Clinical Trial

Major Finding: Combined sEphB4-HSA and pembrolizumab improves overall survival as compared to pembrolizumab alone.

Concept: The regimen was well tolerated, with hypertension being the most commonly reported toxicity.

Impact: Further evaluation of sEphB4-HSA in high-grade urothelial carcinoma is warranted.

sEphB4-HSA PLUS PEMBROLIZUMAB IMPROVES OVERALL SURVIVAL IN UROTHELIAL CARCINOMA

First-line platinum-based chemotherapy as well as antibodies targeting PD-1 or PD-L1 demonstrate low response rates in patients with metastatic urothelial carcinoma (UC); therefore, treatments for these patients remain an unmet clinical need. The EphB4 receptor tyrosine kinase and its ligand EphrinB2 are highly expressed in UC, and blocking their bidirectional signaling using soluble EphB4-human serum albumin (sEphB4-HSA) inhibits tumor growth in preclinical models. Moreover, combining sEphB4-HSA with an anti–PD-1 agent is more effective than each single agent alone. Sadeghi and colleagues therefore initiated a phase II clinical trial to assess the combination of sEphB4-HSA along with the PD-1 inhibitor pembrolizumab in 70 patients with platinum-refractory UC. The primary endpoints for this study were overall survival (OS) and tolerability, with additional endpoints of progression-free survival (PFS), objective response, duration of response (DOR), and toxicity. The study met its primary endpoints with an overall median OS of 14.6 months, with the median OS for patients who were EphrinB2-positive being 21.5 months. Among 63 evaluable patients, the objective response rate was 41%, with a complete response rate of 18% (11 patients). Among the 70 intent-to-treat patients, the median PFS was 4.1 months, while the median DOR was not yet reached. For EphrinB2-positive patients, the ORR was 52% and the complete response rate was 24%. This patient population also had a median PFS of 5.7 months, and the median DOR was not yet reached. Evaluation of toxicity showed that six patients (8.6%) discontinued treatment, with hypertension being the most common toxicity related to sEphB4-HSA. Severe immune-related adverse events were observed in one patient and resulted in death, but other immune-mediated adverse events were resolved with corticosteroids. In summary, this trial shows that the combination of sEphB4-HSA and pembrolizumab improves OS as compared to the historical data for pembrolizumab alone in UC, suggesting further phase III trials are warranted for this regimen in this setting. ■

Sadeghi S, Quinn D, Dorff T, Pal S, Groshen S, Tsao-Wei D, et al. EphrinB2 inhibition and pembrolizumab in metastatic urothelial carcinoma. J Clin Oncol 2022 Aug 19 [Epub ahead of print].

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Rectal Cancer

Major Finding: Transcriptomic and immune features distinguish responses to neoadjuvant therapy in rectal cancer.

Concept: Immune infiltration as well as *IGF2* and *L1CAM* expression are associated with neoadjuvant therapy response.

Impact: This work proposes features that can highlight those patients who might not need subsequent surgery.

TRANSCRIPTOMIC PROFILING HIGHLIGHTS RECTAL TUMORS WITH IMPROVED PROGNOSIS

The standard of care for patients with rectal cancer involves surgical resection, ranging from local excision to extensive removal of the rectum and the mesorectal envelope. Prior to surgery, radiation and chemotherapy are often administered as neoadjuvant therapy, which elicits a clinical response in most patients with locally advanced rectal cancer. A complete response has been associated with low recurrence and excellent survival, leading Chatila and colleagues to explore the genomic and transcriptomic features that distinguish patients for whom organ preservation following neoadjuvant therapy may be an option. DNA sequencing analysis of pretreated primary tumor samples found that most tumors were mismatch repair proficient and microsatellite stable (pMMR/MSS) and that the most frequently altered genes were *APC*, *TP53*, and *KRAS*. Genomic profiles of tumors by rectal location revealed clear differences in Wnt pathway alterations, driven largely by *APC* mutations, with the most frequent being observed in the upper rectum and significantly decreasing as proximity to the anal verge increased, reflecting the observed differences in clinical prognosis of rectal tumors in different regions. Interestingly, no somatic DNA alterations were associated with clinical variables or complete response, although *KRAS* mutations were associated with shorter disease-free survival in patients treated with neoadjuvant chemoradiation followed by consolidative chemotherapy. Conversely, RNA sequencing analysis of pretreatment samples revealed high expression of insulin-like growth factor 2 (*IGF2*) and L1 cell adhesion molecule (*L1CAM*) in tumors from patients who had an incomplete response to neoadjuvant therapy. Moreover, immune signature analysis identified a cluster of immune hot pMMR/MSS tumors that exhibited improved response and disease-free survival and were characterized by extensive immune infiltration, high Th1 cell levels, and high TGFβ signaling, as well as overexpression of genes encoding targets of immune checkpoint blockade. In summary, this study profiles the genomic and transcriptomic landscape of rectal cancer, highlighting features associated with superior response to neoadjuvant therapy that may have the potential to distinguish patients with improved prognosis. ■

Chatila WK, Kim JK, Walch H, Marco MR, Chen CT, Wu F, et al. Genomic and transcriptomic determinants of response to neoadjuvant therapy in rectal cancer. Nat Med 2022;28:1646–55.

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