ERG response to factual errors identified by the manufacturer (please also see erratum document)

Issue 1 [redacted] ICERs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
[redacted]	The results of the ERG's alternative analysis should be redacted.	[redacted]	The ERG notes that it can only consider data as presented in the submission [redacted]

Issue 2 Page 60

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 60 of the ERG report states that 'any consideration by the ERG of subgroups is 'not legitimate'. This is not correct. The clarification letter states that the KM data for patients with non-visceral disease (NVD) has been requested….Given our previous experience with LRiG we anticipate that this will form the basis of a de novo cost effectiveness analysis in this group….we do not believe this to be legitimate'.	Change sentence to 'the forming of a de novo cost effectiveness analysis using the KM data requested by the ERG during the clarification questions is not legitimate'.	This statement notes that 'any consideration by the ERG of subgroups is not legitimate'. This does not correspond to what is written in the clarification response. The clarification refers to the forming of a de novo cost effectiveness analysis which includes the KM data requested.	The ERG has revised the text (new text added is in red font and underlined): Original text : The manufacturer claims that the method of analysis (alternative censoring definition) is 'significantly flawed', and also that any consideration by the ERG of subgroups is 'not legitimate'. Revised text: The manufacturer claims that the method of analysis (alternative censoring definition) is 'significantly flawed', and also that consideration by the ERG of the impact of specified subgroups on modelled estimates of cost-effectiveness is 'not legitimate'.

Issue 3 Page 63

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 63 of the ERG report notes that 'no potential explanations have been offered' when referring to the efficacy of pertuzumab in people with non-visceral disease in CLEOPATRA. This is incorrect, Roche offered explanations, of which some are contained in the sentence that followed in the ERG report.	Delete sentence.	This sentence states that Roche did not provide explanations. This is incorrect and contradicts the following sentence in the ERG report.	The ERG has revised the text (new text added is in red font and underlined): Original text: Despite additional multivariate Cox regression analyses this difference persisted, and no potential explanations have been offered. Revised text: Despite additional multivariate Cox regression analyses this difference persisted, and no potential biological explanations have been offered.

Issue 4 Page 65

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 65 of the ERG report states that 'In the manufacturer's base-case decision analysis, Kaplan-Meier results are used directly up to 35 months post-randomisation, and thereafter an exponential projection is applied to each arm'. This is incorrect, as exponential projection is applied at different time points in each arm. This is to reflect the fact that by incorrectly having the same break point (month 35) in both arms, such an analysis would be using trends observed in the higher risk group to inform the extrapolation of the lower risk group. This explains why the mean duration of PFS is the same for the control arm in the ERG analysis and the Roche analysis, whereas the mean duration is different in the intervention arm. Please refer to the page 50 of the ERG report which states	The description of the manufacturer's model should be consistent with the explanation provided on page 50 of the ERG report. It should also be noted that as a result of randomisation, the proportion of patients who are at lower risk will be the same in both arms. Because duration of PFS is longer in the pertuzumab arm, the subgroup of patients who have a lower risk will progress later on in the pertuzumab arm compared with the control arm. It is therefore incorrect to use the same segment of trial data in both arms (600 days onwards) – this is because the pertuzumab arm analysis will use the higher risk group to inform the	The ERG report contains a factual error and contradicts what is stated in page 50 of the ERG report.	The ERG has revised the text as follows (the new text added is underlined): <u>Original text:</u> In the manufacturer's base-case decision analysis, Kaplan-Meier analysis results are used directly up to 35 months post-randomisation, and thereafter an exponential projection is applied to each trial arm. The exponential parameters are calibrated by least squares minimisation against the Kaplan-Meier results beyond 36 weeks for each arm. This approach leads to mean undiscounted PFS estimates of [redacted] months (pertuzumab) vs [redacted] months (control), a gain of [redacted] months favouring pertuzumab. <u>Revised text:</u> In the manufacturer's base-case decision analysis, Kaplan-Meier analysis results are used directly up to <u>27 months (pertuzumab) and 35 months (control) post-randomisation. A common long-term exponential projection is applied to both arms from 32 months (pertuzumab) or 35 months (control). A separate exponential trend is used in the pertuzumab arm in the period between 27 and</u>

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that 'the model uses investigator assessed progression data…until week 117 in the pertuzumab arm and until week 152 in the control arm'.	extrapolation of the lower risk group in that arm.		32 months. This approach leads to mean undiscounted PFS estimates of [redacted] months (pertuzumab) vs [redacted] months (control), a gain of [redacted] months favouring pertuzumab.