Single Technology Appraisal

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from** Merck Sharpe & Dohme:
   a. Response form
   b. Additional evidence appendix

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Roy Castle Lung Cancer Foundation
   b. British Thoracic Oncology Group

There were no comments on the Draft Guidance received through the NICE website

3. **External Assessment Group critique of company comments on the Draft Guidance**

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

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Consultation on the draft guidance document – deadline for comments 5pm on Thursday 19 September. Please submit via NICE Docs.

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

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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.
0	<u>Executive summary of the company's response to the Draft Guidance</u> The company presents evidence that the trial outcomes in the PD-L1 TPS <50% subgroup, which constitutes a stratified sample of 726 patients from of a triple blinded Randomised Controlled Trial are in line with clinical and biological expectation and evidence that the results in the smaller PD-L1 TPS≥50% are contrary to expectation. This, in addition to the greater unmet need in the PD-L1 TPS<50% population is why the company's submission focused on these patients. As requested by the committee, the company has supplied clinical evidence and an economic model for the Full Licenced Population. The company has updated the model to include the committee's preferred baseline age of 67 along with a Standardised Mortality Ratio for cured patients. These updates increased the ICERs somewhat. The company has conducted a number of scenario analyses on the model that aim to meet the concerns outlined by the committee in the Draft Guidance including Treatment Effect Waning, exploration of downstream transition probabilities (e.g. by considering cure in the LR state), adjustment of the cure percentage to meet long term recurrence rates and adjustment of DM

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	outcomes post routine follow-up to reflect trial outcomes. These scenario analyses either made little difference to ICERs or slightly improved the cost-effectiveness of pembrolizumab. For the PD-L1 TPS<50% subgroup, the range of credible ICERs was largely between £20,000 - £30,000/QALY gained, indicating pembrolizumab is cost-effective in this group with little associated decision-uncertainty. For the Full Licenced Population, the range of ICERs was wider but the best fitting model had an ICER only slightly above £30,000/QALY gained. This estimate is likely conservative given the unexpected overperformance of the control arm for PD-L1 TPS≥50% patients and the wealth of data supporting the clinical effectiveness of pembrolizumab in these NSCLC patients.
1	Trial results versus expectation **Summary points:** • **Overall, the Draft Guidance (DG) reads as if it is the results in the PD-L1<50% sub-population, which constituted 72% of the licensed population, that cannot be explained, which does not reflect the body of evidence in NSCLC and may lead to inaccurate conclusions about the clinical effectiveness in this subpopulation.** • **While the treatment effect in the PD-L1 ≥50% subgroup was expected to be better than in the PD-L1 <50% subgroup, the appropriate interpretation of the data is that the treatment effect in the PD-L1 ≥50% subgroup was worse than expected, as opposed to the treatment effect in the PD-L1 <50% subgroup being better than expected.** • **The outcomes in the PD-L1<50% subpopulation, which accounts for 72% of the licensed population were as expected in both the placebo and pembrolizumab arms based on the pre-specified target DFS HR in the trial population, consistency of the results with those in the two pre-specified subgroups (PD-L1 <1% and 1-49%) which are also stratification factors, and consistency of placebo outcomes with another RCT in this setting.** • **The treatment effect in the PD-L1≥50% subpopulation was substantially worse than expected, this is largely due to control arm patients having much longer disease-free survival (DFS) in this smaller sub-population versus the rest of the control arm. This is the element of the trial outcomes that is contrary to biological expectation.** • **Trials in the adjuvant setting are inherently at some risk of sampling bias, particularly in smaller subgroups. This is because it is unknowable whether a patient has truly been cured by their radical treatment plan prior to randomisation. Approximately 30%-40% of patients enrolled in any adjuvant NSCLC trial are already cured and will not experience recurrent disease. While the very large sample size of KEYNOTE-091 offsets these risks in the overall population (and in the PD-L1<50% group, which has a large sample size), it is possible the smaller PD-L1≥50% subgroup does not contain the same proportion of patients who were truly cured prior to initiation of the trial within it, which may explain the results within that subgroup.**

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We would like to clarify what the expected results of KEYNOTE-091 were. The trial was designed in collaboration with EORTC, a scientific body independent of MSD and was powered to detect a disease-free survival (DFS) HR of 0.75 in the overall population and a DFS HR of 0.55 in the PD-L1TPS ≥50% subgroup(1). This was based on a number of randomised controlled trials (RCTs) of pembrolizumab in late-stage NSCLC where pembrolizumab has demonstrated effectiveness regardless of PD-L1 expression but where the greatest treatment effect was always seen in the PDL1≥50% subgroup.

Of note, other RCT designs assessing adjuvant immunotherapies in early-stage NSCLC showed target DFS HRs that are relatively consistent with KEYNOTE-091, more specifically:

- IMpower010 (adjuvant atezolizumab vs best supportive care) was designed to have 91% power to detect a DFS HR of 0.73 for the DFS analysis in the stage II–IIIA population, 76% power to detect a DFS HR of 0.78 in the stage IB-IIIA population (the overall population) and 90% power to detect a DFS HR of 0.65 in stage II–IIIA population with tumours expressing PD-L1 on 1% or more of tumour cells. A median DFS duration of 34 months was expected for the best supportive care group in both stage II-IIIA population and PD-L1 ≥1% subgroup(2) i.e. within the trial design, DFS in the control arm was expected to be the same regardless of PD-L1 expression.

- BR31 (adjuvant durvalumab vs placebo) provided 80% power to detect an HR for DFS of 0.725 in all participants with stage IB-IIIA NSCLC and 0.645 in the PD-L1 ≥1% subgroup. Similarly to KEYNOTE-091, use of prior adjuvant chemotherapy was permitted but not required(3).

- ANVIL (adjuvant nivolumab vs observation) was powered to detect co-primary endpoint of a 33% improvement in DFS favouring nivolumab, corresponding to a DFS HR of 0.67. Similarly to KEYNOTE-091, use of prior adjuvant chemotherapy was permitted but not required(4).

Based on the above, it is reasonable to presume that the statistical plans for these trials were based on the expected DFS benefits regardless of PD-L1 expression and increasing confidence in the role of immune check-point inhibitors in patients with higher PD-L1 expression.

The treatment effect for pembrolizumab in the PD-L1 TPS <50% (DFS HR=0.72) and full licenced population (DFS HR=0.76) appear to be in line with the KEYNOTE-091 statistical plan as well as that of other trials evaluating immunotherapies in early-stage NSCLC, especially when considering that these groups reflect the majority of the study populations and that the patients unable to have adjuvant chemotherapy were included in the power calculations and would be expected to have a worse outcome due to lack of fitness.

It is stated in the Draft Guidance document that the results from the PD-L1 TPS < 50% subgroup are not considered convincing, given their *post hoc* nature. However, the fact that PD-L1 TPS <1% and 1-49% are prespecified subgroups and stratification factors strengthens the validity of their results. Given that the PD-L1 TPS <50% subpopulation effectively combines these two prespecified subgroups and the results are consistent with those in these subgroups (Table 1), it is extremely unlikely that the results in the PD-L1 <50% subpopulation are merely due to chance.

Table 1. DFS by PD-L1 subgroups – IA3

PD-L1 Subgroup	DFS HR (95% CI)
Overall (Prior Adjuvant Chemotherapy)	0.76 (0.64, 0.91)

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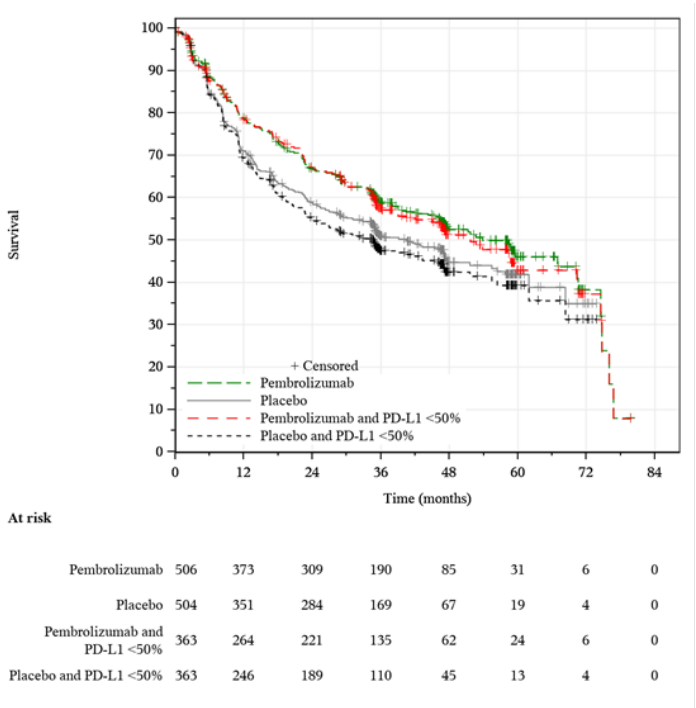
<50%	0.72 (0.58, 0.89)
1-49%	0.70 (0.51, 0.96)
<1%	0.75 (0.56, 0.99)

Abbreviations: DFS: Disease-free Survival; HR: Hazard Ratio; IA3: Interim Analysis 3; PD-L1: PD-L1: Programmed Cell Death - Ligand 1.
Source: KEYNOTE-091 EPAR EMEA/H/C/003820/II/0121(5)

The DFS data show that the treatment effect in the PD-L1 TPS <50% subpopulation is similar to that observed in the licensed population (Prior Adjuvant Chemotherapy population) (DFS HR 0.72 vs 0.76 for the PD-L1 TPS <50% and licensed population, respectively - Table 1 and Figure 1). This is not surprising giving that the PD-L1 TPS <50% subpopulation accounts for 72% of the licensed population. The figure below shows the small impact the addition of the relatively small PD-L1≥50% subpopulation has on the KM curves.

Figure 1. Kaplan-Meier Curve of Disease-Free Survival Based on Investigator Assessment for the Prior Adjuvant Chemotherapy Population and PD-L1 TPS <50% subpopulation - (Intention-to-Treat Population)



Database Cutoff Date: 24JAN2023
Abbreviations: PD-L1: PD-L1: Programmed Cell Death - Ligand 1; TPS: Tumour Proportion Score.

The results in the population in which the Marketing Authorisation was granted were considered valid by the regulators such as the European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA, who relied upon EMA's decision via EC decision Reliance Procedure), as the baseline characteristics were balanced between treatment arms, and from a statistical perspective, the use of adjuvant chemotherapy was a stratification factor and pre-specified subgroup(5).

The Marketing Authorisation granted for the Prior Adjuvant Chemotherapy population (i.e., irrespective of PD-L1 status) is reflective of treatment with pembrolizumab being considered efficacious and safe in all PD-L1 subgroups within this population. The views of the regulator, and

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the magnitude of the observed treatment effect for the licensed population and PD-L1<50% subgroup being in line with expectations, should give the NICE committee confidence that the data in the PD-L1 TPS <50% are supported by biologically plausible mechanisms. This is also demonstrated by other indications in NSCLC where pembrolizumab has been approved by the regulators and then recommended by NICE (TA683(6), TA770(7)) irrespective of the PD-L1 expression i.e., including the PD-L1 TPS <50%.

It is important to note that the absolute outcomes for the PD-L1<50% subgroup in the placebo arm are in line with the published literature i.e. IMpower010, while noting that the populations from the two trials are very similar but do not fully overlap (stage IB-IIIA in KEYNOTE-091 vs stage II-IIIA in IMpower010) (Table 2). The company notes that median DFS in the ≥50% placebo group of KEYNOTE-091 was approximately 2 years longer than DFS in all the other control arm groups, which were similar to each other.

Table 2. Summary of median Disease-Free Survival by PD-L1 expression for the control arm in IMpower010 and KEYNOTE-091 trials

	Study: IMpower010[a]		KEYNOTE-091[b]		
	PD-L1 ≥50%	PD-L1<1-49%	PD-L1≥50%	PD-L1 <50%	PD-L1 <1-49%
Disease-Free Survival	**BSC** **N[c]=114**	**BSC** **N[d]=114**	**Placebo** **N[e]=141**	**Placebo** **N[f]=363**	**Placebo** **N[g]=165**
Median DFS (95%CI)	35.7 [29.7-NE]	31.4 [24.0-NE]	57.82 [36.40; NR]	34.5 [23.3, 46.4]	32.89 [22.28; 47.21]
	c: Number of participants: intention-to-treat population with PD-L1 ≥50% stage II-IIIA NSCLC	d: Number of participants: intention-to-treat population with PD-L1 1-49% stage II-IIIA NSCLC	e: Number of participants: intention-to-treat population with Adjuvant Chemotherapy and PD-L1 ≥50%	f: Number of participants: intention-to-treat population with Adjuvant Chemotherapy and PD-L1 <50%	g: Number of participants: intention-to-treat population with Adjuvant Chemotherapy and PD-L1 1-49%

a: Database Cutoff Date: 21JAN2021(8)
b: Database Cutoff Date: 24JAN2024(9)
Abbreviations: BSC: best supportive care; NE: not evaluable; NSCLC: non-small cell lung cancer; PD-L1: Programmed Cell Death - Ligand 1.

The DFS HR for the PD-L1 TPS ≥50% group was 0.83. Based on the target DFS HR in this subgroup (HR=0.55), it appears that only the HR in the PD-L1≥50% group is against the expectations, with the outcomes in the placebo arm being substantially better in this subgroup than in any other PD-L1 subgroups.

The overperformance of the DFS curve of the placebo arm for the PD-L1 ≥50% subgroup can clearly be seen in the KM curves below (Figure 2). While there is a substantial overlap of the KM curves for the PD-L1 <1% and 1-49% subgroups (green and grey lines), the KM curve for the PD-L1 ≥50% subgroup reflects better outcomes for the placebo arm in this subgroup (red line). This is further confirmed by the DFS rates at multiple time points being similar for the PD-L1 <1% and 1-49% subgroups but not for the PD-L1 ≥50% subgroup (Table 3). The consistency in outcomes for the PD-L1 <1% and 1-49% subgroups along with the better-than-expected outcomes in the PD-L1 ≥50% subgroup clearly suggest an overperforming control group in the latter, as opposed to underperforming in the other PD-L1 subgroups.

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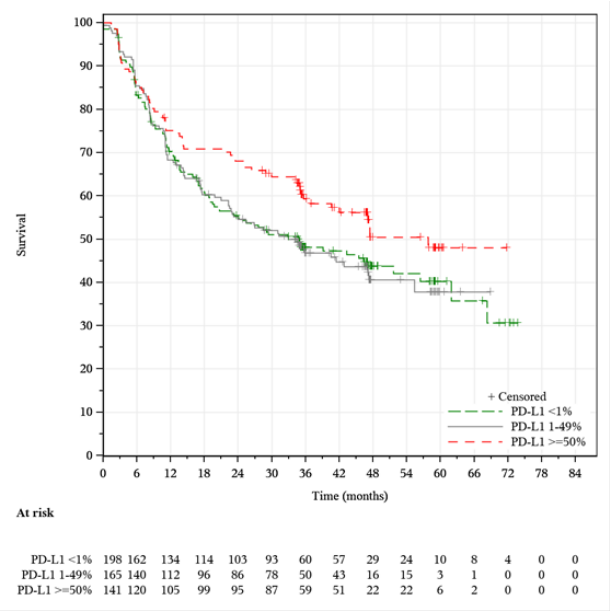
Figure 2. Kaplan-Meier Curve of Disease-Free Survival by PD-L1 expression Based on Investigator Assessment - Placebo Arm - Participants with Prior Adjuvant Chemotherapy (ITT Population)



Database Cutoff Date: 24JAN2023
Abbreviations: PD-L1: Programmed Cell Death - Ligand 1.

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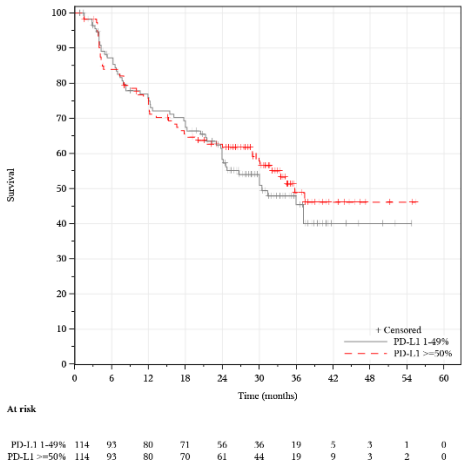
Table 3. Summary of Disease-Free Survival Rate Over Time by PD-L1 expression Based on Investigator Assessment - Participants with Adjuvant Chemotherapy (Intention-to-Treat Population)

	Study: KEYNOTE 091[a]		
Disease-Free Survival Based on Investigator Assessment (Primary Censoring Rule)	**PD-L1 ≥50%** **Placebo** **N[b]=141**	**PD-L1 <1-49%** **Placebo** **N[c]=165**	**PD-L1 <1%** **Placebo** **N[d]=198**
Kaplan-Meier Rate at Specified Timepoint, % [95%-CI][e]			
Month 12	75.2 [67.1; 81.5]	68.3 [60.6; 74.8]	70.2 [63.3; 76.1]
Month 18	70.9 [62.6; 77.6]	60.2 [52.3; 67.3]	60.7 [53.4; 67.2]
Month 24	68.0 [59.6; 75.0]	54.5 [46.6; 61.8]	55.4 [48.1; 62.1]
Month 30	64.4 [55.9; 71.7]	52.0 [44.0; 59.3]	51.1 [43.8; 57.9]
Month 36	59.3 [50.5; 67.0]	46.8 [38.8; 54.4]	48.1 [40.7; 55.0]
Month 42	56.1 [47.1; 64.2]	44.7 [36.6; 52.5]	47.2 [39.9; 54.2]
Month 48	50.4 [40.2; 59.8]	40.5 [31.9; 49.0]	43.8 [36.2; 51.0]
Median DFS (95% CI)	57.82 [36.40; NR]	32.89 [22.28; 47.21]	34.76 [20.47; 51.62]
a: Database Cutoff Date: 24JAN2023 e: From the product-limit (KM) method for censored data	b: Number of participants: intention-to-treat population with Adjuvant Chemotherapy and PD-L1 ≥50%	c: Number of participants: intention-to-treat population with Adjuvant Chemotherapy and PD-L1 1-49%	d: Number of participants: intention-to-treat population with Adjuvant Chemotherapy and PD-L1 < 1%

Abbreviations: DFS: Disease-free Survival; KM: Kaplan-Meier; NR: Not Reached; PD-L1: Programmed Cell Death - Ligand 1.

Of note, this trend for the PD-L1 ≥50% subgroup was not observed for the placebo arm in the IMpower010 trial, with no substantial differences in outcome between the PD-L1 subgroups (Figure 3).

Figure 3. Kaplan-Meier Curves of DFS of IMpower010 Control Arm (Best Supportive Care) by PD-L1 expression



Participants: control arm (best supportive care) with stage II-IIIA NSCLC
Database Cutoff Date: 21JAN2021
Note: Published Kaplan-Meier (KM) curves from IMpower010(8) were digitized, and the pseudo-IPD data were extracted to estimate the number of participants at risk over time and event rates.

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	Pseudo-IPD extraction is a manual process where visual identification of event times in published KM curves is required. Therefore, some minor differences of the results from those published can be expected. Abbreviations: IPD: Individual Patient Data; NSCLC: non-small cell lung cancer; PD-L1: Programmed Cell Death - Ligand 1. Importantly, PD-L1 was actually found to be a negative prognostic factor in early-stage lung cancer in a meta-analysis of 50 studies of patients not treated with PD-L1/PD-1 inhibitors (10). More specifically, the results of the meta-analysis in subgroups by TNM stage revealed that increased PD-L1 expression was associated with poor prognosis for lung cancer patients in early stage I-III (HR =1.51, 95% CI: 1.23–1.86). There was no statistically significant effect in advanced stage IV (HR =0.66, 95% CI: 0.33–1.33). It should be noted that high heterogeneity was found across all subgroups and the meta-analysis in advanced stage was informed by only three small studies. Since there is little evidence from the dozens of studies in the literature that PD-L1 is a positive prognostic factor for outcomes in the absence of immunotherapy treatment, the interpretation of the scientific community, and that advanced by the clinicians at ACM1 was that the differentiated outcomes observed in KEYNOTE-091 are more likely a chance finding rather than reflecting the reality of the natural history of NSCLC by PD-L1 status. In conclusion, while the treatment effect in the PD-L1 ≥50% subgroup was expected to be better than in the PD-L1 <50% subgroup, the appropriate interpretation of the data is that the treatment effect in the PD-L1 ≥50% subgroup was worse than expected, as opposed to the treatment effect in the PD-L1 <50% subgroup being better than expected. DFS in the placebo arm in the <50% subpopulation is consistent with another RCT in this setting and the treatment effect is consistent with what the trial was powered to detect via a large triple blinded RCT, given the clinical knowledge derived from many other RCTs of pembrolizumab in NSCLC. The company's view is that the biological plausibility of the observed data in this group is therefore not in question. All studies in the adjuvant setting are at some risk of sampling bias, as it is not known how many patients were genuinely cured by their radical treatment plan (i.e. surgery with adjuvant chemotherapy) and therefore will never experience recurrent disease. This issue can be ameliorated by enrolling a large sample size into the trial, as in KEYNOTE-091, but smaller subgroups, such as the PD-L1≥50% remain at greater risk of a chance finding that is contrary to clinical expectation. However, the biology of resected NSCLC is less well-studied than that in the advanced setting.
2	Selection of the PDL1<50% sub-population **Summary point: In not requesting reimbursement in the subgroup with unexpected and unexplained results, the company's intent was to increase the certainty and applicability of the cost-effectiveness estimates to UK clinical practice rather than decreasing it.** As demonstrated in comment 1, the results in the PDL1≥50% subgroup were unexpected and do not reflect the natural history of PD-L1≥50% NSCLC, which should be no different than the other PD-L1 subgroups. Rather than select the PD-L1 <50% on the basis of the observed data, the proposed positioning is the result of the exclusion of the subgroup with unexpected and unexplained results (i.e., PD-L1 ≥50% subgroup, where there is lower unmet need because another effective treatment option is currently being used in clinical practice). While some clinicians have expressed their interest in using pembrolizumab in this subgroup, these results would have impacted the degree of certainty over the effectiveness and cost-effectiveness assessment. MSD opted for a simplified and pragmatic approach by excluding the PD-L1 ≥50% subgroup to increase the certainty about the applicability of

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	the cost-effectiveness estimates to UK clinical practice rather than decreasing it. This was also informed by our UK advisory boards, where it was confirmed that, based on the differences in HRs between the trials, atezolizumab would remain the treatment of choice in this patient population, even if pembrolizumab was available. Nevertheless, we provide the clinical effectiveness and cost-effectiveness results for the full licensed population (Prior Adjuvant Chemotherapy population) as part of our response to this consultation. Please see MSD Response to the Draft Guidance document provided separately for the full technical details.
3	Sample size of PDL1<50% subpopulation **Summary point: the sample size of the subpopulation (n=726 patients) is adequately large, especially within the context of oncology treatments appraised by NICE, and this reduces the risk of chance findings.** We would like to clarify that, whilst the sample size of the subpopulation is smaller than the licensed population, a subpopulation of 726 patients, which account for 72% of the population on which the Marketing Authorization is based (n=1,010), should be considered adequately large. This is also supported by the lack of additional imbalances between trial arms in this subpopulation and the narrow confidence interval. Therefore, it is reasonable to conclude that the risk that the results are due to chance is limited and the findings are not expected to have deviated substantially from the true treatment effect. MSD feel that stating in the Draft Guidance document that the smaller sample size prevents reliable conclusions being drawn can mislead stakeholders about the extent of the uncertainty in the clinical effectiveness evidence. KEYNOTE-091 is a large, triple-blinded RCT with treatment effects in line with its statistical analysis plan (except in one notable subgroup) and with highly statistically significant data. Of note, other technologies recommended by NICE in early-stage NSCLC were based on much smaller sample sizes e.g. TA823 (atezolizumab as adjuvant treatment, n=229)(11) and TA876 (nivolumab with chemotherapy as neoadjuvant treatment, n=358) (12).
4	Treatment effect waning **Summary point**: **as explained at ACM1, both of the company's analyses already included treatment waning as a natural consequence of the data (and the disease setting, in which hazards are expected to converge as both arms eventually include only cured patients). For the avoidance of doubt, we have added treatment waning to the model and, as expected, this has a very limited impact on the results.** Treatment effect waning already happens in the company's model because the DFS HR gradually attenuates and equals 1 at 7 years. There is no (or negligible, depending on curve selection) modelled benefit for pembrolizumab thereafter. Follow up in KEYNOTE-091 is relatively long compared to most oncology trials considered by NICE and the gap between the end of follow-up (~5 years) and the DFS HR equalling 1 (~7 years) is already short. In the company's base case analysis there was a short projected benefit after the trial but the hazard ratio became 1 soon after. Imposing treatment waning assumptions very slightly influences the company's base case (see Figure 8). In the company's alternative scenario the hazard ratio become 1 by the end of KEYNOTE-091 follow-up so treatment waning assumptions have no effect on the model. In the EAG's base case, where the DFS hazard ratio is modelled to favour placebo for almost the whole time horizon, treatment waning assumptions would theoretically benefit pembrolizumab as the hazard ratio would move back from above 1 to 1. In section 3.8 of the Draft Guidance (DG) document, the committee express their wish that treatment effect waning is explored in the model. As explained at the meeting, "treatment effect waning" in NICE appraisals has historically meant the attenuation of the hazard ratio to 1 over time. This will

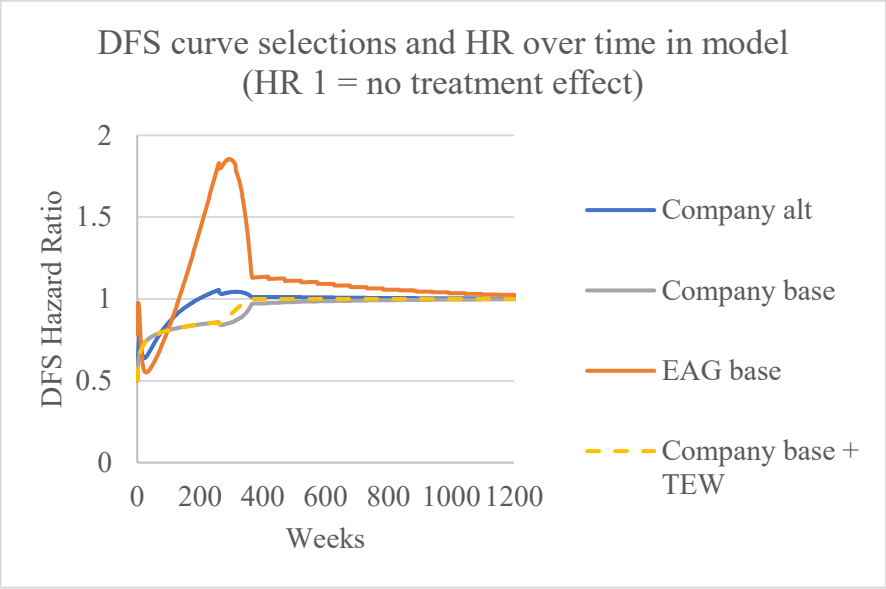
naturally happen in all adjuvant treatment settings anyway because only cured patients will be left in both arms of the model after a certain time point.

At ACM1, the company then explained that the DFS ratio already trends to 1 very soon after follow-up in the company's analyses. This is due to a combination of the natural attenuation of the hazards in the projected curves and the imposition of the cure assumption from years 5-7, which eliminates 95% of the difference in the hazards anyway.

Given that the HR reaches the clinically expected HR of 1 soon after follow-up using conventionally projected survival curves it is unclear why it would be desirable that additional assumptions about further reductions in treatment effect would be layered on top of the model.

We implemented a sensitivity analysis where treatment waning from 5-7 years is imposed. These time points were chosen because there are already 5 years of KM data from KEYNOTE-091 so it would make little sense to impose an assumption on top of the survival curves within the observed follow-up time. The behaviour of the DFS HR in the model is illustrated in the Figure below:-

Figure 4. DFS Hazard Ratios over time in the model PD-L1<50% subgroup under different DFS curve selections



The company note that in the EAG's preferred settings there is a permanent disbenefit for pembrolizumab eventually resulting in greater DFS for placebo, which is not clinically plausible. This is the result of the EAG selecting a constant transition for DF->LR in the pembrolizumab arm alone and a zero transition for DF->DM in the placebo arm alone.

We are concerned that section 3.8 of the DG document misrepresents the modelling choices as a dichotomy between "no treatment waning" in the company's analysis and "treatment waning explored" in the EAG's analysis. The company would instead characterise this choice as "treatment waning accounted for appropriately in line with clinical expectation" in the company's analysis and "treatment effect modelled to favour placebo for the time horizon of the model so that DFS eventually becomes higher in the placebo arm" in the EAG's analysis.

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	As a result of the above considerations we would note that section 3.8 of the DG document has multiple factual inaccuracies: treatment waning was applied in the model because the DFS HR attenuated to 1 shortly after trial follow up and the benefits of pembrolizumab were not sustained throughout the time horizon of the model (if benefit here means 'treatment effect').
5	Adaptions to the economic model The company has made some changes to the model to reflect the preferences expressed by the committee in the Draft Guidance:- 1. Treatment waning functionality added 2. Sensitivity analysis examining possibility for cure in LR state added 3. Baseline age changed to 67 4. Additional model supplied in which the survival curve parameters, time on treatment and subsequent treatments have been adjusted to reflect the full licensed population 5. SMR of 1.453 added to cured patients (consistent with the committee's preference in NICE ID5094) 6. Sensitivity analyses relating to cure proportions and long term recurrence conducted
6	Economic model results in the licensed population The company has supplied an additional model for the licensed population. This model is identical to the base case model except that the DFS survival curve parameters have been replaced with those for the licensed population, the Time on Treatment has been adjusted appropriately and the downstream treatments have been adjusted to reflect that patients in the ≥50% will be eligible for pembrolizumab and atezolizumab monotherapy. The proportions eligible for different DM treatments have been taken from KEYNOTE-091 for the full licensed population. Treatments in LR are unaltered. The results of the model are as expected; the DFS HR is similar but slightly higher in the licensed population because of the overperforming control arm in the PDL1≥50% subgroup and so the ICER results are slightly higher. Given that the PDL1≥50% subgroup is not that large and the treatment effect is not very different, adding them back in has not influenced the ICERs by much. There is some uncertainty about the optimal approach to survival curve selection (weighted MSE statistics are supplied in a separate document). Again, the company has not selected constant or zero transitions in its DFS survival curve selections and suggests 3 options are most plausible:- 1. Pembro (log-normal/log-normal), placebo (log-normal, log-normal) 2. Pembro (generalised gamma/log-normal), placebo (generalised gamma/log-normal) 3. Pembro (log-normal/log-normal), placebo (generalised gamma/log-normal) Option 1 uses the best fitting curves (weighted MSE) for pembrolizumab and then fits the same models for placebo. Option 2 uses the best fitting models for placebo and then fits the same for pembrolizumab and option 3 uses the best fitting models for each arm. Option 3 has the best visual

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	fit to both arms but the trade-off is that it uses a different parametric model between the arms for the DF->LR transition.
7	Reprogramming the model to account for downstream time varying transition probabilities **Summary point: the company has not reprogrammed the model to truly take account of this but on investigation via sensitivity analyses, it appears there are no obvious advantages in complicating the model this way. This is because:-** • **For the LR health state, there is either no or little difference in projected cumulative incidence between the arms, depending on DFS curve selection. Sensitivity analyses benefited pembrolizumab.** • **For DM patients, there is no strong evidence from key trials that the exponential distributions are inaccurate.** LR patients The most obvious potential for an influential time dependent downstream transition in the economic model is within the LR health state, where the advisory board estimated around 10-20% of patients might actually be cured by the interventions they were offered. Implementing truly time dependent downstream transition probabilities is computationally complex and there wasn't the time during this consultation response to explore this fully. The company has, however, conducted exploratory analyses to investigate how this would effect the ICER if it could be properly implemented. The first thing to note is that the projected cumulative incidence of LR between the arms under most model selection assumptions is very similar; if generalised gamma curves are used it is actually exactly the same, other plausible curve selection options can results in a range of +2% to -2% incremental LR incidence within the model. Therefore, *a priori*, any adjustment to LR transition probabilities affects only a very small proportion of patients differentially between the arms and should not be expected to have a large influence on the ICER. Given that we would effectively be adding about the same amount of LR life years to both arms and the incremental costs and QALYs will barely change. In order to undertake exploratory analysis the company calculated the mean discounted life years for a cured patient (11.3 years based on life tables with SMR 1.453 applied) and an uncured LR patient (2.6 years based on the RWE TP used in the model [calculations are in 'LR life years calculation tab in the model'). Assuming a midpoint of 15% cure, this suggests that the mean discounted life years for a given patient in the LR health state might actually be 3.9 instead of 2.6 (15%*12+85%*3) i.e that the model has underestimated mean LR life years by a factor of approximately 1.5. The company imposed an LR cure assumption similar to the DFS cure assumption within the economic model and varied it until the mean discounted LR life years in the placebo arm of the model were 1.5* higher than the base case. It should be noted that while useful for illustrative purposes this method is imperfect as patients would be transitioning in and out of the LR state and, in reality, this transition probability would be highly dynamic but this method is useful in order to adjust the overall mean LR life years in exploratory scenario analyses examining the possible direction and magnitude of bias in the model.

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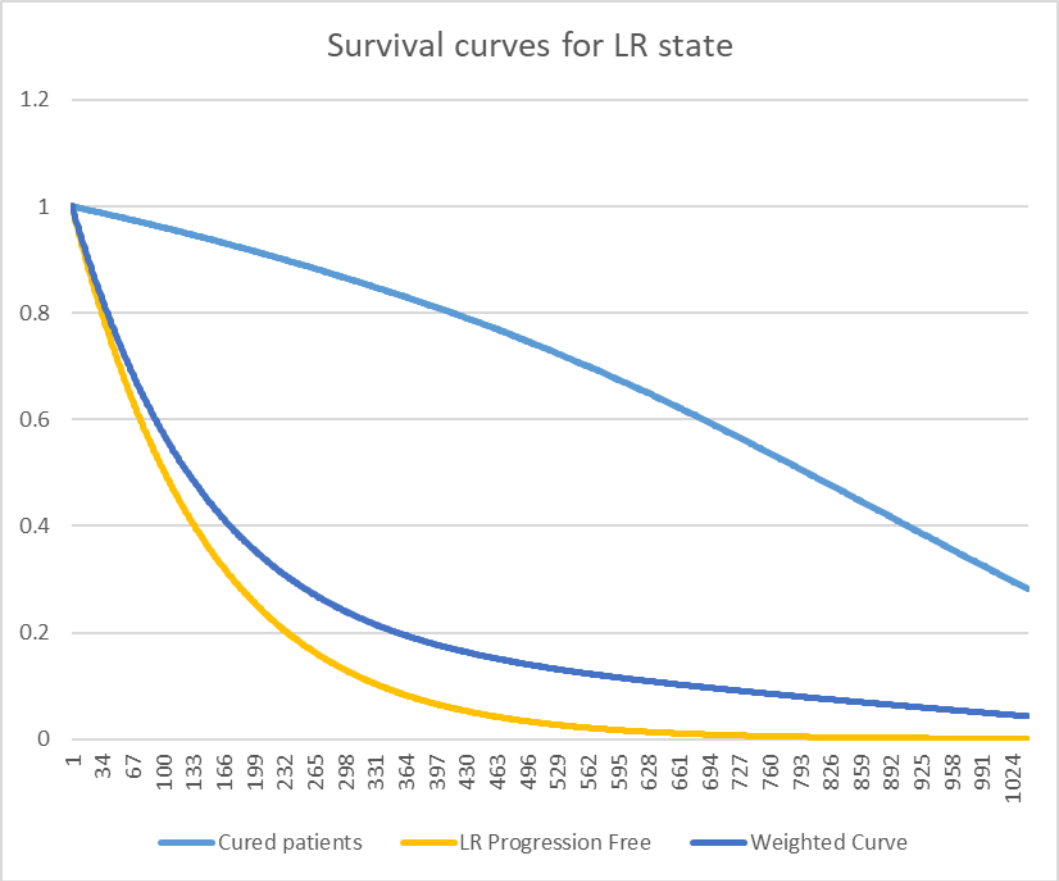
Figure 5. The weighted curve represents a situation where 85% of LR patients are uncured and 15% of patients are cured



In the instance where no calibration is applied, extending LR life years has the expected negligible effect on the ICER because the number of LR patients is very similar in both arms. In the base case where the LR outcomes are calibrated to match the trial and there are more LR patients alive at 5 years, reducing the LR TPs via the imposition of a cure benefits pembrolizumab because there are more patients to benefit. This reduces the ICER. While this analysis is exploratory, the company's interpretation is that this could be describing a real phenomenon; during the 2023 advisory board, it was established as plausible that pembrolizumab exposed patients recur at disease stages that make them more amenable to treatment. It may therefore be that a greater proportion of LR patients in the pembrolizumab arm achieve a cure than in the placebo arm and this could even be the post-DFS treatment effect that was observed in KEYNOTE-091. Overall, the company's interpretation of these analyses is that, were we able to fully incorporate time-dependency in the LR health state, the effect would either be neutral or would benefit pembrolizumab.

DM Patients

The outcomes for DM patients have more potential to affect the model's results because there are many more DM patients in the placebo arm. We examined the survival analysis of the available data from the key trials in the DM health state, namely the KEYNOTE-189 and 407 trials. We discovered that the exponential survival models that are currently in use in the KEYNOTE-091 economic model are in the middle of the pack of standard survival models for OS in these studies and that differences in AIC/BIC were relatively small. There is therefore no obvious reason to reject the

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	exponential models as either under or overestimating outcomes for patients treated with pembrolizumab+chemotherapy in the DM health state. For osimertinib, the company believes it more plausible that an exponential model overestimates than underestimates the OS on that drug if the effect is believed to be strong at first and wear off over time. Evidence from the FLAURA trial(13) is more supportive of this than the converse situation. However, halving survival on osimertinib only changes the ICER by £10. This is because it is used to exactly the same extent in both arms and in a small proportion of DM patients. A time varying transition probability theoretically has the ability to influence time on treatment in the DM state within the model. The company checked the mean cycles estimated by the model ('ToT_Advanced' tab) versus those observed in the KEYNOTE-407(14) and KEYNOTE-189(15) studies and found that they were well estimated overall (1 cycle fewer and 1 greater, respectively). The mean cycles on osimertinib are not reported in the literature but in the EAG report it is confirmed that osimertinib costs do not influence the ICER much even if they are set to extreme values. The consequence of under or estimating the ToT by a small amount due to curve fitting prior to stopping rules can therefore reasonably be considered to be negligible. On the balance of probability, it is more likely that the company has underestimated ToT in the DM health state than overestimated it. The reason for this is that OS observed in the registry data was higher than OS observed in the DM trials. The clinical explanation for this is that incident DM patients who are picked up through regular post-resection monitoring are likely to have DM that has recurred at a less advanced state than the *de novo* metastatic patients who were recruited into clinical trials. It is known that a large proportion of *de novo* metastatic patients are diagnosed in A&E and through symptomatic presentation, as opposed to incidental findings whereas patients recurring after surgery in the trials were typically diagnosed on regular routine follow up scans. Therefore, the company believes it is more likely that the DM health state costs bias the ICER against pembrolizumab than for it. We did not have time to quantify the magnitude of this bias during the DG response period.

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Figure 6. KEYNOTE-189 data showing exponential model is the central estimate for OS on pembrolizumab and fits the curve well

[redacted]

Figure 7. Figure showing OS in KEYNOTE-407, exponential model is central but may overestimate OS (and therefore overestimate the KEYNOTE-091 ICER slightly)

[redacted]

KN189 OS	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
LogNormal	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
GenGamma	[redacted]	[redacted]

KN407 OS	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
LogNormal	[redacted]	[redacted]
LogLogistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

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	GenGamma [redacted] [redacted]
8	Mixture cure modelling Validatory mixture cure models were provided at Clarification Questions response in line with Table 19 from TA761(16). This type of modelling of DFS is not compatible with the competing risks structure of the economic model so the company has not performed any additional analyses. Fitting 4 separate mixture cure models for the individual competing risks transitions is theoretically possible but would suffer from a smaller sample size and relative immaturity of the curves, leading to cure fractions that could be highly variable and treatment effects that are difficult to interpret. The company's view is that additional experimental survival analysis on DFS is not necessary; KEYNOTE-091 is a large trial with long follow-up in a disease area where the epidemiology is relatively well known. The model already contains dozens of survival analysis options and the long-term differences among these curves are controlled by the cure assumption. Disease free patients are no longer followed up after 5 years in clinical practice because there is clinical confidence that this represents cure for the vast majority of patients. Late recurrences beyond this point do occur but are already accounted for in the model where the model's estimates appear to match a long-term cohort study highlighted in this appraisal and TA823.
9	Validation of OS **Summary point: OS in the placebo arm of the trial match what has been observed in patient matched registry data when adjusting for differences in mean age. The model predicted observed OS well in the placebo arm but a temporary calibration ensures the model matches the observed data in the pembrolizumab arm.** The patient characteristics of the SEER-Medicare cohort (n=1,761 patients) are broadly aligned with those of KEYNOTE-091 trial patients, including histology and stage, as the inclusion criteria applied to the SEER cohort ensured patients were aligned with the KEYNOTE-091 trial population. The difference in mean age, due to SEER-Medicare cohort being restricted to age 65+, has been accounted for in the model. The OS in the placebo arm accurately match the observed data from SEER if the mean age in the model is set to match the mean age in SEER (73.8):- *Figure 8. Modelled OS and Real World Data OS from SEER Medicare (model mean age adjusted to 73.8 to match), prior to temporary calibration*

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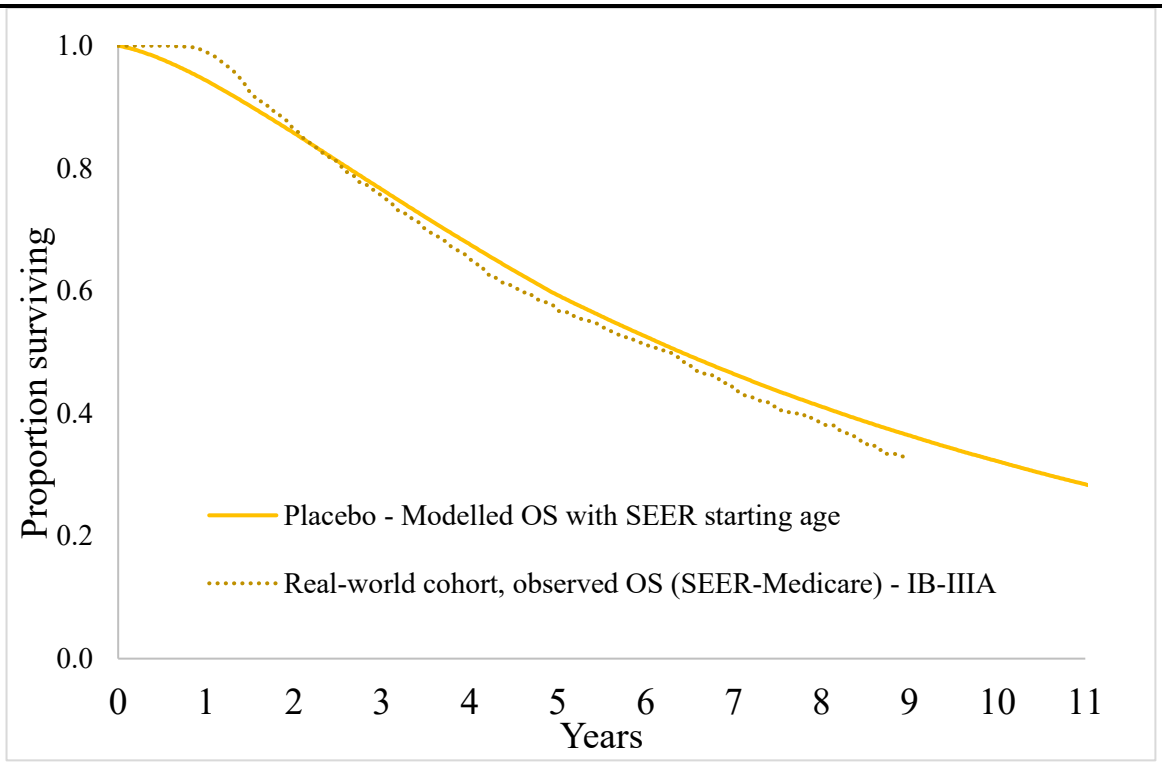

The OS in the placebo arm of the model accurately matched the placebo OS observed in KEYNOTE-091, suggesting that the model reasonably accurately captures the natural history of resected NSCLC.

The economic model underestimated the OS that was seen in the pembrolizumab arm of the model. This is because the model *a priori* assumed there would be no post DFS advantage for either treatment. However, a post DFS advantage was observed for pembrolizumab and the potential reasons for this were discussed extensively in section B.3.3.2, "Calibration of downstream transitions to observed OS" subsection of the CS. The model was therefore temporarily calibrated to reflect the post-DFS survival that was seen in the trial. After 5 years, this advantage instantaneously ends, potentially biasing the model against pembrolizumab but, given the uncertainty, the company agreed to follow the EAG's advice on this point in the updated base case prior to ACM1.

Figure 9. Modelled and observed OS without temporary calibration (<50% subgroup)

[redacted]

Figure 10. Modelled and observed OS with temporary calibration (<50% subgroup)

[redacted]

Figure 11. Observed versus modelled OS for Full Licenced Population without temporary calibration

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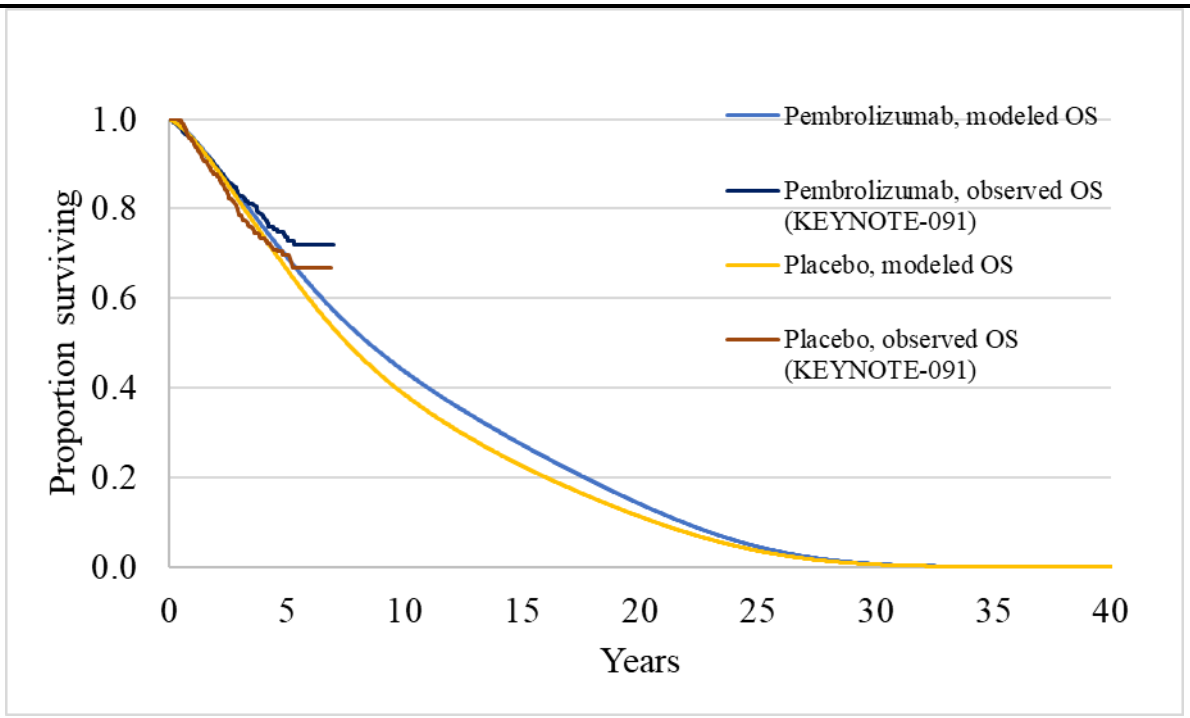
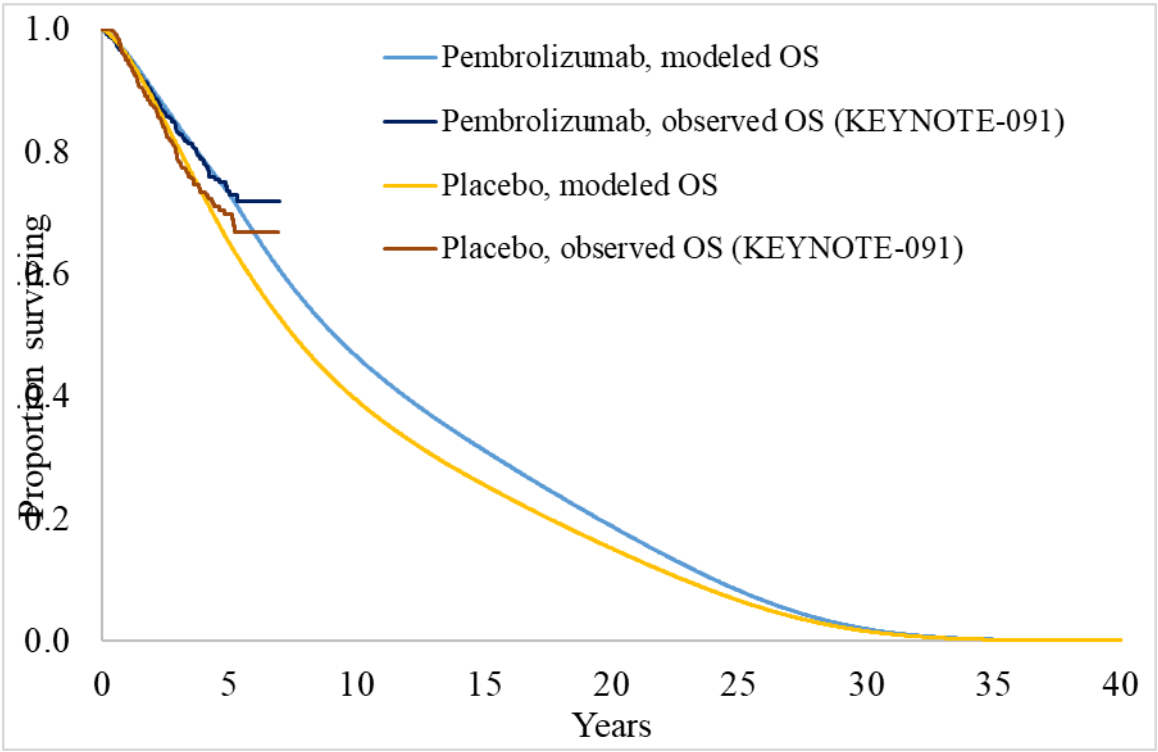


Figure 12. Observed versus modelled OS for Full Licenced Population with temporary calibration



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10 Modelling late recurrences in line with epidemiological literature

Summary point: the company's base case analysis already does this and the EAG's does not. Additional sensitivity analyses varying the cure assumptions along with the DFS curve selections have been undertaken.

During Clarification Questions, the EAG highlighted a long term study(17) that had been used to validate late stage recurrences in the adjuvant atezolizumab appraisal (NICE TA823(11)). It is reported in this study that the cumulative incidence between 10.2 and 19.8 years is approximately 0.8% of the total resected population. The company confirmed that the corresponding figures in its economic model was 0.77% in the pembrolizumab arm and 0.73% in the placebo arm, which ostensibly appeared similar. The table below lists the late stage recurrence data in the licensed and PD-L1 <50% population models under different assumptions. The imposition of a greater starting age (67 rather than 64) and an SMR of 1.453 reduces the numbers at risk in later model cycles and therefore the incident cases in the downstream part of the model. In the original long term cohort study, patients had a mean age of 64 at resection, the same as in KEYNOTE-091, which may mean that long term incidence data would be slightly lower than 0.8% in the UK population. Nevertheless, the model contains the ability to change the cure assumption so that late stage recurrences can match 0.8% in the placebo arm for any curve selection and the company has provided some sensitivity analyses around this. It should be noted that sensitivity analyses lowering the cure point with the EAG's preferred curve selection (e.g. to the 75% cure percentage referenced in section 3.7 of the Draft Guidance document are not credible as they lead to significant crossing of the DFS curves. Ultra late recurrences are calculated from the cumulative incidence curves in the Trace_AdjReg sheets in the model (sum of LR and DM recurrences between 10.2 and 19.8 years).

Table 4. Long term incidence produced by various DFS curve selections and cure percentages in the <50% subgroup and the Full Licensed Population (FLP)

Population	Model Selection	10-20y incidence pembro	10-20y incidence placebo
<50%	Company original base case	0.77%	0.73%
	Age 67 and SMR 1.453 applied		
<50%	Company base case	0.59%	0.55%
<50%	Company alternative	0.53%	0.37%
<50%	EAG base case	0.95%	0.13%
<50%	Company base case and Cure=92.5%	0.86%	0.80%
<50%	Company alternative and Cure=88.8%	1.20%	0.80%
FLP	Best fitting pembro	0.52%	0.57%
FLP	Best fitting placebo	0.84%	0.38%
FLP	Best fitting both	0.52%	0.38%
FLP	Best fitting pembro and Cure = 93%	0.73%	0.80%
FLP	Best fitting placebo and Cure =89.3%	1.70%	0.80%
FLP	Best fitting both and Cure=89.3%	1.10%	0.80%

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	There are some caveats with using long term cohort studies like this to validate the predictions made by the economic model. Obtaining very long term follow-up data on resected NSCLC of the sort required to validate the long term predictions of the model is challenging. The generalisability of any study where the initial resections took place 20 years ago is uncertain. The company's view is that the documentation of rare ultra-late recurrences in the literature suggest that the DFS transition probabilities in the model should have the property of declining, but not zero or constant hazards and that the model should allow for a small number of both types of recurrences to occur throughout its time horizon in both arms but the exact long-term recurrence rate is not known with certainty. The appropriateness of using the precise figure of 0.8% as a model selection criteria is therefore uncertain. Selecting a zero hazards curve for the placebo arm only, as in the EAG base, case implies that there will be no long term DM recurrences in the placebo arm. Given that half of incident cases of NSCLC are metastatic and that disease is often occult until it is advanced, this does not appear to make clinical sense, particularly when applied to one arm only. The company also reiterates that a transition with constant hazards is also conceptually inappropriate for projection when a large and increasing proportion of patients are cured.
11	<u>Modifiable risk ratio</u> Modifiable risk ratios are already present in the model for all downstream transitions. They are used in calibration to set the short term outcomes equal to those observed in the trial. It is unclear what additional analyses the committee wanted using these but the company is happy to provide any relevant sensitivity analyses if requested prior to ACM2.
12	<u>SMR for cured patients</u> In Section 3.13 of the Draft Guidance document, the committee request that the company impose a Standardised Mortality Raio of 1.5 to 1.6 on cured patients. This is based on an un-referenced estimate from a clinician consulted by the ID3907 EAG. In the appraisal for NICE ID5094, which was a very similar indication and took place at the same committee meeting on August 7th 2024, the committee requested an SMR of 1.453. This was based on an epidemiological study sourced by the ID5094 EAG for that appraisal. Since the data sourced by the EAG for ID5094 is equally applicable to both appraisals and constitutes more robust evidence, the company have instead implemented this value in the model. The company would like to point out that this source represents the overall SMR of patients who were disease free at 5 years, inclusive of both lung cancer and non-lung cancer mortality. Since the model already accounts for the additional mortality associated with recurrent lung cancer after 5 years, the figure of 1.453 is double counting and should be seen as an upper estimate by the committee.
13	<u>Company's updated analyses in response to the Draft Guidance</u> The company has updated the model in line with the items in comment 5 and produced a range of cost-effectiveness results under the following assumptions:-

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- Baseline age = 67
- SMR = 1.453
- Cure point 5-7 years (95% unless otherwise mentioned)
- Temporary calibration of post DFS outcomes to match trial to 5 years
- Osimertinib discount 0%

Key scenario analyses include:-

- Results for Full Licensed Population (FLP)
- Different curve selection options for DF->LR and DF->DM
- No DM adjustment after 5 years (patients survival is no longer than in the DM trials)
- A % of patients in LRR health state assumed cured after years 5-7 to inflate LRR life years
- Cure proportion varied in order to meet target of 0.8% ultra late recurrences

Table 5: Results of the company's scenario analyses following ACM1

Population	Model Selection	Inc Costs	Inc QALYs	Inc LYs	ICER
<50%	Company ACM1 base case	[redacted]	[redacted]	1.1	[redacted]
Age 67 and SMR 1.453 applied					
<50%	Company base case	[redacted]	[redacted]	0.94	[redacted]
<50%	Company alternative	[redacted]	[redacted]	0.84	[redacted]
<50%	EAG base case	[redacted]	[redacted]	0.64	[redacted]
<50%	Company base case and Cure=92.5%	[redacted]	[redacted]	0.94	[redacted]
<50%	Company alternative and Cure=88.8%	[redacted]	[redacted]	0.83	[redacted]
<50%	Company alternative and LRR cure 95%	[redacted]	[redacted]	1.01	[redacted]
<50%	Company base case and LRR cure 87%	[redacted]	[redacted]	1.05	[redacted]
<50%	Company alternative and TEW 5-7y	[redacted]	[redacted]	0.83	[redacted]
<50%	Company base case and TEW 5-7y	[redacted]	[redacted]	0.93	[redacted]
<50%	Company alternative and no DM adjust	[redacted]	[redacted]	0.92	[redacted]

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<50%	Company base case and no DM adjust	[redacted]	[redacted]	1.02	[redacted]
<50%	Company alternative, cure=88.8%, TEW=5-7, LRR cure 95%, no DM adjust	[redacted]	[redacted]	1.12	[redacted]
FLP	Best fitting pembro	[redacted]	[redacted]	0.82	[redacted]
FLP	Best fitting placebo	[redacted]	[redacted]	0.64	[redacted]
FLP	Best fitting both	[redacted]	[redacted]	0.72	[redacted]
FLP	Best fitting pembro and Cure = 93%	[redacted]	[redacted]	0.82	[redacted]
FLP	Best fitting placebo and Cure =89.3%	[redacted]	[redacted]	0.63	[redacted]
FLP	Best fitting both and Cure=89.3%	[redacted]	[redacted]	0.72	[redacted]
FLP	Best fitting both and LRR cure 85%	[redacted]	[redacted]	0.79	[redacted]
FLP	Best fitting both, cure=89.3%, TEW 5-7 years, LRR cure 85%, no DM adjust	[redacted]	[redacted]	0.88	[redacted]

Overall, the effect of the committee's preferences was to increase the ICERs somewhat versus the ACM1 analyses. This was primarily due to the increased age and the SMR versus the company's original base case meaning that cured patients now gain fewer QALYs.

ICERs increased when incorporating the PD-L1≥50% subgroup into the analysis albeit not by much in two of the three DFS curve selection options. This was firstly because this is a relatively small group within the trial and therefore their ability to influence the KM curves was minimal and secondly because, although the HR summary statistic was slightly worse, the survival analysis takes into account the whole pattern of hazards over the follow up time and the resulting survival curves were not much different to those in the original submission.

There is one set of curves in the Full Licensed Population where the ICER increased by a large amount. This was when the best fitting curves for the placebo arm were applied to the pembrolizumab arm. This unfortunately resulted in a relatively poor visual fit in the pembrolizumab arm. In the converse situation, applying the best fitting pembrolizumab curves to the placebo arm also resulted in a relatively poor visual fit. This may be reason enough to fit separate types of models to the different arms and simply select the best fitting curves for each.

Scenario analyses which varied the cure point to ensure the model matched a target ultra late recurrence rate only had a small effect on the ICERs. This scenario analysis was not presented when applied to the original EAG base case (section 3.7 of the DG) as it would have led to substantial crossing of the DFS curves.

Scenario analyses examining incorporating cure in the LRR state reduced the ICERs. This is because although the projected cumulative incidence of LRR is very similar between the arms, there were more surviving LR patients in the pembrolizumab arm at 5 years to benefit from the cure assumption. The company note that the magnitude of benefit seen in this sensitivity analysis is

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	highly uncertain but that it would either be neutral or favour pembrolizumab if pembrolizumab allowed a greater percentage of LRR patients to have successful treatment with curative intent. Scenario analyses examining whether removing the DM survival adjustment so that survival rates post year 5 matched those observed in the DM trials rather than being inflated to account for the differential prognosis between *de novo* and recurrent metastatic patients reduced ICERs by £1.5k-£3k. The company's view is that this is plausible since patients are not followed up routinely in practice after 3 years it may be that DM disease is more likely to be relatively more advanced by the time a recurrence occurs i.e. a post 5-year incident DM patient is more similar to a *de novo* DM patient prognostically. There are a number of reasons to consider it plausible that the ICERs are overestimated:- 1. ToT for downstream treatments is more likely overestimated than underestimated as recurring DM patients are potentially likely to stay on treatment for longer than *de novo* DM patients. This means the cost offsets associated with adjuvant pembrolizumab may be underestimated. 2. The calibrated post-DFS survival advantage for pembrolizumab ends immediately at 5 years rather than tapering, which may bias the results against pembrolizumab. 3. The results in the Full Licenced Population are likely biased against what would be seen in practice because it is unlikely PD-L1≥50% patients on standard care would have outcomes any better than those with PD-L1<50%. 4. The SMR of 1.453 double counts non-cancer and recurrent-cancer related mortality, the latter of which was already accounted for in the model. 5. In a scenario where DM survival was equal to the trials after 5 years rather than being increased to account for the difference between de novo and recurrent patients, the ICERs were reduced by £1.5k-£3k. 6. Scenario analyses on imposing an LRR cure assumption benefited pembrolizumab. The company therefore consider that the range of uncertainty around the true ICER for the PD-L1<50% subgroup lies within the typical NICE cost-effectiveness threshold of £20,000-£30,000/QALY gained. Importantly, there are no credible sensitivity analyses where the ICER is (much) higher than £30,000/QALY gained and several where the ICERs are closer to £20,000/QALY indicating that the decision risk is low. The company is uncertain about the degree to which NICE committees can take this into account but the population expected to be eligible for adjuvant pembrolizumab is also low, which indicates a low "absolute" decision risk. Most stage II-IIIA NSCLC patients are now expected to receive neo-adjuvant chemo-immunotherapy in the NHS and so will not be eligible for adjuvant pembrolizumab. The company's Budget Impact Model accounted for this and suggested that the eligible population is only ~135 patients per year. The range of ICERs for the Full Licenced Population is wider. The re-inclusion of the subgroup for whom the results are contrary to clinical expectation and in whom pembrolizumab is unlikely to be used makes the results of the economic model more uncertain. Even so, fitting the best fitting models to the DFS curves indicates that the base case ICER is not much higher than £30,000/QALY gained. When the company's sensitivity analyses are applied to the best fitting curves, the ICER drops below £30,000/QALY gained. Given the overperformance of the placebo arm for the PD-

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	L1≥50% population and the wealth of evidence that pembrolizumab is particularly effective for these patients, the model's results for the Full Licenced Population are very likely to be conservative. The company's view is that the clinical evidence in the PD-L1<50% subgroup is in line with expectation, that use of pembrolizumab meets a patient need that is currently unmet in the NHS and that the economic evidence indicates the decision risk is low in recommending it for use.
	<u>Comments on statements within the Draft Guidance (DG) document</u> DG page 6 – Appropriate comparators The reason for not considering durvalumab and osimertinib appropriate comparators is not related to the proposed population. These technologies would not be considered appropriate comparators even if the proposed positioning reflected the full licensed population. Durvalumab is a perioperative treatment and the decision point in the clinical pathway is not the same as for the KEYNOTE-091 population, with the KEYNOTE-091 population being a downstream subset of those included in trials of perioperative treatment. Osimertinib is recommended under the Cancer Drugs Fund (CDF) and, therefore, cannot be considered a relevant comparator in this appraisal regardless of the proposed population. The company notes it is only available for EGFR patients and would be the treatment of choice in this population if EGFR status is known. DG page 7 - Efficacy data presented in the DG document It is noted that the DFS and OS results have been shown in the DG for the overall population, full licensed population (prior adjuvant chemotherapy population) and PD-L1 TPS<50% subpopulation, in line with the data presented in the submission. In the spirit of transparency, DFS and OS data in the overall population were presented in the submission as being the primary and secondary endpoints of the trial. However, this population is broader than the licensed population so reimbursement in this population could not be pursued. Our view is that presenting the data in the overall population in the DG could mislead stakeholders into believing this population was not selected for pursuing reimbursement due to the more unfavourable results when in reality, there is no licence in this population. DG page 9 – Use of pembrolizumab The statement regarding the clinical experts explaining in the submissions that they expect more people to have adjuvant pembrolizumab, should refer more clearly to the Marketing Authorisation of pembrolizumab being broader than that of atezolizumab and to this technology (pembrolizumab) improving outcomes of more patients compared to current standard of care (active monitoring). The statement currently appears to imply that more people would be expected to use pembrolizumab as a result of pembrolizumab being used in the PD-L1 TPS ≥50% subgroup as well. While they noted that using pembrolizumab for patients with PD-L1 ≥50% will give patients the option of a treatment that is given less frequently, it is also stated that all [PD-L1] subgroups benefitted from pembrolizumab in the KEYNOTE-091 trial, which confirms the biological plausibility of the results in the proposed population. General consensus at the 2023 advisory board was that clinicians would continue to use atezolizumab to treat patients with early-stage NSCLC and PD-L1 ≥50% on tumour cells and therefore only the remainder of the patients would likely be candidates for adjuvant pembrolizumab. DG page 10 – The two statements "*the results of KEYNOTE-091 could not be clinically explained*" and "*the company and the clinical experts could not explain the results from this post-hoc subgroup*" are potentially misleading. The results in the <50% subgroup are as expected. The results in the PD-L1 ≥50% subgroup are unexpected and are potentially the result of more genuinely cured patients (a patient variable that is unknowable at randomisation) being randomised into that subgroup during the randomisation process.

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Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

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	DG page 11 – The statement about the committee that "*considered that the findings could be the result of chance*" can mislead stakeholders about the extent of the uncertainty in the findings. The population in question is a stratified sample of 726 patients from a prospective, triple-blinded RCT. The magnitude of the hazard ratio broadly matches clinical expectation based on the trial design and the results of other pembrolizumab RCTs in NSCLC, and the confidence interval is narrow and the upper bound well below 1. The outcomes on placebo match the data observed in another relevant RCT. This considerably reduces the risk of the outcomes in the PD-L1<50% subgroup being "the result of chance". DG page 12 – issues around age "*added to the uncertainty around the effectiveness of adjuvant pembrolizumab*" is misleading. In the paragraph above it is confirmed by the clinical experts that age is not a treatment effect modifier. The company view this as especially true in this instance where the difference between the mean age in the trial and those receiving a comparable intervention in UK clinical practice is quite small. DG page 16 – there are many references to the model not capturing treatment effect waning, which are incorrect. Equalisation of hazards is expected in the adjuvant setting as only cured patients remain in both arms after a certain time period. The hazards equalise in both the company's analyses in line with this expectation. The EAG's model selection results in a situation where placebo is modelled to have a benefit over pembrolizumab for almost the whole time horizon of the model as opposed to capturing treatment waning. DG page 21 – "*This was because the large clinical benefits associated with this population were unexpected, based on a post hoc subgroup and could not be clinically explained*" is a factual inaccuracy. As explained above (DG – page 10) and more extensively under comment 1, the benefits in this subpopulation were as expected. It is the results in the PD-L1≥50% group that are not in line with expectations.

Insert extra rows as needed

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Single technology appraisal

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

Response to the Draft Guidance document Appendix

September 2024

File name	Version	Contains confidential information	Date
NICE ID3907 MSD Response to Draft Guidance document [CON]	1.0	Yes	19/09/2024

Contents

Appendix 1: Clinical Effectiveness results

Clinical effectiveness results for the licensed population

The clinical effectiveness results for the licensed population (Prior Adjuvant Chemotherapy Population) from the protocol-prespecified interim analysis 3 (IA3- database cutoff date of 24-JAN-2023) are presented below.

The median duration of follow-up (defined as the time from randomization to the date of death or the database cut-off date if the participant is still alive) for participants in the Prior Adjuvant Chemotherapy Population was [redacted] months in the pembrolizumab group and [redacted] months in the placebo group. Details of participants' follow-up duration were provided in the submission (Table 16, page 52 of DG Committee Papers [redacted]).

Baseline characteristics

Please note that baseline characteristics for the Prior Adjuvant Chemotherapy population were presented in the submission (Table 11, page 43 of DG Committee Papers [redacted]).

Primary outcome: Disease-free survival (DFS)

In the Prior Adjuvant Chemotherapy Population, the IA3 results demonstrated a clinically meaningful benefit associated with pembrolizumab (median 53.8 months vs 40.5 months; HR: 0.76 [95% CI: 0.64, 0.91]) (Table 1, also available in DG Committee Papers [redacted], page 56). These are overall consistent with the DFS improvements observed in the PD-L1 <50% TPS subpopulation.

Table 1. Analysis of Disease-Free Survival – Prior Adjuvant Chemotherapy Population (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median DFS[a] (Months) (95% CI)	DFS Rate at Month 12 in %[a] (95% CI)	vs. Placebo	
							Hazard Ratio[b] (95% CI)[b]	p-Value[c]
Pembrolizumab	506	225 (44.5)	15754.5	1.4	53.8 (46.2, 70.4)	78.7 (74.8, 82.1)	0.76 (0.64, 0.91)	0.00150
Placebo	504	262 (52.0)	14614.8	1.8	40.5 (32.9, 47.4)	71.0 (66.8, 74.7)	---	---

[a] From product-limit (Kaplan-Meier) method for censored data.

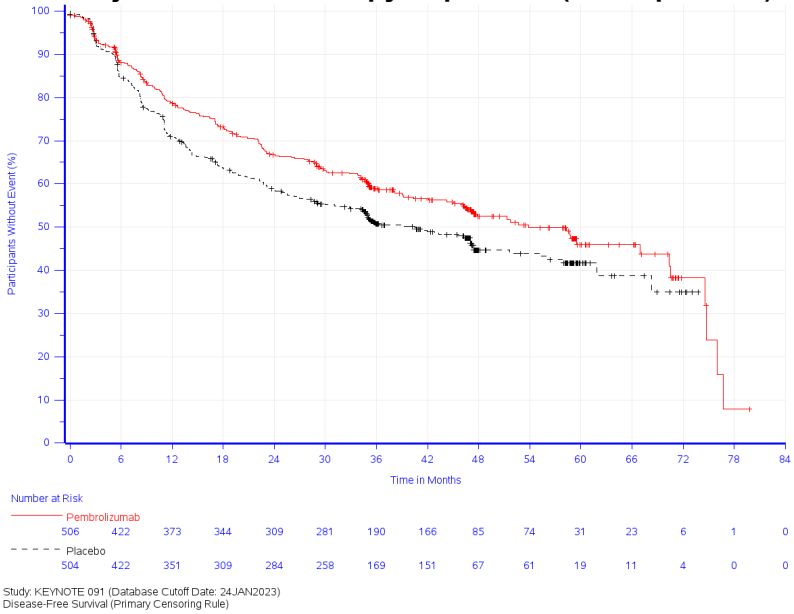
[b] Based on the multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).

[c] One-sided p-value based on the Wald Test in the multivariate Cox regression model.

Database Cutoff Date: 24JAN2023

Source: KEYNOTE-091 EPAR EMEA/H/C/003820/II/0121(1).

Figure 1. Kaplan-Meier Estimates of Disease-Free Survival (Primary Censoring Rule) – Prior Adjuvant Chemotherapy Population (ITT Population)



Source: KEYNOTE-091 EPAR EMEA/H/C/003820/II/0121(1).

The DFS Kaplan-Meier curves separated at approximately Month 6 and remained separated through the period assessed (Figure 1). The separation between the DFS curves remains consistent throughout most of the follow-up period ([redacted]%, [redacted]%, [redacted]% and [redacted]% at 12, 24, 36 and 48 month, respectively), suggesting a sustained treatment effect (Table 2). After 48 months, the heavy censoring (e.g. [redacted] disease-free patients and only 31 at risk at month 60) prevents any reliable conclusions.

Table 2. Summary of DFS Rate Over Time (Primary Censoring Rule) - Prior Adjuvant Chemotherapy Population (ITT Population)

	Pembrolizumab (N=506)	**Placebo (N=504)**
DFS rate at 12 Months in (95% CI)[a]	[redacted]	[redacted]
DFS rate at 18 Months in (95% CI)[a]	[redacted]	[redacted]
DFS rate at 24 Months in (95% CI)[a]	[redacted]	[redacted]
DFS rate at 30 Months in (95% CI)[a]	[redacted]	[redacted]
DFS rate at 36 Months in (95% CI)[a]	[redacted]	[redacted]
DFS rate at 42 Months in (95% CI)[a]	[redacted]	[redacted]
DFS rate at 48 Months in (95% CI)[a]	[redacted]	[redacted]
DFS rate at 54 Months in (95% CI)[a]	[redacted]	[redacted]
DFS rate at 60 Months in (95% CI)[a]	[redacted]	[redacted]
[a] From the product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 24JAN2023		

Source: Data on File. KEYNOTE-091 IA3 Statistical Report(2).

The most common type of first DFS event in both groups was recurrence. Overall, fewer participants in the pembrolizumab group experienced disease recurrence compared with the placebo group (Table 3). The most frequent type of recurrence was distant metastases, which occurred less frequently in the pembrolizumab group, similarly with what was presented for the PD-L1 TPS<50% subpopulation ([redacted]% vs [redacted]% in the pembrolizumab and placebo arm, respectively). The percentage of patients with local and/or regional recurrence was lower in the pembrolizumab group compared to the placebo group, consistently to what was observed in the PD-L1 TPS<50% subpopulation ([redacted]% vs [redacted]% in the pembrolizumab and placebo arm, respectively)

Table 3. Disease Status - Prior Adjuvant Chemotherapy Population (ITT Population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	506		504	
Type of First Event in DFS Analysis				
No event	281	(55.5)	242	(48.0)
Event	225	(44.5)	262	(52.0)
Not disease-free at baseline	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Local and/or regional recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Distant metastasis	[redacted]	[redacted]	[redacted]	[redacted]
Both	[redacted]	[redacted]	[redacted]	[redacted]
New malignancy	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
New malignancy includes the second primary and second malignancies. Database Cutoff Date: 24JAN2023				

Source: Data on File. KEYNOTE-091 IA3 Statistical Report(2).

Secondary outcomes: Overall survival (OS)

In the Prior Adjuvant Chemotherapy Population, 113 (22.3%) and 138 (27.4%) OS events were observed in the pembrolizumab and placebo group, respectively, corresponding to HR of 0.79 [95% CI: 0.62, 1.01]) (Table 4, also available in DG Committee Papers [redacted], page 61).

The median OS was not reached for either treatment group confirming due to the relative early time of the analysis with respect to the OS endpoint (Figure 2). The observed OS rate over time is presented in Table 5.

Table 4. Analysis of Overall Survival – Prior Adjuvant Chemotherapy Population (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS[a] (Months) (95% CI)	OS Rate at Month 12 in %[a] (95% CI)	vs. Placebo	
							Hazard Ratio[b] (95% CI)[b]	p-Value[c]
Pembrolizumab	506	113 (22.3)	22810.0	0.5	Not Reached (., .)	95.6 (93.4, 97.1)	0.79 (0.62, 1.01)	0.03224
Placebo	504	138 (27.4)	22313.1	0.6	Not Reached (., .)	95.0 (92.7, 96.6)	---	---

[a] From product-limit (Kaplan-Meier) method for censored data.

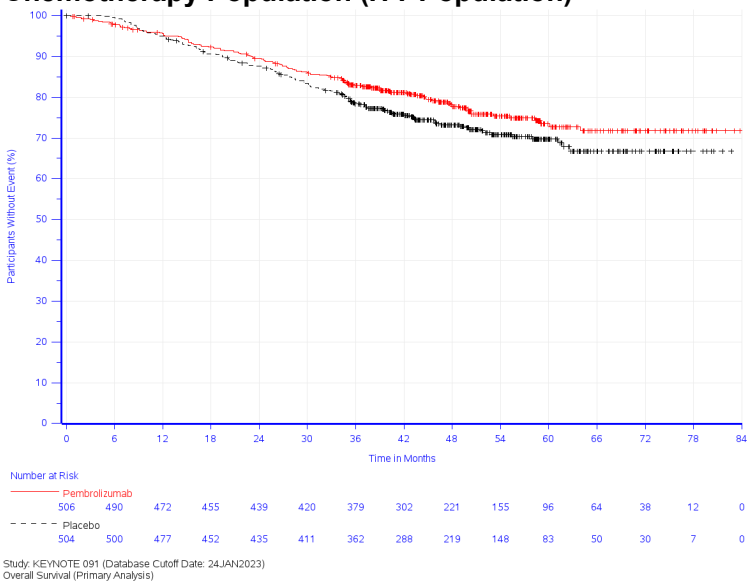
[b] Based on the multivariate Cox regression model with treatment adjusted by the following covariates: stage (IB vs. II vs. IIIA), PD-L1 status (≥50% vs. 1-49% vs. <1%), region (Western Europe vs. Eastern Europe vs. Rest of World vs. Asia), histology (squamous vs. non-squamous), and smoking status (never vs. former/current).

[c] One-sided p-value based on the Wald Test in the multivariate Cox regression model.

Database Cutoff Date: 24JAN2023

Source: KEYNOTE-091 EPAR EMEA/H/C/003820/II/0121(1).

Figure 2. Kaplan-Meier Estimates of Overall Survival (Primary Analysis) - Prior Adjuvant Chemotherapy Population (ITT Population)



Source: KEYNOTE-091 EPAR EMEA/H/C/003820/II/0121(1).

Table 5. Summary of Overall Survival Rate Over Time - Prior Adjuvant Chemotherapy Population (ITT Population)

	Pembrolizumab (N=506)	**Placebo (N=504)**
OS rate at 12 Months in (95% CI)[a]	[redacted]	[redacted]
OS rate at 18 Months in (95% CI)[a]	[redacted]	[redacted]
OS rate at 24 Months in (95% CI)[a]	[redacted]	[redacted]
OS rate at 30 Months in (95% CI)[a]	[redacted]	[redacted]
OS rate at 36 Months in (95% CI)[a]	[redacted]	[redacted]
OS rate at 42 Months in (95% CI)[a]	[redacted]	[redacted]
OS rate at 48 Months in (95% CI)[a]	[redacted]	[redacted]
OS rate at 54 Months in (95% CI)[a]	[redacted]	[redacted]
OS rate at 60 Months in (95% CI)[a]	[redacted]	[redacted]
[a] From the product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 24JAN2023		

Source: Data on File. KEYNOTE-091 IA3 Statistical Report(2).

Appendix 2: DFS survival analysis for the Full Licensed Population

Table 6. Comparison of different parametric functions used to model DFS in the pembrolizumab arm for patients who received adjuvant chemotherapy: Fit with observed data and long-term extrapolations by weighted MSE

Color key:

Predicted survival curve is lower than for placebo when using the same distributions for placebo (excluded from consideration as base case)

a. Approach #1: Parametric models separately fitted to each treatment arm: Pembrolizumab

Rank by MSE *(out of all 67 combinations under approaches 1-3)*	**Parametric functions**		**MSE vs. observed DFS**	**Predicted DFS (%)**						**Predicted OS (%)**					
	DF → LR	**DF → DM**		**4 yrs**	**5 yrs**	**7 yrs**	**10 yrs**	**20 yrs**	**30 yrs**	**4 yrs**	**5 yrs**	**7 yrs**	**10 yrs**	**20 yrs**	**30 yrs**
1	Log-normal	Log-normal	0.0001116	53	47	39	33	19	4	71	64	52	40	19	4
5	Log-logistic	Log-normal	0.0001471	52	46	37	31	18	3	71	64	52	39	18	4
8	Log-normal	Generalized gamma	0.0001567	52	46	37	30	17	3	71	64	51	38	18	3
9	Log-normal	Log-logistic	0.0001578	52	46	37	31	18	3	71	64	51	38	18	4
10	Weibull	Log-normal	0.0001607	52	46	37	29	17	3	71	64	52	38	17	3
11	Generalized gamma	Log-normal	0.0001629	52	46	36	29	17	3	71	64	52	38	17	3
14	Gamma	Log-normal	0.0001637	52	46	36	29	17	3	71	64	52	38	17	3
15	Log-normal	Gompertz	0.0001639	52	47	39	33	19	4	71	64	52	40	19	4
21	Log-normal	Weibull	0.0001784	52	46	36	29	17	3	71	64	51	37	17	3
22	Gompertz	Log-normal	0.0001819	52	46	37	30	17	3	71	64	52	38	18	3
23	Log-normal	Gamma	0.0001912	52	46	36	29	16	3	71	64	51	37	17	3
25	Exponential	Log-normal	0.0002521	52	45	35	28	16	3	71	64	52	37	16	3
26	Log-logistic	Gompertz	0.0002575	51	46	37	31	18	4	71	64	51	39	18	4
27	Log-logistic	Log-logistic	0.0002597	52	45	36	29	16	3	71	64	51	37	17	3
28	Log-logistic	Generalized gamma	0.0002605	52	45	35	28	16	3	71	64	51	37	17	3
30	Weibull	Gompertz	0.0002779	51	45	36	30	17	3	71	64	51	38	17	3
31	Generalized gamma	Gompertz	0.0002811	51	45	36	30	17	3	71	64	51	38	17	3
32	Gamma	Gompertz	0.0002823	51	45	36	29	17	3	71	64	51	38	17	3
33	Weibull	Log-logistic	0.0002865	51	45	35	28	16	3	71	64	51	36	16	3
34	Weibull	Generalized gamma	0.0002884	52	45	35	27	15	3	71	64	51	36	16	3

35	Generalized gamma	Log-logistic	0.0002907	51	45	35	27	15	3	71	64	51	36	16	3
36	Gamma	Log-logistic	0.0002922	51	45	35	27	15	3	71	64	51	36	16	3
37	Generalized gamma	Generalized gamma	0.0002927	52	45	34	27	15	3	71	64	51	36	16	3
38	Gamma	Generalized gamma	0.0002943	52	45	34	27	15	3	71	64	51	36	16	3
39	Log-logistic	Weibull	0.0002991	52	45	35	27	15	3	71	64	51	36	16	3
40	Log-logistic	Gamma	0.0003212	52	45	34	27	15	3	71	64	50	36	16	3
41	Gompertz	Gompertz	0.0003275	51	45	36	30	17	4	71	64	51	38	18	4
42	Gompertz	Log-logistic	0.0003280	51	45	35	28	16	3	71	64	51	37	16	3
43	Gompertz	Generalized gamma	0.0003292	51	45	35	28	16	3	71	64	51	36	16	3
44	Weibull	Weibull	0.0003317	51	45	34	26	15	3	71	64	51	36	15	3
45	Generalized gamma	Weibull	0.0003367	51	45	34	26	15	3	71	64	51	36	15	3
47	Gamma	Weibull	0.0003385	51	45	34	26	15	3	71	64	51	36	15	3
48	Weibull	Gamma	0.0003562	51	45	34	26	15	3	71	64	50	35	15	3
49	Generalized gamma	Gamma	0.0003617	51	45	34	26	14	3	71	64	50	35	15	3
50	Gamma	Gamma	0.0003636	51	45	34	26	14	3	71	64	50	35	15	3
51	Gompertz	Weibull	0.0003748	51	45	34	27	15	3	71	64	51	36	16	3
52	Gompertz	Gamma	0.0004012	51	45	34	27	15	3	71	64	50	35	15	3
53	Exponential	Gompertz	0.0004344	51	45	35	28	16	3	71	64	51	37	16	3
54	Exponential	Log-logistic	0.0004436	51	44	33	26	15	3	71	64	51	36	15	3
55	Exponential	Generalized gamma	0.0004473	51	44	33	26	14	3	71	64	51	36	15	3
56	Log-normal	Exponential	0.0005035	51	44	34	26	14	3	72	64	49	34	15	3
57	Exponential	Weibull	0.0005059	51	44	33	25	14	3	71	64	50	35	14	3
58	Exponential	Gamma	0.0005397	51	44	32	25	14	3	71	64	50	35	14	3
60	Log-logistic	Exponential	0.0007571	51	43	32	24	13	3	72	64	49	33	14	3
61	Weibull	Exponential	0.0008146	51	43	31	23	13	2	72	64	49	33	13	3
62	Generalized gamma	Exponential	0.0008234	51	43	31	23	13	2	72	64	49	33	13	3
63	Gamma	Exponential	0.0008266	51	43	31	23	13	2	72	64	49	33	13	2
64	Gompertz	Exponential	0.0009071	51	43	32	24	13	3	72	64	49	33	14	3
66	Exponential	Exponential	0.0011365	51	43	30	22	12	2	72	64	49	32	13	2

b. Approach #2: Parametric proportional hazards models jointly fitted with a time-constant treatment effect: Pembrolizumab

Rank by MSE *(out of all 67 combinations under approaches 1-3)*	**Parametric functions**		**MSE vs. observed DFS**	**Predicted DFS (%)**						**Predicted OS (%)**					
	DF → LR	**DF → DM**		**4 yrs**	**5 yrs**	**7 yrs**	**10 yrs**	**20 yrs**	**30 yrs**	**4 yrs**	**5 yrs**	**7 yrs**	**10 yrs**	**20 yrs**	**30 yrs**

6	Weibull	Gompertz	0.0001510	52	47	38	32	18	4	70	64	53	40	19	4
17	Gompertz	Gompertz	0.0001667	52	47	41	35	21	4	70	64	53	42	21	4
20	Exponential	Gompertz	0.0001746	52	46	37	31	17	3	70	64	53	40	18	4
24	Gompertz	Weibull	0.0001960	52	46	37	30	17	3	71	64	51	38	17	3
29	Weibull	Weibull	0.0002688	52	45	35	27	15	3	71	64	51	36	16	3
46	Exponential	Weibull	0.0003382	52	45	34	26	15	3	71	64	51	36	15	3
59	Gompertz	Exponential	0.0007301	51	44	33	25	14	3	72	64	49	34	15	3
65	Weibull	Exponential	0.0009474	51	43	31	23	12	2	72	64	49	33	13	2
67	Exponential	Exponential	0.0011365	51	43	30	22	12	2	72	64	49	32	13	2

c. Approach #3: Parametric proportional hazards models jointly fitted with a time-varying treatment effect: Pembrolizumab

Rank by MSE *(out of all 67 combinations under approaches 1-3)*	**Parametric functions**		**MSE vs. observed DFS**	**Predicted DFS (%)**						**Predicted OS (%)**					
	DF → LR	**DF → DM**		**4 yrs**	**5 yrs**	**7 yrs**	**10 yrs**	**20 yrs**	**30 yrs**	**4 yrs**	**5 yrs**	**7 yrs**	**10 yrs**	**20 yrs**	**30 yrs**
2	Weibull	Gompertz	0.0001381	52	47	39	33	19	4	70	64	53	41	19	4
3	Exponential	Gompertz	0.0001386	52	47	39	33	19	4	70	64	53	41	19	4
4	Gompertz	Exponential	0.0001438	52	45	35	28	16	3	71	64	51	36	16	3
7	Gompertz	Weibull	0.0001541	52	46	37	30	17	3	71	64	51	38	17	3
12	Weibull	Weibull	0.0001633	52	46	35	28	16	3	71	64	51	37	16	3
13	Exponential	Weibull	0.0001635	52	46	35	28	16	3	71	64	51	37	16	3
16	Gompertz	Gompertz	0.0001654	52	47	40	35	20	4	70	63	53	42	21	4
18	Exponential	Exponential	0.0001670	52	45	34	26	14	3	71	64	50	35	15	3
19	Weibull	Exponential	0.0001675	52	45	34	26	14	3	71	64	50	35	15	3

Abbreviations: DF, disease-free; DFS, disease-free survival; DM, distant metastases; LR, local-regional recurrence; MSE, mean squared error; OS, overall survival.

Table 7. Comparison of different parametric functions used to model DFS in the placebo arm for patients who received adjuvant chemotherapy: Fit with observed data and long-term extrapolations

Color key:

Predicted survival curve is higher than for pembrolizumab when using the same distributions for pembrolizumab (excluded from consideration as base case)

a. Approach #1: Parametric models separately fitted to each treatment arm: Placebo

Rank by MSE *(out of all 67 combinations under approaches 1-3)*	Parametric functions		MSE vs. observed DFS	Predicted DFS (%)						Predicted OS (%)					
	DF → LR	DF → DM		4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
1	Generalized gamma	Gompertz	0.0001780	46	42	37	33	19	4	68	61	50	39	19	4
2	Generalized gamma	Log-normal	0.0002686	45	40	33	28	16	3	68	61	48	35	16	3
3	Generalized gamma	Generalized gamma	0.0002790	45	40	33	28	16	3	68	60	48	35	16	3
4	Gompertz	Gompertz	0.0002843	46	42	36	32	19	4	68	61	49	38	19	4
5	Log-normal	Gompertz	0.0003096	45	40	34	28	16	3	68	61	49	37	17	3
6	Log-logistic	Gompertz	0.0003698	45	40	33	27	16	3	68	61	49	36	16	3
7	Generalized gamma	Log-logistic	0.0003751	44	39	32	26	15	3	68	60	47	33	15	3
8	Weibull	Gompertz	0.0004056	45	40	32	26	14	3	68	61	49	36	15	3
9	Exponential	Gompertz	0.0004280	45	40	31	25	14	3	68	61	49	35	15	3
10	Gamma	Gompertz	0.0004320	45	40	31	25	14	3	68	61	49	35	15	3
11	Generalized gamma	Weibull	0.0004642	45	39	31	25	15	3	69	60	47	33	15	3
12	Gompertz	Log-normal	0.0005000	45	40	32	27	16	3	68	61	48	34	16	3
13	Gompertz	Generalized gamma	0.0005103	45	40	32	27	16	3	68	61	48	34	16	3
16	Generalized gamma	Gamma	0.0005477	45	39	31	25	14	3	69	61	46	32	14	3
17	Gompertz	Log-logistic	0.0006132	44	39	31	26	15	3	68	60	47	33	15	3
18	Log-normal	Log-normal	0.0006153	44	39	30	24	14	3	69	61	47	33	14	3
19	Log-normal	Generalized gamma	0.0006347	44	38	30	24	14	3	69	61	47	33	14	3
21	Log-logistic	Log-normal	0.0007276	44	38	29	23	13	3	69	61	47	33	14	3
23	Log-logistic	Generalized gamma	0.0007475	44	38	29	23	13	3	69	61	47	32	13	3
24	Gompertz	Weibull	0.0007494	45	39	30	25	14	3	69	61	47	32	14	3
26	Log-normal	Log-logistic	0.0007844	44	38	29	23	13	3	68	60	46	32	13	3
27	Weibull	Log-normal	0.0008160	44	38	28	22	12	2	69	61	47	32	13	2
29	Weibull	Generalized gamma	0.0008366	44	38	28	22	12	2	69	61	47	32	13	2
30	Gompertz	Gamma	0.0008496	45	39	30	24	14	3	69	61	46	32	14	3
31	Exponential	Log-normal	0.0008569	44	38	28	21	12	2	69	61	47	32	13	2
32	Gamma	Log-normal	0.0008637	44	38	28	21	12	2	69	61	47	32	13	2
33	Exponential	Generalized gamma	0.0008787	44	38	28	21	12	2	69	61	47	32	13	2
34	Gamma	Generalized gamma	0.0008858	44	38	28	21	12	2	69	61	47	32	12	2
35	Log-logistic	Log-logistic	0.0009031	43	37	28	22	12	2	68	60	46	31	13	2
36	Log-normal	Weibull	0.0009510	44	38	28	22	12	2	69	61	46	31	13	2
37	Weibull	Log-logistic	0.0009920	44	37	27	21	11	2	69	60	46	31	12	2

39	Exponential	Log-logistic	0.0010406	44	37	27	20	11	2	69	60	46	31	12	2
40	Gamma	Log-logistic	0.0010488	44	37	27	20	11	2	69	60	46	31	12	2
41	Log-normal	Gamma	0.0010870	44	37	28	21	12	2	69	61	46	31	12	2
42	Log-logistic	Weibull	0.0010881	44	37	27	21	12	2	69	61	46	31	12	2
44	Weibull	Weibull	0.0012038	44	37	27	20	11	2	69	61	46	30	12	2
45	Log-logistic	Gamma	0.0012320	44	37	27	20	11	2	69	61	46	30	12	2
46	Exponential	Weibull	0.0012596	44	37	26	19	11	2	69	61	46	30	11	2
48	Gamma	Weibull	0.0012689	44	37	26	19	11	2	69	61	46	30	11	2
49	Weibull	Gamma	0.0013617	44	37	26	19	11	2	69	61	46	30	11	2
50	Exponential	Gamma	0.0014239	44	37	26	19	10	2	69	61	46	30	11	2
51	Gamma	Gamma	0.0014342	44	37	26	19	10	2	69	61	46	30	11	2
55	Generalized gamma	Exponential	0.0018868	43	36	26	19	10	2	69	60	44	27	11	2
56	Gompertz	Exponential	0.0021085	43	35	25	18	10	2	69	60	44	27	11	2
59	Log-normal	Exponential	0.0027897	42	34	23	16	9	2	70	60	43	26	9	2
61	Log-logistic	Exponential	0.0029301	42	34	22	16	8	2	70	60	43	26	9	2
62	Weibull	Exponential	0.0030995	42	34	22	15	8	1	70	60	43	26	8	2
63	Exponential	Exponential	0.0032239	42	34	22	14	8	1	70	60	43	26	8	1
66	Gamma	Exponential	0.0032448	42	34	21	14	8	1	70	60	43	26	8	1

b. Approach #2: Parametric proportional hazards models jointly fitted with a time-constant treatment effect: Placebo

Rank by MSE *(out of all 67 combinations under approaches 1-3)*	**Parametric functions**		**MSE vs. observed DFS**	**Predicted DFS (%)**						**Predicted OS (%)**					
	DF → LR	**DF → DM**		**4 yrs**	**5 yrs**	**7 yrs**	**10 yrs**	**20 yrs**	**30 yrs**	**4 yrs**	**5 yrs**	**7 yrs**	**10 yrs**	**20 yrs**	**30 yrs**
14	Gompertz	Gompertz	0.0005235	44	40	33	28	16	3	68	60	48	36	17	3
20	Weibull	Gompertz	0.0006843	44	39	30	25	14	3	68	61	48	34	15	3
28	Exponential	Gompertz	0.0008241	44	38	30	23	13	3	68	61	48	34	14	3
38	Gompertz	Weibull	0.0010033	44	38	28	22	13	3	69	61	46	31	13	3
47	Weibull	Weibull	0.0012661	44	37	26	20	11	2	69	61	46	30	11	2
52	Exponential	Weibull	0.0014583	44	36	26	19	10	2	69	61	46	30	11	2
57	Gompertz	Exponential	0.0024140	42	35	24	17	10	2	70	60	43	27	10	2
60	Weibull	Exponential	0.0028595	42	34	22	15	8	1	70	60	43	26	9	2
64	Exponential	Exponential	0.0032239	42	34	22	14	8	1	70	60	43	26	8	1

c. Approach #3: Parametric proportional hazards models jointly fitted with a time-varying treatment effect: Placebo

Rank by MSE *(out of all 67 combinations under approaches 1-3)*	**Parametric functions**		**MSE vs. observed DFS**	**Predicted DFS (%)**						**Predicted OS (%)**					
	DF → LR	**DF → DM**		**4 yrs**	**5 yrs**	**7 yrs**	**10 yrs**	**20 yrs**	**30 yrs**	**4 yrs**	**5 yrs**	**7 yrs**	**10 yrs**	**20 yrs**	**30 yrs**
15	Gompertz	Gompertz	0.0005444	44	39	32	27	16	3	68	61	48	35	16	3
22	Exponential	Gompertz	0.0007436	44	38	30	24	13	3	68	61	48	34	14	3
25	Weibull	Gompertz	0.0007527	44	38	30	24	13	3	68	61	48	34	14	3
43	Gompertz	Weibull	0.0011440	44	37	28	21	12	2	69	61	46	31	12	2
53	Exponential	Weibull	0.0014717	44	36	26	19	10	2	69	61	46	29	11	2
54	Weibull	Weibull	0.0014853	44	36	25	19	10	2	69	61	46	29	11	2
58	Gompertz	Exponential	0.0026572	42	35	23	17	9	2	70	60	43	26	10	2
65	Exponential	Exponential	0.0032239	42	34	22	14	8	1	70	60	43	26	8	1
67	Weibull	Exponential	0.0032484	42	34	21	14	8	1	70	60	43	26	8	1

Abbreviations: DF, disease-free; DFS, disease-free survival; DM, distant metastases; LR, local-regional recurrence; MSE, mean squared error; OS, overall survival.

Appendix 3: Subsequent treatment market shares

Table 8. Subsequent treatment market shares by I/O eligibility status and adjuvant treatment arm – Prior Adjuvant Chemotherapy Population (full licensed population)

	Pembrolizumab		**Active monitoring**
First line:	**I/O-eligible (1L)**	**I/O-ineligible (1L)**	**I/O-eligible (1L)**
Pembrolizumab	19.1%	0%	19.1%
Atezolizumab	4.8%	0%	4.8%
Osimertinib	15%	15%	15%
Pembrolizumab + carboplatin + paclitaxel	29.8%	0%	29.8%
Pembrolizumab + pemetrexed + platinum	31.3%	0%	31.3%
Platinum-doublet chemotherapy (PDC)	0%	85%	0%
Second line:	**IO-eligible (2L)**	**IO-ineligible (2L)**	**IO-eligible (2L)**
Docetaxel	30%	30%	30%
Pemetrexed + platinum	30%	30%	30%
No active treatment (BSC)	40%	40%	40%

[redacted]

Appendix 4: New sensitivity analyses programmed into the model

The company has programmed the following new sensitivity analyses into the model:-

- Treatment effect waning on DFS:

  The economic model includes the ability to implement a more rapid treatment effect waning on the DFS curve for the pembrolizumab arm. When applied, the cause-specific hazards of transitions originating from the DF state in the pembrolizumab arm will linearly converge to those in the routine surveillance arm, with a user-modifiable time point for the initiation and completion of the attenuation. Past the selected complete attenuation time-point, the transition probabilities from the DF state in the pembrolizumab arm will match those from the routine surveillance arm from the DF health state. If the transition probability is lower in the placebo arm, the transition probability in the pembrolizumab arm will be left unchanged. This prevents the treatment waning function from positively impacting the survival extrapolations for the adjuvant treatment, in cases where transition probabilities from the DF state are lower in the placebo arm than in the adjuvant treatment arm during certain cycles. Switch is on the Specifications tab.

- Cure rate on LR state:

  The model includes the functionality to apply a cure assumption in the LR health state for both arms. Upon applying the cure assumption, the per-cycle risks of DM from the LR state (as estimated under the scenario with no cure assumption) are reduced by the user-specified percentage for patients in the LR health state during the selected time point. The same percentage per-cycle risk reduction is also applied to the transitions rates from LR to death, subject to the constraint that this risk is always at least as high as the background mortality in each cycle. The model allows for user-modifiable time points, for when the reduction in risk to initiate and complete attenuation. Due to the memoryless property of the Markov model, the per-cycle risk reduction are applied to all patients the LR health state within the selected time point, including newly entered patients and remaining patients from previous cycles. Switch is on the specifications tab.

Appendix 5: Disaggregated model results for the Full Licensed Population (FLP)

Costs (£)	Pembrolizumab	Placebo	Incremental (Pembrolizumab vs. Placebo)
Costs, total and by category	[redacted]	[redacted]	[redacted]
Adjuvant treatment costs	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Subsequent treatment costs in LR state	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Radiotherapy costs	[redacted]	[redacted]	[redacted]
Salvage surgery costs	[redacted]	[redacted]	[redacted]
Subsequent treatment costs in DM state	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
Terminal care costs	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
Costs, total and by state	[redacted]	[redacted]	[redacted]

Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
Death (one-time terminal care costs)	[redacted]	[redacted]	[redacted]

Effectiveness

Quality-adjusted life years (QALYs), total and by state	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]
AE-related disutility	[redacted]	[redacted]	[redacted]
Age-related disutility	[redacted]	[redacted]	[redacted]
Life years (LYs), total and by state	[redacted]	[redacted]	[redacted]
Disease-free	[redacted]	[redacted]	[redacted]
Local-regional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]

Incremental outcomes (adjuvant pembrolizumab vs. comparator)

Incremental costs (£)	[redacted]	[redacted]	[redacted]
Incremental QALYs	[redacted]	[redacted]	[redacted]
Incremental LYs	[redacted]	[redacted]	[redacted]
Incremental costs per QALY gained	[redacted]	[redacted]	[redacted]
Incremental costs per LY gained	[redacted]	[redacted]	[redacted]

References

1. European Medicines Agency (EMA). EMEA/H/C/003820/II/0121. Keytruda European Public Assessment Report (EPAR). Available from: https://www.ema.europa.eu/documents/variation-report/keytruda-h-c-003820-ii-0121-epar-assessment-report-variation_en.pdf. . 2023.
2. MSD. Data on File. KEYNOTE-091 IA3 Statistical Report.

Response to the National Institute for Health and Care Excellence's Draft Guidance Consultation Document - Pembrolizumab for adjuvant treatment of resected non small cell lung cancer. [ID 3907]

This response is submitted by Roy Castle Lung Cancer Foundation.

- We are disappointed that the Committee's preliminary decision is not to recommend Pembrolizumab in this indication.

- We welcome the Committee's conclusion in 3.1, that there is an unmet need for treatment that reduces the risk of recurrence after complete resection, in this patient group.

- We note that the company has made submission, in the adjuvant setting, after surgery and chemotherapy, for those non small cell lung cancer patients, with PD-L1 TPS< 50%. It should be noted that no other immunotherapy agent is available for this patient group.

- We understand the complexities of this appraisal

    - The company submission in a narrower patient population, than the study and the licenced indication.
      [From a patient perspective, as noted in 3.4, the PD-L1 TPS>50% group, would have the potential advantage of Pembrolizumab being given 6 weekly, rather than 3 / 4 weekly (as with Atezolizumab, available in this indication, via the CDF)].
    - The KEYNOTE-091 study showing poorer results for the PD-L1 TPS> 50% patient group, as compared with those in the PD-L1 TPS< 50% patient group. We would, of course normally expect to see a greater effect in those with higher expression.

- However, we would highlight the trial evidence of clinical benefit (section 3.3), found in the PD-L1 TPS<50% patient group and in the trial study population overall. Delaying or reducing the risk of recurrence in this patient group is of vital and obvious importance. Once the cancer has recurred, potentially curative treatment is no longer an option.

- We, therefore, urge the Committee to reconsider their decision.

[redacted]

Roy Castle Lung Cancer Foundation
September 2024

NICE National Institute for Health and Care Excellence

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 19 September. Please submit via NICE Docs.

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

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NICE National Institute for Health and Care Excellence

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Yes diamond funding BTOG annual conference April 2024 £60,000+ VAT
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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NICE National Institute for Health and Care Excellence

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 19 September. Please submit via NICE Docs.

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	*Has all of the relevant evidence been taken into account?* REPLY: PDL1 <1%, 1-50% and >50% were stratification factors in the KN091 trial and appear in all the Forest plots presenting results. The population of <50% in the KN091 trial is now referred to in this document as the 'narrower' population and yet this population accounts for 726 of the 1177 randomised patients in this trial. The use of the word 'narrower' and 'smaller' leads the reader to think that this is a small subpopulation of the trial and that this subgroup could not have statistical power to show a difference between pembrolizumab or placebo, and the continued use of this word is thus misleading and biases the reader. e.g The committee states: *It explained that **the smaller** sample size of this post hoc subgroup, which was a subpopulation of the prespecified population (see section 3.3)* The committee states *This is narrower than the population it is licensed for. Usual treatment for people in this narrower population (i.e. the <50%) is active monitoring.' In*correct, as pembrolizumab is licensed and FDA approved for all PDL1 subgroups, and atezolizumab is licensed and FDA approved, for all patients with PDL1>1%. The CDF approval for atezolizumab in the UK is only for >50%. This evidence has not been taken into account and again this sentence is misleading to an uninformed reader. The relevant evidence on the biomarker (PDL1) that was used in the trial design did not give appropriate weight to the fact that the use of PDL1 in operable disease was an extrapolation from the advanced disease PDL1 experience. There is both an unmet need in patients who have had surgery and need adjuvant chemotherapy and are PDL1 <50%. There is a danger that some patients with operable disease, PDL1 <50%, who, rather than going straight to surgery will be given neoadjuvant chemotherapy and immunotherapy (TA876) or perioperative (both neoadjuvant and adjuvant) treatment with a risk of overtreatment with resulting toxicities. The UNMET need is also the patient – often now picked up on screening, who has a small tumour, thus initial surgery is the standard of care. After careful staging and postoperatively the pathology of the tumour may suggest a higher stage and fits the criteria for adjuvant chemotherapy. If PDL1 <50% - an arbitrary cut off, currently these patients receive no further treatment until relapse. These are real clinical situations and day to day cases in an MDT.
2	*Has all of the relevant evidence been taken into account?* I believe all the relevant nuances of the data and how the market is being carved up were not considered to provide the best interpretation of the data available. The reporting and dissection of current adjuvant therapy and the interpretation of the Impower 010 trial was not reviewed in the context of how and why MSD presented only data for the <50% PDL1 expression patients.

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Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 19 September. Please submit via NICE Docs.

	MSD have the positive experience of recently going to the FDA and getting approval on the basis of a subgroup of the whole trial – the subgroup who had adjuvant chemotherapy. This was not a primary endpoint, **but was a stratification factor, PDL1 was also a stratification factor**. This is now the licensed population for pembrolizumab – all patients must have at least one cycle of adjuvant chemotherapy and does not include mention of PDL1. MSD believed I imagine, that if they presented the whole trial to UK NICE that the PDL1 high subgroup (451 patient out of 1177) would have dominated the discussion – and this is the subgroup with already an approved treatment in the UK (atezolizumab TA 823). It is unfortunate that a non significant small subgroup is dominating the discussion of a larger significant subgroup. The primary endpoint of the Impower 010 trial and FDA approval of atezolizumab is for all patients with PDL1>1%. In their hierarchically testing for the primary endpoint, PDL1>50% was not part of the analysis. PDL1 >50% was a secondary endpoint. The CDF has approved atezolizumab for the subgroup of PDL1>50% which was significant but not the primary endpoint. MSD have had FDA approval for the subgroup of the whole trial who received chemotherapy, irrespective of PDL1 status. Thus I think MSD must have believed that the most relevant data for the UK, would be that data which addresses the unmet need – and indeed this is what clinicians have been expecting – that all patients in the adjuvant setting irrespective of PDL1 status would have access to one immunotherapy drug – as the 2 trials are overall so large and so similar in size and patient characteristics. Like for the Impower 010 assessment, PFS in Keynote 091 is mature and OS is also significant now. The EAG in one sentence imply this was *the smallest subgroup and that the data analysis was data driven rather than biological plausibility*. So again this was not the smallest subgroup of the trial and yes clinicians believe that it is biological plausibility that pembrolizumab and atezolizumab are active in all subgroups. It is mentioned that MSD should have presented the whole trial or the dataset they presented to the FDA. It is a shame that the review progressed this far to NOT get to the point of being considered strong enough for an economic evaluation that would be meaningful. While NICE is quick to use a cut of >/<50% PDL1 – this is by extrapolating from the significance of this cut in advanced stage NSCLC trials, other things that we have learned from the use of immunotherapy in metastatic disease was not considered. For example in advanced disease, we have all seen responses, independent of actual PDL1 expression rates – responses and outcomes are improved in the reported trials, even in PDL1 negative subgroups. In general PDL1 is seen as a biomarker that can be heterogenous and there can have mixed expression rates and difference in results with antibodies used within the same tissue sample. We believe that given the overall results of both Impower 010 and Keynote 091, that both these drugs are active in the adjuvant setting for NSCLC.

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3	*Are the recommendations sound and a suitable basis for guidance to the NHS?* REPLY: The recommendations do not appear balanced in the review of the 2 large trials. The Impower 010 trial data on 229 patients with PDL1>50% out of the total 1005 patients randomised was approved for the UK and is on the CDF on the basis of a secondary endpoint. MSD presented their data on what they considered relevant for the unmet need in the UK of 726 patients with PDL1<50% of the 1177 randomised – and yet NICE considered this data as not enough as it was an ad hoc analysis in the trial design – although it was a stratification factor and therefore normally results are reported and presented at some point.
4	*Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?* Reply: The committee believed that increasing AGE was an issue. *The EAG was also concerned that age may be a treatment effect modifier.* None of the 2 adjuvant trials (Impower 010 and Keynote 091) show age to be a prognostic factor for lack of treatment effect or toxicity and again a bigger body of data from the advanced disease trials does not hold up age an independent factor for withholding immunotherapy on the basis of efficacy or toxicty.
5	*Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* With more patients presenting with early stage lung cancer through screening, we expect average age to go down over the next 5 years. The summaries of clinical and cost effectiveness have to be respected and accepted as done by specialists in the field. But it is surprising that so many experts can come up with varying results. It would be a shame that the influx of early stage disease patients, though screening, might miss out on an adjuvant therapy that would prolong their working life or good health life even more.

Insert extra rows as needed

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EAG response to stakeholder feedback

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135657.

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1 Introduction

The National Institute for Health and Care Excellence (NICE) undertook stakeholder engagement due to concerns around the company's positioning of pembrolizumab for adults whose tumours have PD-L1 biomarker expression on less than 50% of their tumour cells. This is a narrower population than its marketing authorisation. There were also concerns expressed by the committee on baseline age in the trial informing the company's model being lower compared to the population in current NHS practice. In addition, the committee believed there was significant uncertainty in the model and certain additional aspects required further exploration such as treatment waning and alternate ways to model post recurrence mortality. In addition, the committee suggested the model did not capture the additional mortality faced by disease-free patients compared to general population.

In response to stakeholder engagement, responses were received from Roy Castle Lung Cancer Foundation, the British Thoracic Oncology Group and MSD UK (the marketing company for pembrolizumab).

This report contains the External Assessment Group (EAG) critique of the responses to stakeholder engagement and updated EAG cost-effectiveness analyses. It should be noted that some of the data provided in the response by the company were marked as commercial-in-confidence, and the EAG critique of these data is provided in a confidential appendix.

2 Clinical effectiveness

2.1 Trial results versus expectation

The company state that the fact that PD-L1 TPS <1% and 1-49% were prespecified subgroups, and stratification factors in the KEYNOTE-091 trial[1], strengthens the validity of these results and decreases the possibility that the results of the PD-L1 <50% subgroup that combines these two subgroups were due to chance. As previously addressed in the EAG report, the EAG acknowledges the prespecified subgroups and stratification factors strengthens the validity of their results compared to if these had not been prespecified but notes that the KEYNOTE-091 trial was powered to detect a difference in DFS in the overall trial population and in the PD-L1 ≥50% subgroup. No a priori power calculation was undertaken for the PD-L1 <50% subgroup and so the results for this subgroup are inherently more subject to bias compared to the populations the trial was appropriately powered to assess. In addition, as discussed in Section 2.3. the possibility of the results being due to chance cannot be entirely ruled out and the choice to focus on the PD-L1 TPS <50% subgroup may have been data-driven regardless of the validity of the results. Within this framework, the company highlights that results between the different PD-L1 subgroups and the overall (Prior Adjuvant Chemotherapy) population, i.e. the full licensed population, referred to as FLP henceforward, are consistent suggesting they are unlikely to be due to chance. The EAG notes these results show DFS HRs were consistent irrespectively of PD-L1 expression, with no robust evidence demonstrating a significant difference between the individual categories and the FLP.

Table 1. DFS by PD-L1 subgroups – IA3 (adapted from company DG response, Table 1)

PD-L1 Subgroup	DFS HR (95% CI)
Overall (Prior Adjuvant Chemotherapy)	0.76 (0.64 to 0.91)
<50%	0.72 (0.58 to 0.89)
1-49%	0.70 (0.51 to 0.96)
<1%	0.75 (0.56 to 0.99)

To support its assertion that the unexpected clinical findings for the PD-L1 ≥50% subgroup of the KEYNOTE-091 trial were due to an ''overperforming'' control arm within this subgroup, the company compared the median DFS of the placebo group in the PD-L1 ≥50% subgroup with that of the placebo groups of other PD-L1 expression subgroups of the KEYNOTE-091 trial (<50% and <1-49%) as well as with the placebo groups of the equivalent PD-L1 expression subgroups in the Impower010 trial[2] (≥50% and <1-49%) across multiple time points. This showed the median DFS in the PD-L1 ≥50%

placebo group in KEYNOTE-091 was approximately 2 years longer compared to the placebo groups in other trials (Table 2 in the company's DG response). The company emphasised the DFS HR for the PD-L1 TPS ≥50% group (0.83) being substantially higher than the target DFS HR in this subgroup (0.55) and the DFS in this subgroup being substantially better than any other PD-L1 subgroups across multiple time points (Figure 2 and Table 3 in the company's DG response), indicated findings for the PD-L1 ≥50% group were against clinical expectations. The EAG notes that its EAG report appropriately covers this issue raised by the company. The EAG considers the evidence presented by the company does not conclusively demonstrate an "overperformance" of the placebo group in KEYNOTE-091. As acknowledged by the company in response to clarification questions, the possibility of the difference in the results of the PD-L1 ≥50% placebo group and other placebo groups could be due to an imbalance in unobserved and hence unknown factors such as molecular biomarkers. The EAG considers that naïve comparisons between trials should be treated with caution.

The company reported that in a meta-analysis of 50 studies (24 of which were in NSCLC), PD-L1 was shown to be a negative prognostic factor as increased PDL-1 expression was associated with poor prognosis in early-stage NSCLC (I-III).[3] The EAG notes that statistically significant results were only found for TNM stage subgroup analyses and there was uncertainty around the effect estimate. The EAG also notes that as highlighted by the company, there was no statistically significant effect in advanced stage (stage IV), thus no definitive conclusion on PD-L1 being a negative prognostic factor for NSCLC can be drawn based on this evidence. In addition, the EAG notes that in the subgroup analyses by TNM stage I-III for which statistically significant results were found, not all studies included focused on NSCLC while limitations in the included studies such as the variability in cut-off values for PD-L1 expression used among studies may limit the reliability of the findings.

Finally, the company reported that due to its smaller size (compared to the overall trial population and the PD-L1 <50% subgroup), the PD-L1 ≥50% subgroup of the KEYNOTE-091 trial is at greater risk of sampling bias. Specifically, the company notes that there is a risk that the subgroup contains a larger proportion of patients who may have been cured by their radical treatment plan prior to randomisation compared to larger samples, such as the FLP or the PD-L1 <50% subgroup, and that this could explain the results within the PD-L1 ≥50% subgroup. The EAG notes that one of the stratification factors for KEYNOTE-091 was PD-L1 TPS (<1% vs 1–49% vs ≥50%), and as such, randomisation should have ensured that the pembrolizumab and placebo groups had balanced populations at the beginning of the trial. If the company's assertion that more patients in the

placebo group of the PD-L1 ≥50% subgroup had received a definitive cure due to surgery prior to randomisation is true, then it seems likely that the same would also be true for the pembrolizumab group of the PD-L1 ≥50% subgroup. This would likely have a limited impact on any estimated relative difference between the two groups, as assessed by a DFS HR. However, if the company is asserting that the ITT population was appropriately randomised but "by chance" more patients who had received definitive cure due to surgery prior to randomisation were disproportionately allocated to the placebo group of the PD-L1 ≥50% subgroup, then this would result in disproportionately fewer patients who had a definitive cure due to surgery being allocated to the PD-L1 <50% subgroup. The overall result of this would be an "overperformance" of the placebo group in the PD-L1 ≥50% subgroup and an "underperformance" of the placebo group in the PD-L1 <50% subgroup; i.e. compared to placebo, pembrolizumab would have a reduced HR for DFS in the PD-L1 ≥50% and an improved HR for DFS in the PD-L1 <50% subgroup. In this situation, the EAG considers it likely that the ITT population may be the only robust estimate of DFS available from the trial.

2.2 Selection of the PD-L1 <50% subgroup

The company highlights its choice to exclude the PD-L1 ≥50% subgroup and seek approval in people with PD-L1 <50% was driven by its intent to increase the certainty and applicability of the cost-effectiveness to UK clinical practice which would be compromised by the unexpected and unexplained results of the former subgroup. The EAG notes the company's rationale for focusing on the PD-L1 <50% subgroup being their aim to exclude the subgroup with 'unexpected and unexplained' results rather than selecting the PD-L1 <50% based on observed data, highlights that the company's choice was not driven by findings with biological or clinical plausibility.

In addition, the company emphasised the unmet need for treatment in the PD-L1 ≥50% subgroup is lower due to other effective treatment options currently being used in clinical practice. However, the EAG notes that while atezolizumab is available via the CDF for people with PD-L1 TPS 50% or more, there are no routinely commissioned treatments available for this subgroup. The EAG also notes that the Roy Castle Lung Cancer Foundation highlighted a potential advantage for patients with PD-L1 TPS >50% being treated with pembrolizumab 6 weekly instead of 3 or 4 weekly with atezolizumab. The EAG notes that with both pembrolizumab and atezolizumab being administered intravenously, the less frequent administration of pembrolizumab has the potential to reduce the demand for intravenous therapy services in hospitals. Moreover, the British Thoracic Oncology Group considered the PD-L1 <50% TPS to be an arbitrary cut-off, emphasising that the Marketing

Authorisation population (i.e. the FLP in KEYNOTE-091) is considered eligible for chemotherapy irrespectively of PD-L1 expression further highlighting an unmet need in the FLP.

2.3 Sample size of the PDL-1 <50% subgroup

The company emphasises that the PD-L1 <50% subgroup (n=726) from KEYNOTE-091 accounts for 72% of the KETNOTE-091 trial's FLP (n=1,010). The results of the FLP are the basis for the Marketing Authorisation for pembrolizumab and the company considers that since the PD-L1 <50% subgroup includes a large proportion of the population upon which the MHRA based its decision, it is a robust subgroup. In addition, the company asserts it should be considered adequately large, particularly within the context of oncology treatments appraised by NICE.

The EAG notes, that while the sample of the PD-L1 <50% subgroup is "relatively large", it is still smaller than the original sample upon which the study was powered and was not subject to an *a priori* power calculation. Thus, results for the subgroup are likely to be less robust compared to results from an appropriately powered *a priori* subgroup. While the EAG agrees that the results in this subgroup may be valid, there is a risk that they are due to chance and so it is possible that the company's choice to seek approval in this subgroup may have been data-driven (regardless of the findings being due to chance or not).

2.4 Clinical effectiveness results for the full licensed population

In response to the committee's requests, the company provided the results for the FLP (Prior Adjuvant Chemotherapy Population) from the protocol-prespecified interim analysis 3 (IA3 – database cut-off date of 24-JAN-2023). The EAG notes that the median DFS in IA3 results in the FLP was 53.8 months (95% CI: 46.2 to 70.4) in the pembrolizumab group and 40.5 months (95% CI: 32.9 to 47.4) in the placebo group. Median DFS was 13.3 months longer in the pembrolizumab group compared to the placebo group, with 225 (44.5%) and 262 (52%) DFS events occurring in each group respectively. This corresponded to a 24% relative reduction in the risk of disease recurrence or death with pembrolizumab compared to placebo (HR: 0.76, 95% CI: 0.64 to 0.91).

The EAG notes, the results of the FLP were consistent with the DFS improvements shown for the PD-L1 <50% TPS subgroup. Similarly to the PD-L1<50% subgroup, the most common type of first DFS event in both treatment groups of the FLP was recurrence with the most frequent type of recurrence being distant metastases. In line with what was observed in the PD-L1<50% subgroup, in the FLP

fewer participants in the pembrolizumab group experienced disease recurrence, distant metastases and local/regional recurrence compared to placebo.

In terms of overall survival (OS), in the FLP there were fewer deaths in in the pembrolizumab group (113 [22.3%]) compared to the placebo group (138 [27.4%]) that corresponded to HR of 0.79 (95% CI: 0.62 to 1.01). The EAG notes that as for PD-L1 <50%, the median OS for the FLP was not reached for either treatment group, highlighting the immaturity of the OS data due to the relative early time of the analysis.

2.5 Conclusions of the clinical effectiveness evidence

The EAG considers that a definitive conclusion about the findings of KEYNOTE-091 being due to an overperforming control arm in the PD-L1 TPS ≥50% subgroup cannot be drawn based on the evidence presented by the company and comparisons between the control arm of the PD-L1 TPS ≥50% subgroup and control arms from other trials should be treated with caution. In addition, the meta-analysis cited by the company does not provide any conclusive evidence of PD-L1 being a negative prognostic factor to support the company's assertion that the placebo group in the PD-L1 ≥50% subgroup performed better than expected. The EAG also notes that the risk of sampling bias in the PD-L1 ≥50% subgroup being larger compared to the larger subgroups of KEYNOTE-091 cannot explain the differential trial results for the placebo group in that subgroup, as PD-L1 TPS was a stratification factor and randomisation should have resulted in balanced populations between pembrolizumab and placebo. Any substantial impact on the treatment effect due to sampling bias and the disproportionate allocation of patients cured prior to randomisation in the placebo group of the PD-L1 ≥50% subgroup, would suggest a wider issue relating to the randomisation of the trial and would have resulted in disproportionately fewer patients being allocated in the PD-L1 <50% subgroup, which in turn would result in the underperformance of the placebo group in that subgroup.

The EAG agrees that PD-L1 TPS <1% and 1-49% being prespecified subgroups and stratification factors in the KEYNOTE-091 trial increases the validity of the results of the PD-L1 <50% subgroup that encompasses them. However, the EAG recommends caution in the interpretation of the results as PD-L1 TPS <50% had not been a prespecified efficacy population and while its sample size is not "small", it is smaller than that used in the a priori power calculation undertaken for the ITT population of KETNOTE-091 and hence its results are inherently more subject to bias.

The EAG notes the results for the FLP and PD-L1 <50% subgroup and the FLP were overall consistent, with improvements achieved by pembrolizumab in terms of DFS and OS. In conclusion, the EAG notes that although the risk of findings in the PD-L1 <50% subgroup being due to chance is low, it cannot be entirely ruled out and considering this was not a prespecified subgroup and the lack of sufficient evidence to provide a biological explanation for the findings, its selection may have been data-driven.

3 Cost effectiveness

3.1 Comment 4. Treatment effect waning

The company state that their version of the model already incorporates treatment waning due to the natural convergence of hazards for both placebo and pembrolizumab to 1 after the cure-point. The company state there is no modelled benefit for pembrolizumab following this point, although this is likely only referring to hazard benefit as pembrolizumab retains significant DFS benefit for the total time horizon following 7 years as can be shown in Figure 2 and Figure 1. If the time horizon is changed to 7 years, the incremental QALY benefit for pembrolizumab is more than halved in both the full licensed population (FLP) and PD-L1 <50% subgroup populations.

Figure 1. Modelled and observed DFS time horizon company base case (PD-L1 <50% subgroup)

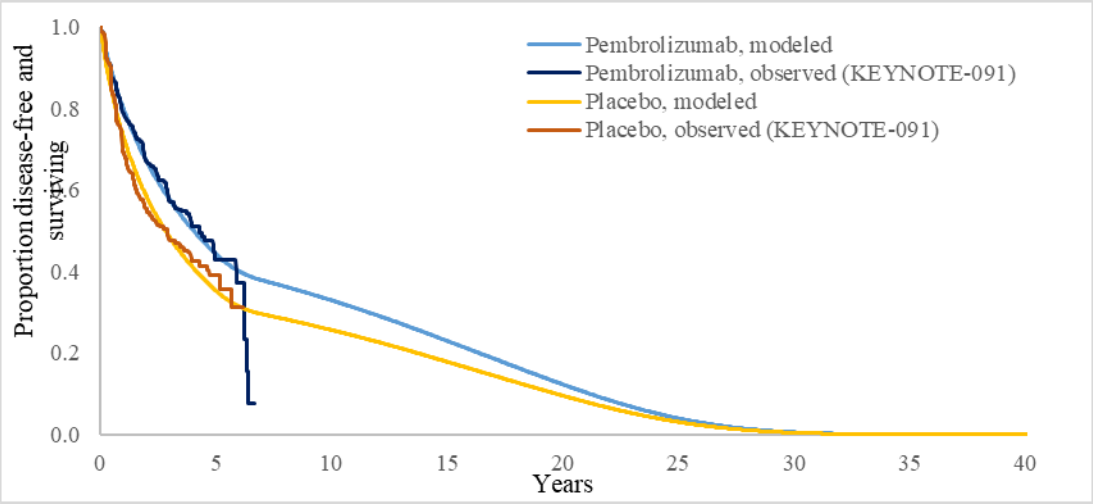
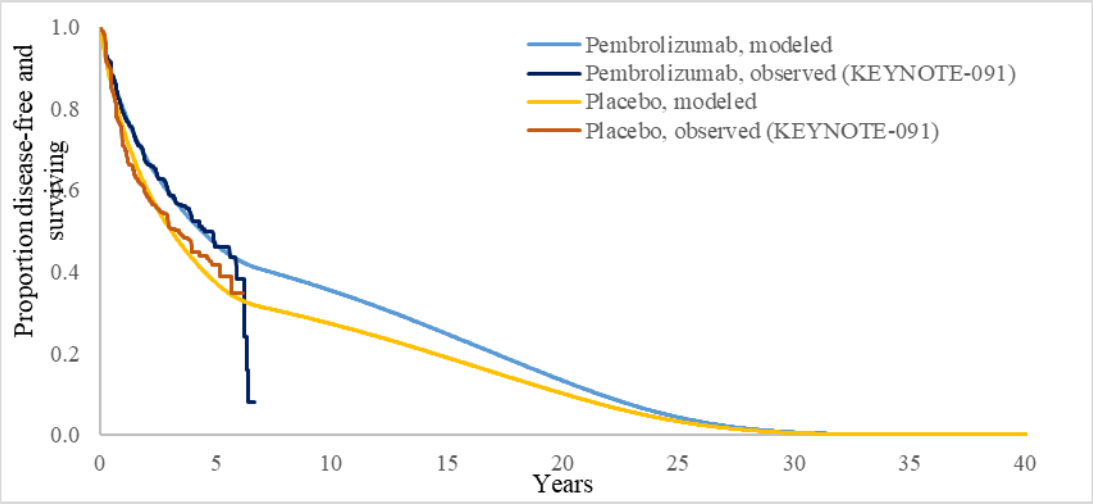


Figure 2. Modelled and observed DFS time horizon company base case (Full licenced population)



The company has implemented a manual waning solution that involves equalising the pembrolizumab hazards with that of placebo. This only effects patients in the pembrolizumab arm. It should be noted that waning itself is not the issue but was proposed by the EAG at ACM 1 as a solution to the problem of the company base case parametric curves providing a poor fit for the KM data towards the end of the trial period, particularly in the placebo arm.

As previously illustrated, a significant portion of the benefit for pembrolizumab comes from projections of DFS post-trial, therefore a poor fit to data towards the end of the trial period has a significant impact on cost-effectiveness. This can be seen in Figure 3. This then results in a subsequent impact on OS as can be seen in Figure 4 (the area that does not appear to fit the data has been circled)

Figure 3. Modelled and observed DFS 7 years company base case (PD-L1<50% subgroup)

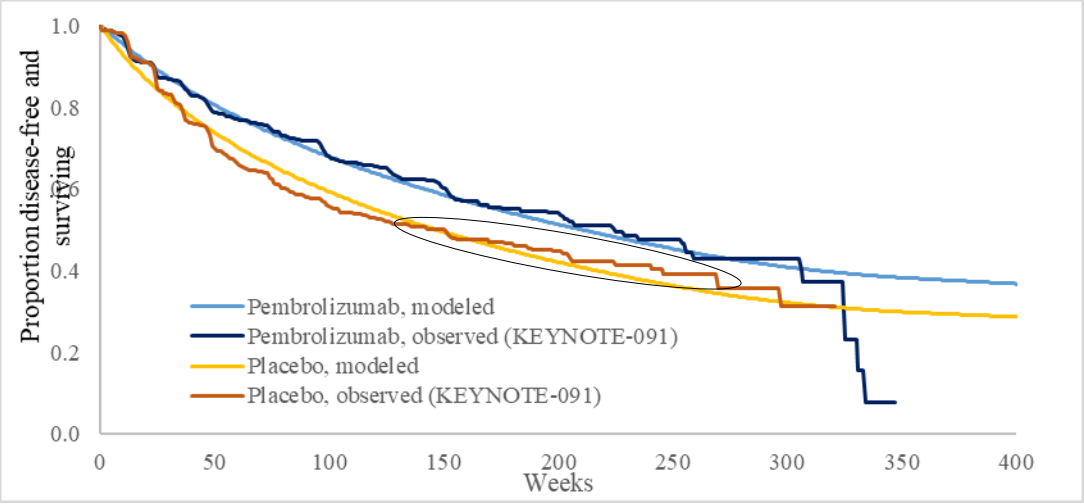


Figure 4. Modelled and observed OS 7 years company base case (PD-L1<50% subgroup)

The issue is even more apparent in the FLP, as can be seen in Figure 5 (the area that does not appear to fit the data has been circled). It is clear that using the company base case curves, results in a deviation from the trial DFS data, in the last 2 years of the trial.

Figure 5. Modelled and observed DFS 7 years company base case (Full licenced population)

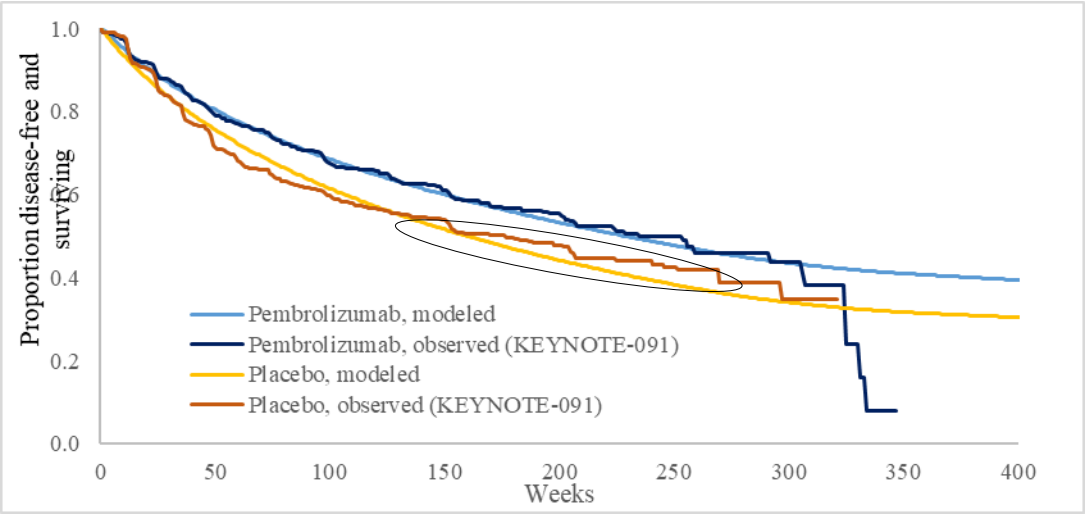
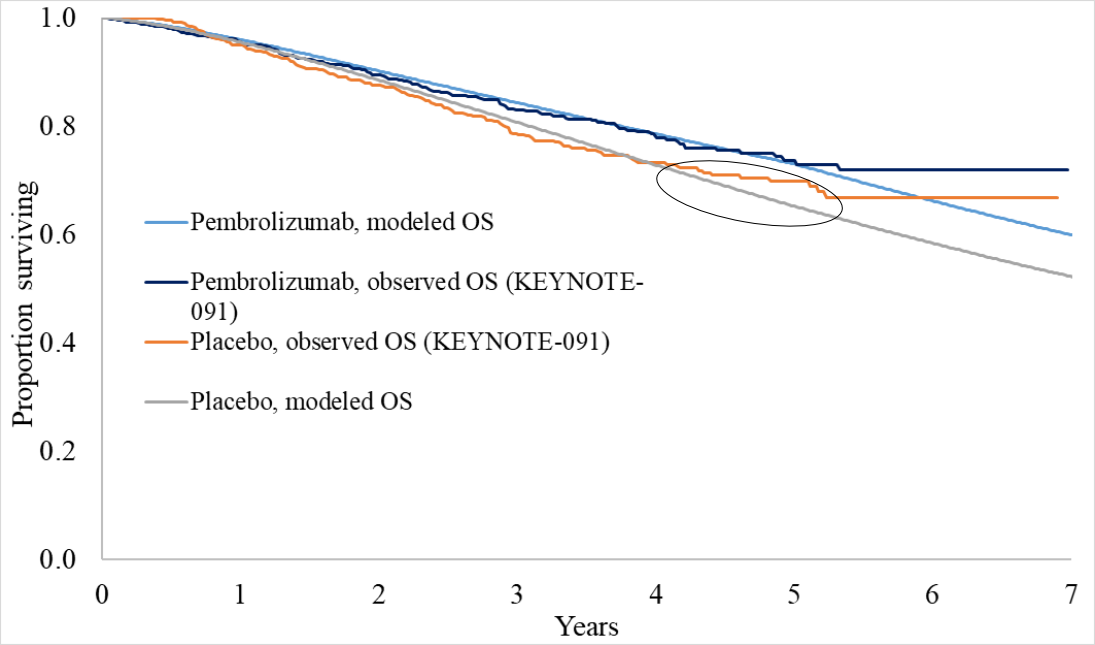


Figure 6. Modelled and observed OS 7 years company base case (Full licenced population)



The company base case scenario always appeared to have a good match to the KM data for pembrolizumab, although there was a slightly better fitting combination of curves available, but this was not the case for placebo. Therefore, the company's approach to adding waning on top of the company base case involves changing the fit of the "more appropriate" pembrolizumab curve and leaving the "less appropriate" placebo curve unchanged.

However, the committee stated clearly in the draft guidance from ACM 1 that there was insufficient evidence to deviate from the TSD14 guidance of using the same parametric function in both treatment arms[4]. Therefore, the EAG has opted to adopt the alternative company base case curves of generalised gamma for DF to LR and log-normal for DF to DM. This curve selection partially resolves the issue but there is still a poor fit for the final few years in the placebo arm for PD-L1<50% subgroup and FLP as demonstrated in Figure 7 and Figure 8

Figure 7. Modelled and observed DFS 7 years Generalised gamma and Log-normal (PD-L1<50% subgroup)

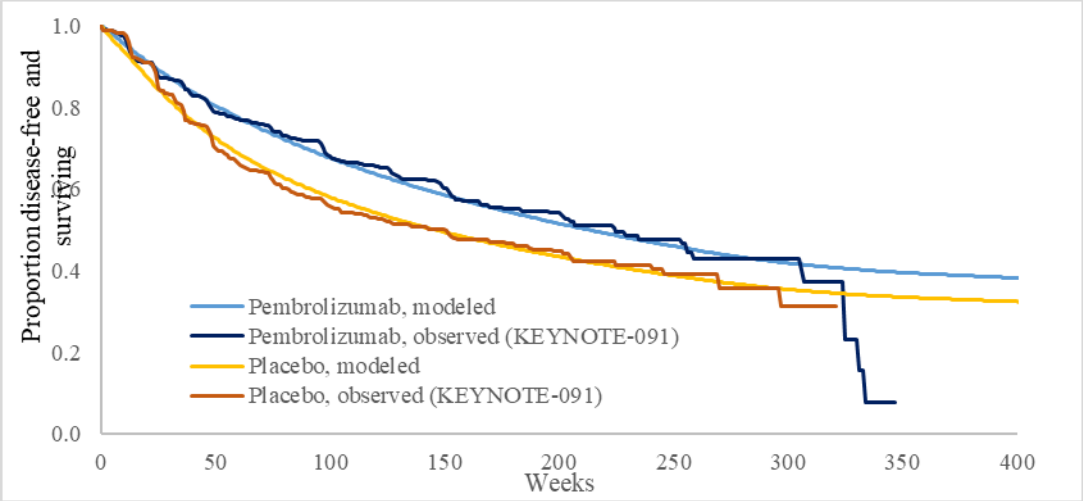
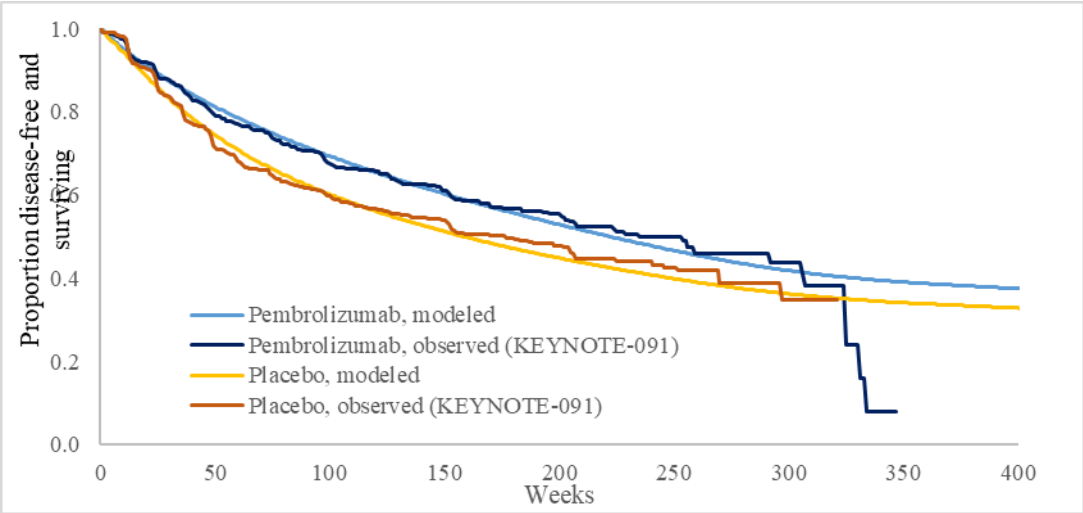


Figure 8. Modelled and observed OS 7 years Generalised gamma and Log-normal (Full licenced population)



The EAG has provided a scenario selecting the best fitting curves, by MSE (mean square errors) of observed DFS, for placebo. The company stated in their response that this was generalised gamma and log-normal but using MSE it is generalised gamma and Gompertz, for x an y respectively. In the appendix provided by the company they state that using this combination was excluded for consideration as predicted survival curve is higher than for pembrolizumab when using the same distributions for pembrolizumab. When the EAG attempted to apply the Generalized gamma to DF to LR and Gompertz to DF to DM transitions in both arms, pembrolizumab retained a higher DFS throughout the entire time horizon in both the PD-L1<50% subgroup and the FLP.

Nevertheless, to avoid potentially implausible results for this scenario, particularly when altering the cure percentage to match long-term recurrences (see Section 3.3), the EAG scenario prevented this

from occurring in the model by setting a rule that DFS for pembrolizumab can never fall below placebo. The fit of these curves shows significant improvement in the placebo arm with minimal impact to pembrolizumab, compared to the EAG base case, in the PD-L1<50% subgroup.

Figure 9. Modelled and observed DFS 7 years Generalised gamma and Gompertz (PD-L1<50% subgroup)

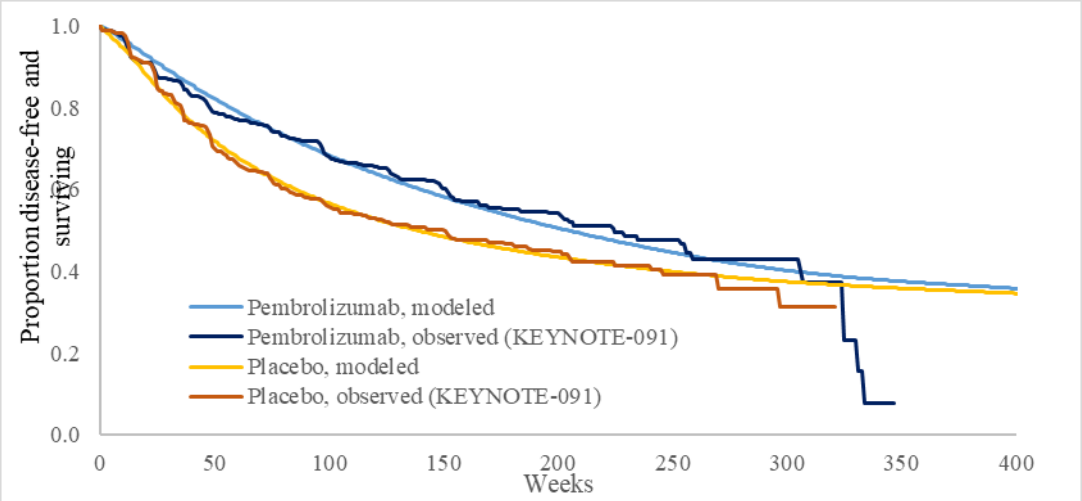


Figure 10. Modelled and observed OS 7 years Generalized gamma and Gompertz (PD-L1<50% subgroup)

[redacted]

However, this curve selection is not the EAG base case as, in the full licensed population, it appears to cause the same issue as the company base case, for pembrolizumab, resulting in a poor fit in the last two years for the active treatment as can be seen in Figure 11. It also does not fully resolve the poor OS fit for placebo as seen in Figure 12. Additional figures comparing the different parametric curves can be found in the appendix in Section **Error! Reference source not found.**.

Figure 11. Modelled and observed DFS 7 years Generalized gamma and Gompertz (Full licenced population)

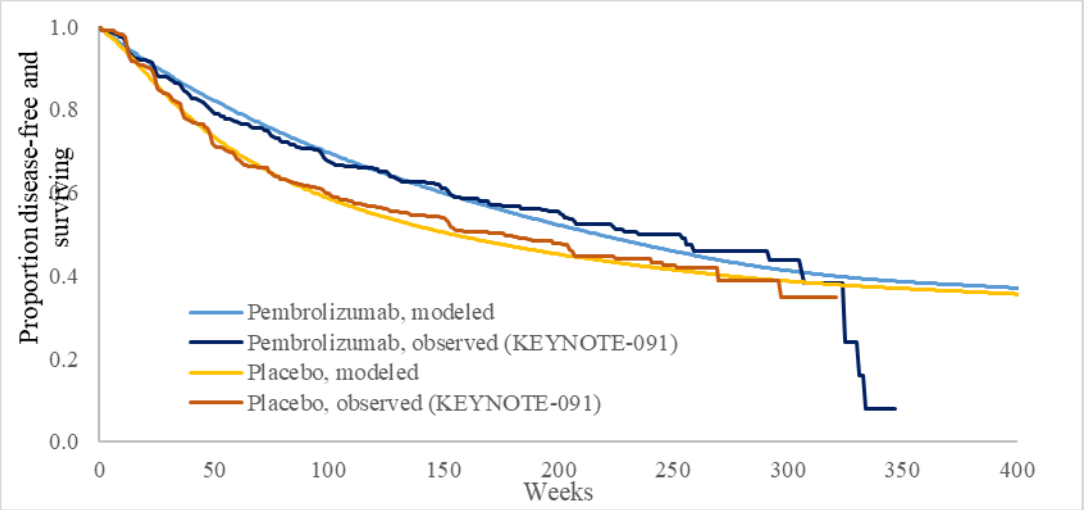
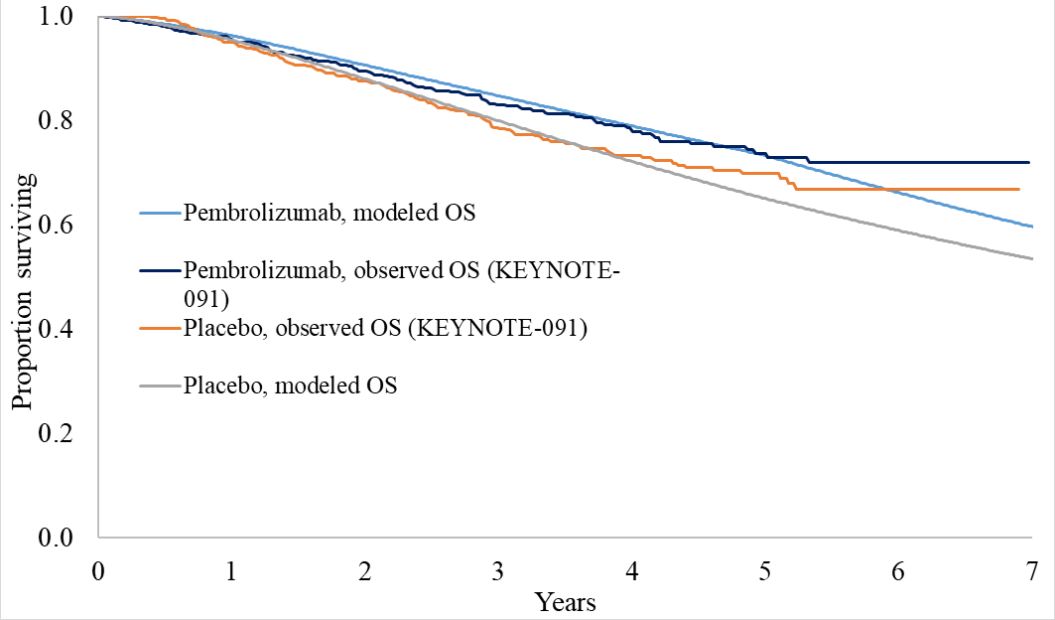


Figure 12. Modelled and observed OS 7 years Generalized gamma and Gompertz (Full licenced population)



3.2 Comment 7. Reprogramming the model to account for downstream time varying transition probabilities

In response to the concerns about the downstream uncertainty from LR patients, the company has undertaken exploratory analysis around the potential for patients who experience this to be cured by the interventions available. In their scenario analysis they demonstrate that altering the survival of LRR patients does not significantly impact cost-effectiveness. This limits the uncertainty from assumptions made for patients in this state, such as the use of non-time-varying models.

However, in the DM state the company case is less clear. They note the relatively small difference in AIC and BIC between models selected, which is also true for DFS models which have been acknowledged as having the largest impact on cost-effectiveness results. The company show that the exponential curve extrapolation roughly sits in the middle of other extrapolations and that picking other extrapolations is unlikely to have a big impact. This is illustrated in Figure 13 and Figure 14 showing extrapolations for KEYNOTE-189 and KEYNOTE-407 OS. These trials were on squamous and non-squamous patients respectively. However, in the squamous patient trial (keynote 407) representing about 25% of all DM patients[5], there is very significant difference in long term projections depending on the curve selected.

Figure 13. KEYNOTE-189 data showing exponential model is the central estimate for OS on pembrolizumab and fits the curve well

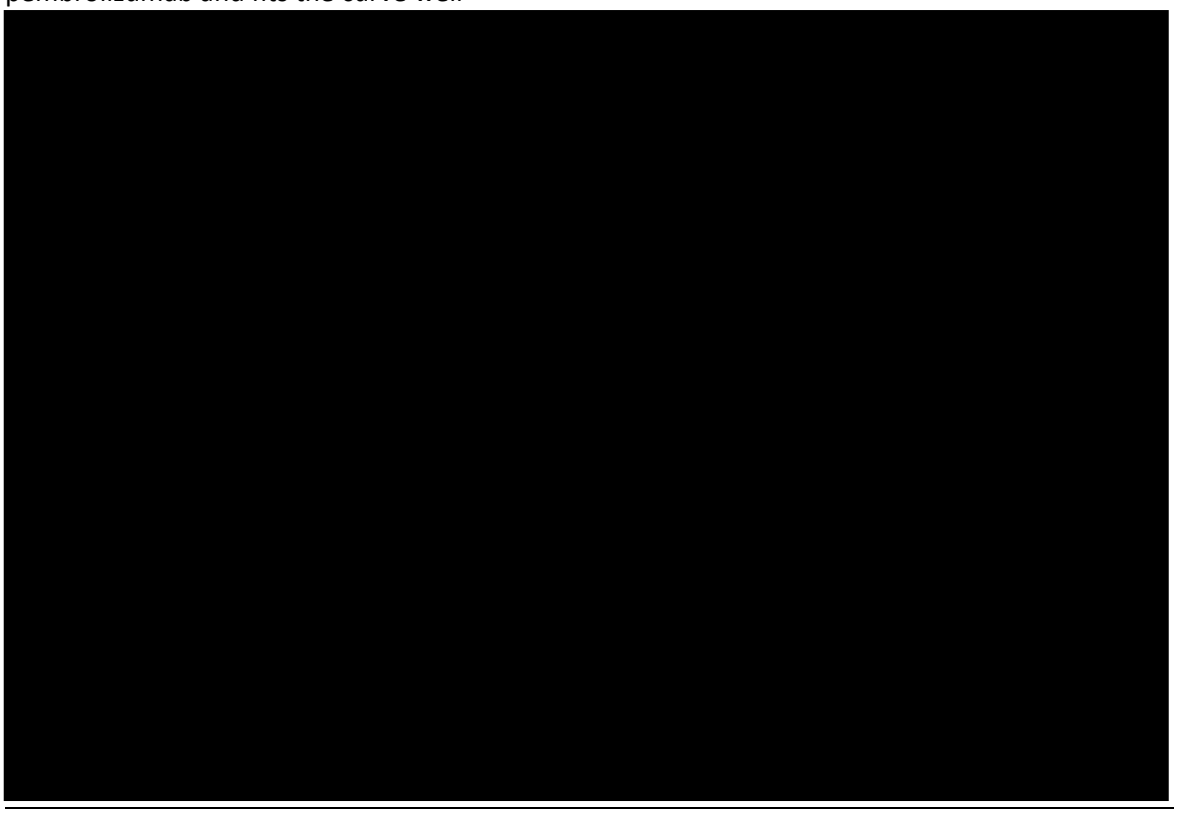
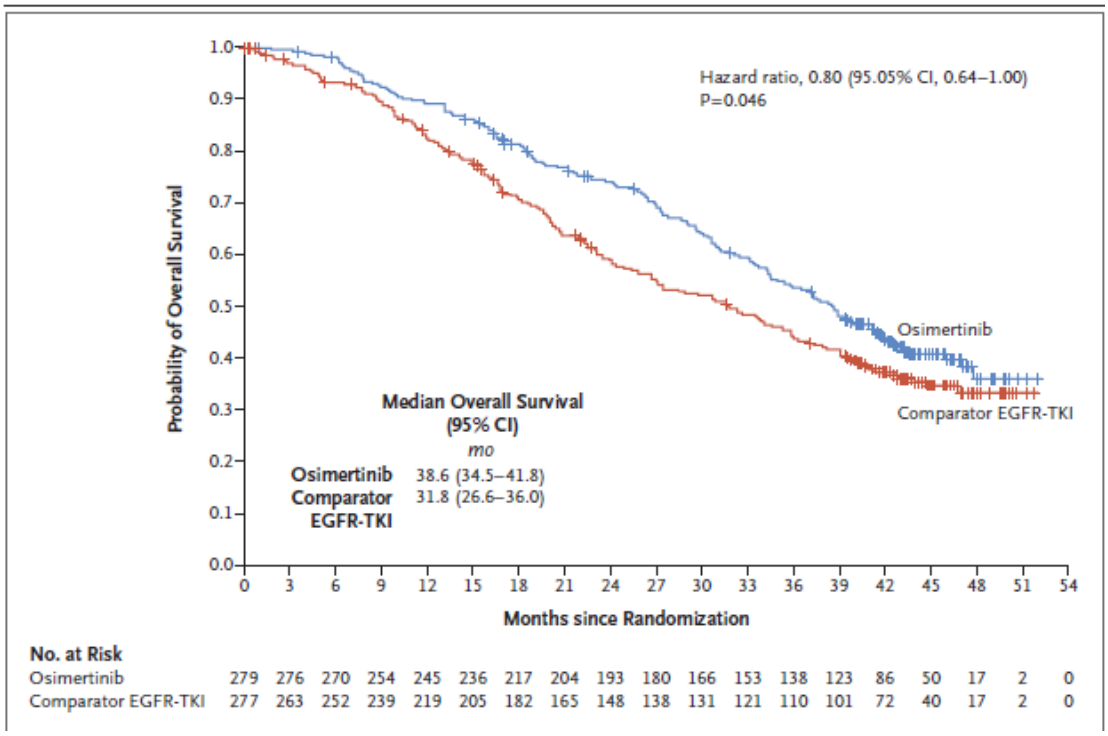


Figure 14. Figure showing OS in KEYNOTE-407, exponential model is central but may overestimate OS (and therefore overestimate the KEYNOTE-091 ICER slightly)

The company makes the case that, to the extent there is uncertainty for OS in DM patients, it is likely OS is overestimated (i.e. a more accurate model would have a positive impact on cost-effectiveness as more placebo patients enter the DM health state). Although this is solely in relation to osimertinib. The company notes that the effect of osimertinib is believed to be strong at first and wears off over time based on evidence from the FLAURA trial as shown in Figure 15[6]. It should be noted this only impacts [redacted] of patients based on market share. The EAG acknowledges that uncertainty in the LR health state is likely to have little impact, although uncertainty for DM patients is still significant.

Figure 15. Overall survival osimertinib vs EGFR-TKI FLAURA trial



3.3 Comment 10. Modelling late recurrences in line with epidemiological literature

The company has undertaken additional analyses in order to ensure the long-term incidence of late recurrences corresponds to the literature value for 10-20 year recurrences of 0.8%[7]. They note that their original base case approximately matched the literature value. However, in order for the updated base case analysis to include the ACM 1 committee recommendations of a standardised mortality ratio (an SMR chosen by the company of 1.453) and a baseline age of 67, the cure percentage would need to be changed. At present the companies updated base case does not use this altered cure percentage.

As noted in the initial EAG report the 95% reduction is an arbitrary figure initially selected in NICE TA823[8] to match the long term recurrence rate. While it is an interesting observation that the original company base case did not require alteration to the cure percentage to match the 10 to 20 year recurrence rate, this does not suggest any greater validity to this combination of assumptions. Given the new combination of assumptions does not match long term recurrences, the EAG recommends using the adjusted cure rate to ensure 10-20 year recurrences match the literature. This would mean using 92.5% for PD-L1 <50% subgroup population or 93% for FLP, assuming the updated company base case were adopted.

3.4 Comment 12. Standardised mortality ratio (SMR) for cured patients

In the draft guidance the committee requested the company impose an SMR for cured patients. The committee has requested that an SMR of 1.453 be used. This figure is taken from Janssen-Heijnen *et al*. 2012[9] and looks at conditional 5-year relative survival for every additional year survived after initial diagnosis.

The company note that using the value from this paper double counts mortality from late-stage recurrences which are already accounted for in the model. The EAG agrees with this assessment, the paper states that this excess mortality is, in part, driven by late recurrences. It also lists second tumours, late side effects of treatment, or a higher comorbidity mortality rate associated with cancer-related risk factors as potential explanations for the higher mortality.

Therefore, using this value should be seen as an upper estimate as late-stage recurrences can occur in the model and do contribute to a higher than general population mortality for the overall population. However, since this value does include mortality from other sources and no more appropriate value is available the EAG have included it into the base case in line with the company base case. In addition, whilst the EAG acknowledges that including this SMR is a conservative assumption, removing the SMR has minimal impact on the ICER compared to altering the parametric curve selection, as can be seen in Table 5 and Table 6 in Section 5.2.

4 Company's revised cost-effectiveness results

4.1 Company revisions as a result of ACM1

In comment 13, the company accepts a number of changes to the model, although they now believe that all ICERs are overestimated. The company accepts an updated baseline age to 67, an SMR of 1.453 and have presented results for the full licensed population (FLP) alongside the PD-L1 <50% subgroup. These results can be found in Table 4 below.

Table 2. Company's base case results

Intervention	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
ACM 1 company base case							
Pembrolizumab	[redacted]	[redacted]	[redacted]	–	–	–	–

SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACM 2 company base case (PD-L1<50% subgroup)							
Pembrolizumab	[redacted]	[redacted]	[redacted]	–	–	–	–
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACM 2 company base case (FLP)							
Pembrolizumab	[redacted]	[redacted]	[redacted]	–	–	–	–
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FLP, full licensed population; ICER, incremental cost-effectiveness ratio; LY, life year; PD-L1, Programmed Cell Death Ligand 1; QALY, quality-adjusted life-year

4.2 Scenario analysis

The company has conducted multiple scenarios (Table 3). The EAG has rerun these analyses. The company ACM1 base case presented is notably different from what was previously presented although this is likely due to an error in reporting. When the EAG ran the company ACM1 base case using the latest version of the model it produced the same results previously presented at ACM 1. The EAG was unable to recreate scenarios involving no DM adjustments and contacted the company for further clarity on how these were produced.

Table 3. Scenario analysis conducted by the company

Scenario	Incremental costs (£)	Incremental QALYs	Incremental LYs	ICER
Base-Case*	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1<50% subgroup Age 67 and SMR 1.453 applied				
Company updated base case	[redacted]	[redacted]	[redacted]	[redacted]
Company alternative	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case	[redacted]	[redacted]	[redacted]	[redacted]
Company base case and Cure=92.5%	[redacted]	[redacted]	[redacted]	[redacted]
Company alternative and Cure=88.8%	[redacted]	[redacted]	[redacted]	[redacted]
Company alternative and LRR cure 95%	[redacted]	[redacted]	[redacted]	[redacted]
Company base case and LRR cure 87%*	[redacted]	[redacted]	[redacted]	[redacted]
Company alternative and TEW 5-7y	[redacted]	[redacted]	[redacted]	[redacted]
Company base case and TEW 5-7y	[redacted]	[redacted]	[redacted]	[redacted]
Company alternative and no DM adjust	[redacted]	[redacted]	[redacted]	[redacted]

Company base case and no DM adjust	[redacted]	[redacted]	[redacted]	[redacted]
Company alternative, cure=88.8%, TEW=5-7, LRR cure 95%, no DM adjust*	[redacted]	[redacted]	[redacted]	[redacted]
Full licenced population Age 67 and SMR 1.453 applied				
Best fitting curve for pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Best fitting curve for placebo	[redacted]	[redacted]	[redacted]	[redacted]
Best fitting curves for pembrolizumab and placebo	[redacted]	[redacted]	[redacted]	[redacted]
Best fitting curve for pembrolizumab and Cure = 93%	[redacted]	[redacted]	[redacted]	[redacted]
Best fitting curve for placebo and Cure =89.3%	[redacted]	[redacted]	[redacted]	[redacted]
Best fitting curves for pembrolizumab and placebo and Cure=89.3%	[redacted]	[redacted]	[redacted]	[redacted]
Best fitting curves for pembrolizumab and placebo and LRR cure 85%	[redacted]	[redacted]	[redacted]	[redacted]
Best fitting both, cure=89.3%, TEW 5-7 years, LRR cure 85%, no DM adjust*	[redacted]	[redacted]	[redacted]	[redacted]

*The EAG notes that for this scenario the EAG result differed from the company

Abbreviations: AE, adverse event; DM, distant metastases; DFS, disease free survival; FLP, full licensed population; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; LY, life-years; PD-L1, Programmed Cell Death Ligand 1; RDI, relative dose intensity; Q6W, every 6 weeks.

5 EAG's cost-effectiveness results

5.1 EAG base case

Since the committee at ACM 1 considered that the chosen extrapolations for pembrolizumab and placebo should come from the same family of curves, the updated EAG base case includes matching parametric curves for pembrolizumab and placebo (generalised gamma for DF->LR and lognormal for DF->DM). It also uses a cure rate of 91% or 89% depending on if the PD-L1 <50% subgroup or FLP is used, these percentages were derived to match the placebo arms late recurrence rate to the literature value for 10-20 year recurrences of 0.8%[7]. In addition, the EAG base case adopts the SMR of 1.453 and the baseline age of 67, now applied in the company base case, due to recommendation by the committee in ACM 1.

Table 4. EAG's base case results

Intervention	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
ACM 1 EAG base case							
Pembrolizumab	[redacted]	[redacted]	[redacted]	–	–	–	–
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACM 2 (PD-L1<50% subgroup)							
Pembrolizumab	[redacted]	[redacted]	[redacted]	–	–	–	–
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACM 2 (FLP)							
Pembrolizumab	[redacted]	[redacted]	[redacted]	–	–	–	–
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FLP, full licensed population; ICER, incremental cost-effectiveness ratio; LY, life year; PD-L1, Programmed Cell Death Ligand 1; QALY, quality-adjusted life-year

5.2 EAG scenario analyses

The following additional sensitivity analyses were also undertaken using the EAG's preferred analysis. For the scenario using placebo favoured curves, a scenario is provided with the cure percentage adjusted to ensure long term recurrences match the literature and with the EAG base case cure percentage:

Table 5. Scenarios applied to the EAG preferred base case analysis (PD-L1<50% subgroup)

	Results per patient	Pembrolizumab	Placebo	Incremental value
0	**EAG preferred analysis (cure 91%)**			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
1	Placebo favoured curves (Generalized gamma and Gompertz) (cure 91%)			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
2	Placebo favoured curves (Generalized gamma and Gompertz) (cure 73%)			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
3	Differential cure point 6 years for placebo 7 for pembrolizumab (cure 91%)			

	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
4	Differential cure point 5 years for placebo 7 for pembrolizumab (cure 91%)			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
5	Remove calibration (cure 91%)			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
6	Remove SMR (cure 91%)			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]

*The EAG notes that for this scenario the company reapplied the calibration

Abbreviations: FLP, full licensed population; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; PD-L1, Programmed Cell Death Ligand 1; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year;

Table 6. Scenarios applied to the EAG preferred base case analysis (FLP)

	Results per patient	Pembrolizumab	Placebo	Incremental value
0	**EAG preferred analysis (cure 89%)**			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
1	Placebo favoured curves (Generalized gamma and Gompertz) (cure 89%)			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
2	Placebo favoured curves (Generalized gamma and Gompertz) (cure 74%)			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
3	Differential cure point 6 years for placebo 7 for pembrolizumab (cure 89%)			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
4	Differential cure point 5 years for placebo 7 for pembrolizumab (cure 89%)			
	total costs (£)	[redacted]	[redacted]	[redacted]

	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
5	Remove calibration (cure 89%)			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	[redacted]	[redacted]	[redacted]
6	Remove SMR (cure 89%)			
	total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]

*The EAG notes that for this scenario the company reapplied the calibration

Abbreviations: FLP, full licensed population; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; PD-L1, Programmed Cell Death Ligand 1; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year;

6 References

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7 Appendices

7.1 Additional figures comparing parametric modelling approaches

7.1.1 DFS curve selections and HR over time

The curves below show the hazard ratio over time for the EAG base case and the company base case and EAG alternative curves. This can be seen in for the PD-L1 <50% subgroup and in for the FLP.

Figure 16. DFS curve selections and HR over time (PD-L1 <50% subgroup)

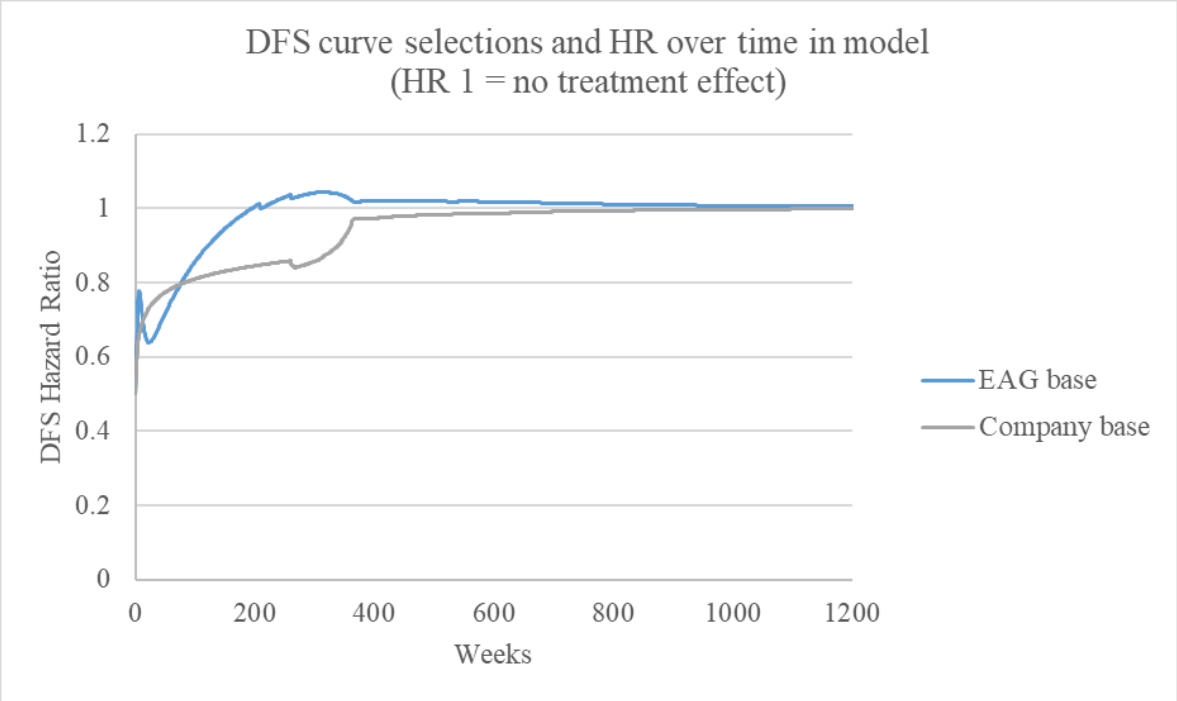
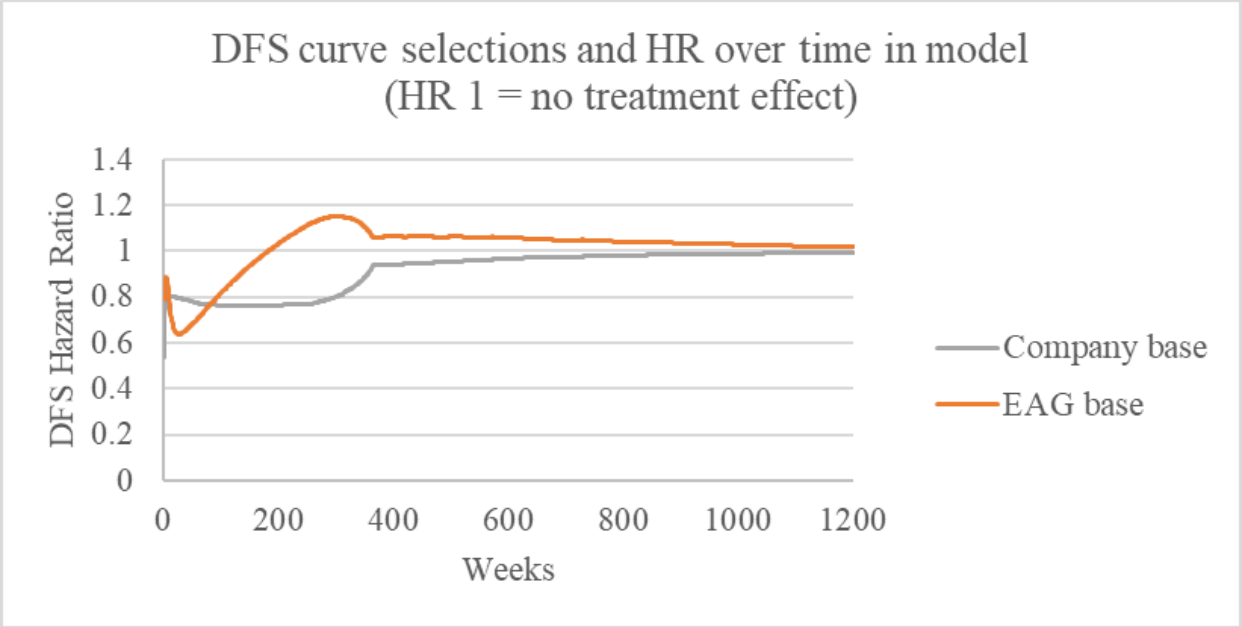


Figure 17. DFS curve selections and HR over time (Full licensed population)



7.1.2 Modelled DFS

The curves below show the modelled DFS for pembrolizumab versus placebo in the company and EAG base case along with the EAG additional scenario using placebo favoured curves. These three curves are shown in Figure 18, Figure 19 and Figure 20 for the PD-L1 <50% subgroup and Figure 21, Figure 22 and Figure 23 for the full licensed population.

FLP@

Figure 18. Modelled DFS company base case (PD-L1 <50% subgroup)

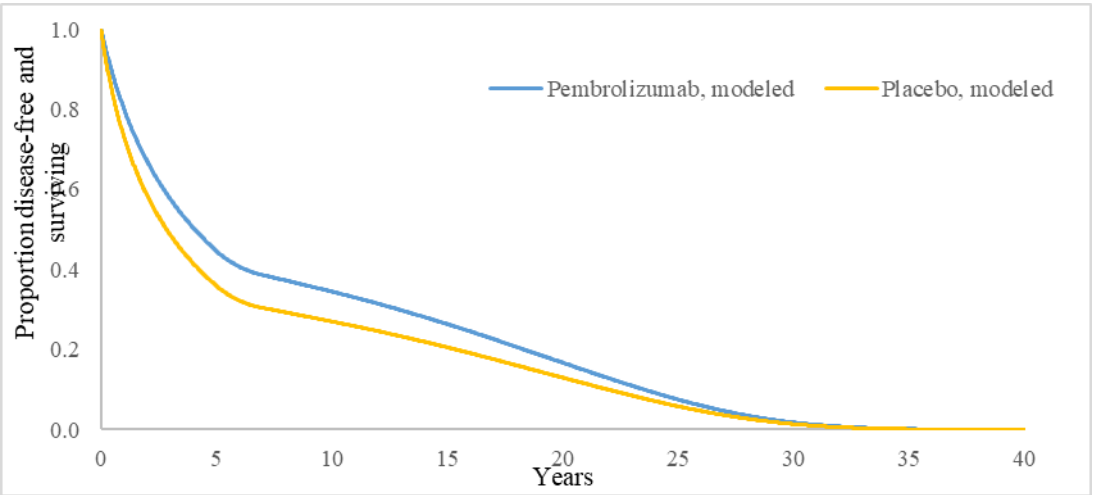


Figure 19. Modelled DFS EAG base case (PD-L1 <50% subgroup)

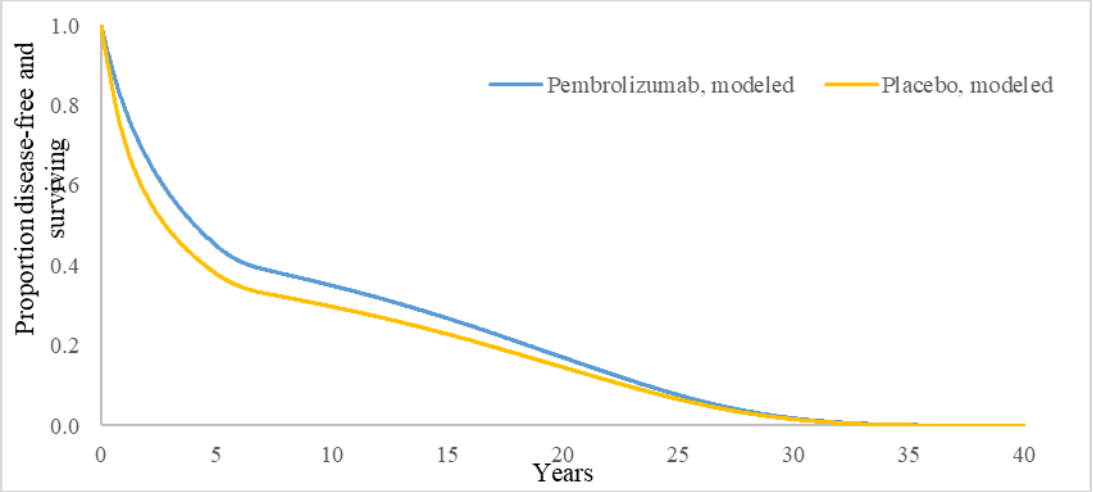


Figure 20. Modelled DFS EAG pembrolizumab favoured (PD-L1 <50% subgroup)

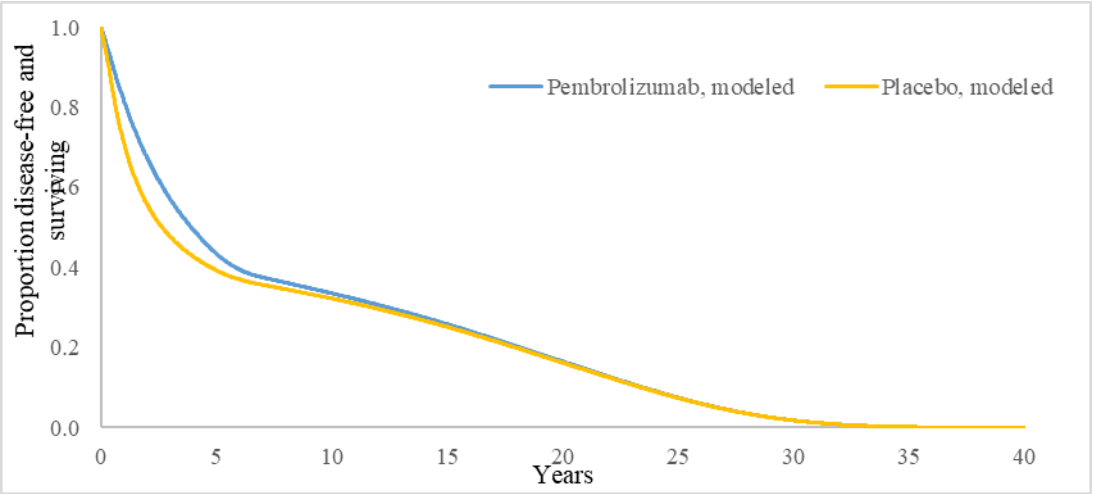


Figure 21. Modelled DFS company base case (Full licensed population)

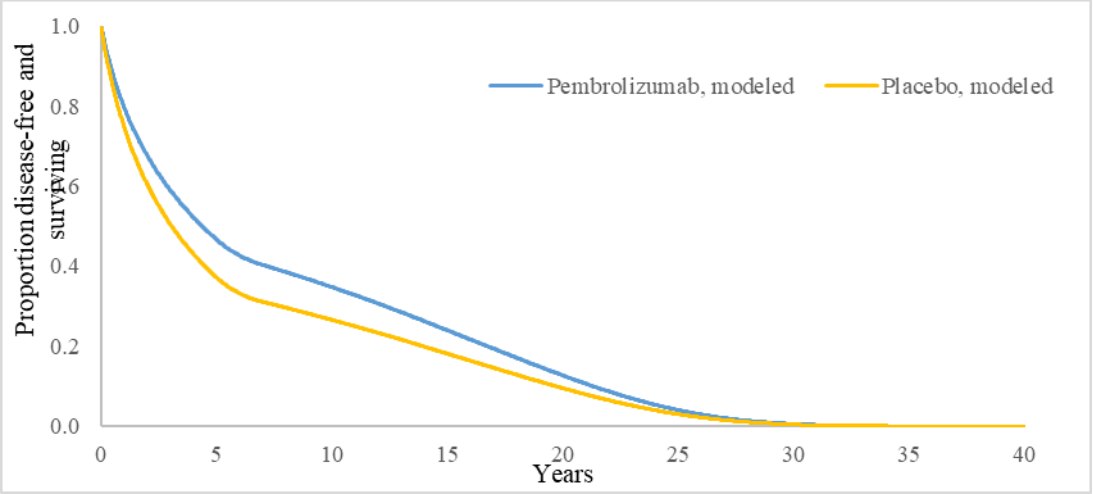


Figure 22. Modelled DFS EAG base case (Full licensed population)

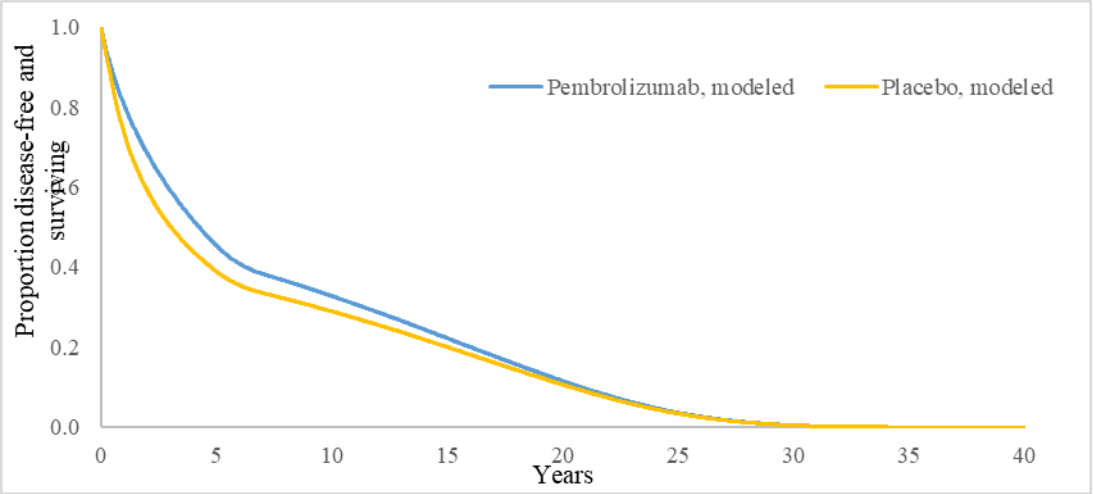


Figure 23. Modelled DFS EAG pembrolizumab favoured (Full licensed population)