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# Oncology Treatment Pathways<sup>®</sup>

Diagnostic Testing & Personalized Medicine

## Trastuzumab Deruxtecan Enters Treatment Paradigm for Gastrointestinal Cancer Subtypes

Jason Harris

**FAM-TRASTUZUMAB DERUXTECAN-NXKI** (Enhertu) represents a potential new standard of care for adults with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.

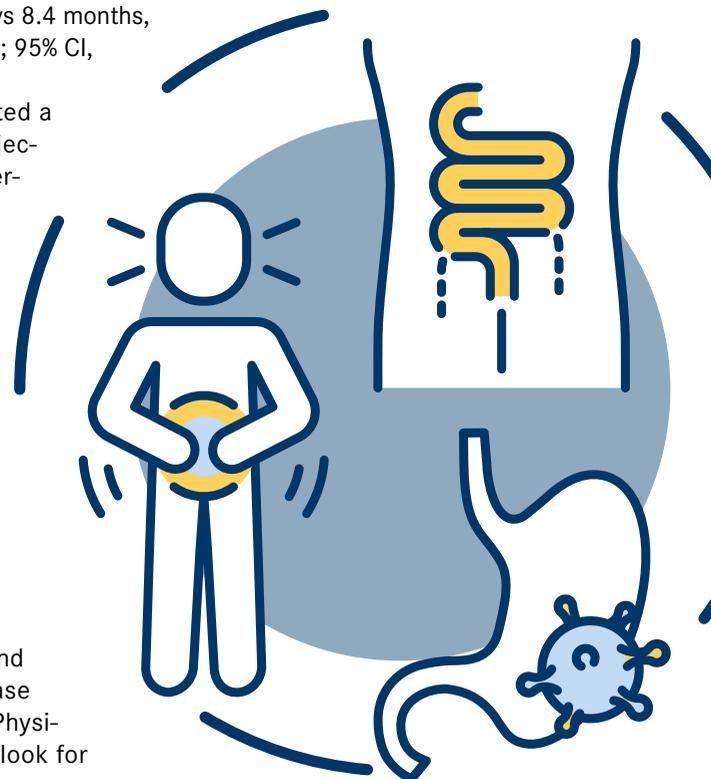
The FDA approved the new indication for the HER2-directed antibody-drug conjugate (ADC) on January 15, 2021, for patients who previously received trastuzumab (Herceptin)-based therapy. The agency initially approved the drug in December 2019 for patients with previously treated unresectable or metastatic HER2-positive breast cancer.

The latest indication is based on findings from the phase 2 DESTINY-Gastric01 trial (NCT03329690). The data demonstrated that treatment with trastuzumab deruxtecan resulted in an improvement in median overall survival compared

with physician’s choice of irinotecan or paclitaxel, at 12.5 vs 8.4 months, respectively (HR, 0.59; 95% CI, 0.39-0.88;  $P=$ .0097).<sup>1</sup>

The ADC also elicited a higher confirmed objective response rate versus chemotherapy. In the 126 patients who received trastuzumab deruxtecan, the response rate was 40.5% compared with 11.3% in the 62 patients who received chemotherapy ( $P < .0001$ ).

Notably, the indication includes a boxed warning for embryo-fetal harm and interstitial lung disease (ILD)/pneumonitis. Physicians are advised to look for



cough, dyspnea, fever, and other respiratory symptoms.

In an interview with *OncLive*®, Yelena Y. Janjigian, MD, chief of the Gastrointestinal Medical Oncology Service at Memorial Sloan Kettering Cancer Center in New York, New York, talked about what the approval of trastuzumab deruxtecan means for patients with this disease and the importance of reaffirming the presence of HER2 throughout therapy.

## **OncLive: What was noteworthy about the patient response to this drug?**



Yelena Y. Janjigian, MD,

**Janjigian:** In the main cohort of the study, all patients were HER2 positive; the HER2 low-expressing cohort was presented separately. A study in

the *New England Journal of Medicine*<sup>2</sup> looked at patients who were HER2 immunohistochemistry [IHC] 3+ or IHC 2+ based on archival samples, not samples taken at the most recent progression. What was remarkable about the study is that, despite having a heavily pretreated patient population in the third-line setting, the overall response is clinically meaningful and has not been previously demonstrated by any HER2-directed agents in later lines of therapy.

## **Could trastuzumab deruxtecan become the new standard of care in patients with previously treated gastric or GEJ cancers?**

It's important to note that the DESTINY-Gastric01 study focused on patients in later lines—third line or beyond. Despite that, the FDA approved use of trastuzumab deruxtecan after progression

of disease on trastuzumab; in other words, potentially in the second-line setting, third line, and beyond. What also is interesting to note is that the FDA label does suggest and encourage biopsies at the time of progression. That's very important to note because 20% to 30% of tumors lose HER2 overexpression after progression on a trastuzumab-based therapy. Therefore, if you're going to go after HER2 as a target, it would be important to confirm that it is still present in the tumor.

Studies are underway to evaluate and understand how this drug could be used in the first-line setting and its potential in that setting. Right now in first-line settings, we're focused on combinations with anti-PD-1-based therapies; regimens [include] pembrolizumab [Keytruda] plus trastuzumab in combination with first-line fluoropyrimidine oxaliplatin-based therapy, which is being explored in the phase 3 setting in the KEYNOTE-811 trial (NCT03615326).

## **Can you describe the mechanism of action for this drug?**

Trastuzumab deruxtecan is an antibody-drug conjugate that uses a trastuzumab-based inhibition with a crosslinking agent and a chemotherapy payload that is quite potent. The cytotoxic ratio to targeted agent ratio is higher than other ADCs that were studied before, such as TDM-1 [ado-trastuzumab emtansine; Kadcyla]. Here, trastuzumab deruxtecan uses 8 chemotherapy payload molecules to a HER2-directed molecule. The agent that's being used is the topoisomerase inhibitor DM1. It's really a potent agent, and it is active in gastrointestinal malignancies, particularly in gastric cancer.

## **In terms of safety, how does trastuzumab deruxtecan compare with existing therapies?**

This drug is typically well tolerated. Adverse effects related to cytotoxic chemotherapy, such as decreased white blood cell count and gastrointestinal toxicity, could be seen. One adverse effect that's important to note and to be aware of is ILD, which is an effect related to HER2 inhibition and HER2 binding in normal epithelial cells and lung interstitial cells. That's something to be on the lookout for, particularly since in the breast cancer studies and colorectal cancer studies treatment-related deaths were reported from ILD.

In gastric cancer, there were no treatment-related deaths reported thus far, and with close monitoring, dose interruptions, and dose reductions, the patients did well. ILD is something to monitor your patients for, both radiographically and clinically.

## **What is next in the treatment of HER2-positive gastric cancers?**

Trastuzumab deruxtecan has shown efficacy in [this] disease. It's important to build on that efficacy and continue to try to understand which patients need to continue on HER2 inhibition and which patients need to be changed to other types of therapy because of loss of HER2. I would encourage biopsies in the second-line setting to confirm that the target is present before switching therapy. Use of next-generation sequencing, as well as liquid biopsies or circulating tumor DNA, has helped us understand the heterogeneity of HER2 expression and gastric and esophageal cancer. We need to continue to test our patients for HER2 standard [therapy] in the first-line setting and retest again in second line. ■

# Genomics, AI, and Demography Will Remake Cancer Care by 2030

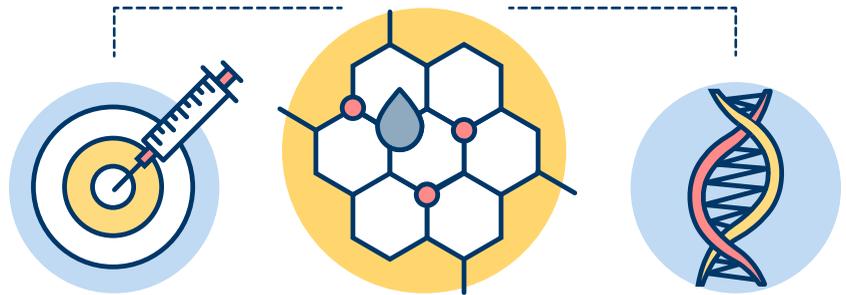
Jason Harris

**A WAVE OF APPROVALS** and a rapidly evolving treatment landscape could make the next decade a watershed period in breast cancer care, according to George W. Sledge Jr, MD.

“We are entering a decade which may finally lead to the effective control of not just breast cancer, but of many human cancers,” Sledge said during the Giants of Cancer Care® Lecture, “Breast Cancer in 2030: Where Are We Going?” presented at the 38th Annual Miami Breast Cancer Conference®. “I find this incredibly exciting every day [as I look to] my assistant professors and the fellows who [will] follow beyond them because I think they will hopefully see the final ability to beat these awful cancers.” Sledge is a professor of medicine in the Division of Oncology at the Stanford University Medical Center. He was the 2018 Giants of Cancer Care® award winner in breast cancer for his work with paclitaxel and the development of CLEVER, a biomedical informatics tool that can identify distant metastatic relapse and locoregional relapse with high accuracy.

## Genomic Revolution and AI

The “genomic revolution” and the “big data revolution” have already begun but will make real strides affecting treatment for patients with cancer, especially as the cost of genomic sequencing continues to drop as the technology improves. This trend will allow for more, if not all, patients with cancer to undergo panel testing for pathogenic mutations and next-generation sequencing, and Sledge anticipates the identification of smaller subpopula-



tions who may benefit from specific targeted therapies.

“Dynamic evolutionary changes will be mapped in real time and will dictate therapy,” Sledge said. “Our therapies in the past have all been based upon, in essence, population-based studies. But in the future, if we’re able to see clonal evolution of a particular mutation that allows a cancer to escape, say, from aromatase inhibitor therapy with popping up of an ESR1 mutation [we might be able to] measure that and intervene to prevent the tumor from growing. I think this will be increasingly likely as new studies are performed.”

“I suspect in a decade from now we will have a much better handle on which patients benefit from which drugs and indeed we’ll have new drugs to look for those specific targeted areas,” Sledge said. Furthermore, Sledge said that physicians will be able to harness artificial intelligence (AI)-based approaches to supplement imaging results, improve interpretation of patient data, and improve prediction models for breast cancer.

Sledge cited results from McKinney et al assessing the ability of an AI system to predict breast cancer. Compared with human experts, the AI produced an absolute reduction in false positives of 5.7% in the United States and an absolute reduction of

9.4% in false negatives. The AI system outperformed all human readers by an absolute margin of 11.5% on average.<sup>1</sup>

In its most basic form, investigators and physicians will use big data to improve pattern recognition. Sledge expects machine-based radiology, pathology, and radiation planning will be ubiquitous by 2030.

“I’m not here to say that the machines will replace radiologists, pathologists, or radiation physicists, but they’ll absolutely be an adjunct,” Sledge said. “AI-based approaches will increasingly direct all aspects of cancer therapy, and I suspect provide real-time clinical decision support for [clinicians] and patients in the clinic. While early attempts to do this, such as IBM’s Watson, have not been particularly successful, I think it’s only a matter of time before we will increasingly see something like this work.”

## Demography to Reshape Oncology Care

Sledge turned his attention away from the machine and back toward humanity as he explained his final prediction for the next decade: the effect of demographic changes. “Demography is going to be a major driver for [how we approach care],” Sledge said.

For the first time in US history, Americans aged 65 years or older are projected to outnumber children aged

18 years or younger by the year 2034, accounting for 23.4% and 19.8% of the population, respectively.<sup>2</sup>

“As a result of this basic demographic change, demand [for oncologists] will continue to grow because there will be more cases of invasive cancers in the United States, including breast cancer,” Sledge noted. A study published by the American Society of Clinical Oncology noted that nearly a fifth (19.7%) of oncologists are nearing retirement age of 64 years or older and only 15.6% of oncologists are early in their career at age 40 or below (N = 12,940).<sup>3</sup>

As the oncology workforce and ancillary service providers, such as pharmacists, face impending shortages, the number of survivors of cancer is set to increase. Close to a quarter of all cancer survivors will be patients with breast cancer, Sledge said, estimating that there will be approximately 5 million survivors of breast cancer in the next decade. “We’re not very good at taking care of survivors of cancer. We lack the mechanisms...to take care of the special needs of long-term survivors.” Additional consequences that are locked in by demography include low numbers of available oncologists, poor distribution of care providers, and financial stresses that increase with each new approved drug. “It’s wonderful that we’ve had a new drug every year in the breast cancer space, but they are all very expensive both to the health care system and individuals,” Sledge said.

In conclusion, Sledge acknowledged the folly of prediction, noting that he likely missed something important and much of what he said may be proven wrong or irrelevant. “But in 2030, if you remember this talk, please give me credit for the stuff I got right.” ■

For full references, visit [OncLive.com](https://www.onclive.com)

## New HER2-Targeting Therapies Jostle for a Place in the Treatment Lineup

Denise Myshko

**THE INTRODUCTION OF NEW** therapies for patients with recurrent HER2-positive metastatic breast cancer (mBC) has resulted in a crowded landscape for third-line treatments and beyond, raising questions about how best to sequence a wealth of options, according to Sara A. Hurvitz, MD.

There are now 8 HER2-targeting agents available for patients with mBC, Hurvitz said; these include 3 new drugs that the FDA approved in the past 15 months.<sup>1</sup> Meanwhile, additional regimens are in development that may further change the paradigm.

“This continues to be an incredibly exciting time for the treatment of HER2-positive breast cancer given all these new agents but we are challenged to understand how to best sequence these agents, which really will require us to take into account the unique safety profile and efficacy profile of each of these agents,” Hurvitz said during a presentation at the *38th Annual Miami Breast Cancer Conference®*. Hurvitz is director of the Breast Cancer Clinical Research Program UCLA and codirector of the Santa Monica-UCLA Outpatient Hematology/Oncology Practice.

As it stands now, she said, the gold standard for first-line HER2-positive mBC is the combination of trastuzumab (Herceptin), pertuzumab (Perjeta), and a taxane. For second-line therapy, she said the first choice is ado-trastuzumab emtansine (T-DM1; Kadcyla), although the tucatinib (Tukysa) triplet approved in April 2020 may become another option in this setting. In that

regimen, tucatinib is combined with trastuzumab and capecitabine.

In the third-line setting, there are at least 8 choices, including 3 new drugs and an expanded indication for a fourth agent, which have been approved since December 2019.<sup>1</sup> Besides the tucatinib regimen, the recent additions to the treatment toolkit comprise the new drugs fam-trastuzumab deruxtecan-nxki (Enhertu) monotherapy and margetuximab-cmkb (Margenza) plus chemotherapy, as well as an expanded indication for neratinib (Nerlynx) combined with capecitabine.

### Wave of Recent Approvals

During her presentation, Hurvitz reviewed data for the 4 recently approved therapies in detail and described efforts to advance their use in ongoing clinical studies.

Trastuzumab deruxtecan, an antibody-drug conjugate, gained an accelerated approval in December 2019 for patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2-based regimens in the metastatic setting.

The decision was based on findings from the phase 2 DESTINY-Breast01 trial (NCT03248492), a multicenter, single-arm in which 184 patients received trastuzumab deruxtecan. Hurvitz pointed out that 92% of participants had visceral disease and the population had undergone a median of 6 prior lines of therapy, including 1 patient who had received 27 lines of treatment in the metastatic setting.

“We were blown away to see the

objective response rates [ORRs],” Hurvitz said. Updated data presented at the 2020 San Antonio Breast Cancer Symposium (SABCS) showed an ORR of 61.4%, with a median duration of response of 20.8 months, median progression-free survival (PFS) of 19.4 months, and a median overall (OS) of 24.6 months.<sup>2</sup> Hurvitz noted that patients receiving the drug should be monitored for interstitial lung disease, which was fatal in 2.7% of patients.

The drug is being evaluated in a number of phase 3 trials, including DESTINY-Breast02 (NCT03523585), the confirmatory study for the approval, which is comparing trastuzumab deruxtecan versus investigator’s choice of capecitabine plus either trastuzumab or lapatinib (Tykerb) in patients with mBC who previously received T-DM1.

The phase 3 DESTINY-Breast03 trial (NCT03529110) is testing whether trastuzumab deruxtecan can bump T-DM1 as the preferred choice in the second-line setting; the study directly compares the 2 drugs in a randomized population. This study is recruiting patients with mBC who previously received trastuzumab plus a taxane.

In February 2020, neratinib received an expanded indication in combination with capecitabine for patients with advanced or metastatic HER2-positive breast cancer who have received 2 or more prior HER2-directed regimens in the metastatic setting. The approval for the tyrosine kinase inhibitor (TKI) was based on the phase 3 NALA trial (NCT01808573), in which patients were randomized to receive capecitabine with either neratinib or lapatinib.

Notably, the dose of capecitabine was lower in neratinib arm (1500 mg/m<sup>2</sup>) than it was in the lapatinib cohort (2000 mg/m<sup>2</sup>) because of concerns about diarrhea. Patients

treated with neratinib also received loperamide starting with the first dose to mitigate diarrhea. Nevertheless, about 24% of patients developed diarrhea of grade 3 or 4 severity with neratinib versus 13% with lapatinib.<sup>3</sup> “This is a big limiting factor for the use of this agent,” Hurvitz said.

In findings from an updated analysis, PFS was 8.8 months in the neratinib arm versus 6.6 months with lapatinib ( $P = .003$ ). Neratinib also improved outcomes for patients with stable central nervous system (CNS) disease at baseline, according to data from the NALA trial presented at SABCS 2020. The mean PFS was 7.8 months in the neratinib arm versus 5.5 months in the lapatinib arm (HR, 0.66; 95% CI, 0.41-1.05;  $P = .074$ ).<sup>4</sup>

Efficacy against CNS disease also is one of the striking features of tucatinib therapy, a TKI that gained FDA approval in May 2020 in combination with trastuzumab and capecitabine for patients with HER2-positive mBC, including patients with brain metastases, who have received 1 or more prior anti-HER2-based regimens in the metastatic setting.

Hurvitz said the pivotal phase 2 HER2CLIMB trial (NCT02614794), in which patients were randomized to receive capecitabine/trastuzumab in combination with either tucatinib or placebo, “was designed to interrogate” tucatinib’s efficacy against brain metastases. In all, 48% of the study’s 612 participants had CNS metastases that were stable or actively progressing.

“This drug hit a homerun at its first reporting,” Hurvitz said. The median PFS in patients receiving tucatinib was 7.8 months (95% CI, 7.5-9.6) compared with 5.6 months (95% CI, 4.2-7.1) for patients who had placebo (HR, 0.54; 95% CI, 0.42-0.71;  $P < .001$ ). The median

OS was 21.9 months (95% CI, 18.3-31.0) in the tucatinib arm compared with 17.4 months (95% CI, 13.6-19.9) in the control arm (HR, 0.66; 95% CI, 0.50-0.87;  $P = .005$ ). Among the patients with brain metastases, PFS at 1 year was 24.9% in the tucatinib arm and 0% in the placebo group (HR, 0.48; 95% CI, 0.34-0.69;  $P < .001$ ).<sup>5</sup>

In terms of adverse events (AEs), Hurvitz noted an increased risk of hand-foot syndrome and diarrhea, although the incidence of grade 3/4 diarrhea was only 12.9% versus 8.6% in the placebo arm,<sup>5</sup> which she said compares favorably with the neratinib data. Tucatinib’s HER2 selectivity “reduces the risk of diarrhea and you don’t need to use upfront loperamide with this agent,” she said.

Although the pivotal tucatinib study was a third-line trial, the FDA approved the regimen in the second line, probably because of its “incredible activity” in patients with brain metastases, Hurvitz said. The question now is whether tucatinib can advance past T-DM1 monotherapy in the second-line setting. In the phase 3 HER2CLIMB-02 trial (NCT03975647), the combination of tucatinib plus T-DM1 is being compared with placebo plus T-DM1.

Margetuximab, which was approved in December 2020 in combination with chemotherapy for patients with HER2-positive breast cancer who have received 2 or more prior anti-HER2 regimens, “is a uniquely designed trastuzumab,” Hurvitz said.

“It has the same Fab portion that targets HER2 but the Fc portion is engineered to more tightly bind to the patient’s immune effector cells, NK [natural killer] cells and dendritic cells at the Fc receptor,” she said. “We know that about 85% of patients will have an Fc receptor genotype that indicates weaker

binding affinity for antibodies. Engineering this to more tightly bind may benefit patients.”

The chimeric monoclonal antibody was approved based on findings from the phase 3 SOPHIA trial (NCT02492711), which demonstrated a PFS benefit for margetuximab plus chemotherapy over trastuzumab plus chemotherapy. Median PFS in the margetuximab arm was 5.8 months (95% CI, 5.52-6.97) compared with 4.9 months (95% CI, 4.17-5.59) in the control arm (HR, 0.76; 95% CI, 0.59-0.98;  $P = .033$ ).<sup>6</sup>

Hurvitz said the PFS benefit appears to be restricted to participants who were carriers of the CD16A receptor with a 158F allele. Additionally, she noted, there was a median 4.3-month difference in OS in the margetuximab arm compared with the control arm (23.7 vs 19.4 months, respectively) in patients who were CD16A-158F carriers, although it was not statistically significant ( $P = .087$  by unstratified log rank). These patients comprised 437 of trial participants, or 86% of those who were genotyped (506 patients of 536).

In terms of AEs, Hurvitz said margetuximab has a favorable profile. “The tolerability of this agent is really quite good,” she said. “The only thing that is increased compared with trastuzumab is infusion-related reactions. It is a good, tolerable agent we can now combine.”

Moving forward, Hurvitz anticipates that margetuximab will be used more frequently in patients who are F allele carriers. She said an assay is being developed to identify these patients. ■

For full references, visit [OncLive.com](https://www.onclive.com)

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## Agents Targeting MET, RET, and Previously “Undruggable” KRAS Advance Treatment in NSCLC

By Hayley Virgil

**APPROXIMATELY 40% OF PATIENTS** with lung cancer harbor genetic abnormalities, said Melissa L. Johnson, MD, who stressed that next-generation sequencing (NGS) must be performed to ensure that patients are being matched with the correct targeted therapy.

In February 2021, the FDA granted an accelerated approval to tepotinib (Tepmetko) for use in patients with metastatic non-small cell lung cancer (NSCLC) harboring *MET* exon 14 skipping alterations.<sup>1</sup> The regulatory decision was based on data from the phase 2 VISION trial (NCT02864992), which showed that the *MET* inhibitor induced an objective response rate (ORR) of 43%.<sup>2</sup>

In May 2020, the FDA gave the green light to capmatinib (Tabrecta) for use in patients with metastatic *MET* exon 14 skipping-mutated

NSCLC based on data from the phase 2 GEOMETRY mono-1 study (NCT02414139), which showed that the agent elicited an ORR of 67.9%.<sup>3</sup> In the same month, selpercatinib (LOXO-292; Retevmo) also received regulatory approval from the FDA for use in patients with *RET* alteration-positive NSCLC, after the agent induced an ORR of 64%.<sup>4</sup> The FDA approval of **pralsetinib (Gavreto)** followed close behind, in September 2020, when it was indicated for patients with *RET* fusion-positive NSCLC after having elicited an ORR of 57%.<sup>4,5</sup>

Although several therapies have been developed to target these oncogenic drivers, there has been a dearth of *KRAS*-targeted therapies; this changed with the emergence of agents like sotorasib (formerly AMG 510) and adagrasib (MRTX849).

“*KRAS* has been very difficult to target for 30 years. Some of the problem is that *KRAS* cycles between guanosine triphosphate on and guanosine diphosphate [GDP] off, so it’s not in the same state all the time. Both *KRAS* G12C inhibitors [that have been developed] lock *KRAS* in its GDP-bound off state,” explained Johnson. “It was the discovery of this solvent II binding pocket that is visible or accessible when the *KRAS* protein is in its GDP-bound off state that allowed these drugs to be developed. It’s a cool story, and I’m watching the development of drugs in this space absolutely with interest.”

In an interview With *OncoLive*® during a 2020 Institutional Perspective in Cancer webinar on Lung Cancer, Johnson, an associate director of lung cancer research at

Sarah Cannon Research Institute, discussed the implications of recent advances made in the development of oncogenetargeted agents in NSCLC.

## **OncLive®: Which targeted agents have been recently added to the National Comprehensive Cancer Network (NCCN) guidelines in NSCLC?**



Melissa L. Johnson, MD

For these oncogenic drivers, *KRAS* does not yet have an FDA-approved indication. We have known about *KRAS* mutations for more than

30 years and how relevant they are in the development of lung cancers, but they have been very hard to treat. That being said, 2 drugs with encouraging clinical trial data [read out] in 2020: sotorasib, a direct *KRAS* G12C inhibitor made by Amgen, and adagrasib, a direct *KRAS* G12C inhibitor made by Mirati. I would anticipate that we would see the approvals of these drugs in years to come, and then they'll be added to the NCCN guidelines.

[Regarding] *MET* alterations, [a patient] can have *MET* exon 14 [*MET*ex14] skipping alterations or amplification of *MET* gene copy number. A high gene copy number—6 or higher per cell—is what we consider therapeutically relevant. In the past, crizotinib [Xalkori] was approved for patients with *MET* gene amplifications; more recently, [it was approved] for [those with] *MET*ex14 skipping [mutations]. Just [last] year, capmatinib was added to the NCCN guidelines after it was FDA approved for [use] in patients with *MET*ex14 skipping mutations, as well as in those with a *MET* gene copy number higher than 10.

Tepotinib is another *MET* tyrosine kinase inhibitor [TKI] [that has emerged in the paradigm]; it is not yet approved but received a breakthrough therapy designation from the FDA. I would anticipate, likewise, that this TKI will be added to the NCCN guidelines [in the near future].

Finally, the 2 drugs selpercatinib [Retevmo] and pralsetinib [Gavreto] were [FDA] approved for patients with *RET* fusion-positive lung cancer and so were both added to the NCCN guidelines.

## **What were some of the lessons learned from the GEOMETRY mono-1 and VISION studies with regard to NGS?**

[These studies produced] the positive results we saw with capmatinib and tepotinib, respectively. First, the GEOMETRY study looked at patients with either *MET*ex14 skipping mutations or *MET* elevated gene copy number. Various cohorts were examined; they included patients with gene copy number 4 to 6, 6 to 10, and 10 and higher. One of the take-home lessons from this study was that although we would expect patients with *MET*ex14 skipping mutations to respond to these *MET*-directed TKIs, patients with high levels of gene copy number also responded.

It's really important to look at the NGS report and know that it's not just a couple of copy numbers of *MET* that are sufficient for [patients] to be treated with capmatinib but, rather, more than 10. That's an important distinction that I don't believe we've spoken about in lung cancer before; it's something we have discussed in breast cancer with *HER2* overexpression versus gene copy number.

The VISION study [NCT02864992] evaluated tepotinib in that same group of patients with *MET* al-

terations. Here, the interesting take-home lesson was that *MET* alterations were found by analyzing tissue or blood; it didn't matter which medium was used. The response rate when [patients were] treated with tepotinib was in the 40% to 50% range. This seems to be another alteration you can find in the plasma if you don't have adequate tissue to do your NGS.

## **If tepotinib is approved down the line, what factors do you consider when choosing an agent for your patients with MET alterations?**

We have used crizotinib in the past because it was the only show in town. We know that it targets not just *MET*; it is also an *ALK* and a *ROS1* inhibitor. I do believe that both capmatinib and tepotinib are more potent *MET* inhibitors, so [if] tepotinib is approved, I will likely choose that or capmatinib over crizotinib. All the *MET*-directed therapies have a similar adverse effect [AE] profile in terms of edema, weight gain, nausea, and diarrhea. Beyond that, picking one and learning to use it is probably what I will do.

## **Shifting to developments made with RET-targeted treatments, what are some of the key players that have changed care for these patients?**

These are some of my favorite drugs. Where I practice in Tennessee, we see a lot of *RET* fusions—maybe more than we see *EGFR* or *ALK*, which is interesting. We've used selpercatinib in clinical trials for a while. Both this drug and pralsetinib are great in that they are highly potent for *RET* translocation. Patients feel really well and the AE profile is quite mild. Some hypertension [is reported], as well as a little

bit of edema, but both are very well-tolerated drugs.

In the most recent months, we have also started to hear about how selpercatinib appears to have good intracranial penetration; this is a relevant end point for all of our oncogene-driven cancers in NSCLC. It's good to see that these drugs penetrate the blood-brain barrier and can be relied upon to treat those sanctuary sites.

### What research efforts are being made to overcome acquired resistance to RET inhibitors?

With every TKI, as you're able to identify the acquired resistance mutations, you can begin to develop inhibitors of that resistance; those efforts are ongoing. I'm also really excited about the recent development of several SHIP2 inhibitors; they seem to work for many oncogenic drivers that are developing resistance, maybe in combination with an EGFR inhibitor or a RET inhibitor. One of the mechanisms of resistance that has been reported for patients with RET rearrangements is the development of *MET* amplification; this is also a mechanism of resistance for patients with EGFR-driven cancers.

We at Sarah Cannon, and others, were able to identify a group of patients who developed *MET* amplifications as the resistance mechanism to selpercatinib. When these patients were treated with selpercatinib and crizotinib together, [we were able to] overcome resistance for these patients. This type of Whac-A-Mole approach is sometimes difficult because different TKIs may have overlapping toxicity. However, because selpercatinib is such a well-tolerated drug, it was tolerated in combination with crizotinib quite nicely. In the future, we will begin to



**KRYSTAL-1 [NCT03785249]** was the phase 1/2 study of the direct **KRAS G12C drug adagrasib**; it was a traditional phase 1 study that enrolled all-comers, all [patients with] **solid tumors** that harbored a **KRAS G12C mutation**.

investigate resistance mechanisms for these patients, just like [we have for patients with] EGFR-positive disease, by identifying the mechanisms of resistance and developing combination strategies.

### Shifting to KRAS, which was once considered to be an undruggable target, what was learned from the KRYSTAL-1 study?

KRYSTAL-1 [NCT03785249] was the phase 1/2 study of the direct KRAS G12C drug adagrasib; it was a traditional phase 1 study that enrolled all-comers, all [patients with] solid tumors that harbored a KRAS G12C mutation. The dose escalation [portion of the trial] went fairly rapidly, and 600 mg twice daily was the dose chosen for the expansion [portion of the research]. Combination efforts [were explored] in [patients with] NSCLC, as well as with colorectal cancer [CRC], ovarian cancer, and other solid tumors [harboring] the mutation.

In the NSCLC expansion portion [of the trial], the response rate was more than 40% for patients who had KRAS G12C mutations, which is exciting and in the realm of so many other oncogene drivers that we developed inhibitors for over the years. Adagrasib is well tolerated, [although] nausea and some gastrointestinal upset are commonly reported [with this agent], and some reversible transaminase

elevation and creatine elevation were also reported. In general, this is a drug that I believe is here to stay. I look forward to watching its development in lung cancer, [where] it is being combined with pembrolizumab [Keytruda] for patients with PD-L1-expressing cancers. In CRC, it's being combined with cetuximab [Erbix]. Exactly what the combinatorial paths are [going to be] beyond the path to registration is an area to watch.

### Is there anything else that you would like to add?

Although *MET* alterations account for somewhere between 2% and 6% of all lung cancers and *RET* rearrangements happen in about 2% of lung cancers, KRAS mutations happen in a larger number, [ranging from] 25% to 30% [of patients]. Taken together, [these alterations account for] close to 40% of [all] lung adenocarcinomas. If you add that to *EGFR*, *ALK*, *ROS1*, and the *BRAF* alterations, you can see the many therapeutic options for patients with NSCLC over and above chemoimmunotherapy. The take-home lesson is how important NGS is to find these patients so that they can be treated with the appropriate targeted therapy, either instead of or in addition to chemoimmunotherapy. ■

For full references, visit [Onclive.com](https://www.onclive.com)

