NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small-cell lung cancer [ID1566]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small-cell lung cancer [ID1566]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to company comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from Bristol Myers Squibb**
   a. Main response
   b. Appendix A
   c. Appendix B
   d. Appendix C1
   e. Appendix C2

3. **Evidence Review Group critique of company comments on the ACD**

There were no comments on the ACD from other consultee and commentator organisations, from experts or through the NICE website.

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

NICE National Institute for Health and Care Excellence

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Consultation on the appraisal consultation document – deadline for comments 5:00pm on 29 April 2021 **email:** 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:	[redacted]

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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 we have demonstrated nivolumab + ipilimumab + chemotherapy is an effective treatment option that has the potential to improve outcomes for patients with advanced non-small cell lung cancer (NSCLC). Specific comments are detailed below.
1	**Why the committee made these recommendations pages, 3-4 and Sections 3.3, 3.18** Pembrolizumab plus pemetrexed and platinum chemotherapy for non-squamous NSCLC is included as a comparator – in both the bulleted list and the first paragraph of page 3 with no explanation that this was not included in the final scope. As final guidance for pembrolizumab plus pemetrexed and platinum chemotherapy for non-squamous NSCLC was published the day prior to the appraisal committee meeting for this topic, following a period of time in the Cancer Drugs Fund, we understand that NICE now consider it a relevant comparator. However, it is important that the ACD makes clear that this change to the final scope has been made by NICE at the ACD stage. The ACD currently reads as if this was an error in the company submission. We therefore suggest changing the wording as follows: • From *"Nivolumab combination has not been compared with pembrolizumab plus pemetrexed and platinum chemotherapy, which is widely used in the NHS."* • To *"Nivolumab combination has not been compared with pembrolizumab plus pemetrexed and platinum chemotherapy, as at the time of scoping it was not approved for routine use in the NHS in England. However, it has since been recommended and is used in the NHS and therefore a consideration in this appraisal."* This aligns with the detail as presented in **Section 3.3**. In line with the committee's conclusion, and **Section 3.18** we have now included pembrolizumab plus pemetrexed and platinum chemotherapy for the treatment of non-squamous NSCLC in the cost-effectiveness model and provide the results of these analyses in Appendix A. As stated in the ACD, pembrolizumab plus carboplatin and paclitaxel is not recommended for routine commissioning and is not considered standard of care in England. It is therefore not an in-scope comparator and analyses have not been included. Although other immuno-oncology (IO) monotherapy and combination therapies are recommended in England for the first line treatment of NSCLC, survival is still poor and there remains a need for more effective treatment options. It is therefore important that all evidence or new treatment modalities such as IO-IO plus chemotherapy are assessed in this context. These have the potential to improve outcomes and ensure that clinicians can prescribe the systemic anti-cancer therapy regimen most suitable for individual patients. BMS remains committed to working with NICE and NHS England to achieving access for the nivolumab combination in untreated advanced NSCLC for those patients who will benefit.

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Why the committee made these recommendations and Section 3.22

"It is unlikely that collecting more data in the Cancer Drugs Fund would resolve the uncertainty in the modelling"

Much of the uncertainty in the modelling is due to the lack of long-term follow-up and anticipated long-term treatment effect of the nivolumab combination in this setting. [redacted] Additional database locks are planned for both trials and these will help to reduce this uncertainty, increase confidence in the current analyses and facilitate a comparison of long-term outcomes across the currently approved IO regimens. Table 1 through Table 4 show the landmark OS and PFS results for CheckMate-9LA versus CheckMate-227 [redacted]. Data available in Appendix C show the [redacted] overall survival and progression free survival curves for CheckMate-9LA and CheckMate-227.

Table 1. Non-Squamous PD-L1 < 50% Landmark Outcomes

Trial	Year 1 (%)	Year 2 (%)	Year 3 (%)
Overall Survival			
CheckMate 9LA	[redacted]		
CheckMate 227	[redacted]	[redacted]	[redacted]
Progression-Free Survival			
CheckMate 9LA	[redacted]		
CheckMate 227	[redacted]	[redacted]	[redacted]

Table 2. Squamous PD-L1 < 50% Landmark Outcomes

Trial	Year 1 (%)	Year 2 (%)	Year 3 (%)
Overall Survival			
CheckMate 9LA	[redacted]		
CheckMate 227	[redacted]	[redacted]	[redacted]
Progression-Free Survival			
CheckMate 9LA	[redacted]		
CheckMate 227	[redacted]	[redacted]	[redacted]

Table 3. Non-Squamous PD-L1 All-Comers Landmark Outcomes

Trial	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)
Overall Survival				
CheckMate 9LA	[redacted]	[redacted]		
CheckMate 227	[redacted]	[redacted]	[redacted]	[redacted]
Progression-Free Survival				
CheckMate 9LA	[redacted]	[redacted]		
CheckMate 227	[redacted]	[redacted]	[redacted]	[redacted]

Table 4. Squamous PD-L1 All-Comers Landmark Outcomes

Trial	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)
Overall Survival				
CheckMate 9LA	[redacted]	[redacted]		
CheckMate 227	[redacted]	[redacted]	[redacted]	[redacted]
Progression-Free Survival				
CheckMate 9LA	[redacted]	[redacted]		
CheckMate 227	[redacted]	[redacted]	[redacted]	[redacted]

The tables above demonstrate that outcomes [redacted].

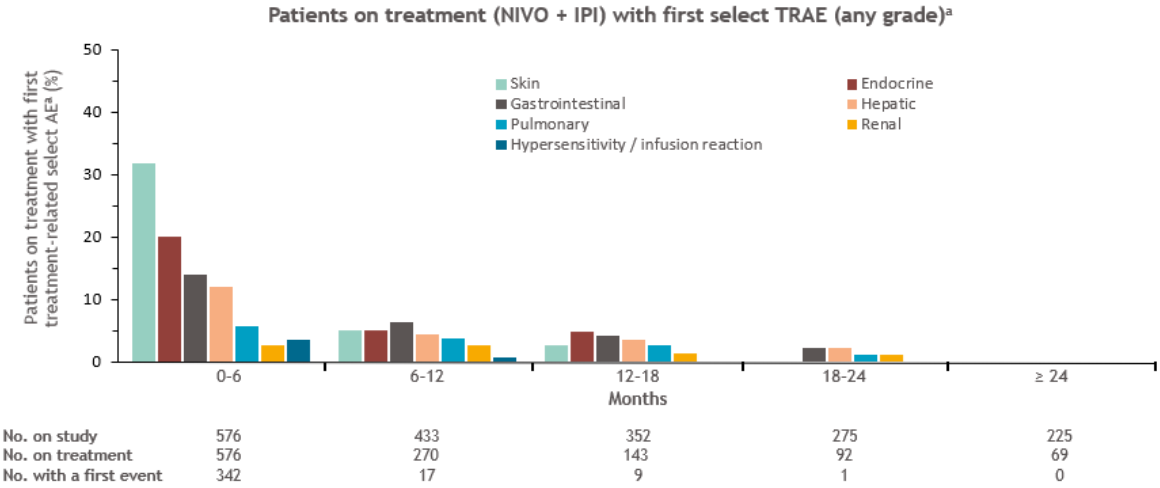
We therefore consider that the nivolumab combination does meet the criteria for inclusion in the Cancer Drugs Fund, as the collection of further data would reduce the uncertainty in the cost-effectiveness estimates and would facilitate a long-term comparison versus other IO combination therapies.

3

Section 3.7

"It concluded that nivolumab combination was likely to be less well tolerated than other chemo-immunotherapy combinations, so more specialist management would be needed to address severe toxicities"

We disagree that the tolerability of the nivolumab combination will require more specialist management than other available options in 1L NSCLC. Clinicians are experienced in treating patients with the nivolumab + ipilimumab combination in other indications (such as melanoma and renal cell carcinoma) and managing adverse events associated with IO therapies such as nivolumab and ipilimumab. The limited course of chemotherapy means that the adverse events typically associated with chemotherapy (such as anaemia, neutropenia and thrombocytopenia) are less prevalent during treatment with this combination. An analysis of the CheckMate 227 data over time shows that adverse events (AEs) with the nivolumab + ipilimumab combination tend to occur early in treatment but are managed effectively and reduce with later cycles (Figure 1).

	Figure 1. Treatment-related select adverse events over time in patients treated with nivolumab + ipilimumab in CheckMate-227.  No. on study 576 433 352 275 225 No. on treatment 576 270 143 92 69 No. with a first event 342 17 9 1 0 a Select AEs were events with a potential immunological cause that required frequent monitoring/intervention; percentages were for patients who had events of any grade reported between first dose and 30 days after last dose of study treatment. Source: Ramalingham et al., 2020 We have conducted an indirect treatment comparison of AEs for nivolumab + ipilimumab + chemotherapy and the pembrolizumab + chemotherapy regimens in the first line setting. There were no statistically significant differences in the odds of AEs leading to discontinuation of the study drug (any drug within the regimen) between the nivolumab + ipilimumab + chemotherapy, or the two pembrolizumab-containing regimens, either for grades 3/4/5 or grade 1-5 AEs. Similarly, in the indirect comparisons of treatment-related grade 3/4 or 3/4/5 AEs, no significant differences were observed in the comparison between nivolumab + ipilimumab + chemotherapy and any of the relevant comparators, further supporting our assumption that no additional specialist management is required, compared with standard of care.
4	**Section 3.10** *"The committee agreed that there was uncertainty about the validity of applying survival curves derived from the ITT data across all the subgroups. It concluded that survival curves should be modelled separately for each subgroup."* We have provided the analyses according to the committees preferred assumptions – using the overall survival data for the separate histology and PD-L1 subgroups. In addition, we provide a scenario analysis in which the histology-specific, PD-L1 all-comers data are used. This is consistent with the data used for decision-making in the recent CDF-exit submission for pembrolizumab + chemotherapy in non-squamous NSCLC (TA683). Nonetheless, it is important to note that CheckMate-9LA was not stratified or powered for analyses of the combined histology/PD-L1 subgroups. Histology was a stratification factor, providing some rationale for analysing data by histology subgroup, however not for the combined histology and PD-L1 subgroups, which as well as not being pre-specified, include low patient numbers. Additionally, PD-L1 is not an effect modifier due to the mechanism of action for the combination, as seen in the trial data, providing further rationale to support analyses for the histology subgroups but not the combined histology/PD-L1 subgroups.

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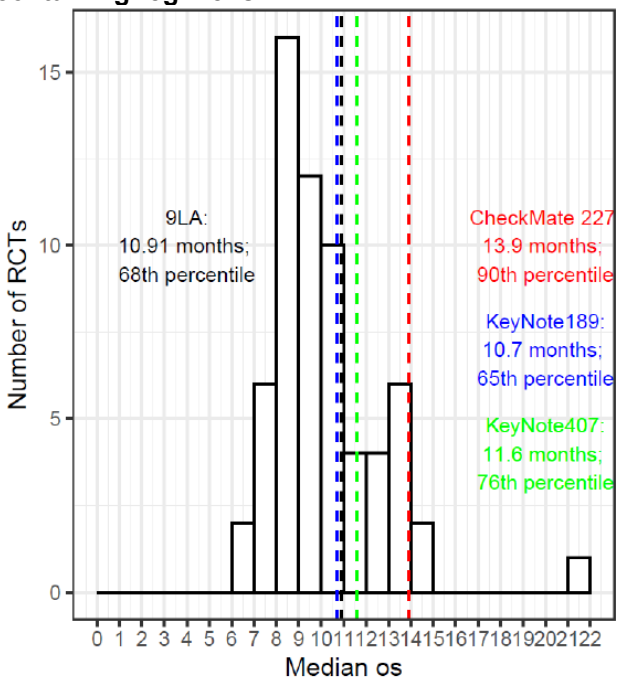
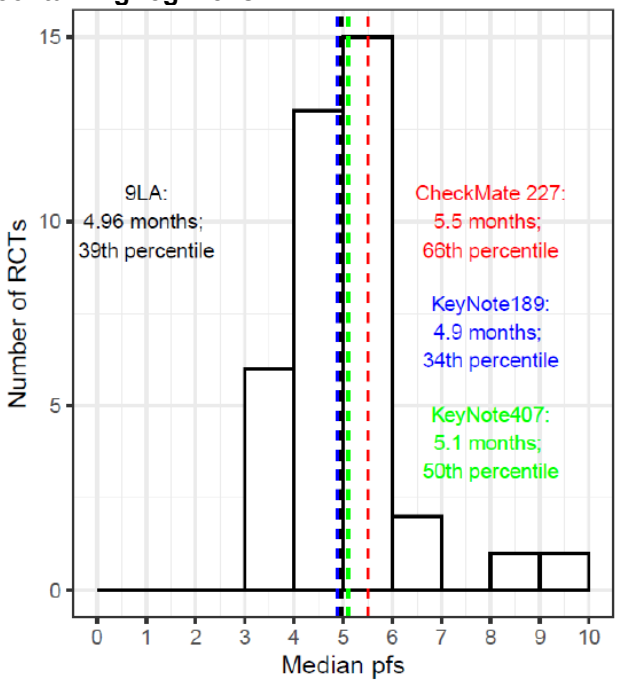
5	**Section 3.11** *"The committee concluded that the survival curves for people having platinum-doublet chemotherapy should be based on the CheckMate-227 data alone"* We disagree that the platinum-doublet chemotherapy survival curves should be based on CheckMate-227 alone. We prefer to use the original approach that is aligned with the approach for the nivolumab + ipilimumab + PDC arm, in which the CheckMate-9LA trial is utilised up to 13 months and conditional survival from the CheckMate-227 trial is applied following this point. As CheckMate-9LA is the registrational trial for this indication, it is most appropriate for use for the estimation of survival benefit of patients on PDC, to preserve the benefits of comparing between arms of a randomised controlled trial. CheckMate-227 data are then used to inform the long-term survival in both arms in relative terms from when most of the censoring occurs in CheckMate-9LA. This relative survival would capture any long-term effects of e.g., subsequent therapies used in CheckMate-227. Utilising CheckMate-227 naïvely to inform the absolute survival for the chemotherapy arm, would to a large extent disregard the data from the registrational trial for this indication. As presented below, utilising CheckMate-227 alone is very clearly selectively choosing the "worst case" comparator data available. As noted in our response to clarification questions, although median OS in the chemotherapy arm was lower in CheckMate-9LA than in CheckMate-227, in CheckMate-9LA it was within the range that has recently been reported in other phase 3 first-line NSCLC studies, which had similar patient populations (e.g., median OS, 10.7-11.3 months in KeyNote-189 and 11.3-11.6 months KeyNote-407). BMS has undertaken a systematic literature review and network meta-analysis of first line therapies for the treatment of advanced NSCLC in patients without sensitising EGFR mutations or ALK translocations. Sixty-seven randomised controlled trial arms of platinum doublet chemotherapy containing regimens published up until March 2020 were identified. Of these, 63 presented median OS in the relevant PD-L1 all-comer population. As shown in Figure 2, the median OS reported for the chemotherapy arm of CheckMate-9LA is above the overall median (68th percentile), and similar to the medians for both KeyNote-189 and 407 (65th and 76th percentile respectively), while the median OS for CheckMate-227 is substantially higher (in the 90th percentile).

Figure 2. Median OS in 63 randomised controlled arms of platinum doublet chemotherapy containing regimens.



Median progression-free survival was presented for 38 trial arms in the relevant PD-L1 all-comer population. As shown in Figure 3, the median PFS reported for the chemotherapy arms of CheckMate-9LA Keynote-189 and KeyNote-407 are similar, with CheckMate-227 slightly higher.

Figure 3. Median PFS in 38 randomised controlled arms of platinum doublet chemotherapy containing regimens.



	Limited real-world evidence from the UK are available. [redacted]. This suggests that the OS seen in clinical practice in the UK for patients treated with chemotherapy is lower even than that in CheckMate-9LA and less than half that reported in CheckMate-227. Based on the above, it would be inappropriate to use survival estimate from the chemotherapy arm of CheckMate-227 in this appraisal as these seem to be outliers. CheckMate-9LA is the registrational trial for this indication and as can be seen from the figures above, the chemotherapy survival estimates are well aligned with those from other trials, and particularly KeyNote-189 and -407 which were considered to be representative of the UK in other recent NICE appraisals. It would be inconsistent for the committee to assume a higher OS for patients treated with PDC in comparisons with the nivolumab combination than was considered valid in the similar appraisal of pembrolizumab + chemotherapy (TA683), published last month.
6	**Section 3.12** *"The committee concluded that a treatment effect lasting 3 to 5 years after starting treatment was appropriate for decision making, for consistency with previous immunotherapy appraisals in NSCLC."* As noted during technical engagement, although long-term information on duration of treatment effect of nivolumab + ipilimumab + chemotherapy in the first line setting is not available, the 3-year data cut for CheckMate-227 show a clear continued treatment effect beyond the 2-year treatment stop. Further, evidence from nivolumab in second line NSCLC demonstrates a robust and durable treatment effect of IO therapy in patients with NSCLC that is relevant to this appraisal. Moreover, there is a growing body of evidence across other tumour types that dual IO therapy will have a robust treatment effect beyond discontinuation when compared to single-IO therapy. In the CheckMate-067 trial (in advanced melanoma), the median treatment-free interval for patients receiving dual-IO therapy of nivolumab + ipilimumab was greater than patients receiving single IO therapy (nivolumab alone or ipilimumab alone) after five-years of follow up. Patients on dual-IO therapy achieved a median treatment-free interval of 18.1 months, compared to 1.8 months and 1.9 months for single-IO therapy with nivolumab alone and ipilimumab alone, respectively. This demonstrates a substantial and lasting treatment effect associated with nivolumab + ipilimumab (Larkin et al. 2019). In renal cell carcinoma, recently published data from CheckMate-214 shows that after 4 years of follow up, 59 patients had achieved a complete response and 156 a partial response. Of these patients, 27 of 59 complete responders and 67 of 156 partial responders had discontinued treatment with nivolumab + ipilimumab but had not received any subsequent therapy. Again, demonstrating a robust and lasting treatment effect following dual-IO therapy (Albiges et al. 2020). While we maintain that duration of treatment effect for nivolumab + ipilimumab + PDC will last beyond 3 to 5 years, the updated economic analysis considers a treatment effect duration of 5 years. This is aligned with the ERG-preferred assumption and the committee-preferred assumption.

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<table>
<tr><td>7</td><td>Section 3.13
“A time-to-death approach meant that people entering the model had a different health related quality of life depending on the treatment arm they were assigned to.”

This could be further clarified – TTD utility values did not differ across treatment arms, in that utility values for each time-to-death category were consistent. Any differences in utility values between arms were due to the proportion of patients within each proximity to death category. We propose the following wording:

“A time-to-death approach meant that people entering the model had a different health related quality of life depending on the treatment arm they were assigned to, due to the proportion of patients within each proximity to death category.”

As argued in more detail at technical engagement, we do feel that the TTD approach to incorporating utility values can allow us to better capture the clinical progression of patients within the progressed-disease health state.
While we maintain that TTD utility values are an appropriate way to incorporate utility values and is increasingly being used and accepted in this indication (Hatswell et al. 2020), we have accepted the use health state utility values in line with the committee’s preferred assumption in the updated economic analysis.</td></tr>
<tr><td>8</td><td>Section 3.17
“It understood that the company and ERG agreed that nivolumab combination did not meet the criteria for end of life treatments for:
• non-squamous NSCLC and a PD-L1 TPS below 50%”

Although, at the time of submission, based on results of the IMPower-150 trial, we anticipated that end of life would not apply in the non-squamous PD-L1 <50% subgroup, new real-world evidence has since been published that suggests the overall survival seen in trials of IO + chemotherapy combinations may not be reflected in clinical practice with currently approved IO therapies, and median OS is less than 24 months in all subgroups.

Waterhouse et al (2021) report a recent retrospective study of patients in the Flatiron database with stage IIIB to IV NSCLC, treated with IO plus chemotherapy (predominantly pembrolizumab + chemotherapy, used in over 98% of patients) between 1 January 2016 and 30 June 2020. The reported median overall survival in patients with both squamous and non -squamous NSCLC was substantially lower than those reported in the KeyNote-407 and KeyNote-189 trials as shown in the table below.

Median overall survival for patients treated with pembrolizumab + chemotherapy in a US retrospective study and the registrational trials.
<table>
<tr><th></th><th colspan="3">Waterhouse 2021 real world evidence</th><th colspan="3">KeyNote-407 and -189 randomised controlled trials</th></tr>
<tr><th></th><th>N</th><th>Median OS (months)</th><th>95% CI</th><th>N</th><th>Median OS (months)</th><th>95% CI</th></tr>
<tr><td>Squamous</td><td>814</td><td>10.6</td><td>9.3–11.8</td><td>278</td><td>17.1</td><td>14.4–19.9</td></tr>
<tr><td>Non-squamous</td><td>3,457</td><td>12.0</td><td>11.3–12.8</td><td>410</td><td>22.0</td><td>19.5–25.2</td></tr>
</table>
Sources: Waterhouse et al. (2021); Paz-Ares et al. (2020), Gadgeel et al. (2020)

In contrast, available real-world evidence on the use of nivolumab in lung cancer suggests that the outcomes in clinical practice are similar to those achieved in the randomised controlled trials. In the CDF-exit reviews for nivolumab in second line NSCLC (TA655 and GID-TA10513), the real-world</td></tr>
</table>

<table>
<tr><td></td><td>SACT data provided evidence to support that the OS achieved in the trials was reflected in clinical practice, and the longer follow-up in the trials demonstrated that the predicted long-term OS was achieved in practice as reported by Popat et al., 2021 at World Conference on Lung Cancer.

These data demonstrate not only that there remains a need for additional treatment options in first line NSCLC, but also that, based on median overall survival of less than 24 months, and an anticipated survival benefit of greater than 3 months following treatment with the nivolumab combination, NICE's end-of-life criteria apply across all populations in this appraisal.</td></tr>
<tr><td>9</td><td>Section 3.21
"The committee agreed that the most plausible ICERs for nivolumab combination .... were above the range normally considered to be a cost- effective use of NHS resources"

In Appendix A, we provide updated cost-effectiveness analyses that reflect the ACD response assumptions detailed in the table below.

<table>
<tr><td></td><td>Appraisal Committee's preferred assumption</td><td>ACD response economic analysis</td></tr>
<tr><td>Survival curves by subgroups</td><td>Apply separate survival curves by histology (NSQ and SQ) and PD-L1 status</td><td>Apply separate survival curves by histology (NSQ and SQ) and PD-L1 status</td></tr>
<tr><td>PDC Survival Modelling</td><td>Survival for people having PDC should be modelled using CheckMate-227 data alone</td><td>Model survival for people having PDC based on CheckMate-9LA followed by CheckMate-227</td></tr>
<tr><td>Treatment effect duration</td><td>3 – 5 years</td><td>5 years as per the ERG and Appraisal Committee's preferred assumption</td></tr>
<tr><td>Utility values</td><td>Progression-based utility values</td><td>Progression-based utility values</td></tr>
<tr><td>Composition of platinum-doublet chemotherapy</td><td>Separate chemotherapy regimen distributions should be used</td><td>Separate chemotherapy regimen distributions are used</td></tr>
<tr><td>Proportion of subsequent therapy</td><td>Subsequent therapy proportion should be based on CheckMate-227</td><td>Subsequent therapy based on CheckMate-227</td></tr>
<tr><td>Relative dose intensity</td><td>Minimal impact on ICER results and likely to lie between company and ERG approach</td><td>Retained company-preferred approach</td></tr>
</table>
</td></tr>
</table>

Cost-effectiveness results for the non-squamous PD-L1 < 50% population are presented in Table 5.

Table 5. Cost-Effectiveness Results for Non-Squamous PD-L1<50% NSCLC

	Total costs	Total LYs	Total QALYs	ICER
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	[redacted]	£50,890
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	Dominated
Pembrolizumab + platinum + pemetrexed	[redacted]	[redacted]	[redacted]	Dominated

Cost-effectiveness results for the non-squamous PD-L1 all-comers population are presented in Table 6.

Table 6. Cost-Effectiveness Results for Non-Squamous NSCLC

	Total costs	Total LYs	Total QALYs	ICER
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	[redacted]	£34,581
Pembrolizumab + platinum + pemetrexed	[redacted]	[redacted]	[redacted]	Dominated

Cost-effectiveness results for the squamous PD-L1 < 50% population are presented in Table 7.

Table 7. Cost-Effectiveness Results for Squamous PD-L1<50% NSCLC

	Total costs	Total LYs	Total QALYs	ICER
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	[redacted]	£55,590

Cost-effectiveness results for the squamous PD-L1 all-comers population are presented in Table 8.

Table 8. Cost-Effectiveness Results for Squamous NSCLC

	Total costs	Total LYs	Total QALYs	ICER
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	[redacted]	£58,692

Insert extra rows as needed

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Checklist for submitting comments

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

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

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

APPENDIX A. UPDATED COST-EFFECTIVENESS SCENARIOS

This document contains the updated base case analyses for Nivolumab + ipilimumab combined with PDC in the following populations, requested by NICE based on the current treatment landscape in the UK:

- Non-Squamous histology, PD-L1 < 50%
- Squamous histology, PD-L1 < 50%

Further analyses are presented in the following populations:

- Non-Squamous histology, PD-L1 All-Comers
- Squamous histology, PD-L1 All-Comers

The analyses have been conducted using the committee's preferred survival curves by histology (NSQ and SQ) and PD-L1 status. Further, additional FP NMA models were explored and selection for inclusion in the cost-effectiveness model to facilitate comparison with comparators included in the updated scope. Methods and model selection approach remain consistent with previously submitted FP NMA models. Results of these analyses are presented in more detail in Appendix B.

As argued in the original submission and during technical engagement and presented below we argue that modelling of treatment effect should not be split by both histology and PD-L1 status, as CheckMate-9LA was not stratified or powered for analyses of the combined histology/PD-L1 subgroups. Histology was a stratification factor, providing some rationale for analysing data by histology subgroup, however not for the combined histology and PD-L1 subgroups, which as well as not being pre-specified, include low patient numbers.

Given the update to the scope to include pembrolizumab + pemetrexed + PDC as a comparator for the Non-Squamous subgroup, the Non-Squamous histology and PD-L1 All-Comers data is also fully aligned with the relevant decision problem. The Non-Squamous histology data (not restricted by PD-L1 status) is likely to be more robust due to increased patient numbers and therefore less uncertainty than when the data are split by PD-L1 status as well as histology. The analysis using Squamous histology and PD-L1 All-Comers data is similarly more robust and thus has been applied for the Squamous subgroup. However, for completeness analyses of relative treatment effect for the Non-Squamous comparison have been conducted both based on histology only and histology with PD-L1 status, but the histology specific analyses have been used in the base case.

There were challenges associated with conducting the NMAs in the Non-Squamous subgroup, due to the shape of the long-term data in KeyNote-189 and the immaturity of the data from all trials. As shown in Figure 1 and Figure 2, towards the end of the available data the pembrolizumab + pemetrexed + PDC curves begin to converge towards the PDC curves. Although expected for a combination of single IO + chemotherapy these curves converged in a manner such that the resulting long-term hazards from the NMA for patients in the pembrolizumab + pemetrexed + PDC is greater than those in the PDC arm. Such long-term increased risk for patients treated with IO + chemotherapy compared with PDC might not be seen as clinically plausible. As would be expected, the late convergence towards the PDC arm has an impact on the long-term predictions for pembrolizumab + pemetrexed + PDC

hazard ratio versus nivolumab + ipilimumab + PDC. However, as explored through scenario analyses the impact on outcomes or cost-effectiveness is limited.

Figure 1. Overall Survival from KeyNote-189 – NSQ Histology PD-L1 < 50%

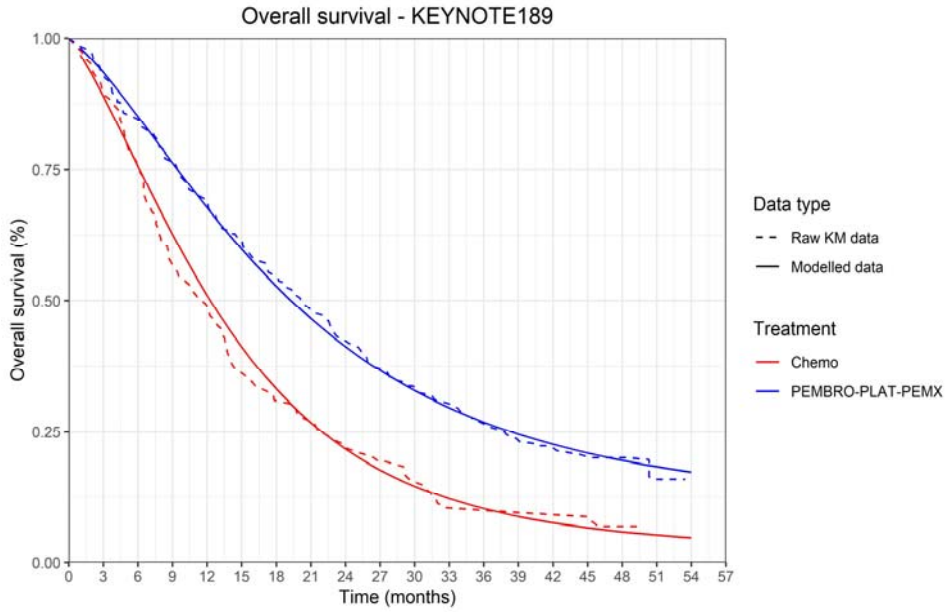
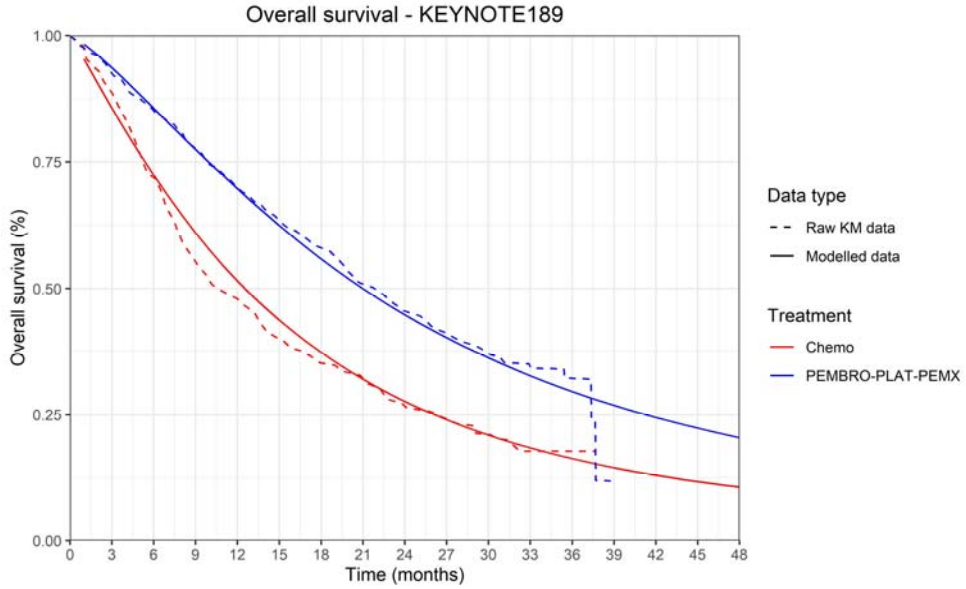


Figure 2. Overall Survival from KeyNote-189 – NSQ Histology



The results of the FP NMAs explored are shown in Figure 3 and Figure 4. As shown in Figure 3, the hazard ratio versus nivolumab + ipilimumab + PDC of pembrolizumab + pemetrexed + PDC dips below the hazard ratio of nivolumab + ipilimumab + PDC versus PDC after approximately 60 months. For clarity, this does not suggest that the absolute survival of patients on pembrolizumab + pemetrexed + PDC necessarily is poorer in the long-term than patients on PDC. Instead, these results suggest that the probability of death at a given timepoint of patients on pembrolizumab + pemetrexed + PDC is greater beyond a certain timepoint, approximately 60-months, than patients on PDC.

Figure 3. HRs of NIVO-IPI-Chemo vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC

Figure 4. HRs of NIVO-IPI-Chemo vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 All-Comers in first-line advanced NSCLC

To mitigate the potentially clinically implausible long-term predictions of hazards for pembrolizumab + pemetrexed + PDC being higher than those for PDC a cap function has been incorporated into the model. This cap ensures that the long-term hazard ratios of pembrolizumab + pemetrexed + PDC versus nivolumab + ipilimumab + PDC cannot dip below that of PDC versus nivolumab + ipilimumab + PDC. The resulting adjusted hazard ratios versus nivolumab + ipilimumab + PDC over time shown in Figure 5 and Figure 6. This cap function was applied to the base case analyses.

Figure 5. HRs of NIVO-IPI-Chemo vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (adjusted)

Figure 6. HRs of NIVO-IPI-Chemo vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 All-Comers in first-line advanced NSCLC (adjusted)

Non-Squamous Histology Cost-Effectiveness Results

Non-Squamous Histology and PD-L1 < 50%

To provide the most reliable and the most conservative analysis, the FP NMA including Non-Squamous PD-L1 All-Comers data is used in the base case analysis along with the cap in the model to ensure that predicted long-term hazard of pembrolizumab + pemetrexed + PDC is not above that of PDC.

As presented earlier it has been demonstrated that the treatment effect of nivolumab + ipilimumab + PDC does not differ across PD-L1 subgroups, and the FP NMA in the Non-Squamous histology is the most appropriate to inform the Non-Squamous PD-L1 < 50% comparison. Using this data is also the most conservative approach, because the HR versus Nivolumab + ipilimumab combined with PDC over time are higher in the Non-Squamous PD-L1 All-Comers FP NMA than in the Non-Squamous PD-L1<50% NMA.

Table 1 shows the cost-effectiveness results in patients with Non-Squamous NSCLC with PD-L1 < 50%. This analysis uses survival curves based on data from the NSQ PD-L1 < 50% population. Data from NSQ PD-L1 All-Comers FP NMA is applied to these survival curves to define the relative effectiveness of comparators not included in the CheckMate-9LA trial.

Table 1. Cost-Effectiveness Results for Non-Squamous PD-L1<50% NSCLC

	Total costs	Total LYs	Total QALYs	ICER
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	[redacted]	£50,890
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	Dominated
Pembrolizumab + pemetrexed + PDC	[redacted]	[redacted]	[redacted]	Dominated

Non-Squamous Histology and PD-L1 < 50% – Without long-term hazard ratio adjustment

Table 2 shows the base case analysis, without the long-term adjustment of the pembrolizumab + pemetrexed + PDC hazard ratio. Adding this cap does not have a large impact on the cost-effectiveness results as the cap does not become active until approximately 60-months, and only reduces total QALYs in the pembrolizumab + pemetrexed + PDC by 0.01.

Table 2. Cost-Effectiveness Results for Non-Squamous PD-L1<50% NSCLC – Without long-term hazard ratio adjustment

	Total costs	Total LYs	Total QALYs	ICER
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	[redacted]	£50,890
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	Dominated
Pembrolizumab + pemetrexed + PDC	[redacted]	[redacted]	[redacted]	Dominated

Non-Squamous Histology and PD-L1 < 50% – Using NSQ PD-L1 < 50% FP NMA

Table 3 shows a scenario analysis in which the FP NMA using the data from the NSQ PD-L1 < 50% data are used, instead of NSQ PD-L1 All-Comers.

Table 3. Cost-Effectiveness Results for Non-Squamous PD-L1<50% NSCLC - Using NSQ PD-L1 < 50% FP NMA

	Total costs	Total LYs	Total QALYs	ICER
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	[redacted]	£50,890
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	Dominated
Pembrolizumab + pemetrexed + PDC	[redacted]	[redacted]	[redacted]	Dominated

Non-Squamous Histology and PD-L1 < 50% – Using NSQ PD-L1 < 50% FP NMA without long-term hazard ratio adjustment

Table 4 shows a further scenario analysis in which the FP NMA using the data from the NSQ PD-L1 < 50% data are used, without long-term adjustment of the pembrolizumab + pemetrexed + PDC hazard ratio.

Table 4. Cost-Effectiveness Results for Non-Squamous PD-L1<50% NSCLC - Using NSQ PD-L1 < 50% FP NMA without long-term hazard ratio adjustment

	Total costs	Total LYs	Total QALYs	ICER
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	[redacted]	£50,890
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	Dominated
Pembrolizumab + pemetrexed + PDC	[redacted]	[redacted]	[redacted]	Dominated

Non-Squamous Histology and PD-L1 < 50% - Using previously submitted FP NMA

Table 5 shows the cost-effectiveness results in patients with Non-Squamous NSCLC with PD-L1 < 50%. This scenario uses the previously submitted FP NMA and shows results versus atezolizumab + bevacizumab + carboplatin + paclitaxel which are consistent with the updated FP NMA submitted.

Table 5. Cost-Effectiveness Results for Non-Squamous PD-L1<50% NSCLC

	Total costs	Total LYs	Total QALYs	ICER
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	[redacted]	£50,890
Atezolizumab + bevacizumab + carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	Dominated

Non-Squamous Histology and PD-L1 All-Comers

Table 6 shows the cost-effectiveness results in patients with Non-Squamous NSCLC (using NSQ survival curves not restricted by PD-L1 status).

This scenario fully aligns the survival curves used for Nivolumab + ipilimumab combined with PDC and PDC arms with the FP NMA data used for Pembrolizumab + platinum + pemetrexed. This is also fully aligned with the approved population for Pembrolizumab + platinum + pemetrexed. The Non-Squamous histology data (not restricted by PD-L1 status) is likely to be more robust due to increased patient numbers and therefore less uncertainty than when the data are split by PD-L1 status as well as histology.

Table 6. Cost-Effectiveness Results for Non-Squamous NSCLC

	Total costs	Total LYs	Total QALYs	ICER
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	[redacted]	£34,581
Pembrolizumab + pemetrexed + PDC	[redacted]	[redacted]	[redacted]	Dominated

Squamous Histology Cost-Effectiveness Results

Squamous Histology and PD-L1 < 50%

Table 7 shows the base case cost-effectiveness results in patients with Squamous NSCLC with PD-L1 < 50%

Table 7. Cost-Effectiveness Results for Squamous PD-L1<50% NSCLC

	Total costs	Total LYs	Total QALYs	ICER
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	[redacted]	£55,590

Squamous Histology and PD-L1 All-Comers

For completeness and to align with the analyses presented in the Non-Squamous population, Table 8 shows the cost-effectiveness results in patients with Squamous NSCLC (not restricted by PD-L1 status).

Table 8. Cost-Effectiveness Results for Squamous NSCLC

	Total costs	Total LYs	Total QALYs	ICER
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab combined with PDC	[redacted]	[redacted]	[redacted]	£58,692

Summary of Curve Selection Results

A summary of the base case curve selections for OS and PFS in each subgroup is provided in Table 9 and Table 10.

Table 9. Summary of OS Curve Selection

	Nivolumab + Ipilimumab + PDC	PDC
PD-L1 < 50% Non-Squamous	Log-logistic	Spline Odds 2 Knot
PD-L1 < 50% Squamous	Log-logistic	Log-logistic
Squamous[a]	Lognormal	Lognormal
Non-Squamous[a]	Lognormal	Log-logistic

[a] Selected distributions for Squamous and Non-Squamous subgroups based on statistical fit only and not formally validated with a clinician

Table 10. Summary of PFS Curve Selection

	Nivolumab + Ipilimumab + PDC	PDC
PD-L1 < 50% Non-Squamous	Spline Odds 1 Knot	Spline Odds 2 Knot
PD-L1 < 50% Squamous	Spline Normal 1 Knot	Spline Hazards 2 Knot
Squamous[a]	Spline Odds 2 Knot	Loglogistic
Non-Squamous[a]	Spline Odds 1 Knot	Loglogistic

[a] Selected distributions for Squamous and Non-Squamous subgroups based on statistical fit only and not formally validated with a clinician

BRISTOL-MYERS SQUIBB COMPANY

NIVOLUMAB

Fractional Polynomial NMA Non-Interventional Study Report for Study CA209-9LA

FRACTIONAL POLYNOMIAL NMA OF 1ST LINE IMMUNOTHERAPIES FOR ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

Non-squamous networks of evidence

Indication:	1st line non-small cell lung cancer (NSCLC)
Study Initiation Date:	9-Apr-2020
Study Completion Date:	Ongoing
Study Period:	Prior to May 12, 2020
Report Date:	30-March-2021
Document Control Number:	Version 1.0
Previous Version(s) of this Report:	N/A

THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH THE INTERNATIONAL SOCIETY FOR PHARMACOEPIDEMIOLOGY GUIDELINES FOR GOOD PHARMACOEPIDEMIOLOGY PRACTICES

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1 NSQ HISTOLOGY & PD-L1 < 50% NETWORK

1.1 NSQ & PD-L1 <50% (CheckMate NSQ histology and PD-L1 <50%): Overall survival - Constant HR model

In this current section, a constant hazard ratio (HR) model is presented for overall survival in the target population of patients with non-squamous histology and PD-L1 expression levels <50%. This is a parsimonious model choice that provided reasonably good fit to the data, given that the proportional hazards assumption did not appear to be violated in IMpower 150 or KeyNote 189. However, the hazards did not appear to be proportional in CheckMate 227, which may potentially be seen in the longer-term follow-up from CheckMate 9LA. This constant HR model did not capture the temporal dynamics in terms of relative effects over time for CheckMate 227, or potentially for the longer-term projections of CheckMate 9LA.

In section 1.2, a time-varying HR model is presented, based on the same input data. The latter model is able to capture these temporal dynamics, with only a small decrement to model fit (2 units difference in the deviance information criterion [DIC]).

***Table** 1: RCTs included in the network meta-analysis of overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Study	PD-L1	Histology	Treatment 1	Treatment 2	HR (95% CI)
ERACLE - Galetta (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	0.93 (0.60 - 1.43)
PRONOUNCE - Zinner (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	1.07 (0.84 - 1.37)
IMpower 150	< 50%	NSq	ATEZO-BEV15-PD	BEV15-PD	0.81 (0.65 - 1.02)
KeyNote 189	< 50%	NSq	PEMBRO-PLAT-PEMX	PLAT-PEMX	0.57 (0.45 - 0.73)
CheckMate 227	< 50%	NSq	NIVO-IPI	PLAT-PEMX*	[redacted]
CheckMate 9LA	< 50%	NSq	NIVO-IPI-PLAT-PEMX*	PLAT-PEMX*	[redacted]

**Note: This is the nonsq regimen within the checkmate trial(s)*

***Table** 2: Data sources of RCTs included in the network meta-analysis of overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Study	Author	Year	Publication type
ERACLE	Galetta	2015	Manuscript

Study	Author	Year	Publication type
PRONOUNCE	Zinner	2015	Manuscript
IMpower150	Socinski	2018	ASCO conference
KEYNOTE189	Gray	2020	WCLC conference
CheckMate 9LA	BMS	April 2020	IPD on file
CheckMate 227	BMS	April 2020	IPD on file

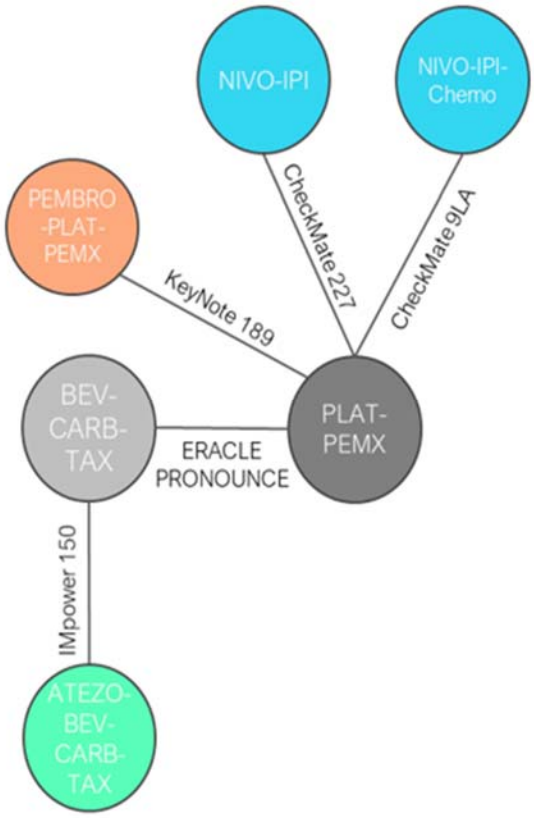
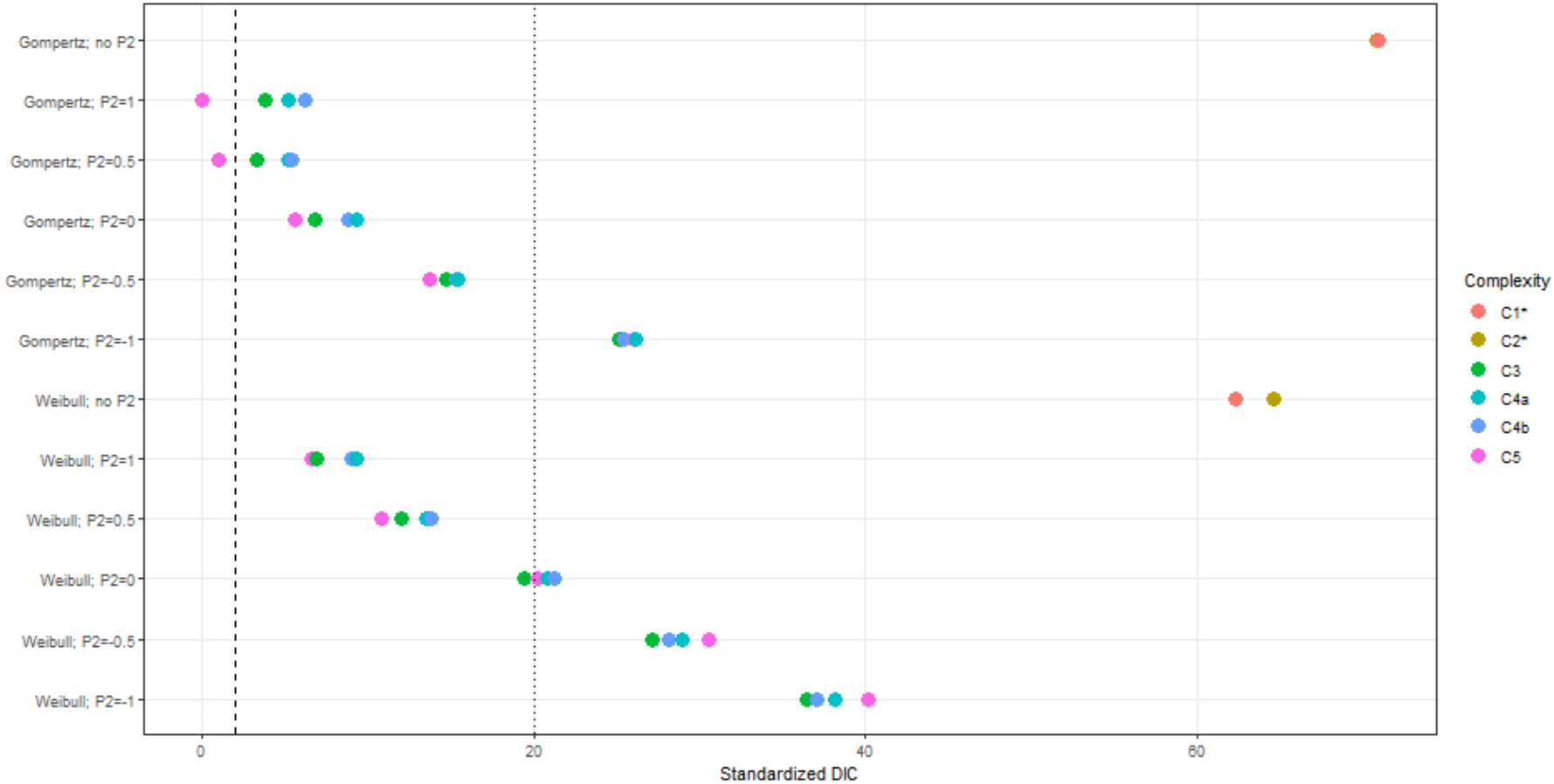


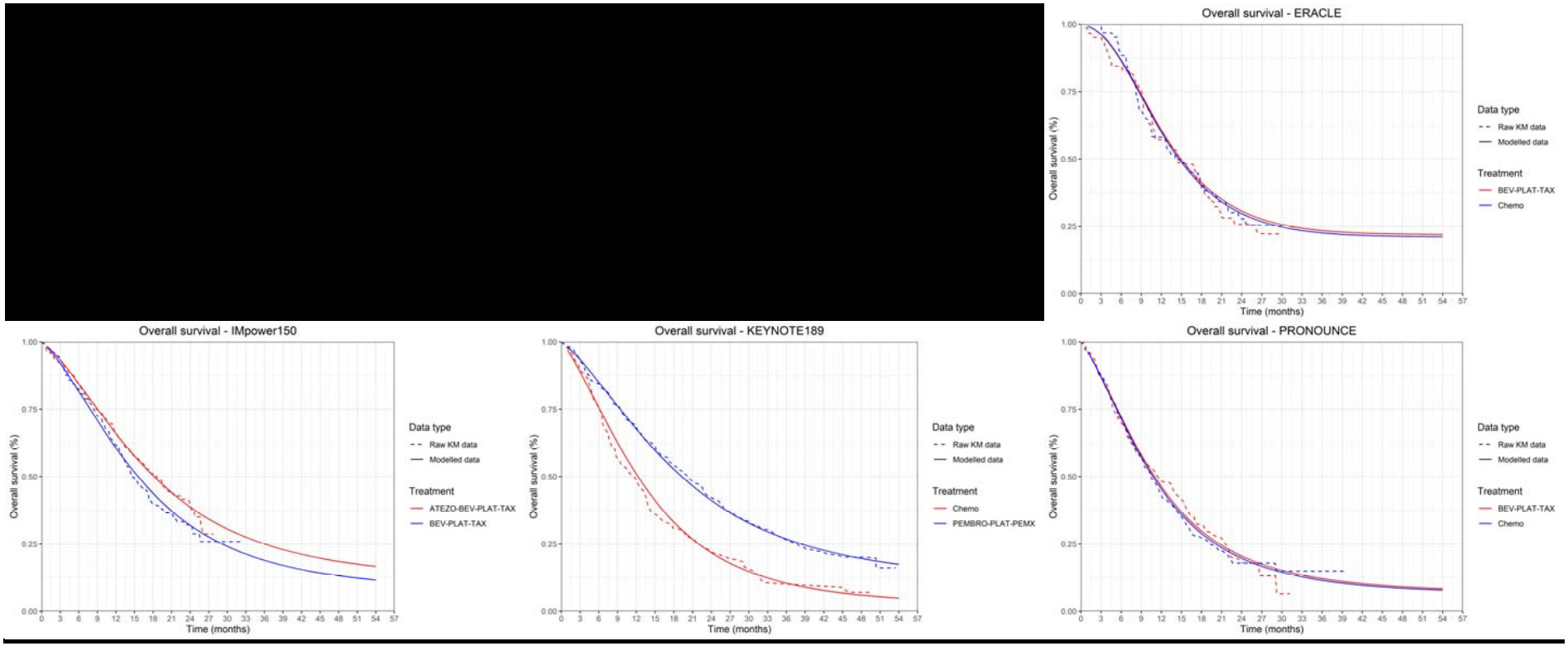
***Figure** 1: Network diagram for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

***Figure** 2: Model fit statistics for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*



Abbreviations: DIC = deviance information criterion
Selected model: p1p0.5; treatment effect on scale

***Figure** 3: Comparison of fractional polynomial model fit to Kaplan-Meier curves of contributing RCTs for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*



Note: mu parameters are study specific, while d parameters are meta-analyzed. From model: p1p0.5; treatment effect on scale

***Table** 3: Mu_mean parameters for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Parameter	Estimate	Variance	Correlation (12)	Correlation (13)	Correlation (23)
Mu_mean1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Estimate	Variance	Correlation (12)	Correlation (13)	Correlation (23)
Mu_mean2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Please note that the following estimates for mu are *not* outputs of the NMA - these have been provided as a baseline onto which treatment effects can be added; however, the choice of reference curve should be updated as appropriate. Currently, these are estimated using the average mus of the reference treatment (Chemo).*
Estimates obtained from the following model: p1p0.5; treatment effect on scale

***Table** 4: d parameters for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Treatment	d1 Estimate	d1 Variance
Chemo	[redacted]	[redacted]
BEV-PLAT-TAX	[redacted]	[redacted]
ATEZO-BEV-PLAT-TAX	[redacted]	[redacted]
PEMBRO-PLAT-PEMX	[redacted]	[redacted]
NIVO-IPI	[redacted]	[redacted]
NIVO-IPI + Chemo	[redacted]	[redacted]

Estimates obtained from the following model: p1p0.5; treatment effect on scale

The model estimates can be incorporated into a fractional polynomial model of the functional form:

$$log\ hazard = (Mu1 + d1) + Mu2*t + Mu3*t^{(0.5)}$$

Study-specific estimates for Mu1, Mu2, and Mu3, which define the reference curve, are provided, and can be replaced with updated estimates, against which differences can be applied.

Hazard ratios for treatment X vs treatment Y at any time t can be calculated using the formula below:

$$EXP((d1[X] - d1[Y]))$$

***Figure** 4: HRs of NIVO-IPI-Chemo vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 21 months of follow-up.*
Estimates obtained from the following model: p1p0.5; treatment effect on scale
Dashed lines represent 95% credible intervals

***Table** 5: HRs of NIVO-IPI-Chemo vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Comparator	HR (95% CrI)
Chemo	[redacted]
BEV-PLAT-TAX	[redacted]
ATEZO-BEV-PLAT-TAX	[redacted]
PEMBRO-PLAT-PEMX	[redacted]
NIVO-IPI	[redacted]

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 21 months of follow-up. HRs shaded in grey are projections and not an observed finding.*
Estimates obtained from the following model: p1p0.5; treatment effect on scale

***Table** 6: HRs of NIVO-IPI vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Comparator	HR (95% CrI)
Chemo	[redacted]
BEV-PLAT-TAX	[redacted]
ATEZO-BEV-PLAT-TAX	[redacted]

Comparator	HR (95% CrI)
PEMBRO-PLAT-PEMX	[redacted]
NIVO-IPI-Chemo	[redacted]

HRs shaded in grey are projections and not an observed finding.
Estimates obtained from the following model: p1p0.5; treatment effect on scale

***Table** 7: Correlation matrix for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Parameter	d[BEV-PLAT-TAX,1]	d[ATEZO-BEV-PLAT-TAX,1]	d[PEMBRO-PLAT-PEMX,1]	d[NIVO-IPI,1]	d[NIVO-IPI-Chemo,1]
d[BEV-PLAT-TAX,1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[ATEZO-BEV-PLAT-TAX,1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[PEMBRO-PLAT-PEMX,1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[NIVO-IPI,1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[NIVO-IPI-Chemo,1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Estimates obtained from the following model: p1p0.5; treatment effect on scale

1.2 NSQ & PD-L1 <50% (CheckMate NSQ histology and PD-L1 <50%): Overall survival - Time-varying Model

See section 1.1 for a constant HR model based on the same input data, and associated explanation.

***Table** 8: RCTs included in the network meta-analysis of overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Study	PD-L1	Histology	Treatment 1	Treatment 2	HR (95% CI)
ERACLE - Galetta (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	0.93 (0.60 - 1.43)
PRONOUNCE - Zinner (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	1.07 (0.84 - 1.37)
IMpower 150	< 50%	NSq	ATEZO-BEV15-PD	BEV15-PD	0.81 (0.65 - 1.02)
KeyNote 189	< 50%	NSq	PEMBRO-PLAT-PEMX	PLAT-PEMX	0.57 (0.45 - 0.73)
CheckMate 227	< 50%	NSq	NIVO-IPI	PLAT-PEMX*	[redacted]
CheckMate 9LA	< 50%	NSq	NIVO-IPI-PLAT-PEMX*	PLAT-PEMX*	[redacted]

**Note: This is the nonsq regimen within the checkmate trial(s)*

***Table** 9: Data sources of RCTs included in the network meta-analysis of overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Study	Author	Year	Publication type
ERACLE	Galetta	2015	Manuscript
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CheckMate 227	BMS	April 2020	IPD on file

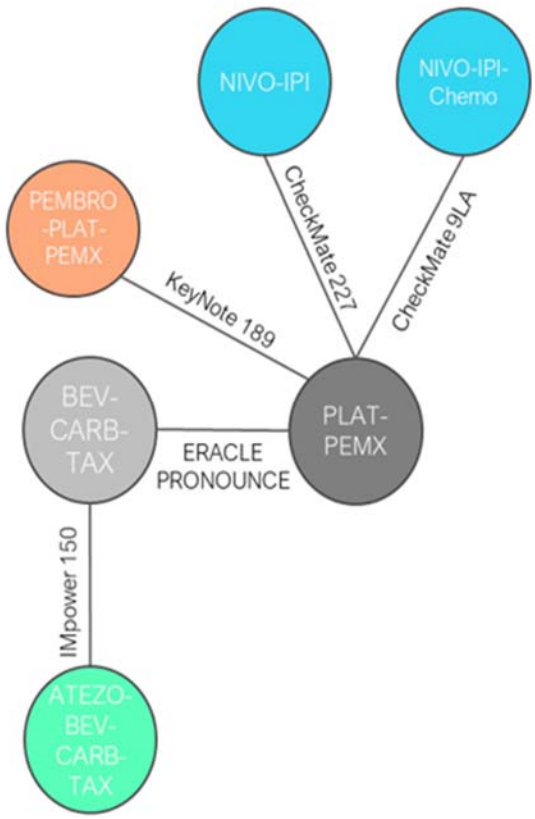
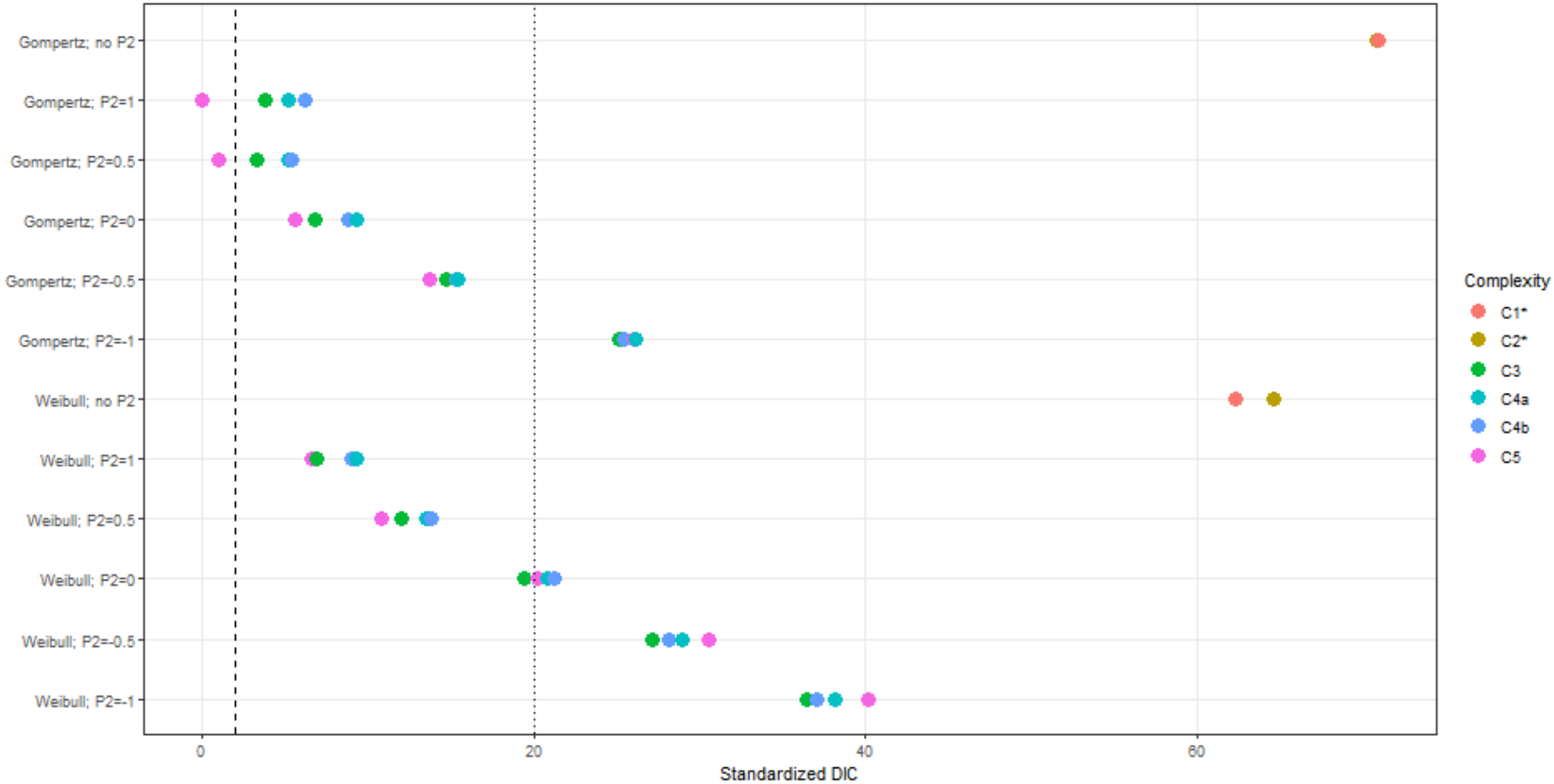


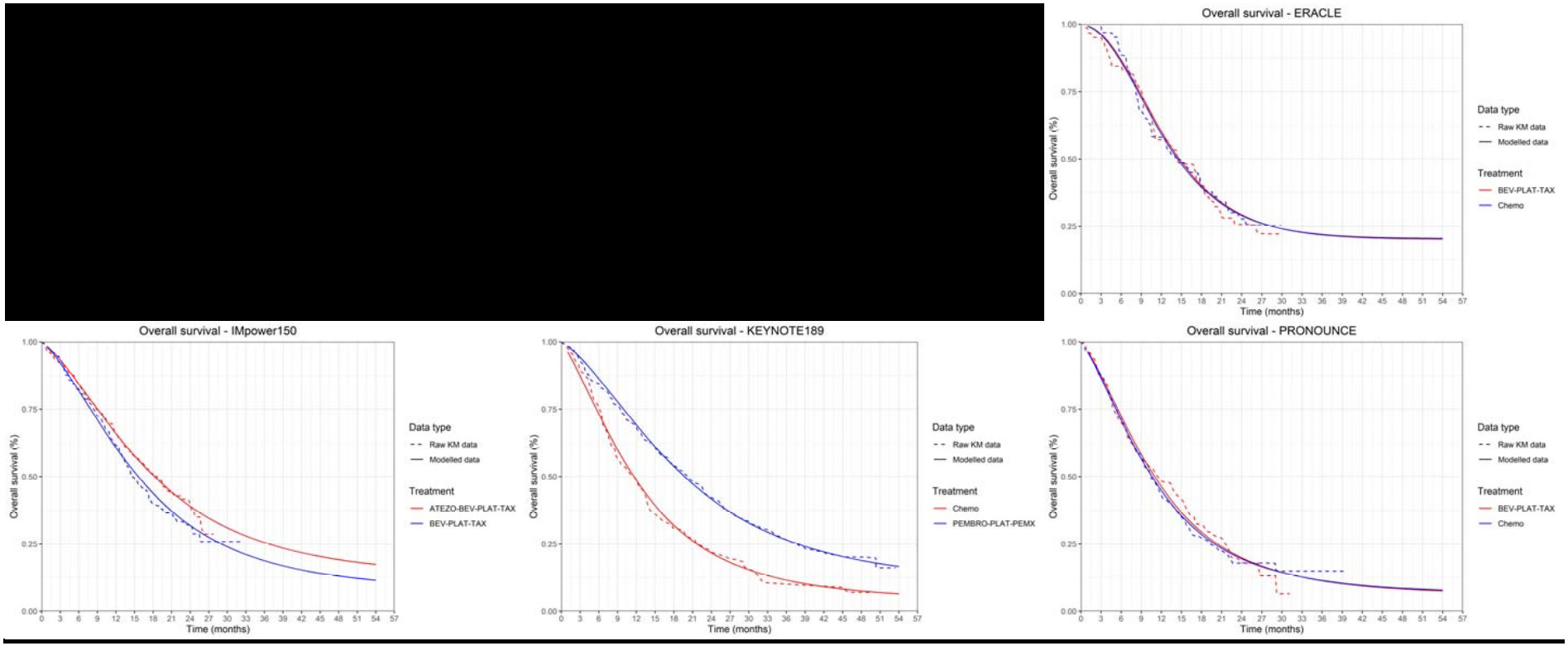
***Figure** 5: Network diagram for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

***Figure** 6: Model fit statistics for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*



Abbreviations: DIC = deviance information criterion
Selected model: p1p0.5; treatment effect on scale, 2nd shape

***Figure** 7: Comparison of fractional polynomial model fit to Kaplan-Meier curves of contributing RCTs for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*



Note: mu parameters are study specific, while d parameters are meta-analyzed. From model: p1p0.5; treatment effect on scale, 2nd shape

***Table** 10: Mu_mean parameters for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Parameter	Estimate	Variance	Correlation (12)	Correlation (13)	Correlation (23)
Mu_mean1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Estimate	Variance	Correlation (12)	Correlation (13)	Correlation (23)
Mu_mean2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Please note that the following estimates for mu are *not* outputs of the NMA - these have been provided as a baseline onto which treatment effects can be added; however, the choice of reference curve should be updated as appropriate. Currently, these are estimated using the average mus of the reference treatment (Chemo).*
Estimates obtained from the following model: p1p0.5; treatment effect on scale, 2nd shape

***Table** 11: d parameters for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Treatment	d1 Estimate	d1 Variance	d3 Estimate	d3 Variance	d23 Correlation
Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO-BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO-PLAT-PEMX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI + Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Estimates obtained from the following model: p1p0.5; treatment effect on scale, 2nd shape

The model estimates can be incorporated into a fractional polynomial model of the functional form:

$$log\ hazard = (Mu1 + d1) + Mu2*t + (Mu3 + d3)*t^{(0.5)}$$

Study-specific estimates for Mu1, Mu2, and Mu3, which define the reference curve, are provided, and can be replaced with updated estimates, against which differences can be applied.

Hazard ratios for treatment X vs treatment Y at any time t can be calculated using the formula below:

$$EXP((d1[X] - d1[Y]) + (d3[X] - d3[Y])*t^{(0.5)})$$

***Figure** 8: HRs of NIVO-IPI-Chemo vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 21 months of follow-up.*
Estimates obtained from the following model: p1p0.5; treatment effect on scale, 2nd shape
Dashed lines represent 95% credible intervals

***Table** 12: HRs of NIVO-IPI-Chemo vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Comparator	Timepoint (months)	HR (95% CrI)
Chemo	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
ATEZO-BEV-PLAT-TAX	1	[redacted]

Comparator	Timepoint (months)	HR (95% CrI)
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
PEMBRO-PLAT-PEMX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
NIVO-IPI	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 21 months of follow-up. HRs shaded in grey are projections and not an observed finding.*
Estimates obtained from the following model: p1p0.5; treatment effect on scale, 2nd shape

***Table** 13: HRs of NIVO-IPI vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Comparator	Timepoint (months)	HR (95% CrI)
Chemo	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
	1	[redacted]
	6	[redacted]

Comparator	Timepoint (months)	HR (95% CrI)
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
ATEZO-BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
PEMBRO-PLAT-PEMX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
NIVO-IPI-Chemo	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]

HRs shaded in grey are projections and not an observed finding.
Estimates obtained from the following model: p1p0.5; treatment effect on scale, 2nd shape

***Table** 14: Correlation matrix for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Parameter	d[BEV-PLAT-TAX,1]	d[ATEZO-BEV-PLAT-TAX,1]	d[PEMBRO-PLAT-PEMX,1]	d[NIVO-IPI,1]	d[NIVO-IPI-Chemo,1]	d[BEV-PLAT-TAX,3]	d[ATEZO-BEV-PLAT-TAX,3]	d[PEMBRO-PLAT-PEMX,3]	d[NIVO-IPI,3]	d[NIVO-IPI-Chemo,3]
d[BEV-PLAT-TAX,1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[ATEZO-BEV-PLAT-TAX,1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[PEMBRO-PLAT-PEMX,1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[NIVO-IPI,1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[NIVO-IPI-Chemo,1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[BEV-PLAT-TAX,3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[ATEZO-BEV-PLAT-TAX,3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[PEMBRO-PLAT-PEMX,3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[NIVO-IPI,3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[NIVO-IPI-Chemo,3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Estimates obtained from the following model: p1p0.5; treatment effect on scale, 2nd shape

1.3 NSQ & PD-L1 <50% (CheckMate NSQ histology and PD-L1 <50%): Progression-free survival

***Table** 15: RCTs included in the network meta-analysis of progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Study	PD-L1	Histology	Treatment 1	Treatment 2	HR (95% CI)
ERACLE - Galetta (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	0.79 (0.53 - 1.17)
PRONOUNCE - Zinner (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	1.06 (0.84 - 1.34)
IMpower 150	< 50%	NSq	ATEZO-BEV15-PD	BEV15-PD	0.68 (0.56 - 0.82)
KeyNote 189	< 50%	NSq	PEMBRO-PLAT-PEMX	PLAT-PEMX	0.61 (0.49 - 0.77)
CheckMate 227	< 50%	NSq	NIVO-IPI	PLAT-PEMX*	[redacted]
CheckMate 9LA	< 50%	NSq	NIVO-IPI-PLAT-PEMX*	PLAT-PEMX*	[redacted]

**Note: This is the nonsq regimen within the checkmate trial(s)*

***Table** 16: Data sources of RCTs included in the network meta-analysis of progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Study	Author	Year	Publication type
ERACLE	Galetta	2015	Manuscript
PRONOUNCE	Zinner	2015	Manuscript
IMpower150	Socinski	2018	NEJM manuscript
KEYNOTE189	Gray	2020	WCLC conference
CheckMate 9LA	BMS	April 2020	IPD on file
CheckMate 227	BMS	April 2020	IPD on file

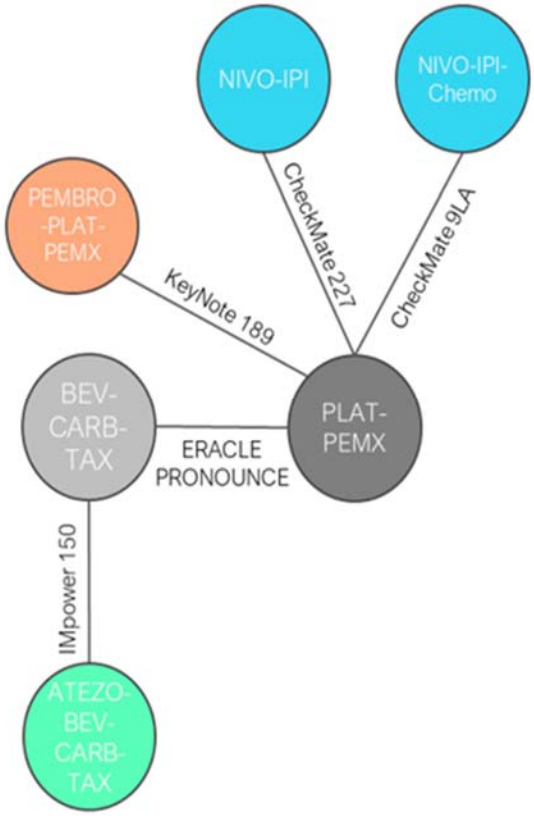
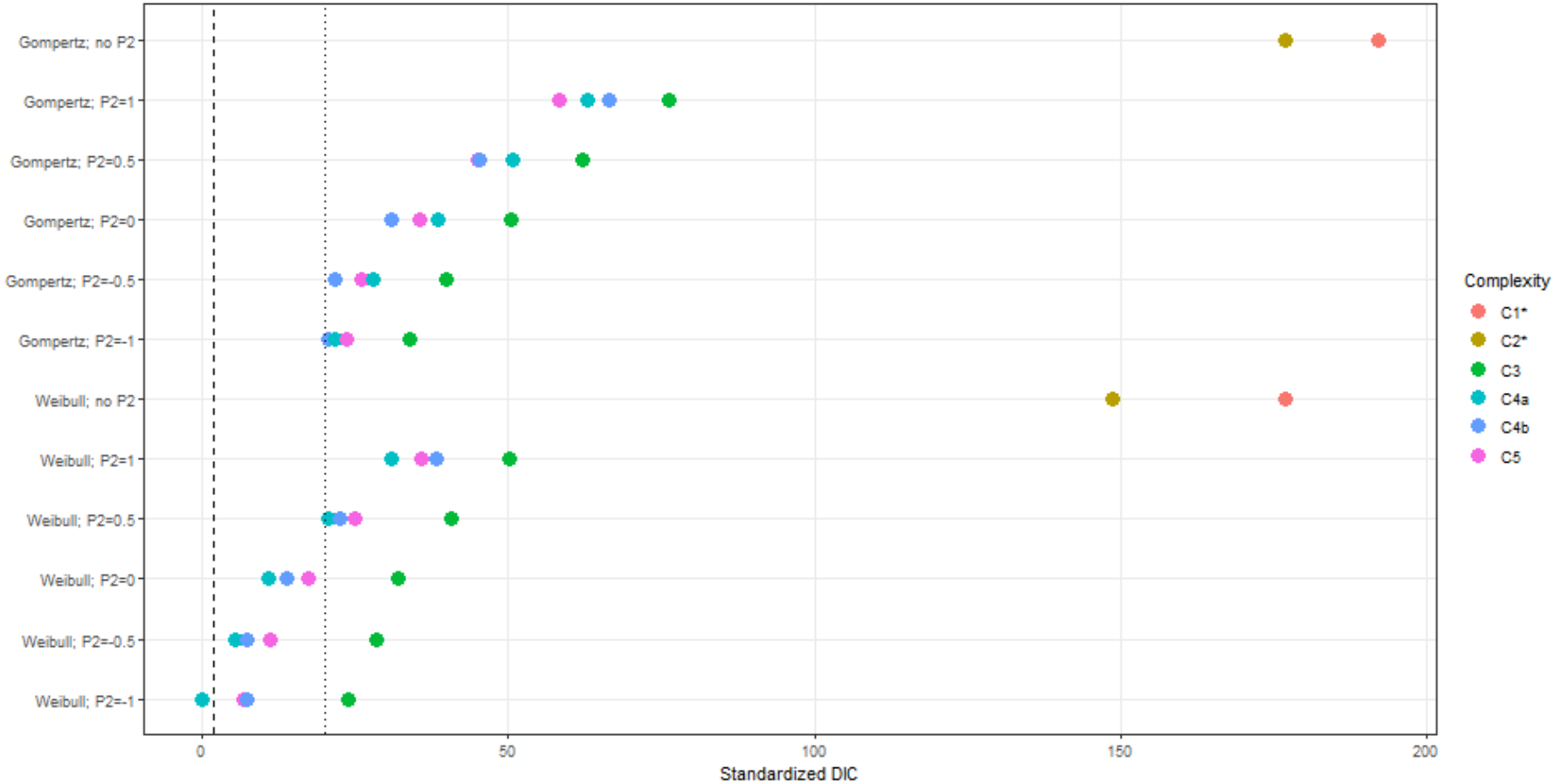


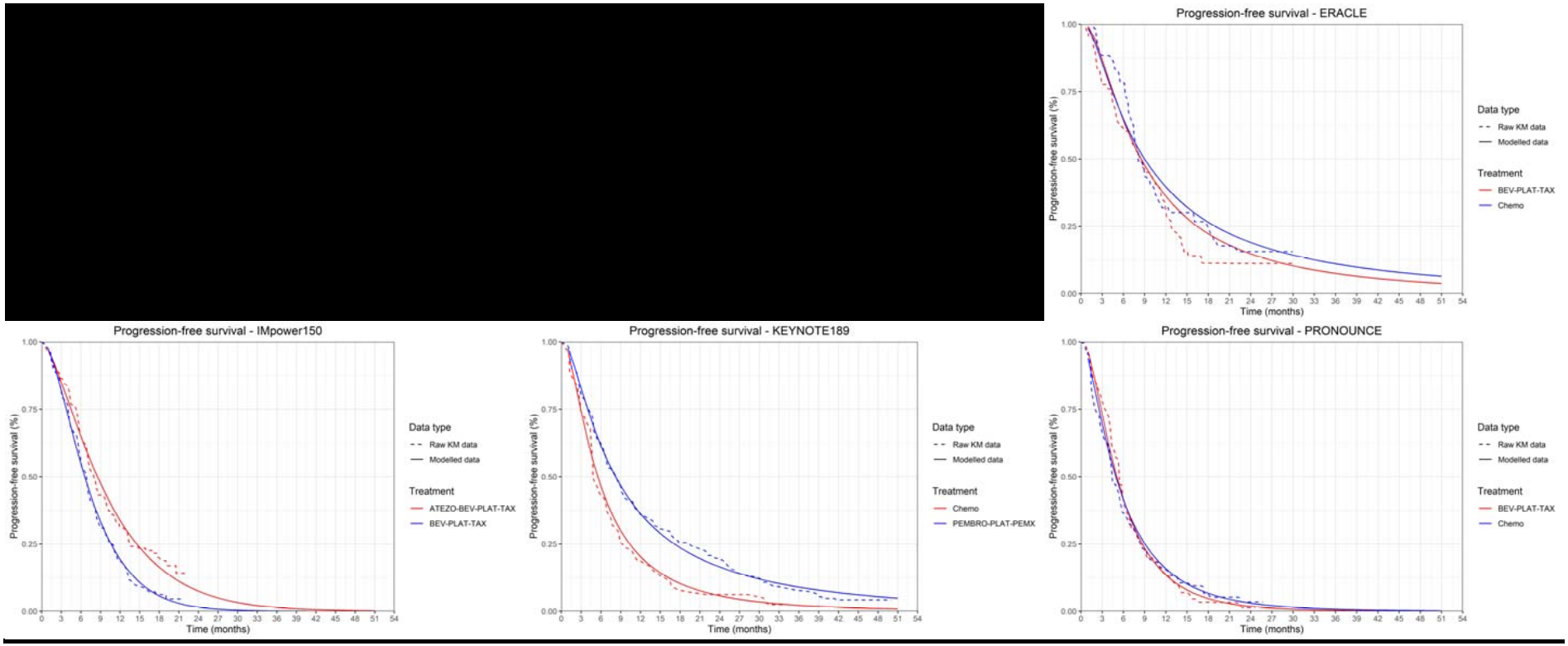
***Figure** 9: Network diagram for progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

***Figure** 10: Model fit statistics for progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*



Abbreviations: DIC = deviance information criterion
Selected model: p0p-1; treatment effect on scale, 2nd shape

***Figure** 11: Comparison of fractional polynomial model fit to Kaplan-Meier curves of contributing RCTs for progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*



Note: mu parameters are study specific, while d parameters are meta-analyzed. From model: p0p-1; treatment effect on scale, 2nd shape

***Table** 17: Mu_mean parameters for progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Parameter	Estimate	Variance	Correlation (12)	Correlation (13)	Correlation (23)
Mu_mean1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Please note that the following estimates for mu are *not* outputs of the NMA - these have been provided as a baseline onto which treatment effects can be added; however, the choice of reference curve should be updated as appropriate. Currently, these are estimated using the average mus of the reference treatment (Chemo).*
Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape

***Table** 18: d parameters for progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Treatment	d1 Estimate	d1 Variance	d3 Estimate	d3 Variance	d23 Correlation
Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO-BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO-PLAT-PEMX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI + Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape

The model estimates can be incorporated into a fractional polynomial model of the functional form:

$$log\ hazard = (Mu1 + d1) + Mu2*ln(t) + (Mu3 + d3)*(1/t)$$

Study-specific estimates for Mu1, Mu2, and Mu3, which define the reference curve, are provided, and can be replaced with updated estimates, against which differences can be applied.

Hazard ratios for treatment X vs treatment Y at any time t can be calculated using the formula below:

$$EXP((d1[X] - d1[Y]) + (d3[X] - d3[Y])*(1/t))$$

***Figure** 12: HRs of NIVO-IPI-Chemo vs comparators over time for progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 18 months of follow-up.*
Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape
Dashed lines represent 95% credible intervals

***Table** 19: HRs of NIVO-IPI-Chemo vs comparators over time for progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Comparator	Timepoint (months)	HR (95% CrI)
Chemo	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
ATEZO-BEV-PLAT-TAX	1	[redacted]

Comparator	Timepoint (months)	HR (95% CrI)
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
PEMBRO-PLAT-PEMX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
NIVO-IPI	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 18 months of follow-up. HRs shaded in grey are projections and not an observed finding.*
Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape

***Table** 20: HRs of NIVO-IPI vs comparators over time for progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Comparator	Timepoint (months)	HR (95% CrI)
Chemo	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
	1	[redacted]
	6	[redacted]

Comparator	Timepoint (months)	HR (95% CrI)
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
ATEZO-BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
PEMBRO-PLAT-PEMX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
NIVO-IPI-Chemo	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]

HRs shaded in grey are projections and not an observed finding.
Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape

***Table** 21: Correlation matrix for progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% and NSQ for KN189, IMP150, CM9LA, and CM227; PD-L1 all-comers and NSQ for all other RCTs)*

Parameter	d[BEV-PLAT-TAX,1]	d[ATEZO-BEV-PLAT-TAX,1]	d[PEMBRO-PLAT-PEMX,1]	d[NIVO-IPI,1]	d[NIVO-IPI-Chemo,1]	d[BEV-PLAT-TAX,3]	d[ATEZO-BEV-PLAT-TAX,3]	d[PEMBRO-PLAT-PEMX,3]	d[NIVO-IPI,3]	d[NIVO-IPI-Chemo,3]
d[BEV-PLAT-TAX,1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[ATEZO-BEV-PLAT-TAX,1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[PEMBRO-PLAT-PEMX,1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[NIVO-IPI,1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[NIVO-IPI-Chemo,1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[BEV-PLAT-TAX,3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[ATEZO-BEV-PLAT-TAX,3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[PEMBRO-PLAT-PEMX,3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[NIVO-IPI,3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
d[NIVO-IPI-Chemo,3]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape

2 NSQ HISTOLOGY NETWORK

2.1 PD-L1 all-comers (CheckMate mixed histology): Overall survival

***Table** 22: RCTs included in the network meta-analysis of overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*

Study	PD-L1	Histology	Treatment 1	Treatment 2	HR (95% CI)
ERACLE - Galetta (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	0.93 (0.60 - 1.43)
PRONOUNCE - Zinner (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	1.07 (0.84 - 1.37)
IMpower 150	All-comers	NSq	ATEZO-BEV15-PD	BEV15-PD	0.80 (0.67 - 0.95)
IMpower 130	All-comers	NSq	ATEZO-CARB-NabTAX	PLAT-NabTAX	0.79 (0.64 - 0.98)
KeyNote 189	All-comers	NSq	PEMBRO-PLAT-PEMX	PLAT-PEMX	0.56 (0.46 - 0.69)
CheckMate 227	All-comers	Mixed	NIVO-IPI	PLAT-PEMX or CARB-TAX	[redacted]
CheckMate 9LA	All-comers	Mixed	NIVO-IPI-PLAT-PEMX or GEM	PLAT-PEMX or GEM	[redacted]

***Table** 23: Data sources of RCTs included in the network meta-analysis of overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*

Study	Author	Year	Publication type
ERACLE	Galetta	2015	Manuscript
KEYNOTE189	Rodriguez-Abreu	2020	ASCO conference poster
PRONOUNCE	Zinner	2015	Manuscript
IMpower150	SocinskiAACR	2020	AACR conference slides
IMpower130	West	2019	Lancet manuscript
CheckMate 9LA	BMS	April 2020	IPD on file
CheckMate 227	BMS	April 2020	IPD on file

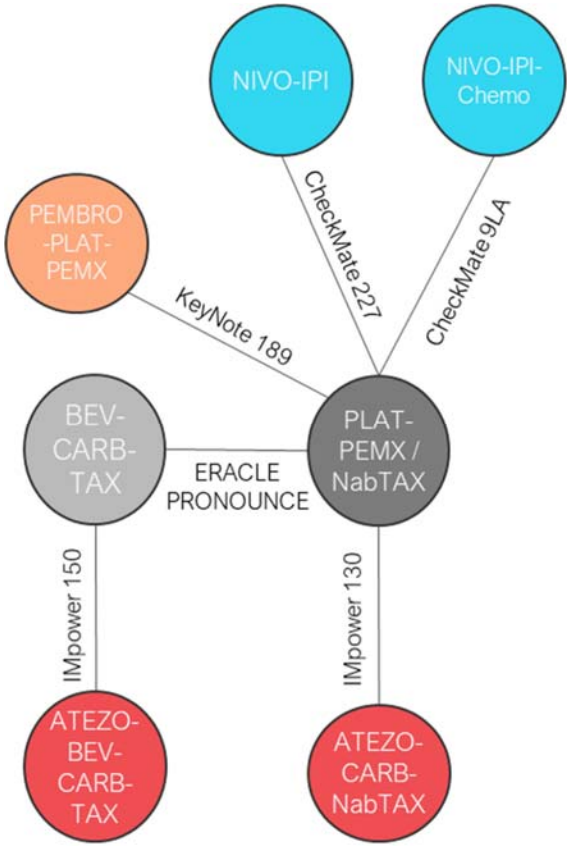
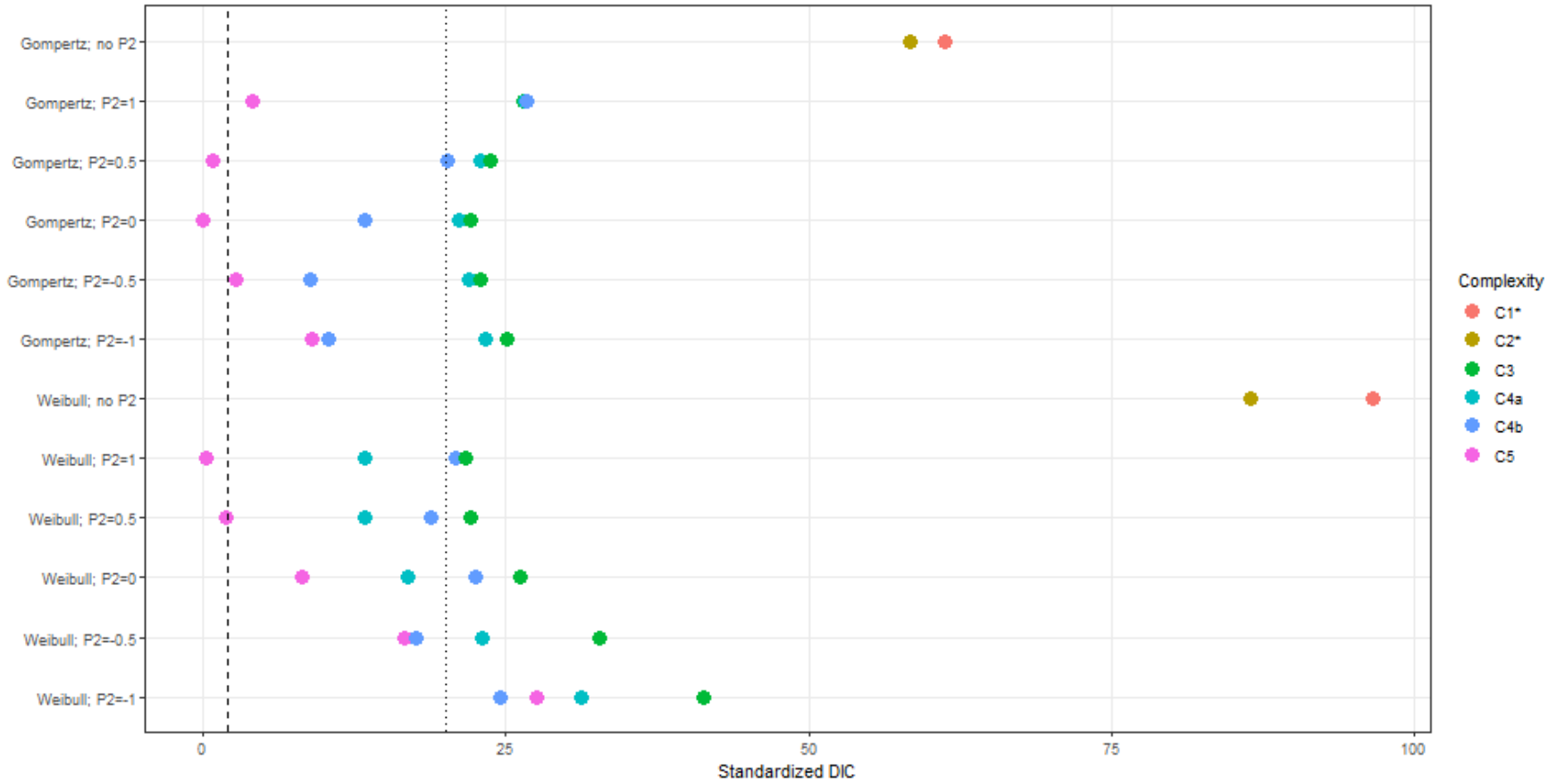


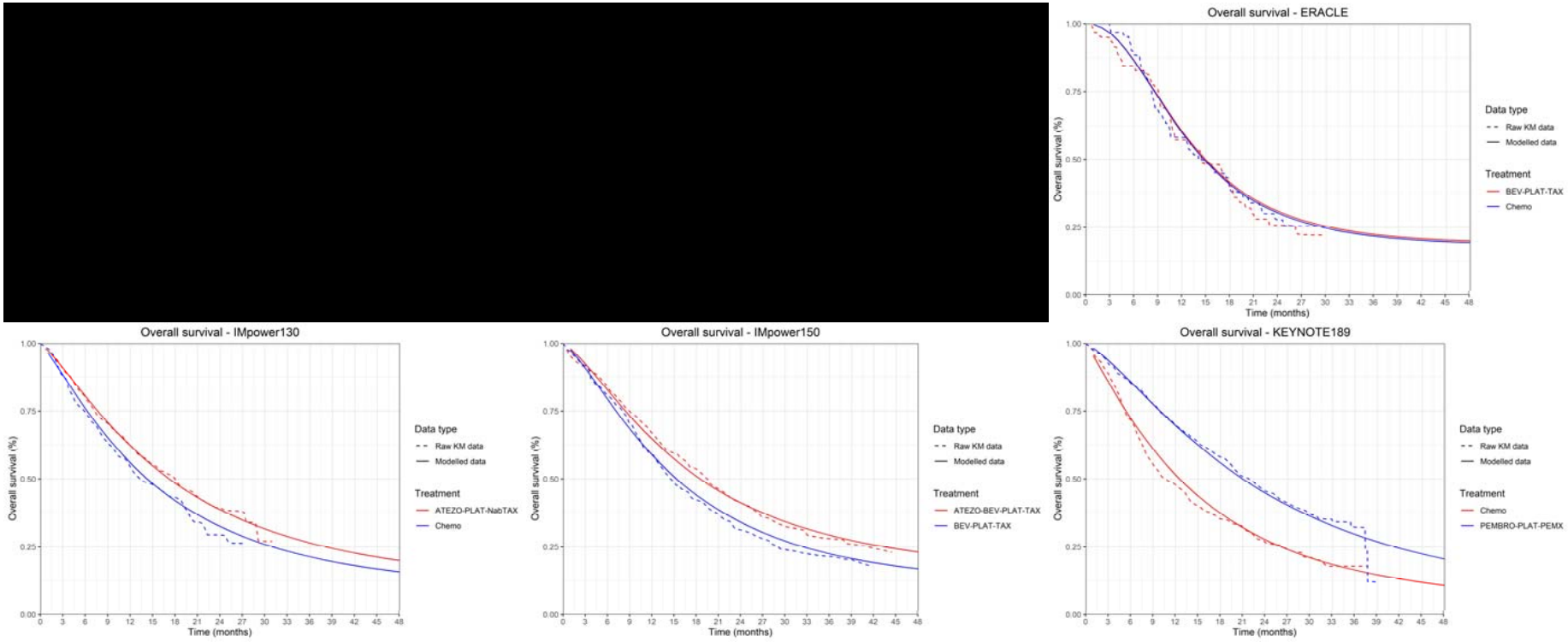
***Figure** 13: Network diagram for overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*

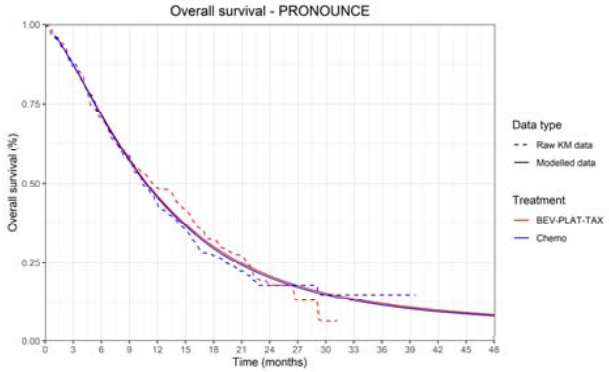
***Figure** 14: Model fit statistics for overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*



Abbreviations: DIC = deviance information criterion
Selected model: p1p0; treatment effect on scale, 2nd shape

***Figure** 15: Comparison of fractional polynomial model fit to Kaplan-Meier curves of contributing RCTs for overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*





Note: mu parameters are study specific, while d parameters are meta-analyzed. From model: p1p0; treatment effect on scale, 2nd shape

***Table** 24: Mu_mean parameters for overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*

Parameter	Estimate	Variance	Correlation (12)	Correlation (13)	Correlation (23)
Mu_mean1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Please note that the following estimates for mu are *not* outputs of the NMA - these have been provided as a baseline onto which treatment effects can be added; however, the choice of reference curve should be updated as appropriate. Currently, these are estimated using the average mus of the reference treatment (Chemo).*
Estimates obtained from the following model: p1p0; treatment effect on scale, 2nd shape

***Table** 25: d parameters for overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*

Treatment	d0 Estimate	d0 Variance	d2 Estimate	d2 Variance	d02 Correlation
Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO-BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO-PLAT-NabTAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	d0 Estimate	d0 Variance	d2 Estimate	d2 Variance	d02 Correlation
PEMBRO-PLAT-PEMX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI + Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Estimates obtained from the following model: p1p0; treatment effect on scale, 2nd shape

***Figure** 16: HRs of NIVO-IPI-Chemo vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 21 months of follow-up.*
Estimates obtained from the following model: p1p0; treatment effect on scale, 2nd shape
Dashed lines represent 95% credible intervals

***Table** 26: HRs of NIVO-IPI-Chemo vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*

Comparator	Timepoint (months)	HR (95% CrI)
Chemo	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
ATEZO-BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]

Comparator	Timepoint (months)	HR (95% CrI)
	36	[redacted]
	48	[redacted]
ATEZO-PLAT-NabTAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
PEMBRO-PLAT-PEMX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
NIVO-IPI	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 21 months of follow-up.*
Estimates obtained from the following model: p1p0; treatment effect on scale, 2nd shape

***Table** 27: HRs of NIVO-IPI vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*

Comparator	Timepoint (months)	HR (95% CrI)
Chemo	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]

Comparator	Timepoint (months)	HR (95% CrI)
	24	[redacted]
	36	[redacted]
	48	[redacted]
ATEZO-BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
ATEZO-PLAT-NabTAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
PEMBRO-PLAT-PEMX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
NIVO-IPI-Chemo	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]

Estimates obtained from the following model: p1p0; treatment effect on scale, 2nd shape

2.2 PD-L1 all-comers (CheckMate mixed histology): Progression-free survival

***Table** 28: RCTs included in the network meta-analysis of progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*

Study	PD-L1	Histology	Treatment 1	Treatment 2	HR (95% CI)
ERACLE - Galetta (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	0.79 (0.53 - 1.17)
PRONOUNCE - Zinner (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	1.06 (0.84 - 1.34)
IMpower 150	All-comers	NSq	ATEZO-BEV15-PD	BEV15-PD	0.71 (0.59 - 0.85)
IMpower 130	All-comers	NSq	ATEZO-CARB-NabTAX	PLAT-NabTAX	0.64 (0.54 - 0.77)
KeyNote 189	All-comers	NSq	PEMBRO-PLAT-PEMX	PLAT-PEMX	0.50 (0.41 - 0.61)
CheckMate 227	All-comers	Mixed	NIVO-IPI	PLAT-PEMX or CARB-TAX	[redacted]
CheckMate 9LA	All-comers	Mixed	NIVO-IPI-PLAT-PEMX or GEM	PLAT-PEMX or GEM	[redacted]

***Table** 29: Data sources of RCTs included in the network meta-analysis of progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*

Study	Author	Year	Publication type
ERACLE	Galetta	2015	Manuscript
KEYNOTE189	Rodriguez-Abreu	2020	ASCO conference poster
PRONOUNCE	Zinner	2015	Manuscript
IMpower130	West	2019	Lancet manuscript
IMpower150	SocinskiNEJM	2018	NEJM manuscript
CheckMate 9LA	BMS	April 2020	IPD on file
CheckMate 227	BMS	April 2020	IPD on file

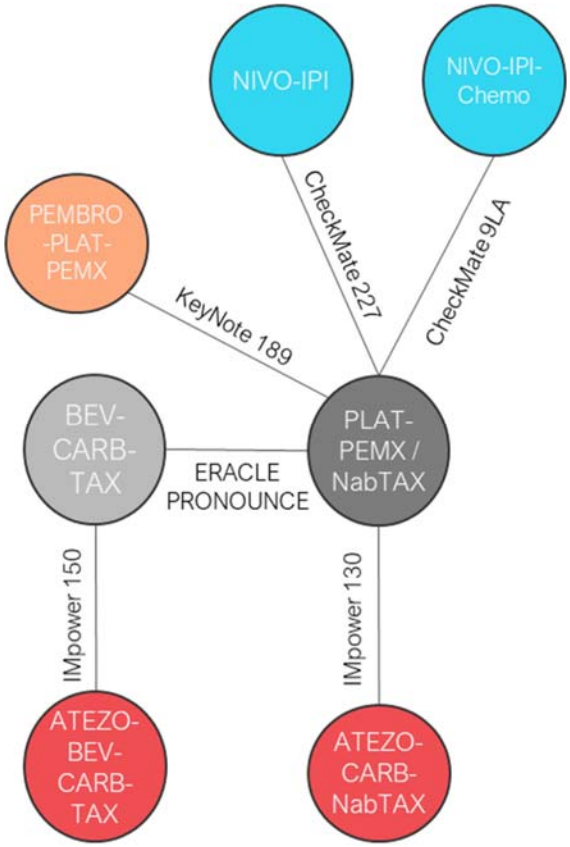
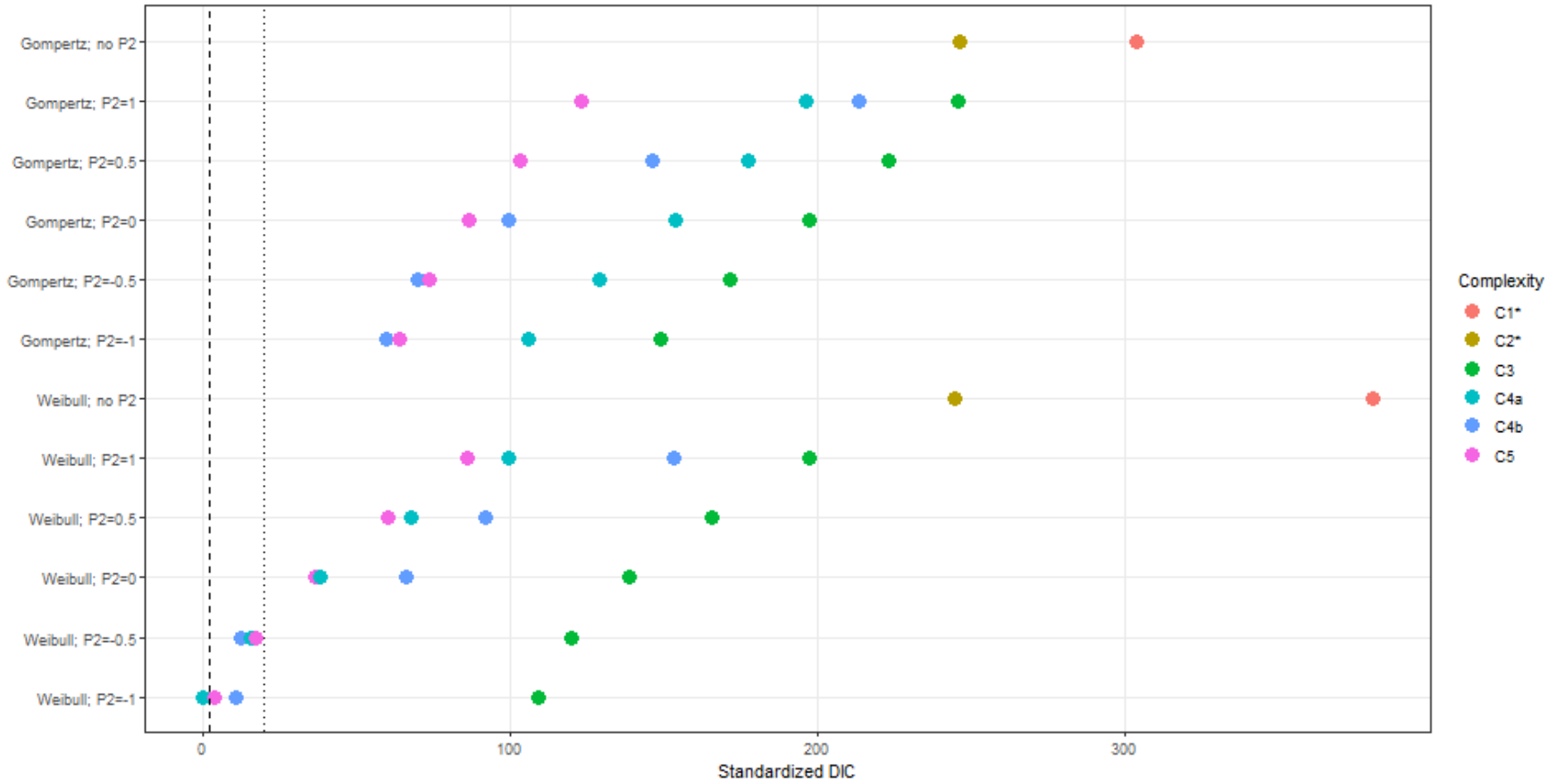


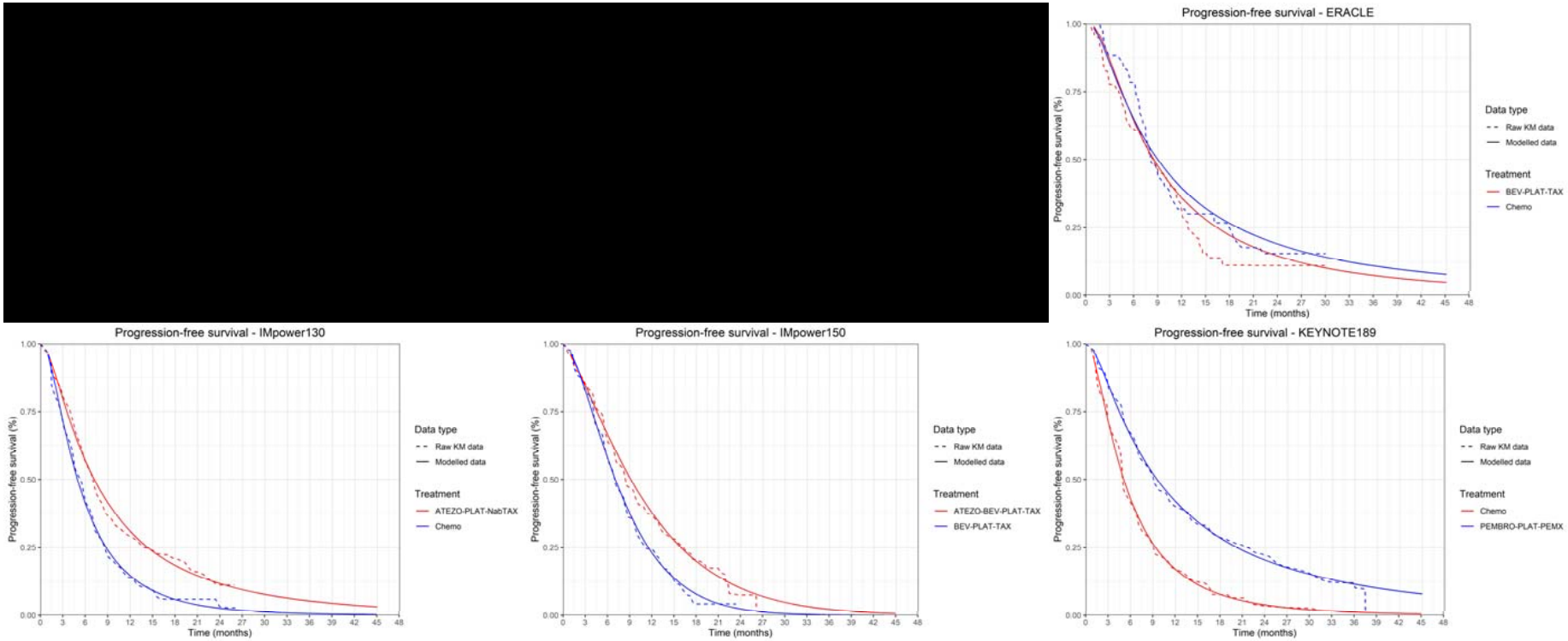
***Figure** 17: Network diagram for progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*

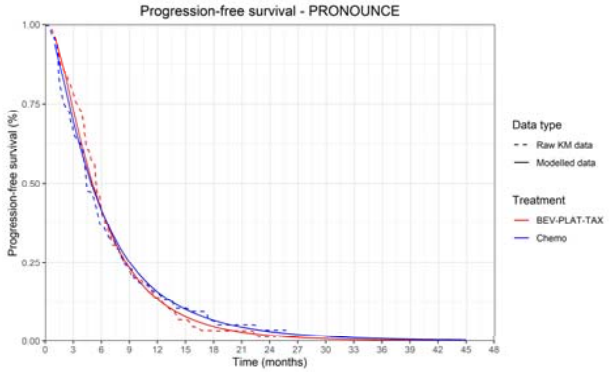
***Figure** 18: Model fit statistics for progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*



Abbreviations: DIC = deviance information criterion
Selected model: p0p-1; treatment effect on scale, 2nd shape

***Figure** 19: Comparison of fractional polynomial model fit to Kaplan-Meier curves of contributing RCTs for progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*





Note: mu parameters are study specific, while d parameters are meta-analyzed. From model: p0p-1; treatment effect on scale, 2nd shape

***Table** 30: Mu_mean parameters for progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*

Parameter	Estimate	Variance	Correlation (12)	Correlation (13)	Correlation (23)
Mu_mean1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Please note that the following estimates for mu are *not* outputs of the NMA - these have been provided as a baseline onto which treatment effects can be added; however, the choice of reference curve should be updated as appropriate. Currently, these are estimated using the average mus of the reference treatment (Chemo).*
Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape

***Table** 31: d parameters for progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*

Treatment	d0 Estimate	d0 Variance	d2 Estimate	d2 Variance	d02 Correlation
Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO-BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO-PLAT-NabTAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	d0 Estimate	d0 Variance	d2 Estimate	d2 Variance	d02 Correlation
PEMBRO-PLAT-PEMX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI + Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape

***Figure** 20: HRs of NIVO-IPI-Chemo vs comparators over time for progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 18 months of follow-up.*
Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape
Dashed lines represent 95% credible intervals

***Table** 32: HRs of NIVO-IPI-Chemo vs comparators over time for progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*

Comparator	Timepoint (months)	HR (95% CrI)
Chemo	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
ATEZO-BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]

Comparator	Timepoint (months)	HR (95% CrI)
ATEZO-PLAT-NabTAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
PEMBRO-PLAT-PEMX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
NIVO-IPI	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 18 months of follow-up.*
Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape

***Table** 33: HRs of NIVO-IPI vs comparators over time for progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; mixed histology for CM9LA and CM227, NSQ histology for all other RCTs)*

Comparator	Timepoint (months)	HR (95% CrI)
Chemo	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
ATEZO-BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]

Comparator	Timepoint (months)	HR (95% CrI)
	36	[redacted]
ATEZO-PLAT-NabTAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
PEMBRO-PLAT-PEMX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
NIVO-IPI-Chemo	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]

Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape

2.3 PD-L1 <50% (CheckMate mixed histology): Overall survival

***Table** 34: RCTs included in the network meta-analysis of overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*

Study	PD-L1	Histology	Treatment 1	Treatment 2	HR (95% CI)
ERACLE - Galetta (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	0.93 (0.60 - 1.43)
PRONOUNCE - Zinner (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	1.07 (0.84 - 1.37)
IMpower 150	<50%	NSq	ATEZO-BEV15-PD	BEV15-PD	0.81 (0.65 - 1.02)
IMpower 130	<50%	NSq	ATEZO-CARB-NabTAX	PLAT-NabTAX	0.78 (0.62 - 1.00)
KeyNote 189	<50%	NSq	PEMBRO-PLAT-PEMX	PLAT-PEMX	0.56 (0.44 - 0.72)
CheckMate 227	All-comers	Mixed	NIVO-IPI	PLAT-PEMX or CARB-TAX	[redacted]
CheckMate 9LA	All-comers	Mixed	NIVO-IPI-PLAT-PEMX or GEM	PLAT-PEMX or GEM	[redacted]

***Table** 35: Data sources of RCTs included in the network meta-analysis of overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*

Study	Author	Year	Publication type
ERACLE	Galetta	2015	Manuscript
IMpower150	SocinskiASCO	2018	ASCO conference slides
PRONOUNCE	Zinner	2015	Manuscript
IMpower130	CappuzzoESMO	2018	ESMO conference slides
KEYNOTE189	Rodriguez-Abreu	2020	ASCO conference poster
CheckMate 9LA	BMS	April 2020	IPD on file
CheckMate 227	BMS	April 2020	IPD on file

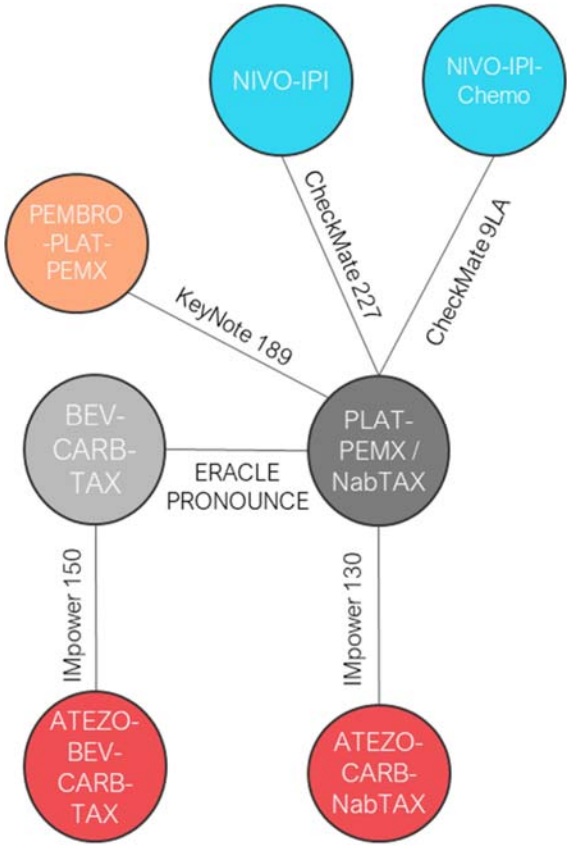
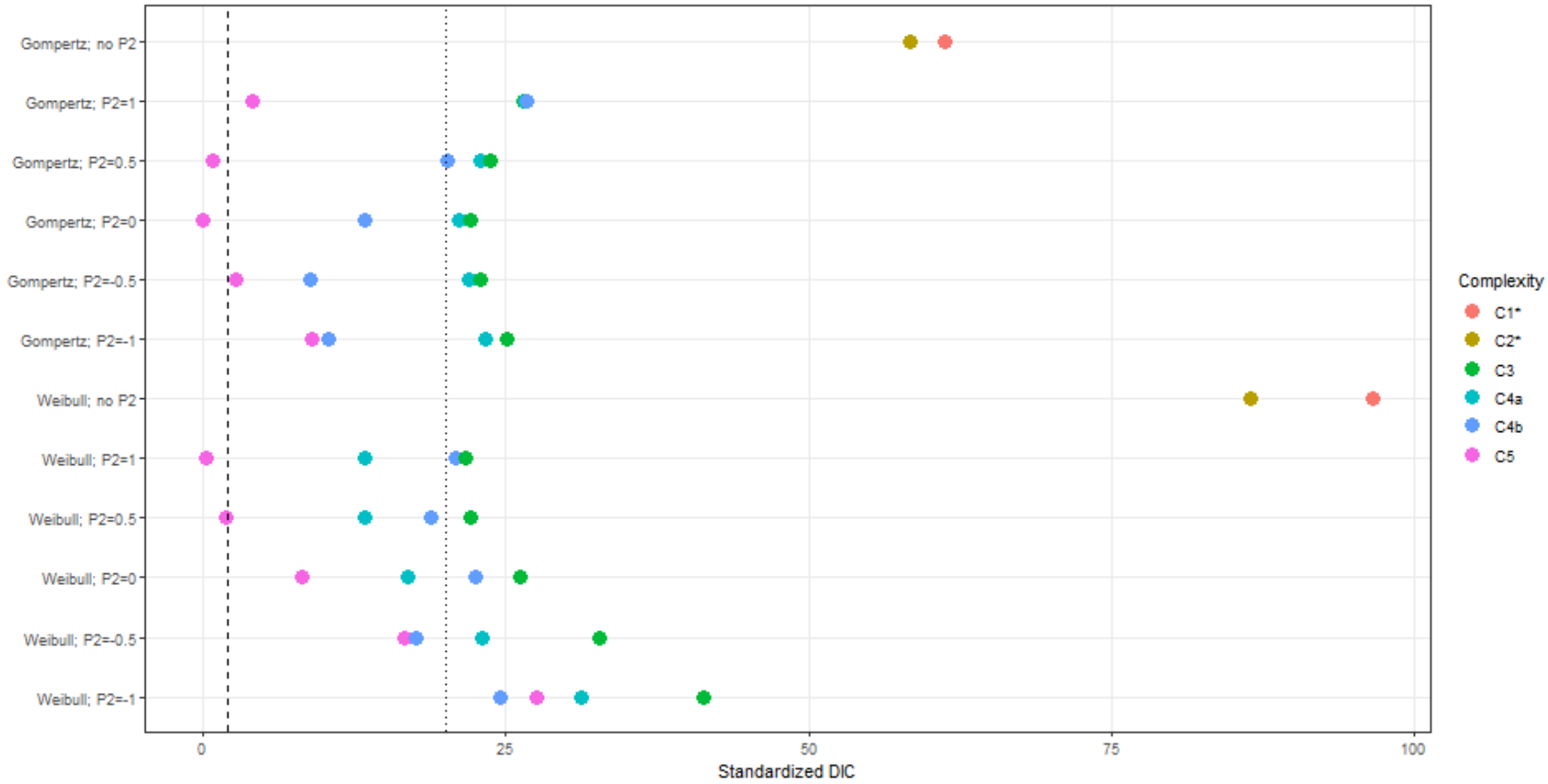


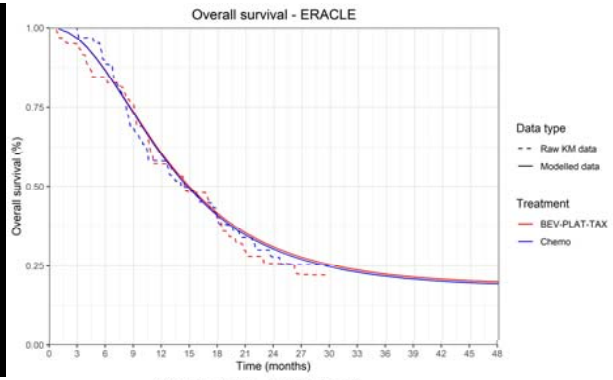
***Figure** 21: Network diagram for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*

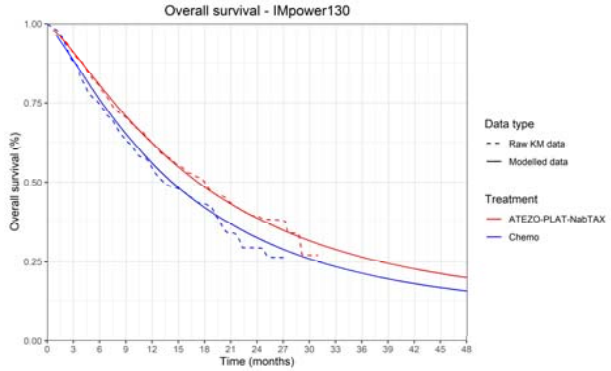
***Figure** 22: Model fit statistics for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*

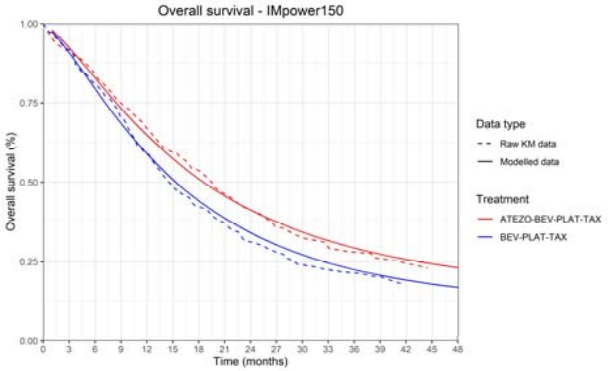


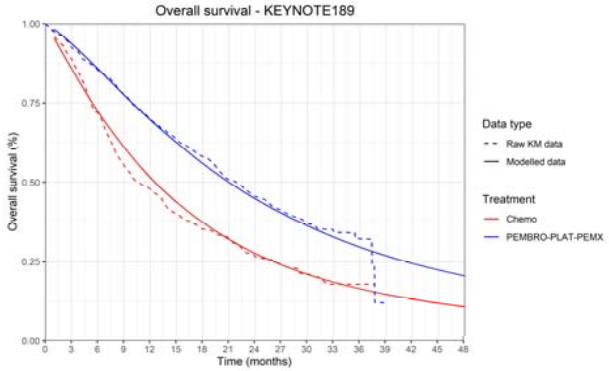
Abbreviations: DIC = deviance information criterion
Selected model: p1p-0.5; treatment effect on scale, 2nd shape

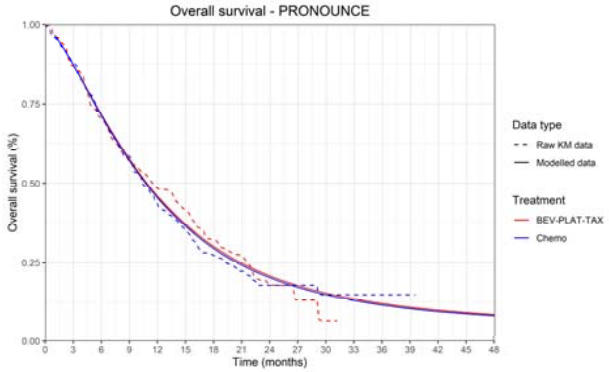
***Figure** 23: Comparison of fractional polynomial model fit to Kaplan-Meier curves of contributing RCTs for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*











Note: mu parameters are study specific, while d parameters are meta-analyzed. From model: p1p-0.5; treatment effect on scale, 2nd shape

***Table** 36: Mu_mean parameters for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*

Parameter	Estimate	Variance	Correlation (12)	Correlation (13)	Correlation (23)
Mu_mean1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Please note that the following estimates for mu are *not* outputs of the NMA - these have been provided as a baseline onto which treatment effects can be added; however, the choice of reference curve should be updated as appropriate. Currently, these are estimated using the average mus of the reference treatment (Chemo).*
Estimates obtained from the following model: p1p-0.5; treatment effect on scale, 2nd shape

***Table** 37: d parameters for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*

Treatment	d0 Estimate	d0 Variance	d2 Estimate	d2 Variance	d02 Correlation
Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO-BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO-PLAT-NabTAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	d0 Estimate	d0 Variance	d2 Estimate	d2 Variance	d02 Correlation
PEMBRO-PLAT-PEMX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI + Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Estimates obtained from the following model: p1p-0.5; treatment effect on scale, 2nd shape

***Figure** 24: HRs of NIVO-IPI-Chemo vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 21 months of follow-up.*
Estimates obtained from the following model: p1p-0.5; treatment effect on scale, 2nd shape
Dashed lines represent 95% credible intervals

***Table** 38: HRs of NIVO-IPI-Chemo vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*

Comparator	Timepoint (months)	HR (95% CrI)
Chemo	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
ATEZO-BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]

Comparator	Timepoint (months)	HR (95% CrI)
	36	[redacted]
	48	[redacted]
ATEZO-PLAT-NabTAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
PEMBRO-PLAT-PEMX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
NIVO-IPI	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 21 months of follow-up.*
Estimates obtained from the following model: p1p-0.5; treatment effect on scale, 2nd shape

2.4 PD-L1 <50% (CheckMate mixed histology): Progression-free survival

***Table** 39: RCTs included in the network meta-analysis of progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*

Study	PD-L1	Histology	Treatment 1	Treatment 2	HR (95% CI)
ERACLE - Galetta (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	0.79 (0.53 - 1.17)
PRONOUNCE - Zinner (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	1.06 (0.84 - 1.34)
IMpower 150	<50%	NSq	ATEZO-BEV15-PD	BEV15-PD	0.68 (0.56 - 0.82)
IMpower 130	<50%	NSq	ATEZO-CARB-NabTAX	PLAT-NabTAX	0.67 (0.55 - 0.82)
KeyNote 189	<50%	NSq	PEMBRO-PLAT-PEMX	PLAT-PEMX	0.55 (0.43 - 0.70)
CheckMate 227	All-comers	Mixed	NIVO-IPI	PLAT-PEMX or CARB-TAX	[redacted]
CheckMate 9LA	All-comers	Mixed	NIVO-IPI-PLAT-PEMX or GEM	PLAT-PEMX or GEM	[redacted]

***Table** 40: Data sources of RCTs included in the network meta-analysis of progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*

Study	Author	Year	Publication type
ERACLE	Galetta	2015	Manuscript
IMpower150	SocinskiNEJM	2018	NEJM manuscript
PRONOUNCE	Zinner	2015	Manuscript
IMpower130	CappuzzoESMO	2018	ESMO conference slides
KEYNOTE189	GadgeelASCO	2019	ASCO conference poster
CheckMate 9LA	BMS	April 2020	IPD on file
CheckMate 227	BMS	April 2020	IPD on file

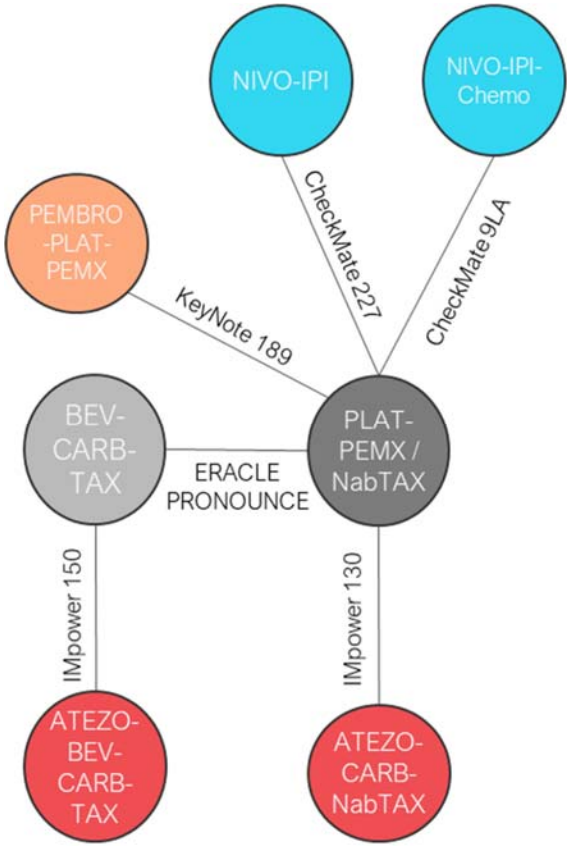
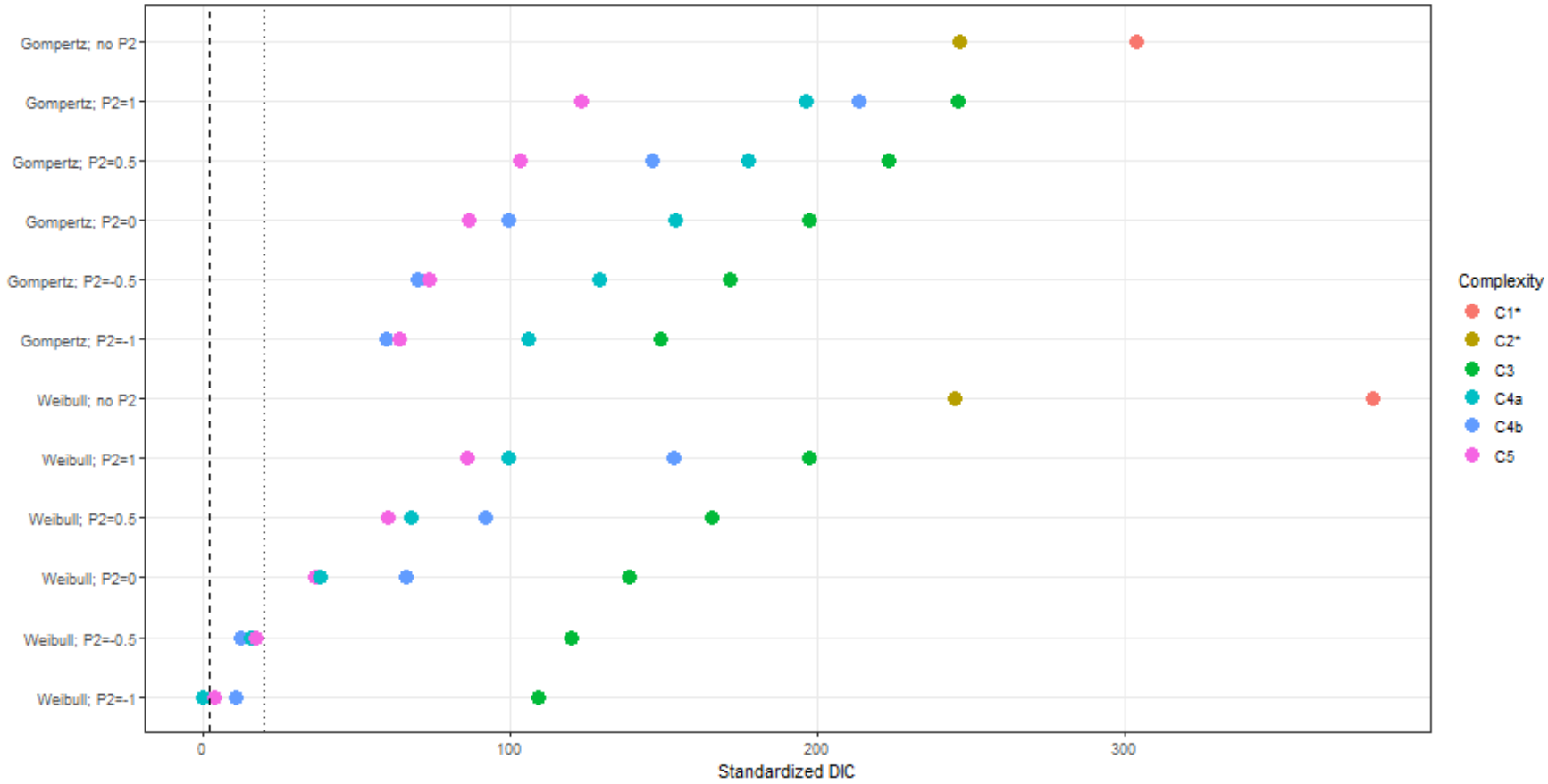


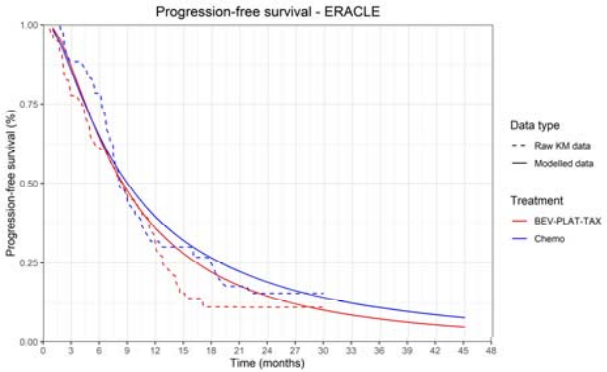
***Figure** 25: Network diagram for progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*

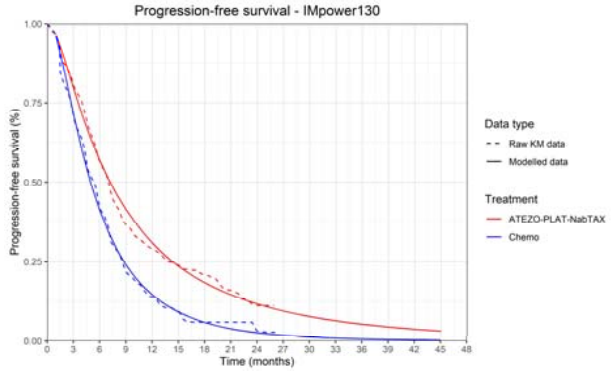
***Figure** 26: Model fit statistics for progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*

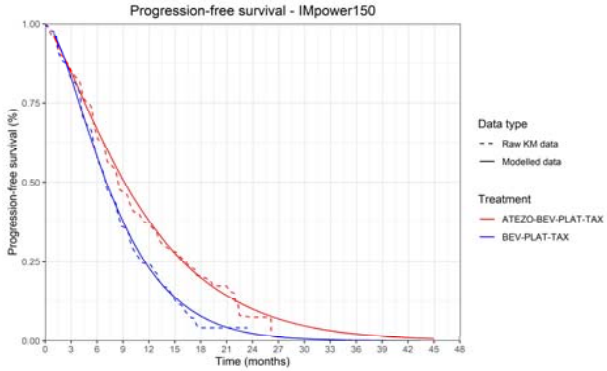


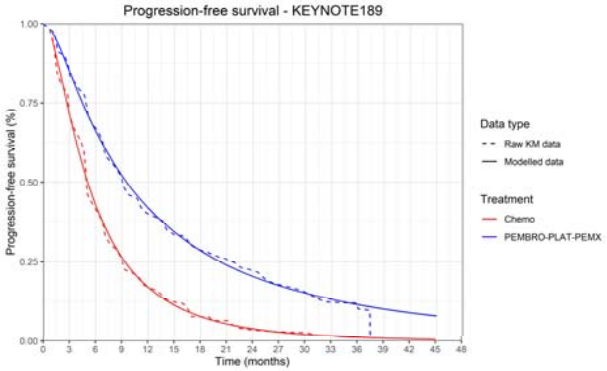
Abbreviations: DIC = deviance information criterion
Selected model: p0p-1; treatment effect on scale, 2nd shape

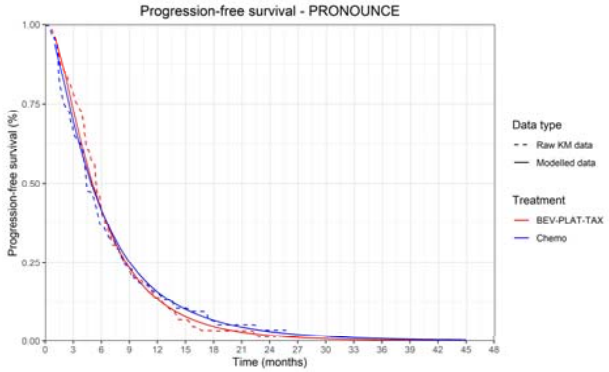
***Figure** 27: Comparison of fractional polynomial model fit to Kaplan-Meier curves of contributing RCTs for progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*











Note: mu parameters are study specific, while d parameters are meta-analyzed. From model: p0p-1; treatment effect on scale, 2nd shape

***Table** 41: Mu_mean parameters for progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*

Parameter	Estimate	Variance	Correlation (12)	Correlation (13)	Correlation (23)
Mu_mean1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Please note that the following estimates for mu are *not* outputs of the NMA - these have been provided as a baseline onto which treatment effects can be added; however, the choice of reference curve should be updated as appropriate. Currently, these are estimated using the average mus of the reference treatment (Chemo).*
Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape

***Table** 42: d parameters for progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*

Treatment	d0 Estimate	d0 Variance	d2 Estimate	d2 Variance	d02 Correlation
Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO-BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO-PLAT-NabTAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	d0 Estimate	d0 Variance	d2 Estimate	d2 Variance	d02 Correlation
PEMBRO-PLAT-PEMX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI + Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape

***Figure** 28: HRs of NIVO-IPI-Chemo vs comparators over time for progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 18 months of follow-up.*
Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape
Dashed lines represent 95% credible intervals

***Table** 43: HRs of NIVO-IPI-Chemo vs comparators over time for progression-free survival for the target population of NSQ histology and PD-L1 < 50% in first-line advanced NSCLC (data inputs: PD-L1 < 50% for IMP150, IMP130, and KN189; PD-L1 all-comers for all other RCTs)*

Comparator	Timepoint (months)	HR (95% CrI)
Chemo	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
ATEZO-BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
ATEZO-PLAT-NabTAX	1	[redacted]

Comparator	Timepoint (months)	HR (95% CrI)
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
PEMBRO-PLAT-PEMX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
NIVO-IPI	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 18 months of follow-up.*
Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape

2.5 PD-L1 all-comers (CheckMate NSQ histology): Overall survival

***Table** 44: RCTs included in the network meta-analysis of overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*

Study	PD-L1	Histology	Treatment 1	Treatment 2	HR (95% CI)
ERACLE - Galetta (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	0.93 (0.60 - 1.43)
PRONOUNCE - Zinner (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	1.07 (0.84 - 1.37)
IMpower 150	All-comers	NSq	ATEZO-BEV15-PD	BEV15-PD	0.80 (0.67 - 0.95)
IMpower 130	All-comers	NSq	ATEZO-CARB-NabTAX	PLAT-NabTAX	0.79 (0.64 - 0.98)
KeyNote 189	All-comers	NSq	PEMBRO-PLAT-PEMX	PLAT-PEMX	0.56 (0.46 - 0.69)
CheckMate 227	All-comers	NSq	NIVO-IPI	PLAT-PEMX*	[redacted]
CheckMate 9LA	All-comers	NSq	NIVO-IPI-PLAT-PEMX*	PLAT-PEMX*	[redacted]

**Note: This is the nonsq regimen within the checkmate trial(s)*

***Table** 45: Data sources of RCTs included in the network meta-analysis of overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*

Study	Author	Year	Publication type
ERACLE	Galetta	2015	Manuscript
KEYNOTE189	Rodriguez-Abreu	2020	ASCO conference poster
PRONOUNCE	Zinner	2015	Manuscript
IMpower150	SocinskiAACR	2020	AACR conference slides
IMpower130	West	2019	Lancet manuscript
CheckMate 9LA	BMS	April 2020	IPD on file
CheckMate 227	BMS	April 2020	IPD on file

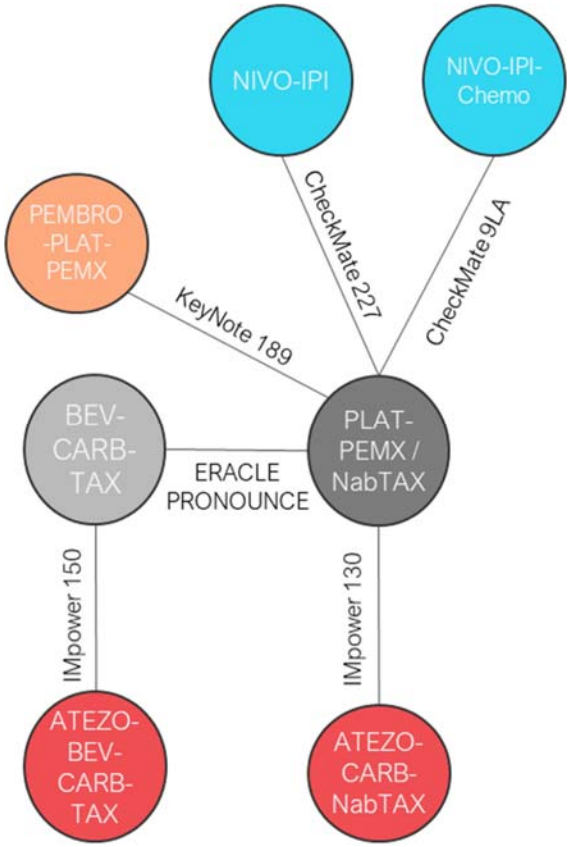
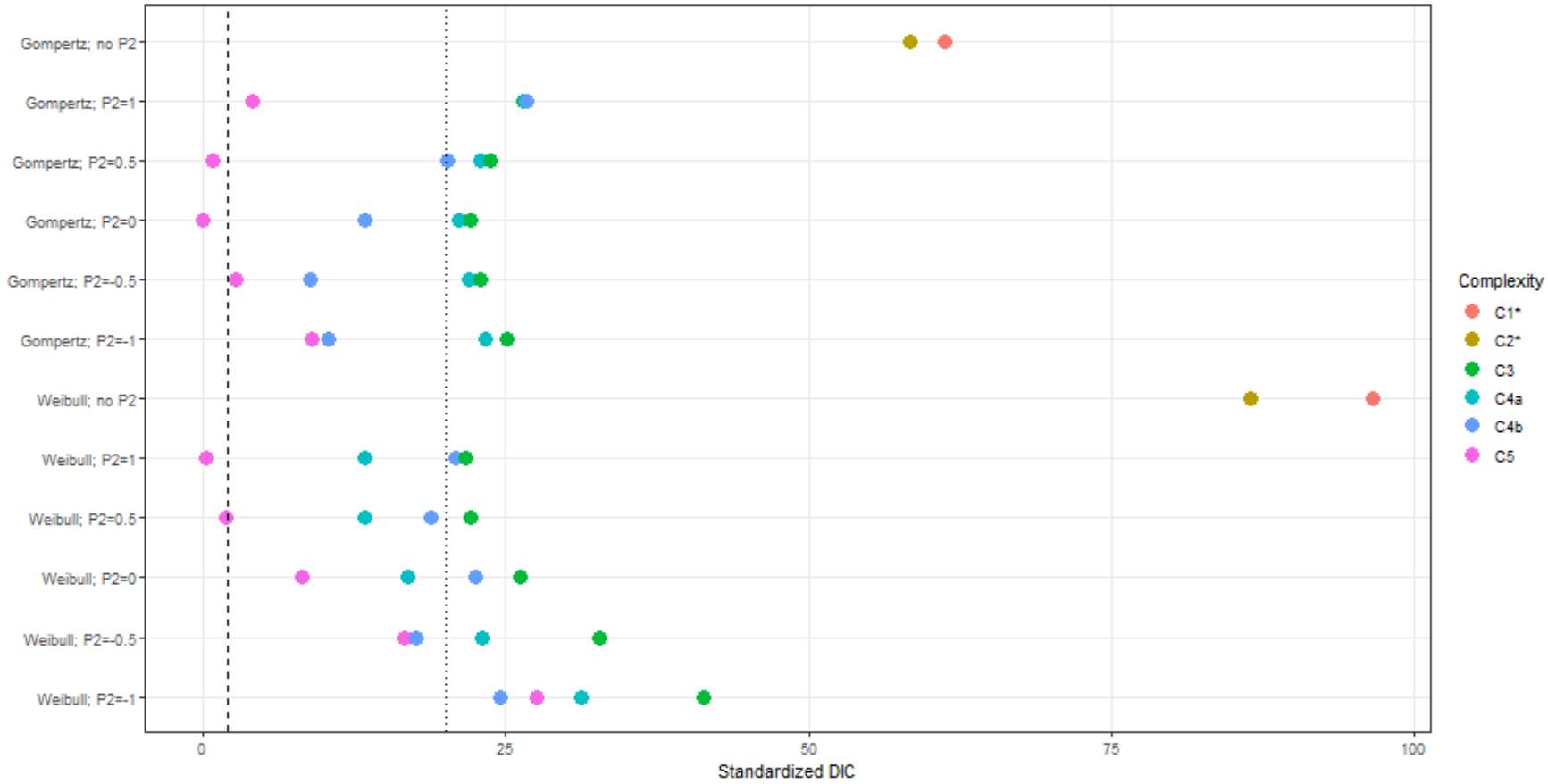


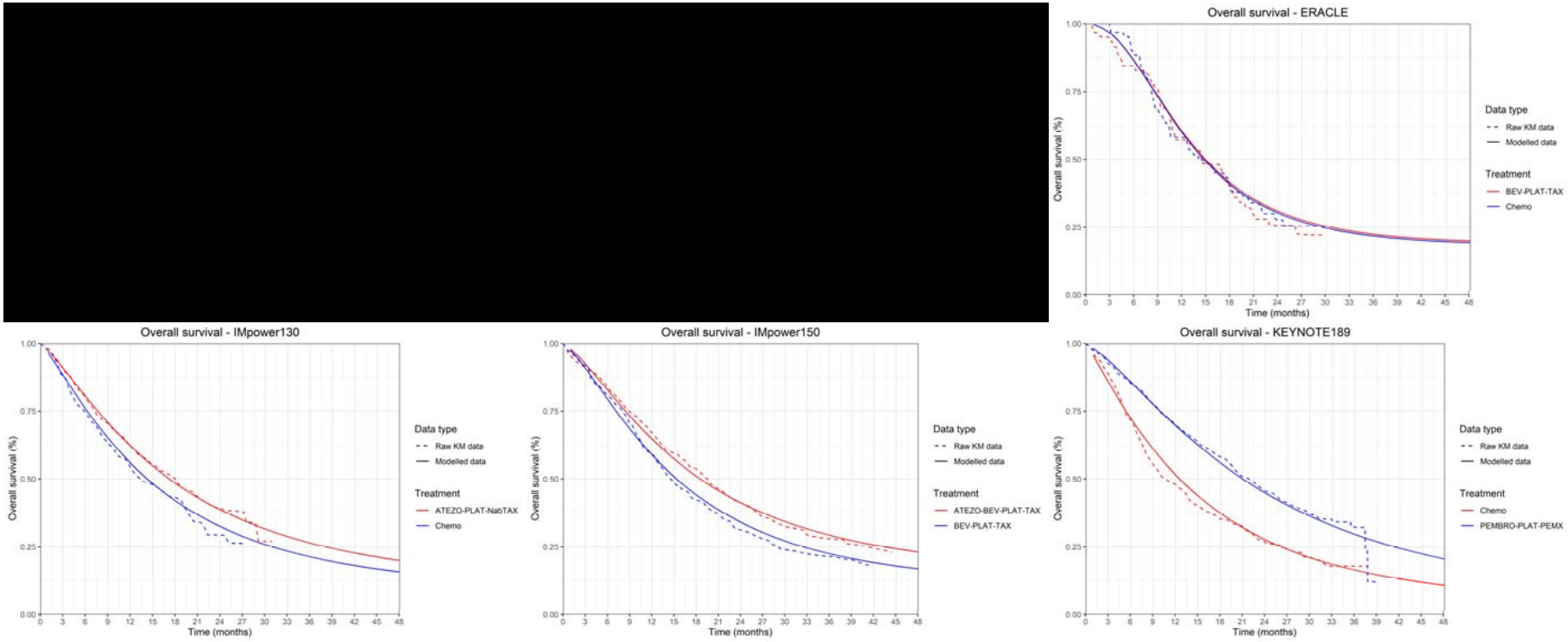
***Figure** 29: Network diagram for overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*

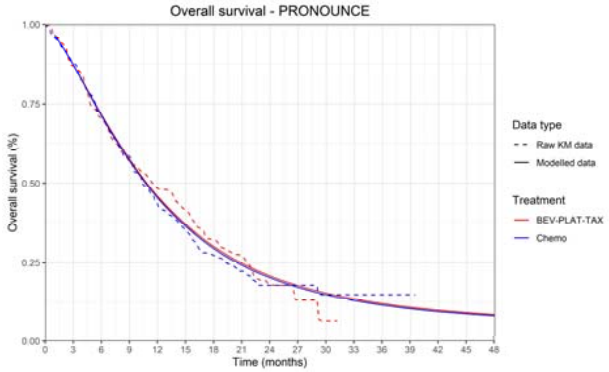
***Figure** 30: Model fit statistics for overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*



Abbreviations: DIC = deviance information criterion
Selected model: p0p1; treatment effect on scale, 1st shape

***Figure** 31: Comparison of fractional polynomial model fit to Kaplan-Meier curves of contributing RCTs for overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*





Note: mu parameters are study specific, while d parameters are meta-analyzed. From model: p0p1; treatment effect on scale, 1st shape

***Table** 46: Mu_mean parameters for overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*

Parameter	Estimate	Variance	Correlation (12)	Correlation (13)	Correlation (23)
Mu_mean1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Please note that the following estimates for mu are *not* outputs of the NMA - these have been provided as a baseline onto which treatment effects can be added; however, the choice of reference curve should be updated as appropriate. Currently, these are estimated using the average mus of the reference treatment (Chemo).*
Estimates obtained from the following model: p0p1; treatment effect on scale, 1st shape

***Table** 47: d parameters for overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*

Treatment	d0 Estimate	d0 Variance	d1 Estimate	d1 Variance	d01 Correlation
Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO-BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO-PLAT-NabTAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	d0 Estimate	d0 Variance	d1 Estimate	d1 Variance	d01 Correlation
PEMBRO-PLAT-PEMX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI + Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Estimates obtained from the following model: p0p1; treatment effect on scale, 1st shape

***Figure** 32: HRs of NIVO-IPI-Chemo vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 21 months of follow-up.*
Estimates obtained from the following model: p0p1; treatment effect on scale, 1st shape
Dashed lines represent 95% credible intervals

***Table** 48: HRs of NIVO-IPI-Chemo vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*

Comparator	Timepoint (months)	HR (95% CrI)
Chemo	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
ATEZO-BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]

Comparator	Timepoint (months)	HR (95% CrI)
	36	[redacted]
	48	[redacted]
ATEZO-PLAT-NabTAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
PEMBRO-PLAT-PEMX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]
NIVO-IPI	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
	48	[redacted]

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 21 months of follow-up.*
Estimates obtained from the following model: p0p1; treatment effect on scale, 1st shape

2.6 PD-L1 all-comers (CheckMate NSQ histology): Progression-free survival

***Table** 49: RCTs included in the network meta-analysis of progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*

Study	PD-L1	Histology	Treatment 1	Treatment 2	HR (95% CI)
ERACLE - Galetta (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	0.79 (0.53 - 1.17)
PRONOUNCE - Zinner (2015)	All-comers	NSq	PLAT-PEMX	BEV15-PD	1.06 (0.84 - 1.34)
IMpower 150	All-comers	NSq	ATEZO-BEV15-PD	BEV15-PD	0.71 (0.59 - 0.85)
IMpower 130	All-comers	NSq	ATEZO-CARB-NabTAX	PLAT-NabTAX	0.64 (0.54 - 0.77)
KeyNote 189	All-comers	NSq	PEMBRO-PLAT-PEMX	PLAT-PEMX	0.50 (0.41 - 0.61)
CheckMate 227	All-comers	NSq	NIVO-IPI	PLAT-PEMX*	[redacted]
CheckMate 9LA	All-comers	NSq	NIVO-IPI-PLAT-PEMX*	PLAT-PEMX*	[redacted]

**Note: This is the nonsq regimen within the checkmate trial(s)*

***Table** 50: Data sources of RCTs included in the network meta-analysis of progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*

Study	Author	Year	Publication type
ERACLE	Galetta	2015	Manuscript
KEYNOTE189	Rodriguez-Abreu	2020	ASCO conference poster
PRONOUNCE	Zinner	2015	Manuscript
IMpower130	West	2019	Lancet manuscript
IMpower150	SocinskiNEJM	2018	NEJM manuscript
CheckMate 9LA	BMS	April 2020	IPD on file
CheckMate 227	BMS	April 2020	IPD on file

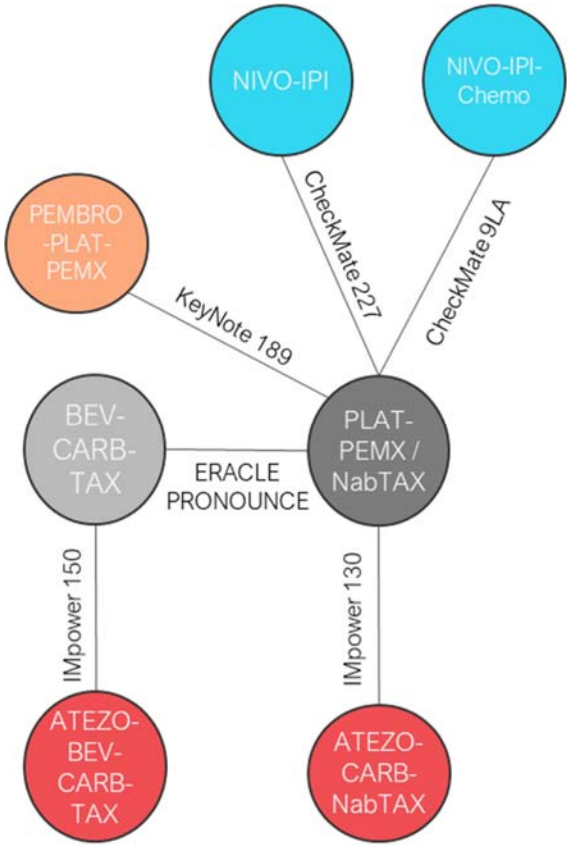
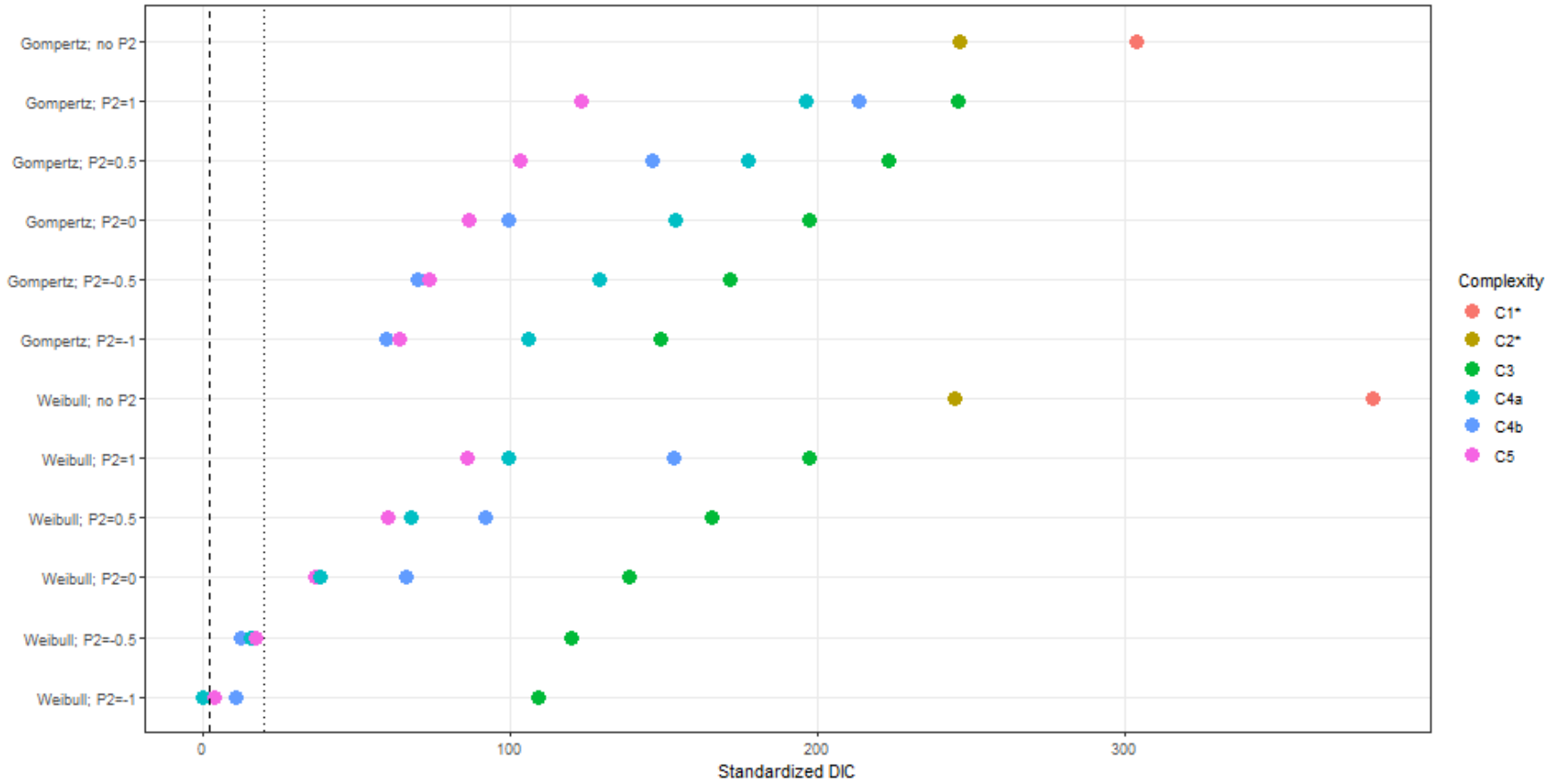


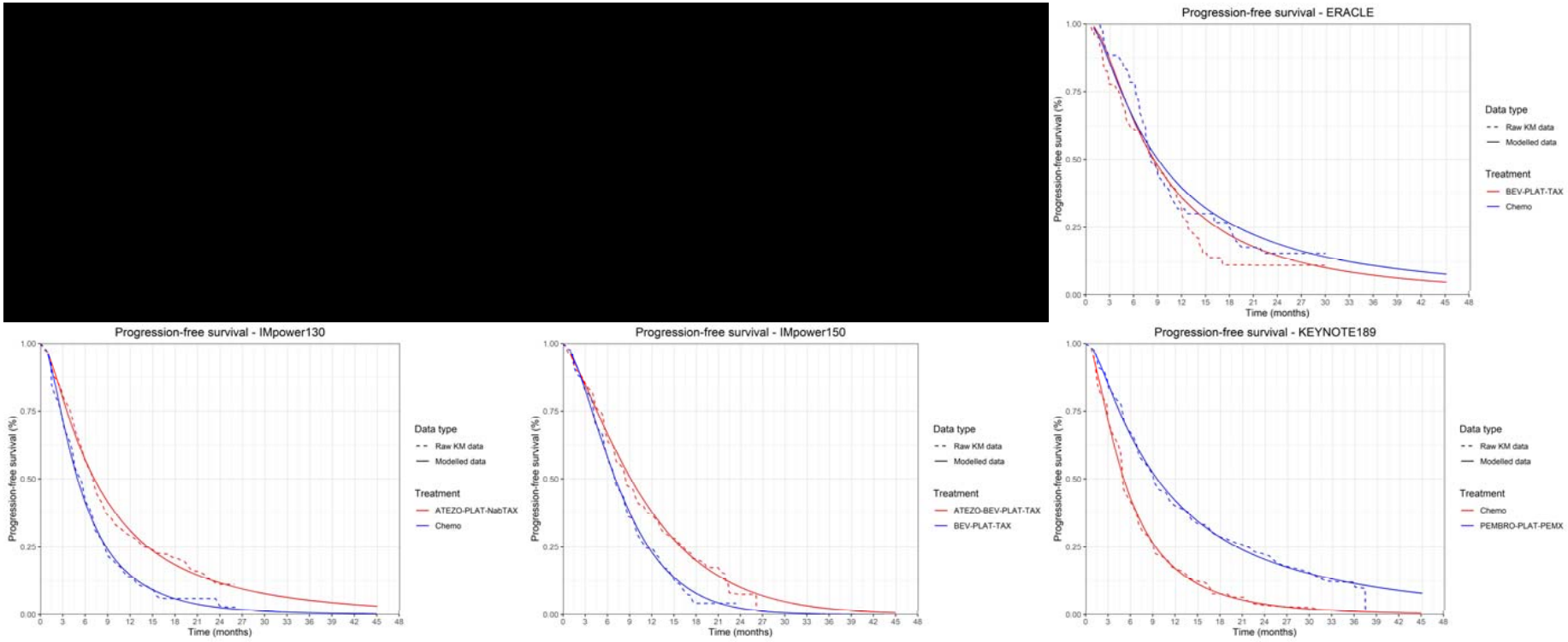
***Figure** 33: Network diagram for progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*

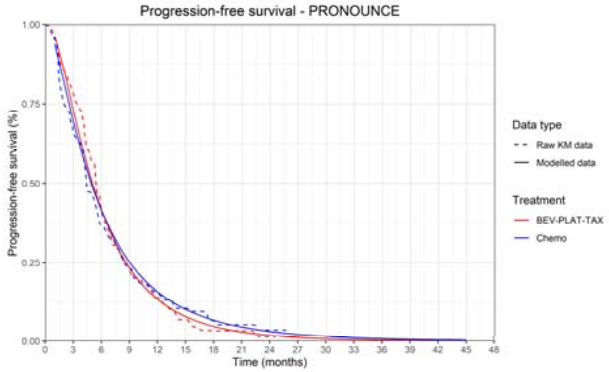
***Figure** 34: Model fit statistics for progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*



Abbreviations: DIC = deviance information criterion
Selected model: p0p-1; treatment effect on scale, 2nd shape

***Figure** 35: Comparison of fractional polynomial model fit to Kaplan-Meier curves of contributing RCTs for progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*





Note: mu parameters are study specific, while d parameters are meta-analyzed. From model: p0p-1; treatment effect on scale, 2nd shape

***Table** 51: Mu_mean parameters for progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*

Parameter	Estimate	Variance	Correlation (12)	Correlation (13)	Correlation (23)
Mu_mean1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mu_mean3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Please note that the following estimates for mu are *not* outputs of the NMA - these have been provided as a baseline onto which treatment effects can be added; however, the choice of reference curve should be updated as appropriate. Currently, these are estimated using the average mus of the reference treatment (Chemo).*
Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape

***Table** 52: d parameters for progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*

Treatment	d0 Estimate	d0 Variance	d2 Estimate	d2 Variance	d02 Correlation
Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO-BEV-PLAT-TAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ATEZO-PLAT-NabTAX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	d0 Estimate	d0 Variance	d2 Estimate	d2 Variance	d02 Correlation
PEMBRO-PLAT-PEMX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO-IPI + Chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape

***Figure** 36: HRs of NIVO-IPI-Chemo vs comparators over time for progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 18 months of follow-up.*
Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape
Dashed lines represent 95% credible intervals

***Table** 53: HRs of NIVO-IPI-Chemo vs comparators over time for progression-free survival for the target population of NSQ histology and PD-L1 all-comers in first-line advanced NSCLC (data inputs: PD-L1 all-comers for all RCTs; NSQ histology for all RCTs)*

Comparator	Timepoint (months)	HR (95% CrI)
Chemo	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
ATEZO-BEV-PLAT-TAX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
ATEZO-PLAT-NabTAX	1	[redacted]

Comparator	Timepoint (months)	HR (95% CrI)
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
PEMBRO-PLAT-PEMX	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
NIVO-IPI	1	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]

**Note NIVO-IPI-Chemo becomes a projection and not an observed finding following 18 months of follow-up.*
Estimates obtained from the following model: p0p-1; treatment effect on scale, 2nd shape

Overall Survival and Progression Free Survival in the ITT population in CheckMate 9LA [redacted] and CheckMate 227 Part 1 [redacted]

Objective

To describe OS and PFS results including the KM curves and corresponding HRs in the ITT population for nivolumab + ipilimumab+chemotherapy and chemotherapy based on all randomized subjects in CM9LA [redacted] and Part 1 ITT population for nivolumab + ipilimumab and chemotherapy based on all randomised subjects in CM227 ([redacted])

Background

OS and PFS outcomes based on 2019 DBL interim analyses and 2020 DBL analysis for CM-9LA comparing nivolumab + ipilimumab + chemotherapy to chemotherapy were previously presented by Reck et al at ASCO 2020 and published in The Lancet Oncology, Paz-Ares et al. 2021.

OS and PFS outcomes based on February 2020 (3-year DBL) analysis for CM-227 Part 1A (PD-L1 ≥1%), comparing nivolumab + ipilimumab to chemotherapy, nivolumab alone to chemotherapy, and nivolumab + ipilimumab to nivolumab alone, and Part 1B (PD-L1 <1%), comparing nivolumab + ipimlimumab to chemotherapy, and nivolumab + chemotherapy to chemotherapy, were previously presented by Ramalingam et al at ASCO 2020.

Here we present i) OS and PFS Kaplan-Meier curves, median OS and PFS, OS and PFS HRs (95%CI), and OS and PFS rates for nivolumab + ipilimumab + chemotherapy and chemotherapy arms in CM9LA ITT population ii) OS and PFS Kaplan-Meier curves, median OS and PFS, OS and PFS HRs (95%CI), and OS and PFS rates for nivolumab + ipilimumab and chemotherapy arms in CM227 Part 1 ITT population

Results

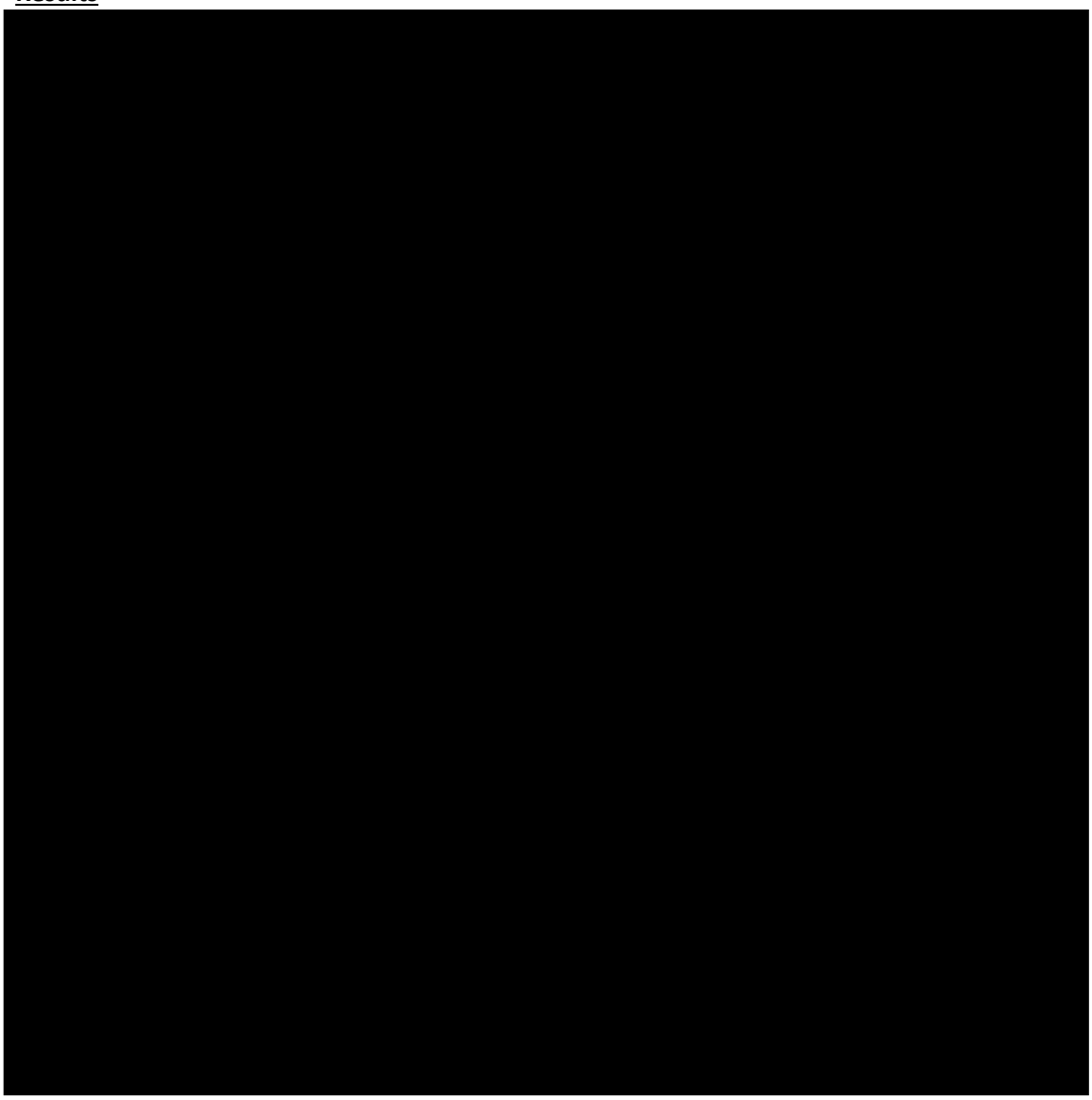


Figure 1. Kaplan-Meier Plot of Overall Survival - All Randomized Subjects, Global Population CM9LA - Nivolumab+Ipilimumab+Chemotherapy and Chemotherapy

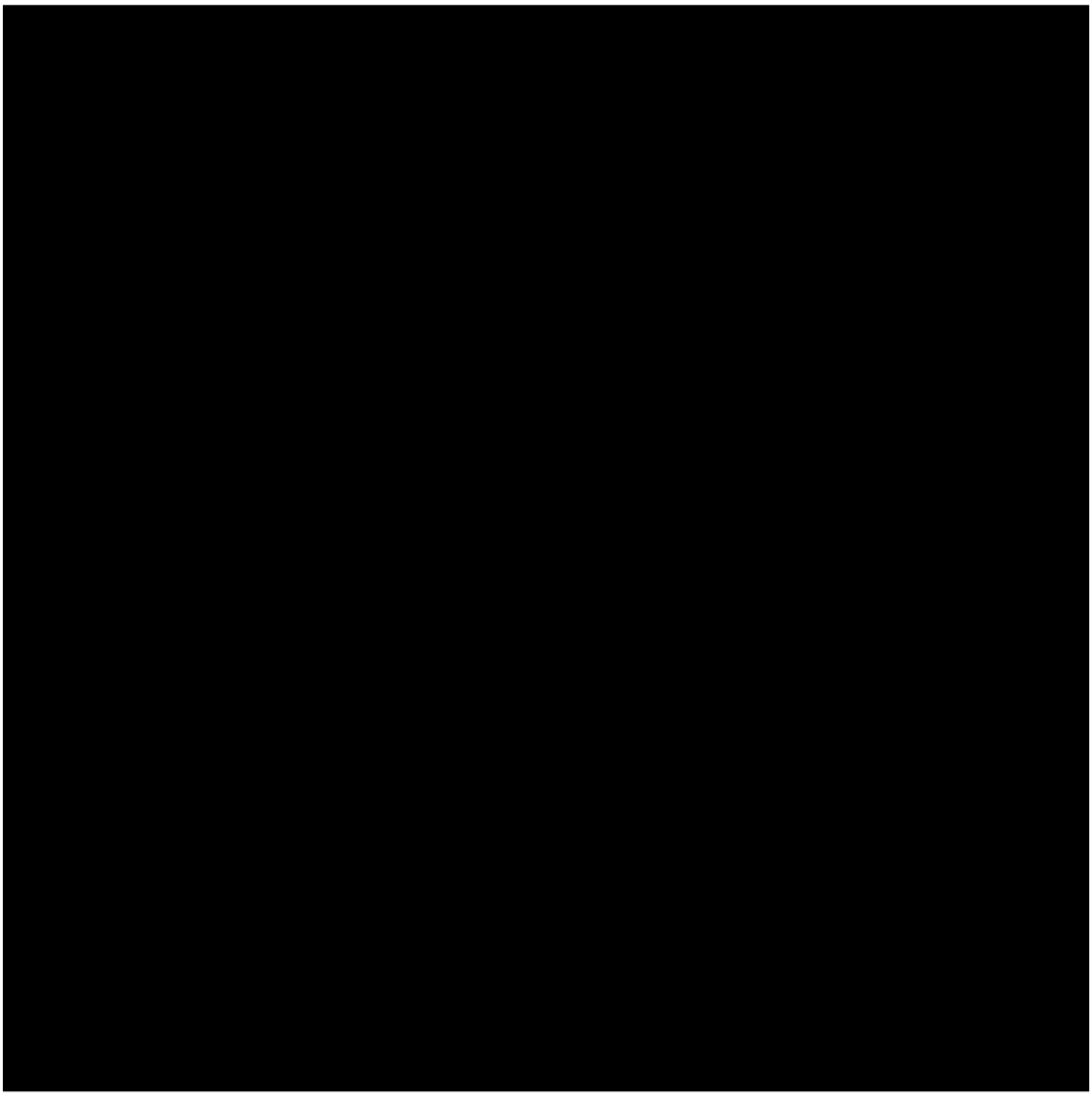


Figure 2. Kaplan-Meier Plot of PFS per BICR - All Randomized Subjects, Global Population CM9LA - Nivolumab+Ipilimumab+Chemotherapy and Chemotherapy

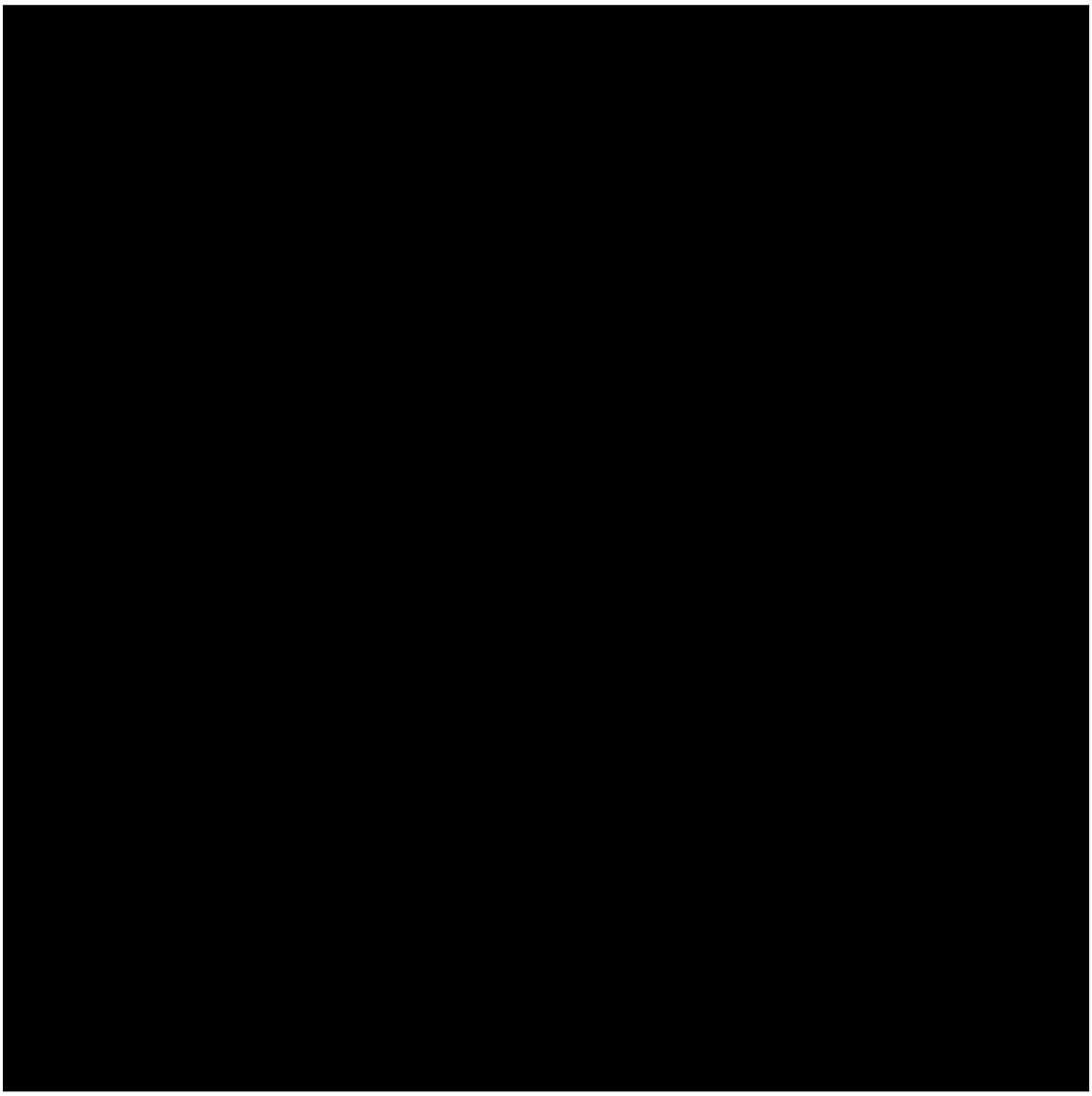


Figure 3. Kaplan-Meier Plot of Overall Survival - All Randomized Subjects, Global Population CM227 Part 1 - Nivolumab+Ipilimumab and Chemotherapy

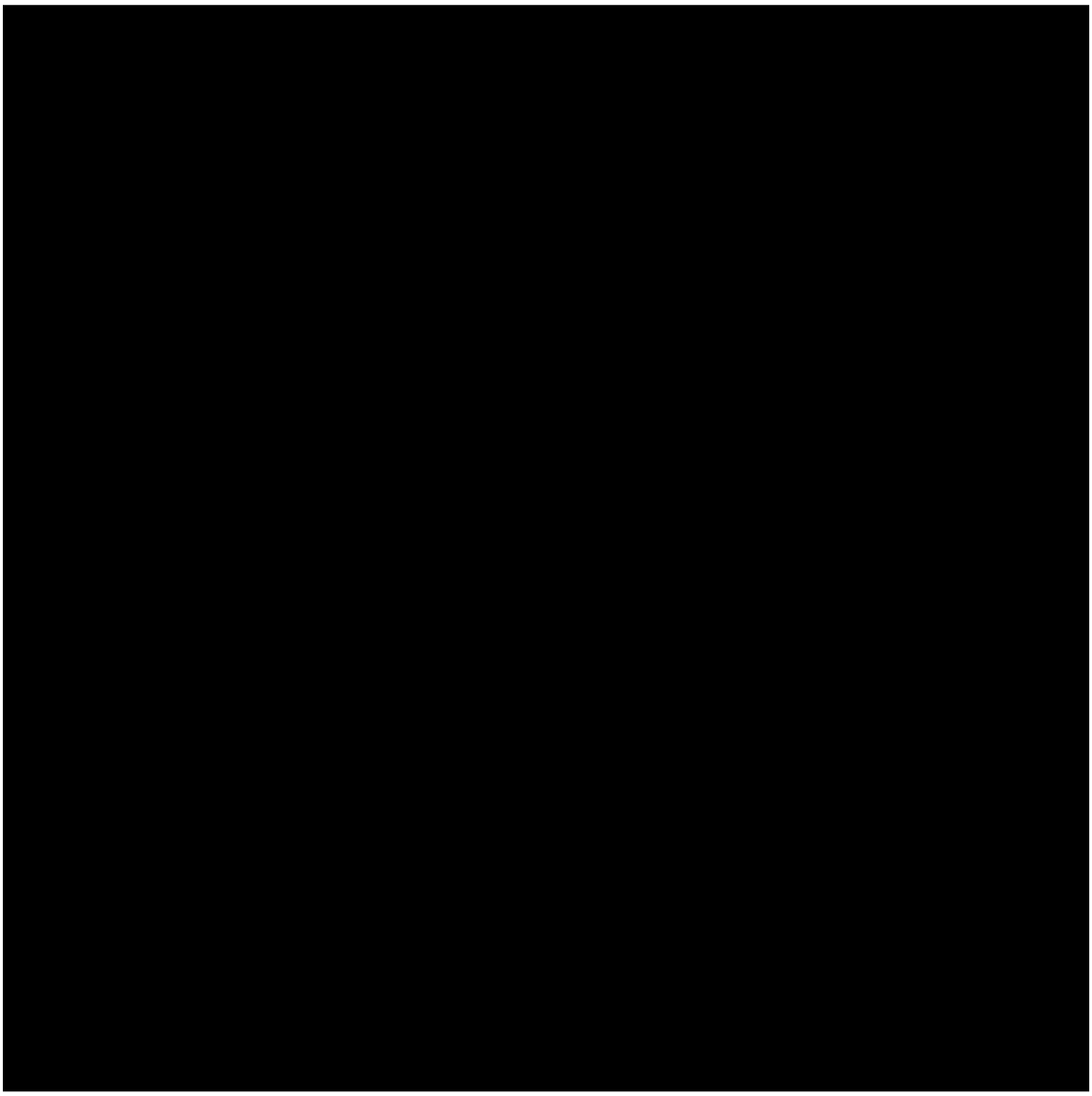


Figure 4. Kaplan-Meier Plot of PFS per BICR - All Randomized Subjects, Global Population CM227 Part 1 - Nivolumab+Ipilimumab and Chemotherapy

Table 1. Overall Survival Summary - All Randomized Subjects, Global Population CM9LA - Nivolumab+Ipilimumab+Chemotherapy and Chemotherapy

Table 2. PFS per BICR Summary - All Randomized Subjects, Global Population CM9LA - Nivolumab+Ipilimumab+Chemotherapy and Chemotherapy

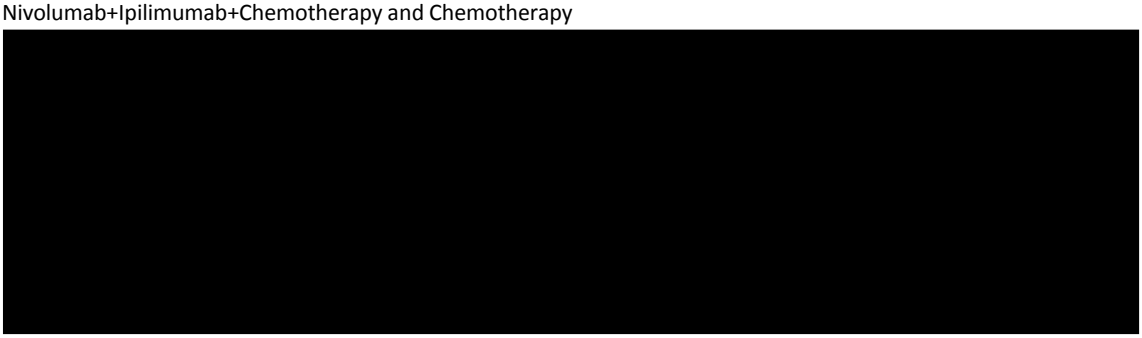


Table 3. Overall Survival Summary - All Randomized Subjects, Global Population CM227 Part 1 - Nivolumab+Ipilimumab and Chemotherapy

Table 4. PFS per BICR Summary - All Randomized Subjects, Global Population CM227 Part 1 - Nivolumab+Ipilimumab and Chemotherapy

References

Reck, et al. Nivolumab + ipilimumab + 2 cycles of platinum-doublet chemotherapy vs 4 cycles chemotherapy as first-line treatment for stage IV/recurrent NSCLC: CheckMate 9LA, ASCO 2020

Paz-Ares, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2021; 22: 198-211

Ramalingam, et al. Nivolumab + ipilimumab versus platinum-doublet chemotherapy as first-line treatment for advanced non-small cell lung cancer: Three-year update from CheckMate 227 Part 1, ASCO 2020

Overall Survival and Progression Free Survival by Non-Squamous and Squamous Histology in CheckMate 9LA [redacted] and CheckMate 227 Part 1 [redacted]

Objective

To describe OS and PFS results including the KM curves and corresponding HRs in histology subgroups defined by stratification (Non-Squamous and Squamous) for nivolumab + ipilimumab+chemotherapy and chemotherapy based on all randomized subjects in CM9LA [redacted] and Part 1 population for nivolumab + ipilimumab and chemotherapy based on all randomised subjects in CM227 [redacted]

Background

OS and PFS outcomes based on 2019 DBL interim analyses and 2020 DBL analysis for CM-9LA comparing nivolumab + ipilimumab + chemotherapy to chemotherapy were previously presented by Reck et al at ASCO 2020 and published in The Lancet Oncology, Paz-Ares et al. 2021.

OS and PFS outcomes based on February 2020 (3-year DBL) analysis for CM-227 Part 1A (PD-L1 ≥1%), comparing nivolumab + ipilimumab to chemotherapy, nivolumab alone to chemotherapy, and nivolumab + ipilimumab to nivolumab alone, and Part 1B (PD-L1 <1%), comparing nivolumab + ipimlimumab to chemotherapy, and nivolumab + chemotherapy to chemotherapy, were previously presented by Ramalingam et al at ASCO 2020.

Here we present i) OS and PFS Kaplan-Meier curves, median OS and PFS, OS and PFS HRs (95%CI), and OS and PFS rates for nivolumab + ipilimumab + chemotherapy and chemotherapy arms in CM9LA by Non-Squamous and Squamous histology ii) OS and PFS Kaplan-Meier curves, median OS and PFS, OS and PFS HRs (95%CI), and OS and PFS rates for nivolumab + ipilimumab and chemotherapy arms in CM227 Part 1 by Non-Squamous and Squamous histology

Results

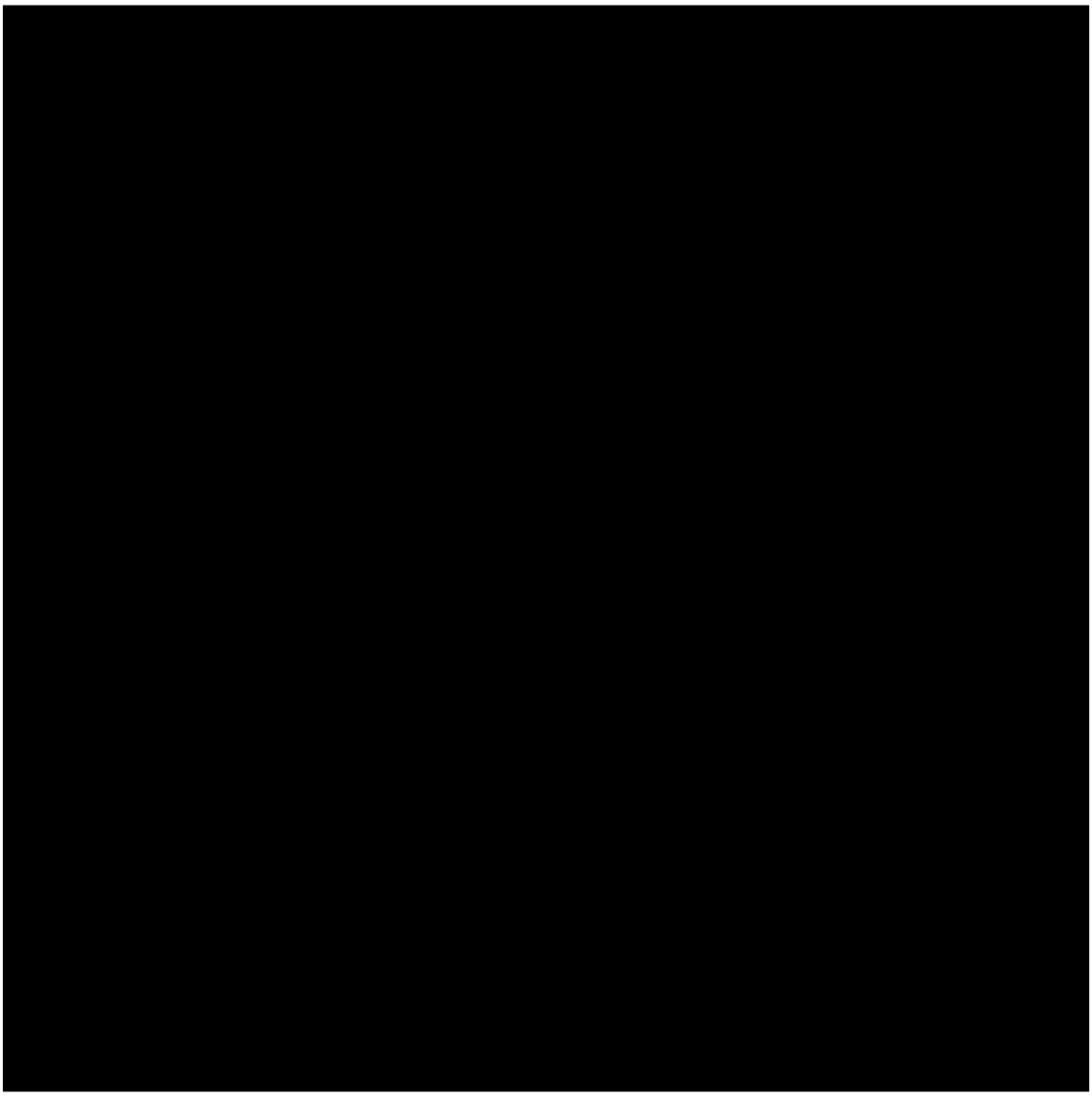


Figure 1. Kaplan-Meier Plot of Overall Survival by Squamous histology - All Randomized Subjects, Global Population CM9LA - Nivolumab+Ipilimumab+Chemotherapy and Chemotherapy

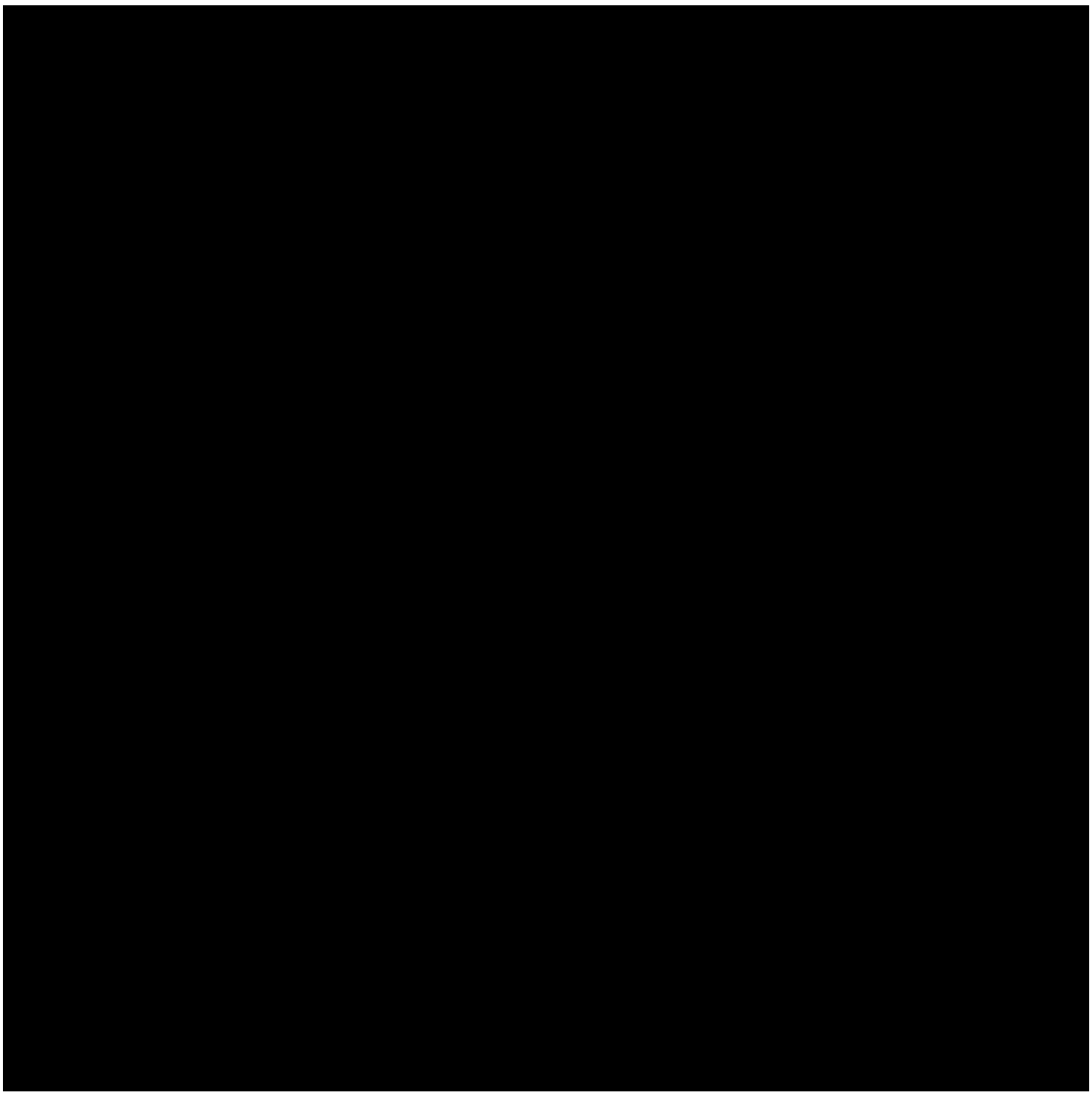


Figure 2. Kaplan-Meier Plot of Overall Survival by Non-Squamous histology - All Randomized Subjects, Global Population CM9LA - Nivolumab+Ipilimumab+Chemotherapy and Chemotherapy

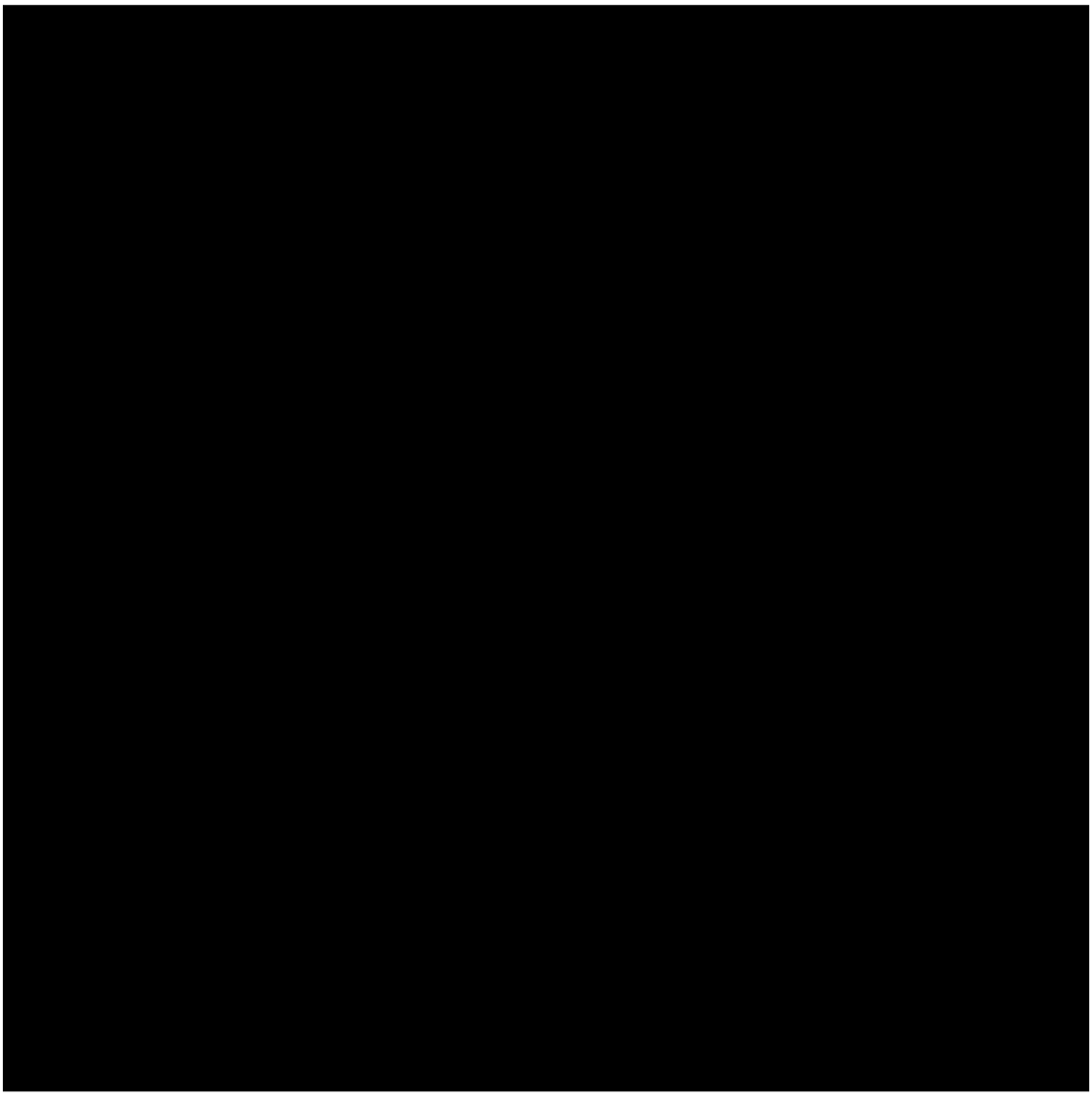


Figure 3. Kaplan-Meier Plot of PFS per BICR by Squamous histology - All Randomized Subjects, Global Population CM9LA - Nivolumab+Ipilimumab+Chemotherapy and Chemotherapy

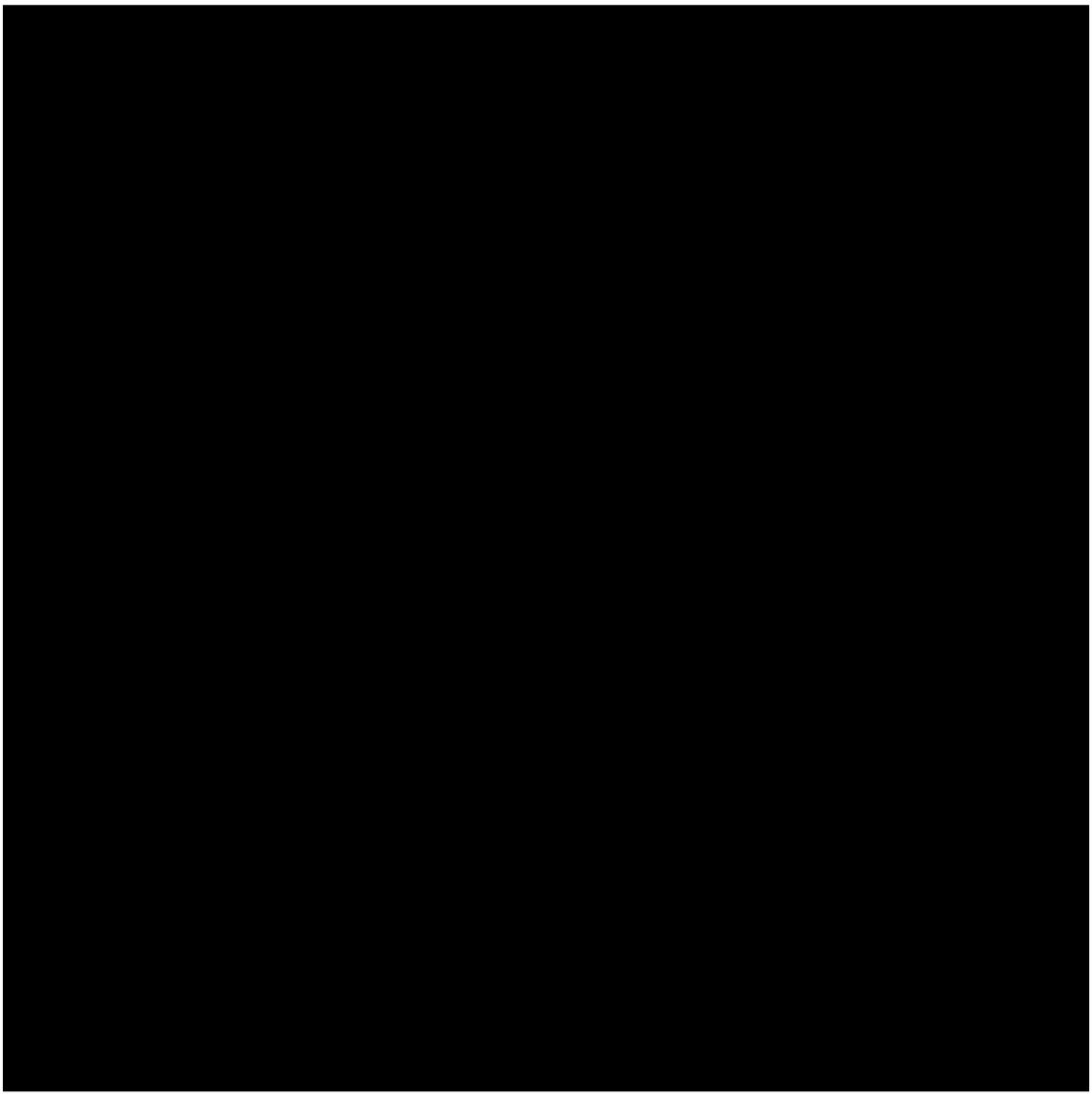


Figure 4. Kaplan-Meier Plot of PFS per BICR by Non-Squamous histology - All Randomized Subjects, Global Population CM9LA - Nivolumab+Ipilimumab+Chemotherapy and Chemotherapy

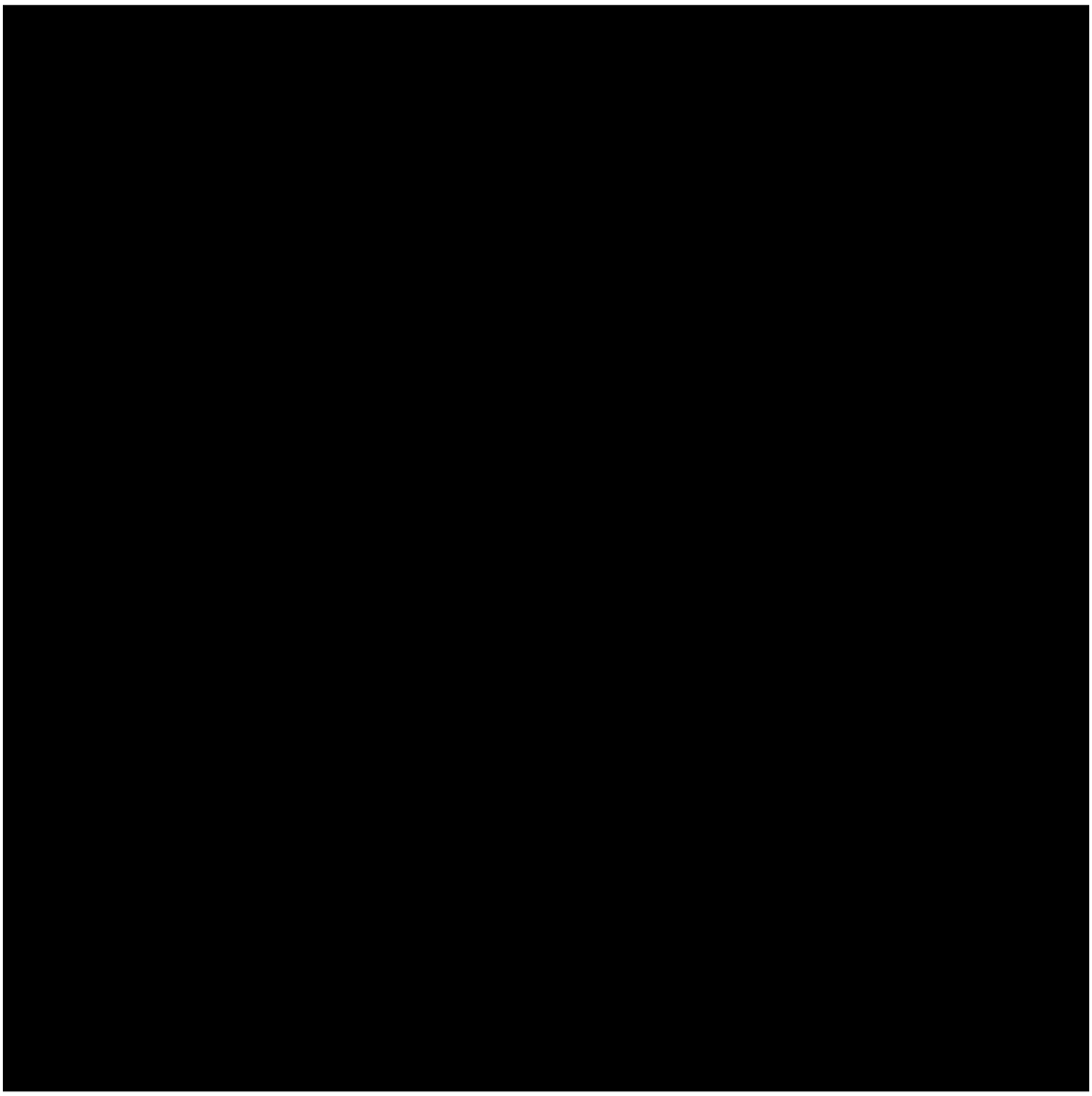


Figure 5. Kaplan-Meier Plot of Overall Survival by Squamous histology - All Randomized Subjects, Global Population CM227 Part 1- Nivolumab+Ipilimumab and Chemotherapy

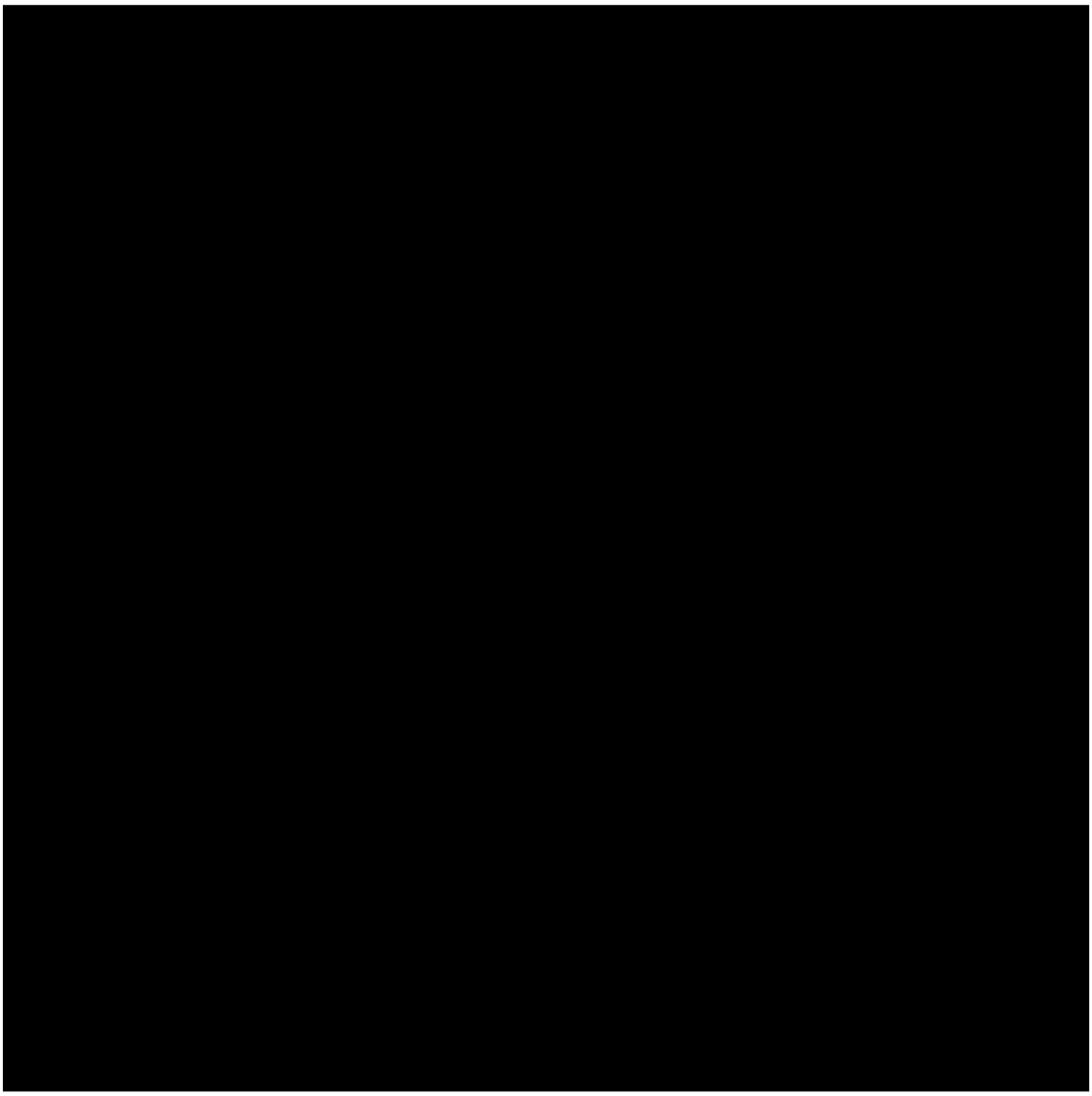


Figure 6. Kaplan-Meier Plot of Overall Survival by Non-Squamous histology - All Randomized Subjects, Global Population CM227 Part 1- Nivolumab+Ipilimumab and Chemotherapy

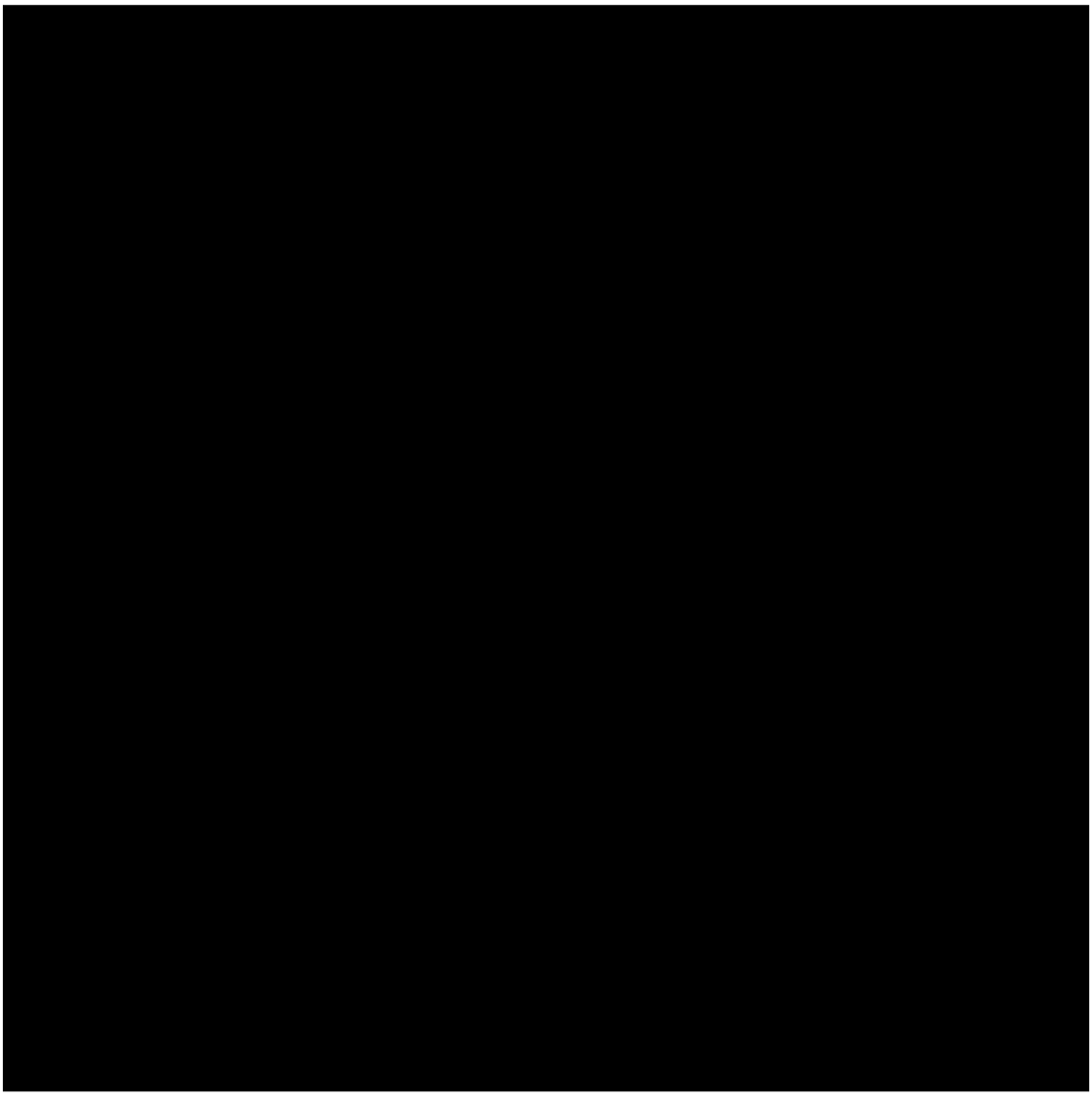


Figure 7. Kaplan-Meier Plot of PFS per BICR by Squamous histology - All Randomized Subjects, Global Population CM227 Part 1 - Nivolumab+Ipilimumab and Chemotherapy

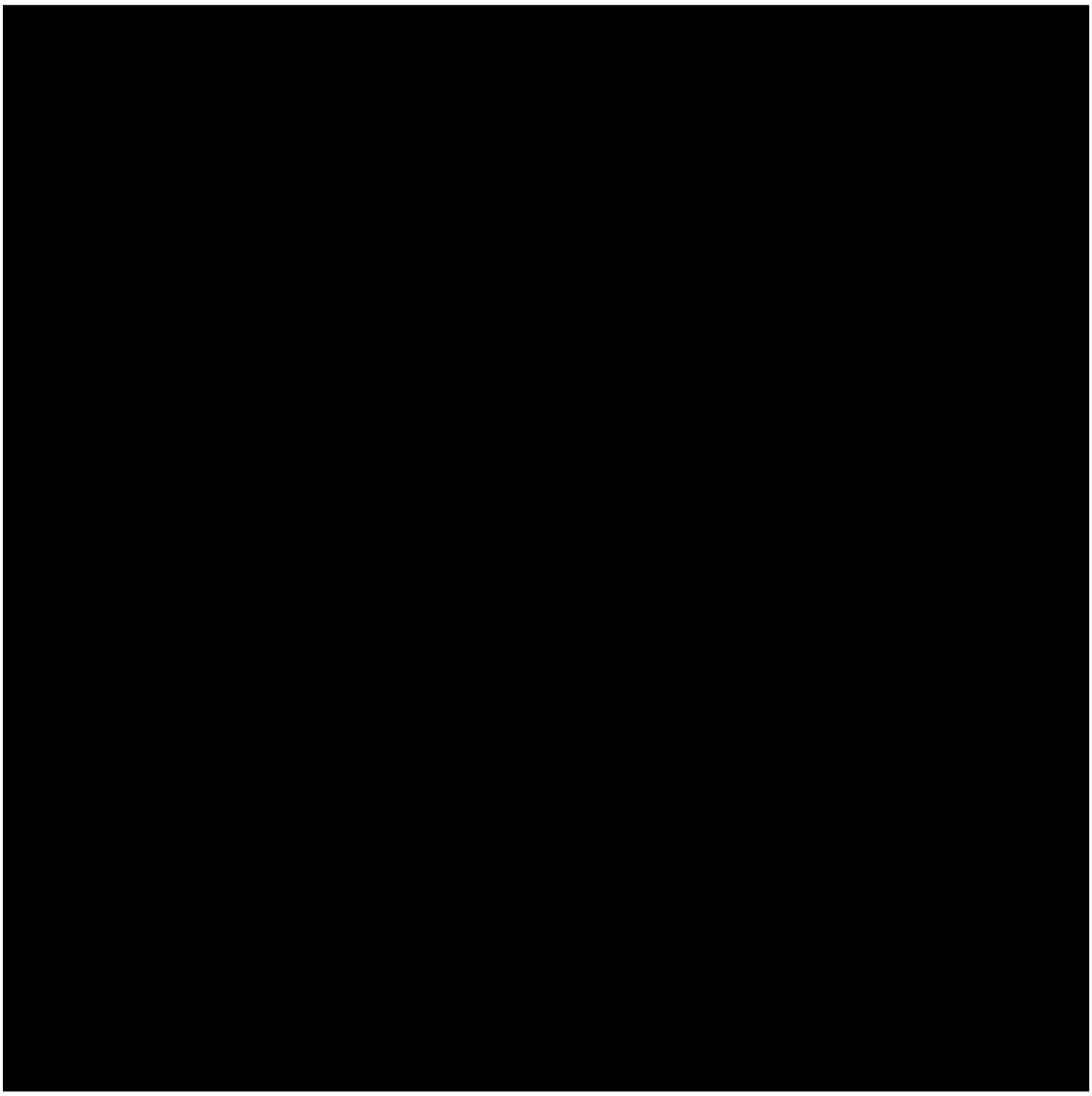


Figure 8. Kaplan-Meier Plot of PFS per BICR by Non-Squamous histology - All Randomized Subjects, Global Population CM227 Part 1 - Nivolumab+Ipilimumab and Chemotherapy

Table 1. Overall Survival Summary by Squamous histology - All Randomized Subjects, Global Population CM9LA - Nivolumab+Ipilimumab+Chemotherapy and Chemotherapy

Table 2. Overall Survival Summary by Non-Squamous histology - All Randomized Subjects, Global Population CM9LA - Nivolumab+Ipilimumab+Chemotherapy and Chemotherapy

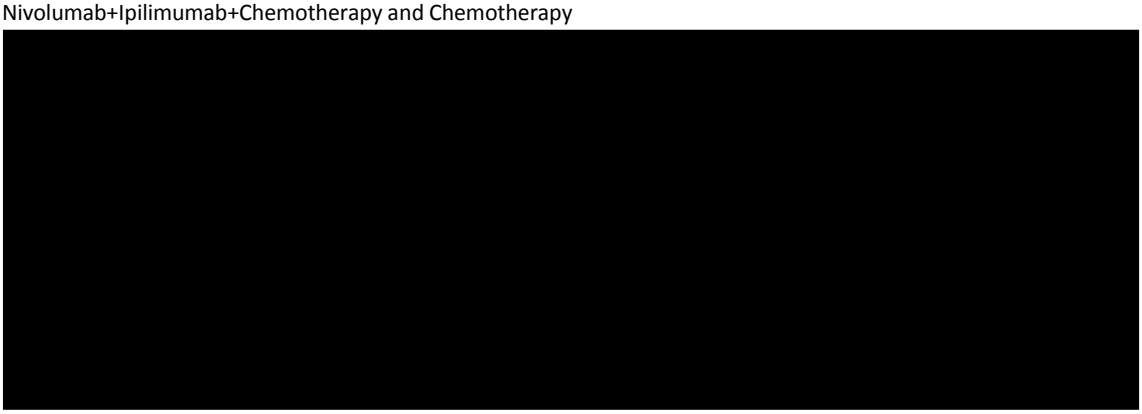


Table 3. PFS per BICR Summary by Squamous histology - All Randomized Subjects, Global Population CM9LA - Nivolumab+Ipilimumab+Chemotherapy and Chemotherapy

Table 4. PFS per BICR Summary by Non-Squamous histology - All Randomized Subjects, Global Population CM9LA - Nivolumab+Ipilimumab+Chemotherapy and Chemotherapy

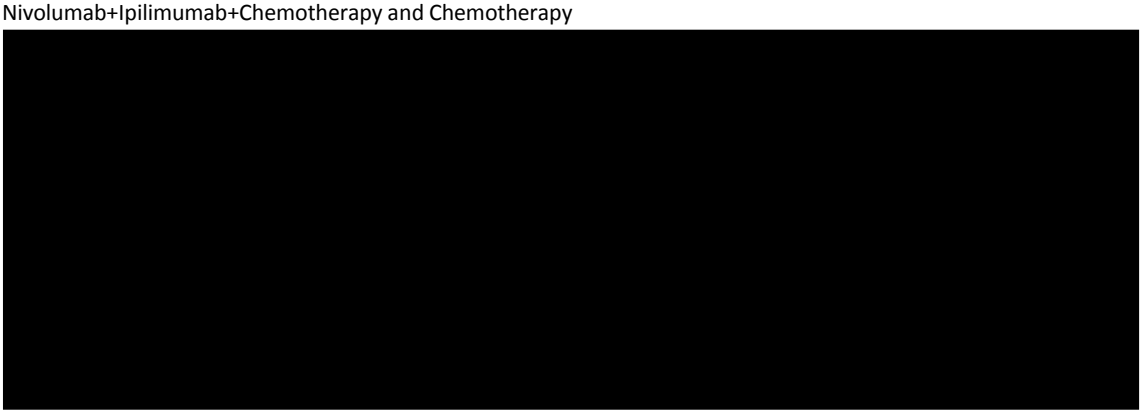


Table 5. Overall Survival Summary by Squamous histology - All Randomized Subjects, Global Population CM227 Part 1 - Nivolumab+Ipilimumab and Chemotherapy

Table 6. Overall Survival Summary by Non-Squamous histology - All Randomized Subjects, Global Population CM227 Part 1 - Nivolumab+Ipilimumab and Chemotherapy

Table 7. PFS per BICR Summary by Squamous histology - All Randomized Subjects, Global Population CM227 Part 1 - Nivolumab+Ipilimumab and Chemotherapy

Table 8. PFS per BICR Summary by Non-Squamous histology - All Randomized Subjects, Global Population CM227 Part 1 - Nivolumab+Ipilimumab and Chemotherapy

References

Reck, et al. Nivolumab + ipilimumab + 2 cycles of platinum-doublet chemotherapy vs 4 cycles chemotherapy as first-line treatment for stage IV/recurrent NSCLC: CheckMate 9LA, ASCO 2020

Paz-Ares, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2021; 22: 198-211

Ramalingam, et al. Nivolumab + ipilimumab versus platinum-doublet chemotherapy as first-line treatment for advanced non-small cell lung cancer: Three-year update from CheckMate 227 Part 1, ASCO 2020

Single Technology Appraisal (STA)

Nivolumab with ipilimumab and chemotherapy for untreated advanced non-small-cell lung cancer

ERG commentary on the response submitted by the company to the ACD

Produced by **CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD**

Date **07/05/2021**

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in [redacted], all academic-in-confidence (AIC) data are highlighted in [redacted].

1 OVERVIEW

The evidence review group (ERG) was requested by NICE to provide a critique of the additional evidence submitted by the company in response to the appraisal consultation document (ACD).

Due to the limited time available, the additional work undertaken by the ERG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission. However, the ERG has checked the implementation of any proposed changes and ensured replication of the results presented by the company.

The company's revised models incorporate the ERG- and committee-preferred utility values and the results of updated network meta-analyses (NMAs) to include pembrolizumab combination therapy as an additional comparator. However, the ERG noted an error in the model submitted by the company that resulted in the duration of treatment benefit for pembrolizumab + PDC always being applied for the patients' lifetime, regardless of the scenario selected. Results presented in Sections 3 and 4 reflect the analysis that has been corrected by the ERG.

The revised models did not incorporate the commercial access agreement for pemetrexed and the PAS for atezolizumab, bevacizumab and pembrolizumab. The ERG has provided additional results of the analyses with these costs applied in a separate confidential appendix.

2 DESCRIPTION AND CRITIQUE OF ADDITIONAL EVIDENCE

Within their response to the ACD, the company raised a number of concerns regarding the assumptions made in the ACD, which they attempted to address through the presentation of additional analyses. These are discussed by the ERG in turn below.

2.1 Inclusion of pembrolizumab plus pemetrexed and platinum chemotherapy as a comparator for non-squamous NSCLC

2.1.1 Decision problems

In the original submission, there were three decision problems of interest, since the comparators for decision problems 2 and 4 were identical. However, with the inclusion of pembrolizumab + PDC as a comparator for decision problems 1 and 2 after the first committee meeting, there are now four decision problems and subpopulations of interest, each with a different set of comparators. These are summarised in Table 1.

Table 1 Comparators in the decision problem within each subpopulation

Original decision problem		
PD-L1	**Non-squamous**	**Squamous**
< 50%	*Decision problem 1* • Atezolizumab + BEV + PDC • PDC	*Decision problem 3* • PDC
≥ 50%	*Decision problem 2* • Pembrolizumab monotherapy • PDC	*Decision problem 4* • Pembrolizumab monotherapy • PDC

Post-ACD decision-problem		
PD-L1	**Non-squamous**	**Squamous**
< 50%	*Decision problem 1* • Atezolizumab + BEV + PDC • ***Pembrolizumab + PDC*** • PDC	*Decision problem 3* • PDC
≥ 50%	*Decision problem 2* • Pembrolizumab monotherapy • ***Pembrolizumab + PDC*** • PDC	*Decision problem 4* • Pembrolizumab monotherapy • PDC

2.1.2 Updated indirect treatment comparisons: critique of methods

In the ACD response, the company provided new indirect treatment comparisons (using fractional polynomial network meta-analysis [FP NMA]) to compare pembrolizumab + PDC vs nivolumab + ipilimumab + PDC vs PDC in a non-squamous population (combined decision problems 1 and 2). However, this revised NMA excluded pembrolizumab monotherapy as a comparator. New NMAs are also presented for the non-squamous histology and PD-L1 < 50% population (decision problem 1). There is no comparative evidence for pembrolizumab monotherapy vs pembrolizumab in combination with PDC in the non-squamous (NSQ) PD-L1 ≥ 50% population (decision problem 2). Table 2 summarises new or updated NMAs (indirect comparisons) in the company's ACD response.

Table 2 Summary of the indirect comparisons provided in the company submission and ACD response.

	Network meta-analysis	
Population*	**Post technical engagement**	**ACD response**
Mixed histology and PD-L1 ≥ 50% **(relevant to decision problem 2&4**)**	***Analysis 1*** **Data used from CheckMate-9LA and CheckMate-227:** The full ITT population. **Treatments compared:** • Nivolumab + Ipilimumab + PDC • Pembrolizumab monotherapy • PDC	***Analysis ACD1*** Not updated in ACD response.
Non-squamous histology and PD-L1 < 50% **(relevant to decision problem 1)**	***Analysis 2*** **Data used from CheckMate-9LA and CheckMate-227:** subgroup data of non-squamous and PD-L1 < 50% **Treatments compared:** • Nivolumab + Ipilimumab + PDC	***Analysis ACD2a*** ***(company response to ACD, Appendix B, section 1)***

	• Atezolizumab + Bevacizumab + PDC • PDC	**Data used from CheckMate-9LA and CheckMate-227:** subgroup data of non-squamous and PD-L1 < 50% **Data used for other studies:** subgroup data of non-squamous and PD-L1 < 50% where available **Treatments compared:** • Nivolumab + Ipilimumab + PDC • Atezolizumab + Bevacizumab + PDC • Pembrolizumab + PDC • PDC **Additional studies:** • KEYNOTE-189
		Analysis ACD2b ***(company response to ACD, Appendix B, section 2.3/2.4)*** **Data used from CheckMate-9LA and CheckMate-227:** Histology all-comers and PD-L1 all-comers (ITT) **Data used for other studies:** subgroup data of non-squamous and PD-L1 < 50% where available **Treatments compared:** • Nivolumab + Ipilimumab + PDC • Atezolizumab + Bevacizumab + PDC • Pembrolizumab + PDC • PDC **Additional studies:** • KEYNOTE-189 • IMpower 130
Non-squamous histology and PD-L1 all-comers (relevant to decison problems 1 & 2)	Not reported in company submission	***Analysis ACD3a*** ***(company response to ACD, Appendix B, sections 2.1/2.2)*** **Data used from CheckMate-9LA and CheckMate-227:** Histology all-comers and PD-L1 all-comers (ITT). **Data used for other studies:** subgroup data of non-squamous and PD-L1 all comers **Treatments compared:** • Nivolumab + Ipilimumab + PDC • Atezolizumab + Bevacizumab + PDC • Pembrolizumab + PDC • PDC **Additional studies:** • KEYNOTE-189 • IMpower 130
	Not reported in company submission	***Analysis ACD3b*** ***(company response to ACD, Appendix B, sections 2.5/2.6)*** **Data used from CheckMate-9LA and CheckMate-227:** subgroup data of non-squamous and PD-L1 all-comers.

		Data used for other studies: subgroup data of non-squamous and PD-L1 all comers **Treatments compared:** • Nivolumab + Ipilimumab + PDC • Atezolizumab + Bevacizumab + PDC • Pembrolizumab + PDC • PDC **Additional studies:** • KEYNOTE-189 • IMpower 130

*For population 3 (squamous, PD-L1 < 50%), the only relevant comparator is PDC. There is already direct evidence comparing nivolumab + ipilimumab + limited PDC and PDC from CheckMate-9LA, hence an indirect comparison in this sub-population was not required.
** ITC for consolidated populations 2 + 4 (any histology and PD-L1 ≥ 50%) was used due to sample size limitations. The company stated that the models, in which PD-L1 ≥ 50% subgroup data from CheckMate-9LA were used were deemed clinically implausible based on a priori assumptions.
NOTE: only treatment comparisons of interest are added to this table

None of the updated NMAs included [redacted] The hazard ratio estimated from CheckMate-9LA for nivolumab + ipilimumab + PDC vs PDC [redacted]; however, it is uncertain to what extent this will impact the relative treatment effect estimated from the NMAs. All updated analyses included the additional KEYNOTE-189 trial which compared pembrolizumab + PDC with PDC, so that this new comparator could be included in the decision problem for non-squamous histology (decision problems 1 and 2). The pseudo-IPD for the subgroup of patients with PD-L1 < 50% in the KEYNOTE-189 trial was constructed by combining the reconstructed pseudo-IPD from the Kaplan-Meier curves for the PD-L1 < 1% and the PD-L1 1-49% groups, presented in the sources noted by the company (Appendix B, company's response to the ACD and subsequent company clarifications).

There were inconsistencies in the hazard ratios reported for the same sub-populations in the KEYNOTE-189 trial. This seems to be due to different sources being used for data extraction. For OS, the ACD2a analysis uses the Gray 2020 WCLC conference[1] (based on an August 2020 cut-off date) as a source, with estimated HR 0.57 95% CI (0.45 – 0.73) [App B Table 1]. However, the ACD2b analysis uses the Rodriguez-Abreu 2020 ASCO poster[2] (based on a May 2019 cut-off date), HR 0.56 (0.44 – 0.72) [App B Table 37], although they should represent the same subgroup of patients. There is a similar discrepancy for the PFS results.[3] The differences are small but it is unclear why different sources were used by the company. It is important to note that all NMAs except the non-squamous histology and PD-L1 < 50% (relevant to decision problem 1) used data from the Rodriguez-Abreu 2020 poster, which is an older data cut of KEYNOTE-189 than Gray 2020. The median follow-up was 18.8 months (range, 0.2 to 38.8 months) compared with 46.3 months (range,

41.8 to 54.1 months) presented in the Gray 2020 conference poster. The older data cut from the Rodriguez-Abreu poster was used in the company's base case. The reasons for this choice are unclear but, in principle, it would have been preferable to use the latest data cut as that provides more mature evidence.

Some new NMAs also included an additional study, IMpower 130,[4] comparing a different atezolizumab combination to PDC (Table 2). As this intervention is not a relevant comparator for any of the decision problems under consideration it is unclear why this additional study was included. Due to the nature of the indirect comparisons, the inclusion of this additional study is unlikely to affect the results for the comparisons of interest, beyond contributing information to the shape of the fractional polynomial models selected. Nevertheless, justification for its inclusion in the NMAs should have been presented.

The ERG did not have access to any of the data used in the new NMAs and did not have sufficient time to validate all FP model choices. The company stated that the methods for model choice were the same as in the original company submission which were appropriate. However, the ERG was concerned that some of the Kaplan-Meier and fitted curve plots provided by the company appeared inconsistent and could not be validated. The company later provided sources for some data and corrections to some plots but these could not be fully validated due to lack of time. The company did confirm that the ERG's concerns regarding incorrect figures did not affect the numerical analysis results which were correctly incorporated into the model (it was only a figure copying error).

2.1.3 Updated indirect treatment comparisons: critique of results

The company noted challenges associated with conducting the NMAs in the non-squamous subgroup (results presented in Figure 1), due to the shape of the long-term data of KEYNOTE-189[2] and the immaturity of the data from other trials (although it is unclear why a more recent source of data was not used – see section 2.1.2). The company applied a cap function into the base case analyses, which ensures that the long-term hazard ratios of pembrolizumab + pemetrexed + PDC versus nivolumab + ipilimumab + PDC cannot dip below that of PDC versus nivolumab + ipilimumab + PDC, which would be clinically implausible.

Although this is not an ideal adjustment, as noted by the company, the impact on outcomes or cost-effectiveness is limited. However, it does provide counter-intuitive results when conducting scenarios under the company's preferred assumptions, when relative treatment effects were estimated and applied relative to nivolumab + ipilimumab + PDC and the survival of PDC was modelled using independently generated survival curves from CheckMate-9LA and CheckMate-227 data (rather than using the relative effects from the FP NMA). Under these scenarios, life years generated for pembrolizumab + PDC increases (i.e. has a greater benefit) when the duration of treatment benefit

decreases. This is because the pembrolizumab per-cycle rate of death becomes greater than that of PDC after a certain amount of time. The duration of treatment benefit for all immunotherapies is implemented in the model by setting the rate of death equal to that of PDC after the appropriate amount of time (i.e. 3 to 5 years after starting treatment, under the Committee-preferred assumptions). Applying a limited duration of benefit means that the survival rate for pembrolizumab + PDC actually increases when it is set to that of PDC. When PDC is the baseline treatment for which all relative effects are applied to (as per the Committee's preferred assumption), this counter-intuitive scenario no longer occurs.

Figure 1 HRs of NIVO-IPI-Chemo vs comparators over time for overall survival for the target population of NSQ histology and PD-L1 all-comers (NMA ACD3b) (Fig 4 in Appendix A of the company's ACD response)

As a result of KeyNote-189 being added to the network, the company selected an alternative FP model to the one used for the NMA post-Technical Engagement. The ERG compared the number of life years estimated in the non-squamous PD-L1 < 50% population under the same modelling assumptions to demonstrate how the update of the network impacted upon the projected survival estimates (Table 3). Subsequently, the number of life years increased with nivolumab + ipilimumab + PDC, and decreased with atezolizumab + bevacizumab + PDC.

Table 3 Comparison of mean life years in the non-squamous PD-L1 < 50% population

	Life years (NMA post-TE)	**Life years (NMA post-ACD)**
3-year duration of benefit after starting treatment		
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]
Atezolizumab + bevacizumab + PDC	[redacted]	[redacted]
5-year duration of benefit after starting treatment		
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]
Atezolizumab + bevacizumab + PDC	[redacted]	[redacted]
Modelling assumptions: PDC survival modelled with CM-227 with subgroup specific data (non-squamous PD-L1<50%), relative treatment effects for nivo+ipi+PDC and for atezo+bev+PDC modelled with NMA ACD2a		

2.2 Long-term data collection

The company disagreed with the committee's recommendation that nivolumab combination does not meet the criteria for inclusion in the cancer drugs fund (CDF). This decision was based on further data collected being unlikely to be sufficient to reduce the key uncertainties affecting the cost-effectiveness results. The company consider that much of the uncertainty in the modelling is '*due to the lack of long-term follow-up and anticipated long-term treatment effect of the nivolumab combination in this setting*' which can be resolved with further data collection, thus meeting criteria for inclusion in the CDF. The ERG considers there to be a number of issues regarding the resolution of uncertainty including issues highlighted in the original ERG report and those highlighted in the company's ACD response.

In the original ERG report, the assessment that a 2-year data collection period would be unable to resolve a key outstanding area of uncertainty was predominantly based on the proposed duration of treatment benefit. This was a key driver of cost-effectiveness in both the company-preferred and ERG-preferred models. The company had assumed a lifelong survival benefit for patients receiving first-line immunotherapy, however the ERG preferred to limit the benefit of treatment to 5 years after treatment initiation as per previous TAs.[5-7] It was the uncertainty around this key issue of a lifelong duration of benefit (i.e. a cure in some patients) that was deemed unresolvable with up to 2 years of further data collection. Subsequently, a 5-year duration of benefit was accepted by the company in response to the ACD, which is considered the upper limit of the committee-preferred assumption of 3-5 years. However, rather than implement this as 5 years from the initiation of treatment to align with committee preference and previous TAs, the company's updated base case assumes the duration of benefit is 5 years after the discontinuation of treatment (i.e. 7 years after initiation). See Section 2.6 for further detail. Although the issue of lifelong treatment benefit has now been resolved, the ERG would like to reiterate that even with CDF data collection, the maximum duration of treatment benefit that could be observed is 5 years from the point of treatment initiation as per the upper limit of the committee's preference.

A further issue of uncertainty and one raised in the company's ACD response is that of the long-term survival benefits of nivolumab combination. The company have provided results from [redacted]. Overall survival and progression free survival in the nivolumab + ipilimumab arms are reported for the PD-L1 all comers population and the PD-L1 < 50% population, separately for squamous and non-squamous patients in Tables 1 to 4 of the company's ACD response. The full set of data reported separately for squamous and non-squamous patients is provided in Appendix C2. The ERG used these data to adapt Tables 3 to 4 from the company's ACD response (see Table 4 and Table 5 in this report). The ERG was unable to verify the results reported for patients with PD-L1 < 50

(Tables 1 to 2 of the company's response to ACD). The impact [redacted] on the hazard ratios for overall survival is presented in Table 6.

The ERG agrees that these data support a [redacted] receiving nivolumab + ipilimumab compared to PDC. However, as these data were not included in the new indirect treatment comparisons including pembrolizumab + PDC, the efficacy of nivolumab + ipilimumab in the long-term, compared to other immunotherapy combination therapies, is uncertain.

Finally, any data collected in the CDF regarding the long-term outcomes of patients receiving nivolumab + ipilimumab will be influenced by subsequent therapies received in CheckMate-9LA which are not in line with current UK practice. As detailed in the ERG report, 17% of the trial participants on nivolumab receiving subsequent therapy received an immunotherapy, and 16% received a targeted therapy. In the UK, patients receiving immunotherapy first line who receive subsequent therapy would receive docetaxel, which is reflective of UK clinical practice and in line with the second-line marketing authorisation of cancer immunotherapies. Any benefits (or harms) of the subsequent immunotherapies are included in the data used in the model, limiting the generalisability of the results. This also has implications for the costs of treatment and the subsequent cost-effectiveness (see Section 2.9).

Table 4 Non-Squamous PD-L1 All-Comers Landmark Outcomes (adapted from Tables 1-4 of the company's ACD response and Table 1-8 of Appendix C2).

Trial	Year 1 (%)		Year 2 (%)		Year 3 (%)		Year 4 (%)	
Overall Survival								
	Nivo+ipi	PDC	Nivo+ipi	PDC	Nivo+ipi	PDC	Nivo+ipi	PDC
CheckMate 9LA	[redacted]	[redacted]	[redacted]	[redacted]				
CheckMate 227	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-Free Survival								
CheckMate 9LA	[redacted]	[redacted]	[redacted]	[redacted]				
CheckMate 227	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Some values were reported differently in the company ACD response: [redacted]

Table 5 Squamous PD-L1 All-Comers Landmark Outcomes (adapted from tables 1-4 of the company's ACD response and Table 1-8 of Appendix C2).

Trial	Year 1 (%)		Year 2 (%)		Year 3 (%)		Year 4 (%)	
Overall Survival								
	Nivo+ipi	PDC	Nivo+ipi	PDC	Nivo+ipi	PDC	Nivo+ipi	PDC
CheckMate 9LA	[redacted]	[redacted]	[redacted]	[redacted]				
CheckMate 227	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-Free Survival								
CheckMate 9LA	[redacted]	[redacted]	[redacted]	[redacted]				
CheckMate 227	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Some values were reported differently in the company ACD response: [redacted]

Table 6 Survival data for histology and PD-L1 subgroups using [redacted] for CheckMate 9LA and CheckMate 227 (Adapted from Table 11 and 15 of the ERG report and appendix B, C1 and C2 of the company's ACD response).

	ITT	NSQ<50	NSQ≥50	SQ<50	SQ≥50	SQ	NSQ	<1% 1-49%	≥ 50%
CheckMate9LA									
Nivo N	361	[redacted]	[redacted]	[redacted]	[redacted]	109	229	262	76
PDC N	358	[redacted]	[redacted]	[redacted]	[redacted]	110	223	235	98
HR (1-yr data cut)	0.66 (0.55-0.80)	[redacted]	[redacted]	[redacted]	[redacted]	0.62 (0.45-0.86)	0.69 (0.55-0.87)	0.62 (0.45-0.85) 0.61 (0.44-0.84)	0.66 (0.44-0.99)
HR used in NMA	[redacted]	[redacted]	-	-	-	-	[redacted]	-	-
HR ([redacted])	[redacted]	-	-	-	-	[redacted]	[redacted]	-	-
CheckMate227									
Nivo N	583	[redacted]	[redacted]	[redacted]	[redacted]	164	419	378	205
PDC N	583	[redacted]	[redacted]	[redacted]	[redacted]	164	419	391	192
HR (3-yr data cut)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.69 (0.52-0.92)	0.85 (0.69-1.04)	[redacted]	[redacted]
HR used in NMA	[redacted]	[redacted]	-	-	-	-	[redacted]	-	-
HR ([redacted])	[redacted]	-	-	-	-	[redacted]	[redacted]	-	-

2.3 Tolerability of nivolumab combination therapy

The company stated in their response to the ACD that an indirect treatment comparison was carried to compare adverse events for nivolumab + ipilimumab + PDC and the pembrolizumab + PDC regimens in the first line setting. However, neither further details nor results of these comparisons were available to the ERG so we cannot comment further.

The company also present a plot describing how some treatment-related adverse events occur over time (company's response to ACD, Figure 1). However, it is unclear how this figure should be interpreted in light of treatment discontinuations that will also occur over time.

2.4 Subgroup-specific survival analysis

"The committee agreed that there was uncertainty about the validity of applying survival curves derived from the ITT data across all the subgroups. It concluded that survival curves should be modelled separately for each subgroup."

In their updated base case analysis, the company implemented the survival curves for the separate histology and PD-L1 subgroups, which were originally provided during the technical engagement period and were based on the 1-year data-cut for CheckMate-9LA and 3-year data-cut for CheckMate-227. As discussed in Section 2.2, [redacted].

In addition, the company also provided a scenario analysis in which the histology-specific, PD-L1 all-comers data were used to model survival, for consistency with the appraisal of pembrolizumab + chemotherapy in non-squamous NSCLC (TA683). However, the company did not provide details of the curve fitting process for these two subgroups and thus the ERG was unable to validate their approach. Plots of overall survival extrapolated over the time horizon of the model were generated by the ERG from the company model (Figure 2 and Figure 3, Table 7 and Table 8). Note that survival up to 1 year is informed by the observed data from CheckMate-9LA, and survival thereafter is informed from survival models fit to data from CheckMate-227, and assumes that there is a treatment benefit duration for immunotherapies for 5 years after *discontinuing* treatment.

Figure 2 Overall survival in the non-squamous population (generated from company model)

Figure 3 Overall survival in the squamous population (generated from company model)

Table 7 Landmark OS for the company-selected parametric models – nivolumab + ipilimumab + limited PDC (adapted from the economic model)

	Distribution	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 5 (%)	Year 10 (%)
PD-L1 < 50% Non-Squamous	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 < 50% Squamous	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Squamous	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-Squamous	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 8 Landmark PFS for the company-selected parametric models – nivolumab + ipilimumab + limited PDC (adapted from the economic model)

	Distribution	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 5 (%)	Year 10 (%)
PD-L1 < 50% Non-Squamous	Spline Odds 1 Knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 < 50% Squamous	Spline Normal 1 Knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Squamous	Spline Odds 2 Knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-Squamous	Spline Odds 1 Knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.5 Platinum-doublet chemotherapy based on the CheckMate-227 data alone

The committee concluded that the survival curves for people having platinum-doublet chemotherapy should be based on the CheckMate-227 data alone. In the economic model, this is implemented using the ERG-scenario which uses the CheckMate-227 data only for the PDC arm and relative effects from the FP NMA (which captures changing hazard over time) including CheckMate-227. In their response to the ACD, the company disagreed with this conclusion suggesting that it was more appropriate to base survival in the PDC arm on CheckMate-9LA as it is the registrational trial for this indication. In addition, the company suggest "*utilising CheckMate-227 alone is very clearly selectively choosing the "worst case" comparator data available"*, and that median OS in CheckMate-9LA was *"within the range that has recently been reported in other phase 3 first-line NSCLC studies, which had similar patient populations (e.g., median OS, 10.7-11.3 months in KeyNote-189 and 11.3-11.6 months KeyNote-407)"*.

Committees' 5-year survival rate preference for PDC in previous NSCLC STAs ranged from 5-11% in TA531;[8] the range was slightly higher in TA584 at 9-12% although the committee considered these results with reference to those used in TA531.[7] In TA683, the 5-year survival estimate of 5-11% was considered plausible by committee.[9] The model predicts that 5-year survival for PDC in CheckMate-227 alone is 10.5%; in the hybrid approach using CheckMate-9LA followed by CheckMate-227, 5-year survival is 9%. Both fall within the range considered in previous STAs.

As detailed in the original ERG report, the ERG considers that the PDC arm in CheckMate-227 appears to be better for the purpose of decision making in the NHS, compared to CheckMate-9LA. This is due to subsequent therapy, which was numerically lower in CheckMate-9LA than in CheckMate-227 with 27.9% vs. 40.8%, respectively. The ERG considers the proportion of patients with subsequent therapy in CheckMate-227 to be closer to the anticipated proportion in NHS practice (see Section 4.2.6.2 and Section 4.2.8.3, ERG report). It is important to consider whether the baseline

survival represents what would be expected in clinical practice, as often patients included in randomised trials are not very representative of patients expected to be treated in the NHS.

In their ACD response, the company suggest the committee-preferred scenario of using PDC survival from CheckMate-227 and the relative effects from the FP NMA naively informs absolute survival for the PDC arm. This is an incorrect interpretation as the analysis is not conducted naively, the relative treatment effects estimated from the FP NMA are applied to the baseline survival curve, therefore maintaining the randomised nature of the relative treatment effects.

The company presented results from a systematic literature review for first line therapies for the treatment of advanced NSCLC in patients without sensitising EGFR mutations or ALK translocations showing the median OS and PFS and the percentile in which the results of CheckMate-9LA and CheckMate-227 fall (Figures 2 and 3, page 7, Company ACD response). However, as the ERG has not seen the search strategies or extracted data, it is difficult to comment on how comparable the results are. For example, details of the recruitment period and the baseline characteristics of those included in studies would be required to assess comparability and relevance to the current decision problem.

The company also describe [redacted] This shows survival below that presented in CheckMate-227, however with no access to the database or the opportunity to scrutinise the analysis it is again difficult to comment on how comparable the results are. The ERG does, however, agree with the company that limited real world evidence from the UK are available.

Based on this, the ERG concurs with the committee that the PDC arm in CheckMate-227 appears to be better for the purpose of decision making in the NHS, and will retain this in the base-case (see Section 4).

2.6 Duration of treatment benefit

"The committee concluded that a treatment effect lasting 3 to 5 years after starting treatment was appropriate for decision making, for consistency with previous immunotherapy appraisals in NSCLC."

The company maintains that duration of treatment effect for nivolumab + ipilimumab + PDC will last beyond 3 to 5 years, citing evidence from an analysis of five-years of follow up data from the CheckMate-067 trial that evaluated nivolumab + ipilimumab in advanced melanoma to demonstrate a durable response.[10] However, the updated economic analysis provided by the company considers a treatment effect duration of 5 years *after the discontinuation of treatment* (i.e. 7 years after starting treatment, given a maximum two year treatment duration for nivolumab), which is a more optimistic assumption than was preferred by the Committee.

In Section 4, the ERG provides the results of scenarios aligned with the committee-preferred assumption, which consider a treatment effect duration of 3 years after starting treatment, representing a conservative lower limit of the ICER, and of 5 years after starting treatment representing an optimistic, upper limit to the range of plausible ICER.

2.7 Quality of life

"A time-to-death approach meant that people entering the model had a different health related quality of life depending on the treatment arm they were assigned to."

The company accepted the use of progression-based health state utility values in line with the committee's preferred assumption in the updated economic analysis. The company also suggested an alternative wording for the ACD, which the ERG considers to be appropriate and further clarifies the committee's position while remaining concise.

2.8 End of life status within the non-squamous PD-L1 < 50% subgroup

"It understood that the company and ERG agreed that nivolumab combination did not meet the criteria for end of life treatments for:

- *non-squamous NSCLC and a PD-L1 TPS below 50%"*

The company presented evidence from an observational dataset of non-squamous NSCLC patients, demonstrating that median OS for immunotherapy + chemotherapy regimens currently used in practice is less than 24 months in a real-world setting.[11] The median survival in the non-squamous population was 12.0 months, compared to 22.0 months in the controlled trial for pembrolizumab + PDC (KeyNote-189).[3]

The company assert that overall survival seen in trials of immunotherapy + chemotherapy combinations may not be reflected in clinical practice. The ERG noted key differences between the observational and the trial populations: patients in the observational dataset had a more severe performance status, were older and more likely to have unstable brain metastases. They were also

treated in the USA with different treatment patterns to the UK, and substantially fewer patients in the present real-world analysis went on to receive second-line treatment (23%) compared with results reported from pivotal clinical trials (30 %–59 % of patients in clinical trials of pembrolizumab or atezolizumab combination therapies). Whether the observational dataset is more reflective of a UK population that may receive nivolumab for untreated, advanced NSCLC is uncertain; however, it is worth noting that in the recent NICE appraisal of pembrolizumab + PDC (TA683), clinical advisors considered that the population of KeyNote-189 was generalisable to the UK population, and end of life criteria was judged on the basis of mean survival predicted by the model, which was informed by data from KeyNote-189 (actual mean life years gained are redacted in the appraisal documents; however, it was noted that mean survival of pembrolizumab + PDC was not statistically different to that of pembrolizumab monotherapy, which had a mean survival of 28 months).

There is currently very little long-term observational evidence for survival of patients on first-line nivolumab to demonstrate whether an extension in survival of 3 months would also be observed in practice. The company highlighted evidence from trial and observational analyses of nivolumab monotherapy as a second-line treatment for NSCLC, in order to demonstrate that the efficacy of nivolumab would be similar in practice to the trial setting (median OS 9.2 months estimated by observational data, compared with 12.21 months in CheckMate-057).[12] It is possible that there is a similar decline in efficacy for nivolumab in practice when patients with more severe characteristics are treated when compared to the corresponding trial and that a 3-month extension to life may not be observed, but the ERG considers that this is uncertain and not yet supported by evidence.

The ERG notes that both the median and the mean survival are considered when judging whether end of life (EOL) criteria apply. The median survival is typically lower than the mean estimate, especially for those receiving immunotherapies, where a proportion of patients will experience notably extended survival. The mean survival is more representative of the expected survival in the cohort as a whole. Therefore, a median OS of 22.0 months for pembrolizumab + PDC in KeyNote-189 likely has an associated mean value that is greater than 24 months. The company's economic analysis of cost-effectiveness in the non-squamous PD-L1 < 50% population predicts that the mean (undiscounted) life years gained for all immunotherapies are greater than 24 months (Table 9).

Table 9 Mean (undiscounted) life years, predicted by company analysis

	Non-squamous, PD-L1 < 50%	**Non-squamous**	**Squamous, PD-L1 < 50%**	**Squamous**
2 years survival?	Atezo+bev+PDC: 2.61 PDC: 2.15 Pembro+PDC: 2.77	PDC: 2.38 Pembro+PDC: 3.24	PDC: 1.26	PDC: 1.29
0.25-year extension to survival?	Nivo+Ipi+PDC: 3.56	Nivo+Ipi+PDC: 4.17	Nivo+Ipi+PDC: 2.48	Nivo+Ipi+PDC: 2.80

Meets EOL criteria?	**No, survival is > 2 years**	**No, survival is > 2 years**	**Yes**	**Yes**

The ERG considers that the evidence is not sufficiently compelling to demonstrate that the EOL criteria are met in the non-squamous PD-L1 < 50% population. Additionally, EOL criteria are not met in the PD-L1 ≥ 50% subgroups where pembrolizumab monotherapy is a comparator, with greater than 24 months mean survival (ERG report, Section 7). As such, the ERG considers that the EOL criteria are only met in the squamous PD-L1 < 50% population, where the only comparator to nivolumab + ipilimumab + PDC is PDC. A similar conclusion was also made in the recent appraisal of pembrolizumab + PDC (TA683[9]) regarding EOL criteria in each subgroup of non-squamous patients.

2.9 Other issues

As described in Section 2.2, the nivolumab + ipilimumab + PDC survival data from CheckMate-9LA captures the effects of subsequent immunotherapies and targeted therapies which are not in line with current UK practice. The survival benefits of the subsequent therapies are inherently included in the cost-effectiveness of nivolumab + ipilimumab + PDC. Despite the benefits being included, the company's economic model does not include the cost of these therapies, rather the cost of docetaxel is applied as it is assumed 100% of patients receiving subsequent therapy received docetaxel (as would happened in NHS practice). The ERG considers a more consistent approach would have been to apply the costs of the subsequent immunotherapies used in CheckMate-9LA and/or CheckMate-227. Although the resulting costs may be less generalisable to UK practice, there is a consistency in applying the relevant costs of all therapies used to match the observed effects of these therapies, in order to prevent under or overestimation of cost-effectiveness. A similar issue was highlighted in the recent appraisal of pembrolizumab for urothelial carcinoma after platinum-containing chemotherapy (TA692), in which committee found it inconsistent to include the potential benefits of retreatment without the costs, concluding that both should either be included or excluded. The inclusion of these costs has not been explored in scenario analysis by the ERG, as although data are available for subsequent therapies in CheckMate-9LA and CheckMate-227, the corresponding data for the other comparators outside of CheckMate-9LA are not available.

3 RESULTS OF THE COMPANY'S SCENARIOS

A summary of assumptions underlying the company's updated cost-effectiveness analysis following the ACD is detailed in Table 10.

Table 10 Summary of assumptions in the economic analysis following the first Committee meeting

	Appraisal Committee's preferred assumption	**Company's economic analysis following the ACD**
Survival curves by subgroups	Apply separate survival curves by histology (NSQ and SQ) and PD-L1 status	Apply separate survival curves by histology (NSQ and SQ) and PD-L1 status
PDC survival modelling	Survival for people having PDC modelled using CheckMate-227 data alone	Model survival for people having PDC based on CheckMate-9LA followed by CheckMate-227
Treatment effect duration	3 – 5 years after starting treatment	5 years after discontinuation of treatment
Utility values	Progression-based utility values	Progression-based utility values
Composition of platinum-doublet chemotherapy	Separate chemotherapy regimen distributions	Separate chemotherapy regimen distributions are used
Proportion of subsequent therapy	Subsequent therapy proportion based on CheckMate-227	Subsequent therapy proportion based on CheckMate-227
Relative dose intensity	Minimal impact on ICER results and likely to lie between company and ERG approach	Retained company-preferred approach

The company's cost-effectiveness results for the non-squamous PD-L1 < 50% and the squamous PD-L1 < 50% subpopulations are presented in Table 11. The company did not provide comparative evidence for pembrolizumab monotherapy vs pembrolizumab + PDC in the non-squamous PD-L1 ≥ 50% population, and so results for this subgroup cannot be presented. For completeness, the ERG also provides the results of the PD-L1 ≥ 50% population under the company's preferred assumptions. In addition, the company also presented results for the squamous and the non-squamous subpopulations.

These results include the confidential PAS discounts [redacted]. Results with the PAS discounts for pembrolizumab, atezolizumab, bevacizumab and pemetrexed are provided in a confidential appendix separate to this report.

In the non-squamous, PD-L1 < 50% population, nivolumab + ipilimumab + limited PDC generated [redacted] incremental QALYs, and had higher total lifetime costs compared with PDC. The ICER was £50,890 per QALY gained. Nivolumab + ipilimumab + limited PDC dominated atezolizumab + bevacizumab + PDC and pembrolizumab + platinum + pemetrexed, as it generated higher QALYs and had lower total lifetime costs. However, these results may be unreliable due to a large number of uncertainties in the NMAs used to estimate relative effects (Section 2.1).

In the squamous, PD-L1 < 50% population, nivolumab + ipilimumab + limited PDC generated [redacted] incremental QALYs, and had higher total lifetime costs than PDC. The ICER was £55,590 per QALY gained.

Table 11 Results of the company's cost-effectiveness analyses

	Total costs	Total LYs[1]	Total QALYs	ICER
Decision problem 1: Non-squamous, PD-L1 < 50% [2]				
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]	[redacted]	£50,890
Atezolizumab + bevacizumab + PDC	[redacted]	[redacted]	[redacted]	Dominated
Pembrolizumab + PDC [4]	[redacted]	[redacted]	[redacted]	Dominated
Decision problem 1 & 2: Non-squamous [2]				
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]	[redacted]	£34,581
Pembrolizumab + PDC [4]	[redacted]	[redacted]	[redacted]	Dominated
Decision problem 3: Squamous, PD-L1 < 50%				
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]	[redacted]	£55,590
Decision problem 3&4: Squamous				
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]	[redacted]	£58,692
Decision problem 2&4: PD-L1 ≥ 50% [3]				
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]	[redacted]	£33,886
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	£187,288

[1] LYG are discounted at 3.5%
[2] Relative effects estimated from NMA ACD 3b (PD-L1 all comers & NSQ)
[3] Relative effects estimated from NMA ACD1 (PD-L1 ≥ 50%, CM-9LA and CM-227 ITT population)
[4] Results presented for pembrolizumab + PDC are based on the model corrected by the ERG

4 RESULTS OF THE ERG ANALYSES

The results of the ERG alternative base case analyses are presented in Table 12 for the non-squamous PD-L1 < 50% population (decision problem 1), Table 13 for the squamous PD-L1 < 50% population (decision problem 3) and Table 14 for the PD-L1 ≥ 50% population (decision problem 2 and 4). These results include the PAS discounts for nivolumab and ipilimumab. Results with the confidential PAS discounts for the remaining comparators are presented in a confidential appendix separate to this report.

The analyses account for the following assumptions, to align with the Committee's preferences:

- A 3- and 5-year duration of treatment benefit after starting treatment;

- Survival of patients receiving PDC modelled using subgroup-specific data from CheckMate-227, with relative treatment effects for nivolumab + ipilimumab + PDC estimated from the FP NMA;
- Relative effects estimated from NMA ACD2a (using subgroup data of non-squamous and PD-L1 < 50%).

Table 12 Results of the ERG cost-effectiveness analysis – non-squamous PD-L1 < 50%

	Total costs	Total LYs[1]	Total QALYs	ICER
3-year duration of benefit after starting treatment				
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]	[redacted]	£53,636
Atezolizumab + bevacizumab + PDC	[redacted]	[redacted]	[redacted]	Dominated
Pembrolizumab + PDC	[redacted]	[redacted]	[redacted]	Dominated
5-year duration of benefit after starting treatment				
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]	[redacted]	£40,077
Atezolizumab + bevacizumab + PDC	[redacted]	[redacted]	[redacted]	Dominated
Pembrolizumab + PDC	[redacted]	[redacted]	[redacted]	Dominated
[1] LYG are discounted at 3.5%				

Table 13 Results of the ERG cost-effectiveness analysis -squamous PD-L1 < 50%

	Total costs	Total LYs[1]	Total QALYs	ICER
3-year duration of benefit after starting treatment				
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]	[redacted]	£66,829
5-year duration of benefit after starting treatment				
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]	[redacted]	£58,737
[1] LYG are discounted at 3.5% Survival modelled under company assumptions (using CheckMate-9LA and CheckMate-227 data for survival curves), no NMAs were available based on the squamous subpopulations				

Table 14 Results of the ERG cost-effectiveness analysis - PD-L1 ≥ 50%

	Total costs	Total LYs[1]	Total QALYs	ICER
3-year duration of benefit after starting treatment				
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	£57,437
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]	[redacted]	Dominated
5-year duration of benefit after starting treatment				
Platinum doublet chemo	[redacted]	[redacted]	[redacted]	-
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	£47,357
Nivolumab + ipilimumab + PDC	[redacted]	[redacted]	[redacted]	Dominated
[1] LYG are discounted at 3.5%				

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