Dear [redacted],

Thank you for the opportunity to comment on the MTA Report: Erlotinib and gefitinib for treating non-small cell lung cancer that has progressed following prior chemotherapy (ID620). Please find below our comments which are focused on three topics:

1. **Clinical Relevance of the Assessment Group Conclusions for the EGFR M- subgroup**
2. **Suggested Research requirement for RCT evidence in second line NSCLC treatment of EGFR M+ patients**
3. **The Overall Survival Benefit of Gefitinib and EGFR-TKIs**

If you have any further questions please let me know.

Best regards,

[redacted]
AstraZeneca UK Ltd

Summary

- Gefitinib is licensed in the UK for the treatment of EGFR M+ only patient population, therefore the analyses and conclusions for EGFR M- patients presented by the Assessment Group are outside both license and established UK clinical practice.
- Gefitinib is clinically appropriate for the treatment of Caucasian EGFR M+ patients (with a lower population level prevalence of the EGFR mutation than observed in Asia). This is in line with clinical guidelines, clinical opinion, evidence base and other HTA body recommendations.
- AZ believes clinical equipoise for an RCT supporting the use of post-progression treatments following prior chemotherapy for patients with activating EGFR mutations no longer exists unless rescue therapy with an EGFR-TKI in the chemotherapy arm was allowed, which would defy the purpose of such a study.
- The AG have utilised the sub-group data of the BR.21 trial for the clinically irrelevant cost effectiveness analyses for the EGFR M- population. However the AG have not utilised the post-hoc analyses/ sub-group data that AZ submitted for the clinically appropriate EGFR M+ patient population.
- The evidence outlined in our submission indicates that the inclusion of gefitinib in the clinical treatment pathway is likely to be associated with an increase life-expectancy compared to patients who do not receive an EGFR-TKI.
- Post-hoc analyses of the ISEL, INTEREST and IPASS study show a consistent trend of increased overall survival in aNSCLC EGFR M+ patients when gefitinib was included in the treatment sequence versus the patients in the control arm who had not received a EGFR-TKI in the post randomisation treatment sequence.

1. Clinical Relevance of the Assessment Group Conclusions for the EGFR M- subgroup

- Gefitinib is licensed in the UK for the treatment of EGFR M+ only patient population, therefore the analyses and conclusions for EGFR M- patients presented by the Assessment Group are outside both license and established UK clinical practice.
- Gefitinib is clinically appropriate for the treatment of Caucasian EGFR M+ patients (with a lower population level prevalence of the EGFR mutation than observed in Asia). This is in line with clinical guidelines, clinical opinion, evidence base and other HTA body recommendations.

The Assessment Group (AG) concludes in the MTA report that "The largest group of patients to whom the results of this appraisal apply is the EGFR M- patient population." AstraZeneca (AZ) does not agree with the clinical relevance of this conclusion in the context of EGFR-TKI treatment of NSCLC that has progressed following prior chemotherapy.

The scope of this MTA is to appraise the clinical and cost effectiveness of erlotinib and gefitinib within their licensed indications for the treatment of NSCLC following prior chemotherapy. In line with the licensed indication of gefitinib and the scope of the MTA, the objective of the AstraZeneca submission was to demonstrate the clinical benefit of gefitinib therapy in EGFR M+ aNSCLC following prior chemotherapy. Therefore the analyses and conclusions for EGFR M- or EGFR-unknown patients presented by the Assessment Group are outside both gefitinib license and established UK practice.

It is well established that EGFR-TKIs are clinically appropriate for the treatment of NSCLC patients that are EGFR M+. Sixty percent to 80% of tumours from East Asian never-smokers with lung adenocarcinoma harbour EGFR mutations, whereas only 30% to 50% of tumours from North American/European counterparts have such mutations (1). This is validated by the European Society for Medical Oncology (ESMO) Clinical Guidelines for Metastatic NSCLC that states "Any patient with a tumour bearing an activating (sensitizing) EGFR mutation should receive an EGFR-TKI as second-line therapy, if not received previously." (2)

Current NICE recommendations correctly position EGFR-TKI treatment for the first-line treatment of locally advanced or metastatic NSCLC EGFR M+ population only. Patients should receive their most appropriate treatment first as the majority of patients will *only* receive first line treatment due to rapid progression and associated deterioration in health often seen once first line therapy has failed (3, 4). However, due to delays in receiving and interpreting EFGR mutation test results together with the national requirement to initiate a NSCLC patient onto first definitive treatment within 62 days from urgent GP referral, a small percentage of aNSCLC EGFR M+ patients receive chemotherapy as first line treatment in the UK, confirming that there is a small UK patient pool who would meet the eligibility criteria for gefitinib treatment as stated in this second line appraisal. NICE Lung Cancer Quality Standard 12 states that NSCLC patients should be offered second-line systemic therapy that is tailored to the pathological subtype of the tumour and individual predictive factors Second line EGFR-TKI treatment for the EGFR M+ patient population is further validated by recent Health technology appraisal decisions for erlotinib in Australia and New Zealand (5).

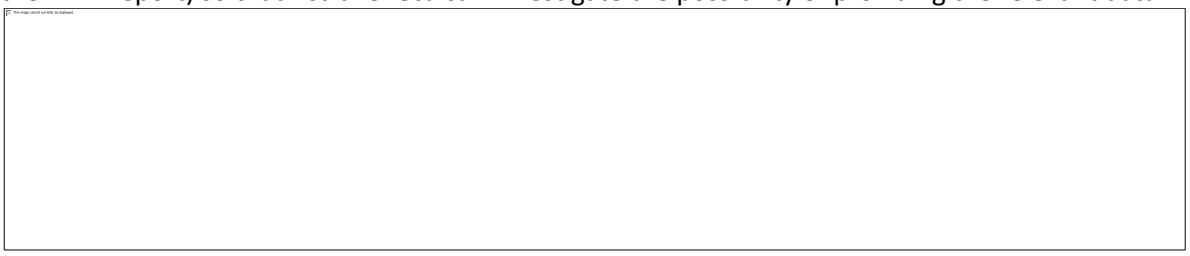
2. Suggested Research requirement for RCT evidence in second line NSCLC treatment of EGFR M+ patients

- AZ believes clinical equipoise for an RCT supporting the use of post-progression treatments following prior chemotherapy for patients with activating EGFR mutations no longer exists unless rescue therapy with an EGFR-TKI in the chemotherapy arm was allowed, which would defy the purpose of such a study.
- The AG have utilised the sub-group data of the BR.21 trial for the clinically irrelevant cost effectiveness analyses for the EGFR M- patient population. However the AG have not utilised the post-hoc analyses/ sub-group data that AZ submitted for the clinically appropriate EGFR M+ patient population.

The AG states "The results of the manufacturer's post-hoc analysis of clinical data from the control arm of the IPASS trial are relevant to the decision problem. However, these findings, and others, require careful and detailed validation in a robustly designed RCT before they can be used to inform decision-making in this complex clinical area." AZ believes an RCT supporting the use of post-progression treatments following prior chemotherapy for patients with activating EGFR mutations would be unethical unless rescue therapy with an EGFR-TKI in the chemotherapy arm was allowed which would defy the purpose of such a study. In addition, traditional 'high quality' RCTs in oncology will always be hampered by patient "cross-over" to comparator treatment; for it is unethical to deny patients access to established treatments of recognised clinical benefit or risk randomisation to a less effective control in this clinical setting.

The AG group acknowledge that the gefitinib trials conducted by AZ were of acceptable methodological quality (see MTA report, page 30) but based their review of the clinical effectiveness evidence on whether or not there was an RCT conducted solely in the specific EGFR M+ patient population. The discovery of the EGFR-TKIs and the identification of the role of *EGFR* genetic mutations in the early 2000s heralded a paradigm shift for aNSCLC patients harbouring *EGFR* mutations sensitive to EGFR-TKIs. Given the clear ethical imperative to pursue only genuine scientific questions, the need to avoid randomising patients to less effective treatments in this clinical setting, and the further ethical issues preventing cross-over to an active alternative following treatment failure, clinical equipoise for an RCT to demonstrate this benefit no longer exists. The rationale for this is in agreement with conclusions made by the European Genomics Project (6) who state "We note that the prospective part of our study was not a randomized clinical trial but an observational diagnostic intervention study. Unfortunately, obtaining overall survival data in a randomized fashion requires prohibiting patients from crossing to the other treatment, an irresponsible measure in this setting."

Refining between-patient variability in treatment response using molecular/genetic markers will inevitably lead to smaller patient populations, subgroups within trials and post-hoc analyses. This is emphasised by the decision of the AG to utilise the sub-group data of the BR.21 trial for the clinically irrelevant EGFR M- cost effectiveness analyses. However the AG have not utilised the post-hoc analyses/ sub-group data that AZ submitted for the clinically appropriate EGFR M+ patient population. Therefore, can the AG provide clarity on the highlighted wording below (see page 107 of the MTA report) so that AstraZeneca can investigate the possibility of providing the relevant data:



3. The Overall Survival Benefit of Gefitinib and EGFR-TKIs

- The evidence outlined in our submission indicates that the inclusion of gefitinib in the clinical treatment pathway is likely to be associated with an increase life-expectancy compared to patients who do not receive an EGFR-TKI.
- Post-hoc analyses of the ISEL, INTEREST and IPASS study show a consistent trend of increased overall survival in aNSCLC EGFR M+ patients when gefitinib was included in the treatment sequence versus the patients in the control arm who had not received a EGFR-TKI in the post randomisation treatment sequence.

Since AZ believes clinical equipoise for an RCT supporting the use of post-progression treatments following prior chemotherapy for patients with activating EGFR mutations no longer exists unless rescue therapy with an EGFR-TKI in the chemotherapy arm was allowed (see Section 2), AZ submitted other appropriate sources of evidence to demonstrate the overall survival benefit of gefitinib and EGFR-TKIs (see Section 6 of the AstraZeneca submission). Over the past 30 years the life expectancy for aNSCLC cancer patients has improved from 6 to 8 months observed with chemotherapy to 19.3 to 35.5 months for EGFR M+ aNSCLC patients treated with an EGFR-TKI (7).

Post-hoc analyses of the ISEL, INTEREST and IPASS study detailed in the AZ submission show a consistent trend of increased overall survival in aNSCLC EGFR M+ patients when gefitinib was included in the treatment sequence versus the patients in the control arm who had not received a EGFR-TKI in the post randomisation treatment sequence.

RCTs of first line doublet therapy in non-selected Asian aNSCLC patients reporting the incidence of post-progression use of a EGFR-TKI following initial randomised doublet chemotherapy suggest that median overall survival without subsequent EGFR-TKI exposure would be approximately 11.2 months; in contrast the median overall survival with 100% of patients receiving a subsequent EGFR-TKI would be approximately 20.7 months (see AZ submission, page 38). Real world observational studies consistently indicate an increased life expectancy attributable to gefitinib/ EGFR-TKI following introduction of EGFR-TKI in the clinical pathway for aNSCLC patients. (,8, 9, 10).

The evidence outlined in this section (and in our submission) indicates that the inclusion of gefitinib in the clinical treatment pathway is associated with an increase life-expectancy compared to patients who do not receive an EGFR-TKI. This conclusion is reinforced by a recently published paper by Ohashi et al who conducted a similar approach to the analyses presented and reached a similar conclusion (1).

References

1. Ohashi K, Maruvka YE, Michor F, Pao W. Epidermal growth factor receptor tyrosine kinase inhibitor-resistant disease. J.Clin.Oncol. 2013 Mar 10;31(8):1070-1080.
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3. Hensing TA, Schell MJ, Lee JH, Socinski MA. Factors associated with the likelihood of receiving second line therapy for advanced non-small cell lung cancer. Lung Cancer 2005 Feb;47(2):253-259.
4. Younes RN, Pereira JR, Fares AL, Gross JL. Chemotherapy beyond first-line in stage IV metastatic non-small cell lung cancer. Rev.Assoc.Med.Bras. 2011 Nov-Dec;57(6):686-691.
5. Australian Pharmaceutical Benefits Advisory Committee (PBAC) Meetings Outcomes – July 2013. http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2013-07/deferrals
6. The Clinical Lung Cancer Genome Project (CLCGP) and Network Genomic Medicine (NGM). A Genomics-Based Classification of Human Lung Tumors. Sci Transl Med 2013; 5(209) 209ra153
7. NSCLC Meta-Analyses Collaborative Group. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J.Clin.Oncol. 2008 Oct 1;26(28):4617-4625
8. Takano T, Fukui T, Ohe Y, Tsuta K, Yamamoto S, Nokihara H, et al. EGFR mutations predict survival benefit from gefitinib in patients with advanced lung adenocarcinoma: a historical comparison of patients treated before and after gefitinib approval in Japan. J.Clin.Oncol. 2008 Dec 1;26(34):5589-5595.
9. Kim ST, Uhm JE, Lee J, Sun JM, Sohn I, Kim SW, et al. Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small cell lung cancer who failed previous chemotherapy. Lung Cancer 2012 Jan;75(1):82-88.
10. Shi et al. Comparison of Survival in Patients with Advanced Lung Adenocarcenoma treated before and after Gefitinib approval in China. Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO 2013;Abs 1331.

Abbreviations

aNSCLC	Advanced Non Small Cell Lung Cancer
EGFR	Epidermal Growth Factor Receptor
EGFR M-	Mutation negative
EGFR M+	Mutation Positive
EGFR-TKI	Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor
INTEREST	IRESSA NSCLC Trial Evaluating REsponse and Survival versus Taxotere
IPASS	IRESSA Pan-Asia Study
IRESSA	Gefitinib
ISEL	IRESSA Survival Evaluation in Lung Cancer
MTA	Multiple Technology Appraisal
NSCLC	Non Small Cell Lung Cancer
QoL	Quality of Life
RCT	Randomised Controlled Trial