NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [ID1477]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [ID1477]

Contents:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Sanofi	**Sanofi would like to thank the appraisal committee for recognising the potential benefit IsaPd could bring to patients at 4th line after the failure of 3 prior therapies.** Sanofi is pleased that the committee agree that there remains a need for effective treatment options for previously treated multiple myeloma, and that people would welcome new options. This is particularly true at 4th line (4L) after the failure of 3 prior therapies where the unmet need has been clearly demonstrated through strong uptake into the early access to medicines scheme (EAMS) which opened in December 2019 and ran until marketing authorisation in June 2020. At the close of the scheme after 5 months 'academic / commercial in confidence information removed' had been enrolled. We recognise that there are other options available for the treatment of multiple myeloma via routine and Cancer Drugs Fund (CDF) commissioning and are happy that committee accepts the company positioning of isatuximab in combination with pomalidomide and dexamethasone (IsaPd) at 4L. Moreover, we are satisfied the committee has agreed that the subgroup analysis from the ICARIA-MM trial for people who have had 3 previous treatments is appropriate for decision making. In the submitted company base case, pomalidomide in combination with dexamethasone (Pd) was presented as the comparator to the combination of IsaPd at 4L. Sanofi agree with the committee that Pd is the only relevant comparator in this position. Furthermore, we are pleased that the committee has recognised the clinical benefit due to IsaPd because it delays the progression of relapsed and refractory multiple myeloma (RRMM) and increases how long people live compared with Pd. Sanofi are also encouraged that the committee concluded IsaPd met the criteria to be considered a life-extending, end-of-life treatment and so should be judged against the higher £50k/QALY threshold.	Comment noted. Please find detailed responses to the individual comments in the relevant sections of this table below. Some detailed responses relate to the updated cost-effectiveness analysis and clinical evidence submitted by the company after the first committee meeting (not reproduced in this document - please see the committee papers for full details of the evidence).
Sanofi	**Sanofi are disappointed that the committee were not able to recommend IsaPd at this stage. On the basis of the information provided within our response, which demonstrates IsaPd can be considered plausibly cost-effective, we urge the committee to reconsider this preliminary decision.** In summary, in order to address the committees concerns we have provided the following: 1. Exploration and discussion of the uncertainty surrounding the extrapolation of OS data from the ICARIA-MM trial	Comments noted. The committee acknowledged the uncertainty surrounding the extrapolation of overall survival data in their decision-making. They concluded that there is a range of plausible distributions to estimate overall survival in each trial arm and the

	2. A revised cost-effectiveness base case for 4th line patients along with scenario analyses 3. An updated cost-effectiveness analysis that includes the committees preferred assumptions 4. Proposal for inclusion in the CDF 5. Discussion on the challenges associated with the assessment of branded combinations in the current STA framework and cost-effectiveness scenarios exploring the impact of removing the backbone pomalidomide cost for the IsaPd combination. 6. New cost-effectiveness analyses for 3rd line patients versus PanVd (+ scenario analyses) A commercial discussion with NHSE/NICE has been scheduled for the 8th July. The net prices for isatuximab utilised in this response align with our response to technical engagement academic / commercial in confidence information removed. It is important to note that this appraisal is further complicated by the existence of a confidential PAS for pomalidomide **which is not and cannot be known to Sanofi.** The ICERs presented in this document are therefore not the true ICERs which will be lower depending on the level of discount on pomalidomide. **Sanofi encourage the appraisal committee to reconsider their preliminary decision in the context of the unmet need at later lines of therapy, the data that could be collected were IsaPd to be recommended for use on the CDF and ask that the committee exert a degree of flexibility in their decision making given the challenge associated with appraising branded combination therapies.**	company's alternative survival analysis using surrogates for overall survival is not robust (see FAD section 3.11 to14). The committee agreed that the uncertainty in the current evidence base was too high for it to be confident that the most plausible ICER range was below the range NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life. It therefore concluded that it could not recommend isatuximab plus pomalidomide and dexamethasone for routine use in adults with relapsed and refractory multiple myeloma (see FAD section 3.26) The committee concluded that isatuixmab plus pomalidomide and dexamethasone had plausible potential to be cost-effective at the company's price for isatuximab including a commercial arrangement and therefore recommended its use in adults with relapsed and refractory multiple myeloma within the cancer drugs fund (CDF) after 3 previous lines of treatment (including

		lenalidomide and a proteasome inhibitor) when the company's commercial offer as part of the managed access agreement is used (see FAD section 3.27) The committee concluded that, in line with the NICE guide to the methods of technology appraisal (2013), all relevant costs should be included (see FAD section 3.21) The committee concluded that there is unmet need for new effective treatment options for people who have had 2 previous lines of treatment (see FAD section 3.4). The committee concluded at its first meeting that it would focus its discussion on people who have had 3 previous lines of treatment. The committee heard from clinical experts that currently many clinicians use lenalidomide after 2 previous lines of treatment, with ixazomib and dexamethasone in the CDF or with dexamethasone. The clinical experts agreed that the company's positioning after 3 previous lines of treatment was appropriate (see FAD section

		3.3). The committee concluded at the second meeting that the cost-effectiveness analysis after 2 previous lines of treatment is not robust enough for decision making (see FAD section 3.24)
Sanofi	**The committee has concluded that the clinical data are immature, but the Weibull distribution gives the most plausible OS estimates** Extrapolations for OS at 4L in the model are based on immature data which comprises only ~30% of possible events and this high level of uncertainty means that a range of plausible assumptions for long term survival of IsaPd should be considered in the context of CDF entry rather than relying on the most punitive estimation. In this section we validate our original assumptions and discuss alternative approaches to the extrapolation of long-term outcomes. T**he currently available ICARIA-MM data are more highly censored than data sets used by NICE in previous assessments** Median OS was not reached in ICARIA-MM at the time of the data cut. At the cut-off date, 69% of the 4L patients were still alive (78.8% in IsaPd arm and 60.3% in Pd arm with median follow-up of 11.6 months) and were, consequently, censored in the data analysis. At the time of the analysis, the probability of surviving 12 months was 0.780 (95% CI; 0.638, 0.872) in the IsaPd arm and 0.619 (95% CI; 0.474; 0.735) in the Pd arm. While censored data in oncology trials are to be expected, this level of censoring is more than that seen with other treatments assessed by NICE in the 4L setting for RRMM (Table 1). **Table 1: Censoring levels across treatments recommended at 4L** Note: Ixazomib (TA505) has not been included since it only has a conditional marketing authorisation. No data on censoring for PANORAMA-2 was identified. **Independently fitting the data for OS makes no material difference to the outcomes.** The ERG concluded in their report that independently fitted curves may be more appropriate than the jointly fitted models presented by the company (Section 4.2.4.2.2 of ERG report). We have fitted the	Comments noted. The committee acknowledged the uncertainty surrounding the extrapolation of overall survival data in their decision-making. They concluded that there is a range of plausible distributions to estimate overall survival in each trial arm including the exponential or the lognormal extrapolation for isatuximab plus pomalidomide and dexamethasone and the independently fitted Weibull for pomalidomide plus dexamethasone (see FAD section 3.13). The committee acknowledged that the clinical data from ICARIA-MM at the current data cut is immature and that more data from this trial would help to reduce the clinical uncertainties in the evidence (see FAD section 3.27) The committee also acknowledged the longer-term

	OS data independently and found that the fits and conclusions from the associated statistical analysis made no material difference to the originally proposed estimates. However we agree that in this case it is plausible that the curves could follow different trajectories due to the significantly different pharmacological properties for the triplet IsaPd combination vs. Pd. Current OS fits are based on extremely immature survival data and we discuss this in detail below where we concur with the committee assumptions around the Weibull fit for the Pd arm but not for the IsaPd extrapolation. The results for the independent curve fitting exercise are provided in an Appendix. **Lack of clinical experience with IsaPd in UK practice highlights uncertainty in predicting long term outcomes at 4L for triplet based anti-CD38 therapy but outcomes for Pd are more certain.** How well the extrapolated curves fit to the empirical data from the trial is important but we agree with the committee that it is less informative for both IsaPd and Pd given the different levels of censoring in the arms and that other ways of validating the curve selection are needed, for example, by seeking clinical opinion. However, there is no clinical experience of IsaPd use outside of the ICARIA-MM trial or EAMS programme and there is no observed long-term survival experience from using any triplet therapy at 4L such as IsaPd in the UK. (EAMS ran for 5 months making long term outcomes hard to predict from this real world UK clinical experience to date) This makes it difficult for UK clinicians to be able to predict with certainty, what the most plausible extrapolations for IsaPd would be based on only ~20% of OS data. On the other hand, there is substantially more experience with Pd at 4L and also more literature precedent. Since the NICE approval of pomalidomide in 2017, approximately a third of patients have been treated with this doublet combination. To date numerous studies have been published documenting its use in RRMM in heavily pre-treated patients. We have inspected the literature and have plotted long-term outcomes for Pd taken from the key studies to examine in the round, the treatment effect for patients with RRMM. The results of this analysis are provided in Figure 1 and the list of publications considered can be found in an Appendix. **Figure 1: Long term outcomes from pomalidomide trials and the Weibull extrapolation from the ICARIA-MM Pd arm** The clinical experts at the committee meeting concurred that the Weibull extrapolation is the most appropriate for Pd in the UK clinical setting as did the experts we spoke to during the validation exercise	follow-up data from the daratumumab trials and considered this when assessing the plausibility of each distribution to estimate overall survival (see FAD section 3.13) The committee concluded that the company's alternative survival analysis using surrogates for overall survival is not robust (see FAD section 3.14)

	carried out for the submission. We have overlaid the ICARIA-MM Pd Weibull fit for Pd (black dashed line) in Figure 1 to test this assumption. Whilst cross trial comparisons should be interpreted with caution visual inspection of the diagram shows that this fit matches the available evidence well compared to the exponential curve (blue dashed line). Given the literature precedent and clinical validation **we concur with the committee's view that the Weibull estimator may be appropriate for the Pd setting.** However, these results **do not validate** the committee preference for the Weibull fit for IsaPd, a triplet-based monoclonal (mAb) therapy with a different and enhanced mode of action in combination with pomalidomide. Considerable uncertainty remains, not least due to lack of longer-term clinical experience in the UK. In the following sections we present some clinical arguments derived from the trial data to support the expectation of longer survival with IsaPd as predicted by the exponential and follow up with an alternative approach to estimating outcomes for the model which is evidence based. In a later section we discuss the pharmacological reasons for differences in the long-term outcomes between IsaPd and Pd. **Duration and depth of response supports longer term survival projections with IsaPd.** Achievement of minimal residual disease negative (MRD-ve) status is known to be a prognostic factor for prolonged PFS and OS and as such MRD as a surrogate end point is now being considered for inclusion in clinical trials (4),(5). The published evidence to date is mainly focused earlier in the pathway on newly diagnosed patients where MRD status has been more routinely measured. However, a very recent metanalysis of published data has found that even in relapsed refectory multiple myeloma where MRD -ve status is generally considered to be harder to reach, MRD negativity can be achieved and is very important for long term outcomes (4). In this study MRD-ve patients were calculated to have an PFS HR of 0.30 (95% CI, 0.18 – 049). Similarly, studies have found that partial to very good (partial) response rates are also prognostic of better outcomes overall. For example a newly published analysis of median OS by response status supports the view that patients who respond (definitions below) to daratumumab monotherapy have better median OS compared to those with stable or progressive disease (36-month OS rate for responders (partial response or better) was 60.2% compared to those with stable 29.5% and progressive disease 12.5% (6). The median OS for responders (partial response or better) was not reached (95% CI 29.2–not estimable). This is in contrast to patients with a minimal response or stable disease who had a median OS of 18.5 months (95% CI 15.1–22.4) and patients with progressive disease or without an evaluable response who had median OS of 3.5 months (95% CI 1.5–6.6).	

	We have examined the outcomes for patients treated in ICARIA-MM in a similar way and assessed the association between depth of response (including MRD-ve, MRD+ve and very good partial response (VGPR) or better, partial response (PR) and less than PR) and long-term outcomes. Although data are currently immature from ICARIA-MM, similar results to those reported for daratumumab (6) are seen for IsaPd in terms of depth of response and these are correlated with improved long-term outcomes in both arms in 4L patients. In the ICARIA-MM trial MRD status was only recorded for a small number of patients who achieved a stringent complete response (SCR) or a complete response (CR) (14 patients in the IsaPd arm and 2 patients in the Pd arm). The true CR rate is likely to have been underestimated in the clinical trial due to the interference of isatuximab with M protein measurements. This was investigated using a mass spectrometry technique and the true CR rate from the ICARIA-MM trial was assessed to have been underestimated by between 10-17% (7). Nonetheless of the 14 in the IsaPd arm 8 were MRD-ve (8/14 = 57%) at a minimum sensitivity of 1 in 105 nucleated cells. Neither of the patients with MRD measurement in the Pd arm achieved MRD-ve status. In the ITT population, after a median follow-up of 11.6 months in the Isa-Pd arm, 100% of MRD-ve patients were progression free and alive. In the IsaPd arm, median PFS was longer with increased depth of response: (MRD−ve patients, not reached (NR); ≥VGPR and MRD+ve, 15.21 months; partial response (PR), 11.53 months; less than PR, 3.29 months). This pattern was also observed for 1-year OS probabilities (100% > 92.9% > 82.4% > 46.4%, respectively) (8). Similar results have been seen in the 4L population: academic / commercial in confidence information removed Clinicians currently have little expectation of achieving MRD-ve status for patients in late lines of therapy and so it is noteworthy that a significant proportion of those with MRD status recorded achieved MRD negativity in the IsaPd arm. The PFS and OS outcomes are plotted against response in Figure 2 and Figure 3 overleaf. **Figure 2: academic / commercial in confidence information removed** **Figure 3: academic / commercial in confidence information removed**	

	The results show that depth of response, including MRD negativity, was improved with IsaPd and was clearly associated with better long-term survival outcomes. Obviously, the downward trajectory in the overall measures of PFS and OS in the earlier months of the trial are driven mainly by the patients with less than partial response. Outcomes for patients with partial response or better will drive the tails of the OS curves and so these results remain highly uncertain for IsaPd. The opinion of clinicians (n=5, not 3 as noted in the ACD) we have sought directly, suggests that there will be some patients for whom MM therapies are effective for prolonged periods beyond cessation of treatment even at 4L and these patients will have long OS which can extend into many years. The findings from the clinical trials presented above are supportive of this opinion. Further supporting evidence comes from looking at OS in ICARIA-MM by using similar definitions of response used in Usmani 2020 (6): i.e those who responded to treatment, minimal response or stable disease, and progressive disease. Although data are immature in ICARIA-MM, patients treated with Pd and with a minimal response or stable disease had a median overall survival of 13.9 months. Median overall survival was not reached in Pd patients who were responding or with progressive disease. At study cut-off, median overall survival was not reached in patients responding to treatment with IsaPd or in those with minimum response or stable disease (Table 2). **Table 2: academic / commercial in confidence information removed** sCR: stringent complete response, CR: complete response, VGPR: very good partial response, PR: partial response [a] Interaction test from the Cox proportional hazard model including the factor, treatment effect and the treatment by factor interaction In summary, while it is clear that the extrapolations for overall survival from ICARIA-MM are highly uncertain at first data cut with ~70% of patients still alive, it is worth considering that more than half of the patients in the 4L IsaPd cohort achieved MRD-ve status or partial response or better. OS for these patients is almost completely unknown and so we believe these results provide clinical evidence to support the rationale that the punitive Weibull extrapolation of overall survival in the economic model is not a reasonable choice for IsaPd. **It is reasonable to anticipate improved overall survival with triplet based anti-CD38 therapy compared to monotherapy anti-CD38 therapy, based on the evidence.**	

	Daratumumab monotherapy is the only other anti-CD38 therapy available currently at 4L and so it is useful to compare and contrast these results with the ICARIA-MM data. The positive recommendation for daratumumab in the CDF was supported by evidence from two single arm pivotal trials: SIRIUS and GEN501 reporting outcomes based on 31 months of follow-up (TA510) (1). Recently, final OS data were published for these monotherapy studies. The publication reports OS for 148 patients who received daratumumab 16 mg/kg (42 patients in GEN501 part 2; 106 patients in SIRIUS), with a median follow-up of 36.6 months. The median overall survival reported was 20.5 months (95% CI 16.6–28.1) and 3-year overall survival rate of 36.5% (28.4–44.6) (6). Patients entering the daratumumab studies GEN501 and SIRIUS are similar to those in ICARIA-MM 4L cohort (See Appendix 3). In order to compare the outcomes we have overlaid the daratumumab OS KM data with that of the ICARIA-MM OS KM estimators (Figure 4). The daratumumab KM OS is intermediate between IsaPd and Pd and whilst cross trial comparisons should be treated with caution this indicates that longer term, better outcomes with the triplet based anti-CD38 IsaPd might be expected. This assumption should be considered in the light of the compelling emerging evidence of the enhanced clinical benefits from the immunomodulatory effect of the anti-CD38 class and moreover the addition of an IMiD (pomalidomide) to isatuximab which is likely to further improve the body's own natural immune defences (This effect is discussed in a following section). **Figure 4: Overlay of the 4L OS KM data from ICARIA-MM and GEN501 and SIRIUS (6)** Using the data from this analysis, we fitted parametric extrapolations to the OS curves reported for daratumumab. (details are provided in an Appendix). The exponential was found to be the best fit based on the Bayesian information criteria (BIC), whereas the Log normal was the best fit based on the Akaike information criterion (AIC) and AICc. Visually, the lognormal provided the better fit. However, using both distributions we extrapolated out to 10 years in order to approximate the proportion of patients predicted to be alive at 5 years and 10 years. The landmark method approach presented below compares the predicted estimates for survival to corresponding estimates for IsaPd predicted in our model (Table 4). **Table 3: Estimated proportion of patients alive at 5 years and 10 years for Daratumumab and IsaPd**	

	It is reasonable to assume that a triplet anti-CD38 may have better outcomes than monotherapy as we have discussed above and in detail in a following section. The 3-year overall survival rate on daratumumab monotherapy was reported to be 36.5% (6). **This is longer than that predicted with IsaPd at 5 years with either the exponential or Weibull estimates** and so our estimates for isatuximab may be highly conservative in the short term. Bearing in mind the better fit to the lognormal distribution is based on the much longer follow data up for daratumumab, these results in Table 3 above suggest that our projections of overall survival with IsaPd using the exponential fit may be conservative compared with daratumumab. The committee preferred assumption of Weibull fit for the IsaPd OS data is also contrary to the observed daratumumab outcomes. Usmani et al. (6) reports median OS for daratumumab monotherapy at 20.5 months and the Weibull extrapolation from the observed OS data in ICARIA-MM is 27.7 months. Given the considerable difference in the observed median PFS at 4L for these patients (daratumumab: 4.0 months vs. IsaPd: 13.3 months) it is reasonable to assume that a larger difference between the two therapies at median OS would be observed than 7 months. These observations are also supported by the results from a survey carried out by Sanofi for the purposes of this response. 21 English haematologist/haem-oncologists were asked about their perceptions of survival for RRMM patients treated at 4L in the UK. 86% (N = 21) of the experts surveyed said they would expect patients receiving fourth-line treatment with a triplet regimen which includes a monoclonal antibody (mAb) to have much longer OS than similar patients receiving an mAb as monotherapy (mean of an additional 12.2 months). **Exploratory analyses using PFS as a surrogate for overall survival of IsaPd** We have established, based on literature precedent and clinical opinion, that the committee preferred assumption of the Weibull extrapolation using the ICARIA-MM data for Pd PFS is likely to be suitable for decision making so in the following section we concentrate on overall survival in the IsaPd arm. Given the highly censored survival data for IsaPd we have considered an alternative method to extrapolate OS. The most widely used surrogate for OS in oncology is PFS and this relationship has been established for multiple myeloma. Moreover, it has been shown that it varies by line and treatment type. The PFS data from the 4L IsaPd patients in ICARIA-MM provides an estimate for median PFS and so whilst still not mature these data are likely to provide sufficient information for a	

PFS:OS extrapolation to be used. Alternative methods to achieve this extrapolation are discussed in the next section.

Estimating a suitable range of ratios to use in the analysis.

In a pragmatic search of the literature we identified 3 potential sources for estimating this relationship. These references are provided below.

- Cartier S, Zhang B, Rosen VM, et al. Relationship between treatment effects on progression-free survival and overall survival in multiple myeloma: a systematic review and meta-analysis of published clinical trial data. Oncol Res Treat. 2015;38(3):88-94. doi:10.1159/000375392 (9)
- Félix J, Aragão F, Almeida JM, et al. Time-dependent endpoints as predictors of overall survival in multiple myeloma. BMC Cancer. 2013;13:122. Published 2013 Mar 16. doi:10.1186/1471-2407-13-122 (10)
- Dimopoulos M, Sonneveld P, Nahi H, et al. Progression-Free Survival as a Surrogate Endpoint for Overall Survival in Patients with Relapsed or Refractory Multiple Myeloma. Value in Health 2017; 20:9 PA408. DOI:https://doi.org/10.1016/j.jval.2017.08.064 (11)

The paper by Cartier only examines the association between the HR and ln(HR) for PFS and the HR and ln(HR) for OS so was not relevant for an analysis attempting to project treatment specific OS based on treatment specific PFS (as opposed to treatment effects expressed as an HR) (9). The papers by Dimopoulos (11) and Felix (10) examine the associations between median PFS and median OS. These studies are based on literature reviews and PFS and OS data are reported as the average of the medians identified. (See Table 4 below).

Table 4: Key findings from Felix and Dimopoulos

It is important to note that the Dimopoulos et al. ratio is based on RRMM studies which are the appropriate patients for the comparison here. This is not the case for Felix et al. which covers earlier lines of treatment. Therefore, we have included Felix et al. as a sensitivity analysis.

Given the time frame of the Dimopolous et al. literature review, carried out for the purposes of their analysis (RCTs published between 1970 to 2017) it is unlikely to include studies with anti-CD38 treatments. Older drug regimens are known to have poorer outcomes. The authors of the DSU review

	evaluating the relationship between PFS and OS in advanced metastatic cancers highlight that, within the context of HTA, evidence on PFS:OS ratios from within the same drug class should be used (12). This is preferable to mixing drug classes for estimation purposes. So on the basis of the DSU recommendation and the lack of other evidence we also explored the PFS:OS ratio based on daratumumab monotherapy published in the daratumumab NICE submission (1). PFS and OS from the integrated analysis of the two pivotal daratumumab studies for RRMM are provided below in Table 5 and Table 6. **Table 5: Relationship of PFS to OS in the daratumumab studies as reported in daratumumab submission (based on 31.1 months follow -up)** We have used these data to estimate the relationship between median PFS and median OS for daratumumab further. Not all of the data for the two studies is available in order for us to be able to derive a ratio to extrapolate PFS:OS for IsaPd. Table 7 shows the available median PFS and OS from the two trials individually as well as integrated analysis for both studies combined. The cells in yellow are calculated from the reported values assuming the median for the overall is approximately a weighted average of the two trials. **Table 6: Relationship of PFS to OS in the daratumumab studies as reported in Usmani 2020 (based on 36.6 months follow-up) (6)** Values in yellow computed Based on this, it would appear that, for the combined analysis of the two daratumumab trials, the ratio is 20.5 to 4.2 = 4.8. Data from the SIRIUS trial alone, which NICE considered more appropriate for decision making, suggests the ratio is 5.0 (18.6 to 3.7). Therefore, the published evidence suggests ratios of PFS:OS may lie between 1.7 and 5.0. We have included 1.7, 2.9 and 5.0 in our scenarios below. **Exploratory analyses: Simulation of OS data for use in the economic model.** The most straightforward way to predict OS for IsaPd from PFS data is to apply a deceleration factor (DF) to the committee agreed PFS distribution for IsaPd which was the lognormal. It is important to	

	note that we found the best fit extrapolation for the final long-term OS data for daratumumab was also lognormal (see section above) and so it is not unreasonable to project the PFS lognormal fit forwards. We have set the upper and lower bounds for the DF as the daratumumab ratio of 5.0 and the Felix et al. of 1.7, with the Dimopoulos et al. ratio of 2.9 as the most plausible key scenario. These are shown in Figure 5 overleaf plotted as green dashed lines. **Figure 5: Overlays of the extrapolations for deceleration factors 2.9, 4 and 5 along with the exponential fit for IsaPd and the Weibull extrapolation for Pd.** DF 1.7 is not a plausible factor as this extrapolation lies well below the exponential (and even below the original committee preferred IsaPd Weibull in the first 5 years). DF 5.0 is derived from the anti-CD38 daratumumab long term data (and so arguably could be the most appropriate to use from a class perspective) but does not follow the observed KM data and provides a fit which may be overly optimistic. Of the three deceleration factors, DF 2.9 is likely to be the most plausible as it is derived from the literature review of RRMM therapies. A limitation is the lack of anti-CD38 therapies in this analysis making it potentially conservative for the purposes of this appraisal. The fit derived from this validates the exponential distribution (shown in blue) in the first 6 years and estimates the same median OS. However, visual fit to the KM data is less good than the exponential and may provide optimistic outcomes in the later years. Nonetheless, estimates for longer term survival are unknown and the pharmacological properties of the IsaPd triplet suggest that better long-term outcomes may be plausible. We have established above the importance of considering patient response as a prognostic factor for long term outcomes and we know that more than half of the patients in the ICARIA-MM trial at 4L had partial response or better. We have noted that these patients have very little OS data associated with them. This means that the survival curves are likely to be steep at the outset as the patients with less than partial response leave the cohort and to flatten later as patients with better response live longer. The extent to which these responding patients survive is unknown, but it is clinically plausible based on the mechanisms of action of the triplet therapy discussed in the next issue section, that a small minority might live for a considerable period. The ICERs for these decelerated fits are provided in the results section below.	

	Given the shape of the most plausible curve derived from DF2.9 we have also explored an alternative approach in which the best use of all the available data is made. A partially synthetic KM estimator was constructed using observed event times for patients who died and imputed times for those who were censored for OS. Imputed event times were calculated by multiplying PFS times by the deceleration factor (i.e., 2.9). Patients with and imputed OS time who experienced a PFS event are assumed to experience an OS event (i.e., died) at the imputed time while patients with an imputed OS time who were censored on PFS (i.e., no PFS event) are censored at the imputed OS time We justify this on the basis that for censored patients PFS is at least as great as the PFS censored time and so the imputed OS time must be similarly at least as great as 2.9 times the censored PFS time. The partially synthetic KM data are shown below in Figure 6 overlaid with the best fit to these data which was the exponential (followed by the log normal). Full details of the curve fitting exercise are provided in Appendix 4. **Figure 6: Synthesised OS KM data and best fit extrapolation** This new fit to the partially synthetic data is compared to the original company base case exponential curve in Figure 7 overleaf. We have included the Weibull fit to the Pd data for reference. **Figure 7: Comparison of the fits to the partially synthetic and observed KM data.** The fit to the partially synthetic KM data provides a slightly less optimistic view of OS than the exponential (Median $OS_{Syth\ KM}$ = 31.1 months vs. Median OS_{expo} = 33.9 months) but does follow the trajectory very closely. Although simplistic, these analyses have demonstrated that the original company base case extrapolation using the exponential estimator is likely to be valid. The approach using the partially synthetic KM data may be more informative than extrapolations based on only a very small amount of observed OS data. In the section below we present the ICERs for these analyses. **Updated cost effectiveness results for the comparison of IsaPd with Pd at 4L** academic / commercial in confidence information removed **Updated cost effectiveness results and scenario analyses**	

	Having established that the most plausible extrapolation for the Pd arm for the model is the Weibull, we present here three equivalent analyses examining IsaPd extrapolations: the exponential extrapolation for the IsaPd arm; the decelerated PFS:OS IsaPd Lognormal curve and the fitted data to the partially synthetic IsaPd KM data. We provide full sensitivity analyses for these comparisons and also scenarios which include the deceleration factor for the PFS:OS extrapolations. Table 7 overleaf shows the deterministic and probabilistic cost effectiveness estimates using the Weibull extrapolation for Pd OS and the exponential extrapolation for IsaPd OS at academic / commercial in confidence information removed isatuximab PAS discount. Table 8 overleaf presents the same results with academic / commercial in confidence information removed. Scatter plots and CEACs are provided in Appendix 5. All results are reported using list price for pomalidomide. List price for daratumumab is also used. We are unaware of the agreed daratumumab NHSE access price but as a final in-market PAS does not yet exist since it is provided on the CDF, it would be inappropriate to include any further discount to list in the economic modelling. **Table 7: Cost effectiveness results for the Weibull Pd OS and exponential extrapolation for IsaPd OS with academic / commercial in confidence information removed PAS discount** **Table 8: academic / commercial in confidence information removed** Table 9 below presents the analysis using DF 2.9 for the IsaPd PFS:OS extrapolation and provides deterministic and probabilistic cost effectiveness estimates using the Weibull extrapolation for Pd OS at academic / commercial in confidence information removed isatuximab PAS discount. Table 10 overleaf presents the same results with academic / commercial in confidence information removed. Again, in both cases all other drugs are included in the model at their list prices. **Table 9: Cost effectiveness results for the Weibull Pd OS and DF 2.9 to estimate IsaPd OS with academic / commercial in confidence information removed PAS discount** **Table 10: academic / commercial in confidence information removed** Table 11 overleaf presents the analysis using the fitted data to the partially synthetic IsaPd KM and provides deterministic and probabilistic cost effectiveness estimates using the Weibull extrapolation for Pd OS at academic / commercial in confidence information removed isatuximab PAS discount. Table 12 overleaf presents the same results with academic / commercial in confidence information removed Again, in both cases all other drugs are included in the model at their list prices.	

	Table 11: Cost effectiveness results for the Weibull Pd OS and the fitted data to the partially synthetic IsaPd KM with academic / commercial in confidence information removed PAS discount **Table 12: academic / commercial in confidence information removed** Table 13 below presents results for scenarios in which the deceleration factor is varied. Note that all other drugs are included in the model at their list prices. **Table 13: Scenario analysis** **Summary** In this section we have examined the historical data for Pd and concur with committee assumption that the Weibull fit to the Pd KM data is the likely best estimator for long term outcomes with pomalidomide treatment. We have provided further rationale for the choice of the exponential fit to the IsaPd OS data originally used in the company base case and provided alternatives to the direct extrapolation of the OS IsaPd KM data making best use of the available data. In doing so, we have shown that the predictions made by the exponential distribution in the original company model are credible and according to the recently published daratumumab data (6), the exponential could be a conservative estimate. In recognition of the uncertainty inherent in this appraisal we have provided several alternative cost effectiveness results. The deterministic ICERs for these range from £73,934 to £99,038 at academic / commercial in confidence information removed PAS and academic / commercial in confidence information removed. Note that these do not incorporate the PAS prices for any other products which are unknown to us. Sensitivity analyses including CEAC, scatter plots and one-way sensitivity analysis are included in the appendices. These new analyses including the academic / commercial in confidence information removed discount offered should give the committee confidence to recommend isatuximab for inclusion on the CDF. This decision will provide interim access for patients with high need and resolve the remaining uncertainty in the evidence base. In the next section we discuss the clinical plausibility of the better prognosis for patients treated with triplet therapies including an IMiD and an anti-CD38.	

Sanofi	**The immunomodulatory effect of isatuximab in combination with pomalidomide is a critical part of the mode of action for IsaPd and is likely to be reflected in extended OS.** **Isatuximab has multiple modes of action** CD38 is considered a good target for the treatment of multiple myeloma because MM cells overexpress several surface adhesion molecules including CD38. This contrasts strongly with the much lower levels of expression of CD38 on normal cells. Anti-CD38 mAbs including isatuximab have been shown to have broadly three different mechanisms of action (MoA) which are summarised below with particular reference to isatuximab (Table 14). The first two MoAs target MM cells. The third MoA, immunomodulation is also now understood to be an important part of the efficacy shown by the anti-CD38 class. [For examples see: Jain, 2020 (13), Krejcik, 2016 (14), Adams, 2019 (15), Feng 2017 (16)] Table 14: The multiple mechanisms of action for isatuximab **Targeting the body's immune system is a key component of the anti-CD38 MoA** Reducing immunosuppressive cells improves the body's innate ability to fight disease, so alongside the MOAs associated with killing tumour cells directly, it is critical to recognise immunomodulation as part of the mechanistic action of isatuximab in the context of overall survival. Multiple myeloma (MM) cells have a strong relationship with the bone marrow microenvironment which supports their proliferation and survival. In MM changes take place in the bone marrow microenvironment that lead to loss of functional immune surveillance (17). These changes are associated with increasing levels of immunosuppressive cells such as Regulatory T cells (Treg) and B cells. Tregs are the most extensively studied immunosuppressive cell subset in cancer immunology including MM (16). Tregs modulate the response (function and proliferation) of other immune cells. Increased levels of Tregs cause immune dysfunction, allowing the tumour to go unchecked. Elimination of Tregs, "removes the breaks on the immune system" and targets the tumour for elimination. Levels of Tregs often correlate with tumour burden and disease progression in MM. This is because the frequency of Tregs gradually increases in the bone marrow microenvironment with more progressive MM and accumulation of Treg in this tumour microenvironment is associated with reduced survival [(16) and references therein]. These data also suggest that myeloma patients have elevated levels of activated Tregs in comparison to healthy controls suggesting the normal immunosurveillance is dysregulated.	Comments noted. The committee acknowledged that isatuximab has a different mechanism of action and heard from the ERG that is was reasonable to use a different distribution to extrapolate the overall survival data for isatuximab plus pomalidomide and dexamethasone to that used for pomalidomide and dexamethasone and considered this in its decision-making (see FAD sections 3.13 and 3.22). The committee concluded that an increasing relative treatment effect of isatuximab plus pomalidomide and dexamethasone over time is potentially plausible but is highly uncertain because of the immaturity of the ICARIA-MM data (see FAD section 3.22). The committee noted that ICARIA-MM was ongoing, and that further data from this trial could help reduce the clinical uncertainties. The committee concluded that while isatuximab plus pomalidomide and dexamethasone could not be recommended for routine use, it did meet the criteria to be considered for inclusion in

	It has been found that all immunosuppressive cells such as TRegs express high levels of CD38 similar to that found on malignant MM plasma cells and these are targeted by CD38 directed antibodies such as isatuximab (17). Therefore, in targeting CD38, Isatuximab also inhibits the suppressive function of TRegs and other immunosuppressive cells by reducing their numbers, decreasing immune inhibitory cytokine production, and blocking their trafficking. This results in improved anti-tumour immune responses. Thus, CD38-directed antibodies target not only MM-cells but also immunosuppressive cells such as the TRegs. It is also of note that in this way the anti-CD38s inhibit growth and survival factor transfer from bone marrow stromal cells which is also necessary for MM cell proliferation. This has also been similarly reported in association with daratumumab Several reviews have been published very recently highlighting the importance of the immunomodulatory mode of action in MM therapy (17),(18) and several in-vivo and in-vitro studies have examined the phenomenon (14),(15),(16). Very recently a publication examining patients with RRMM treated with the anti-CD38 therapy daratumumab directly assessed Treg levels in this context. The results indicated an association between durable response and immunomodulatory mechanisms. The authors state that immunomodulatory effects obtained by depleting CD38+ Tregs may prove to be more important than any direct effects of daratumumab. Isatuximab has been shown to similarly deplete Tregs and like daratumumab to also further enhance NK− and CD8+ T effector cell-mediated anti-tumour immune responses. This latter point means that use of the anti-CD38 class may restore immune effector cell function as well as depleting immunosuppressive cells (16). **The synergistic effect of IMiDs and anti-CD38 therapies is significant** It is well known that the combination of the immunomodulatory drugs (IMiDs) lenalidomide and pomalidomide with the anti-CD38 therapies has synergistic benefit (19). MM impacts the regulation of multiple cellular compartments of the bone marrow, with plasma cells at the heart of the dysregulation. IMiDs have a wide range of modes of actions which not only include direct targeting of MM cells but influence the dysfunctional bone marrow microenvironment. The combination of an IMiD and an anti-CD38, utilises multiple effector mechanisms which enhance not only plasma cell destruction, but also augments host tumour cell immune response. Existing data also demonstrates that treatment with an IMiD, elevates the levels of CD38 on the activated/induced Treg population, and therefore priming them for directed targeting by anti-CD38 therapies. Hence upregulation of CD38 expression on these cells is likely to provide a deeper immunomodulatory response when IMiDs are used combination with the anti-CD38s for the reasons discussed above. This may be critical for sustained myeloma disease control and improved patient outcomes.	the CDF after 3 previous lines of treatment (including lenalidomide and a proteasome inhibitor) when the company's commercial offer as part of the managed access agreement is used (see section FAD section 3.27)

	In addition, while patients develop resistance against the direct anti-MM effects of IMiDs, several analyses have revealed that their T- and NK-cell activating properties remained largely intact, making IMiDs ideal partners for combination immunotherapies (17). **The immunomodulatory effect is likely to extend beyond treatment duration** As discussed above, very recently the median overall survival for daratumumab monotherapy was published. Median OS in daratumumab treated patients was 20.5 months (95% CI 16.6 to 28.1) (6) and Janssen attribute this at least in part to the immunomodulatory mechanism of action of daratumumab or the inhibition of growth and survival factor transfer from bone marrow stromal cells. We believe that the outcomes for IsaPd treated patients are likely to be much improved over even these impressive results through the contribution from the synergistic immunomodulatory actions of pomalidomide and isatuximab in combination. It is worth reiterating that in the 4L population median PFS for daratumumab treated patients was 3.7 months in the SIRIUS study (20) and median PFS was 13.31 months (7.425; NC) in ICARIA-MM for IsaPd treated patients. A naive comparison of these results suggests the triplet therapeutic option provides significantly more benefit than monotherapy which is likely due in part to the immunomodulatory effects discussed above. In summary, targeting CD38 with Isatuximab induces immunomodulatory effects which both relieve immunosuppression and trigger anti-MM immunity. This helps to restore the pre-existing anti-MM T-cell responses in the bone marrow microenvironment and can be thought of as 'resetting' the immune system. This is likely to provide benefits much beyond the duration of treatment with IsaPd. Given the lack of mature OS data from ICARIA-MM we have discussed above various approaches to the extrapolation of the outcomes data over time including the use of PFS to estimate OS. The weight of the evidence presented suggests that the original company extrapolations for OS using the exponential estimator are plausible and that the new analyses presented above for the PFS:OS relationship are likely to hold true. However, we do recognise the considerable uncertainty in the data at this point in time. For these reasons we are confident that a period in the CDF will provide the clarity needed to validate the expected longer median OS duration and determine the true benefit due to the triplet combination of IsaPd.	
Sanofi	**Subsequent treatments in ICARIA-MM do not reflect NHS clinical practice AND adjusting trial data for subsequent treatments not available in clinical practice is appropriate but more information is needed** Sanofi agree that the subsequent treatments in ICARIA-MM do not reflect UK clinical practise with respect to daratumumab monotherapy and lenalidomide use following 4L treatment. This is not dissimilar to other trials in this line of treatment (1). Clinical experts, on the day of the AC meeting, noted that there were no standard 5th line treatments and treatments at this point in the pathway would	Comment noted. The committee acknowledged that the subsequent treatments given in ICARIA-MM, in particular lenalidomide and daratumumab, did not reflect NHS clinical practice (see section 3.9). The committee

	likely be ineffective. The experts also stated that the subsequent therapies in ICARIA-MM were unlikely to affect the survival results in the 4L population. Therefore, we believe the base case which includes costs and benefits for subsequent therapies without adjustment can be considered appropriate from a cost-effectiveness perspective. To address the impact of subsequent therapies we did perform an analysis using the approach of applying HR from Cox model in the IPCW to the Pd arm (21). It is our understanding that the committee accepted this analysis but would like to see the co-variates used and the range of weights estimated. These have now been provided as a confidential reference (22). We also noted the committee's preference to see approach where individual patient data (IPD) are reconstructed from the weighted panel data set and parametric curve fitted to both arms of the trial. The reconstructed KM OS curves reported in Appendix 6. Using this method produced counter-intuitive results. The OS curve with censoring on receipt of daratumumab and lenalidomide and with IPCW adjustment are slightly higher for both groups compared with the uncensored unadjusted estimates. As the IPCW curves are supposed to reflect the counterfactual wherein patients would not have received daratumumab or lenalidomide, one would expect these censored and adjusted curves to be lower than the uncensored unadjusted curves if lenalidomide and daratumumab have a beneficial impact on OS. These results highlight the lack of robustness of the results given the small number of patients in this analysis (70% - 80% censored patients and results based on 10 to 16 patients) and likely to be biased by unmeasured factors that are associated with receipt of daratumumab or lenalidomide and survival. It may also support the view expressed by clinicians, that adjustment for subsequent therapies make no valid difference to overall survival following 4L treatment. Given the lack of clinical face validity of this approach, it was not considered feasible to implement in the model.	preferred to adjust both the survival data and costs associated with these treatments, but the company did not provide the requested analysis (see FAD section 3.16). The committee heard from the clinical experts that treatments given at this point in the treatment pathway (after 4 or more previous lines of treatment) would likely be ineffective (see FAD section 3.9). The committee concluded that without the appropriate and fully reported adjustment analyses, it was reasonable to remove the costs of lenalidomide and daratumumab from the analysis, particularly because clinical experts suggested that treatments received at fifth line or later would be likely to have minimal effects on survival (see FAD section 3.17).
Sanofi	**The committee state that no analyses reflect their preferred assumptions** The committee concluded that none of the company's or the ERG's analyses reflected the committee's preferences. The committee would have preferred to see analyses that fulfilled the following 4 requirements shown in Table 15. In order to satisfy the request, we have carried out this analysis and have provided comments on technical aspects below in Table 15. **Table 14: Committee preferred assumptions** The results are presented below in Table 16 and Table 17. As above, these ICERs are based on the list prices for the comparator treatments.	Comments noted. At the second meeting, the committee considered that an increasing relative treatment effect of isatuximab plus pomalidomide and dexamethasone over time is potentially plausible, but highly uncertain because of the immaturity of the clinical data

	It is informative to place this committee preferred scenario in the context of the previous discussion. In particular, with respect to the much more mature data from the daratumumab studies. The survival curves for the truncated Weibull with waning at 3 years (blue line), the Weibull (green line) and the company preferred exponential (purple line) are shown in Figure 8 overleaf. In the committee preferred analysis only ~1% of patients remain alive in the IsaPd arm at 6.5 years and none by 7.5 years which is equivalent to the 7.5-year outcome for the Weibull estimation. Inspection of Figure 8 reveals that with **no waning** applied to the Weibull curve (Green fit) there are less than 2% of patients alive at 10 years. We have discussed at length the likely impact of the pharmacological properties of the IsaPd triplet on long term outcomes and have noted the difference in observed daratumumab monotherapy PFS at 4.1 months vs. the observed IsaPd median PFS at 13.3 months. We have shown in the daratumumab landmark analysis above (Table 3) that with the most plausible fitting curve ~11% of patients are alive at 10 years. This suggests to us that incorporating waning in this analysis is not appropriate. We have also discussed in the previous section how long-term outcomes for patients may be strongly correlated with response to therapy and how those patients with partial response or better are likely to survive for longer. This means that any waning effect is likely to be already incorporated into the most plausible estimates for survival that we have put forward. The exponential curve predicts 10 year survival at 8.6% which, considered in the light of the arguments above may be conservative because it falls under the most plausible daratumumab landmark at 10 years (Table 3). This further validates our extrapolation choices. Whilst we do not know the PAS price for pomalidomide, under the committee preferred assumptions we believe it is likely that isatuximab **would not be cost effective even at £0 price**. (When no discount is included for pomalidomide in the model the required discount to achieve an ICER of £50,000 is academic / commercial in confidence information removed. This is a perverse finding given the clear clinical benefit demonstrated by IsaPd over existing treatments and recognised unmet need at 4L.	from ICARIA-MM (see FAD section 3.22).

Sanofi	**We urge the AC to consider the context of this appraisal. The current system (including the NICE process and methods) is not sufficiently flexible to cope with the assessment of branded combination treatments and therefore does not sufficiently recognise their value** The clinical paradigm for oncology is changing rapidly as diseases are increasingly well understood and combinations of older drugs (which in most cases are not generic) with newer, more effective agents are becoming ubiquitous. Using drugs that work by different mechanisms in combination has been shown many times improve the probability and magnitude of therapeutic response and reduce drug resistance. As such, isatuximab in combination with pomalidomide and dexamethasone has demonstrated significant clinical benefits through a randomised comparative phase 3 trial in the difficult-to-treat patient group with lenalidomide and proteasome inhibitor refractory (double refractory) disease. Despite the very promising clinical evidence, the cost-effective price of isatuximab is significantly constrained by the confidential discounted price for the combination partner pomalidomide. The pomalidomide PAS is unknown to us but resulted in a recommendation from NICE very close to the WTP for EoL drugs. We have shown above that under the committee's preferred assumptions, isatuximab would not be cost-effective even if priced at £0 (academic / commercial in confidence information removed). Under the reimbursement system in the UK that does not disaggregate value, it is difficult to demonstrate the cost-benefit of combination treatments generally and specifically for IsaPd at 4L with no knowledge of the comparator price nor flexibility in the threshold. This issue has been widely discussed but no solutions currently exist (23). In this appraisal, the ICER is driven by (1) costs of using pomalidomide, a high cost drug, in combination with isatuximab and (2) additional PFS (5.5 months) incurring the costs of both isatuximab and pomalidomide. With no knowledge of the pomalidomide discount we nonetheless believe that we have provided a persuasive case that IsaPd can be cost-effective. However, under the NICE preferred Weibull assumptions for overall survival, isatuximab cannot meet the NICE threshold for cost-effectiveness. Pomalidomide, has already been accepted by NICE as a cost-effective treatment, therefore the additional costs arising from its prolonged use as a background therapy could theoretically be removed. This approach has been discussed in the NICE DSU review and used in other HTA	The committee did not consider it to be appropriate to remove pomalidomide costs from the isatuximab plus pomalidomide and dexamethasone arm. This was because the NICE methods guide states that all relevant costs should be included in analysis (see FAD section 3.21)

	submissions (23),(24). Indeed, committees have requested alternative analyses that explore the removal of backbone costs (24),(25). This can be done in two ways. Approach 1 is by removing the costs of Pd on the IsaPd arm for the period of time which is common to both IsaPd and Pd (Approach 1, Figure 9). The idea here is that for the period of time that Pd would be used in combination with isatuximab, only the incremental cost of isatuximab should be included in the costs. The resulting ICER of academic / commercial in confidence information removed demonstrates just how much the additional pomalidomide use is driving the cost-effectiveness of IsaPd (Table 18). Another approach is by removing the additional Pd costs in the IsaPd arm (Approach 2, Figure 9). This ICER seems appropriate and provides useful insight for the overall assessment of the cost-effectiveness of isatuximab. Removing these costs reduces the base case ICER from academic / commercial in confidence information removed at the list price for pomalidomide (Table 18) Even in the face of this substantial challenge, the analyses presented within the earlier sections of our response demonstrate that, at the academic / commercial in confidence information removed discount offered by Sanofi, it is plausible that IsaPd could be considered cost-effective (under credible assumptions) despite being assessed within a framework that does not work for and penalises branded combinations. **Sanofi are committed to working with the ABPI, NHSE and NICE to seek a solution to this issue to ensure that this does not result in patients being denied access to valuable treatments in the future but would emphasise that there is an unmet need for isatuximab now and that these patients cannot wait for a permanent solution to be developed.**	
Sanofi	**The committee have concluded that Isatuximab plus pomalidomide and dexamethasone does not meet the Cancer Drug Fund (CDF) criteria** According to the criteria for a positive recommendation via CDF, there must be plausible potential for IsaPd to satisfy the criteria for routine commissioning, but significant clinical uncertainty remaining which needs more investigation. This might be through data collection in NHS clinical practice or continuing company sponsored clinical studies. In this appraisal the clinical uncertainty, the plausible extrapolation for long term overall survival and the confidential price of pomalidomide are key determinants for whether the IsaPd combination can be plausibly cost-effective for the NHS.	The committee noted that ICARIA-MM was ongoing, and that further data from this trial could help reduce the clinical uncertainties. The committee concluded that while isatuximab plus pomalidomide and dexamethasone could not be recommended for routine use, it did meet the criteria to be considered for inclusion in

	The current uncertainty regarding long term survival is undeniable and we are pleased that the appraisal committee has accepted that this is due to the large proportion of patients still alive at the 2018 data cut. However, there were some concerns raised which we address below. **Insufficient time for data to be collected via CDF on overall survival, time on treatment and subsequent therapies in practice** • ICARIA-MM study will provide further data to reduce uncertainty and validate extrapolations for long term survival The outcomes presented in this appraisal are based on a data cut from almost 2 years ago (October 2018). Given the high level of censoring at this cut off it is clear that there is significant need for further time to allow more mature data to become available from the trial. The original power calculations for the study suggested that 220 deaths would be needed to achieve 79.3% power in the ITT population. An interim data cut is planned after ~90% of these 220 deaths have been recorded. This is predicted to occur in early academic / commercial in confidence information removed, providing a further 2 years of outcomes data. The results from this interim analysis are expected to become available in academic / commercial in confidence information removed. The final OS analysis with ~220 events is again event-driven and is anticipated between academic / commercial in confidence information removed. Once these final OS data are recorded, which will provide almost academic / commercial in confidence information removed more data than currently available, the trial data will be sufficiently powered to enable the extrapolations for IsaPd and Pd to be calculated more robustly at both 3L and 4L. (It is worth noting that clear separation of the 4L OS KM data is evident almost from the outset providing a clue as to the potential benefit of IsaPd vs. SoC). Until this time, it is difficult to determine with certainty what the most appropriate extrapolations for the OS data are but with the current building evidence base for next generation and triplet combination therapies it is highly likely that the Weibull estimator offers extremely conservative view of long term outcomes for IsaPd at 4L or at 3L. We have provided arguments to support this view above. Evidence for 3L outcomes will also be more mature and can be used to inform comparison, particularly vs Pd. The case for the 3L positioning is made in a following section. Other CDF agreements at 4L in RRMM have demonstrated that the Public Health England/NHSE databases can inform uncertainties in overall survival and subsequent therapies (1). Table 19 details how uncertainties in the current IsaPd evidence base can be addressed with further evidence collection in the CDF and when this data may become available.	the CDF after 3 previous lines of treatment (including lenalidomide and a proteasome inhibitor) when the company's commercial offer as part of the managed access agreement is used (see section FAD section 3.27) The committee concluded that it is not appropriate to use isatuximab plus pomalidomide and dexamethasone when disease is refractory to a previous anti-CD38 monoclonal antibody (see FAD section 3.8)

Table 15: Areas of uncertainty for IsaPd and how these can be addressed via the CDF

Insufficient patients available at 4L to inform data collection due to 2nd line (2L) use of daratumumab via the CDF

It is important to note that **daratumumab is not a relevant comparator due to its position on the CDF at both 2L and 4L** so should not feature in the decision-making process during this appraisal. The following information is provided to show that in real world clinical practice the proposed place in therapy for IsaPd remains an area of unmet need for patients entering 4L naïve to anti-CD38 treatment today and will do so for several years to come.

There will be sufficient patients eligible for IsaPd at 4L over the CDF period allowing adequate data collection to be performed from both the ICARIA-MM final OS cut and NHSE/PHE databases:

- Daratumumab with bortezomib and dexamethasone (DVd) has been recommended via CDF in April 2019. While uptake of this combination is increasing at 2L, based on the estimated progression-free survival on DVd (26 months), the length of time between 2L and 3L (5 months (26)) and the anticipated time on 3L treatment before progressing to 4L (e.g. PFS on PanVd is 7.8 months [TA380](3)), we estimate that it would take at least 3 years for the patients receiving DVd to reach 4L. This is likely to be beyond the lifetime of the CDF duration for IsaPd.
- Patients presently receiving treatment at 3L, or who were not eligible for DVd at 2L, will progress to 4L and be eligible for IsaPd. academic / commercial in confidence information removed,. The rapid uptake in the EAMS programme suggests that even with daratumumab monotherapy available at 4L, there remains a place for IsaPd which clinicians tell us may be the preferred choice as an anti-CD38 triplet therapy over monotherapy due to likely improved outcomes. It is also expected that IsaPd will displace Pd at 4L were it to be recommended.
- Finally, the NICE position paper states that **treatments in the CDF are not relevant to the decision problem as long term reimbursement decisions and in-market price are unknown therefore the impact on eligible patient numbers due to treatment funded via CDF earlier in the treatment pathway should not influence decision making at 4L** (27).
- Whilst the patient pool eligible for an anti-CD38 at 4L will undoubtably dwindle, at the end of the CDF period there will still be an unmet need and some patients will require IsaPd

	treatment. These may be people treated with a prior anti-CD38 who have not become refractory or patients who are naïve to anti-CD38. It is true that at the time of isatuximab exit from the CDF, the treatment landscape is likely to have evolved with newly recommended treatments (such as lenalidomide at 1st/2nd line) becoming more embedded in clinical practice, routine commissioning for DVd at 2L may be available, and the pomalidomide price may have also changed if the elotuzumab appraisal is re-started (ID1467) or a generic is launched. Pd may move to 3rd line position. Nonetheless there is **demonstrable unmet need today at 4L** and we are concerned that these patients with poor prognosis and very limited life expectancy may be denied access to a life-extending drug on the basis of speculation around changes to a pathway that are irrelevant to them. **Conclusion** The analyses provided in this response indicate that IsaPd could be considered plausibly cost-effective. We acknowledge these analyses are currently very uncertain but data being collected and that could be collected during a potential MAA, could be used to validate the overall survival extrapolations (the key driver of uncertainty) presented within this response, dramatically reducing the existing level of uncertainty. **Sanofi therefore suggest that IsaPd is an ideal candidate for the CDF.**	
Sanofi	**Sanofi recognises that there is an emerging unmet need for new effective third line (3L) treatment options, after 2 previous treatments.** Recognising the committee request for further discussion and analysis to address the emerging gap in the treatment pathway at 3L we provide an exploration of the 3L position for IsaPd below. AT the outset it is important to note that whilst DVd is in the pathway at 2L, it is provided on the CDF and so should not feature in the decision making for this appraisal. It is discussed below in terms of the pathway and how it may affect patient flow in the future. Our base case population was fourth line (4L) patients who have received 3 prior lines of therapy. This is where clinicians have told us the current unmet need is. The rapid uptake of patients into the Early Access Medicines Scheme (EAMS) at 4L (academic / commercial in confidence information removed in 5 months), reinforces the high unmet at 4L need despite the recent availability of daratumumab via the CDF at 2L. Recent market research by IQVIA show that lenalidomide-based regimens are still the	The committee concluded that there is unmet need for new effective treatment options for people who have had 2 previous lines of treatment (see FAD section 3.4). The committee concluded at its first meeting that it would focus its discussion on people who have had 3 previous lines of treatment. The committee heard from clinical experts that currently many clinicians use lenalidomide after 2 previous lines of treatment, with ixazomib and dexamethasone

	predominant treatments at 3L (March/April 2020) either routinely commissioned or via the CDF in combination with ixazomib (approximately 65%) and that daratumumab in combination with bortezomib and dexamethasone (DVd) is increasingly being used at 2L via the CDF (most up to date estimate is 27%) (Figure 10) (28). We acknowledge that the treatment paradigm is changing with the recent approval of lenalidomide earlier in the pathway (untreated multiple myeloma and after 1 previous treatment) and it is likely that there will be increasing numbers of patients at 3L who have had prior lenalidomide exposure. This can be seen by the market research data above. Currently the main outcomes at 2L are as follows: Median progression-free survival (PFS) for lenalidomide plus dexamethasone (Rd) at 2L is estimated to be 48.1 weeks (95% CI: 36.4, 62.1) (29). DVd at 2L provides a median PFS of 26 months compared with bortezomib plus dexamethasone alone at 8 months (hazard ratio [HR] 0.23, 95% confidence interval [CI] 0.16 to 0.33; p<0.0001) (30). Based on these clinical outcomes, we expect DVd to remain one of the main treatments of choice at 2L with Rd used in those patients for whom DVd is not an option. Therefore, recognising currently there may be some patients at 3L who would be eligible for IsaPd we did submit evidence comparing IsaPd to Pd in patients with 2 prior lines (i.e. 3L patients) in our original dossier. This analysis was derived from outcomes for patients from ICARIA-MM who had received two prior lines of therapy. The 3L cohort in ICARIA-MM is smaller than the 4L cohort (N=90 vs N=110), and although the current data are extremely immature for overall survival (Figure 11) clear separation of the curves is observed for progression-free survival.(Figure 12). In response to the request by the appraisal committee, we have conducted a cost-effectiveness analysis versus PanVd at 3L and this is reported here. The cost-effectiveness is based on a matched-adjusted indirect comparison (MAIC) reported in an Appendix 7. (Originally reported in Appendix K to the company submission). As PANORAMA-2 does not report outcomes by line, the MAIC has been performed using the ITT population of ICARIA. Below are the MAIC-adjusted KM curves for PFS and OS for IsaPd (Figure 13 and Figure 14). Estimates of PFS and OS for PanVd were obtained by applying the MAIC-adjusted HR for PanVd vs. IsaPd to the unweighted 3L PFS and OS for IsaPd. The application of these MAIC-adjusted HRs in this fashion was considered reasonable as tests of the linearity of Schoenfeld residuals for the comparison was not statistically significant. HRs derived using the results of the ITC of trials for treatments for PanVd are shown in Table 20 below.	in the CDF or with dexamethasone. The clinical experts agreed that the company's positioning after 3 previous lines of treatment was appropriate (see FAD section 3.3). The committee concluded at the second meeting that the cost-effectiveness analysis after 2 previous lines of treatment is not robust enough for decision making (see FAD section 3.24)

	Based on the MAIC, IsaPd has more favourable PFS than PanVd, with a HR that is greater than 1.0 (based on the 95% CI) and is statistically significant for PanVd versus IsaPd. While the HR for OS also numerically favours IsaPd, it is not statistically different from PanVd (based on the 95% CIs). **Updated cost effectiveness results for the comparison of IsaPd with Pd at 3L** academic / commercial in confidence information removed **Results for the updated base case and scenario analyses** Below we present the results for the exponential distributions for the IsaPd arm for PanVd based on best statistical fit for IsaPd arm. Given the immaturity of the 3L data and the limitation of cost-effectiveness based on a less-than-robust MAIC vs PanVd these analyses should be considered exploratory. Table 21 below shows the deterministic cost effectiveness estimates using the exponential extrapolation for IsaPd OS at academic / commercial in confidence information removed PAS discount. The cost effectiveness estimates calculated at 3L are heavily dependent on the estimates for OS which were also derived from the trial data. As the data is so immature and the patients treated in this earlier setting are likely to have a longer prognosis for OS there so there is unsurprisingly little separation of the observed OS data for the two arms. This leads to high estimates for the IsaPd vs. Pd ICER at 3L. Table 22 overleaf presents the same results with academic / commercial in confidence information removed. All results are provided in an Appendix. All results are reported using list price for all other treatments. The ICERs presented here therefore not the true ICERs which will be lower depending on the level of discount on pomalidomide. The deterministic cost effectiveness estimates derived from this analysis are presented below (Table 21). These are based on exponential distribution for all time-to-event inputs based on best fitting curves (lowest BIC). Although we have endeavoured to provide the most robust analysis possible there are a significant number of limitations in making this comparison versus PanVd, as were noted for the equivalent 4L comparison provided in Appendix K.4 of the company submission. The most relevant being that PANORAMA-2 does not report outcomes by line of treatment and that MAIC-adjusted HR for PanVd	

	vs. IsaPd using ITT data are applied to unweighted 3L PFS and OS for IsaPd. This means that the results from these 3L analyses should be interpreted with caution. We have previously provided analyses versus Pd as we maintain that PanVd is not a valid comparator at 3L or at 4L. The clinical experts consulted by us and present at the NICE committee meeting have stated that PanVd is used 5L and that very few patients would get PanVd at 3L. This is validated by the market research we have carried out and that was presented in the company submission dossier. No treatments evaluated by NICE at 3L or 4L have included PanVd as a valid comparator. End of life (EoL) has been accepted at 4L by the committee. We also believe that the EoL criteria might apply at 3L. Although the survival data are very immature at 3L, the analysis above using the PFS data to predict OS shows that it is likely that IsaPd will offer an extension to life of more than 3 months (estimated LYG= 3.6). As the treatment pathway for RRMM evolves with more effective treatments being used earlier in the pathway, it is likely that the survival observed at 3L may look more like the survival currently associated with 4L. In the literature, the term 'double refractory' usually refers to a patient that has progressed on or within 60 days of receiving both a proteasome inhibitor and an immunomodulatory drug (including lenalidomide). Clinical outcomes for this group of patients have been historically poor, with a median overall survival of between 9-13 months (31),(32). Until recently, the first point at which a patient could receive lenalidomide in the UK was at 3L, meaning that most patients meeting the definition of double refractory in the UK were actually 4L patients. In moving lenalidomide earlier in the pathway, to 1L (transplant ineligible) or 2L, a patient could be now be considered 'double refractory' at 3L if they had progressed on or within 60 days following a PI and an IMiD. It is difficult to estimate the clinical outcomes for this group of patients in the UK as the change to the pathway is so recent. However, the ICARIA-MM control arm (Pd) represents a group of 3L patients who have failed both a PI and lenalidomide. The refractory rate to lenalidomide in the Pd arm was 92% and double refractory rate was 70% (33). The OS data for the ICARIA-MM 3L Pd arm is immature, but it reasonable to assume based on the curves it may not extend beyond 2 years. In addition, ELOQUENT-3, a randomised phase 2 study, looked at elotuzumab in combination with Pd in patients who had received ≥2 lines of therapy including lenalidomide and a PI. The control arm in this trial (Pd) showed a lenalidomide refractory rate of 82% and double refractory rate at 72%. The Pd OS in this trial was 17.4 months (34).	

	This group of 'double refractory' patients at 3L are particularly relevant to this discussion as on the whole, they are CD38 naïve and could benefit from an anti-CD38 therapy especially in combination with an IMiD, such as IsaPd. In moving lenalidomide to earlier lines of therapy, patients receive this clinical benefit earlier in the pathway and efficacious novel combination therapies are needed following relapse to both a PI and lenalidomide. It is reasonable to assume that patients who are double refractory at 3L receiving standard of care therapies would have a survival of less than 2 years and would benefit from a CD38 therapy and particularly in combination. We accept that whether 3L treatment meets the end of life criteria is uncertain, but we believe this it is plausible for some patients and that this uncertainty could be addressed by further data collection were IsaPd to be recommended for use on the CDF. **IsaPd has the potential to be a highly effective option at 3L however we acknowledge that the currently available data are very immature and current cost-effectiveness analyses are extremely uncertain. As the ICARIA data matures the true potential for IsaPd at 3L will be revealed.**	
Sanofi	**The committee believe that the model adequately captures the benefits of IsaPd and so it is not innovative.** In our original submission we stated that IsaPd represents a step-change in the management of double-refractory patients who have received 3 prior lines of treatment, including lenalidomide. However, the committee concluded that it had not been presented with any evidence of additional benefits from treatment with IsaPd. We agree that the model captured all of the health-related quality of life benefit observed in the ICARIA-MM study but do not agree that further benefits from treatment with IsaPd would not be realised in real world clinical practice. These may not be captured in the QALY but are nonetheless of critical importance to patients. The ACD recognises the psychological impact for patients approaching the end of the treatment pathway, where further treatment options are limited. We heard in committee the value that myeloma patients place on hope for new treatment even at later lines of therapy and that this is critical for mental wellbeing of not only the patient but also their family and friends. Patients do not want to feel abandoned at the end of lives when there is the potential for a new treatment option. Literature precedent exists to demonstrate this element of value in cancer therapies. It has been found from a willingness to pay exercise that cancer patients have a strong preference for the 'hopeful gamble' of a larger survival gain over the 'safe bet' with a narrower 'spread' of outcomes (35). This was echoed in committee when the patient expert explained that patients value treatments that delay the disease	The committee acknowledged that there is an unmet need at fourth line and understood that there is a psychological impact for patients approaching the end of the treatment pathway. It understood that patients and clinicians' value more treatments choices at this part of the pathway and that caregivers are also impacted by the condition (see FAD section 3.1). The committee concluded that the model adequately captured all health-related quality-of-life benefits of isatuximab plus pomalidomide and dexamethasone and that is had not been presented with any evidence of additional

	progressing, which outweighs the negative impact of their side effects. From the patient perspective it is clear that providing the care that they themselves value should be an important part of the allocative decision and so the element of hope should be particularly taken into account during the decision-making process for this appraisal. Most of the care for patients with MM is episodic and provided in the outpatient setting. This means that caregivers are essential for the optimal outcomes of patients with MM as the disease progresses. Therefore, caregivers face similar challenges to those faced by the patient. They are required to take in complex information, perform often complicated or technical procedures such as line care or injections, assist the patient with activities of daily living, and attend multiple appointments. Along with the emotional distress of living with or knowing a loved one suffering from an incurable disease, all of these additional process elements can contribute to reductions in the health-related quality of life of carers. Unexpected changes to plans of care based on patient progression are not uncommon and this also adds stress for patient and carer alike and significantly impact carers. (36) Moreover, unexpected changes to plans of care based on patient progression are not uncommon in RRMM and this also adds stress for patient and carer (36). The impact of hope for patients with RRMM has been discussed above and in this context, carers face a difficult and conflicting challenge. They must prepare for the possibility of death for their loved one whilst needing to reinforce an atmosphere of hope in order to help the patient manage day to day tasks of living with MM. All of these complex and interacting elements contribute to reductions in the QoL of carers (36). It is worth noting that RRMM is a disease of later life and so very often partners of patients assuming a caregiving role are older people, potentially coping with the health issues associated with later life themselves. The NICE DSU document on modelling carer health-related quality of life in NICE technology appraisals notes that there have been several instances where committees have considered the impact on carer related QoL and so precedent exists (37). Whilst the level of distress of caregivers is not routinely screened for and is therefore difficult to quantify in RRMM, for the purposes of this appraisal it should be a significant part of the deliberative decision-making process. Finally, it is critical to recognise that the triplet IsaPd combination was granted positive innovative medicine (PIM) status by the MHRA and became available through EAMS in December 2019. The scheme ran until marketing authorisation in early June 2020. [For details see: https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-isatuximab-in-combination-with-pomalidomide-and-dexamethasone-for-adult-patients. Accessed 23/06/2020].	benefits from treatment with isatuximab plus pomalidomide and dexamethasone (see FAD section 3.28)

	The early access to medicines scheme (EAMS) aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. In doing so it recognises that the medicine provides significant new innovation in a setting where there is a lack of effective treatments. Isatuximab is the first triplet myeloma therapy to have been granted EAMS status and at closure of the scheme academic / commercial in confidence information removed patients had enrolled. This is despite the disruption due to COVID-19. The fact that there remained steady uptake during this time indicates the strong clinical and patient appetite for this treatment. Finally, we are concerned that despite the high unmet need demonstrated through EAMS, the strong clinical data from ICARIA-MM and the clear patient preference for life extending medicines at the end of life that people with RRMM will be denied access to a highly effective, life extending medicine because there isn't an innovative process to assess branded combinations.	
Myeloma UK	**Significant clinical benefit** As stated in our appraisal submission, a study conducted jointly by Myeloma UK, the EMA and the University of Groningen showed that, achieving a lasting remission from treatment was the most important factor for most (three quarters of all) participants. The ICARIA trial demonstrated a significant PFS advantage (11.5 months vs 6.5) months and a much higher response rate (31.8% vs 8.5% for very good partial response.) In addition, this triplet combination which includes a monoclonal antibody and immunomodulatory agent, is the first time that such a combination would be available in the treatment pathway. Given the heterogenous nature of myeloma, delivering access to treatments with different mechanisms of action is vital. This combination would deliver a totally new treatment opportunity to patients at fourth line.	Comments noted. The committee acknowledged that isatuximab plus pomalidomide and dexamethasone was likely to extend progression-free and overall survival compared with pomalidomide plus dexamethasone after 3 previous lines of treatment, but noted that median follow up was short, the subgroup was small and the data were immature (see FAD section 3.7)
Myeloma UK	**Unmet need and anti-CD38 therapies** Although there are approved treatment options for patients at fourth line, there is still significant unmet need for this patient population who do not have access to a novel triplet combination.	The committee recalled that clinical experts explained that using an anti-CD38 antibody treatment again later in the treatment pathway would be appropriate if it had been

	A 2016 study[1] showed that around 15% of patients progress to fourth line. Given the treatment advances that have been made and are now available in the treatment pathway it is reasonable to conclude that this figure will now be higher. The Committee discussed the impact of introducing isatuximab into the treatment pathway following the combination of daratumumab, velcade and dexamethasone (DVD) which is currently approved at second line via the Cancer Drugs Fund (CDF). In our response to the technical engagement report we agreed with clinical advice that, in the absence of data from the ICARIA or other trials, patients refractory to daratumumab should not receive isatuximab at fourth line. However, in line with ICARIA inclusion criteria, it should be available to patients who had been exposed to daratumumab but who are not refractory. The Cancer Drugs Fund clinical lead expressed concern that the amount of data that could be collected through the CDF would be limited due to the number of patients who would be refractory to daratumumab at second line. We believe that it is too early in the use of DVD at second line to reach conclusions about the numbers of patients who will reach fourth line refractory to anti-CD38 therapy. Velcade is well known to be challenging as a long term treatment option due to the incidence of peripheral neuropathy and could result in many patients being unable to complete a course of DVD to progression. In addition, DVD is approved through the CDF and, in line with NICE guidance, it cannot be assumed that it will be routinely commissioned. We therefore argue that there is no clear evidence that numbers of patients at fourth line who are still responsive to anti-CD38 therapy will be too low to make CDF data collection viable. As the Committee acknowledges, the myeloma treatment pathway is rapidly evolving and issues around treatment sequencing are increasingly challenging. We agree with the CDF clinical lead that it is not the role of the CDF to be a proxy for clinical trials which should be undertaken by industry. However, we also argue that the increasing difficulty in predicting with confidence how future HTA decisions will impact the pathway means there is a strong case for flexibility in decision making.	stopped for reasons other than disease progression. The clinical experts also stated that they would not use an anti-CD38 antibody again if the disease had been refractory to one in a previous line of treatment. The committee concluded that it is not appropriate to use isatuximab plus pomalidomide and dexamethasone when disease is refractory to a previous anti-CD38 monoclonal antibody (see FAD section 3.8).
Myeloma UK	**Overall survival and the CDF** We appreciate that having data on overall survival (OS) is vital to understanding a treatment's real value. However, advances in myeloma treatment mean that it is increasingly challenging to produce	The committee noted that ICARIA-MM was ongoing, and that further data from this trial could help reduce the clinical

	OS data within the timelines of a clinical trial, and ensure that patients are not missing out on the most promising new treatments. Clearly the CDF is the key policy mechanism for delivering access to treatments in this category. We are therefore obviously disappointed that, as it stands, the Committee does not consider that isatuximab, pomalidomide and dexamethasone has plausible potential to be cost effective at the current price. There is very clear evidence that this treatment is significantly better than the standard comparator (and good reason given what we know about the efficacy of MAB/IMid combinations that it would also deliver benefit compared to CDF funded daratumumab monotherapy). Myeloma patients at fourth line face a significant disease and psychological burden. In the face of this, it would be hugely disappointing if an effective new treatment which is clearly superior to existing treatment options was not approved. We therefore hope that all avenues will be explored by the company, NICE and NHS England to enable a positive recommendation via the CDF.	uncertainties. The committee concluded that while isatuximab plus pomalidomide and dexamethasone could not be recommended for routine use, it did meet the criteria to be considered for inclusion in the CDF after 3 previous lines of treatment (including lenalidomide and a proteasome inhibitor) when the company's commercial offer as part of the managed access agreement is used (see section FAD section 3.27)
UK Myeloma Forum	**Has all of the relevant evidence been taken into account?** There is clearly an unmet clinical need for patients with RRMM. This condition remains incurable and there are a dwindling number of patients alive beyond 4th line. It is therefore important to give the best therapies available early in the pathway to give the most benefit. There is clearly a survival benefit with the addition of isatuximab to PomDex. This improved PFS is matched by favorable quality of life and toxicity data. This is important for patients who often have significant co-morbid issues related to multiple myeloma such as bone disease and renal problems, and the effect of toxicities of prior treatment (such as neuropathy).	Comments noted. The committee acknowledged that isatuximab plus pomalidomide and dexamethasone was likely to extend progression-free and overall survival compared with pomalidomide plus dexamethasone after 3 previous lines of treatment, but noted that median follow up was short, the subgroup was small and the data were immature (see FAD section 3.7) The committee recommended isatuximab plus pomalidomide and dexamethasone for use

		within the Cancer Drugs Fund as an option for treating relapsed and refractory multiple myeloma in adults who have had lenalidomide and a proteasome inhibitor and whose disease has progressed on their last treatment, only if they have had 3 previous lines of treatment and the conditions in the managed access agreement for isatuximab plus pomalidomide and dexamethasone are followed.
UK Myeloma Forum	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Using the best treatment at 4th line that is available to patients. In current practice patients will receive daratumumab 4th line (CDF) and PomDex at 5th line. We know that it is best to combine the anti-CD38 monoclonal antibodies with an immunomodulatory drug (IMID). Rather than separating these therapies at 4th and 5th line it will have most benefit when we combine our most potent IMID with an anti-CD38 monoclonal antibody at 4th line. Given that there will be a limited number of patients able to receive treatment at 5th line they are being disadvantaged by not receiving the most appropriate combination at 4th line.	Comments noted. The committee concluded that the appropriate comparator was pomalidomide and dexamethasone after 3 previous lines of treatment (see section 3.5). The NICE position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product states that treatments that have been recommended by NICE for use in the Cancer Drugs Fund cannot be considered established practice. Therefore, products recommended for use in the Cancer Drugs Fund after

		1 April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals.
UK Myeloma Forum	**Are the recommendations sound and a suitable basis for guidance to the NHS?** Using the technology at 3rd line. The committee accepted that IsaPD is appropriately compared to PomDex at 4th line, however it raised concern about whether it should be considered as a 3rd line. We recognize the attempt of the committee to horizon scan and identify the up and coming unmet need which is 3rd line, currently for patients to receive IsaPD they need to have received lenalidomide beforehand. This technology naturally fits into 4th line at the moment but appreciate that with the increasing use of lenalidomide in 1st and 2nd line this is a diminishing population. The exception being those on the transplant-eligible pathway. As such, the vagrancies of the myeloma pathway, whilst challenging, are not dealt with by this appraisal outcome currently. This results in lack of equity of access if patients receiving treatment currently can not receive this technology at 4th line given its clear benefit over PomDex. Applicability for use in the Cancer Drugs Fund. One of the reasons stated for not meeting the Cancer Drug Fund criteria is that most patients will have received an anti-CD38 monoclonal antibody before they get to 4th line. Whilst there will be a large number of patients who will receive daratumumab at 2nd line (in combination with bortezomib and dexamethasone, DVd; CDF), there are a proportion of patients who will not receive daratumumab at second line (CDF) due to early progression on bortezomib given as initial therapy or who developed significant neurotoxicity and so can't receive this combination at 2nd line. In addition, DVd was only available on the CDF in 2019. There is therefore a large number of patients who have never received an anti-CD38 monoclonal antibody before 4th line. They would gain clear clinical benefit from receiving IsaPD and though they are a group of diminishing numbers over coming years they still exist and should not be ignored.	The committee acknowledged that there is an unmet need at fourth line and understood that there is a psychological impact for patients approaching the end of the treatment pathway. It understood that patients and clinicians' value more treatments choices at this part of the pathway and that caregivers are also impacted by the condition (see FAD section 3.1) The committee concluded that there is unmet need for new effective treatment options for people who have had 2 previous lines of treatment (see FAD section 3.4). The committee concluded at its first meeting that it would focus its discussion on people who have had 3 previous lines of treatment. The committee heard from clinical experts that currently many clinicians use lenalidomide after 2 previous

		lines of treatment, with ixazomib and dexamethasone in the CDF or with dexamethasone. The clinical experts agreed that the company's positioning after 3 previous lines of treatment was appropriate (see FAD section 3.3). The committee concluded at the second meeting that the cost-effectiveness analysis after 2 previous lines of treatment is not robust enough for decision making (see FAD section 3.24). The committee recalled that clinical experts explained that using an anti-CD38 antibody treatment again later in the treatment pathway would be appropriate if it had been stopped for reasons other than disease progression. The clinical experts also stated that they would not use an anti-CD38 antibody again if the disease had been refractory to one in a previous line of treatment. The committee concluded that it is not appropriate to use isatuximab plus pomalidomide and dexamethasone when disease is refractory to a previous anti-CD38 monoclonal antibody

		(see FAD section 3.8)
UK Myeloma Forum	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** This technology naturally fits into 4th line at the moment but appreciate that with the increasing use of lenalidomide in 1st and 2nd line this is a diminishing population. The exception being those on the transplant-eligible pathway. As such, the vagrancies of the myeloma pathway, whilst challenging, are not dealt with by this appraisal outcome currently. This results in lack of equity of access if patients receiving treatment currently can not receive this technology at 4th line given its clear benefit over PomDex.	The committee acknowledged that there is an unmet need at fourth line and understood that there is a psychological impact for patients approaching the end of the treatment pathway. It understood that patients and clinicians' value more treatments choices at this part of the pathway and that caregivers are also impacted by the condition (see FAD section 3.1) The committee recommended isatuximab plus pomalidomide and dexamethasone for use through the Cancer Drugs Fund as an option for relapsed and refractory multiple myeloma, It is only recommended if people have had 3 previous lines of treatment (including lenalidomide and a proteasome inhibitor), and their disease progressed on the last treatment. The conditions in the managed access agreement must be followed (see FAD section 3.27). The committee concluded that there is unmet need for new

		effective treatment options for people who have had 2 previous lines of treatment (see FAD section 3.4). The committee concluded at its first meeting that it would focus its discussion on people who have had 3 previous lines of treatment. The committee heard from clinical experts that currently many clinicians use lenalidomide after 2 previous lines of treatment, with ixazomib and dexamethasone in the CDF or with dexamethasone. The clinical experts agreed that the company's positioning after 3 previous lines of treatment was appropriate (see FAD section 3.3). The committee concluded at the second meeting that the cost-effectiveness analysis after 2 previous lines of treatment is not robust enough for decision making (see FAD section 3.24)

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Patient expert 1	**Better fourth line treatment – than existing authorised treatments** POM/DEX (TA573 / Jan 2017)	Comments noted. The committee concluded that the appropriate comparator was

	Although the evidence presented by Sanofi from the ICARIA trial was interim and based upon a sub-set of data, nevertheless the data demonstrated a significant advantage when compared with POM/DEX for relapsed and refractory patients. There was a PFS advantage (11.5 months vs 6.5) and the indication of an OS advantage of c.10%. Importantly the trial reported a higher response rate (60.4% vs 35.3% for some level of response; 31.8% vs 8.5% for very good partial response). DARATUMUMAB (TA510 / CDF / March 2018) – Not a comparator We know from US experience that DARA monotherapy is less effective than triplet combinations in which it is included. Initial FDA approval of DARA monotherapy occurred in November 2015 and was quickly followed up over the next four years by approvals for triplet combinations combining it with Proteasome Inhibitors (PIs) (Velcade), Immunomodulatory drugs (IMiDs) (Lenalidomide and Pomalidomide) and a corticosteroid (DEX). The availability of the unique combination therapy of ISA/POM/DEX is equivalent to the FDA authorisation for DARA/POM/DEX given for relapsed/refractory patients given three years ago in June 2017. The US experience suggests that it is highly likely that ISA/POM/DEX is more effective than the authorised DARA monotherapy for UK myeloma patients. *Conclusion: Based upon evidence to date from the ICARIA trial and US experience the ISA/POM/DEX triplet treatment is more effective than current approved treatments through NICE and the CDF, and could relegate them in clinical decisions about patient treatment.*	pomalidomide and dexamethasone after 3 previous lines of treatment (see section 3.5). The committee acknowledged that isatuximab plus pomalidomide and dexamethasone was likely to extend progression-free and overall survival compared with pomalidomide plus dexamethasone after 3 previous lines of treatment, but noted that median follow up was short, the subgroup was small and the data were immature (see FAD section 3.7) The committee also acknowledged the longer-term follow-up data from the daratumumab trials and considered this when assessing the plausibility of each distribution to estimate overall survival (see FAD section 3.13) Daratumumab monotherapy was not included as a comparator for this appraisal. The NICE position statement: consideration of products recommended for use in the

		Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product states that treatments that have been recommended by NICE for use in the Cancer Drugs Fund cannot be considered established practice. Therefore, products recommended for use in the Cancer Drugs Fund after 1 April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals.
Patient expert 1	**Anti-CD38 drug for "first time" users** The anti-CD38 monoclonal antibody (MAB) drug DARA (with VELcade and DEX) was made available through the Cancer Drugs Fund (CDF) in April last year (TA573) for 2nd line treatment, and hence is not strictly a comparator in NICE deliberations. However, in reality some patients would already have had the opportunity to be treated with DARA at 2nd line, and potentially in the future if authorisation continues outside the CDF after January 2021. The Committee were concerned that there could be two anti-CD38 drugs in the myeloma treatment pathway. There are, however, two key groups of patients who would benefit from anti-CD38 treatment at 4th line despite its use at 2nd line in the pathway: • Those patients who have missed the opportunity to access MAB therapy through DARA/VEL/DEX (DVD) - namely those beyond 2nd line who are currently on 3rd line treatment or in remission prior to 4th line treatment. • Those patients who either are judged not clinically suitable for DVD at 2nd line treatment or who have to stop DVD due to suffering from adverse effects With regard to the first group, in a study published in July 2016[i] it was stated that some 15% of myeloma patients survive to receive 4th line treatment (and may be more now given progressively longer survival times over the last 4 years). In the UK, with a myeloma incidence of 5,700 per annum[ii]	The committee recalled that clinical experts explained that using an anti-CD38 antibody treatment again later in the treatment pathway would be appropriate if it had been stopped for reasons other than disease progression. The clinical experts also stated that they would not use an anti-CD38 antibody again if the disease had been refractory to one in a previous line of treatment. The committee concluded that it is not appropriate to use isatuximab plus pomalidomide and dexamethasone when disease

	(and an updated prevalence of 24,000), this suggests that currently some 855 myeloma patients per annum (or 3600 patients at some time) will currently require 4th line treatment, many of whom will have missed the opportunity for anti-CD38 treatment at 2nd line. *Conclusion: The ISA/POM/DEX provides "first time" users of an anti-CD38 drug who are currently on 3rd line treatment or in remission prior to 4th line treatment and therefore missed DARA treatment, or were not prescribed or stopped DARA at 2nd line, to have the opportunity to be treated with drugs other than PIs and IMiDs.*	is refractory to a previous anti-CD38 monoclonal antibody (see FAD section 3.8)
Patient expert 1	**Unique triplet combination** As we are aware, myeloma cells mutate over time and the opportunity for an anti-CD38 drug to be used (in an effective triplet regime) to fight the cancer provides the best chance of providing longer PFS and prolonging life. Patients at 4th line who have only been treated with PIs and IMiDs typically have a life expectancy of less than 12 months. PIs, IMiDs and MABs each have different mechanisms of action to fight against myeloma cells, and hence a combination of ISA (MAB) + POM (IMiD) + DEX (corticosteroid) would be a unique therapy available for routine authorisation. This has the potential to extend patient life at a crucial point in their treatment journey. Importantly, ISA/POM/DEX meets NICE's end of life criteria, unlike DARA monotherapy[iii] . Additionally, the MHRA considered the triplet to be "Promising Innovative Medicine" - the first treatment for relapsed and refractory patients to be recognised. *Conclusion: ISA/POM/DEX is a unique triplet therapy which combines three separate mechanisms for treating myeloma, and is recognised as both meeting NICE's end of life criteria and being innovative.*	Comments noted. The committee acknowledged that the technology had a different mechanism of action and considered this in its decision-making (see FAD sections 3.13 and 3.22)
Patient expert 1	**Unmet need** Relapsed and refractory patients at 4th line treatment are coming to the end of their myeloma journey. Additionally, they are aware that the depth of response to treatment decreases with each additional line of therapy and therefore they will have less time in remission than previous lines of treatment provided. Their prognosis is worse than at any time in their journey to date. The physical and psychological burden that this situation imposes on patients and carers is enormous, including disease-related effects such as pain and fatigue, loss of mobility, increasing reliance on carers, lack of control, concern for partners left behind after their demise, and loss of hope and self-worth.	The committee acknowledged that there is an unmet need at fourth line and understood that there is a psychological impact for patients approaching the end of the treatment pathway. It understood that patients and clinicians' value more treatments choices at this part of the pathway and that caregivers are also impacted

	As we are aware, loss of a positive mental attitude to fight a chronic illness such as myeloma can impact adversely upon life expectancy[iv] and therefore affect both patients' quality of life and remaining length of life. Patients therefore need the reassurance to trust and have confidence that they have access to the best possible treatment regime to give them a few more months/years of life. They deserve no less. *Conclusion: 4th line patients have an unmet need, both physically and psychologically to continue their fight against myeloma. They deserve the best treatment available* **CONCLUSION** I recognise that the appraisal committee has a difficult decision to make when considering whether or not to give authorisation for this therapy. There are issues, inter alia, concerning immature trial data, sub-group analysis, comparator data and cost effectiveness which the committee have considered and weighed prior to the issue of the ACD. However, I would hope that in reconsidering their decision the committee will recognise that the outcome will have considerable physical and psychological impact upon the lives of relapsed and refractory patients at this critical point in their myeloma journey. I hope that the points above will be taken into consideration, the plight of patients put at the heart of their decision-making and result in granting authorisation for this unique and innovative triplet therapy which provides clear clinical benefit over any other approved treatment at 4th line.	by the condition (see FAD section 3.1)
Clinical expert 1	I welcome the opportunity to comment on this consultation document. I was disappointed that isatuximab plus pomalidomide and dexamethasone has not been recommended for treating patients with relapsed and refractory multiple myeloma in line with its marketing authorisation. I would like to point out a few important issues related to the clinical interpretation of the evidence. There is clearly an unmet clinical need for patients with relapsed and refractory multiple myeloma. This condition remains incurable and there are a dwindling number of patients alive beyond 4th line. It is therefore important to give the best therapies available early in the pathway to give the most benefit. There is clearly a survival benefit with the addition of isatuximab to pomalidomide and dexamethasone. This improved PFS is matched by favorable quality of life and toxicity data. This is supported by published trial data and also personal experience of using this technology in clinical practice. This is important for patients who often have significant co-morbid issues related to multiple	The committee acknowledged that there is an unmet need at fourth line and understood that there is a psychological impact for patients approaching the end of the treatment pathway. It understood that patients and clinicians' value more treatments choices at this part of the pathway and that caregivers are also impacted by the condition (see FAD

	myeloma such as bone disease and renal problems, and the effect of toxicities of prior treatment (such as neuropathy). Whilst isatuximab necessitates additional day care attendance this does not adversely affect patient quality of life.	section 3.1) The committee acknowledged that isatuximab plus pomalidomide and dexamethasone was likely to extend progression-free and overall survival compared with pomalidomide plus dexamethasone after 3 previous lines of treatment, but noted that median follow up was short, the subgroup was small and the data were immature (see FAD section 3.7)
Clinical expert 1	Using the technology at 3rd line. The committee accepted that isatuximab with pomalidomide and dexamethasone is appropriately compared to pomalidomide at 4th line, however it raised concern about whether it should be considered as a 3rd line. Whilst there may be merit in patients receiving this treatment at 3rd line, it is most suited to patients at 4th line in the current pathway. For patients to receive pomalidomide with istuximab they need to have received lenalidomide beforehand. This technology naturally fits into 4th line at the moment. Currently most patients are receiving lenalidomide with ixazomib and dexamethasone at 3rd line. Whilst a group of non-transplant eligible patients receive lenalidomide upfront (first line), a large number of patients treated upfront (transplant eligible) and beyond will not receive lenalidomide until 3rd line. The vagrancies of the myeloma pathway, whilst challenging, are not appropriately dealt with by this appraisal. It is important to deal with the current cohort of patients going through the treatment pathway rather than trying to second guess potential treatment choices in future. It is unfair to patients receiving treatment currently not to receive this technology at 4th line given its clear benefit over pomalidomide.	The committee acknowledged that there is an unmet need at fourth line and understood that there is a psychological impact for patients approaching the end of the treatment pathway. It understood that patients and clinicians' value more treatments choices at this part of the pathway and that caregivers are also impacted by the condition (see FAD section 3.1) The committee concluded that there is unmet need for new effective treatment options for

		people who have had 2 previous lines of treatment (see FAD section 3.4). The committee concluded at its first meeting that it would focus its discussion on people who have had 3 previous lines of treatment. The committee heard from clinical experts that currently many clinicians use lenalidomide after 2 previous lines of treatment, with ixazomib and dexamethasone in the CDF or with dexamethasone. The clinical experts agreed that the company's positioning after 3 previous lines of treatment was appropriate (see FAD section 3.3). The committee concluded at the second meeting that the cost-effectiveness analysis after 2 previous lines of treatment is not robust enough for decision making (see FAD section 3.24) Isatuximab, plus pomalidomide and dexamethasone, is recommended for use within the Cancer Drugs Fund as an option for treating relapsed and refractory multiple myeloma in adults who have had lenalidomide and a proteasome

		inhibitor, and whose disease has progressed on their last therapy, only if they have had 3 previous lines of treatment and the conditions in the management access agreement for isatuximab with pomalidomide and dexamethasone are followed (see FAD section 3.27)
Clinical expert 1	Using the best treatment at 4th line that is available to patients. In current practice patients will receive daratumumab 4th line (CDF) and pomalidomide at 5th line. We know that it is best to combine the anti-CD38 monoclonal antibodies with an immunomodulatory drug (IMID). Rather than separating these therapies at 4th and 5th line it will have most benefit when we combine our most potent IMID with an anti-CD38 monoclonal antibody at 4th line. Given that there will be a limited number of patients able to receive treatment at 5th line they are being disadvantaged by not receiving the most appropriate combination at 4th line.	Comments noted. The committee concluded that the appropriate comparator was pomalidomide and dexamethasone after 3 previous lines of treatment (see section 3.5). The NICE position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product states that treatments that have been recommended by NICE for use in the Cancer Drugs Fund cannot be considered established practice. Therefore, products recommended for use in the Cancer Drugs Fund after 1 April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant

		appraisals.
Clinical expert 1	Applicability for use in the Cancer Drugs Fund. One of the reasons stated for not meeting the Cancer Drug Fund criteria is that most patients will have received an anti-CD38 monoclonal antibody before they get to 4th line. Whilst there will be a large number of patients who will receive daratumumab at 2nd line (in combination with bortezomib and dexamethasone, CDF), there are a sizeable number of patients who will not receive daratumumab at second line (CDF) due to early progression on bortezomib given as initial therapy or who developed significant neurotoxicity and so can't receive this combination at 2nd line. In addition, daratumumab with bortezomib and dexamethasone was only available on the CDF in 2019. There is therefore a large number of patients who have never received an anti-CD38 monoclonal antibody before 4th line. They would gain clear clinical benefit from receiving isatuximab with pomalidomide and dexamethasone. This large group of patients should not be ignored.	The committee noted that ICARIA-MM was ongoing, and that further data from this trial could help reduce the clinical uncertainties. The committee concluded that while isatuximab plus pomalidomide and dexamethasone could not be recommended for routine use, it met the criteria to be considered for inclusion in the Cancer Drugs Fund, when the company's commercial offer as part of the managed access agreement is used (see section FAD section 3.27). Isatuximab, plus pomalidomide and dexamethasone, is recommended for use within the Cancer Drugs Fund as an option for treating relapsed and refractory multiple myeloma in adults who have had lenalidomide and a proteasome inhibitor, and whose disease has progressed on their last therapy, only if they have had 3 previous lines of treatment and the conditions in the management access agreement for isatuximab with pomalidomide and

		dexamethasone are followed (see FAD section 3.27)
Clinical expert 1	Isatuximab with pomalidomide and dexamethasone is a step change for patients with relapsed and refractory multiple myeloma. There is clear benefit of an anti-CD38 monoclonal antibody with an immunomodulatory drug (IMID) which result in the greatest clinical benefit. This technology combines the most potent available IMID, namely pomalidomide with a well-tolerated anti CD38 monoclonal antibody.	The committee acknowledged that there is an unmet need at fourth line and understood that there is a psychological impact for patients approaching the end of the treatment pathway. It understood that patients and clinicians' value more treatments choices at this part of the pathway and that caregivers are also impacted by the condition (see FAD section 3.1). The committee concluded that the model adequately captured all health-related quality-of-life benefits of isatuximab plus pomalidomide and dexamethasone and that is had not been presented with any evidence of additional benefits from treatment with isatuximab plus pomalidomide and dexamethasone (see FAD section 3.28)
Clinical expert 1	Subsequent treatment in ICARIA do not reflect NHS clinical practice. Whilst this is a true statement, it is important to note that responses reported are as expected in routine clinical practice. Unfortunately at 5th line and beyond responses and clinical outcomes are poor irrespective of what therapies are given at stage meaning that outcomes reported are generalisable to the population of patients treated in routine NHS practice. In conclusion, I would be grateful if the committee can reconsider allowing use of isatuximab with pomalidomide and dexamethasone within its marketing authorisation at 4th line in the NHS.	Comment noted. The committee acknowledged that the subsequent treatments given in ICARIA-MM, in particular lenalidomide and daratumumab, did not reflect NHS clinical practice (see section 3.9). The committee

		preferred to adjust both the survival data and costs associated with these treatments, but the company did not provide the requested analysis (see FAD section 3.16). The committee heard from the clinical experts that treatments given at this point in the treatment pathway (after 4 or more previous lines of treatment) would likely be ineffective (see FAD section 3.9). The committee concluded that without the appropriate and fully reported adjustment analyses, it was reasonable to remove the costs of lenalidomide and daratumumab from the analysis, particularly because clinical experts suggested that treatments received at fifth line or later would be likely to have minimal effects on survival (see FAD section 3.17)

Comments received from commentators

No comments received

Comments received from members of the public

No comments received

Dear Linda,

RE: Appraisal Consultation Document for isatuximab in combination with pomalidomide and dexamethasone for the treatment of relapsed refractory multiple myeloma (ID 1477)

Sanofi are encouraged to see that the appraisal consultation document (ACD) recognised the unmet need for multiple myeloma (MM) patients at later stages in the pathway and that the clinical data available for the isatuximab in combination with pomalidomide and dexamethasone (IsaPd) combination are very promising. At 4th line, the unmet need for IsaPd has been clearly demonstrated via rapid uptake through the Early Access to Medicines Scheme (EAMS) for isatuximab ([redacted] patients in 5 months). Sanofi were disappointed however that the committee were not able to recommend IsaPd at this stage. On the basis of the information provided within our response, which demonstrates IsaPd is plausibly cost-effective, we would urge the committee to reconsider their preliminary decision and consider a recommendation for isaPd via the cancer drugs fund.

Our attached response document contains:

1. An updated cost-effectiveness analysis that includes the committee's preferred assumptions
2. Exploration and discussion of the uncertainty surrounding the extrapolation of overall survival (OS) data from the ICARIA-MM trial
3. Revised cost-effectiveness analyses for 4th line patients
4. New cost-effectiveness analysis for 3rd line patients versus panobinostat in combination with bortezomib and dexamethasone (PanVd)
5. Proposal for inclusion in the cancer drugs fund (CDF)
6. Discussion on the challenges associated with the assessment of branded combinations in the current Single Technology Appraisal (STA) framework and cost-effectiveness scenarios exploring the impact of removing the backbone pomalidomide cost for the IsaPd combination.

[redacted]. This appraisal is further complicated by the existence of a confidential Patient Access Scheme (PAS) for pomalidomide which is not and cannot be known to Sanofi.

A brief summary of our response is provided below.

Sanofi have provided cost-effectiveness analyses using the committee's preferred assumptions. Taken together these assumptions result in a highly conservative analysis (in which IsaPd is not cost-effective when isatuximab is priced at £0) and we would urge the committee to consider alternative plausible assumptions, particularly in the context of potential inclusion of IsaPd in the CDF. The key area of uncertainty is the extrapolation of overall survival data from the ICARIA-MM trial. As acknowledged at the appraisal committee meeting (ACM), it is very difficult to select the most plausible extrapolations given the limited OS data available and the limited experience clinicians currently have with IsaPd. There are a range of clinically plausible curves and it is this range that should be taken into account in the committee's decision making rather than reliance on a single curve. In time, the ICARIA-MM survival data will mature and greater clinical experience with IsaPd will be gained. This will reveal which of these survival curves are most reflective of longer-term survival for IsaPd.

There is now considerable clinical experience and data to inform long term survival for pomalidomide in combination with dexamethasone (Pd). The Weibull curve is used in our revised analyses as this is supported by clinical opinion, reflects the committee's preferred assumption and is reinforced by existing data for Pd. At the present time, the greatest clue in terms of the long-term survival associated with IsaPd may come from the long term survival data available for another anti-CD38 therapy, daratumumab. Daratumumab monotherapy is currently available at 4th line via the CDF and long term OS data have recently become available (median OS = 20.5 months (95% CI 16.6–28.1)(1). Given the combination of an immunomodulatory drug (e.g. pomalidomide) and an anti-CD38 is known to have a synergistic effect, one would expect a triplet therapy including an anti-CD38 offered at the same stage in the treatment pathway to be associated with at least equivalent survival to daratumumab monotherapy. This would imply that the committee's preferred extrapolation (Weibull) is highly conservative. It is also worth considering that more than half of the patients in the 4th line IsaPd cohort achieved partial response or better and some were even MRD-ve. OS for these patients is almost completely unknown, again suggesting that current extrapolations are likely to be conservative.

There is substantial evidence to suggest that there is a relationship between progression-free survival (PFS) and OS in MM but that this may differ by line and treatment type (2, 3). In order to further understand the OS that might be expected given the available PFS data for IsaPd, we have used a PFS to OS surrogacy relationship informed by the available literature to create OS curves for IsaPd based on the available IsaPd PFS data. Although this approach obviously has limitations, it may actually be more informative than extrapolations based on only a very small amount of OS data. Given the limited OS data available (78.8% in IsaPd arm and 60.3% in Pd arm censored), any cost-effectiveness analysis presented will be associated with substantial uncertainty. Our response presents 3 analyses that use credible and clinically plausible assumptions which result in deterministic incremental cost-effectiveness ratios (ICER) of [redacted]. These ICERs are based on the pomalidomide list price and will be lower once the PAS price is taken into account.

Our original submission was made for patients at 4th line as this is where the current unmet need for IsaPd is. However, as per comments made at the ACM we acknowledge that the MM pathway is evolving and that 3rd line positioning may be relevant in the future. We have therefore provided a cost-effectiveness analysis for this group vs. PanVd as requested (analysis vs. pomalidomide was already presented in the company submission). However, it is important to acknowledge that this analysis is associated with a greater level of uncertainty given the smaller number of patients in the ICARIA-MM 3L subgroup and that a MAIC using ITT evidence was required to compare to the 3L comparator specified in the scope PanVd.

Sanofi are committed to collecting further survival data both at 3rd and 4th line through ICARIA-MM. Final OS data is expected between Oct 2021 and Mar 2022 (data cut in original submission was Oct 2018) at which point we anticipate we would have 65% of completed events in the 4th line population, and around 90% in the intention-to-treat (ITT) population. Ultimately this data will provide greater clarity regarding which OS curves are most appropriate and will greatly reduce the existing level of uncertainty in analysis of cost-effectiveness. For this reason, we feel IsaPd is a suitable candidate for the CDF.

Despite the very promising clinical evidence for IsaPd, the cost-effectiveness of IsaPd is significantly constrained by the existing price for pomalidomide and its approval at/close to the end-of-life threshold. The underlying system failure is demonstrated by the fact that implementing the committee preferred assumptions, isatuximab is not cost-effective at zero price. This issue has been widely discussed, but no solution currently exists (4). The analyses contained within our response demonstrate that at the [redacted] proposed by Sanofi it is plausible that IsaPd could be cost-effective despite being

assessed within a framework that does not work for branded combinations. Sanofi are committed to working with the ABPI, NHS England and NICE to seek a solution to this issue to ensure that this does not result in patients being denied access to valuable treatments in the future but would emphasise that there is an unmet need for isatuximab now and that these patients cannot wait for a permanent solution to be developed.

Sanofi encourage the appraisal committee to reconsider their preliminary decision in the context of the new analyses presented, the unmet need at later lines of therapy, the data that could be collected were IsaPd to be recommended for use on the CDF and ask that the committee exert a degree of flexibility in their decision-making given the challenge associated with demonstrating cost-effectiveness for branded combination therapies.

Kind Regards,

[redacted]
Sanofi UK & Ireland

Cc Helen Knight

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NICE National Institute for Health and Care Excellence

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [ID1477]

Consultation on the appraisal consultation document – deadline for comments 5pm on **25 June 2020**

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Sanofi
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	Richard Hudson

NICE National Institute for Health and Care Excellence

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [ID1477]

Consultation on the appraisal consultation document – deadline for comments 5pm on **25 June 2020**

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Sanofi would like to thank the appraisal committee for recognising the potential benefit IsaPd could bring to patients at 4th line after the failure of 3 prior therapies.** Sanofi is pleased that the committee agree that there remains a need for effective treatment options for previously treated multiple myeloma, and that people would welcome new options. This is particularly true at 4th line (4L) after the failure of 3 prior therapies where the unmet need has been clearly demonstrated through strong uptake into the early access to medicines scheme (EAMS) which opened in December 2019 and ran until marketing authorisation in June 2020. At the close of the scheme after 5 months 'academic / commercial in confidence information removed' had been enrolled. We recognise that there are other options available for the treatment of multiple myeloma via routine and Cancer Drugs Fund (CDF) commissioning and are happy that committee accepts the company positioning of isatuximab in combination with pomalidomide and dexamethasone (IsaPd) at 4L. Moreover, we are satisfied the committee has agreed that the subgroup analysis from the ICARIA-MM trial for people who have had 3 previous treatments is appropriate for decision making. In the submitted company base case, pomalidomide in combination with dexamethasone (Pd) was presented as the comparator to the combination of IsaPd at 4L. Sanofi agree with the committee that Pd is the only relevant comparator in this position. Furthermore, we are pleased that the committee has recognised the clinical benefit due to IsaPd because it delays the progression of relapsed and refractory multiple myeloma (RRMM) and increases how long people live compared with Pd. Sanofi are also encouraged that the committee concluded IsaPd met the criteria to be considered a life-extending, end-of-life treatment and so should be judged against the higher £50k/QALY threshold.
2	**Sanofi are disappointed that the committee were not able to recommend IsaPd at this stage. On the basis of the information provided within our response, which demonstrates IsaPd can be considered plausibly cost-effective, we urge the committee to reconsider this preliminary decision.** In summary, in order to address the committees concerns we have provided the following: 1. Exploration and discussion of the uncertainty surrounding the extrapolation of OS data from the ICARIA-MM trial

	2. A revised cost-effectiveness base case for 4th line patients along with scenario analyses 3. An updated cost-effectiveness analysis that includes the committees preferred assumptions 4. Proposal for inclusion in the CDF 5. Discussion on the challenges associated with the assessment of branded combinations in the current STA framework and cost-effectiveness scenarios exploring the impact of removing the backbone pomalidomide cost for the IsaPd combination. 6. New cost-effectiveness analyses for 3rd line patients versus PanVd (+ scenario analyses) A commercial discussion with NHSE/NICE has been scheduled for the 8th July. The net prices for isatuximab utilised in this response align with our response to technical engagement academic / commercial in confidence information removed. It is important to note that this appraisal is further complicated by the existence of a confidential PAS for pomalidomide **which is not and cannot be known to Sanofi.** The ICERs presented in this document are therefore not the true ICERs which will be lower depending on the level of discount on pomalidomide. **Sanofi encourage the appraisal committee to reconsider their preliminary decision in the context of the unmet need at later lines of therapy, the data that could be collected were IsaPd to be recommended for use on the CDF and ask that the committee exert a degree of flexibility in their decision making given the challenge associated with appraising branded combination therapies.**
3	**The committee has concluded that the clinical data are immature, but the Weibull distribution gives the most plausible OS estimates** Extrapolations for OS at 4L in the model are based on immature data which comprises only ~30% of possible events and this high level of uncertainty means that a range of plausible assumptions for long term survival of IsaPd should be considered in the context of CDF entry rather than relying on the most punitive estimation. In this section we validate our original assumptions and discuss alternative approaches to the extrapolation of long-term outcomes. T**he currently available ICARIA-MM data are more highly censored than data sets used by NICE in previous assessments** Median OS was not reached in ICARIA-MM at the time of the data cut. At the cut-off date, 69% of the 4L patients were still alive (78.8% in IsaPd arm and 60.3% in Pd arm with median follow-up of 11.6 months) and were, consequently, censored in the data analysis. At the time of the analysis, the probability of surviving 12 months was 0.780 (95% CI; 0.638, 0.872) in the IsaPd arm and 0.619 (95% CI; 0.474; 0.735) in

the Pd arm. While censored data in oncology trials are to be expected, this level of censoring is more than that seen with other treatments assessed by NICE in the 4L setting for RRMM (Table 1).

Table 1: Censoring levels across treatments recommended at 4L

Treatment	Appraisal	Trials	% censored	CDF
Daratumumab monotherapy	TA510 (1)	SIRIUS GEN501	42%	YES
Pomalidomide	TA427 (2)	MM-003	42%	NO
Panobinostat	TA380 (3)	PANORAMA 1	54%	NO

Note: Ixazomib (TA505) has not been included since it only has a conditional marketing authorisation.
No data on censoring for PANORAMA-2 was identified.

Independently fitting the data for OS makes no material difference to the outcomes.

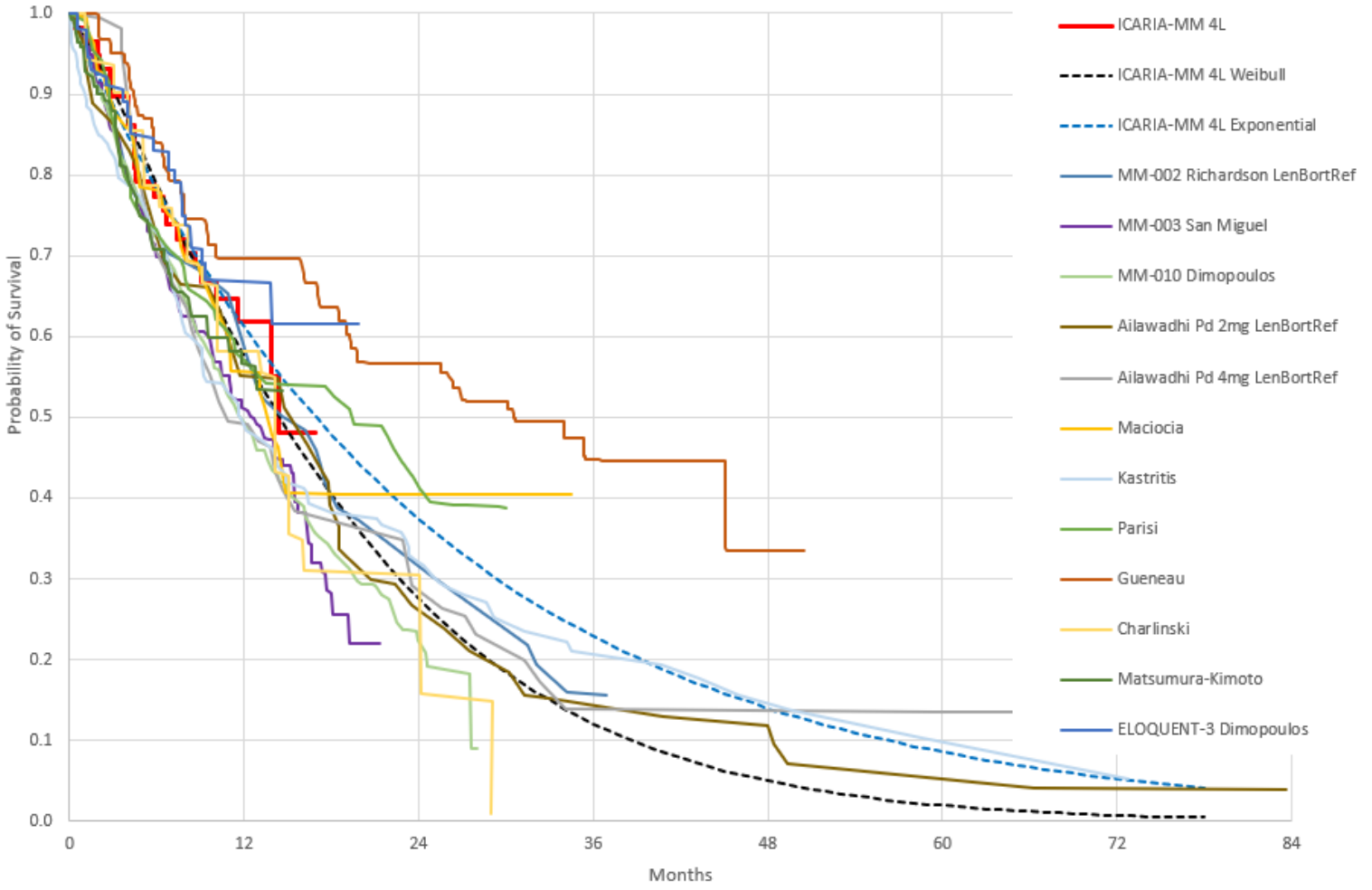
The ERG concluded in their report that independently fitted curves may be more appropriate than the jointly fitted models presented by the company (Section 4.2.4.2.2 of ERG report). We have fitted the OS data independently and found that the fits and conclusions from the associated statistical analysis made no material difference to the originally proposed estimates. However we agree that in this case it is plausible that the curves could follow different trajectories due to the significantly different pharmacological properties for the triplet IsaPd combination vs. Pd. Current OS fits are based on extremely immature survival data and we discuss this in detail below where we concur with the committee assumptions around the Weibull fit for the Pd arm but not for the IsaPd extrapolation. The results for the independent curve fitting exercise are provided in an Appendix.

Lack of clinical experience with IsaPd in UK practice highlights uncertainty in predicting long term outcomes at 4L for triplet based anti-CD38 therapy but outcomes for Pd are more certain.

How well the extrapolated curves fit to the empirical data from the trial is important but we agree with the committee that it is less informative for both IsaPd and Pd given the different levels of censoring in the arms and that other ways of validating the curve selection are needed, for example, by seeking clinical opinion. However, there is no clinical experience of IsaPd use outside of the ICARIA-MM trial or EAMS

	programme and there is no observed long-term survival experience from using any triplet therapy at 4L such as IsaPd in the UK. (EAMS ran for 5 months making long term outcomes hard to predict from this real world UK clinical experience to date) This makes it difficult for UK clinicians to be able to predict with certainty, what the most plausible extrapolations for IsaPd would be based on only ~20% of OS data. On the other hand, there is substantially more experience with Pd at 4L and also more literature precedent. Since the NICE approval of pomalidomide in 2017, approximately a third of patients have been treated with this doublet combination. To date numerous studies have been published documenting its use in RRMM in heavily pre-treated patients. We have inspected the literature and have plotted long-term outcomes for Pd taken from the key studies to examine in the round, the treatment effect for patients with RRMM. The results of this analysis are provided in Figure 1 and the list of publications considered can be found in an Appendix.

Figure 1: Long term outcomes from pomalidomide trials and the Weibull extrapolation from the ICARIA-MM Pd arm



	The clinical experts at the committee meeting concurred that the Weibull extrapolation is the most appropriate for Pd in the UK clinical setting as did the experts we spoke to during the validation exercise carried out for the submission. We have overlaid the ICARIA-MM Pd Weibull fit for Pd (black dashed line) in Figure 1 to test this assumption. Whilst cross trial comparisons should be interpreted with caution visual inspection of the diagram shows that this fit matches the available evidence well compared to the exponential curve (blue dashed line). Given the literature precedent and clinical validation **we concur with the committee's view that the Weibull estimator may be appropriate for the Pd setting.** However, these results **do not validate** the committee preference for the Weibull fit for IsaPd, a triplet-based monoclonal (mAb) therapy with a different and enhanced mode of action in combination with pomalidomide. Considerable uncertainty remains, not least due to lack of longer-term clinical experience in the UK. In the following sections we present some clinical arguments derived from the trial data to support the expectation of longer survival with IsaPd as predicted by the exponential and follow up with an alternative approach to estimating outcomes for the model which is evidence based. In a later section we discuss the pharmacological reasons for differences in the long-term outcomes between IsaPd and Pd. **Duration and depth of response supports longer term survival projections with IsaPd.** Achievement of minimal residual disease negative (MRD-ve) status is known to be a prognostic factor for prolonged PFS and OS and as such MRD as a surrogate end point is now being considered for inclusion in clinical trials (4),(5). The published evidence to date is mainly focused earlier in the pathway on newly diagnosed patients where MRD status has been more routinely measured. However, a very recent metanalysis of published data has found that even in relapsed refectory multiple myeloma where MRD -ve status is generally considered to be harder to reach, MRD negativity can be achieved and is very important for long term outcomes (4). In this study MRD-ve patients were calculated to have an PFS HR of 0.30 (95% CI, 0.18 – 049). Similarly, studies have found that partial to very good (partial) response rates are also prognostic of better outcomes overall. For example a newly published analysis of median OS by response status supports the view that patients who respond (definitions below) to daratumumab monotherapy have better median OS compared to those with stable or progressive disease (36-month OS rate for responders (partial response or better) was 60.2% compared to those with stable 29.5% and progressive disease 12.5% (6). The median OS for responders (partial response or better) was not reached (95% CI 29.2–not estimable). This is in contrast to patients with a minimal response or stable disease who had a median OS of 18.5 months (95% CI 15.1–22.4) and patients with progressive disease or without an evaluable response who had median OS of 3.5 months (95% CI 1.5–6.6).

	We have examined the outcomes for patients treated in ICARIA-MM in a similar way and assessed the association between depth of response (including MRD-ve, MRD+ve and very good partial response (VGPR) or better, partial response (PR) and less than PR) and long-term outcomes. Although data are currently immature from ICARIA-MM, similar results to those reported for daratumumab (6) are seen for IsaPd in terms of depth of response and these are correlated with improved long-term outcomes in both arms in 4L patients. In the ICARIA-MM trial MRD status was only recorded for a small number of patients who achieved a stringent complete response (SCR) or a complete response (CR) (14 patients in the IsaPd arm and 2 patients in the Pd arm). The true CR rate is likely to have been underestimated in the clinical trial due to the interference of isatuximab with M protein measurements. This was investigated using a mass spectrometry technique and the true CR rate from the ICARIA-MM trial was assessed to have been underestimated by between 10-17% (7). Nonetheless of the 14 in the IsaPd arm 8 were MRD-ve (8/14 = 57%) at a minimum sensitivity of 1 in 105 nucleated cells. Neither of the patients with MRD measurement in the Pd arm achieved MRD-ve status. In the ITT population, after a median follow-up of 11.6 months in the Isa-Pd arm, 100% of MRD-ve patients were progression free and alive. In the IsaPd arm, median PFS was longer with increased depth of response: (MRD−ve patients, not reached (NR); ≥VGPR and MRD+ve, 15.21 months; partial response (PR), 11.53 months; less than PR, 3.29 months). This pattern was also observed for 1-year OS probabilities (100% > 92.9% > 82.4% > 46.4%, respectively) (8). Similar results have been seen in the 4L population: academic / commercial in confidence information removed Clinicians currently have little expectation of achieving MRD-ve status for patients in late lines of therapy and so it is noteworthy that a significant proportion of those with MRD status recorded achieved MRD negativity in the IsaPd arm. The PFS and OS outcomes are plotted against response in Figure 2 and Figure 3 overleaf.

Figure 2: academic / commercial in confidence information removed

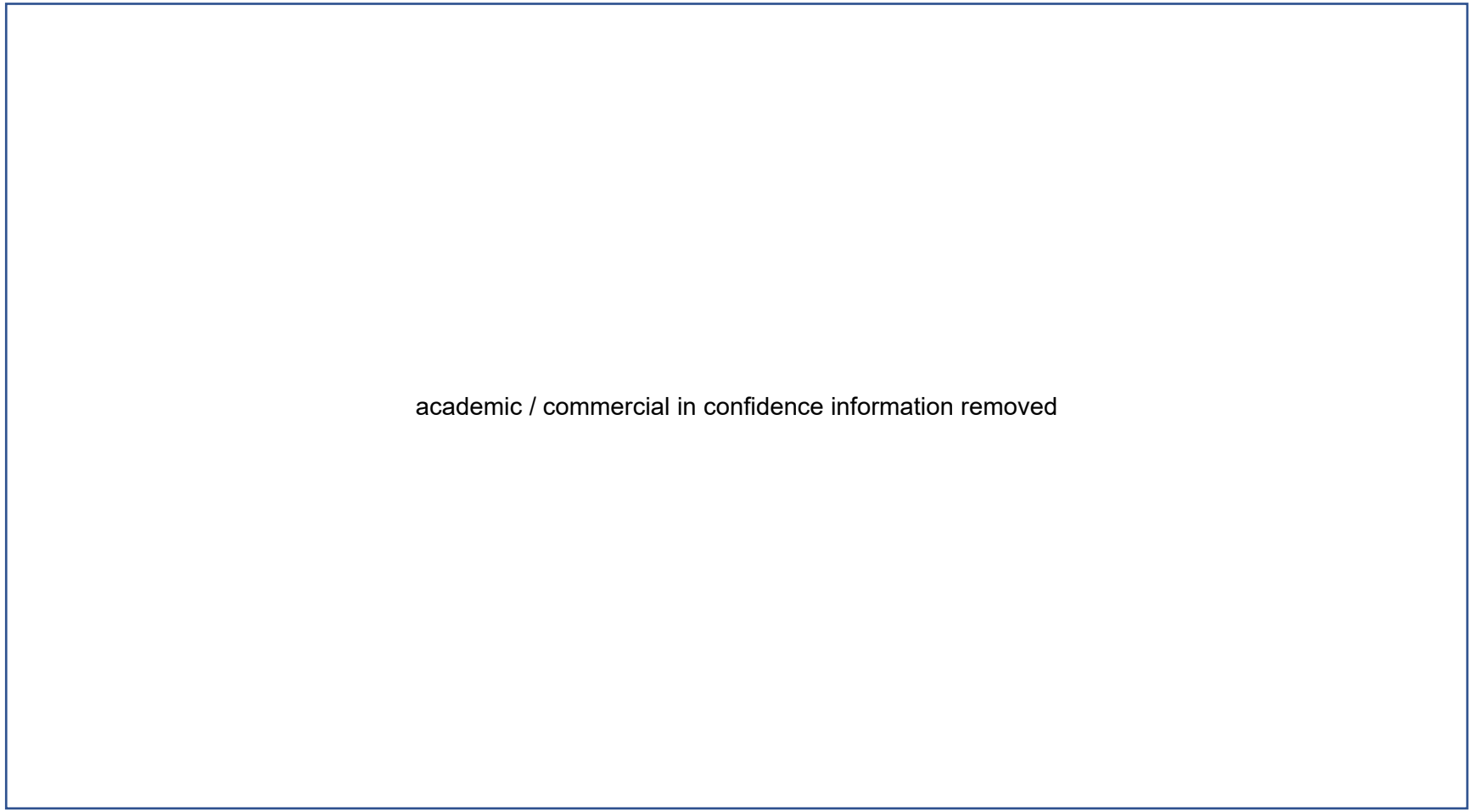


Figure 3: academic / commercial in confidence information removed

academic / commercial in confidence information removed

The results show that depth of response, including MRD negativity, was improved with IsaPd and was clearly associated with better long-term survival outcomes. Obviously, the downward trajectory in the overall measures of PFS and OS in the earlier months of the trial are driven mainly by the patients with less than partial response. Outcomes for patients with partial response or better will drive the tails of the OS curves and so these results remain highly uncertain for IsaPd.

The opinion of clinicians (n=5, not 3 as noted in the ACD) we have sought directly, suggests that there will be some patients for whom MM therapies are effective for prolonged periods beyond cessation of treatment even at 4L and these patients will have long OS which can extend into many years. The findings from the clinical trials presented above are supportive of this opinion.

Further supporting evidence comes from looking at OS in ICARIA-MM by using similar definitions of response used in Usmani 2020 (6): i.e those who responded to treatment, minimal response or stable disease, and progressive disease. Although data are immature in ICARIA-MM, patients treated with Pd and with a minimal response or stable disease had a median overall survival of 13.9 months. Median overall survival was not reached in Pd patients who were responding or with progressive disease. At study cut-off, median overall survival was not reached in patients responding to treatment with IsaPd or in those with minimum response or stable disease (Table 2).

Table 2: academic / commercial in confidence information removed

academic / commercial in confidence information removed
academic / commercial in confidence information removed

	academic / commercial in confidence information removed

sCR: stringent complete response, CR: complete response, VGPR: very good partial response, PR: partial response
[a] Interaction test from the Cox proportional hazard model including the factor, treatment effect and the treatment by factor interaction

In summary, while it is clear that the extrapolations for overall survival from ICARIA-MM are highly uncertain at first data cut with ~70% of patients still alive, it is worth considering that more than half of the patients in the 4L IsaPd cohort achieved MRD-ve status or partial response or better. OS for these patients is almost completely unknown and so we believe these results provide clinical evidence to support the rationale that the punitive Weibull extrapolation of overall survival in the economic model is not a reasonable choice for IsaPd.

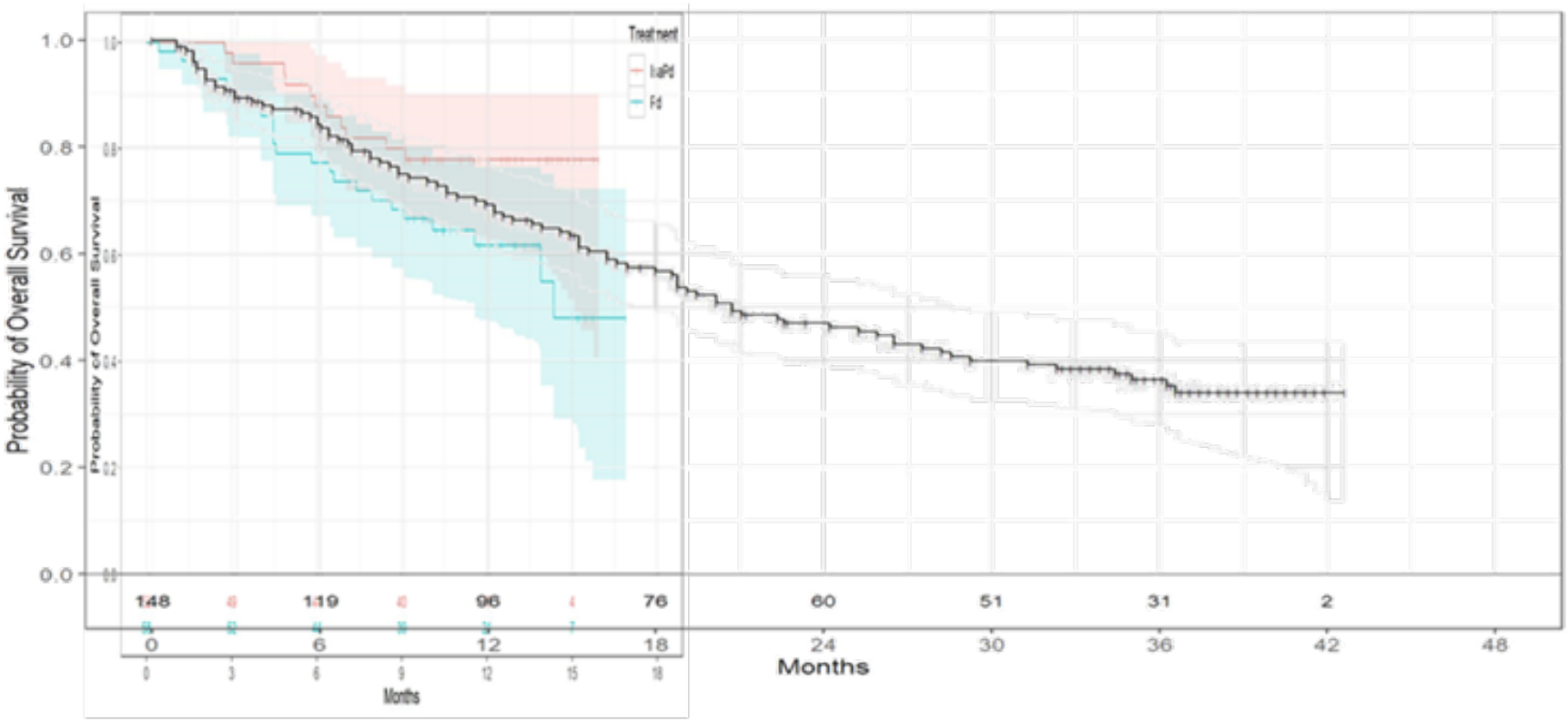
It is reasonable to anticipate improved overall survival with triplet based anti-CD38 therapy compared to monotherapy anti-CD38 therapy, based on the evidence.

Daratumumab monotherapy is the only other anti-CD38 therapy available currently at 4L and so it is useful to compare and contrast these results with the ICARIA-MM data. The positive recommendation for daratumumab in the CDF was supported by evidence from two single arm pivotal trials: SIRIUS and GEN501 reporting outcomes based on 31 months of follow-up (TA510) (1).

Recently, final OS data were published for these monotherapy studies. The publication reports OS for 148 patients who received daratumumab 16 mg/kg (42 patients in GEN501 part 2; 106 patients in SIRIUS), with a median follow-up of 36.6 months. The median overall survival reported was 20.5 months (95% CI 16.6–28.1) and 3-year overall survival rate of 36.5% (28.4–44.6) (6).

Patients entering the daratumumab studies GEN501 and SIRIUS are similar to those in ICARIA-MM 4L cohort (See Appendix 3). In order to compare the outcomes we have overlaid the daratumumab OS KM data with that of the ICARIA-MM OS KM estimators (Figure 4). The daratumumab KM OS is intermediate between IsaPd and Pd and whilst cross trial comparisons should be treated with caution this indicates that longer term, better outcomes with the triplet based anti-CD38 IsaPd might be expected. This assumption should be considered in the light of the compelling emerging evidence of the enhanced clinical benefits from the immunomodulatory effect of the anti-CD38 class and moreover the addition of an IMiD (pomalidomide) to isatuximab which is likely to further improve the body's own natural immune defences (This effect is discussed in a following section).

Figure 4: Overlay of the 4L OS KM data from ICARIA-MM and GEN501 and SIRIUS (6)



Using the data from this analysis, we fitted parametric extrapolations to the OS curves reported for daratumumab. (details are provided in an Appendix). The exponential was found to be the best fit based on the Bayesian information criteria (BIC), whereas the Log normal was the best fit based on the Akaike information criterion (AIC) and AICc. Visually, the lognormal provided the better fit. However, using both distributions we extrapolated out to 10 years in order to approximate the proportion of patients predicted to be alive at 5 years and 10 years.

The landmark method approach presented below compares the predicted estimates for survival to corresponding estimates for IsaPd predicted in our model (Table 4).

Table 3: Estimated proportion of patients alive at 5 years and 10 years for Daratumumab and IsaPd

Year	Daratumumab (approximate)		IsaPd	
	Exp	Lognormal	Exponential	Weibull
5-y	~17%	~24%	29.4%	17.0%
10-y	~3%	~11%	8.6%	1.6%

It is reasonable to assume that a triplet anti-CD38 may have better outcomes than monotherapy as we have discussed above and in detail in a following section. The 3-year overall survival rate on daratumumab monotherapy was reported to be 36.5% (6). **This is longer than that predicted with IsaPd at 5 years with either the exponential or Weibull estimates** and so our estimates for isatuximab may be highly conservative in the short term. Bearing in mind the better fit to the lognormal distribution is based on the much longer follow data up for daratumumab, these results in Table 3 above suggest that our projections of overall survival with IsaPd using the exponential fit may be conservative compared with daratumumab.

The committee preferred assumption of Weibull fit for the IsaPd OS data is also contrary to the observed daratumumab outcomes. Usmani et al. (6) reports median OS for daratumumab monotherapy at 20.5 months and the Weibull extrapolation from the observed OS data in ICARIA-MM is 27.7 months. Given the considerable difference in the observed median PFS at 4L for these patients (daratumumab: 4.0 months vs. IsaPd: 13.3 months) it is reasonable to assume that a larger difference between the two therapies at median OS would be observed than 7 months.

These observations are also supported by the results from a survey carried out by Sanofi for the purposes of this response. 21 English haematologist/haem-oncologists were asked about their perceptions of survival for RRMM patients treated at 4L in the UK. 86% (N = 21) of the experts surveyed said they would expect patients receiving fourth-line treatment with a triplet regimen which includes a monoclonal antibody (mAb) to have much longer OS than similar patients receiving an mAb as monotherapy (mean of an additional 12.2 months).

Exploratory analyses using PFS as a surrogate for overall survival of IsaPd

We have established, based on literature precedent and clinical opinion, that the committee preferred assumption of the Weibull extrapolation using the ICARIA-MM data for Pd PFS is likely to be suitable for decision making so in the following section we concentrate on overall survival in the IsaPd arm.

Given the highly censored survival data for IsaPd we have considered an alternative method to extrapolate OS. The most widely used surrogate for OS in oncology is PFS and this relationship has been established for multiple myeloma. Moreover, it has been shown that it varies by line and treatment type. The PFS data from the 4L IsaPd patients in ICARIA-MM provides an estimate for median PFS and so whilst still not mature these data are likely to provide sufficient information for a PFS:OS extrapolation to be used. Alternative methods to achieve this extrapolation are discussed in the next section.

Estimating a suitable range of ratios to use in the analysis.

In a pragmatic search of the literature we identified 3 potential sources for estimating this relationship. These references are provided below.

- Cartier S, Zhang B, Rosen VM, et al. Relationship between treatment effects on progression-free survival and overall survival in multiple myeloma: a systematic review and meta-analysis of published clinical trial data. Oncol Res Treat. 2015;38(3):88-94. doi:10.1159/000375392 (9)
- Félix J, Aragão F, Almeida JM, et al. Time-dependent endpoints as predictors of overall survival in multiple myeloma. BMC Cancer. 2013;13:122. Published 2013 Mar 16. doi:10.1186/1471-2407-13-122 (10)
- Dimopoulos M, Sonneveld P, Nahi H, et al. Progression-Free Survival as a Surrogate Endpoint for Overall Survival in Patients with Relapsed or Refractory Multiple Myeloma. Value in Health 2017; 20:9 PA408. DOI:https://doi.org/10.1016/j.jval.2017.08.064 (11)

The paper by Cartier only examines the association between the HR and ln(HR) for PFS and the HR and ln(HR) for OS so was not relevant for an analysis attempting to project treatment specific OS based on treatment specific PFS (as opposed to treatment effects expressed as an HR) (9). The papers by Dimopoulos (11) and Felix (10) examine the associations between median PFS and median OS. These studies are based on literature reviews and PFS and OS data are reported as the average of the medians identified. (See Table 4 below).

Table 4: Key findings from Felix and Dimopoulos

Study	Mean of Median PFS (months)	Mean of Median OS (months)	Ratio PFS:OS	Scope of the literature review
Felix et al. 2013 (10)	22.5	39.1	1.7	All studies published between January 1970 and February 2011 that assessed OS in MM using TTP, PFS, or EFS as a primary endpoint. 153 studies included: (230 treatment arms, 22,696 patients and mean study duration of 3.8 years)
Dimopoulos et al. 2017 (11)	8.26	24.34	2.9	RCTs published between 1970 to 2017 including RRMM patients. 22 RCTs were included (42 treatment arms, 7,884 patients)

It is important to note that the Dimopoulos et al. ratio is based on RRMM studies which are the appropriate patients for the comparison here. This is not the case for Felix et al. which covers earlier lines of treatment. Therefore, we have included Felix et al. as a sensitivity analysis.

Given the time frame of the Dimopolous et al. literature review, carried out for the purposes of their analysis (RCTs published between 1970 to 2017) it is unlikely to include studies with anti-CD38 treatments. Older drug regimens are known to have poorer outcomes. The authors of the DSU review evaluating the relationship between PFS and OS in advanced metastatic cancers highlight that, within the context of HTA, evidence on PFS:OS ratios from within the same drug class should be used (12). This is preferable to mixing drug classes for estimation purposes. So on the basis of the DSU recommendation and the lack of other evidence we also explored the PFS:OS ratio based on daratumumab monotherapy published in the daratumumab NICE submission (1).

PFS and OS from the integrated analysis of the two pivotal daratumumab studies for RRMM are provided below in Table 5 and Table 6.

Table 5: Relationship of PFS to OS in the daratumumab studies as reported in daratumumab submission (based on 31.1 months follow -up)

	Based on integrated analysis of MMY2002/GEN501	**Based on Janssen model predictions**
PFS	Median 4.0 months	Median 4.4 months
OS	Median 20.1 months	Median 20.9 months

We have used these data to estimate the relationship between median PFS and median OS for daratumumab further. Not all of the data for the two studies is available in order for us to be able to derive a ratio to extrapolate PFS:OS for IsaPd. Table 7 shows the available median PFS and OS from the two trials individually as well as integrated analysis for both studies combined. The cells in yellow are calculated from the reported values assuming the median for the overall is approximately a weighted average of the two trials.

Table 6: Relationship of PFS to OS in the daratumumab studies as reported in Usmani 2020 (based on 36.6 months follow-up) (6)

Trial	N	Percent	Median PFS	Median OS
SIRIUS	106	72%	3.7	18.6
GEN501	42	28%	5.6	25.3
Combined	148	100%	4.2	20.5

Values in yellow computed

Based on this, it would appear that, for the combined analysis of the two daratumumab trials, the ratio is 20.5 to 4.2 = 4.8. Data from the SIRIUS trial alone, which NICE considered more appropriate for decision making, suggests the ratio is 5.0 (18.6 to 3.7).

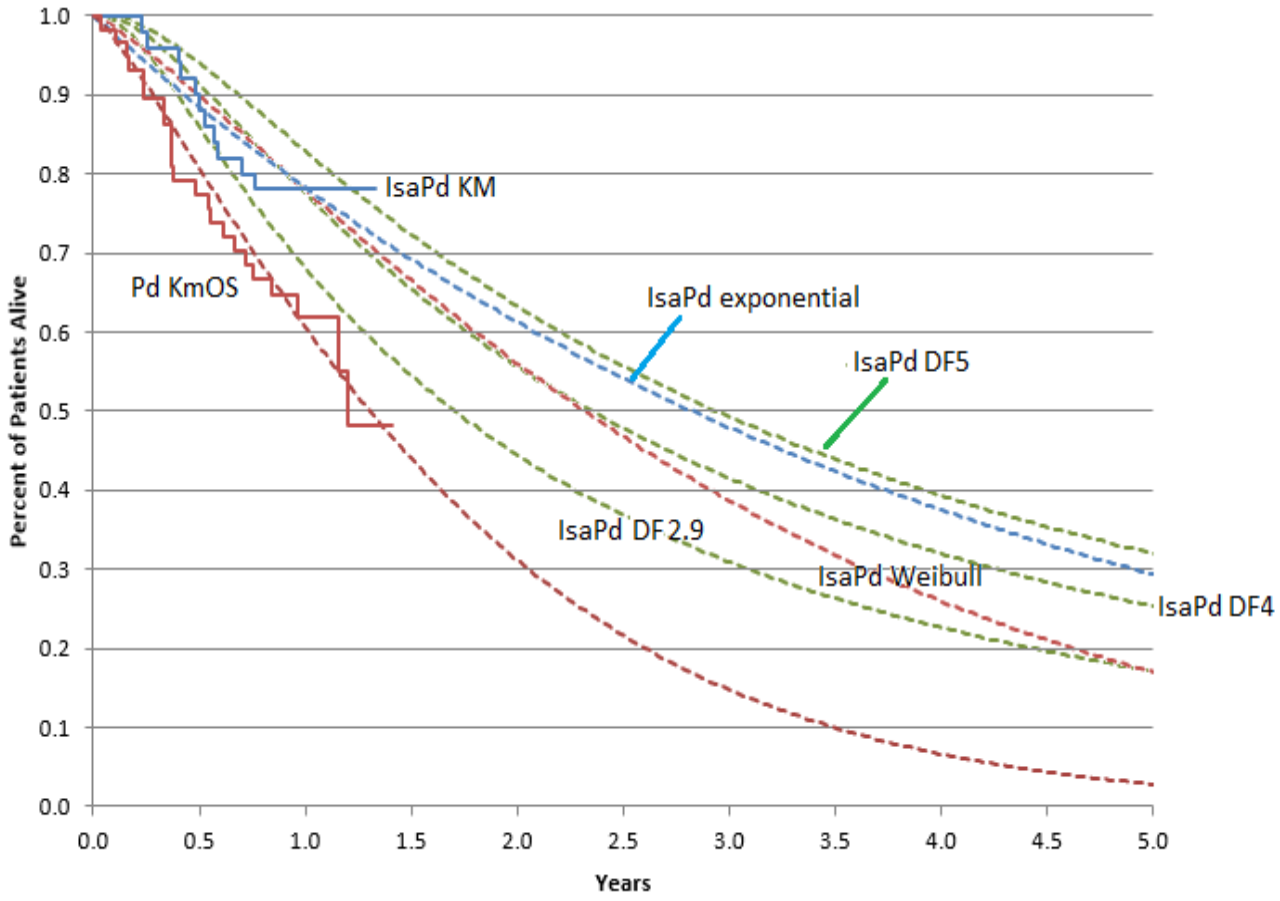
Therefore, the published evidence suggests ratios of PFS:OS may lie between 1.7 and 5.0. We have included 1.7, 2.9 and 5.0 in our scenarios below.

Exploratory analyses: Simulation of OS data for use in the economic model.

The most straightforward way to predict OS for IsaPd from PFS data is to apply a deceleration factor (DF) to the committee agreed PFS distribution for IsaPd which was the lognormal. It is important to note that we found the best fit extrapolation for the final long-term OS data for daratumumab was also lognormal (see section above) and so it is not unreasonable to project the PFS lognormal fit forwards.

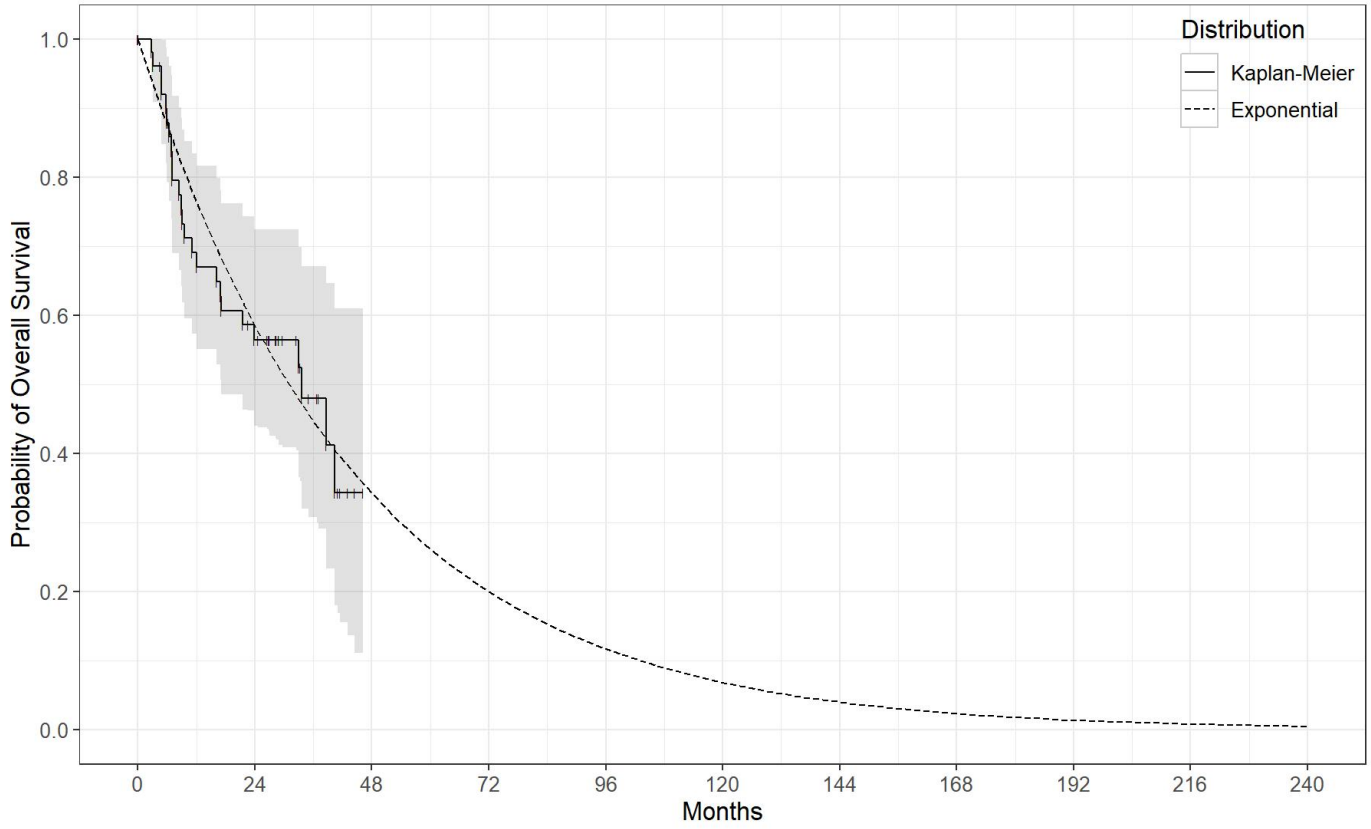
We have set the upper and lower bounds for the DF as the daratumumab ratio of 5.0 and the Felix et al. of 1.7, with the Dimopoulos et al. ratio of 2.9 as the most plausible key scenario. These are shown in Figure 5 overleaf plotted as green dashed lines.

Figure 5: Overlays of the extrapolations for deceleration factors 2.9, 4 and 5 along with the exponential fit for IsaPd and the Weibull extrapolation for Pd.



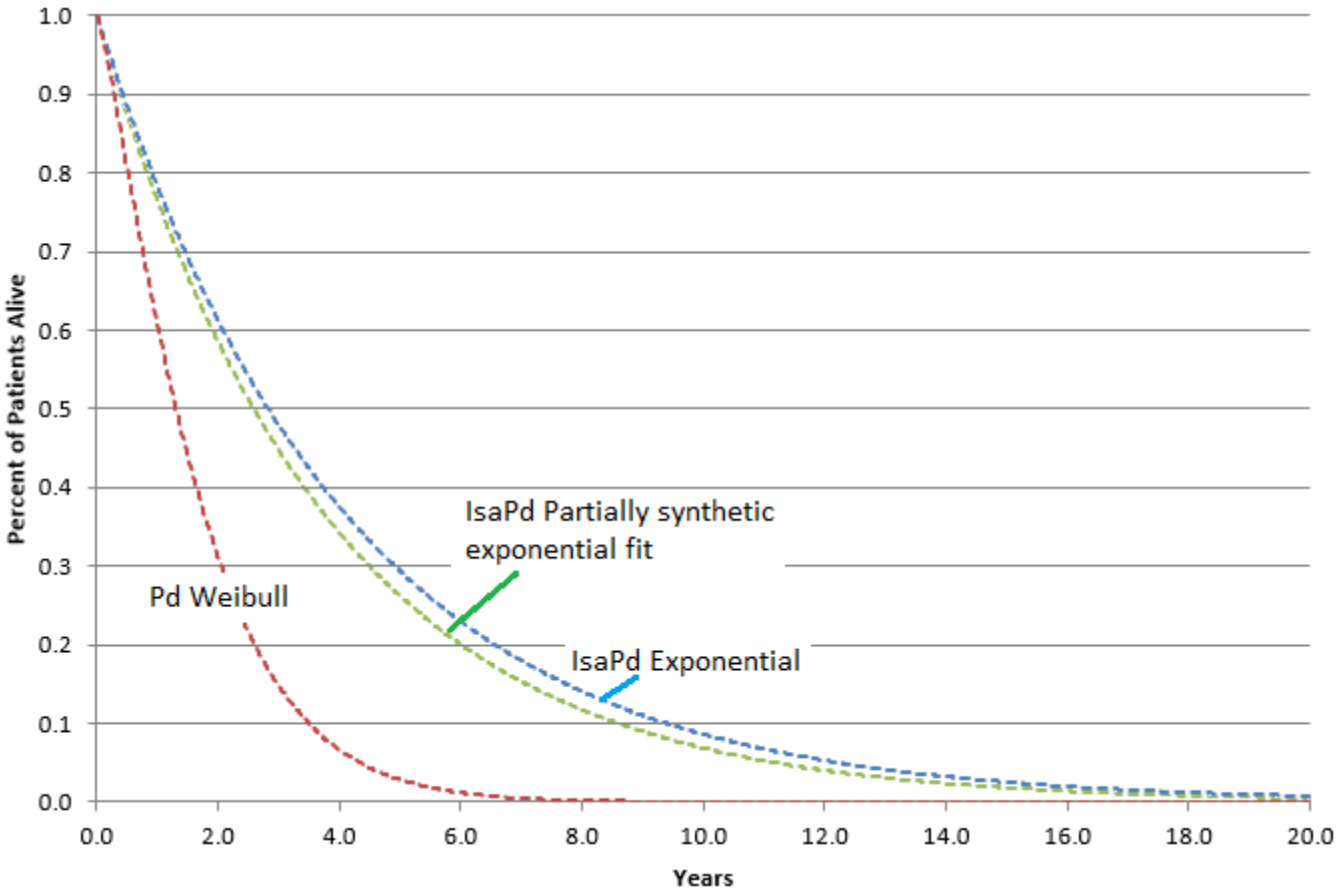
	DF 1.7 is not a plausible factor as this extrapolation lies well below the exponential (and even below the original committee preferred IsaPd Weibull in the first 5 years). DF 5.0 is derived from the anti-CD38 daratumumab long term data (and so arguably could be the most appropriate to use from a class perspective) but does not follow the observed KM data and provides a fit which may be overly optimistic. Of the three deceleration factors, DF 2.9 is likely to be the most plausible as it is derived from the literature review of RRMM therapies. A limitation is the lack of anti-CD38 therapies in this analysis making it potentially conservative for the purposes of this appraisal. The fit derived from this validates the exponential distribution (shown in blue) in the first 6 years and estimates the same median OS. However, visual fit to the KM data is less good than the exponential and may provide optimistic outcomes in the later years. Nonetheless, estimates for longer term survival are unknown and the pharmacological properties of the IsaPd triplet suggest that better long-term outcomes may be plausible. We have established above the importance of considering patient response as a prognostic factor for long term outcomes and we know that more than half of the patients in the ICARIA-MM trial at 4L had partial response or better. We have noted that these patients have very little OS data associated with them. This means that the survival curves are likely to be steep at the outset as the patients with less than partial response leave the cohort and to flatten later as patients with better response live longer. The extent to which these responding patients survive is unknown, but it is clinically plausible based on the mechanisms of action of the triplet therapy discussed in the next issue section, that a small minority might live for a considerable period. The ICERs for these decelerated fits are provided in the results section below. Given the shape of the most plausible curve derived from DF2.9 we have also explored an alternative approach in which the best use of all the available data is made. A partially synthetic KM estimator was constructed using observed event times for patients who died and imputed times for those who were censored for OS. Imputed event times were calculated by multiplying PFS times by the deceleration factor (i.e., 2.9). Patients with and imputed OS time who experienced a PFS event are assumed to experience an OS event (i.e., died) at the imputed time while patients with an imputed OS time who were censored on PFS (i.e., no PFS event) are censored at the imputed OS time We justify this on the basis that for censored patients PFS is at least as great as the PFS censored time and so the imputed OS time must be similarly at least as great as 2.9 times the censored PFS time. The partially synthetic KM data are shown below in Figure 6 overlaid with the best fit to these data which was the exponential (followed by the log normal). Full details of the curve fitting exercise are provided in Appendix 4.

Figure 6: Synthesised OS KM data and best fit extrapolation



This new fit to the partially synthetic data is compared to the original company base case exponential curve in Figure 7 overleaf. We have included the Weibull fit to the Pd data for reference.

Figure 7: Comparison of the fits to the partially synthetic and observed KM data.



The fit to the partially synthetic KM data provides a slightly less optimistic view of OS than the exponential (Median $OS_{Syth\ KM}$ = 31.1 months vs. Median OS_{expo} = 33.9 months) but does follow the trajectory very closely.

Although simplistic, these analyses have demonstrated that the original company base case extrapolation using the exponential estimator is likely to be valid. The approach using the partially synthetic KM data may be more informative than extrapolations based on only a very small amount of observed OS data. In the section below we present the ICERs for these analyses.

Updated cost effectiveness results for the comparison of IsaPd with Pd at 4L

academic / commercial in confidence information removed

Updated cost effectiveness results and scenario analyses

Having established that the most plausible extrapolation for the Pd arm for the model is the Weibull, we present here three equivalent analyses examining IsaPd extrapolations: the exponential extrapolation for the IsaPd arm; the decelerated PFS:OS IsaPd Lognormal curve and the fitted data to the partially synthetic IsaPd KM data. We provide full sensitivity analyses for these comparisons and also scenarios which include the deceleration factor for the PFS:OS extrapolations.

Table 7 overleaf shows the deterministic and probabilistic cost effectiveness estimates using the Weibull extrapolation for Pd OS and the exponential extrapolation for IsaPd OS at academic / commercial in confidence information removed isatuximab PAS discount. Table 8 overleaf presents the same results with academic / commercial in confidence information removed. Scatter plots and CEACs are provided in Appendix 5. All results are reported using list price for pomalidomide. List price for daratumumab is also used. We are unaware of the agreed daratumumab NHSE access price but as a final in-market PAS does not yet exist since it is provided on the CDF, it would be inappropriate to include any further discount to list in the economic modelling.

Table 7: Cost effectiveness results for the Weibull Pd OS and exponential extrapolation for IsaPd OS with academic / commercial in confidence information removed PAS discount

Outcome	Deterministic results		Probabilistic results	
	IsaPd	Pd	IsaPd	Pd
Totals, discounted				
Costs (£)	academic / commercial in confidence information removed		academic / commercial in confidence information removed	
LYs				
QALYs				
Difference IsaPd vs Pd				
Costs (£)		113,837		123,573
LYs		2.020		2.158
QALYs		1.309		1.393
ICER IsaPd vs Pd				
Cost (£) per life-year saved		56,359		57,255
Cost (£) per QALY saved		86,984		88,698

Table 8: academic / commercial in confidence information removed

academic / commercial in confidence information removed

academic / commercial in confidence information removed

Table 9 below presents the analysis using DF 2.9 for the IsaPd PFS:OS extrapolation and provides deterministic and probabilistic cost effectiveness estimates using the Weibull extrapolation for Pd OS at academic / commercial in confidence information removed isatuximab PAS discount. Table 10 overleaf presents the same results with academic / commercial in confidence information removed. Again, in both cases all other drugs are included in the model at their list prices.

Table 9: Cost effectiveness results for the Weibull Pd OS and DF 2.9 to estimate IsaPd OS with academic / commercial in confidence information removed PAS discount

Outcome	Deterministic results		Probabilistic results	
	IsaPd	Pd	IsaPd	Pd
Totals, discounted				
Costs (£)	**academic / commercial in confidence information removed**		**academic / commercial in confidence information remove**	
LYs				
QALYs				
Difference IsaPd vs Pd				
Costs (£)		114,621		124,379
LYs		2.413		2.431

QALYs		1.550		1.562
ICER IsaPd vs Pd				
Cost (£) per life-year saved		47,493		51,158
Cost (£) per QALY saved		73,934		79,628

Table 10: academic / commercial in confidence information removed

academic / commercial in confidence information removed
academic / commercial in confidence information removed

Table 11 overleaf presents the analysis using the fitted data to the partially synthetic IsaPd KM and provides deterministic and probabilistic cost effectiveness estimates using the Weibull extrapolation for Pd OS at academic / commercial in confidence information removed isatuximab PAS discount. Table 12 overleaf presents the same results with academic / commercial in confidence information removed Again, in both cases all other drugs are included in the model at their list prices.

Table 11: Cost effectiveness results for the Weibull Pd OS and the fitted data to the partially synthetic IsaPd KM with academic / commercial in confidence information removed PAS discount

Outcome	Deterministic results		Probabilistic results	
	IsaPd	Pd	IsaPd	Pd
Totals, discounted				
Costs (£)	academic / commercial in confidence information removed		academic / commercial in confidence information removed	
LYs				
QALYs				
Difference IsaPd vs Pd				
Costs (£)		113,302		122,547
LYs		1.751		1.814
QALYs		1.144		1.182
ICER IsaPd vs Pd				
Cost (£) per life-year saved		64,692		67,544
Cost (£) per QALY saved		£99,038		103,717

Table 12: academic / commercial in confidence information removed

academic / commercial in confidence information removed

academic / commercial in confidence information removed

Table 13 below presents results for scenarios in which the deceleration factor is varied. Note that all other drugs are included in the model at their list prices.

Table 13: Scenario analysis

Scenario name	Justification	ICER vs Pd (£/QALY)
Deceleration factor = 1.7	Taken from Felix et al. 2013 (10)	160,297
Deceleration factor = 5.0	Derived from the daratumumab studies	37,052

Summary

In this section we have examined the historical data for Pd and concur with committee assumption that the Weibull fit to the Pd KM data is the likely best estimator for long term outcomes with pomalidomide treatment.

We have provided further rationale for the choice of the exponential fit to the IsaPd OS data originally used in the company base case and provided alternatives to the direct extrapolation of the OS IsaPd KM data making best use of the available data. In doing so, we have shown that the predictions made by the exponential distribution in the original company model are credible and according to the recently published daratumumab data (6), the exponential could be a conservative estimate.

	In recognition of the uncertainty inherent in this appraisal we have provided several alternative cost effectiveness results. The deterministic ICERs for these range from £73,934 to £99,038 at academic / commercial in confidence information removed PAS and academic / commercial in confidence information removed. Note that these do not incorporate the PAS prices for any other products which are unknown to us. Sensitivity analyses including CEAC, scatter plots and one-way sensitivity analysis are included in the appendices. These new analyses including the academic / commercial in confidence information removed discount offered should give the committee confidence to recommend isatuximab for inclusion on the CDF. This decision will provide interim access for patients with high need and resolve the remaining uncertainty in the evidence base. In the next section we discuss the clinical plausibility of the better prognosis for patients treated with triplet therapies including an IMiD and an anti-CD38.
4	**The immunomodulatory effect of isatuximab in combination with pomalidomide is a critical part of the mode of action for IsaPd and is likely to be reflected in extended OS.** **Isatuximab has multiple modes of action** CD38 is considered a good target for the treatment of multiple myeloma because MM cells overexpress several surface adhesion molecules including CD38. This contrasts strongly with the much lower levels of expression of CD38 on normal cells. Anti-CD38 mAbs including isatuximab have been shown to have broadly three different mechanisms of action (MoA) which are summarised below with particular reference to isatuximab (Table 14). The first two MoAs target MM cells. The third MoA, immunomodulation is also now understood to be an important part of the efficacy shown by the anti-CD38 class. [For examples see: Jain, 2020 (13), Krejcik, 2016 (14), Adams, 2019 (15), Feng 2017 (16)]

Table 14: The multiple mechanisms of action for isatuximab

Targeting MM cells		Immune system targeting
Fc-dependent immune effector mechanisms	**Direct effects**	**Immunomodulatory effects**
Complement-dependent cytotoxicity	Caspase-dependent apoptotic pathway	Elimination of CD38-positive immune suppressor cells, such as T_{Regs}, regulatory B cells, and myeloid-derived suppressor cells
Antibody-dependent cell-mediated cytotoxicity (ADCC)	Lysosome-mediated cell death pathway	Inhibition of growth and survival factor transfer from bone marrow stromal cells.
Antibody-dependent cellular phagocytosis (ADCP)		

Targeting the body's immune system is a key component of the anti-CD38 MoA

Reducing immunosuppressive cells improves the body's innate ability to fight disease, so alongside the MOAs associated with killing tumour cells directly, it is critical to recognise immunomodulation as part of the mechanistic action of isatuximab in the context of overall survival.

Multiple myeloma (MM) cells have a strong relationship with the bone marrow microenvironment which supports their proliferation and survival. In MM changes take place in the bone marrow microenvironment that lead to loss of functional immune surveillance (17). These changes are associated with increasing levels of immunosuppressive cells such as Regulatory T cells (T_{reg}) and B cells. T_{regs} are the most extensively studied immunosuppressive cell subset in cancer immunology including MM (16). T_{regs} modulate the response (function and proliferation) of other immune cells. Increased levels of Tregs cause immune dysfunction, allowing the tumour to go unchecked. Elimination of T_{regs}, "removes the breaks on the immune system" and targets the tumour for elimination.

	Levels of T_{regs} often correlate with tumour burden and disease progression in MM. This is because the frequency of T_{regs} gradually increases in the bone marrow microenvironment with more progressive MM and accumulation of T_{reg} in this tumour microenvironment is associated with reduced survival [(16) and references therein]. These data also suggest that myeloma patients have elevated levels of activated T_{regs} in comparison to healthy controls suggesting the normal immunosurveillance is dysregulated. It has been found that all immunosuppressive cells such as T_{Regs} express high levels of CD38 similar to that found on malignant MM plasma cells and these are targeted by CD38 directed antibodies such as isatuximab (17). Therefore, in targeting CD38, Isatuximab also inhibits the suppressive function of T_{Regs} and other immunosuppressive cells by reducing their numbers, decreasing immune inhibitory cytokine production, and blocking their trafficking. This results in improved anti-tumour immune responses. Thus, CD38-directed antibodies target not only MM-cells but also immunosuppressive cells such as the T_{Regs}. It is also of note that in this way the anti-CD38s inhibit growth and survival factor transfer from bone marrow stromal cells which is also necessary for MM cell proliferation. This has also been similarly reported in association with daratumumab Several reviews have been published very recently highlighting the importance of the immunomodulatory mode of action in MM therapy (17),(18) and several in-vivo and in-vitro studies have examined the phenomenon (14),(15),(16). Very recently a publication examining patients with RRMM treated with the anti-CD38 therapy daratumumab directly assessed T_{reg} levels in this context. The results indicated an association between durable response and immunomodulatory mechanisms. The authors state that immunomodulatory effects obtained by depleting CD38+ T_{regs} may prove to be more important than any direct effects of daratumumab. Isatuximab has been shown to similarly deplete T_{regs} and like daratumumab to also further enhance NK− and CD8+ T effector cell-mediated anti-tumour immune responses. This latter point means that use of the anti-CD38 class may restore immune effector cell function as well as depleting immunosuppressive cells (16). **The synergistic effect of IMiDs and anti-CD38 therapies is significant** It is well known that the combination of the immunomodulatory drugs (IMiDs) lenalidomide and pomalidomide with the anti-CD38 therapies has synergistic benefit (19). MM impacts the regulation of multiple cellular compartments of the bone marrow, with plasma cells at the heart of the dysregulation. IMiDs have a wide range of modes of actions which not only include direct targeting of MM cells but influence the dysfunctional bone marrow

	microenvironment. The combination of an IMiD and an anti-CD38, utilises multiple effector mechanisms which enhance not only plasma cell destruction, but also augments host tumour cell immune response. Existing data also demonstrates that treatment with an IMiD, elevates the levels of CD38 on the activated/induced T_{reg} population, and therefore priming them for directed targeting by anti-CD38 therapies. Hence upregulation of CD38 expression on these cells is likely to provide a deeper immunomodulatory response when IMiDs are used combination with the anti-CD38s for the reasons discussed above. This may be critical for sustained myeloma disease control and improved patient outcomes. In addition, while patients develop resistance against the direct anti-MM effects of IMiDs, several analyses have revealed that their T- and NK-cell activating properties remained largely intact, making IMiDs ideal partners for combination immunotherapies (17). **The immunomodulatory effect is likely to extend beyond treatment duration** As discussed above, very recently the median overall survival for daratumumab monotherapy was published. Median OS in daratumumab treated patients was 20.5 months (95% CI 16.6 to 28.1) (6) and Janssen attribute this at least in part to the immunomodulatory mechanism of action of daratumumab or the inhibition of growth and survival factor transfer from bone marrow stromal cells. We believe that the outcomes for IsaPd treated patients are likely to be much improved over even these impressive results through the contribution from the synergistic immunomodulatory actions of pomalidomide and isatuximab in combination. It is worth reiterating that in the 4L population median PFS for daratumumab treated patients was 3.7 months in the SIRIUS study (20) and median PFS was 13.31 months (7.425; NC) in ICARIA-MM for IsaPd treated patients. A naive comparison of these results suggests the triplet therapeutic option provides significantly more benefit than monotherapy which is likely due in part to the immunomodulatory effects discussed above. In summary, targeting CD38 with Isatuximab induces immunomodulatory effects which both relieve immunosuppression and trigger anti-MM immunity. This helps to restore the pre-existing anti-MM T-cell responses in the bone marrow microenvironment and can be thought of as ‘resetting’ the immune system. This is likely to provide benefits much beyond the duration of treatment with IsaPd. Given the lack of mature OS data from ICARIA-MM we have discussed above various approaches to the extrapolation of the outcomes data over time including the use of PFS to estimate OS. The weight of the evidence presented suggests that the original company extrapolations for OS using the exponential estimator are plausible and that the new analyses presented above for the PFS:OS relationship are likely to hold true. However, we do recognise the considerable uncertainty in the data at this point in time. For these reasons we are confident that a period in the CDF will provide the clarity needed to validate the expected longer median OS duration and determine the true benefit due to the triplet combination of IsaPd.

	Subsequent treatments in ICARIA-MM do not reflect NHS clinical practice AND adjusting trial data for subsequent treatments not available in clinical practice is appropriate but more information is needed Sanofi agree that the subsequent treatments in ICARIA-MM do not reflect UK clinical practise with respect to daratumumab monotherapy and lenalidomide use following 4L treatment. This is not dissimilar to other trials in this line of treatment (1). Clinical experts, on the day of the AC meeting, noted that there were no standard 5th line treatments and treatments at this point in the pathway would likely be ineffective. The experts also stated that the subsequent therapies in ICARIA-MM were unlikely to affect the survival results in the 4L population. Therefore, we believe the base case which includes costs and benefits for subsequent therapies without adjustment can be considered appropriate from a cost-effectiveness perspective. To address the impact of subsequent therapies we did perform an analysis using the approach of applying HR from Cox model in the IPCW to the Pd arm (21). It is our understanding that the committee accepted this analysis but would like to see the co-variates used and the range of weights estimated. These have now been provided as a confidential reference (22). We also noted the committee's preference to see approach where individual patient data (IPD) are reconstructed from the weighted panel data set and parametric curve fitted to both arms of the trial. The reconstructed KM OS curves reported in Appendix 6. Using this method produced counter-intuitive results. The OS curve with censoring on receipt of daratumumab and lenalidomide and with IPCW adjustment are slightly higher for both groups compared with the uncensored unadjusted estimates. As the IPCW curves are supposed to reflect the counterfactual wherein patients would not have received daratumumab or lenalidomide, one would expect these censored and adjusted curves to be lower than the uncensored unadjusted curves if lenalidomide and daratumumab have a beneficial impact on OS. These results highlight the lack of robustness of the results given the small number of patients in this analysis (70% - 80% censored patients and results based on 10 to 16 patients) and likely to be biased by unmeasured factors that are associated with receipt of daratumumab or lenalidomide and survival. It may also support the view expressed by clinicians, that adjustment for subsequent therapies make no valid difference to overall survival following 4L treatment. Given the lack of clinical face validity of this approach, it was not considered feasible to implement in the model.
5	**The committee state that no analyses reflect their preferred assumptions** The committee concluded that none of the company's or the ERG's analyses reflected the committee's preferences. The committee would have preferred to see analyses that fulfilled the following 4 requirements shown in Table 15. In order to satisfy the request, we have carried out this analysis and have provided comments on technical aspects below in Table 15.

Table 15: Committee preferred assumptions

Committee requirement	Company comment
Used a Weibull extrapolation for estimating overall survival.	Implemented in the analysis as per original model settings.
Adjusted for subsequent trial treatments not used in NHS clinical practice, with methods fully reported.	Implemented in the analysis as per original model settings. Further information on how the adjustment was carried out is provide above and in a confidential appendix.
Applied the drug wastage and relative dose intensity assumptions from the company's base case.	No change - As per the original company base case.
Included a waning of the relative treatment effect for isatuximab plus pomalidomide and dexamethasone compared with pomalidomide plus dexamethasone.	We disagree with this request as discussed in the following section. Also, there is no obvious time at which a waning effect should occur. Therefore, we have chosen to implement an immediate switch to HR = 1 between the arms at the time when ~90% of patients had discontinued treatment. This was chosen on the basis that we heard in committee a preference for short term maintenance of treatment effect. This equates to 3 years in the model.

The results are presented below in Table 16 and Table 17. As above, these ICERs are based on the list prices for the comparator treatments.

Table 16: Committee preferred scenario using Weibull extrapolation for Pd OS and exponential extrapolation for IsaPd OS with academic / commercial in confidence information removed PAS discount

Outcome	Deterministic results		Probabilistic results	
	IsaPd	Pd	IsaPd	Pd
Totals, discounted				
Costs (£)	academic / commercial in confidence information removed		academic / commercial in confidence information removed	
LYs				
QALYs				
Difference IsaPd vs Pd				
Costs (£)		111,355		117,207
LYs		0.775		0.789
QALYs		0.531		0.539
ICER IsaPd vs Pd				
Cost (£) per life-year saved		143,698		148,614
Cost (£) per QALY saved		209,730		217,505

Table 17: academic / commercial in confidence information removed

academic / commercial in confidence information removed

academic / commercial in confidence information removed

It is informative to place this committee preferred scenario in the context of the previous discussion. In particular, with respect to the much more mature data from the daratumumab studies.

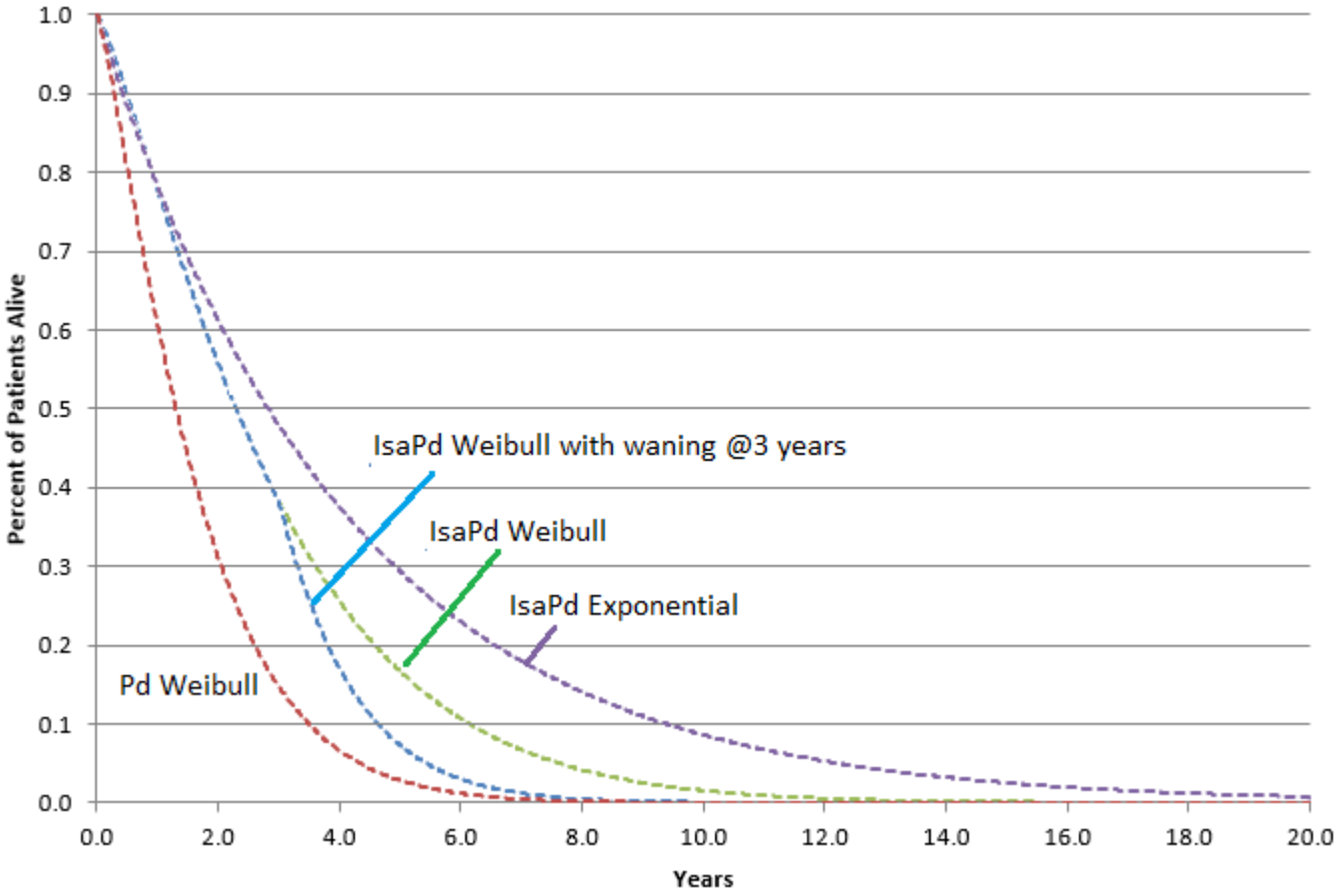
The survival curves for the truncated Weibull with waning at 3 years (blue line), the Weibull (green line) and the company preferred exponential (purple line) are shown in Figure 8 overleaf. In the committee preferred analysis only ~1% of patients remain alive in the IsaPd arm at 6.5 years and none by 7.5 years which is equivalent to the 7.5-year outcome for the Weibull estimation.

Inspection of Figure 8 reveals that with **no waning** applied to the Weibull curve (Green fit) there are less than 2% of patients alive at 10 years. We have discussed at length the likely impact of the pharmacological properties of the IsaPd triplet on long term outcomes and have noted the difference in observed daratumumab monotherapy PFS at 4.1 months vs. the observed IsaPd median PFS at 13.3 months. We have shown in the daratumumab landmark analysis above (Table 3) that with the most plausible fitting curve ~11% of patients are alive at 10 years. This suggests to us that incorporating waning in this analysis is not appropriate.

We have also discussed in the previous section how long-term outcomes for patients may be strongly correlated with response to therapy and how those patients with partial response or better are likely to survive for longer. This means that any waning effect is likely to be already incorporated into the most plausible estimates for survival that we have put forward.

	The exponential curve predicts 10 year survival at 8.6% which, considered in the light of the arguments above may be conservative because it falls under the most plausible daratumumab landmark at 10 years (Table 3). This further validates our extrapolation choices. Whilst we do not know the PAS price for pomalidomide, under the committee preferred assumptions we believe it is likely that isatuximab **would not be cost effective even at £0 price**. (When no discount is included for pomalidomide in the model the required discount to achieve an ICER of £50,000 is academic / commercial in confidence information removed. This is a perverse finding given the clear clinical benefit demonstrated by IsaPd over existing treatments and recognised unmet need at 4L.

Figure 8: Comparison of the Weibull, truncated Weibull with waning and exponential fit.



6	**We urge the AC to consider the context of this appraisal. The current system (including the NICE process and methods) is not sufficiently flexible to cope with the assessment of branded combination treatments and therefore does not sufficiently recognise their value** The clinical paradigm for oncology is changing rapidly as diseases are increasingly well understood and combinations of older drugs (which in most cases are not generic) with newer, more effective agents are becoming ubiquitous. Using drugs that work by different mechanisms in combination has been shown many times improve the probability and magnitude of therapeutic response and reduce drug resistance. As such, isatuximab in combination with pomalidomide and dexamethasone has demonstrated significant clinical benefits through a randomised comparative phase 3 trial in the difficult-to-treat patient group with lenalidomide and proteasome inhibitor refractory (double refractory) disease. Despite the very promising clinical evidence, the cost-effective price of isatuximab is significantly constrained by the confidential discounted price for the combination partner pomalidomide. The pomalidomide PAS is unknown to us but resulted in a recommendation from NICE very close to the WTP for EoL drugs. We have shown above that under the committee's preferred assumptions, isatuximab would not be cost-effective even if priced at £0 (academic / commercial in confidence information removed). Under the reimbursement system in the UK that does not disaggregate value, it is difficult to demonstrate the cost-benefit of combination treatments generally and specifically for IsaPd at 4L with no knowledge of the comparator price nor flexibility in the threshold. This issue has been widely discussed but no solutions currently exist (23). In this appraisal, the ICER is driven by (1) costs of using pomalidomide, a high cost drug, in combination with isatuximab and (2) additional PFS (5.5 months) incurring the costs of both isatuximab and pomalidomide. With no knowledge of the pomalidomide discount we nonetheless believe that we have provided a persuasive case that IsaPd can be cost-effective. However, under the NICE preferred Weibull assumptions for overall survival, isatuximab cannot meet the NICE threshold for cost-effectiveness. Pomalidomide, has already been accepted by NICE as a cost-effective treatment, therefore the additional costs arising from its prolonged use as a background therapy could theoretically be removed. This approach has been discussed in the NICE DSU review and used in other HTA submissions (23),(24). Indeed, committees have requested alternative analyses that explore the removal of backbone costs (24),(25).

	This can be done in two ways. Approach 1 is by removing the costs of Pd on the IsaPd arm for the period of time which is common to both IsaPd and Pd (Approach 1, Figure 9). The idea here is that for the period of time that Pd would be used in combination with isatuximab, only the incremental cost of isatuximab should be included in the costs. The resulting ICER of academic / commercial in confidence information removed demonstrates just how much the additional pomalidomide use is driving the cost-effectiveness of IsaPd (Table 18). Another approach is by removing the additional Pd costs in the IsaPd arm (Approach 2, Figure 9). This ICER seems appropriate and provides useful insight for the overall assessment of the cost-effectiveness of isatuximab. Removing these costs reduces the base case ICER from academic / commercial in confidence information removed at the list price for pomalidomide (Table 18)

Figure 9: Diagram illustrating 2 approaches to removing backbone costs

Table 18: Impact on the base case ICER of removing additional cost of Pd on the IsaPd arm

academic / commercial in confidence information removed

Even in the face of this substantial challenge, the analyses presented within the earlier sections of our response demonstrate that, at the academic / commercial in confidence information removed discount offered by Sanofi, it is plausible that IsaPd could be considered cost-effective (under credible assumptions) despite being assessed within a framework that does not work for and penalises branded combinations.

Sanofi are committed to working with the ABPI, NHSE and NICE to seek a solution to this issue to ensure that this does not result in patients being denied access to valuable treatments in the future but would emphasise that there is an unmet need for isatuximab now and that these patients cannot wait for a permanent solution to be developed.

7	**The committee have concluded that Isatuximab plus pomalidomide and dexamethasone does not meet the Cancer Drug Fund (CDF) criteria** According to the criteria for a positive recommendation via CDF, there must be plausible potential for IsaPd to satisfy the criteria for routine commissioning, but significant clinical uncertainty remaining which needs more investigation. This might be through data collection in NHS clinical practice or continuing company sponsored clinical studies. In this appraisal the clinical uncertainty, the plausible extrapolation for long term overall survival and the confidential price of pomalidomide are key determinants for whether the IsaPd combination can be plausibly cost-effective for the NHS. The current uncertainty regarding long term survival is undeniable and we are pleased that the appraisal committee has accepted that this is due to the large proportion of patients still alive at the 2018 data cut. However, there were some concerns raised which we address below. **Insufficient time for data to be collected via CDF on overall survival, time on treatment and subsequent therapies in practice** • ICARIA-MM study will provide further data to reduce uncertainty and validate extrapolations for long term survival The outcomes presented in this appraisal are based on a data cut from almost 2 years ago (October 2018). Given the high level of censoring at this cut off it is clear that there is significant need for further time to allow more mature data to become available from the trial. The original power calculations for the study suggested that 220 deaths would be needed to achieve 79.3% power in the ITT population. An interim data cut is planned after ~90% of these 220 deaths have been recorded. This is predicted to occur in early academic / commercial in confidence information removed, providing a further 2 years of outcomes data. The results from this interim analysis are expected to become available in academic / commercial in confidence information removed. The final OS analysis with ~220 events is again event-driven and is anticipated between academic / commercial in confidence information removed. Once these final OS data are recorded, which will provide almost academic / commercial in confidence information removed more data than currently available, the trial data will be sufficiently powered to enable the extrapolations for IsaPd and Pd to be calculated more robustly at both 3L and 4L. (It is worth noting that clear separation of the 4L OS KM data is evident almost from the outset providing a clue as to the potential benefit of IsaPd vs. SoC). Until this time, it is difficult to determine with certainty what the most appropriate extrapolations for the OS data are but with the current building evidence base for next generation and triplet combination therapies it is highly likely that the Weibull estimator offers extremely conservative view of long term outcomes for IsaPd at 4L or at 3L. We have provided arguments to support this view above. Evidence for 3L outcomes will also be more mature and can be used to inform comparison, particularly vs Pd. The case for the 3L positioning is made in a following section.

Other CDF agreements at 4L in RRMM have demonstrated that the Public Health England/NHSE databases can inform uncertainties in overall survival and subsequent therapies (1). Table 19 details how uncertainties in the current IsaPd evidence base can be addressed with further evidence collection in the CDF and when this data may become available.

Table 19: Areas of uncertainty for IsaPd and how these can be addressed via the CDF

Area of uncertainty	Data source	When will this be available	How will this address the uncertainty
Immature OS data	ICARIA-MM	Current data cut – October 2018 Interim OS – academic / commercial in confidence information removed Final data cut is academic / commercial in confidence information removed	There are 99 completed events (32%) in the current data cut. At the interim analysis for OS, it is expected that there will be 50%-60% completed events in the 4L population. The final OS analysis data cut will provide academic / commercial in confidence information removed of additional overall survival data when an anticipated 65% of OS events are expected in the 4L population.
Subsequent therapies	ICARIA-MM	Final data cut is between Oct academic / commercial in confidence information removed	More complete data will be available on which IPCW analysis can be performed to adjust for post study treatments.
Immature OS data, TTD	NHSE Blueteq	For the duration of the MAA	Refractory status by line of treatment, total number of patients starting treatment, time on treatment, reasons for discontinuation

Immature OS data, generalisability of outcomes to English patients and subsequent therapies used in routine practise	PHE/SACT	For the duration of the MAA	Patient baseline characteristics, treatment duration, subsequent treatment (where possible) and survival status (number of death events and time to death following the first dose of IsaPd can be collected via Public Health England)
TTD	PHE databases	For the duration of the MAA	Time on treatment can be used to validate TTD curves or be used as a proxy for PFS

Insufficient patients available at 4L to inform data collection due to 2nd line (2L) use of daratumumab via the CDF

It is important to note that **daratumumab is not a relevant comparator due to its position on the CDF at both 2L and 4L** so should not feature in the decision-making process during this appraisal. The following information is provided to show that in real world clinical practice the proposed place in therapy for IsaPd remains an area of unmet need for patients entering 4L naïve to anti-CD38 treatment today and will do so for several years to come.

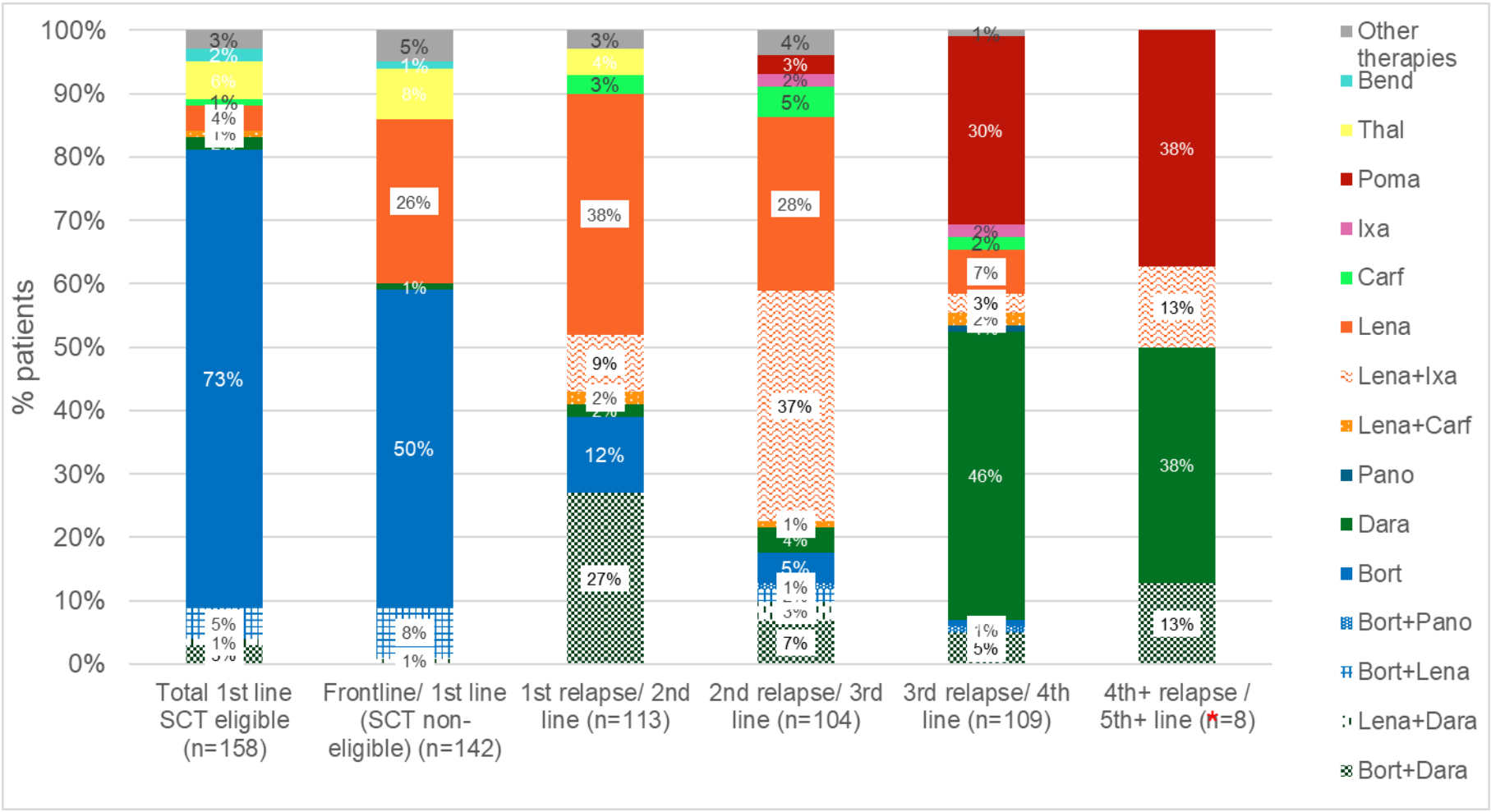
There will be sufficient patients eligible for IsaPd at 4L over the CDF period allowing adequate data collection to be performed from both the ICARIA-MM final OS cut and NHSE/PHE databases:

- Daratumumab with bortezomib and dexamethasone (DVd) has been recommended via CDF in April 2019. While uptake of this combination is increasing at 2L, based on the estimated progression-free survival on DVd (26 months), the length of time between 2L and 3L (5 months (26)) and the anticipated time on 3L treatment before progressing to 4L (e.g. PFS on PanVd is 7.8 months [TA380](3)), we estimate that it would take at least 3 years for the patients receiving DVd to reach 4L. This is likely to be beyond the lifetime of the CDF duration for IsaPd.
- Patients presently receiving treatment at 3L, or who were not eligible for DVd at 2L, will progress to 4L and be eligible for IsaPd. academic / commercial in confidence information removed,. The rapid uptake in the EAMS programme suggests that even with daratumumab monotherapy available at 4L, there remains a place for IsaPd which clinicians tell us may be the preferred choice as

	an anti-CD38 triplet therapy over monotherapy due to likely improved outcomes. It is also expected that IsaPd will displace Pd at 4L were it to be recommended. • Finally, the NICE position paper states that **treatments in the CDF are not relevant to the decision problem as long term reimbursement decisions and in-market price are unknown therefore the impact on eligible patient numbers due to treatment funded via CDF earlier in the treatment pathway should not influence decision making at 4L** (27). • Whilst the patient pool eligible for an anti-CD38 at 4L will undoubtably dwindle, at the end of the CDF period there will still be an unmet need and some patients will require IsaPd treatment. These may be people treated with a prior anti-CD38 who have not become refractory or patients who are naïve to anti-CD38. It is true that at the time of isatuximab exit from the CDF, the treatment landscape is likely to have evolved with newly recommended treatments (such as lenalidomide at 1st/2nd line) becoming more embedded in clinical practice, routine commissioning for DVd at 2L may be available, and the pomalidomide price may have also changed if the elotuzumab appraisal is re-started (ID1467) or a generic is launched. Pd may move to 3rd line position. Nonetheless there is **demonstrable unmet need today at 4L** and we are concerned that these patients with poor prognosis and very limited life expectancy may be denied access to a life-extending drug on the basis of speculation around changes to a pathway that are irrelevant to them. **Conclusion** The analyses provided in this response indicate that IsaPd could be considered plausibly cost-effective. We acknowledge these analyses are currently very uncertain but data being collected and that could be collected during a potential MAA, could be used to validate the overall survival extrapolations (the key driver of uncertainty) presented within this response, dramatically reducing the existing level of uncertainty. **Sanofi therefore suggest that IsaPd is an ideal candidate for the CDF.**
8	**Sanofi recognises that there is an emerging unmet need for new effective third line (3L) treatment options, after 2 previous treatments.** Recognising the committee request for further discussion and analysis to address the emerging gap in the treatment pathway at 3L we provide an exploration of the 3L position for IsaPd below.

	AT the outset it is important to note that whilst DVd is in the pathway at 2L, it is provided on the CDF and so should not feature in the decision making for this appraisal. It is discussed below in terms of the pathway and how it may affect patient flow in the future. Our base case population was fourth line (4L) patients who have received 3 prior lines of therapy. This is where clinicians have told us the current unmet need is. The rapid uptake of patients into the Early Access Medicines Scheme (EAMS) at 4L (academic / commercial in confidence information removed in 5 months), reinforces the high unmet at 4L need despite the recent availability of daratumumab via the CDF at 2L. Recent market research by IQVIA show that lenalidomide-based regimens are still the predominant treatments at 3L (March/April 2020) either routinely commissioned or via the CDF in combination with ixazomib (approximately 65%) and that daratumumab in combination with bortezomib and dexamethasone (DVd) is increasingly being used at 2L via the CDF (most up to date estimate is 27%) (Figure 10) (28).

Figure 10: Relative proportions of treatments received at each line (March/April 2020) (28)



	We acknowledge that the treatment paradigm is changing with the recent approval of lenalidomide earlier in the pathway (untreated multiple myeloma and after 1 previous treatment) and it is likely that there will be increasing numbers of patients at 3L who have had prior lenalidomide exposure. This can be seen by the market research data above. Currently the main outcomes at 2L are as follows: Median progression-free survival (PFS) for lenalidomide plus dexamethasone (Rd) at 2L is estimated to be 48.1 weeks (95% CI: 36.4, 62.1) (29). DVd at 2L provides a median PFS of 26 months compared with bortezomib plus dexamethasone alone at 8 months (hazard ratio [HR] 0.23, 95% confidence interval [CI] 0.16 to 0.33; p<0.0001) (30). Based on these clinical outcomes, we expect DVd to remain one of the main treatments of choice at 2L with Rd used in those patients for whom DVd is not an option. Therefore, recognising currently there may be some patients at 3L who would be eligible for IsaPd we did submit evidence comparing IsaPd to Pd in patients with 2 prior lines (i.e. 3L patients) in our original dossier. This analysis was derived from outcomes for patients from ICARIA-MM who had received two prior lines of therapy. The 3L cohort in ICARIA-MM is smaller than the 4L cohort (N=90 vs N=110), and although the current data are extremely immature for overall survival (Figure 11) clear separation of the curves is observed for progression-free survival.(Figure 12).

Figure 11: Kaplan Meier plot for 3rd line- IsaPd vs Pd- Overall Survival

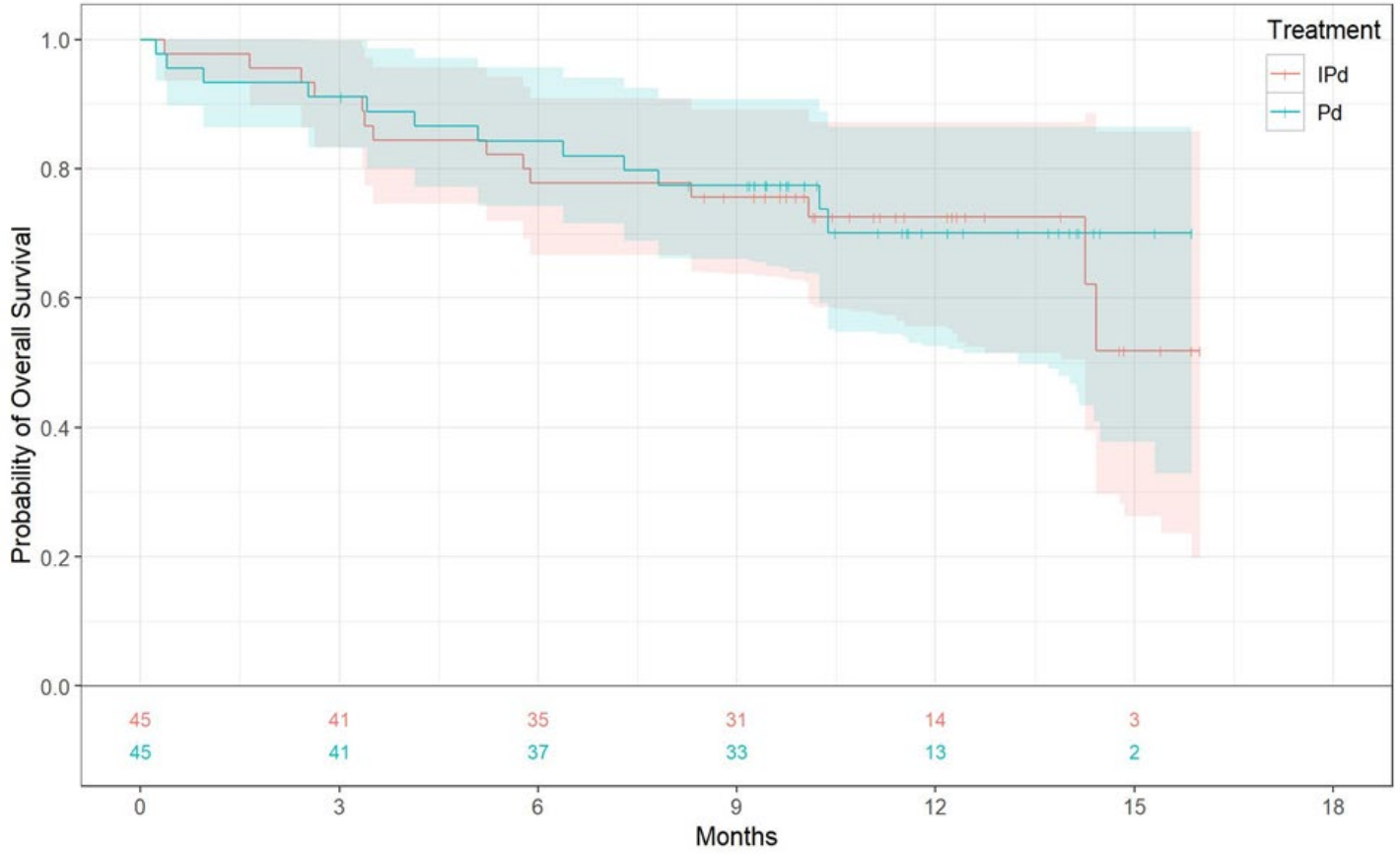
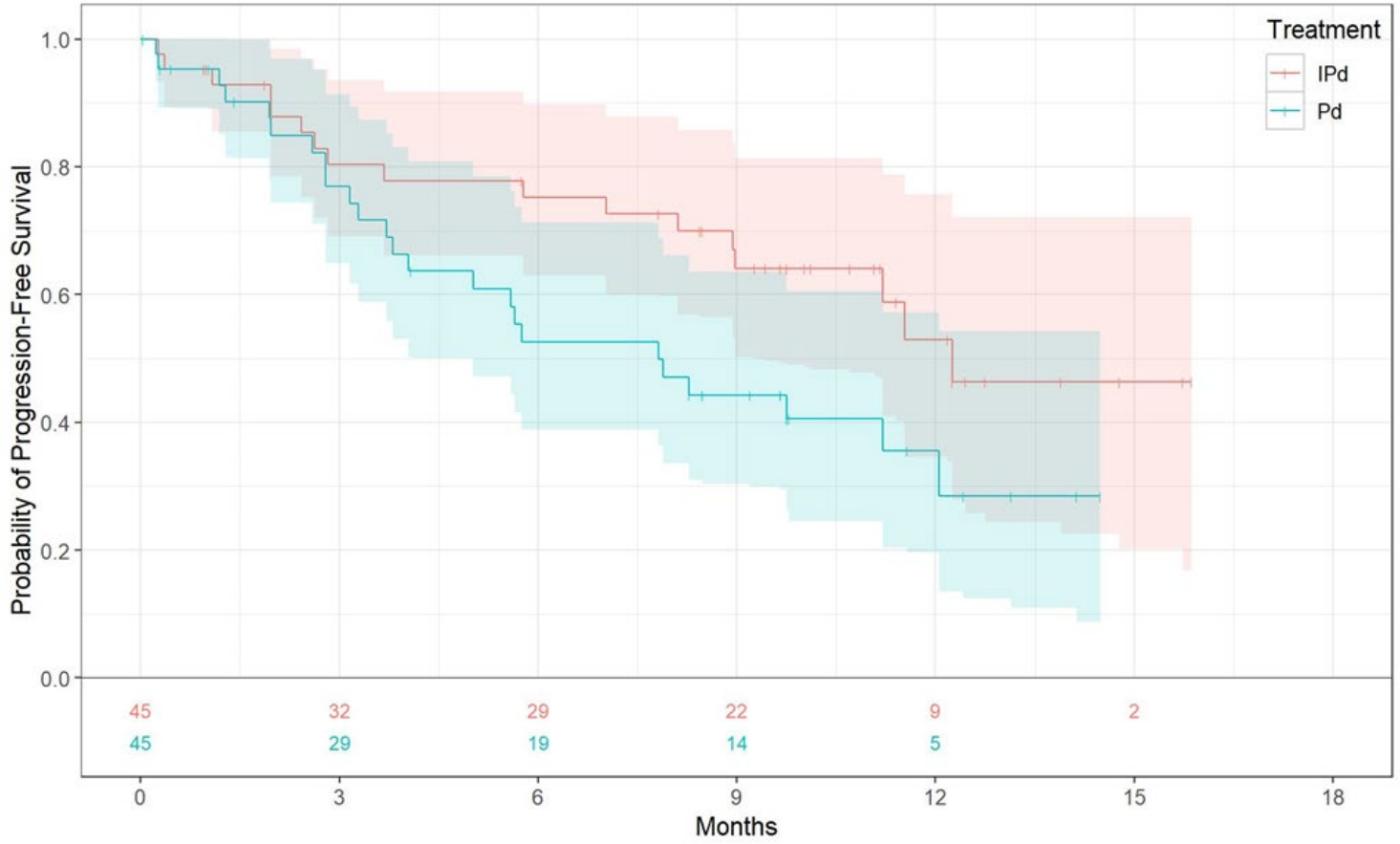


Figure 12: Kaplan Meier plot for 3rd line- IsaPd vs Pd- Progression free survival



In response to the request by the appraisal committee, we have conducted a cost-effectiveness analysis versus PanVd at 3L and this is reported here. The cost-effectiveness is based on a matched-adjusted indirect comparison (MAIC) reported in an Appendix 7. (Originally reported in Appendix K to the company submission). As PANORAMA-2 does not report outcomes by line, the MAIC has been performed using the ITT population of ICARIA. Below are the MAIC-adjusted KM curves for PFS and OS for IsaPd (Figure 13 and Figure 14).

Figure 13: MAIC-Adjusted PFS for IsaPd and PanVd

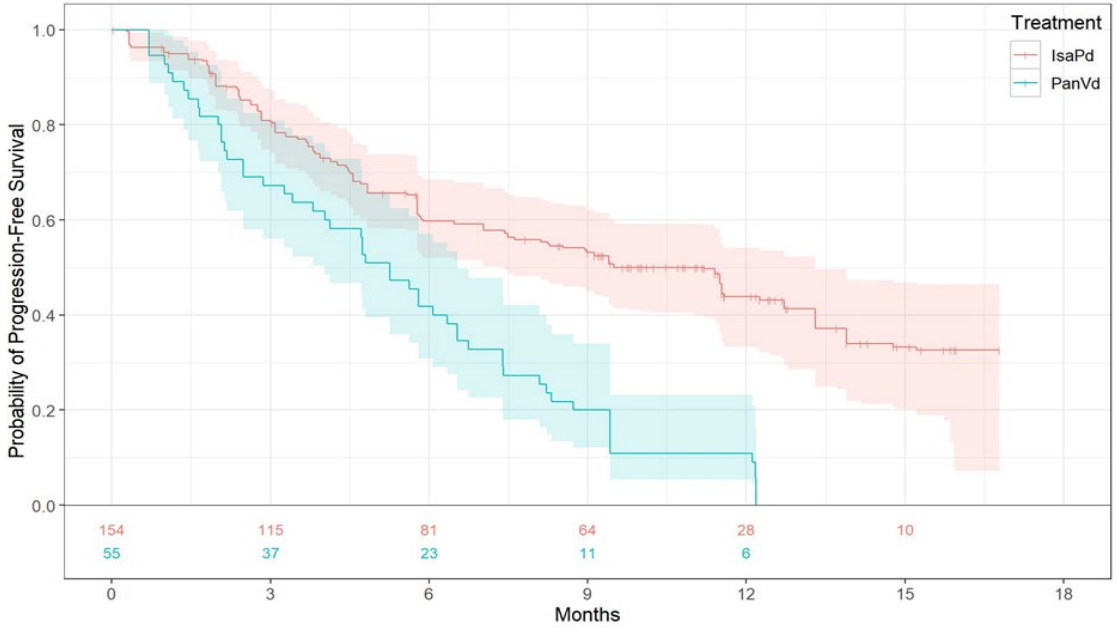
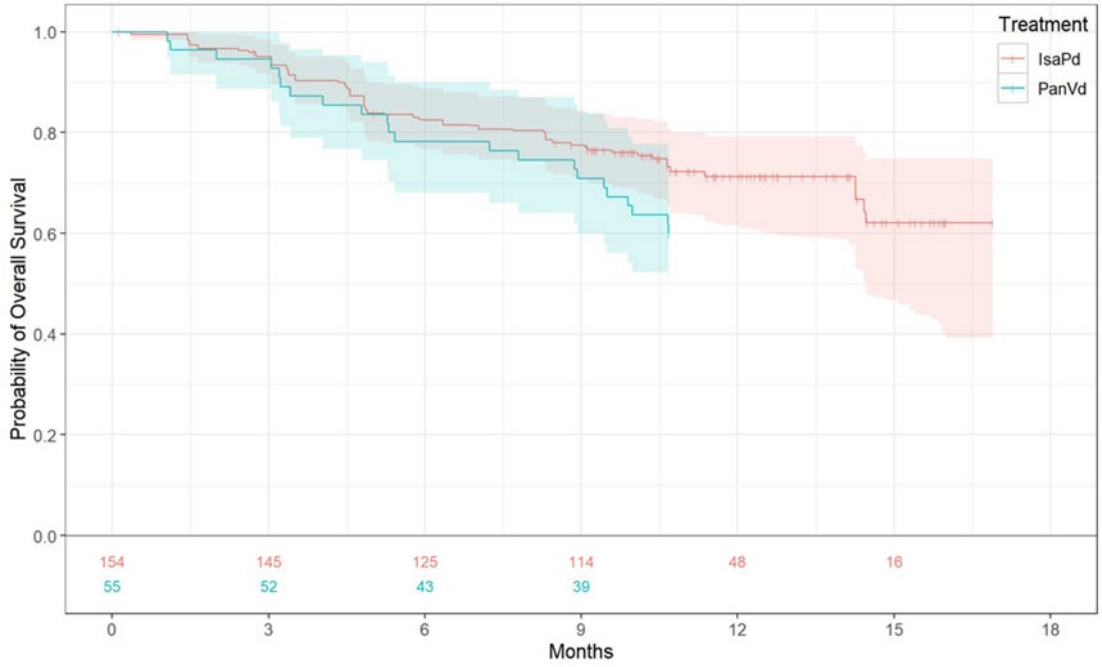


Figure 14: MAIC-Adjusted OS for IsaPd and PanVd



Estimates of PFS and OS for PanVd were obtained by applying the MAIC-adjusted HR for PanVd vs. IsaPd to the unweighted 3L PFS and OS for IsaPd. The application of these MAIC-adjusted HRs in this fashion was considered reasonable as tests of the linearity of Schoenfeld residuals for the comparison was not statistically significant. HRs derived using the results of the ITC of trials for treatments for PanVd are shown in Table 20 below.

Table 20: HRs for PFS and OS from MAIC of HRs from Trials of Patients with RRMM

Comparator	HR vs. IsaPd (95% CI)	
	PFS	OS
PanVd	2.71 (1.90, 3.86)	1.56 (0.92, 2.63)

Based on the MAIC, IsaPd has more favourable PFS than PanVd, with a HR that is greater than 1.0 (based on the 95% CI) and is statistically significant for PanVd versus IsaPd. While the HR for OS also numerically favours IsaPd, it is not statistically different from PanVd (based on the 95% CIs).

Updated cost effectiveness results for the comparison of IsaPd with Pd at 3L

academic / commercial in confidence information removed

Results for the updated base case and scenario analyses

Below we present the results for the exponential distributions for the IsaPd arm for PanVd based on best statistical fit for IsaPd arm. Given the immaturity of the 3L data and the limitation of cost-effectiveness based on a less-than-robust MAIC vs PanVd these analyses should be considered exploratory.

Table 21 below shows the deterministic cost effectiveness estimates using the exponential extrapolation for IsaPd OS at academic / commercial in confidence information removed PAS discount. The cost effectiveness estimates calculated at 3L are heavily dependent on the estimates for OS which were also derived from the trial data. As the data is so immature and the patients treated in this earlier setting are likely to have a longer prognosis for OS there so there is unsurprisingly little separation of the observed OS data for the two arms. This leads to high estimates for the IsaPd vs. Pd ICER at 3L. Table 22 overleaf presents the same results with academic / commercial in

confidence information removed. All results are provided in an Appendix. All results are reported using list price for all other treatments. The ICERs presented here therefore not the true ICERs which will be lower depending on the level of discount on pomalidomide.

The deterministic cost effectiveness estimates derived from this analysis are presented below (Table 21). These are based on exponential distribution for all time-to-event inputs based on best fitting curves (lowest BIC).

Table 21: Cost effectiveness results using exponential OS for IsaPd vs. PanVd at 3L with academic / commercial in confidence information removed PAS discount

<table>
<tr><th rowspan="2">Outcome</th><th colspan="2">Deterministic results</th></tr>
<tr><th>IsaPd</th><th>PanVd</th></tr>
<tr><td colspan="3">Totals, discounted</td></tr>
<tr><td>Costs (£)</td><td rowspan="3">academic / commercial in confidence information removed</td><td rowspan="3">academic / commercial in confidence information removed</td></tr>
<tr><td>Lys</td></tr>
<tr><td>QALYs</td></tr>
<tr><td colspan="3">Difference IsaPd vs. PanVd</td></tr>
<tr><td colspan="2">Costs (£)</td><td rowspan="3">academic / commercial in confidence information removed</td></tr>
<tr><td colspan="2">Lys</td></tr>
<tr><td colspan="2">QALYs</td></tr>
<tr><td colspan="3">ICER (IsaPd) vs comparator</td></tr>
<tr><td colspan="2">Cost (£) per life-year saved</td><td rowspan="2">academic / commercial in confidence information removed</td></tr>
<tr><td colspan="2">Cost (£) per QALY saved</td></tr>
</table>

Abbreviations: IsaPd, isatuximab+ pomalidomide+ dexamethasone; LY, life year; PanVd, panobinostat + bortezomib + dexamethasone; QALY, quality-adjusted life year.

Table 22: academic / commercial in confidence information removed

academic / commercial in confidence information removed

Abbreviations: IsaPd, isatuximab+ pomalidomide+ dexamethasone; LY, life year; PanVd, panobinostat + bortezomib + dexamethasone; QALY, quality-adjusted life year.

Although we have endeavoured to provide the most robust analysis possible there are a significant number of limitations in making this comparison versus PanVd, as were noted for the equivalent 4L comparison provided in Appendix K.4 of the company submission. The most relevant being that PANORAMA-2 does not report outcomes by line of treatment and that MAIC-adjusted HR for PanVd vs. IsaPd using ITT data are applied to unweighted 3L PFS and OS for IsaPd. This means that the results from these 3L analyses should be interpreted with caution.

We have previously provided analyses versus Pd as we maintain that PanVd is not a valid comparator at 3L or at 4L. The clinical experts consulted by us and present at the NICE committee meeting have stated that PanVd is used 5L and that very few patients would get PanVd at 3L. This is validated by the market research we have carried out and that was presented in the company submission dossier. No treatments evaluated by NICE at 3L or 4L have included PanVd as a valid comparator.

	End of life (EoL) has been accepted at 4L by the committee. We also believe that the EoL criteria might apply at 3L. Although the survival data are very immature at 3L, the analysis above using the PFS data to predict OS shows that it is likely that IsaPd will offer an extension to life of more than 3 months (estimated LYG= 3.6). As the treatment pathway for RRMM evolves with more effective treatments being used earlier in the pathway, it is likely that the survival observed at 3L may look more like the survival currently associated with 4L. In the literature, the term 'double refractory' usually refers to a patient that has progressed on or within 60 days of receiving both a proteasome inhibitor and an immunomodulatory drug (including lenalidomide). Clinical outcomes for this group of patients have been historically poor, with a median overall survival of between 9-13 months (31),(32). Until recently, the first point at which a patient could receive lenalidomide in the UK was at 3L, meaning that most patients meeting the definition of double refractory in the UK were actually 4L patients. In moving lenalidomide earlier in the pathway, to 1L (transplant ineligible) or 2L, a patient could be now be considered 'double refractory' at 3L if they had progressed on or within 60 days following a PI and an IMiD. It is difficult to estimate the clinical outcomes for this group of patients in the UK as the change to the pathway is so recent. However, the ICARIA-MM control arm (Pd) represents a group of 3L patients who have failed both a PI and lenalidomide. The refractory rate to lenalidomide in the Pd arm was 92% and double refractory rate was 70% (33). The OS data for the ICARIA-MM 3L Pd arm is immature, but it reasonable to assume based on the curves it may not extend beyond 2 years. In addition, ELOQUENT-3, a randomised phase 2 study, looked at elotuzumab in combination with Pd in patients who had received ≥2 lines of therapy including lenalidomide and a PI. The control arm in this trial (Pd) showed a lenalidomide refractory rate of 82% and double refractory rate at 72%. The Pd OS in this trial was 17.4 months (34). This group of 'double refractory' patients at 3L are particularly relevant to this discussion as on the whole, they are CD38 naïve and could benefit from an anti-CD38 therapy especially in combination with an IMiD, such as IsaPd. In moving lenalidomide to earlier lines of therapy, patients receive this clinical benefit earlier in the pathway and efficacious novel combination therapies are needed following relapse to both a PI and lenalidomide. It is reasonable to assume that patients who are double refractory at 3L receiving standard of care therapies would have a survival of less than 2 years and would benefit from a CD38 therapy and particularly in combination. We accept that whether 3L treatment meets the end of life criteria is uncertain, but we believe this it is plausible for some patients and that this uncertainty could be addressed by further data collection were IsaPd to be recommended for use on the CDF.

	IsaPd has the potential to be a highly effective option at 3L however we acknowledge that the currently available data are very immature and current cost-effectiveness analyses are extremely uncertain. As the ICARIA data matures the true potential for IsaPd at 3L will be revealed.
9	**The committee believe that the model adequately captures the benefits of IsaPd and so it is not innovative.** In our original submission we stated that IsaPd represents a step-change in the management of double-refractory patients who have received 3 prior lines of treatment, including lenalidomide. However, the committee concluded that it had not been presented with any evidence of additional benefits from treatment with IsaPd. We agree that the model captured all of the health-related quality of life benefit observed in the ICARIA-MM study but do not agree that further benefits from treatment with IsaPd would not be realised in real world clinical practice. These may not be captured in the QALY but are nonetheless of critical importance to patients. The ACD recognises the psychological impact for patients approaching the end of the treatment pathway, where further treatment options are limited. We heard in committee the value that myeloma patients place on hope for new treatment even at later lines of therapy and that this is critical for mental wellbeing of not only the patient but also their family and friends. Patients do not want to feel abandoned at the end of lives when there is the potential for a new treatment option. Literature precedent exists to demonstrate this element of value in cancer therapies. It has been found from a willingness to pay exercise that cancer patients have a strong preference for the 'hopeful gamble' of a larger survival gain over the 'safe bet' with a narrower 'spread' of outcomes (35). This was echoed in committee when the patient expert explained that patients value treatments that delay the disease progressing, which outweighs the negative impact of their side effects. From the patient perspective it is clear that providing the care that they themselves value should be an important part of the allocative decision and so the element of hope should be particularly taken into account during the decision-making process for this appraisal. Most of the care for patients with MM is episodic and provided in the outpatient setting. This means that caregivers are essential for the optimal outcomes of patients with MM as the disease progresses. Therefore, caregivers face similar challenges to those faced by the patient. They are required to take in complex information, perform often complicated or technical procedures such as line care or injections, assist the patient with activities of daily living, and attend multiple appointments. Along with the emotional distress of living with or knowing a loved one suffering from an incurable disease, all of these additional process elements can contribute to reductions in the health-related quality of life of carers. Unexpected changes to plans of care based on patient progression are not uncommon and this also adds stress for patient and carer alike and significantly impact carers. (36) Moreover, unexpected changes to plans of care based on patient progression are not uncommon in RRMM and this also adds stress for patient and carer (36). The impact of

	hope for patients with RRMM has been discussed above and in this context, carers face a difficult and conflicting challenge. They must prepare for the possibility of death for their loved one whilst needing to reinforce an atmosphere of hope in order to help the patient manage day to day tasks of living with MM. All of these complex and interacting elements contribute to reductions in the QoL of carers (36). It is worth noting that RRMM is a disease of later life and so very often partners of patients assuming a caregiving role are older people, potentially coping with the health issues associated with later life themselves. The NICE DSU document on modelling carer health-related quality of life in NICE technology appraisals notes that there have been several instances where committees have considered the impact on carer related QoL and so precedent exists (37). Whilst the level of distress of caregivers is not routinely screened for and is therefore difficult to quantify in RRMM, for the purposes of this appraisal it should be a significant part of the deliberative decision-making process. Finally, it is critical to recognise that the triplet IsaPd combination was granted positive innovative medicine (PIM) status by the MHRA and became available through EAMS in December 2019. The scheme ran until marketing authorisation in early June 2020. [For details see: https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-isatuximab-in-combination-with-pomalidomide-and-dexamethasone-for-adult-patients. Accessed 23/06/2020]. The early access to medicines scheme (EAMS) aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. In doing so it recognises that the medicine provides significant new innovation in a setting where there is a lack of effective treatments. Isatuximab is the first triplet myeloma therapy to have been granted EAMS status and at closure of the scheme academic / commercial in confidence information removed patients had enrolled. This is despite the disruption due to COVID-19. The fact that there remained steady uptake during this time indicates the strong clinical and patient appetite for this treatment. Finally, we are concerned that despite the high unmet need demonstrated through EAMS, the strong clinical data from ICARIA-MM and the clear patient preference for life extending medicines at the end of life that people with RRMM will be denied access to a highly effective, life extending medicine because there isn't an innovative process to assess branded combinations.

Insert extra rows as needed

Checklist for submitting comments

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [ID1477]

Consultation on the appraisal consultation document – deadline for comments 5pm on **25 June 2020**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

ACD response
Appendices

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma
[ID1477]

June 2020

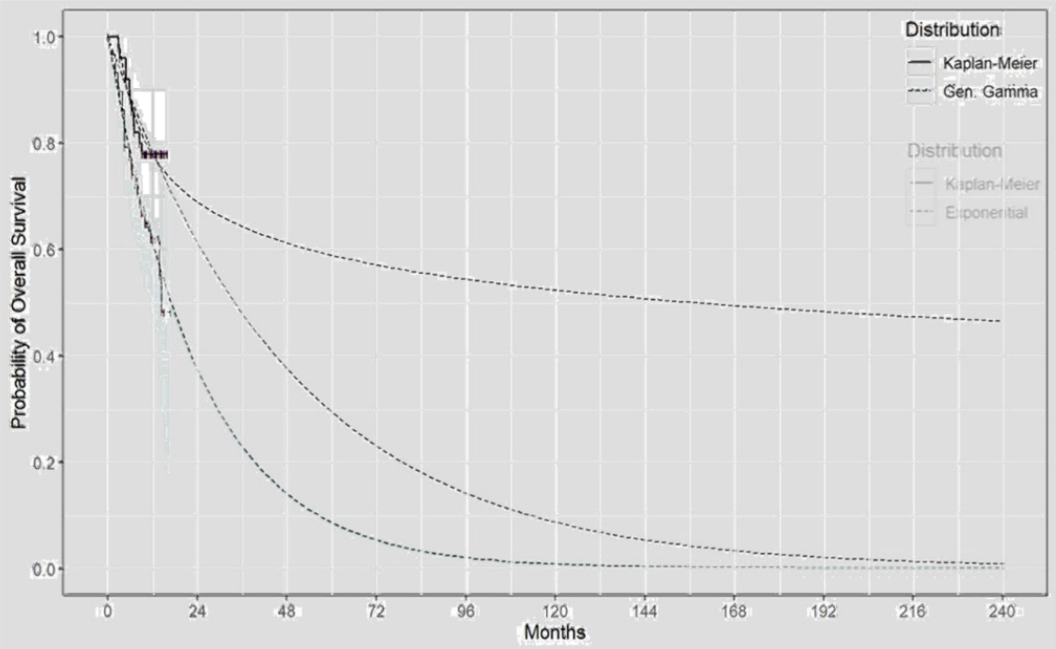
Table of Contents

Appendix 1: Independent fits for the OS curves

Summary

The curve fitting exercise for OS, found that the exponential was the best fitting distribution for Pd (based on BIC) whereas for IsaPd the generalized gamma has the lowest BIC and the exponential has the second lowest BIC. However, the projections for the generalized gamma are overly optimistic. The chart below, which is an overlay of the individually and jointly fitted exponential distributions for IsaPd and Pd, along with the gamma for IsaPd, shows that the individually and jointly fitted exponentials for IsaPd and Pd are identical. It also highlights the overly optimistic projections from the gamma. The exponential is also the best fitting curve for TTD for both IsaPd and Pd when the two study arms are fitted independently.

Independently fitted OS 4L curves



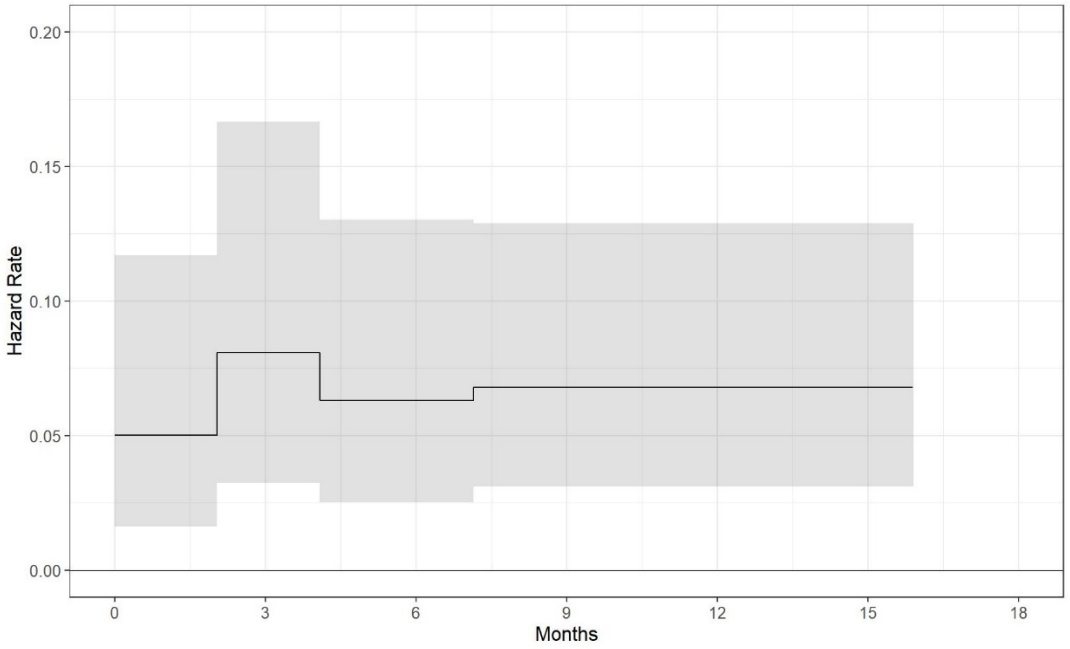
This analysis suggests that using the individually rather than jointly fitted curves for OS and TTD would not impact the selection of the distributions for these time-to-event outcomes. Since model results are determined almost entirely by these two outcomes, the use of the alternate approach of fitting curves individually rather than jointly as in the base case would have no material effect on the model inputs or results.

TTD IsaPd curve fitting results

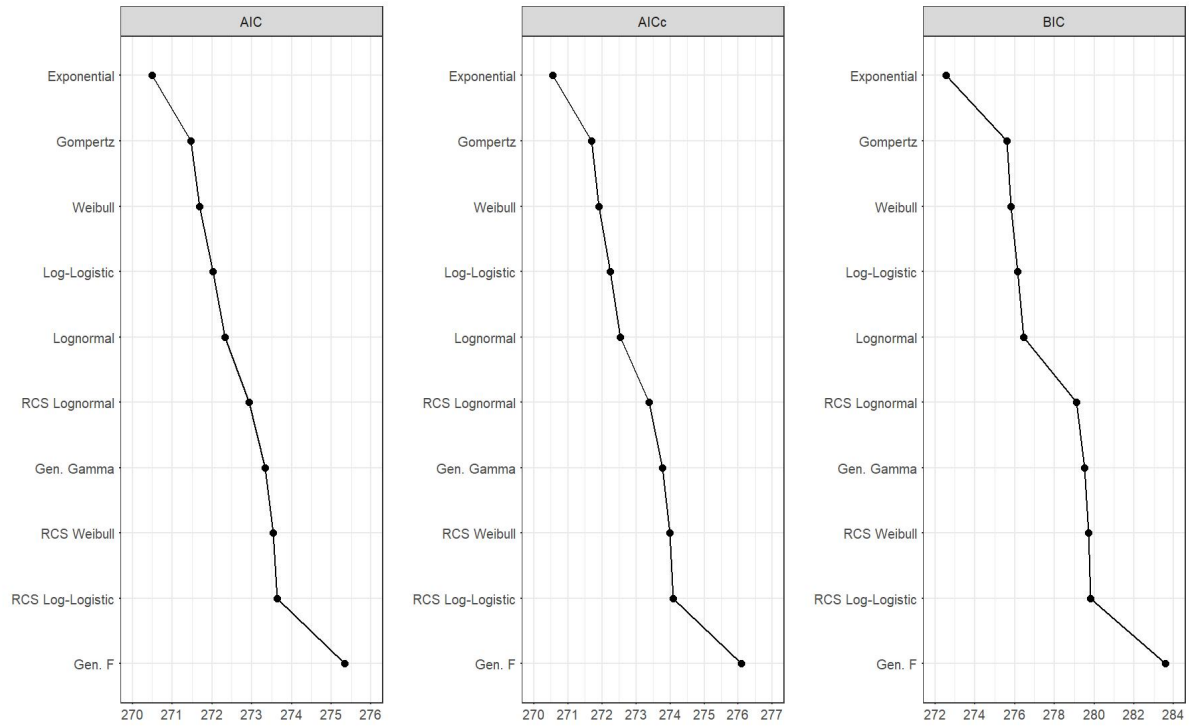
Kaplan Meier, TTD for IsaPd

academic / commercial in confidence information removed

Hazard rates, TTD



Fit Statistics, TTD



Time to Discontinuation to End of Trial Follow-Up, TTD

academic / commercial in confidence information removed

Time to Discontinuation to End of Trial Follow-Up, TTD (continued)

academic / commercial in confidence information removed

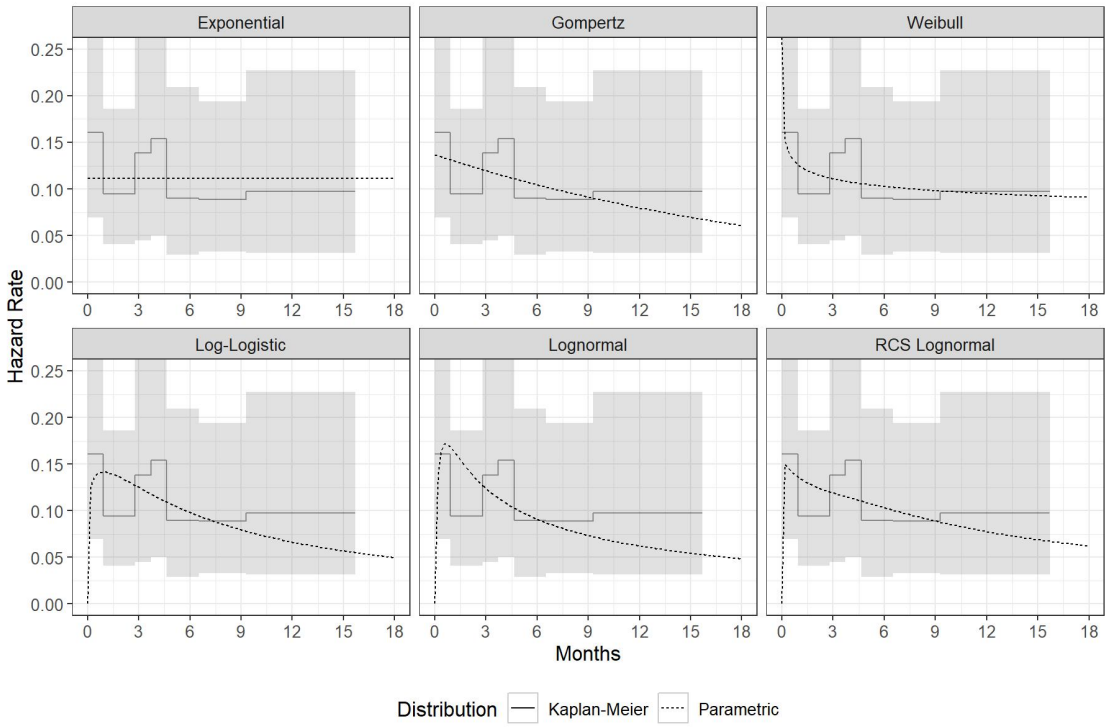
Time to Discontinuation to 20 years, TTD

academic / commercial in confidence information removed

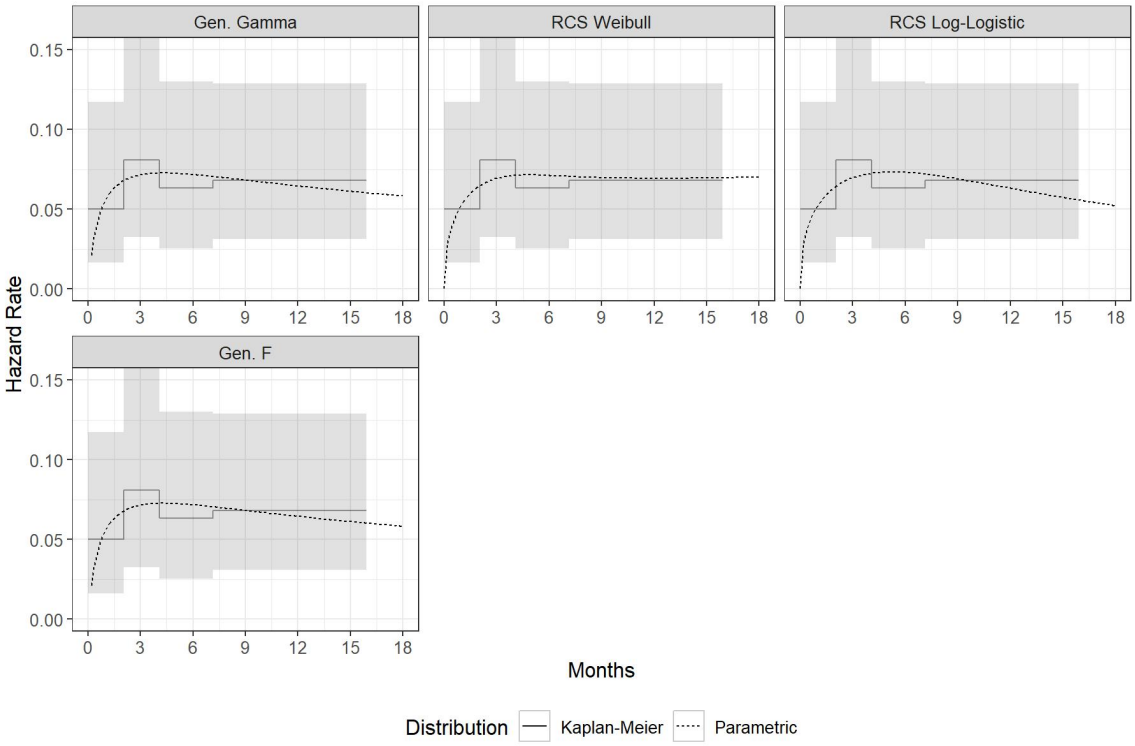
Time to Discontinuation to 20 years, TTD

academic / commercial in confidence information removed

Hazard rate to End of Trial Follow-Up

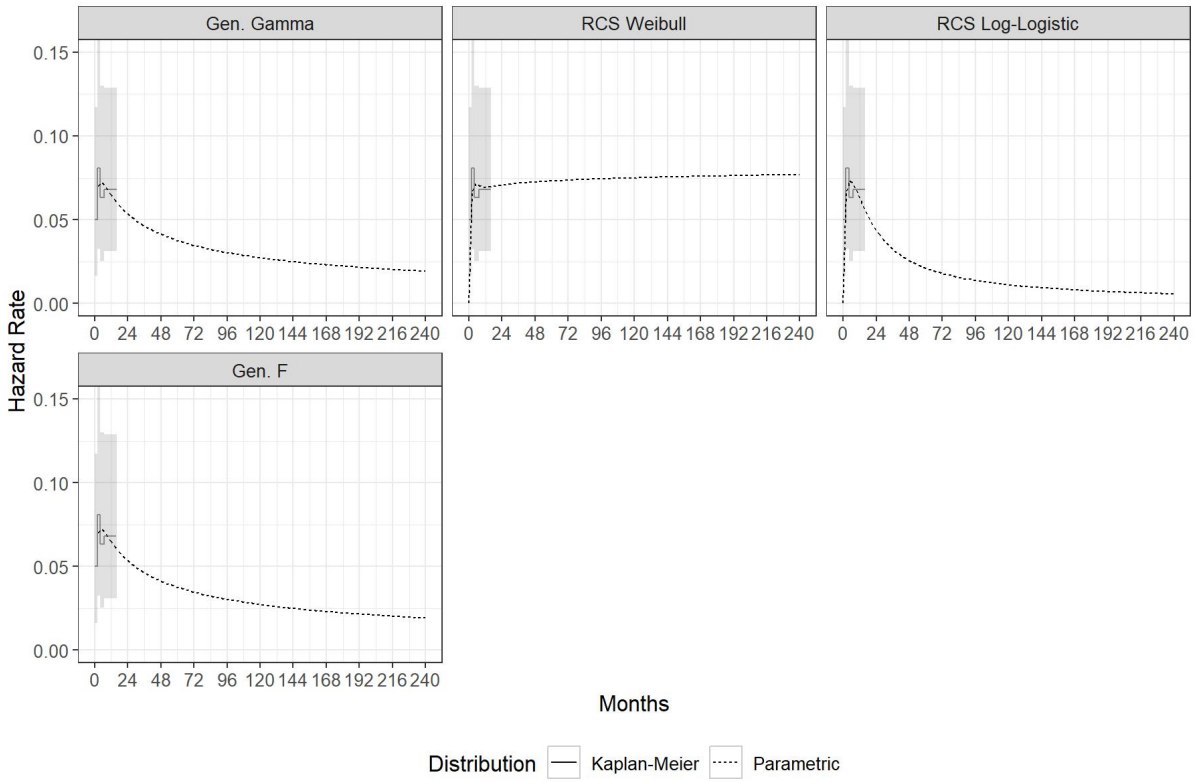


Hazard rate to End of Trial Follow-Up



Hazard rate to 20 years

academic / commercial in confidence information removed



TTD to End of Trial Follow-Up – exponential

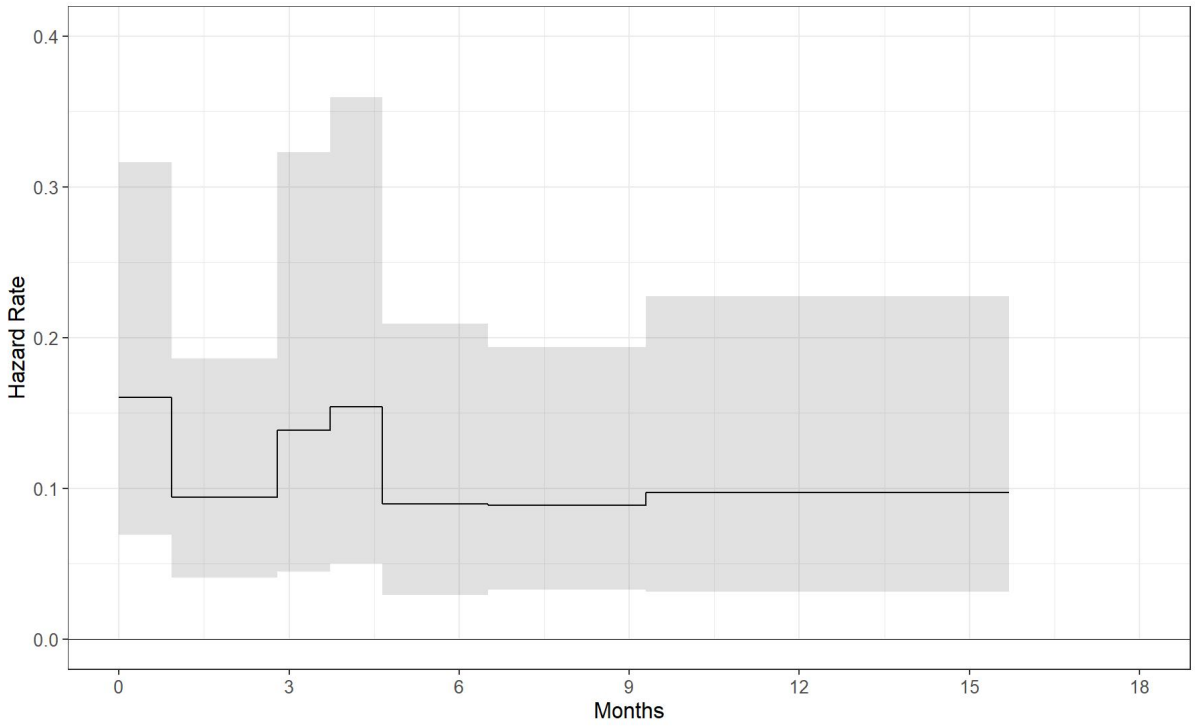
academic / commercial in confidence information removed

TTD to 20 years follow up- exponential

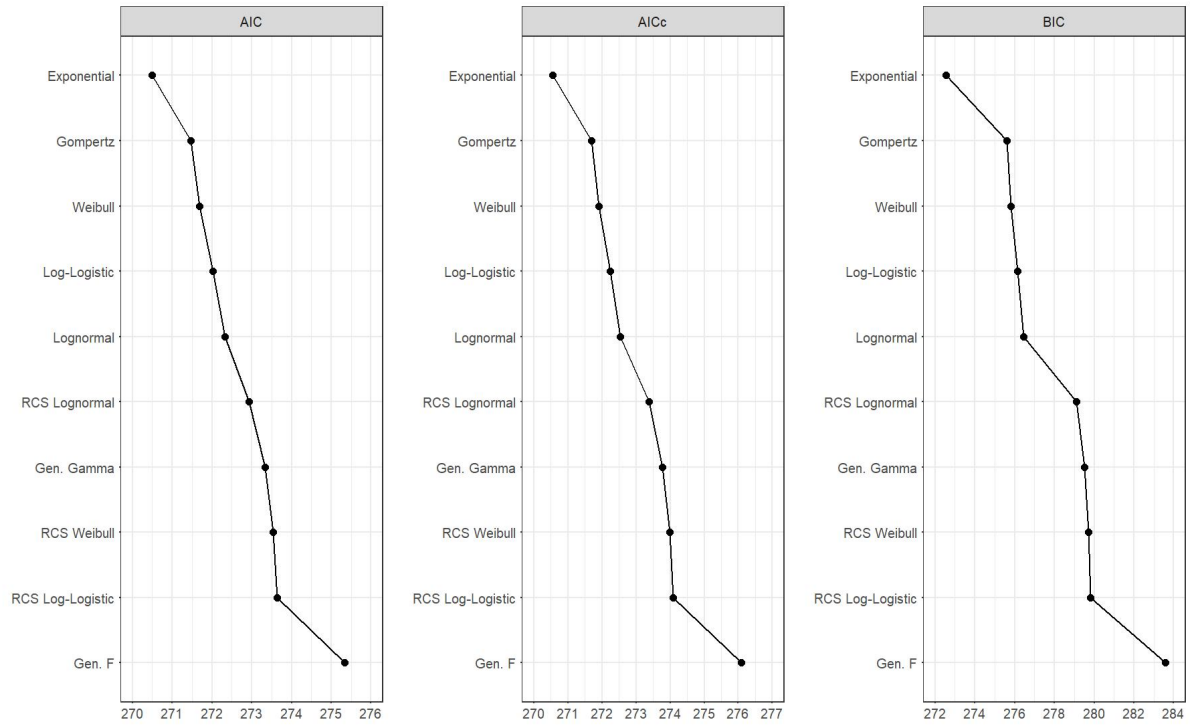
TTD: Pd

Kaplan Meier, TTD

TTD, Hazard rates



Fit statistics, TTD



Time to discontinuation to End of Trial Follow-Up

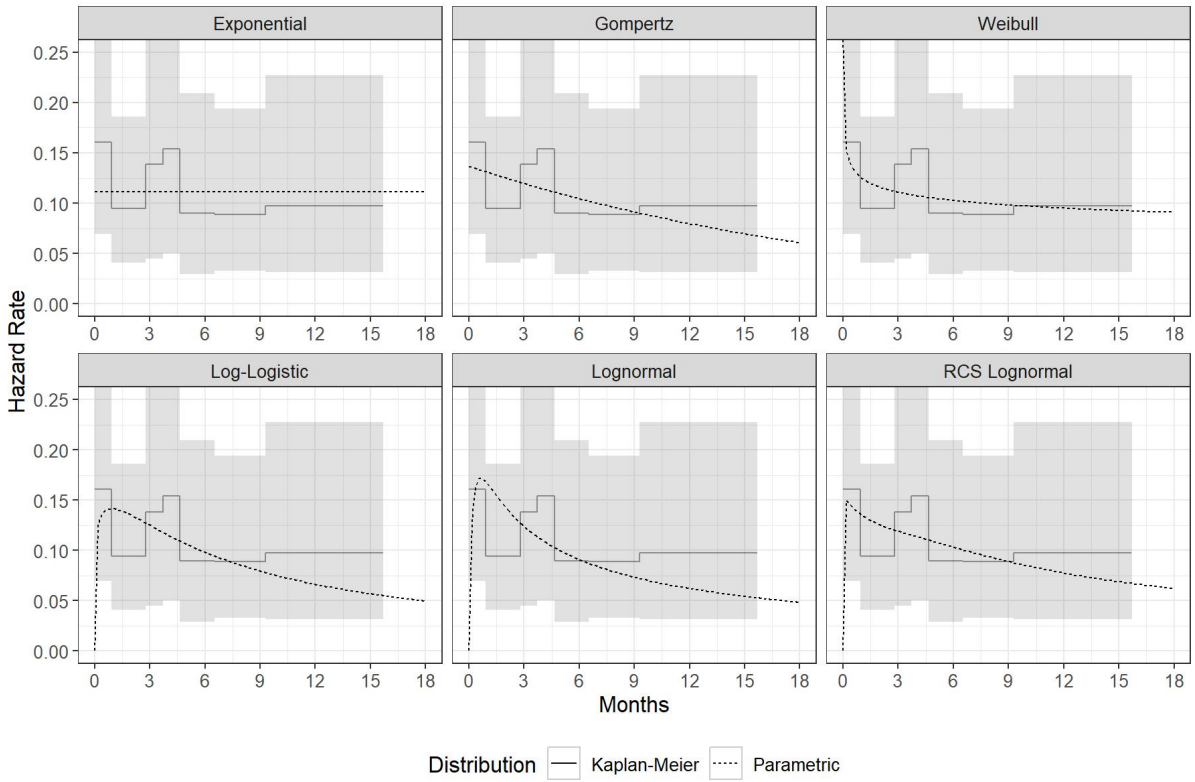
academic / commercial in confidence information removed

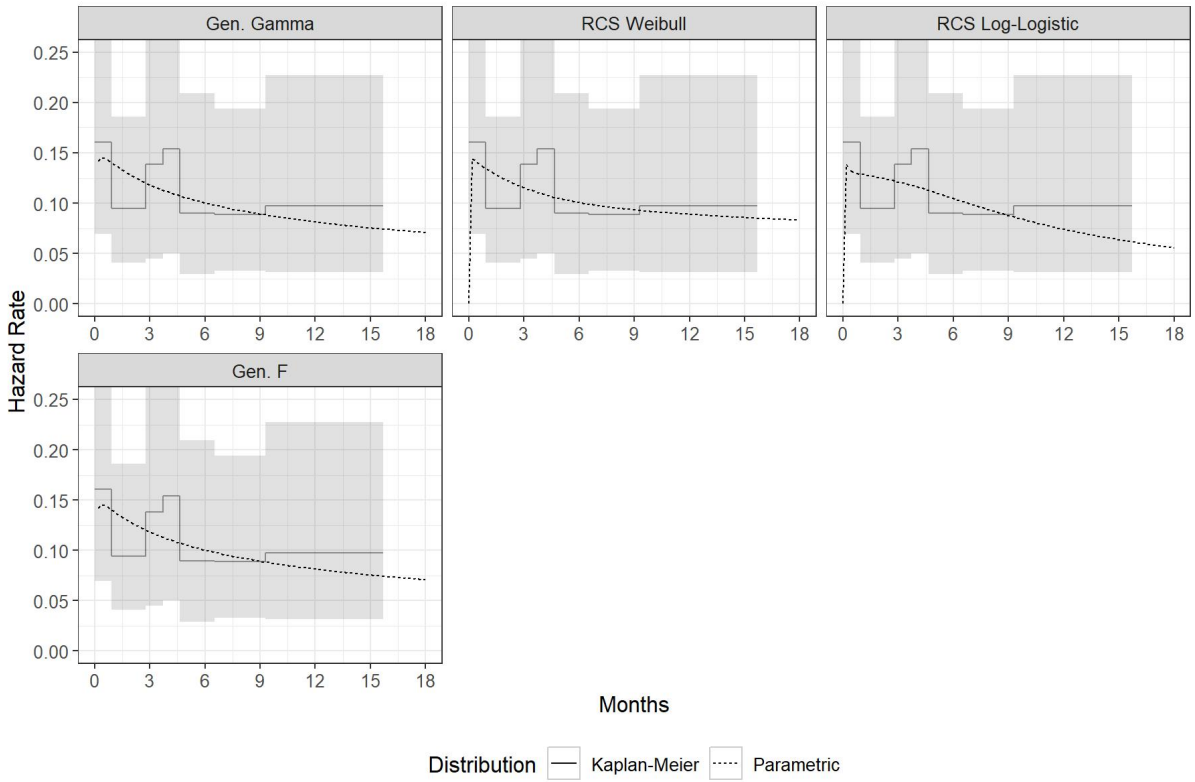
academic / commercial in confidence information removed

Time to discontinuation, to 20 years, TTD

academic / commercial in confidence information removed

Hazard rates, to End of Trial Follow-Up





Hazard Rates, to 20 years

academic / commercial in confidence information removed

TTD, Exponential, to End of Trial Follow-Up

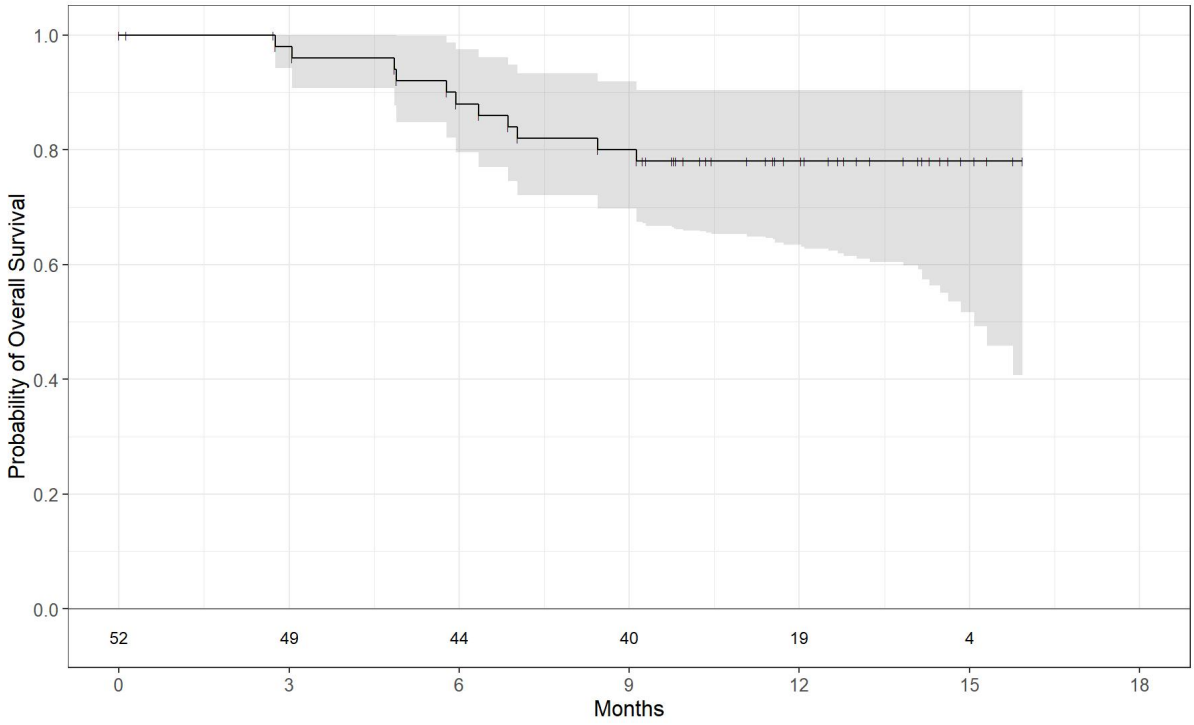
academic / commercial in confidence information removed

TTD, exponential, to 20 years

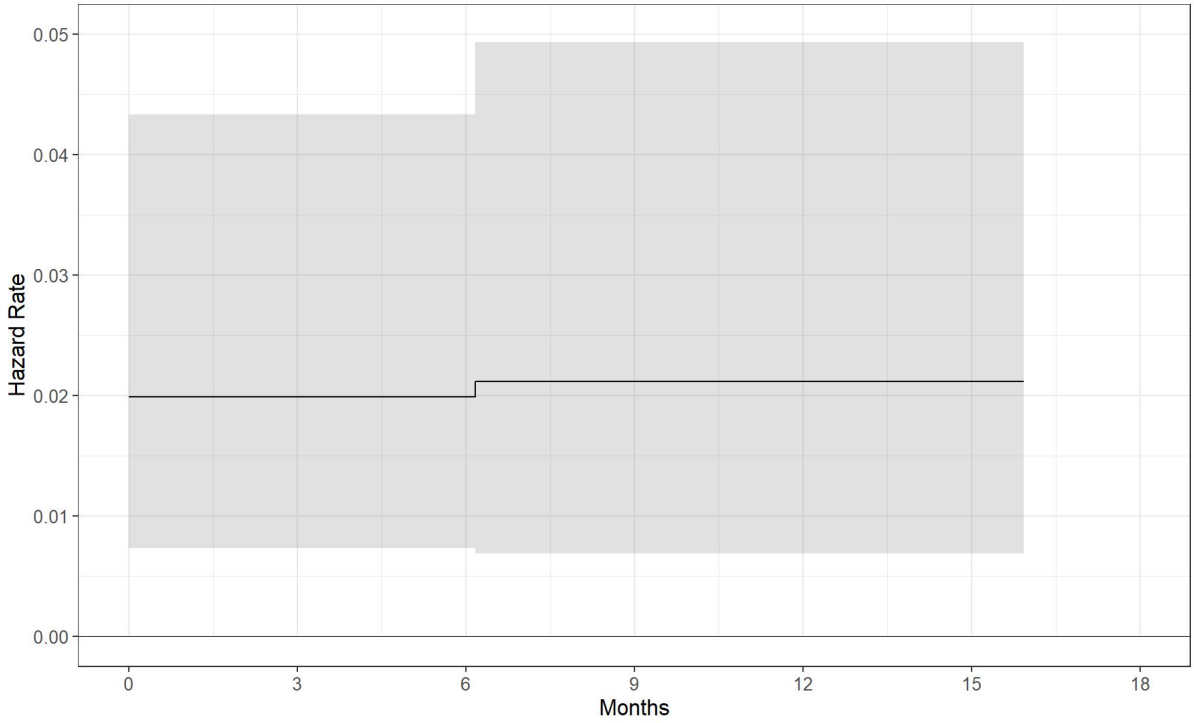
academic / commercial in confidence information removed

OS: IsaPd

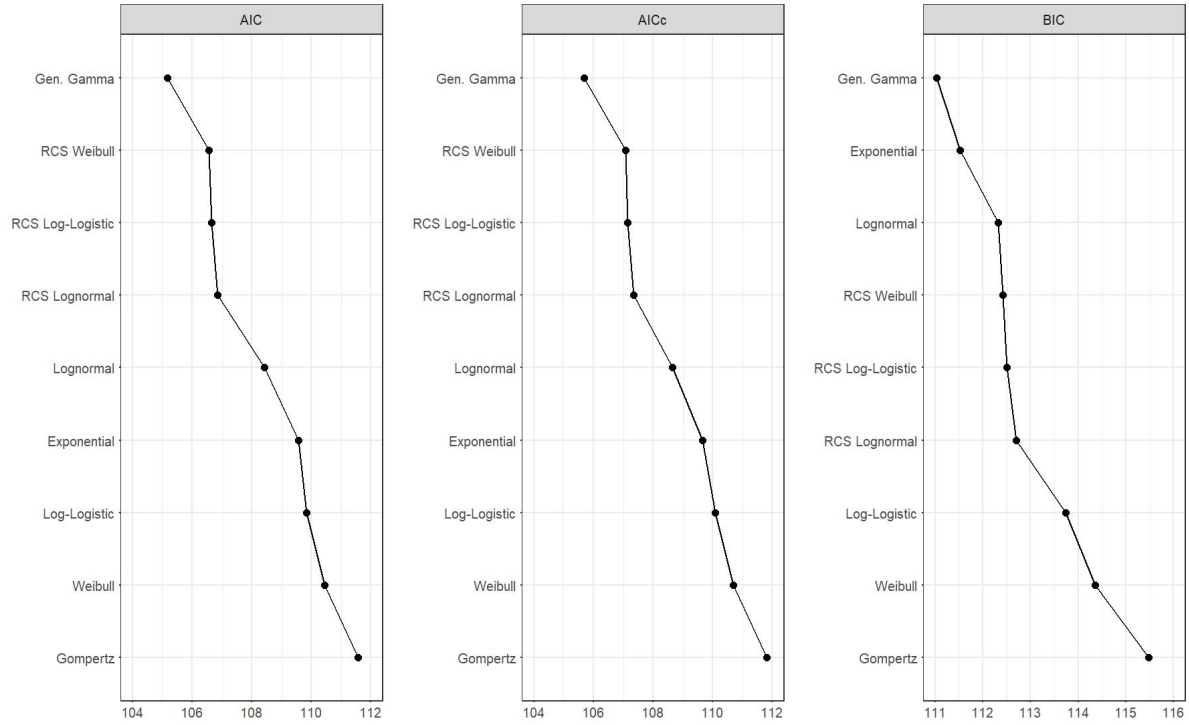
Kaplan Meier, OS



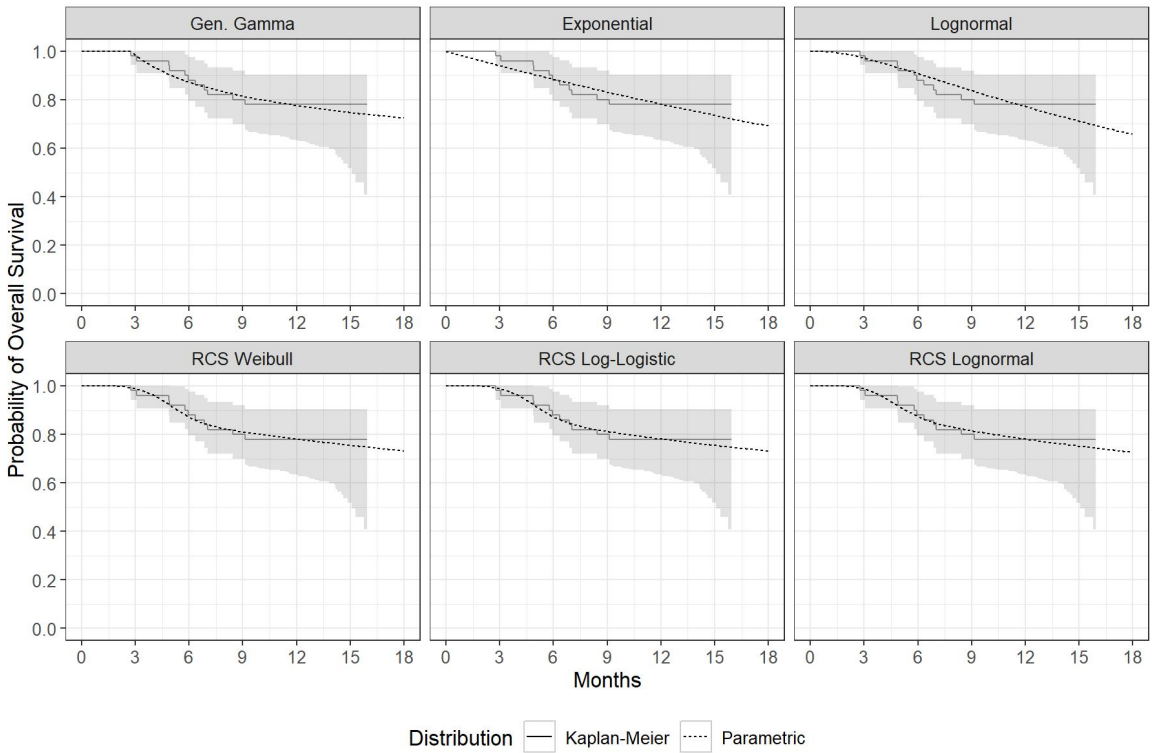
Hazard rates, OS

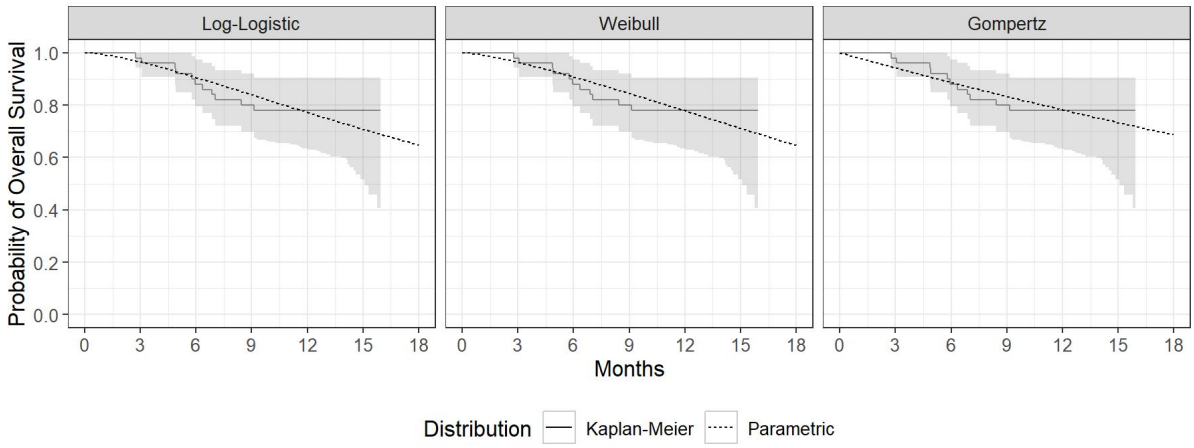


Fit statistics, OS

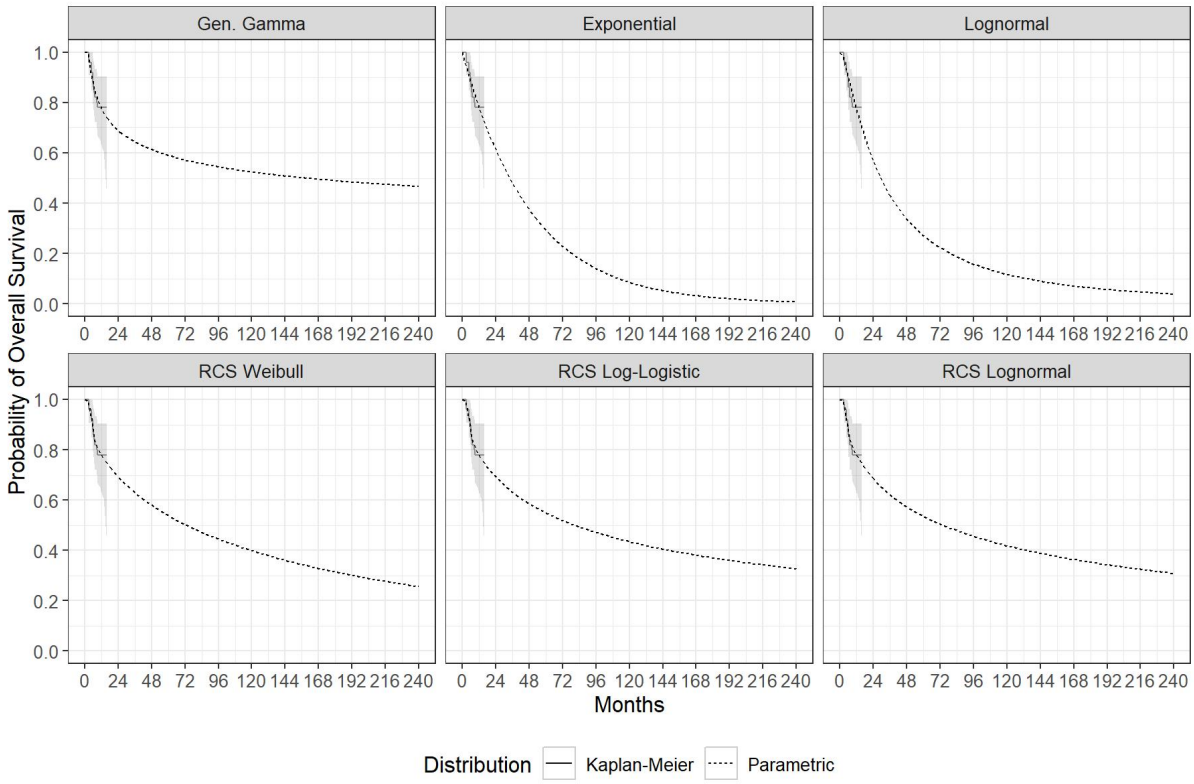


OS, to End of Trial Follow-Up

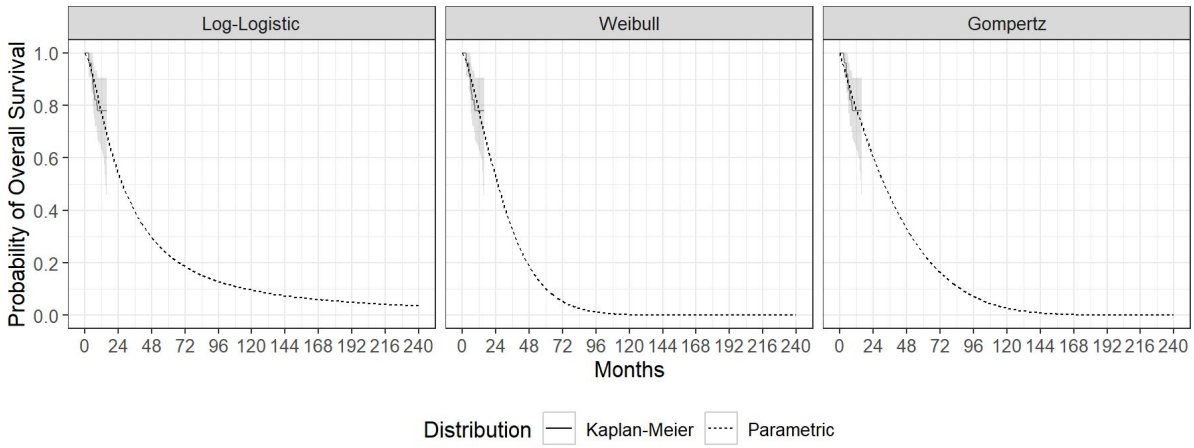




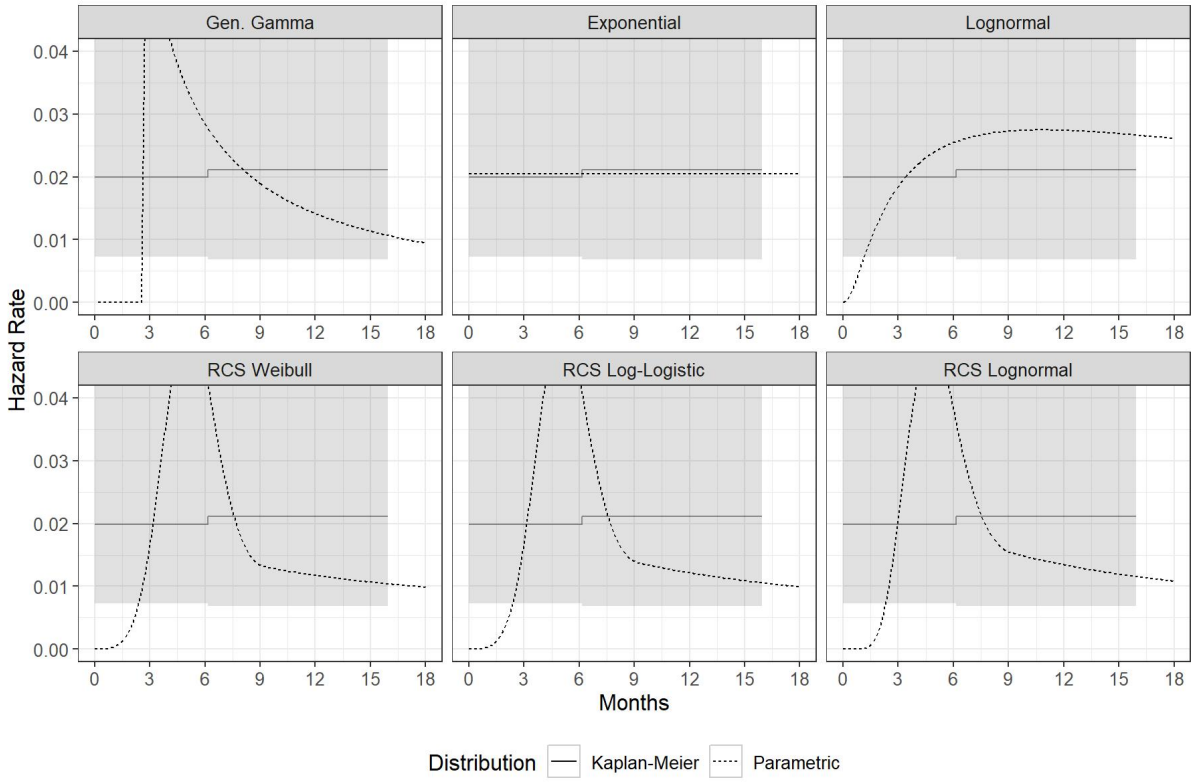
OS to 20 years

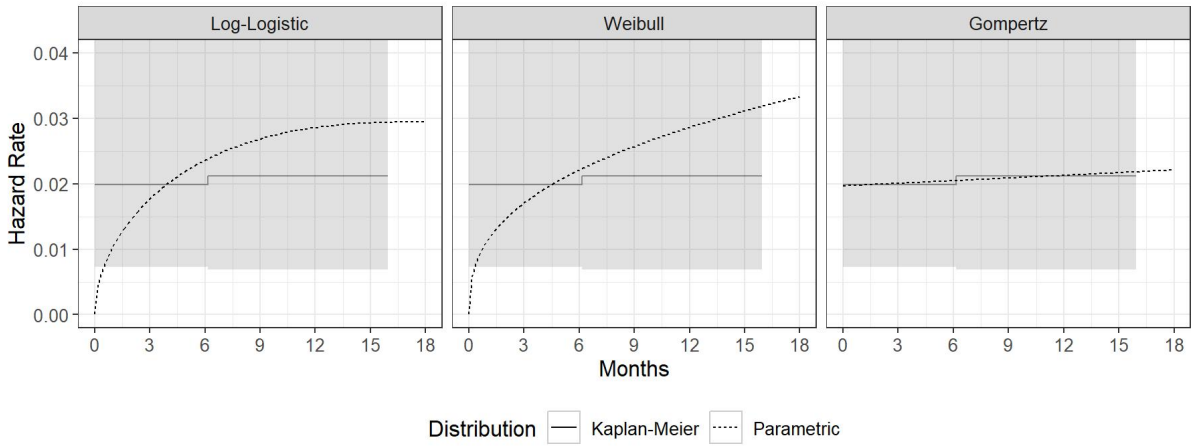


OS to 20 years

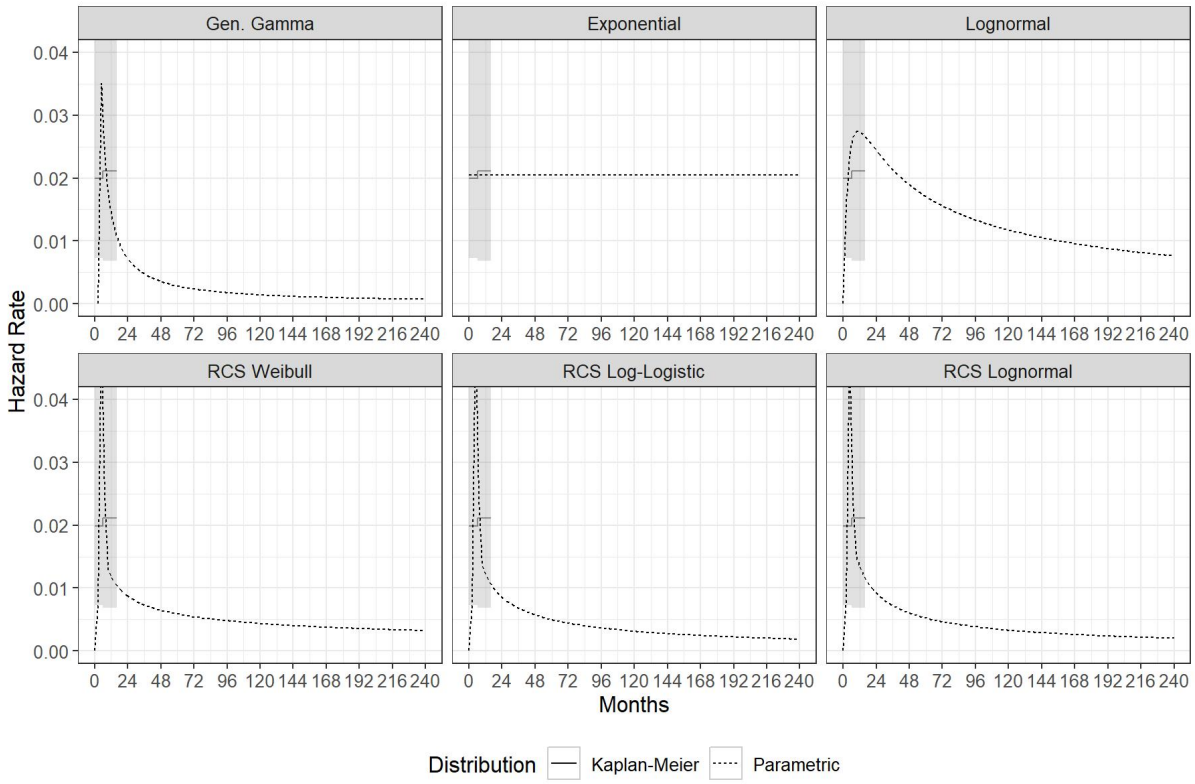


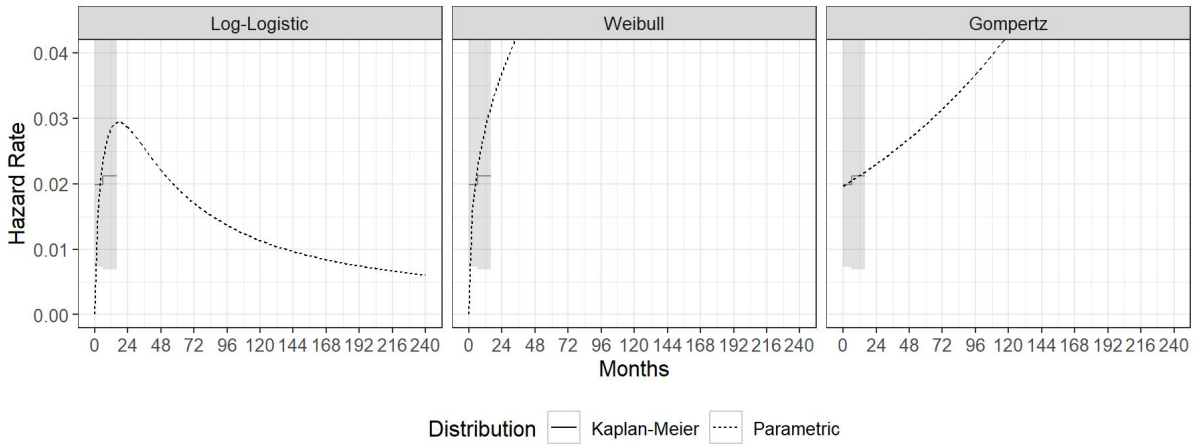
Hazard rates, to End of Trial Follow-Up



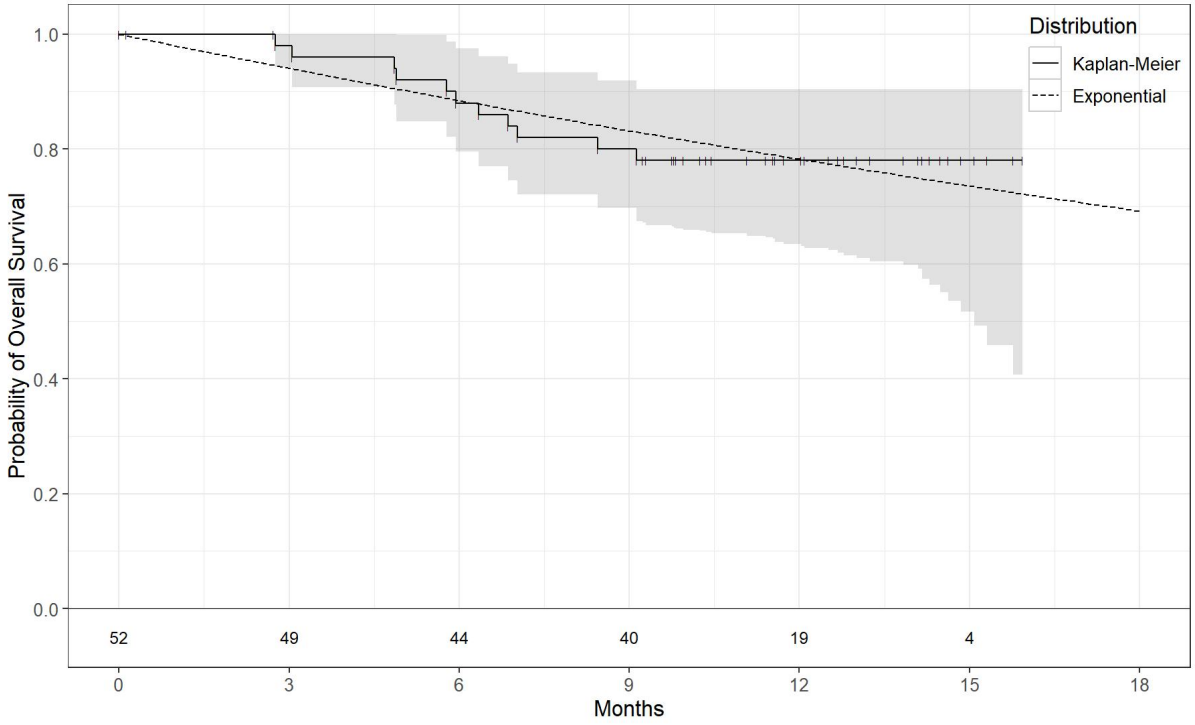


Hazard rates to 20 years

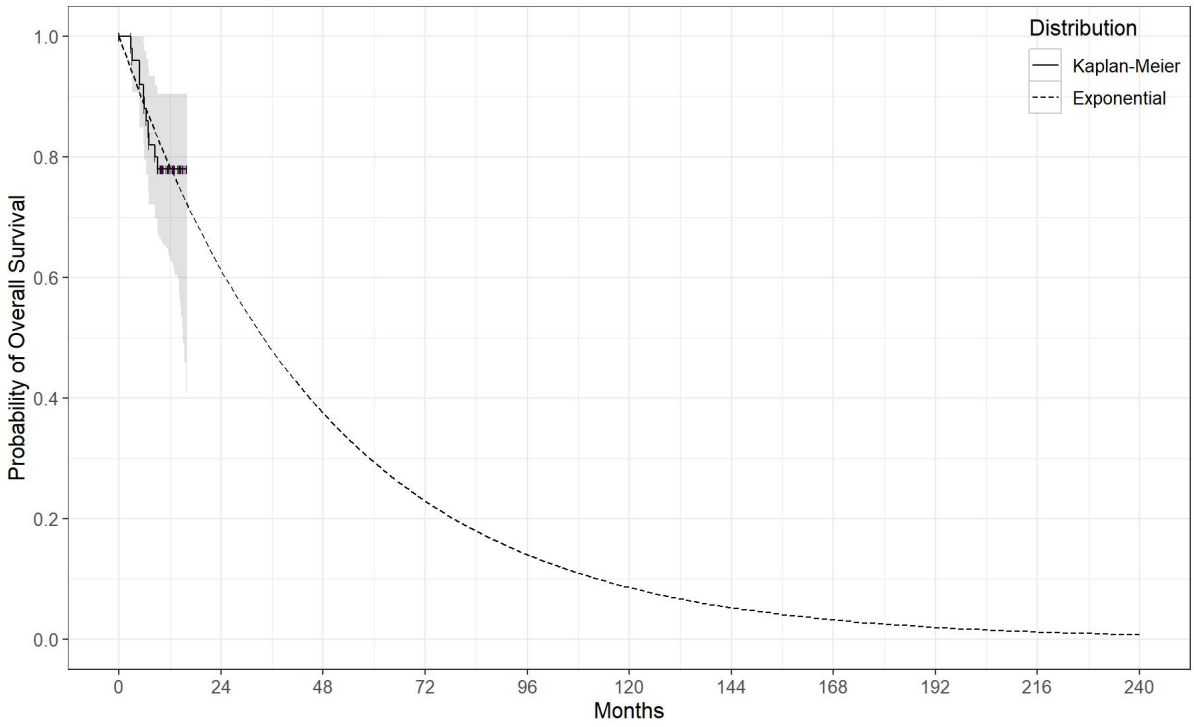




OS to End of Trial Follow-Up

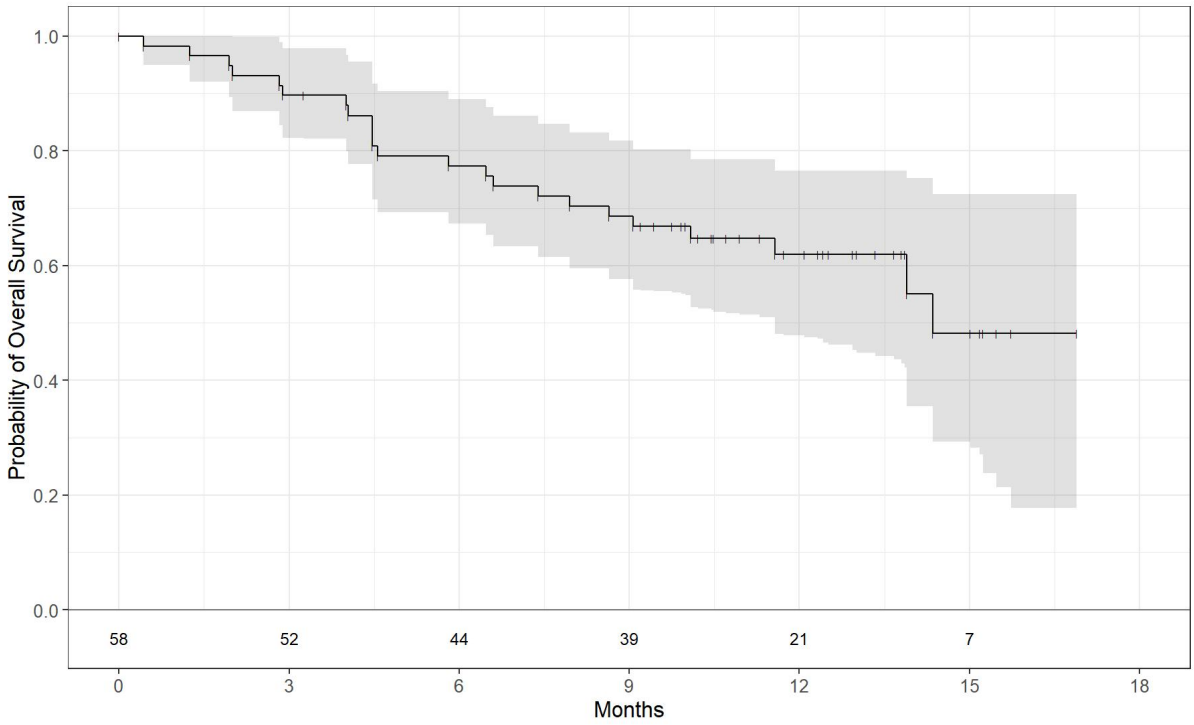


OS, to 20 years

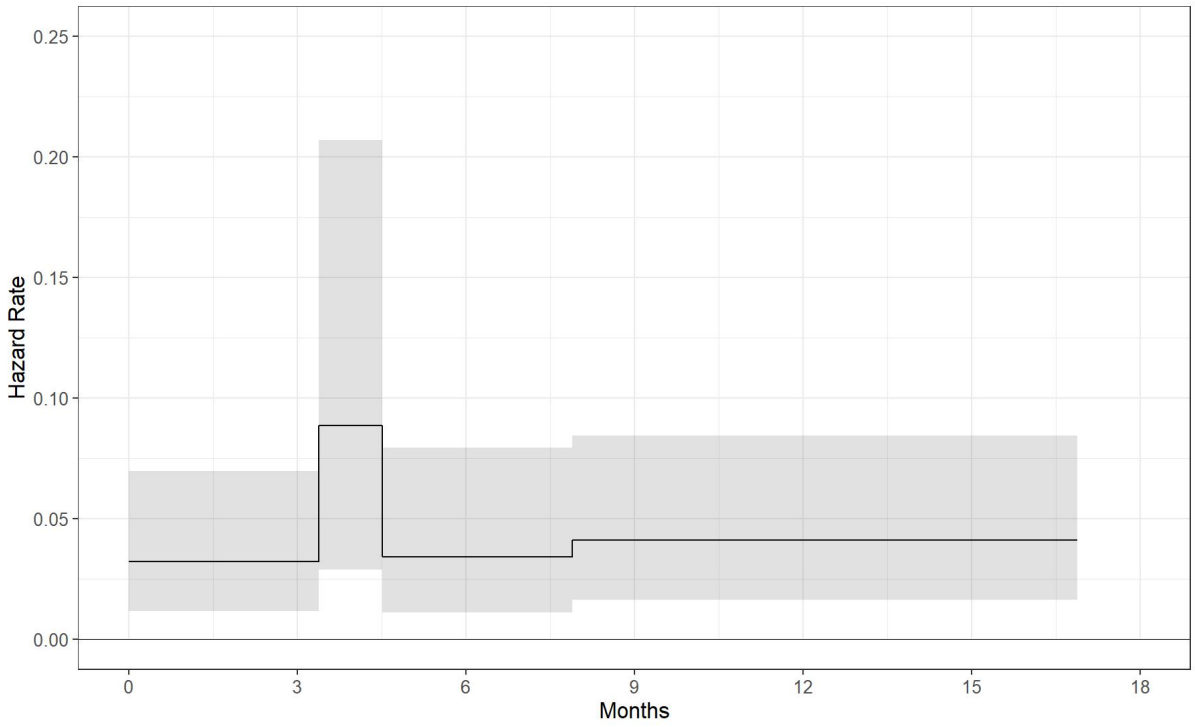


OS: Pd

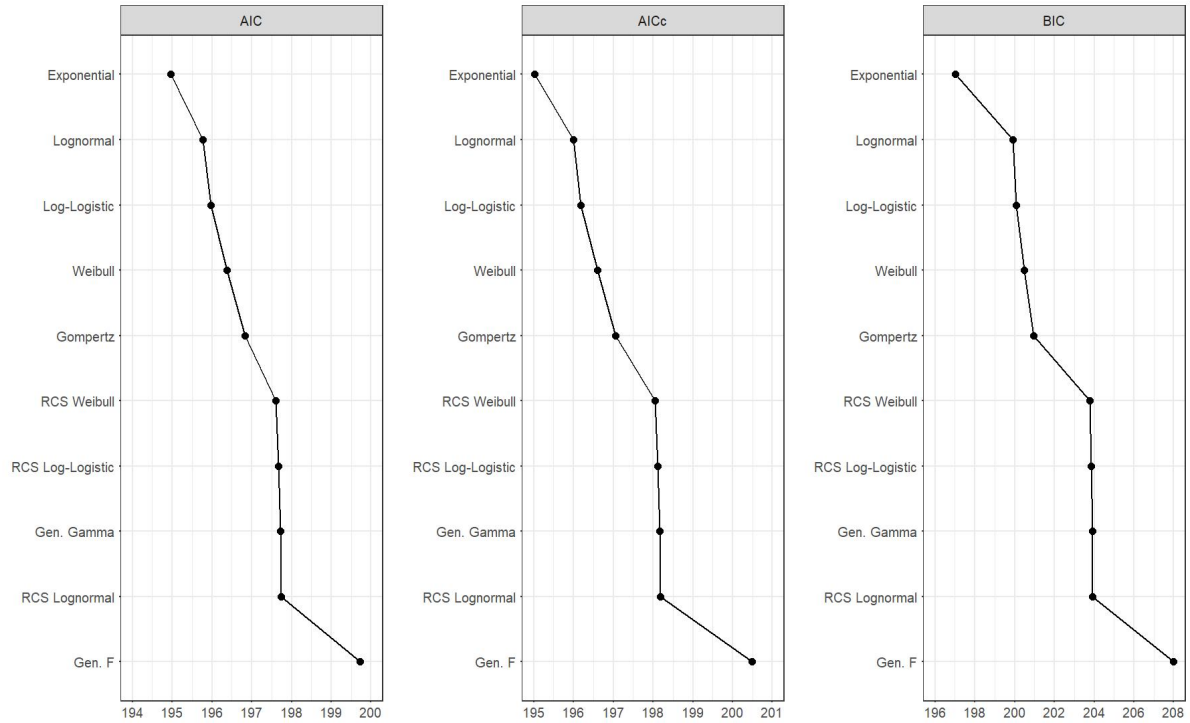
Kaplan Meier: OS



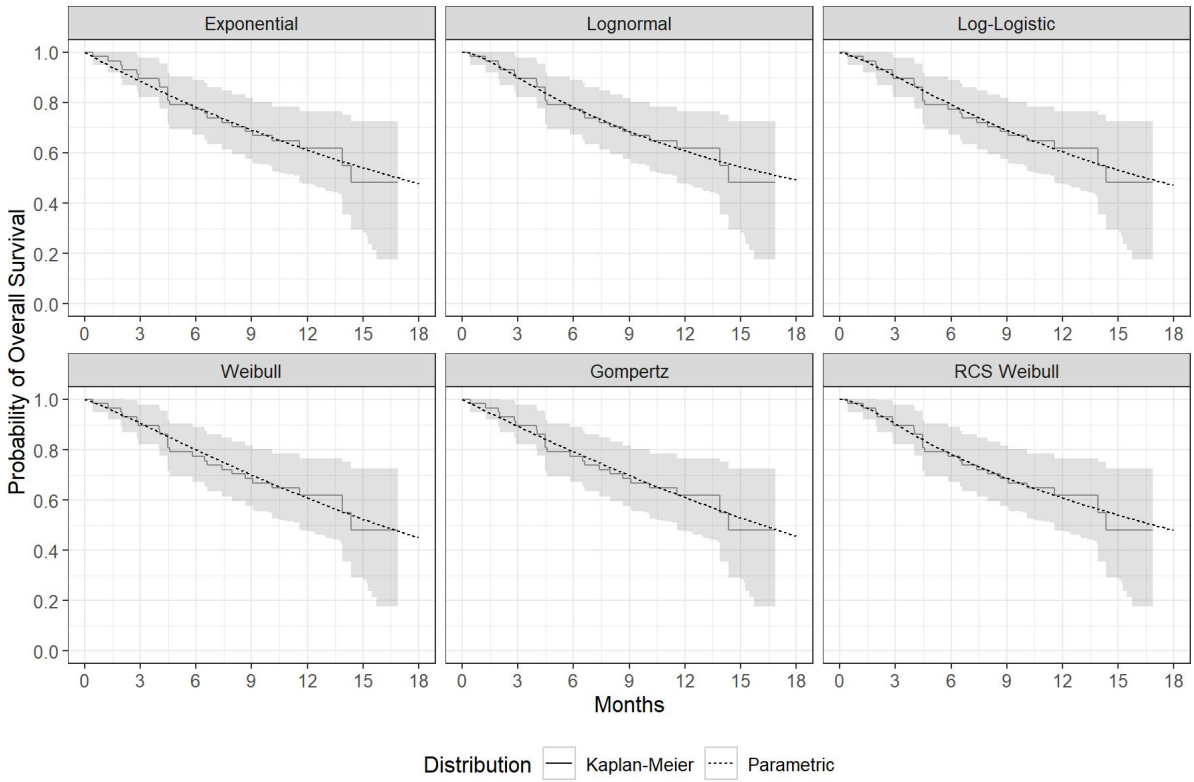
Hazard rates, OS

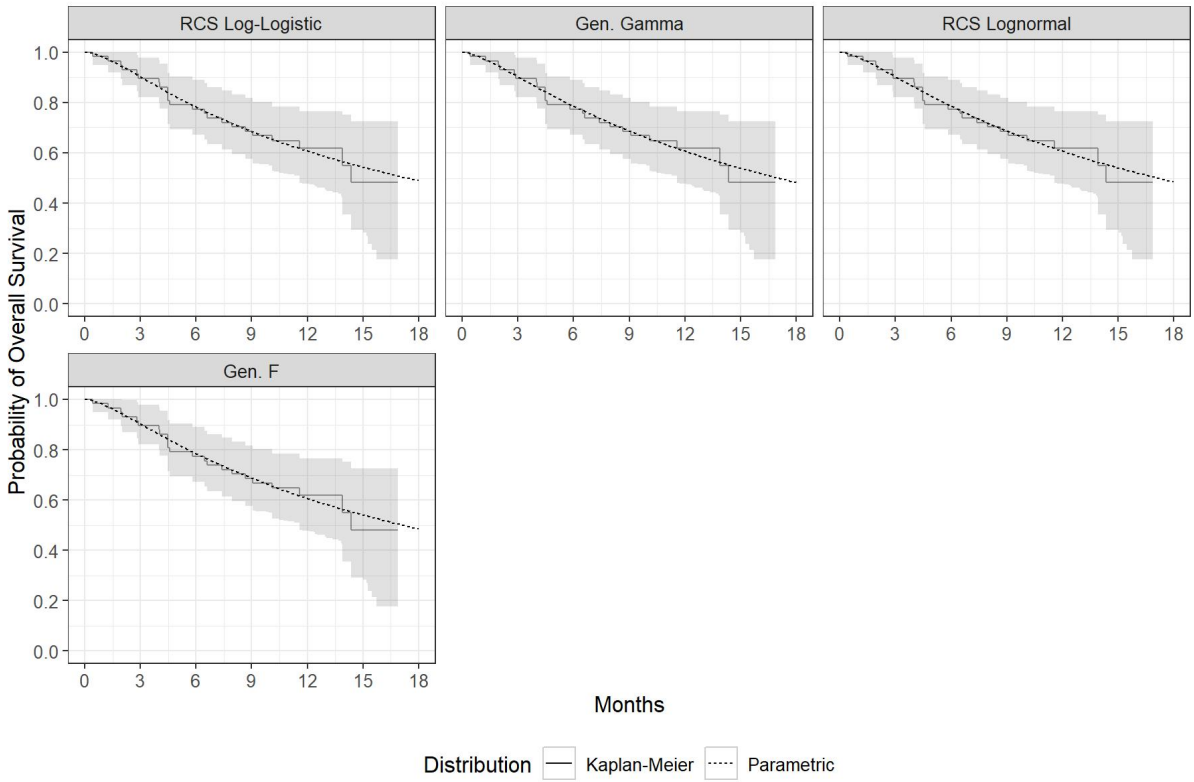


Fit statistics

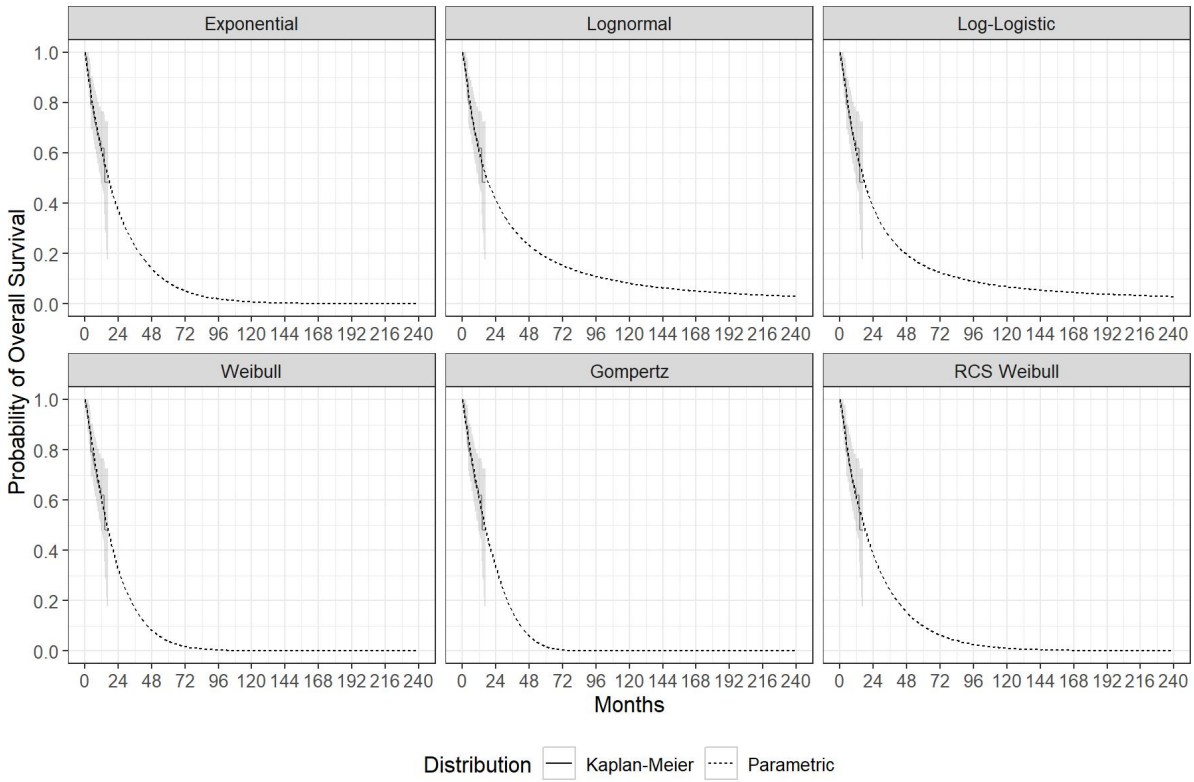


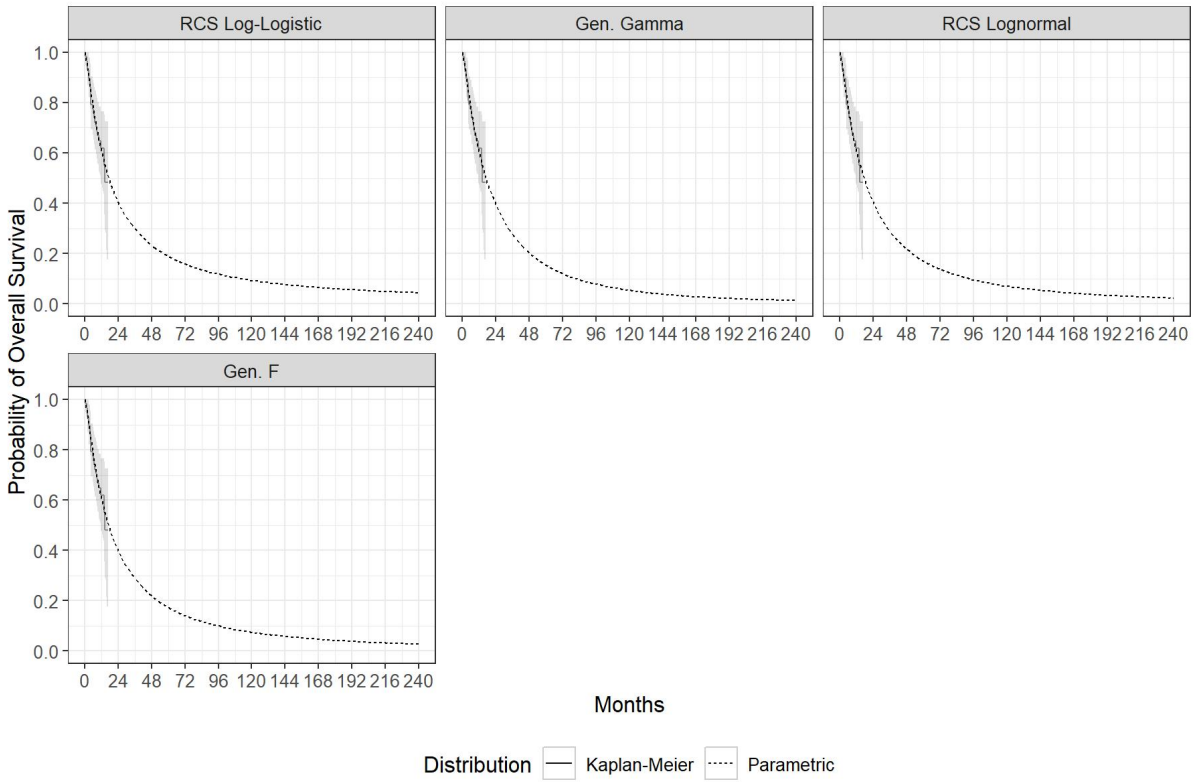
OS to End of Trial Follow-Up



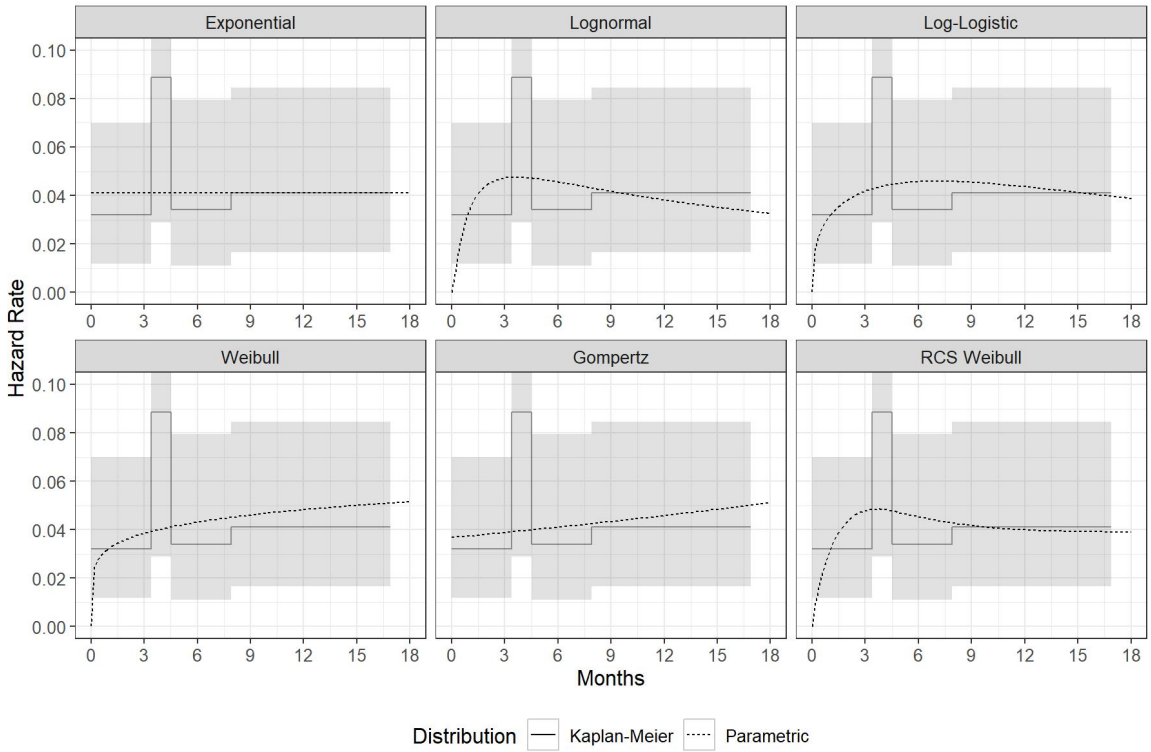


OS to 20 years

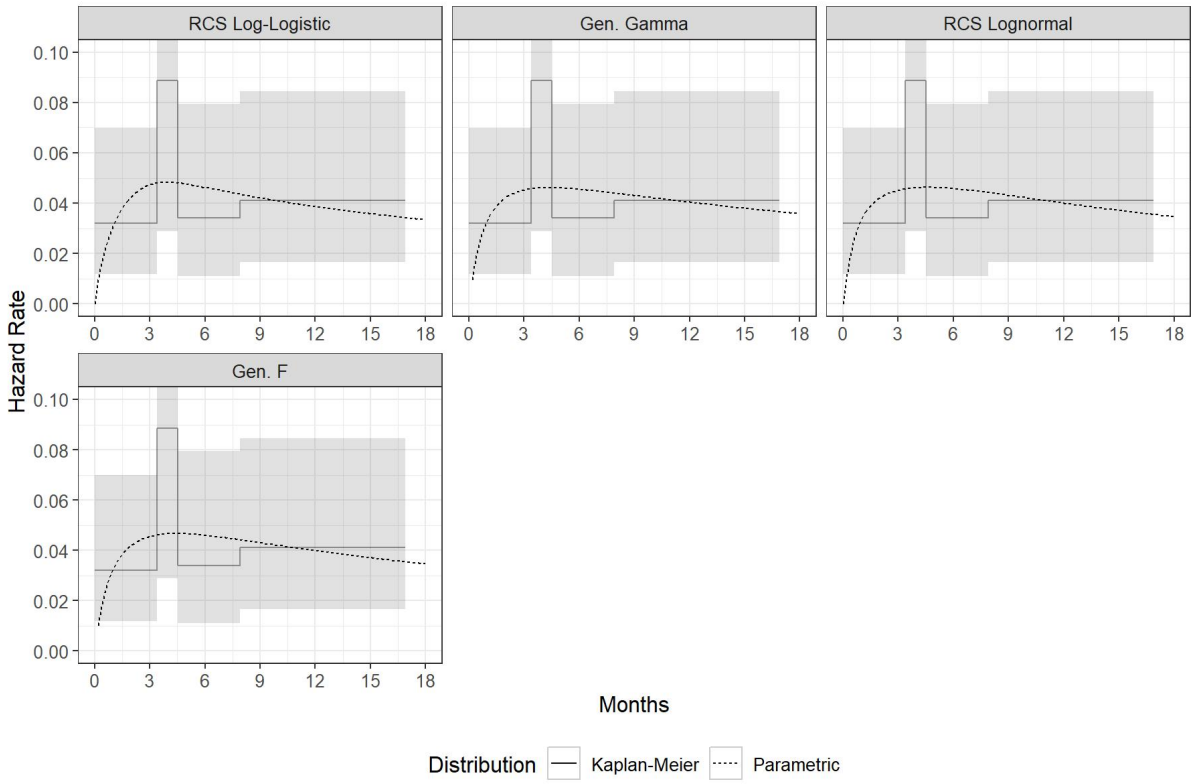




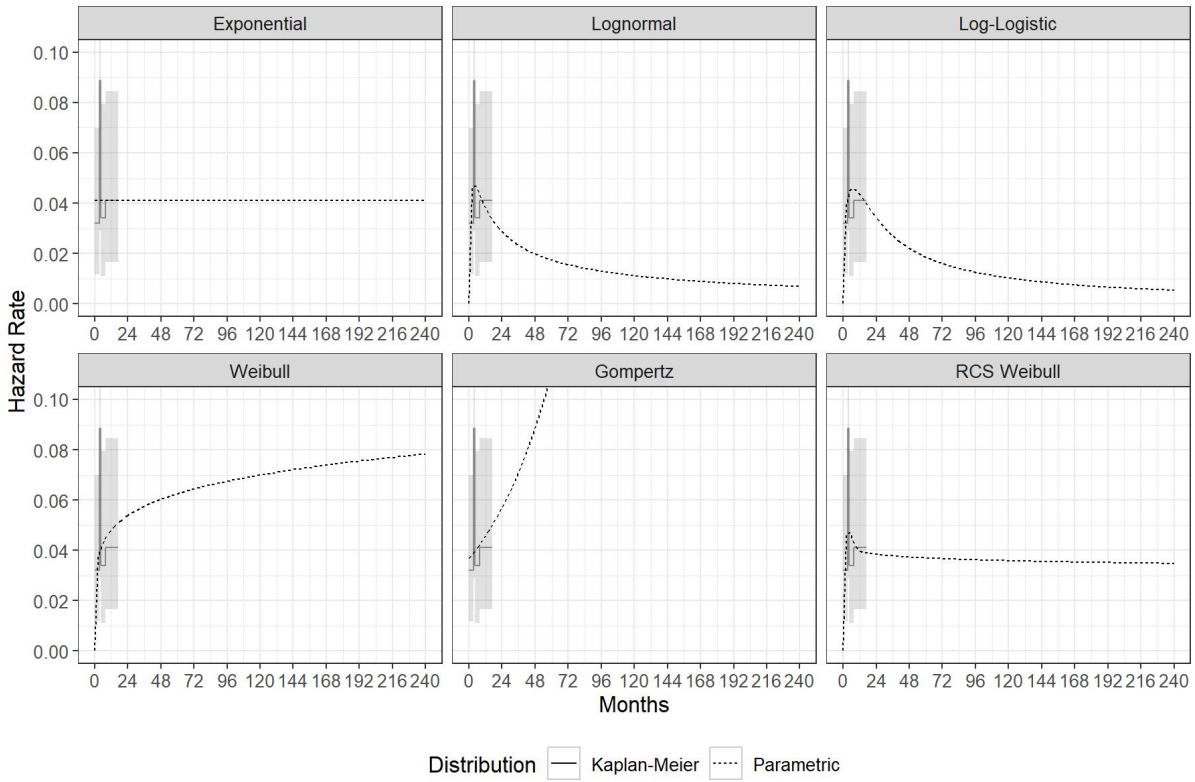
Hazard rates, end of trial follow-up

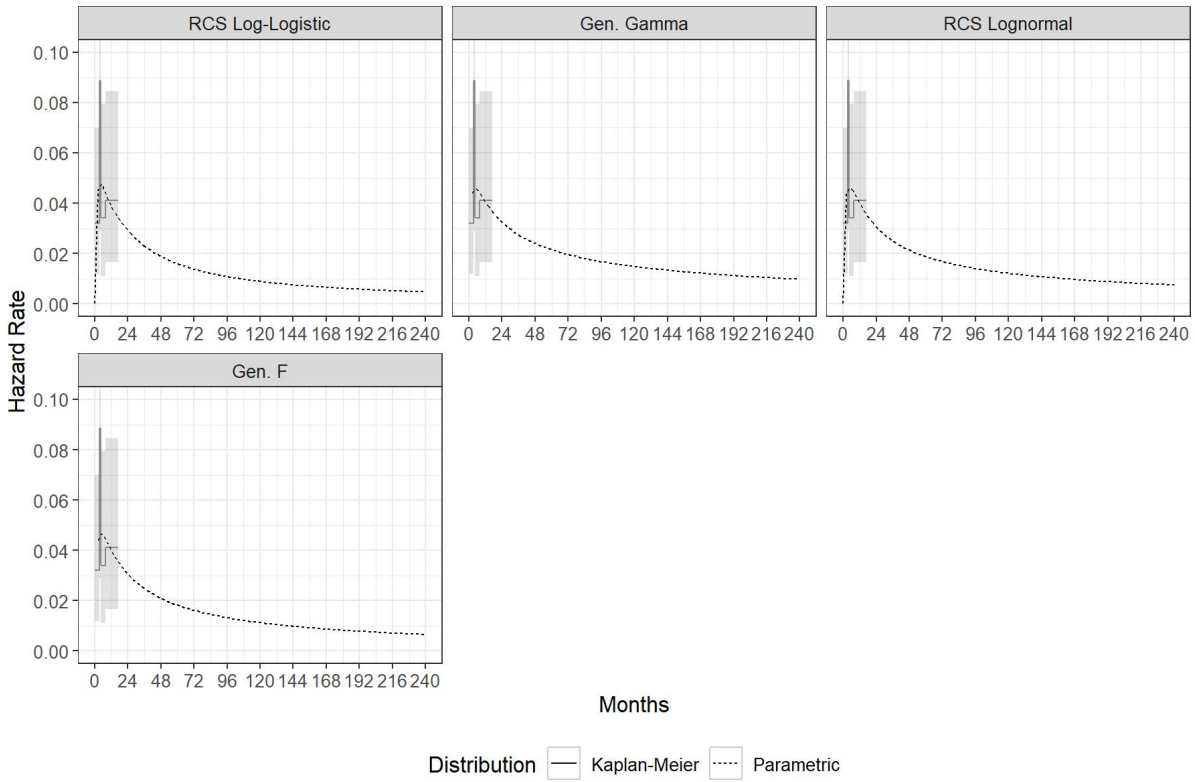


Hazard rates, end of trial follow-up

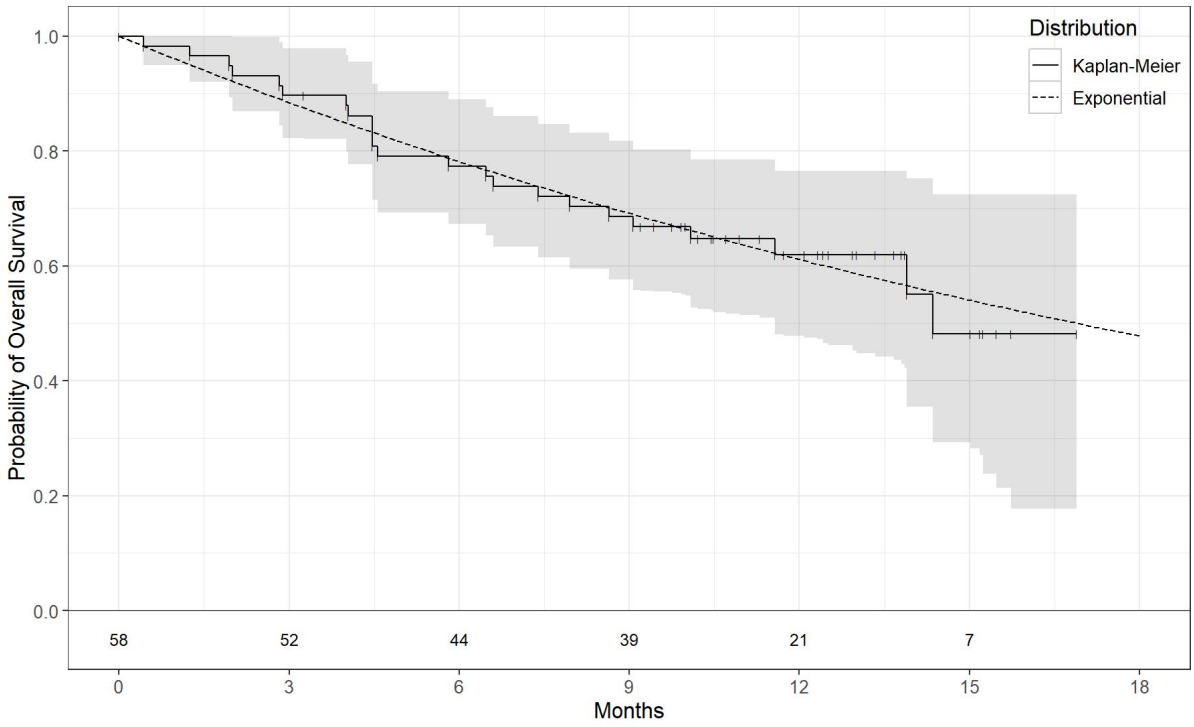


Hazard Rates, to 20 years

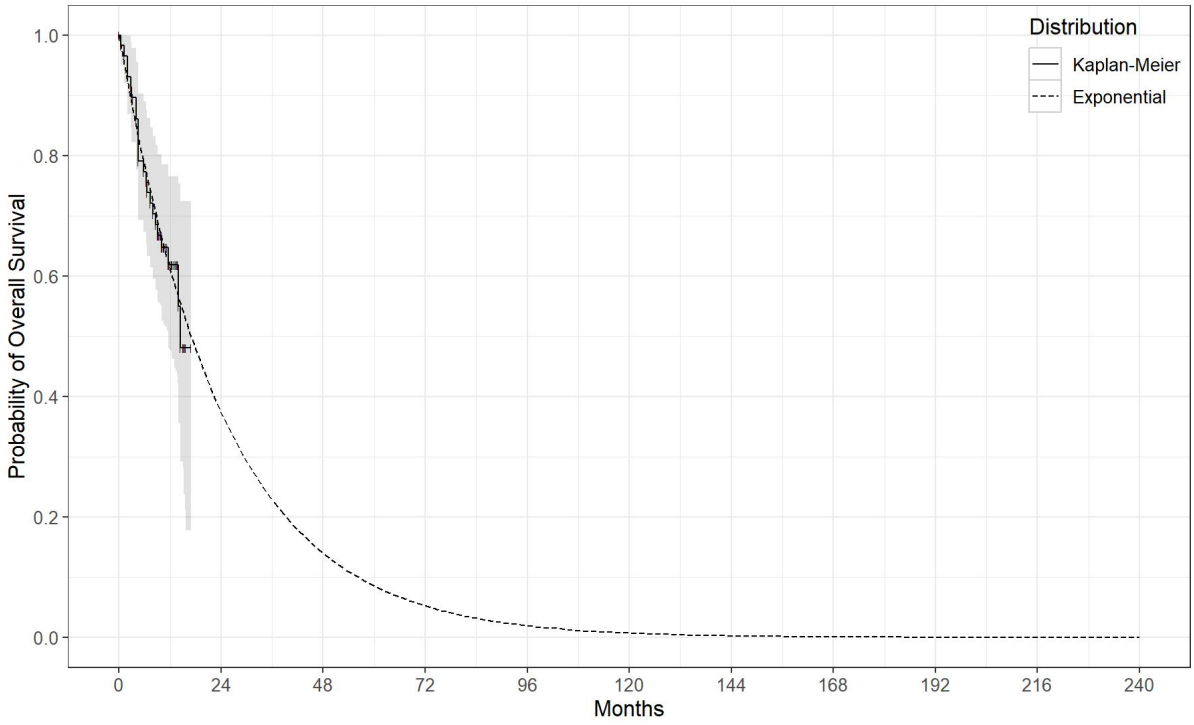




OS to end of the trial follow-up



Overall survival to 20 years



Appendix 2: Long term outcomes from pomalidomide trials

Author	Year	Description	N	Median N Prior lines	Treatment	Subgroup	N	Median PFS	Median OS
Lacy et al.(1)	2009	Phase 2 trial		4	Pd		60	11.6	NR
Lacy et al.(2)	2010	Retrospective analysis of cohort of Len refractory patients with Pd at Mayo Clinic from November 2008 to April 2009		4	Pd (64%)		34	4.8	13.9
San Miguel et al.(3)	2013	MM-03 MC Phase 3 RCT	455	5	Pomalidomide+low dose dexamethasone		302	4.0	12.7
					High dose dexamethasone		153	1.9	8.9
Leleu et al.(4)	2013	Multicentre RCT of 2 dose regimens	57	5	Pd 21/28		43	5.4	14.9
					Pd 28/28		14	3.7	14.8
Richardson et al.(5)	2014	MM-02 Phase 2 RCT	221	5	P+Ld		113	4.2	16.5
					P+Hd		108	2.7	15.6
Dimopoulos et al.(6)	2016	MM-010 STRATUS Phase 3b single arm study	682	5	Pd 4 mg 21/28			4.6	11.9
Ailawadhi et al.(7)	2016	Large, multi-cohort clinical trial testing various doses and treatment schedules of	345	3.5	2 mg Pd	Lenalidomide refractory	35	5.0	25.2
				6	2 mg Pd	Lenalidomide and	35	6.3	14.7

Author	Year	Description	N	Median N Prior lines	Treatment	Subgroup	N	Median PFS	Median OS
		pomalidomide and dexamethasone (Pom/dex) in patients with refractory multiple myeloma				Bortezomib refractory			
				6	4 mg Pd	Lenalidomide and Bortezomib refractory	35	3.5	9.2
				3	2/4 mg Pd	All	343	N/A	NA
Parisi et al.(8)	2019	Retrospective analysis of Italian patients in MM-1010 or MM-015	76	>=4	Pd	4L	22	49.6% @18months	57.3% @18months
						5L+	54	17.6% @18 months	53.2% @18 months
Maciocia et al.(9)	2017	Retrospective analysis of all patients treated with pomalidomide at five UK centres between 2013 and 2016	85 (75 with sufficient data)	3	Pd	UK Series all	85	4.5	9.7
				3		UK Series Resp Avail	70	5.2	13.7
				5		MM-003	302	N/A	N/A
Dimopoulos et al.(10)	2018	Phase 3 Trial of elotuzumab plus pomalidomide and dexamethasone vs. Pd		3	Pd		57	4.7	NR

Author	Year	Description	N	Median N Prior lines	Treatment	Subgroup	N	Median PFS	Median OS
Matsumura-Kimoto et al.(11)	2018	Retrospective analysis of RRMM patients in Japanese registration group from May 2015 to March 2016	108	4	4mg Pd			4.4*	53% @ 1 year
Charlinski et al.(12)	2018	Retrospective analysis of Polish patients from 12 sites between October 2014 and March 2017	50	4	4mg Pd		50	10.0	14.0
Kastritis et al.(13)	2019	Retrospective analysis of RRMM patients treated at University hospital in Athens	147	3	4mg Pd			5.0	12.1
Gueneau et al.(14)	2018	All RRMM patients treated with PD for RRMM in university hospital in France between 8/2013 and 10/2015		2-3	Pd		63	N/A	30.5

Author	Year	Description	N	Median N Prior lines	Treatment	Subgroup	N	Median PFS	Median OS
Sriskandarajah et al.(15)	2016	Patients treated with pomalidomide containing regimens (pomalidomide and dexamethasone 30/39; cyclophosphamide, pomalidomide and dexamethasone 9/39) at the Royal Marsden separate from a clinical trial protocol		4	Pd		30	5.1	13.1
					Cyclo Pd		9		
Baz et al.(16)	2016	"Phase 2 RCT in pts with RRMM with >2 prior therapies"		3	Pd		36	4.4	NR
Scott et al. (17)	2017	Retrospective assessment of the outcomes of a 'real world' cohort of Australian patients treated with pomalidomide in compassionate access program		5	Pd (64%)		87	3.4	7.5

Author	Year	Description	N	Median N Prior lines	Treatment	Subgroup	N	Median PFS	Median OS
		between 2010 and 2015							
Jandial et al. (18)	2018	Outcomes with generic pomalidomide for a total of 24 RRMM patients from May 2017 to May 2018 at institute in Chandigarh, India		4	17/24 Pd 7 triplet		24	6.0	N/A
Mele et al. (19)	2019	Multicenter retrospective analysis of 103 consecutive patients with RRMM, treated with POM LoDEX as salvage therapy at 12 haematological centers in Puglia and Basilicata		3	Pd		103	10.0	16.0

*Time to treatment failure (progression) in 47 patients, NR – not reached

Appendix 3: Comparison of the baseline patient characteristics from ICARIA-MM, patients in 4L and Daratumumab monotherapy trials GEN501 and SIRIUS pooled patients (Usmani 2020)

Baseline demographics	ICARIA-MM – Patients in 4L		GEN501 and SIRIUS Pooled patients (N=148)
	Pd (N=58)	IsaPd (N=52)	
Age, years, mean (SD)	64.2 (8.9)	66.1 (8.5)	NR
Age, years, median (Min;Max), [IQR]	65.5 (41 ; 80)	68.0 (39 ; 79)	64.0 [58 - 70]
Age group, years, n (%)			
<65	27 (46.6)	19 (36.5)	NR
65–74	22 (37.9)	26 (50.0)	52 (35%)
≥75	9 (15.5)	7 (13.5)	16 (11%)
Sex, n (%)			
Male	27 (46.6)	30 (57.7)	69 (47%)
Female	31 (53.4)	22 (42.3)	79 (53%)
Race, n (%)			
White	51 (87.9)	42 (80.8)	NR
Black or African American	1 (1.7)	0	NR
Asian	5 (8.6)	5 (9.6)	NR
Native Hawaiian or other Pacific Islander	0	2 (3.8)	NR
Missing/Not reported	1 (1.7)	3 (5.8)	NR
Ethnicity, n (%)			
Hispanic or Latino	1 (1.7)	3 (5.8)	NR
Not Hispanic or Latino	51 (87.9)	42 (80.8)	NR

ECOG PS, n (%)			
0	30 (51.7)	21 (40.4)	41 (28%)
1	23 (39.7)	25 (48.1)	97 (66%)
2	5 (8.6)	6 (11.5)	10 (7%)
≥1 extramedullary plasmacytomas, n (%)	NR	NR	18 (12%)
Geographical region, n (%)			
Western Europe	29 (50.0)	19 (36.5)	NR
Eastern Europe	10 (17.2)	13 (25.0)	NR
North America	0	3 (5.8)	NR
Asia	5 (8.6)	5 (9.6)	NR
Other countries‡	14 (24.1)	12 (23.1)	NR
Regulatory region, n (%)			
Western countries	33 (56.9)	27 (51.9)	NR
Other countries‡‡	25 (43.1)	25 (48.1)	NR
Creatinine clearance (MDRD), n (%)			
≥60 mL/min	34/57 (59.6)*	30/48 (62.5)*	89 (60)
<60 mL/min	23/57 (40.4)*	18/48 (37.5)*	59 (40)
≥30 to <60 mL/min	NR	NR	54 (37)
<30 mL/min	NR	NR	5 (3)
Bone marrow plasma cells (%)			
≤30	NR	NR	85 (57)
>30 to ≤60	NR	NR	26 (18)
>60	NR	NR	35 (24)
Years since diagnosis, median, (IQR)	NR	NR	5.1 (3.9 – 7.8)
Number of previous lines of therapy, median, (IQR)	3.0	3.0	5.0 (4 – 7)
>3 previous lines of therapy, n (%)	NR	NR	133 (76)
Previous ASCT, n (%)	NR	NR	116 (78)

Previous proteasome inhibitor†, n (%)			
Any	NR	NR	148 (100)
Bortezomib	NR	NR	147 (99)
Carfilzomib	NR	NR	61 (41)
Previous immunomodulatory drug†, n (%)			
Any	NR	NR	146 (99)
Lenalidomide	NR	NR	145 (98)
Pomalidomide	NR	NR	82 (55)
Thalidomide	NR	NR	66 (45)
Refractory to treatment, n (%)			
Last line of therapy	NR	NR	135 (91)
IMiD and PI	36 (62.1)	38 (73.1)	128 (87)
IMiD, PI and alkylating agent	NR	NR	100 (68)
Bortezomib	30 (51.7)	31 (59.6)	125 (85)
Carfilzomib	15 (25.9)	10 (19.2)	58 (39)
Lenalidomide	51 (87.9)	48 (92.3)	124 (84)
Ixazomib	7 (12.1)	6 (11.5)	
Pomalidomide	NR	NR	82 (55)
Thalidomide	NR	NR	41 (28)
Alkylating agent only	NR	NR	107 (72)

NR; not reported, IQR; interquartile range, ASCT; autologous stem-cell transplantation, ECOG; Eastern Cooperative Oncology Group, IMiD; immunomodulatory drug, PI; proteasome inhibitor

‡Other countries=Australia, New Zealand, Turkey and Russia

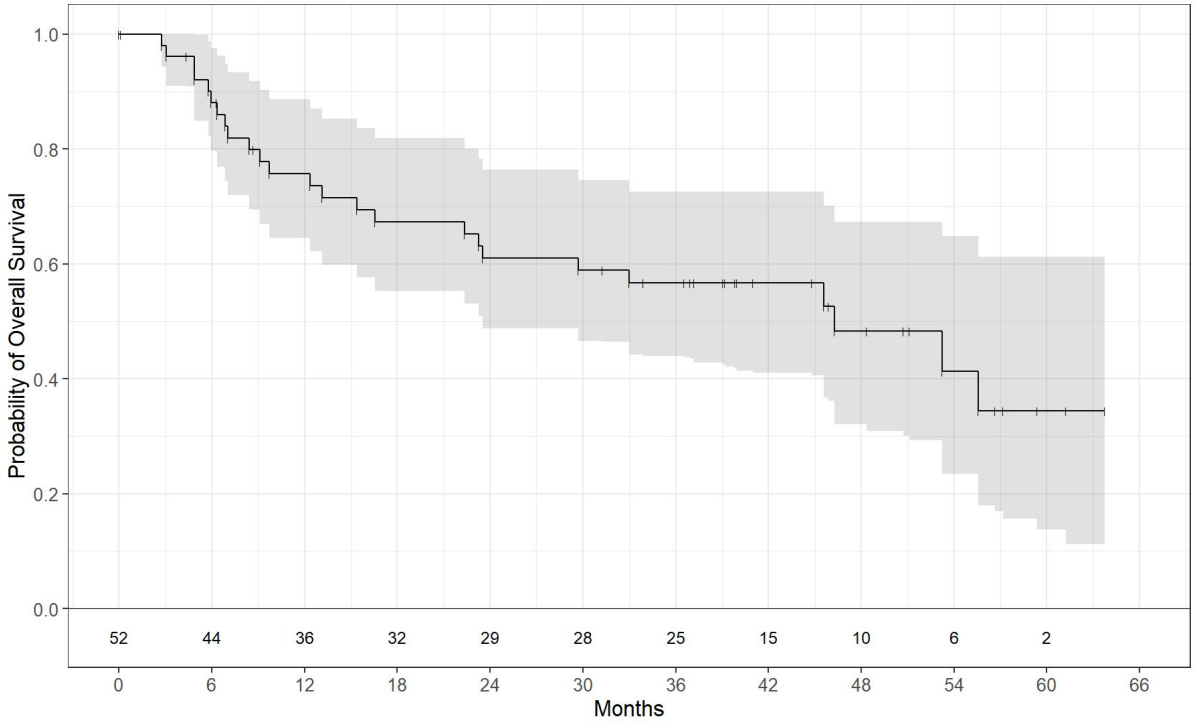
‡‡Other countries=Czech Republic, Hungary, Poland, Slovakia, Japan, Korea, Republic of Taiwan (Province of China), Turkey and Russia

*% calculated using the number of patients with at least one event (n) over the number of patients assessed for each parameter (N1) at baseline

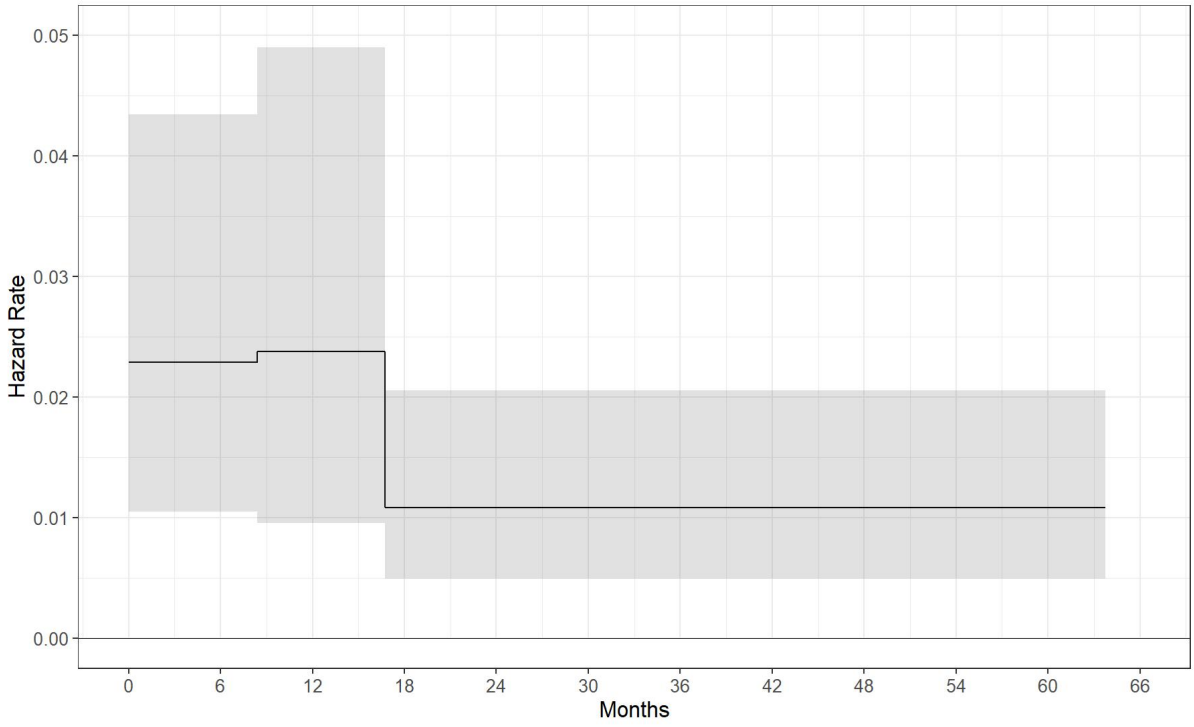
†Patients could have received more than one of these therapies

Appendix 4: Curve fitting exercise to the semi-synthetic KM data at 4L

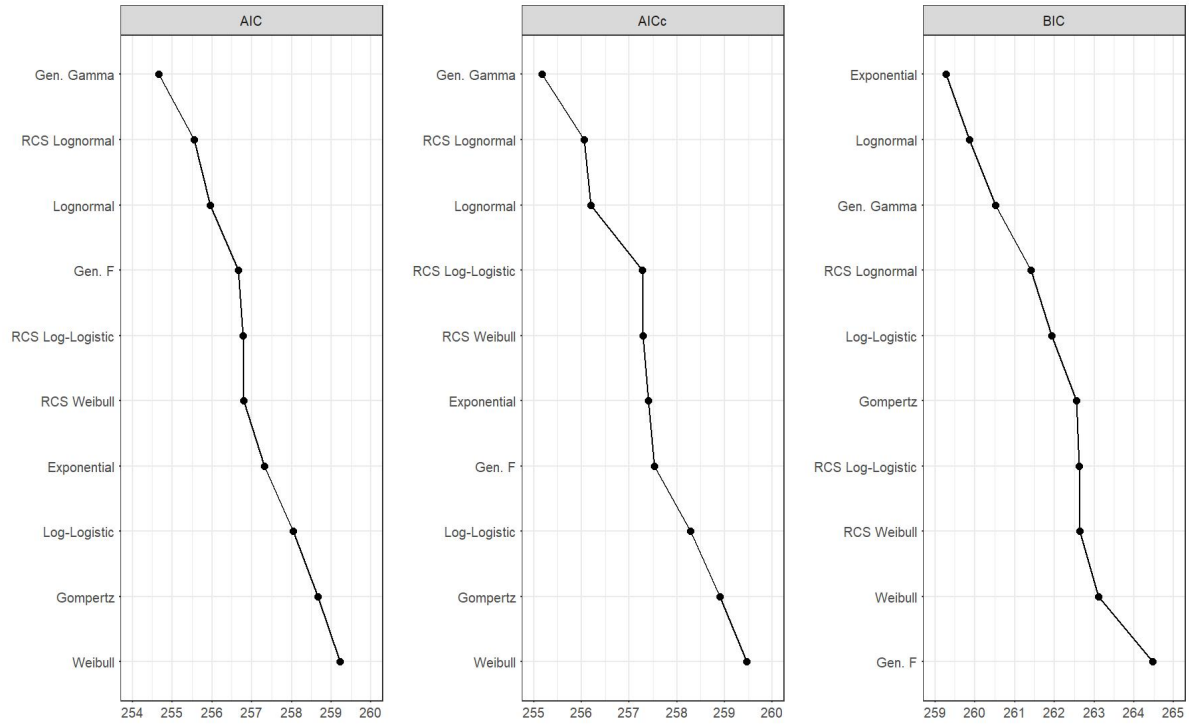
Kaplan Meier data, OS



Hazard rates



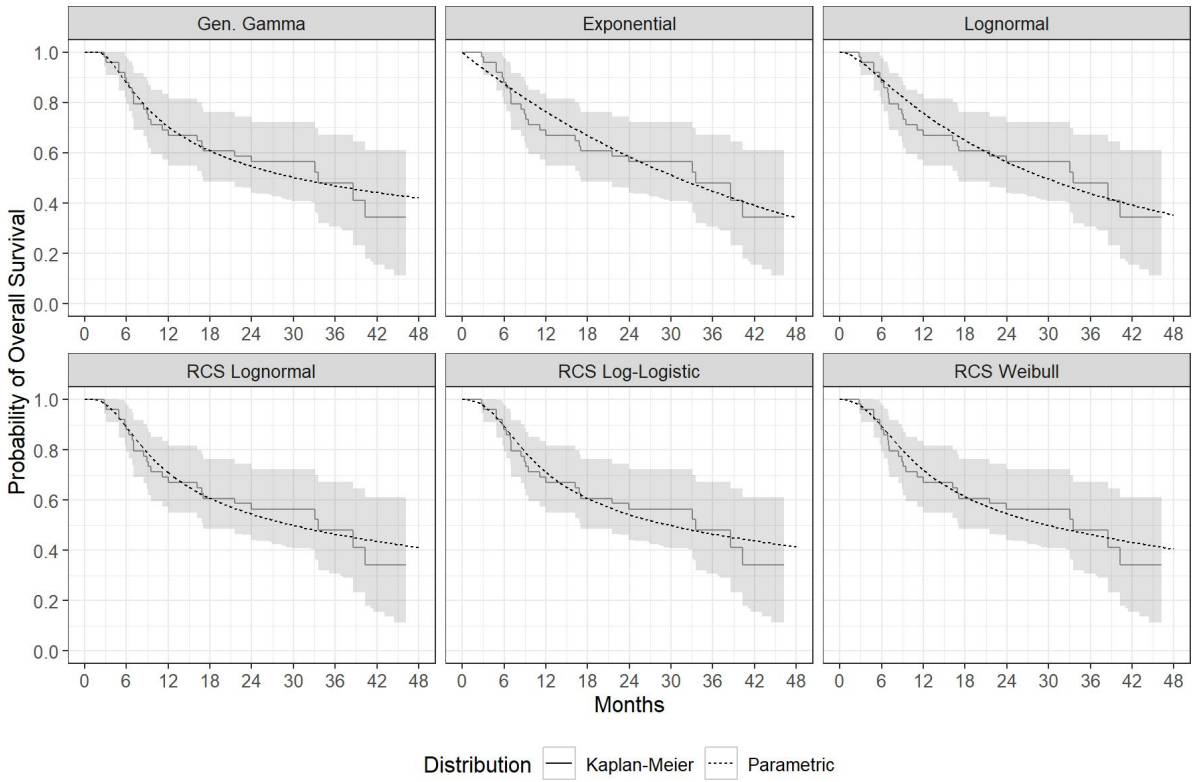
Fit Statistics, OS

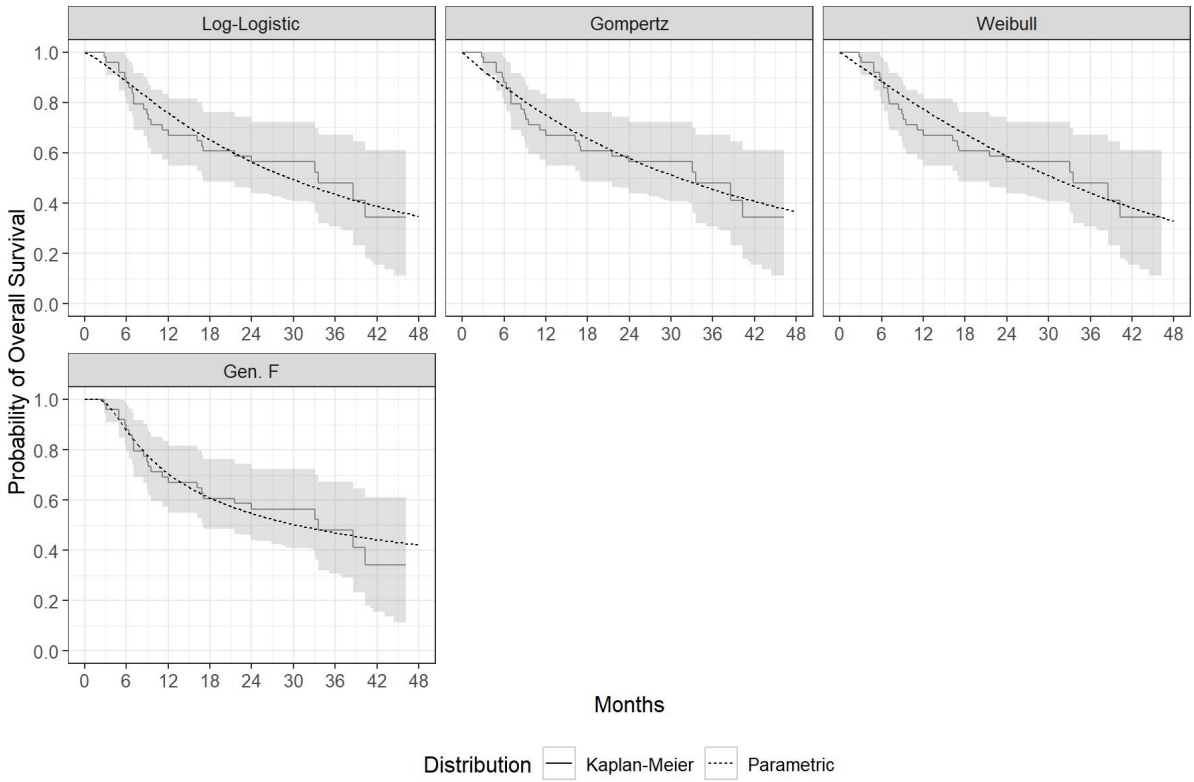


Fit Statistics, OS

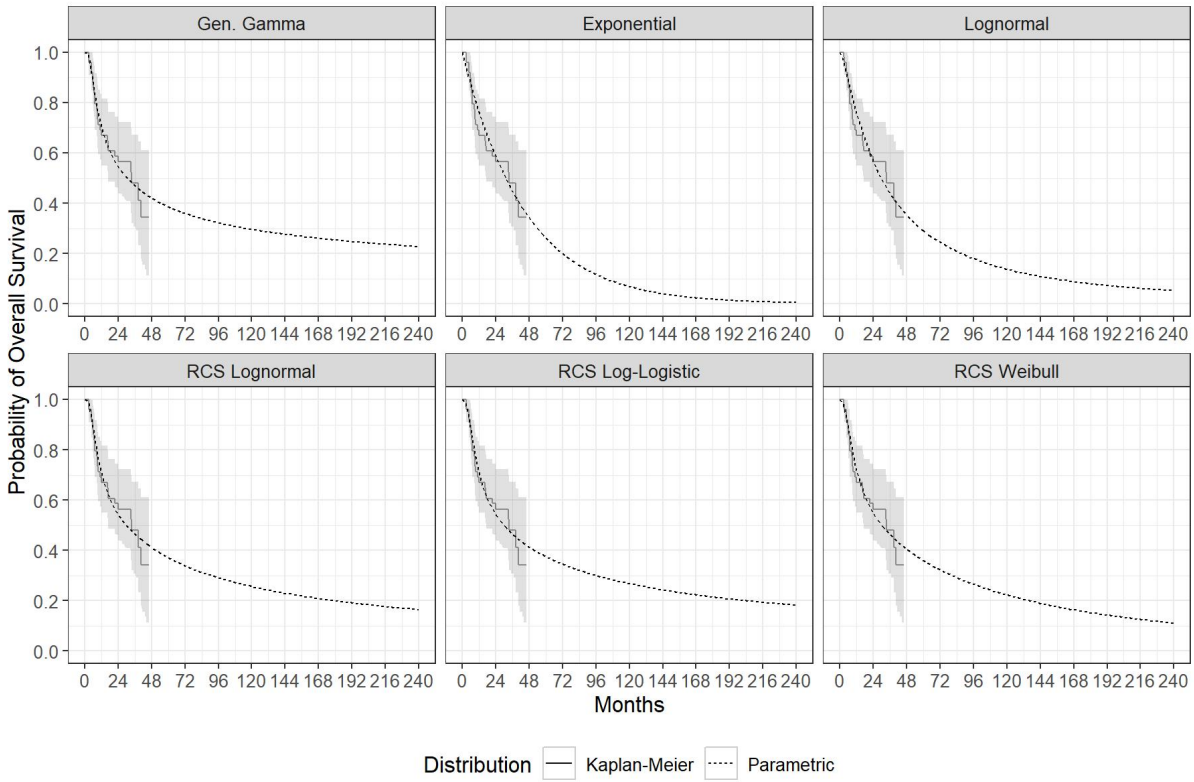
Distribution	Converged	DF	-2LL	AIC	AICc	BIC
Exponential	TRUE	1	255.3	257.3	257.4	259.3
Lognormal	TRUE	2	252.0	256.0	256.2	259.9
Gen. Gamma	TRUE	3	248.7	254.7	255.2	260.5
RCS Lognormal	TRUE	3	249.6	255.6	256.1	261.4
Log-Logistic	TRUE	2	254.0	258.0	258.3	261.9
Gompertz	TRUE	2	254.7	258.7	258.9	262.6
RCS Log-Logistic	TRUE	3	250.8	256.8	257.3	262.6
RCS Weibull	TRUE	3	250.8	256.8	257.3	262.6
Weibull	TRUE	2	255.2	259.2	259.5	263.1
Gen. F	TRUE	4	248.7	256.7	257.5	264.5

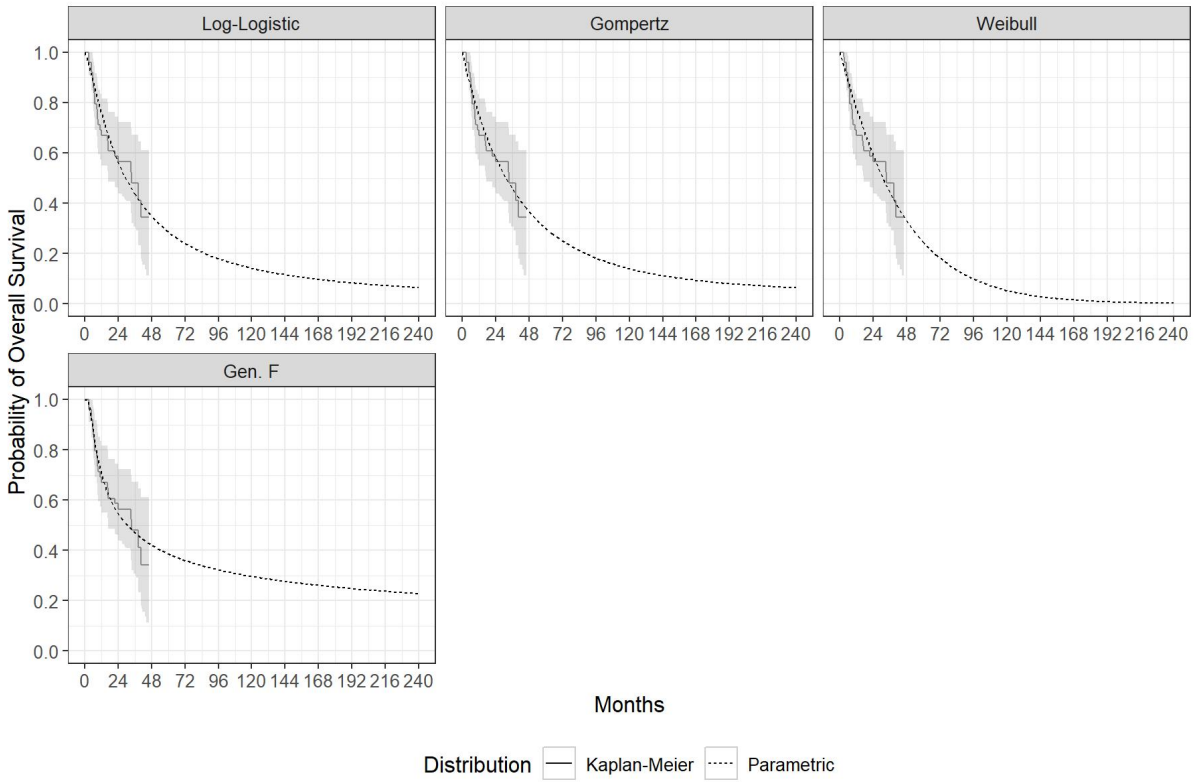
Overall Survival to End of Trial Follow-Up, OS



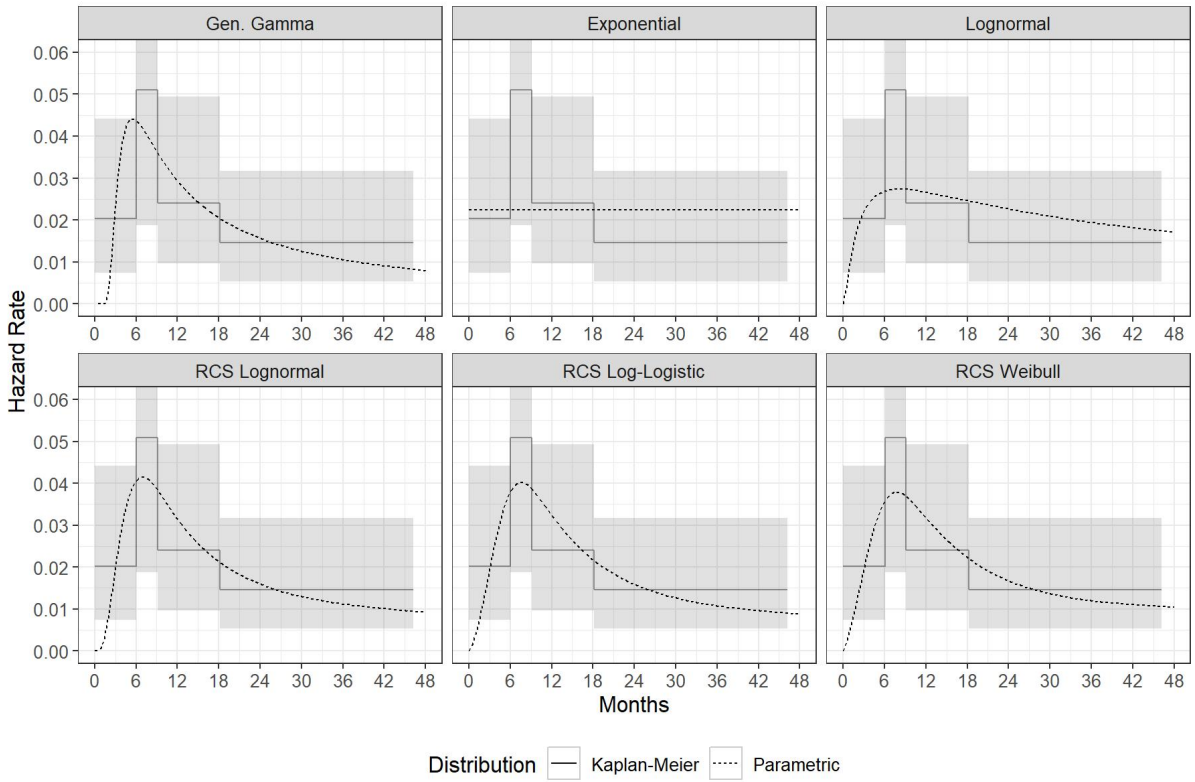


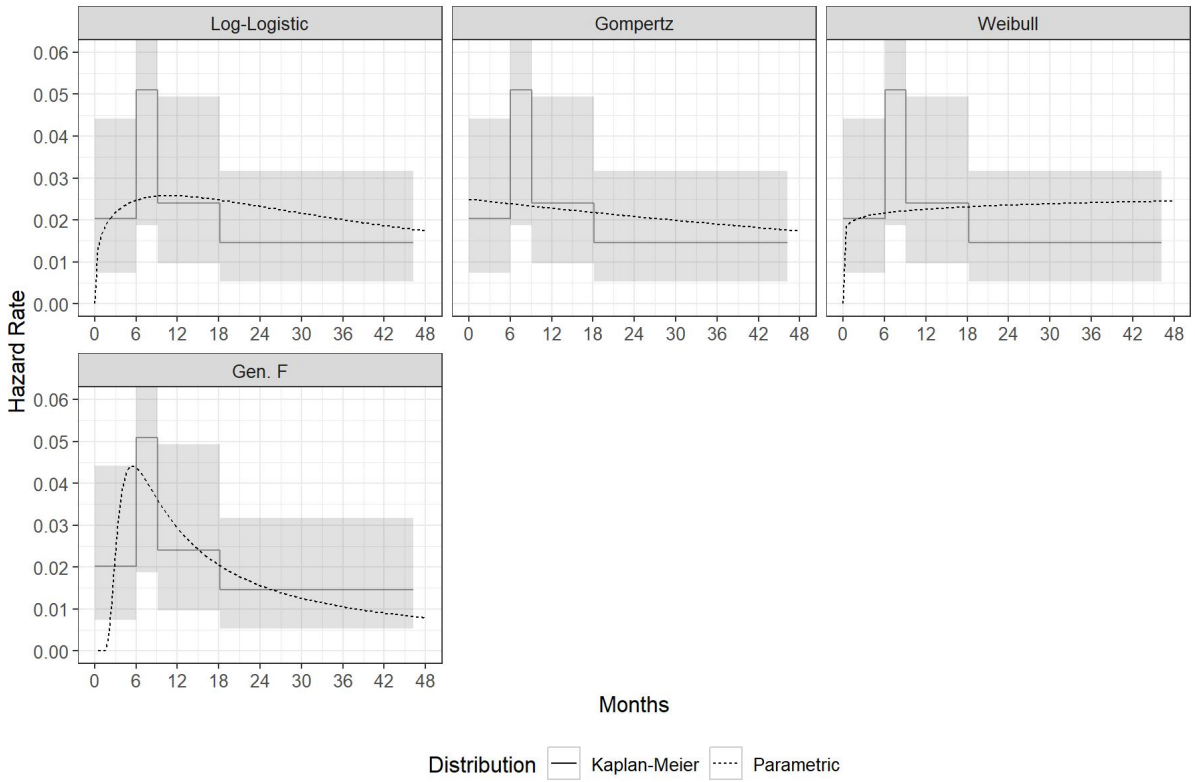
Overall Survival to 20 years



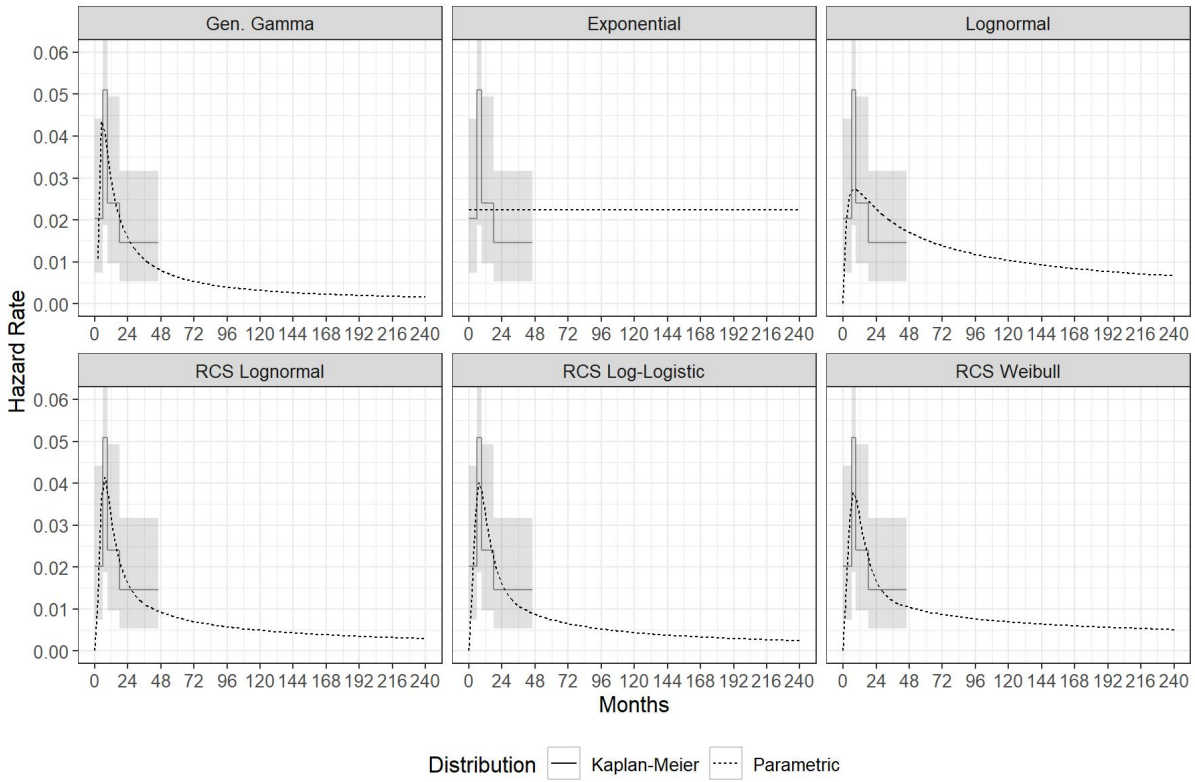


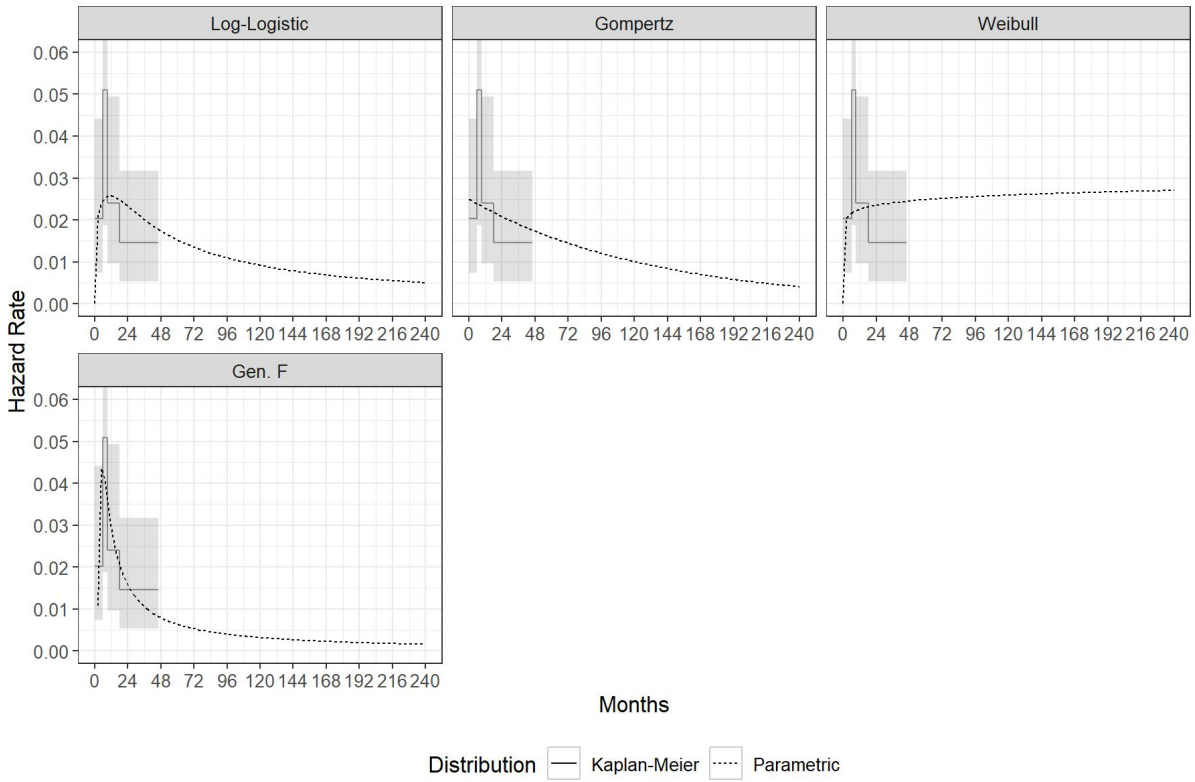
Hazard rates to the end of trial follow up



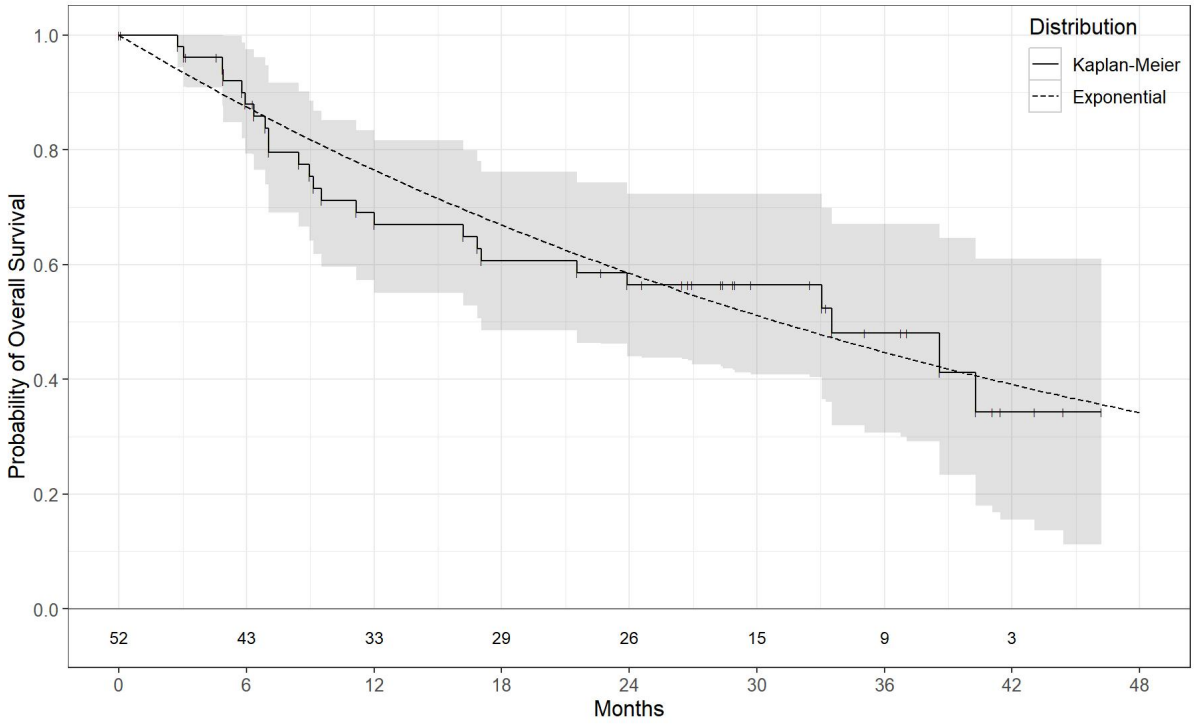


Hazard rates to 20 years

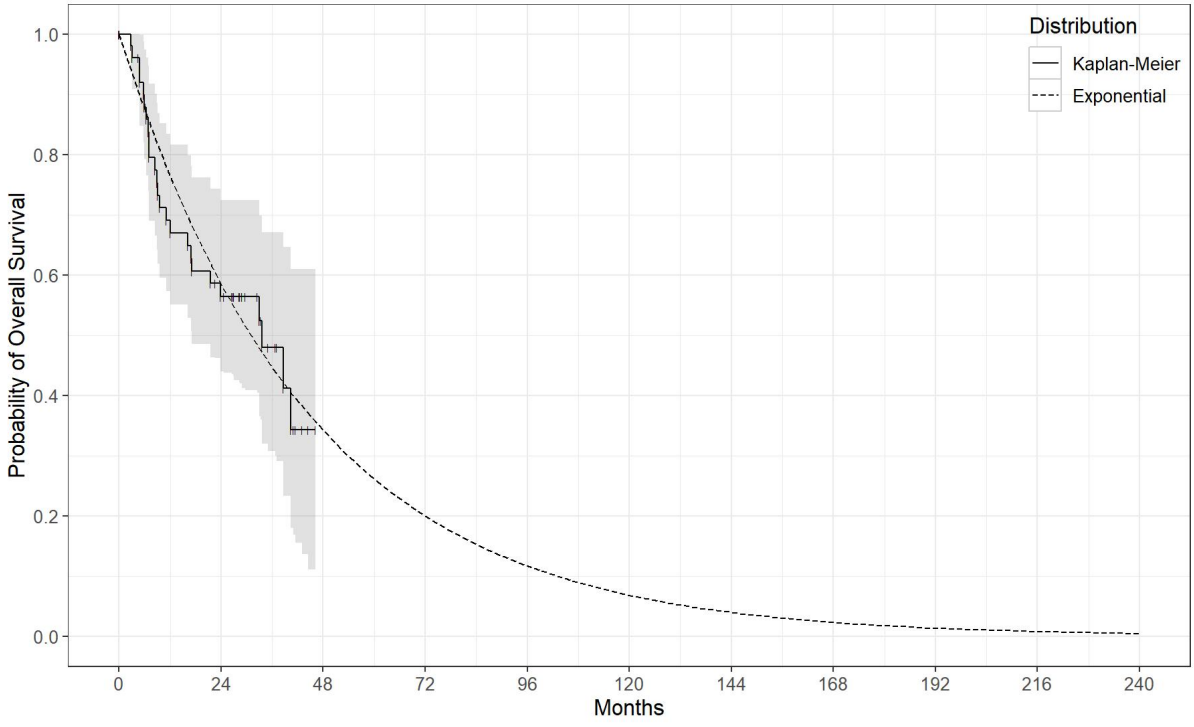




Overall survival to end of trial follow up, exponential



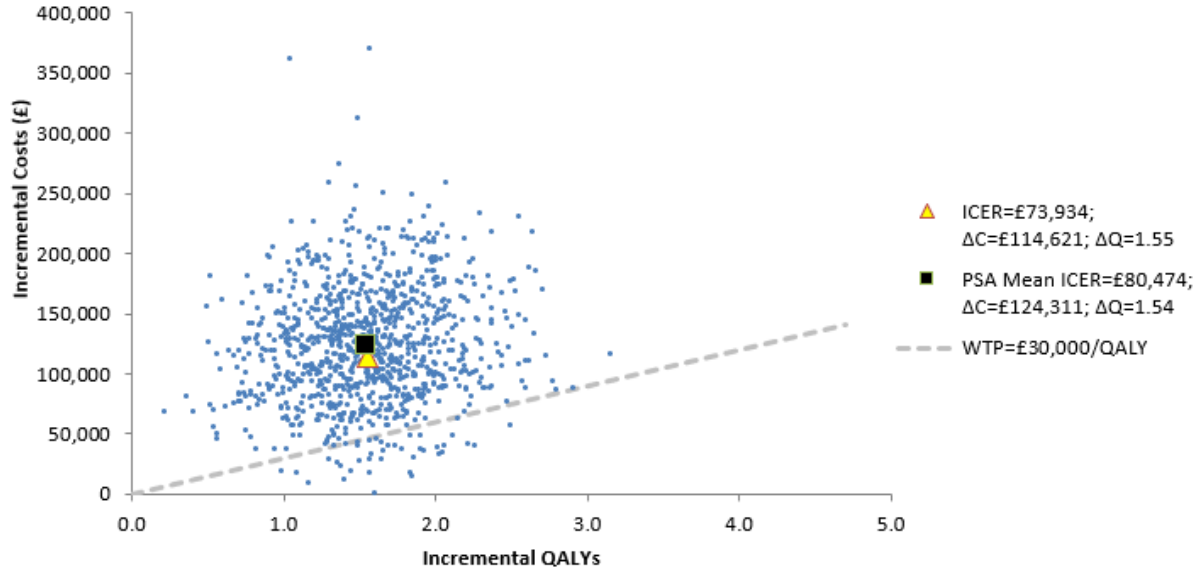
Overall survival to 20 years, exponential



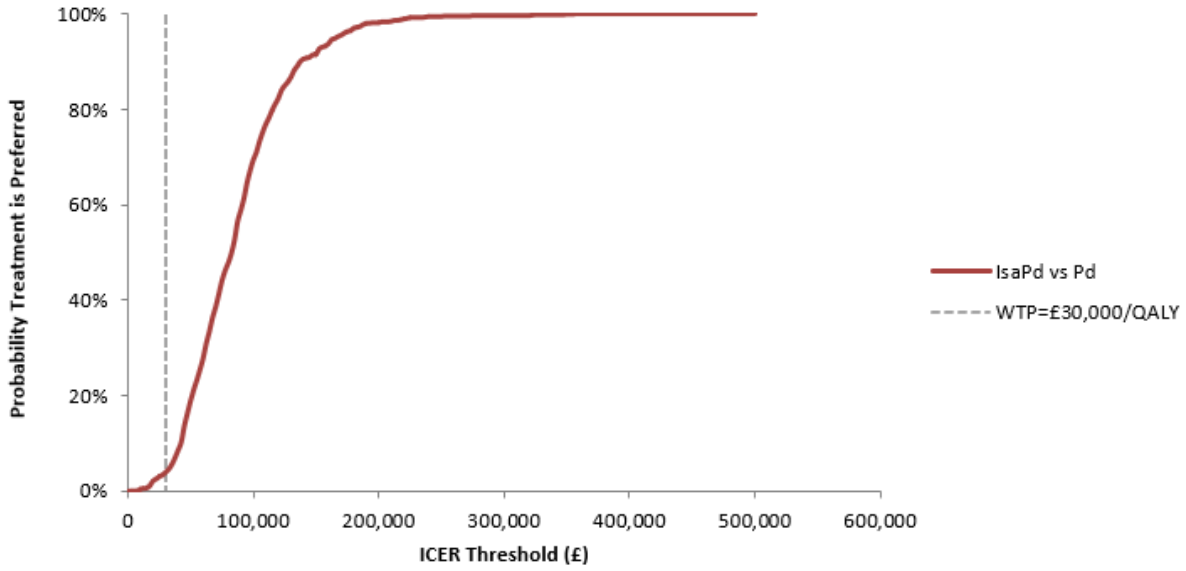
Appendix 5: Scatter plots and Cost effectiveness acceptability curves – 4L

Results using Weibull for Pd OS and Exponential for IsaPd OS academic / commercial in confidence information removed at 4L

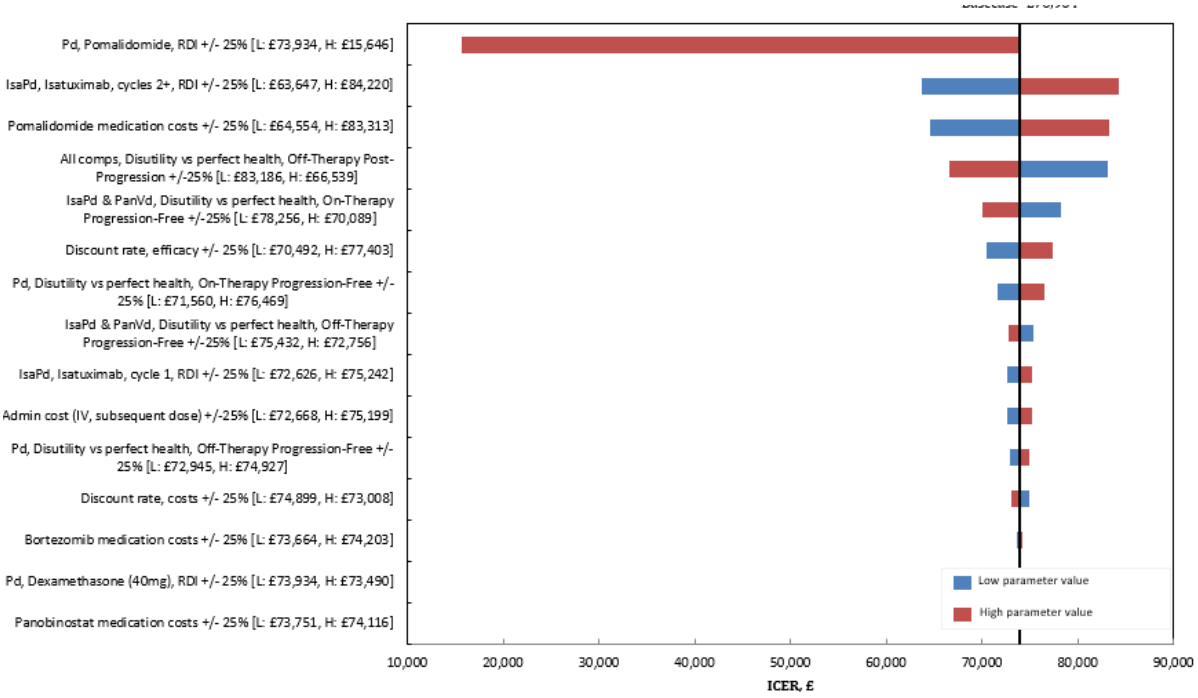
Scatter plot of simulations on cost-effectiveness plane



CEAC curves



Tornado diagram

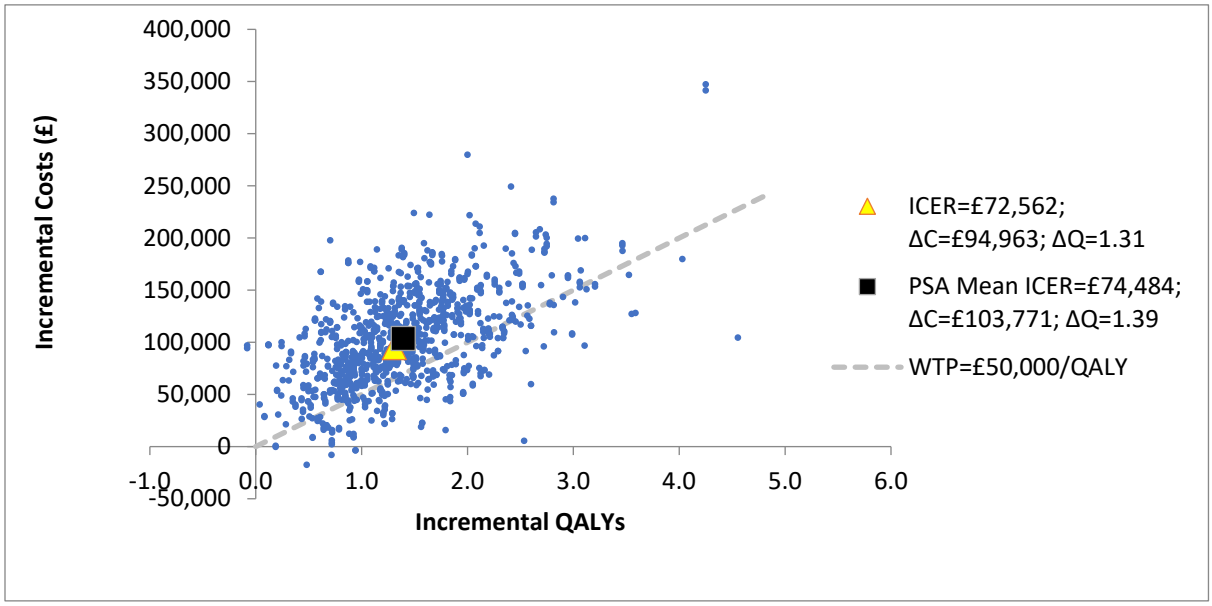


Scenarios

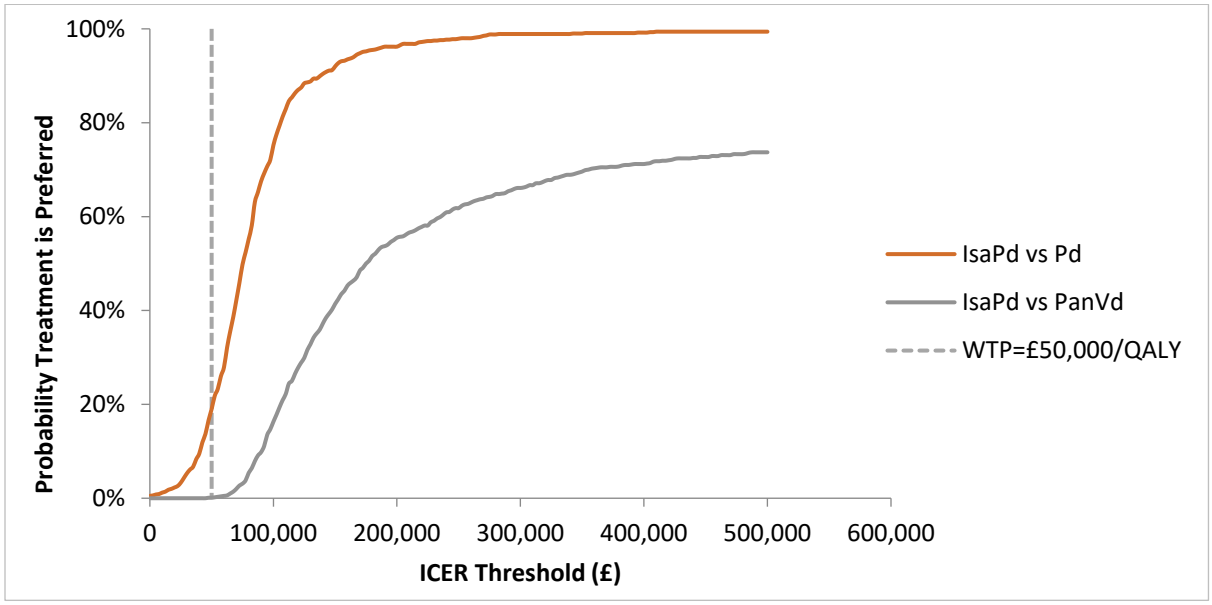
Basecase	£73,934
No medication wastage	£60,028
EQ-5D-5L utilities	£71,566
No PAS discount for Pom	£73,934
% receiving subsequent therapy and duration of subsequent therapy based on KOL feedback	£80,830
% receiving subsequent therapy based on HTA submissions	£73,934
Duration of AEs based on KOL feedback	£73,934
Favorable distributions for IsaPd	£59,922
Unfavorable distributions for IsaPd	£167,637
Other costs from dara NICE submission	£71,151
Treatment discontinued upon progression, lognormal (R) (best BIC)	£114,084
Treatment discontinued upon progression, exponential	£64,646
5-year time horizon	£135,502
10-year time horizon	£89,531
20-year time horizon	£73,934
1.5% effectiveness discount rate	£66,113
1.5% effectiveness and cost discount rates	£68,144
Isa dosing based on ICARIA weight distribution	£88,441
Favorable inputs	£58,249
Unfavorable inputs	£177,130
No Dara Subsequent Tx – IPCW HR OS	£96,532
No Dara or Len Subsequent Tx – IPCW HR OS	£104,680

Results using Weibull for Pd OS and Exponential for IsaPd OS academic / commercial in confidence information removed at 4L

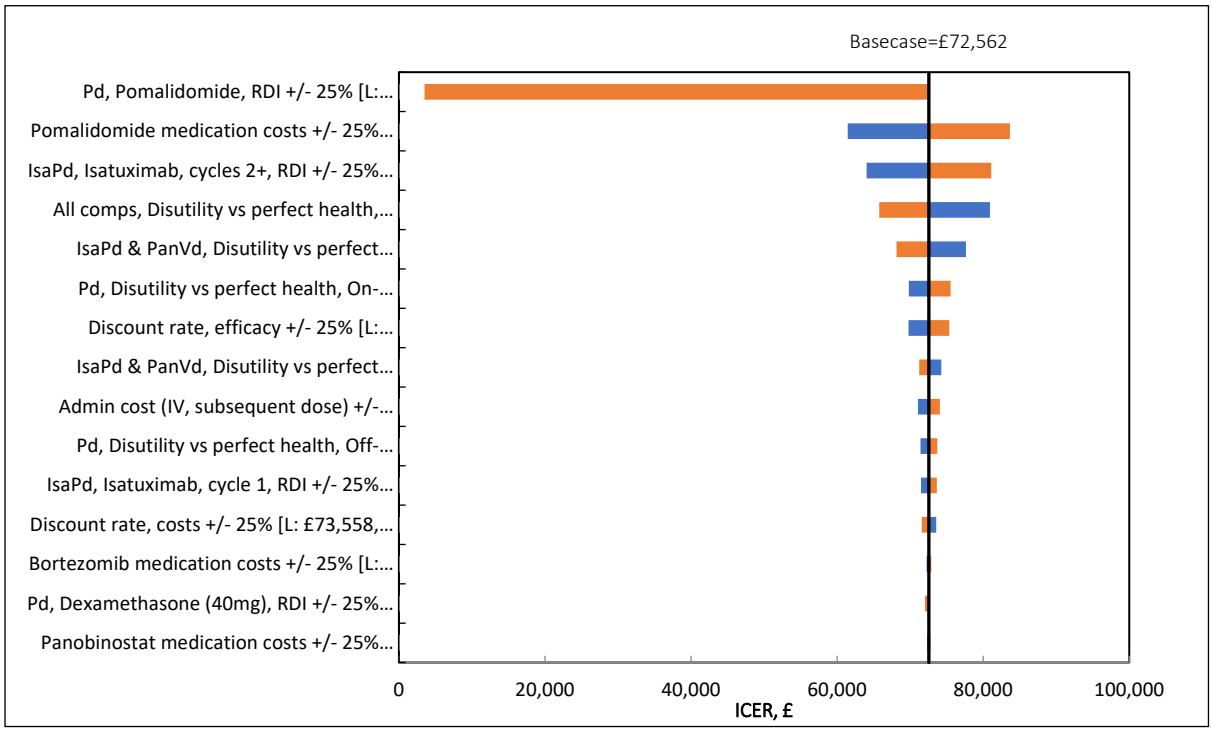
Scatter plot of simulations on cost-effectiveness plane



CEAC curves



Tornado diagram



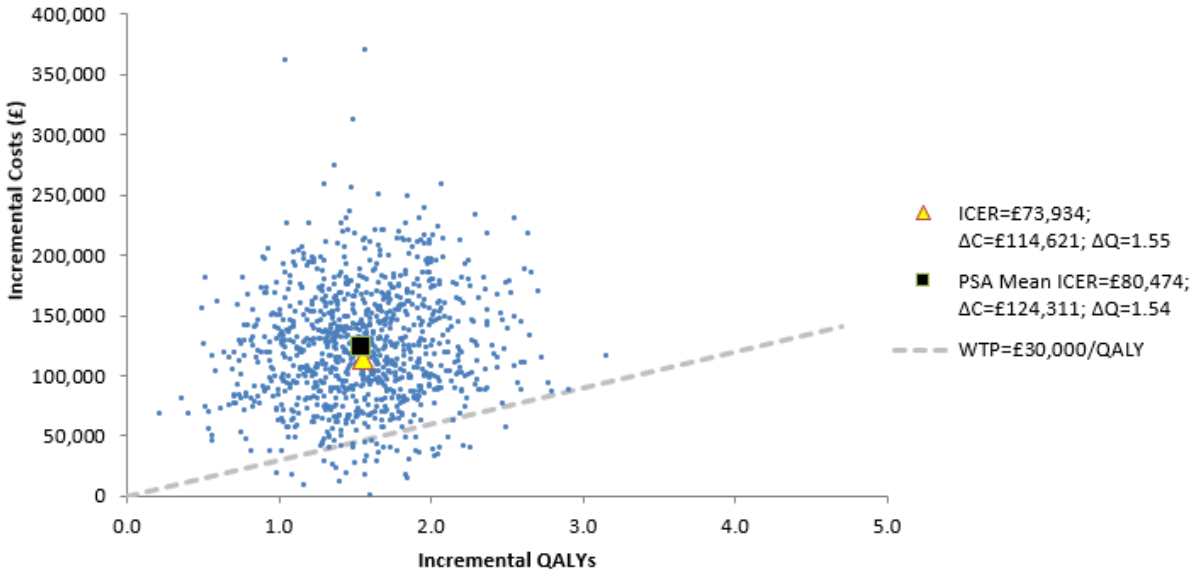
Scenario analyses

Base case	£72,562
No medication wastage	£57,000
EQ-5D-5L utilities	£70,499
No PAS discount for Pom	£72,562
% receiving subsequent therapy and duration of subsequent therapy based on KOL feedback	£80,731
% receiving subsequent therapy based on HTA submissions	£72,562
Duration of AEs based on KOL feedback	£72,562
Favourable distributions for IsaPd	£48,319
Unfavourable distributions for IsaPd	£141,716
Other costs from dara NICE submission	£69,821
Treatment discontinued upon progression, lognormal (R) (best BIC)	£114,012
Treatment discontinued upon progression, exponential	£62,267
5-year time horizon	£115,486
10-year time horizon	£80,127
20-year time horizon	£72,562
1.5% effectiveness discount rate	£66,217

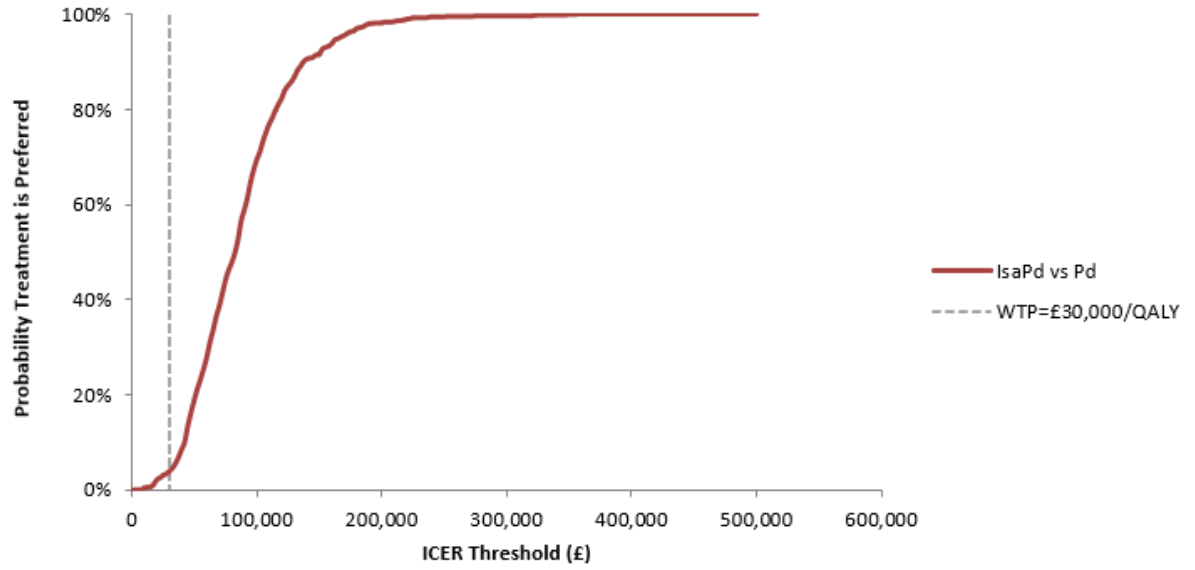
1.5% effectiveness and cost discount rates	£68,347
Isa dosing based on ICARIA weight distribution	£104,170
Favorable inputs	£58,249
Unfavorable inputs	£151,209
No Dara Subsequent Tx – IPCW HR OS	£83,600
No Dara or Len Subsequent Tx – IPCW HR OS	£90,132

Results using Weibull for Pd OS and DF2.9 to estimate IsaPd OS academic / commercial in confidence information removed at 4L

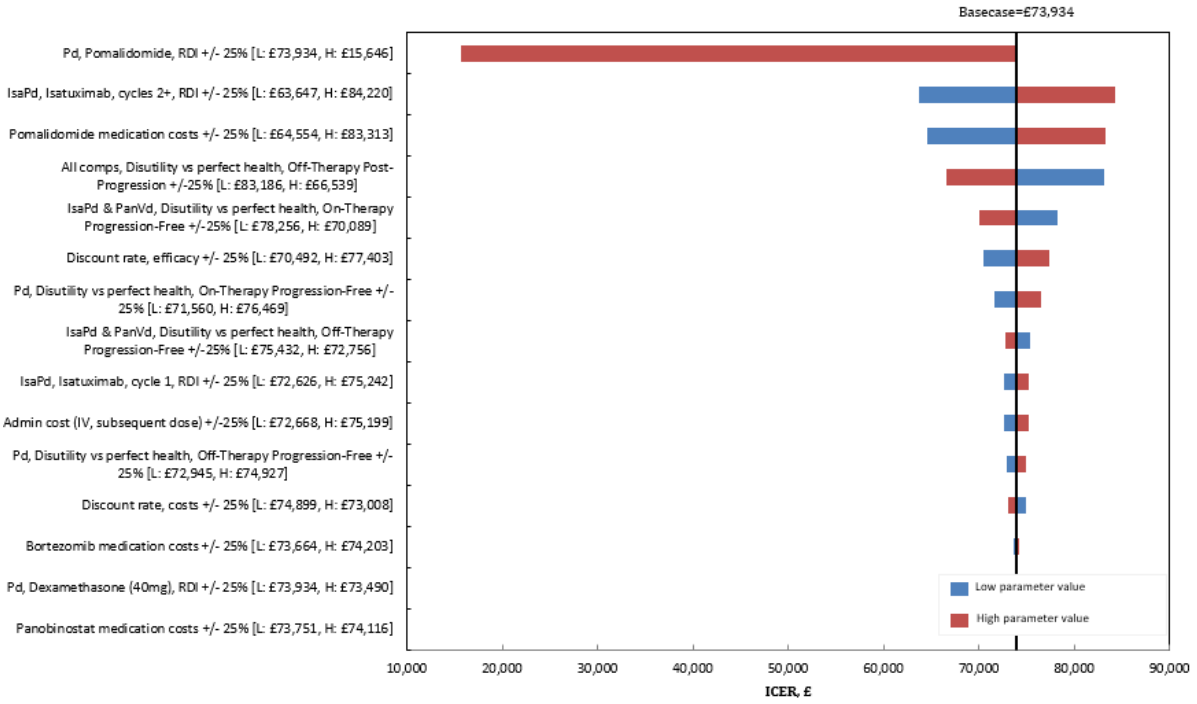
Scatter plot of simulations on cost-effectiveness plane



CEAC curves



Tornado diagram

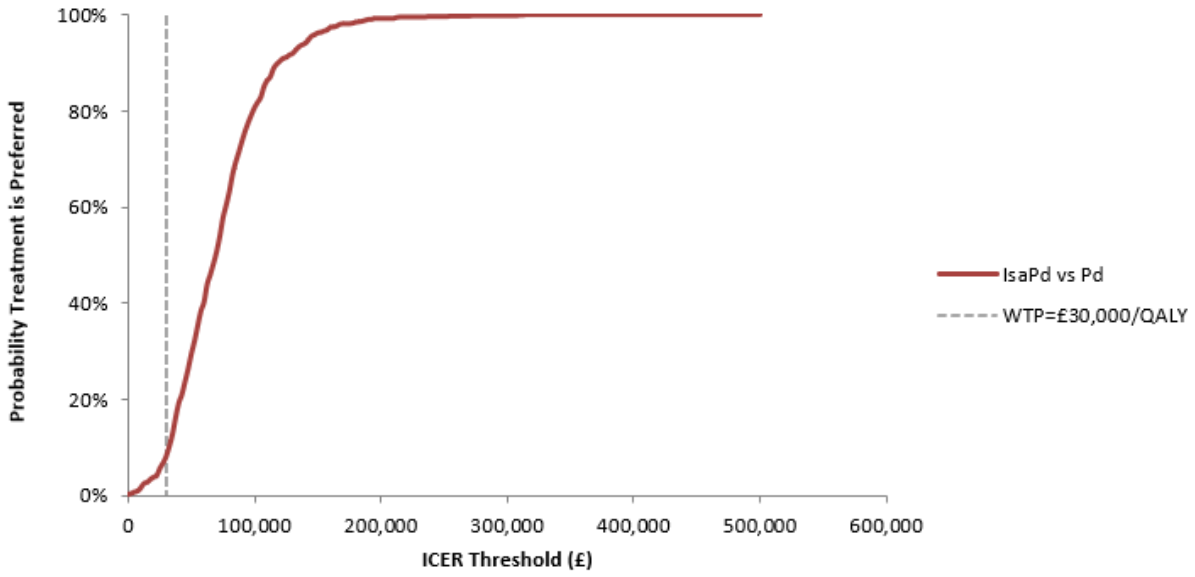


Scenarios

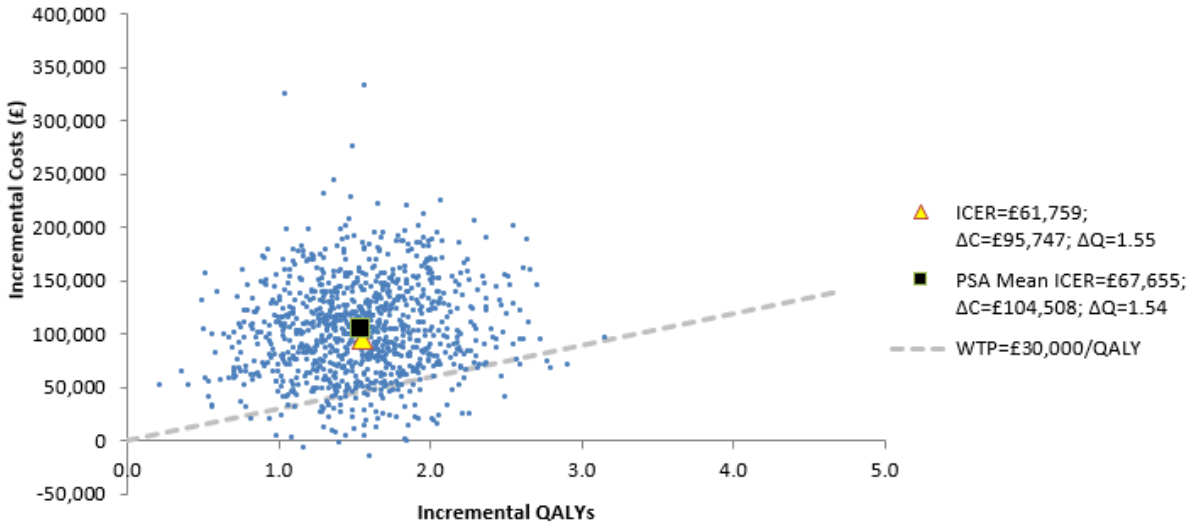
Basecase	£73,934
No medication wastage	£60,028
EQ-5D-5L utilities	£71,566
No PAS discount for Pom	£73,934
% receiving subsequent therapy and duration of subsequent therapy based on KOL feedback	£80,830
% receiving subsequent therapy based on HTA submissions	£73,934
Duration of AEs based on KOL feedback	£73,934
Favorable distributions for IsaPd	£59,922
Unfavorable distributions for IsaPd	£167,637
Other costs from dara NICE submission	£71,151
Treatment discontinued upon progression, lognormal (R) (best BIC)	£114,084
Treatment discontinued upon progression, exponential	£64,646
5-year time horizon	£135,502
10-year time horizon	£89,531
20-year time horizon	£73,934
1.5% effectiveness discount rate	£66,113
1.5% effectiveness and cost discount rates	£68,144
Isa dosing based on ICARIA weight distribution	£88,441
Favorable inputs	£58,249
Unfavorable inputs	£177,130
No Dara Subsequent Tx – IPCW HR OS	£96,532
No medication wastage	£104,680

Results using Weibull for Pd OS and DF2.9 to estimate IsaPd OS academic / commercial in confidence information removed at 4L

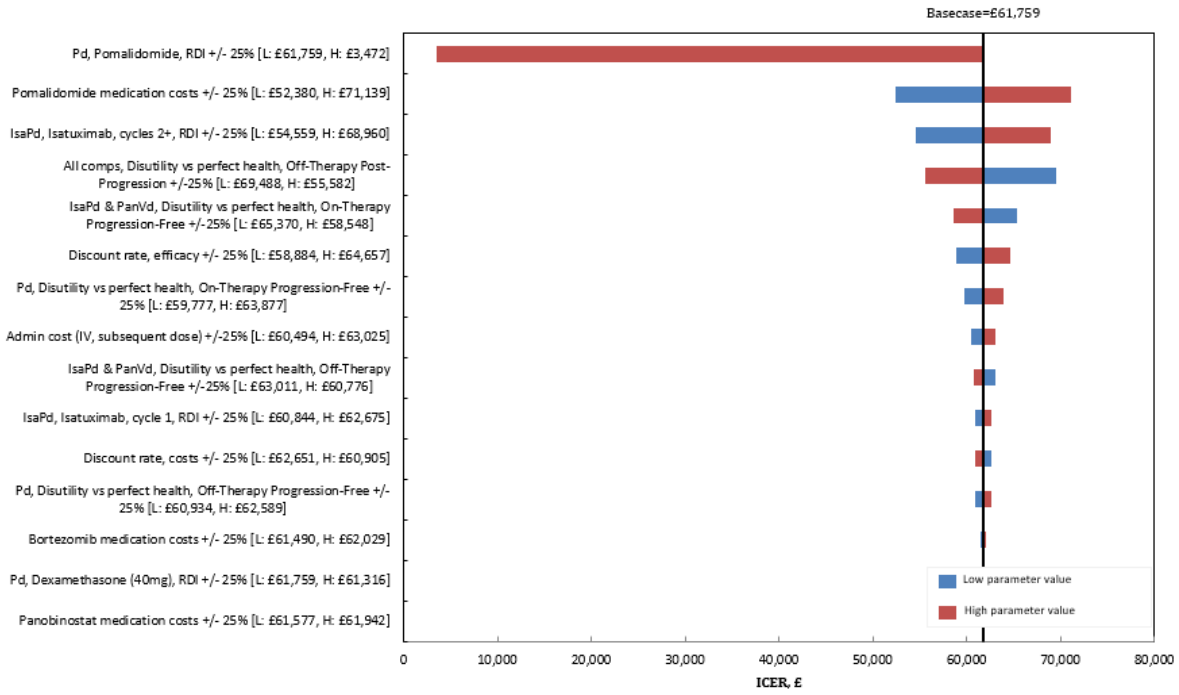
Scatter plot of simulations on cost-effectiveness plane



CEAC curves



Tornado diagram

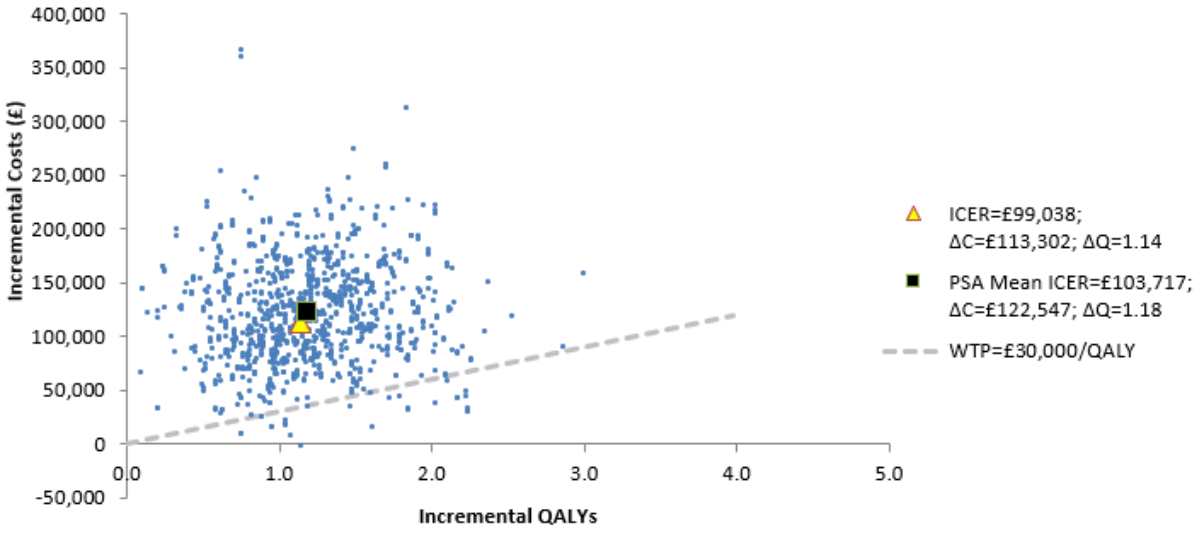


Scenarios

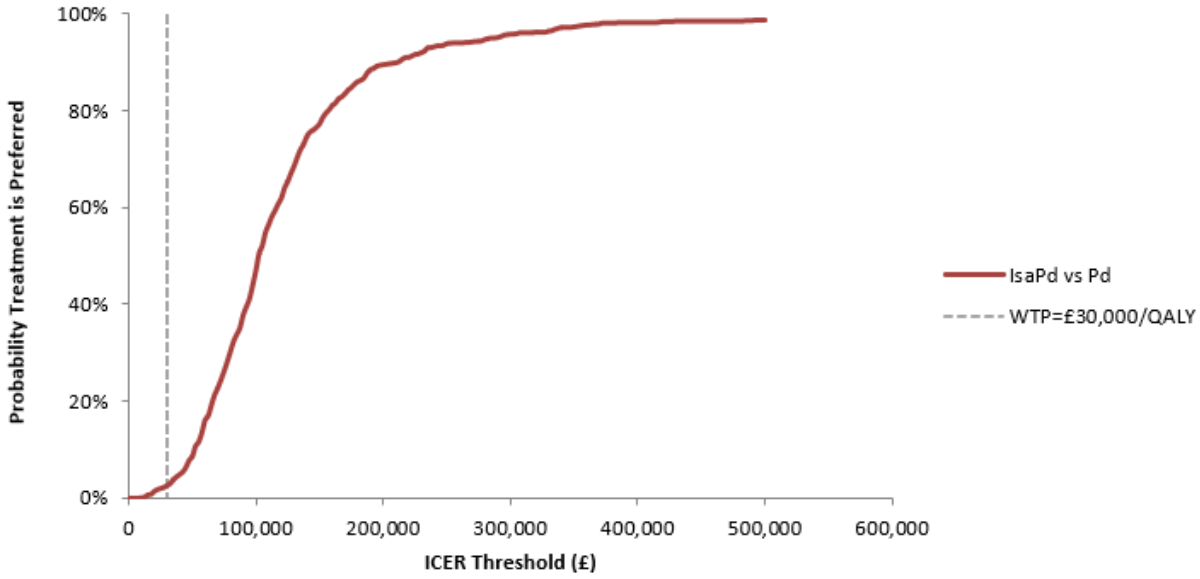
Base case	£61,759
No medication wastage	£48,623
EQ-5D-5L utilities	£59,781
No PAS discount for Pom	£61,759
% receiving subsequent therapy and duration of subsequent therapy based on KOL feedback	£68,656
% receiving subsequent therapy based on HTA submissions	£61,759
Duration of AEs based on KOL feedback	£61,759
Favorable distributions for IsaPd	£48,319
Unfavorable distributions for IsaPd	£141,716
Other costs from dara NICE submission	£58,976
Treatment discontinued upon progression, lognormal (R) (best BIC)	£97,201
Treatment discontinued upon progression, exponential	£53,069
5-year time horizon	£112,189
10-year time horizon	£74,655
20-year time horizon	£61,759
1.5% effectiveness discount rate	£55,227
1.5% effectiveness and cost discount rates	£57,103
Isa dosing based on ICARIA weight distribution	£88,441
Favorable inputs	£58,249
Unfavorable inputs	£151,209
No Dara Subsequent Tx – IPCW HR OS	£83,600
No Dara or Len Subsequent Tx – IPCW HR OS	£90,132

Results using Weibull for Pd OS and semi-synthetic OS for IsaPd OS academic / commercial in confidence information removed at 4L

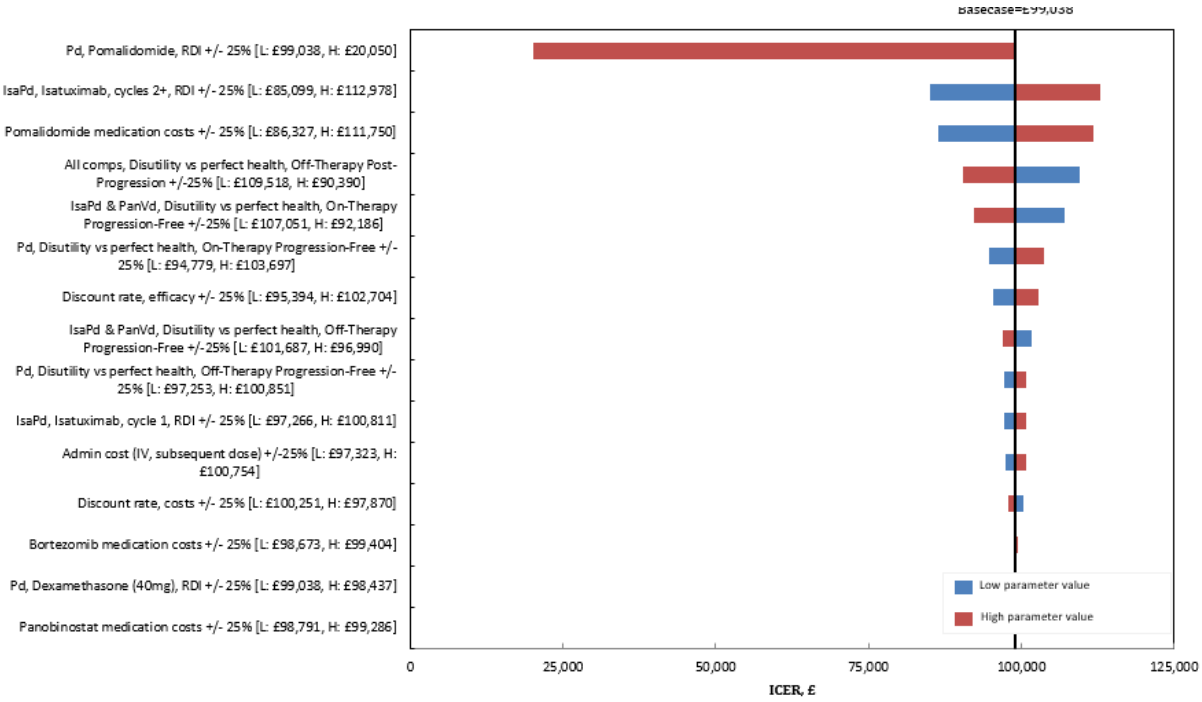
Scatter plot of simulations on cost-effectiveness plane



CEAC curves



Tornado diagram

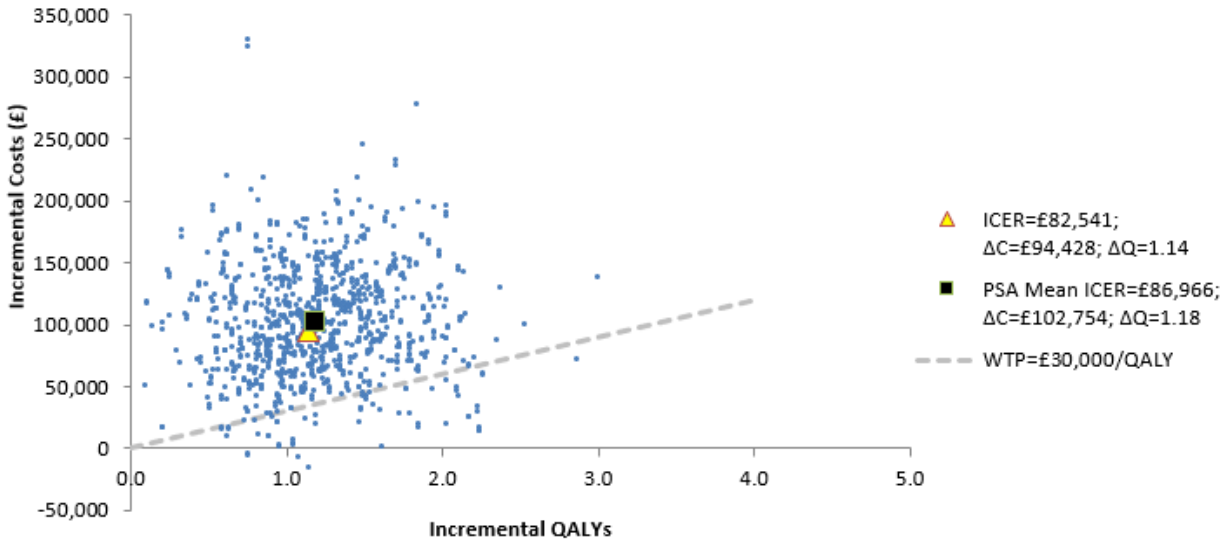


Scenarios

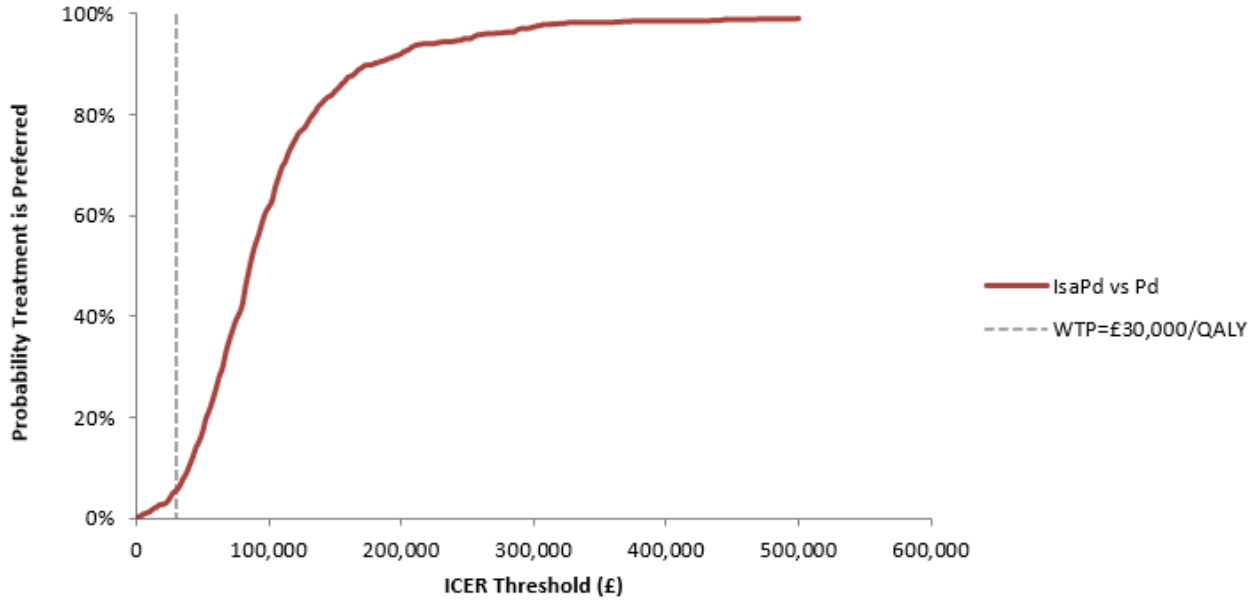
Base case	£99,038
No medication wastage	£80,195
EQ-5D-5L utilities	£96,637
No PAS discount for Pom	£99,038
% receiving subsequent therapy and duration of subsequent therapy based on KOL feedback	£108,384
% receiving subsequent therapy based on HTA submissions	£99,038
Duration of AEs based on KOL feedback	£99,038
Favorable distributions for IsaPd	£59,922
Unfavorable distributions for IsaPd	£167,637
Other costs from dara NICE submission	£96,336
Treatment discontinued upon progression, lognormal (R) (best BIC)	£151,694
Treatment discontinued upon progression, exponential	£86,452
5-year time horizon	£153,759
10-year time horizon	£107,959
20-year time horizon	£99,038
1.5% effectiveness discount rate	£90,745
1.5% effectiveness and cost discount rates	£93,347
Isa dosing based on ICARIA weight distribution	£118,698
Favorable inputs	£58,249
Unfavorable inputs	£177,130
No Dara Subsequent Tx – IPCW HR OS	£96,532
No Dara or Len Subsequent Tx – IPCW HR OS	£104,680

Results using Weibull for Pd OS and semi-synthetic OS for IsaPd OS academic / commercial in confidence information removed at 4L

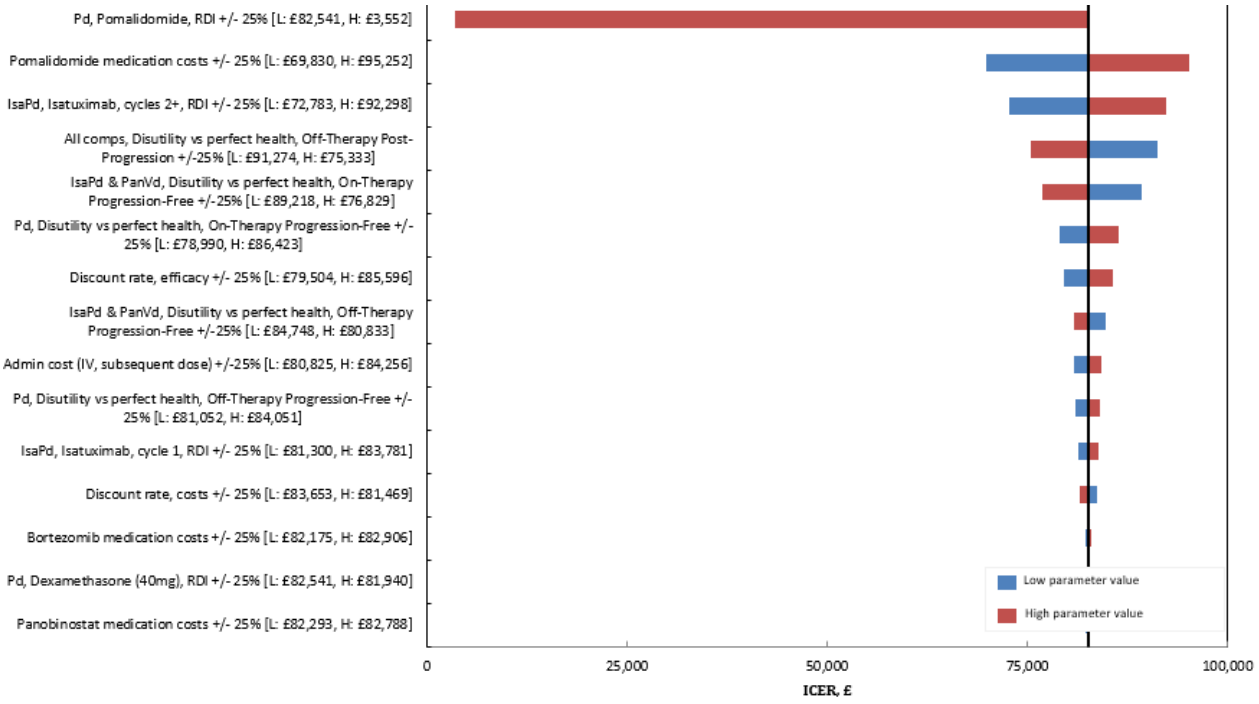
Scatter plot of simulations on cost-effectiveness plane



CEAC curves



Tornado diagram

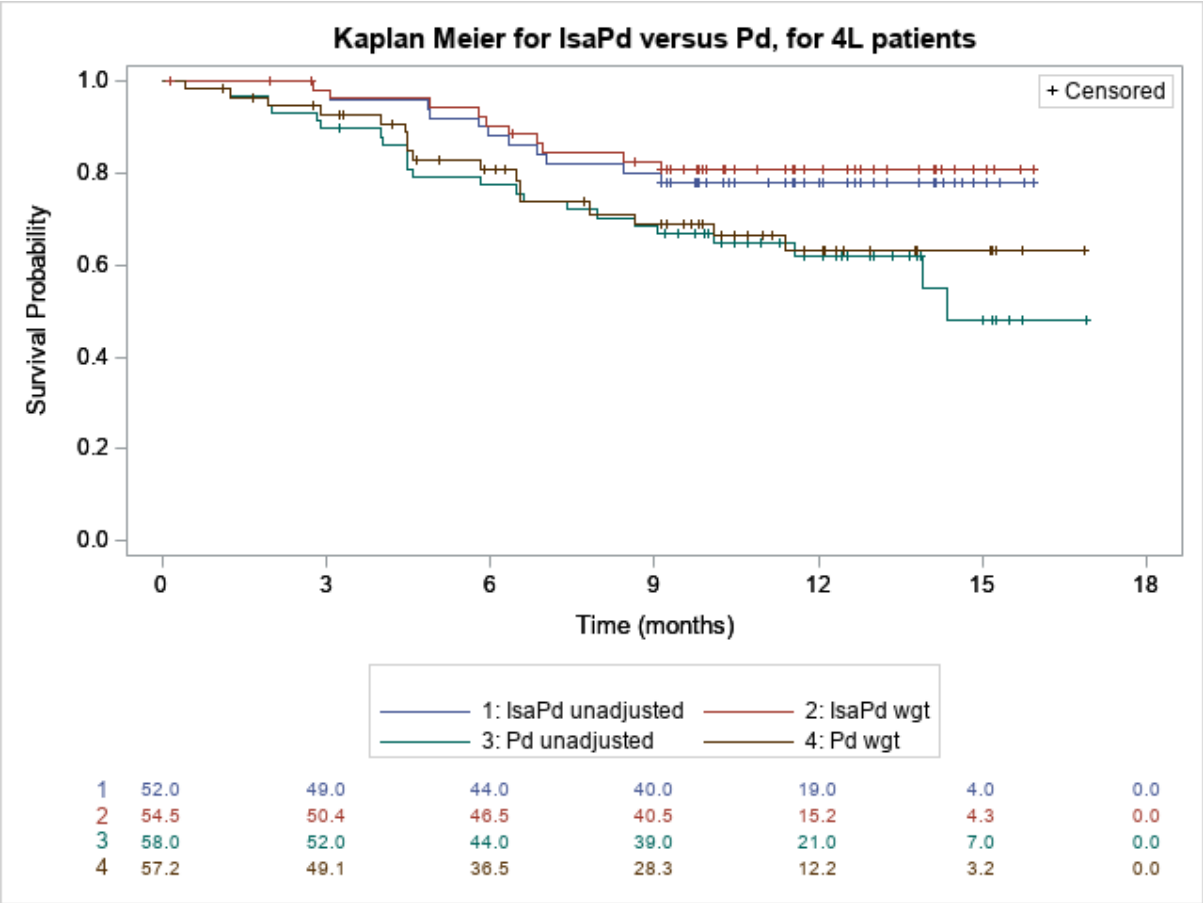


Scenarios

Base case	**£82,541**
No medication wastage	£64,739
EQ-5D-5L utilities	£80,539
No PAS discount for Pom	£82,541
% receiving subsequent therapy and duration of subsequent therapy based on KOL feedback	£91,886
% receiving subsequent therapy based on HTA submissions	£82,541
Duration of AEs based on KOL feedback	£82,541
Favourable distributions for IsaPd	£48,319
Unfavourable distributions for IsaPd	£141,716
Other costs from dara NICE submission	£79,838
Treatment discontinued upon progression, lognormal (R) (best BIC)	£128,959
Treatment discontinued upon progression, exponential	£70,764
5-year time horizon	£127,236
10-year time horizon	£89,913
20-year time horizon	£82,541
1.5% effectiveness discount rate	£75,629
1.5% effectiveness and cost discount rates	£78,017
Isa dosing based on ICARIA weight distribution	£118,698
Favourable inputs	£58,249
Unfavourable inputs	£151,209
No Dara Subsequent Tx – IPCW HR OS	£83,600
No Dara or Len Subsequent Tx – IPCW HR OS	£90,132

Appendix 6: Reconstructed KM OS curves using IPCW weights

Reconstructed KM OS curves based on the analysis of OS in 4L patients with censoring on receipt of dara or len and inverse probability of censoring weighting (IPCW) to adjust for informative censoring



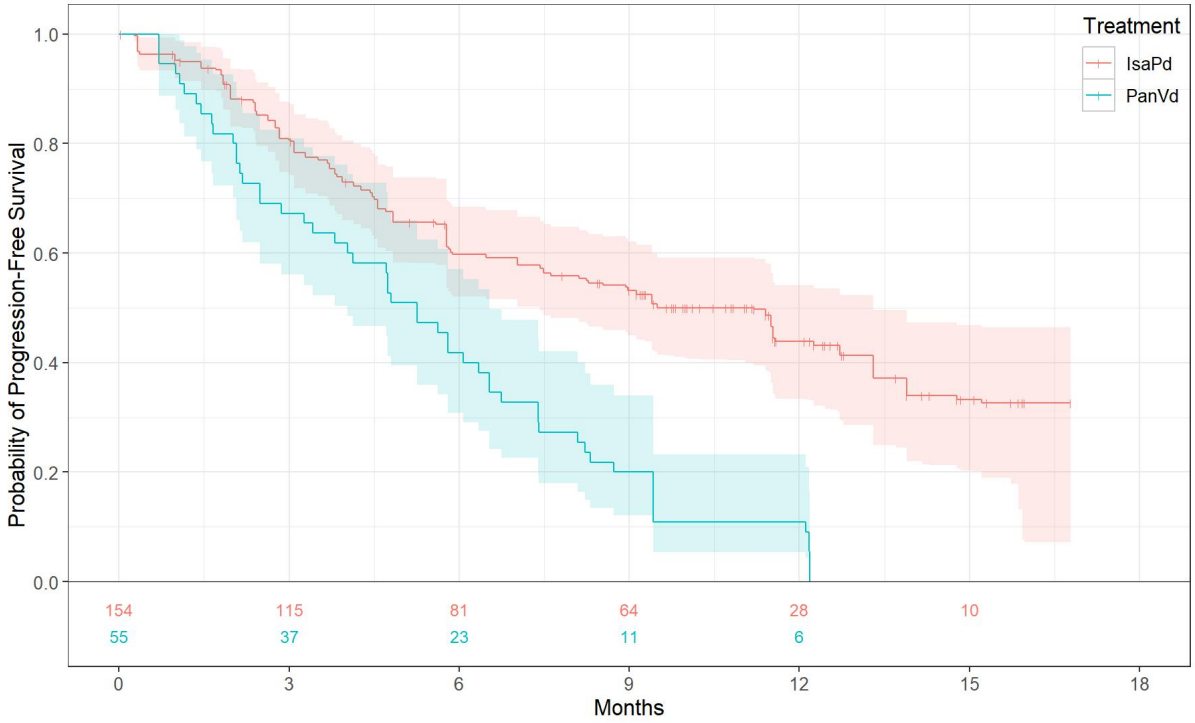
Appendix 7: Further details on the Matching Adjusted Indirect Comparison (MAIC) to PanVd

(Full details of the MAIC are reported in Appendix K4 of company submission – only a summary is provided here of the key outcomes)

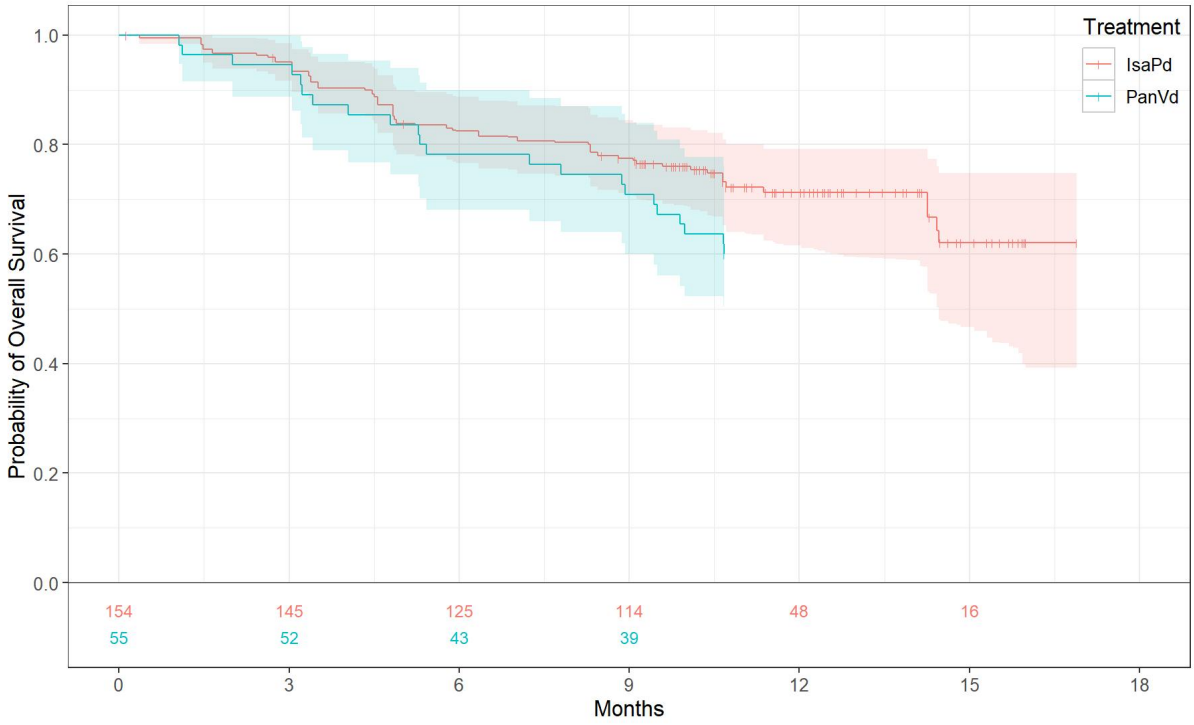
Estimates of PFS, PFS on treatment, TTD, and OS for PanVd were based on estimates of the relative effectiveness of these treatments derived from unanchored comparisons of PFS and OS for the MAIC-adjusted IsaPd arm of ICARIA-MM and the single arm PANORAMA-2 trial of PanVd. As the systematic literature review revealed that a connected evidence network linking IsaPd to PanVd could not be constructed, the comparison of IsaPd to PanVd required an unanchored comparison. To control for differences between trials in patient characteristics that might bias such comparisons, a MAIC was conducted wherein patients in the IsaPd arm of the ICARIA-MM trial were weighted so that their baseline characteristics would match the aggregate statistics on the characteristics in the PANORAMA-2 trial. Patient-level failure time data for PanVd were reconstructed from published KM curves using and adaptation of a published algorithm by Guyot. The MAIC-adjusted KM curves for PFS and OS for IsaPd and PanVd are shown below.

MAIC-Adjusted PFS and OS for IsaPd and PanVd

PFS



OS



For the comparison to PanVd at 3L, the MAIC-adjusted HR for PanVd vs. IsaPd are applied to the unweighted 3L PFS and OS for IsaPd. Below are the trial data for PFS and OS in the 3L population to which these HR are applied.

HRs for PFS and OS from ITC of HRs from Trials of Patients with RRMM

Comparator	HR vs. IsaPd (95% CI)	
	PFS	OS
PanVd	2.71 (1.90, 3.86)	1.56 (0.92, 2.63)

a. Progression-Free Survival

As summarized in the table below, the restricted lognormal distribution was used for PFS for IsaPd and Pd for the 3L population based on BIC, visual fit, treatment effect diagnostics, and clinical plausibility. A more detailed discussion of the rationale for the selection of this distribution is provided in the remainder of this section.

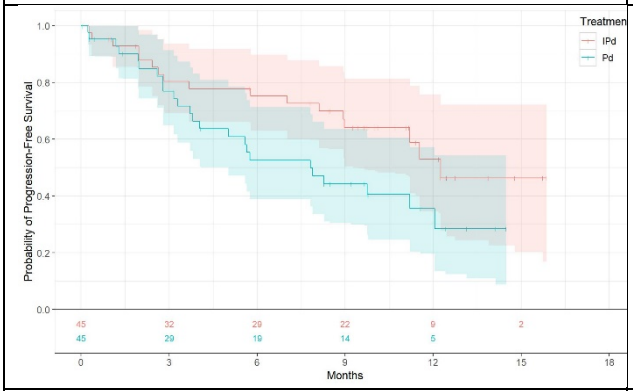
Parametric Distribution Used for PFS for IsaPd and Pd for 3L Population

Chosen distribution	Exponential
BIC rank	First
Visual inspection	Good visual fit to the observed KM survival curves
Treatment effect	Proportional hazards model appropriate based on treatment effect diagnostics
Clinical plausibility	Although no external data are available to validate the long-term projections, distribution yields projection of PFS for Pd that are below 10% at three years, below 5% at five years and close to zero by 10 years, which are not unreasonable given the relatively poor prognosis of these patients.
Comment	Yields projection of benefit that is within the range of estimates from all distributions

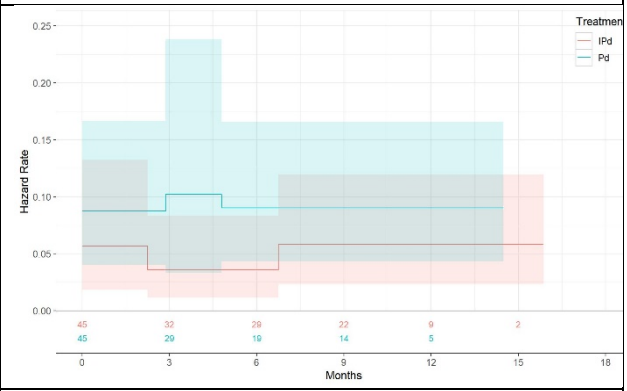
KM survival distributions, hazard rates, HRs, and Schoenfeld residuals, transformation diagnostics, and treatment effect diagnostics for PFS by treatment group for 3L patients in the ICARIA-MM trial are reported in the figure below. The hazard rates for Pd and IsaPd are relatively stable; hazard rates for IsaPd are lower than those for Pd throughout the follow-up period. The test of the linearity of the Schoenfeld residuals is not statistically significant, suggesting that a PH distribution (e.g., exponential, Weibull, Gompertz) may not be inappropriate. The cumulative hazard function (log of survival by time) has a slightly decreasing slope (with the exception of the tail of the distribution where the numbers at risk are small), suggesting that distributions with diminishing hazards may not be inappropriate. The treatment effect diagnostics indicate that PH, proportional odds, and AFT models may all be appropriate.

Progression-Free Survival for the 3L Population of ICARIA-MM, by Randomized Treatment

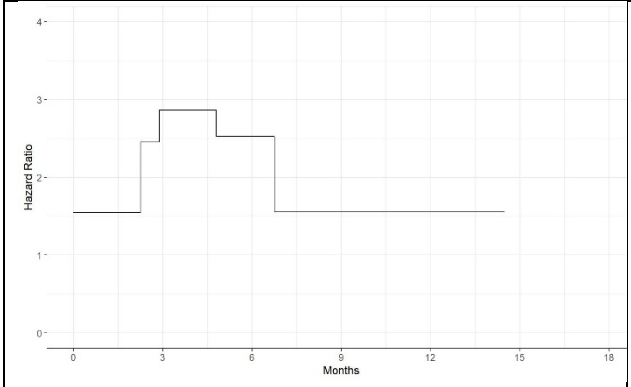
A. Kaplan-Meier Survival Distribution



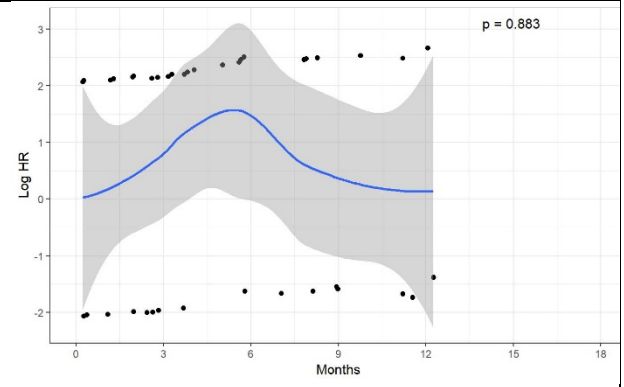
B. Hazard Rates



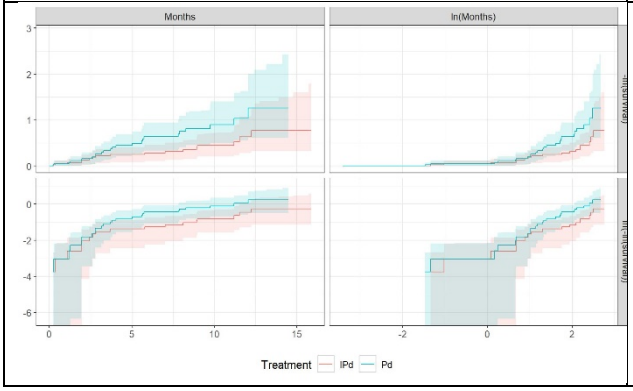
C. Hazard Ratio



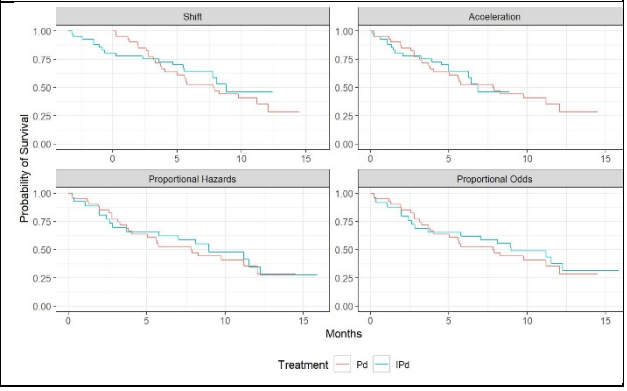
D. Schoenfeld Residuals



E. Transformation Diagnostics



F. AFT Treatment Effect Diagnostic

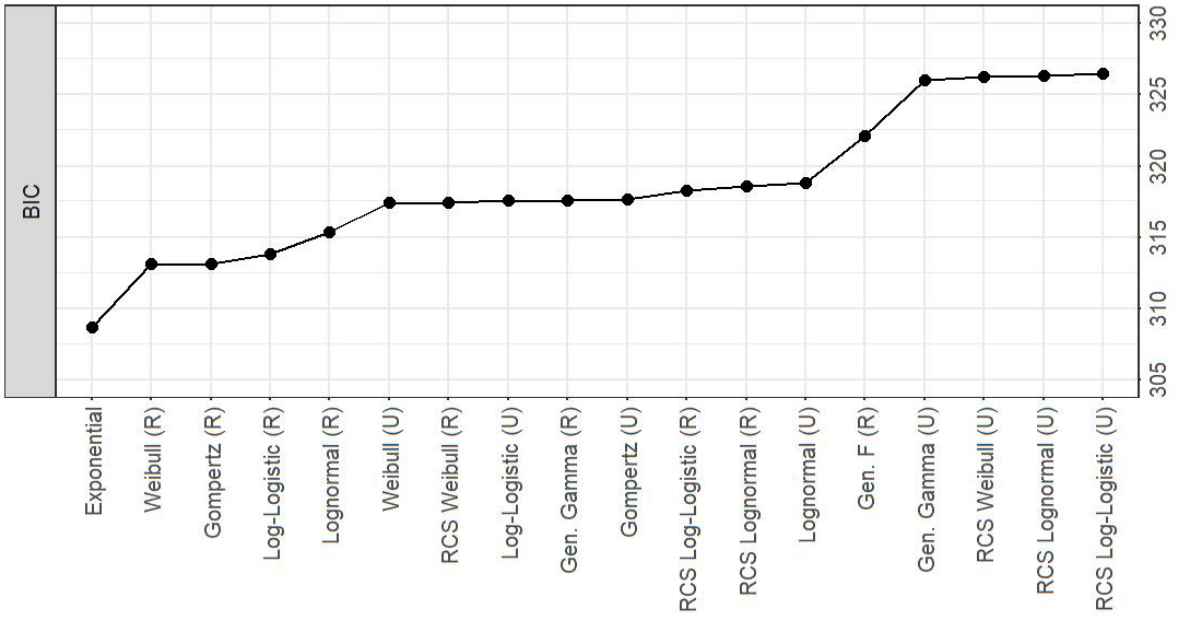


Source: Analyses of ICARIA-MM data

A ranking of parametric distributions fit to PFS by the fit statistics are shown in the figure below. The top six distributions, according to BIC statistics were as follows:

- Exponential
- Weibull (R);
- Gompertz (R);
- Log-logistic (R);
- Lognormal (R); and,
- Weibull (U).

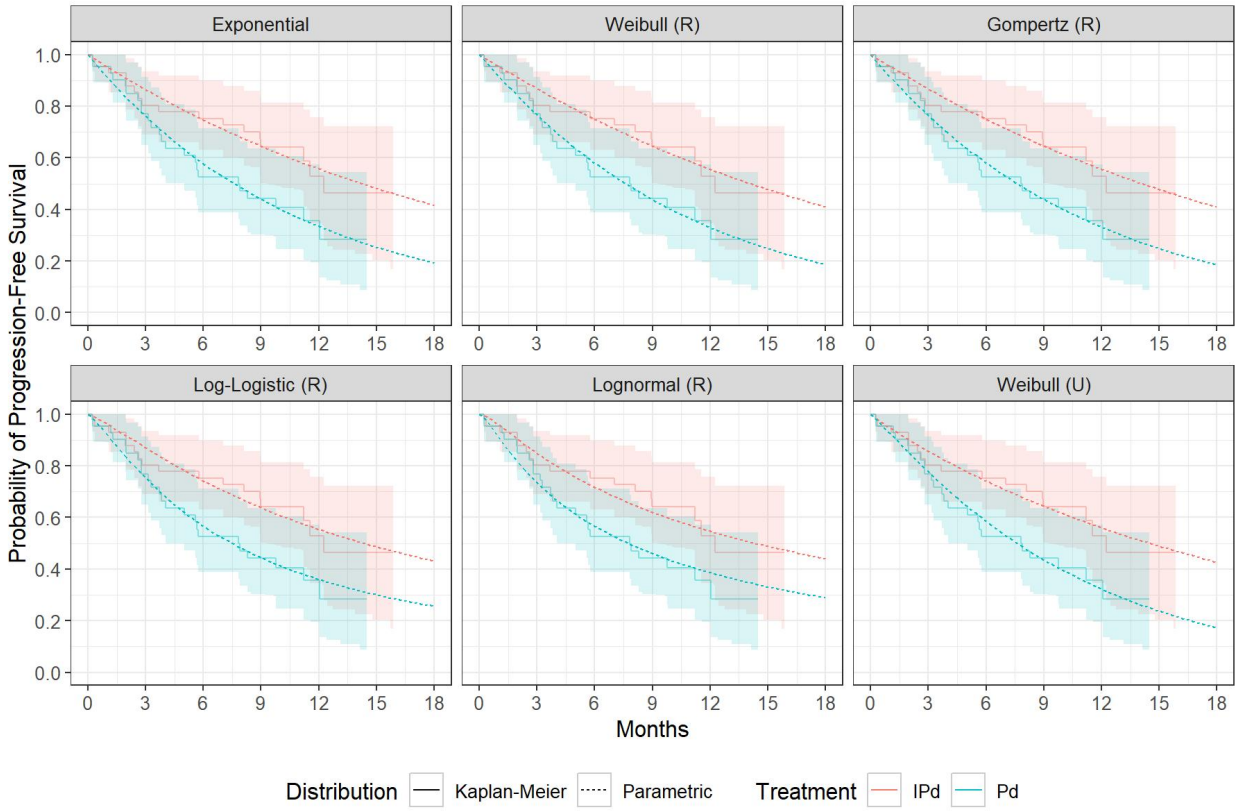
Figure 1. Fit Statistics for Parametric Distributions Fit to PFS for the 3L Population of ICARIA-MM



BIC: Bayesian Information Criterion (Smaller is Better)

Parametric survival distributions for PFS during the trial period for the six best fitting distributions based on BIC are shown in in the figure below (distributions are ranked by BIC going left to right, top to bottom). All of the top fitting parametric distributions have relatively good fit to the KM distribution. All the other distributions generate projections of PFS at 18 months for Pd ranging from approximately 15% to 25% and for IsaPd ranging from 40% to 45%.

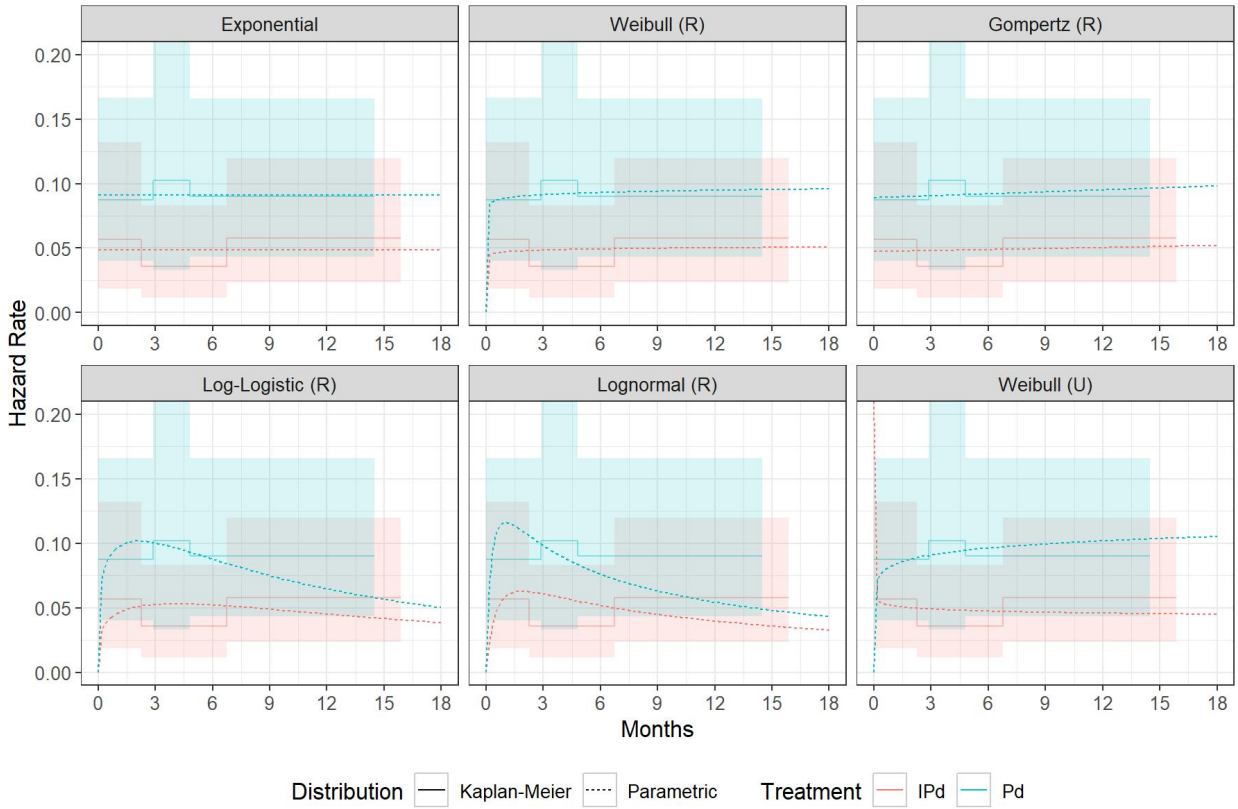
Parametric Survival Distributions Fit to PFS for the 3L Population in ICARIA-MM, by Randomized Treatment



Source: Analyses of ICARIA-MM data

Hazard rates during the trial follow-up for the top six best fitting parametric survival distributions based on BIC for PFS are compared with non-parametric hazards in the figure below. The hazard rates for the exponential, restricted Weibull and restricted Gompertz are relatively stable over time with very slight increases seen for the restricted Weibull and restricted Gompertz. The rates for the restricted log-logistic and the restricted lognormal initially increase and then gradually decrease over time. The hazard rate for Pd appears to increase slightly and for IsaPd decrease slightly for the unrestricted Weibull distribution.

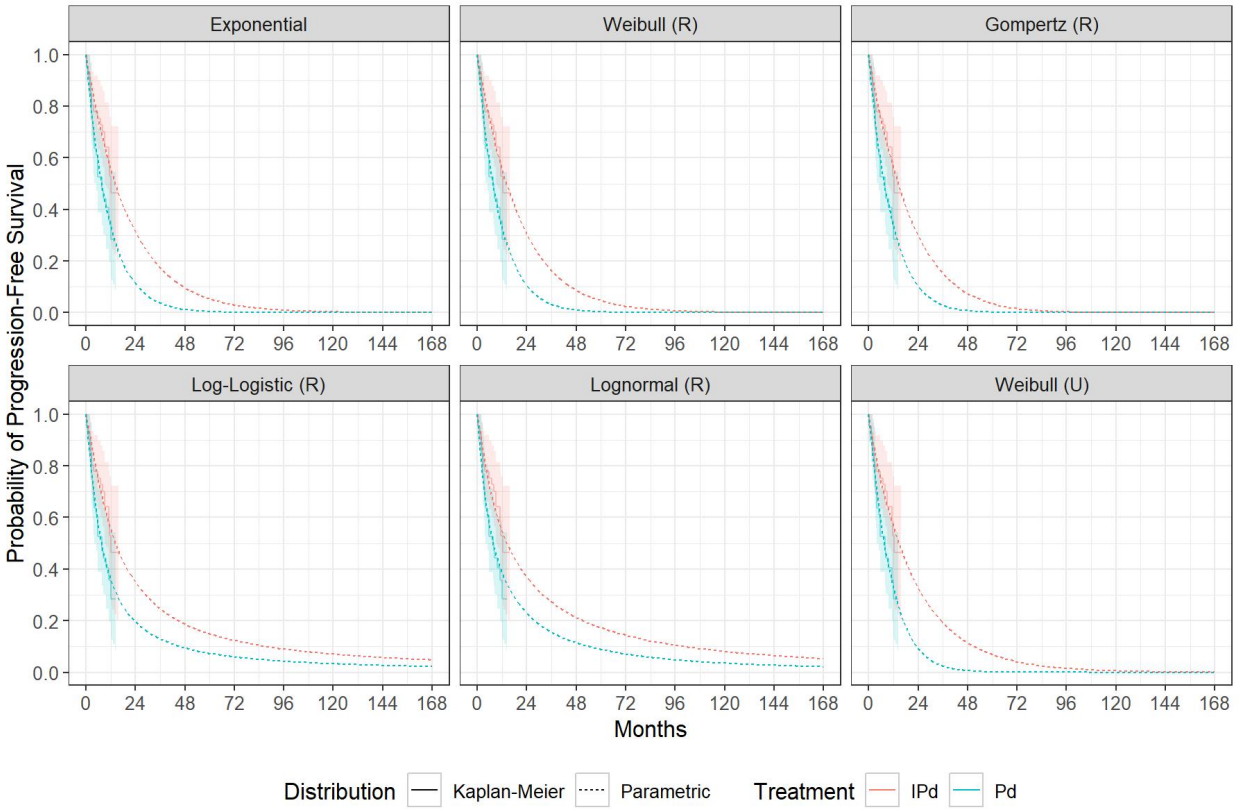
Hazard Rates for Parametric Survival Distributions Fit to PFS for the 3L Population from ICARIA-MM, by Randomized Treatment



Source: Analyses of ICARIA-MM data

Long-term projections of PFS (out to 15 years) for these six distributions are shown in in the next figure. PFS is generally projected to be less than 20% for both IsaPd and Pd at 5 years and less than approximately 10% for both IsaPd and Pd by 120 months.

Long-Term Projections of PFS Based on Parametric Survival Distributions Fit to PFS for the 3L Population in ICARIA-MM, by Randomized Treatment



Source: Analyses of ICARIA-MM data

RSMT for PFS to end of trial follow-up and 15 years are shown in the table below. Projected RMST for PFS after 15 years with Pd ranges from 10.4 months (unrestricted Weibull) to 20.6 months (restricted lognormal). For IsaPd, RMST at 15 years ranges from 15.1 months (unrestricted generalized gamma) to 41.1 months (unrestricted lognormal). The exponential distribution yields a projected RMST at 15 years for IsaPd (20.5 months) that is within the range of estimates from the various distributions considered. The projected difference in RMST for IsaPd versus Pd in PFS through 15 years ranges from 3.6 to 24.2 months. The difference in RMST for IsaPd versus Pd in PFS through 15 years for the exponential distribution is 9.6 months, which is within the range of estimates.

RMST for PFS to End of Trial Follow-up and 15 Years Among the 3L Population of ICARIA-MM, by Randomized Treatment Arm

Distribution	End of Trial Follow-up			15 Years		
	IsaPd	Pd	Difference	IsaPd	Pd	Difference
Kaplan-Meier	10.2	7.7	2.5			
Exponential	10.4	8	2.4	20.5	10.9	9.6
Gen. F (R)	10.4	8	2.4	20.6	11	9.6
Gen. Gamma (R)	10.4	8	2.4	20.5	11	9.5
Gen. Gamma (U)	10.4	8	2.4	15.1	11.5	3.6

Distribution	End of Trial Follow-up			15 Years		
	IsaPd	Pd	Difference	IsaPd	Pd	Difference
Gompertz (R)	10.4	8	2.4	19.1	10.6	8.5
Gompertz (U)	10.4	8	2.4	19.8	10.5	9.3
Log-Logistic (R)	10.4	8.1	2.3	31.3	18.9	12.4
Log-Logistic (U)	10.4	8	2.4	36.7	16.5	20.2
Lognormal (R)	10.2	8.2	2	33.4	20.6	12.8
Lognormal (U)	10.3	8	2.3	41.1	16.9	24.2
RCS Log-Logistic (R)	10.4	8.1	2.3	29.9	18.1	11.8
RCS Log-Logistic (U)	10.4	8	2.4	35.8	15.5	20.3
RCS Lognormal (R)	10.2	8.2	2	26.7	16.5	10.2
RCS Lognormal (U)	10.3	8	2.3	35.2	13.1	22.1
RCS Weibull (R)	10.4	8	2.4	21.3	11.2	10.1
RCS Weibull (U)	10.3	8	2.3	22.7	11	11.7
Weibull (R)	10.4	8	2.4	19.9	10.7	9.2
Weibull (U)	10.4	8.1	2.3	21.8	10.4	11.4
			0			
Minimum	7.7	10.2	2	15.1	10.4	3.6
Maximum	8.2	10.4	2.5	41.1	20.6	24.2

Source: Analyses of ICARIA-MM data

The restricted lognormal distribution was used in the base case based on visual and statistical goodness of fit. Also, this distribution yields projections of the benefit of IsaPd on PFS that within the range of estimates from the various distributions considered. Although no external data are available to validate the long-term projections, this distribution yields projection of PFS for Pd that are close to zero by 10 years, which are not unreasonable given the relatively poor prognosis of these patients. Treatment effect diagnostics suggest that proportional hazards models such as the exponential are not inappropriate. The plot of the cumulative hazard function is suggestive of a diminishing hazard over time consistent with this distribution.

b. Progression-Free Survival On Treatment

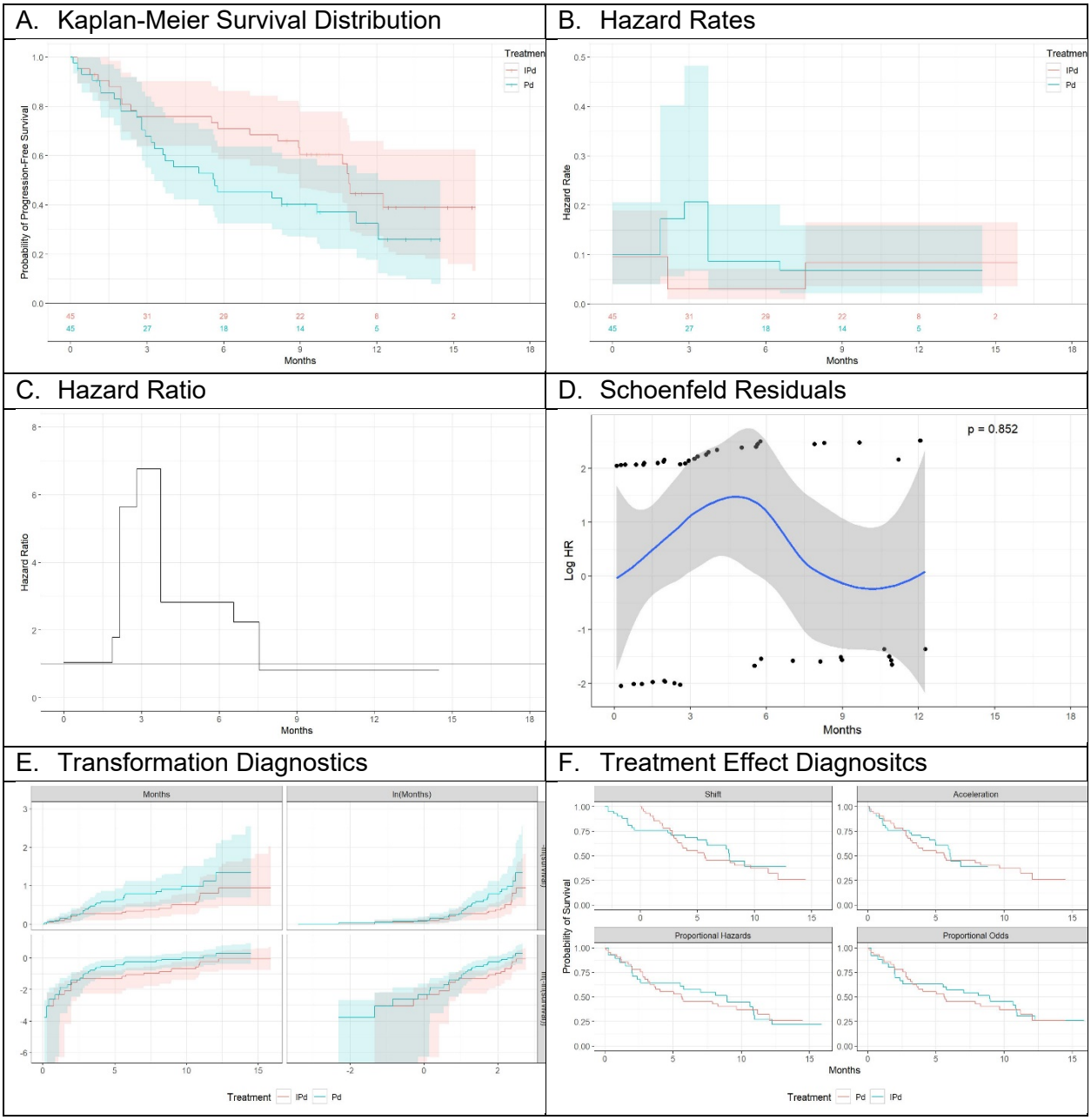
As summarized in the next table, the exponential distribution was used for PFS on treatment for IsaPd and Pd for the analysis of the 3L population based on BIC, visual fit, treatment effect diagnostics, and clinical plausibility. A more detailed discussion of the rationale for the selection of this distribution is provided in the remainder of this section.

Parametric Distribution Used for PFS On Treatment for IsaPd and Pd for 3L Population

Distribution	Exponential
BIC rank	First
Visual inspection	Relatively good visual fit to the observed KM curves
Treatment effect	AFT treatment effect consistent with treatment effect diagnostics
Clinical plausibility	No external data are available to assess clinical plausibility of long-term projections
Comment	Predicted RMST for Pd, IsaPd, and the difference between IsaPd and Pd that are in the middle of the ranges of estimates from the various distributions considered

KM survival distributions, hazard rates, HRs, and Schoenfeld residuals, transformation diagnostics, and treatment effect diagnostics for PFS on treatment by treatment group for 3L patients in the ICARIA-MM trial reported in the figure below. The hazard rates for the IsaPd and Pd groups overlap at about 7.5 months, where rates for IsaPd prior to that time point were lower than the hazards for Pd; rates are higher for IsaPd vs. Pd after 7.5 months. The p-value on the test of linearity of Schoenfeld residuals is not statistically significant suggesting that a PH distribution may not be inappropriate. The slope of the cumulative hazard function for IsaPd is somewhat diminishing (except for an increasing slope at the tail when relatively few patients remain at risk), suggesting a declining hazard over time. The treatment effect diagnostics suggest that an AFT model may be most appropriate, and that models with proportional odds treatment effects may provide a particularly good fit.

PFS on Treatment for the 3L Population of ICARIA-MM, by Randomized Treatment



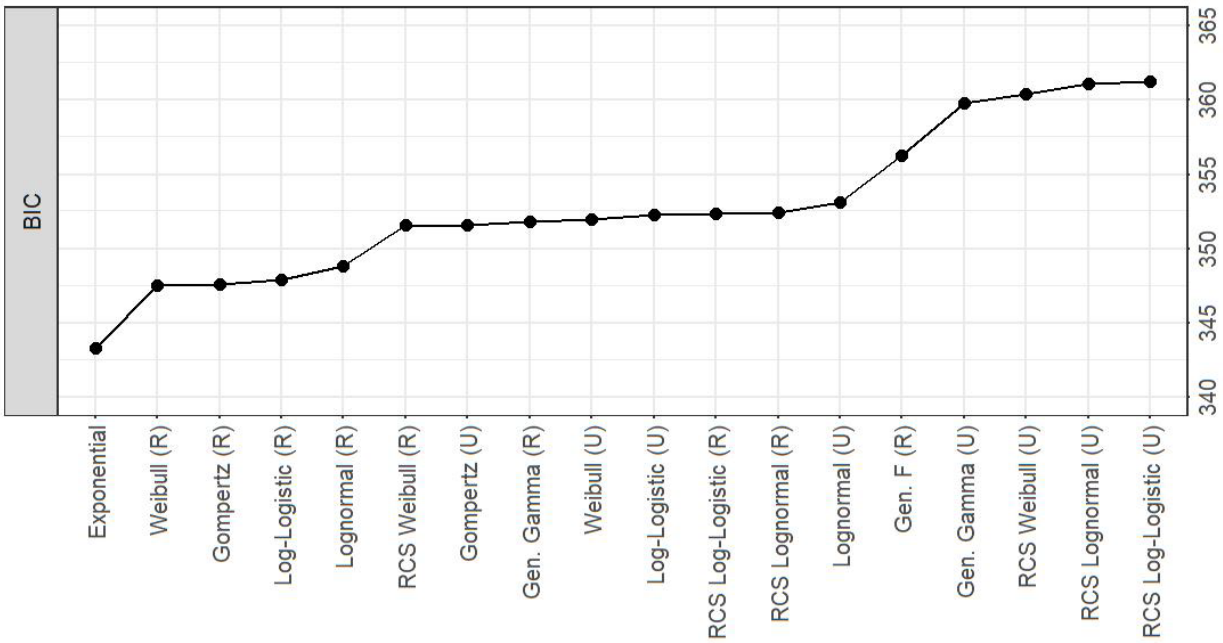
Source: PAI Analyses of ICARIA-MM data

A ranking of parametric distributions fit to PFS on treatment by the fit statistics are shown in the figure below. The top six distributions, according to BIC statistic were as follows:

- Exponential;
- Weibull (R);
- Gompertz (R);
- Log-logistic (R);
- Lognormal (r); and,

- RCS Weibull (R).

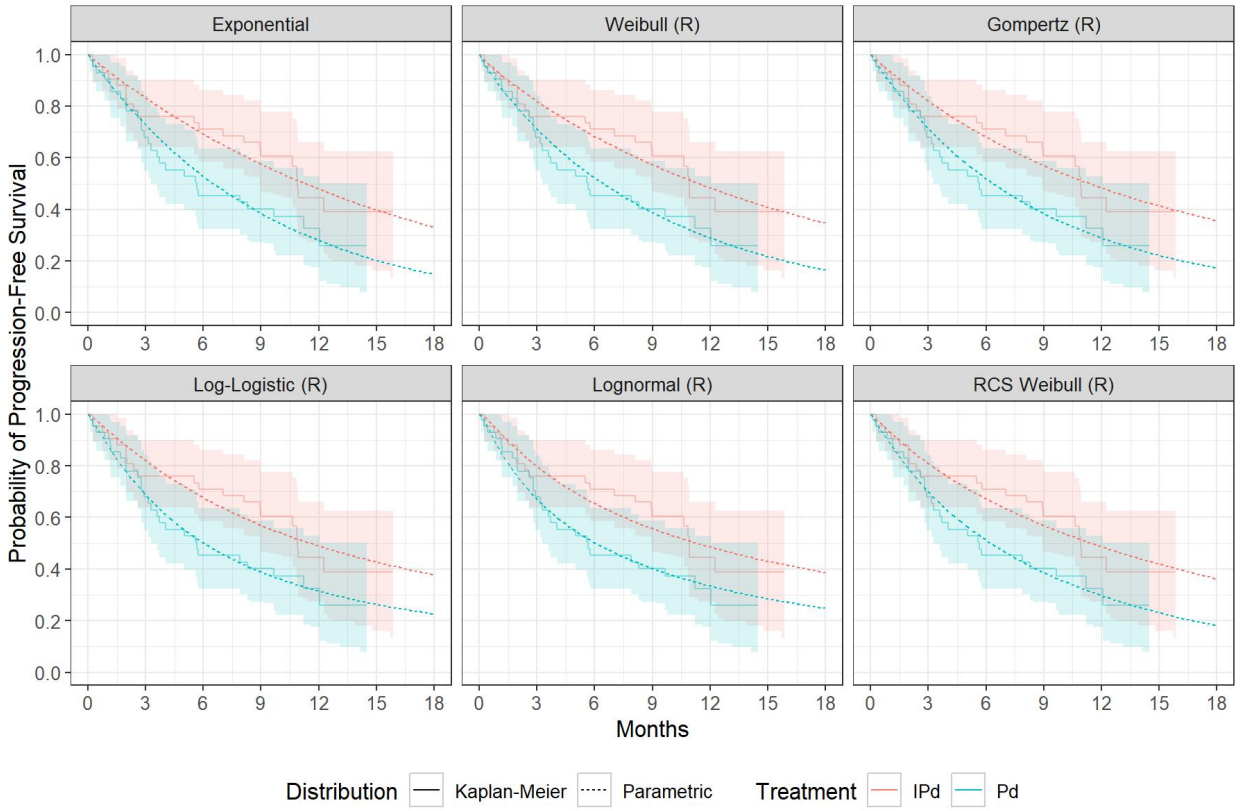
Fit Statistics for Parametric Distributions Fit to PFS On Treatment for the 3L Population of ICARIA-MM



BIC: Bayesian Information Criterion (Smaller is Better)

Parametric survival distributions for PFS on treatment during the trial period for the top six best fitting distributions based on BIC are shown below (distributions are ranked by BIC going left to right, top to bottom). All of the top-fitting distributions based on BIC also have relatively good visual fit to the KM curves.

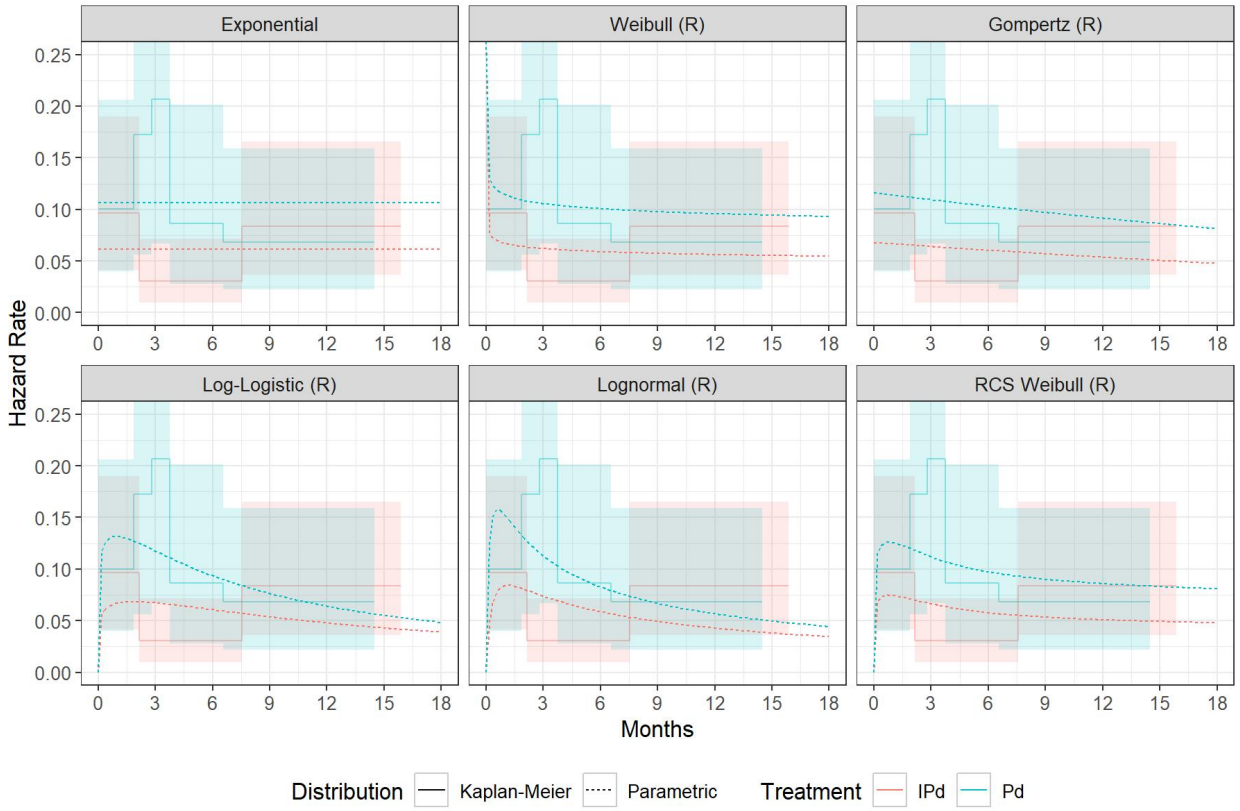
Parametric Survival Distributions Fit to PFS On Treatment for the 3L Population in ICARIA-MM, by Randomized Treatment



Source: PAI Analyses of ICARIA-MM data

Hazard rates during the trial follow-up for PFS on treatment for the top six best fitting parametric survival distributions are compared with non-parametric hazards below. The hazard rates for the exponential distribution remain stable over time while the rates for the restricted Weibull and restricted Gompertz decrease over time. Hazard rates for the restricted log-logistic, restricted lognormal, and restricted RCS Weibull increase initially and then gradually decrease over time. For all of the top six distributions, the hazard for IsaPd is projected to be lower than that for Pd throughout the trial follow-up.

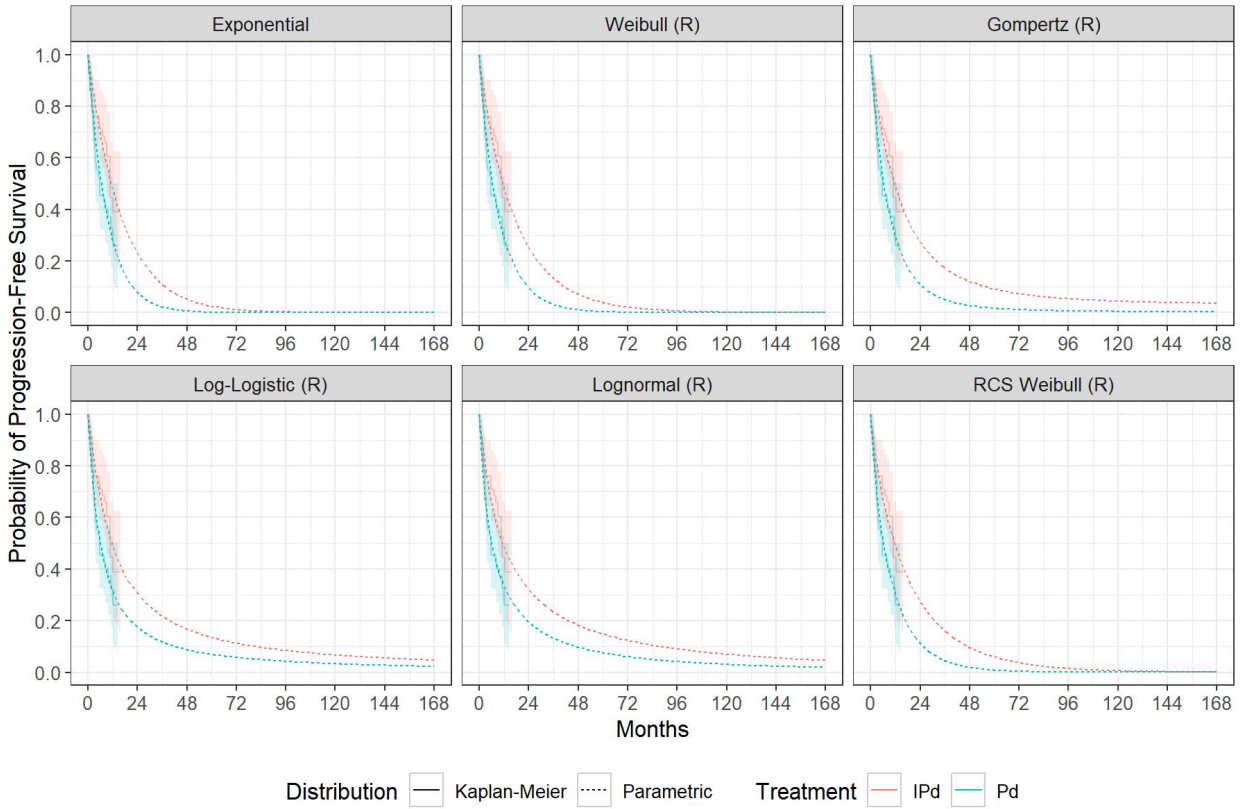
Hazard Rates for Parametric Survival Distributions Fit to PFS On Treatment for the 3L Population from ICARIA-MM, by Randomized Treatment



Source: PAI Analyses of ICARIA-MM data

Long-term projections of PFS on treatment out to 15 years for these six distributions are shown below. All of these distributions yield projections of PFS on treatment that are less than 20% after 5 years and less than 10% after 10 years.

Long-Term Projections of PFS On Treatment Based on Parametric Survival Distributions fit to PFS for the 3L Population in ICARIA-MM, by Randomized Treatment



Source: PAI Analyses of ICARIA-MM data

RSMT for PFS on treatment to end of trial follow-up and 15 years are shown in the table below. Projected RMST for PFS on treatment after 15 years with Pd ranges from 9.4 (exponential) to 20.5 months (unrestricted Gompertz) and for IsaPd ranges from 12.3 (unrestricted generalized gamma) to 32.2 months (restricted generalized F). The difference in RMST for IsaPd versus Pd in PFS through 15 years ranges from -5.8 (unrestricted Gompertz) to 15.7 months (unrestricted lognormal). The restricted exponential yields predicted RMST for IsaPd that is in the range of estimates and for Pd that at the low end of the range of estimates from the various distributions considered.

RMST for PFS On Treatment to End of Trial Follow-up and 15 Years among the 3L Population of ICARIA-MM, by Randomized Treatment Arm

Distribution	End of Trial Follow-up			15 Years		
	IsaPd	Pd	Difference	IsaPd	Pd	Difference
Kaplan-Meier	9.3	7	2.3			
Exponential	9.6	7.4	2.2	16.3	9.4	6.9
Gen. F (R)	9.5	7.3	2.2	20.1	11.1	9
Gen. Gamma (R)	9.5	7.3	2.2	20	11	9
Gen. Gamma (U)	9.6	7.3	2.3	12.3	12	0.3
Gompertz (R)	9.5	7.4	2.1	23.9	11.2	12.7

Distribution	End of Trial Follow-up			15 Years		
	IsaPd	Pd	Difference	IsaPd	Pd	Difference
Gompertz (U)	9.6	7.3	2.3	14.7	20.5	-5.8
Log-Logistic (R)	9.6	7.4	2.2	28.5	17.5	11
Log-Logistic (U)	9.6	7.3	2.3	30.4	16.4	14
Lognormal (R)	9.4	7.4	2	29.5	18	11.5
Lognormal (U)	9.4	7.3	2.1	32.2	16.5	15.7
RCS Log-Logistic (R)	9.6	7.3	2.3	28	17.1	10.9
RCS Log-Logistic (U)	9.6	7.3	2.3	29.7	16.1	13.6
RCS Lognormal (R)	9.4	7.4	2	24.9	15.3	9.6
RCS Lognormal (U)	9.5	7.3	2.2	28.4	13.3	15.1
RCS Weibull (R)	9.5	7.3	2.2	19.3	10.5	8.8
RCS Weibull (U)	9.5	7.3	2.2	17.9	11	6.9
Weibull (R)	9.5	7.4	2.1	17.5	9.9	7.6
Weibull (U)	9.5	7.4	2.1	17.3	9.9	7.4
Min	9.3	7	2	12.3	9.4	-5.8
Max	9.6	7.4	2.3	32.2	20.5	15.7

Source: PAI Analyses of ICARIA-MM data

Based on the analyses above, the restricted lognormal distribution should be used for PFS on treatment based statistical goodness of fit (lowest BIC), relatively good visual fit, AFT treatment effect consistent with treatment effect diagnostics, and predicted difference between IsaPd and Pd in RMST that is in the range of estimates from the various distributions considered.

c. Time to Discontinuation

As summarized in the table that follows the exponential distribution was used for TTD for IsaPd and Pd for the 3L population based on BIC, visual fit, treatment effect diagnostics, and clinical plausibility. A more detailed discussion of the rationale for the selection of this distribution is provided in the remainder of this section.

Parametric Distribution Used for TTD for IsaPd and Pd for 3L Population

Distribution	Exponential
BIC rank	First
Visual fit	Projection yields good visual fit to the observed KM survival curves
Treatment Effect	Test of linearity of Schoenfeld residuals not statistically significant suggesting PH assumption is reasonable
Clinical plausibility	No long-term data to assess clinical plausibility
Comment	RMST at 15 years for IsaPd is at low end of range of estimates and therefore will yield relatively low estimates of costs and favorable ICER for IsaPd

KM survival distributions, hazard rates, HRs, Schoenfeld residuals, transformation diagnostics, and treatment effect diagnostics for TTD by treatment group for 3L patients in the ICARIA-MM trial are reported in the figure that follows. The hazard rates for IsaPd are relatively stable and

mostly lower than the hazards for Pd throughout the follow-up period. Although the HR for IsaPd vs. Pd generally increases over the follow-up of the trial, the test of non-proportionality is not statistically significant, suggesting PH distributions (exponential, Weibull, Gompertz) are not inappropriate. The cumulative hazard plots are approximately linear suggesting relative constant hazards. The treatment effect diagnostics indicate that PH, proportional odds, and AFT models may all be appropriate.

TTD for the 3L Population of ICARIA-MM, by Randomized Treatment

A. Kaplan-Meier Survival Distribution

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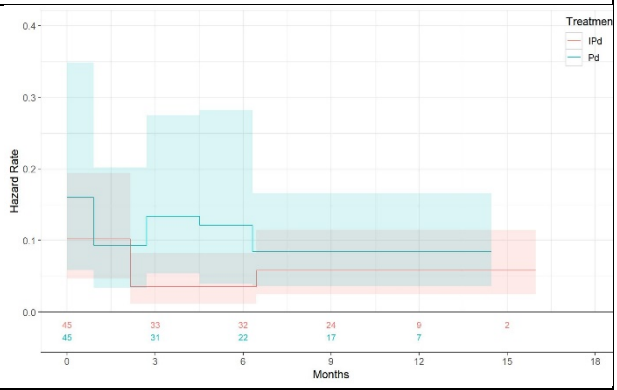
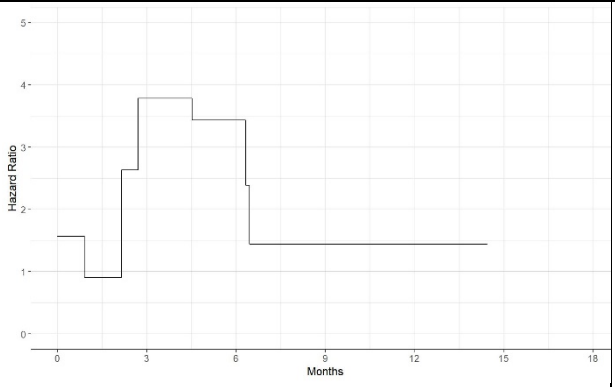
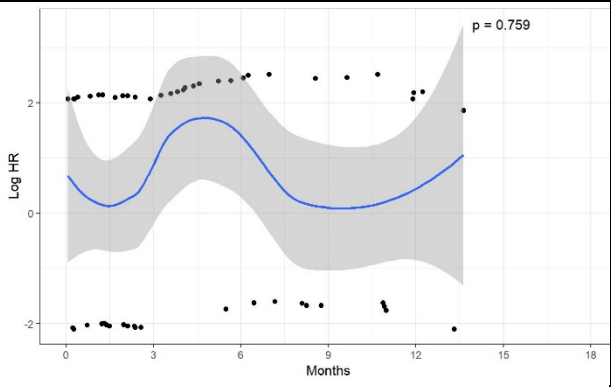
B. Hazard Rates



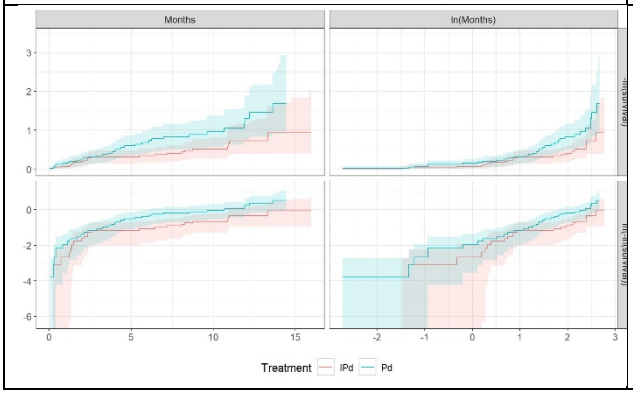
C. Hazard Ratio



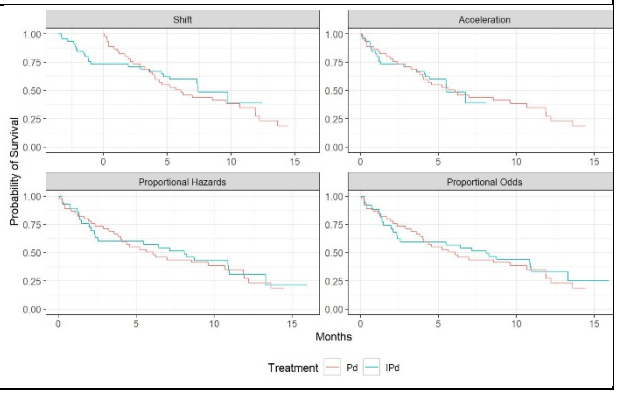
D. Schoenfeld Residuals



E. Transformation Diagnostics



F. Treatment Effect Diagnostics

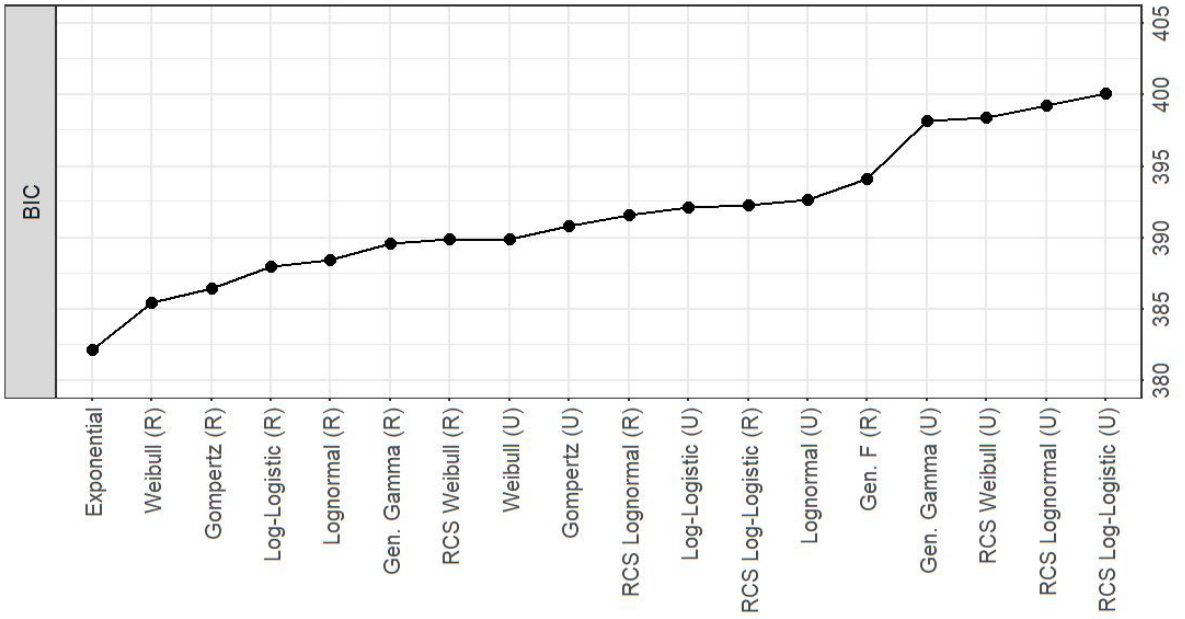


Source: PAI Analyses of ICARIA-MM data

A ranking of parametric distributions fit to TTD by the fit statistics are shown in Figure 20. The top six distributions, according to BIC statistic were as follows:

- Exponential;
- Weibull (R);
- Gompertz (R);
- Log-logistic (R);
- Lognormal (R); and,
- Generalized gamma (R).

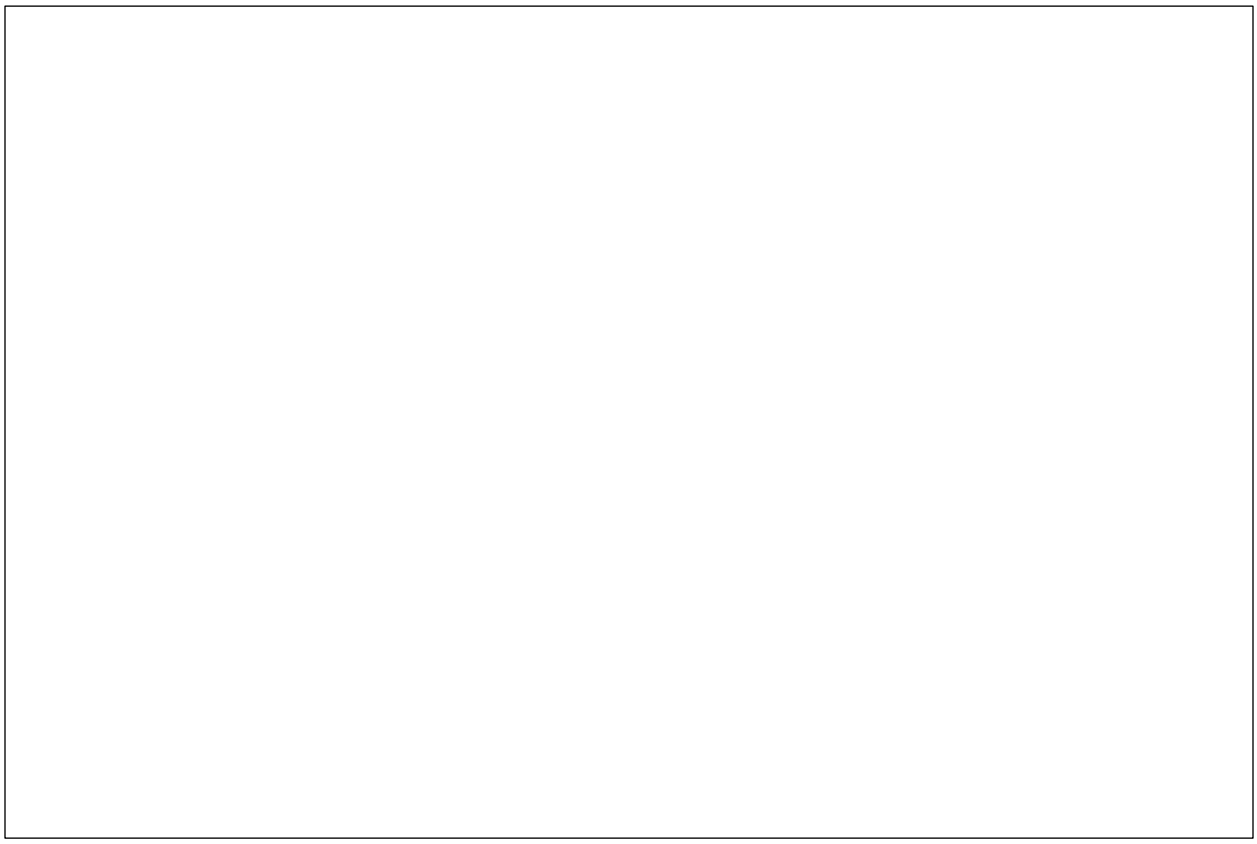
Fit Statistics for Parametric Distributions Fit to TTD for the 3L Population of ICARIA-MM



BIC: Bayesian Information Criterion (Smaller is Better)

Parametric survival distributions for TTD during the trial period for the six best fitting distributions based on BIC are shown in the figure below (distributions are ranked by BIC going left to right, top to bottom). In visual inspection of the survival distributions, the exponential has a good fit to the KM curves.

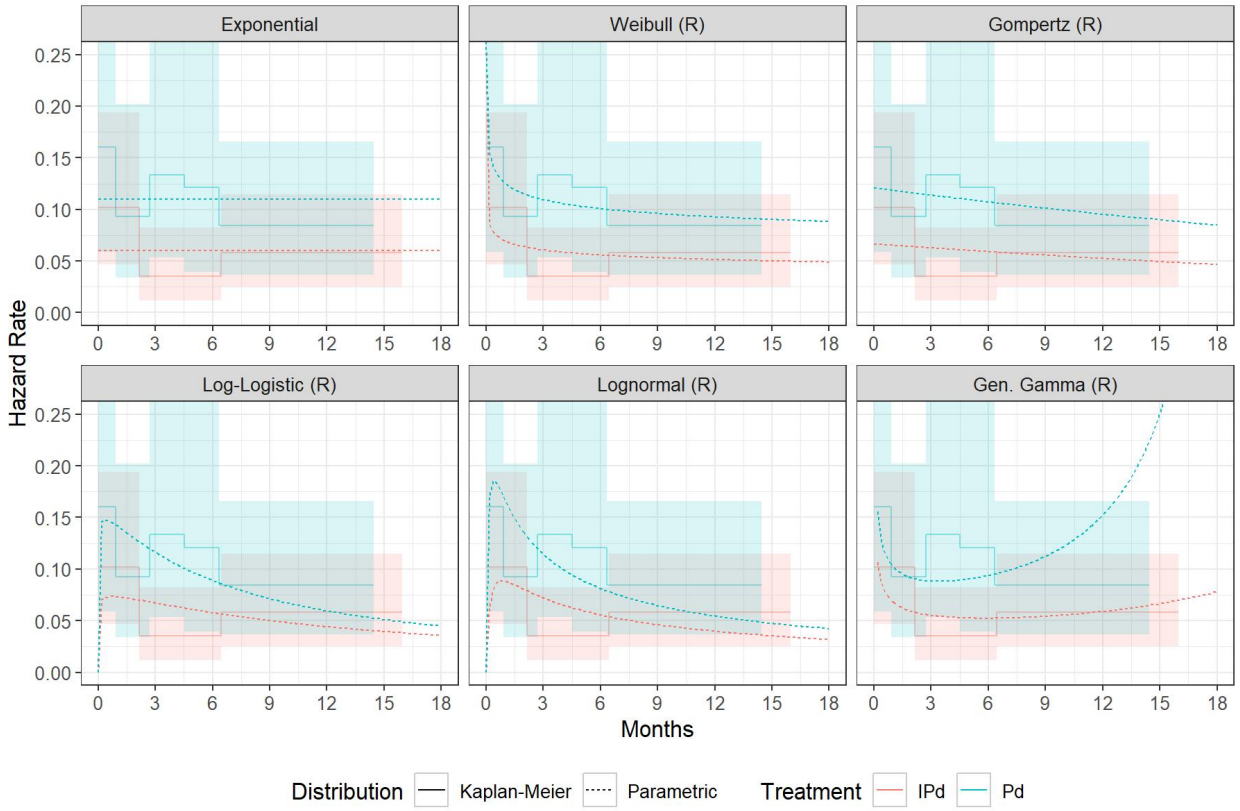
Parametric Survival Distributions Fit to TTD for the 3L Population in ICARIA-MM, by Randomized Treatment



Source: PAI Analyses of ICARIA-MM data

Hazard rates during the trial follow-up for PFS for the top six best fitting parametric survival distributions are compared with non-parametric hazards in the next figure. Some of the top six best fitting distributions yield hazard rates that increase initially and then decrease over time, while others show relatively constant or decreasing hazards over time. The projected hazard rates for Pd based on the restricted generalized gamma curve are increasing at a very high rate, which is not consistent with the observed hazard rates. For all of the top six distributions, the hazard for IsaPd is projected to be lower than that for Pd throughout the trial follow-up.

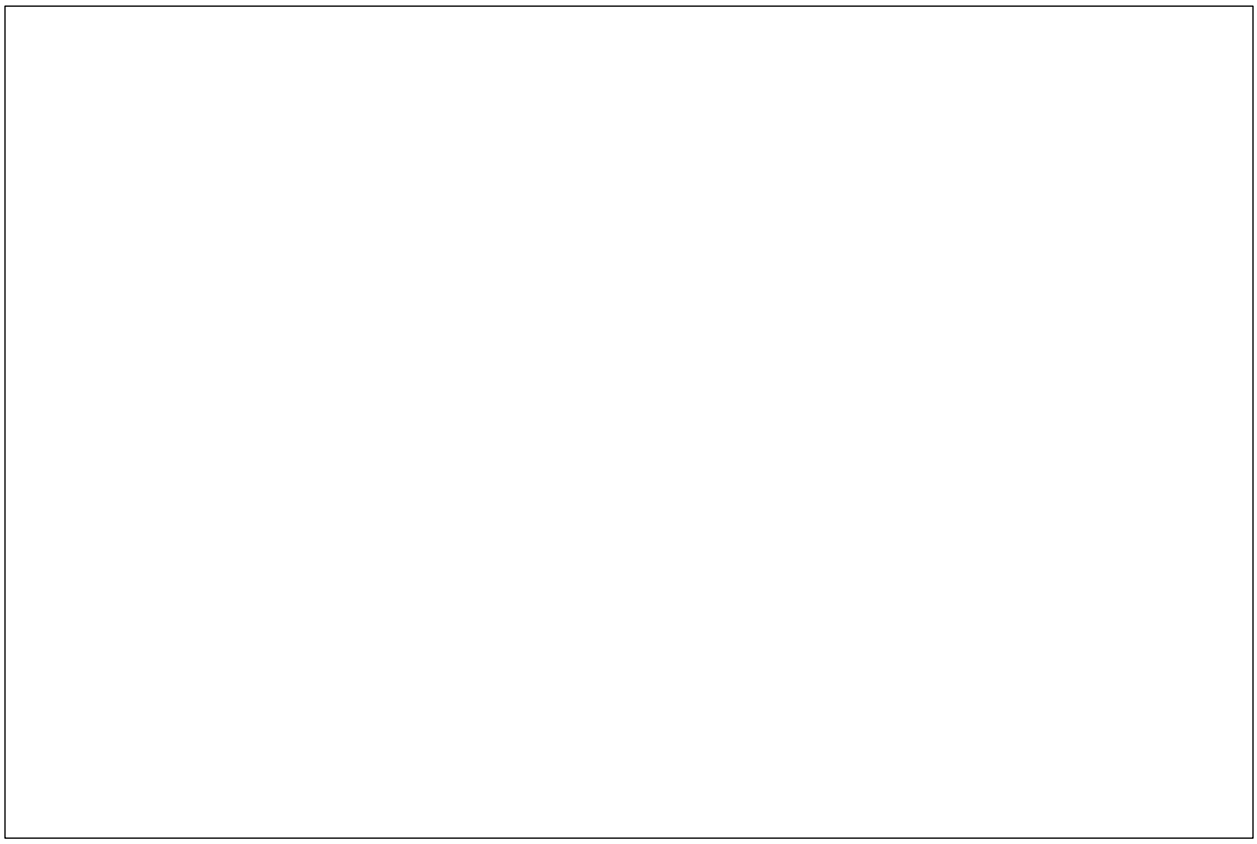
Hazard Rates for Parametric Survival Distributions Fit to TTD for the 3L Population from ICARIA-MM, by Randomized Treatment



Source: PAI Analyses of ICARIA-MM data

Long-term projections of TTD out to 15 years for these six distributions are shown in the figure that follows. All the distributions yield projections of TTD for both IsaPd and Pd of below 10% by 10 years. The exponential distribution shows a relatively steep decline and is below 10% in both arms by 48 months and reaches 0% in both arms by 84 months. As long-term data on TTD for patients receiving IsaPd or Pd are unavailable, it is not feasible to assess the external validity of these projections.

Long-Term Projections of TTD Based on Parametric Survival Distributions fit to TTD for the 3L Population in ICARIA-MM, by Randomized Treatment



Source: PAI Analyses of ICARIA-MM data

RSMT to end of trial follow-up and 15 years for TTD are shown in the table below. Projected RMST for TTD after 15 years with Pd ranges from 7.8 months (unrestricted generalized gamma) to 18.6 months (restricted log-logistic) and for IsaPd ranges from 13.2 months (restricted generalized gamma) to 36.8 months (unrestricted RCS log-logistic). The projected difference in RMST for IsaPd versus Pd in TTD through 15 years ranges from 5.3 months (restricted generalized gamma) to 9.2 months (restricted Gompertz). The RMST for IsaPd based on the exponential distribution is the 17th percentile of the distributions examined. That for Pd is the 22nd percentile.

RMST for TTD to End of Trial Follow-up the 3L Population of ICARIA-MM, by Randomized Treatment Arm

Distribution	End of Trial Follow-up			15 Years		
	IsaPd	Pd	Difference	Pd	IsaPd	Difference
Kaplan-Meier	academic / commercial in confidence information removed					
Exponential						
Gen. F (R)						
Gen. Gamma (R)						
Gen. Gamma (U)						

Gompertz (R)	academic / commercial in confidence information removed
Gompertz (U)	
Log-Logistic (R)	
Log-Logistic (U)	
Lognormal (R)	
Lognormal (U)	
RCS Log-Logistic (R)	
RCS Log-Logistic (U)	
RCS Lognormal (R)	
RCS Lognormal (U)	
RCS Weibull (R)	
RCS Weibull (U)	
Weibull (R)	
Weibull (U)	
Min	
Max	

Source: PAI Analyses of ICARIA-MM data

Lacking external data to validate the long-term projections of TTD, the exponential distribution was selected for the 3L population, as this distribution has the lowest BIC, good visual fit, and the test of linearity of Schoenfeld residuals suggest that the PH assumption (required by exponential distribution) is not violated. It should be noted that RMST at 15 years for IsaPd for the exponential distribution is near the lower end of the range of estimates and therefore will yield a relatively low estimate of the cost of IsaPd and a relatively favorable ICER.

d. Overall Survival

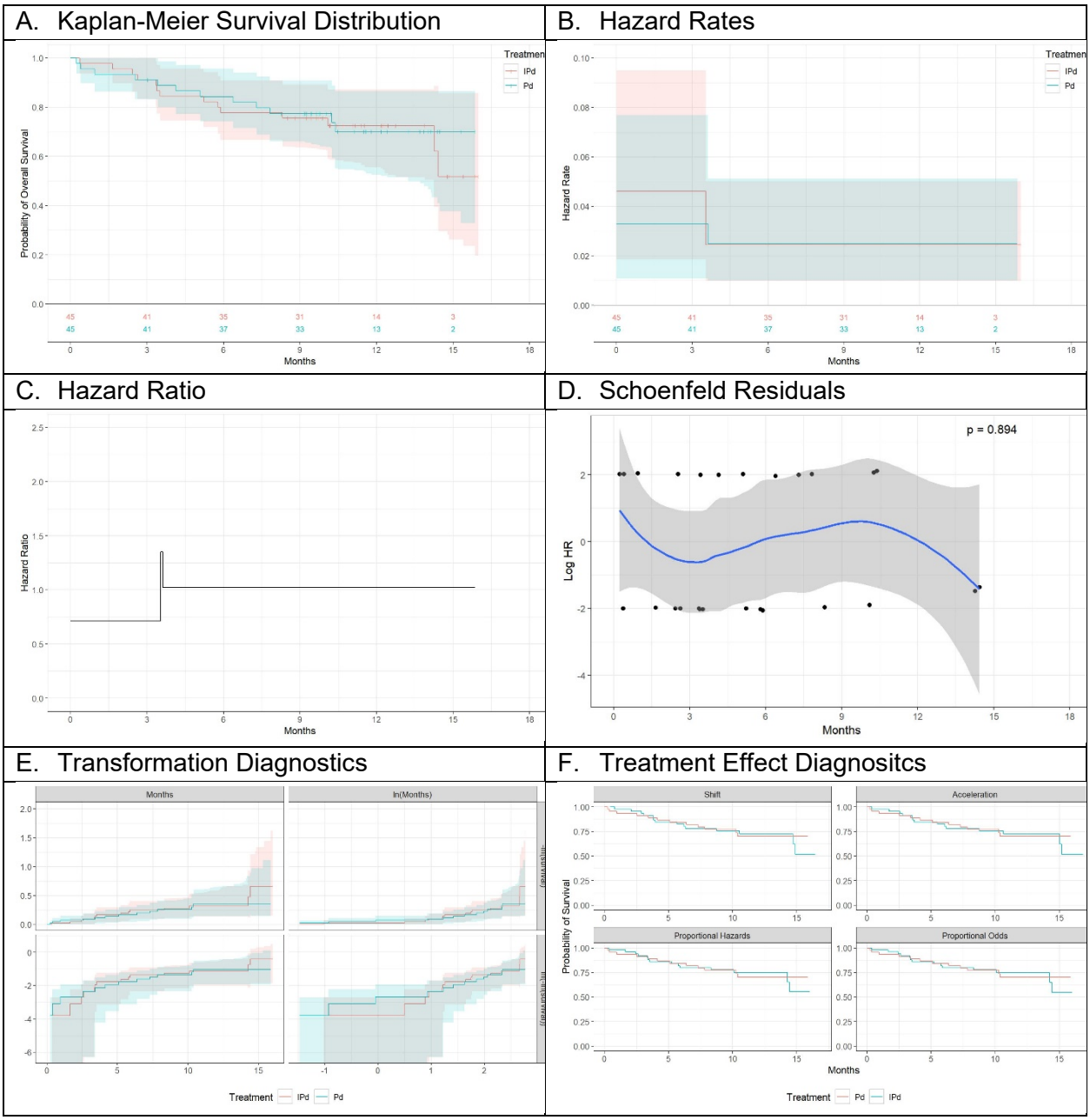
As summarized in the next table, the exponential distribution was used for OS for IsaPd and Pd in analysis of the 3L population based on BIC, visual fit, treatment effect diagnostics, and clinical plausibility. A more detailed discussion of the rationale for the selection of this distribution is provided in the remainder of this section.

Parametric Distribution Used for OS for 3L Population

Distribution	Exponential
BIC rank	First
Visual inspection	Acceptable, though possibly underestimate OS for IsaPd at the tail of the distribution.
Treatment effect	PH treatment effect consistent with treatment effect diagnostics and test of linearity of Schoenfeld residuals
Clinical plausibility	No long-term data to assess clinical plausibility
Comment	Projected RMST at 15 years for Pd, IsaPd, and the difference between IsaPd and Pd were approximately in the middle of the range of estimates generated by all the distributions considered

KM survival distributions, hazard rates, HRs, and Schoenfeld residuals, transformation diagnostics, and treatment effect diagnostics for OS by treatment group for 3L patients in the ICARIA-MM trial are reported in the next figure. The hazard rates for the IsaPd and Pd group are relatively stable and largely overlapping throughout the follow-up period. The test of the linearity of the Schoenfeld residuals is not statistically significant, suggesting that a PH distribution may not be inappropriate. The cumulative hazard function (log of survival by time) has a relatively constant slope for both arms (with the exception of the tail of the distribution Pd where the numbers at risk are small), suggesting that a PH distribution may not be inappropriate. The treatment effect diagnostics indicate that PH, proportional odds, and AFT models may all be appropriate.

Overall Survival for the 3L Population of ICARIA-MM, by Randomized Treatment



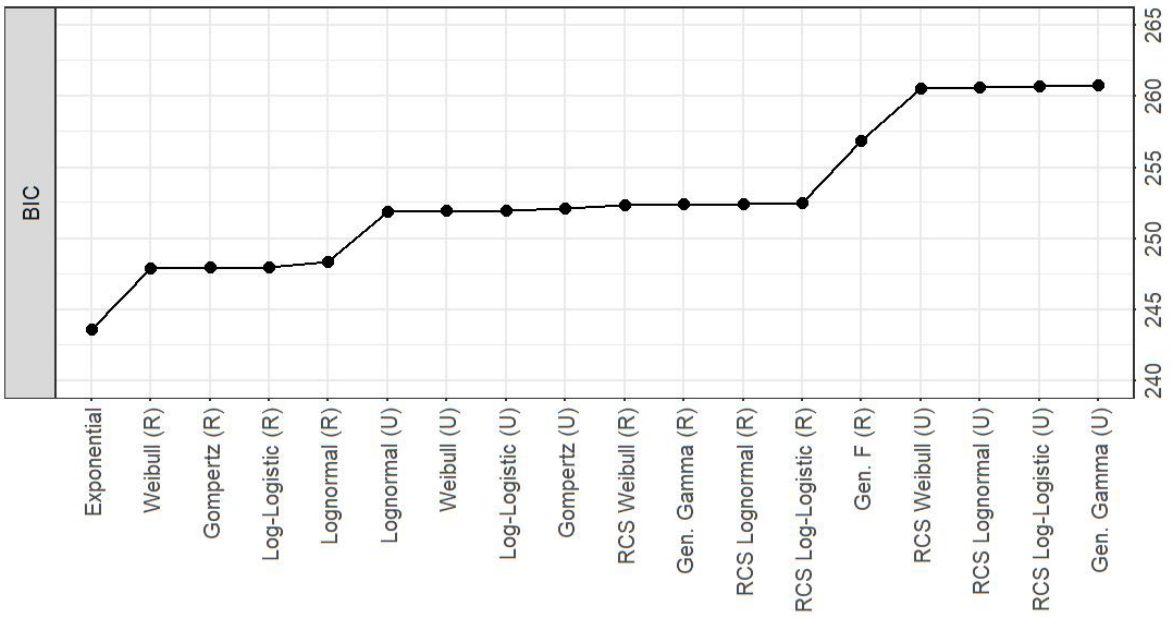
Source: PAI Analyses of ICARIA-MM data

A ranking of parametric distributions fit to OS by the fit statistics are shown in the figure below. The top six distributions, according to BIC statistic were as follows:

- Exponential
- Weibull (R);
- Gompertz (R);
- Log-logistic (R);
- Lognormal (R); and,

- Lognormal (U).

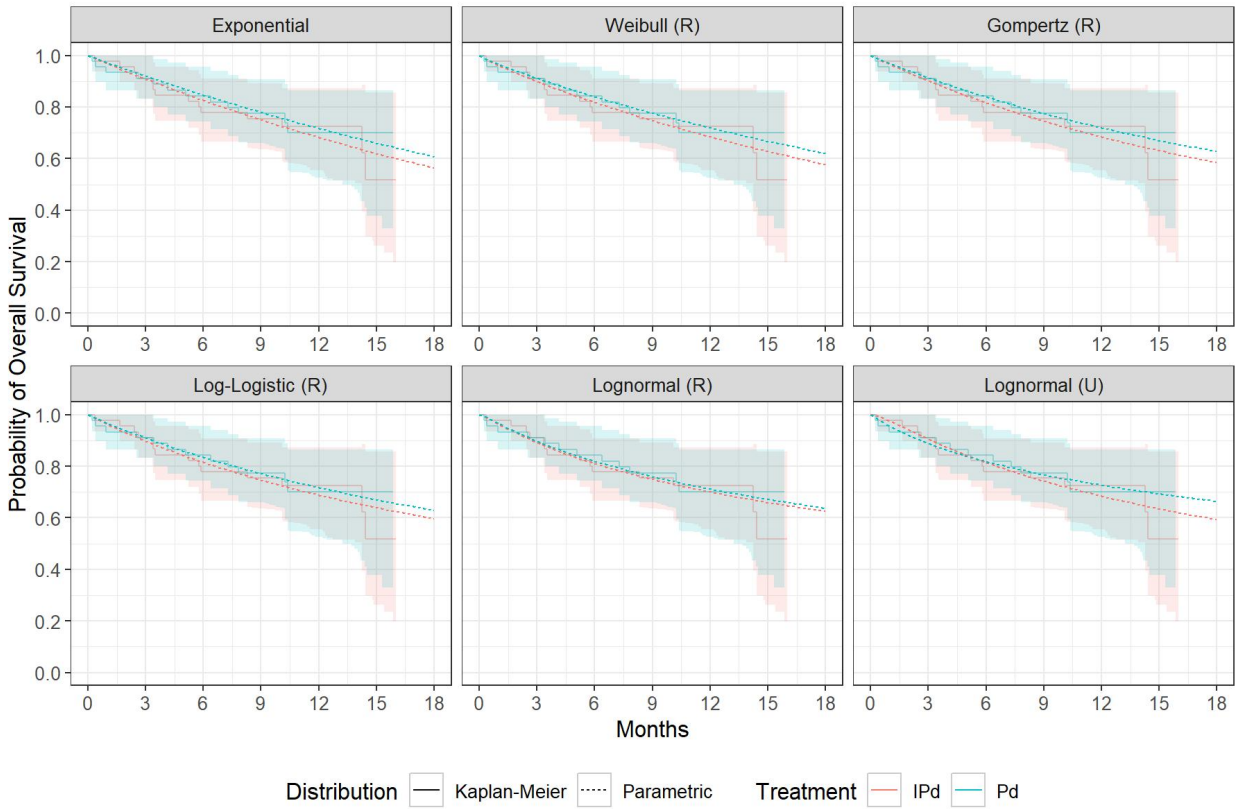
Figure 2. Fit Statistics for Parametric Distributions Fit to OS for the 3L Population of ICARIA-MM



BIC: Bayesian Information Criterion (Smaller is Better)

Parametric survival distributions for OS during the trial period for the six best fitting distributions based on BIC are shown in the figure below (distributions are ranked by BIC going left to right, top to bottom). The top six best fitting distributions all tend to have good visual fit to the KM curves for both IsaPd and the Pd arm.

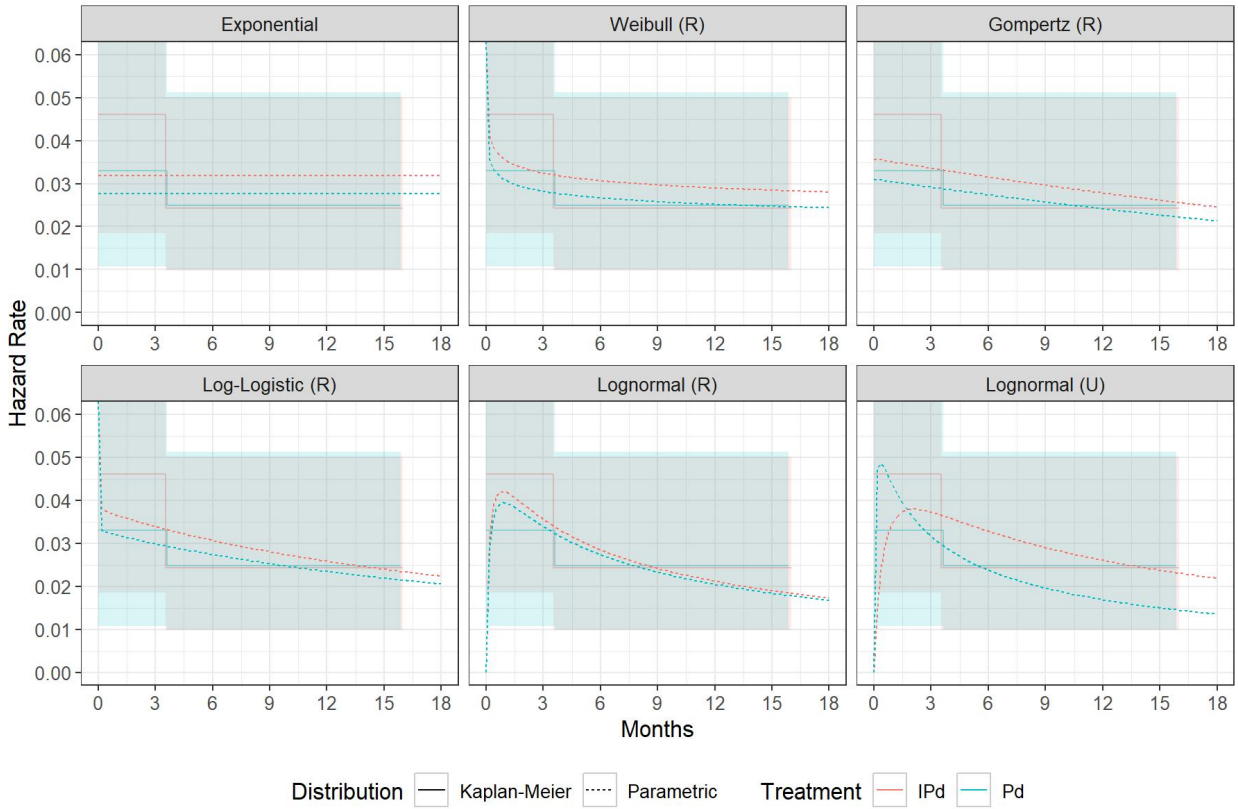
Parametric Survival Distributions Fit to OS for the 3L Population in ICARIA-MM, by Randomized Treatment



Source: PAI Analyses of ICARIA-MM data

Hazard rates during the trial follow-up for the top six best fitting parametric survival distributions based on BIC for OS are compared with non-parametric hazards in the figure below. The exponential has constant hazards while the restricted Weibull, restricted Gompertz, and restricted log-logistic have decreasing hazards. The restricted and unrestricted lognormal distributions have hazards that initially increase and then gradually decreasing for both arms. For most of the curves, the hazard rates for IsaPd are consistently lower than for Pd; however, in the unrestricted lognormal, the curves cross at about 2 months and the rates for IsaPd are higher than those for Pd for the remainder of the observation period.

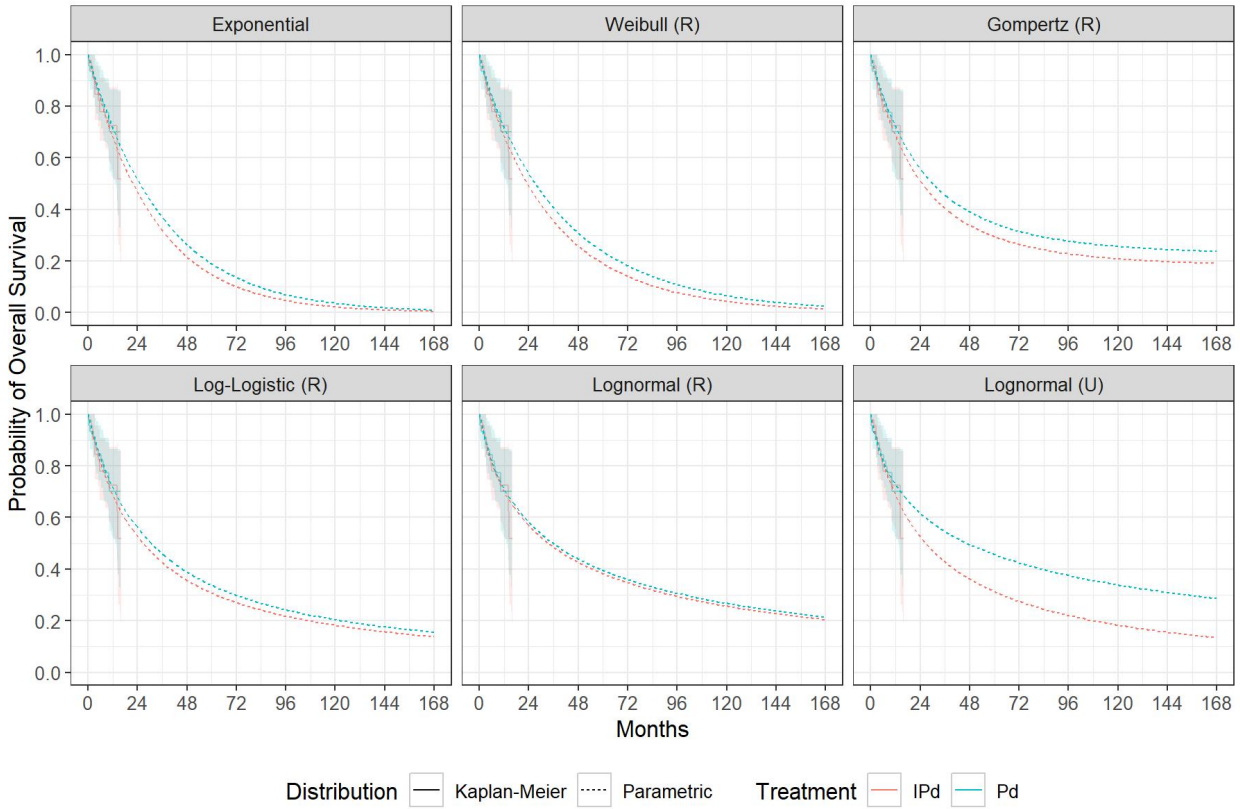
Hazard Rates for Parametric Survival Distributions Fit to OS for the 3L Population from ICARIA-MM, by Randomized Treatment



Source: PAI Analyses of ICARIA-MM data

Long-term projections of OS (out to 15 years) for these six distributions are shown in the next figure. The exponential distribution, selected for the 3L population, and restricted Weibull show a separation between the IsaPd and Pd arms, with 0% of the patients in the IsaPd and Pd arms remaining alive at about 14 years (168 months). The restricted Gompertz, restricted log-logistic, restricted lognormal, and unrestricted lognormal all predict over 10% of patients in both the IsaPd and Pd arms remaining alive at 14 years (168 months).

Long-Term Projections of OS Based on Parametric Survival Distributions Fit to OS for the 3L Population in ICARIA-MM, by Randomized Treatment



Source: Analyses of ICARIA-MM data

RSMT for OS to end of trial follow-up and 15 years are shown in the table below. Projected RMST for OS after 15 years with Pd ranges from 35.8 months (exponential) to 95.1 months (unrestricted Gompertz) and for IsaPd ranges from 26.9 months (unrestricted Gompertz) to 63.6 months (restricted lognormal). The difference in projected RMST for OS after 15 years with IsaPd versus Pd ranges from -68.2 months (unrestricted Gompertz) to -1.9 months (unrestricted lognormal). The exponential distribution yields projections of RMST for OS for Pd (35.8 months) and IsaPd (31.2 months) that are within the ranges if a;; the distributions. The difference in RMST for OS for IsaPd vs. Pd (-4.6 months) is upper end of the range of values (78th percentile) for the distributions considered.

RMST for OS to End of Trial Follow-up and 15 Years among the 3L Population of ICARIA-MM, by Randomized Treatment Arm

	End of Trial Follow-up			15 Years		
Distribution	**IsaPd**	**Pd**	**Difference**	**IsaPd**	**Pd**	**Difference**
Kaplan-Meier	12.2	12.6	-0.4			12.2
Exponential	12.5	12.8	-0.3	31.2	35.8	12.5
Gen. F (R)	12.4	12.8	-0.4	41.7	46.8	12.4
Gen. Gamma (R)	12.4	12.8	-0.4	41.6	46.7	-5.1
Gen. Gamma (U)	12.5	12.7	-0.2	44.9	61.1	-16.2

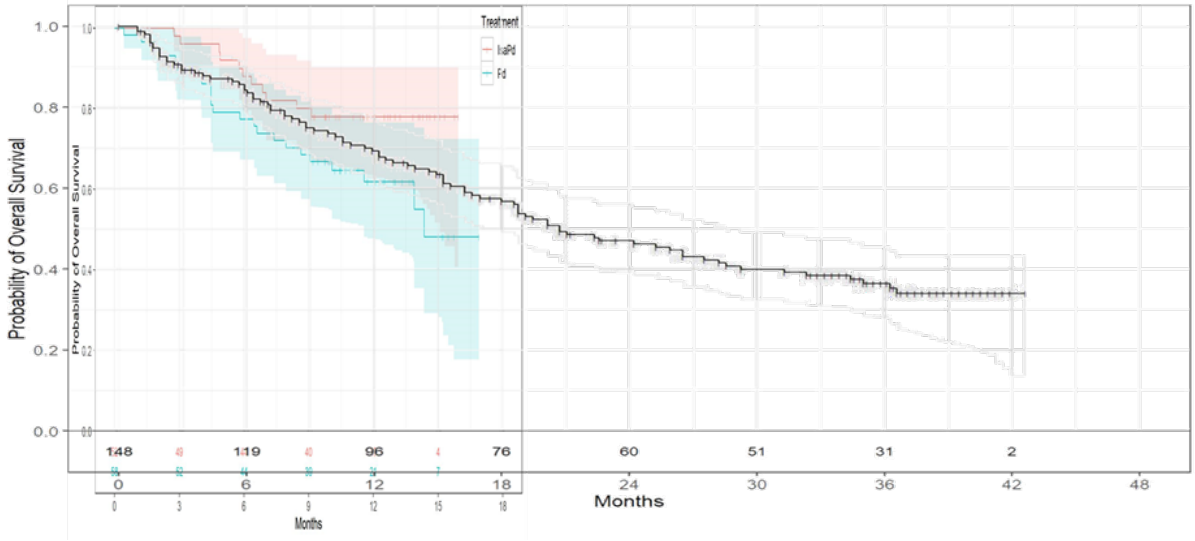
Distribution	End of Trial Follow-up			15 Years		
	IsaPd	Pd	Difference	IsaPd	Pd	Difference
Gompertz (R)	12.4	12.8	-0.4	54.5	62.4	-7.9
Gompertz (U)	12.5	12.8	-0.3	26.9	95.1	-68.2
Log-Logistic (R)	12.4	12.8	-0.4	53	57.3	-4.3
Log-Logistic (U)	12.5	12.7	-0.2	46.1	65.3	-19.2
Lognormal (R)	12.5	12.6	-0.1	63.6	65.5	-1.9
Lognormal (U)	12.4	12.7	-0.3	53.2	75.2	-22
RCS Log-Logistic (R)	12.4	12.8	-0.4	53.2	57.5	-4.3
RCS Log-Logistic (U)	12.5	12.8	-0.3	52.6	62.3	-9.7
RCS Lognormal (R)	12.5	12.7	-0.2	55.9	58.1	-2.2
RCS Lognormal (U)	12.4	12.7	-0.3	51.4	66.1	-14.7
RCS Weibull (R)	12.4	12.8	-0.4	38.2	44	-5.8
RCS Weibull (U)	12.4	12.8	-0.4	38.2	48.9	-10.7
Weibull (R)	12.4	12.8	-0.4	35.3	40.7	-5.4
Weibull (U)	12.5	12.7	-0.2	29.6	49.3	-19.7
Min	12.2	12.6	-0.4	26.9	35.8	-68.2
Max	12.5	12.8	-0.1	63.6	95.1	-1.9

Source: Analyses of ICARIA-MM data

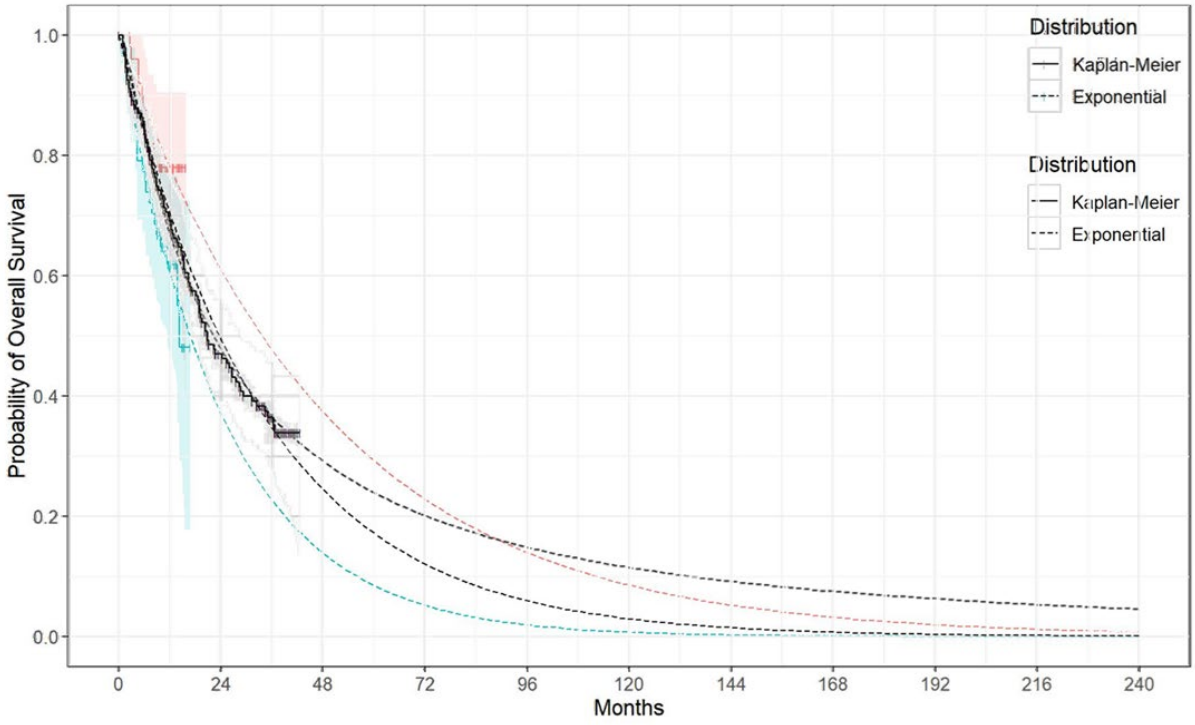
Based on the analyses above, the exponential distribution was used for the 3L population for OS based statistical goodness of fit (lowest BIC), acceptable visual fit, PH treatment effect consistent with treatment effect diagnostics and test of linearity of Schoenfeld residuals. The difference in RMST for OS for IsaPd versus Pd for the exponential distribution is in the upper end of the range of values for the distributions considered, and therefore may be relatively optimistic in terms of the projected benefits of IsaPd versus Pd.

Appendix 8: Long term daratumumab monotherapy evidence

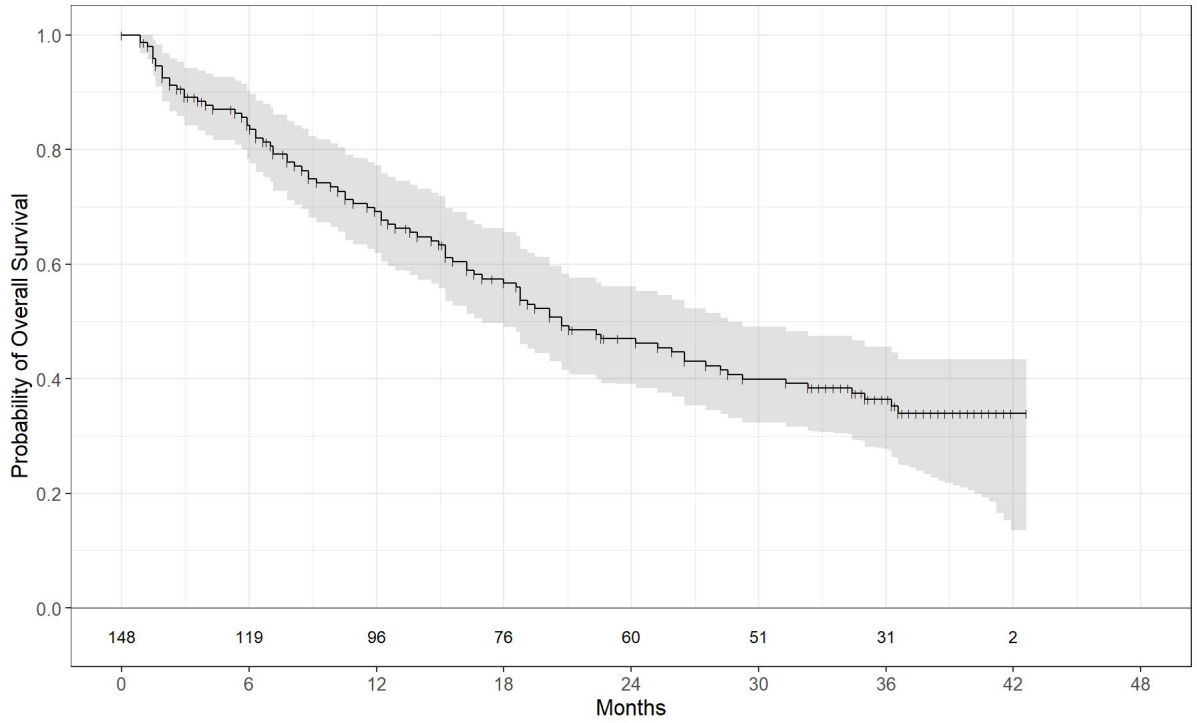
Overlaid the KM curves for OS for IsaPd and Pd vs. the long-term Dara OS data



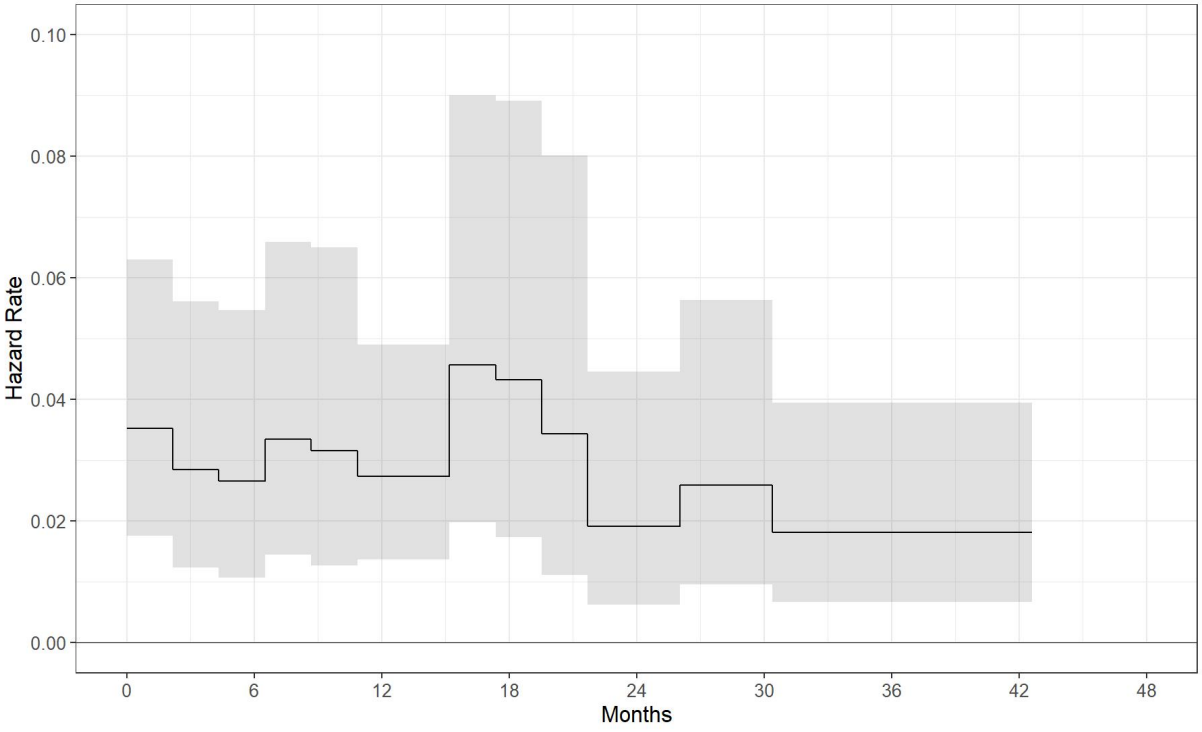
Exponential and lognormal distributions for dara (the black lines, lognormal is higher) with the exponential for IsaPd and Pd.



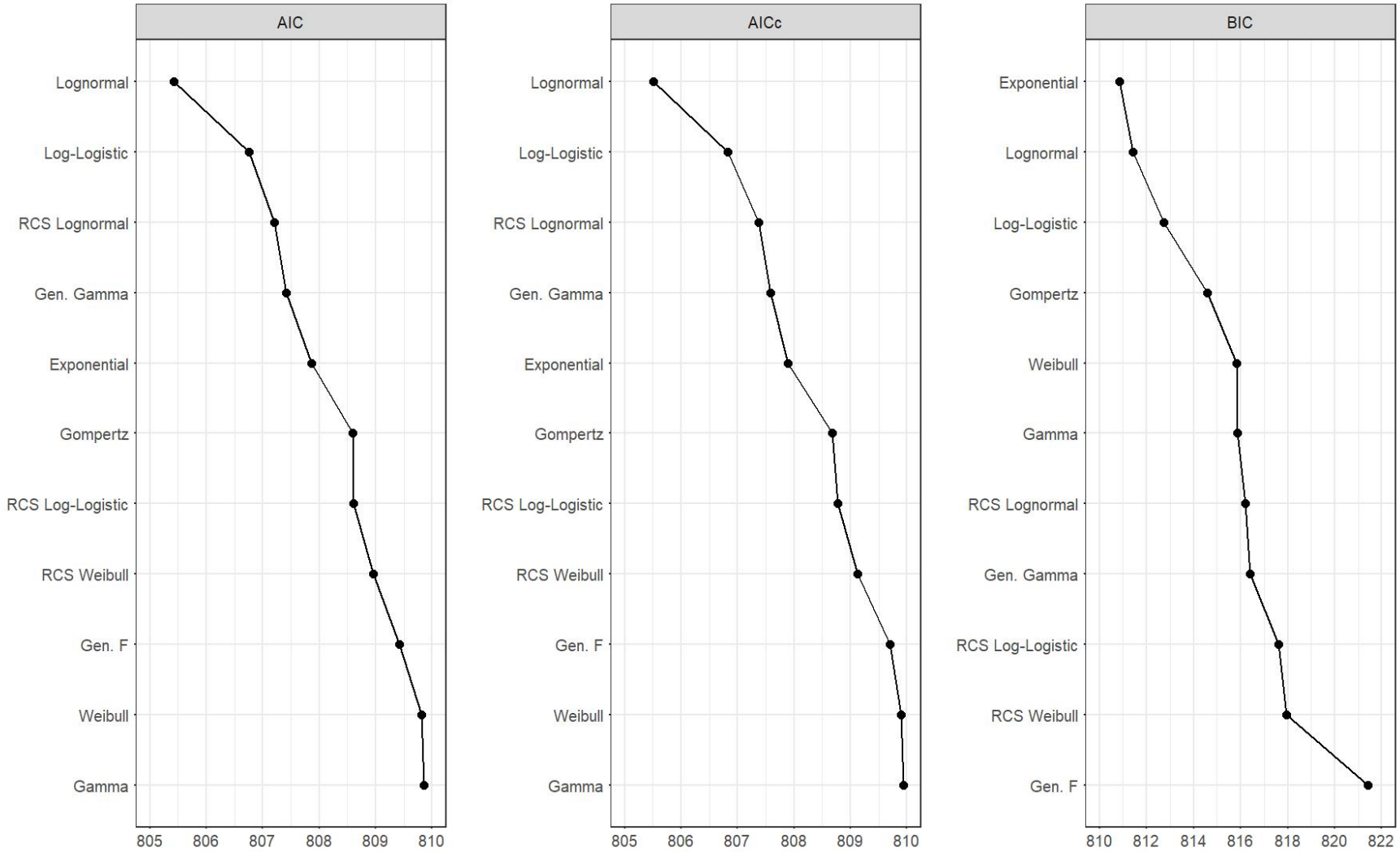
Kaplan-Meier, OS



Hazard Rates, OS



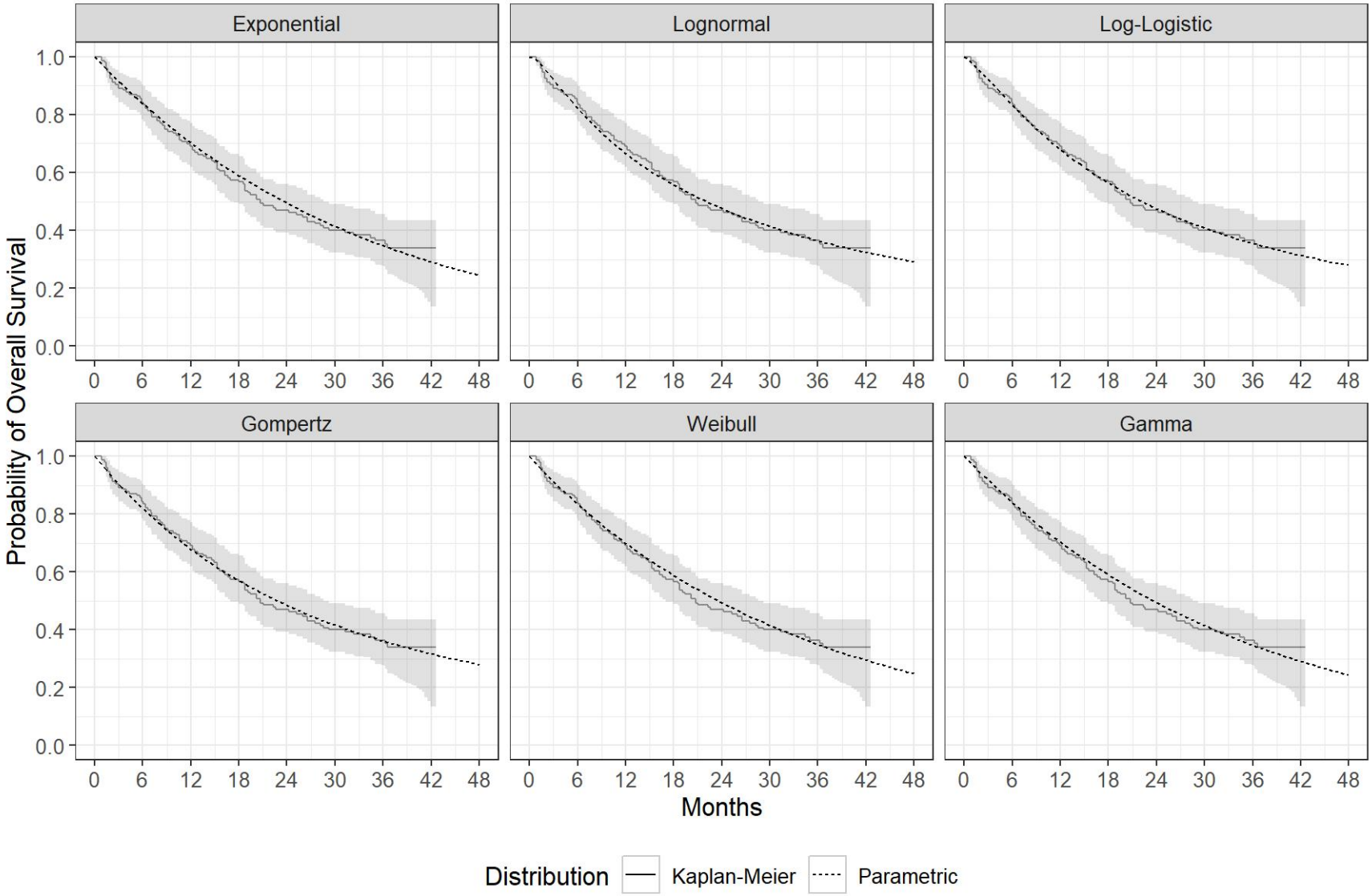
Fit Statistics, OS

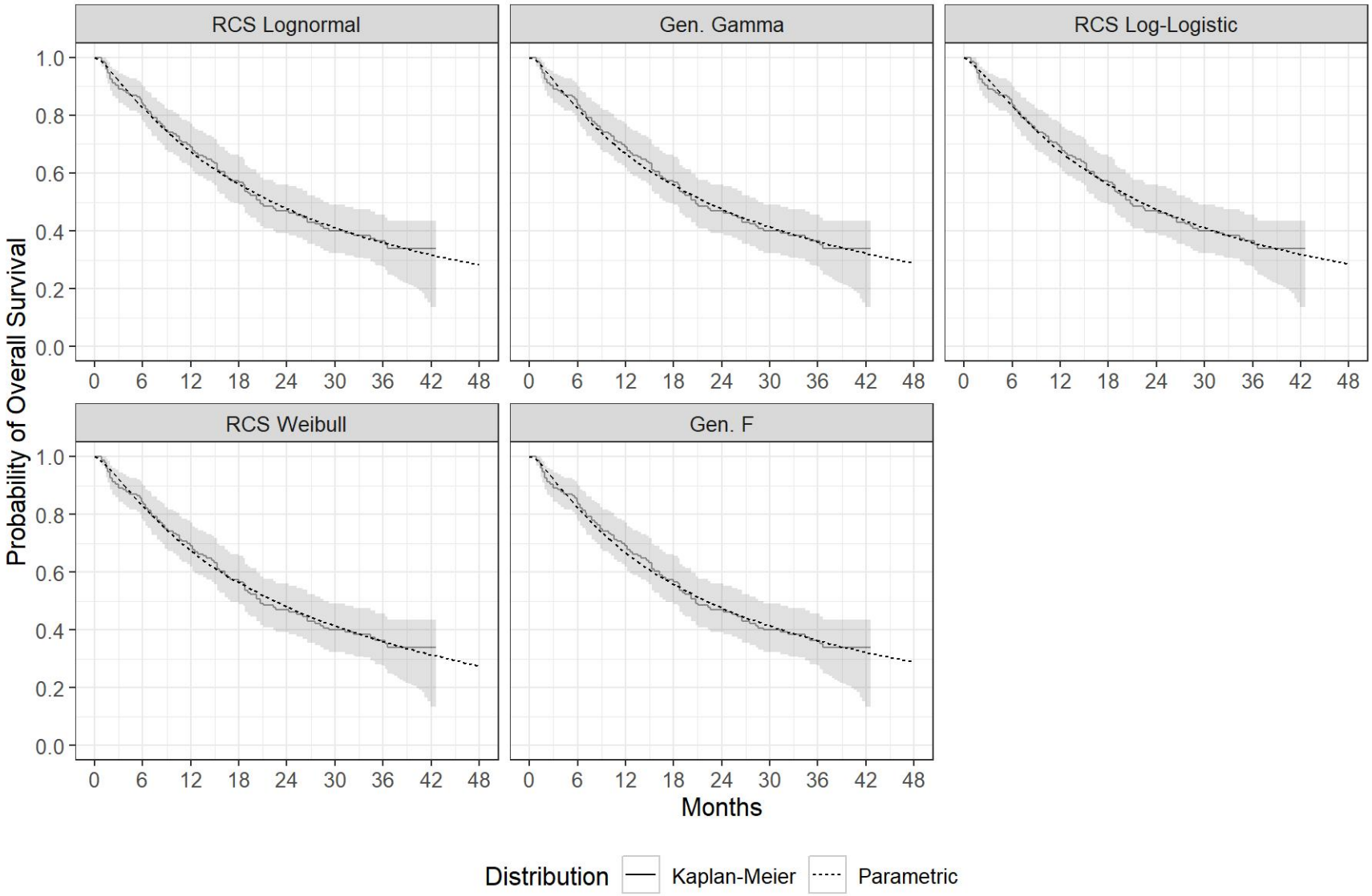


Fit Statistics, OS

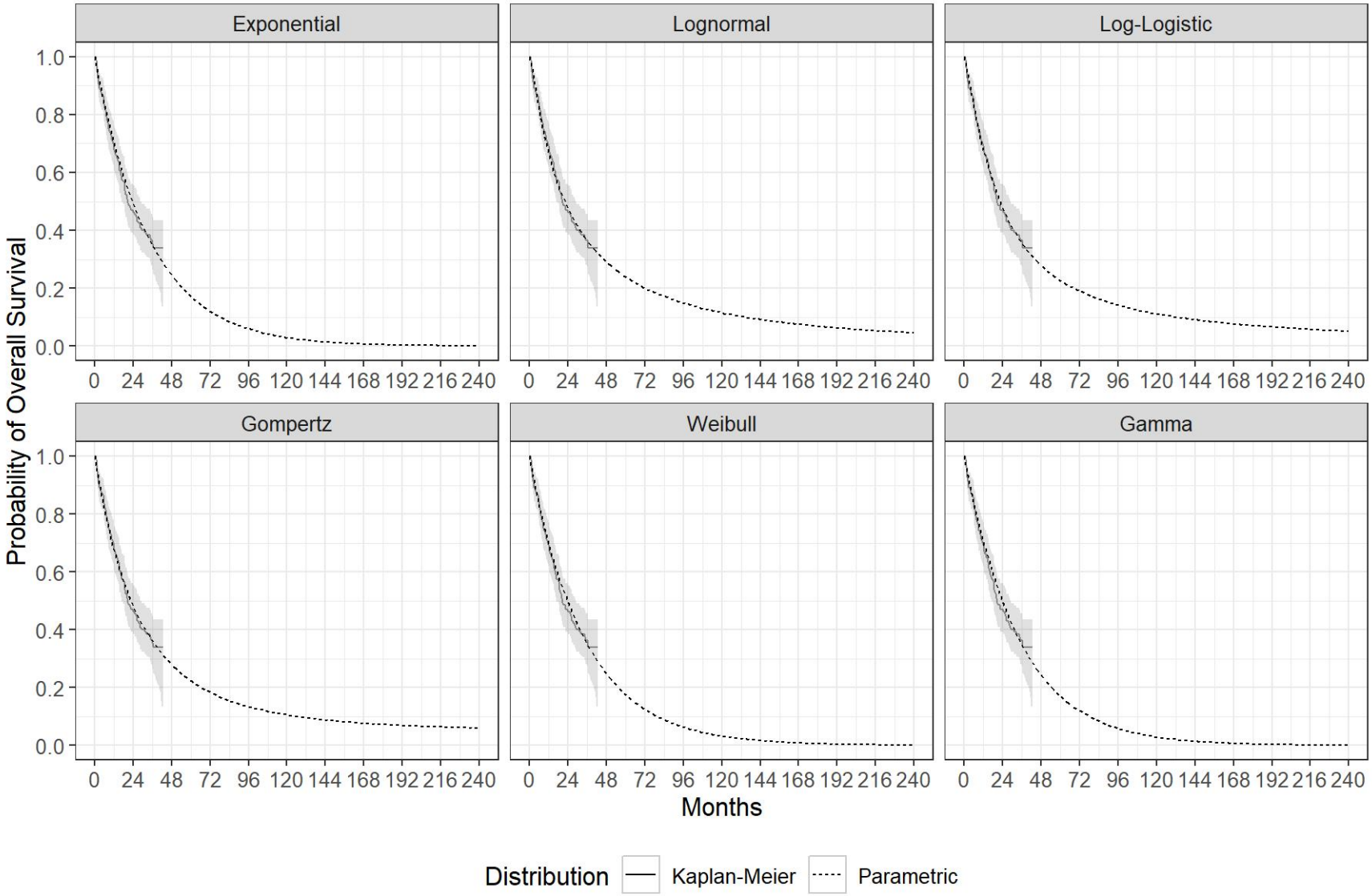
Distribution	Converged	DF	-2LL	AIC	AICc	BIC
Exponential	TRUE	1	805.9	807.9	807.9	810.9
Lognormal	TRUE	2	801.4	805.4	805.5	811.4
Log-Logistic	TRUE	2	802.7	806.7	806.8	812.7
Gompertz	TRUE	2	804.6	808.6	808.7	814.6
Weibull	TRUE	2	805.8	809.8	809.9	815.8
Gamma	TRUE	2	805.9	809.9	809.9	815.9
RCS Lognormal	TRUE	3	801.2	807.2	807.4	816.2
Gen. Gamma	TRUE	3	801.4	807.4	807.6	816.4
RCS Log-Logistic	TRUE	3	802.6	808.6	808.8	817.6
RCS Weibull	TRUE	3	803.0	809.0	809.1	817.9
Gen. F	TRUE	4	801.4	809.4	809.7	821.4

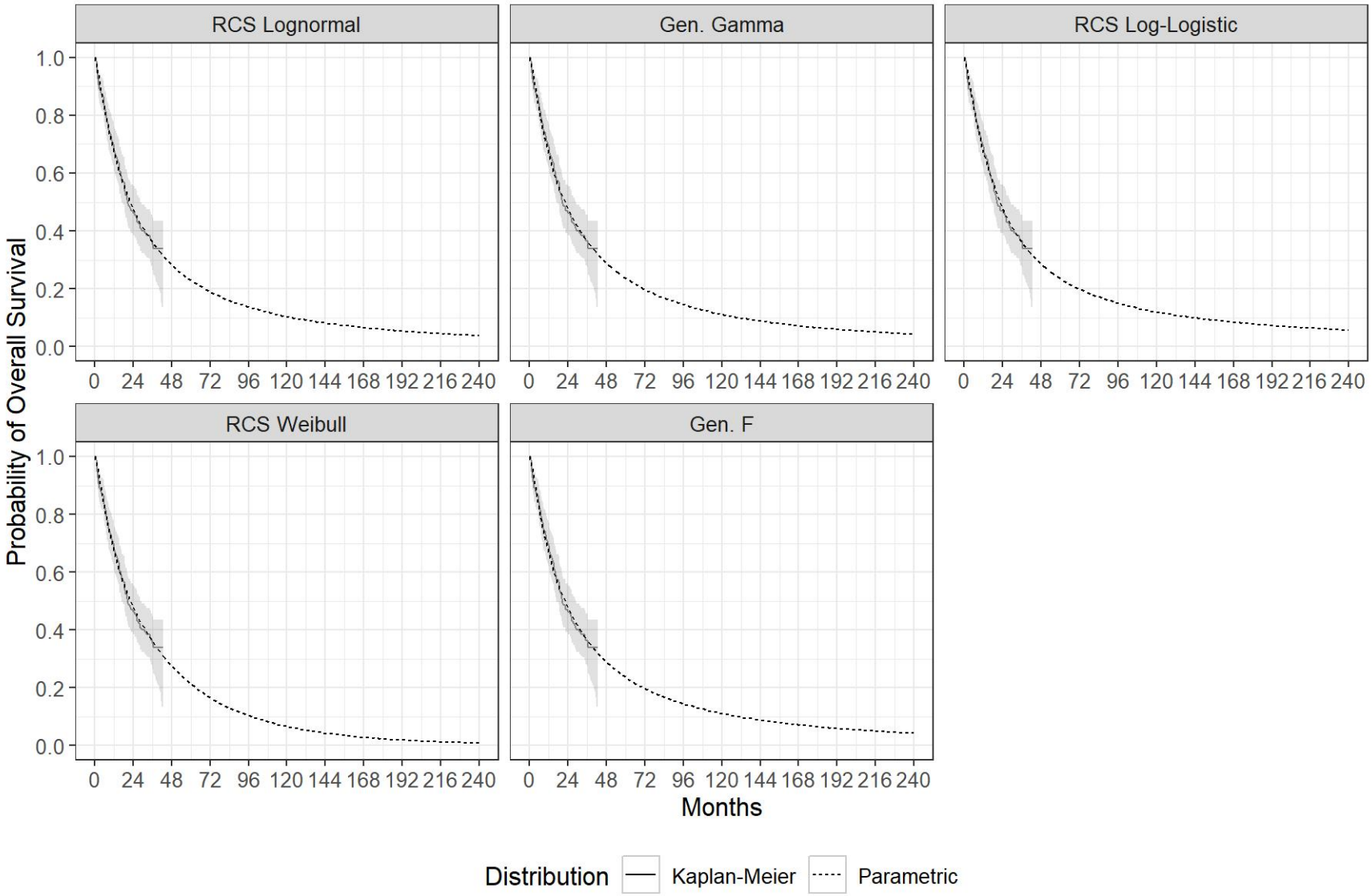
Overall Survival to End of Trial Follow-Up, OS



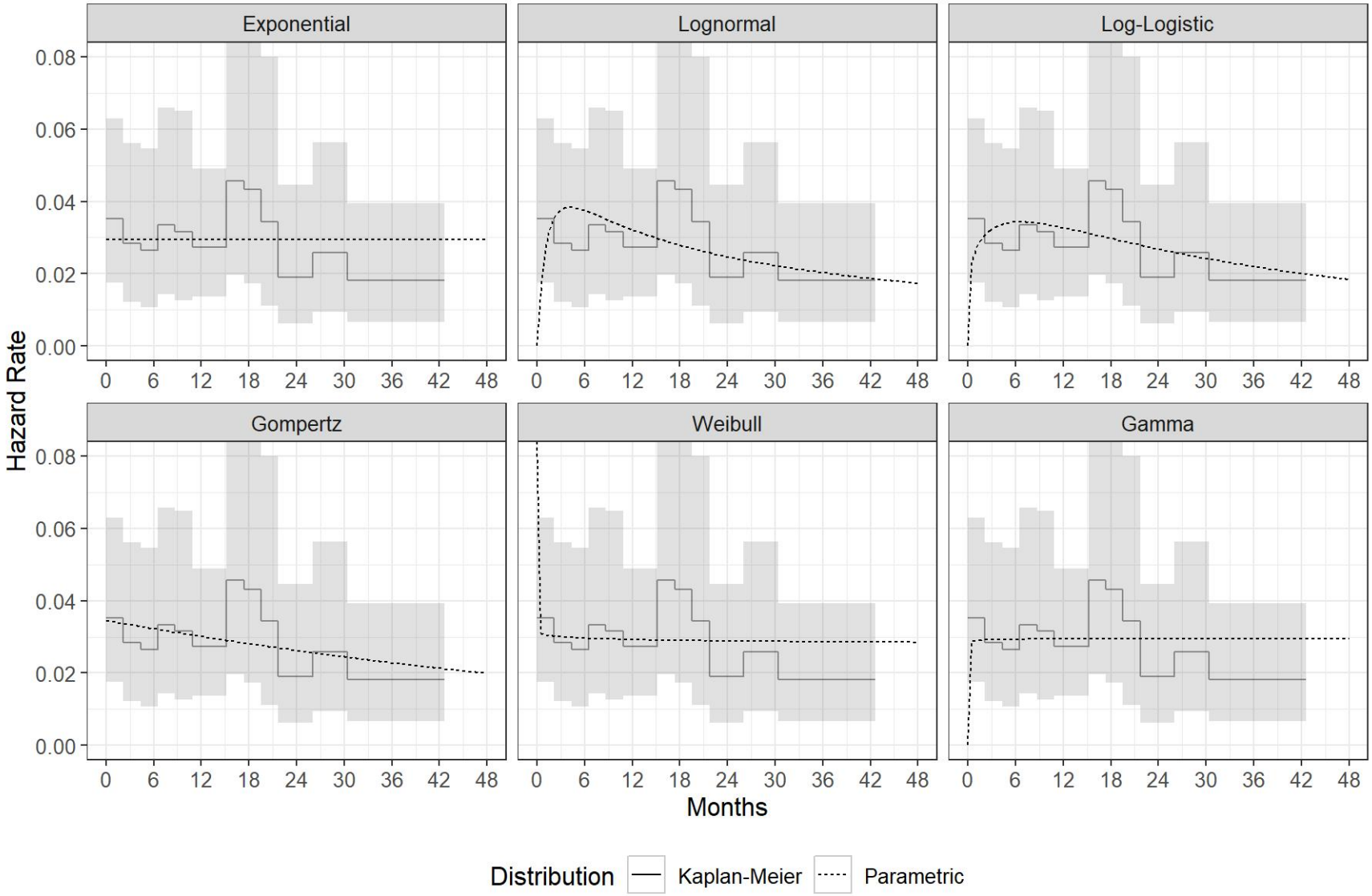

RCS Lognormal
Gen. Gamma
RCS Log-Logistic
RCS Weibull
Gen. F
Probability of Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
6
12
18
24
30
36
42
48
Months
Distribution
Kaplan-Meier
Parametric

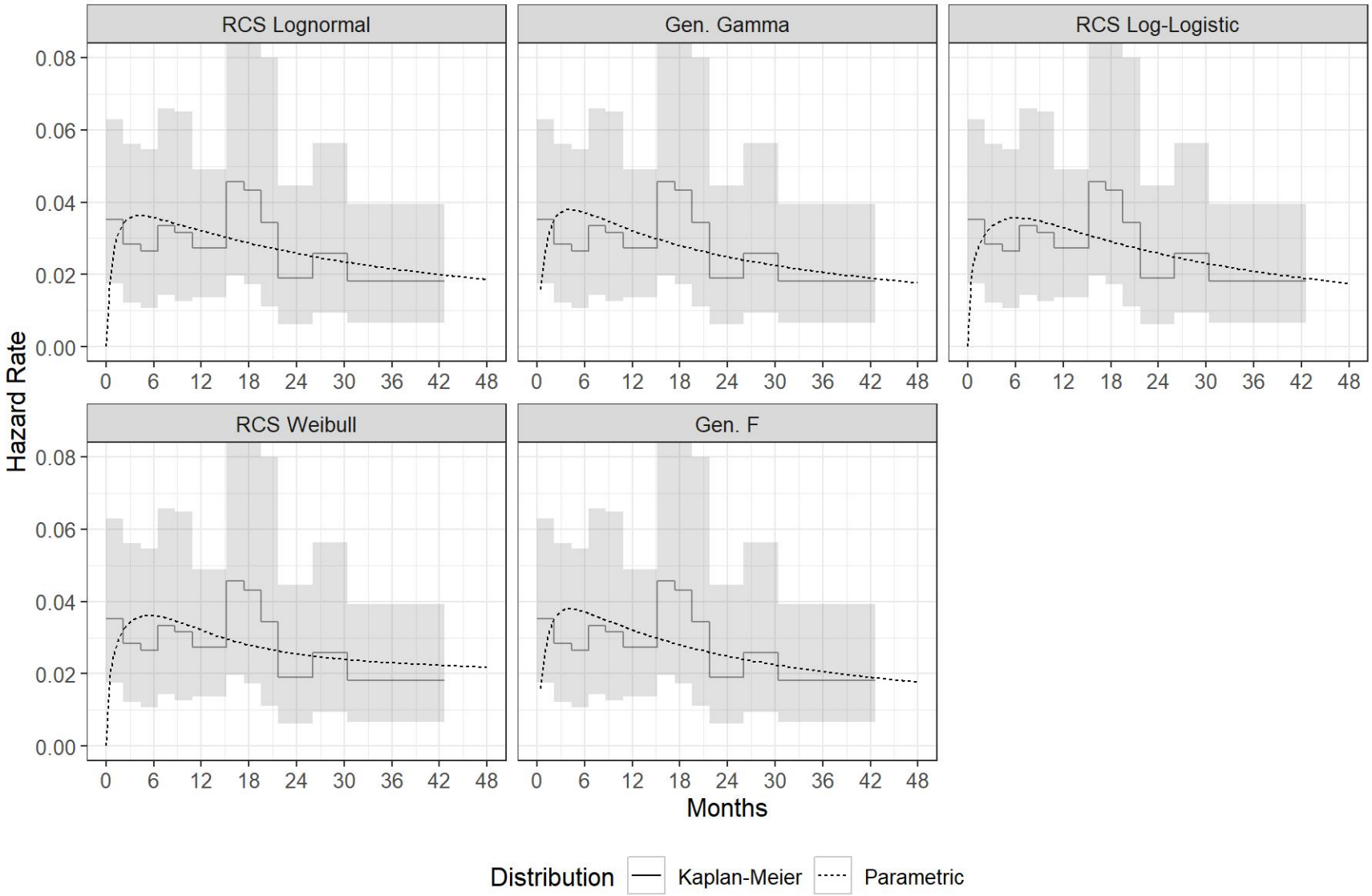
Overall Survival to 20 years, OS



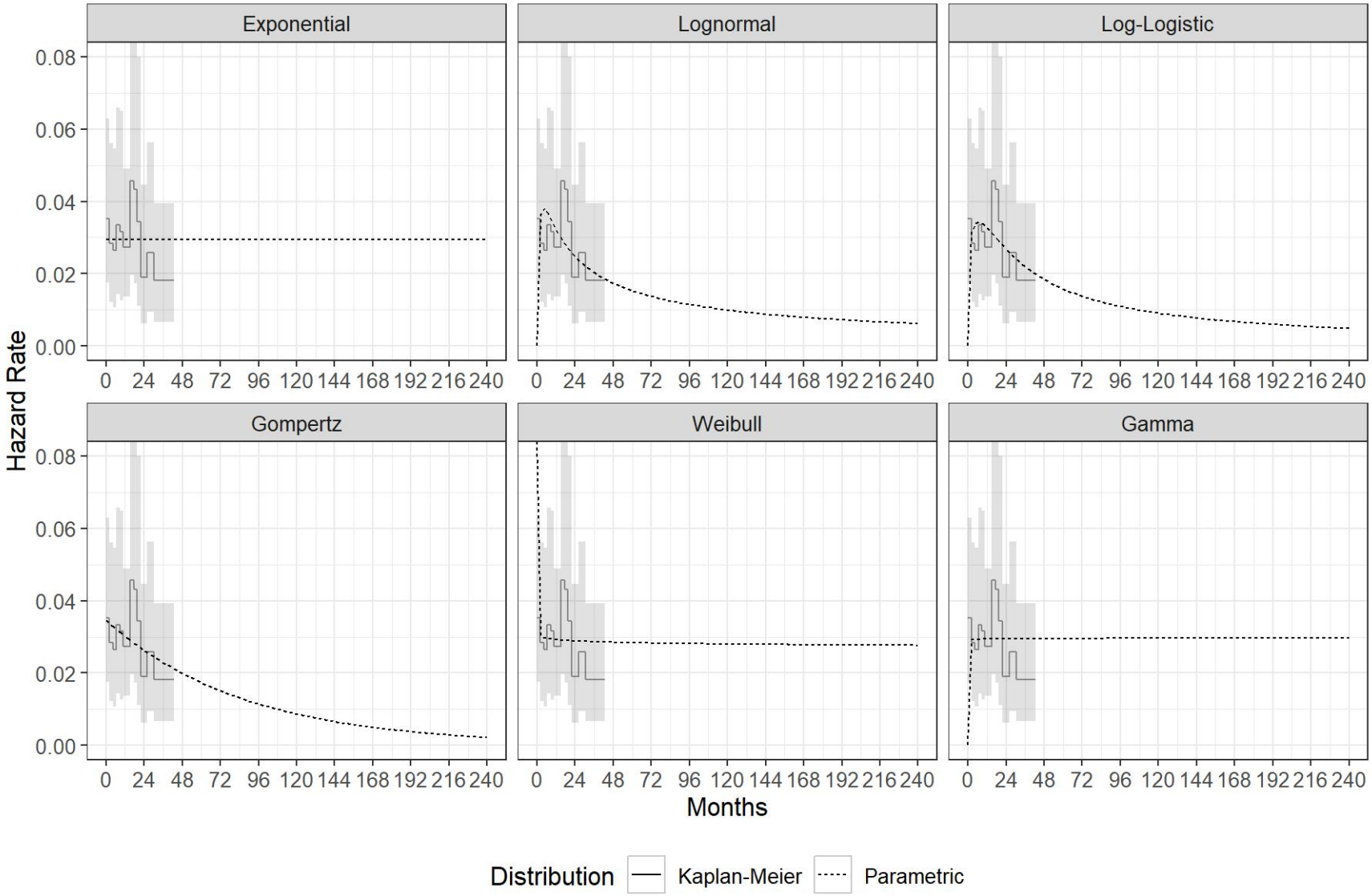

RCS Lognormal
Gen. Gamma
RCS Log-Logistic
RCS Weibull
Gen. F
Probability of Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
0 24 48 72 96 120 144 168 192 216 240
Months
Distribution
Kaplan-Meier
Parametric

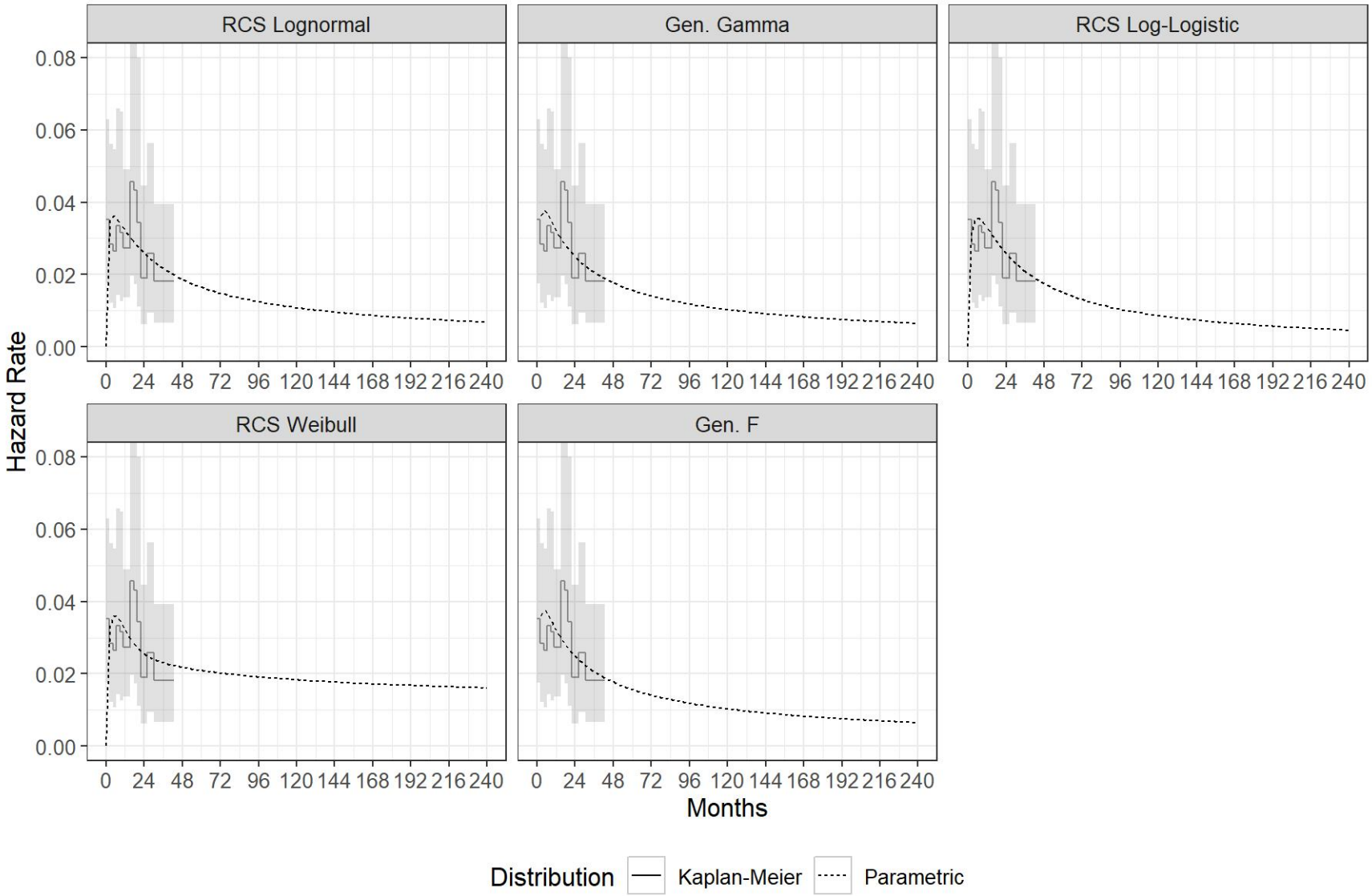
Hazard Rate to End of Trial Follow-Up, OS




RCS Lognormal
Gen. Gamma
RCS Log-Logistic
RCS Weibull
Gen. F
Hazard Rate
0.00
0.02
0.04
0.06
0.08
0
6
12
18
24
30
36
42
48
Months
Distribution
Kaplan-Meier
Parametric

Hazard Rate to 20 years, OS

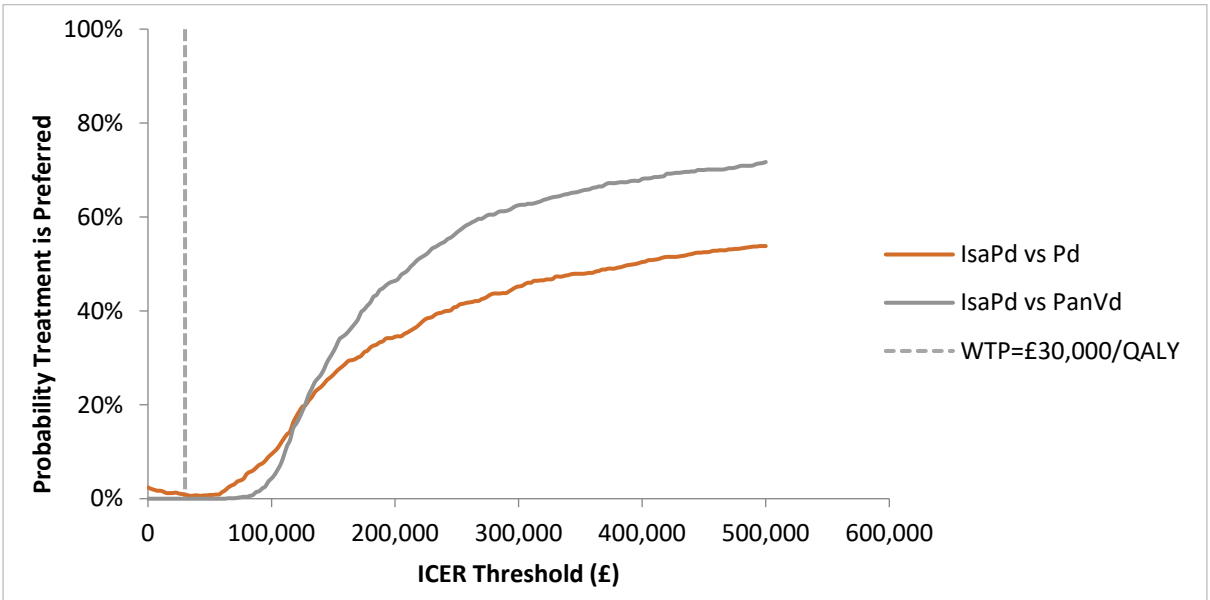



RCS Lognormal
Gen. Gamma
RCS Log-Logistic
RCS Weibull
Gen. F
Hazard Rate
0.08
0.06
0.04
0.02
0.00
0 24 48 72 96 120 144 168 192 216 240
Months
Distribution
Kaplan-Meier
Parametric

Appendix 9: Scatter plots and Cost effectiveness acceptability curves – 3L

Results using Exponential for IsaPd OS and PanVd (academic / commercial in confidence information removed PAS)

CEAC curves



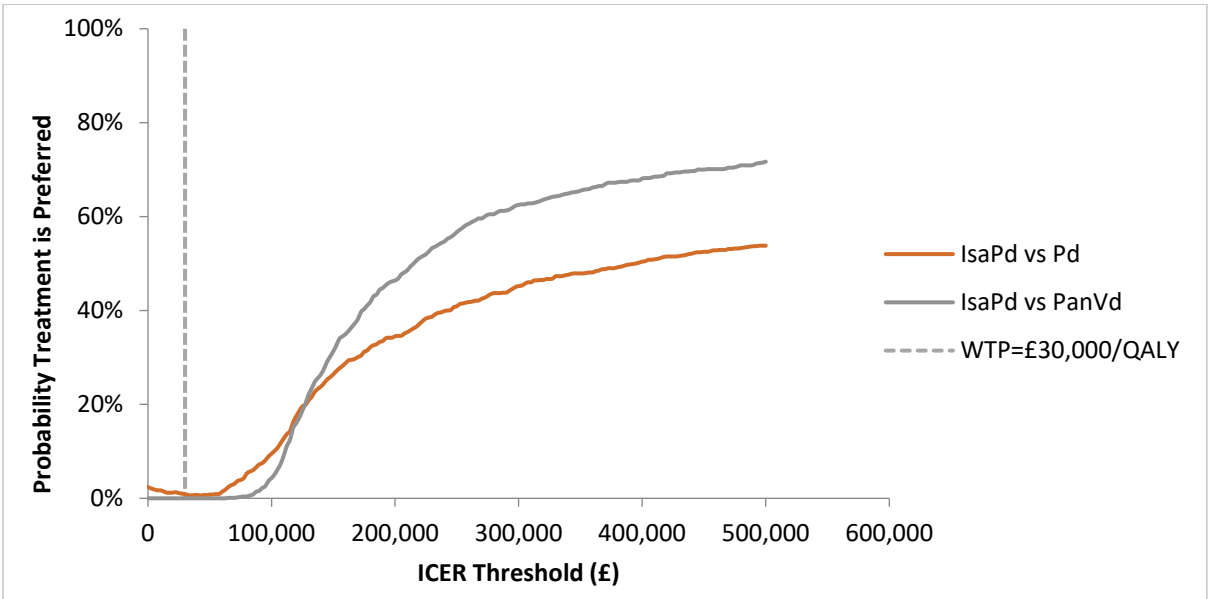
Scenario analyses

Scenario	Vs PanVd
Basecase	£300,537
No medication wastage	£271,661
EQ-5D-5L utilities	£264,904
No PAS discount for Pom	£300,537
% receiving subsequent therapy and duration of subsequent therapy based on KOL feedback	£274,649
% receiving subsequent therapy based on HTA submissions	£351,271
Duration of AEs based on KOL feedback	£308,855
Favourable distributions for IsaPd	#N/A
Unfavourable distributions for IsaPd	#N/A
Other costs from dara NICE submission	£298,342
Treatment discontinued upon progression, lognormal (R) (best BIC)	£485,230
Treatment discontinued upon progression, exponential	£292,991
5-year time horizon	£375,470
10-year time horizon	£310,634
20-year time horizon	£300,537
1.5% effectiveness discount rate	£283,503
1.5% effectiveness and cost discount rates	£290,871

Isa dosing based on ICARIA weight distribution	£341,735
Favourable inputs	#N/A
Unfavourable inputs	#N/A
No Dara Subsequent Tx – IPCW HR OS	£78,282
No Dara or Len Subsequent Tx – IPCW HR OS	£85,230
PFS:OS Deceleration Factor of 1.7	£125,782
PFS:OS Deceleration Factor of 2.9	£78,610
PFS:OS Deceleration Factor of 3.5	£68,788
PFS:OS Deceleration Factor of 4	£63,080
PFS:OS Deceleration Factor of 5	£55,317
IsaPd OS Exponential	£1,730,466

Results using Exponential for IsaPd OS and PanVd (academic / commercial in confidence information removed) 3L

CEAC curves



Scenario analyses

Scenario	Vs PanVd
Basecase	£265,966
No medication wastage	£239,272
EQ-5D-5L utilities	£234,432
No PAS discount for Pom	£265,966
% receiving subsequent therapy and duration of subsequent therapy based on KOL feedback	£240,077
% receiving subsequent therapy based on HTA submissions	£316,700
Duration of AEs based on KOL feedback	£273,326
Favourable distributions for IsaPd	#N/A
Unfavourable distributions for IsaPd	#N/A
Other costs from dara NICE submission	£263,771
Treatment discontinued upon progression, lognormal (R) (best BIC)	£436,093

Treatment discontinued upon progression, exponential	£259,161
5-year time horizon	£331,568
10-year time horizon	£274,874
20-year time horizon	£265,966
1.5% effectiveness discount rate	£250,891
1.5% effectiveness and cost discount rates	£257,736
Isa dosing based on ICARIA weight distribution	£341,735
Favourable inputs	#N/A
Unfavourable inputs	#N/A
No Dara Subsequent Tx – IPCW HR OS	£69,562
No Dara or Len Subsequent Tx – IPCW HR OS	£75,704
PFS:OS Deceleration Factor of 1.7	£111,533
PFS:OS Deceleration Factor of 2.9	£69,847
PFS:OS Deceleration Factor of 3.5	£61,167
PFS:OS Deceleration Factor of 4	£56,123
PFS:OS Deceleration Factor of 5	£49,262
IsaPd OS Exponential	£1,529,605

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Response to ACD - ERG Clarification questions

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1477]

3rd July 2020

ERG Question 1a: *'Can we request that the company tabulate the patient characteristics for the studies in Table 1? Similarly, to how they have in Appendix 3 when comparing the daratumumab and isatuximab studies'.*

We have provided a table comparing the baseline characteristics for ICARIA, SIRIUS, GEN501, MM-003 and PANORAMA-1 below.

Table 1: Comparison of baselines characteristics of patients in ICARIA-MM 4L, GEN501+SIRIUS, MM-003 and PANORAMA-1

Baseline demographics	ICARIA-MM – Patients in 4L		GEN501 and SIRIUS Pooled patients (N=148) (1),(2)	MM-003 (ITT population) (3),(4)		PANORAMA-1 (5),(6) N=768	
	Pd (N=58)	IsaPd (N=52)		Pd N=302	High dose dexamethasone N=153	PanVd N=387	Placebo-Vd N=381
Age, years, mean (SD)	64.2 (8.9)	66.1 (8.5)	NR	63.6 (9.3)	63.7 (9.6)	62.4 (9.34)	61.8 (9.43)
Age, years, median (Min;Max), [IQR]	65.5 (41 ; 80)	68.0 (39 ; 79)	64.0 [58 - 70]	64 (35 ; 84)	65 (35 ; 87)	63.0 (28 ; 84)	63.0 (32 ; 83)
Age group, years, n (%)							
<65	27 (46.6)	19 (36.5)	NR	NR	NR	225 (58.1)	220 (57.7)
>65	NR	NR	NR	135 (44.7)	72 (47.1)	162 (41.9)	162 (41.9)
65–74	22 (37.9)	26 (50.0)	52 (35)	NR	NR	127 (33)	133 (35)
≥75	9 (15.5)	7 (13.5)	16 (11)	24 (8)	12 (8)	35 (9)	28 (7)
Sex, n (%)							
Male	27 (46.6)	30 (57.7)	69 (47)	181 (59.9)	87 (56.9)	202 (52)	205 (54)
Female	31 (53.4)	22 (42.3)	79 (53)	121 (40)	66 (43)	185 (48)	176 (46)
Race, n (%)							
White	51 (87.9)	42 (80.8)	NR	244 [a] (80.8)	113 [a] (73.9)	249 (64)	250 (66)
Black or African American	1 (1.7)	0	NR	NR	NR	5 (1)	17 (4)
Asian	5 (8.6)	5 (9.6)	NR	NR	NR	128 (33)	104 (27)
Native Hawaiian or other Pacific Islander	0	2 (3.8)	NR	NR	NR	NR	NR

Other	NR	NR	NR	NR	NR	5 (1)	10 (3)
Missing/Not reported	1 (1.7)	3 (5.8)	NR	NR	NR	NR	NR
Ethnicity, n (%)							
Hispanic or Latino	1 (1.7)	3 (5.8)	NR	NR	NR	NR	NR
Not Hispanic or Latino	51 (87.9)	42 (80.8)	NR	NR	NR	NR	NR
ECOG PS, n (%)							
0	30 (51.7)	21 (40.4)	41 (28)	110 (36.4)	36 (23.5)	175 (45)	162 (43)
1	23 (39.7)	25 (48.1)	97 (66)	138 (45.7)	86 (56.2)	191 (49)	186 (49)
2	5 (8.6)	6 (11.5)	10 (7)	52 (17.2)	25 (16.3)	19 (5)	29 (8)
Missing	0	0	0	2 (<1)	3 (2)	2 (<1)	3 (<1)
≥1 extramedullary plasmacytomas, n (%)	NR	NR	18 (12)	NR	NR	NR	NR
ISS Stage, n (%)							
Stage I	24 (41.4)	25 (48.1)	NR	197 (65.2)	93 (60.8)	156 (40)	152 (40)
Stage II	14 (24.1)	17 (32.7)	NR			104 (27)	92 (24)
Stage III	19 (32.8)	9 (17.3)	NR	93 (30.8)	54 (35.3)	77 (20)	86 (23)
Missing/Not assessed	NR	NR	NR	12 (4.0)	6 (3.9)	50 (13)	51 (13)
Geographical region, n (%)							
Western Europe	29 (50.0)	19 (36.5)	NR	NR	NR	NR	NR
Eastern Europe	10 (17.2)	13 (25.0)	NR	NR	NR	NR	NR
North America	0	3 (5.8)	NR	NR	NR	NR	NR
Asia	5 (8.6)	5 (9.6)	NR	NR	NR	NR	NR
Other countries‡	14 (24.1)	12 (23.1)	NR	NR	NR	NR	NR
Regulatory region, n (%)							
Western countries	33 (56.9)	27 (51.9)	NR	NR	NR	NR	NR
Other countries‡‡	25 (43.1)	25 (48.1)	NR	NR	NR	NR	NR
Creatinine clearance (MDRD), n (%)							

≥60 mL/min	34/57 (59.6)*	30/48 (62.5)*	89 (60)	205 (68)	93 (60.8)	376 (97.2)	378 (99.2)
<60 mL/min	23/57 (40.4)*	18/48 (37.5)*	59 (40)[b]	95 (31)[b]	59 (39)[b]	NR	NR
≥30 to <60 mL/min	NR	NR	54 (37)	93 (30.7)	56 (36.6)	NR	NR
<30 mL/min	NR	NR	5 (3)	2 (0.7)	3 (2.0)	NR	NR
Missing	NR	NR	NR	2 (0.7)	1 (0.7)	2 (< 1)	3 (< 1)
Bone marrow plasma cells (%)							
≤30	NR	NR	85 (57)	NR	NR	NR	NR
>30 to ≤60	NR	NR	26 (18)	NR	NR	NR	NR
>60	NR	NR	35 (24)	NR	NR	NR	NR
Years since diagnosis, median, [IQR], (Min;Max)	NR	NR	5.1 [3.9 – 7.8]	5·3 (0·6 ; 30·0)	6·1 (0·9 ; 21·1)	3.09 [c] (0.2 – 25.67)	3.24 [c] (0.2 – 25)
Number of previous lines of therapy, median, [IQR], (Min;Max)	3.0	3.0	5.0 [4 – 7]	5 [d] (2 ; 14)	5 [d] (2 ; 17)	1.0 (1 ; 4)	1.0 (1 ; 4)
>3 previous lines of therapy, n (%)	58 (100)	52 (100)	133 (76)	NR	NR	NR	NR
Previous ASCT, n (%)	NR	NR	116 (78)	214 (70.9)	105 (68.6)	215 (56)	224 (59)
Previous proteasome inhibitor†, n (%)							
Any	NR	NR	148 (100)	NR	NR	NR	NR
Alkylators	NR	NR	NR	299 (99.0)	150 (98.0)	310 (80.1)	301 (79.0)
Bortezomib	NR	NR	147 (99)	302 (100)	153 (100)	169 (43.7)	161 (42)
Carfilzomib	NR	NR	61 (41)	NR	NR	NR	NR
Previous immunomodulatory drug†, n (%)							
Any	NR	NR	146 (99)	NR	NR	NR	NR
Lenalidomide	NR	NR	145 (98)	302 (100)	153 (100)	72 (18.6)	85 (22)
Pomalidomide	NR	NR	82 (55)	NR	NR	NR	NR
Thalidomide	NR	NR	66 (45)	173 (57.3)	93 (60.8)	205 (53.0)	188 (49)
Other prior treatments, n (%)							

Dexamethasone	NR	NR	NR	295 (97.7)	152 (99.3)	308 (80)	315 (83)
Refractory status, n (%)							
Refractory	NR	NR	NR	249 (82)	125 (82)	NR	NR
Relapsed	NR	NR	NR	NR	NR	247 (64)	235 (62)
Relapsed and refractory**	58 (100)	52 (100)	NR	NR	NR	134 (35)	141 (37)
Refractory to treatment, n (%)							
Last line of therapy	NR	NR	135 (91)	NR	NR	NR	NR
IMiD and PI	36 (62.1)	38 (73.1)	128 (87)	225 (74.5)	113 (73.9)	NR	NR
IMiD, PI and alkylating agent	NR	NR	100 (68)	NR	NR	NR	NR
Bortezomib	30 (51.7)	31 (59.6)	125 (85)	238 (78.8)	121 (79.1)	NR	NR
Carfilzomib	15 (25.9)	10 (19.2)	58 (39)	NR	NR	NR	NR
Lenalidomide	51 (87.9)	48 (92.3)	124 (84)	286 (94.7)	141 (92.2)	NR	NR
Ixazomib	7 (12.1)	6 (11.5)	NR	NR	NR	NR	NR
Pomalidomide	NR	NR	82 (55)	NR	NR	NR	NR
Thalidomide	NR	NR	41 (28)	90 (29.8)	48 (31.4)	NR	NR
Alkylating agent only	NR	NR	107 (72)	NR	NR	NR	NR
Intolerant to bortezomib	NR	NR	NR	45 (14.9)	23 (15.0)	NR	NR

NR; not reported, IQR; interquartile range, ASCT; autologous stem-cell transplantation, ECOG; Eastern Cooperative Oncology Group, IMiD; immunomodulatory drug, PI; proteasome inhibitor

**Excluding primary refractory

‡Other countries=Australia, New Zealand, Turkey and Russia

‡‡Other countries=Czech Republic, Hungary, Poland, Slovakia, Japan, Korea, Republic of Taiwan (Province of China), Turkey and Russia

*% calculated using the number of patients with at least one event (n) over the number of patients assessed for each parameter (N1) at baseline

†Patients could have received more than one of these therapies

[a] ,Race/ethnicity was not permitted to be collected by law in some regions

[b] ,Sum of two rows below

[c] ,Reported in months, converted to years

[d] ,Defined as number of prior anti-myeloma therapies

ERG Question 1b: ***Request from the ERG to 'tabulate the patient characteristics for the studies in Figure 1'.***

We have provided a table below comparing the baseline characteristics for ICARIA-MM vs. all studies included in Figure 1 of Sanofi response to ACD document

Table 2: Comparison of baseline characteristics of patients in ICARIA-MM vs pomalidomide publications included in Figure 1 of Sanofi response to ACD

Baseline characteristics	ICARIA-MM 4L		MM-002 Richardson et al. 2014 (7)		San-Miguel et al. 2013 (4) MM-003 (ITT population)		Dimopolous et al. 2016 (8) MM-010 (ITT Pop) N=682	Ailawadhi et al. 2018 (9) 2mg/4mg		Maciocia et al. 2017 (10)		Kastritis et al. 2019 (11) N=147	Parisi et al. 2019 (12) n=76	Gueneau et al. 2018 (13) N=63	Charlinski et al. 2018 (14) N=50	Matsumura-Kimoto et al. 2018 (15) N=108	ELOQUENT-1 Dimopoulos et al. 2018 (16)	
	Pd N=58	IsaPd N=52	Pd N= 113	Pom alone N= 108	Pd N=302	Hi-Dex N=153		2mg N= 35	4mg N= 35	UK series (all) N=85	UK series (response avail) N=70						Elo group N=60	Control group N=57
Age, years, mean (SD)	64.2 (8.9)	66.1 (8.5)	NR	NR	63.6 (9.3)	63.7 (9.6)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Age, years, median (Min;Max)/range	65.5 (41; 80)	68.0 (39; 79)	64 (34; 88)	61 (37;88)	64 (35; 84)	65 (35; 87)	66 (37; 88)	62 (39;77)	61 (45;77)	66 (40; 89)	61 (41; 82)	64 (38; 86)	63 (43; 83)	66 (40;85)	63 (40;84)	69 (34;90)	69 (43;81)	66 (36;81)
Age group, years, n (%)																		
<65	27 (46.6)	19 (36.5)	(55%)	(64%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	22 (37)	22 (39)
>65	NR	NR	(45%)	(36%)	135 (44.7)	72 (47.1)	369 (54.1)	NR	NR	48 (56.5)	37 (53)	NR	NR	NR	16 (32.0)	NR	NR	NR
65–74	22 (37.9)	26 (50.0)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
≥75	9 (15.5)	7 (13.5)	NR	NR	24 (8)	12 (8)	87 [c] (12.8)	NR	NR	15 [c] (17.6)	9 [c] (13)	NR	NR	NR	5 [g] (10.0)	NR	13 (22)	12 (21)
>70	NR	NR	NR	NR	NR	NR	213 (31.2)	NR	NR	NR	NR	51 (35)	NR	NR	NR	NR	NR	NR
Sex, n (%)																		
Male	27 (46.6)	30 (57.7)	55%	53%	181 (59.9)	87 (56.9)	381 (55.9)	27 (77)	21 (60)	50 (59)	41 (59)	51%	43 (56.5)	37 (59)	22 (44.0)	45 (42)	32 (53)	35 (61)
Female	31 (53.4)	22 (42.3)	45%	47%	121 (40)	66 (43)	301 (44.1)	8 (22)	14 (40)	35 (41)	29 (41)	49%	33 (43.4)	26 (41)	28 (32.0)	63 (58)	28 (47)	22 (39)

Baseline characteristics	ICARIA-MM 4L		MM-002 Richardson et al. 2014		San-Miguel et al. 2013 MM-003 (ITT population)		Dimopolous et al. 2016 MM-010 (ITT Pop) N=682	Ailawadhi et al. 2018 2mg/4mg		Maciocia et al. 2017		Kastritis et al. 2019 N=147	Parisi et al. 2019 n=76	Gueneau et al. 2018 N=63	Charlinski et al. 2018 N=50	Matsumura-Kimoto et al. 2018 N=108	ELOQUENT-1 Dimopoulos et al. 2018	
	Pd N=58	IsaPd N=52	Pd N= 113	Pom alone N= 108	Pd N=302	Hi-Dex N=153		2mg N= 35	4mg N= 35	UK series (all) N=85	UK series (response avail) N=70						Elo group N=60	Control group N=57
Race, n (%)																		
White	51 (87.9)	42 (80.8)	NR	NR	244 [a] (80.8)	113 [a] (73.9)	NR	31 (88.6)	29 (82.9)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Black or African American	1 (1.7)	0	NR	NR	NR	NR	NR	3 (8.6)[f]	4 (11.4)[f]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Asian	5 (8.6)	5 (9.6)	NR	NR	NR	NR	NR			NR	NR	NR	NR	NR	NR	NR	NR	NR
Native Hawaiian or other Pacific Islander	0	2 (3.8)	NR	NR	NR	NR	NR			NR	NR	NR	NR	NR	NR	NR	NR	NR
Other	NR	NR	NR	NR	NR	NR	NR			NR	NR	NR	NR	NR	NR	NR	NR	NR
Missing/Not reported	1 (1.7)	3 (5.8)	NR	NR	NR	NR	NR	1 (2.9)	2 (5.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ethnicity, n (%)																		
Hispanic or Latino	1 (1.7)	3 (5.8)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Not Hispanic or Latino	51 (87.9)	42 (80.8)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
ECOG PS, n (%)																		
0	30 (51.7)	21 (40.4)	28%	28%	110 (36.4)	36 (23.5)	614 (90.0)	13 (37.1)	13 (37.1)	NR	NR	NR	37 (48.6)	NR	34 (68.0)	NR	NR	NR
1	23 (39.7)	25 (48.1)	60%	66%	138 (45.7)	86 (56.2)		18 (51.4)	18 (51.4)	NR	NR	NR		NR		NR	NR	NR
2	5 (8.6)	6 (11.5)	12%	10%	52 (17.2)	25 (16.3)	68 (10.0)	4 (11.4)	4 (11.4)	NR	NR	NR	29 (38.1)	NR	16 (32.0)	NR	NR	NR
3	NR	NR	0%	2%	NR	NR		0%	0%	NR	NR	NR	NR	NR		NR	NR	NR
3 or more	NR	NR	NR	NR	NR	NR	NR	0%	0%	NR	NR	NR	NR	NR	0	NR	NR	NR
Missing	0	0	NR	NR	2 (<1)	3 (2)	NR	0%	0%	NR	NR	NR	NR	NR	0	NR	NR	NR
ISS Stage, n (%)																		

Stage I	24 (41.4)	25 (48.1)	7%	7%	197 (65.2)	93 (60.8)	414 (60.7)	NR	NR	8 (9.4)	7 (10)	NR	18 (23.6)	10 (16)	13 (26.0)	29 (27)	53 (88)	50 (88)
Stage II	14 (24.1)	17 (32.7)	26%	27%				NR	NR	13 (15.3)	12 (17)	NR	21 (27.6)	43 (68)	15 (30.0)	38 (35)		
Stage III	19 (32.8)	9 (17.3)	67%	66%	93 (30.8)	54 (35.3)	236 (34.6)	NR	NR	NR	10 (14)	NR	37 (48.6)	10 (16)	22 (44.0)	35 (32)	7 (12)	7 (12)
Missing/Not assessed	NR	NR	NR	NR	12 (4.0)	6 (3.9)	32 (4.7)	NR	NR	48 (56.5)	41 (59)	NR	NR	0	0	6 (6)	NR	NR
Creatinine clearance (MDRD), n (%)																		
≥60 mL/min	34/57 (59.6)*	30/48 (62.5)*	NR	NR	205 (68)	93 (60.8)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
<60 mL/min	23/57 (40.4)*	18/48 (37.5)*	NR	NR	95 (31)[b]	59 (39)[b]	237 (34.8)	NR	NR	32 [e] (37.6)	25 [e] (36)	50 [e] (34)	NR	NR	14 (28.0)	NR	NR	NR
≥30 to <60 mL/min	NR	NR	NR	NR	93 (30.7)	56 (36.6)	NR	NR	NR	NR	NR	NR	NR	NR	[h]	NR	NR	NR
>50 mL/min	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	59 (77.6)	NR		NR	NR	NR
30 – 50 mL/min	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	13 (17.1)	NR		NR	NR	NR
<30 mL/min	NR	NR	NR	NR	2 (0.7)	3 (2.0)	NR	NR	NR	NR	NR	NR	4 (5.2)	NR		NR	NR	NR
Missing	NR	NR	NR	NR	2 (0.7)	1 (0.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Years since diagnosis, median, (Min;Max)/range	NR	NR	NR	NR	5·3 (0.6; 30)	6·1 (0.9; 21.1)	NR	4.75 (1.0–20.7)	6.0 (1.1-17.2)	4 (<1; 18)	5 (<1; 11)	4.6 (0.7; 15)	NR	3.2 (0.5;19.6)	4.5 (0.5;24.9)	3.4 (0.33 ;10.6)	4.8 (0.5;21.9)	4.4 (0.7;17.5)
Number of previous lines of therapy, median, (Min;Max)/range	3.0	3.0	5 [d] (2; 13)	5 [d] (1; 12)	5 [d] (2; 14)	5 [d] (2; 17)	5 [d] (2; 18)	6 (3-9)	6 (2-11)	3 [d] (1; 8)	3 [d] (2; 7)	3 [d] (1;9)	NR	NR	NR	4 (1;10)	3 (2;8)	3 (2;8)
>3 previous lines of therapy, n (%)	58 (100)	52 (100)	NR	NR	NR	NR	NR	NR	NR	NR	NR	67 (46)	NR	2-3: n=37 (59);	2-3: n=20 (40);	<4: n=66 (61);	2 or 3: n= 30 (60);	2 or 3: n=36 (63);

> 2 prior lines of therapy, n (%)	58 (100)	52 (100)	95%	95%	NR	NR	637 [d] (93.4)	NR	NR	73 (85.9)	62 (89)	NR	NR	≥4: n=26 (41)	4-5: n=26 (52); >5: n=4 (8)	>5: n=42 (39)	>4: n=24 (40)	>4: 21 (37)
≤2 prior lines of therapy, n (%)	0	0	5%	5%	NR	NR	NR	NR	NR	NR	NR	31 (21)	NR					
Previous ASCT, n (%)	NR	NR	74%	76%	214 (70.9)	105 (68.6)	451 (66.1)	27 (77.1)	27 (77.1)	51 (60.0)	NR	78 (53)	NR	50 (79)	29 (58.0)	36 (33)	31 (52)	33 (58)
Previous proteasome inhibitor†, n (%)																		
Alkylators	NR	NR	NR	NR	299 (99.0)	150 (98.0)	NR	NR	NR	NR	NR	NR	NR	NR	50 (100)	NR[i]	NR	NR
Bortezomib	NR	NR	NR	NR	302 (100)	153 (100)	682 (100.0)	35 (100	35 (100)	84 (98.8)	NR	143 (97)	NR	63 (100)	50 (100)		60 (100)	57 (100)
Carfilzomib	NR	NR	17%	29%	NR	NR	24 (3.5)	0%	0%	NR	NR	NR	NR	NR	4 (8.0)		9 (15)	16 (28)
Ixazomib	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	5 (8)	2 (4)
Previous immunomodulatory drug†, n (%)																		
Lenalidomide	NR	NR	NR	NR	302 (100)	153 (100)	682 (100)	35 (100)	35 (100)	85 (100)	NR	147 (100)	NR	63 (100)	49 (98.0)	NR[i]	59 (98)	57 (100)
Pomalidomide	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR		NR	NR
Thalidomide	NR	NR	67%	67%	173 (57.3)	93 (60.8)	372 (54.5)	22 (63)	20 (76.9)	70 (82.4)	NR	103 (70)	NR	NR	50 (100)		25 (42)	19 (33)
Other prior treatments, n (%)																		
Dexamethasone	NR	NR	99%	99%	295 (97.7)	152 (99.3)	666 (97.7)			NR	NR	NR	NR	NR	NR	NR[i]	NR	NR
Lenalidomide and bortezomib	NR	NR	100%	100%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	48 (96%)		NR	NR
Melphalan	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR		38 (63)	36 (63)
Daratumumab	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR		1 (2)	2 (4)
Doxorubicin	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR		18 (30)	15 (26)
Lenalidomide as last prior therapy, %	NR	NR	39%	39%	NR	NR	NR	NR	NR	NR	NR	62 (42.5)	NR	NR	NR		NR	NR

Refractory status, n (%)																		
Refractory	NR	NR	NR	NR	249 (82)	125 (82)	NR	NR	NR	NR	NR	NR	NR	NR	23 (46.0)	NR	NR	NR
Relapsed	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	27 (54.0)	NR	0 [j]	3 [j] (5)
Relapsed and refractory**	58 (100)	52 (100)	NR	NR	NR	NR	NR	35 (100)	35 (100)	NR	NR	138 (94)	NR	63 (100)	NR	108 (100)	NR	NR
Bortezomib relapsed and refractory	NR	NR	NR	NR	NR	NR	NR	35 (100)	35 (100)	40 (47.1)	NR	NR	NR	24 (38.1)	NR	79 (73)	NR	NR
Refractory to treatment, n (%)																		
IMiD and PI	36 (62.1)	38 (73.1)	62%	61%	225 (74.5)	113 (73.9)	547 (80.2)	35 (100)	35 (100)	62 (72.9)	NR	NR	NR	19 (30.2)	8 (16.0)	58 (54)	41 (68)	41 (72)
Bortezomib	30 (51.7)	31 (59.6)	71%	70%	238 (78.8)	121 (79.1)	571 (83.7)	35 (100)	35 (100)	23 (27.1)	NR	104 (71)	NR	24 (38.1)	14 (28.0)	79 (73)	NR	NR
Carfilzomib	15 (25.9)	10 (19.2)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lenalidomide	51 (87.9)	48 (92.3)	78%	80%	286 (94.7)	141 (92.2)	654 (95.9)	35 (100)	35 (100)	NR	NR	NR	NR	37 (58.7)	24 (48.0)	73 (68)	54 (90)	48 (84)
Ixazomib	7 (12.1)	6 (11.5)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pomalidomide	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Thalidomide	NR	NR	NR	NR	90 (29.8)	48 (31.4)	NR	NR	NR	NR	NR	NR	NR	NR	31 (62.0)	NR	NR	NR
Alkylating agent only	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Intolerant to bortezomib	NR	NR	NR	NR	45 (14.9)	23 (15.0)	NR	NR	NR	7 (8.2)	NR	NR	NR	NR	NR	17 (16)	NR	NR

NR; not reported, ASCT; autologous stem-cell transplantation, ECOG; Eastern Cooperative Oncology Group, IMiD; immunomodulatory drug, ISS; International Staging System, PI; proteasome inhibitor, Hi-Dex; High dose dexamethasone

**Excluding primary refractory

*% calculated using the number of patients with at least one event (n) over the number of patients assessed for each parameter (N1) at baseline

†Patients could have received more than one of these therapies

[a] Race/ethnicity was not permitted to be collected by law in some regions

[b] Sum of two rows below

[c] Reported as >75

[d] Defined as number of prior anti-myeloma therapies/regimen or treatments

[e] eGFR, estimated glomerular filtration rate

[f] reported as Non-White

[g] reported as >75 years

[h] <45ml/min reported in 5 (10%) patients

[i] prior treatments included anthracyclines, BTZ, cisplatin, corticosteroids, cyclophosphamide, etoposide, LEN, melphalan, panobinostat, ranimustine, thalidomide, vincristine, radiation therapy, and clinical trials of cell therapy or new drugs. HDT/ASCT with high-dose melphalan had been administered in 36 patients (33%) – no exact proportions reported for each treatment

ERG question 2a: ***We would also like to have details of subsequent treatments post-progression which may differ due to the date the study was conducted*.**

We have tabulated the post study therapies used SIRIUS, GEN501, MM-003 and PANORAMA-1 in Table 2 below.

We acknowledge that treatment is constantly evolving, and these post study treatments may not reflect current UK clinical practice at 5L.

In our response to the technical report to issue 5, we provided further information from a survey of three UK clinical experts to comment on the distribution of subsequent treatments used in ICARIA and how these would reflect current clinical practice. They suggested that treatment in the 5L+ setting was less regimented and that patients receive several different therapies depending on their preference, performance status and prognosis. The main treatments that the clinical experts suggested were bendamustine, bortezomib, thalidomide, melphalan, etoposide and panobinostat.

It is worth reflecting that the clinical experts at committee explained that treatments at this point in the pathway would likely be ineffective. The experts considered that 5L+ treatment in ICARIA-MM was unlikely to affect the survival results in the ICARIA-MM subgroup. (ACD page 12, section 3.9). This might also be the case for the studies presented below in Table 3.

Table ***3: Subsequent therapies used in ICARIA-MM 4L patients, GEN501 + SIRIUS, MM-003 and PANORAMA-1***

Subsequent therapies, %	**ICARIA-MM 4L †**		**GEN501 and SIRIUS Pooled patients (N=148) ‡ (2)**	**MM-003 (ITT population)* (3)**		**PANORAMA-1 ** (5) N=768**	
	Pd (N=58)	**IsaPd (N=52)**		**Pd N=302**	**High dose dexamethasone N=153**	**PanVd N=387**	**Placebo-Vd N=381**
≥1 subsequent anti-myeloma drug	NR	NR	NR	44.4	60.1	NR	NR
Patients with subsequent therapy (%)	NR	NR	80	NR	NR	38	49
Immunomodulatory drugs	NR	NR	NR	NR	NR	20	29
Thalidomide	0.0	3.57	NR	NR	NR	NR	NR
Lenalidomide	2.38	14.29	15.5	NR	NR	NR	NR
Pomalidomide	7.14	7.14	33.8	0.3	48.4[a]	NR	NR
Proteosome inhibitor	NR	NR	NR	NR	NR	NR	NR
Bortezomib	16.67	25.0	24.3	17.9	15.7	11	13
Carfilzomib	21.43	17.86	28.4	NR	NR	NR	NR
Monoclonal antibodies	NR	NR	NR	NR	NR	3	1
Daratumumab	38.10	7.14	NR	NR	NR	NR	NR
Alkylating agents	NR	NR	NR	NR	NR	15	22
Bendamustine	11.9	10.71	NR	11.3	8.5	NR	NR
Cyclophosphamide	NR	NR	31.8	21.2	11.1	NR	NR
Melphalan	0.0	10.71	NR	NR	NR	NR	NR

Other anti-myeloma drugs							
Etoposide	0.0	10.71	NR	NR	NR	NR	NR
Panobinostat	0.0	3.57	NR	NR	NR	NR	NR
Dexamethasone	NR	NR	58.1	29.1	23.5	NR	NR
Steroids	NR	NR	NR	NR	NR	26	33
Autologous stem cell transplant	NR	NR	NR	NR	NR	2	3

†Because of the large number of different subsequent therapies received, only the ten most frequently received treatments in ICARIA-MM were included in the model.
‡The most common (given to >20% of patients) subsequent therapies. 31 December 2015 data cut-off, presented in Daratumumab submission, more recent data cut is available in Usmani et al. 2020.
* 01 September 2013 data cut, presented in NICE submission for pomalidomide.
**No data on subsequent therapies were found in published submission documents for pomalidomide, hence data from the publication is used.
[a], An additional 11 patients crossed over to the POM+DEX arm during the study after IDMC review

ERG question 2b*: Request from the ERG to 'provide details of subsequent treatments post-progression which may differ due to the date the study was conducted' for the studies shown in Figure 1 of ACD response*

We have provided a table comparing the subsequent treatments post-progression for all studies included in Figure 1 of Sanofi response to ACD document below. Note that those studies that are not present in table below did not report subsequent treatments (Table 4).

Table 4: *Subsequent therapies used in ICARIA-MM vs pomalidomide publications presented in Figure 1 of Sanofi response to ACD*

Subsequent therapies, %	**ICARIA-MM 4L †**		**San-Miguel et al. 2013 (4) MM-003 (ITT population)***		**Kastritis et al. 2019 (11) N=147**
	Pd (N=58)	**IsaPd (N=52)**	**Pd N=302**	**Hi-Dex N=153**	
≥1 subsequent anti-myeloma drug	NR	NR	44.4	60.1	NR
Patients with subsequent therapy (%)	NR	NR	NR	NR	57.5
Immunomodulatory drugs (IMiD)	NR	NR	NR	NR	NR
Thalidomide	0.0	3.57	NR	NR	NR
Lenalidomide	2.38	14.29	NR	NR	NR
Pomalidomide	7.14	7.14	0.3	48.4[a]	NR
Proteosome inhibitor (PI)	NR	NR	NR	NR	NR
Bortezomib	16.67	25.0	17.9	15.7	NR
Carfilzomib	21.43	17.86	NR	NR	7**
IMiD and PI	NR	NR	NR	NR	13
Monoclonal antibodies	NR	NR	NR	NR	12
Daratumumab	38.10	7.14	NR	NR	NR
Alkylating agents	NR	NR	NR	NR	NR
Bendamustine	11.9	10.71	11.3	8.5	NR
Cyclophosphamide	NR	NR	21.2	11.1	NR
Melphalan	0.0	10.71	NR	NR	NR
Other anti myeloma drugs	NR	NR	NR	NR	NR
Etoposide	0.0	10.71	NR	NR	NR
Panobinostat	0.0	3.57	NR	NR	NR
Dexamethasone	NR	NR	29.1	23.5	NR
Steroids	NR	NR	NR	NR	NR
Conventional chemotherapy	NR	NR	NR	NR	10

IMiD with chemotherapy	NR	NR	NR	NR	5.5
Bortezomib and chemotherapy	NR	NR	NR	NR	7.5
Autologous stem cell transplant	NR	NR	NR	NR	NR

NR; not reported

†Because of the large number of different subsequent therapies received, only the ten most frequently received treatments in ICARIA-MM were included in the model.

* 01 September 2013 data cut, presented in NICE submission for pomalidomide.

** carfilzomib and dexamethasone

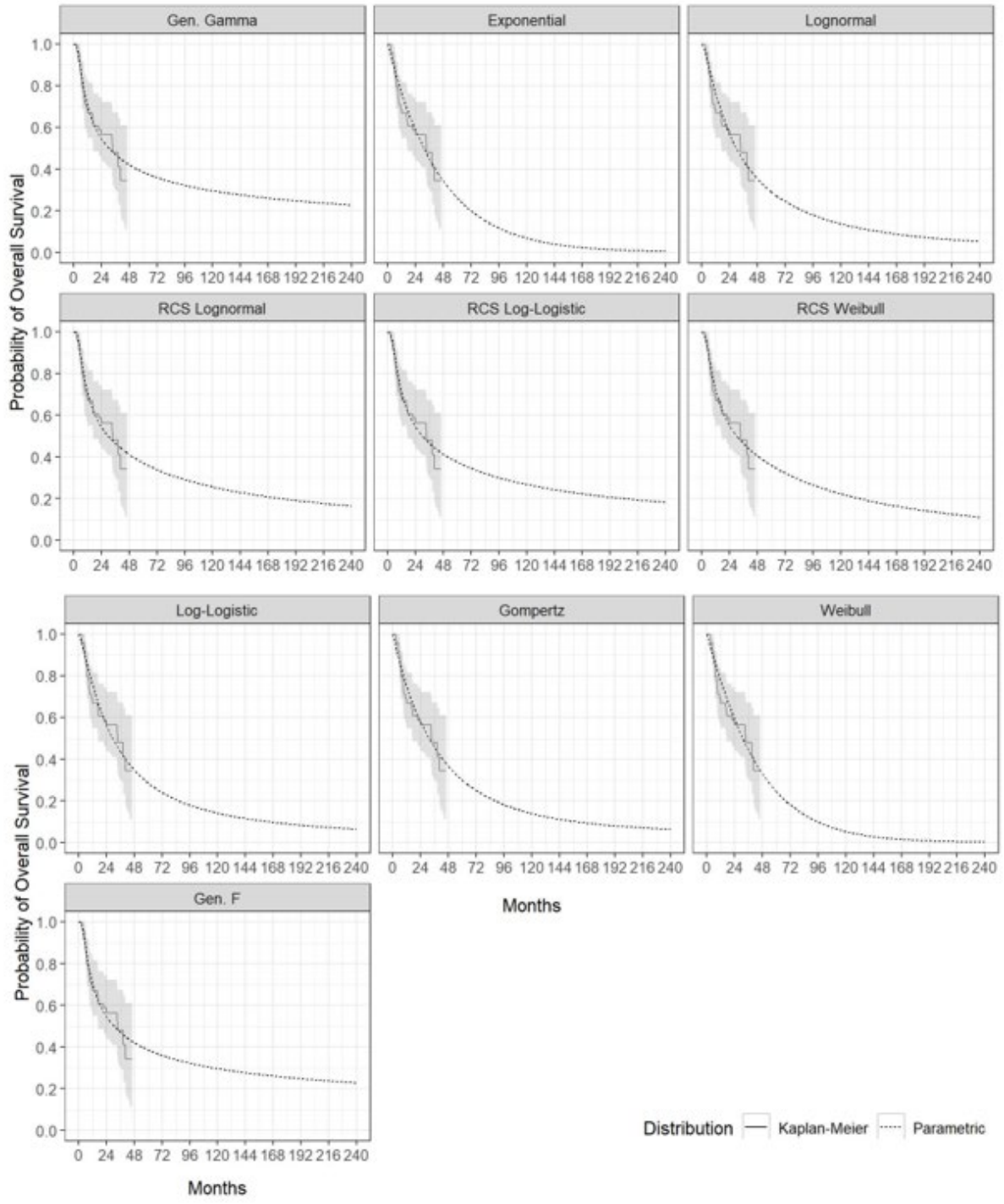
[a], An additional 11 patients crossed over to the POM+DEX arm during the study after IDMC review

Additional Sanofi comment: Further observations on the curve fitting exercise to the semi-synthetic KM OS data

We have provided information about the curve fitting exercise carried out for the semi-synthetic KM OS data in our ACD response. We would like to take this opportunity to provide further observations on the chosen curve.

Figure 1 overleaf is reproduced from Appendix 3 to the ACD submission. It can be seen from these extrapolations that the two most conservative fits are the exponential and the Weibull.

Figure 1. Fitted curves to the semi-synthetic KM OS data



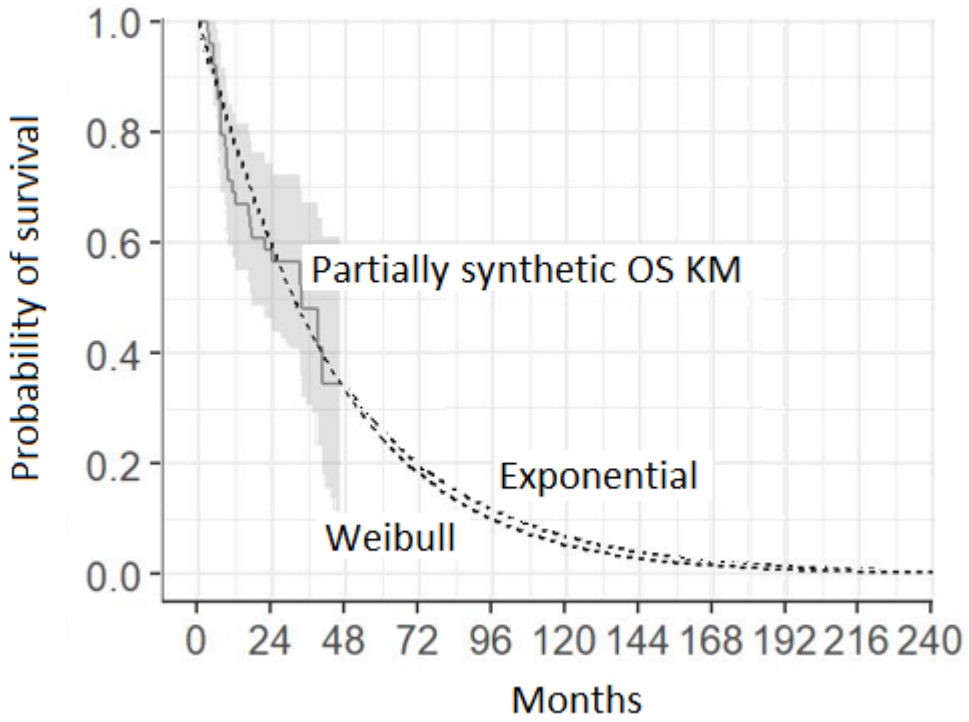
The exponential fit provides the lowest BIC and all fit statistics are lower for the exponential than for the Weibull indicating a better fit to the KM data for the exponential estimator (Table 5).

Table 5. Fit Statistics, OS

Distribution	Converged	DF	-2LL	AIC	AICc	BIC
Exponential	TRUE	1	255.3	257.3	257.4	259.3
Lognormal	TRUE	2	252.0	256.0	256.2	259.9
Gen. Gamma	TRUE	3	248.7	254.7	255.2	260.5
RCS Lognormal	TRUE	3	249.6	255.6	256.1	261.4
Log-Logistic	TRUE	2	254.0	258.0	258.3	261.9
Gompertz	TRUE	2	254.7	258.7	258.9	262.6
RCS Log-Logistic	TRUE	3	250.8	256.8	257.3	262.6
RCS Weibull	TRUE	3	250.8	256.8	257.3	262.6
Weibull	TRUE	2	255.2	259.2	259.5	263.1
Gen. F	TRUE	4	248.7	256.7	257.5	264.5

It is clear from Figure 1 that all of the other curves apart from the Weibull provide more optimistic views of long-term survival and so the choice between Weibull and exponential is the most conservative. In order to compare the two curves, we have overlaid them in Figure 2 below.

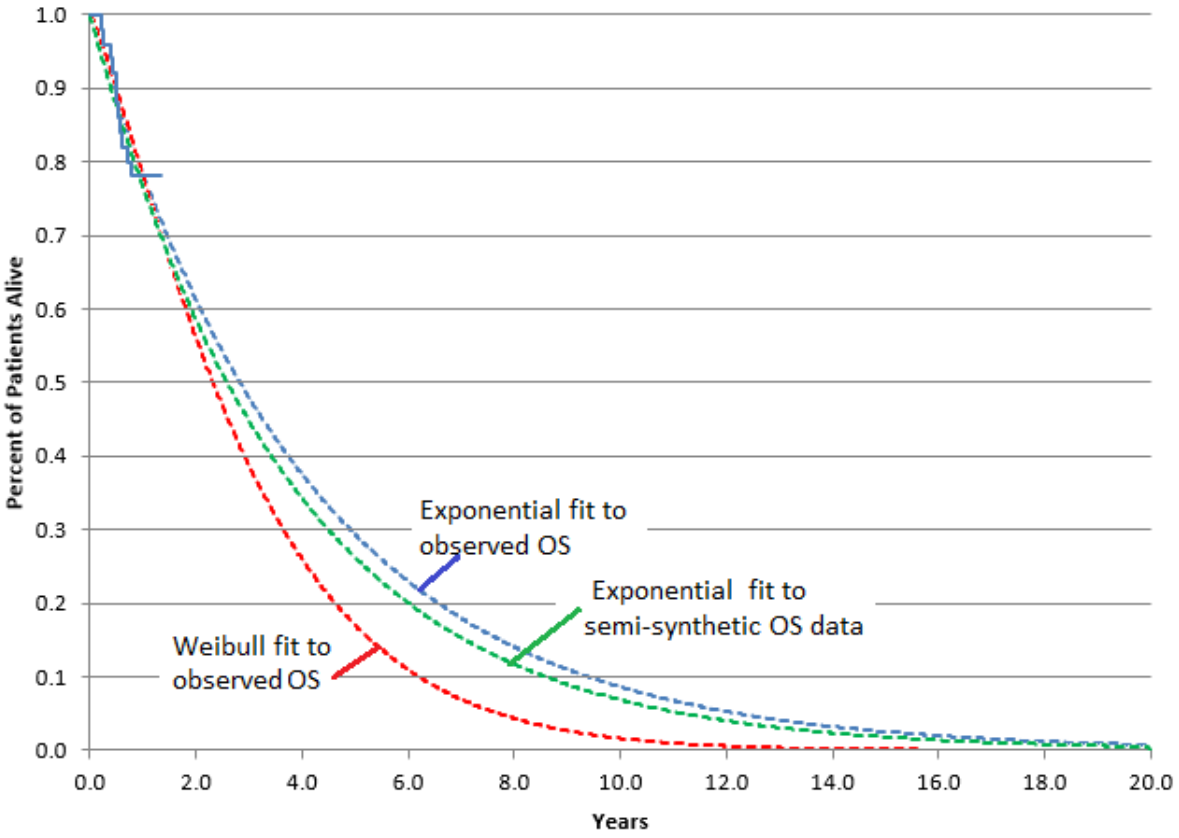
Figure 2. Overlay of the exponential and the Weibull fits to the semi-synthetic KM OS data



When the curves are fitted to the more complete semi-synthetic KM OS data both curves follow almost identical trajectories indicating that with more information the Weibull estimator predicts very similar long-term outcomes.

Figure 3 overleaf compares the original exponential fit (in blue) to the semi synthetic fit (in green) and the Weibull fit to the original OS data (in red).

Figure 3. Comparison of the fits to the partially synthetic and observed KM data.



When Figure 3 is compared to Figure 2 above it is evident that the original IsaPd exponential fit (blue) tracks much more closely to the Weibull fit to the semi synthetic data (Figure 2) than the Weibull fit to the observed data in red (Figure 3). This suggests that the original Weibull fit simply didn't have enough information to provide a secure estimate because it changes so much with more data. The exponential fit remains almost unchanged and could therefore be considered the more robust estimator.

Conclusion

The committee stated that their original preference for the curve fit to the observed IsaPd OS data from ICARIA was the Weibull based on shorter expectation of survival. We believe that our original choice (which was agreed by the ERG and Tech team), of the exponential fit based on fit statistics, plausibility of clinical outcomes for a triplet combination at 4th line and some clinical opinion remains the best estimate.

We have shown here that the original Weibull estimate is too conservative because when more data is introduced it predicts a longer tail almost identical to the exponential estimate.

Of the two most conservative curves (Weibull and exponential) in this new curve fitting exercise the exponential is the most plausible choice because it has the lowest fit statistics and face validity for long term survival. We hope that this analysis provides the committee with assurance that the new company base case of Weibull for the Pd arm and exponential for the IsaPd arm is the most appropriate.

Calculation supporting removal of backbone costs for Pomalidomide in combination with dexamethasone (Pd)

The results supporting the removal of Pd costs were done outside the Sanofi Excel model. Using the model with Weibull extrapolation for OS on Pd and exponential extrapolation for PS on IsaPd, the costs of removing Pd are calculated by adjusting only the costs of isatuximab and pomalidomide drug costs. All other costs related to (administration, health-state costs, adverse events, subsequent therapies and terminal care costs) remain the same as these are not expected to change with price changes on isatuximab and Pd. All outcomes related to LYG and QALYs were also assumed to remain the same.

Where isatuximab prices have been included, [redacted] are considered, unless stated otherwise.

Below we outline the steps taken to estimate the costs for Approach 1 and Approach 2 in the ACD response.

- Step 1: We estimated the total costs in the model when Pd is set to zero price in order to estimate the total costs of isatuximab in the IsaPd arm ([redacted])
- Step 2: We estimated the costs of Pd when isatuximab is set to zero price ([redacted])
- Step 3: Using the model estimated costs for Pd arm ([redacted]) we estimated the additional cost of Pd on the IsaPd arm ([redacted])

These costs were then used to estimate the impact on the ICER in Approach 1 and 2.

Table 6. Estimating total costs when setting isatuximab and Pd to zero

	Total cost
Isatuximab at list price **Pd at 0 price**	[redacted]
Isatuximab at [redacted] discount **Pd at 0 price**	[redacted]
Pd at list price **Isatuximab at 0 price**	[redacted]
Additional cost of Pd	[redacted]

Table 7: Disaggregated costs for all cost in the base case

Cost Category (£), Discounted	**IsaPd**	**Pd**
Medication	[redacted]	[redacted]
Administration	[redacted]	[redacted]
Progression-free	[redacted]	[redacted]
Post progression	[redacted]	[redacted]
Total	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]

Subsequent therapy	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]

Table 8: Total LYG and QALY estimated in the base case

	IsaPd	Pd
Total LYG	[redacted]	[redacted]
Total QALY	[redacted]	[redacted]

Approach 1 – Here the cost of IsaPd is calculated as the cost of Isatuximab for the duration of therapy at [redacted] plus the additional cost of Pd ([redacted]). All other costs and outcomes remain the same (Table 9).

Table 9: Approach 1

Cost Category (£), Discounted	IsaPd	Pd
Medication	[redacted]	[redacted]
Administration	[redacted]	[redacted]
Progression-free	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]
Total	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]
Total	[redacted]	[redacted]
Total costs	[redacted]	[redacted]
Total LYG	[redacted]	[redacted]
Total QALY	[redacted]	[redacted]
Incremental costs	[redacted]	
Incremental QALY	[redacted]	
Cost/QALY	[redacted]	

Approach 2 – In this calculation, the cost of IsaPd is the sum of the cost of isatuximab ([redacted]) and the cost of Pd as per the comparator arm (i.e. for the period of time that is the same on the IsaPd arm and the Pd arm) i.e. [redacted]. As above all other costs and outcomes remain the same (Table 10).

Table 10: Approach 2

Cost Category (£), Discounted	IsaPd	Pd
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
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Introduction

Myeloma UK welcomes the opportunity to comment on the NICE Appraisal Consultation Document (ACD) on isatuximab in combination with pomalidomide and dexamethasone.

We understand the challenges NICE faces in this appraisal which are recurring themes in health technology assessments of myeloma treatments. Particularly the lack of data on overall survival and the cost effectiveness challenges of combination treatments where the key anti-myeloma drugs are made by different companies.

We were pleased that the Committee recognised that pomalidomide and dexamethasone is the only relevant comparator at fourth line, that the treatment met the criteria for end of life treatment and that the Committee acknowledged the need for effective treatment options for relapsed myeloma.

Significant clinical benefit

As stated in our appraisal submission, a study conducted jointly by Myeloma UK, the EMA and the University of Groningen showed that, achieving a lasting remission from treatment was the most important factor for most (three quarters of all) participants.

The ICARIA trial demonstrated a significant PFS advantage (11.5 months vs 6.5) months and a much higher response rate (31.8% vs 8.5% for very good partial response.)

In addition, this triplet combination which includes a monoclonal antibody and immunomodulatory agent, is the first time that such a combination would be available in the treatment pathway. Given the heterogenous nature of myeloma, delivering access to treatments with different mechanisms of action is vital. This combination would deliver a totally new treatment opportunity to patients at fourth line.

Unmet need and anti-CD38 therapies

Although there are approved treatment options for patients at fourth line, there is still significant unmet need for this patient population who do not have access to a novel triplet combination.

A 2016 study[1] showed that around 15% of patients progress to fourth line. Given the treatment advances that have been made and are now available in the treatment pathway it is reasonable to conclude that this figure will now be higher.

The Committee discussed the impact of introducing isatuximab into the treatment pathway following the combination of daratumumab, velcade and dexamethasone (DVD) which is currently approved at second line via the Cancer Drugs Fund (CDF). In our response to the technical engagement report we agreed with clinical advice that, in the absence of data from the ICARIA or other trials, patients refractory to daratumumab should not receive isatuximab at fourth line. However, in line with ICARIA inclusion criteria, it should be available to patients who had been exposed to daratumumab but who are not refractory.

[1] Yong, K et al: Multiple myeloma: patient outcomes in real-world practice. BJH July 2016. Figure 2 (https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.14213

The Cancer Drugs Fund clinical lead expressed concern that the amount of data that could be collected through the CDF would be limited due to the number of patients who would be refractory to daratumumab at second line.

We believe that it is too early in the use of DVD at second line to reach conclusions about the numbers of patients who will reach fourth line refractory to anti-CD38 therapy. Velcade is well known to be challenging as a long term treatment option due to the incidence of peripheral neuropathy and could result in many patients being unable to complete a course of DVD to progression. In addition, DVD is approved through the CDF and, in line with NICE guidance, it cannot be assumed that it will be routinely commissioned.

We therefore argue that there is no clear evidence that numbers of patients at fourth line who are still responsive to anti-CD38 therapy will be too low to make CDF data collection viable.

As the Committee acknowledges, the myeloma treatment pathway is rapidly evolving and issues around treatment sequencing are increasingly challenging. We agree with the CDF clinical lead that it is not the role of the CDF to be a proxy for clinical trials which should be undertaken by industry. However, we also argue that the increasing difficulty in predicting with confidence how future HTA decisions will impact the pathway means there is a strong case for flexibility in decision making.

Overall survival and the CDF

We appreciate that having data on overall survival (OS) is vital to understanding a treatment's real value. However, advances in myeloma treatment mean that it is increasingly challenging to produce OS data within the timelines of a clinical trial, and ensure that patients are not missing out on the most promising new treatments.

Clearly the CDF is the key policy mechanism for delivering access to treatments in this category. We are therefore obviously disappointed that, as it stands, the Committee does not consider that isatuximab, pomalidomide and dexamethasone has plausible potential to be cost effective at the current price.

There is very clear evidence that this treatment is significantly better than the standard comparator (and good reason given what we know about the efficacy of MAB/IMid combinations that it would also deliver benefit compared to CDF funded daratumumab monotherapy).

Myeloma patients at fourth line face a significant disease and psychological burden. In the face of this, it would be hugely disappointing if an effective new treatment which is clearly superior to existing treatment options was not approved. We therefore hope that all avenues will be explored by the company, NICE and NHS England to enable a positive recommendation via the CDF.

[redacted]

[redacted]

25 June 2020

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [ID1477]

ACD comments from [redacted] on behalf of the UK Myeloma Forum

Q1 - Has all of the relevant evidence been taken into account?

There is clearly an unmet clinical need for patients with RRMM. This condition remains incurable and there are a dwindling number of patients alive beyond 4th line. It is therefore important to give the best therapies available early in the pathway to give the most benefit. There is clearly a survival benefit with the addition of isatuximab to PomDex. This improved PFS is matched by favorable quality of life and toxicity data. This is important for patients who often have significant co-morbid issues related to multiple myeloma such as bone disease and renal problems, and the effect of toxicities of prior treatment (such as neuropathy).

Q2 - Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Using the best treatment at 4th line that is available to patients. In current practice patients will receive daratumumab 4th line (CDF) and PomDex at 5th line. We know that it is best to combine the anti-CD38 monoclonal antibodies with an immunomodulatory drug (IMID). Rather than separating these therapies at 4th and 5th line it will have most benefit when we combine our most potent IMID with an anti-CD38 monoclonal antibody at 4th line. Given that there will be a limited number of patients able to receive treatment at 5th line they are being disadvantaged by not receiving the most appropriate combination at 4th line.

Q3 - Are the recommendations sound and a suitable basis for guidance to the NHS?

Using the technology at 3rd line. The committee accepted that IsaPD is appropriately compared to PomDex at 4th line, however it raised concern about whether it should be considered as a 3rd line. We recognize the attempt of the committee to horizon scan and identify the up and coming unmet need which is 3rd line, currently for patients to receive IsaPD they need to have received lenalidomide beforehand. This technology naturally fits into 4th line at the moment but appreciate that with the increasing use of lenalidomide in 1st and 2nd line this is a diminishing population. The exception being those on the transplant-eligible pathway. As such,

the vagrancies of the myeloma pathway, whilst challenging, are not dealt with by this appraisal outcome currently. This results in lack of equity of access if patients receiving treatment currently can not receive this technology at 4th line given its clear benefit over PomDex.

Applicability for use in the Cancer Drugs Fund. One of the reasons stated for not meeting the Cancer Drug Fund criteria is that most patients will have received an anti-CD38 monoclonal antibody before they get to 4th line. Whilst there will be a large number of patients who will receive daratumumab at 2nd line (in combination with bortezomib and dexamethasone, DVd; CDF), there are a proportion of patients who will not receive daratumumab at second line (CDF) due to early progression on bortezomib given as initial therapy or who developed significant neurotoxicity and so can't receive this combination at 2nd line. In addition, DVd was only available on the CDF in 2019. There is therefore a large number of patients who have never received an anti-CD38 monoclonal antibody before 4th line. They would gain clear clinical benefit from receiving IsaPD and though they are a group of diminishing numbers over coming years they still exist and should not be ignored.

Q4 - Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

This technology naturally fits into 4th line at the moment but appreciate that with the increasing use of lenalidomide in 1st and 2nd line this is a diminishing population. The exception being those on the transplant-eligible pathway. As such, the vagrancies of the myeloma pathway, whilst challenging, are not dealt with by this appraisal outcome currently. This results in lack of equity of access if patients receiving treatment currently can not receive this technology at 4th line given its clear benefit over PomDex.

ISATUXIMAB / POMALIDOMIDE / DEXAMETHASONE (ID 1477)

PATIENT EXPERT RESPONSE TO ACD

ALAN CHANT

Thank you for the opportunity to respond to the Appraisal Consultation Document for the above triplet for treating relapsed and refractory myeloma at 4th line.

I would like to make the following points in support of the proposed treatment for your consideration:

1. Better fourth line treatment – than existing authorised treatments

POM/DEX (TA573 / Jan 2017)

Although the evidence presented by Sanofi from the ICARIA trial was interim and based upon a sub-set of data, nevertheless the data demonstrated a significant advantage when compared with POM/DEX for relapsed and refractory patients. There was a PFS advantage (11.5 months vs 6.5) and the indication of an OS advantage of c.10%. Importantly the trial reported a higher response rate (60.4% vs 35.3% for some level of response; 31.8% vs 8.5% for very good partial response).

DARATUMUMAB (TA510 / CDF / March 2018) – Not a comparator

We know from US experience that DARA monotherapy is less effective than triplet combinations in which it is included. Initial FDA approval of DARA monotherapy occurred in November 2015 and was quickly followed up over the next four years by approvals for triplet combinations combining it with Proteasome Inhibitors (PIs) (Velcade), Immunomodulatory drugs (IMiDs) (Lenalidomide and Pomalidomide) and a corticosteroid (DEX).

The availability of the unique combination therapy of ISA/POM/DEX is equivalent to the FDA authorisation for DARA/POM/DEX given for relapsed/refractory patients given three years ago in June 2017.

The US experience suggests that it is highly likely that ISA/POM/DEX is more effective than the authorised DARA monotherapy for UK myeloma patients.

Conclusion: Based upon evidence to date from the ICARIA trial and US experience the ISA/POM/DEX triplet treatment is more effective than current approved treatments through NICE and the CDF, and could relegate them in clinical decisions about patient treatment.

2. Anti-CD38 drug for "first time" users

The anti-CD38 monoclonal antibody (MAB) drug DARA (with VELcade and DEX) was made available through the Cancer Drugs Fund (CDF) in April last year (TA573) for 2nd line treatment, and hence is not strictly a comparator in NICE deliberations.

However, in reality some patients would already have had the opportunity to be treated with DARA at 2nd line, and potentially in the future if authorisation continues outside the CDF after January 2021.

The Committee were concerned that there could be two anti-CD38 drugs in the myeloma treatment pathway. There are, however, two key groups of patients who would benefit from anti-CD38 treatment at 4th line despite its use at 2nd line in the pathway:

- Those patients who have missed the opportunity to access MAB therapy through DARA/VEL/DEX (DVD) - namely those beyond 2nd line who are currently on 3rd line treatment or in remission prior to 4th line treatment.
- Those patients who either are judged not clinically suitable for DVD at 2nd line treatment or who have to stop DVD due to suffering from adverse effects

With regard to the first group, in a study published in July 2016[1] it was stated that some 15% of myeloma patients survive to receive 4th line treatment (and may be more now given progressively longer survival times over the last 4 years). In the UK, with a myeloma incidence of 5,700 per annum[2] (and an updated prevalence of 24,000), this suggests that currently some 855 myeloma patients per annum (or 3600 patients at some time) will currently require 4th line treatment, many of whom will have missed the opportunity for anti-CD38 treatment at 2nd line.

Conclusion: The ISA/POM/DEX provides "first time" users of an anti-CD38 drug who are currently on 3rd line treatment or in remission prior to 4th line treatment and therefore missed DARA treatment, or were not prescribed or stopped DARA at 2nd line, to have the opportunity to be treated with drugs other than PIs and IMiDs.

3. Unique triplet combination

As we are aware, myeloma cells mutate over time and the opportunity for an anti-CD38 drug to be used (in an effective triplet regime) to fight the cancer provides the best chance of providing longer PFS and prolonging life. Patients at 4th line who have only been treated with PIs and IMiDs typically have a life expectancy of less than 12 months.

PIs, IMiDs and MABs each have different mechanisms of action to fight against myeloma cells, and hence a combination of ISA (MAB) + POM (IMiD) + DEX (corticosteroid) would be a unique therapy available for routine authorisation. This has the potential to extend patient life at a crucial point in their treatment journey.

Importantly, ISA/POM/DEX meets NICE's end of life criteria, unlike DARA monotherapy[3] . Additionally, the MHRA considered the triplet to be "Promising Innovative Medicine" - the first treatment for relapsed and refractory patients to be recognised.

Conclusion: ISA/POM/DEX is a unique triplet therapy which combines three separate mechanisms for treating myeloma, and is recognised as both meeting NICE's end of life criteria and being innovative.

4. Unmet need

Relapsed and refractory patients at 4th line treatment are coming to the end of their myeloma journey. Additionally, they are aware that the depth of response to treatment decreases with each additional line of therapy and therefore they will have less time in remission than previous lines of treatment provided. Their prognosis is worse than at any time in their journey to date.

The physical and psychological burden that this situation imposes on patients and carers is enormous, including disease-related effects such as pain and fatigue, loss of mobility, increasing reliance on carers, lack of control, concern for partners left behind after their demise, and loss of hope and self-worth.

As we are aware, loss of a positive mental attitude to fight a chronic illness such as myeloma can impact adversely upon life expectancy[4] and therefore affect both patients' quality of life and remaining length of life.

Patients therefore need the reassurance to trust and have confidence that they have access to the best possible treatment regime to give them a few more months/years of life. They deserve no less.

Conclusion: 4th line patients have an unmet need, both physically and psychologically to continue their fight against myeloma. They deserve the best treatment available.

CONCLUSION

I recognise that the appraisal committee has a difficult decision to make when considering whether or not to give authorisation for this therapy.

There are issues, inter alia, concerning immature trial data, sub-group analysis, comparator data and cost effectiveness which the committee have considered and weighed prior to the issue of the ACD.

However, I would hope that in reconsidering their decision the committee will recognise that the outcome will have considerable physical and psychological impact upon the lives of relapsed and refractory patients at this critical point in their myeloma journey. I hope that the points above will be taken into consideration, the plight of patients put at the heart of their decision-making and result in granting authorisation for this unique and innovative triplet therapy which provides clear clinical benefit over any other approved treatment at 4th line.

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[1] Yong, K et al: Multiple myeloma: patient outcomes in real-world practice. BJH July 2016. Figure 2 (https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.14213

[2] Myeloma UK Annual Report 2019; Page 7 https://www.myeloma.org.uk/wp-content/uploads/2020/04/Myeloma-UK-Annual-Report-Financial-Statements-2019.pdf

[3] Nice Guideline TA505: Committee Discussion 3.17

[4] Numerous studies including: Spiegel, D: Minding the Body: Psychotherapy and Cancer Survival. PubMed August 2013. https://pubmed.ncbi.nlm.nih.gov/23980690/

Response to ACD published for Isatuximab plus pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma (issued May 2020).

Author: Neil Rabin, Clinical Expert **25th June 2020**

I welcome the opportunity to comment on this consultation document. I was disappointed that isatuximab plus pomalidomide and dexamethasone has not been recommended for treating patients with relapsed and refractory multiple myeloma in line with its marketing authorisation. I would like to point out a few important issues related to the clinical interpretation of the evidence.

1. There is clearly an unmet clinical need for patients with relapsed and refractory multiple myeloma. This condition remains incurable and there are a dwindling number of patients alive beyond 4th line. It is therefore important to give the best therapies available early in the pathway to give the most benefit. There is clearly a survival benefit with the addition of isatuximab to pomalidomide and dexamethasone. This improved PFS is matched by favorable quality of life and toxicity data. This is supported by published trial data and also personal experience of using this technology in clinical practice. This is important for patients who often have significant co-morbid issues related to multiple myeloma such as bone disease and renal problems,

and the effect of toxicities of prior treatment (such as neuropathy). Whilst isatuximab necessitates additional day care attendance this does not adversely affect patient quality of life.

2. Using the technology at 3rd line. The committee accepted that isatuximab with pomalidomide and dexamethasone is appropriately compared to pomalidomide at 4th line, however it raised concern about whether it should be considered as a 3rd line. Whilst there may be merit in patients receiving this treatment at 3rd line, it is most suited to patients at 4th line in the current pathway. For patients to receive pomalidomide with istuximab they need to have received lenalidomide beforehand. This technology naturally fits into 4th line at the moment. Currently most patients are receiving lenalidomide with ixazomib and dexamethasone at 3rd line. Whilst a group of non-transplant eligible patients receive lenalidomide upfront (first line), a large number of patients treated upfront (transplant eligible) and beyond will not receive lenalidomide until 3rd line. The vagrancies of the myeloma pathway, whilst challenging, are not appropriately dealt with by this appraisal. It is important to deal with the current cohort of patients going through the treatment pathway rather than trying to second guess potential treatment choices in future. It is unfair to patients receiving treatment currently not to receive this technology at 4th line given its clear benefit over pomalidomide.
3. Using the best treatment at 4th line that is available to patients. In current practice patients will receive daratumumab 4th line (CDF) and pomalidomide at 5th line. We know that it is best to combine the anti-

CD38 monoclonal antibodies with an immunomodulatory drug (IMID). Rather than separating these therapies at 4th and 5th line it will have most benefit when we combine our most potent IMID with an anti-CD38 monoclonal antibody at 4th line. Given that there will be a limited number of patients able to receive treatment at 5th line they are being disadvantaged by not receiving the most appropriate combination at 4th line.

4. Applicability for use in the Cancer Drugs Fund. One of the reasons stated for not meeting the Cancer Drug Fund criteria is that most patients will have received an anti-CD38 monoclonal antibody before they get to 4th line. Whilst there will be a large number of patients who will receive daratumumab at 2nd line (in combination with bortezomib and dexamethasone, CDF), there are a sizeable number of patients who will not receive daratumumab at second line (CDF) due to early progression on bortezomib given as initial therapy or who developed significant neurotoxicity and so can't receive this combination at 2nd line. In addition, daratumumab with bortezomib and dexamethasone was only available on the CDF in 2019. There is therefore a large number of patients who have never received an anti-CD38 monoclonal antibody before 4th line. They would gain clear clinical benefit from receiving isatuximab with pomalidomide and dexamethasone. This large group of patients should not be ignored.
5. Isatuximab with pomalidomide and dexamethasone is a step change for patients with relapsed and refractory multiple myeloma. There is clear benefit of an anti-CD38 monoclonal antibody with an

immunomodulatory drug (IMID) which result in the greatest clinical benefit. This technology combines the most potent available IMID, namely pomalidomide with a well-tolerated anti CD38 monoclonal antibody.

6. Subsequent treatment in ICARIA do not reflect NHS clinical practice. Whilst this is a true statement, it is important to note that responses reported are as expected in routine clinical practice. Unfortunately at 5th line and beyond responses and clinical outcomes are poor irrespective of what therapies are given at stage meaning that outcomes reported are generalisable to the population of patients treated in routine NHS practice.

In conclusion, I would be grateful if the committee can reconsider allowing use of isatuximab with pomalidomide and dexamethasone within its marketing authorisation at 4th line in the NHS.

Yours sincerely

Dr Neil Rabin

Consultant Haematologist

University College London Hospital (UCLH)

and the North Middlesex University Hospital

Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma. A Single Technology Appraisal. The ERG's response to the company's response to the ACD.

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Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Matt Stevenson and Aline Navega Biz critiqued the health economic analysis submitted by the company. John Stevens critiqued the statistical analyses provided by the company. Emma Hock critiqued the comparability of new studies identified by the company. All authors were involved in drafting and commenting on the final report.

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1 Background

NICE appraised isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (IsaPd) at an appraisal committee on the 13th of May 2020. This resulted in an Appraisal Consultation Document (ACD) which did not recommend the use of IsaPd for treating relapsed and refractory multiple myeloma in adults who have had at least 2 treatments (including lenalidomide and a proteasome inhibitor) and whose disease has progressed on the last treatment.[1]

On the 26th June 2020, the Evidence Review Group (ERG) received documents, via NICE, from the company (Sanofi) which provided additional analyses and an alternative Patient Access Scheme (PAS).[2] The 62-page comment response, the 76-page Appendices and the revised economic model are collectively referred to as the company's response to the ACD.

The previous PAS was a simple discount of [redacted]% applied to the cost of isatuximab. [redacted] The proposed PAS has not been formally agreed, although the company states that a meeting is scheduled on the [redacted] to discuss the offer.

In this document the ERG summarises the substantive comments raised by the company and, where appropriate, provides a critique of these issues.

2 Comments raised by the company in its response to the ACD

For brevity, the position of the company has been summarised by the ERG. The section headings follow the numbering of the company's comments in its response to the ACD. The first two numbered comments by the company are generic in thanking the committee for recognising the benefits of IsaPd, and signposting what follows in the remaining seven comments. As such, we will only summarise comments 3 to 9 in sections 2.1 to 2.7. The ERG critique is contained in Chapter 3.

2.1 New analyses related to the overall survival models used for pomalidomide plus dexamethasone and IsaPd

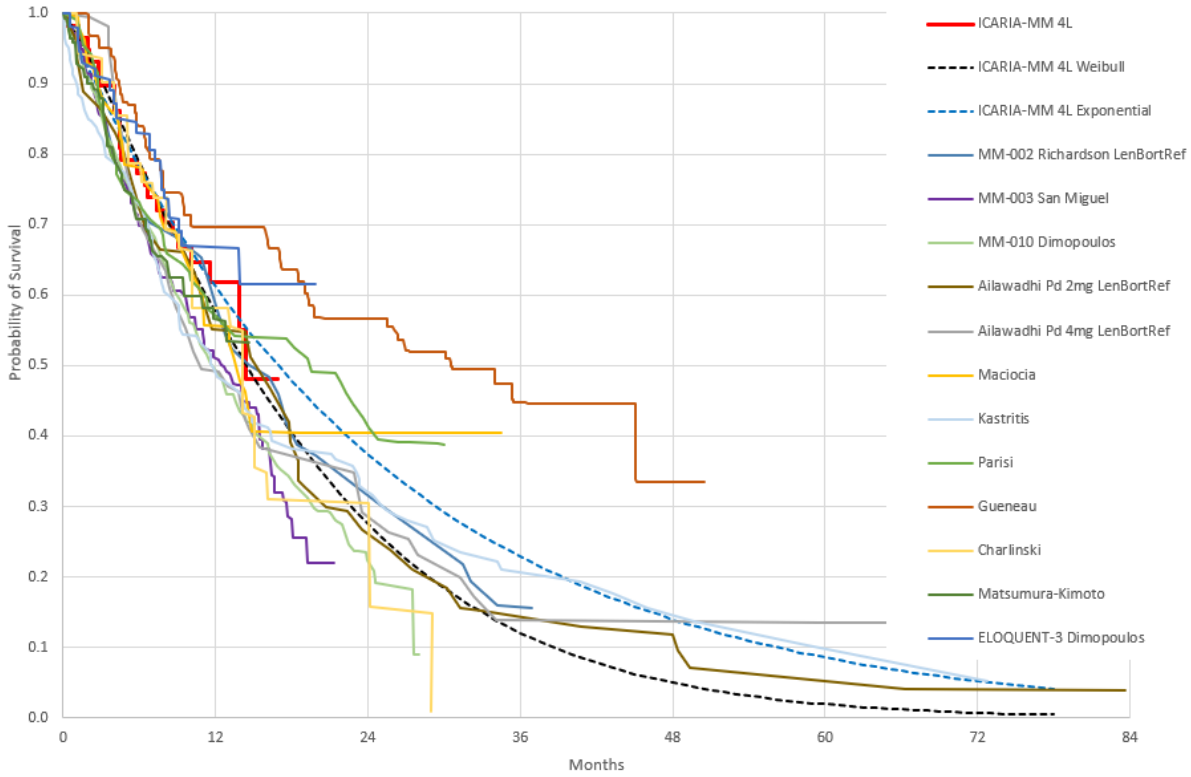
Within the ACD the committee stated that its preference was for Weibull distributions for both pomalidomide plus dexamethasone (Pd) and IsaPd to estimate overall survival (OS). This contrasts with the company's initial submission that preferred the exponential distribution for both Pd and IsaPd. The ERG had commented that the BIC values were similar for the exponential, Weibull and lognormal distributions and had provided analyses for all three acknowledging that there was considerable uncertainty in the long-term estimates for OS.

The company provided additional evidence relating to OS, noting that the data are '*extremely immature*' supporting the committee's use of a Weibull distribution for Pd, but maintaining that an exponential distribution would be more appropriate for IsaPd.

To support the use of a Weibull distribution for Pd OS data the company plotted long-term outcomes from key studies containing Pd. This plot is replicated in Figure 1. Based on this plot, and the evidence of clinical experts at the meeting, and clinical experts spoken to by the company, the company stated that '*we concur with the committee's view that the Weibull estimator may be appropriate for the Pd setting*'.

The company posit that there are reasons to suspect that IsaPd would be associated with longer survival that is better represented by an exponential distribution than a Weibull distribution. Four broad reasons have been provided for this hypothesis: 1) that the duration and depth of response supports longer-term survival projections; 2) that it would be reasonable to expect that triplet therapy containing an anti-CD38 therapy (isatuximab) would improve survival compared with anti-CD38 monotherapy (daratumumab), and that an exponential distribution is the best fit to more mature daratumumab data; 3) that exploratory analyses assuming relationships between progression-free survival (PFS) and OS indicate longer survival; and 4) creation of '*synthetic OS KM data*' where an exponential distribution provides a best fit to these data. The key arguments of each point are summarised below.

Figure 1: Long-term outcomes from Pd studies



2.1.1 Duration and depth of response

The company highlights a recent meta-analysis showing that patients with minimal residual disease (MRD) have better prognosis than those without MRD with a hazard ratio (HR) of 0.30 (95% confidence interval (CI) 0.18 – 0.49).[3] Additionally, patients who respond to daratumumab monotherapy have better median OS compared to those who did not.[4]

The company present data on OS conditional on response status, from fourth-line (4L) patients in ICARIA-MM, some of which are replicated in Table 1. The company highlight the percentage difference in responders between IsaPd ([redacted]) compared with Pd ([redacted]) stating that "*OS for these patients is almost completely unknown and so we believe these results provide clinical evidence to support the rationale that the punitive Weibull extrapolation of overall survival in the economic model is not a reasonable choice for IsaPd*".

Table 1: OS conditional on response status in ICARIA-MM-4L patients

	Pd			IsaPd			
Best Overall Response	N	Events (%)	Median OS (months)	N	Events (%)	Median OS (months)	HR: IsaPd vs Pd (95% CI)
Responders (Partial response or greater)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minimal response or stable disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NC – Non-calculable

2.1.2 Using daratumumab data

Daratumumab, like isatuximab, is an anti-CD38. Daratumumab monotherapy is licensed for use in England through the cancer drugs fund (CDF) supported by data from two studies: SIRIUS and GEN501. More mature OS data are available for daratumumab than for IsaPd in ICARIA-MM, with a median follow up of 36.6 months. The company states that the patients enrolled in GEN501 and SIRIUS are similar to those at 4L in the ICARIA-MM study and have provided a comparison of the baseline patient characteristics from ICARIA-MM (for patients in 4L) pooled patients from GEN501 and SIRIUS[4] in Appendix 3 of the Company's response to the ACD.

The company perform a naive indirect comparison to show that the OS survival function for daratumumab lies between those of Pd and IsaPd and state that "*whilst cross trial comparisons should be treated with caution this indicates that longer term, better outcomes with the triplet based anti-CD38 IsaPd might be expected.*"

The company fit parametric models to the daratumumab survival data with the exponential distribution being the best fit using the Bayesian information criteria (BIC) with the lognormal distribution being the best fit using the Akaike information criteria (AIC).

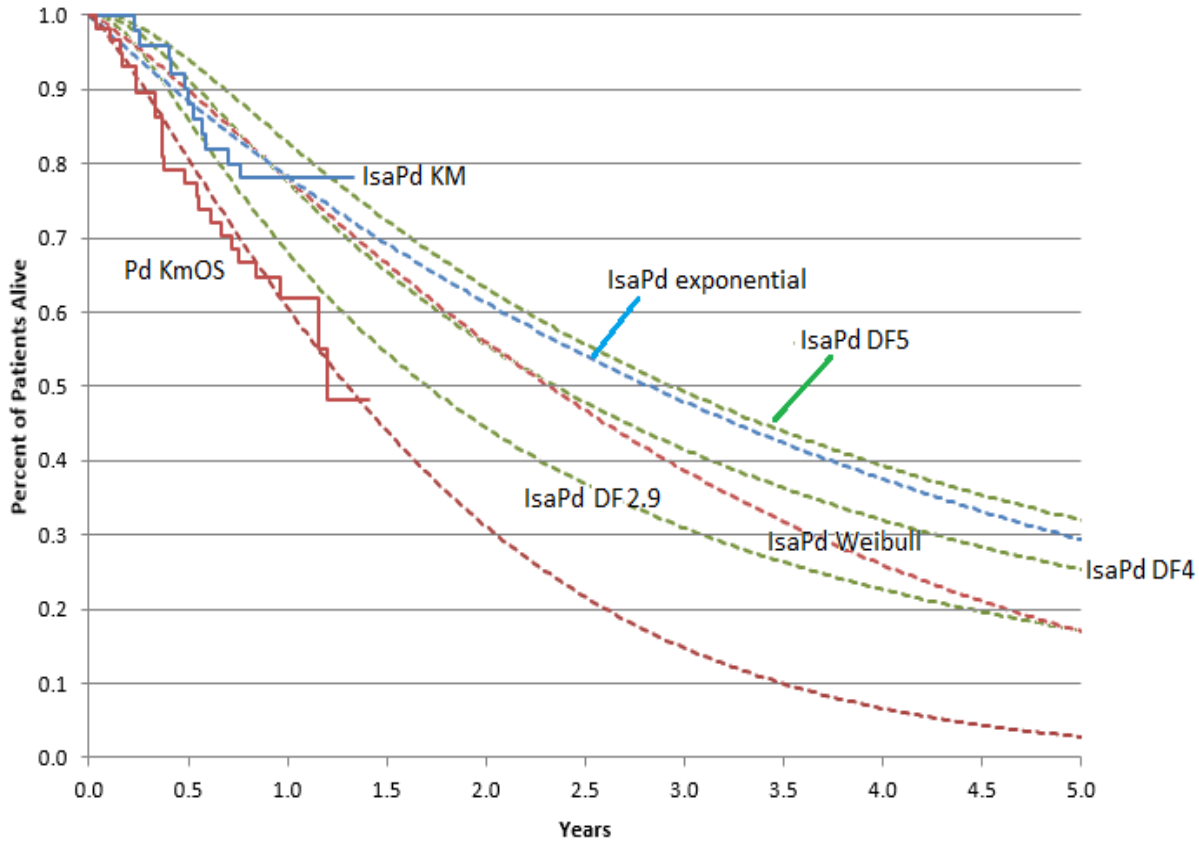
The company provide data on the approximate survival for daratumumab monotherapy at 5 years (~17%) and 10 years (~3%) when using an exponential distribution and compares those with the estimates for IsaPd (17% and 2%) from a Weibull distribution respectively and contends that the Weibull distribution for IsaPd would underestimate OS as "*it is reasonable to anticipate improved overall survival with triplet based anti-CD38 therapy compared to monotherapy anti-CD38 therapy*."

2.1.3 Using PFS as a surrogate for OS

The company considers an alternative method for calculating OS given the highly censored OS data. A pragmatic literature search was undertaken with two papers identified that provide an association between median PFS and median OS in multiple myeloma.[5, 6] The company prefers the Dimopoulos *et al*.[6] paper as it includes relapsed and/or refractory multiple myeloma (RRMM), which is more relevant to the population in the decision problem, and where the ratio of median OS to median PFS was reported to be 2.9, based on 22 randomised controlled trials. Felix *et al*.[5] report a ratio of median OS to median PFS of 1.7 based on 153 studies. In addition to the literature review the company assessed data for daratumumab from the SIRIUS study which gave a ratio of median OS to median PFS of 5.0.

The company applied each ratio of median OS to median PFS to the committee-accepted lognormal distribution for PFS by use of deceleration factors (DF) (1.7; 2.9; and 5.0) to produce lognormal distributions with which to estimate the OS survival function for IsaPd patients. The company comments that the lognormal distribution was one of the better fits to the longer-term daratumumab OS data. A plot of the KM survival functions for OS for both Pd and IsaPd were provided, together with the fitted Weibull survival function used for Pd, an exponential distribution fitted to the IsaPd OS data and the three lognormal survival functions generated by using the DFs. This figure is replicated in Figure 2. The company states that "*DF 1.7 is not a plausible factor as this extrapolation lies well below the exponential (and even below the original committee preferred IsaPd Weibull in the first 5 years). DF 5.0 is derived from the anti-CD38 daratumumab long term data (and so arguably could be the most appropriate to use from a class perspective) but does not follow the observed KM data and provides a fit which may be overly optimistic.*" The DF of 2.9 which came from studies with RRMM patients is shown to be similar to the exponential distribution used by the company in its original submission for estimates over the initial six years with the lognormal distribution having greater survival rates beyond this time point due its decreasing hazard.

Figure 2: The estimates of OS from analyses using PFS as a surrogate of OS

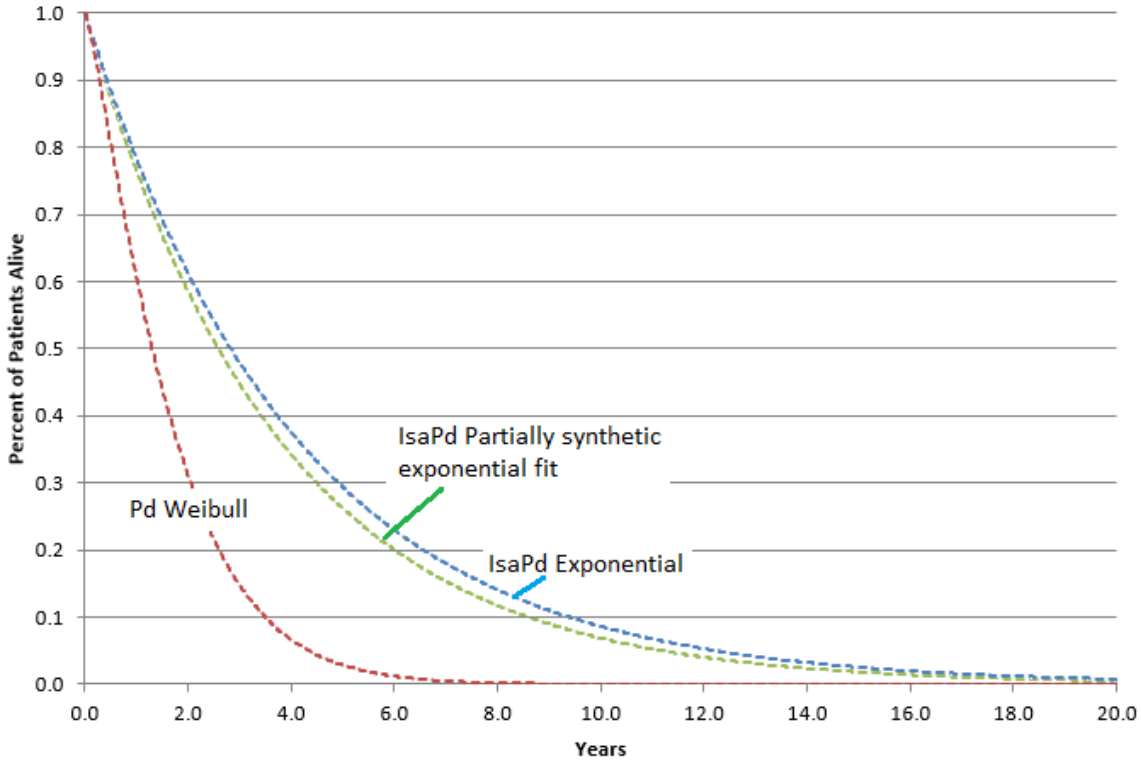


2.1.4 Creation of synthetic KM OS data

Having noted that the DF of 2.9 provided plausible results the company undertook further analyses using observed PFS and OS data where both events occurred, using the relationship between OS and PFS to estimate OS events where a PFS event had occurred and leaving both PFS and OS censored if there was no PFS event. The resulting output was called 'synthetic KM data' by the company. The best fitting distribution to the synthetic KM data, based on BIC was an exponential, although all bar the generalised F distribution had similar values. The Weibull distribution appeared to provide a similar fit to the exponential distribution. The company report the goodness-of-fit statistics relating to the synthetic KM data in Appendix 4 of its response to the ACD.

The company plotted the Weibull survival function fitted to the Pd OS data, the exponential survival function fitted to the IsaPd OS data, and the exponential survival function fitted to the synthetic KM data. This has been reproduced in Figure 3. It is seen that the exponential survival function fitted to the synthetic KM data is similar to that fitted to the full ICARIA-MM 4L patient population who received IsaPd.

Figure 3: The estimate of OS from the synthetic KM OS data



2.2 Multiple modes of action of IsaPd and the potential to extend overall survival and the impact of subsequent treatments

The company provides detail on the mechanisms of action associated with anti-CD38 therapies and how these are believed to benefit the patient by relieving immunosuppression and triggering anti-multiple myeloma immunity. Further, the company point to the synergistic benefits when an anti-CD38 therapy is used in combination with an immunomodulatory drug, such as pomalidomide.[7] The company states that '*this is likely to provide benefits much beyond the duration of treatment with IsaPd*' and supports the use of alternative estimates of OS detailed in Section 2.1

Comment 4 of the company's response to the ACD also discusses the impact of subsequent treatments in ICARIA-MM. agreeing that these '*do not reflect UK clinical practise with respect to daratumumab monotherapy and lenalidomide use following 4L treatment.*' Citing clinical advice that fifth-line

treatments would likely be ineffective the company states a preference for an analysis that includes the costs and benefits for subsequent therapies without adjustment.

The company states that its understanding was that the Appraisal Committee accepted its previous analysis applying a HR to data produced for Pd from an inverse probability of censoring weights approach. The company have provided further detail on the covariates used and the range of weights estimated.

Additionally, as directed by the committee, the company reconstructed individual patient data from the weighted panel data set and fitted parametric models to both the IsaPd and the Pd arm. The company states that the results produced are counter-intuitive with survival being slightly higher when the counterfactual is estimated for patients not receiving either daratumumab or lenalidomide which the company acknowledges could be due to "*unmeasured factors that are associated with receipt of daratumumab or lenalidomide and survival*". The company states that '*given the lack of clinical face validity of this approach, it was not considered feasible to implement in the model.*'

2.3 Analyses relating to the committee's preferred scenario

The ACD stated that none of the company's or the ERG's analyses reflected the committee's preferences, which were detailed. The committee's preferences were: the use of a Weibull distribution to estimate both IsaPd and Pd OS adjustments for subsequent treatments not used in the NHS along with details on the methods used; using drug wastage and relative dose intensity from the company's base case; and including a waning of the relative treatment effect for IsaPd compared with Pd following discontinuation of isatuximab, such that hazards were equal for people surviving a long time after cessation of isatuximab treatment.

The company has performed an analysis to take these points into consideration although it implemented a waning treatment effect by setting the HR to 1 when approximately 90% of patients in the IsaPd arm had discontinued treatment, which was at 3 years. The company comments that when a waning treatment effect is applied to the IsaPd Weibull distribution that < 2% of patients are alive at 10 years which is significant less than that associated with daratumumab monotherapy (~11%). The company did not remove the costs of daratumumab and lenalidomide when adjusting for subsequent treatments as it did in its response to the technical engagement.

2.4 Challenges presented by the combined use of branded interventions

The company states that '*The current system (including the NICE process and methods) is not sufficiently flexible to cope with the assessment of branded combination treatments and therefore does not sufficiently recognise their value*'. The company notes that the price of isatuximab at which IsaPd

is cost-effective is constrained by the price of pomalidomide, which has a confidential PAS, '*but resulted in a recommendation from NICE very close to the WTP for EoL drugs*.' The company declares that under the committee's preferred scenario (see Section 2,3) that isatuximab cannot meet the NICE threshold for cost-effectiveness.

The company provides analyses showing the impact on the incremental cost effectiveness ratio (ICER) when employing two alternative methods for incorporating the price of Pd. The first approach includes the costs of Pd in the IsaPd arm only when the Pd costs have stopped in the Pd arm, which is only considering the excess Pd costs in the IsaPd arm. The second approach sets the costs of Pd in the IsaPd arm to that of the Pd arm.

The company conclude its response by stating that "*we are concerned that despite the high unmet need demonstrated through EAMS, the strong clinical data from ICARIA-MM and the clear patient preference for life extending medicines at the end of life that people with RRMM will be denied access to a highly effective, life extending medicine because there isn't an innovative process to assess branded combinations.*"

2.5 The potential for IsaPd to be included in the CDF

The appraisal committee did not believe that IsaPd was a candidate for the CDF although acknowledged that further data collection may reduce uncertainties in the evidence. In Comment 7 the company reiterate that the data from ICARIA-MM are immature and that further results from the study are anticipated in [redacted], with a final OS analysis expected between [redacted]. The company also states that data on the effectiveness of IsaPd in third-line would also become more mature, that more data on subsequent treatments would become available, that treatment duration time would have further data and that data from an English context would be generated.

In the ACD the committee determined that the amount of data collected on IsaPd at 4L would be limited by the use of daratumumab (another anti-CD38 therapy) as a second-line treatment. The company cites a NICE position paper that states that "*products recommended for use in the CDF should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals*."[8]

2.6 Unmet need for new third-line treatments in multiple myeloma

In the ACD it is stated that there is an unmet need for new, effective third-line (3L) options. Although clinical experts stated that position IsaPd at 4L was appropriate the committee concluded that it would

welcome evidence for IsaPd at 3L. The company maintain that clinicians believe that the current unmet need is at 4L and highlight a rapid uptake of IsaPd at 4L in the Early Access Medicine Scheme (EAMS) ([redacted] patients in 5 months). Data is presented on the use of lenalidomide, which is a pre-requisite for IsaPd treatment; these show that lenalidomide is predominantly used at 3L or later.

However, as patients at 3L may be eligible for IsaPd the company conducted cost-effectiveness analyses of IsaPd comparing with Pd using ICARIA-MM data, and with PanVd using a matching-adjusted indirect comparison (MAIC). Due to the limitations of the MAIC, the company highlights that the comparison with PanVd should be considered exploratory, and may not be relevant as clinical experts at the appraisal committee stated that PanVd would be used at fifth-line, as market research undertaken by the company (Figure 10 of the company's response to the ACD) show little, or no, use of PanVd at 3L.

The company believes that it NICE's end of life criteria may be met in 3L, as patients who had lenalidomide prior to 3L patients could be double refractory to both a proteasome inhibitor and an immunomodulatory agent. The company states that "*The OS data for the ICARIA-MM 3L Pd arm is immature, but it reasonable to assume based on the curves it may not extend beyond 2 years.*" The company also states that if IsaPd were to be recommended in the CDF then uncertainty in efficacy data could be reduced. The company did not provide results for IsaPd vs Pd in its response to the ACD.

2.7 Innovative nature of IsaPd

The committee believed that any innovative nature of IsaPd was adequately captured in the company's model. In its response the company did not agree that "*further benefits from treatment with IsaPd would not be realised in real world clinical practice. These may not be captured in the QALY but are nonetheless of critical importance to patients.*" The company states that '*the element of hope should be particularly taken into account during the decision-making process for this appraisal*' stating that there is a strong preference amongst cancer patients to take a hopeful gamble over an option with a narrower spread of outcomes.[9]

The company also detail that there would be reductions in the health-related quality of life of carers, with carers often being older people with potential health issues themselves. The company contend that '*for the purposes of this appraisal it should be a significant part of the deliberative decision-making process*'.

2.8 Results produced by the company

The probabilistic results produced by the company for key scenarios are shown in Table 2 when a PAS of [redacted] is used and in Table 3 when a PAS of [redacted] is used. More details are provided in the company's response to the ACD.

Table 2: Key probabilistic results produced by the company assuming a [redacted] PAS discount

Scenario	Inc Costs (£)	Inc QALYs	Cost per QALY gained (£)
Company's interpretation of Committee's base case	117,207	0.539	217,505
Company's base case	123,573	1.393	88,698
Using DF of 2.9†	124,311	1.545	80,474
Using the partially synthetic IsaPd KM	122,547	1.182	103,717
Removing the costs of Pd Approach 1 (deterministic)♪	[redacted]	[redacted]	[redacted]
Removing the costs of Pd Approach 2 (deterministic)♪	[redacted]	[redacted]	[redacted]
Company's base case for 3L population (IsaPd vs Pd)††	[redacted]	[redacted]	[redacted]

Inc – incremental; QALY - quality-adjusted life year

† The model produced a slightly different answer to that reported in the company's response to the ACD.

†† Analyses run by ERG.

♪ Not presented in the company's response to the ACD.

Table 3: Key probabilistic results produced by the company assuming a [redacted] PAS discount

Scenario	Inc Costs (£)	Inc QALYs	Cost per QALY gained (£)
Company's interpretation of Committee's base case	[redacted]	[redacted]	[redacted]
Company's base case	[redacted]	[redacted]	[redacted]
Using DF of 2.9†	[redacted]	[redacted]	[redacted]
Using the partially synthetic IsaPd KM	[redacted]	[redacted]	[redacted]††
Removing the costs of Pd Approach 1 (deterministic)†	[redacted]	[redacted]	[redacted]
Removing the costs of Pd Approach 2 (deterministic)†	[redacted]	[redacted]	[redacted]
Company's base case for 3L population (IsaPd vs Pd)†††	[redacted]	[redacted]	[redacted]

Inc – incremental; QALY - quality-adjusted life year

† *The model produced a slightly different answer to that reported in the company's response to the ACD.*

†† *Corrected typographical error in the company's response to the ACD.*

††† *Analyses run by ERG*

3 ERG critique of the company's response to the ACD

The subsections in this section correspond to those in Section 2.

3.1 New analyses related to the overall survival models used for Pd and IsaPd

The ERG compared the Pd arms considered in Figure 1 with the ICARIA-MM study. A greater proportion of the ICARIA-MM 4L Pd arm patients had an ECOG of 0 at baseline (51.7%) than in MM-02 (28%), MM-03 (36.4%) and Ailawadhi *et al*.[10] (37.1%) studies, and a greater proportion of patients with an ECOG or 0 or 1 (91.4%) than in the Parisi *et al*. (48.6%) and the Charlinski *et al*.[11] study (68.0%). A smaller proportion of the ICARIA-MM 4L Pd arm patients had an ECOG of 1 (39.7%) or 2 (8.6%) at baseline than in the MM-02 study (60% and 12%, for ECOG of 1 and 2, respectively), the MM-03 study (45.7% and 17.2%, respectively) and the Ailawadhi *et al*. 2018 study (51.4% and 11.4%, respectively), and a smaller proportion of patients with an ECOG of 2 than the Parisi *et al*. 2019 study (38.1%) and an ECOG of 2 or 3 than the Charlinski *et al*. study (32.0%; no patients had an ECOG of 3 in the ICARIA-MM study). This suggests that there was a greater proportion of patients with more impairment in most of the other Pd studies, compared with the ICARIA-MM study 4L patients, which may impact on long-term prognosis.

Compared with the Pd arms considered in Figure 1, the ICARIA-MM 4L Pd arm patients had a lower median number of previous lines of therapy (3.0) at baseline than patients in the MM-02 study (5.0), the MM-03 study (5.0), the Dimopolous *et al*.[12] (5.0), the Ailawadhi *et al*. study (6.0) and the Matsumura-Kimoto *et al*.[13] study (4.0). Again, this may suggest that patients in most of the other Pd studies may have a worse prognosis over the longer-term than the ICARIA-MM 4L study Pd arm patients.

Other than ICARIA-MM, only the MM-03 study and the Kastritis *et al*.[14] study reported subsequent therapies. Neither of these studies reported subsequent use of daratumumab, thalidomide or lenalidomide. A smaller proportion of patients in the Kastritis *et al*. study had subsequent carfilzomib (7%) than patients in the Pd arm of ICARIA-MM at 4L (21.43%), and a smaller proportion of patients in the MM-03 study had subsequent pomalidomide (0.3%) than patients in the Pd arm of ICARIA-MM at 4L (7.14%). There are no other notable differences in subsequent therapies where the subsequent therapies were reported among the Pd arms of all three studies. Some subsequent therapies were not reported for ICARIA-MM, but were reported among patients in the MM-03 study, including cyclophosphamide and dexamethasone, and likewise, some subsequent therapies not reported for ICARIA-MM were reported among patients in the Kastritis *et al*. study, including IMiD and PI, other monoclonal antibodies than daratumumab, and conventional chemotherapy. Given that the ICARIA-MM study is the only study where subsequent CD-38 therapy has been reported, it is possible that

patients in the Pd arm of the ICARIA-MM study (at 4L) have a slightly better longer-term prognosis than those in the other Pd study.

The data presented are inconclusive regarding the best distribution to model OS and therefore there is no reason to dispute the opinion of the clinical experts that attended the appraisal committee that the hazard for those on Pd is increasing. The ERG notes that these clinical experts were unlikely to be as familiar with IsaPd OS as with Pd OS, and that it is reasonable for distributions used to model survival data to be different according to the treatment because of differences in the mechanism of action of treatments.

Patients are heterogeneous and follow survival functions according to differences in risk factors. The aim of a survival analysis is to identify a survival function that is a reasonable representation of the average (i.e. marginal) survival function ignoring heterogeneity between patients or averaging over the distribution of risk factors in the population. Six of the ten models used by the company to model OS data are members of the Generalised F distribution family. The company is presenting an argument to support its assertion that that the marginal survival function for the IsaPd OS data is reasonably represented by an exponential distribution. There are two particular features of an exponential distribution that are notable:

- An exponential distribution assumes that the average hazard of death is constant across the lifetime of patients
- An exponential distribution also arises as a mixture of Weibull distributions with fixed shape parameter, $\nu > 1$.[15]

Hence, the company is asserting that either: 1) the marginal risk of death ignoring all relevant risk factors is constant over the lifetime of patients such that the shape parameter of the Weibull distribution is one with probability one, or 2) there are groups of patients with common shape parameter but different scale parameters in whom the marginal risk of death is increasing over time.

The company acknowledges that the evidence from ICARIA-MM is *immature* so that estimates of survival functions and mean OS for IsaPd and Pd will be uncertain. The company presents several arguments and supporting analyses for an alternative model for the IsaPd OS data but accepts the ACs preferred model for Pd. In general, the company has made assertions about the choice of model for IsaPd based on the 'expected' survival function with no account taken of uncertainty; no information is provided about parameter estimates or the range of likely values that are consistent with the sample data. The company presented KM OS survival functions from 12 published studies of Pd to support the assertion that a Weibull distribution best represents Pd OS data (Figure 1). However, the company did

not fit any parametric models to these data and did not provide any supporting evidence that the data-generating process is a Weibull distribution for each study.

The ERG does not consider that it is reasonable to assert with probability one that parameters take particular values *and* that a model is the true model. Furthermore, the company has not presented any evidence to show that there are groups of patients with common shape parameter but different scale parameters in whom the marginal risk of death is increasing over time.

3.1.1 Duration and depth of response

The ERG could not identify the data reported by the company; Munshi *et al*.[3] report that in patients with a complete response the presence of minimal residual disease was associated with a shorter PFS compared with those without minimal residual disease – HR 0.44 (CI 0.34 – 0.56).

The company stated that "*in the ICARIA-MM trial MRD status was only recorded for a small number of patients who achieved a stringent complete response (SCR) or a complete response (CR) (14 patients in the IsaPd arm and 2 patients in the Pd arm*)." The ERG accepts that PFS and OS may differ according to best overall response and MRD status, although the evidence from ICARIA-MM is uncertain. Similarly, the effect of IsaPd relative to Pd may be greater in patients defined as responders and as having minimal response or stable disease compared to patients with progressive disease, although the evidence from ICARIA-MM is uncertain (Table 1).

The company asserted that PFS and OS events in the earlier months of ICARIA-MM are mainly in patients with less than partial response and patients with partial response or better will have events later. The ERG suggests that this would be consistent with a higher hazard rate at the beginning of the study as patients with poor prognosis dies and a decreasing hazard rate as an increasing proportion of patients with partial response or better remain at risk.

The company presented OS data conditional on response status in Table 1.Whilst there was no statistically significant difference in HRs when interaction between response level, treatment effect and the treatment effect by response level interaction were considered (p=0.39) there appeared to be a trend to show increased median survival for those with better response and a trend for a lower percentage of patients with better response level to have an OS event which could support the hypothesis of longer survival in those with better response.

3.1.2 Using daratumumab data

The ERG agrees that there are no large differences in the patient characteristics between the 4L patients from ICARIA-MM and the pooled GEN501 and SIRIUS patients, although there are some differences on some characteristics. The pooled patient population of GEN501 and SIRIUS appears to be younger than the ICARIA-MM 4L population, in particular than the IsaPd arm, with a lower proportion of patients aged ≥75 years (11% [GEN501 and SIRIUS] vs. 37.9% [ICARIA-MM 4L Pd] and 50.0% [ICARIA-MM 4L IsaPd]) and a lower proportion of patients aged 65-74 years (35% [GEN501 and SIRIUS] vs. 15.5% [ICARIA-MM 4L Pd] and 13.5% [ICARIA-MM 4L IsaPd]). The proportion of male patients in the pooled GEN501 and SIRIUS study data (47%) is comparable with the ICARIA-MM 4L Pd arm patients (46.6%), but slightly lower than in the ICARIA-MM 4L IsaPd arm (57.7%). A greater proportion of the pooled GEN501/SIRIUS patients had an ECOG of 1 (66%) compared with the ICARIA-MM 4L Pd (39.7%) and IsaPd (48.1%) arms, with a lower proportion having an ECOG of 2 (7%, 8.6% and 11.5%, respectively) and a lower proportion with an ECOG of 0 (28%, 51.7% and 40.4%, respectively). The pooled GEN501/SIRIUS patients had received more lines of therapy (median of 5.0 lines) than patients in the Pd and IsaPd arms of ICARIA-MM 4L (both with a median of 3.0 lines). The GEN501 and SIRIUS studies are reasonably similar to the ICARIA-MM study, with a similar treatment schedule, although the GEN501 and SIRIUS studies recruited patients at 4L and later, whereas ICARIA-MM recruited patients at 3L and later.

In terms of subsequent therapies, as noted in the ERG report, a much greater proportion of the ICARIA-MM 4L patients in the Pd arm received subsequent daratumumab (38.10%) than in the IsaPd arm (7.14%), and subsequent daratumumab was not reported for the GEN501 and SIRIUS pooled patients. A greater proportion of the GEN501 and SIRIUS pooled patients received subsequent pomalidomide (33.8%) and carfilzomib (28.4%) than among the ICARIA-MM 4L Pd arm (7.14% for pomalidomide and 21.43% for carfilzomib) and IsaPd arm patients (7.14% for pomalidomide and 17.86% for carfilzomib). A similar proportion of the GEN501 and SIRIUS pooled patients (24.3%) and the ICARIA-MM 4L IsaPd arm patients (25.0%) received subsequent bortezomib, which was a greater proportion than among the of ICARIA-MM 4L Pd arm patients (16.67%).

It is reasonable to suppose that the data-generating process of treatments of the same class follow the same underlying model, although with study-specific parameter values that reflect the mix of patients in a study. Daratumumab monotherapy is the only other anti-CD38 therapy available currently at 4L, and the company utilised evidence from a pooled analysis of two single arm pivotal studies, SIRIUS (106 patients) and GEN501, (42 patients in part 2) reporting outcomes based on a median follow-up of

36.6 months. The company cautions against making inferences using unadjusted, arm-based comparisons of the pooled data from SIRIUS and GEN501. The ERG similarly cautions against making inferences based on pooling data from different studies. Indeed, given that the objective was to assess whether treatments of the same class follow the same underlying model, the ERG would prefer to see an assessment of the exchangeability of evidence from SIRIUS and GEN501 separately with respect to a preferred model.

The company asserts that patients entering the daratumumab studies GEN501 and SIRIUS are similar to those in ICARIA-MM 4L, although the ERG does not necessarily consider that this is relevant for the purpose of identifying a plausible model according to a class of treatments. Information to support the choice of model to represent the pooled SIRIUS and GEN501 data is presented in the company's Appendix 8. The ERG considers that a visual inspection of the empirical hazard function (company's response to the ACD Appendix 8, Page 88) suggests a decreasing rather than constant hazard. While information criterion (AIC/AICc/BIC) only provide an assessment of the extent to which a model fits the observed data and not how to choose between models with respect to their extrapolated survival functions, there is no material difference between the BIC values for the exponential, lognormal and log-logistic distributions. As usual different information criterion reach different conclusions and they suggest that a range of models reasonably represents the observed data. The empirical and fitted hazard functions are presented in the company's response to the ACD Appendix 8 (Pages 95-96). The ERG notes that the Gompertz distribution is implausible on the basis that it suggests that the shape parameter is negative which would mean that some patients tend to immortality. The fitted Weibull hazard function does suggest that the shape parameter, ν, is close to but less than one over the observed period but seems to generate a hazard function that does not appear to follow the empirical hazard function. Of the three models with the lowest BIC, the ERG prefers the log-logistic distribution, which appears to be consistent with a shape parameter β greater than one; no information is provided concerning the uncertainty about parameter estimates. As stated previously, the ERG would like to see evidence that the models are consistent across the SIRIUS and GEN50 data.

The empirical hazard function for IsaPd from ICARIA-MM (CS, Appendix K.1.3) was similar to the empirical hazard function of the pooled SIRIUS and GEN501 data over a comparable period. Hence, the ERG sees no reason to assume that the hazard function for IsaPd is constant over the lifetime of patients, although the exponential distribution is believed to be preferable to a Weibull distribution with an increasing hazard as the ERG does not believe the hazard is increasing. The ERG has also conducted analyses using a lognormal distribution for IsaPd OS as this could not be ruled out based on the data available.

The ERG believes, however, that if a different distribution is used for IsaPd OS than for Pd OS then it is not appropriate to continue to use the jointly-fitted Weibull distribution for Pd and that the independent Weibull distribution should be used. The ERG has explored the impact of using independent distributions in sensitivity analyses.

3.1.3 Using PFS as a surrogate for OS

The ERG acknowledges that PFS is correlated with OS within patients. However, unlike with continuously distributed multivariate data, there are no formal multivariate distributions with which to analyse time-to-event data and it is necessary to resort to statistical modelling to allow for correlation. The company used two alternative approaches to model the relationship between PFS and OS.

The company presented the results of two meta-analyses estimating the relationship between median PFS and median OS[5, 6] and estimated the ratio of median PFS to median OS using data from SIRIUS[16], GEN501 and the pooled data from SIRIUS and GEN501.[4] Felix[5] did not include treatment in the anti-CD38 class and the company considered results from this meta-analysis in a sensitivity analysis. The ERG notes that the report of the Dimopoulos meta-analysis is an abstract of a workshop and not a paper in a peer reviewed journal. The ERG notes that the ratio of median PFS to median OS is itself an uncertain parameter. However, no information is provided about the relationship by treatment class, the heterogeneity in the ratio of median PFS to median OS between studies, or the predictive distribution of the ratio of median PFS to median OS in a new treatment class or in a new study. The company asserts that the published evidence suggests that the ratios of median PFS to median OS may lie between 1.7 and 5.0, and has used 1.7[5], 2.9[6]s] and 5.0[16] in scenario analyses. The ERG notes that these estimates ignore uncertainty about their true values. The company uses these point estimates in two ways to estimate the IsaPd OS survival function from evidence about PFS.

The company stated that, "*the most straightforward way to predict OS for IsaPd from PFS data is to apply a deceleration factor (DF) to the committee agreed PFS distribution for IsaPd which was the lognormal*." The ERG notes that the median of a lognormal distribution is the mean on the log-scale [i.e. $\text{Med}_{OS} = exp\,(\mu_{os})$ and $\text{Med}_{PFS} = exp(\mu_{PFS})$] so that knowledge of the ratio provides information only about the location parameter of the OS distribution function. The ERG assumes that the company has used the same shape parameter as estimated for PFS, which may not be appropriate. The company presents a case for the most plausible ratio on the basis of how well the estimated OS survival function represents the OS KM survival function without considering uncertainty associated with both estimates. Of particular concern is that the sample OS data from ICARIA-MM is not included in the analysis. The ERG suggests that a better use of the sample data and external information would

be through a proper Bayesian analysis in which the external information is used to formulate a prior distribution for the ratio of medians that is updated using the sample evidence from the study.

3.1.4 Creation of synthetic OS data

The company generated a partially synthetic OS Kaplan-Meir survival function using observed event times for patients who died and imputed event times for those who were censored. Imputed event times were generated by multiplying the observed PFS times by the ratio of median PFS to median OS (i.e. 2.9). Patients with an imputed OS event time who experienced a PFS event were assumed to experience an OS event at the imputed time, whereas patients with an imputed OS time who were censored for PFS were censored at the imputed OS time.

This approach does make use of the observed OS data for patients who have an event. However, as before, the process ignores uncertainty in the scaling factor. The ERG's preferred approach is one that models relationships between population parameters rather than one that adjusts data and assumes it to be observed.

The company stated that an exponential distribution best represented the 'synthetic' data, although based on BIC (company's response to ACD Appendix 4) there was little to choose between exponential, lognormal, generalised gamma and 'restricted cubic spine Weibull' distributions.

3.2 Multiple modes of action IsaPd and the potential to extend overall survival and the impact of subsequent treatments

The ERG believes that the analyses undertaken by the company as detailed in Section 2.1 and critiqued in Section 3.1 take into consideration the potential benefits associated with multiple modes of action associated with IsaPd.

The ERG believes that the company's position is contradictory as it suggests that fifth-line treatments are likely to be ineffective but prefers to use unadjusted costs and benefits for subsequent therapies, including expensive treatments not recommended in England. Removing the costs of subsequent treatments not recommended would appear more consistent. The ERG explored this scenario in sensitivity analyses.

The EGR notes that it is not necessary to use hazard ratios when adjusting for subsequent treatments. It is possible that the use of a hazard ratio to adjust for subsequent treatments is generating what the company believes to be counter-intuitive results. It is also possible that subsequent treatments are having minimal effect on survival post-4L and that while the adjusted survival functions suggest improved survival, there is also greater uncertainty associated with the adjusted results.

3.3 Analyses relating to the committee's preferred scenario

The ERG notes that in the company's revised base case survival models were fitted separately to each treatment arm in the treatment effect is not constant and there is already the potential for a waning treatment effect. It would have been helpful if the company had reported the appropriate measure of relative treatment effect over the lifetime of patients to allow an assessment of whether and when the models predict a waning treatment effect.

The ERG believes that the committee intended the costs of daratumumab and lenalidomide to be removed from the company's analysis as these interventions are not recommended in England after 4L.

3.4 Challenges presented by the combined use of branded interventions

As this relates to NICE's process the ERG has no comment to make on this issue, bar stating that there is no dispensation in the NICE methods guide to provide additional QALY weights where these are generated by more than one branded intervention.[17]

3.5 The potential for IsaPd to be included in the CDF

The ERG believes that this question is primarily for the appraisal committee discussion but makes the following observations. Firstly, that it the ICARIA-MM study is due to provide results in the relatively near future then uncertainty can be reduced without resort to the CDF, particularly as patients newly treated would likely also have immature survival data during the CDF period.

Secondly, the NICE position paper on interventions that have gone into the CDF[8] does not explicitly cover a situation where the potential recruitment of patients for an intervention considered for the CDF is impacted on by an intervention already in the CDF. It does state that CDF interventions should neither be comparators nor included in a treatment sequence, which has been adhered to by the appraisal committee.

3.6 Unmet need for new 3L treatments in multiple myeloma

The ERG agrees with the company that the comparison of IsaPd with PanVd in 3L is redundant as the committee decided that PanVd was not used until after 4L in England.

Whilst the company did not provide a comparison of IsaPd vs Pd at 3L this could be run within the model. However, the analysis indicated that Pd dominated IsaPd, which the ERG believes is not credible. The ERG did not have time to fully check the modelling undertaken by the company.

The company states that IsaPd may meet the end of life criteria, although the ERG is sceptical of this claim, as data from Pd at 3L, presented in Figure 11 of the company's response to the ACD shows a probability of survival of approximately 80% after 7 months, and of over 70% at 15 months. The ERG acknowledges that there are no deaths in the Pd arm after about 10.5 months and that the number of patients at risk is small so that events cause a steep step in the KM survival function, but believes that average survival would be in excess of 2 years. The estimated survival time at 3L for patients receiving Pd in the company's model was [redacted] years.

3.7 Innovative nature of IsaPd

The ERG comments that the company does not discuss the likely loss of hope or increased carer burden associated with treatments that would be displaced from routine commissioning if IsaPd was to receive a positive recommendation from NICE. As such, the net impact on societal health, which could be negative, is unknown. It is also not known to what extent increased hope may be captured within the anxiety and depression dimension of the EQ-5D.

3.8 Results produced by the company

The ERG replicated the results provided by the company. However, the ERG believes that the appraisal committee intended that the costs of daratumumab and lenalidomide should be removed when the adjustment was undertaken. Accordingly, the ERG has re-run the committee's preferred assumptions removing the costs of daratumumab and lenalidomide.

In the company's base case, the costs of daratumumab and lenalidomide were also maintained. The ERG ran analyses removing these costs, but were unable to adjust the survival data, as the HR produced by the company could not be applied to the Weibull distribution for Pd OS whilst maintaining an exponential distribution for IsaPd OS. Although this represents a limitation, the ERG notes that the HR did not change significantly when daratumumab and lenalidomide were removed [redacted] and thus, the analysis provides an indicative ICER.

The ERG also believes that it is more appropriate to use the independent Weibull distribution for Pd OS than the jointly-fitted Weibull distribution. The ERG also believes that results using an independent lognormal distribution for IsaPd OS may be informative to the committee.

4 Analyses undertaken by the ERG

The ERG could not run all of its desired sensitivity analyses. The model produced an error when using an independent lognormal distribution for IsaPd OS in PSA, and also the results in PSA when using an independent Weibull distribution for Pd OS in PSA were the same as when a jointly-fitted Weibull distribution was used, despite the deterministic results being different. These limitations were discovered too near to the report deadline to allow the company time to resolve these.

To indicate the impact of using an independent lognormal distribution for IsaPd and an independent Weibull distribution for Pd, deterministic results have been presented in Table 4 ([redacted] PAS) and Table 5 ([redacted] PAS). This provides information to the committee on which to make inferences on the probabilistic results. Probabilistic results are shown in Table 6 (using a PAS discount of [redacted]) and in Table 7 (using a PAS discount of [redacted]).

Table 4: Exploratory deterministic results produced by the ERG assuming a [redacted] PAS discount

Scenario	Inc Costs (£)	Inc QALYs	Cost per QALY gained (£)
Company's interpretation of Committee's base case	111,355	0.531	209,730
ERG's interpretation of Committee's base case	133,357	0.531	251,169
Company's base case (exponential for IsaPd OS, jointly-fitted Weibull for Pd OS)	113,837	1.309	86,984
Company's base case removing the costs of daratumumab and lenalidomide	135,839	1.309	103,796
Company's base case but using an independent Weibull for Pd OS and removing the costs of daratumumab and lenalidomide	135,704	1.266	107,219
Company's base case but using a lognormal for IsaPd OS and using independent Weibull for Pd OS and removing the costs of daratumumab and lenalidomide.	135,958	1.344	101,136

Inc – incremental; QALY - quality-adjusted life year

Table 5: Exploratory deterministic results produced by the ERG assuming a [redacted] PAS discount

Scenario	Inc Costs (£)	Inc QALYs	Cost per QALY gained (£)
Company's interpretation of Committee's base case	[redacted]	[redacted]	[redacted]
ERG's interpretation of Committee's base case	[redacted]	[redacted]	[redacted]
Company's base case (exponential for IsaPd OS, jointly-fitted Weibull for Pd OS)	[redacted]	[redacted]	[redacted]
Company's base case removing the costs of daratumumab and lenalidomide	[redacted]	[redacted]	[redacted]
Company's base case but using an independent Weibull for Pd OS and removing the costs of daratumumab and lenalidomide	[redacted]	[redacted]	[redacted]
Company's base case but using a lognormal for IsaPd OS and using independent Weibull for Pd OS and removing the costs of daratumumab and lenalidomide.	[redacted]	[redacted]	[redacted]

Inc – incremental; QALY - quality-adjusted life year

Table 6: Exploratory probabilistic results produced by the ERG assuming a [redacted] PAS discount

Scenario	Inc Costs (£)	Inc QALYs	Cost per QALY gained (£)
ERG's interpretation of Committee's base case	140,296	0.539	260,352
Company's base case removing the costs of daratumumab and lenalidomide.	146,662	1.393	105,271

Inc – incremental; QALY - quality-adjusted life year

Table 7: Exploratory probabilistic results produced by the ERG assuming a [redacted] PAS discount

Scenario	Inc Costs (£)	Inc QALYs	Cost per QALY gained (£)
ERG's interpretation of Committee's base case	[redacted]	[redacted]	[redacted]
Company's base case removing the costs of daratumumab and lenalidomide.	[redacted]	[redacted]	[redacted]

Inc – incremental; QALY - quality-adjusted life year

5 Discussion

The company responded to the ACD with additional analyses of the data from ICARIA-MM and supporting evidence from studies of Pd and daratumumab (another anti-CD38 intervention). Given the additional evidence, in particular longer follow-up of patients treated with daratumumab in SIRIUS and GEN50, the ERG believes that, if the choice for the distribution to represent IsaPd OS was between an exponential or a Weibull distribution, then an exponential distribution would be preferred as the hazard is unlikely to be increasing over time. The ERG also comments that a lognormal distribution could not be ruled out on the basis that the hazard might be decreasing as sicker patients die early leaving those at lower risk of death and has presented results using this distribution too, although these results could only be calculated deterministically due to the model producing an error when run probabilistically.

The company's base case maintained a jointly-fitted Weibull distribution for Pd survival despite using an exponential distribution for IsaPd OS. The ERG believes this is inappropriate and has provided results using an independently-fitted Weibull distribution for Pd OS, although these results could only be calculated deterministically as when run probabilistically the independently fitted Weibull produced the same results as the jointly-fitted Weibull indicating an error.

There were differences in the company's and the ERG's interpretation of the Appraisal Committee's base case related to whether the costs of daratumumab and lenalidomide should be included. If these costs are removed the ICER for IsaPd increases compared to Pd.

The probabilistic cost per QALY gained changes according to the assumed distribution used to estimate OS for IsaPd. Without considering PAS for interventions other than isatuximab the ICER assuming a [redacted] PAS is estimated by the ERG to be £105,271 using an exponential distribution for IsaPd OS. Using a Weibull distribution markedly increases the ICER, whilst the use of a lognormal distribution decreases the ICER. When using a PAS of [redacted] the ICERs when using an exponential distribution for IsaPd OS is [redacted]. If the subsequent costs of daratumumab and lenalidomide are included in the analyses then the ICER becomes more favourable to IsaPd, being £88,698 using a PAS of [redacted] and [redacted] when using a PAS of [redacted]. These ICERs will be slightly higher if an independently fitted Weibull is used for Pd survival rather than a jointly-fitted Weibull.

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