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NRG-GY020: Phase III randomized trial of radiation +/- MK-3475 (pembrolizumab) for newly diagnosed early-stage high intermediate risk (HIR) mismatch repair deficient (dMMR) endometrioid endometrial cancer

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Background

Currently, vaginal brachytherapy (VBT) is recommended as adjuvant therapy for HIR EC. Immunotherapy (IO) is highly effective for patients with recurrent dMMR EC. We hypothesized that the addition of IO to radiation (RT) would improve recurrence free survival (RFS) in early stage dMMR EC.

Methods

NRG-GY020 was a randomized, phase III open-label superiority trial and included patients with newly diagnosed, early-stage, HIR (GOG-249 criteria), dMMR endometrioid EC. Patients in both arms received VBT; only patients with stage II and IB grade 3 were allowed to receive external beam pelvic radiation (EBRT). Patients were randomized 2:1 to 1 year of pembrolizumab 400 mg IV every 6 weeks starting within 7 days of RT, vs RT alone. The primary analysis compared the proportion of RFS at 3 years (RFS3) between RT+pembro and RT using normal approximations. Patients who reached RFS3 were considered treatment successes, whereas patients who recurred or died of any cause or who came off study within 3 years for any other reason were considered treatment failures. Secondary analyses included a log-rank test, Cox proportional hazards models, and Kaplan-Meier (KM) curves with comparisons at 3 years.

Results

Between 2/2020-8/2022, 168 patients were enrolled. Median age was 66, 77% were white; 20% had stage IA, 63% IB, 17% stage II, with 82% grade 2/3 EC. Most patients (70%) received VBT alone, while 30% received EBRT +/- VBT. The RT+pembro arm experienced more grade 3/4 toxicity (43% vs 15%), mostly grade 3 lymphopenia and hypertension. At data cutoff (median follow up 45.5 months), the standardized statistic comparing the two proportions was $Z=-0.48$ ($p=0.68$). RFS3 was 73% for RT vs 70% for RT+pembro; 10/56 (18%) recurrences in the RT and 12/112 (11%) in the RT+pembro arm, and 5 (9%) and 22 (20%) failures for other reasons, respectively. KM estimated RFS was 81% in the RT vs 88% in the RT+ pembro arm (HR 0.72 (95%CI 0.33,1.61; $p=0.21$)). 3-year overall survival (OS) was 96% in both arms.

Conclusions

The addition of pembrolizumab to RT did not meet the pre-specified criteria for superiority. RT alone (VBT and/or EBRT) remains the standard in HIR dMMR endometrioid EC.

Clinical trial identification

NCT04214067.

Legal entity responsible for the study

NCI/CTEP/NRG Oncology and the Authors.

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Disclosure

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