CLINICAL UPDATE

Current Developments in the Management of Solid Tumors

The Use of Zenocutuzumab for *NRG1* Fusion–Positive Tumors

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H&O What type of testing is used to detect clinically relevant gene fusions?

AS Gene fusions can be detected using DNA- or RNA-based assays; however, RNA is typically superior. Most currently available DNA-based assays sequence the exons and select introns from cancer-related genes. NRG1 has very large introns that cannot be tiled on a DNA-based panel. Fusion breakpoints can occur in introns, so RNA-based assays can more reliably detect gene fusions.

H&O How reliable is liquid biopsy for detecting gene fusions?

AS Liquid biopsies can vary in terms of their ability to detect gene fusions. The sensitivity depends on: (1) the genes, introns, and exons that are covered within the panel; (2) the bioinformatic approach to analyzing the circulating tumor DNA (ctDNA); and (3) the variable shedding of ctDNA by different tumors. Both tumor type and stage of disease can influence the tumor shedding. For the majority of fusions and assays, liquid biopsies are still not quite as sensitive as tumor biopsies.

H&O Now that the *NRG1* gene fusion is newly actionable, what can you tell us about it?

AS NRG1, also known as neuregulin, is a ligand that binds to human epidermal growth factor receptor 3 (HER3). In normal cells, upon binding of NRG1 to HER3, HER3 then dimerizes with HER2, and that heterodimer leads to increased downstream signaling of the phosphoinositide 3-kinase and protein kinase B, or PI3K/AKT, pathway. *NRG1* fusions are oncogenic fusions that create a chimeric ligand. The ligand itself is abnormal and that can drive this signaling in a constitutively active way. How *NRG1* fusions do this is thought to be either increased expression of the ligand and/or tethering of NRG1 to the cell membrane, localizing NRG1 to where HER3 (its receptor) is, and causing increased signaling through proximity.

NRG1 is actionable in that researchers are able to target *NRG1* fusions and disrupt signaling for therapeutic benefit. There are several ways of targeting this particular pathway. Different approaches are currently being studied; however, zenocutuzumab (Zeno, Merus) is the option that has the most data specific to *NRG1* fusion–positive patients. Zenocutuzumab is a HER2/HER3 bispecific antibody that docks on HER2 and blocks NRG1 from binding to HER3; however, it also physically blocks the interaction of HER2 and HER3, so there are 2 ways that zenocutuzumab prevents signaling through the HER2/HER3 heterodimer. Monoclonal HER3 antibodies that prevent NRG1 from binding to HER3 can also block *NRG1* fusion signaling. Afatinib (Gilotrif, Boehringer Ingelheim) and other tyrosine kinase inhibitors are different in that they can inhibit the tyrosine kinase domain of HER2. Afatinib blocks downstream of ligand binding but prevents signaling from the HER2/HER3 heterodimer by blocking the tyrosine kinase activity. Tyrosine kinase inhibitors have been anecdotally described as therapeutically useful in patients who have *NRG1* fusions.

H&O How do patients with *NRG1*-positive fusions respond to currently available standard-of-care treatment options?

AS This is an important question because researchers are still learning about the natural history of patients with

NRG1-positive cancers. The eNRGy trial, the largest cohort of these patients described thus far, looked at more than 100 patients with non–small cell lung cancer (NSCLC) with *NRG1* fusions and retrospectively analyzed their response to standard-of-care treatments, including chemotherapy, immunotherapy, and combination chemotherapy/immunotherapy. The NRG1-positive NSCLC patients in the trial tended to respond very poorly to standard-of-care therapy. It seems that the group of patients who have this genetic fusion do less well than the NSCLC patients without it when given the standard therapies that are currently approved today. Whether that is also true of other diseases, including pancreatic cancer and other histologies, is being actively investigated.

H&O How can targeting pathogenic gene fusions, such as *NRG1*, improve outcomes in patients with advanced cancer?

AS *NRG1* fusions can be targeted using therapies that block the increased signaling from the NRG1/HER3/HER2 pathway. We have seen that by inhibiting this constitutive activation of signaling, cancers can shrink and be stabilized for long periods of time. The largest data set is from a clinical trial evaluating the HER2/HER3 bispecific antibody zenocutuzumab in patients with *NRG1* fusion–positive solid tumors. This is a large basket trial that is currently underway, and initial results have been presented. The data show that in patients with advanced cancer, there are impressive clinical responses across cancer types. Efficacy has been observed in NSCLC, pancreatic cancer, breast cancer, and other diseases, with both tumor shrinkage and disease stabilization for prolonged periods.

Additionally, afatinib—the tyrosine kinase inhibitor that, as I mentioned, inhibits HER2 kinase activity—has been found to be effective in *NRG1* fusion–positive cancers. There is currently no large prospective clinical trial to determine what the response rate is to afatinib. However, many case reports and case series as well as the NRG registry trial have included some data showing that the response rates to afatinib are clinically relevant.

Clearly, *NRG1* is a targetable genetic alteration. In my own experience, we have patients who have been on these treatments for years without growth of very difficult-to-treat cancers, like NSCLC and pancreatic cancer. This is especially notable in a population that seems to have poor outcomes with standard treatments.

H&O Which patients might benefit from precision oncologic treatment with zenocutuzumab?

AS NRG1 fusions are found in less than 1% of solid tumor patients overall but can be seen across different solid tumors. They are enriched in otherwise driver-negative NSCLC, in invasive mucinous adenocarcinomas of the lung (eg, in a rarer subtype of NSCLC), and in KRAS wild-type pancreatic cancer. The majority of patients with pancreatic cancer (over 90%) have KRAS mutations. The small population of patients who do not have KRAS mutations are enriched for *NRG1* fusions. Beyond that, *NRG1* fusions have been identified in breast cancer, in cholangiocarcinoma, and in a long list of other solid tumors. We believe and hope that targeted therapy may be effective in any patient with an oncogenic *NRG1* fusion. However, the majority of the data to date have been in patients with lung cancer and in those with pancreatic cancer, which make up the majority of patients enrolled in the clinical trials.

H&O What is important for oncologists to understand about the efficacy data on zenocutuzumab?

AS The observed efficacy of zenocutuzumab in a heavily pretreated patient population is very promising particularly because *NRG1* fusion–positive patients tend to have diseases with few alternative therapies and poor prognoses. For pancreatic cancer, there are very few effective options after standard first-line chemotherapy. In NSCLC, although chemoimmunotherapy in general is an effective treatment option, Drilon and colleagues have shown that it is not very effective in this particular subset of NSCLC patients. It is important when looking at the efficacy data to understand that this is a population of patients for which there are truly limited therapeutic options.

Most patients who responded to zenocutuzumab had symptomatic and radiographic improvement very quickly, achieving a response at the time of their first scan. Within a week or two of their first infusion, patients have said that they are starting to get their strength and appetite back, their cough is better, they are not requiring as much oxygen, and they are starting to go back to the gym and to work. Patients responding to zenocutuzumab generally report improved quality of life.

H&O What are some of the key findings on the safety profile of zenocutuzumab?

AS Zenocutuzumab is extremely well tolerated. The majority of adverse events observed during the eNRGy clinical trial were grade 1 or grade 2. There was no grade 3 side effect seen in more than 2% of the patients. Notably, many HER2-targeted therapies have gastrointestinal toxicity, and cardiac toxicity is a prominent concern. In this trial, there were very few clinically significant gastrointestinal or cardiac toxicities.

Zenocutuzumab does carry the risk of an infusion-related reaction as the drug is going in. This type of reaction was observed in about 12% of patients. However, patients can typically continue the infusion and do not have to come off the study because of this. Antihistamines and corticosteroids are generally effective at preventing and/or treating these infusion reactions.

H&O What has been your personal clinical experience with zenocutuzumab? Is there any advice you would share with your peers?

AS I have seen many patients who have very few or no alternative treatment options clinically benefit from this treatment. The side effect profile, as I mentioned, is one of the best attributes of zenocutuzumab, and patients generally feel better on the treatment. I have had patients enter the study with significant weight loss and severe chemotherapy-related side effects, and within weeks of being in the trial, they are able to function better and return to routine activities.

In terms of the durability, I have had patients in the study since 2019 who have had essentially no side effects. Truthfully, it is tough to get some patients off this trial. Even when the disease does start to slowly progress, some patients ask to stay on the drug because they have felt so good on it. It has benefited them from both a cancer perspective and a quality-of-life perspective.

H&O How do you see zenocutuzumab being incorporated into current oncologic practice?

AS The clinical trial of zenocutuzumab enrolled NRG1-positive patients who had previously received standard-of-care therapy or who were considered ineligible for or refused standard-of-care therapy. Consequently, the majority of patients in the study had previously been treated with chemotherapy or chemoimmunotherapy. In patients who have previously been treated with standard-of-care therapies, zenocutuzumab is an excellent treatment option and something that I would encourage all patients with *NRG1* fusion–positive cancers to consider, in particular patients with lung or pancreatic cancer.

One outstanding question is whether zenocutuzumab should be started earlier, potentially as first-line therapy, in patients who have *NRG1* fusion–positive lung cancer, given the available data showing that these patients do poorly on chemoimmunotherapy. A large clinical trial would be necessary to definitively answer that question, and given the rarity of the alteration, such a trial will likely not be conducted. However, some clinicians may choose zenocutuzumab as first-line therapy, particularly in patients who they anticipate will have severe toxicity from standard therapies.

My advice to oncologists on incorporating zenocutuzumab into their practice is that if a mild infusion reaction happens to not necessarily give up on the treatment. In all cases of an infusion reaction in the trial, we were able to stop the infusion, give the patient supportive care, and resume therapy either that day or at a subsequent visit. However, the safety of this approach should be evaluated on a case-by-case basis, taking into account the patient's comorbidities.

Disclosures

Dr Schram has served on the advisory board of Relay Therapeutics, Mersana, Merus, PMV Pharma, Schrodinger, Repare Therapeutics, Revolution Medicine, and Endeavor Biomedicines; has consulted for Blueprint Bio, Flagship Pioneering, and Redona Therapeutics; has served on the Steering Committee of Merus, Pfizer, and Relay Therapeutics; has received research funding paid to institution from AstraZeneca, ArQule, BeiGene/Springworks, Black Diamond Therapeutics, Elevation Oncology, Kura, Lilly, Merus, Northern Biologics, Pfizer, PMV Pharma, Relay, Repare Therapeutics, Revolution Medicine, and Surface Oncology; and has received food and beverage from PUMA and Repare Therapeutics.

Suggested Reading

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