Immunotherapy Reshapes First-Line Treatment for Advanced Endometrial Cancer

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Endometrial cancer is a common gynecologic malignancy, and for patients with advanced or recurrent disease, treatment options have historically centered on chemotherapy. Recent advancements in immunotherapy have shown promise across various solid tumors, prompting investigation into its role in endometrial cancer. This study provides further insights into the efficacy of combining an immune checkpoint inhibitor with standard chemotherapy in this patient population.

KEY TAKEAWAYS

- The Pivot: First-line treatment for advanced or recurrent endometrial cancer now includes pembrolizumab in combination with chemotherapy.
- The Data: Pembrolizumab plus chemotherapy significantly improved progression-free survival (PFS) compared to chemotherapy alone, with hazard ratios favoring pembrolizumab across both mismatch repair-deficient (0.45) and mismatch repair-proficient (0.64) groups.
- The Action: Clinicians should consider pembrolizumab plus paclitaxel-carboplatin as a first-line option for eligible patients with advanced or recurrent endometrial cancer, irrespective of their mismatch repair status.

Background on Endometrial Cancer Treatment

Endometrial cancer is a significant health concern, with advanced or recurrent disease posing considerable challenges. Historically, the standard first-line treatment for these patients has involved a combination of paclitaxel and carboplatin chemotherapy. While effective for many, there remains a need for therapies that can extend progression-free survival and improve overall outcomes. Immunotherapy, particularly immune checkpoint inhibitors, has demonstrated efficacy in various solid tumors by harnessing the body's immune system to target cancer cells. This success has led to investigations into its potential role in endometrial cancer management1.

Study Design and Patient Cohort

The NRG GY018 study was a phase 3 randomized trial designed to evaluate the efficacy and safety of pembrolizumab in combination with chemotherapy for advanced or recurrent endometrial cancer. The study included women aged 18 years or older who had newly diagnosed stage III or IVA endometrial cancer with measurable disease, or stage IVB or recurrent endometrial cancer, with or without measurable disease. A total of 810 patients were randomized in a 1:1 ratio to receive either pembrolizumab or placebo, in combination with paclitaxel-carboplatin. Following the initial chemotherapy phase, patients continued with maintenance pembrolizumab or placebo for up to 24 months1.

Primary and Secondary Endpoints

The primary endpoint of the NRG GY018 study was investigator-assessed progression-free survival (PFS). Key secondary endpoints included overall survival (OS) and safety. Exploratory analyses also assessed PFS by blinded independent central review (BICR) and further examined outcomes based on mismatch repair (MMR) status. Mismatch repair status is a crucial biomarker in endometrial cancer, influencing response to certain therapies. The study aimed to determine if the addition of pembrolizumab would improve outcomes across both mismatch repair-deficient (MMR-d) and mismatch repair-proficient (MMR-p) patient populations1.

Key Findings: Progression-Free Survival

The study demonstrated that pembrolizumab plus chemotherapy significantly improved investigator-assessed progression-free survival compared to placebo plus chemotherapy, irrespective of mismatch repair status. For patients with MMR-proficient disease, the hazard ratio (HR) for PFS by BICR was 0.64 (95% confidence interval [CI]: 0.49-0.85; P=0.0008), favoring the pembrolizumab arm. In the MMR-deficient cohort, the benefit was even more pronounced, with an HR of 0.45 (95% CI: 0.27-0.73; P=0.0005) for PFS by BICR, also favoring pembrolizumab. These results indicate a substantial reduction in the risk of disease progression or death with the addition of pembrolizumab to standard chemotherapy1.

Overall Survival and Exploratory Analyses

While overall survival data were immature at the time of this report, the hazard ratios for OS consistently favored the pembrolizumab arm across both MMR-proficient and MMR-deficient groups. For MMR-proficient patients, the 1-sided nominal P-value was 0.1157, with an HR of 0.79 (95% CI: 0.53-1.17). In the MMR-deficient group, the 1-sided nominal P-value was 0.0617, with an HR of 0.55 (95% CI: 0.25-1.19). Although these OS findings did not reach statistical significance at this interim analysis, the trends suggest a potential long-term survival benefit that warrants continued follow-up. The consistent improvement in PFS across both MMR subgroups highlights the broad applicability of this combination therapy1.

Clinical Implications and Future Directions

The findings from the NRG GY018 study provide strong evidence supporting the integration of pembrolizumab into the first-line treatment regimen for patients with advanced or recurrent endometrial cancer, regardless of their mismatch repair status. The significant improvement in progression-free survival represents a meaningful clinical advance for this patient population, offering a new standard of care. These results have already influenced clinical practice guidelines, establishing pembrolizumab plus chemotherapy as a preferred initial treatment option.

Why this matters for clinical practice today

For clinicians managing advanced or recurrent endometrial cancer, these data underscore the importance of incorporating immunotherapy early in the treatment course. The consistent benefit observed across both MMR-deficient and MMR-proficient subgroups simplifies treatment stratification, allowing for broader application of this effective combination. While overall survival data are still maturing, the robust PFS improvement provides a clear rationale for adopting this regimen, potentially delaying disease progression and improving quality of life for patients. It also emphasizes the need for continued research into biomarkers that might further refine patient selection and predict response to immunotherapy.

Limitations and Next Steps

A primary limitation of the current report is the immaturity of the overall survival data. While the trends are encouraging, definitive conclusions regarding long-term survival benefits will require further follow-up. Additionally, while the study included a large and diverse patient population, further research may explore specific subgroups or molecular characteristics that could predict an even greater response to this combination therapy. Future studies might also investigate the optimal duration of maintenance therapy and the potential for de-escalation strategies. Continued monitoring for long-term safety and efficacy will be crucial as this regimen becomes more widely adopted in clinical practice1.

REFERENCES

1. 1. Eskander RN, Sill MW, Beffa L, et al. Pembrolizumab plus chemotherapy in advanced or recurrent endometrial cancer: overall survival and exploratory analyses of the NRG GY018 phase 3 randomized trial. Nat Med. 2025;31(5):1539-1546. doi:10.1038/s41591-025-03566-1