1)Price comparisons of the IVDs listed.

RESPONSE: The costs for the different commercially available PCR- based tests for EGFR range around the same order of magnitude. For Therascreen and for Cobas, the cost for one test ranges between 100 to 1000 US dollar worldwide, per patient. In particular, in one exploratory survey we did, the cost was so reported: 700 USD in Venezuela, 150 USD in Pakistan, 400 USD in Thailand and Brazil. In Hungary, the preferred test is based on Sanger's sequencing, costing 120 USD per exon, namely 300-400 USD per patient. All of them represent the cost reported by laboratories on the pricing list, and what is requested commonly to patients to pay or governments to reimburse (so it includes the equipment, capital investments, facility- level costs and workforce). However, the cost of a single kit for a single patients for EGFR PCR, as an average cost in low- middle income countries, is estimated around 4,5 USD per patient.

2)Quality control requirements for running this IVD.

RESPONSE: EGFR Test Mutant Control and negative control are included in each run of up to 30 samples, provided by the seller. According to ASCO/CAP guidelines to assure quality testing and appropriate diagnostic performance, laboratories should use EGFR test methods that are able to detect mutations in specimens with at least 20 % cancer cell content, with an EGFR mutation testing able to detect all individual mutations that have been reported with a frequency of at least 1% of EGFR-mutated lung adenocarcinomas.

3)Health economic justification for introducing this IVD in LMICs.

RESPONSE: Evidence based on modelling exercises suggest that the treatment of advanced EGFR mutated NSCLC patients may result in an improvement of health economic outcomes, for the improvement of the safety profile and of the control of the disease, against chemotherapy. A systematic review and cost-effectiveness analysis on the long-term consequences in terms of costs and quality-adjusted life years or QALYs estimated using a Markov model showed a more sustainable approach with PCR- based assays than the gold standard Sanger's sequencing, as reported in the original submission. When compared to double chemotherapy frontline, tyrosine kinase inhibitors were more cost-effective than cisplatin-pemetrexed; this model considered the cost of the medicines, the healthcare utilization and intensity and included the costs related to the management of toxicities (DOI: https://doi.org/10.1016/j.jval.2015.04.008). One systematic review on the cost- effectiveness of EGFR TKI against doublet chemotherapy in China (n=7 studies), reported that geftinib dominates the chemotherapy with an ICER of ¥ 13499.7/QALY (DOI: https://doi.org/10.1016/j.jval.2015.09.1183).

4)Any comment on testing in TKI resistant cases?

RESPONSE: The submission specified that the use of PCR- based techniques to assess the mutational status of EGFR in NSCLC is intended exclusively frontline, for the use of either erlotinib, gefitinib or afatinib – consistently with the indications and use of EGFR TKI in the WHO EML. The identification of possible mechanisms of resistance to EGFR TKI is useful for patients receiving and progressing to one of the three TKIs, to detect the resistance mutation T790M

(a half of the cases), targetable with osimertinib, a new generation TKI. However, as osimertinib is not listed as an essential medicine on the EML, the use of this IVD is not intended here for resistant cases. Moreover, the identification of non- T790M EGFR alterations is commonly of interest for research and not clinical practice. In principle, though upfront rare alterations of primary resistance may occur, again it is outside the scope of this submission to assess the benefit of EGFR TKI in such rare cases, as to provide a treatment algorithm.