PD-1 Checkpoint Inhibitor Shows Promise for Anal Cancer

Zynyz immunotherapy added to chemotherapy extended progression-free survival and may improve overall survival.

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Incyte's PD-1 checkpoint inhibitor Zynyz (retifanlimab) plus chemotherapy significantly improved progression-free survival in previously untreated patients with advanced anal cancer, according to late-breaking study results presented at the European Society for Medical Oncology Congress (#ESMO2024) in Barcelona.

This Phase III trial—which included people living with HIV—is the first and largest study of a first-line checkpoint inhibitor for advanced anal cancer, a disease with "high unmet medical need," said presenter Sheela Rao, MD, of the Royal Marsden National Health Service Foundation Trust. Based on these findings, she suggested that Zynyz plus platinum-based chemotherapy may represents "a new standard of care" for patients with advanced squamous cell anal cancer.

Anal cancer, like cervical cancer, is usually caused by the human papillomavirus (HPV), a common sexually transmitted infection. The virus triggers abnormal cell growth (dysplasia), which can progress to precancerous lesions and, ultimately, invasive cancer. Anal cancer is distinct from rectal cancer, which is related to colon cancer. Anal cancer is uncommon among the general population, but people living with HIV are at greater risk. HPV vaccines lower the risk of acquiring the virus, and anal screening and early treatment of precancerous lesions can prevent progression to cancer, but these are underutilized.

The POD1UM-303/InterAACT2 trial (NCT04472429) evaluated the safety and efficacy of Zynyz for adults with inoperable locally recurrent or metastatic squamous cell anal carcinoma who were not previously treated with systemic chemotherapy. (Another trial, PODIUM-202, showed promising results for patients with locally advanced or metastatic anal cancer who experienced disease progression after platinum-based chemotherapy.)

"Advanced squamous cell anal carcinoma is an often-neglected rare condition that, despite its increasing incidence and the often poor prognosis, has had the same standard-of-care treatment for decades with very few trials," Rao said in an Incyte news release. Treatment typically involves chemotherapy and radiation, but relapse is common.

Zynyz is a monoclonal antibody that targets PD-1, an immune checkpoint protein on T cells that regulates immune function. Some tumors can hijack PD-1 to turn off immune responses. Drugs that block the interaction between PD-1 and its PD-L1 receptor on cancer cells can release the brakes and restore T-cell activity. In 2023, the Food and Drug Administration (FDA) granted accelerated approval of Zynyz for advanced Merkel cell carcinoma. None of the currently approved checkpoint inhibitors are specifically indicated for anal cancer, though some can be used to treat solid tumors with specific genetic features regardless of location.

PODIUM-303 enrolled 308 participants. About 70% were women, most were white and the median age was 62 years. People with well-controlled HIV on antiretroviral therapy were eligible, making up 4% of the study population. Most patients had previously received radiation therapy. Around 90% had PDL-1 positive tumors, which is associated with better response to PD-1 checkpoint inhibitors.

The participants were randomly assigned to receive IV infusions of Zynyz or a placebo, both in combination with platinum-based chemotherapy (carboplatin and paclitaxel), for up to six monthly cycles, followed by Zynyz or placebo alone for up to a year. Those who experienced disease progression in the placebo group could cross over to Zynyz.

Progression-free survival time was 9.3 months for people in the Zynyz group versus 7.4 months for those in the placebo group, reflecting a 37% reduction in the risk of disease progression or death. The overall response rates (tumor regression) were 56% and 44%, respectively, and the median duration of response was about twice as long with Zynyz (14.0 versus 7.2 months). Overall survival data are not yet mature but so far appear to favor Zynyz by about six months (29.2 versus 23.0 months), Rao reported.

Treatment was generally safe and well tolerated, but side effects were common. Most people in both groups experienced severe (Grade 3 or higher) treatment-emergent adverse events. The most common side effects in the Zynyz plus chemotherapy group were anemia, nausea and hair loss. One concern with checkpoint inhibitors that restoring immune response against cancer can also activate the immune system more broadly, leading to excessive inflammation. In this study, 46% of Zynyz recipients experienced immune-mediated adverse events, compared with 24% in the placebo group. HIV-positive participants maintained viral suppression and did not experience additional or worse side effects.

Based on these findings, Incyte indicated that it plans to file for FDA approval of Zynyz for anal cancer by the end of the year.

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