Zenocutuzumab Shines in PDAC

An investigational first-in-class therapy for tumors harboring *NRG1* fusions shows early efficacy, albeit in a modest number of patients so far. The response rate with zenocutuzumab (MCLA-128; Merus) appears especially striking in pancreatic ductal adenocarcinoma (PDAC), said Alison Schram, MD, of Memorial Sloan Kettering Cancer Center in New York, NY. She presented data from the ongoing phase I/II eNRGy trial during the American Society of Clinical Oncology 2021 Annual Meeting, June 4–8.

"Chromosomal rearrangements involving *NRG1* are rare oncogenic drivers," Schram said, "and enriched in *KRAS*–wild-type pancreatic cancer, as well as in invasive mucinous adenocarcinoma of the lung," a subtype of non–small cell lung cancer (NSCLC). Through RNA sequencing, numerous fusion partners with NRG1 have been identified, she added, including ATP1B1, CD74, and SDC4.

Zenocutuzumab, a bispecific antibody, targets HER2 and HER3, working via a "dock and block" mechanism, explained Merus's CEO Bill Lundberg, MD. First, "it docks onto HER2, which is abundant, so it's highly concentrated on the cell surface and can then bind HER3, blocking interactions with NRG1—HER3's ligand—or with NRG1 fusions." By preventing HER2–HER3 dimerization, zenocutuzumab also halts downstream activation of cell-proliferative PI3K/mTOR signaling. As well, it induces enhanced antibody-dependent cellular cytotoxicity.

eNRGy has enrolled 61 patients to date, all with locally advanced, metastatic, or inoperable *NRG1* fusion–positive (*NRG1+*) cancers. Schram reported results for 45 evaluable patients across three cohorts: 12 with PDAC; 24 with NSCLC; and nine with various other solid tumors, including cholangiocarcinoma. The objective response rates (ORR) were 42%, 29%, and 22%, respectively.

In the PDAC group, another 50% experienced stable disease, and of 11 patients assessed for the tumor biomarker CA19-9—often used to monitor efficacy—"all had sustained declines of more than 50% while on treatment."

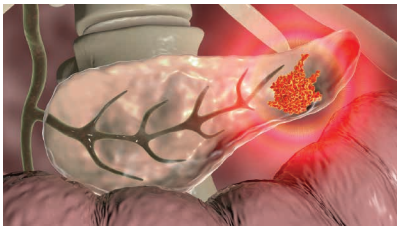
"The median age in this cohort was 47.5 years, consistent with prior findings that *NRG1+* PDAC tends to occur in younger patients," Schram observed. "Since the approval of a PARP inhibitor [olaparib (Lynparza; AstraZeneca)] for PDAC, genomic sequencing has become more common, so in this context, if *KRAS*–wild-type turns up and your patient is young, I'd consider looking for *NRG1* fusions as well."

Zenocutuzumab was "extremely well tolerated," Schram said, with low-grade fatigue, anemia, and diarrhea being the main side effects, and a "notable absence" of severe gastrointestinal, skin, or cardiac toxicities.

With eNRGy, "we now have the first prospective clinical validation of *NRG1* fusions as actionable oncogenic drivers," Schram concluded, and "the first demonstration of effective targeting of a genomically altered ligand" rather than receptors such as TRK or RET.

Thus far, "all approved fusion-targeting drugs are small molecules—for instance, larotrectinib [Vitrakvi; Bayer]," said study discussant Ignacio Garrida-Laguna, MD, PhD, of Huntsman Cancer Institute in Salt Lake City, UT. Zenocutuzumab is therefore "proof-of-concept that antibody-based therapies can also hit" fusion oncoproteins. "The drug's size is undisclosed, but it would be interesting to learn more about its potential to cross the blood–brain barrier and treat brain metastases" in NSCLC.

As well, "we need to learn if *NRG1* fusions are prognostic in PDAC—analysis of real-world datasets with annotated genomic information will be critical," Garrida-Laguna said. Because zenocutuzumab "looks incredibly effective" against this notoriously difficult-to-treat cancer, "it begs the question of what ORR and 'n' of patients would support an accelerated approval," he added. "For context, vemurafenib [Zelboraf; Genentech] was approved for Erdheim Chester disease with efficacy data in only 26 patients."



Currently, zenocutuzumab holds orphan drug designation for PDAC and fast-track status for metastatic *NRG1+* cancers that have progressed on standard therapy. An update on its path to registration, which Merus indicated could be tumor-agnostic or tumor-specific, is expected by the first half of 2022. *–Alissa Poh* ■

Ovarian Cancer Screening Falls Short

According to one of the largest clinical trials ever performed, ovarian cancer screening does not decrease disease mortality in the general population (Lancet 2021;397:2182–97). If population screening is to become a reality, researchers need to identify more sensitive methods to detect ovarian cancer earlier and in larger numbers of women, findings of the UKCTOCS study suggest.

Ovarian cancer screening is not standard practice, even among women at elevated risk, because there's scant evidence it improves survival. The only other large clinical trial to assess its effectiveness, which enrolled more than 78,000 participants, detected no benefit from ultrasound and tests for the ovarian cancer biomarker CA125 (JAMA 2011;305:2295–303).

In 2016, interim results from the UKCTOCS trial, which began in 2001, hinted that screening might work after all. Researchers enrolled more than 202,000 women in the UK and randomly assigned them to one of three groups in a 1:1:2 ratio: One was offered annual screening with ultrasound; the second was offered CA125 testing, with ultrasound follow-up for participants whose results suggested higher risk; and the third received no screening. Researchers tracked participants even after screening ended in 2011. With a median follow-up