# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Final draft guidance

# Pembrolizumab with chemoradiotherapy for untreated locally advanced cervical cancer

## 1 Recommendations

1.1 Pembrolizumab with chemoradiotherapy (external beam radiation therapy followed by brachytherapy) can be used, within its marketing authorisation, as an option for untreated International Federation of Gynecology and Obstetrics (FIGO) 2014 stages 3 to 4A locally advanced cervical cancer in adults. Pembrolizumab can only be used if the company provides it according to the commercial arrangement (see section 2).

### What this means in practice

Pembrolizumab with chemotherapy must be funded in the NHS in England for the condition and population in the recommendation, if it is considered the most suitable treatment option. It must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that pembrolizumab with chemoradiotherapy provides benefits and value for money, so it can be used routinely across the NHS in this population.

### Why the committee made this recommendation

Usual treatment for FIGO 2014 stages 3 to 4A locally advanced cervical cancer is chemoradiotherapy.



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Clinical trial evidence shows that pembrolizumab with chemoradiotherapy increases how long people have before their cancer gets worse and how long they live compared with chemoradiotherapy alone.

Despite uncertainties in the economic model, the cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, pembrolizumab plus chemoradiotherapy can be used.

# 2 Information about pembrolizumab

## Marketing authorisation indication

2.1 Pembrolizumab (Keytruda, MSD) 'in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of FIGO 2014 Stage 3 – 4A locally advanced cervical cancer in adults who have not received prior definitive therapy'.

## Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for pembrolizumab.

## Price

2.3 Pembrolizumab costs £2,630 per 100-mg vial (excluding VAT; BNF online accessed January 2026), or around £91,000 for a year of treatment.

2.4 The company has a commercial access agreement. This makes pembrolizumab available to the NHS with a discount. The size of the discount is commercial in confidence.

## Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for MSD will be included here when guidance is published.



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# 3 Committee discussion

The evaluation committee considered evidence submitted by MSD, a review of this submission by the external assessment group (EAG) and responses from stakeholders. See the committee papers for full details of the evidence.

## Locally advanced cervical cancer

3.1 Locally advanced cervical cancer refers to cervical cancer that has spread beyond the cervix but is still confined to the pelvic region, without distant metastasis. It typically includes International Federation of Gynecology and Obstetrics (FIGO) stages 3 to 4A, in which the condition may involve:

- the pelvic wall
- the lower third of the vagina
- nearby organs like the bladder or rectum.

These stages are associated with a significantly poorer prognosis compared with early-stage cancer, making treatment more complex and urgent. The company submitted results from a 2016 survey from Jo's Cervical Trust of 35 women diagnosed with cervical cancer. The women reported an often challenging and disruptive experience. After diagnosis, many felt isolated when having to make decisions and worried about future fertility. They said treatment, particularly chemoradiotherapy and radiotherapy, was physically and emotionally demanding, with common side effects such as nausea, fatigue, anxiety and feelings of loneliness. These effects markedly affected daily life, including family routines, intimate relationships and employment, sometimes leading to early retirement. Financial burdens because of increased living costs and loss of income added to the stress of managing the condition. The committee concluded that there is a high disease burden for people with locally advanced cervical cancer.



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# Clinical management

## Treatment options

3.2 Usual treatment for locally advanced cervical cancer is chemoradiotherapy, which combines external beam radiotherapy (EBRT) and brachytherapy with weekly cisplatin chemotherapy. If the cancer recurs or spreads and tumours express PD-L1 with a combined positive score (CPS) of at least 1, a subsequent option is pembrolizumab plus chemotherapy. This is in line with NICE's technology appraisal guidance on pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer (from here TA939). Other options are chemotherapy alone or no further active treatment. The clinical experts explained that the goal of chemoradiotherapy is cure, with a complete response expected at around 3 months, and relapse typically occurs early. One clinical expert noted that cure rates with standard chemoradiotherapy are considered good. But around 20% to 25% of people have a relapse or are not fully cured, leaving scope for improvement. For stages 3 to 4A of cervical cancer, 1 expert estimated the chance of cure as being under 50%, making treatments that increase cure rates particularly important. The clinical experts suggested that adding pembrolizumab to chemoradiotherapy could lead to a cure in 10% to 15% more people. The committee concluded that there is an unmet need for treatments that improve cure rates in locally advanced cervical cancer. It agreed that standard chemoradiotherapy without pembrolizumab is the relevant comparator, in line with the NICE scope.

# Clinical effectiveness

## Key clinical trial: KEYNOTE-A18

3.3 The main clinical evidence was from KEYNOTE-A18, which was an international, phase 3, double-blind, randomised, placebo-controlled trial. It compared pembrolizumab plus chemoradiotherapy with placebo plus chemoradiotherapy for untreated locally advanced cervical cancer. In line



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with the marketing authorisation, the company presented data from people with FIGO 2014 stages 3 to 4A cancer. The final analysis of the trial showed that adding pembrolizumab to chemoradiotherapy statistically significantly improved progression-free survival, with a hazard ratio of 0.63 (95% confidence interval 0.48 to 0.82; p=0.0002). It also statistically significantly improved overall survival, with a hazard ratio of 0.64 (95% confidence interval 0.46 to 0.88; p=0.0031). The committee concluded that adding pembrolizumab to standard chemoradiotherapy for locally advanced cervical cancer statistically significantly improved progression-free and overall survival.

## Generalisability of KEYNOTE-A18 to the NHS

3.4 The EAG thought that KEYNOTE-A18 was broadly relevant to the NHS population of stages 3 to 4A locally advanced cervical cancer. But it noted some differences:

- The chemoradiotherapy regimen used in KEYNOTE-A18 (cisplatin, EBRT, brachytherapy) reflected UK practice. But the total radiation dose in the trial was lower than that recommended in current NHS guidelines. This introduced uncertainty about whether relative treatment effects would differ if higher doses were used in practice.
- KEYNOTE-A18 used the FIGO 2014 staging system, whereas UK practice now uses FIGO 2018. The EAG's clinical experts said that mapping from FIGO 2014 to 2018 was possible.

The clinical experts at the committee meeting said that KEYNOTE-A18 was applicable to NHS clinical practice in terms of the population and the treatment the participants had. They explained that it can be difficult to treat locally advanced cervical cancer with an adequate dose of radiation in clinical practice, so patients may not have the recommended dose. At consultation, 1 clinical expert said that, although the trial permitted some lower radiotherapy doses (primarily for the Japan cohort), median delivered doses were comparable to



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those in UK practice. The committee acknowledged the differences identified by the EAG but was satisfied that KEYNOTE-A18 was applicable to NHS clinical practice.

## Subsequent treatments

3.5 The EAG noted that a large proportion of people with disease progression in KEYNOTE-A18 had subsequent treatment. The subsequent treatment mix was very different from what people would normally have in the NHS. The company considered the exact proportions of people who had subsequent treatment, and the treatments they had, to be confidential so they cannot be reported here. The clinical experts said that people who have not had a complete response to chemoradiotherapy in the first 3 months (as noted in section 3.2, around 50% are likely to have a relapse) are offered palliative chemotherapy with pembrolizumab, in line with TA939.

The company noted in its submission that retreatment with immunotherapy was only allowed on the NHS if the cancer progresses at least 6 months after the initial course of pembrolizumab is finished. The committee queried whether someone who had first-line pembrolizumab alongside chemoradiotherapy could be offered pembrolizumab again, and whether there would be any benefit. It noted that the EAG's clinical experts had mixed views on retreatment with pembrolizumab. One said they were unlikely to use it again because there was no evidence to support its efficacy and safety. Another said that they might consider retreatment, given the limited treatment options available in the second-line setting.

The clinical experts at the committee meeting said that they had not seen any evidence of benefit from offering pembrolizumab again, so were not sure of its value. They said that the preference was to use it with the aim of a cure earlier in the pathway. The NHS England clinical lead said that pembrolizumab was available as a second-line treatment to allow clinical



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choice. The committee concluded that there was a lack of evidence for the value of pembrolizumab retreatment, and that the extent of its use and potential benefit in clinical practice for cervical cancer is uncertain.

## Economic model

### Company's modelling approach

3.6 The company's original economic model took a cohort-level semi-Markov approach, with 4 health states:

- progression free
- progressed disease 1
- progressed disease 2
- death.

Clinical data from KEYNOTE-A18 was used for transitions from the progression-free health state. Data from the KEYNOTE-826 trial (see section 3.10) for transitions after progression. The EAG said it was broadly satisfied with the model. But the need for calibration to fit overall survival (see section 3.10) and uncertainty about long-term benefits (see section 3.7) and cure assumptions (see section 3.8) made the results highly uncertain. The committee agreed that the results of the model were highly uncertain (see section 3.8 and section 3.10).

After consultation on the draft guidance, the company submitted a new model with 3 health states, progression free, progressed disease and dead, using data from KEYNOTE-A18 for transitions after progression. The company said it changed its model from a 4-state to a 3-state model because the data from KEYNOTE-A18 was too immature to be used in a 4-state model. That is, there was not enough data to provide reliable estimates of treatment effect. It preferred to use the full post-progression dataset to maintain patient numbers, rather than splitting them into the separate transitions needed for a 4-state model and so



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smaller, less reliable subsets. The committee thought that the updated model also had a high degree of uncertainty associated with it (see sections 3.11 to 3.13).

## Long-term survival modelling

3.7 The company's original submission estimated long-term progression-free survival and time to progression using standard parametric models based on the interim analysis of KEYNOTE-A18. At clarification, the company updated its analyses, using flexible parametric survival models, based on the final analysis of KEYNOTE-A18. It chose a 1-knot odds restricted cubic spline (RCS) model to estimate progression-free survival in the placebo plus chemoradiotherapy arm. This was because it was the best statistical fit and had a good hazard fit. It chose the same model for the pembrolizumab plus chemoradiotherapy arm for consistency. The company also estimated time to progression using 1-knot odds RCS models for both treatment arms, again for consistency with the progression-free survival modelling.

The company got clinical expert advice on the plausibility of the survival curves based on interim data from the original company submission. But it did not get clinical input on the updated curves. The EAG's clinical experts said that the predictions from the 1-knot odds RCS models were reasonable. But they thought that longer follow up was needed to be confident the benefits would be maintained long term. The EAG noted that the model-predicted overall survival did not reflect that of the final results of KEYNOTE-A18 (see section 3.10). It said that further input from clinical experts about the plausibility of the company's modelled progression-free survival and overall-survival estimates would be valuable. The clinical experts at the committee meeting agreed with the EAG's clinical experts that the estimated survival curves for progression-free survival and time to progression looked plausible and in line with their experience. The committee concluded that the results for progression-free survival and



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time to progression using the 1-knot odds RCS model (company's and EAG's base cases) were clinically plausible.

## Cure assumption

3.8 Based on clinical advice, the company's original economic model assumed that some people in both treatment groups (pembrolizumab plus chemoradiotherapy and chemoradiotherapy alone) would be cured after initial treatment. From year 5, the probability of progression declined, reaching a 95% reduction by year 7 and staying at 5% from then on. For anyone considered cured, the transition to progressed disease was set to zero, and mortality risk matched that of the general population (adjusted using a standardised mortality ratio for cancer survivors). These cure assumptions applied only to first-line treatments and not after progression. The company said that these assumptions reflected clinical practice. That is, if someone's cervical cancer has not come back by 5 years, they are typically discharged and considered functionally cured.

The EAG noted that the way cure was implemented in the model was based on arbitrary assumptions and that the proportion of people who may be cured was uncertain. It said that the company could have used an evidence-based approach to estimate cure, by attempting a mixture cure approach. The company thought that its assumptions were robust, given the trial follow up and the natural history of locally advanced cervical cancer. The clinical experts agreed that it was appropriate to assume a proportion of people are cured. They said that, usually, if someone remained progression free for 2 to 3 years, they were likely to be cured. They added that occasionally someone could relapse after 5 years, but this was rare. As noted in section 3.2, in their experience, around 50% of people are cured with chemoradiotherapy, and adding pembrolizumab would increase this. The committee agreed that a cure assumption was appropriate in principle, but that the assumptions used to implement cure were not evidence based.



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After consultation on the draft guidance, the company retained its original cure assumption. It clarified that the modelled cure proportions estimated that around 9% more people would be cured if pembrolizumab was added to chemoradiotherapy. But it also provided supporting evidence from mixture cure models of progression-free survival, as requested by the committee. It did not carry out mixture cure modelling for overall survival. It said that this was because the overall-survival data from KEYNOTE-A18 was too immature (and no further data cuts were expected). But the company suggested that progression-free survival was linked to overall survival, so progression-free survival benefits implied overall-survival benefits.

The mixture cure model distributions generally showed higher cure proportions for pembrolizumab plus chemoradiotherapy than for chemoradiotherapy alone. The exceptions were generalised gamma and Gompertz, which generated implausibly low cure estimates. The company did a sensitivity analysis censoring all events after 200 weeks. This was to test the robustness of the mixture-cure model results and to explore how a small number of late events might affect the cure proportion. The difference in cure fractions remained and was larger than the original mixture-cure model results. The EAG said that the company's mixture cure modelling was useful and supported its cure assumption. It agreed that mixture cure modelling for overall survival was likely to be very uncertain. It thought that the company's assertion of a link between overall and progression-free survival was broadly reasonable. This was based on advice from its clinical experts, who said that anyone who was progression free for a substantial amount of time could be considered cured. The EAG said that the sensitivity analysis censoring events at 200 weeks should be interpreted with caution. This was because it ignored 2 late events in the pembrolizumab plus chemoradiotherapy arm of model. The committee accepted that the mixture cure models were further evidence that a larger proportion of people who had



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pembrolizumab plus chemoradiotherapy would be cured than if they had chemoradiotherapy alone. But it noted that none of the models presented by the company (excluding the scenario analysis censoring events at 200 weeks) showed as large a difference as the company's base-case model. The committee concluded that the company's base-case estimate of the extent to which pembrolizumab increases cure rates when added to chemoradiotherapy was potentially optimistic. It also concluded that the true size of the benefit was uncertain.

### Treatment effect waning for pembrolizumab

3.9 The company's original economic model assumed that the full treatment effect of pembrolizumab would be maintained for 5 years after starting treatment. Between years 5 and 7, the proportion of people benefiting from pembrolizumab decreased linearly from 100% to 0%. From year 7 onwards it remained at 0%. This waning assumption applied to pembrolizumab in both first- and second-line settings. The company said that this assumption was in line with previous NICE technology appraisals, in particular TA939. The EAG said that longer follow up from KEYNOTE-A18 was needed to confirm or refute the assumption. Clinical advice to the EAG was that assuming the treatment effect wanes over time would have a limited effect on first-line treatment benefit for pembrolizumab plus chemoradiotherapy. This was because, by year 7, the baseline risk of progression for chemoradiotherapy alone is expected to be close to zero. The committee thought that pembrolizumab treatment waning was appropriate in the first- and second-line settings, for consistency with TA939.

After consultation on the draft guidance, the company's updated base-case model did not include waning for pembrolizumab when used after progression. The company said that this was because post-progression outcomes depend more on whether someone has had pembrolizumab previously than on later treatment. The EAG said that this approach was inconsistent because waning was included in the company's subsequent



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treatment trade-off calculations (see section 3.12). This meant that waning was applied to a proportion of people whose cancer had progressed. But a scenario analysis including post-progression waning for pembrolizumab showed that it did not have much effect on the incremental cost-effectiveness ratio (ICER). Because post-progression waning for pembrolizumab had a negligible impact on the modelling results, the committee did not discuss this further.

## Trial and model-predicted overall survival

3.10 The company's original economic model estimated overall survival using:

- models fitted to progression-free survival and time-to-progression data from KEYNOTE-A18
- post-progression survival data from KEYNOTE-826 (a trial of pembrolizumab plus chemotherapy for persistent, recurrent or metastatic cervical cancer)
- structural assumptions on cure, treatment effect waning and subsequent treatments.

The model predictions did not fit well with the observed overall survival from the final analysis of KEYNOTE-A18. To address this, the company applied calibration factors to transition probabilities out of the first progression state, forcing modelled overall survival to better fit observed overall survival. The company noted that this approach had also been used in NICE's technology appraisal guidance on pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer. The EAG said that calibration was pragmatic but 'not ideal'. It could not determine the exact cause of the overall-survival discrepancy but suggested likely contributors were:

- failing to account for competing risks when deriving progression and death probabilities



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- possible misspecification of parametric survival models used for transitions
- using data from KEYNOTE-826, which may not fully represent the KEYNOTE-A18 progressed population.

The company suggested that the most likely reason for the overall-survival mismatch was using KEYNOTE-826 for progressed disease states in the model. It said that data from KEYNOTE-826 was used in the economic analysis because KEYNOTE-A18 did not have enough long-term data after progression. To improve comparability with KEYNOTE-A18, the company restricted its analyses of KEYNOTE-826 to the subgroup of people with a CPS of 1 or more who had had chemoradiotherapy. The EAG said that using KEYNOTE-826 for post-progression modelling was pragmatic. It also said that the subgroup of people with a CPS of 1 or more and prior chemoradiotherapy was broadly comparable to the population in KEYNOTE-A18 at progression. But it noted that unmeasured prognostic differences left uncertainty.

The clinical experts said that pembrolizumab worked in different ways in KEYNOTE-A18 and KEYNOTE-826. In KEYNOTE-A18, they said that using pembrolizumab at the same time as chemoradiotherapy would have had a big impact on the primary tumour. This would have enabled local control and so improved survival. In KEYNOTE-826, people had recurrent metastatic cancer and treatment was systemic rather than local, so would not have had the same impact. The committee noted that the populations in the 2 trials were also different. In KEYNOTE-826, no one had had prior pembrolizumab, so it did not capture the post-progression benefit of immunotherapy.

The committee discussed how the differences in mechanisms of the cancer and treatment context noted by the EAG and clinical experts may have affected outcomes. It discussed how using KEYNOTE-826



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data in the model could have led to an underestimate of overall-survival benefits for pembrolizumab over the KEYNOTE-A18 duration. This was why the company applied calibration factors. The committee thought that this was likely to be the main factor driving the mismatch in overall survival between the model predictions and the observed data from KEYNOTE-A18. It noted that the model appeared to underestimate overall survival in the follow-up period of KEYNOTE-A18. But, longer term, this was not supported by evidence. At the first committee meeting, the committee concluded that using direct data from KEYNOTE-A18 rather than from KEYNOTE-826 for the progressed disease states for the pembrolizumab arm of the model may help reduce uncertainty.

### Overall-survival estimates using updated 3-state transition model

3.11 After consultation on the draft guidance, the company submitted a new 3-state transition model using KEYNOTE-A18 post-progression survival data to estimate overall survival (see section 3.10). The company said that using KEYNOTE-A18 post-progression data markedly improved how well modelled overall survival fitted the observed data. But it noted that there was still some underfitting at the end of the curves. It suggested that this was because the model was underestimating post-progression survival life years for pembrolizumab more than it underestimated it for chemotherapy alone. The EAG thought that the new modelled overall-survival estimate had a worse fit to the observed survival data. It said that, as with the 4-state model, it was unclear why. But it thought that it could be because:

- competing risks in deriving progression or death risks were not accounted for properly
- parametric survival models informing overall-survival-related transition probabilities (progression-free survival, time to progression and post-progression survival) were misspecifed.



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The EAG noted that the company's approach to estimating subsequent treatments (see section 3.12) meant that it still partly relied on the costs and quality-adjusted life years (QALYs) estimated using data from KEYNOTE-826 and used in the previous 4-state model. The committee shared the EAG's concerns that the new modelled overall-survival estimate was a poor fit to the observed survival data (see section 3.13).

### Subsequent treatment trade-off

3.12 The survival estimates in the updated model relied only on data from KEYNOTE-A18, which had a very different subsequent treatments mix from the NHS, as noted in section 3.5. So, the company had to adjust the model to reflect UK clinical practice. It did this by adding the net QALY and cost payoffs from the original 4-state model into the progressed disease state, which used data from KEYNOTE-826 (see section 3.10). The EAG said that this approach was inconsistent because:

- It meant that the model still combined data from KEYNOTE-A18 (post-progression survival) and KEYNOTE-826 (QALYs and costs). These trials had populations with prognostic differences.
- It added extra QALYs (from increased active treatment) without adjusting the survival curves. So, the modelled overall survival was misleading.
- The company's base-case model excluded treatment waning for subsequent pembrolizumab treatment. But waning was included when calculating QALYs and costs using the trade-off method; so waning applied only to the difference in treatment distributions.

Because of these issues, the EAG said that the company's approach was unlikely to solve the inherent limitation of KEYNOTE-A18 not reflecting the subsequent treatment mix in the NHS. The committee shared the EAG's concerns about the company's subsequent treatment trade-off approach and acknowledged the substantial uncertainties (see section 3.13).



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### The committee's conclusions on the company's updated overall-survival modelling

3.13 The committee discussed the issues around survival modelling with the company's original 4-state model and its updated 3-state model. It acknowledged that the company had attempted to reduce the uncertainty around using KEYNOTE-826 data in its original 4-state model by producing the 3-state model using only KEYNOTE-A18 post-progression survival data. But the committee noted how this introduced further uncertainty. This was because of the mismatch between the subsequent treatments in KEYNOTE-A18 and the NHS, with the need to 'bolt on' costs and QALYs using the subsequent treatment trade-off approach (see section 3.12). Also, it still partly relied on KEYNOTE-826 data. The committee agreed that the new model of overall survival did not provide a markedly better fit to the observed trial overall-survival data. It acknowledged that, without more mature overall-survival data from KEYNOTE-A18, further modelling was unlikely to resolve the uncertainty. It concluded that both the 4-state and 3-state models had unresolvable uncertainty associated with them. But in the absence of other evidence, it concluded they could be used for decision making.

### Retreatment with pembrolizumab

3.14 The company's economic model assumed that people could have pembrolizumab again after disease progression if it was at least 2.5 years after starting first-line pembrolizumab plus chemoradiotherapy. For these 'late progressors', the model assumed that:

- 51% would have pembrolizumab plus chemotherapy (with or without bevacizumab)
- 29% would have chemotherapy (with or without bevacizumab)
- 20% would have no further active treatment.

The model assumed no reduction in effectiveness when pembrolizumab was used again. The committee recalled its earlier



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conclusion that the extent and potential benefit of retreatment with pembrolizumab in clinical practice is uncertain (see section 3.5). After consultation on the draft guidance, the company provided scenarios exploring a lower and zero rate of retreatment with pembrolizumab. It also explored reducing the efficacy of pembrolizumab when used as retreatment. Although it noted that there was no evidence for this and no other NICE technology appraisal guidance had required reduced efficacy in this context. These scenarios had a small impact on the ICER. The committee was reassured by the scenario. It concluded that it accepted the company's base-case assumption around pembrolizumab retreatment.

## Equality

### Sex and age

3.15 Cervical cancer affects women, trans men, and non-binary people registered female at birth, often of working age with caring responsibilities. Also, younger people are frequently affected. Sex and age are protected characteristics under the Equality Act 2010. But because the committee's recommendations do not restrict access to treatment for some people over others, the committee agreed these were not potential equalities issues that could be addressed in a NICE technology appraisal.

### Socioeconomic deprivation

3.16 The company and clinical experts noted that deprived groups (when considering factors such as income, education, having English as a first language, and availability of human papillomavirus (HPV) immunisation and cervical screening) are affected more by cervical cancer. Incidence and mortality are higher in the most deprived groups. A clinical expert noted the practical barriers to adherence to the treatment schedule, including the time and travel costs for frequent hospital visits needed for pembrolizumab infusions. They said that the extended treatment schedule (chemoradiotherapy followed by pembrolizumab for up to 2 years) may be



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particularly difficult to manage for people with caring responsibilities, inflexible work or people from more deprived backgrounds. This is because of the need for repeated face-to-face reviews before each infusion. The other clinical expert agreed that people with stages 3 to 4A locally advanced cervical cancer were often from the most deprived groups. But they emphasised that each extra treatment appointment was an opportunity to engage, offer treatment with the potential to cure and assess for relapse. So, extra visits would not disadvantage deprived groups. They also highlighted that people may not come to follow-up appointments but are likely to attend for treatment.

The company presented a distributional cost-effectiveness analysis (DCEA) indicating a social gradient in incidence and outcomes. Also, it explored net health benefits by Index of Multiple Deprivation. It used the University of York's health equity impact calculator. It noted that the ICD10 code used in the calculations was an overall code that includes all stages of cervical cancer, not just stages 3 to 4A. The company noted the substantial gradient in incidence across deprivation groups and suggested that this would be even steeper for stages 3 to 4A cervical cancer. The EAG noted several methodological limitations to the DCEA including:

- that the population was not specific to locally advanced cervical cancer
- the lack of sensitivity analyses to test uncertainty
- the lack of reporting for some assumptions.

During the committee meeting, the company confirmed that the DCEA assumed equal uptake of treatment across groups. The committee considered whether this assumption was appropriate, noting the earlier comments that the extended treatment schedule may be a barrier to treatment for people from deprived backgrounds. But it was reassured by the additional comments that the extra appointments needed were an opportunity to further engage with people from deprived groups and potentially improve outcomes. The committee acknowledged the



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uncertainties with the DCEA. It thought that issues around uptake of treatment could not be addressed in a NICE technology appraisal. The committee recognised that cervical cancer, especially in the advanced stages, is concentrated in and has poorer outcomes in deprived groups. So, pembrolizumab has the potential to improve health inequalities. It noted that if practical barriers affect uptake in more deprived groups, the health inequality benefit may not be realised. But it was reassured that those barriers may not appear in practice. It concluded that there was a potential health inequalities benefit associated with pembrolizumab and it took this into account when it agreed its maximum preferred ICER (see section 3.19).

### Ethnicity and language

3.17 A clinical expert noted that in some areas (for example, London) many people with cervical cancer have been born outside the UK in places where HPV vaccination and screening may be less routine. They also said that language can be a barrier to understanding and engaging with care. Race is a protected characteristic under the Equality Act 2010. There is potential for indirect discrimination if access is hindered by service delivery factors (for example, frequent in-person infusions) that disproportionately impact groups with caring responsibilities, lower incomes or limited English proficiency. But the committee concluded that these were implementation issues that the NHS could mitigate through service organisation rather than issues that could be addressed in a NICE technology appraisal.

## Uncaptured benefits

3.18 The committee considered whether there were any uncaptured benefits of pembrolizumab. It did not identify additional benefits not captured in the economic modelling. So, the committee concluded that all additional benefits of pembrolizumab had already been taken into account.



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## Cost-effectiveness estimates

### Acceptable ICER

3.19 The NICE technology appraisal and highly specialised technologies guidance: the manual notes that, above a most plausible ICER of £25,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee recalled the potential to reduce health inequalities for more deprived groups (see section 3.16). It also noted the high levels of uncertainty, specifically:

- the size of the additional cure proportion when pembrolizumab is added to chemoradiotherapy (see section 3.8)
- the mismatch between observed trial overall survival and model-predicted overall survival for both the 4-state and 3-state economic models, and the need for the company to apply calibration factors to force a fit for the 4-state model (see section 3.10)
- the difference in subsequent treatments between KEYNOTE-A18 and the NHS, which meant that the company had to use a 'subsequent treatment trade-off approach' in its updated 3-state model to add QALYs and costs from the original 4-state model, which used data from KEYNOTE-826 (see section 3.12).

So, the committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£25,000 to £35,000 per QALY gained).

### The committee's preferred assumptions and cost-effectiveness estimate

3.20 The committee recalled its conclusion that the 3-state and 4-state models were both associated with a high degree of uncertainty but were suitable



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for decision making (see section 3.13). It also recalled that no further data was expected from KEYNOTE-A18 and that additional modelling was unlikely to resolve the uncertainty. The committee appreciated the high unmet need for treatments that improve cure rates in locally advanced cervical cancer. In the absence of further evidence to determine which modelling approach generated the most plausible results, it concluded that its preferred ICER was the midpoint between the company's 2 base-case estimates. The committee's preferred model assumptions were in line with the company's base case (despite noting the considerable uncertainty associated with these), including:

- that some people would be cured in both arms of the model, with a larger proportion having pembrolizumab plus chemoradiotherapy being cured than the proportion having chemoradiotherapy (see section 3.8)
- no waning for pembrolizumab as a subsequent treatment (see section 3.9)
- that people could have retreatment with pembrolizumab if their cancer came back at least 2.5 years after their initial treatment with pembrolizumab plus chemotherapy (see section 3.14)

The committee's preferred ICER cannot be reported here because of confidential discounts for pembrolizumab and 1 of the comparator drugs.

## Conclusion

3.21 The committee recognised that pembrolizumab plus chemoradiotherapy is a clinically effective treatment for untreated FIGO 2014 stages 3 to 4A untreated locally advanced cervical cancer. Using the committee's preferred assumptions, the ICER was within the range that NICE considers a cost-effective use of NHS resources. So, pembrolizumab can be used in the NHS.



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# 4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has untreated locally advanced cervical cancer



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and the healthcare professional responsible for their care thinks that pembrolizumab with chemoradiotherapy is the right treatment, it should be available for use, in line with NICE's recommendations.

# 5 Evaluation committee members and NICE project team

## Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

## Chair

**Radha Todd and Raju Reddy**
Chairs, technology appraisal committee A

## NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager, and an associate director or principal technical adviser.

**Emilene Coventry**
Technical lead

**Zoe Charles**
Technical adviser



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**Jennifer Upton**

Project manager

**Ian Watson**

Associate director

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