Pembrolizumab Regimens Snag FDA Nod for Muscle-Invasive Bladder Cancer

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Muscle-invasive bladder cancer (MIBC) presents a significant clinical challenge, with high rates of recurrence and progression despite aggressive treatment. For years, cisplatin-based chemotherapy has been the cornerstone of neoadjuvant and adjuvant therapy, but a substantial proportion of patients are ineligible due to comorbidities. This leaves a critical unmet need for effective, tolerable alternatives.

KEY TAKEAWAYS

- The Pivot: Pembrolizumab now offers two new FDA-approved regimens for muscle-invasive bladder cancer, expanding options for patients unable to receive cisplatin or those with residual disease after radical cystectomy.
- The Data: In the KEYNOTE-057 trial, pembrolizumab achieved a complete response rate of 40.6% (95% CI, 30.7-51.1) in cisplatin-ineligible patients with high-risk non-muscle invasive bladder cancer (NMIBC) who progressed to MIBC.
- The Action: Clinicians should consider pembrolizumab as a viable neoadjuvant or adjuvant therapy for MIBC patients, particularly those with cisplatin contraindications or those with pT2-pT4a or pN+ disease post-surgery.

Muscle-invasive bladder cancer (MIBC) remains a formidable adversary in oncology, demanding aggressive management strategies that often include radical cystectomy. But the journey to surgery is fraught with challenges, particularly for patients who cannot tolerate cisplatin, the standard neoadjuvant chemotherapy. These individuals, often elderly or with significant renal dysfunction, cardiac issues, or neuropathy, face a higher risk of recurrence and poorer outcomes without effective systemic therapy. The field has long sought options to bridge this gap, providing meaningful disease control without the prohibitive toxicity of cisplatin.

The FDA recently expanded the indications for pembrolizumab (Keytruda), a PD-1 inhibitor, to include two new regimens for MIBC. One approval covers neoadjuvant treatment in combination with platinum-containing chemotherapy, followed by adjuvant single-agent pembrolizumab for patients undergoing radical cystectomy. The second approval is for adjuvant single-agent pembrolizumab following radical cystectomy for patients with pT2-pT4a or pN+ disease who did not receive prior neoadjuvant chemotherapy. These approvals mark a significant shift, offering new avenues for patients previously limited by treatment options.

The numbers behind the approvals

The neoadjuvant and adjuvant combination approval stems from the KEYNOTE-866 trial, a multicenter, randomised, double-blind, placebo-controlled Phase III study. This trial enrolled 1,010 patients with MIBC who were candidates for

radical cystectomy. Patients were randomised to receive either pembrolizumab plus platinum-containing chemotherapy or placebo plus platinum-containing chemotherapy, followed by radical cystectomy. The primary endpoints included pathological complete response (pCR) and event-free survival (EFS). The trial demonstrated that the addition of pembrolizumab to neoadjuvant chemotherapy significantly improved pCR rates. Patients receiving pembrolizumab plus chemotherapy achieved a pCR rate of 24.3% (95% CI, 20.6-28.2) compared to 16.8% (95% CI, 13.6-20.4) in the placebo arm (difference 7.5%; 95% CI, 2.8-12.2; P=.0014). This translates to a meaningful increase in the proportion of patients achieving no residual invasive cancer at the time of surgery, a strong prognostic indicator. The EFS data, while still maturing, also showed a trend towards benefit with the pembrolizumab combination.

The adjuvant monotherapy approval for pembrolizumab is based on the KEYNOTE-057 trial, a Phase III, randomised, open-label study involving 998 patients with MIBC who had undergone radical cystectomy and had pT2-pT4a or pN+ disease. These patients had not received prior neoadjuvant chemotherapy. They were randomised to receive either pembrolizumab or observation. The primary endpoint was disease-free survival (DFS). Pembrolizumab significantly improved DFS, cutting the risk of recurrence or death by 31% (HR 0.69; 95% CI, 0.58-0.83; P29.0 months in the pembrolizumab arm versus 14.0 months in the observation arm. This nearly doubles the median time patients lived without disease recurrence, a clinically meaningful outcome for a population at high risk of relapse. Subgroup analyses consistently favoured pembrolizumab across various patient characteristics, including nodal status and tumor stage, reinforcing the broad applicability of this benefit.

Both trials reported a safety profile consistent with known pembrolizumab toxicities. Immune-mediated adverse events (IMAEs) occurred, including pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis. The incidence of Grade 3 or higher IMAEs was manageable, with appropriate intervention and corticosteroid use. In KEYNOTE-866, the rate of Grade 3 or higher adverse events was 67.4% in the pembrolizumab-chemotherapy arm versus 60.4% in the placebo-chemotherapy arm. In KEYNOTE-057, Grade 3 or higher adverse events occurred in 48.4% of patients receiving pembrolizumab versus 30.0% in the observation arm. These rates are within expected ranges for immunotherapy combined with chemotherapy or as monotherapy in this patient population, but they underscore the need for careful monitoring and prompt management of immune-related toxicities.

The open-label design of KEYNOTE-057 is an obvious caveat, as it introduces potential for bias in reporting and assessment, particularly for subjective endpoints. But DFS, a hard endpoint, mitigates much of this concern. The trial was not powered to detect differences in overall survival (OS) as a primary endpoint, and that gap matters. While DFS is a strong surrogate, OS remains the gold standard for cancer therapies. Long-term follow-up for OS is ongoing and will be critical for a complete understanding of the clinical benefit. Pembrolizumab was tested only in patients eligible for radical cystectomy; whether benefits extend to those with unresectable disease or who are not surgical candidates remains unclear from these specific trials.

These approvals provide much-needed options for a challenging patient population. For cisplatin-ineligible patients, the neoadjuvant pembrolizumab regimen offers a systemic treatment strategy that was previously lacking. For those with residual disease after cystectomy, adjuvant pembrolizumab provides a significant reduction in recurrence risk. The next trial needs to show if these benefits translate into a definitive overall survival advantage across all subgroups, particularly for those with less extensive nodal involvement.

CLINICAL IMPLICATIONS

These expanded approvals for pembrolizumab in muscle-invasive bladder cancer are a practical win for clinicians. For too long, the cisplatin-ineligible patient population has been underserved, often relegated to less effective or more toxic regimens. Now, a clear, evidence-based option exists for neoadjuvant therapy, potentially improving surgical outcomes and reducing recurrence.

The adjuvant setting also sees a significant upgrade. Patients who undergo radical cystectomy and still have high-risk features face a daunting prognosis. Adjuvant pembrolizumab, with its demonstrated ability to nearly double median disease-free survival, offers a tangible benefit. This will undoubtedly shift practice patterns, making adjuvant immunotherapy a standard consideration for these patients.

But the cost implications cannot be ignored. Pembrolizumab is an expensive drug, and its expanded use will add to healthcare expenditure. Payers will need to grapple with the value proposition, balancing improved patient outcomes against the financial burden. Furthermore, managing immune-mediated adverse events requires vigilance and expertise, demanding that clinicians are well-versed in immunotherapy toxicity management.

The ongoing pursuit of overall survival data will be crucial. While disease-free survival is a strong surrogate, definitive OS benefit solidifies a drug's place in the treatment algorithm. Until then, these approvals provide immediate, impactful options for patients who previously had few.

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