SUMMIT REWIND

A LOOK BACK AT KEY SESSIONS FROM THE 2022 NCODA FALL SUMMIT

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NCODA

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PROFESSIONAL STUDENT ORGANIZATION

Empowering The Future Generation of Oncology Leaders

> "Being a part of the NCODA Professional Student Organization (PSO) community is such a remarkable experience. Together, we keep each other updated and informed on current clinical oncology practices, while also providing opportunities that aid in developing leadership skills."

- Jonathan Rivera
PharmD Candidate | Class of 2023
University of North Texas Health Science Center

ABOUT PSO

Our focus is to offer an international community for healthcare students with a passion in oncology and pharmaceutical industry. The NCODA Professional Student Organization (PSO) was established for students interested in oncology, association management, healthcare advocacy and policy, and industry leadership.

PSO BENEFITS

- First professional student organization for students interested in oncology/association management/industry leadership
- Opportunities to attend NCODA international meetings
- International public presentation opportunities
- Create educational materials to help impact cancer care
- International publishing opportunities ***(ForumRewind, SummitRewind, Inspire & Oncolytics Today publications)***
- Increased networking opportunities with oncology clinical and industry professionals, and key opinion leaders
- Access to over 50+ hours of oncology video education (Student Educational Talks)
- Oncology clinical practice experience and mentorship
- Healthcare advocacy and policy experience
- Additional student opportunities:
  - 1-year post-graduate oncology fellowships
  - International elective APPE rotation in oncology
  - Participate in NCODA's international clinical oncology competition

Locations of Established PSO Chapters

FOR MORE INFORMATION OR TO SUGGEST NEW CHAPTERS
Email **Cooper Bailey** at **cooper.bailey@ncoda.org**
Scan to visit, or check out **www.ncoda.org/professional-student-organizations**

NCODA is a grassroots, not-for-profit organization, founded to strengthen oncology organizations with medically integrated pharmacy (MIP) services.

SUMMITREWIND provides summaries of key sessions from NCODA's annual Fall Summit written by members of Professional Student Organization chapters from across North America. To view slides from presentations, scan the QR code at the end of the summaries.

Notable On The Cover: (Center middle) **Neal Dave**, PharmD, Executive Director of Pharmacy Operations at Texas Oncology and the 2018 *NCODA Living the Mission Award* recipient, kicks off the 2022 Fall Summit by reading NCODA's Mission and Vision. (Center lower) **Jim Schwartz**, RPh, Corporate Pharmacy Manager at Texas Oncology and NCODA President, introduces keynote speaker, **William Roth**. (Right lower) **David Nash**, MD, MBA, Founding Dean Emeritus at Jefferson College of Public Health, provides a keynote presentation.

SUMMITREWIND is published by NCODA, Inc. and is issued annually in print and online.

An Overview of FGFR Inhibitors & Unprecedented and Unexpected: Immunotherapy in Early-Stage Rectal Cancer

PRESENTERS: **Roger Orr**, PharmD, BCOP | Florida Cancer Specialists and Research Institute; **Courtney Cavalieri**, PharmD, BCOP | Huntsman Cancer Institute

SYNOPSIS: This dual presentation discussed the current place of FGFR inhibitors and dostarlimab in oncology practice. FGFR inhibitors have been included in several clinical trials to establish their efficacy and to identify side effects. Orr discussed the treatment regimens, dosing, and patient-specific considerations for each FGFR inhibitor. Cavalieri provided an overview on colon cancer staging and current treatment regimens for patients diagnosed with early-stage rectal cancer. She then summarized the findings and implications of a study that utilized immunotherapy with dostarlimab in place of chemoradiation.

PRESENTATION: **Overview of FGFR:** FGFR inhibitors block downstream MAPK and PI3K/AKT pathways, thereby preventing tumor proliferation in patients with carcinomas. There are currently three FGFR inhibitors available, erdafitinib, pemigatinib and infigratinib (which will be discontinued in March 2023).

This drug class has some specific adverse drug events that require close monitoring by the oncology team. These include hyperphosphatemia, ocular toxicity, stomatitis, nail toxicities, palmar-plantar erythrodysesthesia and CYP3A4 interactions. Orr recommended early intervention to treat these side effects.

Dostarlimab in Early-Stage Rectal Cancer: For patients diagnosed with early-stage rectal cancer, treatment aims to cure. While being cured is a reasonable outcome, therapy comes with long-term complications and toxicities. Treatment typically consists of surgery, radiation and chemotherapy. A new study looked at a small group of early-stage rectal cancer patients who had dMMR-MSI-H disease using dostarlimab as a neoadjuvant therapy. After six months of dostarlimab, the patients underwent a standard long course of chemoradiation. Remarkably, after treatment, 100% of these patients were cured and did not have to undergo further treatment. This discovery will need further investigation, but gives hope to rectal cancer patients.

TAKEAWAY POINTS:

- FGFR inhibitors have a unique set of side effects that require frequent monitoring, but they are manageable with appropriate interventions.
- In a new study, dostarlimab treatment for six months provided a 100% cure rate for patients with early-stage rectal cancer.

Summary by **Lola Botero**, PharmD Candidate (2024), University of Arizona.

Scan the QR codes at right to view slides from presentations.

Resources for Nurses to Improve Patient's Compliance and Adherence to Oral Oncolytic Regimens

PRESENTERS: **April Hallatt**, BSN, RN, OCN | Indiana University Health Ball Memorial Cancer Center; **Amanda McCauley**, BSN, RN, OCN | Norton Cancer Institute

SYNOPSIS: McCauley detailed a number of resources available for nurses to best support patient adherence to oral oncolytic regimens. She delivered an in-depth review of the NCODA website, giving particular attention to the "Resources" tab. Hallatt then outlined the relevance and importance of patient adherence for treatment success. She summarized different factors that can contribute to poor adherence, followed by defining clinician-patient based interventions to promote adherence.

PRESENTATION: McCauley discussed the tabs on the NCODA website, including "Events," "Accreditation" and "NCODA University." Her main emphasis was placed on the Resources tab as she highlighted key member resource offerings, including Treatment Support Kits (TSKs). TSKs allow clinicians to provide their patients with a comprehensive set of products and educational materials to best manage adverse events during oral anticancer treatment. Further patient education can be obtained through the Oral Chemotherapy Education (OCE) library. NCODA CONNECT is a virtual platform that allows members to participate in committees and share insights, as well as access medication tracking forms and patient follow-up templates.

Hallatt shifted gears by distinguishing *compliance* from *adherence*. She emphasized the negative connotation compliance can carry as it implies obedience to the healthcare practitioner. Instead, she encouraged using adherence as the word of choice. She quoted the World Health Organization, stressing "adherence is the single most important modifiable factor that compromises treatment outcomes." Promotion of self-efficacy and resilience are strategies clinicians can use to maximize patient adherence. Moreover, nurturing honest and accessible communication through telehealth, mobile applications and patient support programs will ensure patients are comfortable conveying their needs.

DISCUSSION:

Q: Who contributes to the writing of the OCE sheets?

A: They are a collaboration between nurses, pharmacists and pharmacy technicians.

TAKEAWAY POINTS:

- Proper medication adherence is enabled by collaboration between patient and clinician.
- Promotion of self-efficacy and resilience are proactive interventions to best support a patient's care.

Summary by **Brandon Handfield**, PharmD Candidate (2023), University of Toronto.

SESSION SLIDES: Scan the QR code at right to view slides from this presentation.

The Roles of Pharmacy Technicians in Patient Care & Healthcare Leadership Within the Pharmacy

PRESENTERS: Ericka Valdez | Texas Oncology; **Ashley Kohler-Gerber**, CPhT, CSPT | American Oncology Network

SYNOPSIS: Valdez discussed how pharmacy technicians are uniquely qualified to serve the role of clinical research coordinators (CRC).

Kohler-Gerber discussed leadership opportunities for pharmacy technicians, including nontraditional roles.

PRESENTATION: Valdez discussed the role of a clinical research coordinator (CRC) by presenting their responsibilities and how CRCs fit into the process of clinical trials. She explained that pharmacy technicians can serve as a CRC, and why they are qualified to fill this role.

As a CRC, pharmacy technicians need to understand the complete process of a clinical trial. This includes working with other healthcare providers, following protocols, monitoring patient safety and helping the entire team work in unison for a successful clinical trial.

Valdez concluded by reiterating that these specific skills that pharmacy technicians possess are why she believes they can transition and excel in the role of a CRC.

Kohler-Gerber explained why pharmacy technicians are necessary and important to the healthcare team, including the value they add to patient care, and how pharmacy technicians can expand their career within pharmacy.

She outlined her own journey into a leadership role within the pharmacy technician field, but noted that not every pharmacy technician path will be the same.

She said expanding into a leadership role does not always specifically mean management and provided some examples. These included pharmacy technicians sitting on state boards of pharmacy and specializing in billing and reimbursement.

She also discussed qualities that she believes pharmacy technicians should have that will help them grow into leadership roles.

TAKEAWAY POINTS:

- Pharmacy technicians are qualified to serve as CRCs and taking on the role can be a great path for pharmacy technicians to expand their careers.
- There are numerous ways pharmacy technicians can expand into leadership roles. These opportunities can vary based on practice setting and personal interests.

Summary by **Parker Lenheiser**, PharmD Candidate (2024), Texas Tech University.

Scan the QR codes at right to view slides from presentations.

What Color Bag is Best? A Practical Review of White, Brown, Clear and Gold Bagging

PRESENTER: Jorge Garcia, PharmD, MS, MHA, MBA, FACHE | Miami Cancer Institute/ Baptist Health South Florida

SYNOPSIS: Garcia reviewed the definitions of different "bagging" models and their impact on the health system's medication distribution process. After discussing the operational, quality and safety barriers of white bagging and brown bagging, he summarized key emerging regulations and provider mitigation strategies to resolve concerns associated with these models.

PRESENTATION: White bagging and brown bagging describe the processes of delivering healthcare-administered medications from an external payer-restricted specialty pharmacy to the healthcare provider (white bagging) or to the patient, who then brings the medication to the provider for administration (brown bagging).

Garcia said payers adopt these strategies as cost-saving initiatives that may present better convenience for the patient. However, from the health system's perspective, these practices lead to fragmentation of care, bypass operational and clinical safety checks, and raise concerns for supply chain integrity and patient safety. The lack of ability to control product quality, handling and turnaround time results in treatment delay, increased provider liability and compromised patient safety.

In addressing solutions to these challenges, Garcia cited letters submitted by professional health system organizations to regulatory bodies regarding the safety concerns associated with white and brown bagging. Garcia also highlighted that a number of states are in the process of passing regulations to limit payer-mandated white and brown bagging practices. Lastly, he discussed health system and provider mitigation strategies, including joining advocacy efforts and shifting towards clear bagging and gold bagging, where medications are dispensed in the health system's internal specialty pharmacy to ensure delivery of quality pharmaceutical care.

TAKEAWAY POINTS:

- Increasingly prevalent payer-mandated brown and white bagging practices bypass health systems' safety checks and raise concerns for patient safety, drug chain of custody and quality of care.
- Regulations are emerging at the state level to address the safety concerns of white and brown bagging.
- Clear bagging and gold bagging may serve as alternatives to improve health systems' ability to control the distribution process and maintain the quality of care.

Summary by **Cindy Chan**, PharmD Candidate (2024), University of Minnesota.

SESSION SLIDES: Scan the QR code at right to view slides from this presentation.

Addressing Burnout, Retention and Engagement in Oncology Practices Today

PRESENTER: Stephanie Broussard, MSSW, LCSW-S, APHSW-C | Texas Oncology

SYNOPSIS: Broussard discussed how fundamental self-care is essential to any individual aiming for long-term success and prosperity. Working conditions have a well-known impact — either positive or negative — on employee health.

Broussard emphasized that everyone, regardless of career or background, is susceptible to burnout and they need to know what can be done to prevent it.

PRESENTATION: Broussard defined burnout as "feelings of depletion, exhaustion, isolation, negativism and cynicism of your job, along with fantasies of escape." Despite burnout being present long before the COVID-19 pandemic, this catastrophe exacerbated occupational stress on healthcare workers on a global level.

According to Broussard, although self-care is becoming more recognized as a necessity by organizations to prevent burnout, they tend to implement strategies that either don't really benefit their employees, or the needs of their employees are too expensive to provide.

Healthcare professionals must proactively protect their mental well-being so that they're capable of helping others. This led to the creation of **The Emotional PPE Project**. Just as healthcare workers need physical personal protective equipment (PPE) to keep them physically safe, there must be protective processes in place to protect their mental health. Along with implementation of personal defense mechanisms, organizations need to make more of an effort to show their employees that they are valued.

In essence, when addressing burnout, prevention is key. Broussard stressed the importance of maintaining balance of eight critical dimensions of wellness: intellectual, sensual, nutritional, spiritual, physical, contextual, relational and emotional domains. Mastering this balance allows you to prioritize pivotal principles, beliefs, and values that give purpose to our life.

Equally as important, organizations must begin to tie in a culture of self-care and well-being to the company's core values and beliefs.

TAKEAWAY POINTS:

- The COVID-19 pandemic showed that healthcare workers are valuable to our society, but it didn't show them that they are valued.
- Everyone needs to establish a self-care plan surrounding the eight dimensions of wellness, as well to as practice emotional PPE.

Summary by **Reem Holozadah**, PharmD Candidate (2024), Northeast Ohio Medical University.

SESSION SLIDES: Scan the QR code at right to view slides from this presentation.

Thanatology for Oncology Healthcare Professionals

PRESENTER: Robert Mancini, PharmD, BCOP, FHOPA | St. Luke's Cancer Institute

SYNOPSIS: Mancini presented on thanatology — the study of death and the practices associated with it — and how it applies both academically and clinically in a healthcare setting.

PRESENTATION: Mancini emphasized the importance of understanding how to communicate with others when going through a tragic event. "All healthcare professionals are death educators and we never stop teaching this subject," he said.

Not only does thanatology effect patients, but also the healthcare team as well through related guilt or blame that they put on themselves. Healthcare professionals often feel that they failed to cure the patient, made the wrong medical decision or made things worse.

"When it comes to dealing with death or grief in a healthcare setting, it's okay to feel, to cry, to be sad," Mancini said. In order to heal, he emphasized that it's extremely important to rely on your co-workers, take breaks and talk to others.

Mancini stated that while 95% of nursing and medical schools teach about the topic of thanatology, only 68% of pharmacy schools include some form of death education. Most pharmacists feel that they are not prepared for the end-of-life care conversation with patients, and they often rely heavily on their peers — nurses and doctors — to help them through it. He noted that 93% of pharmacists said their pharmacy degree did not prepare them for these types of interactions.

Mancini said that the topic of death is discussed almost every day in a healthcare setting, and every professional should be able to communicate with the patient and their family about what is going to happen, as well as be able to walk them through the process. Both patients and their families will turn to anyone they can during this difficult time. This is a skill that every healthcare professional needs to learn when they're going through their respective schooling.

TAKEAWAY POINTS:

- It is important that healthcare professionals understand how to communicate with others through a tragic event.
- Healthcare teams should rely on each other, take breaks and talk to one another in order to heal.
- Education about end-of-life care conversations should be taught in pharmacy school in order for pharmacists to feel that they are prepared for those discussions.

Summary by **Shannyn Gilchrist-Oates**, PharmD Candidate (2024), University of North Texas Health Science Center.

SESSION SLIDES: Scan the QR code at right to view slides from this presentation.

Addressing Financial Assistance Obstacles to Support Patient Advocacy

MODERATOR: Caitlyn Boltik, CPhT | Riverside Regional Medical Center

PRESENTER: Rich Citrenbaum, PharmD | Patient Access Network (PAN) Foundation; **Tim Limback** | Sanofi; **Deanna Schaffner** | Exelixis

SYNOPSIS: Charitable foundation grants and patient assistance programs (PAPs) were reviewed as well as barriers to financial assistance. Discussion on how to overcome the barriers followed.

PRESENTATION: Citrenbaum outlined the 21 oncology funds that the PAN Foundation supports. He encouraged everyone to take advantage of funds for all types of cancer. Some do not run out of money the way others do, but PAN's FundFinder (**fundfinder.panfoundation.org**) can be used to track funding status for nine charitable organizations. A new transportation fund has been launched to assist patients with the cost of traveling and can cover hotel stays.

Schaffner explained how the Medicare Part D "donut hole" places an enormous burden on patients. Patients should be told that high out-of-pocket costs will subside once catastrophic coverage kicks in. Foundation grants can help with high out-of-pocket costs, while PAPs can help with the donut hole and deductible.

Prior authorization (PA) was discussed as one of the largest barriers. It is important to know that some manufacturers provide appeal letters to make the appeal process easier. PAPs usually require a PA denial and one appeal denial, but some require multiple appeal denials.

Limback addressed that most foundations have a 90-day look back period, which he encouraged use of for retrospective patient reimbursement. He encouraged attendees to enroll and renew patients online in an effort to expedite the process and reserve phone access to those who absolutely need it.

DISCUSSION:

Q: (For Schaffner) How long is the turnaround time once a PAP application is submitted?

A: I can only speak for my company (Exelixis), but we try to get patients turned around within 48 hours.

TAKEAWAY POINTS:

- Free trials and samples are commonly available to patients as a bridge or short-term solution.
- If a patient is denied because of income for foundations, they may still qualify for PAPs.
- Patients can obtain a second grant from the PAN foundation if the original grant is depleted.

Summary by **Sarah Gillaspie**, PharmD Candidate (2024), Virginia Commonwealth University.

SESSION SLIDES: Scan the QR code at right to view slides from this presentation.

WHAT COULD THE CHANCE FOR A **PROGRESSION-FREE AND TREATMENT-FREE PERIOD** MEAN FOR YOUR PATIENTS WITH CLL/SLL?

Indication

- VENCLEXTA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

- **VEN+G regimen: Designed to be completed after 12 months** (twelve 28-day treatment cycles): GAZYVA® (obinutuzumab) is administered in Cycles 1–6, and VENCLEXTA is taken orally 400 mg/day from Cycle 3, Day 1, after the first two cycles of GAZYVA and the 5-week VENCLEXTA dose ramp-up[1]

- **VEN+R regimen: Designed to be completed after 24 months** (twenty-four 28-day treatment cycles after the 5-week VENCLEXTA dose ramp-up): rituximab is administered in Cycles 1–6; VENCLEXTA is taken orally 400 mg/day from Cycle 1, Day 1 of rituximab through Cycle 24[1]

- **CLL14 trial design and primary endpoint:** In a randomized clinical trial of 432 patients (VEN+G: N=216; GClb: N=216) with previously untreated CLL and with a median follow-up of 28 months (range: 0–36 months), **VEN+G reduced the risk of progression or death by 67% vs GClb (HR=0.33; 95% CI: 0.22–0.51 [*P*<0.0001]). Median PFS was not reached in either arm**[1]

- **MURANO trial design and primary endpoint:** In a randomized clinical trial of 389 patients (VEN+R: N=194; BR: N=195) with previously treated CLL and with a median follow-up of 23.4 months (range: 0–37.4+ months), **VEN+R reduced the risk of progression or death by 81% vs BR (HR=0.19; 95% CI: 0.13–0.28 [*P*<0.0001]). Median PFS not reached in VEN+R vs 18.1 months in BR (95% CI: 15.8–22.3)**[1]

VEN+G=VENCLEXTA + GAZYVA; VEN+R=VENCLEXTA + rituximab; GClb=GAZYVA + chlorambucil; HR=hazard ratio; CI=confidence interval; PFS=progression-free survival; BR=bendamustine + rituximab; 1L=first line; R/R=relapsed/refractory.

Important Safety Information

Contraindication

- Concomitant use of VENCLEXTA with *strong* CYP3A inhibitors at initiation and during ramp-up phase is contraindicated in patients with CLL/SLL due to the potential for increased risk of tumor lysis syndrome (TLS).

Tumor Lysis Syndrome

- Tumor lysis syndrome, including fatal events and renal failure requiring dialysis, has occurred in patients treated with VENCLEXTA.
- VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS at initiation and during the ramp-up phase in all patients, and during reinitiation after dosage interruption in patients with CLL/SLL. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENCLEXTA and at each dose increase. TLS, including fatal cases, has been reported after a single 20 mg dose.
- In patients with CLL/SLL who followed the current (5 week) dose ramp-up and the TLS prophylaxis and monitoring measures, the rate of TLS was 2% in the VENCLEXTA CLL/SLL monotherapy trials. The rate of TLS remained consistent with VENCLEXTA in combination with obinutuzumab or rituximab. With a 2- to 3-week dose ramp-up and higher starting dose in patients with CLL/SLL, the TLS rate was 13% and included deaths and renal failure.
- The risk of TLS is a continuum based on multiple factors, particularly reduced renal function, tumor burden, and type of malignancy. Splenomegaly may also increase the risk of TLS in patients with CLL/SLL.
- Assess all patients for risk and provide appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases. Interrupt dosing if needed; when restarting VENCLEXTA follow dose modification guidance in the Prescribing Information.
- Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, which may increase the risk of TLS at initiation and during the ramp-up phase, and requires VENCLEXTA dose reduction.

Neutropenia

- In patients with CLL, Grade 3 or 4 neutropenia developed in 63% to 64% of patients and Grade 4 neutropenia developed in 31% to 33% of patients when treated with VENCLEXTA in combination and monotherapy studies. Febrile neutropenia occurred in 4% to 6% of patients.
- Monitor complete blood counts. Interrupt dosing for severe neutropenia and resume at same or reduced dose. Consider supportive measures including antimicrobials and growth factors (e.g., G-CSF).

Infections

- Fatal and serious infections such as pneumonia and sepsis have occurred in patients treated with VENCLEXTA. Monitor patients for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and 4 infection until resolution and resume at same or reduced dose.

Immunization

- Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery occurs. Advise patients that vaccinations may be less effective.

Embryo-Fetal Toxicity

- VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment and for 30 days after the last dose.

Increased Mortality in Patients with Multiple Myeloma when VENCLEXTA is Added to Bortezomib and Dexamethasone

- In a randomized trial (BELLINI; NCT02755597) in patients with relapsed or refractory multiple myeloma, the addition of VENCLEXTA to bortezomib plus dexamethasone, a use for which VENCLEXTA is not indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with VENCLEXTA in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.

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With **fixed-duration VENCLEXTA** regimens, offer your patients the **power to stop treatment** and the chance for:

A TARGET STOP DATE	• VENCLEXTA-based regimens give patients a target treatment completion date[1] • A defined end to treatment that encourages compliance and optimizes clinical outcomes[2,3]
LIMITED TIME ON TREATMENT	• No additional VENCLEXTA regimen exposure after completing treatment[1]
A TREATMENT-FREE PERIOD	• Fixed duration offers patients a return to life without a daily reminder of their treatment and disease
FIXED TREATMENT, FIXED COST	• No additional VENCLEXTA regimen patient out-of-pocket costs after completing treatment per the recommended dosing*

*Coverage and patient out-of-pocket costs for VEN+G and VEN+R vary by health plan. Patients may still incur out-of-pocket costs for other treatments or tests as directed by their healthcare providers.

To learn more, scan the code or visit **VENCLEXTAHCP.COM/CLL**

Explore over 5 years of follow-up data for VENCLEXTA in both 1L and R/R CLL

Adverse Reactions

- **In patients with CLL receiving combination therapy with obinutuzumab,** serious adverse reactions were most often due to febrile neutropenia and pneumonia (5% each). The most common adverse reactions (≥20%) of any grade were neutropenia (60%), diarrhea (28%), and fatigue (21%). Fatal adverse reactions that occurred in the absence of disease progression and with onset within 28 days of the last study treatment were reported in 2% (4/212) of patients, most often from infection.
- **In patients with CLL receiving combination therapy with rituximab,** the most frequent serious adverse reaction (≥5%) was pneumonia (9%). The most common adverse reactions (≥20%) of any grade were neutropenia (65%), diarrhea (40%), upper respiratory tract infection (39%), fatigue (22%), and nausea (21%). Fatal adverse reactions that occurred in the absence of disease progression and within 30 days of the last VENCLEXTA treatment and/or 90 days of the last rituximab were reported in 2% (4/194) of patients.
- **In patients with CLL/SLL receiving monotherapy,** the most frequent serious adverse reactions (≥5%) were pneumonia (9%), febrile neutropenia (5%), and sepsis (5%). The most common adverse reactions (≥20%) of any grade were neutropenia (50%), diarrhea (43%), nausea (42%), upper respiratory tract infection (36%), anemia (33%), fatigue (32%), thrombocytopenia (29%), musculoskeletal pain (29%), edema (22%), and cough (22%). Fatal adverse reactions that occurred in the absence of disease progression and within 30 days of venetoclax treatment were reported in 2% of patients in the VENCLEXTA monotherapy studies, most often (2 patients) from septic shock.

Drug Interactions

- Concomitant use with a P-gp inhibitor or a strong or moderate CYP3A inhibitor increases VENCLEXTA exposure, which may increase VENCLEXTA toxicities, including the risk of TLS. Consider alternative medications or adjust VENCLEXTA dosage and monitor more frequently for adverse reactions. Resume the VENCLEXTA dosage that was used prior to concomitant use of a P-gp inhibitor or a strong or moderate CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.
- Patients should avoid grapefruit products, Seville oranges, and starfruit during treatment as they contain inhibitors of CYP3A.
- Avoid concomitant use of strong or moderate CYP3A inducers.
- Monitor international normalized ratio (INR) more frequently in patients receiving warfarin.
- Avoid concomitant use of VENCLEXTA with a P-gp substrate. If concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before VENCLEXTA.

Lactation

- Advise women not to breastfeed during treatment with VENCLEXTA and for 1 week after the last dose.

Females and Males of Reproductive Potential

- Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for 30 days after the last dose.
- Based on findings in animals, VENCLEXTA may impair male fertility.

Hepatic Impairment

- Reduce the dose of VENCLEXTA for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more frequently for adverse reactions. No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Please see Brief Summary of full Prescribing Information on the following pages.

References: 1. VENCLEXTA Prescribing Information. **2.** Greer JA, Amoyal N, Nisotel L, et al. A systematic review of adherence to oral antineoplastic therapies. *Oncologist*. 2016;21(3):354-376. **3.** Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. *CA Cancer J Clin*. 2009;59(1):56-66.

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US-VENC-220303/October 2022

VENCLEXTA®
venetoclax tablets 10mg, 50mg, 100mg

VENCLEXTA® (venetoclax tablets)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

VENCLEXTA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Acute Myeloid Leukemia

VENCLEXTA is indicated in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

CONTRAINDICATIONS

Concomitant use of VENCLEXTA with *strong* CYP3A inhibitors at initiation and during the ramp-up phase is contraindicated in patients with CLL/SLL due to the potential for increased risk of tumor lysis syndrome *[see Drug Interactions]*.

WARNINGS AND PRECAUTIONS

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in patients treated with VENCLEXTA *[see Adverse Reactions]*.

VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS at initiation and during the ramp-up phase in all patients, and during reinitiation after dosage interruption in patients with CLL/SLL. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENCLEXTA and at each dose increase. TLS, including fatal cases, has been reported after a single 20 mg dose of VENCLEXTA.

In patients with CLL/SLL who followed the current (5-week) dose ramp-up and the TLS prophylaxis and monitoring measures, the rate of TLS was 2% in the VENCLEXTA CLL/SLL monotherapy trials. The rate of TLS remained consistent with VENCLEXTA in combination with obinutuzumab or rituximab. With a 2- to 3-week dose ramp-up and higher starting dose in patients with CLL/SLL, the TLS rate was 13% and included deaths and renal failure *[see Adverse Reactions]*.

In patients with AML who followed the current 3-day ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 1.1% in patients who received VENCLEXTA in combination with azacitidine (VIALE-A). In patients with AML who followed a 4-day ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 5.6% and included deaths and renal failure in patients who received VENCLEXTA in combination with low-dose cytarabine (VIALE-C) *[see Adverse Reactions]*.

The risk of TLS is a continuum based on multiple factors, particularly reduced renal function, tumor burden, and type of malignancy. Splenomegaly may also increase the risk of TLS in patients with CLL/SLL.

Assess all patients for risk and provide appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases. Interrupt dosing if needed; when restarting VENCLEXTA, follow dose modification guidance *[see Dosage and Administration in the full Prescribing Information and see Use in Specific Populations]*.

Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, which may increase the risk of TLS at initiation and during the ramp-up phase of VENCLEXTA. For patients with CLL/SLL, coadministration of VENCLEXTA with strong CYP3A inhibitors at initiation and during the 5-week ramp-up phase is contraindicated *[see Contraindications]*. For patients with AML, reduce the dose of VENCLEXTA when coadministered with strong CYP3A inhibitors at initiation and during the 3- or 4-day ramp-up phase. For patients with CLL/SLL or AML, reduce the dose of VENCLEXTA when coadministered with moderate CYP3A4 inhibitors or P-gp inhibitors *[see Drug Interactions]*.

Neutropenia

In patients with CLL, Grade 3 or 4 neutropenia developed in 63% to 64% of patients and Grade 4 neutropenia developed in 31% to 33% of patients when treated with VENCLEXTA in combination and monotherapy studies. Febrile neutropenia occurred in 4% to 6% of patients *[see Adverse Reactions]*.

In patients with AML, baseline neutrophil counts worsened in 95% to 100% of patients treated with VENCLEXTA in combination with azacitidine, decitabine, or low-dose cytarabine. Neutropenia can recur with subsequent cycles.

Monitor complete blood counts throughout the treatment period. Consider supportive measures, including antimicrobials and growth factors (e.g., G-CSF).

Infections

Fatal and serious infections, such as pneumonia and sepsis, have occurred in patients treated with VENCLEXTA *[see Adverse Reactions]*.

Monitor patients for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and 4 infection until resolution.

Immunization

Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery occurs. The safety and efficacy of immunization with live attenuated vaccines during or following VENCLEXTA therapy have not been studied. Advise patients that vaccinations may be less effective.

Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. In an embryo-fetal study conducted in mice, administration of venetoclax to pregnant animals at exposures equivalent to that observed in patients at a dose of 400 mg daily resulted in post-implantation loss and decreased fetal weight.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for 30 days after the last dose *[see Use in Specific Populations]*.

Increased Mortality in Patients with Multiple Myeloma when VENCLEXTA is Added to Bortezomib and Dexamethasone

In a randomized trial (BELLINI; NCT02755597) in patients with relapsed or refractory multiple myeloma, the addition of VENCLEXTA to bortezomib plus dexamethasone, a use for which VENCLEXTA is not indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with VENCLEXTA in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.

ADVERSE REACTIONS

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

- Tumor Lysis Syndrome *[see Warnings and Precautions]*
- Neutropenia *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*

Clinical Trials Experience

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

In CLL/SLL, the safety population reflects exposure to VENCLEXTA as monotherapy in patients in M13-982, M14-032, and M12-175 and in combination with obinutuzumab or rituximab in patients in CLL14 and MURANO. In this CLL/SLL safety population, the most common adverse reactions (≥20%) for VENCLEXTA were neutropenia, thrombocytopenia, anemia, diarrhea, nausea, upper respiratory tract infection, cough, musculoskeletal pain, fatigue, and edema.

In AML, the safety population reflects exposure to VENCLEXTA in combination with decitabine, azacitidine, or low-dose cytarabine in patients in M14-358, VIALE-A, and VIALE-C. In this safety population, the most common adverse reactions (≥30% in any trial) were nausea, diarrhea, thrombocytopenia, constipation, neutropenia, febrile neutropenia, fatigue, vomiting, edema, pyrexia, pneumonia, dyspnea, hemorrhage, anemia, rash, abdominal pain, sepsis, musculoskeletal pain, dizziness, cough, oropharyngeal pain, and hypotension.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

VENCLEXTA in Combination with Obinutuzumab

The safety of VENCLEXTA in combination with obinutuzumab (VEN+G) (N=212) versus obinutuzumab in combination with chlorambucil (GClb) (N=214) was evaluated in CLL14, a randomized, open-label, actively controlled trial in patients with previously untreated CLL. Patients randomized to the VEN+G arm were treated with VENCLEXTA and obinutuzumab in combination for six cycles, then with VENCLEXTA as monotherapy for an additional six cycles. Patients initiated the first dose of the 5-week ramp-up for VENCLEXTA on Day 22 of Cycle 1 and once completed, continued VENCLEXTA 400 mg orally once daily for a total of 12 cycles. The trial required a total Cumulative Illness Rating Scale (CIRS) >6 or CLcr <70 mL/min, hepatic transaminases and total bilirubin ≤2 times upper limit of normal and excluded patients with any individual organ/system impairment score of 4 by CIRS except eye, ear, nose, and throat organ system. The median duration of exposure to VENCLEXTA was 10.5 months (range: 0 to 13.5 months) and the median number of cycles of obinutuzumab was 6 in the VEN+G arm.

Serious adverse reactions were reported in 49% of patients in the VEN+G arm, most often due to febrile neutropenia and pneumonia (5% each). Fatal adverse reactions that occurred in the absence of disease progression and with onset within 28 days of the last study treatment were reported in 2% (4/212) of patients, most often from infection.

In the VEN+G arm, adverse reactions led to treatment discontinuation in 16% of patients, dose reduction in 21%, and dose interruption in 74%. Neutropenia led to discontinuation of VENCLEXTA in 2% of patients, dose reduction in 13%, and dose interruption in 41%.

Table 1 presents adverse reactions identified in CLL14.

Table 1. Adverse Reactions (≥10%) in Patients Treated with VEN+G in CLL14

Adverse Reaction	VENCLEXTA + Obinutuzumab (N = 212)		Obinutuzumab + Chlorambucil (N = 214)	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Blood and lymphatic system disorders				
Neutropenia[a]	60	56	62	52
Anemia[a]	17	8	20	7
Gastrointestinal disorders				
Diarrhea	28	4	15	1
Nausea	19	0	22	1
Constipation	13	0	9	0
Vomiting	10	1	8	1
General disorders and administration site conditions				
Fatigue[a]	21	2	23	1
Infections and infestations				
Upper respiratory tract infection[a]	17	1	17	1

[a]Includes multiple adverse reaction terms.

Other clinically important adverse reactions (All Grades) reported in <10% of patients treated with VEN+G are presented below:

Blood and lymphatic system disorders: febrile neutropenia (6%)

Infection and infestations (all include multiple adverse reaction terms): pneumonia (9%), urinary tract infection (6%), sepsis (4%)

Metabolism and nutrition disorder: tumor lysis syndrome (1%)

During treatment with VENCLEXTA monotherapy after completion of VEN+G, the adverse reaction that occurred in ≥10% of patients was neutropenia (26%). The grade ≥3 adverse reactions that occurred in ≥2% of patients were neutropenia (23%) and anemia (2%).

Table 2 presents laboratory abnormalities CLL14.

Table 2. New or Worsening Clinically Important Laboratory Abnormalities (≥10%) in Patients Treated with VEN+G in CLL14

Laboratory Abnormality[a]	VENCLEXTA + Obinutuzumab (N = 212)		Obinutuzumab + Chlorambucil (N = 214)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Leukopenia	90	46	89	41
Lymphopenia	87	57	87	51
Neutropenia	83	63	79	56
Thrombocytopenia	68	28	71	26
Anemia	53	15	46	11
Chemistry				
Blood creatinine increased	80	6	74	2
Hypocalcemia	67	9	58	4
Hyperkalemia	41	4	35	3
Hyperuricemia	38	38	38	38

[a]Includes laboratory abnormalities that were new or worsening, or with worsening from baseline unknown.

Grade 4 laboratory abnormalities that developed in ≥2% of patients treated with VEN+G included neutropenia (32%), leukopenia and lymphopenia (10%), thrombocytopenia (8%), hypocalcemia (8%), hyperuricemia (7%), blood creatinine increased (3%), hypercalcemia (3%), and hypokalemia (2%).

VENCLEXTA in Combination with Rituximab

The safety of VENCLEXTA in combination with rituximab (VEN+R) (N=194) versus bendamustine in combination with rituximab (B+R) (N=188) was evaluated in MURANO. Patients randomized to VEN+R completed the scheduled ramp-up (5 weeks) and received VENCLEXTA 400 mg once daily, in combination with rituximab for 6 cycles followed by VENCLEXTA monotherapy, for a total of 24 months after ramp-up. At the time of analysis, the median duration of exposure to VENCLEXTA was 22 months and the median number of cycles of rituximab was 6 in the VEN+R arm.

Serious adverse reactions were reported in 46% of patients in the VEN+R arm, with most frequent (≥5%) being pneumonia (9%). Fatal adverse reactions that occurred in the absence of disease progression and within 30 days of the last VENCLEXTA treatment and/or 90 days of last rituximab were reported in 2% (4/194) of patients.

In the VEN+R arm, adverse reactions led to treatment discontinuation in 16% of patients, dose reduction in 15%, and dose interruption in 71%. Neutropenia and thrombocytopenia each led to discontinuation of VENCLEXTA in 3% of patients. Neutropenia led to dose interruption of VENCLEXTA in 46% of patients.

Table 3 presents adverse reactions identified in MURANO.

Table 3. Adverse Reactions (≥10%) in Patients Treated with VEN+R in MURANO

Adverse Reaction	VENCLEXTA + Rituximab (N = 194)		Bendamustine + Rituximab (N = 188)	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Blood and lymphatic system disorders				
Neutropenia[a]	65	62	50	44
Anemia[a]	16	11	23	14
Gastrointestinal disorders				
Diarrhea	40	3	17	1
Nausea	21	1	34	1
Constipation	14	<1	21	0
Infections and infestations				
Upper respiratory tract infection[a]	39	2	23	2
Lower respiratory tract infection[a]	18	2	10	2
Pneumonia[a]	10	7	14	10
General disorders and administration site conditions				
Fatigue[a]	22	2	26	<1

[a]Includes multiple adverse reaction terms.

Other clinically important adverse reactions (All Grades) reported in <10% of patients treated with VEN+R are presented below:

Blood and lymphatic system disorders: febrile neutropenia (4%)

Gastrointestinal disorders: vomiting (8%)

Infections and infestations: sepsis (<1%)

Metabolism and nutrition disorders: tumor lysis syndrome (3%)

During treatment with VENCLEXTA monotherapy after completion of VEN+R combination treatment, adverse reactions that occurred in ≥10% of patients were upper respiratory tract infection (21%), diarrhea (19%), neutropenia (16%), and lower respiratory tract infections (11%). The Grade 3 or 4 adverse reactions that occurred in ≥2% of patients were neutropenia (12%) and anemia (3%).

Table 4 presents laboratory abnormalities identified in MURANO.

Table 4. New or Worsening Clinically Important Laboratory Abnormalities (≥10%) in Patients Treated with VEN+R in MURANO

Laboratory Abnormality	VENCLEXTA + Rituximab (N = 194)		Bendamustine + Rituximab (N = 188)	
	All Grades[a] (%)	Grade 3 or 4 (%)	All Grades[a] (%)	Grade 3 or 4 (%)
Hematology				
Leukopenia	89	46	81	35
Lymphopenia	87	56	79	55
Neutropenia	86	64	84	59
Anemia	50	12	63	15
Thrombocytopenia	49	15	60	20
Chemistry				
Blood creatinine increased	77	<1	78	1
Hypocalcemia	62	5	51	2
Hyperuricemia	36	36	33	33
Hyperkalemia	24	3	19	2

[a]Includes laboratory abnormalities that were new or worsening, or with worsening from baseline unknown.

Grade 4 laboratory abnormalities that developed in ≥2% of patients treated with VEN+R included neutropenia (31%), lymphopenia (16%), leukopenia (6%), thrombocytopenia (6%), hyperuricemia (4%), hypocalcemia (2%), hypoglycemia (2%), and hypermagnesemia (2%).

VENCLEXTA as Monotherapy

The safety of VENCLEXTA was evaluated in pooled data from three single-arm trials (M13-982, M14-032, and M12-175). Patients received VENCLEXTA 400 mg orally once daily after completing the ramp-up phase (N=352). The median duration of treatment with VENCLEXTA at the time of data analysis was 14.5 months (range: 0 to 50 months). Fifty-two percent of patients received VENCLEXTA for more than 60 weeks.

In the pooled dataset, the median age was 66 years (range: 28 to 85 years), 93% were White, and 68% were male. The median number of prior therapies was 3 (range: 0 to 15).

Serious adverse reactions were reported in 52% of patients, with the most frequent (≥5%) being pneumonia (9%), febrile neutropenia (5%), and sepsis (5%). Fatal adverse reactions that occurred in the absence of disease progression and within 30 days of venetoclax treatment were reported in 2% of patients in the VENCLEXTA monotherapy studies, most often (2 patients) from septic shock.

Adverse reactions led to treatment discontinuation in 9% of patients, dose reduction in 13%, and dose interruption in 36%. The most frequent adverse reactions leading to drug discontinuation were thrombocytopenia and autoimmune hemolytic anemia. The most frequent adverse reaction (≥5%) leading to dose reductions or interruptions was neutropenia (8%).

Table 5 presents adverse reactions identified in these trials.

Table 5. Adverse Reactions Reported in ≥10% (All Grades) or ≥5% (Grade ≥3) of Patients with Previously Treated CLL/SLL Who Received VENCLEXTA Monotherapy

Adverse Reaction	VENCLEXTA (N = 352)	
	All Grades (%)	Grade ≥3 (%)
Blood and lymphatic system disorders		
Neutropenia[a]	50	45
Anemia[a]	33	18
Thrombocytopenia[a]	29	20
Lymphopenia[a]	11	7
Febrile neutropenia	6	6
Gastrointestinal disorders		
Diarrhea	43	3
Nausea	42	1
Abdominal pain[a]	18	3
Vomiting	16	1
Constipation	16	<1
Mucositis[a]	13	<1
Infections and infestations		
Upper respiratory tract infection[a]	36	1
Pneumonia[a]	14	8
Lower respiratory tract infection[a]	11	2
General disorders and administration site conditions		
Fatigue[a]	32	4
Edema[a]	22	2
Pyrexia	18	<1
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[a]	29	2
Arthralgia	12	<1
Respiratory, thoracic, and mediastinal disorders		
Cough[a]	22	0
Dyspnea[a]	13	1
Nervous system disorders		
Headache	18	<1
Dizziness[a]	14	0
Skin and subcutaneous tissue disorders		
Rash[a]	18	<1

Adverse reactions graded using NCI Common Terminology Criteria for Adverse Events version 4.0.

[a]Includes multiple adverse reaction terms.

Table 6 presents laboratory abnormalities reported throughout treatment that were new or worsening from baseline. The most common (>5%) Grade 4 laboratory abnormalities observed with VENCLEXTA monotherapy were hematologic laboratory abnormalities, including neutropenia (33%), leukopenia (11%), thrombocytopenia (15%), and lymphopenia (9%).

Table 6. New or Worsening Laboratory Abnormalities in ≥40% (All Grades) or ≥10% (Grade 3 or 4) of Patients with Previously Treated CLL/SLL Who Received VENCLEXTA Monotherapy

Laboratory Abnormality	VENCLEXTA (N = 352)	
	All Grades[a] (%)	Grade 3 or 4 (%)
Hematology		
Leukopenia	89	42
Neutropenia	87	63
Lymphopenia	74	40
Anemia	71	26
Thrombocytopenia	64	31
Chemistry		
Hypocalcemia	87	12
Hyperglycemia	67	7
Hyperkalemia	59	5
AST increased	53	3
Hypoalbuminemia	49	2
Hypophosphatemia	45	11
Hyponatremia	40	9

[a]Includes laboratory abnormalities that were new or worsening, or worsening from baseline unknown.

Important Adverse Reactions in CLL/SLL

Tumor Lysis Syndrome

Tumor lysis syndrome is an important identified risk when initiating VENCLEXTA.

CLL14

The incidence of TLS was 1% (3/212) in patients treated with VEN+G *[see Warnings and Precautions]*. All three events of TLS resolved and did not lead to withdrawal from the trial. Obinutuzumab administration was delayed in two cases in response to the TLS events.

MURANO

The incidence of TLS was 3% (6/194) in patients treated with VEN+R. After 77/389 patients were enrolled in the trial, the protocol was amended to incorporate the current TLS prophylaxis and monitoring measures. All events of TLS occurred during the VENCLEXTA ramp-up period and were resolved within two days. All six patients completed the ramp-up and reached the recommended daily dose of 400 mg of VENCLEXTA. No clinical TLS was observed in patients who followed the current 5-week ramp-up schedule and TLS prophylaxis and monitoring measures. Rates of laboratory abnormalities relevant to TLS for patients treated with VEN+R are presented in Table 4.

Monotherapy Studies (M13-982 and M14-032)

In 168 patients with CLL treated according to recommendations described in sections 2.1 and 2.2, the rate of TLS was 2%. All events either met laboratory TLS criteria (laboratory abnormalities that met ≥2 of the following within 24 hours of each other: potassium >6 mmol/L, uric acid >476 µmol/L, calcium <1.75 mmol/L, or phosphorus >1.5 mmol/L), or were reported as TLS events. The events occurred in patients who had a lymph node(s) ≥5 cm and/or absolute lymphocyte count (ALC) ≥25 x 10^9/L. All events resolved within 5 days. No TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures was observed in these patients. All patients had CLcr ≥50 mL/min. Laboratory abnormalities relevant to TLS were hyperkalemia (17% all Grades, 1% Grade ≥3), hyperphosphatemia (14% all Grades, 2% Grade ≥3), hypocalcemia (16% all Grades, 2% Grade ≥3), and hyperuricemia (10% all Grades, <1% Grade ≥3).

In the initial Phase 1 dose-finding trials, which had shorter (2-3 week) ramp-up phase and higher starting doses, the incidence of TLS was 13% (10/77; 5 laboratory TLS, 5 clinical TLS), including 2 fatal events and 3 events of acute renal failure, 1 requiring dialysis. After this experience, TLS risk assessment, dosing regimen, TLS prophylaxis and monitoring measures were revised.

Acute Myeloid Leukemia

VENCLEXTA in Combination with Azacitidine

The safety of VENCLEXTA in combination with azacitidine (VEN+AZA) (N=283) versus placebo in combination with azacitidine (PBO+AZA) (N=144) was evaluated in VIALE-A, a double-blind, randomized trial, in patients with newly diagnosed AML. At baseline, patients were ≥75 years of age or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr <45 mL/min, or other comorbidity. Patients were randomized to receive VENCLEXTA 400 mg orally once daily after completion of the ramp-up phase in combination with azacitidine (75 mg/m^2 either intravenously or subcutaneously on Days 1-7 of each 28-day cycle) or placebo in combination with azacitidine. Among patients who received VEN+AZA, the median duration of exposure to VENCLEXTA was 7.6 months (range: <0.1 to 30.7 months).

Serious adverse reactions were reported in 83% of patients who received VEN+AZA, with the most frequent (≥5%) being febrile neutropenia (30%), pneumonia (22%), sepsis (excluding fungal; 19%), and hemorrhage (6%). Fatal adverse reactions occurred in 23% of patients who received VEN+AZA, with the most frequent (≥2%) being pneumonia (4%), sepsis (excluding fungal; 3%), and hemorrhage (2%).

Adverse reactions led to permanent discontinuation of VENCLEXTA in 24% of patients, dose reductions in 2%, and dose interruptions in 72%. Adverse reactions which led to discontinuation of VENCLEXTA in ≥2% of patients were sepsis (excluding fungal; 3%) and pneumonia (2%). The most frequent adverse reaction leading to dose reduction was pneumonia (0.7%). Adverse reactions which required a dose interruption in ≥5% of patients included febrile neutropenia (20%), neutropenia (20%), pneumonia (14%), sepsis (excluding fungal; 11%), and thrombocytopenia (10%). Among patients who achieved bone marrow clearance of leukemia, 53% underwent dose interruptions for absolute neutrophil count (ANC) <500/microliter.

Table 7 presents adverse reactions identified in VIALE-A.

Table 7. Adverse Reactions (≥10%) in Patients with AML Who Received VEN+AZA with a Difference Between Arms of ≥5% for All Grades or ≥2% for Grade 3 or 4 Reactions Compared with PBO+AZA in VIALE-A

Adverse Reaction	VENCLEXTA + Azacitidine (N = 283)		Placebo + Azacitidine (N = 144)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Nausea	44	2	35	<1
Diarrhea[a]	43	5	33	3
Vomiting[b]	30	2	23	<1
Stomatitis[c]	18	1	13	0
Abdominal pain[d]	18	<1	13	0
Blood and lymphatic system disorders				
Febrile neutropenia	42	42	19	19
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[e]	36	2	28	1
General disorders and administration site conditions				
Fatigue[f]	31	6	23	2
Edema[g]	27	<1	19	0
Vascular disorders				
Hemorrhage[h]	27	7	24	3
Hypotension[i]	12	5	8	3
Metabolism and nutrition disorders				
Decreased appetite[j]	25	4	17	<1
Skin and subcutaneous tissue disorders				
Rash[k]	25	1	15	0
Infections and infestations				
Sepsis[l] (excluding fungal)	22	22	16	14
Urinary tract infection[m]	16	6	9	6
Respiratory, thoracic and mediastinal disorders				
Dyspnea[n]	18	4	10	2
Nervous system disorders				
Dizziness[o]	17	<1	8	<1

[a]Includes diarrhea and colitis.
[b]Includes vomiting and hematemesis.
[c]Includes stomatitis, mouth ulceration, mucosal inflammation, cheilitis, aphthous ulcer, glossitis, and tongue ulceration.
[d]Includes abdominal pain, abdominal pain upper, abdominal discomfort, and abdominal pain lower.
[e]Includes arthralgia, back pain, pain in extremity, musculoskeletal pain, bone pain, myalgia, neck pain, non-cardiac chest pain, arthritis, musculoskeletal chest pain, musculoskeletal stiffness, spinal pain, and musculoskeletal discomfort.
[f]Includes fatigue and asthenia.
[g]Includes edema peripheral, edema, generalized edema, eyelid edema, face edema, penile edema, periorbital edema, and swelling.
[h]Includes epistaxis, hematuria, conjunctival hemorrhage, hemoptysis, hemorrhoidal hemorrhage, gingival bleeding, mouth hemorrhage, hemorrhage intracranial, vaginal hemorrhage, cerebral hemorrhage, gastrointestinal hemorrhage, muscle hemorrhage, skin hemorrhage, upper gastrointestinal hemorrhage, anal hemorrhage, eye hemorrhage, gastritis hemorrhagic, hemorrhage, hemorrhage urinary tract, hemorrhagic diathesis, hemorrhagic stroke, hemorrhagic vasculitis, lower gastrointestinal hemorrhage, mucosal hemorrhage, penile hemorrhage, post procedural hemorrhage, rectal hemorrhage, retinal hemorrhage, shock hemorrhagic, soft tissue hemorrhage, subdural hemorrhage, tongue hemorrhage, urethral hemorrhage, vessel puncture site hemorrhage, vitreous hemorrhage, and wound hemorrhage.
[i]Includes hypotension and orthostatic hypotension.
[j]Includes decreased appetite and hypophagia.
[k]Includes rash, rash maculo-papular, rash macular, drug eruption, rash papular, rash pustular, eczema, rash erythematous, rash pruritic, dermatitis acneiform, rash morbilliform, dermatitis, eczema asteatotic, exfoliative rash, and perivascular dermatitis.
[l]Includes sepsis, escherichia bacteremia, escherichia sepsis, septic shock, bacteremia, staphylococcal bacteremia, klebsiella bacteremia, staphylococcal sepsis, streptococcal bacteremia, enterococcal bacteremia, klebsiella sepsis, pseudomonal bacteremia, pseudomonal sepsis, urosepsis, bacterial sepsis, clostridial sepsis, enterococcal sepsis, neutropenic sepsis, and streptococcal sepsis.
[m]Includes urinary tract infection, escherichia urinary tract infection, cystitis, urinary tract infection enterococcal, urinary tract infection bacterial, pyelonephritis acute, and urinary tract infection pseudomonal.
[n]Includes dyspnea, dyspnea exertional, and dyspnea at rest.
[o]Includes dizziness and vertigo.

Other clinically important adverse reactions (All Grades) at ≥10% that did not meet criteria for Table 7 or <10% are presented below:

Hepatobiliary disorders: cholecystitis/cholelithiasis[a] (4%)

Infections and infestations: pneumonia[b] (33%)

Metabolism and nutrition disorders: tumor lysis syndrome (1%)

Nervous system disorders: headache[c] (11%)

Investigations: weight decreased (13%).

[a]Includes cholecystitis acute, cholelithiasis, cholecystitis, and cholecystitis chronic.

[b]Includes pneumonia, lung infection, pneumonia fungal, pneumonia klebsiella, atypical pneumonia, lower respiratory tract infection, pneumonia viral, lower respiratory tract infection fungal, pneumonia hemophilus, pneumonia pneumococcal, and pneumonia respiratory syncytial viral.

[c]Includes headache and tension headache.

Table 8 presents laboratory abnormalities identified in VIALE-A.

Table 8. New or Worsening Laboratory Abnormalities (≥10%) in Patients with AML Who Received VEN+AZA with a Difference Between Arms of ≥5% for All Grades or ≥2% for Grade 3 or 4 Reactions Compared with PBO+AZA in VIALE-A

Laboratory Abnormality	VENCLEXTA + Azacitidine		Placebo + Azacitidine	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Neutrophils decreased	98	98	88	81
Platelet decreased	94	88	94	80
Lymphocytes decreased	91	71	72	39
Hemoglobin decreased	61	57	56	52
Chemistry				
Bilirubin increased	53	7	40	4
Calcium decreased	51	6	39	9
Sodium decreased	46	14	47	8
Alkaline phosphatase increased	42	1	29	<1
Blood bicarbonate decreased	31	<1	25	0

The denominator used to calculate the rate varied from 85 to 144 in the PBO+AZA arm and from 125 to 283 in the VEN+AZA arm based on the number of patients with at least one post-treatment value.

VENCLEXTA in Combination with Azacitidine or Decitabine

The safety of VENCLEXTA in combination with azacitidine (N=67) or decitabine (N=13) was evaluated in M14-358, a non-randomized trial of patients with newly diagnosed AML. At baseline, patients were ≥75 years of age, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr <45 mL/min, or other comorbidity. Patients received VENCLEXTA 400 mg orally once daily after completion of the ramp-up phase in combination with azacitidine (75 mg/m^2 either intravenously or subcutaneously on Days 1-7 of each 28-day cycle) or decitabine (20 mg/m^2 intravenously on Days 1-5 of each 28-day cycle).

Azacitidine

The median duration of exposure to VENCLEXTA when administered in combination with azacitidine was 6.5 months (range: 0.1 to 38.1 months). The safety of VENCLEXTA in combination with azacitidine in this trial is consistent with that of VIALE-A.

Decitabine

The median duration of exposure to VENCLEXTA when administered in combination with decitabine was 8.4 months (range: 0.5 to 39 months).

Serious adverse reactions were reported in 85% of patients who received VENCLEXTA with decitabine, the most frequent (≥10%) being sepsis (excluding fungal; 46%), febrile neutropenia (38%), and pneumonia (31%). One (8%) fatal adverse reaction of bacteremia occurred within 30 days of starting treatment.

Permanent discontinuation of VENCLEXTA due to adverse reactions occurred in 38% of patients. The most frequent adverse reaction leading to permanent discontinuation (≥5%) was pneumonia (8%).

Dosage reductions of VENCLEXTA due to adverse reactions occurred in 15% of patients. The most frequent adverse reaction leading to dose reduction (≥5%) was neutropenia (15%).

Dosage interruptions of VENCLEXTA due to adverse reactions occurred in 69% of patients. The most frequent adverse reactions leading to dose interruption (≥10%) were neutropenia (38%), febrile neutropenia (23%), leukopenia (15%), and pneumonia (15%).

The most common adverse reactions (≥30%) were febrile neutropenia (69%), fatigue (62%), constipation (62%), musculoskeletal pain (54%), dizziness (54%), nausea (54%), abdominal pain (46%), diarrhea (46%), pneumonia (46%), sepsis (excluding fungal; 46%), cough (38%), pyrexia (31%), hypotension (31%), oropharyngeal pain (31%), edema (31%), and vomiting (31%). The most common laboratory abnormalities (≥30%) were neutrophils decreased (100%), lymphocytes decreased (100%), white blood cells decreased (100%), platelets decreased (92%), calcium decreased (85%), hemoglobin decreased (69%), glucose increased (69%), magnesium decreased (54%), potassium decreased (46%), bilirubin increased (46%), albumin decreased (38%), alkaline phosphatase increased (38%), sodium decreased (38%), ALT increased (31%), creatinine increased (31%), and potassium increased (31%).

VENCLEXTA in Combination with Low-Dose Cytarabine

VIALE-C

The safety of VENCLEXTA in combination with low-dose cytarabine (VEN+LDAC) (N=142) versus placebo with low-dose cytarabine (PBO+LDAC) (N=68) was evaluated in VIALE-C, a double-blind randomized trial in patients with newly diagnosed AML. At baseline, patients were ≥75 years of age, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr <45 mL/min, or other comorbidity. Patients were randomized to receive VENCLEXTA 600 mg orally once daily after completion of a 4-day ramp-up phase in combination with low-dose cytarabine (20 mg/m^2 subcutaneously once daily on Days 1-10 of each 28-day cycle) or placebo in combination with low-dose cytarabine. Among patients who received VEN+LDAC, the median duration of exposure to VENCLEXTA was 3.9 months (range: <0.1 to 17.1 months).

Serious adverse reactions were reported in 65% of patients who received VEN+LDAC, with the most frequent (≥10%) being pneumonia (17%), febrile neutropenia (16%), and sepsis (excluding fungal; 12%). Fatal adverse reactions occurred in 23% of patients who received VEN+LDAC, with the most frequent (≥5%) being pneumonia (6%) and sepsis (excluding fungal; 7%).

Adverse reactions led to permanent discontinuation of VENCLEXTA in 25% of patients, dose reductions in 9%, and dose interruptions in 63%. The most frequent adverse reaction (>2%) which resulted in permanent discontinuation of VENCLEXTA was pneumonia (6%). Adverse reactions which required a dose reduction in ≥1% of patients were pneumonia (1%) and thrombocytopenia (1%), and the adverse reactions which required a dose interruption in ≥5% of patients included neutropenia (20%), thrombocytopenia (15%), pneumonia (8%), febrile neutropenia (6%), and sepsis (excluding fungal; 6%). Among patients who achieved bone marrow clearance of leukemia, 32% underwent dose interruptions for ANC <500/microliter.

Table 9 presents adverse reactions identified in VIALE-C.

Table 9. Adverse Reactions (≥10%) in Patients with AML Who Received VEN+LDAC with a Difference Between Arms of ≥5% for All Grades or ≥2% for Grade 3 or 4 Compared with PBO+LDAC in VIALE-C

Adverse Reaction	VENCLEXTA + Low-Dose Cytarabine (N = 142)		Placebo + Low-Dose Cytarabine (N = 68)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Nausea	42	1	31	0
Diarrhea	28	3	16	0
Vomiting	25	<1	13	0
Abdominal pain[a]	15	<1	9	3
Stomatitis[b]	15	1	6	0
Blood and lymphatic system disorders				
Febrile neutropenia	32	32	29	29
Infections and infestations				
Pneumonia[c]	29	19	21	21
Vascular Disorders				
Hemorrhage[d]	27	8	16	1
Hypotension[e]	11	5	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[f]	23	3	18	0
General Disorders and Administration Site Conditions				
Fatigue[g]	22	2	21	0
Nervous System Disorders				
Headache	11	0	6	0

[a]Includes abdominal pain, abdominal pain upper, abdominal discomfort, and abdominal pain lower.
[b]Includes stomatitis, mouth ulceration, aphthous ulcer, glossitis, mucosal inflammation, and tongue ulceration.
[c]Includes pneumonia, lung infection, lower respiratory tract infection, pneumonia fungal, lower respiratory tract infection fungal, pneumocystis jirovecii pneumonia, pneumonia aspiration, pneumonia cytomegaloviral, and pneumonia pseudomonal.
[d]Includes epistaxis, conjunctival hemorrhage, hemoptysis, gastrointestinal hemorrhage, gingival bleeding, mouth hemorrhage, upper gastrointestinal hemorrhage, hematuria, retinal hemorrhage, catheter site hemorrhage, cerebral hemorrhage, gastric hemorrhage, gastritis hemorrhagic, hemorrhage intracranial, hemorrhage subcutaneous, lip hemorrhage, mucosal hemorrhage, pharyngeal hemorrhage, post procedural hemorrhage, pulmonary alveolar hemorrhage, pulmonary hemorrhage, tooth pulp hemorrhage, uterine hemorrhage, and vascular access site hemorrhage.
[e]Includes hypotension and orthostatic hypotension.
[f]Includes back pain, arthralgia, pain in extremity, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, arthritis, bone pain, musculoskeletal chest pain, and spinal pain.
[g]Includes fatigue and asthenia.

Other clinically important adverse reactions (All Grades) at ≥10% that did not meet criteria for Table 9 or <10% are presented below:

Hepatobiliary disorders: cholecystitis/cholelithiasis[a] (1%)

Infections and infestations: sepsis[b] (excluding fungal; 15%), urinary tract infection[c] (8%)

Metabolism and nutrition disorders: decreased appetite (19%), tumor lysis syndrome (6%)

Nervous system disorders: dizziness[d] (9%)

Respiratory, thoracic, and mediastinal disorders: dyspnea[e] (10%)

Investigations: weight decreased (9%).

[a]Includes cholecystitis and cholecystitis acute.

[b]Includes sepsis, bacteremia, septic shock, neutropenic sepsis, staphylococcal bacteremia, streptococcal bacteremia, bacterial sepsis, Escherichia bacteremia, pseudomonal bacteremia, and staphylococcal sepsis.

[c]Includes urinary tract infection and escherichia urinary tract infection.

[d]Includes dizziness and vertigo.

[e]Includes dyspnea and dyspnea exertional.

Table 10 describes laboratory abnormalities identified in VIALE-C.

Table 10. New or Worsening Laboratory Abnormalities (≥10%) in Patients with AML Who Received VEN+LDAC with Difference Between Arms of ≥5% for All Grades or ≥2% for Grade 3 or 4 Reactions Compared with PBO+LDAC in VIALE-C

Laboratory Abnormality	VENCLEXTA + Low-Dose Cytarabine		Placebo + Low-Dose Cytarabine	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Platelets decreased	97	95	92	90
Neutrophils decreased	95	92	82	71
Lymphocytes decreased	92	69	65	24
Hemoglobin decreased	63	57	57	54
Chemistry				
Bilirubin increased	61	7	38	7
Albumin decreased	61	6	43	4
Potassium decreased	56	16	42	14
Calcium decreased	53	8	45	13
Glucose increased	52	13	59	9
AST increased	36	6	37	1
Alkaline phosphatase increased	34	1	26	1
ALT increased	30	4	26	1
Sodium increased	11	3	6	1

The denominator used to calculate the rate varied from 38 to 68 in the PBO+LDAC arm and from 65 to 142 in the VEN+LDAC arm based on the number of patients with at least one post-treatment value.

M14-387

The safety of VENCLEXTA in combination with low-dose cytarabine (N=61) was evaluated in M14-387, a non-randomized, open- label trial of patients with newly diagnosed AML. At baseline, patients were ≥75 years of age, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr <45 mL/min, or other comorbidity. Patients received VENCLEXTA 600 mg orally once daily after completion of the ramp-up phase in combination with low-dose cytarabine (20mg/m^2 subcutaneously on Days 1-10 of each 28-day cycle). The safety of VENCLEXTA in combination with low-dose cytarabine is consistent with that of VIALE-C.

DRUG INTERACTIONS

Effects of Other Drugs on VENCLEXTA

Strong or Moderate CYP3A Inhibitors or P-gp Inhibitors

Concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor increases venetoclax C_{max} and $AUC_{0\text{-}INF}$, which may increase VENCLEXTA toxicities, including the risk of TLS *[see Warnings and Precautions]*.

Concomitant use with a strong CYP3A inhibitor at initiation and during the ramp-up phase in patients with CLL/SLL is contraindicated *[see Contraindications]*.

In patients with CLL/SLL taking a steady daily dosage (after ramp-up phase), consider alternative medications or adjust VENCLEXTA dosage and monitor more frequently for adverse reactions.

In patients with AML, adjust VENCLEXTA dosage and monitor more frequently for adverse reactions.

Resume the VENCLEXTA dosage that was used prior to concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor.

Avoid grapefruit products, Seville oranges, and starfruit during treatment with VENCLEXTA, as they contain inhibitors of CYP3A.

Strong or Moderate CYP3A Inducers

Concomitant use with a strong CYP3A inducer decreases venetoclax C_{max} and $AUC_{0\text{-}INF}$, which may decrease VENCLEXTA efficacy. Avoid concomitant use of VENCLEXTA with strong CYP3A inducers or moderate CYP3A inducers.

Effect of VENCLEXTA on Other Drugs

Warfarin

Concomitant use of VENCLEXTA increases warfarin C_{max} and $AUC_{0\text{-}INF}$, which may increase the risk of bleeding. Monitor international normalized ratio (INR) more frequently in patients using warfarin concomitantly with VENCLEXTA.

P-gp Substrates

Concomitant use of VENCLEXTA increases C_{max} and $AUC_{0\text{-}INF}$ of P-gp substrates, which may increase toxicities of these substrates. Avoid concomitant use of VENCLEXTA with a P-gp substrate. If a concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before VENCLEXTA.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action, VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. There are no available data on VENCLEXTA use in pregnant women to inform a drug-associated risk. Administration of venetoclax to pregnant mice during the period of organogenesis was fetotoxic at exposures 1.2 times the human exposure at the recommended dose of 400 mg daily based on AUC. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal data

In embryo-fetal development studies, venetoclax was administered to pregnant mice and rabbits during the period of organogenesis. In mice, venetoclax was associated with increased post-implantation loss and decreased fetal body weight at 150 mg/kg/day (maternal exposures approximately 1.2 times the human exposure at the recommended dose of 400 mg once daily). No teratogenicity was observed in either the mouse or the rabbit.

Lactation

Risk Summary

There are no data on the presence of VENCLEXTA in human milk or the effects on the breastfed child or milk production. Venetoclax was present in the milk when administered to lactating rats *(see Data)*.

Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with VENCLEXTA and for 1 week after the last dose.

Data

Animal Data

Venetoclax was administered (single dose; 150 mg/kg oral) to lactating rats 8 to 10 days post-parturition. Venetoclax in milk was 1.6 times lower than in plasma. Parent drug (venetoclax) represented the majority of the total drug-related material in milk, with trace levels of three metabolites.

Females and Males of Reproductive Potential

VENCLEXTA may cause fetal harm when administered to pregnant women *[see Use in Specific Populations]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating VENCLEXTA.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for 30 days after the last dose.

Infertility

Based on findings in animals, VENCLEXTA may impair male fertility.

Pediatric Use

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

Juvenile Animal Toxicity Data

In a juvenile toxicology study, mice were administered venetoclax at 10, 30, or 100 mg/kg/day by oral gavage from 7 to 60 days of age. Clinical signs of toxicity included decreased activity, dehydration, skin pallor, and hunched posture at ≥30 mg/kg/day. In addition, mortality and body weight effects occurred at 100 mg/kg/day. Other venetoclax-related effects were reversible decreases in lymphocytes at ≥10 mg/kg/day; a dose of 10 mg/kg/day is approximately 0.06 times the clinical dose of 400 mg on a mg/m^2 basis for a 20 kg child.

Geriatric Use

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Of the 352 patients with previously treated CLL/SLL evaluated for safety from 3 open-label trials of VENCLEXTA monotherapy, 57% (201/352) were ≥65 years of age and 18% (62/352) were ≥75 years of age. No clinically meaningful differences in safety and effectiveness were observed between older and younger patients in the combination and monotherapy studies.

Acute Myeloid Leukemia

Of the 283 patients who received VENCLEXTA with azacitidine in VIALE-A, 96% were ≥65 years of age and 60% were ≥75 years of age.

Of the 13 patients who received VENCLEXTA in combination with decitabine in M14-358, 100% were ≥65 years of age and 62% were ≥75 years of age.

Of the 142 patients who received VENCLEXTA in combination with low-dose cytarabine in VIALE-C, 92% were ≥65 years of age and 57% were ≥75 years of age.

Clinical studies of VENCLEXTA in patients with AML did not include sufficient numbers of younger adults to determine if patients 65 years of age and older respond differently from younger adults.

Renal Impairment

Due to the increased risk of TLS, patients with reduced renal function (CLcr <80 mL/min, calculated by Cockcroft-Gault formula) require more intensive prophylaxis and monitoring to reduce the risk of TLS when initiating treatment with VENCLEXTA *[see Warnings and Precautions]*.

No dose adjustment is recommended for patients with mild, moderate or severe renal impairment (CLcr ≥15 mL/min).

Hepatic Impairment

No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Reduce the dose of VENCLEXTA for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more frequently for adverse reactions.

OVERDOSAGE

There is no specific antidote for VENCLEXTA. For patients who experience overdose, closely monitor and provide appropriate supportive treatment; during ramp-up phase interrupt VENCLEXTA and monitor carefully for signs and symptoms of TLS along with other toxicities. Based on venetoclax large volume of distribution and extensive protein binding, dialysis is unlikely to result in significant removal of venetoclax.

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Ref: 20070720 Revised: June 2022

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Updates In Treatment of Metastatic Melanoma & Metastatic Uveal Melanoma

PRESENTERS: **Jocelyn Joseph**, PharmD, BCOP | MD Anderson Cancer Center; **Anna Jan**, PharmD, BCOP, MD Anderson Cancer Center

SYNOPSIS: Joseph reviewed updates in treatment recommendations for adults with newly diagnosed stage IV metastatic melanoma. She discussed literature that supported the use of LAG-3 inhibitors in treatment and their place in therapy. She compared the safety profile of nivolumab and relatlimab to nivolumab plus ipilimumab. Jan reviewed treatment options for uveal melanoma. She discussed the role of new treatment options for metastatic uveal melanoma and described the administration and management of toxicities associated with the treatment options for uveal melanoma.

PRESENTATION: Joseph discussed the role of immune checkpoint inhibitors in the treatment of metastatic melanoma patients and how advancements in these therapies are providing newer treatment opportunities. She noted that in the treatment of metastatic melanoma, there are three main types of medications used: PD-1 inhibitors, BRAF and MEK inhibitors and dual checkpoint inhibitors. The data currently shows that using checkpoint inhibitors with different mechanisms of action results in enhanced T-cell function and overall better response rate. She reviewed the response rates of nivolumab +relatlimab and discussed their role in the treatment of metastatic melanoma. The data suggested that combination therapy with a LAG-3 agent performed better in treating patients with stage IV metastatic melanoma.

Jan discussed the impact of different therapies for metastatic uveal melanoma. While it is a rare disease, it is the most common form of intraocular melanoma. She discussed tebentafusp, which is a new Category 1 recommendation per the National Comprehensive Cancer Network guidelines for individuals with HLA-A*02:01-positive unresectable or metastatic uveal melanoma. She reviewed an article that was published in the *New England Journal of Medicine* that compared tebentafusp to other treatment options and found that the median survival rate increased from 16 months to 21.7 months, and progression-free survival rate increased from 19% to 31% at six months.

TAKEAWAY POINTS:

- LAG-3 therapies like relatlimab have compelling data for their use in metastatic melanoma.
- Tebentafusp has been shown to be more effective than current treatments available for HLA-A*02:01-positive unresectable or metastatic uveal melanoma.

Summary by **Nitin Joshi**, PharmD Candidate (2023), ETSU Bill Gatton College of Pharmacy.

Scan the QR codes at right to view slides from presentations.

Updates in HER2-Low Breast Cancer & Updates in ITP: From TPO to SYK

PRESENTERS: **Sydney Schultz**, PharmD | Mayo Clinic; **Alexis Kuhn**, PharmD, BCOP | Mayo Clinic

SYNOPSIS: Schultz discussed the results of the DESTINY-Breast04 trial and the adverse events that may occur with treatment of trastuzumab deruxtecan. Kuhn discussed therapeutic updates for immune thrombocytopenia (ITP) in both children and adults.

PRESENTATION: Schulz discussed the treatment landscape of HER2-low categorized breast cancer. The subgroup, HER2-low, includes patients who were previously considered to be triple-negative, as well as those who were considered to be HER2-positive. According to Schulz, about 60% of patients previously considered HER2-negative are now considered HER2-low. The treatment discussed was trastuzumab deruxtecan, an antibody drug conjugate that differs from traditional TDM1 therapy.

Schulz presented the bystander effect as the biggest difference between traditional TDM1 and T-DXd therapy. This effect was described as the antiHER-2-directed antibody acting as a homing system that brings the cytotoxic payload to cells expressing the HER2 protein. Because of the tetrapeptide-based cleavable linker, the topoisomerase 1 inhibitors payload breaks away from the antibody and the membrane permeability allows the cytotoxic payload to affect the neighboring cells.

The DESTINY-Breast04 trial for this therapy was randomized in a 2:1 fashion of HER2-low, unresectable and/or metastatic breast cancer patients. Patients received trastuzumab deruxtecan or physician's choice. The primary endpoint was progression-free survival with HER2-low expression.

Kuhn discussed updates in ITP therapy for adults and pediatrics. ITP has three distinct duration-based phases including "new," "persistent" and "chronic." The ASH guideline update form 2019 included treatment options for both pediatrics and adults. Kuhn presented information for persistent and chronic phases with first-line options being TPO agonists and splenectomy being reserved as a last-line therapy.

TAKEAWAY POINTS:

- The DESTINY-Breast04 trial showed a prolongation of overall survival from 16.8 months with chemotherapy vs 23.4 months with T-DXd.
- Nausea, vomiting and lung toxicity proved to be higher in the T-DXd group than in the physician's choice group.
- While adult patients may progress to chronic ITP, the incidence of children progressing to the chronic stage is low.

Summary by **Kimi Breede**, PharmD Candidate (2024), ETSU Bill Gatton College of Pharmacy.

Scan the QR codes at right to view slides from presentations.

The Impact of Equity and Diversity Challenges Amongst Oncology Patients

PRESENTERS: Kashyap Patel, MD | Carolina Blood and Cancer Care Associates; **Margaret Caldwell**, Patient

SYNOPSIS: Patel discussed the importance of addressing cancer patients' equity and diversity challenges and how they have managed them at Carolina Blood and Cancer Care Associates.

PRESENTATION: Patel stated that five different areas primarily impact oncology patients' outcomes based on social determinants of health. He noted that lack of diversity in next-generation sequencing and related tests negatively impacts outcomes.

He went on to discuss the lack of diversity in genetic databases for patients outside of European descent, which complicates the availability for actions to be taken on those with varying ancestries. Lack of testing results in improper care and an increase in cost to the healthcare system.

Another impacting factor was the lack of screening for patients. Patel believes we must take a bottom-up approach to increase access to tumor testing and genetics to implement actual change.

He discussed payer-related factors that provide a barrier to care and financial toxicities, including medical debt and food and housing issues. To manage this, his practice has partnered with local programs in the area to help provide housing and food for his patients in need.

Patel emphasized that the most crucial way to overcome apprehension is to establish a human connection with patients. Caldwell noted that she would not be alive today if Patel had not gone the extra mile to connect with her.

DISCUSSION:

Q: What are two things that we can take back to our practices?

A: Create a third-party insurance fund to help supplement all healthcare costs. Focus on the patient as a human being, not a tumor, and talk about the financial impact on the patient and not just the healthcare system.

Q: How do we increase trial participation in underrepresented populations?

A: Help the patient understand and make them comfortable with the trial and ultimately establish a more human connection with the patient.

TAKEAWAY POINTS:

- The five main areas impacting outcomes are lack of Next-generation sequencing, cancer screenings, access to clinical trials, payer-related factors and financial toxicities.
- Fixing these issues requires making a human connection with patients and keeping them at the center of the practice.

Summary by **Charles Burke**, PharmD Candidate (2023), University of Florida.

SESSION SLIDES: Scan the QR code at right to view slides from this presentation.

Drug Interactions for Oral Chemotherapy Management

PRESENTER: Paige Reid, PharmD | Texas Oncology

SYNOPSIS: Reid addressed the importance of understanding how herbal products, dietary supplements and common foods can cause interactions with chemotherapy.

PRESENTATION: Many patients take herbals and supplements to maintain health and prevent, alleviate or cure disease.

Patients undergoing chemotherapy or have cancer may utilize Complementary and Alternative Medicine (CAM) for various reasons, including coping with treatment side effects, comforting worries or trying to treat or cure their cancer. Commonly used herbal products to be familiar with include black cohosh, saw palmetto, red yeast rice, DHEA, echinacea, St. John's Wort, ginkgo and ginseng. Patients using these products alone or in combination with other medication therapy may experience side effects including, but not limited to, GI distress, increased risk of hormone-sensitive cancers, hepatotoxicity, increased risk of bleeding and drug metabolism interactions.

Cancer affects every aspect of a patient's health, including appetite and diet. Common foods can cause interactions with a patient's chemotherapy in addition to herbal and natural supplements. Patients should be counseled on "good foods" to fuel their bodies, including plant-based proteins, healthy fats and carbs, and vitamins and minerals.

It is also important for both healthcare providers and patients to be aware of how recent meals and fat content of meals can interfere with bioavailability and absorption times of oral chemotherapy agents.

Additionally, patients receiving cancer treatment have compromised immune systems and should limit the risk of exposure to foodborne illness. Foods to consume with caution include grapefruit juice, orange juice, raw meats and uncooked foods.

TAKEAWAY POINTS:

- Medication reconciliation is a great opportunity to inquire about a patient's use of herbal products, supplements and dietary habits.
- It is important to determine the therapeutic benefit of patients taking herbal products and supplements and have a conversation to address the necessity of them taking it.
- Be knowledgeable about frequently used products and research for natural products that patients report taking.

Summary by **Maddie Lee**, PharmD Candidate (2024), Drake University .

SESSION SLIDES: Scan the QR code at right to view slides from this presentation.

Molecular Testing for Non-Small Cell Lung Cancer

PRESENTER: Jill Kolesar, PharmD, BCOP | University of Kentucky

SYNOPSIS: Kolesar encouraged utilizing next-generation sequencing (NGS) through molecular tumor boards (MTBs), to target specific receptors for patients battling Non-Small Cell Lung Cancer. Using NGS not only improves outcomes, but it also diminishes the chance of resistance to anticancer agents. Her efforts in molecular cell testing have helped transform the idea of cancer as an acute death sentence to more of a chronic disease state

PRESENTATION: According to the World Health Organization, lung cancer has been a leading cause of death for worldwide for years due to the complexity of the cancer. Fortunately, researchers have been working to create targeted therapies to prolong survival.

The Molecular Tumor Board at the University of Kentucky was created to bridge the gap between patients and doctors related to targeted therapies and genomics sequencing. MTBs act as consultant services and review each patient's case individually. Information is entered in electronic health records, along with recommended therapy to be administered. Often to ensure patients receive proper targeted therapy, more tests are required per MTB standards.

To see the true impact of MTB, Kolesar and her team assembled a case-control study from 2017-2019 to compare the results of patients who had molecular testing done and were placed on targeted therapy against the patients who did not. Results showed that patients who had molecular testing prior to receiving therapy had an eight times higher survival rate than patients who did not receive testing.

Kolesar and her team decided to take the study a step further and asked if it mattered where patients got treated, comparing community to academic settings. In both settings, the number of patients receiving their targeted therapy was about equal, meaning location of therapy did not matter.

Overall, it is shown that molecular testing is very useful in increasing a patient's life expectancy.

TAKEAWAY POINTS:

- MTB next-generation sequencing technique is effective in increasing survival with patient battling non-small cell lung cancer regardless of location.
- A future goal of MTB is to reach more patients who have a socioeconomic barrier.

Summary by **Janaya Mott**, PharmD Candidate (2025), Shenandoah University.

SESSION SLIDES: Scan the QR code at right to view slides from this presentation.

Legislative Roundtable: Reform, Leadership & Policy Updates

MODERATOR: Jessica Nagro, PhRMA

PRESENTERS: Jasey Cárdenas | McKesson, **John McDonald III** | New York State Assembly member, **Jerrica Mathis**, MSEd | Cardinal Health

SYNOPSIS: The panel talked about the impact of the Inflation Reduction Act of 2022 (IRA) on the pricing of drugs. Panelists discussed how the midterm elections would affect the IRA. They encouraged professionals in the oncology field to get more involved and suggested ways they can promote change by being involved in legislation.

PRESENTATION: Congress passed the IRA in August 2022 and it was signed into law by President Biden. Mathis discussed the drug-pricing changes and how they will benefit the patients. Some of the benefits include limiting drug price increases and pricing negotiations for Medicare Part D, with manufacturers getting penalized for refusing to negotiate. Legislation approved $3 billion for the fiscal year 2022 to implement drug price negotiations over the 2021-2023 period. Cárdenas mentioned the impact IRA will have on providers as they won't be caught up in the middle of negotiations and, inevitably, hurt patient care.

McDonald talked about the importance of the midterm elections and how they will affect pharmacy. He stressed the importance of the two parties coming together, noting, "Government usually works best when people are divided. People will have to compromise and it forces parties to start talking about legislation." Bipartisan agreement could lead to greater transparency.

All presenters stressed the importance of pharmacy involvement with the legislation. McDonald said, "Pharmacists don't realize how impactful they are in the legislative process."

McDonald and Mathis challenged the audience to invite legislators to their pharmacies to show what they do in practice.

Cárdenas said that legislators aren't aware of the medical process. Allowing legislators to understand what pharmacies do helps them do their job better.

DISCUSSION:

Q: What are the biggest challenges facing oncology?

A: Bipartisan agreement to increase access to patient care.

TAKEAWAY POINTS:

- IRA is going to change the landscape of how drug pricing is negotiated.
- The importance of the profession of pharmacy being involved with legislation.

Summary by **Sam Palmatier**, PharmD Candidate (2024), University of Minnesota.

Oncology Legislation Tracker: Scan the QR code at right to view NCODA's Oncology State Legislation Tracker.

Anatomy of a Collaborative Practice Agreement

PRESENTERS: **Benyam Muluneh**, PharmD, BCOP | University of North Carolina Medical Center; **Jessie Modlin**, PharmD, BCOP | St. Luke's Health System, Idaho

SYNOPSIS: Muluneh discussed the misconceptions, changing of interpretation, benefits and challenges involved with Collaborative Practice Agreements (CPAs). Modlin analyzed the legal considerations, important components involved and resources available to start or modify CPAs.

PRESENTATION: Modlin introduced a call to action from the Hematology/Oncology Pharmacy Association (HOPA) that discussed CPAs, including labs and symptom management of oral oncolytics. This stressed that CPAs should exist where oncology pharmacists are critically involved in the interdisciplinary care team.

Modlin reviewed the importance of thoroughly reviewing the laws and regulations due to the ambiguity among the different states, and utilizing that information to determine and define what those important components of the CPA will be. Included with the legal considerations and components, Muluneh discussed in detail the misconceptions surrounding CPAs and how interpretation of the laws have changed over time compared to initially being more prescriptive.

Muluneh further discussed that utilizing CPAs has shown improvement in patient education, adherence, frequency of clinical assessments, toxicity management and financial outcomes. He also discussed the challenges of provider status, available billing codes for pharmacists, familiarity by payer, direct and indirect billing, and facility fee billing.

DISCUSSION:

Q: When making changes to therapy using a CPA, do you usually inform the prescribing physician or NP?

A: Muluneh and Modlin agreed that it depends on the patient scenario such as dose change, therapy change, or adverse reactions being experienced.

Q: How do you overcome physician resistance to CPAs in a small practice, or when APP staff perform most of the functions within the scope of pharmacy and CPAs are not mandated or part of state law?

A: Practices must understand what is important to the physicians. It's important to build trust and promote areas of the pharmacist's expertise that don't overlap with the physician's. Start small by taking one simple task off the physician's agenda to make their day easier.

TAKEAWAY POINT:

• It is important to build a foundation of trust and utilize the CPA to continue to grow and augment your patient care practices.

Summary by **Abbey Pendley**, PharmD Candidate (2024), Auburn University.

SESSION SLIDES: Scan the QR code at right to view slides from this presentation.

The 4-1-1 on 420: A Clinical and Legal Review of Medical Cannabis

PRESENTER: **Maya Leiva**, PharmD, BCOP | Inova Schar Cancer Institute

SYNOPSIS: Leiva discussed clinical strategies and pharmacology regarding medical cannabis. Leiva also talked about the challenges regarding its legality for medical and recreational use across the United States – as well as changing legislation that may shift these conversations.

PRESENTATION: Leiva discussed in detail the major relevant cannabinoids and their potential benefits. The National Academy of Sciences commissioned and published a large systematic review in 2017. The review determined that medical cannabinoids, such as CBD and THC, may prove beneficial in multiple indications including chronic pain, chemotherapy-related nausea and vomiting, AIDS-related cachexia, neuropathic pain, anxiety disorders, and sleep disorders. Proper dosing and safety should be considered for any medical indication. Though there are no real dosing guidelines for CBD, the average daily doses range from one to three grams. For symptom control and functional improvement, the lowest dose of THC should be targeted. Dosing should be adjusted or increased based on patient response. Although marijuana-based products are federally classified as Schedule I drugs, individual states have their own regulations regarding use of recreational and medicinal marijuana. The H.R. 3617 "MORE Act" was passed by Congress in April 2022. This act has now been moved to the Senate, and if passed, would remove marijuana from the list of Schedule Substances from the federal Controlled Substances Act, as well as eliminate criminal penalties.

DISCUSSION:

Q: Why are clinical trials that include cannabinoids, particularly THC, such a challenge when there's so much interest?

A: The main challenges surround the chain of custody and getting the DEA and FDA approval for Schedule I drug trials.

Q: Besides immunotherapy, are there any oral oncolytics that have a contradiction with cannabis?

A: Drugs that rely on T-cell activation in the tumor microenvironment may be of concern. However, this is not an absolute contraindication and interactions have not been thoroughly studied.

TAKEAWAY POINTS:

• Cannabinoids may prove useful to patient's well-being in a variety of different indications, including but not limited to, chemotherapy-related nausea and vomiting.

• Patients should start on the lowest effective dose and be increased based on response and tolerability.

Summary by **Nathan Uk**, PharmD Candidate (2024), University of Minnesota.

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