National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	MSD	We suggest [redacted]	Thank you for your comment. The wording of the draft remit is written as per the current NICE style to ensure consistency across all scopes and appraisals. No changes were made to the scope.
	British Gynaecological Cancer Society	Generally happy, please expand in particular to consider PDL1, TMB and MSI status (see later on)	Thank you. No action required.
	Jo's Cervical Cancer Trust	Yes, we believe so [the wording of the remit is appropriate].	Thank you. No action required.

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Timing Issues	MSD	We anticipate that the proposed appraisal should be scheduled to enable NICE to issue final guidance soon after regulatory approval. Information regarding anticipated regulatory timelines presented in UK PharmaScan accurately reflect current expectations.	Thank you for your comment. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme.
	British Gynaecological Cancer Society	Routine [timing].	Thank you. No action required.
	Jo's Cervical Cancer Trust	There is currently a lack of choice / options for women with late stage cervical cancer with just one life prolonging drug with limited results (e.g. 3-4 months), therefore being able to offer increased options is important. Current chemotherapy options have challenging side effects and therefore a drug that can reduce these and improve quality of life is important. Anecdotally we are hearing reports of an increase in women with advanced stage cancers entering pathways due to later diagnosis as a result of the COVID pandemic and we need to ensure that we are not failing this group.	Thank you for your comment. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme.

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Additional comments on the draft remit	MSD	No further comment.	Noted. No action required.
	British Gynaecological Cancer Society	No additional comments.	Noted. No action required.
	Jo's Cervical Cancer Trust	No additional comments.	Noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	MSD	We suggest a change to the wording used to define the stages for clarity. Locally advanced cancer is defined as stage 1B2 to 4A (1) and metastatic is defined as cervical cancer at stage IVB (2) The word 'metastatic' should be removed from "there were 2,591 newly diagnosed cases of metastatic cervical cancer". The number referenced is the total number of registrations in England during 2017 for cervical cancer. Data from Public Health England (3) shows the percentage of people diagnosed at each stage during 2018 was 46.4% for stage 1, 16.1% stage 2, 6.5% stage 3, 8.8% stage 4 and 22.1% had missing stage information. Using these numbers would mean 228 patients diagnosed in 2017 with stage 4 (metastatic) cervical cancer.	Thank you for your comment. The background section of the scope has been updated to include the definitions of the stages and remove the word 'metastatic'.
	British Gynaecological Cancer Society	Please expand to: 1]include Gynaecologic Oncology Group prognostic model to predict treatment response to cisplatin-based chemotherapy (Black race, Performance status,	Thank you for your comment. The background section of the scope aims to

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		pelvic disease, prior treatment with cisplatin, recurrence within 1 year of diagnosis) (Moore Gynaecol Oncology 2010) 2]the additional benefit that bevacizumab offers when combined to platinum paclitaxel backbone 3]effect of PDL1, TMB-tumour and MSI-H impact on response to pembrolizumab 4]assessment of prior therapies, residual toxicities and performance status in selecting appropriate second line therapy, options include pembrolizumab, chemotherapy and palliative / Best supportive care 5]The published available data is beyond the first line setting. Does company have data in the first line setting?	provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. No changes were made to the scope.
	Jo's Cervical Cancer Trust	Yes [the background information is accurate and complete].	Thank you. No action required.
The technology/ intervention	MSD	Yes [the description of the technology is accurate].	Thank you. No action required.
	British Gynaecological Cancer Society	It [the technology description] needs updating to include particularly Tumour Mutational Burden Data. Also to discuss Microsatellite instability / deficient mismatch repair data	Thank you for your comment. The technology section is intended only to briefly outline the technology; it is not designed to be exhaustive in its detail. No changes were made.
	Jo's Cervical Cancer Trust	We believe so [the description of the technology is accurate].	Thank you. No action required.

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Population	MSD	We suggest “Adults (18 and over)” for clarity. The primary endpoints will be assessed in combined positive score (CPS) ≥1 to <10, ≥10 and all-comers. Currently no data has been presented on outcomes by these groups.	Thank you for your comment. The wording of the population is written as per the current NICE style to ensure consistency across all scopes and appraisals. Ages are only added for children and adolescents. No changes were made to population wording. The combined positive score of PD-L1 expression level has been added to the ‘Other considerations’ section of the scope.
	British Gynaecological Cancer Society	Possibly of Black ethnicity	Thank you for your comment. The committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population.

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	Jo's Cervical Cancer Trust	Yes [the population is defined appropriately].	Thank you. No action required.
Comparators	MSD	We suggest the removal of etoposide in combination with platinum therapy. According to Royal Surrey guidelines (4) this is used in the treatment of small cell cervical cancer (SCCC). SCCC accounts for 3% of all cervical cancers (5). After reviewing publicly available cancer alliance guidelines, we also suggest the removal of 'paclitaxel alone'. Only one Cancer Alliance lists paclitaxel as an option for palliative treatment but in the second line setting. Bevacizumab in combination with paclitaxel and cisplatin or carboplatin, should be included as per BGCS guidelines (6). • Platinum chemotherapy (cisplatin or carboplatin) alone or in combination with paclitaxel or topotecan or etoposide • Paclitaxel alone.	Thank you for your comment. At the scoping stage of the appraisal, identification of comparators should be inclusive. Because etoposide is used in cervical cancer, it has been retained in the scope. Any exclusion from the decision problem in the company submission should be fully justified and will be considered during the course of the appraisal. Following the discussions at the scoping Zoom, bevacizumab in combination with paclitaxel and carboplatin has been added to the scope for people who receive it via the Cancer Drugs Fund. We acknowledge paclitaxel alone is used

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			in second line setting so it has been removed.
	British Gynaecological Cancer Society	First line systemic therapy in the UK is generally accepted to be platinum + taxane +/- bevacizumab. If you wish to look at the combination regimen of Pembro + other SACT in the first line for cervical cancer, then your comparison groups should be: 1] platinum + taxane +bevacizumab (in the UK this is mainly carboplatin + paclitaxel + bevacizumab) 2) platinum taxane without bevacizumab (in the UK this is mainly carboplatin and paclitaxel).	Thank you for your comment. Following the discussions at the scoping Zoom, bevacizumab in combination with paclitaxel and carboplatin has been added to the scope for people who receive it via the Cancer Drugs Fund.
	Jo's Cervical Cancer Trust	Yes [these are the standard treatments currently used in the NHS with which the technology should be compared].	Thank you. No action required.
Outcomes	MSD	We suggest the inclusion of "duration of response"	Thank you for your comment. It is not considered necessary to specify 'duration of response' as an outcome in addition to 'progression-free survival' that is already included in the scope. No changes were made.

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	British Gynaecological Cancer Society	Appropriate outcome data, please also seek any randomised data against chemotherapy.	Thank you. No action required.
	Jo's Cervical Cancer Trust	Yes [these outcome measures capture the most important health related benefits (and harms) of the technology].	Thank you. No action required.
Economic analysis	MSD	None identified, no further comment.	Noted. No action required.
	British Gynaecological Cancer Society	No comments.	Noted. No action required.
	Jo's Cervical Cancer Trust	No comments.	Noted. No action required.
Equality and Diversity	MSD	None identified, no further comment.	Noted. No action required.
	British Gynaecological Cancer Society	Ensure that patients of Black ethnicity are adequately assessed / represented	Thank you for your comment. The population in the scope is 'Adults with untreated recurrent, persistent or metastatic cervical cancer'. The appraisal committee will assess the technology using the data presented to it in the company

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			submission documents. No action required.
	Jo's Cervical Cancer Trust	No comments.	Noted. No action required.
Other considerations	MSD	Patients with squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix were eligible to be recruited to KEYNOTE-826.	Thank you for your comment. Following discussion at the scoping Zoom, adenosquamous carcinoma and poorly differentiated carcinoma have been added to the list of subgroups that will be considered if the evidence allows.
	British Gynaecological Cancer Society	Pembrolizumab for second line cervical cancer systemic therapy is an available option in NCCN guidelines. Technology has the potential to improve outcomes in selected patients with recurrent, persistent or metastatic cervical cancer, such subgroups that are most likely to benefit should be explored as well as overall groups and groups defined by histology (squamous vs adenocarcinomas). 1]include Gynaecologic Oncology Group prognostic model to predict treatment response to cisplatin-based chemotherapy (Black race, Performance status, pelvic disease, prior treatment with cisplatin, recurrence within 1 year of diagnosis) (Moore Gynaecol Oncology 2010)	Thank you for your comment. Following discussions at the scoping Zoom, subgroups defined by histology, pelvic disease status, programmed death-ligand 1 (PD-L1) expression and tumour mutational burden were included in the scope.

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		2]effect of PDL1, TMB-tumour and MSI-H impact on response to pembrolizumab 3]assessment of prior therapies, residual toxicities and performance status in selecting appropriate second line therapy, options include pembrolizumab, chemotherapy and palliative / Best supportive care	Subgroups specified within Gynaecologic Oncology Group prognostic model (except pelvic disease) were not added to the scope because they included groups protected by equality legislation or were not considered relevant to the decision problem. Subgroups defined by microsatellite instability (MSI) were not added because MSI is rare and not assessed in clinical practice.
	Jo's Cervical Cancer Trust	As touched on earlier there is a lack of life prolonging treatments for cervical cancer patients. This treatment would give more equality to patients allowing greater options in terms of advanced stage care that is long overdue.	Thank you. No action required.
Innovation	MSD	MSD considers pembrolizumab to be innovative in its potential to make a significant and substantial positive impact on health-related benefits. Pembrolizumab in combination with chemotherapy has the potential to improve outcomes for patients receiving treatment in adults with recurrent, persistent or metastatic cervical cancer.	Thank you for your comment. The submissions can expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on

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		Pembrolizumab would be the first anti-PD-1 pathway targeting agent to be approved for the first line treatment of adults with recurrent, persistent or metastatic cervical cancer, and would represent a step-change in the management of these patients.	health-related benefits that are unlikely to be included in the QALY calculation during the assessment. No action required.
	British Gynaecological Cancer Society	Technology has the potential to improve outcomes in selected patients with recurrent, persistent or metastatic cervical cancer, such subgroups that are most likely to benefit should be explored as well as overall groups. Please see under Background information.	Thank you for your comment. The submissions can expand on the potential innovative nature of the technology, in particular its potential to make a significant and substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during the assessment. No action required.
	Jo's Cervical Cancer Trust	It would be considered innovative as it is using technology not currently used in the treatment of cervical cancer. Feedback we have received is that the health-related benefits are that it is well tolerated by private patients in the UK as well as throughout Europe with fewer side effects.	Thank you for your comment. The submissions can expand on the potential innovative nature of the technology, in particular its potential to make a significant and

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			substantial impact on health-related benefits that are unlikely to be included in the QALY calculation during the assessment. No action required.
Questions for consultation	MSD	**Have all relevant comparators for pembrolizumab with chemotherapy been included in the scope?** • **Which treatments are considered to be established clinical practice in England for untreated recurrent, persistent or metastatic cervical cancer?** • **What are the most commonly used chemotherapy regimens used in clinical practice for untreated recurrent, persistent or metastatic cervical cancer?** A: We expect the first line treatment used would be systemic chemotherapy with cisplatin/paclitaxel or carboplatin/paclitaxel doublets with or without bevacizumab depending on any patient risk factors as per the BGCS guidelines. **Are the outcomes listed appropriate?** A: Yes; we do however ask that the "Duration of response" is also included in the list of outcomes **Are the subgroups suggested in 'Other considerations' appropriate?** A: No further comment	Thank you for your comment. No action required.

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		Are there any other subgroups of people in whom pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? A: None at this time **Where do you considered pembrolizumab will fit into the existing NICE pathway, Cervical cancer (2018).** A: We anticipate that the use of pembrolizumab in combination with chemotherapy will be in the first line setting. **In particular, please tell us if the proposed remit and scope:** • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which pembrolizumab will be licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access pembrolizumab;** • **could have any adverse impact on people with a particular disability or disabilities.** **Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.** A: No impact **Do you consider pembrolizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?**	

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		A: Yes **Do you consider that the use of pembrolizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** A: We do not consider that there will be substantial health-related benefits that are unlikely to be included in the QALY calculation. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** N/A **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** A: None.	
	British Gynaecological Cancer Society	No comments.	Noted. No action required.
	Jo's Cervical Cancer Trust	No comments.	Noted. No action required.
	MSD	No further comment.	Noted. No action required.

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Additional comments on the draft scope	British Gynaecological Cancer Society	No comments.	Noted. No action required.
	Jo's Cervical Cancer Trust	No comments.	Noted. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Novartis Pharmaceutical UK Ltd