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Letter to the editor, Reply to: Lee and Matulonis: Immunotherapy and radiation combinatorial trials in gynecologic cancer: A potential synergy?

In a recent review published in *Gynecologic Oncology*, titled "Immunotherapy and radiation combinatorial trials in gynecologic cancer: A potential synergy?" (Lee and Matulonis, 2019), authors Larissa Lee and Ursula Matulonis provide a timely review of adding immunotherapy to chemotherapy and radiotherapy. Preclinical (Sharabi et al., 2015) and clinical studies (Johnson and Jagsi, 2016) have previously described synergistic activity with the combination of radiation and immunotherapy. In their review the authors outline many clinical trials that are currently underway that are exploring safety and efficacy of immunotherapy/radiotherapy combinations in the metastatic and definitive setting (Lee and Matulonis, 2019). It should be noted, however, that the list of trials in the review is by no means exhaustive and, therefore, we want to raise awareness of a large phase 3 trial that recently started recruiting patients in order to examine the efficacy and safety of the anti-programmed death ligand-1 (PD-L1) antibody durvalumab combined with standard of care (SoC) concurrent chemoradiation therapy (CCRT) in locally advanced cervical cancer. This randomized, multicenter, international, double-blind, placebo-controlled study called "CALLA" (NCT03830866), will enroll approximately 714 newly diagnosed, immunotherapy-naïve patients with adenocarcinoma, squamous or adenosquamous cervical carcinoma (2009 FIGO Stages IB2 – IVA), making it one of the largest trials in this patient population (Monk et al., 2019).

Patients will be randomized 1:1 to receive either durvalumab intravenously [IV]) or placebo every 4 weeks. All patients will receive cisplatin or carboplatin administered concurrently with external beam radiation therapy plus brachytherapy. Randomization is stratified by disease stage (FIGO Stage < Ill and N positive, Stage ≥ III and N negative, or FIGO Stage ≥ III and N positive) and region (US, Canada, EU, South Korea, and Japan versus the rest of the world). The primary endpoint is investigator-assessed progression-free survival (per RECIST v1.1 or histopathologic confirmation of local tumor progression). Secondary endpoints are overall survival, objective response and complete response rates, duration of response in patients with a complete response, incidence of local or distant disease progression or secondary malignancy, disease-related symptoms, and health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-CX24). Pharmacokinetics, immunogenicity, and safety of durvalumab will also be assessed. Patient enrollment is ongoing.

The clinical activity associated with potentiating the proinflammatory effects of CCRT suggests that administering durvalumab in combination with CCRT may have clinical benefits, including increasing the response rate to CCRT, improving the complete response rate, and decreasing the number of patients who progress on CCRT. Safety observations in other tumor types have demonstrated that concurrent administration of CCRT and immunotherapy has generally been well tolerated (Chao et al., 2018; Jabbour et al., 2018; Powell et al., 2018). The safety of administration of durvalumab and CCRT, for example, is supported by results from the PACIFIC study, which showed that durvalumab administered within 42 days of completion of CCRT had a well-tolerated and manageable safety profile that was consistent with the established safety profile to date (Antonia et al., 2017). Therefore, the CALLA trial was commenced to evaluate the efficacy and safety of concurrent administration of durvalumab and CCRT in patients with cervical cancer.

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Author contributions

All authors equally contributed to this manuscript.

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