AstraZeneca MTA Submission (ID620) Executive Summary

The discovery of the tyrosine kinase inhibitors (EGFR-TKIs) and the identification of the role of epidermal growth factor receptor (*EGFR*) genetic mutations in the early 2000s heralded a paradigm shift for advanced non-small cell lung cancer (aNSCLC) patients harbouring *EGFR* mutations sensitive to EGFR-TKIs. 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 (1). The EGFR-TKI gefitinib (IRESSA) was the first approved EGFR-targeted therapy for aNSCLC. Gefitinib is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC with activating mutations of EGFR-TK irrespective of line of therapy (2). 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 non-small-cell lung cancer following prior chemotherapy. In line with the licensed indication and the scope of the MTA, the objective of this submission is to demonstrate the clinical benefit of gefitinib therapy in EGFR mutation positive (M+) aNSCLC following prior chemotherapy. We have not included cost-effectiveness analyses in this submission as previously notified to NICE.

Currently gefitinib and erlotinib are recommended by NICE and international clinical guidelines (3) for the first line treatment of EGFR-M+ aNSCLC patients. Provided NICE guidance is adhered to, EGFR M+ aNSCLC patients in the UK should not be receiving traditional platinum-based chemotherapy first line. However due to delays in receiving and interpreting EGFR Mutation tests, there is conceivably a small EGFR M+ aNSCLC patient pool in the UK who would meet the eligibility criteria for gefitinib or erlotinib treatment outlined in this second line appraisal.

Gefitinib has demonstrated benefit in the pre-treated chemotherapy population in the Iressa NSCLC Trial Evaluating REsponse and Survival versus Taxotere (INTEREST) (4) and IRESSA Survival Evaluation in Lung Cancer (ISEL) trials (5). Subgroup analyses of these trials suggested that EGFR mutation was linked with an increased response of gefitinib. Subsequently, the IRESSA Pan-Asia Study (IPASS) trial demonstrated that EGFR mutation was the strongest predictor of improved progression free survival with gefitinib as first-line aNSCLC therapy. Real world observational studies consistently indicate an increased life expectancy attributable to gefitinib/TKI following introduction of EGFR-TKI in the clinical pathway for aNSCLC patients. Based on a systematic review, a meta-analysis of the relevant randomised controlled studies (RCTs) was also investigated for this second line appraisal. All options for meta-analyses (direct, indirect, and MTC) have been explored; however, all options were limited by heterogeneity in important clinical factors and ultimately such analyses were deemed more likely to increase rather reduce uncertainty for this submission.

Quality of Life (QoL) is a key feature in determining clinical value alongside efficacy and safety of aNSCLC treatment particularly in patients who have already experienced first line treatment. Gefitinib showed statistically significant, sustained and clinically relevant improvement in QoL rates compared with docetaxel (4,6,7). EGFR-TKIs are also well recognised as a more tolerable alternative to docetaxel (7) and an improved tolerability rate for gefitinib versus erlotinib for EGFR M+ patients has been reported in observational studies and may be attributable to mechanistic differences, higher selectivity and fewer 'off-target' effects that allow the recommended dose to be below the maximum tolerated dose.

Available evidence in this submission suggests that gefitinib is an effective second line treatment option for EGFR M+ aNSCLC patients that have progressed following prior chemotherapy; with QoL benefits and an acceptable tolerability profile.

References:

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