FDA Expands Chemo-Free Bladder Cancer Combo for Curative Setting

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High-risk, non-muscle-invasive bladder cancer (NMIBC) presents a persistent challenge for urologists, particularly when patients cannot tolerate cisplatin-based chemotherapy. The standard of care, Bacillus Calmette-Guérin (BCG), often falls short, leading to recurrence and progression to muscle-invasive disease. This unmet need has driven the search for effective, less toxic alternatives.

KEY TAKEAWAYS

- The Pivot: The FDA expanded the indication for a chemotherapy-free combination, offering a new first-line option for cisplatin-ineligible patients with locally advanced or metastatic urothelial carcinoma.
- The Data: The combination reduced the risk of disease progression or death by 38% (HR 0.62; 95% CI, 0.49-0.79; PThe Action: Clinicians should consider this combination for cisplatin-ineligible patients with advanced urothelial carcinoma, particularly those with PD-L1 expression, as a frontline treatment.

Urothelial carcinoma, especially in its advanced or metastatic forms, has historically relied on platinum-based chemotherapy as the backbone of first-line treatment. But a significant proportion of patients, up to half in some cohorts, are deemed ineligible for cisplatin due to comorbidities like renal dysfunction, hearing loss, or peripheral neuropathy. For these patients, carboplatin-based regimens offer inferior efficacy, leaving a substantial therapeutic gap. The FDA's recent expanded approval for enfortumab vedotin-ejfv plus pembrolizumab addresses this critical population, providing a chemotherapy-free alternative for first-line treatment of locally advanced or metastatic urothelial carcinoma in cisplatin-ineligible patients.1

This expanded indication stems from the EV-302/KEYNOTE-A39 trial, a global, multicenter, open-label, randomized Phase III study. The trial enrolled 886 patients with previously untreated locally advanced or metastatic urothelial carcinoma who were eligible for cisplatin- or carboplatin-containing chemotherapy. Patients were randomized 1:1 to receive either enfortumab vedotin-ejfv in combination with pembrolizumab or platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin). The primary endpoints were overall survival (OS) and progression-free survival (PFS), assessed by blinded independent central review. Secondary endpoints included objective response rate (ORR), duration of response (DoR), and safety.1

The numbers

The combination of enfortumab vedotin-ejfv and pembrolizumab significantly improved both overall survival and progression-free survival compared to chemotherapy. Patients receiving the combination lived a median of 31.5 months, compared to 16.1 months for those on chemotherapy (HR 0.47; 95% CI, 0.38-0.58; P12.5 months in the combination arm versus 6.3 months in the chemotherapy arm (HR 0.45; 95% CI, 0.38-0.54; PObjective response rates were also higher

with the combination, reaching 68% (95% CI, 63.9-72.6) compared to 44% (95% CI, 39.4-48.4) with chemotherapy. Complete responses were observed in 12% of patients in the combination arm versus 4% in the chemotherapy arm. The duration of response was also longer with the combination, though specific median values were not yet mature at the time of the primary analysis. These efficacy benefits were consistent across prespecified subgroups, including those defined by PD-L1 expression, age, and visceral metastatic disease.1

Safety profiles were consistent with the known toxicities of each agent. Grade 3 or higher treatment-related adverse events occurred in 56% of patients in the combination arm and 70% in the chemotherapy arm. Peripheral neuropathy, a common adverse event with enfortumab vedotin-ejfv, occurred in 67% of patients in the combination arm (Grade 3 or higher in 7%), while skin reactions were seen in 64% (Grade 3 or higher in 17%). Hyperglycemia was reported in 14% (Grade 3 or higher in 7%). These rates are manageable, but clinicians must remain vigilant for these specific toxicities. The trial was open-label, which is an obvious caveat, but the primary endpoints were assessed by a blinded independent central review, mitigating some of the bias concerns.1

The EV-302/KEYNOTE-A39 trial included patients eligible for cisplatin, which means the data directly supports the use of this combination as a new standard of care for all eligible patients, not just those ineligible for cisplatin. This broadens the impact significantly beyond the initial cisplatin-ineligible population. The trial's robust design and clear efficacy signals provide strong evidence for this shift. Still, the long-term implications of managing chronic toxicities, particularly peripheral neuropathy, will require careful post-marketing surveillance and real-world data collection. The trial was not powered to detect differences in rare adverse events, and that gap matters for long-term patient management.1

CLINICAL IMPLICATIONS

The EV-302/KEYNOTE-A39 results are a clear win for patients with advanced urothelial carcinoma. For too long, cisplatin-ineligible patients faced inferior outcomes with carboplatin-based regimens. This chemotherapy-free combination offers a substantial improvement in both survival and progression-free survival, setting a new benchmark for first-line treatment.

Clinicians now have a compelling alternative to chemotherapy, one that delivers superior efficacy with a manageable, albeit distinct, toxicity profile. The median overall survival of 31.5 months is particularly striking, nearly doubling that of chemotherapy. This is not a marginal gain; it represents a significant extension of life for patients with a historically poor prognosis.

The shift away from chemotherapy as the default first-line option for advanced urothelial carcinoma is overdue. While the combination does introduce its own set of adverse events, such as peripheral neuropathy and skin reactions, these are generally predictable and manageable with proactive monitoring. The data supports a re-evaluation of current treatment algorithms, placing this combination at the forefront for eligible patients.

The next step involves understanding how this combination performs in real-world settings, particularly in patients with more complex comorbidities not fully represented in a clinical trial. Furthermore, identifying biomarkers beyond PD-L1 that predict an even greater response would refine patient selection. For now, the message is clear: the chemotherapy-free era for advanced urothelial carcinoma has arrived.

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