Single technology appraisal (STA)
Trabectedin for the treatment of advanced metastatic soft tissue sarcoma

Appraisal consultation document

Joint comments from:

Patient group stakeholders
- Sarcoma UK
- Rarer Cancers Forum
- Macmillan Cancer Support

Professional stakeholders
- Institute of Cancer Research
- Royal College of Physicians
- British Sarcoma Group
- NCRI Sarcoma CSG
- Royal College of Pathologists
- Royal College of Radiologists
- Association of Cancer Physicians
- Joint Collegiate Council for Oncology

i) Do you consider that all of the relevant evidence has been taken into account?

It appears that the Appraisal Committee considered all the available published evidence on the efficacy of trabectedin in sarcomas. However, because the randomised phase II study that led to a licence being granted by the EMEA was a comparison between two different active schedules of administration there is concern that the benefit associated with the drug, also seen in single arm phase II trials, has not been adequately appreciated.

The ACD expresses concern that the prognosis of the patients in the randomised trial was somewhat better than in historical series. This may be partly explained by the large percentage of patients with liposarcoma in the study. These patients have a somewhat better median progression free and overall survival, often due to relatively indolent disease, when compared with leiomyosarcoma. However, it should also be noted that the median overall survival of patients in the inferior arm was only 11.8 months, in spite of an incidence of partial response and prolonged stable disease in this group, but the median overall survival of patients in the standard arm was 13.8 months. Although not statistically significant, this improvement, which is commensurate with the improvement in progression-free survival, is consistent with a treatment effect, rather than being entirely explained by patient selection.

ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are

appropriate?

Subject to the comments above we accept that the summary of clinical effectiveness is a reasonable interpretation of the evidence. These are firm data and although there has been no phase 3 randomised controlled trials, the evidence indicates significant survival benefit. The EMEA gave marketing authorisation on an exceptional basis, recognising the extreme rarity of the indication for which trabectedin is used.

The resource impact on the NHS has, however, been seriously overestimated. In the final concluding paragraph of the ACD, in which it is acknowledged that trabectedin is probably capable of extending the life of patients with metastatic soft tissue sarcoma by an average of 3 months, a figure of 500-600 patients is quoted. This makes the unreasonable assumption that all patients with metastatic sarcoma would be eligible for treatment. The licence for trabectedin is currently for patients who have progressive disease after treatment with an anthracycline and ifosfamide or are unsuitable for these therapies. The number of patients who remain fit enough for further chemotherapy after doxorubicin and ifosfamide is reduced progressively with each line of treatment.

Responses to an e-mail questionnaire of sarcoma centres in the UK indicates that for smaller centres with about 50-100 new sarcoma patients a year, the number being considered for trabectedin therapy is in the range of 1-3 per annum. At the Royal Marsden Hospital, which currently sees >650 new patients with soft tissue sarcoma a year, the mean number of applications for treatment with trabectedin over the last 2 years is less than 30 per annum. The incidence of soft tissue sarcoma in the UK including gastrointestinal stromal tumour (GIST) is in the region of 3000; if GIST (which is not treated with conventional chemotherapy) is excluded one is left with a figure in the region of 2400. The best estimate currently available for the number of patients suitable for trabectedin use is approximately 110 per annum, about half of whom currently receive it. This surely needs to be taken into account when considering the resource impact on the NHS.

We have grave concerns about the evidence used for the cost effectiveness analysis, or rather the academic exercise conducted in the absence of evidence. The absence of real quality of life data has led to an analysis which might be described as conducted to meet bureaucratic requirements and as such its use to possibly deny patients access to an effective treatment can be questioned.

We recognise that the cost of trabectedin is high and we support the current way of addressing that situation by the manufacturer proposing a risk-sharing agreement. The Committee has every right to express its concerns about cost in the only way open to it, effectively inviting the manufacturer to negotiate. However we question whether this is a proper way of conducting an Appraisal or a proper way of negotiating prices as it generates cost and effort for all stakeholders which would otherwise be unnecessary if a separate process were set up for evaluating ultra-orphan drugs.

In its own “Social Value Judgements” NICE indicates that *“NICE does not expect to receive referrals from the Secretary of State for Health to evaluate ‘ultra-orphan drugs’ (drugs used to treat very rare diseases or conditions). This is*

because the Department of Health currently has other mechanisms to assess the availability of ultra-orphan drugs in the NHS."

The Cancer Reform Strategy clearly states *"We therefore propose that as a default position all new cancer drugs and significant new licensed indications will be referred to NICE, providing that NICE agrees that there is a sufficient patient population and evidence base on which to carry out an appraisal and that there is not a more appropriate alternative mechanism for appraisal."*

The relevant population base is tiny (approximately 110 per annum as indicated above) and the ACD states that the evidence available was limited. This was reinforced to NICE during the scoping phase of the project and the patient groups also indicated their concern that an Appraisal was being conducted at all for such a rare indication. No proper answer has been given to those concerns, and an Appraisal has taken place regardless. The scoping exercise thus looks 'tokenistic', especially as the Appraisal Committee confirms the concerns that were expressed.

We accept that NICE remains under ministerial control and that it has no discretion on performing an Appraisal if instructed by ministers to do so. Even so, it would be in the interests of transparency for a clear statement to be made about how NICE consulted with the Departments of Health over the limited evidence and the decisions that were made that may affect the credibility of an Appraisal.

We welcome the Appraisal Committee's judgement that trabectedin meets the performance criteria for a life-extending end-of-life treatment. We feel it is unfortunate that the cost effectiveness analysis failed to deliver an ICER which the Committee felt it could accept, and regret that significant issues now arise because of the need to develop an analysis using a non-sarcoma health economics model.

iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

No. The negative impact of an unfavourable FAD by NICE is such that treatment with trabectedin in the UK would effectively cease outside the private sector. Anecdotal personal experience indicates that this would result in a significant detriment to quality of life and overall survival for sarcoma patients. The point that was made during the STA hearing, which is clear from the reports of the phase II trials, e.g. le Cesne et al, is that median progression-free and overall survival figures do not adequately represent the true benefit of this agent. The lack of cumulative specific organ toxicities, unlike ifosfamide or doxorubicin, combined with the ability of trabectedin to control metastatic disease for long periods of time in a significant minority of patients with sarcoma, translate into a very large improvement in disease control in these patients.

We are also concerned that the Appraisal Committee has de facto indicated that

there is a new limit for an ICER (cost per QALY), without offering any guidance to what that may be. This lack of transparency is not consistent with past experience where a reference guide has always existed. To establish a new limit for a rare tumour group may be an accident of timing but it appears like discrimination, given the tiny numbers of patients affected and the low overall impact on the NHS.

iv) Are there any equality related issues that need special consideration that are not covered in the ACD?

Yes, there is a growing need to identify rarity as an equality issue.

There are intrinsic inequalities associated with all extremely rare diseases and also specifically with soft tissue sarcoma that are not addressed in the ACD. We emphasised to the Appraisal the heterogeneity of this disease group but the ACD ignores the fact that within the overall cohort of patients with soft tissue sarcoma who might benefit from treatment with trabectedin there are subsets of patients who are more likely to benefit than others, e.g. those with uterine leiomyosarcoma and myxoid liposarcoma.

Such patients may experience a much higher than average response rate and more durable benefit. They will be unjustifiably discriminated against for having a rare disease by making a blanket decision that trabectedin is not to be used.

Ignoring such heterogeneity would not be considered in a more common tumour. Were all breast cancers included in the appraisal of trastumuzab? Were all leukaemias included in the appraisal of imatinib? What would have been the effect of such inclusion? Why should all sarcomas be included in the appraisal of trabectedin?

We acknowledge that currently there are regional variations in access to treatment but at least under the current arrangement bodies such as the London Cancer New Drugs Group, representing PCTs in London, are free to make the decision, as they have done, to recommend the use of trabectedin within specialist sarcoma centres. A negative decision by NICE is a denial of choice and has a disproportionate effect on small subgroups of sarcoma patients. The ultimate inequality of such a decision is that access to trabectedin would be based on the ability to pay for it, regardless of differential response.

Given the poor standards of care that many sarcoma patients still have to face (the NICE Sarcoma Improving Outcomes Guidance implementation is behind its original schedule) and the erratic standards for referral of sarcoma patients to specialist treatment centres in some regions of England, it is also an equality issue that there are patients, already suffering from delayed or inappropriate treatment, for whom an effective treatment may not become available.

Again we recognise the cost factor, and express our hope that can be resolved and that the Appraisal Committee will feel able to use the discretions given to it to correct this situation.