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Pembrolizumab for locally advanced cervical cancer

We read with great interest the results from the ENGOT-cx11/GOG-3047/KEYNOTE-A18 trial reported by Domenica Lorusso and colleagues.[1] The improvement in progression-free survival is exciting but difficult to interpret without additional radiation details and sites of progression. The total equivalent dose in 2 Gy fractions is reported as 87 Gy (IQR 83–92), which suggests that 25% of patients received less than 83 Gy. Data from EMBRACE-1 show that the minimum dose that covers 90% of the target volume of 85 Gy is required to offer a 95% chance of local control at 3 years for squamous cell cancers, and an even higher dose is needed for adenocarcinomas.[2] Additional information on volume and dose received by the high-risk cervix target and the technique of brachytherapy would be helpful. In addition, the protocol suggested a total dose of 60 Gy (equivalent dose in 2 Gy fractions) to enlarged lymph nodes;[1] however, the total dose delivered to nodes and their size was not reported, which is important as more than 80% of participants were node-positive. The overall imaging response rate of 76–79% in both treatment groups and complete response rate of about 50% are lower than the response rates reported in most modern series with advanced radiation techniques. Clarification regarding some of the radiation details would be helpful to aid interpretation of the results, especially regarding whether the effect of adding pembrolizumab is local, regional, or distant (or a combination). Given EMBRACE-II[3] is investigating the effect of modern radiotherapy techniques, including intensity-modulated radiation therapy, image-guided radiation therapy, prophylactic para-aortic region radiation therapy for disease with more than two positive nodes, integrated boost to nodes, and adaptive brachytherapy, it is important to try to understand the results of ENGOT-cx11/GOG-3047/KEYNOTE-A18 in the context of the highest standard of chemoradiation treatment.

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1 Lorusso D, Xiang Y, Hasegawa K, et al. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): a randomised, double-blind, phase 3 clinical trial. *Lancet* 2024; **403:** 1341–50.

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3 Pötter R, Tanderup K, Kirisits C, et al. The EMBRACE II study: the outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. *Clin Transl Radiat Oncol* 2018; **9:** 48–60.

We read with interest the Article by Domenica Lorusso and colleagues about the ENGOT-cx11/GOG-3047/KEYNOTE-A18 trial.[1] This phase 3 study showed that pembrolizumab, when administered in combination with chemoradiotherapy, resulted in a statistically significant improvement in progression-free survival, compared with chemoradiotherapy alone, for patients with locally advanced cervical cancer. However, the results are difficult to interpret.

Although the total physical dose received by the cervix was provided in the Article, no information was provided regarding the minimal dose received by 90% of the high-risk clinical target volume, which is strongly associated with local control rate and progression-free survival.[2] Currently, it is inconceivable to compose a study on image-guided brachytherapy for cervical cancer without incorporating such dose information. The EMBRACE-I study has already shown that if an adequate dose of more than 85 Gy is delivered to 90% of the high-risk clinical target volume, a local control rate of 90% can be expected.[2] Therefore, it is possible that the poor quality of brachytherapy in this study led to a local control rate far inferior to that of the EMBRACE-I trial. Had high-quality brachytherapy been conducted and better local control achieved, it is likely that no statistically significant additional effect of pembrolizumab would have been observed. If this is the case, it would be challenging to consider the combination of pembrolizumab and chemoradiotherapy as a new standard of care. These points should be addressed by the authors.

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1 Lorusso D, Xiang Y, Hasegawa K, et al. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): a randomised, double-blind, phase 3 clinical trial. *Lancet* 2024; **403:** 1341–50.
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We commend Domenica Lorusso and colleagues for their Article[1] reporting a phase 3 clinical trial that analysed the comparison between pembrolizumab or placebo combined with chemoradiotherapy in the treatment of newly diagnosed, high-risk, locally advanced cervical cancer. However, the strength of evidence in this study could be enhanced by further discussion of some issues.

First, on the basis of previous evidence,[2] pembrolizumab was approved by the US Food and Drug Administration for first-line or second-line treatment in patients with PD-L1-positive (combined positive score ≥1) cervical cancer. The study's conclusions would be more easily understood if the authors could provide the rationale for the inclusion of participants with PD-L1-negative (combined positive score <1) tumours. Previous studies[3,4] found that patients with PD-L1-negative status also benefited from pembrolizumab treatment in terms of progression-free survival and overall survival, although prognosis seemed to be better among patients with PD-L1-positive status. In this study,[1] participants were also categorised by PD-L1 combined positive scores (≥1 and <1). Furthermore, Lorusso and colleagues indicated that the key secondary endpoints included progression-free survival and overall survival by PD-L1 status. However, figure 2 of their Article does not provide an analysis of progression-free survival for these two stratified groups. We recommend the inclusion of detailed information on progression-free survival and overall survival for participants with varying levels of PD-L1 expression.

Second, in the comparison of adverse events between the two treatment methods, we suggest the inclusion of the p value for the difference between the two groups. This recommendation stems from the incidence rates in table 2 of their Article, which seem to indicate higher occurrences of both treatment-related adverse events and immune-mediated adverse events in the pembrolizumab–chemoradiotherapy group, with a greater difference in the incidence of immune-mediated adverse events, in particular.

Third, participants in this study included individuals with squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma, but specific case numbers were not provided. There is evidence that PD-L1 is expressed by most cervical squamous cell carcinomas but not necessarily by other histological types of cervical cancer (such as adenocarcinoma).[2,5] Moreover, a previous study showed a statistically significant difference in response rates to pembrolizumab treatment between patients with PD-L1-positive cervical cancer and those with PD-L1-negative cervical cancer.[2]

Fourth, in figure 3 of their Article, only overall survival for the two treatments is displayed, and the hazard ratios for comparisons of overall survival of various subgroups are not provided. Differences in overall survival have been shown among protocol-specified subgroups for the treatment of persistent, recurrent, or metastatic cervical cancer using pembrolizumab combined with chemotherapy or placebo combined with chemotherapy.[4] We recommend the reporting of these results.

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1 Lorusso D, Xiang Y, Hasegawa K, et al. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): a randomised, double-blind, phase 3 clinical trial. *Lancet* 2024; **403:** 1341–50.
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Regarding the Article by Domenica Lorusso and colleagues on ENGOT-cx11/GOG-3047/KEYNOTE-A18,[1] this trial finally shows the long-awaited progress in patients with high-risk locally advanced cervical cancer: addition of pembrolizumab to chemoradiation statistically significantly improved progression-free survival at 24 months. We do not want to question the results of a randomised controlled trial or the potential role of pembrolizumab, but we would like to focus attention on the central treatment component, which is chemoradiotherapy, including brachytherapy.