Expanding the Standard of Care: Dostarlimab for Advanced Endometrial Cancer

Endometrial cancer (EC) is the most prevalent uterine malignancy and ranks as the fourth most common cancer among women in the United States. The American Cancer Society projects that nearly 70,000 women will be diagnosed in 2026, with an estimated 14,000 deaths expected as a result.1 Of all gynecologic cancers, EC has the second highest mortality rate after ovarian cancer.2

Treatment options have improved significantly since the development of novel targeted or immunotherapies, such as dostarlimab (Jemperli; GSK)—a monoclonal antibody approved by the FDA in combination with carboplatin and paclitaxel chemotherapy, followed by dostarlimab as a single agent, for the treatment of adult patients with mismatch repair-deficient (dMMR) advanced or recurrent EC.3

As immunotherapy becomes an integral component of first-line treatment in this setting, pharmacists are increasingly called upon to support safe and effective use of dostarlimab. Understanding the mechanism and clinical evidence to anticipating, monitoring, and managing the complex toxicity profile associated with PD-1 inhibition, is crucial for ensuring optimal patient outcomes.

EC Survival Rates

Survival outcomes in endometrial cancer are shaped by a combination of factors, including stage at diagnosis, tumor histology, and molecular characteristics such as MMR status.3

Survival by Stage

At the population level, 5-year relative survival rates in the U.S. and comparable high-income countries follow a clear pattern tied to extent of disease. When all stages are combined, survival hovers around 80% to 85%. For women diagnosed with localized disease confined to the uterus, that figure rises to approximately 95% to 96%. Regional spread to nearby tissues or lymph nodes brings survival down to the 70% to 75% range, and distant or metastatic disease carries a markedly worse prognosis, with only about 15% to 20% of patients alive at 5 years.3

The Role of Histology and Molecular Features

Not all endometrial cancers behave the same way. Non-endometrioid subtypes tend to be more aggressive, carry a higher risk of recurrence, and generally have worse survival compared to low-grade endometrioid tumors at equivalent stages.3

Molecular profiling, particularly MMR status, has become increasingly important in understanding prognosis and guiding treatment. dMMR/ microsatellite instability-high tumors have shown meaningful responsiveness to immunotherapy, which can meaningfully improve outcomes in the recurrent and advanced settings. MMR-proficient (pMMR) tumors, which are more prevalent, represent a significant unmet need. They tend to respond less robustly to immunotherapy alone, making treatment more challenging.3

Advanced and Recurrent Disease

For patients with metastatic endometrial cancer, the prognosis has historically been poor, consistent with the 15% to 20% 5-year survival figure cited above. However, the treatment landscape is evolving. Newer regimens combining PD-1 inhibitors such as dostarlimab with platinum-based chemotherapy, followed by immunotherapy maintenance, have demonstrated meaningful improvements in overall survival across both dMMR and pMMR patient populations in clinical trials. Notably, in dMMR patients, overall survival (OS) had not yet been reached at the time of analysis in some trials.3

Dostarlimab

Dostarlimab works by targeting the PD-1 receptor on T cells to keep the immune system from mounting an excessive response. Tumors exploit this mechanism by coating themselves with PD-L1 and PD-L2 molecules, which latch onto PD-1 and effectively shut down T cells before they can eliminate cancer cells. By binding to PD-1, dostarlimab physically

blocks PD-L1 and PD-L2 from making that connection. With the checkpoint disengaged, T cells regain their ability to recognize and destroy tumor cells.4

The RUBY Trial

RUBY was a phase 3, randomized, double-blind, placebo-controlled trial enrolling adults with primary advanced (stage III–IV) or first recurrent EC who were chemotherapy-naïve in the advanced or recurrent setting. The trial included both dMMR/MSI-H and pMMR/MSS tumors, and enrolled patients with a range of histologic subtypes—including serous, clear cell, carcinosarcoma, and endometrial carcinoma—reflecting the diversity of disease seen in clinical practice.3

Patients were randomized to 1 of 2 arms: dostarlimab plus carboplatin and paclitaxel followed by dostarlimab maintenance, or placebo plus carboplatin and paclitaxel followed by placebo maintenance. During the combination phase, patients received carboplatin and paclitaxel alongside either dostarlimab 500 mg intravenously (IV) or placebo every 3 weeks for six cycles. This was followed by a maintenance phase in which dostarlimab 1000 mg IV or placebo was administered every 6 weeks. Treatment continued for up to 3 years in total, inclusive of the combination phase.3

The trial's co-primary end points were progression-free survival (PFS) in the dMMR/MSI-H subgroup and in the overall population. The key secondary end point was OS, assessed in both the dMMR/MSI-H subgroup and the all-comer population. Additional end points included objective response rate, duration of response, safety and tolerability, and health-related quality of life.3

Efficacy

In the dMMR/MSI-H subgroup, dostarlimab plus chemotherapy produced marked improvements in both PFS and OS compared to chemotherapy alone. Median OS in this group had not been reached in the dostarlimab arm at the time of analysis, pointing to a substantial and durable survival benefit.3

Across the overall population, the dostarlimab arm demonstrated a significant improvement in PFS, along with an approximately 16-month improvement in median OS compared to placebo. In the pMMR/MSS subgroup, improvements in OS and PFS were more modest, though still clinically meaningful. This subgroup is particularly important given that pMMR tumors account for roughly 70% to 75% of all endometrial cancer cases, making even incremental gains in this population significant at a population level.3

Safety

The safety profile was consistent with what would be expected from the combination of platinum-taxane chemotherapy and a PD-1 inhibitor. Chemotherapy-related toxicities were observed alongside immune-mediated adverse events (AEs), which included endocrinopathies such as thyroid disorders and rare cases of type 1 diabetes, as well as hepatitis, colitis, pneumonitis, nephritis, and dermatologic and musculoskeletal manifestations. Immune-related adverse events were generally manageable using established treatment algorithms—dostarlimab was held or discontinued for grade 3 or 4 events, and high-dose corticosteroids were used as first-line management. For steroid-refractory toxicities, escalation to additional immunosuppressive agents such as anti-TNF therapy or vedolizumab was employed as needed.3

Toxicity Management

Patients on dostarlimab plus chemotherapy face a dual toxicity burden. The expected effects of carboplatin and paclitaxel layered on top of immune-mediated AEs driven by PD-1 blockade. An important feature of immune-mediated toxicity is its unpredictability in timing: some reactions emerge early, within the first 4 to 6 weeks, while others can appear months or even more than a year after starting treatment—and in some cases, after therapy has already been stopped.3

Immune-Mediated Adverse Events

Endocrine toxicities are among the most common. Thyroid dysfunction occurs frequently and can be subtle enough to go undetected without routine laboratory monitoring. Adrenal insufficiency and hypophysitis are less common but can present insidiously with fatigue, hypotension, and hyponatremia. Type 1 diabetes is a rarer but important complication, sometimes presenting abruptly as diabetic ketoacidosis, and can emerge after prolonged exposure. Cases have been reported after approximately 2 years on a PD-1 inhibitor.3

Gastrointestinal and hepatic toxicities include colitis and diarrhea, which are often low-grade and manageable, but grade 3 to 4 events can be severe, occasionally requiring hospitalization and high-dose corticosteroids. Immune-mediated hepatitis presents as elevated liver enzymes and bilirubin, and careful differentiation from chemotherapy-related liver toxicity, viral hepatitis, or hepatic disease progression is essential.3

Pulmonary toxicity, specifically pneumonitis, is relatively infrequent but carries serious consequences if missed. It can appear at any point from the earliest treatment cycles to beyond 30 weeks.3

Dermatologic reactions such as rash and pruritus are common and generally manageable. Severe cutaneous reactions—including Stevens-Johnson—are rare but are recognized label events and should remain on the differential in cases of severe or atypical skin involvement.3

Renal, musculoskeletal, and other immune-mediated effects round out the spectrum. Nephritis may manifest as a rising creatinine or declining GFR. Inflammatory arthritis and myalgias can be significant enough to warrant rheumatology involvement. Neurologic and cardiac immune-mediated are uncommon but potentially life-threatening and require prompt recognition.3

Timing and Monitoring

The variability of immune-mediated toxicity has direct implications for monitoring strategy. Rash and thyroid abnormalities may surface within the first few cycles, while conditions such as type 1 diabetes, inflammatory arthritis, and late-onset pneumonitis can emerge months to years into treatment. This underscores the importance of baseline testing before initiating systemic therapy including HIV, hepatitis B, and hepatitis C screening, as well as tuberculosis and hepatitis risk assessment in patients who may ultimately need anti-TNF therapy. 3

Management Principles

Toxicity management is graded and stepwise. For grade 1 or mild events, treatment is generally continued with close monitoring, and low-dose steroids may be considered for select toxicities. Grade 2 events typically warrant holding the immunotherapy agent, initiating moderate-dose corticosteroids, and resuming only once the toxicity has resolved to grade 1 or below and the patient is on no more than 10 mg of prednisone equivalent daily.3

Grade 3 to 4 events often mandate permanent discontinuation of the PD-1 inhibitor. Management in these cases involves high-dose corticosteroids with a slow taper over at least 4 weeks, with escalation to second-line immunosuppressive agents such as anti-TNF therapy or vedolizumab for steroid-refractory cases.3

The Pharmacist’s Role

Pharmacists play an integral role in the safe and effective use of dostarlimab across the full treatment continuum. Key responsibilities include verifying dosing and baseline labs prior to initiation, educating patients on the distinction between immune-related and chemotherapy-related side effects, and supporting timely toxicity recognition and management. Because immune-mediated AEs can emerge at any point, ongoing pharmacist engagement is essential throughout the entire course of therapy.

As dostarlimab becomes standard of care for a broader population of patients with advanced and recurrent endometrial cancer, pharmacists are also well-positioned to contribute at the systems level through protocol development, formulary oversight, and the integration of graded toxicity management criteria into clinical workflows. In a treatment regimen of this complexity, the pharmacist's role extends well beyond dispensing.

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