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.

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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

In response to Naoya Murakami and colleagues, we welcome the opportunity to further describe the delivery of high-quality radiotherapy in this study. Rigorous site validation was required before study enrolment. Sites followed the International Commission on Radiation Report 89 for prescribing, recording, and reporting brachytherapy for cervical cancer[6] and the GEC-ESTRO brachytherapy guidelines.[7] External-beam radiotherapy plan approval by an external vendor was required before random assignment of participants, and the brachytherapy plan was submitted within 2 weeks of completion of external-beam radiotherapy. Overall treatment time was not to exceed 50 days (with extension to a maximum of 56 days for unforeseen delays). Geographical variance in the total radiation dose, number of fractions, and methodology of application was permitted only after consultation with the study sponsor. Continuous evaluation by an independent data monitoring committee assured that radiotherapy was consistent with the current standard of care. Despite the challenges associated with the COVID-19 pandemic and the Russia–Ukraine war, brachytherapy was started in 95% or more of patients and total radiation therapy was performed within 56 days in 75% of the population.

We agree with Binhua Dong and colleagues that PD-L1 expression as a predictor of treatment response in cervical cancer is of interest. Our results show a clinically meaningful improvement in progression-free survival with the addition of pembrolizumab to chemoradiotherapy versus chemoradiotherapy alone in the subgroup of patients with a PD-L1 combined positive score of 1 or higher, consistent with the results in the intention-to-treat population. A treatment benefit was also seen in the subgroup with a PD-L1 combined positive score of less than 1; however, these results warrant cautious interpretation due to the low number of events (≤7 per treatment group) and the small number of patients in this subgroup (n=50, ~5% of the study population), representative of patients with locally advanced cervical cancer in this setting. Thus, requiring PD-L1 testing of all patients to identify the approximately 5% with a PD-L1 combined positive score of less than 1 might prove unnecessarily burdensome. Furthermore, the proposed post-hoc subgroup analysis combining PD-L1 expression status with histology could yield small, unbalanced subgroups and, consequently, inconclusive results. As statistical significance of overall survival had not yet been established at this analysis, subgroup analyses were not done; however, the overall survival results in protocol-specified subgroups have since been reported.[8]

Regarding the higher incidence of immune-mediated adverse events in the pembrolizumab–chemoradiotherapy group, this result is expected with the addition of immunotherapy and is primarily driven by low-grade endocrinopathies. Most immune-mediated events were non-serious and manageable with supportive care. Per the study protocol, between-group differences in adverse events were summarised using descriptive statistics (ie, no hypothesis testing); thus, p values are not available.

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