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Pembrolizumab for previously treated solid tumours with high microsatellite instability or mismatch repair deficiency [ID4036]

Produced by Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Center+ (UMC+)

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Contributions of authors

Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Willem Witlox acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Sabine Grimm, Bradley Sugden, Teebah Abu-Zarah, Thomas Otten, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Mark Perry and Mubarak Patel acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report, and provided general guidance.

Abbreviations

5-FU	5-fluorouracil
AE	Adverse event
aEC	Advanced endometrial cancer
AEOSI	Adverse Event of Special Interest
AiC	Academic in Confidence
AIC	Akaike Information Criterion
Anti-PD-1	Anti programmed death 1
ASaT	All subjects as treated
ASC	Active symptom control
ASCO	American Society of Clinical Oncology
BHM	Bayesian hierarchical model
BIC	Bayesian information criterion
BRAF	Gene that encodes the B-Raf protein
CADTH	Canadian Agency for Drugs and Technologies in Health
CAPOX	Oxaliplatin + capecitabine
CEA	Cost-effectiveness analysis
CI	Confidence interval
CiC	Commercial in Confidence
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRD	Centre for Reviews and Dissemination
CS	Company submission
CTCAE	Common Terminology Criteria for Adverse Events
DAE	Discontinuation due to adverse event
DALY	Disability-adjusted life year
DCR	Disease control rate
DIC	Deviance Information Criterion
dMMR	DNA mismatch repair deficient
DNA	Deoxyribonucleic acid
DOR	Duration of response
DR	Date range
DSU	Decision Support Unit
EAG	Evidence Assessment Group
ECI	Event of clinical interest
ECM	Established clinical management
ECOG	Eastern Cooperative Oncology Group
EED	Economic Evaluation Database
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC	European Organisation for the Research and Treatment of Cancer
QLQ-C30	Quality of Life Questionnaire C30
EQ-5D	EuroQol 5D Quality of Life Instrument
ESMO	European Society of Medical Oncology
ESS	Effective sample size
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FDA	Food and Drug Administration
FE	Fixing errors
FOLFIRI	Folinic acid, fluorouracil, irinotecan
FOLFOX	Folinic acid, fluorouracil, oxaliplatin
FOLFOXIRI	Folinic acid, fluorouracil, irinotecan, oxaliplatin

FV	Fixing violations
G-CSF	Granulocyte colony-stimulating factor
h	Hour
HCRU	Health care resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
HTAD	Health Technology Assessment Database
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
iNHB	Incremental net health benefit
IPD	Individual participant data
IRC	Independent Radiologist Review Committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan–Meier
KRAS	Kirsten rat sarcoma virus gene
KSR	Kleijnen Systematic Reviews Ltd
LY	Life year
mAB	Monoclonal antibody
MAIC	Matching-adjusted indirect comparison
mCRC	Metastatic colorectal cancer
MeSH	Medical Subject Heading
mFOLFIRI	Modified folinic acid, fluorouracil, irinotecan
mFOLFOX	Modified folinic acid, fluorouracil, oxaliplatin
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MJ	Matters of judgement
MMR	Mismatched repair
MSD	Merck Sharp and Dohme
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
MSS	Microsatellite stable
NA	Not applicable
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Non-estimable
NL	The Netherlands
NR	Not reached
NRAS	Enzyme encoded by the NRAS gene
NTRK	Neurotrophin receptor tyrosine kinase
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PF	Progression-free
PFS	Progression-free survival
pMMR	Proficient mismatch repair

PPP	Platinum pre-treated population
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRO	Patient-reported outcome
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q3W	Once every three weeks
QALY	Quality-adjusted life year
QoL	Quality of life
RAS	Rat sarcoma virus
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SD	Search date
SD	Stable disease
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SoC	Standard of care
STA	Single Technology Appraisal
STM	State transmission models
TA	Technology Appraisal
TAS-102	Tipiracil hydrochloride
ToT	Time on treatment
TPC	Treatment of physician's choice
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTP	Time to progression
UK	United Kingdom
UMC+	University Medical Center+
US	United States
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
WES	Whole exome sequencing
XELOX	Capecitabine plus oxaliplatin

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 relates to the clinical effectiveness, and Section 1.5 relates to the cost effectiveness. Other key issues are discussed in Section 1.6 while a summary is presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report Section
1	Inappropriate exclusion of comparators from the company decision problem.	2.3
2	External validity of the trial evidence to the UK target population.	3.2.3.2
3	Adverse event data for KEYNOTE-158 were aggregated, and not presented for each separate tumour site.	3.2.7.1
4	Mismatch in MSI-H/dMMR status between pembrolizumab population and comparator population.	3.4.3
5	High risk of bias in comparative efficacy.	3.4
6	Populations were aggregated across all tumour sites based on their MSI-H/dMMR status. However, MSI-H/dMMR status for most comparators was unknown and heterogeneity between tumour sites seems substantial.	4.2.2
7	Treatment baskets were used to inform SoC per tumour site, which may bias the costs and outcomes of SoC in the economic model.	4.2.4
8	The selection of patients in the comparator studies was not based on their MSI-H/dMMR status, which introduced (methodological) uncertainty in the estimation the relative effectiveness of pembrolizumab.	4.2.6
9	The suitability of the Bayesian hierarchical model approach in the context of this submission was questionable.	4.2.6
10	The time-to-death utility approach to model the HRQoL of tumour sites included in KEYNOTE-158 was questionable.	4.2.8
11	Assumptions regarding the modelling of subsequent treatments were questionable.	4.2.9
12	Testing costs to identify patients with MSI-H/dMMR were not included in the company's base-case analysis.	4.2.9
13	Severity estimates were based on the company's modelling of QALYs, which was subject to limitations, and therefore uncertain.	4.2.10
14	The majority of the company's scenario analyses could not be reproduced and lacked face validity.	5.2

dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; MSI-H = microsatellite instability-high; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life year; SoC = standard of care; TSD = Technical Support Document; UK = United Kingdom

1.2 Overview of key model outcomes

National Institute for Health and Care Excellence technology appraisals compare how much a new technology improves length (overall survival) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increased progression-free survival (PFS) for pembrolizumab in the colorectal cancer (CRC) indication (QALYs in the progression-free (PF) health state increased by [redacted] [redacted] of total QALYs] compared with standard of care (SoC)) and increased time-to-death in the other indications (QALYs in time to treatment discontinuation (TTD) 360+ days increased by [redacted] [redacted] of total QALYs]).
- Increased overall survival (OS) for pembrolizumab (survival increased by [redacted] years compared with SoC).

Overall, the technology is modelled to affect costs by:

- The higher treatment costs (additional costs of [redacted] compared with SoC).
- The higher resource use costs (additional costs of [redacted] compared with SoC).

The modelling assumptions that have the greatest effect on the overall indication net health benefit (NHB; based on the company's deterministic sensitivity analyses) were:

- Administration costs of oral chemotherapy
- Proportion of CRC patients receiving subsequent therapy after pembrolizumab
- Utility values by Grothey 2013[1] to inform health-related quality of life (HRQoL) in CRC

Based on the company's scenario analyses, modelling assumptions that have the greatest effect on the overall indication NHB were related to:

- Treatment waning
- QALYs and costs discounting
- Survival modelling of OS and PFS in the pembrolizumab arm

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there is a lack of evidence from certain comparators (Table 1.2).

Table 1.2: Issue 1: Inappropriate exclusion of comparators from the company decision problem

Report Section	**2.3**
Description of issue and why the EAG has identified it as important	Nivolumab + ipilimumab, irinotecan + raltitrexed and ECM were designated as relevant comparators by the NICE scope, but not included in the decision problem. The company presented an argument that nivolumab + ipilimumab would not be an appropriate comparator to pembrolizumab at the second line stage, as nivolumab + ipilimumab would only be used where pembrolizumab had not been used first line, but this is the very population of the decision problem. ECM was listed as a separate comparator in the NICE scope. This raises a question as to what it might entail, given that other treatments were separately listed and that those other treatments could also be regarded as a type of ECM. However, the company did not clear resolve this ambiguity by stating that the comparators that they considered could have been considered as a whole as

Report Section	2.3
	ECM. This then leaves open the possibility that some treatments, which might be regarded as ECM were not considered. Therefore, the company might not have considered all relevant comparators in their analysis of evidence. Failure to consider all these potentially relevant comparators may yield spurious conclusions about pembrolizumab efficacy.
What alternative approach has the EAG suggested?	Inclusion of these comparators in the decision problem, and therefore extending the scope of comparators used in the analyses.
What is the expected effect on the cost effectiveness estimates?	The omission of these comparators may have contributed to a spurious inflation of cost effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Inclusion of these comparators in the decision problem, and therefore extending the scope of comparators used in the analyses.
EAG = Evidence Assessment Group; ECM = established clinical management; NICE = National Institute for Health and Care Excellence	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified a number of concerns with the evidence presented on the clinical effectiveness, namely the potentially reduced external validity of the trial evidence (see Table 1.3) as well as the aggregation of adverse events (Table 1.4), the mismatch between pembrolizumab and comparators in microsatellite instability-high (MSI-H)/deoxyribonucleic acid (DNA) mismatch repair deficient (dMMR) status (Table 1.5) and the lack of transparency in the derivation of comparator data used for the health economic analysis (Table 1.6).

Table 1.3: Issue 2: External validity of the trial evidence to the UK target population

Report Section	3.2.3.2
Description of issue and why the EAG has identified it as important	For colorectal and gastric cancer, and to a lesser extent small intestine cancer, the EAG notes large differences in ethnicity between the trials and the UK data provided by the company. The UK data are not specifically in people with MSI-H/dMMR, and the EAG recognises that it is possible that the ethnic proportions in a more relevant UK subgroup with MSI-H/dMMR status might be more closely aligned with the trial data (which is in an MSI-H/dMMR population). However, given evidence that ethnicity is not strongly linked to MSI-H/dMMR status, it is unlikely that the ethnic make-up of a UK MSI-H/dMMR subgroup would be appreciably different to the ethnic make-up of the UK data presented by the company. Given that the UK data may reflect the ethnic proportions of the specific UK target population, there are possible discrepancies between the trial data and the UK target population.
What alternative approach has the EAG suggested?	A subgroup analysis for ethnicity might demonstrate if ethnicity is an effect modifier. If it is, then the possible discrepancies in ethnicity between trial and UK target population may reduce the applicability of trial findings.
What is the expected effect on the cost effectiveness estimates?	Unknown. This will depend on the effect of ethnicity on outcomes.
What additional evidence or analyses might help to resolve this key issue?	A subgroup analysis for ethnicity might demonstrate if ethnicity is an effect modifier. If it is, then the possible discrepancies in

Report Section	3.2.3.2
	ethnicity between trial and UK target population may reduce the applicability of trial findings.
dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; MSI-H = microsatellite instability-high; UK = United Kingdom	

Table 1.4: Issue 3: Aggregation of AE data for KEYNOTE-158

Report Section	3.2.7.1
Description of issue and why the EAG has identified it as important	Aggregation of data were not performed for the clinical efficacy outcomes from KEYNOTE-158, but the four tumour sites were combined for appraisal of AEs. It is possible that an aggregated result could obscure high levels of AEs in a single tumour site
What alternative approach has the EAG suggested?	Subgrouping of the aggregated data is required.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Subgrouping of the aggregated data and comparative analysis of these sub-grouped data.
AE = adverse event; EAG = Evidence Assessment Group	

Table 1.5: Issue 4: Mismatch in MSI-H/dMMR status between pembrolizumab population and comparator population

Report Section	3.4.3
Description of issue and why the EAG has identified it as important	The ITC uses pembrolizumab trials in the MSI-H/dMMR population and comparator trials that are *not* in the MSI-H/dMMR population. However, MSI-H/dMMR may be a treatement effect modifier. The company provided evidence that suggested MSI-H/dMMR status may worsen prognosis. This suggests that the mismatch might have a conservative effect, i.e., it may reduce rather than enhance apparent pembrolizumab effectiveness. However, the company also cites clinical opinion suggesting that MSI-H/dMMR status may improve the effectiveness of immunotherapy treatment. This additional effect may increase uncertainty of the magnitude and direction of any effect modification.
What alternative approach has the EAG suggested?	The EAG has suggested that pembrolizumab data in people *without* MSI-H/dMMR status be compared to the non-MSI-H/dMMR comparator data. This may have disadvantages in terms of reduced external validity, but the advantages in terms of enhanced internal validity may be greater.
What is the expected effect on the cost effectiveness estimates?	There is the potential for the cost effectiveness to have been spuriously increased by the mismatch.
What additional evidence or analyses might help to resolve this key issue?	The EAG has suggested that pembrolizumab data in people *without* MSI-H/dMMR status be compared to the non-MSI-H/dMMR comparator data. This may have disadvantages in terms of reduced external validity, but the advantages in terms of enhanced internal validity may be greater.
dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; ITC = indirect treatment comparison; MSI-H = microsatellite instability-high	

Table 1.6: Issue 5: High risk of bias in comparative efficacy

Report Section	3.4.3
Description of issue and why the EAG has identified it as important	Having presented the ITC and MAIC evidence, with its limitations as described above, the company concludes that the ITC and MAIC evidence is not fit for purpose for the economic analysis, and that the health economic strategy will therefore be based upon the following approach: *"parametric survival distributions were fitted to the comparator pseudo-IPD with the most clinically plausible extrapolation chosen for use in the base case"*. The EAG agree that all methods are limited, including the non-responder-based analysis, as acknowledged by the company. However, although the base case method has the advantage of not assuming proportional hazards, it still uses non-randomised controlled data with no adjustment for confounding. Therefore, all methods imply a high risk of bias in comparative efficacy for pembrolizumab in all cancers.
What alternative approach has the EAG suggested?	Given the serious limitations of all approaches, there seems to be little that can be suggested to reduce the risk of bias.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Given the serious limitations of all methods of survival estimation, the EAG suggests the use of external validation and clinical expert opinion to test the independently fitted parametric survival curves, alongside other criteria, in line with TSD 14 (see key issue 8).
EAG = Evidence Assessment Group; IPD = individual participant data; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; TSD = technical support document	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The main EAG results are reproduced using confidential patient access schemes in a confidential appendix. The key issues in the cost effectiveness evidence are discussed in the issue Tables below.

Table 1.7: Issue 6: Model structure – Aggregating tumour sites results

Report Section	4.2.2
Description of issue and why the EAG has identified it as important	The company aggregated populations across all tumour sites based on their MSI-H/dMMR status to generate outcomes for the overall indication. However, MSI-H/dMMR status for most comparators was unknown and heterogeneity between tumour sites seems substantial.
What alternative approach has the EAG suggested?	Further justification, supported by evidence, as to the appropriateness of aggregating results across tumour sites.
What is the expected effect on the cost effectiveness estimates?	The impact on cost effectiveness results (direction of influence and magnitude) differs per tumour site.
What additional evidence or analyses might help to resolve this key issue?	Further justification, supported by evidence, as to the appropriateness of aggregating results across tumour sites.
dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; MSI-H = microsatellite instability-high	

Table 1.8: Issue 7: Intervention and comparators – Treatment baskets to inform SoC

Report Section	4.2.4
Description of issue and why the EAG has identified it as important	Treatment baskets were used to inform SoC per tumour site, comprising a mixture of single comparators and pooled comparators. The comparator effectiveness and costs are therefore based on the average clinical effectiveness and weighted average costs across the treatments included in the comparator basket which may bias the costs and outcomes of SoC in the economic model.
What alternative approach has the EAG suggested?	The EAG presented fully incremental analyses results per tumour site. Present fully incremental analysis results moving forward.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	NA
EAG = Evidence Assessment Group; NA = not applicable; SoC = standard of care	

Table 1.9: Issue 8: Treatment effectiveness and extrapolation – Methodology for estimation of relative effectiveness

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	Except for paclitaxel in gastric cancer and paclitaxel/doxorubicin in endometrial cancer, the selection of patients in the comparator studies was not based on their MSI-H/dMMR status. This introduced uncertainty in the estimation the relative effectiveness of pembrolizumab. There is methodological uncertainty about how to best analyse the data.
What alternative approach has the EAG suggested?	A non-responder scenario analysis, assuming that patients treated with pembrolizumab from KEYNOTE-158 and KEYNOTE-164 who do not achieve a partial or complete response have survival outcomes (OS and PFS) that are consistent with patients who received a comparator treatment within established clinical practice.
What is the expected effect on the cost effectiveness estimates?	The scenario analysis resulted in an increased ICER.
What additional evidence or analyses might help to resolve this key issue?	Full NICE DSU TSD 14 and 21 details that support the optimal parametric curves to extrapolate the non-responder OS and PFS KM data. Provide further details on the implementation of the non-responder analysis into the economic model and elaborate on how this analysis also affects the modelled pembrolizumab life years and QALY gains.
dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; DSU = Decision Support Unit; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; MSI-H = microsatellite instability-high; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; TSD = Technical Support Document	

Table 1.10: Issue 9: Treatment effectiveness and extrapolation – BHM approach for modelling of pembrolizumab OS and PFS

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The EAG questions the suitability of the BHM approach in the context of this submission. The BHM approach would only be appropriate if the assumption that the different tumour sites can be considered subgroups of an overarching MSI-H/dMMR solid tumour population is justified.
What alternative approach has the EAG suggested?	Apply the BHM approach only to comparable tumour sites, justified and supported by clinical arguments and evidence rather than statistical arguments. Modelling the KEYNOTE-164 data for the colorectal cancer (CRC) tumour site separately and applying the BHM approach only to the tumour sites included in the KEYNOTE-158 basket trial. Provide further justification on the use of a BHM approach for time-to-event outcomes rather than response outcomes.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Apply the BHM approach only to comparable tumour sites, justified and supported by clinical arguments and evidence rather than statistical arguments. Modelling the KEYNOTE-164 data for the CRC tumour site separately and applying the BHM approach only to the tumour sites included in the KEYNOTE-158 basket trial. Further elaboration on the suitability of the BHM approach for time-to-event outcomes rather than response outcomes.
BHM = Bayesian hierarchical modelling; CRC = colorectal cancer; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; MSI-H = microsatellite instability-high	

Table 1.11: Issue 10: Health-related quality of life - Time-to-death approach for modelling the HRQoL of tumour sites in KEYNOTE-158

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	The company used a time-to-death utility approach to model the HRQoL of tumour sites included in KEYNOTE-158. The EAG questioned this, as it is not part of the NICE DSU TSD guidance on utilities and lacks details on statistical analyses, it seems inconsistent with the progression-based model structure, and it lacks face validity.
What alternative approach has the EAG suggested?	The EAG uses the more conservative health state-based approach of modelling utilities as a function of progression status in its base-case.
What is the expected effect on the cost effectiveness estimates?	Using the health state-based approach of modelling utilities increased the ICER.
What additional evidence or analyses might help to resolve this key issue?	Provide full details of the statistical analyses for the various models that were considered.
DSU = Decision Support Unit; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; TSD = Technical Support Document	

Table 1.12: Issue 11: Resources and costs – Modelling of subsequent treatments

Report Section	4.2.9
Description of issue and why the EAG has identified it as important	The EAG questions the assumptions that (1) the proportions of patients receiving subsequent treatments are equal regardless of initial treatment and that (2) the modelled subsequent treatments are reflective of UK clinical practice.
What alternative approach has the EAG suggested?	Further evidence and justification to support these assumptions.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Further evidence and justification to support these assumptions.
EAG = Evidence Assessment Group; UK = United Kingdom	

Table 1.13: Issue 12: Resources and costs - Testing costs to identify patients with MSI-H/dMMR

Report Section	4.2.9
Description of issue and why the EAG has identified it as important	The company did not include testing costs to identify patients with MSI-H/dMMR in their base-case analysis.
What alternative approach has the EAG suggested?	The EAG adopted the company's scenario analysis including testing costs in its base-case.
What is the expected effect on the cost effectiveness estimates?	The inclusion of testing costs slightly increased the ICER.
What additional evidence or analyses might help to resolve this key issue?	Evidence to support the assumptions that 1) testing in colorectal cancer (CRC) and endometrial cancer is routinely commissioned in the NHS, and 2) 50% of patients of the remaining tumour sites already receive these tests.
CRC = colorectal cancer; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; MSI-H = microsatellite instability-high; NHS = National Health Service	

Table 1.14: Issue 13: Severity – Approach for estimation of severity

Report Section	4.2.10
Description of issue and why the EAG has identified it as important	Severity estimates are based on the company's modelling of QALYs, which is subject to limitations in the data used, and therefore uncertain. The company's time-to-death approach to estimating HRQoL leads to a [redacted] QALY multiplier for two tumour sites (gastric and small intestine) than the alternative, more conventional health state (progression-) based approach to modelling HRQoL.
What alternative approach has the EAG suggested?	Use the health state (progression-) based approach to modelling HRQoL.
What is the expected effect on the cost effectiveness estimates?	ICERs will [redacted] with the alternative approach suggested by the EAG.
What additional evidence or analyses	QALY estimates from NICE TAs in populations with MSI-H/dMMR status.

Report Section	4.2.10
might help to resolve this key issue?	
dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; MSI-H = microsatellite instability-high; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life year; TA = technology appraisal	

Table 1.15: Issue 14: Reproducibility and face validity of scenario analyses

Report Section	5.2
Description of issue and why the EAG has identified it as important	The EAG was unable to reproduce the majority of the scenario analyses reported in Table 93 of the CS. The results of some scenario's (e.g., pembrolizumab OS, PFS – BHM Weibull) also lacked face validity, i.e., the EAG found an increased NHB compared to the company's base-case while the company reported a decreased NHB in CS, Table 93.
What alternative approach has the EAG suggested?	Further justification for the differences between the EAG and company scenario analyses and the lack of face validity should be provided. In addition, step by step details should be provided on how the company's scenario analyses can be reproduced in the economic model.
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Further justification for the lack of reproducibility and face validity of the company's scenario analyses should be provided. In addition, step by step details should be provided on how the company's scenario analyses can be reproduced in the economic model.
BHM = Bayesian hierarchical modelling; CS = company submission; EAG = Evidence Assessment Group; NHB = net health benefit; OS = overall survival; PFS = progression-free survival	

1.6 Other key issues: summary of the EAG's view

There were no other key issues.

1.7 Summary of the EAG's view

The CS base-case ICER (probabilistic) for the overall indication was £12,637 per QALY gained (Table 1.16). The estimated EAG base-case ICER (probabilistic) for the overall indication, based on the EAG preferred assumptions highlighted in Section 6.1, was £16,531 per QALY gained. The estimated deterministic base-case ICERs (based on a fully incremental analysis per tumour site) for colorectal cancer, endometrial cancer, gastric cancer, small intestine cancer and cholangiocarcinoma were £13,845, £17,785, £27,387, £21,970, and £15,250 per QALY gained, respectively. The most influential adjustments were the 1.2 QALY multipliers for tumour sites except cholangiocarcinoma, and the health state-based approach to estimate utility values. The ICER increased most in the scenario analysis using a non-responder analysis to estimate the relative effectiveness of pembrolizumab.

In conclusion, there is large remaining uncertainty about the effectiveness and cost effectiveness of pembrolizumab, which can be partly resolved by the company by conducting further analyses. This includes providing an estimation of the OS and PFS relative effectiveness of pembrolizumab in patients that all had a positive MSI-H/dMMR status, an analysis applying the Bayesian hierarchical model (BHM) approach only to comparable tumour sites based on clinical arguments and evidence, full details of the statistical analyses for the various time-to-death models that were considered for the estimation of HRQoL, further justification for assumptions made regarding the modelling of subsequent

treatments and costs for MSI-H/dMMR testing, and further justification for the lack of reproducibility and face validity of scenario analyses. Therefore, the EAG believes that the CS nor the EAG report contains an unbiased ICER of pembrolizumab compared with relevant comparators.

Table 1.16: Summary of EAG's preferred assumptions and ICER

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]
CS base-case						
Pembrolizumab	[redacted]	[redacted]				
SoC	£33,759	[redacted]	[redacted]	[redacted]	£12,796	1.85
Matter of judgement (1-Tumour site distribution based on UK epidemiological data)						
Pembrolizumab	[redacted]	[redacted]				
SoC	£32,561	[redacted]	[redacted]	[redacted]	£13,415	1.78
Matter of judgement (2-Health state-based approach to estimate utility values)						
Pembrolizumab	[redacted]	[redacted]				
SoC	£33,759	[redacted]	[redacted]	[redacted]	£13,744	1.63
Matter of judgement (3-Inclusion of MSI-H/dMMR testing costs)						
Pembrolizumab	[redacted]	[redacted]				
SoC	£33,759	[redacted]	[redacted]	[redacted]	£12,987	1.83
Matter of judgement (4-1.2 QALY multipliers for tumour sites except cholangiocarcinoma)						
Pembrolizumab	[redacted]	[redacted]				
SoC	£33,759	[redacted]	[redacted]	[redacted]	£13,974	1.58
Deterministic EAG base-case						
Pembrolizumab	[redacted]	[redacted]				
SoC	£32,561	[redacted]	[redacted]	[redacted]	£16,856	1.14
Probabilistic EAG base-case						
Pembrolizumab	[redacted]	[redacted]				
SoC	£33,138	[redacted]	[redacted]	[redacted]	£16,531	1.20
Scenario analysis (5-Non-responder analysis)						
Pembrolizumab	[redacted]	[redacted]				
SoC	£36,020	[redacted]	[redacted]	[redacted]	£20.336	0.72

[1]iNHB for willingness-to-pay of £30,000 per QALY
CS = company submission; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; MSI-H = microsatellite instability-high; QALY = quality-adjusted life-year; SoC = standard of care; UK = United Kingdom

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
Population	• Adults with unresectable or metastatic MSI-H or dMMR CRC previously treated with fluoropyrimidine-based combination therapy. • Adults with advanced or recurrent MSI-H or dMMR endometrial cancer, whose disease has progressed on or following treatment with a platinum-containing therapy and who are not candidates for curative surgery or radiation. • Adults with unresectable or metastatic MSI-H or dMMR gastric, small intestine, or biliary cancer, whose disease has progressed on or following at least one prior therapy.	• Adults with unresectable or metastatic MSI-H or dMMR CRC previously treated with fluoropyrimidine-based combination therapy. • Adults with advanced or recurrent MSI-H or dMMR endometrial cancer, whose disease has progressed on or following treatment with a platinum-containing therapy and who are not candidates for curative surgery or radiation. • Adults with unresectable or metastatic MSI-H or dMMR gastric, small intestine, or biliary cancer, whose disease has progressed on or following at least one prior therapy	In line with final NICE scope	No comment
Intervention	Pembrolizumab	Pembrolizumab	In line with final NICE scope	No comment
Comparator(s)	For people with previously treated MSI-H or dMMR with unresectable or metastatic CRC:	For people with previously treated MSI-H or dMMR with	*For people with previously*	The rationale for not using

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
	• Established management without pembrolizumab • Nivolumab with ipilimumab • Single-agent irinotecan (after FOLFOX) • FOLFIRI (after either FOLFOX or CAPOX) • Raltitrexed (if 5-fluorouracil and folinic acid are not suitable) • Trifluridine-tipiracil For people with previously treated MSI-H or dMMR with advanced or recurrent endometrial cancer: • Established management without pembrolizumab • Chemotherapy, including: • Carboplatin and paclitaxel • Paclitaxel monotherapy • Doxorubicin monotherapy • Carboplatin monotherapy • Hormone therapy (such as medroxyprogesterone acetate and megestrol) For people with previously treated MSI-H or dMMR with unresectable or metastatic gastric, small intestine, or biliary cancer: • Established management without pembrolizumab	unresectable or metastatic CRC: • FOLFIRI/FOLFOX/FOLFO4/ mFOLFOX6 (70% of eligible patients) • Trifluridine-tipiracil (30% of eligible patients For people with previously treated MSI-H or dMMR with advanced or recurrent endometrial cancer: • Chemotherapy, including paclitaxel, doxorubicin and carboplatin For people with previously treated MSI-H or dMMR with unresectable or metastatic gastric, small intestine and biliary cancer: *Gastric cancer* • Paclitaxel • FOLFIRI *Small intestine cancer* • FOLFIRI/FOLFOX *Biliary cancer* • FOLFOX • FOLFIRI	*treated MSI-H or dMMR with unresectable or metastatic colorectal cancer:* Single-agent irinotecan and raltitrexed are not considered relevant comparators in this appraisal as clinical expert opinion confirmed that they are not routinely used in clinical practice unless other treatments are contra-indicated. Nivolumab with ipilimumab is not considered a relevant comparator in this appraisal. Given that nivolumab with	nivolumab with ipilimumab as a comparator in the decision problem (for the sub-population with CRC) is not clearly explained, despite this comparator being requested in the NICE scope. The rationale for not using single-agent irinotecan and raltitrexed as a comparator in the decision problem (for the sub-population with CRC), which was requested in the NICE scope, is based on clinical opinion that this agent is

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
			ipilimumab cannot be used to treat patients who received any prior treatment with an anti-PD-1 antibody, and pembrolizumab is the SoC for patients with untreated metastatic CRC with MSI-H or dMMR, nivolumab with ipilimumab will be the treatment of choice for a small subset of people who receive fluoro-pyrimidine-based combination chemotherapy in first-line when the MSI-H/dMMR status is not yet confirmed or	rarely prescribed in clinical practice. There is a need for the company back up the rationale with more objective evidence. For the sub-population with endometrial cancer, the decision problem appears sufficiently similar to the NICE scope in terms of chemotherapy. The rationale for excluding hormone therapy appears to be valid. The NICE scope includes 'established management

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
			where the progression of the disease requires fast acting chemo-therapy. Clinical expert opinion suggested that these patients will routinely receive nivolumab with ipilimumab unless there are comorbidities. In these instances, which are expected to occur in a small proportion of patients (subset of the subset) pembrolizumab may be a suitable option. *For people with previously treated MSI-H or dMMR with*	without pembrolizumab' as a valid comparator for all three sub-populations (colorectal tumours, endometrial tumours and gastric, biliary, or small intestine tumours). This aspect of the NICE scope implies that any comparator, provided it is currently used in UK clinical practice, is a valid comparator. However, 'established management without pembrolizumab' has not been included in the

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
			advanced or recurrent endometrial cancer: Based on clinical expert consultation, SoC is chemotherapy such as paclitaxel, doxorubicin and carboplatin. Hormone therapy is only used with palliative intent if all other treatment options are exhausted, or patients cannot tolerate further lines of chemotherapy which is not the proposed positioning for pembrolizumab. *For people with previously*	decision problem for these three sub-populations. Failure to include this criterion in the decision problem means that the company does not have to consider all relevant comparators in their evidence. If established management options have not been included amongst the specified comparators in the decision problem this will lead to a biased evaluation of the evidence.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
			treated MSI-H or dMMR with unresectable or metastatic gastric, small intestine and biliary cancer: Established clinical management without pembrolizumab has been identified based on European guidelines and clinical expert consultation. With regard to small intestine cancer, clinical experts identified FOLFOX/ FOLFIRI as the treatment of choice but did not expect MSD to find any published evidence on	

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
			efficacy. This was confirmed in the SLR which only identified evidence for nab-paclitaxel, which is used in the CEA.	
Outcomes	• OS • PFS • RR • DOR • Adverse effects of treatment • HRQoL	• OS • PFS • RR • DOR • Adverse effects of treatment • HRQoL	NA	No comment
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. • The availability and cost of biosimilar and generic products should be taken into account. • The use of pembrolizumab for this indication is conditional on the presence of either MSI-H or dMMR classified tumours. The	Cost effectiveness of the treatments specified are expressed in terms of incremental cost per QALY. The economic analysis implements a lifetime time horizon for estimating clinical and cost effectiveness. Costs are included from an NHS and PSS perspective and use sources reflecting the current prices available to the NICE (with the exception of	Previous appraisals and clinical opinion suggest testing is well established in colorectal and endometrial cancer and so for consistency testing costs are not included in the base-case. However, testing costs for the remaining	Testing costs to identify patients with MSI-H/ dMMR were explored by the company in a scenario analysis, but not included in their base-case. The EAG adopted the company's scenario analysis including

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
	economic modelling should include the costs associated with diagnostic testing for MSI-H or dMMR in people with solid tumours who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See Section 4.8 of the Guidance Development Manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introductionto-health-technology-evaluation).	therapies available with a confidential discount). Testing costs are not included in the base-case analysis.	tumour sites are explored in scenario analyses.	testing costs in its base-case.
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Tumour site • Previous therapy	Cost effectiveness analysis for each tumour site are provided.	No additional subgroup analysis was performed.	No comments.
Special considerations including issues related to equity or equality		No issues with equity or equality have been identified.		

Based on Table 1 and pages 10 to 12 of the CS[2]
CAPOX = oxaliplatin plus capecitabine; CEA = cost effectiveness analysis; CRC = colorectal cancer; CS = company submission; DOR = duration of response; dMMR = DNA mismatch repair deficient: DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; FOLFIRI = folinic acid, fluorouracil, irinotecan; FOLFOX = folinic acid, fluorouracil, oxaliplatin; HRQoL = health-related quality of life; mFOLFOX = modified folinic acid, fluorouracil, oxaliplatin; MSD = Merck Sharp and Dohme; MSI-H = microsatellite instability-high; NA = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OS = overall survival; PD-1 = programmed death 1; PFS = progression-free survival; PSS = Personal Social Services; QALY = quality-adjusted life year; RR = response rate; SLR = systematic literature review; SoC = standard of care; UK = United Kingdom

2.1 Population

The population defined in the scope comprises:

1. Adults with unresectable or metastatic microsatellite instability-high (MSI-H) or deoxyribonucleic acid (DNA) mismatch repair deficient (dMMR) colorectal cancer previously treated with fluoropyrimidine-based combination therapy.
2. Adults with advanced or recurrent MSI-H or dMMR endometrial cancer, whose disease has progressed on or following treatment with a platinum-containing therapy and who are not candidates for curative surgery or radiation.
3. Adults with unresectable or metastatic MSI-H or dMMR gastric, small intestine, or biliary cancer, whose disease has progressed on or following at least one prior therapy.

The population in the decision problem is in line with the National Institute for Health and Care Excellence (NICE) scope.

EAG comment: No comment.

2.2 Intervention

The intervention (pembrolizumab) is in line with the scope.

Pembrolizumab (KEYTRUDA®, Merck Sharp and Dohme; MSD) is a humanised monoclonal anti-programmed cell death-1 antibody, which binds to the programmed death ligand 1 (PD-L1) receptor, thereby blocking its interaction with ligands PD-L1 and programmed death ligand 2 (PD-L2). The programmed cell death protein (PD-1) receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. PD-L1 and PD-L2 are expressed in antigen-presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.[2]

EAG comment: No comment.

2.3 Comparators

The comparators in the decision problem differ to those in the NICE scope (see Table 2.1).

EAG comment:

- The rationale for not using nivolumab plus ipilimumab as a comparator in the decision problem (for the sub-population with colorectal cancer) is not clearly explained, despite this comparator being requested in the NICE scope. The company have been asked to provide a clearer explanation. The company explained that [redacted] of patients with metastatic colorectal cancer (CRC) and confirmed MSI-H/dMMR would be offered pembrolizumab as *first-line* treatment (as per technology appraisal 709 (TA709)), and therefore second line pembrolizumab treatment (which is the line of therapy relevant to the current company submission (CS)) would only be considered for 10% of patients with metastatic CRC and confirmed MSI-H/dMMR. For this subset, the first-line therapy would usually be a chemotherapy agent, with nivolumab plus ipilimumab offered as the *first choice* second-line agent. This would seem to imply that nivolumab + ipilimumab is a comparator, i.e. the company's own description of the care pathway states that, at the position of pembrolizumab in this appraisal, which is second line following chemotherapy, nivolumab + ipilimumab would be used. Therefore, it does not seem correct when the company argue (see Table 2.1) that nivolumab + ipilimumab is ruled out because it is not appropriate following pembrolizumab fist line: *"Given that nivolumab with ipilimumab cannot be used to treat patients who received any prior treatment with an anti-PD-1 antibody, and pembrolizumab is the standard of care for patients with untreated metastatic colorectal cancer with MSI-H or dMMR, nivolumab with ipilimumab will be the treatment of choice*

for a small subset of people who receive fluoropyrimidine-based combination chemotherapy in first-line when the MSI-H/MMR status is not yet confirmed or where the progression of the disease requires fast acting chemotherapy." This 'small proportion' is the very population in the decision problem. Therefore, it would seem reasonable to regard nivolumab + ipilimumab as a valid comparator to second line pembrolizumab in CRC. This has been deemed a key issue.

- The rationale for not using single-agent irinotecan and raltitrexed as a comparator in the decision problem (for the sub-population with CRC), which was requested in the NICE scope, is based on clinical opinion that this agent is rarely prescribed in clinical practice. There is a need for the company to back up the rationale with more objective evidence, which it was asked to do in the clarification questions. The company responded by reiterating that *"single-agent irinotecan and raltitrexed are not considered relevant comparators in this appraisal as clinical expert opinion confirmed that they are not routinely used in clinical practice unless other treatments are contraindicated. This is well established and supported by opinion from TA716".* The EAG does not think this response provides a more objective rationale than previously provided, as again it is based on subjective opinion. The uncertainty about the validity of excluding this comparator is therefore a key issue.
- For the sub-population with endometrial cancer, the decision problem appears sufficiently similar to the NICE scope in terms of chemotherapy. The rationale for excluding hormone therapy appears to be valid.
- The NICE scope includes 'established management without pembrolizumab' as a valid comparator for all three sub-populations (colorectal tumours, endometrial tumours and gastric, biliary, or small intestine tumours). It might be reasonable to consider that ECM is a general term for any comparator, provided it is currently used in clinical practice in England and Wales. However, the NICE scope also specifies comparators in the same list, which leaves open the possibility that ECM might include comparators not listed in the NICE scope. Unfortunately, in the company's consideration of appropriate comparators, 'established management without pembrolizumab' has not been included explicitly in the decision problem, except under the gastric, small intestine and biliary cancer heading (see Table 2.1). Failure to include this term in the decision problem means that the company might not have considered all relevant comparators in their evidence (only the specified ones are to be covered). The company were asked to list all established clinical management options for each of the tumour sub-populations so the EAG can evaluate if all relevant comparators are included amongst those listed in the decision problem. The company responded by directing the EAG to the response to QB4a in the response to the request for clarification[3], but, again the term 'established clinical management without pembrolizumab' was only mentioned in relation to 'gastric, small intestine, and biliary cancer' If some established management options have not been included amongst the specified comparators in the decision problem this will lead to a biased evaluation of the evidence. Therefore, this is deemed a key issue.

2.4 Outcomes

The NICE final scope lists the following outcome measures:

- Overall survival (OS)
- Progression-free survival (PFS)
- Response rate (RR)
- Duration of response (DOR)
- Adverse effects of treatment
- Health-related quality of life (HRQoL)

These were all included in the decision problem.

EAG comment: No comment.

2.5 Other relevant factors

Subgrouping for tumour site and previous therapy was advised by the NICE scope if the evidence allowed. The decision problem states that cost effectiveness evidence for each tumour site has been carried out, but there is no information about subgrouping for previous therapy.

Pembrolizumab was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) on 16 May 2022 for treatment of the following MSI-H or dMMR tumours in adults with:

- Unresectable or metastatic CRC after previous fluoropyrimidine-based combination therapy
- Advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation
- Unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

Pembrolizumab received Food and Drug Administration (FDA) approval in 2019 for the treatment of MSI-H solid tumours in children and adults.

According to the company, no equality issues related to the use of pembrolizumab for treatment of MSI-H or dMMR solid tumours are foreseen (CS[2], Section B.1.4).

EAG comment:

- Subgrouping was carried out for tumour site where possible (only the KEYNOTE-158 trial had >1 tumour site). An overall analysis was not also carried out.
- Subgrouping for previous treatment was not carried out and there is no rationale given for this. This might be an important subgrouping analysis if previous treatment in the United Kingdom (UK) target population differs from that in the trials. The company have been asked to provide a rational approach in the clarification letter. The company responded by stating that *"no subgroup analysis by previous treatment was performed neither in the KEYNOTE-158 nor in the KEYNOTE-164 trials. Considering the small sample size within each tumour type and the inherent exploratory nature of subgroup analyses, no valid and reliable conclusions can be drawn about the effectiveness of the technology in subgroups".* The EAG would argue that until such subgroup analyses are performed it is unknown whether there will be sufficient statistical power. In addition, even if insufficient power exists, this does not prohibit a considered comparison of point estimates that might uncover potential threats to external validity that should be of interest to the committee. The company continued by stating that *"also, in KEYNOTE-158 the subgroup analysis by previous treatment across the four tumour types would potentially lead to misleading results as it would not take into account the heterogeneity across histologies".* The EAG notes that the appropriate approach would be to stratify each stratum of tumour type by previous treatment (rather than stratifying the entire cohort by treatment type) which would circumvent this problem. The company continues by saying, *"in KEYNOTE-164, two cohorts of patients (Cohort A and B) were enrolled based on previous lines of chemotherapy (at least two lines and one line of fluoropyrimidine-based combination therapies for cohort A and B, respectively). As shown in the response to A34, no substantial differences in prior treatments is seen within and between the two cohorts with 100% of participants being previously treated with fluoropyrimidine-based combination therapies."* The EAG would state in response that although there was homogeneity in previous fluoropyrimidine-based combination therapies, there was heterogeneity with respect to other treatments.

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

A systematic literature review (SLR) was conducted by the company to identify available evidence on the efficacy and safety of pembrolizumab and relevant comparators for each of the tumour sites of interest. The findings will be reported separately for each of the SLRs conducted.

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.[2] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[4, 5] The EAG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS details the five SLRs undertaken to identify relevant clinical evidence for the efficacy and safety of pembrolizumab and the relevant comparators, across the five tumour sites of interest. The original searches were between August and November 2022 and in the case of searches for small intestine cancer, this was updated in February 2023 in response to the EAG's request for clarification.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

Resource	Endometrial cancer	Small intestine cancer	Gastric cancer	Biliary cancer	Colorectal cancer
Electronic databases					
Embase (Ovid)	DR: 2000-2022/08/26 SD: 29/08/22	DR: 2000-2023/02/17 SD: 17/02/23	DR: 2000-2022/08/26 SD: 29/08/22	DR: 2000-2022/08/26 SD: 29/08/22	DR: 2000-2022/08/31 SD: 29/08/31
MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily (Ovid)	DR: 2000-2022/08/26 SD: 29/08/22	DR: 2000-2023/02/16 SD: 17/02/23	DR: 2000-2022/08/26 SD: 29/08/22	DR: 2000-2022/08/26 SD: 29/08/22	DR: 2000-2022/08/31 SD: 29/08/31
CENTRAL (EBM Reviews Ovid)	DR:2000-2022/07 SD: 29/08/22	DR: 2000-2023/01 SD: 17/02/23	DR:2000-2022/07 SD: 29/08/22	DR:2000-2022/07 SD: 29/08/22	DR:2000-2022/07 SD: 29/08/22
Conferences searches via Northern Light Life Sciences Conference Abstracts					
ASCO 2019-2022	DR: 2019-2022/wk36 SD: 22/09/22	DR: 2019-2022/wk44 SD: 14/11/22	DR: 2019-2022/wk35 SD: 06/09/22	DR: 2019-2022/wk36 SD: 22/09/22	DR: 2019-2022/wk40 SD: 13/10/22
ESMO 2019-2022	DR: 2019-2022/wk36 SD: 22/09/22	DR: 2019-2022/wk44 SD: 14/11/22	DR: 2019-2022/wk35 SD: 06/09/22	DR: 2019-2022/wk36 SD: 22/09/22	DR: 2019-2022/wk40 SD: 13/10/22
Trials registries					
ClinicalTrials.gov	31/10/22	15/11/22	30/11/22	29/9/22	20/10/22

ASCO = American Society of Clinical Oncology; CS = company submission; DR = date range; ESMO = European Society for Medical Oncology; SD = search date

EAG comment:

General

- Searches were carried out across a good range of databases. Two relevant conference proceedings and the ClinicalTrials.gov registry were also searched. Where appropriate strategies utilised a recognised randomised controlled trial (RCT) study design filter from the Scottish Intercollegiate Guidelines Network (SIGN).
- The EAG noted a number of reporting errors which were rectified by the company at clarification. The EAG would draw attention to current best practice which recommends that the database search strategies to be presented exactly as run, rather than copied into a tabular format, as item 8 of the PRISMA-S reporting checklist recommends.[6] The Cochrane Handbook also recommends that *"...bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors".*[7]
- The company confirmed that separate searches specific to adverse events (AEs) were not conducted. Instead *"adverse events were considered relevant outcomes for study selection in the PICOS criteria, and the database searches did not restrict to clinical efficacy outcomes".*[3] Best practice suggests that it is unlikely that efficacy searches that include study design filters for RCTs will be sensitive enough to identify all safety data. Ideally, searches for AEs should be carried out alongside the efficacy searches.[8]
- The database searches for the clinical effectiveness SLR contained a limit for English language items only. Language limits should be used with caution as they risk missing potentially relevant records, however given the large numbers of records retrieved by the searches, the EAG considers this pragmatic approach acceptable. However, a more cautious approach may have been to exclude non-English papers at screening rather than at the searching stage. If translation was not possible at that point, the exclusion of the references could have been clearly documented in the PRISMA flowchart in a more transparent manner.

Small Intestine Cancer SLR

- The EAG noted that the structure for the small intestine cancer SLR, was much more complex than the approach taken by the other SLRs. The strategies also contained a number of issues, including missing synonyms for combined chemotherapy regimen (see Capeox, missing terms include XELOX, CAPOX, CAPE-OX or OxCap) and non-consequential redundant lines. The strategies for Embase, MEDLINE and CENTRAL also contained errors regarding line combinations in the interventions facet (see line #34 in the Embase strategy).[9] Of more concern, the strategies did not include terms for pembrolizumab. Given that a search combining a facet for small intestinal cancer and study design, similar to the searches for the other tumour sites, would have resulted in the smallest overall results set (n=902 without the interventions facet in the Embase search), the EAG asked to rerun these searches in line with the approach taken by the other SLRs: i.e., small intestine cancer + adapted Scottish Intercollegiate Guidelines Network (SIGN) RCT filter (Limits: 2000-date/English only) and screen the results to ensure that no relevant papers were missed by the original search. The company responded that *"due to the limited time available, it was not feasible to remove intervention terms entirely for this search. To capture all potentially relevant studies based on the comparators of interest, we have revised the search strategies with the following changes:*
    - *Added pembrolizumab*
    - *Updated CAPOX (added all synonyms)*
    - *Removed redundant oxaliplatin lines*

- *Added nab-paclitaxel*
- *Updated leucovorin synonyms (added folinic acid)".*[3]

- Whilst the EAG would have preferred to see the searches in the requested format, which would have been more transparent due to the complex nature of the line combinations in the interventions facet, all of the major errors appear to have been corrected in the updated searches and the EAG agrees that the searches are now fit for purpose. For further discussion regarding the additional single-arm trial on pembrolizumab in patients with previously treated advanced small bowel adenocarcinoma located by these searches please see Section 3.1.5.2.
- The EAG noted a disparity in the number of hits reported for the conference searches between the PRISMA flowchart (n=0) and the strategies listed in Section D1.2.2. (ASCO = 19, ESMO = 6), the company confirmed that the numbers reported in D1.2.2. were correct and provided an updated PRISMA flowchart.

Biliary Cancer SLR

- The EAG noted a disparity for the number of search results reported for the conference searching between the strategies listed in Section D1.4.1 (n=225) and the numbers listed in the PRISMA flowchart (n=370). The company confirmed that the numbers reported in the PRISMA flowchart were correct and provided both the strategies of two update searches and details of an additional 47 abstracts identified by additional searches that were not yet indexed in the Northern Light database at the time of searching.

Colorectal Cancer SLR

- The company confirmed that a reporting error had occurred in the PRISMA flowchart for the number of search results reported for the conference searching and provided an updated PRISMA flow diagram depicting the 1,506 conference abstract records recorded in the searches in Section D1.5.2.

3.1.2 Inclusion criteria

3.1.2.1 Endometrial cancer

An SLR was originally conducted to identify RCTs, single-arm and non-randomised trials evaluating the efficacy of interventions used for the treatment of advanced endometrial carcinoma patients with disease progression after prior therapy. This 'global SLR' had a broad scope, where any intervention recommended in treatment guidelines (e.g., National Comprehensive Cancer Network, (NCCN), European Society for Medical Oncology (ESMO)), in addition to those based on consultation with clinical experts in the UK, was of interest. However, only interventions specifically reflecting the current clinical practice in the UK were identified and selected at full-text screening stage (*'UK-specific SLR'*). The UK-specific eligibility criteria used in the search strategy for studies are presented in Table 3.2.

Table 3.2: Eligibility criteria used in search strategy for evidence in the endometrial cancer subgroup

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients with advanced (metastatic and/or unresectable) endometrial carcinoma by histology Patients previously treated for advanced disease Female adults (≥18 years)	Performance status of 2 or higher (or equivalent) Stage I or II disease CNS metastasis Previously treated with anti-PD-1*/PD-L1 agents

Criteria	Inclusion criteria	Exclusion criteria
	ECOG performance status of 0-1 (or equivalent) Recurrent disease when stage not specified	
Interventions	Paclitaxel monotherapy Doxorubicin monotherapy Carboplatin monotherapy Carboplatin and paclitaxel Pembrolizumab	Radiation without chemotherapy Surgical intervention without systemic treatment Other non-pharmacologic treatments (e.g., hyperthermia)
Comparators	Unrestricted	–
Outcomes	At least one of the following outcomes: OS Progression-free survival (PFS) Time to progression (TTP) Duration of response (DOR) Objective response rate (ORR), disease control rate (DCR), and number of patients with complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) when available Any-cause and treatment-related adverse events (AEs) Any-cause and treatment-related grade 3-5 AEs Any-cause and treatment-related serious AEs (SAEs) Discontinuation due to AEs (DAEs) Patient-reported outcomes (e.g., EQ-5D, EORTC QLQ-C30)	–
Study design	Randomised controlled trials (RCTs) Non-randomised trials Single-arm trials	Case reports Case series Observational studies
Time	From 2000 onward	
Language	English language	

Based on Table 6 of CS appendices[9]
* Anti-PD-1 are drugs that suppress the programmed cell death 1 protein, thereby upregulating the immune response
AE = adverse event; CNS = central nervous system; CR = complete response; CS = company submission; DAE = discontinuation due to adverse event; DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer - Quality of Life questionnaire C30; EQ-5D = EuroQol 5D quality of life instrument; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = Programmed death-ligand 1; PFS = progression-free survival; PR = partial response; SAE = serious adverse event; SD = stable disease; TTP = time to progression

EAG comment: It is important to note that the protocol above represents a revised protocol, only containing interventions deemed by the company to represent current UK practice, which is different to the inclusive original protocol. This post-hoc protocol change is a risk of bias.

3.1.2.2 Small intestine cancer

An SLR was conducted to identify RCTs, single-arm and non-randomised trials evaluating the efficacy of interventions used for the treatment of advanced small intestine cancer who progressed on prior

therapy. This 'global SLR' had a broader scope, where any intervention recommended in treatment guidelines (e.g., NCCN, ESMO), in addition to those based on consultation with clinical experts in the UK, was of interest.

Table 3.3: Eligibility criteria used in search strategy for evidence in the small intestine cancer subgroup

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients with advanced (unresectable and/or metastatic) small intestine or small bowel adenocarcinoma Patients who were previously treated for advanced disease Adults (≥18 years) ECOG performance status 0 or 1 Recurrent disease when stage not specified Irrespective of MSI-H or dMMR status	ECOG performance status 2 or higher (or equivalent) Stage I or II disease Central nervous system metastasis Previously treated with anti-PD-1*/ PD-L1 agents
Interventions	FOLFOX ± bevacizumab CAPOX ± bevacizumab FOLFOXIRI ± bevacizumab 5-FU + leucovorin ± bevacizumab Capecitabine ± bevacizumab Paclitaxel (including nab-paclitaxel) Docetaxel	Radiation without chemotherapy Surgical intervention without systemic treatment Other non-pharmacologic treatments (e.g., hyperthermia)
Comparators	Unrestricted	–
Outcomes	At least one of the following outcomes: OS; PFS; TTP; DOR; ORR and number of patients with CR, PR, SD, or PD when available; drug-related AEs; grade 3-5 AEs (all, drug related); DAEs; SAEs; PROs (e.g., EQ-5D, EORTC QLQ-C30)	–
Study design	Randomised controlled trials Controlled clinical trials Non-randomised clinical trials, including single-arm interventional studies	Case reports Case series
Time	From 2000 onward	–
Language	English language	–

Based on Table 15 of CS appendices[9]

* Anti-PD-1 are drugs that suppress the programmed cell death 1 protein, thereby upregulating the immune response

5-FU = fluorouracil; AE = adverse event; CAPOX = oxaliplatin plus capecitabine; CR = complete response; CS = company submission; DAE = discontinuation due to adverse event; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer - Quality of Life questionnaire C30; EQ-5D = EuroQol 5D quality of life instrument; FOLFOX = folinic acid, fluorouracil, oxaliplatin; FOLFOXIRI = folinic acid, fluorouracil, irinotecan, oxaliplatin; MSI-H = microsatellite instability-high; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = Programmed death-ligand 1; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; SAE = serious adverse event; SD = stable disease; TTP = time to progression

EAG comment:

- Pembrolizumab is not included as an intervention or comparator. The company was asked to explain how an SLR that does not include pembrolizumab will be of relevance to this submission. The

company stated that, *"the search strategy included search terms specific for interventions that were deemed representative of the standard therapies at the time of the regulatory evaluation and therefore search terms for pembrolizumab were not included. The search strategy has been revised to include pembrolizumab as search term and resulted in the identification of three additional studies. Please see response to A5 and A6 for details of the studies identified."*

- In the response to A5 the company stated that *"the new search identified an additional single-arm trial on pembrolizumab in patients with previously treated advanced small bowel adenocarcinoma (Pedersen, 2021).*[10] *Of the 40 patients treated with pembrolizumab in the trial, only four had MSI-H tumour. Patients in this study (regardless of MSI-H status) were older than in KEYNOTE-158 (median age 63 years [29–85] vs 58 [21 to 77]), and a greater number of patients had two prior lines of therapy (67.5% vs 22.2%), but they were similar for proportion of males and race. The study shows better PFS results for MSI-H patients compared to KEYNOTE-158 for the same tumour site whereas median OS was not reached in neither study. However, the results are likely be impacted by the small sample size, (only two PFS and OS events occurred), and should be interpreted with caution."*
- The EAG agrees that the very small number of patients with MSI-H status in Pedersen 2021 may diminish the value of its contribution to the clinical effectiveness evidence [10] The data provided by the company in Table 3.4 are not informative, and perusal of the primary source does not provide more information, other than that the number of progression and death events in this subgroup were 2/4 and 2/4 respectively. The results of Pedersen 2021[10] will therefore not be added to the clinical evidence section in this report.
- In the response to A6, the company state that the other 2 articles of relevance were Maio 2022[11] and Marabelle 2020[12], which provided data already available from KEYNOTE-158.
- Therefore, the new search conducted by the company does not appear to have picked up any significant new papers that should be added to the clinical efficacy evidence.

Table 3.4: PFS and OS results for KEYNOTE-158 and Pedersen 2021

	KEYNOTE-158 (small intestine cancer), n=27	**Pedersen 2021, n=4**
Median PFS (95% CI), months	23.4 (4.3, NR)	NE (2.5, NE)
Median OS (95% CI), months	Not reached (16.2, NR)	NE (2.5, NE)
Based on Table 1 in company response to clarification questions[3] CI = confidence interval NE = non-estimable; NR = not reached; OS = overall survival; PFS = progression-free survival		

3.1.2.3 Gastric cancer

An SLR was conducted to identify RCTs evaluating the efficacy of interventions used for the treatment of advanced gastric cancer patients who progressed on prior therapy. This represents a post-hoc change to the original SLR protocol, where non-randomised and single-arm studies were originally also included. This protocol change was for pragmatic reasons, relating to the large number of studies yielded by the search. This 'global SLR' had a broad scope, where any intervention recommended in treatment guidelines (e.g., NCCN, ESMO), in addition to those based on consultation with clinical experts in the UK, was of interest. However, only interventions specifically reflecting the current clinical practice in the UK were identified and selected at full-text screening stage ('UK-specific SLR').

Table 3.5: Eligibility criteria used in search strategy for evidence in the gastric cancer subgroup

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients with advanced (unresectable and/or metastatic) gastric cancer by histology Patients previously treated for advanced disease Adults (≥18 years) ECOG performance status of 0-1 (or equivalent) Recurrent disease when stage not specified	Performance status of 2 or higher (or equivalent) Stage I or II disease Central nervous system metastasis Previously treated with anti-PD-1*/ PD-L1 agents
Interventions	Pembrolizumab 5-FU 5-FU plus methotrexate/leucovorin FOLFIRI/mFOLFIRI Irinotecan Irinotecan + cisplatin Paclitaxel Docetaxel Docetaxel + cisplatin Docetaxel + oxaliplatin	Other systemic therapies Radiation without chemotherapy Surgical intervention without systemic treatment Non-pharmacologic treatments (e.g., hyperthermia)
Comparators	Unrestricted	--
Outcomes	At least one of the following outcomes: OS, PFS, time to disease progression, objective response, CR, PR, SD, PD	--
Study design	Randomised controlled trials	Non-randomised controlled trials Single-arm trials Observational studies Case reports Case series
Time	From 2000 onward	
Language	English language	

Based on Table 26 of CS appendices[9]
* Anti-PD-1 are drugs that suppress the programmed cell death 1 protein, thereby upregulating the immune response
5-FU = fluorouracil; CR = complete response; CS = company submission; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = folinic acid, fluorouracil, irinotecan; mFOLFIRI = modified folinic acid, fluorouracil, irinotecan; OS = overall survival; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response; SD = stable disease

EAG comment:

- The outcomes of quality of life and AEs are not included, although these outcomes are in the NICE scope and decision problem. The lack of these outcomes in the SLR means that otherwise relevant studies restricted to these outcomes would not be included. The company have been asked to add these outcomes to the review and include any additional relevant studies if required. The company

responded by stating that the table in the CS had been incorrect and that HRQoL and AEs had actually been included for this SLR. The EAG is satisfied with this response.

- Only RCTs are included, which was a pragmatic decision secondary to the large numbers of trials identified. This represents a post-hoc change to the protocol, as the original SLR was reported to include non-randomised and single-arm trials as well. This therefore creates a risk of bias.
- The restriction to RCTs is also at odds with the main clinical evidence submission, where non-randomised and single-arm trials are included. Given this, the company has been asked how it can be sure that all relevant non-randomised and single-arm trials related to gastric cancer are included in the main clinical evidence submission. The company responded by stating that *"while the use and selection of single-arm trials is justified in the context of rare malignancies such as some of the MSI-H cancers, a large amount of evidence was expected to be found in the unselected population with previously treated gastric cancer. Therefore, a pragmatic choice was made to limit the selection to RCTs which would have provided the most robust form of evidence that could be used as the source for comparator efficacy"*. The EAG notes that no RCTs for pembrolizumab versus the comparators were found, forcing the company to look at separate comparator data. Therefore, if potentially useful non-randomised evidence directly comparing pembrolizumab to the comparators were missed by the RCT-only approach, this would constitute a limitation.
- It is important to note that the protocol above represents a revised protocol, only containing interventions deemed by the company to represent current UK practice, which is different to the inclusive original protocol. This post-hoc protocol change is a risk of bias.

3.1.2.4 Biliary cancer

An SLR ('global SLR') was performed to identify RCTs, single-arm and non-randomised trials evaluating the efficacy of interventions recommended in treatment guidelines (e.g., NCCN, ESMO), in addition to those based on consultation with clinical experts in the UK, for the treatment of patients with advanced biliary cancer who have progressed on prior therapy. However, only interventions reflecting the current clinical practice in the UK have been identified and selected at full-text screening stage ('UK-specific SLR').

Table 3.6: Eligibility criteria used in search strategy for evidence in the biliary cancer subgroup

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients with advanced (unresectable and /or metastatic) biliary adenocarcinoma (gall bladder of biliary tree – intrahepatic or extrahepatic cholangiocarcinoma) Previously treated for advanced disease Adults (≥18 years) ECOG performance status of 0-1 (or equivalent) Recurrent disease when stage not specified	Performance status of 2 or higher (or equivalent) Stage I or II disease CNS metastasis Previously treated with anti-PD-1*/PD-L1 agents Ampulla of Vater cancers
Interventions	Pembrolizumab 5-FU plus leucovorin mFOLFIRI* (irinotecan plus 5-FU plus leucovorin) mFOLFOX* (oxaliplatin plus 5-FU plus leucovorin) XELOX/CAPOX (oxaliplatin plus capecitabine) Oxaliplatin plus natrium folinate plus 5-FU	Radiation without chemotherapy Surgical intervention without systemic treatment Other non-pharmacologic treatments (e.g., hyperthermia)
Comparators	Unrestricted	–
Outcomes	At least one of the following outcomes: OS	

Criteria	Inclusion criteria	Exclusion criteria
	PFS Time to progression DOR ORR, disease control rate, and number of patients with CR, PR, SD, or PD when available Any-cause and treatment-related AEs Any-cause and treatment-related Grade 3-5 AEs Any-cause and treatment-related SAEs Discontinuation due to AEs Patient-reported outcomes (e.g., EQ-5D, EORTC QLQ-C30)	–
Study design	RCTs Non-randomised trials Single-arm trials	Case reports Case series Observational (prospective, retrospective) studies
Time	From 2000 onward	–
Language	English language	–

Based on Table 35 of CS appendices[9]
* Anti-PD-1 are drugs that suppress the programmed cell death 1 protein, thereby upregulating the immune response
5-FU = fluorouracil; AE = adverse event; CAPOX = oxaliplatin plus capecitabine; CNS = central nervous system; CR = complete response; CS = company submission; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer - Quality of Life questionnaire C30; EQ-5D = EuroQol 5D quality of life instrument; mFOLFIRI = modified folinic acid, fluorouracil, irinotecan; mFOLFOX = modified folinic acid, fluorouracil, oxaliplatin; ORR = objective response rate; OS= overall survival; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response; RCT =randomised controlled trial; SAEs = serious adverse events; SD = stable disease;

EAG comment: It is important to note that the protocol above represents a revised protocol, only containing interventions deemed by the company to represent current UK practice, which is different to the inclusive original protocol. This post-hoc protocol change is a risk of bias.

3.1.2.5 Colo-rectal cancer

An SLR was performed to identify RCTs, in addition to non-RCT for pembrolizumab, evaluating the efficacy of interventions used globally ('global SLR') for the treatment of patients with advanced CRC who have progressed on at least one prior line of therapy. However, only interventions reflecting the current clinical practice in the UK have been identified and selected at full-text screening stage ('UK-specific SLR').

Table 3.7: Eligibility criteria used in search strategy for evidence in the CRC subgroup

Category	Inclusion Criteria	Exclusion Criteria
Population	Patients with histologically proven locally advanced unresectable or metastatic (unresectable stage III or stage IV) CRC: Previously treated for advanced disease Adult (≥18 years) ECOG 0 or 1 Recurrent disease when stage not specified Irrespective of MSI-H or dMMR status	ECOG 2 or higher Populations with stage I or II disease Studies in patient with CNS metastasis Studies in patients previously treated with anti-PD-1* /PD-L1
Interventions	Globally used treatments: Second-line or beyond setting:	Radiation without chemotherapy

Category	Inclusion Criteria	Exclusion Criteria
	Fluorouracil plus leucovorin plus oxaliplatin (FOLFOX) in combination with bevacizumab, aflibercept, ramucirumab, cetuximab, or panitumumab Fluorouracil plus leucovorin plus irinotecan (FOLFIRI) in combination with bevacizumab, aflibercept, ramucirumab, cetuximab, or panitumumab Capecitabine plus oxaliplatin (CAPOX) in combination with bevacizumab Third-line or beyond setting: Regorafenib TAS-102 (trifluridine/tipiracil) Treatments relevant to clinical practice in the UK:* Second-line or beyond setting: Pembrolizumab Nivolumab plus ipilimumab FOLFOX/FOLFOX4/mFOLFOX6 FOLFIRI TAS-102 (trifluridine/tipiracil) Third-line or beyond setting: Regorafenib	Surgical intervention without systemic treatment Other non-pharmacologic treatments (e.g., hyperthermia) Treatments targeting liver metastases
Comparators	Unrestricted	–
Outcomes	At least one of the following outcomes: OS PFS TTP DOR ORR and number of patients with CR, PR, SD, and PD, when available. Drug-related AEs Grade 3-5 AEs (all, drug-related) Discontinuation due to AE SAEs Patient-reported outcomes (e.g., EQ-5D, EORTC QLQ-C30)	–
Study design	For non-pembrolizumab studies RCTs For studies on pembrolizumab: RCTs Non-randomised trials Single-arm trials	For non-pembrolizumab studies Non-RCTs, including single-arm trials Case series Case reports Observational (prospective, retrospective) studies For studies on pembrolizumab: Case series

Category	Inclusion Criteria	Exclusion Criteria
		Case reports Observational (prospective, retrospective) studies
Time	From 2000 onwards	–
Language	English language	–

Based on Table 15 of CS appendices[9]

* Anti-PD-1 are drugs that suppress the programmed cell death 1 protein, thereby upregulating the immune response

AE = adverse event; CNS = central nervous system; CR = complete response; CRC = colorectal cancer; CS = company submission; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer - Quality of Life questionnaire C30; EQ-5D = EuroQol 5D quality of life instrument; FOLFIRI = folinic acid, fluorouracil, irinotecan; FOLFOX = folinic acid, fluorouracil, oxaliplatin; mFOLFOX = modified folinic acid, fluorouracil, oxaliplatin; MSI-H = microsatellite instability-high; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response; RCT =randomised controlled trial; SAEs = serious adverse events; SD =stable disease; TAS-102 = tipiracil hydrochloride; TTP = time to progression; UK = United Kingdom

EAG comment:

- Nivolumab with ipilimumab is included as a comparator, whereas it is not included in the main clinical evidence submission. The EAG has been asked why it is appropriate to include it in the SLR but not in the main clinical evidence submission. The company responded by stating that, *"the inclusion of nivolumab with ipilimumab in the SLR eligibility criteria for the interventions/comparators was based on MSD original understanding of the treatments that pembrolizumab would displace if it was recommended. Further insights into the treatment pathway for colorectal cancer in the metastatic setting and patient eligibility to licensed treatments, allowed MSD to revise the list of relevant comparators of pembrolizumab in this appraisal, which is presented in the decision problem (Table 1 of document B of company submission), and excludes nivolumab with ipilimumab for the reasons described in the response to A18."* The EAG accepts this response as an explanation of the apparent contradiction. However, as explained in Section 2.3, please note that the EAG does not agree that nivolumab with ipilimumab should necessarily be excluded as a comparator.
- It is important to note that the protocol above represents a revised protocol, only containing interventions deemed by the company to represent current UK practice, which is different to the inclusive original protocol. This post-hoc protocol change is a risk of bias.

3.1.3 Critique of data extraction

The following applies to all the SLRs conducted across the different cancer types.

Two reviewers, working independently, reviewed all titles and abstracts and proceedings identified by the search according to the selection criteria, apart from outcome criteria, which were only applied during the screening of full-text publications. All studies identified as eligible studies during title and abstract screening were then screened at a full-text stage by the same two reviewers. The full-text studies identified at this stage were included for data extraction. Following reconciliation between the two investigators, a third reviewer was included to reach a consensus on any remaining discrepancies.

Two reviewers, working independently, extracted data from the final list of included studies. All data of interest (study, treatment and patient characteristics, and outcomes) were extracted from primary

publications, whereas only additional data reported for relevant outcomes of interest or subgroups of interest were extracted from subsequent publications. Any discrepancies between reviewers were resolved through discussion, involving a third reviewer if necessary. Data were stored and managed in a Microsoft Excel workbook.

EAG comment: No comment.

3.1.4 Quality assessment

The following applies to all the SLRs conducted across the different cancer types.

Two independent reviewers assessed study quality. Following reconciliation between the two investigators, a third investigator was included to reach a consensus for any remaining discrepancies. The Cochrane risk of bias tool version 2 was used to assess the risk of bias in RCTs.[13] This instrument is used to evaluate five key domains: 1) bias arising from the randomisation process, 2) bias due to deviations from intended interventions, 3) bias due to missing outcome data, 4) bias in the measurement of the outcome, and 5) bias in the selection of the reported result. The domains were assessed independently and in aggregate for an overall risk of bias judgment based on the following scale: low risk of bias, some concerns, or high risk of bias.

The Newcastle-Ottawa scale was used to assess the quality of single-arm and non-randomised studies.[14] This instrument was used to evaluate the quality of these studies based on 1) study group and selection, 2) comparability of the groups within studies (not applicable for single-arm studies), and 3) the ascertainment of either the exposure or outcomes of interest for case-control or cohort studies. Ranking of the study quality was done by using a 'star system' in which a study can be given a maximum of one star for each numbered item within the "Selection" and "Exposure" categories and a maximum of two stars for "Comparability" category.

EAG comment: No comment.

3.1.5 Evidence synthesis

3.1.5.1 Endometrial cancer

A total of 6,137 citations were identified from database searches of MEDLINE, Embase, and CENTRAL. After removing 1,145 duplicate citations, a total of 4,992 citations were screened. This led to the exclusion of 4,789 citations and resulted in the identification of 203 citations eligible for full-text screening. Of these, 141 were excluded, one for duplicate publication, 31 for study design, 77 for population, eight for intervention, 20 for outcome, four for other reasons (e.g., protocols, abstracts not identified from conference search, and full-text unavailable for review). This resulted in the inclusion of 62 citations from the main database searches. Searches of conference proceedings and the United States (US) trial registry, as well as handsearch of the bibliography of previously published SLRs resulted in the identification of 238 additional citations for screening, of which 29 were included. Overall, a total of 91 citations representing 61 unique trials met the eligibility criteria of the global SLR.

Of the 61 trials identified in the global SLR, 45 were excluded from the UK-specific SLR because they had evaluated interventions deemed 'not of interest' by the company. The remaining 16 trials (represented in 33 citations) consisted of three single-arm trials and 13 RCTs.

Of these 16 trials, four trials (three single-arm trials and one RCT) evaluating pembrolizumab were identified. Of these, KEYNOTE-146 and KEYNOTE-775 investigated the efficacy and safety of pembrolizumab in combination with lenvatinib and therefore are not in line with the intervention of interest in this appraisal (pembrolizumab monotherapy). Roque 2021 was reported to be a Phase 2

single-arm trial evaluating pembrolizumab in patients with recurrent MSI-H endometrial cancer analysed by whole exome sequencing (WES). Results from this trial are discussed in Document B, Section B.3.14.1.3 on the validation of the cost effectiveness analysis, but are not in the clinical effectiveness section. KEYNOTE-158 was the only study investigating the efficacy of pembrolizumab in the approved indication deemed relevant to this appraisal by the company.

Table 3.8: List of publications included in the UK-specific SLR

Trial ID	Registry number	Principal publication	Principal publication title	Associated publications
Angioli 2007	--	Angioli 2007	Liposome-encapsulated doxorubicin citrate in previously treated recurrent/metastatic gynecological malignancies	--
Hirai 2004	--	Hirai 2004	Phase II trial of 3-h infusion of paclitaxel in patients with adenocarcinoma of endometrium: Japanese Multicenter Study Group	--
Homesley 2008	--	Homesley 2008	A phase ii trial of weekly 1-hour paclitaxel as second-line therapy for endometrial and cervical cancer	--
KEYNOTE-146/Study 111	NCT02501096	Makker 2020	Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer	Makker 2019a; Makker 2019b; Makker 2020
KEYNOTE-158	NCT02628067	O'Malley 2019	Pembrolizumab in patients with msi-h advanced endometrial cancer from the keynote-158 study	Maio 2022, O'Malley 2022, O'Malley 2022
KEYNOTE-775	NCT03517449	Lorusso 2021	Health-related quality of life (HRQoL) in advanced endometrial cancer (aEC) patients (pts) treated with lenvatinib plus pembrolizumab or treatment of physician's choice (TPC).	Colombo 2021, Colombo 2021, Makker 2022, Makker 2022, Makker 2021, Makker 2022, Yonemori 2022
Lincoln 2003	--	Lincoln 2003	Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: A gynecologic oncology group study	--
McMeekin 2015	NCT00883116	McMeekin 2015	Phase iii randomized trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer	CT.gov 2015
Muggia 2002	--	Muggia 2002	Phase ii trial of the pegylated liposomal doxorubicin in	--

Trial ID	Registry number	Principal publication	Principal publication title	Associated publications
			previously treated metastatic endometrial cancer: A gynecologic oncology group study	
Nishio 2003	--	Nishio 2003	Weekly 1-h paclitaxel infusion in patients with recurrent endometrial cancer: A preliminary study	--
Roque 2021	NCT02899793	Roque 2021	A phase II evaluation of pembrolizumab in recurrent microsatellite instability-high (MSI-H) endometrial cancer patients with Lynch-like versus MLH-1 methylated characteristics (NCT02899793)	Bellone 2021, Bellone 2022
Scambia 2020	NCT02725268	Scambia 2020	Randomized phase ii study of sapanisertib (sap) + paclitaxel (pac) versus pac alone in patients (pts) with advanced, recurrent, or persistent endometrial cancer	CT.gov 2020a
Vandenput 2009	--	Vandenput 2009	Leuven Dose-Dense Paclitaxel/Carboplatin Regimen in Patients With Primary Advanced or Recurrent Endometrial Carcinoma	--
Vandenput 2012	--	Vandenput 2012	Weekly paclitaxel-carboplatin regimen in patients with primary advanced or recurrent endometrial carcinoma	--
Van Wijk 2003	--	Van Wijk 2003	Phase ii study of carboplatin in patients with advanced or recurrent endometrial carcinoma. A trial of the eortc gynaecological cancer group	--
Vergote 2015	--	Vergote 2015	Phase II study of weekly paclitaxel/carboplatin in combination with prophylactic G-CSF in the treatment of gynecologic cancers: A study in 108 patients by the Belgian Gynaecological Oncology Group	--

Based on Table 7 of the CS appendices[9]
aEC = advanced endometrial cancer; EORTC = European Organisation for the Research and Treatment of Cancer; G-CSF = Granulocyte colony-stimulating factor; HRQoL = health-related quality of life; MSI-H = microsatellite instability-high; SLR = systematic literature review; TPC = treatment of physician's choice; UK =United Kingdom

EAG comment:

- The CS claims that *"...except for paclitaxel in gastric cancer and paclitaxel/doxorubicin in endometrial, there were no published data available specifically in MSI-H/dMMR-specific populations"*. However, the EAG were able to find a trial of nivolumab with ipilimumab in this population. The company were asked to comment on the appropriateness of this trial to the decision

problem. The company were also asked to clarify if all studies were examined for subgroup data in the decision problem population. Finally, if some relevant clinical effectiveness data have been omitted from the CS, then the company were used to use this in the ITC comparisons. The company responded by stating that *"the study identified by the EAG was not used to perform an indirect treatment comparison as it evaluated an intervention MSD does not consider a relevant comparator in this appraisal for the reasons provided in the response to A18"*. The EAG does not agree with the arguments provided by the company in the clarification letter response[3] that nivolumab and ipilimumab is not an appropriate comparator, and therefore does not agree that the study in question should be included. This has been deemed a key issue.

- The specific reasons for the exclusion of 45 trials from the UK-specific SLR are not provided in Table 8 of the appendices. A general reason (*"interventions not of interest"*) is given in the text on page 14 of the appendices, but more detailed reasons for the exclusion of each study would be helpful to allow us to assess the validity of the exclusions. In the clarification questions, the company were asked if the company could provide specific reasons why each of the 45 trials is 'not of interest'. The company responded that *"the 45 citations excluded from the endometrial cancer UK-specific SLR …. were excluded because the interventions evaluated were not relevant to the UK clinical practice. As explained in the Appendix of the company submission, these 'global SLRs' had a broader scope and interventions specifically reflecting the current clinical practice in the UK were identified and selected at full-text screening stage ('UK-specific SLR'). This resulted in a number of studies being considered relevant to the 'global SLR' but excluded from the UK-specific SLR as eligibility criteria for the interventions were not met. Tables…. below provide details of the interventions evaluated in the excluded studies which were considered not relevant to current clinical practice in the UK"*. The tables provided listed the interventions deemed unsuitable for UK practice, and the EAG noted that none were the comparators used in the indirect treatment comparison (ITC). Given the company's definition of relevant comparators, these exclusions appear appropriate. However, given that the NICE scope allowed any established comparator, some of these exclusions may not be justified.

3.1.5.2 Small intestine cancer

Searching MEDLINE, Embase, and CENTRAL, 215 citations were identified. In the title and abstract screening phase, 39 duplicates were removed, 169 citations were excluded, and seven citations were moved forward into the full-text screening phase. In the full-text screening phase, four citations were excluded due to population, one due to intervention, and one due to study design. The only remaining study was single-arm trial (Overman 2018) that evaluated nab-paclitaxel that is not considered a relevant comparator.

EAG comment: There were no trials identified using pembrolizumab. This was due to pembrolizumab not being included as an intervention or comparator in the protocol. It is therefore unknown if relevant pembrolizumab trials relating to small intestine cancer exist in addition to KEYNOTE-158. This very serious issue has also been raised as an EAG comment in Section 3.1.2.2.

3.1.5.3 Gastric cancer

A total of 17,535 abstracts were identified across Embase, MEDLINE, and CENTRAL. After removing 4,375 duplicate records, 13,160 records were screened, resulting in the exclusion of 12,191 abstracts. The remaining 969 records were progressed to full-text screening, where 762 full-text publications were excluded for the following reasons: 73 due to study design, 625 due to population, 10 due to outcome, 49 due to intervention, and five due to other reasons (e.g., language, study protocol). A total of 207 full-text publications were included at this stage. An additional 825 citations were identified through

conference search (n=812), search of the US clinical trial registry (n=12), and handsearch of the grey literature (n=1); of these, 61 were included the evidence base. Overall, a total of 268 publications (representing 206 unique clinical trials) were of interest for the global SLR.

Of the 206 trials included in the global evidence base, 165 were excluded from the UK-specific SLR because they were not RCTs (n=142) or had evaluated interventions not of interest (n=23). The remaining 65 citations (representing 41 unique RCTs) were included in the evidence base.

Following clinical expert consultation, the final list of comparators reflecting current clinical practice in the UK were narrowed down by the company to paclitaxel and FOLFIRI (folinic acid, fluorouracil, irinotecan). Based on this, of the 41 trials that met the eligibility criteria for inclusion in the SLR, only 24 corresponding to 45 publications are considered relevant to this appraisal. A complete list of publications included after full-text review is available in Table 3.9. The studies not considered relevant for this appraisal by the company are shaded in the table.

Table 3.9: List of publications included in the UK SLR

Trial	Primary/ secondary	Author, year	Title
KEYNOTE-061	Primary	Shitara 2018	Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (keynote-061): A randomised, open-label, controlled, phase 3 trial
	Secondary	Shitara 2021	Molecular determinants of clinical outcomes with pembrolizumab versus paclitaxel in a randomized, open-label, phase 3 trial in patients with gastroesophageal adenocarcinoma
	Secondary	Fuchs 2020	Pembrolizumab versus paclitaxel for previously treated patients with pd-l1-positive advanced gastric or gastroesophageal junction cancer (gc): Update from the phase iii keynote-061 trial
	Secondary	Chao 2021	Assessment of pembrolizumab therapy for the treatment of microsatellite instability-high gastric or gastroesophageal junction cancer among patients in the keynote-059, keynote-061, and keynote-062 clinical trials
	Secondary	Van Cutsem 2021	Health-related quality of life in advanced gastric/gastroesophageal junction cancer with second-line pembrolizumab in KEYNOTE-061
	Secondary	Cutsem 2019	Impact of pembrolizumab (pembro) versus paclitaxel on health-related quality of life (hrqol) in patients with advanced gastric or gastroesophageal junction (gej) cancer that has progressed after first-line chemotherapy (keynote-061)
	Secondary	Fuchs 2022	Pembrolizumab versus paclitaxel for previously treated PD-L1-positive advanced gastric or gastroesophageal junction cancer: 2-year update of the randomized phase 3 KEYNOTE-061 trial
Yi 2012	Primary	Yi 2012	Randomised phase ii trial of docetaxel and sunitinib in patients with metastatic gastric cancer who were previously treated with fluoropyrimidine and platinum
RAINBOW	Primary	Wilke 2014	Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (rainbow): A double-blind, randomised phase 3 trial
	Secondary	Al-Batran 2016	Quality-of-life and performance status results from the phase iii rainbow study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated gastric or gastroesophageal junction adenocarcinoma
	Secondary	Cascinu 2021	Tumor response and symptom palliation from rainbow, a phase iii trial of ramucirumab plus paclitaxel in previously treated advanced gastric cancer
	Secondary	De Vita 2019	Ramucirumab and paclitaxel in patients with gastric cancer and prior trastuzumab: Subgroup analysis from rainbow study
	Secondary	Kim 2018	Exposure-response relationship of ramucirumab in east asian patients from rainbow: A randomized clinical trial in second-line treatment of gastric cancer

Trial	Primary/ secondary	Author, year	Title
	Secondary	Muro 2016	Subgroup analysis of east asians in rainbow: A phase 3 trial of ramucirumab plus paclitaxel for advanced gastric cancer
	Secondary	Shitara 2016	Subgroup analyses of the safety and efficacy of ramucirumab in japanese and western patients in rainbow: A randomized clinical trial in second-line treatment of gastric cancer
	Secondary	Van Cutsem 2020	Biomarker analyses of second-line ramucirumab in patients with advanced gastric cancer from rainbow, a global, randomized, double-blind, phase 3 study
	Secondary	Yamaguchi 2021	Quality of life associated with ramucirumab treatment in patients with advanced gastric cancer in japan: Exploratory analysis from the phase iii rainbow trial
	Secondary	Muro 2019	Is ramucirumab and paclitaxel therapy beneficial for second-line treatment of metastatic gastric or junctional adenocarcinoma for patients with ascites? Analysis of rainbow phase 3 trial data
	Secondary	Muro 2018	Age does not influence efficacy of ramucirumab in advanced gastric cancer: Subgroup analyses of regard and rainbow
	Secondary	Klempner 2020	Impact of frontline doublet versus triplet therapy on clinical outcomes: Exploratory analysis from the rainbow study
SHINE	Primary	Van Cutsem 2017	A randomized, open-label study of the efficacy and safety of azd4547 monotherapy versus paclitaxel for the treatment of advanced gastric adenocarcinoma with fgfr2 polysomy or gene amplification
AIO	Primary	Thuss-Patience 2011	Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer - a randomised phase iii study of the arbeitsgemeinschaft internistische onkologie (aio)
JACCRO GC-05	Primary	Tanabe 2015	Phase ii/iii study of second-line chemotherapy comparing irinotecan-alone with s-1 plus irinotecan in advanced gastric cancer refractory to first-line treatment with s-1 (jaccro gc-05)
Sym 2013	Primary	Sym 2013	A randomized phase ii study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mfolfiri) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy
Shitara 2014	Primary	Shitara 2014	Randomised phase ii study comparing dose-escalated weekly paclitaxel vs standard-dose weekly paclitaxel for patients with previously treated advanced gastric cancer
ABSOLUTE	Primary	Shitara 2017	Nab-paclitaxel versus solvent-based paclitaxel in patients with previously treated advanced gastric cancer (absolute): An open-label, randomised, non-inferiority, phase 3 trial
	Secondary	Takashima 2019	Peritoneal metastasis as a predictive factor for nab-paclitaxel in patients with pretreated advanced gastric cancer: An exploratory analysis of the phase iii absolute trial

Trial	Primary/ secondary	Author, year	Title
Satoh 2015	Primary	Satoh 2015	Randomized phase ii trial of nimotuzumab plus irinotecan versus irinotecan alone as second-line therapy for patients with advanced gastric cancer
TyTAN	Primary	Satoh 2014	Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of her2-amplified advanced gastric cancer in asian populations: Tytan - a randomized, phase iii study
Roy 2013	Primary	Roy 2013	A randomized phase ii study of pep02 (mm-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma
JCOG0407	Primary	Nishina 2016	Randomized phase ii study of second-line chemotherapy with the best available 5-fluorouracil regimen versus weekly administration of paclitaxel in far advanced gastric cancer with severe peritoneal metastases refractory to 5-fluorouracil-containing regimens (jcog0407)
TRICS/UMIN 000002571	Primary	Nishikawa 2015	Randomised phase iii trial of second-line irinotecan plus cisplatin versus irinotecan alone in patients with advanced gastric cancer refractory to s-1 monotherapy: Trics trial
CCOG0701	Primary	Nakanishi 2016	Phase ii multi-institutional prospective randomized trial comparing s-1 plus paclitaxel with paclitaxel alone as second-line chemotherapy in s-1 pretreated gastric cancer (ccog0701)
SUN-CASE	Primary	Moehler 2016	Sunitinib added to folfiri versus folfiri in patients with chemorefractory advanced adenocarcinoma of the stomach or lower esophagus: A randomized, placebo-controlled phase ii aio trial with serum biomarker program
	Secondary	Nagel 2018	Cytokeratin-18 fragments predict treatment response and overall survival in gastric cancer in a randomized controlled trial
Maruta 2007	Primary	Maruta 2007	A clinical study of docetaxel with or without 5'dfur as a second-line chemotherapy for advanced gastric cancer
T-ACT Study	Primary	Makiyama 2020	Randomized, phase ii study of trastuzumab beyond progression in patients with her2-positive advanced gastric or gastroesophageal junction cancer: Wjog7112g (t-act study)
RADPAC	Primary	Lorenzen 2020	Phase iii randomized, double-blind study of paclitaxel with and without everolimus in patients with advanced gastric or esophagogastric junction carcinoma who have progressed after therapy with a fluoropyrimidine/platinum-containing regimen (radpac)
Lee 2017	Primary	Lee 2017	A multicenter randomized phase ii study of docetaxel vs. Docetaxel plus cisplatin vs. Docetaxel plus s-1 as second-line chemotherapy in metastatic gastric cancer patients who had progressed after cisplatin plus either s-1 or capecitabine
KCSG ST10-01	Primary	Lee 2019	A phase iii study to compare the efficacy and safety of paclitaxel versus irinotecan in patients with metastatic or recurrent gastric cancer who failed in first-line therapy (kcsg st10-01)

Trial	Primary/ secondary	Author, year	Title
Kondo 2000	Primary	Kondo 2000 [15]	A phase iii randomized study comparing doxifluridine and 5-fluorouracil as supportive chemotherapy in advanced and recurrent gastric cancer
KNUH2008047	Primary	Kim 2015	Multi-center randomized phase ii study of weekly docetaxel versus weekly docetaxel-plus-oxaliplatin as a second-line chemotherapy for patients with advanced gastric cancer
DREAM	Primary	Kang 2018	Efficacy and safety findings from dream: A phase iii study of dhp107 (oral paclitaxel) versus IV Paclitaxel in patients with advanced gastric cancer after failure of first-line chemotherapy
WJOG 4007	Primary	Hironaka 2013	Randomized, open-label, phase iii study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: Wjog 4007 trial
TCOG GI-0801/BIRIP	Primary	Higuchi 2014	Biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for advanced gastric cancer: A randomised phase iii trial (tcog gi-0801/birip trial)
Fushida 2016	Primary	Fushida 2016	Paclitaxel plus valproic acid versus paclitaxel alone as second-or third-line therapy for advanced gastric cancer: A randomized phase ii trial
COUGAR-02	Primary	Ford 2014	Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (cougar-02): An open-label, phase 3 randomised controlled trial
GOLD	Primary	Bang 2017	Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (gold): A double-blind, randomised, placebo-controlled, phase 3 trial
Bang 2015	Primary	Bang 2015	Randomized, double-blind phase ii trial with prospective classification by atm protein level to evaluate the efficacy and tolerability of olaparib plus paclitaxel in patients with recurrent or metastatic gastric cancer
RAINBOW-Asia	Primary	Xu 2021	Efficacy and safety of weekly paclitaxel with or without ramucirumab as second-line therapy for the treatment of advanced gastric or gastroesophageal junction adenocarcinoma (RAINBOW-Asia): a randomised, multicentre, double-blind, phase 3 trial
	Secondary	CT.gov 2017	A Study of Paclitaxel With or Without Ramucirumab (LY3009806) in Participants With Gastric or Gastroesophageal Cancer
NCT00991952	Primary	CT.gov 2009	Irinotecan Hydrochloride With or Without Alvocidib in Treating Patients With Advanced Stomach or Gastroesophageal Junction Cancer That Cannot Be Removed By Surgery
NCT01579578	Primary	CT.gov 2012	Assess the Efficacy of AZD8931 in Combination With Paclitaxel Versus Paclitaxel Alone in Patients With Gastric Cancer

Trial	Primary/ secondary	Author, year	Title
Xiaoying 2019	Primary	Xiaoying 2019	Comparison of efficacy and safety of second-line palliative chemotherapy with paclitaxel plus raltitrexed and paclitaxel alone in patients with metastatic gastric adenocarcinoma: A randomized phase ii trial
Wang 2021	Primary	Wang 2021	Apatinib plus paclitaxel versus placebo plus paclitaxel as second-line therapy in patients with gastric cancer with peritoneal carcinomatosis: A double-blind, randomized phase ii trial
KEYNOTE-063	Primary	Chung 2021	Pembrolizumab versus paclitaxel for previously treated advanced gastric or gastroesophageal junction cancer (KEYNOTE-063): A randomized, open-label, phase 3 trial in Asian patients
	Secondary	Cheol 2020	Pembrolizumab vs paclitaxel as second-line treatment for asian patients with pd-l1-positive advanced gastric or gastroesophageal cancer (gc) in the phase iii keynote-063 trial
BRIGHTER	Primary	Shah 2022	Randomized, Double-Blind, Placebo-Controlled Phase III Study of Paclitaxel +/- Napabucasin in Pretreated Advanced Gastric or Gastroesophageal Junction Adenocarcinoma
		NCT02178956, CT.gov 2014	A Study of BBI608 Plus Weekly Paclitaxel to Treat Gastric and Gastro-Esophageal Junction Cancer
OGSG0701	Primary	Kawase 2021	Randomized phase II study of Irinotecan-11 versus Paclitaxel versus each combination chemotherapy with S-1 for advanced gastric cancer that is refractory to S-1 or S-1 plus CDDP: OGSG0701
GATSBY	Primary	Thuss-Patience 2017	Trastuzumab emtansine versus taxane use for previously treated her2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (atsby): An international randomised, open-label, adaptive, phase 2/3 study
	Secondary	Shitara 2020	Efficacy of trastuzumab emtansine in Japanese patients with previously treated HER2-positive locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma: A subgroup analysis of the GATSBY study
	Secondary	Shah 2019	Biomarker analysis of the GATSBY study of trastuzumab emtansine versus a taxane in previously treated HER2-positive advanced gastric/gastroesophageal junction cancer
Kang 2012	Primary	Kang 2012	Salvage chemotherapy for pretreated gastric cancer: A randomized phase iii trial comparing chemotherapy plus best supportive care with best supportive care alone
Lu 2019	Primary	Lu 2019	Combination of apatinib mesylate and second-line chemotherapy for treating gastroesophageal junction adenocarcinoma

Based on Table 27 of the CS appendices[9]
CS = company submission; SLR =systematic literature review; UK = United Kingdom

EAG comment:

- The limitation of studies to those with the comparators paclitaxel and FOLFIRI is in line with the decision problem, but not in line with the NICE scope, which allowed any comparator established in UK practice for this population. As previously noted in Section 2.3, this narrowing of the scope may have led to some important evidence of clinical relevance being missed out.
- The specific *"not of interest"* reasons for the exclusion of 23 trials from the UK-specific SLR are not provided in Table 28 of the appendices. Detailed reasons for the exclusion of each study would be helpful to allow us to assess the validity of the exclusions. In the clarification questions, the company were asked if the company could provide specific reasons why each of the 23 trials is 'not of interest'. The company responded that *"the …. 23 citations excluded from the gastric cancer UK-specific SLR were excluded because the interventions evaluated were not relevant to the UK clinical practice. As explained in the Appendix of the company submission, these 'global SLRs' had a broader scope and interventions specifically reflecting the current clinical practice in the UK were identified and selected at full-text screening stage ('UK-specific SLR'). This resulted in a number of studies being considered relevant to the 'global SLR' but excluded from the UK-specific SLR as eligibility criteria for the interventions were not met. Tables….below provide details of the interventions evaluated in the excluded studies which were considered not relevant to current clinical practice in the UK"*. The tables provided listed the interventions deemed unsuitable for UK practice, and the EAG noted that none were the comparators used in the ITC. Given the company's definition of relevant comparators, these exclusions appear appropriate. However, given that the NICE scope allowed any established comparator, some of these exclusions may not be justified.
- None of the 41 'included' studies are in the clinical evidence section of the CS.[2] It is assumed that this is because none of these studies covered the population with H-MSI/dMMR, and/or they were used in the ITC. However, this is unclear. The company has been asked to explain this. The company responded by stating that *"in the gastric cancer SLR, 24 studies corresponding to 45 publications were considered relevant to this appraisal as evaluating interventions of interest in line with the decision problem. Of the 24 studies, three studies namely Chao et al. 2013 (KEYNOTE-061), Sym et al. 2013, and Moehler et al. 2016 (SUNCASE) (19) were selected and used in the ITC"*. The EAG is satisfied with this response.

3.1.5.4 Biliary cancer

A total of 5,183 citations were identified through database searches of MEDLINE, Embase, and CENTRAL. After removing 891 duplicate citations, a total of 4,292 citations were screened. This led to the exclusion of 3,924 citations and resulted in the identification of 368 citations eligible for full-text screening. Of these, 322 were excluded: four for duplicate publication, 17 for study design, 180 for population, 33 for intervention, 68 for outcome, and 20 for other reasons (e.g., protocols, abstracts not identified from conference search, and full-text unavailable for review). This resulted in the inclusion of 46 citations from the main database searches. Searches of conference proceedings and the US trial registry, as well as handsearch of the bibliography of previously published SLRs resulted in the identification of 791 additional citations for screening, of which 29 were included. Overall, a total of 75 citations representing 54 unique trials met the eligibility criteria of the global SLR.

Of the 54 trials identified in the global SLR, 46 did not evaluate the interventions relevant to the routine practice in the UK and were therefore excluded. The remaining nine trials (represented in 15 citations) were retained, which consisted of five single-arm trials and four RCTs. Two trials evaluating pembrolizumab were identified, of which KEYNOTE-028 is a Phase 1b study investigating a not approved dosage of pembrolizumab (10 mg/kg every two weeks). Therefore, the company decided that it is not in line with the intervention of interest in this appraisal. KEYNOTE-158 was the only study investigating the efficacy of pembrolizumab in the approved indication deemed by the company to be relevant to this appraisal.

Table 3.10: Trial and treatment characteristics of included studies

Trial ID	Registry number	Publications	Study design	Publication type	Treatment	N	Trial start date	Primary completion date	Region	Multicenter
Single-arm trials										
Hwang 2015	NCT01127555	Hwang 2015	Phase II, open-label	Full-text	mFOLFOX3 (oxaliplatin plus 5-fluorouracil plus leucovorin)	30	April, 2010	June, 2012	South Korea	Yes
KEYNOTE-028	NCT02054806	Piha-Paul 2020; Yung-Jue 2019	Phase Ib, open-label	Full-text	Pembrolizumab	24	February, 2014	April, 2021	International	Yes
KEYNOTE-158	NCT02628067	Piha-Paul 2020; Yung-Jue 2019; Marabelle 2020; Maio 2022	Phase II, open-label	Full-text	Pembrolizumab	104	December, 2015	June, 2026	International	Yes
Kim 2019b	NCT02350686	Kim 2019	Phase II, open-label	Full-text	XELOX (capecitabine plus oxaliplatin)	50	May, 2015	December, 2019	South Korea	Yes
Sinn 2013	NCT00356161	Sinn 2013	Phase II, open-label	Full-text	Oxaliplatin plus natrium folinate plus 5-fluorouracil	37	April, 2002	January 2010	Germany	No

Trial ID	Registry number	Publications	Study design	Publication type	Treatment	N	Trial start date	Primary completion date	Region	Multicenter
RCTs										
ABC-06	NCT01926236; EudraCT, 2013-001812-30	Lamarca 2021, Lamarca 2019, Lamarca 2022	Phase III, open-label	Full-text	Arm 1: ASC Arm 2 : ASC plus mFOLFOX (oxaliplatin plus leucovorin plus 5-fluorouracil)	162	February, 2014	January, 2018	United Kingdom	Yes
Choi 2021	NCT03464968	Choi 2021, Won 2020	Phase II, open-label	Full-text	Arm 1: mFOLFOX (oxaliplatin plus leucovorin plus 5-fluorouracil) Arm 2: mFOLFIRI (irinotecan plus leucovorin plus 5-fluorouracil)	118	July, 2015	February, 2020	Korea	Yes
NALIRICC	NCT03043547; EudraCT: 2016-003709-33	Vogel 2022	Phase II, open-label	Conference abstract	Arm 1: nal-Irinotecan plus 5- fluorouracil plus leucovorin Arm 2: 5-flurouracil plus leucovorin	100	October, 2017	December, 2021	Germany	Yes

Trial ID	Registry number	Publications	Study design	Publication type	Treatment	N	Trial start date	Primary completion date	Region	Multicenter
NIFTY	NCT03524508	Yoo 2021, Changhoon 2021, Yoo 2022	Phase IIb, open-label	Conference abstract/poster	Arm 1: Liposomal irinotecan plus 5- fluorouracil plus leucovorin	174	September, 2018	September, 2020	Korea	Yes
					Arm 2: 5-fluorouracil plus leucovorin					

Based on Table 36 on the CS appendices [9]
ASC = active symptom control; CS = company submission

3.1.5.5 Colorectal cancer

The search retrieved a total of 39,745 records. After the removal of duplicates, the abstracts of 30,856 records were screened. Of the 1,424 records that proceeded to the full-text screening phase, 49 records describing 25 unique RCTs evaluating globally used treatments for patients with advanced CRC who had disease progression after at least one prior line of therapy were identified. Six records describing four unique non-RCTs evaluating pembrolizumab monotherapy were also identified. To identify RCTs evaluating treatments relevant to clinical practice in the UK, a decision rule was applied to include only those trials evaluating the following interventions: nivolumab plus ipilimumab, FOLFIRI, FOLFOX, FOLFOX4, mFOLFOX6, TAS-102, or regorafenib (third-line and beyond patients). After application of this decision rule, 36 records describing 15 unique trials and six records describing four unique non-RCTs evaluating pembrolizumab monotherapy were included in the SLR.

Following clinical expert consultation, the final list of comparators reflecting current clinical practice in the UK has been narrowed down to the following chemotherapy regimens: FOLFOX, FOLFIRI and TAS-102. Based on this, of the 15 RCTs trials that met the eligibility criteria for inclusion in the SLR, only 14 corresponding to 34 records are considered relevant to this appraisal.

Four trials evaluating pembrolizumab have been identified, of which Le 2015 and KEYNOTE-028 are Phase 2 and 1b studies, respectively, investigating a not approved dosage of pembrolizumab (10 mg/kg every two weeks) and therefore were not regarded by the company to be in line with the intervention of interest in this appraisal. Michalaki 2020 is an American Society of Clinical Oncology (ASCO) conference abstract with limited information about patient characteristics (e.g., previous lines of therapy), study methodology and outcomes. Whilst it met the eligibility criteria for the SLR, it was not possible to assess its relevance to this appraisal. KEYNOTE-164 was the only study investigating the efficacy of pembrolizumab in the approved indication deemed by the company to be relevant to this appraisal.

A complete list of publications included after full-text review is available in Table 3.11. The studies not considered relevant for this submission are shaded in the table.

Table 3.11: List of included trials in UK-specific SLR

Trial ID	Registry number	Principal publication	Principle publication title	Associated publication(s)
Studies on pembrolizumab (single-arm trials)				
KEYNOTE-028	NCT02054806	O'Neil 2017	Safety and antitumor activity of the anti-pd-1 antibody pembrolizumab in patients with advanced colorectal cancer	--
KEYNOTE-164	NCT02460198	Le 2020	Phase ii open-label study of pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: Keynote-164	Diaz 2020, Le 2021
Le 2015	NCT01876511	Le 2015	PD-1 Blockade in Tumors with Mismatch-Repair Deficiency	--
Michalaki 2020	--	Michalaki 2020	Safety and efficacy of pembrolizumab monotherapy in patients with advanced colorectal msi-h/dmmr cancers	--
Non-pembrolizumab studies (RCTs)				
BEYOND	EudraCT 2017-004519-38	Aparicio 2022	Randomized phase II trial of FOLFIRI-panitumumab compared with FOLFIRI alone in patients with RAS wild-type circulating tumor DNA metastatic colorectal cancer beyond progression to first-line FOLFOX-panitumumab: the BEYOND study (GEMCAD 17-01)	--
Cao 2015	--	Cao 2015	A multi-center randomized phase ii clinical study of bevacizumab plus irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) compared with FOLFIRI alone as second-line treatment for Chinese patients with metastatic colorectal cancer	--
CAPRI-GOIM	EudraCT 2009-014041-81	Ciardiello 2016	Cetuximab continuation after first progression in metastatic colorectal cancer (CAPRI-GOIM): A randomized phase II trial of FOLFOX plus cetuximab versus FOLFOX	--
CONCUR	NCT01584830	Li 2015	Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer	Xu 2020

Trial ID	Registry number	Principal publication	Principle publication title	Associated publication(s)
			(CONCUR): A randomised, double-blind, placebo-controlled, phase 3 trial	
ECOG 3200	--	Giantonio 2007	Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group study E3200	Reddy 2005
Li 2018	NCT01661270	Li 2018	Aflibercept plus FOLFIRI in Asian patients with pretreated metastatic colorectal cancer: A randomized phase iii study	--
Liu 2015	--	Liu 2015	A randomized phase ii clinical study of combining panitumumab and bevacizumab, plus irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) compared with FOLFIRI alone as second-line treatment for patients with metastatic colorectal cancer and KRAS mutation	--
Moore 2016	NCT01111604	Moore 2016	Randomized phase II study of modified FOLFOX6 in combination with ramucirumab or icrucumab as second-line therapy in patients with metastatic colorectal cancer after disease progression on first-line irinotecan-based therapy	--
Peeters 2010	NCT00339183	Peeters 2010	Randomized phase iii study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer	Bennet 2011, Peeters 2014, Peeters 2015
RAISE	NCT01183780	Tabernero 2015	Ramucirumab versus placebo in combination with secondline FOLFIRI in patients with metastatic colorectal cancer that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study	Cohn 2017, Lim 2019, Obermannova 2016, Tabernero 2018, Yoshino 2017, Yoshino 2019
RECOURSE	NCT01607957	Mayer 2015	Randomized trial of tas-102 for refractory metastatic colorectal cancer	Longo-Munoz 2017, Van Cutsem 2017, Van Cutsem 2018

Trial ID	Registry number	Principal publication	Principle publication title	Associated publication(s)
TERRA	NCT01955837	Xu 2018	Results of a randomized, double-blind, placebo-controlled, phase iii trial of trifluridine/tipiracil (TAS-102) monotherapy in Asian patients with previously treated metastatic colorectal cancer: The TERRA study	--
VELOUR	NCT00561470	Van Cutsem 2012[16]	Addition of Aflibercept to Fluorouracil, Leucovorin, and Irinotecan Improves Survival in a Phase III Randomized Trial in Patients With Metastatic Colorectal Cancer Previously Treated With an Oxaliplatin-Based Regimen	Chau 2014, Joulain 2013, Ruff 2015, Ruff 2018, Tabernero 2014, Van Cutsem 2016, Van Cutsem 2020
Xie 2014	--	Xie 2014[17]	Safety and efficacy of second-line treatment with folinic acid, 5-fluorouracil and irinotecan (FOLFIRI) in combination of panitumumab and bevacizumab for patients with metastatic colorectal cancer	--
Yoshino 2012	JapicCTI-090880	Yoshino 2012[18]	TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial	--

Based on Table 45 of the CS appendices[9]

CS = company submission; dMMR = mismatch repair deficiency; DNA = deoxyribonucleic acid; KRAS = Kirsten rat sarcoma virus gene; MSI-H = microsatellite instability-high; PD-1 = Programmed cell death protein 1; RAS = rat sarcoma virus; RCT = randomised controlled trial; SLR = systematic literature review; UK = United Kingdom

EAG comment:

- The limitation of studies to those with the comparators FOLFOX, FOLFIRI and trifluridine-tipiracil (TAS-102) is in line with the decision problem, but not in line with the NICE scope, which allowed any comparator established in UK practice for this population, and also specified nivolumab. As previously noted in section 2.3, this narrowing of the scope may have led to some important evidence of clinical relevance being missed out.
- Roque 2021 (and associated papers Bellone 2021 and Bellone 2022) is highlighted as a relevant pembrolizumab trial in the endometrial cancer SLR. Although this was included in the cost effectiveness section of the CS[2], it was not presented in the clinical effectiveness section. The company have been asked to explain why this trial was not included as clinical effectiveness evidence in the CS[2] alongside KEYNOTE-158. The company responded by stating that *"Roque et al. 2021 refers to a conference abstract for the relevant study of patients with recurrent MSI-H endometrial cancers treated with pembrolizumab. Bellone et al. 2022 provides further data and KM functions for OS and PFS for the same study. This is a small investigator led study of 24 evaluable patients, compared with the 83 endometrial cancer patients observed in KEYNOTE-158. Patients in Bellone et al. 2022 were older (mean age 69 vs. 64.3) and the majority (50%) were FIGO stage 1 compared to KEYNOTE-158 where endometrial patients were disease stage IV or IVB (97.6%). Also, in Bellone et al. 2022 six patients (25%) harboured Lynch/Lynch- like tumours and 18 (75%) had sporadic endometrial cancer whereas details on the molecular pathways originating MSI-H/dMMR tumours are not available for KEYNOTE-158. Data from this study are therefore uncertain given the small patient population and may represent a healthier but older patient population not thought to be consistent with pivotal trials related to the licence. Comparison of Bellone et al. 2022 OS data with those from KEYNOTE-158 endometrial cancer patients shows outcomes are comparable although Bellone et al. 2022 has a shorter maximum follow up period. PFS data are similar between the two studies (but slightly improved for Bellone study) and any interpretation of tangible differences between the studies should be treated with caution given the small patient numbers. In summary:*

  Median PFS (Bellone study vs KEYNOTE-158): 25.8 months vs. 21.9 months

  Median OS (Bellone study vs KEYNOTE-158): 40 months vs. Not reached

  ORR (Bellone vs KN-158): 58% vs. 50.6%"

  The EAG does not agree with the company's reasons for not including the data from Bellone 2022 in the clinical effectiveness evidence. The data are probably underpowered, but the point estimates may still be informative, and therefore contribute to a fuller understanding of the clinical effects of pembrolizumab. Furthermore, although the patient population in Bellone is different to that in KEYNOTE-158, it falls within the scope of the decision problem. However, the EAG does not regard the exclusion of the study as a key issue, given that its inclusion would increase, rather than diminish, the positive pembrolizumab effects provided from KEYNOTE-158.
- KEYNOTE-028 and Le 2015 were excluded on the basis of dosage. However, the dosage of pembrolizumab is not specified in either the NICE scope nor the decision problem (nor, interestingly, in the protocol of the SLR). The company has been asked to clarify why these trials were omitted from the clinical evidence. With regard to KEYNOTE-028, the company responded by stating that, *"whilst neither the NICE scope nor the decision problem specify the dosage of pembrolizumab, the scope of this appraisal is to evaluate the clinical effectiveness and cost-effectiveness of pembrolizumab in the licensed indication. According to the Summary of Product Characteristics (SmPC) (20), the recommended dose of pembrolizumab in adults is either 200 mg every 3 weeks or*