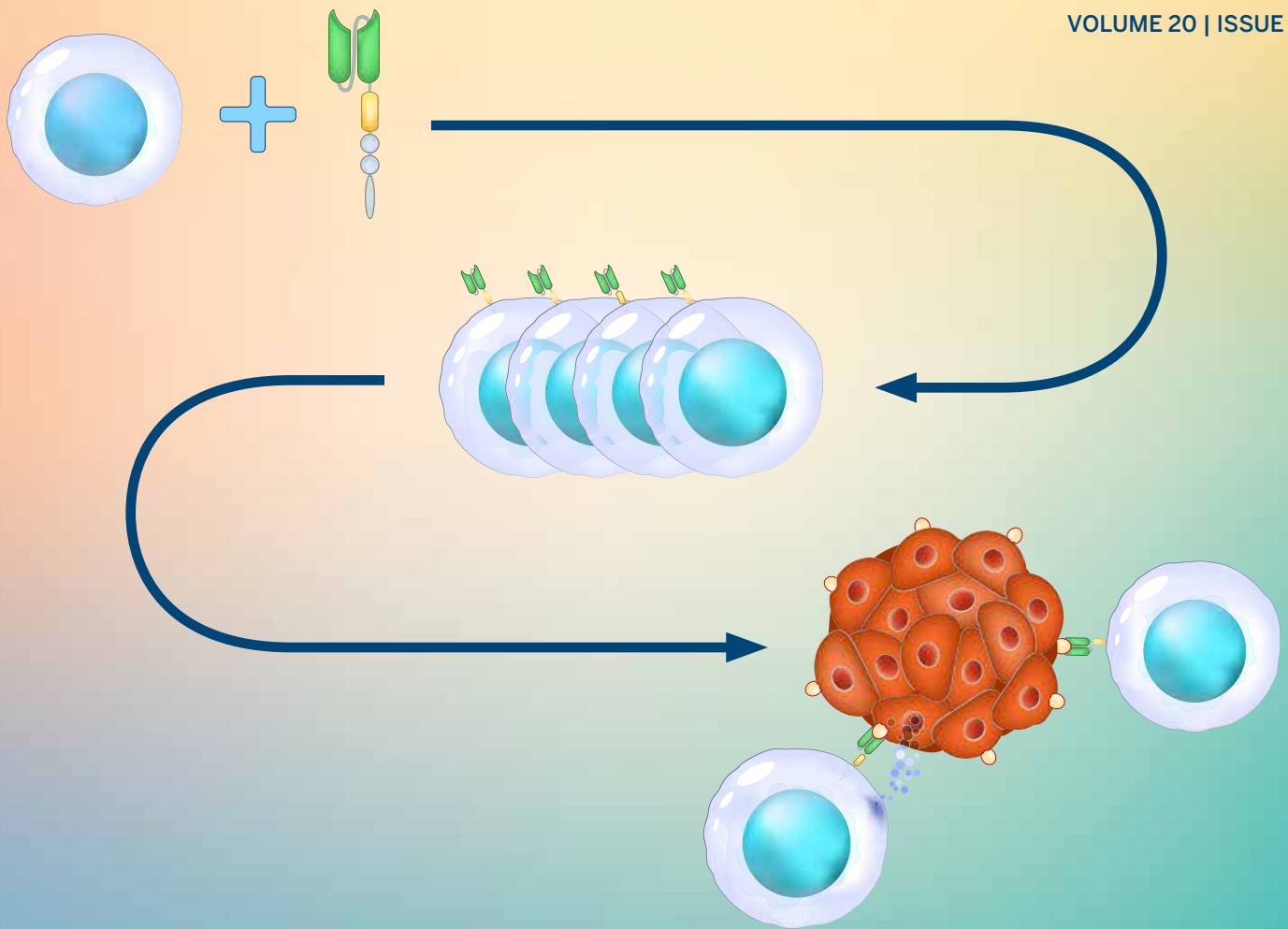


HOPA NEWS

Pharmacists Optimizing Cancer Care

VOLUME 20 | ISSUE 4



Lymphoma Bispecific T-cell Engagers' Place in Therapy

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Pharmacists Optimizing Cancer Care®

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Lymphoma Bispecific T-cell Engagers' Place in Therapy



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Introduction

Approximately 40% of non-Hodgkin lymphoma is diffuse large B-cell lymphoma (DLBCL)^{1,2} making it the most commonly diagnosed subtype with a five-year relative survival rate of 64.7%. In the first-line setting, patients achieve a 60-70% cure rate. Once patients progress into the second-line setting, response rates decrease dramatically to 26%, leaving an unmet need in the third-line setting and beyond.² The standard first-line treatment options for DLBCL include chemotherapy and immunotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or Pola-R-CHP (polatuzumab, rituximab, cyclophosphamide, doxorubicin, prednisone). For the second-line setting, treatment selection may vary between an autologous hematopoietic stem cell transplant (HSCT), anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, or non-curative chemotherapy and immunotherapy.

Bispecific T-cell engagers (BiTE) are a novel new treatment option for DLBCL patients in the third-line setting and beyond. BiTE therapies are beginning to evolve the treatment landscape for lymphoma, filling a treatment gap for patients post anti-CD19 CAR T-cell therapy in relapsed or refractory DLBCL in the third-line setting. Two BiTE agents, epcoritamab and glofitamab, were granted United States Food and Drug Administration (FDA) approval this year in adult patients with relapsed or refractory DLBCL who have received two or more prior lines of systemic therapies.^{1,3} They are both CD20:CD3 BiTE therapies with differences in structure and administration.⁴

Overview of Epcoritamab and Glofitamab

Epcoritamab is a full length IgG1 bispecific antibody with a 1:1 structure administered subcutaneously (SQ) until disease progression or unacceptable toxicity.⁵ It binds to a specific epitope on CD20 to allow for co-administration with other CD20 targeted medications and is currently being studied in combination with other chemotherapy agents.⁶ Glofitamab is also a full length IgG1 bispecific antibody with a unique 2:1 structure and is administered intravenously (IV) with a fixed duration of 12 cycles.⁷ This structure has an extra Fab fragment which allows for bivalent binding to CD20. Glofitamab can also be co-administered with other CD20 targeted medications and is currently being studied in combination with chemotherapy and other CD20 targeted medications due to its novel structure. Both drugs are administered in stepwise dosing

to help decrease the risk of cytokine release syndrome (CRS) which is the main adverse effect for both agents.^{1,3}

Epcoritamab is given in a 28-day cycle and requires two step-up doses before administering the target dose weekly.¹ Patients receive 0.16 mg SQ on day 1, then 0.8 mg SQ on day 8, followed by the target dose of 48 mg SQ on day 15 and beyond. Once patients have completed three cycles of epcoritamab 48 mg SQ weekly, the frequency changes from weekly to biweekly administration for cycles 4 through 9. Starting on cycle 10 and beyond, patients receive epcoritamab 48 mg SQ monthly until disease progression or unacceptable toxicity. Premedication with an antihistamine, acetaminophen, and steroid is required for cycle 1, with additional steroids given for three days after administration to prevent CRS. Premedication only continues after cycle 1 if patients experience grade 2 or 3 CRS.

On cycle 1 day 1 of glofitamab, patients only receive obinutuzumab.³ This serves as a preventative measure for CRS by debulking the tumor burden prior to exposure to glofitamab on cycle 1 day 8. The weekly step-up dosing for glofitamab is 2.5 mg

IV on cycle 1 day 8, then 10 mg IV on cycle 1 day 15. The target dose is administered starting on cycle 2 day 1 at 30 mg IV and is given every 21 days up to 12 cycles. The first three doses are administered over a 4-hour infusion and glofitamab can then be infused over 2 hours if no CRS occurs. Premedication with an antihistamine, acetaminophen, and steroid is required prior to glofitamab cycles 1, 2 and 3. It is recommended to continue premedication if patients experience CRS.

For both BiTE therapies, prophylaxis for *Pneumocystis jiroveci* and herpes virus are recommended.^{1,3} Any delays in treatment may require re-administering

the step-up doses; this is important to consider, especially if treatment is interrupted during the initial step-up doses. Neither BiTE therapy has any known drug-drug interactions, which allows them to be easily combined with other treatments. Epcoritamab does have approval for High Grade B-cell Lymphoma (HGBL) (double and triple hit) while neither of them have FDA approval in Primary Mediastinal B-cell Lymphoma (PMBL) patient population.

Overview of Clinical Studies

Epcoritamab was FDA approved based on a dose-expansion phase 1 and 2 study in patients with relapsed or refractory large B-cell lymphoma who had received at least two prior lines of therapy.⁶ The primary endpoint was overall response rate (ORR). There were 157 patients treated with at least one dose with a median follow up of 10.7 months. The ORR was 63.1% with a complete response (CR) rate of 38.9%. Of the 61 patients who had previously received

"As anti-CD19 CAR T-cell therapy continues to be used in the second-line setting, BiTE therapies are fulfilling an unmet need in the third-line setting post anti-CD19 CAR T-cell therapy."

anti-CD19 CAR T-cell therapy, 21 patients (34.4%) achieved a CR. About half of the patients (49.7%) experienced any grade CRS, with grade 3 or higher occurring in 2.5% of patients. The median time to CRS was 21-24 hours post-administration, with most events occurring in cycle 1; 61% of the CRS cases occurred on cycle 1 day 15 and were mainly grade 1 in severity. Any grade of immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 6% of patients with a median time to onset of 3 days; one fatal ICANS event occurred.

Glofitamab was FDA approved based on a Phase 2 study in patients with relapsed or refractory DLBCL who had received at least two prior lines of therapy.⁷ The primary endpoint was CR rate. There were 154 patients who received at least one dose with a median follow up of 12.6 months. For the primary endpoint, 39% of patients achieved a CR. Of the 52 patients who had previously received anti-CD19 CAR T-cell therapy, 18 patients (34.6%) achieved a CR. More than half of the patients (63%) experienced any grade CRS, with grade 3 or higher occurring in 4% of patients. The median time to CRS was 13.5 hours post-administration, with most events occurring in cycle 1; 54.5% of the CRS cases occurred on cycle 1 day 8 and were mainly grade 1 in severity. Any grade of ICANS occurred in 8% of patients with no fatal events occurring.

Sequencing and Clinical Implications

These FDA approvals raise the question of appropriate sequencing in the third-line DLBCL space. The current National Comprehensive Cancer Network (NCCN) guidelines include BiTE therapies, anti-CD19 CAR T-cell therapy, loncastuximab tesirine, and selinexor as category 2A recommendations in the third-line setting, making it difficult to determine which treatment option is most appropriate for a patient.⁸ Currently the only potential curative option in the third-line setting would be anti-CD19 CAR T-cell therapy, but this treatment is more commonly utilized in the second-line setting, which limits the number of curative treatment options available. Nearly half of the patients who receive anti-CD19 CAR T-cell therapy in the third-line setting relapse, leaving an unmet need for patients who progress.

Of the available treatment options listed in the NCCN guidelines for the third-line setting, there are reservations about the use of loncastuximab and selinexor.⁹ For the overall patient population, loncastuximab had an ORR of 48.3% with 35% of patients achieving a CR. Although there were 15 patients studied post anti-CD19 CAR T-cell therapy with loncastuximab, given its similar target to anti-CD19 CAR T-cell therapy, there is hesitancy to use it right after progression. Despite the recommendations in the NCCN guidelines to use selinexor post anti-CD19 CAR T-cell therapy, Kalakonda et al. did not specify whether patients received prior anti-CD19 CAR T-cell therapy and included 38 patients post autologous HSCT.⁹ For the overall patient population, selinexor had an ORR of 28% with 12% of patients achieving a CR. In comparison to loncastuximab and selinexor, epcoritamab and glofitamab included a higher

number of patients who had previously received anti-CD19 CAR T-cell therapy, 61 and 51 patients respectively, with a little over a third of patients (34% for both agents) achieving a CR, supporting the NCCN recommendation to be used post anti-CD19 CAR T-cell therapy.¹⁰ If patients have received anti-CD19 CAR T-cell therapy, BiTE therapies have demonstrated excellent response rates versus the other NCCN recommended options of loncastuximab tesirine and selinexor. In the post-autologous HSCT setting, BiTE therapies have not shown to be curative yet and therefore for eligible patients with curative intent, anti-CD19 CAR T-cell therapy is the treatment of choice over BiTE therapies. If patients are ineligible for anti-CD19 CAR T-cell therapy, BiTE therapies are a promising option in the third-line setting.

Although direct comparisons between trials cannot be made, overall both the epcoritamab and glofitamab trials have similar response rates and safety profile (Table 1). Important counseling points and monitoring for pharmacists includes reviewing CRS and ICANS symptoms and the importance of recognizing and treating promptly. The main differences between the two medications are administration and duration of treatment; epcoritamab is administered SQ with a shorter infusion chair time, has more frequent dosing, and is given indefinitely whereas glofitamab is administered IV with a longer infusion chair time, less frequent dosing overall, and is given at a fixed duration of 12 cycles. When determining which BiTE therapy to select for a patient, it is crucial to consider patient preference.

Some patient specific risk factors to consider that put patients at higher risk for CRS complications are age \geq 65 years, high tumor burden, and circulating tumor cells. Loncastuximab and epcoritamab are the only agents that have FDA approval in HGBL, which provides an option in the third-line setting for patients post anti-CD19 CAR T-cell therapy. Preparation, time, and resources are needed to administer anti-CD19 CAR T-cell therapy which can delay treatment for patients and can require bridging treatment. One of the advantages to BiTE therapies is that they can be quickly acquired and administered which is beneficial for patients who cannot wait for the anti-CD19 CAR T-cell process. There are clinical trials researching both BiTE therapies, epcoritamab and glofitamab, in earlier lines of treatment.

Conclusion

FDA approvals with unique and novel BiTE therapies in the DLBCL space have produced exciting response data and challenge the current treatment landscape. Patient specific goals and factors influence decisions on what to treat with in the third-line setting. As anti-CD19 CAR T-cell therapy continues to be used in the second-line setting, BiTE therapies are fulfilling an unmet need in the third-line setting post anti-CD19 CAR T-cell therapy. Important safety considerations include CRS and ICANS, which require pharmacists to appropriately educate and monitor patients closely. ●●

Table 1. Epcoritamab and Glofitamab Comparison Chart

	Epcoritamab	Glofitamab
Administration	SQ	IV
Frequency	28-day cycles: Weekly (Cycles 1-3) Biweekly (Cycles 4-9) Monthly (Cycles 10+)	21-day cycles: Weekly (Cycle 1) Every 21 days (Cycles 2-12)
Infusion Time	Injection	4 hours (cycle 1 days 8, 15 and cycle 2 day 1) 2 hours (cycle 3+ if no CRS observed)
Premedications	<u>Recommended for cycle 1 only (if no grade 2+ CRS observed):</u> Antihistamine Acetaminophen Steroids (on days 1-4)	*Obinutuzumab (only given on cycle 1 day 1) <u>Recommended for cycles 1, 2, and 3 (if no CRS observed):</u> Antihistamine Acetaminophen Steroids
Duration of Treatment	Indefinitely	Up to 12 cycles
Efficacy		
ORR	63.1%	52%
CR	39%	39%
Safety		
Any grade CRS	49.7%	63%
Median time to CRS	21-24 hours	13.5 hours
Highest risk of CRS	Cycle 1 Day 15	Cycle 1 Day 8
Any grade ICANS	6%	8%
FDA Indication(s)	R/R DLBCL R/R HGBL	R/R DLBCL

SQ: subcutaneous; IV: intravenous; ORR: overall response rate; CR: complete response; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome.

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Reflections of a New Residency Program Director



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Last month marked my one-year anniversary as the Post Graduate Year-2 Adult Oncology Residency Program Director (RPD) at Memorial Sloan Kettering (MSK). I had worked hard for many years in hopes of becoming an RPD and felt honored to transition into this role at MSK. Becoming RPD brought tremendous change, growth, and a healthy dose of self-reflection over the past 12 months. First and foremost, I believe the core quality of a successful RPD is the ability to find joy in mentorship. Additionally, the foundation of a strong program is based on your understanding of resources, the empowerment of your team, and creating experiences that meet the needs of residents.

Through mentorship many of us found our paths to oncology pharmacy. A common trait connecting residency programs and members of professional organizations is the desire to pay this guidance and training forward to others. Within residency programs, including our programs at MSK, mentorship is a strong thread which weaves together preceptors and has fostered the growth of residents. Examples of strategies that have benefited our program include providing continuity and actionable guidance, and setting clear expectations. To

provide continuity, we have incorporated rotation hand-offs that highlight resident strengths with a special focus on sustainability of the achievement, concrete examples of how to improve during the next rotation, and ensuring the resident remains on track for graduation. Preceptors for both the preceding and upcoming rotations attend, as well as the mentor for the resident. The structure and intent of these hand-offs has continued to evolve since the program's inception. During each hand-off we recap goals for the month and address progress, including whether previous development strategies proved to be sustainable and applicable across specialties. For example, one of our residents identified that reviewing primer papers or lengthy references prior to rotation led to information paralysis. Through trial and error, we together identified that an alternative approach of providing podcasts and online lectures helped tremendously with rotation preparation.

"I ultimately learned that tailoring experiences to better suit the interests of both the preceptor and resident can improve job satisfaction and achievement of professional goals."

This preparatory method subsequently became a sustainable strategy for future rotations and an actionable item for preceptors as they helped identify appropriate content. Hand-off discussions changed throughout the year to align with ASHP Competency Areas, Goals, and Objectives (CAGOs) and resident learning styles. We use a similar method when assessing progress on research projects during Residency Research Subcommittee meetings, continuing education lectures, and academic lectures provided at pharmacy schools. Regarding setting clear expectations, this is a skill that develops with experience. To enhance this ability, we developed methods for preceptor training centered around the idea of mentorship. This year, MSK Residency Program Coordinators (RPC) spearheaded our first ever new preceptor orientation. During this experience, RPCs provided actionable strategies for

precepting including setting realistic expectations dependent on the residents' individual experience and providing constructive feedback. We have found that, through mentorship, our program continues to evolve as does professional development within the team.

In addition to motivated mentors, the greatest resource available to RPDs is the ASHP Accreditation Standard for Residency Programs. When transitioning into this role, I reviewed the ASHP Accreditation Standard and our Pharmacy Residency Manual concurrently. It helped me to make the connection between the ASHP Standards, CAGOs,

and existing learning experiences within our program. I was fortunate to become RPD for an already well-established program, however, for an RPD potentially developing a new program, I highly recommend creating the basics of your manual by nearly copying the ASHP Standards and then further embellishing—you cannot go wrong. The newest version of the ASHP Accreditation Standard for residency programs became effective on July 1st, 2023.¹ Along with other programs throughout the country, we proactively revamped our manual and syllabi to ensure we are following the updated Standards. An exciting addition to the latest Standard is the prioritization of well-being and resilience training. Burnout among pharmacy residents is an unfortunate reality and has been observed within our own program. We are hopeful that implementing this longitudinal experience will improve overall well-being by enhancing self-awareness, communication, and utilization of wellness resources. This requirement has also created

≡ Reflection on Personal Impact and Growth ≡

an opportunity for additional preceptor engagement and joint professional development. Many of you may also discover that members of your team have firsthand experiences and training that will empower them to effectively lead this longitudinal experience.

During this past year I have learned to delegate tasks to best suit team member's career goals, interests, and strengths. As a new RPD I found it challenging at times to delegate responsibilities due to fear of contributing to burnout. I ultimately learned that tailoring experiences to better suit the interests of both the preceptor and resident can improve job satisfaction and achievement of professional goals. For example, a preceptor looking for research opportunities might have great interest in mentoring a resident project but decide not to volunteer due to lack of experience.

Providing mentorship to this preceptor along with guidance from the Resident Research Subcommittee can pave the way for successful project completion and professional development.

This past year as RPD has been an adventure and I am looking forward to the future. I have truly learned that the success of the program lies within the team and that the desire to mentor connects us. I am excited for continued collaboration with fellow members of HOPA and ASHP, and for connecting with residency programs throughout the nation as we shape our legacy. If you are thinking about becoming an RPD, go for it! Understanding your resources and leveraging your team will set you up for success on your journey. The reward of seeing residents succeed is immense and has enriched my life—I am hopeful it will do the same for you.



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BCOP Recertification Framework Update – A Piece of Good News!



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Did you know that soon, board-certified pharmacists will be able to earn recertification units for various professional activities? Beginning January 1, 2024, board-certified pharmacists starting a new certification cycle will be able to earn up to 20 continuing professional development (CPD) units to count towards the 100 required for recertification (for Board Certified Oncology Pharmacy [BCOP] and other Board of Pharmacy Specialties [BPS] certifications). Units can be applied for activities that align with the exam content outline, such as: teaching and precepting learners, attending CME (continuing medical education) sessions, scholarly activities, and selected workplace activities.¹ With this CPD initiative, BPS hopes to encourage oncology pharmacists to diversify their continuing educational activities and recognize the effort and time that board-certified pharmacists devote towards educating current and future pharmacists and elevating our profession.

The CPD-Recertification pilot program is a response from BPS to feedback from board-certified pharmacists who expressed the need for flexible, contemporary, interactive, and cost-effective activities as part of maintaining continued competence in their specialty practice area. BPS representatives collaborated with other professional organizations that have used a CPD framework to design a quality program. Under the current process, board-certified pharmacists can maintain their certification over a seven-year period by one of two pathways: 1) Pass the recertification exam OR 2) Earn 100 assessed CPE (continuing pharmacy education) units through a BPS-approved professional development program. Under the updated framework, the two pathways are: 1) Pass the recertification exam **and complete 20 CPD units** OR 2) earn at least **80 assessed CPE units** through a BPS-approved professional development program (**i.e. BCOP credits**) **and complete up to 20 CPD units.**

"Units can be applied for activities that align with the exam content outline, such as: teaching and precepting learners, attending CME sessions, scholarly activities, and selected workplace activities."

In summary, if your board certification is up for recertification, or you are ready to obtain your board certification, then you will need to:

1. Log into MyBPS **annually** and follow the prompts to complete the reflect and plan portion of the CPD requirement.
2. Within six months post completion of a CPD activity, complete the learn and evaluate portion for that CPD activity.
3. Earn and document two units each year over the seven year cycle.

Of note, the CPD program is within the pilot phase. BPS will continue to gather data and feedback to optimize and finalize the program. Therefore, content may change to reflect program optimization efforts. Please refer to CPD FAQs for more information and future updates.²

Below, we will share the BPS answers to commonly asked questions.

What is CPD?

CPD activities are self-selected/self-reported activities that contribute to your commitment of lifelong learning. These CPD activities may come from the following seven categories:

1. Assessed CPE via BPS-approved professional development program(s)
2. CPE and CPD portfolios
3. Academic, Professional, and Interprofessional Study
4. Teaching and Precepting Learners
5. Scholarly Activities
6. Workplace Activities
7. Leadership and Professional Service

Board-certified pharmacists may earn up to 10 CPD units per activity, depend-

ing on the type of activity. There are maximums for CPD units that can be earned per year and per recertification cycle. Another notable feature of this CPD framework is that if you participate in BPS-approved, assessed CPE, but don't pass the post-activity assessment for BPS recertification credit, you can count the ACPE credit earned as CPD units. Please refer to the CPD FAQs for details.

Who is eligible to take advantage of CPD starting in 2024?

Board-certified pharmacists, including BCOPs, who start a new certification cycle beginning in 2024 and onward are eligible. This includes pharmacists newly certified in 2023 and board-certified pharmacists who successfully recertify in 2023.

For example: If your cycle begins in 2025, then you are eligible to take advantage of the new CPD-recertification framework in 2025. If your cycle starts in 2026, then you are eligible in 2026, and so on.

PRACTICE MANAGEMENT (continued)

How to record CPD units?

Board-certified pharmacists will track recertification progress in the MyBPS portal over the seven-year period. Board-certified pharmacists, including BCOPs, falling within the updated framework will record a minimum of two units per year (BPS-approved, assessed CPE or self-selected, self-reported CPD activities) to maintain an active certification. A CPD cycle consists of five phases: Reflect, Plan, Learn, Evaluate, and Apply.

Reflect and Plan: this is completed **annually**.

- **Goal:** Help create learning goals and plan for the year.
- **Reflect:** Consider potential learning needs related to your current practice and professional development. Consider the content outline relevant to your specialty certification. What knowledge, behaviors, attitudes, or skills did you identify as an area for growth?
- **Plan:** Consider the CPD activity selected to promote the acquisition of the competency identified in your reflection. Document the SMART goal or learning objectives related to the CPD activity.
- Follow prompts when logged into MyBPS portal.



Learn and Evaluate: This is completed **within six months** of completion of the CPD activities.

- **Goal:** Record and assess the impact of the activity and how the new knowledge could be applied in your daily practice.
- **Learn:** Document via MyBPS CPD activity self-reporting portal and evidence upload feature.
- **Evaluate:** Assess the impact of your learning. Describe how your professional development or practice was/will be impacted by this learning.
- Follow prompts when logged into MyBPS portal.

Apply: Utilize the newly acquired knowledge in your daily practice.

How to document steps after logging into MyBPS (available to eligible pharmacists after January 1, 2024)?

To document CPD activities, log in to MyBPS. In the “Recertification” section, under the “Action” column, click “Report Activity.” Click the orange “Add Activity Record” button. Read the attestation before clicking the checkbox of acknowledgement. From the “Activity Type” dropdown menu, select the CPD activity you wish to report. Follow the instructions on the subsequent page and complete the required fields, including the “Evaluate” box. Upload your evidence of completion in the “Supporting documents” field by clicking the green “Add files” button. Click “Save” when you are ready to proceed.

To document your Annual Reflection & Plan, log in to MyBPS. In the “Recertification” section, under the “Action” column, click “Report

Activity.” Click the orange “Add Activity Record” button. Read the attestation before clicking the checkbox of acknowledgement. From the “Activity Type” dropdown menu, select “Annual Reflection & Plan Submission.” In the “Date” field, select a date within the year for which this reflection and plan are applicable. Respond to the “Reflect and Plan” prompts. Click “Save” when you are ready to proceed.

From the confirmation screen stating “Record has been added,” you may click “Add new activity” to report additional CPD activities or click “Return to transcript” to review all CPE and CPD completed for recertification so far. If you notice an error in CPD activities that you’d like to correct, click the “Edit” tab. In the action column, click “Edit/Del.” To delete the record, click “Delete record” above the “Activity Type” drop down. This cannot be undone. If you wish to edit the record, make appropriate changes, and click “Save” when finished. CPD activities completed the year prior cannot be edited or deleted (i.e., 2024 activities cannot be edited/deleted in 2025).

What are some examples of CPD activities?

1. BPS-approved, assessed CPE (i.e. BCOP credits)
 - You will complete 80 units of assessed CPE via BPS-approved professional development program(s). For the remaining 20 units, you can choose to complete any combination of assessed CPE via BPS-approved professional development program(s) or one or more of the newly approved self-selected, self-reported CPD activities. For example, you could complete an additional 20 units from BPS-approved professional development programs to satisfy the 100 unit recertification requirement. You do not need to complete the 80 units of assessed CPE via BPS-approved professional development programs before completing the newly approved CPD activities. The necessary plan, reflect, and evaluate components MUST be completed regardless of the mix of CPD activities.
2. CPE and CPD portfolios
 - You completed CPE from your employer titled, “Survivorship and Onco-Primary Care: Screenings and Treatment of the Whole Patient Before and After Cancer Care,” which corresponds with domains 1 and 2 of the content outline. One contact hour (0.1 CEU) will be awarded 1 CPD unit. There is a maximum of 10 units per year and 10 units per 7-year cycle.
3. Academic, Professional, and Interprofessional Study
 - You completed a semester-long course titled, “Health Information Systems Analysis and Design” for your Master’s Degree in Health Informatics, which corresponds with domain 3 of the content outline. One course will be awarded 5 CPD units. There is a maximum of 5 units per year and 10 units per 7-year cycle.
4. Teaching and Precepting Learners
 - You gave a CPE presentation at HOPA’s Annual Meeting titled, “Knowledge Gaps for Cancer Therapy-Related Cardiovascular Toxicities,” which corresponds with domain 2 of the content outline. One hour of teaching will be awarded 2 CPD units. There is a maximum of 10 units per year and 10 units per 7-year cycle.

- You developed and provided a lecture to PharmD students titled, “Long-Term Complications of Cancer Therapy,” which aligns with domain 2 of the content outline. One hour of teaching will be awarded 2 CPD units. There is a maximum of 10 units per year and 10 units per 7-year cycle.
 - You precepted a pharmacy resident during a 5-week outpatient infusion center elective rotation, which corresponds with domain 2 of the content outline. Ten hours of precepting will be awarded 1 CPD unit. There is a maximum of 2 units per year and 10 units per 7-year cycle.
5. Scholarly Activities
- You authored a peer-reviewed journal article titled, “Evolution and Innovation in Hematopoietic Cell Transplantation and Cellular Immunotherapy: Critical Updates in Therapeutics,” which aligns with domain 2 of the content outline. One article will be awarded 5 CPD units. There is a maximum of 5 units per year and 10 units per 7-year cycle.
6. Workplace Activities
- You led a quality improvement project at your institution resulting in the update of an outdated order set to reflect new supportive care guidelines, which aligns with domain 2 of the content outline. Ten hours of participation will be awarded 1 CPD unit. There is a maximum of 5 units per year and 10 units per 7-year cycle.

7. Leadership and Professional Service

- You participated as BPS Item Writer for the BCOP examination, which aligns with domains 1, 2, and 3 of the content outline. Two CPD units will be awarded. There is a maximum of 2 units per year and 10 units per 7-year cycle.

If you have questions that were not addressed by the FAQs page, please visit the contact us page on the BPS website.³ To expedite your request, select “CPD” from the first drop down menu when submitting an e-ticket. For additional information on the CPD framework, please refer to the BPS Podcast, “What is CPD? Explaining Continuing Professional Development in Pharmacy, with Michelle Estevez.”⁴

This news was brought to you by the BPS Oncology Specialty Pharmacy Council and Board of Directors. The Oncology Pharmacy Specialty Council is made up of at least ten BCOPs and up to two additional members (each of whom may or may not be BCOPs), from different practice settings, backgrounds, and expertise.⁵ Our main objective is to promote, preserve, and elevate the Board Certification Standards and the value of being BCOPs. We work to serve you, the current and future BCOPs.

Please accept our sincere appreciation for all you do for our profession and our patients! ●●

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Quality Leadership Roles within Healthcare Organizations: Q&A with Two Pharmacist Leaders



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Clinical Pharmacy Specialist - Medical Oncology
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Quality positions within pharmacy are critical to ensure the safety, efficacy and overall quality of products and services. These roles are vital in oncology to maintain compliance with stringent regulations, implement quality control measures, and continuously improve pharmacy operations for safe and effective medication use. In this article, we interview two pharmacy quality experts regarding their roles and career in quality and quality improvement.

Describe your current job responsibilities and typical workday.

Dr. Man: My responsibilities encompass several areas: quality improvement (QI), medication safety, and policy management. A typical workday for me is dynamic, shaped by ongoing initiatives and project prioritization. I am the primary preceptor for the QI longitudinal rotation in our PGY-2 Medication Use Safety and Policy residency program, dedicating my time to provide QI related training and leading various QI initiatives. Additionally, I serve as a coach for our system network's Clinical Process Improvement Leadership Program, offering guidance and expertise to participating teams. Within the realm of medication safety, I am responsible for a range of tasks aimed at ensuring the safe and effective use of medications. This encompasses adverse drug reaction monitoring, medication use evaluations, and outpatient pharmacy safety event follow-up. Within my role in policy management, I serve as the co-chair of the pharmacy policy committee. This position entails close collaboration with a diverse team of stakeholders to maintain and update policies and procedures, ensuring that the practices align with safety standards and regulatory compliance.

Dr. DiMarco: My responsibilities include both operational and clinical activities in the inpatient oncology pharmacy and two outpatient infusion centers. A typical workday consists of multi-disciplinary meetings with physicians, advanced practice providers, and nursing regarding clinical initiatives, reviews of policies, protocols,

guidelines, and formulary additions, and planning for a transition to a new infusion center in the Spring of 2024. I am also the Sidney Kimmel Cancer Center (SKCC) Pharmacy Quality Lead. In this role, I support the quality structure of the Oncology Service Line and help to identify priorities and provide education to pharmacy staff at all Jefferson locations with the goal of providing patient-centered cancer care across the enterprise.

What training(s) did you complete that allowed you to perform your role, and of these, what training or experiences did you find the most valuable?

Dr. Man: I have undergone a well-rounded training journey to equip myself for my current role. This journey includes completing a PGY-1 Pharmacy Residency, which laid a solid foundation by exposing me to pharmacy operations and providing essential clinical knowledge. I've pursued additional training to further enhance my skills in healthcare quality improvement and safety, including the American Society of Clinical Oncology (ASCO) Quality Training Program (QTP), the Clinical Process Improvement Leadership Program (CPIP), and the American Society of Health-System Pharmacist (ASHP) Medication Safety Certificate. I found the ASCO QTP training particularly instrumental in my role due to its comprehensive understanding of various QI methodologies and the practical tools it equipped me with, which are directly applicable to leading diverse projects in various settings.

Dr. DiMarco: From a management perspective, I did not have any formal training. From a quality perspective, I completed the HOPA-ASCO 1-day QTP program which was a great introduction to quality and is what really got me interested in learning more about quality improvement. SKCC - Jefferson Health was the first in the nation to submit an application for the ASCO Patient Centered Cancer Care Certification, and that is when I first started to get involved in quality improvement and eventually led to the Quality Pharmacy Lead position. I completed the ASCO-HOPA QTP 6 month course which was incredibly valuable and changed the way I approach problems and process improvement; I use the lessons I've learned from QTP nearly every day.

Can you share a success story of a process you helped improve?

Dr. Man: Institutional policies are the backbone of our operations, guiding our staff in fulfilling their roles effectively. However, we noticed a limited level of engagement with policy updates, which

"I think that is just the reality of process improvement. Things get better, or more efficient, over time, and we always keep an open mind when additional suggestions are made."

QUALITY INITIATIVES (continued)

prompted this initiative. We adopted the Plan-Do-Study-Act (PDSA) cycle methodology to guide the QI journey. Our process began with an analysis of pre-intervention data from the policy access log to identify the program. We then designed and administered a survey to assess staff members' ability to navigate the policy management system, their awareness of policy updates, and their preferred communication channels for receiving updates. Utilizing descriptive statistics, we summarized the survey responses, providing valuable diagnostic insights. Additionally, we implemented a Statistical Process Control (SPC) chart to monitor the process change over time, ensuring continuous improvement. Through interventions that included establishing a formal communication channel for policy updates and improving accessibility to relevant content, our efforts resulted in a two-fold increase in the policy access rate compared to the baseline.

Dr. DiMarco: I wish I had a nice and pretty process improvement success story, but my honest answer is that I can't think of a single process that was a success from start to finish. There is constant re-evaluation and adjustments are made based on end-user feedback. I think that is just the reality of process improvement. Things get better, or more efficient, over time, and we always keep an open mind when additional suggestions are made. One example of this is our recent guideline revision for treatment of chemotherapy extravasations. What started out as a guideline update due to drug shortages and availability turned into the realization that the EPIC orders were also in need of review and optimization. Then, once the new orders were built and ready to go, we had an extravasation in the infusion center. The next day, we received feedback that the guideline was helpful, but there was still a delay in treatment because the pharmacist and technician couldn't find the antidote in the pharmacy. After that, we designated an area for the extravasation antidotes in both the inpatient and outpatient pharmacies which contains all possible antidotes and supplies needed.

What techniques have you used to identify potential areas for process improvement in your organization?

Dr. Man: I've found that fostering collaboration with different departments and stakeholders is instrumental in identifying potential areas for quality or process improvement. This entails working closely with cross-functional teams to assess current processes and identify gaps or inefficiencies. Through collaborative discussions and data analysis, potential areas where processes may not align with best practices or where opportunities exist to optimize workflow are pinpointed. Involving team members from different backgrounds and expertise provides diverse perspectives essential for uncovering improvement opportunities. Inclusive approaches such as regular meetings and forums aid in identifying potential areas for improvement that may not be immediately apparent. By combining collaborative efforts with thorough gap analyses, the focus remains on ensuring that process improvement initiatives are well-informed, data-driven, and centered on enhancing patient care and overall organizational efficiency.

What are some of the biggest challenges you have faced when trying to improve quality in your organization?

Dr. DiMarco: My two biggest challenges are staffing and time management. We have had pretty consistent staff turnover, which makes it difficult to keep quality improvement projects going and to start larger projects. However, our lack of staffing has forced us to become creative and continue quality work with limited resources. Time management is also a challenge because since COVID the number of Zoom® meetings has increased, making it really difficult to have any downtime in between to work on projects, like for example a long-term QTP project. I think that's why the 1-day program was so helpful because it gave a small slice of a quality improvement work, and then when I entered the 6 month course I was able to experience what a longitudinal project looks like. QTP also taught me the different phases of quality work and how exciting it can be to start a project, but inevitably, projects can feel overwhelming, and the team can lose morale. It can still be hard to stay focused when other job responsibilities start to pile up as well, but normalizing this "low" phase has made it easier to recognize it and find ways to bring the project back to life. ●●

Waldenström Macroglobulinemia: What is the Best Way to BTK?



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Waldenström macroglobulinemia (WM) is an indolent hematologic malignancy that is characterized by a lymphoplasmacytic lymphoma (LPL) infiltrate in the bone marrow and the presence of a monoclonal IgM paraprotein.¹ Patients with non-IgM LPL are not considered to have WM but will typically have similar outcomes and management. Overall, WM is considered a rare disease, accounting for only 1% of all cases of non-Hodgkin lymphomas, with an age-adjusted incidence in the United States of 9.2 cases per million in men and 3 cases per million in women.^{1,2}

WM can present similar to other indolent lymphoid malignancies, with patients experiencing clinical manifestations such as lymphadenopathy, splenomegaly, constitutional symptoms, and peripheral cytopenias secondary to bone marrow infiltration.³ Due to the circulating IgM paraprotein, patients with WM can have unique complications including hyperviscosity syndrome, cryoglobulinemia, cold agglutinin syndrome, peripheral neuropathy, amyloidosis, and acquired von Willebrand disease. Much like other indolent lymphomas, not all patients will require immediate treatment, but rather indications for starting treatment often include symptomatic disease.⁴ Many factors should be considered when selecting treatment for patients with WM, including their disease presentation, patient-specific characteristics, patient preferences, anticipated toxicities, and the genomic profile and molecular features of the disease.

One of the molecular features unique to WM is the presence of the activating myeloid differentiation factor 88 (*MYD88*) L265P mutation (*MYD88*^{L265P}), which is present in up to 90% of patients with WM.³ The *MYD88* gene encodes for the adaptor protein for toll-like receptor, which triggers interleukin-1 receptor associated kinase-1 and -4 and Bruton tyrosine kinase (BTK), which then mediates nuclear factor kappa B activation. *MYD88* mutations are not specific to WM, as they do occur in other lymphomas such as marginal zone lymphoma and certain subtypes of diffuse large B-cell lymphoma,⁵ but can help to differentiate between WM and an IgM myeloma. *MYD88* wild type disease (*MYD88*^{WT}) can be present in 5-10% of WM cases and is associated with shorter overall survival and a higher risk of transformation to an aggressive lymphoma.

The other most common mutation observed in WM is in CXC motif chemokine receptor 4 (*CXCR4*^{MUT}), which may be present in 30-40% of patients with WM.^{6,7} *CXCR4* mutations cause gain-of-function activity and lead to enhanced activation of AKT and ERK and subsequent MAPK1/2 pathway signaling that can result in

sustained survival of WM cells. *CXCR4*^{MUT} disease is associated with a distinct clinical phenotype compared to *CXCR4* wild-type disease (*CXCR4*^{WT}) and patients often present with higher serum IgM levels, have a higher burden of disease in their bone marrow, and have a higher risk of developing sequelae such as hyperviscosity syndrome and acquired von Willebrand disease.⁷

Treatment options for WM, whether treatment-naïve or relapsed/refractory disease, per the International Workshop for WM recommendations include anti-CD20 monoclonal antibodies, time-limited chemoimmunotherapy, proteasome inhibitor-based regimens, and BTK inhibitors.⁴ All four BTK inhibitors (the covalent BTK inhibitors ibrutinib, acalabrutinib and zanubrutinib, and non-covalent BTK inhibitor pirtobrutinib) have been evaluated for the treatment of WM in varying capacities, however not all are approved for WM at this time.⁸⁻¹¹ In 2015, ibrutinib received United

States Food and Drug Administration (FDA) approval for the treatment of WM, hallmarking the first regulatory approval of a drug for this rare disease. In 2018, ibrutinib plus rituximab received approval for WM. Subsequently in 2021, zanubrutinib received FDA approval as well for WM. With the multiple regulatory approvals and various trials evaluating BTK inhibitors in WM, one must ask, what is the best way to use BTK inhibitors in WM? Which is the optimal BTK inhibitor in WM? Should they be paired with rituximab? What is the impact of genomic profiling on BTK inhibitor response? Should we be using a BTK inhibitor upfront or time-limited chemoimmunotherapy for WM?

Overall, BTK inhibition represents an efficacious means of treating WM as these

agents have demonstrated high response rates in the treatment of WM, with most trials observing >90% of patients responding to therapy.³ Ibrutinib and zanubrutinib have been evaluated head-to-head in the open-label, randomized phase III ASPEN trial.¹⁰ In the recently published final analysis of this trial (median follow-up of 44.4 months), zanubrutinib exhibited numerically higher rates of very good partial response and complete response (VGPR + CR) compared to ibrutinib (36.3% vs. 25.3%; *p*=0.07). Median progression free survival (PFS) and overall survival were not reached in either arm. From a safety standpoint, there were similar incidences of adverse events observed between zanubrutinib and ibrutinib. However, there were differences in the types of adverse events, primarily cardiovascular events. Exposure-adjusted incidence of atrial fibrillation and hypertension were lower with zanubrutinib versus ibrutinib (*p*<0.05). Conversely, there was a higher rate of neutropenia with zanubrutinib. From ASPEN, zanubrutinib demonstrated a numerically higher rate of quality responses and a significantly improved cardiovascular safety profile compared to ibrutinib.

"Overall, BTK inhibition represents an efficacious means of treating WM as these agents have demonstrated high response rates in the treatment of WM, with most trials observing >90% of patients responding to therapy."

CLINICAL PEARLS (continued)

How does the genomic profile of WM impact BTK inhibition? With ibrutinib monotherapy, patients with *CXCR4^{MUT}* disease had shorter PFS, delayed treatment response, and a lower rate of quality response compared to those with *CXCR4^{WT}*. In this phase II trial, patients with *MYD88^{WT}* disease had no major responses and shorter PFS than those with *MYD88^{L265P}* disease, however, there was a very small sample size of these patients.¹² In the phase III iNNOVATE trial, which compared rituximab-ibrutinib to rituximab-placebo, the clinical benefit of ibrutinib when added to rituximab was observed regardless of mutational status.⁸ In ASPEN, there were numerically higher rates of response and improved time to response observed in patients with *CXCR4^{MUT}* disease with zanubrutinib compared to ibrutinib.¹⁰ Additionally, a *MYD88^{WT}* disease cohort of ASPEN demonstrated similar response rates with zanubrutinib relative to patients with *MYD88^{L265P}* disease, however, these two groups of patients were not being directly compared.

What about the addition of rituximab to BTK inhibition? The phase III iNNOVATE trial demonstrated that the addition of ibrutinib to rituximab improved outcomes relative to rituximab alone in WM.⁸ ASPEN compared two BTK inhibitors head-to-head without the addition of an anti-CD20 monoclonal antibody.¹⁰ Adding rituximab to ibrutinib appears to overcome some of the resistances imposed by *CXCR4* mutations to ibrutinib, however, there is no data currently to suggest that rituximab needs to be added to zanubrutinib in WM.

What about acalabrutinib and pirtobrutinib? While both agents have been evaluated in early phase clinical trials in cohorts containing WM patients, neither agent currently has regulatory approval for WM. Acalabrutinib has been evaluated in a phase II trial of treatment-naïve and relapsed/refractory patients, demonstrating a 93% overall response rate.⁹ As it has demonstrated significant efficacy, acalabrutinib can be considered in the treatment of WM, but more likely as alternative to another BTK inhibitor that has more

supporting data and regulatory approval. In the phase I/II BRUIN trial, the non-covalent BTK inhibitor pirtobrutinib demonstrated a 68% major response rate among patients with heavily pretreated WM, including patients who had received a prior covalent BTK inhibitor.¹¹ With the paucity of treatment options in heavily pretreated WM, pirtobrutinib could become a reasonable treatment option in later lines of therapy for WM.

How does BTK inhibition in WM compare against other treatment options? Outside of being compared against rituximab monotherapy, this is a question that has not yet been evaluated or answered in the literature, as there are no randomized controlled trials comparing BTK inhibitors to chemoimmunotherapy or proteasome inhibitor-based regimens in WM. A recently published meta-analysis of controlled and uncontrolled trials demonstrated that bendamustine-rituximab elicited higher response rates compared to ibrutinib- and bortezomib-based therapies in WM.¹³ Randomized controlled trials comparing treatment options in WM are needed to answer this question. Chemoimmunotherapy and bortezomib-based treatment offers a time-limited therapy approach, and may also have lower overall costs relative to BTK inhibitor-based treatment.

So, then what is the best way to BTK in WM? Overall, BTK inhibitors offer high response rates in WM. Zanubrutinib showed numerically improved quality responses and time to response compared to ibrutinib monotherapy, including in patients with various genomic profiles. Zanubrutinib also has an improved cardiovascular safety profile compared to ibrutinib. Ibrutinib may be best paired with rituximab in WM, particularly in patients with *CXCR4* mutations, however this further adds to therapy cost, complexity, and safety. Moving forward, other BTK inhibitors may have a larger role in WM, such as pirtobrutinib among those patients who have already had a covalent BTK inhibitor. ●●

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I'm a Green ESFJ - But Does it Matter?: Personality Assessments in Onboarding



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I'm an ESFJ, what are you? Maybe an INTP? Or are you "High I" and "Low C"? Maybe you avoided acronyms totally, and are more of an achiever, maximizer, harmony, consistency, activator? I'm also a "green", but that may be a combination of a "white" and "yellow" in your color test. But "red" is "red", regardless of the test, right?

At least one of these personality descriptors probably sounds familiar to you – maybe all of them do! Myers-Briggs Type Indicator, DiSC® Assessment, CliftonStrengths® Assessment (previously StrengthsFinder®), the Birkman Method, and the Color Code Personality Test are just some of the personality evaluations utilized by employers and residency program leaders to provide introductory assessments of new hires or residents.¹⁻⁵

Upon starting my post-graduate year (PGY)-1 residency, I took the Birkman Method quiz to determine what personality color type I was. We discovered that in our large PGY-1 class, nearly three quarters fell into two color categories. These categories weren't surprising when we read the details: motivated/sociable and analyzers/planners. These seemed like common traits among pharmacy residents. However, a few of my co-residents fell into the other two color categories. While we all had marks under every color, some of the traits in these smaller groups could be thought of as "less desirable," like introverted/cautious and decisive/demanding. This led to some immediate tensions among co-residents and some inadvertent "us and them-ing." The color test was canceled. No more color categorizing.

When I started my PGY-2 residency, I took the Myers-Briggs Type Indicator and CliftonStrengths® Assessments. All residents met with the director of pharmacy and program leaders to discuss our results. The discussion was informative and felt like a positive introduction to my co-residents. While I don't recall the results being formally referenced the rest of the year, several residents posted their personality combination in their workspace.

Though these are very personal experiences and perceptions, I think they're illustrative of some pros and cons of using formal assessments with new residents. At Mayo Clinic – Rochester for the PGY-2 Oncology Residency program, we don't formally use any of these assessments during the onboarding or orientation period. But we do discuss their utility during our Teaching Rotation, including

pros, cons, and impact on the learner's experience. The assessments we specifically review include the Pharmacists' Inventory of Learning Styles (PILS), the Thomas-Kilmann Conflict Mode Instrument, and the ReganStein Color Personality Test.⁶⁻⁸ We chose these because they are free (bonus!) and represent a good variety of personality assessments.

The PILS assessment asks you to think of recent situations where you had to learn something new to solve a problem, then answer 17 questions on a Likert scale (usually, sometimes, rarely, hardly) with each answer assigned a letter (A, B, C, D).⁶ You then tally how many A's, B's, C's, and D's you have, with the top earner representing your dominant learning style. The four learning styles include Accommodator, Assimilator, Converger, and Diverger and correlate with how you may learn best. The breakdown of these

styles shares insight into the resident's preferential approaches to processing, teaching, learning, and relating to others, as well as some specific educational needs. This can foster excellent discussion early in the year on how a learner may prepare for topic discussions or be most successful on a rotation. This assessment also avoids stigmatizing language that can make a learner feel like one style is "better" than another. It focuses on actions to make each style a success, versus emphasizing challenges with them.

The Thomas-Kilmann Conflict Mode Instrument may not be as kind in its categorizing as the PILS assessment. This is a 30-question assessment where you're instructed to consider situations in which your wishes differ from someone else,

then to choose between two responses that would be most typical of your behavior.⁷ At times, neither option may be how you would respond, but you're still instructed to select an option closest to your own behavior. You can collect tallies in five different categories: Competing, Collaborating, Compromising, Avoiding, and Accommodating. You can further plot out your individual category scores on a bell-curve graphic with percentiles based on scores of real world practicing leaders. Unlike PILS, the descriptions of these categories are laced with negative connotations ("Competing is assertiveness and uncooperative – an individual pursues his own concerns at the other person's expense."). Despite most test-takers having a few marks in every category, inevitably someone has the most tallies in the less-desirable style, resulting in someone feeling the need to defend or explain away the assuredly errant results. Leaving a learner feeling "boxed-in" is one of the cons to some of these personality assessments. No one ever wants to feel "other'd", especially when making a first impression at a new institution.

"However, caution is encouraged to use assessments that best suit the goals of your onboarding and avoids putting residents in a "box" where they may be impacted personally and professionally for the rest of their residency year."

THE RESIDENT'S CUBICLE (continued)

While leadership may never reference these assessments again or share them with preceptors, the learner doesn't know that. This leaves a learner starting the year in a vulnerable position, likely the opposite intention of an onboarding assessment.

The last assessment we discuss is the ReganStein Color Personality Test – one of many varieties of color tests. This one is a 27-question assessment where you select one word or phrase per grouping that best describes you.⁸ Your tallies correlate to one of four colors (red, yellow, blue, green), generally divided by extroversion and introversion. While the color descriptions can at times leave the tester feeling stigmatized, the summaries do share situations where this personality type is actually ideal, as well as

tendencies, weaknesses, areas for personal growth, and what they may need from others.

Overall, the use of onboarding assessments can be incredibly valuable. They can give residency leaders worthwhile insight into their new residents, but also allow co-residents to learn more about their colleagues and their own personal learning styles early in the year. However, caution is encouraged to use assessments that best suit the goals of your onboarding and avoids putting residents in a “box” where they may be impacted personally and professionally for the rest of their residency year. These should be just one part of a well-rounded onboarding process to set your learners up for success. ●●

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Kelsea Seago, PharmD, BCOP

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Relapsing and remitting, increasingly resistant, incurable – all unchanged circumstances that so often accompany a diagnosis of multiple myeloma despite significant advances in the treatment landscape over the past decade.^{1,2} But, are we getting closer to changing the narrative? Bispecific T-cell engagers (BiTEs) are the latest novel immunotherapies in the multiple myeloma treatment repertoire, and emerging data on their efficacy in heavily pretreated and refractory patients is promising.² BiTEs exhibit their effect in multiple myeloma by binding to CD3 on T-cells in addition to a tumor-associated antigen on the surface of malignant cells.² Currently approved BiTE therapies for multiple myeloma include teclistamab (Tecvayli), talquetamab (Talvey), and elranatamab (Elrexfio), with additional agents in the pipeline.³

In October 2022, teclistamab became the first BiTE therapy United States Food and Drug Administration (FDA) approved for multiple myeloma.³ Change sentence to: Studied in the MajesTEC-1 trial, teclistamab binds to CD3 on T-cells and B-cell maturation antigen (BCMA) on myeloma cells to target and kill the multiple myeloma cells.⁴ The approval quickly demonstrated that implementation of these novel agents would be a feat in and of itself. These agents are costly to both institutions and patients, pose significant logistical challenges, and require frequent patient monitoring along with careful consideration of site of care, and repeat dosing on varying schedules. Luckily, prior experience with blinatumomab, a BiTE utilized in acute lymphoblastic leukemia plagued with similar challenges, likely provided a buildable foundation for anti-myeloma BiTE implementation at academic medical centers and community oncology practice sites alike.⁵ Teclistamab remained the exclusive BiTE therapy on the market for multiple myeloma until talquetamab and elranatamab gained FDA approval within a single week in August 2023.³ Talquetamab was studied in the MonumentAL-1 trial and targets both CD3+ and G protein-coupled receptor, family C, group 5, member D (GPC5D) expressed on multiple myeloma cells.⁶ Elranatamab redirects T cells to mediate killing of BCMA-expressing myeloma cells and was evaluated in the MagnetisMM-3 study.⁷ While the emergence of anti-myeloma BiTE serves as another beacon of hope for the disease state, it also contributes to the already complex clinical decision-making process for many practitioners treating patients with relapsed and refractory multiple myeloma.

"For candidates fit enough for CAR T-cell or BiTE therapies, some additional deciding factors to consider include patient preference, social determinants of health, urgency of treatment necessity, prior therapies received, and any unique toxicities associated with the agents."

Not only are BiTEs novel to this malignancy, but BCMA-targeting chimeric antigen receptor (CAR) T-cell therapies idecabtagene vicleucel and ciltacabtagene autoleucel were also approved in March 2021 and February 2022, respectively.³ Though CAR T-cell therapy has been approved for over two-and-a-half years, early vector shortages and ongoing site access limitations have dampened the number of patients able to receive these therapies to date.⁸ Therefore, many clinicians are facing the clinical conundrum of determining where BiTEs best fit in the treatment of multiple myeloma with minimal data to use as guidance. By navigating this clinically challenging landscape, the data needed to best answer this question is actively being created. So, in the meantime, how do we choose?

When determining a patient's next line of therapy for relapsed and refractory multiple myeloma, the decision must always be patient centered. For candidates fit enough for CAR T-cell or BiTE therapies, some additional deciding factors to consider include patient preference, social determinants of health, urgency of treatment necessity, prior therapies received, and any unique toxicities associated with the agents.²

Social determinants of health (SDOH) may very likely impact a patient's realistic treatment options in this stage of their disease. For patients yet to receive BiTE or CAR T-cell therapy, determining whether a patient can logistically manage to stay close to the treatment facility for an extended length of time accompanied by a stable caregiver and refrain from driving for eight weeks is a helpful initial step.^{8,9,10} Typically, these stipulations are encouraged or required to receive CAR T-cell therapy, meaning some patients are better suited for BiTE therapy solely based on SDOH.⁸ Each of the available BiTE therapies is administered subcutaneously with similar recommendations surrounding inpatient administration of step-up dosing due to the risk of cytokine release syndrome (CRS) and neurotoxicity, though centers may have varying practices related to site of care based on institutional infrastructure.^{4,6,7} When choosing a BiTE based on SDOH, it's also prudent to consider how the patient can receive care close to home or travel less frequently. Connecting a patient with a community oncologist and assisting with local BiTE initiation or transfer of care after step-up dosing is often necessary. Additionally, considering the frequency of dosing may be helpful for patients with travel barriers or for those still in the workforce, even if care is being provided locally. After step-up dosing, teclistamab is dosed once per week indefinitely and elranatamab is dosed weekly through week 25 followed by every two weeks thereafter.^{4,7} However, talquetamab offers dosing

FEATURE (continued)

frequency choices with the potential for weekly or every two-week administration immediately after the completion of step-up dosing, which may be beneficial for some patients based on SDOH.⁶ The cost of the BiTE therapy must also be considered. Patient assistance is available for eligible patients through each of the respective manufacturers, but proactively assessing a patient's insurance status and coverage details is crucial in determining realistic therapy options. Additionally, the institutional financial impact may be a barrier despite adequate patient financial access. Uniquely, elranatamab has financial assistance available for institutions through the Elrexfio™ Inpatient Free Drug Program. This program may allow qualifying hospitals to initiate elranatamab with more financial ease through manufacturer-supplied 44-mg single-use vials for inpatient administration of step-up dosing.¹¹ Hence, understanding a patient's SDOH and addressing the financial hurdles of BiTE implementation are important factors in choosing therapy for a relapsed or refractory multiple myeloma patient.

Likewise, assessing the rate of relapse while also considering prior therapies received is imperative for this patient population. CAR T-cell therapy requires patient-specific manufacturing that may take up to five weeks from vein to vein, while BiTE therapies are ready for immediate use.⁸ On the contrary, in patients who have received prior CAR T-cell or BiTE therapy, there is encouraging data demonstrating that transitioning to another T-cell redirecting therapy results in a higher overall response rate (ORR) versus other types of therapies.¹² This data highlights the benefit of sequencing these agents, even if the optimal approach is still unknown. With talquetamab and elranatamab being new to the market, many centers may still be in the process of assessing these agents for addition to hospital formulary or lean towards teclistamab based on prescribing comfort for patients currently needing immediate therapy. However, in patients progressing after teclistamab or for institutions with additional BiTEs already on formulary, talquetamab may be an enticing option as the first and only anti-myeloma therapy to target GPRC5D.¹⁰

Furthermore, any available clues related to optimal BiTE sequencing must be considered from the trials that brought these BiTEs to market in addition to an understanding of any associated unique toxicities. Though there are no direct comparisons of the anti-myeloma BiTE therapies or large trials assessing the best approach to sequencing T-cell redirecting therapies, the available data on BiTEs does offer some insight to use as guidance. Cohort C of the MajesTEC-1 trial evaluated the response to teclistamab in patients who had received prior anti-BCMA treatment with an antibody drug conjugate (ADC) or CAR T-cell therapy. Twenty-five patients in Cohort C were evaluated for efficacy of teclistamab, and two patients had previously received both a BCMA-targeted ADC and CAR T-cell therapy. The results demonstrated an ORR of 40%, with 20% of patients achieving complete response (CR) or better.

Importantly, responses were rapid with a time to first response of 1.2 months and time to best response of 2.1 months. The median duration of response was not reached.¹³ In assessing the available sequencing data for talquetamab, the MonumenTAL-1 study included 58 patients who had received prior BCMA-directed therapy. Thirty-three of these patients were deemed refractory to a prior BCMA targeted ADC or BiTE, and 16 patients in this subset received the talquetamab dose recommended for a phase II trial. Of these 16 patients, 50% responded, which was similar to the response rates seen in all triple-class-exposed and penta-drug-exposed patients in addition to those with high-risk cytogenetics.^{14,15} This trial proves that sequencing talquetamab after available anti-BCMA CAR T-cell or BiTE therapy can still induce a high rate of response despite prior T-cell redirection. Of note, talquetamab was shown to commonly induce unique adverse effects such as skin, nail, and oral toxicities likely related to its target, as well as hypophosphatemia, decreased appetite, and weight loss.¹⁵ Similarly, outcomes with elranatamab in patients with prior anti-BCMA exposure was evaluated in cohort B of the MagnetisMM-3 trial. A pooled analysis from this trial in addition to MagnetisMM-1 and MagnetisMM-9 was recently presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2023 with encouraging results for 86 patients who had previously received a BCMA-directed ADC or CAR T-cell therapy, with 9.3% of patients previously receiving both. The ORR was 45.3%, and 17.4% of patients achieved at least a CR. In responding patients, median time to response was 1.9 months while duration of response was not reached. Progression free survival was 4.8 months, and overall survival was not reached by 10 months of follow-up. Hematologic adverse events and the occurrence of CRS appear slightly lower with elranatamab, though cross-trial comparison of other agents is limited.^{16,17} Further clinical trials on combining these agents with other anti-myeloma medications and with each other are already ongoing. Presented at ASCO 2023 Annual Meeting, the phase Ib RedirecTT-1 trial assessed 63 patients with triple-class-exposed relapsed or refractory multiple myeloma treated with a dual BiTE regimen consisting of teclistamab and talquetamab, resulting in an impressive ORR of 84%.¹⁸ Future reporting from these trials in addition to real-world data and toxicity experience will continue to shed light on the best approach to sequencing and combining these therapies.

While BiTE therapies offer a unique approach to the treatment of relapsed and refractory multiple myeloma with impressive clinical outcomes, the optimal way in which to utilize them is not yet known. Through careful assessment of individual patient preference, SDOH, rate of disease progression, prior therapies received, review of the available data, and consideration of any unique toxicities, clinicians must craft patient-centered treatment plans for patients needing T-cell redirection with BiTEs on a case-by-case basis. ●●

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HELP PATIENTS ANSWER THESE + OTHER QUESTIONS ABOUT IMMUNO-ONCOLOGY FOR CANCER CARE

IMMUNE CHECKPOINT INHIBITORS

What are Immune Checkpoint Inhibitors?

How do they work?

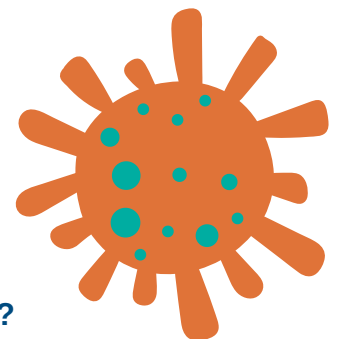
What are the Side Effects?

CELLULAR THERAPY

What is CAR T-Cell Therapy?

What are the Side Effects?

Is financial support available?



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Burnout: A Caregiver's Perspective



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Over time, cancer treatment has increasingly shifted to the outpatient setting, reducing inpatient admissions and length of stay. As a result, informal caregivers, such as family members or friends, play an increasingly larger role in the daily care of the cancer patient, assisting with tasks that were often completed by trained providers. The role of the caregiver may vary, but often includes a broad range of tasks: assisting with activities of daily living, providing companionship, emotional and financial support, treatment administration and compliance, symptom identification and management, and sharing the decision-making role with the patient.^{1,2}

While assuming the role of a caregiver can be rewarding and provide satisfaction and purpose, caregiving can also be demanding and lead to emotional, physical, and spiritual distress and financial difficulties—all of these contributing to caregiver burnout.^{3,4,5} Most healthcare systems focus on the care of the cancer patient, failing to identify caregiver burnout and provide guidance to support the caregiver along the cancer care continuum. This article conveys two caregivers' perspectives on caregiver burnout: how it manifests, factors contributing to burnout, how to cope with caregiver burnout, and what we can do better to alleviate it.

What was your understanding of caregiver burnout before experiencing it yourself? How did it manifest?

KH

I assumed that caregiver burnout was something reserved for spouses, or at least someone living with the patient. I thought that it would manifest as annoyance or depression, lower energy output, compromised productivity. I do not live with the patient (my mother, who lives with my father), but I did experience caregiver burnout that, to be honest, I am still working through. I didn't disengage immediately, but I began to over time. My relationships with everyone besides the patient suffered. Sleep became difficult, which over time

led to completely giving up my favorite hobbies: most notably, running, which is a substantial part of my identity. The most surprising feature for me was that I became angry, not toward the patient, but I realized I resented anyone else in our family or our circle who seemed able to find time to rest and care for themselves. Physically, I realized I had new, regular headaches and gained weight.

SW

My dad was diagnosed with stage IV colon cancer the summer before my sophomore year in high school. I am an only child and so, my Mama and I tag teamed his care. She was primary, but as she was working to keep income coming in, I helped to pick him up from appointments. We did this for almost 4 years and then he died. Fast forward 5 years and my Mama was diagnosed with stage IV colon cancer as well. Motivated by things experienced with Daddy, I decided to go to pharmacy school, so at the time Mama was diagnosed I was in my third year. When I started my APPEs, my preceptors were amazing and worked with me, so that I could take her to and from chemotherapy and be there for her. As I had been in school with my dad (high school and freshman year of college), juggling these priorities was not new for me. However, what was new was it was just me and my mom. She went from caregiver to patient and I went from extra help to primary caregiver. She was fit and able to

"It can happen to any of us. We aren't exempt, just because we know the system. In fact, we may be even more susceptible to burnout."

work, take herself to appointments, and take care of herself for a while. Then she had brain metastases that caused peripheral vision loss and from then on she did not drive much, so I would take her to chemotherapy every other week and to all of her appointments. She had two craniotomies and stereotactic body radiotherapy for her brain metastases, was in a clinical trial, and had several lines of therapy. She was treated for colon cancer for almost 9.5 years before she died. So much of it was just my life, our normal, we settled into a routine and we made it work. During this time, I lived 2.5 hours away as the closest job I could initially get out of residency as an oncology pharmacist was there. There was a lot of driving and a lot of times where it was hard for me to manage it all, though my supervisors and colleagues were amazing and made it as easy on me as they could. There were times where we did tag team to have others drive her depending on the circumstance, though there were still times where even when this occurred, I would have to unexpectedly drive down as a new complication occurred. I would not say that I truly had caregiver burnout because I loved my Mama and was happy to help her, I just sometimes felt pulled in so many directions and there were times where I felt torn between helping her and living my life. My friends and family were very supportive and helped when they could, but I also liked being the one that helped the most because we had a bond and a routine.

What factors contributed most to burnout?**KH**

Volume and Denial. Volume: While I assumed that working in Oncology would actually be beneficial, I suspect now, with hindsight, that I became burned out faster because my exposure to cancer and healthcare was constant. The subject matter was relentless. Denial: I was unprepared in part because I assumed that her husband would be a proxy; however, between technology issues, health literacy, and an inability to accept the prognosis, he was unable to provide meaningful support.

SW

I think my burnout was more so in my job. Being an inpatient hematology/oncology pharmacist dealing with cancer every day and dealing with it in my personal life was hard, as there was no real escape. Then when Mama died, she died at the hospital where I worked, so I found myself really struggling at being able to provide the same care that I did being in that environment. I sought out a change in scenery and a new job at a different place, which has really helped with my mental health and career burnout feelings. I also was a bit lost, not having her to take care of anymore as that was a big part of my identity for so long. In some ways the job helped with that because I did know my role there, but once I changed jobs, I had to re-define that and find my footing again.

What can we, as pharmacists and members of the healthcare team, do to help alleviate caregiver burnout?**KH**

My team is using a quality-of-life questionnaire that asks frank and uncomfortable questions, which I have found may help identify who the caregivers are. The survey has also inspired deeper conversations with patients that might help us offer additional resources to the family. In my experience, I was initially hesitant to call myself a caregiver, OR to admit to being “burned out” because I didn’t feel I could be. It shouldn’t be warranted: I came home to my house and my family most nights. I did not take time away from work. I was tired and angry, not depressed. I could justify reduced productivity. I was just being pulled in too many directions. I would like to see more resources with more questions and more open and inclusive wording. I would like to see more literature directed to supporting family as a whole or addressing stress and strain of cancer on friends and family members. I think I could have identified what I was going through earlier if I was not reticent to adopt the terminology.

SW

I talk to my caregivers just as much if not more than my patients. Make them feel supported because if they do not or if they do not take care of themselves, it is hard to take care of their loved one. You can’t pour from an empty cup. I have linked them (with permission) with other caregivers in similar situations and talked to them about resources available.

What advice would you share with someone struggling with caregiver burnout? What coping mechanisms have you found helpful? What ways have you found to take care of yourself during particularly stressful times?**KH**

I hated to approach my husband and ask him to do anything else for me when I knew that he was doing so much to maintain the home and take care of our children, but I asked him to help me structure my days to allow - if nothing else - 30 minutes to myself. Usually that is spent running, or exercising, or walking, or just being outside. The accountability of his asking how I’ll spend my 30 minutes has been truly helpful. I see a therapist regularly, and during the most stressful periods, I saw her as frequently as twice a month. We are fortunate to be able to afford a cleaning service twice a month that has helped me from being constantly overwhelmed. I have taken a couple of sick days, which I had never really done since I started primarily working from home.

SW

Grace. Give yourself grace and know that you are enough, exactly as you are and exactly what you can do is enough. Remember the things that bring you joy and make time for them. Fill your cup however and whenever you can. Remember that it is okay to ask for help. You do not have to carry the burden alone and do it all alone; others will help, but you have to ask for it. There is no shame or weakness in asking for and receiving help. Others like having a purpose and feeling as if they contributed as well. There are also a lot of therapists that specialize in helping caregivers; they are definitely a resource worth pursuing and can be very helpful for processing and developing coping strategies. I did not go to my therapist until after my mom died. I tried a couple, but I was not very committed. Looking back, it would have been helpful for me to have been more committed sooner.

Please feel free to share anything else about caregiver burnout and your experience that you think would be helpful for HOPA News readers to know.**KH**

It can happen to any of us. We aren’t exempt, just because we know the system. In fact, we may be even more susceptible to burnout. And it is hard, knowing things. Balancing knowing guidelines and outcomes and side effects with applying that knowledge to someone we love is taxing in a way that I can’t explain. Some days it is impossible to reconcile the clinical side of this patient case with the fact that this patient is my mother.

SW

I think there needs to be more of a focus on helping young caregivers: the ones trying to start careers, date, start families, all while juggling caregiving. There really is not a whole lot out there. There needs to be more resources about how to utilize things like family and medical leave, how to fill out certain paperwork, and how to re-find yourself and your purpose post-caregiving.

SECTION

A cancer diagnosis affects both patients and their caregivers. When asked whether the healthcare team discussed caregiver burnout, provided information, or made referrals to resources during the cancer care process, both KH and SW answered “no”.

Healthcare providers must be aware of the needs of the caregiver and must improve access to multidisciplinary assistance to address the multifaceted needs of today’s cancer patient caregiver. ●●

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REDEFINE EXPECTATIONS IN 3L mCRC¹

LONSURF in combination with bevacizumab

INDICATION

LONSURF is indicated as a single agent or in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Severe Myelosuppression: In the 1114 patients who received LONSURF as a single agent, LONSURF caused severe or life-threatening myelosuppression (Grade 3-4) consisting of neutropenia (38%), anemia (17%), thrombocytopenia (4%) and febrile neutropenia (3%). Three patients (0.3%) died due to neutropenic infection/sepsis; four other patients (0.5%) died due to septic shock. A total of 14% of patients received granulocyte-colony stimulating factors. In the 246 patients who received LONSURF in combination with bevacizumab, LONSURF caused severe or life-threatening myelosuppression (Grade 3-4) consisting of neutropenia (52%), anemia (5%), thrombocytopenia (4%) and febrile neutropenia (0.4%). One patient (0.4%) died due to abdominal sepsis and two other patients (0.8%) died due to septic shock. A total of 29% of patients received granulocyte-colony stimulating factors. Obtain complete blood counts prior to and on Day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for severe myelosuppression and resume at the next lower dosage.

Embryo-Fetal Toxicity: LONSURF can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 6 months after the final dose.

USE IN SPECIFIC POPULATIONS

Lactation: It is not known whether LONSURF or its metabolites are present in human milk. There are no data to assess the effects of LONSURF or its metabolites on the breastfed child or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with LONSURF and for 1 day following the final dose.

Male Contraception: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose.

Geriatric Use: Patients 65 years of age or older who received LONSURF in combination with bevacizumab had a higher incidence of the following hematologic laboratory abnormalities compared to patients younger than 65 years: Grade 3 or 4 neutropenia (60% vs 46%) and Grade 3 or 4 thrombocytopenia (5% vs 4%).

Renal Impairment: No adjustment to the starting dosage of LONSURF is recommended in patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min). Reduce the starting dose of LONSURF for patients with severe renal impairment (CLcr of 15 to 29 mL/min) to a recommended dosage of 20 mg/m².

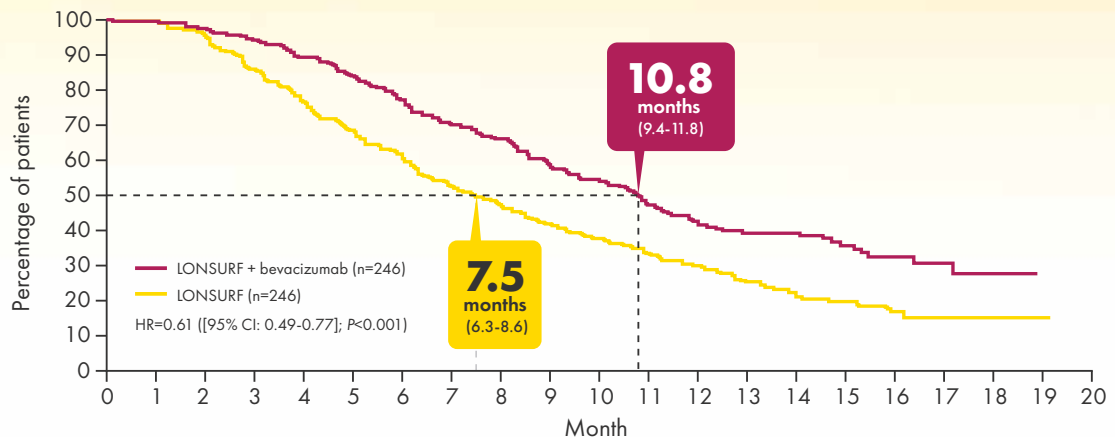
Scan this QR code or visit LONSURFhcp.com
to learn more about this combination regimen



LONSURF + bevacizumab IMPROVED OVERALL SURVIVAL¹

EFFICACY: PRIMARY ENDPOINT

Median OS increased by >3 months



No. at risk

LONSURF + bevacizumab	246	244	239	230	217	203	183	160	149	131	119	104	88	69	52	37	24	13	2	0	0
LONSURF	246	242	230	205	184	163	143	120	108	95	85	76	63	44	24	16	10	5	2	1	0

Results were consistent across subgroups regardless of age, sex, location of primary disease, number of metastatic sites, RAS mutation status, and prior bevacizumab treatment.²

SUNLIGHT Study Design¹

SUNLIGHT was a phase 3, international, randomized, open-label study to evaluate the efficacy and safety of LONSURF used in combination with bevacizumab vs LONSURF alone in patients with previously treated mCRC. The primary endpoint was OS and a secondary endpoint was PFS.

3L, third-line; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival.

SELECTED IMPORTANT SAFETY INFORMATION (cont'd)

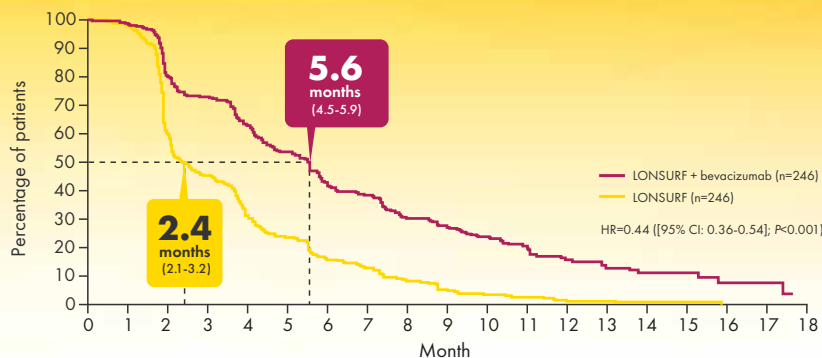
USE IN SPECIFIC POPULATIONS (cont'd)

Hepatic Impairment: Do not initiate LONSURF in patients with baseline moderate or severe (total bilirubin > 1.5 times ULN and any AST) hepatic impairment. Patients with severe hepatic impairment (total bilirubin > 3 times ULN and any AST) were not studied. No adjustment to the starting dosage of LONSURF is recommended for patients with mild hepatic impairment.

ADVERSE REACTIONS

Serious adverse reactions occurred in 25% of patients. The most frequent serious adverse reactions ($\geq 2\%$) were intestinal obstruction (2.8%), and COVID-19 (2%). Fatal adverse reactions occurred in 1.2% of patients who received LONSURF in combination with bevacizumab, including rectal fistula (0.4%), bowel perforation (0.4%) and atrial fibrillation (0.4%).

LONSURF + bevacizumab IMPROVED PROGRESSION-FREE SURVIVAL^{1,2}



EFFICACY: SECONDARY ENDPOINT
Median PFS increased by >3 months

No. at risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
LONSURF + bevacizumab	246	242	198	179	153	128	99	89	70	61	52	43	25	18	13	7	4	2	0
LONSURF	246	236	147	109	74	56	36	29	19	12	8	6	2	2	1	1	0	0	0

SELECTED IMPORTANT SAFETY INFORMATION (cont'd) ADVERSE REACTIONS (cont'd)

The most common adverse reactions or laboratory abnormalities ($\geq 20\%$ in incidence) in patients treated with LONSURF in combination with bevacizumab vs LONSURF alone were neutropenia (80% vs 68%), anemia (68% vs 73%), thrombocytopenia (54% vs 29%), fatigue (45% vs 37%), nausea (37% vs 27%), increased aspartate aminotransferase (34% vs 28%), increased alanine aminotransferase (33% vs 23%), increased alkaline phosphatase (31% vs 36%), decreased sodium (25% vs 20%), diarrhea (21% vs 19%), abdominal pain (20% vs 18%), and decreased appetite (20% vs 15%).

Please see brief summary of Prescribing Information below and on adjacent pages.

References: 1. LONSURF. Prescribing Information. Taiho Oncology, Inc; 2023. 2. Prager GW, Taieb J, Fakih M, et al. Trifluridine-tipiracil and bevacizumab in refractory metastatic colorectal cancer. *N Engl J Med.* 2023;388:1657-1667. doi:10.1056/NEJMoa2214963

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LONSURF (trifluridine and tipiracil) tablets, for oral use Initial U.S. Approval: 2015

Brief Summary of Prescribing Information

For complete Prescribing Information, consult official package insert.

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer

LONSURF, as a single agent or in combination with bevacizumab, is indicated for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Myelosuppression

In the 1114 patients who received LONSURF as a single agent, LONSURF caused severe or life-threatening myelosuppression (Grade 3-4) consisting of neutropenia (38%), anemia (17%), thrombocytopenia (4%) and febrile neutropenia (3%). Three patients (0.3%) died due to neutropenic infection/sepsis; four other patients (0.5%) died due to septic shock. A total of 14% of patients received granulocyte-colony stimulating factors.

In the 246 patients who received LONSURF in combination with bevacizumab, LONSURF caused severe or life-threatening myelosuppression (Grade 3-4) consisting of neutropenia (52%), anemia (5%), thrombocytopenia (4%) and febrile neutropenia (0.4%). One patient (0.4%) died due to abdominal sepsis and two other patients (0.8%) died due to septic shock. A total of 29% of patients received granulocyte-colony stimulating factors. Obtain complete blood counts prior to and on Day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for severe myelosuppression and resume at the next lower dosage [see Dosage and Administration (2.2) in the full Prescribing Information].

5.2 Embryo-Fetal Toxicity

Based on animal studies and its mechanism of action, LONSURF can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dosage levels resulting in exposures lower than those achieved at the recommended dosage of 35 mg/m² twice daily. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use an effective method of contraception during

treatment with LONSURF and for at least 6 months after the final dose [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

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

- Severe Myelosuppression [see Warnings and Precautions (5.1)]

6.1 Clinical Trials Experience

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

The data described in the WARNINGS AND PRECAUTIONS section and below reflect exposure to LONSURF at the recommended dose in 533 patients with metastatic colorectal cancer in RECOURSE, 246 patients with metastatic colorectal cancer treated with LONSURF as monotherapy in SUNLIGHT and 335 patients with metastatic gastric cancer in TAGS. Among the 1114 patients who received LONSURF as a single agent, 12% were exposed for 6 months or longer and 1% were exposed for 12 months or longer. The most common adverse reactions or laboratory abnormalities ($\geq 10\%$) were neutropenia, anemia, thrombocytopenia, fatigue, nausea, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

Among the 246 patients with metastatic colorectal cancer treated with LONSURF in combination with bevacizumab in SUNLIGHT, 39% were exposed for 6 months or longer, and 14% were exposed for 12 months or longer. The most common adverse reactions or laboratory abnormalities ($\geq 20\%$) were neutropenia, anemia, thrombocytopenia, fatigue, nausea, increased AST, increased ALT, increased alkaline phosphatase, decreased sodium, diarrhea, abdominal pain, and decreased appetite.

Metastatic Colorectal Cancer

LONSURF as a single agent

The safety of LONSURF was evaluated in RECOURSE, a randomized (2:1), double-blind, placebo-controlled trial in patients with previously treated metastatic colorectal cancer [see Clinical Studies (14.1) in the full Prescribing Information]. Patients received LONSURF 35 mg/m²/dose (n=533) or placebo (n=265) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. In RECOURSE, 12% of patients received LONSURF for more than 6 months and 1% of patients received LONSURF for more than 1 year.

The study population characteristics were: median age 63 years; 61% male; 57% White, 35% Asian, and 1% Black.

The most common adverse reactions or laboratory abnormalities ($\geq 10\%$ in incidence) in patients treated with LONSURF at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

In RECURSE, 3.6% of patients discontinued LONSURF for an adverse reaction and 14% of patients required a dose reduction. The most common adverse reactions or laboratory abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

Table 3 and Table 4 list the adverse reactions and laboratory abnormalities (graded using CTCAE v4.03), respectively, observed in RECURSE.

Table 3 Adverse Reactions ($\geq 5\%$) in Patients Receiving LONSURF and at a Higher Incidence ($>2\%$) than in Patients Receiving Placebo in RECURSE

Adverse Reactions	LONSURF (N=533)		Placebo (N=265)	
	All Grades (%)	Grades 3-4* (%)	All Grades (%)	Grades 3-4* (%)
General				
Asthenia/fatigue	52	7	35	9
Pyrexia	19	1.3	14	0.4
Gastrointestinal				
Nausea	48	1.9	24	1.1
Diarrhea	32	3	12	0.4
Vomiting	28	2.1	14	0.4
Abdominal pain	21	2.4	19	3.8
Stomatitis	8	0.4	6	0
Metabolism and nutrition				
Decreased appetite	39	3.6	29	4.9
Infections†				
	27	7	16	4.9
Nervous system				
Dysgeusia	7	0	2.3	0
Skin and subcutaneous tissue				
Alopecia	7	0	1.1	0

*No Grade 4 definition for nausea, abdominal pain, or fatigue in National Cancer Institute Common Terminology

† Incidence reflects 64 preferred terms in the Infections and Infestations system organ class.

Table 4 Laboratory Abnormalities in RECURSE

Laboratory Parameter*	LONSURF		Placebo	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematologic				
Anemia†	77	18	33	3
Neutropenia	67	38	0.8	0
Thrombocytopenia	42	5	8	0.4

* Worst Grade at least one grade higher than baseline, with percentages based on number of patients with post-baseline samples, which may be < 533 (LONSURF) or 265 (placebo)

† One Grade 4 anemia adverse reaction based on clinical criteria was reported

In RECURSE, pulmonary emboli occurred more frequently in LONSURF-treated patients (2%) compared to no patients on placebo.

LONSURF in combination with bevacizumab

The safety of LONSURF in combination with bevacizumab was evaluated in SUNLIGHT, an international, randomized, open label study in patients with previously treated metastatic colorectal cancer [see Clinical Studies (14.1) in the full Prescribing Information].

The study population characteristics were: median age 63 years (20 to 90 years); 52% male; 88% White, 1.4% Black, 0.2% Asian, 0.2% American Indian or Alaska Native, and 9.6% were unknown; and baseline ECOG performance status 0 (46%), 1 (54%), or 2 (0.2%).

Serious adverse reactions occurred in 25% of patients. The most frequent serious adverse reactions ($\geq 2\%$) were intestinal obstruction (2.8%), and COVID-19 (2%). Fatal adverse reactions occurred in 1.2% of patients who received LONSURF in combination with bevacizumab, including rectal fistula (0.4%), bowel perforation (0.4%) and atrial fibrillation (0.4%).

Permanent treatment discontinuation due to an adverse reaction occurred in 13% of patients. The adverse reaction which resulted in permanent treatment discontinuation in $\geq 2\%$ of patients was fatigue.

Dosage reductions due to an adverse reaction or laboratory abnormality occurred in 7% of patients. At least one dose reduction in 3.7% of patients was required for neutropenia.

Dosage interruptions due to an adverse reaction occurred in 11% of patients who received LONSURF in combination with bevacizumab. The adverse reaction that required dosage interruption in $\geq 2\%$ of patients was nausea.

The most common adverse reactions or laboratory abnormalities ($\geq 20\%$ in incidence) in patients treated with LONSURF in combination with bevacizumab were neutropenia, anemia, thrombocytopenia, fatigue, nausea, increased aspartate aminotransferase, increased alanine aminotransferase, increased alkaline phosphatase, decreased sodium, diarrhea, abdominal pain, and decreased appetite. Table 5 and Table 6 list the adverse reactions and laboratory abnormalities, respectively, observed in SUNLIGHT.

Table 5: Adverse Reactions ($\geq 5\%$) in SUNLIGHT

Adverse Reactions	LONSURF + Bevacizumab (N=246) (%)		LONSURF (N=246) (%)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Gastrointestinal disorders				
Nausea	37	1.6	27	1.6
Diarrhea*	21	1.2	19	2.4
Abdominal pain*	20	2.8	18	3.7
Vomiting*	19	0.8	15	1.6
Stomatitis*	13	< 0.4	4.1	0
Constipation	11	0	11	0.8
General disorders and administration site conditions				
Fatigue*	45	5	37	8
Pyrexia	4.9	0	6	0.4
Infections and infestations*				
	31	8	24	8
Metabolism and nutrition disorders				
Decreased appetite	20	< 0.8	15	1.2
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	18	1.2	11	2
Nervous system disorder				
Headache	8	0	3.7	0
Vascular disorders				
Hypertension*	11	6	2	1.2
Hemorrhage*	10	1.2	3.7	0.8
Renal and urinary disorders				
Proteinuria	6	0.8	1.2	0

*Represents a composite of multiple related terms

Table 6: Select Laboratory Abnormalities ($\geq 10\%$) in SUNLIGHT

Laboratory parameters	LONSURF + Bevacizumab ^a		LONSURF ^a	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Neutrophils decreased	80	52	68	39
Hemoglobin decreased	68	5	73	11
Platelets decreased	54	4.1	29	0.8
Chemistry				
Aspartate aminotransferase increased	34	2.1	28	1.2
Alanine aminotransferase increased	33	3.3	23	0.4
Alkaline phosphatase increased	31	0.8	36	1.2
Sodium decreased	25	2.1	20	3.3
Potassium increased	17	0	15	0
Potassium decreased	12	0.8	12	2.5
Creatinine increased	12	0.8	15	0

^aEach test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: LONSURF + bevacizumab group (n=242 patients) and LONSURF group (range: 240 to 242 patients).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data and its mechanism of action [see *Clinical Pharmacology (12.2) in the full Prescribing Information*], LONSURF can cause fetal harm. LONSURF caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation at doses resulting in exposures lower than or similar to human exposures at the recommended clinical dose (see *Data*). There are no available data on LONSURF use in pregnant women. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

Trifluridine/tipiracil was administered orally once daily to female rats during organogenesis at dose levels of 15, 50, and 150 mg/kg [trifluridine (FTD) equivalent]. Decreased fetal weight was observed at FTD doses ≥ 50 mg/kg (approximately 0.33 times the FTD exposure at the clinical dose of 35 mg/m² twice daily). At the FTD dose of 150 mg/kg (approximately 0.92 times the FTD exposure at the clinical dose of 35 mg/m² twice daily) embryo-lethality and structural anomalies (kinked tail, cleft palate, ectrodactyly, anasarca, alterations in great vessels, and skeletal anomalies) were observed.

8.2 Lactation

Risk Summary

There are no data on the presence of trifluridine, tipiracil or its metabolites in human milk or its effects on the breastfed child or on milk production. In nursing rats, trifluridine and tipiracil or their metabolites were present in breast milk (see *Data*). Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with LONSURF and for 1 day following the final dose.

Data

Radioactivity was excreted in the milk of nursing rats dosed with trifluridine/tipiracil containing ¹⁴C-FTD or ¹⁴C-tipiracil (TPI). Levels of FTD-derived radioactivity were as high as approximately 50% of the exposure in maternal plasma an hour after dosing with trifluridine/tipiracil and were approximately the same as those in maternal plasma for up to 12 hours following dosing. Exposure to TPI-derived radioactivity was higher in milk than in maternal plasma beginning 2 hours after dosing and continuing for at least 12 hours following administration of trifluridine/tipiracil.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating LONSURF [see *Use in Specific Populations (8.1)*].

Contraception

LONSURF can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*].

Females

Advise females of reproductive potential to use effective contraception during treatment with LONSURF and for at least 6 months after the final dose.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose [see *Nonclinical Toxicology (13.1) in the full Prescribing Information*].

8.4 Pediatric Use

Safety and effectiveness of LONSURF in pediatric patients have not been established.

Juvenile Animal Toxicity Data

Dental toxicity including whitening, breakage, and malocclusion (degeneration and disarrangement in the ameloblasts, papillary layer cells and odontoblasts) were observed in rats treated with trifluridine/tipiracil at doses ≥ 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m² twice daily).

8.5 Geriatric Use

Of the 1114 patients with metastatic colorectal cancer or gastric cancer who received single agent LONSURF in clinical studies, 45% were 65 years of age or over, and 11% were 75 and over. In the 246 patients who received LONSURF in combination with bevacizumab; 41% were 65 years of age or over, and 10% were 75 and over. While these studies were not designed to detect a difference

in efficacy, no overall differences were observed in patients 65 or older versus younger patients with either LONSURF as a single agent or LONSURF in combination with bevacizumab.

Patients 65 years of age or older who received LONSURF as a single agent had a higher incidence of the following hematologic laboratory abnormalities compared to patients younger than 65 years: Grade 3 or 4 neutropenia (46% vs 32%), Grade 3 anemia (20% vs 14%), and Grade 3 or 4 thrombocytopenia (6% vs 3%). Patients 65 years of age or older who received LONSURF in combination with bevacizumab had a higher incidence of the following hematologic laboratory abnormalities compared to patients younger than 65 years: Grade 3 or 4 neutropenia (60% vs 46%) and Grade 3 or 4 thrombocytopenia (5% vs 4%).

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min as determined by the Cockcroft-Gault formula). Reduce the dose of LONSURF for patients with severe renal impairment (CLcr of 15 to 29 mL/min) [see *Dosage and Administration (2.3) in the full Prescribing Information*]. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end stage renal disease.

8.7 Hepatic Impairment

No adjustment to the starting dosage of LONSURF is recommended for patients with mild hepatic impairment. Do not initiate LONSURF in patients with baseline moderate or severe (total bilirubin >1.5 times ULN and any AST) hepatic impairment [see *Clinical Pharmacology (12.3) in the full Prescribing Information*].

17 PATIENT COUNSELING INFORMATION

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

Severe Myelosuppression

Advise patients to immediately contact their healthcare provider if they experience signs or symptoms of infection and advise patients to keep all appointments for blood tests [see *Warnings and Precautions (5.1)*].

Gastrointestinal Toxicity

Advise patients to contact their healthcare provider for severe or persistent nausea, vomiting, diarrhea, or abdominal pain [see *Adverse Reactions (6.1)*].

Administration Instructions

Advise patients that LONSURF is available in two strengths and they may receive both strength tablets to provide the prescribed dosage.

Advise patients to take LONSURF with food [see *Dosage and Administration (2.1) in the full Prescribing Information*].

Advise patients not to retake doses of LONSURF that are vomited or missed and to continue with the next scheduled dose.

Advise patients that anyone else who handles their medication should wear gloves [see *References (15) in the full Prescribing Information*].

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.2), Use in Specific Populations (8.3)*].

Advise female patients of reproductive potential to use effective contraception during treatment with LONSURF and for at least 6 months after the final dose [see *Warnings and Precautions (5.2), Use in Specific Populations (8.3)*].

Advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose [see *Use in Specific Populations (8.3), Nonclinical Toxicology (13.1) in the full Prescribing Information*].

Lactation

Advise women not to breastfeed during treatment with LONSURF and for 1 day following the final dose [see *Use in Specific Populations (8.2)*].



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LON-PM-US-1722

Duration of Response to Poly (ADP-Ribose) Polymerase Inhibitors for Maintenance Treatment of Ovarian Cancer in Patients With Germline or Somatic Homologous Recombination Deficiency



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Olaparib, the first poly (ADP-ribose) polymerase (PARP) inhibitor approved by the United States Food and Drug Administration (FDA) was initially indicated for monotherapy in patients with ovarian cancer and germline *BRCA* mutations after ≥ 3 lines of chemotherapy.¹ Since that time, olaparib, rucaparib and niraparib have gained FDA approvals for use in the maintenance setting, including patients without homologous recombination deficiency (HRD).²⁻⁴

Before reviewing the mechanism of PARP inhibitors, it is important to examine the role of PARP proteins. PARP proteins play an essential role in base excision repair, a mechanism used to repair single-stranded deoxyribonucleic acid (DNA) breaks. PARP inhibitors target these proteins, inhibiting their ability to bind and initiate the repair process. An accumulation of single-stranded DNA breaks can result in double-stranded DNA breaks which are restored via homologous recombination repair (HRR).^{5,6}

HRR is a complex process that includes many proteins and genes, most notably *BRCA1* and *BRCA2*.⁶ When harboring a mutation in *BRCA1*, *BRCA2*, or other HRR genes, cells are considered to have HRD and must use an alternative repair mechanism to fix double-stranded DNA breaks.⁷ By pairing HRD with a PARP inhibitor, a concept referred to as synthetic lethality is exploited, and the impairment of multiple DNA repair mechanisms leads to more certain cell death.⁵⁻⁷

Germline and somatic mutations are two different types of HRR mutations; both lead to HRD.⁷ The key differences between the mutations include the inheritance pattern, the location of the mutations, and the manner in which they change over time. Approximately 41-50% of ovarian carcinomas are estimated to exhibit HRD.⁵ We have limited data directly comparing the duration of response with maintenance PARP inhibitors for patients with germline or somatic HRD. Defining this response could provide clarity for practitioners regarding the expected duration of response to PARP inhibitor maintenance therapy based on the type of mutation harbored.

In this retrospective study, we aimed to determine if germline or somatic HRD impacted the duration of response to PARP inhibitors used for the maintenance treatment of ovarian cancer, regardless of the line of therapy.

Methods

A single-center, retrospective chart review was conducted for patients who received a PARP inhibitor for front-line or subsequent-line maintenance treatment from May 1, 2017, to September 1, 2020. Patients were aged ≥ 18 years with ovarian, fallopian tube, or primary peritoneal cancer who received follow-up care at the University of Kansas Health System. The patients had previously undergone tumor molecular testing or next-generation sequencing to determine their HRD status. Patients were considered to have HRD if they exhibited mutations in any of the following genes: *BRCA1*, *BRCA2*, *EMSY*, *PTEN*, *RAD51C*, *RAD51D*, *RAD50*, *ATM*/*ATR*, *FANC*, *BARD1*, *BRIP1*, *CHEK1*, *CHEK2*, *FAM175A*, *NBN*, *PALB2*, *MRE11A*, *MMR*, and *TP53*.⁵

The primary end point of time to next treatment (TTNT) was defined as the time from PARP inhibitor initiation to day 1 of subsequent chemotherapy and was compared between 3 patient cohorts: the presence of germline HRD, the presence of somatic HRD, or no known HRD. The event of interest occurs when a patient starts the subsequent treatment. TTNT is a helpful measure of the duration of clinical benefit and has advantages over standard end points for our study. TTNT and progression free survival (PFS) have similar interpretations, but the event of PFS is disease progression. Because clinician-assessed disease progression is more difficult to abstract during chart review, the surrogate marker of TTNT was chosen to measure clinical benefit.

Cox Proportional Hazards (CoxPH) models were used to test the association between TTNT and HRD mutation and were fit using the CoxPH function. A subsequent CoxPH model was fit adjusting for PARP inhibitor line of therapy (front-line or subsequent line). Since very few patients had experienced the event ($n=28$, 37.8%), restricted mean time to subsequent treatment was used to represent the average event-free time up to 25 months, which was the latest follow-up time recorded among cohorts.⁸

Results

Of 139 charts reviewed, 74 patients met eligibility criteria. Germline and somatic HRD were identified in 14 and 23 patients, respectively. A total of 2 PATIENTS had both germline and somatic HRD. We assumed that germline HRD takes precedence over somatic HRD based on the known predisposition of inherited cancers with germline mutations.⁷ These patients were included

"Our study helps to answer if the duration of response to PARP inhibitor maintenance therapy differs based on whether an HRD mutation is germline or somatic."

in the germline HRD cohort. The remaining 37 patients had no known HRD.

PARP inhibitor maintenance therapy was used in the front-line setting for 46% of the patients, whereas the other 54% received PARP inhibitors in the subsequent maintenance setting. The most common PARP inhibitor received was olaparib (n=52; 70%), followed by niraparib (n=18; 24%) and rucaparib (n=4; 5%). Additional patient demographics are shown in **Table 1**. Based on Fisher's

exact test of independence between the baseline characteristics and the 3 cohorts, the only characteristic that was significantly different was the PARP inhibitor received.

In all, 33 (44.6%) patients had relapsed disease while receiving PARP inhibitor maintenance therapy, and 28 (84.8%) of those patients received subsequent chemotherapy. These 28 patients were considered events in the TTNT analysis. The remaining 5 patients had not yet started subsequent chemotherapy at the

Table 1. Baseline Characteristics

Characteristic	Overall (n=74)	Germline HRD (n=14)	Somatic HRD (n=23)	No known HRD (n=37)	P value
Median age (range), y	67 (34-90)	62 (38-81)	66 (37-78)	67 (34-90)	0.19
Race					0.47
White, n (%)	68 (92)	12 (86)	21 (91)	35 (95)	
Non-White, n (%)	6 (8)	2 (14)	2 (9)	2 (5)	
Diagnosis					0.41
Ovarian/fallopian tube cancer, n (%)	65 (88)	12 (86)	22 (96)	31 (84)	
Primary peritoneal cancer, n (%)	9 (12)	2 (14)	1 (4)	6 (16)	
Histology type					1
High-grade serous, n (%)	69 (93)	14 (100)	21 (91)	34 (92)	
Clear cell, n (%)	2 (3)	0	1 (4)	1 (3)	
Other, n (%)	3 (4)	0	1 (4)	2 (5)	
Stage at diagnosis					1
Stage III, n (%)	48 (65)	9 (64)	14 (61)	25 (68)	
Stage IV, n (%)	23 (31)	4 (29)	7 (30)	12 (32)	
Unknown, n (%)	3 (4)	1 (7)	2 (9)	0	
Neoadjuvant chemotherapy					0.50
Yes, n (%)	41 (55)	6 (43)	13 (57)	22 (59)	
No, n (%)	33 (45)	8 (57)	10 (43)	15 (41)	
Response to platinum chemotherapy					0.90
Partial, n (%)	16 (22)	2 (14)	4 (17)	10 (27)	
Complete, n (%)	53 (72)	12 (86)	17 (74)	24 (65)	
Other/Unknown	5 (7)	0	2 (9)	3 (8)	
Maintenance line of therapy					0.18
Front-line, n (%)	34 (46)	8 (57)	13 (57)	13 (35)	
Subsequent line, n (%)	40 (54)	6 (43)	10 (43)	24 (65)	
PARP inhibitor					0.002
Olaparib, n (%)	52 (70)	12 (86)	20 (87)	20 (54)	
Niraparib, n (%)	18 (24)	1 (7)	1 (4)	16 (43)	
Rucaparib, n (%)	4 (5)	1 (7)	2 (9)	1 (3)	
CA-125 at PARP inhibitor initiation					0.60
<35 U/mL, n (%)	58 (78)	12 (86)	19 (83)	27 (73)	
≥35 U/mL, n (%)	16 (22)	2 (14)	4 (17)	10 (27)	
HRD mutation					0.41
BRCA1, n (%)	20 (27%)	7 (50%)	13 (57%)	0	
BRCA2, n (%)	21 (28%)	4 (29%)	17 (74%)	0	
Other,* n (%)	10 (14%)	4 (29%)	6 (26%)	0	

*Other HRD mutations included CHEK2, TP53, PALB2, and BRIP1.

CA, cancer antigen; HRD, homologous recombination deficiency; PARP, poly (ADP-ribose) polymerase.

HIGHLIGHTS OF MEMBERS' RESEARCH (continued)

time of data collection and were not considered as events in the TTNT analysis.

The estimated restricted mean TTNT was 13 months for the patients with no known HRD versus 20.7 months for the patients with germline HRD (no known vs germline, HR, 0.25; 95% CI, 0.07-0.83; $P=.02$). Similarly, the estimated restricted mean TTNT was 19.5 months for the patients with somatic HRD (no known vs somatic, HR, 0.33; 95% CI, 0.12-0.89; $P=.03$). There was no significant difference in TTNT between the patients with germline HRD and the patients with somatic HRD (germline vs somatic, HR, 0.74; 95% CI, 0.17-3.13; $P=.68$; **Table 2** and **Figure 1**). The Cox proportional hazard model was then further adjusted for PARP inhibitor maintenance line of therapy (**Figure 2**).

The mean TTNT remained the same for the 3 cohorts, but the HRs associated with mutation status did change. The patients with no known HRD had a significantly shorter TTNT compared with the patients with germline HRD (no known vs germline, 13 months vs 20.7 months; HR, 0.25; 95% CI, 0.07-0.86; $P=.03$). Likewise, the patients with no known HRD had a significantly shorter TTNT compared with patients with somatic HRD (no known vs somatic, 13 months vs 19.5 months; HR, 0.35; 95% CI, 0.13-0.96; $P=.04$). Again, the TTNT was not significantly different between patients with germline HRD and patients with somatic HRD (germline vs somatic, 20.7 months vs 19.5 months; HR, 0.71; 95% CI, 0.17-3.04; $P=.65$).

Discussion

PARP inhibitors have gained several FDA approvals for use in ovarian cancer in the maintenance setting, including patients without HRD. Our study confirmed that patients with no known HRD had a significantly shorter time to subsequent chemotherapy compared to those with germline or somatic HRD. However, there was no significant difference in the duration of response to PARP inhibitor maintenance therapy if a patient had a germline or somatic mutation and the response to PARP inhibitor therapy was preserved regardless of whether it was used in the front-line or subsequent-line maintenance setting.

Our study helps to answer if the duration of response to PARP inhibitor maintenance therapy differs based on whether an HRD mutation is germline or somatic. As the number of indications expands for PARP inhibitors, understanding the impact of gene mutations on response to therapy can guide clinicians in selecting the appropriate maintenance therapy.

This study has limitations. Data collection and accuracy are limited to the completeness and accuracy of the electronic medical record. Because our providers do not use tumor molecular testing that calculates an HRD score, HRD was determined simply by the presence of a mutation in one of the HRR genes. The PARP inhibitor received by patients with no known HRD was significant when compared to the other cohorts. This finding is not unexpected since niraparib was the first PARP inhibitor to be FDA approved in the

Table 2. Cox Proportional Hazard Model Results by HRD Mutation

Parameter	Germline HRD mutation (n=14)	No known HRD mutation (n=37)	Somatic HRD mutation (n=23)	No known HRD mutation (n=37)	Germline HRD mutation (n=14)	Somatic HRD mutation (n=23)
Events, n	3	20	5	20	3	5
Estimated restricted mean TTNT, mo ^a	20.7	13	19.5	13	20.7	19.5
Hazard ratio (95% CI)	0.25 (0.07-0.83)		0.33 (0.12-0.89)		0.74 (0.17-3.13)	
P value	.02		.03		.68	

^aRestricted mean at 25 months.

CI indicates confidence interval; HRD, homologous recombination deficiency; TTNT, time to next treatment.

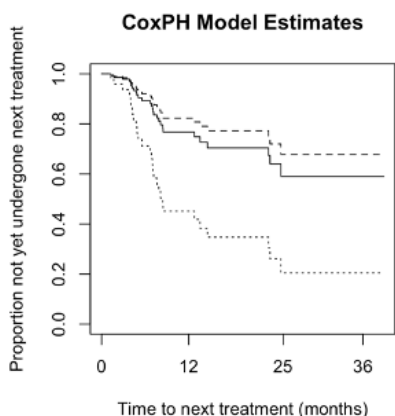


Figure 1. Progression Estimate by HRD Mutation

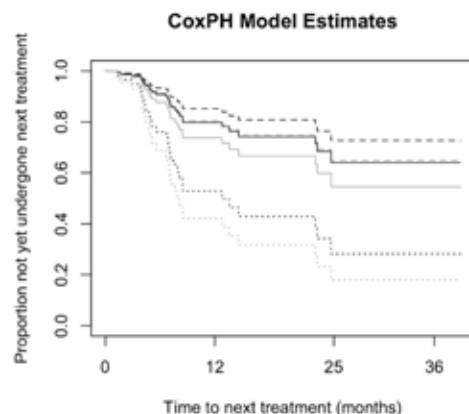


Figure 2. Progression Estimate by HRD Mutation and PARP Inhibitor Line of Therapy

maintenance setting regardless of HRD. While no direct comparisons have been made between the PARPi, no difference in efficacy is expected. The small sample size may hinder the statistical power for detecting differences and associations between the groups.

Conclusion

In this single-center, retrospective chart review, patients with germline or somatic HRD receiving PARP inhibitors for maintenance

treatment of ovarian cancer had a significantly longer TTNT compared with patients with no known HRD, regardless of use in the front-line or subsequent-line setting. There was no difference in TTNT between patients with germline HRD or somatic HRD. Patients and providers may expect similar periods of response regardless of germline or somatic HRD or maintenance line of therapy. ●●

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Precision Oncology - Challenges and Considerations for the Oncology Pharmacist



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Put simply, precision oncology is the use of molecular profiling to help provide the right treatment to the right patient at the right time.¹ In practice, precision oncology is a highly complex approach to personalized medicine in the treatment of patients with cancer. It strives toward accurate, efficient, and effective diagnostic testing and treatment, and uses a variety of testing techniques.^{2,3} In order to successfully utilize precision oncology, not only do clinicians need to know how and what to test, but they must be able to interpret molecular profiling results and identify matched therapies.⁴ Due to its complexities and challenges, pharmacists can be a valuable resource for implementing precision oncology into practice and overcoming logistical challenges and access barriers.

The first incidence of precision medicine in oncology was in 1998 with the discovery of the BCR-ABL rearrangement in chronic myeloid leukemia (CML). This led to the development of imatinib, which received United States (US) Food and Drug Administration (FDA) approval in 2001.⁵ Other examples of early discoveries in precision oncology can be seen in the identification and targeting of the oncogene HER2 and tumor suppressor genes *BRCA1* and *BRCA2*.⁶ Over the past decade, significant advances have been made in precision oncology. A prime example of this can be seen in the treatment of non-small cell lung cancer (NSCLC). The treatment of advanced NSCLC has been transformed due to precision oncology, and it is reported that approximately half of patients are identified as candidates for targeted agents instead of chemotherapy based on biomarker testing.⁵ Other examples are the FDA approval of tumor-agnostic therapies based on genomic biomarkers. These include the approval of pembrolizumab for microsatellite-instability-high (MSI-H) or tumor mutational burden-high (TMB-H) solid tumors, dabrafenib and trametinib for BRAF V600E-mutated solid tumors, and seliprecitinib for all RET fusion-positive cancers.⁷ Guidelines have incorporated precision oncology into their treatment recommendations, with the American Society of Clinical Oncology (ASCO) publishing specific guidelines on molecular testing and the National Comprehensive Cancer Network (NCCN) incorporating biomarker testing in each of their tumor-specific guidelines.⁵

Precision oncology can be daunting for many practitioners due to the complexity and variety of tests that are available. It is reported that nearly 60 nucleic acid-based tests have been approved

by the US Center for Devices and Radiological Health for utilization in oncology.⁸ Next-generation sequencing (NGS), which is a method of sequencing large volumes of DNA and RNA to identify genetic variants, is the most frequently used test in precision oncology. NGS can detect a range of genomic variants, including single nucleotide variants and insertions or deletions, which can result in non-functional proteins that may be oncogenic drivers and ideal targets for therapy.⁵ However, proteomics, transcriptomics, and metabolomics tests are growing in accuracy and accessibility.³ Several considerations must be made when selecting the right molecular test; these include the choice of assay, cost, tissue quantity and quality, and turnaround time.⁵ Advances in NGS technologies have shifted practices from single-target tests to comprehensive genomic

profiling panels (CGP), which can improve turnaround times and time to therapy initiation.^{8,9} Liquid biopsies for circulating tumor DNA (ctDNA) or tumor cells may be useful in situations where tissue biopsies are not feasible, or if tumor heterogeneity is suspected. ctDNA can assess shed DNA from multiple sites, and may be a safer and less expensive option than the tissue biopsy of multiple sites.^{10,11}

After identifying who and what to test, clinicians then face the task of interpreting and applying these results to their patients. Genomic variants can be present yet may not be drivers of pathogenesis,

and mutations expressed at lower allele frequencies may be less successful targets for treatment. The tumor type can also contribute to differences in responses to targeted therapy.¹² Determining if a variant is actionable should include an assessment of whether the variant is a driver of pathogenesis, if there are available therapies that target the variant, and what level of evidence exists for the use of a specific therapy against this variant in the specific tumor type.¹³ Precision oncology databases can be a valuable resource for interpreting results. OncoKB is an FDA-recognized precision oncology database that provides a catalog of pathogenic mutations which are ranked based on evidence of clinical actionability. These databases are a helpful tool, but may face challenges when keeping up-to-date with rapidly emerging data.^{7,9}

There are many practical challenges to the widespread adoption of precision oncology in clinical practice, including inexperience, lack of resources, and cost. Lack of confidence among oncologists in using and interpreting genomic testing can hinder the use of precision oncology in clinical practice. A survey of 1,281 oncologists in the United States found that only 38.2% felt confident in using NGS, highlighting the need for education among healthcare professionals. Pharmacists are well-positioned to have an integral role in providing education to oncologists and other healthcare

"There are many practical challenges to the widespread adoption of precision oncology in clinical practice, including inexperience, lack of resources, and cost."

providers on the utility of precision medicine in oncology, as well as helping to develop internal policies for the use of biomarker testing.¹⁴ Molecular tumor boards can also help to facilitate multidisciplinary input by bringing together experts in precision oncology, but their implementation can be especially challenging at smaller institutions and in community practice.⁹ Cost is another significant barrier to precision oncology, as both sequencing tests and specific therapies can be expensive. Although many insurance companies cover specific tests based on the tumor and indication, reimbursement can be limited for whole-genome sequencing and CGP. Furthermore, off-label therapies can be difficult to access due to insurance and drug costs, which can result in delays of care. Pharmacists can be a valuable resource to identify coverage gaps and financial resources to avoid these gaps in care when prescribing off-label therapies based on genomic testing.¹

Additionally, there are many ethical considerations for precision medicine in oncology. Specifically, gaps between advances in drug development and drug delivery can increase health disparities due to unequal access to technology and resources.⁹ A retrospective study in over 23,000 patients with NSCLC, breast, and colorectal cancers found significant disparities in rates of NGS testing and clinical trial enrollment between patients of African American and White races.¹⁵ In general, it is estimated that only 3-5% of patients are enrolled in clinical trials with precision oncology; these low enrollment rates are often due to access issues and patient ineligibility due to advanced disease and comorbidities. To advance the use of

precision oncology, it is imperative that clinical trials be designed that improve on the rates of matching patients to drugs and expand access based on location and eligibility criteria.¹⁰

Precision medicine is an area in oncology that continues to expand dramatically. Future areas of consideration include novel approaches to drug development based on genomic alterations, improvements in clinical trial design, adoption of more widespread guidelines for comprehensive genomic testing, and the expansion of available tests to further characterize drivers of carcinogenesis. Pharmacists are well-positioned to have an important role in the implementation and analysis of genomic testing. The pharmacist's role in precision oncology may include recommending and interpreting genomic testing, making treatment recommendations, providing patient education, and obtaining off-label medications. In patients who receive off-label therapies or combination regimens which have not been well-studied, pharmacists are capable of making recommendations on appropriate monitoring, dose adjustments, and side effect management. Due to their knowledge of pharmacotherapy, molecular genetics, and cancer biology, pharmacists should be involved in molecular tumor boards and the implementation of institutional workflows for genomic testing, as well as clinical trial design. A multidisciplinary approach to precision oncology, which incorporates oncologists, pharmacists, nurses, and other healthcare providers, is imperative to providing the right care to the right patient and improving access to individualized medicine for all patients. ●●

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Board Update

So Much to Celebrate



LeAnne Kennedy, PharmD, BCOP, CPP, FHOPA
HOPA President (2023-2024)
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With the holidays upon us I hope everyone can enjoy your seasonal traditions – and maybe even start some new ones. As a first-time grandma, I know my family will have plenty of long-standing *and brand-new* ways to celebrate.

HOPA's Celebrates 20 Years

Our association turns 20 next year and staff and the Board of Directors are planning several ways to recognize HOPA's contributions to optimizing cancer care. Look for timelines of oncology pharmacy milestones, as well as key moments in HOPA's history. But looking back is only part of the celebration.

Annual Conference 2024 (AC24) will be held April 3-6 in Tampa, Florida. In addition to registering for the conference, we invite you to get your ticket to step aboard the Yacht Starship on the evening of Friday, April 5. Registration for both AC24 and the gala is now open on our website.

Practice Management 2023 was a Success

In November, about 250 members and other oncology pharmacy professionals gathered in Austin, Texas for PM23. Thank you to the PM Committee for thoughtful programming, including round-table discussions to allow attendees time to reflect on – and share – lessons learned in managing oncology pharmacy practices. Also of note were the Oral Anticancer Agents Collaborative Research Launch and the Industry Relations Council Summit, both of which took place in Austin ahead of PM23.

New Board of Directors Members have been Elected

At the time of this writing, voting had not yet closed but by now, three new Board members have been elected and will begin their terms in April of 2024. The revised HOPA Bylaws will also have been voted on and approved. Thank you to the Nominations and Governance Committees for your work on these important operational and leadership initiatives.

Member Awards will be Announced, along with a New Class of HOPA Fellows

Thank you to everyone who nominated HOPA members, everyone who completed your Fellows application, and to the Recognition Committee who makes our annual awards program a success. Award winners and fellows will be announced soon, and we will celebrate them during AC24 in April.

One Last Appeal to Donate to the HOPA Research Grant Fund

This year's grantees have been selected for the HOPA Research Fund Award (RFA). The RFA relies on donations to help support pharmacist-led research. Please donate on our website to the fund as part of your year-end giving. A gift of any amount is appreciated; donations of \$10, \$15, or \$25 all add up. Thank you in advance for your consideration.

Thank you for all you do for hematology/oncology pharmacy and for HOPA and I will see you in the new year! ●●



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