NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

Contents:

The following documents are made available to consultees and commentators:

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

2. **Comments on the Appraisal Consultation Document from Bristol-Myers Squibb Pharmaceuticals**
   - **Company response**
   - **Company response appendices**

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Evidence Review Group critique of company comments on the ACD**
   - **ERG ACD response critique**
   - **ERG ACD response critique addendum**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Appraisal title

Single Technology Appraisal

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

Type of stakeholder:

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 Social Care 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 document (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 and Social Care, 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.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Unknown	Not applicable	This was once a disease of men in industry which undoubtedly will be hitting its peak. You consultation hasn't addressed the issue now being seen in hospitals of women and younger people in general presenting with this disease. The demographic is changing.	Thank you for the comments. . The committee noted that this disease is no longer restricted to men working in industry and the Final Appraisal Document (FAD) notes "*although mesothelioma was once a disease of men in industry, it is also now being seen in women and younger people."* And *"The committee concluded that malignant pleural mesothelioma is an aggressive disease with a poor prognosis and there is an unmet need for new treatment options."*
2	Patient	Not applicable	I'm a female 56-year-old mesothelioma patient. I'm a wife and mother of an 18-year-old. Having survived breast cancer at age 29 I was given 6-8 months to live in June 2020 in the midst of The Covid pandemic. In this situation when you are told there are basically no treatment options it is difficult to put into words how it feels. Your life is over through no fault of your own. At this point you are faced with truths that are very difficult to bear. I didn't knowingly expose myself to asbestos. I never worked in heavy industry. What was once a predominately older man's disease is now affecting people just like me and younger. I don't believe this disease has peaked, although for the older male industrial workers it probably has. There are a new generation of much younger mesothelioma patients coming through. This is something that should provoke thought. To give a patient a glimmer of hope that their life may be extended and even have good quality for a period of time is a powerful thing. For those of us who have mesothelioma the importance of having some options for treatment are a lifeline of hope. It could provide a precious gift of time. Please think carefully on your decision. We all deserve a chance of a future	

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3	Patient group	Gruppo Italiano Mesothelioma	**Has all of the relevant evidence been taken into account?** We do not think so . The extreme Survival Fragility Index and the heavy Censoring rate heavily affects the results shown in the intervention arm . The survival of pats on Ipi/Nivo does not top that of other trials (i.e Chemo/Bevacizumab) and shows a very mild superiority in non epithelial when compared to Chemo alone. Unfortunately the censoring rate in the control arm of IPI/Nivo disallows to conclude for any superiority in this subset of patients either. Full Results on preparation and available in strict confidentiality **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** No they are not. This is a brief breakdown: the estimated drug cost for Cisplatin/Pemetrexed $46,225 for six cycles whereas the US patent on bevacizumab expired in 2019 and the drug's European patent expires in 2022. On the other hand the combined cost for Ipilimumab/Nivolumab is approximately $153,800 for four cycles The analysis of the data provided in the trial does not justify the high cost of the Ipi/Nivo **Are the recommendations sound and a suitable basis for guidance to the NHS?** At the moment we have no evidence enough to recommend IPI/Nivo for any subtype of Meso Remind the strictly confidential full analysis in preparation for submission is available for your perusal and considerations **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?** No	Thank you for your comments. NICE considers all evidence and statements submitted by the company and relevant stakeholders during the appraisal process. Please refer to the FAD for details on how these were considered by the committee.
4	Unknown	University of Hull	**Has all of the relevant evidence been taken into account?** No the national mesothelioma audit 2020 has not been included and this is pertinent as it shows 40% received sact The committee have not considered the fact that more and more patients are accessing immunotherapy through legal means i.e. suing those companies that exposed patients to asbestos for the cost of treatment. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The comparison with registry data is not justified as this will included PS 3 and 4 patients where as the trial does not, thereby skewing the survival.	Thank you for the comments. NICE considers all relevant evidence and statements submitted by the company and stakeholders during the appraisal process. Please refer to section 3.3 of the FAD for details on how these were considered by the committee.

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			The comments about PDL1 are spurious as many tumour sites have initiated such measurements when immunotherapy has been introduced into practice. **Are the recommendations sound and a suitable basis for guidance to the NHS?** no **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?**	Based on the evidence available, nivolumab plus ipilimumab is recommended, within its market authorisation, for untreated unresectable malignant pleural mesothelioma in adults and with ECOG status of 0 or 1. This recommendation applies to all adult patients with the condition and with ECOG status of 0 or 1. Supply and source of the medication in practice is beyond the remit of NICE committee so cannot be addressed by NICE recommendation.
5	Unknown	Unknown	In the last paragraph under why the committee made the recommendations, there is a sentence that states 'because its cost effectiveness is uncertain, it is not recommended for routine use in the NHS.' but then in the last sentence in the paragraph it states 'Nivolumab plus ipilimumab does not meet the criteria to be considered for the Cancer Drugs Fund because it currently does not have the potential to be cost effective.' It's a bit confusing reading that cost-effectiveness is uncertain then going on to read that it does not have the potential to be cost effective. Suggest for some consistency here	Thank you for your comment. The current FAD concludes "*The committee concluded that it could recommend nivolumab plus ipilimumab for treatment of malignant pleural mesothelioma, within its marketing authorisation."*
7	Company	Bristol Myers Squibb	Section 3.7. Second-line treatments used in Checkmate 743 do not reflect UK clinical practice We agree with the ERG and appraisal committee that current second line treatments for MPM are not established due to a lack of relevant guidelines, no standard of care therapy and the recent use of nivolumab monotherapy as a second line treatment during the COVID-19 pandemic. Moreover, we agree that adjusting overall survival for second-line immunotherapies would better reflect the difference between nivolumab plus ipilimumab and chemotherapy. We have performed a treatment switching analysis using the new 3-year database lock data cut in which the chemotherapy arm OS data have been adjusted to account for patients that switch to second-line immunotherapies. Full details of the analysis are presented in Appendix C. The cost-effectiveness results were explored using two methods for adjusting for treatment switching (Appendix C, section 3.7). The revised base case ICER using the 3-year database lock (Appendix B, Table	

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			10) reduced from £75,322 to [redacted] and [redacted] using the IPCW and two-stage methods, respectively. Please note, there is also a typographical error in Section 3.7 on page 10 where the fact that 24% of patients received vinorelbine second line is stated twice.	
8			Section 3.8. Nivolumab plus ipilimumab improves overall survival compared with chemotherapy, but its effect may be overestimated This section of the ACD concludes that "nivolumab plus ipilimumab reduces the risk of death in people with malignant pleural mesothelioma compared with chemotherapy, but that the interim trial analysis may have overestimated the magnitude of this difference", this statement is not supported and based on the evidence we present here we consider it inaccurate. In the ACD, it is stated that "overall survival with chemotherapy was around 20% at 3 years on the Kaplan–Meier curve of the trial data. This is much higher than the 8% to 10% survival at 3 years from UK registry and UK audit data" and note that changes in mesothelioma management may explain this difference. However, this would also suggest the current efficacy benefit of nivolumab + ipilimumab is currently underestimated versus UK practice. The ACD later states that "The committee also recognised that early results from trials that report benefit are likely to overestimate the treatment effect of the drug under investigation." We are unaware of any evidence to support this statement; indeed, prior trials of IO therapies have consistently shown that early analyses underestimate the survival benefit of IO therapies – due to the delayed effect vs. chemotherapy and the longer-term survival benefit in some patients. Antonia et al. (2019) reported a pooled analysis of four trials of nivolumab in previously treated non-small cell lung cancer (NSCLC; CheckMate 017, 057, 063 and 003) when a minimum of four-years follow-up were available. Across all four studies, OS benefits with nivolumab were maintained with this additional long-term data. Borghaei et al. (2021) have now published 5-year follow-up data for CheckMate-017 and -057 and nivolumab continues to demonstrate a survival benefit versus docetaxel, exhibiting a 5-times greater OS rate (Five-year pooled OS rate of 13.4% for nivolumab-treated patients vs. 2.6% for docetaxel-treated patients (Figure 1). This clearly shows that the anticipated benefit of nivolumab based on the early results has been sustained or improved through 5-years of follow-up. Rothwell et al. (2020) use the example of nivolumab in the second line treatment of NSCLC as a case study of the impact of uncertainty in survival on HTA decision-making in the UK and demonstrate that in this case, the early clinical data under-estimated the long-term OS benefit that became apparent following additional follow-up in the Cancer Drugs Fund. Figure 1. Overall survival of all treated patients in the pooled CheckMate-017 and 057 trials at the 5-year database lock	Thank you for your comment and for providing the longer term data from Checkmate743. Please see section xx in the FAD for how these were considered by the committee.

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			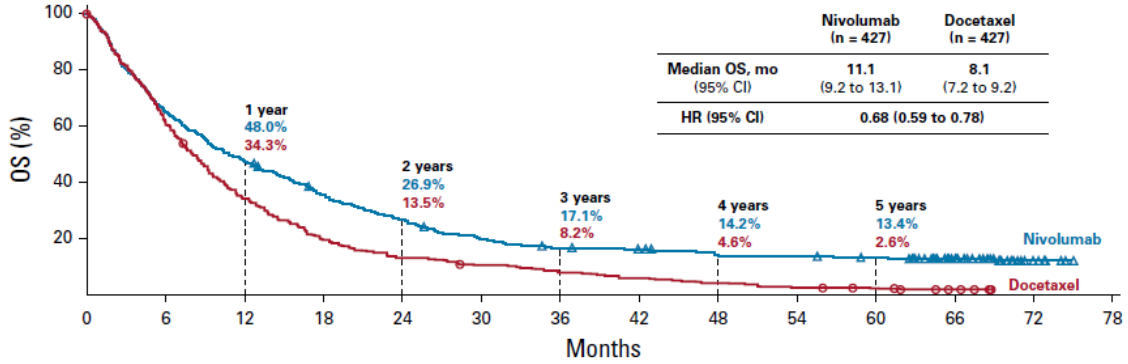 Source: Borghaei et al. (2021) Based on this, the statement in the ACD “nivolumab plus ipilimumab reduces the risk of death in people with malignant pleural mesothelioma compared with chemotherapy, but that the interim trial analysis may have overestimated the magnitude of this difference” is not supported by evidence. In section 3.24 of the ACD, the committee note that further evidence on the long-term effect of nivolumab plus ipilimumab is required. Longer term data from CheckMate-743 are now available and are presented in Appendix A, these demonstrate consistent hazard-ratios for OS with this additional follow-up vs. that presented in our submission. There is a continuing OS benefit for patients treated with nivolumab + ipilimumab vs. those treated with chemotherapy, however additional follow-up, such as in the CDF, would further reduce uncertainty. Updated survival analyses based on this data cut has been conducted and outcome of these analyses are presented in Appendix B.	
9			Section 3.9. Nivolumab plus ipilimumab had no impact on progression-free survival We agree that there are limitations with PFS as an outcome measure in MPM. However, since the committee note in Section 3.24 that further evidence is required, the longer-term data now available are presented in Appendix A. These data show that with longer follow-up (minimum of 35.5 months vs 22.1 months in the analysis in the original submission), a PFS benefit for nivolumab + ipilimumab is beginning to become apparent. Furthermore, patients treated with nivolumab + ipilimumab demonstrate a durable response with 28% of responders treated with nivolumab + ipilimumab remaining in response compared with none of those treated with chemotherapy. It is likely that this continued response in the nivolumab + ipilimumab arm will translate into further PFS and OS benefits as follow-up continues.	Thank you for your comment. Please see section 3.9 of the FAD.
10			Section 3.10. The effect of nivolumab plus ipilimumab compared with chemotherapy may be modified by	Thank you for this comment.

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			histological subtype In Appendix D we provide further analyses for histology subgroups. Nonetheless, BMS maintain that given the high unmet need, consistent efficacy of nivolumab + ipilimumab across histologies, and lack of alternative treatments in this indication, the use of nivolumab + ipilimumab should not be limited by histology. There remain issues with histological subtyping in MPM, as the tumours are heterogeneous in nature, and, in clinical practice, histological subtype can be a broad spectrum that is hard to define. Evidence shows that the plasticity of tumour cells means that epithelioid cells can mutate to sarcomatoid cells within the tumour over time and biphasic disease can be misdiagnosed as epithelioid. Indeed, clinicians advise that samples from different areas may have different histology and tumours may also evolve over time. Therefore, histology should not be used in clinical decision-making. In terms of nivolumab + ipilimumab, the CheckMate-743 trial was not powered to assess efficacy by histology subgroups, therefore any differences seen may be due to chance and should not drive treatment decisions. Furthermore, as treatment options are so limited, there is a need for new effective treatments for all patients with MPM, regardless of histology. In CheckMate-743 an OS benefit was observed in epithelioid and non-epithelioid subgroups, with similar median OS for nivolumab + ipilimumab in both histology subgroups. The treatment effect of nivolumab + ipilimumab versus PDC was more pronounced in the non-epithelioid subgroup (HR, 0.46) than in the epithelioid subgroup (HR, 0.86) at the original analysis, and this was maintained in the latest data cut presented in Appendix A. The results of the cost-effectiveness analyses by histology subgroup should always be interpreted in the context of these uncertainties. Any selection strategy by histology in this population would likely be associated with significant opportunity costs, particularly in terms of foregone health benefits of patients that could benefit from efficient treatment.	Please see section 3.10 of the FAD for how the evidence was considered by the committee.
11			Section 3.14. A 2-year stopping rule for nivolumab plus ipilimumab and a 6-cycle stopping rule for chemotherapy is appropriate We are pleased that the appraisal committee agreed that the stopping rule is appropriate. However, we disagree with the point made that “protocol violations related to the 2-year stopping rule in the trial means that the results may overestimate the treatment effect of nivolumab plus ipilimumab”. In the CheckMate-743 trial, two patients remained on therapy after 24 months. However, assessment of the time-to-treatment discontinuation data suggests that they did not receive additional doses but a short delay in their final dose, likely due to scheduling/logistics. No patients received nivolumab or ipilimumab beyond month 26. Therefore, the impact of this in terms of efficacy would be negligible.	Thank you for your comment,
			Section 3.15. The model structure is acceptable, but the extrapolations are uncertain We agree that there is uncertainty in the survival extrapolations, but the new clinical data with additional follow-up and subsequent survival analyses presented in Appendix B help to reduce that uncertainty; additional follow-up during a period in the CDF would address this concern further. Furthermore, the accrual of progression-free life years after the trial is often seen with immuno-oncology therapies, where PFS is below chemotherapy initially but has a long-term benefit for responders. As noted in response to comment 3 above,	Thank you for your comment. Please see section 3.16 and section 3.19 for committee’s considerations on these.

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			the most recent data cut with minimum 3-year follow-up demonstrates continued PFS and DoR in patients treated with nivolumab + ipilimumab.	
			Section 3.16. Using a log-logistic distribution to extrapolate overall survival for both treatments is appropriate When applied to the PDC arm data, the log-logistic distribution results in clinically implausible long-term survival predictions. As previously presented, the clinicians consulted specifically stated that the predicted long-term survival with the log-logistic distribution is too optimistic. It is also important to note that the selection of spline models was not primarily motivated by the within trial fit, as the ACD seems to insinuate. On the contrary, the spline 2-knots normal distribution was primarily selected based on the plausibility of its long-term survival predictions. As such, BMS consider that the spline 2-knots normal distribution is a both statistically and clinically plausible model.	Thank you for your comment. Section 3.18 of the FAD states *"The committee concluded that the log-logistic distribution was appropriate for extrapolating overall survival in both arms, but that how long the treatment effect would continue in the long term was somewhat uncertain."*
			Section 3.17. The extrapolated progression-free survival is uncertain As noted in response 3 we agree that there are limitations with PFS as an outcome measure in MPM and that there will always be uncertainties related to immature data. However, the additional data now available (presented in Appendix A) shows that nivolumab + ipilimumab continues to show a long-term benefit compared with PDC and reduces some of the uncertainty related to PFS benefits.	Thank you for your comment. Please see section 3.19 of the FAD. "
			Section 3.18. Continued treatment benefit up to 5 years is acceptable BMS maintain the argument that adjustment at an arbitrary 5-year timepoint results in an unfounded and clinically implausible change in the hazard for the long-term survivors. Continued benefit of nivolumab plus ipilimumab over 5 years is likely based on observations from other immunotherapy trials and populations with long-term follow-up close to or exceeding 5 years, such as CheckMate-017 and -057 described above (Borghaei et al., 2021), CheckMate-065 (Wolchok et al., 2021) and CheckMate 227 (Paz-Ares et al., 2021). In the ACD it is stated that "It noted that the company based its argument on expert opinion, but it was not clear how the company chose the expert or elicited the expert's opinion." The clinical experts we consulted were selected based on their expertise, knowledge and experience in MPM. As MPM is a rare condition, it is treated by a few specialists at large oncology centres in the UK.	Thank you for your comment. The FAD states *"The ERG considered it appropriate to assume that the treatment effect would wane 5 years after treatment starts and 3 years after treatment stops. It acknowledged that this duration was arbitrary, but had been accepted in other NICE technology appraisals, including nivolumab for treating recurrent or metastatic squamous cell carcinoma of the head and neck after platinum-based chemotherapy. During its first meeting, the committee also noted the evidence presented by the company in their response to clarification questions, which suggested that the treatment effect of immunotherapies is maintained for up to 4 years in non-small-cell lung cancer (Antonia et al.*

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				2019). However, the Cancer Drugs Fund clinical lead noted that some tumours treated with immunotherapies relapsed. The committee considered that there appeared to be a continuing benefit after stopping treatment, but it was unclear how long it would last, therefore it would be reasonable to assume some treatment effect waning."
			Section 3.20. The company's modelling of second-line treatments may underestimate the cost-effectiveness estimate for nivolumab plus ipilimumab As noted in Comment 1, as part of a reanalysis of the trial data provided in Appendix C we include an analysis in which the clinical results are adjusted for second-line treatments. This better reflects the difference between nivolumab + ipilimumab and chemotherapy and results in an improved OS benefit for nivolumab + ipilimumab vs chemotherapy (reduced hazard ratio) and a reduced ICER. The cost-effectiveness results were explored using two methods for adjusting for treatment switching (Appendix C, section 3.7). The revised base case ICER using the 3-year database lock (Appendix B, Table 10) reduced from £75,322 to [redacted] and [redacted] using the IPCW and two-stage methods, respectively.	Thank you for your comment. Please see the response to comment 1.
			Section 3.21. Nivolumab plus ipilimumab is likely to meet the end of life criteria We agree with the committee's conclusion that nivolumab plus ipilimumab in this indication meets end of life criteria. We also agree that there is some uncertainty about the current OS benefit seen in patients of different histological sub-types. A period in the CDF and the collection of data via the SACT during this time would provide additional real-world evidence on subtypes and therefore reduce this uncertainty.	Thank you for your comment. Please see section 3.24 of the FAD.

NICE National Institute for Health and Care Excellence

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

Consultation on the appraisal consultation document – deadline for comments 5pm on Monday 20 September. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Bristol Myers Squibb
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	Eleni Theodorou

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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.
	Thank you for giving us the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. We are disappointed with the Committee's draft recommendation as nivolumab + ipilimumab is an effective treatment option that has the potential to improve outcomes for patients with untreated unresectable mesothelioma (MPM). In this rare, highly aggressive disease in which no new treatments have been licensed since 2009, and no other trials have shown a clinically meaningful improvement in OS, the statistically and clinically meaningful survival benefit is of great importance to patients and their families. Specific comments are detailed below.
1	**Section 3.7. Second-line treatments used in Checkmate 743 do not reflect UK clinical practice** We agree with the ERG and appraisal committee that current second line treatments for MPM are not established due to a lack of relevant guidelines, no standard of care therapy and the recent use of nivolumab monotherapy as a second line treatment during the COVID-19 pandemic. Moreover, we agree that adjusting overall survival for second-line immunotherapies would better reflect the difference between nivolumab plus ipilimumab and chemotherapy. We have performed a treatment switching analysis using the new 3-year database lock data cut in which the chemotherapy arm OS data have been adjusted to account for patients that switch to second-line immunotherapies. Full details of the analysis are presented in Appendix C. The cost-effectiveness results were explored using two methods for adjusting for treatment switching (Appendix C, section 3.7). The revised base case ICER using the 3-year database lock (Appendix B, Table 10) reduced from £75,322 to [redacted] and [redacted] using the IPCW and two-stage methods, respectively. Please note, there is also a typographical error in Section 3.7 on page 10 where the fact that 24% of patients received vinorelbine second line is stated twice.
2	**Section 3.8. Nivolumab plus ipilimumab improves overall survival compared with chemotherapy, but its effect may be overestimated** This section of the ACD concludes that "nivolumab plus ipilimumab reduces the risk of death in people with malignant pleural mesothelioma compared with chemotherapy, but that the interim trial analysis may have overestimated the magnitude of this difference", this statement is not supported and based on the evidence we present here we consider it inaccurate. In the ACD, it is stated that "overall survival with chemotherapy was around 20% at 3 years on the Kaplan–Meier curve of the trial data. This is much higher than the 8% to 10% survival at 3 years from UK registry and UK audit data" and note that changes in mesothelioma management may explain this difference. However, this would also suggest the current efficacy benefit of nivolumab + ipilimumab is currently underestimated versus UK practice. The ACD later states that "The committee also recognised that early results from trials that report benefit are likely to overestimate the treatment effect of the drug under investigation." We are unaware of any evidence to support this statement; indeed, prior trials of IO therapies have consistently shown that early analyses underestimate the survival benefit of IO therapies – due to the delayed effect vs. chemotherapy and the longer-term survival benefit in some patients.

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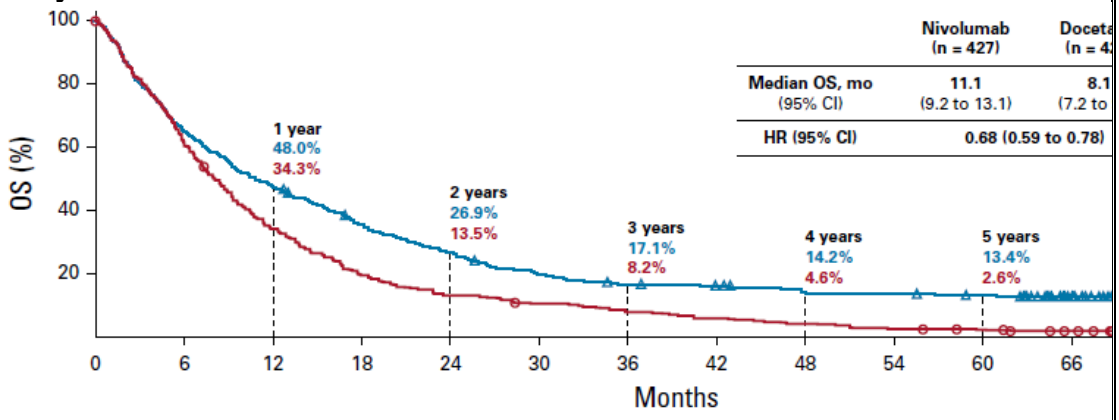
	Antonia et al. (2019) reported a pooled analysis of four trials of nivolumab in previously treated non-small cell lung cancer (NSCLC; CheckMate 017, 057, 063 and 003) when a minimum of four-years follow-up were available. Across all four studies, OS benefits with nivolumab were maintained with this additional long-term data. Borghaei et al. (2021) have now published 5-year follow-up data for CheckMate-017 and -057 and nivolumab continues to demonstrate a survival benefit versus docetaxel, exhibiting a 5-times greater OS rate (Five-year pooled OS rate of 13.4% for nivolumab-treated patients vs. 2.6% for docetaxel-treated patients (Figure 1). This clearly shows that the anticipated benefit of nivolumab based on the early results has been sustained or improved through 5-years of follow-up. Rothwell et al. (2020) use the example of nivolumab in the second line treatment of NSCLC as a case study of the impact of uncertainty in survival on HTA decision-making in the UK and demonstrate that in this case, the early clinical data under-estimated the long-term OS benefit that became apparent following additional follow-up in the Cancer Drugs Fund. **Figure 1. Overall survival of all treated patients in the pooled CheckMate-017 and 057 trials at the 5-year database lock**  **No. of patients at risk** Nivolumab 427 280 205 150 113 84 70 64 55 54 50 30 Docetaxel 427 264 145 84 57 45 34 26 19 12 9 4 Source: Borghaei et al. (2021) Based on this, the statement in the ACD “nivolumab plus ipilimumab reduces the risk of death in people with malignant pleural mesothelioma compared with chemotherapy, but that the interim trial analysis may have overestimated the magnitude of this difference” is not supported by evidence. In section 3.24 of the ACD, the committee note that further evidence on the long-term effect of nivolumab plus ipilimumab is required. Longer term data from CheckMate-743 are now available and are presented in Appendix A, these demonstrate consistent hazard-ratios for OS with this additional follow-up vs. that presented in our submission. There is a continuing OS benefit for patients treated with nivolumab + ipilimumab vs. those treated with chemotherapy, however additional follow-up, such as in the CDF, would further reduce uncertainty. Updated survival analyses based on this data cut has been conducted and outcome of these analyses are presented in Appendix B.
3	**Section 3.9. Nivolumab plus ipilimumab had no impact on progression-free survival** We agree that there are limitations with PFS as an outcome measure in MPM. However, since the committee note in Section 3.24 that further evidence is required, the longer-term data now available are presented in Appendix A.

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Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

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	These data show that with longer follow-up (minimum of 35.5 months vs 22.1 months in the analysis in the original submission), a PFS benefit for nivolumab + ipilimumab is beginning to become apparent. Furthermore, patients treated with nivolumab + ipilimumab demonstrate a durable response with 28% of responders treated with nivolumab + ipilimumab remaining in response compared with none of those treated with chemotherapy. It is likely that this continued response in the nivolumab + ipilimumab arm will translate into further PFS and OS benefits as follow-up continues.
4	**Section 3.10. The effect of nivolumab plus ipilimumab compared with chemotherapy may be modified by histological subtype** In Appendix D we provide further analyses for histology subgroups. Nonetheless, BMS maintain that given the high unmet need, consistent efficacy of nivolumab + ipilimumab across histologies, and lack of alternative treatments in this indication, the use of nivolumab + ipilimumab should not be limited by histology. There remain issues with histological subtyping in MPM, as the tumours are heterogeneous in nature, and, in clinical practice, histological subtype can be a broad spectrum that is hard to define. Evidence shows that the plasticity of tumour cells means that epithelioid cells can mutate to sarcomatoid cells within the tumour over time and biphasic disease can be misdiagnosed as epithelioid. Indeed, clinicians advise that samples from different areas may have different histology and tumours may also evolve over time. Therefore, histology should not be used in clinical decision-making. In terms of nivolumab + ipilimumab, the CheckMate-743 trial was not powered to assess efficacy by histology subgroups, therefore any differences seen may be due to chance and should not drive treatment decisions. Furthermore, as treatment options are so limited, there is a need for new effective treatments for all patients with MPM, regardless of histology. In CheckMate-743 an OS benefit was observed in epithelioid and non-epithelioid subgroups, with similar median OS for nivolumab + ipilimumab in both histology subgroups. The treatment effect of nivolumab + ipilimumab versus PDC was more pronounced in the non-epithelioid subgroup (HR, 0.46) than in the epithelioid subgroup (HR, 0.86) at the original analysis, and this was maintained in the latest data cut presented in Appendix A. The results of the cost-effectiveness analyses by histology subgroup should always be interpreted in the context of these uncertainties. Any selection strategy by histology in this population would likely be associated with significant opportunity costs, particularly in terms of foregone health benefits of patients that could benefit from efficient treatment.
5	**Section 3.14. A 2-year stopping rule for nivolumab plus ipilimumab and a 6-cycle stopping rule for chemotherapy is appropriate** We are pleased that the appraisal committee agreed that the stopping rule is appropriate. However, we disagree with the point made that "protocol violations related to the 2-year stopping rule in the trial means that the results may overestimate the treatment effect of nivolumab plus ipilimumab". In the CheckMate-743 trial, two patients remained on therapy after 24 months. However, assessment of the time-to-treatment discontinuation data suggests that they did not receive additional doses but a short delay in their final dose, likely due to scheduling/logistics. No patients received nivolumab or ipilimumab beyond month 26. Therefore, the impact of this in terms of efficacy would be negligible.
6	**Section 3.15. The model structure is acceptable, but the extrapolations are uncertain** We agree that there is uncertainty in the survival extrapolations, but the new clinical data with additional follow-up and subsequent survival analyses presented in Appendix B help to reduce that uncertainty; additional follow-up during a period in the CDF would address this concern further. Furthermore, the accrual of progression-free life years after the trial is often seen with

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	immuno-oncology therapies, where PFS is below chemotherapy initially but has a long-term benefit for responders. As noted in response to comment 3 above, the most recent data cut with minimum 3-year follow-up demonstrates continued PFS and DoR in patients treated with nivolumab + ipilimumab.
7	**Section 3.16. Using a log-logistic distribution to extrapolate overall survival for both treatments is appropriate** When applied to the PDC arm data, the log-logistic distribution results in clinically implausible long-term survival predictions. As previously presented, the clinicians consulted specifically stated that the predicted long-term survival with the log-logistic distribution is too optimistic. It is also important to note that the selection of spline models was not primarily motivated by the within trial fit, as the ACD seems to insinuate. On the contrary, the spline 2-knots normal distribution was primarily selected based on the plausibility of its long-term survival predictions. As such, BMS consider that the spline 2-knots normal distribution is a both statistically and clinically plausible model.
8	**Section 3.17. The extrapolated progression-free survival is uncertain** As noted in response 3 we agree that there are limitations with PFS as an outcome measure in MPM and that there will always be uncertainties related to immature data. However, the additional data now available (presented in Appendix A) shows that nivolumab + ipilimumab continues to show a long-term benefit compared with PDC and reduces some of the uncertainty related to PFS benefits.
9	**Section 3.18. Continued treatment benefit up to 5 years is acceptable** BMS maintain the argument that adjustment at an arbitrary 5-year timepoint results in an unfounded and clinically implausible change in the hazard for the long-term survivors. Continued benefit of nivolumab plus ipilimumab over 5 years is likely based on observations from other immunotherapy trials and populations with long-term follow-up close to or exceeding 5 years, such as CheckMate-017 and -057 described above (Borghaei et al., 2021), CheckMate-065 (Wolchok et al., 2021) and CheckMate 227 (Paz-Ares et al., 2021). In the ACD it is stated that “It noted that the company based its argument on expert opinion, but it was not clear how the company chose the expert or elicited the expert’s opinion.” The clinical experts we consulted were selected based on their expertise, knowledge and experience in MPM. As MPM is a rare condition, it is treated by a few specialists at large oncology centres in the UK.
10	**Section 3.20. The company’s modelling of second-line treatments may underestimate the cost-effectiveness estimate for nivolumab plus ipilimumab** As noted in Comment 1, as part of a reanalysis of the trial data provided in Appendix C we include an analysis in which the clinical results are adjusted for second-line treatments. This better reflects the difference between nivolumab + ipilimumab and chemotherapy and results in an improved OS benefit for nivolumab + ipilimumab vs chemotherapy (reduced hazard ratio) and a reduced ICER. The cost-effectiveness results were explored using two methods for adjusting for treatment switching (Appendix C, section 3.7). The revised base case ICER using the 3-year database lock (Appendix B, Table 10) reduced from £75,322 to [redacted] and [redacted] using the IPCW and two-stage methods, respectively.
11	**Section 3.21. Nivolumab plus ipilimumab is likely to meet the end of life criteria** We agree with the committee’s conclusion that nivolumab plus ipilimumab in this indication meets end of life criteria. We also agree that there is some uncertainty about the current OS benefit seen in patients of different histological sub-types. A period in the CDF and the collection

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	of data via the SACT during this time would provide additional real-world evidence on subtypes and therefore reduce this uncertainty.

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1 APPENDIX A. CHECKMATE 743: 3-YEAR UPDATE

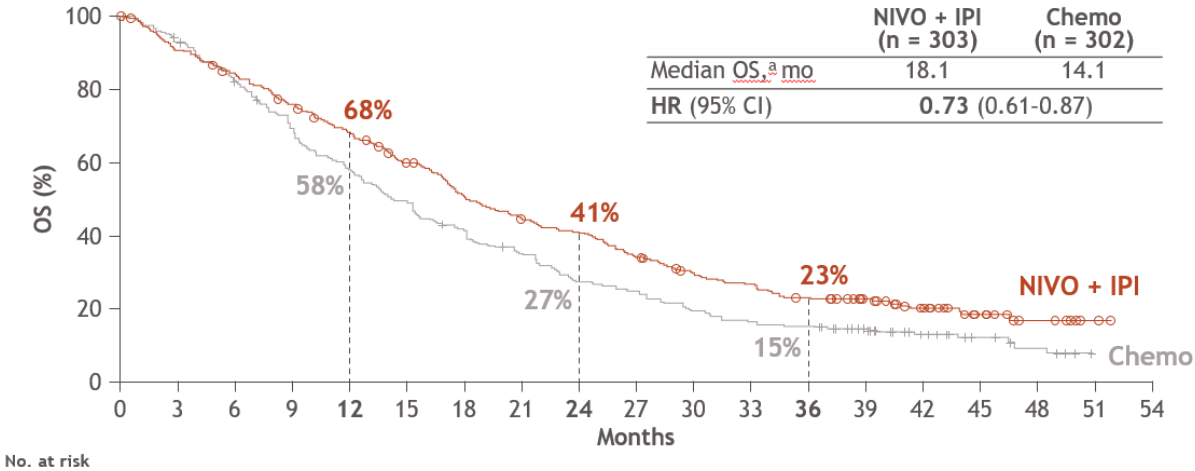
1.1 Introduction

An additional CheckMate-743 database lock took place on 7 May 2021, with a minimum of 35.5 months follow-up (Peters et al., 2021). Results from this latest data cut are presented below and used in updated economic analyses.

1.2 Overall survival

Figure 1 shows the OS Kaplan-Meier curves for nivolumab + ipilimumab and pemetrexed + cisplatin/carboplatin. At 3 years, 23% of patients in the nivolumab + ipilimumab arm remained alive compared with 15% in the chemotherapy arm. Thus, with a minimum 3-year follow-up nivolumab + ipilimumab continues to demonstrate sustained OS benefit compared to chemotherapy when patients have been off therapy for one year, regardless of histology (Peters et al., 2021).

Figure 1. Kaplan Meier plot for nivolumab + ipilimumab vs. pemetrexed + cisplatin/carboplatin for OS



[a]95% CIs were 16.8–21.0 (NIVO + IPI) and 12.4–16.3 (chemo).

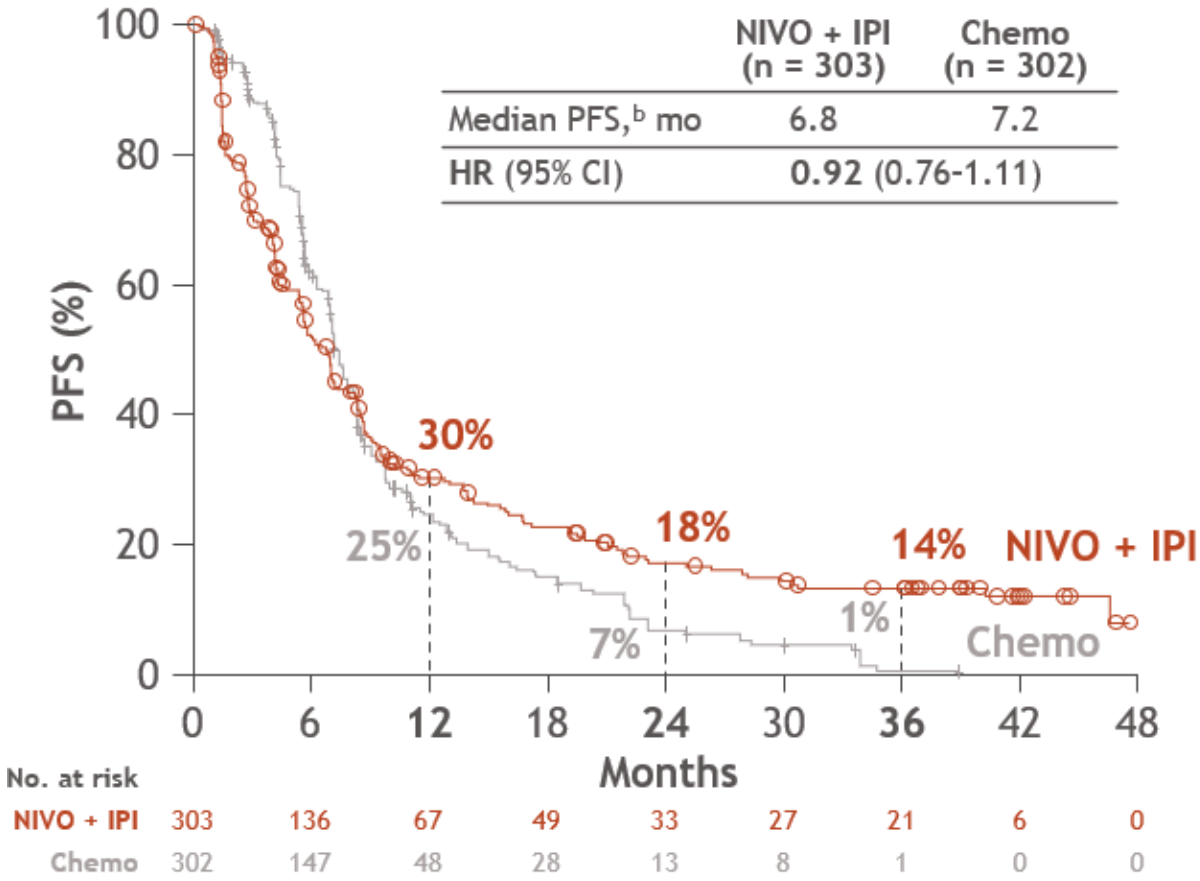
mOS: median OS; OS: overall survival

Source: Peters et al. (2021)

1.3 Progression-free survival

The Kaplan-Meier curves for PFS in the nivolumab + ipilimumab and pemetrexed + cisplatin/carboplatin arms are shown in Figure 2. At 3-years follow-up, 14% of nivolumab + ipilimumab patients remained progression-free compared with only 1% of chemotherapy-treated patients (Peters et al., 2021).

Figure 2. Kaplan Meier plot for nivolumab + ipilimumab vs. pemetrexed + cisplatin/carboplatin for PFS[a]



[a]Per BICR; [b]95% CIs were 5.6–7.4 (NIVO + IPI) and 6.9–8.0 (chemo).

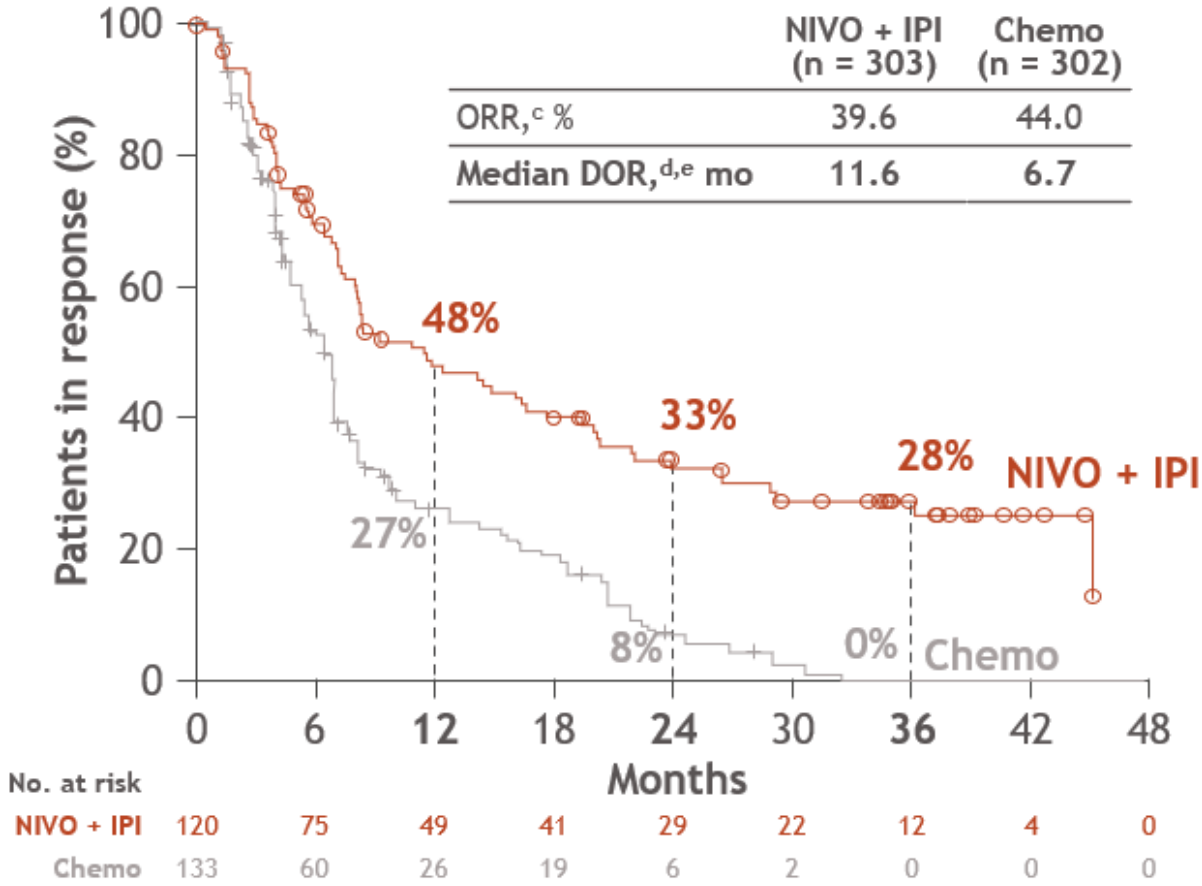
PFS: progression-free survival

Source: Peters et al. (2021)

1.4 Response

At the 3-year database lock, complete response was reached in 3 more patients (totally 8 [2.6%]) in nivolumab + ipilimumab, compared to zero in patients in the chemotherapy arm. Patients in the nivolumab + ipilimumab arm also had a higher chance of achieving durable responses than those in the chemotherapy arm, regardless of histology (Peters et al., 2021). At 36 months, 28% of responders treated with nivolumab + ipilimumab remained in response compared with none of those treated with chemotherapy (Figure 3).

Figure 3. Kaplan Meier plot for nivolumab + ipilimumab vs. pemetrexed + cisplatin/carboplatin for DoR



[c]8 patients (7 with epithelioid histology and 1 with non-epithelioid histology) treated with NIVO + IPI and 0 patients treated with chemo had CR; [d]DOR was calculated in patients with a response (NIVO + IPI: n = 120, chemo: n = 133); [e]95% CIs were 8.2–16.8 (NIVO + IPI) and 5.6–7.1 (chemo).

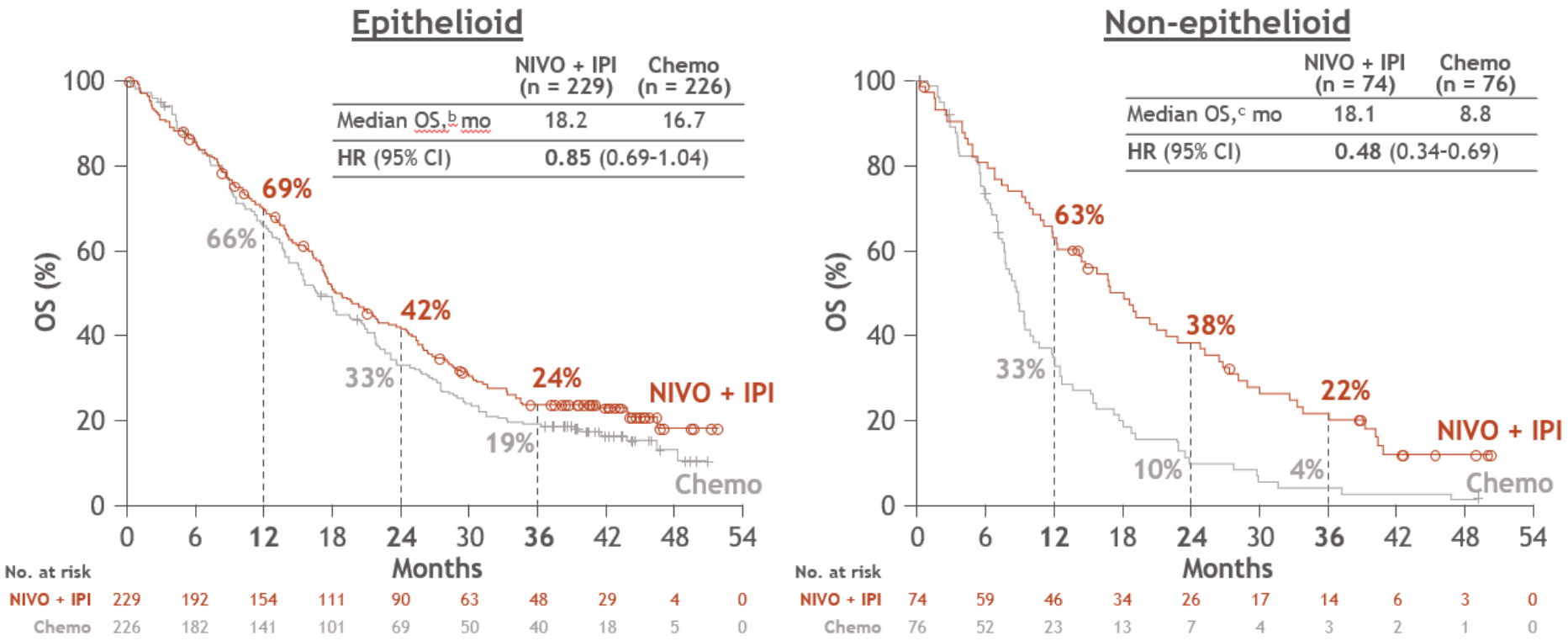
DoR: Duration of response

Source: Peters et al. (2021)

1.5 Subgroup data

Overall survival by histology is presented in Figure 4. It is important to note that since CheckMate-743 was not powered for these subgroup analyses, differences in the efficacy results in subgroups may therefore have been caused by chance.

Figure 4. **Figure 1: Kaplan Meier plot for nivolumab + ipilimumab vs. pemetrexed + cisplatin/carboplatin for OS by histology[a]**



[a]Histology per CRF; [b]95% CIs were 16.9–21.9 (NIVO + IPI) and 14.9–20.3 (chemo); [c]95% CIs were 12.2–22.8 (NIVO + IPI) and 7.4–10.2 (chemo).

Source: Peters et al. (2021)

1.6 Safety

No additional safety signals were observed during the additional follow-up (Peters et al., 2021).

2 APPENDIX B. UPDATED SURVIVAL ANALYSIS

2.1 Survival analysis of the 3-year data cut

As with the originally submitted survival analysis modelling was conducted using the FlexSurv package in R and modelled using the FlexSurvReg function. Parametric survival models were fitted to individual patient-level data from the CheckMate-743 trial. For each endpoint, seven parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma, and generalised gamma) and six spline based models (Spline 1 knot hazard, Spline 2 knot hazard, Spline 1 knot odds, Spline 2 knot odds, Spline 1 knot normal and Spline 2 knot normal) were considered for the extrapolation of “all-comers” patient-level data. The following sections provide details of the survival models for the following outcomes based on the 3-year data cut:

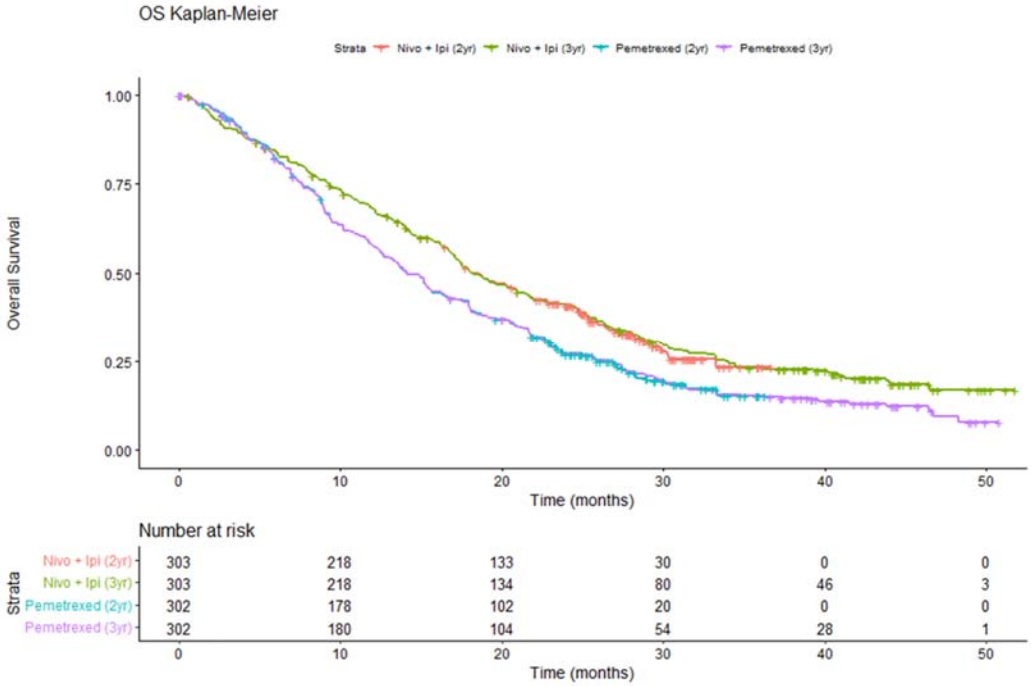
- Overall survival (see Section 2.2)
- Progression-free survival (see Section 2.3)

A summary of the revised cost-effectiveness results using the updated survival analysis results is presented in Section 2.4.

2.2 Overall survival

Figure 5 shows the OS KM curves for nivolumab + ipilimumab and pemetrexed + cisplatin or carboplatin for the 2-year and 3-year data cuts.

Figure 5. CheckMate-743: Kaplan-Meier plot of overall survival (all randomised patients)

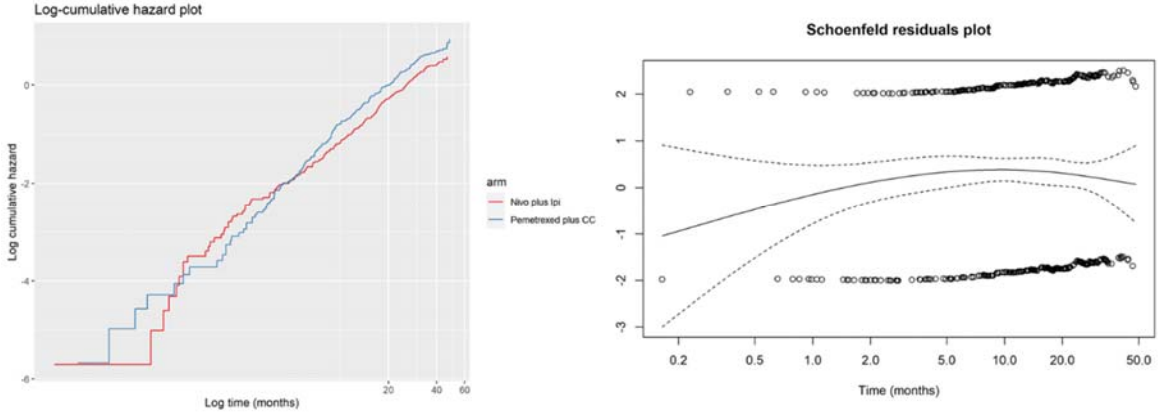


Ipi = ipilimumab; Nivo = nivolumab; OS = overall survival.
Source: BMS data on file (2021).

2.2.1 Testing of proportional hazards assumption

Visual inspection of the log-cumulative hazards and Schoenfeld residuals plots was undertaken to assess proportionality of treatment effects over time. As with the analysis of the 2-year data cut, a Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time failed to reject the proportional hazards assumption at a 5% significance level (P = 0.496). Visual inspection of the Schoenfeld residuals plot demonstrates a relatively but not completely linear pattern (Figure 6). However, inspection of the log-cumulative hazards plot reveals that the cumulative hazard for nivolumab + ipilimumab and PDC crosses at multiple time points, which could be seen, per definition, to falsify the assumption of proportional hazards. Therefore, aligned with the analysis submitted based on the 2-year data cut non proportionality was assumed for the updated survival analysis with only independent models fitted and incorporated into the updated economic model.

Figure 6. **Log-cumulative hazard plot and Schoenfeld residuals plot for nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin for overall survival**



2.2.2 Assessing goodness-of-fit of parametric survival models within the trial period

2.2.2.1 Nivolumab + ipilimumab

Table 1 summarises the goodness-of-fit statistics for independent survival models fitted to the OS endpoint of nivolumab + ipilimumab. As shown, several of the models have AIC values with a difference of less than 4 to the distribution with the lowest AIC; these can be considered the best fitting models based on the Burnham and Anderson (2004) rule of thumb.

Table 1. **Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for nivolumab + ipilimumab**

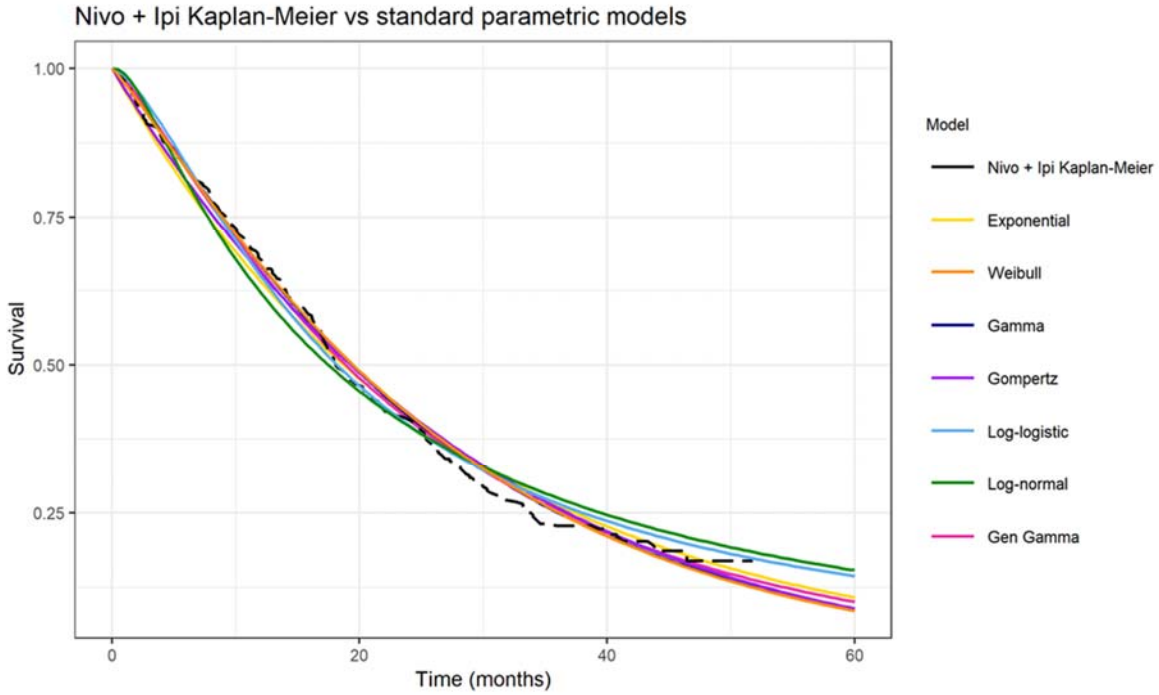
Independent model	AIC rank	AIC	BIC
Gamma	1	1991.72	1999.15
Spline normal 1 knot	2	1991.95	2003.10
Spline odds 1 knot	3	1992.21	2003.35
Weibull	4	1992.55	1999.98
Generalised Gamma	5	1992.95	2004.10
Spline hazard 1 knot	6	1993.52	2004.67
Spline odds 2 knots	7	1993.64	2008.50
Spline normal 2 knots	8	1993.94	2008.80
Log-logistic	9	1994.05	2001.48
Spline hazard 2 knots	10	1994.44	2009.29
Exponential	11	1994.76	1998.48

Independent model	AIC rank	AIC	BIC
Gompertz	12	1995.85	2003.29
Log-normal	13	2004.10	2011.53

AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 7 shows the standard parametric models for nivolumab + ipilimumab compared with the CheckMate-743 KM data for OS. Visually, most of the curves fit some sections of the KM data well but overestimate or underestimate other parts of the KM data. All models except log-logistic and log-normal underpredict the later part of the data; the same was seen for the previous data cut. Thus, most standard parametric models are anticipated to underestimate the long-term survival for nivolumab + ipilimumab. For the spline models (Figure 8), all distributions have a reasonable visual fit to the KM data from CheckMate-743.

Figure 7. Independent parametric models overlaying the overall survival Kaplan-Meier data for nivolumab + ipilimumab



KM = Kaplan-Meier; Nivo + Ipi = nivolumab + ipilimumab; OS = overall survival.

Figure 8. Independent spline models for nivolumab + ipilimumab overlaying the CheckMate-743 Kaplan-Meier data

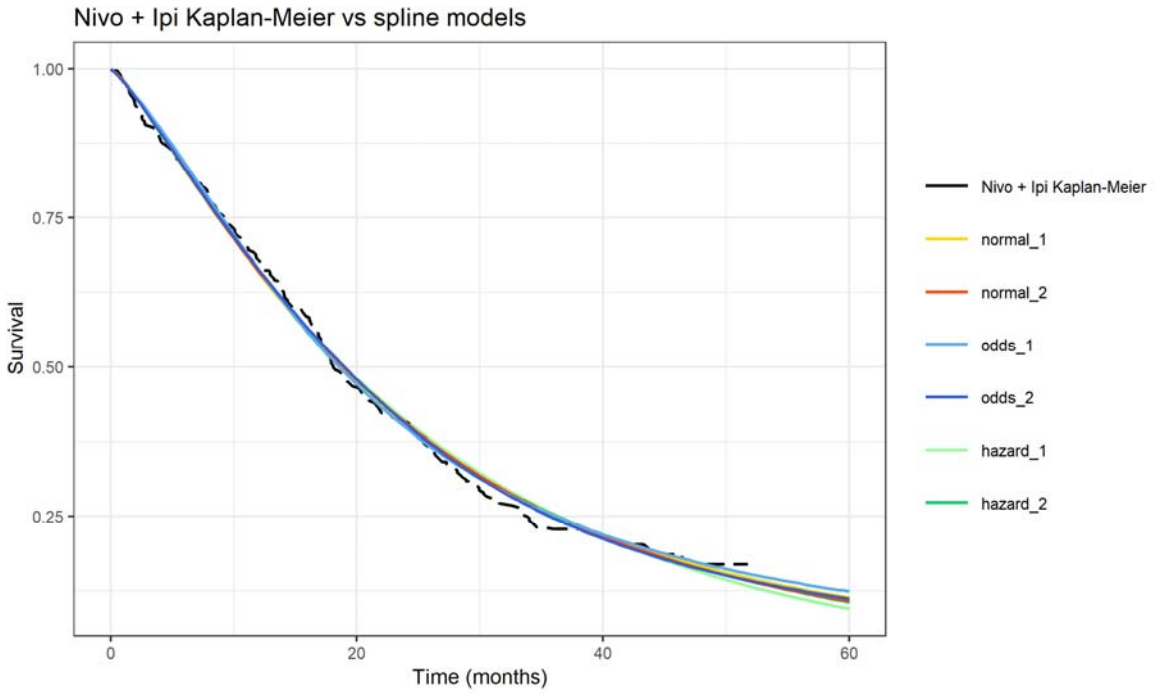


Table 2 presents the landmark OS for each distribution as well as the CheckMate-743 trial and MAPS trial Kaplan-Meier data.

Table 2. Landmark absolute overall survival analysis for independent parametric distributions fitted to nivolumab + ipilimumab

		Absolute survival (%)						
Data set	**Curve**	**6 mos**	**Yr 1**	**Yr 2**	**Yr 3**	**Yr 5**	**Yr 10**	**Yr 20**
CheckMate-743	Kaplan-Meier	84.0	67.9	40.8	23.2	-	-	-
MAPS	Kaplan-Meier	88.8	63.4	33.6	15.7	8.1	-	-
Nivolumab + ipilimumab extrapolation	Weibull	83.2	66.9	41.6	25.1	8.6	0.5	0.0
	Gamma	83.4	66.8	41.4	25.0	8.9	0.6	0.0
	Gompertz	81.2	65.5	41.7	25.8	9.0	0.3	0.0
	Generalised gamma	83.2	65.9	40.7	25.3	10.1	1.2	0.0
	Exponential	80.1	64.1	41.1	26.3	10.8	1.2	0.0
	Log-logistic	83.9	65.0	39.8	26.5	14.4	5.7	2.1
	Log-normal	81.2	62.2	39.6	27.5	15.4	5.5	1.5
	Spline 1 knot hazard	83.1	66.0	41.0	25.3	9.5	0.8	0.0
	Spline 2 knot hazard	83.9	66.2	40.0	25.3	10.6	1.3	0.0

Data set	Curve	Absolute survival (%)						
		6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 20
	Spline 1 knot odds	84.2	66.4	39.7	25.1	12.4	4.2	1.3
	Spline 2 knot odds	83.4	66.1	40.4	24.7	11.2	3.3	0.9
	Spline 1 knot normal	83.5	66.0	40.1	25.2	11.4	2.6	0.4
	Spline 2 knot normal	83.2	66.1	40.6	25.1	10.9	2.3	0.3

mos = months; Yr = year.

2.2.2.2 Pemetrexed plus cisplatin or carboplatin

Table 3 summarises the goodness-of-fit statistics for independent survival models fitted to the OS endpoint of pemetrexed + cisplatin or carboplatin. As for the nivolumab + ipilimumab arm, the differences in AIC and BIC values suggest that some of the distributions (specifically Gompertz, log-normal, and exponential) have a poorer fit to the trial data than other distributions.

Table 3. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for pemetrexed + cisplatin or carboplatin

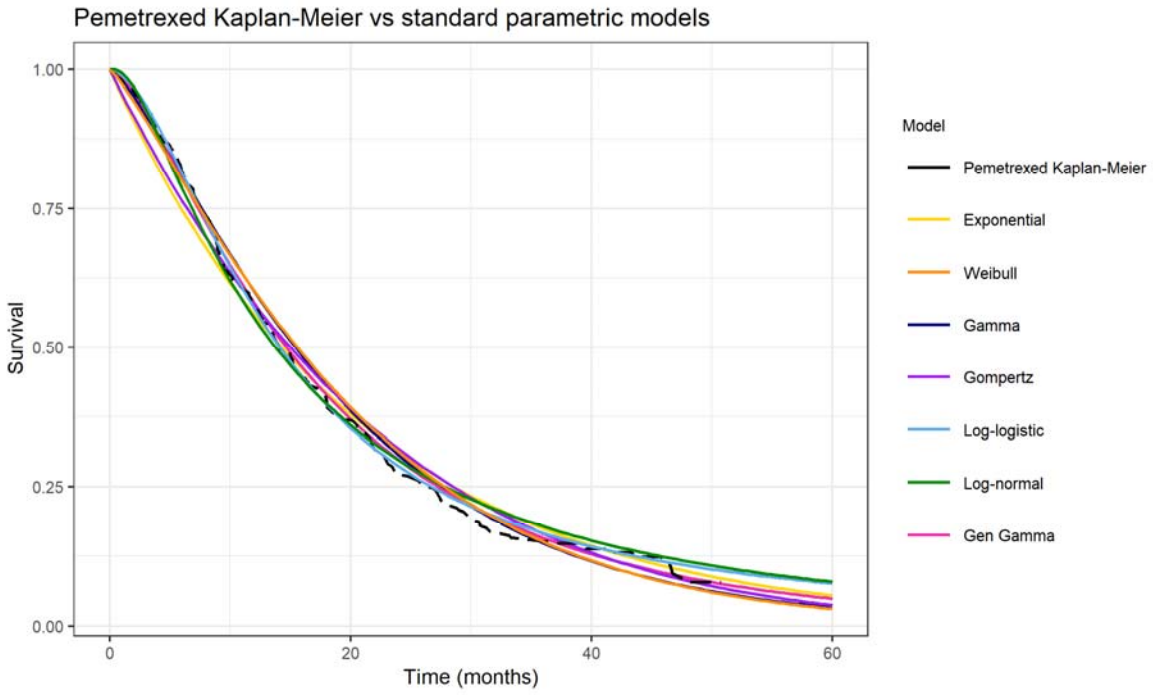
Independent model	AIC rank	AIC	BIC
Log-logistic	1	1,986.84	1,994.26
Spline odds 1 knot	2	1,987.46	1,998.59
Spline odds 2 knots	3	1,989.41	2,004.25
Spline normal 1 knot	4	1,989.57	2,000.70
Spline normal 2 knots	5	1,989.61	2,004.45
Spline hazard 2 knots	6	1,990.21	2,005.05
Spline hazard 1 knot	7	1,991.03	2,002.16
Generalised Gamma	8	1,991.08	2,002.21
Gamma	9	1,993.42	2,000.84
Weibull	10	1,997.24	2,004.66
Log-normal	11	1,998.90	2,006.32
Exponential	12	2,006.58	2,010.29
Gompertz	13	2,006.92	2,014.34

AIC = Akaike information criterion; BIC = Bayesian information criterion.

This can also be confirmed with regards to visual fit in Figure 9 showing the independent parametric models for pemetrexed + cisplatin or carboplatin overlaid on the KM data from

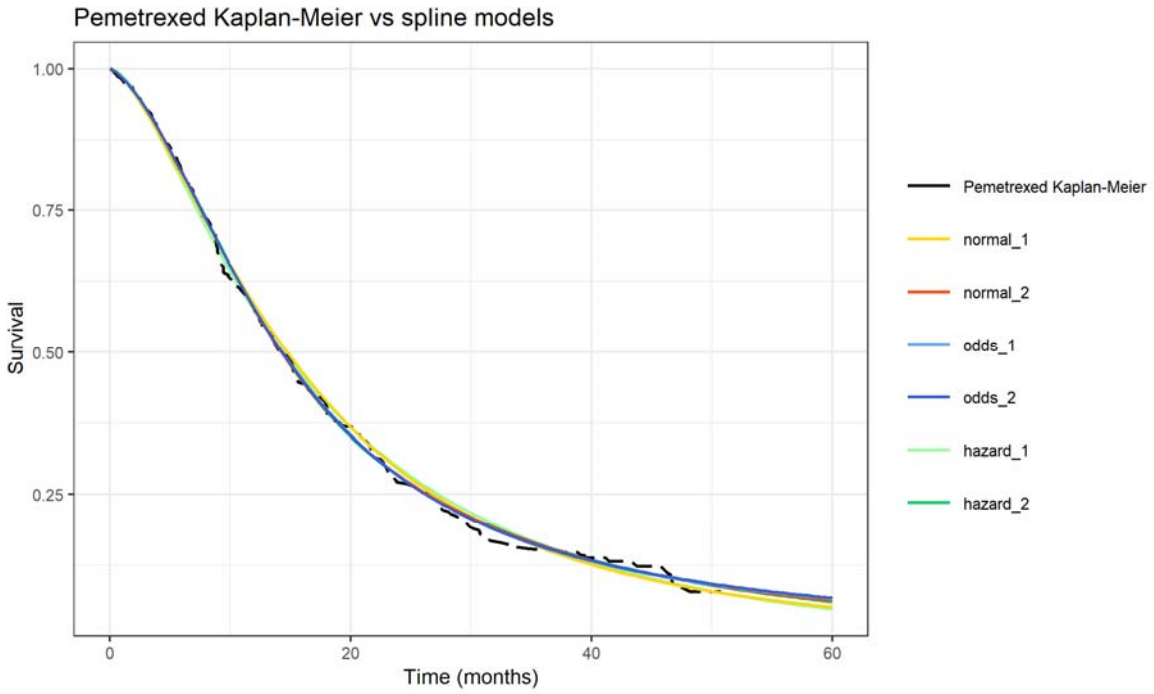
CheckMate-743 where these three distributions underestimate the initial part of the KM data. The exponential, log-logistic, and log-normal distributions also slightly overestimate survival at the end of the trial. As for nivolumab + ipilimumab, all spline models have a good visual fit to the KM data from CheckMate-743 (Figure 10).

Figure 9. Independent parametric models overlaying the overall survival Kaplan-Meier data for pemetrexed + cisplatin or carboplatin



CM = CheckMate; ITT = intent to treat; OS = overall survival.

Figure 10. Independent splines models overlaying the overall survival Kaplan-Meier data for pemetrexed + cisplatin or carboplatin



KM = Kaplan-Meier; OS = overall survival

Table 4 presents the landmark OS for each distribution and the CheckMate-743 trial and MAPS trial Kaplan-Meier data.

Table 4. Landmark absolute overall survival analysis for independent parametric distributions fitted to pemetrexed + cisplatin or carboplatin

		Absolute survival (%)						
Data set	Curve	6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 20
CheckMate-743	Kaplan-Meier	82.0	57.7	27.2	15.4	-	-	-
MAPS	Kaplan-Meier	88.8	63.4	33.6	15.7	8.1	-	-
Pemetrexed + cisplatin or carboplatin extrapolation	Weibull	80.1	60.2	31.2	15.1	3.0	0.0	0.0
	Gamma	80.9	60.1	30.6	14.8	3.3	0.1	0.0
	Gompertz	76.4	57.7	31.7	16.5	3.7	0.0	0.0
	Generalised gamma	80.3	58.0	29.7	15.7	4.9	0.4	0.0
	Exponential	74.7	55.8	31.2	17.4	5.4	0.3	0.0
	Log-logistic	81.4	57.0	28.6	16.6	7.6	2.4	0.7
	Log-normal	78.7	55.2	29.7	17.8	7.9	1.9	0.3
	Spline 1 knot hazard	80.3	57.6	29.7	16.0	4.8	0.3	0.0

Data set	Curve	Absolute survival (%)						
		6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 20
	Spline 2 knot hazard	81.7	57.8	28.2	16.0	6.1	0.7	0.0
	Spline 1 knot odds	81.5	57.5	28.2	15.6	6.6	1.9	0.5
	Spline 2 knot odds	81.6	57.7	28.2	15.7	6.8	2.0	0.6
	Spline 1 knot normal	80.8	58.5	29.3	15.4	5.2	0.7	0.1
	Spline 2 knot normal	81.7	57.6	28.3	15.9	6.3	1.2	0.2

Mos = months; Yr = year.

2.2.3 Selection of base-case distributions

As presented earlier, several of the distributions had a statistical fit (AIC/BIC) that was similar to the best fitting distribution. However, of the standard parametric distributions shown in Figure 11 and Figure 13, only log-logistic and log-normal presented a hazard function for both arms in line with the hazard function identified from analyses of the data from the MAPS trial. For the PDC arm, generalised gamma also provided a declining hazard over time, although not as marked a decline as for log-logistic and log-normal. All other distributions had constant or increasing hazards over time. For the spline models, only spline 1 knots hazard did not show a potentially appropriate hazard function for both the nivolumab + ipilimumab arm and PDC arm (Figure 12 and Figure 14).

Figure 11. Nivolumab + ipilimumab independent parametric hazard function

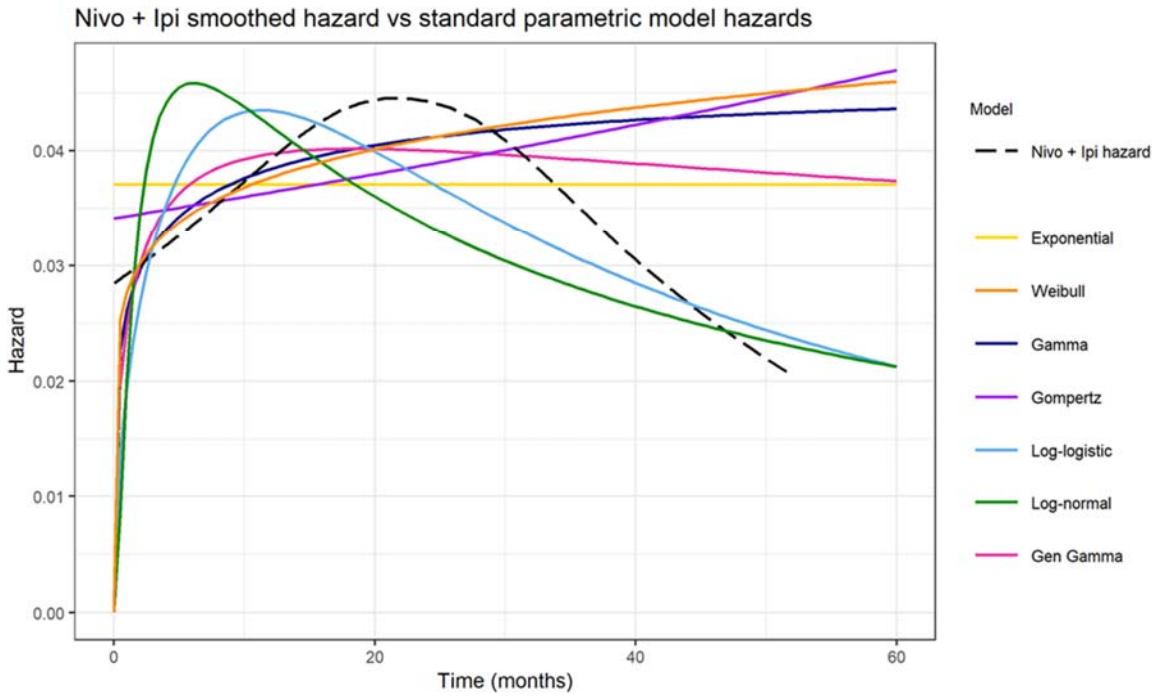


Figure 12. Nivolumab + ipilimumab independent spline hazard function

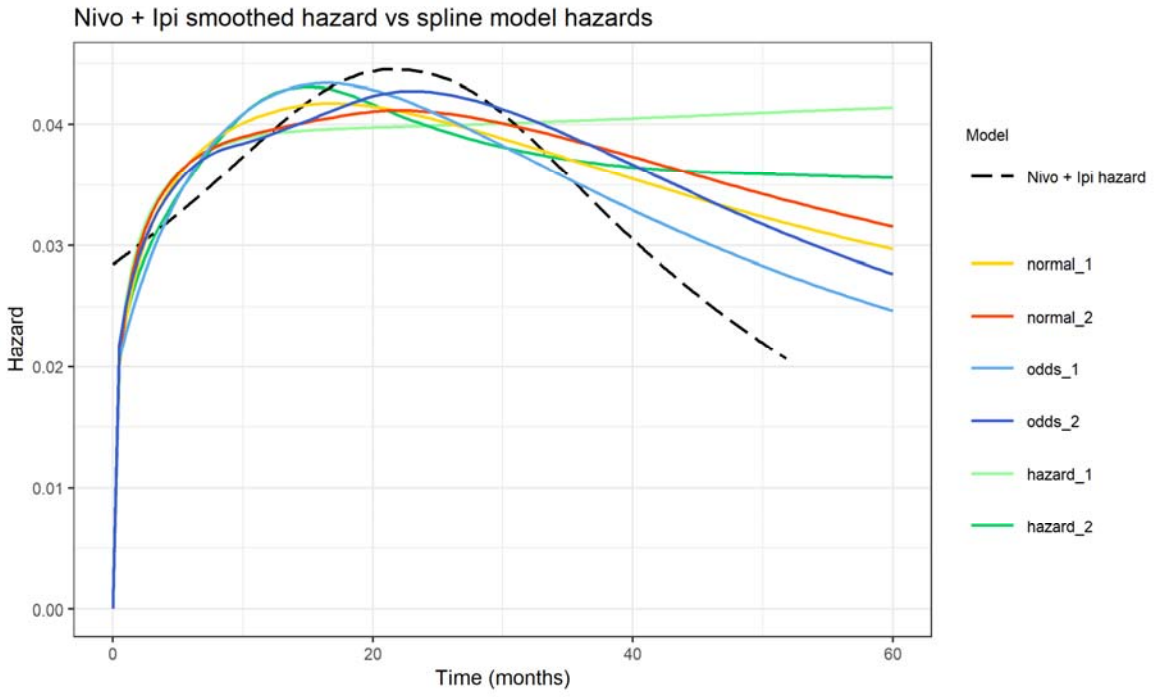
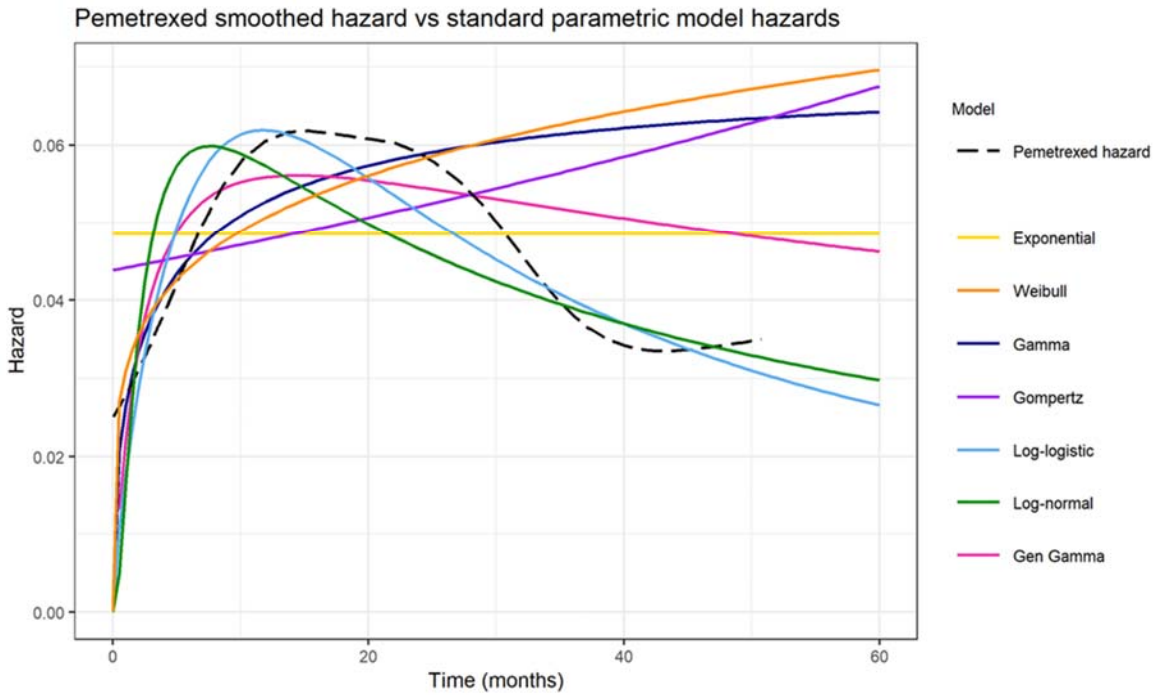
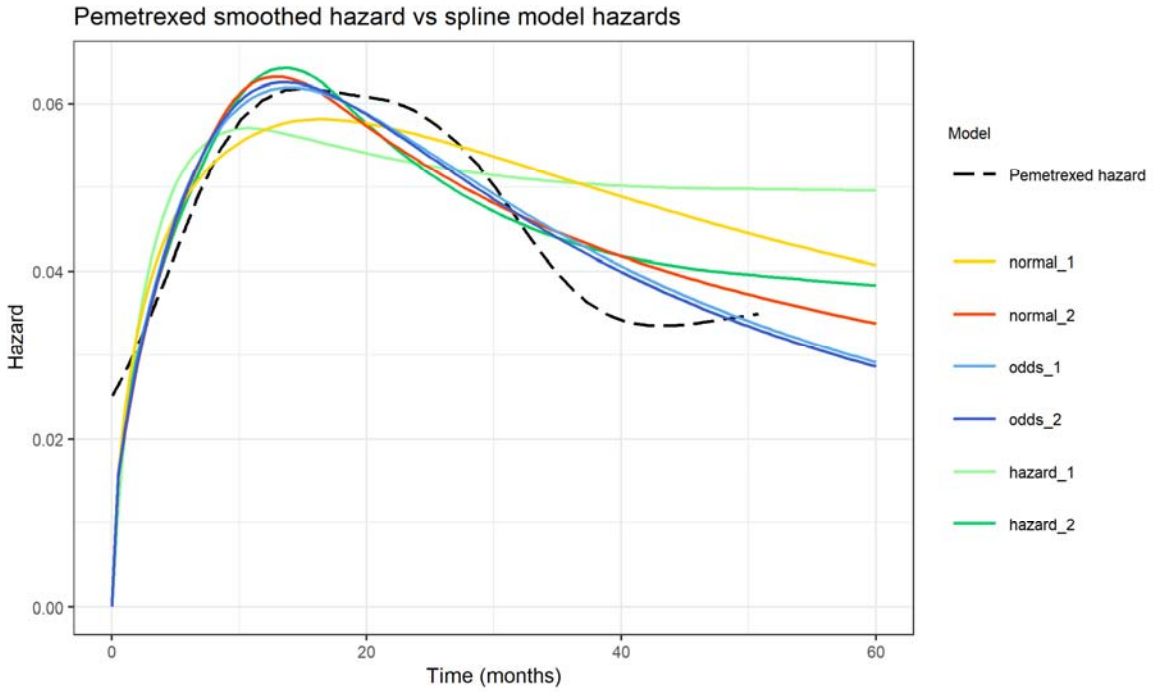


Figure 13. PDC independent parametric hazard function



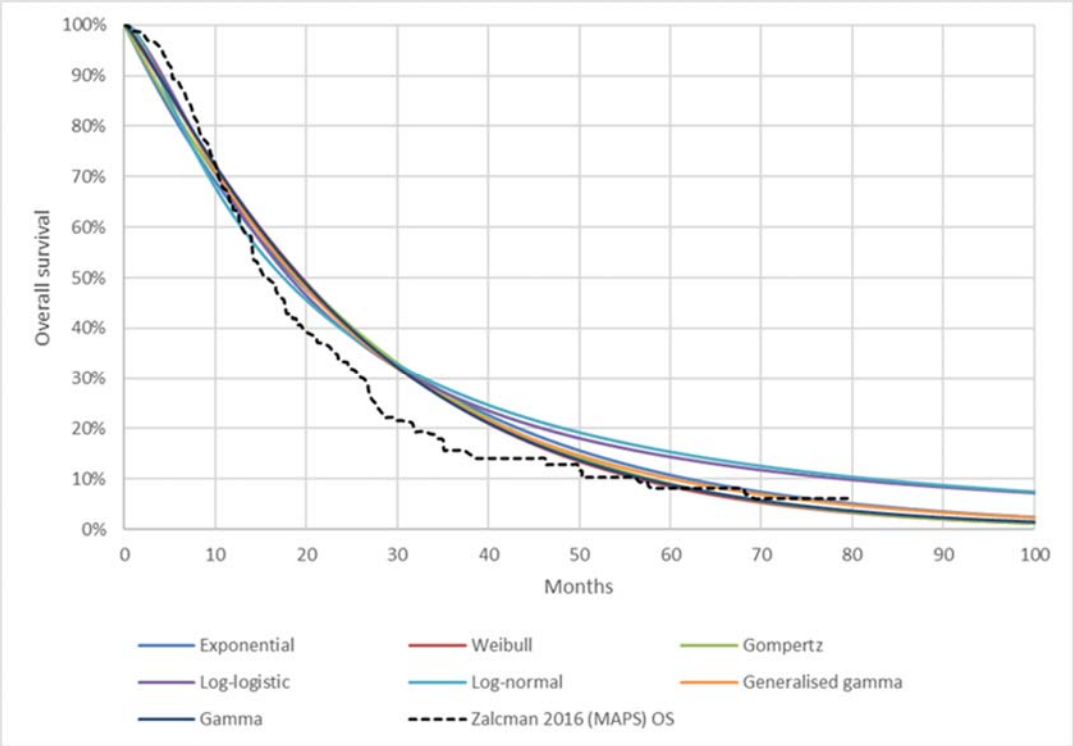
PDC = platinum-based doublet chemotherapy.

Figure 14. PDC independent spline hazard function



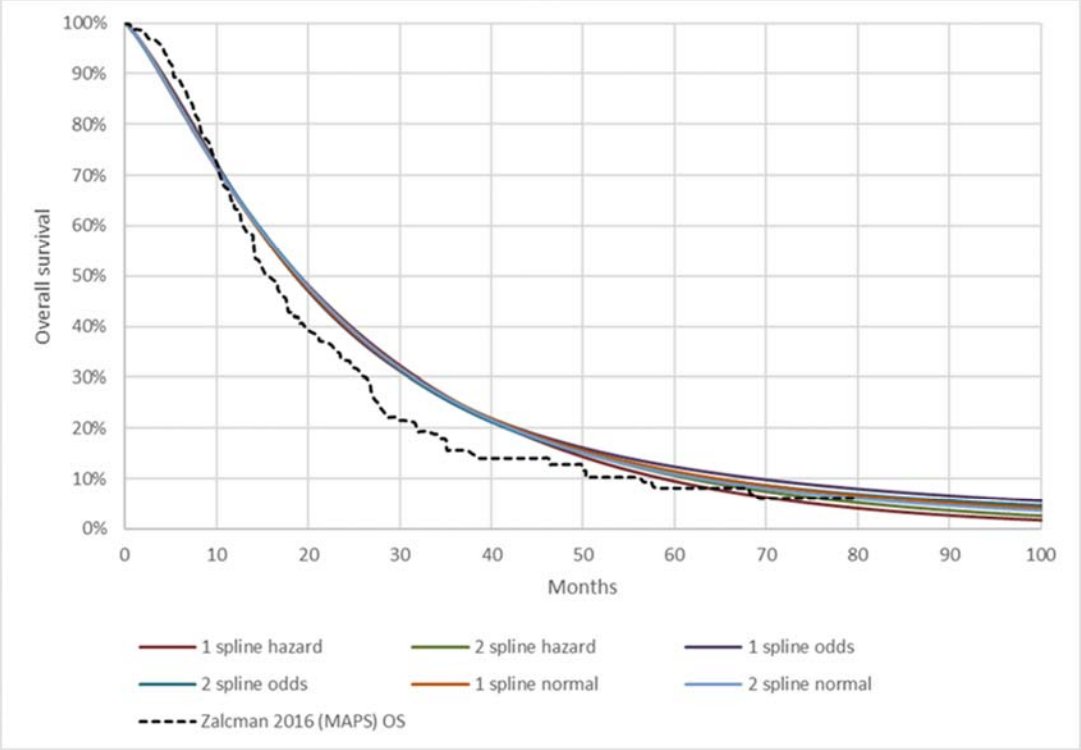
The deviation in hazard function for most of the distributions fitted to the CheckMate-743 data also result in the absolute survival not fulfilling the criteria of being slightly below the survival from MAPS for the PDC arm, and above that observed in the MAPS trial for the nivolumab + ipilimumab arm (Figure 15 to Figure 18).

Figure 15. Independent parametric models overlaying the MAPS OS Kaplan-Meier data for nivolumab + ipilimumab



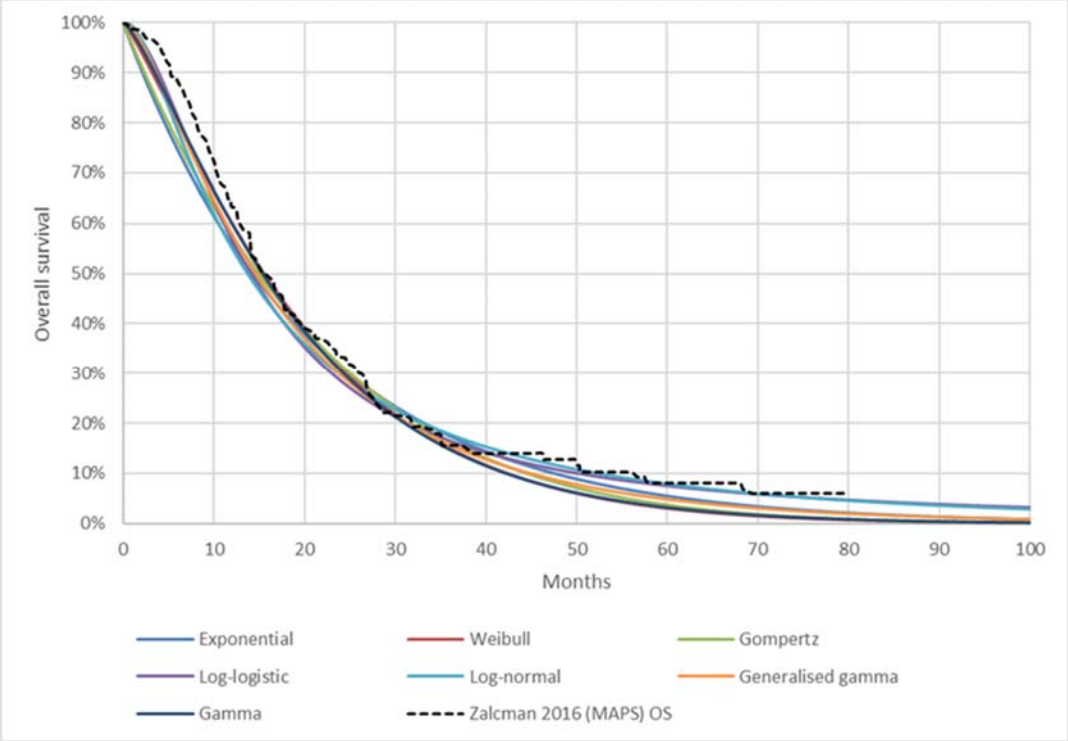
OS = overall survival.

Figure 16. Independent spline-based models overlaying the MAPS OS Kaplan-Meier data for nivolumab + ipilimumab



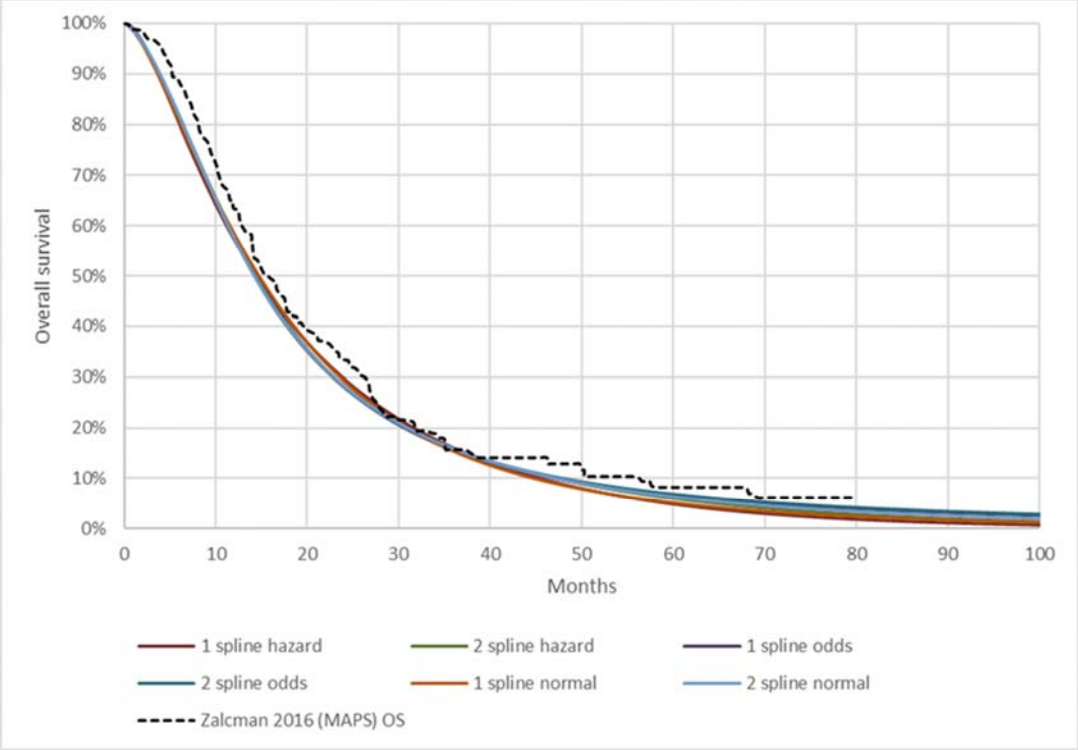
OS = overall survival.

Figure 17. Independent parametric models overlaying the MAPS OS Kaplan-Meier data for PDC



OS = overall survival; PDC = platinum-based doublet chemotherapy.

Figure 18. Independent spline-based models overlaying the MAPS OS Kaplan-Meier data for PDC



OS = overall survival; PDC = platinum-based doublet chemotherapy.

Table 5 summarises the final overall assessment of fit for all distributions as follows:

- Based on the Burnham and Anderson (2004) rule of thumb, it was considered that a difference in AIC less than 4 with respect to the lowest AIC was appropriate, between 4 and 10 was neutral, and more than 10 was inappropriate in line with previous ERG arguments in a NICE assessment of cancer treatments (NICE, 2019).
- Based on the Raftery (1995) rule of thumb, it was considered that a difference in BIC more than 10 with respect to the BIC for distribution with the lowest BIC was inappropriate.
- Distributions with increasing hazard rates at the start and declining hazards long-term were considered appropriate; hazard rates declining from the beginning were considered neutral; the remaining distributions were considered inappropriate.

- Based on clinical input, distributions with predicted survival at 5-year, 7.5-year and 10-year of around 5%, 2% and 0%, respectively for PDC patients would be appropriate. Distributions predicting survival above 2% at 10 years or higher than that observed for PDC in MAPS were considered inappropriate. For nivolumab + ipilimumab, predicted survival that is lower than that observed for PDC in MAPS was considered inappropriate and survival around 5% at 10 years would be considered appropriate.

Table 5. Summary of assessment of selection criteria for distributions

Distribution	Distribution	AIC	BIC	Appropriate hazard function	Plausible survival predictions
Nivolumab + ipilimumab	Weibull	✓	✓	✗	✗
	Gamma	✓	✓	✗	✗
	Gompertz	✗	✓	✗	✗
	Generalised gamma	✓	✓	✗	✗
	Exponential	✓	✓	✗	✗
	Log-logistic	✓	✓	✓	✓
	Log-normal	✗	✗	✓	✓
	Spline 1 knot hazard	✓	✓	✗	✗
	Spline 2 knot hazard	✓	✗	✓	✗
	Spline 1 knot odds	✓	✓	✓	✗
	Spline 2 knot odds	✓	✓	✓	✗
	Spline 1 knot normal	✓	✓	✓	✗
	Spline 2 knot normal	✓	✓	✓	✗
Pemetrexed + cisplatin or carboplatin	Weibull	✗	✗	✗	✗
	Gamma	✗	✓	✗	✗
	Gompertz	✗	✗	✗	✗
	Generalised gamma	✗	✓	-[a]	✓
	Exponential	✗	✗	✗	✓
	Log-logistic	✓	✓	✓	✗
	Log-normal	✗	✗	✓	✗
	Spline 1 knot hazard	✗	✓	✗	✓
	Spline 2 knot hazard	✓	✗	✓	✗
	Spline 1 knot odds	✓	✓	✓	✗
	Spline 2 knot odds	✓	✓	✓	✗
	Spline 1 knot normal	✓	✓	✓	✓

Distribution	Distribution	AIC	BIC	Appropriate hazard function	Plausible survival predictions
	Spline 2 knot normal	✓	✗	✓	✓

AIC = Akaike information criterion; BIC = Bayesian information criterion.

[a] The generalised gamma distribution has been marked as neutral, although it has an increasing hazard initially with long-term declining hazards the long-term decline in hazards is less pronounced than would be expected from the MAPS data.

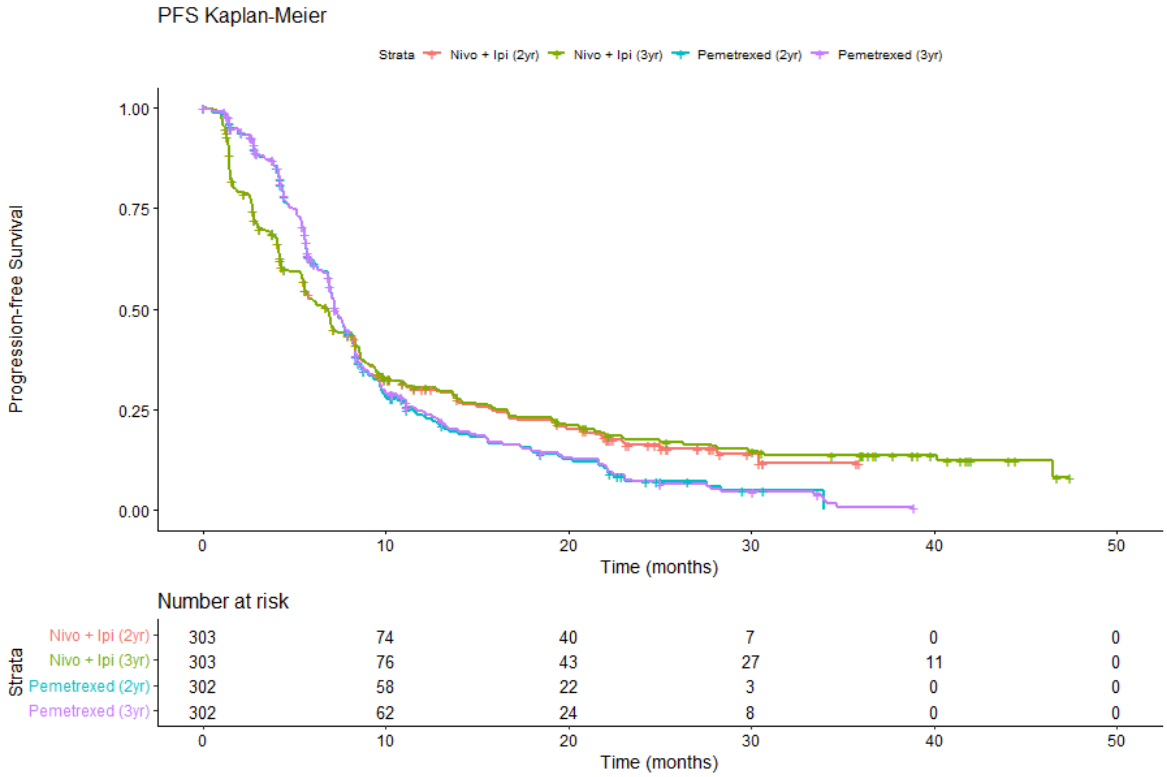
Based on the overall assessment presented in Table 5, log-logistic is the only distribution for nivolumab + ipilimumab that is considered appropriate for all criteria. Therefore, the log-logistic distribution appears to be the most appropriate distribution for the nivolumab + ipilimumab arm, aligned with the analyses based on the 2-year data. The only other distribution not leading to inappropriate long-term survival predictions for nivolumab + ipilimumab was the log-normal. This distribution had a poorer fit to the trial data but had an appropriate hazard function and slightly more optimistic long-term survival than the log-logistic distribution. Given that all other distributions except for log-logistic and log-normal resulted in implausible long-term predictions (key function of the extrapolations), none of those were considered potential candidates for nivolumab + ipilimumab.

For PDC, the only distribution deemed appropriate for all criteria was the Spline 1 knot normal. Of the other functions predicting clinically valid long-term survival, generalized gamma had a slightly deviating hazard function and Spline 2 knot normal had a 19 deviation in BIC. Both of these deviations from the heuristic could perhaps have been acceptable hadn't the Spline 1 knot normal fulfilled all criteria. However, based on the above Spline 1 knot normal was selected as the best distribution for the PDC arm.

2.3 Progression-free survival

Figure 19 presents the KM curves for PFS in the nivolumab + ipilimumab and pemetrexed + cisplatin or carboplatin arms.

Figure 19. CheckMate-743: Kaplan-Meier plot of progression-free survival by blinded independent central review (all randomised patients)



Ipi = ipilimumab; Nivo = nivolumab; PFS = progression-free survival.

Notes: Per adapted mRECIST for pleural mesothelioma lesions and/or RECIST v1.1 for non-pleural lesions.

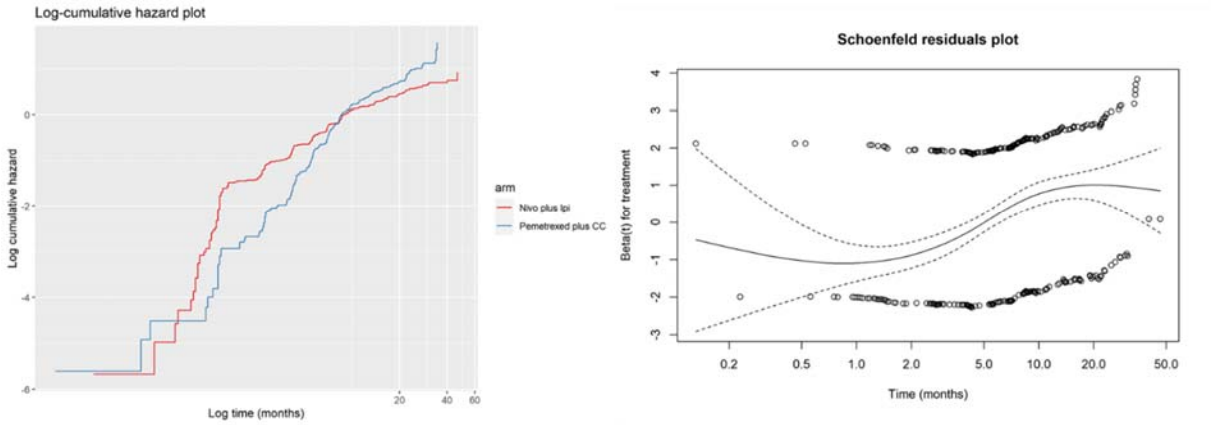
Chemo in figure refers to platinum-based doublet chemotherapy.

Source: BMS data on file (2021).

2.3.1 Testing of proportional hazards assumption

Visual inspection of the log-cumulative hazards and Schoenfeld residuals plots was undertaken to assess proportionality of treatment effects over time. Visually, it would appear the proportional hazards assumption does not hold given the non-linearity and crossover seen in the log-cumulative plot (Figure 20). A Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time use confirmed the rejection of the null hypothesis of proportional hazards ($P < 0.001$). Therefore, only independent parametric curves were considered appropriate for modelling PFS and are reported here.

Figure 20. Log-cumulative hazard plot and Schoenfeld residuals plot for nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin



2.3.2 Assessing goodness of fit of parametric survival models

2.3.2.1 Nivolumab + ipilimumab

Table 6 provides a summary of the AIC and BIC goodness-of-fit statistics reported for the parametric distributions of the independent survival models for PFS fitted to the nivolumab + ipilimumab arm of CheckMate-743. As shown in Table 6, there were large differences in AIC and BIC between the best fitting distribution and most other distributions, indicating that several of the distributions would have a poor fit to the trial data. In fact, none of the other standard distributions were within the difference in AIC (< 4 from the best fitting distribution) proposed by Burnham and Anderson (2004) and only 2 spline models fulfilled that criterion (Spline normal 1 knot and 2 knots).

Table 6. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to progression-free survival data for nivolumab + ipilimumab

Arm	Distribution	AIC ranked	AIC	BIC
Nivolumab + ipilimumab	Generalised gamma	1	1,514.64	1,525.78
	Spline normal 1 knot	2	1,515.61	1,526.75
	Spline normal 2 knots	3	1,516.71	1,531.57
	Spline odds 2 knots	4	1,518.76	1,533.61
	Spline hazard 2 knots	5	1,520.29	1,535.14
	Spline odds 1 knot	6	1,520.69	1,531.83
	Spline hazard 1 knot	7	1,521.01	1,532.15
	Log-normal	8	1,527.08	1,534.51

Arm	Distribution	AIC ranked	AIC	BIC
	Log-logistic	9	1,533.79	1,541.22
	Gompertz	10	1,547.65	1,555.07
	Weibull	11	1,579.00	1,586.43
	Gamma	12	1,585.49	1,592.91
	Exponential	13	1,586.25	1,589.96

AIC = Akaike information criterion; BIC = Bayesian information criterion.

AS can be seen from Figure 21 the poor statistical fit of most standard distributions is also translating into poor visual fit to the KM data. The spline models however provide a reasonable fit to the KM data (Figure 22).

Figure 21. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for nivolumab + ipilimumab

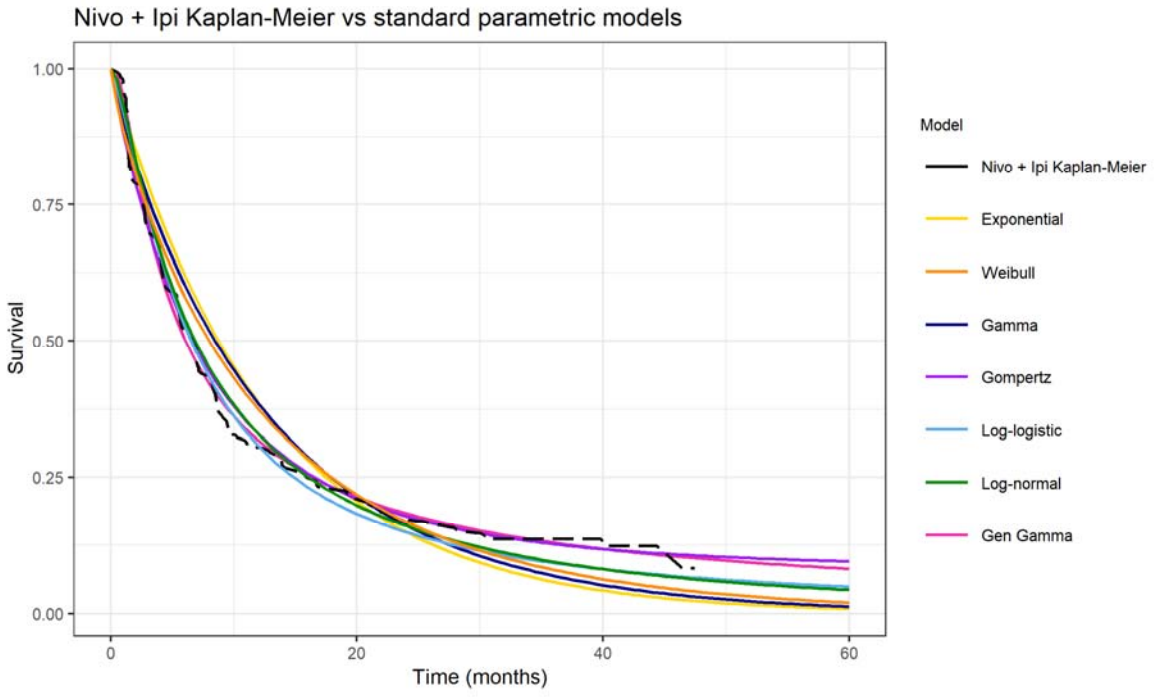
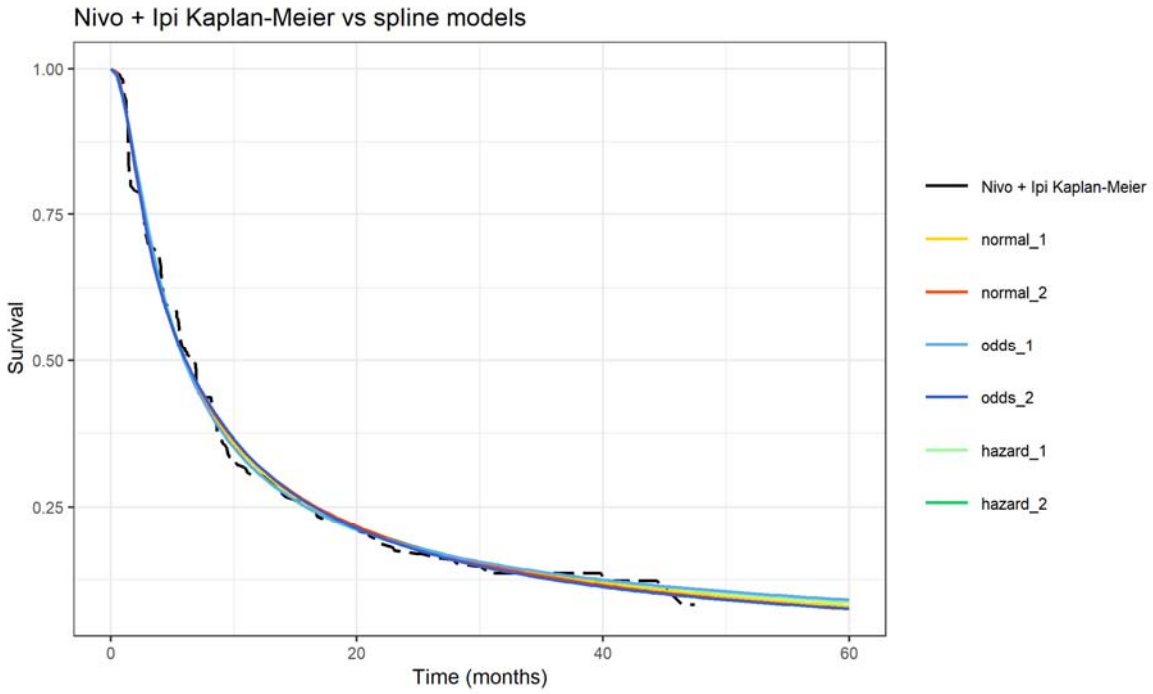


Figure 22. Independent splines models overlaying the progression-free survival Kaplan-Meier data for nivolumab + ipilimumab



The landmark PFS analysis presented in Table 7 shows that the distributions with the best statistical and visual fit to the data resulted in relatively similar long-term predictions of PFS. Thus, based on the statistical and visual fit to the data and selecting the simplest model, the generalised gamma distribution was selected as the best fitting distribution to use for PFS for nivolumab + ipilimumab. This selection is also aligned with the distribution used in the original submission.

Table 7. Landmark absolute progression-free survival analysis for independent parametric distributions fitted to nivolumab + ipilimumab

		Absolute survival (%)						
Data set	**Curve**	**6 mos**	**Yr 1**	**Yr 2**	**Yr 3**	**Yr 5**	**Yr 10**	**Yr 20**
CheckMate-743	Kaplan-Meier	52.1	30.0	17.5	13.6	-	-	-
Nivolumab + ipilimumab extrapolation	Weibull	58.2	37.5	16.8	8.0	2.0	0.1	0.0
	Gamma	60.4	38.5	16.1	6.9	1.3	0.0	0.0
	Gompertz	52.9	33.0	17.8	12.7	9.5	8.4	8.4
	Generalised gamma	50.5	31.7	18.4	13.0	8.2	4.3	2.2
	Exponential	62.2	38.7	15.0	5.8	0.9	0.0	0.0
	Log-logistic	52.9	30.7	14.9	9.3	4.9	2.0	0.8

Data set	Curve	Absolute survival (%)						
		6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 20
	Log-normal	54.2	32.9	16.1	9.5	4.3	1.2	0.2
	Spline 1 knot hazard	50.2	30.7	18.3	13.4	8.6	4.1	1.5
	Spline 2 knot hazard	50.0	31.6	18.6	13.1	7.8	3.1	0.9
	Spline 1 knot odds	49.9	30.8	18.4	13.6	9.1	5.2	2.9
	Spline 2 knot odds	50.5	32.1	18.2	12.5	7.6	3.7	1.8
	Spline 1 knot normal	50.0	31.5	18.5	13.1	8.0	3.7	1.5
	Spline 2 knot normal	50.3	32.1	18.5	12.8	7.6	3.3	1.2

Mos = Months; Yr = Year.

2.3.2.2 Pemetrexed plus cisplatin or carboplatin

Table 8 shows the goodness-of-fit statistics for the independent parametric distributions according to AIC/BIC criteria for the pemetrexed + cisplatin or carboplatin arm of CheckMate-743. As for nivolumab + ipilimumab, there were large differences in AIC and BIC between the best fitting distribution and most other distributions. Of the standard distributions only Loglogistic was within 4 in difference of AIC from the best fitting distribution based on AIC. Log-logistic was however the best fitting distribution based on BIC (which punishes more complex models).

Table 8. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to progression-free survival data for pemetrexed + cisplatin or carboplatin

Independent model	AIC rank	AIC	BIC
Spline normal 2 knots	1	1,414.45	1,429.30
Spline odds 2 knots	2	1,415.18	1,430.03
Spline hazard 2 knots	3	1,415.38	1,430.22
Log-logistic	4	1,417.91	1,425.34
Spline odds 1 knot	5	1,419.03	1,430.17
Spline hazard 1 knot	6	1,424.97	1,436.10
Spline normal 1 knot	7	1,427.34	1,438.48
Generalised gamma	8	1,429.38	1,440.52
Gamma	9	1,434.51	1,441.94

Independent model	AIC rank	AIC	BIC
Log-normal	10	1,435.73	1,443.16
Weibull	11	1,446.53	1,453.95
Gompertz	12	1,473.95	1,481.38
Exponential	13	1,480.67	1,484.39

AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 23 shows the independent parametric models with best statistical fit to the data for pemetrexed + cisplatin or carboplatin compared with the KM data from CheckMate-743. None of the distributions fully capture the middle part of the KM curve, but the log-logistic fits slightly better than the other distributions. Log-logistic however provide the best visual fit overall and appear to fit the tail of the KM curve better than the other distributions together with log-normal. With regards to visual fit Figure 24 shows that even the flexible spline models don't provide a particularly good fit to the full data.

Figure 23. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for pemetrexed + cisplatin or carboplatin

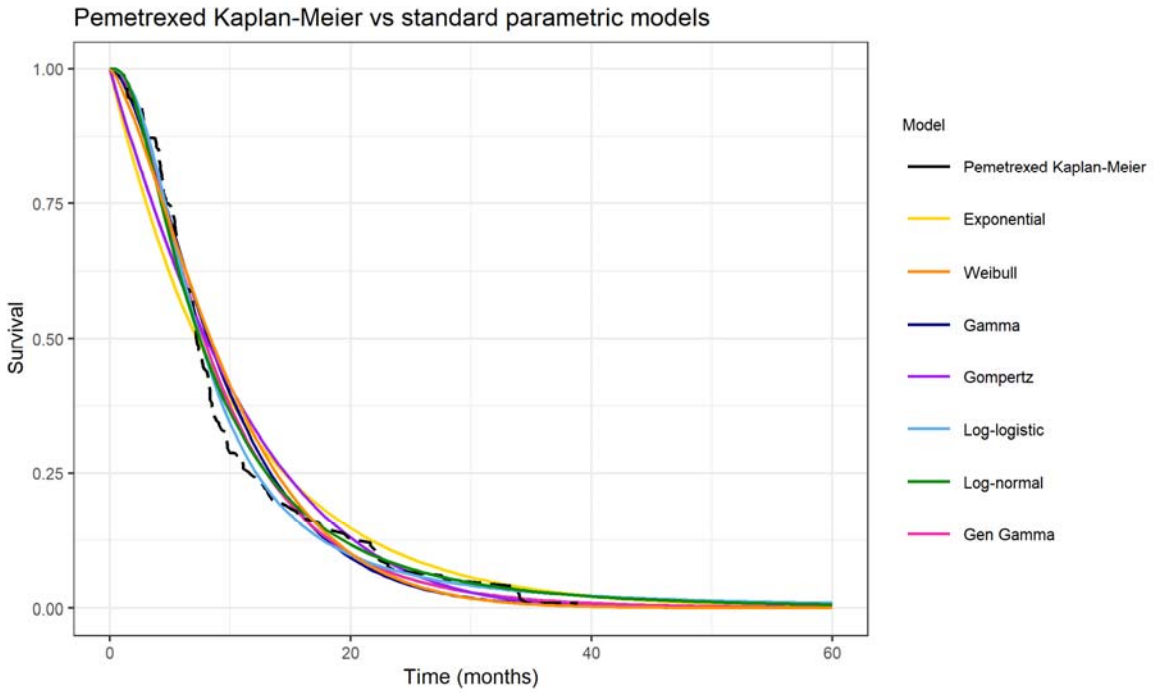


Figure 24. Independent splines models overlaying the progression-free survival Kaplan-Meier data for pemetrexed + cisplatin or carboplatin

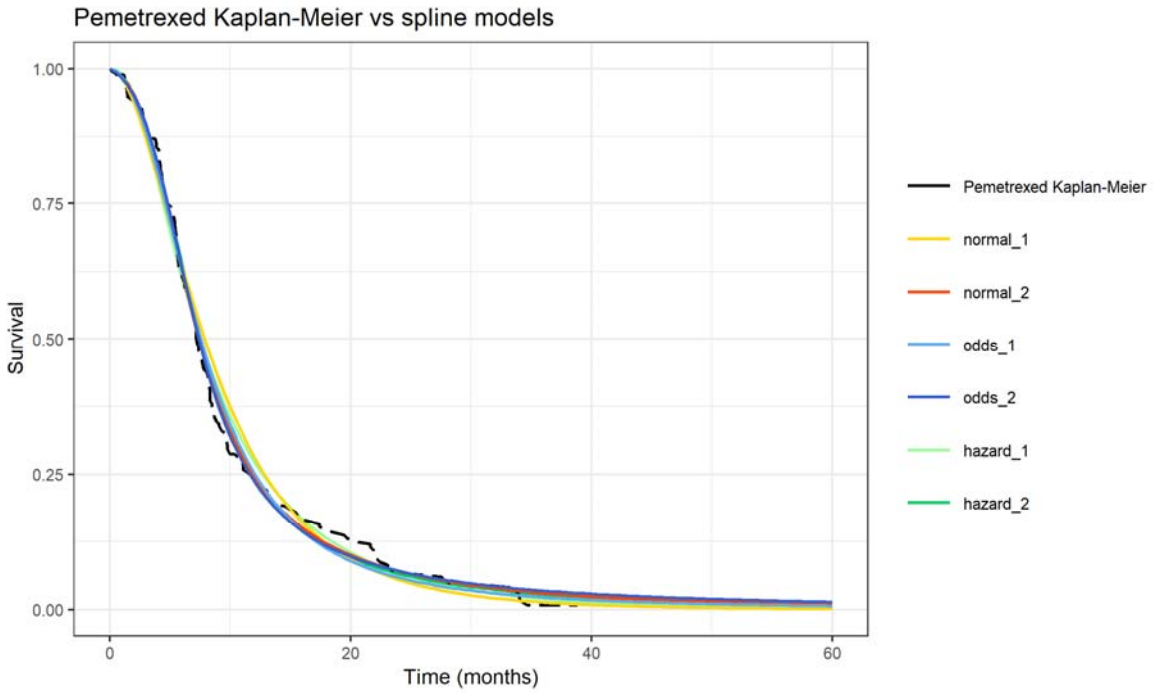


Table 9 presents the landmark survival analysis. The table shows that log-logistic would result in the most optimistic long-term PFS extrapolation of the standard distributions for PDC and therefore also could be seen as a conservative assumption in comparison to nivolumab + ipilimumab. The 2 knot spline model that had slightly better AIC than log-logistic also provides relatively similar predicted survival but with a slightly higher BIC due to added complexity. Thus, as for the original submission, log-logistic was selected as the best fitting distribution for PDC.

Table 9. Landmark absolute progression-free survival analysis for independent parametric distributions fitted to pemetrexed + cisplatin or carboplatin

	Curve	Absolute survival (%)						
Data set	Start year	6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 20
CheckMate-743	Kaplan-Meier	62.1	24.7	7.1	0.8	-	-	-
Pemetrexed + cisplatin or carboplatin extrapolation	Weibull	64.4	32.0	5.2	0.6	0.0	0.0	0.0
	Gamma	64.7	30.2	4.9	0.7	0.0	0.0	0.0
	Gompertz	60.2	33.3	7.4	1.0	0.0	0.0	0.0
	Generalized Gamma	62.6	28.6	6.0	1.4	0.1	0.0	0.0
	Exponential	56.3	31.7	10.0	3.2	0.3	0.0	0.0

Data set	Curve Start year	Absolute survival (%) 6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 20
	Log-logistic	62.2	25.6	6.7	2.8	0.9	0.2	0.0
	Log-normal	60.4	28.3	7.9	2.9	0.6	0.0	0.0
	Spline hazard 1 knot	61.2	27.3	6.8	2.0	0.2	0.0	0.0
	Spline hazard 2 knots	64.0	24.3	6.6	2.8	0.7	0.0	0.0
	Spline odds 1 knot	62.8	25.2	5.9	2.3	0.7	0.1	0.0
	Spline odds 2 knots	63.2	23.7	7.1	3.5	1.4	0.4	0.1
	Spline normal 1 knot	63.5	28.2	5.5	1.3	0.1	0.0	0.0
	Spline normal 2 knots	62.7	24.6	7.1	3.0	0.9	0.1	0.0

Mos = months; Yr = year.

2.4 Cost-effectiveness results

Table 10 presents total costs, life-years gained (LYGs), QALYs, and incremental costs per QALY for nivolumab + ipilimumab versus PDC based on the 3-year data cut with an updated nivolumab PAS of [redacted]. Compared with PDC, nivolumab + ipilimumab generated 0.667 incremental QALYs and 0.817 incremental LYGs, and the nivolumab + ipilimumab–treated cohort had higher total lifetime costs. The ICER was £75,322 per QALY gained.

Table 10. Base-case incremental results of nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin in first-line unresectable MPM

Technologies	Total costs (£)	Total LYGs	Total QALYs	Inc. costs, £	Inc. LYs	Inc. QALYs	Incremental costs per QALY, £
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	50,260	0.817	0.667	75,322

Inc = Incremental; LYG = life-year gained; QALY = quality-adjusted life-year.

Base case overall survival distributions: nivolumab + ipilimumab = log-logistic; pemetrexed + cisplatin or carboplatin = spline normal 1 knot.

Base case progression-free survival distributions: nivolumab + ipilimumab = generalized gamma; pemetrexed + cisplatin or carboplatin = log-logistic.

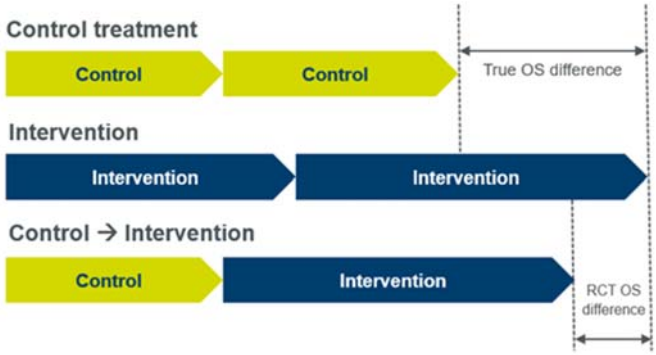
3 APPENDIX C. TREATMENT SWITCHING ANALYSIS

As per the available trial results, after study treatment (nivolumab+ ipilimumab or chemotherapy) was discontinued, 44.9% of nivolumab + ipilimumab-treated patients and 42.4% of chemotherapy-treated patients proceeded to receive subsequent systemic therapy with 4.0% of nivolumab+ ipilimumab and 21.5% of chemotherapy subjects receiving subsequent immunotherapy (anti PD-1/PD-L1, anti CTLA-4, other). This inflated the performance of the chemotherapy arm, preventing an intention-to-treat (ITT) analysis from providing an unbiased comparison of randomised treatments, as is usually required in HTA. Most subjects in the chemotherapy arm switched to immunotherapy after experiencing progression; very few patients in the chemotherapy arm switched prior to progression.

3.1 Potential Impact of Treatment switching

A treatment switching analysis of OS and PFS provides an adjustment for switching/crossover from the control treatment to the experimental treatment in the subsequent line of treatment (Figure 25). OS and PFS were selected as co-primary endpoints as the trial protocol hypothesized that OS can potentially be affected by cross-over therapy to any PD-1/PD-L1 or CTLA-4 targeted therapy that is commercially available or within other clinical trials, whereas PFS is not affected by cross-over, and will help detect any benefit of nivolumab + ipilimumab over the comparator, in particular if OS is confounded by cross-over.

Figure 25. Impact of Treatment Switching



3.2 Definition of Treatment switching in CM743 trial

Treatment switching is defined as initiation of an IO therapy in the chemotherapy arm.

3.3 Treatment switching adjustment methods

Simple and common methods that are not recommended in the literature or in HTA guidance are excluding switchers and censoring on switch. These methods are linked to bias since switching is likely to be related to prognostic factors. Recommended adjustment methods provide a counterfactual estimate for the treatment switchers that accounts for prognostic factors, exploiting the experience of the non-switchers in the sample. The appropriateness of each method depends on the context of switching in the study.

3.4 Treatment switching recommended methods

Different approaches to treatment switching adjustment are described in Table 11.

Table 11. Advanced Treatment Switching Methods and Descriptions

Methods	Description
Inverse Probability Censoring Weights (IPCW)	▪ This method adjusts estimates of a treatment effect in Chemotherapy arm in the presence of any type of informative censoring. ▪ Baseline and visit data are used to model the probability of treatment switching. ▪ Weights are calculated that act to substitute data from patients who are censored at switch with data from similar patients who do not switch treatment.
Two-Stage Estimation (TSE)	▪ This method effectively recognize that the clinical trial is randomized up until the point of disease progression, but beyond that point it essentially becomes an observational study. ▪ If switch occurs before progression, it is assumed that patients switched because of a strong suspicion of progression and date of progression is moved to the date of switch. ▪ Post-progression survival (PPS) in switchers and non-switchers is compared so that a shrinkage or 'acceleration' factor can be estimated to generate counterfactual PPS in switchers.
Rank Preserving Structural Failure Time Model (RPSFTM)	▪ This method estimates an acceleration factor such that no treatment effect is seen when both arms of the trial are compared using counterfactual survival times, i.e., the method works on a hypothetical setting to evaluate what would be the survival times of patients in the absence of any treatment effect. ▪ This acceleration factor is then used to adjust post-switch survival times.
Iterative Parameter Estimation (IPE)	▪ The Iterative Parameter Estimation (IPE) adjustment method is used as an extension of the RPSFTM as it estimates the parameters of the model with the help of a parametric failure time distribution. ▪ The method works around the same assumptions of RPSFTM, however, As the counterfactual survival times must follow a parametric failure time distribution, this method may encounter convergence issues.

3.5 Rationale for choosing IPCW as primary methods

Two-stage estimation (TSE) has been used by HTA to estimate counterfactual survival times for patients who switch treatments – that is, survival times that would have been observed in the absence of switching. However, when switchers do not die during the study, counterfactual censoring times are estimated inducing informative censoring. Re-censoring is usually applied alongside TSE to avoid informative censoring, but it reduces follow-up. RPSFTM and IPE assume that the treatment effect is the same for all participants regardless of when treatment is received. This is unlikely to hold in a RCT.

IPCW represents a robust technique for addressing informative censoring, assuming no unmeasured confounders which leverages data gathered throughout the trial to assess the treatment effect. The IPCW method artificially censors patients at the point of treatment switch; this may introduce bias if probability of switch is associated with any prognostic factors. Weights for the observations associated with remaining patients according to their baseline and time-varying demographic and disease-related characteristics are estimated to adjust for any potential confounding created by the artificial censoring. Thus, IPCW is selected as our primary and preferred method from a HTA perspective and especially considering existence of non-trivial informative censoring - switching prior to progression.

3.6 Results

In this section Table 12 presents the overall results of the treatment switching analysis. Figure 26 to Figure 28 and Table 13 to Table 16 presents the results of the survival analysis based on the treatment switching analysis. Table 17 presents the interpretation of the analysis and selection of distributions to be used in the economic analysis for the treatment switching scenario.

Table 12. Median OS and HR and associated 95% CIs in Chemotherapy arm for ITT and treatment switching adjusted analyses

	OS Analysis				PFS Analysis*			
Model	Median	95% CI of Median	HR	95% CI of HR	Median	95% CI of Median	HR	95% CI of HR
ITT	[redacted]							
IPCW	[redacted]							
Two-stage	[redacted]							
RPSFTM	[redacted]							

	OS Analysis				PFS Analysis*			
Model	Median	95% CI of Median	HR	95% CI of HR	Median	95% CI of Median	HR	95% CI of HR
IPE (exponential fit)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Two-stage method is not applicable for PFS analysis as a secondary baseline cannot be defined from progression

Figure 26. Comparison of ITT and treatment switching adjusted chemotherapy arm OS and PFS

Table 13. Table 3: IPCW adjusted chemotherapy arm OS - Goodness of fit

AIC rank	Model	AIC	BIC
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]		

Table 14. Two-Stage adjusted chemotherapy arm OS - Goodness of fit

AIC rank	Model	AIC	BIC
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]

Table 15. Landmark Survival Probabilities - IPCW adjusted chemotherapy arm OS

Model	6 months	1 Year	2 Years	3 Years	5 Years	10 Years	20 Years
ITT KM (unadjusted)	82.0%	57.7%	27.2%	15.4%	-	-	-
[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]
[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]
[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]

Model	6 months	1 Year	2 Years	3 Years	5 Years	10 Years	20 Years
[redacted]							

Table 16. Landmark Survival Probabilities - Two-stage adjusted chemotherapy arm OS

Model	6 months	1 Year	2 Years	3 Years	5 Years	10 Years	20 Years
ITT KM (unadjusted)	82.0%	57.7%	27.2%	15.4%	-	-	-
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							

Figure 27. Combined parametric and spline models for IPCW adjusted chemotherapy arm OS

Figure 28. Combined parametric and spline fits for Two-stage adjusted chemotherapy arm OS

Table 17. Interpretations of Results and conclusions of Treatment switching analysis of OS and PFS

OS Analysis	PFS Analysis

OS Analysis	PFS Analysis
[redacted]	

3.7 Cost-effectiveness results

Table 18 presents total costs, life-years gained (LYGs), QALYs, and incremental costs per QALY for nivolumab + ipilimumab versus PDC, investigating the impact of the treatment switching analysis. Separate results are presented for the IPCW and two-stage adjustment methods; the base case ICER (Table 10) reduced from £75,322 to [redacted]

Table 18. Base-case incremental results of nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin adjusted for treatment switching

Technologies	Total costs (£)	Total LYGs	Total QALYs	Inc. costs, £	Inc. LYs	Inc. QALYs	Incremental costs per QALY, £
IPCW method							

Technologies	Total costs (£)	Total LYGs	Total QALYs	Inc. costs, £	Inc. LYs	Inc. QALYs	Incremental costs per QALY, £
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two-stage method							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Inc = Incremental; LYG = life-year gained; QALY = quality-adjusted life-year.

Note: the OS and PFS survival distributions are the same as the ITT base case analysis (Table 10).

4 APPENDIX D. HISTOLOGY SPECIFIC SUBGROUP ANALYSES

4.1 Summary of histology specific subgroup analyses

4.1.1 Survival analysis of the 3-year data cut

Survival analysis for the histology subgroups were conducted following the same approach as for the ITT population described in Section 2.1. However, given the paucity of external clinical data for the subgroups there were considerable limitations with regards to external validation of the long-term survival predictions in the selection of the most appropriate distributions.

However, as presented in the company submission the results from CheckMate-743 shows that survival for the histology subgroups is expected to be similar for patients treated with nivolumab + ipilimumab. For the PDC population on the other hand, patients with epithelioid histology would be expected to have a higher long-term survival compared to the non-epithelioid patients. Thus, selection of distributions for nivolumab + ipilimumab was guided by being similar to the log-logistic distribution selected for the ITT population. For PDC, selection of distributions was primarily guided by visual and statistical fit with the premise that epithelioid should have a higher long-term survival than ITT and non-epithelioid a lower survival than ITT.

4.1.2 Selection of base-case distributions

Based on the criteria presented above, Table 19 presents the selected distributions for the subgroup exploratory scenarios.

Table 19. Base-case distributions selected for the histology subgroups

Population	Treatment	Outcome	Distribution
Epithelioid	Nivolumab + ipilimumab	OS	Log-logistic
		PFS	Generalised Gamma
	PDC	OS	Spline odds 1 knot
		PFS	Log-logistic
Non-epithelioid	Nivolumab + ipilimumab	OS	Log-logistic
		PFS	Spline 2 knots normal
	PDC	OS	Log-normal
		PFS	Gamma

Full results of the survival analysis for the subgroups including Kaplan-Meier data, statistical fits, visual fits, and landmark survival data for the histology-specific subgroups are presented in the following sections:

- Epithelioid overall survival (Section 4.2)
- Epithelioid progression-free survival (Section 4.3)
- Non-epithelioid overall survival (Section 4.4)
- Non-epithelioid progression-free survival (Section 4.5)

4.1.3 Cost-effectiveness results

Table 20 presents total costs, life-years gained (LYGs), QALYs, and incremental costs per QALY for nivolumab + ipilimumab versus PDC by histology subgroup, using the distributions presented in Table 19.

Table 20. Base-case incremental results of nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin by histology subgroup

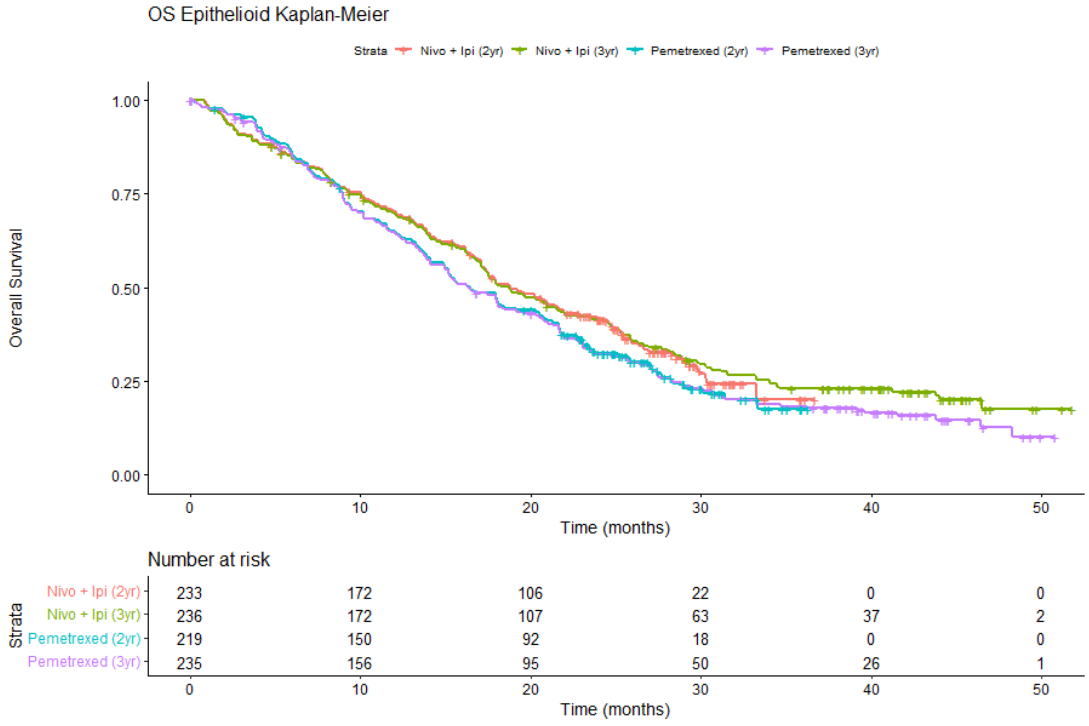
Technologies	Total costs (£)	Total LYGs	Total QALYs	Inc. costs, £	Inc. LYs	Inc. QALYs	Incremental costs per QALY, £
Epithelioid							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	50,972	0.596	0.462	110,323
Non-epithelioid							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	52,373	1.441	1.072	48,871

Inc = Incremental; LYG = life-year gained; QALY = quality-adjusted life-year.

4.2 Epithelioid overall survival

Figure 29 shows the OS KM curves for nivolumab + ipilimumab and pemetrexed + cisplatin or carboplatin for the 2-year and 3-year data cut combined.

Figure 29. CheckMate-743: Kaplan-Meier plot of overall survival (all randomised patients)



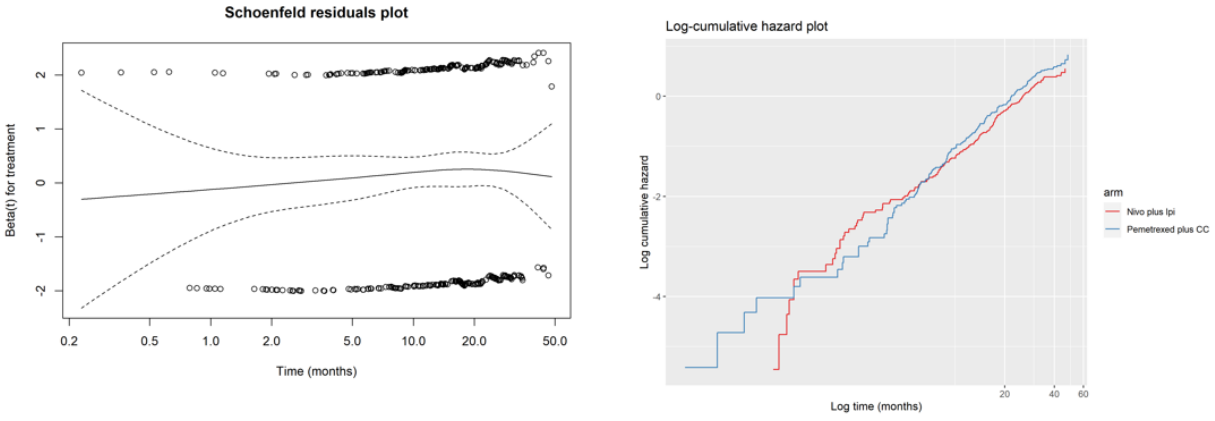
Ipi = ipilimumab; Nivo = nivolumab; OS = overall survival.

Source: BMS data on file (2021).

4.2.1 Testing of proportional hazards assumption

The log-cumulative hazards log-cumulative hazards and Schoenfeld residuals plots are presented in Figure 30. Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time resulted in a p-value of 0.41.

Figure 30. Log-cumulative hazard plot and Schoenfeld residuals plot for nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin for overall survival



4.2.2 Assessing goodness-of-fit of parametric survival models within the trial period

4.2.2.1 Nivolumab + ipilimumab

Table 21 summarises the goodness-of-fit statistics for independent survival models fitted to the OS endpoint of nivolumab + ipilimumab.

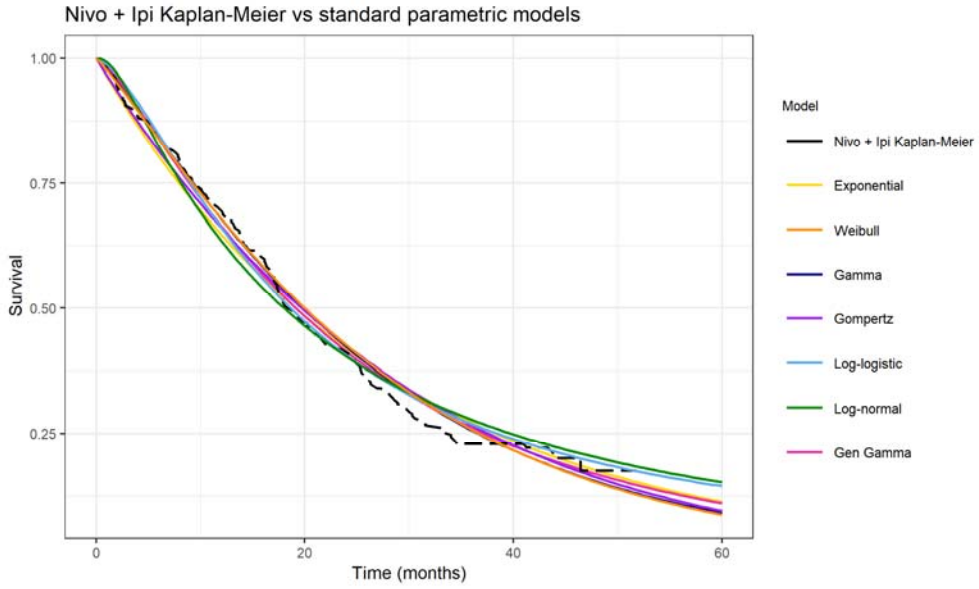
Table 21. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for nivolumab + ipilimumab

Independent model	AIC rank	AIC	BIC
Spline normal 1 knot	1	1,543.18	1,553.56
Spline odds 1 knot	2	1,543.83	1,554.22
Log-logistic	3	1,544.29	1,551.21
Gamma	4	1,544.72	1,551.64
Generalised Gamma	5	1,545.28	1,555.67
Spline normal 2 knots	6	1,545.36	1,559.21
Weibull	7	1,545.76	1,552.68
Spline odds 2 knots	8	1,545.89	1,559.74
Spline hazard 1 knot	9	1,546.31	1,556.70
Spline hazard 2 knots	10	1,546.57	1,560.42
Exponential	11	1,547.80	1,551.26
Gompertz	12	1,549.19	1,556.11
Log-normal	13	1,549.24	1,556.16

AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 31 shows the independent standard parametric models for nivolumab + ipilimumab compared with the CheckMate-743 KM data for OS. Figure 32 shows the equivalent for the independent spline models.

Figure 31. Independent parametric models overlaying the overall survival Kaplan-Meier data for nivolumab + ipilimumab



KM = Kaplan-Meier; Nivo + Ipi = nivolumab + ipilimumab; OS = overall survival.

Figure 32. Independent spline models for nivolumab + ipilimumab overlaying the CheckMate-743 Kaplan-Meier data

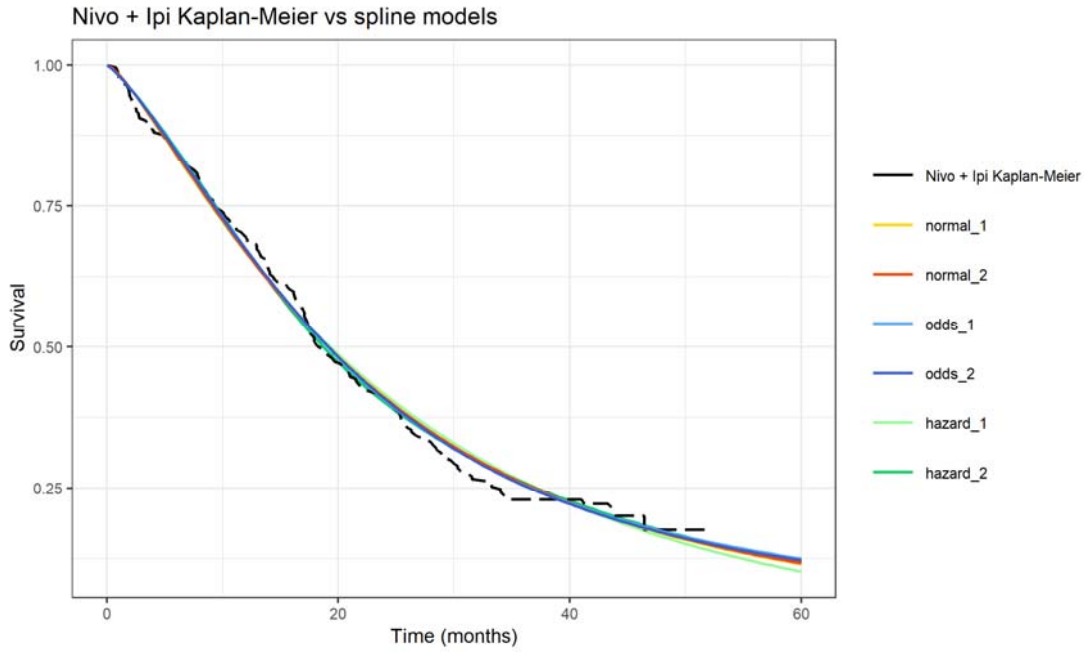


Table 22 presents the landmark OS for each distribution and the CheckMate-743 trial.

Table 22. Landmark absolute overall survival analysis for independent parametric distributions fitted to nivolumab + ipilimuma

		Absolute survival (%)						
Data set	Curve	6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 20
CheckMate-743	Kaplan-Meier	85	70	41	23	-	-	-
Nivolumab + ipilimumab extrapolation	Weibull	84	68	43	26	9	0	0
	Gamma	84	68	42	26	9	1	0
	Gompertz	82	66	43	27	10	0	0
	Generalised gamma	84	66	41	26	11	2	0
	Exponential	80	65	42	27	11	1	0
	Log-logistic	85	66	41	27	15	6	2
	Log-normal	83	63	40	28	15	5	1
	Spline 1 knot hazard	84	67	42	26	10	1	0
	Spline 2 knot hazard	85	67	40	26	12	2	0
	Spline 1 knot odds	85	67	41	26	12	4	1
	Spline 2 knot odds	85	67	41	25	12	4	1
	Spline 1 knot normal	84	67	41	26	12	3	0
	Spline 2 knot normal	84	67	41	26	12	3	0

mos = months; Yr = year.

4.2.2.2 Pemetrexed plus cisplatin or carboplatin

Table 23 summarises the goodness-of-fit statistics for independent survival models fitted to the OS endpoint of pemetrexed + cisplatin or carboplatin.

Table 23. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for pemetrexed + cisplatin or carboplatin

Independent model	AIC rank	AIC	BIC
Spline odds 1 knot	1	1,547.50	1,557.88
Log-logistic	2	1,548.47	1,555.39
Spline odds 2 knots	3	1,549.26	1,563.10
Spline normal 1 knot	4	1,549.27	1,559.65
Spline normal 2 knots	5	1,549.73	1,563.58
Spline hazard 2 knots	6	1,549.98	1,563.82
Gamma	7	1,550.86	1,557.78

Independent model	AIC rank	AIC	BIC
Generalised Gamma	8	1,551.85	1,562.23
Spline hazard 1 knot	9	1,552.39	1,562.77
Weibull	10	1,552.94	1,559.87
Gompertz	11	1,560.86	1,567.78
Exponential	12	1,561.75	1,565.21
Log-normal	13	1,563.03	1,569.96

AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 33 shows the independent parametric models for pemetrexed + cisplatin or carboplatin overlaid on the KM data from CheckMate-743. Figure 34Figure 32 shows the equivalent for the independent spline models.

Figure 33. Independent parametric models overlaying the overall survival Kaplan-Meier data for pemetrexed + cisplatin or carboplatin

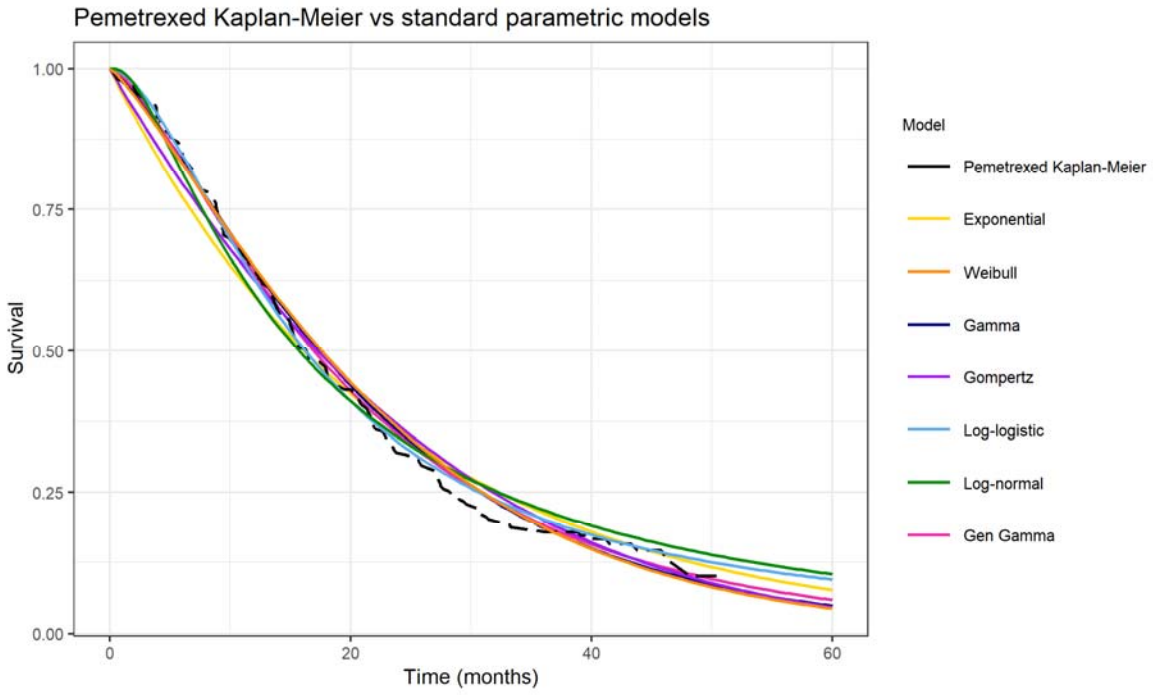


Figure 34. Independent splines models overlaying the overall survival Kaplan-Meier data for pemetrexed + cisplatin or carboplatin

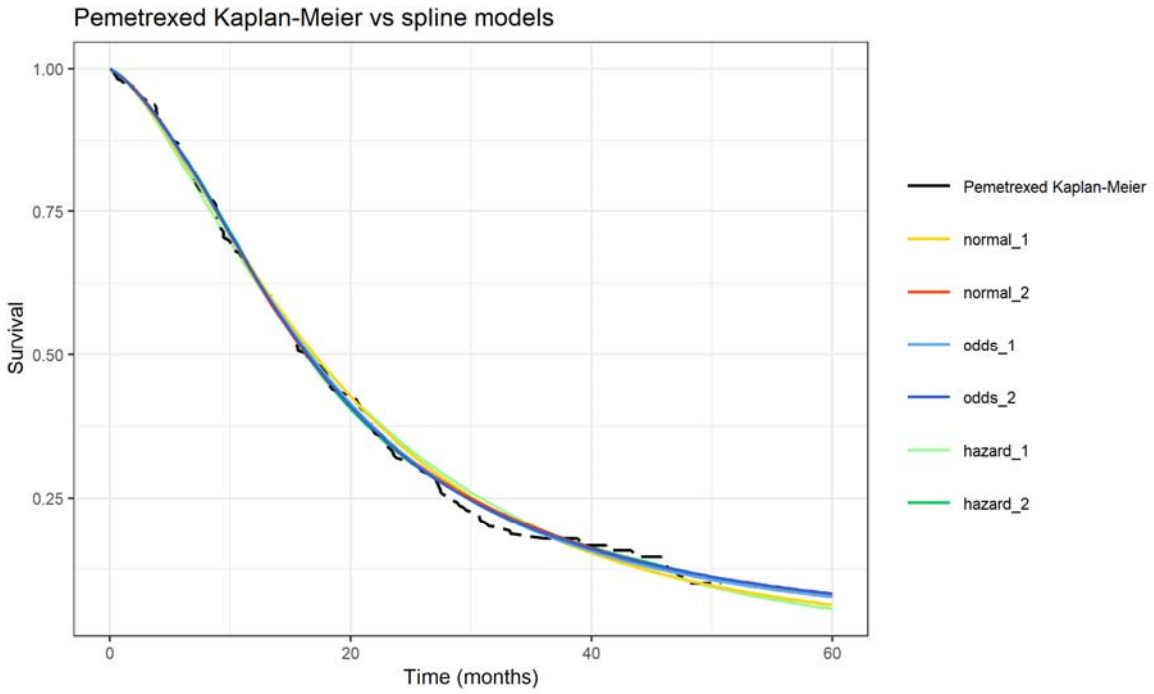


Table 22 presents the landmark OS for each distribution and the CheckMate-743 trial.

Table 24. Landmark absolute overall survival analysis for independent parametric distributions fitted to pemetrexed + cisplatin or carboplatin

		Absolute survival (%)						
Data set	**Curve**	**6 mos**	**Yr 1**	**Yr 2**	**Yr 3**	**Yr 5**	**Yr 10**	**Yr 20**
CheckMate-743	Kaplan-Meier	85	65	32	18	-	-	-
Pemetrexed + cisplatin or carboplatin extrapolation	Weibull	83	65	36	19	4	0	0
	Gamma	84	65	36	19	5	0	0
	Gompertz	80	63	37	20	5	0	0
	Generalized Gamma	84	64	35	19	6	0	0
	Exponential	77	60	36	21	8	1	0
	Log-logistic	85	63	34	20	9	3	1
	Log-normal	82	60	35	22	10	3	1
	Spline hazard 1 knot	83	63	35	19	6	0	0
	Spline hazard 2 knots	85	64	33	19	8	1	0
	Spline odds 1 knot	85	64	33	19	8	2	1
	Spline odds 2 knots	85	64	33	19	8	2	1

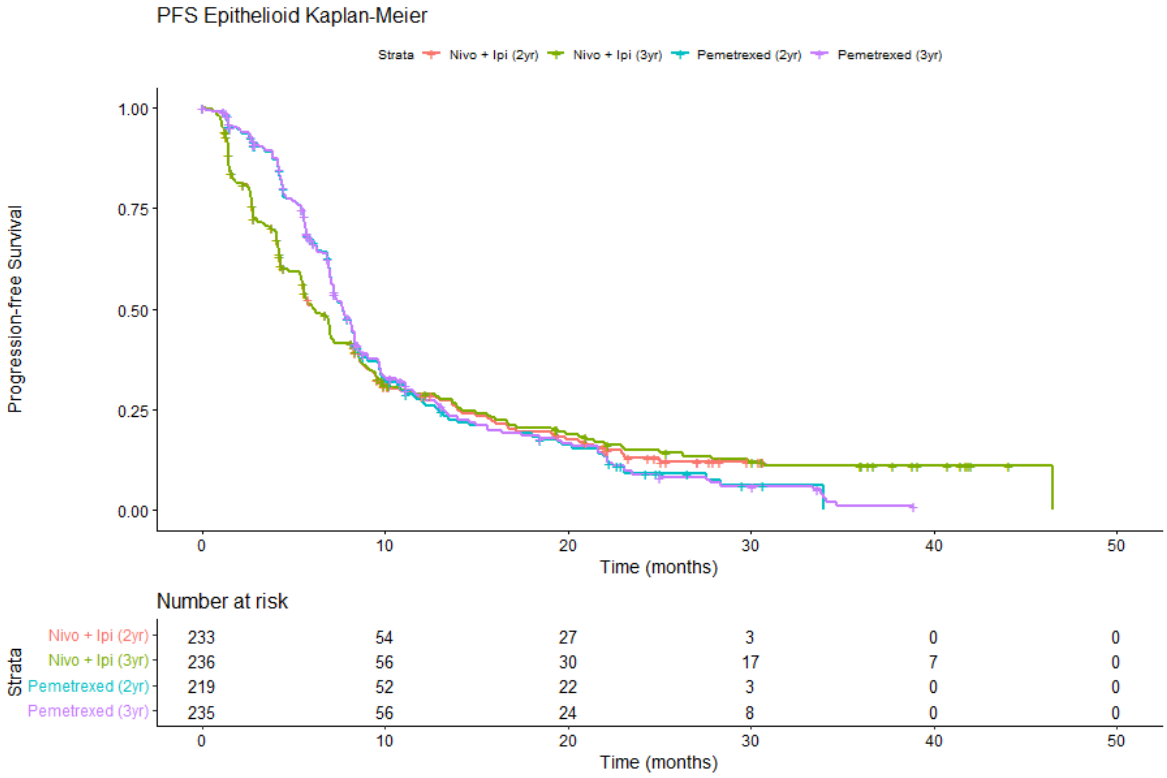
Data set	Curve	Absolute survival (%)						
		6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 20
	Spline normal 1 knot	84	64	35	19	6	1	0
	Spline normal 2 knots	85	64	33	19	8	2	0

Mos = months; Yr = year.

4.3 Epithelioid progression free-survival

Figure 35 shows the PFS KM curves for nivolumab + ipilimumab and pemetrexed + cisplatin or carboplatin for the 2-year and 3-year data cut combined.

Figure 35. CheckMate-743: Kaplan-Meier plot of progression-free survival (all randomised patients)

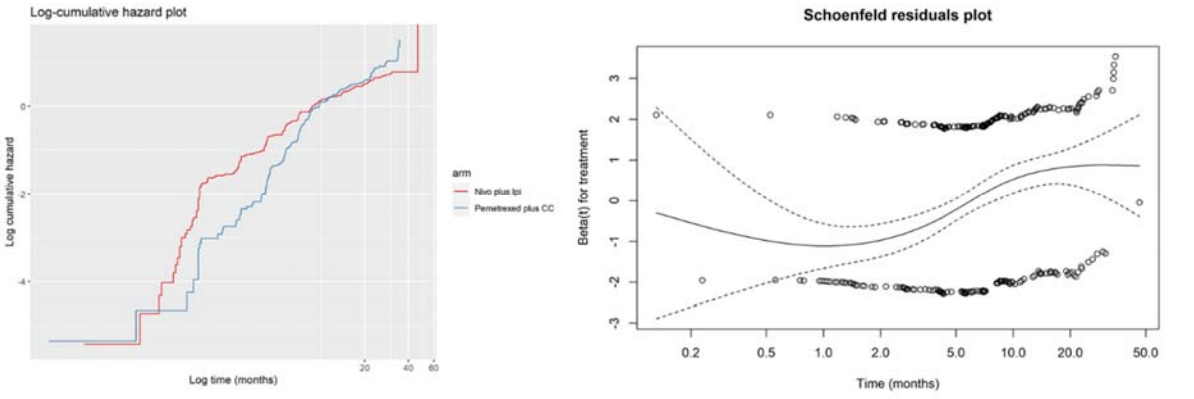


Ipi = ipilimumab; Nivo = nivolumab; PFS = progression-free survival.
Source: BMS data on file (2021).

4.3.1 Testing of proportional hazards assumption

The log-cumulative hazards log-cumulative hazards and Schoenfeld residuals plots are presented in Figure 36. Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time resulted in a p-value of <0.001.

Figure 36. Log-cumulative hazard plot and Schoenfeld residuals plot for nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin for progression-free survival



4.3.2 Assessing goodness-of-fit of parametric survival models within the trial period

4.3.2.1 Nivolumab + ipilimumab

Table 25 summarises the goodness-of-fit statistics for independent survival models fitted to the PFS endpoint of nivolumab + ipilimumab.

Table 25. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to progression-free survival data for nivolumab + ipilimumab

Independent model	AIC rank	AIC	BIC
Generalised Gamma	1	1,190.46	1,200.85
Spline normal 1 knot	2	1,190.65	1,201.04
Spline hazard 1 knot	3	1,192.34	1,202.73
Spline normal 2 knots	4	1,192.39	1,206.24
Spline odds 1 knot	5	1,192.42	1,202.81
Spline odds 2 knots	6	1,193.34	1,207.20
Spline hazard 2 knots	7	1,193.57	1,207.42
Log-normal	8	1,194.60	1,201.52
Log-logistic	9	1,197.91	1,204.84
Gompertz	10	1,213.30	1,220.23
Weibull	11	1,233.05	1,239.98
Exponential	12	1,234.05	1,237.51
Gamma	13	1,235.79	1,242.72

AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 37 shows the independent standard parametric models for nivolumab + ipilimumab compared with the CheckMate-743 KM data for PFS. Figure 38Figure 32 shows the equivalent for the independent spline models.

Figure 37. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for nivolumab + ipilimumab

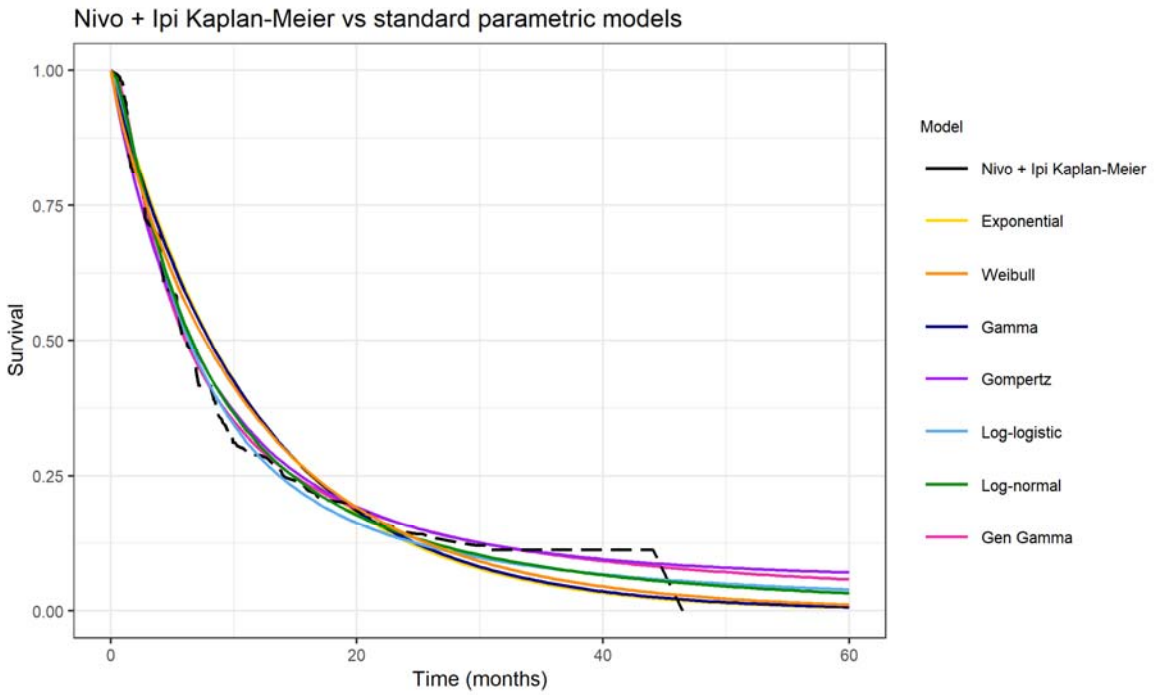


Figure 38. Independent spline models overlaying the progression-free survival Kaplan-Meier data for nivolumab + ipilimumab

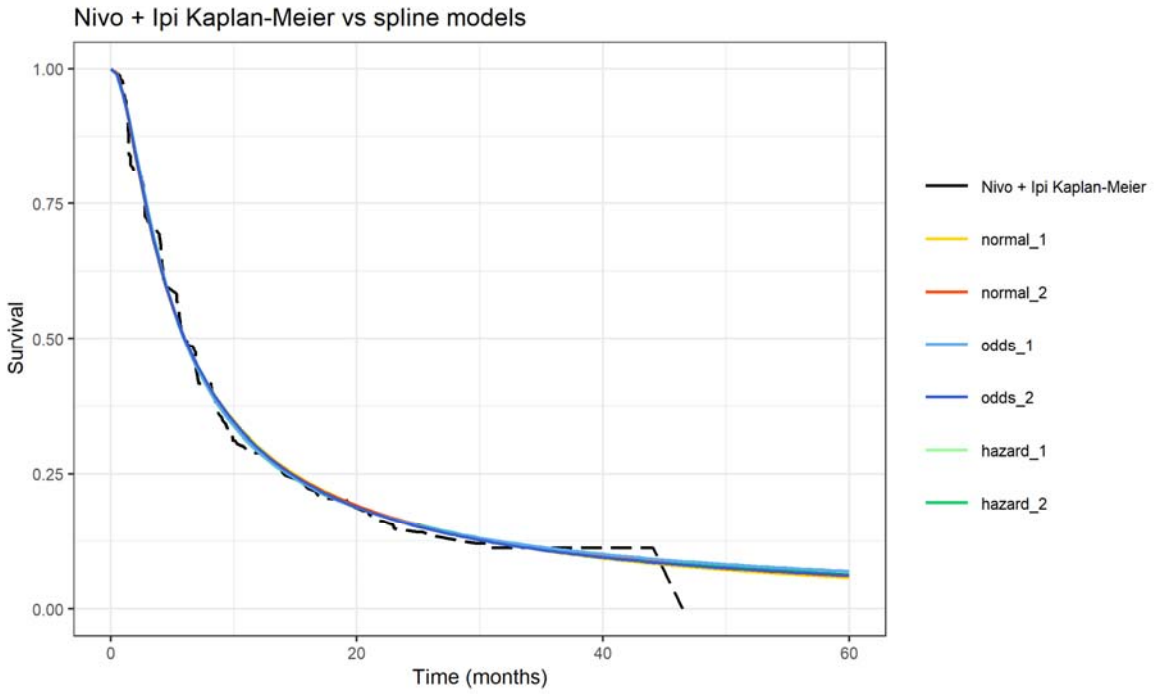


Table 26 presents the landmark PFS for each distribution and the CheckMate-743 trial.

Table 26. Landmark absolute PFS analysis for independent parametric distributions fitted to nivolumab + ipilimumab

		Absolute survival (%)						
Data set	**Curve**	**6 mos**	**Yr 1**	**Yr 2**	**Yr 3**	**Yr 5**	**Yr 10**	**Yr 20**
CheckMate-743	Kaplan-Meier	51	29	15	11	-	-	-
Nivolumab + ipilimumab extrapolation	Weibull	57	35	14	6	1	0	0
	Gamma	59	36	13	5	1	0	0
	Gompertz	52	32	16	10	7	6	6
	Generalised gamma	50	30	16	10	6	2	1
	Exponential	60	36	13	5	1	0	0
	Log-logistic	52	29	13	8	4	1	1
	Log-normal	53	31	14	8	3	1	0
	Spline 1 knot hazard	50	29	16	11	7	3	1
	Spline 2 knot hazard	50	29	16	11	6	2	1
	Spline 1 knot odds	50	29	16	11	7	4	2
	Spline 2 knot odds	50	30	16	11	6	3	1

Data set	Curve	Absolute survival (%)						
		6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 20
	Spline 1 knot normal	50	30	16	10	6	2	1
	Spline 2 knot normal	50	30	16	11	6	2	1

mos = months; Yr = year.

4.3.2.2 Pemetrexed plus cisplatin or carboplatin

Table 27 summarises the goodness-of-fit statistics for independent survival models fitted to the PFS endpoint of pemetrexed + cisplatin or carboplatin.

Table 27. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to progression-free survival data for pemetrexed + cisplatin or carboplatin

Independent model	AIC rank	AIC	BIC
Spline normal 2 knots	1	1,134.61	1,148.44
Spline hazard 2 knots	2	1,135.75	1,149.59
Spline odds 2 knots	3	1,135.77	1,149.61
Log-logistic	4	1,137.47	1,144.39
Spline odds 1 knot	5	1,138.96	1,149.34
Spline hazard 1 knot	6	1,142.77	1,153.15
Spline normal 1 knot	7	1,144.37	1,154.75
Generalised Gamma	8	1,145.95	1,156.33
Gamma	9	1,148.73	1,155.64
Log-normal	10	1,151.46	1,158.38
Weibull	11	1,156.94	1,163.86
Gompertz	12	1,176.28	1,183.20
Exponential	13	1,181.60	1,185.06

AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 39 shows the independent parametric models for pemetrexed + cisplatin or carboplatin overlaid on the KM data from CheckMate-743. Figure 40Figure 32 shows the equivalent for the independent spline models.

Figure 39. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for pemetrexed + cisplatin or carboplatin

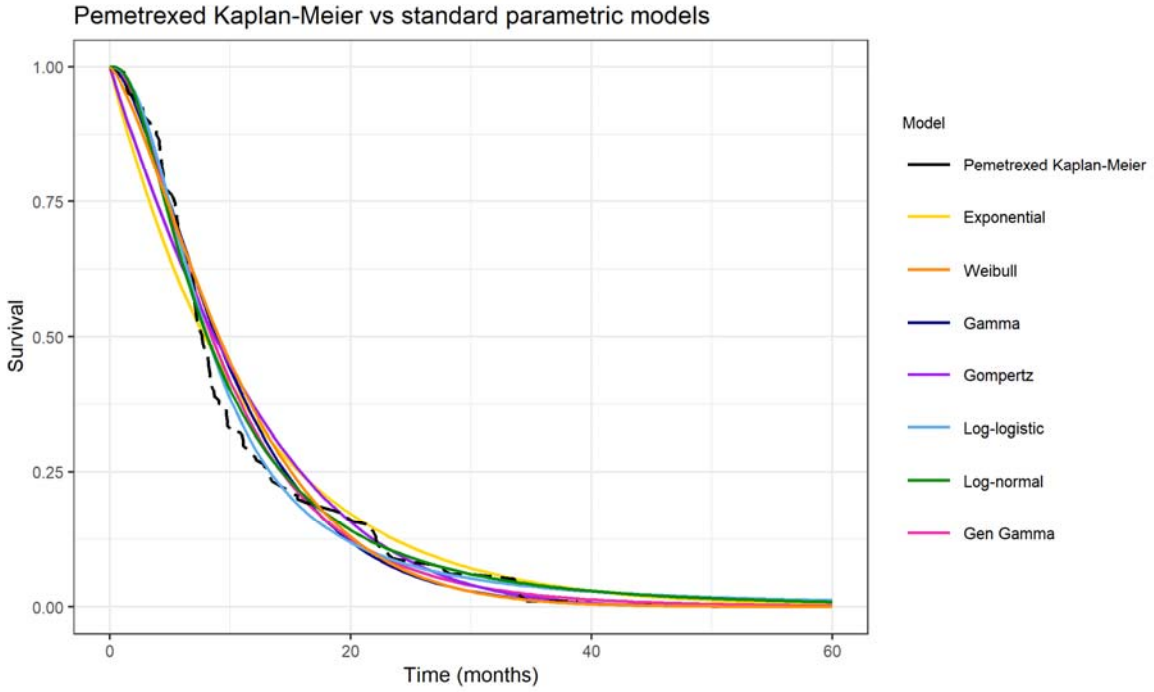


Figure 40. Independent splines models overlaying the progression-free survival Kaplan-Meier data for pemetrexed + cisplatin or carboplatin

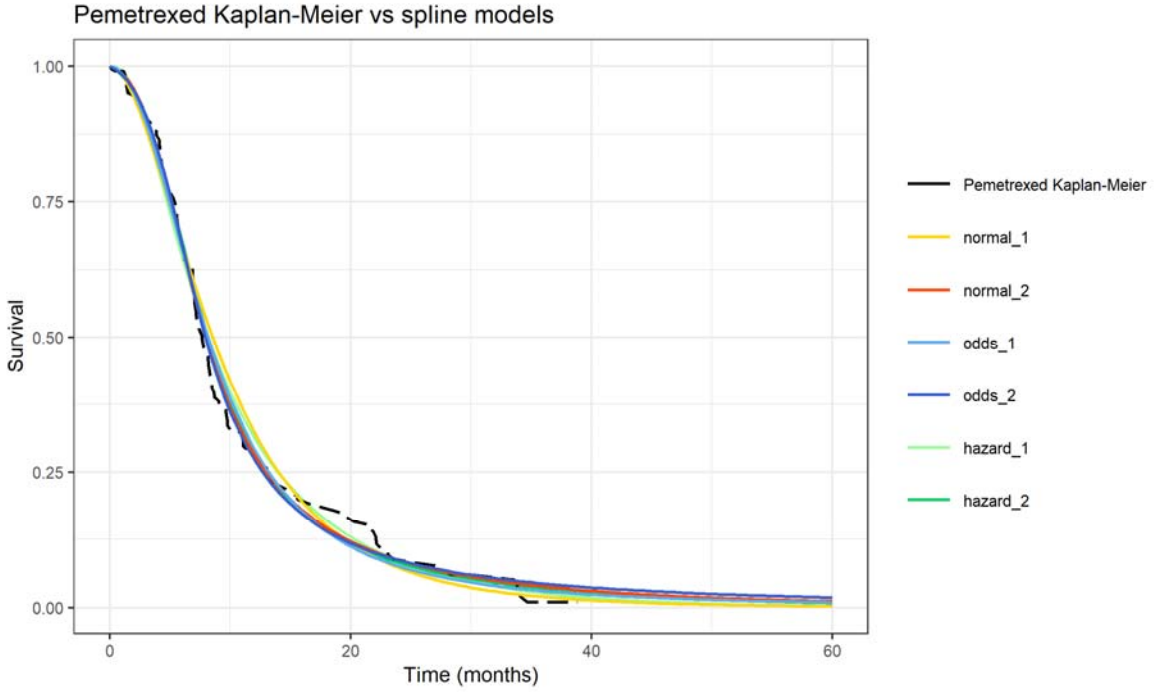


Table 28 presents the landmark OS for each distribution and the CheckMate-743 trial.

Table 28. Landmark absolute overall survival analysis for independent parametric distributions fitted to pemetrexed + cisplatin or carboplatin

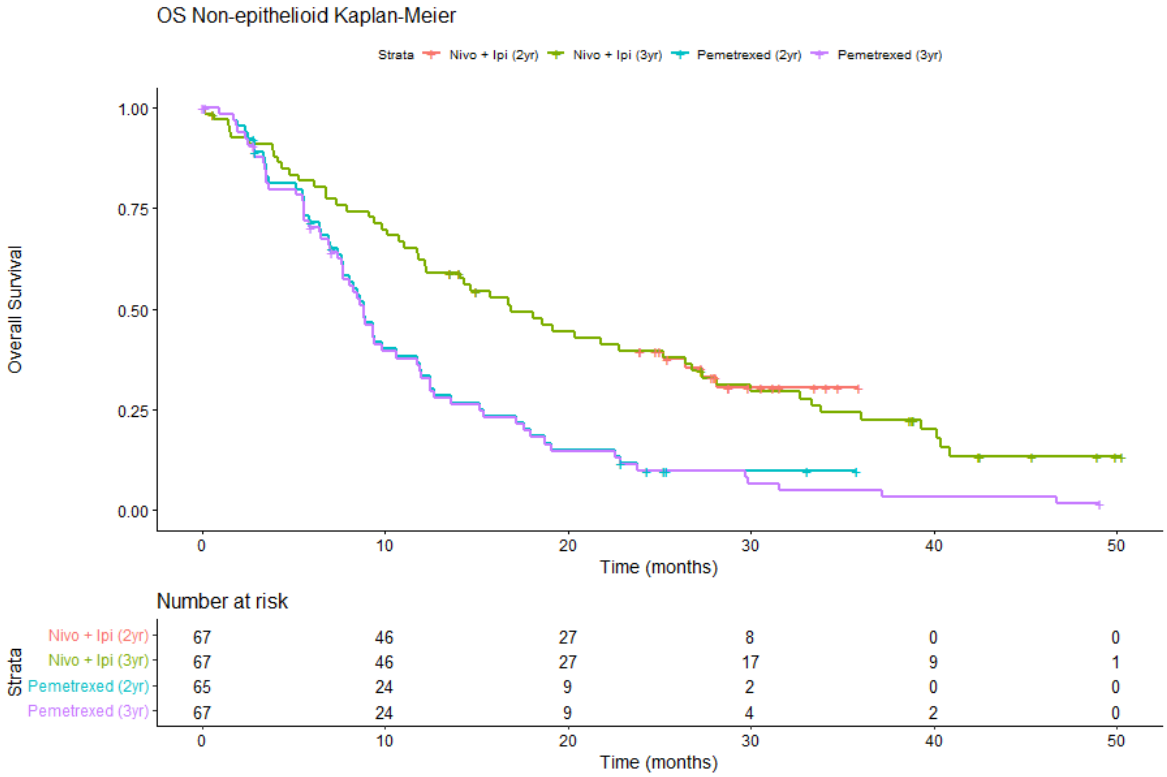
		Absolute survival (%)						
Data set	**Curve**	**6 mos**	**Yr 1**	**Yr 2**	**Yr 3**	**Yr 5**	**Yr 10**	**Yr 20**
CheckMate-743	Kaplan-Meier	68	28	9	1	-	-	-
Pemetrexed + cisplatin or carboplatin extrapolation	Weibull	67	36	7	1	0	0	0
	Gamma	68	35	7	1	0	0	0
	Gompertz	63	37	10	2	0	0	0
	Generalized Gamma	66	33	8	2	0	0	0
	Exponential	59	35	12	4	1	0	0
	Log-logistic	66	29	8	4	1	0	0
	Log-normal	64	32	10	4	1	0	0
	Spline hazard 1 knot	65	31	9	3	0	0	0
	Spline hazard 2 knots	68	28	8	4	1	0	0
	Spline odds 1 knot	66	29	8	3	1	0	0
	Spline odds 2 knots	67	27	9	4	2	1	0
	Spline normal 1 knot	67	32	7	2	0	0	0
	Spline normal 2 knots	67	28	9	4	1	0	0

Mos = months; Yr = year.

4.4 Non-epithelioid overall survival

Figure 41 shows the OS KM curves for nivolumab + ipilimumab and pemetrexed + cisplatin or carboplatin for the 2-year and 3-year data cut combined.

Figure 41. CheckMate-743: Kaplan-Meier plot of overall survival (all randomised patients)



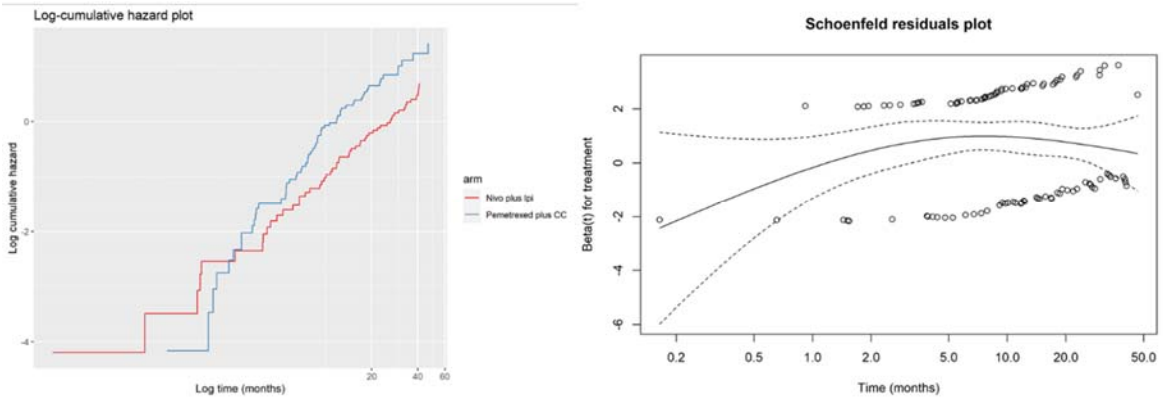
Ipi = ipilimumab; Nivo = nivolumab; OS = overall survival.

Source: BMS data on file (2021).

4.4.1 Testing of proportional hazards assumption

The log-cumulative hazards log-cumulative hazards and Schoenfeld residuals plots are presented in Figure 42. Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time resulted in a p-value of 0.40.

Figure 42. Log-cumulative hazard plot and Schoenfeld residuals plot for nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin for overall survival



4.4.2 Assessing goodness-of-fit of parametric survival models within the trial period Independent models

4.4.2.1 Nivolumab + ipilimumab

Table 29 summarises the goodness-of-fit statistics for independent survival models fitted to the OS endpoint of nivolumab + ipilimumab.

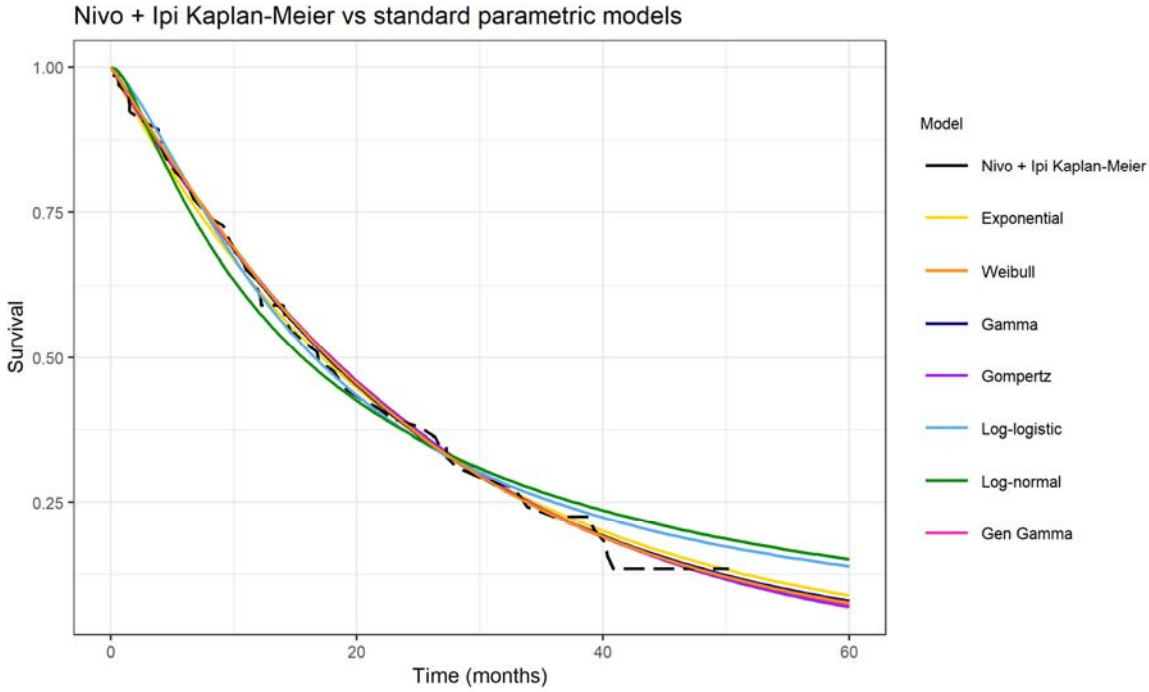
Table 29. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for nivolumab + ipilimumab

Independent model	AIC rank	AIC	BIC
Exponential	1	448.52	450.73
Weibull	2	450.13	454.55
Gamma	3	450.16	454.58
Gompertz	4	450.22	454.63
Spline hazard 1 knot	5	452.13	458.75
Generalised Gamma	6	452.13	458.75
Spline normal 1 knots	7	452.38	459.00
Spline odds 1 knot	8	452.84	459.46
Log-logistic	9	452.96	457.37
Spline hazard 2 knots	10	454.07	462.90
Spline normal 2 knots	11	454.22	463.05
Spline odds 2 knots	12	454.50	463.33
Log-normal	13	457.08	461.49

AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 43 shows the independent parametric models for pemetrexed + cisplatin or carboplatin overlaid on the KM data from CheckMate-743. Figure 44Figure 32 shows the equivalent for the independent spline models.

Figure 43. Independent parametric models overlaying the overall survival Kaplan-Meier data for nivolumab + ipilimumab



KM = Kaplan-Meier; Nivo + Ipi = nivolumab + ipilimumab; OS = overall survival.

Figure 44. Independent spline models for nivolumab + ipilimumab overlaying the CheckMate-743 Kaplan-Meier data

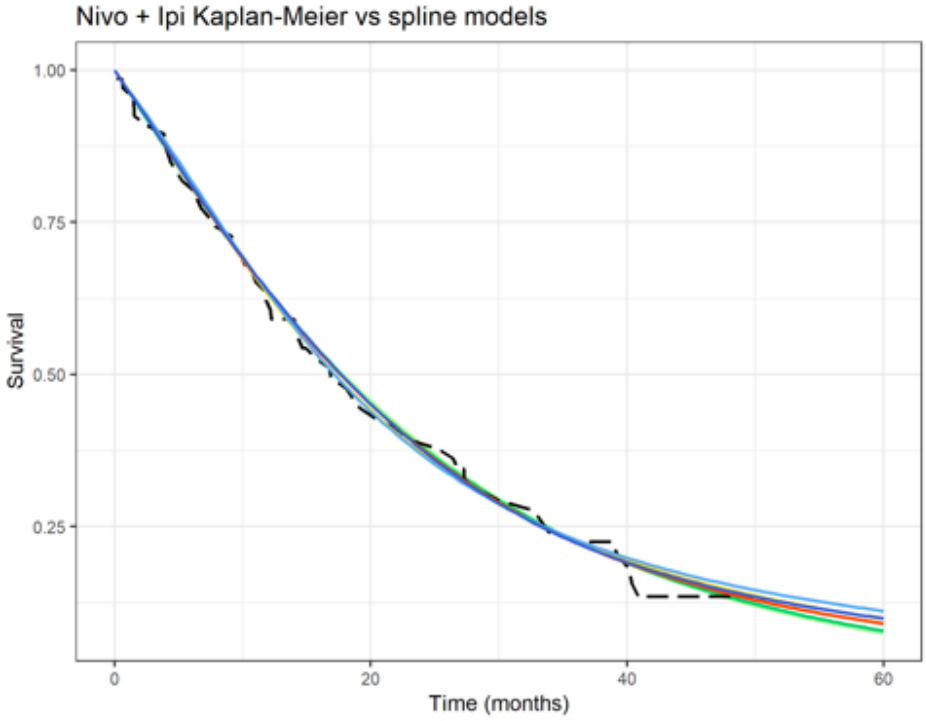


Table 30 presents the landmark OS for each distribution and the CheckMate-743 trial.

Table 30. Landmark absolute overall survival analysis for independent parametric distributions fitted to nivolumab + ipilimumab

		Absolute survival (%)						
Data set	**Curve**	**6 mos**	**Yr 1**	**Yr 2**	**Yr 3**	**Yr 5**	**Yr 10**	**Yr 20**
CheckMate-743	Kaplan-Meier	81.8	62.1	39.5	24.2	-	-	-
Nivolumab + ipilimumab extrapolation	Weibull	80.6	63.5	38.3	22.7	7.7	0.4	0.0
	Gamma	80.4	63.1	38.2	22.8	8.0	0.6	0.0
	Gompertz	80.0	63.5	38.9	22.9	7.0	0.1	0.0
	Generalised gamma	80.6	63.6	38.4	22.7	7.5	0.4	0.0
	Exponential	78.5	61.7	38.1	23.5	8.9	0.8	0.0
	Log-logistic	80.9	61.3	37.2	25.0	13.9	5.7	2.2
	Log-normal	76.8	58.0	37.1	26.1	15.1	5.9	1.8
	Spline 1 knot hazard	80.6	63.6	38.4	22.6	7.5	0.4	0.0
	Spline 2 knot hazard	81.0	63.6	38.0	22.6	7.9	0.5	0.0
	Spline 1 knot odds	81.8	63.4	36.8	22.8	11.2	3.8	1.2

Data set	Curve	Absolute survival (%)						
		6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 20
	Spline 2 knot odds	81.0	63.7	37.6	22.4	9.9	2.9	0.8
	Spline 1 knot normal	81.3	63.1	37.0	22.6	9.9	2.2	0.3
	Spline 2 knot normal	80.9	63.5	37.7	22.4	9.1	1.7	0.2

mos = months; Yr = year.

4.4.2.2 Pemetrexed plus cisplatin or carboplatin

Table 31 summarises the goodness-of-fit statistics for independent survival models fitted to the OS endpoint of pemetrexed + cisplatin or carboplatin.

Table 31. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to overall survival data for pemetrexed + cisplatin or carboplatin

Independent model	AIC rank	AIC	BIC
Log-normal	1	419.97	424.38
Log-logistic	2	420.21	424.62
Spline normal 1 knot	3	421.77	428.38
Generalised Gamma	4	421.82	428.44
Spline hazard 1 knot	5	421.84	428.46
Spline odds 1 knot	6	422.14	428.76
Spline normal 2 knots	7	423.28	432.10
Spline hazard 2 knots	8	423.60	432.42
Gamma	9	423.92	428.33
Spline odds 2 knots	10	424.14	432.96
Weibull	11	426.67	431.08
Exponential	12	430.07	432.28
Gompertz	13	431.45	435.86

AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 45 shows the independent parametric models for pemetrexed + cisplatin or carboplatin overlaid on the KM data from CheckMate-743. Figure 46Figure 32 shows the equivalent for the independent spline models.

Figure 45. Independent parametric models overlaying the overall survival Kaplan-Meier data for pemetrexed + cisplatin or carboplatin

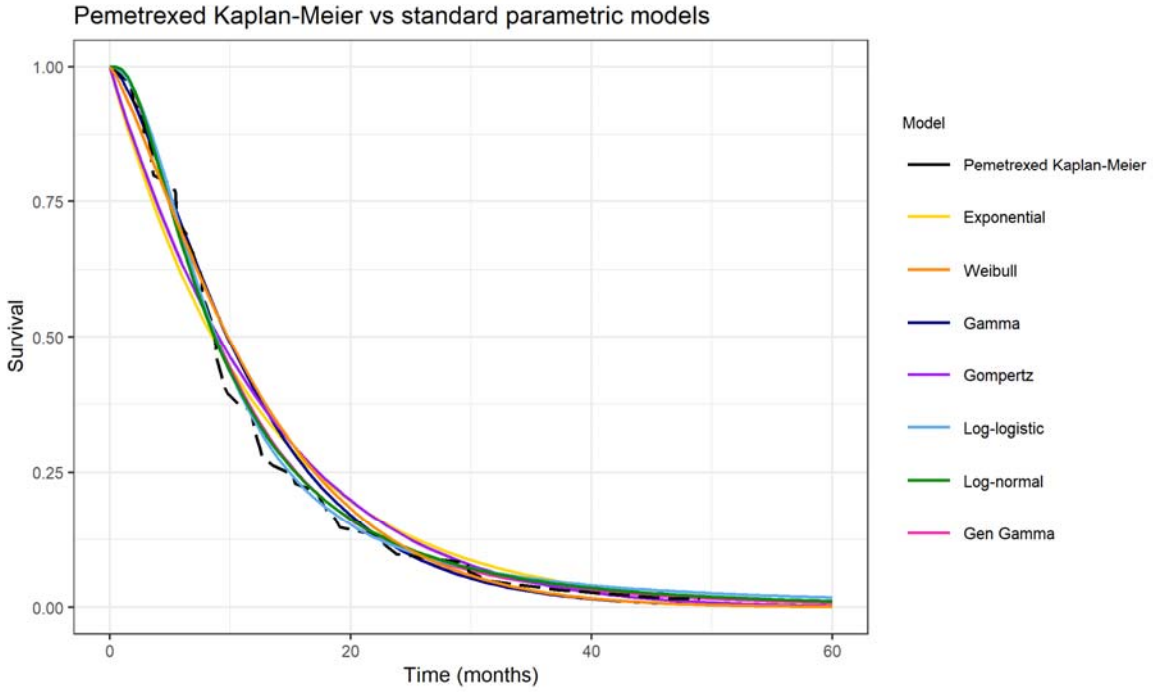


Figure 46. Independent splines models overlaying the overall survival Kaplan-Meier data for pemetrexed + cisplatin or carboplatin

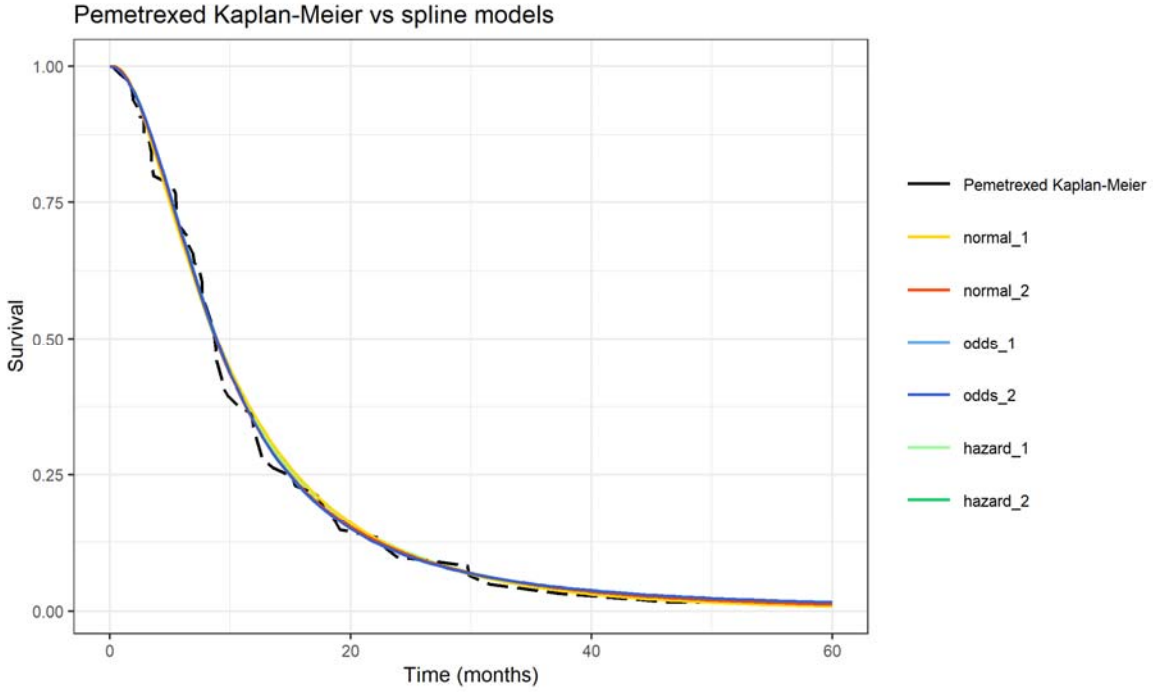


Table 32 presents the landmark OS for each distribution and the CheckMate-743 trial.

Table 32. Landmark absolute overall survival analysis for independent parametric distributions fitted to pemetrexed + cisplatin or carboplatin

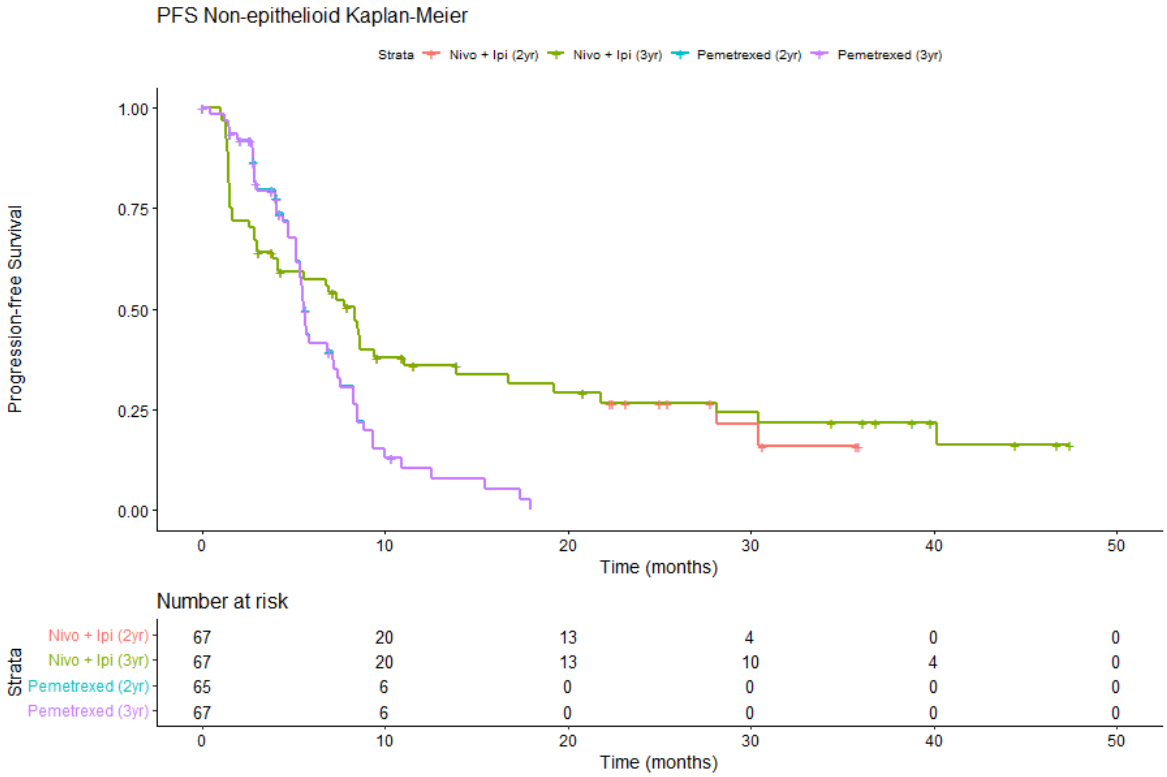
		Absolute survival (%)						
Data set	**Curve**	**6 mos**	**Yr 1**	**Yr 2**	**Yr 3**	**Yr 5**	**Yr 10**	**Yr 20**
CheckMate-743	Kaplan-Meier	70.4	32.8	9.8	4.9	-	-	-
Pemetrexed + cisplatin or carboplatin extrapolation	Weibull	69.0	41.0	11.8	2.8	0.1	0.0	0.0
	Gamma	70.3	40.1	10.8	2.6	0.1	0.0	0.0
	Gompertz	63.6	39.3	13.8	4.2	0.3	0.0	0.0
	Generalised gamma	67.6	35.8	11.3	4.3	0.9	0.0	0.0
	Exponential	61.4	37.7	14.2	5.3	0.8	0.0	0.0
	Log-logistic	68.9	34.4	11.0	5.0	1.8	0.4	0.1
	Log-normal	66.9	35.2	11.6	4.7	1.1	0.1	0.0
	Spline 1 knot hazard	68.1	35.0	11.3	4.5	0.9	0.0	0.0
	Spline 2 knot hazard	69.2	34.6	10.8	4.5	1.1	0.0	0.0
	Spline 1 knot odds	69.1	34.5	10.6	4.7	1.6	0.4	0.1
	Spline 2 knot odds	69.1	34.5	10.6	4.7	1.6	0.4	0.1
	Spline 1 knot normal	67.8	35.9	11.1	4.2	0.9	0.1	0.0
	Spline 2 knot normal	68.9	34.4	10.9	4.6	1.2	0.1	0.0

Mos = months; Yr = year.

4.5 Non-epithelioid progression free-survival

Figure 47 shows the PFS KM curves for nivolumab + ipilimumab and pemetrexed + cisplatin or carboplatin for the 2-year and 3-year data cut combined.

Figure 47. CheckMate-743: Kaplan-Meier plot of progression-free survival (all randomised patients)



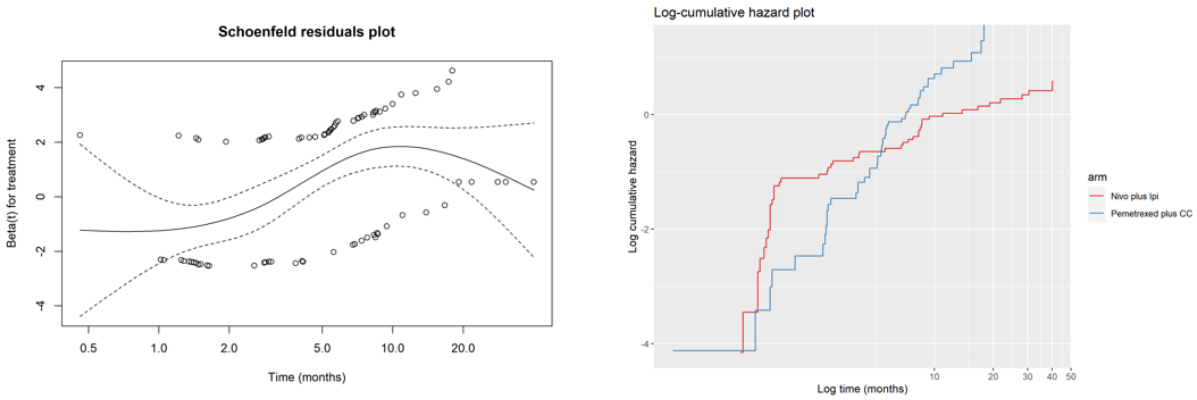
Ipi = ipilimumab; Nivo = nivolumab; OS = overall survival.

Source: BMS data on file (2021).

4.5.1 Testing of proportional hazards assumption

The log-cumulative hazards log-cumulative hazards and Schoenfeld residuals plots are presented in Figure 48. Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time resulted in a p-value of <0.001.

Figure 48. Log-cumulative hazard plot and Schoenfeld residuals plot for nivolumab + ipilimumab versus pemetrexed + cisplatin or carboplatin for progression-free survival



4.5.2 Assessing goodness-of-fit of parametric survival models within the trial period Independent models

4.5.2.1 Nivolumab + ipilimumab

Table 33 summarises the goodness-of-fit statistics for independent survival models fitted to the PFS endpoint of nivolumab + ipilimumab.

Table 33. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to progression-free survival data for nivolumab + ipilimumab

Independent model	AIC rank	AIC	BIC
Spline normal 2 knots	1	318.64	327.45
Spline on odds 2 knots	2	320.94	329.75
Spline on hazard 2 knots	3	323.81	332.62
Spline normal 1 knot	4	326.53	333.13
Spline on odds 1 knot	5	329.87	336.47
Spline on hazard 1 knot	6	331.07	337.67
Log-normal	7	332.20	336.60
Log-logistic	8	335.17	339.58
Gompertz	9	335.42	339.82
Weibull	10	344.11	348.51
Gamma	11	347.08	351.48
Exponential	12	350.15	352.34
Generalised Gamma[a]	13	NA	NA

AIC = Akaike information criterion; BIC = Bayesian information criterion.

[a] Model failed to converge.

Figure 49 shows the independent parametric models for pemetrexed + cisplatin or carboplatin overlaid on the KM data from CheckMate-743. Figure 50Figure 32 shows the equivalent for the independent spline models.

Figure 49. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for nivolumab + ipilimumab

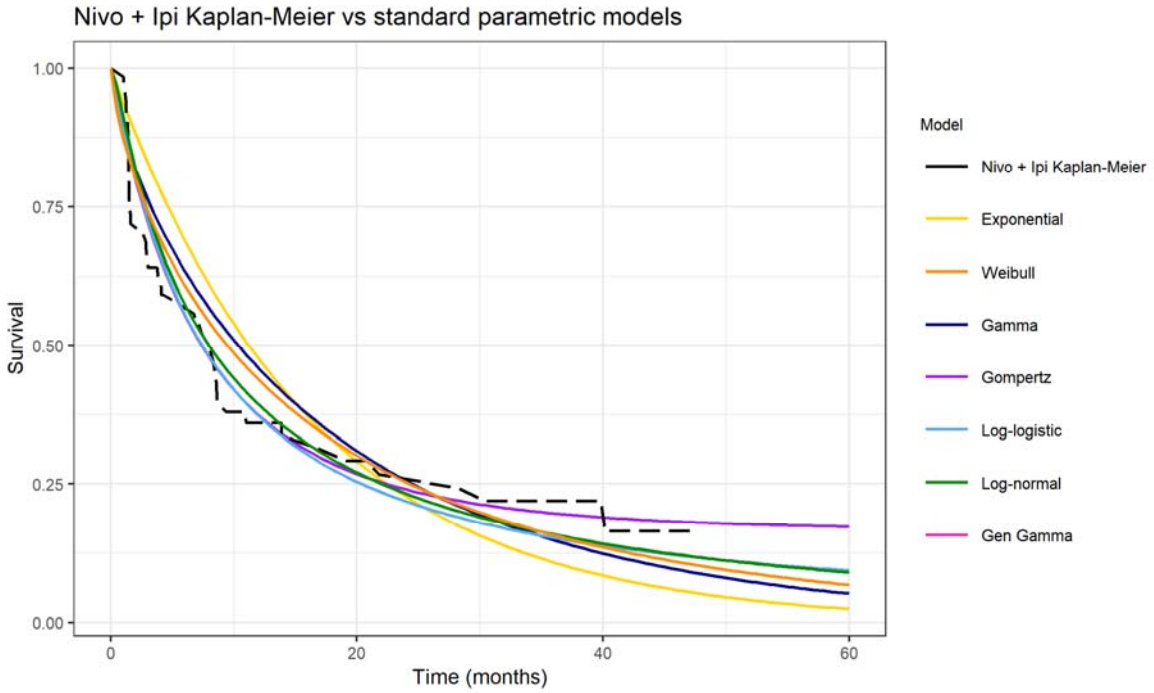


Figure 50. Independent spline models overlaying the progression-free survival Kaplan-Meier data for nivolumab + ipilimumab

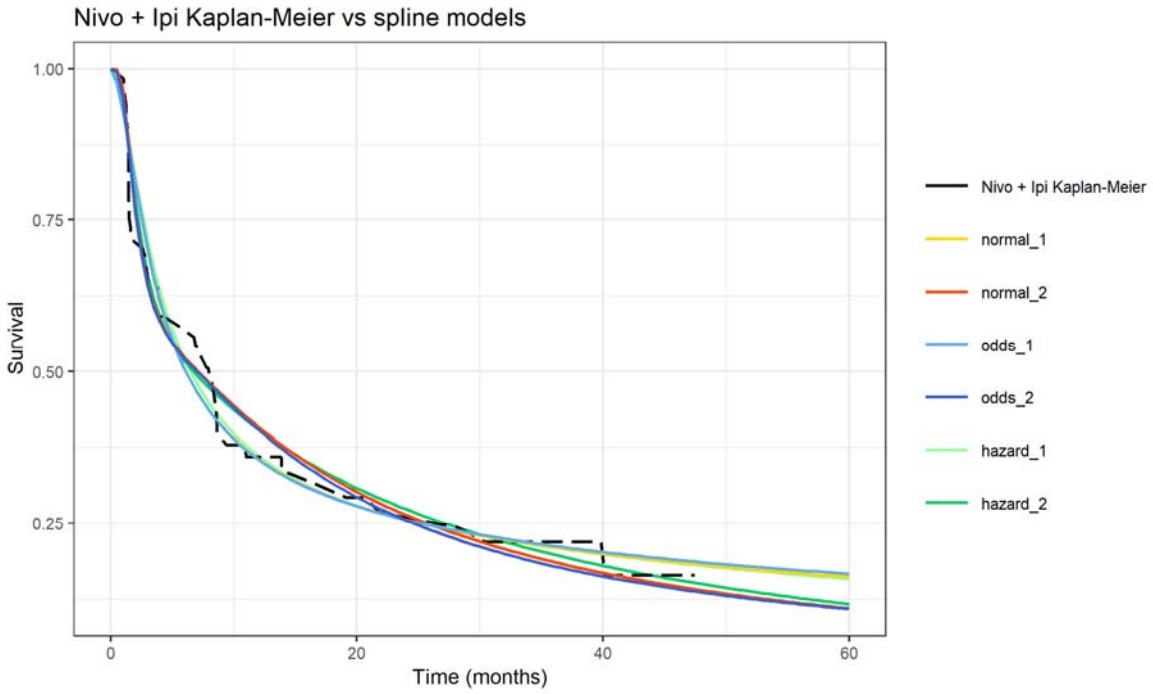


Table 34 presents the landmark OS for each distribution and the CheckMate-743 trial.

Table 34. Landmark absolute progression free-survival analysis for independent parametric distributions fitted to nivolumab + ipilimumab

		Absolute survival (%)						
Data set	**Curve**	**6 mos**	**Yr 1**	**Yr 2**	**Yr 3**	**Yr 5**	**Yr 10**	**Yr 20**
CheckMate-743	Kaplan-Meier	57.4	35.9	26.8	21.9	-	-	-
Nivolumab + ipilimumab extrapolation	Weibull	60.9	43.8	25.3	15.7	6.8	1.1	0.1
	Gamma	63.5	45.9	25.6	14.8	5.2	0.4	0.0
	Gompertz	55.5	37.4	24.0	19.7	17.3	16.7	16.7
	Generalised gamma	50.5	31.7	18.4	13.0	8.2	4.3	2.2
	Exponential	69.0	47.6	22.7	10.8	2.5	0.1	0.0
	Log-logistic	55.8	37.3	21.9	15.3	9.4	4.6	2.2
	Log-normal	57.5	39.3	23.2	15.9	9.0	3.6	1.2
	Spline 1 knot hazard	51.9	36.1	25.5	20.9	15.8	10.0	5.6
	Spline 2 knot hazard	51.7	40.4	27.3	19.8	11.7	4.3	1.0
	Spline 1 knot odds	50.4	35.5	25.6	21.2	16.7	11.8	8.2
	Spline 2 knot odds	52.2	40.4	25.5	17.9	10.9	5.3	2.5

Data set	Curve	Absolute survival (%)						
		6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 20
	Spline 1 knot normal	50.3	35.6	25.5	21.0	16.1	10.8	6.9
	Spline 2 knot normal	52.4	40.9	26.4	18.6	11.0	4.6	1.6

mos = months; Yr = year.

4.5.2.2 Pemetrexed plus cisplatin or carboplatin

Table 35 summarises the goodness-of-fit statistics for independent survival models fitted to the PFS endpoint of pemetrexed + cisplatin or carboplatin.

Table 35. Statistical goodness-of-fit indicator (AIC/BIC) values for independent parametric models fitted to progression-free survival data for pemetrexed + cisplatin or carboplatin

Independent model	AIC rank	AIC	BIC
Gamma	1	271.81	276.22
Weibull	2	272.55	276.96
Spline on odds 1 knot	3	272.89	279.50
Spline normal 1 knot	4	272.96	279.57
Log-logistic	5	273.49	277.90
Generalised Gamma	6	273.68	280.30
Spline on hazard 1 knot	7	273.74	280.36
Spline on hazard 2 knots	8	274.03	282.85
Spline normal 2 knots	9	274.47	283.29
Spline on odds 2 knots	10	274.87	283.69
Log-normal	11	277.41	281.82
Gompertz	12	280.85	285.26
Exponential	13	294.02	296.23

AIC = Akaike information criterion; BIC = Bayesian information criterion.

Figure 51 shows the independent parametric models for pemetrexed + cisplatin or carboplatin overlaid on the KM data from CheckMate-743. Figure 52Figure 32 shows the equivalent for the independent spline models.

Figure 51. Independent parametric models overlaying the progression-free survival Kaplan-Meier data for pemetrexed + cisplatin or carboplatin

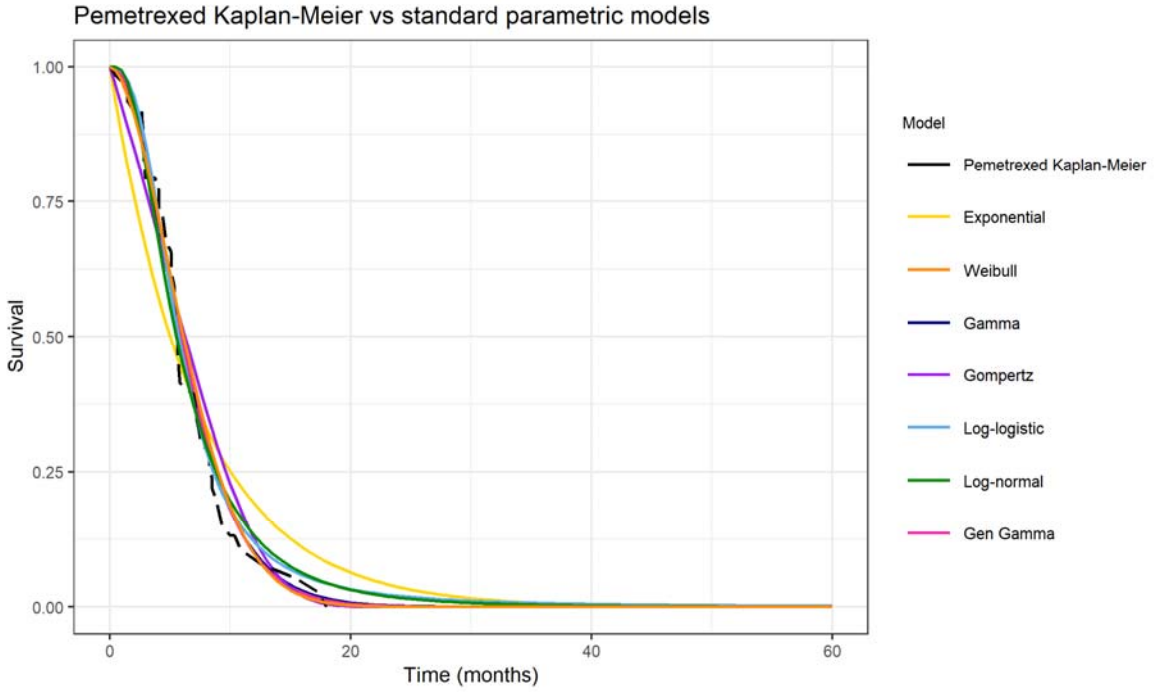


Figure 52. Independent splines models overlaying the progression-free survival Kaplan-Meier data for pemetrexed + cisplatin or carboplatin

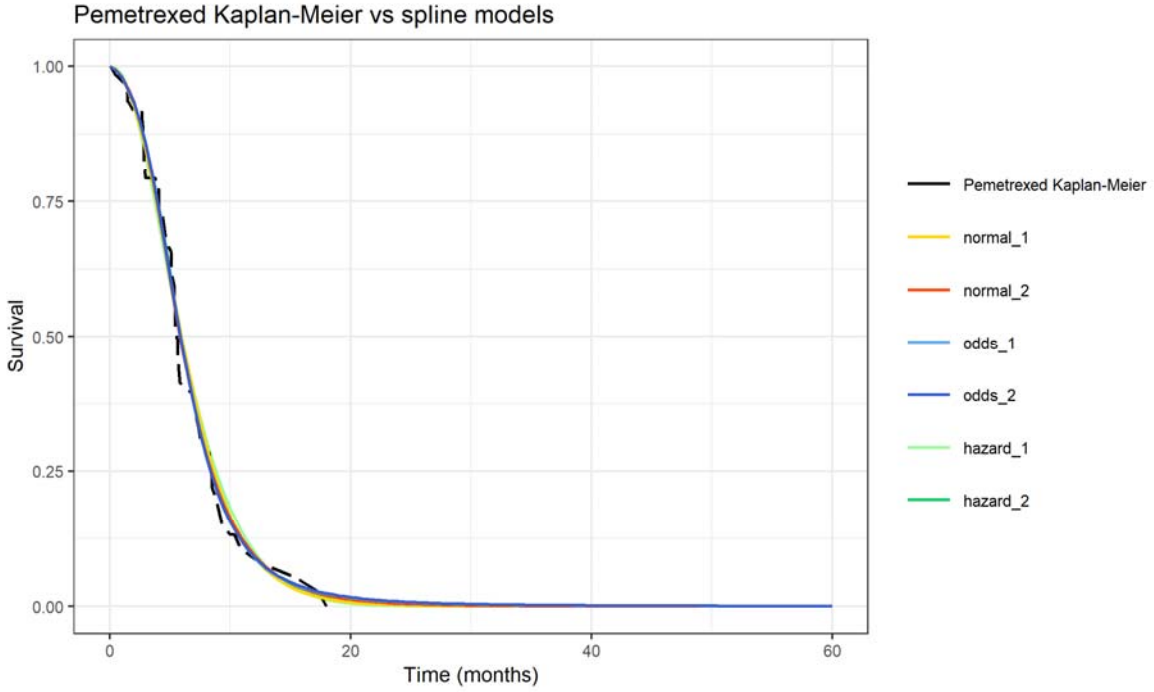


Table 36 presents the landmark OS for each distribution and the CheckMate-743 trial.

Table 36. Landmark absolute progression-free survival analysis for independent parametric distributions fitted to pemetrexed + cisplatin or carboplatin

		Absolute survival (%)						
Data set	Curve	6 mos	Yr 1	Yr 2	Yr 3	Yr 5	Yr 10	Yr 20
CheckMate-743	Kaplan-Meier	41.4	10.5	-	-	-	-	-
Pemetrexed + cisplatin or carboplatin extrapolation	Weibull	51.2	9.7	0.0	0.0	0.0	0.0	0.0
	Gamma	48.7	10.1	0.2	0.0	0.0	0.0	0.0
	Gompertz	52.0	12.5	0.0	0.0	0.0	0.0	0.0
	Generalised Gamma	49.4	9.8	0.1	0.0	0.0	0.0	0.0
	Exponential	43.7	19.1	3.6	0.7	0.0	0.0	0.0
	Log-logistic	47.0	11.9	2.0	0.7	0.2	0.0	0.0
	Log-normal	45.4	13.2	1.7	0.3	0.0	0.0	0.0
	Spline hazard 1 knot	49.1	10.0	0.1	0.0	0.0	0.0	0.0
	Spline hazard 2 knots	48.7	9.2	0.4	0.0	0.0	0.0	0.0
	Spline odds 1 knot	48.6	8.9	0.8	0.2	0.0	0.0	0.0
	Spline odds 2 knots	48.4	9.0	0.9	0.2	0.0	0.0	0.0
	Spline normal 1 knot	49.6	9.0	0.3	0.0	0.0	0.0	0.0
	Spline normal 2 knots	48.0	9.4	0.5	0.1	0.0	0.0	0.0

Mos = months; Yr = year.

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

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

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

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 was once a disease of men in industry which undoubtedly will be hitting its peak. You consultation hasn't addressed the issue now being seen in hospitals of women and younger people in general presenting with this disease. The demographic is changing.

Name	[redacted]
Comments on the ACD:	

General:

I'm a female 56-year-old mesothelioma patient. I'm a wife and mother of an 18-year-old. Having survived breast cancer at age 29 I was given 6-8 months to live in June 2020 in the midst of The Covid pandemic.

In this situation when you are told there are basically no treatment options it is difficult to put into words how it feels.

Your life is over through no fault of your own. At this point you are faced with truths that are very difficult to bear.

I didn't knowingly expose myself to asbestos. I never worked in heavy industry. What was once a predominately older man's disease is now affecting people just like me and younger. I don't believe this disease has peaked, although for the older male industrial workers it probably has. There are a new generation of much younger mesothelioma patients coming through.

This is something that should provoke thought.

To give a patient a glimmer of hope that their life may be extended and even have good quality for a period of time is a powerful thing. For those of us who have mesothelioma the importance of having some options for treatment are a lifeline of hope. It could provide a precious gift of time.

Please think carefully on your decision. We all deserve a chance of a future.

Name	[redacted] Gruppo Italiano Mesothelioma
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

We do not think so .
The extreme Survival Fragility Index and the heavy Censoring rate heavily affects the results shown in the intervention arm . The survival of pats on Ipi/Nivo does not top that of other trials (i.e Chemo/Bevacizumab) and shows a very mild superiority in non epithelial when compared to Chemo alone. Unfortunately the censoring rate in the control arm of IPI/Nivo disallows to conclude for any superiority in this subset of patients either.
Full Results on preparation and available in strict confidentiality

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
No they are not. This is a brief breakdown: the estimated drug cost for Cisplatin/Pemetrexed $46,225 for six cycles whereas the US patent on bevacizumab expired in 2019 and the drug's European patent expires in 2022.
On the other hand the combined cost for Ipilimumab/Nivolumab is approximately $153,800 for four cycles
The analysis of the data provided in the trial does not justify the high cost of the Ipi/Nivo

Are the recommendations sound and a suitable basis for guidance to the NHS?
At the moment we have no evidence enough to recommend IPI/Nivo for any subtype of Meso
Remind the strictly confidential full analysis in preparation for submission is available for your perusal and considerations

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?
No

Name	[redacted] University of Hull
Comments on the ACD:	

Has all of the relevant evidence been taken into account?
No the national mesothelioma audit 2020 has not been included and this is pertinent as it shows 40% received sact
The committee have not considered the fact that more and more patients are accessing immunotherapy through legal means i.e. suing those companies that exposed patients to asbestos for the cost of treatment.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
The comparison with registry data is not justified as this will included PS 3 and 4 patients where as the trial does not, thereby skewing the survival.
The comments about PDL1 are spurious as many tumour sites have initiated such measurements when immunotherapy has been introduced into practice.

Are the recommendations sound and a suitable basis for guidance to the NHS?
no

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?

Name	[redacted]
Comments on the ACD:	

General:
In the last paragraph under why the committee made the recommendations, there is a sentence that states 'because its cost effectiveness is uncertain, it is not recommended for routine use in the NHS.' but then in the last sentence in the paragraph it states 'Nivolumab plus ipilimumab does not meet the criteria to be considered for the Cancer Drugs Fund because it currently does not have the potential to be cost effective.' It's a bit confusing reading that cost-effectiveness is uncertain then going on to read that it does not have the potential to be cost effective. Suggest for some consistency here

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Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

Consultation on the appraisal consultation document – deadline for comments 5pm on Monday 20 September. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities.	

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	Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**	
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Bristol Myers Squibb	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A	
Name of commentator person completing form:	Eleni Theodorou	

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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.	ERG response
	Thank you for giving us the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. We are disappointed with the Committee's draft recommendation as nivolumab + ipilimumab is an effective treatment option that has the potential to improve outcomes for patients with untreated unresectable mesothelioma (MPM). In this rare, highly aggressive disease in which no new treatments have been licensed since 2009, and no other trials have shown a clinically meaningful improvement in OS, the statistically and clinically meaningful survival benefit is of great importance to patients and their families. Specific comments are detailed below.	The company have submitted a new cost effectiveness model with updated results. Notably, the company have updated their survival analysis with new data. The updated model employs one of the ERG preferred adjustments (the switch to treatment-independent utilities from 3 years onwards) but does not include treatment-waning and the use of parametric distributions to model time-to-treatment discontinuation (use of mean number of doses instead). The impact of the latter is relatively small, but the impact of potential treatment waning is significant. The ERG provides scenario analyses in the addendum.
1	**Section 3.7. Second-line treatments used in Checkmate 743 do not reflect UK clinical practice** We agree with the ERG and appraisal committee that current second line treatments for MPM are not established due to a lack of relevant guidelines, no standard of care therapy and the recent use of nivolumab monotherapy as a second line treatment during the COVID-19 pandemic. Moreover, we agree that adjusting overall survival for second-line immunotherapies would better reflect the difference between nivolumab plus ipilimumab and chemotherapy. We have performed a treatment switching analysis using the new 3-year database lock data cut in which the chemotherapy arm OS data have been adjusted to account for patients that switch to second-line immunotherapies. Full details of the analysis are presented in Appendix C. The cost-effectiveness results were explored using two methods for adjusting for treatment switching (Appendix C, section 3.7). The revised base case	The ERG can confirm that appropriate methods, as reflected in TSD 18,[1] of adjustment for treatment switching in the comparator arm of the trial were used, as reported in Appendix C to company comments on the ACD.[2] Also, Table 12 of the appendices shows little difference between the various methods in chemotherapy arm median survival or the hazard ratio (HR) of nivolumab plus ipilimumab vs. chemotherapy.

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	ICER using the 3-year database lock (Appendix B, Table 10) reduced from £76,844 to [redacted] and [redacted] using the IPCW and two-stage methods, respectively. Please note, there is also a typographical error in Section 3.7 on page 10 where the fact that 24% of patients received vinorelbine second line is stated twice.	
2	**Section 3.8. Nivolumab plus ipilimumab improves overall survival compared with chemotherapy, but its effect may be overestimated** This section of the ACD concludes that "nivolumab plus ipilimumab reduces the risk of death in people with malignant pleural mesothelioma compared with chemotherapy, but that the interim trial analysis may have overestimated the magnitude of this difference", this statement is not supported and based on the evidence we present here we consider it inaccurate. In the ACD, it is stated that "overall survival with chemotherapy was around 20% at 3 years on the Kaplan–Meier curve of the trial data. This is much higher than the 8% to 10% survival at 3 years from UK registry and UK audit data" and note that changes in mesothelioma management may explain this difference. However, this would also suggest the current efficacy benefit of nivolumab + ipilimumab is currently underestimated versus UK practice. The ACD later states that "The committee also recognised that early results from trials that report benefit are likely to overestimate the treatment effect of the drug under investigation." We are unaware of any evidence to support this statement; indeed, prior trials of IO therapies have consistently shown that early analyses underestimate the survival benefit of IO therapies – due to the delayed effect vs. chemotherapy and the longer-term survival benefit in some patients. Antonia et al. (2019) reported a pooled analysis of four trials of nivolumab in previously treated non-small cell lung cancer (NSCLC; CheckMate 017, 057, 063 and 003) when a minimum of four-years follow-up were available. Across all four studies, OS benefits with nivolumab were maintained with this additional long-term data. Borghaei et al. (2021) have	As reported in the Appendix A, the latest data cut shows that overall survival at three years is lower than reported in the CS i.e., 15% vs. 20%.[2] The HR in the latest data-cut is however little changed: 0.73 (95% CI: 0.61-0.87) vs. 0.74 (96.6% CI: 0.60 to 0.9). Therefore, the ERG would agree with the company in disputing the applicability to Checkmate 743 of the assertion: "…that early results from trials that report benefit are likely to overestimate the treatment effect of the drug under investigation." The ERG would also dispute the applicability of the trials cited by the company in different populations, e.g. CheckMate 017, 057, 063 and 003 in NSCLC, but direct evidence from Checkmate 743 for inference up to 3 years and perhaps up to 5 years means that evidence from these other trials is probably of little value.

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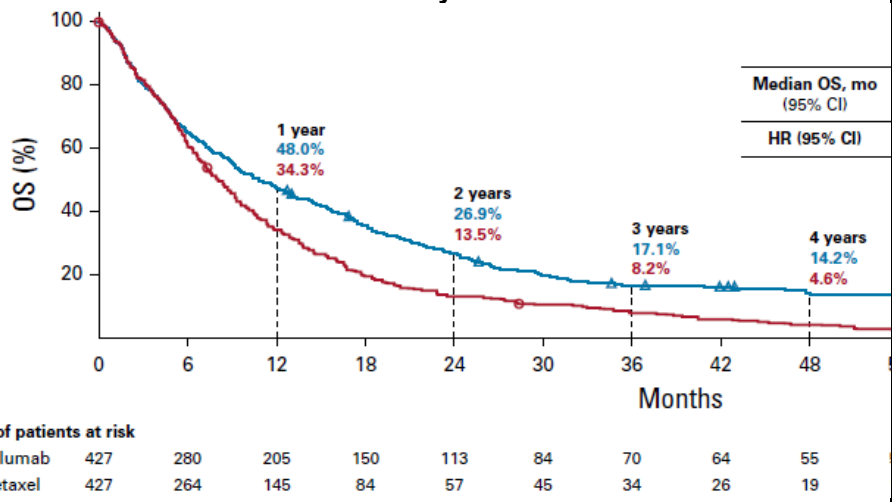
	now published 5-year follow-up data for CheckMate-017 and -057 and nivolumab continues to demonstrate a survival benefit versus docetaxel, exhibiting a 5-times greater OS rate (Five-year pooled OS rate of 13.4% for nivolumab-treated patients vs. 2.6% for docetaxel-treated patients (Figure 1). This clearly shows that the anticipated benefit of nivolumab based on the early results has been sustained or improved through 5-years of follow-up. Rothwell et al. (2020) use the example of nivolumab in the second line treatment of NSCLC as a case study of the impact of uncertainty in survival on HTA decision-making in the UK and demonstrate that in this case, the early clinical data under-estimated the long-term OS benefit that became apparent following additional follow-up in the Cancer Drugs Fund. **Figure 1. Overall survival of all treated patients in the pooled CheckMate-017 and 057 trials at the 5-year database lock**  **No. of patients at risk** Nivolumab 427 280 205 150 113 84 70 64 55 Docetaxel 427 264 145 84 57 45 34 26 19 Source: Borghaei et al. (2021)	

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	Based on this, the statement in the ACD "nivolumab plus ipilimumab reduces the risk of death in people with malignant pleural mesothelioma compared with chemotherapy, but that the interim trial analysis may have overestimated the magnitude of this difference" is not supported by evidence. In section 3.24 of the ACD, the committee note that further evidence on the long-term effect of nivolumab plus ipilimumab is required. Longer term data from CheckMate-743 are now available and are presented in Appendix A, these demonstrate consistent hazard-ratios for OS with this additional follow-up vs. that presented in our submission. There is a continuing OS benefit for patients treated with nivolumab + ipilimumab vs. those treated with chemotherapy, however additional follow-up, such as in the CDF, would further reduce uncertainty. Updated survival analyses based on this data cut has been conducted and outcome of these analyses are presented in Appendix B.	
3	**Section 3.9. Nivolumab plus ipilimumab had no impact on progression-free survival** We agree that there are limitations with PFS as an outcome measure in MPM. However, since the committee note in Section 3.24 that further evidence is required, the longer-term data now available are presented in Appendix A. These data show that with longer follow-up (minimum of 35.5 months vs 22.1 months in the analysis in the original submission), a PFS benefit for nivolumab + ipilimumab is beginning to become apparent. Furthermore, patients treated with nivolumab + ipilimumab demonstrate a durable response with 28% of responders treated with nivolumab + ipilimumab remaining in response compared with none of those treated with chemotherapy. It is likely that this continued response in the nivolumab + ipilimumab arm will translate into further PFS and OS benefits as follow-up continues.	Appendix A shows that the point estimate for PFS has moved below 1 and the 95% CI shifted down for the latest data-cut vs. the one in the CS: 0.92 (0.76-1.11) vs. 1.00 (0.82-1.21).[2] Given that at 3 years 14% of nivolumab + ipilimumab patients remained progression-free compared with only 1% of chemotherapy-treated patients, it is reasonable to expect that there might be a gain, albeit small, in PFS with nivolumab + ipilimumab.
4	**Section 3.10. The effect of nivolumab plus ipilimumab compared with chemotherapy may be modified by histological subtype**	Figure 1 of the appendices shows that the HR for epithelioid histology is considerable higher than with non-epthelioid (0.85 vs. 0.48 and that the 95%

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	In Appendix D we provide further analyses for histology subgroups. Nonetheless, BMS maintain that given the high unmet need, consistent efficacy of nivolumab + ipilimumab across histologies, and lack of alternative treatments in this indication, the use of nivolumab + ipilimumab should not be limited by histology. There remain issues with histological subtyping in MPM, as the tumours are heterogeneous in nature, and, in clinical practice, histological subtype can be a broad spectrum that is hard to define. Evidence shows that the plasticity of tumour cells means that epithelioid cells can mutate to sarcomatoid cells within the tumour over time and biphasic disease can be misdiagnosed as epithelioid. Indeed, clinicians advise that samples from different areas may have different histology and tumours may also evolve over time. Therefore, histology should not be used in clinical decision-making. In terms of nivolumab + ipilimumab, the CheckMate-743 trial was not powered to assess efficacy by histology subgroups, therefore any differences seen may be due to chance and should not drive treatment decisions. Furthermore, as treatment options are so limited, there is a need for new effective treatments for all patients with MPM, regardless of histology. In CheckMate-743 an OS benefit was observed in epithelioid and non-epithelioid subgroups, with similar median OS for nivolumab + ipilimumab in both histology subgroups. The treatment effect of nivolumab + ipilimumab versus PDC was more pronounced in the non-epithelioid subgroup (HR, 0.46) than in the epithelioid subgroup (HR, 0.86) at the original analysis, and this was maintained in the latest data cut presented in Appendix A. The results of the cost-effectiveness analyses by histology subgroup should always be interpreted in the context of these uncertainties. Any selection strategy by histology in this population would likely be associated with significant opportunity costs, particularly in terms of foregone health benefits of patients that could benefit from efficient treatment.	CI for the former overlaps 1.[2] Although there remains some uncertainty, this confirms that there the effectiveness of nivolumab is modified by histological subtype.

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5	**Section 3.14. A 2-year stopping rule for nivolumab plus ipilimumab and a 6-cycle stopping rule for chemotherapy is appropriate** We are pleased that the appraisal committee agreed that the stopping rule is appropriate. However, we disagree with the point made that "protocol violations related to the 2-year stopping rule in the trial means that the results may overestimate the treatment effect of nivolumab plus ipilimumab". In the CheckMate-743 trial, two patients remained on therapy after 24 months. However, assessment of the time-to-treatment discontinuation data suggests that they did not receive additional doses but a short delay in their final dose, likely due to scheduling/logistics. No patients received nivolumab or ipilimumab beyond month 26. Therefore, the impact of this in terms of efficacy would be negligible.	Given that the two patients who received nivolumab + ipilimumab received delayed doses after 24 months rather than additional doses, the ERG considers this issue resolved.
6	**Section 3.15. The model structure is acceptable, but the extrapolations are uncertain** We agree that there is uncertainty in the survival extrapolations, but the new clinical data with additional follow-up and subsequent survival analyses presented in Appendix B help to reduce that uncertainty; additional follow-up during a period in the CDF would address this concern further. Furthermore, the accrual of progression-free life years after the trial is often seen with immuno-oncology therapies, where PFS is below chemotherapy initially but has a long-term benefit for responders. As noted in response to comment 3 above, the most recent data cut with minimum 3-year follow-up demonstrates continued PFS and DoR in patients treated with nivolumab + ipilimumab.	It seems indeed plausible that the new clinical data with additional follow-up and subsequent survival analyses presented in Appendix B help to reduce that uncertainty; additional follow-up during a period in the CDF would address this concern further.[2] The ERG comment related to the model structure related to the plausibility and uncertainties of the partitioned survival model extrapolations. The impact of the limitations related to the partitioned survival model (highlighted in NICE DSU TSD 19), such as the extrapolations of PFS and OS while assuming structural independence between these endpoints, is likely related to the LYs that are accumulated beyond the observed data.[3] As stated in Section 5.1 (and Table 5.2) of the ERG report, based on the original CS, approximately [redacted] of the LYs are gained beyond the observed data period for nivolumab + ipilimumab compared with PDC while this is even larger ([redacted] for PF LYs. The company unfortunately did not provide information on the LYs that are accumulated beyond the observed data based on the new data-cut data. Hence, the impact of the limitations related to the partitioned survival model, including the extrapolations remains unclear and would potentially warrant additional exploration by the company (e.g. providing information regarding the LYs that are accumulated beyond the observed data).

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7	**Section 3.16. Using a log-logistic distribution to extrapolate overall survival for both treatments is appropriate** When applied to the PDC arm data, the log-logistic distribution results in clinically implausible long-term survival predictions. As previously presented, the clinicians consulted specifically stated that the predicted long-term survival with the log-logistic distribution is too optimistic. It is also important to note that the selection of spline models was not primarily motivated by the within trial fit, as the ACD seems to insinuate. On the contrary, the spline 2-knots normal distribution was primarily selected based on the plausibility of its long-term survival predictions. As such, BMS consider that the spline 2-knots normal distribution is a both statistically and clinically plausible model.	See previous ERG comment on this issue from ERG report section 4.2.6: "Specifically, the log-logistic distribution for both treatment arms is considered a plausible alternative, as illustrated in CS Table 32 considering the goodness of fit (AIC and BIC), the appropriateness of the hazard function as well as survival extrapolations (i.e. aligned with the MAPS data). Moreover, the CS section "Heuristics for selection of survival extrapolation for OS based on external validation" describes identical hazard functions for both PDC and nivolumab + ipilimumab (i.e. the hazard function of the selected distribution should have an initial increase in hazards followed by long-term decreasing hazards) that is consistent with the log-logistic distribution. Therefore, the log-logistic distribution is used for both treatment arms in the ERG base-case." In addition, it should be noted that the company have presented updated survival analyses informed by the new data cut. The company now use the spline 1-knot normal model to inform OS in the PDC arm in the base-case. The ERG considers that this is likely appropriate, given the available data. However, uncertainty remains and further data may shed further light on the appropriateness of these extrapolations.
8	**Section 3.17. The extrapolated progression-free survival is uncertain** As noted in response 3 we agree that there are limitations with PFS as an outcome measure in MPM and that there will always be uncertainties related to immature data. However, the additional data now available (presented in Appendix A) shows that nivolumab + ipilimumab continues to show a long-term benefit compared with PDC and reduces some of the uncertainty related to PFS benefits.	See ERG response to Comment 3 and Comment 6.
9	**Section 3.18. Continued treatment benefit up to 5 years is acceptable** BMS maintain the argument that adjustment at an arbitrary 5-year timepoint results in an unfounded and clinically implausible change in the hazard for the long-term survivors. Continued benefit of nivolumab plus ipilimumab over 5 years is likely based on observations from other immunotherapy trials and populations with long-term follow-up close to or exceeding 5 years, such as CheckMate-017 and -057 described above (Borghaei et al., 2021),	Figures 11-14 in the Appendices do not support the waning of the treatment effect within the first 4-5 years, although a lot of patients continue to be right-censored for this analysis.[2] There is no evidence for either the presence or the absence of treatment waning after 5 years and so this remains uncertain. The ERG prefers to represent this uncertainty using scenario analysis.

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	CheckMate-065 (Wolchok et al., 2021) and CheckMate 227 (Paz-Ares et al., 2021). In the ACD it is stated that "It noted that the company based its argument on expert opinion, but it was not clear how the company chose the expert or elicited the expert's opinion." The clinical experts we consulted were selected based on their expertise, knowledge and experience in MPM. As MPM is a rare condition, it is treated by a few specialists at large oncology centres in the UK.	
10	**Section 3.20. The company's modelling of second-line treatments may underestimate the cost-effectiveness estimate for nivolumab plus ipilimumab** As noted in Comment 1, as part of a reanalysis of the trial data provided in Appendix C we include an analysis in which the clinical results are adjusted for second-line treatments. This better reflects the difference between nivolumab + ipilimumab and chemotherapy and results in an improved OS benefit for nivolumab + ipilimumab vs chemotherapy (reduced hazard ratio) and a reduced ICER. The cost-effectiveness results were explored using two methods for adjusting for treatment switching (Appendix C, section 3.7). The revised base case ICER using the 3-year database lock (Appendix B, Table 10) reduced from £76,844 to [redacted] and [redacted] using the IPCW and two-stage methods, respectively.	See ERG response to Comment 1.
11	**Section 3.21. Nivolumab plus ipilimumab is likely to meet the end of life criteria** We agree with the committee's conclusion that nivolumab plus ipilimumab in this indication meets end of life criteria. We also agree that there is some uncertainty about the current OS benefit seen in patients of different histological sub-types. A period in the CDF and the collection of data via the SACT during this time would provide additional real-world evidence on subtypes and therefore reduce this uncertainty.	The ERG agrees that there is uncertainty in whether the survival gain for the epithelioid subgroup is at least 3 months given the median survival of 18.2 vs. 16.7 months shown in Figure 4 of the appendices.[2]

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- 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

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Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

Consultation on the appraisal consultation document – deadline for comments 5pm on Monday 20 September. Please submit via NICE Docs.

- 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.

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ERG References

[1] Latimer NR, Abrams KR. *NICE DSU technical support document 16. Adjusting survival time estimates in the presence of treatment switching*. Sheffield: University of Sheffield, 2014 [accessed 21.9.21]. 57p. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD16_Treatment_Switching.pdf

[2] National Institute for Health and Care Excellence. *Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]: ACD company appendices v0.1 (20.09.21)*. London: NICE, 2021. 69p.

[3] Woods B, Sideris E, Palmer S, Latimer N, M. S. *NICE DSU technical support document 19. Partitioned survival analysis for decision modelling in health care: a critical review [Internet]*. Sheffield: University of Sheffield, 2017 [accessed 2.2.21]. 72p. Available from: http://nicedsu.org.uk/wp-content/uploads/2017/06/Partitioned-Survival-Analysis-final-report.pdf

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma [ID1609]

ADDENDUM: Response to ACM 2

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 22/12/2021

1. Post-ACM 2 company response critique

Post-ACM 2, the company were asked the following: "Please explore the following uncertainties using data from the most recent data cut in May 2021, specifically (by priority):

1. How treatment effect changes over time, as implied by the company's and ERG's chosen distributions for overall and progression-free survival; and as implied by the Kaplan-Meier curves of CheckMate 743

2. Scenario analyses assuming treatment effect waning starting at different time points (for example, waning from 5 years or 10 years onwards)

3. Removing the costs of non-NHS second-line treatments from both arms in the model

4. Clearer reporting of the 4 treatment switching methods considered and used to adjust for non-NHS second-line treatments, and sufficient justification for the IPCW method chosen

5. Adjusting the treatment effect for second-line treatments in subgroups; and explore the treatment effect overtime implied by the selected distributions in subgroups" Additional comments regarding treatment switching scenarios

The following is a critique of the company response.{, 2021 #232}

1. How treatment effect changes over time, as implied by the company's and ERG's chosen distributions for overall and progression-free survival; and as implied by the Kaplan-Meier curves of CheckMate 743

The company presented modelled treatment effect for OS for both the company preferred (log-logistic for nivolumab + ipilimumab and 1 knot spline normal for PDC) and ERG preferred (log-logistic for nivolumab + ipilimumab and log-logistic for PDC) distributions along with the smooth hazard ratio (HR) in Figure 1. Based on this, the ERG considers that it is not possible to rule out either the company's or the ERG's modelled treatment effect, especially given that the end of the smoothed hazard curve is likely to have only a small number of patients (reflected in very wide confidence intervals) and may therefore not be very informative. For the non-epithelioid subgroup, whilst the mean HR remains relatively constant (with a small trend towards 1), the confidence intervals become wide towards the end owing to small sample sizes. This is similar also for the epithelioid subgroup, except for small downward trend away from 1 in the mean HR towards the end of the time horizon. The ERG considers that uncertainty remains about the applicability of treatment waning as the confidence intervals towards the end of the curves are wide.

2. Scenario analyses assuming treatment effect waning starting at different time points (for example, waning from 5 years or 10 years onwards)

The ERG appreciates the company's treatment waning scenario analyses, which could be verified. It is to be noted that these are conditional on the company's choice of distributions for OS and no crossover adjustment. Results for the subgroups were not provided.

3. Removing the costs of non-NHS second-line treatments from both arms in the model

The ERG considers the company's approach as valid.

4. Clearer reporting of the 4 treatment switching methods considered and used to adjust for non-NHS second-line treatments, and sufficient justification for the IPCW method chosen

These methods were reported in Appendix A in the form of a statistical report, updated as version 2.0.{, 2021 #231}{, 2021 #236} The company set out the rationale for adjusting for treatment switching to any PD-1/PD-L1 or CTLA-4 targeted therapy. They also provided the distribution of timing of switching in relation to progression: for the ITT population, 19 (6.3%) before and 46 (15.2%) after, as well as the distribution by months since randomization. For the epithelioid and non-epithelioid subgroups these figures were: [redacted] before and [redacted]%) after and [redacted]%) before and [redacted] after respectively (Table 2, Appendix A). Switching adjustment was performed on the 3-year database lock (7 May 2021) data of CheckMate 743 trial.{, 2021 #236}

The covariates used for the adjustment were provided in Table 7 for the IPCW method and Table 8 for the Two-stage and IPE methods: the same covariates were used for both the IPE and the RPSFTM method.{, 2021 #231} There was no explicit justification for the choice of covariates, A sensitivity analysis was conducted to compare a model with all chosen covariates ("Full model") with a model with only "significant" covariates, although what was meant by "significant" was not reported. A justification for the IPCW method as the base case was provided with emphasis on there having been informative censoring i.e. pre-progression, which would undermine the assumption required for the Two-stage method of switching on progression only. It was also argued that switching to one of several types of immunotherapy would imply that the common treatment effect assumption necessary for the IPE and the RPSFTM methods would be violated. For the IPCW method, stabilised weights were used. The company also reported the method for handling missing data, assuming no event if Grade 3 AE missing, the mean of ECOG and EQ5D if missing at baseline and LOCF if missing at follow-up.

In the update to Appendix A, the company presented an analysis by histology subgroups. The company reported that the same methods as for adjusting the ITT population were followed. The results for each method of adjustment are reproduced in Table 1.{, 2021 #236}

Table 1.1: Median OS and HR and associated 95% CIs in Chemotherapy arm for treatment switching adjusted analyses

	Epithelioid				Non-epithelioid			
Model	**Median**	**95% CI of Median**	**HR**	**95% CI of HR**	**Median**	**95% CI of Median**	**HR**	**95% CI of HR**
ITT without any stratification factor	[redacted]							
ITT with gender as stratification factor	[redacted]							
IPCW without any as stratification factor	[redacted]							
IPCW with gender as stratification factor	[redacted]							
Two-stage estimation without any stratifictaio factor and without re-censoring	[redacted]							
Two-stage estimation with gender	[redacted]							

	Epithelioid				Non-epithelioid			
as stratification factor and without re-censoring								
Two-stage estimation without any stratifictaio factor and with re-censoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two-stage estimation with gender as stratification factor and with re-censoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RPSFTM without stratification and without re censoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RPSFTM with gender as stratification factor and	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Epithelioid				Non-epithelioid			
without re censoring								
RPSFTM without stratification and with re censoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RPSFTM with gender as stratification factor and with re censoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
IPE (exponential fit) without stratification and without re censoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPE (exponential fit) with gender as stratification factor and without re censoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPE (exponentia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Epithelioid				Non-epithelioid			
l fit) without stratificatio n and with re censoring								
IPE (exponentia l fit) with gender as stratificatio n factor and with re censoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Source: Appendix A, Statistical report, versions 2.0, Table 31.{, 2021 #236}								

ERG comment

The company have provided more detail in the methods of switching adjustment and some justification of the choice of IPCW method. The ERG would agree that the Two-stage method is of questionable validity given that about 40% (calculated from the numbers above) of switching occurred pre-progression. It might be less questionable for the epithelioid subgroup given that the equivalent figure is 22%, but twice as many non-epithelioid patients switched pre-progression. It also seems questionable that there would be a common treatment effect on switching to an immunotherapy that is not necessarily that to which patients were randomised i.e. not nivolumab plus ipilimumab, thus making the IPE and RPSFTM methods of questionable validity. This would lead to the conclusion that the IPCW method might be preferred. However, its validity depends crucially on the satisfaction of the "no unmeasured confounders" assumption, which entails the identification of all baseline and time-dependent confounding factors and correct model specification. This might be problematic given the lack of justification for the choice of covariates. Given this lack of justification and the need to identify all confounders, the ERG prefers the "Full model". There can also be a lack of overlap (of the distributions of covariates between the switchers and non-switchers).{Latimer, 2018 #230} It is possible that some of the predicted propensity scores are close to zero, implying an excessively large weight, leading to instability in the IPCW method.{Latimer, 2014 [accessed 21.9.21] #227} However, none of the weights were reported to exceed 1.67 for the ITT population (Table 12 in Appendix A), 2.51 in the epithelioid subgroup (Table 34, Appendix A) or 1.98 in the non-epithelioid subgroup (Table 37, Appendix A).{, 2021 #236} There is also the potential for lack of reliability of the IPCW method given the need to adjust for a large number of covariates and if the sample size is small or number of patients who do not switch is low.{Latimer, 2018 #230} In this case, the percentage who do not switch might be regarded as relatively high (about 80% regardless of histology subgroup, calculated from the figures above): as shown in simulations any of the methods of adjustment are likely to provide a less biased estimate than use of the ITT population if less than about 60% of patients eligible to switch do so.{Latimer, 2018 #230}

The effect of treatment switching adjustment on the histological subgroups, as shown in Table 1.1 above, is a little more substantial, but, as intuitively expected, if the treatment effect changes it only improves. In the epithelioid subgroup the HR deceases from [redacted] using the IPCW method with a range from [redacted], depending on method and whether gender is included as a stratification factor. The 95% confidence interval also moves from crossing to not crossing the point of no difference using the IPCW and Two-stage methods. In the non-epithelioid subgroup the HR does not change with the IPCW method unless gender included as a stratification factor and the range is from [redacted] depending on method and whether gender is included as a stratification factor.

Of course, even if the IPCW method might be preferred theoretically, as the ERG have already pointed out in the critique of the response to ACM1 for the ITT analysis,{National Institute for Health and Care Excellence, 2021 #228}{Armstrong, 2021 #233} robustness at least has been demonstrated regardless of histological subgroup by the outcomes being very similar no matter which method is used.

5. Adjusting the treatment effect for second-line treatments in subgroups; and explore the treatment effect overtime implied by the selected distributions in subgroups" Additional comments regarding treatment switching scenarios

The company's treatment switching scenarios in subgroups show a modest decrease in the ICER in the non-epithelioid subgroup, and a larger decrease in the ICER in the epithelioid subgroup. The cause for the larger effect in the epithelioid subgroup is unclear: it may be due to the larger starting ICER, or may be caused by more uncertainty in the data, or by differences in treatment switching. Different treatment

switching adjustment methods also result in small differences in the ICER in the non-epithelioid subgroup, and larger differences in the epithelioid subgroup.

With regard to the survival analysis performed conditional on treatment switching adjustments, the company argued that model choice should not be based on statistical fit alone, but should provide a good fit to landmark survival probabilities and should be in agreement with the curve selection based on the results of ITT analysis. The ERG considers that the agreement with the ITT analysis may be relevant, however, it is not clear whether this is a necessary condition considering that it may be plausible to have different hazard patterns in these fundamentally different subgroups. The ERG therefore tested the model with the best statistical fit as an alternative scenario analysis for the ITT population and subgroups. Results show that the treatment switching scenarios for the ITT and epithelioid populations are sensitive to the chosen survival model (Table 2).

Table 2: Subgroups - ERG scenarios based on company's updated post-ACD model (deterministic)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
ITT: Company's revised base-case, no treatment switching							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	50,260	0.871	0.667	75,322
ITT: Company's revised base-case, with treatment switching (IPCW)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	51,475	1.010	0.751	68,582
ITT: Company's revised base-case, with treatment switching (IPCW), use log-logistic instead of 1 spline normal							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	50,801	0.885	0.672	75,623
ITT: ERG scenario (company base-case + parametric TTD, log-logistic for PDC OS) and tx switching (IPCW)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	51,513	0.885	0.672	76,683
ITT: ERG scenario (company base-case + parametric TTD, log-logistic for PDC OS, tx waning 5 years) and tx switching (IPCW)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	51,692	0.779	0.582	88,744
Epithelioid: Company's revised base-case, no treatment switching							

Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	49,957	0.596	0.462	108,125
Epithelioid: Company's revised base-case, with treatment switching (IPCW)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	51,112	0.725	0.539	94,775
Epithelioid: Company's revised base-case, with treatment switching (IPCW), use log-logistic instead of 1 spline odds							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	50,607	0.632	0.482	105,087
Epithelioid: ERG scenario (company base-case + parametric TTD, log-logistic for PDC OS) and tx switching (IPCW)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	51,318	0.632	0.482	106,565
Epithelioid: ERG scenario (company base-case + parametric TTD, log-logistic for PDC OS, tx waning 5 years) and tx switching (IPCW)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	51,211	0.547	0.418	122,578
Non-epithelioid: Company's revised base-case, no treatment switching							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	51,358	1.441	1.072	47,923

Non-epithelioid: Company's revised base-case, with treatment switching (IPCW)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	52,015	1.477	1.093	47,584
Non-epithelioid: Company's revised base-case, with treatment switching (IPCW), use log-logistic instead of lognormal							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	51,966	1.468	1.087	47,817
Non-epithelioid: ERG scenario (company base-case + parametric TTD, log-logistic for PDC OS) and tx switching (IPCW)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	52,678	1.468	1.087	48,472
Non-epithelioid: ERG scenario (company base-case + parametric TTD, log-logistic for PDC OS, tx waning 5 years) and tx switching (IPCW)							
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	
Pemetrexed + cisplatin or carboplatin	[redacted]	[redacted]	[redacted]	53,040	1.252	0.903	58,738