

15th October 2009

NHS
**National Institute for
Health and Clinical Excellence**

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Dear [REDACTED] and [REDACTED]

Re: Single Technology Appraisal – Gefitinib for the first-line treatment of locally advanced or metastatic non-small cell lung cancer

The Evidence Review Group Liverpool Reviews and Implementation Group (LRiG) and the technical team at NICE have now had an opportunity to take a look at submission received on the 24th September by AstraZeneca. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports, and you may want to respond to the points raised and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by **17:00, 29th October 2009**. 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.

Please underline all confidential information, and separately highlight information that is submitted under '**commercial in confidence**' in red, and all information submitted under '**academic in confidence**' in yellow.

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

If you have any further queries on the technical issues raised in this letter then please contact Fay McCracken – Technical Lead (Fay.Mccracken@nice.org.uk) Any procedural questions should be addressed to Jeremy Powell – Project Manager (Jeremy.Powell@nice.org.uk) in the first instance.

Yours sincerely

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Section 4.5 – Issues relating to current UK clinical practice

- A1. **Priority question:** Please provide further details of actual EGFR-TK mutation testing currently taking place within the UK (e.g. number of tests conducted in each centre, type of test used, number/proportion of EGFR mutation positive, mutation negative, and mutation unknown patients etc).
- A2. **Priority question:** Please clarify whether the ARMS test (as used in the IPASS study) is the same test as is proposed by AstraZeneca for use in UK clinical practice.

Section 6.3.1 – Summary of methodology of relevant RCTs

- A3. Please clarify how patient compliance with gefitinib therapy was monitored during the IPASS trial.
- A4. Please clarify the rate of patient compliance with gefitinib therapy during the IPASS trial.
- A5. Please clarify whether patients received monthly packs/bottles of gefitinib tablets.
- A6. Please clarify the proportion of patients in the IPASS trial who received second-line treatment by treatment arm. The MS states that patients whose tumour progressed after first line treatment were offered the opportunity to switch to other treatments.
- A7. Please specify the post-progression chemotherapies given by treatment arm in the IPASS trial and the proportions of patients receiving each of these post-progression chemotherapies.

Section 6.3.3 – Patient numbers

- A8. The MS states that forty patients were non-compliant with the trial protocol in the IPASS trial and others “did not significantly deviate at entry” (pg 20 of the MS). Please provide the number of patients in each arm of the IPASS trial broken down by type of protocol deviation.
- A9. Please provide the number of patients who deviated from the IPASS trial protocol by treatment arm and were included in the analysis data set.
- A10. Please provide a full list of protocol deviations for the IPASS trial.
- A11. Please clarify the assumptions undertaken to incorporate data points from patients who deviated from the IPASS trial protocol.

Section 6.4 – Results of relevant comparative RCTs

- A12. Please clarify at what point during the IPASS trial patients were tested for mutation status.
- A13. Please clarify whether patients were tested for mutation status of their tumours more than once during the IPASS trial. If yes, please provide details on whether the mutation status of tumours changed over time.

- A14. Please clarify the number of centres in which patients were invited to provide samples for testing.
- A15. Please clarify the number of patients in each centre who were invited to provide samples.
- A16. Please clarify the number of patients in each centre who agreed to provide samples.
- A17. Please clarify the number of patients who were EGFR M+, M- and M unknown in each of the centres.
- A18. Please provide additional information on why so few IPASS trial patients provided samples.
- A19. Please clarify why so few samples were evaluable for IPASS trial patients.
- A20. Please provide a per protocol analysis for the overall population in the IPASS trial. In the analysis of a non-inferiority trial, it is usual to perform an intention to treat (ITT) analysis and a per protocol (PP) analysis.
- A21. Please provide a per protocol analysis for EGFR M+ patients in the IPASS trial.

Section 6.6 - Indirect/mixed treatment comparisons

- A22. **Priority question:** Please provide a network diagram for each outcome of interest (overall survival, progression free survival and objective response rate). The network of randomised controlled trials comparing doublet chemotherapies in the first-line treatment of advanced NSCLC (MS, Figure 16) is not sufficiently informative since it is not presented by the outcome of interest.
- A23. **Priority question:** Please provide all data points used in the mixed treatment comparison (MTC) analyses including WinBUGS codes used for each analysis. The MS does not explicitly present the data points used in each analysis (direct evidence) and it is not clear what assumptions were made on the prior distributions.
- A24. **Priority question:** Please provide the rationale for selecting the following adverse events to be included in the MTC: anaemia, diarrhoea, fatigue, febrile neutropenia, nausea and vomiting, and neutropenia (pg 48 of the MS) and not including adverse events such as rash/acne, neurotoxicity, haematologic toxicity, hair loss etc.

Section 7.2.3 – Comparator technology

- A25. Please provide clarification for the exclusion of docetaxel as a comparator. The scope for the appraisal specified 'platinum based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or cinorelbine); or pemetrexed in combination with platinum based chemotherapy (carboplatin or cisplatin); or best supportive care'.

Section 7.2.9.7 – Additional infrastructure for the technology

- A26. **Priority question:** Please clarify the description of EGFR-TK mutation testing by providing more detailed information on the infrastructure required to set up a universal and standardised method of testing in England and Wales.
- A27. **Priority question:** Please outline the anticipated length of time it would take to set up a universal and standardised method of testing for EGFR-TK mutations in England and Wales.
- A28. **Priority question:** Please provide details of the different types of EGFR-TK mutation tests currently available.
- A29. **Priority question:** Please clarify what the associated accuracy rates of the different EGFR-TK mutation tests are.
- A30. **Priority question:** Please clarify whether any of the EGFR-TK mutation tests can use cytology rather than histology specimens.
- A31. **Priority question:** Please provide details on how AstraZeneca will ensure that the EGFR test proposed for use in UK clinical practice is robust. In the Summary of Product Characteristics leaflet for gefitinib, under special warnings and precautions, it states: "When assessing the EGFR-TK mutation status of a patient, it is important that a well validated and robust methodology is chosen to avoid false negative or false positive determinations".

Appendix 6 - Baseline characteristics for EGFR M+ patients

- A32. Please provide the same description of baseline characteristics for the EGFR M+ population in the IPASS trial as is presented for the overall population i.e. ethnic group, tumour histology, disease stage at entry, time from diagnosis to randomisation, stage classification at diagnosis.

Section B: Clarification on cost-effectiveness data

Section 7.2.6 - Framework

- B1. Please provide the frequency distribution of number of cycles of chemotherapy received by patients for each treatment arm in the IPASS trial.
- B2. Please clarify how the disutility decrement for certain adverse events (e.g. hair loss, fatigue, anaemia, rash) may impact on HRQoL throughout the course of treatment. The assumption outlined in Table 22 (pg 85 of the MS) states that the disutility associated with the adverse events was applied only for a single cycle (21 days).

Economic model - Individual patient data (IPD)

- B3. **Priority question:** Please provide access to anonymised individual patient data for the IPASS trial in order to validate key aspects of the submitted model including the modelling of overall survival and progression-free survival, the choice of parameter values, and structural assumptions.
- B4. **Priority question:** Please also provide individual patient data for the following data fields for each EGFR mutation status positive patient in the IPASS trial:
- unique anonymised patient identifier
 - gender (male / female)
 - smoking status (never / ever)
 - histology (adeno / other)
 - disease stage at entry (IIIB / IV)
 - trial arm (gefitinib or paclitaxel)
 - performance status at entry (0 / 1 / 2)
 - responder to first-line therapy (yes / no)
 - days from randomisation to disease progression/withdrawal or to censoring re-progression/withdrawal
 - censoring for progression/withdrawal (yes / no)
 - days from randomisation to death or to censoring re-death
 - censoring for death (yes / no)
 - cycles of trial medication administered
 - cycles of second line chemotherapy administered
 - type of second line chemotherapy administered (agent(s) or "none")
 - days from randomisation to start of second line chemotherapy

Economic model - MTC results

- B5. **Priority question:** The submitted model (row 54 of 'Parameters' worksheet) that the MTC included evidence relating to pemetrexed/cisplatin as a comparator, yielding a value for the hazard ratio for overall survival of 0.745. Please provide the corresponding hazard ratios for pemetrexed/cisplatin for progression free survival and adverse events.

Section C: Textual clarifications and additional points

References

- C1. Some referenced and unreferenced data in the submission resides in documents not in the public domain or only available in abstract form. For purposes of clarification and verification please provide the following:
- **Priority:** An electronic copy of the full Clinical Study Report for the IPASS trial including the trial protocol (original and amended) and all figures, tables and other results pertaining to the EGFR M+ population.
 - **Priority:** The original source of the data which describes the North East Japan Gefitinib Study Group trial (Reference 20) (Kobayashi 2009). Please also clarify why data from the abstract reported in Tables 4 and 5 (pg 40) and Figure 14 (pg 44) of the MS do not match the data reported in the referenced abstract (e.g. there are fewer patients described in the abstract).
- C2. **Priority question:** Please provide more details on the First-SIGNAL trial (reference 21).
- C3. Please provide a full set of electronic references.