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1 World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human participants. *JAMA* 2024; published online Oct 19. https://www.doi.org/10.1001/jama.2024.21972.

2 Jeyaraman M, Balaji S, Jeyaraman N, Yadav S. Unraveling the ethical enigma: artificial intelligence in healthcare. *Cureus* 2023; **15:** e43262.

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.

MK reports consulting fees from Theragenics, Pfizer, and Adaptiiv; reports being a member of the data and safety monitoring board for Alessa and GT Medical; reports receiving book royalties from Springer; and is the Vice President of the American Brachytherapy Society. SB reports being an employee of Varian, receiving fees for consulting from Elsevier, and being a member of the data and safety monitoring board for Xoft.

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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.

2 Schmid MP, Lindegaard JC, Mahanshetty U, et al. Risk factors for local failure following chemoradiation and magnetic resonance image-guided brachytherapy in locally advanced cervical cancer: results from the EMBRACE-I study. *J Clin Oncol* 2023; **41:** 1933–42.

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.

NM, NO, and NS report grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan. NM has received payments or honoraria from lectures, presentations, speakers bureaus, manuscript writing, or educational events from Elekta, Chiyoda Technol, Boston Scientific, AstraZeneca, MedicaLine, Teleflex, and Bayer. NO and NS have received payments or honoraria from lectures, presentations, speakers bureaus, manuscript writing, or educational events from Elekta, Chiyoda Technol, and Boston Scientific. YT declares no competing interests. During the preparation of this work, the authors used QuilBot and Microsoft Copilot in order to improve the standard of English. After using these tools, the