Looking Forward to a New Wave of Breast Cancer Therapies

Joyce A. O’Shaughnessy, MD
POLYCYTHEMIA VERA

Severity, impact, and implications of symptom burden in PV

Patients with polycythemia vera (PV) experience a unique constellation of troublesome symptoms. These can vary in intensity and/or emerge throughout the course of PV, including in patients whose disease is well controlled by other measures. However, consistently monitoring symptoms and therapy may help patients with PV achieve their individual quality of life (QoL) goals.

PV is a myeloproliferative neoplasm (MPN) characterized by abnormal proliferation of mature myeloid cells. Symptom burden in PV and other MPNs may also be severe, similar to that seen in acute myeloid leukemia, non-Hodgkin lymphoma, or metastatic cancer. Patients with PV are also at risk for thrombotic events (up to 40%), and transformation to post-PV myelofibrosis (MF; ~10%) or acute myeloid leukemia (AML; ~3%). Given the prevalence of symptoms and the burden they may impose on patients, symptom alleviation is a major objective in the evaluation of patients with PV.

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Although PV is chronic, symptoms can be dynamic, changing throughout the course of the disease. Given their dynamic nature and potential to reveal aspects of the underlying biology, it is essential to monitor symptoms when PV is diagnosed and regularly as the disease is being managed. The occurrence of a new event such as thrombosis, diabetes diagnosis, or change in medication may affect symptoms. Symptom monitoring can help healthcare professionals interpret how the variety of clinical changes have affected the patient’s disease along with helping to recognize the potentially subtle signs of disease progression.

Tracking Symptoms in PV

Surrogates of disease burden such as risk scores and blood cell counts often fail to correlate with symptomatic burden, but validated patient reported outcome (PRO) tools may permit objective and rapid assessment of the symptom burden in patients with PV. To assess the unique spectrum of symptomatology seen in patients with MPNs, we developed the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) and the more concise MPN-SAF Total Symptom Score (MPN-SAF TSS), commonly known as the MPN-10. This tool includes the most representative and pertinent MPN-related symptoms—fatigue, vascular symptoms, constitutional symptoms, and spleen-related symptoms. The importance of recognizing symptoms in MPNs and the value of surveys to quantify PROs was substantiated by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms, which incorporated symptom burden assessment as part of routine evaluation of patients with PV in 2017.

The MPN-10 is designed to assess the unique spectrum of symptomatology seen in patients with MPNs.

Visit mpnconnect.com/mpn-resources.aspx for the MPN-10 form and additional resources

At our clinic, we provide the MPN-10 to patients during the check-in process. This opens a discussion between patient and HCP. I document the MPN-10 sum score into the patient’s chart and refer to it at future visits. By providing an objective, quantitative PRO, these surveys provide data that facilitate management decisions.

Evaluating Symptom Burden to Assess the Patient’s Condition

With these data, we then thoroughly examine the patients for signs of disease such as splenomegaly and ask probing questions to gain a deeper understanding of symptom burden. Despite nearly 90% of patients reporting symptoms at

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diagnosis, physicians estimate that only 60% of patients present with symptoms.\textsuperscript{14} This is likely because of the nature of symptoms in PV that causes them to not be readily apparent to physicians. At our clinic we have noted that serial assessment of symptom burden using PRO tools allows for direct assessment of the patient experience and has demonstrated in clinical trial settings to be a sensitive clinical indicator of disease progression.\textsuperscript{5,12}

Some of the key symptoms I look for are fatigue, abdominal discomfort, early satiety, headaches, bone pain, pruritus, and depression. I also pay close attention to the overall QoL, which can be affected by both the severity and the multitude of symptoms in PV.\textsuperscript{15} Older individuals may not report their symptoms, regarding them as a natural sign of aging, or patients may have grown accustomed to the symptoms as they gradually emerged during the long course of PV. The erroneous acceptance of this new, symptomatic “normal” can be corrected by educating patients about PV.

Incorporating Symptoms into the Clinical Assessment Routine

Providing individualized care – which encompasses PV disease-related factors, any comorbidities, and the patient’s personal health and wellness goals – is the ultimate goal when I treat patients with PV. Developing a routine to track symptoms and other factors can facilitate this. As physicians, even if we do a thorough job when asking patients with PV about what symptoms they are experiencing, we may easily miss the severity of the symptoms – especially in patients who have a large number of different symptoms. The continuum of disease and patient characteristics combined with the chronic nature of PV emphasizes the need to routinely monitor and track therapy, disease signs, and symptoms. Overall, this can be thought of as reading the patient’s diary of disease to get a complete picture of the impact of PV on both their underlying biology and their lifestyle goals. Patients with PV can live for many years with a severe symptom burden, and trying to optimize QoL is paramount.

Robyn M. Scherber, MD, MPH
Assistant Professor of Medicine, Department of Hematology & Oncology, Mays Cancer Center at UT Health San Antonio

This article, sponsored by Incyte Corporation, is based on a paid interview with Robyn M. Scherber, MD, MPH an Assistant Professor of Medicine, Department of Hematology & Oncology at Mays Cancer Center, conducted on May 29, 2018.

Our editors collaborate with renowned cancer centers across the country to bring you reports on cutting-edge developments in oncology research and treatment. For this month’s Partner Perspectives, go to page 46.
The breast cancer treatment landscape has been changing rapidly, thanks to FDA approvals of novel drugs and new indications for established therapies. Joyce A. O’Shaughnessy, MD, a 2016 Giants of Cancer Care® award winner who has helped create the current therapeutic paradigm, shares her insights into new and emerging options.
CHOLANGIOCARCINOMA TREATMENT IS ON OUR RADAR

With cholangiocarcinoma in our sights, QED is committed to developing therapy for FGFR-driven diseases.

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Breast Cancer Momentum Is Encouraging

When it comes to developing targeted treatment approaches, clinical investigators who specialize in breast cancer have been particularly adept. Consider these examples: Therapeutic strategies aimed at hormonal functions have been used for more than 100 years and continue to be refined today with CDK4/6 inhibitors. In the modern era, the anti-HER2 monoclonal antibody trastuzumab (Herceptin) became one of the first biomarker-targeted anticancer agents to enter clinical practice more than 20 years ago; today, numerous novel drugs directed at the same pathway are in development.

Now we are in the midst of another wave of innovation. In less than 6 months, the FDA approved 3 novel drugs and granted a new indication for a fourth agent. This burst of activity comes on top of several 2019 milestones, including the approval of the first checkpoint inhibitor for breast cancer, atezolizumab (Tecentriq), for PD-L1-positive triple-negative disease, and the first PI3K-directed agent, alpelisib (Piqray), for PIK3CA-mutated, HER2-negative metastatic settings.

The rapid pace of development means practicing oncologists must enhance their knowledge base. In this issue of OncologyLive®, we feature the insights of one of the best possible guides to the new landscape: Joyce A. O’Shaughnessy, MD. A 2016 Giants of Cancer Care® award winner, O’Shaughnessy has played a pivotal role in advancing care for patients with breast cancer in numerous ways. As a physician-scientist, she has contributed key findings to chemotherapy, preventive therapy, molecularly targeted agents, and immunotherapy. She also has investigated next-generation sequencing approaches that help individualize care.

Meanwhile, O’Shaughnessy is moving forward with the peer education that forms another important aspect of her approach. She is scheduled to lead 3 Physicians’ Education Resource® (PER®), conferences this year: the 19th Annual International Congress on the Future of Breast Cancer® (IBC) in New York, New York, on July 17 and 18 (IBC East) and in San Diego, California, on July 31 and August 1 (IBC West), and the 18th Annual School of Breast Oncology® on November 5 to 7 in Atlanta, Georgia. (The meetings are scheduled as live events. For updates, visit GoToPER.com).

Although the coronavirus disease 2019 pandemic has thrown our entire health care system into disarray, it is heartening to know that this vital work continues. Our content team is dedicated to bringing you information about the latest developments throughout the cancer spectrum in this publication and on OncLive.com.

As always, thank you for reading and stay safe.

Mike Hennessy Sr
Chairman and Founder
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From the Editor

Clinical Trials Should Reflect Molecular Advances, Real-World Patients

by MAURIE MARKMAN, MD

THE FUNDAMENTAL VALUE of the randomized phase 3 trial in the development of credible medical care and public health policy needs no justification. For more than a half-century in the United States and other countries, ineffective and potentially harmful approaches for treating medical conditions have been removed or prevented from entering the clinician’s armamentarium. This happens after failing to achieve a prospectively defined measurable outcome in an appropriately designed and conducted randomized phase 3 trial.

The importance of this methodology has been particularly poignant in the establishment of a robust approach to the use of pharmaceutical agents, including in the oncology space. Today, it would be impossible to envision medical care in this country where the selection of therapeutics was not based on the conduct, completion, and subsequent publication of randomized phase 3 trial findings, built on studies involving comparisons of thousands of novel concepts over the preceding decades for the purpose of optimizing successful care for individual patients in terms of efficacy and toxicity. From the earliest moments of medical school instruction, through residency and fellowship training, physicians are taught the primacy of the randomized phase 3 trial in the hierarchy of evidence-based medicine.

MOLECULAR PROFILING MAKES A DIFFERENCE

However, with our rapidly expanding knowledge of the complexity and heterogeneity of basic molecular biology, it is increasingly clear that past assumptions regarding the homogeneity of various populations included within these studies has been in error, and sometimes, seriously so.

For example, 30 years ago when clinical trials in metastatic lung cancer were conducted, populations were simply divided into 2 relatively large subgroups: small cell and non–small cell. Today, it is understood that there are several highly clinically relevant subgroups of patients with advanced/metastatic lung cancer, some of which may represent a very small percentage (<3%-5%) of the entire population. And, although it may be reasonable to conduct a randomized phase 3 trial over an acceptable period of time that involves 20% to 30% of the large population of patients with non–small cell lung cancer, it is increasingly clear that approach is highly questionable if one is attempting to initiate and complete such a study that only involves 2% to 3% of these patients. How long would society and, most importantly, patients and their families with these molecularly defined cancer subgroups be willing to wait for an answer to the question of the clinical utility of a novel therapeutic approach?

It is quite easy to find multiple highly clinically relevant situations in the oncology domain where the dogma regarding the requirement for definitive randomized trials is increasingly problematic. Consider, for example, a recent report of a randomized phase 2 trial examining the novel targeted agent capivasertib, which is designed to target several potentially clinically relevant molecular abnormalities (PIK3CA/AKT1/PTEN) in patients with triple-negative breast cancer.1 Of note, approximately 10% to 15% of breast cancers are classified as triple negative. The study, conducted over 3 years at 42 academic centers in 6 countries, included 140 patients with previously untreated locally advanced or metastatic triple-negative breast cancer. Overall, the study revealed no statistically significant impact on progression-free survival (PFS), the primary trial end point (HR, 0.74; 2-sided P = .11). However, of the approximately 25% of patients in the study population with available samples who were found to have the hypothesized relevant molecular targets, the HR for PFS was 0.30 (P = .01), whereas there was no impact...
From the Editor

on PFS (HR, 1.13; P = .61) in the subgroup without these abnormalities. Similar results were observed for the impact of therapy on overall survival in the entire patient population and 2 relevant subpopulations.

So how does one move forward to confirm the clinical value of this observation in a molecularly defined group of women with breast cancer such that the FDA might approve this (or any other) novel antineoplastic agent? Should a definitive randomized phase 3 trial be required and, if so, how many years—or perhaps decades—would be necessary to complete such a study? This question is particularly relevant in this instance considering that the FDA already has approved alpelisib (Piqray) for patients with another subtype of PIK3CA-mutated breast cancer based on phase 3 trial findings.²

AUTHENTIC STUDY POPULATIONS ARE NEEDED

Further, it is increasingly recognized that the population of individuals who participate in definitive phase 3 randomized trials that establish the standard of care in the cancer arena are strikingly unrepresentative of the real-world population encountered by oncologists. One recently published peer-reviewed article—an example of the many that could be cited—emphasizes this point.³ In an examination of the National Cancer Database from 2004 through 2015 for the proportion of individuals (total sample size, 12,097,681) receiving their initial course of therapy for cancer in the United States, investigators found that 0.1% (1 in 1000 patients) were enrolled in a clinical trial, and this population quite poorly represented the overall population with a malignancy in this country in such areas as age, comorbidities, and race.³

Unfortunately, this status quo for defining optimal therapy continues to be the gold standard demanded by a large sector of academics involved in statistical evaluations of medical care, as well as by many regulators.

And, disturbingly, the pushback against change has perhaps only intensified, despite increasingly overwhelming evidence of serious issues with this status quo.

How else does one explain the recent publication of a commentary in the New England Journal of Medicine that describes the process of randomization as “magic” and real-world evidence as “myth”?⁴ Fortunately, with the rapidly evolving revolution in our understanding of the fundamental molecular biology of health and disease and the introduction of increasingly beneficial health-related strategies based on that knowledge (eg, wellness, prevention, screening, treatment), we as a society are beginning to appropriately ignore such biased rhetoric.

REFERENCES


**FDA Clears First Therapy for UTUC**

The approval of mitomycin gel (UGN-101; Jelmyto) for the treatment of low-grade upper tract urothelial cancer (UTUC) offers patients a therapeutic alternative to radical surgery.

The agent’s approval is based on results from the pivotal phase 3 OLYMPUS trial (NCT02793128), which showed that mitomycin gel induced a complete response rate of 58% in this patient population (n = 71).

Among the 41 patients who achieved a complete response, 19 (46%) continued to respond at 12 months, which was another major efficacy benchmark in the study. Additionally, 7 patients experienced disease recurrence at the 12-month assessment point and 9 continued to be followed. The median duration of response was not reached (range, 0-18.8+ months).

UTUC corresponds to a subset of urothelial cancers that arise in the lining of the kidney or the ureter and can block the ureter or kidney, causing swelling, infections, and impairment of kidney function in some patients. UTUCs can develop as low-grade or high-grade tumors; low-grade tumors are the rarer of the 2, affecting 6000 to 8000 patients per year in the United States.

**Pemigatinib Scores Indication for FGFR2+ Cholangiocarcinoma**

Treatment options for patients with previously treated locally advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements have expanded with the approval of pemigatinib (Pemazyre).

The FGFR inhibitor’s indication in this setting is based on interim findings from the multicohort phase 2 FIGHT-202 study (NCT02924376). Data for the cohort of patients with FGFR2 fusions or rearrangements (n = 107) demonstrated that at median follow-up of 15 months, single-agent pemigatinib led to a 36% objective response rate consisting of 3 (2.8%) complete responses and 35 (33%) partial responses. Further, 50 (46.7%) patients showed stable disease, for a disease control rate of 82%. The median duration of response was 7.5 months with an acceptable safety profile.

This objective response rate translated to a longer median progression-free survival in this cohort. The median progression-free survival was 6.9 months, compared with 2.1 months in a cohort of patients with other FGF/FGFR genetic alterations (n = 20) and 1.7 months in a cohort of patients without FGF/FGFR mutations (n = 18).

Of note, cholangiocarcinoma is often diagnosed at a late or advanced stage when the prognosis is poor, and existing therapies such as combination gemcitabine/cisplatin have limited efficacy.

**Ibrutinib/Rituximab Regimen Is Approved for Frontline CLL/SLL**

Ibrutinib (Imbruvica) is now approved for use in combination with rituximab (Rituxan) for the frontline treatment of adults with chronic lymphocytic leukemia or small lymphocytic lymphoma.

The doublet therapy’s expanded approval is based on findings from the phase 3 E1912 trial (NCT02048813), which demonstrated a statistically significant improvement in progression-free survival in patients who received the regimen versus those who were treated with standard fludarabine, cyclophosphamide, and rituximab (HR, 0.34; 95% CI, 0.22-0.52; P <.0001).

At a median follow-up of 37 months, the median progression-free survival was not reached in either arm, investigators said.

The HR for overall survival also favored the 2-drug approach over fludarabine, cyclophosphamide, and rituximab (HR, 0.34; 95% CI, 0.15-0.79; P = .009) and safety data were consistent with the known tolerability of ibrutinib.

Ibrutinib and rituximab’s supplemental new drug application was reviewed under Project Orbis, an initiative of the FDA Oncology Center of Excellence that provides a framework for the concurrent submission and review of oncology therapies among international partners. For example, the FDA, Health Canada, and the Australian Therapeutic Goods Administration collaboratively reviewed the doublet’s application.

**A New Dose of Trastuzumab Biosimilar Is Approved**

Trastuzumab-dttb (SB3; Ontruzant), a biosimilar approved for patients with HER2-overexpressing breast cancer or metastatic gastric or gastroesophageal junction adenocarcinoma, can now be administered at a 420-mg dose.

The FDA’s clearance of trastuzumab-dttb’s new dosage is based on data sets from 7 clinical trials, which demonstrated similarity in survival outcomes and safety between the biosimilar and reference trastuzumab (Herceptin) in patients with HER2-positive adjuvant and metastatic breast cancer, as well as HER2-positive metastatic gastric cancer.

The trastuzumab biosimilar was initially approved in January 2019 as a 150-mg single-dose vial after findings from a phase 3 study (NCT02149524) of the product showed that trastuzumab-dttb induced a rate of breast pathological complete response similar to trastuzumab in patients with HER2-positive breast cancer. Safety outcomes were also similar between the biosimilar and trastuzumab.

**Maintenance Niraparib Gets Green Light for Ovarian Cancer**

Niraparib (Zejula) is now approved as a maintenance therapy for adults with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to frontline platinum-based chemotherapy.

The PARP inhibitor’s indication in this setting is based on findings from the phase 3 PRIMA study (ENGOT-OV26/GOG-3012; NCT02655016), which showed that maintenance niraparib conferred a superior median progression-free survival (PFS) benefit compared with placebo in the first-line setting. The median PFS in the niraparib arm was 13.8 months versus 8.2 months in the placebo group, translating to a 38% reduction in the risk of disease progression or death (HR, 0.62; 95% CI, 0.50-0.76; P <.001).

This benefit extended to patients with tumors that test positive for homologous recombination deficiency. In this subset, the median PFS was 21.9 months compared with 10.4 months with placebo (HR, 0.34; 95% CI, 0.15-0.79; P <.001). PRIMA enrolled 733 patients. Investigators randomized patients 2:1 to receive niraparib (n = 487) or placebo (n = 246). Upon the initiation of the PRIMA study, niraparib was given at 300 mg. Patients who weighed less than 77 kg or had platelet counts below 150K/µL received niraparib at 200 mg.
THERAPEUTIC OPTIONS FOR pretreated HER2-positive breast cancer now include tucatinib (Tukysa) as part of a triplet regimen with a tolerable safety profile that promises improved quality of life.

On April 17, 2020, the FDA approved tucatinib in combination with trastuzumab (Herceptin) and capcitabine (Xeloda) for adults with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received at least 1 prior anti–HER2-based regimen in the metastatic setting. Tucatinib is a HER2-directed tyrosine kinase inhibitor.

The approval is based on findings from the phase 2 HER2CLIMB study (NCT02614794), which demonstrated the triplet’s capacity to improve survival in patients with and without brain metastases. In the overall population, the median progression-free survival (PFS) with the 3-agent approach was 7.8 months versus 5.6 months with trastuzumab and capcitabine alone. Among those with brain metastases, median PFS was 7.6 months in the tucatinib arm versus 5.4 months in the control group.

In an interview with OncologyLive®, Erika P. Hamilton, MD, director of the Breast Cancer and Gynecologic Research Program at Sarah Cannon Research Institute in Nashville, Tennessee, discussed the regimen’s potential in earlier lines of therapy and how HER2CLIMB’s inclusion of patients with brain metastases has the power to move the needle in clinical investigations of therapies in this subgroup.

**Q What was noteworthy about the efficacy data?**

HER2CLIMB had 4 end points looking at progression-free survival, overall survival, overall response rate, and then progression-free survival among patients with brain metastases. The trial met all 4 of these end points, so it was a win across the board.

The activity in the population of patients with brain metastases really stood out. We have a lot of good therapies for breast cancer, but many of them do not cross the blood-brain barrier, so patients with brain metastases comprise a very high-risk patient population that is known to have worse outcomes. To have a drug that not only [meets end points] across the board but also benefits patients with brain metastases is meaningful. There is a statistic from the trial that [shows] the progression-free survival at 1 year among patients with brain metastases was 0% if they were not receiving tucatinib [compared with] a quarter of patients with brain metastases who remained on the trial at 1 year and were [receiving tucatinib].

**Q Why is HER2CLIMB’s inclusion of a broad population of patients with brain metastases important?**

In oncology trials, we commonly allow patients with brain metastases only if they have been treated with local therapy, such as resection or radiation and are stable 4 weeks after they finish local treatment. This trial was very different. HER2CLIMB allowed 3 different populations of patients with brain metastases to enroll: this traditional population with stable, pretreated brain metastases; metastases that had never been treated; and metastases that were treated and had progressed after. It was a very high-risk population.

Right now, I think that there is a lot of talk about how important clinical trials are and many patients’ trouble accessing them. We know that the best treatment option for a patient is enrolling on a clinical trial. There is also a lot of talk about how our inclusion criteria are a little too [strict], maybe [strict] than they need to be, and historically, there has been some fear from drug companies because they do not want to include patients who may be sicker, not have optimal organ function, or in this case, have actively progressing brain metastases and may not do as well on therapy.

I think it was progressive, wise, and brave to allow these patients on the trial, who probably stood to benefit the most. After this trial, because it is the first one to do so, I think there will be many more companies who will follow suit.

**Q How well is the tucatinib triplet regimen tolerated?**

We normally give HER2 therapy in conjunction with chemotherapy. Capcitabine is an oral chemotherapy that tends to be pretty well tolerated. It does not cause hair loss, and it also does not cause a patient’s [white blood cell] counts to drop [significantly], so it is a favored chemotherapy partner in breast cancer. Trastuzumab is our most widely used HER2 antibody, and we learned that having a dual HER2 blockade such as trastuzumab with pertuzumab [Perjeta] or in this case, trastuzumab and tucatinib, can [lead to] additive [efficacy]. It is a very good combination, and I think that what is unique about tucatinib is this [agent] does not add a whole lot of toxicity.

The most common adverse events we saw in the trial were diarrhea, hand-foot syndrome, nausea, and fatigue, and those are the most common side effects of capcitabine as a single agent. The addition of tucatinib added some liver dysfunction, about a 5% grade 3 elevation in liver function tests that was reversible.

The most important [characteristic] of tucatinib that is unlike other HER2 [agents] that we are familiar with like lapatinib [Tykerb] and neratinib [Nerylnx] is that tucatinib is specific and only blocks HER2, which makes it better tolerated than some of our more traditional options for HER2-positive breast cancer. Lapatinib and neratinib not only block HER2, but they also block HER1, or EGFR, and toxicities of rash and diarrhea come from EGFR [inhibition].

**Q What are the next steps for the use of this regimen?**

Can we move tucatinib earlier [in the treatment paradigm]? There is a lot of excitement around the brain metastases data, but I do not see this as a drug that I would only use in patients with brain metastases because it is an active regimen for the 52% of patients on the trial who did not have brain metastases. Because our systemic therapies are effective for HER2-positive breast cancer, these women are living longer and longer. Up to 50% of people with this disease will eventually develop brain metastases, which is quite a bit higher than some other types of cancer, so using a drug like tucatinib, even in the absence of brain metastases—that can get into the brain and work—may prevent brain metastases. I think an important question to ask moving forward is if we use tucatinib earlier, could we prevent brain metastases?

I am currently enrolling [patients in] the HER2CLIMB-02 trial [NCT03975647] of tucatinib in combination with T-DM1 [Kadcyla; ado-trastuzumab emtansine] or T-DM1 alone in the second-line setting.
FDA approval—April 17, 2020
FDA grants approval for tucatinib (Tukysa) in combination with trastuzumab (Herceptin) and capecitabine (Xeloda) for adults with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received at least 1 prior anti–HER2-based regimen in the metastatic setting.

Mechanism of action:
Tucatinib is a HER2-targeted tyrosine kinase inhibitor that obstructs HER2 and HER3 phosphorylation, to block downstream MAPK and AKT signaling and cell proliferation. In vivo, tucatinib hindered the growth of HER2-expressing tumors. Notably, tucatinib and trastuzumab have demonstrated increased antitumor activity in vitro and in vivo versus either agent alone.

How supplied:
50- and 150-mg tablets
Dosing:
- 300 mg twice daily in combination with a standard dosage of trastuzumab and 1000 mg/m² of capecitabine until disease progression or unacceptable toxicity.
- Advise patients to take tucatinib tablets approximately 12 hours apart and at the same time each day with or without a meal. Patients should only swallow tucatinib tablets whole: do not ingest tablets if broken or cracked.

Company: Seattle Genetics, Inc

PVOTAL EFFICACY DATA FOR APPROVAL
HER2CLIMB (NCT02614794), a randomized (2:1) placebo-controlled trial, enrolled 612 patients with HER2-positive unresectable locally advanced or metastatic breast cancer who received prior trastuzumab, pertuzumab (Perjeta), and ado-trastuzumab emtansine (T-DM1; Kadcyla) separately or in combination in the neoadjuvant, adjuvant, or metastatic setting. Patients with brain metastases were permitted to participate provided that they were neurologically stable and did not require immediate radiation or surgery.

Efficacy results for approval in the HER2CLIMB trial

Baseline patient characteristics

<table>
<thead>
<tr>
<th>Age in Primary End Point Analysis Population</th>
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<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
</tr>
<tr>
<td>&lt;65 years</td>
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<tr>
<td>7.8 (7.5-9.6)</td>
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<tr>
<td>&gt;65 years</td>
</tr>
<tr>
<td>5.6 (4.2-7.1)</td>
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Patients with brain metastases in total population, % (n = 291)

<table>
<thead>
<tr>
<th>Unreated metastases</th>
<th>Treated but stable metastases</th>
<th>Treated but radiographically progressing brain metastases</th>
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<tbody>
<tr>
<td>23%</td>
<td>40%</td>
<td>37%</td>
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Median lines of prior therapy (range)

<table>
<thead>
<tr>
<th>Systemic therapy</th>
<th>Systemic therapy in metastatic setting</th>
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<tbody>
<tr>
<td>4 (range, 2-17)</td>
<td>3 (range, 1-14)</td>
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Hormone receptor status, %

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<th>ER- and PR-</th>
<th>Other</th>
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<tr>
<td>39.4%</td>
<td>38.1%</td>
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</table>

Location of other metastases (%)

<table>
<thead>
<tr>
<th>Lung</th>
<th>Liver</th>
<th>Bone</th>
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<tbody>
<tr>
<td>50.0%</td>
<td>33.8%</td>
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References

WARNINGS AND PRECAUTIONS

• Diarrhea: Tucatinib can cause severe diarrhea, which may lead to dehydration, acute kidney injury, or death. Administer antidiarrheal therapy as needed. Interrupt therapy, reduce the dose, or permanently discontinue treatment based on severity of adverse event.
• Hepatotoxicity: Severe hepatotoxicity has been reported. Monitor alanine aminotransferase, aspartate aminotransferase, and bilirubin prior to initiating tucatinib, every 3 weeks during treatment, and as clinically indicated. Interrupt therapy, reduce the dose, or permanently discontinue based on severity.
• Embryo-Fetal Toxicity: Tucatinib can cause fetal harm. Warn women of reproductive age of the potential risk to a fetus and recommend effective contraception.

COMMONLY REPORTED ADVERSE EVENTS IN THE HER2CLIMB STUDY

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Tucatinib + trastuzumab + capecitabine (n = 404)</th>
<th>Placebo + trastuzumab + capecitabine (n = 197)</th>
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</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade 3/4</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesiain syndrome</td>
<td>63%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>58%</td>
<td>3.7%</td>
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<tr>
<td>Hepatotoxicity</td>
<td>42%</td>
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<td>Vomiting</td>
<td>36%</td>
<td>3.0%</td>
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<tr>
<td>Stomatitis</td>
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<td>2.5%</td>
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</table>
Breast Cancer Pioneer 
Looks Forward to a New Wave of Therapies

by CHRISTINA T. LOGUIDICE

THE DEGREE TO WHICH nature and nurture affect disease has long been debated in medicine, and it is an issue that esteemed breast cancer researcher and medical oncologist Joyce A. O’Shaughnessy, MD, has been working to unravel for her patients throughout a career that spans more than 30 years.

O’Shaughnessy’s care approach strives to consider the whole patient, from determining the importance of germline and somatic mutations and other molecular disease markers, to applying the ever-advancing knowledge at the bedside, to advocating for guidelines and policies that help improve overall quality of life and increase the chances of favorable long-term outcomes for patients and survivors. These efforts include advocating for insurance coverage of nutrition and exercise programs to help overcome treatment-related adverse events and reduce risk of recurrence.

Her endeavors have led to some encouraging outcomes, including for patients with unmet needs who would normally have a poor prognosis. O’Shaughnessy’s practice-changing work in oncology and efforts to educate other clinicians on advances in the field resulted in her becoming a recipient of the 2016 Giants of Cancer Care® award in the community outreach/education category. She is the Celebrating Women Chair in Breast Cancer Research, Baylor University Medical Center, Texas Oncology, and chair, Breast Cancer Program, US Oncology Research.

After a burst of FDA approvals of novel drugs and formulations in less than 18 months, O’Shaughnessy is looking forward to integrating these advancements into clinical practice. Over the next few years, many additional new agents are expected to be approved for breast cancer, and others are likely to receive expanded indications, O’Shaughnessy said in an interview with OncologyLive®.

“It’s truly an exciting and hopeful time in breast cancer because many of the novel agents recently approved and in late-stage development will ultimately improve the long-term outcomes of high-risk early-stage patients, thereby decreasing the global burden of metastatic breast cancer, and there’s no indication that the pace of discovery will slow down any time soon,” she said.

The nature of these emerging therapies and how they fit into the treatment paradigm are among the topics that O’Shaughnessy will tackle this year as she continues her role as a leading breast cancer physician-scientist and educator. She will serve as program chair and co-chair, respectively, for the 19th Annual International Congress on the Future of Breast Cancer® (IBC), which will be held in New York City on July 17 and 18, 2020, (IBC East) and in San Diego, California, on July 31 and August 1, 2020, (IBC West).

The conferences, which are among many medical meetings with which O’Shaughnessy is involved, are hosted by Physicians’ Education Resource®, LLC (PER®). Each meeting features more than 25 sessions that will cover a broad range of novel and practical topics in breast cancer, including new risk-reduction strategies, new algorithms for treating hormone receptor–positive metastatic disease, and the potential emergence of HER2-low breast cancer as a unique subtype. (The meetings currently are scheduled as live events. For updates, visit GoToPER.com).
Additionally, in perhaps her most unusual education project, O’Shaughnessy will chair the 18th Annual School of Breast Oncology®, an intensive 3-day deep dive into the latest data and their clinical implications about breast cancer biology, diagnostics, prevention, and treatment. The program, also hosted by PER®, will take place November 5 through November 7, 2020, in Atlanta, Georgia.

THE IMPORTANCE OF LEARNING FROM EXCEPTIONAL RESPONDERS: A PATIENT STORY

A patient who greatly influenced O’Shaughnessy’s translational and clinical research direction is a woman named Donna, now 68 years old, who was initially diagnosed with triple-negative breast cancer (TNBC) in 2008 at age 56.

As is characteristic of TNBC, Donna experienced multiple recurrences of treatment-refractory disease in her thoracic and supravacular lymph nodes. She had undergone several surgical resections and rounds of radiation therapy and had been treated with multiple cytotoxic agents, including taxanes, carboplatin, anthracyclines, alkylators, and antimetabolites. In 2011, she was referred to O’Shaughnessy to be considered for enrollment into a clinical trial. At that time, she had a 3-cm involved left supraclavicular lymph node and no other disease.

“We biopsied the lymph node and performed next-generation sequencing but didn’t find a specific mutation to target therapeutically. Her cancer contained an FOXM1 amplicon and somatic loss-of-function mutation in SMARCA4, which is part of the SWI/SNF family that is involved in double-strand DNA repair, among other things,” O’Shaughnessy said in an interview with OncologyLive®.

Donna was enrolled into a clinical trial assessing dactolisib (BEZ235), an oral agent that inhibits PI3K, mTOR, and the DNA repair protein DNA-PK. “Her cancer responded with a decrease in the size of the left supraclavicular lymph node, but after approximately 6 weeks on therapy, the node began growing very rapidly. This was a definite change in the tempo of her disease, which heretofore had been growing slowly,” O’Shaughnessy said.

The enlarging supravacular lymph node was resected, as was a subpectoral lymph node a few months later, which was the patient’s only site of recurrent disease at that time. Shortly after the second resection, however, she developed very rapidly growing internal mammary lymph nodes, some of which were substernal and pushing her sternum out, causing considerable pain.

“I treated her with 6 cycles of high-dose nab-paclitaxel [Abraxane] and cisplatin every 3 weeks and obtained a complete response [CR] on CT scan after 2 cycles of therapy. She has been without evidence of disease since 2012,” O’Shaughnessy said.

O’Shaughnessy has analyzed the molecular characteristics of Donna’s serial tumor specimens, including by reverse-phase protein arrays to understand protein pathway activation within her breast cancer. “I think what happened is that the BEZ235 remodeled her cancer by interrupting signaling through the PI3K pathway, inhibited DNA-PK, and shifted signaling in the cancer over to the highly proliferative MAP kinase, MEK/ERK-driven pathway. And BEZ235 increased the degree of homologous recombination deficiency in her breast cancer, which I think was present because of the somatic SMARCA4 loss-of-function mutation seen on next-generation sequencing. These changes likely increased the sensitivity of her cancer to DNA-damaging agents, including cisplatin. So, though Donna had never benefited from chemotherapy before, her remodeled tumor became exquisitely sensitive to cisplatin and nab-paclitaxel following treatment with BEZ235,” O’Shaughnessy explained.

O’Shaughnessy’s experience with Donna, an exceptional responder, shifted the direction of her research toward conducting small, translational pilot trials aimed at increasing BRCA1ess in metastatic TNBCs, defined as disruptive DNA repair traits that sporadic cancers share with BRCA1/2-mutated tumors. The goal of increasing BRCA1ess is to enhance the effectiveness of DNA-damaging agents and checkpoint inhibitors. She currently has ongoing clinical trials using PI3K/mTOR inhibitors, a combination of TAK-228 and TAK-117 called PIKTOR (NCT03193853) and LY3023414 (NCT04032080), to evaluate whether these agents can increase homologous recombination deficiency in patients with pretreated metastatic TNBCs.

O’Shaughnessy has always loved science, but it was a personal experience that set her on the path to medicine. When
O’Shaughnessy was in high school, her 5-year-old sister, Teri, developed acute lymphoblastic leukemia, and she watched as her sister was treated on a series of pediatric leukemia clinical trials. Teri succumbed to her disease in 1975, when she was just 10 years old.

At the time, O’Shaughnessy was a student at the College of the Holy Cross in Worcester, Massachusetts, and, after her sister’s death, she decided that cancer research would become her life’s mission. Fortunately, the dean of Holy Cross was very supportive and provided her with funding for her initial study that summer, and she then spent much of her senior year in college studying tumor virology at the Worcester Foundation for Biomedical Research in nearby Shrewsbury, Massachusetts.

After graduating college, O’Shaughnessy went on to pursue her medical degree from Yale University Medical School in New Haven, Connecticut, where she conducted research and wrote her graduation thesis on the biochemical mechanisms of antileukemic agents under the mentorship of 2 very dedicated oncologists, Edwin C. Cadman, MD, and Christopher C. Benz, MD.

Although O’Shaughnessy was initially interested in hematological malignancies because of her sister, a post-fellowship opportunity to transition to the National Cancer Institute’s Clinical Breast Cancer Division to work with her mentor, Kenneth Cowan, MD, PhD, in 1990 cemented her focus on breast cancer. She has since made a considerable impact on the field.

When she first started caring for patients with breast cancer, the treatment landscape was barren, and there had been no improvement in cure rates since the 1930s. Conservative estimates suggest that more than 1 million women died from breast cancer in the United States between 1950 and 1990 alone; a clear trend toward improved survival was not seen until the mid-1990s.

Today, many patients with breast cancer, including those with metastatic disease and the aggressive subtypes, are experiencing improved survival rates due to the rapid pace of discovery, clinical development, and FDA approval of new agents.

O’Shaughnessy’s contributions to the breast cancer armamentarium include key research into the chemotherapeutics gemcitabine, capecitabine, and eribulin mesylate; the CDK4/6 inhibitors abemaciclib (Verzenio) and ribociclib (Kisqali); the immune checkpoint inhibitor pembrolizumab (Keytruda); and numerous targeted therapies including HER2 and PARP inhibitors.

Unlike in the past, when researchers searched for broad-spectrum cancer therapies, today’s treatments are increasingly targeting molecular markers in well-defined breast cancer subtypes. O’Shaughnessy shared her insights on some of the emerging therapies on the horizon that are likely to reshape breast cancer care.

**RECENT DRUG APPROVALS IN BREAST CANCER**

**Neratinib**

Neratinib (Nerlynx) is an orally available tyrosine kinase receptor inhibitor of EGFR, HER2, and HER4. On February 25, 2020, the drug received FDA approval for a new indication as a combination therapy with capecitabine for adult patients with advanced or metastatic HER2-positive breast cancer who have received 2 or more previous anti-HER2-based regimens in the metastatic setting. It was previously approved in 2017 as a single agent for the extended adjuvant treatment of adults with early-stage HER2-positive breast cancer following adjuvant trastuzumab (Herceptin)-based therapy.

Neratinib’s new indication was approved based on data from the multicenter, open-label NALA trial (NCT01808573), which randomly assigned patients 1:1 to receive neratinib 240 mg orally once daily on days 1 to 21 with capecitabine 750 mg/m² given orally twice daily on days 1 to 14 for each 21-day cycle (n = 307) or to lapatinib (Tykerb) 1250 mg orally once daily on days 1 to 21 with capecitabine 1000 mg/m² given orally twice daily on days 1 to 14 for each 21-day cycle (n = 314). The primary end points were progression-free survival (PFS) and overall survival (OS), whereas secondary end points included objective response rate and response duration. Primary and secondary outcome measures were improved with neratinib plus capecitabine versus lapatinib plus capecitabine (TABLE 1).

“One year of neratinib is a very important therapy for patients with high-risk estrogen receptor-positive breast cancer in the adjuvant setting. I offer it in combination with endocrine therapy following neoadjuvant pertuzumab [Perjeta] and adjuvant T-DM1 [ado-trastuzumab emtansine; Kadcyla], as it substantially reduces the risk of breast cancer recurrence. In my practice, I have seen that neratinib plus capecitabine is an effective combination for patients with HER2-positive brain metastases,” O’Shaughnessy said.

**Trastuzumab Deruxtecan**

Fam-trastuzumab deruxtecan-nxki (Enhertu) is a HER2-directed antibody and topoisomerase inhibitor conjugate. On December 20, 2019, the FDA granted accelerated approval to trastuzumab deruxtecan for patients with unresectable metastatic HER2-positive breast cancer who received 2 or more previous anti-HER2-based regimens in the metastatic setting.

Approval was based on data from the 2-part, open-label, single-group, multicenter, phase 2 DESTINY-Breast01 (NCT03248492) trial, which included 184 patients who had undergone a median of 6 previous treatments and received the recommended dose of trastuzumab deruxtecan (5.4 mg per/kg of body weight).

**TABLE 1. NALA TRIAL EFFICACY RESULTS**

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Neratinib + capecitabine</th>
<th>Lapatinib + capecitabine</th>
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<tbody>
<tr>
<td><strong>Primary end points</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>5.6 (4.9-6.9)</td>
<td>5.5 (4.3-5.6)</td>
</tr>
<tr>
<td>PFS rate at 12 months</td>
<td>29%</td>
<td>15%</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>21.0 (17.7-23.8)</td>
<td>18.7 (15.5-21.2)</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>32.8%</td>
<td>26.7%</td>
</tr>
<tr>
<td>Median response duration, months (95% CI)</td>
<td>8.5 (5.6-11.2)</td>
<td>5.6 (4.2-6.4)</td>
</tr>
</tbody>
</table>

ORR, objective response rate; OS, overall survival; PFS progression-free survival.
EXPLORE TIL IMMUNOTHERAPY

TIL MANUFACTURING AT IOVANCE STARTS WITH ISOLATING TUMOR-INFILTRATING LYMPHOCYTES (TIL)
from a surgically resected piece of a patient’s tumor. The isolated TIL, which may recognize multiple patient-specific antigens expressed by the tumor, are expanded to billions of cells. Prior to infusion of TIL, the patients are treated with non-myeloablative lymphodepletion preconditioning to remove the suppressive tumor micro-environment. Once the TIL are infused, the patients receive up to 6 doses of IL-2 to support expansion and anti-tumor activity of the TIL.

22 DAY PROCESS, ONE-TIME THERAPY

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TO LEARN MORE ABOUT THE TRIALS
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VISIT CLINICALTRIALS.GOV
Metastatic Melanoma: NCT02360579
Cervical Cancer: NCT03108495
Head and Neck Cancer: NCT03083873
Multiple Solid Tumors: NCT03645928
(Melanoma, HNSCC, NSCLC)

TIL Therapy is an investigational therapy and has not been approved for any indication by the United States Food and Drug Administration (USFDA) or any other regulatory agency. The safety and efficacy of this therapy has not been determined.
In the intention-to-treat analysis, 112 patients had a response to therapy (60.9%; 95% CI, 53.4-68.0), with a CR rate of 6.0% and a partial response rate of 54.9%. The median duration of response was 14.8 months (95% CI, 13.8-16.9), and the median duration of PFS was 16.4 months (95% CI, 12.7-not reached). 7

Several phase 3 trials are ongoing, including DESTINY-Breast02 (NCT03523585), which is evaluating trastuzumab deruxtecan versus the investigator’s choice in patients with HER2-positive, unresectable, or metastatic breast cancer previously treated with standard-of-care HER2 therapies, including T-DM1; DESTINY-Breast03 (NCT03529110), which is comparing trastuzumab deruxtecan versus T-DM1 in patients with HER2-positive, unresectable, or metastatic breast cancer previously treated with trastuzumab and a taxane; and DESTINY-Breast04 (NCT03734029), which is assessing trastuzumab deruxtecan versus the investigator’s choice for HER2-low breast cancer that has spread or is unresectable. All 3 trials are currently recruiting patients.

### TABLE 2. SELECT TRIALS OF PROMISING REGIMENS IN THE BREAST CANCER PIPELINE

<table>
<thead>
<tr>
<th>Agent</th>
<th>Key trials (ClinicalTrials.gov identifier)</th>
<th>Patient population</th>
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<tbody>
<tr>
<td><strong>AKT inhibitors</strong></td>
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<tr>
<td>Capivasertib (AZD5363)</td>
<td>Phase 3: Capivasertib/paclitaxel vs placebo/paclitaxel (CAPItello290; NCT03997123)</td>
<td>Treatment-naive locally advanced unresectable or mTNBC</td>
</tr>
<tr>
<td>Ipatasertib (RG7440)</td>
<td>Phase 3: Ipatasertib + atezolizumab and paclitaxel given in various combinations and +/- placebo (NCT04177108)</td>
<td>Treatment-naive locally advanced unresectable or mTNBC</td>
</tr>
<tr>
<td><strong>Antibody-drug conjugates</strong></td>
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<tr>
<td>Fam-trastuzumab deruxtecan-nxki (Enhertu)</td>
<td>Phase 3: Trastuzumab deruxtecan vs physician’s choice of treatment (ie, capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel) (DESTINY-Breast04; NCT03734029)</td>
<td>HER2-low, unresectable, and/or metastatic BC previously treated with chemotherapy</td>
</tr>
<tr>
<td>Ladiratuzumab vedotin (SGN-LIV1A)</td>
<td>Phase 1/2: Single-arm trial of ladiratuzumab vedotin + pembrolizumab (NCT03310957)</td>
<td>Locally advanced or mTNBC</td>
</tr>
<tr>
<td>Sacituzumab govitecan (Trodelvy)</td>
<td>Phase 3: Sacituzumab govitecan vs physician’s choice of treatment (ie, eribulin, capecitabine, gemcitabine, vinorelbine) (ASCENT; NCT02574455)*</td>
<td>Refractory/relapsed mTNBC</td>
</tr>
<tr>
<td>Vic-trastuzumab duocarmazine (SYD985)</td>
<td>Phase 3: SYD985 vs physician’s choice of treatment (ie, lapatinib or trastuzumab + capecitabine; trastuzumab + vinorelbine or eribulin) (TULIP; NCT03262935)</td>
<td>Unresectable locally advanced or metastatic HER2+ BC progressing during or after ≥2 HER2-targeting regimens for locally advanced/metastatic disease or progression during or after T-DM1 treatment</td>
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<tr>
<td><strong>CDK4/6 inhibitors</strong></td>
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<tr>
<td>Abemaciclib (Verzenio)</td>
<td>Phase 3: 2 years of abemaciclib + standard adjuvant ET vs standard adjuvant ET (monarchE; NCT03155997)*</td>
<td>High-risk, node-positive, early-stage, HR+/HER2- BC</td>
</tr>
<tr>
<td>Palbociclib (Ibrance)</td>
<td>Phase 3: 2 years of palbociclib + standard adjuvant ET for ≥5 years vs standard adjuvant ET for ≥5 years (PALLAS; NCT02513394)*</td>
<td>HR+/HER2- early BC</td>
</tr>
<tr>
<td>Ribociclib (Kisqali)</td>
<td>Phase 3: Standard ET + palbociclib or placebo for 13 cycles (PENELOPE-B; NCT01864746)*</td>
<td>Pre- and postmenopausal women with HR+/HER2-normal early BC at high risk of relapse because pCR was not achieved following neoadjuvant taxane-containing chemotherapy</td>
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<tr>
<td><strong>Checkpoint inhibitors</strong></td>
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<tr>
<td>Durvalumab (Imfinzi)</td>
<td>Phase 3: Durvalumab vs chemotherapy as maintenance therapy (SAFIR02-IMMUNO; NCT02299999 substudy)*</td>
<td>Metastatic BC</td>
</tr>
<tr>
<td>Elacestrant</td>
<td>Phase 3: Elacestrant vs standard of care (eg, fulvestrant, anastrozole, letrozole, exemestane) (EMERALD; NCT03778931)</td>
<td>ER+/HER2- advanced BC that has relapsed or progressed after at least 1 but ≤2 prior lines of ET including CDK4/6 inhibitor therapy</td>
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<tr>
<td><strong>Oral taxanes</strong></td>
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<tr>
<td>Oral paclitaxel with encequidar (OPE; Oraxol)</td>
<td>Phase 3: OPE vs IV paclitaxel (NCT02594371)*</td>
<td>Metastatic BC suitable for treatment with IV paclitaxel monotherapy</td>
</tr>
<tr>
<td>Tesetaxel</td>
<td>Phase 2: Tesetaxel (27 mg/m² on day 1 of a 21-day cycle) plus a reduced dose of capecitabine (1650 mg/m² daily for 14 days of each 21-day cycle) (CONTESSA 2; NCT03858972)</td>
<td>HER2-/HR+ locally advanced or metastatic BC not previously treated with a taxane in the neoadjuvant, adjuvant, or metastatic setting and not treated with &gt;1 chemotherapy regimen for advanced disease</td>
</tr>
</tbody>
</table>

BC, breast cancer; ER, estrogen receptor; ET, endocrine therapy; HR, hormone receptor; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; pCR, pathological complete response; T-DM1, ado-trastuzumab emtansine.

*Trial is active but not recruiting.
November 5 – 7, 2020
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- Current guidelines and evolving evidence on locoregional treatment options
- Systemic therapies for early-stage and advanced/metastatic breast cancer

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O’Shaughnessy said she is excited about the potential for trastuzumab deruxtecan, which may redefine how women with HER2-low–expressing breast cancers (1+/2+ on immunohistochemistry) are treated if it receives an expanded indication. “Trastuzumab deruxtecan represents an exciting new strategy because the antibody against HER2, trastuzumab, binds to the breast cancer cells even in the setting of low HER2 expression, enabling the powerful chemotherapy drug, deruxtecan, to be delivered to these and even neighboring HER2-negative cells—the so-called bystander effect,” O’Shaughnessy said. “If the phase 3 DESTINY-Breast04 trial is positive, and the early phase 1/2 data do appear promising, we will have a new subtype of breast cancer, HER2-low, to target with this new agent,” she said.

Approval of trastuzumab deruxtecan in the setting of HER2-low expression would potentially affect a large number of patients, as this group has been estimated to be 2.5 times that of the current HER2-positive population.8

Sacituzumab Govitecan
Sacituzumab govitecan-hziy (Trodelvy) gained an accelerated approval on April 22, 2020, for the treatment of patients with metastatic TNBC who have received 2 or more prior therapies for metastatic disease. It is an antibody-drug conjugate that combines a humanized monoclonal antibody with SN-38 in a way that enables high concentrations of SN-38 to be delivered to tumors.10

In a phase 1/2 multicenter trial (NCT01631552) that included 108 patients, investigator assessment showed an objective response rate of 33.3%, with 3 CRs and 33 partial responses. The median duration of response was 7.7 months. Post hoc assessment by independent central review showed a response rate of 34.3% and median duration of response of 9.1 months. The clinical benefit rate was 45.4%, the median PFS was 5.5 months (95% CI, 4.1-6.3), and the median OS was 13.0 months (95% CI, 11.2-13.7).10

Sacituzumab govitecan is being assessed in the phase 3 ASCENT study (NCT02574455) in patients with relapsed or refractory metastatic TNBC who have been treated with 2 or more anticancer agents. The study, which has an estimated enrollment of 529 patients, is randomizing participants 1:1 to receive either sacituzumab govitecan (10 mg/kg on days 1 and 8 of a 21-day cycle) or physician’s choice of chemotherapy (eribulin, capecitabine, gemcitabine, or vinorelbine).

Tucatinib
On April 17, 2020, the FDA approved tucatinib (Tukysa) in combination with trastuzumab and capecitabine for patients with locally advanced or unresectable metastatic HER2-positive breast cancer, including patients with brain metastases previously treated with HER2-targeting therapies.11 It is an oral, small-molecule tyrosine kinase receptor inhibitor that is highly selective for HER2.

In the phase 2 HER2CLIMB trial (NCT02614794), the PFS rate at 1 year was 33.1% among those who received the tucatinib-containing regimen versus 12.3% for participants who took placebo, trastuzumab, and capecitabine; the median PFS was 7.8 months (95% CI, 7.5-9.6) and 5.6 months (95% CI, 4.2-7.1), respectively, (HR, 0.54; 95% CI, 0.42-0.71; P < .001).12

At 2 years, the OS rate was 44.9% in the tucatinib group and 26.6% in the comparator arm; the median OS was 21.9 months (95% CI, 18.3-31.0) and 17.4 months (95% CI, 13.6-19.9), respectively, (HR, 0.66; 95% CI, 0.50-0.88; P = .005). Among the patients with brain metastases, PFS at 1 year was 24.9% in the tucatinib-combination group and 0% in the placebo-combination group, and the median PFS was 7.6 months (95% CI, 6.2-9.5) and 5.4 months (95% CI, 4.1-5.7), respectively.12

HER2CLIMB is the first completed randomized trial to include and show benefit in patients with HER2-positive breast cancer and brain metastases.13

NOVEL THERAPIES IN LATE-STAGE DEVELOPMENT
Margetuximab
Margetuximab is being assessed in the phase 3 SOPHIA trial (NCT02492711), which is comparing this agent in combination with chemotherapy versus trastuzumab plus chemotherapy in patients with HER2-positive metastatic breast cancer previously treated with anti-HER2-targeted therapies. Margetuximab is a crystallizable fragment-engineered anti-HER2 monoclonal antibody that is similar to trastuzumab, targeting the same epitope and exerting similar antiproliferative effects but with enhanced immune activity against HER2-expressing tumor cells.14

The second interim OS analysis, which was planned after 270 deaths (cutoff September 2019), showed a median OS of 21.6 months (95% CI, 18.86-24.05) for the margetuximab-containing regimen versus 19.8 months (95% CI, 17.54-22.28) for trastuzumab-based therapy plus chemotherapy, a finding that did not reach statistical significance (stratified log-rank P = .326).15 The final prespecified OS analysis is planned after 385 deaths and projected to occur in the second half of 2020. However, exploratory analysis of patients carrying a specific genotype of CD16a, the CD16a 158F allele, had a larger OS benefit with margetuximab. In the second interim analysis, their median OS was prolonged by 4.3 months versus trastuzumab (23.7 vs 19.4 months, respectively; HR, 0.79; 95% CI, 0.61-1.04; nominal P = .087). Approximately

Joyce A. O’Shaughnessy, MD, with Sara A. Hurvitz, MD, who will co-chair the 19th Annual International Congress on the Future of Breast Cancer® West, in July 2020.
85% of participants in the SOPHIA trial had the CD16A 158F allele, which represents its prevalence in the general human population. In contrast, the patients who did not have the CD16A 158F allele (15%) had a better survival outcome with the trastuzumab combination.

On December 19, 2019, based on the SOPHIA data, margetuximab's manufacturer, MacroGenics, announced it had submitted a biologics license application to the FDA. It previously received fast-track designation for margetuximab on January 23, 2018. Pembrolizumab: Neoadjuvant and First-Line Metastatic Settings Pembrolizumab, a humanized, anti–PD-1 monoclonal antibody, is showing promise when added to chemotherapy in the neoadjuvant and first-line metastatic settings for women with TNBC or hormone receptor–positive/HER2-negative disease.

In February 2020, both the phase 2 adaptively randomized I-SPY2 trial (NCT01042379) and the phase 3 randomized KEYNOTE-522 trial (NCT03036488) reported positive results in the neoadjuvant setting, and the KEYNOTE-355 (NCT02819518) trial investigators announced that pembrolizumab in combination with chemotherapy had met the study’s primary end point of PFS in the first-line setting in patients with metastatic TNBC whose tumors had PD-L1 combined positive scores of 10% or greater. The I-SPY2 trial assessed pembrolizumab in combination with taxane- and anthracycline-based neoadjuvant chemotherapy in 250 women with early-stage breast cancer. The addition of pembrolizumab to standard neoadjuvant chemotherapy more than doubled pathological CR (pCR) rates compared with chemotherapy alone for both hormone receptor–positive/HER2-negative disease and TNBC. Final estimated pCR rates, evaluated in March 2017, were 44% versus 17%, 30% versus 13%, and 60% versus 22% for pembrolizumab plus neoadjuvant chemotherapy versus standard neoadjuvant chemotherapy in the HER2-negative, hormone receptor–positive/HER2-negative, and TNBC cohorts, respectively.

The KEYNOTE-522 trial randomly assigned patients who were treatment naïve and had stage II or stage III TNBC in a 2:1 ratio to receive neoadjuvant therapy with pembrolizumab plus paclitaxel and carboplatin (n = 784) or placebo plus paclitaxel and carboplatin (n = 390). Both groups then received an additional 4 cycles of pembrolizumab or placebo, as well as doxorubicin-cyclophosphamide or epirubicin-cyclophosphamide. After definitive surgery, patients received adjuvant pembrolizumab or placebo every 3 weeks for up to 9 cycles. The first interim analysis, which included the first 602 patients who underwent randomization, showed a pCR of 64.8% (95% CI, 59.9-69.5) in the pembrolizumab-chemotherapy group and 51.2% (95% CI, 44.1-58.3) in the placebo-chemotherapy group (P < .001). After a median follow-up of 15.5 months, 58 patients (7.4%) in the pembrolizumab-chemotherapy group and 46 patients (11.8%) in the placebo-chemotherapy group had disease progression that precluded definitive surgery, had local or distant recurrence or a second primary tumor, or died from any cause.

EMERGING TREATMENT STRATEGIES: 2021 AND BEYOND O’Shaughnessy said that many other agents in earlier phases of clinical development across the breast cancer spectrum are also showing considerable promise, with FDA approvals anticipated over the next few years. Some of the agents she mentioned are outlined in Table 2 on page 18.

“In 2021, I hope we have clinical availability of an antibody-drug conjugate called SYD985 [vic-trastuzumab duocarmazine], which is another promising anti-HER2-based therapy currently being evaluated in the phase 3 TULIP trial [NCT03262933]. And, importantly, I’m hoping the ongoing phase 3 adjuvant trials of palbociclib [Ibrance], abemaciclib, and ribociclib are also positive and become standards of care for patients with high-risk estrogen receptor–positive breast cancer,” she said.

Other agents that O’Shaughnessy believes are likely to influence the standard management of patients with breast cancer in the future include the ATK inhibitors capivasertib and ipatasertib; the checkpoint inhibitors atezolizumab (Tecentriq), nivolumab (Opdivo), and durvalumab (Imfinzi) in the neoadjuvant and adjuvant settings; the selective estrogen receptor degrader elacestrant; the novel antibody-drug conjugate ladiratuzumab vedotin (SGN-LIV1A); and the oral taxanes OPE (oral paclitaxel with encequidar) and tesetaxel.

The door was opened for checkpoint inhibitor therapy in breast cancer on March 8, 2019, when the FDA approved atezolizumab, a PD-L1 inhibitor, in combination with nab-paclitaxel for patients with unresectable locally advanced or metastatic TNBC whose tumors exhibit PD-L1 expression of 1% or more on tumor-infiltrating immune cells.

KEEPING UP WITH THE EVER-CHANGING TREATMENT LANDSCAPE The many treatments O’Shaughnessy discussed are only a sampling of what is yet to come, as breast cancer continues to receive a tremendous amount of investment. A 2019 report in the Journal of the National Comprehensive Cancer Network that examined cancer funding by nonprofit organizations found that, in 2015, breast cancer initiatives received $460 million of the $6 billion generated by the 119 cancer-related nonprofits included in the study. This funding has enabled the development of significant therapeutic advances for patients with breast cancer but has created a challenge for oncologists in learning about and applying ever-evolving new information in their practices. Attending meetings such as the Miami Breast Cancer Conference, IBC East, IBC West, and the School of Breast Oncology is a way oncologists and other practitioners can make sure they are up to date on all the key advances that will help their patients, O’Shaughnessy explained.

“There are many new data oncologists can apply tomorrow in their practices, but they have to know which patients and when they may benefit from new therapies, and what the risks are,” she said.

For example, tucatinib became available for patients through an expanded-access program before the FDA approved it. “These are the types of topics we cover in depth at our meetings and applying ever-evolving new information in their practices. Attending meetings such as the Miami Breast Cancer Conference, IBC East, IBC West, and the School of Breast Oncology is a way oncologists and other practitioners can make sure they are up to date on all the key advances that will help their patients, O’Shaughnessy explained.

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ENHERTU monotherapy: durable efficacy

EXPECTATIONS

NOW APPROVED

(n=111; 95% CI: 13.8, 16.9)c

(n=111/184; 95% CI: 52.9, 67.4)b

4.3% CR (n=8) and 56.0% PR (n=103)

14.8 month mDORc,d

60.3% ORR

aORR (CR+PR) in ITT population.1 bORR 95% CI calculated using Clopper-Pearson method.1 cMedian DOR based on Kaplan-Meier estimate.1 95% CI calculated using Brookmeyer-Crowley method.1 dDOR based on a median duration of follow-up of 11.1 months.1

CI, confidence interval; CR, complete response; DOR, duration of response; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; ICR, independent central review; ITT, intent-to-treat; mBC, metastatic breast cancer; mDOR, median duration of response; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.


Please see additional Important Safety Information and a Brief Summary of full Prescribing Information on following pages.

IMPORTANT SAFETY INFORMATION

Interstitial Lung Disease / Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU, ILD occurred in 9% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 2.6% of patients treated with ENHERTU. Median time to first onset was 4.1 months (range: 1.2 to 8.3). Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD/pneumonitis by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg prednisolone or equivalent). Upon improvement, follow by gradual taper (e.g., 4 weeks).

ENHERTU was assessed in a single-arm trial of 184 females with HER2+ unresectable and/or mBC who had received ≥2 prior anti-HER2 therapies. Patients received ENHERTU 5.4 mg/kg IV once every 3 weeks until disease progression or unacceptable toxicity. The major efficacy outcomes were confirmed ORR assessed by ICR using RECIST v1.1 and DOR.1

Important Safety Information (continued)

WARNINGS AND PRECAUTIONS

INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.

- Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

Please see additional Important Safety Information and a Brief Summary of full Prescribing Information on following pages.

Visit ENHERTUhcp.com for more information.
ENHERTU monotherapy: durable efficacy

ENHERTU was assessed in a single-arm trial of 184 females with HER2+ unresectable and/or mBC who had received ≥2 prior anti-HER2 therapies. Patients received ENHERTU 5.4 mg/kg IV once every 3 weeks until disease progression or unacceptable toxicity. The major efficacy outcomes were confirmed ORR assessed by ICR using RECIST v1.1 and DOR.¹

**60.3% ORR**

(n=111/184; 95% CI: 52.9, 67.4)ᵇ

4.3% CR (n=8) and 56.0% PR (n=103)

**14.8 month mDOR**

(c,d)

(n=111; 95% CI: 13.8, 16.9)ᶜ

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**Important Safety Information (continued)**

**WARNINGS AND PRECAUTIONS**

**Interstitial Lung Disease / Pneumonitis**

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU, ILD occurred in 9% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 2.6% of patients treated with ENHERTU. Median time to first onset was 4.1 months (range: 1.2 to 8.3).

Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg prednisolone or equivalent). Upon improvement, follow by gradual taper (e.g., 4 weeks).


Please see additional Important Safety Information and a Brief Summary of full Prescribing Information on following pages.
**Important Safety Information**

**Indication**

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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**WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY**

- Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.

- Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

**Contraindications**

None.

**WARNINGS AND PRECAUTIONS**

**Interstitial Lung Disease / Pneumonitis**

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU, ILD occurred in 9% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 2.6% of patients treated with ENHERTU. Median time to first onset was 4.1 months (range: 1.2 to 8.3).

Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg prednisolone or equivalent). Upon improvement, follow by gradual taper (e.g., 4 weeks).

**Neutropenia**

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU, a decrease in neutrophil count was reported in 30% of patients and 16% had Grade 3 or 4 events. Median time to first onset was 1.4 months (range: 0.3 to 18.2). Febrile neutropenia was reported in 1.7% of patients.

Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, ENHERTU may require dose interruption or reduction. For Grade 3 neutropenia (Absolute Neutrophil Count [ANC] <1.0 to 0.5 x 10^9/L) interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 10^9/L) interrupt ENHERTU until resolved to Grade 2 or less. Reduce dose by one level. For febrile neutropenia (ANC <1.0 x 10^9/L and temperature >38.3°C or a sustained temperature of ≥38°C for more than 1 hour), interrupt ENHERTU until resolved. Reduce dose by one level.

**Left Ventricular Dysfunction**

Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. In the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, two cases (0.9%) of asymptomatic LVEF decrease were reported. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF <50% prior to initiation of treatment.

Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. Permanently discontinue ENHERTU if LVEF of <40% or absolute decrease from baseline of >20% is confirmed. When LVEF is >45% and absolute decrease from baseline is 10-20%, continue treatment with ENHERTU. When LVEF is 40-45% and absolute decrease from baseline is <10%, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks. When LVEF is 40-45% and absolute decrease from baseline is 10-20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose. When LVEF is <40% or absolute decrease from baseline is >20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks.
When LVEF is <40% or absolute decrease from baseline is >20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF of <40% or absolute decrease from baseline of >20% is confirmed, permanently discontinue ENHERTU. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure.

**Embryo-Fetal Toxicity**

ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months after the last dose of ENHERTU.

**Adverse Reactions**

The safety of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study DS8201-A-J101. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31).

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were interstitial lung disease, pneumonia, vomiting, cellulitis, hypokalemia, and intestinal obstruction. Fatalities due to adverse reactions occurred in 4.3% of patients including interstitial lung disease (2.6%), and the following events occurred in one patient each (0.4%): acute hepatic failure/acute kidney injury, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 9% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 33% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, thrombocytopenia, leukopenia, upper respiratory tract infection, fatigue, nausea, and ILD. Dose reductions occurred in 18% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, and neutropenia.

The most common adverse reactions (frequency ≥20%) were nausea (79%), fatigue (59%), vomiting (47%), alopecia (46%), constipation (35%), decreased appetite (32%), anemia (31%), neutropenia (29%), diarrhea (29%), leukopenia (22%), cough (20%), and thrombocytopenia (20%).

**Use in Specific Populations**

- **Pregnancy:** ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months following the last dose of ENHERTU.
- **Lactation:** There are no data regarding the presence of ENHERTU in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.
- **Females and Males of Reproductive Potential:** Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: Females: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 7 months following the last dose. Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months following the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.
- **Pediatric Use:** Safety and effectiveness of ENHERTU have not been established in pediatric patients.
- **Geriatric Use:** Of the 234 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 26% were ≥65 years and 5% were ≥75 years. No overall differences in efficacy were observed between patients ≥65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged ≥65 years (53%) as compared to younger patients (42%).
- **Hepatic Impairment:** In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor.

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or fda.gov/medwatch.

Please see a Brief Summary of full Prescribing Information on following pages.
ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use

Initial U.S. Approval: 2019

BRIEF SUMMARY: See package insert for full prescribing information.

WARNING: INTERSTITIAL LUNG DISEASE AND EMBRYO-FETAL TOXICITY

- Interstitial Lung Disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and the need to immediately report symptoms [see Dosage and Administration (2.2) in the full prescribing information, Warnings and Precautions (5.1)].

- Embryo-Fetal Toxicity: Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception [see Warnings and Precautions (5.4), Use in Specific Populations (8.1), Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) in the full prescribing information]. Advise patients of the potential risks to a fetus.

Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months after the last dose of ENHERTU [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Interstitial Lung Disease / Pneumonitis [see Warnings and Precautions (5.1)]
- Neutropenia [see Warnings and Precautions (5.2)]
- Left Ventricular Dysfunction [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study DS8201-A-J101 (NCT02564900). ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31).

In the pooled 234 patients, the median age was 56 years (range: 28-96), 74% of patients were ≤65 years, 99.6% of patients were female, and the majority were White (51%) or Asian (42%). Patients had an ECOG performance status of 0 (58%) or 1 (42%) at baseline. Ninety-four percent had visceral disease, 31% had bone metastases, and 13% had brain metastases.

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were interstitial lung disease, pneumonia, vomiting, nausea, neutropenia, hypokalemia, and intestinal obstruction. Fatalities due to adverse reactions occurred in 4.3% of patients including interstitial lung disease (2.6%), and the following events occurred in one patient each (0.4%): acute hepatic failure/acute kidney injury, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 9% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 33% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, thrombocytopenia, leukopenia, upper respiratory tract infection, fatigue, nausea, and ILD. Dose reductions occurred in 18% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, and neutropenia.

The most common adverse reactions (frequency ≥20%) were nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anemia, neutropenia, diarhea, leukopenia, cough, and thrombocytopenia.

Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities observed in ENHERTU-treated patients.

Table 3: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients in DESTINY-Breast01 and Study DS8201-A-J101

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ENHERTU 5.4 mg/kg</th>
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<tbody>
<tr>
<td></td>
<td>All Grades N=234</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>79</td>
</tr>
<tr>
<td>Vomiting</td>
<td>47</td>
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<tr>
<td>Constipation</td>
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<td>Diarrhea</td>
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<td><strong>General Disorders and Administration Site Conditions</strong></td>
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<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
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<tr>
<td>Alopecia</td>
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<td>Rasha</td>
<td>10</td>
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</tbody>
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(continued)
ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use

5. WARNINGS AND PRECAUTIONS

• Respiratory symptoms. Permanently discontinue ENHERTU in all patients with new onset or worsening of respiratory symptoms. Monitor for and promptly investigate signs and symptoms of interstitial lung disease (ILD) or pneumonitis, including cough or dyspnea. Withholding ENHERTU may be appropriate if the symptoms stabilize or improve, and may be restarted at a lower dose. If symptom recurrence occurs, ENHERTU should be permanently discontinued.

• Embryo-fetal harm. Advise patients of these risks and the need for effective contraception during and for at least 4 months after the last dose of ENHERTU. There is a regulated distribution program through the ENHERTU REMS to ensure that women are adequately counseled about the potential hazards to the fetus. Refer to “Instructions for Use” for more information about the ENHERTU REMS program.

• Based on its mechanism of action, ENHERTU can cause fetal harm when administered to pregnant women. There are no available data on the use of ENHERTU in pregnant women. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fetal pulmonary hypoplasia, skeletal abnormalities, and neonatal death [see Data]. Based on its mechanism of action, the topoisomerase inhibitor component of ENHERTU, DXI, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells [see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) in the full prescribing information]. Advise patients of the potential risks to a fetus.

There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months following the last dose of ENHERTU [see Clinical Considerations].

• The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

• There were no animal reproductive or developmental toxicity studies conducted in vivo with ENHERTU. Rodents exposed to DXI during organogenesis have demonstrated decreased fetal weight, decreased fetal ossification, and increased incidences of fetal cleft palate. The potential for DXI to cause similar fetal findings in humans has not been evaluated. In addition, neutralizing activity of anti-ENHERTU antibodies has not been assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ENHERTU can cause fetal harm when administered to a pregnant woman. There are no available data on the use of ENHERTU in pregnant women. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fetal pulmonary hypoplasia, skeletal abnormalities, and neonatal death [see Data]. Based on its mechanism of action, the topoisomerase inhibitor component of ENHERTU, DXI, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells [see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) in the full prescribing information]. Advise patients of the potential risks to a fetus.

There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months following the last dose of ENHERTU [see Clinical Considerations].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received ENHERTU during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Human Data

There are no available data on the use of ENHERTU in pregnant women. In postmarketing reports in pregnant women receiving a HER2-directed antibody, cases of oligohydramnios manifesting as fetal pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported. These case reports described oligohydramnios in pregnant women who received a HER2-directed antibody either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after use of a HER2-directed antibody was stopped.

Animal Data

There were no animal reproductive or developmental toxicity studies conducted with fam-trastuzumab deruxtecan-nxki.

8.2 Lactation

Risk Summary

There is no data regarding the presence of fam-trastuzumab deruxtecan-nxki in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.

Table 3: Common Adverse Reactions (>10% All Grades or ≥2% Grades 3 or 4) in Patients in DESTINY-Breast01 and Study DS8201-A-J101

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ENHERTU 5.4 mg/kg</th>
<th>N=234</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3 or 4 %</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>32</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>12</td>
<td>3.4</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>22</td>
<td>6</td>
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<tr>
<td>Thrombocytopenia</td>
<td>20</td>
<td>3.4</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gough</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
<td>1.3</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>9</td>
<td>2.6</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Infections and Infestation</td>
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<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>15</td>
<td>0.6</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>14</td>
<td>0.9</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>10</td>
<td>0.9</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>11</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Events were graded using NCI-CTCAE version 4.03. N=number of patients exposed; PT = preferred term.

Table 3: Common Adverse Reactions (>10% All Grades or ≥2% Grades 3 or 4) in Patients with Unresectable or Metastatic HER2-positive Breast Cancer Treated with ENHERTU

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>ENHERTU 5.4 mg/kg</th>
<th>N = 234</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3 or 4 %</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>70</td>
<td>7</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>70</td>
<td>7</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>62</td>
<td>16</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>37</td>
<td>3.4</td>
</tr>
</tbody>
</table>

(continued)
8.3 Females and Males of Reproductive Potential

Pregnancy Testing
Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU.

Contraception
Females
ENHERTU can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 7 months following the last dose.

Males
Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months following the last dose [see Nonclinical Toxicology (13.1) in the full prescribing information].

Infertility
Based on findings in animal toxicity studies, ENHERTU may impair male reproductive function and fertility [see Nonclinical Toxicology (13.1) in the full prescribing information].

8.4 Pediatric Use
Safety and effectiveness of ENHERTU have not been established in pediatric patients.

8.5 Geriatric Use
Of the 234 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 26% were 65 years or older and 5% were 75 years or older. No overall differences in efficacy were observed between patients ≥65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (53%) as compared to younger patients (42%).

8.6 Renal Impairment
No dose adjustment of ENHERTU is required in patients with mild (creatinine clearance (CLcr) ≥60 and <90 mL/min) or moderate (CLcr ≥30 and <60 mL/min) renal impairment [see Clinical Pharmacology (12.3) in the full prescribing information]. No data are available in patients with severe renal impairment.

8.7 Hepatic Impairment
No dose adjustment of ENHERTU is required in patients with mild (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment. In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor, DXd [see Dosage and Administration (2.2) in the full prescribing information]. No data are available in patients with severe (total bilirubin >3 to 10 times ULN and any AST) hepatic impairment [see Clinical Pharmacology (12.3) in the full prescribing information].

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Interstitial Lung Disease
• Inform patients of the risks of severe or fatal ILD. Advise patients to contact their healthcare provider immediately for any of the following: cough, shortness of breath, fever, or other new or worsening respiratory symptoms [see Warnings and Precautions (5.1)].

Neutropenia
• Advise patients of the possibility of developing neutropenia and to immediately contact their healthcare provider should they develop a fever, particularly in association with any signs of infection [see Warnings and Precautions (5.2)].

Left Ventricular Dysfunction
• Advise patients to contact their healthcare provider immediately for any of the following: new onset or worsening shortness of breath, cough, fatigue, swelling of ankles/legs, palpitations, sudden weight gain, dizziness, loss of consciousness [see Warnings and Precautions (5.3)].

Embryo-Fetal Toxicity
• Inform female patients of the potential risk to a fetus. Advise female patients to contact their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.4), Use in Specific Populations (8.1)].

• Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 7 months after the last dose [see Use in Specific Populations (8.3)].

• Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months after the last dose [see Use in Specific Populations (8.3)].

Lactation
• Advise women not to breastfeed during treatment and for 7 months after the last dose of ENHERTU [see Use in Specific Populations (8.2)].

Infertility
• Advise males of reproductive potential that ENHERTU may impair fertility [see Use in Specific Populations (8.3)].

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USPI-ENH-C1-1219-r001-B
First-Line Systemic Strategies Continue to Evolve in HCC

by JASON HARRIS

THE COMBINATION OF ATEZOLIZUMAB (Tecentriq) and bevacizumab (Avastin) is likely to become the new frontline standard in unresectable hepatocellular carcinoma (HCC) in the near future, according to Anthony B. El-Khoueiry, MD, associate professor of clinical medicine at University of Southern California Norris Comprehensive Cancer Center in Los Angeles. For the time being, however, sorafenib (Nexavar) and lenvatinib (Lenvima) remain the current standard of care.

El-Khoueiry reviewed sequencing in first-line therapy for HCC as part of the virtual platform for the 5th Annual School of Gastrointestinal Oncology™ (SOGO®), hosted by Physicians’ Education Resource®, LLC (PER®). “We have multiple systemic therapy options now available in this disease, which is fantastic for patients,” he said. “This all happened within the span of 2 to 3 years. It’s becoming critical to transition patients from liver-directed therapy to systemic therapy at the right time.” (TIMELINE)

In January, Roche submitted a supplemental biologics license application to the FDA for the combination of atezolizumab and bevacizumab for the treatment of patients with unresectable HCC who have not received prior systemic therapy based on findings from the phase 3 IMbrave150 study (NCT03434379). Ann-Lii Cheng, MD, director of the National Taiwan University Cancer Center, presented the data in November at the European Society for Medical Oncology Asia 2019 Congress.¹

The combination induced a 42% reduction in the risk for death (HR, 0.58; 95% CI, 0.42-0.79; $P = .0006$) and a 41% reduction in the risk for disease progression or death versus sorafenib (HR, 0.59; 95% CI, 0.47-0.76; $P < .0001$).

After a median follow-up of 8.6 months, the median overall survival (OS) was not reached in the combination arm compared with 13.2 months in the sorafenib arm. The 6-month OS rate also favored the combination, 85% versus 72%, respectively.

The combination arm also significantly improved median progression-free survival (6.8 vs 4.3 months; HR, 0.59; 95% CI, 0.47, 0.76; $P < .0001$). The 6-month progression-free survival rate was 55% in the experimental arm versus 37% in the sorafenib arm.

Atezolizumab plus bevacizumab induced an overall response rate (ORR) more than twice as high as sorafenib (27% vs 12%, $P < .0001$) based on independent assessment using RECIST 1.1 guidelines.

Per IMbrave150 protocol, 501 patients were randomly assigned to atezolizumab plus bevacizumab or sorafenib alone. Investigators administered 1200 mg of IV atezolizumab on day 1 of each 21-day cycle; IV bevacizumab was given at 15 mg/kg on day 1 of each 21-day cycle. Oral sorafenib was administered at 400 mg twice daily on days 1 to 21 of each 21-day cycle. In both arms, treatment was given until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

“This is the first study in 11 years to show an improvement in survival with a new first-line treatment option compared to sorafenib, which has been the standard of care throughout this time,” Cheng said in a news release. “Atezolizumab plus bevacizumab has the potential to be a practice-changing treatment option in hepatocellular carcinoma.”

El-Khoueiry had some caveats about the combination. Mature data are not yet available, and he noted that all patients in the IMbrave150 study were required to have an endoscopy within the previous 6 months and varices had to be treated. He added that physicians should avoid extrapolating the data and treating patients beyond Child-Pugh A liver function because of an...
increased risk for portal hypertension and variceal bleeding.

“We can’t just take everyone to this without the appropriate caution,” he said, adding that sorafenib or lenvatinib will remain the best choice for patients with contraindications to bevacizumab or atezolizumab.

**SHAKING UP THE STANDARD PROVES DIFFICULT**

The FDA approved lenvatinib for use in this patient population based on findings from the phase 3 REFLECT trial, which were first presented at the 2017 American Society of Clinical Oncology Annual Meeting and later published in the *Lancet*. Findings from REFLECT demonstrated that the primary end point of OS was noninferior for lenvatinib versus sorafenib (13.6 vs 12.3 months; HR, 0.92; 95% CI, 0.79-1.06).2,3

The ORR was 24.1% with lenvatinib (n = 478) versus 9.2% with sorafenib (n = 476; OR, 3.13; 95% CI, 2.15-4.56; P <.00001). The complete response rate was 1.3% in the lenvatinib group and 0.4% with sorafenib.

“They’re noninferior. Both are valid options,” El-Khoueiry said of lenvatinib and sorafenib. “But if we have patients who are symptomatic, who need a response, we may gravitate toward lenvatinib.”

In a post hoc analysis of the REFLECT trial presented at the 2020 Gastrointestinal Cancers Symposium, patients with unresectable HCC treated with lenvatinib demonstrated a median OS of 23.0 months, compared with 9.6 months in those randomized to first-line sorafenib. The HR was 0.71, although this difference fell just short of statistical significance (95% CI, 0.51-1.01).4

Investigators had hoped that nivolumab (Opdivo), which is active in second-line therapy, would become another treatment option in the first line. They compared the anti-PD-1 monoclonal antibody versus sorafenib in the phase 3 CheckMate 459 trial (NCT02576509). Patients with advanced HCC were assigned to 240-mg IV nivolumab every 2 weeks (n = 371) or 400-mg twice-daily oral sorafenib (n = 372).5

The median OS was 16.4 months for nivolumab and 14.7 months for sorafenib (HR, 0.85; 95% CI, 0.72-1.02; P = .0752), which did not meet the predefined threshold for statistical significance.

However, nivolumab induced an ORR of 15% versus 7% for sorafenib, and nivolumab produced superior health-related quality of life and reduced treatment burden, leading investigators to consider a role for the immune checkpoint inhibitor in patients with unresectable HCC.

**EMERGING OPTIONS**

El-Khoueiry said investigators are exploring a variety of drug combinations for first-line treatment in ongoing trials, noting that the use of these will likely be decided on a case-by-case basis by evaluating the risk-benefit ratio for each individual patient.

*CONTINUED ON PAGE 32*
Primary Location of GEJ Tumors Affects Treatment

by DENISE MYSHKO

TREATMENT APPROACHES ARE BEING refined by the primary location of gastroesophageal junction (GEJ) tumors, said Stephen C. Yang, MD, during the 5th Annual School of Gastrointestinal Oncology® (SOGO®) meeting.

“The site does matter because it influences therapy,” said Yang, associate vice chair for faculty development, and professor of surgery and medical oncology at Johns Hopkins University School of Medicine in Baltimore, Maryland. “A multidisciplinary approach remains necessary for all of these tumors. It not only involves the esophageal group but also the gastric group at our institution.”

But Yang said there has been confusion about whether junction tumors should be treated as esophageal or gastric cancer. The confusion, he said, could be related to the fact that there are several ways to classify these tumors.

CLASSIFYING A TUMOR: GASTRIC OR ESOPHAGEAL

The most commonly used classification for assessing and planning treatment of GEJ tumors is the Siewert classification, which has been used since the 1980s.1 Type I is similar to esophageal cancers by epidemiology and histology and type III is similar to distal gastric cancers with intestinal and diffuse histologic types and no association with reflux, Yang said. Type I GEJ tumors are 1 to 5 centimeters above the GEJ and type III starting 2 cm below the junction. Type II tumors begin 1 cm above the junction and type III 2 to 5 cm distal to GEJ.

Less commonly used systems, Yang said, are the Union for International Cancer Control and Nishi’s Japanese Classification of Esophageal Cancer.

Yang noted in his presentation that the National Comprehensive Cancer Network had adopted the Siewert classification. The guidelines describe Siewert types I and II tumors as being esophageal and suggests clinicians follow recommendations for esophageal cancer. Siewert type III tumors are described as gastric cancer.2

Yang suggested clinicians consider the molecular and genomic classifications, especially for gastroesophageal adenocarcinoma, which is the primary histologic cell type in GEJ tumors. He pointed to a recent study3 in Cancer Discovery that found similarities between adenocarcinomas of the stomach and esophagus and their definitive distinction from squamous cell carcinomas of the esophagus. The authors suggest that a “single-target, single-drug” rationale has proved too simplistic for GEJ adenocarcinoma because of the genomic instability and heterogeneity of this disease.

“The gastroesophageal junction tumors are [characterized by] mostly chromosomal instability but also share other genomic characteristics similar to gastric cancer but are still primarily associated with esophageal cancer,” Yang said. “A small component has genomic stable types that have microsatellite instability and also a small percentage are associated with the Epstein-Barr virus.”

Yang said the variability of GEJ tumors has made treatment challenging. Controversies for GEJ tumors include the following: how best to stage these tumors, should induction or radiation be added to the regimen, what is the best surgical approach, and whether to add adjuvant therapies and under which situations.

“No trials have specifically addressed this for true type II GEJ tumors,” he said. Yang said that the histology of the stomach away from the tumor may be the key to determining which classification these borderline tumors fall under. It’s important to determine if the rest of the mucosa is healthy, noted Yang. If there is atrophy of the mucosa, the presence of Helicobacter pylori, or the patient has a history of reflux, it likely that the tumor is primarily gastric cancer. On the other hand, if the mucosa is healthy and there is H pylori, it is most likely esophageal.

TREATMENT APPROACHES

Another controversy, Yang said, is the surgical approach and whether surgery should take more of the esophagus or more of the stomach. He cited a 2015 study, a retrospective analysis of 266 patients with surgically resectable GEJ adenocarcinomas from 2003 to 2013.4 The analysis reported that a positive circumferential resection margin was more common with gastrectomy (29%) versus esophagectomy (11%; P = .025). Further, no significant differences in mortality, morbidity, or disease recurrence were found.

Yang said another question that remains is whether to use induction or adjuvant radiation. A retrospective data analysis from the Surveillance, Epidemiology, and End Results registry database showed that adjuvant radiation therapy was associated...
with a survival benefit as compared with neoadjuvant radiation therapy for the treatment of patients with type II GEJ cancer. A total of 1497 patients with resectable GEJ cancer were identified, with 746 receiving adjuvant radiation therapy and 751 receiving neoadjuvant radiation therapy. Adjuvant radiation had a significantly lower death risk (HR, 0.84; 95% CI, 0.73-0.97; $P = .0168$) as well as a significantly lower disease-specific death risk (HR, 0.84; 95% CI, 0.72-0.97; $P = .0211$).

“The individualized surgical approach remains critical not only preoperatively but also intraoperatively for decision making,” Yang said.

**REFERENCES**

1. Curtis N, Noble F, Bailey L, Kelly J, Byrne P, Underwood T. The relevance of the Siewert classification in the era of multimodal surgery, particularly with regard to a pancreaticoduodenectomy, said Michael A. Choti, MD, chief of surgery at Banner MD Anderson Cancer Center in Gilbert, Arizona. In a video interview, Choti discusses the benefit of neoadjuvant chemotherapy in pancreatic cancer.

**MORE ON Onclive.com**

**Benefits of Neoadjuvant Chemotherapy in Pancreatic Cancer**

Although the guideline recommendations for pancreatic cancer suggest up-front surgery, data from recent studies demonstrate that neoadjuvant chemotherapy is superior to up-front surgery. In a video interview, Choti discusses the benefit of neoadjuvant chemotherapy in pancreatic cancer.

**REFERENCES**


**CONTINUED FROM PAGE 30**

CheckMate 9DW (NCT04039607) is a phase 3 trial evaluating nivolumab plus ipilimumab (Yervoy) versus sorafenib or lenvatinib. The nivolumab/ipilimumab combination is approved in the second-line setting.

In the HIMALAYA trial (NCT03298451), investigators are comparing durvalumab (Imfinzi) monotherapy versus durvalumab plus tremelimumab versus sorafenib in patients who are ineligible for locoregional therapy. The COSMIC-312 study (NCT03755791) compares cabozantinib (Cabometyx) with or without atezolizumab versus sorafenib.

One promising option to emerge recently is lenvatinib plus pembrolizumab (Keytruda). In July 2019, the FDA granted the combination a breakthrough therapy designation for patients with advanced unresectable HCC that is not amenable to locoregional therapy based on updated interim findings from the multicenter phase 1b KEYNOTE-524 trial (NCT03006926).

In the study, investigators administered 1V pembrolizumab at 200 mg every 3 weeks and lenvatinib at 12 mg daily for patients weighing at least 60 kg, and 8 mg/day for patients weighing less than 60 kg.

Interim data presented at the 2019 American Association for Cancer Research Annual Meeting showed that the combination induced an investigator-assessed ORR of 36.7% (95% CI, 19.9%-56.1%) via mRECIST criteria and 50.0% by mRECIST per independent radiology review committee. At the time of the August 23, 2018, data cutoff, 60% of patients remained on study treatment.

Llovet et al presented updated data at the 2019 European Society for Medical Oncology Congress. The ORR including unconfirmed responses was 44.8% and 34 patients (50.7%) remained on treatment at the June 30, 2019, data cutoff.

El-Khoueiry noted that “there is a price to pay for the combination.” In the data released at the 2019 American Association for Cancer Research Annual Meeting, the rate of grade 3 or higher adverse events was 73%, with a 50% rate of serious adverse events and 4 (13%) fatalities.

“There’s definitely higher toxicity with the combination,” El-Khoueiry said. “We’ll see how this evolves with a bigger data set.”

The combination is currently being evaluated versus lenvatinib monotherapy in the ongoing LEAP-002 trial (NCT03713593).
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Chasing a Cure for GBM: Investigators Test Multiple Regimens in Novel Trial

by RACHEL NAROZNIAK, MA

INVESTIGATORS ARE CHANGING the standard randomized controlled trial (RCT) design to more expeditiously identify experimental therapies for patients with glioblastoma (GBM), the deadliest form of brain cancer.1

GBM kills 95% of patients within 5 years of diagnosis, with more than half of patients dying in the first 15 months; that prognosis makes a customary RCT structure that could span 1 to 4 years in length impractical. Investigators of the first global adaptive phase 2/3 GBM Adaptive Global Innovative Learning Environment (AGILE) platform trial (NCT03970447) are implementing a multiarm, 2-stage approach to concurrently evaluate single-agent and combination regimens.1,2

“We felt that there needed to be a way to test multiple therapies in a randomized study, determine whether or not there are signals, confirm those signals, and move forward with new drug applications,” said Timothy F. Cloughesy, MD, global principal investigator of the GBM AGILE trial and director of the Neuro-Oncology Program of the Brain Research Institute at the University of California, Los Angeles.

GBM AGILE is recruiting 550 patients with IDH1 R132H wild-type newly diagnosed (ND) grade IV GBM or recurrent GBM (FIGURE). Investigators will stratify patients by 3 subtypes of GBM: ND methylated GBM, ND unmethylated GBM, or recurrent disease, and randomize them to a treatment arm in the trial’s first stage.

At present, GBM AGILE investigators are evaluating treatment interventions in patients either with ND unmethylated GBM or recurrent disease.

Patients with ND GBM who are randomized to the control arm will receive radiation therapy (RT) at 60 Gy in combination with temozolomide (Temodar) at 75 mg/m² for 6 weeks, followed by maintenance temozolomide. The maintenance phase would begin 2 to 6 weeks after RT, starting with 150 mg/m² on days 1 to 5 of a 28-day cycle, followed by 200 mg/m² on days 1 to 5 of the second and subsequent cycles. In the experimental arm, patients with ND GBM will also be treated with RT and temozolomide but will receive the experimental regimen instead of maintenance temozolomide.

For those with recurrent disease, participants in the control arm will be treated with lomustine (Gleostine) started at 110 mg/m² per day on day 1 of a 42-day cycle for a maximum of 6 cycles; in the experimental arm, patients with recurrent disease type will receive an investigational therapy.

The first experimental agent to be tested is regorafenib (Stivarga), a multikinase inhibitor that the FDA has approved for metastatic colorectal cancer, metastatic gastrointestinal stromal tumor, and hepatocellular carcinoma. In the GBM AGILE trial, regorafenib will be administered at 160 mg daily for 3 weeks of every 4-week cycle.

As the study progresses, investigators will open additional treatment arms to explore other regimens. They also will assess patients for potential biomarkers that could be used to direct therapy.

Across stages 1 and 2 of GBM AGILE, the primary end point of the study is overall survival (OS). Secondary end points include progression-free survival, tumor response, and duration of response.

TAILORING TRIAL TO THE DISEASE
GBM AGILE investigators will closely assess the anticancer activity of the control and experimental interventions in the ND and recurrent disease populations. In stage 1 of the study, investigators will stop enrolling patients in a treatment arm if the arm completes accrual (n ≤150) or if the arm’s therapy demonstrates futility or unacceptable toxicity.3

In stage 1 of the GBM AGILE study, investigators will use a dynamic assignment strategy known as adaptive randomization to direct a higher proportion of new participants to the superior treatment arm.4

FIGURE. Multiple Regimens in Newly Diagnosed and Recurrent GBM Study

PHASE 2/3 GBM AGILE TRIAL (NCT03970447)

<table>
<thead>
<tr>
<th>Eligibility criteria</th>
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</thead>
<tbody>
<tr>
<td>Newly diagnosed GBM</td>
<td>Recurrent GBM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Histologically confirmed grade IV GBM/gliosarcoma following surgical resection or biopsy</td>
<td>• Histologically confirmed GBM/gliosarcoma at first or second recurrence after initial standard, control, or experimental therapy. Therapy must have included RT.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Availability of tumor tissue following procedure</td>
<td>• No prior VEGF-targeted therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Karnofsky PS ≥70% within 14 days of randomization</td>
<td>• Availability of tumor tissue from initial definitive surgery or recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Karnofsky PS ≥70% within 14 days of randomization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DOR, duration of response; GBM, glioblastoma; OS, overall survival; PFS, progression-free survival; PS, performance status; RT, radiation therapy.

*Regorafenib is the first experimental agent to be tested. Other regimens will be evaluated as new investigational arms open.
“Adaptive randomization allows us to identify the therapies that are working best for patients. The randomization probabilities would adjust based on current data from the ongoing trial,” Cloughesy said.

This predefined algorithm will identify the treatments with the greatest efficacy based on the survival benefit that these therapies confer when compared with a common control. It will also select the GBM population for which these interventions are most promising. Those therapies deemed promising will “graduate” to stage 2.

For this stage, investigators will use fixed randomization to evaluate the efficacy of these therapies in the algorithm-defined population to confirm findings from the first stage of the trial. Each stage 2 cohort will enroll 50 patients.

The design of the 2-stage study supports swifter patient registration, as well as a more rapid regulatory review process and subsequent clinical adoption of the treatments that display signals in the second stage of the GBM AGILE study.

Equally important, GBM AGILE’s unique model means that investigators can more rapidly identify and expel the treatments that do not show signals indicative of therapeutic benefit than they would in traditional RCTs. “[Recognizing] early futility has huge value because if you find early futility and stop enrollment, you have determined that the therapy is not going to confer benefit, and you didn’t have to run a large, costly phase 3 study to get that answer,” Cloughesy said.

Of note, data from the treatments that do not demonstrate a sufficient survival advantage in the first stage to justify further study in stage 2, but nevertheless suggest a potential benefit, will become available to GBM specialists and can be used to support the development of biomarker hypotheses as well as further therapeutic investigations in the field.

“Our goal is to identify the effective drugs, get rid of the ineffective drugs, and also identify the drugs that have a signal, [but one] that isn’t quite as strong [as others],” Cloughesy said, adding that drug developers can draw upon data from the GBM AGILE study to determine whether they would like to appropriately power and pursue a trial of an agent that was found to have a more minimal signal in the phase 2/3 study.

**PURSUITING PARADIGM CHANGE**

The GBM AGILE study is a clinical endeavor that has been years in the making and owes its dynamic design to the collaborative interplay of more than 130 oncologists, pathologists, statisticians, imagers, neurosurgeons and academic, industry, and government researchers, who have worked collectively to cultivate this investigative model since 2015.

GBM AGILE is a “group effort” that was initiated in response to a series of unsuccessful clinical trials in GBM, according to Cloughesy. “The rationale for GBM AGILE comes from the setting of GBM, where in the [past] few years, there have been several negative phase 3 studies. They were expensive, costing several hundred million dollars, and it seemed that we weren’t [facilitating investigations] very well,” Cloughesy said. “Then, the disease gets the reputation that drugs can’t be developed in glioblastoma—that they’re just bound to fail.”

In ND GBM, the standard of care is temozolomide, which was approved for use in combination with RT and as a maintenance therapy in 2005. Existing data show that the median OS with temozolomide and concurrent RT is 14.6 months versus 12.1 months with RT alone, supporting the doublet regimen’s application in this setting.

Patients with ND GBM receive temozolomide with RT after maximal surgical resection, which rarely eradicates GBM tumor cells in their totality due to the invasive nature of the disease. Although adjuvant temozolomide and RT are administered to reduce the risk of disease recurrence, nearly all cases of GBM that initially respond to frontline treatment eventually recur.

In contrast to ND GBM, there is no established standard of care for recurrent disease. Interventions for recurrent GBM can include surgical resection, reirradiation, nitrosoureas, temozolomide rechallenge, or treatment with tyrosine kinase inhibitors or bevacizumab (Avastin).

Bevacizumab was indicated for use in patients with GBM in 2017, after findings from the phase 3 EORTC 26101 study (NCT01290939) showed that adding the VEGF inhibitor to lomustine reduced the risk of disease progression or death by 48%. Administering bevacizumab with lomustine extended the median progression-free survival versus single-agent lomustine (4.2 vs 1.5 months; HR, 0.52; 95% CI, 0.41-0.64) but notably did not result in a significant improvement in OS (HR, 0.91; \( P = .4578 \)).

The modest survival benefits that exist in all GBM therapies afford patients with GBM, coupled with the lack of curative options, translate to a need for more efficacious treatment options for a disease that accounts for 45% of all malignant brain tumors and more than 12,000 cases annually in the United States.

**LEADING A MOVEMENT IN GBM**

GBM AGILE investigators and the trial’s broad network of clinical collaborators believe that the platform format of the study has the potential to not only identify better therapies for this deadly disease but also reduce the time and costs associated with their development around the world.

“We wanted to facilitate this evaluation in 1 environment to boost development in glioblastoma, and we also wanted to do this in multiple jurisdictions beyond the United States,” Cloughesy said. GBM AGILE is actively enrolling patients in the United States, and international locations in Canada, China, and Europe are also expected to open at a later date, according to Cloughesy.

Whereas the coronavirus disease 2019 (COVID-19) pandemic has prompted the suspension of many clinical trials across the nation, GBM AGILE has continued to accrue patients. “We have continued to add sites during this time and enrollment has remained steady, so we’ve been happy to see that,” Cloughesy said. “At their institutions, people [ask], what’s a necessary study going forward? Glioblastoma is almost 100% fatal. COVID-19 is incredibly serious, but glioblastoma will continue to be serious even after we’ve learned how to deal with COVID-19. We still need to learn how to deal with glioblastoma.”

For a full list of references, see the article at OncLive.com.
Trastuzumab Deruxtecan Shows Promise in HER2+ NSCLC

by JESSICA HERGERT

FAM-TRASTUZUMAB DERUXTECAN-NXKI (Enhertu; DS-8201), a HER2-directed antibody-drug conjugate, demonstrated significant clinical activity in patients with non-small cell lung cancer (NSCLC), according to findings from a phase 1 study published in Cancer Discovery.\(^1\)\(^2\)

In the analysis, 55.6% of patients with HER2-overexpressing or HER2-mutant NSCLC (n = 18) had a confirmed objective response, with a median duration of response of 10.7 months (95% CI, 6.9-11.5). Nine patients had a progression-free survival (PFS) event (50.0%) and the median PFS was 11.3 months (95% CI, 7.2-14.3).

Participants with NSCLC were among 60 patients with HER2-overexpressing nonbreast or nongastric cancers and/or HER2-mutant solid tumors treated with trastuzumab deruxtecan during the study (NCT02564900).

In December 2019, the FDA approved the drug for patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more HER2-directed regimens for metastatic disease.

Research interest in testing trastuzumab deruxtecan in other cancers with HER2 aberrations has been growing. In NSCLC, HER2 gene amplification and mutations have been identified as oncogenic drivers, while overexpression has been associated with poor prognosis.\(^2\)

Investigators in the trastuzumab deruxtecan study note that HER2 activating mutations have been identified in approximately 1% to 3% of NSCLC samples, while HER2 overexpression, as assessed by immunohistochemistry (IHC2+ or IHC3+) has been found in 10% to 30% of specimens.\(^2\)

Among patients with NSCLC in the study, 61.1% (n = 11) had tumors with HER2 mutations, 11.1% (n = 2) were IHC3+, and 5.6% (n = 1) were IHC2+.

Patients with HER2-mutated NSCLC derived the most benefit compared with other nonbreast, nongastric solid tumors (TABLE).\(^2\)

These patients had an objective response rate of 72.7% (95% CI, 39.0%-94.0%) and a median duration of response of 9.9 months (95% CI, 6.9-11.5). Further, the disease control rate was 90.9% and the median PFS was 11.3 months (95% CI, 8.1-14.3).

Investigators noted that there are no currently approved HER2-targeting therapies for patients with NSCLC and certain other cancers where HER2 aberrations have been observed. However, certain patients are eligible for treatment with VEGF inhibitors. Overexpression of HER2 in human tumor cells is closely associated with increased angiogenesis and expression of VEGF.\(^3\)

“We are very excited by the results of this preliminary study,” senior investigator Bob T. Li, MD, of Memorial Sloan Kettering Cancer Center, said in a press release.\(^1\) “[Trastuzumab deruxtecan] shows early promise for transforming the standard of care for patients with HER2-overexpressing or HER2-mutated cancers and we look forward to continuing this important research in future clinical trials.”

A phase 2 study testing trastuzumab deruxtecan in patients with HER2-overexpressing or HER2-mutant NSCLC is under way (NCT03505710). The study seeks to enroll 170 patients.

**FINDINGS SUPPORT BROADER EFFICACY**

In the phase 1 study, patients were evaluated in 3 subgroups: colorectal cancer (CRC; n = 20), NSCLC (n = 18), and “other” cancers, which included salivary gland (n = 8), esophageal (n = 2), endometrial (n = 2), biliary tract (n = 2), Paget disease (n = 2), pancreatic (n = 1), uterine cervix carcinoma (n = 1), extraskeletal myoid chondrosarcoma (n = 1), and small intestine adenocarcinoma (n = 1).

Additionally, 2 patients with HER2-mutated breast cancer were included in the “other” cancers subgroup.

The total population experienced a confirmed objective response rate of 28.3% with a median PFS of 7.2 months (95% CI, 4.8-11.1) for patients with pretreated HER2-overexpressing or HER2-mutated cancer. Overall survival was 23.4 months (95% CI, 15.6-not estimable).

Confirmed responses were reported in 6 tumor types: HER2-overexpressing NSCLC, CRC, salivary gland cancer, biliary tract cancer, endometrial cancer, and HER2-mutant breast and NSCLC (FIGURE).\(^1\) Nearly all patients with HER2-mutated cancer experienced disease control.

*HER2-targeted therapies have proven successful for patients with breast and...**

**TABLE. Outcomes of HER2-directed Therapy in NSCLC Versus Other Cancers\(^2\)**

<table>
<thead>
<tr>
<th>Outcome(^a)</th>
<th>NSCLC (n = 18)</th>
<th>HER2-mutant (n = 11)</th>
<th>CRC (n = 20)</th>
<th>Other cancers (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR (95% CI)</td>
<td>55.6% (30.8%-78.5%)</td>
<td>72.7% (39.0%-94.0%)</td>
<td>5% (0.1%-24.9%)</td>
<td>27.3% (10.7%-50.2%)</td>
</tr>
<tr>
<td>Confirmed DCR (95% CI)</td>
<td>83.3% (58.6%-96.4%)</td>
<td>90.9% (58.7%-99.8%)</td>
<td>80% (56.3%-94.3%)</td>
<td>81.8% (59.7%-94.8%)</td>
</tr>
<tr>
<td>Median TTR, months (95% CI)</td>
<td>1.4 (1.2-2.8)</td>
<td>1.4 (1.2-1.4)</td>
<td>3.0 (NE)</td>
<td>1.6 (1.4-3.0)</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>10.7 (6.9-11.5)</td>
<td>9.9 (6.9-11.5)</td>
<td>13.4 (NE)</td>
<td>NR (3.0-NE)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>11.3 (7.2-14.3)</td>
<td>11.3 (8.1-14.3)</td>
<td>4.0 (2.7-5.6)</td>
<td>11.0 (2.8-NE)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NR (17.3-NE)</td>
<td>17.3 (17.3-NE)</td>
<td>15.6 (4.8-NE)</td>
<td>23.4 (9.6-NE)</td>
</tr>
</tbody>
</table>

CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; NE, not estimable; NR, not reached.

NSCLC, non–small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTR, time to response.

\(^a\)Assessment by independent central review.

\(^b\)TTR measured from registration to the time when criteria for complete response or partial response were first met.
LUNG CANCER

Additional previous anticancer regimens therapy and 16 had prior immunotherapy. having received at least 5 therapies. anticancer regimens with 33.3% of patients observed. Patients had a median of 3.0 prior first dose of trastuzumab deruxtecan was tile range, 15.9-44.0) months between disease. A median time of 28.8 (interquar -trastuzumab deruxtecan. 3+ CRC experienced disease control with PFS rate of 85% for a median 4.0 months was achieving a confirmed response. However, a this study, with only 1 of these patients 6 weeks of therapy.

Of note, patients with CRC did not derive effects. Additional treatment options are urgently needed for these patients.” Of 60 patients treated with the antibody-drug conjugate, 51 were evaluable for tumor shrinkage. Moreover, 80.4% of these patients showed tumor shrinkage from baseline after 6 weeks of therapy.

Of note, patients with CRC did not derive as significant benefit as other patients in this study, with only 1 of these patients achieving a confirmed response. However, a PFS rate of 85% for a median 4.0 months was noted and 100% of patients with HER2 IHC 3+ CRC experienced disease control with trastuzumab deruxtecan.

At baseline, all patients had visceral disease. A median time of 28.8 (interquartile range, 15.9-44.0) months between initial diagnosis and administration of the first dose of trastuzumab deruxtecan was observed. Patients had a median of 3.0 prior anticancer regimens with 33.3% of patients having received at least 5 therapies.

Fifty-six patients underwent prior chemotherapy and 16 had prior immunotherapy. Additional previous anticancer regimens included HER2-targeted therapy (n = 17), hormonal therapy (n = 3), VEGF inhibitors (n = 28), EGFR inhibitors (n = 17), and ALK inhibitors (n = 1). Also, 66.7% of patients underwent previous cancer surgery and 51.7% underwent previous radiotherapy.

Regarding HER2 expression as assessed by a central laboratory, there were 36.7% of patients in the total population with HER2 IHC 3+, 15% with IHC 2+, 18.3% with IHC 1+, and 20% with IHC 0.

Patients were a median of 58 years old (range, 23-83) and just over half (51.7%) were female. The trial enrolled patients from Japan (n = 38) and the United States (n = 22).

In the trial, patients received a 6.4-mg/kg dose of trastuzumab deruxtecan intravenously once every 3 weeks. A previous phase 1 dose-escalation and expansion study established this regimen as the maximum-tolerated dose without dose-limiting toxicities among patients with HER2-positive breast and gastric cancer.

Regarding this study, trastuzumab deruxtecan was generally well tolerated among patients. The frequency of all-grade treatment-emergent adverse events (TEAEs) was similar across tumor types; gastrointestinal and hematologic TEAEs were the most common all-grade TEAE experience.

“Therapies that target HER2 can be selectively directed to HER2-overexpressing or HER2-mutated cancer cells, which could improve efficacy and help reduce toxicities caused by off-target effects on normal cells,” lead author Junji Tsurutani, MD, PhD, of Showa University in Tokyo, Japan, said in the press release.

Every patient experienced at least 1 TEAE; the most common were nausea (n = 26), vomiting (n = 24), and decreased appetite (n = 15).

Regardless of causality, 62.7% of patients had grade 3 or higher TEAEs including anemia (n =15), decreased neutrophil count (n = 12), decreased platelet count (n = 9), decreased white blood cell count (n = 11), decreased appetite (n = 4), elevated aspartate aminotransferase levels (n = 3), febrile neutropenia (n = 3), and hyponatremia (n = 3).

Five patients discontinued treatment due to toxicity. Moreover, 2 of these events were due to pneumonitis and 1 was due to interstitial lung disease (ILD), which is a toxicity of concern reported in HER2-positive breast cancer, the indication for which trastuzumab deruxtecan received FDA accelerated approval in December 2019.

Additionally, 23.7% of patients required dose reduction and 37.3% required dose interruption as a result of TEAEs. There were 5 TEAE-related patient deaths reported. One of these deaths was a result of respiratory failure brought on by ILD.

“The safety profile of trastuzumab deruxtecan is consistent with the previously reported breast and gastric cancer cohorts from this phase 1 study,” said Li. “ILD is an important identified TEAE that may be serious—even fatal—and thus requires monitoring and prompt intervention. Further research is required to minimize and manage this risk.”

**REFERENCES**


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**FIGURE. Clinical Activity Outcomes in Phase 1 Study**

<table>
<thead>
<tr>
<th>Stage</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC (n = 18)</td>
<td>2.0%</td>
<td>11.1%</td>
<td>55.6%</td>
<td>27.8%</td>
<td>1.7%</td>
</tr>
<tr>
<td>CRC (n = 20)</td>
<td>10.0%</td>
<td>75.0%</td>
<td>22.7%</td>
<td>4.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Other cancers (n = 18)</td>
<td>4.4%</td>
<td>54.5%</td>
<td>26.7%</td>
<td>15.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Total population (n = 56)</td>
<td>6.7%</td>
<td>54.5%</td>
<td>26.7%</td>
<td>15.8%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

CR, complete response; CRC, colorectal cancer; DCR, disease control rate; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease.

*Assessment by independent central review.
Novel Vaccine Improves Relapse-Free Survival in Ovarian Cancer

by GINA COLUMBUS

FRONTLINE MAINTENANCE TREATMENT

with Vigil, a novel tumor cell vaccine, demonstrated an improvement in relapse-free survival (RFS) compared with placebo in patients with stage III/IV ovarian cancer, especially in those with BRCA1/2 wild-type disease, according to clinical trial findings.

Results from the phase 2 VITAL study (NCT02346747) showed that the median RFS favored the Vigil arm over placebo in the overall patient population (n = 91) at 12.6 months versus 8.4 months, respectively (HR, 0.69; P = .065).

However, when stratified by BRCA status, the RFS improvement was found to be statistically significant in the patients with BRCA1/2 wild-type tumors (n = 67) in the Vigil arm at 19.4 months compared with 14.8 months in the control arm (HR, 0.459; P = .007) from the time of randomization. Moreover, the median overall survival (OS) was not reached with Vigil and was 41.4 months with placebo from the time of randomization (HR, 0.417; P = .020).

“Having the first maintenance therapy that is specific [to BRCA1/2] wild-type patients and shows a survival benefit both in [relapse]-free and overall survival is significant in my mind,” lead study author Rodney P. Rocconi, MD, Elsie Colle Chair in Oncology Research, associate director of Clinical Research, and professor of gynecologic oncology at USA Mitchell Cancer Institute in Mobile, Alabama, said in an interview with OncologyLive®.

“The second thing is that we’re getting almost to the point where we thought immunotherapy would not work in ovarian cancer. This vaccine shows that by a different approach, or a different set of methods, the door is not shut on immunotherapy in ovarian cancer; there are ways to go about this,” added Rocconi, who was scheduled to present these data during the 2020 Society of Gynecologic Oncology Annual Meeting.

The overall prognosis for patients with advanced epithelial ovarian cancer is poor, and those with BRCA1/2 wild-type disease, which Rocconi said comprises 85% of all patients with ovarian cancer, have become an unmet need, he explained. Additionally, elevated TGF-β expression is found to also correlate with poor prognosis in this disease.

Vigil immunotherapy is defined as a tumor cell vaccine comprised of autologous harvested tumor tissue that is transfected with a DNA plasmid encoding granulocyte-macrophage colony-stimulating factor and bifunctional shRNA-furin, which leads to control of TGF-β expression. The genetically modified therapy is administered into the intradermal layers of patient’s upper arm.

“One thing [about this vaccine that makes it] a little bit different is that it’s not a global, immunologic therapy; it’s very targeted and very specific,” said Rocconi. “We are harvesting a patient’s cancer at the time of surgery prior to chemotherapy, and we create vaccines to the neoantigens that are on that cancer cell. By doing that, the vaccine is attracted or targeted to that own individual patient’s cancer cells.”

In the double-blind, placebo-controlled, randomized trial, investigators sought to evaluate whether a frontline maintenance approach with Vigil would improve RFS in this patient population. Investigators randomized 91 patients with advanced-stage ovarian cancer who achieved complete clinical response to frontline surgery and chemotherapy to receive Vigil at 1 × 10⁷ cells/mL (n = 46) or placebo (n = 45) monthly for 12 doses or fewer.

To be eligible for enrollment, patients must have had stage IIIb, IIIc, or IV high-grade papillary serous/clear cell/endometrioid ovarian, fallopian tube, or primary peritoneal cancer; could not have received prior chemotherapy or investigational agents before tissue acquisition for Vigil manufacture; could not have had another malignancy; had an ECOG performance status score of 0 to 2 before diagnostic laparoscopy or debulking laparotomy; and must have had no prior history of hypersensitivity reactions with taxanes or platinum-based therapy.

Through BRCA1/2 testing, it was determined that 74% of patients had BRCA1/2 wild-type disease and 26% harbored BRCA1/2 mutations. The key end points were RFS, safety, and proportion of recurrences. The median time from surgery to randomization was 6.9 months in the Vigil arm versus 6.6 months in the control group.

Moreover, additional findings showed that in the overall cohort, recurrences were observed in 54% of patients treated with Vigil immunotherapy compared with 76% of patients who received placebo (χ² P = .014). When stratified by BRCA4 status, 51% of the patients with BRCA1/2 wild-type disease who were treated with Vigil experienced disease relapse versus 79% of those in the same patient population who received placebo (χ² P = .023).

However, in the population with BRCA1/2-mutant disease, there was no benefit observed with the use of Vigil.

Additionally, 23% and 46% of patients on the Vigil and placebo arms had died, respectively. Regarding safety, there was no additional toxicity in the Vigil arm compared with the control group. Grade 2/3 adverse events (AEs) occurred in 8% of patients treated with Vigil compared with 18% of those in the control group. The most common AEs of this severity in the Vigil arm were bone pain and fatigue, whereas nausea and musculoskeletal pain were most common in the placebo arm. No grade 4/5 AEs were observed.

“If we are able to move this forward and get an indication for this from the FDA, this would be the first agent that specifically benefits the BRCA1/2 wild-type [population, leading to] fewer recurrences and hopefully longer lives,” Rocconi concluded.

REFERENCE

Ipatasertib (GDC-0068, RG7440): An investigational, ATP-competitive AKT inhibitor¹,²
Currently Enrolling in Breast Cancer

**IPATunity170**

**Phase III • NCT04177108**

A Study of Ipatasertib in Combination With Atezolizumab and Paclitaxel as a Treatment for Participants With Locally Advanced or Metastatic Triple-Negative Breast Cancer

A randomized, double-blind, placebo-controlled study of patients with

- Locally advanced or metastatic TNBC
- No prior systemic therapy for mTNBC

N=1155

**Study Endpoints**

**Primary Outcome Measures:**

- PFS (investigator-assessed), defined as the time from randomization to the first occurrence of disease progression* or death from any cause
- OS, defined as the time from randomization to death from any cause

**Selected Secondary Outcome Measures:**

- ORR, defined as the proportion of patients with a CR or PR on 2 consecutive occasions ≥4 weeks apart*
- DoR, defined as the time from the first occurrence of a documented objective response to disease progression* or death from any cause
- GHS/QoL scores†
- PFS, OS, ORR, and DoR in PIK3CA/AKT1/PTEN-altered tumors

**Selected Eligibility Criteria**

- Histologically documented TNBC that is locally advanced or metastatic and is not amenable to resection with curative intent
- Measurable disease according to RECIST v1.1
- ECOG performance status of 0 or 1
- No prior systemic therapy for inoperable LA/mTNBC
- No history of diabetes requiring insulin

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- Email: global-roche-genentech-trials@gene.com

*As determined by the investigator through the use of RECIST v1.1.
†As assessed using selected questions from EORTC QLC-C30.

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Community Practices Offer Telehealth Tips

by DENISE MYSHKO

THE NEED TO ADAPT EFFECTIVELY and provide consistent care to patients with cancer during the public health threat caused by coronavirus disease 2019 (COVID-19) has prompted the expanded use of telehealth. Regulations on telehealth have been relaxed, and this affords oncology practices the opportunity to better serve this high-risk patient population during the COVID-19 crisis while mitigating the spread of the pandemic.

“Circumstances on the ground have radically changed in a short period of time where we recognize that telehealth technologies can be used in a public health emergency,” Ryan Howe, deputy director of the Hospital and Ambulatory Policy Group at the Centers for Medicare & Medicaid Services (CMS), said during a webinar on April 3, 2020, hosted by the Community Oncology Alliance (COA).

“We’ve really had to think strategically about how to manage [patients with cancer],” said Debra Patt, MD, MPH, MBA, a breast cancer specialist and executive vice president of Texas Oncology in Austin. “We cannot really stop operations...and if patients do not receive therapy for the months that we expect coronavirus to persist in our community, then their cancer will progress, and they will have an adverse outcome.”

Telehealth has enabled practices such as Texas Oncology to dramatically reduce clinic volumes, creating a safer environment for patients who still require treatment administered at health care facilities.

“We have a desire to decrease the volume in our clinic by a large margin. By taking out all the follow-up patients, we were able to reduce our volume by 80%, making it a safer environment for our most vulnerable patients,” Patt said.

Telemedicine also gives clinics the opportunity for family consultations and important conversations about patients’ prognoses and whether they need advanced-care planning.

“With a patient with advanced cancer, this conversation is urgent, but you can’t have other people in the clinic now,” Patt said. “We have had to think strategically about how to manage patients. By reducing volume, we’ve created a safer environment that allows patients to get the care they need.”

POLICY CHANGES ENABLE EXPANSION Before the pandemic, statutory provisions limited the use of telehealth services that Medicare would cover. Patients had to live in a designated rural area and could access telehealth only in a health care setting (as opposed to their homes), and physicians had to be licensed in the state in which the patient resided.1,2 Because of such limitations, telehealth had little uptake prior to the pandemic, particularly among oncology practices.

Although more than 50 US health systems already had in place telehealth technology to allow clinicians to see patients at their home, few oncologists had embraced the technology.3,4

On March 17, 2020, CMS waived the setting of care and geographic restrictions that had been place. By expanding this benefit on a temporary and emergency basis under the Coronavirus Preparedness and Response Supplemental Appropriations Act,2 CMS has authorized Medicare to pay for office, hospital, and other visits furnished via telehealth across the country, including in the patient’s home. The action, however, does not mean that state or local licensure is automatically waived; the American Medical Association (AMA) advises practices to check state requirements.5

CMS is allowing licensed providers to render services outside their state of enrollment as well. The agency has indicated these are temporary waivers for the COVID-19 crisis, although several speakers at the COA webinar have indicated they would like to see these changes persist.

“CMS has been incredibly responsive. They have listened to what we have said and what we have asked for in terms changes for telehealth. Telehealth has been a virtual lifeline,” said Ted Okon, executive director at COA, said during the webinar.

Additionally, the Office for Civil Rights at the US Department of Health & Human Services said it would not impose penalties for noncompliance with requirements related to the Health Insurance Portability and Accountability Act (HIPAA) during the COVID-19 public health emergency.6 Some of the technologies being used for telehealth may not fully comply with the requirements of the HIPAA rules.

Private payers have followed CMS’ lead and made changes to their policies as well. The American Society of Clinical Oncology (ASCO) has put together a guide...
with information and updates about payers’ changes. Payers listed in ASCO’s guideline have issued temporary changes to their coverage for telehealth services. For example, they may waive member cost sharing for a covered telemedicine service or allow providers to bill for a standard face-to-face visit for all virtual care services, including those not related to COVID-19.

On April 30, CMS released an updated rule increasing payments for some visits via telehealth.\(^7\) In response to requests from ASCO, CMS is increasing payments for telephone evaluation and management visits to match payments for similar office and outpatient visits, which will increase payments from a range of about $14 to $41 to about $46 to $110. The payments are retroactive to March 1, 2020.

**HOW PRACTICES IMPLEMENT TELEHEALTH**

The AMA has developed a step-by-step guide to implementing telehealth based on insights from across the medical community,\(^4\) although the guide stresses that the process is not always straightforward. Licensure and reimbursement are 2 of the most common challenges to scaling telehealth in practice, and the AMA suggests that investing time in understanding the complexities will save time and resources later.

Speakers at COA’s webinar offered insight into their telehealth initiatives. For example, Texas Oncology, with 221 sites throughout the state and about 60,000 new patients a year, has been using telemedicine for 5 years, but because of statutory limitations, this was primarily a clinic-to-clinic operation, Patt said.

“We’ve previously used telemedicine to bridge the gaps in medical subspecialties and that is meaningful, but its use case was limited,” she said.

Texas Oncology began expanding its telemedicine services in February 2020. The first phase was to onboard about 15% of the clinicians to complement triage for acute care evaluations.

The second phase started in March, with onboarding for about 80% of clinicians for acute care, established visits, and new patient consultations. By early April, Texas Oncology had 500 doctors, 150 advanced practice providers, and 900 support staff who had access to the telemedicine program.

Patt said she would like to see CMS expand coverage of telehealth for preventive services and would like the expanded services to be available throughout 2020.

“There is a discordant narrative regarding expected duration of illness for the pandemic. Some practices have been reluctant to adopt changes because this may last only a month. That is a limitation. If CMS had a policy allowing this to last for the year, it would facilitate adoption.”

Bud Pierce, MD, PhD, a physician with Oregon Oncology Specialists, noted that the loosening of CMS regulations has also enabled practices to innovate. “As a long-time practitioner, I love doing this now, and it’s so powerful to take into the future to take better care of our patients. Let’s use technology to be innovative. One of the main impediments to innovation in medicine is rules and laws. We need to be paid for the work we do,” he said.

Oregon Oncology Specialists, which has 4 sites (soon to be 7) and sees 3000 new patients a year, has used Zoom over the past few weeks to conduct follow-up visits with several older patients who were concerned about coming to the office.

“We’re using Zoom because we weren’t doing any telemedicine before this. This was so much better than a phone visit. It’s important to see patients. You get so much more from that,” he said.

But Patt cautioned clinicians about using some technologies. “It’s great that CMS has allowed for the noncompliant platforms such as FaceTime, Skype, and Zoom during the health crisis, but these are not long-term solutions,” she noted. Texas Oncology is using the VSee telemedicine platform, which is encrypted and HIPAA compliant.

Dennis Zoet, chief business development officer at Cancer & Hematology Centers of Western Michigan, said his group is using Doxy.me because it is easy for patients and is HIPAA compliant.

“This is the right vendor for my practice right now; I don’t know if this is the right vendor for my practice 6 months post-COVID-19 emergency implementation,” he said during the webinar.

Cancer & Hematology Centers of Western Michigan, which has 5 locations and saw 8000 new patients in 2019, was able to make telehealth available quickly. The practice signed up on March 18 and had the first virtual visit 2 days later. At the time of the webinar, 53 staff had been trained on the platform and the practice had 22 stations available for virtual visits, with 400 scheduled virtual visits.

Zoet offered a few lessons learned from his practice’s implementation, as well as points to consider.

After 1 patient came to the office instead of doing a virtual visit and other patients said they did not have a usable or charged device, he implemented a training program for appointment schedulers and included a script for them to follow when speaking with patients.

“The patients are so appreciative, they are enjoying it, although they are experiencing some hiccups,” he said. “We also are doing quick surveys of 5 minutes to get feedback from the doctors and we have support for them as well.”

Mission Cancer & Blood in Des Moines, Iowa, is having nurses set up the telehealth appointments.

“The appointment scheduler is not a clinical person, and to now explain to the patient why we are switching them to a telehealth visit is a clinical discussion,” said Phil Stover, JD, MBA, the practice’s CEO. “We wanted this to be a clinical team assuring the patient we are taking care of them. That has helped us with streamlining the implementation.”

Mission Cancer & Blood, which has 3 main locations, also created a handbook for its providers with policies and procedures; information about One Touch Telehealth, the platform they are using; troubleshooting information; and how-to’s for engaging patients.

For a full list of references, see the article at OncLive.com.
**INDICATION**

NUBEQA® (darolutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC).

**IMPORTANT SAFETY INFORMATION**

**Embryo-Fetal Toxicity:** Safety and efficacy of NUBEQA have not been established in females. NUBEQA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment with NUBEQA and for 1 week after the last dose.

**Adverse Reactions**

Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥ 1% of patients who received NUBEQA were urinary retention, pneumonia, and hematuria. Overall, 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Adverse reactions occurring more frequently in the NUBEQA arm (≥2% over placebo) were fatigue (16% vs. 11%), pain in extremity (6% vs. 3%) and rash (3% vs. 1%). Clinically significant adverse reactions occurring in ≥2% of patients treated with NUBEQA included ischemic heart disease (4.0% vs. 3.4% on placebo) and heart failure (2.1% vs. 0.9% on placebo).

**Drug Interactions**

Effect of Other Drugs on NUBEQA — Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure, which may

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“METASTASIS-FREE SURVIVAL (MFS) IS JUST THE HALF OF IT”
NUBEQA®—Focus on both MFS and tolerability\(^{1,2}\)

**40 MONTHS**

**PROVEN TOLERABILITY**

More than double the median MFS with NUBEQA + ADT\(^*\) vs 18 months with ADT alone\(^*\)

\[(HR: 0.41; 95\% CI: 0.34-0.50; P<0.0001)\]

Three adverse reactions occurred more frequently with NUBEQA + ADT (≥2% over ADT alone): fatigue (16% vs 11%), pain in extremity (6% vs 3%), and rash (3% vs 1%)

**SAME RATE OF PERMANENT DISCONTINUATION**

9% of men permanently discontinued due to adverse reactions whether on NUBEQA + ADT or ADT alone

Dose interruptions and reductions due to adverse reactions occurred in 13% and 6%, respectively, of patients treated with NUBEQA + ADT.

The most frequent reasons for permanent discontinuation in patients treated with NUBEQA + ADT included cardiac failure (0.4%) and death (0.4%). The most frequent reasons for dose interruptions included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%). The most frequent reasons for dose reductions included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled, international, multicenter phase III study (ARAMIS) in nmCRPC patients with a prostate-specific antigen doubling time of ≤10 months. 1509 patients were randomized 2:1 to receive either 600 mg NUBEQA twice daily (n=955) or matching placebo (n=554). All patients received concurrent ADT [treatment with GnRH analog or previous bilateral orchiectomy]. The primary endpoint was MFS, defined as the time from randomization to the time of first evidence of BICR-confirmed distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, \(^{99m}\)Tc bone scan by BICR, unacceptable toxicity, or withdrawal. OS data were not mature at the time of final MFS analysis (57% of the required number of events).\(^{1,2}\) The planned final OS analysis has been conducted and mature data on OS will be presented at an upcoming scientific meeting.

\(^{*}\)NUBEQA + ADT, 95% CI: 34.3-NR.  \(^{1}\)ADT alone, 95% CI: 15.5-22.3.

Start new patients with up to 2 months free.\(^{\dagger}\)

Visit NUBEQAhcp.com

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**TOLERABILITY**

Decrease NUBEQA activity. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamidine exposure, which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed.

**Effects of NUBEQA on Other Drugs** — NUBEQA is an inhibitor of breast cancer resistance protein (BCRP) transporter. Concomitant use of NUBEQA increases the exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug. Consult the approved product labeling of the BCRP substrate when used concomitantly with NUBEQA.

\(^{\dagger}\)The NUBEQA Free Trial Program provides 2 months’ supply of NUBEQA at no cost to patients who meet the program eligibility requirements and agree to the terms and conditions. For full terms and conditions, please call DUDE Access Services at 1-833-337-3833 or visit NUBEQAhcp.com to download the Patient Service Request Form with full terms and conditions.

ADT=androgen deprivation therapy; HR=hazard ratio; CI=confidence interval; NR=not reached; GnRH=gonadotropin-releasing hormone; BCRP=breast cancer resistance protein; CT=computed tomography; MRI=magnetic resonance imaging; OS=overall survival.

Please see the following page for brief summary of full Prescribing Information.
7 Drug Interactions

7.1 Effect of Other Drugs on NUBEQA

Combined P-gp and Strong or Moderate CYP3A4 Inducer

Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure which may decrease NUBEQA activity [see Clinical Pharmacology (12.3)]. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Combined P-gp and Strong CYP3A4 Inhibitors

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure [see Clinical Pharmacology (12.3)] which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed [see Dosage and Administration (2.3)].

7.2 Effects of NUBEQA on Other Drugs

Breast Cancer Resistance Protein (BCRP) Substrates

NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and Cmax of BCRP substrates [see Clinical Pharmacology (12.3)], which may increase the risk of BCRP substrate-related toxicities.

Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug. Consult the approved product labeling of the BCRP substrate when used concomitantly with NUBEQA.

8 Use in Specific Populations

8.1 Pregnancy

Risk Summary

The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy [see Clinical Pharmacology (12.1)]. Animal embryo-fetal developmental toxicology studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.

8.2 Lactation

Risk Summary

The safety and efficacy of NUBEQA have not been established in females. There are no data on the presence of darolutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on the mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Use in Specific Populations (8.1, 8.3)].

Infertility

Males

Based on animal studies, NUBEQA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

Safety and effectiveness of NUBEQA in pediatric patients have not been established.

8.5 Geriatric Use

Of the 954 patients who received NUBEQA in ARAMIS, 88% of patients were 65 years and over, and 49% were 75 years and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment

Patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m²) who are not receiving hemodialysis have a higher exposure to NUBEQA and reduction of the dose is recommended [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]. No dose reduction is needed for patients with mild or moderate renal impairment (eGFR 30–89 mL/min/1.73 m²). The effect of end stage renal disease (eGFR <15 mL/min/1.73 m²) on darolutamide pharmacokinetics is unknown.

8.7 Hepatic Impairment

Patients with moderate hepatic impairment (Child–Pugh Class B) have a higher exposure to NUBEQA and reduction of the dose is recommended [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]. No dose reduction is needed for patients with mild hepatic impairment. The effect of severe hepatic impairment (Child–Pugh C) on darolutamide pharmacokinetics is unknown.

10 Overdosage

There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.

Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to systemic toxicity in patients with intact hepatic and renal function [see Clinical Pharmacology (12.3)].

In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.
with NUBEQA included ischemic heart disease (4.0% versus 3.4% on placebo) and heart failure
1 Includes fatigue and asthenia

Initial U.S. Approval: 2019
to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to
increase in frequency compared to placebo. Table 2 shows laboratory test abnormalities related

Table 1 shows adverse reactions in ARAMIS reported in the NUBEQA arm with a ≥2% absolute
The most frequent adverse reactions requiring dosage reduction in patients treated with

Permanent discontinuation due to adverse reactions occurred in 9% of patients receiving

analog or had a bilateral orchiectomy. The median duration of exposure was 14.8 months

patients in the ARAMIS study received a concomitant gonadotropin-releasing hormone (GnRH)

If needed for patients with mild or moderate renal impairment (eGFR 30-89 mL/min/1.73 m2). The
hemodialysis have a higher exposure to NUBEQA and reduction of the dose is recommended

Patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m 2) who are not receiving

Nonclinical Toxicology (13.1)
Based on animal studies, NUBEQA may impair fertility in males of reproductive potential

NUBEQA only on the basis of the exposure-response relationship. Darolutamide is a substrate of
Breast Cancer Resistance Protein (BCRP) Substrates
[see Dosage and Administration (2.2)]

[see Clinical Pharmacology (12.3)]

in vitro
chromosome aberration assay in human peripheral

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References: 1. NUBEQA (darolutamide) [prescribing information]. Whippany,
NJ: Bayer HealthCare Pharmaceuticals Inc.; July 2019. 2. Fizazi K, Shore N,
Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate
Chemotherapy Findings Help Clarify Sequencing Options in mCRPC

by BRITTANY LOVELY

ALTHOUGH NUMEROUS THERAPIES have been introduced for patients with metastatic castration-resistant prostate cancer (mCRPC), the question of how to optimally sequence treatments for those who experience progression remains a vexing clinical challenge.

Two leading experts in genitourinary cancers unpacked their approach during a wide-ranging OncLive Insights® video program. Daniel P. Petrylak, MD, is a professor of medicine and urology and coleader of Cancer Signaling Networks at Yale Cancer Center in New Haven, Connecticut. Nicholas J. Vogelzang, MD, is a medical oncologist at Comprehensive Cancer Centers of Nevada in Las Vegas. Both are recipients of a Giants of Cancer Care® award in the genitourinary cancer category.

THE SHIFTING LANDSCAPE

The biggest change in the prostate cancer field in the past 5 years involves moving agents from the castration-resistant setting into the hormone-sensitive disease state, Petrylak said. However, as these options expand and shuffle the treatment landscape, clinicians must decipher the best course of action to not only prolong survival but also maintain quality of life.

“My goal in treating patients is to make sure that they receive every class of drug that we have available to them, whether that be immune therapy, whether that be next-generation antiandrogens, whether that be DNA-damaging agents like radium and the PARP inhibitors, [as well as] the chemotherapeutic agents,” said Petrylak. “If we can do that, then I feel that I’ve accomplished the best possible care for my patients in this situation.”

Both Petrylak and Vogelzang said that they do not shy away from using docetaxel, especially for newly diagnosed patients, even if patients are hesitant to begin chemotherapy.

“I’m personally still using a lot of docetaxel, and I find that if you approach the patient right when they’re diagnosed, they’re not so negative about it,” Vogelzang said. “But also, more importantly, you say, ‘Look, then I’ve got all these androgen receptor inhibitors that I could use after the docetaxel.’”

The introduction of novel therapies that target androgen activity, such as enzalutamide (Xtandi), apalutamide (Erleada), and the combination of abiraterone acetate (Zytiga) with prednisone, has opened up the treatment landscape, Petrylak said: “We have competing drugs, each of which has its own advantages and disadvantages, [and] we’ve seen less of a use of docetaxel in this particular space.”

He noted that he takes an approach similar to Vogelzang’s, discussing both long- and short-term adverse events (AEs) associated with each treatment option with his patients.

“Particularly with docetaxel, we know that patients can [experience] some neuropathy and neutropenia. But when you do the 6 cycles of treatment, you’re done. It’s over with; you don’t have to worry about taking a pill. We know that abiraterone [plus] prednisone does have some cardiovascular effects,” Petrylak said. “So, if a patient has cardiac dysfunction, I’m going to lean away from giving abiraterone and prednisone and perhaps [choose] docetaxel, apalutamide, or enzalutamide.”

SEQUENCING THERAPY

For patients who develop resistance to initial androgen-deprivation therapy, next steps for treatment choice depend on evidence of metastases (M0 or M1) by conventional imaging and whether the patient is symptomatic, according to National Comprehensive Cancer Network guidelines (FIGURE). Options include secondary hormonal therapies with modern antiandrogens, such as apalutamide, enzalutamide, darolutamide (Nubeqa), and the androgen metabolism inhibitor abiraterone.

WORKUP FOR PROGRESSION

Imaging

• Chest CT
• Bone imaging
• Abdominal/pelvic CT or MRI with and without contrast

Molecular Testing

• Clinical/pathologic features: any T; any N, M1
• Recommended: HRm
• Consider: MSI or dMMR

dMMR, mismatch repair deficiency; HRm, homologous recombination repair gene mutations; M1, distant metastasis; MSI, microsatellite instability; N, regional lymph nodes; T, primary tumor.
For patients with distant metastases (M1), first-line regimens with category 1 recommendations consist of abiraterone, docetaxel, enzalutamide, and sipuleucel-T (Provenge), as well as radium-223 chloride (Xofigo) for those with symptomatic bone metastases.\(^1\)

Second-line recommendations depend on the therapies used in the first-line mCRPC setting and whether molecular testing reveals an aberration that suggests use of the PARP inhibitor olaparib (Lynparza) for patients with homologous recombination repair mutations or the anti-FD-1 inhibitor pembrolizumab (Keytruda) for those with microsatellite instability (MSI)-high tumors or mismatch repair deficiency. Docetaxel has a category 1 recommendation after first-line abiraterone or enzalutamide, whereas preferred regimens after first-line docetaxel are abiraterone, enzalutamide, or the chemotherapy cabazitaxel (Jevtana).

For patients who progress or whose prostate-specific antigen (PSA) levels rise despite androgen-targeting therapy, deciphering the best course of treatment presents a challenge. Sequencing regimens based on available data factor into approaches following front-line treatment, as do insurance hurdles.

**FIGURE.** Chemotherapy in Metastatic Castration-Resistant Prostate Cancer

*National Comprehensive Cancer Network Guideline recommendations*\(^\)\(^a\)

**Adenocarcinoma**\(^a\)

- **First-line preferred regimen:**
  - Docetaxel (category 1)
- **Second-line treatment:**
  - Preferred regimen after first-line abiraterone or enzalutamide
  - Docetaxel (category 1)
  - Other recommendations after first-line abiraterone or enzalutamide:
    - Cabazitaxel
    - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies
    - After first-line docetaxel:
      - Cabazitaxel (category 1)
    - Other considerations after first-line docetaxel:
      - Consider docetaxel rechallenge
      - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies
    - Subsequent treatments if visceral metastases are present:
      - Prefered regimens:
        - Cabazitaxel (category 1)
        - Docetaxel rechallenge
      - Other recommendations:
        - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies

**Small cell/neuroendocrine prostate cancer**

- **First-line and subsequent options:**
  - Cisplatin/etoposide
  - Carboplatin/etoposide
  - Docetaxel/carboplatin
  - Atezolizumab/carboplatin/etoposide (category 3)

\(^a\)Guidelines include extensive information for androgen-targeting agents, PARP inhibitors, and immunotherapy in this disease setting.

\(^\)Patients with disease progression on a given therapy should not repeat that therapy, with the exception of docetaxel, which can be given in the second- or subsequent-line metastatic castration-resistant prostate cancer setting if given in the castration-naïve setting.

\(^\)If visceral metastases are present, all recommendations are category 2B.

“What I often tell the patient is, ‘Look, the cancer that we started treating you with way back when with androgen deprivation therapy and perhaps docetaxel, now after AR [androgen receptor] inhibition,…has evolved,’ Vogelzang said. ‘The tumor is now a different tumor.’

**New Role for Cabazitaxel**

Petrylak noted that results from the CARD trial (NCT02485691) helped clarify some of the questions surrounding which therapy to use after progression. The findings demonstrated that cabazitaxel, a next-generation taxane already approved for mCRPC after prior docetaxel-containing therapy, is a more effective choice for subsequent therapy than continued use of agents that target androgen signaling.\(^2\)

“The CARD trial was a study that looked at sequential treatments in castrate-resistant disease. Generally, we would use next-generation antiandrogens like abiraterone or enzalutamide first, then go on to docetaxel,” Petrylak said. ‘The question has always been ‘What’s the next step?’ A lot of people will try another next-generation agent or, of course, go on chemotherapy. And the thought was ‘Well, chemotherapy is more toxic; we don’t want to use it in this situation,’ but the CARD trial helps answer that particular question.”

The study involved 255 patients with mCRPC with castrate levels of serum testosterone (<0.5 ng/mL) whose disease had progressed after prior docetaxel and within 12 months of receiving either abiraterone or enzalutamide. Progression was defined according to RECIST criteria or by the appearance of at least 2 new bone lesions or rising PSA levels.

Patients were randomized to receive cabazitaxel (25 mg/m\(^2\) every 3 weeks) or antiandrogen therapy with either abiraterone (1000 mg once daily) plus prednisone (5 mg twice daily) or enzalutamide (160 mg once daily), depending on which agent they had previously received. Participants in the cabazitaxel arm also received oral prednisone (10 mg daily) and prophylactic granulocyte colony-stimulating factor.

After a median follow-up of 9.2 months, median imaging-based progression-free survival (PFS) was 8.0 months in the cabazitaxel arm (\(n = 129\)) and 3.7 months in the abiraterone/enzalutamide arm (\(n = 126\)), with a cabazitaxel-favoring HR of 0.54 (95% CI, 0.40-0.73; \(P < .001\)). The data also supported the efficacy of cabazitaxel in overall survival (median 13.6 vs 11.0 months; HR, 0.64; 95% CI, 0.46-0.89; \(P = .008\)).

“[These results] lend a lot of credence to the idea that the tumor has evolved away from androgen receptor dependence to a more neuroendocrine, more chemo-responsive [tumor],” Vogelzang said.

Investigators also seek to determine whether dual chemotherapy with cabazitaxel in combination with carboplatin can address the resistance to therapies that inhibit androgen signaling in progressive mCRPC. The combination showed early signs of efficacy in a phase 1/2 trial (NCT01505868), and a randomized phase 3 study is planned.\(^3\)

Another available option for clinicians is sipuleucel-T, an autologous cellular immunotherapy approved by the FDA in 2010 to treat asymptomatic or minimally symptomatic patients with mCRPC.\(^4\) Sipuleucel-T is designed to induce an immune response targeted against prostatic acid phosphatase, an antigen expressed in most prostate cancers. The agent typically is administered...
in 3 intravenous infusions every 2 weeks (at approximately weeks 0, 2, and 4). Emerging data show that sipuleucel-T may be more effective if administered earlier in the treatment timeline, according to Petrylak. “Before the PSA gets to 22 is one of the thoughts,” he said. “I think that it’s underused and underappreciated. It is a process that has activity and a proven survival benefit.”

**FUTURE OF TARGETED AGENTS**

PARP inhibitors are poised to make an impact on the future of treatment for patients with refractory prostate cancer, Petrylak noted, adding that that efficacy has been seen only in small patient populations thus far. “The issue is really trying to assess [these small patient populations]. Number 1, we all have to check our patients molecularly now. This is now an absolute. You have to check them for MSI. You have to check them now for DNA repair mutations, because we can make an impact on our patient’s care by administering drugs based upon these particular markers,” he said.

Several exciting trials recently released data for using PARP inhibitors in castrate-resistant disease, Petrylak added, citing the PROfound study (NCT02987543). The phase 3 randomized trial met its primary end point of radiographic PFS.

The trial recruited 387 patients with mCRPC who had disease progression after receiving newer hormone-targeting agents and had BRCA1, BRCA2, or ATM (cohort A) alteration or 1 or more of 12 gene alterations associated with homologous recombination repair (cohort B). Patients were randomized 2:1 to receive either olaparib (300 mg twice daily) or physician’s choice of abiraterone (1000 once daily) plus prednisone (5 mg twice daily) or enzalutamide (160 mg once daily).

The benefit of olaparib was observed regardless of previous treatment with or without taxane therapy. However, the greatest benefit was observed in cohort A, with a radiographic PFS of 7.4 months with olaparib versus 3.6 months with other hormonal agents in patients previously treated with taxane therapy (HR, 0.34; 95% CI, 0.25-0.47). “It’s very exciting that we’ve been able to select patients with a different molecular mutation and then administer a drug based upon that mutation,” Petrylak said. He added that approximately 20% of all patients with castration-resistant prostate cancer and 10% of all patients have BRCA1 or BRCA2 alterations.

Vogelzang posed the question “If you’re testing early on all patients, and if you don’t find a BRCA [mutation] or a DNA repair deficiency, would you retest your patients?” Petrylak said that he does retest. “[There] could be a clonal evolution of something that may not be picked up in the original test,” he explained. “But I’m also excited about drugs that are trying to induce BRCA, and I think that this is going to be the next step in this particular pathway. How can we induce the cell to downregulate the DNA repair pathway such that you are sensitive to a PARP inhibitor?”

**MAINTAINING QUALITY OF LIFE**

Petrylak emphasized the importance of open communication between patient and physician, especially with regard to expected and reported AEs, throughout the treatment process for mCRPC. “If we catch a fever early, if we catch fatigue early, we may be able to do some things to fix those, so that the patient can tolerate chemotherapy better,” he said. Overcoming patient fear and aversion to chemotherapy goes hand in hand with maintaining open communication.

Karim Fizazi, MD, PhD, and colleagues presented quality-of-life results from the CARD trial at the 2020 American Society of Clinical Oncology Genitourinary Cancers Symposium. The analysis evaluated changes in pain and health-related quality of life with the primary end points of pain response and time to pain progression, symptomatic skeletal events, and patient-reported outcomes.

The pain response, defined as a decrease of 30% or more from baseline in Brief Pain Inventory–Short Form pain intensity score, was 45.0% in the cabazitaxel arm (n = 111) versus 19.3% in the enzalutamide/abiraterone arm (n = 109; P <.0001). The percentage of patients with the probability of not having pain progression after 12 months was 66.2% versus 45.3%, respectively. The median time to first symptomatic skeletal event was not reached (NR) in the cabazitaxel arm (95% CI, 20.0-NR) versus 16.7 months (95% CI, 10.8-NR) in the enzalutamide/abiraterone arm (HR, 0.59; 95% CI, 0.35-1.01; P = .05). Changes in quality-of-life domains measured through the Functional Assessment of Cancer Therapy–Prostate questionnaire also favored cabazitaxel.

The authors concluded that use of cabazitaxel should be considered over a second androgen-signaling–targeted inhibitor in patients who have progression within 12 months following treatment with docetaxel and another inhibitor aimed at androgen signaling. Petrylak noted that quality-of-life data did not show much of a difference between the study drugs. “That tells us that the activity of the drugs may actually be helping overcome some of the adverse effects,” Petrylak said, adding that fatigue is an AE that needs to be monitored “very, very carefully” in patients receiving enzalutamide.

**REFERENCES**


Higher-Risk Myelodysplastic Syndromes (HR-MDS): Lacking Treatment Advances in Over a Decade

BY JUSTIN WATTS, MD

MYELODYSPLASTIC SYNDROMES (MDS) are a heterogenous, molecularly-driven group of rare bone marrow cancers that occur when the blood-forming cells in the marrow become abnormal, or dysplastic, and are unable to correctly make new blood cells. It is estimated that there are 14,000 new cases of MDS reported every year in the U.S., with most cases diagnosed in people aged 60 or older.

There are several roadblocks to diagnosing MDS, mostly related to symptoms being vague and attributed to other, less serious illnesses. This can cause the diagnosis and subsequent treatment to be delayed, which can result in disease progression. Symptoms include fever, easy bruising or bleeding, loss of appetite, fatigue, weakness, shortness of breath, pale skin and frequent or severe infections.

MDS can be initially identified by a complete blood count (CBC) with differential test, and a peripheral blood smear, which detect signs of MDS like anemia, abnormal myeloblasts (“blasts”) or other abnormalities. A diagnosis is then confirmed by the presence of persistent cytopenias and the identification of cytogenetic abnormalities, dysplasia or increased blasts (less than 20%) in the bone marrow as determined by a bone marrow aspiration and biopsy test.

A risk score is then determined, most often by the Revised International Prognostic Scoring System (IPSS-R), to help determine a patient’s prognosis and the appropriate treatment option. The risk score is based on the percentage of blasts and the chromosomal abnormalities present in the bone marrow cells, combined with the severity of cytopenias, and it ranges from very low-risk to very high-risk. Patients with “higher-risk” disease – defined as intermediate, high or very high on the IPSS-R scale – account for 43% of people diagnosed with MDS.

There has historically been a lack of consensus regarding the classification of MDS, with some considering MDS to be more of a bone marrow disorder than a cancer. While lower-risk MDS can sometimes behave indolently and be observed without treatment, it is important to realize that higher-risk MDS (HR-MDS) is a fatal bone marrow cancer that is progressive in nature, and fast diagnosis and intervention is critical.

Because higher-risk patients have more severe symptoms, and ultimately lower rates of overall survival (OS), prompt diagnosis and treatment is critical. Current treatment options do not provide benefit for all patients, and survival is limited with the currently approved therapies. If left untreated, the median survival rate is 9.6 months to 3 years upon diagnosis. Furthermore, approximately 40% of people living with HR-MDS will transform to acute myeloid leukemia (AML), another aggressive blood cancer with poor survival outcomes. AML progresses rapidly and is typically fatal within weeks or months if untreated.

There have been significant advances in the development of targeted treatment options for other cancers. However, there are no targeted therapies available to patients with HR-MDS.

Recent research shows that overall cancer mortality rates have declined by 29% from 1991 to 2017, especially in lung, colorectal, breast and prostate cancers, as well as melanoma, lymphoma and some types of leukemia. For patients living with these cancers, early detection has been a key component of improved survival rates. An equally critical component has been the scientific community’s dedication to researching, developing and bringing innovative...
medicines to patients that specifically target and attack certain types of cancer cells in malignancies like lung cancer, melanoma, lymphoma and certain types of leukemia.1,3

The ultimate goal of HR-MDS treatment is to induce remission, slow disease progression and to manage symptoms to help maintain quality of life. However, there is room to improve upon the current standard of care – hypomethylating agent (HMA) monotherapy – which provides limited benefit in most patients. Specifically, not every patient responds to HMA monotherapy, and most of the patients that do respond will eventually experience disease progression or lose their response.1,4

Other options like allogeneic stem cell transplantation (ASCT) have the potential to cure HR-MDS, but many patients may not be eligible because they may be too frail or sick to tolerate the procedure or may not have a suitable donor.1,5-6 Due to age or comorbidities, only 6% to 14% of people living with HR-MDS undergo ASCT. Even patients who are eligible to receive ASCT have relatively poor outcomes, as transplant-related mortality ranges from 20% to 37%.7,10,11

In the event that neither chemotherapy nor ASCT are options, supportive care alternatives, such as transfusions or blood cell growth factors can help manage symptoms, but have no efficacy against the disease itself.1,5,11

A significant need remains for targeted therapies for those living with HR-MDS.

For over a decade, there has been little advancement in treatment options for people living with HR-MDS despite poor patient outcomes. Continued research is critical to potentially bring a targeted therapeutic option to HR-MDS patients, not only to improve OS, but also to manage symptoms and preserve quality of life. Though there has been little progress in HR-MDS treatment options over the last decade, late-stage clinical studies are actively investigating novel agents in combination with HMAs to improve efficacy and patient outcomes while maintaining safety and tolerability. Due to its aggressive nature and poor survival rates, people living with HR-MDS urgently need new treatment options that are more effective at inducing remission and slowing or preventing disease progression to ultimately improve the survival and quality of life of patients living with this disease. ■

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Sponsored by Takeda Oncology

REFERENCES
2. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Myelodysplastic Syndromes, Chronic Myeloproliferative Disorders, and Chronic Myelomono-
Scoring System Stratifies Risk of Heart Failure in Patients With Acute Leukemia

by NICHOLE TUCKER

BASELINE CLINICAL CHARACTERISTICS coupled with measurable cardiac parameters can be used to predict the risk of heart failure (HF) among adults with acute leukemia who receive anthracycline-based therapy, according to recent study findings.1

Investigators developed a 21-point scoring system to evaluate the potential for HF among patients with newly diagnosed acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL). The formula stratifies patients into high-, moderate-, or low-risk groups.

Although prior research has shown that patients with hematologic malignancies experience the highest rates of symptomatic HF and cardiac death compared with other patients with cancer treated with anthracyclines, investigators said data are limited when it comes to evaluating comorbidities in those with acute leukemia.

“Our hope, in creating this risk score system, is to help clinicians identify patients with the highest risk for potential cardiac damage, so they can more closely monitor the patients via a multidisciplinary approach,” said Scherrer-Crosbie, director of the Cardiac Ultrasound Laboratory and a professor of cardiovascular (CV) medicine in the Perelman School of Medicine at the University of Pennsylvania in Philadelphia.

To examine these factors, investigators identified adults (≥18 years of age) treated with anthracyclines for newly diagnosed AML or ALL at the Hospital of the University of Pennsylvania between January 2004 and April 2018. In all, 450 patients with adequate baseline records who were followed for a median of 16 months (range, 1-132 months) were included in the analysis. The description of symptomatic HF was based on the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials.

Among those in the study, symptomatic HF developed in 8.9% of the patients (n = 40), which included 1 patient with decompensated HF who died. The median time to development of HF was 10 months (range, 1-76). Death due to a noncardiac cause occurred in 47.8% of patients (n = 215).1

At baseline, 67% of patients in the study had AML (n = 301) and 33% had ALL (n = 149). Forty-eight percent of patients were male (average age, 51 years; ± 15). The most common baseline CV disease characteristics were current/previous smoking history (40%), having 2 or more CV risk factors (39%), hypertension (36%), and hypercholesterolemia (22%).

Investigators found that patients who developed HF were typically older and had a higher incidence of previous HF, atrial fibrillation, and preexisting CV diseases.

RISK SCORE COMPRISSES 6 VALUES

The scoring system assigns point values to 6 factors: baseline global longitudinal strain greater than -15%, left ventricular ejection fraction less than 50%, preexisting CV disease, AML, anthracycline dose of 250 mg/m2 or greater, and age greater than 60 years (TABLE).1 Patients were then divided by scores into low (0-6 points), moderate (7-13 points), and high (14-21 points) risk groups.

Overall, the 1-year estimated cumulative incidence of HF for the low-, moderate-, and high-risk groups was 1.0%, 13.6%, and 35.0%, respectively.

The risk of HF and noncardiac mortality was found to be higher in patients with AML (11.6% and 52.8%, respectively) than in those with ALL (3.4% and 34.9%; P < .001). Contributing factors to this finding included greater doses of anthracyclines in patients with AML and that patients in the AML group tended to be older. After adjusting for these risk factors, however, patients with AML still faced a greater risk of symptomatic HF (HR, 2.77; 95% CI, 1.01-7.63; P = .048).

For patients with ALL, investigators modified the risk score to exclude an AML diagnosis. Using a 17-point formula, investigators estimated the cumulative risk of HF incidence at 1 year in patients with ALL at less than 0.1% for the low-risk group, 3.6% for the moderate-risk group, and 17.0% for the high-risk cohort (P < .001).

An exploratory analysis was also conducted to show the relationship between risk score and overall mortality. It was discovered that the risk score was associated with all-cause death (HR, 1.36; 95% CI, 1.23-1.50; P < .001). Patients in low-risk to moderate-risk groups had a greater overall survival time than high-risk patients (P < .001). Only global longitudinal strain greater than -15% was found to be independently related to all-cause death (HR, 1.73; 95% CI, 1.30-2.31; P < .001).

Limitations of the study include the fact that it was conducted at a single center and that the score has not been validated in a separate cohort, investigators said. A large prospective, multicenter study is needed to further validate the formula.

For a full list of references, see the article at OncLive.com.

TABLE. Variables Included to Predict the Risk of Heart Failure After Leukemia Therapy1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score points</th>
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<tbody>
<tr>
<td>GLS &gt;-15%</td>
<td>6</td>
</tr>
<tr>
<td>Preexisting CV disease</td>
<td>4</td>
</tr>
<tr>
<td>Leukemia type (AML)</td>
<td>4</td>
</tr>
<tr>
<td>EF &lt;50%</td>
<td>4</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td>1</td>
</tr>
<tr>
<td>Anthracycline dose ≥250 mg/m²</td>
<td>2</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukemia; CV, cardiovascular; EF, ejection fraction; GLS, global longitudinal strain.
Hard-to-Target WNT Pathway Gets a Fresh Look

by JANE DE LARTIGUE, PHD

RESEARCH INTEREST IN TARGETING

the WNT pathway, a critical regulator of embryonic development and adult tissue homeostasis, has ebbed and flowed in the almost 40 years since its discovery.1,2 Yet finding the right balance between efficacy and safety has thus far proved elusive, and the field is littered with failures.2

The pull remains strong, however, and investigators continue to find innovative ways to attack the WNT pathway beyond targeting the major molecular players. Myriad drugs with varied mechanisms of action are currently in the pipeline but are still in the early stages of clinical development (TABLE).

Investigators recently uncovered a potential role for WNT signaling in immune evasion by cancer cells.3-5 Activation of WNT signaling is enriched in tumors with low levels of infiltrating T cells.3 This raises the possibility that WNT inhibitors could make immunologically cold tumors more responsive to immunotherapy. Drug developers are seeking to capitalize on this link through combination therapy with immune checkpoint inhibitors.

DKN-01, an antibody targeting the WNT pathway inhibitor DKK1 (dickkopf-related protein 1), has been shown to participate in innate immunity.6 The combination of DKN-01 and the PD-1 inhibitor pembrolizumab (Keytruda) has recently showed promise in patients with gastroesophageal adenocarcinoma who had high DKK1 expression.7 DKN-01 is being tested in numerous clinical trials across a range of malignancies.

A COMPLEX NETWORK

The first mammalian WNT gene was described in 1982.1 In the intervening years, painstaking research has painted a picture of the WNT genes—19 of which have now been identified—as orchestrators of an evolutionarily conserved and highly complex pathway that plays a fundamental role in embryonic development and the maintenance of many adult tissues.8-12

WNTs serve as ligands for a family of 10 Frizzled (FZD) receptors. Although certain ligands have a higher affinity for particular receptors, in general they are highly promiscuous in their binding.12 Receptor-ligand interaction triggers the membrane recruitment and activation of disheveled (DVL), which relays WNT signals from the cell surface to intracellular downstream effectors.9-12

Beyond this basic outline of WNT signal transduction, variations in several key molecular components mark the existence of several different WNT signaling cascades with distinct cellular outcomes. The best characterized of these cascades is dubbed the canonical, or β-catenin-dependent, pathway (FIGURE 9-12). In the absence of WNT ligands, β-catenin is retained in the cytoplasm by a multiprotein complex composed of axin, adenomatous polyposis coli (APC), GSK3β and CK1α. This aptly named “destruction complex” phosphorylates the β-catenin protein, ultimately targeting it for degradation by the proteasome.9-12

The canonical pathway is activated upon WNT ligand binding to FZD and its coreceptor LRP5/6, which leads to inhibition of the destruction complex. Thus spared from phosphorylation and degradation, β-catenin is stabilized and subsequently moves into the nucleus, where it interacts with TCF/LEF transcription factors to drive transcription of WNT target genes, which coordinate a plethora of cellular functions.9-12

Two main noncanonical WNT pathways have also been characterized; in addition to being β-catenin independent, they involve coreceptors and downstream signaling mediators that differ from those implicated in the canonical pathway. The WNT/planar cell

FIGURE. Canonical View of WNT Signaling9-12

The WNT pathway has several mechanisms of activation. This illustration depicts the most fully characterized view of the signaling network as dependent on β-catenin. Other descriptions include 2 pathways that function independently of β-catenin.
polarity (PCP) pathway involves coreceptors such as ROR1 and PTK7, as well as downstream signaling by Rho GTPases and JNK, and plays key roles in cell division, morphology, and migration.

**CANCERS ASSOCIATED WITH ABBERRANT WNT ACTIVITY**

Owing to their pleiotropic functions in key cellular processes, both canonical and non-canonical forms of WNT signaling have been implicated in carcinogenesis, although the role of the former is better understood.

Its best known association with cancer is the APC gene, which occur in more than 80% of colorectal carcinomas (CRCs) and are associated with familial adenomatous polyposis, a hereditary cancerous condition that takes its name from the gene.

A 2012 report from The Cancer Genome Atlas Research Network estimated that up to 93% of sporadic CRCs contain at least 1 alteration in a known WNT pathway component. Beyond APC mutations, other abnormalities in WNT signaling include mutations in RNF43 and gene fusions involving RSPO family members, which encode proteins that regulate FZD degradation. RNF43 mutations and RSPO fusions are found in approximately 18% and 10% of CRCs, respectively. WNT signaling abnormalities have been found across a range of other cancer types and in a variety of pathway components. An estimated 25% to 35% of hepatocellular carcinomas (HCCs) and more than half of breast cancers, for example, display heightened activity of the WNT pathway. The basal-like breast cancer subtype seems to be particularly susceptible, and WNT pathway activation has been shown to be associated with poorer prognosis.

**A DOUBLE-EDGED SWORD**

WNT’s central role in many cellular processes, including those underlying hallmarks of malignant transformation, has led to substantial interest in targeting the pathway. Investigators have evaluated a host of drugs with different mechanisms of action, and several have entered clinical trials. Hampered by significant toxicity or lack of efficacy, however, none have made it past the early stages of clinical development.

Efforts to target the major molecular players have yielded several anticancer drugs. OncoMed Pharmaceuticals began developing the anti-FZDI/2/5/7/8 antibody vantictumab and ipafrecept, a fusion protein comprising a truncated FZD8 fused to the Fc region of immunoglobulin G1 that was designed to act as a decoy receptor for WNT ligands. Bayer pulled out of a licensing deal for the 2 drugs in 2017, and no clinical trials are ongoing for either agent.

Phase 1 clinical trials of vantictumab and ipafrecept were recently terminated prematurely because of concerns about bone toxicity, a common on-target toxic effect of inhibiting the WNT pathway, which plays a critical role in normal bone homeostasis. In a phase 1b study in 26 patients with untreated metastatic pancreatic cancer (NCT02050178), ipafrecept in combination with nab-paclitaxel (Abraxane) and gemcitabine was well tolerated, with no dose-limiting toxicities (DLTs) or fragility fractures, and 34.6% of patients had partial responses (PRs).

Tabituximab barzuxetan (OTSA101-DTPA-90Y) is an anti-FZD10 antibody radiolabeled with yttrium 90 that investigators are testing in patients with synovial sarcoma, in which FZD10 is frequently found to be overexpressed. In a first-in-human study (NCT01469975), the best response in 3 of 8 patients treated with tabituximab barzuxetan was stable disease (SD), which lasted up to 21 weeks for 1 patient. That trial was halted because of slow accrual, but a similar study is ongoing (NCT04176016).

Several β-catenin inhibitors have also been developed. PRI-724 and CWP232291 (CWP291) block the interaction between β-catenin and its transcriptional coactivator CREB-binding protein to prevent WNT target gene transcription. Ongoing development of these drugs as anticancer agents is somewhat unclear. CWP291 in combination with cytarabine is undergoing phase 1/2 clinical testing in patients with relapsed/refractory acute myeloid leukemia (NCT03055286), with anticipated study completion in October 2020.

**NONCANONICAL SIGNALING**

Research has further revealed the complexities of WNT signal transduction, clarifying that some components have tumor-suppressive rather than tumor-promoting effects, depending on the context. One example is WNT5A, which has been shown to play a protective role in several tumor types. Foxy-5 is a novel hexapeptide molecule that mimics WNT5A and binds to and activates FZD2 and FZD5 to restore WNT5A function in tumors with low expression level. Investigators have conducted 2 clinical trials in patients with breast, colon, or prostate cancer (NCT02020291, NCT02655952), but no results have been available.

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**Clinical Implications**

**WNT Signaling Abnormalities in Cancer Types**

The WNT family is a group of proteins implicated in many cellular functions including:

1. Organ formation
2. Stem cell renewal
3. Cell survival

**WNT in cancers:**

- **CRC:** Pathway is upregulated in both microsatellite instable and microsatellite stable CRCs
- **Breast:** More than half of breast cancers have activation of WNT, which is associated with lower overall survival
- **NSCLC:** There is evidence that WNT/β-catenin signaling helps maintain lung cancer “stemness.” WNT ligands and receptors have been found in the bone marrow microenvironment.
- **CML:** Patients in blast crisis have shown evidence of WNT activation.

- **Ovarian:** WNT signaling plays a critical role in chemoresistance and is involved in the maintenance and propagation of ovarian cancer stem cells.

CML, chronic myeloid leukemia; CRC, colorectal cancer; NSCLC, non–small cell lung cancer.
released to date. A phase 2 study of Foxy-5 as neoadjuvant treatment for patients with WNT5A-low colon cancer is ongoing (NCT03883802).

Also notable is that WNT5A functions in the noncanonical WNT pathway. Several other novel drugs have also been designed to target coreceptors involved in the WNT/PCP pathway, ROR1 and PTK7.

Cirmtuzumab is an anti-ROR1 antibody that has demonstrated promise in preclinical trials. Cirmtuzumab functioned synergistically with the Bruton tyrosine kinase inhibitor ibrutinib (Ibrance) to reduce tumor cell proliferation in cells and xenografts derived from patients with chronic lymphocytic leukemia (CLL).26

Data from a phase 1/2 study (NCT03088878) of the combination showed an overall response rate (ORR) of 67%, with 1 confirmed complete response (CR) with no morphologic evidence of CLL in the marrow, 1 clinical CR, and 6 PRs.27 Following this success, investigators opened an expansion cohort to include patients with mantle cell lymphoma. Interim data demonstrated a 50% CR rate in evaluable patients (n = 12). Notably, 4 patients achieved PR and 2 had stable disease (SD). The best ORR was 83%.28

<table>
<thead>
<tr>
<th>Drug (developer)</th>
<th>Mechanism of action</th>
<th>Cancer types</th>
</tr>
</thead>
<tbody>
<tr>
<td>2X-121 (Oncology Venture US)</td>
<td>Dual PARP 1/2 and tankyrase 1/2 inhibitor</td>
<td>Ovarian, breast</td>
</tr>
<tr>
<td>WTN974 (LGK974) (Novartis)</td>
<td>Porcupine inhibitor</td>
<td>WNT ligand-dependent solid tumors</td>
</tr>
<tr>
<td>ETC-1922159 (EDDC)*</td>
<td>Porcupine inhibitor</td>
<td>Advanced, unresectable solid malignancies</td>
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<tr>
<td>RXC004 (Redx Pharma Pty)</td>
<td>Porcupine inhibitor</td>
<td>Advanced malignancies</td>
</tr>
<tr>
<td>CGX1321 (Careagen Inc)</td>
<td>Porcupine inhibitor</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>XNW7201 (Sinovent Pty Ltd)</td>
<td>Porcupine inhibitor</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Tabituximab barzuxetan (Radiolabeled OTSA101-DTPA) (OncoTherapy Science Inc)</td>
<td>Anti-FZD10 antibody</td>
<td>Synovial sarcoma</td>
</tr>
<tr>
<td>Foxy-5 (WntResearch AB)</td>
<td>WNT5A mimic hexapeptide</td>
<td>WNT5A-low colon cancer</td>
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<tr>
<td>BI 905677 (Boehringer Ingelheim)</td>
<td>LRPS/6 antagonist nanobody</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>CWP232291 (CWP291) (JW Pharmaceutical)</td>
<td>Peptide mimic; inhibits WNT/β-catenin-dependent gene transcription</td>
<td>Acute myeloid leukemia</td>
</tr>
<tr>
<td>DKN-01 (Leap Therapeutics)</td>
<td>Anti-DKK1 antibody</td>
<td>Biliary tract, carcinosarcoma, epithelial endometrial, epithelial ovarian, HCC, esophagealgastric, DKK1-elevated prostate</td>
</tr>
<tr>
<td>SM08502 (Samumed LLC)</td>
<td>CLK2/3 inhibitor</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Cofetuzumab pelidotin (PF-06647020; PTK7-ADC) (AbbVie/Pfizer)</td>
<td>ADC: anti-PTK7 antibody conjugated to auristatin-0101</td>
<td>Triple-negative breast cancer</td>
</tr>
<tr>
<td>MCLA-158 (Merus)</td>
<td>LGR5/EGFR bispecific antibody</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Cirmtuzumab (Oncternal Therapeutics Inc)</td>
<td>Anti-ROR1 antibody</td>
<td>B-cell lymphoid malignancies, HER2-negative breast cancer</td>
</tr>
</tbody>
</table>

ADC, antibody-drug conjugate.

*EDDC indicates the Experimental Drug Development Centre, an Agency for Science, Technology and Research entity.
Cofetuzumab pelidotin (PF-06647020) is an antibody-drug conjugate comprising a PTK7-targeted antibody linked to an auristatin payload. In a phase 1 study (NCT02222922), 112 patients with advanced solid tumors were treated at doses ranging from 0.2 to 3.7 mg/kg. Investigators noted 2 DLTs at the 3.7-mg/kg dose, and the recommended phase 2 dose was 2.8 mg/kg. Most AEs were grade 1 or 2, most commonly nausea, alopecia, and fatigue. The ORR was 27% in patients with ovarian cancer (n = 44), 16% in patients with non-small cell lung cancer (n = 25), and 21% in those with triple-negative breast cancer (n = 29).²⁹

**ADDITIONAL TARGETS DKN-01**

Investigators presented results from the phase 1 P102/KEYNOTE-731 (NCT02013154) study of DKN-01 in combination with pembrolizumab at the 2020 Gastrointestinal Cancers Symposium.³ To date, 34 patients with gastroesophageal adenocarcinoma had been enrolled. Among the 10 response-evaluable patients with high DKK1 expression levels, the ORR was 50% (all PRs), and the disease control rate (DCR) was 80%. In contrast, patients with low DKK1 expression levels (n = 15) had an ORR of 0% and a DCR of 20%.⁷

DKN-01 also recently showed promise in a phase 2 basket trial in patients with endometrial or ovarian cancer, both as monotherapy and in combination with paclitaxel (NCT03395080).³⁰

In a pooled analysis of all patients treated with DKN-01 monotherapy (n = 51), 21.6% of patients had WNT activating mutations and demonstrated a longer median PFS (168 vs 56 days) as compared to patients without WNT activating mutations. Median OS was not reached in the WNT activating mutation group versus 328 days in the non-WNT activating mutation group.

Further, DKK1 high expression was associated with WNT activating mutations and was associated with greater clinical benefit in patients treated with monotherapy. RNAscope expression data was available for 32 of the 51 patients treated with monotherapy. Patients with DKK1-high tumors (n = 7) experienced longer PFS (168 vs 56 days) and OS (450 vs 276 days) compared with those who had DKK1-low tumors (n = 25) per RNAscope assay results.³⁰

In total, 54 patients were treated with DKN-01 plus paclitaxel. The combination generated robust response in patients with paclitaxel-experienced endometrioid endometrial cancer (n = 22). Twelve patients had SD and 10 had progressive disease (PD). In 6 evaluable pretreated carcinosarcoma patients, 2 patients achieved partial response, 1 had SD, and 3 had PD.³⁰

**Porcupine Enzymes**

Another focus has been on the development of porcupine (PORCN) inhibitors. PORCN is an enzyme involved in the posttranslational modification of WNT ligands, which is essential for WNT secretion. As such, PORCN inhibitors should cause a complete shutdown of all WNT signaling.³⁰

Five PORCN inhibitors are currently in clinical testing (Table). WNT974, a first-in-class, selective, oral PORCN inhibitor, demonstrated preclinical activity as monotherapy in patients with solid tumors when evaluated based on AXIN2 suppression, a marker of WNT pathway activity.³¹ Updated data from the phase 1 trial’s combination arm (NCT01351103) were presented at the 2020 American Association for Cancer Research Annual Meeting. WNT974 plus spartalizumab, an anti-PD-1 monoclonal antibody, demonstrated clinical activity as monotherapy in patients with solid tumors (including colon, endometrial, and ovarian cancer) and non-small cell lung cancer (n = 25), 33,34 with an ORR of 27% and 21% in those with triple-negative breast cancer (n = 29). ²⁹

**SM08502**

SM08502 is an inhibitor of CLK2/3, proteins that play a role in RNA splicing. Alternative splicing is an important mechanism to regulate the expression of WNT-related genes; thus, CLK2/3 inhibition offers a way to indirectly target the WNT pathway.³³ Potent inhibition of tumor growth was observed in xenograft mouse models treated with SM08502 alone (gastrointestinal cancer) or in combination with standard-of-care chemotherapy (pancreatic cancer),³³,³⁴ and the FDA has granted SM08502 an orphan drug designation for the treatment of pancreatic cancer.³³ Results from a phase 1 study in advanced solid tumors (NCT03355066) are eagerly awaited.

**PARP**

Oncology Venture is developing 2X-121, a dual inhibitor of the PARP 1 and 2 proteins as well as PARP family members tankyrases 1 and 2, known alternatively as PARP5A and 5B, respectively. Tankyrase enzymes increase the degradation of axin by the proteasome.³⁶ In a phase 1 study (NCT01618136) in 41 patients with advanced solid tumors treated at 6 dose levels of 2X-121 (50, 100, 200, 400, 600, and 800 mg once daily), 2 patients with ovarian cancer experienced PRs. Additionally, 13 patients achieved SD, which lasted more than 24 weeks for 8 patients (7 of whom had pancreatic cancer).³⁷

The company also developed Drug Response Predictor (DRP) technology, which uses artificial intelligence algorithms to predict patients who will respond to a drug based on the expression of 414 genes. Investigators administered the 2X-121 DRP to 13 patients in the above study and it accurately identified patients with PRs and durable SD.³⁷

Jane de Lartigue, PhD, is a freelance medical writer and editor based in Gainesville, Florida.
INDICATION
CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

SELECT IMPORTANT SAFETY INFORMATION
HEMORRHAGE
- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage occurred between 13-44%. Grade 3-5 hemorrhage incidence ranged from 2-5%.
- Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in REGARD and RAINBOW; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown.
- Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

Please see Brief Summary of Prescribing Information and Important Safety Information for CYRAMZA on subsequent pages.
CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

Adding CYRAMZA to paclitaxel nearly doubles the response vs paclitaxel alone\(^1,2\)

<table>
<thead>
<tr>
<th>ORR (Complete and Partial Response): Supportive Outcome Measure</th>
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<tbody>
<tr>
<td>RAINBOW ORR: percent of patients (95% CI)(^1)</td>
</tr>
<tr>
<td>CYRAMZA + paclitaxel (n=330) 28%</td>
</tr>
<tr>
<td>Placebo + paclitaxel (n=335) 16%</td>
</tr>
</tbody>
</table>

ORR DOES NOT INCLUDE STABLE DISEASE

- Disease progression and tumor response were assessed by investigators in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1\(^2\)
- 2 complete response in CYRAMZA-treated patients and 1 complete response in the placebo-treated patients

**CYRAMZA plus paclitaxel significantly extended OS and PFS\(^1\)**

<table>
<thead>
<tr>
<th>Overall Survival: Major Outcome Measure Median-Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYRAMZA + paclitaxel (n=330) 9.6 MONTHS* (8.5, 10.8)</td>
</tr>
<tr>
<td>Placebo + paclitaxel (n=335) 7.4 MONTHS* (6.3, 8.4)</td>
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</tbody>
</table>

Hazard ratio=0.81 (0.68, 0.96); \(P=0.017\)

- The percentage of deaths at the time of analysis was 78% (256 patients) and 78% (260 patients) in the CYRAMZA plus paclitaxel and placebo plus paclitaxel treatment arms, respectively

<table>
<thead>
<tr>
<th>PFS: Supportive Outcome Measure Median-Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYRAMZA + paclitaxel (n=330) 4.4 MONTHS* (4.2, 5.3)</td>
</tr>
<tr>
<td>Placebo + paclitaxel (n=335) 2.9 MONTHS* (2.8, 3.0)</td>
</tr>
</tbody>
</table>

Hazard ratio=0.64 (0.54, 0.75); \(P<0.001\)

- The percentage of events at the time of analysis was 85% (279 patients) and 88% (296 patients) in the CYRAMZA plus paclitaxel and placebo plus paclitaxel treatment arms, respectively

STUDY DESIGN: The phase III RAINBOW trial evaluated the efficacy and safety of CYRAMZA plus paclitaxel vs placebo plus paclitaxel in patients with locally advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- and platinum-containing chemotherapy. Major efficacy outcome measure was OS. Supportive efficacy outcome measures were PFS and ORR. All patients were ECOG PS 0 or 1. Prior to enrollment, 93% of patients had progressed during treatment or within 4 months after the last dose of first-line chemotherapy for metastatic disease. Twenty-five percent of patients had received anthracycline in combination with platinum/fluoropyrimidine therapy, while 75% did not. Patients were randomized 1:1 to CYRAMZA 8 mg/kg (n=330) or placebo (n=335) every 2 weeks (on days 1 and 15) of each 28-day cycle. Patients in both arms received paclitaxel 80 mg/m\(^2\) on days 1, 8, and 15 of each 28-day cycle.\(^1,3\)

SELECT IMPORTANT SAFETY INFORMATION

**GASTROINTESTINAL PERFORATIONS**
- CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from <1-2%.
- Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

**IMPAIRED WOUND HEALING**
- Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF or VEGFR pathway. CYRAMZA, a VEGFR\(^2\) antagonist, has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds.
- Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 28 days following a major surgical procedure and until the wound is fully healed. Discontinue CYRAMZA in patients who develop wound healing complications that require medical intervention.

Please see Important Safety Information on next page and Brief Summary of Prescribing Information for CYRAMZA on subsequent pages.
**Warnings and Precautions**

**Hypertension**
- Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or until stable.
- Hypertension occurs in <1-3% of patients treated with CYRAMZA. 6-15% of patients who received CYRAMZA had Grade 3-5 hypertension.
- Most patients who experienced hypertension improved with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

**Infusion-Related Reactions (IRR)**
- Infusion-related reactions (IRR), including severe and life-threatening IRR, occurred in CYRAMZA clinical studies. The majority of IRR across trials occurred during or following a first or second CYRAMZA infusion.
- Severe (Grade ≥3) IRR occurred between <1-9%. Grade 3-5 IRR incidence was <1%.
- IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR.
- Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR.

**Impaired Wound Healing**
- Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF or VEGFR pathway. CYRAMZA, a VEGFR2 antagonist, has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds.
- Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 28 days following a major surgical procedure and until the wound is fully healed.

**Arterial Thromboembolic Events (ATE)**
- Arterial Thromboembolic Events (ATE) incidence ranged from <1-2%.
- The incidence of all Grade ATE ranged from <1-2%.
- Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

**Proteinuria Including Nephrotic Syndrome**
- Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade proteinuria ranged from 3-20%. Grade ≥3 proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%.
- Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio. If the result of the urine dipstick is 2+ or greater, perform a 24-hour urine collection for protein measurement.

**Thyroid Dysfunction**
- Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of Grade 1-2 hypothyroidism ranged from <1-3%; there were no reports of Grade 3-5 hypothyroidism. Monitor thyroid function during treatment with CYRAMZA.

**Lactation**
- Breastfeeding is not recommended during treatment with CYRAMZA and for 2 months after the last dose.

**Most Common Adverse Reactions—CYRAMZA Administered as a Single Agent ( REGARD)**
- The most commonly reported adverse reactions (all Grades; Grade 3-4) occurring in ≥5% of patients receiving CYRAMZA and ≥2% higher than placebo in REGARD were hypertension (16% vs 8%; 8% vs 3%), diaphoresis (14% vs 9%; 1% vs 2%), headache (12% vs 3%; 0% vs 0%), and hypotension (4% vs 3%; 1% vs 1%).
- The most common serious adverse reactions with CYRAMZA were anemia (3.8%) and intestinal obstruction (2.1%).
- Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.
- Clinically relevant adverse reactions reported in ≥1% and ≤5% of CYRAMZA-treated patients in REGARD were neutropenia (4.7%), epistaxis (4.0%), rash (2.4%), intestinal obstruction (2.1%), and arterial thromboembolic events (1.7%).

**Most Common Adverse Reactions—CYRAMZA Administered in Combination with Paclitaxel (RAINBOW)**
- The most commonly reported adverse reactions (all Grades; Grade ≥3) occurring in ≥5% of patients receiving CYRAMZA with paclitaxel and ≥2% higher than placebo with paclitaxel in RAINBOW were fatigue/asthenia (57% vs 44%; 12% vs 9%), neutropenia (54% vs 31%; 41% vs 19%), diarrhea (32% vs 23%; 4% vs 2%), epistaxis (3% vs 7%; 9% vs 5%), hypotension (25% vs 6%; 15% vs 3%), peripheral edema (25% vs 14%; 2% vs 1%), stomatitis (20% vs 7%; 1% vs 1%), proteinuria (17% vs 6%; 1% vs 0%), thrombocytopenia (13% vs 6%; 2% vs 2%), hyperuricemia (11% vs 5%; 1% vs 1%), and gastrointestinal hemorrhage events (10% vs 6%; 4% vs 2%).
- The most common serious adverse reactions in patients who received CYRAMZA with paclitaxel were neutropenia (3.7%) and febrile neutropenia (2.4%).

**References:**
CYRAMZA® (ramucirumab) injection, for intravenous use

Brief Summary: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE

Gastric Cancer

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage

CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage occurred between 13-44%. Grade 3-5 hemorrhage incidence ranged from 2-3%. Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in REGARD and RAINBOW; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

Gastrointestinal Perforations

CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from <1-2%. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF or VEGFR pathway. CYRAMZA, a VEGFR2 antagonist, has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds. Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 28 days following a major surgical procedure and until the wound is fully healed. Discontinue CYRAMZA in patients who develop wound healing complications that require medical intervention.

Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATEs), including myocardial infarction, cardiac arrest, cerebrovascular events, and cerebral ischemia, occurred across clinical trials. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade ATE was 2-3%. Grade 3-5 ATE incidence was 1-2%. Permanently discontinue CYRAMZA in patients who experience an ATE.

Hypertension

An increased incidence of severe hypertension occurred in patients receiving CYRAMZA. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension occurred between 11-26%. Grade 3-5 hypertension incidence ranged from 6-15%. Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Withhold CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions

Infusion-related reactions (IRR), including severe and life threatening IRR, occurred in CYRAMZA clinical trials. The majority of IRR across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRR included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR occurred between <1-9%. Grade 3-5 IRR incidence was <1%. Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3-4 IRR.

Worsening of Pre-existing Hepatic Impairment

Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatic encephalopathy, was reported in patients with Child-Pugh B or C cirrhosis who received single agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration. Based on safety data from RAINBOW, in patients with Child-Pugh A liver cirrhosis, the pooled incidence of hepatic encephalopathy and hepatic encephalopathy was 6% compared to patients who received placebo (0%).

Posterior Reversible Encephalopathy Syndrome

Posterior Reversible Encephalopathy Syndrome (PRES) also known as Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in <0.1% of 1916 patients enrolled in five clinical studies with CYRAMZA. Symptoms of PRES include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension. Confirm the diagnosis of PRES with magnetic resonance imaging and permanently discontinue CYRAMZA in patients who develop PRES. Symptoms may resolve or improve within days, although some patients with PRES can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome

Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade proteinuria ranged from 3-20%. Grade ≥3 proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%. Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio. If the result of the urine dipstick is ≥2+ or greater, perform a 24-hour urine collection for protein measurement. Withhold CYRAMZA for urine protein levels that are 2 or more grams over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to less than 2 grams over 24 hours. Permanently discontinue CYRAMZA for urine protein levels greater than 3 grams over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction

Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of Grade 1-2 hypothyroidism ranged from <1-3%; there were no reports of Grade 3-5 hypothyroidism. Monitor thyroid function during treatment with CYRAMZA.

Embryo-Fetal Toxicity

Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF and VEGFR2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for 3 months after the last dose.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described in the Warnings and Precautions section reflect exposure to CYRAMZA in 1916 patients from five studies: REGARD, RAINBOW, RAISE, REVEL, and REACH-2.

Gastric Cancer

The safety of CYRAMZA was evaluated in REGARD and RAINBOW. Patients in both trials had locally advanced or metastatic gastric cancer (including GEJ adenocarcinoma) and had previously received platinum- or fluoropyrimidine-containing chemotherapy. Patients had Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Both trials excluded patients with uncontrolled hypertension, major surgery within 26 days, or patients receiving chronic anti-platelet therapy other than once daily aspirin. REGARD excluded patients with bilirubin ≥1.5 mg/dL and RAINBOW excluded patients with bilirubin >1.5 times the upper limit of normal (ULN).

CYRAMZA Administered as a Single Agent (REGARD)

Patients received either CYRAMZA 8 mg/kg or placebo intravenously every two weeks. Patients randomized to CYRAMZA received a median of 4 doses; the median duration of exposure was 8 weeks and 32 (14% of 236) patients received CYRAMZA for at least six months. The most common serious adverse reactions with CYRAMZA were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients versus 8.7% of patients who received placebo.

The most common adverse reactions (all grades) observed in CYRAMZA-treated patients at a rate of ≥10% and ≥2% higher than placebo were hypertension and diarrhea. Table 1 provides the frequency and severity of adverse reactions (CTCAE, version 4.0) in REGARD.

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>CYRAMZA (N=236)</th>
<th>Placebo (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Grades (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensiona</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 1: Adverse Reactions Occurring in ≥5% of Patients with a ≥2% Difference Between Arms in REGARD

Vascular

Hypertensiona

Diarrhea

Headache

Metabolism and Nutrition

Hyponatremia

a Hypertension is a consolidated term.

Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients in REGARD were neutropenia (4.7%), epistaxis (4.7%), rash (4.2%), intestinal obstruction (2.1%), and arterial thromboembolic events (1.7%).

Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including Grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and IRR. In REGARD, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria versus 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in REGARD was 0.8% and the rate of IRR was 0.4%.

CYRAMZA Administered in Combination with Paclitaxel (RAINBOW)

Patients received paclitaxel 80 mg/m² on Days 1, 8, and 15 of each 28-day cycle with either CYRAMZA 8 mg/kg or placebo intravenously every two weeks. Patients randomized to CYRAMZA received a median of 9 doses; the median duration of exposure was 18 weeks, and 93 (28% of 327) patients received CYRAMZA for at least six months.

The most common serious adverse reactions in patients who received CYRAMZA with paclitaxel were neutropenia (3.7%) and febrile neutropenia (2.4%). 19% of patients who received CYRAMZA with paclitaxel received granulocyte colony-stimulating factors. Adverse reactions resulting in discontinuation of any component of the CYRAMZA with paclitaxel combination in ≥2% of patients in RAINBOW were neutropenia (4%) and thrombocytopenia (5%). The most common adverse reactions (all grades) observed...
in patients who received CYRAMZA with paclitaxel at a rate of ≥30% and ≥2% higher than placebo with paclitaxel were fatigue/asthenia, neutropenia, diarrhea, and epistaxis. Table 2 provides the frequency and severity of adverse reactions (CTCAE, version 4.0) in RAINBOW.

Table 2: Adverse Reactions Occurring in >5% of Patients with a ≥2% Difference Between Arms in RAINBOW

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>CYRAMZA with Paclitaxel (N=327)</th>
<th>Placebo with Paclitaxel (N=329)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>≥ Grade 3 (%)</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/Asthenia</td>
<td>57 (18%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>25 (8%)</td>
<td>2 (0%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>54 (17%)</td>
<td>41 (13%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>31 (10%)</td>
<td>19 (6%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13 (4%)</td>
<td>2 (0%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32 (10%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>20 (6%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Gastrointestinal bleed</td>
<td>10 (3%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>31 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (8%)</td>
<td>15 (5%)</td>
</tr>
<tr>
<td>Renal and Urinary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>17 (5%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>11 (3%)</td>
<td>1 (0%)</td>
</tr>
</tbody>
</table>

* Neutropenia, gastrointestinal hemorrhage events, hypertension, proteinuria, and hypoalbuminemia are consolidated terms.
* Includes 1 fatal event in the CYRAMZA arm.

Clinically relevant adverse reactions reported in ≥1% and <5% of patients receiving CYRAMZA with paclitaxel were sepsis (3.1%), including 5 fatal events, and gastrointestinal perforations (1.2%).

**Immunogenicity**

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to CYRAMZA with the incidences of antibodies to other products may be misleading.

In clinical trials, 86/2880 (3%) of CYRAMZA-treated patients tested positive for treatment-emergent anti-ramucirumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in 14 of the 86 patients who tested positive for treatment-emergent anti-ramucirumab antibodies.

**Postmarketing Experience**

The following adverse reactions have been identified during postapproval use of CYRAMZA. Because such reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- **Blood and lymphatic system:** Thrombotic microangiopathy
- **Neoplasms benign, malignant and unspecified:** Hemangioma
- **Hematology:** Hemangioma, Neoplasms benign, malignant and unspecified.
- **Thrombotic microangiopathy**
- **Hypersensitivity**
- **Drug interstitial lung disease**

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to a pregnant woman. There are no available data on CYRAMZA use in pregnant women. Animal models link angiogenesis, VEGF and VEGFR2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise a pregnant woman of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

**Data**

Animal Data

No animal studies have been specifically conducted to evaluate the effect of ramucirumab on reproduction and fetal development. In mice, loss of the VEGFR2 gene resulted in embryofetal death and these fetuses lacked organized blood vessels and blood islands in the yolk sac. In other models, VEGFR2 signaling was associated with development and maintenance of endometrial and placental vascular function, successful blastocyst implantation, maternal and fetal-placental vascular differentiation, and development during early pregnancy in rodents and non-human primates. Disruption of VEGF signaling has also been associated with developmental anomalies including poor development of the cranial region, forelimbs, forebrain, heart, and blood vessels.

**Lactation**

**Risk Summary**

There is no information on the presence of ramucirumab in human milk or its effects on the breastfed child or on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential risk for serious adverse reactions in breastfed children from ramucirumab, advise women not to breastfeed during treatment with CYRAMZA and for 2 months after the last dose.

**Females and Males of Reproductive Potential**

**Pregnancy Testing**

Verify the pregnancy status of females of reproductive potential prior to initiating.

**Contraception**

Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to a pregnant woman.

**Females**

Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for 3 months after the last dose.

**Infertility**

**Females**

Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

**Pediatric Use**

The safety and effectiveness of CYRAMZA in pediatric patients have not been established.

**Juvenile Animal Toxicity Data**

In animal studies, effects on epiphyseal growth plates were identified. In cynomolgus monkeys, anatomical pathology revealed adverse effects on the epiphyseal growth plate (thickening and osteochondropathy) at all doses tested (5-50 mg/kg). Ramucirumab exposure at the lowest weekly dose tested in the cynomolgus monkey was 0.2 times the exposure in humans at the recommended dose of ramucirumab as a single agent.

**Geriatric Use**

Of the 563 CYRAMZA-treated patients in REGARD and RAINBOW, 205 (36%) were 65 and over, while 41 (7%) were 75 and over. Overall, no differences in safety or effectiveness were observed between these subjects and younger subjects.

Of the 1253 patients in REVEL, 455 (36%) were 65 and over and 84 (7%) were 75 and over. Of the 627 patients who received CYRAMZA with docetaxel in REVEL, 237 (38%) were 65 and over, while 45 (7%) were 75 and over. In an exploratory subgroup analysis of REVEL, the hazard ratio for overall survival in patients less than 65 years old was 0.74 (95% CI: 0.62, 0.87) and in patients 65 years and over was 1.10 (95% CI: 0.89, 1.36).

Of the 529 patients who received CYRAMZA with FOLFIRI in RAISE, 209 (40%) were 65 and over, while 51 (10%) were 75 and over. Overall, no differences in safety or effectiveness were observed between these subjects and younger subjects.

Of the 197 patients who received CYRAMZA in REACH-2, 95 (48%) were 65 years and over, while 37 (19%) were 75 years and over. Overall, no differences in efficacy were observed between these subjects and younger subjects.

**Hepatic Impairment**

No dose adjustment is recommended for patients with mild (total bilirubin within ULN and aspartate aminotransferase (AST) >ULN or total bilirubin >1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment. Clinical deterioration was reported in patients with Child-Pugh B or C cirrhosis who received single agent CYRAMZA.

**Additional information can be found at www.cyramza.com**

**Lilly**

Eli Lilly and Company, Indianapolis, IN 46285, USA

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RB-G HCP BS 18NOV2019
MRD in Acute Lymphoblastic Leukemia: Why, How, When, and Whom to Test?

by CHRISTINA T. LOGUIDICE

ADVANCEMENTS IN THE TREATMENT

landscape for adult patients with acute lymphoblastic leukemia (ALL) has led to improved rates of complete remission at some point during their treatment course. But although 80% to 90% achieve complete remission, 50% of adult patients ultimately experience relapse and have poor outcomes.1 Studies in both adult and pediatric patients with ALL have demonstrated a strong correlation between minimal or measurable residual disease (MRD) and risk for relapse, leading investigators to explore the prognostic significance MRD holds for this patient population.2

Patients with ALL who achieve complete remission can potentially harbor a large number of leukemic cells in the bone marrow below the threshold of detection of conventional morphologic methods and has been shown to be a useful prognostic tool in clinical studies.3,5 “We initially called this minimal residual disease, but people are moving to call this measurable residual disease. I like that term because it reminds me that all the tests we use have levels of detection, and people who are MRD negative can relapse. We know that they still have residual disease there, it’s just too low for our limits of detection,” Litzow said.

There is no consensus on what sensitivity threshold indicates MRD positivity but at least 1 cancer cell in 10,000 normal cells (≥0.01%) is commonly used.4 A 2017 meta-analysis that included 13,637 adult and pediatric patients found MRD status to be a strong indicator of therapeutic benefit, noting “minimal residual disease is a biomarker of disease in the powerful sense that MRD is the disease.”5 Patients who became MRD negative early in the course of treatment had a reduced risk of relapse and were more likely to have longer overall survival. The 10-year

WHY MRD TESTING IS IMPORTANT

The panelists discussed a variety of prognostic factors that need to be taken into consideration when caring for patients with ALL, including demographic, clinical, and biologic/genetic factors, as well as patients’ response to treatment.1,4 “We still need to consider the individual patient…but I think we’re finding that measurable residual disease is replacing some of our traditional risk factors that we’ve relied on in the past,” Litzow said.

MRD refers to the presence of leukemic cells below detectable levels when assessed with conventional morphologic methods and

Mark R. Litzow, MD

Participating in the panel are, from left, Rachel E. Rau, MD; Mark R. Litzow, MD; Jae Park, MD; and Ryan D. Cassaday, MD.

“UPDATE ON MRD TESTING IN ACUTE LYMPHOBLASTIC LEUKEMIA”

MODERATOR

Mark R. Litzow, MD
Professor of Medicine
Head, Acute Leukemia Group
Mayo Clinic
Rochester, MN
Chair, ECOG-ACRIN Leukemia Committee
Philadelphia, PA

PANELISTS

Ryan D. Cassaday, MD
Associate Professor
Division of Hematology
University of Washington School of Medicine
Assistant Professor
Clinical Research Division
Fred Hutchinson Cancer Research Center
Seattle, WA

Jae Park, MD
Associate Attending Physician
Division of Hematologic Oncology
Director, Adult Acute Lymphoblastic Leukemia Division
Memorial Sloan Kettering Cancer Center
New York, NY

Rachel E. Rau, MD
Assistant Professor
Department of Pediatrics
Section of Hematology-Oncology
Baylor College of Medicine
Houston, TX

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Participating in the panel are, from left, Rachel E. Rau, MD; Mark R. Litzow, MD; Jae Park, MD; and Ryan D. Cassaday, MD.
event-free survival for patients who achieved MRD negativity versus those who did not was 64% versus 21% for adult patients and 77% versus 32% for pediatric patients. The value of achieving MRD was consistently observed across therapies, disease subtypes, and MRD assessment methods, time performed, and sensitivity threshold.3

HOW TO ENSURE A HIGH-QUALITY MRD TEST RESULT

MRD testing requires obtaining a high-quality sample from the patient’s bone marrow. The panelists explained that the highest-quality sample comes from the first pull of the marrow aspirate, with a 2-mL or 3-mL sample after the needle is introduced into the bone marrow being ideal. “You don’t want that first pull to be 10 mL and just hemodilut,” panelist Ryan D. Cassaday, MD, said.

Having to undertake subsequent pulls also compromises the MRD result. A 50% reduction in leukemic cells has been observed in samples from second pulls. As the number of pulls increases, there is increasing dilution of leukemic cells. “If there is total dilution of the sample, it is no longer really relevant for testing,” panelist Jae Park, MD, said.

Subsequently, if the oncologist is not the one obtaining the bone marrow aspirate for evaluation, Park recommended discussing the importance of obtaining a good specimen on the first pull with the provider performing the procedure.

Another important consideration the panelists discussed is knowing where the specimen is going to be tested and which test is being used. “The most common tool or method used to measure MRD, at least in the United States, is multiparameter flow cytometry. It’s fast and relatively reliable,” Cassaday said. Flow cytometry differentiates ALL cells from normal leukocytes. However, because of variability in technique, the sample should be assessed at a facility that provides excellent, reference-laboratory quality flow cytometry, such as the type offered by the University of Washington, he noted. “If it’s being run as an in-house assay, it’s worth talking to the pathologists about,” he said, noting it would be important to ask questions about the sensitivity of the assay and how many colors are being used. To detect leukemic cells at a sensitivity threshold of less than 0.01%, at minimum a 6-color flow cytometry needs to be performed.3 “If the level of sensitivity is 0.1% or worse, it’s going to be very hard to be able to utilize the data for MRD-directed therapy because you’re going to be falsely reassured,” he said.

Other standard techniques for MRD testing include polymerase chain reaction (PCR) and next-generation sequencing (NGS), which can detect leukemic cells at a sensitivity threshold of less than \(1 \times 10^{-6} (<0.0001\%)\).3 In Europe they base a lot of their MRD assessments on PCR. It’s a more labor-intensive strategy, but it tends to be more sensitive when done in proper laboratories,” Cassaday said. PCR detects clonal rearrangements in immunoglobulin (Ig) heavy chain genes and/or T-cell receptor (TCR) genes and can detect gene fusions such as BCR-ABL.1 “They worked out a system to standardize and then centralize [MRD assessment] that we just don’t have here in the United States. One exception to that is probably the BCR-ABL quantitative PCR that we can use for Ph [Philadelphia chromosome]-positive patients and a few other examples of fusion oncogenes that we can use for RT-PCR [reverse transcriptase PCR] that are probably more reliably sensitive than most standard flow cytometry,” he said.

NGS is the newest modality being used to assess MRD. Like PCR, it detects clonal rearrangements in Ig heavy chain genes and/or TCR genes.3 “You have to have a [baseline] specimen from the leukemia to be able to identify the sequence, which is not necessarily an assured thing. And it takes a little bit more of a turnaround time,” Cassaday explained. Compared with flow cytometry, which can yield results in less than 1 day, NGS results may take up to a week.4 He also noted that it is not yet clear how NGS can be used to guide treatment decision making in clinical practice but that “it’s certainly an important and potentially useful tool that is hopefully going to become more integrated into clinical trials so we can use it a bit more reliably.”

WHEN AND WHOM TO TEST FOR MRD

According to Litzow, the National Comprehensive Cancer Network (NCCN) guidelines are used to guide MRD testing in adult patients. These guidelines suggest MRD assessment should be undertaken upon completion of the initial induction and then periodically based on regimen and response.2 “The general timing that we do [when] testing for MRD is after induction 1, which is usually the 4-week time point given whatever regimen they used, whether it’s hyper-CVAD 1a [cyclophosphamide, vincristine, doxorubicin, dexmethasone] versus a pediatric or pediatric-inspired regimen, or some of the other regimens,” Park said. “I think that’s a clear time point to get them tested, but you can argue that on the basis of that 4-week MRD, we don’t necessarily make treatment-change decisions at that time, but it identifies our higher-risk patients,” he said.

Park added that follow-up MRD testing is typically performed at the 3-month mark for most patients, regardless of whether they are getting induction 2, consolidation, or another cycle of hyper-CVAD. “The NCCN guidelines loosely use the term induction. After induction, after initial consolidation, some of these regimens have a long consolidation so I personally check every time I do a bone marrow biopsy, the bone marrow aspiration,” he said. He explained that throughout consolidation, he makes recommendations based on the regimen, with testing generally occurring every 2 or 3 months while patients are being treated.

MRD assessments should also be undertaken during maintenance therapy, but Park explained that testing frequency in this setting has also not been well defined for adult patients. “For certain regimens, they have done protocols every 3 months for the first year and every 6 months for the second year, but it all depends. One thing we want to emphasize is this: If it is not induction 1, consolidation, then you stop monitoring them. If they are MRD positive, then you change the management. If they are MRD negative, you want to follow that MRD level to make sure that those are staying negative to, again, optimize the management based on the level,” he said.
Panelist Rachel E. Rau, MD, said that MRD timing is approached slightly differently in pediatric patients. Although the induction period for pediatric regimens is 4 to 5 weeks, the utility of MRD testing at this time point is lineage dependent. “In B-cell ALL, that early time point is highly prognostic. In T-cell ALL, it takes a little longer to clear [leukemic cells] so it doesn’t seem to have the same impact on outcome, and, therefore, a second time point for the patients with T-cell ALL seems to be most critical in terms of clearance and correlation with outcome,” Rau said. She noted in the patients with T-cell ALL, the second time point for MRD testing is generally after 2 months of additional therapy following induction, although it varies by consortium.

Rau noted that several interesting data in the pediatric population indicate that patients with certain genotypes do well even if their MRD shows leukemic cells above the level associated with more favorable outcomes (ie, >0.01). She explained that a study published by investigators at the University of California found that the patients with favorable cytogenetics tended to do well even if their MRD was slightly higher at the end of induction. Two favorable pediatric cytogenetic subsets include patients with hyperdiploidy and those with ETV6-RUNX1 fusions. She noted that when they examined the Children’s Oncology Group data for these patients, they found differences. Patients with hyperdiploidy (ie, double trisomy of chromosomes 4 and 10) and an MRD between 0.1% and 0.01% did fine with standard nonintensified postinduction therapy. In contrast, patients with ETV6-RUNX1 fusions who had an MRD in the same range did not do well unless their postinduction therapy was intensified. “For that small amount of disease, it is worthwhile to intensify or change the therapy that has been previously working or just continue with it? Hopefully, we can address these issues in large trials to really answer them, rather than borrowing the data piece-meal,” Park said.

He noted that patients with T-cell lymphoblastic lymphoma are an exception because they rarely have blood or bone marrow involvement. In these patients, he said, there are no good prognostic tools. “We do PET [positron emission tomography] scan assessment,” he said. Cassady agreed, saying he also uses PET scans in this population at times. “It’s a really challenging population to apply risk-directed therapy and response assessments to. In my experience, fortunately, those patients tend to do pretty well, so transplant is usually not something I’m thinking about for most of those folks, but there is definitely a subset that does not do well and, unfortunately, it’s hard to know who those patients are,” he said.

**REFERENCES**

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