Single Technology Appraisal

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]

Contents:

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NICE National Institute for Health and Care Excellence

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day **3 March 2025**. Please submit via NICE Docs.

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

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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.	Not applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	BMS has no link to the tobacco industry.
Name of commentator person completing form:	Gabriel Okorogheye, Associate Director, Health Economics & Outcomes Research (HEOR) Lead, Market Access & External Affairs, BMS UK.
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	In summary, BMS feel that: • All of the relevant evidence has not been taken into account. • Available overall survival (OS) evidence from CheckMate 8HW and CheckMate 142 has not been taken into account (Comments 3 and 19). • The summaries of the clinical and cost effectiveness evidence are not reasonable interpretations of the evidence.

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	• Evidence submitted by the external assessment group (EAG) in January 2025 contains unspecified model changes and it is unclear if these changes were present in model outcomes presented to the committee ahead of the appraisal committee meeting (ACM) (Comment 2). • Clinical evidence submitted to NICE does not support uncertainty in the comparative evidence for nivolumab with ipilimumab, and challenges in the transitivity of the progression-free survival (PFS) network are unfounded (Comment 4). • The provisional recommendations are not a suitable basis for guidance to the NHS. "The recommendation is unreasonable in the light of the evidence submitted to NICE" [p7 of NICE guide to the methods of technology appraisal 2013]. • The PFS validation and adjustment activities undertaken by the EAG are entirely inappropriate in the context of recent publications (Andre et al. 2025[1]) demonstrating that PFS outcomes are vastly different between the locally confirmed (intention to treat [ITT]) and centrally confirmed populations (Comments 5 and 18). • The EAG base case analysis uses the efficacy of nivolumab plus ipilimumab to inform post-progression survival in patients who received 1L chemotherapy treatment, while also applying the lower cost of pembrolizumab to the majority of patients. This inappropriately assigns an inflated survival benefit to lower cost therapy sequences (Comment 21). • The EAG apply treatment waning at two years, despite evidence to refute it (Comment 22). Further, the methodology used by the EAG to implement treatment waning grossly overestimates the efficacy of pembrolizumab in both PFS and OS when compared with outcomes from KEYNOTE-177 ([redacted]% at five years in the economic model versus 34.0% in KEYNOTE-177). • Pembrolizumab modelled time on treatment is derived using PFS fractional polynomial network meta-analysis (FPNMA) outcomes applied to nivolumab plus ipilimumab time to discontinuation (TTD), resulting in implausible time on treatment that is shorter than that for chemotherapy, which does not fit with KEYNOTE-177 observations (Comments 23 and 24). A cost-effectiveness appendix has been provided by BMS, with analyses designed to address the committee's concerns and uncertainties. The approach outlined in this appendix provides a significantly better fit to the observed clinical data than the EAG approach and also takes into account clinical expert opinion provided to NICE.
2	**<u>Uncertainty in EAG model following EAG report</u>** The NICE Technical team have shared two versions of the EAG adapted company model with BMS. 1. The model used to develop the EAG report, shared in September 2024. 2. The model used to inform the document "Addendum: Comparison of Updated Kaplan Meier Data to Model Predictions and Updated Subsequent Treatment Data", requested by BMS and shared after the ACM in late January 2025. Upon examination of the January 2025 model, it was apparent that unspecified amendments had been made versus the September 2024 model, outside of the committee preferred assumptions, and used to populate the addendum document.

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	Several of these amendments have since been identified (including use of per protocol time on treatment estimation and amendment of proportion female) but others remain unidentified. There was no discussion or agreement at the ACM or in the appraisal consultation document (ACD) to fundamental changes to the model unrelated to the HST committee's preferred assumptions. To demonstrate the extent of discordance between the September 2024 and January 2025 versions of the model shared by the EAG, the EAG base case in the September 2024 model showed an incremental cost-effectiveness ration (ICER) of £49,333/quality-adjusted life year (QALY) compared with chemotherapy, whereas the January 2025 version returned an ICER of £91,439/QALY. By NICE's own guidance, to ensure that the appraisal process is as transparent as possible, it is essential that evidence on which the appraisal committee's decisions are based is made available to stakeholders and is publicly available. In contradiction of this aim, if the model had not been requested by BMS, it is unclear whether these changes would have come to light. Due to the lack of transparency regarding model changes, BMS have implemented their updates in the original September 2024 model as there can be no confidence in the January 2025 version received. BMS have sought to assess if these model changes were apparent in the document "Addendum: Comparison of Updated Kaplan Meier Data to Model Predictions", provided to the committee ahead of the ACM and used for decision making. Most cost outcomes are redacted due to confidential patient access scheme (PAS) discounts for comparators, making a factual accuracy check impossible, but QALY outcomes appear to align with the September 2024 model. BMS has assumed that only model changes specified by the appraisal committee are intended and have developed its own version of the EAG base case analysis, based on the September 2024 model shared by the EAG. This BMS version of the EAG base case combined with committee preferred assumptions has been used to inform the economic analysis presented in the document in response to the draft guidance.
3	**<u>Availability of OS data and translation of PFS into OS benefit</u>** In response to recent requests from NICE, BMS have commissioned an analysis of the immature OS data from CheckMate 8HW. Only a very limited number of BMS personnel have been unblinded to these data in order to maintain trial integrity. These data have been submitted to NICE. These OS data have been utilised to confirm the projected outcomes for both PFS and OS. This addresses a key uncertainty noted by the appraisal committee. It should also be noted that CheckMate 142 OS data were provided as part of the company submission and evidence across cohort 2 (≥second line [2L+] nivolumab with ipilimumab) and cohort 3 (first line [1L] nivolumab with ipilimumab), totalling 146 patients, showed a consistent benefit of nivolumab with ipilimumab on OS. In support of the OS data demonstrating the benefit of nivolumab with ipilimumab, the submitted approach regarding translation of PFS into OS benefit is aligned with the white paper on surrogate endpoints in cost-effectiveness analysis developed by NICE in collaboration with its international partners.[2] In line with the recommendations in this white paper, CheckMate 142 data provided at company submission showed a strong correlation between PFS and OS for cohort 1 (2L+ nivolumab monotherapy), cohort 3 (1L nivolumab with ipilimumab) and combined cohort 2 (2L+ nivolumab with ipilimumab) and cohort 3 from CheckMate 142.[3] The correlation coefficients for

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	cohorts were: 0.83 for 2L+ nivolumab (Plackett Copula), 0.92 for 1L nivolumab with ipilimumab (Frank Copula), and 0.85 for 1L and 2L+ nivolumab with ipilimumab (Plackett Copula). There is also strong evidence from the published literature supporting the relationship between PFS and OS benefit. Ye et al. 2020[4] conducted a meta-analysis of 40 randomised trials investigating PD-1/PD-L1 targeting immunotherapies which found a strong correlation of 0.84 (1L monotherapy trials) between PFS and OS. Ye et al. concluded that improvements in PFS are likely to translate into OS. This is also in line with all other nivolumab with ipilimumab indications assessed by NICE, where PFS benefit translated into OS benefit (TA400,[5] TA716,[6] TA724[7], TA780[8] and TA818[9]). Further, BMS provided a clear biological rationale for the link between PFS and OS in Section B.2.10.2 and clarification question A23, supported by expert opinion obtained by BMS and NICE, and shared by the clinical experts at the ACM, as outlined in section 3.12 of the draft advice. In particular, clinical expert opinion received by NICE stated that nivolumab with ipilimumab is likely to improve OS and improve cure rate. BMS reported the PFS data transparently and conducted scenario analyses to assess the impact of the assumption. In light of the weight of trial evidence, published literature support and clinical expert opinion, is surprising that the EAG and the appraisal committee considered scenarios with no OS benefit to be clinically plausible. In combination with the recently provided CheckMate 8HW OS evidence, this uncertainty can be considered to be addressed.
4	**Transitivity of the PFS network and uncertainty in the comparative evidence** The draft guidance states on page 13 that there are important limitations with the analysis, which mean the results are uncertain. However, this is not a reasonable interpretation of the evidence. Lack of central testing for deficient mismatch repair (dMMR) or high microsatellite instability (MSI-H) in KEYNOTE-177 does not violate the transitivity of the network meta-analysis (NMA; section 3.9 of the draft guidance). The testing approach was the same in both CheckMate 8HW and KEYNOTE-177 for the randomised populations used in the comparison. The presence of an additional, post-randomisation, central test in CheckMate 8HW is not relevant to the NMA. In the CheckMate 8HW trial, 15% of locally confirmed cases in the ITT population were determined not to be dMMR or MSI-H when centrally tested and were therefore unlikely to respond to immunotherapy (see Comment 9). A robust NMA requires the assumption that a similar number of locally confirmed patients would not have been centrally confirmed if such testing had been carried out in KEYNOTE-177. While the EAG is correct to highlight this assumption and note that use of central testing is important for preventing non-differential ascertainment bias, absence of central confirmation in KEYNOTE-177 does not in itself violate the assumption of transitivity. As can be seen in the BMS analysis appendix, outcomes are relatively similar between the pembrolizumab arm of KEYNOTE-177 and the nivolumab arm of CheckMate 8HW, indicating that these populations are comparable. Hence, the use of the locally confirmed population to inform the NMA for both studies maintains transitivity and may underestimate the efficacy of all immunotherapies in the NMA and so can be considered conservative.

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	The draft guidance cites the EAG as explaining that this central assessment prevented a like-for-like comparison between CheckMate 8HW and KEYNOTE-177 (page 12, section 3.9), but as described above, this is not the case. Additionally, the EAG note that transitivity of the network relies on the assumption of a class treatment effect for chemotherapy (page 12, section 3.9), with heterogeneity within the comparator groups (EAG report p19). However, this is based on a slightly higher number of patients receiving a bevacizumab-containing regimen in KEYNOTE-177 (70.0% versus [redacted]% in CheckMate 8HW). It is stated on page 12 that the EAG notes "there was some heterogeneity of outcomes in the chemotherapy arms of CheckMate 8HW and KEYNOTE-177, but they were similar enough for comparison" [p12 of the draft consultation]. Based on this evidence, it can be seen that KEYNOTE-177 and CheckMate 8HW are sufficiently similar to enable an indirect comparison. The FPNMA is a robust indirect treatment comparison (ITC) of two phase 3 randomised controlled trials of the relevant comparators. Frequently, NICE committees appraising oncology treatments do not have this luxury and need to assess unanchored ITCs of single arm studies. The Committee concurs that the BMS fractional polynomial NMA (FPNMA) was appropriate to assess the treatment effect of nivolumab with ipilimumab compared to pembrolizumab, but this conclusion is not reflected in the draft guidance. However, if transitivity is still considered a challenge for consideration of the ITC evidence, an unanchored matching adjusted indirect comparison (MAIC) may be considered an alternative appropriate method. Outcomes from an unanchored MAIC between KEYNOTE-177 and CheckMate 8HW were provided as part of the company submission and used to inform a cost-effectiveness scenario analysis. These outcomes supported the beneficial impact of nivolumab with ipilimumab over pembrolizumab. It is also important to note that data are now available to compare nivolumab monotherapy across all lines from CheckMate 8HW and pembrolizumab from KEYNOTE-177. Consistent with the cost-effectiveness modelling results, PFS outcomes from these trial arms are highly similar. Given the difference in PFS outcomes between the centrally confirmed and locally confirmed cohort of CheckMate 8HW, this would suggest that a similar numbers of patients in KEYNOTE-177 would have been centrally confirmed if assessed. In conclusion, the evidence demonstrates that KEYNOTE-177 and CheckMate 8HW are sufficiently similar to enable a robust ITC using FPNMA, which provides a reliable assessment of the treatment effect of nivolumab with ipilimumab compared to pembrolizumab. While potential transitivity challenges have been raised, both the conservative approach to maintain transitivity and the consistency in outcomes, including new data comparing nivolumab monotherapy with pembrolizumab, reinforces the validity of the analysis and supports the beneficial impact of nivolumab with ipilimumab. Additionally, unanchored MAIC analyses further corroborate these findings.
5	**<u>Validation of PFS outcomes to CheckMate 8HW nivolumab monotherapy</u>** Ahead of the ACM, the EAG provided the document "Addendum: Comparison of Updated Kaplan Meier Data to Model Predictions" in which they compared modelled pembrolizumab curve outcomes, based on a locally confirmed population, to the

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	observed outcomes from a centrally confirmed nivolumab monotherapy arm of CheckMate 8HW. Upon finding that modelled outcomes did not align with the observed values, the EAG applied an adjustment to the ITC hazard ratios (HRs) in order to align pembrolizumab PFS with observed nivolumab PFS. However, this is an inherently biased comparison. As shown in a recent publication of the CheckMate 8HW data (Andre et al. 2025[1]), PFS outcomes are vastly different between the locally confirmed (ITT) and centrally confirmed populations. For nivolumab monotherapy, median PFS in the centrally confirmed population is 39.3 months, whereas in the locally confirmed population this is 18.4 months. As such, the EAG approach of adjusting the modelled pembrolizumab outcomes is inappropriate as it overestimates PFS for pembrolizumab and should have been considered more carefully before being presented to the Appraisal Committee. An alternative approach to modelling pembrolizumab PFS has been provided as a scenario in a separate appendix, informed by the views of the clinical experts that nivolumab monotherapy and pembrolizumab would be expected to have similar outcomes. In this approach, the nivolumab monotherapy time to progression (TTP) Kaplan-Meier data in the CheckMate 8HW locally confirmed all lines population is extrapolated using standard parameterisations. Nivolumab with ipilimumab TTP extrapolations were not updated, as the extrapolations originally presented within the economic model reflect a locally confirmed 1L population, which is more appropriate to the indication. This approach more closely mirrored the observed pembrolizumab PFS values from KEYNOTE-177 than the approach of applying the nivolumab with ipilimumab versus nivolumab monotherapy adjusted HR to estimate pembrolizumab PFS, although still provided an overestimation compared with observed values. Nonetheless, BMS maintain that because of the methodological robustness of the FPNMA compared with the application of nivolumab monotherapy data, the FPNMA outcomes should be retained in the base case analysis.
6	Page 4. Section 1.2 The draft guidance states “There is no evidence available to show whether nivolumab with ipilimumab increases how long people live compared with chemotherapy or pembrolizumab.” This is incorrect, as CheckMate 142 demonstrates that nivolumab with ipilimumab increases OS compared with chemotherapy or pembrolizumab, although it is a noncomparative study. Further, there is a wealth of evidence to support a survival benefit for nivolumab with ipilimumab in other cancers. Based on this, it would be more correct to say ““There is limited evidence available to show whether nivolumab with ipilimumab increases how long people live compared with chemotherapy or pembrolizumab.”
7	Page 4, section 2.2 The Summary of Product Characteristics provided in the hyperlink is the EMA Summary of Product Characteristics. [redacted]
8	Page 8 Section 3.4

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	The draft guidance describes that BMS stated "withholding the interim overall survival analysis was essential to preserve the statistical integrity of the trial, and avoid introducing bias that might lead to incorrect conclusions about overall survival". The company did not withhold OS data and did not state that it was withholding this data. The company remained blinded to OS data, so had no OS data to withhold. The reasoning stated here refers to why the company could not, at the time, be unblinded to the data managed by the independent Data Monitoring Committee. As noted in comment 3, a highly confidential analysis of OS data has now been made available to NICE in response to requests from NICE.
9	Page 8 Section 3.4 In relation to the clinical trial, the draft guidance states "the company further explained that dMMR or MSI-H status can be locally confirmed, or centrally confirmed with greater accuracy at regional laboratories." However, this is not what the company explained in relation to local versus central testing. In CheckMate 8HW, the locally confirmed (ITT) population had their MSI/MMR status confirmed at one of the investigator sites and were randomised on that basis. BMS then centrally confirmed status using a standardised test, resulting in the centrally confirmed population. Patients in KEYNOTE-177 did not have their MSI-H/dMMR status centrally confirmed, and therefore the enrolled population is comparable with the locally confirmed (ITT) population in CheckMate 8HW. In CheckMate 8HW, 15% of the locally confirmed population were false positive, also known as microsatellite stable/mismatch repair proficient patients (MMS/pMMR). This is clinically significant, as trials show that patients with MSS/pMMR disease do not to respond to immune-oncology therapies. The implication is that, in order to be unbiased, comparisons between results from the ITT population in KEYNOTE-177 and the centrally confirmed population in CheckMate 8HW should not be made. The cost-effectiveness model uses the locally confirmed population from both trials in order to maintain comparability of the evidence base. The EAG approach of adjusting the modelled pembrolizumab curve outcomes, based on a locally confirmed population, to match the observed outcomes from a centrally confirmed nivolumab monotherapy arm of CheckMate 8HW introduces significant bias in favour of pembrolizumab.
10	Page 8 Section 3.4 The draft guidance contains the factually inaccurate statement "it noted that, at the time of the interim analysis (October 2023), the information fraction was 80%". The information fraction was 80% for PFS and should not be considered to apply automatically to other endpoints. Further fatalities needed to occur before the information fraction for OS would reach 80%. BMS attempted to correct this error in the EAG report factual accuracy check, requesting that the EAG clarify that the information fraction for primary endpoint (PFS by blinded independent central review [BICR]) was 80%. However, the EAG did not believe that this was a factual accuracy error. Given the high rate of cross over and subsequent immunotherapy use in the patients randomised to receive chemotherapy, and the low event rate in the nivolumab with ipilimumab arm, there is a high degree of uncertainty in the statement "that overall-survival data at this time would likely closely parallel the final overall-survival data".

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	As noted in comment 3, a highly confidential analysis of OS data has now been made available to NICE in response to requests from NICE.
11	Page 9 Section 3.5 "The committee discussed that it would have preferred to see comparative overall-survival data from CheckMate 8HW (see section 3.4). It concluded that overall-survival data from a small cohort of a non- randomised trial was informative but highly uncertain" CheckMate 142 has extended, 60-month OS follow-up, which also demonstrated strong correlation across both nivolumab and ipilimumab arms (cohorts 2 and 3), which in total treated 164 patients. Therefore, the OS data from CheckMate 142 should not be described as highly uncertain.
12	Page 11 Section 3.8 The draft guidance states: "The company explained that the most appropriate indirect treatment comparison was the FPNMA, and that the alternatives were presented as validating analyses only." This is not entirely correct. It is correct that BMS believe that the most appropriate ITC approach is the FPNMA, as agreed by the EAG. Additionally, it is correct that the constant hazard NMA is presented for completeness and as a validation exercise. However, the anchored MAIC and unanchored MAIC are provided in order to assess the uncertainty around the outcomes for the FPNMA and are particularly important in the context of the EAG comments on transitivity of the NMA network. As can be seen, all ITC approaches consistently provide evidence of the benefit of nivolumab with ipilimumab over pembrolizumab.
13	Page 11 Section 3.8 The draft guidance contains a factual inaccuracy. The statement "This was statistically significant up to 12 months against all treatments, and up to 60 months for all treatments except pembrolizumab" does not reflect that the FPNMA primary analysis demonstrated statistically significant benefits for nivolumab with ipilimumab over pembrolizumab at all time points. Only one of the other two FPNMA scenario analyses estimated that the credible intervals would cross the null at 24 to 60 months. In support of this result, the EAG report stated that this finding suggested "confidence in the finding that the benefits of nivolumab with ipilimumab consistently outweigh the comparators."
14	Page 13 Section 3.10 This section omits a key point raised by BMS at the ACM discussion as an inaccuracy. This issue is that the observed nivolumab data is not in the same population as the pembrolizumab data in the model (as explained in comment number 5). In brief, the company explained at the ACM that the nivolumab monotherapy data referred to in the EAG's exploratory analysis was for the centrally confirmed sub-population, whereas the modelled data for pembrolizumab was from the model which used the ITT (locally confirmed) population. An in depth of explanation of the issues with this approach is provided in comment 9. Following the appraisal

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	committee meeting, BMS published data demonstrating that median PFS in the nivolumab monotherapy arm for the centrally confirmed population is 39.3 months, whereas in the locally confirmed population this is 18.4 months. However, even in the context of the data already available for nivolumab with ipilimumab at the time of the ACM, this should have been considered inappropriate and biased towards pembrolizumab. Further, the data provided by BMS in the addendum included previously treated patients (43%[1]) while the modelled pembrolizumab data was based on previously untreated patients only. The direction of bias for this assessment is unclear. Nivolumab plus ipilimumab efficacy may be similar between treatment lines based on CheckMate 8HW evidence whereas PD-L1 monotherapy efficacy may be slightly decreased for previously treated patients versus previously untreated patients based on OS from KEYNOTE-164 and KEYNOTE-177, respectively. However, it is clear that the EAG should not have used the data for previously treated patients without clearly understanding any potential bias. After the ACM, on January 25th, BMS published PFS by BICR Kaplan-Meier data for nivolumab versus nivolumab with ipilimumab in the ITT (locally confirmed) population (Andre et al. 2025[1]). Median PFS for nivolumab monotherapy arm was 18.4 months in the locally confirmed cohort, which is comparable to the 16.5 months seen for pembrolizumab monotherapy in KEYNOTE-177. This validates the assertion that it is inappropriate to compare a centrally confirmed population with a locally confirmed population.
15	Page 13 Section 3.10 The draft guidance states that “the committee noted that most people in the ad-hoc analysis were having first-line treatment (the exact number is confidential and cannot be reported here)”[10]. At the ACM, NICE did not have access to a breakdown of the data by line of therapy, so the committee could not have considered the patient characteristics or make such a definitive statement. After the ACM, on Saturday 25th January, BMS published these data at the ASCO GI congress[11] and in the Lancet[1]. Within the ‘all treatment lines’ cohort used to inform the EAG’s validation analysis, 57% of the patients were treated in the 1L setting, with 43% receiving treatment in the 2L, 3L or beyond. Thus, any conclusions are speculative and do not fully reflect the 1L population that is relevant for decision making purpose. Nonetheless, the population characteristics are not strictly relevant, as the comparison did not compare a like-for-like patient population. It is particularly concerning that the EAG did not correctly define the patient population in the analysis submitted to the appraisal committee.
16	Page 14 Section 3.10 When discussing the EAG’s validation analysis, the draft guidance notes that any impact on the applicability of the CheckMate 8HW population to the modelled population would also impact on the nivolumab with ipilimumab data, but that this was not the case. However, the EAG’s fit to the modelled data noticeably underpredicts nivolumab with ipilimumab PFS across the observed data period. While the magnitude of under prediction is less than that for pembrolizumab, the nivolumab with ipilimumab arm remains impacted, so that the draft guidance statement is incorrect.

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17	Section 3.10 This section is based on the false assumption of equivalency between outcomes in locally confirmed and centrally confirmed patients and does not reflect the differences in outcomes in locally confirmed dMMR/MSI-H patients that are not centrally confirmed (in other words, locally misdiagnosed patients). Following the appraisal committee meeting, BMS published data demonstrating that median PFS in the nivolumab monotherapy arm for the centrally confirmed population is 39.3 months, whereas in the locally confirmed population this is 18.4 months. As such, comparing model outcomes based on the locally confirmed outcomes and trial data for the centrally confirmed cohort is entirely inappropriate and biased towards pembrolizumab (as noted above). In CheckMate 8HW and KEYNOTE-177, patients were randomised based on local testing. In CheckMate 8HW, tissue samples were then centrally tested to confirm MSI-H/dMMR status which found that 15% of local tests returned false positives, i.e. patients with MSS/pMMR. Patients with MSS/pMMR disease are not known to respond to treatment with immuno-oncology therapies hence, as expected, the PFS curves for the ITT (locally confirmed population) were lower than for the centrally confirmed population modelled by the EAG. KEYNOTE-177 is likely to have had a proportion of patients who were locally confirmed dMMR/MSI-H but would not have been centrally confirmed if assessed, and therefore likely to include a proportion of patients who did not have MSI-H/dMMR disease. Thus, comparing a centrally confirmed dMMR/MSI-H cohort for nivolumab monotherapy versus a locally confirmed cohort for pembrolizumab is inherently biased, as you would expect the centrally confirmed cohort to have higher PFS outcomes.
18	Section 3.10 BMS acknowledge that clinical experts anticipate similar results for nivolumab monotherapy and pembrolizumab as they have a similar mode of action. However, that does not mean that identical results are expected, particularly when comparing different patient populations. The below points summarise the methodological issues with the EAG's approach, as endorsed by the HST committee. 1. The starting point for the EAG's approach is the assumption that pembrolizumab is identical and interchangeable with nivolumab. They then assume that a model incorporating data based on the 1L prescribing of pembrolizumab from the KEYNOTE-177 randomised controlled trial (RCT) with local testing of dMMR or MSI-H is incorrect as it does not accurately predict: • PFS for a different product (nivolumab) • PFS aggregated across multiple lines of therapy (first, second, third line and beyond). • PFS in a cohort with centrally tested dMMR or MSI-H with 15% of non-MSI-H/dMMR patients removed This was inappropriate in the context of the data already available for nivolumab with ipilimumab at the time of the ACM showing that PFS outcomes are substantially different between the locally assessed and centrally

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	assessed cohort. It stands to reason that the model does not predict outcomes for an alternative drug in a population who had previously received treatment and with a different method of identifying dMMR or MSI-H, likely containing a proportion of patients who would be insensitive to treatment with immunotherapy. 2. The EAG seek to justify their use of data that contain a mix of first and later lines of therapy by noting that the company cost-effectiveness model predictions for 1L nivolumab with ipilimumab are reflected in the five-year Kaplan-Meier plot of PFS for all lines of therapy. Whilst in this case the EAG are comparing the correct treatments with each other, they are still ignoring line of therapy and the difference in the presence/absence of MSS/pMMR patients in the population. The coincidence that the model predictions for nivolumab with ipilimumab are similar to the five-year Kaplan-Meier plot of PFS for all lines of therapy is no justification for ignoring RCT data for pembrolizumab and assuming nivolumab in all lines can be considered an adequate substitute. 3. The EAG then proceeded to adjust the HR for TTP for pembrolizumab in the cost-effectiveness model to reflect the Kaplan-Meier results for nivolumab monotherapy in all lines of treatment. The issues with this element of the EAG approach include: • The data shared by BMS had a constant HR of [redacted]. The EAG have adjusted FPNMA values by a value of 0.6 with no justification for selecting a different value to the one calculated by the CheckMate 8HW trial statisticians. • In section 3.8 of the draft guidance, it is correctly noted that the most appropriate method to conducting an ITC between nivolumab with ipilimumab and pembrolizumab is with an FPNMA. “The FPNMA is a particularly useful approach for capturing non-linear relationships between treatment effects and covariates, and when the assumption of proportional hazards does not hold. The EAG agreed with the company that this was the case in CheckMate 8HW, so estimating a time-varying hazard ratio was most appropriate”[10]. However, in the exploratory analysis the EAG are applying a constant HR, assuming a uniform difference between the treatment arms, which directly contradicts the approach advocated when robust RCT data are being used in the ITC. • Additionally, in the implementation of the exploratory analysis in the cost-effectiveness model, instead of substituting one HR for another the EAG have multiplied the FPNMA base case HR by the HR they have selected. There is no methodological justification provided for this non-standard method of applying a new value in this way. This substantially overestimates the efficacy unnecessarily in favour of pembrolizumab, as demonstrated in the analysis appendix provided by BMS. • It should be noted that the EAG exploratory analysis consistently underpredicts the efficacy of nivolumab with ipilimumab. However, this is to be expected given the limitations summarised above. 4. It is BMS’ opinion that by substituting the data for nivolumab monotherapy in all lines of therapy for pembrolizumab in the 1L the committee is: • deviating from the decision problem comparators. • incorporating a comparator that is not licensed in the UK or approved by NICE in this indication.

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]

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	• deviating from the decision problem population (all lines vs 1L in the scope).
19	<u>The company's semi-Markov model and assumptions that progression free survival translates to overall survival</u> On page 14 it states "The EAG noted that, within this model structure, gains in progression-free survival directly equate to a gain in the estimated overall survival. Because overall-survival data was not provided from CheckMate 8HW, the EAG was unable to validate this assumption" [p14, draft guidance[10]]. It is important to clarify this point for commentators and consultees that are not familiar with decision analytic modelling. The model does not assume that PFS equals OS. In the model patients can remain in the PFS state or progress directly to death or the progressed state. In the progressed state patients can remain in that state or they can progress to the death state. Summing the number of patients in the PFS state and the progressed state will give OS. On page 15 of the EAG report, it states "the company's model assumed equal post-progression survival across all arms in the model (see section 3.9). The EAG highlighted that this means the model assumes that progression-free survival in each arm translates into overall survival".[10] This is incorrect and should be clarified; instead, the differences in OS between treatments is driven by the differences in PFS applied in the model. Given that the combination of nivolumab with ipilimumab is proving to be so efficacious, BMS have limited data on mortality. As a result, the model conservatively assumes that all treatments in the model have the same rate of mortality once patients enter the progressed state. It is unlikely that patients receiving 1L chemotherapy or pembrolizumab will have equal survival to patients receiving nivolumab with ipilimumab following progression. There is no clinical evidence to suggest that patients could progress sooner but remain alive longer once they have progressed. Further, the appraisal committee concluded that lack of OS data was a substantial limitation that contributes a high degree of uncertainty to the cost-effectiveness analysis.[10] BMS are surprised that the HST committee feels that the absence of OS data creates a high degree of uncertainty in the appraisal of two established immuno-oncology treatments with evidence from other tumours demonstrating sustained benefit out to 10 years. BMS will reflect on the HST committee's feedback on the challenges of appraising immuno-oncology treatments with substantial survival gains and late OS trial results. In addition, BMS are surprised with the committee conclusions in the context of the white paper on surrogate endpoints in cost-effectiveness analysis developed by NICE in collaboration with its international partners, as outlined in comment 3.[2] The company provided evidence in line with the recommendations outlined in the white paper (robust evidence of a strong correlation between PFS and OS, a clear biological rationale and clinical expert support). Further, BMS reported the PFS data transparently and conducted scenario analyses to assess the impact of the assumption. It is therefore surprising that the EAG and the appraisal committee considered scenarios with no OS benefit to be clinically plausible.

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]

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	BMS have provided immature OS data for the EAG and the HST committee to confirm that the beneficial impact on PFS outcomes seen in the CheckMate 8HW trial result in better OS for nivolumab with ipilimumab compared to both chemotherapy and nivolumab monotherapy. As a result, this uncertainty should be considered resolved. The OS data should be utilised to confirm the projected outcomes for both PFS and OS.
20	Page 15 Section 3.12 BMS believe that there is a typographical error, and the following sentence should be referring to CheckMate 8HW and not CheckMate 142, "The EAG also highlighted some immature safety endpoint death data from CheckMate 142 (this data is considered confidential by the company and cannot be reported here" [p15, draft guidance[10]].
21	<u>Post-progression survival</u> The HST committee agreed with the EAG that a scenario requested in response to the clarification questions (B21a) should be used to model 2L treatment for patients receiving 1L chemotherapy. Some time was devoted to this topic at the ACM, but it was not fully explored. As the appraisal focuses on 1L treatment, BMS devoted the majority of its time to modelling 1L treatments. BMS took a pragmatic approach to modelling the 2L treatment for chemotherapy as pembrolizumab is the key comparator in this appraisal. The clinical experts at the ACM confirmed that the majority of patients are treated with pembrolizumab in the 1L. The rapidly developed scenario of 2L nivolumab with ipilimumab for patients receiving 1L treatment with chemotherapy has substantial challenges. The scenario assumes all patients are able to receive nivolumab with ipilimumab and receive the subsequent survival benefits. However, this lacks face validity, as some patients will be unable to receive a doublet immunotherapy. As a result, patients who receive 1L chemotherapy generate more life years than patients receiving pembrolizumab. This contradicts the findings of TA709 (Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency). Further, this post-progression survival was used within the EAG base case analysis, which included use of chemotherapy and pembrolizumab as 2L therapy after 1L chemotherapy. The revised model assumes that patients that start (first line) on chemotherapy go on to either have chemotherapy (4%) pembrolizumab (56%) or nivolumab plus ipilimumab (40%). However, there are large differences in the relative efficacies of nivolumab with ipilimumab, pembrolizumab and chemotherapy. The EAG scenario applies the efficacy of nivolumab (PD-1) plus ipilimumab (CTLA-4), but the majority of patients receive the cost of pembrolizumab (PD-1). To use the terminology of the EAG, this divorces cost from effects. The EAG are overestimating efficacy and underestimating the cost of subsequent treatment. As a result, the chemotherapy arm benefits from the improved effectiveness of nivolumab with ipilimumab with the reduced costs of pembrolizumab and chemotherapy, which biases outcomes in the modelled chemotherapy arm, magnifying the face validity challenges.

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	BMS has provided an additional scenario that includes modelling of survival outcomes of nivolumab with ipilimumab, pembrolizumab and chemotherapy as subsequent treatment. OS data from relevant studies in the 2L setting were digitised and used to derive exponential functions that could be applied in the economic model and weighted by subsequent treatment usage to derive a survival curve reflecting all three subsequent therapies. When added to the company base case, this had a large impact on resource use in favour of nivolumab plus ipilimumab. This scenario returned a dominant ICER when applied to both the company and EAG base case.
22	Time to progression and treatment waning The HST committee "concluded that equal hazards for nivolumab with ipilimumab and pembrolizumab should be assumed after 2 years of treatment" (p19, draft guidance[10]). The EAG rationale for this approach can be summarised as follows: • Clinical expert opinion: advice to the EAG highlighted that an infinitely increasing treatment effect is not reasonable, as clinical response to immunotherapies tends to occur in the first year of treatment. However, this does not imply that hazards should be equal at two years. Further, clinical expert opinion provided to NICE note the potential for nivolumab with ipilimumab to improve the rate of cure in this population, particularly for patients who respond to treatment. Newly available data from the locally confirmed all treatment lines population shows that 63% of patients in the nivolumab with ipilimumab arm achieve an objective response (28% complete response). This response is durable (median duration of response not reached) and Kaplan-Meier data show that only a small proportion of patients lose this response once achieved.[1] Although analysis is not yet available, it is reasonable to assume that patients with a complete or partial response comprise the majority of patients without a PFS event at two years. As a result, it is not plausible to assume that patients who have not progressed by two years have an increased risk of progression after this point, in either treatment arm. • Low patient numbers from two years: at two years, 67/202 patients remain at risk for PFS in the nivolumab with ipilimumab arm of CheckMate 8HW but only 4/101 in the chemotherapy arm, which was suggested would make the ITC evidence uncertain. However, despite low patient numbers, the FPNMA showed statistically significant benefits for nivolumab with ipilimumab over pembrolizumab from 6 months to five years. BMS has shared evidence from CheckMate 8HW of a statistically significant benefit for nivolumab with ipilimumab over nivolumab monotherapy,[1] showing adequate patient numbers out to four years, indicating stable clinical efficacy well beyond 2 years. • Apparent ongoing OS benefit for nivolumab with ipilimumab: the EAG note that the model appears to have an OS benefit for nivolumab with ipilimumab after hazards are equalised at two years. However, the figure provided by the EAG excludes background mortality. When background mortality is included, there is no ongoing OS benefit for nivolumab with ipilimumab over pembrolizumab after hazards are equalised at two years.

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	• The EAG also noted that the steep jump in the HR for PFS "may not be completely realistic" (page 136, EAG report). In response to the draft consultation, BMS have conducted additional analyses (provided as a separate appendix) designed to address the committee's concerns and address uncertainty. These analyses demonstrate that application of treatment waning at any point, but especially at two years, biases the outcomes in favour of pembrolizumab and fails to reflect the observed evidence from KEYNOTE-177 and CheckMate 8HW.
23	<u>Time to treatment discontinuation</u> The HST committee "preferred the EAG's alternative assumption of applying the hazard ratio used for time to progression to the TTD Kaplan–Meier curve for nivolumab with ipilimumab" (p20, draft guidance[10]) to estimate pembrolizumab time on treatment. Time to treatment discontinuation (TTD) is not influenced by progression alone. While more patients discontinued due to disease progression during KEYNOTE-177 (50 [32.7%] patients in the pembrolizumab arm), a significant number discontinued due to adverse events (22 [14.4%] patients) and other reasons.[12] Similarly, application of the PFS NMA outcomes onto the nivolumab with ipilimumab TTD data fails to appreciate the potential differences in hazard profile between PFS and TTD outcomes. Further, the EAG approach has the unintended consequence that modelled time on treatment is longer for chemotherapy than for pembrolizumab, which does not fit with data from KEYNOTE-177 and is not clinically plausible. Clinician opinion given during the ACM and noted in the draft guidance warned against comparing across KEYNOTE-177 and CheckMate 8HW to determine TTD: these trials were done at different times, and knowledge about the clinical benefits of staying on an immunotherapy has increased over that time, which may have influenced in-trial decisions to stop treatment later with increased prescriber confidence and experience. In the interests of resolving the lack of data for pembrolizumab in as robust a method as possible, BMS have included the TTD from the September 2024 database lock for the nivolumab monotherapy arm to inform pembrolizumab modelled time on treatment (see provided appendix). This analysis demonstrates further cost savings for nivolumab plus ipilimumab compared with pembrolizumab and a more cost-effective ICER. BMS are assuming that line of therapy would have a minimal impact on TTD, particularly as there is limited impact when comparing 1L nivolumab with ipilimumab TTD and the equivalent data for all treatment lines.
24	<u>Time to treatment discontinuation</u> On page 19 of the draft consultation, the EAG noted that the data presented are the mean duration of treatment data, which uses the same definition in both trials, so it is not affected by censoring. However, this misunderstands the differences in the endpoints and the extent to which each are affected by follow up. CheckMate 8HW collected two sets of data describing the duration of treatment: • Time to discontinuation: Measures time from randomisation to the patient's last dose, regardless of study end or follow-up duration. TTD provides a robust, long-term view of treatment duration. • Time on treatment: Measures time from randomisation to the study end or the patient's last dose, whichever comes first. Time on treatment is influenced by

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	follow-up duration and may underestimate treatment time, particularly for ongoing therapies. CheckMate 8HW collected data on both TTD and time on treatment to provide a complete view of patient treatment duration, making it more reliable for capturing full treatment time. In contrast, KEYNOTE-177 only reported time on treatment which is limited by follow-up time and might not reflect actual treatment duration for patients still on therapy at study closure. TTD is the more robust endpoint and it also tends to be longer compared with time on treatment, due to the impact of censoring instead of including patients with ongoing treatment as events at last dose. Further, KEYNOTE-177 was conducted earlier than CheckMate 8HW, meaning the trials were performed during different periods of clinical practice, with evolving clinician experience in immunotherapy prescribing and management. In summary, an ITC between CheckMate 8HW and KEYNOTE-177 time on treatment data would be uncertain due to: • Different Endpoints: CheckMate 8HW reported TTD, which fully reflects treatment duration, while KEYNOTE-177 relied only on time on treatment, which can underestimate treatment time. • Impact of follow-up: Time on treatment is dependent on follow-up duration, while TTD is unaffected, leading to inherent differences in data accuracy. • Time gap between trials: KEYNOTE-177 (started in 2015) was conducted years before CheckMate 8HW (started in 2019), during which prescriber confidence, experience, and understanding of immunotherapies evolved significantly, influencing treatment patterns. In line with this evolving clinical practice, clinicians highlighted during the appraisal committee that comparisons between these trials are problematic because knowledge of the clinical benefits of staying on immunotherapies improved over time. This could result in later discontinuation decisions in CheckMate 8HW versus earlier stopping in KEYNOTE-177. In conclusion, comparing treatment duration between CheckMate 8HW and KEYNOTE-177 is inappropriate due to differences in endpoints (TTD vs. time on treatment, study follow-up designs, and the time gap between trials. The evolution of clinical practice and prescriber confidence over these years further complicates drawing fair comparisons of treatment patterns across these studies.
25	<u>Resource use</u> BMS are happy to accept the resource use assumptions favoured by the EAG and the HST committee. However, we would like to note that BMS do not have any issues with the resource use estimates selected in TA866, TA716, TA709, TA668, TA439 and TA405 by other manufacturers and EAGs and endorsed by other NICE committees.
26	<u>Acceptable ICER</u> The first bullet point, treatment effect because of lack of OS data, has been addressed, as per comment 3. BMS are sharing immature OS data with NICE as part of this response, to address the HST's concerns regarding uncertainty. The OS data should be utilised to confirm the projected outcomes for both PFS and OS.

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	The second bullet point, FPNMA, has been addressed in comment 4. BMS do not agree that there is a violation of transitivity or class treatment effect assumptions that prevent the FPNMA from being appropriate to assess the treatment effect of nivolumab with ipilimumab compared with pembrolizumab. Further, in cases where transitivity assumption is violated, then an unanchored MAIC is the most appropriate approach. BMS has conducted this analysis and included it in the company submission alongside the FPNMA. The unanchored MAIC provided similar outcomes to the FPNMA, although outcomes were slightly higher for pembrolizumab. As such, the transitivity of the FPNMA network should not be considered a source of uncertainty that would require a lower acceptable ICER, as this has already been addressed. The HST committee feel there is a high level of uncertainty relating to whether PFS can be assumed to translate to OS. However, as described in detail in comment 3, there is substantial, robust evidence to indicate that PFS is appropriate to inform OS in this setting.
27	<u>Surgery in patients with unresectable disease</u> BMS agree with clinical expert opinion that clinical experience with people with dMMR or MSI-H metastatic colorectal cancer suggests that up to about one-third of people who had had unresectable disease could have resectable disease after treatment with nivolumab with ipilimumab. This could allow them to have potentially curative surgery and improve the chance of long-term survival. Further, BMS note clinical expert advice provided to NICE that nivolumab with ipilimumab is likely to result in an increased cure rate versus current standard of care. The current economic model does not reflect either assertion from clinicians. While these are plausible outcomes, BMS acknowledge that it may not be possible to robustly include this within the economic model. As a result, it should be more explicitly noted in Section 3.18 of the draft guidance that the economic model outcomes are conservative and underestimate the potential value of nivolumab with ipilimumab.
28	<u>Committee's preferred assumptions</u> BMS accept the HST committee's preferred assumptions of: 1. the EAG's approach to resource use: a) oncologist visits aligning with treatment administration visits, then tapering once people are off treatment, and stopping when people are discharged at 5 years. b) costs for 2L treatment aligning with those for 1L treatment. c) palliative care costs aligned to people having palliative care in line with UK practice. d) costs for subsequent lines of treatment applied using a payoff approach (see section 3.17). 2. the committee also agreed with the following minor changes to the company's model preferred by the EAG: a) Health Survey England data rather than trial body weight used to calculate wastage. b) using trial data rather than market share to model the split of treatments included in the chemotherapy comparator. c) no half-cycle correction for TTD. BMS agree with:

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	3. using data from the Cancer Drugs Fund clinical lead on subsequent treatment use after immunotherapy and chemotherapy to inform the subsequent treatments used in the model. • BMS note that the data on subsequent treatment use after chemotherapy must be implemented for efficacy as well as costs. BMS has a provided a robust scenario that includes survival data for pembrolizumab and chemotherapy as well as nivolumab with ipilimumab (as described in comment 21). BMS disagree strongly with the following EAG assumptions that the HST committee initially favoured after the ACM: 4. application of an HR to the modelled time to progression curve for pembrolizumab to improve visual fit to the 5-year Kaplan–Meier PFS data for nivolumab alone (see section 3.10). • As described in comments 5 and 18, the EAG has adjusted ITC HRs for modelled pembrolizumab curve outcomes, based on a locally confirmed population, to match observed outcomes from a centrally confirmed nivolumab monotherapy arm of CheckMate 8HW. Data provided for the locally confirmed cohort demonstrates how inappropriate this approach was and highlights how poorly the EAG revised base case matches observed data. 5. post-progression survival for people after 1L chemotherapy taken from exponential fit to cohort 2 of CheckMate 142 OS to reflect expectation of improved survival with nivolumab with ipilimumab. • The EAG scenario applies the efficacy of nivolumab (PD-1) with ipilimumab (CTLA-4) but the majority of patients receive the cost of pembrolizumab (PD-1) (as described in comment 21). BMS note that the data on subsequent treatment use after chemotherapy must be implemented for efficacy as well as costs. 6. treatment effect from the FPNMA only applies to the first 2 years of the model and after this, hazards are equal for pembrolizumab and nivolumab with ipilimumab. • As noted in comment 22, clinical advice to the EAG highlighted that an infinitely increasing treatment effect is not reasonable, as clinical response to immunotherapies tends to occur in the first year of treatment. However, clinical expert opinion provided to NICE note the potential for nivolumab with ipilimumab to improve the rate of cure in this population, particularly for patients who respond to treatment. CheckMate 8HW data demonstrate a high rate of response for nivolumab with ipilimumab arm and an extended duration of response. As a result, it is plausible to suggest that outcomes are maintained. Further, there is no evidence to support equal hazards at two years. 7. time on treatment for pembrolizumab assumed to be lower than time on treatment for nivolumab with ipilimumab, based on applying the HR used for TTP to the TTD Kaplan–Meier curve for nivolumab with ipilimumab. • Comments 23 and 24 summarise the concerns with this approach. TTD is not influenced by progression alone and clinical data show that a large proportion of patients discontinue due to adverse events and other reasons.

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	Further, the EAG approach has the unintended consequence that modelled time on treatment is longer for chemotherapy than for pembrolizumab, which does not fit with data from KEYNOTE-177. A cost-effectiveness appendix has been provided by BMS, with analyses designed to address the committee's concerns and uncertainties. The approach outlined in this appendix provides a significantly better fit to the observed clinical data than the EAG approach and also takes into account clinical expert opinion provided to NICE.

Insert extra rows as needed

Checklist for submitting comments

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Single Technology Appraisal

Nivolumab plus ipilimumab for untreated metastatic colorectal cancer with high microsatellite instability or deficient mismatch repair [ID1136]

Appendix: BMS analysis following draft guidance

March 2025

File name	Version	Contains confidential information	Date
	V1	Yes	3rd March 2025

Executive summary

Following the appraisal committee meeting, BMS has conducted additional analyses to address the committee's concerns and adapt assumptions/approaches implemented by the EAG which do not align with observed clinical data or appropriate methodology.

A summary of the economic model updates is presented in Table 1 and an updated base case analysis is presented in Section 6. Table 2 below provides a summary of the amendments made by BMS against the EAG approach and committee preferences, alongside the rationale for these amendments.

Given the significant challenges in the EAG approach and the lack of alignment with clinical expert opinion, BMS strongly believes it is crucial for clinical experts to attend the second meeting to validate an updated approach. Their presence will ensure that their valuable insights are fully considered, allowing for a more robust and informed decision-making process.

Table 1. Summary of updates to economic model inputs

Model input	Committee preferred assumption	BMS updated base case	Section reference	Scenario
Subsequent treatment costs	Costs for subsequent lines of treatment applied using payoff approach.	Payoff approach used in line with committee-preferred assumptions. However, time on treatment aligned with observed time on treatment from key studies	Section 1	Payoff approach, with updated time on treatment from key studies (Table 5)
Subsequent treatments following first-line chemotherapy	2.2% FOLFIRI 1.8% FOLFOX 56% PEMBRO 40% NIVO + IPI	As committee-preferred assumptions	-	Scenario encompassing all committee preferred assumptions applied in updated BMS base case analysis (Table 21)
Resource use	Oncologist visits align with treatment administration visits and once patients are off treatment taper off and stop when patients are discharged at 5 years. Resource use costs for 2nd line treatment align with those for 1st line treatment. Palliative care costs align to patients receiving palliative care in line with UK practice.	As committee-preferred assumptions	-	
Population weight	Use HSE data to calculate wastage	As committee-preferred assumptions	-	
Chemotherapy comparator	Use trial data for the split of treatments included in the chemotherapy comparator.	As committee-preferred assumptions	-	
Half-cycle correction	No half-cycle correction for TTD.	As committee-preferred assumptions	-	

Model input	Committee preferred assumption	BMS updated base case	Section reference	Scenario
Time on treatment for pembrolizumab arm	Time on treatment for PEMBRO is derived from CM8HW NIVO + IPI TTD adjusted using PFS HR derived from NMA	PEMBRO time on treatment is derived from CM8HW NIVO monotherapy arm TTD	Section 2	PEMBRO time on treatment is derived from CM8HW NIVO monotherapy arm TTD (Table 8)
Initial pembrolizumab TTP outcomes	PEMBRO TTP is derived by the PFS HR obtained from the FP-NMA, adjusted by 0.6	PEMBRO TTP is derived by the PFS HR obtained from the FP-NMA, without adjustment	Section 3	PEMBRO TTP informed by CM8HW NIVO + IPI vs NIVO PFS HR or informed by NIVO monotherapy TTP (Table 12)
Long-term pembrolizumab TTP outcomes	Hazards for PEMBRO and NIVO + IPI set equal at 2 years.	Removed following inclusion of NIVO monotherapy TTP	Section 4	Treatment waning at six years (Table 13)
Post progression survival following first-line chemotherapy	PPS for patients after chemotherapy taken from exponential fit to CM142 OS to reflect expectation of improved survival with NIVO + IPI.	PPS taken from exponential fit to OS data CM142 (NIVO+IPI), KEYNOTE-164 (PEMBRO) and CRYSTAL (chemotherapy), weighted by proportion receiving each therapy	Section 5	PPS taken from exponential fit to OS data CM142 (NIVO+IPI), KEYNOTE-164 (PEMBRO) and CRYSTAL (chemotherapy), weighted by proportion receiving each therapy (Table 18)

Abbreviations: CM8HW, CheckMate 8HW; FOLFIRI, Folinic acid, fluorouracil and irinotecan; FOLFOX, Folinic acid, fluorouracil and oxaliplatin; FP, fractional polynomial; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; NMA, network meta-analysis; OS, overall survival, PEMBRO, pembrolizumab; PFS, progression-free survival; PPS post-progression survival; QALY, quality adjusted life-years; TTD, Time-to-discontinuation; TTP, time-to-progression

Table 2. Rationale for amending EAG approach and committee-preferred assumptions

Item	EAG approach	Company-updated approach	Rationale
Subsequent treatment costs – time on treatment	Applied subsequent treatment as the cost of a course on entry to the progressed disease state and assumed a mean time on treatment for NIVO+IPI and PEMBRO based on the mean time-on-treatment in CM8HW	Updated the time on subsequent treatment for PEMBRO and NIVO + IPI to use median time-to-discontinuation (TTD) from CM8HW	TTD censors patients with ongoing treatment at the time of last dose, whereas time-on-treatment measures the time between randomisation and final dose, irrespective of whether a patient is still receiving treatment. As a result, time on treatment underestimates therapy duration for any studies where patients are still receiving treatment and the approach taken by the EAG of using time on treatment underestimates treatment costs. Duration of first line therapy applies TTD data, so BMS have updated the economic analysis to reflect this in the subsequent treatment setting. The EAG base case assumed a mean time on treatment for NIVO + IPI and PEMBRO in the 2nd line of [redacted] based on the mean time on treatment in CM8HW.[1] The updated BMS base case applies a mean time on treatment of [redacted] based on median TTD in CM8HW.[1]
Time on treatment for pembrolizumab arm	Apply the HR from the PFS NMA to the curve fit to NIVO+IPI TTD data.	PEMBRO time on treatment is derived from CM8HW NIVO monotherapy arm TTD.	The analysis performed by the EAG assumes that discontinuation of treatment is solely down to disease progression and does not consider discontinuation due to adverse events. This is inconsistent with data from CheckMate 8HW and KEYNOTE-177, and is inconsistent with clinical opinion, as evidenced by results from a clinician survey performed by the company. Recognising the similar clinical efficacy of NIVO and PEMBRO described in the committee meeting, the company's amended approach uses TTD data for the NIVO monotherapy arm from CM8HW to model time on treatment for PEMBRO. This amended approach addresses concerns from the committee around the appropriateness of assuming equal TTD, addresses the risks associated with a naïve comparison between trials and offers improved robustness over the EAG approach. Mean time on treatment for the pembrolizumab arm was [redacted] months in the EAG base case analysis. The updated BMS base case applies nivolumab monotherapy TTD from CM8HW, with a mean of [redacted] months.

Item	EAG approach	Company-updated approach	Rationale
Initial pembrolizumab TTP outcomes	PEMBRO TTP is derived by the PFS HR obtained from the FP-NMA, adjusted by 0.6	PEMBRO TTP is derived by the PFS HR obtained from the FP-NMA, without adjustment	The EAG applied the adjustment to the FP-NMA HRs in order to match PFS for PEMBRO to the observed NIVO monotherapy data in the centrally confirmed all treatment lines cohort. This not appropriate for the following reasons: • Comparison of outcomes in a centrally confirmed population versus modelled outcomes for a locally confirmed population is subject to considerable bias (Table 9). • The EAG has provided no evidence or source for the adjustment factor, implying that there is no methodological rationale. • PEMBRO outcomes from the EAG base case are greatly increased versus observed nivolumab monotherapy outcomes in the locally confirmed population. Using unadjusted FP-NMA values ensures a robust ITC evidence base to provide comparative evidence for PEMBRO versus NIVO + IPI, with supportive evidence from extensive scenario analyses assessing alternative approaches. In the EAG base case, PEMBRO PFS at 1 year was [redacted], compared with observed data of 55.3% for PEMBRO from KEYNOTE-177[2,3] and [redacted] for NIVO from CM8HW. By comparison, the BMS updated base case predicts PEMBRO PFS at one year of [redacted].
Treatment waning	Assumes that treatment effect only applies to the first two years of the model and that after this timepoint hazards are equal for PEMBRO and NIVO+IPI	Removed following inclusion of NIVO monotherapy TTP.	BMS have shared evidence from CM8HW providing evidence of a statistically significant benefit for NIVO + IPI over NIVO monotherapy. At four years, 56 (of 354) patients remained at risk for PFS in the NIVO + IPI arm, with 31 (of 353) patients in the NIVO arm, indicating a stability of clinical efficacy well beyond 2 years. As noted by the clinical experts during the appraisal committee, NIVO monotherapy and PEMBRO would be expected to have similar outcomes, so that this benefit can be inferred for NIVO + IPI versus PEMBRO. Further supportive evidence is available from CM067, where the PFS benefits of NIVO+IPI over NIVO monotherapy are maintained after a minimum follow up of ten years. As outlined in the committee papers, clinical expert opinion to the committee states that “a sub-set of these cancers patients will have a complete response to treatment and may be cured; others will benefit from a prolonged period of progression free survival,” further highlighting that applying a treatment waning effect would be inappropriate in these patients. In addition, the FP-NMA demonstrated statistically significant benefit for NIVO + IPI versus PEMBRO between 6 months and 60 months. Considering the available evidence, it is unclear why the EAG have selected a treatment waning effect.

Item	EAG approach	Company-updated approach	Rationale
Post-progression survival following first-line chemotherapy	Implausible to assume that chemotherapy at second-line (after prior immunotherapy) is equally effective compared with second-line immunotherapy (after prior chemotherapy)	Enabled the modelling of outcomes of NIVO+IPI, PEMBRO and chemotherapy as a subsequent treatment following chemotherapy	The EAG's base case included costs of PEMBRO, NIVO + IPI and chemotherapy as second-line therapy after first-line chemotherapy. However, all patients in the chemotherapy arm receive survival outcomes for NIVO + IPI and there are large differences in the relative efficacies of NIVO + IPI, PEMBRO and chemotherapy. As a result, the chemotherapy arm benefits from the improved effectiveness of NIVO + IPI with the reduced costs of PEMBRO and chemotherapy, which biases outcomes in the modelled chemotherapy arm. In order to align costs and benefits for the chemotherapy arm, BMS has adapted the economic model to enable modelling of outcomes of NIVO + IPI, PEMBRO and chemotherapy as subsequent treatment. In the EAG base case, [redacted] of patients in the chemotherapy arm remain alive at 5 years, compared with [redacted] in the NIVO + IPI arm and [redacted] in the PEMBRO arm. By comparison, the BMS updated base case predicts that [redacted] of patients remain alive at five years, compared with [redacted] for PEMBRO and [redacted] for NIVO + IPI.

Abbreviations: CM8HW, CheckMate 8HW; FP, fractional polynomial; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; NMA, network meta-analysis; OS, overall survival, PEMBRO, pembrolizumab; PFS, progression-free survival; PPS post-progression survival; QALY, quality adjusted life-years; TTD, Time-to-discontinuation; TTP, time-to-progression

Approach to economic analyses

All scenario analyses and model amendments are presented versus the company and EAG base cases, in line with best practice.

The company has added the post-ACM committee preferences (distribution of subsequent treatments and derivation of PEMBRO TTP by adjusting the FP-NMA by 0.6) into the EAG model received in September 2024. The EAG model provided following the appraisal committee meeting in January 2025 was not used, as unspecified model updates had been conducted, limiting confidence in the results (Table 3). Several of these amendments have since been identified (including use of per protocol time on treatment estimation and amendment of proportion female) but others remain unidentified. There was no discussion or agreement at the appraisal committee meeting or ACD to fundamental changes to the model unrelated to the HST committee's preferred assumptions.

Table 3. Summary of the EAG base case in the September 2024 model and January 2025 model (NIVO+IPI list price)

		Versus PEMBRO			Versus chemotherapy		
		Inc costs	Inc QALYs	ICER (£/QALY)	Inc costs	Inc QALYs	ICER (£/QALY)
EAG base case	EAG report	[redacted]	[redacted]	£19,150	[redacted]	[redacted]	£49,333
	EAG model September 2024	[redacted]	[redacted]	£19,150	[redacted]	[redacted]	£49,333
	EAG model January 2025	[redacted]	[redacted]	*£19,227*	[redacted]	[redacted]	*£91,439*
EAG base case with TTP adjustment	EAG model September 2024	[redacted]	[redacted]	£57,334	[redacted]	[redacted]	£48,233
	EAG model January 2025	[redacted]	[redacted]	*Dominant*	[redacted]	[redacted]	*£91,439*
	EAG addendum 1 - January 2025	[redacted]	[redacted]	Not reported	Not reported		
	EAG addendum 2 - January 2025	[redacted]	[redacted]	*Dominant*	Not reported		
EAG base case with updated subs. treatments	EAG model September 2024	[redacted]	[redacted]	£19,641	[redacted]	[redacted]	£27,873
	EAG model January 2025	[redacted]	[redacted]	*£19,227*	[redacted]	[redacted]	*£68,694*
	EAG addendum 2 - January 2025	[redacted]	[redacted]	*£19,227*	[redacted]	[redacted]	*£68,694*
Revised EAG base case	EAG model September 2024	[redacted]	[redacted]	£57,334	[redacted]	[redacted]	£27,873
	EAG model January 2025	[redacted]	[redacted]	*Dominant*	[redacted]	[redacted]	*£68,694*
	EAG addendum 2 - January 2025	[redacted]	[redacted]	*Dominant*	[redacted]	[redacted]	*£68,694*

EAG, external assessment group; ICER, incremental cost-effectiveness ratio; LY, life year; NIVO+IPI, nivolumab with ipilimumab; PEMBRO, pembrolizumab; QALY, quality-adjusted life year

Therefore, BMS has implemented the committee-preferred approach (adjustment of FP-NMA HRs and subsequent treatment following first line chemotherapy) within the original September 2024 EAG model.

1 Subsequent treatment costs – time on treatment

The EAG applied subsequent treatment as the cost of a course on entry to the progressed disease state. BMS has amended the base case analysis to include this approach.

In addition, the EAG assumed a mean time on treatment for NIVO + IPI and PEMBRO based on the mean time on treatment in CM8HW (13.26 months[4]). However, as previously identified, the economic model applies TTD to inform

modelled time on treatment in the first line setting. TTD censors patients with ongoing treatment at time of last dose, whereas the time on treatment clinical trial endpoint measures time from randomisation to last dose regardless of whether patients are still receiving treatment.

As a result, use of the time on treatment clinical trial endpoint in the second-line model setting underestimates the cost of treatment. Time to treatment discontinuation should be used in the preferred modelling assumptions.

1.1 BMS scenario

BMS have updated the time on subsequent treatment for PEMBRO and NIVO + IPI to use median time to discontinuation from CM8HW, as outlined in Table 4.

Table 4. Time on subsequent treatment

Subsequent treatment	Weeks on subsequent treatment
FOLFIRI	20.16, aligned with TA709
FOLFOX	20.16, aligned with TA709
PEMBRO	[redacted] weeks, aligned with CM8HW median time to discontinuation for NIVO + IPI locally confirmed 1L cohort
NIVO + IPI	[redacted] weeks, aligned with CM8HW median time to discontinuation for NIVO + IPI locally confirmed 1L cohort

1.2 Economic model results

An overview of outcomes from this scenario is presented in Table 5. Amendment of subsequent treatment time increased subsequent treatment costs for the chemotherapy arm in the EAG base case. By contrast, this assumption reduced subsequent treatment costs in the company base case, when including use of the payoff approach in line with committee preferences.

Table 5. Impact of amended time on subsequent treatment (with NIVO + IPI PAS)

NIVO + IPI vs chemotherapy		Company base case	Company base case with amended time on treatment*	Updated EAG base case**	EAG base case** with amended time on treatment
Chemotherapy	Inc costs	[redacted]	[redacted]	[redacted]	[redacted]
	Inc QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	£1,831	£3,678	Dominant	Dominant

* Payoff approach used in line with committee-preferred assumptions.
**BMS reproduction of EAG base case post-ACM, due to unspecified model amendments in revised EAG model (shared with BMS after the appraisal committee meeting) that do not align with committee preferences (see section "Approach to economic analyses")
Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Inc, incremental; IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; QALYs, quality-adjusted life years.

BMS have amended their base case analysis from a per cycle subsequent treatment cost to reflect the committee-preferred approach of applying the cost of subsequent treatment upon entry in the progressed disease state (i.e. the payoff approach). However, the ICERs used for decision-making should incorporate median time to discontinuation from CM8HW to model time on subsequent treatment for PEMBRO and NIVO + IPI rather than mean time on treatment as the latter underestimates the cost of subsequent treatment as described above, and biasing the analysis against NIVO + IPI.

2 Time on treatment for pembrolizumab arm

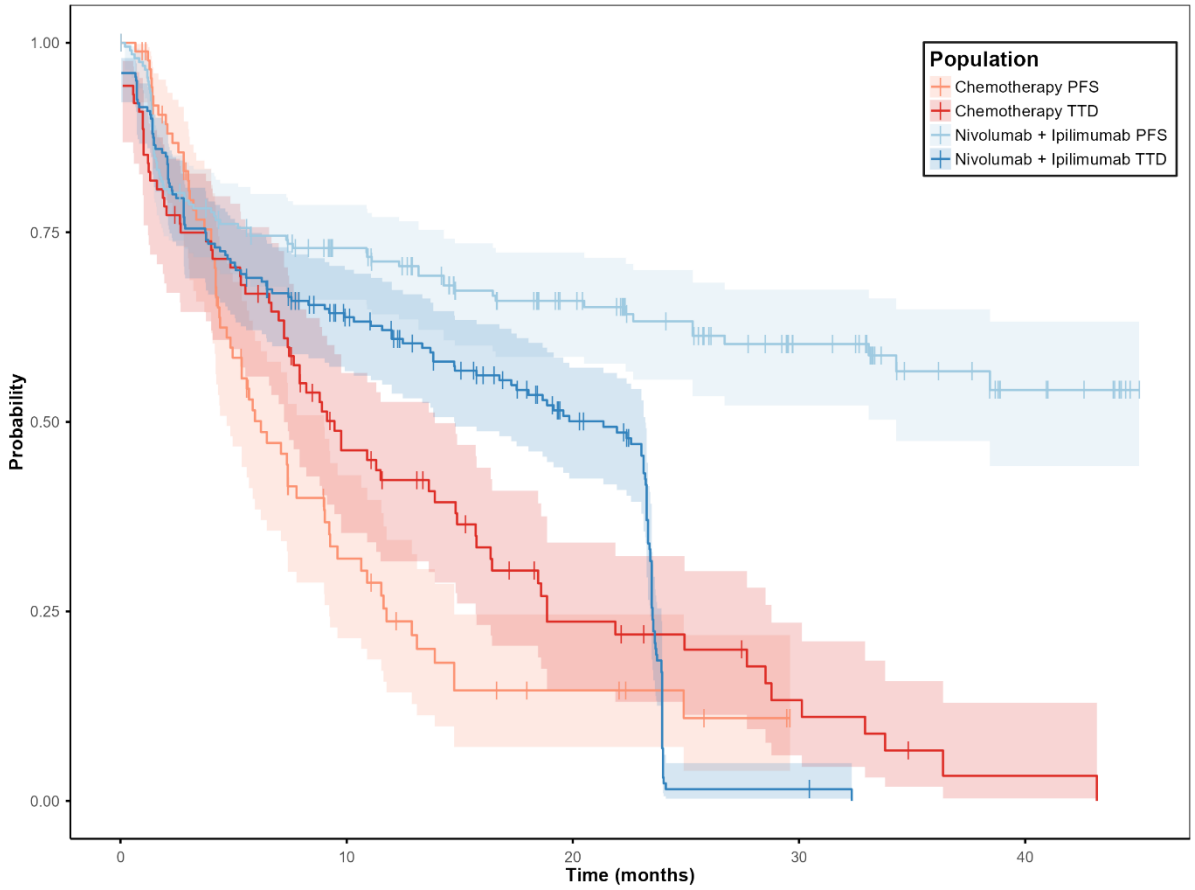
In order to inform modelled time on treatment for the pembrolizumab (PEMBRO) arm, the External Assessment Group (EAG) applied the hazard ratio (HR) from the progression-free survival (PFS) network meta-analysis (NMA) to the curve fit to nivolumab (NIVO) plus ipilimumab (IPI) time to discontinuation (TTD) data from CM8HW. The stated rationale for this approach is that this would provide a more reasonable estimate of relative time on treatment that would be expected than if PEMBRO was less effective in preventing progression.

However, it should be noted that progression is only one of the factors impacting TTD for immunotherapies. During CheckMate 8HW (CM8HW), a similar number of patients in the NIVO + IPI arm discontinued due to disease progression (38 patients) as discontinued due to adverse events (36 patients).[1,4] While more patients

discontinued due to disease progression during KEYNOTE-177 (50 patients in the pembrolizumab arm), a significant number discontinued due to adverse events (22 patients) and other reasons.[2] As such, progression cannot be considered the only factor driving a difference in TTD.

Similarly, application of the PFS FPNMA outcomes onto the NIVO + IPI TTD data fails to appreciate the potential differences in hazard profile between PFS and TTD outcomes. TTD Kaplan-Meier data are not available for pembrolizumab from KEYNOTE-177. TTD Kaplan-Meier data for NIVO + IPI and chemotherapy from CM8HW do not closely resemble PFS Kaplan-Meier data, as shown in Figure 1. As a result, applying outcomes from the PFS NMA to derive pembrolizumab TTD is likely to overestimate risk of discontinuation early in the model, where it is most influential.

Figure 1. CM8HW KM curves for PFS per BICR and TTD in all randomised subjects (interim analysis)[4]



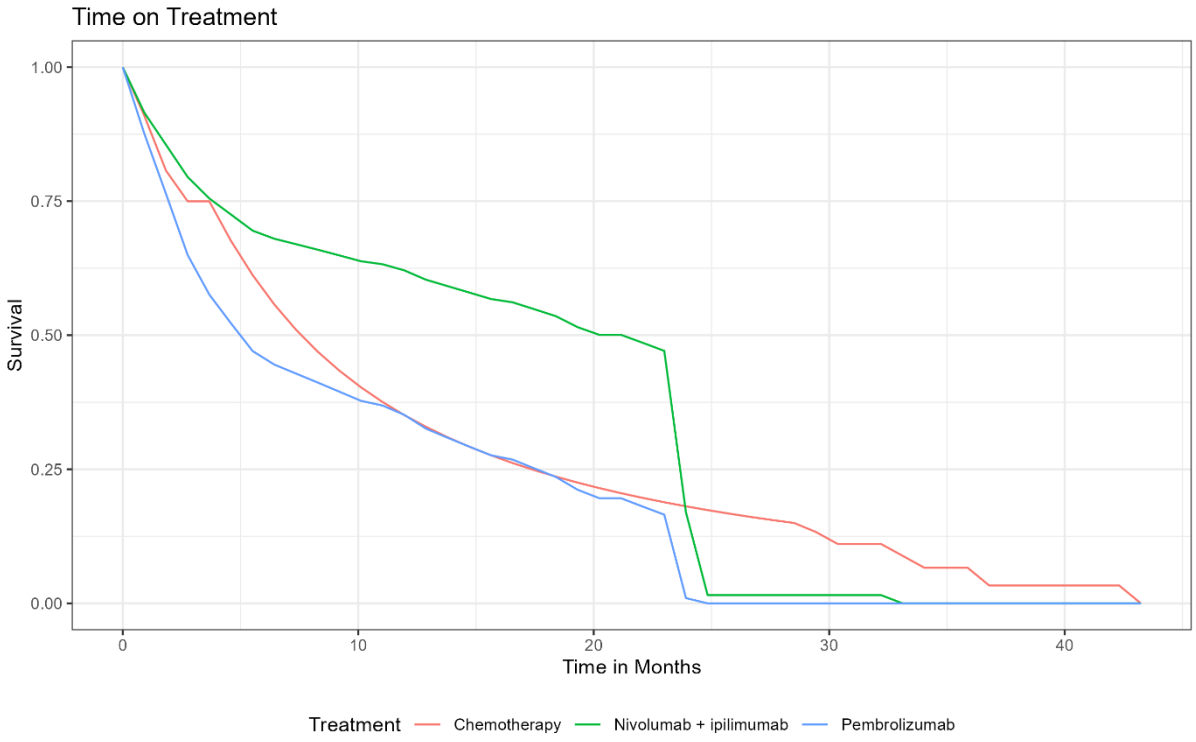
Abbreviations: BICR, blinded independent central review; CI, confidence interval; IPI, ipilimumab; NA, not available; NIVO, nivolumab; PFS, progression-free survival

Additionally, the EAG assumptions do not align fully with clinical opinion. To inform this response, BMS has undertaken a clinician survey that elicited the views (including around treatment discontinuation and TTD) of four UK clinicians experienced in using immunotherapies for the treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC).[5] One clinician felt that TTD for NIVO + IPI would be similar to that observed PEMBRO, while another felt it would shorter than for PEMBRO and two believed it would be longer, indicating that this EAG assumption may not be accepted by clinicians.[5] CM8HW data presented in Table 6 and Figure 3 align with clinician opinion in that NIVO + IPI TTD is similar to PD-L1 monotherapy TTD.

Further, the EAG has used evidence from CM8HW to inform TTD evidence for PEMBRO, which has been modelled using KEYNOTE-177. Clinician opinion during the appraisal committee, noted in the draft guidance, warned against comparing across KEYNOTE-177 and CM8HW to determine TTD, as these trials were conducted at different times, and knowledge about the clinical benefits of staying on an immunotherapy has increased over that time. Increased experience from clinicians may have influenced decisions to stop treatment later following increased prescriber confidence and familiarity.

Application of PFS HR to inform PEMBRO modelled time on treatment lacks face validity. Modelled time on treatment for PEMBRO is presented in Figure 2. As can be seen, PEMBRO time on treatment in the EAG base case analysis is lower than that of chemotherapy for the majority of the modelled horizon, which is inconsistent with outcomes from KEYNOTE-177 (presented in TA709) which demonstrated higher PFS for PEMBRO compared with chemotherapy and lower discontinuation.[2,6] Therefore, the EAG approach for modelling PEMBRO time on treatment produces outcomes which do not align with observed efficacy and safety data for PEMBRO.

Figure 2. PEMBRO time on treatment in EAG base case analysis



2.1 BMS scenario

BMS noted the committee conclusion that it was not appropriate to assume equal TTD for nivolumab plus ipilimumab and pembrolizumab because of the risk of bias in the naive comparison between trials and the clinical plausibility of this assumption. However, given the flaws in the EAG approach, noted above, BMS has sought an alternative approach that is more robust.

As noted by the EAG, NIVO and PEMBRO are both PD-L1 inhibitors and are often considered clinically similar and to have similar effectiveness. As data are available from the CM8HW NIVO monotherapy arm, TTD data from this arm have been used to inform modelled time on treatment for PEMBRO. This amended approach addresses concerns from the committee around the appropriateness of assuming equal TTD and addresses the risks associated with a naïve comparison between trials. Additionally, it offers improved robustness over the EAG approach.

A summary of CM8HW TTD data is provided in Table 6. NIVO monotherapy data are only reported for all treated patients while modelled NIVO + IPI data uses the data

for the first-line treatment cohort only, in line with the primary endpoint and the appraisal indication. As such, data are provided for NIVO + IPI and chemotherapy for both patient cohorts to aid interpretation.

As the NIVO monotherapy TTD Kaplan-Meier data is near complete at the end of CM8HW follow-up (Figure 3), this data has been applied directed in the economic model to estimate PEMBRO modelled time on treatment.

Table 6. CM8HW time to treatment discontinuation summary

	CheckMate 8HW outcomes					**Committee preferred model assumption**
	All treated patients			**First line patients**		**First line patients**
	NIVO	**NIVO + IPI**	**CHEMO**	**NIVO + IPI**	**CHEMO**	**PEMBRO (estimated)**
N	[redacted]	[redacted]	[redacted]	200	88	-
Mean (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM8HW, CheckMate 8HW; CHEMO, chemotherapy, CI, confidence interval; IPI, ipilimumab, NIVO, nivolumab.

Figure 3. CM8HW TTD Kaplan-Meier data (locally confirmed all lines cohort)

Abbreviations: NAR, number at risk

2.2 Economic model results

As can be seen in Table 7, amendment of modelled time on treatment to include NIVO monotherapy TTD increased time on treatment in the PEMBRO arm, reducing incremental costs for NIVO + IPI. While this is expected for the EAG scenario, this amendment also slightly increases modelled time on treatment for PEMBRO when applied in the company base case analysis. As a result, cost-effectiveness improved in both the company and EAG scenarios (Table 8).

Table 7. Proportion of patients on first line PEMBRO treatment in scenario (without half cycle correction)

Proportion of patients on first-line PEMBRO	Company base case	Company base case with amended time on treatment	Updated EAG base case	EAG base case with amended time on treatment
Day 196 (approx. 0.5 years)	[redacted]	[redacted]	[redacted]	[redacted]
Day 364 (approx. 1 year)	[redacted]	[redacted]	[redacted]	[redacted]
Day 560 (approx. 1.5 years)	[redacted]	[redacted]	[redacted]	[redacted]
Day 728 (approx. 2 years)	[redacted]	[redacted]	[redacted]	[redacted]
Day 924 (approx. 2.5 years)	1.5%	0.9%	0	0.9%

Abbreviations: EAG, external assessment group; PEMBRO, pembrolizumab

Table 8. Impact of amended time on treatment (with NIVO + IPI PAS)

NIVO + IPI vs PEMBRO	Company base case	Company base case with amended time on treatment	Updated EAG base case*	EAG base case* with amended time on treatment
Inc. costs	[redacted]	[redacted]	[redacted]	[redacted]
Inc. QALYs	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	Dominant	Dominant	Dominant	Dominant

*BMS reproduction of EAG base case post-ACM, due to unspecified model amendments in revised EAG model (shared with BMS after the appraisal committee meeting) that do not align with committee preferences (see section "Approach to economic analyses").
Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Inc, incremental; IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years.

Because of the risk of bias in the naive comparison between CheckMate 8HW and KEYNOTE-177, and the clinical plausibility of this assumption, the ICERs considered for decision making should use TTD data for the NIVO arm from the CM8HW NIVO monotherapy arm to inform modelled time on treatment for PEMBRO.

3 Initial pembrolizumab TTP outcomes

Following availability of CM8HW NIVO monotherapy data for the centrally confirmed dMMR/MSI-H all treatment lines cohort, the EAG applied an adjustment of 0.6 to the HRs derived from the FP-NMA in order to match PFS for PEMBRO to the observed NIVO monotherapy data. It is not valid to compare this cohort of patients against the modelled population due to the high potential for bias, as outlined in Table 9.

Table 9. Comparison of appraisal population of interest and the BMS addendum CM8HW population of interest

Appraisal population of interest	BMS addendum CM8HW population	Likely bias from comparison
Locally confirmed patients (aligning with KEYNOTE-177 and NHS use of local testing laboratories)	Centrally confirmed patients	Centrally confirmed patients have improved outcomes versus locally confirmed patients
First line (previously untreated patients)	All treatment lines (43% previously treated in BMS addendum CM8HW population[7])	Direction of bias is unclear. NIVO + IPI efficacy may be similar between treatment lines based on CM8HW evidence. PD-L1 monotherapy efficacy may be slightly decreased for previously treated patients versus previously untreated patients based on OS from KEYNOTE-164 and KEYNOTE-177, respectively.

The stated rationale for this adjustment is that clinical advisors expect PEMBRO and NIVO to have similar outcomes. However, PEMBRO and NIVO should not be considered identical or interchangeable, particularly when comparing outcomes across different patient populations.

Further, the EAG have provided no evidence or source for this adjustment factor. The PFS data shared by BMS for the centrally confirmed population had a constant HR of 0.62, while the locally confirmed population had a HR of 0.64.[7] As such, it appears that there is no methodological rationale for applying the 0.6 HR to the FP-NMA variable HRs beyond matching the observed NIVO monotherapy PFS.

Further, it is inappropriate to adjust the FP-NMA HRs using a constant factor. The draft guidance correctly concludes that the most appropriate method to conducting an indirect treatment comparison of NIVO + IPI versus PEMBRO is with a FP-NMA. The EAG agreed that use of a time-varying hazard ratio was most appropriate. However, in the exploratory analysis the EAG are applying a constant adjustment, assuming a uniform difference between the treatment arms, which directly contradicts the approach agreed to be most appropriate for the NMA.

However, it should be noted that this comparison is using two different populations and as such is inherently flawed. While the CM8HW NIVO monotherapy interim analysis reported on the all treatment lines cohort (including previously treated 2L,

3L, 3L+ patients), the economic model is assessing a first-line cohort and is informed by an FP-NMA for NIVO + IPI in the first-line setting versus PEMBRO in the first-line setting. More importantly in the context of immunotherapy efficacy, the CM8HW NIVO monotherapy interim analysis reported on patients with centrally confirmed dMMR/MSI-H mCRC whereas the economic model used data informed by patients with locally confirmed dMMR/MSI-H mCRC for all treatment arms. This distinction of locally confirmed versus centrally confirmed status was found to be highly impactful for NIVO + IPI during CM8HW. As seen in Figure 4, NIVO + IPI and NIVO monotherapy PFS outcomes are lower at all timepoints for the locally confirmed cohort when compared with the centrally confirmed cohort. For nivolumab monotherapy, median PFS in the centrally confirmed population is 39.3 months, whereas in the locally confirmed population this is 18.4 months.[7] On this basis, the EAG comparison of the modelled PFS with the interim analysis centrally confirmed cohort is not appropriate.

Figure 4. CM8HW progression-free survival in centrally confirmed (A) and locally confirmed (B) patients (reproduced from Andre et al. 2025[7])

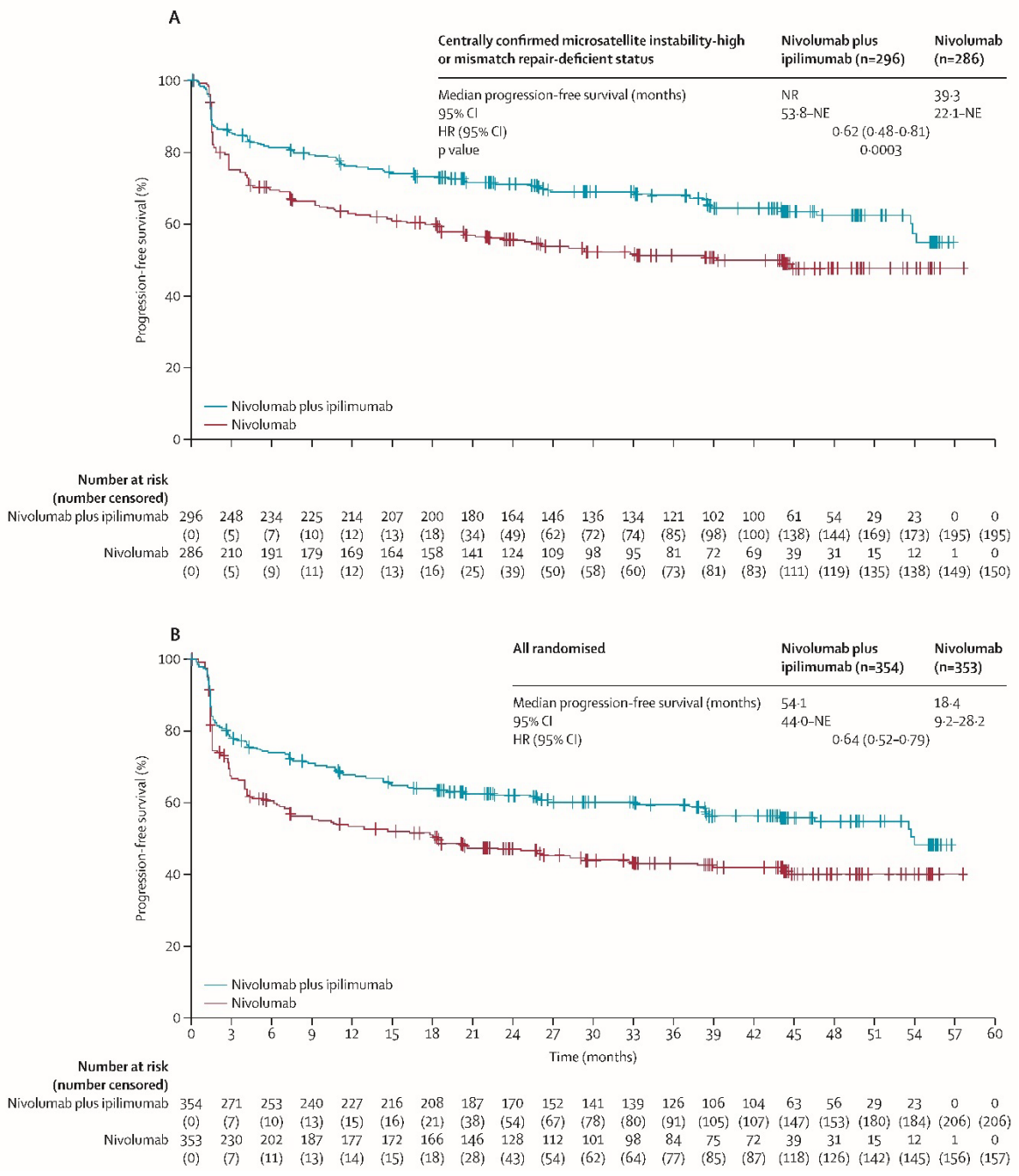


Table 10 and compare outcomes between CM8HW NIVO monotherapy, KEYNOTE-177 PEMBRO arm and the EAG base case. Additionally, modelled PEMBRO outcomes for scenarios based on more robust indirect comparison approaches are provided for contrast. The modelled scenario that most closely reflects the observed data is the unanchored MAIC scenario. The scenario applying the CM8HW NIVO monotherapy TTP extrapolation to inform PEMBRO TTP predicts PFS outcomes that

provide a close fit to CM8HW and KEYNOTE-177 data but overestimates observed outcomes at five years. Although the constant HR NMA has been presented for validation and is not the most methodologically robust approach, the outcomes more closely match observed outcomes than the EAG approach using an adjustment factor on FP-NMA HRs. Other ITC scenarios underestimate PEMBRO outcomes.

As can be seen, the EAG revised base case adjusting the FP-NMA by 0.6 exceeds all other PFS outcomes, including observed outcomes for CM8HW NIVO monotherapy arm in locally confirmed dMMR/MSI-H patients. The estimates of PEMBRO PFS produced by the EAG substantially exceed the observed outcome in KEYNOTE-177 by 8.1% in year 1 rising to 14.0% in year 5. As a result, this approach is overly bias towards PEMBRO and should not form the basis of a final ICER for NICE decision making.

Table 10. Comparison of economic model PFS outcomes, CheckMate 8HW NIVO monotherapy arm and KEYNOTE-177 PEMBRO arm

Model scenario		**1 year PFS, %**	**3-year PFS, %**	**5-year PFS, %**
KEYNOTE-177[2,3] PEMBRO arm (locally confirmed dMMR/MSI-H, first line)		55.3%	42.7%	34.0%
CheckMate 8HW NIVO monotherapy arm (locally confirmed dMMR/MSI-H, all lines)		[redacted]	[redacted]	[redacted]
Modelled PEMBRO scenarios using NMA outcomes applied to company base case	FP-NMA	[redacted]	[redacted]	[redacted]
	Anchored MAIC	[redacted]	[redacted]	[redacted]
	Unanchored MAIC	[redacted]	[redacted]	[redacted]
	Constant HR NMA	[redacted]	[redacted]	[redacted]
Modelled PEMBRO scenario using CM8HW outcomes applied to company base case[7]	NIVO monotherapy PFS HR (0.64)	[redacted]	[redacted]	[redacted]
	NIVO monotherapy TTP extrapolation	[redacted]	[redacted]	[redacted]
EAG revised base case (including constant adjustment of 0.6 to thew FP-NMA HR)		[redacted]	[redacted]	[redacted]

Abbreviations: CM8HW, CheckMate 8HW; dMMR, mismatch repair deficient, EAG, External Assessment Group; FP, fractional polynomial; HR, hazard ratio, IPI, ipilimumab; KM, Kaplan-Meier; MAIC, matching adjusted indirect comparison; MSI-H, microsatellite instability-high; NIVO, nivolumab; NMA, network meta-analysis; PEMBRO, pembrolizumab; PFS, progression-free survival

3.1 Comparison of BMS approach and EAG approach

Table 11 outlines key differences between the approach taken by the EAG and the BMS approach, particularly focussing on the EAG's unwarranted adjustment of a methodologically robust FP-NMA HR, in the absence of any evidence base. Additionally, it critiques the use of different populations to inform the model. The table below outlines these differences, emphasising the significant limitations of comparing centrally confirmed NIVO data (proxy for PEMBRO) to locally confirmed populations and demonstrating how BMS adjustments rectify these inconsistencies to produce results more accurately aligned with trial evidence.

Table 11. Comparison of EAG revised approach versus BMS exploratory scenario approach

	EAG	BMS	Explanation
Approach	Adjusted HR to FP-NMA using NIVO monotherapy data, then applied to PEMBRO	PEMBRO TTP is derived by the PFS HR obtained from the FP-NMA, without adjustment	As outlined above, the EAG approach of adjusting the FP-NMA HRs vastly overestimates PEMBRO outcomes. The current BMS approach provides a better fit to the available data and is more methodologically robust.
dMMR / MSI-H Confirmation	Centrally confirmed population (sub-population)	All treated population (locally confirmed)	In CM8HW and KEYNOTE-177, patients were randomised based on local testing. In CM8HW, tissue samples were then centrally tested to confirm MSI-H/dMMR status. In 15% of cases, the local test was found to have incorrectly identified the patients as MSI-H/dMMR (false positive, MSS/pMMR). MSS/pMMR patients are known not to response to IO, hence, as expected, the PFS curves for the ITT (locally confirmed population) were lower than for the centrally confirmed population modelled by the EAG. The EAG adjustment is based on the centrally confirmed NIVO patient sub-population compared to NIVO+IPI's all treated population (locally tested and centrally confirmed), creating an inconsistent, non-like-for-like comparison that biases efficacy in favour of PEMBRO, based on the NIVO data mentioned. In the UK context, it is expected that testing will be conducted in local centres but the quality of testing will be consistent with the central testing used in the trial, ensuring patients are not incorrectly identified as MSI-H/dMMR (false positives, MSS/pMMR) and consequently receiving these treatments unnecessarily. This implies that the efficacy and cost-effectiveness estimates for NIVO+IPI are conservative, as the base case is based on the entire treated population, which includes patients mistakenly identified and who would not achieve similar outcomes to the centrally confirmed population.
Assumptions applied in model	Assume CM8HW NIVO data is applicable to PEMBRO using centrally conformed population (sub-population)	Assumes FP-NMA provides true reflection of comparative efficacy of NIVO + IPI versus PEMBRO in the locally confirmed cohort	The EAG's base case significantly exceeds all other PFS outcomes, including CM8HW NIVO results. The EAG approach is overly biased towards PEMBRO and should not inform the final ICER for NICE decision-making. The BMS adjustments resolves this issue, producing results aligned with expectations from the appropriate trial data and evidence base.

Abbreviations: CM8HW, CheckMate 8HW; dMMR, mismatch repair deficient; EAG, External Assessment Group; FP, fractional polynomial; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; ITT, intention-to-treat; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NIVO, nivolumab; NMA, network meta-analysis; PEMBRO, pembrolizumab; PFS, progression-free survival; pMMR, mismatch repair proficient; TTP, time-to-progression

3.2 BMS scenario analysis

BMS noted the views of the clinical experts during the appraisal committee that NIVO monotherapy and PEMBRO would be expected to have similar outcomes. In the absence of direct data for PEMBRO, two options were considered to derive TTP model inputs for PEMBRO:

- **NIVO monotherapy PFS HR:** Adjustment of NIVO + IPI TTP curves using the PFS HR for NIVO + IPI versus NIVO monotherapy in the CM8HW locally confirmed all lines population (0.64).[7]
- **NIVO monotherapy TTP extrapolation:** Extrapolation of NIVO monotherapy TTP Kaplan-Meier data in the CM8HW locally confirmed all lines population using standard parameterisations.

This later approach has the advantage of leveraging a direct within-trial comparison and is more typical than applying an adjustment factor to ITC HRs in order to match PFS to observed data.

3.2.1 Extrapolation of NIVO monotherapy TTP

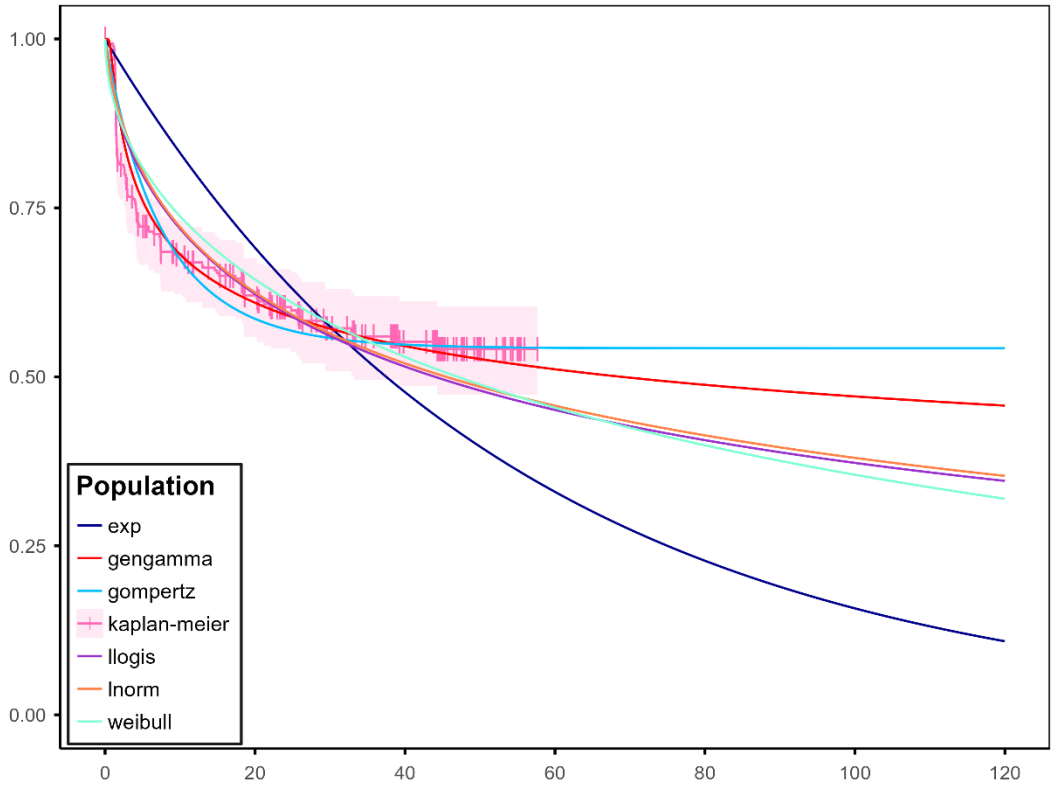
Extrapolation of NIVO monotherapy TTP is informed by the interim analysis of the CM8HW study using a data cutoff of September 2024, with data for the locally confirmed all treatment lines population. NIVO + IPI TTP extrapolations were not updated, as the extrapolations originally presented within the economic model reflect a locally confirmed first line population, which is more appropriate to the indication of interest.

Standard parametric models (exponential, generalised gamma, Gompertz, log-logistic, lognormal, Weibull) were fit to the available CM8HW data for NIVO monotherapy. These parameterisations are presented in Figure 5.

Of the parametric models, the exponential and Gompertz can be excluded based on unrealistic extrapolations, with the exponential predicting a steep decline in TTP and the Gompertz predicting an unrealistically high long-term TTP. The remaining models reflect the hazard profile of the observed data, demonstrating reduced

hazards over time. The generalised gamma appears to provide the best fit to the observed data, which is reflected in the goodness of fit statistics. Although the predicted mean survival for the generalised gamma extrapolation can be considered potentially long, this can be considered a conservative approach to informing the extrapolation of PEMBRO. Further, the generalised gamma was applied for NIVO + IPI so application for PEMBRO is recommended for consistency.

Figure 5. CM8HW NIVO monotherapy TTP standard parametric extrapolations (locally confirmed all lines population; Aug 2024 data cutoff)



Fit Name	AIC	BIC	Parameters	Median (Months)	Mean (Months)
Exp.	1169.85	1173.51	lambda: 0.0185	37.50 (30.32, 45.83)	54.10 (43.74, 66.11)
Weibull	1095.32	1102.63	shape: 0.5316; scale: 93.7252	47.04 (33.08, 67.49)	168.45 (106.87, 269.60)
Gompertz	1062.07	1069.38	shape: -0.1035; rate: 0.0633	N/A (28.24, N/A)	N/A
L. logistic	1083.90	1091.21	shape: 0.6343; scale: 44.0174	44.02 (28.80, 67.55)	N/A
Lognormal	1069.96	1077.27	mu: 3.8178; sigma: 2.5803	45.50 (29.98, 70.82)	1269.87 (511.82, 3638.15)
Gen. Gamma	1014.30	1025.27	mu: 0.8328; sigma: 1.6382; Q: -3.8098	68.94 (32.64, 159.82)	N/A

3.3 Economic model results

As shown in Table 12, using the HR for NIVO monotherapy versus NIVO + IPI PFS to derive PEMBRO TTP reduced PFS and OS in the PEMBRO arm compared with

the updated EAG base case analysis, resulting in higher incremental QALYs for NIVO + IPI versus PEMBRO. Similar results were observed when using NIVO TTP extrapolations to inform PEMBRO TTP.

By contrast, applying the NIVO monotherapy HR to derive PEMBRO TTP within the original company base case analysis increased PEMBRO PFS and OS, so that incremental QALYs for NIVO + IPI vs PEMBRO were reduced. The application of NIVO monotherapy TTP extrapolations to inform PEMBRO had a similar impact.

The NIVO monotherapy TTP extrapolation approach more closely mirrored the observed PFS values compared to applying the NIVO+IPI versus NIVO monotherapy adjusted HR, although it still overestimated the observed PFS, as shown in Table 10 and . Although this is a plausible conservative approach, use of the FP-NMA remains the most methodologically robust option. Clinical experts consistently state the opinion that NIVO and PEMBRO have similar efficacy outcomes. However, application of NIVO monotherapy data in this manner assumes that NIVO and PEMBRO have identical efficacy, which has not been demonstrated. Hence, a robust ITC is required to provide comparative evidence for PEMBRO versus NIVO + IPI. As a result, the FP-NMA outcomes are retained in the revised BMS base case analysis.

Table 12. Impact of using CM8HW NIVO monotherapy data to inform PEMBRO TTP (with NIVO + IPI PAS)

NIVO + IPI vs PEMBRO		**Company base case**	**Company base case with NIVO TTP**	**Updated EAG base case***	**EAG base case* with NIVO TTP****
NIVO monotherapy PFS HR	Inc costs	[redacted]	[redacted]	[redacted]	[redacted]
	Inc QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	Dominant	Dominant	Dominant	Dominant
NIVO monotherapy TTP extrapolation	Inc costs	[redacted]	[redacted]	[redacted]	[redacted]
	Inc QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	Dominant	Dominant	Dominant	Dominant

*BMS reproduction of EAG base case post-ACM, due to unspecified model amendments in revised EAG model (shared with BMS after the appraisal committee meeting) that do not align with committee preferences (see section “Approach to economic analyses”).
** Excludes EAG preferred assumptions for adjustment of FP-NMA outcomes and equal hazards at two years.

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Inc, incremental; IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years.

4 Treatment waning

The EAG model includes the assumption that the treatment effect only applies to the first 2 years of the model and after this timepoint hazards are equal for PEMBRO and NIVO + IPI. The rationale for this is that clinical expert advice to the EAG highlighted that an infinitely increasing treatment effect is not reasonable as response to immunotherapies tends to occur in the first year of treatment.

The EAG also noted that at two years, 67 (out of 202) patients remain at risk for progression in the NIVO + IPI arm of the CM8HW trial but only 4 (out of 101) patients remain at risk in the chemotherapy arm. It considered this to add uncertainty to efficacy comparisons following this timepoint. However, BMS has shared evidence from CM8HW providing evidence of a statistically significant benefit for NIVO + IPI over NIVO monotherapy.[7] At four years, [redacted] ([redacted]) patients remaining at risk for PFS in the NIVO + IPI arm and [redacted] ([redacted]) patients in the NIVO arm indicating a stability in this clinical efficacy well beyond 2 years. As noted by the clinical experts during the appraisal committee, NIVO monotherapy and PEMBRO would be expected to have similar outcomes, so that this benefit can be inferred for NIVO + IPI versus PEMBRO. Supportive evidence is available for CheckMate 067 in patients with melanoma, where the PFS benefits of NIVO + IPI versus NIVO are maintained after minimum follow up of ten years.[8] As such, it is not plausible to assume loss of treatment effect at two years based on low patient numbers.

Further, despite low patient numbers, the FP-NMA demonstrated statistically significant benefit for NIVO + IPI versus pembrolizumab between 6 months ([redacted] and 60 months [redacted]. This benefit was statistically significant across scenarios and across model fits, which the EAG report states suggests “confidence in the finding that the benefits of NIVO + IPI consistently outweigh the comparators”. In the context of this clear evidence that an improved hazard ratio is maintained across the CM8HW time horizon (and potentially for up to ten years), it is unclear why the EAG selected treatment waning to start at two years.

The EAG also noted that steep jump in the hazard ratio for PFS (reproduced in Figure 6) “may not be completely realistic” (EAG report, page 136). This is justified on the basis that the EAG scenario is considered to translate into continued improved treatment effect in OS (Figure 7, reproduced from the EAG report, page 136). However, it should be noted that the data to inform Figure 7 excludes background mortality, which is applied to model deaths for patients who have not yet progressed. Given that there is a significant PFS advantage for NIVO + IPI versus PEMBRO, background mortality is highly impactful over the long-term. When background mortality is included within this data, the subsequent plot shows that there is no ongoing OS benefit for NIVO + IPI over PEMBRO, as shown in Figure 8. As such, this is not a justification for an implausible jump in PFS hazard ratio without evidence.

Figure 6. Treatment effect on TTP assuming effect treatment effect waning after 2 years (reproduced from EAG report)

Figure 7. Treatment effect on PD-D transition assuming treatment effect waning after 2 years (reproduced from EAG report)

Figure 8. Treatment effect on OS assuming treatment effect waning after 2 years

On the basis of clear evidence showing sustained effectiveness, it remains unclear why the EAG has chosen to implement treatment waning impacting immediately at two years.

4.1 Economic model results

Given that there is robust evidence to support a statistically significant benefit on hazard ratio to at least six years, a conservative scenario was undertaken to demonstrate the impact of treatment waning at six years. This analysis is consistent both with prior NICE appraisals and available clinical evidence.[9]

As can be expected, addition of treatment waning at six years slightly improved QALY accrual in the EAG base case analysis and slightly worsened QALY accrual in the company base case analysis, though all ICERs returned dominance for NIVO+IPI compared with PEMBRO (Table 13). Although amending to a 6-year treatment waning assumption improves the fit of the EAG base case scenario to observed PFS data, this remains higher than plausible (PFS [redacted]% at five years in the PEMBRO arm of the economic model versus 34.0% for the PEMBRO treatment arm during KEYNOTE-177). As a result, this scenario has not been applied in the BMS updated base case analysis.

Table 13. Impact of treatment waning at six years (with NIVO + IPI PAS)

NIVO + IPI vs PEMBRO	Company base case	Company base case with waning at 6 years	EAG base case*	EAG base case* with waning at 6 years
Inc costs	[redacted]	[redacted]	[redacted]	[redacted]
Inc QALYs	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	Dominant	Dominant	Dominant	Dominant

*BMS reproduction of EAG base case post-ACM, due to unspecified model amendments in revised EAG model (shared with BMS after the appraisal committee meeting) that do not align with committee preferences (see section "Approach to economic analyses").
Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Inc, incremental; IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; QALYs, quality-adjusted life years.

Applying treatment waning at the 6-year timepoint results in NIVO+IPI being dominant compared with pembrolizumab when applied to both the EAG and company base case analyses. The sensitivity of model outcomes to treatment waning between seven and ten years is illustrated in Table 14.

Table 14. Impact of treatment waning on company and base case analysis

NIVO + IPI vs PEMBRO	Company base case with waning at 7 years	Company base case with waning at 8 years	Company base case with waning at 9 years	Company base case with waning at 10 years
Inc costs	[redacted]	[redacted]	[redacted]	[redacted]
Inc QALYs	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	Dominant	Dominant	Dominant	Dominant
NIVO + IPI vs PEMBRO	**EAG base case* with waning at 7 years**	**EAG base case* with waning at 8 years**	**EAG base case* with waning at 9 years**	**EAG base case* with waning at 10 years**
Inc costs	[redacted]	[redacted]	[redacted]	[redacted]
Inc QALYs	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	Dominant	Dominant	Dominant	Dominant

*BMS reproduction of EAG base case post-ACM, due to unspecified model amendments in revised EAG model (shared with BMS after the appraisal committee meeting) that do not align with committee preferences (see section "Approach to economic analyses").
Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Inc, incremental; IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; QALYs, quality-adjusted life years.

As there is clear evidence that an improved hazard ratio for NIVO+IPI over pembrolizumab is maintained to five years using the FP-NMA, and there is evidence of maintained clinical benefit of NIVO+IPI over NIVO (considered clinically equivalent to pembrolizumab) after ten years of follow-up, there is no clinical basis for implementing treatment waning a treatment waning of NIVO+IVI against pembrolizumab at two years. BMS have performed a scenario applying a waning of NIVO+IPI treatment effect compared with pembrolizumab from six years to remain conservative.

5 Post progression survival following first-line chemotherapy

The EAG considered that it was implausible to assume that chemotherapy as second-line treatment (after first-line immunotherapy) was equally effective as second-line immunotherapy (after first-line chemotherapy). As part of the clarification questions BMS provided a scenario analysis using OS data from cohort 2 of CheckMate 142 to inform post-progression survival (PPS) after chemotherapy, which the appraisal committee considered to be more plausible.

However, the scenario applying NIVO + IPI OS to inform PPS was used as part of the EAG base case analysis, which applied costs for PEMBRO, NIVO + IPI and chemotherapy as second-line therapy after first-line chemotherapy. There is a large difference between effectiveness of NIVO + IPI, PEMBRO and chemotherapy, as outlined in Table 15. As a result, the chemotherapy arm benefits from the improved effectiveness of NIVO + IPI with the reduced costs of PEMBRO and chemotherapy, which biases outcomes in favour of the modelled chemotherapy arm.

Table 15. Overview of reported OS outcomes for second-line therapies

Therapy	Study	Median OS	OS at two years	OS at three years	OS at four years
NIVO + IPI	CM142 cohort 2[10]	Not reached	75%	71%	71%
PEMBRO	KEYNOTE-164[11]	36.1 months	59%	51%	44%
Chemotherapy (FOLFOX)	Van Cutsem 2011[12]	11.9 months	Not reported	Not reported	Not reported

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; OS, overall survival

5.1 BMS scenario

In order to align costs and benefits for the chemotherapy arm, BMS has adapted the economic model to enable modelling of survival outcomes of NIVO + IPI, PEMBRO and chemotherapy as subsequent treatment following first line chemotherapy.

OS Kaplan-Meier data from KEYNOTE-164[11] and Van Cutsem 2011[12] were digitised and exponential parameterisations were fitted to the available data (Figure 9 and Figure 10). While these exponential functions were not the most appropriate fits to the available data (Table 16 and Table 17), overall outcomes were reflective of the efficacy of the respective therapies. More importantly, the resultant simple exponential fits could be applied in the model and weighted by usage to derive a survival reflecting all three subsequent therapies and dynamically updated whenever the proportion receiving subsequent therapy is amended.

Figure 9. PEMBRO OS data exponential parameterisation (KEYNOTE-164[11])

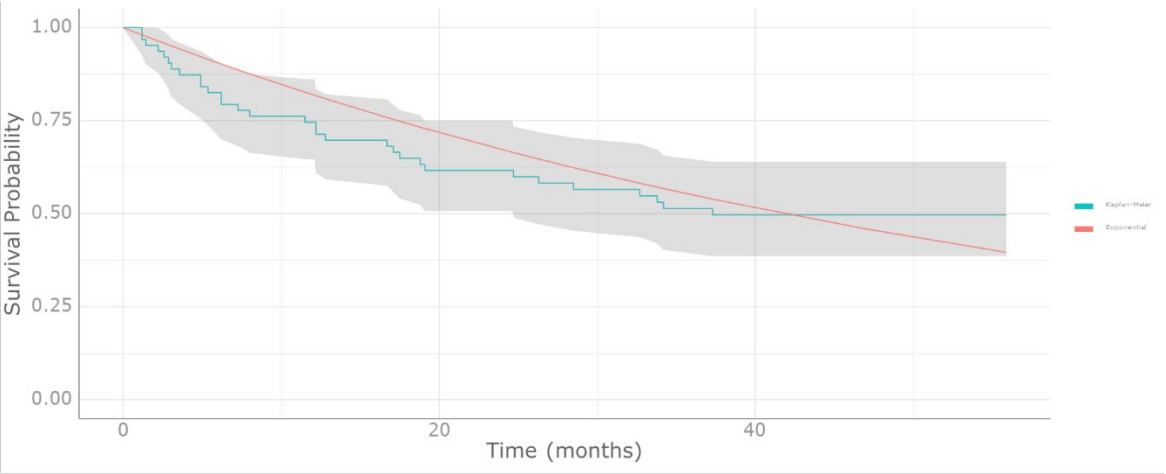


Table 16. PEMBRO OS data parameterisations (KEYNOTE-164[11])

Model	AIC	BIC	Parameters	Median survival	Reduced mean survival
Exponential	318.31	320.45	rate = 0.0165	41.9	36.47
Weibull (PH)	315.68	319.96	shape = 0.7203; scale = 0.0452	44.22	35.56
Weibull (AFT)	315.68	319.96	shape = 0.7203; scale = 73.5604	44.22	35.56
Gompertz	310.81	315.1	shape = -0.044; rate = 0.0348	47.43	34.73
Log-logistic	313.44	317.72	shape = 0.8671; scale = 42.1662	42.17	34.89
Log-normal	311.25	315.54	meanlog = 3.7687; sdlog = 1.9365	43.32	35.07
Generalised Gamma	310.01	316.44	mu = 2.3064; sigma = 1.9248; Q = -1.9028	48.32	34.66
Original Data	-	-	-	37.3	34.67

Figure 10. FOLFOX OS data exponential parameterisation (Van Cutsem 2011[12])

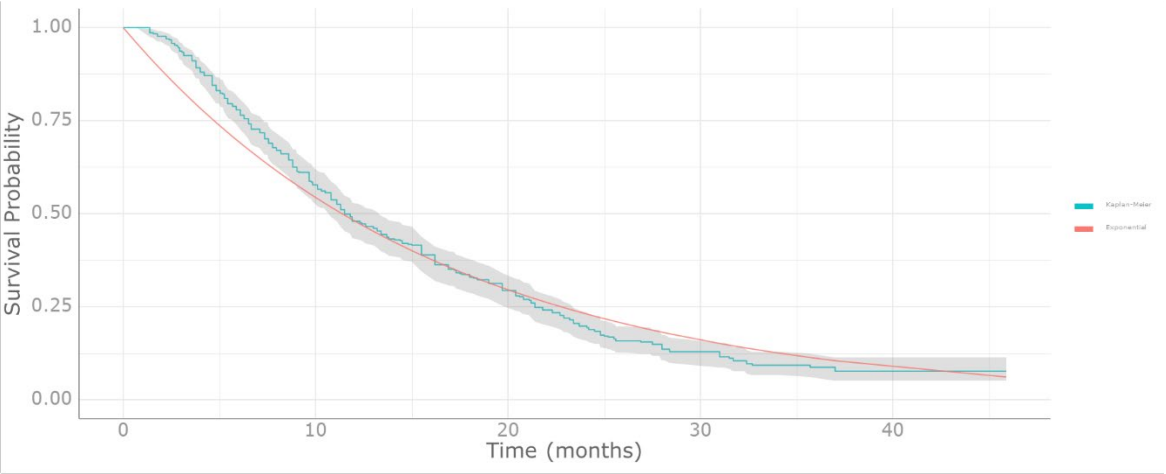


Table 17. FOLFOX OS data parameterisations (Van Cutsem 2011[12])

Model	AIC	BIC	Parameters	Median survival	Reduced mean survival
Exponential	2857.48	2861.54	rate = 0.061	11.37	15.4
Weibull (PH)	2810.21	2818.33	shape = 1.3656; scale = 0.0207	13.1	15.5
Weibull (AFT)	2810.21	2818.33	shape = 1.3656; scale = 17.1265	13.1	15.5
Gompertz	2841.73	2849.85	shape = 0.024; rate = 0.0463	12.79	15.35
Log-logistic	2791.11	2799.23	shape = 1.9869; scale = 11.8534	11.85	15.65
Log-normal	2783.3	2791.42	meanlog = 2.4614; sdlog = 0.8597	11.72	15.58
Generalised Gamma	2784.86	2797.04	mu = 2.5049; sigma = 0.8503; Q = 0.1099	11.87	15.54
Original Data	-	-	-	11.5	15.67

5.2 Economic model results

As can be seen in Table 18, amendment of chemotherapy arm PPS to a weighted exponential rate reflecting OS for FOLFOX and PEMBRO increased chemotherapy PPS versus the company base case and reduced PPS versus the EAG base case. When added to the EAG base case, this had little impact on accrual of costs, with a minor impact on resource use. However, as part of the company base case, this had a large impact on resource use, due to higher disease management costs, and also

increased subsequent treatment costs due to inclusion of pembrolizumab. NIVO+IPI presents a highly cost-effective use of NHS resources according to both the company and the EAG base case analyses, and in the company and EAG base case analyses with amended PPS.

Table 18. Impact of amended post-progression survival for first-line chemotherapy arm (with NIVO + IPI PAS)

NIVO + IPI vs chemotherapy	Company base case	Company base case with amended PPS*	EAG base case**	EAG base case** with amended PPS
Inc costs	[redacted]	[redacted]	[redacted]	[redacted]
Inc QALYs	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	£1,831	Dominant	Dominant	Dominant

* Also applies committee preferences for subsequent treatment composition
**BMS reproduction of EAG base case post-ACM, due to unspecified model amendments in revised EAG model (shared with BMS after the appraisal committee meeting) that do not align with committee preferences (see section "Approach to economic analyses").
Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Inc, incremental; IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; PPS, post-progression survival; QALYs, quality-adjusted life years.

It is essential that the benefits of subsequent treatment are aligned with the costs. In order to align with the committee's preferred assumptions for subsequent treatment, survival outcomes should reflect the efficacy of NIVO+IPI, PEMBRO and chemotherapy as subsequent treatments.

6 BMS updated base case analysis

As outlined in the Overview, all analyses are run using the EAG model provided in September 2024 due to the unidentified model updates included within the January 2025 version. As can be seen in Table 19 and Table 20, the BMS amended base case provides an improved fit to observed data compared with the EAG base case; however, the addition of a treatment waning assumption to the BMS amended base case results in poorer fit to observed data.

The amended base case presented in Table 21 and Table 22 results in lower incremental QALYs. However, ICERs remain cost-effective.

Table 19. Comparison of PEMBRO PFS outcomes from economic model, CheckMate 8HW NIVO monotherapy arm and KEYNOTE-177 PEMBRO arm

Model scenario	1 year PFS, %	3-year PFS, %	5-year PFS, %
KEYNOTE-177[2,3] PEMBRO arm (locally confirmed dMMR/MSI-H, first line)	55.3%	42.7%	34.0%
CheckMate 8HW NIVO monotherapy arm (locally confirmed dMMR/MSI-H, all lines)	[redacted]	[redacted]	[redacted]
BMS amended base case	[redacted]	[redacted]	[redacted]
EAG revised base case (including constant adjustment of 0.6 to the FP-NMA HR)	[redacted]	[redacted]	[redacted]

Abbreviations: CM8HW, CheckMate 8HW; dMMR, mismatch repair deficient, EAG, External Assessment Group; FP, fractional polynomial; HR, hazard ratio; MSI-H, microsatellite instability-high; NIVO, nivolumab; NMA, network meta-analysis; PEMBRO, pembrolizumab; PFS, progression-free survival

Table 20. Comparison of PEMBRO OS outcomes from economic model, CheckMate 8HW NIVO monotherapy arm and KEYNOTE-177 PEMBRO arm

Model scenario	1 year OS, %	3-year OS, %	5-year OS, %
KEYNOTE-177[2,3] PEMBRO arm (locally confirmed dMMR/MSI-H, first line)	77.8%	61.4%	54.8%
BMS amended base case	[redacted]	[redacted]	[redacted]
EAG revised base case (including constant adjustment of 0.6 to the FP-NMA HR)	[redacted]	[redacted]	[redacted]

Abbreviations: CM8HW, CheckMate 8HW; dMMR, mismatch repair deficient, EAG, External Assessment Group; FP, fractional polynomial; HR, hazard ratio; MSI-H, microsatellite instability-high; NIVO, nivolumab; NMA, network meta-analysis; PEMBRO, pembrolizumab; PFS, progression-free survival

BMS maintain that it is inappropriate to apply treatment waning in ICERs used for decision-making because the modelled values with treatment waning are discordant compared with observed trial results from KEYNOTE-177. Notably, the EAG's revised base case shows a one-year PFS rate 8.1% higher than observed outcomes from KEYNOTE-177, while the difference between modelled and observed outcomes at the 5-year timepoint rises to 14.0%. Further, applying a 2-year waning period in the company base case inflates 5-year PFS to 56.9%. These outputs demonstrate that the treatment waning approaches incorporated within the model generate unrealistic outcomes for PFS.

The impracticality of the EAG's treatment waning approach is further demonstrated when comparing the observed and modelled OS outcomes: KEYNOTE-177 shows a 1-year OS of 77.8% for pembrolizumab, whereas the EAG revised base case predicts 1-year OS of 89.3%. The inflated OS outcomes in the EAG revised base case continue at 5 years, where the model overestimates pembrolizumab OS by 7%. Therefore, the EAG analysis drastically exaggerates outcomes for pembrolizumab compared with available clinical evidence and is biased against NIVO+IPI.

In comparison, the OS outputs generated in the BMS amended base case is more closely aligned with observed clinical evidence. At 5 years in KEYNOTE-177, OS is measured at 54.8% which closely compares with the output from the amended BMS base case (56.6%). This close alignment between observed and BMS-modelled OS outcomes is disrupted when treatment waning is applied at two years, when 5-year OS is inflated to 67.3%, further demonstrating the impracticality of incorporating treatment waning into the analyses.

PFS outputs for NIVO monotherapy from CheckMate 8HW are also closely aligned with observed PFS in KEYNOTE-177. Consistent outcomes across trials confirm the accuracy of BMS's estimates without unnecessary waning, further validating the approach taken in the BMS model.

In summary, applying treatment waning is misleading and inflates outcomes for pembrolizumab compared with NIVO + IPI. The BMS base case without waning more closely aligns with trial results, providing a more realistic and evidence-based estimation. Further, clinical opinion presented within the committee papers (page 526) states that "a sub-set of these cancers patients will have a complete response to treatment and may be cured;" therefore, it would be inappropriate to model treatment waning in these patients.

Table 21. BMS preferred model assumptions (with NIVO + IPI PAS)

Model scenario	Section	PEMBRO			Chemotherapy		
		Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. costs	Inc. QALYs	ICER (£/QALY)
Company submission base case analysis	-	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£1,831
Accepted committee-preferred assumptions*	-	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Time on treatment for PEMBRO arm amended to CM8HW NIVO monotherapy arm	2.1	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£1,831
Post progression survival following first-line chemotherapy informed by all subsequent therapies	5.2	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Subsequent treatment time on treatment updated for chemotherapy arm	1.2	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant
Updated BMS base case (cumulative)	-	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	Dominant

*Includes committee preferences for: subsequent treatments following first-line chemotherapy (2.2% FOLFIRI; 1.8% FOLFOX; 56% PEMBRO; 40% NIVO + IPI); resource use assumptions; using HSE data to calculate wastage; using trial data for the split of treatments included in the chemotherapy comparator arm; no half-cycle correction for TTD.

Abbreviations: CM8HW, CheckMate 8HW; FOLFIRI, Folinic acid, fluorouracil and irinotecan; FOLFOX, Folinic acid, fluorouracil and oxaliplatin; HR, hazard ratio; HSE, Health Survey England; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; PEMBRO, pembrolizumab; QALY, quality-adjusted life year; TTD, time to discontinuation; TTP, time to progression

Table 22. BMS preferred model assumptions (without NIVO + IPI PAS)

Model scenario	Section	PEMBRO			Chemotherapy		
		Inc. costs	Inc. QALYs	ICER (£/QALY)	Inc. costs	Inc. QALYs	ICER (£/QALY)
Company submission base case analysis	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Accepted committee-preferred assumptions*	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on treatment for PEMBRO arm amended to CM8HW NIVO monotherapy arm	2.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post progression survival following first-line chemotherapy informed by all subsequent therapies	5.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment time on treatment updated for chemotherapy arm	1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated BMS base case (cumulative)	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Includes committee preferences for: subsequent treatments following first-line chemotherapy (2.2% FOLFIRI; 1.8% FOLFOX; 56% PEMBRO; 40% NIVO + IPI); resource use assumptions; using HSE data to calculate wastage; using trial data for the split of treatments included in the chemotherapy comparator arm; no half-cycle correction for TTD.

Abbreviations: CM8HW, CheckMate 8HW; FOLFIRI, Folinic acid, fluorouracil and irinotecan; FOLFOX, Folinic acid, fluorouracil and oxaliplatin; HR, hazard ratio; HSE, Health Survey England; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; PEMBRO, pembrolizumab; QALY, quality-adjusted life year; TTD, time to discontinuation; TTP, time to progression

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nivolumab plus ipilimumab for untreated metastatic colorectal cancer with high microsatellite instability or deficient mismatch repair [ID1136]

Appendix 2: CheckMate 8HW OS

[redacted]

March 2025

File name	Version	Contains confidential information	Date
	V1	Yes	3rd March 2025

Overview of OS evidence

This document presents the BMS submission (ID1136), which is based on interim analysis 1 from the November 2023 data cutoff (DBL). To enhance the committee's decision-making process, BMS is sharing key OS results from the most recent analysis, dated September 2024 DBL.

This was not a pre-planned analysis, and BMS sought approval and authorisation from our global headquarters. The analysis of the immature OS data was conducted after the DBL in response to the NICE draft guidance requesting OS data to reduce uncertainty.

To preserve trial integrity, only a very limited number of BMS personnel have been unblinded to these data. We kindly request that this data be used to validate the modelling outputs and to conclude that the PFS benefit of NIVO+IPI translates into an OS benefit.

Outcomes for NIVO + IPI versus CHEMO in locally confirmed first line patients are presented in Figure 1 and Table 1 while outcomes for NIVO + IPI versus NIVO in all randomised locally confirmed (all treatment lines) patients are presented in Figure 2 and Table 1. Outcomes are based on a minimum follow-up of [redacted]. In both comparisons, [redacted]

Figure 1. CM8HW Overall survival Kaplan-Meier – NIVO + IPI vs CHEMO in locally confirmed patients (first line)

Statistical model for HR: Stratified Cox proportional hazard model by tumour sidedness (left vs. right) as entered into the IRT.
Symbols represent censored observations.

Figure 2. CM8HW Overall survival Kaplan-Meier – NIVO + IPI vs NIVO in locally confirmed patients (all treatment lines)

Statistical model for hazard ratio: Stratified Cox proportional hazard model by tumour sidedness (left vs. right) and prior lines of therapy (0, 1, >= 2) as entered into the IRT.
Symbols represent censored observations.

Table 1. CM8HW OS Kaplan-Meier outcomes

	First line locally confirmed patients		All lines locally confirmed patients	
	NIVO + IPI (N = 202)	**CHEMO (N = 101)**	**NIVO + IPI (N = 354)**	**NIVO (N = 353)**
Median OS (months, 95% CI)				
OS at 6 months (%, 95% CI)				
OS at 12 months (%, 95% CI)				
OS at 18 months (%, 95% CI)				
OS at 24 months (%, 95% CI)				
OS at 30 months (%, 95% CI)				
OS at 36 months (%, 95% CI)				

Abbreviations: CHEMO, chemotherapy; CM8HW, CheckMate 8HW; IPI, ipilimumab; N.A., not available; NIVO, nivolumab; OS, overall survival

Comparison of CM8HW OS and modelled outcomes

As can be seen in Table 2 and Figure 3, predicted model OS is overestimated at year 1 for NIVO + IPI. However, by year 2, modelled outcomes have an improved fit to the observed data and by year 3 the fit can be considered plausible for the company base case.

By contrast, Table 3 and Figure 4 indicate that the company base case may closely reflect PEMBRO outcomes. By contrast, outcomes for PEMBRO from the EAG base case appear more similar to NIVO + IPI observed outcomes.

Based on this evidence, it is demonstrable that PFS benefit translates into an OS benefit. Although the economic model slightly overpredicts for NIVO+IPI, the overprediction is significantly greater for PEMBRO and CHEMO. As a result, the cost-effectiveness comparisons can be viewed as conservative.

Table 2. Comparison of NIVO + IPI OS outcomes from economic model and CheckMate 8HW NIVO + IPI arm

Model scenario	1 year OS, %	2-year OS, %	3-year OS, %	5-year OS, %
CheckMate 8HW NIVO + IPI arm (locally confirmed dMMR/MSI-H, first line)	[redacted]	[redacted]	[redacted]	[redacted]
BMS amended base case NIVO + IPI OS	[redacted]	[redacted]	[redacted]	[redacted]
EAG revised base case (including FP-NMA HR adjustment of 0.6) NIVO + IPI OS*	[redacted]	[redacted]	[redacted]	[redacted]

* Outcomes for the NIVO + IPI arm remain unchanged between the BMS base case and the EAG base case
Abbreviations: CM8HW, CheckMate 8HW; dMMR, mismatch repair deficient, EAG, External Assessment Group; FP, fractional polynomial; HR, hazard ratio; MSI-H, microsatellite instability-high; NIVO, nivolumab; NMA, network meta-analysis; PEMBRO, pembrolizumab; PFS, progression-free survival

Table 3. Comparison of PEMBRO OS outcomes from economic model, CheckMate 8HW NIVO monotherapy arm and KEYNOTE-177 PEMBRO arm

Model scenario	1 year OS, %	2-year OS, %	3-year OS, %	5-year OS, %
KEYNOTE-177[1,2] PEMBRO arm (locally confirmed dMMR/MSI-H, first line)	77.8%	68.0%	61.4%	54.8%
CheckMate 8HW NIVO monotherapy arm (locally confirmed dMMR/MSI-H, all lines)	[redacted]	[redacted]	[redacted]	[redacted]
BMS amended base case PEMBRO OS	[redacted]	[redacted]	[redacted]	[redacted]
EAG revised base case (including FP-NMA HR adjustment of 0.6) PEMBRO OS	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM8HW, CheckMate 8HW; dMMR, mismatch repair deficient, EAG, External Assessment Group; FP, fractional polynomial; HR, hazard ratio; MSI-H, microsatellite instability-high; NIVO, nivolumab; NMA, network meta-analysis; PEMBRO, pembrolizumab; PFS, progression-free survival

Figure 3. Comparison of CM8HW OS outcomes for NIVO + IPI and chemotherapy (locally confirmed, first line cohort) versus modelled survival for NIVO + IPI and chemotherapy

Figure 4. Comparison of CM8HW OS outcomes for NIVO + IPI and NIVO (locally confirmed, all treatment lines cohort) versus modelled survival for NIVO + IPI and PEMBRO

1 References

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2. National Institute for Health and Care Excellence. Technology appraisal [TA709]. Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency. June 2021. Available from: https://www.nice.org.uk/guidance/ta709 [accessed on 13/03/24].

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Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day **3 March 2025**. 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):	Individual (clinical expert).

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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.	Bristol-Myers Squibb - I received (i) an honorarium of £1,400 for attending a UK advisory board meeting with BMS on 26/03/24 and (ii) an honorarium of £280 for attending a UK advisory board meeting with BMS on 24/10/24. In these meetings, we discussed (a) management of dMMR/MSI-High colorectal cancer in the UK, and (b) the landscape of management of metastatic colorectal cancer through all lines of therapy in the UK. These were broadly based and part of BMS wishing to understand different aspects of how colorectal cancer is managed across the UK, including regional and devolved nation differences. These have been previously been disclosed to NICE for this appraisal and are unchanged.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	Richard Wilson, Professor of Gastrointestinal Oncology, School of Cancer Sciences, University of Glasgow and Honorary Consultant in Medical Oncology, Beatson West of Scotland Cancer Centre.

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.
Example 1	We are concerned that this recommendation may imply that ……..

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1	I share the frustration of the committee that the overall survival data was not made available to us for this appraisal. I understand that this was part of the Statistical Analysis Plan for the trial, but would have preferred that flexibility had been shown by BMS and this data confidentially released given the number of events that have already occurred and the high likelihood that this OS analysis would be consistent with their planned final OS analysis.
2	I believe that, given the consistency between the first-line (small and non-randomised as it was) cohort data from CheckMate 142 with the CheckMate 8HW data for all efficacy endpoints, this data is highly informative for this appraisal.
3	I strongly believe that the panel ICER estimates (that these will be more than £25,000 per QALY gained) fail to take in to account the significant number of patients who will need no further lines of therapy for their cancer for many years, and that a proportion of patients who receive ipilimumab and nivolumab in this setting are likely to be alive and cancer free for at least 10 years (and hence likely to be cured).
4	A larger subgroup of patients with dMMR/MSI-H metastatic CRC are aged under 50 years old at time of diagnosis than we see in the population of patients with pMMR/MSS metastatic CRC, mainly due to a germline predisposition from Lynch Syndrome. Hence, ipilimumab/nivolumab will have a significantly higher efficacy benefit in patients with young onset CRC compared to average age onset CRC.
5	In the treatment of patients with untreated unresectable or metastatic dMMR/MSI-H CRC with current standard care SACT (chemotherapy +/- EGFR inhibitors and pembrolizumab monotherapy), those with tumoural activating RAS or BRAF mutations and those with liver metastases have a worse prognosis than those without these baseline features. This is not seen in the CheckMate 8HW trial results. Hence, those patients in these poor prognosis subgroups will receive significantly better outcomes from ipilimumab/nivolumab compared to other available SACT.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and

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separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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

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Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]: A Single Technology Appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School
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Date completed	10/03/2025
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Competing interests	None.
Acknowledgments	The authors acknowledge the administrative support provided by Mrs Sue Whiffin and Ms Jenny Lowe (both PenTAG).

1. EXECUTIVE SUMMARY

The purpose of this addendum is to provide the EAG's response to the company's ACD response ahead of AC2.

The EAG noted that the company provided additional data which partially addressed the EAG's concerns. This included interim overall survival (OS) data for the CM8HW trial. However, nivolumab monotherapy data were only provided for the all treated population rather than the first line setting that is relevant for this appraisal. The EAG further noted that the new information was used selectively to inform the base case and that the OS data did not inform the model.

The EAG made two key changes to the revised company base case:

- Use of nivolumab TTP data as a proxy for pembrolizumab outcomes based upon the hazard ratio reported in Andre et al 2025[1] rather than the FP NMA; the EAG considered this to provide a more reliable source of information, given the potential issues with transitivity in the NMA and clinical expectation of similar effectiveness for nivolumab and pembrolizumab.
- Use of subsequent time to discontinuation data based upon the mean first-line time to discontinuation estimates in the model. The EAG considered this more appropriate than using medians derived from NIVO + IPI data only but would have preferred the company to supply estimates from previously treated trials.

Table 1 shows the impact of the changes when all treatments are shown at list price. When the nivolumab monotherapy data is used, rather than the FP NMA, incremental QALYs reduced from [redacted]Use of TTD consistent with the first line inputs in the model for subsequent immune oncology treatment reduced the list price costs on the chemotherapy arm by [redacted]. A separate cPAS appendix is provided showing the results with all relevant price discounts included.

The EAG noted that the projections supplied [redacted]. [redacted]. The EAG were unable to do further analyses to adjust for the impact of this with the data and timeframe available.

Table 1: Company revised base case (list price)

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER £/QALY
Company revised base case					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO outcomes modeled using HR for NIVO monotherapy					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consistent immunotherapy TTD for 1st and 2nd line treatment					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative impact of EAG revised base case					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: Treatment effect waning after 4 years					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: Treatment effect waning after 10 years					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHEMO, chemotherapy; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; QALY, quality-adjusted life-year; TTD, time to discontinuation

2. RESPONSES TO COMPANY COMMENTS

2.1. Comment 1: Summary of company position

The company put forward its position that the draft guidance (DG) issued by NICE was inaccurate, as it did not consider all of the relevant evidence, was not a reasonable interpretation of the clinical and economic evidence and was not a suitable basis for guidance to the NHS. The EAG has offered its response to each point in turn.

2.2. Comment 2: Uncertainty in EAG model following EAG report

The EAG accepted the company's clarification. The issues in the January version of the model sent to the company resulted from the redaction process, which inadvertently affected the proportion of female patients in the cohort, the time on treatment parameter, and the cost of cetuximab. As these issues happened during the redaction of confidential data, they were not present in the January version of the model incorporating the company's PAS and other commercial discounts, where these values were correctly specified and aligned with the results from the model sent in September. These issues were corrected in the redacted version of the model. The EAG noted that the company starting from the version supplied with the EAG report did not pose a major issue as the only change conducted since then relevant to this analysis was inputting new data from Peter Clark on the composition of subsequent treatments, which the company have accurately replicated.

2.3. Comment 3: Availability of OS data and translation of PFS into OS benefit

The EAG agreed that uncertainty in relation to the OS benefit of NIVO + IPI over chemotherapy has been addressed. The EAG noted that OS data from CM8HW was not provided for nivolumab monotherapy in first line patients. Therefore, uncertainty in the comparison to pembrolizumab has not been fully addressed.

The EAG noted that the observed OS data and the original model projections provided by the company were [redacted] (Figure 3 of Appendix 2 of the company response). The EAG maintained it was therefore appropriate to note the considerable uncertainty that lack of provision of OS data caused in being able to validate model projections in the company's initial submission. As noted in the EAG assessment report, the model had original assumed that gains in TTP directly translated to gains in OS. This was not an assumption tested in the surrogacy analysis presented by the company and is [redacted].

2.4. Comment 4: Transitivity of the PFS network and uncertainty in the comparative evidence

The EAG previously noted that all randomised patients were the most appropriate population to include in the network, as this reflected the absence of central testing in the KN177 trial (post-randomisation). The EAG agreed that the absence of central testing in all randomized patients did not itself violate the assumption of transitivity, although could have added a level of uncertainty as the analysis assumed a similar rate of misclassification between the two trials of dMMR/ MSI-H status.

The company provided newly published data to compare nivolumab monotherapy across all lines from CheckMate 8HW and pembrolizumab from KEYNOTE-177. The EAG noted that these PFS outcomes were quite different between the locally confirmed (ITT) and centrally confirmed populations. For nivolumab monotherapy, median PFS in the centrally confirmed population was 39.3 months, whereas in the locally confirmed population this was 18.4 months. Centrally confirmed participants had nearly twice as long PFS as locally confirmed participants. Median PFS for chemotherapy in CM8HW for all randomised participants was [redacted] compared to 5.9 (4.4, 7.9) for the centrally confirmed population. Furthermore, although the PFS HR for local vs. central testing for NIVO + IPI vs nivolumab monotherapy were similar,[1] which is reassuring, the HRs for PFS for NIVO + IPI vs chemotherapy (Table 18 and Table 19 document B) were not similar. The EAG re-iterated that, post-randomisation, central testing would have only supported the avoidance of non-differential ascertainment bias, whereby the true effect was diluted because of misclassification of dMMR/ MSI-H status using local testing, which the EAG believed is supported by this evidence.

As the company and the EAG were using a time-varying function of the hazard ratio, and the FP NMA does not rely on proportionality, it would be necessary to see a new FP NMA with the appropriate curve – which accurately reflects how the hazard ratio changes over time based upon the NIVO + IPI vs nivolumab monotherapy data – to be fully reassured that this is no longer an issue.

The EAG agreed that transitivity of the network is not violated by the slightly higher number of patients receiving a bevacizumab-containing regimen in KEYNOTE-177, as they were similar enough for comparison.

2.5. Comment 5: Validation of PFS outcomes to CheckMate 8HW nivolumab monotherapy

The company supplied additional evidence from a newly published paper (André et al, 2025[1]) that showed that PFS outcomes are quite different between the locally confirmed (ITT) and centrally confirmed populations. For nivolumab monotherapy, median PFS in the centrally confirmed population was 39.3 months, whereas in the locally confirmed population this was 18.4 months. The EAG noted this discrepancy between the results and central and local testing. Centrally confirmed participants had nearly twice as long PFS as locally confirmed participants. Median PFS for chemotherapy in CM8HW for all randomised participants was [redacted] compared to 5.9 (4.4, 7.9) for the centrally confirmed population. The EAG provided commentary on the implications for the NMA in response to Comment 4.

2.6. Comment 6: Evidence for increased life expectancy

At the time of the first Committee meeting, data had not been presented to demonstrate a survival benefit for NIVO + IPI from the randomised controlled trial. The EAG noted that data from naïve comparisons and other indications should be interpreted with a high level of caution. Fortunately, the company have now provided overall survival data from CM8HW, which [redacted]

2.7. Comment 7: Summary of Product Characteristics

The EAG agreed that the Summary of Product Characteristics (SmPC) hyperlinked in the DG is the European (EMA) SmPC rather than the UK one. The company states that [redacted] The EAG report referred throughout to the draft UK SmPC, not the EMA one.

2.8. Comment 8: Withholding of overall survival data

The EAG thanked the company for provision of overall survival data to allow a more accurate assessment to be conducted. The EAG noted that the company have been able to put in place arrangements to provide this data.

2.9. Comment 9: Central versus local testing

The EAG accepted the company's clarification regarding definitions of central versus local testing. The EAG noted that, now data has been provided in the locally tested population for

nivolumab, there was no need to use data in the centrally tested population to inform the model. This data was not available at the time of the first Committee meeting.

2.10. Comment 10: Information fraction of 80%

The EAG accepted the company's clarification regarding their position that the information fraction of 80% should not be generalised beyond PFS. However, this was no longer relevant given that interim OS data have since been provided.

2.11. Comment 11: Preference for comparative overall survival data

The EAG noted that the modelled projections, which were produced with access to CheckMate 142, were [redacted] to the observed Kaplan Meier data from CM8HW.

2.12. Comment 12: Most appropriate indirect treatment comparison

The EAG previously concluded that the FP NMA was the most appropriate for decision making. This is because the constant-hazard NMA violated the proportional hazards assumption. The EAG noted that the anchored and unanchored MAIC were presented in order to assess the uncertainty around the outcomes for the FP NMA.

2.13. Comment 13: Results of network meta-analysis

The EAG recognized that this comment was referring to the primary network section in the EAG report (section 3.4.1.4). The EAG agreed that the NICE Draft Guidance transposed the information from the EAG report incorrectly. The EAG assessment report noted that the CrIs did not cross the null, and that NIVO + IPI significantly and consistently outweighed both chemotherapy and pembrolizumab between 6 and 60 months. This was in line with the company's observation.

2.14. Comment 14: Population differences between nivolumab and pembrolizumab

The EAG noted that the relevant data to make a more robust comparison were not available at the time of the first Committee meeting. The additional analysis supplied by the EAG, based upon the data available, indicated that the model predicted the observed results for NIVO + IPI relatively accurately, despite the differences in patient population (confirmation and line of treatment), but underpredicted the observed data for nivolumab (assuming pembrolizumab and nivolumab had similar effectiveness). Shortly before the first Committee meeting, the company

provided additional data to the EAG. These data were used by the EAG to provide an exploratory analysis highlighting the large impact use of nivolumab monotherapy data rather than the FP NMA for relative effectiveness could have on cost-effectiveness results. The EAG did not imply that this was the most robust analysis that could be conducted if all data had been provided. The company were asked to integrate the nivolumab monotherapy data into their model at the time they provided the addendum, but they did not do so.

The company have since provided an updated base case, which used data from nivolumab monotherapy in the locally confirmed all treated population as a proxy for pembrolizumab TTD, although not for TTP, which continued to rely on the FP NMA. The company noted that median PFS in the locally confirmed all-comers population was similar for nivolumab monotherapy to the first line population for pembrolizumab (18.4 vs 16.5 months).

Clinical advice to the EAG was that response rates are generally higher in the first line setting compared to the second line setting or later. Clinicians believed it would be reasonable to expect that the relative gain of combination immunotherapy over single agent immunotherapy is greater in the first line setting. The use of nivolumab data from all treated patients may therefore provide somewhat of a conservative estimate, although use of relative rather than absolute effects was expected to limit the scale of the impact.

The EAG noted that the company has not supplied data for nivolumab monotherapy in first line patients to allow a more robust comparison to be made.

2.15. Comment 15: Breakdown by line of therapy

The EAG noted that the company has now provided information on the proportion of patients receiving treatment at second line or beyond (43%). The EAG noted that this proportion could be calculated based upon the numbers at risk supplied in the Kaplan Meier data available at the first Committee meeting. The EAG noted that the addendum supplied by the company to the EAG prior to the Committee meeting did not provide any clear description of what population it pertained to, nor how this differed from the decision problem population and the information previously supplied. The EAG also reiterated that the fit of the modelled projections to the NIVO + IPI arm despite differences in population was very good and that this was not the case for the comparison of the projections of pembrolizumab vs the nivolumab monotherapy arm. Given that central vs local testing impacted both nivolumab and NIVO + IPI similarly (hazard ratios were

similar in the two populations in Andre et al.[1]) and the difference in relative effects due to line of treatment was also expected to be limited, it was reasonable to point out this discrepancy.

2.16. Comment 16: Fit to the modelled data

The EAG noted that the fit to the NIVO + IPI data was reasonable and therefore the EAG did not consider it necessary to undertake further adjustment within exploratory analysis. The EAG further noted that the analysis was presented as exploratory only, in lieu of the company providing their own robust analysis using the nivolumab monotherapy data in the correct population and line and was presented to demonstrate the potentially large impact of underpredicted pembrolizumab outcomes.

2.17. Comment 17: Assumption of equivalency between outcomes in locally confirmed and centrally confirmed patients

The company correctly highlighted that locally confirmed and centrally confirmed patient outcomes for immunotherapies differ. At the time of the Committee meeting the EAG did not have access to data for nivolumab monotherapy for centrally confirmed patients. The EAG responded to the points raised in relation to the NMA in Comment 4.

2.18. Comment 18: Clinical advice regarding similar results for nivolumab monotherapy and pembrolizumab as they have a similar mode of action

The EAG noted that the analysis being discussed was presented as exploratory sensitivity analysis only for exactly the reasons noted by the company and that the company did not provide the EAG with the data needed to provide a more robust estimate. The EAG noted that the company have not provided the data required to provide a more robust estimate (in particular, outcomes for nivolumab monotherapy relative to NIVO + IPI in the first line centrally confirmed population).

The EAG acknowledged the company's agreement that "clinical experts anticipate similar results for nivolumab monotherapy and pembrolizumab as they have a similar mode of action."

2.19. Comment 19: Semi-Markov model and assumptions that progression free survival translates to overall survival

The EAG noted, as per the original assessment report, that the assumption of equal post progression survival made in the companies' model was only reasonable where subsequent treatments are not expected to introduce differential effectiveness. Similar subsequent

treatments (and therefore an expectation of similar effectiveness) was a reasonable assumption in the comparison to pembrolizumab but not in the comparison to chemotherapy. Fortunately, OS data were since provided to inform a more robust comparison to chemotherapy.

The EAG noted that the model did not rely on a traditional surrogacy analysis of the type that is the main focus of the white paper cited by the company,[2] instead making an assumption of equal post progression survival. In addition, the whitepaper contains many recommendations which the previous analysis did not follow. In particular:

- The model should be built so that the effect of treatment on final outcomes by the surrogate and the duration of that effect are modifiable parameters that can be explored within the model. Additionally, it should be possible to remove the effect of the surrogate to allow a full exploration of its impact on the results.
- Scenario analysis should be presented (for example, testing assumptions around relationship of surrogate to final outcome considering best and worst-case scenarios) with justification for the range selected

The whitepaper also discusses the need for consideration of the generalisability of evidence relating to the surrogacy relationship to the decision problem. The EAG noted that the evidence of surrogacy provided by the company came from 45 patients from CM142 cohort 3 (NIVO + IPI in first line); MSI-H status was only centrally confirmed in 10 of these cases. No attempt was made to determine whether the relationship between PFS and OS observed in CM142 was replicated in other data sources such as KEYNOTE 177. The EAG did not consider this to be "robust evidence."

2.20. Comment 20: Potential typographical error

The EAG agreed that there is a typographical error in the DG and consider the company's proposed correction reasonable.

2.21. Comment 21: Post-progression survival

The EAG agreed the company did not provide sufficiently robust analysis to incorporate the impacts of subsequent treatment fully in terms of their impact on costs and effectiveness for the first Committee meeting. The EAG noted that this was requested in clarification questions. The EAG were pleased to see the company provide a new scenario to address this. The EAG noted

that there were several limitations with this scenario analysis which are discussed further in Section 3.1.5.

2.22. Comment 22: Time to progression and treatment waning

The EAG noted that the company have now provided additional data which allowed for a more robust comparison. Commentary on the new company analyses is provided in Section 3.1.

2.23. Comment 23: Time to treatment discontinuation

The EAG considered that use of nivolumab monotherapy data to reflect expected outcomes for pembrolizumab is more robust, which is why this data was requested at clarification stage. The EAG noted that Andre et al. (2025)[1] indicates a lower median duration of treatment for nivolumab compared to NIVO + IPI [20·5 months (IQR 3·8–23·6) vs 16·4 months (3·7–23·5)] indicating that the EAG were correct to be concerned about the company's original assumption of equal TTD. The EAG noted the data provided was for all treated patients and not specific to first line. The EAG provided commentary on the new company base case assumptions in Section 3.1.2.

2.24. Comment 24: Time to treatment discontinuation vs time on treatment

The EAG considered that an indirect comparison is no longer required as nivolumab monotherapy data has been provided.

2.25. Comment 25: Resource use

The company accepted the EAG base case resource use estimates.

2.26. Comment 26: Acceptable ICER

The EAG noted that additional data have now been provided.

2.27. Comment 27: Surgery in people with unresectable disease

The EAG sought clinical expert advice on the potential for curative surgery and were informed that most patients with metastatic colorectal cancer do not have curative surgery, even with a good response to systemic anti-cancer therapy (SACT). Exceptions were those with liver only metastases who have a good but not complete response to SACT, who may then have resection of the colorectal primary and resection/ablation of liver metastases. The clinical expert advising the EAG considered that very few patients (10% or fewer) with metastatic or

unresectable dMMR/MSI-H colorectal cancer treated with NIVO + IPI would be able to subsequently have surgery. This was because most would have too many sites of metastatic disease for resection, or they would get a complete response with durable control in all sites of disease and not need surgery. The expert also thought that the choice of drug (NIVO + IPI relative to pembrolizumab) would have little impact on the numbers receiving surgery. The EAG noted that few patients received subsequent surgery in the CM8HW trial: NIVO + IPI n = [redacted] chemotherapy n = [redacted].

The company also noted that this possibility cannot be robustly included in the economic model. The EAG agreed with this. The EAG did not consider that lack of inclusion of the potential for curative surgery has led to an underestimation of the potential value of NIVO + IPI, as expert advice to the EAG was that rates of surgery would be similar for NIVO + IPI and pembrolizumab and, regardless, the impact would already be captured in the observed OS data.

2.28. Comment 28: Committee's preferred assumptions

The EAG noted the company's comments and reviewed the revised cost-effectiveness analysis in the Section below.

3. RESPONSE TO ADDITIONAL EVIDENCE DOCUMENTS

3.1. Analysis appendix 1: Model updates

3.1.1. Time on subsequent treatment

The EAG noted that the new analysis presented represented an improvement from the original company base case, which assumed that all patients on NIVO + IPI or pembrolizumab received exactly 2 years of treatment.

The EAG appreciated the provision of the source of information for the duration of chemotherapy.

The EAG would have preferred it if the company had used the mean time to discontinuation data from previously treatment information from trials run by the company as opposed to data from CM8HW, which the EAG had used as a placeholder in the absence of more relevant data. The EAG also noted that the company update reported using a median rather than a mean – which is not preferred as use of medians does not reflect the fundamental principles of economic analysis – and that the company assumed the same time to discontinuation with NIVO + IPI as for pembrolizumab, which is also not preferred.

The mean time on treatment for first line NIVO + IPI and pembrolizumab taken from the model based upon the AUC method was [redacted] and [redacted]weeks, rather than the [redacted]weeks used in the company analysis. The EAG preferred to use these data for consistency with the first line inputs in the mode. However, the EAG flagged that these data are not ideal and that data from previously treated trials would have been preferred.

3.1.2. Time on treatment for pembrolizumab

The EAG considered the idea of using mean time on treatment data from nivolumab monotherapy in CM8HW to be an improvement on the analysis previously provided by the company, which assumed the same duration of treatment for NIVO + IPI and pembrolizumab.

The EAG noted that its base case applied the same HR to TTD as for PFS, due to lack of another suitable alternative given nivolumab monotherapy data had not been provided by the company and TTD data were not available for PEMRBO.

Unfortunately, the EAG noted some issues with the new data provided by the company:

- The mean TTD for NIVO + IPI in Table 6 ([redacted] months in all treated and [redacted] months in first line) did not match the previously provided figure of [redacted] (Table 64, CS) TTD was slightly lower in first line patients relative to all treated patients for both NIVO + IPI and chemotherapy, which meant that applying naïve TTD information for nivolumab from the all treated population would slightly over-estimate TTD

Given the issues observed with implementation of the new company analysis, the EAG analysed TTD data for NIVO + IPI vs. nivolumab (Figure 3, appendix 1) as a surrogate for NIVO + IPI vs. pembrolizumab. [redacted]. The EAG compared mean survival based upon the area under the curve using these curve fits and concluded that the mean survival estimates were similar/higher to that included in the revised company base case, and therefore accepted the company base case estimates.

3.1.3. Initial pembrolizumab TTP outcomes

The company update to use nivolumab monotherapy data from the locally confirmed population was an improvement in the analysis provided. The EAG were disappointed not to see this within the new company base case.

The EAG agreed with the choice of the generalised gamma curve as the most plausible fit to the nivolumab monotherapy data, in line with the choice made for NIVO + IPI. The EAG noted that the data used included previously treated patients, which represents a limitation. However, the EAG also noted that outcomes were similar for NIVO + IPI across first line and all treated patients. In the CS, in the first line population, the median PFS was [redacted] in the NIVO + IPI arm for all randomised subjects, while in the chemotherapy arm the median PFS was [redacted] In the all-treated population,[1] median PFS was not reached with NIVO + IPI (95% CI 53·8 to not estimable) and was 39·3 months with nivolumab (22·1 to not estimable; HR 0·62, 95% CI 0·48–0·81; p=0·0003).

The EAG scrutinised data from Andre 2025[1] for comparisons between NIVO + IPI and nivolumab monotherapy for evidence of non-proportional hazards in PFS for the ITT population. Apart from an expected step at the start of the curve that includes early progressors, proportional hazards did not appear to be meaningfully violated in these curves.

The EAG considered the impact of TTP on model fit to the observed OS data in each of the three scenarios (Figure 1). The EAG noted that the observed fit was consistently poor for NIVO + IPI ([redacted]) and was much better for nivolumab using either the FP NMA or generalized gamma curve fit to the nivolumab monotherapy data and naïve comparison. However, in these scenarios, the difference between NIVO + IPI and pembrolizumab [redacted]. The EAG therefore preferred to use the hazard ratio from Andre 2025[1] in its base case.

Figure 1: Comparison of model fit to observed OS data

a) Company base case using FP NMA for pembrolizumab

[redacted]

Abbreviations: FP NMA, fractional polynomial network meta-analysis; OS, overall survival

b) Use of NIVO data as a proxy for PEMBRO based upon the Andre 2025 hazard ratio

Abbreviations: NIVO, nivolumab; PEMBRO, pembrolizumab

c) Use of NIVO data as a proxy for PEMBRO based upon generalised gamma curve fit to Andre 2025 data (naïve comparison)

Abbreviations: NIVO, nivolumab; PEMBRO, pembrolizumab

3.1.4. Treatment effect waning

The EAG first noted that application of treatment effect waning does not indicate, as the company appear to imply, that a stable benefit is not assumed and that a significant benefit is not observed. The EAG rather assumed in its base case, at the time of the first Committee meeting, that hazards would be equal after two years. I.e., that there would be the same risk of an event occurring in the long term. The assumption being made was that the benefit of NIVO + IPI relative to other treatments is observed in the first two years (whilst patients are still on treatment) and that after this point patients will either already have been observed to be complete responders or not.

The EAG were pleased to see data presented now for the comparison of NIVO + IPI and nivolumab – which provided data for a reasonable number of patients remaining at risk for just under four years. The EAG was unclear why the company stated that there were robust data to support a lack of treatment effect waning for six years.

The company cited data from advanced melanoma to support long-term durability of treatment effect. The EAG noted that melanoma is a different disease, and that melanoma is highly responsive to immunotherapy due to several key factors related to its tumor biology and immune microenvironment. (For example, high tumor mutational burden, inflated tumor micro-environment, exhibition of upregulated interferon-γ pathways and expression of PD-L1.) The EAG further noted that the performance of PD-1/PD-L1 inhibitors has not been consistent across different tumor types. Therefore, this evidence cannot be directly translated to a colorectal cancer setting.

The EAG did note, however, that provision of OS data did provide some reassurance of the durability of a long-term treatment effect and therefore no longer considered treatment effect waning in its base case. Instead, the EAG tested the impact of treatment effect waning at four and ten years in scenario analysis.

3.1.5. Post progression survival

The EAG were pleased to see the company had provided an update to their analysis to better reflect expected survival for subsequent treatments. The EAG had originally requested this at clarification questions stage. The EAG noted, however, that the company analysis continued to assume an exponential distribution for all treatments, which is acknowledged not to be a good fit by the company. The tables presented by the company were misleading as they implied similar

mean survival for all the fitted curves. It would appear, however, that the company presented the restricted mean survival (labelled reduced survival) rather than the lifetime modelled survival (Tables 16 and 17, Appendix 1 of company response). Figure 9 of Appendix 1 of the company response indicated the exponential curve to be a poor visual fit to data for pembrolizumab. The EAG noted that the use of an exponential fit was flagged previously as unrealistic in Key Issue 3 of the original EAG assessment report. The use of an exponential fit would be expected to underestimate survival for immune-oncology treatments where a profile of decreasing hazards (plateau) is often observed in the longer term. This biased against chemotherapy as the increase in treatment costs was unlikely to be proportional due to a 2-year stopping rule being applied for all patients receiving pembrolizumab and a reasonable proportion receiving NIVO + IPI.

The EAG also noted that the survival curves were informed by naïve analysis of different trials. The EAG noted that using naïve comparison introduces limitations, such as differences in trial settings and populations, as no adjustment is performed for these differences. However, the EAG considered the relevant trials to be of high quality, so this may not be a major issue.

The EAG note that the companies revised base case is [redacted] when comparing the model to the observed data. The EAG, however, remains concerned about [redacted].

Figure 2: KM vs model projection vs CHEMO base case (company and EAG)

[redacted]

[redacted]Abbreviations: CHEMO, chemotherapy; EAG, External Assessment Group; KM, Kaplan-Meier

3.1.6. Overall comments

The EAG noted that the revised company base case [redacted] (Table 2) and, as noted previously, [redacted] observed survival for NIVO + IPI.

Table 2: Revised base case comparison to observed survival for PEMBRO (adapted from Table 19 and 20, Appendix 1 company response)

Model scenario	1 year, %	3-year, %	5-year, %
Progression-free survival			
KEYNOTE-177[3,4] PEMBRO arm (locally confirmed dMMR/MSI-H, first line)	55.3%	42.7%	34.0%
CheckMate 8HW NIVO monotherapy arm (locally confirmed dMMR/MSI-H, all lines)	[redacted]	[redacted]	[redacted]
Company amended base case	[redacted]	[redacted]	[redacted]
Overall survival			
KEYNOTE-177[3,4] PEMBRO arm (locally confirmed dMMR/MSI-H, first line)	77.8%	61.4%	54.8%
Company amended base case	[redacted]	[redacted]	[redacted]

Abbreviations: dMMR/MSI-H , mismatch repair-deficient/microsatellite instability-high; NIVO, nivolumab; PEMBRO, pembrolizumab

3.2. Analysis appendix 2: CheckMate 8HW overall survival

The company supplied an appendix with OS data from CM8HW at the September 2024 datacut. The company noted that this was not a pre-planned analysis and that the data are interim and immature. The EAG accepted this, while noting the importance of OS data for model validation. Outcomes in the analysis were based on a minimum follow-up of [redacted]Figure 3: CM8HW Overall survival Kaplan-Meier – NIVO + IPI vs CHEMO in locally

confirmed patients (first line)[redacted]Abbreviations: CHEMO, chemotherapy; NIVO + IPI, nivolumab with ipilimumab
Note: Statistical model for HR; Stratified Cox proportional hazard model by tumour sidedness (left vs. right) as entered into the IRT. Symbols represent censored observations.

[redacted]Figure 4: CM8HW Overall survival Kaplan-Meier – NIVO + IPI vs NIVO in locally confirmed patients (all treatment lines)

Abbreviations: NIVO + IPI, nivolumab with ipilimumab
Note: Statistical model for hazard ratio; Stratified Cox proportional hazard model by tumour sidedness (left vs. right) and prior lines of therapy (0, 1, >= 2) as entered into the IRT. Symbols represent censored observations.

Table 3: CM8HW OS Kaplan-Meier outcomes

	First line locally confirmed patients		All lines locally confirmed patients	
	NIVO + IPI (N = 202)	CHEMO (N = 101)	NIVO + IPI (N = 354)	NIVO (N = 353)
Median OS (months, 95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OS at 6 months (%, 95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OS at 12 months (%, 95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OS at 18 months (%, 95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OS at 24 months (%, 95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OS at 30 months (%, 95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OS at 36 months (%, 95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHEMO, chemotherapy; CM8HW, CheckMate 8HW; IPI, ipilimumab; N.A., not available; NIVO, nivolumab; OS, overall survival

[redacted]The data presented showed [redacted]The American Society of Clinical Oncology (ASCO) often suggests a 20% or greater relative improvement in median overall survival as a benchmark for a clinically meaningful benefit.[5] According to this threshold, it [redacted]The EAG noted that the modelled projections were [redacted] to the observed data.

4. EAG ADDITIONAL ANALYSES AND REVISED BASE CASE

Table 4: Base case assumptions

Company revised base case	EAG revised base case
Subsequent treatment data for NIVO + IPI and NIVO stated to be median TTD from CM8HW in the locally confirmed 1L cohort for NIVO + IPI (Table 4, Appendix 1)	The EAG preferred to use first line TTD taken from the model based upon the use of AUC method. This was preferred for consistency with the first line inputs in the model. However, the EAG flagged that these data were not ideal and that data from previously treated trials would have been preferred.
Pembrolizumab TTP is derived from the FP-NMA	Model pembrolizumab outcomes using HR for nivolumab monotherapy vs NIVO + IPI

Abbreviations: AUC, area under the curve; CM8HW, CheckMate 8HW; EAG, external assessment group; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; TTD, time to discontinuation; TTP, time to progression

Table 5: Company revised base case (list price)

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER £/QALY
Company revised base case					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHEMO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHEMO, chemotherapy; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; QALY, quality-adjusted life year

Table 6: EAG revised base case (list price)

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER £/QALY
PEMBRO outcomes modeled using HR for NIVO monotherapy					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHEMO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consistent immunotherapy TTD for 1st and 2nd line treatment					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER £/QALY
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHEMO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative impact of EAG revised base case					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHEMO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHEMO, chemotherapy; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; QALY, quality-adjusted life year

EAG scenarios:

Table 7: Treatment effect waning (list price)

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER £/QALY
Treatment effect waning after 4 years					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHEMO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment effect waning after 10 years					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHEMO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHEMO, chemotherapy; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; QALY, quality-adjusted life year

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