Matulonis’ Passion Drives Gynecologic Cancer Research Into the Next Era

PEER EXCHANGE
Targeted Treatment Boom Reshapes Differentiated THYROID CANCER Landscape

OncPathways
First Steps Down the HER3 Pathway in NSCLC Signal Early Success

CONFERENCE HIGHLIGHTS
26th Annual International Congress on Hematologic Malignancies Leading Experts Provide Updates Across HEMATOLOGIC MALIGNANCIES

THE US ONCOLOGY NETWORK
Progress in PROSTATE CANCER Options Creates Excitement

Scan the QR code to watch the first-of-its-kind 24-hour online program for health care professionals, by health care professionals.
For your patient with non-metastatic castration-resistant prostate cancer (nmCRPC)

HELP HIM LIVE FOR WHAT HE LOVES

MEN LIVED 2X LONGER WITHOUT CANCER SPREADING\(^1,2\)
40.4 months vs 18.4 months for ADT alone
HR: 0.41, 95% CI: 0.34-0.50; \(P=0.0001\) (intent-to-treat).

REDUCED RISK OF DEATH BY NEARLY A THIRD\(^1,3\)
31% reduction in the risk of death vs ADT alone
Secondary endpoint: HR: 0.69, 95% CI: 0.53-0.88; \(P=0.003\). Medians not estimable.

PROVIDED THE RELIEF OF AN EXTRA 15 MONTHS WITHOUT PAIN PROGRESSION\(^1,3\)*
40.3 months vs 25.4 months for ADT alone
Secondary endpoint: HR: 0.65, 95% CI: 0.53-0.79; \(P=0.0001\).

INDICATION
NUBEQA\(^{\circledast}\) (darolutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.

IMPORTANT SAFETY INFORMATION

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

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

Adverse reactions occurring more frequently in the NUBEQA arm (≥2% over placebo) were fatigue (16% vs 11%), pain in extremity (6% vs 3%) and rash (3% vs 1%).

Clinically significant adverse reactions occurring in ≥2% of patients treated with NUBEQA included ischemic heart disease (4.0% vs 3.4% on placebo) and heart failure (2.1% vs 0.9% on placebo).

Drug Interactions
**Effect of Other Drugs on NUBEQA** – Combined P-gp and strong or moderate CYP3A4 inducers decrease NUBEQA exposure, which may decrease NUBEQA activity. Avoid concomitant use.

Combined P-gp and strong CYP3A4 inhibitors increase NUBEQA exposure, which may increase the risk of NUBEQA adverse reactions. Monitor more frequently and modify NUBEQA dose as needed.

**Effects of NUBEQA on Other Drugs** – NUBEQA inhibits breast cancer resistance protein (BCRP) transporter. Concomitant use increases exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use where possible. If used together, monitor more frequently for adverse reactions, and consider dose reduction of the BCRP substrate.

NUBEQA inhibits OATP1B1 and OATP1B3 transporters. Concomitant use may increase plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor more frequently for adverse reactions and consider dose reduction of these substrates.

Review the prescribing information of drugs that are BCRP, OATP1B1, and OATP1B3 substrates when used concomitantly with NUBEQA.

Metastasis-free survival (MFS) was the primary endpoint, and overall survival (OS) was a key secondary endpoint.\(^1\)

*Time to pain progression was defined as at least a 2-point worsening from baseline of pain score on BPI-SF (a validated health-related quality-of-life instrument) or initiation of opioids and reported in 28% of all patients on study.

Study design
The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled phase III study (ARAMIS) in nmCRPC patients on ADT with a PSA doubling time ≤ 10 months. 1509 patients were randomized 2:1 to 600 mg NUBEQA twice daily \(n=955\) or placebo \(n=554\). MFS was defined as time from randomization to time of first evidence of BICR-confirmed distant metastasis or death from any cause ≤ 33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, \(^{99m}\)Tc bone scan by BICR, unacceptable toxicity, or withdrawal.\(^{1,2}\)

ADT=androgen deprivation therapy; HR=hazard ratio; CI=confidence interval; BPI-SF= Brief Pain Inventory Short Form; PSA=prostate-specific antigen; BICR=blinded independent central review; CT=computed tomography; MRI=magnetic resonance imaging.

Please see the following page for the brief summary of Prescribing Information.
NUBEQA® (darolutamide) tablets, for oral use
Initial U.S. Approval: 2019

BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE NUBEQA® is indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer (mCRPC).

2. CONTRAINDICATIONS None.

5.1 Embryo-Fetal Toxicity The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm when administered to a pregnant female (see Clinical Pharmacology (12.1)). Adverse male with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA (see Use in Specific Populations (8.4)).

5.2 Nursing Mothers NUBEQA may impair fertility in males of reproductive potential (see Nonclinical Toxicology (13.1)).

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

5.4 Geriatric Use Of the 9,545 patients who received NUBEQA in ARMS, 84% of patients were 65 years and older, and 49% were 75 years and older. No overall differences in safety or efficacy were observed between these patients and younger patients.

6.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.

ARMS, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had non-metastatic castration-resistant prostate cancer (mCRPC). In this study, patients received either NUBEQA at a dose of 600 mg or a placebo, twice a day. All patients in the ARMS study received a concurrent peripherally-inhibiting hormone (GnRH) agonist or had a bilateral orchectomy. The median duration of exposure was 14.4 months (range: 0.1 to 44.3 months) in patients who received NUBEQA. Overall, adverse events occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in the 1% of patients who received NUBEQA included urinary retention, pneumonia, and hematuria. Overall, 3.8% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), and severe physical health deterioration (0.1%), and pulmonary embolism (0.1%) for NUBEQA. Permanently discontinued due to adverse reactions occurred in 9% of patients receiving NUBEQA or placebo. The most frequent adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), death (0.4%), and diarrhea (0.2%).

Table 1 shows adverse reactions in ARMS reported in the NUBEQA arm with a 5% absolute increase in frequency compared to placebo. Table 2 shows laboratory test abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ARMS study.

Table 1: Adverse Reactions in ARMS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NUBEQA (n=4,347)</th>
<th>Placebo (n=1,926)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any Grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>6.6%</td>
<td>0.9%</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insomnia</strong></td>
<td>3.5%</td>
<td>0.9%</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td>2.9%</td>
<td>0.8%</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>0.5%</td>
<td>0.8%</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>0.4%</td>
<td>0.2%</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>0.4%</td>
<td>0.1%</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>0.4%</td>
<td>0.2%</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td>0.3%</td>
<td>0.1%</td>
</tr>
<tr>
<td><strong>Decreased Hgb</strong></td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td><strong>Hypercalcemia</strong></td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td><strong>Increased AST</strong></td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td><strong>Increased Alk Phos</strong></td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Table 2: Laboratory Test Abnormalities in ARMS

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>NUBEQA (n=4,347)</th>
<th>Placebo (n=1,926)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any Grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neutrophil count</strong></td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Hematocrit</strong></td>
<td>0.5%</td>
<td>0.4%</td>
</tr>
<tr>
<td><strong>AST increased</strong></td>
<td>0.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td><strong>Alkaline phosphatase</strong></td>
<td>0.5%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Review the prescribing information of the BCP, OATP1B1, and OATP1B3 substrates when used concomitantly with NUBEQA.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Contraception

Based on the mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA (see Use in Specific Populations (8.4)).

9. NONCLINICAL TOXICOLOGY

9.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of darolutamide have not been conducted.

Darolutamide was clastogenic in vitro in CHO/hescR-cell micronucleus assay in human peripheral blood lymphocytes. Darolutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in the In vivo comet assay mouse micronucleus assay and the Comet assay in the liver and epididymus of the rat.

Fertility studies in animals have not been conducted with darolutamide. In repeat-dose toxicity studies in male rats and dogs (2 times the clinical exposure based on AUC 0-24 h), no adverse effects on fertility were observed in males or females.

9.2 Human Reproduction

Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with NUBEQA.

9.3 Pregnancy

Inform patients to take their dose of two tablets (twice daily). NUBEQA should be taken with food. Each tablet should be swallowed whole.

Inform patients that in the event of a missed daily dose of NUBEQA, to take any missed dose, as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose (see Dosage and Administration (2.2)).

9.4 Lactation

Inform patients that NUBEQA can be a harmful to a developing fetus and can cause loss of pregnancy (see Use in Specific Populations (8.4)).

Inform male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA (see Warnings and Precautions (5.1) and Use in Specific Populations (8.5)).

9.5 Pediatric Use

Inform male patients that NUBEQA may impair fertility (see Use in Specific Populations (8.5)).

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CONCEPTS

Publisher’s Note

Programs to Address Disparities in Oncology Clinical Trials Garner Nationwide Interest

A RECENT REPORT BY the American Cancer Society highlighted persistently lower survival rates among Black patients with cancer compared with White patients with cancer in most malignancies, underscoring the need for increased diversity in clinical trials.1 Another report found that race was only reported in 63% of trials leading to FDA approvals of oncology drugs from 2008 to 2018 and that only 22% of the population of Black patients expected in the US cancer incidence and 44% of Hispanic patients were represented in trials compared with 98% of White patients.2

Considering these disparities, an ongoing collaboration focused on increasing racial and ethnic diversity in clinical trial patient populations between the Association of Community Cancer Centers (ACCC) and the American Society of Clinical Oncology (ASCO) is gaining traction among cancer research institutions. The pilot project was first announced in the summer of 2020 and planned to involve 40 to 50 sites across the United States in the testing of a research site self-assessment tool and an implicit bias training program. Seventy-five cancer research sites in the community and academic settings have applied and been invited to participate in the expanded project, which commenced in the summer of 2021.3

Networks have been seeking to tackle disparities in health care delivery in various ways. For example, Benny Weksler, MD, MBA, FACS, FACCP, system chief of the Thoracic Surgery, Division of Thoracic and Esophageal Surgery at Allegheny Health Network (AHN) Cancer Institute, told OncologyLive® efforts are being made at his institution to address disparities are starting at the time of screening patients for lung cancer.

One key initiative run by AHN is the nurse navigation program, which tracks patients or potential patients with lung cancer to ensure they all undergo proper screening and treatment, Weksler said. If a patient is turned down by a surgeon, the institution works to ensure that the patient receives the care they need. Additionally, the use of electronic flags and stops in medical records has amplified care for all patients, regardless of racial background. By electronically noting recommendations from other doctors, such as the need to quit smoking or meeting the requirements for lung cancer screening, other physicians can better provide continuous care for patients over time, Weksler added.

As always, thank you for reading.

Mike Hennessy Jr
President and CEO
MJH Life Sciences®

REFERENCES


For more on how leading institutions and investigators are bridging gaps in care, scan the QR code to sign up for the OncLive® newsletter or visit our Disparities in Cancer Care page at onclive.com/clinical/disparities-in-cancer-care.

TOC, CONTINUED FROM PAGE 4
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- Evaluate the role of PARP inhibitors across gynecologic malignancies, including ovarian cancer
- Outline the reasoning for pursuing immunotherapy approaches in gynecologic malignancies, such as cervical and endometrial cancers
- Explain the latest data and emerging trends in gynecologic malignancies, place these updates in clinical context, and evaluate the therapeutic implications
- Summarize evidence-based approaches for identification and management of potential adverse events associated with treatments

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- Hear a debate-style presentation featuring 2 experts—each offering an opposing viewpoint on the treatment options for homologous recombination-proficient (HRP) ovarian cancer—and weigh in on who you think has the most persuasive argument
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HERE SHOULD BE LITTLE or no debate with the statement that clinical trials serve as the primary source of data employed to favorably affect outcomes for patients who receive a diagnosis of cancer. However, much can be said regarding well-described deficiencies in the existing trial process and, unfortunately, the often ineffective efforts to improve this critical component of cancer care and research. This includes the time required to design, initiate, and complete highly clinically relevant studies, the staggering costs required to complete many studies (particularly phase 3 randomized trials), never-ending debates regarding meaningful study end points, and the exclusion of individuals who represent the real-world demographics of patients receiving cancer care (eg, age, common comorbidities).

One must add to this list the smaller size of molecularly defined patient subgroups within individual cancer types, which make it more difficult to conduct “gold-standard” randomized studies within a reasonable period of time. Further, there is the questionable relevance of existing and rather antiquated trial-based toxicity scales developed in a long-past era where standard systemic antineoplastic drug therapy focused almost exclusively on the short-term intermittent intravenous delivery of several cycles of cytotoxic agents. As advanced cancers increasingly become serious “chronic illnesses,” with treatments including combination regimens with oral and daily dosing strategies potentially delivered over a period of years rather than a few weeks or months, the critical question of objectively measuring the actual effects on patient-reported outcomes and experienced quality of life becomes ever more important.

Additional issues regarding cancer clinical trials need to be considered, including how truly paradigm-changing study results in a specific setting might be optimally implemented in routine practice. Equally important is how clinicians should view trial outcomes when several alternative strategies may be employed but no direct comparative data exist to assist in the decision-making process.

INTERPRETING PUBLISHED DATA
This commentary highlights a particular concern that has received limited discussion in the oncology literature. How does one interpret unexpected, perhaps highly provocative, but less than conclusive peer-reviewed study results that may be of considerable direct relevance to patient welfare? An example might include settings where it was uncertain when, if ever, formal regular approval from the FDA would occur. How might oncologists consider using these published data to potentially optimize the opportunity for a favorable clinical outcome for an individual patient?

A recent example of this phenomenon from outside the oncology realm is that of the potential use of high-titer COVID-19 convalescent plasma to prevent or treat the complications of a serious viral infection. Although widely discussed in the medical and lay literature, data from several well-designed randomized trials published in high-impact peer-reviewed journals failed to demonstrate the benefits of this strategy.1-3 However, a more recent report from a randomized trial involving 1225 participants from 23 study sites concluded that “early administration of high-titer SARS-CoV-2 convalescent plasma reduced outpatient hospitalizations by more than 50%. High-titer convalescent plasma is an effective outpatient COVID-19 treatment with the advantages of low cost, wide availability, and rapid resilience to variant emergence from viral genetic drift in the face of a changing pandemic.”4 Of course, these various trials were conducted at somewhat different times with diverse study populations. But the question being addressed in this commentary is how should individual clinicians and the medical community interpret these outcomes and how might the results affect the treatment of serious COVID-19 infections?

“Issues regarding cancer clinical trials need to be considered, including how truly paradigm-changing study results in a specific setting might be optimally implemented in routine practice. Equally important is how clinicians should view trial outcomes when several alternative strategies may be employed but no direct comparative data exist to assist in the decision-making process.”
Turning to the cancer arena it is not difficult to find recent examples of intriguing study results that either seriously challenge or raise concerns regarding the current clinical paradigm but unfortunately do not yet provide a definitive answer to the questions they address.

INFLUENCE ON TIMELY DECISION-MAKING
For the purpose of this all-too-brief discussion, let us consider the provocative report involving patients with advanced melanoma treated with immunotherapy at a single center from January 1, 2012, to December 31, 2020, recently published in a high-impact oncology journal. A total of 481 individuals were treated, but the specific study population analyzed here included only those with stage IV disease (n = 299). In the analysis, patients who had at least 20% of infusions administered after 4:30 PM experienced a shorter median overall survival of 4.8 years (95% CI, 3.9-not estimable) vs not reached among those who received treatment earlier in the day (HR, 2.04; 95% CI, 1.04-4.00; P = .038). The investigators concluded, “This result remained robust to multivariable proportional hazards adjustment.”

Of note, intriguing preclinical data exist related to the potential relevance of circadian rhythm on immune function, and findings from at least 1 additional small nonrandomized clinical experience supported the conclusions of this report.

Of course, the study being a nonrandomized retrospective analysis, leads to the usual criticisms associated with all such observational studies. As a result, there appeared the not surprising editorial response that “prospective randomized trials should identify optimal timing of infusions of immune checkpoint inhibitors, which might be sex specific and tailored to individual patients’ circadian biomarkers.”

There is nothing wrong with this anticipated academic conclusion, but what about the patient with advanced melanoma scheduled to begin therapy tomorrow, or the next day or the next week, with a commercially available checkpoint inhibitor? Should the infusions be scheduled preferentially in the morning rather than the afternoon, even in the absence of definitive evidence-based “gold standard” data from a well-written, rigorously conducted, and analyzed phase 3 randomized study, one subjected to peer review and published in an appropriately high-impact medical journal? Co-pays, insurance approval, formulary committee, added costs to an oncology practice or hospital outpatient program, or inclusion in National Comprehensive Cancer Network guidelines are not standing in the way of this decision.

One might also inquire as to what the oncologist would want if this were a family member or friend, or whether patients in this situation should perhaps be given a summary of the existing data and determine its relevance for themselves.

REFERENCES
BEHIND THE SCIENCE
Silver Lining of Telehealth Amid the COVID-19 Pandemic

Although telehealth eliminates the physical interaction between physician and patient, Sikander Ailawadhi, MD, of Mayo Clinic in Jacksonville, Florida, believes there is a silver lining: improved administration of care to patients with rare cancer diagnoses. Ailawadhi cited patients with Waldenström macroglobulinemia, a rare disease in which expertise is relatively limited. With telehealth, geographic barriers expanded, allowing patients unprecedented access to evaluation by specialists. Ricardo Costa, MD, of Moffitt Cancer Center in Tampa, Florida, added that telehealth expanded opportunities for patients to receive second opinions and participate in clinical trials that leverage virtual follow-up visits.

TO WATCH, VISIT bit.ly/3t3jAAj.

SECOND OPINION
Promoting Shared Guidelines for Breast Cancer Screenings

Despite a consensus among national health organizations regarding the benefits of routine mammographic screening in patients 50 years and older, screening recommendations for patients aged 40 to 49 years vary, according to Randy C. Miles, MD, MPH, of Massachusetts General Hospital in Boston. Individuals in this age group are less likely to develop breast cancer, but if they do, they are more likely to present with aggressive disease. Miles said that contradictory guidelines can do a disservice to the shared decision-making process between physician and patient when assessing the benefit-to-harm ratio of screening.

TO WATCH, VISIT bit.ly/3KsUFvQ.

WELL-BEING CHECKUP
Daily Interaction With Patients Can Spark Newfound Meaning for Physicians

Eunice Wang, MD, of Roswell Park Comprehensive Cancer Center in Buffalo, New York, began her career in the laboratory. At the time, she thought she would devote her life to unraveling the underlying mechanisms that drive cancer biology. However, small encounters with patients made a big difference in shifting her perspective. Although the emotional weight of the job is hard to bear at times, Wang said being surrounded by patients reminds her that oncologists need to keep working to advance care. She cites patients’ strength, fortitude, and persistence even in the face of the unknown as inspiration for her perseverance.

TO WATCH, VISIT bit.ly/3D4bysZ.
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Pacritinib Advances Care for Intermediate- or High-Risk Myelofibrosis

The FDA has granted an accelerated approval to pacritinib (Vonjo) for the treatment of adult patients with intermediate-risk or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis with a platelet count below 50 × 10^9/L. The recommended dosage is 200 mg orally twice daily.

The decision was based on findings from the phase 3 PERSIST-2 trial (NCT02055781), in which investigators evaluated efficacy among those with platelet count less than 50 × 10^9/L. Among those who received pacritinib at the 200-mg twice-daily dose (n = 31) 29.0% (95% CI, 14.2%-48.0%) experienced a reduction in spleen volume of at least 35% vs 3.1% (95% CI, 0.1%-16.2%) of those who received best available therapy (BAT; n = 32), which included agents such as ruxolitinib (Jakafi), watch-and-wait approaches, or symptom-directed treatment.

Additionally, 26% of patients who received the twice-daily dose experienced a reduction in TSS of at least 50% using the Modified Myelofibrosis Symptom Assessment Form compared with 9% of those who received BAT. The developer, CTI BioPharma Corp, is expected to demonstrate confirmatory findings of the agent in the phase 3 PACIFICA trial (NCT03165734).

To Read More, visit bit.ly/3pQYNHe.

Cilta-cel Enters Arena for Relapsed/Refractory Multiple Myeloma

The FDA has approved cilta-cabtagene autoleucel (cilta-cel; Carvykti) for the treatment of adult patients with relapsed or refractory multiple myeloma following 4 or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

The approval was based on data from the phase 1b/2 CARTITUDE-1 trial (NCT03548207), in which patients who received the therapy (n = 97) had an objective response rate of 98% (95% CI, 92.7%-99.7%). Additionally, the stringent complete response rate was 78% (95% CI, 68.8%-86.1%). The median duration of response was 21.8 months.

Further findings showed that among those who achieved a complete response or better, the 12-month progression-free survival rate was 85% (95% CI, 72.0%-91.8%). In those who achieved a very good partial response, this rate was 62% (95% CI, 42.1%-76.9%).

Notably, there is a box warning regarding cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, parkinsonism and Guillain-Barré syndrome, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, and prolonged and/or recurrent cytopenias.

To Read More, visit bit.ly/3tR0mNz.

Neoadjuvant Nivolumab Plus Chemotherapy Increases Treatment Options for Resectable NSCLC

The FDA has approved nivolumab (Opdivo) plus platinum-doublet chemotherapy for adult patients with resectable non–small cell lung cancer (NSCLC) in the neoadjuvant setting.

The regulatory decision was based on findings from the phase 3 CheckMate 816 trial (NCT02998528), in which investigators found that the combination (n = 179) resulted in a significant improvement in event-free survival (EFS) vs chemotherapy alone (n = 179) in patients with newly diagnosed, resectable, histologically confirmed stage IB, II, or IIA NSCLC and measurable disease.

Specifically, median EFS with nivolumab plus chemotherapy was 31.6 months (95% CI, 30.2–not reached) vs 20.8 months (95% CI, 14.0-26.7) with chemotherapy alone (HR, 0.63; 95% CI, 0.45-0.87; P = .0052).

Moreover, the combination resulted in a pathologic complete response rate of 24% (95% CI, 18.0%-31.0%) vs 2.2% (95% CI, 0.6%-5.6%) with chemotherapy alone (P < .0001).

Results from a prespecified interim analysis for overall survival resulted in a HR of 0.57 (95% CI, 0.38-0.87), which did not cross the boundary for statistical significance.

To Read More, visit bit.ly/3J1norm.

Regulators Push Back PDUFA Date for BLA/sNDA of Ublituximab Plus Umbralisib in CLL and SLL

The FDA has extended the Prescription Drug User Fee Act (PDUFA) goal date to June 25 for the biologics license application (BLA) and supplemental new drug application (sNDA) seeking the approval of ublituximab plus umbralisib (Ukoniq; U2) in patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

The BLA/sNDA submissions were supported by findings from the phase 3 UNITY-CLL trial (NCT02612311), which compared U2 with obinutuzumab (Gazyva) plus chlorambucil in 421 evaluable patients with treatment-naive or relapsed/refractory CLL.

The FDA announced it was investigating umbralisib after initial findings revealed a potential increased risk of death in those who received the agent. As of September 2021, an imbalance was observed in favor of the control arm (HR, 1.23); however, no statistically significant difference was noted. When excluding deaths associated with COVID-19, the 2 arms were approximately balanced (HR, 1.04).

The regulatory agency notified the developer, TG Therapeutics, Inc, that the updated overall survival analyses that had been submitted in February represented a major amendment to the applications.

To Read More, visit bit.ly/31179Jv.
Levels of HER2 expression within the HER2-negative classification merit consideration

When standard treatment options for HER2-negative mBC are exhausted, additional therapies for varying levels of HER2 expression are needed to reshape how the story unfolds.

Daiichi Sankyo and AstraZeneca are committed to furthering the research and development of potential treatment options for women with mBC across the spectrum of HER2 expression.

Pacritinib Paves a “Unique Lane” of Treatment for Select Myelofibrosis

by Jackie Collins

PATIENTS WHO DEVELOP post-essential thrombocytopenia myelofibrosis (PET-MF) or post-polycythemia vera myelofibrosis (PPV-MF), which are associated with significant symptom burden and bone marrow failure, have limited therapies available for effective treatment. Unlike primary myelofibrosis, the biology of these 2 presents a challenge for investigators at the time of diagnosis and initiation of treatment.1 However, progress in prognostic scoring systems and a deeper understanding of associated cytogenetics of the disease have led investigators to develop novel agents for the treatment of patients with PET-MF and PPV-MF.1

The JAK2/IRAK1 inhibitor pacritinib (Vonjo) was granted accelerated approval by the FDA for the treatment of adult patients with intermediate or high-risk primary or secondary PET-MF or PPV-MF and with a platelet count below 50 × 10^9/L. The approval was based on findings from PERSIST-2 (NCT02055781), a phase 3 trial in which the primary end points were a reduction in spleen volume of at least 35% and a total symptom score (TSS) reduction of at least 50% at 24 weeks.

The approval marks the first treatment specifically for patients with cytopenic myelofibrosis, according to Ruben A. Mesa, MD, director of the Mays Cancer Center at The University of Texas Health San Antonio MD Anderson Cancer Center.

“[Pacritinib] is an important additional JAK2 inhibitor with a unique lane for patients with marked thrombocytopenia or even the broader cytopenic myelofibrosis,” Mesa said in an interview with OncologyLive®.

“This is a disease where multiple therapies are needed.”

ROAD TO APPROVAL

In PERSIST-2, patients with PET-MF and PPV-MF with enlarged spleens and platelet counts of 100 × 10^9/L or less were randomly assigned to receive 200-mg pacritinib at a twice-daily dose (n = 107), 400-mg once-daily dose (n = 104), or best available therapy (BAT; n = 100), which included agents such as ruxolitinib (Jakafi), watch-and-wait approaches, or symptom-directed treatment.2

The recommended dosage of pacritinib is 200 mg orally twice daily.3 During the course of the trial, the toxicity profile of the 400-mg dose was deemed unsafe.

Investigators evaluated efficacy among those participants with platelet count of less than 50 × 10^9/L. Of those who received pacritinib at the 200-mg twice-daily dose (n = 31), 29.0% (95% CI, 14.2%-48.0%) experienced a reduction in spleen volume of at least 35% vs 3.1% (95% CI, 0.1%-16.2%) of those who received BAT (n = 32).²

Additionally, 26% of patients who received the twice-daily dose experienced a reduction in TSS of at least 50% using the Modified Myelofibrosis Symptom Assessment Form compared with 9% of those who received BAT.²

“Pacritinib is somewhat distinct in that it is able to improve splenomegaly, a very important area of burden in myelofibrosis that has not been able to be safely used in patients with severe thrombocytopenia or a platelet count of [below 50 × 10^9/L with other agents],” Mesa said. “And, [pacritinib] can be given at full dose.”

Pacritinib had a predictable and manageable safety profile. In an analysis of the safety population, the most common all-grade adverse effects (AEs) among those who received pacritinib twice daily (n = 104) were diarrhea (48%), thrombocytopenia (34%), nausea (32%), anemia (24%), and peripheral edema (20%). For the 98 patients in the safety population who received BAT, the most common all-grade AEs were thrombocytopenia (23%), diarrhea (15%), nausea (15%), and peripheral edema (15%).²

Ruxolitinib and fedratinib (Inrebic), both included as BAT options, have been used off label for patients with myelofibrosis whose platelet counts are above 50 × 10^9/L, but they are typically given at a significantly reduced dose.

“[Ruxolitinib and fedratinib] can improve splenomegaly but have the [adverse] effect of potentially causing anemia; thrombocytopenia is the dose-limiting toxicity,” Mesa said. Pacritinib can be given at full dose for this patient population, Mesa explained.

Treatment with pacritinib also favorably affected transfusion burden among these patients. Specifically, among patients who were not transfusion independent at baseline, treatment with pacritinib reduced red blood cell (RBC) transfusion burden at week 24 on study.¹ Eight of 36 patients who received the twice-daily dose and were not transfusion independent vs 3 of 35 patients who received BAT experienced a reduction in burden.

Further, at week 24, among 44 patients who had hemoglobin (Hb) at least 10 g/dL at baseline who received pacritinib, 25% had an Hb increase of at least 2 g/dL or RBC transfusion independence for at least 8 weeks. Among the 41 patients who received BAT, only 12% achieved a clinical benefit.

Although these data were not included in the approval, Mesa noted that it marks an important clinical factor for this treatment. “There has been, for some patients, improvement in anemia or even turning patients from transfusion dependent to transfusion independent,” Mesa said.

The approval of pacritinib for patients with PET-MF or PPV-MF is not tied to a specific line of therapy. “In particular, [for] patients with a platelet count [below 50 × 10^9/L],” Mesa said, “it will be the most unique for any amount of thrombocytopenia under [below 100 × 10^9/L]. There clearly is activity in the PERSIST-1 study [NCT01773187] where it was not limited only to patients with thrombocytopenia; it is active for patients who have a normal platelet count. In those settings, it will be more in the second-line setting or potentially in combinations.”

Considering the significance of JAK inhibitors in myelofibrosis, breakthroughs will be needed in terms of monitoring. Moreover, when looking at progression-free and overall survival, it is important to further examine how the data correlate with the exact degree of splenomegaly shrinkage or symptom improvement, as well as the overall effect on the biology of the disease. Overall, the realm of correlational studies will be important to further understand the utility of these agents in myelofibrosis, Mesa said.

Future investigative efforts include those monitoring molecular markers, as well as inflammatory markers that may change rapidly, Mesa said. “There is a range of different phenotypes within the disease and many new mechanisms of action are being identified, [such as] IRAK1, as an additional, important new target.” As these breakthroughs continue to reshape the treatment of patients with myelofibrosis, it will be important to note that if there are multiple therapies, it will be necessary to have more evidence-based ways of sequencing them, Mesa said.

REFERENCES


**Drug Spotlight**

**FDA approval—February 28, 2022**

The FDA grants accelerated approval to pacritinib (Vonjo) for the treatment of adult patients with intermediate or high-risk primary or secondary (post–polycythemia vera or post–essential thrombocythemia) myelofibrosis with a platelet count below 50 × 10^9/L.

**Mechanism of action**
- Pacritinib is an oral kinase inhibitor with activity against wild-type JAK2, mutant JAK2V617F form, and FLT3. Pacritinib does not inhibit JAK1 and has demonstrated inhibitory activity against IRAK1.

**How supplied**
- 100 mg capsules
- 200 mg orally twice daily

**Company**
- CTI BioPharma Corp

**BASELINE PATIENT CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Pacritinib</th>
<th>BAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years, range)</td>
<td>Pacritinib (n = 74)</td>
</tr>
<tr>
<td></td>
<td>BAT (n = 72)</td>
</tr>
<tr>
<td>Median palpable spleen length, cm (range)</td>
<td>Pacritinib (n = 74)</td>
</tr>
<tr>
<td></td>
<td>BAT (n = 72)</td>
</tr>
</tbody>
</table>

**Type of myelofibrosis diagnosis at baseline**
- Pacritinib
- BAT

**Number of prior therapies at baseline**

<table>
<thead>
<tr>
<th>Pacritinib</th>
<th>BAT</th>
</tr>
</thead>
</table>
| 0 | 0%
| 1 | 22%
| 2 | 25%
| 3 | 23%
| ≥ 3 | 22%

**Efficacy in the PERSIST-2 Trial**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pacritinib (n = 31)</th>
<th>BAT (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 35% SVR (95% CI)</td>
<td>29% (14.2%-48.0%)</td>
<td>3.1% (0.1%-16.2%)</td>
</tr>
<tr>
<td>≥ 50% reduction in TSS (95% CI)</td>
<td>23% (9.6%-41.1%)</td>
<td>13% (3.5%-29.0%)</td>
</tr>
</tbody>
</table>

**TOTAL SYMPTOM SCORE (TSS)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pacritinib (n = 44)</th>
<th>BAT (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin ≥ 2 g/dL or RBC transfusion independence for ≥ 8 weeks</td>
<td>25%</td>
<td>12%</td>
</tr>
</tbody>
</table>

**Additional Efficacy Data**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pacritinib (n = 37)</th>
<th>BAT (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced RBC transfusion burden at week 24</td>
<td>22%</td>
<td>9%</td>
</tr>
</tbody>
</table>

**Commonly Reported Adverse Effects in the PERSIST-2 Trial**

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Pacritinib (n = 106)</th>
<th>BAT (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grade</td>
<td>Grade 3/4</td>
<td>All grade</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48%</td>
<td>4%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>34%</td>
<td>32%</td>
</tr>
<tr>
<td>Nausea</td>
<td>32%</td>
<td>1%</td>
</tr>
<tr>
<td>Anemia</td>
<td>24%</td>
<td>22%</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>20%</td>
<td>1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19%</td>
<td>0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15%</td>
<td>1%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15%</td>
<td>1%</td>
</tr>
</tbody>
</table>

**Warnings and Precautions**

- Hemorrhage
- Diarrhea
- Thrombocytopenia
- Prolonged QT interval

- Major adverse cardiac event
- Thrombosis
- Secondary malignancies
- Risk of infection

**References**

THE FIRST EVER TARGETED THERAPY FOR RESECTABLE EGFRm NSCLC

The first and only EGFR TKI to help prevent disease recurrence or death

ADJUVANT TAGRISSO: DELIVERING OVERWHELMING EFFICACY

TAGRISSO demonstrated extraordinary disease-free survival in resected EGFRm NSCLC patients¹-³

Consistent results with or without prior adjuvant chemotherapy²⁺

• Patients in the ADAURA trial are treated with ORAL TAGRISSO FOR 3 YEARS or until disease recurrence or unacceptable toxicity

*Median DFS was not reached for TAGRISSO (95% CI: 38.8, NE) and was 19.6 months (95% CI: 16.6, 24.5) for control arm.¹

†Control arm=placebo.

*Exploratory subgroup results for patients with adjuvant chemotherapy was HR=0.23 (95% CI: 0.15, 0.40).²

CI, confidence interval; DFS, disease-free survival; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive; IASLC, International Association for the Study of Lung Cancer; L858R, exon 21 leucine 858 arginine substitution; NE, not estimable; CI, confidence interval; DFS, disease-free survival; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive; IASLC, International Association for the Study of Lung Cancer; L858R, exon 21 leucine 858 arginine substitution; NE, not estimable; NSCLC, non-small cell lung cancer; QoL, quality of life; TKI, tyrosine kinase inhibitor.

INDICATION

• TAGRISSO is indicated as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test

SELECT SAFETY INFORMATION

• There are no contraindications for TAGRISSO

• Interstitial lung disease (ILD)/pneumonitis occurred in 3.7% of the 1479 TAGRISSO-treated patients; 0.3% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed

AstraZeneca

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ADAURA study design: Phase III, double-blind, randomized, placebo-controlled trial in 682 patients with completely resected stage IB, II, and IIIA NSCLC with or without adjuvant chemotherapy. NSCLC patients had centrally confirmed EGFR mutations (exon 19 deletion or L858R mutation). Patients were stratified by stage (IB vs II vs IIIA), EGFR mutation (exon 19 deletion or L858R), and race (Asian vs non-Asian). Patients were randomized to either TAGRISSO (n=339, 80 mg orally, once daily) or placebo (n=343). The maximum interval between surgery and randomization was 26 weeks with adjuvant chemotherapy and 10 weeks without adjuvant chemotherapy. The primary endpoint of the study was DFS by investigator assessment in stage II/IIIA patients. The secondary endpoints were DFS in the overall population (stage IB/II/IIIA), DFS rate at 2, 3, 4, and 5 years, overall survival (stage II/IIIA and overall population), safety, and health-related QoL. The planned treatment duration was 5 years or until disease recurrence/unacceptable toxicity.1

SELECT SAFETY INFORMATION

- Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSO-treated patients. Of the 1479 TAGRISSO-treated patients in clinical trials, 0.8% were found to have a QTc >500 msec, and 3.1% of patients had an increase from baseline QTc >60 msec. No QTc-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia.

- Cardiomyopathy occurred in 3% of the 1479 TAGRISSO-treated patients. 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10% from baseline and to <50% LVEF occurred in 3.2% of 1233 patients who had baseline and at least one follow-up LVEF assessment. In the ADAURA study, 1.5% (5/325) of TAGRISSO-treated patients experienced LVEF decreases ≥10% from baseline and a drop to <50%. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO.

- Keratitis was reported in 0.7% of 1479 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist.

- Postmarketing cases consistent with Stevens-Johnson syndrome (SJS) and erythema multiforme major (EMM) have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if SJS or EMM is suspected and permanently discontinue if confirmed.

- Postmarketing cases of cutaneous vasculitis including leukocytoclastic vasculitis, urticarial vasculitis, and IgA vasculitis have been reported in patients receiving TAGRISSO. Conduct periodic monitoring with ECGs and electrolytes in patients with connective tissue disease or vasculitis. Withhold TAGRISSO if cutaneous vasculitis is suspected, evaluate for systemic involvement, and consider dermatology consultation. If no other etiology can be identified, consider permanent discontinuation of TAGRISSO based on severity.

- Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose.

- Most common (≥20%) adverse reactions, including laboratory abnormalities, were leukopenia, lymphopenia, thrombocytopenia, diarrhea, anemia, rash, musculoskeletal pain, nail toxicity, neutropenia, dry skin, stomatitis, fatigue, and cough.

Tagrisso is indicated for adult patients with metastatic EGFR T790M mutation-positive NSCLC with disease progression on or after EGFR TKI therapy who have been previously treated with an EGFR TKI for the treatment of EGFR mutation-positive NSCLC.
Serious adverse reactions were reported in 18% of patients treated with TAGRISSO and 28% when co-administering with a strong CYP3A4 inducer. No serious adverse reaction was reported in 2% or more patients treated with TAGRISSO. One patient (0.4%) treated with TAGRISSO experienced a fatal adverse reaction (ILD/pneumonitis).

Table 4. Adverse Reactions Occurring in >10% of Patients Receiving TAGRISSO in FLAURA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=279)</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=277)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3/4 (%)</td>
<td>All Grades (%)</td>
<td>Grade 3/4 (%)</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>38</td>
<td>≤ 1</td>
<td>38</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td></td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>44</td>
<td>≤ 1</td>
<td>44</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>51</td>
<td>0.7</td>
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</tr>
<tr>
<td>Neutropenia</td>
<td>42</td>
<td>≤ 1</td>
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<tr>
<td>Metabolic and Nutritional Disorders</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Increased weight</td>
<td>12</td>
<td>≥ 1</td>
<td>12</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cough</td>
<td>17</td>
<td>0.4</td>
<td>17</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>0.4</td>
<td>10</td>
</tr>
<tr>
<td>Neurologic Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>22</td>
<td>1.1</td>
<td>21</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>10</td>
<td>0.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Skin Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>58</td>
<td>1.1</td>
<td>58</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>1.8%</td>
<td>1.4%</td>
<td></td>
</tr>
<tr>
<td>QTc interval prolongation</td>
<td>1.4%</td>
<td>1.1%</td>
<td></td>
</tr>
</tbody>
</table>

Clinically relevant adverse reactions in FLAURA in >10% of patients receiving TAGRISSO were alopecia (7%), epistaxis (6%), interstitial lung disease (3.9%), urticaria (2.2%), palmar-palm erythrodysesthesia syndrome (1.4%), QTc interval prolongation (1.1%), and rash (0.4%). EGFR TKI internal control measurement represents the incidence of patients who had a ≥1% change in baseline and at least one on-study laboratory measurement available (TAGRISSO range: 267 - 273 and EGFR TKI comparator range: 244 - 247).

Table 5. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in FLAURA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>N/A</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>38</td>
<td></td>
</tr>
<tr>
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<td>Lymphopenia</td>
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<tr>
<td>Decreased platelets</td>
<td>25</td>
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<tr>
<td>Lymphopenia</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
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<td></td>
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<tr>
<td>Increased weight</td>
<td>12</td>
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</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
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</tr>
<tr>
<td>Cough</td>
<td>17</td>
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<tr>
<td>Nausea</td>
<td>10</td>
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<tr>
<td>Neurologic Disorders</td>
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<tr>
<td>Fatigue</td>
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<td>Cardiac Disorders</td>
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<td>Prolonged QT interval</td>
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<td>Skin Disorders</td>
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<td>Rash</td>
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<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
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</tr>
<tr>
<td>QTc interval prolongation</td>
<td>1.4%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

Clinical relevant laboratory abnormalities in FLAURA that occurred in ≥20% of patients receiving TAGRISSO were increased blood creatinine (7%), and reduced hemoglobin (4%). EGFR TKI comparator (gefitinib or erlotinib) laboratory abnormalities were anemia (7%), and increased AST (8%). Laboratory abnormalities of ≥1% change from baseline and at least one on-study laboratory measurement available (TAGRISSO range: 267 - 273 and EGFR TKI comparator range: 244 - 247).

Table 6. Adverse Reactions Occurring in >10% of Patients Receiving TAGRISSO in AURA2

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=279)</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=277)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3/4 (%)</td>
<td>All Grades (%)</td>
<td>Grade 3/4 (%)</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>35</td>
<td>0.4</td>
<td>30</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td></td>
<td>20</td>
<td>1.7</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>47</td>
<td>0.7</td>
<td>51</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased weight</td>
<td>12</td>
<td>≥ 1</td>
<td>12</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>17</td>
<td>0.4</td>
<td>16</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>0.4</td>
<td>10</td>
</tr>
<tr>
<td>Neurologic Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>22</td>
<td>1.1</td>
<td>21</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>10</td>
<td>0.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Skin Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>58</td>
<td>1.1</td>
<td>58</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>1.8%</td>
<td>1.4%</td>
<td></td>
</tr>
<tr>
<td>QTc interval prolongation</td>
<td>1.4%</td>
<td>1.1%</td>
<td></td>
</tr>
</tbody>
</table>

Clinically relevant adverse reactions in AURA2 in >10% of patients receiving TAGRISSO were epistaxis (6%), interstitial lung disease (3.9%), alopecia (3.9%), epistaxis (2.2%), palmar-palm erythrodysesthesia syndrome (1.8%), QTc interval prolongation (1.1%), leukopenia (1.1%), and erythema multiforme (0.7%). EGFR TKI internal control measurement represents the incidence of patients who had a ≥1% change from baseline and at least one on-study laboratory measurement available (TAGRISSO range: 267 - 273 and EGFR TKI comparator range: 244 - 247).

Table 7. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in AURA3

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>N/A</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
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<td></td>
</tr>
<tr>
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<td>1.1%</td>
</tr>
</tbody>
</table>

Clinically relevant laboratory abnormalities in AURA3 that occurred in ≥20% of patients receiving TAGRISSO were anemia (5%), and increased AST (8%). EGFR TKI comparator (gefitinib or erlotinib) laboratory abnormalities were neutropenia (12%), and increased AST (8%). Laboratory abnormalities of ≥1% change from baseline and at least one on-study laboratory measurement available (TAGRISSO range: 267 - 273 and EGFR TKI comparator range: 244 - 247).

Table 8. Other Drugs Taken During Treatment

<table>
<thead>
<tr>
<th>Other Drug</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin)</td>
<td>130%</td>
</tr>
</tbody>
</table>

TAGRISSO® (osimertinib) tablets, for oral use

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

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Rev. 1/21 US-56124 8/21
Matulonos’ Passion Drives Gynecologic Cancer Research Into the Next Era

SPECIALIZATION IN ONCOLOGY\textsuperscript{1} research affords investigators the opportunity to dive into tumor biology and uncover unique approaches to care. But specialization does not mean siloed approaches. Cross-functional team collaboration coupled with insights gained from patient interactions in the clinic and input from external collaborators are all vital to contributing to the rapidly changing treatment landscape, according to Ursula A. Matulonis, MD, a pillar of gynecologic cancer research and the embodiment of collaborative spirit.

From her start in gynecologic oncology drug development to her present-day position as chief of the Division of Gynecologic Oncology at the Dana-Farber Cancer Institute (Dana-Farber), coleader of the Gynecologic Cancer Program within the Dana-Farber/Harvard Cancer Center, and professor of medicine at Harvard Medical School in Boston, Massachusetts, Matulonis’ career has been built on the foundation of fostering and developing collaborative environments and programs to push the unmet needs of patients with gynecologic cancers into the research spotlight.

In her roles, Matulonis noted that she is coleader of the administrative corps with D’Andrea and Spriggs, as well as the developmental research program with D’Andrea and Kevin M. Elias, MD, who is director of the Gynecologic Oncology Laboratory at Brigham and Women’s Hospital and an assistant professor of obstetrics, gynecology, and reproductive biology at Harvard Medical School.\textsuperscript{2} “The [developmental program] provides grants to fledgling new projects that may eventually serve as a different project within the SPORE grant. It’s been super fun, [and] it is a 5-year grant, so we’re busy at work at the moment.”

In addition to her ongoing leadership and investigative efforts at Dana-Farber, Matulonis will return as the cochair of the upcoming 13th Annual International Symposium on Ovarian Cancer and Other Gynecologic Malignancies\textsuperscript{3}, a 1-day program to be hosted by Physicians’ Education Resource\textsuperscript{4}, LLC (PER\textsuperscript{5}), on May 14, 2022.

“I’ve cochaired [the symposium] for a number of years now, [and it] really [is] a group effort,” Matulonis said. “[The agenda] is very fun to put working hard—collaboration is critical. No one can operate singularly, it just doesn’t work that way,” Matulonis said.

There is no better way to highlight the collaborative spirit at work than through her latest achievement, securing a Specialized Program of Research Excellence (SPORE) grant from the National Cancer Institute.\textsuperscript{1} The Ovarian Cancer SPORE will focus on the development of combination drugs for low-grade serous cancers, the initiation of trials to evaluate combination therapies to overcome PARP inhibitor resistance, and the development of novel neoantigen vaccine development to enhance immune response to checkpoint inhibitors for patients with ovarian cancer.\textsuperscript{1,2}

“This is something I’ve worked for years to develop and something I’ve worked really hard to get off the ground with others,” Matulonis said. “I’m not the sole person here, but a lot of hard work finally came to fruition in 2020. I colead [the program] with my basic science colleagues, Alan D. D’Andrea, MD, and David Spriggs, MD, at Massachusetts General Hospital,” she said. D’Andrea is the director of the Susan F. Smith Center for Women’s Cancers at Dana-Farber. Spriggs is the director of the Gynecologic Oncology Program at Massachusetts General Hospital Cancer Center.

“I’ve certainly learned, from [the SPORE] grant and from the gynecologic program within Dana-Farber, that many individuals need to be incorporated from an expert standpoint—surgeons, oncologists, medical oncologists, radiation oncologists, pathologists, basic scientists—everyone [must] have a seat at the table,” Matulonis said.

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together, and it changes over time. You truly have the experts in the field talking about their cancer [specialties, and it’s going to be interesting [this year] because we’ve got the world’s experts presenting.”

International presenters at this year’s meeting include Nicoletta Colombo, MD, PhD; Philipp Harter, MD, PhD; Susana Banerjee, MBBS, PhD, MA, FRCP; Domenica Lorusso, MD, PhD; and Ana Oaknin, MD, PhD. The assembled faculty will approach an agenda that has undergone a shift in recent years, moving away from an ovarian cancer–dominated agenda to one that reflects the trends in the field of subspecialties of gynecologic malignancies.

“I remember a few years ago, our focus was on the use of PARP inhibitors [in ovarian cancer], the adverse effects, when to use a PARP inhibitor, which PARP inhibitor to use, and so on,” Matulonis said. “This year, the top billing goes to cervical cancer because of what’s happened in the past year—the leapfrogging of immunoncology agents into [the treatment paradigm for] patients with newly diagnosed advanced cancer or those with recurrent cervical cancer.”

LAYING THE FOUNDATION FOR RESEARCH AND INNOVATION

Matulonis graduated from Albany Medical College in 1987 during what she referred to as “the dark ages of oncology.” Her first interest was hematologic malignancies, a field she thought she would pursue as she was drawn to the underlying biology. “I realized there was a whole world of solid tumors out there,” Matulonis said, noting that her interest in breast and gynecologic cancers was fostered during her fellowship at Dana-Farber.

“I was doing both breast and gynecologic cancers at Dana-Farber in the late 1990s, early 2000s, and no one was running a gynecologic program. I found women’s cancers compelling because they’re incredible cancers from a biology standpoint. There was not much drug development happening and we had limited therapies, so that propelled me to want to do a better job for our patients.”

Around 2004, the programs split into 2 divisions, and Matulonis chose to follow the pathway paved by recent advances with PARP inhibitors for gynecologic cancers. “What really drove the program forward and gave us footing and foundation were PARP inhibitors. I was one of the US principal investigators of Study 19 [NCT00753545], the results of which were published in the New England Journal of Medicine in 2012.”

The trial evaluated olaparib (Lynparza) as maintenance treatment for patients with platinum-sensitive, relapsed, high-grade serious ovarian cancer, demonstrating a significant progression-free survival (PFS) benefit. “That was a pivotal study. At that moment, there was nothing going on in ovarian cancer. In 2006, there was carboplatin/gemcitabine [for] platinum-sensitive cancer, but there had not been anything [new] since then. It was interesting to use these drugs [and] to see how they worked. They had activity, and Study 19 [illuminated] the concept that patients with BRCA-mutated tumors elicited much more benefit than nonmutated cancers. But even [patients with] nonmutated cancers had activity.”

Investigators solidified olaparib’s role in the treatment landscape with results of the SOLO-1 trial (NCT01844986), and Matulonis turned her attention to another novel agent, niraparib (Zejula), serving as the US principal investigator of the phase 3 NOVA trial (NCT01847274). “That was an incredibly exciting time [and] sealed my interest in new drug development for ovarian cancer,” Matulonis said.

At the time that these agents were expanding the treatment landscape, Matulonis had a hand in another area of growth—the gynecologic cancer research team at Dana-Farber. With an influx of investigative efforts under her purview, Matulonis built out a team that would help to support not only the management of the grants and funding but also the processes required to move drug development from bench to bedside, including compliance standards. “I was able to grow the team from 2 or 3 medical oncologists up to 9 and build a team that includes research managers, data managers, research nurses, regulatory individuals, program managers—approximately 40 [team members].”

As a professor at Harvard Medical School, Matulonis said that position places her in a role that is meant to elevate the junior faculty. “I am at a certain point in my career, where my job is to make sure junior faculty are actively doing research, generating their own ideas, [and] writing their own trials,” Matulonis said. “My job is to be incredibly supportive and help them be successful.”

OBSERVATIONS FROM A DIVerging LANDSCAPE

The various histologies that fall under the gynecologic cancer umbrella do not respond to a one-size-fits-all approach. For example, patients with cervical cancer represent a significant unmet need in the clinic, as mortality rates worsen rather than improve in these subtypes. Endometrial cancer and ovarian cancer also have their own unique challenges for investigators at various stages.

“Each cancer is its own cancer, and there is a lot to think about individually,” Matulonis said.

AGENDA HIGHLIGHTS

13th Annual International Symposium on Ovarian Cancer and Other Gynecologic Malignancies

Treatment of gynecologic malignancies is a dynamic field with recent advances shifting the treatment paradigm to provide significant clinical benefit. The 1-day, educational, and scientific meeting will feature presentations from experts in gynecologic cancers on the latest diagnostic, therapeutic, and supportive care strategies for patients with ovarian, endometrial, and cervical malignancies.

“I can guarantee attendees that the agenda has been extremely well thought out, based on emerging trends in gynecologic cancer treatment,” said cochair Ursula A. Matulonis, MD. “We have been able to reach beyond US-based experts and have the world’s experts talking. There will be interactive discussions with the participants, case presentations, and opportunities for discourse.”

Some sessions of note include the following:

› Biological Rationale and Biomarkers for Immunotherapy in Cervical Cancer presented by Bradley J. Monk, MD, FACS, FACOG

› DDR and PARP Inhibitors in Ovarian Cancer presented by Panagiotis A. Kontstantinopoulos, MD, PhD

› Low-Grade Serious Ovarian Cancer presented by Susana Banerjee, MBBS, MA, FRCP, PhD

› Medical Crossfire®: Cytoreductive Surgery in Recurrent Ovarian Cancer: Does One Size Fit All? debate between Philipp Harter, MD, PhD, and Ritu Salani, MD, MBA

› Immunotherapy in Endometrial Cancer presented by Matthew A. Powell, MD

For more information scan the QR code or visit bit.ly/3iCbmZR.

Integration of Immuno-ology Agents

Data for immuno-ology (IO) agents have shown varying success across the gynecologic landscape, including among those with cervical cancer, ovarian cancer, endometrial cancer, and the tangentially related uterine cancer, according to Matulonis.

Pembrolizumab (Keytruda) has been integrated into the standard of care for patients with cervical cancer in combination and as a single agent based on PD-L1 expression, microsatellite instability-high (MSI-H), and mismatch repair deficient tumors (dMMR), respectively.Recently, the addition of pembrolizumab to chemotherapy with or without bevacizumab
TABLE 1. Tumor Agnostic Approvals for Patients With Gynecologic Cancers^6,10,11

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Drug</th>
<th>Patients</th>
<th>ORR (95% CI)</th>
<th>CR</th>
<th>PR</th>
<th>Additional Gynecologic Cancer Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>dMMR</td>
<td>Dostarlimab</td>
<td>adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options</td>
<td>41.6% (34.9%-48.6%)</td>
<td>9.1%</td>
<td>32.5%</td>
<td>for the treatment of patients with dMMR recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen</td>
</tr>
<tr>
<td>Pivotal trial: GARNET (NCT02715284)</td>
<td></td>
<td>(n = 209)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSI-H</td>
<td>Pembrolizumab</td>
<td>adult patients with unrespectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options</td>
<td>39.6% (31.7%-47.9%)</td>
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<tr>
<td>TMB</td>
<td>Pembrolizumab</td>
<td>adult and pediatric patients with unrespectable or metastatic TMB-high (≥ 10 mut/Mb) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options</td>
<td>29% (21%-39%)</td>
<td>4%</td>
<td>25%</td>
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<tr>
<td>Pivotal trial: KEYNOTE-158 (NCT02628067)</td>
<td></td>
<td>(n = 102)</td>
<td>(n = 70)</td>
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^6,10,11

For patients with endometrial cancer, combination IO therapy with tyrosine kinase inhibitor lenvatinib (Lenvima) plus pembrolizumab demonstrated a significant improvement in PFS vs chemotherapy alone in patients treated with pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic TMB-high (≥ 10 mut/Mb) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

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Tisotumab vedotin doesn’t have a marker, it’s tissue factor,” Matulonis said, noting that the FDA approval does not indicate that tissue factor must be present. “However, there are other ADCs in development that require a biomarker, namely mirvetuximab soravtansine, which is being considered for accelerated approval.”

At the Society of Gynecologic Oncology 2022 Annual Meeting on Women’s Cancer, Matulonis presented data from the single-arm phase 3 SORAYA trial (NCT04296890), which assessed the efficacy of mirvetuximab soravtansine in patients with platinum-resistant ovarian cancer who had received 1 to 3 prior lines of therapy, experienced disease recurrence within 6 months of the last platinum-based regimen, and who have high folate receptor-alpha (FRA) expression. The ADC is designed with a FA-receptor antibody, a cleavable linker, and maytansinoid DM4 payload. The overall response rate (ORR) among 105 treated patients was 32.4% (95% CI, 23.6%-42.2%), consisting of 5 complete responses and 29 partial responses. The agent elicited the highest response among patients who had prior treatment with a PARP inhibitor (n = 50), with an ORR of 38.0% (95% CI, 24.7%-52.8%).^13

"For patients with ovarian cancer, introduction of [IO] agents [are] a different story," Matulonis said. “The only approval for an IO agent in ovarian cancer is tumor agnostic for those patients with MSI-H or tumor mutational burden-high [TMB-H] disease, but IO does not have any formal indications.”

The tumor agnostic approvals for patients with solid tumors align with indications awarded to dostarlimab-gxly (Jemperli) for patients with dMMR recurrent or advanced solid tumors and pembrolizumab for patients with unrespectable or metastatic TMB-H disease (TABLE 1).^6,10,11

Antibody-Drug Conjugates

Matulonis said a few other trends in the space include finding a place for antibody-drug conjugates (ADCs) and turning a focus on developing novel targeted therapies. “The development of targeted specific drugs to specific tumors may come from novel ADCs,” Matulonis said.

In September 2021, the FDA approved the tissue factor-directed antibody and microtubular inhibitor conjugate, tisotumab vedotin-tftv (Tivdak), for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. The approval was based on data from 101 patients treated in the phase 2 innovaTV 204 trial (NCT03438396), in which the agent elicited an objective response rate of 24% (95% CI, 15.9%-33.3%), with a median duration of response of 8.3 months (95% CI, 4.2- not reached). Tisotumab vedotin doesn’t have a marker, it’s tissue factor,” Matulonis said, noting that the FDA approval does not indicate that tissue factor must be present. “However, there are other ADCs in development that require a biomarker, namely mirvetuximab soravtansine, which is being considered for accelerated approval.”

At the Society of Gynecologic Oncology 2022 Annual Meeting on Women’s Cancer, Matulonis presented data from the single-arm phase 3 SORAYA trial (NCT04296890), which assessed the efficacy of mirvetuximab soravtansine in patients with platinum-resistant ovarian cancer who had received 1 to 3 prior lines of therapy, experienced disease recurrence within 6 months of the last platinum-based regimen, and who have high folate receptor-alpha (FRA) expression. The ADC is designed with a FRa-binding antibody, a cleavable linker, and maytansinoid DM4 payload. The overall response rate (ORR) among 105 treated patients was 32.4% (95% CI, 23.6%-42.2%), consisting of 5 complete responses and 29 partial responses. The agent elicited the highest response among patients who had prior treatment with a PARP inhibitor (n = 50), with an ORR of 38.0% (95% CI, 24.7%-52.8%).

“Antibody-Drug Conjugates Matulonis said a few other trends in the space include finding a place for antibody-drug conjugates (ADCs) and turning a focus on developing novel targeted therapies. “The development of targeted specific drugs to specific tumors may come from novel ADCs,” Matulonis said. In September 2021, the FDA approved the tissue factor-directed antibody and microtubular inhibitor conjugate, tisotumab vedotin-tftv (Tivdak), for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. The approval was based on data from 101 patients treated in the phase 2 innovaTV 204 trial (NCT03438396), in which the agent elicited an objective response rate of 24% (95% CI, 15.9%-33.3%), with a median duration of response of 8.3 months (95% CI, 4.2- not reached). Tisotumab vedotin doesn’t have a marker, it’s tissue factor,” Matulonis said, noting that the FDA approval does not indicate that tissue factor must be present. “However, there are other ADCs in development that require a biomarker, namely mirvetuximab soravtansine, which is being considered for accelerated approval.”
“These results position mirvetuximab soravtansine to become a practice-changing, biomarker-driven, standard-of-care treatment option for patients with FRa-positive, platinum-resistant ovarian cancer,” Matulonis said at the meeting.

The Status of PARP in Ovarian Cancer

With 3 PARP approvals in the first-line maintenance setting, the use of these agents is deeply embedded in the treatment of patients with ovarian cancer (TABLE 2). However, there is a long road ahead for investigators, as resistance mechanisms present barriers to their continued efficacy.

Matulonis has been on that road since 2011, when early data demonstrated that a synergistic effect existed with the combination of PI3K and PARP inhibitors in breast cancer with or without BRCA mutations. In 2019, Matulonis and Dana-Farber colleague Panagiotis A. Konstantinopoulos, MD, PhD, published data from a phase 1 study (NCT01623349) of the combination of olaparib and alpelisib (Piqray), an α-specific PI3K inhibitor in patients with recurrent triple-negative breast cancer or high-grade serous ovarian cancer. Konstantinopoulos is the director of translational research in gynecologic oncology at Dana-Farber and an associate professor of medicine at Harvard Medical School.

Efficacy data from the trial showed that among the 28 patients with epithelial ovarian cancer 36% had a partial response, 50% had stable disease, and 11% had progressive disease. One patient (4%) was un evaluable for response using RECIST 1.1. Of note, 8 patients had stable disease for at least 6 months at the time of analysis. In early 2021, the phase 3 trial EPIK-O (NCT04729387) was initiated to evaluate alpelisib plus olaparib or single-agent cytotoxic chemotherapy in adult patients with platinum-resistant or refractory high-grade serous ovarian cancer with no germline BRCA mutation. Patients in the experimental arm received the maximum-tolerated dose determined in the previous study (alpelisib 200 mg orally once daily and olaparib 200 mg orally twice daily).

“It took 10 years, but we finally got to the point where this could potentially serve as a study to support an FDA approval,” Matulonis said. “It’s early on, but it’s pretty exciting.”

### TABLE 2. PARP Inhibitor Maintenance Therapies for Ovarian Cancer

<table>
<thead>
<tr>
<th>PARP Inhibitor</th>
<th>Indication</th>
<th>Outcome</th>
<th>Efficacy for approval in all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>The treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with ≥3 prior lines of chemotherapy</td>
<td>Olaparib (n = 137)</td>
<td>Placebo (n = 118)</td>
</tr>
<tr>
<td></td>
<td>ORR (95% CI)</td>
<td>34% (26%-42%)</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>CR</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PR</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Rucaparib</td>
<td>For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy</td>
<td>Rucaparib (n = 236)</td>
<td>Placebo (n = 118)</td>
</tr>
<tr>
<td></td>
<td>Median PFS, months</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR, 0.36; 95% CI, 0.30-0.45; P &lt; .0001</td>
<td>13.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Efficacy in HRD group*</td>
<td>Rucaparib (n = 130)</td>
<td>Placebo (n = 66)</td>
</tr>
<tr>
<td></td>
<td>Median PFS, months</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR, 0.23; 95% CI, 0.16-0.34; P &lt; .0001</td>
<td>16.6</td>
<td></td>
</tr>
<tr>
<td>Niraparib</td>
<td>For the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to first-line, platinum-based chemotherapy</td>
<td>Niraparib (n = 487)</td>
<td>Placebo (n = 246)</td>
</tr>
<tr>
<td></td>
<td>Median PFS, months (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR, 0.62; 95% CI, 0.50-0.76; P &lt; .0001</td>
<td>13.8 (11.5-14.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Efficacy in HRD group</td>
<td>Niraparib (n = 247)</td>
<td>Placebo (n = 126)</td>
</tr>
<tr>
<td></td>
<td>Median PFS, months (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR, 0.43; 95% CI, 0.31-0.59; P &lt; .0001</td>
<td>21.9 (19.3-NE)</td>
<td></td>
</tr>
</tbody>
</table>

CR, complete response; HRD, homologous recombination deficient; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial response.

*Includes patients with deleterious germline or somatic BRCA mutation or high genomic loss of heterozygosity.

PASSION REFLECTED IN WORDS

Looking back at how the trajectory of her career has led her to become a prominent leader of the next generation of investigators, Matulonis’ favorite quotes echo her sentiments of her current positions. “One of my favorite quotes is from Buzz Lightyear, ‘To infinity and beyond.’ That’s my go-to—think big. Another is from Billie Jean King, ‘Pressure is a privilege,’ which is etched into the National Tennis Center in Queens, [New York],” she said. “There’s a lot of pressure [in our work,] but what we do really is a privilege. All the faculty are hardworking, and I try to make sure they’re not completely overlapping in terms of what kind of research they’re doing.

“I know some are pursuing drug development [and] some are working solely on novel immunotherapies. [Elizabeth H. Stover, MD, PhD] is working on rare tumors … We are charging faculty with coming up with new ideas about how to tackle clinical problems, then giving them the resources to do that.”

Although Matulonis noted that at times her role is somewhat akin to being an air traffic controller, her passion for the work is evident in the way she speaks of inspiring the next wave of innovation in the field. “I see it as a mission of mine because of the need for new drug development and new treatment strategies for our patients,” she said.

“It is imperative that we train the next generation competently and well. To be a successful faculty member, to stay in academics, those individuals [must] feel that they are productive, that they are enjoying what they’re doing, [and] that they feel fulfilled. That’s important, I want to keep them engaged.”

For a full list of references, see the article at OneLive.com.
Indication
VONJO™ (pacritinib) is indicated for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera [PPV] or post-essential thrombocythemia [PET]) myelofibrosis (MF) with a platelet count below $50 \times 10^9/L$.

This indication is approved under accelerated approval based on spleen volume reduction. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

VONJO is available as 100 mg capsules, for oral use.

Important Safety Information
CONTRAINDICATIONS
VONJO is contraindicated in patients concomitantly using strong CYP3A4 inhibitors or inducers as these medications can significantly alter exposure to pacritinib, which may increase the risk of adverse reactions or impair efficacy.

Please see Important Safety Information and Brief Summary on the following pages and full Prescribing Information at VONJO.com.

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Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with VONJO, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

**Risk of Infection:** Another JAK inhibitor has increased the risk of serious infections (compared to best available therapy) in patients with myeloproliferative neoplasms. Serious bacterial, mycobacterial, fungal, and viral infections may occur in patients treated with VONJO. Delay starting VONJO with VONJO until active serious infections have resolved. Observe patients receiving VONJO for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.

**DRUG INTERACTIONS**

**Effect of Other Drugs on VONJO:** VONJO is predominantly metabolized by CYP3A4. Coadministration of VONJO with strong CYP3A4 inhibitors or inducers are contraindicated. Avoid concomitant use of VONJO with moderate CYP3A4 inhibitors or inducers.

**Effect of VONJO on Other Drugs:** VONJO is an inhibitor of CYP1A2, CYP3A4, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic cation transporter 1 (OCT1) in vitro. Concomitant administration of VONJO with these substrates may increase their plasma concentrations. Avoid coadministration of VONJO with drugs that are sensitive substrates of CYP1A2, CYP3A4, P-gp, BCRP or OCT1.

### ADVERSE REACTIONS

**Fatal adverse reactions occurred in 8% of patients receiving VONJO 200 mg twice daily and in 9% of patients treated with best available therapy (BAT). The fatal adverse reactions among patients treated with VONJO 200 mg twice daily included events of disease progression (3%), and multiorgan failure, cerebral hemorrhage, meningoencephalitis, and acute myeloid leukemia in <1% of patients each, respectively.**

Serious adverse reactions occurred in 47% of patients treated with VONJO 200 mg twice daily and in 31% of patients treated with BAT. The most frequent serious adverse reactions occurring ≥3% patients receiving VONJO 200 mg twice daily were anemia (8%), thrombocytopenia (6%), pneumonia (6%), cardiac failure (4%), disease progression (3%), pyrexia (3%), and squamous cell carcinoma of skin (3%).

Permanent discontinuation due to an adverse reaction occurred in 15% of patients receiving VONJO 200 mg twice daily compared to 12% of patients treated with BAT. The most frequent reasons for permanent discontinuation in ≥2% of patients receiving VONJO 200 mg twice daily included anemia (3%) and thrombocytopenia (2%).

The most common adverse reactions in ≥20% of patients (N=106) were diarrhea, thrombocytopenia, nausea, anemia, and peripheral edema.

### USE IN SPECIFIC POPULATIONS

**Pregnancy:** There are no available data on VONJO use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Advise pregnant women of the potential risk to a fetus. Consider the benefits and risks of VONJO for the mother and possible risks to the fetus when prescribing VONJO to a pregnant woman.

**Lactation:** There are no data on the presence of pacritinib in either human or animal milk, the effects on the breastfed child, or the effects on milk production. It is not known whether VONJO is excreted in human milk. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with VONJO, and for 2 weeks after the last dose.

**Infertility:** Pacritinib reduced male mating and fertility indices in BALB/c mice. Pacritinib may impair male fertility in humans.

**Pediatric Use:** The safety and effectiveness of VONJO in pediatric patients have not been established.

**Hepatic Impairment:** Administration of a single dose of VONJO 400 mg to subjects with hepatic impairment resulted in a decrease in the geometric mean area under the concentration curve (AUC) of pacritinib by 85%, 36%, and 45% in subjects with mild [Child-Pugh A], moderate [Child-Pugh B], or severe hepatic impairment [Child-Pugh C], respectively, compared to subjects with normal hepatic function. Avoid use of VONJO in patients with moderate [Child-Pugh B] or severe hepatic impairment [Child-Pugh C].

**Renal Impairment:** Administration of a single dose of VONJO 400 mg to subjects with renal impairment resulted in approximately 30% increase in maximal concentration (Cmax) and AUC of pacritinib in subjects with eGFR 15 to 29 mL/min and eGFR <15 mL/min on hemodialysis compared to subjects with normal renal function (eGFR ≥90 mL/min). Avoid use of VONJO in patients with eGFR <30 mL/min.

Please see Brief Summary on the following pages and full Prescribing Information at VONJO.com.

US-PAC-200045 02/2022
5.1 Hemorrhage
Serious (11%) and fatal (2%) hemorrhages have occurred in VONJO-treated patients with platelet counts <100 x 10^9/L. Serious (13%) and fatal (2%) hemorrhages have occurred in VONJO-treated patients with platelet counts <50 x 10^9/L. Grade ≥3 bleeding events (defined as requiring transfusion or invasive intervention) occurred in 15% of patients treated with VONJO compared to 7% of patients treated with control arm. Due to hemorrhage, VONJO dose reductions, dose interruptions, or permanent discontinuations occurred in 3%, 3%, and 5% of patients, respectively.

Avoid use of VONJO in patients with active bleeding and hold VONJO 7 days prior to any planned surgical or invasive procedures. Assess platelet counts periodically, as clinically indicated. Manage hemorrhage using treatment interruption and medical intervention.

5.2 Diarrhea
VONJO caused diarrhea in approximately 48% of patients compared to 15% of patients treated with the control arm. The median time to resolution in VONJO-treated patients was 2 weeks. The incidence of reported diarrhea decreased over time with 41% of patients reporting diarrhea in the first 8 weeks of treatment, 15% in Weeks 8-16, and 8% in Weeks 16-24. Diarrhea resulted in treatment interruption in 3% of VONJO-treated patients. None of the VONJO-treated patients reported diarrhea that resulted in treatment discontinuation. Serious diarrhea adverse reactions occurred in 2% of patients treated with VONJO compared to no such adverse reactions in patients in the control arm. Control preexisting diarrhea before starting VONJO treatment. Manage diarrhea with anti-diarrheal medications, fluid replacement, and dose modification. Treat diarrhea with anti-diarrheal medications promptly at the first onset of symptoms. Interrupt or reduce VONJO dose in patients with significant diarrhea despite optimal supportive care.

5.3 Thrombocytopenia
VONJO can cause worsening thrombocytopenia. VONJO dosing was reduced due to worsening thrombocytopenia in 2% of patients with preexisting moderate to severe thrombocytopenia (platelet count <100 x 10^9/L). VONJO dosing was reduced due to worsening thrombocytopenia in 2% of patients with preexisting severe thrombocytopenia (platelet count <50 x 10^9/L). Monitor platelet count prior to VONJO treatment and as clinically indicated during treatment. Interrupt VONJO in patients with clinically significant worsening of thrombocytopenia that lasts for more than 7 days. Restart VONJO at 50% of the last given dose once the toxicity has resolved. If toxicity recurs, hold VONJO. Restart VONJO at 50% of the last given dose once the toxicity has resolved.

5.4 Prolonged QT Interval
VONJO can cause prolongation of the QTc interval. QTc prolongation of >500 msec was higher in VONJO-treated patients than in patients in the control arm (1.4% vs 1%). QTc increase from baseline by 60 msec or higher was greater in VONJO-treated patients than in control arm patients (1.9% vs 1%). Adverse reactions of QTc prolongation were reported for 3.8% of VONJO-treated patients and 2% of control arm patients. No cases of torsades de pointes were reported.

Avoid use of VONJO in patients with a baseline QTc of >480 msec. Avoid use of drugs with significant potential for QTc prolongation in combination with VONJO. Correct hypokalemia prior to and during VONJO treatment. Manage QTc prolongation using VONJO interruption and electrolyte management.

5.5 Major Adverse Cardiac Events (MACE)
Another Janus kinase (JAK) inhibitor has increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with VONJO, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur.

5.6 Thrombosis
Another JAK inhibitor has increased the risk of thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

5.7 Secondary Malignancies
Another JAK inhibitor has increased the risk of lymphoma and other malignancies, excluding non-melanoma skin cancer (NMSC), (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which VONJO is not indicated. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with VONJO, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

5.8 Risk of Infection
Another JAK inhibitor has increased the risk of serious infections (compared to best available therapy) in patients with myeloproliferative neoplasms. Serious bacterial, mycobacterial, fungal, and viral infections may occur in patients treated with VONJO. Delay starting therapy with VONJO until active serious infections have resolved. Observe patients receiving VONJO for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.

5.9 Interactions With CYP3A4 Inhibitors or Inducers
Coadministration of VONJO with strong CYP3A4 inhibitors or inducers is contraindicated. Avoid concomitant use of VONJO with moderate CYP3A4 inhibitors or inducers.

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

- Hemorrhage [see Warnings and Precautions (5.1)]
- Diarrhea [see Warnings and Precautions (5.2)]
- Thrombocytopenia [see Warnings and Precautions (5.3)]
- Prolonged QT Interval [see Warnings and Precautions (5.4)]
- Major Adverse Cardiac Events [see Warnings and Precautions (5.5)]
- Thrombosis [see Warnings and Precautions (5.6)]
- Secondary Malignancies [see Warnings and Precautions (5.7)]
- Risk of Infection [see Warnings and Precautions (5.8)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The safety of VONJO was evaluated in the randomized, controlled PERSIST-2 trial. In PERSIST-2, key eligibility criteria included adults with intermediate or high-risk primary or secondary (PPV or PET) MF with splenomegaly and a platelet count ≤100 × 10⁹/L. Prior JAK inhibitor therapy was permitted. Patients received VONJO at 200 mg twice daily (n=106), 400 mg once daily (n=104), or best available therapy (BAT) n=98. Forty-seven (44%) of the 106 patients treated with VONJO 200 mg twice daily had a baseline platelet count of <50 × 10⁹/L. The 400 mg once daily dose could not be established to be safe, so further information on this arm is not provided.

In PERSIST-2, among the 106 patients treated with VONJO 200 mg twice daily, the median baseline hemoglobin was 9.7 g/dL, and the median drug exposure was 25 weeks. Fifty-four percent of patients were exposed for 6 months, and 18% were exposed for approximately 12 months. Accounting for dose reductions, the average daily dose (mean relative dose intensity) and median daily dose (median relative dose intensity) were 380 mg (95%) and 400 mg (100%), respectively, for patients receiving VONJO twice daily.

The median age of patients who received VONJO 200 mg twice daily was 67 years (range: 39 to 85 years), 59% were male, 86% were White, 3% were Asian, 2% were Native Hawaiian or Other Pacific Islander, 0% were Black, 9% did not report race, and 87% had an Eastern Cooperative Oncology Group performance status of 0 to 1.

Serious adverse reactions occurred in 47% of patients treated with VONJO 200 mg twice daily and in 31% of patients treated with BAT. The most frequent serious adverse reactions occurring in ≥2% patients receiving VONJO 200 mg twice daily were anemia (8%), thrombocytopenia (6%), pneumonia (6%), cardiac failure (4%), disease progression (3%), pyrexia (3%), and squamous cell carcinoma of skin (3%). Fatal adverse reactions occurred in 8% of patients receiving VONJO 200 mg twice daily and in 9% of patients treated with BAT. The fatal adverse reactions among patients treated with VONJO 200 mg twice daily included events of disease progression (3%), and multiorgan failure, cerebral hemorrhage, meningoencephalitis, and acute myeloid leukemia in <1% of patients each, respectively.

Permanent discontinuation due to an adverse reaction occurred in 15% of patients receiving VONJO 200 mg twice daily compared to 12% of patients treated with BAT. The most frequent reasons for permanent discontinuation in ≥2% of patients receiving VONJO 200 mg twice daily included anemia (3%) and thrombocytopenia (2%).

Drug interruptions due to an adverse reaction occurred in 27% of patients who received VONJO 200 mg twice daily compared to 10% of patients treated with BAT. The most frequent reasons for drug interruption in ≥2% of patients receiving VONJO 200 mg twice daily were anemia (5%), thrombocytopenia (4%), diarrhea (3%), nausea (3%), cardiac failure (3%), neutropenia (2%), and pneumonia (2%).

Dosage reductions due to an adverse reaction occurred in 12% of patients who received VONJO 200 mg twice daily compared to 7% of patients treated with BAT. Adverse reactions requiring dosage reduction in ≥2% of patients who received VONJO 200 mg twice daily included thrombocytopenia (2%), neutropenia (2%), conjunctival hemorrhage (2%), and epistaxis (2%). The most common adverse reactions in ≥20% of patients (N=106) were diarrhea, thrombocytopenia, nausea, anemia, and peripheral edema.

Table 5 summarizes the common adverse reactions in PERSIST-2 during randomized treatment.

Table 5  Adverse Reactions Reported in ≥10% Patients Receiving VONJO (200 mg Twice Daily) or BAT During Randomized Treatment in PERSIST-2

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>VONJO (200 mg Twice Daily) (N=106)</th>
<th>Best Available Therapy (N=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Gradesa</td>
<td>Grade ≥3</td>
<td>All Gradesa</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>44 4 5 0</td>
<td>24 22 15 14</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>34 32 23 18</td>
<td>11 11 9 8</td>
</tr>
<tr>
<td>Nausea</td>
<td>32 31 11 1</td>
<td>20 20 14 14</td>
</tr>
<tr>
<td>Anemia</td>
<td>24 22 15 14</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>13 13 13 13</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19 19 19 19</td>
<td>0</td>
</tr>
<tr>
<td>Nervousness</td>
<td>15 15 15 15</td>
<td>10 10 10 10</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15 15 15 15</td>
<td>10 10 10 10</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>12 12 12 12</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10 10 10 10</td>
<td>0</td>
</tr>
<tr>
<td>Flatulence</td>
<td>10 10 10 10</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>8 8 8 8</td>
<td>0</td>
</tr>
</tbody>
</table>

a Grade by CTCAE Version 4.03.

In a clinical drug interaction study, a single dose of VONJO 400 mg was administered following treatment with clarithromycin, a strong CYP3A4 inhibitor. Clarithromycin was administered as 500 mg twice daily for 5 days, which is a submaximal regimen for CYP3A4 inhibition. Compared to VONJO administered alone, the area under the concentration curve (AUC) and maximal concentration (Cmax) of pacritinib increased by 80% and 30%, respectively, upon coadministration with clarithromycin. The increase in exposure to pacritinib may be even higher when tested following a longer treatment with clarithromycin that results in maximal CYP3A4 inhibition. The impact of moderate CYP3A4 inhibitors on the pharmacokinetics of VONJO has not been investigated in clinical studies. Coadministration of VONJO with strong CYP3A4 inhibitors is contraindicated. Avoid concomitant use of VONJO with moderate CYP3A4 inhibitors.

In a clinical drug interaction study, a single dose of VONJO 400 mg was administered following treatment with rifampin, a strong CYP3A4 inducer, at 600 mg once daily for 10 days. Compared to VONJO administered alone, the AUC and Cmax of pacritinib decreased by 87% and 51%, respectively, upon coadministration with rifampin. The impact of moderate CYP450 inducers on the pharmacokinetics of VONJO has not been investigated in clinical studies. Coadministration of VONJO with strong CYP450 inducers is contraindicated. Avoid concomitant use of VONJO with moderate CYP450 inducers.
8 USE IN SPECIFIC POPULATIONS (cont.)

8.1 Pregnancy (cont.)
In a pre- and post-natal development study in mice, pregnant animals were
dosed with pacritinib from implantation through lactation at 30, 100, or
250 mg/kg/day. Maternal toxicity was noted at 250 mg/kg and associated
with increased gestation length and dystocia, lowered mean birth weights
and neonatal survival, and transiently delayed startle response, learning,
and memory development at weaning.

8.2 Lactation
Risk Summary
There are no data on the presence of pacritinib in either human or animal milk,
the effects on the breastfed child, or the effects on milk production. It is not
known whether VONJO is excreted in human milk. Because of the potential for
serious adverse reactions in the breastfed child, advise patients that
breastfeeding is not recommended during treatment with VONJO, and for
2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential
Infertility
Males
Pacritinib reduced male mating and fertility indices in BALB/c mice. Pacritinib
may impair male fertility in humans.

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

8.5 Geriatric Use
Clinical studies of VONJO did not include sufficient numbers of subjects aged 65
and over to determine whether they respond differently from younger subjects.

8.6 Hepatic Impairment
Administration of a single dose of VONJO 400 mg to subjects with hepatic
impairment resulted in a decrease in the geometric mean AUC of pacritinib by
8.5%, 36%, and 45% in subjects with mild [Child-Pugh A], moderate [Child-Pugh
B], or severe hepatic impairment [Child-Pugh C], respectively, compared to
subjects with normal hepatic function. Avoid use of VONJO in patients with
moderate [Child-Pugh B] or severe hepatic impairment [Child-Pugh C].

8.7 Renal Impairment
Administration of a single dose of VONJO 400 mg to subjects with renal
impairment resulted in approximately 30% increase in Cmin and AUC of pacritinib
in subjects with eGFR 15 to 29 mL/min and eGFR <15 mL/min on hemodialysis
compared to subjects with normal renal function (eGFR ≥90 mL/min). Avoid use
of VONJO in patients with eGFR <30 mL/min.

17 PATIENT COUNSELING INFORMATION
See FDA approved patient labeling (Patient Information).
Discuss the following with patient prior to and during treatment with VONJO:
Current therapy with another kinase inhibitor
Advise patients who are currently taking a kinase inhibitor that they must taper
or discontinue their current kinase inhibitor therapy according to the package
insert for that drug prior to starting VONJO.

Hemorrhage
Advise patients that VONJO can cause hemorrhage and instruct them to consult
their healthcare provider right away if bleeding occurs. Advise patients about
how to recognize bleeding and of the urgent need to report any unusual
bleeding to their physician. Patients should urgently seek emergency medical
attention for any bleeding that cannot be stopped.

Diarrhea
Advise patients that VONJO can cause diarrhea. Advise patients to stay hydrated
while taking VONJO and to inform their physician if they experience diarrhea.
Instruct patients to initiate anti-diarrheal medications (eg, loperamide) if
diarrhea occurs. Advise patients to urgently seek emergency medical attention
if diarrhea becomes severe.

Thrombocytopenia
Advise patients that VONJO is associated with thrombocytopenia, and of the
need to monitor complete blood counts before and during treatment.

Prolonged QT Interval
Advise patients to consult their healthcare provider immediately if they feel
faint, lose consciousness, or have signs or symptoms suggestive of arrhythmia.
Advise patients with a history of hypokalemia of the importance of monitoring
their electrolytes.

Major Adverse Cardiac Events (MACE)
Advise patients that events of MACE including myocardial infarction, stroke, and
cardiovascular death, have been reported in clinical studies with another JAK
inhibitor used to treat rheumatoid arthritis, a condition for which VONJO is not
indicated. Advise patients, especially current or past smokers or patients with
other cardiovascular risk factors, to be alert for the development of signs and
symptoms of cardiovascular events.

Thrombosis
Advise patients that events of deep vein thrombosis (DVT) and pulmonary
embolism (PE) have been reported in clinical studies with another JAK inhibitor
used to treat rheumatoid arthritis, a condition for which VONJO is not indicated.
Advise patients to tell their healthcare provider if they develop any signs or
symptoms of a DVT or PE.

Secondary Malignancies
Advise patients, especially current or past smokers and patients with a known
secondary malignancy (other than a successfully treated NMSC), that
lymphoma and other malignancies (excluding NMSC) have been reported in
clinical studies with another JAK inhibitor used to treat rheumatoid arthritis, a
condition for which VONJO is not indicated.

Infections
Advise patients that treatment with another JAK inhibitor has increased the risk
of serious infections in patients with myeloproliferative neoplasms and that
serious bacterial, mycobacterial, fungal, and viral infections may occur in
patients treated with VONJO. Inform patients of the signs and symptoms of
infection and to report any such signs and symptoms promptly.

Nausea and Vomiting
Advise patients that nausea and vomiting may occur during treatment with
VONJO. Instruct them on how to manage nausea and vomiting and to immediately
inform their healthcare provider if nausea/vomiting become severe.

Drug-Drug Interactions
Advise patients to inform their healthcare providers of all medications they are
taking, including prescription and over-the-counter medications, vitamins,
herbal products, and dietary supplements.

Dosing
Advise patients to take VONJO twice a day, with or without food or drink, at
similar times each day. Instruct patients to swallow the VONJO capsules whole
and not to open, break, or chew the capsules. Instruct patients that if they miss
a dose of VONJO, to skip the dose and take the next dose when it is due and
return to the normal schedule. Warn patients not to take 2 doses to make up for
the missed dose. Instruct patients to discontinue VONJO 7 days prior to any
surgery or invasive procedures (such as cardiac catheterization, coronary
stenting, or varicose vein ablation) due to the risk of bleeding and to only
restart VONJO on the instruction of their healthcare provider. Patients should
not change or stop taking VONJO without first consulting their physician.

Lactation
Advise patients to avoid breastfeeding while taking VONJO and for 2 weeks after
the final dose.

Additional information can be found at VONJO.com.

Manufactured and marketed by:
CTI BioPharma Corp.
3101 Western Ave #800
Seattle, WA 98121

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US-PAC-2100050 02/2022
Targeted Therapies Plus Chemotherapy Provide Path Around Acquired Resistance in AML

by KYLE DOHERTY

TARGETED THERAPIES, SPECIFICALLY those agents directed at mutated proteins and aberrant protein-to-protein interactions, have been shown to improve survival among patients with relapsed or refractory acute myeloid leukemia (AML). However, developed resistance to targeted therapies has proved to be a problem, according to a presentation by Eytan M. Stein, MD, during the 26th Annual International Congress Hematologic Malignancies®: Focus on Leukemias, Lymphomas, and Melanomas.

“The challenge of single-agent inhibitors is [acquired] resistance,” Stein, director of the Program for Drug Development in Leukemia in the Division of Hematologic Malignancies at Memorial Sloan Kettering Cancer Center in New York, New York, said. “We can overcome the resistance by moving agents upfront in combination with broadly active standard-of-care agents [such as] chemotherapy.”

ADDRESSING RAS PATHWAY MUTATIONS FLT3 Approximately 30% of patients with AML display mutations in the Fms-like tyrosine kinase 3 receptor (FLT3). Among these patients, 23% have FLT3 internal tandem duplications (FLT3 ITD) and 7% have FLT3 tyrosine kinase domain (FLT3 TKD) mutations. Several agents have been investigated in the space; however, a lack of prolonged efficacy remains a challenge for their integration into clinical practice.

Investigators evaluated midostaurin, a multitargeted tyrosine kinase inhibitor, in patients with wild-type or FLT3-mutant relapsed/refractory AML or myelodysplastic syndromes in a phase 2B study (NCT00045942). Among the 95 patients enrolled, 35 had FLT3-mutant disease and 57 had wild-type disease. Patients were treated with 50 mg or 100 mg of midostaurin twice daily.

Patients with FLT3-mutant disease experienced an overall response rate (ORR) of 71%, with all responses being blast responses. Patients with wild-type disease had an ORR of 56% and 24 patients had a blast response. The study authors concluded that midostaurin displayed hematologic activity in both patients with FLT3-mutant and wild-type disease but that there were no clear differences in the blast responses when stratified by type of FLT3 mutation or dose of study drug.

“Midostaurin is a relatively weak FLT3 inhibitor,” Stein said. “[Investigators observed] some decrease in the level of blast, but nothing that was good enough to be a true complete remission [CR]. In the relapsed or refractory setting, midostaurin has very little, if any, significant clinical activity.”

In the phase 3 QuANTUM-R trial (NCT02039726), the potent, selective type 2 FLT3 inhibitor quizartinib was compared with salvage chemotherapy in patients with relapsed/refractory FLT3 ITD–positive AML. Patients were randomized 2:1 to receive either quizartinib (n = 245) or salvage chemotherapy (n = 122), and the primary end point of the study was overall survival (OS). At a median follow-up of 23.5 months (range, 15.4-32.3), the median OS in the quizartinib group was 6.2 months (range, 5.3-7.2) compared with 4.7 months (range, 4.0-5.5) in the chemotherapy group (HR, 0.76; 95% CI, 0.58-0.98; P = .02).

Stein noted that although a survival benefit was observed with single-agent quizartinib, the FDA did not approve the drug; however, it has been approved for use in Japan.

In a similar phase 3 study (NCT02421939), the FLT3 inhibitor gilteritinib (Xospata) was compared with salvage chemotherapy in patients with relapsed/refractory AML harboring a FLT3-ITD mutation. Patients were randomized 2:1 to receive either gilteritinib (n = 247) or salvage chemotherapy (n = 124). The primary end points of the trial were OS and CR/CR with partial hematologic recovery (CRh) rate. Patients treated with gilteritinib experienced a median OS of 9.3 months vs 5.6 months in the salvage chemotherapy arm (HR, 0.665; 95% CI, 0.518-0.853; 2-sided P = .0013).

“You will notice in both of these studies...”
that there is a tail to the curve, where almost no patients end up surviving very long," Stein said. “And if you just gave these patients FLT3 inhibitors and didn’t follow that up with an allogeneic stem cell transplant, I would argue that nearly all of these patients end up relapsing by a year after going on therapy, whether they go on quizartinib or gilteritinib.”

Stein explained that the 3 most common mutations among patients who relapsed on gilteritinib were FLT3 F691L, NRAS, and KRAS. The FLT3 F691L mutation is a “gatekeeper mutation” that can prevent the binding of gilteritinib, reducing efficacy and ultimately leading to resistance against the agent, Stein said. Mutations in the RAS pathway then become the driving mutations in disease growth via clonal evolution.3

**IDH1/2**

Another mutation type common in patients with AML are mutations of isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase 2 (IDH2), which are observed in up to 25% of patients with AML. Patients with an IDH1 or IDH2 mutation experience an increase in intracellular β-hydroxylutarate, freezing the cell in an undifferentiated state, Stein said. IDH1 and IDH2 are mutations of clinical interest because if effectively drugged and the intracellular β-hydroxylutarate is decreased, cells will begin differentiating again—and patients will go into a complete clinical remission, Stein explained.

The IDH1 inhibitor ivosidenib (Tibsovo) was examined as a single agent in patients with relapsed/refractory AML harboring an IDH1 mutation in a phase 1 trial (NCT02074839). In the primary efficacy population (n = 125), the median OS was 9.0 months (95% CI, 7.1-10.0). Among patients who experienced a CR or CRh (n = 38), the median OS was 18.8 months (95% CI, 14.2- not estimable [NE]). Similar to patients treated with FLT3 inhibitors, a drop-off in survival was seen around 12 to 16 months because of relapse, Stein noted.4

Enasidenib (Idhifa), an IDH2 inhibitor, was also tested as a single agent in patients with IDH2-mutant AML in a phase 1/2 trial (NCT01915498). The efficacy results with enasidenib were very similar to those seen with ivosidenib, Stein noted. Specifically, the median OS was 8.8 months (95% CI, 7.8-9.9) among all treated patients (n = 214), and the median OS for patients who achieved a CR (n = 42) was 18.9 months (95% CI, 14.5-24). Investigators observed the same drop in survival at the tail of the curve.3

“The most common causes of relapse [among patients treated with IDH inhibitors] are RTK pathway mutations and [new] mutations in IDH,” Stein said. “One of the mutations in IDH can be a second-site mutation that can prevent drug binding. The other mutations that we see in IDH are what we call isoform switching. Isoform switching is a mechanism of clonal evolution. When you have a patient with IDH2-mutant AML and you give them an IDH2 inhibitor, there are some cases where IDH1 mutation then pops up and takes over driving the disease.”

Stein went on to explain that the same mechanism of isoform switching can occur with IDH1-mutant disease switching to IDH2-mutant disease. Any new targeted therapy will eventually experience problems with resistance, more likely through second-site mutations or clonal evolution, Stein said.

### Table. Select Combination Therapy Trials in AML8-11

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**FLT3 inhibitor + chemotherapy**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Midostaurin (n = 360)</th>
<th>Placebo (n = 357)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>74.7 (31.5-NR)</td>
<td>25.6 (18.6-42.9)</td>
</tr>
<tr>
<td>CR*</td>
<td>HR, 0.78; 95% CI, 0.63-0.96; P = .009</td>
<td>59%</td>
</tr>
<tr>
<td>Median time to CR, days (range)</td>
<td>35 (20-60)</td>
<td>35 (20-60)</td>
</tr>
</tbody>
</table>

**IDH inhibitor + chemotherapy**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ivosidenib (n = 60)</th>
<th>Enasidenib (n = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NR (NC-NC)</td>
<td>25.6 (25.5-NR)</td>
</tr>
<tr>
<td>12-month OS rate</td>
<td>78%</td>
<td>76%</td>
</tr>
<tr>
<td>CR</td>
<td>68%</td>
<td>55%</td>
</tr>
<tr>
<td>CR/CRp</td>
<td>8%</td>
<td>19%</td>
</tr>
</tbody>
</table>

**Dual IDH inhibition**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ivosidenib plus azacitidine (n = 72)</th>
<th>Placebo plus azacitidine (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median EFS, months</td>
<td>24.0</td>
<td>HR, 0.44; 95% CI, 0.27-0.73; P = .0005</td>
</tr>
<tr>
<td>CR (95% CI)</td>
<td>47.2% (35.3%-59.3%)</td>
<td>14.9% (7.7%-25.0%)</td>
</tr>
<tr>
<td>Median duration of CR, months (95% CI)</td>
<td>62.5% (50.3%-73.6%)</td>
<td>18.9% (10.7%-29.7%)</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>HR, 0.33; 95% CI, 0.16-0.69; P = .0011</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE. Select Combination Therapy Trials in AML8-11**

**RATIFY (NCT00651261): a phase 3 trial evaluating induction chemotherapy including cytara bine and daunorubicin, consolidation high-dose cytarabine, plus midostaurin or placebo in patients with FLT3-mutant AML**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Median OS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (95% CI)</td>
<td>47.2% (35.3%-59.3%)</td>
</tr>
<tr>
<td>Median duration of CR, months (95% CI)</td>
<td>62.5% (50.3%-73.6%)</td>
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<tr>
<td>ORR (95% CI)</td>
<td>HR, 0.33; 95% CI, 0.16-0.69; P = .0011</td>
</tr>
</tbody>
</table>

**WINTER HEME**

**Select Combination Therapy Trials in AML**

- **RATIFY (NCT00651261): a phase 3 trial evaluating induction chemotherapy including cytara bine and daunorubicin, consolidation high-dose cytarabine, plus midostaurin or placebo in patients with FLT3-mutant AML.**
- **IDH1 inhibitor + chemotherapy**
- **IDH2 inhibitor + chemotherapy**
- **FLT3 inhibitor + chemotherapy**
- **Dual IDH inhibition**

**TACKLING RESISTANCE**

To overcome problems with resistance, targeted therapies are being examined in combination with intensive chemotherapy or a dual inhibitor approaches **(TABLE).** Midostaurin plus chemotherapy was evaluated in patients with AML harboring an FLT3 mutation in the phase 3 RATIFY trial (NCT00651261). The study design consisted of 1 to 2 cycles of induction chemotherapy (cytarabine plus daunorubicin) plus midostaurin or placebo. If patients achieved CR, consolidation high-dose cytarabine was administered in combination with midostaurin or placebo for 4 cycles. If CR persisted, patients received single-agent targeted therapy for 12 cycles.

Patients treated with the combination experienced a median OS of 74.7 months (95% CI, 31.5-not reached) compared with 25.6 months among patients who received placebo (HR, 0.78; 95% CI, 0.63-0.96; P = .009).8

Another phase 3 trial combining a targeted therapy with chemotherapy, OnAUNTUM-First (NCT02668653) displayed positive topline results. The trial met its primary end point for OS, and the combination was found to be manageable in terms of safety. Updated results will be reported at an upcoming medical meeting.9

Similarly positive results have been observed when IDH inhibitors are combined with induction chemotherapy, followed by consolidation,
and single-agent maintenance therapy. In the phase 1 AG120-221-C-001 study (NCT02632708), patients with IDH1 mutations received enasidenib 500 mg once daily, and those with IDH2 mutations received enasidenib 100 mg once daily. Consolidation therapy with continuous enasidenib or enasidenib was administered to patients who had partial response. Maintenance therapy with enasidenib or enasidenib was offered to patients in remission at the end of consolidation.

For those treated with enasidenib, the median OS was not reached, and the 12-month survival probability was 78% when evaluated after induction on day 1. Among patients treated with enasidenib plus chemotherapy, the median OS was 25.3 months (95% CI, 25.5-NE) and the 12-month survival probability was 74%. Stein noted that the same design is now being done as a randomized phase 3 trial in Europe.

In the phase 3 study (NCT02677922), ivosidenib was combined with azacitidine (Onureg) and evaluated in patients with AML harboring an IDH1 mutation. Patients treated with the combination (n = 100) experienced a median OS of 24.0 months compared with 7.9 months among the 100 patients who received placebo plus azacitidine (HR, 0.44; 95% CI, 0.27-0.73; P = .0005). In March 2022, the FDA granted a priority review to the application of the combination as a treatment for patients with untreated IDH1-mutant AML.

[These results] argue that we should be combining some of these targeted agents, [such as] FLT3 inhibitors and IDH inhibitors, with intensive chemotherapy to eliminate the most common source of clonal evolution, which is RAS-mutant disease, Stein said. "Maybe there will be other better targeted therapies for KRAS-mutant disease, but combining targeted therapies with more broadly active treatments like chemotherapy and hypomethylating agents is really the way to go."
ENGINEERED FOR A CHALLENGING LANDSCAPE

In the world of EGFR+ mNSCLC, few challenges have been tougher to navigate than EGFR exon 20 insertion mutations.1-10

Until RYBREVANT®—the first and only bispecific antibody built for the treatment of adult patients with locally advanced or mNSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.11

INDICATION
RYBREVANT® (amivantamab-vmwj) is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

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

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Infusion-Related Reactions
RYBREVANT® can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population, IRR occurred in 66% of patients treated with RYBREVANT®. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVANT® due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT® as recommended. Administer RYBREVANT® via a peripheral line on Week 1 and Week 2. Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT® infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT® based on severity.

Interstitial Lung Disease/Pneumonitis
RYBREVANT® can cause interstitial lung disease (ILD)/pneumonitis.

Based on the safety population, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT®, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT® due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT® in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

Dermatologic Adverse Reactions
RYBREVANT® can cause rash (including dermatitis acniform), pruritus and dry skin. Based on the safety population, rash occurred in 74% of patients treated with RYBREVANT®, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT® was permanently discontinued due to rash in 0.7% of patients.

Toxic epidermal necrolysis occurred in one patient (0.3%) treated with RYBREVANT®.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT®. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.
In a multicenter, open-label, multicohort study11*,

Results for tough-to-treat disease

- 3.7% of patients achieved a CR
- 36% of patients achieved a PR

**ORR**

40%

95% CI: 29%, 51% (n=81)

- Efficacy was evaluated by ORR* and DOR11

**MEDIAN DOR WAS 11.1 MONTHS**11†

(95% CI: 6.9, NE)11†

*CHRYSALIS was a multicenter, open-label, multicohort study conducted to assess the safety (n=129) and efficacy (n=81) of RYBRENT® in adult patients with locally advanced or metastatic NSCLC. Efficacy was evaluated in 81 patients with locally advanced or metastatic NSCLC who had EGFR exon 20 insertion mutations as determined by prospective local testing, whose disease had progressed on or after platinum-based chemotherapy. RYBRENT® was administered intravenously at 1500 mg for patients ≤80 kg once weekly for 4 weeks, then every 2 weeks thereafter, starting at Week 5, until disease progression or unacceptable toxicity.†

†According to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by Blinded Independent Central Review (BICR).11†

Based on Kaplan-Meier estimates.11†

The safety of RYBRENT® was evaluated in the CHRYSALIS study (n=129):11†

- The warnings and precautions included infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity.11†

- The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (25%), cough (25%), constipation (23%), and vomiting (22%).†

- The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).†

- IRRs occurred in 66% of patients treated with RYBRENT®, the majority of which may occur with the first infusion.†

Based on the safety population, N=302.

The innovation you’ve been waiting for.

RYBRENThcp.com

CR, complete response; DOR, duration of response; EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; mNSCLC, metastatic non–small cell lung cancer; NE, not estimable; ORR, overall response rate; PR, partial response.

If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or difficulty improving within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBRENT® based on severity.

Ocular Toxicity

RYBRENT® can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population, keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBRENT®. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBRENT® based on severity.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBRENT® can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBRENT®.

Adverse Reactions

The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (25%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).

Please see Brief Summary of all Prescribing Information for RYBRENT® on subsequent pages.


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RYBRENT (amivantamab-vmwy) injection, for intravenous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

RYBRENT is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1) in Full Prescribing Information], whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14) in Full Prescribing Information]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

RYBRENT can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population [see Adverse Reactions], IRR occurred in 68% of patients treated with RYBRENT. Among patients receiving treatment for 1 Week 1 Day 1, 85% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 82% and 1.3% of patients permanently discontinued RYBRENT due to IRR.

Premedicate with antihistamines, antipyrretics, and glucocorticoids and infuse RYBRENT as recommended [see Dosage and Administration (2.3) in Full Prescribing Information]. Administer RYBRENT via a peripheral line on Week 1 and Week 2 [see Dosage and Administration (2.6) in Full Prescribing Information].

Monitor patients for any signs and symptoms of infusion reactions during RYBRENT infusion in a setting where cardiopulmonary resuscitation medications and equipment are available. Interruption of infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBRENT based on severity [see Dosage and Administration (2.4) in Full Prescribing Information].

Interstitial Lung Disease/Pneumonitis

RYBRENT can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population [see Adverse Reactions], ILD/pneumonitis occurred in 3.3% of patients treated with RYBRENT, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBRENT due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBRENT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed [see Dosage and Administration (2.4) in Full Prescribing Information].

Dermatologic Adverse Reactions

RYBRENT can cause rash (including dermatitis acutiform, pruritus and dry skin. Based on the safety population [see Adverse Reactions], rash occurred in 74% of patients treated with RYBRENT, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBRENT was permanently discontinued due to rash in 0.7% of patients [see Adverse Reactions].

Toxic epidermal necrolysis (TEN) occurred in one patient (0.3%) treated with RYBRENT.

Instruct patients to avoid direct sunlight and use broad-spectrum UV protection [see Adverse Reactions]. Alcohol-free emollient cream is recommended for dry skin.

If skin reactions develop, start topical corticosteroids and oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBRENT based on severity [see Dosage and Administration (2.4) in Full Prescribing Information].

Ocular Toxicity

RYBRENT can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population [see Adverse Reactions], keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBRENT. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBRENT based on severity [see Dosage and Administration (2.4) in Full Prescribing Information].

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBRENT can cause fetal harm when administered to a pregnant woman. Administration of other EGFR inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryolethality, and abortion. Advise female patients of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBRENT. [see Use in Specific Populations].

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Infusion-Related Reactions [see Warnings and Precautions]
- Interstitial Lung Disease/Pneumonitis [see Warnings and Precautions]
- Dermatologic Adverse Reactions [see Warnings and Precautions]
- Ocular Toxicity [see Warnings and Precautions]

Clinical Trials Experience

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

The safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to RYBRENT as a single agent in the CHRYsalis study in 302 patients with locally advanced or metastatic NSCLC who received a dose of 1050 mg (for patients <80 kg) or 1400 mg (for patients ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter. Among 302 patients who received RYBRENT, 36% were exposed for 6 months or longer and 12% were exposed for greater than one year. In the safety population, the most common (≥20%) adverse reactions were rash, infusion-related reaction, paronychia, musculoskeletal pain, dyspnea, nausea, edema, cough, fatigue, stomatitis, constipation, vomiting and pruritus. The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased phosphorus, decreased albumin, increased glucose, increased gamma-glutamyl transferase, decreased sodium, decreased potassium, and increased alkaline phosphatase.

The data described below reflect exposure to RYBRENT at the recommended dosage in 129 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy. Among patients who received RYBRENT, 44% were exposed for 6 months or longer and 12% were exposed for greater than one year.

The median age was 62 years (range: 36 to 84 years); 61% were male; 55% were Asian, 35% were White, and 2.3% were Black; and 82% had baseline body weight <80 kg.

Serious adverse reactions occurred in 30% of patients who received RYBRENT. Serious adverse reactions in ≥2% of patients included pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 2 patients (1.5%) due to pneumonia and 1 patient (0.8%) due to sudden death.

Permanent discontinuation of RYBRENT due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYBRENT in ≥1% of patients were pneumonia, IRR, pneumonitis/ILD, dyspnea, pleural effusion, and rash.

Dose interruptions of RYBRENT due to an adverse reaction occurred in 78% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 59% of patients. Adverse reactions requiring dose interruption in ≥5% of patients included dyspnea, nausea, rash, vomiting, fatigue, and diarrhea.

Dose reductions of RYBRENT due to an adverse reaction occurred in ≥2% of patients. Adverse reactions requiring dose reductions in ≥2% of patients included rash and paronychia.

The most common adverse reactions (≥20%) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased albumin, decreased phosphorus, decreased potassium, increased glucose, increased alkaline phosphatase, increased gamma-glutamyl transferase, and decreased sodium.
Table 1: Adverse Reactions (≥ 10%) in Patients with NSCLC with Exon 20 Insertion Mutations Whose Disease Has Progressed on or after Platinum-based Chemotherapy and Received RYBRENTM in CHRYSLASIS

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>RYBRENTM (N=129)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3 or 4 (%)</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>64</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>14</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>Infusion related reaction</td>
<td>64</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>33</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Edema*</td>
<td>27</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paronychia</td>
<td>50</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>10</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>47</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea†</td>
<td>37</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Cough†</td>
<td>25</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>26</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>23</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain†</td>
<td>11</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage†</td>
<td>19</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>15</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy†</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Headache†</td>
<td>10</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

* Rash: acne, dermatitis, dermatitis acriform, eczema, eczema atactic, palmar-plantar erythrodysaesthesia syndrome, perineal rash, rash, rash erythematous, rash macule-papular, rash papular, rash vesicular, skin exfoliation, toxic epidermal necrosis
1 Fatigue: asthenia, fatigue
2 Edema: eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema, peripheral swelling
4 Pneumonia: atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, and pulmonary sepsis
5 Musculoskeletal pain: arthritis, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain
6 Dyspnea: dyspnea, dyspnea exertional
7 Cough: cough, productive cough, upper airway cough syndrome
8 Stomatitis: aphthous ulcer, cheilitis, glossitis, mouth ulceration, mucosal inflammation, pharyngeal inflammation, stomatitis
9 Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and epigastric discomfort
10 Hemorrhage: epistaxis, gingival bleeding, hemothria, hemoptysis, hemorrhage, mouth hemorrhage, mucosal hemorrhage
11 Peripheral neuropathy: hypoesthesia, neuralgia, paresthesia, peripheral sensory neuropathy
12 Headache: headache, migraine

Clinically relevant adverse reactions in <10% of patients who received RYBRENT included ocular toxicity, ILD/pneumonitis, and toxic epidermal necrosis (TEN).

Table 2: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients With Metastatic NSCLC With EGFR Exon 20 Insertion Mutations Whose Disease Has Progressed on or After Platinum-based Chemotherapy and Who Received RYBRENTM in CHRYSLASIS

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RYBRENTM (N=129)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3 or 4 (%)</td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>79</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>56</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>53</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>46</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>38</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>33</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>33</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>27</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Increased gamma-glutamyl transferase</td>
<td>27</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>26</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>36</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

* The denominator used to calculate the rate was 126 based on the number of patients with a baseline value and at least one post-treatment value.

Immunogenicity

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

In CHRYSLASIS, 3 of the 28 (1%) patients who were treated with RYBRENT and evaluable for the presence of anti-drug antibodies (ADA), tested positive for treatment-emergent anti-amivantamab-vmjw antibodies (one at 27 days, one at 59 days and one at 184 days after the first dose) with titers of 1:40 or less. There are insufficient data to evaluate the effect of ADA on the pharmacokinetics, safety, or efficacy of RYBRENT.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action and findings in animal models, RYBRENT can cause fetal harm when administered to a pregnant woman. There are no available data on the use of RYBRENT in pregnant women or animal data to assess the risk of RYBRENT in pregnancy. Disruption or deletion of EGFR in animal models resulted in impairment of embryofetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR or MET signaling has resulted in embryolethality, malformations, and post-natal death in animals (see Data). Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

No animal studies have been conducted to evaluate the effects of amivantamab-vmjw on reproduction and fetal development; however, based on its mechanism of action, RYBRENT can cause fetal harm or developmental anomalies. In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development) and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/foetuses of mice with disrupted EGFR signaling. Similarly, knock out of MET or its ligand HGF was embryonic lethal due to severe defects in placental development, and fetuses displayed defects in muscle development in
multiple organs. Human IgG1 is known to cross the placenta; therefore, amivantamab-vmjw has the potential to be transmitted from the mother to the developing fetus.

**Lactation**

**Risk Summary**

There are no data on the presence of amivantamab-vmjw in human milk on milk production, or its effects on the breastfed child. Because of the potential for serious adverse reactions from RYBREVANT in breast-fed infants, advise women not to breast-feed during treatment with RYBREVANT and for 3 months after the final dose.

**Females and Males of Reproductive Potential**

RYBREVANT can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations].

**Pregnancy Testing**

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

**Contraception**

**Females**

Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT.

**Pediatric Use**

The safety and efficacy of RYBREVANT have not been established in pediatric patients.

**Geriatric Use**

Of the 129 patients treated with RYBREVANT, 41% were 65 years of age or older, and 9% were 75 years of age or older. No clinically important differences in safety or efficacy were observed between patients who were ≥65 years of age and younger patients.

**PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information).

**Infusion-Related Reactions**

Advise patients that RYBREVANT can cause infusion-related reactions, the majority of which may occur with the first infusion. Advise patients to alert their healthcare provider immediately for any signs or symptoms of infusion-related reactions [see Warnings and Precautions].

**Interstitial Lung Disease/Pneumonitis**

Advise patients of the risks of interstitial lung disease (ILD)/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms [see Warnings and Precautions].

**Dermatologic Adverse Reactions**

Advise patients of the risk of dermatologic adverse reactions. Advise patients to limit direct sun exposure, to use broad spectrum UVA/UVB sunscreen, and to wear protective clothing during treatment with RYBREVANT [see Warnings and Precautions]. Advise patients to apply alcohol free emollient cream to dry skin.

**Ocular Toxicity**

Advise patients of the risk of ocular toxicity. Advise patients to contact their ophthalmologist if they develop eye symptoms and advise discontinuation of contact lenses until symptoms are evaluated [see Warnings and Precautions].

**Paronychia**

Advise patients of the risk of paronychia. Advise patients to contact their healthcare provider for signs or symptoms of paronychia [see Adverse Reactions].

**Embryo-Fetal Toxicity**

Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with RYBREVANT and for 3 months after the final dose, and to inform their healthcare provider of a known or suspected pregnancy. [see Warnings and Precautions, Use in Specific Populations].

**Lactation**

Advise women not to breastfeed during treatment with RYBREVANT and for 3 months after the final dose [see Use in Specific Populations].

Product of Ireland

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Janssen Biotech, Inc.

Horsham, PA 19044

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antibody test that detects cancer cells in the blood, is one such test available to investigators to identify patients with hematologic malignancies. However, improvements with mass spectrometry, such as those demonstrated in the PROMISE study (NCT03689595), may replace SPEP in the future, according to Ghobrial. Investigators for the PROMISE study set out to identify high-risk populations, specifically Black Americans and those with a first- or second-degree relative with a blood cancer, with precursor conditions to multiple myeloma, such as monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma. A total of 7600 patients were identified and evaluated using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) as well as SPEP and immunofixation.

“We wanted to see what was the lowest level that you could detect by SPEP [and to determine] the lowest you cannot detect by SPEP but can detect by mass spectrometry using a new AI [artificial intelligence]-informed algorithm to quantify the immunoglobulins and the light chains,” Ghobrial said.

The level to detect MGUS was determined as 0.2 g/L. “These were true monoclonal proteins [and] not abnormalities in the assay,” Ghobrial said. The overall prevalence of MGUS, as detected by MALDI-TOF MS, was 13% compared with 6% by SPEP in the high-risk population. Interestingly, because we had [access to] survival data [in the] electronic health record of every patient, we were able to [identify] the survival and comorbidities associated with MGs,” Ghobrial explained, adding that worse overall survival was observed with MG detection. Despite MGUS being more common among patients with myeloma, Ghobrial said that it is also associated with macroglobulinemia. “We’re starting to step back and say this is an immune dysregulation that may not be just about myeloma.”

Despite bone marrow biopsy being the gold standard for diagnosing and monitoring patients, there is an urgent need for robust early-detection methods that are tumor biology-based as well as minimally invasive, Ghobrial noted (FIGURE). Once cells are extracted, you can perform whole genome sequencing, RNA sequencing, anything else you want,” she said.

The samples were enriched with CD138 and enumerated using the CellSearch platform at Dana-Farber Cancer Institute. One or more circulating tumor cells were detected in 84% of patients, with 74% of patients with MGUS and 84% of patients with smoldering multiple myeloma having successful enumeration. Higher circulating tumor cell counts were also associated with risk classification. A median of 4, 21, and 59 circulating tumor cells was detected in the low-, intermediate-, and high-risk smoldering multiple myeloma groups, respectively.

“If you use the 2/20/20 [3-risk-factors stratification model] that we use for patients with smoldering myeloma and add on circulating tumor cells, we were able to find that circulating tumor cells [were associated with] worse outcomes and faster [disease] progression,” Ghobrial said. “The presence of circulating tumor cells tells you that there is a more biological indication of advancement of the disease beyond just an enumeration of tumor burden in those patients.”

Investigators also compared results with bone marrow biopsy using conventional methods such as FISH and whole genome sequencing without amplification, which allowed them to perform the tests on individuals with a lower tumor burden. “If you have only 20 or 30 cells, you need genomic amplification to try and conduct genome sequencing,” Ghobrial said. “We have

CTCs, circulating tumor cells; ctDNA, circulating tumor DNA; FISH, fluorescence in situ hybridization.
been able to detect every single translocation or copy number alteration [as determined by] FISH in circulating tumor cells and also in the bone marrow. Cancer cell fraction, the number of mutations, and the number of clones that you can detect in the blood were also more significant than what you detect in the bone marrow.

“We were surprised that you can detect everything in the blood that you found in the bone marrow. Rarely [do] we find something in the bone marrow, but the blood always gave us more mutations and a higher cancer cell fraction of certain mutations, which indicates that maybe the clones that are capable of circulating in the blood have an enhanced ability to be more important for us to understand biologically what happens with circulating clones vs bone marrow clones.”

Ghobrial then returned to her discussion of leveraging the immune system and noted that her future research is dedicated to showing these advances. “If you do immune single-cell sequencing in bone marrow, and now we can do it in the blood, they reflect each other,” she said. In examples pulled from unpublished data, Ghobrial highlighted that there was significant compositional and transcriptional change that could predict which patients would progress to myeloma in the future once markers were identified. “However, what we try to do here is also using immune cell markers to decide whether a patient will have a biomarker of response to therapy, as well as after treatment, whether you have a normalization of your immune system, what we called post immune normalization, and whether that can be predictive for long-term remission.”

Ghobrial concluded that a lot of work needs to be done to improve understanding of early detection, prediction of response to therapy, prognostic biomarkers, and monitoring patients. “In the future, these approaches will [leverage] multiomics instead [of just] methylation,” she said. “Hopefully [liquid biopsy] will be a clinical tool that we can use for our patients instead of using only bone marrow or lymph node biopsies or other [invasive] biopsies.”

**REFERENCES**


**WINTER HEME**

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**Treatment and Sequencing Options Continue to Evolve in Relapsed/Refractory DLBCL**

by **CHRIS RYAN**

**THE EMERGENCE OF NOVEL AGENTS.** Including chimeric antigen receptor (CAR) T-cell therapies and antibody-drug conjugates, plus existing options such as chemoinmunotherapy and bone-marrow transplant, have to raise questions about the sequencing of these treatments in patients with diffuse large B-cell lymphoma (DLBCL), according to Grzegorz S. Nowakowski, MD.

“We have now multiple agents that are approved, and if you imagine possible permutations and combinations of those, the number gets quite high,” said Nowakowski, a professor of medicine and oncology in the Lymphoma Program at Mayo Clinic in Rochester, Minnesota, in a presentation at the 26th Annual International Congress on Hematologic Malignancies®. “[We] clearly won’t be able to study those [permutations] in randomized settings. We will see more and more real-world data on sequencing of therapy [and] how to best choose therapy in the future. And this field is likely to evolve even more in the near future with bispecifics coming to this space.”

**EMERGING AGENTS TACKLE RELAPSED DISEASE**

Frontline standard of care for patients with DLBCL is rituximab (Rituxan) plus cyclophosphamide, doxorubicin, hydrochloride, vincristine, and prednisone (R-CHOP). This approach results in a cure for approximately 50% of patients. Those who progress and are transplant eligible will receive high-dose chemotherapy in the second-line setting. Around half of patients will be eligible for autologous stem cell transplant (ASCT), with approximately 10% to 15% of patients achieving a cure.

Several regimens have emerged in the past 3 years in the second- and third-line settings for patients who are ineligible for ASCT, or who have disease progression, or for those who relapse. These include the ADC polatuzumab vedotin-piiq (Polivy) plus bendamustine and rituximab (BR); selinexor (Xpovio); tafasitamab-cxix (Monjuvi) plus lenalidomide (Revlimid); and loncastuximab tesirine-lpyl (Zynlonta).

In June 2019, the FDA granted an accelerated approval to polatuzumab vedotin in combination with BR for patients with relapsed/refractory DLBCL who have received at least 2 prior therapies. A phase 2 study (NCT02257567) tested the efficacy of polatuzumab vedotin plus BR in patients with relapsed/refractory DLBCL or follicular lymphoma who received at least 1 line of prior treatment, and who were transplant ineligible or had progressed after ASCT. Patients in the DLBCL arm (n = 40) achieved an objective response rate (ORR) of 45% with polatuzumab vedotin vs an ORR of 17.5% with BR alone (n = 40).

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Additionally, in June 2020, the FDA approved selinexor for adult patients with relapsed/refractory DLBCL who have received at least 2 lines of prior therapy. The phase 2b SADAL trial (NCT02227251) explored selinexor in patients with relapsed/refractory DLBCL who had received 2 to 5 lines of prior treatment. Data from the single-arm study showed that among the 127 patients who received selinexor at a 60-mg dose the overall response rate was 28% ORR (95% CI, 20.7%-37.0%), with a median duration of response of 9.3 months (95% CI, 4.8-23.0), and a median overall survival (OS) of 9.1 months (95% CI, 6.6-15.1).

In July 2020, the combination of tafasitamab and lenalidomide was approved by the FDA for patients with DLBCL who were ineligible for ASCT. This combination elicited an ORR of 60% (95% CI, 48.0%-71%) among the 80 patients treated in the phase 2 L-MIND trial (NCT02399085), including a complete response (CR) rate of 43% (95% CI, 32.4%-53.4%).

“What was really encouraging about this study was [the median] progression-free survival [PFS] of 16.2 months and [the median] OS of 31.6 months, which was very significant,” Nowakowski said. “[These] 2 standard end points looked extremely favorable in this study, and [the] responses appeared to be quite durable.”

Furthermore, the RE-MIND trial (NCT04150328) compared combination data from L-MIND with real-world data of lenalidomide monotherapy in transplant-ineligible patients with relapsed/refractory DLBCL. In a matched analysis set analysis of 76 patients from each study, those in the combination arm had a significantly better ORR at 67.1% vs those in the lenalidomide arm at 34.2% (odds ratio, 3.89; P < 0.001).

In April 2021, the FDA approved loncastuximab tesirine for patients with relapsed/refractory DLBCL who have received at least 2 prior lines of systemic therapy. This humanized anti-CD19 antibody is stochastically conjugated through a cathepsin-cleavage valine-alanine linker to a pyrrolobenzodiazepine dimer toxin, causing DNA crosslinking. This agent was explored in the phase 2 LOTIS-2 trial (NCT03589469), where it elicited an ORR of 16.7% including a CR rate of 3.0%.

ANTICANCER IMMUNOONCOLOGY: NONMYELOSUPPRESSIVE STRATEGIES

THE TREATMENT OPTIONS FOR POST CAR T RELAPSE

Should CAR T-cell therapy shift to earlier settings in DLBCL, Nowakowski acknowledged that work would remain to address the need for more post-CAR T-cell therapy treatment options. Long-term follow-up data of patients with relapsed/refractory DLBCL who received tisagenlecleucel (Yescarta) showed that at 5 years approximately 60% of patients experienced disease relapse. These patients can be quite challenging to treat,” Nowakowski said. “We know the outcome of patients post CAR T-relapse is extremely poor. Median OS is only [5.3] months, and patients who relapse early—by day 30—have particularly poor outcomes, with [an OS] of 3.75 months.”

Despite investigative efforts to explore therapeutic options, Nowakowski explained that prolonged cytopenias represented a major barrier to enrollment in clinical trials for patients with aggressive B-cell lymphomas who progress after CD19-directed CAR T-cell therapy. Across 4 clinical trials exploring selinexor, polatuzumab plus BR, fasiltamab plus lenalidomide, and loncastuximab tesirine, 47% of patients were excluded. Additionally, time from CD19-directed CAR T-cell therapy to disease progression was shorter in patients who were ineligible for enrollment (median 1.1 months; range, 0.5-4.7) vs those who were eligible for enrollment (median, 3.0 months; range, 0.9-2.7; P = .004).

“Unless we change the inclusion criteria and change our clinical trials, [these agents are] not a viable option for many patients post CAR T-cell relapse,” said Nowakowski.

Nonmyelosuppressive strategies, including immunotherapy and targeted therapy, have demonstrated clinically beneficial outcomes for those who experience relapse after CAR T-cell therapy. They may represent preferential options. For example, results of a single-center study in France examining the use of lenalidomide in patients following CAR T-cell therapy relapse showed that treatment with lenalidomide at the time of relapse may elicit a high response rate.

A total of 33 patients who experienced disease progression after tisagenlecleucel and 26 who experienced disease progression following axicabtagene ciloleucel (Yescarta) were included in the analysis. Among the 41 patients who received lenalidomide, 30 received the agent in combination with rituximab, 1 received it in combination with obinutuzumab (Gazyva), and 10 received it monotherapy. The ORR was 27.1%, including a CR in 9 patients. Notably, 11 patients who started treatment before day 15 following CAR T-cell infusion experienced a higher ORR at 63.6% and a higher CR rate at 36.4%. The median PFS was 101 days, and the median OS was 225 days among all treated patients.

Notably, Nowakowski also commented that an older treatment option, radiation therapy, could represent another route for patients following relapse on CAR T-cell therapy. "All of us who see patients post CAR T-cell therapy know that relapses could be [found in] somewhat unusual [places]. Sometimes they are localized, sometimes they are in unusual spaces,” Nowakowski said. "If you do have a localized relapse, radiation can provide durable stable disease, during which a patient can [have hematologic] recovery and become a candidate for other therapy,” he concluded.

REFERENCES
Indications

IBRANCE® (palbociclib) 125 mg capsules and tablets are indicated for the treatment of adult patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer (mBC) in combination with:

• an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men, or
• fulvestrant in patients with disease progression following endocrine therapy

Important Safety Information

Neutropenia was the most frequently reported adverse reaction in PALOMA-2 (80%) and PALOMA-3 (83%). In PALOMA-2, Grade 3 (56%) or 4 (10%) decreased neutrophil counts were reported in patients receiving IBRANCE plus letrozole. In PALOMA-3, Grade 3 (55%) or Grade 4 (11%) decreased neutrophil counts were reported in patients receiving IBRANCE plus fulvestrant. Febrile neutropenia has been reported in 1.8% of patients exposed to IBRANCE across PALOMA-2 and PALOMA-3.

One death due to neutropenic sepsis was observed in PALOMA-3. Inform patients to promptly report any fever. Monitor complete blood count prior to starting IBRANCE, at the beginning of each cycle, on Day 15 of first 2 cycles and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Please see Important Safety Information throughout, followed by Brief Summary of Prescribing Information for capsules and tablets.
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**Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis**

can occur in patients treated with CDK4/6 inhibitors, including IBRANCE when taken in combination with endocrine therapy. Across clinical trials (PALOMA-1, PALOMA-2, PALOMA-3), 1.0% of IBRANCE-treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3 or 4, and no fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported.

**Monitor patients** for pulmonary symptoms indicative of ILD/pneumonitis (e.g., hypoxia, cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed pneumonitis, interrupt IBRANCE immediately and evaluate the patient. Permanently discontinue IBRANCE in patients with severe ILD or pneumonitis.

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**IBRANCE COMBINATION THERAPY HAS HELPED CHANGE THE STORY OF HR+/HER2- MBC**

**Evaluated in a broad range of patients**

**PALOMA-2:**
- IBRANCE + letrozole
  - First line in mBC
    - (No prior lines of mBC therapy)
  - With or without prior (neo)adjuvant chemotherapy
  - Postmenopausal women
  - 30-89 years of age (median=62)
  - Visceral/nonvisceral (including bone-only)
  - DFI: De novo metastatic, ≤12 months, >12 months

**PALOMA-3:**
- IBRANCE + fulvestrant
  - First line or later in mBC
    - (For patients who progressed on or after ET in the adjuvant or metastatic setting)
  - Up to 1 prior line of chemotherapy for mBC
  - Pre-/peri-/postmenopausal women
  - 30-88 years of age (median=57)
  - Visceral/nonvisceral (including bone-only)
  - DFI: ≤24 months, >24 months

**The #1 prescribed FDA-approved oral combination treatment for HR+/HER2- mBC**

- **5+ YEARS** since initial FDA approval
- **14,000+ PRESCRIBERS** have chosen IBRANCE
- **115,000+ PATIENTS** prescribed IBRANCE

**Explore the clinical evidence on the following pages**

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**Important Safety Information (cont.)**

Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with CDK4/6 inhibitors, including IBRANCE when taken in combination with endocrine therapy. Across clinical trials (PALOMA-1, PALOMA-2, PALOMA-3), 1.0% of IBRANCE-treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3 or 4, and no fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g., hypoxia, cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed pneumonitis, interrupt IBRANCE immediately and evaluate the patient. Permanently discontinue IBRANCE in patients with severe ILD or pneumonitis.
STRENGTH IN FIRST LINE

**IBRANCE + LETROZOLE AS INITIAL MBC THERAPY**

In a 2:1 randomized, double-blind, Phase 3 trial of postmenopausal women with ER+/HER2- mBC (N=666)\(^1\)

**Compelling 10-month mPFS improvement vs placebo + letrozole**

- **Primary endpoint:** Investigator-assessed progression-free survival (PFS)\(^3\)
- **24.8 months mPFS** (n=444) vs **14.5 months mPFS** with placebo + letrozole (n=222); (95% CI: 22.1-NE vs 12.9-171); \(HR=0.58\) (95% CI: 0.46-0.72); \(P<0.0001\)
- Number of PFS events: 194 (43.7%) with IBRANCE + letrozole vs 137 (61.7%) with placebo + letrozole
- **ORR** (secondary endpoint): **55.3%** (95% CI: 49.9-60.7) of patients with measurable disease achieved an objective response with IBRANCE + letrozole vs **44.4%** (95% CI: 36.9-52.2) with placebo + letrozole (IBRANCE + letrozole n=338; placebo + letrozole n=171)\(^5\)
- At the time of final analysis of PFS, OS (secondary endpoint) data were not mature. Patients will continue to be followed for the final analysis

*CIF=confidence interval; HR=hazard ratio; mPFS=median progression-free survival; NE=not estimable; ORR=overall response rate; OS=overall survival.

*ORR was defined as the number (%) of patients with confirmed complete response or partial response.\(^2\)*

**Adverse reactions**

The **most common adverse reactions (≥10%)** of any grade reported in PALOMA-2 for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (50% vs 6%), infections (60% vs 42%), leukopenia (39% vs 2%), fatigue (37% vs 28%), nausea (35% vs 26%), alopecia (33% vs 16%), stomatitis (30% vs 14%), diarrhea (26% vs 19%), anemia (24% vs 9%), rash (18% vs 12%), asthenia (17% vs 12%), thrombocytopenia (16% vs 1%), vomiting (16% vs 17%), decreased appetite (15% vs 9%), dry skin (12% vs 6%), pyrexia (12% vs 9%), and dysgeusia (10% vs 5%).

**Important Safety Information (cont.)**

Based on the mechanism of action, IBRANCE can cause **fetal harm**. Advise females of reproductive potential to use effective contraception during IBRANCE treatment and for at least 3 weeks after the last dose. IBRANCE may impair fertility in males and has the potential to cause genotoxicity. Advise male patients to consider sperm preservation before taking IBRANCE. Advise male patients with female partners of reproductive potential to use effective contraception during IBRANCE treatment and for 3 months after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy. Advise women **not to breastfeed** during IBRANCE treatment and for 3 weeks after the last dose because of the potential for serious adverse reactions in nursing infants.

The **most common adverse reactions (≥10%)** of any grade reported in PALOMA-2 for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (80% vs 6%), infections (60% vs 42%), leukopenia (39% vs 2%), fatigue (37% vs 28%), nausea (35% vs 26%), alopecia (33% vs 16%), stomatitis (30% vs 14%), diarrhea (26% vs 19%), anemia (24% vs 9%), rash (18% vs 12%), asthenia (17% vs 12%), thrombocytopenia (16% vs 1%), vomiting (16% vs 17%), decreased appetite (15% vs 9%), dry skin (12% vs 6%), pyrexia (12% vs 9%), and dysgeusia (10% vs 5%).

The **most frequently reported Grade ≥3 adverse reactions (≥5%)** in PALOMA-2 for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (66% vs 2%), leukopenia (25% vs 0%), infections (7% vs 3%), and anemia (5% vs 2%).

Lab abnormalities of any grade occurring in PALOMA-2 for IBRANCE plus letrozole vs placebo plus letrozole were decreased WBC (97% vs 25%), decreased neutrophils (95% vs 20%), anemia (78% vs 42%), decreased platelets (63% vs 14%), increased aspartate aminotransferase (52% vs 34%), and increased alanine aminotransferase (43% vs 30%).

The **most common adverse reactions (≥10%)** of any grade reported in PALOMA-3 for IBRANCE plus fulvestrant vs placebo plus fulvestrant were neutropenia (83% vs 4%), leukopenia (53% vs 5%), infections (47% vs 31%), fatigue (41% vs 29%), nausea (34% vs 28%), anemia (30% vs 13%), stomatitis (28% vs 13%), diarrhea (24% vs 19%), thrombocytopenia (23% vs 0%), vomiting (19% vs 15%), alopecia (18% vs 6%), rash (17% vs 6%), decreased appetite (16% vs 8%), and pyrexia (13% vs 5%).

Please see Important Safety Information throughout, followed by Brief Summary of Prescribing Information for capsules and tablets.
STRENGTH IN FIRST LINE OR LATER

**IBRANCE + FULVESTRANT IN MBC AFTER PROGRESSION ON ENDOCRINE THERAPY**

In a 2:1 randomized, double-blind, Phase 3 trial of women with HR+/HER2- mBC who progressed on or after ET in the adjuvant or metastatic setting (N=521)^1

**Doubled mPFS vs placebo + fulvestrant**

- **Primary endpoint:** Investigator-assessed PFS^2
  
  - 9.5 months mPFS (n=347) vs **4.6 months mPFS** with placebo + fulvestrant (n=174); (95% CI: 9.2-11.0 vs 3.5-5.6); 
    **HR=0.46** (95% CI: 0.36-0.59); **P<0.0001**
  
  - Number of PFS events: 145 (41.8%) with IBRANCE + fulvestrant vs 114 (65.5%) with placebo + fulvestrant
  
  - ORR* (secondary endpoint): **24.6%** (95% CI: 19.6-30.2) of patients with measurable disease achieved an objective response with IBRANCE + fulvestrant vs **10.9%** (95% CI: 6.2-17.3) with placebo + fulvestrant (IBRANCE + fulvestrant n=267; placebo + fulvestrant n=138)^3
  
  - A final OS (secondary endpoint) analysis was conducted with 310 events (~60% of trial population) having occurred. These data show a numerical difference in favor of IBRANCE + fulvestrant vs placebo + fulvestrant that did not reach statistical significance^4
    
    - Median OS was 34.9 months (95% CI: 28.8-40.0) with IBRANCE + fulvestrant vs 28.0 months (95% CI: 23.6-34.6) with placebo + fulvestrant (HR=0.81 [95% CI: 0.64-1.03]; P=0.09); a difference of 6.9 months
    
    - This difference in median OS was similar to the improvement in mPFS previously seen with the addition of IBRANCE to fulvestrant in PALOMA-3^5

**Adverse reactions**

The **most common adverse reactions (≥10%)** of any grade reported in PALOMA-3 for IBRANCE plus fulvestrant vs placebo plus fulvestrant were neutropenia (83% vs 4%), leukopenia (53% vs 5%), infections (47% vs 31%), fatigue (41% vs 29%), nausea (34% vs 28%), anemia (30% vs 13%), stomatitis (28% vs 13%), diarrhea (24% vs 19%), thrombocytopenia (23% vs 0%), vomiting (19% vs 15%), alopecia (18% vs 6%), rash (17% vs 6%), decreased appetite (16% vs 8%), and pyrexia (13% vs 5%).

**Get the results for updated analyses at IBRANCEhcpp.com or from your IBRANCE representative**

**Important Safety Information (cont.)**

The most frequently reported Grade ≥3 adverse reactions (≥5%) in PALOMA-3 for IBRANCE plus fulvestrant vs placebo plus fulvestrant were neutropenia (66% vs 1%) and leukopenia (31% vs 2%).

Lab abnormalities of any grade occurring in PALOMA-3 for IBRANCE plus fulvestrant vs placebo plus fulvestrant were decreased WBC (99% vs 26%), decreased neutrophils (96% vs 14%), anemia (78% vs 40%), decreased platelets (62% vs 10%), increased aspartate aminotransferase (43% vs 48%), and increased alanine aminotransferase (56% vs 34%).

Avoid concurrent use of **strong CYP3A inhibitors**. If patients must be administered a strong CYP3A inhibitor, reduce the IBRANCE dose to 75 mg. If the strong inhibitor is discontinued, increase the IBRANCE dose (after 3-5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Grapefruit or grapefruit juice may increase plasma concentrations of IBRANCE and should be avoided. Avoid concomitant use of **strong CYP3A inducers**.

The dose of **sensitive CYP3A substrates** with a narrow therapeutic index may need to be reduced as IBRANCE may increase their exposure.

For patients with **severe hepatic impairment** (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg. The pharmacokinetics of IBRANCE have not been studied in patients requiring hemodialysis.

**References:**
Patients should be encouraged to take their dose of IBRANCE at approximately the same time each day.

**DOSAGE AND ADMINISTRATION**

**Recommended Dose and Schedule.** The recommended dose of IBRANCE is 125 mg capsules taken orally once daily, as a single dose, on Days 1-21 of each 28-day treatment cycle, with or without concomitant endocrine therapy. Patients should continue taking IBRANCE at the same time each day. If the patient vomits or misses a dose, an additional dose is not needed.

**Dose Reduction.** If dose reduction is required, the first recommended dose reduction is to 100 mg/day and the second dose reduction is to 75 mg/day. If further dose reduction below 75 mg/day is indicated, discontinue the treatment.

**Dose Modification and Management – Hematologic Toxicities**

Monitor complete blood counts prior to the start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and in clinically indicated situations.

For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, monitor complete blood counts for subsequent cycles every 3 months, prior to the beginning of a cycle and as clinically indicated.

**CTCAE Grade**

**Day 1 Change: Withdraw IBRANCE, repeat complete blood count monitoring within 1 week. When recovered to Grade ≤2, start the next dose at the same cycle.**

**Day 15 of first 2 cycles:**

- If Grade 1 or 2 neutropenia, Grade 1 or 2 leukopenia, or Grade 1 or 2 anemia continue at the time of the next scheduled dose, repeat complete blood count monitoring on Day 22. If Grade 4 on Day 22, see Grade 4 dose modification guidelines below.

**Grade 3 neutropenia**

- At any time: Withdraw IBRANCE until recovery to Grade ≤2.
- At any time: Withdraw IBRANCE until recovery to Grade ≤2. **Resume at the next lower dose.**

**Grade 4**

- At any time: Withdraw IBRANCE until recovery to Grade ≤2.
- At any time: Withdraw IBRANCE until recovery to Grade ≤2. **Resume at the next lower dose.**

**Grading according to CTCAE 4.0:**

- **Absolute neutrophil count (ANC): Grade 1: <500 µL; Grade 2: <1500 µL/mm³; Grade 3: 1500 – <5000 µL/mm³; Grade 4: ≥5000 µL/mm³.**

**Dose Modification and Management – Non-Hematologic Toxicities**

**CTCAE Grade**

**Day 1 Change:**

- Withhold until symptoms resolve to:
  - Grade ≥1;
  - Grade ≤2 (if not considered a safety risk for the patient). **Resume at the next lower dose.**

**Grading according to CTCAE 4.0:**

- **Non-hematologic toxicities**
  - **Skin and subcutaneous toxicities**
    - Alopecia
    - Fatigue
    - Anemia
    - Rash
    - Pruritus

**Adverse Reactions (≥10%) in Study 1**

**Adverse Reaction**

**IBRANCE + Letrozole (N=444)**

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
</table>
| Infections and infestations
| Infec| 6% | 0 | 42 | 3 |
| Blood and lymphatic system disorders
| Neutropenia | 50 | 0 | 6 | 1 |
| Leukopenia | 59 | 0 | 6 | 1 |
| Anemia | 24 | 1 | 9 | 0 |
| Thrombocytopenia | 16 | 1 | 9 | 0 |
| Metabolism and nutrition disorders
| Dehydration | 15 | 0 | 9 | 0 |
| Nervous system disorders
| Dysesthesia | 0 | 0 | 5 | 0 |
| Gastrointestinal disorders
| Stomatitis | 30 | 0 | 0 | 0 |
| Nausea | 35 | 1 | 0 | 26 |
| Diarrhea | 26 | 1 | 0 | 19 |
| Vomiting | 39 | 1 | 0 | 0 |
| Skin and subcutaneous toxicities
| Alopecia | 33 | 0 | 0 | 16 |
| Fatigue | 17 | 0 | 0 | 0 |
| Anemia | 17 | 0 | 0 | 0 |
| Rash | 30 | 0 | 0 | 0 |
| Pruritus | 12 | 0 | 0 | 0 |

**Adverse Reactions (≥3%) in Study 1**

**Adverse Reaction**

**IBRANCE + Letrozole (N=444)**

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
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</table>
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| Blood and lymphatic system disorders
| Neutropenia | 50 | 0 | 6 | 1 |
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| Skin and subcutaneous toxicities
| Alopecia | 33 | 0 | 0 | 16 |
| Fatigue | 17 | 0 | 0 | 0 |
| Anemia | 17 | 0 | 0 | 0 |
| Rash | 30 | 0 | 0 | 0 |
| Pruritus | 12 | 0 | 0 | 0 |

**Pharmacokinetic Data**

- Peak palbociclib exposure (Cmax) increased by 41% when coadministered with fulvestrant.
- There is no information regarding the presence of palbociclib in human milk, nor its effect on the nursing infant.

**Fertility and Pregnancy**

- Patients of reproductive potential are advised to use effective contraception during treatment with IBRANCE and for at least 3 weeks after treatment.

- Male patients should have a negative sperm count prior to initiating IBRANCE.

**Other**

- Transaminase elevations, hyperglycemia, pancreatic islet cell vacuolation, and kidney tubule vacuolation) were present with fulvestrant.

- Anemia was evaluated in Study 1 (PALOMA-2). The data described below reflect exposure to IBRANCE in 444 out of 666 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of IBRANCE plus letrozole in Study 1. The median duration of treatment for IBRANCE plus letrozole was 19.8 months while the median duration of treatment for placebo plus letrozole arm was 13.8 months.

- Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving IBRANCE plus letrozole. No dose reduction was allowed for letrozole in Study 1.

- Permanent discontinuation associated with an adverse reaction occurred in 43 of 444 (9.7%) patients receiving IBRANCE plus letrozole and in 13 of 666 (2.0%) patients assigned to placebo plus letrozole. The most common adverse reactions (≥10%) in patients in the IBRANCE plus letrozole arm by descending frequency were neutropenia, leucopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthma, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia.

- The most frequently reported Grade ≥3 adverse reactions (≥5%) in patients receiving IBRANCE plus letrozole by descending frequency were neutropenia, leucopenia, infections, and anemia.
The estimated background risk of major birth defects and miscarriage for the indicated population category is 2% to 4%. In the estimated background population, 2% to 4% of patients receiving IBRANCE plus fulvestrant were reported to have had a first pregnancy at doses of up to 300 mg/kg/d with maternal systemic exposures approximately 4 times the human exposure (AUC) at the recommended dose. In embryo-fetal development studies in rats and rabbits, palbociclib was administered orally throughout organogenesis. There was no evidence of palbociclib embryotoxicity at doses up to 300 mg/kg/d with maternal systemic exposures approximately 4 times the human exposure (AUC) at the recommended dose.

Lactation. There is no information regarding the presence of palbociclib in human milk, nor its effects on milk production or the breastfed infant. Because of the potential for serious adverse reactions in breastfeeding infants from IBRANCE, advise a lactating woman not to breastfeed during treatment with IBRANCE and for 3 weeks after the last dose.

Females and Males of Reproductive Potential. Based on animal studies, IBRANCE can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should have a negative pregnancy test prior to starting treatment with IBRANCE. IBRANCE (CRCh tail class A) harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with IBRANCE and for at least 3 weeks after the last dose. Based on animal studies, IBRANCE may impair fertility in males of reproductive potential.

Pediatric Use. The safety and efficacy of IBRANCE in pediatric patients has not been studied.

Hepatic Impairment. No dose adjustment is required in patients with mild or moderate hepatic impairment (child-pugh class A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg once daily for 21 consecutive days followed by 7 days of drug-free treatment to comprisem the hepatic excretory functional toxicokinetic trial study was conducted in 15 patients with advanced solid tumors in subjects with varying degrees of hepatic function, the palbociclib unbound exposure (unbound AUC) was increased by 17% in subjects with mild hepatic impairment, and increased by 34% and 77% in subjects with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function. Peak palbociclib unbound exposure (unbound AUC) increased by 19% in moderate hepatic impairment and severe hepatic impairment, respectively, relative to subjects with normal hepatic function. Review the Full Prescribing Information for the known aromatase inhibitor or fulvestrant for dose modifications related to hepatic impairment.

Renal Impairment. No dose adjustment is required in patients with mild, moderate, or severe renal impairment (CrCl ≥15 mL/min). Based on a pharmacokinetic trial in subjects with varying degrees of renal function, the total palbociclib exposure (AUC(0-∞)) increased by 39%, 42%, and 31% with mild (CrCl 30-50 mL/min), moderate (CrCl <30-50 mL/min), and severe (CrCl <30-50 mL/min) renal impairment, respectively, relative to subjects with normal renal function. Peak palbociclib unbound exposure (unbound AUC) increased by 19% in moderate renal impairment and severe renal impairment, respectively, relative to subjects with normal renal function. The pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis.

OVERDOSAGE

There is no known antidote for IBRANCE. The treatment of overdose of IBRANCE should consist of general supportive measures.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Malignant Hypertension

• Advise patients to immediately report any signs or symptoms of myelosuppression or infection, such as fever, chills, dizziness, shortness of breath, weakness or any increased tendency to bleed anywhere or bruise.

Intestinal Lymph Disease/Pneumonitis

• Advise patients to immediately report any signs or symptoms of myelosuppression or infection, such as fever, chills, dizziness, shortness of breath, weakness or any increased tendency to bleed anywhere or bruise.
E-Selectin Presents a Favorable Path Forward for AML Populations

by BRITTANY LOVELY

ACHIEVEMENT OF COMPLETE REMISSION (CR) and the depth of that remission are 2 of the most critical needs that investigators seek to address in acute myeloid leukemia (AML). Compared with other leukemias, patients with AML have the lowest 5-year survival rate at 29.5% vs 70.6% for those with chronic lymphocytic leukemia, 87.2% for those with chronic myeloid leukemia, and 69.9% for those with acute lymphocytic leukemia.1,2 Investigators have noted that acquired resistance to standard therapies, such as induction chemotherapy with anthracycline and cytarabine, and the persistence of leukemia stem cells tracked in minimal residual disease (MRD) are 2 hurdles for developing effective treatments for patients.

"Remissions can be achieved with both intensive and non-intensive therapies in sometimes up to 70% of patients [with AML], but a major issue with a vast majority of patients is [relapse] unless they are bridged to allogeneic stem cell transplant," David Sallman, MD, said in an interview with OncologyLive®. "A big issue is having some leftover amount of disease after frontline therapies, which [is] predictive of poor outcomes even in [individuals] who are ultimately bridged to transplant. Improving the depth of remission and targeting leukemic stem cells that may be left behind [are] of paramount importance to further improve outcomes to therapy."

Sallman is an assistant member in the Department of Malignant Hematology at Moffitt Cancer Center in Tampa, Florida.

UNMASKING RESIDUAL DISEASE WITH E-SELECTIN

A recent avenue of exploration for investigators is to inhibit the activity that promotes the self-renewal of leukemic stem cells and draw out persistent cells masked in the bone marrow tumor microenvironment. Specifically, investigators are exploring novel agents engineered to target adhesion factors, which can mobilize persistent leukemic stem cells from the bone marrow niche.3

"Normal hematopoietic stem cells reside in the bone marrow in these specialized microenvironments, which refer to the stem cell niche," Geoffrey L. Uy, MD, said in an interview. "Evidence suggests that leukemia stem cells occupy specific niches within the bone marrow. This interaction confers protection against genotoxic stresses, such as chemotherapy."

Uy is a professor of medicine in the Division of Oncology, Section of Bone Marrow Transplantation at Washington University School of Medicine in St Louis and a bone marrow transplant specialist and medical oncologist at Siteman Cancer Center in Missouri. One adhesion molecule and associated pathway of interest is E-selectin, which is expressed on the vascular endothelium and has known interactions with leukemic stem cells through binding with ligands such as CD44. Activation of the E-selectin pathway induces activity that can result in the protection of these cells and the promotion of cytotoxic chemotherapy resistance.4,5

"E-selectin is normally expressed on endothelial cells and is upregulated in response to inflammation, which includes IL-1, tumor necrosis factor, and lipopolysaccharide," Uy explained. "When E-selectin is upregulated, it binds to E-selectin ligands present on leukocytes and is an important mechanism for these leukocytes to traffic to areas of inflammation. In the bone marrow microenvironment, we know that E-selectin is present in the bone marrow sinusoids. It is expressed at high levels, and the E-selectin ligands are expressed on tumor cells. We think that this interaction confers specific protective effects to these AML blasts, and plenty of data have shown that specific pathways are activated, such as PI3K, AKT, and NFkB that can be important for leukemia cell survival."

Disrupting the E-selectin pathway opens the door for investigators to capitalize on the known effects of intensive chemotherapy regimens, such as MEC (mitoxantrone, etoposide, and cytarabine). An agent of interest in this space is the novel E-selectin antagonist uproleselan. Investigators have observed preclinical and clinical activity of uproleselan in combination with MEC, specifically in a phase 1/2 study (NCT02306291) in a cohort of older patients (aged ≥ 60 years) with newly diagnosed AML and in a cohort of patients with relapsed or refractory AML, administered in the salvage setting.6

FIGURE. Phase 3 Trial of Uproleselan in Relapsed/Refractory AML

NCT03616470

Eligibility criteria

- Aged ≥ 18 years and ≤ 75 years
- Patients with relapsed or refractory AML
- ≤ 1 prior stem cell transplant
- Has not received the chemotherapy regimen to be used for induction on this trial
- Is considered medically eligible to receive the trial-specific induction chemotherapy regimen

End points

Primary
- OS
- Select secondary
- Rate of severe oral mucositis
- ORR
- Duration of remission
- AEs
- Pharmacokinetic exposure

<table>
<thead>
<tr>
<th>Randomized 1:1 (N = 388)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uproleselan plus MEC or FAI</td>
</tr>
<tr>
<td>Placebo plus MEC or FAI</td>
</tr>
</tbody>
</table>

AEs, adverse events; AML, acute myeloid leukemia; EFS, event-free survival; FAI, fludarabine, cytarabine and idarubicin; MEC, mitoxantrone, etoposide and cytarabine; ORR, overall response rate; OS, overall survival.

Uproleselan clears the path for chemotherapy

The treatment schema for the phase 1/2 trial called for the administration of uproleselan 24 hours following induction chemotherapy as a 20-minute intravenous (IV) infusion. Three doses of uproleselan were assessed, and the recommended phase 2 dose (RP2D) was determined as 10 mg/kg because it did not result in dose-limiting toxicities in more than 33% of patients.7

Induction chemotherapy regimens in the trial...
were as follows. Patients with relapsed/refractory AML received standard MEC (daily mitoxantrone 10 mg/m² via 15-20 minute IV, daily etoposide 100 mg/m² IV over 60 minutes, and daily cytarabine 1000 mg/m² IV over 60 minutes for 5 days), and older patients with newly diagnosed AML received conventional 7 + 3 induction chemotherapy (24-hour continuous daily infusion of cytarabine 200 mg/m² on days 1-7 in combination with 12 mg/m² idarubicin on days 1-3 via daily IV bolus). Induction therapy lasted 8 days and 10 days, respectively. If remission was achieved patients, were offered optional consolidation therapy.

Among those treated with the RP2D in the relapsed/refractory cohort (n = 54), the overall response rate (ORR) was 41%, with 35% of patients reporting a CR and 10 patients having a response lasting at least 12 months. Thirteen patients were evaluable for MRD assessment, 4 patients were positive and 9 as MRD negative, defined as having at least 10⁻⁹ leukemic cells.

The median overall survival (OS) was 8.8 months (95% CI, 9.7-11.4), and the median event-free survival (EFS) was 1.5 months (95% CI, 1.3-2.8). Notably, assessed by E-selectin ligand expression, those with at least 10% expression (n = 21) had a greater median OS (10.7 months; 95% CI, 5.9-not applicable [NA]) vs those with 10% expression or less (5.2 months; 95% CI, 0.9-9.4). This benefit extended to those who had a CR lasting at least 12 months and to those who underwent transplant following uproleselan. In the cohort of older patients (n = 25), the ORR was 72% with a CR rate of 52%. Among those evaluable for MRD assessment, 4 patients were positive and 5 were negative. The median OS was 12.6 months (95% CI, 9.9-NA), and the median EFS was 9.2 months (95% CI, 3.0-12.6).

In terms of safety, the agent was well tolerated and demonstrated no clear additive toxicities.

“Ther are no significant drug interactions [with chemotherapy], such as QT prolongation or CYP3A4 interactions. [Uproleselan] is easy to add to different chemotherapy backbones,” Uy said of the phase 1/2 data. “One of the potential benefits of this drug is that it may protect patients against chemotherapy-induced mucositis. Gastrointestinal toxicity can be quite significant in patients receiving induction chemotherapy for leukemia, [and uproleselan] may protect against [this] important cause of morbidity in this population.”

Leveraging these findings, trials have commenced to further explore the efficacy of uproleselan in both populations. “The major key when you’re thinking of any trial in the intensive chemotherapy option is really a randomized trial,” Sallman said, noting that the phase 3 trial in the relapsed/refractory patient population will be of particular interest because those who progress following more than 1 line of therapy have the worst outcomes.

**UNPACKING THE ROLE OF UPROLESelan ACROSS AML**

Investigators have expanded the scope of this evaluation with the initiation of the phase 3 GMI-1271-301 trial (NCT03616470). The phase 3 study is designed to evaluate chemotherapy with either uproleselan or placebo in patients with relapsed/refractory AML. Enrollment was completed in November 2021. Patients were randomly assigned to receive uproleselan or placebo in combination with 1 cycle of induction MEC or fludarabine, cytarabine, and idarubicin. Consolidation therapy, which can last up to 3 cycles, will consist of either uproleselan or placebo in combination with high-dose or intermediate-dose cytarabine (Figure). The primary end point of the study is OS. Secondary outcome measures include ORR and rate of severe oral mucositis following treatment. EFS, duration of remission, and safety will also be assessed.

Investigators are also seeking to explore the efficacy of uproleselan in a secondary cohort of patients from the phase 1/2 study—those with newly diagnosed AML who are 60 years and older and fit for 7 + 3 chemotherapy—in the phase 2/3 A041701 (NCT03701308) trial. Sponsored by the National Cancer Institute and the Alliance for Clinical Trials in Oncology, the study completed enrollment at the end of 2021. Patients were randomly assigned to 7 + 3 chemotherapy with or without uproleselan. If CR was achieved, patients proceeded to consolidation therapy; those without CR proceeded to a second induction cycle. The primary end point of the phase 2 portion of the trial is EFS. Should the results meet the prespecified end point, the data will transfer confidentially to GlycoMimetics Inc, the developer of the agent, to support filing for FDA approval.

**REFERENCES**


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Chemoimmunotherapy Anchors Front Line in Metastatic TNBC

by ANITA T. SHAFFER

PATIENTS WITH NEWLY DIAGNOSED metastatic triple-negative breast cancer (TNBC) should undergo PD-L1 expression testing on tumors to determine whether they are candidates for frontline chemoimmunotherapy, according to Kevin Kalinsky, MD, MS.

The emergence of immune checkpoint inhibitor (ICI) therapy for patients with PD-L1-positive TNBC is among the advancements in the past several years that are shaping the treatment landscape for this breast cancer subtype. Other milestones include the approval of saci

TABLE 1. Outcomes by PD-L1 Expression in KEYNOTE-522

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ITT population</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pembrolizumab plus chemotherapy</td>
<td>Placebo plus chemotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 566)</td>
<td>(n = 281)</td>
<td></td>
</tr>
<tr>
<td>Median OS, months</td>
<td>17.2</td>
<td>15.5</td>
<td></td>
</tr>
<tr>
<td>18-month OS rate</td>
<td>47.8%</td>
<td>41.8%</td>
<td></td>
</tr>
<tr>
<td>24-month OS rate</td>
<td>35.5%</td>
<td>30.4%</td>
<td></td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>7.5</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td>12-month PFS rate</td>
<td>29.3%</td>
<td>20.8%</td>
<td></td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>40.8%</td>
<td>37.0%</td>
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</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CPS ≥ 10</th>
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<tbody>
<tr>
<td></td>
<td>Pembrolizumab plus chemotherapy</td>
<td>Placebo plus chemotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 220)</td>
<td>(n = 103)</td>
<td></td>
</tr>
<tr>
<td>Median OS, months</td>
<td>23.0</td>
<td>16.1</td>
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</tr>
<tr>
<td>18-month OS rate</td>
<td>58.3%</td>
<td>44.7%</td>
<td></td>
</tr>
<tr>
<td>24-month OS rate</td>
<td>48.2%</td>
<td>34.0%</td>
<td></td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>9.7</td>
<td>5.6</td>
<td></td>
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<tr>
<td>12-month PFS rate</td>
<td>39.1%</td>
<td>23.0%</td>
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<tr>
<td>ORR (95% CI)</td>
<td>52.7%</td>
<td>40.8%</td>
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<table>
<thead>
<tr>
<th>Outcome</th>
<th>CPS ≥ 1</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Pembrolizumab plus chemotherapy</td>
<td>Placebo plus chemotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 425)</td>
<td>(n = 211)</td>
<td></td>
</tr>
<tr>
<td>Median OS, months</td>
<td>17.6</td>
<td>16.0</td>
<td></td>
</tr>
<tr>
<td>18-month OS rate</td>
<td>48.4%</td>
<td>41.4%</td>
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</tr>
<tr>
<td>24-month OS rate</td>
<td>37.7%</td>
<td>29.5%</td>
<td></td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>7.6</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>12-month PFS rate</td>
<td>31.7%</td>
<td>19.4%</td>
<td></td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>44.9%</td>
<td>38.9%</td>
<td></td>
</tr>
</tbody>
</table>

Kevin Kalinsky, MD, MS

FRONTLINE IMMUNOTHERAPY

In July 2021, the FDA granted regular approval to pembrolizumab (Keytruda), a PD-1 inhibitor, in combination with chemotherapy for patients with unresectable or metastatic TNBC with PD-L1 positivity, defined as a combined positive score (CPS) of 10 or greater via immunohistochemistry (IHC) testing.

The PD-L1 IHC 22C3 pharmDx assay has been designated as the companion diagnostic for the indication. At the same time, the FDA approved pembrolizumab for patients with high-risk, early-stage TNBC in combination with chemotherapy as neoadjuvant treatment and then continued as a single agent as adjuvant treatment after surgery.

The indications in all settings are based on data from the phase 3 KEYNOTE-522 (NCT03036488) trial in patients with locally recurrent unresectable or metastatic TNBC who had not previously received chemotherapy in the metastatic setting, regardless of PD-L1 expression status.

In the metastatic setting, 847 patients were randomized 2:1 to receive pembrolizumab at 200 mg (n = 566) or placebo (n = 281) every 3 weeks in combination with nab-paclitaxel (Abraxane), paclitaxel, or gemcitabine plus carboplatin.

The primary end points were progression-free survival (PFS) and overall survival (OS) for participants with PD-L1-positive tumors (CPS ≥ 10 and CPS ≥ 1) and in the intention-to-treat (ITT) population.

After a median follow-up of 44.1 months, the median OS in patients with a CPS score of 10 or greater was 23.0 months in the pembrolizumab arm compared with 16.1 months with placebo (HR, 0.73; 95% CI, 0.55-0.95; 1-sided P = .0093), according to findings from the final analysis presented at the 2021 European Society for Medical Oncology Congress. Median PFS for this population was 9.7 months (95% CI, 7.6-11.3) with pembrolizumab compared with 5.6 months (95% CI, 5.3-7.3) with placebo (HR, 0.66; 95% CI, 0.50-0.88). Pembrolizumab therapy also resulted in a 52.7% objective response rate (ORR) in patients with a CPS score of 10 or greater compared with 40.8% with placebo.
Although median OS was higher among patients with a CPS score of 1 or greater and in the ITT population, the results did not reach the thresholds for statistical significance (HR, 0.86 and 0.89, respectively). In the subgroup of participants with a CPS score of less than 10, the pembrolizumab-containing regimen was not superior to the placebo arm (HR, 1.04). 4

The regular approval for pembrolizumab in metastatic TNBC converted an accelerated approval that the FDA had granted for the agent in November 2020 and solidified a place for ICI therapy in the treatment paradigm for this breast cancer subtype. 1 In August 2021, Genentech voluntarily withdrew an accelerated approval indication for atezolizumab (Tecentriq), a PD-L1 inhibitor, in combination with nab-paclitaxel for patients with metastatic TNBC with tumors expressing PD-L1 after the agent did not reach its primary PFS end point in a confirmatory trial. 3

**Sacituzumab Govitecan**

In the recurrent setting, sacituzumab govitecan has been introduced into the TNBC paradigm as a later-line therapy for patients with previously treated metastatic disease, but its robust single-agent activity shows its potential to have a much more pronounced improvement in PFS and OS compared with chemotherapy (HR for disease progression or death, 0.43; 95% CI, 0.35-0.54; P < .0001). The median OS, respectively, was 11.8 months (95% CI, 10.5-13.8) and 6.9 months (95% CI, 5.9-7.7), which translated into an HR for death of 0.51 (95% CI, 0.41 to 0.62; P < .0001). 5

Like other ADCs, sacituzumab govitecan has 3 main components: an antibody coupled with a cytotoxic payload joined by a linker. The agent is comprised of a humanized monoclonal antibody directed at Trop-2, an antigen expressed on the surface of tumor cells in more than 90% of breast cancers; SN-38, the active metabolite of irinotecan and a topoisomerase I inhibitor; and a hydrolysable linker. 6

Although sacituzumab govitecan is directed at Trop-2, the ASCENT trial did not require that patients’ tumors exhibit a certain expression level for inclusion. In a biomarker analysis of Trop-2 expression among 290 assessable ASCENT participants, investigators found sacituzumab govitecan was more effective than chemotherapy among patients with metastatic TNBC with a high H-score (200-300) and medium H-score (100-200) via IHC testing in terms of median PFS, ORR, and OS (TABLE 2). 7 Efficacy outcomes also were numerically higher for patients with low Trop-2 levels (HR score, 0 to < 100) who received sacituzumab govitecan (n = 27) than for those who had chemotherapy (n = 32), but the number of participants in the subgroup was too small to reach definitive conclusions, investigators said. 8

The potential for broader applications for sacituzumab govitecan in breast cancer is being explored in numerous clinical trials. These include the phase 3 TROPICS-02 trial

**TABLE 2. Outcomes by Trop-2 Expression in ASCENT**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trop-2 high (&gt;200-300)</th>
<th>TPC (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>6.9 (5.8-7.4)</td>
<td>2.5 (1.5-2.9)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>14.2 (11.3-17.5)</td>
<td>6.9 (5.3-8.9)</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>44% (33%-55%)</td>
<td>1% (0%-8%)</td>
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</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trop-2 medium H-score (100-200)</th>
<th>TPC (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>5.6 (2.9-8.2)</td>
<td>2.2 (1.4-4.3)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>14.9 (6.9-NE)</td>
<td>6.9 (4.6-10.1)</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>38% (23%-55%)</td>
<td>11% (3%-27%)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trop-2 low H-score (0 to &lt;100)</th>
<th>TPC (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>2.7 (1.4-5.8)</td>
<td>1.6 (1.4-2.7)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>9.3 (7.5-17.8)</td>
<td>7.6 (5.0-9.6)</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>22% (9%-42%)</td>
<td>6% (1%-21%)</td>
</tr>
</tbody>
</table>

**ADVANTAGE. It’s an important agent in this subtype of breast cancer.”**

Sacituzumab govitecan demonstrated an improvement in PFS and OS compared with single-agent chemotherapy among patients with relapsed or refractory metastatic TNBC in the phase 3 ASCENT trial (NCT02574455). 8,9 Based on the study findings, the FDA granted regular approval to sacituzumab govitecan in April 2021 as monotherapy for patients with unresectable locally advanced or metastatic TNBC who have received 2 or more prior systemic therapies, including at least 1 for metastatic disease. This decision converted a 2020 accelerated approval in the same indication to full approval. 10

In ASCENT, 529 patients with TNBC were randomized 1:1 to receive sacituzumab govitecan at 10 mg/kg (n = 267) or physician’s choice of chemotherapy (n = 262), with investigators prespecifying single-agent eribulin (Halaven), capecitabine, gemcitabine, or vinorelbine. The primary end point was PFS by blinded independent central review in patients without known brain metastases. Findings were reported after a median follow-up of 17.7 months.

Among 468 patients in this population, sacituzumab govitecan therapy resulted in a median PFS of 5.6 months (95% CI, 4.3-6.3) compared with 1.7 months (95% CI, 1.5-2.6) for those who received chemotherapy (HR for disease progression or death, 0.41; 95% CI, 0.32-0.52; P < .001). Sacituzumab govitecan also demonstrated improvement in median OS, a secondary end point. In patients without brain metastases, the median OS was 12.1 months (95% CI, 10.7-14.0) in the sacituzumab govitecan arm vs 6.7 months (95% CI, 5.8-7.7) in the chemotherapy group (HR for death, 0.48; 95% CI, 0.38-0.59; P < .001). 8

Sacituzumab govitecan also improved median PFS and OS in the full population, which included 61 patients with brain metastases. In the full population, the median PFS was 4.8 months (95% CI, 4.1-5.8) with sacituzumab govitecan and 1.7 months (95% CI, 1.5-2.5) with chemotherapy (HR for disease progression or death, 0.43; 95% CI, 0.35-0.54; P < .0001). The median OS, respectively, was 11.8 months (95% CI, 10.5-13.8) and 6.9 months (95% CI, 5.9-7.7), which translated into an HR for death of 0.51 (95% CI, 0.41 to 0.62; P < .0001). 9

Kevin Kalinsky, MD, MS, discusses how antibody-drug conjugates (ADCs) have solidified their role as an important therapy for patients with HER2-positive breast cancer, and how they might be leveraged in other disease subtypes.

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**Kalinsky on the Potential of ADCs Across Breast Cancer Subtypes**

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The potential for broader applications for sacituzumab govitecan in breast cancer is being explored in numerous clinical trials. These include the phase 3 TROPICS-02 trial.
(NCT03901339), which is ongoing but no longer recruiting participants, comparing sacituzumab govitecan with physician’s choice of single-agent chemotherapy in patients with hormone receptor-positive, HER2-negative metastatic breast cancer with disease progression after at least 2 prior chemotherapy regimens. The German Breast Group is conducting the phase 3 SASCIA trial (NCT04395565) testing sacituzumab govitecan with physician’s choice of capcitabine or platinum-based chemotherapy as postneoadjuvant treatment for patients with HER2-negative breast cancer, including TNBC and hormone receptor-positive disease.6

GENETIC BIOMARKERS
All patients diagnosed with recurrent or metastatic breast cancer should undergo tumor testing for BRCA1/2 mutations to determine if they are candidates for PARP inhibitor therapy, according to National Comprehensive Cancer Network (NCCN) breast cancer treatment guidelines. The FDA has approved 2 PARP inhibitors, olaparib (Lynparza) and talazoparib (Talzenna), in HER2-negative breast cancer settings, but the NCCN panel believes these agents could be considered for use in patients with any breast cancer subtype with a BRCA1/2 mutation.11 Specifically, olaparib is approved for the treatment of adult patients with deleterious or suspected deleterious BRCA, HER2-negative metastatic breast cancer who have received chemotherapy in the neoadjuvant, adjuvant, or metastatic setting.12 Talazoparib is indicated for patients with BRCA-mutated HER2-negative locally advanced or metastatic breast cancer.13

The FDA approved olaparib based on data from the phase 3 OlympiAD trial (NCT02000622), in which patients with previously treated BRCA-mutated HER2-negative metastatic breast cancer were randomized 2:1 to receive olaparib tablets (300 mg twice daily) or standard single-agent chemotherapy (capecitabine, eribulin, or vinorelbine). Of the 302 patients treated during the study, approximately 50% had TNBC at baseline.12 For the overall study population, median PFS with olaparib was 7.0 months compared with 4.2 months with chemotherapy (HR for disease progression or death, 0.58; 95% CI, 0.43-0.80; \( P < .001 \)). A subgroup analysis showed that patients with TNBC derived a greater benefit from olaparib therapy (HR, 0.43; 95% CI, 0.29-0.63) compared with participants with hormone receptor-positive disease (HR, 0.82; 95% CI, 0.55-1.26).14

The indication for talazoparib is based on findings from the phase 3 EMBRACA study (NCT01945775), in which patients were randomized 2:1 to receive talazoparib capsules (1 mg once daily) or physician’s choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). Approximately 44% of the 431 patients randomized during the study had TNBC at baseline. In the full population, the median PFS for patients in the talazoparib arm was 8.6 months (95% CI, 7.2-9.3) vs 5.6 months (95% CI, 4.2-6.7) in the chemotherapy arm (HR for progression or death, 0.54; 95% CI, 4.2-6.7; \( P < .001 \)). Results from a subgroup analysis suggested patients with hormone receptor-positive disease received a greater benefit from talazoparib (HR, 0.47; 95% CI, 0.32-0.70) than those with TNBC (0.60; 95% CI, 0.41-0.87).13,15

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

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For adults with polycythemia vera (PV) who have had an inadequate response to or are intolerant of hydroxyurea (HU)

**EVERY DAY COUNTS. JAKAFI CAN HELP.**

PV is a hematologic malignancy that can become advanced in a subset of patients

In a subset of patients, these characteristics may indicate advanced PV despite treatment with HU at the maximum tolerated dose and phlebotomy.

<table>
<thead>
<tr>
<th>Hct ≥45%</th>
<th>WBC count &gt;1 x 10^9/L</th>
<th>Disease-related SYMPTOMS</th>
</tr>
</thead>
</table>

In the phase 3 RESPONSE* trial, Jakafi demonstrated superior results vs BAT

---

**Composite Primary Endpoint**

23% (25/110) of patients receiving Jakafi achieved Hct control and ≥35% spleen volume reduction at week 32 vs <1% (1/112) of patients receiving BAT (P < 0.0001)

BAT, best available therapy; Hct, hematocrit; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; TSS, Total Symptom Score; WBC, white blood cell.

*The RESPONSE (Randomized study of Efficacy and Safety in Polycythemia vera with JAK Inhibitor ruxolitinib versus Best available care) trial was a randomized, open-label, active-controlled phase 3 trial comparing Jakafi with BAT in 222 patients with PV. Patients enrolled in the study had been diagnosed with PV for at least 24 weeks, had an inadequate response to or were intolerant of HU, required phlebotomy for Hct control, and exhibited splenomegaly. All patients were required to demonstrate Hct control between 40% and 45% prior to randomization. After week 32, patients were able to cross over to Jakafi treatment.

The composite primary endpoint was defined as Hct control without phlebotomy eligibility and a ≥35% spleen volume reduction as measured by CT or MRI. To achieve the Hct control endpoint, patients could not become eligible for phlebotomy between weeks 8 and 32. Phlebotomy eligibility was defined as Hct >45% that is ≥3 percentage points higher than baseline or Hct >48% (lower value).

BAT included HU (60%), interferon/pegylated interferon (12%), anagrelide (7%), pipobroman (2%), lenalidomide/halofantrine (5%), and observation (15%).

Jakafi 95% CI, 0.15-0.32; BAT 95% CI, 0.00-0.05.

---

**Indications and Usage**

Jakafi is indicated for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea.

**Important Safety Information**

- Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.

- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary.

- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi.

- Severe neutropenia (ANC <0.5 x 10^9/L) was generally reversible by withholding Jakafi until recovery.

- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.

- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination.

- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate.

- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment.

- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines.

- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation.

- Non-melanoma skin cancers (NMSC) including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations.

- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

- Another JAK-inhibitor has increased the risk of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, and stroke (compared to those treated with tumor TNF blockers) in patients with...
For adults with polycythemia vera (PV) who have had an inadequate response to or are intolerant of hydroxyurea (HU)

• Manage thrombocytopenia by reducing the dose or temporarily interrupting

In the phase 3 RESPONSE* trial, Jakafi demonstrated superior results† vs BAT‡

‡BAT included HU (60%), interferon/pegylated interferon (12%), anagrelide (7%), pipobroman (2%), lenalidomide/thalidomide (5%), and observation (15%).11

• Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment
treatment of active TB should be based on the overall risk-benefit determination

In a subset of patients, these characteristics may

Consulting their physician. When discontinuing or interrupting Jakafi for reasons

evaluate and treat any intercurrent illness and consider restarting or increasing

failure. If any of these occur after discontinuation or while tapering Jakafi,

nonhematologic adverse reactions (incidence ≥20%) were infections (pathogen not specified) and viral infections

• Avoid concomitant use with fluconazole doses greater than 200 mg. Dose modifications may be required when administering Jakafi with fluconazole
doses of 200 mg or less, or with strong CYP3A4 inhibitors, or in patients with renal or hepatic impairment. Patients should be closely monitored and the
dose titrated based on safety and efficacy

Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking
Jakafi should not breastfeed during treatment and for 2 weeks after the final
dose

Please see Brief Summary of Full Prescribing Information for Jakafi on the following pages. To learn more about Jakafi, visit HCP.Jakafi.com


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Brief Summary: For Full Prescribing Information, see package insert.

Indications and Usage: Myelofibrosis Jakafi is indicated for treatment of intermediate or high-risk myelofibrosis (MF) associated with erythrocytosis following primary MF, post-polycythemia vera MF and post-essential thrombocytemia MF in adults. Polycythemia Vera Jakafi is indicated for treatment of polycythemia vera (PV) in adults who have an inadequate response to or are intolerant of hydroxyurea. Acute Graft-Versus-Host Disease Jakafi is indicated for treatment of steroid-refractory acute graft-versus-host disease (aGVHD) in adult and pediatric patients 12 years and older. Chronic Graft-Versus-Host Disease Jakafi is indicated for treatment of chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older.

Contraindications: None.

Warnings and Precautions: Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [see Adverse Reactions (6.1) in Full Prescribing Information]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [see Dosage and Administration (2) in Full Prescribing Information]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 × 10⁹/L) was generally reversible by withholding Jakafi until recovery. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [see Dosage and Administration (2) in Full Prescribing Information]. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines. Tuberculosis Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors are indicated but are not limited to, residence or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. Progressive Multifocal Leuкоencephalopathy Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate. Herpes Zoster Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected. Hepatitis B Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine transaminase and aspartate transaminase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. Symptomatic Anemia Following Interruption or Discontinuation of Treatment with Jakafi Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. Withholding Jakafi may result in exacerbation of symptoms. Non-Melanoma Skin Cancer (NMSC) Non-melanoma skin cancers, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. Lipid Elevations Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical judgment and management of hyperlipidemia. Major Adverse Cardiovascular Events (MACE) Another JAK-inhibitor has increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Thrombosis Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. In patients with MF and PV treated with Jakafi in clinical trials, the rates of thromboembolic events were similar in Jakafi and control treated patients. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately. Secondary Malignancies Another JAK-inhibitor has increased the risk of lymphomas and other malignancies excluding NMSC (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi, particularly in patients with a known secondary malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers. Adverse Reactions The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling: Thrombocytopenia, Anemia and Neutropenia [see Warnings and Precautions (5.1) in Full Prescribing Information]. Risk of Infection [see Warnings and Precautions (5.2) in Full Prescribing Information] • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [see Warnings and Precautions (5.3) in Full Prescribing Information] • Non-Melanoma Skin Cancer [see Warnings and Precautions (5.4) in Full Prescribing Information] • Lipid Elevations [see Warnings and Precautions (5.5) in Full Prescribing Information] • Major Adverse Cardiovascular Events (MACE) [see Warnings and Precautions (5.6) in Full Prescribing Information] • Diabetic Retinopathy [see Warnings and Precautions (5.7) in Full Prescribing Information] • Secondary Malignancies [see Warnings and Precautions (5.8) in Full Prescribing Information]. 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. Myelofibrosis The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 × 10⁹/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 × 10⁹/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse reactions were thrombocytopenia and anemia [see Table 2]. Thrombocytopenia, anemia and neutropenia are dose-related effects. The three most frequent nonhematologic adverse reactions were bruising, dizziness and headache [see Table 1]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common nonhematologic adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 1: Myelofibrosis: Nonhematologic Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (N=158)</th>
<th>Placebo (N=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Body Weight Loss</td>
<td>45</td>
<td>15</td>
</tr>
<tr>
<td>Gastroesophageal Reflux Infections</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

* National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
  1 includes cutaneous, eczematous, hematosidero, injection site hemato, periodontal hemato, vessel punch site hemato, increased tendency to bruise, petechiae, purpura
  2 includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthis
  3 includes urinary tract infection, cystitis, unspesific, urinary tract infection bacterial, urinary infection, pyuria, pyuria, bacteria, urine bacteria identified, nitrite urine present
  4 includes weight increased, abnormal weight gain
  5 includes herpes zoster and post zoster erythema

Description of Selected Adverse Reactions: Anemia

In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transplants during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 times greater in patients treated with Jakafi compared to placebo treated patients. Thrombocytopenia in the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50 × 10⁹/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens. Discontinuation...
Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-controlled Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=151)</th>
<th>Jakafi (N=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades 1 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td></td>
<td>Grade 4 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td></td>
<td>Grade 4 (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td></td>
<td>Grade 4 (%)</td>
<td>Grade 3 (%)</td>
</tr>
</tbody>
</table>

- Hematology
  - Anemia: 72 < 1 < 1 58 0 0
  - Neutrophilia: 27 5 < 1 24 3 < 1
- Chemistry
  - Hyperbilirubinemia: 3 0 < 1 10 1 < 1

Additional Data from the Placebo-controlled Study
- 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. • 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was < 1% for Jakafi with no Grade 3 or 4 AST elevations. • 17% of patients treated with Jakafi and < 1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was < 1% for Jakafi with no Grade 3 or 4 cholesterol elevations.

Polycthemia Vera in a randomized, open-label, active-controlled study, 110 patients with PV resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy (see Clinical Studies (14.2) in Full Prescribing Information). The most frequent adverse reaction was anemia.

Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi. Table 3 presents the most frequent nonhematologic adverse reactions occurring up to Week 32.

Table 3: Polycthemia Vera: Nonhematologic Adverse Reactions Occurring in > 5% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (N=151)</th>
<th>Grade 3 (N=151)</th>
<th>Grade 4 (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13</td>
<td>0</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Muscle Spasm</td>
<td>8</td>
<td>0</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Constipation</td>
<td>8</td>
<td>0</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Anemia</td>
<td>82</td>
<td>13</td>
<td>75</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>75</td>
<td>6</td>
<td>75</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>12 0 13 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12</td>
<td>0</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Constipation</td>
<td>8</td>
<td>0</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Muscle Spasm</td>
<td>8</td>
<td>0</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

- Selected laboratory abnormalities are listed in Table 6 below
- National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03
- Grouped terms that are composites of applicable adverse reaction terms.
- Clinically relevant laboratory abnormalities are shown in Table 4.

Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>72 &lt; 1 &lt; 1</td>
<td>58 0 0</td>
<td></td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>27 5 &lt; 1 24</td>
<td>3 &lt; 1</td>
<td></td>
</tr>
</tbody>
</table>
| Chemistry            | Hyperbilirubinemia: 3 0 < 1 10 1 < 1

Table 5: Acute Graft-versus-Host Disease: Nonhematologic Adverse Reactions Occurring in > 15% of Patients in the Open-label, Single-Cohort Study

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Jakafi (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Infections</td>
<td>55</td>
</tr>
<tr>
<td>Edema</td>
<td>51</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>49 &lt; 1 &lt; 20</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>32 28</td>
</tr>
<tr>
<td>Dizziness</td>
<td>32</td>
</tr>
<tr>
<td>Viral infections</td>
<td>31</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>25</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24</td>
</tr>
<tr>
<td>Rash</td>
<td>23</td>
</tr>
<tr>
<td>Headache</td>
<td>21</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16</td>
</tr>
</tbody>
</table>

- Selected laboratory abnormalities are listed in Table 6 below
- National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03
- Grouped terms that are composites of applicable adverse reaction terms.

Table 6: Acute Graft-versus-Host Disease: Selected Laboratory Abnormalities Worsening from Baseline in the Open-Label, Single Cohort Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>75</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>75</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td>Hyperbilirubinemia</td>
<td>11 1</td>
<td></td>
</tr>
</tbody>
</table>

Clinical trials are generally reversible by withholding Jakafi until resolution of adverse events and the steps to take if they occur.

Other: Increased the dose of Jakafi. Instruct patients not to increase the dose of Jakafi. Instruct patients not to increase the dose of Jakafi.
and effectiveness of Jakafi for treatment of myelofibrosis or polycythemia vera in pediatric patients with steroid-refractory aGVHD has not been established in pediatric patients younger than 12 years old. The safety and effectiveness of Jakafi for treatment of cGVHD after failure of one or two lines of systemic therapy has been evaluated for treatment of children 12 years and older. Use of Jakafi in pediatric patients with cGVHD after failure of one or two lines of systemic therapy is supported by evidence from adequate and well-controlled trials of Jakafi in adults and adolescents [see Clinical Studies (14.3, 14.4) in Full Prescribing Information] and additional pharmacokinetic and safety data in pediatric patients. The safety and effectiveness of Jakafi for treatment of cGVHD has not been established in pediatric patients younger than 12 years old. Jakafi was evaluated in a single-arm, dose-escalation study (NCT01164163) in 27 pediatric patients with relapsed or refractory solid tumors (Cohort A) and 20 with leukemias or myeloproliferative neoplasms (Cohort B). The patients had a median age of 14 years (range, 2 to 21 years) and included 18 children (age 2 to < 12 years), and 14 adolescents (age 12 to < 17 years). The dose levels tested were 15, 21, 29, 39, or 50 mg/m² twice daily in 28-day cycles with up to 6 patients per dose group. Overall, 38 (81%) patients were treated with no more than a single cycle of Jakafi, while 3, 1, 2, and 3 patients received 2, 3, 4, and 5 or more cycles, respectively. A protocol-defined maximal tolerated dose was not observed, but since few patients were treated for multiple cycles, tolerability with continued use was not assessed adequately to establish a recommended Phase 2 dose higher than the recommended dose for adults. The safety profile in children was similar to that seen in adults. Juvenile Animal Toxicity Data Administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures (e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis) occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at exposures that are at least 27% the clinical exposure at the maximum recommended dose of 25 mg twice daily. Geriatric Use Of the total number of patients with MF in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. Clinical studies of Jakafi in patients with cGVHD did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Of the total number of patients with cGVHD treated with Jakafi in clinical trials, 11% were 65 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. Renal Impairment Total exposure of ruxolitinib and its active metabolites increased with moderate (Clcr 30 to 59 mL/min) and severe (Clcr 15 to 29 mL/min) renal impairment, and ESRD (Clcr less than 15 mL/min) on dialysis. [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Modify Jakafi dosage as recommended [see Dosage and Administration (2.6) in full Prescribing Information]. Hepatic Impairment Exposure of ruxolitinib increased with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment [see Clinical Pharmacology (12.3) in full Prescribing Information].
ALTERATIONS IN GENES ASSOCIATED with homologous recombination repair (HRR) are present in up to 30% of patients with metastatic castration-resistant prostate cancer (mCRPC). Although these mutations, such as in BRCA1/2, are prognostic of poor outcomes, they have also been revealed to confer sensitivity to PARP inhibition. Investigators explored the outcomes of adding a PARP inhibitor—niraparib (Zejula)—to an enhanced androgen-signaling inhibitor—abiraterone acetate (Zytiga)—to optimize outcomes for patients with mCRPC with HRR mutations.

Data from the phase 3 MAGNITUDE trial (NCT03748641), presented during the 2022 Genitourinary Cancer Symposium, showed that at a median follow-up of 16.7 months, the niraparib combination resulted in a 47% reduction in the risk of disease progression or death in patients harboring BRCA1/2 mutations. The median progression-free survival (PFS) was 16.6 months with the combination vs 10.9 months with placebo plus abiraterone acetate (HR, 0.53; 95% CI, 0.36-0.79; P = .0014). Among all patients with HRR gene alterations, the median PFS was 16.5 months vs 13.7 months, respectively (HR, 0.73; 95% CI, 0.56-0.96; P = .0217).

The investigative regimen also prolonged time to cytotoxic chemotherapy, delayed time to symptomatic progression, and nearly doubled the median time to prostate-specific antigen increase to cytotoxic chemotherapy, delayed time to symptomatic progression, and nearly doubled the median time to prostate-specific antigen increase across gene alterations. "When we focused on the [patients with] HRR-positive deleterious mutations, we saw that if we focus on the BRCA2 subset alone, there was a statistically and clinically significant outcome as a primary end point," said Eleni Efstatthiou, MD, PhD, an author on the study, in an interview with OncologyLive®. "However, [I believe that] when you look across the group, we are soon going to see interesting data on gene-by-gene analyses that [will be] quite compelling."

Efstatthiou, section chief of Genitourinary Medical Oncology at Houston Methodist Oncology Partners in Texas, provided her top takeaways from the recent trial results and how these data will influence the next phase of research.

3 QUESTIONS WITH ELENI EFSTATTHIOU, MD, PHD

Q What should be known in terms of safety with this combination? It was surprising to see the acceptable tolerability [of this approach]. The safety profile was better than I had expected. However, looking carefully at the safety profile [and the data that were] presented, we need to keep in mind that we mainly want to focus on the [noninferiority margin]. We have used abiraterone acetate, and we understand there are cardiovascular implications. However, now we need to learn how to use PARP inhibition. When it comes to cardiovascular events, we did not see any difference at this time, which is a very good thing.

Another aspect that we need to focus on are the more subjective findings, such as the extent of fatigue that 2 agents combined may add. This will be more evident in real-world practice. We must always remember that when we [enroll] the patients in a trial, we have criteria that are stringent about their physical condition or performance status. [There will be] some more information to come, but the combination seems safe, as long as we monitor patients well.

Q What are the top takeaways from MAGNITUDE your colleagues should be aware of?

We have come a long way. [We have gone] from the introduction of an agent such as abiraterone acetate in our clinics, to introducing more precise targeted agents in combination with androgen-signaling inhibition. We have been taking these steps forward over the past 2 years, applying assays that [help us] determine how to better target this disease, and always taking into consideration the patient and their safety. That is what we like to call the therapeutic index: having a good ratio of efficacy and safety. Overall, we are making progress.

My cautionary statement [would be that] sometimes, we try to oversimplify, and we try to make [certain approaches] accessible to everyone. I would disagree with that notion. Many [investigators] who participated in this trial were adamant about being precise in determining the patient cohort who would derive the maximum benefit [from this combination].

We are now met with a question: Will we persist in following the precision medicine approach and reach improvement in both efficacy and safety [outcomes], or will we revert to a more agnostic approach? [I do not have an answer for this, but] many variables will come into play. We will listen to what the FDA says, and we will take it from there.

Q What are the next steps in this space?

The next big question [will focus on whether we] can make a difference in the lives of men who are diagnosed with metastatic hormone-naïve prostate cancer who harbor such mutations. We know that such a trial is ongoing. Moreover, can we introduce a trial design where we include men with locally advanced prostate cancer who harbor such mutations?

We know that men who harbor such mutations, whether germline or somatic, have a grim prognosis. As long as we are able to identify these [early on]—and [this is one reason] I am a big proponent of early genetic testing—then we can target it. This is the future, and it might just lead to an incremental change and cure. I know I am saying a big word, but that is how we make things happen.

REFERENCE

ctDNA Assays Open the Door for Earlier Detection, Intervention in Breast Cancer

by CHRIS RYAN

CIRCULATING TUMOR DNA (ctDNA) has many potential applications in breast cancer, and evidence shows that its prognostic potential may be superior to pathologic complete response (CR), a commonly used tool in the field. The improved sensitivity of ctDNA is likely to lead to optimized treatment strategies and improved outcomes, explained Pat W. Whitworth, MD.

“If we can detect disease when [it is] at a very minimal state, [around] when we’re giving adjuvant treatment, that puts us in a position to potentially eradicate that disease,” Whitworth said. “We have a number of findings and studies that show patients who clear their ctDNA stay clear [and] do not relapse.”

Following neoadjuvant chemotherapy, pathologic CR has been an effective tool for stratifying patients with advanced breast cancer into low- and high-risk populations based on the achievement of response. However, measurements for pathologic CR require invasive procedures to obtain tissue samples and, among those with residual disease, it may not provide robust evidence to support its use as a prognostic tool for early metastatic recurrence.1

The minimally invasive plasma analysis afforded with the use of ctDNA analysis provides a complementary and potentially alternative prognostic factor to further stratify patients with residual disease. The use of plasma analysis also offers the potential for patient-specific designs, using custom panels based on the clonal somatic variants present in the primary tumor.1

In an interview with OncologyLive®, Whitworth, director of the Nashville Breast Center in Tennessee, discussed the implementation of an individualized ctDNA assay in clinical research. He explained how data from past studies are informing the use of ctDNA and talked about the potential of these assays to guide treatment decisions in patients with breast cancer.

What unmet need would ctDNA assays fill in breast cancer treatment decisions? We are always looking for ways to detect minimal residual disease [MRD], or disease that we can’t find any other way in patients. For a long time, [there has been] excitement about the ability to detect ctDNA in patients. Initially, [we used ctDNA] to look at activating or driving mutations we knew were associated with certain cancers. We were hoping, at the time, that [that information] would not only guide treatment decisions but would also let us know if the disease was gone or present.

Unfortunately, the ctDNA panels that detect driver mutations are subject to selection pressure. In other words, if a patient has treatment that is effective against that clone of cells, we will often see that ctDNA marker go away. But the tumor [may have] more tricks up its sleeve and have other driver mutations that will take over. Following those [and] trying to monitor for MRD, or [another marker] that suggests a patient needs treatment, did not work out too well.

What is exciting about these new panels is that they are based primarily on single nucleotide polymorphisms [and] single nucleotide variants that are different when you look at the patient’s germline. That is usually done by looking at normal white blood cells and [comparing] those with the tumor. Tumors have some mutations that [are only a result of] mistakes during the reproduction of the cells. You might have some single nucleotide polymorphisms and housekeeping genes or other genes that aren’t really related to the tumor. These tend to be far more stable than driver mutations that are subject to selection pressure.

What are the potential advantages of leveraging ctDNA assays compared with a polymerase chain reaction (PCR) assay? We use PCR as an indicator of the effectiveness of the neoadjuvant chemotherapy that the patient has had. If the tumor disappears in the breast, that is a good indicator that if there were cancer cells elsewhere in the body, they’re gone. That is what we have used for a while, and if the tumor doesn’t go away, we tend to give patients a new treatment depending on the subtype of the tumor.

[Results of] the phase 2 I-SPY 2 trial [NCT01042379] demonstrated that if you take patients who had complete disappearance of their ctDNA signature—the customized panel that was developed on [a specific] patient’s tumor when compared [with] that patient’s germline white blood cells—at the end of neoadjuvant treatment, the ctDNA level went down to 0 or was undetectable. Those patients have a very good prognosis, very similar to patients who have a pathologic CR. The interesting thing is that this was true even when patients did not have a pathologic CR. This is one of the things that we hope will guide our treatment decisions.

The most near-term value for these ctDNA panels will not necessarily be to make treatment decisions, especially like withholding treatment, but more on the order of detecting MRD far earlier than we might detect with ordinary clinical measurements [such as] imaging.

If we can detect disease when it is at a very minimal state, [such as] when we are giving adjuvant treatment, that puts us in a position to potentially eradicate that disease. We have [data from] several studies that show [that] patients who clear their ctDNA and stay clear do not relapse. Right now, it is a very exciting area, which is primarily used to monitor the effectiveness of treatment, not necessarily to replace pathologic CR. I am most interested in that because of the findings from the I-SPY 2 trial, which showed that patients who had disappearance of ctDNA, even if they did not have a pathologic CR, also had a very good prognosis.

What are the clinical implications of the data from these trials? There are several potential applications. The holy grail [is that ctDNA provides] a way of telling whether the patient has a meaningful tumor present in the body that needs treatment. These assays can be used on the front end of treatment to risk stratify patients that have high levels of ctDNA. This customized panel [is] made new again for every individual patient. Those patients that have high levels [of ctDNA], or do not have disappearance of those levels after surgery, have higher risk. We know that from previous studies in colorectal cancer and in breast cancer. But you can also monitor the effectiveness of treatment during neoadjuvant treatment. In the I-SPY 2 trial, some patients cleared their ctDNA partway through their taxane treatment at the first part of their neoadjuvant treatment. Others did not clear [ctDNA] until after their doxorubicin and cyclophosphamide treatment. You could see where the patient responded and what the patient responded to. You want to see some complete clearance of ctDNA at the completion of neoadjuvant treatment, although you do not see that in all cases. [None of the] patients who did not clear their ctDNA had a pathologic CR.

This puts us in a position to change treatment if we do not see any change in the ctDNA level.
Advances in Learning Health Care Systems Strive to Optimize Cancer Care

by KYLE DOHERTY

AS TECHNOLOGY AND CANCER CARE continue to become intertwined at every level, there is an imperative need to effectively process and use vast amounts of data to provide the highest level of care for patients. Learning health care systems represent an evolving model of cancer data integration and application that has the potential to positively affect care for many patients.

“What we try to do [with learning health care systems] is to make it easier for providers to take all the information at their disposal and use it in real time to come up with the best treatment option and care plan for their patient,” Duncan Allen, MHA, the senior vice president of clinical services at OneOncology in Nashville, Tennessee, said in an interview with OncologyLive. “We need to make sure that the systems we’re using can ‘talk’ to each other. Do we have the right data, infrastructure, and interfacing in place, from when a new approval comes out to the time when providers are putting that new therapeutic regimen into practice?”

A TRACK RECORD OF EFFICACY

The Institute of Medicine describes the ideal learning health care system as one where, “…science, informatics, incentives, and culture are aligned for continuous improvement and innovation— with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience.”1

The American Society of Clinical Oncology’s CancerLinQ (Learning Intelligence Network for Quality) is a learning health care system designed to collect clinical data from electronic medical records (EMRs) and provide clinical decision support based on available guidelines. The developers of CancerLinQ also designed the learning health system to capture processes and outcomes, allowing investigators to track trends and identify areas of unmet need (FIGURE).1

Results of a prototype leveraging CancerLinQ showed that the system was able to accumulate data from 130,000 cases of patients with previously treated breast cancer from the individual EMR systems of 5 large practices, surpassing the original target goal of 30,000 cases.1 The system then used the data to provide recommendations via a decision-support dialogue box within an open-source EMR that can be accessed by the clinician. Additionally, 10 Breast Cancer Quality Oncology Practice Initiative performance measures with compliance ratings were accessible. The system also included software that enabled the clinician to visualize the data set. The CancerLinQ prototype was assembled in 5 months.1

Nearly a decade after the initial design, investigators continue to use the CancerLinQ system. For example, in 2021, Ray et developed a prognostic tool using CancerLinQ data to predict risk of death within 30 days of a clinical encounter in patients with metastatic breast cancer (MBC). Data drawn from the EMR included age, vital signs, laboratory values, performance status, pain score, and time since chemotherapy, as well as estrogen receptor, progesterone receptor, or HER2 status from January 2000 to June 2020.2

The system identified 9270 patients, representing 586,801 encounters. The model had a prediction accuracy of 86%, positive predictive value of 50%, sensitivity of 70%, and specificity of 88%. Specifically, predictors of mortality within 30 days for patients with MBC included chemotherapy within 1 year but not the past 30 days (odds ratio [OR] 1.92; 95% CI, 1.67-2.20), opiate use (OR, 1.71; 95% CI, 1.17-2.52), and high pain score with no opiate use (OR, 1.27; 95% CI, 1.10-1.48).2 CancerLinQ is currently used by more than 100 oncology practices and contains real-world data representing more than 6 million patients.1

BUILDING ON THE EXISTING MODEL

A major proposed addition to the learning health care system is the integration of genomic data. Targeted therapies that require precise knowledge to be effective—ie, mutations are being expressed in a disease—are becoming increasingly prevalent in cancer care. The addition of genomic profiling to the learning health care system will allow clinicians to quickly identify agents that will be effective for a patient depending on their specific mutations. Similarly, these data can be used to match patients with the appropriate clinical trials for their unique disease, Allen explained.

To achieve this, investigators have determined that the primary infrastructure elements of the learning health care system must include a common cancer genomic profiling (CGP) vendor, a common EMR system, integrated genomic results, and access to clinical trials. The CGP and EMR systems are then integrated to include clinical and genomic data together; these data are then moved into the point of care so to be easily accessed by the clinician.4

![FIGURE. Core Tenants of ASCO’s CancerLinQ](http://example.com/figure.png)

ASCO, American Society of Clinical Oncology; CGP, common cancer genomic profiling; CGP, Common Oncology Practice Initiative; EMR, electronic medical record; QOPI, Quality Oncology Practice Initiative.
“The biggest elements are data and information consumption, making sure that you have solutions across the types of information that a provider requires to be practicing at the top of their license [and] then making sure you have the right connectivity built so it can be seamless for clinicians to figure out what treatment is best for their patients,” Allen said.

One of the biggest roadblocks to incorporating genomic profiling in a learning health care system is working to ensure that all patients who are eligible for genomic profiling receive it. Strategies to overcome this challenge include increased patient education efforts by clinicians to help patients understand all their treatment options.

In the hematology space, investigators who are part of the American Society of Hematology Research Collaborative, a nonprofit organization, are seeking build a data infrastructure platform designed to support learning health systems. The goal of the project is to provide the most effective treatments to improve the lives of patients by generating and applying clinical evidence from clinical, administrative, laboratory, and patient-reported sources. The organization is comprised of 2 primary initiatives: the data hub and the clinical trials network.

The data hub draws on information from EMR integration, direct data entry via electronic data capture, and external data sources to better develop clinical care delivery sites for hematologic diseases. It optimizes the exchange of information via interconnected dashboards, queries, and research contributions, highlighting gaps in care and patient outcomes.

Multiple myeloma was chosen as an initial disease area of focus for the initiative because data sharing opportunities using real-world data are especially timely. Additionally, investigators note that multiple myeloma represents a prime opportunity for the learning health care system model because large data sets are required for the development and validation of prognostic biomarkers and because therapy sequencing decisions becoming more complex.

Investigators designed the data hub to encompass disease-specific end points, clinical guidelines, and other evidence-based documents to serve as core metrics. Baseline computable phenotypes (e-phenotypes) for various clinical concepts are formed using value sets from clinical terms drawn from EMR documentation codes. Data that may not be reliably recorded in individual patient EMRs are also sourced, leveraging local research data and/or disease-progression metrics. All data are funneled into the site dashboard, where trends may be referenced by the clinician.

The collective plans to develop a comprehensive e-phenotype knowledge base, with an emphasis on being able to easily share this information and having the e-phenotypes mature and inform treatment decisions over time. Developers plan to create algorithms based on an inclusive list of codes used to determine the sensitivity for capturing information to predict the positive value of the proposed concept. Machine learning and artificial intelligence can then be used to determine contributors to the e-phenotypes when rules do not exist or are not applicable.

“What we can do today that we weren’t able to do 15 to 20 years ago is take aggregated patient information that is deidentified and HIPAA [Health Insurance Portability and Accountability Act] compliant and utilize it in making the best treatment decisions for patients,” Allen said.

“With all the information we’ve gathered, including clinical, genomic, financial, and operational data, we can help select the best therapeutic regimen for our patients. From a patient perspective, they significantly benefit from how the field of informatics has developed to a state where we can leverage big data to make much [better] decisions.”

A WORK IN PROGRESS

It is important to note that learning health care systems are not perfect by any means and that constant work is being done to improve and optimize the model, Allen said. In many instances, connectivity issues impede fast and accurate communication between the EMR and CGP vendors. Fragmentation of the workflow can negate many advantages provided by the learning health care system model.

To address these shortcomings, firms such as OneOncology are using physician-driven councils to provide ongoing feedback on the systems they are building. These physician advisory boards can help inform the developers of learning health care systems with the areas to focus next, the biggest issues for practicing oncologists in the clinic, and how to continue to streamline the systems for ease and speed of use. Clinicians are also working to improve the interoperability between different EMR systems to better facilitate their integration into a learning health care system model.

“Like everything [today], health care is getting smarter,” Allen said. “Much of that intelligence is driven from how you marry data together to extract more value. The future of learning health care systems is that they’re much more automated. You’ll see more consolidation, especially in the oncology space, around partners where people are coming up with full suites of software that can help [further] unlock the learning health care system approach.”

For a full list of references, see the article at OncLive.com.
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Progress in Prostate Cancer Options Creates Excitement

by MARK T. FLEMING, MD

PROSTATE CANCER IS THE most common cancer in men and the second-leading cause of cancer-related deaths in men in the US. Over the past few years, a number of life-prolonging treatment options for patients with advanced prostate cancer have been developed. Unfortunately, many patients eventually experience disease progression and require several lines of subsequent therapy. Durable control with each subsequent treatment is often short.

However, hope is on the horizon. Promising results have come from the VISION trial (NCT03511664), which evaluated the use of lutetium Lu 177 vipivotide tetraxetan (Pluvitivo; formerly 177Lu-PSMA-617) for patients with advanced prostate cancer. Investigators also are utilizing smarter approaches to treatment and research as they recognize that not all prostate cancers are the same.

RECENT TRIAL RESULTS AND APPROVALS GENERATE OPTIMISM

Results of the phase 3 VISION trial are exciting. VISION investigators evaluated in metastatic castration-resistant prostate cancer (mCRPC) following administration of an androgen receptor-targeting drug and systemic chemotherapy. Risk of death was reduced approximately 40% and a 4-month improvement in median overall survival was observed when lutetium Lu 177 vipivotide tetraxetan was added to standard therapy (TABLE 1). The FDA approved the targeted radioligand for the treatment of patients with prostate-specific membrane antigen (PSMA)-positive mCRPC who have previously been treated with androgen-receptor pathway and taxane-based chemotherapy in March 2022. Physicians have been eagerly awaiting the approval of this promising treatment option for patients, which likely will become the new standard of care.

VISION results also are expected to drive a surge of clinical trials to determine if the same efficacy is found when lutetium Lu 177 vipivotide tetraxetan is employed earlier in the course of the disease. These trials could examine the outcomes of the agent in the prechemotherapy space prior to when an individual becomes symptomatic, as well as in the hormone-sensitive metastatic period clinical space.

COUPLING PSMA DIAGNOSTIC TARGETS WITH THERAPEUTIC TARGETS

With the FDA approval of lutetium Lu 177 vipivotide tetraxetan, physicians have 2 PSMA-targeted treatment options as well as targeted diagnostic tests. For example, pittufo lastat F-18 (Pylarify), a PSMA-targeting PET imaging agent, has been approved by the FDA. This cutting-edge nuclear medicine scan for detecting the PSMA protein found on the surface of prostate cancer cells is exceptionally sensitive.

In the proPSMA trial (ANZCTR1261700005358), PSMA PET-CT scans were 92% accurate in detecting metastatic tumors compared with 65% accuracy for CT and bone scans. By targeting PSMA, the PET-CT scan provides a clear image and additional information on the location and extent of the cancer, which has broad implications for the diagnosis, management, and ongoing monitoring of the disease. This is a major step forward in the battle against prostate cancer, offering not only more sensitive tests to identify the disease but also the opportunity to pair diagnostic targets with therapeutic targets.

A SMARTER APPROACH IS COMING

There is great potential for making significant advances in prostate cancer treatment in the near future. Investigators and physicians are recognizing that not all prostate cancers are the same and that variant histologies and physicians are becoming more mindful of the different features that can affect how patients are treated.

Genomic and molecular testing, as well as next-generation sequencing, are becoming the standard of care used by many physicians, especially those who treat a high volume of patients with prostate cancer. More treatment plans are being developed based on both the molecular and pathological features of the disease. There is evolving evidence that genomics testing can be even more advantageous than traditional guidelines when used for some localized biopsied prostate cancers.

Investigators also are exploring different ways to target DNA repair and immune checkpoint inhibition, and several pathways look very promising. For instance, PTEN is a multi-functional tumor suppressor, which is typically lost in many cancers. Approximately 70% of patients with prostate cancer have loss of expression of PTEN. PTEN is part of the PI3K/AKT/mTOR pathway. To date, mTOR inhibitors have not been very successful in treating patients with PTEN loss, and investigators are examining whether microRNAs could be effective.

MULTIDISCIPLINARY CARE IMPROVES OUTCOMES

Another very positive development for patients with mCRPC...
is the rapid growth of multidisciplinary team (MDT) care in urologic oncology. This care model will become even more important for those with advanced prostate cancer as new treatment options evolve.

Just by the nature of prostate cancer, it is almost a necessity that at least 3 health care providers are involved in patient care: specialists in urology, medical oncology, and radiation oncology. The different perspectives and backgrounds of subspecialty care result in shared decision-making that supports best practices and helps ensure optimal clinical care.

Although multidisciplinary clinics are commonly associated with academic centers, more community-based clinics are building their practices around MDT care. The establishment of MDTs is more complex in the community setting, mainly because of multiple tax IDs. However, community practices, recognizing the many benefits MDT care provides, are striving to offer all critical aspects of outpatient cancer care via tumor boards.

**GREAT PROGRESS AHEAD**

These are very encouraging times. It is wonderful to see patients do well because there are more treatment options available, largely due to research. Today there are therapies that are very effective with less toxicity, enabling physicians to better manage these cancers than in the past. Progress is even being made in treating patients with oligometastatic sites.

If progress continues to occur in diagnostic testing, there also will be a greater opportunity to catch these cancers earlier and cure more patients—the ultimate goal. There is more hope than ever for patients who not so long ago had few options, and there is strong evidence that continued advancements are right around the corner.

**REFERENCES**


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**TABLE 2. proPSMA Design and Outcomes**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Eligible population (n = 302)</th>
<th>Palladium-68 PSMA-11 PET/CT (n = 150)</th>
<th>CT + bone scan (n = 152)</th>
</tr>
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**Conclusions:** PSMA PET-CT is a suitable replacement for CT and bone scans and provides superior accuracy, treatment changes, fewer equivocal results, and lower radiation exposure.
For appropriate patients faced with relapsed/refractory multiple myeloma

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ADC = antibody-drug conjugate; BCMA = B-cell maturation antigen; RRMM = relapsed or refractory multiple myeloma.
**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Ocular Toxicity:** Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%). Among patients with keratopathy (n = 186), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

Keratopathy: Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 6.1% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow-up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

**Visual Acuity Changes:** A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 10% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1.4% of patients. A decrease in visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

**Monitoring and Patient Instruction:** Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity. Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist. Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery. BLENREP is only available through a restricted program under a REMS.

**Thrombocytopenia:** Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 16%, and Grade 4 in 7%. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity.

**Infusion-Related Reactions:** Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8%, and Grade 4 in 1.7%. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity.

**Embryo-Fetal Toxicity:** Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus.

Advises females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose. Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

**ADVERSE REACTIONS**

The pooled safety population described in **WARNINGS AND PRECAUTIONS** reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder.

Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (21%) was the most frequent adverse reaction resulting in permanent discontinuation. Dosage interruptions due to an adverse reaction occurred in 53% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%). Dose reductions due to an adverse reaction occurred in 26% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

The most common adverse reactions (20%) were keratopathy (71%), decreased visual acuity (53%), nausea (24%), blurred vision (22%), pyrexia (22%), infusion-related reactions (21%), and fatigue (20%). The most common Grade 3 or 4 (≥5%) laboratory abnormalities were lymphocytes decreased (22%), platelets decreased (21%), hemoglobin decreased (18%), neutrophils decreased (9%), creatinine increased (5%), and gamma-glutamyl transferase increased (5%).

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

**USE IN SPECIFIC POPULATIONS**

**Lactation:** Because of the potential for serious adverse reactions in the breastfeeding child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

**Females and Males of Reproductive Potential:** Based on findings in animal studies, BLENREP may impair fertility in females and males.

**Geriatric Use:** Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years and older. Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the 95 patients who received BLENREP at the 2.5-mg/kg dose, keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older.

**Renal or Hepatic Impairment:** The recommended dosage has not been established in patients with severe renal impairment (eGFR ≤ 15 mL/min/1.73 m²) or end-stage renal disease (ESRD) with eGFR < 15 mL/min/1.73 m² not on dialysis or requiring dialysis. The recommended dosage has not been established in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 × ULN and any AST).

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.
1 INDICATIONS AND USAGE

BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. This indication is approved under accelerated approval based on response rate [see Clinical Studies (14) of full Prescribing Information].

Changes in visual acuity may be associated with difficulty for driving and reading. Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume, or permanently discontinue, based on severity [see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)].

Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS [see Warnings and Precautions (5.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Ocular Toxicity

Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%) [see Adverse Reactions (6.1)]. Among patients with keratopathy (n = 165), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

Keratopathy

Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 or 4 keratopathy (n = 149), 38% of patients recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes

A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 1% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1.4%. Of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

Monitoring and Patient Instruction

Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity [see Dosage and Administration (2.3) of full Prescribing Information].

Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist [see Dosage and Administration (2.1) of full Prescribing Information].

Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery.

BLENREP is only available through a restricted program under a REMS [see Warnings and Precautions (5.2)].
Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation.

Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

The most common adverse reactions (>20%) were keratopathy, decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue. The most common Grade 3 or 4 (>5%) laboratory abnormalities were lymphocytopenia, decreased platelets, decreased hemoglobin, decreased neutrophils, increased creatinine, and gamma-glutamyl transferase increased.

Table 1 summarizes the adverse reactions in DREAMM-2 for patients who received the recommended dosage of 2.5 mg/kg once every 3 weeks.

**Table 1. Adverse Reactions (≥10%) in Patients Who Received BLENREP in DREAMM-2**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BLENREP N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Keratopathy*</td>
<td>71</td>
</tr>
<tr>
<td>Decreased visual acuity*</td>
<td>53</td>
</tr>
<tr>
<td>Blurred vision†</td>
<td>22</td>
</tr>
<tr>
<td>Dry eye‡</td>
<td>14</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20</td>
</tr>
<tr>
<td><strong>Procedural complications</strong></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions†</td>
<td>21</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12</td>
</tr>
<tr>
<td>Back pain</td>
<td>11</td>
</tr>
<tr>
<td><strong>Metabolic and nutritional disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection‡</td>
<td>11</td>
</tr>
</tbody>
</table>

* Keratopathy was based on slit lamp eye examination, characterized as corneal epithelial changes with or without symptoms.
† Visual acuity changes were determined upon eye examination.
‡ Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.
§ Dry eye included dry eye, ocular discomfort, and eye pruritus.
¶ Fatigue included fatigue and asthenia.
‖ Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthma, hypertension, lethargy, tachycardia.
¶¶ Upper respiratory tract infection included upper respiratory tract infection, nasopharyngitis, rhinovirus infections, and sinusitis.

Clinically relevant adverse reactions in <10% of patients included:
- **Eye Disorders:** Photophobia, eye irritation, infectious keratitis, ulcerative keratitis.
- **Gastrointestinal Disorders:** Vomiting.
- **Infections:** Pneumonia.
- **Infections:** Albuminuria.

Table 2 summarizes the laboratory abnormalities in DREAMM-2.

**Table 2. Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received BLENREP in DREAMM-2**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>62</td>
<td>21</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>49</td>
<td>22</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>57</td>
<td>2</td>
</tr>
<tr>
<td>Albon decreased</td>
<td>43</td>
<td>4</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Gamma-glutamyl transference increased</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Creatinine phosphokinase increased</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>20</td>
<td>2</td>
</tr>
</tbody>
</table>

6.2 Immunogenicity

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

The immunogenicity of BLENREP was evaluated using an electrochemiluminescence (ECL)-based immunassay to test for anti-belantamab mafodotin antibodies. In clinical studies of BLENREP, 2/274 patients (<1%) tested positive for anti-belantamab mafodotin antibodies after treatment. One of 2 patients tested positive for neutralizing anti-belantamab mafodotin antibodies following 4 weeks on therapy. Due to the limited number of patients with antibodies against belantamab mafodotin-blmf, no conclusions can be drawn concerning a potential effect of immunogenicity on pharmacokinetics, efficacy, or safety.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

**Risk Summary**

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (the microtubule inhibitor, MMAF) and it targets actively dividing cells [see Clinical Pharmacology (12.1). Nonclinical Toxicology (13.1) of full Prescribing Information]. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, belantamab mafodotin-blmf has the potential to be transmitted from the mother to the developing fetus. There are no available data on the use of BLENREP in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with BLENREP.

Advise pregnant women of the potential risk to a fetus.

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 outcome. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

**Data**

Animal Data: Animal reproductive or developmental toxicity studies were not conducted with belantamab mafodotin-blmf. The cytotoxic component of BLENREP, MMAF, disrupts microtubule function, is genotoxic, and can be toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.
8.2 Lactation
Risk Summary
There is no data on the presence of belantamab mafodotin-blimf in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child (see Warnings and Precautions (5.5), Use in Specific Populations (8.3)), and it is not known whether belantamab mafodotin-blimf crosses into human milk, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential
BLENREP can cause fetal harm when administered to pregnant women (see Use in Specific Populations (8.1)).

8.4 Pediatric Use
BLENREP has not been studied in patients 18 years and younger (see Nonclinical Toxicology (13.1) of full Prescribing Information). No dose adjustment is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m² as estimated by the Modification of Diet in Renal Disease [MDRD] equation) (see Clinical Pharmacology (12.3) of full Prescribing Information). The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m² not on dialysis or requiring dialysis (see Clinical Pharmacology (12.3) of full Prescribing Information).

8.5 Geriatric Use
The safety and effectiveness of BLENREP in pediatric patients have not been established.

8.6 Renal Impairment
No dose adjustment is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m² as estimated by the Modification of Diet in Renal Disease [MDRD] equation) (see Clinical Pharmacology (12.3) of full Prescribing Information). The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m² not on dialysis or requiring dialysis (see Clinical Pharmacology (12.3) of full Prescribing Information).

8.7 Hepatic Impairment
No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin < upper limit of normal [ULN]) and aspartate aminotransferase (AST) >ULN or total bilirubin 1 to ≤1.5 × ULN and any AST). The recommended dosage of BLENREP has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) (see Clinical Pharmacology (12.3) of full Prescribing Information).

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

Ocular Toxicity
• Advise patients that ocular toxicity may occur during treatment with BLENREP (see Warnings and Precautions (5.1)).
• Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional (see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)).
• Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision (see Warnings and Precautions (5.1)).
“Hammerin’ Hank” Fought the Skeptics to Become the Father of Cancer Genetics

by JASON HARRIS

HENRY T. LYNCH, MD, spent his life fighting one opponent or another. Whether pitted against the other tough boys in his New York City neighborhood, the Axis powers in World War II, the medical establishment that doubted his findings showing a hereditary cause of cancer, or sometimes even his own doctors, the boxer briefly known as “Hammerin’ Hank” always gave as good as he got and usually won.

Eventually, Lynch became known as the “father of cancer genetics” and helped launch the modern era of precision medicine in oncology. He identified the strain of hereditary nonpolyposis colon cancer, now known as Lynch syndrome, and his documentation of hereditary breast-ovarian cancer syndrome led to the identification of BRCA mutations. Lynch, the 2019 Giants of Cancer Care® award winner for prevention/genetics, was the Charles F. and Mary C. Heider Endowed Chair in Cancer Research at Creighton University in Omaha, Nebraska. He died June 2, 2019, at age 91.

“His work in these areas has had a profound effect on cancer screening, prevention, diagnosis, and treatment,” Clifford A. Hudis, MD, CEO of the American Society of Clinical Oncology, said in a statement.

Lynch grew up in a tough neighborhood on New York City’s Upper West Side during the Depression, and his family, like most in that era, struggled mightily. A big, rough-and-tumble kid—he eventually grew to 6 foot 5—Lynch got into a lot of fights growing up. Much of his early life was a constant struggle for survival. Lynch’s son, Patrick M. Lynch, JD, MD, a professor in the Department of Gastroenterology, Hepatology, and Nutrition at The University of Texas MD Anderson Cancer Center in Houston, said his father grew up “virtually with nothing” and never quite got over the poverty of his youth. “Some years ago, we were at dinner in Philadelphia at some conference. It was one of those rare times when it was just him and me and he opened up a little bit,” Patrick Lynch said.

“When he was a kid, he had sort of an artistic flair, and they had a contest at his school for drawing. He had done a very nice piece that...”
won the competition. They had a party to celebrate, but he wasn't invited because he was just a poor kid with holes in his shoes. He described that in histrionic terms—simply being good enough in one way wasn't necessarily enough. I'm not sure why he chose to tell me that story or how it translated into his attitude toward adversity, but it was a telling story for me about just how tough things were for him growing up.*

At the age of 15 or 16—accounts vary—Lynch swiped an older cousin's identification, lied about his age, and enlisted in the US Navy. He was made a gunner and sent first to Europe, then to the Pacific Theater, and finally the Philippines, where he fought to liberate the islands from Imperial Japanese forces. After mustering out in 1946, Lynch spent time as a prizefighter, later telling Omaha's KETV that he was “fair” as a boxer. That career ended at the insistence of his wife, Jane, a psychiatric nurse who would become his research assistant. They had been married for 61 years when she died in 2012.

Lynch got his high school equivalency degree before earning an undergraduate degree at the University of Oklahoma in Norman and a master’s degree in clinical psychology at the University of Denver in Colorado. He received his medical degree from the University of Texas Medical Branch at Galveston and studied for a doctorate in human genetics at The University of Texas at Austin.

In 1967, Lynch landed at Creighton, a small Catholic university. Omaha is not considered a hub of academic and clinical research, but the school allowed Lynch to pursue his research largely free from interference. Lynch was inspired to look for hereditary causes of cancer after a 1961 conversation with a patient with alcoholism, who told him that “everyone in his family had died of colon cancer.”

Moreover, the patient’s family history included ovarian and endometrial cancers, Lynch told The Washington Post: “It was why he drank. He was convinced he was going to die.” Often assisted by Jane and social worker Anne Krush, Lynch traveled throughout rural Nebraska to interview farmers. As noted by David Cantor, PhD, Lynch felt that rural families made ideal participants because they kept careful family history records and often several generations lived in close proximity to one another, making it easy to interview several branches of a single family in a short period.

To augment the interviews, Lynch and his colleagues visited historical archives and libraries and pored over medical records, census data, and the documents from genealogical societies. Over time, they created detailed family pedigrees, and Lynch recognized patterns of disease suggesting that some cancers were hereditary in origin. The prevailing wisdom of the time said that cancer was strictly an environmental phenomenon. Besides, physicians feared that telling patients that cancer can be hereditary could induce fatalism in those who had a family history of the disease and complacency in those who did not. Lynch first described hereditary nonpolyposis colorectal cancer, a form of colon cancer then known as family cancer syndrome and eventually renamed Lynch syndrome, in a 1964 presentation at a meeting of the American Society of Human Genetics. In 1971, he identified hereditary forms of breast and ovarian cancers that, more than 20 years later, investigators determined to be linked to the BRCA1/2 genes, which are associated with an increased risk of breast and ovarian cancers.

Lynch’s boss, physician, and friend Robert “Bo” Dunlay, MD, dean of Creighton University School of Medicine, earned his medical degree at Creighton in 1981 and studied under Lynch. Dunlay said that although Lynch had been publishing data on prevention and hereditary cancers since the late 1960s, his colleagues didn’t take him seriously.

Determined to prove the doubters wrong, Lynch threw himself into his work. Patrick Lynch said his father’s intense focus—his near obsession—helped him battle through skepticism: “He ran into barriers in his work. I wouldn’t say he ignored them, but I guess he was so used to people throwing up barriers.”

Lynch’s ideas finally broke into the mainstream in the 1990s with the discovery of the first cancer genes. His family histories proved invaluable to molecular work on the genetics of some cancers. Genetic testing ultimately proved him right decades after he began drawing up family pedigrees. Today, to identify Lynch syndrome, hospitals and clinics regularly screen tumors for microsatellite instability in patients younger than age 50 who have received a diagnosis of colorectal cancer.

Lynch developed what are today regarded as the cardinal principles of cancer genetics: early age of disease onset, specific patterns of multiple primary cancers, and Mendelian patterns of inheritance in hundreds of extended families worldwide.

Lynch’s drive—or stubbornness, depending on one’s perspective—was legendary long before he died. At 90, he submitted a 10-year research plan. Dunlay recalled attending Lynch’s lectures as a medical student. “He was a huge man to start with and very animated. He would wander around the room and wave his arms,” he recounted. “Because of his size, it was sometimes a little bit frightening. He was so enthusiastic about teaching us about the importance of screening for cancer and the prevention of cancer. He had such a great passion for that subject.”

He said that Lynch, at age 88 and recovering from a broken neck, once tried to sneak off to South America against doctor’s orders to help set up genetic screening clinics. Dunlay cleared Lynch to go to Texas on the first leg of the trip but told him international travel was not an option.

“The very next day, I got a phone call from a colleague who said, ‘I’ve got Henry Lynch in my office asking me to sign paperwork allowing him to go to South America,’” Dunlay said, laughing. “He simply wasn’t going to take no for an answer.”

Tami Richardson-Nelson worked with Lynch for more than 30 years, essentially serving as his information technology department. He was famous for beginning his workday at 3:00 AM, but had to dial back his work schedule as he aged. In his final years, he substituted collaboration and sharing data for traveling to far-flung locales.

“All of his life, he remained dedicated to cancer research,” Richardson-Nelson said. “He lived and died by that research.”

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**2019 Giants of Cancer Care® Inductees**

- Eric R. Winer, MD
- Charles M. Perou, PhD
- Richard Pazdur, MD
- Alan P. Venook, MD
- Bernard J. Escudier, MD
- Beth Y. Karlan, MD
- Frederick R. Appelbaum, MD
- David H. Johnson, MD

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To learn more about Giants of Cancer Care® program and read more about the 2019 class, scan the QR code or visit [bit.ly/3MJ2mjf](bit.ly/3MJ2mjf).
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Treatment Optimization Efforts Seek to Overcome Resistance in Advanced CML

by BRITTANY LOVELY

ADVANCES IN THE DEVELOPMENT of tyrosine kinase inhibitors (TKIs) that target the breakpoint cluster region–Abelson murine leukemia 1 (BCR-ABL1) fusion have changed the treatment landscape for patients with Philadelphia chromosome–positive chronic myeloid leukemia (CML).1 Patients of receive their initial CML diagnosis in the chronic phase, during which time disease may be controlled with treatments with approved TKIs such as imatinib mesylate (Gleevec). Second generation TKIs have elicited durable responses among patients treated in the first- and second-line setting. However, up to 20% of patients may develop resistance via acquired mutations such as the gatekeeper T315I mutation.1

Overcoming resistance mechanisms in this patient population has resulted in the development of the agents asciminib (Scemblix) and ponatinib (Iclusig). Asciminib was granted accelerated approval by the FDA in October 2021 for patients with Philadelphia chromosome–positive CML in any phase who present with a T315I mutation.2

In ASCEMBL, investigators presented updated findings for patients who had at least 48 weeks of treatment with asciminib (n = 157) vs those who received bosutinib (n = 76). Major molecular response (MMR) rates at 48 weeks were 29.3% among those who received asciminib and 13.2% for those who received bosutinib (common treatment difference 16.1%; 95% CI, 5.7%-26.6%).4

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In OPTIC, updated outcomes regarding the benefit/risk analysis of different dosing strategies of ponatinib—cohort A: 45 mg to 15 mg (n = 93); cohort B: 30 mg to 15 mg (n = 93); cohort C: 15 mg (n = 91)—demonstrated that durable responses measured as BCR-ABL1 expression 1% or less was achieved in all cohorts. Patients in cohort A experienced the highest response rate measured as BCR-ABL1 of 1% or less at 12 months at 44.1% (95% CI, 15.1%-73.0%) meeting the prespecified statistical end point. Among those in cohort A who had a T315I mutation at baseline (n = 15), the response rate at 12 months was 60%. More results from the analysis are highlighted in TABLE 2.5-7

UPDATES FROM 2021 ASH

We’re going to start our discussion with the efficacy and safety [data] from ASCEMBL, a phase 3 study of asciminib, which is a first-in-class STAMP inhibitor, vs bosutinib in patients with CML and chronic phase after 2 or more prior TKIs. This is an update after 48 weeks. Dr Jabbour is going take us through this. Maybe if you could start with what is a STAMP [Specifically Targeting the ABL Myristoyl Pocket] inhibitor and why is this active with a T315I mutation?

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JABBOUR [To start,] I want to talk about asciminib, the new kid in block
added to the treatment landscape in CML. Asciminib is different than ponatinib or other TKIs. It binds to the myristoyl pocket to inhibit BCR-ABL1, which is different than the prior TKIs, which use the ATP binding site to inhibit BCR-ABL1. It belongs to what we call the STAMP class of drugs.

Asciminib was already assessed in a phase 1 study [NCT02081378] with the recommended phase 2 dose established as 40 mg twice daily. With dose escalation, investigators determined a 200 mg twice daily dose as appropriate dose for patient harboring the T315I mutation.

ASCEMBL was a randomized phase 3 trial that randomly assigned patients with chronic phase CML who progressed following at least 2 TKIs and who did not have T315I mutations at baseline to asciminib 40 mg twice daily or bosutinib 500 mg once daily—the approved dose for patient who failed prior TKIs. The primary end point was MMR rate at 24 weeks, [data that were previously reported].

[The MMR rate was] 25.5% in favor of asciminib compared with 13.2% for bosutinib. This higher rate of MMR seen with asciminib led to the approval of the drug. Now, what we know as well, the rate of MMR seen with asciminib led to the change of the label of ponatinib being placed on vascular events, therefore the drug was placed on 45 mg per day and in patients at high risk of vascular events were seen in nearly every patient we did see vascular events, unfortunately. These follow-up [were not done yet]. Now with ponatinib at 45 mg per day, [was designed to evaluate] dose optimization of ponatinib. When we lower the dose of ponatinib we can optimize the outcome. In OPTIC, patients who had received at least 2 TKIs were randomly assigned to ponatinib at 45 mg and reduced to 15 mg because of lack of efficacy. Discontinuation because of adverse events at 2021 ASH, we had a long-term follow-up of this study at 48 weeks and the results were still in favor of asciminib. I would like to highlight discontinuation rates with bosutinib compared with asciminib. [Results showed that] 77.6% of patients who received bosutinib had to stop the drug compared with 42.7% with asciminib. Intolerance is an issue here, but the drug was still better than bosutinib.

One good question is why [is there no study] comparing asciminib with ponatinib? That has not been done yet.

Moving on to ponatinib, the agent was approved a long time ago as a third-generation TKI effective against T315I mutations at a dose of 45 mg per day. Ponatinib was evaluated in patients who failed multiple TKIs, 2 or more, or who had a T315I mutation. So the patients who were enrolled were heavily pretreated, with 53% having received more than 3 TKIs.

The vast majority of patients were able to achieve complete response [55%] and responses were durable [not reached at 60 months follow-up]. Now with ponatinib at 45 mg per day, we did see vascular events, unfortunately. These vascular events were seen in nearly every patient at 45 mg per day and in patients at high risk of vascular events, therefore the drug was placed on hold for a short time.

Following the clinical hold, a trial called OPTIC [was designed to evaluate] dose optimization of ponatinib. When we lower the dose of ponatinib we can optimize the outcome. In OPTIC, patients who had received at least 2 TKIs were randomly assigned to ponatinib at 45 mg and reduced to 15 mg once the BCR-ABL1** of 1% or less was obtained; 30 mg reduced to 15 mg once the BCR-ABL1** was at 1% or less; or 15 mg [as a starting dose]. The primary end point was rate of 1% or less BCR-ABL1** at 12 months. In this study, the investigators have shown that dose optimization from 45 mg to 15 mg was the winner. In a way, it does offer the best efficacy and the best safety. This led to the change of the label of ponatinib being administered at 45 mg with reduction to 15 mg.

**DAVIDS** That’s very helpful. I’m curious with asciminib, it’s early still, but have there been any resistance mechanisms identified yet?
This is very important question. In fact, in ASCEMBL we reported mutations in a binding site of asciminib. Similarly, as we have seen with the ATP binding site with the other TKIs, already patients are expressing mutations, and there was a rationale to combine asciminib with other TKIs, and those investigations are ongoing right now.

Other things to consider are that already even with the short follow-up there was a 5% rate of vascular events reported. Mechanistically, we do not know how [these are occurring], but that’s something to keep in mind. Finally, the dose of asciminib is different, whether you prescribe it for non-T315I-mutant disease, which is 40 mg twice daily, or T315I-mutant disease, which is 200 mg twice daily. Of course, price plays a role here because then you have to pay more for those with T315I mutations.

You said that probably we’re not going have head-to-head data for asciminib and ponatinib.

I think ideally that should have happened because we know in the third-line setting the best drug is ponatinib. We should have compared asciminib with ponatinib and the winner will get it all.

Without that comparative data, you have a patient sitting in front of you, how do you weigh the pros and cons of these 2 drugs? How do you decide?

Well, so far with ponatinib we have 10 years of follow-up. It’s extremely effective. I think it’s one of the most effective TKIs available. I start 45 mg in non-T315I-mutant disease and then reduce the dose and maintain the response. We also get to adjust the dose based on dynamic of response later. If a patient receives 45 mg and has adverse events, the dose is reduced to 30 mg and then 15 mg. We’ve shown that dose adjustment did not compromise efficacy.

In the OPTIC trial, the dose adjustment was based on efficacy, so you don’t have to wait for the safety concerns to happen to reduce the dose. By adjusting based on a response and efficacy, we had a better outcome. Therefore, the threshold was determined in 2 ways: No. 1, you do not need full dose all along, and No. 2, reducing the dose based on dynamic of response is better than waiting for safety concerns. This approach will preserve response and give you the best long-term outcome. Therefore, that led to the change of the label of the drug where you adjust the dose based on response. We have plenty of data on that now, and that dose reduction has become the standard of care.

Some great abstracts in CML, very nicely summarized. Another great ASH meeting for this disease as well.
Learn more about how targeting the extrinsic tumor microenvironment is improving treatment for patients with AML

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First Steps Down the HER3 Pathway in NSCLC Signal Early Success

by BRITTANY LOVELY

DISEASE PROGRESSION AND ACQUIRED resistance to approved EGFR tyrosine kinase inhibitors (TKIs) have resulted in a treatment void in the third- and later-line settings for patients with non-small cell lung cancer. Targeted approaches in these settings rely on the identification of overexpression of resistance mechanisms such as MET amplification. Otherwise, options for patients without actionable genomic alterations rely on treatment with chemotherapy, which has limited efficacy.

The identification of an overexpressed, targetable mutation would present a pathway forward for investigators. One such target under exploration is HER3.

Intracellular tyrosine kinase activity is limited in HER3, making this member of the EGFR family a prime target for investigators hoping to overcome resistance in non-small cell lung cancer (NSCLC).1,2 Findings from studies conducted over the past 15 years have identified that PI3K/AKT signaling and the upregulation of HER3 play key roles in the resistance to EGFR-targeted therapies.3

In an analysis of tissue samples from patients with NSCLC, HER3 expression was identified in 82.7% of the primary tumors, 86.6% of lymph nodes, and 91.2% of brain metastases.4 Other studies have noted that overexpression of HER3 (immunohistochemistry [IHC] staining 2+ or 3+) was identified in 42.2% NSCLC tissue samples with 70.7% of samples demonstrating expression at any level (IHC 1+ to 3+).5

Although HER3 expression has been identified as a favorable target, which resulted in several investigational studies, no agents have been approved by the FDA. However, in December 2021 the FDA granted a breakthrough therapy designation to novel antibody-drug conjugate (ADC) patritumab deruxtecan.6

OVERCOMING RESISTANCE HURDLES

Designed with a cell membrane-permeable payload, the development of the first-in-class ADC overcomes the limitations experiences with monoclonal antibodies alone.7 Patritumab deruxtecan leverages a similar linker-payload design used with fam-trastuzumab deruxtecan-nsk1 (Enhertu)—specifically, patritumab deruxtecan covalently linked to a topoisomerase I inhibitor payload using a tetrapeptide-based cleavable linker.8

The first avenue of exploration to harnessing the utility of HER3 expression in NSCLC is in the post EGFR-TKI setting. Investigators have previously noted that tissue samples from patients who developed EGFR-TKI resistance had greater expression of HER3 than prior to treatment.9

Building on the foundational data from preclinical models, a phase 1/2 study (NCT03260491) of patritumab deruxtecan was initiated for patients with metastatic or unresectable NSCLC harboring an EGFR mutation who experienced disease progression after systemic treatment (FIGURE).1 The recommended dose was determined to be 5.6 mg/kg via intravenous infusion once every 3 weeks.

Efficacy analysis was conducted among patients who received the dose in the dose-escalation phase and those enrolled to the dose-expansion cohort (n = 57).1

The confirmed overall response rate (ORR) via independent central review was 39% (95% CI, 26.0-52.4%) with 1 complete response and 21 partial responses reported. Further, 19 patients had stable disease as the best reported response for a disease control rate of 72% (95% CI, 58.5%-83.0%). At a median follow-up of 10.2 months, 32% of patients remained on treatment. The median duration of response was 6.9 months (95% CI, 3.1-not estimable [NE]).

Responses were similar among patients who had received prior osimertinib (Tagrisso) and a platinum-containing chemotherapy regimen (n = 44) with a confirmed ORR of 39% (95% CI, 24.4%-54.5%). One patient had a complete response, 36 had partial responses, and 30 had stable disease for a disease control rate of 68% (95% CI, 52.4%-81.4%).

Survival data for both groups were also similar. Specifically, the median progression-free survival (PFS) among all patients was 8.2 months (95% CI, 4.4-8.3) and the median overall survival (OS) was NE (95% CI, 9.4-NE). In the subgroup of patients who received prior chemotherapy and osimertinib, the median PFS was 8.2 months (95% CI, 4.0-NE) and the median OS was NE (95% CI, 8.2-NE).3

Of note in terms of safety was the incidence of interstitial lung disease (ILD), a known treatment-related adverse effect (TRAE) associated with trastuzumab deruxtecan. The safety analysis was conducted in the subgroup of 57 patients who received the recommended dose and across all dosing cohorts (n = 81). Treatment-related ILD was reported in 4 patients, all of whom were in the 5.6 mg/kg cohort and investigators noted that all cases were resolved with drug discontinuation. Two patients had grade 1 ILD, 1 patient had grade 2 ILD, and 1 patient had grade 3 ILD.

Grade 3 or higher TRAEs were reported among 54% of patients in the 5.6 mg/kg cohort and 47% among all treated patients. The highest incidence of grade 3 TRAEs were thrombocytopenia (30% and 26%, respectively), neutropenia (19% and 15%), and fatigue (14% and 10%).

In a biomarker analysis, investigators used IHC to produce H-scores to quantify expression among 43 available tissue samples from the 5.6-mg/kg cohort. Pretreatment, all samples had HER3 expression with a median H-score of 180 (range, 2-280). Investigators noted that confirmed responses were reported across H-scores, but that those with higher H-scores (≥150) were associated with complete response.1

Further, genomic analysis was conducted prior to treatment with patritumab deruxtecan and identified several EGFR-activating mutations, other EGFR-associated mutations, amplification, and non-EGFR mutations and fusions. Resistance mutations including the gatekeeper T790M mutation presented in 13 patients: 6 had a partial response, 4 had stable disease, 2 had disease progression, and 1 was not evaluable; the ORR was 46%. For those without T790M mutations, 23 patients were reported to have other known EGFR mutations that are associated with resistance. Among these patients the ORR was 35%, comprising 8 patients with partial responses, 7 patients with stable disease, 5 with progressive disease, and 3 who were not evaluable. Finally, among the 21 patients with other or unknown resistance mechanisms, the ORR was 38% with 8 patients with partial responses, 8 with stable disease, 2 with disease progression, and 3 who were not evaluable.1

NEXT STEPS IN INVESTIGATING HER3

Based on the promising early efficacy signals in the phase 1 study, investigators have initiated a phase 2 study, HERTHENA-Lung01 (NCT0461900-4), to evaluate the safety and efficacy of patritumab deruxtecan as a single agent for patients with EGFR-mutated NSCLC in the third-line setting following progression on at least 1 EGFR-TKI and 1 platinum-based chemotherapy regimen. All patients enrolled in the trial will receive patritumab deruxtecan and will be randomly assigned to the fixed dose of...
5.6 mg/kg on day 1 of each 21-day cycle, or an up-titration regimen administered at 3.2 mg/kg in cycle 1, 4.8 mg/kg in cycle 2, and 6.4 mg/kg in cycle 3 forward. The primary outcome is ORR.

To enhance the applicability of patritumab deruxtecan, combination strategies with EGFR-TKIs may prove to be a synergistic treatment option as EGFR-TKIs have influence in the upregulation of HER3. Investigators of a multi-arm, phase 1 study (NCT04676477) are evaluating patritumab deruxtecan in combination with osimertinib in both treatment-naïve and previously treated patients with EGFR-mutant NSCLC. Patients must have received prior osimertinib and experienced disease progression.

The study design of the dose-expansion cohort will include individuals who will receive the combination in the second-line setting and those who will receive the combination as a first-line treatment. Of note, the first-line expansion cohort will only be initiated if the recommended combination dose is efficacious with osimertinib is administered at 80 mg once daily.

Tissue analysis and observational end points of these studies may help to expand knowledge of the biology of HER3 and how it can be further leveraged as a marker for not only this population but in other tumor types where it is highly expressed.

### REFERENCES

Targeted Treatment Boom Reshapes Differentiated Thyroid Cancer Landscape

by CHRISTINA T. LOGUIDICE

DIFFERENTIATED THYROID CANCER

(DTC) makes up approximately 95% of all thyroid cancers and is becoming more prevalent worldwide. A decade ago, treatment options for DTC were limited but today a plethora of targeted treatments are available. “There are not a lot of cancer types [in which] such great research, collaboration, and advancements have happened,” Marcia S. Brose, MD, PhD, FASCO, said during a recent OncLive Peer Exchange® program.

Brose was among a panel of thyroid cancer experts who shared their insights into the evolving DTC treatment landscape. They reviewed the use of VEGF receptor (VEGFR) inhibitors and some of the precision medicine treatments now identified for molecularly selected subsets of patients with DTC, such as BRAF, RET, and TRK inhibitors.

The DTC classification includes papillary thyroid cancer (PTC), follicular thyroid cancer, and Hürthle cell cancer (FIGURE 1). The 2 main lineages, papillary and follicular, have differences in epidemiological profiles and clinical course, noted Giuseppe Barbesino, MD. “Papillary thyroid cancer is the most common type. It is seen across all ages with mostly nodal metastasis, occasionally other organs,” he said. “The follicular type tends to metastasize to the bone, but the lungs can also be involved.”

VEGFR INHIBITORS

Although initial therapy for localized DTC is often effective, tumor recurrences have been observed in up to 30% of patients. During the past 10 years, kinase inhibitors have been introduced for patients with metastatic or recurrent DTC, starting with agents directed at the angiogenic pathway.

“Thyroid cancers are very vascular tumors. They respond very well to VEGFR inhibitors,” Maria E. Cabanillas, MD, said. For this reason, anti-VEGFR inhibitors have become a mainstay of treatment for thyroid cancer across histological subtypes. The panelists focused on 3 VEGFR inhibitors that the FDA has approved for patients with radioactive iodine–refractory DTC: sorafenib (Nexavar) and lenvatinib (Lenvima), which are approved as first-line treatments, and cabozantinib (Cabometyx), which is approved as a second-line treatment. In addition to VEGFRs, each of these drugs inhibits other kinases associated with angiogenesis, tumor growth, and cancer progression.

Demonstrating an overall survival benefit in pivotal VEGFR trials for sorafenib and lenvatinib has proved challenging because patients from the placebo arms were permitted to transition to the study drug, noted Lori J. Wirth, MD, who served as moderator of the Peer Exchange program. “Patients [receiving]
placebo when they had disease progression were allowed to cross over and receive the active drug and the majority of patients all received the active drug...so that could negate an overall survival benefit.”

**Sorafenib**

In 2013, sorafenib became the first VEGFR inhibitor approved by the FDA for patients with radioactive iodine–refractory locally recurrent or metastatic DTC, Brose said. The FDA’s approval was based on data from the phase 3 DECISION trial (NCT00984282), in which investigators randomly assigned 417 patients 1:1 to receive sorafenib (n = 207) or placebo (n = 210). Patients receiving placebo who progressed were allowed to cross over to open-label sorafenib. The primary end point was progression-free survival (PFS) by central independent blinded review.

Sorafenib therapy resulted in significantly improved PFS vs placebo, with a median PFS of 10.8 months (95% CI, 9.1-12.9) vs 5.8 months (95% CI, 5.3-7.8), respectively (HR, 0.59; 95% CI, 0.45-0.76; \( P < .001 \)). Improvement in PFS with sorafenib was seen regardless of whether patients’ tumors harbored BRAF or RAS family mutations. There was no statistically significant difference in the secondary end point of OS between the treatment arms, and the median OS was not reached in either arm.6,7 In the final OS analysis, which adjusted for crossover, the data suggested that the true OS treatment effect with sorafenib was larger than observed in the intention-to-treat (ITT) analysis.8

**Lenvatinib**

The FDA approved lenvatinib for radioactive iodine–refractory locally advanced or metastatic DTC in 2015 based on findings from the phase 3 SELECT study (NCT01321554), whose investigators randomly assigned 392 patients with progressive radioactive iodine–refractory DTC 2:1 to lenvatinib (n = 261) or placebo (n = 131).5,9 As in the DECISION study, patients who progressed on placebo could receive open-label lenvatinib. The primary end point was PFS, with secondary end points including response rate, OS, and safety.

The median PFS was 18.3 months (95% CI, 15.1-not estimable [NE]) in the lenvatinib arm vs 3.6 months (95% CI, 2.2-3.7) in the placebo arm (HR, 0.21; 95% CI, 0.14-0.31; \( P < .001 \)). The response rate was 64.8% (n = 169) in the lenvatinib arm, with 4 complete responses (CRs) and 165 partial responses (PRs), compared with a response rate of 1.5% (n = 2) in 131 patients in the placebo arm, with 2 PRs (odds ratio [OR], 28.87; 95% CI, 12.46-66.86; \( P < .001 \)). The median OS was not reached in either arm.

As of data cutoff in February 2021, 258 patients had been randomly assigned in the ITT population, with 170 receiving cabozantinib and 88 receiving placebo. In the final analysis, which had a longer median follow-up of the ITT population than the preplanned interim analysis (10.1 months vs 6.2 months, respectively), the median PFS was 11.0 months (96% CI, 7.4-13.8) for cabozantinib compared with 1.9 months for placebo (95% CI, 1.9-3.7), which translated into a 78% reduction in risk of progression (HR, 0.22; 95% CI, 0.15-0.32; \( P < .001 \)).10 The ORR was 11.0% (95% CI, 6.9%-16.9%) for cabozantinib vs 0% (95% CI, 0.0%-4.1%) for placebo (TABLE 1).9,11

*The COSMIC-311 setting is very different from the first line and the SELECT and DECISION trials because [the COSMIC-311 patients] were rapidly progressing. It’s important for people to know that when things start to go badly and people have already been on sorafenib, lenvatinib, or both for a long time, many times the speed of the disease has really picked up,” Bose said. Subsequently, she said it is essential for clinicians to line up their next therapy at the first hint that a patient has multiple sites of disease that are progressing. If they have not prepared for this, she warned that the patient could decline so quickly that there would no longer be an opportunity to treat them, especially because some drugs can take weeks to obtain.*

**Managing Toxicities of Anti-VEGFR Therapy**

Inhibition of the VEGF signaling pathway is associated with distinct adverse effects (AEs), some **FIGURE. A Snapshot of Thyroid Cancer**

![Image of thyroid cancer](https://example.com/image1)

Papillary thyroid cancer, the most prevalent thyroid malignancy histology, is depicted at right with branching papillae with fibrovascular cores.

“I think many people have switched to make lenvatinib their first-line therapy based on these really strong results from the SELECT trial,” Brose said.

**Cabozantinib**

Cabozantinib is the latest VEGFR inhibitor to be approved, in September 2021. The FDA approved the agent for adult and pediatric patients 12 years and older with locally advanced or metastatic DTC that has progressed following prior VEGFR-targeted therapy and who are ineligible for or refractory to radioactive iodine.10 Approval was based on data from the phase 3 COSMIC-311 trial (NCT03690388), in which investigators randomly assigned 187 patients 2:1 to cabozantinib (n = 125) or placebo (n = 62).11 All patients had been previously treated with sorafenib, lenvatinib, or both. Crossover to cabozantinib following progression on placebo was allowed. The primary end points were objective response rate (ORR) in the first 100 randomly assigned patients and PFS in all randomly assigned patients (ie, ITT population).

“That trial was halted early because it reached one of its primary end points after only 100 patients had been on study for 6 months. So at its first data analysis point, it reached its primary end point, and the data safety monitoring committee recommended it be stopped because it had already shown its efficacy,” Brose said.

As of data cutoff in February 2021, 258 patients had been randomly assigned in the ITT population, with 170 receiving cabozantinib and 88 receiving placebo. In the final analysis, which had a longer median follow-up of the ITT population than the preplanned interim analysis (10.1 months vs 6.2 months, respectively), the median PFS was 11.0 months (96% CI, 7.4-13.8) for cabozantinib compared with 1.9 months for placebo (95% CI, 1.9-3.7), which translated into a 78% reduction in risk of progression (HR, 0.22; 95% CI, 0.15-0.32; \( P < .001 \)).10 The ORR was 11.0% (95% CI, 6.9%-16.9%) for cabozantinib vs 0% (95% CI, 0.0%-4.1%) for placebo (TABLE 1).9,11
of which can be life threatening if proper precautions are not taken. “The toxicity profiles among these 3 [VEGFR inhibitors] are, I would say, comparable. It’s like a bouquet of flowers with the same flowers. Of course, no 2 bouquets are exactly alike, even if they have the same flowers,” Brose said.

She noted that VEGFR inhibitors are associated with varying degrees of hand-foot skin reactions, diarrhea, and hypertension. With lenvatinib, she said, hypertension is the most significant and worrisome AE initially, as it can happen very quickly. To prevent complications from this AE, she calls in prescriptions for antihypertensives before patients start treatment so they can take those therapies if their blood pressure exceeds 150/90 mm Hg, especially at a time when the clinic might be closed. Regarding the hand-foot skin reactions, she tells patients that taking ibuprofen can be helpful.

Brose emphasized the importance of educating patients about AEs associated with VEGFR inhibitors to ensure these events are caught early on, which minimizes risks and enables patients to remain on treatment. “Most adverse events don’t become grade 3 without being grade 1 or 2 first. And if you can intervene at that point, that can make a huge difference,” she said.

**BRAF INHIBITORS**

Somatic BRAF V600E mutations have been observed in 37% to 50% of patients with PTC and are associated with aggressive tumor features and decreased uptake of radioiodine.2,12 Although BRAF inhibition has elicited antitumor activity against DTC in several clinical trials, the only FDA-approved therapy directed at this pathway is indicated for patients with anaplastic thyroid cancer (ATC), a rare and aggressive undifferentiated tumor type.2,3 In May 2018, the FDA approved the combination of dabrafenib (Tafinlar), a BRAF inhibitor, plus trametinib (Mekinist), a MEK inhibitor, for patients with locally advanced or metastatic ATC with a BRAF V600E mutation and no satisfactory locoregional treatment options.2,3

National Comprehensive Cancer Network guidelines note that BRAF inhibitors can be considered for patients with advanced BRAF-mutated PTC who are not candidates for radiiodine therapy, clinical trials, or other systemic therapy.2,3 During the Peer Exchange program, the panelists noted that BRAF inhibitory agents are particularly interesting because data from small studies have shown they can restore the ability of thyroid cancer cells to take up radioiodine (ie, a redifferentiation therapy), potentially reopening the door to radioiodine treatment.

**Vemurafenib**

Vemurafenib (Zelboraf) was the first BRAF inhibitor assessed in a clinical trial for thyroid cancer, Cabanillas said. It was evaluated in an open-label, nonrandomized, multicenter, phase 2 study (NCT01286753) that enrolled 51 patients with BRAF V600E-mutated metastatic or recurrent PTC. The participants included 26 who had never received VEGFR inhibitor therapy and 25 who previously had had such treatment.12 All patients received vemurafenib 960 mg orally twice daily. The primary end point was investigator-assessed best overall response in the VEGFR inhibitor-naïve cohort.

After a median duration of follow-up of 18.8 months in the VEGFR inhibitor-naïve cohort, the best overall response was PR, which investigators observed in 38.5% (n = 20) of patients (95% CI, 20.2-59.4).2 The median PFS was 18.2 months (95% CI, 15.5-29.3). In the previously treated cohort, after a median follow-up of 12.0 months, the best overall response was a PR in 27.3% of patients (6 of 22 patients, as 3 originally enrolled in this cohort were deemed ineligible or withdrew consent). The median PFS was 8.9 months (95% CI, 5.5-NE).

Cabanillas said that vemurafenib has a slightly different AE profile compared with dabrafenib, noting that it causes more issues with arthropathies and skin toxicities, including hand-foot skin reactions. She said vemurafenib also can cause squamous cell carcinomas of the skin and alopecia (usually just hair thinning), which are class effects of BRAF inhibitors. In the phase 2 trial, grade 3 or 4 AEs occurred in 65% or more of patients in both cohorts, with squamous cell carcinoma of the skin, lymphopenia, and increased γ-glutamyltransferase levels being the most common.

**Dabrafenib**

Dabrafenib was assessed in a randomized phase 2 trial (NCT01723202) that evaluated this agent alone and in combination with trametinib in 53 patients with BRAF-mutated PTC, 25% of whom had been previously treated with a multikinase inhibitor.14,15 In the study, 26 patients received dabrafenib monotherapy and 27 patients received dabrafenib plus trametinib. Crossover from monotherapy to combination therapy was allowed at the time of progression. The study’s primary end point was ORR, defined as PRs plus minor responses (ie, 20%-29% decrease in the sum of diameters of target lesions).

In the monotherapy arm, 11 of 22 evaluate patients responded, including 10 with PRs and 1 with a minor response, for an ORR of 50%. In the combination arm, 13 of 24 assessable patients responded, including 9 with PRs and 4 with minor responses, for an ORR of 54%. The median PFS was 11.4 months (95% CI, 3.8-not reached) among those who received monotherapy and 27.3% of patients (6 of 22 patients, as 3 originally enrolled in this cohort were deemed ineligible or withdrew consent). The median PFS was 11.4 months (95% CI, 3.8-not reached) among those who received monotherapy and 27.3% of patients (6 of 22 patients, as 3 originally enrolled in this cohort were deemed ineligible or withdrew consent). The median PFS was 11.4 months (95% CI, 3.8-not reached) among those who received monotherapy and 27.3% of patients (6 of 22 patients, as 3 originally enrolled in this cohort were deemed ineligible or withdrew consent).

**TABLE. COSMIC-311 Trial Snapshot: Final Analysis**

<table>
<thead>
<tr>
<th>Baseline characteristics*</th>
<th>Cabozantinib (n = 170)</th>
<th>Placebo (n = 88)</th>
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<tr>
<td>Age</td>
<td>65 (31-85)</td>
<td>66 (37-83)</td>
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<td>Histologic subtype</td>
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<td>Papillary</td>
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</tr>
<tr>
<td>Follicular</td>
<td>46%</td>
<td>40%</td>
</tr>
<tr>
<td>Metastatic lesion sites*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>30%</td>
<td>24%</td>
</tr>
<tr>
<td>Liver</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Lung</td>
<td>71%</td>
<td>69%</td>
</tr>
<tr>
<td>Other</td>
<td>75%</td>
<td>80%</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>11.0 (7.4-13.8)</td>
<td>1.9 (1.9-3.7)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>19.4 (15.9-19.4)</td>
<td>NE (NE-NE)</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>11% (6.9-16.9)</td>
<td>0% (0.0-4.1)</td>
</tr>
</tbody>
</table>

DTC, differentiated thyroid cancer; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

*Percentages may not equal 100% due to rounding.

*Patients had multiple metastatic sites.

**CONCLUSIONS**

Somatic BRAF V600E mutations have been observed in 37% to 50% of patients with PTC and are associated with aggressive tumor features and decreased uptake of radioiodine. Although BRAF inhibition has elicited antitumor activity against DTC in several clinical trials, the only FDA-approved therapy directed at this pathway is indicated for patients with anaplastic thyroid cancer (ATC), a rare and aggressive undifferentiated tumor type. In May 2018, the FDA approved the combination of dabrafenib (Tafinlar), a BRAF inhibitor, plus trametinib (Mekinist), a MEK inhibitor, for patients with locally advanced or metastatic ATC with a BRAF V600E mutation and no satisfactory locoregional treatment options. National Comprehensive Cancer Network guidelines note that BRAF inhibitors can be considered for patients with advanced BRAF-mutated PTC who are not candidates for radiiodine therapy, clinical trials, or other systemic therapy. During the Peer Exchange program, the panelists noted that BRAF inhibitory agents are particularly interesting because data from small studies have shown they can restore the ability of thyroid cancer cells to take up radioiodine (ie, a redifferentiation therapy), potentially reopening the door to radioiodine treatment.
RET and TRK inhibitors

RET and NTRK fusions are less frequent actional targets that are mostly found in patients with PTC. “We’re going to see [RET fusions] in about 8% to 10% of PTCs, whereas NTRK fusions we see in about 3%,” Cabanillas said. She discussed 2 RET inhibitors, selpercatinib (Retevmo) and pralsetinib (Gavreto), and 2 TRK inhibitors (kinases encoded by NTRK genes), larotrectinib (Vitrakvi) and entrectinib (Rozlytrek), that the FDA has approved.

Selpercatinib

The FDA granted accelerated approvals for selpercatinib, a selective RET inhibitor, for adult and pediatric patients (≥12 years) with RET fusion-positive, radiodine-refractory advanced or metastatic thyroid cancer, adult and pediatric patients with RET-mutant medullary thyroid cancer (MTC), and adults with RET fusion-positive non-small cell lung cancer (NSCLC).

The RET fusion-positive thyroid cancer indication is based on findings from the phase 1/2 LIBRETTO-001 trial (NCT03157128), which included 19 patients with previously treated RET fusion-positive thyroid cancer. Among these were 13 patients with PTC, 3 with poorly differenti-ated tumors, 1 with Hürthle cell carcinoma, and 2 with ATS. Patients with RET-mutant MTC and RET fusion-positive NSCLC were enrolled in separate cohorts. After the dose-escalation portion of the trial, patients received selpercatinib orally at 160 mg twice daily.

In the RET fusion-positive thyroid cancer cohort, the ORR by independent review was 79% (95% CI, 54%-94%), including 1 CR (5%) and 14 PRs (7%).17 After a median follow-up of 13.7 months, 64% (95% CI, 37%-82%) of patients were progression free at 1 year. All patients included in the study had been previously treated with 1 or more VEGFR inhibitors and had tumors refractory to radiodine, other than participants with ATS, a subtype for which radiodine is not used.

Overall, treatment was well tolerated. The discontinuation rate with selperca-tinib for treatment-emergent AEs was only 2%, Cabanillas said, noting that this was for the entire study population of 531 patients. In those with thyroid cancer, the most common AEs of grade 3 or worse severity included hypertension, increased liver enzymes, hyponatremia, and diarrhea.17

Pralsetinib

Pralsetinib has gained accelerated approvals from the FDA for patients 12 years and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and are radiodine-refractory (if such therapy is appropriate), as well as for adult and pediatric patients with advanced or metastatic RET-mutant MTC and adults with RET fusion-positive NSCLC.18 Its safety and efficacy were established in the phase 1/2 ARROW trial (NCT03037385) in patients with locally advanced or metastatic RET-altered solid tumors, including 20 patients with RET fusion-positive thyroid cancer.19 Among the 9 participants who were evaluable for response, all of whom had PTC, the ORR was 89% (95% CI, 52%-100%), all PRs. Although the median PFS and OS were not reached, 81% of patients were progression free at 1 year and the estimated 1-year OS was 91%.18

“The adverse event profile is similar [to] but not really the same [as that of selpercatinib]. It’s interesting that pralsetinib tends to cause more anemia. [The investigators] also reported more musculoskeletal pain and constipation,” Cabanillas said. Like selpercatinib, pralsetinib was associated with hypertension and increased liver enzymes.20 Both agents can elevate liver enzymes, but Cabanillas has switched from one agent to the other when a patient develops this AE. “It’s been OK on the opposite drug, so that is worth trying,” she said. In the safety population of 142 patients with RET-altered thyroid cancer, the discontinuation rate with pralsetinib was 4%.

Larotrectinib and Entrectinib

Larotrectinib and entrectinib are both approved by the FDA for the treatment of solid tumors harboring NTRK gene fusions (also called TRK fusions), Cabanillas said. She noted that larotrectinib has the most data to support its use in DTC.

Cabanillas and colleagues presented long-term efficacy and safety data for larotrectinib in DTC at the 90th Annual Meeting of the American Thyroid Association in 2021. In an assessment of data from several trials, which included 21 evaluable patients with DTC, the ORR was 86% (95% CI, 64%-97%), which include 2 CRs.21 “There was no best response progression, so these were really stellar outcomes. The median follow-up time was 22 months, and with that, we had a median progression-free survival of 51 months, and overall survival was not reached. But at 2 years, 92% of patients were alive,” she said.

Additionally, no patients discontinued treatment because of AEs, Cabanillas noted. Higher-grade AEs included anemia and low lymphocyte counts. She also noted some dizziness and nausea but said that the dizziness tends to resolve as patients adjust to the therapy.

Regarding entrectinib, Cabanillas said that very little is known about the use of this agent in thyroid cancer. She noted that the only data thus far come from an integrated analysis of 54 patients with advanced or metastatic solid tumors harboring NTRK fusions, only 5 of whom had thyroid cancer, with their subtypes not specifed.22 Among these patients, there was only 1 PR.

“We think it’s probably a similar drug [to larotrec-tinib], but it does have other targets and so may lead to some off-target effects,” she said.

For a full list of references, see the article at OncLive.com
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Not all treatments are sufficient for all patients — which leaves them with less than optimal outcomes.¹ New approaches must be pursued to manage a fuller range of signs and symptoms in myelofibrosis.

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