National Institute for Health and Care Excellence

Health Technology Evaluation

Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer ID6138
Response to stakeholder organisation comments on the draft remit and draft scope

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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Merck Sharp & Dohme (MSD)	MSD agrees the appropriate route is a single technology appraisal.	No action required.
Wording	MSD	The wording of the remit reflects the issues about the appraisal.	No action required.
Timing Issues	MSD	This indication will be the first to be appraised by NICE where an immunotherapy is combined with chemoradiotherapy for cervical cancer.	Comment noted. No action required.
Additional comments on the draft remit	MSD	No comments	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	MSD	• "…which gives rise to 2 subtypes of cancer." There are more than 2 subtypes of cervical cancer (1) MSD suggests changing the wording to "which gives rise to 2 **main subtypes of cervical cancer**". • "The human papilloma virus (HPV) is a major cause of the main types of cervical cancer…" HPV is detected in 99% of cervical cancer cases. (2) MSD suggests changing the wording to "HPV is **the main** cause…" • "High-risk cervical cancer is defined as lymph node positive, with parametrial involvement and positive margins" The BGCS definition of high risk used here alludes to patients who have received surgery ("positive margins"). For locally advanced cervical cancer "surgery is not recommended as it is unlikely to be curative, and the combination of radical surgery and chemoradiotherapy has a high risk of adverse effects and associated morbidity." (3) KEYNOTE-A18 did not recruit patients who had received definitive surgery. (4) Therefore this definition is not relevant to this appraisal. Also the definition only includes lymph node positive patients. KEYNOTE-A18 recruited some stage III-IVA patients who were lymph node negative.	Thank you for your comments. The background information was amended in line with the suggestions from the initial scope consultation. No action required.
Population	MSD	MSD suggests a change to the population wording to be line with the anticipated licence: [redacted]	Comment noted. NICE will appraise pembrolizumab within the terms of its

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			marketing authorisation. No action needed.
Subgroups	MSD	**Histology**: KEYNOTE-A18 does include the histologies mentioned in the scope, however the trial was not powered to investigate any potential differences between these groups. MSD's understanding is that treatment in practice would not be different depending on histology. **CPS**: MSD is unclear as to why a cut off of CPS≥10 has been suggested. Data presented at ESMO 2023 showed 94% of the KEYNOTE-A18 participants were CPS≥1. In addition the objectives of the trial do not include assessing outcomes by CPS status. The proposed licence for KEYNOTE-A18 is not restricted by CPS. Therefore MSD do not consider CPS subgroups to be appropriate. **TMB**: Clinical efficacy based upon Tumour Mutational Burden is not a primary or secondary objective in KEYNOTE-A18. Therefore this data will not be available. It's relevance to this appraisal is unclear.	Comments noted. These subgroups are consistent with previous appraisals in this disease area and will only be considered if evidence allows.
Comparators	MSD	The standard of care is chemoradiotherapy (including cisplatin). The British Gynaecological Cancer Society Cervical Cancer guidelines (2020) recommends • "External beam radiation should be planned to use newer technologies • Concurrent platinum-based chemotherapy should usually be administered • Brachytherapy remains an integral part of the treatment • …Single agent radio-sensitising chemotherapy, preferably cisplatin (weekly 40 mg/m2) should be used unless contraindicated." Therefore MSD agrees with the comparator proposed.	No action required

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Outcomes	MSD	The list of outcomes to be considered are appropriate.	No action required
Equality	MSD	At its clinical advisory board, the company heard about substantial health inequalities related issues for women with stage III-IVa locally advanced cervical cancer, which are related to this patient group's comparative lack of engagement with the national screen programme. These are outlined below in the 'other considerations' section.	Comment noted. The committee will consider any equalities issues during the appraisal. No action required.
Other considerations	MSD	In 2023, the gap in cervical screening uptake was 9.8% between the least and most deprived IMD deciles in England (years 25 to 49).(5) Similarly 2022 age standardised rates of cervical cancer diagnosis were 12.1 per 100,000 in the most deprived quintile compared with 7.3 in the least deprived, a 65% difference between both quintiles.(6) A systematic review by Wearn and Shepard (2024) also highlights that the determinants for screening uptake stretch beyond simply deprivation, with cultural differences and language barriers also contributing to lower screening uptake. (7) Due to the close link between cervical screening uptake and cervical cancer incidence, especially late stage where patients often do not present until the disease has become symptomatic, clinical advice to MSD is that that the availability of additional life extending treatments in this indication would act to reduce inequalities in cancer survival time for the most deprived, ethnic minorities, and those that do not have English as a first language, as well as all groups that are less likely to engage with screening and the health care system as a whole. Relatedly, clinical advisers highlighted that a	Comment noted. See response to equality section.

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		disproportionate number of advanced cervical cancer cases are among migrant women versus those born in the UK.	
Questions for consultation	MSD	*Which treatments are considered to be established clinical practice in the NHS for high risk, locally advanced cervical cancer?* • Please see response to comparator section above. *Where do you consider pembrolizumab with chemoradiation will fit into the existing care pathway for untreated high-risk locally advanced cervical cancer?* • MSD considers pembrolizumab with chemoradiation will be used in place of chemoradiation without pembrolizumab. *Are the subgroups suggested appropriate? 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?* • Please see response to subgroup section above. *Would pembrolizumab with chemoradiation be a candidate for managed access?* • MSD considers pembrolizumab with chemoradiation is a potential candidate for managed access if the committee is unable to make a recommendation for routine commissioning.	No action required. No action required. See response on subgroups section. Comment noted. No action required at this stage.

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		Do you consider that the use of pembrolizumab with chemoradiation can result in any potential 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 committee to take account of these benefits.* • MSD considers relevant health benefits will be captured in the QALY calculation.	No action required
Additional comments on the draft scope	MSD	No comments	No action required

References

1. Cancer Research UK. Types and grades of cervical cancer, 2023. Available from: https://www.cancerresearchuk.org/about-cancer/cervical-cancer/stages-types-grades/types-and-grades. [Accessed 14 Dec 2023]
2. NICE. Cervical cancer and HPV: What causes it? , 2022. Available from: https://cks.nice.org.uk/topics/cervical-cancer-hpv/background-information/causes/. [Accessed 14 Dec 2023]
3. NICE. Cervical cancer and HPV: Scenario Management, 2022. Available from: https://cks.nice.org.uk/topics/cervical-cancer-hpv/management/management/. [Accessed 14 Dec 2023]
4. Merck Sharp & Dohme LLC. Study of Chemoradiotherapy With or Without Pembrolizumab (MK-3475) For The Treatment of Locally Advanced Cervical Cancer, 2023. Available from: https://clinicaltrials.gov/study/NCT04221945#participation-criteria. [Accessed 14 Dec 2023]
5. Cancer Research UK. Health inequalities: Breaking down barriers to cancer screening, 2022. Available from: https://news.cancerresearchuk.org/2022/09/23/health-inequalities-breaking-down-barriers-to-cancer-screening/. [Accessed 29th November 2024]
6. NHS Digital. Cancer Registration Statistics, England, 2022, 2024. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2022. [Accessed 25th November 2024]

7. Wearn A, Shepherd L. Determinants of routine cervical screening participation in underserved women: a qualitative systematic review. Psychol Health. 2024;39(2):145-70.

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

N/A