ARTIFICIAL INTELLIGENCE FOR PAYERS

Can AI solve their practical problems and achieve their loftier goals?
The INOmax DS<sub>ir</sub> Plus Delivery Systems provide innovative design and user experience to support the ever-changing demands of the critical care space and keep patient safety a top priority.\(^*\)

- Delivering specialized, redundant, and customizable alarm features designed to help mitigate the risk of device-related rebound pulmonary hypertension
- Advanced features enable delivery of therapy specifically for the MRI suite
- Integration with neonatal transport systems to support seamless delivery of therapy

**Applications**

The INOmax DS<sub>ir</sub> Plus Delivery Systems deliver INOMAX® (nitric oxide) gas, for inhalation. The INOmax DS<sub>ir</sub> Plus Delivery Systems must only be used in accordance with the indications, usage, contraindications, and warnings and precautions described in the INOMAX package inserts and labeling. The approved patient population is limited to neonates. Refer to the INOMAX Full Prescribing Information prior to use.

**Device Warnings**

- Abrupt discontinuation of INOMAX can lead to worsening oxygenation and increasing pulmonary artery pressure (rebound pulmonary hypertension syndrome). To avoid abrupt discontinuation, use the INOblender<sup>*<sup>®</sup> or backup mode immediately to reinstate INOMAX therapy and refer to the INOMAX package insert.
- If the high NO<sub>2</sub> alarm activates, the delivery system should be assessed for proper setup while maintaining INOMAX delivery.
- Do not connect items that are not specified as part of the system.
- If an alarm occurs, safeguard the patient first before troubleshooting or repair procedures.
- Use only INOMAX, pharmaceutical grade NO/N<sub>2</sub>.

**Use in an MR Environment**

- Only use a size “88” (1,963 liters) cylinder that is marked “MR Conditional. Keep cylinder at 100 gauss or less.” with the DS<sub>ir</sub> Plus MRI while in the scanner room. Use of any other cylinder may create a projectile hazard.
- The INOmax DS<sub>ir</sub> Plus MRI is classified as MR Conditional with MR scanners of 1.5 or 3.0 Tesla strength ONLY in areas where the field strength is less than 100 gauss.
- This device contains ferromagnetic components and hence will experience strong attraction close to the magnet. It should be operated at a fringe field of less than 100 gauss.
- A strong magnetic field such as that from an MRI system can affect the ability of the INOMeter to detect if the cylinder valve is open. This can cause a “Cylinder Valve Closed” alarm to occur when the cylinder valve is actually open. If this alarm occurs, reposition/rotate the INOmax DS<sub>ir</sub> Plus MRI cart outside the 100 gauss area to reduce the magnetic interference in the area of the INOMeter until the cylinder handle graphic on the display turns green. This will resolve the “Cylinder Valve Closed” alarm. Typically the required INOmax DS<sub>ir</sub> Plus MRI cart location adjustment is less than 6 inches (15 cm)/90 degrees. Note that interruption of INOMAX therapy will occur one hour from point when the “Cylinder Valve Closed” alarm is activated if the alarm is not resolved.

Rx Only

Consult the Operation and Maintenance Manual, which may be found at www.inomax.com/training-and-education/device-support-resources, for complete information. For technical assistance, call (877) 566-9466.

For additional information, technical assistance, or a complete list of warnings regarding use of validated ventilators, please refer to the INOmax DS<sub>ir</sub> Plus Operation Manual at inomax.com/dsirplusmanual

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\(^*\)No longer in use for commercial application. \(^*\)This may relate to a medical device and software in development that have not yet been cleared by the FDA.

\(^\dagger\)INOmax Total Care is included at no extra cost to contracted INOMAX customers.

**References:**


While you take care of patients, we remain dedicated to helping advance critical care.

Learn how at inomax.com/inomax-delivery-systems/device-innovation
INOMAX® (nitric oxide gas)
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

Treatment of Hypoxic Respiratory Failure
INOmax® is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilator support and other appropriate agents.

CONTRAINDICATIONS
INOmax is contraindicated in neonates dependent on right-to-left shunting of blood.

WARNINGS AND PRECAUTIONS

Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation
Wean from INOmax. Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOmax therapy immediately.

Hypoxemia from Methemoglobinemia
Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of INOmax; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of INOmax to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOmax, additional therapy may be warranted to treat methemoglobinemia.

Airway Injury from Nitrogen Dioxide
Nitrogen dioxide (NO2) forms in gas mixtures containing NO and O2. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.

If there is an unexpected change in NO2 concentration, or if the NO2 concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO2 analyzer should be recalibrated. The dose of INOmax and/or FiO2 should be adjusted as appropriate.

Worsening Heart Failure
Patients with left ventricular dysfunction treated with INOmax may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOmax while providing symptomatic care.

ADVERSE REACTIONS

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 adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Controlled studies have included 325 patients on INOmax doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax, a result adequate to exclude INOmax mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

In CINRGI, the only adverse reaction (>2% higher incidence on INOmax than on placebo) was hypotension (14% vs. 11%).

Based upon post-marketing experience, accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

DRUG INTERACTIONS

Nitric Oxide Donor Agents
Nitric oxide donor agents such as prilocaine, sodium nitroprusside and nitroglycerine may increase the risk of developing methemoglobinemia.

OVERDOSAGE

Overdosage with INOmax is manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO2. Elevated NO2 may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOmax.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

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The potential of artificial intelligence

It seems like not a day goes by without some news about how artificial intelligence (AI) is reshaping the data-drenched world we now live in. Healthcare produces and depends on oceans of data, so it makes sense that AI would have many potential applications in healthcare.

Note, though, the emphasis on potential. We are still in the early days of AI, an incipient phase when enthusiasm and fleet-footed ideas can outpace pedestrian reality. The potential doesn’t get fully realized till reality shakes off its inertia and has had some time to catch up.

Our cover story this issue kicks off a three-part series about AI. We are starting by taking a look at payers and AI. Next month, we’ll examine some of the practical difficulties of implementing AI. In October, we’ll look at some of the more futuristic scenarios.

There is nothing new about computer programs helping people work in healthcare to process and manage huge amounts of data. The intelligence of AI comes in because these systems adjust and adapt as they process data. AI has been compared to a recipe that tinkers with cooking time or adds and subtracts ingredients as it assesses how the dish is turning out.

As we discuss in this issue, payers are interested in AI because it could pick up on patterns that would identify high-cost claims early and head off some expenditures with low-cost medical interventions or timely services that address the social determinants of health. Some of the earliest application of AI on the provider side have been in radiology; for example, research results reported in *JCO Clinical Cancer Informatics* last month showed how machine learning — which is a form of AI — can read CT scans and distinguish between lung lesions caused by small cell lung cancer and lesions from other causes.

Healthcare will always need human beings — their compassion and the hands-on caring. But the innovation of AI can make the system smarter, more efficient and more equitable. The reality just needs to hurry up and catch up with the potential.

Mike Hennessy Sr.
Chairman and Founder of MJH Life Sciences™
Mission Managed Healthcare Executive® provides healthcare executives at health plans and provider organizations with analysis, insights and strategies to pursue value-driven solutions.
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Kindred Hospitals offer valuable partnership for providers and payors alike and take an innovative approach to managed care and customized contracts across various products. Our physician-led acute care helps improve outcomes and guides patients home or to a lower level of care.

Chronically and critically ill patients often need acute care after their stay in an intensive care or medical/surgical unit. While these medically complex patients make up a small part of overall care delivery, it is critical to identify the appropriate care setting for them in order to decrease the risk of costly rehospitalization.
In Brief

Health insurers see utilization bouncing back in 2022

It is rate-setting season for insurers, although the full picture for 2022 premiums won’t emerge for some months yet. But in early July, Sabrina Corlette, J.D., founder and co-director of the Center on Health Insurance Reforms at Georgetown University, got a jump on what insurers might be charging by reviewing early filings for the individual market in Washington, D.C.; Maine; Oregon; Vermont; and Washington. Corlette found a wide range of possible rate requests: from a 0.1% rate decrease by Providence Health Plan in Oregon to a proposed 28.98% increase by Premera Blue Cross in Washington.

Corlette said in a blog post for the center that the filings indicate that insurers expect utilization of healthcare services in 2022 to return to pre-pandemic levels and that some expect even higher use because of pent-up demand. Providence Health Plan, for example, has included a 7.2% “COVID-19 rebound adjustment,” Corlette reported. Insurers also are bracing for costs associated with COVID-19 long haulers and the worsening of chronic conditions because of delayed or canceled care in 2020 and this year (see our story on page 31).

The filings reveal a range of opinions on the effects of the pandemic on claims, according to Corlette’s review. Harvard Pilgrim Health Care in Maine is projecting that vaccine boosters will add 1% to 2022 claims costs, whereas Maine’s Community Health Options sees its COVID-19-related costs as decreasing by 0.5% because vaccination is less expensive than testing.

Medicaid cost of incomplete payment eats into physician reimbursement

One-quarter of Medicaid claims result in a denial of payment for at least one service included in the claim compared with just 7.3% of claims submitted to Medicare and 4.8% of claims submitted to commercial insurers, according to a National Bureau of Economic Research study published in July.

Abe Dunn, Ph.D., the study’s lead author and an economist in the Bureau of Economic Analysis in the Department of Commerce, and his colleagues set out to examine and quantify the “administrative frictions” in claims for medical services. They came up with a statistic they call the cost of incomplete payments (CIP), which comprises foregone revenues when a claim is denied and the costs associated with the back-and-forth of trying to get payment. Their research shows that CIP eats up 17.4% of the contracted fee of a typical Medicaid visit, 5% of a Medicare fee and 2.8% of commercial insurance fee. “These are significant losses — especially for Medicaid, which offers physicians much lower reimbursement rates than other insurers in the first place,” they wrote. Medicaid’s high CIP is, they argue, tantamount to a tax on physician revenues.

Dunn and his co-authors hope their research opens up another avenue to reducing inequality in healthcare. “Without expanding eligibility or raising reimbursement, improving Medicaid claims administration could help make healthcare for low-income Americans more similar to Medicare or employer-sponsored healthcare,” they said.
In Brief

The FDA’s controversial approval of Aduhelm (aducanumab) has put a spotlight on the accelerated approval pathway that the agency used to approve the drug. Devised in the early 1990s to make AIDS treatment drugs available more quickly, accelerated approval has become increasingly common, especially for drugs that treat cancer. The pathway has allowed drugs of questionable clinical value to get on the market, its critics say. Proponents, which include drugmakers, some patient groups and many physicians, say it has worked by and large as intended, speeding up access to needed therapies and spurring drug discovery in the process.

In an opinion piece published in *JAMA Internal Medicine* in July, three experts on drug approvals and costs outlined plans for reforming the accelerated approval process. One of the authors, Aaron Kesselheim, M.D., J.D., M.P.H., voted against approving Aduhelm as a member of an FDA advisory committee and resigned from the committee after the FDA approved the drug.

Kesselheim, a professor at Harvard Medical School; Bishal Gyawali, M.D., Ph.D., an associate professor at Queen’s University in Kingston, Ontario; and Joseph Ross, M.D., M.H.S., a professor at Yale School of Medicine, believe that the use of surrogate markers — usually a lab value or an imaging test result — instead of clinical end points is one of accelerated approval’s problem areas. They say the use of surrogate markers should be curtailed and that confirmatory trials should have clinical end points. Protocols for those confirmatory trials should be finalized as a condition for accelerated approval, they argue, and if a drug fails in a confirmatory trial, withdrawal of the approval that the FDA gave on an accelerated basis should be automatic.

Kesselheim, Gyawali and Ross also believe that the FDA, drugmakers and patient groups should start a public education campaign so patients know that the evidence for drugs approved on an accelerated basis is less certain and that the agency’s OK might be revoked if confirmatory trial results are negative.

Another one of their ideas: CMS and the Department of Veterans Affairs should use their power as payers to rein in spending on drugs that are on the market by virtue of accelerated approval’s lower thresholds. They could limit the prices they pay or exclude the drugs from mandated coverage.

Listen to our podcasts!

Margaret Murray, CEO of the Association for Community Affiliated Plans and a member of the *Managed Healthcare Executive* Editorial Advisory Board, was recently featured on an episode of MHE’s “Meet the Board” podcast series. Murray spoke with MHE Senior Editor Peter Wehrwein and Associate Editor Briana Contreras about her career and her organization and shared her views about the ACA, equity in healthcare and the Biden administration’s healthcare policies.

The “Meet the Board” podcast series spotlights the brand’s board members and shares their views on current healthcare news with listeners. The series is part of MHE’s home podcast “Tuning In to the C-Suite.” Also featured on the podcast is another subseries, “MHE Talks: Improving Patient Access.” You can find “Tuning In to the C-Suite” or other subseries on Apple, Spotify and iHeart Radio podcasts or on the MHE website. Listen in. Learn a lot.

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8/2/21 9:14 AM
Optimal dosing gets a look

FDA approval of Lumakras was contingent on a trial testing lower doses. It could usher in a new era of optimal dosing instead of the maximum tolerated dosing. **by DEBORAH ABRAMS KAPLAN**

The world of oncology treatment may have just course corrected—slightly. The change? The FDA is signaling to pharmaceutical companies a shift from maximum tolerated dosing (MTD) to optimal dosing. What’s at stake for pharmaceutical companies is lower doses that could affect pricing and income. Drug developers may also need to tweak clinical trial designs. For patients, a new framework based on optimal dosing may mean fewer side effects and same efficacy. For payers, there is the prospect of lower drug costs.

The FDA sent a strong signal about optimal dosing in the first half of 2021 when Amgen sought approval for its KRAS inhibitor Lumakras (sotorasib) as therapy for adults with non-small cell lung cancer whose tumors have a KRAS G12C genetic mutation and who have received at least one prior systemic therapy. The FDA granted approval in late May 2021 but required the pharmaceutical company to conduct a post-approval randomized clinical trial comparing the approved dose of 960 mg daily with a 240-mg dose.

Richard Pazdur, M.D., the FDA’s director of the Oncology Center of Excellence, also stated during Stat’s recap of the 2021 meeting of the American Society of Clinical Oncology that the agency wants other pharmaceutical companies to conduct randomized phase 2 trials such as this prior to registration studies. The goal would be for phase 1 trials to identify the range of doses to study in later trials, instead of just identifying the MTD. This move toward closer study of dosing is a win for the Optimal Cancer Care Alliance (OCCA), which has been pushing for several years for the medical community to find ways to avoid relying only on the MTD as a dosing strategy. Optimal dosing used to be called interventional pharmacoeconomics, explains Mark Ratain, M.D., OCCA treasurer and director of the Center for Personalized Therapeutics at the University of Chicago. The group has been pushing stakeholders to develop new oncology dosing regimens. The strategies include lowering dosing, less frequent dosing, shortening the duration of treatment and, in some cases, substituting one therapy for another.

The oncology community has been slow to accept the optimal dosing concept. Clinicians prefer to adhere to the prescribing guidelines, according to Ratain.

"Oncologists believe in the dogma that more is better," Ratain says. "The FDA finally said more is not better."

Although the post-approval dosing trial for Lumakras was a new mandate, there are other obvious candidates for testing lower doses, Ratain says. Those include Opdivo (nivolumab), Keytruda (pembrolizumab), Imbruvica (ibrutinib) and Tecentriq (atezolizumab), for which, Ratain says, "doses are excessive."

Challenges exist for lowering doses in a manner supported by data from trials. The biggest issue involves paying for the trials. "Pharma certainly is not going to fund them," Ratain says. "The NIH (National Institutes of Health) has not shown any interest in funding these trials. The people interested in developing new drug treatments aren’t interested." But NIH would be a reasonable funder, Ratain says. Research of this kind has been funded by the United Kingdom’s National Health Service. Ratain says the trials would pay for themselves because of the savings in drug costs, which would benefit payers and healthcare systems such as Kaiser Permanente.

Deborah Abrams Kaplan writes about medical and practice management topics.
ENHERTU monotherapy: the antibody-drug conjugate with demonstrated durable response\textsuperscript{1,2}

\begin{tabular}{|c|c|c|}
\hline
\textbf{60.3\% ORR} & \textbf{14.8-month mDOR} & \textbf{16.4-month mPFS} \\
\hline
(n=111/184; 95\% CI: 52.9, 67.4) = 4.3\% CR (n=8) + 56.0\% PR (n=103)\textsuperscript{a} & (n=111; 95\% CI: 13.8, 16.9)\textsuperscript{b} & (N=184; 95\% CI: 12.7, NR)\textsuperscript{c} \\
\hline
\end{tabular}

ENHERTU received accelerated approval from FDA based on tumor response rate and duration of response. FDA has not reviewed the PFS and OS data. Multiple confirmatory Phase 3 studies are underway.\textsuperscript{3}

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 primary endpoint was confirmed ORR assessed by ICR using RECIST v1.1. Secondary endpoints included OS, DOR, PFS, CBR, DCR, and best percent change from baseline in sum of diameters of target lesions by ICR.\textsuperscript{1,2}

\textsuperscript{a}ORR (CR+PR) in ITT population. \textsuperscript{b}DOR based on a median duration of follow-up of 11.1 months. Median DOR based on Kaplan-Meier estimate. \textsuperscript{c}Based upon median duration of follow-up of 11.1 months at data cutoff date of August 1, 2019.\textsuperscript{2}

Median overall survival was not reached in DESTINY-Breast01 at median follow-up of 11.1 months, data cutoff August 1, 2019\textsuperscript{2}

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.

\textbf{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.

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; ICR, independent central review; ITT, intent-to-treat; IV, intravenous; mBC, metastatic breast cancer; mDOR, median duration of response; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

\textbf{Please see additional Important Safety Information and a Brief Summary of full Prescribing Information, including Boxed WARNINGS, on following pages.}
**Median PFS of 16.4 months demonstrated in DESTINY-Breast01 with ENHERTU\(^2\)**

Probability of PFS for patients with HER2+ unresectable or mBC receiving ENHERTU 5.4 mg/kg (N=184)\(^1,2,a\)

![Graph showing median PFS](image)

**Learn more at ENHERTUhcp.com/breast**

**Important Safety Information (cont’d)**

**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 5.4 mg/kg, 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/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate systemic corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks.

\(^a\)Of the 184 patients, 48 had progressive disease and 10 had died by 20 months; data for 126 patients were censored, as indicated by tick marks. Disease progression was assessed using modified RECIST v1.1. Dashed lines indicate the 95% CI. Based upon median duration of follow-up of 11.1 months at data cutoff date of August 1, 2019.\(^2\)

**Contraindications**

- ENHERTU received accelerated approval from FDA based on tumor response rate and duration of response. FDA has not reviewed the PFS and OS data. Multiple confirmatory Phase 3 studies are underway.\(^3\)

**References:**


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### Important Safety Information

#### Indication
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- 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

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**Neutropenia**
Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 62% of patients. Sixteen percent had Grade 3 or 4 decrease in neutrophil count. Median time to first onset of decreased neutrophil count was 23 days (range: 6 to 547). 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. 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. 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. 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.

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Probability of PFS for patients with HER2+ unresectable or mBC receiving Median PFS of 16.4 months demonstrated in Boxed WARNINGS, on following pages.

Please see additional Important Safety Information and a
Important Safety Information (cont’d)

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.

Additional Dose Modifications
Thrombocytopenia
For Grade 3 thrombocytopenia (platelets <50 to 25 x 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose. For Grade 4 thrombocytopenia (platelets <25 x 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less. Reduce dose by one level.

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, nausea, 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 ≥20% adverse reactions, including laboratory abnormalities, were nausea (79%), white blood cell count decreased (70%), hemoglobin decreased (70%), neutrophil count decreased (62%), fatigue (59%), vomiting (47%), alopecia (46%), aspartate aminotransferase increased (41%), alanine aminotransferase increased (38%), platelet count decreased (37%), constipation (35%), decreased appetite (32%), anemia (31%), diarrhea (29%), hypokalemia (26%), and cough (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, including Boxed WARNINGS, on following pages.
Additional Dose Modifications of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose.

**Important Safety Information (cont’d)**

1. **Hepatic Impairment:**
   - Data are available from clinical trials of ENHERTU in patients with impaired liver function (Child-Pugh A or B). Use ENHERTU with caution in patients with impaired liver function, and consider the concomitant use of ENHERTU with another antitumor therapy with a known association with hepatic toxicity.

2. **Geriatric Use:**
   - Advise patients aged 65 years or older to use ENHERTU with caution. Age-related decreases in renal function may increase the risk of adverse reactions in patients with impaired renal function.

**Use in Specific Populations** (8.1, 8.3)

**Adverse Reactions**

The following adverse reactions are included in the labeling:

- **Interstitial Lung Disease/ Pneumonitis**
- **Neutropenia**
- **Left Ventricular Dysfunction**

**6 Adverse Reactions**

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

- **Interstitial Lung Disease/ Pneumonitis**
- **Neutropenia**
- **Left Ventricular Dysfunction**

**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.

**Metastatic Breast Cancer**

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) [see Clinical Studies (14.1) in the full prescribing information]. 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 (44%). Patients had an Eastern Cooperative Oncology Group 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.

Grade 3 or 4 decrease in neutrophil count. Median time to first onset of decreased neutrophil count was 23 days (range: 6 to 547). Febrile neutropenia was reported in 1.7% of patients.

Locally Advanced or Metastatic Gastric Cancer

In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, a decrease in neutrophil count was reported in 72% of patients. Fifty-one percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 16 days (range: 4 to 187). Febrile neutropenia was reported in 4.8% of patients.

**5.3 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. In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF.

Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 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 less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF) [see Dosage and Administration (2.3) in the full prescribing information].

**5.4 Embryo-Fetal Toxicity**

Based on its mechanism of action, ENHERTU can cause fetal harm when administered to a pregnant woman. 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. Based on its mechanism of action, the topoisomerase inhibitor component of ENHERTU, DXd, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells [see 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)].
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, 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 (>20%) adverse reactions, including laboratory abnormalities, were nausea, white blood cell count decreased, hemoglobin decreased, neutrophil count decreased, fatigue, vomiting, alopecia, anemia, thrombocytopenia, leukopenia, upper respiratory tract infection, 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 (>20%) adverse reactions, including laboratory abnormalities, were nausea, white blood cell count decreased, hemoglobin decreased, neutrophil count decreased, fatigue, vomiting, alopecia, aspartate aminotransferase increased, alanine aminotransferase increased, platelet count decreased, constipation, decreased appetite, anemia, diarrhea, hypokalemia, and cough.

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-Gastric01 and Study DS8201-A-J101

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ENHERTU 5.4 mg/kg</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N=234</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>79</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>7</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>14</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>59</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>46</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>32</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>31</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>20</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Intestinal lung disease@</td>
<td>9</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infections and Infestation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection†</td>
<td>15</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>11</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

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

Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

- a Grouped term of abdominal pain includes PTs of abdominal discomfort, gastrointestinal pain, abdominal pain lower, and abdominal pain upper.
- b Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosa blistering. One Grade 1 event of aphthous ulcer was not included in the summary of grouped term stomatitis (from DESTINY-Breast01).
- c Grouped term of fatigue includes PTs of fatigue and asthenia.
- d This Grade 3 event was reported by the investigator. Per NCI CTCAE v.4.03, the highest NCI CTCAE grade for alopecia is Grade 2.
- e Grouped term of rash includes PTs of rash, rash pustular, and rash maculo-papular.
- f Grouped term of anemia includes PTs of anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased.
- g Intestinal lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.
- h All events had fatal outcomes (n=6).
- i Grouped term of headache includes PTs of headache, sinus headache, and migraine.
- j Grouped term of upper respiratory tract infection includes PTs of influenza, influenza-like illness, and upper respiratory tract infection.
- k This Grade 4 event was reported by the investigator. Per NCI CTCAE v.4.03, the highest NCI CTCAE grade for dry eye is Grade 3.

Other clinically relevant adverse reactions reported in less than 10% of patients were:
- Injury, Poisoning and Procedural Complications: infusion-related reactions (2.6%)”
- Blood and Lymphatic System Disorders: febrile neutropenia (1.7%)

### Table 4: Selected Laboratory Abnormalities 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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
</tr>
<tr>
<td></td>
<td>N=234</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>70</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>70</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>62</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>37</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>41</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>38</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>26</td>
</tr>
</tbody>
</table>

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

Frequencies were based on NCI CTCAE v.4.03 grade-derived laboratory abnormalities.

Locally Advanced or Metastatic Gastric Cancer

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01 [see Clinical Studies (14.2) in the full prescribing information]. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg once every three weeks or either irinotecan (N=55) 150 mg/m² biweekly or paclitaxel (N=72) 80 mg/m² weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) in the ENHERTU group and 2.8 months (range: 0.5 to 13.1) in the irinotecan/paclitaxel group.

Serious adverse reactions occurred in 44% of patients receiving ENHERTU 6.4 mg/kg. Serious adverse reactions in >2% of patients who received ENHERTU were decreased appetite, ILD, anemia, dehydration, pneumonia, cholestatic jaundice, pyrexia, and tumor hemorrhage. Fatalities due to adverse reactions occurred in 2.4% of patients: disseminated intravascular coagulation, large intestine perforation, and pneumonia occurred in one patient each (0.8%).

ENHERTU was permanently discontinued in 15% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 62% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia, ILD, pneumonia, lymphopenia, upper respiratory tract infection, diarrhea, and hypokalemia. Dose reductions occurred in 32% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia.

The most common (>20%) adverse reactions, including laboratory abnormalities, were hemoglobin decreased, white blood cell decreased, neutrophil count decreased, lymphocyte count decreased, platelet count
decreased, nausea, decreased appetite, anemia, aspartate aminotransferase increased, fatigue, blood alkaline phosphatase increased, alanine aminotransferase increased, diarrhea, hypokalemia, vomiting, constipation, blood bilirubin increased, pyrexia, and alopecia.

Tables 5 and 6 summarize adverse reactions and laboratory abnormalities observed in patients receiving ENHERTU 6.4 mg/kg in DESTINY-Gastric01.

Table 5: Adverse Reactions in ≥10% All Grades or ≥2% Grades 3 or 4 of Patients Receiving ENHERTU in DESTINY-Gastric01

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>ENHERTU 6.4 mg/kg N=125</th>
<th>Irinotecan or Paclitaxel N=62</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3 or 4 %</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>63</td>
<td>4.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>2.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal paina</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td>Stomatitisb</td>
<td>11</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>60</td>
<td>17</td>
</tr>
<tr>
<td>dehydration</td>
<td>6</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemiaa</td>
<td>58</td>
<td>38</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4.8</td>
<td>4.8</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatiguec</td>
<td>55</td>
<td>9</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal lung diseasec</td>
<td>10</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic function abnormal</td>
<td>8</td>
<td>3.2</td>
</tr>
</tbody>
</table>

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

Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

a Grouped term of abdominal pain includes PTs of abdominal discomfort, gastrointestinal pain, abdominal pain, abdominal pain lower, and abdominal pain upper.

b Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosal blisters.

c Grouped term of anemia includes PTs of anemia, hemoglobin decreased, and hematocrit decreased.

d Grouped term of fatigue includes PTs of fatigue, asthenia, and malaise.

e Intestinal lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.

Other clinically relevant adverse reactions reported in less than 10% of patients were:
- **Cardiac Disorders:** asymptomatic left ventricular ejection fraction decrease (8%) [see Warnings and Precautions (5.3)]
- **Infections and Infestations:** pneumonia (6%)
- **Injury, Poisoning and Procedural Complications:** infusion-related reactions (1.6%)

Table 6: Selected Laboratory Abnormalities Occurring in Patients Receiving ENHERTU in DESTINY-Gastric01

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>ENHERTU 6.4 mg/kg N=125</th>
<th>Irinotecan or Paclitaxel N=62</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemoglobin decreased</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>White blood cell count decreased</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Neutrophil count decreased</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Lymphocyte count decreased</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Platelet count decreased</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspartate aminotransferase increased</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Blood alkaline phosphatase increased</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Alanine aminotransferase increased</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Blood bilirubin increased</td>
<td>24</td>
</tr>
</tbody>
</table>

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

Frequencies were based on NCI CTCAE v.4.03 grade-derived laboratory abnormalities.

6.2 Immunogenicity

As with all therapeutic proteins, there is a 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, comparisons of the incidence of antibodies to ENHERTU in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Treatment-induced anti-fam-trastuzumab deruxtecan-nxki antibodies (ADA) developed in 1.7% (14/807) patients who received ENHERTU across all doses. Due to the limited number of patients who tested positive for ADA, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety. 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 topoisoerase inhibitor component of ENHERTU, DXd, can also cause embryo-fetal death when administered to a pregnant woman because it is genotoxic and targets actively dividing cells [see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) and 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.

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%).

Of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were 65 years or older and 14% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.

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].

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 (2.3) 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 if 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)].
Industry Analysis

Investors pouring billions into digital health ventures

The first half of 2021 saw 372 deals averaging $39.6 million, which is already more than the total value of the deals done in all of 2020. by SUSAN LADIKA

With the COVID-19 pandemic pushing consumers into a new virtual healthcare reality, investors are pouring money into the digital health space like never before. Investment during the first half of the year already has topped the total for all of 2020.

More than $14.7 billion flowed into the digital health sector between January and June 2021, compared with $14.6 billion for the entire calendar year of 2020, according to a report by Rock Health, a venture fund that focuses on digital health. And 2020 was already at a record high for digital health investment. "I don’t think a lot of investors expected to double the pace of last year," says Bill Evans, CEO and managing director of Rock Health.

In the first six months of 2021 there were 372 deals that averaged $39.6 million. In all of 2020, there were 460 deals, and the average size was $31.7 million, according to the Rock Health report.

Investment in digital health began about a decade ago, Evans says. Small startups with a limited amount of investment have grown to become “mature companies in a position to attract large, late-stage funding rounds,” he says.

Investment dollars are coming from the private market, public market, companies seeking acquisition targets, and special acquisition company (SPAC) trusts, according to the Rock Health report. The main categories attracting investment so far this year were research and development, which drew $2.7 billion for the first half of the year; on-demand healthcare, which pulled in $2.6 billion; and fitness and wellness, which gained $2 billion.

Mental health was the top clinical indication drawing investment, attracting $1.5 billion, and companies dealing with cardiovascular disease drew $1.1 billion. Digital health also has seen an increase in funding for startups designed to help people manage substance use disorders.

A report by the consultancy McKinsey & Company documented the much-discussed surge in telehealth because of the COVID-19 pandemic. Overall telehealth utilization for office visits and outpatient care was 78 times higher in April 2020 than in February of that year, according to the report.

Usage has since stabilized as more people are returning to in-person care. As of April, telehealth accounted for approximately 15% of utilization across all specialties.

But it was particularly in demand in the behavioral health field, accounting for 50% of utilization for psychiatry and 30% for substance use treatment. The question now for telehealth is whether the loosened restrictions by payers will continue if the pandemic ebbs and the federal government ends the public health emergency that dates back to January 27, 2020. Rock Health found that an increasing share of investment funding is flowing to direct-to-consumer digital health companies. The largest deals so far this year include Noom, which markets weight-loss services; Ro, a telehealth company that also provides pharmacy services; and Capsule, a digital pharmacy. Noom received $540 million in investment; Ro, $500 million; and Capsule, $300 million.

The large number of mergers and acquisitions is another indication of the vitality of the digital health sector. The first half of the year saw 131 mergers and acquisitions compared with 145 for all of last year, according to Rock Health.

Small startups have grown to become “mature companies in a position to attract large, late-stage funding rounds.”

— BILL EVANS, ROCK HEALTH

Susan Ladika, an independent journalist in Tampa, Florida, covers business and healthcare.
The term “artificial intelligence,” or “AI,” conjures up different images for different people. Some think of older breakthroughs such as world chess champion Garry Kasparov losing in 1997 to IBM’s Deep Blue supercomputer. For others, it is the Netflix or YouTube algorithm whirring along in the background and offering suggestions of what to watch based on what you’ve viewed.

It’s difficult to grasp the pervasiveness and exponential growth capabilities of machine-learning algorithms. In the healthcare sector, programmers are working on advances that will improve patients’ well-being and insurers’ bottom line at the same time.

Some improvements may seem mundane, such as automating claims processing or using chatbots (virtual agents) to handle interactions with policyholders. Yet the financial opportunities for health insurers are far from humdrum. A 2018 Accenture analysis estimated insurers can save $7 billion in 18 months by using AI to automate core administrative functions — the equivalent of $1.5 million in operating income for every 100 full-time employees. And those figures don’t even account for the ability to flag potential instances of fraud.

Then there are the future possibilities of AI, such as orchestrating a seamless patient experience — from selecting specialists within an insurer’s network to prescribing of drugs upon discharge.

At Blue Health Intelligence (BHI), which provides clinical data expertise for Blues plans around the United States, programmers attacked the problem of high-cost claimants, defined as members having annual costs surpassing $250,000. This group comprises fewer than 2 in 1,000 of all claimants but it accounts for 9% of all healthcare costs.

Such patients tend to have rare and/or chronic diseases that involve frequent trips to the emergency department, expensive medications, and high-cost specialty care and testing. If an insurer can identify these patients...
early and intervene before their health worsens and healthcare costs spiral out of control, both patients and payers win, says Roxanna Cross, associate vice president for product management at BHI. “And it’s a perfect problem to be solved with AI,” Cross says.

How so? The calculations are so complex that human beings could never hope to tackle them through traditional methods, but computer programs analyzing massive data sets can. BHI used health insurance claims from 48 million patients, augmented it with U.S. census data, and identified 6,000 variables across clinical and demographic categories. It then applied machine learning to use the information to train models to identify high-cost claimants. The best model was so powerful that it succeeded even for patients with large gaps in their data history, including no prior information on high-cost claims, less than a full year of insurance enrollment and no data on pharmacy claims.

With such information, insurers can reach out to patients and physicians, collaborating to personalize care for those who might have obstacles such as gaps in care, limited mobility due to stroke, or not enough money for prescriptions, Cross says.

“When we have applied these models, we certainly have seen millions of dollars in potential cost savings for a relatively small cohort of patients.”

— ROXANNA CROSS, ASSOCIATE VICE PRESIDENT FOR PRODUCT MANAGEMENT AT BHI

Health. Anthem already had invested tens of millions of dollars in K Health’s AI technology to create an app that helped users understand how doctors diagnosed cases in patients with similar symptoms in the past.

With K Health, the symptom checker is free, but patients also can chat with a doctor for less than a typical copay after answering basic questions about their medical background that are relayed to the physician, says Allon Bloch, a co-founder of K Health who will be the joint venture’s CEO.

“To give you a sense, a retail visit on K Health is $19,” Bloch says. “If you went to a doctor, assuming you’re insured, you’ll pay a copay of $25 to $40; your insurer will pay another $100. People go to a doctor about four times a year. Additionally, a lot of people go to the (emergency room) because their doctor is not available. So what do you do on the weekend? What do you do at night? What do you do if your doctor can’t see you in the next 24 hours? We all deserve a system where it should be 24/7, it should be intelligent, it should be proactive, it should be easy.”

The drive to use AI is moving ahead at breakneck speed. A 2018 Accenture survey of global healthcare executives found 72% of health leaders were piloting or planning AI adoption, 93% said AI projects were on their agenda, only 7% said they were minimally or not at all focused on it.

Claims management improvements are ramping up but not without difficulty, according to a McKinsey & Company report from 2017. If original claims coming from hospitals...
aren’t digitized, there is no way to extract the data. Additionally, structured procedures need to be in place for reviewing claims and deciding when human intervention is required. Also necessary is a structured digitization of results and interventions, ideally including more than two years’ worth of data. Insurers falling short of those requirements are not ready for the leap.

AI can simplify many manual and paper-based processes in the offices of both physicians and insurance companies by utilizing natural language processing, allowing healthcare professionals to input information just by talking, says Mahi Rayasam, Ph.D., partner and leader of healthcare analytics at McKinsey. Such improvement can result in significant cost savings, but it can bring other changes, too. “Essentially, how can physicians be more patient facing and not paper facing?” Rayasam says. “Most of the processes that happen in the insurance industry or in the physicians’ offices in large hospitals — there’s still a lot of paper.”

Using AI to detect and prevent fraud is another way health insurers, as well as the federal government, can save money. In 2016, CMS built the Fraud Prevention System, using advanced analytics to identify, prevent and stop payments that match suspicious patterns. The system helped CMS prevent $527 million in losses to fraud in fiscal year 2016, according to a McKinsey report. In 2020, 56% of insurers surveyed by the Coalition Against Insurance Fraud indicated their company was using AI for fraud detection.

AI also can deliver improved interconnectivity among insurance companies, providers and members. Rayasam says AI could speed up the cumbersome process of patients obtaining prior authorizations, and physicians and patients could get updates on an authorization request through an app instead of a series of phone calls.

Rayasam foresees AI-supported scenarios that will improve the patient experience from start to finish. He gave as a hypothetical example his 1-year-old son having a medical emergency late on a Saturday night.

“What if there was an app that knows the situation I’m in and then recommends four or five locations close to me that are either physicians’ offices or urgent care centers, or emergency departments with no wait time?” Rayasam asks. “And it combines that information with the insurance plan that I have and then tells me if I go to location X, not only will I be able to be seen immediately but it will also cost me less from an out-of-pocket standpoint. And then it links to the doctor, who prescribes a medication. Perhaps the app then would be able to connect me to the pharmacy, and the drug is delivered automatically. Then the claim is adjudicated and the payment is made from my cash account.

“That’s kind of like end-to-end flow, where the technology is enabling a member to take care of their needs right from when they start thinking about it and to close the circle in terms of payments and claims. Today you have to do it in 10 separate transactions. Could you do it through one seamless way? That’s where things are moving.”

AI might also be a way to address healthcare equity issues. For example, two patients of the same age with heart disease and diabetes might both be identified as high-end utilizers of medical care, BHI’s Cross notes. However, claims data might identify someone from a low-income community with a history of lower claims costs. Reasons for those lower costs might include not seeing a doctor due to lack of funds, barriers to transportation or child care issues. In such cases, adjustments can be built into the algorithm to equalize their data.

Telehealth also will figure into cost estimates, Cross says. “I think AI can really help inform individuals who would benefit most from certain interventions, telehealth being one of those, particularly when we’re talking about behavioral health,” Cross observes. “The whole goal of AI is to help pair the right care at the right time at the right place with these high-risk, high-need individuals or the total population. And to intervene earlier.”

Larry Hanover is a freelance writer in southern New Jersey.
Explore recommendations for treating HER2-positive metastatic breast cancer (MBC) with newer HER2-targeted treatment approaches and considerations regarding their adoption into clinical practice, including a rationale for the use of dual HER2-targeted monoclonal antibody therapy.

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- Dual HER2-Targeted Therapy for MBC
- COVID-19 and the Use of HER2-Targeted Therapy for MBC
A

gle-related macular degeneration (AMD) is a disorder of the eye characterized by vision loss in the central area of the retina, also called the macula. It is the leading cause of blindness, accounting for 50% to 60% of new cases each year. In addition to age, ethnicity, smoking and alcohol consumption, and certain gene polymorphisms can also impact likelihood of AMD.

There are 2 clinical subtypes of AMD: non-neovascular (also called dry or atrophic), which represents a majority of cases, and neovascular AMD, also called wet or exudative, which accounts for 10% to 15% of cases. Although the wet subtype represents the minority of cases, it causes the majority of the severe vision loss from AMD. This article reviews the clinical burden and evolving treatment spectrum for wet AMD.

Clinical burden

The pathophysiology of wet AMD is well characterized; overexpression of VEGF plays a significant role in the abnormal growth of blood vessels in the macula. Neovascularization in the subretinal space is typically from the choroidal circulation, but it can be from the retinal circulation less frequently. Leaks that form in these abnormal blood vessels can result in pools of blood and/or subretinal fluid beneath the retina. The exudation of fluid beneath the retina can cause loss of central vision, and it can result in detachment of the retinal pigment epithelium (RPE).

Presentation. The clinical definition of AMD must include the presentation of at least one of its observable disease characteristics. The primary histological hallmark of AMD is the presence of drusen that are at least intermediate in size, between 63 and 125 µm in diameter. Drusen are localized deposits of extracellular material in lesions at the basement membrane of the RPE, and they can be observed as bright yellow objects on ophthalmoscopy and are visible on a dilated eye examination. Alterations or abnormalities of the RPE are also common clinical manifestations of AMD. This occurs as hypopigmentation or hyperpigmentation, but more extreme forms may include geographic atrophy of the RPE. AMD is also defined with the presence of choroidal neovascularization, which is visible as gray/green discoloration in the macular area. Newly formed neovascularization will leak fluorescein dye during a fluorescein dye retinal angiography. AMD may also present with polypoidal choroidal vasculopathy, reticular pseudodrusen or retinal angiomatous proliferation.

It is important to note that the symptomatic presentations of wet and dry AMD are considerably different. For dry AMD, vision loss presents slowly and gradually, taking months or even years. Patients with dry AMD may notice a gradual decrease in the visual acuity of both eyes or the presence of scotomas. Conversely, wet AMD is associated with a rapid onset of vision loss, often in mere days or weeks. Wet AMD typically appears first in a single eye, but within five years, there is more than a 40% risk that wet AMD will develop in the other eye. One of the earliest signs of wet AMD is metamorphopsia, which occurs when a patient perceives a straight line to be curved. Patients with wet AMD may also notice a scotoma in their central vision.

Comorbidities and disease burden. Because risk of AMD increases with age, it is important to consider the presence of other age-related conditions, especially those affecting the eye. Patients with wet AMD are more likely to have comorbidities — hypertension, hypercholesterolemia, emphysema, chronic obstructive pulmonary disease, atherosclerosis, arthritis and coronary artery disease — even when other patient factors such as age, gender and race have been controlled for. Those with wet AMD are also more likely to have ocular comorbidities such as glaucoma, myopia and cataracts. Depending on their severity, comorbidities can increase morbidity and further complicate the disease burden for patients with AMD.

The disorder can have a significant effect on patients’ quality of life and functional status. Visual impairment associated with AMD can impair the ability to perform activities of daily living and affect patient independence by limiting the ability to drive a vehicle safely, which can worsen challenges associated with healthcare access and treatment adherence. Patients with visual impairment are also more likely to experience falls and associated injuries.
Over 33% of patients with severe vision loss may experience disability.¹

Left untreated, wet AMD can result in substantial disease burden as well as significant economic burden for patients, their loved ones and society.⁴ When wet AMD is detected early, it is possible to initiate prompt treatment that can help minimize or even reverse vision loss.⁴,⁶

**Anti-VEGF treatment**

The primary goal of therapy when treating a patient with wet AMD is the optimization of visual outcomes. However, current approaches to care can be associated with considerable treatment burden, so an additional goal in the management of wet AMD is to minimize treatment burden and improve long-term adherence, which can also reduce healthcare costs.⁴,¹⁰ Therefore, an effective treatment approach achieves a balance of visual outcomes and therapeutic tolerability.

Because the overexpression of VEGF is known to play a significant role in the pathophysiology of wet AMD, the American Academy of Ophthalmology’s preferred practice pattern emphasizes the role of anti-VEGF agents in the front-line setting.⁴,¹⁰ Intravitreal injection of anti-VEGF agents is the most effective approach to managing wet AMD and may reduce the likelihood that a patient becomes legally blind.⁴ Anti-VEGF agents are able to limit the progression of wet AMD by limiting choroidal neovascularization, thereby stabilizing or reversing the loss of visual acuity.⁴ As a class, anti-VEGF agents have demonstrated improved visual and anatomic results compared with prior treatment approaches in AMD.⁴ Treatment with anti-VEGF agents has also been associated with reduced mortality risk, saving an estimated one to two years of life.⁴

The first anti-VEGF to earn FDA approval, in 2004, is the selective VEGF antagonist pegaptanib sodium.⁴,¹³ Since then, newer agents in the class have demonstrated greater efficacy, improved cost effectiveness and less toxicity.⁴,¹³,¹⁵

**Ranibizumab.** A recombinant humanized monoclonal antibody with specificity for VEGF, ranibizumab received FDA approval for the treatment of AMD in 2006.⁴,¹⁵ The MARINA trial demonstrated that patients treated with ranibizumab for two years experienced improved visual acuity and prevention of vision loss, whereas the ANCHOR trial demonstrated low rates of ocular adverse events with ranibizumab compared with verteporfin, a mainstay of treatment prior to the advent of anti-VEGF therapy in AMD.⁴,¹⁵,²⁷

**Aflibercept.** Approved for wet AMD in 2011, aflibercept is a recombinant fusion protein that has an effect similar to that of VEGF inhibitors by competing for VEGF binding.³,¹⁸ Investigators compared aflibercept with ranibizumab directly in the VEGF Trap-Eye randomized controlled trials (VIEW 1 and VIEW 2), and aflibercept demonstrated equivalent efficacy (at 52 weeks, 95.1 to 96.3% of aflibercept patients and 94.4% of ranibizumab patients maintained vision) and safety in patients with wet AMD. However, patients treated with aflibercept received fewer injections (every two months after three initial monthly doses vs monthly ranibizumab), on average.¹⁰,¹⁹,²⁰ Compared with ranibizumab, aflibercept is more cost-effective and requires fewer injections, which can improve the overall management of wet AMD by improving the balance between visual acuity outcomes and treatment burden.¹¹

**Brolucizumab.** In October 2019, the FDA approved brolucizumab as a VEGF-A inhibitor for use in patients with wet AMD.⁴,¹¹,²² Efficacy results from the phase 3 HAWK and HARRIER trials have shown that brolucizumab is noninferior to aflibercept at 48 weeks. However, concern has been raised regarding retinal vasculitis and/or retinal vascular occlusions, typically in the presence of intraocular inflammation.４,¹¹,¹² Research on the cost burden of brolucizumab has not yet been studied, so it is unclear how cost-effective this recent treatment option is compared with other available anti-VEGF therapies.¹³

**Safety considerations and individualizing care**

Because a further goal of treatment for wet AMD is to minimize treatment burden, it is essential to consider the safety profiles of available therapies. Short-term safety profiles of current agents appear comparable; long-term adverse event (AE) data for anti-VEGF therapy, particularly regarding the effect of cardiovascular AEs, are insufficient.¹³,²₂ All anti-VEGF agents carry potential risks for systemic arterial thromboembolic events and increased intraocular pressure, but results from the clinical trials studying these risks have been inconclusive.⁴,⁴⁴ It is also important for clinicians to consider ocular AEs — notably, infectious or noninfectious endophthalmitis, serious uveitis, and increased ocular pressure.⁴ Other common ocular AEs across agents in the anti-VEGF class include eye pain, floaters, punctate keratitis, cataracts, vitreous opacities, anterior chamber inflammation, vision disturbance, corneal edema and ocular discharge.⁷

To address the treatment burden of anti-VEGF agents, clinicians must also consider the cost burden associated
with this class of medications. The cost effectiveness of VEGF inhibitors varies greatly across agents in the class, but studies of the overall cost burden show that they have tended to be highly cost-effective compared with prior therapeutic approaches.4,13

Overall, the treatment of wet AMD involves important considerations for safety and efficacy as well as treatment burden for the patient, their loved ones, and the healthcare system. As such, selecting an anti-VEGF agent should be highly individualized.4 Moreover, a personalized approach to anti-VEGF treatment has saved the U.S. government billions of dollars, which has noteworthy implications for the American public health system.4

**Anti-VEGF dosing intervals**

When selecting a therapeutic approach in wet AMD, it is important to consider how to optimize injection intervals for anti-VEGF therapies. At this time, there is no clear consensus about the best approach to dosing frequency.4,13 The frequency of intravitreal injections of anti-VEGF agents is one of the primary causes of high treatment burden for wet AMD, so it is difficult to maintain an optimal treatment schedule.10 If the intervals between treatments are too long, the patient’s wet AMD may be undertreated, which could lead to suboptimal visual outcomes.9 Conversely, if the treatments are given too frequently, patients can be overtreated, which could lead to increased toxicity and greater treatment burden.6 To maximize clinical benefit and minimize treatment burden, there are currently 3 approaches to scheduling treatment of anti-VEGF therapy: treat-and-observe (T&O), treat-and-extend (T&E), and fixed interval (or monthly/bimonthly) injection.4,11

T&O dosing of anti-VEGF therapy (also called individualized discontinuous treatment or pro re nata/as-needed dosing) is a flexible scheduling strategy that aims to maintain visual acuity gains and reduce treatment burden by individualizing injection frequency based on treatment response as measured by the presence or absence of subretinal and/or intraretinal fluid.4,15 However, improvements in visual acuity seen in the early phase of T&O dose scheduling are not typically sustained unless patients are frequently monitored with strict retreatment criteria.10 In one study on the use of T&O regimens with ranibizumab, the safety and efficacy appear comparable to fixed monthly dosing over a year of treatment; however, long-term follow-up shows that the gains in visual acuity are not maintained.4 Because the long-term efficacy of T&O injection intervals has not yet been studied in other anti-VEGF agents, it is important to consider dosing schedule and treatment burden carefully.4

The T&E approach to anti-VEGF dosing, also called proactive flexible T&E or continuous variable dosing, is a flexible strategy that can be adjusted to patient response as well.10,11 T&E dosing can maximize functional and anatomic benefit for visual acuity while easing treatment burden by first stabilizing the disease and then extending treatment in two-week or four-week intervals based on the presence or absence of neovascular activity or subretinal hemorrhage.10,11 Additionally, the T&E approach to dosing can decrease treatment burden by reducing the total number of injections and clinic visits per year without compromising improvements in visual acuity.5,11,13,14

The ALTAIR trial was an open-label phase 4 study of different treatment dosing regimens for aflibercept in treat-ment-naive patients.10 After three months of fixed schedule dosing, patients were randomized to extended or shortened treatment by two weeks in one arm of the study vs four weeks in the other study arm.10 The primary endpoint of the study was mean change in best-corrected visual acuity (BCVA) from baseline to week 52 of the study. At 52 weeks, the groups showed little difference in functional outcome: The two-week adjustment group gained an average of 9.0 letters on the BCVA test and the four-week adjustment arm gained an average of 8.4 letters.10 However, at week 52, patients in the two-week adjustment group had received a mean of 7.2 total injections with a mean last interval at 10.7 weeks, whereas the two-week adjustment group had received 6.9 total injections, on average, with a mean last interval at 11.8 weeks.10 In total, the ALTAIR study demonstrated that, between a two-week or four-week dosing regimen, visual acuity outcomes were comparable, whereas the overall treatment burden was reduced.10

Finally, a fixed interval dosing schedule of monthly or bimonthly anti-VEGF injections, also called a fixed continuous regimen, is an approach that schedules treatment every four or eight weeks without adjustments for response to treatment.4,10 However, reviews of real-world evidence have found that more flexible dosing regimens like T&O or T&E are better able to maximize clinical benefit and minimize treatment burden, so only a minority of retina specialists currently set a fixed schedule of monthly or bimonthly injections for their patients with wet AMD.4,10,11

**Conclusions**

Although wet AMD is responsible for nearly 10% of total blindness worldwide, several treatment approaches can provide clinical benefit by slowing, halting, or even reversing the progression of vision loss.8 Anti-VEGF agents are the most effective therapy, constitute the first line of treat-
ment and are cost-effective. However, prices of anti-VEGF medications range widely, and clinic visits for injections and follow-up can be frequent. To optimize treatment outcomes, it is essential to select a therapy and dosing strategy that balances both clinical benefit and the burdens of cost and clinical visits. As the treatment spectrum expands in the future and new therapeutic approaches emerge, it will become more vital that providers continue to engage in effective communication and shared decision-making to meet the complex needs of patients with wet AMD.

REFERENCES


A WAY IN WITH TRODELVY

TRODELVY attacks tumors with an antibody-drug conjugate (ADC) that binds to Trop-2.1

Based on preclinical data. May not correlate with clinical outcomes.

INDICATIONS
TRODELVY® (sacituzumab govitecan-hziy) is a Trop-2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with:
• Unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.
• Locally advanced or metastatic urothelial cancer (mUC) who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor. 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 confirmatory trials.

IMPORTANT SAFETY INFORMATION
BOXED WARNING: NEUTROPENIA AND DIARRHEA
• Severe or life-threatening neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay.
• Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. Administer atropine, if not contraindicated, for early diarrhea of any severity. At the onset of late diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤Grade 1 and reduce subsequent doses.

CONTRAINDICATIONS
• Severe hypersensitivity reaction to TRODELVY.

WARNINGS AND PRECAUTIONS
Neutropenia: Severe, life-threatening, or fatal neutropenia can occur and may require dose modification. Neutropenia occurred in 61% of patients treated with TRODELVY. Grade 3-4 neutropenia occurred in 47% of patients. Febrile neutropenia occurred in 7%. Withhold TRODELVY for absolute neutrophil count below 1500/mm³ on Day 1 of any cycle or neutrophil count below 1000/mm³ on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever.

Diarrhea: Diarrhea occurred in 65% of all patients treated with TRODELVY. Grade 3-4 diarrhea occurred in 12% of patients. One patient had intestinal perforation following diarrhea. Neutropenic colitis occurred in 0.5% of patients. Withhold TRODELVY for Grade 3-4 diarrhea and resume when resolved to ≤Grade 1. At onset, evaluate for infectious causes and if negative, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures (e.g., fluid and electrolyte substitution) may also be employed as clinically indicated. Patients who exhibit an excessive cholinergic response to treatment can receive appropriate premedication (e.g., atropine) for subsequent treatments.

Hypersensitivity and Infusion-Related Reactions: Serious hypersensitivity reactions including life-threatening anaphylactic reactions have occurred with TRODELVY. Severe signs and symptoms included cardiac arrest, hypotension, wheezing, angioedema, swelling, pneumonitis, and skin reactions. Hypersensitivity reactions within 24 hours of dosing occurred in 37% of patients. Grade 3-4 hypersensitivity occurred in 2% of patients. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.3%. The incidence of anaphylactic reactions was 0.3%. Pre-infusion medication is recommended. Observe patients closely for hypersensitivity and infusion-related reactions during each infusion and for at least 30 minutes after completion of each infusion. Medication to treat such reactions, as well as emergency equipment, should be available for immediate use. Permanently discontinue TRODELVY for Grade 4 infusion-related reactions.
ANNOUNCING 2 NEW FDA APPROVALS FOR TRODELVY

FOR METASTATIC TRIPLE-NEGATIVE BREAST CANCER (mTNBC)

NEW EXPANDED INDICATION

INDICATION: TRODELVY is indicated for the treatment of adult patients with unresectable locally advanced or mTNBC who have received 2 or more prior systemic therapies, at least one of which was for metastatic disease.

GIVING YOU THE ABILITY TO OFFER AN OPTION AS EARLY AS 2L IN THE METASTATIC SETTING

In ASCENT, a phase 3 trial, ~1 out of 8 patients (13%) in the TRODELVY group in the full population received only 1 prior line of systemic therapy in the metastatic setting (in addition to having disease recurrence or progression within 12 months of neoadjuvant/adjuvant systemic therapy).1

FOR METASTATIC UROTHELIAL CANCER (mUC)

NEW INDICATION NOW APPROVED

INDICATION: TRODELVY is indicated for the treatment of adult patients with locally advanced or mUC who received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor.

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 confirmatory trials.

ADVERSE REACTIONS

In the ASCENT study (IMMU-132-05), the most common adverse reactions (incidence ≥25%) were fatigue, neutropenia, diarrhea, nausea, alopecia, anemia, constipation, vomiting, abdominal pain, and decreased appetite. The most frequent serious adverse reactions (SAR) (>1%) were neutropenia (7%), diarrhea (4%), and pneumonia (3%). SAR were reported in 27% of patients, and 5% discontinued therapy due to adverse reactions. The most common Grade 3-4 lab abnormalities (incidence ≥25%) in the ASCENT study were reduced neutrophils, leukocytes, and lymphocytes.

In the TROPHY study (IMMU-132-06), the most common adverse reactions (incidence ≥25%) were diarrhea, fatigue, neutropenia, nausea, any infection, alopecia, anemia, decreased appetite, constipation, vomiting, abdominal pain, and rash. The most frequent serious adverse reactions (SAR) (>5%) were infection (18%), neutropenia (12%, including febrile neutropenia in 10%), acute kidney injury (6%), urinary tract infection (6%), and sepsis or bacteremia (5%). SAR were reported in 44% of patients, and 10% discontinued due to adverse reactions. The most common Grade 3-4 lab abnormalities (incidence ≥25%) in the TROPHY study were reduced neutrophils, leukocytes, and lymphocytes.

DRUG INTERACTIONS

UGT1A1 Inducers: Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Avoid administering UGT1A1 inhibitors with TRODELVY.

UGT1A1 Inducers: Exposure to SN-38 may be substantially reduced in patients concomitantly receiving UGT1A1 enzyme inducers. Avoid administering UGT1A1 inducers with TRODELVY.


Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the next page.
Nausea and Vomiting: Grade 4 infusion-related reactions. Hours of dosing occurred in 37% of patients treated with TRODELVY. Grade 3-4 hypersensitivity occurred in 2% of patients. Labeled cholinergic response to treatment with TRODELVY (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive atropine, if not contraindicated, for early diarrhea of any severity. Late diarrhea may occur. Patients with diarrhea and give fluid and electrolytes as needed. Administer atropine, if not contraindicated, for early diarrhea of any severity. At the onset of late diarrhea, provide fluid and electrolyte replacement as needed for rehydration. At the onset of diarrhea, provide fluid and electrolyte replacement as needed. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤ Grade 1 and reduce subsequent doses. [See Warnings and Precautions and Dosage and Administration] INDICATIONS Also see Clinical Studies TRODELVY (sacituzumab govitecan-hziy) is a 2-derpy dirigent antibody and topoisomerase inhibitor conjugate indicated for the treatment of patients with: Unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease. Locally advanced or metastatic esophageal cancer (mEAC) who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death ligand-1 (PD-L1) inhibitor. 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.

DOSAGE AND ADMINISTRATION Also see Warnings and Precautions: Do NOT substitute TRODELVY for use with other drugs containing vinorelbine or its active metabolite SN-38. The recommended dose of TRODELVY is 30 mg/m² of body surface area administered as a 90-minute intravenous infusion over 1 to 2 hours on Day 1 of each 21-day treatment cycle or neutropenic fever. Withhold TRODELVY for neutropenic fever. Dose modifications may be required due to neutropenia. Dose Modifications for Infusion-related Reactions: Slow or interrupt the infusion rate of TRODELVY if the patient develops an infusion-related reaction. Permanent discontinuation of TRODELVY for the threatening infusion-related reaction. [See Warnings and Precautions] Use in Specific Populations: [See Warnings and Precautions] ADVERSE REACTIONS Use in Specific Populations: [See Warnings and Precautions] ADVERSE REACTIONS
Aduhelm OK engulfed by controversy

Accelerated approval and use of surrogate markers are among the friction points. But some see the OK as spawning a new generation of drug development for treating Alzheimer’s disease. by JAIME ROSENBERG

It seems almost every year the drug pipeline is marked by a landmark approval — a drug that upends the prior way of managing a disease and sets treatment strategies off in a new direction. The 2021 version almost certainly seems to be the FDA’s accelerated approval of Aduhelm (aducanumab).

The approval on June 7 was the first in nearly two decades for a drug for Alzheimer’s disease. It also was the first for a medication with a “disease-modifying” mechanism of action that many believe addresses the underlying pathology of this disease, which affects approximately 6 million Americans.

Aduhelm engendered controversy before it received approval. In 2019, Biogen shelved the development of the treatment after a futility analysis from an independent committee said the treatment would be unlikely to benefit patients. Months later, the company announced that it was reviving the development of Aduhelm after its analysis showed the treatment reduced cognitive decline in patients who took high doses. But in November 2020, an independent advisory panel of experts recommended the FDA not approve the drug.

When Biogen announced the FDA’s accelerated approval of Aduhelm in June, concerns about the drug’s effectiveness in slowing disease progression remained and new concerns emerged as the company announced that the annual price tag would be $56,000. (That is the wholesale acquisition cost price. After debates and discounts, it will be lower for many payers.)

Following the approval, three members of the advisory panel resigned. One of them, Aaron Kesselheim, M.D., J.D., M.P.H., called it “the worst drug approval in U.S. history,” noting side effects such as brain swelling and bleeding, falls, confusion and disorientation associated with taking the drug.

Why the controversy?

One source of controversy about Aduhelm is a schism within the agency itself. Agency documents have shown that FDA statisticians said the data from the two clinical trials used to support the approval did not meet statistical standards but that agency leaders overruled them. Another friction point is that Aduhelm received accelerated approval, a separate approval track designed to get medications on the market faster. The FDA has tended to grant accelerated approvals based on evidence from smaller early-stage trials. But Aduhelm was tested in two fairly large phase 3 trials, so the issue with Aduhelm is not the size of the trials but whether the evidence from them merited an FDA OK. As is often true with accelerated approvals, Aduhelm’s approval was based on a surrogate marker, the effect the drug has on beta-amyloid plaques in the brain.

Approvals based on such surrogate markers are controversial because of the uncertainty about whether the marker translates into improved symptoms and outcomes.

As part of Aduhelm’s approval, Biogen must complete a large trial that confirms that clearing the beta-amyloid plaques does, in fact, have cognitive benefits for patients. Theoretically, if the results do not confirm this, the FDA could revoke the approval. One argument for the Aduhelm approval is that it will stimulate new drug development for Alzheimer’s disease in the same way the accelerated approval of many cancer drugs has led to new approved cancer agents. However, critics of the FDA accelerated approvals say too many have been granted, resulting in a large number of drugs, some of them expensive and many for cancer, getting on the market with limited evidence.

Another subplot in the tortuous
Aduhelm saga are questions about role that beta-amyloid plays in the disease. After several other drugs attacking beta-amyloid failed, many Alzheimer’s disease researchers argued that it was time to move on and figure out another target. The Aduhelm approval threw a life preserver to the beta-amyloid hypothesis. Dennis Selkoe, M.D., an Alzheimer’s researcher at Brigham and Women’s Hospital in Boston, has been among the most prominent proponents of the beta-amyloid hypothesis. In an interview with Managed Healthcare Executive, Selkoe compared Aduhelm’s approval to the 1987 approval of lovastatin, the first statin to decrease low-density lipoprotein (LDL) cholesterol. Although it now is accepted that LDL cholesterol is a main driver of coronary artery disease, there was a lack of consensus on the causal relationship at the time of lovastatin’s approval. The FDA approved lovastatin knowing it lowered cholesterol levels but without having concrete evidence that the treatment could decrease the risk of heart attack and strokes. That evidence, Selkoe says, didn’t come until years later, when studies assessed whether patients on the treatment had better cardiovascular outcome. But he predicts that it may be months rather than years for data to emerge that the treatments targeting beta-amyloid reduce cognitive decline as other treatments targeting beta-amyloid enter the market.

**Competition on the horizon?**

The precedent set by the FDA’s approval of Aduhelm based on beta-amyloid reduction has already started to influence the Alzheimer’s disease drug pipeline. Once thinking it would need to wait for more comprehensive data from a phase 3 trial, Eli Lilly announced in late June that it plans to file for accelerated approval of its Alzheimer’s drug donanemab, later this year based on phase 2 data. What’s notable about the available data on donanemab is not just that the treatment cleared the plaque in the brains of two-thirds of patients but that it also slowed cognitive decline — albeit just by a bit. The 131 patients receiving the treatment had a 32% slowed progression in cognitive decline after 76 weeks compared with the 126 patients receiving a placebo. The treatment was so effective at targeting the plaque in some patients that their beta-amyloid levels dropped to those of healthy people.

Roche also has a drug targeting beta-amyloid in its pipeline. Although a report in June stated that the Swiss pharma giant would be filing for early approval of gantenerumab, the company issued a statement that it would not “comment on speculations” and is continuing with its phase 3 trial. Data from the trial are expected later this year.

Gantenerumab, like Aduhelm, was once shelved based on setbacks in clinical trials before Roche reversed course and resumed development of the treatment with hopes that a higher dose would be more effective. Gantenerumab is delivered subcutaneously for five minutes, which could be an advantage over Aduhelm, which is administered intravenously for longer periods of time.

The price tag Biogen put on Aduhelm added fuel to the controversies engulfing the drug. A report from the Institute for Clinical and Economic Review said the $56,000 yearly cost is not in “reasonable alignment with its clinical benefits” and that it would need to be priced between $3,000 and $8,500 a year to fit under commonly used thresholds of cost effectiveness. Medicare is likely to be the payer most affected by Aduhelm’s approval and price because Alzheimer’s disease is a condition that affects older people almost exclusively. CMS is weighing coverage options that will go a long way toward determining the sales of Aduhelm and any competitors that come to market. Meanwhile, members of Congress have announced investigations of Aduhelm’s approval and price.

In addition to the cost of the drug, treatment with Aduhelm may require expensive brain imaging studies to determine if the plaques of beta-amyloid are present. But Selkoe says most patients can be tested via a spinal tap, which would be less costly than brain scans.

Jaime Rosenberg is a freelance medical writer based in Jersey City, New Jersey.
Throughout the COVID-19 pandemic, people have been understandably hesitant to be in public places, including doctors’ offices. Results of a study done by the CDC in late 2020 showed that 41% of adults were avoiding or postponing their regular medical appointments and annual screenings because they feared they might contract COVID-19. That hesitancy has resulted in delayed or forsaken care of all types, with delays in cardiac care among the most consequential.

"Over the last 15 months, people have feared COVID-19 more than they have feared the signs of heart disease, but it is absolutely critical that they notice and seek treatment for those symptoms," says Philip B. Adamson, M.D., a cardiologist in Oklahoma City. "Millions of people are impacted by heart disease and don’t even realize that an earlier diagnosis can allow for more effective treatment options. Once a patient with heart disease reaches a certain stage, their condition begins to rapidly deteriorate."

Consider the circumstances of Chief Petty Officer Ramon Rinkin, 41, a yeoman in the Navy with a family history of heart disease. When Rinkin, a husband and father of three, began experiencing symptoms of indigestion and heartburn during the pandemic, he brushed them aside.

However, as he was getting ready for work one day, he went into cardiac arrest and collapsed in the bathroom. His wife, Melania, began CPR and called 911. Rinkin went into cardiopulmonary arrest at home and again in the ambulance before arriving at Saint Francis Hospital in Bartlett, Tennessee. He then went into cardiogenic shock and coded once more before interventional cardiologist Raj Dave, M.D., inserted an Impella heart pump. Two weeks later, he walked out of the hospital with his healthy, native heart.

Instances such as this were not uncommon during the pandemic because many people, afraid to go to a doctor or hospital, ignored warning signs of heart issues.

Trevor Huber, D.O., a family physician and president and founder of Modera Clinic in Little Elm, Texas, saw this as a huge problem in the past year, especially during the height of the pandemic.

“We saw a drastic increase in patients (who) were experiencing heart disease and heart attacks and not getting care as quickly as they typically would have because of the fear of contracting COVID-19,” he says. “We found this out months later when they would tell us the symptoms and we realized they had had heart attacks while in quarantine and were too afraid to visit our office.” In fact, one of his patients died on Father’s Day after ignoring warning signs.

“His wife told us (afterward) that he had been experiencing heart attack symptoms for two weeks but put off coming in to visit because of COVID-19 fears,” Huber says. “We had another new patient who we set up for a telemedicine visit because he thought he had COVID-19. Once we began the televisit, we realized he was actually experiencing a heart attack. He was very reluctant to come in even after we discovered this, but, thankfully, we were able to convince him of the urgency and were able to transport him to a hospital to get his blockages opened.”

Oluseyi Princewill, M.D., M.P.H., a cardiologist at MedStar Health in Olney, Maryland, saw a significant decline in office visits for chronic disease management and acute symptoms such as chest pain since March 2020. “We also know that many people heeded the warnings to stay home and not further strain the healthcare system,” she says. “In retrospect, that message should have been coupled with public service announcements about the importance of being seen by a healthcare provider for symptoms concerning heart attacks or strokes.”

Christopher Price, M.D., is a retired cardiologist in the Seattle area.
INDICATIONS

- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.

- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

CONTRAINDICATIONS

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARRANTS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.

- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.

- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

- EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

Please see Brief Summary of full Prescribing Information on the next page.
BRIEF SUMMARY—Please see the EYLEA full Prescribing Information Available on HCPC+EYLEA.US for additional product information.

INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR).

CONTRAINDICATIONS

- Hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intravascular hemolysis.

WARNINGS AND PRECAUTIONS

- Increased Intraocular Pressure

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA (see Adverse Reactions 6.5). Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with subcutaneous endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

- Thromboembolic Events

There is a potential risk of arterial thromboembolic events (ATE) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as sudden stroke, myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thrombotic events in wet AMD studies during the first year was 1.8% (2 of 182) in the combined group of patients treated with EYLEA compared with 0.9% (1 of 129) in the control group. During the second year, the incidence was 3% (6 of 183) in the EYLEA group compared with 1.6% (3 of 186) in the control group. The incidence of the ODME studies from baseline to week 52 was 3.3% (2 of 578) in the combined group of patients treated with EYLEA compared with 1.8% (1 of 57) in the control group. There were no thrombotic events in 157 patients treated with EYLEA in the five-month extension study.

ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity (see Contraindications 4.1)

- Endothelial and Retinal Detachments (see Warnings and Precautions 6.1)

- Increased Intraocular Pressure (see Warnings and Precautions 6.2)

- Thromboembolic Events (see Warnings and Precautions 6.3)

- Ocular or Periocular Infections (see Warnings and Precautions 6.4)

- Active Intraocular Inflammation (see Warnings and Precautions 6.5)

6.1 Clinical Trials Experience

Baseline to Week 52 Baseline to Week 100

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who has a health advisory business named Call Doctor Chris. He notes that the ramification of patients not coming in sooner rather than later with their cardiac symptoms is that they are likely to be more ill upon presentation and to potentially stay longer in the hospital. They also might have more complications from their event.

If a patient with atrial fibrillation is seen in the first 48 hours, they could be cardioverted (when the heart is shocked back into normal rhythm) and discharged the same day. If they wait, their risk of stroke likely will be too high to convert their abnormal rhythm safely.

“They would then need to be treated with blood thinners for a month prior to the shocking,” Price says. “Alternatively, the cardiologist may offer (transesophageal echocardiography)-guided cardioversion, but this requires sedation and other risks and expenses.”

“Also,” Price continues, “by waiting longer than 48 hours in this rhythm, the patient risks the possibility of developing heart failure from this uncontrolled rhythm.”

Continued reluctance

There are many reasons to believe a surge in patients with heart and lung disease is coming. Adamson says he has seen reports that more than one-third of American adults skipped or delayed medical care due to the pandemic. But with vaccination and the resumption of normal activities, most physicians are seeing fewer patients delay care when they have major issues. “However, now we are having difficulty getting patients back in for preventive care and routine visits,” Huber says. “Patients have become accustomed to the convenience of telehealth visits, but there are still visits and tests that require in-person interaction. We’re seeing a continued reluctance among some patients to come back in for those visits.”

Another consequence of not seeing a physician is that patients don’t get to discuss or ask questions about heart disease. “These moments that doctors spend with their patients discussing risk factors and symptoms can have just as much impact as the tests themselves,” Price says.

Elevated blood pressure, blood sugar and cholesterol levels are cardiovascular risk factors. Huber says that without wellness visits it was difficult to help patients stay on top of those risk factors. “This really tied our hands, (and we were unable to treat) problems early on before they led to heart disease,” he says. “We have seen a nationwide increase in mortality, including cardiovascular disease, since the pandemic began.”

In response, he says, his practice has been more aggressive in performing screening tests and obtaining electrocardiograms: “We are doing more testing now than ever to help our patients get a clear picture of their heart health.”

Price will hopes to see more patients following up in the clinic for their routine visits. Since spring, she already has seen a promising uptick.

“We’re optimistic that number will continue to increase as more individuals are fully vaccinated and case numbers continue to decline,” she says. “I urge everyone to follow up with their healthcare providers as soon as possible if they haven’t already been seen or scheduled an appointment. It is also important to control our risk factors. The more we eat right, sleep better, exercise and take care of our mental and heart health, the more likely we are to reduce our risk of severe illness.”

Neil Moat, M.D., a cardiologist and chief medical officer of Abbott’s structural heart business (treatments for valvular heart disease and other conditions) says now that the pandemic may be easing up and people are looking to return to some sense of normalcy, everyone should focus on getting their health — and perhaps especially their heart health — back on track.

“Before the COVID-19 pandemic, heart disease was the leading cause of death worldwide, and that hasn’t changed,” he says. “With individuals deprioritizing medical appointments and everything that’s happened over the past year taking a toll on physical and mental wellness, there’s a risk that undiagnosed and undertreated heart conditions will now start coming to the surface.”

He urges patients to reflect on any changes related to their physical or mental wellness they’ve noticed in the past year, as shifts in things such as stamina, mood and pain levels could be signs of potential heart and cardiovascular issues.

“Discussing any observations and questions with your doctor can help them map out a plan for you, whether that includes exams, lab work or treatment,” Moat says. “As the (population) continues to age, heart disease will remain top of mind for years to come, and its prevalence shows no sign of declining.”

Keith Loria is a freelance writer in the Washington, D.C., area.

“We have seen a nationwide increase in mortality, including cardiovascular disease, since the pandemic began.”

— TREVOR HUBER, D.O., A FAMILY PHYSICIAN AND PRESIDENT AND FOUNDER OF MODERA CLINIC

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There’s good news about cervical cancer. But it’s complicated.

Screening and vaccination against HPV have reduced the incidence of cervical cancer, but researchers say some women are being screened for cervical cancer too often — partly because of vaccination.

Last year, the CDC came out with a report showing that nearly three-quarters (71.5%) of adolescents between the ages of 13 and 17 had received at least one dose of the human papillomavirus (HPV) vaccine. Just over half (54.2%) had completed their vaccination series and were considered up-to-date. Those rates are increasing each year, which is important because nearly 36,000 Americans are receiving diagnoses of cancer that are probably caused by HPV infection each year, according to the CDC.

The most common type of cancer caused by HPV infections in women is cervical cancer. The FDA first approved the HPV vaccine in 2006. Initially indicated for girls and young women, the vaccine is now available starting at age 9 for males and females, through age 45. HPV infection is extremely common among sexually active individuals, but the rising rates of HPV vaccination should, theoretically, lead to decreasing rates of certain types of cancer. New data appear to back that up, and screening also plays an important role. But for cervical cancer, screening has become a conundrum. On the one hand, it seems to be having a meaningful impact, lowering the incidence of cervical cancer and the deaths from the disease. On the other hand, evidence from studies seems to show that it is overused.

Incidence dropping

At the 2021 meeting of the American Society of Clinical Oncology, Cheng-I Liao, M.D., of Kaohsiung Veterans General Hospital in Taiwan, presented new data showing that cervical cancer rates decreased by an average of 1.03% per year in the U.S. from 2001 to 2017. It’s not exactly clear why rates are dropping. Liao and colleagues used the United States Cancer Statistics database for their study, and those data sets do not include screening or vaccination. However, Liao told Managed Healthcare Executive that there’s good reason to believe vaccination is a major driver of the declining rates. “We found in the younger age group, especially in the age group 20 to 24, the cervical carcinoma age-specific incidence decreased more than other age groups,” Liao says. “We usually did not provide screening to this age group, meaning the major effect of the decrease was due to vaccination.”

The annual percentage change in the 20-to-24 age group was 4.63%, more than four times the percentage point decrease among those in the 30-to-34 age group. Those in the 20-to-24 age group in 2017 would have been between the ages of 9 and 13 in 2006, which would have put them in the first cohort of girls and young women for whom HPV vaccination was approved, Liao and colleagues noted in the abstract they presented at the ASCO meeting. Among patients ages 50 and older, rates are also dropping, Liao says that is likely because of screening, not vaccination, but HPV vaccination is not generally recommended for this age group.

Screening on the rise

Even as Liao’s report suggested that screening and vaccination were improving rates of cervical cancer, another report raised concerns about the overuse of screening. Writing in JAMA Network Open in April, Jason D. Wright, M.D., of the Columbia University College of Physicians and Surgeons, and his co-authors reported that women at average risk for cervical cancer were frequently overscreened for the disease. Using a database of 2.3 million commercially insured women, they found that nearly two-thirds (64.7%) of women between the ages of 30 and 65 who underwent cervical cancer screening in 2013 and 2014 were tested again within 36 months of their index test. The American Cancer Society’s 2012 guidelines suggested cervical cancer screening every three years or cotesting with HPV and cytologic testing every five years for women in that age group. The association later updated those guidelines to call for HPV testing every five years.
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Wright and colleagues noted that the overuse of screening can lead to a variety of unnecessary procedures. “Identification of transient HPV infections and low-grade abnormal findings likely to resolve spontaneously often leads to further diagnostic testing with colposcopy and biopsies and, possibly, ablative or excisional procedures,” they wrote. “These procedures are often associated with psychological stress and physical symptoms.” Wright and colleagues also noted that treating preinvasive surgical lesions can have negative consequences on pregnancy, including preterm birth.

**Overscreening issues**

Overscreening also leads to significant costs for the healthcare system. A 2015 study modeled HPV screening scenarios found current screening practices, based on a database of patients in New Mexico, were inefficient and had a lower health benefit compared with guidelines-based screening. By following the screening guidelines perfectly, which at the time called for cytological testing every 3 years, physicians would save money and improve health outcomes.

Liao agrees that overscreening can be a problem, not only because it can lead to extra costs and extra patient management, but also because it is not always a good use of the providers’ time. But Liao adds that said overscreening is also a byproduct of improving rates of cervical cancer.

“When the prevalence and incidence are higher, the proportion of overtreatment in screening is small,” he points out. “When the prevalence and the incidence are reduced by screening or vaccination, the proportion of overtreatment in screening will increase. We should balance the cost and the benefit.” Wright and his co-authors said their research also sheds light on another problem: Many women have conflated cervical cancer screening with regular gynecological exams.

“In our study, we found that 74% of women who did not have extra cervical cancer screenings also did not have a gynecologic examination,” Wright wrote in an essay on Columbia University’s website. “I think in women’s minds, annual gynecological exams and cervical cancer screening tests are indelibly linked. But that doesn’t necessarily need to be the case.”

**Role of guidelines**

For Wright, one major problem is that neither patients nor physicians understand the best practices for screening. “As data on testing strategies evolve, guidelines change frequently and multiple ... professional societies release their own, different screening guidelines, patients and clinicians are often unaware of screening recommendations or may be confused by the lack of consensus among guidelines,” he and his colleagues wrote in *JAMA Network Open*.

Liao says it takes time for new recommendations to filter down to the clinic to the point where they are widely followed. In the meantime, he believes that researchers should keep close tabs on disease status and screening and vaccination rates to ensure that guidelines match the real-world situation. “We should ... provide up-to-date suggestions or guidelines (and) continue to educate our health providers and people,” he says. “We can decrease the probability of overtreatment and save lives and money.”

At the same time, Liao’s research also suggests that the status quo for cervical cancer, where guidelines exist and evolve even if they are not always followed, is better than the alternative. He and colleagues found that rates of other HPV-related cancers, including oropharyngeal, anal and rectal squamous cell carcinoma, are on the rise. Those cancers either cannot be screened for or there is a lack of clear screening guidelines, Liao says. Lori Pierce, M.D., ASCO’s president, said in a news release that the juxtaposition of cervical cancer rates falling while other HPV-related cancers are increasing points to a need for better screening guidelines. “Clearly, this study shows that we still have a great deal of work to do in order to reverse the increasing incidence rates of other HPV-related cancers,” she commented.

**Jared Kaltwasser** is a medical writer who lives in Iowa.