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Racial Disparities in Breast Cancer Mortality Persist, Oncology Pharmacy Can Make a Difference

October is Breast Cancer Awareness Month, providing the opportunity for oncology pharmacy professionals to place a microscope on topics surrounding this disease. At the 15th American Association for Cancer Research (AACR) Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved, Julie R. Palmer, ScD, MPH, explained how racial disparities in breast cancer mortality have remained a problem for over 20 years without signs of amelioration. In 2022, despite the attention paid to this issue in the field, Black women still have a 40% higher mortality rate from breast cancer than White women.

At the AACR conference, Palmer explained further that several research teams are conducting investigations into the causality of this racial disparity. However, she noted the causes are likely multifactorial in nature, indicating the need for further data to paint a clearer picture of the tapestry of issues leading to this ongoing disparity. As the research continues, the goal of addressing treatment issues for all populations with breast cancer remains a focus for oncology pharmacists, who are at the forefront in calling attention to problems related to access issues for medically disadvantaged populations.

In the cover story on page 16, authors Michelle Nguyen; Grace Baek, PharmD, BCOP; Arianne Duong, PharmD, BCOP; and Dane Fritzsche, PharmD, BCOP, discuss oral oncolytics for the treatment of hormone receptor–positive and HER2-negative early-stage breast cancer in the adjuvant setting. The authors provide an overview of 3 recently FDA-approved oral oncolytics that have shown promise in improving disease-free survival for this common disease subtype.

Additionally, on page 33, Sarah Schmidt, PharmD, BCOP, addresses quadruplet vs triplet regimens in up-front multiple myeloma (MM) treatment, as data have demonstrated quadruplet regimens may be a viable option for MM. On page 44, Samantha Brongiel, PharmD, BCOP, discusses the use of FDA approved tebentafusp-tebn (Kimmtrak; Immunocore) for the treatment of adult patients with human leukocyte antigen-A*02:01–positive unresectable or metastatic uveal melanoma. Tebentafusp-tebn represents a new class of drug for the treatment of this disease subtype.

With progress in drug development comes progress in disease treatment, providing more opportunities to address disparities among diverse populations across the United States, with oncology pharmacy at the helm.
Editor’s Note

IT’S BREAST CANCER AWARENESS MONTH, and the annual campaign to raise awareness about the impact of breast cancer and to show support for everyone affected by breast cancer is underway. Many oncology pharmacists participate in programs that promote breast cancer awareness and the importance of screening and early detection. Although many of our efforts are primarily in caring for and supporting patients who are undergoing treatment for breast cancer, oncology pharmacists also participate significantly in conversations, research, and publications of that research.

These efforts by oncology pharmacists have helped to highlight not only disparities in cancer care but also gender-based differences in breast cancer treatment. Further, oncology pharmacists have worked tirelessly to provide additional opportunities to support patients with breast cancer throughout their treatment journey to positively impact patient outcomes.

Oncology Pharmacists Can Drive New Strategies to Resolve Disparities in Breast Cancer Care, Patient Outcomes

LISA E. DAVIS, PHARMD, FCCP, BCPS, BCOP, PHARMACY TIMES ONCOLOGY EDITION™ EDITOR IN CHIEF
For example, a recent publication reported an association between initiation of adjuvant endocrine therapy, short- and long-term adherence, and continuation of therapy in low-income women with breast cancer. Although nonadherence to and early discontinuation of adjuvant endocrine therapy is associated with increased risk of disease recurrence and mortality, longer time to initiation of therapy was associated with poorer adherence and lower short-term continuation of adjuvant therapy in this low-income patient population.

In the publication, data showed 77% of women were adherent and 24% had continued therapy at 1 year, but only 22% and 24% of women were adherent and continued therapy at 5 years, respectively. These data suggest that early interventions to promote timely treatment initiation could positively impact treatment adherence to endocrine therapy. Additional interventions and strategies to promote medication adherence and continuation of therapy, particularly preventing and managing adverse effects (AEs), are also critical, especially because endocrine-associated toxicities account for early treatment discontinuation in approximately 20% of both pre- and postmenopausal women.

Evidence of gender-based differences among patients receiving cancer treatment was published earlier this year from an analysis of data from over 200 trials spanning several decades and involving more than 23,000 men and women. Women had an approximate 34% increased risk of experiencing severe symptomatic, hematologic, and nonhematologic AEs compared with men. With immunotherapy, the risk of serious AEs was even greater, at approximately 50% higher than the risk of serious AEs experienced by men. Although these trials were conducted among patients with different cancer types, the data suggest women are more susceptible to chemotherapy and immunotherapy AEs rather than being more likely to report adverse symptoms.

In their practice settings, oncology pharmacists are experienced and frequently deal with acute treatment toxicities, some of which may evolve into or develop later as chronic toxicities. Women who transition from neoadjuvant and/or adjuvant chemotherapy to adjuvant endocrine therapy will benefit from additional support to ensure adherence to their treatment plan. Thus, pharmacists will find additional opportunities to improve treatment outcomes for patients in these treatment settings and within survivorship programs. However, it is important to keep in mind, as one breast cancer survivor recently reminded me, that the 1 drug viewed by the oncology pharmacist as being the most important to their treatment may be 1 of many drugs that the patient is actually dealing with.

With a heightened and unique awareness of varying perspectives within the breast cancer treatment space, oncology pharmacists are well positioned to consider new strategies and opportunities to enhance our patients’ care. We have a lot work to do to resolve disparities in cancer care and patient outcomes. Further, despite the continued advances in new therapies and treatment options, much of what we can accomplish will be through optimizing delivery of current therapies.
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Breast cancer is the leading type of cancer among women, comprising approximately a third of cancer cases in women in the United States in 2022. Although early detection and screening have improved mortality, breast cancer remains the second leading cause of cancer-related death in women. Hormone receptor–positive (HR+), HER2-negative (HER2–) is the most common breast cancer subtype, accounting for 68% of diagnoses.

Hormonal agents such as tamoxifen and aromatase inhibitors have historically been used in the early-stage setting to reduce the risk of metastatic recurrence. Recently, 3 FDA-approved oral oncolytic medications—abemaciclib (Verzenio; Eli Lilly and Company), olaparib (Lynparza; AstraZeneca), and capecitabine (Xeloda; Genentech)—have shown promising efficacy in improving disease-free survival (DFS). However, these drugs have notably different safety profiles and target populations within the adjuvant setting (Table), making it valuable to assess the clinical trial data and management of key adverse events (AEs) for each drug when making treatment decisions for patients with HR+/HER2– breast cancer.

**Abemaciclib**

Abemaciclib is the first and only CDK4/6 inhibitor approved for use in the adjuvant setting for early-stage breast cancer. In regulated cell division, cyclin D complexes with cyclin-dependent kinases CDK4 and CDK6 to phosphorylate and inhibit tumor-suppressor protein retinoblastoma (Rb). Further, CDK4/6 inhibitors block unchecked cell cycle progression in cancer cells by preventing the inactivation of Rb.
In the randomized, open-label, phase 3 monarchE trial (NCT03155997), investigators evaluated the addition of abemaciclib to physician’s choice of standard-of-care (SOC) adjuvant endocrine therapy (ET) for a total of 2 years vs SOC adjuvant ET alone in patients with high-risk HR+/HER2– early breast cancer. During the trial, the high-risk classification was defined as having lymph node involvement (≤4 positive nodes or 1-3 positive nodes) and 1 or more of the following: tumor size at 5 cm or greater, histologic grade 3, or tumor Ki-67 levels at 20% or greater.

At the median follow-up time of 19.1 months, there was significant improvement in the primary end point...
of invasive disease-free survival (IDFS) with abemaciclib and ET compared with ET alone after 2 years (hazard ratio, 0.71; 95% CI, 0.58-0.87; P < .001). The abemaciclib and ET arm also demonstrated statistically superior benefit in distant relapse-free survival (DRFS) rates at 93.8% vs 90.8% with ET alone (hazard ratio, 0.69; 95% CI, 0.55-0.86; P < .001). Additional follow-up data have been recently published, showing continued benefit in both end points beyond 2 years. This is important given that the overall risk of recurrence is highest within the first 2 to 3 years following diagnosis, particularly among those with high-risk features.9

AEs during the trial were consistent with the safety profile from prior analyses.10,11 Common AEs in the abemaciclib arm were diarrhea (83.5%), neutropenia (45.8%), and fatigue (40.6%). Most AEs were classified as either grade 1 or 2.

During the first month of treatment, most patients experienced diarrhea; time to onset of diarrhea was 6 to 8 days and lasted 6 to 11 days.3 Early recognition and intervention are important for optimizing the management of diarrhea. Antidiarrheal agents such as loperamide can be started at the first sign of loose stools. Patients experiencing diarrhea should notify their care team within 24 hours and increase oral fluid and electrolyte intake to prevent dehydration. For grade 2 diarrhea, dose interruption is recommended until toxicity resolves to grade 1 or lower. The manufacturer has additional guidance for dose adjustments with recurrent grade 2 or grade 3 to 4 diarrhea.

In addition to abemaciclib, palbociclib (Ibrance; Pfizer Inc) and ribociclib (Kisqali; Novartis) are 2 other CDK4/6 inhibitors that have been studied in the adjuvant setting. Palbociclib did not show a benefit in its respective clinical trials.12,13 The clinical trial with ribociclib is ongoing.14

One hypothesis for the lack of improvement in IDFS with the addition of palbociclib to ET concerns the dosing schedule of palbociclib.8,15 Palbociclib is dosed on a cyclical basis around a schedule of 3 weeks on and 1 week off repeated every 28 days, whereas abemaciclib is dosed continuously daily. The difference between continuous vs intermittent dosing may have clinically relevant implications on efficacy in terms of achieving sustained inhibition of cell cycle progression and subsequent tumor cell proliferation. This is especially important in the adjuvant setting where elimination of micrometastatic disease is the goal of treatment.16 This is one theory that has yet to be explored further. It is still unclear why palbociclib has not demonstrated benefit in this setting, but results from the ongoing NATALEE trial (NCT03701334) are eagerly awaited to provide further clarity.

**Olaparib**

Olaparib was approved in 2022 for patients with HER2– early-stage, BRCA-mutated breast cancer at high risk of recurrence.4 BRCA1/2 mutations cause defects in the homologous recombination repair pathway, so tumor cells in patients with BRCA mutations rely on PARP enzymes to repair DNA. In patients with BRCA mutations, the inhibition of PARP enzymes by olaparib synergistically results in cumulative DNA damage by blocking both DNA repair mechanisms, resulting in synthetic lethality and death of tumor cells.

In the phase 3, double-blind, randomized OlympiA trial (NCT02032823), patients with a germline BRCA mutation were randomly assigned to either olaparib or placebo for 1 year following neoadjuvant or adjuvant chemotherapy.17 Of enrolled patients, 82.2% had triple-negative breast cancer (TNBC) and 17.7% of patients had HR+/HER2– disease. IDFS (hazard ratio, 0.58; 95% CI, 0.41-0.82; P < .001) and DRFS (hazard ratio, 0.57; 95% CI, 0.39-0.83; P < .001) were significantly improved in patients who received olaparib vs placebo. Additionally, fewer deaths were reported with olaparib compared with placebo (59 vs 86; hazard ratio, 0.68; 95% CI, 0.44-1.05; P = .02).

The most common AEs were nausea (56.9%), fatigue (40.1%), and anemia (23.5%); these were the main reasons for olaparib discontinu-
Anemia had the greatest frequency of grade 3 or higher events (8.7%). Nausea, generally grade 1 or 2, usually occurred within the first month of treatment, with time to onset of nausea at 5 days.\textsuperscript{18} Olaparib is classified as a moderate/high emetic-risk agent.\textsuperscript{19} The National Comprehensive Cancer Network (NCCN) recommends that patients who are newly starting olaparib take a serotonin receptor antagonist, such as ondansetron, 30 to 60 minutes prior to each dose.\textsuperscript{19} If after the first 2 weeks the patient experiences little to no nausea, it is our practice to have them shift their antiemetic medication to use as needed.

\textbf{Capecitabine}

Capecitabine was approved in 1998 for the treatment of metastatic breast cancer.\textsuperscript{5} It is a prodrug of 5-fluorouracil and inhibits thymidylate synthase, blocking production of essential metabolites needed for DNA and RNA synthesis in tumor cells.

In the multicenter, open-label, randomized, phase 3 CREATE-X trial (JBCRG-04), patients with HR+/HER2– breast cancer or TNBC who did not achieve pathological complete response or had node positivity after standard neoadjuvant chemotherapy were randomly assigned to receive adjuvant capecitabine or placebo every 3 weeks for 6 to 8 cycles.\textsuperscript{20} Adjuvant therapy included ET for at least 5 years in patients with HR+ disease, and radiation therapy if indicated regardless of HR positivity.\textsuperscript{20} The number of patients with TNBC comprised 32.2%, and the remaining 67.8% had HR+ breast cancer. The DFS rate was higher in the capecitabine arm (74.1%) than in the control arm (67.6%) at 5 years (hazard ratio, 0.70; 95% CI, 0.53-0.92; \( P = .01 \)). Overall survival was also higher in those receiving capecitabine (89.2%) than in those who did not (83.6%) at 5 years (hazard ratio, 0.59; 95% CI, 0.39-0.90; \( P = .01 \)).

The results for DFS indicate that the greatest benefit was seen in patients with TNBC.\textsuperscript{20} These results led to the inclusion of capecitabine within the NCCN guidelines as postneoadjuvant therapy, with emphasis on use in patients with TNBC.

Of note, the study consisted of an Asian patient population in which pharmacogenomic and pharmacokinetic differences in the metabolism of capecitabine may contribute to the ability to tolerate the higher starting dose of 1250 mg/m\(^2\) twice daily vs 1000 mg/m\(^2\) (the standard dose commonly used in the United States).\textsuperscript{21} There is also evidence that a lower dietary folate intake predisposes Asian patients to lower incidences of toxicity from capecitabine.\textsuperscript{22}

When assessing the trial results, the investigators observed that the most frequent AE was hand-foot syndrome (HFS; all grades, 73.4%; grade \( \geq 3\), 11.1%).\textsuperscript{20} Other common AEs were mostly grade 1 and included thrombocytopenia and anemia.

The median time to onset for HFS is 79 days but can range from 11 to 360 days.\textsuperscript{2} When counseling patients, oncology professionals should emphasize preventive measures, as HFS is a dose-dependent AE.\textsuperscript{23} It is recommended that patients prophylactically use creams or other moisturizers multiple times per day on the hands and feet to prevent the development of HFS. Other supportive measures include wearing appropriately fitting clothes and shoes to reduce skin friction and avoiding prolonged direct heat exposure.\textsuperscript{24} For grade 2 to 3 HFS, dose interruption is recommended until symptoms resolve or decrease to grade 1 or lower. Following grade 3 HFS, subsequent dose reductions are recommended.

\textbf{Summary}

The use of oral oncolytics in the adjuvant treatment of HR+/HER2– early-stage breast cancer continues to grow. Current use is restricted to specific subgroups of patients with HR+, node-positive disease with high-risk features or HER2– disease with \textit{BRCA} mutations, or in those who did not experience a pathologic complete response after receiving neoadjuvant chemotherapy.\textsuperscript{3,5} Abemaciclib, olaparib, and capecitabine all had low incidences of grade 3 or greater toxicities, and discontinuation due to AEs was low.\textsuperscript{8,17,20} Pharmacists play a key role in monitoring therapy and optimizing supportive care to ensure most AEs can be managed in the outpatient setting. As more oral oncolytic options continue to emerge within this treatment setting, patients can be offered a highly tailored approach to therapy selection to achieve optimal outcomes.
Clinical Forum Recaps

Experts Review Current Treatment Space, Future Directions in Basal Cell Carcinoma

Pharmacist involvement in identifying causes and treatment approaches is essential, as BCC can be a result of prior radiation therapy.

AISLINN ANTRIM, ASSOCIATE EDITOR

BY EDUCATING PATIENTS and providing guidance for treatment, pharmacists can play an essential role in the management of basal cell carcinoma (BCC), explained experts who gathered for a recent Pharmacy Times® Clinical Forum event to discuss their experiences in the field. Moderator Scott A. Soefje, PharmD, MBA, BCOP, FCCP, FHOPA, director of pharmacy cancer care services at Mayo Clinic in Rochester, Minnesota, led the discussion and started with a brief overview of the disease space.

Soefje noted there are more patients with BCC in the United States than all other cancers combined, with BCC and squamous cell carcinoma totaling approximately 3.3 million patients. Notably, BCC accounts for approximately 80% of all skin cancers, Soefje said.

Although BCC is generally curable and rarely metastatic, it can be a devastating disease for patients. Soefje listed several risk factors for BCC, emphasizing radiation from sunlight or cancer treatments. This risk is especially notable among individuals with fair skin or those with lymphoma or other cancers who underwent radiation at a younger age. Patients can develop BCC several decades after radiation treatments for cancer, according to Soefje.

Investigators are also beginning to understand the genetics behind BCC, including new knowledge about the Sonic Hedgehog signaling pathway. “PTCH1...is a mutation associated with the nevoid [BCCs] and plays a part in [BCC] through the whole process,” Soefje said. “We also believe there are other mutations. In fact, another interesting trivia—BCC has more genetic mutations than any other solid tumor on average, at 65 mutations per 100 megabase pairs.”

When working with BCC, Soefje said the first thing to do is stratify the risk based on the location and size. These factors determine the surgical approach and whether the tumor is poorly differentiated, is more aggressive, or has perineural involvement. Patients with a history of prior recurrent disease, prior radiation, and those receiving immunosuppressive drugs are also at a high risk for more severe disease.

Melissa Pozotrigo, PharmD, BCOP, senior clinical oncology pharmacist at OncoHealth, added that in the very early stages, dermatologists may be comfortable treating BCC with topical treatments. Beyond that,
dermatologists may refer patients to an oncologist while remaining involved in the multidisciplinary team.

Following this overview, attendees turned to the treatment landscape in BCC. In the first line for BCC are surgical approaches, which are how solid tumors become curable. When done correctly, surgical approaches lead to high 5-year cure rates, Soefje explained.

Various surgical approaches are also available for BCC, each appropriate for different patient needs. Excising and managing the margins are typically used for patients who are low or moderate risk, whereas Mohs surgery is reserved for patients who are high risk or those who are ineligible for excision-type therapy. Electrodissection and cryosurgery may also be performed for some patients, although Soefje noted that cryosurgery tends to leave more significant blemishes that patients may elect to avoid if possible.

However, because of location or size, some patients may be ineligible for surgical approaches. Pharmaceutical approaches can include a Hedgehog (Hh) signaling pathway inhibitor such as vismodegib (Erivedge; Genentech), which is the first FDA-approved Hh signaling pathway inhibitor for the treatment of locally advanced or metastatic BCC. Sonidegib (Odomzo; Sun Pharmaceutical Industries Limited) is also available and indicated for the treatment of adults with locally advanced BCC that has recurred following surgery or radiation, or for patients who are ineligible for surgery or radiation.

Although adverse effects (AEs) are similar for both treatment options, Soefje noted they have different dosing requirements, timing recommendations with food, and drug interactions for oncology pharmacists to be aware of in relation to patient education and guidance. Additionally, several panelists noted that they almost exclusively use vismodegib with their patients, with one panelist explaining that his reasoning for this preference is due to greater concerns regarding potential drug interactions with sonidegib. For example, sonidegib should not be administered in combination with strong cytochrome P450 3A4 inducers or inhibitors, which could limit the number of patients for which the drug is recommended.

Soefje also asked the panelists whether they had seen patients switch from either vismodegib or sonidegib to the other, particularly due to experiencing intolerance. The panelists explained that despite the availability of an alternative Hh signaling pathway inhibitor, they were more likely to take patients off therapy temporarily rather than switching to another option. Furthermore, after experiencing challenging AEs, some patients have also expressed hesitation about switching to another drug in the same class of medications, the panelists explained.

One of the most common AEs experienced by patients on either vismodegib or sonidegib is a loss or change in the ability to taste. In particular, difficulty tolerating foods or having foods taste bland can be a challenge, so including a nutritionist or dietitian on the multidisciplinary team could help patients maintain a healthy diet and weight.

Furthermore, muscle spasms can also be a challenge for patients on vismodegib or sonidegib, and the attendees noted that this AE can cause patients to discontinue therapy. However, amlodipine or L-carnitine can help to manage these, the panelists said.

Because of low response rates, chemotherapy is not typically recommended for patients with BCC. For these patients, immunotherapy may be a better option. Cemiplimab (Libtayo; Regeneron and Sanofi) is currently the only approved immunotherapy indicated for advanced BCC. One panelist explained that he has found the fixed-dose formulation to be convenient, especially when administered every 3 weeks. However, he noted that clinicians should remain aware of immune-related AEs and occasional infusion-related reactions that could occur.

Finally, the panelists looked at the larger picture of BCC treatment and discussed the pharmacist’s role. They all agreed that pharmacists should be involved from the beginning, even during the diagnostic phase, when pharmacists can help identify risk factors. One panelist noted some skin cancers could be drug induced, so pharmacists can be essential team members when helping to identify causes and treatment approaches.

Pharmacists are also crucial when it comes to educating patients, either about preventive measures, treatments, or financial barriers. Because of the current nursing shortage, one panelist noted that he found pharmacists were becoming even more involved in patient education than ever before, opening up new opportunities for pharmacists to demonstrate the value of their inclusion on multidisciplinary patient care teams.

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With the Affordable Care Act in 2010 came interoperability and meaningful use requirements. Part of these requirements included the implementation of electronic medical records (EMRs), which was a crucial part of achieving these standards.¹ With EMRs, prescribers began sending electronic prescriptions.² EMRs can provide advanced decision support when writing prescriptions, and they include features such as auto populating the quantity prescribed, formulary information, therapeutic duplications, warnings about interactions and other potential clinical or regulatory issues. This system results in enhanced patient care and a more streamlined dispensing process. In addition, electronic prescriptions for controlled substances (EPCS) has become more widely used as a tool to combat the opioid epidemic.³

Some critical goals of EPCS have been to eliminate paper prescriptions by allowing providers to prescribe electronically, making them digital, legible, more secure, and trackable for both pharmacists and providers.⁴ This also has allowed prescriptions to become more readily retrievable in electronic archives for audits or drug utilization reviews, which makes the handling of controlled substance prescriptions more efficient.

With EPCS, states began implementing prescription drug monitoring programs (PDMPs), which are electronic databases that track controlled substance prescriptions. Now PDMPs can support authorities’ and providers’ timely information about patient and prescribing behaviors that contribute to opioid abuse and facilitate a directed and resourceful response. PDMPs have allowed providers to review the patient’s history prior to authorizing a prescription. PDMPs have grown from 35 states in April 2011 to 49 states, the District of Columbia, and Guam in 2022.⁵ ⁶ In addition, the Centers for Medicare & Medicaid Services implemented a mandate for electronic prescribing that started on January 1, 2022. This mandate required all controlled drugs covered by Medicare Part D to be dispensed through EPCS.⁷ Many local and state laws have been implemented to better track controlled substance prescriptions using e-prescribing technology and PDMPs.⁸ The National Association of Boards of Pharmacy system has facilitated the transfer of the PDMPs across state lines, and many states now have working interfaces to make multistate data retrieval easier.

To limit the likelihood of drug abuse and diversion, the Drug Enforcement Administration (DEA) has acknowledged the importance of ensuring that the rules regulating electronic prescriptions do not unintentionally enable abuse and diversion.⁹ As a result, the DEA’s Interim Final Rule on EPCS went into effect in June 2010, allowing for e-prescribing and laying out the rules for its use in the United States.¹⁰ Pharmacies, pharmacy system vendors, prescription system application vendors, and providers were all subject to the rules.

Results
EPCS aimed to reduce prescription opioid addiction, abuse, diversion, and death.¹⁰ Additionally, EPCS can improve efficacy, quality, and safety and ultimately help reduce workload in the dispensing phase.¹¹

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EPCS can also improve efficiency, quality, and safety. EPCS has enhanced patient management and reduced prescription fraud associated with paper prescriptions. EPCS has gained popularity because of its ability to detect and prevent opioid diversion by removing paper prescriptions and allowing cross-referencing of PDMP databases. With up to 9% of opioid paper prescriptions suspected of being forged or fraudulent, the widespread use of EPCS has had an overall substantial influence on opioid prescribing.

EPCS has reduced stealing prescription pads or printing them and writing illegitimate paper prescriptions, altering a legitimate prescription to obtain a higher dose or more dosage units (eg, changing a 10 to a 40), and altering a prescription record at the pharmacy to hide diversion from a pharmacy stock, according to the DEA.

The results of a case study conducted at Yale New Haven Health System between February 2017 and August 2017 showed that the median number of opioid pills prescribed per surgery was reduced from approximately 30 pills before the prescription default modification to approximately 20 pills following the change in the prescription default. Prescriptions issued for 30 pills were reduced from 39.7% before the EPCS to 12.9% after the EPCS adoption, whereas prescriptions written for 12 pills rose from 2.1% before EPCS to 24.6% after EPCS. The number of prescriptions written for 120 pills, a 78% decrease in absolute numbers. In another study done at a dental facility in New York, over 3 months before the required PDMP and between December 1, 2013, and February 28, 2014, after PDMP implementation, the most prescribed opioid analgesics were codeine, hydrocodone, and oxycodone. Following the mandated PDMP’s introduction, there was a general trend toward fewer opioid prescriptions and more nonopioid analgesic prescriptions by the end of the trial, with the total number of opioid analgesics prescribed over 3 months dropping from 5096 to 1120 pills, a 78% decrease in absolute numbers.

**Conclusion**

EMRs, EPCS, and PDMPs have become essential tools in health care. They have curbed prescription errors, facilitated monitoring prescribed controlled substances, increased safety, and reduced possible abuses. In addition, EMRs and EPCS have provided a complete record of controlled substance prescriptions, monitoring both patients and physicians. These have been essential tools for law enforcement initiatives, public health agencies, and pharmacists to combat the opioid epidemic that has affected millions of Americans.

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Navigating Drug Resistance in Chronic Myelocytic Leukemia

Opportunities for further optimization of CML management remain.

CHRONIC MYELOCYTIC LEUKEMIA (CML) arises from abnormal pluripotent hematopoietic progenitor cells promoting excessive production of immature cells in the myeloid lineage, resulting in a hypercellular bone marrow and symptoms such as splenomegaly. In the United States, there are an estimated 8860 new cases annually, with a slightly greater incidence of the disease among men than women. In 2021, 15% of all adult leukemia cases were CML cases, with a median age of patients at diagnosis between 64 and 67 years.1,2

In more than 95% of patients with CML, the excessive production of immature, leukemic cells have a hallmark Philadelphia chromosome (Ph) due to a reciprocal translocation between chromosomes 9 and 22, resulting in the fusion tyrosine kinase BCR-ABL1. RNA expression of BCR-ABL1 is monitored by reverse transcription–quantitative polymerase chain reaction to determine the efficacy of tyrosine kinase inhibitors (TKIs), a mainstay of CML treatment.1,3

CML is subdivided into phases, in part by the percentage of myeloblasts in peripheral blood. Most patients are diagnosed with chronic phase CML (CML-CP); however, additional CML diagnoses include the more advanced accelerated phase (CML-AP) and blast phase (CML-BP).

In unmanaged CML, the disease is expected to progress to CML-BP within 3 to 8 years.4 Although TKIs play a role in all phases of disease, the phase of the disease at diagnosis will influence the initial selection of TKI. For instance, second- or later-generation TKIs are preferred for CML-AP, and TKIs are often combined with intensive chemotherapy for CML-BP. However, a common thread among all phases is the significance of TKI adherence, as data have demonstrated that nonadherence is associated with reduced survival.5

The goal of TKI therapy is to attain complete cytogenetic response (CCyR), signifying no detectable Ph-positive cells in the bone marrow—equivalent to BCR-ABL1 at approximately 1% on the International Scale—in 12 months or earlier following the initiation of therapy.1,6 Attainment of CCyR is associated with low rates of progression to CML-AP and CML-BP, as well as a high rate of overall survival.7 However, failure to meet BCR-ABL1 thresholds at 3, 6, and 12 months into TKI therapy is associated with less durable response, such as higher risk of cytogenetic relapse, and may be indicative of resistance to the TKI. In such cases of potential TKI resistance, the consideration of an alternate agent is strongly recommended.1

Primary Resistance
Primary resistance, or refractoriness, is characterized by an inability to attain time-dependent end points or other end points of response, such as CCyR, upon initiation of TKI therapy.8-10 Several BCR-ABL1-independent mechanisms—
including drug transporters and other pharmacokinetic considerations, such as signaling pathway activation and epigenetic dysregulation—have been implicated as contributing factors to primary resistance. However, these targets vary in terms of druggability, and assessment of these mechanisms (with the exception of drug-drug interactions) is generally not pursued during therapeutic planning.1,8,9,11-14

Adenosine triphosphate (ATP)-binding cassette (ABC) transporters include P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), which are present in primitive normal hematopoietic stem cells, as well as the liver, kidney, and other organs.15 Over-expression of these ABC transporters, due to single nucleotide polymorphisms or other causes, promotes active TKI efflux and decrease in intracellular drug accumulation, with the end result being resistance to imatinib (Gleevec; Novartis).9,16,17

Imatinib dose escalation to address overactive efflux transporters is controversial.9 Combining imatinib with some ABC inhibitors (or chemosensitizers), such as verapamil and valspodar, has historically been poorly tolerated because of the off-target effects of these inhibitors. However, elacridar, a dual P-gp and BCRP inhibitor, in combination with imatinib, has demonstrated promising in vitro efficacy for overcoming resistance to imatinib. Further investigation is required before concomitant chemosensitizers can be applied in clinical practice.18

Polymorphisms of the cellular influx–modulating organic cation transporter (OCT1) have also been proposed as an important factor regulating intracellular imatinib availability.15,19 Low OCT1 activity has been associated with long-term imatinib resistance in CML vs the association of high OCT1 activity with improved major molecular response (MMR) rates.20 However, the clinical applications of the association between low OCT1 activity and imatinib resistance remain unclear, in part due to inconsistent findings for specific OCT1 variants impacting imatinib response.13,19,21

Furthermore, the impact of concomitant medications should be assessed to prevent suboptimal TKI concentrations and responses. Extensive hepatic first-pass metabolism characterizes TKI metabolism; because of this, a current medication list should be assessed for medications and supplements inducing cytochrome P450 (CYP) 3A4 prior to TKI initiation. Depending on the TKI, a dose modification or complete avoidance of strong CYP3A4 inhibitors or inducers may be recommended by prescribing information.21,22 Manufacturer guidance should also be referenced regarding the allowance of—or any dosing interval required between—administrations of TKIs and acid-suppressing agents such as proton pump inhibitors, H₂-receptor antagonists, and antacids. Certain TKIs, such as dasatinib (Sprycel; Bristol Myers Squibb), have poor solubility in acid-suppressed environments.22

Other mechanisms recognized as having a relatively larger impact on BCR-ABL–independent resistance include a bone marrow niche impeding TKI action on CML leukemic stem cells (LSCs), which is marked by CD26 (otherwise known as dipeptidyl peptidase IV/DPP4) and promotion of residual disease; the sustained CML LSC maintenance due to JAK/STAT signaling that promotes signaling for cell growth, invasion, and inflammation; and expansion/self-renewal of CML LSCs due to deregulation of the Wnt/β-catenin pathway.23,24 Various trials have attempted to address these factors affecting BCR-ABL–independent resistance by adding targeted agents to TKI therapy. To date, trialed targeted agents include DPP4 inhibitor vildagliptin, JAK inhibitor ruxolitinib, and Wnt inhibition via a porcupine acyl transferase inhibitor.23-25 Additionally, epigenetic modifications, such as histone acetylation and DNA methylation, contribute to CML LSC persistence and TKI resistance. Further, many targeted agents are under investigation, including histone deacetylase (HDAC) inhibitors—such as pracinostat (SB939), vorinostat (Zolinza; Merck), and panobinostat (Farydak; Secura Bio, Inc)—and sirtuin, or class III HDAC inhibitors such as nicotinamide and tenovin-6.26,27

Secondary Resistance
Secondary resistance, or acquired resistance, is characterized by the initial achievement of response to a TKI that is followed by its loss.8-10 The mechanisms of secondary resistance most commonly encompass factors dependent on BCR-ABL, although BCR-ABL–independent mechanisms may also contribute to secondary resistance.9,14 Emerging BCR-ABL point mutations, ascertained by a BCR-ABL1 mutation analysis via traditional Sanger sequencing or more sensitive next-generation sequencing, are a major contributor to secondary resistance and treatment failure, with the presence of certain mutations dictating the selection of a second-
or subsequent-line TKI (Table).\textsuperscript{1,28} Notable sites of BCR-ABL point mutations are at the P-loop (ATP-binding site), TKI contact site (affecting TKI binding), C-loop (catalytic domain), A-loop (activation loop), and the myristate pocket.\textsuperscript{18}

One point mutation of interest is T315I, which is found in approximately 13\% of patients with CML who experience imatinib resistance.\textsuperscript{29} This mutation confers resistance to most FDA-approved TKIs that are competitive at the ATP-binding site. One exception is the third-generation TKI ponatinib (Iclusig; Takeda), with a carbon-carbon triple bond extending from the purine scaffold that minimizes the impact of steric hindrance caused by the T315I amino acid substitution.\textsuperscript{30} Another option in the setting of T315I mutation is omacetaxine (Synribo; Cephalon, Inc), which inhibits protein synthesis by binding to the A-loop, effectively reducing supply of BCR-ABL and other proteins with short half-lives.\textsuperscript{31,32}

PF-114 is a fourth-generation TKI with a ponatinib-like structure but without VEGF inhibition.\textsuperscript{33} A phase 1/2 trial (NCT02885766) enrolled a CML-CP and CML-AP patient population, 31.4\% of whom had T315I mutation. The patient population was also notable for being heavily pretreated, as 49\% had received 3 or more prior TKIs.\textsuperscript{38} At a dose range of 50 to 600 mg, MMR was attained in 6.3\% of patients with a T315I mutation. Additionally, although the toxicities were not extensively reported, grade 3 psoriasis-like skin lesions were noted as the dose-limiting toxicity.\textsuperscript{38,39}

### Table. Notable BCR-ABL Point Mutations for Common CML Therapies\textsuperscript{1,28}

<table>
<thead>
<tr>
<th>Agent</th>
<th>Avoid use with these BCR-ABL point mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>Various, including Y253F/H, E255K, M351T, F359V, T315I, F317L, Q252H/R</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>T315I, Y253H, E255K/V, F359V/C/I</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>T315I/A, F317L/V/I/C, V299L, Y253H*, E255V/K*, F359V/C*</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>T315I, V299L, G250E, F317L</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>Compound mutations in CML-AP (T315I/E453K)* and CML-BP (T315I/F359C)*</td>
</tr>
<tr>
<td>Omacetaxine</td>
<td>None yet reported</td>
</tr>
</tbody>
</table>

CML, chronic myelocytic leukemia; CML-AP, chronic myelocytic leukemia accelerated phase; CML-BP, chronic myeloid leukemia blast phase; *May confer resistance; could consider alternative agent.

There are also agents in the pipeline that aim to provide additional options for T315I and other point mutations. Olverembatinib (HQP1351; Ascentage Pharma) is a third-generation TKI competitive at the ATP-binding site. Patients take 40 mg orally every other day. Two single-arm, open-label phase 2 trials are investigating olverembatinib, with patients with TKI resistance (T315I-mutated) enrolled into either the CML-CP trial (NCT03883087) or the CML-AP trial (NCT03883100), based on their diagnosis. During the trials, MMR was achieved in 56.1\% of patients with CML-CP and 39.1\% of patients with CML-AP.\textsuperscript{35} Additionally, investigators observed grade 3 or higher adverse events (AEs) at more than 10\% incidence, including hematologic toxicities in both CML-CP and CML-AP cohorts, with grade 3 or higher elevated creatine kinase found to be common among patients with CML-CP.\textsuperscript{35,36}

Also in the pipeline, vodobatinib (K0706; Sun Pharma), a third-generation TKI, was demonstrated to be ineffective against the T315I mutation, but it may confer other benefits with other settings of resistant CML. This agent was examined in an open-label, phase 1/2 trial (NCT02629692) in a patient population with CML/Ph-positive acute lymphoblastic leukemia to determine efficacy for those who are heavily pretreated (3 or more TKIs failed) and/or with comorbidities precluding use of nilotinib (Tasigna; Novartis), dasatinib, and ponatinib. During this trial, MMR was achieved for 47\% of patient groups that included both ponatinib-naïve and postponatinib CML-CP and for 33\% of patients (1 of 3 patients) with CML-AP. Additionally, investigators observed grade 3 or higher AEs that included hematologic toxicities, increased amylase/lipase levels, congestive cardiac failure, hypertension, amnesia, and fatal intracranial hemorrhage.\textsuperscript{37}

PF-114 is a fourth-generation TKI with a ponatinib-like structure but without VEGF inhibition.\textsuperscript{33} A phase 1/2 trial (NCT02885766) enrolled a CML-CP and CML-AP patient population, 31.4\% of whom had T315I mutation. The patient population was also notable for being heavily pretreated, as 49\% had received 3 or more prior TKIs.\textsuperscript{38} At a dose range of 50 to 600 mg, MMR was attained in 6.3\% of patients with a T315I mutation. Additionally, although the toxicities were not extensively reported, grade 3 psoriasis-like skin lesions were noted as the dose-limiting toxicity.\textsuperscript{38,39}
Furthermore, BCR-ABL–independent mechanisms of secondary resistance are garnering interest as potential druggable targets, with the caveat that phase 2 data remain to be seen for most of these agents, including those addressed above. Additionally, aurora kinase inhibitors, such as tozasertib (VX-680; Vertex Pharmaceuticals), danusertib (PHA-739358; Selleck), and alisertib (MLN8237; Takeda) dysregulate cell division and may be effective as a subsequent-line therapy with T315I mutation.40

Investigational agents targeting the RAS/MEK/ERK pathway include inhibitors of farnesyltransferase, such as tipifarnib (Zarnestra; Johnson & Johnson) and lonafarnib (Zokinvy; Eiger BioPharmaceuticals, Inc), which downregulate RAS activation; MEK, such as selumetinib (Koselugo; Alexion Pharmaceuticals, Inc) and trametinib (Mekinist; Novartis); and PKC, such as enzastaurin (DB102; Denovo Biopharma LLC). The PI3K/AKT/mTOR pathway is also under active examination with inhibitors of PI3K, such as pictilisib (GDC-0941; Genentech Inc); mTOR, such as sirolimus (Rapamune; Pfizer Inc) and everolimus (Afinitor; Novartis); and AKT, such as MK-2206.18 Additionally, BCL2 inhibition, using agents such as sabutoclax (BI-97C1; Selleck), obatoclax (GX15-070; Teva Pharmaceuticals), and venetoclax (Venclexta; AbbVie and Genentech), has been implicated in reduction of quiescent CML LSCs.27

TKIs have transformed the treatment landscape of CML and dramatically improved overall survival with newly diagnosed CML, with the estimated 8-year survival rate up from 6% before 1975 to 87% since the advent of imatinib in 2001.40 However, opportunities for continued optimization of CML management remain with numerous mechanisms of primary and secondary resistance to TKIs under investigation. ■

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Assessing Quadruplet vs Triplet Regimens in Up-front Multiple Myeloma Treatment

Research indicates quadruplet regimens may be a viable option for this disease.

**Sarah Schmidt, PharmD, BCOP**

**TRIPLET DRUG REGIMENS** have become the standard of care for patients with multiple myeloma (MM) as first-line therapy, followed by autologous stem cell transplant (ASCT) for eligible patients. Although some individuals may present with poorer performance status allowing only for a 2-drug regimen, a third agent should be added if and when status improves.

Studies show that patients experience improved response rates, depth of response, progression-free survival (PFS), and overall survival (OS) with triplet vs doublet regimens. This is important in newly diagnosed MM because a deeper response, such as achievement of negative measurable residual disease (MRD), can improve long-term survival.

The most common first-line triplet regimen for transplant-eligible candidates is RVd (lenalidomide [Revlimid; Bristol Myers Squibb], bortezomib [Velcade; Takeda Pharmaceuticals U.S.A.], and dexamethasone), with some institutions favoring other regimens such as KRd (carfilzomib [Kyprolis; Amgen], lenalidomide, and dexamethasone). For nontransplant candidates, the preferred up-front therapy is either RVd or Dara-Rd (daratumumab [Darzalex; Janssen Biotech], lenalidomide, and dexamethasone). For nontransplant candidates, the preferred up-front therapy is either RVd or Dara-Rd (daratumumab [Darzalex; Janssen Biotech], lenalidomide, and dexamethasone). For nontransplant candidates, the preferred up-front therapy is either RVd or Dara-Rd (daratumumab [Darzalex; Janssen Biotech], lenalidomide, and dexamethasone). For nontransplant candidates, the preferred up-front therapy is either RVd or Dara-Rd (daratumumab [Darzalex; Janssen Biotech], lenalidomide, and dexamethasone). For nontransplant candidates, the preferred up-front therapy is either RVd or Dara-Rd (daratumumab [Darzalex; Janssen Biotech], lenalidomide, and dexamethasone). For nontransplant candidates, the preferred up-front therapy is either RVd or Dara-Rd (daratumumab [Darzalex; Janssen Biotech], lenalidomide, and dexamethasone).

As with other oncological diseases, it is common to add a targeted agent to the standard of care, such as rituximab (Rituxan; Genentech USA) targeting CD20 in lymphoma or midostaurin (Rydapt; Novartis) targeting FLT3 in acute myeloid leukemia. Targeted agents are also seeing increased use with MM treatment. Important targets in MM include CD38, SLAMF7, and BCMA, which are all highly expressed on MM plasma cells. There are multiple studies assessing quadruplet regimens as initial therapy in MM to determine whether a quadruplet regimen is better than a triplet regimen for treatment of patients with MM.

**GRIFFIN,** a randomized phase 2 trial (NCT02874742), assessed adding daratumumab, an anti-CD38 monoclonal antibody (MAB), to frontline RVd (D-RVd) for transplant-eligible patients with newly diagnosed MM. For 4 cycles, trial patients received either D-RVd or RVd, followed by ASCT, then received D-RVd or RVd consolidation for 2 cycles, with maintenance therapy consisting of lenalidomide or lenalidomide plus daratumumab for 26 cycles. Stringent complete response (sCR) following consolidation was the primary end point, in which D-RVd vs RVd showed improved response after consolidation, 42% vs 32% (P = .068), respectively. After 22 months, this was statistically significant with D-RVd vs RVd showing sCR of 62.6% vs 45.4% (P = .018). During the trial, severe hematologic adverse effects (AEs) were observed to be common for this quadruplet regimen. Following publication of these study results, the
regimen has been added to the National Comprehensive Cancer Network (NCCN) guidelines as an option for initial treatment in transplant-eligible patients.¹

At the American Society of Hematology (ASH) Annual Meeting and Exposition in 2021, updated results from GRIFFIN were presented with a median follow-up of 27.4 months. The data showed that results persisted and deepened at the follow-up point, and after 24 months sCR for D-RVd vs RVd was 66.05% vs 47.4% (P = .0096), respectively.⁴ MRD negativity was higher with D-RVd as well (35.6% vs 14.6%; P = .0007).⁴ This trial is ongoing and more time is needed to determine whether there will be a statistically significant PFS benefit.⁴ However, it is also not clear whether the long-term benefit will be driven from the quadruplet initial regimen or the doublet maintenance, which is not currently the standard of care.

The MASTER trial (NCT03224507) is a nonrandomized study assessing daratumumab added to KRd (Dara-KRd) followed by ASCT and then lenalidomide maintenance in transplant-eligible patients with newly diagnosed MM.⁵ The primary end point was MRD negativity, and 80% of patients achieved this at a median follow-up of 25.1 months.⁵ This trial will also assess whether patients can come off therapy after 2 consecutive MRD negative results, which could have significant impact on quality of life; the current standard of care has been ongoing maintenance therapy.⁵

Elotuzumab (Empliciti; Bristol Myers Squibb), a MAb directed against SLAMF7, is approved in the relapsed/refractory setting in combination with lenalidomide or pomalidomide (Pomalyst; Bristol Myers Squibb) plus dexamethasone. At ASH 2021, results were presented that showed the addition of elotuzumab to the RVd backbone did not result in improved outcomes in the frontline setting for transplant-eligible patients.⁶ The quadruplet regimen compared with RVd showed no difference in PFS, with the OS and AEs showing similar results.⁶

Another study presented at ASH 2021 added isatuximab (Sarclisa; Sanofi-Aventis)—which is approved in the relapsed/refractory setting in combination with dexamethasone and either pomalidomide or carfilzomib—to RVd. This study is one of the first trials to use MRD as the primary end point in transplant-eligible patients with newly diagnosed MM.⁷ Isatuximab is a MAb directed at CD38 and differs from daratumumab in that it induces apoptosis of the MM cells more directly.⁸ The study met its primary end point and isatuximab plus RVd was superior to RVd alone.⁷ MRD negativity rates after induction for RVd were 35.6% and 50.1% for isatuximab plus RVd (odds ratio [OR], 1.83; 95% CI, 1.34-2.51; P < .001).⁷ The trial is ongoing, and PFS and OS have not been reported. However, serious AEs have been observed to be similar between the 2 groups.⁷

In transplant-eligible patients with newly diagnosed MM, a quadruplet regimen has been added to the NCCN guidelines, known as D-VTd (daratumumab, bortezomib, thalidomide [Thalomid; Celgene]).¹ The CASSIOPEIA trial (NCT02541383) randomized patients to bortezomib, thalidomide, and dexamethasone (VTd) with or without daratumumab followed by ASCT in part 1 of the trial.⁹ This trial was conducted in Europe, where thalidomide is used more commonly. In the United States, lenalidomide is used to a greater extent than thalidomide, in part to avoid added toxicity of neuropathy with thalidomide combined with bortezomib. The primary end point of CASSIOPEIA was sCR 100 days after ASCT in which 29% of the D-VTd group vs 20% of the VTd group achieved sCR (OR, 16; 95% CI, 1.21-2.12; P = .0010). MRD negativity was also assessed, showing 64% in the D-VTd group vs 44% in the VTd group (P < .0001). In part 2 of the trial, maintenance therapy was analyzed with either observation or daratumumab, results of which demonstrated that daratumumab maintenance every 8 weeks for 2 years reduced risk of disease progression at a median follow-up of 35.4 months.¹⁰

Investigators are continually seeing improved response rates with novel therapies in MM. Whether quadruplet vs triplet regimens offer improved outcomes remains a question, but some studies have shown promising results in such comparisons. Quadruplets are becoming an option for patients with MM and hopefully time will determine which patients benefit most from these new regimens. ■

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Use of Lutetium Lu-177 Vipivotide Tetraxetan to Treat Metastatic Castration-Resistant Prostate Cancer

The FDA-approved, targeted radiopharmaceutical agent can contribute to a patient’s cumulative radiation exposure.

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ON MARCH 23, 2022, the FDA approved lutetium Lu-177 vipivotide tetraxetan (Pluvicto; Novartis), which is referred to in nuclear medicine literature as $^{177}$Lu–prostate-specific membrane antigen–617 ($^{177}$Lu-PSMA-617), for the treatment of PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). Eligibility for treatment with $^{177}$Lu-PSMA-617 for patients is based on whether they had previously been treated with at least 1 prior androgen receptor pathway inhibitor or with 1 to 2 prior taxane regimens. PSMA-positive disease is defined as at least 1 PSMA-positive metastatic lesion and no PSMA-negative lesions, determined with the FDA-approved gallium Ga 68 gozetotide injection (Locametz; Novartis), which is a radioactive diagnostic agent for PET imaging of PSMA-positive lesions, or another approved PSMA-11 imaging agent. In men with previously treated PSMA-positive mCRPC, the randomized (2:1), multicenter, open-label VISION trial (NCT03511664) evaluated $^{177}$Lu-PSMA-617 in combination with best standard of care (BSoC) (n = 551) against BSoC alone (n = 280). BSoC included abiraterone, enzalutamide, bisphosphonates, local radiation therapy, denosumab, and/or glucocorticoids. Patients were not permitted to receive cytotoxic chemotherapy, systemic radioisotopes, or immunotherapy in combination with $^{177}$Lu-PSMA-617. Based on the results of the trial, investigators observed $^{177}$Lu-PSMA-617 plus BSoC improved median overall survival (OS) and progression-free survival (PFS) compared with BSoC alone. Median OS was 15.3 months in the $^{177}$Lu-PSMA-617 group compared with 11.3 months in the control group (HR for death, 0.62; 95% CI, 0.52-0.74; P < .001). Median PFS was 8.7 months in the $^{177}$Lu-PSMA-617 group compared with 3.4 months in the control group (HR for progression or death, 0.40; 99.2% CI, 0.29-0.57; P < .001).

Mechanism of Action
$^{177}$Lu-PSMA-617 is a radioligand therapeutic agent, with the radionuclide lutetium-177 linked to a moiety that binds to PSMA, which is a transmembrane protein expressed in prostate cancer. Upon binding to PSMA-expressing cells, the beta-minus emission from lutetium-177 delivers radiation to PSMA-expressing cells, which induces DNA damage and can lead to cell death.

Dosage and Administration
$^{177}$Lu-PSMA-617 is dosed at 7.4 GBq (200 mCi) intravenously every 6 weeks for up to 6 treatments, or until disease progression or unacceptable toxicity. Before
administration with $^{177}$Lu-PSMA-617, patients’ vital signs should be collected 15 minutes prior, as well as 30 and 60 minutes after administration.²

$^{177}$Lu-PSMA-617 is a radiopharmaceutical that is recommended to be handled with appropriate safety measures to minimize radiation exposure. $^{177}$Lu-PSMA-617 may be administered intravenously (1-10 minutes) using a disposable syringe fitted with a syringe shield (with or without a syringe pump), as an infusion pump using the gravity method (with or without an infusion pump), or as an infusion using the vial (with a peristaltic infusion pump).²

Adverse Events
For patients who received $^{177}$Lu-PSMA-617, the most common adverse events (AEs) they noted included fatigue, dry mouth, nausea, anemia, decreased appetite, and constipation. During the trial, $^{177}$Lu-PSMA-617 was discontinued in 12% of patients due to any treatment-related AEs. In less than 5% of patients, clinically relevant AEs included dry eye, vertigo, and pancytopenia (including bicytopenia).²

Warnings and Precautions
$^{177}$Lu-PSMA-617 has labeled warnings for risk of radiation exposure, bone marrow suppression, renal toxicity, embryo-fetal toxicity, and infertility. As a targeted radiopharmaceutical, $^{177}$Lu-PSMA-617 contributes to a patient’s cumulative radiation exposure. In accordance with institutional good radiation safety practices and Nuclear Regulatory Commission patient-release guidance, it is important to minimize radiation exposure to patients, health care personnel, and household contacts.

During treatment with $^{177}$Lu-PSMA-617, patients should be counseled to increase oral fluid intake and to void frequently to reduce bladder radiation exposure. Following administration of $^{177}$Lu-PSMA-617, patients also must limit close contact (< 3 ft) with household contacts for 2 days or with children and pregnant women for 7 days. Patients must also refrain from sexual activity for 7 days. Patients should sleep in a separate bedroom from household contacts for 3 days, from children for 7 days, or from pregnant women for 15 days.²

$^{177}$Lu-PSMA-617-may cause severe and life-threatening myelosuppression. In the manufacturer’s labeling, grade 3 to 4 anemia was experienced among 13% of patients, grade 3 to 4 neutropenia in 5% of patients, grade 3 to 4 thrombocytopenia in 8% of patients, and grade 3 to 4 lymphocytopenia in 47% of patients. Complete blood counts should be obtained before each treatment with $^{177}$Lu-PSMA-617. Withhold, dose reduce, or discontinue $^{177}$Lu-PSMA-617 based on the grade of myelosuppression experienced.²

$^{177}$Lu-PSMA-617 can also cause severe renal toxicity. During the trial, 3% of patients experienced grade 3 to 4 acute kidney injury. Because of this, patients should be counseled to remain well hydrated. Additionally, patients’ serum creatinine and calculate creatinine clearance should be monitored before each treatment with $^{177}$Lu-PSMA-617.²

Furthermore, because $^{177}$Lu-PSMA-617 is absorbed into the testes, the recommended cumulative dose of 44.4 GBq of $^{177}$Lu-PSMA-617 results in a radiation absorbed within the range where $^{177}$Lu-PSMA-617 may cause temporary or permanent infertility.²

In women, the safety and efficacy of $^{177}$Lu-PSMA-617 have not been established. All radiopharmaceuticals, including $^{177}$Lu-PSMA-617, have the potential to cause fetal harm. For male patients with female partners of reproductive potential, patients should be advised to use effective contraception during treatment with $^{177}$Lu-PSMA-617 and for 14 weeks after the last dose.²

REFERENCES
Tebentafusp-tebn Use in HLA-A*02:01–Positive Unresectable or Metastatic Uveal Melanoma

The agent is representative of a new class of drug, ImmTAC.

IN JANUARY 2022, the FDA approved tebentafusp-tebn (Kimmtrak; Immunocore) for the treatment of adult patients with human leukocyte antigen (HLA)-A*02:01–positive unresectable or metastatic uveal melanoma.1 The FDA approval was based on results from the IMCgp100-102 trial (NCT02570308), a phase 3, open-label, multicenter trial that included 378 patients with metastatic uveal melanoma.

Uveal melanoma is the most common intraocular cancer in adults and represents 3% to 5% of all melanomas, with an annual incidence in Europe and the United States at approximately 6 per 1 million individuals annually.2 Additionally, up to 50% of patients with uveal melanoma will have metastases, predominantly in the liver. The median overall survival in the metastatic setting is approximately 1 year with current agents.

During several prior studies investigating the role of HLA in uveal melanoma, investigators were able to confirm that a high HLA class I expression (including HLA-A) is associated with a poor prognosis.3 In the United States and Europe, approximately 45% of individuals are HLA-A*02:01 positive.4

Mechanism of Action

Tebentafusp-tebn is representative of a new class of drug, termed immune-mobilizing monoclonal T-cell receptors against cancer (ImmTAC). The ImmTAC molecule is a T cell–redirecting bispecific fusion protein that uses an engineered high-affinity T-cell receptor to target any protein that is presented as a peptide-HLA complex on the target cell surface.

Tebentafusp-tebn consists of a soluble affinity-enhanced HLA-A*02:01–restricted T-cell receptor that is specific for the glycoprotein 100 (gp100) peptide and is fused to an anti-CD3 single-chain variable fragment. Glycoprotein 100 is and at least 1 measurable lesion were included. Exclusion criteria for the patient population during the trial included symptomatic central nervous system metastases, active autoimmune disease and receiving steroids, or active systemic immunosuppressive treatment.

Among previously untreated patients with metastatic uveal melanoma, more patients treated with tebentafusp-tebn achieved 1-year overall survival than those in the control group (73% vs 59%, P < .001). Progression-free survival was also significantly higher in the tebentafusp-tebn group (31% vs 19% at 6 months, P = .01). Additionally, the percentage of patients who had an objective response rate was higher in the tebentafusp-tebn group at 9% vs 5% in the control group, with median duration of response at 9.9 months and 9.7 months, respectively.4

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REFERENCES


expressed via HLA-A*02:01 on the surface of most uveal melanoma tumor cells, and tebentafusp-tebn binds to the HLA-A*02:01-gp100 complex on the target cell surface. This results in recruitment and activation of polyclonal T cells through CD3 to release cytokines and cytolytic mediators against the target uveal melanoma tumor cells.5,6

Dosage and Administration
The selection of patients for treatment with tebentafusp-tebn for unresectable or metastatic uveal melanoma is based on a positive HLA-A*02:01 genotyping test, with the tebentafusp-tebn intravenous (IV) dosing schedule as follows6:

- 20 µg IV on day 1
- 30 µg IV on day 8
- 68 µg IV on day 15
- 68 µg IV once every week thereafter

Patients should be treated with tebentafusp-tebn following the dosing schedule until unacceptable toxicity or disease progression occurs. Patients should be administered tebentafusp-tebn once weekly by IV infusion over a period of 15 to 20 minutes. During the first 3 doses of tebentafusp-tebn, patients are at highest risk of cytokine release syndrome (CRS), which may be serious or life-threatening; for this reason, monitoring during and for at least 16 hours following the infusion is required for the first 3 doses, with subsequent monitoring as clinically indicated following the third dose. If the patient does not experience grade 2 or worse hypotension during or after the third infusion, subsequent doses are better tolerated and a minimum of 30 minutes of monitoring is required following tebentafusp-tebn infusion.6

Adverse Events
The most common treatment-related adverse events (TRAEs) of any grade in the tebentafusp-tebn group were CRS (89%) with symptoms such as pyrexia (76%), chills (47%), hypotension (38%), and skin-related AEs such as rash (83%), pruritus (69%), and erythema (23%). The data also showed serious adverse events (AEs) occurred in 28% of patients receiving tebentafusp-tebn, including CRS (10%), rash (4.5%), pyrexia (2.4%), and hypotension (2%).

Fifty-seven percent of patients in the tebentafusp-tebn group experienced TRAEs in the first 4 weeks of treatment during dose escalation; however, the incidence is decreased with repeated doses.4,6 AEs leading to dose reduction occurred in 5% of patients, with CRS (2.4%) and rash (2%) being the most common causes. AEs leading to permanent discontinuation occurred in 3.3% of patients and include anaphylactic reaction, brain edema, CRS, fatigue, hepatotoxicity, hypotension, and nausea, each occurring at 0.4%. No treatment related deaths were reported in either group.4,6

During the trial, the most common laboratory abnormalities, occurring in 50% or more of patients, were decreased lymphocyte count and increased creatinine, increased glucose, increased aspartate aminotransferase, increased alanine aminotransferase, decreased hemoglobin, and decreased phosphate levels.6

Warnings and Precautions
Tebentafusp-tebn has a black box warning for CRS, which may be serious or life-threatening. Patients should be monitored during and for at least 16 hours following the first 3 infusions, then as clinically indicated.6

Pregnancy and Lactation
Currently, there are no available data with tebentafusp-tebn in pregnant women. However, based on the drug’s mechanism of action, it may cause fetal harm when administered to a pregnant woman. Women taking tebentafusp-tebn should be advised of the potential risk to the fetus, and health care providers should verify the pregnancy status in women of reproductive potential prior to initiating treatment. Women of reproductive potential should also be advised to use effective contraception during treatment and for 1 week following the last dose of tebentafusp-tebn.6

There are also no available data on the presence of tebentafusp-tebn in human milk, the subsequent effect on a breastfed child, or the effects on milk production. As tebentafusp-tebn may be excreted in human milk, patients taking tebentafusp-tebn should also be advised not to breastfeed during treatment and for at least 1 week after the last dose.6

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