authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

*Naoya Murakami, Noriyuki Okonogi, Yasuhisa Terao, Naoto Shikama
n.murakami.zi@juntendo.ac.jp

Juntendo University, Tokyo 113-0033, Japan (NM, NO, YT, NS)

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 Pötter R, Tanderup K, Schmid MP, et al. MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study. *Lancet Oncol* 2021; **22:** 538–47.

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.

We declare no competing interests.

*Binhua Dong, Yong Lu, Yue Wang, Pengming Sun, *Huachun Zou
zouhuachun@fudan.edu.cn

Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, Fujian 350001, China (BD, YW, PS, HZ); School of Public Health, the Key Laboratory of Environmental Pollution Monitoring and Disease Control, Ministry of Education, Guizhou Medical University, Guiyang, China (YL); School of Public Health, Fudan University, Shanghai, China (HZ)

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 Chung HC, Ros W, Delord JP, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol* 2019; **37:** 1470–78.
3 Colombo N, Dubot C, Lorusso D, et al. KEYNOTE-826 Investigators. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med* 2021; **385:** 1856–67.
4 Monk BJ, Colombo N, Tewari KS, et al. First-line pembrolizumab + chemotherapy versus placebo + chemotherapy for persistent, recurrent, or metastatic cervical cancer: final overall survival results of KEYNOTE-826. *J Clin Oncol* 2023; **41:** 5505–11.
5 Li C, Cang W, Gu Y, Chen L, Xiang Y. The anti-PD-1 era of cervical cancer: achievement, opportunity, and challenge. *Front Immunol* 2023; **14:** 1195476.

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.

Major progress—conceptually, through response-adapted treatment[2] and technically, through use of combined intracavitary and interstitial applicators and MRI for treatment planning[2]—enabled the development of image-guided adaptive brachytherapy with unprecedented local tumour control rates,[3] resulting in the integration of this novel treatment modality into international guidelines.[4] We acknowledge the huge efforts involved in conducting a comprehensive quality assurance programme for radiotherapy; however, one might question whether brachytherapy was used to its full potential in ENGOT-cx11/GOG-3047/KEYNOTE-A18. The radiation manual for this trial allowed for a broad variety of brachytherapy techniques, including point-directed target specifications and intracavitary-only applications. With such an approach there is—despite the use of MRI or CT—very little possibility of adapting the dose according to individual tumour extension or, subsequently, optimising local tumour control. Numerous studies have shown the poor representativity of point-directed brachytherapy.[5] Furthermore, reporting brachytherapy dose as total cervix dose does not follow current guidelines[2] and substantially limits the objective evaluation of brachytherapy quality. For better comparability, we would encourage the authors to report state-of-the-art target volumes and related dose-volume histogram parameters. The EMBRACE-I study,[3] as a current benchmark for MRI-based image-guided adaptive brachytherapy, indicates the effect of brachytherapy on overall clinical outcome. Adjusting the EMBRACE-I cohort (n=1318) to the high-risk definition of ENGOT-cx11/GOG-3047/KEYNOTE-A18 (IB2–IIB N1 plus any IIIA–IVA) provides a comparable sub-cohort (KEYMBRACE-I cohort) attaining an outcome similar to that of the experimental treatment group of ENGOT-cx11/GOG-3047/KEYNOTE-A18 (appendix). Of course, such a comparison has to be interpreted with caution, but it reveals a trend indicating an unused radiotherapy potential in ENGOT-cx11/GOG-3047/KEYNOTE-A18. Further progress in chemoradiotherapy should be provided by the EMBRACE II study[6] (clinical results expected in 2025), with a specific new focus on risk-adapted nodal treatment (systematic use of para-aortic radiotherapy and nodal boosts). In consequence, we strongly believe that the true benefit of the combination strategy remains to be investigated. Until then, to aid the understanding of the effect of pembrolizumab, disclosure of local, regional, and distal patterns of recurrence would be of great interest.

Embrace-I was funded by the Medical University of Vienna, Aarhus University Hospital, Elekta, and Varian Medical Systems. MPS report grants and personal fees from Elekta; and consulting fees from MSD. CK reports grants and personal fees from Elekta; and grants from Varian Medical Systems. KT reports grants from Varian Medical Systems, the Danish Cancer Society, and Elekta. All other authors declare no competing interests.

*Maximilian P Schmid, Primoz Petric, Umesh Mahantshetty, Christian Kirisits, Kari Tanderup, Ina Jürgenliemk-Schulz, Jacob Lindegaard, Richard Pötter
maximilian.schmid@akhwien.at

Medical University of Vienna, Department of Radiation Oncology, Comprehensive Cancer Center, 1090 Vienna, Austria (MPS, CK, RP); Department of Radiation Oncology, Zürich University Hospital, Zürich, Switzerland (PP); Homi Bhabha Cancer Hospital and Research Centre, Visakhapatnam, India (UM); Aarhus University Hospital, Department of Oncology, Aarhus, Denmark (KT, JL); University Medical Centre Utrecht, Department of Radiation Oncology, Utrecht, Netherlands (IJ-S)

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 No authors listed. Prescribing, recording and reporting brachytherapy for cancer of the cervix (ICRU Report 89). *J ICRU* 2013; **13:** 1.
3 Pötter R, Tanderup K, Schmid MP, et al. MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicenter prospective cohort study. *Lancet Oncol* 2021; **22:** 538–47.
4 Cibula D, Rosaria Raspollini M, Planchamp F, et al. ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer—update 2023. *Radiother Oncol* 2023; **184:** 109682.
5 Tanderup K, Nielsen SK, Nyvang G-B, et al. From point A to the sculpted pear: MR image guidance significantly improves tumour dose and sparing of organs at risk in brachytherapy of cervical cancer. *Radiother Oncol* 2010; **94:** 173–80.
6 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.

Authors' reply

We thank our colleagues for their interesting comments on our Article[1] and the chance to expand on several study details. Mitchell Kamrava and Sushil Beriwal note that our patients received a lower total cervix equivalent dose in 2 Gy fractions than that reported in EMBRACE-I.[2] Correspondence from Maximilian P Schmid and colleagues suggests an unused radiotherapy potential after adjusting the EMBRACE-I cohort to the high-risk definition in ENGOT-cx11/GOG3047/KN-A18. Such cross-study comparisons are challenging due to differences in endpoints, population risk, enrolment periods, and number of study sites and might yield misleading results. ENGOT-cx11/GOG3047/KN-A18 was a global study conducted in 30 countries, including countries in Asia, where the standard total radiotherapy dose is lower than in other countries.[3,4] Accordingly, we selected planned total radiotherapy dose as a stratification factor (<70 Gy *vs* ≥70 Gy equivalent dose in 2 Gy fractions) to permit the inclusion of patients from Asia. Notably, the treatment benefit of pembrolizumab on progression-free survival across patient subgroups, including those defined by radiotherapy dose and east Asian geography, was generally consistent with that observed in the overall population.[5] We agree that additional details regarding radiation techniques will offer important insights, and these data are planned for a future report.

See **Online** for appendix