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AstraZeneca

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Dear Nicole,

Thank you for the opportunity to review the draft MTA ACD for the ongoing appraisal of erlotinib and gefitinib for NSCLC that has progressed following prior chemotherapy (Review of TA162 and TA175) [ID620]. AstraZeneca agree that EGFR M+ NSCLC patients already treated with non-targeted chemotherapy should have subsequent treatments guided by their unique tumour marker status in order to secure an optimal treatment sequence and would like to raise the following points regarding the proposed ACD.

Clarification around the scope of the recommendation for EGFR M+ patients

AstraZeneca request the committee provide greater clarification for Section 1.2 in order to confirm that these recommendations apply to both EGFR M+ patient populations characterised in Section 4.3.4, 4.3.18, and 4.3.7 of the ACD;

- Patients who have received non-targeted chemotherapy as a consequence of a delayed diagnosis *but who have not yet experienced disease progression and who can be considered as an extension to the first-line setting* (as described in 4.3.4 and 4.3.18) and who fall under the remit of TA 192

- Patients who have received non-targeted chemotherapy as a consequence of a delayed diagnosis *and who have mutation status confirmed at the time of disease progression and can be characterised as second line* (as described in 4.3.7) and who fall under the remit of this appraisal

Clarification regarding the IPASS post-hoc analysis

As described in section 4.3.7, "The Committee agreed that these retrospective analyses [of IPASS data] were based on small numbers, were subject to imbalances in baseline characteristics (and so were highly selective) and lacked statistical power". It should be noted that the AG's examination of baseline characteristics and PFS did not show any evidence of potential selection bias with the exception of racial origin where Chinese and Japanese patients were more likely to receive EGFR-TKI treatment than other patients (p.93 AG Report)

In Section 4.1.8 "The AG stated that median OS results for patients treated with subsequent EGFR-TKI after prior chemo reported in AZ post hoc analysis of IPASS were longer than estimates

previously reported in trials...therefore this finding needs to be validated by evidence from an independent RCT because it would represent an important therapeutic advance". Although data remains limited, the median overall survival results for non-targeted chemotherapy without subsequent cross-over to a TKI and for chemotherapy followed by a TKI are consistent with available existing evidence (Goffin et al 2010; AZ submission p. 39; Inoue et al 2013; Zhou et al 2012; Gridelli et al 2012; Rosell et al 2009).

Assessment report

On page 93 of the AG report, the AG attribute the subsequent gain in overall survival presented in this analysis to gefitinib; however, as correctly described on page 41, this gain should be attributed to TKIs as a minority of patients in this group went on to receive erlotinib.

References

Goffin J, et al. First-line systemic chemotherapy in the treatment of advanced non-small cell lung cancer: a systematic review. J.Thorac.Oncol. 2010 Feb;5(2):260-274

Gridelli C, et al. First-Line Erlotinib Followed by Second-Line Cisplatin-Gemcitabine Chemotherapy in Advanced Non–Small-Cell Lung Cancer: The TORCH Randomized Trial. J Clin Oncol 2012 30:3002-3011

Inoue A, et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Ann Oncol. 2013 Jan;24(1):54-9

Rosell R, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009; 361:958-67

Zhou C, et al. Overall survival (OS) results from OPTIMAL (CTONG0802), a phase III trial of erlotinib (E) versus carboplatin plus gemcitabine (GC) as first-line treatment for Chinese patients with EGFR mutation-positive advanced non-small cell lung cancer (NSCLC). Poster 7520, ASCO, Chicago, Illinois, USA, June 2012.