National Institute for Health and Clinical Excellence

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[redacted]

15 April 2009

Dear [redacted],

Trabectedin for the treatment of advanced metastatic soft tissue sarcoma

Following the clarification letter sent on 16 March for the appraisal of trabectedin for the treatment of soft tissue sarcoma, the Evidence Review Group have identified further issues relating to the clinical and cost effectiveness data presented in the submission about which they request clarification.

We request you to provide a written response to this letter to the Institute by **5pm** on **23 April**.

Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

If you present data that are not already referenced in the main body of your submission and that data are seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

If you have further queries on the technical issues raised in this letter, please contact Whitney Miller (Whitney.Miller@nice.org.uk). Procedural questions

should be addressed to Jeremy Powell (Jeremy.Powell@nice.org.uk) in the first instance.

Regards

Meindert Boysen
Associate Director - Appraisals
Encl. checklist for in confidence information

A: Clinical effectiveness

Ref	Clarification Point
A1	Please indicate if the phase II dacarbazine study is the Buesa 1991 reference.
A2	Please clarify whether the presented overall survival (OS) data were calculated from studies referenced 29-31, or were these data calculated from additional studies? The OS data presented does not appear to be available from references 29-31.
A3	Please indicate if the median OS of 5.9 months was calculated from the end of the ifosfamide therapy (i.e. patients were no longer receiving chemotherapy).
A4	Please provide an explanation as to why only 44 out of 50 patients in the dacarbazine column of Table 19 have gender and WHO severity scores.

B: Cost effectiveness

Ref	Clarification Point
B1	Please provide the rationale behind the following assumption: All patients who receive trabectedin treatment enter the model in the progression-free state, whereas those receiving best supportive care (BSC) enter the model in the progressed disease state. As the utility of being in the progressed disease state is lower than being in progression-free disease, this mismatch in the entry states of the patient appears to bias the model in favour of trabectedin. Further to this, please indicate the likely affect this bias has on the cost per QALY ratio.
B2	Please repeat the analyses using the progression-free survival curve instead of the time-to-progression survival curve.
B3	Please account for all significant variables (including gender) in the adjustment of the survival curves in the revised model, in addition to those

Ref	Clarification Point
	already addressed (i.e., WHO performance score and histopathology (L sarcoma)). Additionally, please explore the effects on the cost per QALY ratio of adjusting the trabectedin survival curve, as opposed to the BSC survival curve.
B4	Please explain the rationale behind the decision to use a monthly time cycle, as opposed to one of 3 weeks. Further to this, please provide justification for mismatch between the costs per cycle (which relate to a 3-week cycle) and the utilities (which refer to one month).
B5	Please resolve the following discrepancy: the model now contains a worksheet ('Costs') that estimates the proportion of patients receiving set number of cycles. The proportion reported appears to be consistent with the raw data provided to the ERG. In this data, 130 out of 136 patients (95.6%) received at least one treatment cycle, however the model reports this value to be 94.1%.
B6	Please explain why the methodology for calculating the cost of treatment differs between the deterministic and probabilistic analyses. The deterministic analyses use a mean number of vials used. Despite these values having an associated standard error, sampling from these is not undertaken. Please explore the impact on the ICER of sampling the number of vials used.
B7	Please present a re-analysis in which management costs, such as palliative care and hospice care for patients in the progressive state, are included.
B8	The submission states that the cost for hospitalisation due to nausea and vomiting (from PA29Z) was selected to represent the costs for adverse events; however, this cost relates to abdominal pain, rather than vomiting as reported. Please also confirm that the average length of stay for hospitalised patients was similar to that of the average patient hospitalised for whichever proxy measure is deemed most appropriate.
B9	Please confirm that the 47% of patients (Table 9) who experienced

Ref	Clarification Point
	neutropenia were calculated from 136 patients. This would be consistent with the assumed beta distribution, but is not clearly marked in the submission.
B10	Please use the method of calculating the number of patients in a health state as the average between time $_{t}$ and time $_{t+1}$ to perform the half-cycle correction.
B11	In the revised model, the BSC survival curve has been adjusted for WHO severity and histology relative to the proportions in the base case analysis. This survival curve is then used for the pooled analysis, despite this being a different mix of severity and histology. As a result, the BSC curve is not compatible with the mix of patients in the pooled analysis. Please adjust the trabectedin and BSC curves to be more consistent with one another. If this is not possible, please comment on the likely effect this incompatibility has on the cost per QALY ratio.
B12	For the pooled analysis, the same proportion of patients treated at each cycle was assumed to be as observed in STS-201. Please use the proportion of patients receiving treatment in the pooled analysis. If this is not possible, please discuss the likely effect this assumption has on the ICER.
B13	Please include probabilistic analyses for the pooled analysis. This will require the variance-covariance matrix of PFS and OS curve.