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

For public – contains no confidential information

Technology appraisal committee D [12th July 2023]

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Company: Merck Sharp & Dohme (MSD)

Pembrolizumab (KEYTRUDA, MSD)

Technology details

Marketing authorisation (MHRA granted 16th May 2022)	Pembrolizumab is indicated for MSI-H or dMMR cancers in adults with: • unresectable or metastatic colorectal cancer after fluoropyrimidine-based combination therapy; • advanced or recurrent endometrial cancer whose disease has progressed on or following treatment with a platinum-containing therapy and are not suitable for curative surgery or radiation; • unresectable or metastatic gastric, small intestine, or biliary cancer, whose disease has progressed on or following at least one prior therapy.
Mechanism of action	• Anti-programmed cell death 1 (PD-1) antibody which blocks immune suppression and reactivates T-cell anti-tumour activity
Administration	• 200 mg every 3 weeks or 400 mg every 6 weeks, intravenous
Additional testing in NHS	• Biomarker testing is done by immunohistochemistry (IHC). • This is standard clinical practice for colorectal or endometrial cancer. • Costing in the model has been assumed for gastric, small intestine and biliary cancer.
Price	• List price: £2,630 per 100 mg vial; Confidential discount applicable

Abbreviations: MSI-H, microsatellite instability high; dMMR, deficient DNA mismatch repair; MHRA, Medicines and Healthcare products Regulatory Agency

Background of mismatch repair deficiency (dMMR) and high microsatellite instability (MSI-H) tumours

MSI-H/dMMR is a molecular biomarker indicating a defective DNA repair process

Deficient mismatch repair systems (dMMR) do not repair DNA mutations → results in microsatellite instability (MSI)

↳ MSI-high (MSI-H) describes cancer cells that have a greater than normal number of microsatellites.

Characteristics and prognosis

- MSI-H and dMMR cancers can demonstrate increased expression of PD-1.
  - ↳ PD-1 expression is associated with superior response to anti-PD-1 inhibitors such as pembrolizumab.
- MSI-H / dMMR disease has one of the highest mutational loads versus other molecular subtypes.
- TA716 (colorectal cancer): 'MSI-H / dMMR is associated with a poorer prognosis and a greater risk of death'.

Epidemiology

- The prevalence of MSI-H varies across tumour sites and disease stage.
- Approximate MSI-H / dMMR population eligible per year:
  - ↳ Colorectal (n=125), Endometrial (n=95), Gastric (n=123), Small intestine (n=34), Biliary (n=19).

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Abbreviations: MSI-H, high microsatellite instability; dMMR, mismatch repair deficiency; PD-1 Anti-programmed cell death 1

Patient perspectives

Effective treatment options are limited for people with inoperable biliary cancer

Submissions from a patient expert and AMMF - The Cholangiocarcinoma (biliary) Charity

- The incidence of biliary cancer is increasing year on year, with mortality mirroring incidence, and many younger adults being diagnosed.
- Often diagnosed late because of a lack of awareness at primary care level and symptoms can be vague and easily attributed to other causes. Late diagnosis often means the cancer is inoperable and a terminal diagnosis.
- People with biliary cancer have an unmet need for:
    - Effective treatments
    - Molecular profiling
        - ↳ Should be accessed at diagnosis or during 1st line treatment but still difficult under the NHS.
        - ↳ People may miss out on therapies that could extend their lives.
        - ↳ NHS testing only available to very few biliary cancer patients, with many seeking this privately.
    - Centres of Expertise
- Pembrolizumab offers a survival extending treatment with good QoL for those with MSI-H/dMMR cancer.

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Abbreviation: MSI-H, high microsatellite instability; dMMR, mismatch repair deficiency; QoL, quality of life

Clinical perspectives

Pembrolizumab expected to significantly improve length and quality of life compared to current treatments

Submission from a clinical expert (Consultant Medical Gastrointestinal (GI) Oncologist)

- MSI-H and dMMR testing is routinely commissioned for CRC, but not for non-CRC GI tumour subtypes.
  - ↳ If this appraisal is positive, pathologist will have to test routinely otherwise would be denying a potential treatment option to these patients.
  - ↳ MSI testing is a cheap and readily available test that should be available to all patients so they can access immunotherapy treatments as early as possible in the treatment pathway as the clinical benefits are superior to SoC therapies.
- Pembrolizumab is a step-change in the management of MSI-H/dMMR tumours.
  - ↳ It addresses an unmet need - currently no access to 3rd line immunotherapy for dMMR metastatic CRC, or in any line for the other tumour types being appraised.
  - ↳ It is innovative and life changing allowing some patients to have possibility of long and productive lives.
- There is very little published real-world evidence of large cohort in this population as it is a rare subgroup.
- Pembrolizumab commonly used for other tumour types in the NHS so implementation and management of side effects unlikely to be a problem.

Abbreviations: MSI-H, high microsatellite instability; dMMR, mismatch repair deficiency; GI; gastrointestinal; CRC, colorectal cancer; SoC, standard of care

Other considerations

Equality considerations

- No equality issues anticipated by the company.

Previous NICE solid tumour appraisals (TA630 & TA644)

- Previous NICE solid tumour appraisals were histology independent and for NTRK fusion-positive tumours.
  - ↳ This appraisal is for 5 specific tumour sites / populations with MSI-H/dMMR status.

Evidence considerations

- Evidence is limited by small patient numbers within each of the 5 tumour sites.

Managed access considerations

- Company submitted a managed access proposal.
- NICE managed access team - further data collection would not resolve the key uncertainties.

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Abbreviations: MSI-H, high microsatellite instability; dMMR, mismatch repair deficiency; NTRK, neurotrophic tyrosine receptor kinase

Key issues

Key - Not resolved: Unresolvable: Resolved:

Issue	Resolved?	Type of uncertainty	ICER impact
Comparators	No – for discussion	Structural	Unknown
Trial generalisability	No – unresolvable	Structural	Unknown
High risk of bias in comparative efficacy*	No – unresolvable	Structural	Unknown
MSI-H/dMMR status mismatch between pembrolizumab and comparator population*	No – unresolvable	Structural	Unknown
Aggregating tumour site results	No – for discussion	Structural	Small
Bayesian hierarchy modelling	No – for discussion	Methodological	Small
Subsequent treatments	No – for discussion	Methodological	Moderate
Severity Modifier	Yes – for discussion	-	Small
Utilities	Yes	-	N/A
Testing costs	Yes	-	N/A
Adverse events	Yes	-	N/A
Comparator treatment baskets	Yes	-	N/A
Scenario analysis face validity	Yes	-	N/A

*Issue 8 in EAR merged into this issue to avoid duplication

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Abbreviations: dMMR, deficient mismatch repair; MSI-H, microsatellite instability high; EAR; evidence assessment report

Decision problem (1/2)

Company population, intervention and outcomes matches the NICE scope

	Final scope	Company	EAG
Population	• Adults with unresectable or metastatic MSI-H or dMMR colorectal cancer 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 1 prior therapy.	N/A	N/A
Intervention	• Pembrolizumab	N/A	N/A
Outcomes	• Overall survival • Progression free survival • Response rate • Duration of response • Adverse effects • Health-related quality of life	N/A	N/A

Abbreviations: MSI-H, microsatellite instability high; dMMR, deficient DNA mismatch repair; N/A, not applicable

Decision problem (2/2)

Company comparators do not match the NICE scope

	Final scope	Company	EAG
Comparators	Colorectal cancer: • ECM without pembrolizumab • Nivolumab with ipilimumab (TA716) • Irinotecan (after FOLFOX) • FOLFIRI (after FOLFOX or CAPOX) • Raltitrexed (if 5-fluorouracil and folinic acid are unsuitable) • Trifluridine-tipiracil (TA405)	Colorectal cancer • FOLFIRI/FOLFOX/ FOLFOX4 /mFOLFOX6 • Trifluridine-tipiracil (TAS-102)	Should include: • Nivolumab with ipilimumab • Irinotecan • Raltitrexed

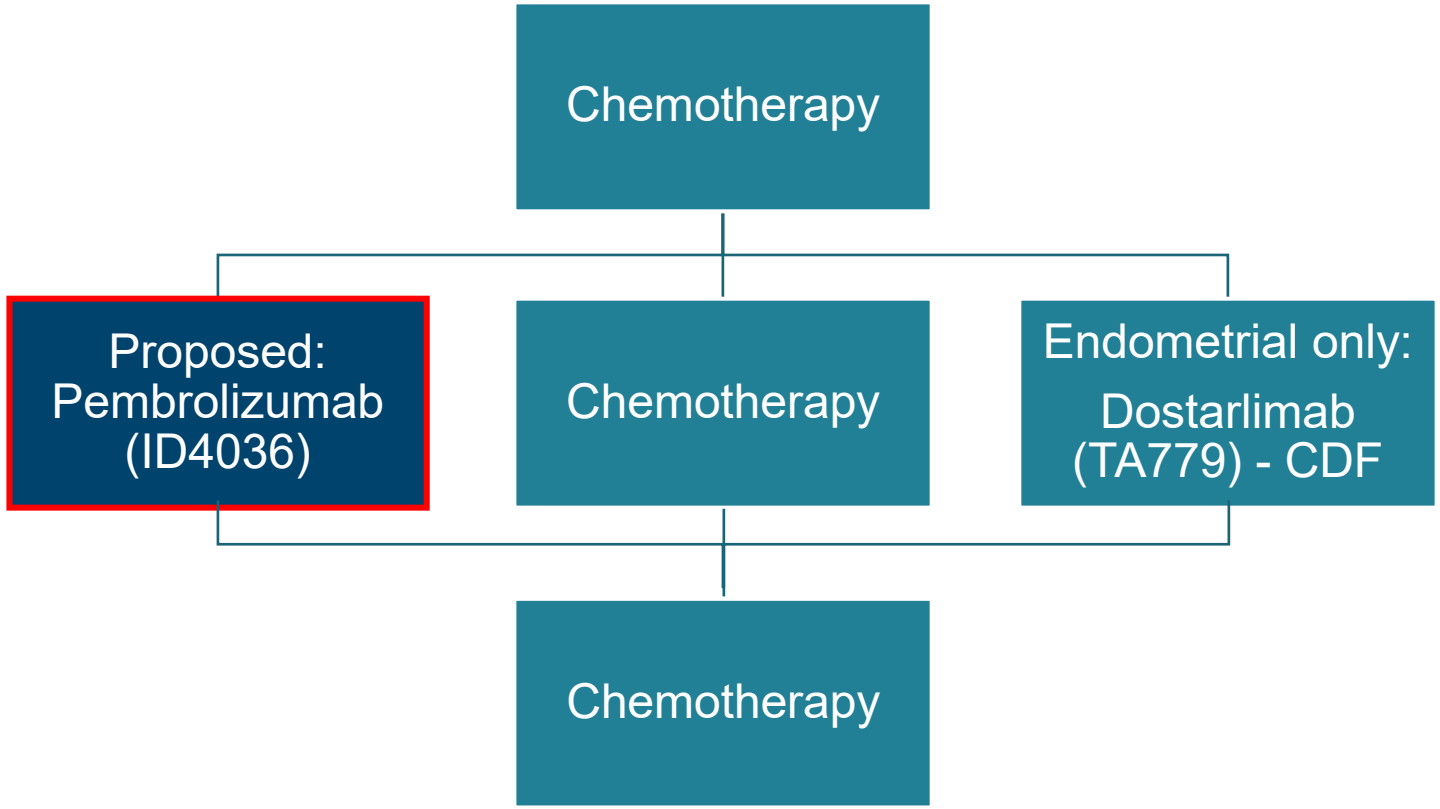
	Endometrial cancer:
	• ECM without pembrolizumab
	• Chemotherapy, including:
	  • Carboplatin and paclitaxel
	  • Paclitaxel, doxorubicin or carboplatin monotherapy
	• Hormone therapy
		Endometrial cancer
		• Chemotherapy, including paclitaxel, doxorubicin and carboplatin
			N/A

	Gastric, small intestine, biliary cancer: • ECM without pembrolizumab	• Gastric: Paclitaxel, FOLFIRI • Small intestine: FOLFIRI/FOLFOX • Biliary: FOLFOX, FOLFIRI	N/A

Abbreviations: ECM, established clinical management; N/A, not applicable

Treatment pathway: MSI-H/dMMR metastatic gastric, small intestine and biliary cancers, and advanced/recurrent endometrial cancers

Pembrolizumab proposed as alternative to second line chemotherapy regimen



Subsequent treatments include:
- Doxorubicin
- Paclitaxel
- Megestrol
- Fulvestrant
- Tamoxifen
- FOLFOX
- FOLFIRI
- Capecitabine
- Fluorouracil + irinotecan
- Gemcitabine + paclitaxel
- Ramucirumab + paclitaxel

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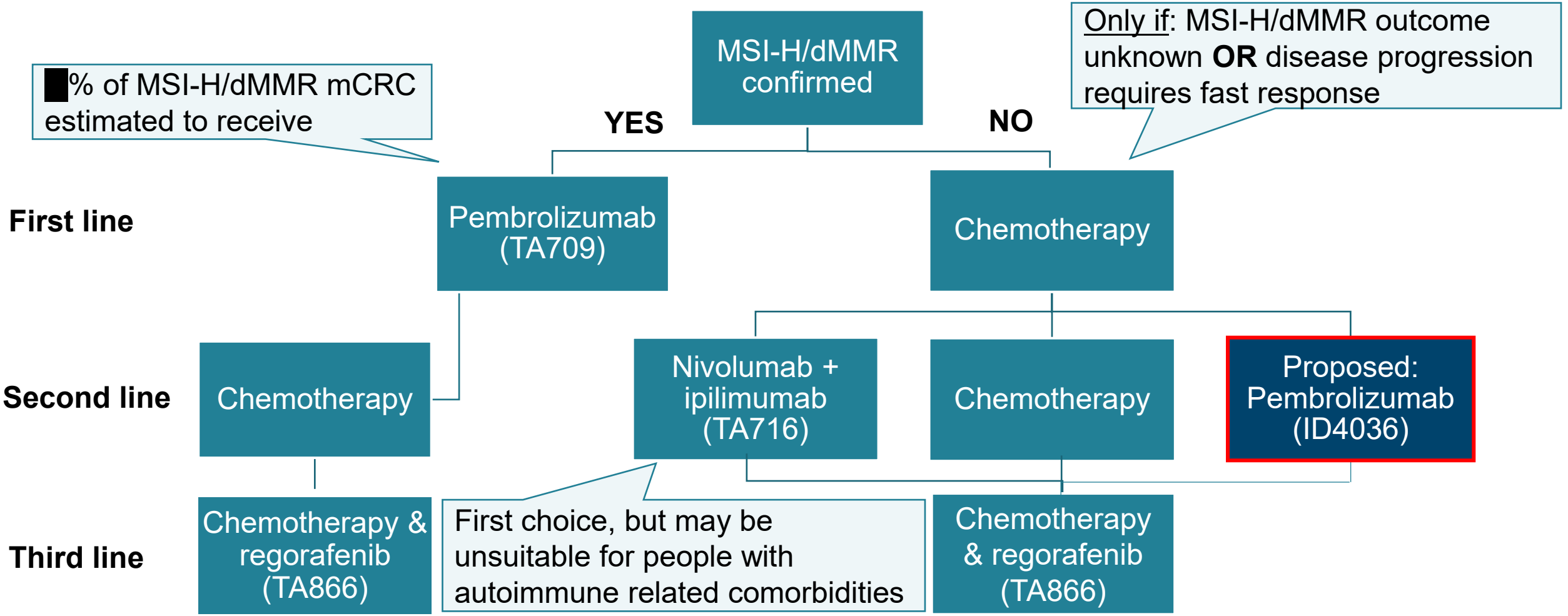
Abbreviations: dMMR, deficient mismatch repair; MSI-H, microsatellite instability high; CDF, cancer drugs fund

Treatment pathway: metastatic MSI-H/dMMR colorectal cancer

Pembrolizumab proposed as alternative to second line chemotherapy regimen



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Abbreviation: dMMR, deficient mismatch repair; MSI-H, microsatellite instability high; mCRC, metastatic colorectal cancer

Key issue: Comparators (1/2)

Company's decision problem excludes 3 scoped comparators

Background

- NICE scope colorectal cancer comparators excluded in the company's decision problem:
  - ↳ 1) nivolumab + ipilimumab, 2) irinotecan, 3) raltitrexed

Company

Nivolumab + ipilimumab

- [redacted]% not have 1st line pembrolizumab (TA709) → instead, chemotherapy then 2nd line nivolumab + ipilimumab.
  - ↳ Very little unmet need - pembrolizumab 2nd line suitable for small proportion of this subset who cannot receive nivolumab + ipilimumab because of comorbidities.
- Nivolumab + ipilimumab preferred in clinical practice as more effective compared to nivolumab alone.
  - ↳ Pembrolizumab results very similar to nivolumab = infer nivolumab + ipilimumab also likely to be superior.
- Would accept restricted CRC recommendation for people unsuitable for nivolumab + ipilimumab.

Irinotecan and raltitrexed:

- Rarely used in clinical practice unless other treatments are contraindicated.
- Similar or lower efficacy compared to alternative options - likely give comparable or more favourable ICERs.

Abbreviations: ICER, incremental cost-effectiveness ratio; CRC, colorectal cancer

Key issue: Comparators (2/2)

Uncertainty remains over suitable comparators for colorectal subgroup

EAG comments

Nivolumab + ipilimumab

- Company - pembrolizumab only to be used for people who are unsuitable with nivolumab with ipilimumab (i.e., those with autoimmune related comorbidities).
  - ↳ But evidence for pembrolizumab versus any colorectal comparator is not specific to this subgroup.

Irinotecan and raltitrexed:

- Exclusion based on subjective clinical opinion is uncertain.
- Evidence of similar/lower efficacy:
  - ↳ not part of systematic review = subject to selection bias of both studies and outcomes included.
  - ↳ not included in cost effectiveness analysis = effect on ICER unknown.

Other considerations

- Clinical expert: people should not miss opportunity to access ≥1 immunotherapy in 1st, 2nd or 3rd line.

↳ Nivolumab + ipilimumab superior 2nd line treatment but will be scenarios where the clinician and/or patient would not want to have 2nd line doublet immunotherapy e.g., increased risk of toxicities.

↳ Pembrolizumab would be valuable option to access in 2nd or 3rd line setting as it would be superior to any current chemotherapy options (e.g., 2nd line irinotecan, raltitrexed, or 3rd line regorafenib or TAS-102).

Should nivolumab + ipilimumab, irinotecan or raltitrexed be included as a comparator for CRC? Is chemotherapy the only comparator relevant for the subgroup unsuitable for nivolumab + ipilimumab ?

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Abbreviations: ICER, incremental cost-effectiveness ratio

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trials

	KEYNOTE-158 (n = 183)	KEYNOTE-164 (n = 124)
Design	Phase 2, non-randomised, single arm, multi-site, open-label study	
Trial population (cohorts relevant to submission)	Adults with advanced dMMR or MSI-H: • Endometrial cancer (n = 83) • Gastric cancer (n = 51) • Small intestine cancer (n = 27) • Biliary cancer (n = 22)	Adults with locally advanced unresectable metastatic dMMR or MSI-H colorectal carcinoma, previously treated with: • ≥ 2 lines of SoC therapies (n=61) • ≥ 1 line of systemic SoC therapy (n=63)
Intervention	Pembrolizumab (200 mg, every 3 weeks)	
Comparator(s)	None	
Primary outcome	Objective response rate*	
Secondary outcomes	Overall survival, progression free survival*, duration of response*, safety and tolerability	
Locations	18 countries. No UK patients.	10 countries. No UK patients.
Used in model?	Yes	Yes
Analysis population: All Subjects as Treated (ASaT)	Participants who had ≥1 dose of pembrolizumab and chance to have been followed for 6 months prior to data cut off.	All allocated participants who had ≥1 dose of pembrolizumab.
*Based on RECIST 1.1 as assessed by independent central radiologic review		

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Abbreviations: MSI-H, high microsatellite instability; dMMR, mismatch repair deficiency; SoC, standard of care

Clinical trial results

Cancer	KEYNOTE-158: Oct 2021; KEYNOTE-164: Feb 2021	
	Median months (95% CI)	24m OS/PFS rate (%)
Overall survival (OS)		
Colorectal	36.1 (24.0, NR)	59.1
Endometrial	NR (48.0, NR)	67.2
Gastric	26.9 (6.6, NR)	50.0
Small intestine	NR (16.2, NR)	62.7
Biliary	14.5 (6.5, 44.8)	50.0
Progression free survival (PFS)		
Colorectal	4.0 ([redacted])	33.8
Endometrial	13.1 (4.9, 25.7)	39.0
Gastric	4.1 (2,1, 24.6)	38.5
Small intestine	23.4 (4.3, NR)	49.8
Biliary	4.2 (2.1, 24.9)	31.8
Note: KEYNOTE-158 has a more recent data cut (Jan 2022) but is commercially confidential.		

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Abbreviations: NR, not reported; OS, overall survival; PFS, progression free survival

Key issue: Trial generalisability (1/2)

Ethnicity differences between trials and UK population for colorectal, gastric and small intestine cancers

Background
- Large ethnicity differences between trials and UK data (not specific to people with MSI-H/dMMR status).

Company
- Limited information available on people with MSI-H.
- Ethnicity subgroup analyses found no meaningful evidence of differences in ORR between race groups.
- No evidence suggests ethnicity is a treatment effect modifier → efficacy outcomes considered generalisable to UK target population and difference found is not expected to affect external validity of trial results.
- Baseline characteristic distributions may be affected by small sample size for each tumour site in the trials.

EAG comments
- Point estimate differences may be important - committee should consider context of applicability.
  - ↳ E.g., Gastric cancer: trial data (28% Asian); UK target population (3% Asian).
  - ↳ Subgroup analysis = ORR results better for Asians - possible higher proportion of Asians in trial may overestimate benefits in UK target population.

Do the ethnicity differences render the trial not generalisable enough for decision making?

Abbreviations: dMMR, deficient mismatch repair; MSI-H, microsatellite instability high; ORR, objective response rate

Key issue: Trial generalisability (2/2)

Age, gender and ethnicity characteristics of trial and UK target populations in each tumour site

Characteristic	Age (years)		Female (%)		Race (%)							
					White		Black		Asian		Mixed/multiple/other	
	Trial	UK*	Trial	UK	Trial	UK	Trial	UK	Trial	UK	Trial	UK
Colorectal n=124	56.1	85-89	44.4	44	67.7	90	5.6	1.4	26.6	2.1	0	0.3
Gastric n=51	66.2	85-89	35	35	63	88	4	2.7	28	3	10	0.5
Small Intestine n=27	57.6	80-84	37	45	82	89	0	2.1	11	3.1	7	0.0***
Endometrial n=83	64.3	75-79	100	100	84	86	4	2.2	6	4.1	7	0.5
Biliary n=22	59.7	85-89**	27	71**	91	84**	0	2.8**	9	6.1**	0	0.0**/***

*Peak rate of diagnosis; **Gallbladder cancer; *** <20 cases
UK statistics: Cancer Research UK (age and sex), Delon 2022 for ethnicity (2013-2017).
Note: UK data for all MSI status.

Key issue: High risk of bias in comparative efficacy

Relative treatment effects explored via unadjusted ITCs, unanchored MAICs and parametric survival models.

Background

- Key clinical evidence from single arm trials = no direct comparison between pembrolizumab and comparators.
- Given proportional hazard violations and limitations of ITCs and MAICs, neither used in analyses.
- Base case: independent parametric survival models fitted to comparator pseudo-IPD for use in the model.

Company

- Single arm trials could bias relative treatment comparisons, but not uncommon in solid tumour indications.
- Non-responder analysis (worst-case scenario) - pembrolizumab non-responders used for comparator efficacy.
- Company and EAG base case include highly conservative treatment effect waning assumption from 7 to 9 years (from start of treatment) to show how cost-effective pembrolizumab remains.

EAG comments

- Serious limitations in all approaches - risk of bias remains in all estimates and base case still informed by non-randomised data that does not adjust for confounding.

Other considerations

- Clinical expert: likely any MSI-H/dMMR comparator data would be too small to estimate relative effectiveness.
- Uncertainties from bias in relative efficacy carried into comparator modelling.
  - ↳ Scenario analyses: non-responder analysis and best/worst case survival curve selections.

What impact does the comparator data have on the relative clinical efficacy estimates?

Abbreviations: ITC, indirect treatment comparison; MAICs, matching-adjusted indirect comparisons; IPD, individual patient data; dMMR, deficient mismatch repair; MSI-H, microsatellite instability high

Key issue: Mismatch in MSI-H/dMMR status between pembrolizumab and comparator population

Background

- Most comparator evidence included in ITC is not from MSI-H/dMMR population

↳ Adjustment for MSI-H/dMMR status not possible – issue if biomarker is a treatment effect modifier.

Company

- Within study comparisons (MSI-H vs non-MSI) show people with MSI-H have:
  - worse prognosis when treated with chemotherapy, and better outcomes when treated with pembrolizumab.
  - clinical experts agree MSI-H/dMMR results in worse prognosis and better response to immunotherapy.
- No adjustment for MSI-H/dMMR is likely to result in conservative estimates of relative efficacy.
  - ↳ ICERs not likely to increase if comparisons performed in the MSI-H/dMMR comparator population.
  - ↳ dMMR/MSI-H considered relevant predictive biomarker of response to pembrolizumab in 5 tumour types.

EAG comments

- Possible MSI-H results in worse prognosis and better response to immunotherapy.
- Company evidence supports that any bias would be conservative (diminish the superiority of pembrolizumab).
  - ↳ But not possible to state likely direction of bias and uncertainty is carried into comparator modelling.

Other considerations

- TA716 concluded that MSI-H/dMMR is associated with a poorer prognosis and a greater risk of death.

Are the ITCs between people with and without MSI-H/dMMR status representative of the treatment effects in the target MSI-H/dMMR populations?

Abbreviations: dMMR, deficient mismatch repair; MSI-H, microsatellite instability high; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparisons

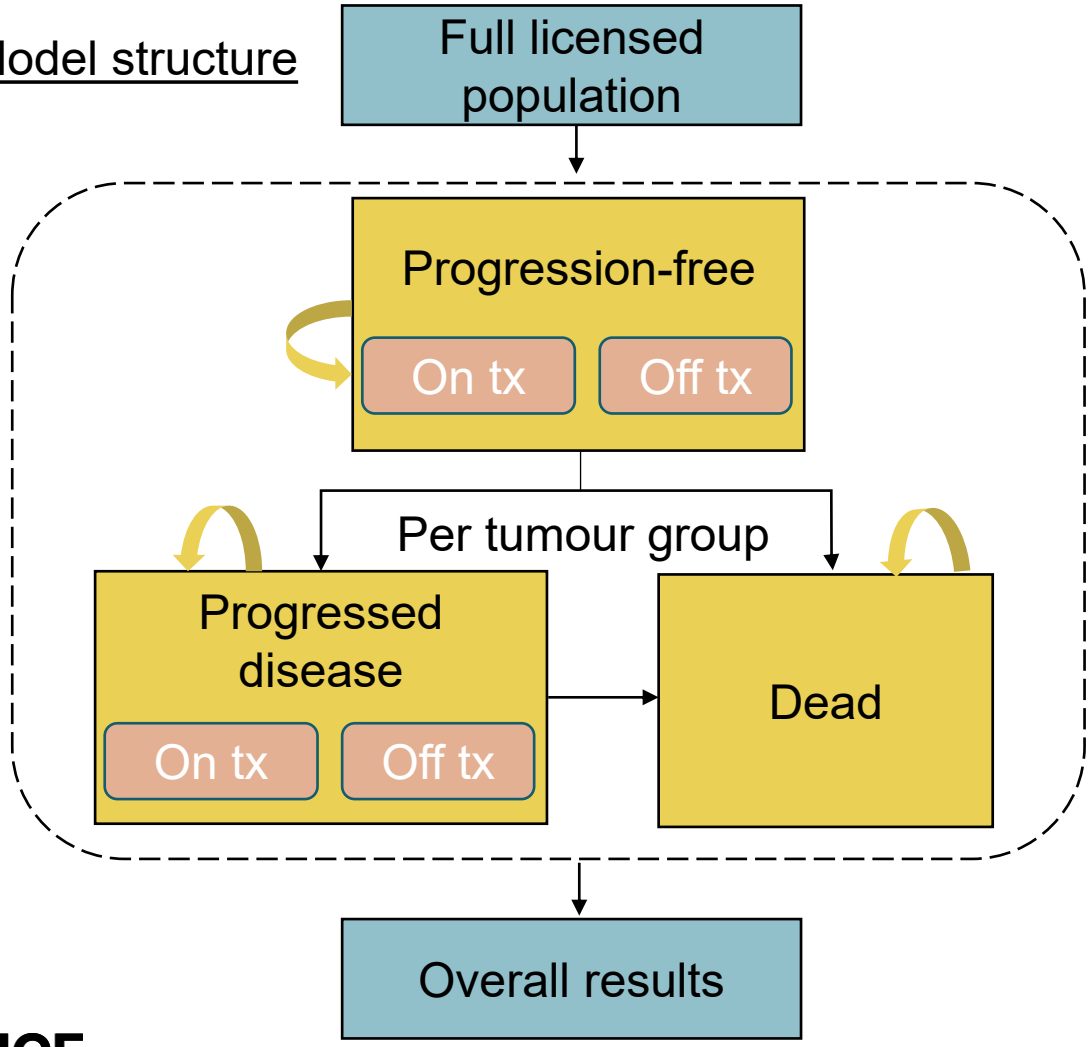
Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

Partitioned survival model with separately modelled tumour sites which aggregate to generate an overall solid tumour outcome, weighted by tumour site prevalence

Model structure



Technology affects **costs** by:

- Higher treatment costs
- Higher resource use costs

Technology affects **QALYs** by:

- Increased OS for pembrolizumab

Assumptions with greatest effect on overall indication NHB:

- *Deterministic sensitivity analyses*
  - Administration costs of oral chemotherapy
  - Proportion of CRC patients receiving subsequent therapy after pembrolizumab
  - Grothey 2013 utility values to inform HRQoL in CRC
- *Scenario analyses*
  - Treatment waning
  - QALYs and costs discounting
  - Pembrolizumab OS and PFS survival modelling

Abbreviations: tx, treatment; QALY, quality-adjusted life year; CRC, colorectal cancer; OS, overall survival; HRQoL, health-related quality of life; PFS, progression free survival; NHB, net health benefits

Key issue: Aggregating tumour site results

Weighting calculations are not an issue that determines cost-effectiveness.

Background

- Multi-cohort model structure used to model each tumour site separately and then aggregate to generate outcomes across all tumour sites (weighted by tumour site distribution across all people with MSI-H/dMMR).

Company

- Individual tumour sites cost-effective and aggregated results cost-effective, therefore, weighting calculations not issue that determines cost-effectiveness.
  - Similar outcomes across chemotherapy comparators in all tumour sites.
- "Aggregation" = weighted averaging of individual total costs, total QALYs and ICERs to produce cost-effectiveness results by tumour site and for the overall indication.
- Aggregation into overall indication results based on epidemiological calculations.

EAG comments

- Question appropriateness of aggregating results, given substantial heterogeneity across each tumour site.
- Unclear why aggregating results is deemed appropriate but recognise tumour specific results are provided.

Is it appropriate to present overall indication results? Should each tumour site be considered individually?

Abbreviations: dMMR, deficient mismatch repair; MSI-H, microsatellite instability high; QALYs, quality-adjusted life years; ICERs, incremental cost-effectiveness ratio; BHM, Bayesian hierarchal modelling; PSM, partitioned survival models

Key issue: Bayesian hierarchical modelling

Modelling approach has minor impact on ICER so not likely a key model driver

Background

- Base case: pembrolizumab OS and PFS modelled using Bayesian hierarchical modelling (BHM).
- BHM: middle ground between assuming complete homogeneity in pembrolizumab efficacy between sites and complete heterogeneity (fitting separate PSM models as though sites are independent trials).

Company

- "True" ICERs somewhere around BHM approach and standard PSMs
- BHM approach: model fit across all five tumour sites, including CRC.
  - EAG: inappropriate to include CRC in BHM given it is a separate trial.
  - Company: reasonable as trials are similar and included in same license, so a CRC site in KEYNOTE-158 would have a comparable sample size to KEYNOTE-164 and results would not differ systematically.
- Scenario: PSM applied to CRC site, BHM applied to other 4 sites - makes little difference to results.

EAG comments

- BHM approach only appropriate if assumption that different tumour sites can be considered subgroups of an overarching MSI-H/dMMR solid tumour population is justified – no evidence provided.
- Acknowledge BHM allows information to be borrowed between tumour sites, given small sample sizes.
  - ↳ But considering OS and PFS differences, seems substantial heterogeneity between tumour sites.
  - ↳ However, modelling individual tumour sites using small sample sizes will likely also introduces bias.

Are the committee happy to use the base case modelling approach?

Abbreviation: ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression free survival; BHM, Bayesian hierarchical modelling; PSM, parametric survival models; CRC, colorectal cancer

Key issue: Subsequent treatments (1/3)

Background

- Modelled subsequent treatments for progressed people were based on KEYNOTE-158 and KEYNOTE-164.
- Subsequent treatments assumed equal regardless the initial line of therapy (pembrolizumab or comparator).

Company

- Trial proportions show that most people receive BSC at 3rd line for advanced metastatic cancer.
- Proportion varies by tumour site (60-80% receiving BSC; 19-41% receiving subsequent treatments).
- Clinicians broadly agreed with proportions.
- Costs vary slightly between pembrolizumab and comparator arms due to differences in progression rates.
- Unclear how subsequent treatments might differ in practice between pembrolizumab and comparators.
- If immunotherapies used in comparator population = higher subsequent treatment costs for comparators.

Other considerations

- Clinical expert: heterogeneity in clinical practice of what chemotherapy type and combinations given.
  ↳ Type of treatment based on many factors e.g., first line treatment, clinical benefits, time to progression, initial treatment toxicity and hang over toxicity, and performance status/fitness to have more lines of chemotherapy.
- Scenarios: doubling pembrolizumab subsequent treatment costs and subsequent treatment costs based on proportional difference in survival benefit between arms.

Abbreviation: BSC, best supportive care; ICERs, incremental cost-effectiveness ratio

Key issue: Subsequent treatments (2/3)

Distribution of subsequent treatments across tumour sites

Tumour site (% receiving subsequent treatments)	**Subsequent treatment distribution (%)**						
Colorectal (26.64)	Regorafenib	Anti-VEGF + chemotherapy	TAS-102	Anti-EGFR + chemotherapy	FOLFOX	FOLFIRI	Fluoropyrimidine monotherapy
	9.68	35.48	6.45	16.13	6.45	19.35	6.45
Endometrial (22.89)	Doxorubicin	Paclitaxel	Megestrol	Fulvestrant	Tamoxifen		
	20.00	20.00	20.00	20.00	20.00		
Gastric (19.61)	FOLFIRI	Irinotecan	Paclitaxel	Ramucirumab + paclitaxel			
	20.00	20.00	20.00	40.00			
Small intestine (40.74)	Gemcitabine + paclitaxel	Ramucirumab + paclitaxel	FOLFOX	FOLFIRI			
	20.00	20.00	20.00	40.00			
Biliary (33.33)	Capecitabine	Fluorouracil + irinotecan	FOLFOX				
	50.00	25.00	25.00				

Abbreviation: EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; TAS-102, tipiracil hydrochloride; VEGF, vascular endothelial growth factor

Key issue: Subsequent treatments (3/3)

Uncertainty in the generalisability of subsequent treatments used in trial to UK population or comparator treatments

EAG comments

- KEYNOTE trials only included people that received pembrolizumab.
  - No evidence provided that subsequent treatment proportions would be same for comparators.
  - Advisory board clinical experts: "[redacted]"
  - [redacted]
    Reasonable to assume proportion receiving subsequent treatments after pembrolizumab would be higher than proportion after comparator treatment.
- KEYNOTE trials did not include patients from the UK.
  - Advisory board clinical experts "[redacted]".
  - Company approach based on simplicity and clinical support - no further justification/evidence provided regarding the generalisability of the modelled subsequent treatments to UK clinical practice.

Are the modelled subsequent treatments reflective of UK clinical practice? Should subsequent treatments be assumed equal for the pembrolizumab and comparator arms?

Severity Modifier

Company and EAG base case: colorectal, endometrial, gastric, small intestine cancer (1.2), biliary cancer (1.7)
↳ Based on proportional QALY shortfall using health state utility values.

QALYs people without the condition (A)

QALYs people with the condition (B)

Health lost with condition

QALY weight	Absolute shortfall (A-B)	Proportional shortfall (A – B) / A
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Tumour site	Health state utility values			Time to death utilities		
	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
Colorectal	[redacted]	[redacted]	1.2	-	-	-
Endometrial	[redacted]	[redacted]	1.2	[redacted]	[redacted]	1.2
Gastric	[redacted]	[redacted]	1.2	[redacted]	[redacted]	1.7
Small intestine	[redacted]	[redacted]	1.2	[redacted]	[redacted]	1.7
Biliary	[redacted]	[redacted]	1.7	[redacted]	[redacted]	1.7

Company: If comparator QALYs reduced by [redacted] in gastric and small intestine sites, highest modifier achieved.
↳ Model may overestimate comparator QALYs e.g., modifiers sensitive to utility method.
EAG: Severity may be over- or under-estimated given the lack of evidence in correct MSI-H/dMMR population.

Abbreviations: QALY: quality-adjusted life year; MSI-H, high microsatellite instability; dMMR, mismatch repair deficiency

How the company incorporated evidence into model

Assumptions	Justification
Population	Patient characteristics based on KN-158 / KN-164.
Tumour site prevalence	Based on KN-158 / KN-164.
Stopping rule	Pembrolizumab 2-year stopping rule applied. No other stopping rules.
Resource costs	
Drug wastage	Not assumed. Relative dose intensities included where available.
Subsequent therapies	Proportion receiving subsequent therapy and mean ToT informed by KN-158/KN-164.
Testing costs	50% testing costs included for gastric, endometrial, and biliary tumour sites.
Utilities	
Utilities values	Endometrial, gastric, small intestine and biliary cancer: HSUV informed by KN-158. Colorectal cancer: HSUV informed by Grothey et al (2013)
AE costs	Included
AE disutilities	Not applied
Survival and time of treatment extrapolations	
Pembrolizumab OS + PFS	Bayesian Hierarchical Modelling
Pembrolizumab TTD	Data applied directly from Kaplan-Meier curve
Comparator OS + PFS	Standard parametric survival modelling
Comparator TTD	Assumed equivalent to PFS for treatments when recommended by clinical experts. For the remaining treatments, exponential distribution fitted to reported median ToT.
Treatment effect waning	Applied to all patients between 7 and 9 years from treatment initiation.

Abbreviations: KN, KEYNOTE; ToT, time on treatment; TTD, time to treatment discontinuation; AE, adverse events; OS, overall survival; PFS, progression free survival; HSUV, health state utility values

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

comparator PAS discounts

Incorporating comparator discounts does not profoundly affect pembrolizumab's cost effectiveness

Company and EAG base case results

Results do not include confidential comparator discounts

3/5 tumour site ICERs are below £20,000 per QALY gained.

Probabilistic fully incremental scenario results

		ICER (vs £20,000 per QALY)	Incremental NHB (£20,000 WTP)	Incremental NHB (£30,000 WTP)
Overall indication (vs SoC):		below	positive	positive
Colorectal	Pooled FOLFOX/FOLFIRI	-	-	-
	TAS-102	above	-	-
	Pembrolizumab	below	positive	positive
Endometrial	Paclitaxel	-	-	-
	Doxorubicin	above	-	-
	Pembrolizumab	below	positive	positive
Gastric	FOLFIRI	-	-	-
	Paclitaxel	above	-	-
	Pembrolizumab	above	negative	positive
Small intestine	Nab-paclitaxel*	-	-	-
	Pembrolizumab	above	negative	positive
Biliary	mFOLFIRI	-	-	-
	mFOLFOX	above	-	-
	Pembrolizumab	below	positive	positive

*FOLFOX/FOLFIRI proxy

Abbreviations: ICER, incremental cost effectiveness ratio; NHB, net health benefits; WTP, willingness-to-pay; QALY, quality-adjusted life years

Scenario analysis: Endometrial, colorectal cancer (1.2), gastric, small intestine and biliary (1.7)

All tumour site ICERs are below £20,000 per QALY gained

Results do not include confidential comparator discounts

		ICER (vs £20,000 per QALY)	Incremental NHB (£20,000 WTP)	Incremental NHB (£30,000 WTP)
Overall indication (vs SoC):		below	Positive	Positive
Colorectal	Pooled FOLFOX /FOLFIRI	-	-	-
	TAS-102	above	-	-
	Pembrolizumab	below	positive	positive
Endometrial	Paclitaxel	-	-	-
	Doxorubicin	above	-	-
	Pembrolizumab	below	positive	positive
Gastric	FOLFIRI	-	-	-
	Paclitaxel	above	-	-
	Pembrolizumab	below	positive	positive
Small intestine	Nab-paclitaxel*		-	-
	Pembrolizumab	below	positive	positive
Biliary	mFOLFIRI	-	-	-
	mFOLFOX	above	-	-
	Pembrolizumab	below	positive	positive

*FOLFOX/FOLFIRI proxy

Abbreviations: ICER, incremental cost effectiveness ratio; NHB, net health benefits; WTP, willingness-to-pay; QALY, quality-adjusted life years

Scenario analysis: Modelling approach

Scenario	Pembrolizumab modelling	Comparator modelling
Base case	Bayesian hierarchical modelling (BHM)	Parametric survival modelling (PSM)
1*	BHM	Non-responder analysis
2*	BHM - worst case curve (minimises QALYs)	PSM – best case curve (maximises QALYs)
3*	BHM - OS: worst case curve, PFS: piecewise	PSM – best case curve (maximises QALYs)
4	PSM - CRC site, BHM - remaining 4 tumours sites	PSM
5	PSM	PSM

*Worst case exploratory analyses

ICER (vs £20,000 per QALY)		Base case	1	2	3	4	5
Overall indication:		below	above	above	above	below	below
Colorectal	Pooled FOLFOX/FOLFIRI	-	-	-	-	-	-
	TAS-102	above	above	above	above	above	above
	Pembrolizumab	below	above	above	below	below	below
Endometrial	Paclitaxel	-	-	-	-	-	-
	Doxorubicin	above	above	above	above	above	above
	Pembrolizumab	below	above	above	above	below	below
Gastric	FOLFIRI	-	-	-	-	-	-
	Paclitaxel	above	above	above	above	above	above
	Pembrolizumab	above	above	above	above	above	above
Small intestine	Nab-paclitaxel*	-	-	-	-	-	-
	Pembrolizumab	above	above	above	above	above	above
Biliary	mFOLFIRI	-	-	-	-	-	-
	mFOLFOX	above	above	above	above	above	above
	Pembrolizumab	below	below	below	below	below	below

* FOLFOX/ FOLFIRI proxy

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life years

Scenario analysis: Subsequent treatments

Scenario 2 has a large impact on colorectal, gastric and small intestine site ICERs

Scenario	Description
Base case	Subsequent treatments assumed the same in pembrolizumab and comparator arms
1	Double subsequent treatment costs for the pembrolizumab arm
2	Subsequent treatment costs based on proportional difference in survival benefit between arms

ICER (vs £20,000 per QALY)		Base case	1	2
Overall indication:		below	above	above
Colorectal	FOLFOX/FOLFIRI	-	-	-
	TAS-102	above	above	above
	Pembrolizumab	below	below	above
Endometrial	Paclitaxel	-	-	-
	Doxorubicin	above	above	above
	Pembrolizumab	below	below	below
Gastric	FOLFIRI	-	-	-
	Paclitaxel	above	above	above
	Pembrolizumab	above	above	above
Small intestine	Nab-paclitaxel*	-	-	-
	Pembrolizumab	above	above	above
Biliary	mFOLFIRI	-	-	-
	mFOLFOX	above	above	above
	Pembrolizumab	below	below	below

*FOLFOX/FOLFIRI proxy

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Other considerations:

- Company have made a managed access proposal.
- NICE managed access team - further data collection would not resolve the key uncertainties.

NICE National Institute for Health and Care Excellence

Thank you.

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Back up slides

NICE appraisals for MSI-H or dMMR tumours or solid tumours

TA	Drug	Recommendation
NICE TA630 (May 2020)	Larotrectinib	Recommended for use within the CDF as an option for treating NTRK fusion-positive solid tumours in adults and children if: • disease is locally advanced/metastatic or surgery could cause severe health problems and they have no satisfactory treatment options.
NICE TA644 (August 2020)	Entrectinib	Recommended for use within the CDF as an option for treating NTRK fusion-positive solid tumours in adults and children 12 years and older if: • disease is locally advanced/metastatic or surgery could cause severe health problems and they have not had an NTRK inhibitor before and they have no satisfactory treatment options.
NICE TA709 (June 2021)	Pembrolizumab	Recommended as an option for untreated metastatic colorectal cancer with MSI-H/dMMR in adults, only if: pembrolizumab is stopped after 2 years and no documented disease progression
NICE TA716 (July 2021)	Nivolumab with ipilimumab	Recommended as an option for treating metastatic colorectal cancer with MSI-H/dMMR after fluoropyrimidine-based combination chemotherapy.
NICE TA779 (March 2022)	Dostarlimab	Recommended for use within the CDF as an option for treating advanced/recurrent endometrial cancer with MSI-H/dMMR in adults who have had platinum-based chemotherapy.

NICE

Abbreviations: MSI-H, high microsatellite instability; dMMR, mismatch repair deficiency; CDF, Cancer Drugs Fund; NTRK, neurotrophic tyrosine receptor kinase; TA, technology appraisal

Clinical results: Pembrolizumab and comparators

Median (months)		Progression free survival (PFS)	Overall survival (OS)
Colorectal	Pooled FOLFOX / FOLFIRI	4.9	11.5
	TAS-102	2.0	7.2
	Pembrolizumab	4.0 ([redacted])	36.1 (24.0, NR)
Endometrial	Paclitaxel	3.7	8.6
	Doxorubicin	3.7	8.6
	Pembrolizumab	13.1 (4.9, 25.7)	NR (48.0, NR)
Gastric	FOLFIRI	2.5	7.5
	Paclitaxel	3.1	7.9
	Pembrolizumab	4.1 (2,1, 24.6)	26.9 (6.6, NR)
Small intestine	Nab-paclitaxel*	2.2	10.3
	Pembrolizumab	23.4 (4.3, NR)	NR (16.2, NR)
Biliary	mFOLFIRI	2.1	6.3
	mFOLFOX	2.7	5.6
	Pembrolizumab	4.2 (2.1, 24.9)	14.5 (6.5, 44.8)

* FOLFOX/ FOLFIRI proxy

NICE

Abbreviations: NR, not reported; OS, overall survival; PFS, progression free survival

Scenario analysis: No severity modifier

Results do not include confidential comparator discounts

ICER in most tumour sites remains below £30,000 per QALY gained

Probabilistic fully incremental scenario results

		ICER (vs £20,000 per QALY)	Incremental NHB (£20,000 WTP)	Incremental NHB (£30,000 WTP)
Overall indication (vs SoC):		above	negative	positive
Colorectal	Pooled FOLFOX /FOLFIRI	-	-	-
	TAS-102	above	-	-
	Pembrolizumab	below	positive	positive
Endometrial	Paclitaxel	-	-	-
	Doxorubicin	above	-	-
	Pembrolizumab	above	negative	positive
Gastric	FOLFIRI	-	-	-
	Paclitaxel	above	-	-
	Pembrolizumab	above	negative	positive
Small intestine	Nab-paclitaxel*	-	-	-
	Pembrolizumab	above	negative	positive
Biliary	mFOLFIRI	-	-	-
	mFOLFOX	above	-	-
	Pembrolizumab	above	negative	positive

*FOLFOX/FOLFIRI proxy

Abbreviations: ICER, incremental cost effectiveness ratio; NHB, net health benefits; WTP, willingness-to-pay

Exploratory scenario: 100% testing cost

Results do not include confidential comparator discounts

Fully incremental scenario results

		ICER (vs £20,000 per QALY)	Incremental NHB (£20,000 WTP)	Incremental NHB (£30,000 WTP)
Overall indication (vs SoC):		below	positive	positive
Colorectal	Pooled FOLFOX /FOLFIRI	-	-	-
	TAS-102	above	-	-
	Pembrolizumab	below	positive	positive
Endometrial	Paclitaxel	-	-	-
	Doxorubicin	above	-	-
	Pembrolizumab	below	positive	positive
Gastric	FOLFIRI	-	-	-
	Paclitaxel	above	-	-
	Pembrolizumab	above	negative	positive
Small intestine	Nab-paclitaxel*	-		
	Pembrolizumab	above	negative	positive
Biliary	mFOLFIRI	-	-	-
	mFOLFOX	above	-	-
	Pembrolizumab	below	positive	positive

*FOLFOX/FOLFIRI proxy