Antibody-Drug Conjugate Shows Clinical Benefit Against Small-Cell Lung Cancer

Patients with brain metastasis experienced responses in the Phase I clinical trial.

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Boston — Zocilurtatug pelitecan (zoci), also known as ZL-1310, an investigational antibody-drug conjugate (ADC) that targets the protein DLL3, demonstrated both safety and capacity to induce anticancer responses in patients with extensive-stage small cell lung cancer (ES-SCLC) according to results from a Phase I clinical trial presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held October 22-26.

SCLC accounts for about 12% of all lung cancer cases in the United States, and the disease is fairly aggressive, with a 9% five-year relative survival rate according to the latest data. “Most patients with extensive-stage small cell lung cancer still experience relapse after standard-of-care therapies with chemotherapy and immunotherapy,” explained presenter Grace K. Dy, MD, director of translational research for thoracic medicine at the Roswell Park Comprehensive Cancer Center.

“DLL3 is a valid target for drug development in SCLC because of its tendency to be highly expressed on SCLC cells. As a newer ADC with modern linker/payload technology, zoci improves on past DLL3-targeting ADC approaches to reduce toxicity and increase the therapeutic index—which we hope will lead to better patient outcomes,” she said.

By attaching a cancer-killing payload of a topoisomerase I inhibitor to an antibody designed to bind to the DLL3 protein on SCLC cancer cells, the drug’s design triggers cell death in SCLC while sparing healthy cells, according to Dy.

In an open-label, multicenter, Phase I clinical trial, Dy and her colleagues tested zoci in 115 patients with ES-SCLC whose disease had progressed after platinum-based chemotherapy. Of those patients, 37 (32%) had ES-SCLC that had metastasized to the brain. These patients had been heavily pretreated with available therapies: 90% with PD-L1 and 44% with two or more prior therapies.

All patients received zoci intravenously every three weeks until their disease progressed or they

experienced unacceptable toxicity, with doses escalating from 0.8 mg/kg to 2.8 mg/kg. Treatment cycles ranged from one to 22, and among patients evaluated, the median number of treatment cycles received was six.

Zoci demonstrated antitumor activity in the 102 patients evaluable at the data cutoff, with a confirmed objective response rate (ORR) of 47% at all dose levels (additional 3% unconfirmed). The researchers observed three complete responses, 45 partial responses (additional three unconfirmed), and 39 stable disease at all dose levels. The 1.6 mg/kg patient cohort had the most objective responses to treatment at 58% confirmed partial response (additional 10% unconfirmed) out of 19 patients with one prior line of therapy. The 32 patients with asymptomatic brain metastasis responded to treatment better than any other patient subgroup with an ORR of 66%, composed of one complete response and 19 partial responses (and an additional unconfirmed response). Responses were also observed in patients with untreated brain metastasis at baseline (8/10).

The team observed responses to treatment even in the four patients whose tumors tested negative for DLL3 expression; in this group, the ORR was 50%. The 10 patients who had received prior treatments targeting DLL3 responded to zoci with a 40% ORR, including one complete and three partial responses.

“These findings show that zoci therapy can achieve impressive response rates in patients with ES-SCLC compared to currently available standard-of-care options,” said Dy.

Patients tolerated zoci reasonably well, Dy said, with treatment-related adverse events (TRAEs) of grade 3 or higher reported in 23 out of 115 patients (20%). The most common TRAEs were anemia and neutropenia (abnormally low neutrophil count in the bloodstream). At 1.2 mg/kg and 1.6 mg/kg doses, adverse events led to dose reduction in 5.6% of patients and no drug discontinuation.

“At the current doses being evaluated as part of the expansion cohort, zoci’s toxicity profile is manageable, with adverse events leading to low rates of dose reduction and discontinuation,” Dy said. “The comparatively high response rates observed in the trial indicates zoci’s potential as a first-line therapy for SCLC, which is currently being investigated.”

“We did observe higher response rates than the second-line therapies that have historically been available for ES-SCLC, but given this trial’s highly selected patient population, we’ll need larger trials to establish zoci’s superiority as a treatment,” she noted.

The study’s limitations include both its size and the fact that the enrolled patients were highly selected on the basis of being eligible for clinical trials in mostly academic centers.

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