility weight of 0.65, the incremental cost per QALY is estimated as £30,314.

At an EST utility weight of 0.6, the incremental cost per QALY is estimated as £31,808.

There is a significant degree of uncertainty with the approach used in these analyses, which implicitly assumes that treatment with trabectedin is associated with greater quality of life compared with treatment with EST. This is further complicated by the

counterintuitive finding that as the QALY difference increases, the incremental cost per QALY also increases. The company submission notes that this is due to the disutility that is also being applied to the trabectedin arm once patients undergo disease progression[3]. It should be remembered that trabectedin delays, rather than prevents, disease progression. This serves to highlight the limitations in the model assumptions, and interpretation of the outputs.

8.3.9.3 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted by assuming distributions around the parameters of the number of cycles of treatment, the dose intensity and the transition probabilities. Based on 1,000 replications the incremental cost per life year gained was estimated as £18,327 (95% confidence interval £12,942 to £27,394). At a willingness to pay threshold of £20,000 and £30,000 per life year gained, the cost effectiveness acceptability curve indicates that the probability of trabectedin being cost effective is around 65% and 99%, respectively. However, it should be noted that the outputs of the PSA are a function of the inputs and this analysis does not address the other potential issues of costs, and uncertainty regarding quality of life aspects of treatment.

8.4 Review of evidence on budget impact:

8.4.1 Description and critique of the company's submission

A simple budget impact analysis is provided based on a reported incidence of STS in Europe, which the company has attempted to extrapolate to the Welsh population. An estimate of the proportion of patients with metastatic STS, and expert opinion on the proportion of patients likely to undergo chemotherapy have been used to derive the number of patients likely to receive trabectedin over the next five years. The cost of trabectedin is based on that assumed in the economic model, which considers the "average" dose and number of treatment cycles received by patients in the pivotal ET-743-STS-201 study[3].

There are several limitations in the budget impact calculations. The crude incidence of STS assumed in the analysis may be an underestimate. In addition, the population estimates for Wales have been incorrectly calculated, which feed through to the number of patients estimated to receive trabectedin each year. The costs of trabectedin in this analysis relate only to the actual acquisition costs of trabectedin and take no account of the need for dexamethasone (although this would actually be a very small component of the drug cost) and also the need for administration by 24-hour IV infusion. As there is not one particular treatment that would be displaced by the introduction of trabectedin following failure of first or second line standard agents, the analysis is not able to provide an accurate net budgetary impact.

8.4.2 Perspective and time horizon

The analysis is conducted from the perspective of NHS Wales over five years commencing from mid 2008[3].

8.4.3 Data sources

8.4.3.1 Incident and prevalent cases

European Society for Medical Oncology (ESMO) recommendations for 2007 indicated that the crude incidence of STS was one to three per 100,000 population per year[23]. The company submission has used the mid-estimate of two per 100,000 as the incidence of STS in Wales[3], and as life expectancy is short, prevalence has been assumed to be the same as the yearly incidence rate. It should be noted that the updated ESMO recommendations, issued in May 2008 (after the company submission to AWMSG was made), quote a revised estimated incidence averaging four per 100,000 population per year in Europe[8], which if extrapolated to Wales would

effectively double the number of patients estimated to be eligible for treatment with trabectedin.

The company submission notes that the mid-2006 population for Wales was 2,965,900 based on Office of National Statistics (ONS) data[24]. The company submission then implies that the population of the UK has grown each year by 0.05% between 2001 and 2006 and attempts to inflate the mid-2006 Welsh population to provide estimates for each of the years 2008 to 2012[3]. However, there is an error in the assumptions used and the calculations conducted. The ONS data indicate that the population of the UK has grown by 0.5% each year (and not 0.05%)[24]. Further, the company submission has actually increased the population estimate from 2006 by 5% each year, and not 0.5%. The population estimates in the company submission are therefore incorrect (the company submission states that the population in 2008 would be 3,269,905, rising to 3,974,590 in 2012; whereas applying a 0.5% increase as per the ONS data would put the 2008 population at 2,995,633 and the 2012 population at 3,055,997). However, due to the low estimated use of further chemotherapy following failure of first/second line standard chemotherapy, this does not translate into large differences in the number of patients that are estimated to be eligible for treatment with trabectedin.

The STS incidence rate of two per 100,000 has then been applied to the Welsh population estimates, which the company submission suggests translates into 65 patients in 2008, rising to 79 patients in 2012 (although the correct figures based on ONS data would be 60 in 2008, rising to 61 in 2012, or double these if the revised incidence rate is used). It is then estimated that 50% of STS patients develop metastatic disease at some point, which would imply that half of the number of patients above would be potentially eligible for trabectedin[3].

8.4.3.2 Rates of adoption

Based on company-sought clinical expert opinion and market research (not verifiable), it is estimated that 85% of patients with metastatic disease receive chemotherapy, of which 10% receive combination therapy with anthracycline and ifosfamide as first-line therapy. Of these, 60% are estimated to then go on to receive second-line therapy. These are patients who would be eligible for treatment with trabectedin as second-line therapy. The company submission estimates this to be two patients in 2008 (which is similar to the 1.5 patients that would be estimated using the correct ONS data). The company data also indicates that 90% of patients who receive chemotherapy receive one single agent as their first-line treatment, of which 75% go on to receive a second single agent as second-line treatment. Of these, 40% are expected to receive a third-line therapy. These are the patients who would be eligible for treatment with trabectedin as third-line therapy. The company submission estimates this as 7 patients (which is similar to the 6.9 patients that would be estimated using the correct ONS data).

Therefore, the company submission estimates that nine patients (two and seven) would be eligible for treatment with trabectedin in 2008. Using the same approach, they estimate that this would rise to 11 patients eligible for treatment with trabectedin in 2012[3] (while the use of the correct ONS data would predict still only nine patients eligible in 2012, or 18 in each year if the revised incidence rate is used).

8.4.3.3 Costs and resource use

The acquisition costs of trabectedin are taken from the economic model data presented in section 8.3.6.1. No consideration is given to the need for dexamathasone (which is only a small component of the costs of treatment) or the need for administration by 24-hour IV infusion. The drug acquisition cost is therefore based on; an assumed body surface are of 1.7m^2, the "average" dose used in study ET-743-STS-201, the BNF list cost of trabectedin vials required to deliver that dose each cycle, and the "average" number of cycles of trabectedin treatment given in study ET-743-STS-201. This is estimated to be £15,179.15[3].

8.4.4 Results

Based on the number of patients estimated in the company submission to be eligible for trabectedin treatment each year, the trabectedin acquisition costs are calculated to be £139,224 in 2008, rising to £169,228 in 2012[3]. These are subject to some uncertainty due to the issue highlighted above. There are no direct savings expected with trabectedin treatment, and there has been no attempt to consider any treatments that may be displaced by trabectedin due to there being no one specific treatment recommended in this patient population.

8.4.5 Sensitivity analysis

No sensitivity analyses have been conducted.

9.0 ADDITIONAL INFORMATION

9.1 Guidance and audit requirements:

The National Institute for Health and Clinical Excellence (NICE) issued cancer services guidance for the treatment of sarcoma in 2006[25]. Key recommendations were:

- Prompt referral for expert diagnosis is crucial
- People should be treated by a specialist multidisciplinary team
- Treatment should be carried out by specialists
- Appropriate support and rehabilitation services should be available to people who are disabled by treatment for sarcoma
- All sarcoma teams should collect data on treatment and care, and take part in training programmes and audits.

Due to the need for treatment by specialists, trabectedin is not suitable for shared care[1,25].

9.2 Related advice:

The European Society for Medical Oncology issued updated recommendations for the diagnosis, treatment and follow-up of patients with STS in May 2008[8]. These recommend chemotherapy as the standard treatment for metastatic disease that is not completely resectable based on anthracyclines as first line treatment (refer to Appendix1 for further details).

9.3 Previous NICE / AWMSG advice:

- Imatinib (Glivec®▼) for the treatment of GIST was the subject of a NICE technology appraisal in October 2004. This recommended imatinib for first line use in people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST. A decision was made in February 2008 to review this guidance[26].

- Sunitinib (Sutent®▼) is not endorsed for use in NHS Wales for the treatment of GIST. This decision, announced 19th February 2008, is due to the marketing authorisation holder not making a submission to AWMSG[27].

9.4 Other points

Trabectedin in the treatment of metastatic STS, and sunitinib in the treatment of GIST, have been proposed as topics for technology appraisal as part of the 18th wave of the NICE work programme[28].

9.5 Patient organisation information

A patient organisation submission by Sarcoma UK and one by The Rarer Cancers Forum were provided to AWMSG members.

GLOSSARY

RECIST criteria

RECIST = Response Evaluation Criteria in Solid Tumours. This defines responses as:

Complete response (CR): disappearance of the tumour/lesion, confirmed at 4 weeks
Partial response (PR): 30% decrease in tumour size, confirmed at 4 weeks
Stable disease (SD): neither PR nor PD criteria met
Progressive disease (PD): 20% increase in tumour size, and no CR, PR or SD documented before increase[29].

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APPENDIX 1. ADDITIONAL CLINICAL INFORMATION

Table 1A. Phase II studies of trabectedin

Reference	Study type	No. of patients	Patient characteristics	Treatment Regimen	Prior Treatment	Outcomes	
Pivotal study							
2, 3,7	Phase II, randomised, open-label study (Blinded independent radiological review panel of tumour assessments)	Randomised n=270 ITT population n=266	Median age: 53 years (range 20-80) ECOG performance status: 0: 49.6% 1: 50.0% 2: 0.4% STS type: Leiomyosarcoma 65.8% Liposarcoma 34.2%	Arm 1: IV trabectedin 1.5mg/m^2 for 24 hours once every three weeks Arm 2: IV trabectedin 0.58mg/m^2 for 3 hours once every week for 3 out of 4 weeks	Virtually all patients had received both anthracycline and ifosfamide. No information regarding next-line treatment was provided.	**Arm1: (Licensed dose)** Median follow-up: 14.7 months Median TTP: 3.7 months (95% CI 2.1 to 5.4) Median PFS: 3.3 months (95% CI 2.1 to 4.6) PFS: 3-month: 51.5% 6-month: 35.5%% Median OS: 13.8 months (95% CI 12.5 to 17.9) 1-year OS: 60.2% (95% CI 52.0 to 68.5)	**Arm 2:** Median follow-up: 10.8 months Median TTP: 2.3 months (95% CI 2.0 to 3.5) Median PFS: 2.3 months (95% CI 2.0 to 3.4) PFS: 3-month: 44.7% 6-month: 27.5% Median OS: 11.8 months (95% CI 9.9 to 13.9) 1-year OS: 49.9% (95%CI 41.4 to 58.4)
Supporting studies							
8	Phase II, single arm study (Independent investigators reviewed hospital records and all available	Included n=104 Efficacy population (treated with ≥1 cycle) n=104	Median age: 53 years (range 18-92) ECOG performance status: 0: 36.5% 1: 63.5% STS type:	IV trabectedin 1.5mg/m^2 for 24 hours once every three weeks	Prior chemotherapy regimens: 1: 75% 2: 23% >2: 2%	Median follow-up: 34 months Median TTP: 105 days (95% CI 75 to 124) PFS: 3-month: 52% 6-month: 29% 12-month: 17%	

	films)		Leiomyosarcoma: 41.0% Synovialosarcoma :17.3% Liposarcoma: 9.6% Other (excl. GIST): 32.1%			Median OS: 278 days (95% CI 238 to 368) 1-year OS: 42%		
9	Phase II, single arm study (Responses were reviewed by an expert committee including two independent radiologists)	Included n=54 Efficacy population (treated with ≥2 cycle) n=54	Median age: 48 years (range 22-71) ECOG performance status: 0: 48% 1: 52% STS type: Leiomyosarcoma: 41% Liposarcoma: 11% GIST: 7% Other: 41%	IV trabectedin 1.5mg/m^2 for 24 hours once every three weeks	Prior chemotherapy regimens: 1: 48% 2: 28% >2: 24% 83% had prior anthracycline and ifosfamide combinations Patients stratified by prior chemotherapy **Group 1** (n=26): 1-2 single agents or 1 combination **Group 2** (n=28): >2 single agents or >1 combination	**All patients** Median follow-up: 26 months Median PFS: 1.9 months (range 0.69 to 30.62 months) PFS: 3-month: 8.8% 6-month: 4.1% Median OS: 12.8 months (range 0.69 to 33.77 months)	**Group 1** Median PFS: 1.76 months PFS: 6-month: 23% Median OS: 13.72 months	**Group 2** Median PFS: 1.9 months PFS: 6-month: 25% Median OS: 7.97 months
10	Phase II, single arm study	Included n=36 Efficacy population (treated with ≥1 cycle) n=36	Median age: 48 years (range 19-68) ECOG performance status: 0: 58% 1: 42% STS type: Leiomyosarcoma: 36% Liposarcoma: 28% Other (excl. GIST): 36%	IV trabectedin 1.5mg/m^2 for 24 hours once every three weeks	Prior chemotherapy regimens: 1: 44% 2: 50% >2: 6% 100% had prior anthracycline and 83% prior ifosfamide	Median follow-up: 38.6 months Median TTP: 1.7 months (95% CI 1.3 to 4.4 months) Median OS: 12.1 months (95% CI 8.1 to 26.5 months) 1-year OS: 53.1% (95% CI 38.7% to 72.8%)		
TTP=time to progression; PFS=Progression-free survival; OS=Overall survival								

Panel 1A. Studies used as historical comparisons for OS with trabectedin.

The company submission refers to four studies[16-19] as historical comparisons for OS with trabectedin. These are stated in the company submission to include two studies of ifosfamide[16,17], a study of dacarbazine[18] and a study of etoposide[19] after failure on standard chemotherapy. The company submission presents OS data from these studies alongside OS data from the pivotal study of trabectedin (ET-743-STS-201). For dacarbazine and etoposide the data is presented as follows:

Dacarbazine: median OS 6.6 months; one-year OS 18%; n=50

Etoposide: median OS 6.3 months; one-year OS 15%; n=26

The dacarbazine data is referenced to a study of high dose ifosfamide (HDI) as first-line treatment in patients with STS[18], and does not appear to relate to patients who received dacarbazine following failure on standard chemotherapy. It is therefore not possible to verify the presented data from the sources provided (although the updated clinical overview provided by the company[14] does include some of the relevant data). The etoposide data was based on a schedule of 50mg/m^2 each day for 21 days out of each four-week cycle[19]. STS patients (mixed types) had previously received one two-drug schedule (usually ifosfamide and doxorubicin) or two one-drug regimens. It is unclear from the referenced study how the median OS and the one-year OS have been calculated as no survival data is reported. The published paper that is referenced notes that in second-line studies the majority of reports indicate that etoposide does not have significant efficacy[19].

For ifosfamide treatment, the OS data is stated to be based on two studies[16,17]. However, there are some inconsistencies in the data reported in the company submission. One report of the data (in the Economics appendix of Form B) suggests median OS to be 5.9 months and 1-year OS to be 20% based on 105 patients, and another report (in the section 3c of Form B) suggests median OS to be 6.6 months based on 86 patients[3]. It is not possible to verify the figures from the actual published manuscripts that are cited as references, but the updated clinical overview includes the latter figures[14]. Both of the ifosfamide studies involved patients receiving the drug as first or second line treatment and it is not clear how the OS data for those patients who receive ifosfamide as second line treatment (the most relevant population to act as a historical comparator) has been combined and calculated. There appear to be some small inconsistencies in the patient numbers reported as providing data from the published studies but there are other issues that limit interpretation of the combined data. One study excluded patients who had received more than one line of therapy, and patients using ifosfamide as second line therapy in that study had only received prior treatment with anthracycline (doxorubicin or epirubicin)[16]. The other study permitted patients to have had combination therapy or two single-agent regimens, and of those 25 patients who had previously received chemotherapy, 13 had received prior ifosfamide treatment[17]. The two studies used very different dosing regimens; one explored dosing regimens of 5g/m^2 continuous infusion over 24 hours once every three weeks or 3g/m^2 infused over four hours for three consecutive days every three weeks[16], and the other study explored HDI 12g/m^2 continuous infusion over three days repeated at four-week intervals[17]. Leiomyosarcoma was the STS type in 46% of patients in the first study[13] and 33% in the second[17]. The second study manuscript notes that a number of studies may indicate that leiomyosarcomas are uniformly resistant to ifosfamide-based therapy, and that the response rate may be higher with bolus/short-term infusion as compared with continuous infusion. These are suggested

as possible reasons for the low response to HDI seen in the study (5% response rate in patients with leioyosarcoma)[17]. Of note, the second study concluded that HDI given as a continuous infusion could not be recommended as the standard treatment of advanced STS even in selected patients[17]. Therefore, there would seem to be several potential issues with comparing this combined data with the data from the trabectedin studies.

A further point to consider is that the updated clinical overview of trabectedin includes details of a literature review of studies of other new investigational agents/regimens[14]. The updated clinical overview determined the median OS in phase II studies with new single agents as chemotherapy in pretreated STS patients to be eight months[14], which is somewhat improved compared with that reported from the combined results of the two phase II trials of ifosfamide. Few details are provided, which warrants caution in the interpretation of this data. However, given that there are low numbers of patients with advanced or metatstatic STS who will be able or willing to undergo further chemotherapy after failure of standard chemotherapy with anthracycline and ifosfamide, it is conceivable that such patients may be offered or accept treatment with other investigational agents that may have improved outcomes compared with that observed from the combined data of the two ifosfamide trials.

Summary of European Society for Medical Oncology updated recommendations (2008) for the diagnosis, treatment and follow-up of patients with STS [8].

The guidelines recommend chemotherapy as the standard treatment for metastatic disease that is not completely resectable based on anthracyclines as first line treatment. The recommendations note that there has been no formal demonstration that multi-agent chemotherapy is superior to single-agent chemotherapy with doxorubicin alone. Nevertheless a higher response rate is expected in sensitive histological types and, therefore, multi-agent chemotherapy with doxorubicin plus ifosfamide may be of choice, especially when a tumour response is felt to be able to give an advantage and the patient's performance status is good. They add that dacarbazine may be added to the regimen. Patients who have already received chemotherapy may be treated with ifosfamide if they did not receive it previously. High-dose ifosfamide may be an option also for patients who have already received standard dose ifosfamide. Trabectedin is considered a second line option in these recommendations.