Patient/carer organisation statement template

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

About you

Your name:

Name of your organisation: Sarcoma UK

Are you (tick all that apply):

- ➳ a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- ➳ an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)

  Director
- other? (please specify)

What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition?

1. **Advantages**
(a) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make.

Sarcomas are a heterogeneous group of cancers of connective tissue. They are collectively very rare and individually can be extremely rare. Bone sarcomas account for about 450 patients each year while soft tissue sarcomas account for approx 2400, of which 750 are GIST. The remaining soft tissue sarcomas total about 1650, of which approximately 1400 patients will be resident in England and Wales.

Soft tissue sarcoma is not a single disease and prognosis varies considerably. Molecular biology is identifying genetic mutations/translocations which distinguish one histotype from another, and establish further sub-types, within what has hitherto been seen as a single disease. It is generally accepted that there are about 50 identifiable sub-types of sarcoma.

When they metastasize sarcomas tend to go to the lungs, occasionally the liver, and more rarely to other organs.. With some sarcomas (eg myxoid chondrosarcoma) it is almost guaranteed to happen quickly although for most there is no certainty but varying degrees of risk/probability. Survival at five years is normally quoted as 50% in the UK but this hides wide differences – limb tumours probably having a 5-year survival closer to 70% while retroperitoneal is probably <10%. The figure is also distorted by the improved survival of GIST patients in recent years following treatment with imatinib.

Soft tissue sarcoma tends to metastasise during the two years following primary diagnosis. This affects about 60% or patients, although distribution is uneven across the various histological sub-types. Thoracic metastectomy is possible in a small percentage of patients and of these 30-40% achieve survival >2 years while 5-year survival has been quoted at 20%. Where metastectomy is not possible, or where a patient relapses following surgery, chemotherapy is the only treatment option.

The indication for which trabectedin is licensed is second-line in metastatic/unresectable soft tissue sarcoma following use of both an anthracycline (usually doxorubicin/adriamycin) and ifosfamide. This means that for patients with prior combination therapy it is a 2nd line treatment, although for those receiving single agent therapy it would be 3rd line. In some sub-types if may even be a 4th or 5th line therapy owing to off-label use of other agents.

Trabectedin addresses an unmet need for patients with a poor prognosis.

Until recently research has failed to find a chemotherapy treatment better than doxorubicin or ifosfamide. These are two of the older generation of cytotoxic chemotherapies, with extensive side effects and, in the case of doxorubicin, a life-time dose limitation because of cardiac side effects. They have been the standard of

care for 20 or more years with doxorubicin in first-line with ifosfamide in second-line (or where doxorubicin is contra-indicated. Combination therapy is being tested.

Treated with doxorubicin and ifosfamide 20-30% of patients have an objective response. Median duration of response is 15 weeks. Median overall survival is approximately one year. Survival at two years is <5% of the treated cohort. The curve has been consistent in 20 years of trials with no difference between the two agents. The latest data were published following ASCO 2007 reporting an EORTC clinical trial of doxorubicin versus alternative schedules of ifosfamide in first-line[1]. A current open clinical trial is comparing doxorubicin versus doxorubicin+ifosfamide in first-line.

Diagnosis with unresectable metastases can come when asymptomatic, presenting both doctors and patients with an awesome dilemma – treat now, or later, or do not treat at all. Treat now and impact on quality of life with highly toxic treatments when quality of life may be precious; treat later and possibly too late to gain any response (however short lived a response may be); or do not treat and accept an accelerating decline, retaining what quality of life is possible for as long as possible.

Trabectedin is offering a new route through this dilemma, a need which has been unmet for years.

It has been possible to identify a number of histotypes and sub-types which do not respond to standard chemotherapy. These include rare histotypes such as clear cell sarcoma and alveolar soft part sarcoma, as well as more common sub-types such as well-differentiated liposarcoma. We can anticipate that some of these histologies will respond to trabectedin but trials are impossible.

Analysis of a sub-set of patients with lLeiomyosarcoma and myxoid Liposarcoma (two of the more common soft tissue sarcomas, together accounting for about 20%-25% of all diagnoses) demonstrates benefit from trabectedin. Phase II trials continue and we understand that synovial sarcoma (a more common histotype which has a known good response to chemotherapy) also shows good response to trabectedin.

Assessing drug activity in soft tissue sarcoma is difficult and objective response measures are a poor assessment of drug effectiveness. Disease stabilisation and freedom from progression are more accurate and relevant indicators of clinical benefit. Van Glabbeke et al[2] analysed the database of the EORTC Soft Tissue and Bone Sarcoma Group looking at 380 patients with advanced disease, treated with a range of new and standard chemotherapy agents in sequential clinical studies They define activity or inactivity in soft tissue sarcoma in terms of 3 and 6 month progression-free survival. A 3 and 6 month PFS of 39% and 14% respectively indicates an active agent, and 21% and 8% respectively indicates an inactive agent.

Four studies have now been carried out with trabectedin in patients with a wide range of sub types. In total 437 patients have been treated[3-6]. These studies have clearly demonstrated the effectiveness of trabectedin in this setting. The 3 and 6 month progression free survival (PFS) estimates of these studies are 38.8 – 53.4% and 24.1 – 37.2%. The best results have been in the randomised phase II study investigating two different schedules of administration, which has shown that the 125 patients treated with a 24 hour infusion of trabectedin had 3 and 6 month progression-free

survival rates of 51.5% and 35.5%[4], indicating significant activity. The work of van Glabbeke et al is important in the context of a rare tumour for which randomised phase III studies are very difficult to run.

There is no effective standard treatment following doxorubicin/ifosfamide. Trabectedin effectively addresses an unmet need.

(b) Please list any short-term and/or long-term benefits that patients expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example family, friends, employers)
- other issues not listed above.

As demonstrated above, when treated with trabectedin the percentage of patients achieving a long stable period of survival is significantly greater than those attaining this state following treatment with doxorubicin or ifosfamide.

Note that all the patients in the trabectedin trials were pre-treated, many heavily. It indicates that trabectedin is not subject to resistance acquired to earlier treatments. In addition the duration of response is generally better, with a median number of five treatments indicating that a significant proportion of patients attain a long duration of stable disease. The treatment is well-tolerated and the common chemotherapy side effects (alopecia, nausea, fatigue) are not found to the same extent.

This is an instance of a treatment addressing an unmet need in second-line, which appears to out-perform long-standing first-line therapy. While this will only be proven through further prospective trials in first-line, these will take many years to deliver results because of the extremely small patient numbers.

Many sarcoma patients have a relatively painfree progress through their disease (apart perhaps from surgical pain) until it becomes irredeemably advanced. Lung metastasis is the principle cause of death and many patients will be asymptomatic when diagnosed with metastases. The younger patient, or patient with a WHO performance status of 0 or 1, is not uncommon and the quality of life which can be achieved in this situation is high, albeit for only a few weeks or months.

Trabectedin will, for some patients, prolong and sustain that quality of life from months into years, addressing a real patient need. It is recognised that it is not a 'cure'.

What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition? (continued)

2. **Disadvantages**
Please list any problems with or concerns you have about the technology.
Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

Very few UK patients have received trabectedin and Sarcoma UK does not promote information about it widely. We do not want to raise expectations when the NHS does not automatically fund it. Clinicians will discuss trabectedin with patients when they consider it appropriate and we can support those patients with information as they seek to arrive at a decision about seeking treatment.

As with most chemotherapeutic agents there is a 'cost' in taking it. It is not free of side effects although these are of lesser intensity than from first-line therapies. It should be remembered that because good liver function is a pre-requisite for prescribing trabectedin the eligible group of patients is a sub-set of the whole metastatic cohort.

3. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

All patients with advanced metastatic cancer wish for a longer life and will consider any treatment which promises the possibility of attaining that goal. Making the final decision about accepting treatment is another matter, a deeply personal decision, and there are patients who decide that further treatment is inappropriate for them. This should not be taken as indicating that there are differences of opinion about the usefulness of a treatment.

4. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

The heterogeneous nature of soft tissue sarcoma means that there are some sub-groups who will benefit more, and some sub-groups who will not benefit at all, from treatment with trabectedin. Until individual patients with some of the rarer histologies are treated and cases reported this information will remain unknown.

Currently, as mentioned earlier, leiomyosarcoma, myxoid liposarcoma and synovial sarcoma respond well to treatment and we can predict that other sub-types will do so

as well, although definitively identifying them is just not possible at this stage in development. Our hope as patients is that those histologies which currently do not respond to the available therapies will respond to trabectedin. It would be grossly unfair for these patients if they were to be denied this chance just because of the rarity of their tumour, in the absence of any kind of clinical trial.

Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list any current standard practice (alternatives if any) used in the UK.

There are no standard treatments other than those already described.

There is growing evidence from clinical trials of the value of a gemcitabine and docetaxel combination in the treatment of leiomyosarcoma. Patients with Angiosarcoma have responded well to pegylated liposomal doxorubicin and to taxanes – off-label use. Aromatase inhibitors have shown benefit for patients with uterine sarcomas testing positive to oestrogen and progesterone hormone receptors.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement in the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc.)

For a metastatic cancer patient attaining stability is an achievement. Maintaining a stable condition and having the ability to return to a 'normal' physical life, even if for a relatively short period, is welcome. Trabectedin holds this promise.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

None.

Research evidence on patient or carer views of the technology

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine NHS care reflects that observed under clinical trial conditions.

There has been no use of this technology as routine NHS care. There have been no case reports or series published covering the few patients so far treated by the NHS (funded through 'exceptional circumstances'). Anecdotal information indicates that patients tolerate the treatment well, as anticipated.

Are there any adverse effects that were not apparent in the clinical trials but have come to light since, during routine NHS care?

None.

Are you aware of any research carried out on patient or carer views of the condition or existing treatments that is relevant to an appraisal of this technology? If yes, please provide references to the relevant studies.

None.

Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients and/or carers if this technology was made available on the NHS?

Approval will have two effects which, while having doubtful clinical value, should not be ignored. The first is that it signals hope, a key factor for patients as they embark on treatment which is palliative rather than curative. The second is that it offers space, the time to achieve, the opportunity to know a grandchild, the ability to help family 'come to terms' with what is happening. These factors may not have much clinical meaning but they are a real benefit to both the patient and their family.

What implications would it have for patients and/or carers if the technology was **not** made available to patients on the NHS?

Information from our German collaborators (Das Lebenshaus in Bad Nauheim) indicates that the take up of trabectedin in Germany far exceeds that in the UK. It is still too early to suggest what additional benefit it is bringing to their patients. Similarly we understand from our clinical contacts that take-up in France is significant.

The new emphasis which NICE is paying to 'seriousness' of a condition, in the context of the Secretary of State's announcement on 5th November 2008, will receive one of its first tests with this treatment. Should trabectedin be refused NHS funding through the NICE appraisal there would be a clear signal to patients with this rare cancer that "we do not matter". This is the first new treatment for advanced soft tissue sarcoma in over 20 years and it is the first sign that some intractable diseases may be treatable with medium and long-term benefit for some patients.

Are there groups of patients that have difficulties using the technology?

Not relevant.

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology.

Trabectedin is not for every patient. Of those treated with trabectedin a number will attain many months of additional life of a high quality, and some will have stable disease for a year or more. Those with the more common histological subtypes leiomyosarcoma and liposarcoma appear to have a higher chance of a long response than others based on data we have today but this is uncertain and it may be that rarer sarcomas will be shown to respond disproportionately better when reviewed retrospectively. As clinical trials of these groups are impossible this chance should not be lost by focussing any approval on the commoner sub-types.

Cost effectiveness of trabectedin is difficult to assess as there are no data. Professor Mike Richards' recent review of additional drugs recommended that the issues facing rare diseases must be addressed by the NHS's regulatory systems. His recommendations have been accepted by the Secretary of State. A decision on whether or not a drug should be used must not be limited by the rarity of the tumour. We are glad that NICE is taking steps through its current consultation to address this issue.

We also believe that there is an equity imperative here. Many millions have and are being been spent annually achieving better survival in more common cancers, a share of which is paid for through taxes paid by those with rarer cancers. Improving the survival rate in these rare soft tissue cancers will entail an annual spend of a fraction of this cost.

Soft tissue sarcoma is an ultra-orphan life-threatening condition. Trabectedin is an innovative treatment addressing an unmet need. It is now recognised that this situation requires special consideration when seeking approval for use, although full details of that process are not available to us when writing this submission. Clinical effectiveness is proven and the patient benefits resulting from this treatment are to be highly valued given the seriousness of the condition. In the absence of any other alternatives to a standard treatment at the advanced stage of this disease, it should receive your approval.

References:

1. Phase III trial of two investigational schedules of ifosfamide compared with standard-dose doxorubicin in advanced or metastatic soft tissue sarcoma: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. Lorigan P, Verweij J, Papai Z, Le Cesne A, Leahy MG, Radford JA, Van Glabbeke MM, Kirkpatrick A, Hogendoorn PC, Blay JY: .J Clin Oncol. 2007 Jul 20;25(21):3144-50.

2. M. Van Glabbeke, J Verweij, I. Judson, O.S. Neilson. Progression-free rate as the principal endpoint for phase II trials in soft tissue sarcoma. European Journal of Cancer, 2002, 38, 543-549.

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4. Yovine A, Riofrio M, Blay JY, Brain E, Alexandre J, Kahatt C, Taamma A, Jimeno J, Martin C, Salhi Y, Cvitkovic E, Misset JL. Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. J Clin Oncol. 2004 Mar 1;22(5):890-9.

5. Garcia-Carbonero R, Supko JG, Manola J, Seiden MV, Harmon D, Ryan DP, Quigley MT, Merriam P, Canniff J, Goss G, Matulonis U, Maki RG, Lopez T, Puchalski TA, Sancho MA, Gomez J, Guzman C, Jimeno J, Demetri GD. Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy. J Clin Oncol. 2004 Apr 15;22(8):1480-90.

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