Aflibercept (Zaltrap) for the treatment of metastatic colorectal cancer

ERG commentary on the additional information submitted by the manufacturer in response to the ACD

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Section 1: Introduction

The ERG was requested by NICE to provide validity checks on the additional evidence submitted by the manufacturer in response to the ACD and to identify any areas of remaining uncertainty. Due to the limited time available, the additional work undertaken by the ERG does not constitute a formal critique of the manufacturer's resubmission and hence does not accord with the procedures and templates applied to the original submission. However, the ERG has checked the implementation of any proposed changes and ensured replication of the results presented by the manufacturer. In addition, the ERG has also undertaken additional scenario analysis to address any remaining issues or areas of uncertainty that it considered was not reflected in the manufacturer's response.

The manufacturer's response to the ACD included:

1. A revised patient access scheme (PAS);
2. An amended version of the economic model (also incorporating a correction to the coding of the probabilistic sensitivity analysis);
3. A revised base case to address areas of uncertainty identified by the ERG and the Appraisal Committee;
4. Cost-effectiveness results from the amended version of the model for revised base-case assumptions (deterministic and probabilistic), as well as for a series of scenario analyses (deterministic analysis);

The ERG considers that the documentation submitted by the manufacturer largely reflects amendments and corrections intended to address the committee's considerations raised within the ACD, as opposed to being based on new data related to aflibercept. The new data proposed in the response specifically relate to the revised PAS and the incorporation of interim baseline EQ-5D data from a Phase IIIb trial (the ASQoP trial) which is now used to inform the utility value applied to the stable disease state in the economic model. The remainder of the changes proposed within the revised base-case all relate to the same evidence previously critiqued by the ERG in the main evaluation report. Consequently, the ERG views of these issues remain largely unaltered

Section 2: Revised Patient Access Scheme (PAS)

The manufacturer has proposed a revised patient access scheme (PAS) which is now incorporated into the revised base-case results. In the revised PAS, aflibercept is now priced at [redacted] per vial (100mg) and [redacted] per vial (200mg); a discount of approximately [redacted] compared to the published list price. In the original PAS used in the previous submission, aflibercept was priced at [redacted] per vial (100mg) and [redacted] per vial (200mg); a discount of approximately [redacted] compared to the published list price.

The ERG has checked the revised economic model and can confirm that the revised PAS has been correctly implemented by the manufacturer.

Section 3: Amended economic model and revised base-case

In response to the ACD the manufacturer submitted an amended economic model and provided results for a revised base-case and additional scenarios. The amended economic model also incorporated a correction for an error subsequently identified by the manufacturer within their original coding for the probabilistic sensitivity analysis (PSA). The manufacturer stated that this error was the reason for the large difference previously noted by the ERG when comparing the deterministic and probabilistic results (approximately £5000-£14,000 difference in the ICER estimates). The manufacturer stated that correcting the error subsequently resulted in similar estimates of the deterministic and probabilistic ICERs, such that the difference in deterministic and probabilistic ICERs presented in the manufacturer's base-case was now only £50.

No details were reported by the manufacturer on the error itself or how this was corrected and hence the ERG cannot validate this specific change. Also it should be noted that, due to time constraints, the manufacturer only compared the deterministic and probabilistic ICERs for the revised base-case results. All subsequent scenarios presented by the manufacturer were based on the deterministic results only. Consequently, it is not possible to conclude that the correction would lead to similar ICERs across all the separate scenarios. Despite these caveats, the ERG considers it unlikely that the difference scenarios would results in large differences in the ICER estimates.

The amended economic model also incorporated several adjustments to the manufacturer's original base-case approach. The adjustments applied in the revised base-case are in response to specific issues raised within the additional ERG analyses presented in the original evaluation report and the committee's considerations of the issues in considering the most plausible ICER for aflibercept outlined in Section 4.6 of the ACD. These areas of uncertainty are summarised below and discussed in more detail in the following sections:

- Correction of AE disutility calculations
- Adjustment to treatment acquisition costs so that they were applied for the entire duration patients were in the "second-line on treatment" state
- Incorporation of ageing disutility based on a starting age of 70
- Use of mean, rather than median estimates from the KOL resource-use survey
- Incorporation of additional administration costs (£15 pharmacy preparation costs)
- Utility of 0.6 for the Progressive Disease Health State
- Assumption of no continued treatment effect (i.e. the application of a hazard ratio equal to 1) after the end of trial follow-up

3.1 Correction of AE disutility calculations

The ERG identified an error in the original model presented by the manufacturer concerning how the disutility of AEs had been incorporated and proposed a correction. The manufacturer has now accepted this correction and the ERG can confirm that this has been appropriately incorporated into the revised base-case results.

3.2 Use of accurate treatment acquisition costs

In the original evaluation report, the ERG questioned the approach used by the manufacturer to estimate the treatment acquisition and administration costs and was concerned that this may have underestimated costs in both treatment groups. The ERG noted that despite the model structure incorporating specific states for "On second-line treatment" and "Discontinued second-line treatment", these were not directly linked to the subsequent calculations of acquisition/administration (and hence the separate states were used to reflect utility differences only). Instead, the costs of second-line treatments were estimated separately from the model structure and were based on a fixed number of cycles (corresponding to the mean overall duration of the combination treatment in each treatment arm observed in the VELOUR trial). The ERG noted that the manufacturer considered this necessary to incorporate dose delays and dose skipping, but also considered that these could have been incorporated within the structure of the model and that the approach used by the manufacturer was inconsistent with that taken for the estimation of utilities. The ERG therefore undertook a separate analysis linking the costing of treatment acquisition and monitoring costs to the structure of the model, ensuring a consistent approach to both costing and utility adjustment.

In their response to the ACD, the manufacturer considered that the Appraisal Committee did not state a clear preference for either approach and hence have retained their original approach to the estimation of treatment acquisition costs within their revised base-case and provided addition justification for this approach. The ERG has evaluated the additional justification provided by the

manufacturer and accepts that given the complex interplay between different components of the treatment regimens (i.e. the duration of different elements may differ), that relating the acquisition and monitoring costs to the structure of the model is difficult and hence accepts that the manufacturer's approach is likely to provide the most accurate estimate. The ERG still considers that this approach leads to inconsistencies between the approaches used to cost treatments and the impact on HRQoL. However, the ERG does not consider that this inconsistency would necessarily bias the results and indeed may actually be marginally conservative towards aflibercept. Consequently, the ERG considers the manufacturer's original approach to be acceptable in light of the additional data provided.

3.3 Application of age-related disutility with a correction for the age of the starting cohort

In the original ERG evaluation report, concerns were noted about both the lack of adjustment for utilities in terms of ageing in the model and also the assumed starting age (60 years – based on the average age of patient's in the VELOUR trial) applied by the manufacturer in their base-case analysis. The ERG considered that a starting age of 70 years was more appropriate based on patients in actual clinical practice based on feedback from our clinical expert and also was consistent with the assumptions employed in previous NICE appraisals for second-line treatment in mCRC. The ERG considered that the approach used in the manufacturer's base case would likely result in an over-estimate of the QALY gains associated with aflibercept.

In the response to the ACD the manufacturer has reiterated their view that the VELOUR trial population is generalisable to patients in the UK likely to be considered eligible for second-line combination therapies and questioned the accuracy of references made in the ACD to the committee's discussion and to the estimates applied by the ERG in their revised base-case. The manufacturer also cites supportive evidence from UK real-world, observational studies of patients with MCRC receiving second-line chemotherapy which they report is consistent with the average of patients in the VELOUR trial.

Consequently, the manufacturer continues to assume a starting age of 60 but has now incorporated age-related disutility in their revised base-case to allow for the impact of ageing. A separate scenario was also presented assuming a starting age of 65. No details were provided by the manufacturer in their response regarding how these real-world studies were identified and consequently the ERG is not able to confirm whether these studies are fully representative of all studies or are potentially selective. Regardless, the ERG still considers that assuming a starting age of 60 is relatively optimistic, based both on the views expressed in the original evaluation report and also based on the mean ages reported in the other real world studies presented by the manufacturer (where 3 of the 4 studies cited had a mean age of 63). However, equally the ERG also accepts that assuming an average

age of 70 may also be too high and hence considers that including the scenario of starting the cohort at 65 years sufficient to reflect the uncertainties previously expressed by the ERG. The ERG also notes that the difference in the ICER estimates between the results based on a starting age of the cohort of 60 or 65 years is relatively minor (approximately £500 difference).

3.4 Median values from survey data

The ERG previously reported a marked difference in the ICER (approximately £5k) when the mean values were used from the KOL survey for community and personal and social care resource use compared to the median values used by the manufacturer in their original base-case analysis. As discussed in the original evaluation report, the ERG considered that mean values are generally considered the most appropriate estimates to inform parameters in cost-effectiveness analysis and also noted that the manufacturer had applied mean resource use estimates from the KOL survey to estimate the cost of AEs management. However, the ERG also considered the rationale provided by the manufacturer regarding their use of median values based on the skewness in the KOL survey data and the relatively small number of respondents (n=6) and hence the ERG also presented an additional set of results in their exploratory analysis based on the median resource use from the KOL survey.

In their response to the ACD, the manufacturer has provided further information which they consider demonstrates that the skewness in the resource use estimates for community and personal and social care is due to a clear outlier, relating to the estimated number of visits from a palliative care team to support patients in the progressed disease state. The manufacturer shows that one estimate from the 6 respondents appears to be a clear outlier and that including this within the mean calculations has a significant impact on the ICER. The manufacturer therefore argues that the inclusion of this estimate is not appropriate. The manufacturer further cites additional supportive evidence from the monthly cost of progression applied in previous TA appraisals (TA242) which they argue is more consistent with the estimates derived from using median as opposed to mean estimates.

Based on their response the manufacturer concluded that using the median was still the most appropriate way to account for the skewed data. However, additional scenario analyses were also undertaken based on:

(i) Using the mean values from the survey data, but excluding the outlier identified for the parameter of the number of visits from the palliative care team;

(ii) Using a per cycle cost of progression based on a previous TA appraisal (TA 242).

While the ERG acknowledges the challenges of using elicitation and expert panels to derive resource utilisation, we also consider that the selection procedure used to identify relevant experts should have ensured that respondents had relevant experience and knowledge of the areas that they were expected

to provide responses for and that this might have avoided the need for post-hoc adjustments (which ultimately is difficult to conclude is reasonable or not). In this instance the ERG considers that the particular estimate does appear to be a potential outlier and hence accepts that the exclusion of this estimate the most pragmatic approach to take in these circumstances. However, the ERG considers the approach taken in the scenario analysis presented by the manufacturer (i.e. using mean values after the exclusion of the outlier) more appropriate than the revised base-case approach which continues to use the median resource use estimates. This approach is also more consistent with the manufacturer's use of mean resource use estimates for AEs. The difference in the ICER based on the manufacturer's revised base-case (i.e. based on the median) and the scenario using the adjusted mean estimate is approximately £1,500.

3.5 Administration costings to reflect increased cost of delivery

The manufacturer acknowledged the ERG's and Committee's concerns that aflibercept may incur additional costs for pharmacy and preparation and administration above those accounted for within the HRG code used in their original model. Consequently, the manufacturer's revised base-case incorporates both an additional £15 preparation cost and a cost of £45 for additional administration per cycle for aflibercept. These estimates were the same as proposed by the ERG in their original critique. The ERG can also confirm that these have been appropriately incorporated within the revised base-case analysis presented by the manufacturer.

3.6 Utility estimate for the Progressive Disease Health State

The manufacturer in their response dismisses the concerns expressed by the ERG regarding their view that the utility values applied in the manufacturer's model appeared high based on comparable estimates reported in the existing literature and compared with population norms; particularly so for progressed disease. The ERG previously expressed concerns regarding the generalisability of the mCRC Utilities study to the mCRC patient population treated in UK routine clinical practice; the relatively small numbers of patients in the study (total n=71, n=36 for stable disease currently receiving second-line treatment and n=32 for progression on or following second-line therapy and currently receiving 3rd line or subsequent lines of therapy or BSC) and the counter-intuitive results reported in one instance.

Having largely dismissed these concerns, the manufacturer has not presented any new scenarios with lower utility values. Regarding the utility value for stable disease the manufacturer has incorporated further interim data from the ASQoP trial based on EQ-5D data for patients receiving aflibercept in combination with FOLFIRI. Estimates from the ASQoP trial are now used to estimate the utility of the stable disease state in the revised base-case analysis (0.78), in preference to the utility value originally derived from the mCRC study ([redacted]).

The ASQoP results are based on an interim data analysis. Of the [redacted] patients who have been screened, [redacted] have received at least 1 cycle of treatment and EQ-5D at baseline was reported for [redacted] patients. No explanation was provided by the manufacturer for why EQ-5D data was only reported for a subset of the patients who appear to have been screened and received at least 1 cycle (i.e. for whom baseline data should be available). The manufacturer subsequently used a weighted average of cycle 3 and 5 (i.e. patients on treatment) to inform the estimate for the stable disease state (0.78) in their revised base-case. The ERG is unclear why the manufacturer used this approach and excluded the baseline utility value (0.77) from this study. The stable disease utility applied in the economic model is applied to patients who may be on and off treatment. The ERG considers that using only patients who have completed 3 or 5 cycles may result in selection bias such that the respondents may be relatively more healthy than the entire sample of patients still in stable disease. The ERG therefore considers the baseline utility value of 0.77 may be a more reasonable basis to inform the utility value for the stable state.

However, the ERG notes that the utility values applied in the revised base-case (0.78) are reasonably consistent with the previous estimates employed based on the original analysis using the mCRC Utilities study and considers the use of the ASQoP trial data a reasonable approach to take based on the higher numbers of patients included. However, the ERG considers the baseline visit value of 0.77 reported in the ASQoP analysis more appropriate to inform stable disease. The manufacturer also presented a separate scenario analysis where they reported the results based on the utility value for the stable disease state based on the mCRC Utilities study estimate of [redacted] (i.e. the value used in the previous submission) and this had only a minor impact on the ICER, increasing the revised base-case ICER by approximately £700. Consequently, the difference between assuming 0.78 and 0.77 is likely to be minor.

The ERG remains concerned the manufacturer continues to apply the utility estimate of 0.71 for progressed disease rather than the value of 0.60 proposed by the ERG. Importantly, no new evidence has been submitted to support this estimate and so the ERG views from their initial review remain unaltered. Hence, we still consider that the alternative estimate proposed of 0.60 to be equally plausible and perhaps more realistic. Although the manufacturer has proposed a subsequent adjustment to the model to account for the deterioration in HRQoL close to the end of life (by applying a utility of 0.3 during the last 2 months of life), the ERG does not consider that this fully addresses their concerns or is based on any empirical evidence. Importantly, no additional scenarios were presented by the manufacturer in their response using the ERG's preferred estimate for progressive disease.

3.7 Overall survival

The ERG previously highlighted the uncertainty surrounding the extrapolation of overall survival and proposed a number of alternative assumptions which we felt were equally plausible as the approach selected by the manufacturer in their original base-case analysis. Importantly, the ERG also noted that these approaches incorporated more pessimistic scenarios than considered by the manufacturer and that the range of scenarios presented by the ERG was more in keeping with existing NICE methodological guidance related to extrapolation by reflecting the extent of possible uncertainty surrounding the extrapolated estimates. Based on the alternative scenarios presented by the manufacturer and the ERG, the ACD states that "the Committee agreed that the ERG's first scenario which assumes equal risk of death for all patients beyond the trial period (hazard ratio equals 1.0) represents an acceptable compromise between the 2 extremes of assuming continuing treatment effect (manufacturer's base case) and allowing for a reversed treatment effect (ERG's second scenario). However, the Committee concluded that, although this was considered the most plausible assumption for extrapolating overall survival, it still considered that great uncertainty exists".

Although the manufacturer has presented separate scenario results based on the approaches considered most acceptable by the Committee, the revised base-case actually uses an alternative assumption reflecting a further scenario not presented by the manufacturer in their original submission or the ERG in their exploratory analysis.

In outlining the rationale for the scenario included in their revised base-case, the manufacturer cites the NICE Methods Guide (2008) which states that "alternative scenarios should be considered to compare the implications of different assumptions around extrapolation of the results. For example, for the duration of treatment effects scenario might include when the treatment benefit in the extrapolated phase is: (i) nil; (ii) the same as during the treatment phase and continues at the same level; or (iii) diminishes in the long term". In their response, the manufacturer argues that the first scenario is the most pessimistic of these assumptions and is represented by the exploratory analysis undertaken by the ERG by assuming a hazard ratio of 1 after the end of trial follow up (30 or 36 months) and further states that this approach was also the basis for generating the Committee's "most plausible" ICER estimates.

The manufacturer response to the ACD considers that it is more plausible to assume that the hazard ratio (HR) increases gradually back to 1 after the end of the observed period after a short period of time (i.e. a further 12 months) rather than assuming that it immediately reverts to 1. Consequently, in their revised base-case the manufacturer applies a tapering effect to the HR at the end of trial follow-up (36 month) such that the HR reverts back in a linear manner to 1 after a further 12 months. That is, the treatment effect is assumed to equal 1 at 48 months, as opposed to at 30 or 36 months based on the scenarios considered most plausible by the Committee in light of the high uncertainty. This approach

resulted in the base-case ICER of £42,242. Separate scenarios were are also presented by the manufacturer based on applying the starting point of the tapering effect to an earlier point (i.e. 24 or 30 months leading to an HR of 1 at 36 or 42 months). The ICERs in these scenarios were less favourable than the base-case, £47,097 to £44,039 per QALY respectively.

Importantly, although the manufacturer claims that the approach supported by the Committee in their deliberations represents the most pessimistic assumption, the manufacturer did not consider the full range of alternative assumptions considered plausible by the ERG and did not consider the possibility that the OS may converge over the extrapolation period (i.e. based on the shape of the respective PFS curves). Despite the Committee's conclusions in the ACD that it appears implausible that the mortality of patients in the progressive state might be increased for a period for patients previously treated with aflibercept relative to those who were not, the ERG maintains its position that this is as equally plausible as any other scenario. Furthermore, the ERG considers that this scenario is entirely justified based on the PFS curves (i.e. indicating that after a particular time point patients remaining on treatment progress at a more rapid rate on aflibercept) and notes that the clinical plausibility of this scenario has been previously considered appropriate by other committees for other vascular endothelial growth factor (VEGF) treatments. The FAD for TA 285 (Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer) reports that "the Committee heard from the clinical specialists that, although not substantiated in clinical practice, it was biologically plausible that bevacizumab could increase PFS, but once the disease has progressed, disease progression could be accelerated once bevacizumab is stopped….. It noted the manufacturer's comment that the overall survival results could have been affected by confounding effects because of the use of post-progression treatments. However, the Committee agreed that the high degree of censoring of PFS estimates and the potential biological action of bevacizumab could also be explanations for the difference in the results" (paragraph 4.8, guidance.nice.org.uk/ta285). Importantly, the additional scenarios considered in the ERG's exploratory analysis assuming that the OS curves converged resulted in significant lower estimates of the mean OS gain for aflibercept, ranging from 2.1 to 2.6 months, and significantly increased the ICER estimates to between £90,824 and £108,945 per QALY.

The ERG therefore does not consider the revised assumption applied in the manufacturer new base-case analysis to be any more plausible than the other scenarios previously considered by the ERG and Committee. Importantly, the revised assumption is not based on any additional data or further re-analysis. The ERG also does not consider that the manufacturer's response and the additional scenarios presented reflect the full range of uncertainties highlighted by the previous ERG report and neither does their revised base-case reflect the conclusions from the Committee based on the ACD.

Section 4: ERG summary of manufacturer response and remaining uncertainties

As previously highlighted the ERG considers that the documentation submitted by the manufacturer largely reflects amendments and corrections intended to address the committee's considerations raised within the ACD, as opposed to being based on new data related to aflibercept. The new data submitted primarily relates to the proposal for a new PAS and the use of an alternative utility estimate for the stable disease state. Both amendments to the model appear reasonable and have been implemented appropriately.

The ERG also considers that the manufacturer has appropriately corrected or altered elements of the model to more appropriately reflect the ERG critique and issues raised by the Committee. However, the ERG considers that there are several important areas of remaining uncertainty which have not been fully addressed in the manufacturer's response. These relate to:

(i) Although the ERG considers the exclusion of the outlier reported in the KOL resource use data to be the most pragmatic approach, we still consider that the use of the mean resource use estimates (excluding the outlier) represents the most appropriate basis for informing the model.

(ii) There remains uncertainty concerning the appropriate starting age to assume in the model and although the manufacturer assumes a starting age of 60, the ERG considers that this is still low compared to patients in routine clinical practice (and lower than 3 of the 4 real world studies reported by the manufacturer in the response)

(iii) In the absence of any further data or information on the utility of progressive disease, the ERG views presented in the original evaluation report have not been altered. Hence, the ERG considers that a utility value of 0.60 (as opposed to 0.71) is more appropriate and this scenario has not been considered by the manufacturer.

(iv) In the absence of any further data or re-analysis of the existing survival data, the ERGs views presented in the original evaluation report have not been altered. Importantly, the ERG maintains its position that there are other equally more plausible (and more pessimistic) scenarios than considered by the manufacturer in both their original submission and their subsequent response. Furthermore, the ERG considers the assumption applied in the manufacturer's revised base case, neither more plausible than any other scenario nor reflective of the position that the Committee appeared to take in outlining the most plausible ICER. Consequently, the ERG considers that the scenarios assuming a HR=1 after 30 or 36 months are more consistent with the Committees conclusions in the ACD.

To address these remaining uncertainties, the ERG has undertaken a range of further exploratory analysis. These scenarios are based on the revised manufacturer model, with the following amendments: (i) resource use estimates from the KOL survey are based on the mean resource use estimates (excluding the potential outlier); (ii) the utility value for stable disease is assumed to be 0.77 (i.e. the baseline value from the ASQoP trial); (iii) the utility value of progressive disease is assumed to be 0.6. Separate scenarios are presented based on starting ages of 60 (Table 1) and 65 (Table 2) and for alternative assumptions related to OS (i.e. HR=1 after 30 or 36 months and applying the tapering effect assumptions also reported by the manufacturer). Due to limited time, the ICER estimates are based on deterministic estimates only.

Table 1: Additional ERG exploratory analysis – assuming a starting age of 60 (utility for stable disease = 0.77**, utility for progressive disease = 0.6, mean resource use estimates for KOL survey – excluding outlier)**

Parameter	Scenario	Incremental costs	Incremental QALYs	ICER
OS	HR = 1 after 36 months	8,716	0.1709	50,991
	HR = 1 after 30 months	8,590	0.1584	54,243
	HR tapers to 1 over 12 month period – start at 30 months	8,703	0.1697	51,296
	HR tapers to 1 over 12 month period – start at 24 months	8,558	0.1552	55,139

Table 2: Additional ERG exploratory analysis – assuming a starting age of 65 (utility for stable disease = 0.77**, utility for progressive disease = 0.6, mean resource use estimates for KOL survey – excluding outlier)**

Parameter	Scenario	Incremental costs	Incremental QALYs	ICER
OS	HR = 1 after 36 months	8,716	0.1688	51,634
	HR = 1 after 30 months	8,590	0.1565	54,890
	HR tapers to 1 over 12 month period – start at 30 months	8,703	0.1676	51,941
	HR tapers to 1 over 12 month period – start at 24 months	8,558	0.1534	55,791

Section 5: Additional ERG comments on End of Life

The mean OS values presented by the manufacturer in Table 1 of their response are based on the Committtee's view on the most plausible assumption to modelling OS benefits (i.e. HR set to 1 after 30 and 36 months). The ERG can confirm that the estimates reported by the manufacturer are correct using a Log-logistic parametric function with a 15 years time horizon.

As stated in their report the ERG says truncating the time horizon is a less appropriate approach to eliminating a treatment benefit than is setting the treatment difference to zero (HR=1). However, as demonstrated in Table 2 of the manufacturer's response the longer the time horizon, the longer the mean survival benefit. It is therefore necessary to consider whether a 15 year time horizon is appropriate in this indication. If 10 or even 5 years was considered long enough to capture the lifetime of all patients with progressed metastatic colorectal cancer, then the mean survival times of 3.4 or 3.7 would be too long. Table 3 below shows the equivalent estimates assuming different time horizons.

Table 3: Mean OS obtained assuming no continued treatment effect after 30 or 36 months – impact of alternative time horizons

Time Horizon	Extrapolation Function	Mean OS (months)
15 years	Log-logistic, with HR = 1 after 30 months	3.4
	Log-logistic, with HR = 1 after 36 months	3.7
10 years	Log-logistic, with HR = 1 after 30 months	3.2
	Log-logistic, with HR = 1 after 36 months	3.5
5 years	Log-logistic, with HR = 1 after 30 months	2.7
	Log-logistic, with HR = 1 after 36 months	2.8