

Trabectedin for the treatment of advanced soft tissue sarcoma

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

Contents

1 Guidance.....	4
2 The technology	5
3 The manufacturer's submission.....	7
4 Consideration of the evidence.....	15
Clinical effectiveness	15
Cost effectiveness	17
5 Implementation.....	21
6 Recommendations for further research.....	22
Appendix A: Appraisal Committee members and NICE project team	23
A Appraisal Committee members	23
B NICE project team.....	26
Appendix B: Sources of evidence considered by the Committee	27
Update information	29

1 Guidance

1.1 Trabectedin is recommended as a treatment option for people with advanced soft tissue sarcoma if:

- treatment with anthracyclines and ifosfamide has failed or
- they are intolerant of or have contraindications for treatment with anthracyclines and ifosfamide.

Trabectedin is only recommended if the company provides it according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with trabectedin that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

2 The technology

- 2.1 Trabectedin (Yondelis, Immedica) is an alkylating agent, which affects cancer cells by damaging DNA. Trabectedin 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. The marketing authorisation was granted under 'exceptional circumstances'. The summary of product characteristics (SPC) states that 'efficacy data are based mainly on liposarcoma and leiomyosarcoma patients'.
- 2.2 Trabectedin is contraindicated in people who have hypersensitivity to trabectedin or to any of the excipients, in those with concurrent serious or uncontrolled infection, in women who are breast-feeding, and in combination with yellow fever vaccine. The SPC states that trabectedin is not indicated for use in children and adolescents, and that creatine phosphokinase, hepatic function and haematological parameters should be monitored regularly during treatment. The SPC lists precautions for use of trabectedin in people with liver or kidney impairment. The SPC reports that the most common adverse reactions are nausea, fatigue, vomiting, weight loss (anorexia), neutropenia, thrombocytopenia, and increases in enzymes in blood indicating abnormal liver function. For full details of adverse events and contraindications, see the SPC.
- 2.3 The SPC for trabectedin states that 'the recommended dose is 1.5 mg/m² body surface area, administered as an intravenous infusion over 24 hours with a 3-week interval between cycles.' The SPC also states that administration of trabectedin through a central venous line is 'strongly recommended'. Anti-emetic prophylaxis with intravenous dexamethasone (20 mg) must be administered to all patients 30 minutes before trabectedin treatment. Dexamethasone may also have hepatoprotective effects. The acquisition cost of trabectedin is £363.00 for a 250-microgram vial and £1,366.00 for a 1-mg (1,000-microgram) vial (excluding VAT; 'British national formulary' [BNF] edition 58). At a dose of 1.5 mg/m², a patient with a body surface area of 1.7 m² would need approximately 2.5 mg of trabectedin per cycle. One such infusion (using two 1-mg vials and two 250-microgram vials of trabectedin) would cost

£3,458. The company has a commercial arrangement. This makes trabectedin available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 The manufacturer's submission

- 3.1 The Appraisal Committee ([appendix A](#)) considered evidence submitted by the manufacturer of trabectedin and a review of this submission by the Evidence Review Group (ERG; [appendix B](#)).
- 3.2 The manufacturer's submission included a phase 2 randomised trial (STS-201) evaluating the efficacy of trabectedin in participants with locally advanced or metastatic soft tissue sarcoma in whom the disease had relapsed or become refractory after treatment with at least 1 anthracycline and ifosfamide, given either in combination or in sequence. All participants had liposarcomas or leiomyosarcomas (L-sarcomas) and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The trial randomised participants to 1 of 2 dosing regimens of trabectedin. One group received the dosage of trabectedin specified in the marketing authorisation (1.5 mg/m² every 3 weeks as a 24-hour intravenous infusion, n=136) and the other group (n=134) received trabectedin at a dosage of 0.58 mg/m² every week as a 3-hour intravenous infusion. In addition, the manufacturer's submission presented 3 uncontrolled phase 2 trials of trabectedin. These included a total of 194 participants with soft tissue sarcoma, of whom 104 had L-sarcomas. Participants in all of these studies had an ECOG performance status of 0 or 1. In the absence of relevant comparator data in the included trials, the manufacturer reported historical control data for patients receiving treatments considered to be equivalent to best supportive care (BSC; see sections 3.7 to 3.9). These data were derived from studies in the database of the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC STBSG).
- 3.3 The primary outcome of the STS-201 trial was time to progression (time between randomisation and the first documentation of disease progression or death as a result of progressive disease); secondary outcomes included progression-free survival, overall survival and best overall response. According to the manufacturer, treatment with trabectedin continued as long as participants derived therapeutic benefit, until the disease progressed, or for at least 2 courses of therapy

beyond a confirmed response. The design of STS-201 permitted crossover for participants in either arm whose disease progressed. The manufacturer acknowledged that the crossover design of the study affected overall survival.

- 3.4 The median time to progression from intention-to-treat analyses was statistically significantly longer (hazard ratio [HR] 0.734, $p=0.032$) for the licensed dosage of trabectedin, with a time to progression of 3.7 months (95% confidence interval [CI] 2.1 to 5.4) compared with 2.3 months (95% CI 2.0 to 3.5) for the comparator dosage of trabectedin. Median overall survival was 13.9 months (95% CI 12.5 to 18.6) for the licensed dosage of trabectedin compared with 11.8 months (95% CI 9.9 to 14.9) for the comparator trabectedin regimen. Median progression-free survival at 3 and 6 months was 51.5% (95% CI 43.0 to 60.1) and 35.5% (95% CI 27.1 to 43.9) respectively for the licensed dosage of trabectedin, compared with 44.7% (95% CI 36.0 to 53.3) and 27.5% (95% CI 19.4 to 35.5) for the comparator trabectedin regimen. The manufacturer reported that in a pre-planned subgroup analysis, efficacy outcomes appeared to be more favourable in patients with liposarcomas than in those with leiomyosarcomas, regardless of the study arm.
- 3.5 The manufacturer reported that the main treatment-related severe (grades 3 and 4) adverse events observed in all studies were transient and reversible, and comprised non-cumulative neutropenia and elevations of hepatic transaminase without clinical consequences. Grade 3 or 4 nausea and vomiting were reported by some participants. The manufacturer stated that unlike with other commonly used cytotoxic agents, no cardiotoxicity or neurotoxicity was observed with trabectedin.
- 3.6 No health-related quality of life data were presented for patients with advanced soft tissue sarcoma and the manufacturer stated that none were obtained from the trials.
- 3.7 Historical control data were used to approximate BSC, with the manufacturer acknowledging the limitations of this approach. To estimate overall survival, data for those in whom treatment with ifosfamide had failed, for those receiving dacarbazine, and for those receiving etoposide were taken from an unpublished analysis of

4 phase 2 studies in the EORTC STBSG database of adults with advanced pre-treated soft tissue sarcoma. To estimate progression-free survival, data for the comparators were taken from a publication reporting on phase 2 studies from the EORTC STBSG database. The studies included in the analysis varied in the treatment given to patients during and before entering the trials. Therefore, the manufacturer selected the pre-treated populations that they considered to be most relevant.

- 3.8 The manufacturer reported that the median overall survival of historical control patients treated with ifosfamide was 6.6 months from start of therapy (95% CI 5.0 to 9.0); a further figure was included by the manufacturer, but was marked as academic-in-confidence and therefore cannot be presented. The manufacturer reported that the median overall survival for those treated with dacarbazine was 6.6 months (95% CI 4.3 to 8.4) and 6.3 months (95% CI 4.4 to 8.9) for those treated with etoposide.
- 3.9 The manufacturer reported that the mean progression-free survival of historical control patients treated with inactive regimens (n=234) was 21% (standard error [SE] \pm 3%) and 8% (SE \pm 2%) at 3 and 6 months respectively. Inactive regimens include treatment with mitozolomide, nimustine, fotemustine, miltefosine, liposomal muramyl tripeptide phosphatidylethanolamide, temozolamide, etoposide, Tomudex or gemcitabine. The corresponding figures for historical control patients treated with active regimens comprising ifosfamide and dacarbazine (n=146) were 39% (SE \pm 4%) and 14% (SE \pm 3%) respectively.
- 3.10 The manufacturer developed its own economic evaluation, comprising a 2-arm state-transition model. The first arm was designed to capture the costs and outcomes associated with treatment with trabectedin; the second arm was designed to capture the costs and outcomes associated with BSC. Administration of other chemotherapies in addition to BSC was explored in a sensitivity analysis. The model included 4 mutually exclusive health states: progression-free after treatment with trabectedin; progressive disease after treatment with trabectedin; progressive disease with BSC; and death. People treated with trabectedin entered the model in the progression-free state, whereas

people treated with BSC entered the model in the progressive disease state. The model cycle length was 1 month with a time horizon of 5 years.

- 3.11 The model used the effectiveness data from the STS-201 trial of trabectedin, which included only participants with L-sarcomas after they had been treated with a regimen containing at least 1 anthracycline and ifosfamide (combined or sequential). To represent the base case, the manufacturer selected effectiveness data from participants receiving a 24-hour infusion of trabectedin every 3 weeks. In a sensitivity analysis, the manufacturer modelled the pooled effectiveness from the 3 initial phase 2 uncontrolled studies of trabectedin. Transition probabilities for the trabectedin arm were estimated from Weibull parameters derived from the patient-level data for time to progression from the STS-201 trial. Weibull curves were fitted to Kaplan–Meier curves for time to progression and overall survival. The Weibull estimates were considered by the manufacturer to be comparable to the Kaplan–Meier curves. Following a request by the ERG, arising because of differences in patient characteristics between the trabectedin and BSC arms, Weibull curves for trabectedin were re-calculated using age, gender and severity as covariates.
- 3.12 The effectiveness data for patients who receive BSC after failure of anthracyclines and ifosfamide were estimated from pooled data from 4 published trials from the EORTC STBSG database. These 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 BSC arms.
- 3.13 Because no studies of quality of life in patients with soft tissue sarcoma were identified, the manufacturer, following discussion with its clinical experts, used health-state utilities for non-small-cell lung cancer as proxies, assuming comparable prognoses and stages of the 2 diseases. Health-state utilities in progression-free and progressive disease states were assumed to be similar for all patients, irrespective of treatment. The utility values for progression-free and progressive disease health states

were assumed to be 0.653 and 0.473 respectively. Admission to hospital as a result of adverse events associated with trabectedin treatment was associated with a utility of 0.610, which was equal to that associated with nausea and vomiting. This was assumed to last 1 month and equated to a quality-adjusted life year (QALY) decrement of 0.004. The utility associated with developing grade 3 or 4 neutropenia was 0.56. This was assumed to last 1 week and equated to a QALY decrement of 0.002. Adverse events were assumed to occur only during the first cycle of trabectedin treatment, and no disutility associated with adverse events was modelled for patients receiving BSC.

- 3.14 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. The manufacturer used patient-level data from the STS-201 trial to calculate the average number of 1-mg and 250-microgram vials used for each patient and the proportion of patients receiving trabectedin in each cycle. The ERG stated that the manufacturer's revised response reported a cost per patient of £23,719 with administration costs excluded, and £25,986 with administration costs and a pre-treatment injection of dexamethasone included. The manufacturer obtained management costs for patients in the progressive disease health state from a cost-of-illness study, and assumed that the costs for the progression-free health state, in the absence of data, were half the costs for the progressive disease health state. Additional costs were included when a patient died. Costs of hospitalisation were average costs and were dependent on patients' diagnoses. The manufacturer did not include costs for treating neutropenia, for treating adverse events in the BSC arm, or for patient monitoring.
- 3.15 With discounting at 3.5% per annum, the manufacturer's revised base-case cost-effectiveness results gave an incremental cost-effectiveness ratio (ICER) of £56,985 per QALY gained for trabectedin compared with BSC, based on an incremental cost of £27,145 and an incremental QALY gain of 0.476. The manufacturer explored uncertainty in 1-way sensitivity and probabilistic sensitivity analyses. The ICER appeared most sensitive to changes in estimates of utility.

- 3.16 The manufacturer presented results for additional scenarios:
- Using pooled effectiveness for trabectedin from 3 uncontrolled phase 2 trials was associated with an ICER of £50,017 per QALY gained.
 - Assuming that 33% and 100% of patients receiving BSC receive further chemotherapy was associated with an ICER of £62,044 and £80,279 per QALY gained respectively.
- 3.17 The ERG stated that the revised method used to estimate the cost of trabectedin was, in general, appropriate. It noted, however, that the model may have underestimated the cost of trabectedin because a few participants were still being treated at the end of the follow-up period, yet the model assumed no patients incurred costs beyond follow-up. The ERG also identified a number of errors in the revised model submitted by the manufacturer. These errors were corrected by the ERG and were shown to have limited impact on the results. The ERG's corrections to the manufacturer's model resulted in an ICER of £56,949 per QALY gained for the base case (compared with the manufacturer's figure of £56,985, see section 3.15) and £49,992 per QALY gained for the pooled analysis (from the 3 phase 2 uncontrolled studies of trabectedin).
- 3.18 The ERG expressed strong concerns over the structure of the model in that people treated with trabectedin entered the model in the progression-free health state, whereas those who received BSC entered in the progressive disease health state, which was associated with a lower estimate of utility than the progression-free health state. The manufacturer conducted a revised scenario analysis (based on the revised method to estimate the cost of trabectedin), which assumed that the utility for the progression-free health state (in the BSC arm) was 0.653 for the first cycle and followed a linear decline over the next 4 cycles to reach the utility for progressive disease (0.473). This manufacturer's analysis was associated with an ICER of £61,064 per QALY gained.
- 3.19 In response to comments received during consultation about the way in which utility was modelled, the ERG presented analyses exploring the impact of different assumptions regarding utility on the ICER. These analyses did not include the model correction (described in section 3.18),

which was estimated to increase the ICERs by approximately £5,000 per QALY gained. One analysis assumed the same utility value for the progressive disease and progression-free health states, and varied this value between 0.4 and 0.9. This caused the ICER to vary from more than £80,000 per QALY gained (with the utility value for both states set to 0.4) to approximately £40,000 per QALY gained (with the utility value for both states set to 0.9). Another analysis explored the difference in the utilities of the progressive disease and progression-free health states by setting the utility for progression-free to 0.653 (the manufacturer's base case) and varying the utility of progressive disease between 0.473 and 0.653. This had little impact on the ICER. The reverse analysis, which set the utility for progressive disease to 0.473 (the manufacturer's base case) and varied the utility for the progression-free health state between 0.473 and 0.9, produced an ICER range of approximately £46,000 to approximately £70,000 per QALY gained.

3.20 The ERG also noted the following uncertainties in the cost-effectiveness estimates presented in the manufacturer's submission:

- The comparability of the BSC and trabectedin arms was unclear. The ERG believed that participants in the STS-201 trial were highly selected and would be expected to have a high rate of survival at the time of inclusion.
- The data based on historical sources were uncertain and data relating to the natural history of disease may not be appropriate for patients who have contraindications for, or are intolerant of, ifosfamide or anthracyclines.
- The ERG was unsure about the comparability of the utility values for patients with soft tissue sarcoma and those with lung cancer, noting that cost-effectiveness results were shown to be sensitive to changes in health-state utilities.

3.21 After the second Appraisal Committee meeting, the manufacturer proposed a patient access scheme for trabectedin for the treatment of advanced soft tissue sarcoma when treatment with anthracyclines and ifosfamide has failed or a person is intolerant of or has contraindications for anthracyclines and ifosfamide. Under this patient access scheme, the acquisition cost of trabectedin to the NHS would be capped at 5 cycles of treatment. The acquisition cost of trabectedin for treatment needed

after the fifth cycle (that is, cycle 6 and beyond) would be met by the manufacturer. The Department of Health considered this would not place an excessive administrative burden on the NHS and accepted the consideration of this scheme by NICE.

- 3.22 The manufacturer submitted an updated cost-effectiveness model incorporating the patient access scheme. The model assumed reimbursement of the acquisition cost of trabectedin from the sixth treatment cycle onwards, and included additional costs to cover the increased operational costs to the NHS of implementing the scheme. The base-case analysis, which assumed equal utility values for the progression-free and progressive disease health states, produced an ICER of £28,712 per QALY gained. This was based on 41% of patients receiving more than 5 cycles of trabectedin, as observed in the STS-201 trial. The manufacturer also presented the scenario analysis with a higher utility value in the progression-free health state (0.653) than in the progressive disease health state (0.473), and incorporating a linear decline (in the BSC arm) of the value in the progression-free health state to the value of the progressive disease health state (see section 3.18). Incorporating the patient access scheme into this scenario reduced the ICER to £34,484 per QALY gained.
- 3.23 The ERG reviewed the updated analyses from the manufacturer and considered that the model had correctly incorporated the patient access scheme. The ERG reiterated that the scenario analysis that assumed that the utility value in the progression-free health state in the BSC arm followed a linear decline to reach the utility value for progressive disease represented the most appropriate estimation of the ICER. Corrections to minor errors noted in the model resulted in an ICER for this scenario of £34,538 per QALY gained.
- 3.24 Full details of all the evidence are in the [manufacturer's submission and the ERG report](#).

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of trabectedin, having considered evidence on the nature of advanced soft tissue sarcoma and the value placed on the benefits of trabectedin by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

- 4.2 The Committee considered the UK treatment pathway for patients with advanced soft tissue sarcoma and noted that trabectedin is licensed for patients with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. The Committee heard from the patient experts and the clinical specialist that there have been no major changes in the treatment of advanced soft tissue sarcoma in the past 20 years and that treatment with trabectedin represents an option for those patients who would otherwise have no licensed treatment options. The Committee heard from the clinical specialist that trabectedin treatment would be managed by specialists in sarcoma units and would usually be administered in an outpatient setting, within existing care structures.
- 4.3 The Committee noted the evidence of clinical effectiveness presented by the manufacturer from the STS-201 trial, which compared 2 dosing regimens for trabectedin and included no alternative treatment as a comparator. The Committee appreciated that because soft tissue sarcoma is a rare condition, the evidence for the comparative effectiveness of trabectedin was limited. The Committee noted that the European Medicines Agency (EMA) had granted trabectedin marketing authorisation under 'exceptional circumstances' based on evidence from a randomised, uncontrolled phase 2 trial of trabectedin in patients with L-sarcomas. The Committee was aware that there were 3 uncontrolled phase 2 trials that included patients with other types of sarcomas. The Committee heard from the clinical specialist that response to treatment

varies according to the type of sarcoma, with some sarcomas being more sensitive to treatment with trabectedin. The Committee was aware that as part of the regulatory process for trabectedin, the manufacturer is committed to exploring the subtypes of soft tissue sarcoma that may best respond to treatment.

- 4.4 The Committee then considered whether the evidence from the 'historical' trials represented patients receiving BSC. Although the Committee was aware of the limitations of historical control data, it noted the 'exceptional circumstances' of the marketing authorisation regarding the difficulties of conducting adequately powered randomised controlled trials against BSC in this patient group, and of exploring factors associated with response to treatment in a reasonable timeframe. The Committee also heard from the clinical specialist that the patients in the 'historical' trials of BSC had been recruited relatively recently, that the general management of advanced soft tissue sarcoma had not changed significantly, and that the duration of the 'historical' control studies was comparable with the trabectedin trial. The Committee therefore concluded that the use of historical controls was appropriate for this disease area but nevertheless needed to be considered with caution.
- 4.5 The Committee noted that there were differences among the patient populations in the randomised trabectedin trial (STS-201) and the 'historical' trials of BSC, mainly with regard to previously received treatment, sarcoma type and ECOG performance status. The clinical specialist informed the Committee that the 3 other uncontrolled phase 2 trials of trabectedin had included patients who were similar to the patients in the 'historical' trials. The Committee therefore accepted that the results could be cautiously generalised to the wider population of patients with advanced soft tissue sarcoma.
- 4.6 The Committee considered the clinical effectiveness data presented by the manufacturer, and noted the median overall survival for patients randomised to the licensed dosage of trabectedin exceeded that for patients receiving BSC. For progression-free survival, patients randomised to the licensed dosage of trabectedin did better than those patients randomised to an active regimen of BSC (see sections 3.4 and 3.9). The Committee noted that there was no evidence on the

effectiveness of trabectedin for patients with contraindications for ifosfamide or anthracyclines. The Committee heard from the clinical specialist, however, that a heart or liver impairment that prevents a patient from receiving ifosfamide or anthracyclines would not prevent a patient from receiving trabectedin.

- 4.7 The Committee understood that most adverse effects associated with trabectedin were reversible and non-cumulative. It heard from the clinical specialist and patient experts that there were fewer, less severe and less frequent adverse reactions associated with trabectedin than with the other chemotherapy agents used to treat soft tissue sarcoma. It understood that the adverse effects associated with trabectedin were manageable, but nevertheless important, as with other chemotherapy agents used to treat soft tissue sarcoma. Based on the clinical effectiveness evidence and the testimony from the clinical specialist and patient experts, the Committee concluded that trabectedin is a clinically effective treatment for advanced soft tissue sarcoma for patients in whom both anthracyclines and ifosfamide have failed, or who are unsuited to receive these agents, allowing for reservations about the use of historical control trials.

Cost effectiveness

- 4.8 The Committee considered evidence on the cost effectiveness of trabectedin for the treatment of advanced soft tissue sarcoma. The Committee noted that overall survival, the acquisition cost of the drug and the utility estimates were the key factors driving the economic model. It heard from the ERG that, given the limited evidence available, the methods used by the manufacturer appeared robust and appropriate. It heard that the administration costs of trabectedin did not greatly affect the outcome of the model. The Committee also heard from the clinical specialist that the scenario submitted by the manufacturer which assumed no benefits of alternative chemotherapy was not clinically plausible. Clinical advice noted that 10% of patients might derive some benefit.
- 4.9 The Committee discussed the estimates of utility used in the model. It accepted the ERG's comment that the model was inappropriate in its

assignment of different utility values to the initial health state of patients depending on the treatment to be received (trabectedin or BSC). The Committee heard from the ERG that the scenario analysis presented by the manufacturer was more appropriate, in which the progressive disease health state in the BSC arm was assigned an initial utility value identical to that of the progression-free health state and then declined linearly over the first 4 cycles of the model (see sections 3.18 and 3.23). The Committee agreed that this scenario represented the most plausible base-case estimation of the ICER.

4.10 The Committee next considered the appropriateness of the use of utilities associated with non-small-cell lung cancer as proxies for those associated with advanced soft tissue sarcoma, given that no utility values exist for advanced soft tissue sarcoma. The Committee heard from the clinical specialist and patient experts that it is not uncommon for patients with advanced soft tissue sarcoma to maintain a quality of life relatively undiminished by the disease for some time, experiencing a rapid decline of quality of life in the final weeks of life, rather than experiencing continued gradual decline over an extended period of time, as often occurs with non-small-cell lung cancer. It heard from the clinical specialist that it may be reasonable to assume that for some proportion of time, patients with advanced soft tissue sarcoma may therefore experience a higher quality of life than patients with non-small-cell lung cancer at a comparable stage of disease. The Committee accepted that these differences could be associated with a different utility profile for patients with advanced soft tissue sarcoma than for those with non-small-cell lung cancer.

4.11 The Committee understood from the ERG's exploratory analyses (see section 3.19) that the way in which utility was modelled influenced the ICER. The Committee had reservations about the use of utility data derived from patients with conditions other than advanced soft tissue sarcoma. The Committee considered that it was very unlikely that the progressive disease and progression-free health states would have the same utility value, and that it was more reasonable to assume a higher utility value for the progression-free state than for the progressive disease state. In the absence of compelling evidence to indicate otherwise, the Committee concluded that the manufacturer's base-case

utility values for progression-free (0.653) and progressive disease (0.473) represented the best estimates available.

4.12 The Committee accepted that the patient access scheme for trabectedin was implemented correctly by the manufacturer in the updated economic model. The Committee noted that the patient access scheme involved capping the maximum acquisition cost of trabectedin per patient at 5 cycles. The Committee heard from the ERG that ICERs incorporating the patient access scheme were insensitive to changes in the operational costs of the scheme. The Committee concluded that the relevant and most appropriate ICER for trabectedin versus BSC on which to base a decision was approximately £34,500 per QALY gained (incorporating the manufacturer's base-case utility values, whereby the utility value in the progression-free health state in the BSC arm followed a linear decline to reach the utility value for progressive disease, and the patient access scheme, see section 3.23).

4.13 The Committee then considered the supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of an additional 3 months or more, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case economic modelling are plausible, objective and robust.

4.14 The Committee discussed whether the benefit provided by trabectedin

for the treatment of advanced soft tissue sarcoma fulfilled the criteria for consideration as a life-extending, end-of-life treatment. The Committee understood that the total number of people with advanced soft tissue sarcoma in England and Wales was approximately 500 to 600, and that the number eligible for treatment with trabectedin may be as low as approximately 110 per year. Noting the limitations of analyses based on data from historical control trials, the Committee considered that life expectancy with BSC alone was likely to be approximately 6 months. The Committee considered the evidence from the trabectedin trial (STS-201) and noted the median overall survival for the licensed dosage was 13.9 months, although the Committee was not convinced that this value had not been overestimated. The Committee did, however, agree that trabectedin provided an improvement in the treatment of advanced soft tissue sarcoma and that it was likely that trabectedin would increase overall survival by more than 3 months. The Committee took the view that the estimates of clinical effectiveness informing the best available estimate of the ICER were sufficiently robust to conclude that trabectedin meets the criteria for being a life-extending, end-of-life treatment.

- 4.15 The Committee considered the best available estimate of the base-case ICER to be approximately £34,500 per QALY gained (see section 4.12). The Committee considered this ICER in light of the end-of-life criteria. The Committee considered that the additional weight that would need to be assigned to the original QALY benefits for the ICER to fall within the current threshold range was acceptable. The Committee concluded that, with the patient access scheme, trabectedin should be recommended as a treatment option for people with advanced soft tissue sarcoma in whom treatment with anthracyclines and ifosfamide has failed, or for those who are intolerant to or have contraindications for anthracyclines and ifosfamide.

5 Implementation

- 5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has advanced soft tissue sarcoma and the doctor responsible for their care thinks that trabectedin is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for further research

- 6.1 The Committee recommends that a study estimating utilities using directly observed health-related quality of life values (such as EQ-5D scores) in people with soft tissue sarcoma is conducted.

Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committee is one of NICE's standing advisory committees. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets 3 times a month except in December, when there are no meetings. There are 4 Appraisal Committees, each with a chair and vice chair. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the [NICE website](#).

Professor Keith Abrams

Professor of Medical Statistics, University of Leicester

Dr Amanda Adler (Chair from September 2009)

Consultant Physician, Addenbrooke's Hospital, Cambridge

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Darren Ashcroft

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Consultant Neurosurgeon, Addenbrooke's Hospital, Cambridge

Mr Tom Wilson

Director of Contracts and Information Management and Technology, Milton Keynes Primary Care Trust

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Whitney Miller

Technical Lead

Joanna Richardson and Eleanor Donegan

Technical Advisers

Jeremy Powell

Project Manager

Appendix B: Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by the School of Health and Related Research (SchARR), University of Sheffield:

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

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I and II also have the opportunity to appeal against the final appraisal determination.

I) Manufacturer/sponsor:

- PharmaMar

II) Professional/specialist and patient/carer groups:

- British Sarcoma Group
- Cancer Research UK
- Rarer Cancers Forum
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians – Medical Oncology Joint Special Committee
- Royal College of Radiologists
- Sarcoma UK

III) Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health
- Welsh Assembly Government
- Department of Health, Social Services and Public Safety for Northern Ireland
- Institute of Cancer Research
- MRC Clinical Trials Unit
- NHS Quality Improvement Scotland

C. The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on trabectedin by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD:

- Professor Ian Judson, nominated by the Royal College of Physicians, on behalf of the National Cancer Research Institute, the Royal College of Physicians, the Royal College of Radiologists, the Association of Cancer Physicians and the Joint Collegiate Council for Oncology – clinical specialist.
- Stella Pendleton, nominated by the Rarer Cancers Forum – patient expert.
- Roger Wilson, nominated by Sarcoma UK – patient expert.

Update information

February 2021: Section 1 of the guidance was updated because the commercial arrangement for trabectedin has changed. Section 2 was also updated because Immedica acquired the marketing and distribution rights to trabectedin in the UK from PharmaMar in 2019.

February 2014: Implementation section updated to clarify that trabectedin is recommended as an option for treating advanced soft tissue sarcoma. Additional minor maintenance update also carried out.

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