National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency ID3802

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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 *Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.*	GSK	Suggested wording is as follows: "[redacted]"	Comment noted. The wording has been updated in light of the comment. It is also kept broad to accommodate any further changes in the marketing authorisation.
	BGCS	Yes	Comment noted. No action required.
Timing Issues	GSK	The proposed submission date of the technology is March 2021. The NHS would benefit from appraisal of this technology at this time due to a high level of unmet need driven by the lack of effective, approved treatment options in	Comment noted. The timing of the technology appraisal is aligned with

Section	Consultee/ Commentator	Comments [sic]	Action
What is the relative urgency of this appraisal to the NHS?		this indication. There has to date been no NICE guidance issued for a medicine in the treatment of endometrial cancer. Of additional note, NHSE recently made the decision to fund nivolumab as an interim treatment option for a similar cohort of endometrial cancer patients. This decision was made to allow for greater flexibility in the management of cancer during COVID-19 pandemic to ensure clinicians have additional treatment options through this time[1]. NHSE's decision to provide a medicine outside of its licensed indication, which has not been referred for NICE appraisal, firstly highlights the vast unmet need in this patient population and, secondly highlights the enthusiasm in the UK clinical community for an immuno-oncology treatment option for this patient population. **References** 1. NHS England interim treatment options during the COVID-19 pandemic (2020). Available at: https://www.nice.org.uk/guidance/ng161/resources/nhs-england-interim-treatment-changes-during-the-covid19-pandemic-pdf-8715724381. Accessed October 2020.	the anticipated regulatory timeline, to provide guidance as soon as possible after regulatory approval. No action required.
	BGCS	There is some urgency with this appraisal. During the Covid pandemic there has been temporary approval for the use of nivolumab in this patient cohort, but without this there will not be the option of immunotherapy despite the effectiveness of the treatment.	Comment noted. The timing of the technology appraisal is aligned with the anticipated regulatory timeline, to provide guidance as soon as possible after regulatory approval. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information *Consider the accuracy and completeness of this information.*	GSK	*Paragraph three* The draft scope should reference the unfavourable prognosis for patients diagnosed with advanced/recurrent endometrial cancer: only 15% of women diagnosed with late-stage disease survive for ≥5 years compared to 92% of women diagnosed at early stage[2]. The median overall survival of women with recurrent, advanced endometrial cancer is reported to be less than 12 months, with progression-free survival ranging from 3 to 6 months based on histology[3-5]. The draft scope states that 17% of EC are mismatch repair deficiency and MSI-High, however, the recently published PETAL study[6] suggests that this may be higher at approximately 26% (Table 4: 132/500 tumours). *Paragraph four* This section focuses on the first treatment of endometrial cancer, and therefore does not sufficiently describe the unmet clinical need in previously treated advanced/recurrent EC which is addressed by dostarlimab. Suggested additional wording: *"No standard of care exists for patients with advanced or recurrent endometrial cancer once they have progressed on or after platinum containing chemotherapy. There are currently no medicines licensed for use within this setting nor are there any NICE guidelines. The BGCS professional guideline contains scant recommendations, which are based on low grade evidence; advising "Second line chemotherapy can be considered in fit patients as either a re-challenge with carboplatin and paclitaxel if the*	Comments noted. Paragraph three References 2 and 6 have been added to the updated scope. Paragraph four Further detail has been added on the treatment of previously treated advanced or recurrent endometrial cancer.

Section	Consultee/ Commentator	Comments [sic]	Action
		treatment free-interval is more than six months, or single agent chemotherapy if less than six months or less fit patients. (Grade D)[7]". The last sentence of this section should be revised to more accurately describe the position of hormone therapy within the endometrial cancer treatment pathway. Suggested wording: *"Hormone therapy is utilised in endometrial cancer in two ways: 1) premenopausal endometrial hyperplasia and early-stage endometrial cancer[8] and 2) as a treatment for advanced endometrial cancer patients unfit for chemotherapy[7]."* **References** 2. Cancer Research UK Uterine Cancer Statistics (2017). Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer#heading-Two. Accessed October 2020. 3. Makker, V., Green, A.K., Wenham, R.M., et. al. New therapies for advanced, recurrent, and metastatic endometrial cancers. Gynecologic oncology research and practice. 2017; 4:19. 4. Huijgens, A. N., & Mertens, H. J. (2013). Factors predicting recurrent endometrial cancer. Facts, views & vision in ObGyn, 5(3), 179–186. 5. Muggia, Franco & Blessing, John & Sorosky, Joel & Reid, Gary. (2002). Phase II Trial of the Pegylated Liposomal Doxorubicin in Previously Treated Metastatic Endometrial Cancer: A Gynecologic Oncology Group Study. Journal of Clinical Oncology: American Society of Clinical Oncology. 20(9). 2360-4. 6. Ryan NAJ, McMahon R, Tobi S, Snowsill T, Esquibel S, et al. (2020) The proportion of endometrial tumours associated with Lynch	

Section	Consultee/ Commentator	Comments [sic]	Action
		syndrome (PETALS): A prospective cross-sectional study. PLOS Medicine 17(9): e1003263. 7. British Gynaecological Cancer Society BGCS Uterine Cancer Guidelines: Recommendations for practice (2017). Available at: https://www.bgcs.org.uk/wp-content/uploads/2019/05/BGCS-Endometrial-Guidelines-2017.pdf. Accessed October 2020. 8. Gressel, G.M., Parkash, V. and Pal, L. (2015), Management options and fertility-preserving therapy for premenopausal endometrial hyperplasia and early-stage endometrial cancer. International Journal of Gynecology & Obstetrics, 131: 234-239.	
	BGCS	The background could also include the data for other immunotherapy agents in MMRd endometrial cancer	Comments noted. The background section aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. No changes made.
The technology/ intervention *Is the description of the technology or technologies accurate?*	GSK	Dostarlimab monotherapy ([redacted], GlaxoSmithKline)	Comment noted. As no confidential information will be released in published document, no changes made.
	BGCS	Yes. New patients with endometrial cancer should be having assessment of MMR status done routinely. There may be patients who relapse for whom it may be necessary to test the tumour (very straightforward).	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Population *Is the population defined appropriately? Are there groups within this population that should be considered separately?*	GSK	Please change to: [redacted]	Comment noted. The population in the scope has been updated in line with the comment.
	BGCS	The population needs to be more clearly defined – is this for patients who have received prior chemotherapy at any time (ie including adjuvant treatment) or only for second line treatment (including recurrence within 6 months of adjuvant platinum based chemotherapy). Would POLE mutant tumours also be included?	Comment noted. During the scoping teleconference, the company clarified that the population is patients who have received prior chemotherapy at any time (including adjuvant treatment), and that people with POLE-mutated tumours are not included.
Comparators *Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be*	GSK	As there is no standard of care for patients once they have progressed on platinum containing chemotherapy, a basket of chemotherapies is likely to be the most appropriate comparator. GSK have undertaken extensive insights gathering exercises through literature searches and with key opinion leaders to understand which treatments are most commonly used in this population. Chemotherapy: 1) *Carboplatin and paclitaxel*	Comments noted. Stakeholders noted during the scoping teleconference that there is no standard of care for patients at this stage, and the use of current treatment options is not supported

described as 'best alternative care'?		**Suggest inclusion** - Expert opinion is that for the majority of patients, carboplatin and paclitaxel will be used as a doublet platinum therapy, which is also highlighted in the BGSC guideline[7].
		2) Doxorubicin
		Suggest inclusion - Expert opinion is that doxorubicin is a comparator, with both the solution for infusion and pegylated liposomal formulations, used in this patient cohort.
		3) *Paclitaxel monotherapy*
		Suggest inclusion - The use of weekly paclitaxel is only supported by anecdotal evidence; but based on its useful activity in ovarian cancer and tolerability, it is an option for selected patients in this patient cohort[7].
		4) *Cyclophosphamide*
		Suggest exclusion - Expert opinion is that cyclophosphamide is not used in this patient cohort and is not a relevant comparator.
		5) Cisplatin
		Suggest exclusion - Expert opinion is that cisplatin monotherapy is not used in this patient cohort and is not a relevant comparator.
		6) Carboplatin
		Suggest exclusion - Expert opinion is that patients who could tolerate carboplatin would be administered carboplatin and paclitaxel combination therapy.
		Hormone therapy – **Suggest exclusion**
		• As mentioned above, hormone therapy is utilised in endometrial cancer in early presenting hormone receptor positive disease. The clinical profile of the patients treated with the hormone therapy is different than the profile of patients in the dostarlimab scope. Furthermore, 50% of patients in the GARNET study had already been
			by robust evidence. Following the discussion, the following comparators have been included in the updated scope:
			• Chemotherapy, including:
			  • carboplatin combined with paclitaxel
			  • paclitaxel monotherapy
			  • doxorubicin monotherapy
			  • carboplatin monotherapy
			• Hormone therapy
			• Best supportive care.
			Carboplatin monotherapy, hormone therapy and best supportive care remain in the updated scope to keep the comparator section inclusive.
			The following comparators have been

Section	Consultee/ Commentator	Comments [sic]	Action
		treated with hormone therapy, demonstrating how it is used at an earlier point in the treatment pathway. • Hormone therapy use in the advanced or recurrent population tends to be reserved for patients not fit for chemotherapy as a palliative treatment as there is no sufficient evidence that hormonal treatment in patients with advanced or recurrent endometrial cancer improves overall survival[7,9,10]. Best supportive care (BSC) – **Suggest exclusion** BSC for this population is not clearly defined. Other care options would include palliative care and surveillance. These options would be considered for patients who would not be able to tolerate further chemotherapy, would be unlikely to have a favourable outcome with further chemotherapy or do not wish to have further treatment. This group of patients would not be considered for treatment with immunotherapies and therefore, BSC is not a suitable comparator for dostarlimab. References: 9. Kokka F, Brockbank E, Oram D, Gallagher C, Bryant A. Hormonal therapy in advanced or recurrent endometrial cancer. Cochrane Database Syst Rev 2010(12):CD007926. 10. Ethier JL, Desautels DN, Amir E, et al. Is hormonal therapy effective in advanced endometrial cancer? A systematic review and meta-analysis. Gynecol Oncol 2017;147(1):158-66.	excluded from the updated scope: cyclophosphamide, cisplatin, radiotherapy and surgery.

Section	Consultee/ Commentator	Comments [sic]	Action
	BGCS	There is no established second line treatment for endometrial cancer. These are all options depending on prior treatments, but there is a large unmet need as outcome so poor with any of these as second line treatment. Radiotherapy and surgery would not be a comparator as they are used for localised relapse and would still be the treatment of choice if appropriate.	Comment noted. Following the discussion at the scoping teleconference, radiotherapy and surgery have been removed as comparators in the updated scope.
Outcomes *Will these outcome measures capture the most important health related benefits (and harms) of the technology?*	GSK	GSK agrees with the proposed outcome measures. Also, to be included: • *Duration of response* As an additional outcome measure to capture the durable and long-term duration of response for patients in this indication.	Comment noted. Duration of response has been added as an outcome measure.
	BGCS	Yes.	Comment noted. No action required.
Economic analysis *Comments on aspects such as the appropriate time horizon.*	GSK	*Paragraph 4* The inclusion of diagnostic testing for microsatellite instability status should be removed from the scope of the economic analysis for the following reasons: • Section 5.9 of the Guide to the Methods of Technology Appraisals referenced in this section of the scope refers to companion diagnostics. No additional companion diagnostics will be required to facilitate the prescribing of dostarlimab.	Comment noted. Stakeholders at the scoping teleconference noted that the testing and identification of dMMR/MSI-H is often available at large centres, although the roll-out across the

Section	Consultee/ Commentator	Comments [sic]	Action
		• Nivolumab is being funded as an interim treatment option for a similar cohort of endometrial cancer patients to allow for greater flexibility in the management of cancer during COVID-19 pandemic which includes the testing required to identify MSI-H or dMMR positive endometrial cancer patients, and therefore should not be assumed as a new cost associated with dostarlimab[1,11]. Testing strategies to identify dMMR/MSI-H positive endometrial cancer patients are proposed to become standard with NICE guidance due to be published on 28th October 2020[12]. BGCS guidelines[7] suggest routine testing for mismatch repair proteins may need to be incorporated into standard care in the UK NHS in the near future. **References** 11. NHS England. National Cancer Drugs Fund List (2020). Available at: https://www.england.nhs.uk/wp-content/uploads/2020/09/national-cdf-list-ver1.169.pdf. Accessed October 2020.	country following DG42 may vary. Where relevant, identification and diagnosis of the condition and the implications of that for the economic modelling may be considered by the committee. The scope remains unchanged.
	BGCS	No additional comments.	Comment noted. No action required.
Equality and Diversity *NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected*	GSK	There are no equality issues identified at this stage.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. 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 [the treatment(s)] is/are/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 the technology;* • *could have any adverse impact on*			

Section	Consultee/ Commentator	Comments [sic]	Action
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.*			
Other considerations *Suggestions for additional issues to be covered by the appraisal are welcome.*	GSK	No additional comment.	Comment noted. No action required.
Innovation *Do you consider the technology 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)?*	GSK	Dostarlimab is a targeted therapy for patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen. There are limited treatment options for previously treated advanced or recurrent endometrial cancer patients. There is no standard of care in the UK clinical setting. Dostarlimab is an innovative technology as it will offer a licensed treatment option to women with advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency. At present, there is no other licensed treatment in Europe. Data from the GARNET trial has been shared at international oncology congresses and locally with experts in this field. The feedback has consistently been that the duration of response and the overall response rate seen with dostarlimab is markedly different than that seen with existing treatment options. Dostarlimab would be a 'step-change' in	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Do you consider that the use of the technology can result in any potential significant and 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.		the management of women with advanced or recurrent endometrial cancer, whose prognosis is poor with current treatment options – *Office for National Statistics cancer survival statistics show that 46% of women diagnosed with late-stage disease survive for ≥1 year*[12,13]. [redacted]. **References** 12. NICE Diagnostics Assessment Programme. Testing strategies for Lynch syndrome in people with endometrial cancer. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-dg10033. Accessed October 2020. 13. Office for National Statistics. Cancer survival by stage at diagnosis for England (2019). Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed. Accessed October 2020.	
	BGCS	Yes. This would offer a significant step forward in treatment for patients with advanced endometrial cancer. Chemotherapy has low response rates and significant toxicity (particular high incidence of persistent peripheral neuropathy).	Comment noted. No action required.
Questions for consultation *Please answer any of the questions for*	GSK	We do not consider radiotherapy and surgery as relevant comparators in this patient population of advanced or recurrent endometrial cancer.	Comment noted. Radiotherapy and surgery have not been included as comparators in the updated scope.

Section	Consultee/ Commentator	Comments [sic]	Action
consultation if not covered in the above sections. If appropriate, please include comments on the proposed process this appraisal will follow (please note any changes made to the process are likely to result in changes to the planned timelines).	BGCS	The additional question would be whether this should be an option for first line relapse with MMRd tumours.	Comment noted. The technology will be appraised in line or within its marketing authorisation.

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

Novartis