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Lung Cancer Treatment Is Continuously Moving Forward

LUNG CANCER IS notoriously deadly. According to the American Cancer Society, carcinoma in the lungs accounts for nearly 25% of all cancer deaths among men and women. More people die of lung cancer each year than from colon, breast, and prostate cancers combined.¹

Lung cancer is also one of the most common forms of carcinoma. In the United States, approximately 235,760 new diagnoses of lung cancer and 131,880 deaths attributed to lung cancer this year.¹

It’s no wonder there are many drug therapies available for patients with the disease as well as potential treatments in the pipeline that may help further improve outcomes. This month, Directions in Oncology Pharmacy® looks closely at lung cancer and provides timely drug information for oncology pharmacists.

In our cover story, on page 36, author Saro Arakelians, PharmD, presents the causes and prevalence of lung cancer, including its risk factors and symptoms. Current treatments on the market, including monotherapies and common drug combinations, are also discussed.

On page 32, the pharmacology of cutting-edge therapies for non-small cell lung cancer (NSCLC), including oral inhibitors, is explored. This information was recently presented at the American Society of Clinical Oncology (ASCO) Annual Meeting.

Additionally, new therapies for NSCLC, which makes up about 84% of all lung cancers,¹ and investigational drugs are heavily featured in this month’s issue.

An article on page 15 highlights a drug that is newly approved by the FDA as well as an investigational treatment that recently received a breakthrough therapy designation. New therapies for mantle cell lymphoma also were the subject of a session at the 2021 ASCO Annual Meeting. This session is recapped on page 34.

Although it is important that oncology pharmacists familiarize themselves with the latest therapies and the drug development pipeline, patients who receive a diagnosis of any type of cancer may require additional support. Patient care may be provided in many different ways.

For example, on page 39, author Jill Drury, PharmD, presents a case study about a patient with pancreatic cancer. The patient receives a consultation with a pharmacist who can assist with medication management.

Financial toxicity for patients with breast cancer is addressed on page 28. Author Justin Lindhorst, MBA, presents the causes and prevalence of cost burden for some patients with breast cancer, as well as the role of the pharmacist in mitigating issues with patients’ ability to pay for care.

As treatments for lung cancer move forward and patient care services continue to expand, the role of the pharmacist in oncology is critical. Our goal, as always, is to provide useful, relevant information that is valuable to these professionals.

Thank you for reading.

Mike Hennessy Sr
CHAIRMAN & FOUNDER

VISIT PHARMACYTIMES.COM FOR REFERENCES.
From the Editor

AS EDITOR-IN-CHIEF OF Directions in Oncology Pharmacy®, I have had the privilege of selecting the finalists for the annual Next Generation Pharmacists® Award over the last decade. Each year we review a bevy of entrants. The applications are typically done by the entrant’s manager or peers. It never ceases to amaze me how these pharmacy professionals continue to advance patient care one year over the next. As expected, much of the focus is on the oncology space. Nearly all of the applicants have obtained multiple certifications in oncology and specialty pharmacy. This month, I think it would be beneficial to share a handful of examples from among the many Next Generation-nominated candidates. Within each there are real-world experiences that many of our readers will hopefully find instructional and perhaps inspirational.

Examples of Innovation in Oncology Specialty Pharmacy

Our first candidate’s onboarding process establishes a relationship with each new patient and creates a patient profile where she is able to accurately assess new oncology therapies. She is able to clarify and adjust those therapies in collaboration with the oncology team where appropriate and counsel her patients thoroughly, including any adverse effect management. Importantly, our candidate is a board certified oncology pharmacist (BCOP) who is well trained to address any drug-related emotional ramifications on medication adverse effects that may present themselves. Most of this candidate’s oncology patients require a weekly check-in to assess progress with their medications, so she creates a strong familiarity and relationship with her patients and their families. Oncology is a complex disease state that often requires many high-cost medications. As a result, our candidate is well versed in working with insurance companies, manufacturers, and grants to eliminate as much cost to the patient as possible.

Our second candidate is managing a busy pediatric hospital pharmacy with a strong focus in oncology. Pediatric oncology patients
require very careful dosing and frequent therapy adjustments based on the variability of younger and smaller patients. This candidate’s efforts have included a focus on reducing prescribing errors in pediatric oncology. The hospital is associated with medical and pharmacy schools, where students are often taught pharmacology classes in tandem between both institutions. This candidate has established a teaching program specifically focused on health care provider prescribing quality improvement, where future practitioners are trained side by side and collaboration becomes part of their future practice DNA. The program consists of oncology prescribing best practices with a pediatric focus. Her program includes information for newly trained pharmacists and medical residents on the best way to prescribe oncology medications and how to prevent potential medication errors. On a practice level, this candidate collaborates with all pediatric hospital departments to enhance bedside delivery. The impact of this activity over the past 12 months is that more than 1000 therapies are reviewed and optimized before the pediatric oncology patient is discharged. Truly, this candidate has a great influence on the care and medication delivery of her oncology pediatric patients.

Our third candidate is a specialty pharmacist and hospital pharmacy director at a large integrated delivery network (IDN) pharmacy. He and his team primarily serve oncology patients. This candidate has a passion for treating each patient holistically and addressing all of their care needs, not just pharmacy. Similar to our first candidate, he is known for going the extra mile to ensure that his patients’ oncology medications are approved through insurance, obtaining critically needed financial assistance through various foundations, as well as reaching out to assist in setting up patients with social support and transportation needs. He is known for creating a deep connection with his patients and the patient’s caregivers. This candidate’s efforts go beyond the institution and include serving on the local Susan G. Komen foundation community advisory board, which connects patients with breast cancer to their group’s support services. Additionally, this candidate has worked with a large pharmaceutical manufacturer’s program that supports patients with metastatic breast cancer to get better access to mammograms and preventive health. Recognizing the importance of integrating outreach programs into his practice, in addition to his work with the Komen foundation, this candidate is involved with the local Leukemia & Lymphoma Society, helping to lead fundraising efforts for its Light The Night and Team In Training initiatives in support of patients with blood cancer.

Our fourth candidate is an oncology pharmacist working in an IDN and managing its oncology clinical pathways program. This program aims to proactively provide patients with the education they need to be successful in their treatment journey and obtain ongoing assessments of a patient’s progress toward their treatment goals. The IDN’s clinical pathways program provides strategies designed around peer-reviewed and approved treatment protocols by cancer type diagnosis, based on selections made by the broader oncology team. Using an implementation process, oncology patients are provided high-touch, patient-centered care pharmacy consultations, allowing the oncology team to intervene early if any issues are spotted, such as adherence, treatment efficacy, or adverse event mitigation issues. As a direct result of this candidate’s efforts over the past 5 years, she has built, updated, and maintained more than 175 unique medication and disease-state-specific evidence-based clinical pathways, including oncology. In doing so, she increased the IDN’s clinical pathway program count in 2020 from about 120 clinical pathways to more than 170. As a result of this candidate’s efforts, the clinical pathways have aided in attaining
excellent proportion of days covered adherence rates year after year. As with our other candidates, this IDN’s program provides information for oncology staff to direct patients to co-pay assistance and patient assistance programs, as needed, to help individuals afford their high-cost oncology medications. It is important to note that 86.49% of patients participating in this IDN’s program were enrolled in co-pay or patient assistance initiatives and, in 2020, a total of $47,265,090 was saved for these patients.

Our fifth candidate also works in an IDN with a focus on clinical oncology program development. This candidate has created countless training guides, work instruction manuals, and checklists for placing oncology patients in the pharmacy system. Additionally, this candidate has helped implement a medical injectable program that allows the IDN’s pharmacy to efficiently work with providers and patients to get them infused or have physician-administered medications sent to providers, while also decreasing medication costs for employer groups. Lastly, this candidate created a workflow to promote the addition of manufacturer patient kits into new-to-therapy patient shipments, which helps patients obtain the information and tools to get started successfully on their new therapy.

Over the next few months, we will announce the final 3 candidates and, ultimately, the winner of the coveted Next Generation Pharmacist® Award in October. In reality every candidate is a champion for the professional and, more importantly, the patient.

Training and Certification
If you are considering focusing your professional career toward an oncology practice, much like the examples above, you have many options. Although it is not mandatory to be certified to practice in oncology, certification has become the gold standard. Many oncology pharmacists turned to specialization in cancer, which led to the development of a certification in pharmacy oncology practice. BCOPs have become an essential member of the care team. Patients and providers have come to know the BCOP as someone who is always available to answer their questions and knows the ins and outs of complex treatment and the extras, such as providing new patient starter kits that contain manufacturer information, calendars, and pamphlets about adverse event management, pictorials of how the drug is dosed, diet advice, and drug monograph information that goes with oncology treatment. Patients are often overwhelmed because of the amount of information and the number of new situations and providers they are interacting with. The BCOP becomes their drug navigator. If you are a pharmacist interested focusing your practice in oncology, you might want to explore becoming a BCOP.

The Board of Pharmacy Specialties created a specific certification for oncology, BCOP, which focuses on the certification of specialists in oncology pharmacy. Certification allows the qualified specialty pharmacist to practice at an advanced level of pharmacy practice in a complicated disease state and work in multiple practice settings. Many BCOPs can be found working in a team-based practice alongside a medical oncologist. In this setting, BCOPs work side by side with oncology teams, review patient histories, and develop cancer treatment plans throughout their oncology patients’ disease. With this expertise in understanding the complex therapies, the BCOP can effectively monitor for, prevent, and manage oncology patient drug-related adverse events. Becoming a BCOP means pharmacists become recognized by the pharmacy profession, their peers, oncology institutions, payers, and other oncology providers as someone who is well qualified to be an oncology therapy expert on the healthcare team.

*Directions in Oncology Pharmacy®* was developed to help raise the bar in oncology pharmacy practice. Our editorial board was selected from a pool of professionals who spend their days on the frontlines of oncology practice and are willing to share their experiences with our readers. We invite you to enjoy this editorial and encourage you to share it with your peers.

*Directions in Oncology Pharmacy®* is fully committed to setting the publication standard through peer-written and reviewed articles focused on the “real world” of oncology pharmacy practice.

We welcome your feedback on this topic and on any topics you would like us to cover in future editions of *Directions in Oncology Pharmacy®*. Please contact me at dsteiber@specialtypharmacytimes.com. We also encourage you and your colleagues to subscribe to this unique journal by logging on to pharmacytimes.com.
Updates in the First-Line Treatment of Advanced Renal Cell Carcinoma

Current guideline recommendations include various combinations of targeted therapy with immunotherapy.

Kelly M. Brunk, PharmD, BCOP, and T.J. Schieber, MBA, PharmD Candidate

The treatment of advanced renal cell carcinoma (aRCC) has drastically changed over the past 30 years. In 1992, the FDA approved the first immunotherapy in aRCC, interleukin 2. More than a decade later, the FDA approved the first targeted agent, sorafenib (Nexavar; Bayer). Since the mid-2000s, the treatment armamentarium for aRCC has expanded with approvals of additional immuno- and targeted therapies.

Current guideline recommendations include various combinations of targeted therapy with immunotherapy. So far in 2021, results from a pair of phase 3 trials—CLEAR (NCT02811861) and CheckMate 9ER (NCT03141177)—were published; the trials evaluated the combination of 2 different tyrosine kinase inhibitors (TKIs) with immunotherapy. To better understand how these 2 trials impact clinical decision-making for first-line treatment of patients with aRCC, these trials were evaluated in the context of other guideline-recommended treatments. These investigational combination immuno- and targeted therapies appear poised to contribute to the evolving treatment landscape of aRCC.

Synergistic Effect of Immune Checkpoint Blockade and Antiangiogenesis

The theory behind the combination stems in part from a main proangiogenic factor, VEGF, which is associated with renal cell carcinoma tumor growth and immunosuppression. VEGF stimulates the growth of blood vessels, leading to tumor angiogenesis, and causes immunosuppression through the promotion of regulatory T cells and inhibition of effector T cells. VEGF-targeted TKIs can control vasculature growth and normalize immune function, leading to better immune cell penetration of tumors especially in the presence of immunotherapy. Because of this control, the combination of a TKI and immunotherapy can have a synergistic antitumor effect.

Lenvatinib Plus Pembrolizumab

The phase 3 CLEAR trial randomized patients to receive either lenvatinib (Lenvima; Eisai Co, Ltd) 20 mg daily plus pembrolizumab (Keytruda; Merck) 200 mg every 21 days (n = 355) or sunitinib (Sutent; Pfizer Inc) 50 mg daily (4 weeks on with 2 weeks off per cycle) (n = 357).
The study showed improved progression free survival (PFS), overall survival (OS), and objective response rate (ORR) with lenvatinib plus pembrolizumab versus sunitinib. The median PFS was longer with lenvatinib plus pembrolizumab than sunitinib (23.9 months vs 9.2 months; P < .001). Median OS was not reached in either arm but favored lenvatinib plus pembrolizumab (P = .005). The ORR was also significantly higher in the lenvatinib plus pembrolizumab group compared with the sunitinib group (71% vs 36.1%; HR, 1.97; 95% CI: 1.69-2.29). The subgroup analysis for PFS and OS trended better for lenvatinib plus pembrolizumab in all subgroups except for the favorable risk subgroup.

The CLEAR trial also evaluated lenvatinib plus everolimus (Afinitor; Novartis) in a third arm compared with sunitinib. Lenvatinib plus everolimus statistically outperformed sunitinib in PFS and ORR but showed no difference in OS. Efficacy results were numerically lower in all categories with lenvatinib plus everolimus compared with lenvatinib plus pembrolizumab. Although caution should be used comparing results between different studies, the PFS, ORR, and complete response were the highest recorded in the lenvatinib plus pembrolizumab group compared with any other trial (see Table6-11).

Any adverse event grade 3 or higher occurred more often with lenvatinib plus pembrolizumab than with sunitinib (82.4% vs 71.8%, respectively). Two of the most common grade 3 or higher adverse events in both arms included diarrhea and hypertension. Discontinuation of at least 1 of the study drugs was seen in 37.2% of the lenvatinib-pembrolizumab arm compared with 14.4% of the sunitinib arm. Dose reductions occurred more frequently with lenvatinib than with sunitinib (68.8% vs 50.3%).

The combination of lenvatinib and pembrolizumab was recently added to the National Comprehensive Cancer Network guidelines as a preferred category 1 recommendation regardless of risk categorization.5

Nivolumab Plus Cabozantinib
The FDA approved nivolumab (Opdivo; Bristol Myers Squibb) plus cabozantinib (Cabometyx; Exelixis, Inc) in January for first-line treatment of aRCC based on results from the CheckMate 9ER study.12

CheckMate 9ER randomized 651 patients to receive cabozantinib 40 mg daily with nivolumab 240 mg every 14 days (n = 323) or sunitinib 50 mg daily (4 weeks on with 2 weeks off per cycle) (n = 328).7 The trial demonstrated a benefit in PFS, OS, and ORR with cabozantinib plus nivolumab compared with sunitinib. The median PFS was twice as long with cabozantinib plus nivolumab (16.6 months vs 8.3 months; HR 0.51; 95% CI: 0.41-0.64; P < .001), and the median OS was not reached but favored the cabozantinib-plus-nivolumab group (HR 0.60; 95% CI: 0.40-0.89; P = .001).7 The confirmed ORR favored cabozantinib plus nivolumab vs sunitinib (55.7% vs. 27.1%; P < .001). In the subgroup analysis, all subgroups trended better with cabozantinib plus nivolumab.7

Adverse events grade 3 or higher were similar across both treatment arms, with 75.3% seen in the cabozantinib-nivolumab arm and 70.6% reported in the sunitinib arm. The more common grade 3 adverse events across groups included diarrhea, palmar-plantar erythrodysesthesia, and hypertension. Treatment discontinuation of at least 1 drug was more common in the cabozantinib plus nivolumab group compared with the sunitinib group (19.7% vs 5.6%, respectively). Dose reductions occurred more...
frequently with cabozantinib than with sunitinib (56.3% vs 51.6%, respectively). The NCCN guidelines have been updated to include cabozantinib plus nivolumab as a preferred first-line option in all risk categories with a category 1 recommendation in intermediate- or poor-risk patients.5

Future Direction
In the first-line treatment setting of aRCC, various therapies have shown improved efficacy compared with sunitinib. However, data comparing these therapies with each other are lacking.6-11 Without direct comparative data, therapy decisions are frequently driven by patient-specific factors or provider preference. Notably, first-line treatment selection may also affect treatment decisions in the subsequent-line setting. Significant overlap exists between the TKIs used in the first-line setting (combined with immunotherapy) and the TKIs in subsequent lines.3 For example, lenvatinib plus everolimus is a therapy option in the subsequent-line setting. If a patient receives pembrolizumab plus lenvatinib in the first-line setting, the combination of lenvatinib plus everolimus may not be appropriate because TKI resistance may develop following disease progression.13

With the many therapy options available, trials evaluating sequencing therapy would benefit clinical practice. New trials are needed to guide practitioners on which first-line therapy options are preferred from direct comparator studies. End points such as PFS2 (time from randomization to second disease progression) could help determine the best sequence of subsequent lines of therapy. Furthermore, the use of sunitinib as a comparator in the first-line setting should be discouraged in new trials of previously untreated RCC, as this is no longer the standard of care.

Several ongoing trials could change therapy protocols. The COSMIC-313 trial (NCT03937219) and the PDIGREE trial (NCT03793166) are evaluating different combinations of ipilimumab (Yervoy; Bristol Myers Squibb), nivolumab, and cabozantinib.14,15 Results of both trials are pending. A novel HIF2A inhibitor, MK-6482 (Belzutifan; Merck), received a priority review from the FDA based on a phase 2 trial of patients with Von Hippel—Lindau disease—associated renal cell carcinoma.16 A phase 3 trial (NCT04195750) is currently underway to compare MK-6482 vs everolimus in patients with aRCC following progression on immunotherapy and a TKI.17

Conclusion
For patients with aRCC, combination therapy with an immune checkpoint inhibitor and a TKI is often the preferred first-line treatment modality. The CLEAR and CheckMate 9ER trials showed promising results, supporting the use of lenvatinib plus pembrolizumab and nivolumab plus cabozantinib, respectively. Among the first-line treatment options, lenvatinib plus pembrolizumab demonstrated the highest ORR and PFS; however, caution should be used when comparing results between trials.6-11 New trials with end points that span multiple lines of therapy are needed to help sequence the therapy of patients with aRCC.

TABLE: Summary of Recent Phase 3 Trials in Advanced Renal Cell Carcinoma6-11

<table>
<thead>
<tr>
<th>Year</th>
<th>Trial name</th>
<th>Agents</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>OS (mo)</th>
<th>PFS (mo)</th>
<th>Statistical benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>CABOSUN</td>
<td>CABO vs SUN</td>
<td>33 vs 12</td>
<td>1.3 vs 0</td>
<td>No benefit</td>
<td>8.2 vs 5.6</td>
<td>ORR, PFS</td>
</tr>
<tr>
<td>2018</td>
<td>CheckMate 214</td>
<td>IPI + NIVO vs SUN</td>
<td>42 vs 27</td>
<td>9 vs 1</td>
<td>NR</td>
<td>11.6 vs 8.4</td>
<td>ORR, OS</td>
</tr>
<tr>
<td>2019</td>
<td>KEYNOTE-426</td>
<td>Pemb + AXI vs SUN</td>
<td>59.3 vs 35.7</td>
<td>5.8 vs 1.9</td>
<td>NR</td>
<td>15.1 vs 11.1</td>
<td>ORR, OS, PFS</td>
</tr>
<tr>
<td>2019</td>
<td>JAVELIN-Renal 101</td>
<td>AVEL + AXI vs SUN</td>
<td>55.2 vs 25.5</td>
<td>4.4 vs 2.1</td>
<td>11.6 vs 10.7</td>
<td>13.8 vs 7.2</td>
<td>PFS</td>
</tr>
<tr>
<td>2021</td>
<td>CheckMate 9ER</td>
<td>NIVO + CABO vs SUN</td>
<td>54.8 vs 28.4</td>
<td>9.3 vs 4.3</td>
<td>NR</td>
<td>16.6 vs 8.3</td>
<td>ORR, OS, PFS</td>
</tr>
<tr>
<td>2021</td>
<td>CLEAR</td>
<td>Pemb + LEN vs SUN</td>
<td>71 vs 36.1</td>
<td>16 vs 4.2</td>
<td>NR</td>
<td>23.9 vs 9.2</td>
<td>ORR, OS, PFS</td>
</tr>
</tbody>
</table>

AVEL, avelumab; AXI, axitinib; CABO, cabozantinib; CR, complete response; IPI, ipilimumab; LEN, lenvatinib; NIVO, nivolumab; NR, not reached; ORR, objective response rate; OS, overall survival; Pemb, pembrolizumab; PFS, progression-free survival; SUN, sunitinib.
Advances in Non–Small Cell Lung Cancer Therapies
New treatments show promise for patients with KRAS G12C–mutated disease.

ADVANCES IN THE lung cancer space are all about biomarkers, explained Alexander Spira, MD, PhD, FACP, director of the Virginia Cancer Specialists Research Institute at The US Oncology Network; and assistant professor of oncology at Johns Hopkins School of Medicine, during a session at the 2021 virtual Community Oncology Alliance Conference.1

In the United States, non–small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers, with most patients (66%) initially receiving a diagnosis of advanced or metastatic disease. One of the most common driver mutations in patients with NSCLC is KRAS G12C, a subset of oncogenic drivers specifically in the KRAS gene.2

KRAS has been one of the primary targets posing a challenge in the lung cancer space. Spira explained that KRAS has been described as an “undruggable target,” which specifically relates to how intricate KRAS is in the signaling pathways for lung cancer.1

Recent data have shown both a high unmet need and poor outcomes associated with the second-line treatment of KRAS G12C–driven NSCLC. Each year, approximately 25,000 new patients diagnosed are with KRAS G12C–mutated NSCLC across the country.2

Spira noted that KRAS has specifically been referred to in the field as “undruggable” for many years; however, it is not for a lack of trying by investigators, as numerous therapies have been thoroughly assessed for potential benefit.1

“They all have failed. So it’s been a very frustrating area,” Spira said during the session. “So how do we target it right now?”1

One drug was recently FDA approved for adult patients with KRAS G12C–mutated locally advanced or metastatic NSCLC who have received at least 1 prior systemic therapy, and another has received a breakthrough therapy designation from the agency.3,4

The accelerated approval of sotorasib (Lumakras; Amgen) follows it being granted priority review by the FDA in February.5 A first-in-class, highly selective, irreversible KRAS G12C inhibitor, sotorasib works by binding KRAS in the inactive state in order to hinder downstream signaling effects.1

The FDA’s decision to approve sotorasib was based on the single-arm, open-label, multicenter study CodeBreaK 100 (NCT03600883).3 During this study, the investigators enrolled 124 patients with KRAS G12C–mutant solid tumors, with the study’s primary end point set as centrally reviewed objective response rate (ORR). To be eligible, patients needed to have received a prior line of systemic anticancer therapy that was consistent with both tumor type and disease stage.1-3

The top-line results from the phase 2 trial demonstrated that 80% of patients achieved disease control, including 3 complete responses (CRs) and 43 partial responses (PRs). The best ORR was approximately 2% CRs, 34% PRs, and 40% stable disease.1

“There’s a pretty deep response that was seen in many of our patients,” Spira said during the session. “It works, and in many of our patients it works very well. [Keep in mind] that many of these patients have multiple lines of therapy, making it of course less likely that you can have a deeper response to tumor volume, so pretty impressive results.”1

The recommended sotorasib dose is 960 mg orally once daily with or without food.3

The most common adverse reactions (≥ 20%) reported in the CodeBreaK 100 trial were diarrhea, »
Recent data have shown both a high unmet need and poor outcomes associated with the second-line treatment of KRAS G12C–driven non–small cell lung cancer.

Musculoskeletal pain, nausea, fatigue, hepatotoxicity, and cough. According to the FDA, the most common laboratory abnormalities (≥25%) were decreased lymphocytes, decreased hemoglobin, increased aspartate aminotransferase, increased alanine aminotransferase, decreased calcium, increased alkaline phosphatase, increased urine protein, and decreased sodium.3

A similar drug that will potentially receive approval from the FDA this year is adagrasib (MRTX849; Mirati Therapeutics, Inc), according to Spira.1 The drug received a breakthrough therapy designation from the FDA in June for the potential treatment of patients with NSCLC who harbor the KRAS G12C mutation following prior systemic therapy.4

Adagrasib was specifically designed to be a differentiated selective inhibitor of KRAS G12C, and Spira noted that this drug was intended to be even more specific than sotorasib, as it is a very potent inhibitor with a very high selectivity for the KRAS G12C protein. Additionally, adagrasib was designed to have a very long half-life, oral bioavailability, and tissue distribution.1

The new designation was based on the phase 1/1b/2 KRYS TAL-1 study (NCT03785249).4 Results from the study demonstrated adagrasib yielded durable responses and broad disease control while also providing extensive coverage throughout the dosing interval.1,5

At a dose of 600 mg given twice daily, adagrasib yielded an ORR of 43% in the phase 1/1b cohort (n = 14) and 45% in the pooled population of the phase 1/1b and 2 cohorts (n = 51).1,5

Furthermore, the results demonstrated a disease control rate of 100% in the phase 1/1b cohort and 96% in the phase 1/1b and 2 cohort, with 57% and 51% of patients having stable disease, respectively. Additionally, in the phase 1/1b cohort, disease progression did not occur, and in the phase 1/1b and 2 cohort, it occurred in 2% of patients.1,5

“Almost never seen before in this phase 1/1b cohort [is] a 100% disease control rate,” Spira said during the session. “I don’t think I’ve ever seen that in a study before. It did drop down to 96% in the pooled population, but it’s pretty remarkable numbers here.”

REFERENCES
Therapies in the Pipeline for Prostate Cancer
New potential medications may continue to expand the role of targeted agents.

IN THE UNITED States, prostate cancer is one of the most common cancers, with nearly 250,000 new diagnoses projected for men in the United States in 2021.1 In recent years, many new therapeutic options have become available for patients with prostate cancer for improving outcomes.

An oral GnRH antagonist, relugolix (Orgovyx; Myovant Sciences and Pfizer Oncology), was approved as a once-daily oral option for patients based on the HERO study (NCT03085095),2 and the role of targeted agents has continued to expand in prostate cancer. Current FDA approvals of 2 PARP inhibitors, olaparib (Lynparza; AstraZeneca) and rucaparib (Rubraca; Clovis Oncology), based on the PROFOUND (NCT02987543) and TRITON2 (NCT02952534) trials, respectively, have provided a new therapeutic option for prostate cancer patients with BRCA mutations.3,4

New potential prostate cancer medications in the pipeline continue the expansion of potential targets.

FDA-approved drugs seeking new indications in prostate cancer

Cabozantinib and Atezolizumab

Cabozantinib (Cabometyx; Exelixis) is a tyrosine kinase inhibitor targeting VEGF, AXL, and MET as pathways to angiogenesis and regulation of immune suppression, among other targets. Atezolizumab (Tecentriq; Genentech) is a monoclonal antibody targeting programmed death ligand 1 (PDL1). Individually, both cabozantinib and atezolizumab have shown some activity in phase 1 trials in prostate cancer.5,6

Possible synergy of the 2 agents in combination was noted in a cohort of the phase 1b COSMIC-021 (NCT03170960) trial in metastatic castrate resistant prostate cancer (mCRPC), in patients having progression on enzalutamide (Xtandi; Astellas and Pfizer) or abiraterone acetate (Zytiga; Janssen Oncology). The overall objective response was 33% in the cohort of 44 patients with authors noting a tolerable safety profile. Subsequent to these findings, further accrual has taken place to expand this cohort.7 On last reporting, patients were receiving cabozantinib 60 mg daily along with atezolizumab 1200 mg every 3 weeks. Cabozantinib is supplied in 20-mg, 40-mg, and 60-mg tablets.8

Talazoparib

Talazoparib (Talzenna; Pfizer Oncology), one of the most potent PARP inhibitors because of its induction of PARP1,9 has been approved as monotherapy in BRCA-mutated human epidermal growth factor receptor 2-negative metastatic breast cancers based on the EMBRACA trial (NCT01945775).10,11

The phase 3 TALAPRO2 trial (NCT03395197) is a 2-armed, randomized controlled trial comparing...
enzalutamide and talazoparib to enzalutamide monotherapy in mCRPC with a BRCA mutation and progression on prior antihormonal therapies. Results of the trial are pending publication, but this may broaden the scope of PARP inhibition in prostate cancer and address possible synergy in using a PARP inhibitor combined with an antihormonal agent, since prior studies investigated PARP inhibitors as monotherapy. The dose of talazoparib in the ongoing TALAPRO-2 trial is 0.5 mg taken once daily, with capsules coming in a 0.25-mg or 1-mg strength.

**Non-FDA Approved Medications Under Investigation in Prostate Cancer**

**ModraDoc006/r**

Intravenous docetaxel (Taxotere; Sanofi) has been a well-established treatment option in prostate cancer since the TAX 327 trial (NCT01989676) demonstrated both a benefit in survival and improvement in quality of life, in 2004. Subsequent to establishing docetaxel as part of standard of care, many oral antihormonal and targeted agents have been approved.

ModraDoc006/r (Modra Pharmaceuticals) is an oral tablet formulation of docetaxel sharing the anti-tumor mechanism of its intravenous counterpart, promoting microtubule assembly while simultaneously inhibiting tubulin activity, which would stabilize microtubules. The bioavailability of oral docetaxel is diminished by both CYP3A4 and P-glycoprotein; as such, ModraDoc006/r has been formulated with ritonavir (Norvir; AbbVie), which inhibits both CYP3A4 and P-glycoprotein.

M18MDP (NCT04028388) is an ongoing phase 2b trial comparing ModraDoc006/r to intravenous docetaxel in patients with mCRPC. Early trends indicate both arms have an impact on prostate-specific antigen (PSA) as well as the primary end point of radiographic progression-free survival, though these data are preliminary. In this trial, ModraDoc006/r tablets were administered weekly on days 1, 8, and 15 of 21-day cycles.

**Onvansertib**

Onvansertib (Cardiff Oncology) is an inhibitor of polo-like kinase 1 (PLK1), which regulates mitotic functions and is highly upregulated in prostate cancer following castration. It is currently being studied in combination with abiraterone and prednisone (Rayos; Horizon) in a phase 2 study (NCT03414034) of patients with mCRPC upon development of resistance to abiraterone, defined as 2 consecutive rises in PSA levels.

Although patients eventually demonstrate resistance to abiraterone after approximately 9 to 16 months of treatment, the hope is that onvansertib can prolong the efficacy of abiraterone. In phase 1 testing, transient and reversible hematologic effects were seen with onvansertib, and current studies are investigating the best dosing for future studies. The dosing schedules being investigated are as follows: 24 mg/m² orally on days 1 to 5 of a 21-day cycle, 18 mg/m² orally on days 1 to 5 of a 14-day cycle, or 12 mg/m² orally on days 1 to 14 of a 21-day cycle.

**Ceralasertib**

Ceralasertib (AZD6738; AstraZeneca) inhibits ATR kinase activity, which is involved in DNA repair. A phase 2 study (NCT03787680) is currently
investigating ceralasertib at a dose of 160 mg orally once daily on days 1 to 7 of 28-day cycle in combination with olaparib 300 mg orally twice daily days 1 to 28 in patients with mCRPC. Patients must have received either 1 previous line of therapy in the metastatic setting or a second-generation anti-androgen such as abiraterone, enzalutamide, or apalutamide within the hormone-sensitive phase of disease with progression while on therapy. The study started in October 2019 and its estimated primary completion date is November 2021.

**Opaganib**

Opaganib (Yeliva; RedHill Biopharma) inhibits sphingosine kinase-2 (SK2), which interferes with cell metabolism. It is currently being studied at a dose of either 250 mg or 500 mg orally, twice daily in combination with either abiraterone or enzalutamide in a phase 2 study (NCT04207255) of patients with mCRPC who have progressed on either enzalutamide or abiraterone. The study started in March 2020 and its estimated primary completion date is January 2022.

There are many targeted therapies in the pipeline for prostate cancer, with some therapies utilizing synergy between already FDA-approved medications. Other therapies are investigating novel potential targets. Although some of the results of these trials are pending, the outlook for patients with prostate cancer could be improved with so many new therapies in the pipeline.

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Specialty Drug Dispensing

Flexibility Is the Key to Success During a Crisis

The pandemic taught the pharmacy to provide a deeper level of personalized care and communication than in the past.

BY PAVLOS PAVLIDIS

“Bend, but don’t break” became the fundamental operating principle at Biologics by McKesson during the COVID-19 pandemic. As an independent specialty pharmacy, Biologics by McKesson provides specialty drugs for patients who have complex diseases, require extra care, or have expensive therapies. It specializes in quick delivery, financial aid assistance, adverse effect management, and adherence support to get medications to patients.

Since COVID-19 emerged, Biologics by McKesson, like many other companies, had to become more flexible. It put aside traditional ways of doing business and found new approaches to respond to the evolving health care landscape. Because it deals with rare disease and oncolytic medications, Biologics by McKesson had to ensure any operational adjustments would not negatively affect patients. By thinking creatively, it found new ways to meet patients’ needs without circumventing quality or compliance.

Many adjustments were made along the way that not only improved the services provided, but also empowered operational resilience, helping the pharmacy anticipate, prevent, and recover from adversity. Several of the modifications ensured that the delivery model was better equipped to respond to unexpected challenges while enhancing patient services.

Keep Patients a Top Priority

Disruptions in national shipping infrastructures became one of the major difficulties following the emergence of COVID-19. Before the pandemic, patients could choose between second-day air shipping, with guaranteed arrival within 2 days, or overnight, arriving by the end of the day. However, as shipping channels were affected by the pandemic, reliably delivering therapies to patients became increasingly difficult and more expensive.

Biologics by McKesson did a bit of soul-searching because the best solution involved substantial cost increases for it, yet it was the right thing to do for patients to ensure continuity of care. The pharmacy instituted a new model that shipped everything from oncology medications to supplemental therapies overnight to patients, with guaranteed...
delivery the next morning. This sent a strong message to patients and biopharma customers that the specialty pharmacy was doing everything in its power to fulfill the commitment to get medications to patients as soon as possible, and the response was overwhelmingly positive. The flexibility built into the delivery system enabled the pharmacy to provide superior service to patients in a time of need, so they did not experience any gaps in care.

Now that many shipping delays have been corrected, Biologics by McKesson is evaluating whether to return to a standard delivery model. Of course, it will always have the option to return to overnight delivery if disruptions occur again.

Empower Flexibility With Reliable Solutions

Coordinating delivery and shipment for rare drugs is complex even in normal times. It is crucial for a specialty pharmacy to ship medications in ways that guarantee not only fast delivery, but also quality and safety. Adjustments are made in response to changing conditions to ensure this. Biologics by McKesson uses only certified vendors that can provide temperature mapping, refrigeration, shipment tracking, and intervention if necessary. This grants the ability to make modifications along the way without fear of losing track of the shipments or endangering their quality. These capabilities proved invaluable when the pandemic started and many flights were affected, causing shipments to be delayed and rerouted.

The deep expertise and advanced technologies of certified vendors provided the specialty pharmacy with reliable solutions to delivery and shipment challenges and have been well worth the expense. Although they may not be the most cost-effective option, these vendors are the best choices to protect the integrity of medications while empowering flexibility within the system. The guarantees these vendors offer remove the risk of quality concerns and ensure patients’ therapies are properly delivered if the pharmacy needs to reroute a shipment in everyday or in emergency situations.

As the transportation landscape was severely disrupted, the performance of delivery carriers became even more important. Early on, Biologics by McKesson realized vendors would face their own challenges as they tried to navigate the widespread service interruptions. Rather than stick with the standard operating procedures, the pharmacy implemented detailed processes and procedures for emergency. This offered the flexibility to better respond and adapt to the changing conditions, enabling a heightened level of coordination and communication with carriers and certified vendors.

Adjust Services to Meet Growing Patient Needs

The pandemic taught the pharmacy to provide a deeper level of personalized care and communication than in the past. Because many patients have compromised immune systems caused by cancer and other conditions, they face an increased risk for COVID-19. To lower their risk of exposure to the virus, many became more homebound and relied on health care services as a lifeline. The specialty pharmacy adapted its operations to become even more patient-centric, recognizing that many individuals could not visit in person with a pharmacist or nurse for guidance. Biologics by McKesson’s highly skilled pharmacy and patient support teams deliver personalized clinical care to help patients understand how to take their medications and manage adverse effects, empowering them to achieve the best outcomes possible.

However, the pharmacy learned that patients needed a higher level of care during this unprecedented time. It provided enhanced counseling to calm their fears about the uncertainty surrounding them. The specialty pharmacy knew that its team was well prepared to take on this additional level of counseling, and patients were grateful and felt more supported than ever.

Meet the Challenges of the Moment With Flexible Solutions

As Biologics by McKesson reshaped its processes and priorities, the lessons learned along the way pointed in 1 direction; it’s critical to be flexible in a crisis. The specialty pharmacy was forced to change its thinking, processes, and services to meet the evolving needs of patients. As a result, patient outcomes improved and business thrived.
Management of Bruton Tyrosine Kinase Inhibitor–Associated Toxicities

Atrial fibrillation, bleeding, infection, and other adverse events may occur with this therapy.

**BY SHAN LI O’CONNOR, PHARMD, BCOP**

**INHIBITION OF BRUTON** tyrosine kinase (BTK) has revolutionized the treatment landscape for patients with B-cell malignancies. By targeting BTK, a critical kinase in proximal B-cell receptor (BCR) signaling, this class of small molecule inhibitors impairs BCR signaling and activation of NF-κB and inhibits cell proliferation and migration.¹

Ibrutinib (Imbruvica; Pharmacyclics and Janssen) was the first effective and selective BTK inhibitor approved by the FDA as a breakthrough therapy in 2013 for the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Its approval introduced the option of chemotherapy-free treatment for this patient population. Since then, ibrutinib has gained approval in other B-cell malignancies, including mantle cell lymphoma (MCL), Waldenström macroglobulinemia, and marginal zone lymphoma.²

Second-generation BTK inhibitor acalabrutinib (Calquence; AstraZeneca), with reduced off-target effects, was approved in 2017 and 2019 for the treatment of MCL and CLL/SLL, respectively.³ Zanubrutinib (Brukinsa; BeiGene), another second-generation BTK inhibitor, was approved in 2019 for the management of relapsed/refractory MCL.⁴

All 3 approved BTK inhibitors act via irreversible covalent binding to C481, found in the adenosine triphosphate–binding pocket of BTK. Mutations in the C481 binding site are known to cause clinical resistance to irreversible BTK inhibition. Third-generation BTK inhibitors currently in clinical studies exhibit reversible noncovalent binding to BTK. These BTK inhibitors act independently of covalent binding to C481 and can achieve target inhibition of both wild-type and C481S-mutated BTK. Therefore, they may overcome resistance mediated by this mutation.⁵,⁶

Toxicities and management of adverse events (AEs) arise throughout therapy with BTK inhibitors. The following toxicities and AEs focus on the 2 approved agents in CLL/SLL.

**Atrial Fibrillation**

Development of atrial fibrillation (AF) has been the most common cause leading to discontinuation of ibrutinib. Male gender, aged 65 years and older, history of valvular heart disease, and hypertension at the time of diagnosis have been identified as independent risk factors for de novo AF. AF occurs initially in about 6% of patients on ibrutinib, increasing to 10% to 15% over 2 years.⁷,⁸ In comparison, the risk of AF in patients on acalabrutinib is slightly lower, ranging from 3.6% to 6%.⁹,¹⁰

For patients with a long history of poorly controlled AF, alternative treatment such as a BCL2 inhibitor may be preferred. For patients with limited risk factors (CHA2DS2-VASc score of 0-1), BTK inhibitors may be reinitiated at the prior dose once symptoms have resolved to baseline. For patients with 2 or more risk factors, management is clinician dependent. Discontinuation of a BTK inhibitor and anticoagulation vs resuming therapy at previous or reduced dose have both been done in practice.¹¹
A β-blocker is preferred over a nondihydropyridine calcium channel blocker (e.g., verapamil and diltiazem) for the management of AF due to lack of drug interaction with BTK inhibitors. Anticoagulation with either a direct oral anticoagulant or enoxaparin is preferred for patients with higher CHA2DS2-VASc scores. Combination of a BTK inhibitor and a vitamin K antagonist is discouraged because of fatal subdural hematoma reported in clinical study.11

**Bleeding**

Minor bleeding such as low-grade ecchymoses and petechiae occurred in up to two-thirds of patients on ibrutinib. Major bleeding occurred less frequently, in 2% to 9% of patients on ibrutinib.7,8 In contrast, major bleeding was seen in only 2% of patients on acalabrutinib monotherapy, with minor bleeding observed in 37% of patients.9,10 Bruising, commonly seen with BTK inhibitors, does not confer an increased risk of major hemorrhage, and therapy can safely continue without interruption.

BTK inhibitors should be held for either 3 days for a minor procedure or 7 days for a major procedure, both before and after, because of the increased peri-procedural bleeding risk. For minor bleeding, holding ibrutinib results in the resolution of bleeding tendency in 2 to 3 days. For severe bleeding, platelet transfusions can be given when appropriate regardless of platelet count. The risk of bleeding increases when patients are on concurrent anticoagulation and antiplatelet therapy. Acalabrutinib may be preferred over ibrutinib for people on dual antiplatelet agents or needing both anticoagulant and antiplatelet therapy.12

**Infection**

Infection of any grade occurred in more than 50% of patients on BTK inhibitors, particularly during the initial treatment period. Pneumonia was the most common infectious complication, occurring in up to 12% of patients. Recent reviews have also highlighted the prevalence of opportunistic infections, including pneumocystis jirovecii (PJP) and aspergillus infection in patients on BTK inhibitors.13 Patients with relapsed/refractory disease, heavily pretreated, and with a known history of infection are at a higher risk for developing infectious complications. CLL guidelines do not specifically address the role of PJP prophylaxis, and practices vary across institutions. However, patients who are at higher risk should consider PJP prophylaxis. Varicella-zoster virus (VZV) reactivation has also been identified while a patient is on BTK inhibitors, and VZV prophylaxis may be appropriate in patients with prior infections.11

**TABLE. Management Recommendations for Adverse Events**11,12

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>• Optimally control baseline hypertension prior to treatment initiation</td>
</tr>
<tr>
<td></td>
<td>• Routinely monitor and initiate appropriate medical therapy or adjust antihypertensive in conjunction with patient’s primary care provider</td>
</tr>
<tr>
<td></td>
<td>• Incidences of hypertension increase over time</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>• Most diarrhea can be managed with supportive care, antimotility agents</td>
</tr>
<tr>
<td></td>
<td>• Taking medication at bedtime can help to mitigate symptoms</td>
</tr>
<tr>
<td></td>
<td>• Consider temporary hold for diarrhea greater than grade 3</td>
</tr>
<tr>
<td>Cytopenia</td>
<td>• Dose reduction or holiday, avoid dose reduction or interruption during early course of therapy</td>
</tr>
<tr>
<td>Headache</td>
<td>• Self-limited with extended treatment, responsive to caffeine</td>
</tr>
<tr>
<td>Fatigue</td>
<td>• Avoid dose reductions for fatigue during early course of therapy</td>
</tr>
<tr>
<td></td>
<td>• Consider drug holiday or dose reduction for severe symptoms</td>
</tr>
<tr>
<td>Arthralgia, myalgia</td>
<td>• Observation and supportive care if symptoms are grade 1 or 2</td>
</tr>
<tr>
<td></td>
<td>• Consider dose reduction if symptoms affect activities of daily living</td>
</tr>
<tr>
<td></td>
<td>• Temporary hold for severe arthralgias, short-course steroids and anti-inflammatory agents may be effective</td>
</tr>
<tr>
<td>Rash</td>
<td>• Self-limiting and respond to topical steroid</td>
</tr>
<tr>
<td>Nail and hair changes</td>
<td>• Brittle nails and hair can be common, incidence increases over time</td>
</tr>
<tr>
<td></td>
<td>• Nail oil to cuticle bed can be helpful</td>
</tr>
</tbody>
</table>

Given the impressive efficacy and activity of BTK inhibitors in the treatment of newly diagnosed and relapsed/refractory CLL, it is vital that the care team become familiar with the management of BTK inhibitor–emergent toxicities.

Visit PharmacyTimes.com for references.
Managing Adverse Events in Cancer Care: Addressing Blood Cell Counts and Drug Management

A proactive approach can ensure that the patient is getting the right therapy at the right time and the right treatment plan with the least amount of waste.

BY DEA BELAZI

SPECIALTY MEDICATIONS ACCOUNTED for 52% of drug spend in 2020, with an increase in drugs approved to treat cancer. In fact, the FDA approved 53 new drugs last year, including 20 with indications related to oncology.

A number of key strategies are available to ensure that oncology patients receive appropriate care and management. With a focus on improved individual outcomes and an enhanced patient experience, a proactive approach to patient engagement can maximize therapeutic opportunities, provide education and information, and help employers and other stakeholders create accountability and predictability around oncology drugs.

The goal is to ensure that the patient is getting the right therapy at the right time and the right treatment plan with the least amount of waste. Preemptive activities should examine patient adherence to their treatment regimen to make sure the individual is considered an appropriate candidate for a particular drug. These initiatives will further reduce waste, minimize adverse effects, and lower health care costs.

Although adverse events resulting from cancer therapy are common, they can be minimized. In a retrospective cohort study, 400 adult patients who had breast, colorectal, or lung cancer and were treated at a comprehensive cancer center were selected by stratified random sampling. The study’s authors concluded that 34% of these patients had at least 1 adverse event and 16% of the patients had 1 or more preventable or mitigable adverse events.

One of the consequences of cancer treatment is a severe low blood cell count, which can lead to serious complications that may delay or prevent the continuation of the cancer therapy regimen. While other considerations exist in treatment, this is one of the key elements of a comprehensive treatment plan.

Low red blood count causes anemia, which often develops gradually with no initial symptoms before the onset of fatigue, shortness of breath, dizziness, rapid heartbeat, and feeling cold. Low white cell count causes neutropenia, which negatively impacts the body’s ability to fight infection. Symptoms may include a temperature of 100.4°F or higher, chills or sweating, diarrhea, painful urination, and persistent cough, among others.

For treatment care teams, it is important to take the most optimal approach to managing adverse events related to low blood cell counts. For instance, when a patient experiences an adverse event, harnessing technology to close the loop between the patient and provider can avoid unneeded spend, speed up the care process, and enhance the patient outcome. Also, staying closely connected to the...
patient through a specialty pharmacy benefit manager (SPBM) can more quickly address any challenges facing the patient or caregiver.

As care coordinators, SPBMs play a role in monitoring and managing cancer patients for adverse events to ensure that the patient is getting the right therapy at the right time, the right treatment plan with the least amount of waste, and site optimization for the right care in the right setting.

Managing Blood Cell Counts During Cancer Treatments

Chemotherapy may lead to low blood counts, causing the possibility of a variety of symptoms, which depend on the type of low blood cell count. SPBMs can provide expertise on supportive therapies for chemotherapy regimens that can impact blood counts.

Because chemotherapy can kill some bone marrow, the body makes fewer white blood cells, raising the chances of the patient contracting febrile neutropenia (FN). Colony-stimulating factors (CSFs), including biosimilars, help prevent infection during chemotherapy and increase the number of white cells in the patient’s blood, lowering the risk for FN.

CSFs include the injectables filgrastim (Neupogen; Amgen), pegfilgrastim (Neulasta; Amgen), and sargramostim (Leukine; Partner Therapeutics). In terms of adverse events, CSFs can cause pyrexia, rash, nausea, vomiting, headache, epistaxis, diarrhea, arthralgia, leukocytosis, spleen rupture, acute respiratory syndrome, and capillary leak syndrome.

The American Society of Clinical Oncology recommends the prophylactic use of CSFs to reduce the risk of FN when the risk of FN is approximately 20% or higher and no other equally effective and safe regimen that does not require CSFs is available. Primary prophylaxis is recommended for the prevention of FN in patients who are at high risk on the basis of age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen.

Dose-dense regimens that require CSFs should be used only within an appropriately designed clinical trial or if supported by convincing efficacy data. Current recommendations for the management of patients exposed to lethal doses of total-body radiotherapy, but not doses high enough to lead to certain death as a result of injury to other organs, include the prompt administration of CSFs.

Guidelines for CSFs:

- **Filgrastim**—This synthetic injection is used to treat neutropenia caused by medicines for treating cancer and helps bone marrow make new white blood cells. One study showed that 5 days of filgrastim use was noninferior to 7 or 10 days of filgrastim use. Given the recognized toxicity and cost of this agent, as well as the impact on health economics and patient morbidity, the shorter duration would be an option for patient care.

- **Pegfilgrastim**—This bone-marrow stimulant is indicated to decrease the incidence of infection in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of FN. It is also indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation and for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

- **Sargramostim**—This granulocyte-macrophage colony stimulating factor (rGM-CSF) is considered medically appropriate for treatment of chemotherapy-induced FN in individuals who have not received prophylactic therapy with a granulocyte CSF and for individuals at risk of developing sepsis, absolute neutrophil count of < 100/mcL, duration of neutropenia expected to be greater than 10 days, pneumonia, or other clinically documented infections, or invasive fungal infection, or for patients hospitalized at the time of fever.

Guidelines for patients with anemia:

- **Erythropoiesis-stimulating agents (ESAs)**—ESAs, including biosimilars, may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose hemoglobin has declined to 10 g/dL. With the exception of selected patients with myelodysplastic syndromes, ESAs should not be offered to most patients with nonchemotherapy-associated anemia. During ESA treatment, hemoglobin may be increased to the lowest concentration needed to avoid transfusions. Iron replacement may be used to improve hemoglobin response and reduce red blood cell transfusions for patients receiving ESA with or without iron deficiency.
Specialty medications for patients undergoing chemotherapy often require specialized clinical support for patient administration, including complex dosing and injected or infused delivery. SPBMs can help ensure adherence while monitoring patients for safety issues and possible adverse effects. SPBM clinical experts have a deep knowledge of possible drug adverse effects and understand ways to mitigate them. These specialists reach out to physicians when patients need additional monitoring or require therapy changes to reduce adverse effects, improve efficacy, and lower patient out-of-pocket costs.

Benefits of a SPBM Partner

SPBMs facilitate ongoing positive patient outcomes through persistence, adherence, compliance, and supportive, collaborative patient management. Professional teams regularly measure and track treatment effectiveness and, across the continuum of providers, validate savings and opportunities for improved outcomes.

SPBMs also offer pharmacists the benefits of technology, analytics, and clinical services designed for oncology cost containment. As a result, they serve as the fulcrum of a central approach to facilitate the care management approach.

For oncologists, SPBMs serve as a hybrid of traditional and innovative approaches that target specific cancer populations. They provide programs that empower both the patient and their caregiver after a diagnosis and referral. SPBMs also play a critical role in providing a personalized approach in treatment options, evidence-based clinical policy bulletins and pathways, utilization management, and other clinical assessments.

SPBMs provide flexible, tailored drug management solutions driven by client needs to increase patient safety, improve health outcomes, identify appropriate sites of care for treatment, reduce waste and cost with effective medication management, and offer negotiated dispensing rates as well as increased transparency.

They deliver significant value for patients by offering specialty pharmacy and infusion networks that specialize in data, analytics, and cost modeling, as well as real-time front-end prescription triage to help patients receive the right care at the right time. These programs also utilize technology to manage and streamline the specialty pharmacy prescription process among the physician, patient, specialty pharmacy, and health insurance plan.

SPBM programs also capture, integrate, and provide prescription data and health care outcome analytics in a real-time platform, providing accurate insights into patient care, provider prescription value, prescription trends, specialty pharmacy performance, dose optimization, treatment paths, and other clinical intervention reports.

Ensure Site of Care Optimization

SPBMs play a key role in optimizing site of care, a key strategy that encourages patients to move from higher-cost settings, such as inpatient hospitals and institutions, to lower-cost settings, such as physicians’ in-office infusion suites, stand-alone infusion centers, home care, and self-administration.17

SPBM programs can also assist caregivers. These individuals helping a family member or friend through cancer treatment may perform a number of activities, including taking the cancer patient to the doctor, making meals, coordinating care services, and providing emotional and spiritual support.

Patient-centric Treatment Monitoring

The best SPBMs take a patient-centric approach to the care continuum that is broadly focused on all aspects of the patient journey, including prevention, diagnosis, treatment, care monitoring for adverse events, and outcomes. Understanding the patient journey is essential to identifying unmet needs and implementing the best medical and nonmedical interventions.

New technologies are allowing providers to diagnose and treat cancers better. To optimize treatment, each stage of the patient journey, including monitoring for low blood cell count, is critical for improving the patient/caregiver experience and outcomes.

SPBMs can ensure that the necessary documentation is in place for patients, caregivers, providers, and pharmacies and that care is being handled appropriately. They consider the whole care of the patient, beyond lab results, to ensure that every need of the patient and caregiver is being met and well managed.

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Breast Cancer, Financial Toxicity, and the Role of Specialty Pharmacy in Reducing Barriers to Care

As health care costs rise and cost-sharing increases, treatment-associated expenses will continue to burden patients.

By Justin Lindhorst, MBA

This year, an estimated 284,200 women will receive a diagnosis of breast cancer. These women will face substantial physical and emotional challenges as they navigate a difficult diagnosis. Patients with breast cancer are also increasingly challenged with significant and persistent financial burden on the road to recovery.

Causes of Health Care Cost Burdens

Financial toxicity caused by the medical and nonmedical costs of breast cancer treatment are negatively impacting women and their clinical outcomes. Rising health care costs and shifts in cost-sharing are contributing to financial toxicity experienced by patients with cancer. New cancer therapies are providing hope and driving better clinical outcomes but also significantly increasing the overall cost of care. Seven percent of all health care spending is associated with cancer, and cancer tops the list of the most costly health conditions in terms of personal expenditures.

The cost of breast cancer treatment varies by age and phase of care, ranging from $20,000 to $100,000 or more. Overall health care costs are increasing as health insurance companies are shifting additional financial responsibility to the patient. From 2006 to 2016, the average health insurance deductible increased from $300 to over $1200, and health insurance cost-sharing often outpaces wage growth. As health care costs rise and cost-sharing increases, financial toxicity will continue to burden patients with breast cancer.

Furthermore, financial challenges are impacting health care access for women without a breast cancer diagnosis, and the impact of COVID-19 has accelerated these issues. During the pandemic—between February 2020 and January 2021—2.5 million women left the United States workforce, compared with 1.8 million men for the same period. Many women who continued to work reported reducing their hours or taking unpaid leave because of increased child care demands brought on by school and day care closures. Additionally, women are forgoing essential health care services,
and skipping tests, treatments, and preventive care appointments at a higher rate than men. A recent study found that financial barriers are impeding women at high risk for breast cancer from accessing preventive screenings and other measures, despite having insurance coverage. Women who did seek health care services reported challenges paying their medical bills.

**Prevalence of Financial Toxicity for Patients With Breast Cancer**

Nearly half of women who receive a breast cancer diagnosis will experience some level of financial toxicity, which occurs disproportionately among minority populations. Current literature suggests women may not be receiving enough counseling and support from their medical providers to adequately address the issue of financial toxicity. One study indicated that only 28% of clinicians felt comfortable discussing out-of-pocket (OOP) costs with their patients.

In a recent survey of patients with breast cancer, 72.8% of 945 respondents felt they did not receive help, at least somewhat, around issues of financial toxicity from their physician or their physician’s staff. In the same study, over half of respondents who expressed wanting to speak to health care providers about the impact of their diagnosis on their employment or finances reported no relevant discussion with their clinical team.

**Pharmacists’ Role in Mitigating Payment Issues**

Specialty pharmacies are uniquely positioned to help patients with breast cancer address issues of financial toxicity. Intake staff regularly interface with patients, prescribers, payers, and pharmaceutical manufacturers. Acting as an intermediary between these parties, the intake team plays a critical role advocating for treatment access and helping reduce financial toxicity. One-on-one consultations help patients understand their OOP costs and identify strategies to minimize financial burden. The intake team often enrolls the patient in manufacturer assistance co-pay programs while providing referrals to charitable organizations assisting with the nonmedical costs associated with cancer care.

According to Lydia Ezekiel, a referral specialist for a national specialty pharmacy, specialty pharmacies play a role in helping patients with breast cancer overcome financial toxicity.

“Our goal is to work within available and appropriate resources to achieve a $0 co-pay,” Ezekiel said. “We delight in informing our patients they will receive their medication at no cost. We also help patients identify resources assisting with transportation, food, or other nonmedical needs.”

Ezekiel also noted that by obtaining patient consent, the team can do extensive research and outreach on the patient’s behalf, referring to charitable organizations without burdening patients with an additional task. However, with so many women in need, a growing number of charities are forced to put patients on waiting lists.

“Many patients meet eligibility criteria for grants but are wait-listed by the foundation due to lack of funds,” said Ezekiel. “We don’t let that slow us down, though. By the time we exhaust all available options, we’ve usually secured some level of support alleviating at least a portion of the financial burden patients are facing.”

Amanda Hasenei is a certified pharmacy technician and referral specialist who has spent over a decade working in the specialty pharmacy space. She said it is not uncommon for patients with breast cancer she sees to be completely overwhelmed with the financial aspects of their care.

“Our first priority is to acknowledge their concerns and assure them they are not alone in the process. We establish goals and priorities around the most...”
immediate financial concerns and then we work relentlessly to overcome them,” said Hasenei.

Strong clinical coordination can also help alleviate financial toxicity. Pharmacists help patients understand their treatment and avoid complications that can result in hospitalization or missed work. One study found a singular oncology specialty pharmacist provided interventions with an estimated annual value of nearly $1 million. The most frequent interventions included medication education, dose adjustments, and medication reconciliation.

Kionna Oleru is a specialty pharmacist who has spent a significant amount of her career serving women with breast cancer. She described the role of a specialty pharmacist in reducing financial toxicity for patients through clinical support.

“Adherence management, validated assessments, and clinical follow-up helps to improve health while decreasing likelihood of delaying or discontinuing treatment. Working together to clinically improve health and make therapy more manageable means less missed work, fewer hospitalizations or doctor appointments, and fewer changes in therapy,” said Oleru.

Conclusions
Women with breast cancer are facing unique financial challenges wrought by rising health care costs, increased cost-sharing, and challenges associated with the pandemic. Research indicates many of these women may not be receiving enough support around the financial impact of their cancer treatment.

Specialty pharmacies have proven their ability to positively impact outcomes for oncology patients, including financial toxicity. Coordinating support across a range of resources and stakeholders, specialty pharmacies are helping alleviate financial toxicity and lighten the burden for patients with breast cancer so they can focus on achieving better health.

References
The Pharmacology of Cutting-Edge Non-Small Cell Lung Cancer Therapies in 2021

The agents that have been evaluated and approved, and those that are coming in the pipeline, make for an exciting time to consider directed therapies.

BY ALANA HIPPENSTEELE

NON–SMALL CELL LUNG cancer (NSCLC) has become the most heterogeneous, molecularly driven cancer in therapeutics, explained R. Donald Harvey, PharmD, BCOP, FCCP, during a session at the virtual 2021 American Society of Clinical Oncology Annual Meeting. The agents that have been evaluated and approved, and those that are coming in the pipeline, make for an exciting time to consider directed therapies in NSCLC.

“Oral MET, RET, and KRAS inhibitors certainly have unique pharmacologic principles that we need to think of when these agents are selected for use, and certainly during and after use as well, as we consider mechanisms of resistance and other aspects of adverse events (AEs), drug interactions, etc,” Harvey said during the session.

Before 2020, significant expansion occurred in the field of non–small cell small molecule therapeutics around the agents being used in clinics today, Harvey explained. Epidermal growth factor receptor (EGFR) inhibition, anaplastic lymphoma kinase (ALK) inhibition, and others provided the foundation for the start to the molecularly derived and molecularly selected population of patients who may be able to be treated with small molecules.

Harvey explained that in this space, over 2020 and 2021, there were FDA approvals of 3 RET inhibitors and 2 MET inhibitors, with more potentially on the horizon in the second half of 2021. Similarly, the first KRAS G12C inhibitor was submitted to the FDA for a new drug application in late 2020, with more potentially to follow.

In terms of the clinical pharmacology characteristics of some of the small molecules, Harvey explained that it is important to note certain valuable points for both patients and practitioners to understand around these agents. For example, in the case of MET skipping variants in the exon 14 region, capmatinib (Tabrecta; Novartis) has some areas worth considering for patients and practitioners alike.

“First, it’s a twice-daily agent with or without food. It has no food effects for absorption. It is a [cytochrome P450 family 3 subfamily A (CYP3A) member 4] and P-glycoprotein substrate, and so should patients be on agents that inhibit those pathways? You need to consider capmatinib exposure and, ideally, avoid moderate and strong inducers of CYP3A as well,” Harvey said during the session.

Additionally, there are some AEs associated with capmatinib. Although it is generally well tolerated, Harvey explained that there can be some rare and serious pneumonitis and transaminitis. Although these are issues that should be monitored closely, pneumonitis and transaminitis are not considered overt or common AEs for capmatinib.

“Each of these agents does have a dose reduction and discontinuation rate. I think it’s important, when we counsel patients and think about therapy initiations, that we consider this in the background, that we may have to dose reduce in certain areas,” Harvey said during the session. “Only about 1 out of 5 patients needed to discontinue these agents within the licensing trials submitted for approval. Specifically, with capmatinib, there’s no effect of age or weight on
pharmacokinetics, and so the dose and exposure are linearly related within each of those areas.”

Additionally, Harvey noted that with tepotinib (Tepmetko; EMD Serono), an important drug interaction that practitioners should stay aware of is with dabigatran (Pradaxa; Boehringer Ingelheim), which is a P-glycoprotein substrate. Since tepotinib is a strong P-glycoprotein inhibitor, it has the potential to significantly increase dabigatran’s Cmax value, Harvey explained. Specifically, clinicians would preferably avoid concurrent use of dabigatran with tepotinib for this reason.

In the RET inhibition space, selpercatinib (Retevmo; Eli Lilly and Company) is the first agent that was approved in this class. For dosing, although selpercatinib has weight-based dosing as an option, most adults will be dosed at 160 milligrams. Additionally, although it is a CYP3A4 substrate, it may also have other CYP and transport protein substrate and interacting potential as well.

For patients treated with selpercatinib, acid-reducing agents should be avoided, Harvey noted. However, if, for example, a proton pump inhibitor is unavoidable, then selpercatinib can be taken by patients with food at least 2 hours before other antacids, outside proton pump inhibitors.

Additionally, selpercatinib has a good tolerability profile in terms of AEs. Although there are some rare but serious occurrences of transaminitis and hemorrhage, overall, the AE profile is reasonable and manageable.

Both selpercatinib and the RET inhibitor pralsetinib (Gavreto; Blueprint Medicines and Genentech) should be held for at least 7 days before elective surgery, and for about 2 weeks after surgery, so healing can occur. This healing period is necessary since RET fusion inhibitors can impair wound healing for many patients, Harvey explained.

For the RET inhibitor pralsetinib, the dosing for patients should be 400 milligrams on an empty stomach. Pralsetinib is also a CYP3A4 substrate with a good tolerability profile and low discontinuation rates. However, approximately 1 in 3 patients were found to need a dose reduction during the licensing trials that were conducted.

For the first KRAS G12C inhibitor sotorasib (Lumakras; Amgen), there is currently not much known, Harvey explained. However, it is known based on the data available that the recommended phase 2 dose and the licensing dose is 960 milligrams.

“It comes in 120 milligram sizes and so it’s 8 tablets that need to be used within that,” Harvey said. “There are ongoing questions of dosing of 240 mg vs 960 mg in a comparison trial that’s been recommended by FDA to be performed.”

For sotorasib, AEs such as diarrhea, fatigue, and nausea are known to occur, with a discontinuation rate of 7%. However, dose reduction data have not been reported.

Additionally, Harvey noted that there are resistance mechanisms that should be considered for patients who are receiving small molecule inhibitors. One resistance mechanism is within the kinase domain itself, whether that be RET, MET, or other aspects of the kinase, while another is the activation of escape alternative pathways.

“When we look specifically at MET, there’s laboratory data suggesting that EGFR activation and/or PI3 kinase upregulation may be responsible for those who develop resistance to the MET inhibitors that are approved,” Harvey said during the session. “RET inhibition, as well, has resistance pathways that need to be considered. There may be new RET mutations within the domain of the gene itself, and there may be MET gene amplifications or KRAS mutations that may lead to RET resistance clinically.”

The occurrence of KRAS G12C resistance shows how these agents work, Harvey explained. The active G12C binding of the KRAS compound to an overarching tumor cell demonstrates the active proliferation and conversion of GDP to GTP, which can go unchecked. With the addition of an inhibitor of the G12C molecule, inhibition of KRAS G12C can lead to growth arrest and subsequent cell death as the GDP-bound cells go into quiescence.

“One mechanism of resistance that’s been identified is that KRAS G12C cells may then undergo an increase in epidermal growth factor, as well as aurora kinase A expression,” Harvey said during the session. “Though those pathways may reengage in an escape mechanism, the G12C can become once again GTP-bound, rather than GDP-bound, and allow for proliferation to occur. This is one mechanism of resistance that’s been identified and there may be others that come forward.”

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FDA-Approved CAR T-Cell Therapies Offer New Treatment Opportunities for Mantle Cell Lymphoma
Between 40% and 50% of patients respond long term without relapsing.

By Aislinn Antrim

With the accelerated approval of brexucabtagene autoleucel (Tecartus; Kite Pharma, Gilead Sciences Inc) for the treatment of adults with mantle cell lymphoma (MCL),\(^1\) chimeric antigen receptor (CAR) T-cell therapies have become key treatments for various cancers, despite their high cost and other challenges, according to a presentation at the 2021 American Society of Clinical Oncology Annual Meeting.\(^2\)

CAR T-cell therapies are genetically modified immune cells, according to presenter Jason Westin, MD, MS, FACP, leader of the diffuse large B-cell lymphoma research team at the University of Texas MD Anderson Cancer Center. He said CAR T cells are usually autologous, although a new allogenic generation is in development.\(^2\)

Westin noted that 4 CAR T-cell therapies have been approved: tisagenlecleucel (Kymriah; Novartis), axicabtagene ciloleucel (Yescarta; Kite Pharma, Gilead Sciences Inc), lisocabtagene maraleucel (Breyanzi; Juno Therapeutics), and brexucabtagene autoleucel. However, Westin focused his presentation on brexucabtagene autoleucel and its approval for MCL.\(^2\)

MCL occurs in approximately 6% of all non-Hodgkin lymphomas in the United States\(^3\) and is typically defined by 11;14 translocation. It has both good and bad features, Westin said, including the fact that it is frequently sensitive to many therapeutics, but often relapses and is considered incurable.\(^2\)

Common therapies include platinum-based chemotherapies and very intensive approaches.\(^3\)

In the MCL treatment space, Westin said historic study results prior to CAR T-cell therapy were abysmal. New outcomes with CAR T cells, however, show a routine 40% to 50% of patients long term who do not relapse.\(^3\)

Brexucabtagene autoleucel, formerly known as KTE-X19, is an anti-CD19 CAR T-cell therapy, Westin said in the presentation. The ZUMA-2 trial (NCT02601313) investigated its use in adults with MCL who have relapsed or are refractory to between 1 and 5 prior therapies, including anthracycline or bendamustine, a CD20 antibody, and a Bruton tyrosine kinase (BTK) inhibitor.\(^4\)

The trial found an overall response rate of 92% for brexucabtagene autoleucel, which Westin said is remarkable. At a median follow-up of 17.5 months, 29 of 60 evaluable patients remained in ongoing responses at data cutoff, and 28 of 40 patients who achieved complete response remain in response. Notably, the median duration of response, progression-free survival, and OS have not yet been reached with a median follow-up of 17.5 months.\(^2,4\)

Westin added that adverse effects are significant, although they tend to diminish in incidence and severity the further out patients get from administration of brexucabtagene autoleucel.\(^2\) Notably, 91% of patients had any grade of cytokine release syndrome, although just 15% had grade 3 or higher.\(^4\)
Finally, Westin said brexucabtagene autoleucel should be administered only in a CAR T-cell center rather than a typical oncology clinic. He said physicians should recommend patients as early as possible in order to get an appointment, receive insurance approval, and begin the long process, which can take 17 days before the genetically modified immune cells are received.²

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New Data Show Promise for Patient Outcomes With Capmatinib

The kinase inhibitor is a promising treatment option for patients with MET exon 14 skipping mutation non–small cell lung cancer.

By Kristen Coppock, MA

New data demonstrate capmatinib (Tabrecta; Novartis) as a promising treatment option for patients with MET exon 14 skipping mutation (METex14) non–small cell lung cancer (NSCLC).¹

A kinase inhibitor, capmatinib is approved by the FDA for the treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping. This approval was based on the phase 2 GEOMETRY (NCT02414139) mono-1 study. Results of the study were presented at the virtual 2021 American Society of Clinical Oncology Annual Conference.²

The findings include data from the GEOMETRY study’s new cohort 7 and updates some previously reported analyses.¹ According to investigators, capmatinib achieved overall response rate (ORR) of 65.6% (95% CI, 46.8-81.4) in the first-line setting for cohort 7, and 67.9% ORR (95% CI, 47.6-84.1) in cohort 5b. In the second-line setting, 51.6% ORR was achieved in the new expansion cohort.¹³

Capmatinib also demonstrated a median duration of response (DOR) of 12.6 months (95% CI, 5.6-not estimable [NE]) among treatment-naïve patients in cohort 5b. DOR for treatment-naïve patients in cohort 7 is NE. Among previously treated patients, DORs of 9.7 months (95% CI, 5.613.0) and 8.4 months (95% CI, 4.2-NE) were found in cohort 4 and cohort 6, respectively.¹³

Additionally, the study found a mature median overall survival (OS) rate of 20.8 months (95% CI, 12.4-22.24) in previously treated patients in cohort 5b, and 13.6 months (95% CI, 8.61-22.24) in previously treated patients in cohort 4. Median OS for cohorts 6 and 7 are not yet reached, according to the authors.¹³

Overall, 160 patients with METex14 who received capmatinib 400 mg twice daily were analyzed. Although data for cohort 7 are still immature, the authors announced that median progression-free survival was 10.8 months (95% CI, 6.8-74.6).²

“This new analysis further supports [capmatinib] as a cornerstone targeted treatment for [patients with] METex14 NSCLC and highlights the importance of biomarker testing,” Juergen Wolf, MD, from the Center for Integrated Oncology, University Hospital of Cologne, Germany, and lead investigator of the GEOMETRY study, said in a press release.² “The impressive overall survival outcome and confirmed outstanding response in the first-line setting will help oncologists decide upon a therapeutic option for patients.”

According to investigators, the safety profile remained unchanged across all GEOMETRY study cohorts (N = 373), with 98.4% of patients reporting at least 1 adverse event (AE) (68.6% grade 3/4) regardless of causality, and 50.9% of patients reporting at least 1 serious AE. In 16.1% of patients, AEs leading to discontinuation (10.5% grade 3/4) were reported.¹³

Serious AEs reported in patients taking capmatinib include lung or breathing problems, liver problems, and risk of photosensitivity. The most commonly reported AEs (≥ 20% all grades) include swelling of the hands or feet, nausea, tiredness, weakness, vomiting, loss of appetite, and changes in certain blood tests.²

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Lung cancer is an aggressive form of cancer that is one of the leading causes of death worldwide and in the United States. This disease may affect anyone, including smokers and nonsmokers. However, the rate of cancer in those with no smoking history is lower.¹

Lung cancer was first identified in 1761 as a distinct disease, although the disease was still rare through the 19th century. In 1929, German physician Fritz Lickint first recognized the potential connection between lung cancer and smoking. The American Cancer Society linked smoking and cancer by 1954 and, a decade later, the US Surgeon General declared smoking a cause for lung and laryngeal cancers.²

Lung cancer today is the third most common cancer in the United States, after skin cancer and breast cancer among women and prostate cancer among men. That said, lung cancer causes more deaths than any other cancer in the country.³ In 2017, there were more than 220,000 new cases of lung cancer reported and about 140,000 people died of this cancer. In other words, for every 100,000 people, 55 new lung cancer cases were reported and 37 of them died of this cancer.³

Lung cancer can be divided into 2 main types: non–small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). About 85% of the lung cancers are the NSCLC type, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Such types are grouped together since their prognoses are typically similar. Adenocarcinomas start in the cells, mainly in current or former smokers, although they can also occur in nonsmokers. It is more common in men and younger populations. Squamous cell carcinoma begins in squamous cells, which line the inside airways of the lungs, near the bronchi. Large cell carcinomas can appear in any part of the lungs.⁵

SCLC occurs in about 15% to 20% of the population. This type of cancer grows faster than NSCLC and responds well to chemotherapy and radiation therapy. However, in the majority of cases, SCLC relapses. Other types of cancer may include lung carcinoid tumors, adenoid cystic carcinomas, lymphomas, sarcomas, and hamartomas.⁴

Lung cancer typically does not have any symptoms in the early stages, which present themselves in the advanced stages. These signs and symptoms may include cough, coughing up blood, shortness of breath,
In 2017, there were more than 220,000 new cases of lung cancer reported and about 140,000 people died of this cancer.

chest pain, weight loss, bone pain, headache, and hoarseness. Medications approved to treat NSCLC include paclitaxel (Abraxane; Bristol Myers Squibb), palbociclib (Ibrance; Pfizer), alectinib (Alecensa; Genentech), bevacizumab (Avastin; Genentech), carboplatin (Paraplatin; Bristol Myers Squibb), ceritinib (Zykadia; Novartis), ramucirumab (Cyramza; Eli Lilly and Company), docetaxel (Taxotere; Sanofi and Aventis), erlotinib (Tarceva; Genentech), gemcitabine (Gemzar; Eli Lilly and Company), durvalumab (Imfinzi; AstraZeneca), pembrolizumab (Keytruda; Merck), lorlatinib (Lorbrena; Pfizer), nivolumab (Opdivo; Eli Lilly and Company), alectinib (Alecensa; Genentech), vinorelbine (Navelbine; Pierre Fabre Pharmaceuticals), and ipilimumab (Yervoy; Bristol Myers Squibb).

When it comes to combination medications for non–small cell lung cancer, 2 options are carboplatin and taxol; and gemcitabine and cisplatin (Platinol; Bristol Myers Squibb). Medications approved for small cell lung cancer may include durvalumab, etoposide (VePesid; Bristol Myers Squibb), everolimus (Afinitor; Novartis), nivolumab, atezolizumab, methotrexate (Rasuvo; Medexus Pharma), and lurbinectedin (Zepzelca; Jazz Pharmaceuticals and PharmaMar).

The most recent addition to this list of medications is amivantamab (Rybrevant; Janssen), which was approved in late May 2021 by the FDA. This drug is a bispecific epidermal growth factor receptor (EGFR)-directed and mesenchymal-epithelial transition (MET) receptor-directed antibody indicated for the treatment of adult patients with NSCLC with EGFR exon 20 insertion mutations.

Amivantamab comes in a 350 mg/mg (50 mg/ml) solution, packaged in a single-dose vial. The most common adverse effects in clinical trials included rash, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. Amivantamab can also create some laboratory abnormalities, such as decreased lymphocytes, decreased albumin levels, decreased phosphate, decreased potassium, and increased alkaline phosphate levels.

With such new medications in the market adding to the variety of options for patients with diagnosed lung cancer, there is a hope for better clinical outcomes, fewer adverse effects, and better prognoses and survival for these patients. With the research advancing on lung cancer, more targeted therapies will be studied in the near future so patients suffering from this debilitating disease can benefit from their effects.

REFERENCES


In 2017, there were more than 220,000 new cases of lung cancer reported and about 140,000 people died of this cancer.
PATIENTS BATTLING CANCER should not be overlooked in any pharmacy setting. Many of these patients are in dire need of support, encouragement, and care coordination. They will endure a grueling process of coping with diagnosis, treatment, and, in cases of recovery, the fear of recurrence. All of these stages will impact the patient emotionally and physically. As the most accessible member of the health care team, the pharmacist can provide information and support that patients with cancer need to get through what might be the most challenging time of their lives. Willingness to help at this crucial time demonstrates a caring and concern that patients likely will never forget.

EM is facing many ups and downs with his treatment options and adverse effects. He presents to you a new list of medications. As the pharmacist, you scan the list and review it against EM’s medication profile and notice some changes. As you conduct your review, you see concern and stress in EM’s face. You explain the concept of pharmacy brown bag and medication therapy management sessions and ask if he would be interested. EM is interested and informs you that he will bring in all of his oral medications the following day.

EM is looking forward to the opportunity to go over his history and current medication list. He has been feeling tired and depressed on top of feeling anxious because of COVID-19. The pandemic had delayed his cancer diagnosis, a scheduled surgery, and genetic testing, in addition to keeping his young, energetic grandchildren away from him. The stress of balancing life in the COVID-19 world is overwhelming and EM feels very alone. You sympathize, offer support, and suggest EM visit you around 3 pm, which is a slower time at your pharmacy. This will allow you to provide him with the best service and safest care.

Brown Bag Consult®
Pancreatic Cancer and Mental Well-Being
The pharmacist can provide information and support that patients with cancer need to get through what might be the most challenging time of their lives.

BY JILL DRURY, PHARMD, BCOP
Many of these patients are in dire need of support, encouragement, and care coordination.

- OTC ibuprofen 200 mg as needed
- OTC loperamide as needed
- hydrocodone bitartrate-acetaminophen 5/325 mg every 4-6 hours as needed for pain
- dronabinol 2.5 mg twice daily before meals (filled at cancer clinic pharmacy)
- fentanyl transdermal patch 50 mcg/h as directed every 3 days (filled at cancer clinic pharmacy)

Your pharmacy profile:

- atorvastatin 20 mg daily
- alprazolam 0.5 mg as needed
- atenolol 25 mg daily
- hydrocodone bitartrate-acetaminophen 5/325 mg every 4-6 hours as needed for pain
- ibuprofen 600 mg twice daily
- sertraline 50 mg daily
- zolpidem 5 mg at bedtime as needed
- olaparib 300 mg twice daily

EM admits that he has started smoking again as it helps him with his pain and nerves. You advise EM about the negative impact of smoking and offer to reach out to his care team to adjust his medications for pain and anxiety. EM tells you he already has stage IV cancer and will not quit smoking. You stress the importance of proper pain and anxiety management.

EM is not consistently taking his atenolol and atorvastatin. He has not seen a cardiologist in over 2 years and he relies on his oncologist and internist for medication refill prescriptions. EM has 4 stents placed when he was in his 50s and has a strong family history of cardiac disease. You take his blood pressure and the best out of 3 reads high in the 170s. EM recently had fluctuations in cholesterol and he talks about changes in his diet. He tells you his appetite is poor and he feels that he hardly eats. EM tells you he feels nauseated and bloated after eating and that makes him feel uncomfortable, so he avoids eating.

You review EM’s dronabinol dose and offer to follow up with the cancer center dietitian for suggestions. He also admits feeling palpitations lately when he is anxious. He has cut out caffeine thinking that was the issue, but the palpitations keep occurring. You urge EM to make a follow-up appointment with his cardiologist for any necessary tests.

EM recently received his first dose of the COVID-19 vaccine and is happy to be able to start seeing his family again soon on a regular basis. He thinks that will help his mood, mobility, and outlook on life. He has been consistently taking his antidepressant medication and hopes to work with you and his care team to discontinue the medication. EM recently received his first dose of the COVID-19 vaccine and is happy to be able to start seeing his family again soon on a regular basis. He thinks that will help his mood, mobility, and outlook on life. He has been consistently taking his antidepressant medication and hopes to work with you and his care team to discontinue the medication. You acknowledge that this is a stressful time and suggest some nonpharmacological ways to reduce stress, help sleep patterns, and ultimately help his spirit. Things like starting a gratitude journal, walking, yoga, or stretching activities sound silly to EM but he acknowledges that they are all good ideas that would make him happier.

EM appreciates your help and suggestions. You offer to contact his providers for necessary follow-up and more support.

About the Author
Jill Drury, PharmD, BCOP, is a clinical pharmacy specialist in Chicago, Illinois, and Milwaukee, Wisconsin.
Advocacy Champion Works to Improve Health Care, Outcomes for Patients With Cancer

Directions in Oncology Pharmacy® is getting to know oncology pharmacy professionals through a series of interviews. In this issue, we talk to Ashley E. Glode, PharmD, BCOP, who was recently named an Advocacy Champion by the American Society of Clinical Oncology (ASCO).

ASHLEY E. GLODE is an assistant professor of pharmacy sciences at the Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Anschutz Medical Campus in Aurora, Colorado. According to the university, Glode is appointed to phase 1 clinical research trials for gastrointestinal and head and neck cancers as well as sarcoma at the University of Colorado Cancer Center. Her clinical practice and research interests lie in improving supportive care interventions and quality of life for patients who are undergoing treatment for cancer.

Q: What motivated you to become a pharmacist and to practice in the oncology space?

A: I had always been interested in health care in one form or another. My family encouraged me to pursue pharmacy, and I loved it. I enjoyed learning the science behind how the human body works and how medication can help fix any issue that arises. In my oncology course in pharmacy school, I was fascinated by the complexities of how cancer can develop and the variety of treatment options available to individualize care. Clinical rotations in school and residency further fueled this passion and, during my oncology residency, I was hooked for life.

Q: You were recently named an Advocacy Champion by ASCO and were entered into the organization’s Senator’s Club. What do these selections mean to you?

A: Being selected as an ASCO Advocacy Champion is a true honor. I can make a difference in the life of the...
“Being involved in advocacy allows me to help patients on a larger scale by educating lawmakers on important bills to improve care for patients with cancer.” —ASHLEY E. GLODE, PHARMD, BCOP

patients I see, but being involved in advocacy allows me to help patients on a larger scale by educating lawmakers on important bills to improve care for patients with cancer. Some of the important initiatives we championed were access to clinical trials for Medicaid enrollees, removal of step therapy requirements for cancer treatment, expansion of telehealth, and funding for cancer research. Being selected to the Senator’s Club is important to me, as it demonstrates my commitment to regular participation in ASCO advocacy activities. I was the only pharmacist selected for the Senator’s Club and 1 of 2 pharmacists selected as an Advocacy Champion.

Q: What do you think is the biggest challenge currently facing oncology pharmacy?
A: I think there are several challenges that impact oncology pharmacists, including burnout and the need to be better at self-care, keeping up with the rapidly evolving treatment options, and financial implications of high-cost cancer care.

Q: What is a recent advancement or success you think is going to impact the oncology pharmacy space?
A: I am really excited about the novel targeted agents being approved for patients with rare mutations. We are moving from a malignancy-specific approach to a tumor-agnostic approach, which may help more patients gain access to lifesaving therapy.

Q: What do you think will be permanently changed in pharmacy by the COVID-19 pandemic?
A: I think the use of technology and telehealth visits will remain an important tool post pandemic. Telehealth has allowed patients to be seen by pharmacists in their homes, when appropriate, allowing for more of their family and caregiver support team to be involved in their treatment discussions.

Q: What do you enjoy most about practicing in oncology pharmacy?
A: I enjoy the evolving treatment landscape and knowing that science is advancing the care I can provide to patients. I also really enjoy the team aspect of caring for patients with cancer and the collaborative multidisciplinary approach that is used to provide optimal treatment.

Q: What is one thing about you that may be unexpected to your patients and students?
A: In pharmacy school, I joined a Student Rainforest Fund trip to the Amazon rainforest. I studied with a shaman and swam with piranhas in the Amazon River.

REFERENCE
Reinforcing Pharmacist Confidence in Current and Emerging Dosing Strategies for Immune Checkpoint Inhibitors

EDUCATIONAL OBJECTIVES

At the completion of this activity, the participant will be able to:
• Compare strategies for dosing of immune checkpoint inhibitors (ICIs) with the same FDA-approved indication
• Distinguish alternative ICI dosing regimens that may be used during the COVID-19 pandemic, including extended-interval dosing regimens and lower-dose regimens
• Identify patient counseling points to set expectations for immune-related adverse events and how to manage them

TARGET AUDIENCE: Pharmacists

ACTIVITY TYPE: Application

RELEASE DATE: July 15, 2021

EXPIRATION DATE: July 15, 2022

ESTIMATED TIME TO COMPLETE ACTIVITY: 2.0 hours

FEE: This lesson is offered for free at www.pharmacytimes.org.

Background

Immune checkpoint inhibitors (ICIs) promote antitumor immunity by blocking receptors on T cells, which serve as negative regulators of immune function, namely cytotoxic T-lymphocyte-associated antigen (CTLA-4) and programmed cell death-1 (PD-1). ICIs have gained Food and Drug Administration (FDA) approval for the treatment of numerous malignancies over the past decade, fueling a renaissance in medical oncology. Treatment indications for these agents are continually expanding, and it is now estimated that more than one-third of all patients with cancer will be eligible to receive an ICI inhibitor at some point during the course of their care.

ICIs have many indications for use as monotherapy, and in recent years have also been approved for use in combination with other types of anticancer therapies. Dosing regimens for ICIs include either fixed dosing, with differing time intervals between doses. Dosing also varies based on whether these agents are FDA approved as monotherapy or as a component of combination therapy. Due to the potential advantages of fixed dosing relative to weight-based dosing, more ICI regimens using fixed dosing are under investigation. As a result, confusion may arise regarding optimal dosing selection for ICIs.

When determining an appropriate ICI dosing strategy, many factors should be considered, including exposure-safety and exposure-efficacy relationships, patient preference, patient-specific factors, such as the presence of comorbidities, including autoimmune disease, and the risk of immune-related adverse events (irAEs).

Given the use of ICIs across multiple malignancies, the increasing number of treatment indications and regimens, and their unique adverse effect (AE) profile, it is important for pharmacists to have a clear understanding of ICI dosing strategies in order to...
ensure maximum clinical benefit. This activity will examine ICI dosing across various malignancies with an evaluation of both fixed dosing versus weight-based ICI dosing, and will review different ICI dosing intervals. Using this information, pharmacists can play a key role in both identifying optimal ICI dosing strategies as well as effectively managing irAEs.

**STAR**

Which factors may lead to confusion on ICI dosing?
What should be considered for each patient when selecting an ICI dosing regimen?

*S = Stop; T = Think; A = Assess; R = Review

**Reviewing Currently Approved ICI Dosing Regimens**

*Initial Methods of Establishing ICI Dosing*

Exposure-safety and exposure-efficacy relationships are essential to evaluate and consider during the development of an anticancer therapy in order to select an appropriate dose. The primary objective of most first-in-human phase 1 clinical trials is to identify the highest dose of an investigational agent with clinically acceptable dose-limiting toxicities (DLTs), commonly referred to as the maximum tolerated dose (MTD). In oncology, the dosing strategy selected for use in later phase trials is known as the recommended phase 2 dose (RP2D). Theoretically, the RP2D for traditional cytotoxic anticancer therapies should be similar to the MTD, as drug exposure is commonly linked to both safety and efficacy. In contrast, many monoclonal antibodies, including ICIs, have lacked a close exposure-safety relationship, leading to no MTD being identified in any of the phase 1 dose-escalation studies for the ICIs currently FDA approved. This has rendered dose-finding strategies focused on MTD less useful for ICIs, and complicated the determination of an appropriate dosing strategy for these agents.

The identification of a biologically efficacious dose (BED) during early-phase drug development using an effect-marker-based strategy has been a helpful complement to MTD-based strategies in these cases. Effect markers are indicators of drug activity, and can be selected from any number of preclinically or clinically relevant attributes, including target saturation (eg, PD-1 occupancy), pharmacodynamic markers, or other objective markers of disease progression such as objective response rate (ORR) and progression-free survival (PFS). The effect-marker strategy was used in the pivotal KEYNOTE-001 trial during the development of the first FDA-approved PD-1 inhibitor pembrolizumab. This was a phase 1 dose-escalation study evaluating pembrolizumab pharmacokinetics (PK) and pharmacodynamics (PD) using interleukin-2 (IL2) stimulation as an effect marker. The BED expected to result in saturation of IL2 was predicted to be pembrolizumab 2 mg/kg every 3 weeks. This dose was shown in model-based, exposure-efficacy analysis using early clinical response measured by ORR, as well as in later clinical trials, to have equivalent clinical benefit to the maximum administered dose of 10 mg/kg every 2 weeks. Thus, for some agents an effect-marker–based strategy may be considered a viable alternative to predict an effective dose rather than the traditional MTD-based strategy.

Early phase trials of the CTLA-4 inhibitor ipilimumab identified a positive exposure-efficacy relationship between doses ranging from 0.3 mg/kg to 10 mg/kg and clinical outcomes including ORR and overall survival (OS). In contrast, anti-PD-1 and anti-PD-L1–based ICIs have generally had a flat or nonsignificant exposure-efficacy relationships with ORR over the range of doses tested, with some variation based on patient and disease characteristics. The primary exception to this rule is avelumab; avelumab demonstrated a significant correlation between area under the curve (AUC) at steady state with PFS and OS and trough concentrations at steady state with PFS and ORR, although it is possible that the analysis of these long-term steady state PK metrics may have been confounded by a potential interaction between tumor volume and reduced drug clearance with clinical response, suggesting the possibility of a more weak exposure-efficacy relationship akin to the other PD-1 and PD-L1 inhibitors.

**Reviewing ICI Dosing Strategies: Weight-Based and Fixed Dosing**

*ICI PK*
ICIs are monoclonal antibodies (mAbs), and dosing of mAbs fundamentally differs from that of cytotoxic small-molecule anticancer therapies. For many small-molecule drugs, body surface area has been used to determine dosing (eg, mg/m²), although this has not been established as a superior method of determining dose as compared with use of either lean or total body weight. Since the approval of the mAb trastuzumab, almost all mAbs have been initially dosed based on body weight (mg/kg). Historically, this dosing has been expected to correct for differences in interpatient drug distribution and elimination.

Small-molecule anticancer agents are eliminated through hepatic and/or renal clearance, which is not possible with mAbs due to their large size. mAbs such as ICIs primarily distribute to the blood plasma and extracellular fluids, then are eliminated through mechanisms unrelated to renal or hepatic function.
first mechanism, proteolytic degradation, is a nonspecific immunoglobulin G elimination pathway that engulfs the antibody into the cellular membrane and catabolizes the protein using lysosomes. This mechanism is slowed down considerably by neonatal Fc receptor expression of the antibody, resulting in prolonged elimination half-life.

The second mechanism of drug elimination is intracellular degradation, triggered by binding of the mAb to its target. Clearance via intracellular degradation is primarily determined by target receptor expression levels and target receptor saturation.

For these reasons, body weight and organ function have been found to have minimal impact on mAb PK and PD.

**Evaluating Alternate Dosing Strategies: Fixed Dosing**

Many ICIs were initially approved for use with dosing based on body weight, with the exception of atezolizumab, cemiplimab, dostarlimab, and durvalumab. (TABLE 1) Since the initial FDA approvals, body weight-based dosing has been found to play a minimal role in the interpatient variability, distribution, and clearance of ICIs, resulting in the reevaluation of weight-based dosing for many ICIs in the postmarketing setting. Newer dosing strategies have been evaluated and approved by the FDA in this setting using PK modeling of efficacy and safety with simulated exposure or early clinical response to the new regimen. The use of population PK analyses among FDA-approved mAbs is increasing, and has been used as the primary method to reevaluate ICI dosing strategies.

The primary disadvantage with simulated PK analyses for ICIs is that the relationship with clinical outcomes, including disease response and potential AEs, is not able to be assessed prospectively. Therefore, monitoring for disease progression and incidence of irAEs with fixed dosing remains important.

Fixed dosing, also known as flat dosing, has been the primary alternative dosing strategy identified for ICIs, which have a wide therapeutic index. Fixed dosing allows for increased patient flexibility and convenience, particularly for agents using

<table>
<thead>
<tr>
<th>Approval</th>
<th>Ipilimumab</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
<th>Atezolizumab</th>
<th>Durvalumab</th>
<th>Avelumab</th>
<th>Cemiplimab</th>
<th>Dostarlimab</th>
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<tbody>
<tr>
<td>Target</td>
<td>CTLA-4</td>
<td>PD-1</td>
<td>PD-1</td>
<td>PD-L1</td>
<td>PD-L1</td>
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<td>60 (first), then 30 if tolerated</td>
<td>60</td>
<td>60</td>
<td>30</td>
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<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<td>6.1</td>
<td>6.9</td>
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<td>5.6</td>
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<td>27</td>
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<td>Doses tested in early phases</td>
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<td>Up to 10 mg/kg q2wk</td>
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<td>Up to 20 mg/kg q3wk</td>
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<td>Up to 10 mg/kg q2wk</td>
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<tr>
<td>Doses of initial FDA approvals</td>
<td>3 mg/kg q3wk x 4 doses</td>
<td>3 mg/kg q2wk</td>
<td>2 mg/kg q3wk</td>
<td>1200 mg q3wk</td>
<td>10 mg/kg q2wk</td>
<td>10 mg/kg q2wk</td>
<td>350 mg q3wk</td>
<td>500 mg q3wk x 4 doses, then 1000 mg q6wk</td>
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<tr>
<td>Current approved dosing*</td>
<td>1 mg/kg q3wk</td>
<td>1 mg/kg q6wk</td>
<td>3 mg/kg q3wk</td>
<td>10 mg/kg q3wk</td>
<td>200 mg q3wk</td>
<td>840 q2wk, 1200 q3wk, 1680 q4wk</td>
<td>10 mg/kg q2wk</td>
<td>10 mg/kg q2wk, 20 mg/kg q3wk, 800 mg q2wk</td>
</tr>
</tbody>
</table>

ADCC, antibody-dependent cellular toxicity. Vss, volume of distribution at steady state.

*See package inserts for specific indications.

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extended-interval dosing. Additionally, fixed dosing may result in reduced interpatient variability as compared to historical dosing based on patient body weight.

The two first ICIs to achieve FDA approval of fixed dosing were nivolumab and pembrolizumab. The effects of body weight on clearance and elimination of pembrolizumab are minimal, and both drug exposure and distribution are similar for body weight-based dosing and fixed dosing. Body weight has more of an effect on nivolumab distribution and clearance, but nivolumab doses ranging from 1 mg/kg to 10 mg/kg have shown equal efficacy, resulting in a wide therapeutic index. Accordingly, the FDA approved fixed dosing strategies for both pembrolizumab and nivolumab in 2016.26 Fixed dosing has since been pursued and approved for all ICIs targeting PD-1 and PD-L1, in order to provide comparable clinical benefit to weight-based regimens with the potential to improve safety and patient ease (TABLE 16-11).

Unlike its PD-1 and PD-L1 counterparts, the CTLA-4 inhibitor ipilimumab is more impacted by body weight, posing a greater risk of irAEs at higher dose levels.21,22 Fixed dosing has not been pursued for ipilimumab for this reason. In fact, one of the major challenges in ICI dosing at present is determining the optimal weight-based dosing of ipilimumab when used as monotherapy or in combination therapy, with the goal of maintaining antitumor effect while simultaneously minimizing the incidence of irAEs. Apart from ipilimumab, there has been no correlation between exposure and safety with any other ICI.

Clinical Data for Fixed Dosing
Nivolumab was the first ICI to receive approval for a new fixed dosing of 240 mg every 2 weeks in September 2016 based on simulations of a population PK model. The analysis demonstrated that the overall exposure to nivolumab from fixed dosing and weight-based dosing was similar.24,25 The slight difference of less than 6% in predicted exposure between regimens was not likely to have a clinically significant effect on safety and efficacy; thus, FDA approved the new dosing.26 Nivolumab was later approved as an extended-interval dosing of 480 mg every 4 weeks in March 2018 using the same methods of PK modeling of exposure, in addition to clinical safety data in 61 patients who transitioned to the new regimen from a previously tolerated, standard dosing of 3 mg/kg every 2 weeks.27-29 The time-averaged steady state exposure of nivolumab 480 mg every 4 weeks was similar with a less than 6% difference to nivolumab 3 mg/kg every 2 weeks. There was an approximate 16% lower trough and 45% higher peak concentration at steady state with 480 mg every 4-week dosing versus 3 mg/kg every 2 weeks. Higher exposure was noted in low body weight patients (less than 70 kg), but was still predicted to be lower than the 10 mg/kg every 2-week dosing deemed safe in early phase clinical trials. In 2020, a combination regimen with fixed-dose nivolumab 360 mg every 3 weeks plus low-dose ipilimumab 1 mg/kg every 6 weeks was approved for both the first-line treatment of non–small cell lung cancer (NSCLC) and first-line treatment of unresectable malignant pleural mesothelioma.6,7 The varied dosing strategies now included in the prescribing information for nivolumab demonstrate the clinical efficacy of fixed dosing for ICIs.

In similar fashion, a population PK model using exposure-response results from patients with advanced melanoma and NSCLC was used to evaluate the potential for fixed dosing with pembrolizumab.17,30 The individual AUC distributions were compared with multiple dosing schemas from early phase trials, including 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, and 10 mg every 2 weeks, and showed similar variability at a fixed dosing strategy of 200 mg every 3 weeks. This indicated that neither dosing strategy was superior based on PK, and that a fixed dosing strategy may be appropriate for pembrolizumab. Based on these data and subsequent clinical trials using this dosing, pembrolizumab received approval by the FDA for 200 mg every 3 weeks for all indications following melanoma.31 In April 2020, the FDA granted accelerated approval to a new extended-interval dosing regimen of 400 mg every 6 weeks for pembrolizumab.32 This approval was again based on PK modeling and exposure-response analyses for the new regimen as compared with pembrolizumab at 2 mg/kg every 3 weeks, 200 mg every 3 weeks, and 10 mg/kg every 2 weeks, as well as interim results from patients enrolled in the KEYNOTE-555 trial.32 Avelumab became the first FDA-approved therapy for metastatic Merkel cell carcinoma in 2017 at a weight-based dosing of 10 mg/kg every 2 weeks, then gained its second monotherapy approval for maintenance treatment of urothelial carcinoma after first-line platinum-based chemotherapy in 2020 at a fixed dose of 800 mg every 2 weeks.10 During consideration of a fixed dosing strategy for avelumab, the 800 mg fixed dose was selected based on studies showing that the median body weight for adults with various types of cancer is approximately 80 kg.33 Using population PK models, exposure simulations used to compare this fixed-dosing strategy with the original 10 mg/kg weight-based dosing showed approximately 12% higher AUC, which was attributed to the median body weight of 70.6 kg in the sampled patients used for the exposure analysis.33 Exposure-safety simulations demonstrated a slightly higher probability of irAEs with fixed dosing (12.6% vs 11.4%), but similar probability of infusion-related reactions whether weight-based
Durvalumab was approved by the FDA in 2017 at a dose of 1500 mg every 4 weeks for extensive stage-small cell lung cancer (ES-SCLC), based on the results of the phase 3 CASPIAN trial. Approval for the extended-interval fixed dosing of 1500 mg every 4 weeks was later expanded to all indications in November 2020. The schedule of this fixed dosing applies to all patients with body weight 30 kg or more; patients weighing less than 40 kg must still use weight-based dosing as per the label. Atezolizumab, cemiplimab, and dostarlimab have never been approved for weight-based dosing for any indication.

or fixed dosing was used. Of note, avelumab has a higher probability of infusion-related reactions (IRRs) as compared with other ICIs of approximately 25%, regardless of dosing strategy. Exposure-efficacy simulations predicted a similar likelihood of objective response between either dosing strategy. Avelumab is now approved at a fixed dose of 800 mg every 2 weeks for all indications. An accelerated approval indication for previous platinum-treated urothelial carcinoma was voluntarily withdrawn in April 2021.

Dostarlimab was approved in 2020 for patients with microsatellite instability-high (MSI-H) cancer, including colorectal cancer, cervical cancer, head and neck squamous cell carcinoma, and endometrial carcinoma. However, the approval was withheld in April 2021 due to an increase in cases of colitis with severe diarrhea and severe enteritis.

### Table 2. Summary of ICI Dosing for Currently Approved Single-Agent Regimens

<table>
<thead>
<tr>
<th>ICI</th>
<th>Adult Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ipilimumab</strong></td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td>• Unresectable or metastatic: 3 mg/kg every 3 weeks for a maximum of 4 doses</td>
</tr>
<tr>
<td></td>
<td>• Adjuvant use: 10 mg/kg every 3 weeks for 4 doses, followed by 10 mg/kg every 6 weeks for up to 5 years</td>
</tr>
<tr>
<td></td>
<td>• Pediatric patients 12 years or older with unresectable or metastatic melanoma</td>
</tr>
<tr>
<td><strong>Nivolumab</strong></td>
<td>Melanoma, NSCLC, RCC, cHL, HNSCC, urethelial carcinoma, MSI-H or dMMR CRC, HCC, ESCC</td>
</tr>
<tr>
<td></td>
<td>• For most indications: 240 mg every 2 weeks or 480 mg every 4 weeks, until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td></td>
<td>• For adjuvant treatment of melanoma: until disease recurrence or unacceptable toxicity for up to 1 year</td>
</tr>
<tr>
<td></td>
<td>• Pediatric patients 12 years or older with MSI-H mCRC: flat dosing for weight over 40 kg; weight-based dosing for weight less than 40 kg</td>
</tr>
<tr>
<td></td>
<td>Note: An accelerated approval indication for refractory small cell lung cancer was voluntarily withdrawn in December 2020.</td>
</tr>
<tr>
<td></td>
<td>Note: Labeled indication for pediatric patients 12 years or older with MSI-H mCRC using weight-based dosing.</td>
</tr>
<tr>
<td><strong>Pembrolizumab</strong></td>
<td>Melanoma, NSCLC, HNSCC, cHL, PMBCL, urethelial carcinoma, MSI-H or dMMR cancer, MSI-H or dMMR colorectal cancer, gastric, esophageal, or GEJ cancer, cervical cancer, HCC, MCC, TMB-H cancer, cSCC</td>
</tr>
<tr>
<td></td>
<td>• For most indications: 200 mg every 3 weeks or 400 mg every 6 weeks, until disease progression or unacceptable toxicity, for up to 24 months</td>
</tr>
<tr>
<td></td>
<td>• For adjuvant treatment of melanoma: until disease recurrence or unacceptable toxicity for up to 1 year</td>
</tr>
<tr>
<td></td>
<td>• Use in pediatric patients with cHL, PMBCL, MCC, MSI-H cancer, and TMB-H cancer: 2 mg/kg (up to 200 mg) every 3 weeks</td>
</tr>
<tr>
<td></td>
<td>Note: An accelerated approval indication for refractory small cell lung cancer was voluntarily withdrawn in March 2021.</td>
</tr>
<tr>
<td><strong>Atezolizumab</strong></td>
<td>Urothelial carcinoma, NSCLC</td>
</tr>
<tr>
<td></td>
<td>• 500 mg every 2 weeks, 1200 mg every 3 weeks or 1680 mg every 4 weeks until disease progression or toxicity</td>
</tr>
<tr>
<td></td>
<td>Note: An accelerated approval indication for prior platinum-treated urothelial carcinoma was voluntarily withdrawn in April 2021.</td>
</tr>
<tr>
<td><strong>Durvalumab</strong></td>
<td>Stage III NSCLC after platinum-based chemoradiotherapy</td>
</tr>
<tr>
<td></td>
<td>• Weight ≥30 kg: 10 mg/kg every 2 weeks or 1500 mg every 4 weeks until disease progression or toxicity (for maximum 12 months)</td>
</tr>
<tr>
<td></td>
<td>• Weight &lt;30 kg: 20 mg/kg every 3 weeks with chemotherapy for 4 cycles, then 10 mg/kg every 2 weeks until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td></td>
<td>Note: An accelerated approval indication for previously treated urothelial carcinoma was voluntarily withdrawn in February 2021.</td>
</tr>
<tr>
<td><strong>Avelumab</strong></td>
<td>MCC, urethelial carcinoma</td>
</tr>
<tr>
<td></td>
<td>• 800 mg every 2 weeks for all indications until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td></td>
<td>• Pediatric patients 12 years or older: metastatic MCC</td>
</tr>
<tr>
<td><strong>Cemiplimab</strong></td>
<td>cSCC, BCC, NSCLC</td>
</tr>
<tr>
<td></td>
<td>• 350 mg every 3 weeks until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td><strong>Dostarlimab</strong></td>
<td>dMMR EC</td>
</tr>
<tr>
<td></td>
<td>• 500 mg every 3 weeks for 4 doses, then 1000 mg every 6 weeks until disease progression or unacceptable toxicity</td>
</tr>
</tbody>
</table>
|                      | **BCC**, basal cell carcinoma; CPS, combined positive score; cHL, classic Hodgkin lymphoma; CRC, colorectal cancer; cSCC, cutaneous squamous cell carcinoma; dMMR, deficient mismatch repair; EC, endometrial carcinoma; ES-SCLC, extensive stage-small cell lung carcinoma; GEJ, gastroesophageal; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; MCC, Merkel cell carcinoma; MSI-H, microsatellite instability-high; NSCLC, non-small cell lung cancer; PMBCL, primary mediastinal B-cell lymphoma; RCC, renal cell carcinoma; TMB-H, tumor mutation burden-high; TNBC, triple negative breast cancer.
the initial approval of atezolizumab 1200 mg every 3 weeks, a shortened-interval (840 mg every 2 weeks) and extended-interval (1680 mg every 4 weeks) dosing strategy for atezolizumab were approved by the FDA in June 2020 for all indications as monotherapy, based on PK modeling and simulations.\textsuperscript{36,37} While early phase trials used weight-based dosing for cemiplimab, it was FDA approved with fixed dosing. No dosing modifications have been made to the prescribing information for cemiplimab, thus the fixed dose of cemiplimab 350 mg every 3 weeks remains its only dosing strategy.\textsuperscript{12,38} The newest ICI, dostarlimab, was similarly approved with a single indication at a dose of 500 mg every 3 weeks for 4 doses, followed by extended-interval dosing at 1000 mg every 6 weeks.\textsuperscript{17}

**ICI Dosing Considerations**

The current dosing, frequencies, infusion duration, and total treatment duration for ICI monotherapy in adult and pediatric indications is summarized in TABLE 2.\textsuperscript{4,14} Many ICIs are now used in combination with other anticancer therapies, depending on the malignancy. Dosing frequency and timing with respect to other therapies are important considerations in combination therapy.

Certain ICIs have unique considerations for dosing, depending on the malignancy. For example, a special consideration with the PD-L1 inhibitor durvalumab is the lower threshold for dosing in patients weighing less than 30 kg in stage III NSCLC and ES-SCLC. The standard fixed dosing recommendation for most patients is durvalumab 1500 mg every 3 weeks when used with chemotherapy, and 1500 mg every 4 weeks when used as monotherapy. However, in patients with a body weight of 30 kg or less, it is recommended to use weight-based dosing of durvalumab 20 mg/kg every 3 weeks during chemotherapy cycles, and durvalumab 10 mg/kg every 2 weeks as monotherapy. Notably, durvalumab is the only ICI with a low body weight threshold for switching between fixed dosing and weight-based dosing built into the prescribing information.

**Financial Impact**

Fixed dosing has the potential to eliminate drug waste created by weight-based dosing and reduce the risk of dosing errors.\textsuperscript{30} However, in some circumstances the reference weights used for fixed dosing may differ from the mean weight of the target population being treated and result in higher economic impact than anticipated.\textsuperscript{39} Thus, strategies to minimize drug cost from ICI dosing have been proposed; namely, dose minimization, using the lesser of both weight-based and fixed-dosing strategies, and vial sharing.\textsuperscript{15,40,41} Dose minimization in the absence of vial sharing is estimated to lower nivolumab drug costs by 9% with no effect on pembrolizumab, while dose minimization plus vial sharing is estimated to lower pembrolizumab drug costs by 19% with no effect on nivolumab costs.\textsuperscript{41} Barriers to these strategies include the removal of weight-based dosing from prescribing information, policies against vial sharing, and lack of smaller vial sizes.\textsuperscript{41} The cost-effectiveness of hybrid dosing strategies may be further explored, due to the potential of reducing cost without compromising clinical outcomes.

Low-dose ICI regimens have also gained interest in an effort to optimize therapeutic efficacy, minimize adverse effects (AEs) and cost, while also improving access to care.\textsuperscript{15,46,47} Phase 1 clinical data have shown high ICI receptor saturation at much lower dose levels than currently FDA approved.\textsuperscript{15} These low-dose ICI regimens have limited data outside of phase 1 trials, although one retrospective study appeared to demonstrate clinical activity using lower doses of nivolumab.\textsuperscript{43} This study was limited by a small sample size and varying baseline characteristics between patients, and the authors concluded that prospective studies are needed before drawing conclusions on low-dose ICI efficacy.\textsuperscript{15}

**Recommendations for ICI Dosing During COVID-19**

Early in the course of the COVID-19 pandemic, patients with cancer were identified as one of the highest risk patient populations for severe complications leading to hospitalization and death due to COVID-19.\textsuperscript{44} In order to reduce the risk of exposure of these patients to SARS-CoV2 in the healthcare setting, many oncology professionals began to delay non-essential procedures, prefer virtual visits and at-home treatment, schedule less frequent in-person follow-up, and defer or discontinue systemic anticancer therapy whenever possible.\textsuperscript{14,45,46} Extended-interval ICI dosing began to receive renewed attention as a therapeutic option, allowing for both evidence-based treatment and minimal exposure to the healthcare environment. Professional societies including the National Comprehensive Cancer Network and European Society for Medical Oncology released temporary recommendations to consider the use of extended-interval ICI dosing for melanoma, NSCLC, and other cancers during the COVID-19 pandemic.\textsuperscript{2,47,48}

Due to the inflammatory nature of COVID-19, there were early concerns about the potential for irAEs to exacerbate or overlap with...
COVID-19 symptoms, leading to poor outcomes.\textsuperscript{24,44} A real-world cohort study of patients with cancer in New York found that ICI use was a predictor of severe disease and hospitalization from COVID-19.\textsuperscript{49} Case reports have also suggested the potential for ICIs to induce hyperactivation of the immune system in the form of cytokine storm, which can delay and complicate recovery from severe COVID-19.\textsuperscript{50} In contrast, the largest real-world COVID-19 patient registry study of adult patients with cancer and COVID-19 showed that those who recently had received immunotherapies were not at higher risk of overall mortality.\textsuperscript{51} Thus, although administration of an ICI may be a risk factor for severe disease, it does not appear to affect survival outcomes.\textsuperscript{49,51} Similar to the treatment of severe irAEs, prompt initiation of corticosteroids is a critical lifesaving intervention in the management of patients experiencing severe COVID-19.\textsuperscript{52} In patients who have tested positive for COVID-19, it has been recommended that treatment with ICIs be delayed until resolution of symptoms or 2 consecutive negative tests.\textsuperscript{45}

The revolutionary development and use of vaccines against COVID-19 now offers the opportunity for patients with cancer to receive protection against SARS-CoV2 and its variants. Vaccination may allow for mitigation of the potential risks of ICI therapy during the pandemic. In patient cases where the decision had been made to delay ICI therapy, vaccination may also allow for continued ICI dosing. The concern had been raised as to whether COVID-19 vaccines themselves may carry a risk of potentiating immune toxicity.\textsuperscript{53} In a real-world, short-term safety analysis of 170 patients vaccinated with the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine while being treated with an ICI, the vaccine was found to be safe and did not increase the risk of irAEs.\textsuperscript{53} Results of a recent case report described a patient with colorectal cancer who developed cytokine release syndrome (CRS) 5 days after receipt of the Pfizer-BioNTech BNT162b2 vaccine while receiving treatment with anti-PD1 monotherapy, although the relation of concomitant ICI therapy with the patient’s development of CRS remains unclear.\textsuperscript{54} Thus, although the overall risk-benefit ratio still remains firmly in favor of vaccination, more studies are needed to definitively evaluate mRNA-based COVID-19 vaccines in this population.

irAEs

\textit{Introduction to irAEs}

Immune checkpoint blockade results in activation of T cells against tumor cells, but may also result in activation against self-antigen, resulting in inflammatory AEs. These unique inflammatory effects mimic naturally occurring autoimmune disease states.\textsuperscript{3,55} The precise mechanism by which irAEs occur is unknown, but possible mechanisms include bystander effects from activated T cells, autoimmune T cells, autoantibodies, pro-inflammatory cytokines, and direct binding of ICIs to targets in normal tissue.\textsuperscript{2,56} Two recent meta-analyses showed that the overall incidence of irAEs is higher for anti-CTLA-4 antibodies than PD-1/PD-L1 inhibitors (72% vs 26.8%), and the incidence of higher-grade irAEs is also higher for anti-CTLA-4 antibodies than PD-1/PD-L1 inhibitors (24% vs 6.1%).\textsuperscript{37,58}
Combination regimens where an ICI is given with another ICI or other anticancer therapy usually result in greater overall incidence of AEs and grade 3 or 4 AEs, including irAEs. Combination PD-1 and CTLA-4 blockade poses a particularly high risk of irAEs, with up to 59% grade 3/4 AEs reported in some clinical trials. Efforts to mitigate the risk of PD-1/CTLA-4 blockade using lower doses of ipilimumab in combination with nivolumab have been somewhat successful, with lower ipilimumab dosing now approved for both metastatic renal cell carcinoma (ipilimumab 1 mg/kg every 3 weeks for 4 doses) and NSCLC (ipilimumab 1 mg/kg every 6 weeks continuously), lowering the rate of grade 3/4 AEs to 46% and 32.8%, respectively.

irAEs usually develop within the first 3 months after treatment initiation and have a later onset as compared with AEs due to chemotherapy. In some cases, irAEs may develop months or, rarely, years after ICI treatment discontinuation. The time to onset of irAEs also varies between ICI monotherapy and combination therapies. irAEs from CTLA-4 inhibitors tend to present earlier than those from PD-1/PD-L1 inhibitors, and irAEs from combination PD-1/CTLA-4 blockade present even earlier than those from monotherapies. Due to the unpredictable onset and nonspecific presentation, irAEs are notoriously difficult to diagnose and manage, and expertise in this realm is needed from pharmacists and other clinicians to promptly identify, assess, and treat these potentially life-threatening events.

Management of irAEs
Management of irAEs is a resource-intensive, multidisciplinary clinical challenge that necessitates clear and open communication between patient and providers to ensure prompt recognition, workup, diagnosis, and initiation of immunosuppression when needed. The inflammatory conditions characterized by irAEs can range from mild dermatologic rash to severe life-threatening myocarditis (FIGURE 1), so extreme care and attention to every case is warranted. Additionally, the timing of irAEs may be weeks to months after therapy initiation, as shown in FIGURE 2. The overlapping AEs of anticancer therapies used in combination regimens, as well as other nonimmune diagnoses common to patients with cancer, can greatly complicate the workup and prompt recognition of whether or not an AE is immune related. Thus, the goal of irAE management is to rapidly recognize and reverse autoimmune attack of the organ system, or in the case of endocrine irAEs, to replace what is no longer produced endogenously due to immune burnout.

In expert consensus guidelines on the management of irAEs, the grade and type of irAE dictate the most appropriate action. The general guideline-based approach to continuing, holding, or discontinuing ICI therapy for irAEs is shown in TABLE 3. Combining irAEs with other nonspecific presentation, irAEs are notoriously difficult to diagnose and manage, and expertise in this realm is needed from pharmacists and other clinicians to promptly identify, assess, and treat these potentially life-threatening events.

![FIGURE 2. ONSET OF IMMUNE-RELATED ADVERSE EVENTS](http://creativecommons.org/licenses/by-nc/4.0/).

**TABLE 3: GENERAL APPROACH TO ICI DOSING MODIFICATION DURING irAE MANAGEMENT**

<table>
<thead>
<tr>
<th>irAE grade</th>
<th>ICI therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>Consider holding ICI depending on risk</td>
</tr>
<tr>
<td>• Continue for arthritis, pruritus, rash, fatigue, mild/asymptomatic endocrine irAEs</td>
<td></td>
</tr>
<tr>
<td>• Hold if neurologic</td>
<td></td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>Hold ICI until improvement to grade ≤1</td>
</tr>
<tr>
<td>• May consider resuming anti-PD1 therapy after resolution of irAE on combination anti-CTLA-4 and anti-PD1 therapy</td>
<td></td>
</tr>
<tr>
<td>• Continue for manageable fatigue and dermatologic irAEs</td>
<td></td>
</tr>
<tr>
<td>• Consider holding ICI if arthritis, dermatologic, or lymphopenia</td>
<td></td>
</tr>
<tr>
<td>• Permanently discontinue if neurologic (hold if neuropathy)</td>
<td></td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>• May consider resuming anti-PD1 therapy after resolution of irAE on combination anti-CTLA-4 and anti-PD1 therapy</td>
<td></td>
</tr>
<tr>
<td>• Hold or consider discontinuing for fatigue, pancreatitis, arthritis, dermatologic</td>
<td></td>
</tr>
<tr>
<td>• Permanently discontinue for any myocarditis/pericarditis</td>
<td></td>
</tr>
<tr>
<td><strong>Grade 4</strong></td>
<td>Permanently discontinue</td>
</tr>
</tbody>
</table>

ICI, immune checkpoint inhibitor; irAE, immune-related adverse event.
noso suppression with high-dose corticosteroids has not been shown to worsen outcomes from ICI therapy.\textsuperscript{56,67} A notable exception to this rule is endocrinopathies, including hypophysitis. High-dose corticosteroids have not been shown to improve outcomes for these patients, and may be associated with worse prognosis.\textsuperscript{68}

Severe irAEs (grade 3 or 4) often require permanent discontinuation of ICI therapy, referral to disease subspecialists, and may frequently require secondary immunosuppressants should the irAE become refractory to high-dose corticosteroids or relapse after initial improvement.\textsuperscript{64} Severe irAEs often require longer courses of high-dose corticosteroid therapy, as well as supportive care interventions to mitigate toxicity from the immunosuppression itself. After resolution of a severe irAE, attempts to rechallenge with ICI dosing are risky and carry an approximately 50% or higher chance of a new or recurrent irAE.\textsuperscript{69}

Further ICI Considerations: Infusion Reactions, Drug Interactions

IRRs for most ICIs are generally infrequent, and thus a relatively minor challenge for the currently approved ICI agents. Due to its higher frequency of IRRs relative to other ICIs, avelumab is the only approved ICI with recommendations for premedication in the prescribing information, which include an antihistamine and acetaminophen before the first 4 infusions to prevent IRRs.\textsuperscript{10} In the case of mild or moderate IRRs, the rate of infusion can be reduced or interrupted; for severe reactions, the infusion should be discontinued. Atezolizumab should be infused over 60 minutes for the first dose, and if tolerated, followed by 30-minute infusions for subsequent doses.\textsuperscript{11} No dose modifications are recommended to mitigate the risk of IRRs from ICIs.

ICIs are not associated with significant drug–drug interactions, as these agents are cleared primarily via proteolytic degradation and intracellular degradation rather than CYP enzymatic pathways or the kidneys.\textsuperscript{16} Drugs and herbal products that interfere with immune activity should be avoided when possible, or used with caution during ICI dosing. One notable drug–herbal interaction that warrants careful consideration and further evaluation is between ICIs and cannabis, a natural immunosuppressant that has been linked in a retrospective cohort study and a prospective study to lower response rates and decrease survival during ICI therapy.\textsuperscript{70,71}

Until other studies are performed to confirm this finding, patients should be made aware of the potential risks of using medical cannabis or other cannabidiol remedies during ICI therapy.

Pharmacist Role in Caring for Patients Receiving ICI Therapy

Given the many ICI treatment regimens, pharmacists can play a key role in assisting with therapy selection based on patient specifics, including disease state, comorbid conditions, and patient preference. They can also assist with the identification

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**FIGURE 3. PHARMACIST’S ROLE IN PREVENTION AND MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS\textsuperscript{63,72}**

1. Know irAE profiles (inflamed organ systems, their presentation, and timing of onset)
2. Identify risk factors (autoimmune disease, organ transplant, combination ICI therapy, etc)
3. Educate patients (train on personal identification of irAEs at home and when to call)

1. Monitor for irAE relapse (develop monitoring plan and backup plan in case of steroid-refractory irAE)
2. Modify immunosuppressive regimen as needed
3. If resuming ICI: educate on risks of rechallenge

1. Recognize irAE potential (remind team, especially in non-oncology settings or those unfamiliar with irAEs)
2. Keep monitoring plan (follow-up on potential irAEs)
3. Review labs to distinguish irAE from non-irAE

ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; PJP, Pneumocystis jirovecii pneumonia; PPI, protein pump inhibitor; T2D, type 2 diabetes.
and management of irAEs. Pharmacists should be involved with patient counseling for ICI therapy, particularly as it relates to recognition and management of irAEs as described in FIGURE 3. By educating patients on irAE recognition, there may be a positive impact on the time to treat AEs, and improve the time to workup and initiation of immunosuppression. It is important to set appropriate expectations before the start of ICI therapy regarding potential for holding therapy or permanent discontinuation of treatment based on tolerability.

During the treatment of irAEs with high-dose corticosteroids, pharmacists can help improve compliance with therapy by designing logical steroid tapering plans, providing patients with a clear medication schedule, and educating on potential steroid-related AEs. As high-dose corticosteroid regimens are often started urgently, the supportive care needs that go along with high-dose corticosteroid therapy may be incidentally omitted. Pharmacists can help to proactively identify these needs and make therapeutic recommendations. Pharmacist interventions include Pneumocystis jiroveci pneumonia (PJP) prophylaxis recommended for patients on daily 20 mg prednisone equivalent or more for 28 days or more; ulcer/gastritis prophylaxis; sleep aids for patients with insomnia after starting corticosteroids; and insulin adjustments for patients with type 2 diabetes.

Furthermore, if secondary immunosuppressive therapy is needed for steroid-refractory irAEs, pharmacists can educate providers on evidence-based options and help guide further monitoring and therapy modifications.

Patients, caregivers, and other members of the health care team should be educated that the occurrence of irAEs in patients on ICI therapy have generally been positive prognostic indicators, with no impact of premature ICI discontinuation and immunosuppression for immune effects on overall efficacy outcomes. Pharmacists in multidisciplinary teams across the clinical spectrum can help improve team awareness of irAE risk, as well as management strategies. As the treatment of irAEs is often acute and time intensive, pharmacists are in a unique position to quickly identify, recommend, and monitor immunosuppressive regimens for patients experiencing these challenging AEs, even in the non-oncology setting. If patients are rechallenged with an ICI after irAEs have been managed and controlled, the patient should be educated on the risk of recurrent irAEs. Furthermore, other anticancer therapies used in ICI combination regimens may need to be adjusted, particularly if suspected to contribute to the AE in question.

Conclusion
Novel dosing strategies for ICI therapy are used in clinical practice, including fixed-dosing and extended-dosing intervals. Pharmacists are in a unique position to assist with therapy selection in patients receiving ICI therapy. Additionally, pharmacists can help provide education to patients, caregivers, and the health care team on the rationale for use of various dosing strategies, as well as identification and management of irAEs.

ADDITIONAL RESOURCES

- National Comprehensive Cancer Network Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities
- Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group
  - https://jitc.biomedcentral.com/articles/10.1186/s40425-017-0300-z
- The Role of Pharmacists in Managing Adverse Events Related to Immune Checkpoint Inhibitor Therapy

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POSTTEST QUESTIONS

1. Combination drug therapy with ipilimumab and nivolumab has been associated with a high incidence of immune-related adverse events (irAEs). To reduce toxicity, the labeled dosing for ipilimumab was changed in which of the following ways? Recommendation for:
   A. Increased dosing frequency
   B. Flat dosing
   C. Dose reduction
   D. Dose interruption

2. Most immune checkpoint inhibitors (ICIs) currently have FDA approval for both weight-based and flat dosing. Which agents only have approval for flat dosing?
   A. Atezolizumab, cemiplimab
   B. Dostarlimab, avelumab
   C. Ipilimumab, nivolumab
   D. Pembrolizumab, durvalumab

3. Dosing strategies for most ICIs are predicted by:
   A. Volume of distribution
   B. Biologically efficacious dosing
   C. Maximum tolerated dose
   D. Exposure-efficacy relationships

4. Compared with weight-based dosing of ICIs, fixed dosing has shown which of the following?
   A. Improved efficacy
   B. Decreased incidence of immune-related adverse events (irAEs)
   C. Comparable drug exposure
   D. Improved adherence

5. Which of the following has been observed among patients with cancer receiving ICIs during the COVID-19 pandemic?
   A. Decreased chance of contracting or spreading COVID-19
   B. Decreased risk of severe complications and death from COVID-19
   C. Increased use of extended-interval ICI dosing to reduce risk of COVID-19 exposure
   D. Increased incidence of ICI-related adverse events due to extended-interval dosing

6. IP is a 49-year-old woman receiving ICI therapy. She is interested in getting the COVID-19 vaccine. Which statement is true regarding vaccine administration? Vaccination is:
   A. Recommended for all patients, regardless of ICI therapy
   B. Not recommended due to increased incidence of irAEs
   C. Recommended after completing at least 1 month of therapy
   D. Recommended only in patients receiving extended-interval dosing

7. GO is a 45-year-old man being actively treated with pembrolizumab for melanoma. He is experiencing transaminitis. What is the most appropriate management strategy?
   A. Continue pembrolizumab.
   B. Hold pembrolizumab and dose reduce once transaminitis has resolved.
   C. Hold pembrolizumab and re-initiate at full dose once transaminitis has resolved.
   D. Discontinue pembrolizumab and do not rechallenge.

8. Which of the following is an appropriate dosing modification strategy to manage grade 3 pneumonitis from ICI therapy?
   A. Continue ICI at full dose
   B. Continue ICI at dose reduction
   C. Withhold ICI until resolution
   D. Permanently discontinue ICI

9. DS is a 72-year-old woman starting cemiplimab for metastatic non-small cell lung cancer. What counseling point should be included in her education session about potential irAEs?
   A. May be prevented with dose modifications.
   B. May be seen months after initiating therapy.
   C. May be prevented with prophylactic corticosteroids.
   D. May be mitigated through extended-interval dosing.

10. What is an important counseling point with avelumab?
    A. Premedication with an antihistamine and acetaminophen is required before the first 4 doses.
    B. Pre- and post-infusion intravenous fluids are required with each dose.
    C. Therapy should be held prior to dental procedures or surgeries.
    D. Monitoring blood pressure and heart rate is required with each dose.
Optimizing Therapy and Coordination of Care for Patients With Chronic Lymphocytic Leukemia Through Specialty Pharmacy Interventions

EDUCATIONAL OBJECTIVES
At the completion of this activity, the participant will be able to:

• Differentiate oral therapies for chronic lymphocytic leukemia (CLL) and proper treatment selection
• Determine the place of targeted treatment options in CLL therapy based on new and emerging safety and efficacy data
• Optimize an integrative approach for specialty pharmacists to manage patients with CLL

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Clinical Presentation and Current Guideline Recommendations on the Selection of Therapy
Chronic lymphocytic leukemia (CLL) is a chronic disorder manifesting as a progressive accumulation of leukemic cells in the blood, bone marrow, and lymphatic tissues.1 It is the most common adult leukemia in Western countries, accounting for 1.1% of all new cancer diagnoses, occurring in older Caucasian men most frequently.2,3 Median age at diagnosis is 70 years, and 5-year relative survival is 87%. In 2021, it is estimated that there will be 21,250 new CLL cases diagnosed, with 4320 deaths linked to CLL.3

Two historical staging systems exist for classification of patients with CLL: the Rai and Binet systems.4,5 Both systems rely on evaluation of nodal involvement and/or size along with hematologic parameters for patient classification. However, given the complexity of prognostic data available now for patients with CLL, these clinical staging symptoms are less predictive of patient outcomes.

Prognosis in patients with CLL is determined by several factors, including immunoglobulin heavy chain variable (IGHV) gene mutation status, cytogenetic abnormalities, and cell surface markers.6 Without regard to stage of CLL, a poorer prognosis and decreased survival are seen in patients with unmutated IGHV, defined as greater than or equal to 98% homology with germline gene sequence, when compared with mutated IGHV.7 Additionally, 80% of patients with untreated CLL have detectable cytogenetic abnormalities. The most common of these include deletion(13q), deletion(11q), trisomy 12, deletion(17p), and deletion(6q).8 Median survival times for these prognostic risk groups are highly variable, and range from 32 to 133 months (TABLE 1). Patients with del(17p) and del(11q) often present with more advanced disease, which results in a shorter treatment-free interval of roughly 9 months, compared with 92 months in patients with del(13q). Cell surface makers of interest include CD38, CD49b,
and ZAP-70. CD49b positivity, defined as greater than or equal to 30% expression, seems to be the strongest flow-cytometry-based predictor of outcomes, and results in both decreased treatment-free survival and overall survival (OS). Both CD38 expression (≥30%) and ZAP-70 (≥20% expression) have been shown to result in shorter progression-free survival (PFS) and OS.

Several different prognostic models have been developed and applied in an effort to better risk-stratify patients with CLL. While none of the currently available prognostic scores are optimal for predicting survival due to recent changes in the treatment landscape for CLL, including the introduction of small-molecule inhibitor therapy, they can be helpful in predicting the likelihood of needing treatment and time to treatment. The International Prognostic Index for CLL (CLL-IPI) uses TP53 and IGHV mutation status, serum beta-2 microglobulin, clinical stage, and patient age to classify patients into 4 groups (ie, low, intermediate, high, and very-high risk). Five-year OS rates are significantly different among the 4 groups at 93%, 79%, 63%, and 23%, respectively. Lastly, the International Prognostic Score for Early-stage CLL (IPS-E) can be used to predict time to first treatment in patients with asymptomatic, early-stage CLL. This tool is simple to calculate, allotting 1 point for presence of unmutated IGHV, absolute lymphocyte count higher than 15 × 10^9/L, and presence of palpable lymph nodes. The 5-year relative risk of initiating treatment in low-risk patients (score = 0) was approximately 8%, approximately 28% in intermediate risk (score = 1), and 61% in high-risk patients (score = 2-3).

Patient presentation is highly variable; as many patients are asymptomatic at time of diagnosis, a “watch and wait” approach may be used for many years. Other patients have a more aggressive disease course, with symptomatic disease necessitating treatment. Indications for treatment in CLL are many, and an elevated white blood cell count alone is generally not sufficient reason to initiate therapy. The International Workshop on CLL 2018 guidelines suggest the following parameters as indications for treatment:

- Documentation of progressive marrow failure (ie, anemia with a hemoglobin <10 grams/dL or thrombocytopenia with platelet count <100,000/mm^3)
- Progressive or symptomatic splenomegaly (≥6 cm below the left costal margin) or symptomatic lymphadenopathy (≥10 cm in longest diameter)
- Progressive lymphocytosis with greater than or equal to 50% increase over 2 months or lymphocyte doubling time less than 6 months
- Autoimmune complications (anemia or thrombocytopenia with poor response to corticosteroids)
- Symptomatic extranodal involvement
- Presence of disease-related symptoms (unintentional weight loss ≥10% of body weight in previous 6 months, significant fatigue, fever ≥100.5 °F for ≥2 weeks without evidence of infection, and/or night sweats 1 month without evidence of infection)

When deciding treatment, patient-specific factors such as age, comorbidities, and performance status should be included in the discussion. Additionally, concomitant medications and potential issues with drug interactions should be considered, as all preferred first-line agents are small-molecule inhibitors with potential for significant drug interactions. Along with presence or absence of del(17p)/TP53 mutation, these are the primary determinants in guiding optimal first-line treatment. Current treatment guidelines for CLL, as recommended by the National Comprehensive Cancer Network (NCCN), are outlined in TABLE 2. Historical data suggest that patients with del(17p) demonstrate a poorer response to traditional chemotherapy agents (eg, bendamustine), making potential therapy options more limited in this population.

### TABLE 1. FREQUENCY OF CYTOGENETIC ABNORMALITIES IN PATIENTS WITH UNTREATED CLL

<table>
<thead>
<tr>
<th>Cytogenetic abnormality</th>
<th>Prognostic risk</th>
<th>Frequency (%)</th>
<th>Median OS</th>
<th>Median treatment-free interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>• del(11q)</td>
<td>Unfavorable</td>
<td>18</td>
<td>6.6 years</td>
<td>13 months</td>
</tr>
<tr>
<td>• del(17p)</td>
<td></td>
<td>7</td>
<td>2.7 years</td>
<td>9 months</td>
</tr>
<tr>
<td>• Normal cytogenetics</td>
<td>Neutral</td>
<td>-</td>
<td>9.3 years</td>
<td>49 months</td>
</tr>
<tr>
<td>• Trisomy 12</td>
<td></td>
<td>16</td>
<td>9.5 years</td>
<td>33 months</td>
</tr>
<tr>
<td>del(13q), as a single mutation</td>
<td>Favorable</td>
<td>55</td>
<td>11.1 years</td>
<td>92 months</td>
</tr>
</tbody>
</table>

When considering treatment options for a patient with CLL, what therapies are recommended for a patient with del(17p)? Without del(17p)?

*S = Stop; T = Think; A = Assess; R = Review
Exploring Emerging Data on Novel Therapies for the Treatment of CLL

The treatment landscape for CLL has changed dramatically over the past 10 years with the introduction of small-molecule inhibitors. Ibrutinib was first approved for use in CLL, and high-level evidence exists for other therapies, including acalabrutinib and venetoclax. Zanubrutinib is listed in national treatment guidelines as an alternative option, primarily based on the level of evidence currently available to support its use.6

Ibrutinib

Ibrutinib is a first-in-class Bruton tyrosine kinase (BTK) inhibitor.14 BTK plays a key part in both B-cell receptor signaling and B-cell development. By inhibiting BTK, B-cell migration and homing mechanisms are altered, which can result in a tran-

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**TABLE 2. CURRENT TREATMENT GUIDELINES FOR CHRONIC LYMPHOCYTIC LEUKEMIA**

<table>
<thead>
<tr>
<th>Patients without del(17p)</th>
<th>First line</th>
<th>Second line and subsequent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frail with comorbidities OR aged ≥65 years and younger patients with significant comorbidities</td>
<td>Preferred: • Acalabrutinib ± obinutuzumab • Ibrutinib • Venetoclax ± obinutuzumab</td>
<td>Preferred: • Acalabrutinib • Ibrutinib • Venetoclax + rituximab • Duvelisib • Idelalisib + rituximab</td>
</tr>
<tr>
<td></td>
<td>Alternate options: bendamustine + anti-CD20 monoclonal antibody, chlorambucil + obinutuzumab, HDMP + rituximab, ibrutinib + obinutuzumab, obinutuzumab, chlorambucil, rituximab</td>
<td>Alternate options: alemtuzumab ± rituximab, chlorambucil + rituximab, reduced dose FCR or PCR, HDMP + rituximab, lenalidomide + rituximab, obinutuzumab, ofatumumab, venetoclax, zanubrutinib, dose-dense rituximab, bendamustine + rituximab, bendamustine + rituximab + ibrutinib/idelalisib</td>
</tr>
<tr>
<td>Age &lt;65 years without significant comorbidities</td>
<td>Preferred: • Acalabrutinib ± obinutuzumab • Ibrutinib • Venetoclax ± obinutuzumab</td>
<td>Preferred: • Acalabrutinib • Ibrutinib • Venetoclax + rituximab • Duvelisib • Idelalisib + rituximab</td>
</tr>
<tr>
<td></td>
<td>Alternate options: bendamustine + anti-CD20 monoclonal antibody, FCR, FR, HDMP + rituximab, ibrutinib + rituximab, PCR</td>
<td>Alternate options: alemtuzumab ± rituximab, bendamustine + rituximab, FC + ofatumumab, FCR, HDMP + rituximab, idelalisib, lenalidomide ± rituximab, obinutuzumab, ofatumumab, PCR, venetoclax, zanubrutinib, bendamustine + rituximab + ibrutinib/idelalisib</td>
</tr>
</tbody>
</table>

| Patients with del(17p) | Preferred first line: • Acalabrutinib ± obinutuzumab • Ibrutinib • Venetoclax ± obinutuzumab | Preferred second line: • Acalabrutinib • Ibrutinib • Venetoclax + rituximab • Duvelisib • Idelalisib + rituximab • Venetoclax |
| | Alternate options: • Alemtuzumab ± rituximab • HDMP + rituximab • Obinutuzumab • Zanubrutinib | Alternate options: • Alemtuzumab ± rituximab • HDMP + rituximab • Idelalisib • Lenalidomide ± rituximab • Ofatumumab • Zanubrutinib |

FCR = fludarabine, cyclophosphamide, rituximab; FR = fludarabine and rituximab; HDMP, high-dose methylprednisolone; PCR = pentostatin, cyclophosphamide, rituximab.
sient lymphocytosis as B cells are pushed out of lymph nodes and into peripheral blood. Ibrutinib was approved by the FDA in 2014 for relapsed/refractory (R/R) CLL based on results of the RESONATE trial, which demonstrated a survival benefit with ibrutinib compared with ofatumumab.15,16

Ibrutinib has also been evaluated in the R/R setting. Ibrutinib plus bendamustine and rituximab (BR) compared with BR alone was evaluated in the phase 3 HELIOS trial, enrolling 578 patients with CLL or small lymphocytic lymphoma (SLL) with 289 participants in each treatment arm.17 Patients with del(17p) were excluded because of known poor response to traditional chemotherapy agents (eg, bendamustine) as were patients with a requirement for anticoagulation, vitamin K antagonists, or strong CYP3A4/5 inhibitors. Ibrutinib was dosed at 420 mg by mouth daily. Patients were treated with 6 cycles of bendamustine intravenous (IV) (70 mg/m²/day x 2 days per cycle) and rituximab (375 mg/m² on cycle 1, day 1; 500 mg/m² on cycles 2-6, day 1). A protocol modification was made after results of the RESONATE trial were released, allowing patients receiving placebo to cross over to receive ibrutinib monotherapy; 31% of patients in the placebo arm crossed over at time of analysis. After a median follow-up of 17 months, PFS in the ibrutinib + BR arm was not reached compared with 13.3 months in the BR-alone arm (P <.0001). PFS at 18 months was 79% in the ibrutinib arm and 24% in the placebo arm (P <.001). Median OS was not reached, with no statistical difference in OS between the treatment groups. Transient cytopenias were noted in both arms, and the frequency of all-grade infection was similar with 70% in each arm. Bleeding events and atrial fibrillation were more common in those patients treated with ibrutinib (31% vs 15% and 7% vs 2%, respectively).17 Ibrutinib is now included in the NCCN guidelines as a category 1 recommendation for second-line treatment in patients without del(17p) who are unable to tolerate purine analogs or those with comorbidities (ie, creatinine clearance <70 mL/min).9

The combination of ibrutinib + rituximab was compared with FCR in previously untreated CLL in the phase 3 E1912 trial.19 This trial excluded patients with del(17p), as these patients have historically shown poor response to FCR. Patients were randomized in a 2:1 fashion to receive ibrutinib 420 mg by mouth daily and rituximab IV (cycle 2, day 1 = 50 mg/m²; cycle 2, day 2 = 325 mg/m²; cycles 3-7, day 1 = 500 mg/m²) or FCR (fludarabine 25 mg/m² IV and cyclophosphamide 250 mg/m² IV on days 1-3, with rituximab [cycle 1, day 1 = 50 mg/m²; cycle 1, day 2 = 325 mg/m²; cycles 2-6, day 1 = 500 mg/m²]) every 28 days. A total of 529 patients were enrolled, with 354 patients assigned to ibrutinib + rituximab and 175 to FCR, with a median follow-up of 33.6 months. The PFS at 3 years was 89.4% in the ibrutinib + rituximab arm compared with 72.9% in the FCR arm (P <.001); however, this difference was not maintained in those with an IGHV mutation. OS at 3 years was also noted to be higher with ibrutinib + rituximab at 98.8% versus 91.5% with FCR. The incidence of grade 3-4 AEs was roughly 80% in both arms, though the rates of grade 3-4 neutropenia (25.6% vs 44.9%) and infectious complications (10.5% vs 20.3%) were lower in the ibrutinib arm. Grade 3-4 hypertension was more common with ibrutinib (18.8%...
Most best uMRD was seen in 77% of those in PB and 60% in BM, results were seen: the overall response rate (ORR) was 96%, the study period. In the fixed-duration cohort of 159 patients, similar randomization to ibrutinib alone or ibrutinib + venetoclax, (P = .1475). For patients without confirmed uMRD and subsequent randomization to ibrutinib alone or ibrutinib + venetoclax, uMRD rates increased to 57% in PB and 54% in BM during the study period. In the fixed-duration cohort of 159 patients, similar results were seen: the overall response rate (ORR) was 96%, the best uMRD was seen in 77% of those in PB and 60% in BM, and the 24-month PFS and OS were 95% and 98%, respectively. These findings were consistent in patients with del(17p). Most AEs were mild (grade 1-2) and occurred early after initiation of combination ibrutinib + venetoclax. The most common AEs across the study period were neutropenia (33%-36%) and hypertension (6%-10%). Based on the lack of robust data, this combination has not yet been incorporated into treatment guidelines.

**Acalabrutinib**

Acalabrutinib is a second-generation BTK inhibitor, with higher BTK selectivity than ibrutinib. It does not inhibit other tyrosine kinase pathways, such as epidermal growth factor receptor, which likely contributes to a more favorable AE profile. The role of acalabrutinib in R/R CLL was investigated in the phase 3 ASCEND trial, assessing acalabrutinib monotherapy compared with investigator’s choice (IC: idelalisib-rituximab [IR] or BR). Acalabrutinib 100 mg by mouth twice daily was given until progressive disease (PD) or unacceptable toxicity. In the idelalisib and rituximab arm, patients received idelalisib 150 mg by mouth twice daily and rituximab IV (375 mg/m² on cycle 1, day 1; then 500 mg/m² IV every 2 weeks x 4 doses, and then every 3 weeks x 3 doses for a total of 8 infusions). In the bendamustine group, patients received bendamustine 70 mg/m² IV on days 1 and 2 of each 28-day cycle with rituximab (375 mg/m² on cycle 1, day 1, then 500 mg/m² on day 1 of cycles 2-6). The primary end point of the study was PFS, and 310 patients were enrolled: 155 received acalabrutinib and 155 received IC. Median age was 67 years, 78% of patients had unmutated IGHV, del(17p) was present in 16% of patients, and 24% had TP53 mutations. After a median follow-up of 16.1 months, 83% of patients treated with acalabrutinib and 56% in the IC arm were deemed to be progression free. PFS was not reached in the acalabrutinib monotherapy arm, compared with 16.5 months with IC treatment. Median OS was not reached in either group. AEs occurring in more than 20% of patients at any grade were dependent on the treatment regimen: headache in patients receiving acalabrutinib, diarrhea and neutropenia in those treated with IR, and neutropenia, infusion-related reactions (IRRs), fatigue, and nausea in patients receiving BR. Atrial fibrillation occurred in 5% of patients treated with acalabrutinib compared with 3% in the IC arm, and bleeding was also more common in acalabrutinib-treated patients (26% vs 7%).

Acalabrutinib is included in the NCCN guidelines as a category 1 treatment recommendation for second-line/subsequent therapy in patients with CLL, regardless of del(17p) status and age.

The ELEVATE-RR trial was a phase 3 study of 533 patients with high-risk, previously treated CLL, which compared acalabrutinib 100 mg by mouth twice (n = 268) with ibrutinib 420 mg by mouth daily (n = 265). The primary outcome was PFS, and median follow-up of the study was 40.9 months. Acalabrutinib was considered noninferior to ibrutinib, as both agents demonstrated a PFS of 38.4 months. Median OS was not reached. However, acalabrutinib demonstrated a better AE profile, with a lower rate of atrial fibrillation (9.4% vs 16%; P = .023), hypertension (9.4% vs 23.2%), arthralgia (15.8% vs 22.8%), and diarrhea (34.6% vs 46%). Higher rates of headache (34.6% vs 20.2%) and cough (28.9% vs 21.3%) were seen with acalabrutinib compared with ibrutinib. Rates of grade 3 or higher infection and Richter transformation were similar between arms, and fewer patients discontinued acalabrutinib due to AEs (14.7% vs 21.3%). This study confirms NCCN recommendations for acalabrutinib in the second-line or greater treatment setting.

Early data for acalabrutinib in treatment-naïve patients came from the phase 1/2 ACE-CL-001 study, which included 99 patients...
who declined treatment with chemotherapy or were considered ineligible for chemotherapy based on comorbidities. Patients with significant cardiac dysfunction, need for anticoagulant therapy, and those on acid-suppressive therapy were excluded from the trial. Initially, acalabrutinib was dosed at 200 mg by mouth daily or 100 mg by mouth twice daily in the phase 2 portion of the study, with the entire cohort transitioned to 100 mg by mouth twice daily based on drug pharmacokinetics and level of BTK occupancy. About half (47%) of patients had high-risk disease based on Rai criteria, 62% had unmutated \textit{IGHV}, and 18% had TP53 aberrations. Most patients (86%) remained on treatment at a median follow-up of 53 months. ORR was 97%, though most of these (90%) were partial responses. Diarrhea (51%), headache (45%), upper respiratory tract infection (44%), and arthralgias (42%) were the most common AEs, and all AEs decreased with longer duration of therapy. Additional AEs such as atrial fibrillation (5%), major hemorrhage (4%), hypertension (22%), and infections (84%) were noted, though most of these were grade 1-2. NCCN guidelines list acalabrutinib as a category 1 treatment option for patients with CLL in the first-line treatment setting.

Combination therapy was investigated with the phase 3 ELEVATE-TN that studied the use of acalabrutinib with or without obinutuzumab against chlorambucil and obinutuzumab in older, treatment-naïve patients. Patients older than 65 years or those aged 18 to 65 years with creatinine clearance 30 to 69 mL/min or a score of greater than 6 on the Cumulative Illness Rating Scale-Geriatric (CIRS-G) were enrolled. Notably, patients with significant cardiac disease or those receiving anticoagulation were excluded. Acalabrutinib was given at a dose of 100 mg by mouth twice daily, with a 1-month lead-in of acalabrutinib in those receiving obinutuzumab to reduce the risk of IRRs. Obinutuzumab was administered according to FDA-approved CLL dosing. Those receiving chlorambucil were treated with 0.5 mg/kg by mouth on days 1 and 15 of each 28-day cycle for 6 cycles. A total of 535 patients were randomly assigned to treatment, with 179 patients receiving acalabrutinib monotherapy, 179 patients receiving acalabrutinib and obinutuzumab, and 177 patients receiving chlorambucil and obinutuzumab. Median patient age in the trial was 70 years, with 84% of patients being older than 65. Most patients were classified as high risk or very-high risk based on their CLL-IPI score (69% and 12%, respectively). Nine percent of patients had del(17p), 18% had del(11q). \textit{TP53} mutation was seen in 11% of patients, unmutated \textit{IGHV} in 63%, and 17% of patients had a complex karyotype. Patients who demonstrated progressive disease while on chlorambucil and obinutuzumab (31%) were allowed to cross over to acalabrutinib monotherapy, which happened in 82% of those cases. After a median follow-up of 28.3 months, median PFS was not reached in the acalabrutinib combination arm compared with 22.6 months in the chlorambucil combination arm \((P < .0001)\). Estimates of PFS at 24 months were 93% with acalabrutinib and obinutuzumab, 87% with acalabrutinib alone, and 47% with chlorambucil and obinutuzumab. Median OS was not reached in any of the treatment groups. Rates of grade 3-4 neutropenia were higher in the acalabrutinib combination arm (30%), compared with 10% in the acalabrutinib-alone arm and 40% in the chlorambucil and obinutuzumab arm. Atrial fibrillation was reported in 3% of patients receiving acalabrutinib combination therapy, 4% of patients on acalabrutinib monotherapy, and 1% of patients on chlorambucil and obinutuzumab. Grade 3 hypertension rates were reported in 2% to 3% across all arms, while bleeding events were highest in the acalabrutinib combination arm (43% vs 39% vs 12%, respectively), though most were grade 1-2. Acalabrutinib with or without obinutuzumab is recommended as first-line therapy in patients with or without del(17p), regardless of age.

**Venetoclax**

Venetoclax inhibits B-cell leukemia/lymphoma 2 protein (BCL2), which is a constitutively overexpressed anti-apoptotic protein in CLL cells. The MURANO trial was an international, randomized, open-label, phase 3 trial that compared venetoclax + rituximab to BR in R/R CLL after 1 to 3 previous therapies. Venetoclax was titrated over 5 weeks due to the risk for tumor lysis syndrome, with a goal maintenance dose of 400 mg by mouth daily, continued for a total of 2 years. IV rituximab was given for a total of 6 cycles (375 mg/m$^2$ on cycle 1, day 1; 500 mg/m$^2$ on cycles 2-6, day 1). Bendamustine dosing was 70 mg/m$^2$ IV, in combination with rituximab. A total of 389 patients were enrolled in the trial, with 194 patients randomized to venetoclax + rituximab and 195 patients receiving BR. Median patient age in both treatment groups was 65 years. After a median follow-up of 23.8 months, PFS at 2 years was not reached in the venetoclax + rituximab arm compared with 17 months in the BR group. Response rates in the venetoclax + rituximab arm were higher in patients with unmutated \textit{IGHV} and \textit{TP53} mutation/del(17p), as well as MRD negativity rates. Venetoclax + rituximab is listed in NCCN guidelines as a category 1 second-line or subsequent treatment recommendation in patients without del(17p).

CLL14 was an open-label, phase 3 trial that investigated the use of fixed-duration venetoclax + obinutuzumab compared with chlorambucil + obinutuzumab in previously untreated CLL. This trial also aimed to include patients with coexisting conditions as evidenced by inclusion of patients with scores of 6 or higher on the CIRS-G or creatinine clearance less than 70 mL/minute. Patients
were randomized in a 1:1 fashion to venetoclax by mouth, started on day 22 of cycle 1 using standard FDA-approved ramp-up CLL dosing. Chlorambucil was dosed at 0.5 mg/kg by mouth on days 1 and 15. Both oral agents were administered for twelve 28-day cycles, and obinutuzumab was given for 6 cycles. A total of 432 patients were enrolled in CLL14, with 216 patients in each treatment arm. Both arms had roughly one-third of patients aged 75 years or older, about 60% of patients with unmutated IGHV, and roughly 10% with mutated TP53. Median follow-up in CLL14 was 28.1 months, and the primary outcome of PFS at 24 months was significantly higher in the venetoclax + obinutuzumab treatment arm compared with the chlorambucil-obinutuzumab–treated arm (88.2% vs 64.1%), which was also seen in patients with unmutated IGHV and TP53 mutations/deletions as in the MURANO trial. Higher rates of MRD negativity in both PB and BM were also seen in the venetoclax + obinutuzumab arm, as were higher rates of complete remission. However, OS was not different between the 2 groups. Myelosuppression was common in both arms, with grade 3-4 neutropenia occurring in about 60% of patients in each arm. Diarrhea was slightly more common in the venetoclax + obinutuzumab arm (4.2% vs 0.5%), as was detection of neoplasms (both benign and malignant, 6.1% vs 3.7%). Updated results from CLL14 demonstrated a median follow-up of 39.6 months, and PFS advantage was still maintained in the venetoclax + obinutuzumab arm compared with chlorambucil-obinutuzumab–treated patients (not reached vs 35.6 months, respectively). Venetoclax, with or without obinutuzumab, is listed as a preferred treatment regimen in those patients who are treatment naïve, with or without del(17p).6

Zanubrutinib
Zanubrutinib is a second-generation BTK inhibitor, which has demonstrated potential advantages regarding off-target effects when compared with first-generation BTK inhibitors, while maintaining clinical efficacy. Additionally, clinical trials with zanubrutinib have allowed patient participation with anticoagulant and antiplatelet medications, most of whom were not allowed in clinical trials with ibrutinib.44 Data from an international, open-label phase 1/2 study included multiple B-cell malignancies, with 122 patients with either newly diagnosed or R/R CLL or SLL.30 High-risk disease was also assessed. Zanubrutinib doses ranged from 40 mg once daily to 320 mg daily, given as 160 mg by mouth twice daily or 320 mg by mouth once daily. For the CLL group, 18% were treatment naïve and had a median follow-up of 27.2 months. The primary end point was safety and tolerability, with response rates and PFS as secondary end points. The most common any-grade AEs occurring in more than 20% of patients included contusion (46%), upper respiratory tract infection (39%), diarrhea (30%), cough (28%), headache (23%), and fatigue (20%). Neutropenia (14%), pneumonia (6%), and anemia (6%) were the most common grade 3 or higher AEs. Other AEs of interest included bleeding (57%), headache (23%), arthralgias/myalgias (19%), hypertension (8%), thrombocytopenia (6%), atrial fibrillation (3%), and major hemorrhage (2%). Treatment was discontinued in 17% of patients, most commonly due to progressive disease. After a median follow-up of 25.1 months, the ORR was 97%, though complete response rates were low (14%). Median PFS was not reached and PFS at 1 year was 97% compared with 89% at 2 years. In patients with del(17p), the ORR was 94% and PFS at 2 years was 75%. These data show the efficacy of zanubrutinib in patients with CLL, regardless of treatment history.30

Zanubrutinib has also been investigated in the international, open-label phase 3 SEQUOIA (BGB-3111-304) trial.31 Arm C specifically evaluated nonrandomized zanubrutinib treatment in patients with CLL or SLL with del(17p) who were treatment naïve. Eligible patients were aged 65 years or older or unsuitable for FCR treatment, and long-term anticoagulation was allowed. A total of 109 patients with CLL were enrolled and the median follow-up was 18.2 months. Best ORR was reported in 94.5% of patients, most of which (87.2%) were partial responses. Median PFS, duration of response, and OS were not reached. Histologic confirmation of transformation occurred in 4 patients, with a median time to disease transformation of 13.6 months. Reported AEs were similar to the phase 1/2 study.31 These data further show potential efficacy of zanubrutinib in the treatment of CLL, and led to the NCCN recommendation for zanubrutinib as a category 2A recommendation for first-line therapy in patients with CLL or SLL, regardless of treatment history.30 Additional phase 3 data for zanubrutinib were recently reported from the ALPINE study, which investigated zanubrutinib 160 mg by mouth twice daily compared with ibrutinib 420 mg by mouth daily in 652 patients with R/R CLL/SLL. An interim analysis after median follow-up of 15 months indicated an ORR of 78.3% with zanubrutinib versus 62.5% with ibrutinib (2-sided, P = .0006). Atrial fibrillation/flutter rates were significantly lower with zanubrutinib (2.5 vs 10.1%,; 2-sided, P = .0014), as were major bleeding events and AEs leading to drug discontinuation or death. Conversely, neutropenia rates were higher with zanubrutinib (28.4% vs 21.7%), though grade 3 or higher infections were lower (12.7% vs 17.9%).32 These data indicate that more selective BTK inhibition may lead to
greater efficacy, with an improved safety profile compared with less-specific BTK inhibitors. Zanubrutinib is recommended by NCCN as a second-line/subsequent treatment in patients who are intolerant to, or have a contraindication to, other BTK inhibitors.

The Role of Specialty Pharmacists in Coordination of Care

While the above oral targeted agents have been solidified as a backbone for therapy in both the front-line and R/R setting for CLL, there are many challenges for clinicians. Generally, these agents require prior authorization with most insurers, are available through limited distribution networks, and can be cost-prohibitive for many patients once authorization is obtained. Pharmacists are well-positioned to assist in managing many of these barriers.

Select patient counseling information for oral agents used in the treatment of CLL are included below as well as in TABLE 3.

1. Acalabrutinib: Acalabrutinib is a second-generation BTK inhibitor. Dosing is generally 100 mg by mouth twice daily, with or without food.
   - Common AEs include anemia, neutropenia, thrombocytopenia, headache, musculoskeletal pain, upper respiratory tract infection, and diarrhea. Less commonly, atrial fibrillation may occur. Due to bleeding risk, consider holding for minor or major surgical procedures.
   - Transient leukocytosis may occur, but is not a sign of disease progression.
   - Drug interactions include gastric acid-reducing agents, which should be avoided or staggered. Acalabrutinib should not be administered with strong CYP3A inhibitors or inducers, and dose adjustments may be recommended with other medications.

2. Ibrutinib: Ibrutinib is a first-generation BTK inhibitor. Dosing for CLL is given at a dose of 420 mg by mouth daily, with or without food, and Seville oranges/grapefruit should be avoided.
   - Like other therapies used to treat CLL, anemia, neutropenia, and thrombocytopenia are common, as are headache, fatigue, rash, musculoskeletal pain, and diarrhea. Less commonly, atrial fibrillation and hypertension may occur. Due to bleeding risk, consider holding for minor or major surgical procedures.
   - Transient lymphocytosis (increased lymphocyte count) may occur, but is not a sign of disease progression and treatment should not be discontinued.
   - Dose adjustments may be required with CYP3A inhibitors, and ibrutinib should not be administered with strong CYP3A inhibitors.

3. Venetoclax: Venetoclax is a BCL2 inhibitor. Dosing for CLL is gradually increased over 3 to 5 weeks due to the risk of tumor lysis syndrome. Venetoclax should be given with food, and Seville oranges/grapefruit/starfruit should be avoided.
   - As with other oral therapies used in the treatment of CLL, anemia, neutropenia, and thrombocytopenia are common as well as nausea, musculoskeletal pain, fatigue, cough, upper respiratory tract infection, and diarrhea. Patients should be assessed for risk of tumor lysis syndrome when initiating venetoclax.
   - Dose adjustments may be required for moderate/strong CYP3A inhibitors or P-gp inhibitors; moderate/strong CYP3A inducers should be avoided, and P-gp substrates should be given 6 hours prior to venetoclax.

4. Zanubrutinib: Zanubrutinib is a second-generation BTK inhibitor. Dosing is either 160 mg by mouth twice daily or 320 mg by mouth daily, with or without food. Capsules should not be opened, broken, or chewed.
   - Common AEs include anemia, neutropenia, thrombocytopenia, headache, anemia, rash, diarrhea, upper respiratory tract infection, bruising, and cough. Less commonly, atrial fibrillation may occur. Due to bleeding risk, consider holding for minor or major surgical procedures.
   - Dose adjustments may be required for coadministration with moderate or strong CYP3A inhibitors; coadministration with moderate or strong CYP3A inducers is not recommended.
When deciding treatment for a patient with CLL, what are considerations for choosing one therapy over another? What are the most common AEs associated with oral therapies? Additionally, patient education and monitoring are areas where pharmacists can play a key role. Many of these agents follow complex schedules of administration, as shown in Table 3.36-39 Therapies may be given in combination with IV therapies, making scheduling and coordination of care important. Pharmacists can play a key role in assuring patient understanding of therapy, and also help set patient expectations for therapy. Specifically, some medications may cause transient leukocytosis at therapy initiation. While this does not indicate a lack of response to therapy, patients should be educated that blood counts may worsen before they improve. Additionally, due to the risk of bleeding associated with the BTK inhibitors, therapy may need to be held for a period of time before and after surgical procedures. These agents can also have significant drug interactions based on their routes of metabolism. CYP3A4 is a major metabolic pathway for oral therapies used in the treatment of CLL, and review of patient medication profiles for possible CYP3A inhibitors or inducers is vital. Review for medications that may increase the risk of a known AE (eg, anticoagulation and increased risk of bleeding in a patient receiving ibrutinib) should also be completed. Additional education points include food or diet interactions, particularly with ibrutinib and venetoclax, and pill burden associated with these therapies (Table 3).
Conclusion
The treatment landscape of CLL is rapidly changing, with many novel single-agent and combination therapy regimens available, there are many nuances involved in selection of the best regimen for a patient, including preexisting medical comorbidities, potential for drug interactions, and need for dose modification of CLL-directed therapies and anticipated AEs. Pharmacists can play a key role in helping patients access these therapies and have a greater understanding of possible AEs, anticipated treatment duration (fixed duration vs indefinite), and goals of therapy.

REFERENCES
21. Wierda WG, Tam CS, Allan JN, et al. Ibrutinib (Ibr) plus venetoclax (Ven) for first-line...

INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety.
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POSTTEST QUESTIONS

1. Which factor generally imparts a good prognosis in patients with chronic lymphocytic leukemia (CLL)?
   A. Unmutated immunoglobulin heavy chain variable gene
   B. Deletion(17p)
   C. Deletion(13q)
   D. CD49b positivity

2. Which first-line treatment would be most appropriate in a 64-year-old patient with CLL with deletion 17p?
   A. Bendamustine + rituximab
   B. Acalabrutinib + obinutuzumab
   C. Fludarabine + cyclophosphamide + rituximab
   D. Ibrutinib + rituximab

3. Which of the following is an appropriate conclusion from the ALPINE trial comparing ibrutinib with zanubrutinib in patients with relapsed or refractory CLL?
   A. Progression-free survival (PFS) was improved with ibrutinib.
   B. Overall incidence of adverse effects was lower with ibrutinib.
   C. Overall response rate was improved with zanubrutinib.
   D. There was no difference in adverse effects.

4. TS is a 70-year-old man initiating second-line therapy with venetoclax for his CLL. Which counseling point is important to include in his education session?
   A. Need to minimize dairy consumption
   B. Monitoring for tumor lysis syndrome
   C. Monitoring blood pressure at home
   D. Common occurrence of alopecia

5. CS is a 75-year-old man preparing to initiate first-line therapy for CLL. He takes pantoprazole for acid reflux. Which agent should be avoided due to potential drug interactions?
   A. Acalabrutinib
   B. Ibrutinib
   C. Venetoclax
   D. Zanubrutinib

6. Which of the following would be important to include in an education session for a patient initiating ibrutinib?
   A. Bleeding risk
   B. Monitor blood glucose
   C. Need for adequate hydration
   D. To be taken with food

7. Which counseling point is important for a patient initiating zanubrutinib?
   A. Dose will be gradually increased
   B. Potential to hold prior to surgery
   C. Avoid grapefruit
   D. Prophylactic antiemetics are recommended

8. Which therapy is the most appropriate to consider for a 70-year-old patient with relapsed CLL who has a del(17p) and a history of atrial fibrillation?
   A. Bendamustine + rituximab
   B. Fludarabine, cyclophosphamide, rituximab
   C. Ibrutinib
   D. Venetoclax

9. The ELEVATE-RR trial compared acalabrutinib with ibrutinib in patients with previously treated, high-risk CLL. Which of the following was an outcome of this study? Compared with ibrutinib, acalabrutinib showed:
   A. Improved overall survival (OS)
   B. Decreased PFS
   C. Decreased incidence of atrial fibrillation
   D. Increased incidence of infection

10. Which of the following was an outcome of the CAPTIVATE study assessing ibrutinib plus venetoclax in patients with untreated CLL?
    A. PFS benefit in patients over age 75
    B. OS benefit only in those patients with del(17p)
    C. Improved disease-free survival in the fixed dose cohort
    D. Improved PFS and OS in patients with del(17p)